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(54) **BILIARY TRACT CANCER DETECTION KIT OR DEVICE, AND DETECTION METHOD**

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C12Q 1/6886	(2018.01)
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C12N 15/09	(2006.01)
G01N 33/53	(2006.01)

(52) **U.S. Cl.**
CPC ***C12Q 1/6886*** (2013.01); ***C12N 15/09*** (2013.01); ***C12Q 1/68*** (2013.01); ***G01N 33/53*** (2013.01); ***G01N 33/566*** (2013.01); ***G01N 37/00*** (2013.01); *C12Q 2600/158* (2013.01); *C12Q 2600/178* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides a kit or device for the detection of biliary tract cancer, and a method for detecting biliary tract cancer. The present invention relates to a kit or device for the detection of biliary tract cancer, comprising a nucleic acid capable of specifically binding to miRNA in a sample of a subject, and a method for detecting biliary tract cancer, comprising measuring the miRNA in vitro.

6 Claims, 4 Drawing Sheets

Specification includes a Sequence Listing.

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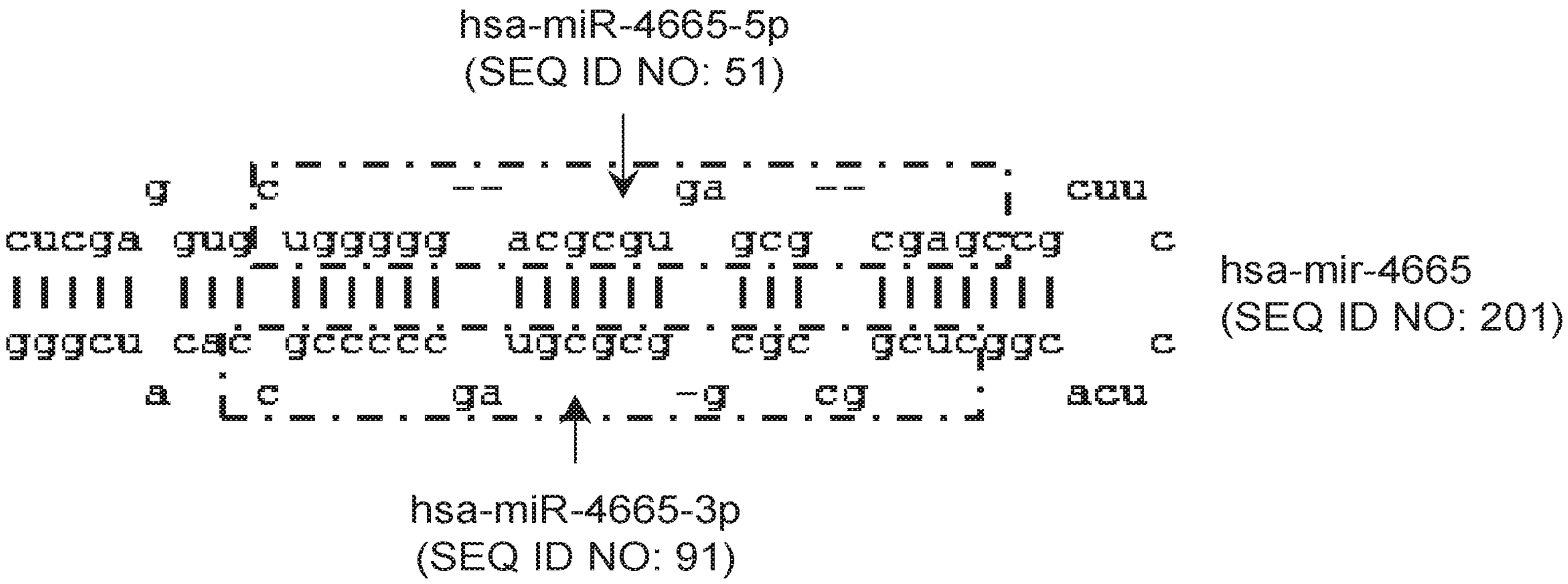
Fig. 1


hsa-miR-4665-5p
(SEQ ID NO: 51)
g c -- ga -- cuu
cucga gug uggggg acgcgu gcg cgagccg c
gggcu cac gccccc ugcgcg cgc gcucggc c
a c ga -g cg acu
hsa-mir-4665
(SEQ ID NO: 201)
hsa-miR-4665-3p
(SEQ ID NO: 91)

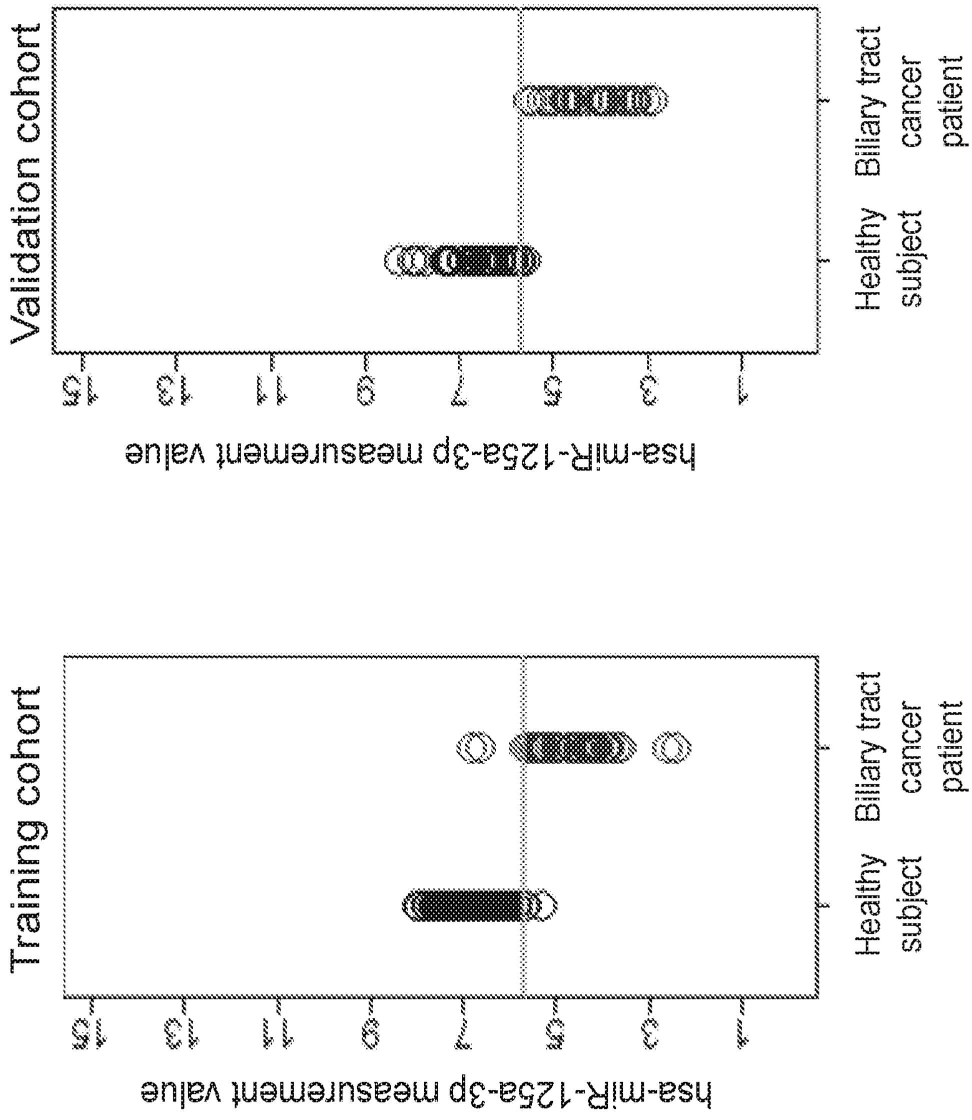

Validation cohort
hsa-miR-125a-3p measurement value
15
13
11
9
7
5
3
1
Healthy subject
Biliary tract cancer patient
Training cohort
hsa-miR-125a-3p measurement value
15
13
11
9
7
5
3
1
Healthy subject
Biliary tract cancer patient

Fig. 2

Fig. 3

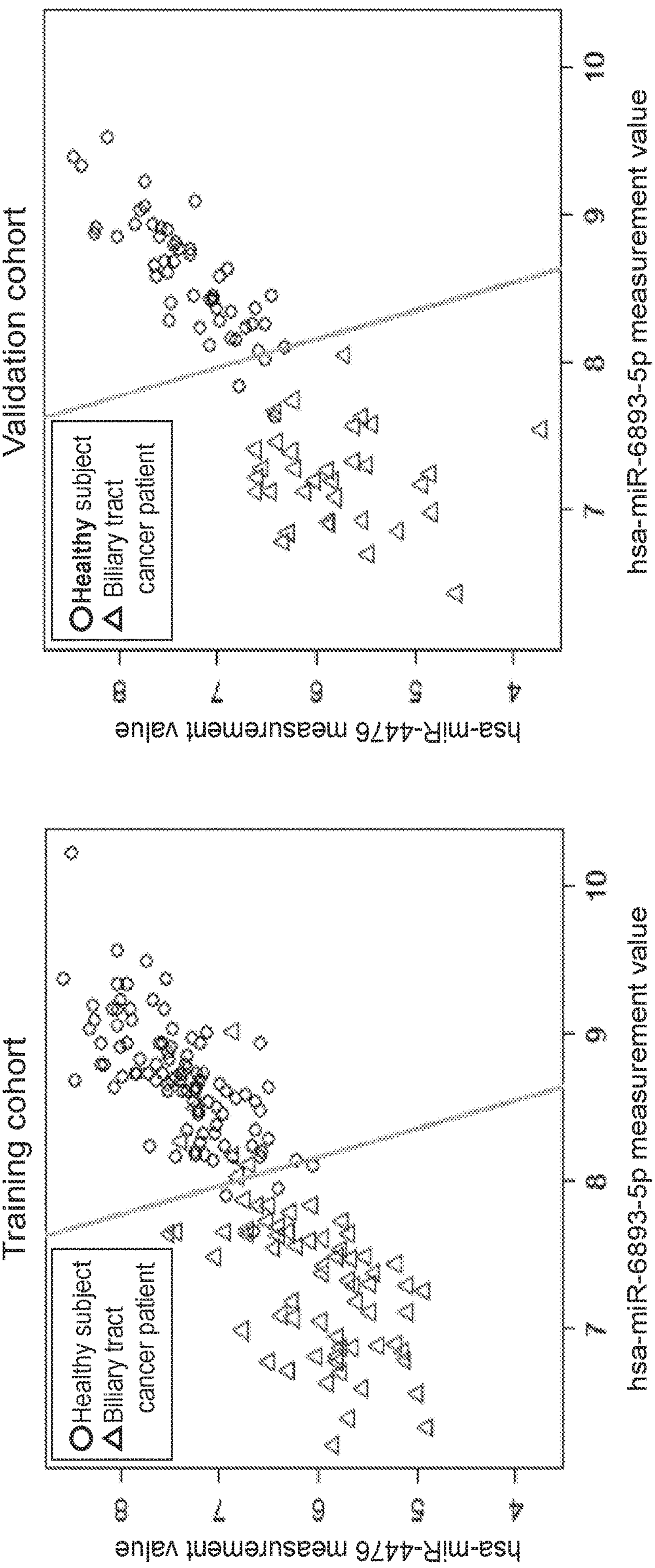
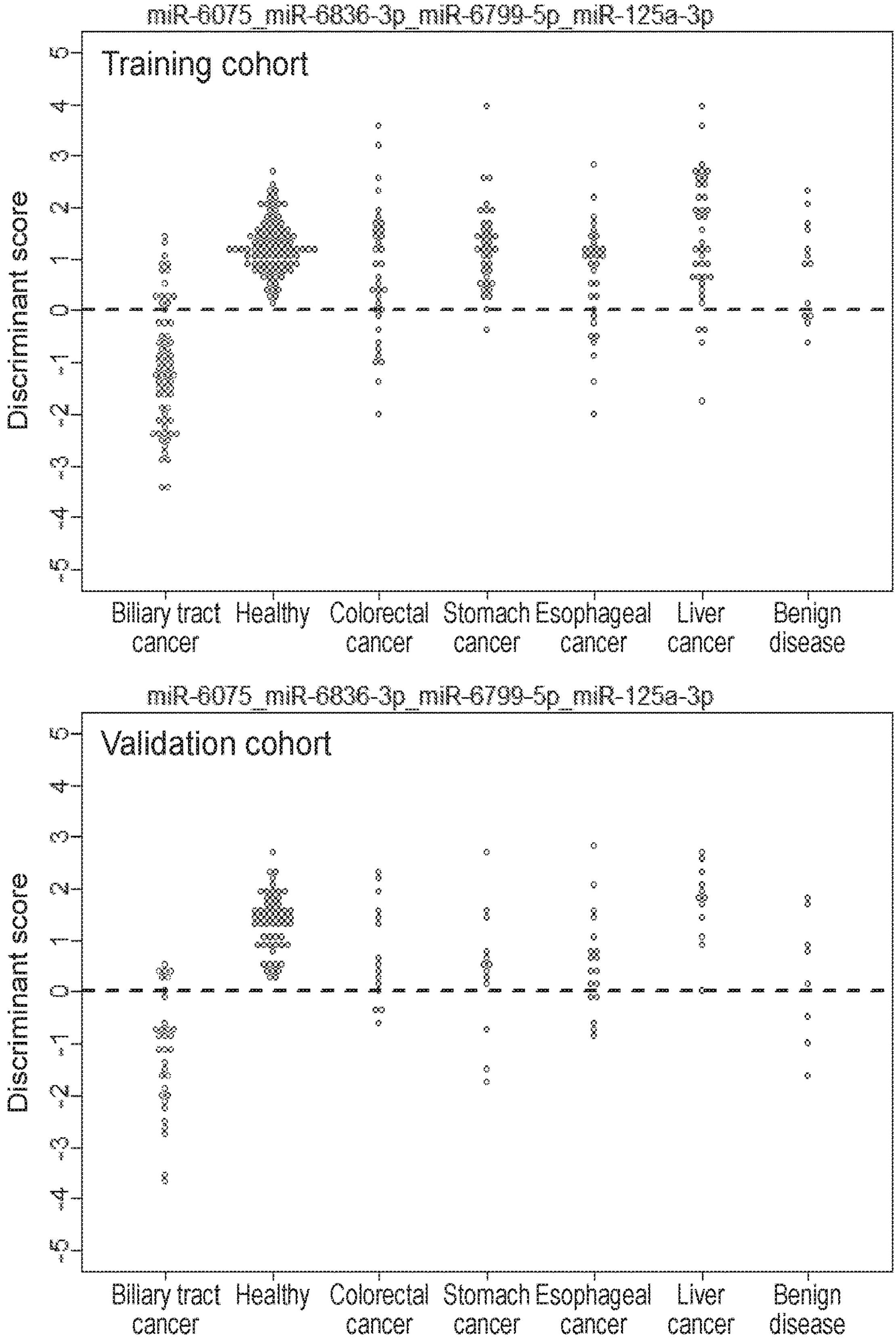

Training cohort
Validation cohort
○ Healthy subject
△ Biliary tract cancer patient
hsa-miR-4476 measurement value
hsa-miR-6893-5p measurement value
4
5
6
7
8
9
10

Fig. 4


miR-6075_miR-6836-3p_miR-6799-5p_miR-125a-3p
Training cohort
Discriminant score
5
4
3
2
1
0
-1
-2
-3
-4
-5
Biliary tract cancer
Healthy
Colorectal cancer
Stomach cancer
Esophageal cancer
Liver cancer
Benign disease
miR-6075_miR-6836-3p_miR-6799-5p_miR-125a-3p
Validation cohort
Discriminant score
5
4
3
2
1
0
-1
-2
-3
-4
-5
Biliary tract cancer
Healthy
Colorectal cancer
Stomach cancer
Esophageal cancer
Liver cancer
Benign disease

BILIARY TRACT CANCER DETECTION KIT OR DEVICE, AND DETECTION METHOD

TECHNICAL FIELD

The present invention relates to a kit or a device for the detection of biliary tract cancer, comprising a nucleic acid capable of specifically binding to a particular miRNA, which is used for examining the presence or absence of biliary tract cancer in a subject, and a method for detecting biliary tract cancer, comprising measuring an expression level of the miRNA using the nucleic acid.

BACKGROUND ART

The biliary tract refers to the entire route of excretion of bile secreted from hepatic cells into the duodenum, and is broadly divided into the intrahepatic bile duct inside the liver and the extrahepatic biliary tree outside the liver. The extrahepatic biliary tree is broadly divided into 3 areas: the extrahepatic bile duct through which the bile is transported from the liver to the duodenum; the gallbladder which temporarily stores and enriches the bile; and the duodenal papilla or the papilla which is an opening site of the bile duct and the main pancreatic duct at the duodenal lumen.

A great majority of biliary tract cancer cases are caused by the malignant transformation of biliary epithelial cells that surround the lumen, and respond, merely weakly, to chemotherapy or radiotherapy. Thus, surgical resection based on early detection is only one radical cure for such biliary tract cancer. However, early biliary tract cancer lacks subjective symptoms. For example, this cancer manifests subjective symptoms such as jaundice or itch only after the bile duct is obstructed with the progression of the cancer so that the bile flows back into a blood vessel. Therefore, biliary tract cancer is often detected in an advanced cancer state. As for intrahepatic bile duct cancer, because the extrahepatic bile duct is rarely obstructed, the disease often progresses asymptomatically without symptoms of jaundice. According to the 2011 statistics of cancer type-specific mortality in Japan disclosed by the Center for Cancer Control and Information Services, National Cancer Center, the number of biliary tract cancer deaths climbed to 18,186 people, and 5-year relative survival rates by cancer type in 2003 to 2005 were in the second lowest position following pancreatic cancer with 22.5% for males and 19.9% for females. Since the biliary tract is closely related to important organs such as the liver and the pancreas, biliary tract cancer is responsible for poor prognosis resulting from its metastasis to these organs.

The biliary tract cancer is broadly divided into three types, extrahepatic bile duct cancer, gallbladder cancer, and papillary cancer, depending on sites of origin. The extrahepatic bile duct cancer is further divided into four types: a cancer that develops in the hepatic portal region which serves as the entrance of the liver (hilar cholangiocarcinoma); a cancer that develops in the upper region from the hepatic portal region to the gallbladder (upper bile duct cancer); a cancer that develops in the middle region from the gallbladder to the pancreas (middle bile duct cancer); and a cancer that develops in the distal region from the pancreas to the duodenal papilla (distal bile duct cancer). A bile duct cancer that develops closer to the liver is known to be more difficult to operate and to have poorer prognosis.

The UICC (Unio Internationalis Contra Cancrum) stages of progression of extrahepatic bile duct cancer, gallbladder cancer, and papillary cancer are defined in "Classification of Biliary Tract Cancer, the 5th edition" (edited by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. KANEHARA & Co., LTD., 2003, p. 109) and classified into stages 0, IA, IB, IIA, IIB, III, IVa, and IVb according to lymph node metastasis, metastasis to extraperitoneal distant organs, macroscopic spread around the bile duct, etc. The UICC stages of progression of intrahepatic bile duct cancer are defined in "TNM Classification of Malignant Tumours, the 7th edition, Japanese version" (UICC Japan National Committee, translated by TNM Committee, KANEHARA & Co., LTD., 2012, p. 110) and classified into stages I, II, III, IVa, and IVb according to lymph node metastasis, metastasis to extraperitoneal distant organs, macroscopic spread around the bile duct, etc.

Limitedly invasive biochemical examination of blood, tumor marker tests, and abdominal ultrasonography are generally used in the initial diagnosis of biliary tract cancer (Non-patent Literature 1). The biochemical examination of blood for the detection of biliary tract cancer employs, for example, alkaline phosphatase, γ-GTP, or bilirubin, which is elevated due to hepatic dysfunction. For example, CEA, CA19-9, DUPAN-2, CA195, CA242, and IL-6 are known as the tumor markers for the detection of biliary tract cancer. As for how to use these tumor markers, a subject is suspected of having a cancer when their concentrations in blood are higher or lower than predetermined reference values. For example, as described in Non-patent Literature 2, the reference value of CEA is set to 5 ng/mL, and the reference value of CA19-9 is set to 37 U/mL. A subject is suspected of having a cancer including biliary tract cancer when their concentrations exhibit these values or higher.

There are reports, albeit at a research stage, on the detection of biliary tract cancer using the expression levels of proteins or genes in biological samples including blood.

Patent Literature 1 describes a method for detecting biliary tract cancer using the expression levels of proteins in biliary tract tissues.

Patent Literature 2 describes a method for diagnosing digestive organ cancers including biliary tract cancer using mRNA genes extracted from cells (mononuclear cells, etc.) in blood.

CITATION LIST

Patent Literature

Patent Literature 1: JP Patent Publication (Kokai) No. 2012-237685 A (2012)

Patent Literature 2: JP Patent Publication (Kokai) No. 2013-223520 A (2013)

Non-Patent Literature

Non-patent Literature 1: "Evidence-based clinical practice guidelines for the management of biliary tract cancers", edited by the publishing committee of the evidence-based clinical practice guidelines for the management of biliary tract cancers. Igakutosho-shuppan Ltd., 2007, p. 38-39

Non-patent Literature 2: Kiyoshi Kurokawa, LAB DATA, 2013, p. 633, 636

SUMMARY OF INVENTION

Problem to be Solved by Invention

An object of the present invention is to find a novel tumor marker for biliary tract cancer and to provide a method that can effectively detect biliary tract cancer using a nucleic acid capable of specifically binding to the marker. As described in Non-patent Literature 1, limitedly invasive biochemical examination of blood, tumor marker tests, and abdominal ultrasonography are generally used in the initial diagnosis of biliary tract cancer. The rate of tumor visualization (probability at which cancer can be detected from images) for biliary tract cancer by the abdominal ultrasonography varies widely from 21 to 90% (Non-patent Literature 1) and is decreased, particularly, for sites of tumors that occupy the lower bile duct. The biochemical examination of blood for the detection of biliary tract cancer employs, for example, alkaline phosphatase, γ-GTP, or bilirubin, which is elevated due to hepatic dysfunction. However, such biochemical examination of blood does not specifically detect biliary tract cancer. For example, CEA, CA19-9, DUPAN-2, CA195, CA242, and IL-6 are known as the tumor markers for the detection of biliary tract cancer. Among them. CEA is known to be elevated by 40 to 70% in biliary tract cancer patients, while CA19-9 is known to be elevated by 50 to 79% in biliary tract cancer patients (Non-patent Literature 1). However, Non-patent Literature 1 states that these tumor markers are not specific for biliary tract cancer and are difficult to use in early diagnosis. Also, Non-patent Literature 1 states that the clinical usefulness of DUPAN-2, CA195, CA242, or IL-6 is not clear. Therefore, in the case of using the conventional tumor markers, there may be the possibility of false detection of other cancers and/or benign tumors and/or benign diseases of the biliary tract and/or peribiliary organs, etc.

As described below, there are reports, albeit at a research stage, on the detection of biliary tract cancer using the expression levels of proteins or genes in biological samples including blood, none of which, however, have yet been brought into practical use.

Patent Literature 1 describes a method for detecting biliary tract cancer using the expression levels of proteins in biliary tract tissues. In this detection method, however, tissue resection by surgical operation is essential for obtaining samples. This step places a great physical burden on patients. Therefore, this method is not favorable as an examination method. In addition, Patent Literature 1 does not describe the specific detection performance, such as accuracy, sensitivity, or specificity for discriminating biliary tract cancer, of this detection method and is thus poorly industrially practical.

Patent Literature 2 describes a method for diagnosing digestive organ cancers including biliary tract cancer using mRNA genes extracted from cells (mononuclear cells, etc.) in blood. This detection method, however, requires dozens to several hundreds of mRNAs to be used in combination and might thus cause increased examination cost and a complicated classification algorithm when actually developed for examination. In addition, the mRNAs are easily decomposable and unstable in blood and are therefore not favorable as analytes.

As mentioned above, the existing tumor markers exhibit low performance in the detection of biliary tract cancer, and neither performance nor detection methods are specifically shown as to the markers at a research stage. Therefore, use of these markers might impose an implementation of needless extra examination due to the false detection of healthy subjects as being biliary tract cancer patients, or might waste therapeutic opportunity because of overlooking biliary tract cancer patients. In addition, the measurement of dozens to several hundreds of genes increases examination cost and is therefore difficult to use in large-scale screening such as medical checkup. Furthermore, the collection of biliary tract tissues for measuring the tumor markers is highly invasive to patients and is not favorable. Hence, there is a demand for a highly accurate biliary tract cancer marker that is detectable from blood, which can be collected in a less invasive manner, and is capable of correctly determining a biliary tract cancer patient as a biliary tract cancer patient and a healthy subject as a healthy subject. Particularly, a highly sensitive biliary tract cancer marker is desired because tumor resection based on early detection is only radical cure for biliary tract cancer.

Means for Solution of Problem

The present inventors have conducted diligent studies to attain the object and consequently completed the present invention by finding several genes usable as markers for the detection of biliary tract cancer from blood, which can be collected with limited invasiveness, and finding that biliary tract cancer can be significantly detected by using nucleic acid(s) capable of specifically binding to any of these markers.

SUMMARY OF INVENTION

Specifically, the present invention has the following features:

(1) A kit for the detection of biliary tract cancer, comprising nucleic acid(s) capable of specifically binding to at least one or more polynucleotide(s) selected from the group consisting of biliary tract cancer markers miR-125a-3p, miR-6893-5p, miR-204-3p, miR-4476, miR-4294, miR-150-3p, miR-6729-5p, miR-7641, miR-6765-3p, miR-6820-5p, miR-575, miR-6836-3p, miR-1469, miR-663a, miR-6075, miR-4634, miR-423-5p, miR-4454, miR-7109-5p, miR-6789-5p, miR-6877-5p, miR-4792, miR-4530, miR-7975, miR-6724-5p, miR-8073, miR-7977, miR-1231, miR-6799-5p, miR-615-5p, miR-4450, miR-6726-5p, miR-6875-5p, miR-4734, miR-16-5p, miR-602, miR-4651, miR-8069, miR-1238-5p, miR-6880-5p, miR-8072, miR-4723-5p, miR-4732-5p, miR-6125, miR-6090, miR-7114-5p, miR-564, miR-451a, miR-3135b, miR-4497, miR-4665-5p, miR-3622a-5p, miR-6850-5p, miR-6821-5p, miR-5100, miR-6872-3p, miR-4433-3p, miR-1227-5p, miR-3188, miR-7704, miR-3185, miR-1908-3p, miR-6781-5p, miR-6805-5p, miR-8089, miR-665, miR-4486, miR-6722-3p, miR-1260a, miR-4707-5p, miR-6741-5p, miR-1260b, miR-1246, miR-6845-5p, miR-4638-5p, miR-6085, miR-1228-3p, miR-4534, miR-5585-3p, miR-4741, miR-4433b-3p, miR-197-5p, miR-718, miR-4513, miR-4446-3p, miR-619-5p, miR-6816-5p, miR-6778-5p, miR-24-3p, miR-1915-3p, miR-4665-3p, miR-4449, miR-6889-5p, miR-486-3p, miR-7113-3p, miR-642a-3p, miR-7847-3p, miR-6768-5p, miR-1290, miR-7108-5p, miR-92b-5p, miR-663b, miR-3940-5p, miR-4467, miR-6858-5p, miR-4417, miR-3665, miR-4736, miR-4687-3p, miR-1908-5p, miR-5195-3p, miR-4286, miR-3679-3p, miR-6791-5p, miR-1202, miR-3656, miR-4746-3p, miR-3184-5p, miR-3937, miR-6515-3p, miR-6132, miR-187-5p, miR-7111-5p, miR-5787, miR-6779-5p, miR-4516, miR-4649-5p, miR-760, miR-3162-5p, miR-3178, miR-940, miR-4271, miR-6769b-5p, miR-4508, miR-6826-5p, miR-6757-5p, miR-3131, and miR-1343-3p.

(2) The kit according to (1), wherein miR-125a-3p is hsa-miR-125a-3p, miR-6893-5p is hsa-miR-6893-5p, miR-204-3p is hsa-miR-204-3p, miR-4476 is hsa-miR-4476, miR-4294 is hsa-miR-4294, miR-150-3p is hsa-miR-150-3p, miR-6729-5p is hsa-miR-6729-5p, miR-7641 is hsa-

miR-7641, miR-6765-3p is hsa-miR-6765-3p, miR-6820-5p is hsa-miR-6820-5p, miR-575 is hsa-miR-575, miR-6836-3p is hsa-miR-6836-3p, miR-1469 is hsa-miR-1469, miR-663a is hsa-miR-663a, miR-6075 is hsa-miR-6075, miR-4634 is hsa-miR-4634, miR-423-5p is hsa-miR-423-5p, miR-4454 is hsa-miR-4454, miR-7109-5p is hsa-miR-7109-5p, miR-6789-5p is hsa-miR-6789-5p, miR-6877-5p is hsa-miR-6877-5p, miR-4792 is hsa-miR-4792, miR-4530 is hsa-miR-4530, miR-7975 is hsa-miR-7975, miR-6724-5p is hsa-miR-6724-5p, miR-8073 is hsa-miR-8073, miR-7977 is hsa-miR-7977, miR-1231 is hsa-miR-1231, miR-6799-5p is hsa-miR-6799-5p, miR-615-5p is hsa-miR-615-5p, miR-4450 is hsa-miR-4450, miR-6726-5p is hsa-miR-6726-5p, miR-6875-5p is hsa-miR-6875-5p, miR-4734 is hsa-miR-4734, miR-16-5p is hsa-miR-16-5p, miR-602 is hsa-miR-602, miR-4651 is hsa-miR-4651, miR-8069 is hsa-miR-8069, miR-1238-5p is hsa-miR-1238-5p, miR-6880-5p is hsa-miR-6880-5p, miR-8072 is hsa-miR-8072, miR-4723-5p is hsa-miR-4723-5p, miR-4732-5p is hsa-miR-4732-5p, miR-6125 is hsa-miR-6125, miR-6090 is hsa-miR-6090, miR-7114-5p is hsa-miR-7114-5p, miR-564 is hsa-miR-564, miR-451a is hsa-miR-451a, miR-3135b is hsa-miR-3135b, miR-4497 is hsa-miR-4497, miR-4665-5p is hsa-miR-4665-5p, miR-3622a-5p is hsa-miR-3622a-5p, miR-6850-5p is hsa-miR-6850-5p, miR-6821-5p is hsa-miR-6821-5p, miR-5100 is hsa-miR-5100, miR-6872-3p is hsa-miR-6872-3p, miR-4433-3p is hsa-miR-4433-3p, miR-1227-5p is hsa-miR-1227-5p, miR-3188 is hsa-miR-3188, miR-7704 is hsa-miR-7704, miR-3185 is hsa-miR-3185, miR-1908-3p is hsa-miR-1908-3p, miR-6781-5p is hsa-miR-6781-5p, miR-6805-5p is hsa-miR-6805-5p, miR-8089 is hsa-miR-8089, miR-665 is hsa-miR-665, miR-4486 is hsa-miR-4486, miR-6722-3p is hsa-miR-6722-3p, miR-1260a is hsa-miR-1260a, miR-4707-5p is hsa-miR-4707-5p, miR-6741-5p is hsa-miR-6741-5p, miR-1260b is hsa-miR-1260b, miR-1246 is hsa-miR-1246, miR-6845-5p is hsa-miR-6845-5p, miR-4638-5p is hsa-miR-4638-5p, miR-6085 is hsa-miR-6085, miR-1228-3p is hsa-miR-1228-3p, miR-4534 is hsa-miR-4534, miR-5585-3p is hsa-miR-5585-3p, miR-4741 is hsa-miR-4741, miR-4433b-3p is hsa-miR-4433b-3p, miR-197-5p is hsa-miR-197-5p, miR-718 is hsa-miR-718, miR-4513 is hsa-miR-4513, miR-4446-3p is hsa-miR-4446-3p, miR-619-5p is hsa-miR-619-5p, miR-6816-5p is hsa-miR-6816-5p, miR-6778-5p is hsa-miR-6778-5p, miR-24-3p is hsa-miR-24-3p, miR-1915-3p is hsa-miR-1915-3p, miR-4665-3p is hsa-miR-4665-3p, miR-4449 is hsa-miR-4449, miR-6889-5p is hsa-miR-6889-5p, miR-486-3p is hsa-miR-486-3p, miR-7113-3p is hsa-miR-7113-3p, miR-642a-3p is hsa-miR-642a-3p, miR-7847-3p is hsa-miR-7847-3p, miR-6768-5p is hsa-miR-6768-5p, miR-1290 is hsa-miR-1290, miR-7108-5p is hsa-miR-7108-5p, miR-92b-5p is hsa-miR-92b-5p, miR-663b is hsa-miR-663b, miR-3940-5p is hsa-miR-3940-5p, miR-4467 is hsa-miR-4467, miR-6858-5p is hsa-miR-6858-5p, miR-4417 is hsa-miR-4417, miR-3665 is hsa-miR-3665, miR-4736 is hsa-miR-4736, miR-4687-3p is hsa-miR-4687-3p, miR-1908-5p is hsa-miR-1908-5p, miR-5195-3p is hsa-miR-5195-3p, miR-4286 is hsa-miR-4286, miR-3679-3p is hsa-miR-3679-3p, miR-6791-5p is hsa-miR-6791-5p, miR-1202 is hsa-miR-1202, miR-3656 is hsa-miR-3656, miR-4746-3p is hsa-miR-4746-3p, miR-3184-5p is hsa-miR-3184-5p, miR-3937 is hsa-miR-3937, miR-6515-3p is hsa-miR-6515-3p, miR-6132 is hsa-miR-6132, miR-187-5p is hsa-miR-187-5p, miR-7111-5p is hsa-miR-7111-5p, miR-5787 is hsa-miR-5787, miR-6779-5p is hsa-miR-6779-5p, miR-4516 is hsa-miR-4516, miR-4649-5p is hsa-miR-4649-5p, miR-760 is hsa-miR-760, miR-3162-5p is hsa-miR-3162-5p, miR-3178 is hsa-miR-3178, miR-940 is hsa-miR-940, miR-4271 is hsa-miR-4271, miR-6769b-5p is hsa-miR-6769b-5p, miR-4508 is hsa-miR-4508, miR-6826-5p is hsa-miR-6826-5p, miR-6757-5p is hsa-miR-6757-5p, miR-3131 is hsa-miR-3131, and miR-1343-3p is hsa-miR-1343-3p.

(3) The kit according to (1) or (2), wherein the nucleic acid is a polynucleotide selected from the group consisting of the following polynucleotides (a) to (e):

(a) a polynucleotide consisting of a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides,

(b) a polynucleotide comprising a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478,

(c) a polynucleotide consisting of a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides,

(d) a polynucleotide comprising a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, and

(e) a polynucleotide hybridizing under stringent conditions to any of the polynucleotides (a) to (d).

(4) The kit according to any one of (1) to (3), wherein the kit further comprises nucleic acid(s) capable of specifically binding to at least one or more polynucleotide(s) selected from the group consisting of other biliary tract cancer markers: miR-6808-5p, miR-6774-5p, miR-4656, miR-6806-5p, miR-1233-5p, miR-328-5p, miR-4674, miR-2110, miR-6076, miR-3619-3p, miR-92a-2-5p, miR-128-1-5p, miR-638, miR-2861, miR-371a-5p, miR-211-3p, miR-1273g-3p, miR-1203, miR-122-5p, miR-4258, miR-4484, miR-4648 and miR-6780b-5p.

(5) The kit according to (4), wherein miR-6808-5p is hsa-miR-6808-5p, miR-6774-5p is hsa-miR-6774-5p, miR-4656 is hsa-miR-4656, miR-6806-5p is hsa-miR-6806-5p, miR-1233-5p is hsa-miR-1233-5p, miR-328-5p is hsa-miR-328-5p, miR-4674 is hsa-miR-4674, miR-2110 is hsa-miR-2110, miR-6076 is hsa-miR-6076, miR-3619-3p is hsa-miR-3619-3p, miR-92a-2-5p is hsa-miR-92a-2-5p, miR-128-1-5p is hsa-miR-128-1-5p, miR-638 is hsa-miR-638, miR-2861 is hsa-miR-2861, miR-371a-5p is hsa-miR-371a-5p, miR-211-3p is hsa-miR-211-3p, miR-1273g-3p is hsa-miR-1273g-3p, miR-1203 is hsa-miR-1203, miR-122-5p is hsa-miR-122-5p, miR-4258 is hsa-miR-4258, miR-4484 is hsa-miR-4484, miR-4648 is hsa-miR-4648, and miR-6780b-5p is hsa-miR-6780b-5p.

(6) The kit according to (4) or (5), wherein the nucleic acid is a polynucleotide selected from the group consisting of the following polynucleotides (f) to (j):

(f) a polynucleotide consisting of a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides,

(g) a polynucleotide comprising a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148,

(h) a polynucleotide consisting of a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides,

(i) a polynucleotide comprising a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, and

(j) a polynucleotide hybridizing under stringent conditions to any of the polynucleotides (f) to (i).

(7) The kit according to any one of (1) to (6), wherein the kit comprises at least two or more nucleic acids capable of specifically binding to at least two or more polynucleotides, respectively, selected from all of the biliary tract cancer markers according to (1) or (2).

(8) A device for the detection of biliary tract cancer, comprising nucleic acid(s) capable of specifically binding to at least one or more polynucleotide(s) selected from the group consisting of biliary tract cancer markers miR-125a-3p, miR-6893-5p, miR-204-3p, miR-4476, miR-4294, miR-150-3p, miR-6729-5p, miR-7641, miR-6765-3p, miR-6820-5p, miR-575, miR-6836-3p, miR-1469, miR-663a, miR-6075, miR-4634, miR-423-5p, miR-4454, miR-7109-5p, miR-6789-5p, miR-6877-5p, miR-4792, miR-4530, miR-7975, miR-6724-5p, miR-8073, miR-7977, miR-1231, miR-6799-5p, miR-615-5p, miR-4450, miR-6726-5p, miR-6875-5p, miR-4734, miR-16-5p, miR-602, miR-4651, miR-8069, miR-1238-5p, miR-6880-5p, miR-8072, miR-4723-5p, miR-4732-5p, miR-6125, miR-6090, miR-7114-5p, miR-564, miR-451a, miR-3135b, miR-4497, miR-4665-5p, miR-3622a-5p, miR-6850-5p, miR-6821-5p, miR-5100, miR-6872-3p, miR-4433-3p, miR-1227-5p, miR-3188, miR-7704, miR-3185, miR-1908-3p, miR-6781-5p, miR-6805-5p, miR-8089, miR-665, miR-4486, miR-6722-3p, miR-1260a, miR-4707-5p, miR-6741-5p, miR-1260b, miR-1246, miR-6845-5p, miR-4638-5p, miR-6085, miR-1228-3p, miR-4534, miR-5585-3p, miR-4741, miR-4433b-3p, miR-197-5p, miR-718, miR-4513, miR-4446-3p, miR-619-5p, miR-6816-5p, miR-6778-5p, miR-24-3p, miR-1915-3p, miR-4665-3p, miR-4449, miR-6889-5p, miR-486-3p, miR-7113-3p, miR-642a-3p, miR-7847-3p, miR-6768-5p, miR-1290, miR-7108-5p, miR-92b-5p, miR-663b, miR-3940-5p, miR-4467, miR-6858-5p, miR-4417, miR-3665, miR-4736, miR-4687-3p, miR-1908-5p, miR-5195-3p, miR-4286, miR-3679-3p, miR-6791-5p, miR-1202, miR-3656, miR-4746-3p, miR-3184-5p, miR-3937, miR-6515-3p, miR-6132, miR-187-5p, miR-7111-5p, miR-5787, miR-6779-5p, miR-4516, miR-4649-5p, miR-760, miR-3162-5p, miR-3178, miR-940, miR-4271, miR-6769b-5p, miR-4508, miR-6826-5p, miR-6757-5p, miR-3131, and miR-1343-3p.

(9) The device according to (8), wherein miR-125a-3p is hsa-miR-125a-3p, miR-6893-5p is hsa-miR-6893-5p, miR-204-3p is hsa-miR-204-3p, miR-4476 is hsa-miR-4476, miR-4294 is hsa-miR-4294, miR-150-3p is hsa-miR-150-3p, miR-6729-5p is hsa-miR-6729-5p, miR-7641 is hsa-miR-7641, miR-6765-3p is hsa-miR-6765-3p, miR-6820-5p is hsa-miR-6820-5p, miR-575 is hsa-miR-575, miR-6836-3p is hsa-miR-6836-3p, miR-1469 is hsa-miR-1469, miR-663a is hsa-miR-663a, miR-6075 is hsa-miR-6075, miR-4634 is hsa-miR-4634, miR-423-5p is hsa-miR-423-5p, miR-4454 is hsa-miR-4454, miR-7109-5p is hsa-miR-7109-5p, miR-6789-5p is hsa-miR-6789-5p, miR-6877-5p is hsa-miR-6877-5p, miR-4792 is hsa-miR-4792, miR-4530 is hsa-miR-4530, miR-7975 is hsa-miR-7975, miR-6724-5p is hsa-miR-6724-5p, miR-8073 is hsa-miR-8073, miR-7977 is hsa-miR-7977, miR-1231 is hsa-miR-1231, miR-6799-5p is hsa-miR-6799-5p, miR-615-5p is hsa-miR-615-5p, miR-4450 is hsa-miR-4450, miR-6726-5p is hsa-miR-6726-5p, miR-6875-5p is hsa-miR-6875-5p, miR-4734 is hsa-miR-4734, miR-16-5p is hsa-miR-16-5p, miR-602 is hsa-miR-602, miR-4651 is hsa-miR-4651, miR-8069 is hsa-miR-8069, miR-1238-5p is hsa-miR-1238-5p, miR-6880-5p is hsa-miR-6880-5p, miR-8072 is hsa-miR-8072, miR-4723-5p is hsa-miR-4723-5p, miR-4732-5p is hsa-miR-4732-5p, miR-6125 is hsa-miR-6125, miR-6090 is hsa-miR-6090, miR-7114-5p is hsa-miR-7114-5p, miR-564 is hsa-miR-564, miR-451a is hsa-miR-451a, miR-3135b is hsa-miR-3135b, miR-4497 is hsa-miR-4497, miR-4665-5p is hsa-miR-4665-5p, miR-3622a-5p is hsa-miR-3622a-5p, miR-6850-5p is hsa-miR-6850-5p, miR-6821-5p is hsa-miR-6821-5p, miR-5100 is hsa-miR-5100, miR-6872-3p is hsa-miR-6872-3p, miR-4433-3p is hsa-miR-4433-3p, miR-1227-5p is hsa-miR-1227-5p, miR-3188 is hsa-miR-3188, miR-7704 is hsa-miR-7704, miR-3185 is hsa-miR-3185, miR-1908-3p is hsa-miR-1908-3p, miR-6781-5p is hsa-miR-6781-5p, miR-6805-5p is hsa-miR-6805-5p, miR-8089 is hsa-miR-8089, miR-665 is hsa-miR-665, miR-4486 is hsa-miR-4486, miR-6722-3p is hsa-miR-6722-3p, miR-1260a is hsa-miR-1260a, miR-4707-5p is hsa-miR-4707-5p, miR-6741-5p is hsa-miR-6741-5p, miR-1260b is hsa-miR-1260b, miR-1246 is hsa-miR-1246, miR-6845-5p is hsa-miR-6845-5p, miR-4638-5p is hsa-miR-4638-5p, miR-6085 is hsa-miR-6085, miR-1228-3p is hsa-miR-1228-3p, miR-4534 is hsa-miR-4534, miR-5585-3p is hsa-miR-5585-3p, miR-4741 is hsa-miR-4741, miR-4433b-3p is hsa-miR-4433b-3p, miR-197-5p is hsa-miR-197-5p, miR-718 is hsa-miR-718, miR-4513 is hsa-miR-4513, miR-4446-3p is hsa-miR-4446-3p, miR-619-5p is hsa-miR-619-5p, miR-6816-5p is hsa-miR-6816-5p, miR-6778-5p is hsa-miR-6778-5p, miR-24-3p is hsa-miR-24-3p, miR-1915-3p is hsa-miR-1915-3p, miR-4665-3p is hsa-miR-4665-3p, miR-4449 is hsa-miR-4449, miR-6889-5p is hsa-miR-6889-5p, miR-486-3p is hsa-miR-486-3p, miR-7113-3p is hsa-miR-7113-3p, miR-642a-3p is hsa-miR-642a-3p, miR-7847-3p is hsa-miR-7847-3p, miR-6768-5p is hsa-miR-6768-5p, miR-1290 is hsa-miR-1290, miR-7108-5p is hsa-miR-7108-5p, miR-92b-5p is hsa-miR-92b-5p, miR-663b is hsa-miR-663b, miR-3940-5p is hsa-miR-3940-5p, miR-4467 is hsa-miR-4467, miR-6858-5p is hsa-miR-6858-5p, miR-4417 is hsa-miR-4417, miR-3665 is hsa-miR-3665, miR-4736 is hsa-miR-4736, miR-4687-3p is hsa-miR-4687-3p, miR-1908-5p is hsa-miR-1908-5p, miR-5195-3p is hsa-miR-5195-3p, miR-4286 is hsa-miR-4286, miR-3679-3p is hsa-miR-3679-3p, miR-6791-5p is hsa-miR-6791-5p, miR-1202 is hsa-miR-1202, miR-3656 is hsa-miR-3656, miR-4746-3p is hsa-miR-4746-3p, miR-3184-5p is hsa-miR-3184-5p, miR-3937 is hsa-miR-3937, miR-6515-3p is hsa-miR-6515-3p, miR-6132 is hsa-miR-6132, miR-187-5p is hsa-miR-187-5p, miR-7111-5p is hsa-miR-7111-5p, miR-5787 is hsa-miR-5787, miR-6779-5p is hsa-miR-6779-5p, miR-4516 is hsa-miR-4516, miR-4649-5p is hsa-miR-4649-5p, miR-760 is hsa-miR-760, miR-3162-5p is hsa-miR-3162-5p, miR-3178 is hsa-miR-3178, miR-940 is hsa-miR-940, miR-4271 is hsa-miR-4271, miR-6769b-5p is hsa-miR-6769b-5p, miR-4508 is hsa-miR-4508, miR-6826-5p is hsa-miR-6826-5p, miR-6757-5p is hsa-miR-6757-5p, miR-3131 is hsa-miR-3131, and miR-1343-3p is hsa-miR-1343-3p.

(10) The device according to (8) or (9), wherein the nucleic acid is a polynucleotide selected from the group consisting of the following polynucleotides (a) to (e):

(a) a polynucleotide consisting of a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides,

(b) a polynucleotide comprising a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478,

(c) a polynucleotide consisting of a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides,

(d) a polynucleotide comprising a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, and

(e) a polynucleotide hybridizing under stringent conditions to any of the polynucleotides (a) to (d).

(11) The device according to any one of (8) to (10), wherein the device further comprises nucleic acid(s) capable of specifically binding to at least one or more polynucleotide(s) selected from the group consisting of other biliary tract cancer markers miR-6808-5p, miR-6774-5p, miR-4656, miR-6806-5p, miR-1233-5p, miR-328-5p, miR-4674, miR-2110, miR-6076, miR-3619-3p, miR-92a-2-5p, miR-128-1-5p, miR-638, miR-2861, miR-371a-5p, miR-211-3p, miR-1273g-3p, miR-1203, miR-122-5p, miR-4258, miR-4484, miR-4648 and miR-6780b-5p.

(12) The device according to (11), wherein miR-6808-5p is hsa-miR-6808-5p, miR-6774-5p is hsa-miR-6774-5p, miR-4656 is hsa-miR-4656, miR-6806-5p is hsa-miR-6806-5p, miR-1233-5p is hsa-miR-1233-5p, miR-328-5p is hsa-miR-328-5p, miR-4674 is hsa-miR-4674, miR-2110 is hsa-miR-2110, miR-6076 is hsa-miR-6076, miR-3619-3p is hsa-miR-3619-3p, miR-92a-2-5p is hsa-miR-92a-2-5p, miR-128-1-5p is hsa-miR-128-1-5p, miR-638 is hsa-miR-638, miR-2861 is hsa-miR-2861, miR-371a-5p is hsa-miR-371a-5p, miR-211-3p is hsa-miR-211-3p, miR-1273g-3p is hsa-miR-1273g-3p, miR-1203 is hsa-miR-1203, miR-122-5p is hsa-miR-122-5p, miR-4258 is hsa-miR-4258, miR-4484 is hsa-miR-4484, miR-4648 is hsa-miR-4648, and miR-6780b-5p is hsa-miR-6780b-5p.

(13) The device according to (11) or (12), wherein the nucleic acid is a polynucleotide selected from the group consisting of the following polynucleotides (f) to (j):

(f) a polynucleotide consisting of a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides,

(g) a polynucleotide comprising a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148,

(h) a polynucleotide consisting of a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides,

(i) a polynucleotide comprising a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, and

(j) a polynucleotide hybridizing under stringent conditions to any of the polynucleotides (f) to (i).

(14) The device according to any one of (8) to (13), wherein the device is for measurement based on a hybridization technique.

(15) The device according to (14), wherein the hybridization technique is a nucleic acid array technique.

(16) The device according to any one of (8) to (15), wherein the device comprises at least two or more nucleic acids capable of specifically binding to at least two or more polynucleotides, respectively, selected from all of the biliary tract cancer markers according to (8) or (9).

(17) A method for detecting biliary tract cancer, comprising measuring an expression level of a target nucleic acid in a sample of a subject using the kit according to any one of (1) to (7) or the device according to any one of (8) to (16); and evaluating in vitro whether or not the subject has biliary tract cancer using the measured expression level and a control expression level for a healthy subject measured in the same way.

(18) The method according to (17), wherein the subject is a human.

(19) The method according to (17) or (18), wherein the sample is blood, serum, or plasma.

<Definition of Term>

The terms used herein are defined as follows.

The term "biliary tract cancer" used herein refers to any malignant tumor formed in the biliary tract. Specifically, the "biliary tract cancer" includes extrahepatic bile duct cancer, gallbladder cancer, papillary cancer, duodenal papilla cancer, intrahepatic bile duct cancer, and the like.

The term "benign tumors and/or benign diseases of the biliary tract and/or peribiliary organs" used herein refers to diseases with nonmalignant tumors in the biliary tract, the liver, and the pancreas.

Abbreviations or terms such as nucleotide, polynucleotide, DNA, and RNA abide by "Guidelines for the preparation of specification which contain nucleotide and/or amino acid sequences" (edited by Japan Patent Office) and common use in the art.

The term "polynucleotide" used herein refers to a nucleic acid, including any of RNA, DNA, and RNA/DNA (chimera). The DNA includes any of cDNA, genomic DNA, and synthetic DNA. The RNA includes all of total RNA, mRNA, rRNA, miRNA, siRNA, snoRNA, snRNA, non-coding RNA and synthetic RNA. The "synthetic DNA" and the "synthetic RNA" used herein refer to DNA and RNA artificially prepared using, for example, an automated nucleic acid synthesizer, on the basis of predetermined nucleotide sequences (which may be any of natural and non-natural sequences). The "non-natural sequence" used herein is intended to be used in a broad sense and includes, for example, a sequence containing substitution, deletion, insertion, and/or addition of one or more nucleotide(s) (i.e., a variant sequence) and a sequence containing one or more modified nucleotide(s) (i.e., a modified sequence), which are different from the natural sequence. As used herein, the term "polynucleotide" is used interchangeably with the term "nucleic acid."

The term "fragment" used herein is a polynucleotide having a nucleotide sequence having a consecutive portion of a polynucleotide and desirably has a length of 15 or more nucleotides, preferably 17 or more nucleotides, more preferably 19 or more nucleotides.

The term "gene" used herein is intended to include not only RNA and double-stranded DNA but also each single-stranded DNA such as a plus strand (or a sense strand) or a complementary strand (or an antisense strand) constituting the duplex. The gene is not particularly limited by its length.

Thus, the "gene" used herein includes all of double-stranded DNA including human genomic DNA, single-stranded DNA (plus strand), single-stranded DNA that has a sequence complementary to the plus strand (complementary strand) including cDNA, microRNA (miRNA), and their fragments, and transcripts, unless otherwise specified. The "gene" includes not only a "gene" represented by a particular nucleotide sequence (or SEQ ID NO) but "nucleic acids" that encode RNAs that have biological functions equivalent to RNA encoded by the gene, for example, a congener (i.e., a homolog or an ortholog), a variant (e.g., a genetic polymorph), and a derivative. Specific examples of such a "nucleic acid" encoding a congener, a variant, or a derivative can include a "nucleic acid" that has a nucleotide sequence that hybridizes under stringent conditions described later to a complementary sequence of a nucleotide sequence represented by any of SEQ ID NOs: 1 to 509 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t. The "gene" is not particularly limited by its functional region and can contain, for example, an expression regulatory region, a coding region, an exon, or an intron. The "gene" may be contained in a cell or may exist alone after being released into the outside of a cell. Alternatively, the "gene" may be in a state enclosed in a vesicle called exosome.

The term "exosome" used herein is a vesicle that is encapsulated by a lipid bilayer and secreted from a cell. The exosome is derived from a multivesicular endosome and may incorporate a biomaterial such as a "gene" (e.g., RNA or DNA) or a protein when released into an extracellular environment. The exosome is known to be contained in a body fluid such as blood, serum, plasma, serum, or lymph.

The term "transcript" used herein refers to RNA synthesized from the DNA sequence of a gene as a template. RNA polymerase binds to a site called a promoter located upstream of the gene and adds ribonucleotides complementary to the nucleotide sequence of the DNA to the 3' end to synthesize an RNA. This RNA contains not only the gene itself but also the whole sequence from a transcription initiation site to the end of a polyA sequence, including an expression regulatory region, a coding region, an exon, or an intron.

The term "microRNA (miRNA)" used herein is intended to mean a 15- to 25-nucleotide non-coding RNA that is transcribed as an RNA precursor having a hairpin-like structure, cleaved by a dsRNA-cleaving enzyme which has RNase III cleavage activity, integrated into a protein complex called RISC, and involved in the suppression of translation of mRNA, unless otherwise specified. The term "miRNA" used herein includes not only a "miRNA" represented by a particular nucleotide sequence (or SEQ ID NO) but a precursor of the "miRNA" (pre-miRNA or pri-miRNA), and miRNAs that have biological functions equivalent thereto, for example, a congener (i.e., a homolog or an ortholog), a variant (e.g., a genetic polymorph), and a derivative. Such a precursor, a congener, a variant, or a derivative can be specifically identified using miRBase Release 20 (http://www.mirbase.org/), and examples thereof can include a "miRNA" that has a nucleotide sequence that hybridizes under stringent conditions described later to a complementary sequence of any particular nucleotide sequence represented by any of SEQ ID NOs: 1 to 509. The term "miRNA" used herein may be a gene product of a miR gene. Such a gene product includes a mature miRNA (e.g., a 15- to 25-nucleotide or 19- to 25-nucleotide non-coding RNA involved in the suppression of translation of mRNA as described above) or a miRNA precursor (e.g., pre-miRNA or pri-miRNA as described above).

The term "probe" used herein includes a polynucleotide that is used for specifically detecting an RNA that results from the expression of a gene, or a polynucleotide derived from the RNA, and/or a polynucleotide complementary thereto.

The term "primer" used herein includes a polynucleotide that specifically recognizes and amplifies an RNA that results from the expression of a gene or a polynucleotide derived from the RNA, and/or a polynucleotide complementary thereto.

In this context, the complementary polynucleotide (complementary strand or reverse strand) means a polynucleotide in a complementary relationship of A:T (U) and G:C base pairs with the full-length sequence of a polynucleotide consisting of a nucleotide sequence defined by any of SEQ ID NOs: 1 to 509 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, or a partial sequence thereof (here, this full-length or partial sequence is referred to as a plus strand for the sake of convenience). However, such a complementary strand is not limited to a sequence completely complementary to the nucleotide sequence of the target plus strand and may have a complementary relationship to an extent that permits hybridization under stringent conditions to the target plus strand.

The term "stringent conditions" used herein refers to conditions under which a nucleic acid probe hybridizes to its target sequence to a larger extent (e.g., a measurement value equal to or larger than a mean of background measurement values+a standard deviation of the background measurement values×2) than that for other sequences. The stringent conditions are dependent on a sequence and differ depending on an environment where hybridization is performed. A target sequence complementary 100% to the nucleic acid probe can be identified by controlling the stringency of hybridization and/or washing conditions. Specific examples of the "stringent conditions" are mentioned later.

The term "Tm value" used herein means a temperature at which the double-stranded moiety of a polynucleotide is denatured into single strands so that the double strands and the single strands exist at a ratio of 1:1.

The term "variant" used herein means, in the case of a nucleic acid, a natural variant attributed to polymorphism, mutation, or the like; a variant containing the deletion, substitution, addition, or insertion of 1 or 2 or more nucleotides in a nucleotide sequence represented by any of SEQ ID NOs: 1 to 509, or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, or a partial sequence thereof; a variant that exhibits percent (%) identity of approximately 90% or higher, approximately 95% or higher, approximately 97% or higher, approximately 98% or higher, approximately 99% or higher to each of these nucleotide sequences or the partial sequences thereof; or a nucleic acid that hybridizes under the stringent conditions defined above to a polynucleotide or an oligonucleotide comprising each of these nucleotide sequences or the partial sequence thereof.

The term "several" used herein means an integer of approximately 10, 9, 8, 7, 6, 5, 4, 3, or 2.

The variant used herein can be prepared by use of a well-known technique such as site-directed mutagenesis or PCR-based mutagenesis.

The term "percent (%) identity" used herein can be determined with or without an introduced gap, using a protein or gene search system based on BLAST or FASTA described above (Zheng Zhang et al., 2000, J. Comput. Biol., Vol. 7, p. 203-214; Altschul, S. F. et al., 1990, Journal of Molecular Biology, Vol. 215, p. 403-410; and Pearson, W. R. et al., 1988, Proc. Natl. Acad. Sci. U.S.A, Vol. 85, p. 2444-2448).

The term "derivative" used herein is meant to include a modified nucleic acid, for example, a derivative labeled with a fluorophore or the like, a derivative containing a modified nucleotide (e.g., a nucleotide containing a group such as halogen, alkyl such as methyl, alkoxy such as methoxy, thio, or carboxymethyl, and a nucleotide that has undergone base rearrangement, double bond saturation, deamination, replacement of an oxygen molecule with a sulfur atom, etc.), PNA (peptide nucleic acid; Nielsen, P. E. et al., 1991, Science, Vol. 254, p. 1497-500), and LNA (locked nucleic acid; Obika, S. et al., 1998, Tetrahedron Lett., Vol. 39, p. 5401-5404) without any limitation.

As used herein, the "nucleic acid" capable of specifically binding to a polynucleotide selected from the biliary tract cancer marker miRNA group described above is a synthesized or prepared nucleic acid and specifically includes a "nucleic acid probe" or a "primer". The "nucleic acid" is utilized directly or indirectly for detecting the presence or absence of biliary tract cancer in a subject, for diagnosing the presence or absence of biliary tract cancer, or the severity of biliary tract cancer, the presence or absence of amelioration or the degree of amelioration of biliary tract cancer, or the therapeutic sensitivity of biliary tract cancer, or for screening for a candidate substance useful in the prevention, amelioration, or treatment of biliary tract cancer. The "nucleic acid" includes a nucleotide, an oligonucleotide, and a polynucleotide capable of specifically recognizing and binding to a transcript represented by any of SEQ ID NOs: 1 to 509 or a synthetic cDNA nucleic acid thereof in vivo, particularly, in a sample such as a body fluid (e.g., blood or urine), in relation to the development of biliary tract cancer. The nucleotide, the oligonucleotide, and the polynucleotide can be effectively used as probes for detecting the aforementioned gene expressed in vivo, in tissues, in cells, or the like on the basis of the properties described above, or as primers for amplifying the aforementioned gene expressed in vivo.

The term "detection" used herein is interchangeable with the term "examination", "measurement", "detection" or "decision support". The term "evaluation" used herein is meant to include diagnosis or evaluation support on the basis of examination results or measurement results.

The term "subject" used herein means a mammal such as a primate including a human and a chimpanzee, a pet animal including a dog and a cat, a livestock animal including cattle, a horse, sheep, and a goat, and a rodent including a mouse and a rat. The term "healthy subject" also means such a mammal without the cancer to be detected.

The term "P" or "P value" used herein refers to a probability at which a more extreme statistic than that is actually calculated from data under a null hypothesis is observed in a statistical test. Thus, smaller "P" or "P value" is regarded as being more significant difference between subjects to be compared.

The term "sensitivity" used herein means a value of (the number of true positives)/(the number of true positives+the number of false negatives). High sensitivity allows biliary tract cancer to be detected early, leading to the complete resection of cancer sites and reduction in the rate of recurrence.

The term "specificity" used herein means a value of (the number of true negatives)/(the number of true negatives+the number of false positives). High specificity prevents needless extra examination for healthy subjects misjudged as being biliary tract cancer patients, leading to reduction in burden on patients and reduction in medical expense.

The term "accuracy" used herein means a value of (the number of true positives+the number of true negatives)/(the total number of cases). The accuracy indicates the ratio of samples that are correctly identified in the discriminant results to all samples, and serves as a primary index for evaluating detection performance.

As used herein, the "sample" that is subject to determination, detection, or diagnosis refers to a tissue and a biological material in which the expression of the gene of the present invention varies as biliary tract cancer develops, as biliary tract cancer progresses, or as therapeutic effects on biliary tract cancer are exerted. Specifically, the "sample" refers to a biliary tract tissue, a peribiliary vascular channel, lymph node, and organ, an organ suspected of having metastasis, the skin, a body fluid such as blood, urine, saliva, sweat, or tissue exudates, serum or plasma prepared from blood, feces, hair, and the like. The "sample" further refers to a biological sample extracted therefrom, specifically, a gene such as RNA or miRNA.

The term "hsa-miR-125a-3p gene" or "hsa-miR-125a-3p" used herein includes the hsa-miR-125a-3p gene (miRBase Accession No. MIMAT0004602) described in SEQ ID NO: 1, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-125a-3p gene can be obtained by a method described in Lagos-Quintana M et al., 2002, Curr Biol, Vol. 12, p. 735-739. Also, "hsa-mir-125a" (miRBase Accession No. MI0000469, SEQ ID NO: 149) having a hairpin-like structure is known as a precursor of "hsa-miR-125a-3p".

The term "hsa-miR-6893-5p gene" or "hsa-miR-6893-5p" used herein includes the hsa-miR-6893-5p gene (miRBase Accession No. MIMAT0027686) described in SEQ ID NO: 2, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6893-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6893" (miRBase Accession No. MI0022740, SEQ ID NO: 150) having a hairpin-like structure is known as a precursor of "hsa-miR-6893-5p".

The term "hsa-miR-204-3p gene" or "hsa-miR-204-3p" used herein includes the hsa-miR-204-3p gene (miRBase Accession No. MIMAT0022693) described in SEQ ID NO: 3, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-204-3p gene can be obtained by a method described in Lim L P et al., 2003, Science, Vol. 299, p. 1540. Also, "hsa-mir-204" (miRBase Accession No. MI0000284, SEQ ID NO: 151) having a hairpin-like structure is known as a precursor of "hsa-miR-204-3p".

The term "hsa-miR-4476 gene" or "hsa-miR-4476" used herein includes the hsa-miR-4476 gene (miRBase Accession No. MIMAT0019003) described in SEQ ID NO: 4, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4476 gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, "hsa-mir-4476" (miRBase Accession No. MI0016828, SEQ ID NO: 152) having a hairpin-like structure is known as a precursor of "hsa-miR-4476".

The term "hsa-miR-4294 gene" or "hsa-miR-4294" used herein includes the hsa-miR-4294 gene (miRBase Accession No. MIMAT0016849) described in SEQ ID NO: 5, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4294 gene can be obtained by a method described in Goff L A et al., 2009, PLoS One, Vol.

4, e7192. Also, “hsa-mir-4294” (miRBase Accession No. MI0015827, SEQ ID NO: 153) having a hairpin-like structure is known as a precursor of “hsa-miR-4294”.

The term “hsa-miR-150-3p gene” or “hsa-miR-150-3p” used herein includes the hsa-miR-150-3p gene (miRBase Accession No. MIMAT0004610) described in SEQ ID NO: 6, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-150-3p gene can be obtained by a method described in Lagos-Quintana M et al., 2002, Curr Biol, Vol. 12, p. 735-739. Also, “hsa-mir-150” (miRBase Accession No. MI0000479, SEQ ID NO: 154) having a hairpin-like structure is known as a precursor of “hsa-miR-150-3p”.

The term “hsa-miR-6729-5p gene” or “hsa-miR-6729-5p” used herein includes the hsa-miR-6729-5p gene (miRBase Accession No. MIMAT0027359) described in SEQ ID NO: 7, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6729-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, “hsa-mir-6729” (miRBase Accession No. MI0022574. SEQ ID NO: 155) having a hairpin-like structure is known as a precursor of “hsa-miR-6729-5p”.

The term “hsa-miR-7641 gene” or “hsa-miR-7641” used herein includes the hsa-miR-7641 gene (miRBase Accession No. MIMAT0029782) described in SEQ ID NO: 8, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-7641 gene can be obtained by a method described in Yoo J K et al., 2013, Arch Pharm Res, Vol. 36, p. 353-358. Also, “hsa-mir-7641-1” and “hsa-mir-7641-2” (miRBase Accession Nos. MI0024975 and MI0024976, SEQ ID NOs: 156 and 157) having a hairpin-like structure are known as a precursor of “hsa-miR-7641”.

The term “hsa-miR-6765-3p gene” or “hsa-miR-6765-3p” used herein includes the hsa-miR-6765-3p gene (miRBase Accession No. MIMAT0027431) described in SEQ ID NO: 9, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6765-3p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, “hsa-mir-6765” (miRBase Accession No. MI0022610, SEQ ID NO: 158) having a hairpin-like structure is known as a precursor of “hsa-miR-6765-3p”.

The term “hsa-miR-6820-5p gene” or “hsa-miR-6820-5p” used herein includes the hsa-miR-6820-5p gene (miRBase Accession No. MIMAT0027540) described in SEQ ID NO: 10, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6820-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, “hsa-mir-6820” (miRBase Accession No. MI0022665, SEQ ID NO: 159) having a hairpin-like structure is known as a precursor of “hsa-miR-6820-5p”.

The term “hsa-miR-575 gene” or “hsa-miR-575” used herein includes the hsa-miR-575 gene (miRBase Accession No. MIMAT0003240) described in SEQ ID NO: 11, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-575 gene can be obtained by a method described in Cummins J M et al., 2006, Proc Natl Acad Sci USA, Vol. 103, p. 3687-3692. Also, “hsa-mir-575” (miRBase Accession No. MI0003582, SEQ ID NO: 160) having a hairpin-like structure is known as a precursor of “hsa-miR-575”.

The term “hsa-miR-6836-3p gene” or “hsa-miR-6836-3p” used herein includes the hsa-miR-6836-3p gene (miRBase Accession No. MIMAT0027575) described in SEQ ID NO: 12, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6836-3p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, “hsa-mir-6836” (miRBase Accession No. MI0022682, SEQ ID NO: 161) having a hairpin-like structure is known as a precursor of “hsa-miR-6836-3p”.

The term “hsa-miR-1469 gene” or “hsa-miR-1469” used herein includes the hsa-miR-1469 gene (miRBase Accession No. MIMAT0007347) described in SEQ ID NO: 13, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1469 gene can be obtained by a method described in Kawaji H et al., 2008, BMC Genomics, Vol. 9, p. 157. Also, “hsa-mir-1469” (miRBase Accession No. MI0007074, SEQ ID NO: 162) having a hairpin-like structure is known as a precursor of “hsa-miR-1469”.

The term “hsa-miR-663a gene” or “hsa-miR-663a” used herein includes the hsa-miR-663a gene (miRBase Accession No. MIMAT0003326) described in SEQ ID NO: 14, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-663a gene can be obtained by a method described in Cummins J M et al., 2006, Proc Natl Acad Sci USA, Vol. 103, p. 3687-3692. Also, “hsa-mir-663a” (miRBase Accession No. MI0003672, SEQ ID NO: 163) having a hairpin-like structure is known as a precursor of “hsa-miR-663a”.

The term “hsa-miR-6075 gene” or “hsa-miR-6075” used herein includes the hsa-miR-6075 gene (miRBase Accession No. MIMAT0023700) described in SEQ ID NO: 15, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6075 gene can be obtained by a method described in Voellenkle C et al., 2012, RNA. Vol. 18, p. 472-484. Also, “hsa-mir-6075” (miRBase Accession No. MI0020352, SEQ ID NO: 164) having a hairpin-like structure is known as a precursor of “hsa-miR-6075”.

The term “hsa-miR-4634 gene” or “hsa-miR-4634” used herein includes the hsa-miR-4634 gene (miRBase Accession No. MIMAT0019691) described in SEQ ID NO: 16, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4634 gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, “hsa-mir-4634” (miRBase Accession No. MI0017261, SEQ ID NO: 165) having a hairpin-like structure is known as a precursor of “hsa-miR-4634”.

The term “hsa-miR-423-5p gene” or “hsa-miR-423-5p” used herein includes the hsa-miR-423-5p gene (miRBase Accession No. MIMAT0004748) described in SEQ ID NO: 17, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-423-5p gene can be obtained by a method described in Kasashima K et al., 2004, Biochem Biophys Res Commun, Vol. 322, p. 403-410. Also, “hsa-mir-423” (miRBase Accession No. MI0001445, SEQ ID NO: 166) having a hairpin-like structure is known as a precursor of “hsa-miR-423-5p”.

The term “hsa-miR-4454 gene” or “hsa-miR-4454” used herein includes the hsa-miR-4454 gene (miRBase Accession No. MIMAT0018976) described in SEQ ID NO: 18, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4454 gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, “hsa-mir-4454” (miRBase Accession No. MI0016800, SEQ ID NO: 167) having a hairpin-like structure is known as a precursor of “hsa-miR-4454”.

The term “hsa-miR-7109-5p gene” or “hsa-miR-7109-5p” used herein includes the hsa-miR-7109-5p gene (miRBase Accession No. MIMAT0028115) described in SEQ ID NO: 19, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-7109-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-7109" (miRBase Accession No. MI0022960. SEQ ID NO: 168) having a hairpin-like structure is known as a precursor of "hsa-miR-7109-5p".

The term "hsa-miR-6789-5p gene" or "hsa-miR-6789-5p" used herein includes the hsa-miR-6789-5p gene (miRBase Accession No. MIMAT0027478) described in SEQ ID NO: 20, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6789-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6789" (miRBase Accession No. MI0022634, SEQ ID NO: 169) having a hairpin-like structure is known as a precursor of "hsa-miR-6789-5p".

The term "hsa-miR-6877-5p gene" or "hsa-miR-6877-5p" used herein includes the hsa-miR-6877-5p gene (miRBase Accession No. MIMAT0027654) described in SEQ ID NO: 21, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6877-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6877" (miRBase Accession No. MI0022724, SEQ ID NO: 170) having a hairpin-like structure is known as a precursor of "hsa-miR-6877-5p".

The term "hsa-miR-4792 gene" or "hsa-miR-4792" used herein includes the hsa-miR-4792 gene (miRBase Accession No. MIMAT0019964) described in SEQ ID NO: 22, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4792 gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4792" (miRBase Accession No. MI0017439, SEQ ID NO: 171) having a hairpin-like structure is known as a precursor of "hsa-miR-4792".

The term "hsa-miR-4530 gene" or "hsa-miR-4530" used herein includes the hsa-miR-4530 gene (miRBase Accession No. MIMAT0019069) described in SEQ ID NO: 23, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4530 gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, "hsa-mir-4530" (miRBase Accession No. MI0016897, SEQ ID NO: 172) having a hairpin-like structure is known as a precursor of "hsa-miR-4530".

The term "hsa-miR-7975 gene" or "hsa-miR-7975" used herein includes the hsa-miR-7975 gene (miRBase Accession No. MIMAT0031178) described in SEQ ID NO: 24, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-7975 gene can be obtained by a method described in Velthut-Meikas A et al., 2013. Mol Endocrinol, online. Also, "hsa-mir-7975" (miRBase Accession No. MI0025751, SEQ ID NO: 173) having a hairpin-like structure is known as a precursor of "hsa-miR-7975".

The term "hsa-miR-6724-5p gene" or "hsa-miR-6724-5p" used herein includes the hsa-miR-6724-5p gene (miRBase Accession No. MIMAT0025856) described in SEQ ID NO: 25, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6724-5p gene can be obtained by a method described in Li Y et al., 2012, Gene, Vol. 497, p. 330-335. Also, "hsa-mir-6724" (miRBase Accession No. MI0022559, SEQ ID NO: 174) having a hairpin-like structure is known as a precursor of "hsa-miR-6724-5p".

The term "hsa-miR-8073 gene" or "hsa-miR-8073" used herein includes the hsa-miR-8073 gene (miRBase Accession No. MIMAT0031000) described in SEQ ID NO: 26, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-8073 gene can be obtained by a method described in Wang H J et al., 2013, Shock, Vol. 39, p. 480-487. Also, "hsa-mir-8073" (miRBase Accession No. MI0025909, SEQ ID NO: 175) having a hairpin-like structure is known as a precursor of "hsa-miR-8073".

The term "hsa-miR-7977 gene" or "hsa-miR-7977" used herein includes the hsa-miR-7977 gene (miRBase Accession No. MIMAT0031180) described in SEQ ID NO: 27, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-7977 gene can be obtained by a method described in Velthut-Meikas A et al., 2013, Mol Endocrinol, online. Also, "hsa-mir-7977" (miRBase Accession No. MI0025753. SEQ ID NO: 176) having a hairpin-like structure is known as a precursor of "hsa-miR-7977".

The term "hsa-miR-1231 gene" or "hsa-miR-1231" used herein includes the hsa-miR-1231 gene (miRBase Accession No. MIMAT0005586) described in SEQ ID NO: 28, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1231 gene can be obtained by a method described in Berezikov E et al., 2007. Mol Cell, Vol. 28, p. 328-336. Also, "hsa-mir-1231" (miRBase Accession No. MI0006321, SEQ ID NO: 177) having a hairpin-like structure is known as a precursor of "hsa-miR-1231".

The term "hsa-miR-6799-5p gene" or "hsa-miR-6799-5p" used herein includes the hsa-miR-6799-5p gene (miRBase Accession No. MIMAT0027498) described in SEQ ID NO: 29, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6799-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6799" (miRBase Accession No. MI0022644, SEQ ID NO: 178) having a hairpin-like structure is known as a precursor of "hsa-miR-6799-5p".

The term "hsa-miR-615-5p gene" or "hsa-miR-615-5p" used herein includes the hsa-miR-615-5p gene (miRBase Accession No. MIMAT0004804) described in SEQ ID NO: 30, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-615-5p gene can be obtained by a method described in Cummins J M et al., 2006. Proc Natl Acad Sci USA, Vol. 103, p. 3687-3692. Also, "hsa-mir-615" (miRBase Accession No. MI0003628, SEQ ID NO: 179) having a hairpin-like structure is known as a precursor of "hsa-miR-615-5p".

The term "hsa-miR-4450 gene" or "hsa-miR-4450" used herein includes the hsa-miR-4450 gene (miRBase Accession No. MIMAT0018971) described in SEQ ID NO: 31, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4450 gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, "hsa-mir-4450" (miRBase Accession No. MI0016795, SEQ ID NO: 180) having a hairpin-like structure is known as a precursor of "hsa-miR-4450".

The term "hsa-miR-6726-5p gene" or "hsa-miR-6726-5p" used herein includes the hsa-miR-6726-5p gene (miRBase Accession No. MIMAT0027353) described in SEQ ID NO: 32, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6726-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6726" (miRBase Accession No. MI0022571, SEQ ID NO: 181) having a hairpin-like structure is known as a precursor of "hsa-miR-6726-5p".

The term "hsa-miR-6875-5p gene" or "hsa-miR-6875-5p" used herein includes the hsa-miR-6875-5p gene (miRBase Accession No. MIMAT0027650) described in SEQ ID NO: 33, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6875-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6875" (miRBase

Accession No. MI0022722, SEQ ID NO: 182) having a hairpin-like structure is known as a precursor of "hsa-miR-6875-5p".

The term "hsa-miR-4734 gene" or "hsa-miR-4734" used herein includes the hsa-miR-4734 gene (miRBase Accession No. MIMAT0019859) described in SEQ ID NO: 34, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4734 gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4734" (miRBase Accession No. MI0017371, SEQ ID NO: 183) having a hairpin-like structure is known as a precursor of "hsa-miR-4734".

The term "hsa-miR-16-5p gene" or "hsa-miR-16-5p" used herein includes the hsa-miR-16-5p gene (miRBase Accession No. MIMAT0000069) described in SEQ ID NO: 35, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-16-5p gene can be obtained by a method described in Lagos-Quintana M et al., 2001, Science, Vol. 294, p. 853-858. Also, "hsa-mir-16-1" and "hsa-mir-16-2" (miRBase Accession Nos. MI0000070 and MI0000115, SEQ ID NOs: 184 and 185) having a hairpin-like structure are known as precursors of "hsa-miR-16-5p".

The term "hsa-miR-602 gene" or "hsa-miR-602" used herein includes the hsa-miR-602 gene (miRBase Accession No. MIMAT0003270) described in SEQ ID NO: 36, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-602 gene can be obtained by a method described in Cummins J M et al., 2006, Proc Natl Acad Sci USA, Vol. 103, p. 3687-3692. Also, "hsa-mir-602" (miRBase Accession No. MI0003615, SEQ ID NO: 186) having a hairpin-like structure is known as a precursor of "hsa-miR-602".

The term "hsa-miR-4651 gene" or "hsa-miR-4651" used herein includes the hsa-miR-4651 gene (miRBase Accession No. MIMAT0019715) described in SEQ ID NO: 37, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4651 gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4651" (miRBase Accession No. MI0017279, SEQ ID NO: 187) having a hairpin-like structure is known as a precursor of "hsa-miR-4651".

The term "hsa-miR-8069 gene" or "hsa-miR-8069" used herein includes the hsa-miR-8069 gene (miRBase Accession No. MIMAT0030996) described in SEQ ID NO: 38, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-8069 gene can be obtained by a method described in Wang H J et al., 2013, Shock. Vol. 39, p. 480-487. Also, "hsa-mir-8069" (miRBase Accession No. MI0025905, SEQ ID NO: 188) having a hairpin-like structure is known as a precursor of "hsa-miR-8069".

The term "hsa-miR-1238-5p gene" or "hsa-miR-1238-5p" used herein includes the hsa-miR-1238-5p gene (miRBase Accession No. MIMAT0022947) described in SEQ ID NO: 39, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1238-5p gene can be obtained by a method described in Berezikov E et al., 2007, Mol Cell, Vol. 28, p. 328-336. Also, "hsa-mir-1238" (miRBase Accession No. MI0006328, SEQ ID NO: 189) having a hairpin-like structure is known as a precursor of "hsa-miR-1238-5p".

The term "hsa-miR-6880-5p gene" or "hsa-miR-6880-5p" used herein includes the hsa-miR-6880-5p gene (miRBase Accession No. MIMAT0027660) described in SEQ ID NO: 40, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6880-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6880" (miRBase Accession No. MI0022727, SEQ ID NO: 190) having a hairpin-like structure is known as a precursor of "hsa-miR-6880-5p".

The term "hsa-miR-8072 gene" or "hsa-miR-8072" used herein includes the hsa-miR-8072 gene (miRBase Accession No. MIMAT0030999) described in SEQ ID NO: 41, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-8072 gene can be obtained by a method described in Wang H J et al., 2013, Shock, Vol. 39, p. 480-487. Also, "hsa-mir-8072" (miRBase Accession No. MI0025908, SEQ ID NO: 191) having a hairpin-like structure is known as a precursor of "hsa-miR-8072".

The term "hsa-miR-4723-5p gene" or "hsa-miR-4723-5p" used herein includes the hsa-miR-4723-5p gene (miRBase Accession No. MIMAT0019838) described in SEQ ID NO: 42, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4723-5p gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4723" (miRBase Accession No. MI0017359, SEQ ID NO: 192) having a hairpin-like structure is known as a precursor of "hsa-miR-4723-5p".

The term "hsa-miR-4732-5p gene" or "hsa-miR-4732-5p" used herein includes the hsa-miR-4732-5p gene (miRBase Accession No. MIMAT0019855) described in SEQ ID NO: 43, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4732-5p gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4732" (miRBase Accession No. MI0017369, SEQ ID NO: 193) having a hairpin-like structure is known as a precursor of "hsa-miR-4732-5p".

The term "hsa-miR-6125 gene" or "hsa-miR-6125" used herein includes the hsa-miR-6125 gene (miRBase Accession No. MIMAT0024598) described in SEQ ID NO: 44, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6125 gene can be obtained by a method described in Smith J L et al., 2012, J Virol, Vol. 86, p. 5278-5287. Also, "hsa-mir-6125" (miRBase Accession No. MI0021259, SEQ ID NO: 194) having a hairpin-like structure is known as a precursor of "hsa-miR-6125".

The term "hsa-miR-6090 gene" or "hsa-miR-6090" used herein includes the hsa-miR-6090 gene (miRBase Accession No. MIMAT0023715) described in SEQ ID NO: 45, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6090 gene can be obtained by a method described in Yoo J K et al., 2012, Stem Cells Dev. Vol. 21, p. 2049-2057. Also, "hsa-mir-6090" (miRBase Accession No. MI0020367, SEQ ID NO: 195) having a hairpin-like structure is known as a precursor of "hsa-miR-6090".

The term "hsa-miR-7114-5p gene" or "hsa-miR-7114-5p" used herein includes the hsa-miR-7114-5p gene (miRBase Accession No. MIMAT0028125) described in SEQ ID NO: 46, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-7114-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-7114" (miRBase Accession No. MI0022965, SEQ ID NO: 196) having a hairpin-like structure is known as a precursor of "hsa-miR-7114-5p".

The term "hsa-miR-564 gene" or "hsa-miR-564" used herein includes the hsa-miR-564 gene (miRBase Accession No. MIMAT0003228) described in SEQ ID NO: 47, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-564 gene can be obtained by a method described in Cummins J M et al., 2006, Proc Natl Acad Sci USA, Vol. 103, p. 3687-3692. Also, "hsa-mir-564" (miR-

Base Accession No. MI0003570, SEQ ID NO: 197) having a hairpin-like structure is known as a precursor of "hsa-miR-564".

The term "hsa-miR-451a gene" or "hsa-miR-451a" used herein includes the hsa-miR-451a gene (miRBase Accession No. MIMAT0001631) described in SEQ ID NO: 48, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-451a gene can be obtained by a method described in Altuvia Y et al., 2005, Nucleic Acids Res, Vol. 33, p. 2697-2706. Also, "hsa-mir-451a" (miRBase Accession No. MI0001729, SEQ ID NO: 198) having a hairpin-like structure is known as a precursor of "hsa-miR-451a".

The term "hsa-miR-3135b gene" or "hsa-miR-3135b" used herein includes the hsa-miR-3135b gene (miRBase Accession No. MIMAT0018985) described in SEQ ID NO: 49, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-3135b gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, "hsa-mir-3135b" (miRBase Accession No. MI0016809, SEQ ID NO: 199) having a hairpin-like structure is known as a precursor of "hsa-miR-3135b".

The term "hsa-miR-4497 gene" or "hsa-miR-4497" used herein includes the hsa-miR-4497 gene (miRBase Accession No. MIMAT0019032) described in SEQ ID NO: 50, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4497 gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, "hsa-mir-4497" (miRBase Accession No. MI0016859, SEQ ID NO: 200) having a hairpin-like structure is known as a precursor of "hsa-miR-4497".

The term "hsa-miR-4665-5p gene" or "hsa-miR-4665-5p" used herein includes the hsa-miR-4665-5p gene (miRBase Accession No. MIMAT0019739) described in SEQ ID NO: 51, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4665-5p gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4665" (miRBase Accession No. MI0017295, SEQ ID NO: 201) having a hairpin-like structure is known as a precursor of "hsa-miR-4665-5p".

The term "hsa-miR-3622a-5p gene" or "hsa-miR-3622a-5p" used herein includes the hsa-miR-3622a-5p gene (miRBase Accession No. MIMAT0018003) described in SEQ ID NO: 52, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-3622a-5p gene can be obtained by a method described in Witten D et al., 2010, BMC Biol, Vol. 8, p. 58. Also, "hsa-mir-3622a" (miRBase Accession No. MI0016013, SEQ ID NO: 202) having a hairpin-like structure is known as a precursor of "hsa-miR-3622a-5p".

The term "hsa-miR-6850-5p gene" or "hsa-miR-6850-5p" used herein includes the hsa-miR-6850-5p gene (miRBase Accession No. MIMAT0027600) described in SEQ ID NO: 53, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6850-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6850" (miRBase Accession No. MI0022696, SEQ ID NO: 203) having a hairpin-like structure is known as a precursor of "hsa-miR-6850-5p".

The term "hsa-miR-6821-5p gene" or "hsa-miR-6821-5p" used herein includes the hsa-miR-6821-5p gene (miRBase Accession No. MIMAT0027542) described in SEQ ID NO: 54, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6821-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6821" (miRBase Accession No. MI0022666, SEQ ID NO: 204) having a hairpin-like structure is known as a precursor of "hsa-miR-6821-5p".

The term "hsa-miR-5100 gene" or "hsa-miR-5100" used herein includes the hsa-miR-5100 gene (miRBase Accession No. MIMAT0022259) described in SEQ ID NO: 55, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-5100 gene can be obtained by a method described in Tandon M et al., 2012, Oral Dis, Vol. 18, p. 127-131. Also, "hsa-mir-5100" (miRBase Accession No. MI0019116, SEQ ID NO: 205) having a hairpin-like structure is known as a precursor of "hsa-miR-5100".

The term "hsa-miR-6872-3p gene" or "hsa-miR-6872-3p" used herein includes the hsa-miR-6872-3p gene (miRBase Accession No. MIMAT0027645) described in SEQ ID NO: 56, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6872-3p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6872" (miRBase Accession No. MI0022719, SEQ ID NO: 206) having a hairpin-like structure is known as a precursor of "hsa-miR-6872-3p".

The term "hsa-miR-4433-3p gene" or "hsa-miR-4433-3p" used herein includes the hsa-miR-4433-3p gene (miRBase Accession No. MIMAT0018949) described in SEQ ID NO: 57, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4433-3p gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, "hsa-mir-4433" (miRBase Accession No. MI0016773, SEQ ID NO: 207) having a hairpin-like structure is known as a precursor of "hsa-miR-4433-3p".

The term "hsa-miR-1227-5p gene" or "hsa-miR-1227-5p" used herein includes the hsa-miR-1227-5p gene (miRBase Accession No. MIMAT0022941) described in SEQ ID NO: 58, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1227-5p gene can be obtained by a method described in Berezikov E et al., 2007, Mol Cell, Vol. 28, p. 328-336. Also, "hsa-mir-1227" (miRBase Accession No. MI0006316. SEQ ID NO: 208) having a hairpin-like structure is known as a precursor of "hsa-miR-1227-5p".

The term "hsa-miR-3188 gene" or "hsa-miR-3188" used herein includes the hsa-miR-3188 gene (miRBase Accession No. MIMAT0015070) described in SEQ ID NO: 59, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-3188 gene can be obtained by a method described in Stark M S et al., 2010, PLoS One, Vol. 5, e9685. Also, "hsa-mir-3188" (miRBase Accession No. MI0014232, SEQ ID NO: 209) having a hairpin-like structure is known as a precursor of "hsa-miR-3188".

The term "hsa-miR-7704 gene" or "hsa-miR-7704" used herein includes the hsa-miR-7704 gene (miRBase Accession No. MIMAT0030019) described in SEQ ID NO: 60, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-7704 gene can be obtained by a method described in Swaminathan S et al., 2013, Biochem Biophys Res Commun, Vol. 434, p. 228-234. Also, "hsa-mir-7704" (miRBase Accession No. MI0025240, SEQ ID NO: 210) having a hairpin-like structure is known as a precursor of "hsa-miR-7704".

The term "hsa-miR-3185 gene" or "hsa-miR-3185" used herein includes the hsa-miR-3185 gene (miRBase Accession No. MIMAT0015065) described in SEQ ID NO: 61, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-3185 gene can be obtained by a method described in Stark M S et al., 2010, PLoS One, Vol. 5, e9685. Also, "hsa-mir-3185" (miRBase Accession No.

MI0014227, SEQ ID NO: 211) having a hairpin-like structure is known as a precursor of "hsa-miR-3185".

The term "hsa-miR-1908-3p gene" or "hsa-miR-1908-3p" used herein includes the hsa-miR-1908-3p gene (miRBase Accession No. MIMAT0026916) described in SEQ ID NO: 62, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1908-3p gene can be obtained by a method described in Bar M et al., 2008, Stem Cells, Vol. 26, p. 2496-2505. Also, "hsa-mir-1908" (miRBase Accession No. MI0008329, SEQ ID NO: 212) having a hairpin-like structure is known as a precursor of "hsa-miR-1908-3p".

The term "hsa-miR-6781-5p gene" or "hsa-miR-6781-5p" used herein includes the hsa-miR-6781-5p gene (miRBase Accession No. MIMAT0027462) described in SEQ ID NO: 63, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6781-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6781" (miRBase Accession No. MI0022626. SEQ ID NO: 213) having a hairpin-like structure is known as a precursor of "hsa-miR-6781-5p".

The term "hsa-miR-6805-5p gene" or "hsa-miR-6805-5p" used herein includes the hsa-miR-6805-5p gene (miRBase Accession No. MIMAT0027510) described in SEQ ID NO: 64, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6805-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6805" (miRBase Accession No. MI0022650, SEQ ID NO: 214) having a hairpin-like structure is known as a precursor of "hsa-miR-6805-5p".

The term "hsa-miR-8089 gene" or "hsa-miR-8089" used herein includes the hsa-miR-8089 gene (miRBase Accession No. MIMAT0031016) described in SEQ ID NO: 65, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-8089 gene can be obtained by a method described in Wang H J et al., 2013, Shock, Vol. 39, p. 480-487. Also, "hsa-mir-8089" (miRBase Accession No. MI0025925, SEQ ID NO: 215) having a hairpin-like structure is known as a precursor of "hsa-miR-8089".

The term "hsa-miR-665 gene" or "hsa-miR-665" used herein includes the hsa-miR-665 gene (miRBase Accession No. MIMAT0004952) described in SEQ ID NO: 66, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-665 gene can be obtained by a method described in Berezikov E et al., 2006. Genome Res. Vol. 16, p. 1289-1298. Also, "hsa-mir-665" (miRBase Accession No. MI0005563, SEQ ID NO: 216) having a hairpin-like structure is known as a precursor of "hsa-miR-665".

The term "hsa-miR-4486 gene" or "hsa-miR-4486" used herein includes the hsa-miR-4486 gene (miRBase Accession No. MIMAT0019020) described in SEQ ID NO: 67, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4486 gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, "hsa-mir-4486" (miRBase Accession No. MI0016847, SEQ ID NO: 217) having a hairpin-like structure is known as a precursor of "hsa-miR-4486".

The term "hsa-miR-6722-3p gene" or "hsa-miR-6722-3p" used herein includes the hsa-miR-6722-3p gene (miRBase Accession No. MIMAT0025854) described in SEQ ID NO: 68, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6722-3p gene can be obtained by a method described in Li Y et al., 2012, Gene, Vol. 497, p. 330-335. Also, "hsa-mir-6722" (miRBase Accession No. MI0022557, SEQ ID NO: 218) having a hairpin-like structure is known as a precursor of "hsa-miR-6722-3p".

The term "hsa-miR-1260a gene" or "hsa-miR-1260a" used herein includes the hsa-miR-1260a gene (miRBase Accession No. MIMAT0005911) described in SEQ ID NO: 69, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1260a gene can be obtained by a method described in Morin R D et al., 2008, Genome Res, Vol. 18, p. 610-621. Also, "hsa-mir-1260a" (miRBase Accession No. MI0006394, SEQ ID NO: 219) having a hairpin-like structure is known as a precursor of "hsa-miR-1260a".

The term "hsa-miR-4707-5p gene" or "hsa-miR-4707-5p" used herein includes the hsa-miR-4707-5p gene (miRBase Accession No. MIMAT0019807) described in SEQ ID NO: 70, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4707-5p gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4707" (miRBase Accession No. MI0017340, SEQ ID NO: 220) having a hairpin-like structure is known as a precursor of "hsa-miR-4707-5p".

The term "hsa-miR-6741-5p gene" or "hsa-miR-6741-5p" used herein includes the hsa-miR-6741-5p gene (miRBase Accession No. MIMAT0027383) described in SEQ ID NO: 71, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6741-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6741" (miRBase Accession No. MI0022586. SEQ ID NO: 221) having a hairpin-like structure is known as a precursor of "hsa-miR-6741-5p".

The term "hsa-miR-1260b gene" or "hsa-miR-1260b" used herein includes the hsa-miR-1260b gene (miRBase Accession No. MIMAT0015041) described in SEQ ID NO: 72, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1260b gene can be obtained by a method described in Stark M S et al., 2010. PLoS One, Vol. 5, e9685. Also, "hsa-mir-1260b" (miRBase Accession No. MI0014197, SEQ ID NO: 222) having a hairpin-like structure is known as a precursor of "hsa-miR-1260b".

The term "hsa-miR-1246 gene" or "hsa-miR-1246" used herein includes the hsa-miR-1246 gene (miRBase Accession No. MIMAT0005898) described in SEQ ID NO: 73, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1246 gene can be obtained by a method described in Morin R D et al., 2008, Genome Res, Vol. 18, p. 610-621. Also, "hsa-mir-1246" (miRBase Accession No. MI0006381, SEQ ID NO: 223) having a hairpin-like structure is known as a precursor of "hsa-miR-1246".

The term "hsa-miR-6845-5p gene" or "hsa-miR-6845-5p" used herein includes the hsa-miR-6845-5p gene (miRBase Accession No. MIMAT0027590) described in SEQ ID NO: 74, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6845-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6845" (miRBase Accession No. MI0022691, SEQ ID NO: 224) having a hairpin-like structure is known as a precursor of "hsa-miR-6845-5p".

The term "hsa-miR-4638-5p gene" or "hsa-miR-4638-5p" used herein includes the hsa-miR-4638-5p gene (miRBase Accession No. MIMAT0019695) described in SEQ ID NO: 75, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4638-5p gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4638" (miRBase Accession

No. MI0017265, SEQ ID NO: 225) having a hairpin-like structure is known as a precursor of "hsa-miR-4638-5p".

The term "hsa-miR-6085 gene" or "hsa-miR-6085" used herein includes the hsa-miR-6085 gene (miRBase Accession No. MIMAT0023710) described in SEQ ID NO: 76, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6085 gene can be obtained by a method described in Voellenkle C et al., 2012. RNA. Vol. 18, p. 472-484. Also, "hsa-mir-6085" (miRBase Accession No. MI0020362, SEQ ID NO: 226) having a hairpin-like structure is known as a precursor of "hsa-miR-6085".

The term "hsa-miR-1228-3p gene" or "hsa-miR-1228-3p" used herein includes the hsa-miR-1228-3p gene (miRBase Accession No. MIMAT0005583) described in SEQ ID NO: 77, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1228-3p gene can be obtained by a method described in Berezikov E et al., 2007, Mol Cell, Vol. 28, p. 328-336. Also, "hsa-mir-1228" (miRBase Accession No. MI0006318, SEQ ID NO: 227) having a hairpin-like structure is known as a precursor of "hsa-miR-1228-3p".

The term "hsa-miR-4534 gene" or "hsa-miR-4534" used herein includes the hsa-miR-4534 gene (miRBase Accession No. MIMAT0019073) described in SEQ ID NO: 78, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4534 gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, "hsa-mir-4534" (miRBase Accession No. MI0016901, SEQ ID NO: 228) having a hairpin-like structure is known as a precursor of "hsa-miR-4534".

The term "hsa-miR-5585-3p gene" or "hsa-miR-5585-3p" used herein includes the hsa-miR-5585-3p gene (miRBase Accession No. MIMAT0022286) described in SEQ ID NO: 79, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-5585-3p gene can be obtained by a method described in Friedlander M R et al., 2012, Nucleic Acids Res, Vol. 40, p. 37-52. Also, "hsa-mir-5585" (miRBase Accession No. MI0019142, SEQ ID NO: 229) having a hairpin-like structure is known as a precursor of "hsa-miR-5585-3p".

The term "hsa-miR-4741 gene" or "hsa-miR-4741" used herein includes the hsa-miR-4741 gene (miRBase Accession No. MIMAT0019871) described in SEQ ID NO: 80, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4741 gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4741" (miRBase Accession No. MI0017379, SEQ ID NO: 230) having a hairpin-like structure is known as a precursor of "hsa-miR-4741".

The term "hsa-miR-4433b-3p gene" or "hsa-miR-4433b-3p" used herein includes the hsa-miR-4433b-3p gene (miRBase Accession No. MIMAT0030414) described in SEQ ID NO: 81, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4433b-3p gene can be obtained by a method described in Ple H et al., 2012, PLoS One, Vol. 7, e50746. Also, "hsa-mir-4433b" (miRBase Accession No. MI0025511, SEQ ID NO: 231) having a hairpin-like structure is known as a precursor of "hsa-miR-4433b-3p".

The term "hsa-miR-197-5p gene" or "hsa-miR-197-5p" used herein includes the hsa-miR-197-5p gene (miRBase Accession No. MIMAT0022691) described in SEQ ID NO: 82, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-197-5p gene can be obtained by a method described in Lagos-Quintana M et al., 2003. RNA, Vol. 9, p. 175-179. Also, "hsa-mir-197" (miRBase Accession No. MI0000239, SEQ ID NO: 232) having a hairpin-like structure is known as a precursor of "hsa-miR-197-5p".

The term "hsa-miR-718 gene" or "hsa-miR-718" used herein includes the hsa-miR-718 gene (miRBase Accession No. MIMAT0012735) described in SEQ ID NO: 83, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-718 gene can be obtained by a method described in Artzi S et al., 2008, BMC Bioinformatics, Vol. 9, p. 39. Also, "hsa-mir-718" (miRBase Accession No. MI0012489. SEQ ID NO: 233) having a hairpin-like structure is known as a precursor of "hsa-miR-718".

The term "hsa-miR-4513 gene" or "hsa-miR-4513" used herein includes the hsa-miR-4513 gene (miRBase Accession No. MIMAT0019050) described in SEQ ID NO: 84, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4513 gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, "hsa-mir-4513" (miRBase Accession No. MI0016879, SEQ ID NO: 234) having a hairpin-like structure is known as a precursor of "hsa-miR-4513".

The term "hsa-miR-4446-3p gene" or "hsa-miR-4446-3p" used herein includes the hsa-miR-4446-3p gene (miRBase Accession No. MIMAT0018965) described in SEQ ID NO: 85, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4446-3p gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, "hsa-mir-4446" (miRBase Accession No. MI0016789, SEQ ID NO: 235) having a hairpin-like structure is known as a precursor of "hsa-miR-4446-3p".

The term "hsa-miR-619-5p gene" or "hsa-miR-619-5p" used herein includes the hsa-miR-619-5p gene (miRBase Accession No. MIMAT0026622) described in SEQ ID NO: 86, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-619-5p gene can be obtained by a method described in Cummins J M et al., 2006, Proc Natl Acad Sci USA, Vol. 103, p. 3687-3692. Also, "hsa-mir-619" (miRBase Accession No. MI0003633, SEQ ID NO: 236) having a hairpin-like structure is known as a precursor of "hsa-miR-619-5p".

The term "hsa-miR-6816-5p gene" or "hsa-miR-6816-5p" used herein includes the hsa-miR-6816-5p gene (miRBase Accession No. MIMAT0027532) described in SEQ ID NO: 87, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6816-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6816" (miRBase Accession No. MI0022661. SEQ ID NO: 237) having a hairpin-like structure is known as a precursor of "hsa-miR-6816-5p".

The term "hsa-miR-6778-5p gene" or "hsa-miR-6778-5p" used herein includes the hsa-miR-6778-5p gene (miRBase Accession No. MIMAT0027456) described in SEQ ID NO: 88, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6778-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6778" (miRBase Accession No. MI0022623, SEQ ID NO: 238) having a hairpin-like structure is known as a precursor of "hsa-miR-6778-5p".

The term "hsa-miR-24-3p gene" or "hsa-miR-24-3p" used herein includes the hsa-miR-24-3p gene (miRBase Accession No. MIMAT0000080) described in SEQ ID NO: 89, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-24-3p gene can be obtained by a method described in Lagos-Quintana M et al., 2001, Science, Vol. 294, p. 853-858. Also, "hsa-mir-24-1" and "hsa-mir-24-2" (miRBase Accession Nos. MI0000080 and

MI0000081. SEQ ID NOs: 239 and 240) having a hairpin-like structure are known as precursors of "hsa-miR-24-3p".

The term "hsa-miR-1915-3p gene" or "hsa-miR-1915-3p" used herein includes the hsa-miR-1915-3p gene (miRBase Accession No. MIMAT0007892) described in SEQ ID NO: 90, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1915-3p gene can be obtained by a method described in Bar M et al., 2008, Stem Cells, Vol. 26, p. 2496-2505. Also, "hsa-mir-1915" (miRBase Accession No. MI0008336, SEQ ID NO: 241) having a hairpin-like structure is known as a precursor of "hsa-miR-1915-3p".

The term "hsa-miR-4665-3p gene" or "hsa-miR-4665-3p" used herein includes the hsa-miR-4665-3p gene (miRBase Accession No. MIMAT0019740) described in SEQ ID NO: 91, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4665-3p gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4665" (miRBase Accession No. MI0017295, SEQ ID NO: 201) having a hairpin-like structure is known as a precursor of "hsa-miR-4665-3p".

The term "hsa-miR-4449 gene" or "hsa-miR-4449" used herein includes the hsa-miR-4449 gene (miRBase Accession No. MIMAT0018968) described in SEQ ID NO: 92, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4449 gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, "hsa-mir-4449" (miRBase Accession No. MI0016792, SEQ ID NO: 242) having a hairpin-like structure is known as a precursor of "hsa-miR-4449".

The term "hsa-miR-6889-5p gene" or "hsa-miR-6889-5p" used herein includes the hsa-miR-6889-5p gene (miRBase Accession No. MIMAT0027678) described in SEQ ID NO: 93, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6889-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6889" (miRBase Accession No. MI0022736, SEQ ID NO: 243) having a hairpin-like structure is known as a precursor of "hsa-miR-6889-5p".

The term "hsa-miR-486-3p gene" or "hsa-miR-486-3p" used herein includes the hsa-miR-486-3p gene (miRBase Accession No. MIMAT0004762) described in SEQ ID NO: 94, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-486-3p gene can be obtained by a method described in Fu H et al., 2005, FEBS Lett, Vol. 579, p. 3849-3854. Also, "hsa-mir-486, hsa-mir-486-2" (miRBase Accession No. MI0002470, MI0023622, SEQ ID NO: 244, 245) having a hairpin-like structure is known as a precursor of "hsa-miR-486-3p".

The term "hsa-miR-7113-3p gene" or "hsa-miR-7113-3p" used herein includes the hsa-miR-7113-3p gene (miRBase Accession No. MIMAT0028124) described in SEQ ID NO: 95, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-7113-3p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-7113" (miRBase Accession No. MI0022964. SEQ ID NO: 246) having a hairpin-like structure is known as a precursor of "hsa-miR-7113-3p".

The term "hsa-miR-642a-3p gene" or "hsa-miR-642a-3p" used herein includes the hsa-miR-642a-3p gene (miRBase Accession No. MIMAT0020924) described in SEQ ID NO: 96, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-642a-3p gene can be obtained by a method described in Cummins J M et al., 2006, Proc Natl Acad Sci USA, Vol. 103, p. 3687-3692. Also, "hsa-mir-642a" (miRBase Accession No. MI0003657. SEQ ID NO: 247) having a hairpin-like structure is known as a precursor of "hsa-miR-642a-3p".

The term "hsa-miR-7847-3p gene" or "hsa-miR-7847-3p" used herein includes the hsa-miR-7847-3p gene (miRBase Accession No. MIMAT0030422) described in SEQ ID NO: 97, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-7847-3p gene can be obtained by a method described in Ple H et al., 2012, PLoS One, Vol. 7, e50746. Also, "hsa-mir-7847" (miRBase Accession No. MI0025517. SEQ ID NO: 248) having a hairpin-like structure is known as a precursor of "hsa-miR-7847-3p".

The term "hsa-miR-6768-5p gene" or "hsa-miR-6768-5p" used herein includes the hsa-miR-6768-5p gene (miRBase Accession No. MIMAT0027436) described in SEQ ID NO: 98, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6768-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6768" (miRBase Accession No. MI0022613, SEQ ID NO: 249) having a hairpin-like structure is known as a precursor of "hsa-miR-6768-5p".

The term "hsa-miR-1290 gene" or "hsa-miR-1290" used herein includes the hsa-miR-1290 gene (miRBase Accession No. MIMAT0005880) described in SEQ ID NO: 99, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1290 gene can be obtained by a method described in Morin R D et al., 2008, Genome Res, Vol. 18, p. 610-621. Also, "hsa-mir-1290" (miRBase Accession No. MI0006352, SEQ ID NO: 250) having a hairpin-like structure is known as a precursor of "hsa-miR-1290".

The term "hsa-miR-7108-5p gene" or "hsa-miR-7108-5p" used herein includes the hsa-miR-7108-5p gene (miRBase Accession No. MIMAT0028113) described in SEQ ID NO: 100, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-7108-5p gene can be obtained by a method described in Ladewig E et al., 2012. Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-7108" (miRBase Accession No. MI0022959, SEQ ID NO: 251) having a hairpin-like structure is known as a precursor of "hsa-miR-7108-5p".

The term "hsa-miR-92b-5p gene" or "hsa-miR-92b-5p" used herein includes the hsa-miR-92b-5p gene (miRBase Accession No. MIMAT0004792) described in SEQ ID NO: 101, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-92b-5p gene can be obtained by a method described in Cummins J M et al., 2006, Proc Natl Acad Sci USA, Vol. 103, p. 3687-3692. Also, "hsa-mir-92b" (miRBase Accession No. MI0003560, SEQ ID NO: 252) having a hairpin-like structure is known as a precursor of "hsa-miR-92b-5p".

The term "hsa-miR-663b gene" or "hsa-miR-663b" used herein includes the hsa-miR-663b gene (miRBase Accession No. MIMAT0005867) described in SEQ ID NO: 102, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-663b gene can be obtained by a method described in Takada S et al., 2008. Leukemia. Vol. 22, p. 1274-1278. Also, "hsa-mir-663b" (miRBase Accession No. MI0006336, SEQ ID NO: 253) having a hairpin-like structure is known as a precursor of "hsa-miR-663b".

The term "hsa-miR-3940-5p gene" or "hsa-miR-3940-5p" used herein includes the hsa-miR-3940-5p gene (miRBase Accession No. MIMAT0019229) described in SEQ ID NO: 103, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-3940-5p gene can be obtained by a method described in Liao J Y et al., 2010, PLoS One, Vol. 5, e10563. Also, "hsa-mir-3940" (miRBase

Accession No. MI0016597, SEQ ID NO: 254) having a hairpin-like structure is known as a precursor of "hsa-miR-3940-5p".

The term "hsa-miR-4467 gene" or "hsa-miR-4467" used herein includes the hsa-miR-4467 gene (miRBase Accession No. MIMAT0018994) described in SEQ ID NO: 104, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4467 gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, "hsa-mir-4467" (miRBase Accession No. MI0016818, SEQ ID NO: 255) having a hairpin-like structure is known as a precursor of "hsa-miR-4467".

The term "hsa-miR-6858-5p gene" or "hsa-miR-6858-5p" used herein includes the hsa-miR-6858-5p gene (miRBase Accession No. MIMAT0027616) described in SEQ ID NO: 105, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6858-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6858" (miRBase Accession No. MI0022704, SEQ ID NO: 256) having a hairpin-like structure is known as a precursor of "hsa-miR-6858-5p".

The term "hsa-miR-4417 gene" or "hsa-miR-4417" used herein includes the hsa-miR-4417 gene (miRBase Accession No. MIMAT0018929) described in SEQ ID NO: 106, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4417 gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, "hsa-mir-4417" (miRBase Accession No. MI0016753, SEQ ID NO: 257) having a hairpin-like structure is known as a precursor of "hsa-miR-4417".

The term "hsa-miR-3665 gene" or "hsa-miR-3665" used herein includes the hsa-miR-3665 gene (miRBase Accession No. MIMAT0018087) described in SEQ ID NO: 107, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-3665 gene can be obtained by a method described in Xie X et al., 2005, Nature, Vol. 434, p. 338-345. Also, "hsa-mir-3665" (miRBase Accession No. MI0016066, SEQ ID NO: 258) having a hairpin-like structure is known as a precursor of "hsa-miR-3665".

The term "hsa-miR-4736 gene" or "hsa-miR-4736" used herein includes the hsa-miR-4736 gene (miRBase Accession No. MIMAT0019862) described in SEQ ID NO: 108, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4736 gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4736" (miRBase Accession No. MI0017373, SEQ ID NO: 259) having a hairpin-like structure is known as a precursor of "hsa-miR-4736".

The term "hsa-miR-4687-3p gene" or "hsa-miR-4687-3p" used herein includes the hsa-miR-4687-3p gene (miRBase Accession No. MIMAT0019775) described in SEQ ID NO: 109, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4687-3p gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4687" (miRBase Accession No. MI0017319, SEQ ID NO: 260) having a hairpin-like structure is known as a precursor of "hsa-miR-4687-3p".

The term "hsa-miR-1908-5p gene" or "hsa-miR-1908-5p" used herein includes the hsa-miR-1908-5p gene (miRBase Accession No. MIMAT0007881) described in SEQ ID NO: 110, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1908-5p gene can be obtained by a method described in Bar M et al., 2008, Stem Cells, Vol. 26, p. 2496-2505. Also, "hsa-mir-1908" (miRBase Accession No. MI0008329, SEQ ID NO: 212) having a hairpin-like structure is known as a precursor of "hsa-miR-1908-5p".

The term "hsa-miR-5195-3p gene" or "hsa-miR-5195-3p" used herein includes the hsa-miR-5195-3p gene (miRBase Accession No. MIMAT0021127) described in SEQ ID NO: 111, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-5195-3p gene can be obtained by a method described in Schotte D et al., 2011, Leukemia. Vol. 25, p. 1389-1399. Also, "hsa-mir-5195" (miRBase Accession No. MI0018174, SEQ ID NO: 261) having a hairpin-like structure is known as a precursor of "hsa-miR-5195-3p".

The term "hsa-miR-4286 gene" or "hsa-miR-4286" used herein includes the hsa-miR-4286 gene (miRBase Accession No. MIMAT0016916) described in SEQ ID NO: 112, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4286 gene can be obtained by a method described in Goff L A et al., 2009, PLoS One, Vol. 4, e7192. Also, "hsa-mir-4286" (miRBase Accession No. MI0015894, SEQ ID NO: 262) having a hairpin-like structure is known as a precursor of "hsa-miR-4286".

The term "hsa-miR-3679-3p gene" or "hsa-miR-3679-3p" used herein includes the hsa-miR-3679-3p gene (miRBase Accession No. MIMAT0018105) described in SEQ ID NO: 113, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-3679-3p gene can be obtained by a method described in Creighton C J et al., 2010, PLoS One, Vol. 5, e9637. Also, "hsa-mir-3679" (miRBase Accession No. MI0016080, SEQ ID NO: 263) having a hairpin-like structure is known as a precursor of "hsa-miR-3679-3p".

The term "hsa-miR-6791-5p gene" or "hsa-miR-6791-5p" used herein includes the hsa-miR-6791-5p gene (miRBase Accession No. MIMAT0027482) described in SEQ ID NO: 114, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6791-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6791" (miRBase Accession No. MI0022636, SEQ ID NO: 264) having a hairpin-like structure is known as a precursor of "hsa-miR-6791-5p".

The term "hsa-miR-1202 gene" or "hsa-miR-1202" used herein includes the hsa-miR-1202 gene (miRBase Accession No. MIMAT0005865) described in SEQ ID NO: 115, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1202 gene can be obtained by a method described in Marton S et al., 2008, Leukemia, Vol. 22, p. 330-338. Also, "hsa-mir-1202" (miRBase Accession No. MI0006334, SEQ ID NO: 265) having a hairpin-like structure is known as a precursor of "hsa-miR-1202".

The term "hsa-miR-3656 gene" or "hsa-miR-3656" used herein includes the hsa-miR-3656 gene (miRBase Accession No. MIMAT0018076) described in SEQ ID NO: 116, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-3656 gene can be obtained by a method described in Meiri E et al., 2010, Nucleic Acids Res. Vol. 38, p. 6234-6246. Also, "hsa-mir-3656" (miRBase Accession No. MI0016056, SEQ ID NO: 266) having a hairpin-like structure is known as a precursor of "hsa-miR-3656".

The term "hsa-miR-4746-3p gene" or "hsa-miR-4746-3p" used herein includes the hsa-miR-4746-3p gene (miRBase Accession No. MIMAT0019881) described in SEQ ID NO: 117, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4746-3p gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4746" (miRBase Accession No. MI0017385, SEQ ID NO: 267) having a hairpin-like structure is known as a precursor of "hsa-miR-4746-3p".

The term "hsa-miR-3184-5p gene" or "hsa-miR-3184-5p" used herein includes the hsa-miR-3184-5p gene (miRBase Accession No. MIMAT0015064) described in SEQ ID NO: 118, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-3184-5p gene can be obtained by a method described in Stark M S et al., 2010, PLoS One, Vol. 5, e9685. Also, "hsa-mir-3184" (miRBase Accession No. MI0014226. SEQ ID NO: 268) having a hairpin-like structure is known as a precursor of "hsa-miR-3184-5p".

The term "hsa-miR-3937 gene" or "hsa-miR-3937" used herein includes the hsa-miR-3937 gene (miRBase Accession No. MIMAT0018352) described in SEQ ID NO: 119, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-3937 gene can be obtained by a method described in Liao J Y et al., 2010, PLoS One, Vol. 5, e10563. Also, "hsa-mir-3937" (miRBase Accession No. MI0016593, SEQ ID NO: 269) having a hairpin-like structure is known as a precursor of "hsa-miR-3937".

The term "hsa-miR-6515-3p gene" or "hsa-miR-6515-3p" used herein includes the hsa-miR-6515-3p gene (miRBase Accession No. MIMAT0025487) described in SEQ ID NO: 120, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6515-3p gene can be obtained by a method described in Joyce C E et al., 2011, Hum Mol Genet, Vol. 20, p. 4025-4040. Also, "hsa-mir-6515" (miRBase Accession No. MI0022227, SEQ ID NO: 270) having a hairpin-like structure is known as a precursor of "hsa-miR-6515-3p".

The term "hsa-miR-6132 gene" or "hsa-miR-6132" used herein includes the hsa-miR-6132 gene (miRBase Accession No. MIMAT0024616) described in SEQ ID NO: 121, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6132 gene can be obtained by a method described in Dannemann M et al., 2012, Genome Biol Evol, Vol. 4, p. 552-564. Also, "hsa-mir-6132" (miRBase Accession No. MI0021277, SEQ ID NO: 271) having a hairpin-like structure is known as a precursor of "hsa-miR-6132".

The term "hsa-miR-187-5p gene" or "hsa-miR-187-5p" used herein includes the hsa-miR-187-5p gene (miRBase Accession No. MIMAT0004561) described in SEQ ID NO: 122, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-187-5p gene can be obtained by a method described in Lim L P et al., 2003, Science, Vol. 299, p. 1540. Also, "hsa-mir-187" (miRBase Accession No. MI0000274, SEQ ID NO: 272) having a hairpin-like structure is known as a precursor of "hsa-miR-187-5p".

The term "hsa-miR-7111-5p gene" or "hsa-miR-7111-5p" used herein includes the hsa-miR-7111-5p gene (miRBase Accession No. MIMAT0028119) described in SEQ ID NO: 123, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-7111-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-7111" (miRBase Accession No. MI0022962. SEQ ID NO: 273) having a hairpin-like structure is known as a precursor of "hsa-miR-7111-5p".

The term "hsa-miR-5787 gene" or "hsa-miR-5787" used herein includes the hsa-miR-5787 gene (miRBase Accession No. MIMAT0023252) described in SEQ ID NO: 124, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-5787 gene can be obtained by a method described in Yoo H et al., 2011, Biochem Biophys Res Commun, Vol. 415, p. 567-572. Also, "hsa-mir-5787" (miRBase Accession No. MI0019797. SEQ ID NO: 274) having a hairpin-like structure is known as a precursor of "hsa-miR-5787".

The term "hsa-miR-6779-5p gene" or "hsa-miR-6779-5p" used herein includes the hsa-miR-6779-5p gene (miRBase Accession No. MIMAT0027458) described in SEQ ID NO: 125, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6779-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6779" (miRBase Accession No. MI0022624, SEQ ID NO: 275) having a hairpin-like structure is known as a precursor of "hsa-miR-6779-5p".

The term "hsa-miR-6808-5p gene" or "hsa-miR-6808-5p" used herein includes the hsa-miR-6808-5p gene (miRBase Accession No. MIMAT0027516) described in SEQ ID NO: 126, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6808-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6808" (miRBase Accession No. MI0022653, SEQ ID NO: 276) having a hairpin-like structure is known as a precursor of "hsa-miR-6808-5p".

The term "hsa-miR-6774-5p gene" or "hsa-miR-6774-5p" used herein includes the hsa-miR-6774-5p gene (miRBase Accession No. MIMAT0027448) described in SEQ ID NO: 127, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6774-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6774" (miRBase Accession No. MI0022619. SEQ ID NO: 277) having a hairpin-like structure is known as a precursor of "hsa-miR-6774-5p".

The term "hsa-miR-4656 gene" or "hsa-miR-4656" used herein includes the hsa-miR-4656 gene (miRBase Accession No. MIMAT0019723) described in SEQ ID NO: 128, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4656 gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4656" (miRBase Accession No. MI0017284, SEQ ID NO: 278) having a hairpin-like structure is known as a precursor of "hsa-miR-4656".

The term "hsa-miR-6806-5p gene" or "hsa-miR-6806-5p" used herein includes the hsa-miR-6806-5p gene (miRBase Accession No. MIMAT0027512) described in SEQ ID NO: 129, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6806-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6806" (miRBase Accession No. MI0022651, SEQ ID NO: 279) having a hairpin-like structure is known as a precursor of "hsa-miR-6806-5p".

The term "hsa-miR-1233-5p gene" or "hsa-miR-1233-5p" used herein includes the hsa-miR-1233-5p gene (miRBase Accession No. MIMAT0022943) described in SEQ ID NO: 130, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1233-5p gene can be obtained by a method described in Berezikov E et al., 2007, Mol Cell, Vol. 28, p. 328-336. Also, "hsa-mir-1233-1" and "hsa-mir-1233-2" (miRBase Accession Nos. MI0006323 and MI0015973, SEQ ID NOs: 280 and 281) having a hairpin-like structure are known as precursors of "hsa-miR-1233-5p".

The term “hsa-miR-328-5p gene” or “hsa-miR-328-5p” used herein includes the hsa-miR-328-5p gene (miRBase Accession No. MIMAT0026486) described in SEQ ID NO: 131, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-328-5p gene can be obtained by a method described in Kim J et al., 2004, Proc Natl Acad Sci USA, Vol. 101, p. 360-365. Also, “hsa-mir-328” (miRBase Accession No. MI0000804, SEQ ID NO: 282) having a hairpin-like structure is known as a precursor of “hsa-miR-328-5p”.

The term “hsa-miR-4674 gene” or “hsa-miR-4674” used herein includes the hsa-miR-4674 gene (miRBase Accession No. MIMAT0019756) described in SEQ ID NO: 132, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4674 gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, “hsa-mir-4674” (miRBase Accession No. MI0017305, SEQ ID NO: 283) having a hairpin-like structure is known as a precursor of “hsa-miR-4674”.

The term “hsa-miR-2110 gene” or “hsa-miR-2110” used herein includes the hsa-miR-2110 gene (miRBase Accession No. MIMAT0010133) described in SEQ ID NO: 133, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-2110 gene can be obtained by a method described in Zhu J Y et al., 2009, J Virol, Vol. 83, p. 3333-3341. Also, “hsa-mir-2110” (miRBase Accession No. MI0010629, SEQ ID NO: 284) having a hairpin-like structure is known as a precursor of “hsa-miR-2110”.

The term “hsa-miR-6076 gene” or “hsa-miR-6076” used herein includes the hsa-miR-6076 gene (miRBase Accession No. MIMAT0023701) described in SEQ ID NO: 134, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6076 gene can be obtained by a method described in Voellenkle C et al., 2012, RNA, Vol. 18, p. 472-484. Also, “hsa-mir-6076” (miRBase Accession No. MI0020353. SEQ ID NO: 285) having a hairpin-like structure is known as a precursor of “hsa-miR-6076”.

The term “hsa-miR-3619-3p gene” or “hsa-miR-3619-3p” used herein includes the hsa-miR-3619-3p gene (miRBase Accession No. MIMAT0019219) described in SEQ ID NO: 135, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-3619-3p gene can be obtained by a method described in Witten D et al., 2010, BMC Biol, Vol. 8, p. 58. Also, “hsa-mir-3619” (miRBase Accession No. MI0016009, SEQ ID NO: 286) having a hairpin-like structure is known as a precursor of “hsa-miR-3619-3p”.

The term “hsa-miR-92a-2-5p gene” or “hsa-miR-92a-2-5p” used herein includes the hsa-miR-92a-2-5p gene (miRBase Accession No. MIMAT00004508) described in SEQ ID NO: 136, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-92a-2-5p gene can be obtained by a method described in Mourelatos Z et al., 2002, Genes Dev, Vol. 16, p. 720-728. Also, “hsa-mir-92a-2” (miRBase Accession No. MI0000094, SEQ ID NO: 287) having a hairpin-like structure is known as a precursor of “hsa-miR-92a-2-5p”.

The term “hsa-miR-128-1-5p gene” or “hsa-miR-128-1-5p” used herein includes the hsa-miR-128-1-5p gene (miRBase Accession No. MIMAT0026477) described in SEQ ID NO: 137, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-128-1-5p gene can be obtained by a method described in Lagos-Quintana M et al., 2002, Curr Biol, Vol. 12, p. 735-739. Also, “hsa-mir-128-1” (miRBase Accession No. MI0000447, SEQ ID NO: 288) having a hairpin-like structure is known as a precursor of “hsa-miR-128-1-5p”.

The term “hsa-miR-638 gene” or “hsa-miR-638” used herein includes the hsa-miR-638 gene (miRBase Accession No. MIMAT0003308) described in SEQ ID NO: 138, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-638 gene can be obtained by a method described in Cummins J M et al., 2006, Proc Natl Acad Sci USA, Vol. 103, p. 3687-3692. Also, “hsa-mir-638” (miRBase Accession No. MI0003653, SEQ ID NO: 289) having a hairpin-like structure is known as a precursor of “hsa-miR-638”.

The term “hsa-miR-2861 gene” or “hsa-miR-2861” used herein includes the hsa-miR-2861 gene (miRBase Accession No. MIMAT0013802) described in SEQ ID NO: 139, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-2861 gene can be obtained by a method described in Li H et al., 2009, J Clin Invest, Vol. 119, p. 3666-3677. Also, “hsa-mir-2861” (miRBase Accession No. MI0013006, SEQ ID NO: 290) having a hairpin-like structure is known as a precursor of “hsa-miR-2861”.

The term “hsa-miR-371a-5p gene” or “hsa-miR-371a-5p” used herein includes the hsa-miR-371a-5p gene (miRBase Accession No. MIMAT0004687) described in SEQ ID NO: 140, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-371a-5p gene can be obtained by a method described in Suh M R et al., 2004. Dev Biol, Vol. 270, p. 488-498. Also, “hsa-mir-371a” (miRBase Accession No. MI0000779, SEQ ID NO: 291) having a hairpin-like structure is known as a precursor of “hsa-miR-371a-5p”.

The term “hsa-miR-211-3p gene” or “hsa-miR-211-3p” used herein includes the hsa-miR-211-3p gene (miRBase Accession No. MIMAT0022694) described in SEQ ID NO: 141, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-211-3p gene can be obtained by a method described in Lim L P et al., 2003. Science, Vol. 299, p. 1540. Also, “hsa-mir-211” (miRBase Accession No. MI0000287, SEQ ID NO: 292) having a hairpin-like structure is known as a precursor of “hsa-miR-211-3p”.

The term “hsa-miR-1273g-3p gene” or “hsa-miR-1273g-3p” used herein includes the hsa-miR-1273g-3p gene (miRBase Accession No. MIMAT0022742) described in SEQ ID NO: 142, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1273g-3p gene can be obtained by a method described in Reshmi G et al., 2011, Genomics, Vol. 97, p. 333-340. Also, “hsa-mir-1273g” (miRBase Accession No. MI0018003, SEQ ID NO: 293) having a hairpin-like structure is known as a precursor of “hsa-miR-1273g-3p”.

The term “hsa-miR-1203 gene” or “hsa-miR-1203” used herein includes the hsa-miR-1203 gene (miRBase Accession No. MIMAT0005866) described in SEQ ID NO: 143, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1203 gene can be obtained by a method described in Marton S et al., 2008, Leukemia, Vol. 22, p. 330-338. Also, “hsa-mir-1203” (miRBase Accession No. MI0006335, SEQ ID NO: 294) having a hairpin-like structure is known as a precursor of “hsa-miR-1203”.

The term “hsa-miR-122-5p gene” or “hsa-miR-122-5p” used herein includes the hsa-miR-122-5p gene (miRBase Accession No. MIMAT0000421) described in SEQ ID NO: 144, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-122-5p gene can be obtained by a method described in Lagos-Quintana M et al., 2002. Curr Biol, Vol. 12, p. 735-739. Also, “hsa-mir-122” (miRBase Accession No. MI0000442, SEQ ID NO: 295) having a hairpin-like structure is known as a precursor of "hsa-miR-122-5p".

The term "hsa-miR-4258 gene" or "hsa-miR-4258" used herein includes the hsa-miR-4258 gene (miRBase Accession No. MIMAT0016879) described in SEQ ID NO: 145, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4258 gene can be obtained by a method described in Goff L A et al., 2009, PLoS One. Vol. 4, e7192. Also, "hsa-mir-4258" (miRBase Accession No. MI0015857, SEQ ID NO: 296) having a hairpin-like structure is known as a precursor of "hsa-miR-4258".

The term "hsa-miR-4484 gene" or "hsa-miR-4484" used herein includes the hsa-miR-4484 gene (miRBase Accession No. MIMAT0019018) described in SEQ ID NO: 146, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4484 gene can be obtained by a method described in Jima D D et al., 2010, Blood, Vol. 116, e118-e127. Also, "hsa-mir-4484" (miRBase Accession No. MI0016845, SEQ ID NO: 297) having a hairpin-like structure is known as a precursor of "hsa-miR-4484".

The term "hsa-miR-4648 gene" or "hsa-miR-4648" used herein includes the hsa-miR-4648 gene (miRBase Accession No. MIMAT0019710) described in SEQ ID NO: 147, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4648 gene can be obtained by a method described in Persson H et al., 2011, Cancer Res, Vol. 71, p. 78-86. Also, "hsa-mir-4648" (miRBase Accession No. MI0017275, SEQ ID NO: 298) having a hairpin-like structure is known as a precursor of "hsa-miR-4648".

The term "hsa-miR-6780b-5p gene" or "hsa-miR-6780b-5p" used herein includes the hsa-miR-6780b-5p gene (miRBase Accession No. MIMAT0027572) described in SEQ ID NO: 148, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6780b-5p gene can be obtained by a method described in Ladewig E et al., 2012. Genome Res, Vol. 22, p. 1634-1645. Also, "hsa-mir-6780b" (miRBase Accession No. MI0022681, SEQ ID NO: 299) having a hairpin-like structure is known as a precursor of "hsa-miR-6780b-5p".

The term "hsa-miR-4516 gene" or "hsa-miR-4516" used herein includes the hsa-miR-4516 gene (miRBase Accession No. MIMAT0019053) described in SEQ ID NO: 466, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4516 gene can be obtained by a method described in Jima D D et al., 2010, Blood., Vol. 116, p. e118-e127. Also, "hsa-mir-4516" (miRBase Accession No. MI0016882, SEQ ID NO: 479) having a hairpin-like structure is known as a precursor of "hsa-miR-4516".

The term "hsa-miR-4649-5p gene" or "hsa-miR-4649-5p" used herein includes the hsa-miR-4649-5p gene (miRBase Accession No. MIMAT0019711) described in SEQ ID NO: 467, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4649-5p gene can be obtained by a method described in Persson H et al., 2011, Cancer Res., Vol. 71, p. 78-86. Also, "hsa-mir-4649" (miRBase Accession No. MI0017276, SEQ ID NO: 480) having a hairpin-like structure is known as a precursor of "hsa-miR-4649-5p".

The term "hsa-miR-760 gene" or "hsa-miR-760" used herein includes the hsa-miR-760 gene (miRBase Accession No. MIMAT0004957) described in SEQ ID NO: 468, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-760 gene can be obtained by a method described in Berezikov E et al., 2006, Genome Res., Vol. 16, p. 289-1298. Also, "hsa-mir-760" (miRBase Accession No. MI0005567, SEQ ID NO: 481) having a hairpin-like structure is known as a precursor of "hsa-miR-760".

The term "hsa-miR-3162-5p gene" or "hsa-miR-3162-5p" used herein includes the hsa-miR-3162-5p gene (miRBase Accession No. MIMAT0015036) described in SEQ ID NO: 469, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-3162-5p gene can be obtained by a method described in Stark M S et al., 2010, PLoS One., Vol. 5, e9685. Also, "hsa-mir-3162" (miRBase Accession No. MI0014192, SEQ ID NO: 482) having a hairpin-like structure is known as a precursor of "hsa-miR-3162-5p".

The term "hsa-miR-3178 gene" or "hsa-miR-3178" used herein includes the hsa-miR-3178 gene (miRBase Accession No. MIMAT0015055) described in SEQ ID NO: 470, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-3178 gene can be obtained by a method described in Stark M S et al., 2010, PLoS One., Vol. 5, e9685. Also, "hsa-mir-3178" (miRBase Accession No. MI0014212, SEQ ID NO: 483) having a hairpin-like structure is known as a precursor of "hsa-miR-3178".

The term "hsa-miR-940 gene" or "hsa-miR-940" used herein includes the hsa-miR-940 gene (miRBase Accession No. MIMAT0004983) described in SEQ ID NO: 471, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-940 gene can be obtained by a method described in Lui W O et al., 2007, Cancer Res., Vol. 67, p. 6031-6043. Also, "hsa-mir-940" (miRBase Accession No. MI0005762, SEQ ID NO: 484) having a hairpin-like structure is known as a precursor of "hsa-miR-940".

The term "hsa-miR-4271 gene" or "hsa-miR-4271" used herein includes the hsa-miR-4271 gene (miRBase Accession No. MIMAT0016901) described in SEQ ID NO: 472, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4271 gene can be obtained by a method described in Goff L A et al., 2009, PLoS One., Vol. 4, e7192. Also, "hsa-mir-4271" (miRBase Accession No. MI0015879, SEQ ID NO: 485) having a hairpin-like structure is known as a precursor of "hsa-miR-4271".

The term "hsa-miR-6769b-5p gene" or "hsa-miR-6769b-5p" used herein includes the hsa-miR-6769b-5p gene (miRBase Accession No. MIMAT0027620) described in SEQ ID NO: 473, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6769b-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res., Vol. 22, p. 1634-1645. Also, "hsa-mir-6769b" (miRBase Accession No. MI0022706, SEQ ID NO: 486) having a hairpin-like structure is known as a precursor of "hsa-miR-6769b-5p".

The term "hsa-miR-4508 gene" or "hsa-miR-4508" used herein includes the hsa-miR-4508 gene (miRBase Accession No. MIMAT0019045) described in SEQ ID NO: 474, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-4508 gene can be obtained by a method described in Jima D D et al., 2010, Blood., Vol. 116, e118-e127. Also, "hsa-mir-4508" (miRBase Accession No. MI0016872, SEQ ID NO: 487) having a hairpin-like structure is known as a precursor of "hsa-miR-4508".

The term "hsa-miR-6826-5p gene" or "hsa-miR-6826-5p" used herein includes the hsa-miR-6826-5p gene (miRBase Accession No. MIMAT0027552) described in SEQ ID NO: 475, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6826-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res., Vol. 22, p. 1634-1645. Also, "hsa-mir-6826" (miRBase Accession No. MI0022671, SEQ ID NO: 488) having a hairpin-like structure is known as a precursor of "hsa-miR-6826-5p".

The term "hsa-miR-6757-5p gene" or "hsa-miR-6757-5p" used herein includes the hsa-miR-6757-5p gene (miRBase Accession No. MIMAT0027414) described in SEQ ID NO: 476, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-6757-5p gene can be obtained by a method described in Ladewig E et al., 2012, Genome Res., Vol. 22, p. 1634-1645. Also, "hsa-mir-6757" (miRBase Accession No. MI0022602. SEQ ID NO: 489) having a hairpin-like structure is known as a precursor of "hsa-miR-6757-5p".

The term "hsa-miR-3131 gene" or "hsa-miR-3131" used herein includes the hsa-miR-3131 gene (miRBase Accession No. MIMAT0014996) described in SEQ ID NO: 477, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-3131 gene can be obtained by a method described in Stark M S et al., 2010, PLoS One., Vol. 5, e9685. Also, "hsa-mir-3131" (miRBase Accession No. MI0014151, SEQ ID NO: 490) having a hairpin-like structure is known as a precursor of "hsa-miR-3131".

The term "hsa-miR-1343-3p gene" or "hsa-miR-1343-3p" used herein includes the hsa-miR-1343-3p gene (miRBase Accession No. MIMAT0019776) described in SEQ ID NO: 478, a homolog or an ortholog of a different organism species, and the like. The hsa-miR-1343-3p gene can be obtained by a method described in Persson H et al., 2011, Cancer Res., Vol. 71, p. 78-86. Also, "hsa-mir-1343" (miRBase Accession No. MI0017320, SEQ ID NO: 491) having a hairpin-like structure is known as a precursor of "hsa-miR-1343-3p".

A mature miRNA may become a variant due to the sequence cleaved shorter or longer by one to several flanking nucleotides, or nucleotide substitution, when cleaved as the mature miRNA from its RNA precursor which has a hairpin-like structure. This variant is called isomiR (Morin R D. et al., 2008, Genome Research, Vol. 18, p. 610-621). miRBase Release 20 shows the nucleotide sequences represented by SEQ ID NOs: 1 to 148 and 466 to 478 as well as a large number of the nucleotide sequence variants and fragments represented by SEQ ID NOs: 300 to 465 and 492 to 509, called isomiRs. These variants can also be obtained as miRNAs having a nucleotide sequence represented by any of SEQ ID NOs: 1 to 148 and 466 to 478.

Specifically, among the variants of polynucleotides that consist of a nucleotide sequence represented by any of SEQ ID NOs: 1, 3, 4, 6, 14, 16, 17, 18, 22, 23, 24, 25, 30, 31, 34, 35, 37, 42, 43, 44, 47, 48, 49, 50, 51, 52, 55, 57, 59, 61, 62, 66, 67, 69, 70, 72, 73, 75, 77, 79, 80, 82, 83, 84, 85, 86, 89, 90, 92, 94, 96, 99, 101, 102, 103, 104, 106, 107, 109, 110, 111, 112, 113, 115, 116, 120, 121, 122, 124, 130, 131, 132, 133, 136, 137, 138, 139, 140, 141, 142, 144, 146, 147, 466, 467, 468, 469, 470, 471, 474, 477, and 478, or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t according to the present invention, examples of the longest variants registered in miRBase Release 20 include polynucleotides represented by SEQ ID NOs: 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412, 414, 416, 418, 420, 422, 424, 426, 428, 430, 432, 434, 436, 438, 440, 442, 444, 446, 448, 450, 452, 454, 456, 458, 460, 462, 464, 492, 494, 496, 498, 500, 502, 504, 506, and 508, respectively.

Also, among the variants of polynucleotides consisting of a nucleotide sequence represented by any of SEQ ID NOs: 1, 3, 4, 6, 14, 16, 17, 18, 22, 23, 24, 25, 30, 31, 34, 35, 37, 42, 43, 44, 47, 48, 49, 50, 51, 52, 55, 57, 59, 61, 62, 66, 67, 69, 70, 72, 73, 75, 77, 79, 80, 82, 83, 84, 85, 86, 89, 90, 92, 94, 96, 99, 101, 102, 103, 104, 106, 107, 109, 110, 111, 112, 113, 115, 116, 120, 121, 122, 124, 130, 131, 132, 133, 136, 137, 138, 139, 140, 141, 142, 144, 146, 147, 466, 467, 468, 469, 470, 471, 474, 477, and 478, or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t according to the present invention, examples of the shortest variants registered in miRBase Release 20 include polynucleotides having sequences represented by SEQ ID NOs: 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 377, 379, 381, 383, 385, 387, 389, 391, 393. 395, 397, 399, 401, 403, 405, 407, 409, 411, 413, 415, 417, 419, 421, 423, 425, 427, 429, 431, 433, 435, 437, 439, 441, 443, 445, 447, 449, 451, 453, 455, 457, 459, 461, 463, 465, 493, 495, 497, 499, 501, 503, 505, 507, and 509, respectively. In addition to these variants and fragments, examples thereof include a large number of isomiR polynucleotides of SEQ ID NOs: 1, 3, 4, 6, 14, 16, 17, 18, 22, 23, 24, 25, 30, 31, 34, 35, 37, 42, 43, 44, 47, 48, 49, 50, 51, 52, 55, 57, 59, 61, 62, 66, 67, 69, 70, 72, 73, 75, 77, 79, 80, 82, 83, 84, 85, 86, 89, 90, 92, 94, 96, 99, 101, 102, 103, 104, 106, 107, 109, 110, 111, 112, 113, 115, 116, 120, 121, 122, 124, 130, 131, 132, 133, 136, 137, 138, 139, 140, 141, 142, 144, 146 and 147 registered in miRBase. Examples of the polynucleotide comprising a nucleotide sequence represented by any of SEQ ID NOs: 1 to 148, 466 to 478 include a polynucleotide represented by any of SEQ ID NOs: 149 to 299, 479 to 491, which are their respective precursors.

The names and miRBase Accession Nos. (registration numbers) of the genes represented by SEQ ID NOs: 1 to 509 are shown in Table 1.

As used herein, the term "capable of specifically binding" means that the nucleic acid probe or the primer used in the present invention binds to a particular target nucleic acid and cannot substantially bind to other nucleic acids.

TABLE 1

SEQ ID NO:	Gene name	miRBase registration No.
1	hsa-miR-125a-3p	MIMAT0004602
2	hsa-miR-6893-5p	MIMAT0027686
3	hsa-miR-204-3p	MIMAT0022693
4	hsa-miR-4476	MIMAT0019003
5	hsa-miR-4294	MIMAT0016849
6	hsa-miR-150-3p	MIMAT0004610
7	hsa-miR-6729-5p	MIMAT0027359
8	hsa-miR-7641	MIMAT0029782
9	hsa-miR-6765-3p	MIMAT0027431
10	hsa-miR-6820-5p	MIMAT0027540
11	hsa-miR-575	MIMAT0003240
12	hsa-miR-6836-3p	MIMAT0027575
13	hsa-miR-1469	MIMAT0007347
14	hsa-miR-663a	MIMAT0003326
15	hsa-miR-6075	MIMAT0023700
16	hsa-miR-4634	MIMAT0019691
17	hsa-miR-423-5p	MIMAT0004748
18	hsa-miR-4454	MIMAT0018976
19	hsa-miR-7109-5p	MIMAT0028115
20	hsa-miR-6789-5p	MIMAT0027478
21	hsa-miR-6877-5p	MIMAT0027654
22	hsa-miR-4792	MIMAT0019964
23	hsa-miR-4530	MIMAT0019069
24	hsa-miR-7975	MIMAT0031178

TABLE 1-continued

SEQ ID NO:	Gene name	miRBase registration No.
25	hsa-miR-6724-5p	MIMAT0025856
26	hsa-miR-8073	MIMAT0031000
27	hsa-miR-7977	MIMAT0031180
28	hsa-miR-1231	MIMAT0005586
29	hsa-miR-6799-5p	MIMAT0027498
30	hsa-miR-615-5p	MIMAT0004804
31	hsa-miR-4450	MIMAT0018971
32	hsa-miR-6726-5p	MIMAT0027353
33	hsa-miR-6875-5p	MIMAT0027650
34	hsa-miR-4734	MIMAT0019859
35	hsa-miR-16-5p	MIMAT0000069
36	hsa-miR-602	MIMAT0003270
37	hsa-miR-4651	MIMAT0019715
38	hsa-miR-8069	MIMAT0030996
39	hsa-miR-1238-5p	MIMAT0022947
40	hsa-miR-6880-5p	MIMAT0027660
41	hsa-miR-8072	MIMAT0030999
42	hsa-miR-4723-5p	MIMAT0019838
43	hsa-miR-4732-5p	MIMAT0019855
44	hsa-miR-6125	MIMAT0024598
45	hsa-miR-6090	MIMAT0023715
46	hsa-miR-7114-5p	MIMAT0028125
47	hsa-miR-564	MIMAT0003228
48	hsa-miR-451a	MIMAT0001631
49	hsa-miR-3135b	MIMAT0018985
50	hsa-miR-4497	MIMAT0019032
51	hsa-miR-4665-5p	MIMAT0019739
52	hsa-miR-3622a-5p	MIMAT0018003
53	hsa-miR-6850-5p	MIMAT0027600
54	hsa-miR-6821-5p	MIMAT0027542
55	hsa-miR-5100	MIMAT0022259
56	hsa-miR-6872-3p	MIMAT0027645
57	hsa-miR-4433-3p	MIMAT0018949
58	hsa-miR-1227-5p	MIMAT0022941
59	hsa-miR-3188	MIMAT0015070
60	hsa-miR-7704	MIMAT0030019
61	hsa-miR-3185	MIMAT0015065
62	hsa-miR-1908-3p	MIMAT0026916
63	hsa-miR-6781-5p	MIMAT0027462
64	hsa-miR-6805-5p	MIMAT0027510
65	hsa-miR-8089	MIMAT0031016
66	hsa-miR-665	MIMAT0004952
67	hsa-miR-4486	MIMAT0019020
68	hsa-miR-6722-3p	MIMAT0025854
69	hsa-miR-1260a	MIMAT0005911
70	hsa-miR-4707-5p	MIMAT0019807
71	hsa-miR-6741-5p	MIMAT0027383
72	hsa-miR-1260b	MIMAT0015041
73	hsa-miR-1246	MIMAT0005898
74	hsa-miR-6845-5p	MIMAT0027590
75	hsa-miR-4638-5p	MIMAT0019695
76	hsa-miR-6085	MIMAT0023710
77	hsa-miR-1228-3p	MIMAT0005583
78	hsa-miR-4534	MIMAT0019073
79	hsa-miR-5585-3p	MIMAT0022286
80	hsa-miR-4741	MIMAT0019871
81	hsa-miR-4433b-3p	MIMAT0030414
82	hsa-miR-197-5p	MIMAT0022691
83	hsa-miR-718	MIMAT0012735
84	hsa-miR-4513	MIMAT0019050
85	hsa-miR-4446-3p	MIMAT0018965
86	hsa-miR-619-5p	MIMAT0026622
87	hsa-miR-6816-5p	MIMAT0027532
88	hsa-miR-6778-5p	MIMAT0027456
89	hsa-miR-24-3p	MIMAT0000080
90	hsa-miR-1915-3p	MIMAT0007892
91	hsa-miR-4665-3p	MIMAT0019740
92	hsa-miR-4449	MIMAT0018968
93	hsa-miR-6889-5p	MIMAT0027678
94	hsa-miR-486-3p	MIMAT0004762
95	hsa-miR-7113-3p	MIMAT0028124
96	hsa-miR-642a-3p	MIMAT0020924
97	hsa-miR-7847-3p	MIMAT0030422
98	hsa-miR-6768-5p	MIMAT0027436
99	hsa-miR-1290	MIMAT0005880
100	hsa-miR-7108-5p	MIMAT0028113
101	hsa-miR-92b-5p	MIMAT0004792
102	hsa-miR-663b	MIMAT0005867
103	hsa-miR-3940-5p	MIMAT0019229
104	hsa-miR-4467	MIMAT0018994
105	hsa-miR-6858-5p	MIMAT0027616
106	hsa-miR-4417	MIMAT0018929
107	hsa-miR-3665	MIMAT0018087
108	hsa-miR-4736	MIMAT0019862
109	hsa-miR-4687-3p	MIMAT0019775
110	hsa-miR-1908-5p	MIMAT0007881
111	hsa-miR-5195-3p	MIMAT0021127
112	hsa-miR-4286	MIMAT0016916
113	hsa-miR-3679-3p	MIMAT0018105
114	hsa-miR-6791-5p	MIMAT0027482
115	hsa-miR-1202	MIMAT0005865
116	hsa-miR-3656	MIMAT0018076
117	hsa-miR-4746-3p	MIMAT0019881
118	hsa-miR-3184-5p	MIMAT0015064
119	hsa-miR-3937	MIMAT0018352
120	hsa-miR-6515-3p	MIMAT0025487
121	hsa-miR-6132	MIMAT0024616
122	hsa-miR-187-5p	MIMAT0004561
123	hsa-miR-7111-5p	MIMAT0028119
124	hsa-miR-5787	MIMAT0023252
125	hsa-miR-6779-5p	MIMAT0027458
126	hsa-miR-6808-5p	MIMAT0027516
127	hsa-miR-6774-5p	MIMAT0027448
128	hsa-miR-4656	MIMAT0019723
129	hsa-miR-6805-5p	MIMAT0027512
130	hsa-miR-1233-5p	MIMAT0022943
131	hsa-miR-328-5p	MIMAT0026486
132	hsa-miR-4674	MIMAT0019756
133	hsa-miR-2110	MIMAT0010133
134	hsa-miR-6076	MIMAT0023701
135	hsa-miR-3619-3p	MIMAT0019219
136	hsa-miR-92a-2-5p	MIMAT0004508
137	hsa-miR-128-1-5p	MIMAT0026477
138	hsa-miR-638	MIMAT0003308
139	hsa-miR-2861	MIMAT0013802
140	hsa-miR-371a-5p	MIMAT0004687
141	hsa-miR-211-3p	MIMAT0022694
142	hsa-miR-1273g-3p	MIMAT0022742
143	hsa-miR-1203	MIMAT0005866
144	hsa-miR-122-5p	MIMAT0000421
145	hsa-miR-4258	MIMAT0016879
146	hsa-miR-4484	MIMAT0019018
147	hsa-miR-4648	MIMAT0019710
148	hsa-miR-6780b-5p	MIMAT0027572
149	hsa-mir-125a	MI0000469
150	hsa-mir-6893	MI0022740
151	hsa-mir-204	MI0000284
152	hsa-mir-4476	MI0016828
153	hsa-mir-4294	MI0015827
154	hsa-mir-150	MI0000479
155	hsa-mir-6729	MI0022574
156	hsa-mir-7641-1	MI0024975
157	hsa-mir-7641-2	MI0024976
158	hsa-mir-6765	MI0022610
159	hsa-mir-6820	MI0022665
160	hsa-mir-575	MI0003582
161	hsa-mir-6836	MI0022682
162	hsa-mir-1469	MI0007074
163	hsa-mir-663a	MI0003672
164	hsa-mir-6075	MI0020352
165	hsa-mir-4634	MI0017261
166	hsa-mir-423	MI0001445
167	hsa-mir-4454	MI0016800
168	hsa-mir-7109	MI0022960
169	hsa-mir-6789	MI0022634
170	hsa-mir-6877	MI0022724
171	hsa-mir-4792	MI0017439
172	hsa-mir-4530	MI0016897
173	hsa-mir-7975	MI0025751
174	hsa-mir-6724	MI0022559
175	hsa-mir-8073	MI0025909
176	hsa-mir-7977	MI0025753
177	hsa-mir-1231	MI0006321
178	hsa-mir-6799	MI0022644

TABLE 1-continued

SEQ ID NO:	Gene name	miRBase registration No.
179	hsa-mir-615	MI0003628
180	hsa-mir-4450	MI0016795
181	hsa-mir-6726	MI0022571
182	hsa-mir-6875	MI0022722
183	hsa-mir-4734	MI0017371
184	hsa-mir-16-1	MI0000070
185	hsa-mir-16-2	MI0000115
186	hsa-mir-602	MI0003615
187	hsa-mir-4651	MI0017279
188	hsa-mir-8069	MI0025905
189	hsa-mir-1238	MI0006328
190	hsa-mir-6880	MI0022727
191	hsa-mir-8072	MI0025908
192	hsa-mir-4723	MI0017359
193	hsa-mir-4732	MI0017369
194	hsa-mir-6125	MI0021259
195	hsa-mir-6090	MI0020367
196	hsa-mir-7114	MI0022965
197	hsa-mir-564	MI0003570
198	hsa-mir-451a	MI0001729
199	hsa-mir-3135b	MI0016809
200	hsa-mir-4497	MI0016859
201	hsa-mir-4665	MI0017295
202	hsa-mir-3622a	MI0016013
203	hsa-mir-6850	MI0022696
204	hsa-mir-6821	MI0022666
205	hsa-mir-5100	MI0019116
206	hsa-mir-6872	MI0022719
207	hsa-mir-4433	MI0016773
208	hsa-mir-1227	MI0006316
209	hsa-mir-3188	MI0014232
210	hsa-mir-7704	MI0025240
211	hsa-mir-3185	MI0014227
212	hsa-mir-1908	MI0008329
213	hsa-mir-6781	MI0022626
214	hsa-mir-6805	MI0022650
215	hsa-mir-8089	MI0025925
216	hsa-mir-665	MI0005563
217	hsa-mir-4486	MI0016847
218	hsa-mir-6722	MI0022557
219	hsa-mir-1260a	MI0006394
220	hsa-mir-4707	MI0017340
221	hsa-mir-6741	MI0022586
222	hsa-mir-1260b	MI0014197
223	hsa-mir-1246	MI0006381
224	hsa-mir-6845	MI0022691
225	hsa-mir-4638	MI0017265
226	hsa-mir-6085	MI0020362
227	hsa-mir-1228	MI0006318
228	hsa-mir-4534	MI0016901
229	hsa-mir-5585	MI0019142
230	hsa-mir-4741	MI0017379
231	hsa-mir-4433b	MI0025511
232	hsa-mir-197	MI0000239
233	hsa-mir-718	MI0012489
234	hsa-mir-4513	MI0016879
235	hsa-mir-4446	MI0016789
236	hsa-mir-619	MI0003633
237	hsa-mir-6816	MI0022661
238	hsa-mir-6778	MI0022623
239	hsa-mir-24-1	MI0000080
240	hsa-mir-24-2	MI0000081
241	hsa-mir-1915	MI0008336
242	hsa-mir-4449	MI0016792
243	hsa-mir-6889	MI0022736
244	hsa-mir-486	MI0002470
245	hsa-mir-486-2	MI0023622
246	hsa-mir-7113	MI0022964
247	hsa-mir-642a	MI0003657
248	hsa-mir-7847	MI0025517
249	hsa-mir-6768	MI0022613
250	hsa-mir-1290	MI0006352
251	hsa-mir-7108	MI0022959
252	hsa-mir-92b	MI0003560
253	hsa-mir-663b	MI0006336
254	hsa-mir-3940	MI0016597
255	hsa-mir-4467	MI0016818
256	hsa-mir-6858	MI0022704
257	hsa-mir-4417	MI0016753
258	hsa-mir-3665	MI0016066
259	hsa-mir-4736	MI0017373
260	hsa-mir-4687	MI0017319
261	hsa-mir-5195	MI0018174
262	hsa-mir-4286	MI0015894
263	hsa-mir-3679	MI0016080
264	hsa-mir-6791	MI0022636
265	hsa-mir-1202	MI0006334
266	hsa-mir-3656	MI0016056
267	hsa-mir-4746	MI0017385
268	hsa-mir-3184	MI0014226
269	hsa-mir-3937	MI0016593
270	hsa-mir-6515	MI0022227
271	hsa-mir-6132	MI0021277
272	hsa-mir-187	MI0000274
273	hsa-mir-7111	MI0022962
274	hsa-mir-5787	MI0019797
275	hsa-mir-6779	MI0022624
276	hsa-mir-6808	MI0022653
277	hsa-mir-6774	MI0022619
278	hsa-mir-4656	MI0017284
279	hsa-mir-6806	MI0022651
280	hsa-mir-1233-1	MI0006323
281	hsa-mir-1233-2	MI0015973
282	hsa-mir-328	MI0000804
283	hsa-mir-4674	MI0017305
284	hsa-mir-2110	MI0010629
285	hsa-mir-6076	MI0020353
286	hsa-mir-3619	MI0016009
287	hsa-mir-92a-2	MI0000094
288	hsa-mir-128-1	MI0000447
289	hsa-mir-638	MI0003653
290	hsa-mir-2861	MI0013006
291	hsa-mir-371a	MI0000779
292	hsa-mir-211	MI0000287
293	hsa-mir-1273g	MI0018003
294	hsa-mir-1203	MI0006335
295	hsa-mir-122	MI0000442
296	hsa-mir-4258	MI0015857
297	hsa-mir-4484	MI0016845
298	hsa-mir-4648	MI0017275
299	hsa-mir-6780b	MI0022681
300	isomiR example 1 of SEQ ID NO: 1	—
301	isomiR example 2 of SEQ ID NO: 1	—
302	isomiR example 1 of SEQ ID NO: 3	—
303	isomiR example 2 of SEQ ID NO: 3	—
304	isomiR example 1 of SEQ ID NO: 4	—
305	isomiR example 2 of SEQ ID NO: 4	—
306	isomiR example 1 of SEQ ID NO: 6	—
307	isomiR example 2 of SEQ ID NO: 6	—
308	isomiR example 1 of SEQ ID NO: 14	—
309	isomiR example 2 of SEQ ID NO: 14	—
310	isomiR example 1 of SEQ ID NO: 16	—
311	isomiR example 2 of SEQ ID NO: 16	—
312	isomiR example 1 of SEQ ID NO: 17	—
313	isomiR example 2 of SEQ ID NO: 17	—
314	isomiR example 1 of SEQ ID NO: 18	—
315	isomiR example 2 of SEQ ID NO: 18	—
316	isomiR example 1 of SEQ ID NO: 22	—
317	isomiR example 2 of SEQ ID NO: 22	—
318	isomiR example 1 of SEQ ID NO: 23	—
319	isomiR example 2 of SEQ ID NO: 23	—
320	isomiR example 1 of SEQ ID NO: 24	—
321	isomiR example 2 of SEQ ID NO: 24	—
322	isomiR example 1 of SEQ ID NO: 25	—
323	isomiR example 2 of SEQ ID NO: 25	—
324	isomiR example 1 of SEQ ID NO: 30	—
325	isomiR example 2 of SEQ ID NO: 30	—
326	isomiR example 1 of SEQ ID NO: 31	—
327	isomiR example 2 of SEQ ID NO: 31	—
328	isomiR example 1 of SEQ ID NO: 34	—
329	isomiR example 2 of SEQ ID NO: 34	—
330	isomiR example 1 of SEQ ID NO: 35	—
331	isomiR example 2 of SEQ ID NO: 35	—
332	isomiR example 1 of SEQ ID NO: 37	—

TABLE 1-continued

SEQ ID NO:	Gene name	miRBase registration No.
333	isomiR example 2 of SEQ ID NO: 37	—
334	isomiR example 1 of SEQ ID NO: 42	—
335	isomiR example 2 of SEQ ID NO: 42	—
336	isomiR example 1 of SEQ ID NO: 43	—
337	isomiR example 2 of SEQ ID NO: 43	—
338	isomiR example 1 of SEQ ID NO: 44	—
339	isomiR example 2 of SEQ ID NO: 44	—
340	isomiR example 1 of SEQ ID NO: 47	—
341	isomiR example 2 of SEQ ID NO: 47	—
342	isomiR example 1 of SEQ ID NO: 48	—
343	isomiR example 2 of SEQ ID NO: 48	—
344	isomiR example 1 of SEQ ID NO: 49	—
345	isomiR example 2 of SEQ ID NO: 49	—
346	isomiR example 1 of SEQ ID NO: 50	—
347	isomiR example 2 of SEQ ID NO: 50	—
348	isomiR example 1 of SEQ ID NO: 51	—
349	isomiR example 2 of SEQ ID NO: 51	—
350	isomiR example 1 of SEQ ID NO: 52	—
351	isomiR example 2 of SEQ ID NO: 52	—
352	isomiR example 1 of SEQ ID NO: 55	—
353	isomiR example 2 of SEQ ID NO: 55	—
354	isomiR example 1 of SEQ ID NO: 57	—
355	isomiR example 2 of SEQ ID NO: 57	—
356	isomiR example 1 of SEQ ID NO: 59	—
357	isomiR example 2 of SEQ ID NO: 59	—
358	isomiR example 1 of SEQ ID NO: 61	—
359	isomiR example 2 of SEQ ID NO: 61	—
360	isomiR example 1 of SEQ ID NO: 62	—
361	isomiR example 2 of SEQ ID NO: 62	—
362	isomiR example 1 of SEQ ID NO: 66	—
363	isomiR example 2 of SEQ ID NO: 66	—
364	isomiR example 1 of SEQ ID NO: 67	—
365	isomiR example 2 of SEQ ID NO: 67	—
366	isomiR example 1 of SEQ ID NO: 69	—
367	isomiR example 2 of SEQ ID NO: 69	—
368	isomiR example 1 of SEQ ID NO: 70	—
369	isomiR example 2 of SEQ ID NO: 70	—
370	isomiR example 1 of SEQ ID NO: 72	—
371	isomiR example 2 of SEQ ID NO: 72	—
372	isomiR example 1 of SEQ ID NO: 73	—
373	isomiR example 2 of SEQ ID NO: 73	—
374	isomiR example 1 of SEQ ID NO: 75	—
375	isomiR example 2 of SEQ ID NO: 75	—
376	isomiR example 1 of SEQ ID NO: 77	—
377	isomiR example 2 of SEQ ID NO: 77	—
378	isomiR example 1 of SEQ ID NO: 79	—
379	isomiR example 2 of SEQ ID NO: 79	—
380	isomiR example 1 of SEQ ID NO: 80	—
381	isomiR example 2 of SEQ ID NO: 80	—
382	isomiR example 1 of SEQ ID NO: 82	—
383	isomiR example 2 of SEQ ID NO: 82	—
384	isomiR example 1 of SEQ ID NO: 83	—
385	isomiR example 2 of SEQ ID NO: 83	—
386	isomiR example 1 of SEQ ID NO: 84	—
387	isomiR example 2 of SEQ ID NO: 84	—
388	isomiR example 1 of SEQ ID NO: 85	—
389	isomiR example 2 of SEQ ID NO: 85	—
390	isomiR example 1 of SEQ ID NO: 86	—
391	isomiR example 2 of SEQ ID NO: 86	—
392	isomiR example 1 of SEQ ID NO: 89	—
393	isomiR example 2 of SEQ ID NO: 89	—
394	isomiR example 1 of SEQ ID NO: 90	—
395	isomiR example 2 of SEQ ID NO: 90	—
396	isomiR example 1 of SEQ ID NO: 92	—
397	isomiR example 2 of SEQ ID NO: 92	—
398	isomiR example 1 of SEQ ID NO: 94	—
399	isomiR example 2 of SEQ ID NO: 94	—
400	isomiR example 1 of SEQ ID NO: 96	—
401	isomiR example 2 of SEQ ID NO: 96	—
402	isomiR example 1 of SEQ ID NO: 99	—
403	isomiR example 2 of SEQ ID NO: 99	—
404	isomiR example 1 of SEQ ID NO: 101	—
405	isomiR example 2 of SEQ ID NO: 101	—
406	isomiR example 1 of SEQ ID NO: 102	—
407	isomiR example 2 of SEQ ID NO: 102	—
408	isomiR example 1 of SEQ ID NO: 103	—
409	isomiR example 2 of SEQ ID NO: 103	—
410	isomiR example 1 of SEQ ID NO: 104	—
411	isomiR example 2 of SEQ ID NO: 104	—
412	isomiR example 1 of SEQ ID NO: 106	—
413	isomiR example 2 of SEQ ID NO: 106	—
414	isomiR example 1 of SEQ ID NO: 107	—
415	isomiR example 2 of SEQ ID NO: 107	—
416	isomiR example 1 of SEQ ID NO: 109	—
417	isomiR example 2 of SEQ ID NO: 109	—
418	isomiR example 1 of SEQ ID NO: 110	—
419	isomiR example 2 of SEQ ID NO: 110	—
420	isomiR example 1 of SEQ ID NO: 111	—
421	isomiR example 2 of SEQ ID NO: 111	—
422	isomiR example 1 of SEQ ID NO: 112	—
423	isomiR example 2 of SEQ ID NO: 112	—
424	isomiR example 1 of SEQ ID NO: 113	—
425	isomiR example 2 of SEQ ID NO: 113	—
426	isomiR example 1 of SEQ ID NO: 115	—
427	isomiR example 2 of SEQ ID NO: 115	—
428	isomiR example 1 of SEQ ID NO: 116	—
429	isomiR example 2 of SEQ ID NO: 116	—
430	isomiR example 1 of SEQ ID NO: 120	—
431	isomiR example 2 of SEQ ID NO: 120	—
432	isomiR example 1 of SEQ ID NO: 121	—
433	isomiR example 2 of SEQ ID NO: 121	—
434	isomiR example 1 of SEQ ID NO: 122	—
435	isomiR example 2 of SEQ ID NO: 122	—
436	isomiR example 1 of SEQ ID NO: 124	—
437	isomiR example 2 of SEQ ID NO: 124	—
438	isomiR example 1 of SEQ ID NO: 130	—
439	isomiR example 2 of SEQ ID NO: 130	—
440	isomiR example 1 of SEQ ID NO: 131	—
441	isomiR example 2 of SEQ ID NO: 131	—
442	isomiR example 1 of SEQ ID NO: 132	—
443	isomiR example 2 of SEQ ID NO: 132	—
444	isomiR example 1 of SEQ ID NO: 133	—
445	isomiR example 2 of SEQ ID NO: 133	—
446	isomiR example 1 of SEQ ID NO: 136	—
447	isomiR example 2 of SEQ ID NO: 136	—
448	isomiR example 1 of SEQ ID NO: 137	—
449	isomiR example 2 of SEQ ID NO: 137	—
450	isomiR example 1 of SEQ ID NO: 138	—
451	isomiR example 2 of SEQ ID NO: 138	—
452	isomiR example 1 of SEQ ID NO: 139	—
453	isomiR example 2 of SEQ ID NO: 139	—
454	isomiR example 1 of SEQ ID NO: 140	—
455	isomiR example 2 of SEQ ID NO: 140	—
456	isomiR example 1 of SEQ ID NO: 141	—
457	isomiR example 2 of SEQ ID NO: 141	—
458	isomiR example 1 of SEQ ID NO: 142	—
459	isomiR example 2 of SEQ ID NO: 142	—
460	isomiR example 1 of SEQ ID NO: 144	—
461	isomiR example 2 of SEQ ID NO: 144	—
462	isomiR example 1 of SEQ ID NO: 146	—
463	isomiR example 2 of SEQ ID NO: 146	—
464	isomiR example 1 of SEQ ID NO: 147	—
465	isomiR example 2 of SEQ ID NO: 147	—
466	hsa-miR-4516	MIMAT0019053
467	hsa-miR-4649-5p	MIMAT0019711
468	hsa-miR-760	MIMAT0004957
469	hsa-miR-3162-5p	MIMAT0015036
470	hsa-miR-3178	MIMAT0015055
471	hsa-miR-940	MIMAT0004983
472	hsa-miR-4271	MIMAT0016901
473	hsa-miR-6769b-5p	MIMAT0027620
474	hsa-miR-4508	MIMAT0019045
475	hsa-miR-6826-5p	MIMAT0027552
476	hsa-miR-6757-5p	MIMAT0027414
477	hsa-miR-3131	MIMAT0014996
478	hsa-miR-1343-3p	MIMAT0019776
479	hsa-mir-4516	MI0016882
480	hsa-mir-4649	MI0017276
481	hsa-mir-760	MI0005567
482	hsa-mir-3162	MI0014192
483	hsa-mir-3178	MI0014212
484	hsa-mir-940	MI0005762
485	hsa-mir-4271	MI0015879
486	hsa-mir-6769b	MI0022706

TABLE 1-continued

SEQ ID NO:	Gene name	miRBase registration No.
487	hsa-mir-4508	MI0016872
488	hsa-mir-6826	MI0022671
489	hsa-mir-6757	MI0022602
490	hsa-mir-3131	MI0014151
491	hsa-mir-1343	MI0017320
492	isomiR example 1 of SEQ ID NO: 479	—
493	isomiR example 2 of SEQ ID NO: 479	—
494	isomiR example 1 of SEQ ID NO: 480	—
495	isomiR example 2 of SEQ ID NO: 480	—
496	isomiR example 1 of SEQ ID NO: 481	—
497	isomiR example 2 of SEQ ID NO: 481	—
498	isomiR example 1 of SEQ ID NO: 482	—
499	isomiR example 2 of SEQ ID NO: 482	—
500	isomiR example 1 of SEQ ID NO: 483	—
501	isomiR example 2 of SEQ ID NO: 483	—
502	isomiR example 1 of SEQ ID NO: 484	—
503	isomiR example 2 of SEQ ID NO: 484	—
504	isomiR example 1 of SEQ ID NO: 487	—
505	isomiR example 2 of SEQ ID NO: 487	—
506	isomiR example 1 of SEQ ID NO: 490	—
507	isomiR example 2 of SEQ ID NO: 490	—
508	isomiR example 1 of SEQ ID NO: 491	—
509	isomiR example 2 of SEQ ID NO: 491	—

The present specification encompasses the contents described in the specifications and drawings of Japanese Patent Application Nos. 2014-120884 and 2014-185733 on which the priority of the present application is based.

Advantageous Effects of Invention

According to the present invention, biliary tract cancer can be detected easily and highly accurately. For example, the presence or absence of biliary tract cancer in a patient can be easily detected by using, as an indicator, the measurement values of several miRNAs in blood, serum, and/or plasma of the patient, which can be collected with limited invasiveness.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** This figure shows the relationship between the nucleotide sequences of hsa-miR-4665-5p represented by SEQ ID NO: 51 and hsa-miR-4665-3p represented by SEQ ID NO: 91, which are produced from a precursor hsa-mir-4665 represented by SEQ ID NO: 201.

FIG. **2** Left diagram: the measurement values of hsa-miR-125a-3p (SEQ ID NO: 1) in healthy subjects (100 persons) and biliary tract cancer patients (67 persons) selected as a training cohort were each plotted on the ordinate. The horizontal line in the diagram depicts a threshold (5.69) that was optimized by Fisher's linear discriminant analysis and discriminated between the two groups. Right diagram: the measurement values of hsa-miR-125a-3p (SEQ ID NO: 1) in healthy subjects (50 persons) and biliary tract cancer patients (33 persons) selected as a validation cohort were each plotted on the ordinate. The horizontal line in the diagram depicts the threshold (5.69) that was set in the training cohort and discriminated between the two groups.

FIG. **3** Left diagram: the measurement values of hsa-miR-6893-5p (SEQ ID NO: 2) in healthy subjects (100 persons, circles) and biliary tract cancer patients (67 persons, triangles) selected as a training cohort were each plotted on the abscissa against their measurement values of hsa-miR-4476 (SEQ ID NO: 4) on the ordinate. The line in the diagram depicts a discriminant function ($0=5.16x+y+48.11$) that was optimized by Fisher's linear discriminant analysis and discriminated between the two groups. Right diagram: the measurement values of hsa-miR-6893-5p (SEQ ID NO: 2) in healthy subjects (50 persons, circles) and biliary tract cancer patients (33 persons, triangles) selected as a validation cohort were each plotted on the abscissa against their measurement values of hsa-miR-4476 (SEQ ID NO: 4) on the ordinate. The line in the diagram depicts the threshold ($0=5.16x+y+48.11$) that was set in the training cohort and discriminated between the two groups.

FIG. **4** Upper diagram: a discriminant (−1.25×hsa-miR-6075-1.06×hsa-miR-6836-3p+0.53×hsa-miR-6799-5p+0.18×hsa-miR-125a-3p+15.41) was prepared by use of Fisher's linear discriminant analysis from the measurement values of hsa-miR-6075 (SEQ ID NO: 15), hsa-miR-6836-3p (SEQ ID NO: 12), hsa-miR-6799-5p (SEQ ID NO: 29), and hsa-miR-125a-3p (SEQ ID NO: 1) in 67 biliary tract cancer patients, 93 healthy subjects, 35 colorectal cancer patients, 37 stomach cancer patients, 32 esophageal cancer patients, 38 liver cancer patients, and 13 benign pancreaticobiliary disease patients selected in a training cohort, and discriminant scores obtained from the discriminant were plotted on the ordinate against the sample groups on the abscissa. The dotted line in the diagram depicts a discriminant boundary that offered a discriminant score of 0 and discriminated between the groups. Lower diagram: discriminant scores obtained from the discriminant prepared from the training cohort as to the measurement values of hsa-miR-6075 (SEQ ID NO:15), hsa-miR-6836-3p (SEQ ID NO: 12), hsa-miR-6799-5p (SEQ ID NO: 29), hsa-miR-125a-3p (SEQ ID NO: 1) in 33 biliary tract cancer patients, 57 healthy subjects, 15 colorectal cancer patients, 13 stomach cancer patients, 18 esophageal cancer patients, 12 liver cancer patients, and 8 benign pancreaticobiliary disease patients selected as a validation cohort were plotted on the ordinate against the sample groups on the abscissa. The dotted line in the diagram depicts the discriminant boundary that offered a discriminant score of 0 and discriminated between the two groups.

DESCRIPTION OF EMBODIMENTS

Hereinafter, the present invention will be further described specifically.

1. Target Nucleic Acid for Biliary Tract Cancer

A primary target nucleic acid as a biliary tract cancer marker for detecting the presence and/or absence of biliary tract cancer or biliary tract cancer cells using the nucleic acid probe or the primer for the detection of biliary tract cancer defined above according to the present invention can be at least one or more miRNA(s) selected from the group consisting of hsa-miR-125a-3p, hsa-miR-6893-5p, hsa-miR-204-3p, hsa-miR-4476, hsa-miR-4294, hsa-miR-150-3p, hsa-miR-6729-5p, hsa-miR-7641, hsa-miR-6765-3p, hsa-miR-6820-5p, hsa-miR-575, hsa-miR-6836-3p, hsa-miR-1469, hsa-miR-663a, hsa-miR-6075, hsa-miR-4634, hsa-miR-423-5p, hsa-miR-4454, hsa-miR-7109-5p, hsa-miR-6789-5p, hsa-miR-6877-5p, hsa-miR-4792, hsa-miR-4530, hsa-miR-7975, hsa-miR-6724-5p, hsa-miR-8073, hsa-miR-7977, hsa-miR-1231, hsa-miR-6799-5p, hsa-miR-615-5p, hsa-miR-4450, hsa-miR-6726-5p, hsa-miR-6875-5p, hsa-miR-4734, hsa-miR-16-5p, hsa-miR-602, hsa-miR-4651, hsa-miR-8069, hsa-miR-1238-5p. hsa-miR-6880-5p, hsa-miR-8072, hsa-miR-4723-5p, hsa-miR-4732-5p, hsa-miR-6125, hsa-miR-6090, hsa-miR-7114-5p, hsa-miR-564, hsa-miR-451a, hsa-miR-3135b, hsa-miR-4497, hsa-miR-4665-5p, hsa-miR-3622a-5p, hsa-miR-6850-5p, hsa-miR-6821-5p, hsa-miR-5100, hsa-miR-6872-3p, hsa-miR-4433-3p, hsa-miR-1227-5p, hsa-miR-3188, hsa-miR-7704, hsa-miR-3185, hsa-miR-1908-3p, hsa-miR-6781-5p, hsa-miR-6805-5p, hsa-miR-8089, hsa-miR-665, hsa-miR-4486, hsa-miR-6722-3p, hsa-miR-1260a, hsa-miR-4707-5p, hsa-miR-6741-5p. hsa-miR-1260b, hsa-miR-1246, hsa-miR-6845-5p, hsa-miR-4638-5p, hsa-miR-6085, hsa-miR-1228-3p, hsa-miR-4534, hsa-miR-5585-3p, hsa-miR-4741, hsa-miR-4433b-3p, hsa-miR-197-5p, hsa-miR-718, hsa-miR-4513, hsa-miR-4446-3p, hsa-miR-619-5p, hsa-miR-6816-5p, hsa-miR-6778-5p, hsa-miR-24-3p, hsa-miR-1915-3p, hsa-miR-4665-3p, hsa-miR-4449, hsa-miR-6889-5p, hsa-miR-486-3p, hsa-miR-7113-3p, hsa-miR-642a-3p, hsa-miR-7847-3p, hsa-miR-6768-5p, hsa-miR-1290, hsa-miR-7108-5p, hsa-miR-92b-5p, hsa-miR-663b, hsa-miR-3940-5p, hsa-miR-4467, hsa-miR-6858-5p, hsa-miR-4417, hsa-miR-3665, hsa-miR-4736, hsa-miR-4687-3p, hsa-miR-1908-5p, hsa-miR-5195-3p, hsa-miR-4286, hsa-miR-3679-3p, hsa-miR-6791-5p, hsa-miR-1202, hsa-miR-3656, hsa-miR-4746-3p, hsa-miR-3184-5p, hsa-miR-3937, hsa-miR-6515-3p, hsa-miR-6132, hsa-miR-187-5p, hsa-miR-7111-5p, hsa-miR-5787, hsa-miR-6779-5p, hsa-miR-4516, hsa-miR-4649-5p, hsa-miR-760, hsa-miR-3162-5p, hsa-miR-3178, hsa-miR-940, hsa-miR-4271, hsa-miR-6769b-5p, hsa-miR-4508, hsa-miR-6826-5p, hsa-miR-6757-5p, hsa-miR-3131, and hsa-miR-1343-3p. Furthermore, at least one or more miRNA(s) selected from the group consisting of other biliary tract cancer markers that can be combined with these miRNAs, i.e., hsa-miR-6808-5p, hsa-miR-6774-5p, hsa-miR-4656, hsa-miR-6806-5p, hsa-miR-1233-5p, hsa-miR-328-5p, hsa-miR-4674, hsa-miR-2110, hsa-miR-6076, hsa-miR-3619-3p, hsa-miR-92a-2-5p, hsa-miR-128-1-5p, hsa-miR-638, hsa-miR-2861, hsa-miR-371a-5p, hsa-miR-211-3p, hsa-miR-1273g-3p, hsa-miR-1203, hsa-miR-122-5p, hsa-miR-4258, hsa-miR-4484, hsa-miR-4648 and hsa-miR-6780b-5p can also be preferably used as a target nucleic acid.

These miRNAs include, for example, a human gene comprising a nucleotide sequence represented by any of SEQ ID NOs: 1 to 148, 466 to 478 (i.e., hsa-miR-125a-3p, hsa-miR-6893-5p, hsa-miR-204-3p, hsa-miR-4476, hsa-miR-4294, hsa-miR-150-3p, hsa-miR-6729-5p, hsa-miR-7641, hsa-miR-6765-3p, hsa-miR-6820-5p, hsa-miR-575, hsa-miR-6836-3p, hsa-miR-1469, hsa-miR-663a, hsa-miR-6075, hsa-miR-4634, hsa-miR-423-5p, hsa-miR-4454, hsa-miR-7109-5p, hsa-miR-6789-5p, hsa-miR-6877-5p, hsa-miR-4792, hsa-miR-4530, hsa-miR-7975, hsa-miR-6724-5p, hsa-miR-8073, hsa-miR-7977, hsa-miR-1231, hsa-miR-6799-5p, hsa-miR-615-5p, hsa-miR-4450, hsa-miR-6726-5p, hsa-miR-6875-5p, hsa-miR-4734, hsa-miR-16-5p, hsa-miR-602, hsa-miR-4651, hsa-miR-8069, hsa-miR-1238-5p, hsa-miR-6880-5p, hsa-miR-8072, hsa-miR-4723-5p, hsa-miR-4732-5p, hsa-miR-6125, hsa-miR-6090, hsa-miR-7114-5p, hsa-miR-564, hsa-miR-451a, hsa-miR-3135b, hsa-miR-4497, hsa-miR-4665-5p, hsa-miR-3622a-5p, hsa-miR-6850-5p, hsa-miR-6821-5p, hsa-miR-5100, hsa-miR-6872-3p, hsa-miR-4433-3p, hsa-miR-1227-5p, hsa-miR-3188, hsa-miR-7704, hsa-miR-3185, hsa-miR-1908-3p, hsa-miR-678 I-5p, hsa-miR-6805-5p, hsa-miR-8089, hsa-miR-665, hsa-miR-4486, hsa-miR-6722-3p, hsa-miR-1260a, hsa-miR-4707-5p, hsa-miR-6741-5p, hsa-miR-1260b, hsa-miR-1246, hsa-miR-6845-5p, hsa-miR-4638-5p, hsa-miR-6085, hsa-miR-1228-3p, hsa-miR-4534, hsa-miR-5585-3p, hsa-miR-4741, hsa-miR-4433b-3p, hsa-miR-197-5p, hsa-miR-718, hsa-miR-4513, hsa-miR-4446-3p, hsa-miR-619-5p, hsa-miR-6816-5p, hsa-miR-6778-5p, hsa-miR-24-3p, hsa-miR-1915-3p, hsa-miR-4665-3p, hsa-miR-4449, hsa-miR-6889-5p, hsa-miR-486-3p, hsa-miR-7113-3p, hsa-miR-642a-3p, hsa-miR-7847-3p, hsa-miR-6768-5p, hsa-miR-1290, hsa-miR-7108-5p, hsa-miR-92b-5p, hsa-miR-663b, hsa-miR-3940-5p, hsa-miR-4467, hsa-miR-6858-5p, hsa-miR-4417, hsa-miR-3665, hsa-miR-4736, hsa-miR-4687-3p, hsa-miR-1908-5p, hsa-miR-5195-3p, hsa-miR-4286, hsa-miR-3679-3p, hsa-miR-6791-5p, hsa-miR-1202, hsa-miR-3656, hsa-miR-4746-3p, hsa-miR-3184-5p, hsa-miR-3937, hsa-miR-6515-3p, hsa-miR-6132, hsa-miR-187-5p, hsa-miR-7111-5p, hsa-miR-5787, hsa-miR-6779-5p, hsa-miR-6808-5p, hsa-miR-6774-5p, hsa-miR-4656, hsa-miR-6806-5p, hsa-miR-1233-5p, hsa-miR-328-5p, hsa-miR-4674, hsa-miR-2110, hsa-miR-6076, hsa-miR-3619-3p, hsa-miR-92a-2-5p, hsa-miR-128-1-5p, hsa-miR-638, hsa-miR-2861, hsa-miR-371a-5p, hsa-miR-211-3p, hsa-miR-1273g-3p, hsa-miR-1203, hsa-miR-122-5p, hsa-miR-4258, hsa-miR-4484, hsa-miR-4648, hsa-miR-6780b-5p, hsa-miR-4516, hsa-miR-4649-5p, hsa-miR-760, hsa-miR-3162-5p, hsa-miR-3178, hsa-miR-940, hsa-miR-4271, hsa-miR-6769b-5p, hsa-miR-4508, hsa-miR-6826-5p, hsa-miR-6757-5p, hsa-miR-3131, and hsa-miR-1343-3p, respectively), a congener thereof, a transcript thereof, and a variant or a derivative thereof. In this context, the gene, the congener, the transcript, the variant, and the derivative are as defined above.

The target nucleic acid is preferably a human gene comprising a nucleotide sequence represented by any of SEQ ID NOs: 1 to 509 or a transcript thereof, more preferably the transcript, i.e., a miRNA or its precursor RNA (pri-miRNA or pre-miRNA).

The first target gene is the hsa-miR-125a-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The second target gene is the hsa-miR-6893-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The third target gene is the hsa-miR-204-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The fourth target gene is the hsa-miR-4476 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The fifth target gene is the hsa-miR-4294 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The sixth target gene is the hsa-miR-150-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The seventh target gene is the hsa-miR-6729-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports

show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The eighth target gene is the hsa-miR-7641 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The ninth target gene is the hsa-miR-6765-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 10th target gene is the hsa-miR-6820-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 11th target gene is the hsa-miR-575 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 12th target gene is the hsa-miR-6836-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 13th target gene is the hsa-miR-1469 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 14th target gene is the hsa-miR-663a gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 15th target gene is the hsa-miR-6075 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 16th target gene is the hsa-miR-4634 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 17th target gene is the hsa-miR-423-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 18th target gene is the hsa-miR-4454 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 19th target gene is the hsa-miR-7109-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 20th target gene is the hsa-miR-6789-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 21st target gene is the hsa-miR-6877-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 22nd target gene is the hsa-miR-4792 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 23rd target gene is the hsa-miR-4530 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 24th target gene is the hsa-miR-7975 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 25th target gene is the hsa-miR-6724-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 26th target gene is the hsa-miR-8073 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 27th target gene is the hsa-miR-7977 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 28th target gene is the hsa-miR-1231 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 29th target gene is the hsa-miR-6799-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 30th target gene is the hsa-miR-615-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 31st target gene is the hsa-miR-4450 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 32nd target gene is the hsa-miR-6726-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 33rd target gene is the hsa-miR-6875-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 34th target gene is the hsa-miR-4734 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 35th target gene is the hsa-miR-16-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 36th target gene is the hsa-miR-602 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 37th target gene is the hsa-miR-4651 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 38th target gene is the hsa-miR-8069 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 39th target gene is the hsa-miR-1238-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 40th target gene is the hsa-miR-6880-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 41st target gene is the hsa-miR-8072 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 42nd target gene is the hsa-miR-4723-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 43rd target gene is the hsa-miR-4732-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 44th target gene is the hsa-miR-6125 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 45th target gene is the hsa-miR-6090 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 46th target gene is the hsa-miR-7114-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 47th target gene is the hsa-miR-564 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 48th target gene is the hsa-miR-451a gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 49th target gene is the hsa-miR-3135b gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 50th target gene is the hsa-miR-4497 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 51st target gene is the hsa-miR-4665-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 52nd target gene is the hsa-miR-3622a-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 53rd target gene is the hsa-miR-6850-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 54th target gene is the hsa-miR-6821-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 55th target gene is the hsa-miR-5100 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 56th target gene is the hsa-miR-6872-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 57th target gene is the hsa-miR-4433-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 58th target gene is the hsa-miR-1227-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 59th target gene is the hsa-miR-3188 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 60th target gene is the hsa-miR-7704 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 61st target gene is the hsa-miR-3185 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 62nd target gene is the hsa-miR-1908-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 63rd target gene is the hsa-miR-6781-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 64th target gene is the hsa-miR-6805-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 65th target gene is the hsa-miR-8089 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 66th target gene is the hsa-miR-665 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 67th target gene is the hsa-miR-4486 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that

change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 68th target gene is the hsa-miR-6722-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 69th target gene is the hsa-miR-1260a gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 70th target gene is the hsa-miR-4707-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 71st target gene is the hsa-miR-6741-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 72nd target gene is the hsa-miR-1260b gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 73rd target gene is the hsa-miR-1246 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 74th target gene is the hsa-miR-6845-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 75th target gene is the hsa-miR-4638-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 76th target gene is the hsa-miR-6085 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 77th target gene is the hsa-miR-1228-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 78th target gene is the hsa-miR-4534 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 79th target gene is the hsa-miR-5585-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports

show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 80th target gene is the hsa-miR-4741 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 81st target gene is the hsa-miR-4433b-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 82nd target gene is the hsa-miR-197-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 83rd target gene is the hsa-miR-718 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 84th target gene is the hsa-miR-4513 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 85th target gene is the hsa-miR-4446-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 86th target gene is the hsa-miR-619-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 87th target gene is the hsa-miR-6816-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 88th target gene is the hsa-miR-6778-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 89th target gene is the hsa-miR-24-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 90th target gene is the hsa-miR-1915-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 91st target gene is the hsa-miR-4665-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 92nd target gene is the hsa-miR-4449 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 93rd target gene is the hsa-miR-6889-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 94th target gene is the hsa-miR-486-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 95th target gene is the hsa-miR-7113-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 96th target gene is the hsa-miR-642a-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 97th target gene is the hsa-miR-7847-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 98th target gene is the hsa-miR-6768-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 99th target gene is the hsa-miR-1290 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 100th target gene is the hsa-miR-7108-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 101st target gene is the hsa-miR-92b-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 102nd target gene is the hsa-miR-663b gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports

show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 103rd target gene is the hsa-miR-3940-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 104th target gene is the hsa-miR-4467 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 105th target gene is the hsa-miR-6858-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 106th target gene is the hsa-miR-4417 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 107th target gene is the hsa-miR-3665 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 108th target gene is the hsa-miR-4736 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 109th target gene is the hsa-miR-4687-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 110th target gene is the hsa-miR-1908-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 111th target gene is the hsa-miR-5195-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 112th target gene is the hsa-miR-4286 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 113th target gene is the hsa-miR-3679-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 114th target gene is the hsa-miR-6791-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports

show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 115th target gene is the hsa-miR-1202 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 116th target gene is the hsa-miR-3656 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 117th target gene is the hsa-miR-4746-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 118th target gene is the hsa-miR-3184-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 119th target gene is the hsa-miR-3937 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 120th target gene is the hsa-miR-6515-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 121st target gene is the hsa-miR-6132 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 122nd target gene is the hsa-miR-187-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 123rd target gene is the hsa-miR-7111-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 124th target gene is the hsa-miR-5787 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 125th target gene is the hsa-miR-6779-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 126th target gene is the hsa-miR-6808-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports

show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 127th target gene is the hsa-miR-6774-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 128th target gene is the hsa-miR-4656 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 129th target gene is the hsa-miR-6806-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 130th target gene is the hsa-miR-1233-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 131st target gene is the hsa-miR-328-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 132nd target gene is the hsa-miR-4674 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 133rd target gene is the hsa-miR-2110 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 134th target gene is the hsa-miR-6076 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 135th target gene is the hsa-miR-3619-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 136th target gene is the hsa-miR-92a-2-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 137th target gene is the hsa-miR-128-1-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 138th target gene is the hsa-miR-638 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 139th target gene is the hsa-miR-2861 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 140th target gene is the hsa-miR-371a-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 141st target gene is the hsa-miR-211-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 142nd target gene is the hsa-miR-1273g-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 143rd target gene is the hsa-miR-1203 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 144th target gene is the hsa-miR-122-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 145th target gene is the hsa-miR-4258 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 146th target gene is the hsa-miR-4484 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 147th target gene is the hsa-miR-4648 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 148th target gene is the hsa-miR-6780b-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 149th target gene is the hsa-miR-4516 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 150th target gene is the hsa-miR-4649-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 151st target gene is the hsa-miR-760 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 152nd target gene is the hsa-miR-3162-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 153rd target gene is the hsa-miR-3178 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 154th target gene is the hsa-miR-940 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 155th target gene is the hsa-miR-4271 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 156th target gene is the hsa-miR-6769b-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 157th target gene is the hsa-miR-4508 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 158th target gene is the hsa-miR-6826-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 159th target gene is the hsa-miR-6757-5p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 160th target gene is the hsa-miR-3131 gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

The 161st target gene is the hsa-miR-1343-3p gene, a congener thereof, a transcript thereof, or a variant or a derivative thereof. None of the previously known reports show that change in the expression of the gene or the transcript thereof can serve as a marker for biliary tract cancer.

2. Nucleic Acid Probe or Primer for Detection of Biliary Tract Cancer

In the present invention, a nucleic acid capable of specifically binding to any of the target nucleic acids as the biliary tract cancer markers described above can be used as a nucleic acid, for example, a nucleic acid probe or a primer, for the detection or diagnosis of biliary tract cancer.

In the present invention, the nucleic acid probe or the primer that can be used for detecting biliary tract cancer or for diagnosing biliary tract cancer enables qualitative and/or quantitative measurement of the presence, expression level, or abundance of a target nucleic acid as the biliary tract cancer marker described above, for example, human-derived hsa-miR-125a-3p, hsa-miR-6893-5p, hsa-miR-204-3p, hsa-miR-4476, hsa-miR-4294, hsa-miR-150-3p, hsa-miR-6729-5p, hsa-miR-7641, hsa-miR-6765-3p, hsa-miR-6820-5p, hsa-miR-575, hsa-miR-6836-3p, hsa-miR-1469, hsa-miR-663a, hsa-miR-6075, hsa-miR-4634, hsa-miR-423-5p, hsa-miR-4454, hsa-miR-7109-5p, hsa-miR-6789-5p, hsa-miR-6877-5p, hsa-miR-4792, hsa-miR-4530, hsa-miR-7975, hsa-miR-6724-5p, hsa-miR-8073, hsa-miR-7977, hsa-miR-1231, hsa-miR-6799-5p, hsa-miR-615-5p, hsa-miR-4450, hsa-miR-6726-5p, hsa-miR-6875-5p, hsa-miR-4734, hsa-miR-16-5p, hsa-miR-602, hsa-miR-4651, hsa-miR-8069, hsa-miR-1238-5p, hsa-miR-6880-5p, hsa-miR-8072, hsa-miR-4723-5p, hsa-miR-4732-5p, hsa-miR-6125, hsa-miR-6090, hsa-miR-7114-5p, hsa-miR-564, hsa-miR-451a, hsa-miR-3135b, hsa-miR-4497, hsa-miR-4665-5p, hsa-miR-3622a-5p, hsa-miR-6850-5p, hsa-miR-6821-5p, hsa-miR-5100, hsa-miR-6872-3p, hsa-miR-4433-3p, hsa-miR-1227-5p, hsa-miR-3188, hsa-miR-7704, hsa-miR-3185, hsa-miR-1908-3p, hsa-miR-6781 -5p, hsa-miR-6805-5p, hsa-miR-8089, hsa-miR-665, hsa-miR-4486, hsa-miR-6722-3p, hsa-miR-1260a, hsa-miR-4707-5p, hsa-miR-6741-5p, hsa-miR-1260b, hsa-miR-1246, hsa-miR-6845-5p, hsa-miR-4638-5p, hsa-miR-6085, hsa-miR-1228-3p, hsa-miR-4534, hsa-miR-5585-3p, hsa-miR-4741, hsa-miR-4433b-3p, hsa-miR-197-5p, hsa-miR-718, hsa-miR-4513, hsa-miR-4446-3p, hsa-miR-619-5p, hsa-miR-6816-5p, hsa-miR-6778-5p, hsa-miR-24-3p, hsa-miR-1915-3p, hsa-miR-4665-3p, hsa-miR-4449, hsa-miR-6889-5p, hsa-miR-486-3p, hsa-miR-7113-3p, hsa-miR-642a-3p, hsa-miR-7847-3p, hsa-miR-6768-5p, hsa-miR-1290, hsa-miR-7108-5p, hsa-miR-92b-5p, hsa-miR-663b, hsa-miR-3940-5p, hsa-miR-4467, hsa-miR-6858-5p, hsa-miR-4417, hsa-miR-3665, hsa-miR-4736, hsa-miR-4687-3p, hsa-miR-1908-5p, hsa-miR-5195-3p, hsa-miR-4286, hsa-miR-3679-3p, hsa-miR-6791-5p, hsa-miR-1202, hsa-miR-3656, hsa-miR-4746-3p, hsa-miR-3184-5p, hsa-miR-3937, hsa-miR-6515-3p, hsa-miR-6132, hsa-miR-187-5p, hsa-miR-7111-5p, hsa-miR-5787, hsa-miR-6779-5p, hsa-miR-4516, hsa-miR-4649-5p, hsa-miR-760, hsa-miR-3162-5p, hsa-miR-3178, hsa-miR-940, hsa-miR-4271, hsa-miR-6769b-5p, hsa-miR-4508, hsa-miR-6826-5p, hsa-miR-6757-5p, hsa-miR-3131, or hsa-miR-1343-3p, or a combination thereof, or a congener thereof, a transcript thereof, or a variant or a derivative thereof, and, optionally in combination therewith, hsa-miR-6808-5p, hsa-miR-6774-5p, hsa-miR-4656, hsa-miR-6806-5p, hsa-miR-1233-5p, hsa-miR-328-5p, hsa-miR-4674, hsa-miR-2110, hsa-miR-6076, hsa-miR-3619-3p, hsa-miR-92a-2-5p, hsa-miR-128-1-5p, hsa-miR-638, hsa-miR-2861, hsa-miR-371a-5p, hsa-miR-211-3p, hsa-miR-1273g-3p, hsa-miR-1203, hsa-miR-122-5p, hsa-miR-4258, hsa-miR-4484, hsa-miR-4648 or hsa-miR-6780b-5p or a combination thereof, a congener thereof, a transcript thereof, or a variant or a derivative thereof.

The expression level of each target nucleic acid described above is increased or decreased (hereinafter, referred to as "increased/decreased) depending on the type of the target nucleic acid in a subject who has biliary tract cancer as compared with a healthy subject. Hence, the nucleic acid of the present invention can be effectively used for measuring the expression level of the target nucleic acid in a body fluid derived from a subject (e.g., a human) suspected of having biliary tract cancer and a body fluid derived from a healthy subject and comparing them to detect biliary tract cancer. The nucleic acid of the present invention can also be effectively used for measuring the expression level of the target nucleic acid in a body fluid derived from a subject (e.g., a human) suspected of having biliary" tract cancer and body fluids derived from a colorectal cancer patient, a stomach cancer patient, an esophageal cancer patient, a liver cancer patient, and a benign pancreaticobiliary disease patient and comparing them to specifically detect biliary tract cancer from other cancers, benign diseases, and the like.

The nucleic acid probe or the primer that can be used in the present invention is a nucleic acid probe capable of specifically binding to a polynucleotide consisting of a nucleotide sequence represented by at least one of SEQ ID NOs: 1 to 125 (preferably SEQ ID NOs: 1, 2, and 4 to 125) and 466 to 478, or a primer for amplifying a polynucleotide consisting of a nucleotide sequence represented by at least one of SEQ ID NOs: 1 to 125 and 466 to 478.

The nucleic acid probe or the primer that can be further used in the present invention may comprise a nucleic acid probe capable of specifically binding to a polynucleotide consisting of a nucleotide sequence represented by at least one of SEQ ID NOs: 126 to 148, or a primer for amplifying a polynucleotide consisting of a nucleotide sequence represented by at least one of SEQ ID NOs: 126 to 148.

Specifically, these nucleic acid probes or primers comprise a combination of one or more polynucleotides selected from a group of polynucleotides comprising nucleotide sequences represented by any of SEQ ID NOs: 1 to 509 or nucleotide sequences derived from the nucleotide sequences by the replacement of u with t, and a group of complementary polynucleotides thereof, a group of polynucleotides respectively hybridizing under stringent conditions (mentioned later) to DNAs consisting of nucleotide sequences complementary to these nucleotide sequences, and a group of complementary polynucleotides thereof, and a group of polynucleotides comprising 15 or more, preferably 17 or more consecutive nucleotides in the nucleotide sequences of these polynucleotide groups. These polynucleotides can be used as nucleic acid probes and primers for detecting the biliary tract cancer markers as target nucleic acids.

More specifically, examples of the nucleic acid probe or the primer that can be used in the present invention include one or more polynucleotide(s) selected from the group consisting of the following polynucleotides (a) to (e):

(a) a polynucleotide consisting of a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides,

(b) a polynucleotide comprising a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478,

(c) a polynucleotide consisting of a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides,

(d) a polynucleotide comprising a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, and

(e) a polynucleotide hybridizing under stringent conditions to any of the polynucleotides (a) to (d).

In addition to at least one or more polynucleotide(s) selected from the group consisting of the polynucleotides (a) to (e), the nucleic acid probe or the primer that can be further used in the present invention may comprise polynucleotide(s) selected from the group consisting of the following polynucleotides (f) to (j):

(f) a polynucleotide consisting of a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides.

(g) a polynucleotide comprising a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148,

(h) a polynucleotide consisting of a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides,

(i) a polynucleotide comprising a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, and

(j) a polynucleotide hybridizing under stringent conditions to any of the polynucleotides (f) to (i).

For these polynucleotides, the "fragment thereof comprising 15 or more consecutive nucleotides" can comprise the number of nucleotides in the range of, for example, 15 consecutive nucleotides to less than the total number of nucleotides of the sequence, 17 consecutive nucleotides to less than the total number of nucleotides of the sequence, or 19 consecutive nucleotides to less than the total number of nucleotides of the sequence, in the nucleotide sequence of each polynucleotide, though the fragment is not limited thereto.

These polynucleotides or fragments thereof used in the present invention may each be DNA or may each be RNA.

The polynucleotides that can be used in the present invention can each be prepared by use of a general technique such as a DNA recombination technique. PCR, or a method using an automatic DNA/RNA synthesizer.

The DNA recombination technique and the PCR can employ a technique described in, for example, Ausubel et al., Current Protocols in Molecular Biology, John Willey & Sons, US (1993), and Sambrook et al., Molecular Cloning—A Laboratory Manual, Cold Spring Harbor Laboratory Press. US (1989).

The human-derived hsa-miR-125a-3p, hsa-miR-6893-5p, hsa-miR-204-3p, hsa-miR-4476, hsa-miR-4294, hsa-miR-150-3p, hsa-miR-6729-5p, hsa-miR-7641, hsa-miR-6765-3p, hsa-miR-6820-5p, hsa-miR-575, hsa-miR-6836-3p, hsa-miR-1469, hsa-miR-663a, hsa-miR-6075, hsa-miR-4634, hsa-miR-423-5p, hsa-miR-4454, hsa-miR-7109-5p, hsa-miR-6789-5p, hsa-miR-6877-5p, hsa-miR-4792, hsa-miR-4530, hsa-miR-7975, hsa-miR-6724-5p, hsa-miR-8073, hsa-miR-7977, hsa-miR-1231, hsa-miR-6799-5p, hsa-miR-615-5p, hsa-miR-4450, hsa-miR-6726-5p, hsa-miR-6875-5p, hsa-miR-4734, hsa-miR-16-5p, hsa-miR-602, hsa-miR-4651, hsa-miR-8069, hsa-miR-1238-5p, hsa-miR-6880-5p, hsa-miR-8072, hsa-miR-4723-5p, hsa-miR-4732-5p, hsa-miR-6125, hsa-miR-6090, hsa-miR-7114-5p, hsa-miR-564, hsa-miR-451a, hsa-miR-3135b, hsa-miR-4497, hsa-miR-4665-5p, hsa-miR-3622a-5p, hsa-miR-6850-5p, hsa-miR-6821-5p, hsa-miR-5100, hsa-miR-6872-3p, hsa-miR-4433-3p, hsa-miR-1227-5p, hsa-miR-3188, hsa-miR-7704, hsa-miR-3185, hsa-miR-1908-3p, hsa-miR-6781-5p, hsa-miR-6805-5p, hsa-miR-8089, hsa-miR-665, hsa-miR-4486, hsa-miR-6722-3p, hsa-miR-1260a, hsa-miR-4707-5p, hsa-miR-6741-5p, hsa-miR-1260b, hsa-miR-1246, hsa-miR-6845-5p, hsa-miR-4638-5p, hsa-miR-6085, hsa-miR-1228-3p, hsa-miR-4534, hsa-miR-5585-3p, hsa-miR-4741, hsa-miR-4433b-3p, hsa-miR-197-5p, hsa-miR-718, hsa-miR-4513, hsa-miR-4446-3p, hsa-miR-619-5p, hsa-miR-6816-5p, hsa-miR-6778-5p, hsa-miR-24-3p, hsa-miR-1915-3p, hsa-miR-4665-3p, hsa-miR-4449, hsa-miR-6889-5p, hsa-miR-486-3p, hsa-miR-7113-3p, hsa-miR-642a-3p, hsa-miR-7847-3p, hsa-miR-6768-5p, hsa-miR-1290, hsa-miR-7108-5p, hsa-miR-92b-5p, hsa-miR-663b, hsa-miR-3940-5p, hsa-miR-4467, hsa-miR-6858-5p, hsa-miR-4417, hsa-miR-3665, hsa-miR-4736, hsa-miR-4687-3p, hsa-miR-1908-5p, hsa-miR-5195-3p, hsa-miR-4286, hsa-miR-3679-3p, hsa-miR-6791-5p, hsa-miR-1202, hsa-miR-3656, hsa-miR-4746-3p, hsa-miR-3184-5p, hsa-miR-3937, hsa-miR-6515-3p, hsa-miR-6132, hsa-miR-187-5p, hsa-miR-7111-5p, hsa-miR-5787, hsa-miR-6779-5p, hsa-miR-6808-5p, hsa-miR-6774-5p, hsa-miR-4656, hsa-miR-6806-5p, hsa-miR-1233-5p, hsa-miR-328-5p, hsa-miR-4674, hsa-miR-2110, hsa-miR-6076, hsa-miR-3619-3p, hsa-miR-92a-2-5p, hsa-miR-128-1-5p, hsa-miR-638, hsa-miR-2861, hsa-miR-371a-5p, hsa-miR-211-3p, hsa-miR-1273g-3p, hsa-miR-1203, hsa-miR-122-5p, hsa-miR-4258, hsa-miR-4484, hsa-miR-4648 and hsa-miR-6780b-5p represented by SEQ ID NOs: 1 to 148, 466 to 478 are known in the art, and their acquisition methods are also known as mentioned above. Therefore, each polynucleotide that can be used as a nucleic acid probe or a primer in the present invention can be prepared by cloning the gene.

Such a nucleic acid probe or a primer can be chemically synthesized using an automated DNA synthesizer. In general, a phosphoramidite method is used in this synthesis, and single-stranded DNA up to approximately 100 nucleotides can be automatically synthesized by this method. The automated DNA synthesizer is commercially available from, for example, Polygen GmbH. ABI, or Applied Biosystems, Inc.

Alternatively, the polynucleotide of the present invention can also be prepared by a cDNA cloning method. The cDNA cloning technique can employ, for example, microRNA Cloning Kit Wako.

In this context, the sequences of the nucleic acid probe and the primer for detecting the polynucleotide that consists of a nucleotide sequence represented by any of SEQ ID NOs: 1 to 148, 466 to 478 do not exist as miRNAs or precursors thereof in vivo. For example, the nucleotide sequences represented by SEQ ID NO: 51 and SEQ ID NO: 91 are produced from the precursor represented by SEQ ID NO: 201. This precursor has a hairpin-like structure as shown in FIG. **1**, and the nucleotide sequences represented by SEQ ID NO: 51 and SEQ ID NO: 91 have mismatch sequences with each other. Therefore, a nucleotide sequence completely complementary to the nucleotide sequence represented by SEQ ID NO: 51 or SEQ ID NO: 91 is not naturally produced in vivo. Likewise, the nucleic acid probe and the primer for detecting the nucleotide sequence represented by any of SEQ ID NOs: 1 to 148 and 466 to 478 each has an artificial nucleotide sequence that does not exist in vivo.

3. Kit or Device for Detection of Biliary Tract Cancer

The present invention also provides a kit or a device for the detection of biliary tract cancer, comprising one or more polynucleotide(s) (which may include a variant, a fragment, or a derivative thereof; hereinafter, also referred to as a polynucleotide for detection) that can be used as a nucleic acid probe or a primer in the present invention for measuring a target nucleic acid as a biliary tract cancer marker.

The target nucleic acid as a biliary tract marker according to the present invention is preferably selected from the following group 1:

miR-125a-3p, miR-6893-5p, miR-204-3p, miR-4476, miR-4294, miR-150-3p, miR-6729-5p. miR-7641, miR-6765-3p. miR-6820-5p, miR-575, miR-6836-3p. miR-1469, miR-663a, miR-6075, miR-4634, miR-423-5p, miR-4454, miR-7109-5p, miR-6789-5p. miR-6877-5p, miR-4792, miR-4530, miR-7975, miR-6724-5p, miR-8073, miR-7977, miR-1231, miR-6799-5p, miR-615-5p, miR-4450, miR-6726-5p, miR-6875-5p, miR-4734, miR-16-5p, miR-602, miR-4651, miR-8069, miR-1238-5p, miR-6880-5p, miR-8072, miR-4723-5p, miR-4732-5p, miR-6125, miR-6090, miR-7114-5p, miR-564, miR-451a, miR-3135b, miR-4497, miR-4665-5p, miR-3622a-5p, miR-6850-5p, miR-6821-5p, miR-5100, miR-6872-3p, miR-4433-3p, miR-1227-5p, miR-3188, miR-7704, miR-3185, miR-1908-3p, miR-6781-5p, miR-6805-5p, miR-8089, miR-665, miR-4486, miR-6722-3p, miR-1260a, miR-4707-5p, miR-6741-5p, miR-1260b, miR-1246, miR-6845-5p, miR-4638-5p, miR-6085, miR-1228-3p, miR-4534, miR-5585-3p, miR-4741, miR-4433b-3p, miR-197-5p, miR-718, miR-4513, miR-4446-3p, miR-619-5p, miR-6816-5p, miR-6778-5p, miR-24-3p, miR-1915-3p, miR-4665-3p, miR-4449, miR-6889-5p, miR-486-3p, miR-7113-3p, miR-642a-3p, miR-7847-3p, miR-6768-5p, miR-1290, miR-7108-5p, miR-92b-5p, miR-663b, miR-3940-5p, miR-4467, miR-6858-5p, miR-4417, miR-3665, miR-4736, miR-4687-3p, miR-1908-5p, miR-5195-3p. miR-4286, miR-3679-3p, miR-6791-5p, miR-1202, miR-3656, miR-4746-3p, miR-3184-5p, miR-3937, miR-6515-3p, miR-6132, miR-187-5p, miR-7111-5p, miR-5787, miR-6779-5p, miR-4516, miR-4649-5p, miR-760, miR-3162-5p, miR-3178, miR-940, miR-4271, miR-6769b-5p, miR-4508, miR-6826-5p, miR-6757-5p, miR-3131, and miR-1343-3p.

An additional target nucleic acid that may be optionally used in the measurement is preferably selected from the following group 2: miR-6808-5p, miR-6774-5p, miR-4656, miR-6806-5p, miR-1233-5p, miR-328-5p, miR-4674, miR-2110, miR-6076, miR-3619-3p, miR-92a-2-5p, miR-128-1-5p, miR-638, miR-2861, miR-371a-5p, miR-211-3p, miR-1273g-3p, miR-1203, miR-122-5p, miR-4258, miR-4484, miR-4648 and miR-6780b-5p.

The kit or the device of the present invention comprises nucleic acid(s) capable of specifically binding to any of the target nucleic acids as the biliary tract cancer markers described above, preferably one or more polynucleotide(s) selected from the nucleic acid probes or the primers described in Section 2 above, specifically, the polynucleotides described in Section 2 above, or variant(s) thereof.

Specifically, the kit or the device of the present invention may comprise at least one or more polynucleotide(s) comprising (or consisting of) a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125, and 466 to 478 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, polynucleotide(s) comprising (or consisting of) a complementary sequence thereof, polynucleotide(s) hybridizing under stringent conditions to any of these polynucleotides, or variant(s) or fragment(s) comprising 15 or more consecutive nucleotides of any of these polynucleotide sequences.

The kit or the device of the present invention may further comprise one or more polynucleotide(s) comprising (or consisting of) a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, polynucleotide(s) comprising (or consisting of) a complementary sequence thereof, polynucleotide(s) hybridizing under stringent conditions to any of these polynucleotides, variant(s) or fragment(s) comprising 15 or more consecutive nucleotides of any of these polynucleotide sequences.

The fragment that may be contained in the kit or the device of the present invention is, for example, one or more, preferably two or more polynucleotides selected from the group consisting of the following polynucleotides (1) to (2):

(1) a polynucleotide comprising 15 or more consecutive nucleotides in a nucleotide sequence derived from a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125, 466 to 478 by the replacement of u with t, or a complementary sequence thereof;

(2) a polynucleotide comprising 15 or more consecutive nucleotides in a nucleotide sequence derived from a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 by the replacement of u with t, or a complementary sequence thereof; and

In a preferred embodiment, the polynucleotide is a polynucleotide consisting of a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125, 466 to 478 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a polynucleotide consisting of a complementary sequence thereof, a polynucleotide hybridizing under stringent conditions to any of these polynucleotides, or a variant thereof comprising 15 or more, preferably 17 or more, more preferably 19 or more consecutive nucleotides.

In a preferred embodiment, the polynucleotide is a polynucleotide consisting of a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a polynucleotide consisting of a complementary sequence thereof, a polynucleotide hybridizing under stringent conditions to any of these polynucleotides, or a variant thereof comprising 15 or more, preferably 17 or more, more preferably 19 or more consecutive nucleotides.

In a preferred embodiment, the fragment may be a polynucleotide comprising 15 or more, preferably 17 or more, more preferably 19 or more consecutive nucleotides.

In the present invention, the size of the polynucleotide fragment is the number of nucleotides in the range of, for example, 15 consecutive nucleotides to less than the total number of nucleotides of the sequence, 17 consecutive nucleotides to less than the total number of nucleotides of the sequence, or 19 consecutive nucleotides to less than the total number of nucleotides of the sequence, in the nucleotide sequence of each polynucleotide.

Specific examples of the aforementioned polynucleotide combination constituting the kit or the device of the present invention can include any combination of the polynucleotides consisting of nucleotide sequences represented by SEQ ID NOs shown in Table 1 mentioned later (SEQ ID NOs: 1 to 148 and 466 to 478 corresponding to the miRNA markers in Table 1) or complementary sequences thereof. However, these are given merely for illustrative purposes, and all of various other possible combinations are included in the present invention.

The aforementioned combination constituting the kit or the device for discriminating a biliary tract cancer patient from a healthy subject according to the present invention is desirably, for example, a combination of two or more of the aforementioned polynucleotides consisting of nucleotide sequences represented by SEQ ID NOs shown in Table 1. Usually, a combination of two of these polynucleotides can produce adequate performance.

Specifically, the combination of two polynucleotides consisting of the nucleotide sequences or the complementary sequences thereof for discriminating a biliary tract cancer patient from a healthy subject is preferably a combination comprising at least one or more of newly found polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1 to 125 and 466 to 478, among the aforementioned combinations of two polynucleotides selected from the polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1 to 148 and 466 to 478.

The combination of polynucleotides with cancer type specificity capable of discriminating a biliary tract cancer patient not only from a healthy subject but also from other cancer patients is preferably, for example, a combination of multiple polynucleotides comprising at least one polynucleotide selected from the group consisting of polynucleotides consisting of the nucleotide sequence represented by SEQ ID NOs: 1, 4, 5, 11, 12, 15, 23, 29, 39, 40, 54, 76, 79, 91, 103, 115, 121, 134, 143, 466, 469, 472, 473, and 474, or complementary sequences thereof (hereinafter, this group is referred to as "cancer type-specific polynucleotide group 1"), with any of the polynucleotides of the other SEQ ID NOs.

The combination of polynucleotides with cancer type specificity capable of discriminating a biliary tract cancer patient not only from a healthy subject but also from other cancer patients is more preferably a combination of multiple polynucleotides selected from the cancer type-specific polynucleotide group 1.

The combination of polynucleotides with cancer type specificity capable of discriminating a biliary tract cancer patient not only from a healthy subject but also from other cancer patients is more preferably a combination comprising at least one polynucleotide selected from the group consisting of polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 4, 5, 12, 15, and 40 or complementary sequences thereof (hereinafter, this group is referred to as "cancer type-specific polynucleotide group 2") included in the cancer type-specific polynucleotide group 1, among the combinations of multiple polynucleotides selected from the cancer type-specific polynucleotide group 1.

The number of the aforementioned polynucleotides with cancer type specificity in the combination can be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more in the combination and is more preferably 4 or more in the combination. Usually, the combination of 4 of the polynucleotides can produce adequate performance.

Non-limiting examples of the combination of the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 4 or a complementary sequence thereof with polynucleotides consisting of nucleotide sequences represented by SEQ ID NOs of three polynucleotides selected from the cancer type-specific polynucleotide group 1 or complementary sequences thereof are listed below.

(1) a combination of SEQ ID NOs: 4, 15, 54, and 115 (markers: miR-4476, miR-6075, miR-6821-5p, and miR-1202);

(2) a combination of SEQ ID NOs: 4, 5, 12, and 76 (markers: miR-4476, miR-4294, miR-6836-3p, and miR-6085):

(3) a combination of SEQ ID NOs: 4., 5, 12, and 115 (markers: miR-4476, miR-4294, miR-6836-3p, and miR-1202);

(4) a combination of SEQ ID NOs: 4, 12, 15, and 474 (markers: miR-4476, miR-6836-3p, miR-6075, and miR-4508);

(5) a combination of SEQ ID NOs: 4, 15, 29, and 115 (markers: miR-4476, miR-6075, miR-6799-5p, and miR-1202).

Non-limiting examples of the combination of the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 5 or a complementary sequence thereof with polynucleotides consisting of nucleotide sequences represented by SEQ ID NOs of three polynucleotides selected from the cancer type-specific polynucleotide group 1 or complementary sequences thereof are listed below.

(1) a combination of SEQ ID NOs: 5, 76, 12, and 115 (markers: hsa-miR-4294, hsa-miR-6085, hsa-miR-6836-3p, and hsa-miR-1202);

(2) a combination of SEQ ID NOs: 5, 76, 54, and 115 (markers: hsa-miR-4294, hsa-miR-6085, hsa-miR-6821-5p, and hsa-miR-1202);

(3) a combination of SEQ ID NOs: 5, 23, 12, and 115 (markers: hsa-miR-4294, hsa-miR-4530, hsa-miR-6836-3p, and hsa-miR-1202);

(4) a combination of SEQ ID NOs: 5, 12, 115, and 91 (markers: hsa-miR-4294, hsa-miR-6836-3p, hsa-miR-1202, and hsa-miR-4665-3p);

(5) a combination of SEQ ID NOs: 5, 1, 23, and 4 (markers: hsa-miR-4294, hsa-miR-125a-3p, hsa-miR-4530, and hsa-miR-4476).

Non-limiting examples of the combination of the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 12 or a complementary sequence thereof with polynucleotides consisting of nucleotide sequences represented by SEQ ID NOs of three polynucleotides selected from the cancer type-specific polynucleotide group 1 or complementary sequences thereof are listed below.

(1) a combination of SEQ ID NOs: 5, 12, 29, and 115 (markers: miR-4294, miR-6836-3p, miR-6799-5p, and miR-1202);

(2) a combination of SEQ ID NOs: 12, 15, 23, and 115 (markers: miR-6836-3p, miR-6075, miR-4530, and miR-1202);

(3) a combination of SEQ ID NOs: 5, 12, 115, and 469 (markers: miR-4294, miR-6836-3p, miR-3162-5p, and miR-1202);

(4) a combination of SEQ ID NOs: 5, 12, 115, and 472 (markers: miR-4294, miR-6836-3p, miR-1202, and miR-4271);

(5) a combination of SEQ ID NOs: 5, 12, 76, and 115 (markers: miR-4294, miR-6085, miR-1202, and miR-6836-3p).

Non-limiting examples of the combination of the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 15 or a complementary sequence thereof with polynucleotides consisting of nucleotide sequences represented by SEQ ID NOs of three polynucleotides selected from the cancer type-specific polynucleotide group 1 or complementary sequences thereof are listed below.

(1) a combination of SEQ ID NOs: 15, 29, 1, and 12 (markers: hsa-miR-6075, hsa-miR-6799-5p, hsa-miR-125a-3p, and hsa-miR-6836-3p);

(2) a combination of SEQ ID NOs: 15, 12, 11, and 143 (markers: hsa-miR-6075, hsa-miR-6836-3p, hsa-miR-575, and hsa-miR-1203);

(3) a combination of SEQ ID NOs: 15, 76, 121, and 39 (markers: hsa-miR-6075, hsa-miR-6085, hsa-miR-6132, and hsa-miR-1238-5p):

(4) a combination of SEQ ID NOs: 15, 76, 54, and 121 (markers: hsa-miR-6075, hsa-miR-6085, hsa-miR-6821-5p, and hsa-miR-6132);

(5) a combination of SEQ ID NOs: 15, 40, 1, and 23 (markers: hsa-miR-6075, hsa-miR-6880-5p, hsa-miR-125a-3p, and hsa-miR-4530).

Non-limiting examples of the combination of the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 40 or a complementary sequence thereof with polynucleotides consisting of nucleotide sequences represented by SEQ ID NOs of three polynucleotides selected from the cancer type-specific polynucleotide group 1 or complementary sequences thereof are listed below.

(1) a combination of SEQ ID NOs: 12, 40, 472, and 473 (markers: miR-6836-3p, miR-6880-5p, miR-4271, and miR-6769b-5p);

(2) a combination of SEQ ID NOs: 12, 23, 40, and 466 (markers: miR-6836-3p, miR-4530, miR-6880-5p, and miR-4516);

(3) a combination of SEQ ID NOs: 12, 23, 40, and 134 (markers: miR-6836-3p, miR-4530, miR-6880-5p, and miR-6076);

(4) a combination of SEQ ID NOs: 15, 40, 121, and 134 (markers: miR-6075, miR-6880-5p, miR-6132, and miR-6076);

(5) a combination of SEQ ID NOs: 15, 40, 54, and 76 (markers: miR-6075, miR-6880-5p, miR-6821-5p, and miR-6085).

The kit or the device of the present invention may also comprise a polynucleotide that is already known or that will be found in the future, to enable detection of biliary tract cancer, in addition to the polynucleotide(s) (which can include variant(s), fragment(s), and derivative(s)) according to the present invention as described above.

The kit of the present invention may also comprise an antibody for measuring a marker for biliary tract cancer examination known in the art, such as CEA, CA19-9. SPan-1, DUPAN-2, CA50, CA195, IL-6, CA242, TAG-72, urinary fucose, POA, or TPS, in addition to the polynucleotide(s) according to the present invention as described above.

These polynucleotides contained in the kit of the present invention may be packaged in different containers either individually or in any combination.

The kit of the present invention may comprise a kit for extracting a nucleic acid (e.g., total RNA) from body fluids, cells, or tissues; a fluorescent material for labeling, an enzyme and a medium for nucleic acid amplification, an instruction manual, etc.

The device of the present invention is a device for cancer marker measurement in which nucleic acids such as the polynucleotides according to the present invention described above are bound or attached to, for example, a solid phase. Examples of the material for the solid phase include plastics, paper, glass, and silicon. The material for the solid phase is preferably a plastic from the viewpoint of easy processability. The solid phase has any shape and is, for example, square, round, reed-shaped, or film-shaped. The device of the present invention includes, for example, a device for measurement by a hybridization technique. Specific examples thereof include blotting devices and nucleic acid arrays (e.g., microarrays, DNA chips, and RNA chips).

The nucleic acid array technique is a technique which involves binding or attaching the nucleic acids one by one by use of a method [e.g., a method of spotting the nucleic acids using a high-density dispenser called spotter or arrayer onto the surface of the solid phase surface-treated, if necessary, by coating with L-lysine or the introduction of a functional group such as an amino group or a carboxyl group, a method of spraying the nucleic acids onto the solid phase using an inkjet which injects very small liquid droplets by a piezoelectric element or the like from a nozzle, or a method of sequentially synthesizing nucleotides on the solid phase] to prepare an array such as a chip and measuring target nucleic acids through the use of hybridization using this array.

The kit or the device of the present invention comprises nucleic acids capable of specifically binding to the polynucleotides of at least one or more, preferably at least two or more, more preferably at least three or more, most preferably at least five or more to all of the biliary tract cancer marker miRNAs, respectively, of the group 1 described above. The kit or the device of the present invention may optionally further comprise nucleic acids capable of specifically binding to the polynucleotides of at least one or more, preferably at least two or more, more preferably at least three or more, most preferably all of five of the biliary tract cancer marker miRNAs, respectively, of the group 2 described above.

The kit or the device of the present invention can be used for detecting biliary tract cancer as described in Section 4 below.

4. Method for Detecting Biliary Tract Cancer

The present invention further provides a method for detecting biliary tract cancer, comprising using the kit or the device of the present invention (comprising the above-mentioned nucleic acid(s) that can be used in the present invention) described in Section 3 above to measure expression level(s) of one or more liver cancer-derived gene(s) being an expression level of biliary tract cancer-derived gene(s) selected from the following group: miR-125a-3p, miR-6893-5p, miR-204-3p, miR-4476, miR-4294, miR-150-3p, miR-6729-5p, miR-7641, miR-6765-3p, miR-6820-5p, miR-575, miR-6836-3p, miR-1469, miR-663a, miR-6075, miR-4634, miR-423-5p, miR-4454, miR-7109-5p, miR-6789-5p, miR-6877-5p, miR-4792, miR-4530, miR-7975, miR-6724-5p, miR-8073, miR-7977, miR-1231, miR-6799-5p. miR-615-5p, miR-4450, miR-6726-5p, miR-6875-5p, miR-4734, miR-16-5p, miR-602, miR-4651, miR-8069, miR-1238-5p, miR-6880-5p, miR-8072, miR-4723-5p, miR-4732-5p. miR-6125, miR-6090, miR-7114-5p, miR-564, miR-451a, miR-3135b, miR-4497, miR-4665-5p, miR-3622a-5p, miR-6850-5p, miR-6821-5p, miR-5100, miR-6872-3p, miR-4433-3p, miR-1227-5p, miR-3188, miR-7704, miR-3185, miR-1908-3p, miR-6781-5p, miR-6805-5p, miR-8089, miR-665, miR-4486, miR-6722-3p, miR-1260a, miR-4707-5p, miR-6741-5p, miR-1260b, miR-1246, miR-6845-5p, miR-4638-5p. miR-6085, miR-1228-3p, miR-4534, miR-5585-3p, miR-4741, miR-4433b-3p, miR-197-5p, miR-718, miR-4513, miR-4446-3p, miR-619-5p, miR-6816-5p, miR-6778-5p, miR-24-3p, miR-1915-3p, miR-4665-3p, miR-4449, miR-6889-5p, miR-486-3p, miR-7113-3p. miR-642a-3p, miR-7847-3p, miR-6768-5p, miR-1290, miR-7108-5p, miR-92b-5p, miR-663b, miR-3940-5p, miR-4467, miR-6858-5p, miR-4417, miR-3665, miR-4736, miR-4687-3p, miR-1908-5p, miR-5195-3p, miR-4286, miR-3679-3p, miR-6791-5p, miR-1202, miR-3656, miR-4746-3p, miR-3184-5p, miR-3937, miR-6515-3p, miR-6132, miR-187-5p, miR-7111-5p, miR-5787 and miR-6779-5p, and optionally an expression level of biliary tract cancer-derived gene(s) selected from the following group: miR-6808-5p, miR-6774-5p. miR-4656, miR-6806-5p, miR-1233-5p, miR-328-5p, miR-4674, miR-2110, miR-6076, miR-3619-3p, miR-92a-2-5p, miR-128-1-5p, miR-638, miR-2861, miR-371a-5p, miR-211-3p, miR-1273g-3p, miR-1203, miR-122-5p, miR-4258, miR-4484, miR-4648, miR-6780b-5p, miR-4516, miR-4649-5p, miR-760, miR-3162-5p, miR-3178, miR-940, miR-4271, miR-6769b-5p, miR-4508, miR-6826-5p, miR-6757-5p, miR-3131, and miR-1343-3p in a sample in vitro, further comparing, for example, the expression level(s) of the gene(s) in the sample (e.g., blood, serum, or plasma) collected from a subject suspected of having biliary tract cancer with a control expression level in the sample collected from a healthy subject (including a non-biliary tract cancer patient), and evaluating the subject as having biliary tract cancer when the expression level(s) of the target nucleic acid(s) is statistically significantly different between the samples.

This method of the present invention enables a limitedly invasive, early diagnosis of the cancer with high sensitivity and high specificity and thereby brings about early treatment and improved prognosis. In addition, exacerbation of the disease or the effectiveness of surgical, radiotherapeutic, and chemotherapeutic treatments can be monitored.

The method for extracting the biliary tract cancer-derived gene from the sample such as blood, serum, or plasma according to the present invention is particularly preferably prepared by the addition of a reagent for RNA extraction in 3D-Gene® RNA extraction reagent from liquid sample kit (Toray Industries, Inc.). A general acidic phenol method (acid guanidinium-phenol-chloroform (AGPC)) may be used, or Trizol® (Life Technologies Corp.) may be used. The biliary tract cancer-derived gene may be prepared by the addition of a reagent for RNA extraction containing acidic phenol, such as Trizol (Life Technologies Corp.) or Isogen (Nippon Gene Co., Ltd.). Alternatively, a kit such as miRNeasy® Mini Kit (Qiagen N.V.) can be used, though the method is not limited thereto.

The present invention also provides use of the kit or the device of the present invention for detecting in vitro an expression product of a biliary tract cancer-derived miRNA gene in a sample derived from a subject.

In the method of the present invention, the kit or the device described above comprising a single polynucleotide or any possible combination of the polynucleotides that can be used in the present invention as described above is used.

In the detection or (genetic) diagnosis of biliary tract cancer according to the present invention, each polynucleotide contained in the kit or the device of the present invention can be used as a probe or a primer. In the case of using the polynucleotide as a primer, TaqMan® MicroRNA Assays from Life Technologies Corp., miScript PCR System from Qiagen N.V., or the like can be used, though the method is not limited thereto.

The polynucleotide contained in the kit or the device of the present invention can be used as a primer or a probe according to a routine method in a method known in the art for specifically detecting the particular gene, for example, a hybridization technique such as Northern blot, Southern blot, in situ hybridization, Northern hybridization, or Southern hybridization, or a quantitative amplification technique such as quantitative RT-PCR. A body fluid such as blood, serum, plasma, or urine of the subject is collected as a sample to be assayed according to the type of the detection method used. Alternatively, total RNA prepared from such a body fluid by the method described above may be used, and various polynucleotides including cDNA prepared on the basis of the RNA may be used.

The kit or the device of the present invention is useful for the diagnosis of biliary tract cancer or the detection of the presence or absence of biliary tract cancer. Specifically, the detection of biliary tract cancer using the kit or the device can be performed by detecting in vitro an expression level of a gene using the nucleic acid probe or the primer contained in the kit or the device in a sample such as blood, serum, plasma, or urine from a subject suspected of having biliary tract cancer. The subject suspected of having biliary tract cancer can be evaluated as having biliary tract cancer when the expression level of a target miRNA marker measured using polynucleotide(s) (including variant(s), fragment(s), and derivative(s) thereof) consisting of a nucleotide sequence represented by at least one or more of SEQ ID NOs: 1 to 125, 466 to 478 or a complementary sequence thereof, and optionally a nucleotide sequence represented by one or more of SEQ ID NOs: 126 to 148 or a complementary sequence thereof in the sample such as blood, serum, plasma, or urine of the subject is statistically significantly different compared with the expression level thereof in the sample such as blood, serum, or plasma, or urine of a healthy subject.

The method of the present invention can be combined with a diagnostic imaging method such as abdominal ultrasonography, CT scanning, endoscopic retrograde cholangiopancreatography, or endoscopic ultrasonography. The method of the present invention is capable of specifically detecting biliary tract cancer and can substantially discriminate biliary tract cancer from the other cancers. Particularly, for pancreatic cancer, some miRNA markers for biliary tract cancer can be commonly used. However, biliary tract cancer can be discriminated from pancreatic cancer on the basis of a discriminant boundary adopted according to a discriminant. Alternatively, biliary tract cancer can be discriminated therefrom by combination with an additional diagnostic method such as the diagnostic imaging method as described above.

The method for detecting the absence of an expression product of a biliary tract cancer-derived gene or the presence of the expression product of a biliary tract cancer-derived gene in a sample using the kit or the device of the present invention comprises; collecting a body fluid such as blood, serum, plasma, or urine of a subject: measuring the expression level of the target gene contained therein using one or more polynucleotide(s) (including variant(s), fragment(s), or derivative(s)) selected from the polynucleotide group of the present invention; and evaluating the presence or absence of biliary tract cancer or to detect biliary tract cancer. Using the method for detecting biliary tract cancer according to the present invention, for example, the presence or absence of amelioration of the disease or the degree of amelioration thereof in a biliary tract cancer patient when a therapeutic drug is administered to the patient for amelioration of the disease can be evaluated or diagnosed.

The method of the present invention may comprise, for example, the following steps (a), (b), and (c):

(a) contacting in vitro a sample derived from a subject with a polynucleotide in the kit or the device of the present invention;

(b) measuring an expression level of the target nucleic acid in the sample using the polynucleotide as a nucleic acid probe or a primer; and

(c) evaluating the presence or absence of biliary tract cancer (cells) in the subject on the basis of a measurement result obtained in the step (b).

Specifically, the present invention provides a method for detecting biliary tract cancer, comprising measuring an expression level of a target nucleic acid in a sample of a subject using nucleic acid(s) capable of specifically binding to at least one or more (preferably at least two or more) polynucleotide(s) selected from the group consisting of miR-125a-3p, miR-6893-5p, miR-204-3p, miR-4476, miR-4294, miR-150-3p, miR-6729-5p, miR-7641, miR-6765-3p, miR-6820-5p, miR-575, miR-6836-3p, miR-1469, miR-663a, miR-6075, miR-4634, miR-423-5p, miR-4454, miR-7109-5p, miR-6789-5p, miR-6877-5p, miR-4792, miR-4530, miR-7975, miR-6724-5p, miR-8073, miR-7977, miR-1231, miR-6799-5p, miR-615-5p, miR-4450, miR-6726-5p, miR-6875-5p, miR-4734, miR-16-5p, miR-602, miR-4651, miR-8069, miR-1238-5p, miR-6880-5p, miR-8072, miR-4723-5p, miR-4732-5p, miR-6125, miR-6090, miR-7114-5p, miR-564, miR-451a, miR-3135b, miR-4497, miR-4665-5p, miR-3622a-5p. miR-6850-5p, miR-6821-5p, miR-5100, miR-6872-3p, miR-4433-3p, miR-1227-5p, miR-3188, miR-7704, miR-3185, miR-1908-3p, miR-6781-5p, miR-6805-5p, miR-8089, miR-665, miR-4486, miR-6722-3p, miR-1260a, miR-4707-5p, miR-6741-5p, miR-1260b, miR-1246, miR-6845-5p, miR-4638-5p, miR-6085, miR-1228-3p, miR-4534, miR-5585-3p, miR-4741, miR-4433b-3p, miR-197-5p, miR-718, miR-4513, miR-4446-3p, miR-619-5p, miR-6816-5p, miR-6778-5p, miR-24-3p. miR-1915-3p, miR-4665-3p, miR-4449, miR-6889-5p, miR-486-3p, miR-7113-3p, miR-642a-3p, miR-7847-3p, miR-6768-5p, miR-1290, miR-7108-5p, miR-92b-5p, miR-663b, miR-3940-5p, miR-4467, miR-6858-5p, miR-4417, miR-3665, miR-4736, miR-4687-3p, miR-1908-5p, miR-5195-3p, miR-4286, miR-3679-3p, miR-6791-5p, miR-1202, miR-3656, miR-4746-3p, miR-3184-5p, miR-3937, miR-6515-3p, miR-6132, miR-187-5p, miR-7111-5p, miR-5787, miR-6779-5p, miR-4516, miR-4649-5p, miR-760, miR-3162-5p, miR-3178, miR-940, miR-4271, miR-6769b-5p, miR-4508, miR-6826-5p, miR-6757-5p, miR-3131, and miR-1343-3p and evaluating in vitro whether or not the subject has biliary tract cancer using the measured expression level and a control expression level of a healthy subject measured in the same way as above.

The term “evaluation” used herein is evaluation support based on results of in vitro examination, not physician’s judgment.

As described above, in a preferred embodiment of the method of the present invention, specifically, miR-125a-3p is hsa-miR-125a-3p, miR-6893-5p is hsa-miR-6893-5p, miR-204-3p is hsa-miR-204-3p, miR-4476 is hsa-miR-4476, miR-4294 is hsa-miR-4294, miR-150-3p is hsa-miR-150-3p, miR-6729-5p is hsa-miR-6729-5p, miR-7641 is hsa-miR-7641, miR-6765-3p is hsa-miR-6765-3p, miR-6820-5p is hsa-miR-6820-5p, miR-575 is hsa-miR-575, miR-6836-3p is hsa-miR-6836-3p, miR-1469 is hsa-miR-1469, miR-663a is hsa-miR-663a, miR-6075 is hsa-miR-6075, miR-4634 is hsa-miR-4634, miR-423-5p is hsa-miR-423-5p, miR-4454 is hsa-miR-4454, miR-7109-5p is hsa-miR-7109-5p, miR-6789-5p is hsa-miR-6789-5p, miR-6877-5p is hsa-miR-6877-5p, miR-4792 is hsa-miR-4792, miR-4530 is hsa-miR-4530, miR-7975 is hsa-miR-7975, miR-6724-5p is hsa-miR-6724-5p, miR-8073 is hsa-miR-8073, miR-7977 is hsa-miR-7977, miR-1231 is hsa-miR-1231, miR-6799-5p is hsa-miR-6799-5p, miR-615-5p is hsa-miR-615-5p, miR-4450 is hsa-miR-4450, miR-6726-5p is hsa-miR-6726-5p, miR-6875-5p is hsa-miR-6875-5p, miR-4734 is hsa-miR-4734, miR-16-5p is hsa-miR-16-5p, miR-602 is hsa-miR-602, miR-4651 is hsa-miR-4651, miR-8069 is hsa-miR-8069, miR-1238-5p is hsa-miR-1238-5p, miR-6880-5p is hsa-miR-6880-5p, miR-8072 is hsa-miR-8072, miR-4723-5p is hsa-miR-4723-5p, miR-4732-5p is hsa-miR-4732-5p, miR-6125 is hsa-miR-6125, miR-6090 is hsa-miR-6090, miR-7114-5p is hsa-miR-7114-5p, miR-564 is hsa-miR-564, miR-451a is hsa-miR-451a, miR-3135b is hsa-miR-3135b, miR-4497 is hsa-miR-4497, miR-4665-5p is hsa-miR-4665-5p, miR-3622a-5p is hsa-miR-3622a-5p, miR-6850-5p is hsa-miR-6850-5p, miR-6821-5p is hsa-miR-6821-5p, miR-5100 is hsa-miR-5100, miR-6872-3p is hsa-miR-6872-3p, miR-4433-3p is hsa-miR-4433-3p, miR-1227-5p is hsa-miR-1227-5p, miR-3188 is hsa-miR-3188, miR-7704 is hsa-miR-7704, miR-3185 is hsa-miR-3185, miR-1908-3p is hsa-miR-1908-3p, miR-6781-5p is hsa-miR-6781-5p, miR-6805-5p is hsa-miR-6805-5p, miR-8089 is hsa-miR-8089, miR-665 is hsa-miR-665, miR-4486 is hsa-miR-4486, miR-6722-3p is hsa-miR-6722-3p, miR-1260a is hsa-miR-1260a, miR-4707-5p is hsa-miR-4707-5p, miR-6741-5p is hsa-miR-6741-5p, miR-1260b is hsa-miR-1260b, miR-1246 is hsa-miR-1246, miR-6845-5p is hsa-miR-6845-5p, miR-4638-5p is hsa-miR-4638-5p, miR-6085 is hsa-miR-6085, miR-1228-3p is hsa-miR-1228-3p, miR-4534 is hsa-miR-4534, miR-5585-3p is hsa-miR-5585-3p. miR-4741 is hsa-miR-4741, miR-4433b-3p is hsa-miR-4433b-3p, miR-197-5p is hsa-miR-197-5p, miR-718 is hsa-miR-718, miR-4513 is hsa-miR-4513, miR-4446-3p is hsa-miR-4446-3p, miR-619-5p is hsa-miR-619-5p, miR-6816-5p is hsa-miR-6816-5p, miR-6778-5p is hsa-miR-6778-5p, miR-24-3p is hsa-miR-24-3p, miR-1915-3p is hsa-miR-1915-3p, miR-4665-3p is hsa-miR-4665-3p, miR-4449 is hsa-miR-4449, miR-6889-5p is hsa-miR-6889-5p, miR-486-3p is hsa-miR-486-3p, miR-7113-3p is hsa-miR-7113-3p, miR-642a-3p is hsa-miR-642a-3p, miR-7847-3p is hsa-miR-7847-3p, miR-6768-5p is hsa-miR-6768-5p, miR-1290 is hsa-miR-1290, miR-7108-5p is hsa-miR-7108-5p, miR-92b-5p is hsa-miR-92b-5p, miR-663b is hsa-miR-663b, miR-3940-5p is hsa-miR-3940-5p, miR-4467 is hsa-miR-4467, miR-6858-5p is hsa-miR-6858-5p, miR-4417 is hsa-miR-4417, miR-3665 is hsa-miR-3665, miR-4736 is hsa-miR-4736, miR-4687-3p is hsa-miR-4687-3p, miR-1908-5p is hsa-miR-1908-5p, miR-5195-3p is hsa-miR-5195-3p, miR-4286 is hsa-miR-4286, miR-3679-3p is hsa-miR-3679-3p, miR-6791-5p is hsa-miR-6791-5p, miR-1202 is hsa-miR-1202, miR-3656 is hsa-miR-3656, miR-4746-3p is hsa-miR-4746-3p, miR-3184-5p is hsa-miR-3184-5p, miR-3937 is hsa-miR-3937, miR-6515-3p is hsa-miR-6515-3p, miR-6132 is hsa-miR-6132, miR-187-5p is hsa-miR-187-5p, miR-7111-5p is hsa-miR-7111-5p, miR-5787 is hsa-miR-5787, miR-6779-5p is hsa-miR-6779-5p, miR-4516 is hsa-miR-4516, miR-4649-5p is hsa-miR-4649-5p, miR-760 is hsa-miR-760, miR-3162-5p is hsa-miR-3162-5p, miR-3178 is hsa-miR-3178, miR-940 is hsa-miR-940, miR-4271 is hsa-miR-4271, miR-6769b-5p is hsa-miR-6769b-5p, miR-4508 is hsa-miR-4508, miR-6826-5p is hsa-miR-6826-5p, miR-6757-5p is hsa-miR-6757-5p, miR-3131 is hsa-miR-3131, and miR-1343-3p is hsa-miR-1343-3p.

In a preferred embodiment of the method of the present invention, specifically, the nucleic acid (specifically, probe or primer) is selected from the group consisting of the following polynucleotides (a) to (e):

(a) a polynucleotide consisting of a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides,

(b) a polynucleotide comprising a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478,

(c) a polynucleotide consisting of a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478, or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides,

(d) a polynucleotide comprising a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, and

(e) a polynucleotide hybridizing under stringent conditions to any of the polynucleotides (a) to (d).

In the method of the present invention, nucleic acid(s) capable of specifically binding to at least one or more polynucleotide(s) selected from the followings: miR-6808-5p, miR-6774-5p, miR-4656, miR-6806-5p, miR-1233-5p. miR-328-5p, miR-4674, miR-2110, miR-6076, miR-3619-3p, miR-92a-2-5p, miR-128-1-5p, miR-638, miR-2861, miR-371a-5p, miR-211-3p, miR-1273g-3p, miR-1203, miR-122-5p, miR-4258, miR-4484, miR-4648, miR-6780b-5p, miR-4516, miR-4649-5p, miR-760, miR-3162-5p, miR-3178, miR-940, miR-4271, miR-6769b-5p, miR-4508, miR-6826-5p, miR-6757-5p, miR-3131, and miR-1343-3p may be further used.

In a preferred embodiment, such a nucleic acid is specifically as follows: miR-6808-5p is hsa-miR-6808-5p, miR-6774-5p is hsa-miR-6774-5p, miR-4656 is hsa-miR-4656, miR-6806-5p is hsa-miR-6806-5p, miR-1233-5p is hsa-miR-1233-5p, miR-328-5p is hsa-miR-328-5p, miR-4674 is hsa-miR-4674, miR-2110 is hsa-miR-2110, miR-6076 is hsa-miR-6076, miR-3619-3p is hsa-miR-3619-3p, miR-92a-2-5p is hsa-miR-92a-2-5p, miR-128-1-5p is hsa-miR-128-1-5p, miR-638 is hsa-miR-638, miR-2861 is hsa-miR-2861, miR-371a-5p is hsa-miR-371a-5p, miR-211-3p is hsa-miR-211-3p, miR-1273g-3p is hsa-miR-1273g-3p, miR-1203 is hsa-miR-1203, miR-122-5p is hsa-miR-122-5p, miR-4258 is hsa-miR-4258, miR-4484 is hsa-miR-4484, miR-4648 is hsa-miR-4648, miR-6780b-5p is hsa-miR-6780b-5p, miR-4516 is hsa-miR-4516, miR-4649-5p is hsa-miR-4649-5p, miR-760 is hsa-miR-760, miR-3162-5p is hsa-miR-3162-5p, miR-3178 is hsa-miR-3178, miR-940 is hsa-miR-940, miR-4271 is hsa-miR-4271, miR-6769b-5p is hsa-miR-6769b-5p, miR-4508 is hsa-miR-4508, miR-6826-5p is hsa-miR-6826-5p, miR-6757-5p is hsa-miR-6757-5p, miR-3131 is hsa-miR-3131, and miR-1343-3p is hsa-miR-1343-3p.

In a preferred embodiment, specifically, such a nucleic acid is further selected from the group consisting of the following polynucleotides (f) to (j):

(f) a polynucleotide consisting of a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof comprising 15 or more consecutive nucleotides,

(g) a polynucleotide comprising a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148.

(h) a polynucleotide consisting of a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, a variant thereof, a derivative thereof, or a fragment thereof that comprises 15 or more consecutive nucleotides,

(i) a polynucleotide comprising a nucleotide sequence complementary to a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a nucleotide sequence derived from the nucleotide sequence by the replacement of u with t, and

(j) a polynucleotide hybridizing under stringent conditions to any of the polynucleotides (f) to (i).

Examples of the sample used in the method of the present invention can include samples prepared from a living tissue (preferably a biliary tract tissue) or a body fluid such as blood, serum, plasma, or urine of the subject. Specifically, for example, an RNA-containing sample prepared from the tissue, a polynucleotide-containing sample further prepared therefrom, a body fluid such as blood, serum, plasma, or urine, a portion or the w % hole of a living tissue collected from the subject by biopsy or the like, or a living tissue excised by surgery can be used, and the sample for measurement can be prepared therefrom.

The subject used herein refers to a mammal, for example, a human, a monkey, a mouse and a rat, without any limitation, and is preferably a human.

The steps of the method of the present invention can be changed according to the type of the sample to be assayed.

In the case of using RNA as an analyte, the detection of biliary tract cancer (cells) may comprise, for example, the following steps (a), (b), and (c):

(a) binding RNA prepared from the sample of a subject or a complementary polynucleotide (cDNA) transcribed therefrom to a polynucleotide in the kit or the device of the present invention;

(b) measuring the sample-derived RNA or the cDNA synthesized from the RNA, bound with the polynucleotide by hybridization using the polynucleotide as a nucleic acid probe or by quantitative RT-PCR using the polynucleotide as a primer; and

(c) evaluating the presence or absence of biliary tract cancer (or biliary tract cancer-derived gene expression) on the basis of the measurement results of the step (b).

For example, various hybridization methods can be used for detecting, examining, evaluating, or diagnosing biliary tract cancer (or biliary tract cancer-derived gene expression) in vitro according to the present invention. For example, Northern blot, Southern blot, RT-PCR, DNA chip analysis, in situ hybridization, Northern hybridization, or Southern hybridization can be used as such a hybridization method.

In the case of using the Northern blot, the presence or absence of expression of each gene or the expression level thereof in the RNA can be detected or measured by use of the nucleic acid probe that can be used in the present invention. Specific examples thereof can include a method which comprises labeling the nucleic acid probe (or a complementary strand) with a radioisotope (^{32}P, ^{33}P, ^{35}S, etc.), a fluorescent material, or the like, hybridizing the labeled product with the living tissue-derived RNA from the subject, which is transferred to a nylon membrane or the like according to a routine method, and then detecting and measuring a signal derived from the label (radioisotope or fluorescent material) on the formed DNA/RNA duplex using a radiation detector (examples thereof can include BAS-1800 II (Fujifilm Corp.)) or a fluorescence detector (examples thereof can include STORM 865 (GE Healthcare Japan Corp.)).

In the case of using the quantitative RT-PCR the presence or absence of expression of each gene or the expression level thereof in the RNA can be detected or measured by use of the primer that can be used in the present invention. Specific examples thereof can include a method which comprises preparing cDNA from the living tissue-derived RNA of the subject according to a routine method, hybridizing a pair of primers (that consist of a plus strand and a reverse strand binding to the cDNA) of the present invention with the cDNA such that the region of each target gene can be amplified with the cDNA as a template, and performing PCR according to a routine method to detect the obtained double-stranded DNA. The method for detecting the double-stranded DNA can include a method of performing the PCR using the primers labeled in advance with a radioisotope or a fluorescent material, a method of electrophoresing the PCR product on an agarose gel and staining the double-stranded DNA with ethidium bromide or the like for detection, and a method of transferring the produced double-stranded DNA to a nylon membrane or the like according to a routine method and hybridizing the double-stranded DNA to a labeled nucleic acid probe for detection.

In the case of using the nucleic acid array analysis, an RNA chip or a DNA chip in which the nucleic acid probes (single-stranded or double-stranded) of the present invention are attached to a substrate (solid phase) is used. Regions having the attached nucleic acid probes are referred to as probe spots, and regions having no attached nucleic acid probe are referred to as blank spots. A group of genes immobilized on a solid-phase substrate is generally called a nucleic acid chip, a nucleic acid array, a microarray, or the like. The DNA or RNA array includes a DNA or RNA macroarray and a DNA or RNA microarray. The term "chip" used herein includes all of these arrays. 3D-Gene® Human miRNA Oligo chip (Toray Industries, Inc.) can be used as the DNA chip, though the DNA chip is not limited thereto.

Examples of the measurement using the DNA chip can include, but are not limited to, a method of detecting and measuring a signal derived from the label on the nucleic acid probe using an image detector (examples thereof can include Typhoon 9410 (GE Healthcare Japan Corp.) and 3D-Gene® scanner (Toray Industries, Inc.)).

The "stringent conditions" used herein are, as mentioned above, conditions under which a nucleic acid probe hybridizes to its target sequence to a larger extent (e.g., a measurement value equal to or larger than a mean of background measurement values+a standard deviation of the background measurement values×2) than that for other sequences.

The stringent conditions are defined by conditions for hybridization and subsequent washing. Examples of the hybridization conditions include, but not limited to, 30° C. to 60° C. for 1 to 24 hours in a solution containing SSC, a surfactant, formamide, dextran sulfate, a blocking agent, etc. In this context, 1×SSC is an aqueous solution (pH 7.0) that contains 150 mM sodium chloride and 15 mM sodium citrate. The surfactant includes, for example, SDS (sodium dodecyl sulfate), Triton, or Tween. The hybridization conditions more preferably comprise 3 to 10×SSC and 0.1 to 1% SDS. Examples of the conditions for the washing, following the hybridization, which is another condition to define the stringent conditions, can include conditions comprising continuous washing at 30° C. in a solution containing 0.5×SSC and 0.1% SDS, at 30° C. in a solution containing 0.2×SSC and 0.1% SDS, and at 30° C. in a 0.05×SSC solution. It is desirable that the complementary strand should maintain its hybridized state with a target plus strand even by the washing under such conditions. Specifically, examples of such a complementary strand can include a strand consisting of a nucleotide sequence in a completely complementary relationship with the nucleotide sequence of the target plus

(+) strand, and a strand consisting of a nucleotide sequence having at least 80%, preferably at least 85%, more preferably at least 90% or at least 95%, for example, at least 98% or at least 99% identity to the strand.

Other examples of the "stringent conditions" for the hybridization are described in, for example, Sambrook, J. & Russel, D., Molecular Cloning, A LABORATORY MANUAL. Cold Spring Harbor Laboratory Press, published on Jan. 15, 2001, Vol. 1, 7.42 to 7.45 and Vol. 2, 8.9 to 8.17, and can be used in the present invention.

Examples of the conditions for carrying out PCR using a polynucleotide fragment in the kit of the present invention as a primer include treatment for approximately 15 seconds to 1 minute at 5 to 10° C. plus a Tm value calculated from the sequence of the primer, using a PCR buffer having composition such as 10 mM Tris-HCL (pH 8.3), 50 mM KCL, and 1 to 2 mM $MgCl_2$. Examples of the method for calculating such a Tm value include Tm value=2×(the number of adenine residues+the number of thymine residues)+4×(the number of guanine residues+the number of cytosine residues).

In the case of using the quantitative RT-PCR, a commercially available kit for measurement specially designed for quantitatively measuring miRNA, such as TaqMan® MicroRNA Assays (Life Technologies Corp.). LNA®-based MicroRNA PCR (Exiqon), or Ncode® miRNA qRT-PCT kit (Invitrogen Corp.) may be used.

For the calculation of gene expression levels, statistical analysis described in, for example, Statistical analysis of gene expression microarray data (Speed T., Chapman and Hall/CRC), and A beginner's guide Microarray gene expression data analysis (Causton H.C. et al., Blackwell publishing) can be used in the present invention, though the calculation method is not limited thereto. For example, twice, preferably 3 times, more preferably 6 times the standard deviation of the measurement values of the blank spots are added to the average measurement value of the blank spots on the DNA chip, and probe spots having a signal value equal to or larger than the resulting value can be regarded as detection spots. Alternatively, the average measurement value of the blank spots is regarded as a background and can be subtracted from the measurement values of the probe spots to determine gene expression levels. A missing value for a gene expression level can be excluded from the analyte, preferably replaced with the smallest value of the gene expression level in each DNA chip, or more preferably replaced with a value obtained by subtracting 0.1 from a logarithmic value of the smallest value of the gene expression level. In order to eliminate low-signal genes, only a gene having a gene expression level of 2^6, preferably 2^8, more preferably 2^{10}, or larger, in 20% or more, preferably 50% or more, more preferably 80% or more of the number of measurement samples can be selected as the analyte. Examples of the normalization of the gene expression level include, but are not limited to, global normalization and quantile normalization (Bolstad, B. M. et al., 2003, Bioinformatics, Vol. 19, p. 185-193).

The present invention also provides a method comprising measuring a target gene or gene expression level in a sample derived from a subject using the polynucleotide, the kit, or the device (e.g., chip) for detection of the present invention, or a combination thereof, preparing a discriminant (discriminant function) with gene expression levels in a sample derived from a biliary tract cancer patient and a sample derived from a healthy subject as supervising samples, and determining or evaluating the presence and/or absence of the biliary tract cancer-derived gene in the sample.

Specifically, the present invention further provides the method comprising: a first step of measuring in vitro an expression level of a target gene (target nucleic acid) in multiple samples known to determine or evaluate the presence or absence of the biliary tract cancer-derived gene in the samples, using the polynucleotide, the kit, or the device (e.g., chip) for detection of the present invention, or a combination thereof: a second step of preparing a discriminant with the measurement values of the expression level of the target gene obtained in the first step as supervising samples: a third step of measuring in vitro an expression level of the target gene in a sample derived from a subject in the same way as in the first step; and a fourth step of substituting the measurement value of the expression level of the target gene obtained in the third step into the discriminant obtained in the second step, and determining or evaluating the presence and/or absence of the biliary tract cancer-derived gene in the sample on the basis of the results obtained from the discriminant, wherein the target gene can be detected using the polynucleotide or using a polynucleotide for detection contained in the kit or the device (e.g., chip). In this context, the discriminant can be prepared by use of Fisher's linear discriminant analysis, nonlinear discriminant analysis based on Mahalanobis' distance, neural network, Support Vector Machine (SVM), or the like, though the method is not limited thereto.

When a clustering boundary is a straight line or a hyperplane, the linear discriminant analysis is a method for determining the association of a cluster using Formula 1 as a discriminant. In Formula 1, x represents an explanatory variable, w represents a coefficient of the explanatory variable, and w_0 represents a constant term.

$$f(x) = w_0 + \sum_{i=1}^{n} w_i x_i \qquad \text{Formula 1}$$

Values obtained from the discriminant are referred to as discriminant scores. The measurement values of a newly offered data set can be substituted as explanatory variables into the discriminant to determine clusters on the basis of the signs of the discriminant scores.

The Fisher's linear discriminant analysis, one type of linear discriminant analysis, is a dimensionality reduction method for selecting a dimension suitable for discriminating classes, and constructs a highly discriminating synthetic variable by focusing on the variance of the synthetic variables and minimizing the variance of data that has the same label (Venables, W. N. et al., Modem Applied Statistics with S. Fourth edition. Springer., 2002). In the Fisher's linear discriminant analysis, direction w of projection is determined so as to maximize Formula 2. In Formula 2, μ represents an average input, ng represents the number of data associated to class g, and μg represents an average input of the data associated to class g. The numerator and the denominator are interclass variance and intraclass variance, respectively, when each data is projected in the direction of the vector w. Discriminant coefficient w_i is determined by maximizing this ratio (Takafumi Kanamori et al., "Pattern Recognition", Kyoritsu Shuppan Co., Ltd. (2009); and Richard O. et al., Pattern Classification Second Edition., Wiley-Interscience, 2000).

Formula 2

$$J(w) = \frac{\sum_{g=1}^{G} n_g(w^T\mu_g - w^T\mu)(w^T\mu_g - w^T\mu)^T}{\sum_{g=1}^{G} \sum_{i:y_i=g} (w^T x_i - w^T\mu_g)(w^T x_i - w^T\mu_g)}$$

$$\text{subject to } \mu = \sum_{i=1}^{n} \frac{x_i}{n},\ \mu_g = \sum_{i:u_i=g}^{n} \frac{x_i}{n_g}$$

The Mahalanobis' distance is calculated according to Formula 3 in consideration of data correlation and can be used as nonlinear discriminant analysis for determining a cluster to which a data point is associated, based on a short Mahalanobis' distance from the data point to that cluster. In Formula 3, μ represents a central vector of each cluster, and S^{-1} represents an inverse matrix of the variance-covariance matrix of the cluster. The central vector is calculated from explanatory variable x, and an average vector, a median value vector, or the like can be used.

$$D(x,\mu)=\{(x-\mu)^t S^{-1}(x-\mu)\}^{1/2}$$ Formula 3

SVM is a discriminant analysis method devised by V. Vapnik (The Nature of Statistical Leaning Theory, Springer, 1995). Particular data points of a data set that has known classes are defined as explanatory variables, and classes are defined as objective variables. A boundary plane called hyperplane for correctly classifying the data set into the known classes is determined, and a discriminant for data classification is determined using the boundary plane. Then, the measurement values of a newly offered data set can be substituted as explanatory variables into the discriminant to determine classes. In this respect, the result of the discriminant analysis may be classes, may be a probability of being classified into correct classes, or may be the distance from the hyperplane. In SVM, a method of nonlinearly converting a feature vector to a high dimension and performing linear discriminant analysis in the space is known as a method for tackling nonlinear problems. An expression in which an inner product of two factors in a nonlinearly mapped space is expressed only by inputs in their original spaces is called kernel. Examples of the kernel can include a linear kernel, a RBF (radial basis function) kernel, and a Gaussian kernel. While highly dimensional mapping is performed according to the kernel, the optimum discriminant, i.e., a discriminant, can be actually constructed by mere calculation according to the kernel, which avoids calculating features in the mapped space (e.g., Hideki Aso et al., Frontier of Statistical Science 6 "Statistics of pattern recognition and learning—New concepts and approaches", Iwanami Shoten, Publishers (2004); Nello Cristianini et al., Introduction to SVM. Kyoritsu Shuppan Co., Ltd. (2008)).

C-support vector classification (C-SVC), one type of SVM, comprises preparing a hyperplane by supervising with the explanatory variables of two groups and classifying an unknown data set into either of the groups (C. Cortes et al., 1995, Machine Learning, Vol. 20, p. 273-297).

Exemplary calculation of the C-SVC discriminant that can be used in the method of the present invention is given below. First, all subjects are divided into two groups, i.e., a biliary tract cancer patient group and a healthy subject group. For example, biliary tract tissue examination can be used for confirming each subject either as a biliary tract patient or as a healthy subject.

Next, a data set consisting of comprehensive gene expression levels of serum-derived samples of the two divided groups (hereinafter, this data set is referred to as a training cohort) is prepared, and a C-SVC discriminant is determined by using genes found to differ clearly in their gene expression levels between the two groups as explanatory variables and objective variables (e.g., −1 and +1) that is this grouping. An optimizing objective function is represented by Formula 4 wherein e represents all input vectors, y represents an objective variable, a represents a Lagrange's undetermined multiplier vector, Q represents a positive definite matrix, and C represents a parameter for adjusting constrained conditions.

Formula 4

$$\min_a \frac{1}{2}a^T Q a - e^T a$$

$$\text{subject to } y^T a = 0,\ 0 \le a_i \le C,\ i = 1, \ldots, l,$$

Formula 5 is a finally obtained discriminant, and a group to which the data point is associated can be determined on the basis of the sign of a value obtained according to the discriminant. In this formula, x represents a support vector, y represents a label indicating the associated group, a represents the corresponding coefficient, b represents a constant term, and K represents a kernel function.

Formula 5

$$f(x) = sgn\left(\sum_{i=1}^{l} y_i a_i K(x_i, x) + b\right)$$

For example, a RBF kernel defined by Formula 6 can be used as the kernel function. In this formula, x represents a support vector, and γ represents a kernel parameter for adjusting the complexity of the hyperplane.

$$K(x_i,x_j)=\exp(-r\|x_i-x_j\|^2),\ r<0$$ Formula 6

In addition, an approach such as neural network, k-nearest neighbor algorithms, decision trees, or logistic regression analysis can be selected as a method for determining or evaluating the presence and/or absence of expression of a biliary tract cancer-derived target gene in a sample derived from a subject, or for evaluating the expression level thereof by comparison with a control derived from a healthy subject.

The method of the present invention can comprise, for example, the following steps (a), (b), and (c):

(a) measuring an expression level of a target gene in tissues containing biliary tract cancer-derived genes derived from biliary tract cancer patients and/or samples that are already known to contain no biliary tract cancer-derived gene derived from healthy subjects, using the polynucleotide, the kit, or the device (e.g., DNA chip) for detection according to the present invention:

(b) preparing the discriminants of Formulas 1 to 3, 5, and 6 described above from the measurement values of the expression level measured in the step (a); and

(c) measuring an expression level of the target gene in a sample derived from a subject using the polynucleotide, the kit, or the device (e.g., DNA chip) for detection according to the present invention, substituting the measurement value into the discriminants prepared in the step (b), and determining or evaluating the presence and/or absence of the biliary tract cancer-derived target gene in the sample, or evaluating the expression level thereof by comparison with a healthy subject-derived control, on the basis of the obtained results. In this context, in the discriminants of Formulas 1 to 3, 5, and 6, x represents an explanatory variable and includes a value obtained by measuring a polynucleotide selected from the polynucleotides described above in Section 2, or a fragment thereof, etc. Specifically, the explanatory variable for discriminating a biliary tract cancer patient from a healthy subject according to the present invention is a gene expression level selected from, for example, the following expression levels (1) to (2):

(1) a gene expression level in the serum of a biliary tract cancer patient or a healthy subject measured by any DNA comprising 15 or more consecutive nucleotides in a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478 or a complementary sequence thereof, and

(2) a gene expression level in the serum of a biliary tract cancer patient or a healthy subject measured by any DNA comprising 15 or more consecutive nucleotides in a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a complementary sequence thereof.

As described above, for the method for determining or evaluating the presence and/or absence of a biliary tract cancer-derived gene in a sample derived from a subject, the preparation of a discriminant requires a discriminant prepared in a training cohort. For enhancing the discrimination accuracy of the discriminant, it is necessary for the discriminant to use genes that show clear difference between two groups in the training cohort when preparing the discriminant.

Each gene that is used for an explanatory variable in a discriminant is preferably determined as follows. First, comprehensive gene expression levels of a biliary tract cancer patient group and comprehensive gene expression levels of a healthy subject group, both of which are in a training cohort, are used as a data set, the degree of difference in the expression level of each gene between the two groups is determined through the use of, for example, the P value of t test, which is parametric analysis, or the P value of Mann-Whitney's U test or Wilcoxon test, which is nonparametric analysis.

The gene can be regarded as being statistically significant when the critical rate (significance level) of the P value obtained by the test is smaller than, for example, 5%, 1%, or 0.01%.

In order to correct an increased probability of type I error attributed to the repetition of a test, a method known in the art, for example, Bonferroni or Holm method, can be used for the correction (e.g., Yasushi Nagata et al., "Basics of statistical multiple comparison methods", Scientist Press Co., Ltd. (2007)). As an example of the Bonferroni correction, for example, the P value obtained by a test is multiplied by the number of repetitions of the test, i.e., the number of genes used in the analysis, and the obtained value can be compared with a desired significance level to suppress a probability of causing type I error in the whole test.

Instead of the test, the absolute value (fold change) of an expression ratio of a median value of each gene expression level between gene expression levels of a biliary tract cancer patient group and gene expression levels of a healthy subject group may be calculated to select a gene that is used for an explanatory variable in a discriminant. Alternatively, ROC curves may be prepared using gene expression levels of a biliary tract cancer patient group and a healthy subject group, and a gene that is used for an explanatory variable in a discriminant can be selected on the basis of an AUROC value.

Next, a discriminant that can be calculated by various methods described above is prepared using any number of genes having large difference in their gene expression levels determined here. Examples of the method for constructing a discriminant that produces the largest discrimination accuracy include a method of constructing a discriminant in every combination of genes that satisfy the significance level being a P value, and a method of repetitively evaluating the genes for use in the construction of a discriminant while increasing the number of genes one by one in a descending order of difference in gene expression level (Furey T S. et al., 2000, Bioinformatics., Vol. 16, p. 906-14). A gene expression level of another independent biliary tract cancer patient or healthy subject is substituted as an explanatory variable into this discriminant to calculate discrimination results of the group to which this independent biliary tract cancer patient or healthy subject is associated. Specifically, the found gene set for diagnosis and the discriminant constructed using the gene set for diagnosis can be evaluated in an independent sample cohort to find a more universal gene set for diagnosis capable of detecting biliary tract cancer and a more universal method for discriminating biliary tract cancer.

Split-sample method is preferably used for evaluating the discriminant performance (generality) of the discriminant. Specifically, a data set is divided into a training cohort and a validation cohort, and gene selection by a statistical test and discriminant preparation are performed using the training cohort. To evaluate the performance of the discriminant, accuracy, sensitivity, and specificity are calculated using a result of discriminant analysis in a validation cohort according to the discriminant and a true group to which the validation cohort is associated. On the other hand, instead of dividing a data set, the gene selection by a statistical test and discriminant preparation may be performed using all of samples, and accuracy, sensitivity, and specificity can be calculated by the discriminant analysis using a newly prepared sample cohort for evaluation of the performance of the discriminant.

The present invention provides a polynucleotide for detection or for disease diagnosis useful in the diagnosis and treatment of biliary tract cancer, a method for detecting biliary tract cancer using the polynucleotide, and a kit and a device for the detection of biliary tract cancer, comprising the polynucleotide. Particularly, in order to select a gene for diagnosis and prepare a discriminant so as to exhibit accuracy beyond a biliary tract cancer diagnostic method using existing tumor markers CEA and CA19-9, a gene set for diagnosis and a discriminant for the method of the present invention can be constructed, which exhibit accuracy beyond CEA and CA19-9, for example, by comparing expressed genes in serum derived from a patient confirmed to be negative using CEA and CA19-9 but finally found to have biliary tract cancer by detailed examination such as computed tomography using a contrast medium, with genes expressed in serum derived from a patient having no biliary tract cancer.

For example, the gene set for diagnosis is set to any combination selected from one or two or more of the polynucleotides based on a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 and 466 to 478 or a complementary sequence thereof as described above; and optionally one or two or more of the polynucleotides based on a nucleotide sequence represented by any of SEQ ID NOs: 126 to 148 or a complementary sequence thereof. Further, a discriminant is constructed using expression levels of the gene set for diagnosis in samples derived from class I biliary tract cancer patients as a result of tissue diagnosis and samples derived from class II healthy subjects as a result of tissue diagnosis. As a result, the presence or absence of biliary tract cancer-derived genes in an unknown sample can be determined with 100% accuracy at the maximum by measuring expression levels of the gene set for diagnosis in an unknown sample.

EXAMPLES

Hereinafter, the present invention is described further specifically with reference to Examples below. However, the scope of the present invention is not intended to be limited by these Examples.

Reference Example 1

<Collection of Samples from Biliary Tract Cancer Patients and Healthy Subjects>

Sera were collected using VENOJECT II vacuum blood collecting tube VP-AS109K60 (Terumo Corp.) from 100 healthy subjects and 67 biliary tract cancer patients (1 case with stage IA, 8 cases with stage IB, 8 cases with stage II, 3 cases with stage IIA, 5 cases with stage IIB, 14 cases with stage III, 2 cases with stage IIIB, 1 case with stage IVa, and 25 cases with stage IVb) confirmed to have no primary cancer in organs other than the biliary tract after acquisition of informed consent, and used as a training cohort. Likewise, sera were collected using VENOJECT II vacuum blood collecting tube VP-AS109K60 (Terumo Corp.) from 50 healthy subjects and 33 biliary tract cancer patients (1 case with stage 0, 2 cases with stage I, 1 case with stage IA, 2 cases with stage IB, 2 cases with stage II, 5 cases with stage IIA, 4 cases with stage IIB, 5 cases with stage III, 1 case with stage IV, 1 case with stage IVa, and 9 cases with stage IVb) confirmed to have no primary cancer in organs other than biliary tract after acquisition of informed consent, and used as a validation cohort.

<Extraction of Total RNA>

Total RNA was obtained from 300 μL of the serum sample obtained from each of 250 persons in total of 150 healthy subjects and 100 biliary tract cancer patients included in the training cohort and the validation cohort, using a reagent for RNA extraction in 3D-Gene® RNA extraction reagent from liquid sample kit (Toray Industries, Inc.) according to the protocol provided by the manufacturer.

<Measurement of Gene Expression Level>

miRNAs in the total RNA obtained from the serum samples of each of 250 persons in total of 150 healthy subjects and 100 biliary tract cancer patients included in the training cohort and the validation cohort were fluorescently labeled using 3D-Gene® miRNA Labeling kit (Toray Industries, Inc.) according to the protocol (ver. 2.20) provided by the manufacturer. The oligo DNA chip used was 3D-Gene® Human miRNA Oligo chip (Toray Industries, Inc.) with attached probes having sequences complementary to 2,555 miRNAs among the miRNAs registered in miRBase Release 20. Hybridization between the miRNAs in the total RNA and the probes on the DNA chip under stringent conditions and washing following the hybridization were performed according to the protocol provided by the manufacturer. The DNA chip was scanned using 3D-Gene® scanner (Toray Industries, Inc.) to obtain images. Fluorescence intensity was digitized using 3D-Gene® Extraction (Toray Industries, Inc.). The digitized fluorescence intensity was converted to a logarithmic value having a base of 2 and used as a gene expression level, from which a blank value was subtracted. A missing value was replaced with a value obtained by subtracting 0.1 from a logarithmic value of the smallest value of the gene expression level in each DNA chip. As a result, the comprehensive gene expression levels of the miRNAs in the sera were obtained for the 100 biliary tract cancer patients and the 150 healthy subjects. Calculation and statistical analysis using the digitized gene expression levels of the miRNAs were carried out using R language 3.0.2 (R Development Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, URL http://www.R-project.org/.) and MASS package 7.3-30 (Venables. W. N. & Ripley, B. D. (2002) Modem Applied Statistics with S. Fourth Edition. Springer, New York. ISBN 0-387-95457-0).

Reference Example 2

<Collection of Samples from Patients with other Cancers and Benign Diseases>

Sera were collected using VENOJECT II vacuum blood collecting tube VP-AS109K60 (Terumo Corp.) from each of 35 colorectal cancer patients, 37 stomach cancer patients, 32 esophageal cancer patients, 38 liver cancer patients, and 13 benign pancreaticobiliary disease patients confirmed to have no cancer in other organs after acquisition of informed consent, and used as a training cohort together with the samples of 67 biliary tract cancer patients (1 case with stage 0, 2 cases with stage I, 1 case with stage IA, 4 cases with stage IB, 8 cases with stage II, 4 cases with stage IIA, 6 cases with stage IIB, 14 cases with stage III, 1 case with stage IIIB, 25 cases with stage IV, and 1 case with stage IVa) and 93 healthy subjects of Reference Example 1. Likewise, sera were collected using VENOJECT II vacuum blood collecting tube VP-AS109K60 (Terumo Corp.) from each of 15 colorectal cancer patients, 13 stomach cancer patients, 18 esophageal cancer patients, 12 liver cancer patients, and 8 benign pancreaticobiliary disease patients confirmed to have no cancer in other organs after acquisition of informed consent, and used as a validation cohort together with the samples of 33 biliary tract cancer patients (1 case with stage IA, 6 cases with stage IB, 2 cases with stage II, 4 cases with stage IIA, 3 cases with stage IIB, 5 cases with stage III, 1 case with stage IIIB, and 11 cases with stage IV) and 57 healthy subjects of Reference Example 1. Subsequent extraction of total RNA and measurement and analysis of gene expression levels were conducted in the same way as in Reference Example 1.

Example 1

<Selection of Gene Marker using Samples in the Training Cohort, and Method for Evaluating Cancer Discriminant Performance of Single Gene Marker using Samples in the Validation Cohort>

In this Example, a gene marker for discriminating a biliary tract cancer patient from a healthy subject was selected from the training cohort, and a method for evaluating biliary tract cancer discriminant performance of each selected gene marker alone was studied in samples of the validation cohort independent from the training cohort.

Specifically, first, the miRNA expression levels of the training cohort and the validation cohort obtained in Reference Example 1 above were combined and normalized by quantile normalization.

Next, genes for diagnosis were selected using the training cohort. Here, in order to acquire diagnostic markers with higher reliability, only genes having the gene expression level of 2^6 or higher in 50% or more of the samples in either of the biliary tract cancer patient group in the training cohort or the healthy subject group in the training cohort were selected. In order to further acquire statistically significant genes for discriminating a biliary tract cancer patient group from a healthy subject group, the P value obtained by two-tailed t-test assuming equal variance as to each gene expression level was corrected by the Bonferroni method, and genes that satisfied $p<0.01$ were acquired as gene markers for use in explanatory variables of a discriminant. The obtained genes are described in Table 2.

In this way, hsa-miR-125a-3p, hsa-miR-6893-5p, hsa-miR-204-3p, hsa-miR-4476, hsa-miR-4294, hsa-miR-150-3p, hsa-miR-6729-5p, hsa-miR-7641, hsa-miR-6765-3p, hsa-miR-6820-5p, hsa-miR-575, hsa-miR-6836-3p, hsa-miR-1469, hsa-miR-663a, hsa-miR-6075, hsa-miR-4634, hsa-miR-423-5p, hsa-miR-4454, hsa-miR-7109-5p, hsa-miR-6789-5p, hsa-miR-6877-5p, hsa-miR-4792, hsa-miR-4530, hsa-miR-7975, hsa-miR-6724-5p, hsa-miR-8073, hsa-miR-7977, hsa-miR-1231, hsa-miR-6799-5p, hsa-miR-615-5p, hsa-miR-4450, hsa-miR-6726-5p, hsa-miR-6875-5p, hsa-miR-4734, hsa-miR-16-5p, hsa-miR-602, hsa-miR-4651, hsa-miR-8069, hsa-miR-1238-5p, hsa-miR-6880-5p, hsa-miR-8072, hsa-miR-4723-5p, hsa-miR-4732-5p, hsa-miR-6125, hsa-miR-6090, hsa-miR-7114-5p, hsa-miR-564, hsa-miR-451a, hsa-miR-3135b, hsa-miR-4497, hsa-miR-4665-5p, hsa-miR-3622a-5p, hsa-miR-6850-5p, hsa-miR-6821-5p, hsa-miR-5100, hsa-miR-6872-3p, hsa-miR-4433-3p, hsa-miR-1227-5p, hsa-miR-3188, hsa-miR-7704, hsa-miR-3185, hsa-miR-1908-3p, hsa-miR-6781-5p, hsa-miR-6805-5p, hsa-miR-8089, hsa-miR-665, hsa-miR-4486, hsa-miR-6722-3p, hsa-miR-1260a, hsa-miR-4707-5p, hsa-miR-6741-5p, hsa-miR-1260b, hsa-miR-1246, hsa-miR-6845-5p, hsa-miR-4638-5p, hsa-miR-6085, hsa-miR-1228-3p, hsa-miR-4534, hsa-miR-5585-3p, hsa-miR-4741, hsa-miR-4433b-3p, hsa-miR-197-5p, hsa-miR-718, hsa-miR-4513, hsa-miR-4446-3p, hsa-miR-619-5p, hsa-miR-6816-5p, hsa-miR-6778-5p, hsa-miR-24-3p, hsa-miR-1915-3p, hsa-miR-4665-3p, hsa-miR-4449, hsa-miR-6889-5p, hsa-miR-486-3p, hsa-miR-7113-3p, hsa-miR-642a-3p, hsa-miR-7847-3p, hsa-miR-6768-5p, hsa-miR-1290, hsa-miR-7108-5p, hsa-miR-92b-5p, hsa-miR-663b, hsa-miR-3940-5p, hsa-miR-4467, hsa-miR-6858-5p, hsa-miR-4417, hsa-miR-3665, hsa-miR-4736, hsa-miR-4687-3p, hsa-miR-1908-5p, hsa-miR-5195-3p, hsa-miR-4286, hsa-miR-3679-3p, hsa-miR-6791-5p, hsa-miR-1202, hsa-miR-3656, hsa-miR-4746-3p, hsa-miR-3184-5p, hsa-miR-3937, hsa-miR-6515-3p, hsa-miR-6132, hsa-miR-187-5p, hsa-miR-7111-5p, hsa-miR-5787 and hsa-miR-6779-5p genes represented by SEQ ID NOs: 1 to 125 related thereto were found as biliary tract cancer markers relative to the healthy subjects.

A discriminant for determining the presence or absence of biliary tract cancer was further prepared by Fisher's linear discriminant analysis with the expression levels of these genes as an indicator. Specifically, any newly found polynucleotide consisting of a nucleotide sequence represented by any of SEQ ID NOs: 1 to 125 among the 125 genes selected in the training cohort was applied to Formula 2 to construct a discriminant. Calculated accuracy, sensitivity, and specificity are shown in Table 3. In this respect, a discriminant coefficient and a constant term are shown in Table 4.

Accuracy, sensitivity, and specificity in the validation cohort were calculated using the discriminant thus prepared, and the discriminant performance of the selected polynucleotides was validated using the independent samples (Table 3). For example, the expression level measurement value of the nucleotide sequence represented by SEQ ID NO: 1 was compared between the healthy subjects (100 persons) and the biliary tract cancer patients (67 persons) in the training cohort. As a result, the gene expression level measurement values were found to be significantly lower in the biliary cancer patient group than in the healthy subject group (see the left diagram of FIG. **2**). These results were also reproducible in the healthy subjects (50 persons) and the biliary tract cancer patients (33 persons) in the validation cohort (see the right diagram of FIG. **2**). Likewise, the results obtained about the other polynucleotides shown in SEQ ID NOs: 2 to 125 showed that the gene expression level measurement values were significantly lower (−) or higher (+) in the biliary tract cancer patient group than in the healthy subject group (Table 2). These results were able to be validated in the validation cohort. For example, as for this nucleotide sequence represented by SEQ ID NO: 1, the number of correctly identified samples in the detection of biliary tract cancer was calculated using the threshold (5.69) that was set in the training cohort and discriminated between the two groups. As a result, 33 true positives, 49 true negatives, 1 false positive, and 0 false negatives were obtained. From these values, 99% accuracy, 100% sensitivity, and 98% specificity were obtained as the detection performance. In this way, the detection performance was calculated as to all of the polynucleotides shown in SEQ ID NOs: 1 to 125, and described in Table 3.

Among the polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1 to 125 shown in Table 2, for example, 62 polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 34, 35, 36, 39, 40, 41, 42, 44, 45, 46, 47, 49, 50, 51, 52, 53, 54, 60, 62, 64, 65, 67, 68, 70, 74, 75, 76, 83, 84, 105, 107 exhibited sensitivity of 100%, 97%, 97%, 100%, 84.8%, 90.9%, 87.9%, 90.9%, 66.7%, 87.9%, 93.9%, 75.8%, 72.7%, 72.7%, 75.8%, 63.6%, 78.8%, 75.8%, 69.7%, 72.7%, 72.7%, 69.7%, 93.9%, 66.7%, 63.6%, 69.7%, 69.7%, 78.8%, 75.8%, 72.7%, 78.8%, 81.8%, 66.7%, 60.6%, 60.6%, 72.7%, 66.7%, 60.6%, 63.6%, 81.8%, 60.6%, 69.7%, 60.6%, 78.8%, 69.7%, 63.6%, 63.6%, 60.6%, 72.7%, 63.6%, 72.7%, 72.7%, 63.6%, 66.7%, 60.6%, 60.6%, 63.6%, 63.6%, 69.7%, 63.6%, 69.7%, 60.6%, respectively, in the validation cohort (Table 3). As seen from Comparative Example mentioned later, the existing markers CEA and CA19-9 had sensitivity of 33.3% and 59.4%, respectively, in the validation cohort (Table 5), demonstrating that, for example, the 62 polynucleotides consisting of the nucleotide sequences represented by SEQ ID Nos: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 34, 35, 36, 39, 40, 41, 42, 44, 45, 46, 47, 49, 50, 51, 52, 53, 54, 60, 62, 64, 65, 67, 68, 70, 74, 75, 76, 83, 84, 105, 107 can discriminate, each alone, biliary tract cancer in the validation cohort with sensitivity beyond the existing tumor marker CA19-9 in blood.

For example, the 9 polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1, 2, 3, 4, 10, 11, 12, 23, and 64 were able to correctly discriminate biliary tract cancer for all of the 6 biliary tract cancer samples of stages 0 and 1 (including IA and IB) contained in the validation cohort. Thus, these polynucleotides can detect even early biliary tract cancer and contribute to the early diagnosis of biliary tract cancer.

Furthermore, these polynucleotides were able to correctly discriminate biliary tract cancer for all of the tumors occupying the extrahepatic bile duct, the intrahepatic bile duct, the gallbladder, or the papilla of the biliary tract in the validation cohort. Particularly, the polynucleotides were able to detect cancer of the lower bile duct or the papilla which reportedly has poor prognosis, and cancer in the intrahepatic bile duct which tends to progress asymptomatically.

Example 2

<Method for Evaluating Biliary Tract Cancer Discriminant Performance by Combination of Multiple Gene Markers using Samples in the Validation Cohort>

In this Example, a method for evaluating biliary tract cancer discriminant performance by a combination of the gene markers selected in Example 1 was studied. Specifically, Fisher's linear discriminant analysis was conducted as to 7,750 combinations of any two of the expression level measurement values of the polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1 to 125 selected in Example 1, to construct a discriminant for determining the presence or absence of biliary tract cancer. Next, accuracy, sensitivity, and specificity in the validation cohort were calculated using the discriminant thus prepared, and the discriminant performance of the selected polynucleotides was validated using the independent samples. The biliary tract cancer discrimination in the validation cohort was carried out using the 7,750 combinations of the expression level measurement values of the polynucleotides. For example, the expression level measurement values of the polynucleotides consisting of the nucleotide sequences represented by SEQ ID NO: 2 and SEQ ID NO: 4 were compared between the healthy subjects (50 persons) and the biliary tract cancer patients (33 persons) in the validation cohort. As a result, a scatter diagram that significantly separated the expression level measurement values of the biliary tract cancer patient group from those of the healthy subject group was obtained in the training cohort (see the left diagram of FIG. **3**). These results were also reproducible in the validation cohort (see the right diagram of FIG. **3**). Likewise, a scatter diagram that significantly separated the expression level measurement values of the biliary tract cancer patient group from those of the healthy subject group was also obtained as to the other combinations of any two of the expression level measurement values of the newly found polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1 to 125. These results were able to be validated in the validation cohort. For example, as for these nucleotide sequences represented by SEQ ID NO: 2 and SEQ ID NO: 4, the number of samples that were correctly or incorrectly identified as biliary tract cancer was calculated using the function ($0=5.16x+y+48.11$) that was set in the training cohort and discriminated between the two groups. As a result, 33 true positives, 48 true negatives, 2 false positives, and 0 false negatives were obtained. From these values, 98% accuracy, 100% sensitivity, and 96% specificity were obtained as the detection performance. In this way, the detection performance was calculated for all combinations of any two of the expression level measurement values of the newly found polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1 to 125. Among them, 124 combinations of the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 1 with polynucleotides consisting of nucleotide sequences represented by the other SEQ ID NOs and their detection performance are described in Table 6 as an example. For example, all of the combinations of the expression level measurement values of the polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1 and 7, SEQ ID NOs: 1 and 9, SEQ ID NOs: 1 and 25, and SEQ ID NOs: 1 and 66 also exhibited sensitivity of 100% in the validation cohort. In this way, 6,316 combinations of the expression level measurement values of the polynucleotides having sensitivity beyond the existing marker CA19-9 (75.8% in Table 5) were obtained in the validation cohort. All of the nucleotide sequences 1 to 125 described in Table 2 obtained in Example 1 were employed at least once in these combinations. These results demonstrated that the combinations of any two of the expression level measurement values of the polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1 to 125 can discriminate biliary tract cancer with sensitivity beyond CA19-9 in the validation cohort.

Among the 7,750 combinations of any two of the expression level measurement values of the polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1 to 125, 1,290 combinations of two of the expression level measurement values were able to correctly discriminate biliary tract cancer for all of the 6 biliary tract cancer samples of stages 0 and 1 (including IA and IB) contained in the validation cohort. The polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1 to 125 were employed at least once in these 1,290 combinations of two thereof. Thus, these polynucleotides can detect even early biliary tract cancer and contribute to the early diagnosis of biliary tract cancer.

Thus, markers capable of detecting biliary tract cancer with excellent sensitivity are obtained even if 3, 4, 5, 6, 7, 8, 9, 10 or more of the expression level measurement values of the polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1 to 125 are combined. For example, the polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1 to 125 selected in Example 1 were ranked in the descending order of their P values which indicate statistical significance, and detection performance was calculated using combinations of one or more miRNAs to which the miRNAs were added one by one from the top to the bottom according to the rank. As a result, the sensitivity in the validation cohort was 100% for 1 miRNA, 100% for 2 miRNAs, 100% for 3 miRNAs, 100% for 5 miRNAs, 100% for 10 miRNAs, 100% for 20 miRNAs, 100% for 50 miRNAs, and 100% for 100 miRNAs. These values of the sensitivity were higher than the sensitivity of the existing tumor marker in blood, demonstrating that even combinations of the multiple miRNAs can serve as excellent markers for the detection of biliary tract cancer. In this context, the combinations of the multiple miRNAs are not limited to the combinations of the miRNAs added in the order of statistically significant difference as described above, and any combination of the multiple miRNAs can be used in the detection of biliary tract cancer.

From these results, it can be concluded that all of the polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1 to 125 serve as excellent diagnostic markers for biliary tract cancer.

TABLE 2

SEQ ID NO:	Gene name	P value after Bonferroni correction	Expression level in biliary tract cancer patient relative to healthy subject
1	hsa-miR-125a-3p	7.84E−45	−
2	hsa-miR-6893-5p	7.26E−41	−
3	hsa-miR-204-3p	3.07E−40	−
4	hsa-miR-4476	1.71E−29	−
5	hsa-miR-4294	4.27E−29	−

TABLE 2-continued

SEQ ID NO:	Gene name	P value after Bonferroni correction	Expression level in biliary tract cancer patient relative to healthy subject
6	hsa-miR-150-3p	7.62E−29	−
7	hsa-miR-6729-5p	3.45E−27	+
8	hsa-miR-7641	3.59E−27	−
9	hsa-miR-6765-3p	1.23E−26	−
10	hsa-miR-6820-5p	1.94E−26	−
11	hsa-miR-575	3.20E−22	−
12	hsa-miR-6836-3p	6.22E−22	+
13	hsa-miR-1469	3.82E−21	+
14	hsa-miR-663a	3.20E−20	+
15	hsa-miR-6075	3.39E−19	+
16	hsa-miR-4634	3.45E−19	+
17	hsa-miR-423-5p	6.05E−19	−
18	hsa-miR-4454	1.09E−18	−
19	hsa-miR-7109-5p	4.48E−17	−
20	hsa-miR-6789-5p	5.28E−17	+
21	hsa-miR-6877-5p	1.97E−16	−
22	hsa-miR-4792	5.75E−16	+
23	hsa-miR-4530	1.17E−15	−
24	hsa-miR-7975	1.25E−15	−
25	hsa-miR-6724-5p	2.90E−15	+
26	hsa-miR-8073	6.32E−15	+
27	hsa-miR-7977	7.95E−15	−
28	hsa-miR-1231	1.10E−14	+
29	hsa-miR-6799-5p	7.45E−14	−
30	hsa-miR-615-5p	1.20E−13	−
31	hsa-miR-4450	1.31E−13	−
32	hsa-miR-6726-5p	6.23E−13	−
33	hsa-miR-6875-5p	9.36E−13	+
34	hsa-miR-4734	1.18E−12	+
35	hsa-miR-16-5p	1.44E−12	−
36	hsa-miR-602	2.13E−12	+
37	hsa-miR-4651	3.44E−12	−
38	hsa-miR-8069	3.87E−12	+
39	hsa-miR-1238-5p	4.47E−12	+
40	hsa-miR-6880-5p	6.68E−12	−
41	hsa-miR-8072	8.97E−12	+
42	hsa-miR-4723-5p	1.09E−11	−
43	hsa-miR-4732-5p	1.18E−11	+
44	hsa-miR-6125	2.42E−11	+
45	hsa-miR-6090	5.45E−11	+
46	hsa-miR-7114-5p	6.03E−11	−
47	hsa-miR-564	7.38E−11	−
48	hsa-miR-451a	1.34E−10	−
49	hsa-miR-3135b	1.77E−10	−
50	hsa-miR-4497	2.01E−10	−
51	hsa-miR-4665-5p	2.05E−10	−
52	hsa-miR-3622a-5p	2.06E−10	−
53	hsa-miR-6850-5p	4.73E−10	+
54	hsa-miR-6821-5p	1.08E−09	−
55	hsa-miR-5100	1.24E−09	−
56	hsa-miR-6872-3p	1.30E−09	−
57	hsa-miR-4433-3p	1.82E−09	+
58	hsa-miR-1227-5p	2.00E−09	+
59	hsa-miR-3188	2.76E−09	+
60	hsa-miR-7704	2.85E−09	−
61	hsa-miR-3185	5.63E−09	+
62	hsa-miR-1908-3p	1.55E−08	+
63	hsa-miR-6781-5p	4.49E−08	+
64	hsa-miR-6805-5p	5.45E−08	+
65	hsa-miR-8089	5.74E−08	−
66	hsa-miR-665	6.09E−08	+
67	hsa-miR-4486	8.43E−08	+
68	hsa-miR-6722-3p	2.27E−07	+
69	hsa-miR-1260a	2.91E−07	−
70	hsa-miR-4707-5p	4.82E−07	+
71	hsa-miR-6741-5p	5.45E−07	−
72	hsa-miR-1260b	6.63E−07	−
73	hsa-miR-1246	8.89E−07	+
74	hsa-miR-6845-5p	1.00E−06	+
75	hsa-miR-4638-5p	1.20E−06	−
76	hsa-miR-6085	1.41E−06	−
77	hsa-miR-1228-3p	1.80E−06	+
78	hsa-miR-4534	3.19E−06	−
79	hsa-miR-5585-3p	3.47E−06	+
80	hsa-miR-4741	6.41E−06	+
81	hsa-miR-4433b-3p	1.18E−05	+
82	hsa-miR-197-5p	1.68E−05	+
83	hsa-miR-718	1.86E−05	+
84	hsa-miR-4513	2.50E−05	−
85	hsa-miR-4446-3p	2.73E−05	+
86	hsa-miR-619-5p	4.93E−05	+
87	hsa-miR-6816-5p	5.01E−05	+
88	hsa-miR-6778-5p	5.27E−05	+
89	hsa-miR-24-3p	7.57E−05	−
90	hsa-miR-1915-3p	8.30E−05	+
91	hsa-miR-4665-3p	8.98E−05	+
92	hsa-miR-4449	1.08E−04	+
93	hsa-miR-6889-5p	1.20E−04	−
94	hsa-miR-486-3p	1.44E−04	+
95	hsa-miR-7113-3p	1.47E−04	+
96	hsa-miR-642a-3p	1.54E−04	−
97	hsa-miR-7847-3p	1.63E−04	−
98	hsa-miR-6768-5p	1.79E−04	−
99	hsa-miR-1290	2.46E−04	+
100	hsa-miR-7108-5p	3.53E−04	+
101	hsa-miR-92b-5p	4.71E−04	+
102	hsa-miR-663b	5.05E−04	+
103	hsa-miR-3940-5p	5.20E−04	+
104	hsa-miR-4467	7.73E−04	+
105	hsa-miR-6858-5p	8.31E−04	+
106	hsa-miR-4417	8.55E−04	+
107	hsa-miR-3665	1.00E−03	+
108	hsa-miR-4736	1.42E−03	+
109	hsa-miR-4687-3p	1.53E−03	−
110	hsa-miR-1908-5p	1.64E−03	+
111	hsa-miR-5195-3p	1.91E−03	−
112	hsa-miR-4286	2.65E−03	−
113	hsa-miR-3679-3p	2.91E−03	+
114	hsa-miR-6791-5p	2.94E−03	+
115	hsa-miR-1202	3.05E−03	−
116	hsa-miR-3656	3.57E−03	+
117	hsa-miR-4746-3p	4.03E−03	+
118	hsa-miR-3184-5p	4.73E−03	+
119	hsa-miR-3937	5.41E−03	+
120	hsa-miR-6515-3p	6.16E−03	+
121	hsa-miR-6132	6.37E−03	−
122	hsa-miR-187-5p	7.26E−03	−
123	hsa-miR-7111-5p	7.97E−03	−
124	hsa-miR-5787	8.07E−03	−
125	hsa-miR-6779-5p	8.44E−03	−

TABLE 3

	Training cohort			Validation cohort		
SEQ ID NO:	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
1	97	94	99	98.8	100	98
2	95.2	91	98	96.4	97	96
3	92.2	83.6	98	92.8	97	90
4	86.2	79.1	91	91.6	100	86
5	88.6	79.1	95	88	84.8	90
6	86.8	80.6	91	81.9	90.9	76
7	86.2	80.6	90	86.7	87.9	86
8	85	82.1	87	89.2	90.9	88
9	88.6	80.6	94	84.3	66.7	96
10	88	79.1	94	86.7	87.9	86
11	88.6	77.6	96	91.6	93.9	90
12	85.6	74.6	93	84.3	75.8	90
13	85.6	71.6	95	83.1	72.7	90
14	82	61.2	96	88	72.7	98
15	83.2	61.2	98	90.4	75.8	100
16	82.6	77.6	86	74.7	63.6	82
17	81.4	67.2	91	79.5	78.8	80
18	81.4	68.7	90	84.3	75.8	90

TABLE 3-continued

	Training cohort			Validation cohort		
SEQ ID NO:	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
19	78.4	70.1	84	75.9	69.7	80
20	82	73.1	88	80.7	72.7	86
21	81.4	70.1	89	80.7	72.7	86
22	82	71.6	89	81.9	69.7	90
23	80.2	70.1	87	86.7	93.9	82
24	74.3	56.7	86	81.9	66.7	92
25	78.4	68.7	85	74.7	63.6	82
26	80.2	65.7	90	81.9	69.7	90
27	78.4	61.2	90	81.9	69.7	90
28	82.6	68.7	92	81.9	78.8	84
29	76.6	67.2	83	80.7	75.8	84
30	77.2	71.6	81	77.1	72.7	80
31	79.6	61.2	92	80.7	78.8	82
32	77.2	55.2	92	75.9	54.5	90
33	74.3	61.2	83	72.3	57.6	82
34	75.4	68.7	80	81.9	81.8	82
35	80.8	64.2	92	81.9	66.7	92
36	74.9	64.2	82	74.7	60.6	84
37	77.2	55.2	92	78.3	54.5	94
38	78.4	61.2	90	79.5	57.6	94
39	79	55.2	95	81.9	60.6	96
40	79.6	65.7	89	83.1	72.7	90
41	79.6	65.7	89	73.5	66.7	78
42	77.8	58.2	91	77.1	60.6	88
43	79	58.2	93	74.7	51.5	90
44	76	64.2	84	77.1	63.6	86
45	73.7	70.1	76	74.7	81.8	70
46	73.1	56.7	84	79.5	60.6	92
47	80.8	59.7	95	81.9	69.7	90
48	80.2	59.7	94	78.3	57.6	92
49	80.8	70.1	88	78.3	60.6	90
50	75.4	59.7	86	77.1	78.8	76
51	76.6	61.2	87	77.1	69.7	82
52	76	46.3	96	77.1	63.6	86
53	76	62.7	85	73.5	63.6	80
54	73.7	59.7	83	67.5	60.6	72
55	77.2	56.7	91	77.1	57.6	90
56	73.7	58.2	84	73.5	57.6	84
57	74.9	65.7	81	68.7	51.5	80
58	74.3	53.7	88	77.1	57.6	90
59	79.6	65.7	89	77.1	51.5	94
60	78.4	71.6	83	71.1	72.7	70
61	74.3	56.7	86	73.5	51.5	88
62	75.4	52.2	91	78.3	63.6	88
63	73.7	64.2	80	71.1	57.6	80
64	74.9	59.7	85	79.5	72.7	84
65	76	64.2	84	78.3	72.7	82
66	75.4	53.7	90	79.5	57.6	94
67	70.1	50.7	83	78.3	63.6	88
68	71.9	52.2	85	75.9	66.7	82
69	71.3	52.2	84	74.7	54.5	88
70	73.1	53.7	86	77.1	60.6	88
71	76.6	58.2	89	75.9	57.6	88
72	71.9	46.3	89	77.1	57.6	90
73	75.4	53.7	90	73.5	48.5	90
74	72.5	47.8	89	75.9	60.6	86
75	75.4	52.2	91	78.3	63.6	88
76	73.1	55.2	85	71.1	63.6	76
77	71.9	53.7	84	69.9	54.5	80
78	75.4	55.2	89	71.1	48.5	86
79	73.7	50.7	89	78.3	51.5	96
80	68.9	50.7	81	69.9	51.5	82
81	72.5	58.2	82	62.7	42.4	76
82	70.1	43.3	88	72.3	51.5	86
83	70.7	52.2	83	75.9	69.7	80
84	71.3	46.3	88	74.7	63.6	82
85	70.7	44.8	88	69.9	42.4	88
86	70.1	40.3	90	72.3	36.4	96
87	68.3	49.3	81	65.1	39.4	82
88	70.7	43.3	89	73.5	45.5	92
89	71.9	44.8	90	75.9	39.4	100
90	71.9	53.7	84	71.1	39.4	92
91	72.5	49.3	88	68.7	51.5	80
92	73.1	44.8	92	72.3	42.4	92
93	67.1	47.8	80	71.1	51.5	84
94	71.3	46.3	88	68.7	45.5	84
95	69.5	50.7	82	74.7	48.5	92
96	69.5	44.8	86	69.5	43.8	86
97	71.3	52.2	84	65.1	45.5	78
98	69.5	40.3	89	74.7	57.6	86
99	71.9	49.3	87	73.5	48.5	90
100	71.3	44.8	89	67.5	36.4	88
101	65.3	34.3	86	69.9	33.3	94
102	68.9	43.3	86	70.7	46.9	86
103	70.7	44.8	88	63.9	33.3	84
104	65.9	40.3	83	69.9	45.5	86
105	70.7	47.8	86	79.5	69.7	86
106	72.5	46.3	90	62.7	27.3	86
107	71.9	49.3	87	72.3	60.6	80
108	74.3	46.3	93	73.5	45.5	92
109	66.5	40.3	84	67.5	36.4	88
110	65.3	41.8	81	68.7	36.4	90
111	69.5	49.3	83	74.7	54.5	88
112	70.1	43.3	88	68.7	42.4	86
113	68.7	43.9	85	66.3	48.5	78
114	74.3	52.9	89	72.3	45.5	90
115	67.7	44.8	83	68.7	42.4	86
116	68.3	37.3	89	67.5	33.3	90
117	70.1	46.3	86	68.7	36.4	90
118	64.7	38.8	82	66.3	39.4	84
119	69.5	40.3	89	63.9	24.2	90
120	68.3	46.3	83	61.4	39.4	76
121	72.5	43.3	92	78.3	54.5	94
122	61.7	37.3	78	67.5	36.4	88
123	69.5	38.8	90	74.7	51.5	90
124	63.5	29.9	86	67.5	33.3	90
125	65.3	38.8	83	68.7	39.4	88

TABLE 4

SEQ ID NO:	Discriminant coefficient	Constant Term
1	1.490	8.485
2	2.192	17.571
3	1.628	20.108
4	1.724	11.587
5	2.263	22.296
6	2.463	15.985
7	8.833	111.338
8	1.386	9.644
9	1.528	12.721
10	3.092	21.901
11	1.550	8.821
12	3.319	29.422
13	3.849	39.694
14	3.265	33.699
15	2.090	18.362
16	5.589	55.229
17	2.126	15.004
18	1.892	21.549
19	5.212	38.369
20	4.357	43.428
21	3.893	27.592
22	1.938	13.174
23	2.212	20.328
24	1.832	17.827
25	4.296	42.971
26	2.836	18.443
27	1.791	17.167
28	3.102	20.737
29	4.166	33.600
30	2.570	16.779
31	1.408	7.919
32	2.548	24.931

TABLE 4-continued

SEQ ID NO:	Discriminant coefficient	Constant Term
33	3.348	30.220
34	5.146	61.548
35	1.007	5.891
36	3.423	22.158
37	4.459	48.437
38	5.239	67.494
39	2.724	18.139
40	2.096	14.981
41	5.185	64.019
42	2.496	21.820
43	1.601	10.850
44	5.154	61.778
45	7.100	92.650
46	4.122	28.093
47	1.389	8.063
48	0.844	7.028
49	2.714	21.126
50	2.184	27.536
51	2.782	26.220
52	2.507	14.755
53	5.248	59.794
54	4.258	36.410
55	2.093	21.342
56	2.375	14.357
57	3.716	27.368
58	6.005	57.298
59	3.141	19.304
60	6.949	95.964
61	2.207	15.598
62	2.528	17.814
63	5.205	54.268
64	5.578	63.641
65	3.305	21.681
66	2.302	16.671
67	2.960	21.294
68	5.934	50.718
69	2.315	15.993
70	3.992	29.367
71	3.564	24.617
72	2.022	17.112
73	1.347	11.081
74	3.284	31.457
75	1.545	9.348
76	4.433	46.093
77	4.257	27.033
78	2.935	19.713
79	1.452	8.384
80	3.495	34.503
81	3.632	29.142
82	3.294	23.460
83	3.861	26.420
84	3.328	20.006
85	2.105	16.080
86	1.341	10.397
87	4.228	42.421
88	2.047	16.460
89	1.719	10.767
90	4.014	44.217
91	4.300	25.371
92	2.984	19.534
93	2.882	20.272
94	2.143	17.783
95	2.782	16.404
96	2.452	18.600
97	3.952	25.528
98	3.062	28.862
99	1.303	7.532
100	4.019	36.628
101	2.486	19.866
102	2.977	26.894
103	4.826	59.068
104	2.101	20.436
105	4.536	33.697
106	4.937	40.293
107	6.731	92.497
108	2.367	14.257
109	3.432	32.608
110	4.107	47.065
111	3.209	22.271
112	2.121	15.790
113	3.358	20.358
114	3.889	35.598
115	3.145	20.800
116	4.368	50.242
117	2.562	16.673
118	2.261	17.941
119	3.886	33.439
120	4.225	28.465
121	3.315	25.324
122	2.292	23.043
123	4.989	37.060
124	4.447	57.475
125	5.665	40.490

TABLE 5-1

Training cohort			
Sample name	Cancer stage	CEA(ng/mL)	CA19-9(U/mL)
B01	IB	2	18.2
B05	IB	2.6	24.7
B06	II	2.6	88.7(+)
B07	IIA	1.5	41.8(+)
B09	IVb	20.3(+)	271.6(+)
B10	IVb	3.4	3170(+)
B11	IVb	51.7(+)	32.1
B12	IVb	2.1	5420(+)
B13	III	5	92.5(+)
B14	III	48.9(+)	1900(+)
B17	IB	0.9	16.4
B18	IIB	4916(+)	1.5
B19	IIIB	1.8	80.1(+)
B21	II	0.7	8.3
B25	III	30.3(+)	1364(+)
B26	IVb	10.4(+)	2226(+)
B27	IVb	39.8(+)	3490(+)
B29	III	1.7	8.2
B33	IVb	5	200.6(+)
B35	IVb	14.6(+)	0.1
B39	IIB	0.8	51.7(+)
B40	III	2.7	36.4
B43	IVa	4.4	85.3(+)
B44	IIB	6.3(+)	67.6(+)
B45	II	2.2	59.2(+)
B48	IB	3.2	33.4
B49	IA	4.3	289(+)
B50	IVb	0.8	
B51	II	6.3(+)	16
B52	IIB	3.6	214.9(+)
B54	II	1	98.3(+)
B55	II	1.7	36.8
B56	II	1.6	6.8
B57	II	6.8(+)	4538(+)
B58	IB	1.8	63.9(+)
B59	IB	10.6(+)	46.4(+)
B61	IIA	0.9	9.5
B62	IB	2.3	11.2
B63	IIB	7.2(+)	385.2(+)
B64	IIA	1.9	48.3(+)
B67	IB	1.6	66.2(+)
B69	III	26.2(+)	76.5(+)
B73	III	3.7	156.6(+)
B74	IVb	4.1	14820(+)
B75	IVb	306.7(+)	2098(+)
B77	IVb	1.2	74.2(+)
B78	IVb	2.3	5.3
B81	III	4.9	240.8(+)
B82	III	7.9(+)	1275(+)
B83	IVb	1.6	1641(+)
B85	IVb	29.7(+)	11130(+)

TABLE 5-1-continued

Training cohort			
Sample name	Cancer stage	CEA(ng/mL)	CA19-9(U/mL)
B86	III	3.5	23.8
B89	IVb	5.2(+)	1920(+)
B90	III	1.6	125.7(+)
B91	IVb	3.2	1175(+)
B92	IIIB	4.9	19750(+)
B93	IVb	None	
B94	III	2.6	2670(+)
B95	IVb	2030(+)	23.8
B96	IVb	15.2(+)	68120(+)
B97	IVb	19.5(+)	2.6
B98	IVb	2.3	4308(+)
B99	IVb	1.3	35.2
B100	IVb	2.4	47(+)
B101	III	3.5	40.3(+)
B102	IVb	0.2	3304(+)
B103	III	2.2	2434(+)
	Sensitivity (%)	31.3	68.2

TABLE 5-2

Validation cohort			
Sample name	Cancer stage	CEA(ng/mL)	CA19-9(U/mL)
B02	IB	3.1	17.1
B03	IIB	3.9	12.9
B04	IIA	2.3	15.8
B08	0	2.7	19.8
B15	IVb	13	328.4
B16	II	1.1	9.6
B20	IIB	2.3	189.8
B22	I	7.8	49.2
B23	III	0.8	8.2
B24	IV	11.6	
B28	III	2.4	64.9
B30	IVb	194.7	4597
B31	IVb	3.4	483.3
B32	IIB	2.7	35.2
B34	III	1.6	123.5
B36	IVb	2.7	3374
B37	III	5.5	145.1
B41	IB	2	27.8
B42	IIA	7	37.8
B46	IA	2.1	38.8
B53	I	2.5	6.4
B60	IIA	2.5	105.5
B65	IIA	1.7	11.9
B66	IIA	4.6	11.1
B68	IIB	1.1	7.2
B70	II	1.6	123.5
B71	IVa	6.5	925
B76	IVb	1482	15.6
B79	IVb	65	6510
B80	IVb	5	229.9
B84	III	3.1	52.5
B88	IVb	76.9	777
P91	IVb	2.3	4308
	Sensitivity (%)	33.3	59.4

In Table 5, 5 ng/ml or lower of CEA was indicated as "–", and 37 U/ml or lower of CA19-9 was indicated as "–", while values exceeding these were "+".

TABLE 6

	Training cohort			Validation cohort		
SEQ ID NO:	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
1_2	97	94	99	100	100	100
1_3	95.8	91	99	100	100	100
1_4	95.8	92.5	98	97.6	100	96
1_5	97.6	95.5	99	98.8	100	98
1_6	96.4	92.5	99	96.4	100	94
1_7	98.8	98.5	99	100	100	100
1_8	98.2	95.5	100	98.8	100	98
1_9	98.8	97	100	100	100	100
1_10	95.8	94	97	97.6	100	96
1_11	97	94	99	98.8	100	98
1_12	96.4	92.5	99	98.8	97	100
1_13	97	94	99	100	100	100
1_14	97	95.5	98	100	100	100
1_15	96.4	92.5	99	98.8	97	100
1_16	97.6	95.5	99	96.4	97	96
1_17	97.6	95.5	99	98.8	100	98
1_18	96.4	92.5	99	98.8	97	100
1_19	98.2	95.5	100	98.8	100	98
1_20	97.6	95.5	99	98.8	100	98
1_21	97.6	95.5	99	98.8	100	98
1_22	98.8	97	100	98.8	97	100
1_23	95.8	91	99	98.8	100	98
1_24	96.4	92.5	99	98.8	97	100
1_25	98.8	97	100	100	100	100
1_26	96.4	92.5	99	96.4	97	96
1_27	95.8	92.5	98	98.8	97	100
1_28	97.6	97	98	100	100	100
1_29	95.8	92.5	98	97.6	97	98
1_30	97	92.5	100	100	100	100
1_31	96.4	92.5	99	97.6	97	98
1_32	97.6	95.5	99	98.8	100	98
1_33	96.4	94	98	100	100	100
1_34	96.4	92.5	99	100	100	100
1_35	96.4	91	100	98.8	100	98
1_36	97	95.5	98	100	100	100
1_37	97	94	99	100	100	100
1_38	97	94	99	98.8	100	98
1_39	96.4	92.5	99	97.6	97	98
1_40	97	95.5	98	100	100	100
1_41	96.4	94	98	98.8	97	100
1_42	97.6	94	100	100	100	100
1_43	95.8	92.5	98	97.6	100	96
1_44	97	94	99	98.8	100	98
1_45	97.6	95.5	99	96.4	100	94
1_46	97	94	99	100	100	100
1_47	97	94	99	97.6	100	96
1_48	95.8	91	99	100	100	100
1_49	98.2	95.5	100	100	100	100
1_50	97	94	99	98.8	100	98
1_51	97	94	99	98.8	100	98
1_52	97	94	99	98.8	100	98
1_53	96.4	94	98	98.8	97	100
1_54	97	94	99	98.8	100	98
1_55	96.4	94	98	97.6	97	98
1_56	95.8	94	97	98.8	97	100
1_57	95.8	92.5	98	100	100	100
1_58	96.4	92.5	99	100	100	100
1_59	95.2	91	98	98.8	100	98
1_60	96.4	94	98	97.6	100	96
1_61	98.2	97	99	100	100	100
1_62	97.6	95.5	99	98.8	100	98
1_63	95.2	89.6	99	97.6	97	98
1_64	94.6	89.6	98	98.8	100	98
1_65	97	94	99	96.4	97	96
1_66	95.8	92.5	98	98.8	97	100
1_67	97	94	99	100	100	100
1_68	97.6	95.5	99	97.6	100	96
1_69	95.8	92.5	98	97.6	97	98
1_70	95.8	94	97	98.8	100	98
1_71	98.2	97	99	98.8	100	98
1_72	95.8	92.5	98	98.8	97	100
1_73	97	94	99	100	100	100
1_74	96.4	94	98	98.8	100	98
1_75	96.4	94	98	97.6	100	96
1_76	96.4	92.5	99	97.6	97	98

TABLE 6-continued

	Training cohort			Validation cohort		
SEQ ID NO:	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
1_77	97	95.5	98	97.6	97	98
1_78	96.4	92.5	99	98.8	97	100
1_79	95.8	91	99	98.8	97	100
1_80	95.8	91	99	100	100	100
1_81	95.8	92.5	98	98.8	100	98
1_82	97	95.5	98	100	100	100
1_83	97.6	95.5	99	96.4	97	96
1_84	97	94	99	98.8	100	98
1_85	97	94	99	98.8	100	98
1_86	95.2	91	98	98.8	97	100
1_87	95.8	92.5	98	100	100	100
1_88	95.8	92.5	98	98.8	97	100
1_89	96.4	94	98	98.8	100	98
1_90	96.4	92.5	99	98.8	100	98
1_91	95.8	94	97	97.6	97	98
1_92	97.6	95.5	99	98.8	100	98
1_93	96.4	94	98	98.8	100	98
1_94	97	94	99	98.8	100	98
1_95	95.8	92.5	98	98.8	97	100
1_96	97.6	94	100	100	100	100
1_97	95.8	91	99	97.6	93.9	100
1_98	97	94	99	98.8	100	98
1_99	95.8	92.5	98	100	100	100
1_100	97	94	99	98.8	100	98
1_101	97.6	95.5	99	100	100	100
1_102	97	94	99	100	100	100
1_103	96.4	94	98	100	100	100
1_104	97.6	97	98	98.8	100	98
1_105	97	94	99	98.8	100	98
1_106	97	94	99	100	100	100
1_107	97	94	99	98.8	100	98
1_108	97	94	99	98.8	100	98
1_109	97.6	95.5	99	100	100	100
1_110	96.4	91	100	98.8	97	100
1_111	95.2	89.6	99	98.8	97	100
1_112	96.4	94	98	97.6	97	98
1_113	97	93.9	99	100	100	100
1_114	97	94	99	100	100	100
1_115	97	94	99	98.8	100	98
1_116	97.6	95.5	99	100	100	100
1_117	97.6	94	100	98.8	100	98
1_118	95.8	92.5	98	98.8	100	98
1_119	97	95.5	98	100	100	100
1_120	97	94	99	100	100	100
1_121	97	94	99	98.8	100	98
1_122	97	92.5	100	100	100	100
1_123	97	95.5	98	97.6	100	96
1_124	98.2	97	99	100	100	100
1_125	95.8	91	99	97.6	97	98

Example 3

<Selection of Gene Marker using all Samples and Method for Evaluating Biliary Tract Cancer Discriminant Performance of Acquired Gene Marker>

In this Example, the samples of the training cohort and the validation cohort used in Examples 1 and Example 2 were integrated, and selection of a gene marker and evaluation of its biliary tract cancer discriminant performance were conducted using all of the samples.

Specifically, the miRNA expression levels in the serum of the 100 biliary tract cancer patients and the 150 healthy subjects obtained in Reference Example 1 above were normalized by quantile normalization. In order to acquire diagnostic markers with higher reliability, only genes having a gene expression level of 2^6 or higher in 50% or more of the samples in either of the biliary tract cancer patient group or the healthy subject group were selected in the gene marker selection. In order to further acquire statistical significance for discriminating a biliary tract cancer patient group from a healthy subject group, the P value obtained by two-tailed t-test assuming equal variance as to each gene expression level was corrected by the Bonferroni method, and genes that satisfied $p<0.01$ were selected as gene markers for use in explanatory variables of a discriminant. The obtained genes are described in Table 7. In this way, hsa-miR-6808-5p, hsa-miR-6774-5p, hsa-miR-4656, hsa-miR-6806-5p, hsa-miR-1233-5p, hsa-miR-328-5p, hsa-miR-4674, hsa-miR-2110, hsa-miR-6076, hsa-miR-3619-3p, hsa-miR-92a-2-5p, hsa-miR-128-1-5p, hsa-miR-638, hsa-miR-2861, hsa-miR-371a-5p, hsa-miR-211-3p, hsa-miR-1273g-3p, hsa-miR-1203, hsa-miR-122-5p, hsa-miR-4258, hsa-miR-4484, hsa-miR-4648 and hsa-miR-6780b-5p genes represented by SEQ ID NOs: 126 to 148 were found as biliary tract cancer markers relative to the healthy subjects, in addition to the genes described in Table 2. As with the polynucleotides shown in SEQ ID NOs: 1 to 125, the results obtained about the polynucleotides shown in SEQ ID NOs: 126 to 148 also showed that the expression level measurement values were significantly lower (−) or higher (+) in the biliary tract cancer patient group than in the healthy subject group (Table 7). These results were able to be validated in the validation cohort. The presence or absence of biliary tract cancer in the newly obtained samples can be determined by the methods described in Examples 1 and 2 by using the gene expression level measurement values described in Table 7 either alone or in combination with the gene expression level measurement values described in Table 2.

TABLE 7

SEQ ID NO:	Gene name	P value after Bonferroni correction	Expression level in biliary tract cancer patient relative to healthy subject
1	hsa-miR-125a-3p	4.28E−69	−
2	hsa-miR-6893-5p	1.09E−65	−
3	hsa-miR-204-3p	6.70E−61	−
4	hsa-miR-4476	7.27E−46	−
5	hsa-miR-4294	1.68E−46	−
6	hsa-miR-150-3p	1.80E−39	−
7	hsa-miR-6729-5p	5.38E−43	+
8	hsa-miR-7641	3.05E−42	−
9	hsa-miR-6765-3p	2.49E−39	−
10	hsa-miR-6820-5p	5.67E−39	−
11	hsa-miR-575	8.34E−40	−
12	hsa-miR-6836-3p	5.59E−31	+
13	hsa-miR-1469	9.68E−31	+
14	hsa-miR-663a	5.12E−34	+
15	hsa-miR-6075	1.26E−32	+
16	hsa-miR-4634	1.02E−21	+
17	hsa-miR-423-5p	1.35E−29	−
18	hsa-miR-4454	1.49E−28	−
19	hsa-miR-7109-5p	4.86E−24	−
20	hsa-miR-6789-5p	1.58E−25	+
21	hsa-miR-6877-5p	2.13E−27	−
22	hsa-miR-4792	2.19E−22	+
23	hsa-miR-4530	5.55E−28	−
24	hsa-miR-7975	1.41E−23	−
25	hsa-miR-6724-5p	6.21E−22	+
26	hsa-miR-8073	6.99E−22	+
27	hsa-miR-7977	1.59E−24	−
28	hsa-miR-1231	9.43E−24	+
29	hsa-miR-6799-5p	1.15E−19	−
30	hsa-miR-615-5p	4.36E−22	−
31	hsa-miR-4450	3.74E−25	−
32	hsa-miR-6726-5p	8.86E−19	−
33	hsa-miR-6875-5p	8.34E−18	+
34	hsa-miR-4734	1.61E−21	+
35	hsa-miR-16-5p	5.06E−19	−
36	hsa-miR-602	6.21E−19	+

TABLE 7-continued

SEQ ID NO:	Gene name	P value after Bonferroni correction	Expression level in biliary tract cancer patient relative to healthy subject
37	hsa-miR-4651	8.62E−19	−
38	hsa-miR-8069	3.51E−17	+
39	hsa-miR-1238-5p	1.46E−20	+
40	hsa-miR-6880-5p	3.97E−20	−
41	hsa-miR-8072	4.77E−19	+
42	hsa-miR-4723-5p	8.13E−18	−
43	hsa-miR-4732-5p	3.25E−17	+
44	hsa-miR-6125	1.01E−16	+
45	hsa-miR-6090	1.38E−17	+
46	hsa-miR-7114-5p	1.97E−15	−
47	hsa-miR-564	3.73E−21	−
48	hsa-miR-451a	4.72E−16	−
49	hsa-miR-3135b	1.59E−11	−
50	hsa-miR-4497	2.02E−19	−
51	hsa-miR-4665-5p	4.12E−17	−
52	hsa-miR-3622a-5p	1.48E−18	−
53	hsa-miR-6850-5p	3.84E−15	+
54	hsa-miR-6821-5p	2.55E−13	−
55	hsa-miR-5100	1.10E−14	−
56	hsa-miR-6872-3p	5.30E−16	−
57	hsa-miR-4433-3p	2.69E−12	+
58	hsa-miR-1227-5p	3.37E−17	+
59	hsa-miR-3188	2.17E−14	+
60	hsa-miR-7704	1.24E−13	−
61	hsa-miR-3185	1.95E−12	+
62	hsa-miR-1908-3p	2.94E−15	+
63	hsa-miR-6781-5p	4.29E−12	+
64	hsa-miR-6805-5p	1.17E−15	+
65	hsa-miR-8089	1.47E−13	−
66	hsa-miR-665	8.11E−15	+
67	hsa-miR-4486	3.16E−13	+
68	hsa-miR-6722-3p	1.65E−13	+
69	hsa-miR-1260a	2.60E−11	−
70	hsa-miR-4707-5p	2.00E−10	+
71	hsa-miR-6741-5p	6.59E−09	−
72	hsa-miR-1260b	5.25E−12	−
73	hsa-miR-1246	1.34E−11	+
74	hsa-miR-6845-5p	1.26E−11	+
75	hsa-miR-4638-5p	3.28E−13	−
76	hsa-miR-6085	5.78E−10	−
77	hsa-miR-1228-3p	3.27E−06	+
78	hsa-miR-4534	3.91E−08	−
79	hsa-miR-5585-3p	6.28E−11	+
80	hsa-miR-4741	3.46E−08	+
81	hsa-miR-4433b-3p	1.39E−05	+
82	hsa-miR-197-5p	8.04E−09	+
83	hsa-miR-718	3.74E−08	+
84	hsa-miR-4513	1.21E−10	−
85	hsa-miR-4446-3p	1.77E−08	+
86	hsa-miR-619-5p	1.39E−08	+
87	hsa-miR-6816-5p	1.57E−06	+
88	hsa-miR-6778-5p	4.15E−09	+
89	hsa-miR-24-3p	7.20E−08	−
90	hsa-miR-1915-3p	7.39E−09	+
91	hsa-miR-4665-3p	2.19E−07	+
92	hsa-miR-4449	1.44E−08	+
93	hsa-miR-6889-5p	4.03E−09	−
94	hsa-miR-486-3p	3.07E−07	+
95	hsa-miR-7113-3p	7.17E−05	+
96	hsa-miR-642a-3p	2.16E−05	−
97	hsa-miR-7847-3p	1.01E−03	−
98	hsa-miR-6768-5p	5.36E−06	−
99	hsa-miR-1290	1.38E−07	+
100	hsa-miR-7108-5p	1.70E−05	+
101	hsa-miR-92b-5p	5.47E−05	+
102	hsa-miR-663b	1.10E−05	+
103	hsa-miR-3940-5p	9.32E−06	+
104	hsa-miR-4467	9.80E−07	+
105	hsa-miR-6858-5p	6.11E−08	+
106	hsa-miR-4417	2.44E−04	+
107	hsa-miR-3665	4.03E−06	+
108	hsa-miR-4736	1.16E−05	+
109	hsa-miR-4687-3p	2.65E−07	−
110	hsa-miR-1908-5p	1.15E−04	+
111	hsa-miR-5195-3p	7.52E−06	−
112	hsa-miR-4286	8.49E−06	−
113	hsa-miR-3679-3p	6.22E−04	+
114	hsa-miR-6791-5p	2.88E−05	+
115	hsa-miR-1202	7.99E−06	−
116	hsa-miR-3656	1.87E−06	+
117	hsa-miR-4746-3p	3.71E−05	+
118	hsa-miR-3184-5p	2.22E−05	+
119	hsa-miR-3937	5.36E−03	+
120	hsa-miR-6515-3p	7.18E−02	+
121	hsa-miR-6132	3.43E−04	−
122	hsa-miR-187-5p	1.16E−06	−
123	hsa-miR-7111-5p	5.89E−05	−
124	hsa-miR-5787	1.91E−04	−
125	hsa-miR-6779-5p	1.86E−03	−
126	hsa-miR-6808-5p	2.64E−06	+
127	hsa-miR-6774-5p	2.50E−05	+
128	hsa-miR-4656	7.70E−05	+
129	hsa-miR-6806-5p	1.02E−04	+
130	hsa-miR-1233-5p	1.23E−04	+
131	hsa-miR-328-5p	1.31E−04	−
132	hsa-miR-4674	2.45E−04	+
133	hsa-miR-2110	5.98E−04	−
134	hsa-miR-6076	6.44E−04	−
135	hsa-miR-3619-3p	9.16E−04	+
136	hsa-miR-92a-2-5p	9.76E−04	−
137	hsa-miR-128-1-5p	1.22E−03	+
138	hsa-miR-638	1.54E−03	+
139	hsa-miR-2861	1.95E−03	−
140	hsa-miR-371a-5p	3.24E−03	−
141	hsa-miR-211-3p	3.44E−03	+
142	hsa-miR-1273g-3p	4.10E−03	+
143	hsa-miR-1203	5.55E−03	−
144	hsa-miR-122-5p	5.81E−03	+
145	hsa-miR-4258	5.82E−03	+
146	hsa-miR-4484	7.10E−03	+
147	hsa-miR-4648	8.55E−03	+
148	hsa-miR-6780b-5p	9.46E−03	+

Example 4

<Method for Evaluating Biliary Tract Cancer-specific Discriminant Performance by Combination of Multiple Gene Markers using Samples in the Validation Cohort>

In this Example, additional gene markers for diagnosis were selected by comparing gene expression levels of miRNAs in sera of biliary tract cancer patients with those of a control group consisting of healthy subjects, colorectal cancer patients, stomach cancer patients, esophageal cancer patients, liver cancer patients, and benign pancreaticobiliary disease patients, in the same way as the method described in Example 1, and targeting the training cohort as the sample group described in Reference Example 2. One or two or more markers selected from the group consisting of the additional gene markers for diagnosis (SEQ ID NOs: 466 to 478; see Table 1) thus selected and the gene markers selected in Example 1 in combination were used to evaluate biliary tract cancer-specific discriminant performance.

Specifically, first, the miRNA expression levels in the training cohort and the validation cohort obtained in Reference Example 2 mentioned above were combined and normalized by quantile normalization. Next, Fisher's discriminant analysis was conducted to construct a discriminant for determining the presence or absence of biliary tract cancer, by using combinations of 1 to 4 expression level measurement values comprising at least one or more of the expression level measurement values of the polynucleotides consisting of the nucleotide sequences represented by SEQ

ID NOs: 1 to 148, 466 to 478. Next, accuracy, sensitivity, and specificity in the validation cohort were calculated using the discriminant thus prepared, with a positive sample group that consists of the biliary tract cancer patient group, and a negative sample group that consists of the healthy subject group, the colorectal cancer patient group, the stomach cancer patient group, the esophageal cancer patient group, the liver cancer patient group, and the benign pancreaticobiliary disease patient group. The discriminant performance of the selected polynucleotides was validated using the independent samples.

Most of polynucleotides consisting of the nucleotide sequences represented by these SEQ ID NOs (SEQ ID NOs: 1 to 148, and 466 to 478 corresponding to the miRNA markers of Table 1) or complementary sequences thereof mentioned above were able to provide relatively high accuracy, sensitivity, and specificity in the determination of the presence or absence of biliary tract cancer, and furthermore, were able to specifically discriminate biliary tract cancer from the other cancers. For example, among the combinations of multiple polynucleotides selected from the group consisting of polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1, 4, 5, 11, 12, 15, 23, 29, 39, 40, 54, 76, 79, 91, 103, 115, 121, 134, 143, 466, 469, 472, 473, and 474 or complementary sequences thereof (the cancer type-specific polynucleotide group 1) listed as polynucleotides capable of specifically binding to target markers, combinations comprising at least one polynucleotide selected from the group consisting of polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 4, 5, 12, 15, and 40 or complementary sequences thereof (the cancer type-specific polynucleotide group 2) were able to specifically discriminate biliary tract cancer from the other cancers with high accuracy.

The number of the polynucleotides with cancer type specificity in the combination mentioned above can be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more for the combination. The combinations of 4 or more polynucleotides were able to exhibit discrimination accuracy of 80% or higher.

Specifically, the discrimination accuracy of the measurement using the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 4 or a complementary sequence thereof is given below. The measurement using alone (one) the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 4 or a complementary sequence thereof exhibited accuracy of 81.9% in the training cohort and accuracy of 76.9% in the validation cohort (Table 8). Also, for example, the measurement using the combinations of two polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 4 or a complementary sequence thereof exhibited the highest accuracy of 86.0% in the training cohort and accuracy of 85.3% in the validation cohort (Table 9; "SEQ ID NO" in the table represents the combinations of SEQ ID NOs of the two polynucleotides used). Furthermore, for example, the measurement using the combinations of three polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 4 or a complementary sequence thereof exhibited the highest accuracy of 89.5% in the training cohort and accuracy of 90.4% in the validation cohort (Table 10; "SEQ ID NO" in the table represents the combinations of SEQ ID NOs of the three polynucleotides used). Furthermore, for example, the measurement using the combinations of four polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 4 or a complementary sequence thereof exhibited the highest accuracy of 91.1% in the training cohort and accuracy of 92.3% in the validation cohort (Table 11; "SEQ ID NO" in the table represents the combinations of SEQ ID NOs of the four polynucleotides used).

Specifically, the discrimination accuracy of the measurement using the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 5 or a complementary sequence thereof is given below. The measurement using alone (one) the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 5 or a complementary sequence thereof exhibited accuracy of 79.0% in the training cohort and accuracy of 80.8% in the validation cohort (Table 8). Also, for example, the measurement using the combinations of two polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 5 or a complementary sequence thereof exhibited the highest accuracy of 81.9% in the training cohort and accuracy of 86.5% in the validation cohort (Table 9). Furthermore, for example, the measurement using the combinations of three polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 5 or a complementary sequence thereof exhibited the highest accuracy of 87.6% in the training cohort and accuracy of 89.7% in the validation cohort (Table 10). Furthermore, for example, the measurement using the combinations of four polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 5 or a complementary sequence thereof exhibited the highest accuracy of 93.0% in the training cohort and accuracy of 91.0% in the validation cohort (Table 11).

Specifically, the discrimination accuracy of the measurement using the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 12 or a complementary sequence thereof is given below. The measurement using alone (one) the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 12 or a complementary sequence thereof exhibited accuracy of 80.6% in the training cohort and accuracy of 76.9% in the validation cohort (Table 8). Also, for example, the measurement using the combinations of two polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 12 or a complementary sequence thereof exhibited the highest accuracy of 86.3% in the training cohort and accuracy of 85.9% in the validation cohort (Table 9). Furthermore, for example, the measurement using the combinations of three polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 12 or a complementary sequence thereof exhibited the highest accuracy of 90.2% in the training cohort and accuracy of 91.7% in the validation cohort (Table 10). Furthermore, for example, the measurement using the combinations of four polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 12 or a complementary sequence thereof exhibited the highest accuracy of 93.0% in the training cohort and accuracy of 94.2% in the validation cohort (Table 11).

Specifically, the discrimination accuracy of the measurement using the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 15 or a complementary sequence thereof is given below. The measurement using alone (one) the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 15 or a complementary sequence thereof exhibited accuracy of 83.8% in the training cohort and accuracy of 84.0% in the validation cohort (Table 8). Also, for example, the measurement using the combinations of two polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 15 or a complementary sequence thereof exhibited the highest accuracy of 89.5% in the training cohort and accuracy of 89.1% in the validation cohort (Table 9). Furthermore, for example, the measurement using the combinations of three polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 15 or a complementary sequence thereof exhibited the highest accuracy of 90.5% in the training cohort and accuracy of 92.3% in the validation cohort (Table 10). Furthermore, for example, the measurement using the combinations of four polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 15 or a complementary sequence thereof exhibited the highest accuracy of 93.0% in the training cohort and accuracy of 94.2% in the validation cohort (Table 11).

Specifically, the discrimination accuracy of the measurement using the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 40 or a complementary sequence thereof is given below. The measurement using alone (one) the polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 40 or a complementary sequence thereof exhibited accuracy of 80.0% in the training cohort and accuracy of 76.9% in the validation cohort (Table 8). Also, for example, the measurement using the combinations of two polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 40 or a complementary sequence thereof exhibited the highest accuracy of 81.9% in the training cohort and accuracy of 86.5% in the validation cohort (Table 9). Furthermore, for example, the measurement using the combinations of three polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 40 or a complementary sequence thereof exhibited the highest accuracy of 86.7% in the training cohort and accuracy of 89.7% in the validation cohort (Table 10). Furthermore, for example, the measurement using the combinations of four polynucleotides comprising at least one polynucleotide consisting of the nucleotide sequence represented by SEQ ID NO: 40 or a complementary sequence thereof exhibited the highest accuracy of 91.4% in the training cohort and accuracy of 91.7% in the validation cohort (Table 11).

The expression level measurement values of the nucleotide sequences represented by SEQ ID NOs: 15, 5, 4, 12, 40 were compared among 67 biliary tract cancer patients, 93 healthy subjects, 35 colorectal cancer patients, 37 stomach cancer patients, 32 esophageal cancer patients, 38 liver cancer patients, and 13 benign pancreaticobiliary disease patients in the training cohort. As a result, a scatter diagram that significantly separated the discriminant score of the biliary tract cancer patient group from the other discriminant scores was obtained in the training cohort (see the upper diagram of FIG. **4**). These results were also reproducible in the validation cohort (see the lower diagram of FIG. **4**).

TABLE 8

	Training cohort			Validation cohort		
SEQ ID NO:	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
4	81.9	82.3	80.6	76.9	78.9	69.7
5	79	79	79.1	80.8	80.5	81.8
11	77.1	76.6	79.1	74.4	73.2	78.8
12	80.6	80.2	82.1	76.9	77.2	75.8
15	83.8	88.7	65.7	84	88.6	66.7
23	76.8	75.8	80.6	70.5	66.7	84.8
29	76.2	74.6	82.1	73.7	70.7	84.8
39	79.7	83.5	65.7	74.4	78.9	57.6
40	80	81	76.1	76.9	76.4	78.8
54	61.9	60.1	68.7	65.4	61.8	78.8
76	76.2	77.4	71.6	69.9	75.6	48.5
91	59.7	60.5	56.7	55.1	53.7	60.6
115	56.2	56.5	55.2	58.3	61	48.5
121	70.2	70.2	70.1	73.1	74.8	66.7
143	70.8	73.8	59.7	67.9	71.5	54.5

TABLE 9

	Training cohort			Validation cohort		
SEQ ID NO:	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
15_121	89.5	93.5	74.6	89.1	91.1	81.8
15_88	85.1	89.9	67.2	86.5	91.1	69.7
15_471	86.7	91.5	68.7	86.5	91.1	69.7
5_40	81.9	83.9	74.6	86.5	86.2	87.9
15_12	86.3	89.1	76.1	85.9	88.6	75.8
15_39	87.3	90.3	76.1	85.9	88.6	75.8
15_29	86.3	89.1	76.1	85.9	88.6	75.8
4_15	86	87.9	79.1	85.3	87	78.8

TABLE 10

	Training cohort			Validation cohort		
SEQ ID NO:	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
15_121_115	90.5	94	77.6	92.3	92.7	90.9
15_121_91	90.2	93.5	77.6	91.7	93.5	84.8
15_12_121	90.2	93.5	77.6	91.7	92.7	87.9
15_121_109	89.8	93.1	77.6	91	92.7	84.8
15_102_121	90.1	93.1	78.8	91	91.9	87.9
15_62_121	90.8	94	79.1	91	91.1	90.9
15_39_121	90.8	94.4	77.6	90.4	91.9	84.8
15_23_121	89.8	93.1	77.6	90.4	90.2	90.9
15_4_121	89.5	91.9	80.6	90.4	90.2	90.9
15_76_121	89.5	93.5	74.6	89.7	91.9	81.8
15_121_31	90.5	94	77.6	89.7	91.9	81.8
15_121_64	89.8	93.5	76.1	89.7	91.9	81.8
15_121_468	90.5	93.1	80.6	89.7	91.9	81.8
15_94_121	90.2	93.5	77.6	89.7	91.1	84.8
15_121_143	89.8	94	74.6	89.7	91.1	84.8
15_121_108	89.5	93.1	76.1	89.7	91.1	84.8
5_39_115	87.6	89.1	82.1	89.7	91.1	84.8
40_12_64	86.7	87.9	82.1	89.7	91.1	84.8
15_20_121	91.4	92.3	88.1	89.1	91.1	81.8
15_11_121	89.2	93.1	74.6	89.1	91.1	81.8
15_121_54	89.5	93.5	74.6	89.1	91.1	81.8
15_121_79	90.2	94.8	73.1	89.1	91.1	81.8
15_121_134	89.2	93.1	74.6	89.1	91.1	81.8
15_121_471	89.2	94	71.6	89.1	91.1	81.8
15_121_474	89.5	93.5	74.6	89.1	91.1	81.8
40_39_121	90.8	94	79.1	89.1	91.1	81.8
15_40_121	91.7	94.4	82.1	89.1	90.2	84.8
15_29_121	90.8	94	79.1	89.1	89.4	87.9
5_40_121	85.7	86.3	83.6	89.1	88.6	90.9

TABLE 10-continued

	Training cohort			Validation cohort		
SEQ ID NO:	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
15_88_471	86	91.1	67.2	88.5	93.5	69.7
15_39_115	86	89.9	71.6	88.5	91.9	75.8
40_39_89	88.9	92.7	74.6	88.5	91.9	75.8
40_4_88	86	86.7	83.6	88.5	91.1	78.8
15_5_115	87.3	89.9	77.6	88.5	90.2	81.8
15_12_115	90.5	93.5	79.1	88.5	90.2	81.8
15_121_466	89.2	93.5	73.1	88.5	90.2	81.8
15_121_145	88.6	93.1	71.6	88.5	90.2	81.8
15_121_135	89.5	92.7	77.6	88.5	90.2	81.8
15_121_89	89.5	93.5	74.6	88.5	89.4	84.8
5_12_115	90.2	90.7	88.1	88.5	89.4	84.8
5_12_91	86.7	87.5	83.6	88.5	88.6	87.9
5_471_115	87.3	88.7	82.1	88.5	88.6	87.9
12_121_468	84.1	85.9	77.6	88.5	88.6	87.9
40_39_79	88.3	91.9	74.6	87.8	93.5	66.7
15_79_471	87.6	92.7	68.7	87.8	92.7	69.7
15_39_102	89.2	92.3	77.3	87.8	91.9	72.7
15_102_115	86	89.9	71.2	87.8	91.1	75.8
15_54_64	85.1	89.5	68.7	87.8	91.1	75.8
15_12_473	86.3	89.5	74.6	87.8	90.2	78.8
15_4_471	88.3	90.7	79.1	87.8	90.2	78.8
15_121_467	89.5	93.5	74.6	87.8	90.2	78.8
15_121_472	91.7	94.4	82.1	87.8	90.2	78.8
40_64_88	82.5	83.9	77.6	87.8	90.2	78.8
15_121_88	89.8	93.5	76.1	87.8	89.4	81.8
15_121_470	91.1	93.1	83.6	87.8	89.4	81.8
15_121_473	89.2	93.5	73.1	87.8	89.4	81.8
15_64_88	84.4	89.9	64.2	87.2	92.7	66.7
15_88_79	86	91.1	67.2	87.2	91.9	69.7
15_108_471	86.7	91.5	68.7	87.2	91.9	69.7
15_102_470	86.9	89.9	75.8	87.2	91.1	72.7
15_11_88	83.8	88.3	67.2	87.2	91.1	72.7
40_4_76	86.3	87.9	80.6	87.2	91.1	72.7
40_39_473	87.6	90.7	76.1	87.2	91.1	72.7
15_12_145	87.6	89.9	79.1	87.2	90.2	75.8
15_23_115	85.7	89.1	73.1	87.2	90.2	75.8
40_39_64	87.3	90.3	76.1	87.2	90.2	75.8
40_20_79	83.2	85.5	74.6	87.2	90.2	75.8
15_11_115	86	90.7	68.7	87.2	89.4	78.8
5_76_115	87.9	88.7	85.1	87.2	89.4	78.8
40_20_64	86.7	87.9	82.1	87.2	89.4	78.8
40_11_64	84.1	85.1	80.6	87.2	89.4	78.8
40_467_64	84.8	86.7	77.6	87.2	89.4	78.8
15_4_29	86.3	87.5	82.1	87.2	88.6	81.8
15_5_121	90.8	93.5	80.6	87.2	87.8	84.8
5_121_79	83.8	85.5	77.6	87.2	87	87.9
5_39_121	86.3	87.9	80.6	87.2	86.2	90.9
15_76_471	86	90.7	68.7	86.5	91.9	66.7
15_94_471	86.3	91.1	68.7	86.5	91.1	69.7
15_31_88	84.4	89.1	67.2	86.5	91.1	69.7
15_31_471	86.3	91.1	68.7	86.5	91.1	69.7
15_54_115	87.6	92.3	70.1	86.5	91.1	69.7
15_109_88	85.1	89.9	67.2	86.5	91.1	69.7
15_109_471	86.7	91.5	68.7	86.5	91.1	69.7
15_467_88	84.1	88.7	67.2	86.5	91.1	69.7
15_64_471	86	91.5	65.7	86.5	91.1	69.7
15_88_145	84.4	89.1	67.2	86.5	91.1	69.7
15_88_134	84.4	89.1	67.2	86.5	91.1	69.7
15_88_473	84.4	89.1	67.2	86.5	91.1	69.7
15_145_471	86.7	91.5	68.7	86.5	91.1	69.7
15_470_471	87.3	91.9	70.1	86.5	91.1	69.7
15_471_135	86.7	91.5	68.7	86.5	91.1	69.7
15_471_89	86.7	91.5	68.7	86.5	91.1	69.7
15_471_472	87	91.9	68.7	86.5	91.1	69.7
15_471_474	87	91.9	68.7	86.5	91.1	69.7
40_39_467	89.8	93.1	77.6	86.5	91.1	69.7
15_40_64	85.4	89.5	70.1	86.5	90.2	72.7
15_23_470	86.3	88.3	79.1	86.5	90.2	72.7
15_39_470	87	89.9	76.1	86.5	90.2	72.7
15_39_471	88.9	92.7	74.6	86.5	90.2	72.7
15_29_31	87	90.3	74.6	86.5	90.2	72.7
15_20_79	85.7	90.3	68.7	86.5	90.2	72.7
40_4_470	86	86.7	83.6	86.5	90.2	72.7
15_40_12	87.3	90.7	74.6	86.5	89.4	75.8

TABLE 10-continued

	Training cohort			Validation cohort		
SEQ ID NO:	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
15_12_467	86.3	89.1	76.1	86.5	89.4	75.8
15_12_143	86.3	89.1	76.1	86.5	89.4	75.8
15_12_108	87.3	90.3	76.1	86.5	89.4	75.8
15_12_470	87.9	89.9	80.6	86.5	89.4	75.8
15_12_471	89.5	92.3	79.1	86.5	89.4	75.8
15_12_89	87	89.9	76.1	86.5	89.4	75.8
15_12_472	87	89.5	77.6	86.5	89.4	75.8
15_12_474	86.7	89.5	76.1	86.5	89.4	75.8
15_23_102	86.3	89.9	72.7	86.5	89.4	75.8
15_39_54	87.3	90.3	76.1	86.5	89.4	75.8
15_29_62	85.7	89.1	73.1	86.5	89.4	75.8
15_102_11	85.7	89.5	71.2	86.5	89.4	75.8
40_23_39	87.9	90.7	77.6	86.5	89.4	75.8
40_39_62	88.6	92.3	74.6	86.5	89.4	75.8
40_39_11	88.3	91.1	77.6	86.5	89.4	75.8
40_39_88	87.9	91.5	74.6	86.5	89.4	75.8
40_64_472	84.4	86.7	76.1	86.5	89.4	75.8
4_39_91	84.4	87.5	73.1	86.5	89.4	75.8
4_76_115	86.7	89.1	77.6	86.5	89.4	75.8
15_40_11	84.4	87.9	71.6	86.5	88.6	78.8
15_20_115	87.6	90.7	76.1	86.5	88.6	78.8
5_40_64	84.1	85.5	79.1	86.5	88.6	78.8
40_62_64	83.2	84.7	77.6	86.5	88.6	78.8
40_121_467	87.6	89.5	80.6	86.5	88.6	78.8
4_62_115	82.2	83.1	79.1	86.5	88.6	78.8
15_5_91	86.3	89.9	73.1	86.5	87.8	81.8
40_12_4	86.3	87.1	83.6	86.5	87.8	81.8
40_12_79	85.7	87.9	77.6	86.5	87.8	81.8
40_4_121	86	87.9	79.1	86.5	87.8	81.8
12_4_468	86.3	87.5	82.1	86.5	87.8	81.8
12_4_115	85.1	85.9	82.1	86.5	87.8	81.8
4_88_115	83.8	83.9	83.6	86.5	87.8	81.8
5_40_88	83.5	84.7	79.1	86.5	87	84.8
5_40_20	84.4	85.1	82.1	86.5	86.2	87.9
5_40_54	82.2	83.9	76.1	86.5	86.2	87.9
5_40_109	82.2	83.9	76.1	86.5	86.2	87.9
5_40_471	82.9	85.1	74.6	86.5	86.2	87.9
5_40_473	82.2	83.5	77.6	86.5	86.2	87.9
40_12_88	85.1	85.5	83.6	86.5	86.2	87.9
40_12_121	87	87.9	83.6	86.5	85.4	90.9
15_88_89	84.8	89.5	67.2	85.9	91.1	66.7
15_40_88	84.8	89.5	67.2	85.9	90.2	69.7
15_39_88	87.3	91.5	71.6	85.9	90.2	69.7
15_39_79	87.9	91.9	73.1	85.9	90.2	69.7
15_62_64	84.8	89.1	68.7	85.9	90.2	69.7
15_62_79	85.7	90.3	68.7	85.9	90.2	69.7
15_466_88	84.1	88.7	67.2	85.9	90.2	69.7
15_88_472	85.1	89.9	67.2	85.9	90.2	69.7
15_88_474	85.1	89.9	67.2	85.9	90.2	69.7
15_143_471	86.3	91.5	67.2	85.9	90.2	69.7
15_468_471	86.7	91.5	68.7	85.9	90.2	69.7
15_469_471	86.3	91.1	68.7	85.9	90.2	69.7
15_134_471	87	91.9	68.7	85.9	90.2	69.7
15_471_115	87.3	92.7	67.2	85.9	90.2	69.7
15_29_88	85.1	88.7	71.6	85.9	89.4	72.7
15_29_469	86.3	89.1	76.1	85.9	89.4	72.7
15_102_467	86.9	90.7	72.7	85.9	89.4	72.7
15_102_64	85.4	89.5	69.7	85.9	89.4	72.7
15_102_79	86.3	90.7	69.7	85.9	89.4	72.7
15_102_471	86.9	91.1	71.2	85.9	89.4	72.7
15_470_115	85.1	88.3	73.1	85.9	89.4	72.7
40_39_94	88.6	91.9	76.1	85.9	89.4	72.7
40_39_466	89.5	93.1	76.1	85.9	89.4	72.7
40_39_31	88.6	92.3	74.6	85.9	89.4	72.7
40_39_468	89.2	92.7	76.1	85.9	89.4	72.7
40_39_471	88.6	92.3	74.6	85.9	89.4	72.7
40_39_472	89.2	92.7	76.1	85.9	89.4	72.7
15_5_23	84.8	87.1	76.1	85.9	88.6	75.8
15_40_470	85.4	87.5	77.6	85.9	88.6	75.8
15_12_31	86.7	89.5	76.1	85.9	88.6	75.8
15_12_54	87	89.9	76.1	85.9	88.6	75.8
15_12_468	86.3	89.1	76.1	85.9	88.6	75.8
15_12_134	86.3	89.1	76.1	85.9	88.6	75.8
15_12_135	86.3	89.1	76.1	85.9	88.6	75.8

TABLE 10-continued

SEQ ID NO:	Training cohort			Validation cohort		
	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
15_23_39	87.9	90.3	79.1	85.9	88.6	75.8
15_39_31	87.3	90.3	76.1	85.9	88.6	75.8
15_39_109	87.3	90.3	76.1	85.9	88.6	75.8
15_39_108	87.3	90.3	76.1	85.9	88.6	75.8
15_39_135	87.3	90.3	76.1	85.9	88.6	75.8
15_39_89	87.3	90.3	76.1	85.9	88.6	75.8
15_39_472	87.3	90.3	76.1	85.9	88.6	75.8
15_29_76	86.3	89.1	76.1	85.9	88.6	75.8
15_29_102	87.3	90.7	74.2	85.9	88.6	75.8
15_29_466	86.3	89.1	76.1	85.9	88.6	75.8
15_29_54	86	88.7	76.1	85.9	88.6	75.8
15_29_143	86.3	89.5	74.6	85.9	88.6	75.8
15_29_134	86	88.7	76.1	85.9	88.6	75.8
15_29_108	86.3	89.1	76.1	85.9	88.6	75.8
15_29_471	87	90.3	74.6	85.9	88.6	75.8
15_29_89	86.7	89.5	76.1	85.9	88.6	75.8
15_29_472	86.3	89.1	76.1	85.9	88.6	75.8
15_121_469	90.5	94.4	76.1	85.9	88.6	75.8
40_4_31	86.3	87.5	82.1	85.9	88.6	75.8
40_39_143	87.6	90.7	76.1	85.9	88.6	75.8
40_39_108	87.3	90.7	74.6	85.9	88.6	75.8
40_20_468	84.1	85.9	77.6	85.9	88.6	75.8
40_31_79	82.9	85.5	73.1	85.9	88.6	75.8
4_76_91	86	87.5	80.6	85.9	88.6	75.8
15_5_4	84.4	85.9	79.1	85.9	87.8	78.8
15_40_23	85.1	88.3	73.1	85.9	87.8	78.8
15_40_115	86.3	89.1	76.1	85.9	87.8	78.8
15_12_23	87.9	91.1	76.1	85.9	87.8	78.8
15_4_54	85.7	87.5	79.1	85.9	87.8	78.8
15_4_88	86.3	87.9	80.6	85.9	87.8	78.8
15_4_143	86.7	88.7	79.1	85.9	87.8	78.8
15_4_468	85.7	87.5	79.1	85.9	87.8	78.8
15_4_469	86	87.9	79.1	85.9	87.8	78.8
15_4_91	89.5	91.9	80.6	85.9	87.8	78.8
5_40_79	83.8	85.9	76.1	85.9	87.8	78.8
5_79_115	84.8	85.9	80.6	85.9	87.8	78.8
40_4_20	85.1	85.5	83.6	85.9	87.8	78.8
40_20_145	85.4	86.7	80.6	85.9	87.8	78.8
40_121_79	84.8	86.7	77.6	85.9	87.8	78.8
4_54_468	84.1	86.7	74.6	85.9	87.8	78.8
15_5_40	83.5	87.5	68.7	85.9	87	81.8
15_12_4	87.6	89.9	79.1	85.9	87	81.8
15_4_102	86.3	87.9	80.3	85.9	87	81.8
15_29_115	89.8	91.9	82.1	85.9	87	81.8
5_20_115	87.6	87.9	86.6	85.9	87	81.8
5_121_115	86.7	88.3	80.6	85.9	87	81.8
5_64_115	86	86.3	85.1	85.9	87	81.8
5_469_91	85.4	86.7	80.6	85.9	87	81.8
40_23_4	85.1	85.1	85.1	85.9	87	81.8
40_4_29	86	85.5	88.1	85.9	87	81.8
40_20_88	81.3	81.9	79.1	85.9	87	81.8
40_31_88	81.3	81.5	80.6	85.9	87	81.8
12_39_121	89.8	91.5	83.6	85.9	87	81.8
12_11_91	84.8	85.5	82.1	85.9	87	81.8
12_31_91	84.4	85.1	82.1	85.9	87	81.8
4_88_91	83.5	83.1	85.1	85.9	87	81.8
5_40_11	81.9	83.9	74.6	85.9	86.2	84.8
5_40_467	83.5	85.5	76.1	85.9	86.2	84.8
5_40_108	81.9	83.9	74.6	85.9	86.2	84.8
5_121_468	86.3	87.5	82.1	85.9	86.2	84.8
40_12_11	84.8	85.9	80.6	85.9	86.2	84.8
4_88_143	82.9	83.5	80.6	85.9	86.2	84.8
5_40_29	81.9	83.1	77.6	85.9	85.4	87.9
5_40_143	82.9	83.5	80.6	85.9	85.4	87.9
5_40_89	82.9	84.3	77.6	85.9	85.4	87.9
12_121_115	83.8	84.7	80.6	85.9	85.4	87.9
12_31_471	85.1	86.3	80.6	85.9	85.4	87.9

TABLE 11

SEQ ID NO:	Training cohort			Validation cohort		
	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
15_40_115_121	91.1	94	80.6	94.2	95.1	90.9
12_15_115_121	93	95.6	83.6	94.2	95.1	90.9
15_115_121_471	91.4	94.8	79.1	94.2	95.1	90.9
15_91_115_121	91.4	94	82.1	94.2	95.1	90.9
12_15_64_115	89.5	92.7	77.6	93.6	95.1	87.9
15_39_115_121	91.1	94.8	77.6	92.9	95.1	84.8
15_20_115_121	92.4	93.1	89.6	92.9	94.3	87.9
15_23_115_121	91.1	93.5	82.1	92.9	93.5	90.9
15_94_115_121	91.4	94	82.1	92.9	93.5	90.9
15_62_115_121	91.4	94.4	80.6	92.9	93.5	90.9
15_115_121_143	90.5	93.5	79.1	92.9	93.5	90.9
15_115_121_134	90.8	94.4	77.6	92.9	93.5	90.9
12_15_91_115	90.2	92.7	80.6	92.3	95.1	81.8
12_15_121_145	89.5	91.5	82.1	92.3	94.3	84.8
15_91_121_143	91.1	94.8	77.6	92.3	94.3	84.8
15_91_121_145	89.8	93.1	77.6	92.3	94.3	84.8
5_12_15_121	90.8	93.1	82.1	92.3	93.5	87.9
12_15_29_121	91.1	94	80.6	92.3	93.5	87.9
12_15_88_121	90.5	93.5	79.1	92.3	93.5	87.9
12_15_79_121	89.8	93.5	76.1	92.3	93.5	87.9
12_15_121_471	90.5	94	77.6	92.3	93.5	87.9
12_15_121_473	90.2	93.5	77.6	92.3	93.5	87.9
15_23_91_121	91.4	93.1	85.1	92.3	93.5	87.9
15_62_91_121	92.1	94.4	83.6	92.3	93.5	87.9
15_102_115_121	91.1	94	80.3	92.3	93.5	87.9
15_108_115_121	90.5	93.5	79.1	92.3	93.5	87.9
12_15_40_121	90.8	94	79.1	92.3	92.7	90.9
4_12_15_121	89.2	91.5	80.6	92.3	92.7	90.9
12_15_20_121	90.8	92.7	83.6	92.3	92.7	90.9

TABLE 11-continued

SEQ ID NO:	Training cohort			Validation cohort		
	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
4_15_115_121	91.1	94	80.6	92.3	92.7	90.9
15_115_121_474	90.5	94	77.6	92.3	92.7	90.9
5_39_102_115	88.5	89.5	84.8	92.3	92.7	90.9
5_39_115_471	89.5	91.1	83.6	92.3	92.7	90.9
12_40_64_473	87	87.9	83.6	92.3	92.7	90.9
15_39_115_471	89.2	93.1	74.6	91.7	95.9	75.8
15_31_91_121	89.5	93.1	76.1	91.7	94.3	81.8
39_40_121_135	91.4	94.4	80.6	91.7	94.3	81.8
15_40_91_121	90.5	93.5	79.1	91.7	93.5	84.8
11_12_15_121	90.2	93.5	77.6	91.7	93.5	84.8
12_15_31_121	90.8	94	79.1	91.7	93.5	84.8
12_15_115_471	91.1	94	80.6	91.7	93.5	84.8
15_91_94_121	90.2	93.5	77.6	91.7	93.5	84.8
15_76_115_121	90.2	93.5	77.6	91.7	93.5	84.8
15_91_102_121	91.1	93.5	81.8	91.7	93.5	84.8
11_15_91_121	90.5	93.5	79.1	91.7	93.5	84.8
15_31_115_121	91.1	94.4	79.1	91.7	93.5	84.8
15_54_91_121	90.2	93.5	77.6	91.7	93.5	84.8
15_91_121_134	90.8	94	79.1	91.7	93.5	84.8
15_91_108_121	90.2	93.5	77.6	91.7	93.5	84.8
15_91_121_471	90.8	93.5	80.6	91.7	93.5	84.8
15_89_91_121	89.5	93.1	76.1	91.7	93.5	84.8
15_91_121_473	90.2	93.5	77.6	91.7	93.5	84.8
15_91_121_474	90.2	93.5	77.6	91.7	93.5	84.8
5_12_39_115	92.1	93.1	88.1	91.7	93.5	84.8
5_39_115_135	87.9	89.5	82.1	91.7	93.5	84.8
5_12_15_115	89.8	92.3	80.6	91.7	92.7	87.9
5_15_115_121	90.8	93.5	80.6	91.7	92.7	87.9
12_15_23_121	90.2	93.1	79.1	91.7	92.7	87.9
4_12_15_115	89.5	92.3	79.1	91.7	92.7	87.9
12_15_76_121	90.2	93.5	77.6	91.7	92.7	87.9
12_15_54_121	91.4	94	82.1	91.7	92.7	87.9
12_15_109_121	90.5	93.5	79.1	91.7	92.7	87.9
12_15_121_468	91.4	94	82.1	91.7	92.7	87.9
12_15_121_134	90.2	93.5	77.6	91.7	92.7	87.9
12_15_108_121	90.8	94	79.1	91.7	92.7	87.9
12_15_89_121	89.8	93.1	77.6	91.7	92.7	87.9
12_15_91_121	92.1	94.4	83.6	91.7	92.7	87.9
12_15_121_474	90.5	94	77.6	91.7	92.7	87.9
4_11_15_121	89.8	92.7	79.1	91.7	92.7	87.9
11_15_102_121	90.1	93.1	78.8	91.7	92.7	87.9
15_54_102_121	90.1	93.1	78.8	91.7	92.7	87.9
15_102_108_121	89.8	92.7	78.8	91.7	92.7	87.9
15_115_121_466	90.5	94	77.6	91.7	92.7	87.9
15_54_115_121	91.4	94.4	80.6	91.7	92.7	87.9
15_109_115_121	91.7	94.4	82.1	91.7	92.7	87.9
15_64_115_121	91.7	95.2	79.1	91.7	92.7	87.9
15_88_115_121	90.2	93.5	77.6	91.7	92.7	87.9
15_79_115_121	91.7	95.6	77.6	91.7	92.7	87.9
15_115_121_145	90.5	94	77.6	91.7	92.7	87.9
15_115_121_468	90.8	93.5	80.6	91.7	92.7	87.9
15_23_121_471	90.8	93.5	80.6	91.7	91.9	90.9
4_15_109_121	90.8	93.1	82.1	91.7	91.9	90.9
15_62_121_471	91.4	94.8	79.1	91.7	91.9	90.9
11_15_115_121	90.5	93.5	79.1	91.7	91.9	90.9
15_39_40_115	88.6	91.5	77.6	91	95.1	75.8
15_31_40_121	89.2	93.1	74.6	91	94.3	78.8
15_23_39_115	87.3	91.1	73.1	91	94.3	78.8
15_31_39_121	91.1	95.2	76.1	91	94.3	78.8
15_79_121_468	91.7	95.6	77.6	91	94.3	78.8
20_39_40_115	90.5	92.7	82.1	91	94.3	78.8
12_15_115_134	90.2	93.5	77.6	91	93.5	81.8
15_39_121_468	91.4	94.4	80.6	91	93.5	81.8
15_39_91_121	91.4	94.8	79.1	91	93.5	81.8
15_31_109_121	90.8	94.4	77.6	91	93.5	81.8
15_31_64_121	90.2	94.4	74.6	91	93.5	81.8
15_64_121_134	89.8	94	74.6	91	93.5	81.8
15_88_91_121	90.5	94.4	76.1	91	93.5	81.8
15_79_91_121	91.4	95.2	77.6	91	93.5	81.8
5_12_91_115	93	93.5	91	91	91.1	90.9
5_12_76_115	90.8	91.9	86.6	89.7	91.9	81.8
4_15_29_115	91.1	92.3	86.6	89.7	91.1	84.8
12_15_23_115	90.2	92.7	80.6	89.7	92.7	78.8
5_12_115_472	91.1	91.5	89.6	89.7	91.1	84.8

TABLE 11-continued

	Training cohort			Validation cohort		
SEQ ID NO:	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
15_39_76_121	91.1	94.4	79.1	89.7	91.9	81.8
12_15_23_115	90.2	92.7	80.6	89.7	99.7	78.8
15_40_121_134	90.8	93.5	80.6	89.7	91.1	84.8
4_5_12_115	89.5	90.3	86.6	89.1	88.6	90.9
5_12_115_469	90.8	91.5	88.1	89.1	91.1	81.8
5_12_115_143	91.1	91.9	88.1	88.5	88.6	87.9
5_12_40_115	90.5	91.1	88.1	88.5	89.4	84.8
5_12_23_115	88.9	89.5	86.6	87.8	88.6	84.8
5_12_29_115	89.8	89.9	89.6	87.8	88.6	84.8
12_40_472_473	86.3	87.5	82.1	87.2	87.8	84.8
1_12_15_29	86.3	88.3	79.1	86.5	88.6	78.8
4_15_54_115	88.9	90.7	82.1	86.5	88.6	78.8
5_54_76_115	87.9	89.1	83.6	86.5	90.2	72.7
4_12_15_474	88.3	90.3	80.6	85.9	87	81.8
15_54_76_79	85.4	90.3	67.2	85.3	89.4	69.7
15_54_76_473	84.8	88.7	70.1	85.3	90.2	66.7
15_54_76_115	88.3	93.5	68.7	85.3	88.6	72.7
15_40_54_76	85.7	89.1	73.1	85.3	88.6	72.7
12_23_40_466	86.3	87.9	80.6	84	84.6	81.8
12_23_40_134	85.7	85.1	88.1	83.3	82.9	84.8
4_5_12_76	85.4	86.3	82.1	82.1	83.7	75.8

Comparative Example 1

<Biliary Tract Cancer Discriminant Performance of Existing Tumor Markers in Blood>

The concentrations of the existing tumor markers CEA and CA19-9 in blood were measured in the training cohort and the validation cohort obtained in Reference Example 1 above. When the concentrations of these tumor markers in blood are higher than the reference values described in Non-patent Literature 2 (CEA: 5 ng/mL. CA19-9: 37 U/mL), subjects are usually suspected of having cancer. Thus, whether or not the concentrations of CEA and CA19-9 in blood exceeded their reference values was confirmed for each sample, and the obtained results were assessed for the ability of these tumor markers to detect cancer in biliary tract cancer patients. The sensitivity of each existing marker in the training cohort and the validation cohort was calculated. The results are shown in Table 5. The sensitivity of CEA and CA19-9 was as low as 31.3% and 68.2%, respectively, in the training cohort, and was as low as 33.3% and 59.4%, respectively, in the validation cohort, demonstrating that neither of the markers is useful in the detection of biliary tract cancer (Table 5).

On the other hand, as shown above in Tables 3 and 4 of Examples 1 and 2, it can be concluded that all of the polynucleotides consisting of the nucleotide sequences represented by SEQ ID NOs: 1 to 125 have combinations of 1, 2 or more polynucleotides exhibiting sensitivity beyond the existing biliary tract cancer markers and thus serve as excellent diagnosis markers.

As shown in these Examples and Comparative Example, the kit, etc, and the method of the present invention can detect biliary tract cancer with higher sensitivity than the existing tumor markers and therefore permit early decision to carry out the surgical resection of a cancer site. As a result, improvement in 5-year survival rate and reduction in the rate of recurrence can be achieved.

INDUSTRIAL APPLICABILITY

According to the present invention, biliary tract cancer can be effectively detected by a simple and inexpensive method. This enables early detection, diagnosis and treatment of biliary tract cancer. The method of the present invention can detect biliary tract cancer with limited invasiveness using the blood of a patient and therefore allows biliary tract cancer to be detected conveniently and rapidly.

All publications, patents, and patent applications cited herein are incorporated herein by reference in their entirety.

SEQUENCE LISTING

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cuggggggag gagacccugc u 21

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guaggggcgu cccgggcgcg cggg 24

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agggccgaag gguggaagcu gc 22

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cggugagcgc ucgcuggc 18

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cccagcagga cgggagcg 18

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auccuaguca cggcacca 18

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uucccagcca acgcacca 18

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gugucugggc ggacagcugc 20

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ggggaggugu gcagggcugg 20

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gggggucccc ggugcucgga uc 22

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uggggauuug gagaaguggu ga 22

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cgggagcugg ggucugcagg u 21

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<400> SEQUENCE: 33

ugagggaccc aggacaggag a 21

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gcugcgggcu gcggucaggg cg                                               22


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<400> SEQUENCE: 35

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cggggugggu gaggucgggc                                                  20


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ggaugguugg gggcggucgg cgu                                              23


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<400> SEQUENCE: 39

gugaguggga gccccagugu gug                                              23


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ugguggagga agagggcagc uc                                               22


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ugggggagcc augagauaag agca                                               24


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uguagagcag ggagcaggaa gcu                                                23


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gcggaaggcg gagcggcgga                                                    20


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ggggagcgag ggcggggc                                                      19


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<400> SEQUENCE: 46

ucuguggagu ggggugccug u                                                  21


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aggcacggug ucagcaggc                                                     19


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aaaccguuac cauuacugag uu                                                 22


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ggcuggagcg agugcagugg ug 22

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cuccgggacg gcugggc 17

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cugggggacg cgugagcgcg agc 23

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caggcacggg agcucaggug ag 22

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gugcggaacg cuggccgggg cg 22

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<400> SEQUENCE: 54

gugcguggug gcucgaggcg ggg 23

<210> SEQ ID NO 55
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<400> SEQUENCE: 55

uucagauccc agcggugccu cu 22

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<400> SEQUENCE: 56

cccaugccuc cugccgcggu c 21

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acaggagugg gggugggaca u 21

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guggggccag gcggugg 17

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agaggcuuug ugcggauacg ggg 23

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cggggucggc ggcgacgug 19

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agaagaaggc ggucggucug cgg 23

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ccggccgccg gcuccgcccc g 21

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cgggccggag gucaagggcg u 21

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uagggggcgg cuuguggagu gu 22

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ccuggggaca ggggauuggg gcag                                              24


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<213> ORGANISM: Homo sapiens

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accaggaggc ugaggccccu                                                   20


<210> SEQ ID NO 67
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<400> SEQUENCE: 67

gcugggcgag gcuggca                                                      17


<210> SEQ ID NO 68
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<400> SEQUENCE: 68

ugcaggggug gggugggcca gg                                                22


<210> SEQ ID NO 69
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<400> SEQUENCE: 69

aucccaccuc ugccacca                                                     18


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<400> SEQUENCE: 70

gccccggcgc gggcggguuc ugg                                               23


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<400> SEQUENCE: 71

gugggugcug gugggagccg ug                                                22


<210> SEQ ID NO 72
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<400> SEQUENCE: 72

aucccaccac ugccaccau                                                    19


<210> SEQ ID NO 73
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

aauggauuuu uggagcagg 19

<210> SEQ ID NO 74
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<400> SEQUENCE: 74

cggggccaga gcagagagc 19

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<400> SEQUENCE: 75

acucggcugc gguggacaag u 21

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<400> SEQUENCE: 76

aaggggcugg gggagcaca 19

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<400> SEQUENCE: 77

ucacaccugc cucgcccccc 20

<210> SEQ ID NO 78
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<400> SEQUENCE: 78

ggauggagga ggggucu 17

<210> SEQ ID NO 79
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<400> SEQUENCE: 79

cugaauagcu gggacuacag gu 22

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<400> SEQUENCE: 80

cgggcugucc ggaggggucg gcu 23

<210> SEQ ID NO 81
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<212> TYPE: RNA
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<400> SEQUENCE: 81

caggaguggg gggugggacg u                                               21


<210> SEQ ID NO 82
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<400> SEQUENCE: 82

cggguagaga gggcaguggg agg                                             23


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<400> SEQUENCE: 83

cuuccgcccc gccgggcguc g                                               21


<210> SEQ ID NO 84
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<400> SEQUENCE: 84

agacugacgg cuggaggccc au                                              22


<210> SEQ ID NO 85
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<400> SEQUENCE: 85

cagggcuggc agugacaugg gu                                              22


<210> SEQ ID NO 86
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<400> SEQUENCE: 86

gcugggauua caggcaugag cc                                              22


<210> SEQ ID NO 87
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

uggggcgggg caggucccug c                                               21


<210> SEQ ID NO 88
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<212> TYPE: RNA
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<400> SEQUENCE: 88

agugggagga caggaggcag gu                                              22


<210> SEQ ID NO 89
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

uggcucaguu cagcaggaac ag                                              22


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<400> SEQUENCE: 90

ccccagggcg acgcggcggg                                                 20


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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

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cucggccgcg gcgcguagcc cccgcc                                          26


<210> SEQ ID NO 92
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<400> SEQUENCE: 92

cgucccgggg cugcgcgagg ca                                              22


<210> SEQ ID NO 93
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

ucggggaguc uggggguccgg aau                                            23


<210> SEQ ID NO 94
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

cggggcagcu caguacagga u                                               21


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<400> SEQUENCE: 95

ccucccugcc cgccucucug cag                                             23


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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

agacacauuu ggagagggaa cc                                              22
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<400> SEQUENCE: 97

cguggaggac gaggaggagg c                                            21


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cacacaggaa aagcggggcc cug                                          23


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<400> SEQUENCE: 99

uggauuuuug gaucaggga                                               19


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guguggccgg caggcgggug g                                            21


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<400> SEQUENCE: 101

agggacggga cgcggugcag ug                                           22


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<400> SEQUENCE: 102

gguggcccgg ccgugccuga gg                                           22


<210> SEQ ID NO 103
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<400> SEQUENCE: 103

guggguuggg gcgggcucug                                              20


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<400> SEQUENCE: 104

uggcggcggu aguuaugggc uu                                           22
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

gugaggaggg gcuggcaggg ac 22

<210> SEQ ID NO 106
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<400> SEQUENCE: 106

ggugggcuuc ccggaggg 18

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agcaggugcg gggcggcg 18

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aggcagguua ucugggcug 19

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uggcuguugg agggggcagg c 21

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cggcggggac ggcgauuggu c 21

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<400> SEQUENCE: 111

auccaguucu cugagggggc u 21

<210> SEQ ID NO 112
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

accccacucc ugguacc 17

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<400> SEQUENCE: 113

cuucccccca guaaucuuca uc                                              22


<210> SEQ ID NO 114
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<212> TYPE: RNA
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<400> SEQUENCE: 114

ccccuggggc ugggcaggcg ga                                              22


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<212> TYPE: RNA
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<400> SEQUENCE: 115

gugccagcug caguggggga g                                               21


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<400> SEQUENCE: 116

ggcgggugcg gggugg                                                     17


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<212> TYPE: RNA
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<400> SEQUENCE: 117

agcggugcuc cugcgggccg a                                               21


<210> SEQ ID NO 118
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<400> SEQUENCE: 118

ugaggggccu cagaccgagc uuuu                                            24


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<400> SEQUENCE: 119

acaggcggcu guagcaaugg ggg                                             23


<210> SEQ ID NO 120
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120
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ucucuucauc uaccccccag                                                  20


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<400> SEQUENCE: 121

agcagggcug gggauugca                                                   19


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<400> SEQUENCE: 122

ggcuacaaca caggacccgg gc                                               22


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<400> SEQUENCE: 123

ugggggagga aggacaggcc au                                               22


<210> SEQ ID NO 124
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<400> SEQUENCE: 124

gggcuggggc gcggggaggu                                                  20


<210> SEQ ID NO 125
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 125

cugggagggg cuggguuugg c                                                21


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<400> SEQUENCE: 126

caggcaggga ggugggacca ug                                               22


<210> SEQ ID NO 127
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<212> TYPE: RNA
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<400> SEQUENCE: 127

acuugggcag gagggacccu guaug                                            25


<210> SEQ ID NO 128
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ugggcugagg gcaggaggcc ugu                                          23


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<400> SEQUENCE: 129

uguaggcaug aggcagggcc cagg                                         24


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<400> SEQUENCE: 130

agugggaggc cagggcacgg ca                                           22


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<400> SEQUENCE: 131

gggggggcag gaggggcuca ggg                                          23


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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

cugggcucgg gacgcgcggc u                                            21


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<400> SEQUENCE: 133

uuggggaaac ggccgcugag ug                                           22


<210> SEQ ID NO 134
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<400> SEQUENCE: 134

agcaugacag aggagaggug g                                            21


<210> SEQ ID NO 135
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<400> SEQUENCE: 135

gggaccaucc ugccugcugu gg                                           22


<210> SEQ ID NO 136
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<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 136

gggugggau uuguugcauu ac                                            22


<210> SEQ ID NO 137
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

cggggccgua gcacugucug aga                                          23


<210> SEQ ID NO 138
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

agggaucgcg ggcggguggc ggccu                                        25


<210> SEQ ID NO 139
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

ggggccuggc ggugggcgg                                               19


<210> SEQ ID NO 140
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 140

acucaaacug ugggggcacu                                              20


<210> SEQ ID NO 141
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 141

gcagggacag caaaggggug c                                            21


<210> SEQ ID NO 142
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 142

accacugcac uccagccuga g                                            21


<210> SEQ ID NO 143
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 143

cccggagcca ggaugcagcu c                                            21


<210> SEQ ID NO 144
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 144

uggaguguga caaugguguu ug                                              22


<210> SEQ ID NO 145
<211> LENGTH: 17
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 145

ccccgccacc gccuugg                                                    17


<210> SEQ ID NO 146
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 146

aaaaggcggg agaagcccca                                                 20


<210> SEQ ID NO 147
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 147

ugugggacug caaaugggag                                                 20


<210> SEQ ID NO 148
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 148

uggggaaggc uuggcaggga aga                                             23


<210> SEQ ID NO 149
<211> LENGTH: 86
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 149

ugccagucuc uaggucccug agacccuuua accugugagg acauccaggg ucacagguga      60

gguucuuggg agccuggcgu cuggcc                                          86


<210> SEQ ID NO 150
<211> LENGTH: 69
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 150

ccgggcaggc agguguaggg uggagcccac uguggcuccu gacucagccc ugcugccuuc      60

accugccag                                                             69


<210> SEQ ID NO 151
<211> LENGTH: 110
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 151

ggcuacaguc uuucuucaug ugacucgugg acuucccuuu gucauccuau gccugagaau      60
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auaugaagga ggcugggaag gcaaagggac guucaauugu caucacuggc              110


<210> SEQ ID NO 152
<211> LENGTH: 70
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 152

aaaagccugu cccuaagucc cucccagccu uccagaguug gugccaggaa ggauuuaggg     60

acaggcuuug                                                             70


<210> SEQ ID NO 153
<211> LENGTH: 76
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 153

ccgaugccuc gggagucuac agcagggcca ugucugugag ggcccaaggg ugcauguguc     60

ucccagguuu cggugc                                                      76


<210> SEQ ID NO 154
<211> LENGTH: 84
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 154

cuccccaugg cccugucucc caacccuugu accagugcug ggcucagacc cugguacagg     60

ccugggggac agggaccugg ggac                                             84


<210> SEQ ID NO 155
<211> LENGTH: 65
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 155

gagggugggc gagggcggcu gagcggcucc aucccccggc cugcucaucc cccucgcccu     60

cucag                                                                  65


<210> SEQ ID NO 156
<211> LENGTH: 61
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 156

ucucguuuga ucucggaagc uaagcagggu ugggccuggu uaguacuugg augggaaacu     60

u                                                                      61


<210> SEQ ID NO 157
<211> LENGTH: 53
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 157

guuugaucuc ggaagcuaag cagggucggg ccugguuagu acuuggaugg gag             53


<210> SEQ ID NO 158
<211> LENGTH: 87
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 158
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gugaggcggg gccaggaggg ugugugggcgu gggugcugcg gggccgucag ggugccugcg 60

ggacgcucac cuggcuggcc cgcccag 87

<210> SEQ ID NO 159
<211> LENGTH: 62
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 159

ccuucugcgg cagagcuggg gucaccagcc cucauguacu ugugacuucu ccccugccac 60

ag 62

<210> SEQ ID NO 160
<211> LENGTH: 94
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 160

aauucagccc ugccacuggc uuaugucaug accuugggcu acucaggcug ucugcacaau 60

gagccaguug gacaggagca gugccacuca acuc 94

<210> SEQ ID NO 161
<211> LENGTH: 63
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 161

ggcuccgcag ggcccuggcg caggcaucca gacagcgggc gaaugccucc cccggccccg 60

cag 63

<210> SEQ ID NO 162
<211> LENGTH: 47
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 162

cucggcgcgg ggcgcgggcu ccggguuggg gcgagccaac gccgggg 47

<210> SEQ ID NO 163
<211> LENGTH: 93
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 163

ccuuccggcg ucccaggcgg ggcgccgcgg gaccgcccuc gugucugugg cggugggauc 60

ccgcggccgu guuuuccugg uggcccggcc aug 93

<210> SEQ ID NO 164
<211> LENGTH: 95
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 164

gacaccacau gcuccuccag gccugccugc ccuccagguc auguuccagu gucccacaga 60

ugcagcacca cggcccaggc ggcauuggug ucacc 95

<210> SEQ ID NO 165
<211> LENGTH: 54
<212> TYPE: RNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 165

ggacaagggc ggcgcgaccg gcccggggcu cuugggcggc cgcguuuccc cucc 54

<210> SEQ ID NO 166
<211> LENGTH: 94
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 166

auaaaggaag uuaggcugag gggcagagag cgagacuuuu cuauuuucca aaagcucggu 60

cugaggcccc ucagucuugc uuccuaaccc gcgc 94

<210> SEQ ID NO 167
<211> LENGTH: 55
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 167

ccggauccga gucacggcac caaauuucau gcguguccgu gugaagagac cacca 55

<210> SEQ ID NO 168
<211> LENGTH: 65
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 168

gucuccuggg gggaggagac ccugcucucc cuggcagcaa gccucuccug cccuuccaga 60

uuagc 65

<210> SEQ ID NO 169
<211> LENGTH: 98
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 169

cgagguaggg gcgucccggg cgcgcgggcg gguccccaggc ugggccccuc ggaggccggg 60

ugcucacugc cccgucccgg cgcccguguc uccuccag 98

<210> SEQ ID NO 170
<211> LENGTH: 64
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 170

aguucagggc cgaagggugg aagcugcugg ugcucaucuc agccucugcc cuuggccucc 60

ccag 64

<210> SEQ ID NO 171
<211> LENGTH: 74
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 171

gcagcccggu gagcgcucgc uggccuggca gugcgucgga agaacagggc gggugggggcc 60

gcgcacaucu cugc 74

<210> SEQ ID NO 172
<211> LENGTH: 56

<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 172

cgaccgcacc cgcccgaagc ugggucaagg agcccagcag gacgggagcg cggcgc 56

<210> SEQ ID NO 173
<211> LENGTH: 68
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 173

gugcaaagag caggaggaca ggggauuuau cucccaaggg agguccccug auccuaguca 60

cggcacca 68

<210> SEQ ID NO 174
<211> LENGTH: 92
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 174

cgcugcgcuu cugggcccgc ggcgggcgug gggcugcccg ggccggucga ccagcgcgcc 60

guagcucccg aggcccgagc cgcgacccgc gg 92

<210> SEQ ID NO 175
<211> LENGTH: 72
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 175

gauuucagug accuggcagc agggagcguc gucaguguuu gacuguuuau gguaugucag 60

ggagcugguu cc 72

<210> SEQ ID NO 176
<211> LENGTH: 49
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 176

uucccagcca acgcaccaaa aaugauaugg gucuguuguc uggagaaac 49

<210> SEQ ID NO 177
<211> LENGTH: 92
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 177

gucagugucu gggcggacag cugcaggaaa gggaagacca aggcuugcug ucuguccagu 60

cugccacccu acccugucug uucuugccac ag 92

<210> SEQ ID NO 178
<211> LENGTH: 69
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 178

gaggagggga ggugugcagg gcuggggguca cugacucugc uuccccugcc cugcauggug 60

uccccacag 69

<210> SEQ ID NO 179

<211> LENGTH: 96
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 179

cucgggaggg gcgggagggg gguccccggu gcucggaucu cgagggugcu uauuguucgg 60

uccgagccug ggucucccuc uucccccccaa cccccc 96

<210> SEQ ID NO 180
<211> LENGTH: 65
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 180

ugucuggggga uuuggagaag uggugagcgc aggucuuugg caccaucucc ccuggucccu 60

uggcu 65

<210> SEQ ID NO 181
<211> LENGTH: 61
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 181

gggggcggga gcuggggucu gcagguucgc acugaugccu gcucgcccug ucuccccgcua 60

g 61

<210> SEQ ID NO 182
<211> LENGTH: 72
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182

gagucugagg gacccaggac aggagaaggc cuauggugau uugcauucuu ccugcccugg 60

cuccauccuc ag 72

<210> SEQ ID NO 183
<211> LENGTH: 70
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 183

cucgggcccg accgcgccgg cccgcaccuc ccggcccgga gcugcgggcu gcggucaggg 60

cgaucccggg 70

<210> SEQ ID NO 184
<211> LENGTH: 89
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 184

gucagcagug ccuuagcagc acguaaauau uggcguuaag auucuaaaau uaucuccagu 60

auuaacugug cugcugaagu aagguugac 89

<210> SEQ ID NO 185
<211> LENGTH: 81
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 185

guuccacucu agcagcacgu aaauauuggc guagugaaau auauauuaaa caccaauauu 60 acugugcugc uuuaguguga c 81

<210> SEQ ID NO 186
<211> LENGTH: 98
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 186

uucucacccc cgccugacac gggcgacagc ugcggcccgc uguguucacu cgggccgagu 60

gcgucuccug ucaggcaagg gagagcagag cccccccug 98

<210> SEQ ID NO 187
<211> LENGTH: 73
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 187

cggcgacggc ggggugggug aggucgggcc ccaagacucg ggguuugccg ggcgccucag 60

uucaccgcgg ccg 73

<210> SEQ ID NO 188
<211> LENGTH: 86
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 188

cgccugagcg ugcagcagga caucuuccug accugguaau aauuagguga gaaggauggu 60

ugggggcggu cggcguaacu caggga 86

<210> SEQ ID NO 189
<211> LENGTH: 83
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 189

gugagugggа gccccagugu gugguugggg ccauggcggg ugggcagccc agccucugag 60

ccuuccucgu cugucugccc cag 83

<210> SEQ ID NO 190
<211> LENGTH: 62
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 190

gaggguggug gaggaagagg gcagcuccca ugacugccug accgccuucu cuccuccccc 60

ag 62

<210> SEQ ID NO 191
<211> LENGTH: 80
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 191

gcgucaagau ggcggcgggg agguaggcag agcaggacgc cgcugcugcc gccgccaccg 60

ccgccuccgc uccagucgcc 80

<210> SEQ ID NO 192
<211> LENGTH: 81
<212> TYPE: RNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 192

aguugguggg ggagccauga gauaagagca ccuccuagag aauguugaac uaaaggugcc 60

cucucuggcu ccucccccaaa g 81

<210> SEQ ID NO 193
<211> LENGTH: 76
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 193

gagggagcug uagagcaggg agcaggaagc uguguguguc cagcccugac cuguccuguu 60

cugccccccag ccccuc 76

<210> SEQ ID NO 194
<211> LENGTH: 96
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 194

gcucuggggc gugccgccgc cgucgcugcc accucccccua ccgcuagugg aagaagaugg 60

cggaaggcgg agcggcggau cuggacaccc agcggu 96

<210> SEQ ID NO 195
<211> LENGTH: 60
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 195

cgcugggucc gcgcgcccug ggccgggcga uguccgcuug ggggagcgag gggcggggcg 60

<210> SEQ ID NO 196
<211> LENGTH: 61
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 196

uccgcucugu ggaguggggu gccugucccc ugccacuggg ugacccaccc cucuccacca 60

g 61

<210> SEQ ID NO 197
<211> LENGTH: 94
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 197

cgggcagcgg gugccaggca cggugucagc aggcaacaug gccgagaggc cggggccucc 60

gggcggcgcc guguccgcga ccgcguaccc ugac 94

<210> SEQ ID NO 198
<211> LENGTH: 72
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 198

cuugggaaug gcaaggaaac cguuaccauu acugaguuua guaaugguaa ugguucucuu 60

gcuauaccca ga 72

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<210> SEQ ID NO 199
<211> LENGTH: 68
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 199

ugcccaggcu ggagcgagug caguggugca gucaguccua gcucacugca gccucgaacu      60

ccugggcu                                                               68


<210> SEQ ID NO 200
<211> LENGTH: 89
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 200

accuccggga cggcugggcg ccggcggccg ggagauccgc gcuuccugaa ucccggccgg      60

cccgcccggc gcccguccgc ccgcggguc                                        89


<210> SEQ ID NO 201
<211> LENGTH: 79
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 201

cucgaggugc ugggggacgc gugagcgcga gccgcuuccu cacggcucgg ccgcggcgcg      60

uagcccccgc cacaucggg                                                   79


<210> SEQ ID NO 202
<211> LENGTH: 83
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 202

aauagagggu gcacaggcac gggagcucag gugaggcagg gagcugagcu caccugaccu      60

cccaugccug ugcacccucu auu                                              83


<210> SEQ ID NO 203
<211> LENGTH: 61
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 203

gugcggaacg cuggccgggg cgggagggga agggacgccc ggccggaacg ccgcacucac      60

g                                                                      61


<210> SEQ ID NO 204
<211> LENGTH: 74
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 204

gugcguggug gcucgaggcg gggguggggg ccucgcccug cuugggcccu cccugaccuc      60

uccgcuccgc acag                                                        74


<210> SEQ ID NO 205
<211> LENGTH: 119
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 205
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ccaugaggag cuggcagugg gauggccugg ggguaggagc guggcuucug gagcuagacc      60

acaugggguuc agaucccagc ggugccucua acuggccaca ggaccuuggg cagucagcu     119


<210> SEQ ID NO 206
<211> LENGTH: 62
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 206

gugggucucg caucaggagg caaggccagg acccgcugac ccaugccucc ugccgcgguc      60

ag                                                                      62


<210> SEQ ID NO 207
<211> LENGTH: 81
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 207

cauccuccuu acgucccacc ccccacuccu guuucuggug aaauauucaa acaggagugg      60

gggugggaca uaaggaggau a                                                 81


<210> SEQ ID NO 208
<211> LENGTH: 88
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 208

guggggccag gcgguggugg gcacugcugg ggugggcaca gcagccaugc agagcgggca      60

uuugaccccg ugccacccuu uuccccag                                          88


<210> SEQ ID NO 209
<211> LENGTH: 85
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 209

ggcgccuccu gcucugcugu gccgccaggg ccuccccuag cgcgccuucu ggagaggcuu      60

ugugcggaua cggggcugga ggccu                                             85


<210> SEQ ID NO 210
<211> LENGTH: 59
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 210

cggggucggc ggcgacgugc ucagcuuggc acccaaguuc ugccgcuccg acgcccggc       59


<210> SEQ ID NO 211
<211> LENGTH: 68
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 211

gaauggaaga agaaggcggu cggucugcgg gagccaggcc gcagagccau ccgccuucug      60

uccauguc                                                                68


<210> SEQ ID NO 212
<211> LENGTH: 80
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 212

cgggaaugcc gcggcgggga cggcgauugg uccguaugug uggugccacc ggccgccggc      60

uccgccccgg cccccgcccc                                                  80


<210> SEQ ID NO 213
<211> LENGTH: 64
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 213

aaccccgggc cggaggucaa gggcgucgcu ucucccuaau guugccucuu uuccacggcc      60

ucag                                                                   64


<210> SEQ ID NO 214
<211> LENGTH: 62
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 214

uggccuaggg ggcggcuugu ggaguguaug ggcugagccu ugcucugcuc ccccgccccc      60

ag                                                                     62


<210> SEQ ID NO 215
<211> LENGTH: 82
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 215

aaggagcacu cacuccaauu ucccuggacu gggggcaggc ugccaccucc uggggacagg      60

ggauuggggc aggauguucc ag                                               82


<210> SEQ ID NO 216
<211> LENGTH: 72
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 216

ucuccucgag ggucucugcc cucuacccag gacucuuuca ugaccaggag gcugaggccc      60

cucacaggcg gc                                                          72


<210> SEQ ID NO 217
<211> LENGTH: 63
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 217

gcaugcuggg cgaggcuggc aucuagcaca ggcgguagau gcuugcucuu gccauugcaa      60

uga                                                                    63


<210> SEQ ID NO 218
<211> LENGTH: 78
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 218

ggccucaggc aggcgcaccc gaccacaugc auggcuggug gcggcgugca ggggucgggu      60

gggccaggcu guggggcg                                                    78
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<210> SEQ ID NO 219
<211> LENGTH: 73
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 219

accuuuccag cucaucccac cucugccacc aaaacacuca ucgcggggUc agagggagug 60

ccaaaaaagg uaa 73

<210> SEQ ID NO 220
<211> LENGTH: 80
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 220

gguuccggag ccccggcgcg ggcggguucu ggggugUaga cgcugcuggc cagcccgccc 60

cagccgaggu ucucggcacc 80

<210> SEQ ID NO 221
<211> LENGTH: 63
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 221

aaugggUggg ugcuggUggg agccgugccc uggccacuca uucggcucuc ucccucaccc 60

uag 63

<210> SEQ ID NO 222
<211> LENGTH: 89
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 222

ucuccguuua ucccaccacu gccaccauua uugcuacugu ucagcaggug cugcuggugg 60

ugauggugau agucuggugg gggcggugg 89

<210> SEQ ID NO 223
<211> LENGTH: 73
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 223

uguauccuug aauggauuuu uggagcagga guggacaccu gacccaaagg aaaucaaucc 60

auaggcuagc aau 73

<210> SEQ ID NO 224
<211> LENGTH: 61
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 224

aacugcgggg ccagagcaga gagcccuugc acaccaccag ccucuccucc cugugcccca 60

g 61

<210> SEQ ID NO 225
<211> LENGTH: 68
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 225

gacucggcug cgguggacaa guccggcucc agaaccugga caccgcucag ccggccgcgg 60

caggggguc 68

<210> SEQ ID NO 226
<211> LENGTH: 110
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 226

gucuaccagg ugugggccca gcuuuacaua guucaugcug aggccgggau uucaugcaga 60

aaacugguug caaaaggugc ugaaggggcu gggggagcac aagggagaag 110

<210> SEQ ID NO 227
<211> LENGTH: 73
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 227

gugggcgggg gcaggugugu gguggguggu ggccugcggu gagcagggcc cucacaccug 60

ccucgccccc cag 73

<210> SEQ ID NO 228
<211> LENGTH: 60
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 228

ugugaaugac cccuuccag agccaaaauc accagggaug gaggaggggu cuuggguacu 60

<210> SEQ ID NO 229
<211> LENGTH: 59
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 229

ugaaguacca gcuacucgag aggucagagg auugcuccug aauagcuggg acuacaggu 59

<210> SEQ ID NO 230
<211> LENGTH: 90
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 230

cgggcggggc ggguccggcc gccuccgagc ccggccggca gcccccggcc uuaaagcgcg 60

ggcuguccgg aggggucggc uuucccaccg 90

<210> SEQ ID NO 231
<211> LENGTH: 102
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 231

uguguucccu auccuccuua ugucccaccc ccacuccugu uugaauauuu caccagaaac 60

aggagugggg ggugggacgu aaggaggaug ggggaaagaa ca 102

<210> SEQ ID NO 232
<211> LENGTH: 75
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 232

ggcugugccg gguagagagg gcagugggag guaagagcuc uucacccuuc accaccuucu 60

ccacccagca uggcc 75

<210> SEQ ID NO 233
<211> LENGTH: 70
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 233

ggccgcggcg cgcaagaugg cggcgggccc gggcaccgcc ccuuccgccc cgccgggcgu 60

cgcacgaggc 70

<210> SEQ ID NO 234
<211> LENGTH: 86
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 234

auucuaggug gggagacuga cggcuggagg cccauaagcu gucuaaaacu ucggcccccca 60

gauuucuggu cuccccacuu cagaac 86

<210> SEQ ID NO 235
<211> LENGTH: 67
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 235

cugguccauu ucccugccau ucccuuggcu ucaauuuacu cccagggcug gcagugacau 60

gggucaa 67

<210> SEQ ID NO 236
<211> LENGTH: 99
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 236

cgcccaccuc agccucccaa aaugcuggga uuacaggcau gagccacugc ggucgaccau 60

gaccuggaca uguuugugcc caguacuguc aguuugcag 99

<210> SEQ ID NO 237
<211> LENGTH: 66
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 237

ccgagugggg cggggcaggu cccugcaggg acugugacac ugaaggaccu gcaccuucgc 60

ccacag 66

<210> SEQ ID NO 238
<211> LENGTH: 73
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 238

guucaagugg gaggacagga ggcaggugug guuggaggaa gcagccugaa ccugccuccc 60

ugacauucca cag 73

```
<210> SEQ ID NO 239
<211> LENGTH: 68
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 239

cuccggugcc uacugagcug auaucaguuc ucauuuuaca cacuggcuca guucagcagg     60

aacaggag                                                              68


<210> SEQ ID NO 240
<211> LENGTH: 73
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 240

cucugccucc cgugccuacu gagcugaaac acaguugguu uguguacacu ggcucaguuc     60

agcaggaaca ggg                                                        73


<210> SEQ ID NO 241
<211> LENGTH: 80
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 241

ugagaggccg caccuugccu ugcugcccgg gccgugcacc cgugggcccc agggcgacgc     60

ggcgggggcg gcccuagcga                                                 80


<210> SEQ ID NO 242
<211> LENGTH: 66
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 242

agcagcccuc ggcggcccgg ggggcgggcg gcggugcccg ucccggggcu gcgcgaggca     60

caggcg                                                                66


<210> SEQ ID NO 243
<211> LENGTH: 59
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 243

cugugucggg gagucugggg uccggaauuc uccagagccu cugugccccu acuucccag      59


<210> SEQ ID NO 244
<211> LENGTH: 68
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 244

gcauccugua cugagcugcc ccgaggcccu ucaugcugcc cagcucgggg cagcucagua     60

caggauac                                                              68


<210> SEQ ID NO 245
<211> LENGTH: 64
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 245

uccuguacug agcugccccg agcugggcag caugaagggc cucggggcag cucaguacag     60
```

gaug 64

<210> SEQ ID NO 246
<211> LENGTH: 59
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 246

cuccagggag acagugugug aggccucuug ccauggccuc ccugcccgcc ucucugcag 59

<210> SEQ ID NO 247
<211> LENGTH: 97
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 247

aucugaguug ggagggucccc ucuccaaaug ugucuugggg ugggggauca agacacauuu 60

ggagagggaa ccucccaacu cggccucugc caucauu 97

<210> SEQ ID NO 248
<211> LENGTH: 103
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 248

gugucggcug uggcgugacu gucccucugu gucccccacu aggcccacug cucaguggag 60

cguggaggac gaggaggagg ccguccacga gcaaugccag cau 103

<210> SEQ ID NO 249
<211> LENGTH: 72
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 249

ccaggcacac aggaaaagcg gggcccuggg uucggcugcu accccaaagg ccacauucuc 60

cugugcacac ag 72

<210> SEQ ID NO 250
<211> LENGTH: 78
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 250

gagcgucacg uugacacuca aaaaguuuca gauuuuggaa cauuucggau uuuggauuuu 60

uggaucaggg augcucaa 78

<210> SEQ ID NO 251
<211> LENGTH: 87
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 251

guguggccgg caggcgggug ggcgggggcg gccgguggga accccgcccc gccccgcgcc 60

cgcacucacc cgcccgucuc cccacag 87

<210> SEQ ID NO 252
<211> LENGTH: 96
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 252

```
cgggccccgg gcgggcggga gggacgggac gcggugcagu guuguuuuuu cccccgccaa      60

uauugcacuc gucccggccu ccggcccccc cggccc                                96


<210> SEQ ID NO 253
<211> LENGTH: 115
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 253

ggugccgagg gccguccggc auccuaggcg ggucgcugcg guaccucccu ccugucugug      60

gcggugggau cccguggccg uguuuuccug guggcccggc cgugccugag guuuc          115


<210> SEQ ID NO 254
<211> LENGTH: 102
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 254

gcuuaucgag gaaaagaucg aggugggguug gggcgggcuc uggggauuug gucucacagc      60

ccggauccca gcccacuuac cuugguuacu cuccuuccuu cu                        102


<210> SEQ ID NO 255
<211> LENGTH: 63
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 255

ugguggcggc gguaguuaug ggcuucucuu ucucaccagc agccccuggg ccgccgccuc      60

ccu                                                                    63


<210> SEQ ID NO 256
<211> LENGTH: 67
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 256

gugaggaggg gcuggcaggg accccuccaa guuggggacg gcagccagcc ccugcucacc      60

ccucgcc                                                                67


<210> SEQ ID NO 257
<211> LENGTH: 73
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 257

gaaaacaacc aggugggcuu cccggagggc ggaacaccca gccccagcau ccagggcuca      60

ccuaccacgu uug                                                         73


<210> SEQ ID NO 258
<211> LENGTH: 105
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 258

gcgggcggcg gcggcggcag cagcagcagg ugcggggcgg cggccgcgcu ggccgcucga      60

cuccgcagcu gcucguucug cuucuccagc uugcgcacca gcucc                     105


<210> SEQ ID NO 259
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<211> LENGTH: 47
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 259

aggcagguua ucugggcugc caucucccac uggcugcuug ccugccu 47

<210> SEQ ID NO 260
<211> LENGTH: 80
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 260

accugaggag ccagcccucc ucccgcaccc aaacuuggag cacuugaccu uuggcuguug 60

gagggggcag gcucgcgggu 80

<210> SEQ ID NO 261
<211> LENGTH: 115
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 261

gagcaaaaac cagagaacaa caugggagcg uuccuaaccc cuaaggcaac uggaugggag 60

accugaccca uccaguucuc ugagggggcu cuugugugu cuacaagguu guuca 115

<210> SEQ ID NO 262
<211> LENGTH: 93
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 262

uacuuauggc accccacucc ugguaccaua gucauaaguu aggagauguu agagcuguga 60

guaccaugac uuaagugugg uggcuuaaac aug 93

<210> SEQ ID NO 263
<211> LENGTH: 68
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 263

cguggugagg auauggcagg gaaggggagu uucccucuau ucccuucccc ccaguaaucu 60

ucaucaug 68

<210> SEQ ID NO 264
<211> LENGTH: 67
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 264

ccagaccccu ggggcugggc aggcggaaag aggucugaac ugccucugcc uccuugguc u 60

ccggcag 67

<210> SEQ ID NO 265
<211> LENGTH: 83
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 265

ccugcugcag aggugccagc ugcagugggg gaggcacugc cagggcugcc cacucugcuu 60

agccagcagg ugccaagaac agg 83

<210> SEQ ID NO 266
<211> LENGTH: 69
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 266

cuuucggcca gcgggacggc auccgaggug ggcuaggcuc gggcccgugg cgggugcggg 60

ggugggagg 69

<210> SEQ ID NO 267
<211> LENGTH: 71
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 267

gugucugugc cggucccagg agaaccugca gaggcaucgg gucagcggug cuccugcggg 60

ccgacacuca c 71

<210> SEQ ID NO 268
<211> LENGTH: 75
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 268

aagcaagacu gaggggccuc agaccgagcu uuuggaaaau agaaaagucu cgcucucugc 60

cccucagccu aacuu 75

<210> SEQ ID NO 269
<211> LENGTH: 106
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 269

agaagaaugc ccaaccagcc cucaguugcu acaguucccu guuguuucag cucgacaaca 60

acaggcggcu guagcaaugg ggggcuggau gggcaucuca augugc 106

<210> SEQ ID NO 270
<211> LENGTH: 57
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 270

cauuggaggg uguggaagac aucugggcca acucugaucu cuucaucuac cccccag 57

<210> SEQ ID NO 271
<211> LENGTH: 109
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 271

ugcuauuguc uuacugcuac agcagggcug gggauugcag uauccgcugu ugcugcugcu 60

cccaguccug ccccugcugc uaccuagucc agccucaccg caucccaga 109

<210> SEQ ID NO 272
<211> LENGTH: 109
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 272

ggucgggcuc accaugacac agugugagac cucgggcuac aacacaggac ccgggcgcug 60

cucugacccc ucgugucuug uguugcagcc ggagggacgc agguccgca 109

<210> SEQ ID NO 273
<211> LENGTH: 72
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 273

cugggggagg aaggacaggc caucugcuau ucguccacca accugacuug auccucucuu 60

cccuccuccc ag 72

<210> SEQ ID NO 274
<211> LENGTH: 55
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 274

gggggcuggg gcgcggggag gugcuagguc ggccucggcu cccgcgccgc acccc 55

<210> SEQ ID NO 275
<211> LENGTH: 64
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 275

gagcucuggg aggggcuggg uuuggcagga caguuuccaa gcccugucuc cucccaucuu 60

ccag 64

<210> SEQ ID NO 276
<211> LENGTH: 59
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 276

ggggccaggc agggaggugg gaccaugggg gccuugcugu gugaccaccg uuccugcag 59

<210> SEQ ID NO 277
<211> LENGTH: 70
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 277

ugugcacuug ggcaggaggg acccuguaug ucuccccgca gcaccgucau cgugucccuc 60

uuguccacag 70

<210> SEQ ID NO 278
<211> LENGTH: 75
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 278

aggcuggcgu gggcugaggg caggaggccu guggccgguc ccaggccucc ugcuuccugg 60

gcucaggcuc gguuu 75

<210> SEQ ID NO 279
<211> LENGTH: 64
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 279

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ugcucuguag gcaugaggca gggcccaggu uccaugugau gcugaagcuc ugacauuccu      60

gcag                                                                   64


<210> SEQ ID NO 280
<211> LENGTH: 82
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 280

gugaguggga ggccagggca cggcaggggg agcugcaggg cuaugggagg ggccccagcg      60

ucugagcccu guccucccgc ag                                               82


<210> SEQ ID NO 281
<211> LENGTH: 82
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 281

gugaguggga ggccagggca cggcaggggg agcugcaggg cuaugggagg ggccccagcg      60

ucugagcccu guccucccgc ag                                               82


<210> SEQ ID NO 282
<211> LENGTH: 75
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 282

uggaguggggg gggcaggagg ggcucaggga gaaagugcau acagccccug gcccucucug      60

cccuuccguc cccug                                                       75


<210> SEQ ID NO 283
<211> LENGTH: 87
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 283

cccaggcgcc cgcucccgac ccacgccgcg ccgccggguc ccuccucccc ggagaggcug      60

ggcucgggac gcgcggcuca gcucggg                                          87


<210> SEQ ID NO 284
<211> LENGTH: 75
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 284

caggggguuug gggaaacggc cgcugaguga ggcgucggcu guguuucuca ccgcggucuu      60

uuccucccac ucuug                                                       75


<210> SEQ ID NO 285
<211> LENGTH: 113
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 285

agcaugacag aggagaggug gagguaggcg agaguaauau aauuucucca ggagaacauc      60

ugagagggga aguugcuuuc cugcccuggc ccuuucaccc uccugaguuu ggg            113


<210> SEQ ID NO 286
```

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<211> LENGTH: 83
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 286

acggcaucuu ugcacucagc aggcaggcug gugcagcccg uggugggga ccauccugcc     60

ugcuguggg uaaggacggc ugu                                              83


<210> SEQ ID NO 287
<211> LENGTH: 75
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 287

ucaucccugg guggggauuu guugcauuac uuguguucua uauaaaguau ugcacuuguc     60

ccggccugug gaaga                                                      75


<210> SEQ ID NO 288
<211> LENGTH: 82
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 288

ugagcuguug gauucggggc cguagcacug ucugagaggu uuacauuucu cacagugaac     60

cggucucuuu uucagcugcu uc                                              82


<210> SEQ ID NO 289
<211> LENGTH: 100
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 289

gugagcgggc gcggcaggga ucgcgggcgg guggcggccu agggcgcgga gggcggaccg     60

ggaauggcgc gccgugcgcc gccggcguaa cugcggcgcu                          100


<210> SEQ ID NO 290
<211> LENGTH: 90
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 290

ggcgccucug cagcuccggc ucccccuggc cucucgggaa cuacaagucc cagggggccu     60

ggcggugggc ggcgggcgga agaggcgggg                                      90


<210> SEQ ID NO 291
<211> LENGTH: 67
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 291

guggcacuca aacugugggg gcacuuucug cucucuggug aaagugccgc caucuuuuga     60

guguuac                                                               67


<210> SEQ ID NO 292
<211> LENGTH: 110
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 292

ucaccuggcc augugacuug ugggcuuccc uuugucaucc uucgccuagg gcucugagca     60
```

```
gggcagggac agcaaagggg ugcucaguug ucacuuccca cagcacggag             110


<210> SEQ ID NO 293
<211> LENGTH: 100
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 293

gaggugggag gauugcuuga gucagggugg uugaggcugc aguaaguugu gaucauacca    60

cugcacucca gccugaguga cagagcaaga ccuugucuca                         100


<210> SEQ ID NO 294
<211> LENGTH: 85
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 294

uccuccccgg agccaggaug cagcucaagc cacagcaggg uguuuagcgc ucuucagugg    60

cuccagauug uggcgcuggu gcagg                                           85


<210> SEQ ID NO 295
<211> LENGTH: 85
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 295

ccuuagcaga gcuguggagu gugacaaugg uguuuguguc uaaacuauca aacgccauua    60

ucacacuaaa uagcuacugc uaggc                                           85


<210> SEQ ID NO 296
<211> LENGTH: 91
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 296

acgccccccg ccccgccacc gccuuggagg cugaccucuu acuuucgguc ggucuucuuc    60

ccugggcuug guuugggggc gggggagugu c                                    91


<210> SEQ ID NO 297
<211> LENGTH: 83
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 297

ggguuuccuc ugccuuuuuu uccaaugaaa auaacgaaac cuguuauuuc ccauugaggg    60

ggaaaaaggc gggagaagcc cca                                             83


<210> SEQ ID NO 298
<211> LENGTH: 72
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 298

ugugggacug caaaugggag cucagcaccu gccugccacc cacgcagacc agccccugcu    60

cuguucccac ag                                                         72


<210> SEQ ID NO 299
<211> LENGTH: 79
<212> TYPE: RNA
```

```
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 299

cagccugggg aaggcuuggc agggaagaca caugagcagu gccuccacuu cacgccucuc     60

ccuugucucc uuucccuag                                                  79


<210> SEQ ID NO 300
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 300

cacaggugag guucuuggga gcc                                             23


<210> SEQ ID NO 301
<211> LENGTH: 15
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 301

acaggugagg uucuu                                                      15


<210> SEQ ID NO 302
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 302

gaggcuggga aggcaaaggg acgu                                            24


<210> SEQ ID NO 303
<211> LENGTH: 15
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 303

gaaggaggcu gggaa                                                      15


<210> SEQ ID NO 304
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 304

caggaaggau uuagggacag gcuuu                                           25


<210> SEQ ID NO 305
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 305

caggaaggau uuagggaca                                                  19


<210> SEQ ID NO 306
<211> LENGTH: 24
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<400> SEQUENCE: 306

cugguacagg ccugggggac aggg                                            24
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<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 307

cugguacagg ccugggg 18

<210> SEQ ID NO 308
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<400> SEQUENCE: 308

cggugggauc ccgcggccgu guuuuc 26

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<211> LENGTH: 15
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<400> SEQUENCE: 309

ggggcgccgc gggac 15

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cggcgcgacc ggcccgggg 19

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<400> SEQUENCE: 311

cggcgcgacc ggcccgggg 19

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<400> SEQUENCE: 312

ugaggggcag agagcgagac uuuucuauuu 30

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<211> LENGTH: 15
<212> TYPE: RNA
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<400> SEQUENCE: 313

ugaggggcag agagc 15

<210> SEQ ID NO 314
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<212> TYPE: RNA
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cggauccgag ucacggcacc a 21

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ggauccgagu cacgg                                                    15


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<212> TYPE: RNA
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<400> SEQUENCE: 316

ggugagcgcu cgcuggc                                                  17


<210> SEQ ID NO 317
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 317

cggugagcgc ucgcu                                                    15


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<400> SEQUENCE: 318

cccagcagga cgggagcgcg g                                             21


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<400> SEQUENCE: 319

aagcuggguc aaggag                                                   16


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<400> SEQUENCE: 320

uccuagucac ggcacca                                                  17


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<400> SEQUENCE: 321

uccuagucac ggcacca                                                  17


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<400> SEQUENCE: 322

uucugggccc gcggcgggcg ugggg                                         25
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<400> SEQUENCE: 323

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<400> SEQUENCE: 324

gggggucccc ggugcucgga ucu                                           23


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<212> TYPE: RNA
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<400> SEQUENCE: 325

ucgggagggg cgggag                                                   16


<210> SEQ ID NO 326
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<400> SEQUENCE: 326

uggggauuug gagaaguggu ga                                            22


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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 327

uggggauuug gagaaguggu ga                                            22


<210> SEQ ID NO 328
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<400> SEQUENCE: 328

gcugcgggcu gcggucaggg cgau                                          24


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<400> SEQUENCE: 329

gcugcgggcu gcggucaggg                                               20


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<400> SEQUENCE: 331

uagcagcacg uaaau                                                       15


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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 332

ggugggugag gucgggcccc aag                                              23


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<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 333

cggggugggu gaggucgggc                                                  20


<210> SEQ ID NO 334
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 334

gggggagcca ugagauaaga gcacc                                            25


<210> SEQ ID NO 335
<211> LENGTH: 20
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 335

ugggggagcc augagauaag                                                  20


<210> SEQ ID NO 336
<211> LENGTH: 23
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<400> SEQUENCE: 336

uguagagcag ggagcaggaa gcu                                              23


<210> SEQ ID NO 337
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<400> SEQUENCE: 337

cagggagcag gaagc                                                       15


<210> SEQ ID NO 338
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<400> SEQUENCE: 338
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cuaguggaag aagauggcgg aag 23

<210> SEQ ID NO 339
<211> LENGTH: 15
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<400> SEQUENCE: 339

uaguggaaga agaug 15

<210> SEQ ID NO 340
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 340

cuccgggcgg cgccgugu 18

<210> SEQ ID NO 341
<211> LENGTH: 18
<212> TYPE: RNA
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<400> SEQUENCE: 341

cuccgggcgg cgccgugu 18

<210> SEQ ID NO 342
<211> LENGTH: 27
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 342

aaaccguuac cauuacugag uuuagua 27

<210> SEQ ID NO 343
<211> LENGTH: 15
<212> TYPE: RNA
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<400> SEQUENCE: 343

gaaaccguua ccauu 15

<210> SEQ ID NO 344
<211> LENGTH: 21
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<400> SEQUENCE: 344

cccaggcugg agcgagugca g 21

<210> SEQ ID NO 345
<211> LENGTH: 15
<212> TYPE: RNA
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<400> SEQUENCE: 345

agcucacugc agccu 15

<210> SEQ ID NO 346
<211> LENGTH: 17
<212> TYPE: RNA
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<400> SEQUENCE: 346

ccuccgggac ggcuggg                                                      17


<210> SEQ ID NO 347
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 347

cuccgggacg gcugg                                                        15


<210> SEQ ID NO 348
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 348

cuggggggacg cgugagcgcg agc                                              23


<210> SEQ ID NO 349
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 349

cuggggggacg cgugagcgcg a                                                21


<210> SEQ ID NO 350
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 350

caggcacggg agcucaggug ag                                                22


<210> SEQ ID NO 351
<211> LENGTH: 17
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 351

caggcacggg agcucag                                                      17


<210> SEQ ID NO 352
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 352

gaucccagcg gugccuc                                                      17


<210> SEQ ID NO 353
<211> LENGTH: 15
<212> TYPE: RNA
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<400> SEQUENCE: 353

gaucccagcg gugcc                                                        15


<210> SEQ ID NO 354
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 354

acaggagugg gggugggaca uaa                                              23


<210> SEQ ID NO 355
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 355

acaggagugg gggugggaca                                                  20


<210> SEQ ID NO 356
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 356

ccuucuggag aggcuuugug cggaua                                           26


<210> SEQ ID NO 357
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 357

ccuucuggag aggcu                                                       15


<210> SEQ ID NO 358
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 358

agaagaaggc ggucggucug cgg                                              23


<210> SEQ ID NO 359
<211> LENGTH: 21
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 359

aagaaggcgg ucggucugcg g                                                21


<210> SEQ ID NO 360
<211> LENGTH: 21
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 360

ccggccgccg gcuccgcccc g                                                21


<210> SEQ ID NO 361
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<212> TYPE: RNA
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<400> SEQUENCE: 361

ccggccgccg gcuccgc                                                     17


<210> SEQ ID NO 362
<211> LENGTH: 22
<212> TYPE: RNA
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 362

accaggaggc ugaggccccu ca                                               22


<210> SEQ ID NO 363
<211> LENGTH: 15
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 363

accaggaggc ugagg                                                       15


<210> SEQ ID NO 364
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 364

gcugggcgag gcuggcauc                                                   19


<210> SEQ ID NO 365
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<212> TYPE: RNA
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<400> SEQUENCE: 365

gcugggcgag gcuggca                                                     17


<210> SEQ ID NO 366
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 366

aucccaccuc ugccaccaaa                                                  20


<210> SEQ ID NO 367
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 367

aucccaccuc ugcca                                                       15


<210> SEQ ID NO 368
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 368

gccccggcgc gggcggguuc ugg                                              23


<210> SEQ ID NO 369
<211> LENGTH: 16
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 369

ggagccccgg cgcggg                                                      16


<210> SEQ ID NO 370
<211> LENGTH: 20
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 370

aucccaccac ugccaccauu                                              20


<210> SEQ ID NO 371
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<212> TYPE: RNA
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<400> SEQUENCE: 371

aucccaccac ugcca                                                   15


<210> SEQ ID NO 372
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 372

gaauggauuu uuggagcagg a                                            21


<210> SEQ ID NO 373
<211> LENGTH: 15
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 373

gaauggauuu uugga                                                   15


<210> SEQ ID NO 374
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 374

acucggcugc gguggacaag uc                                           22


<210> SEQ ID NO 375
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<212> TYPE: RNA
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<400> SEQUENCE: 375

acucggcugc gguggacaag                                              20


<210> SEQ ID NO 376
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<400> SEQUENCE: 376

ccucacaccu gccucgcccc cc                                           22


<210> SEQ ID NO 377
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<212> TYPE: RNA
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<400> SEQUENCE: 377

ucacaccugc cucgc                                                   15


<210> SEQ ID NO 378
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<211> LENGTH: 22
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<400> SEQUENCE: 378

cugaauagcu gggacuacag gu 22

<210> SEQ ID NO 379
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<400> SEQUENCE: 379

ccugaauagc uggga 15

<210> SEQ ID NO 380
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<212> TYPE: RNA
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<400> SEQUENCE: 380

gcgggcuguc cggagggguc ggcuuu 26

<210> SEQ ID NO 381
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 381

gcuguccgga gggguc 16

<210> SEQ ID NO 382
<211> LENGTH: 26
<212> TYPE: RNA
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<400> SEQUENCE: 382

cggguagaga gggcaguggg agguaa 26

<210> SEQ ID NO 383
<211> LENGTH: 15
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 383

cggguagaga gggca 15

<210> SEQ ID NO 384
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 384

ggcggcgggc ccggg 15

<210> SEQ ID NO 385
<211> LENGTH: 15
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 385

ggcggcgggc ccggg 15

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<210> SEQ ID NO 386
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 386

ucuaggu ggg gagacuga                                                    18
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 387

guggggagac ugacgg                                                       16


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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 388

ccagggcugg cagugacaug ggu                                               23


<210> SEQ ID NO 389
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 389

cagggcuggc agugacaug                                                    19


<210> SEQ ID NO 390
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 390

cccaaaaugc ugggauuaca ggca                                              24


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<400> SEQUENCE: 391

gcccaccuca gccuc                                                        15


<210> SEQ ID NO 392
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<212> TYPE: RNA
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<400> SEQUENCE: 392

acuggcucag uucagcagga acag                                              24


<210> SEQ ID NO 393
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 393

uggcucaguu cagca                                                        15
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<212> TYPE: RNA
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<400> SEQUENCE: 394

ccccagggcg acgcggcggg                                                 20


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<400> SEQUENCE: 395

cgcggcgggg gcggc                                                      15


<210> SEQ ID NO 396
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 396

gucccggggc ugcgcgaggc acaggc                                          26


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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 397

ggcccggggg gcggg                                                      15


<210> SEQ ID NO 398
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 398

cggggcagcu caguacagga uac                                             23


<210> SEQ ID NO 399
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 399

agcucaguac aggau                                                      15


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<400> SEQUENCE: 400

agacacauuu ggagagggaa ccuc                                            24


<210> SEQ ID NO 401
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 401

agacacauuu ggagag                                                     16
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 402

ggauuuuugg aucagggaug                                                 20


<210> SEQ ID NO 403
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<400> SEQUENCE: 403

auuuuuggau caggg                                                      15


<210> SEQ ID NO 404
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 404

agggacggga cgcggugcag uguugu                                          26


<210> SEQ ID NO 405
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 405

ggcgggcggg aggga                                                      15


<210> SEQ ID NO 406
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 406

ggcccggccg ugccugaggu uuc                                             23


<210> SEQ ID NO 407
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<400> SEQUENCE: 407

ggcgguggga ucccg                                                      15


<210> SEQ ID NO 408
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 408

guggguuggg gcgggcucu                                                  19


<210> SEQ ID NO 409
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 409
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gugggguuggg gcgggcucu 19

<210> SEQ ID NO 410
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<400> SEQUENCE: 410

uggcggcggu aguuaugggc uucuc 25

<210> SEQ ID NO 411
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<400> SEQUENCE: 411

uggcggcggu aguuaugggc uucuc 25

<210> SEQ ID NO 412
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 412

ggugggcuuc ccggaggg 18

<210> SEQ ID NO 413
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<400> SEQUENCE: 413

ggugggcuuc ccgga 15

<210> SEQ ID NO 414
<211> LENGTH: 18
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<400> SEQUENCE: 414

gcggcggcgg cggcagca 18

<210> SEQ ID NO 415
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<400> SEQUENCE: 415

gcgggcggcg gcggc 15

<210> SEQ ID NO 416
<211> LENGTH: 20
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<400> SEQUENCE: 416

uggcuguugg agggggcagg 20

<210> SEQ ID NO 417
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 417

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ggagggggca ggcuc                                                        15


<210> SEQ ID NO 418
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<400> SEQUENCE: 418

cgcggcgggg acggcgauug gu                                                22


<210> SEQ ID NO 419
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 419

cggcggggac ggcgauu                                                      17


<210> SEQ ID NO 420
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 420

auccaguucu cugagggggc u                                                 21


<210> SEQ ID NO 421
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 421

auccaguucu cugagggggc u                                                 21


<210> SEQ ID NO 422
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 422

accccacucc ugguaccaua gu                                                22


<210> SEQ ID NO 423
<211> LENGTH: 15
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 423

accccacucc uggua                                                        15


<210> SEQ ID NO 424
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 424

cuuccccca guaaucuuca u                                                  21


<210> SEQ ID NO 425
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 425

cuucccccca guaaucuuca u 21

<210> SEQ ID NO 426
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

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<212> TYPE: RNA
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<400> SEQUENCE: 427

gcugcagugg gggag 15

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<400> SEQUENCE: 428

uggcgggugc gggggtuggg 19

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 429

uggcgggugc ggggg 15

<210> SEQ ID NO 430
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 430

caacucugau cucuucaucu a 21

<210> SEQ ID NO 431
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 431

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<210> SEQ ID NO 432
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<400> SEQUENCE: 432

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<400> SEQUENCE: 433

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<400> SEQUENCE: 434

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<211> LENGTH: 21
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<213> ORGANISM: Homo sapiens

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ggcuacaaca caggacccgg g                                            21


<210> SEQ ID NO 436
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<400> SEQUENCE: 436

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<210> SEQ ID NO 437
<211> LENGTH: 15
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<400> SEQUENCE: 437

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<210> SEQ ID NO 438
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agugggaggc cagggcacg                                               19


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<212> TYPE: RNA
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<400> SEQUENCE: 441

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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 442

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<210> SEQ ID NO 443
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<212> TYPE: RNA
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<400> SEQUENCE: 443

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<400> SEQUENCE: 444

uuggggaaac ggccgcugag ugaggcgu                                          28


<210> SEQ ID NO 445
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 445

ggggaaacgg ccgcu                                                        15


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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 446

gggugggau uuguugcauu acuug                                              25


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<211> LENGTH: 20
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 447

gggugggau uuguugcauu                                                    20


<210> SEQ ID NO 448
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 448

cggggccgua gcacugucug aga                                               23


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<211> LENGTH: 20
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<400> SEQUENCE: 449

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<210> SEQ ID NO 450
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 450

ggcgcggagg gcggac                                                     16


<210> SEQ ID NO 451
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<400> SEQUENCE: 451

ggcgcggagg gcgga                                                      15


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<211> LENGTH: 16
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<400> SEQUENCE: 452

ggcggugggc ggcggg                                                     16


<210> SEQ ID NO 453
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 453

ggccucucgg gaacu                                                      15


<210> SEQ ID NO 454
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<212> TYPE: RNA
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<400> SEQUENCE: 454

acucaaacug ugggggcacu uu                                              22


<210> SEQ ID NO 455
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<400> SEQUENCE: 455

acucaaacug ugggggcac                                                  19


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<400> SEQUENCE: 456

ggcagggaca gcaaaggggu gc                                              22


<210> SEQ ID NO 457
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 457

gcagggacag caaagggg                                                 18


<210> SEQ ID NO 458
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<400> SEQUENCE: 458

cagccugagu gacagagcaa g                                             21


<210> SEQ ID NO 459
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 459

acugcacucc agccu                                                    15


<210> SEQ ID NO 460
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 460

guggagugug acaauggugu uugu                                          24


<210> SEQ ID NO 461
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<212> TYPE: RNA
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<400> SEQUENCE: 461

uggaguguga caauggug                                                 18


<210> SEQ ID NO 462
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 462

gaaaaaggcg ggagaagccc ca                                            22


<210> SEQ ID NO 463
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<212> TYPE: RNA
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<400> SEQUENCE: 463

gaaaaaggcg ggaga                                                    15


<210> SEQ ID NO 464
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 464

ugugggacug caaaugggag cu                                            22
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<210> SEQ ID NO 465
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 465

ugugggacug caaaugggag cu 22

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<400> SEQUENCE: 466

gggagaaggg ucggggc 17

<210> SEQ ID NO 467
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<400> SEQUENCE: 467

ugggcgaggg gugggcucuc agag 24

<210> SEQ ID NO 468
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<400> SEQUENCE: 468

cggcucuggg ucugugggga 20

<210> SEQ ID NO 469
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<400> SEQUENCE: 469

uuagggagua gaaggguggg gag 23

<210> SEQ ID NO 470
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 470

ggggcgcggc cggaucg 17

<210> SEQ ID NO 471
<211> LENGTH: 21
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<400> SEQUENCE: 471

aaggcagggc ccccgcuccc c 21

<210> SEQ ID NO 472
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<400> SEQUENCE: 472

gggggaagaa aaggugggg 19

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<211> LENGTH: 23
<212> TYPE: RNA
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<400> SEQUENCE: 473

uggugggugg ggaggagaag ugc                                              23


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<400> SEQUENCE: 474

gcggggcugg gcgcgcg                                                     17


<210> SEQ ID NO 475
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<400> SEQUENCE: 475

ucaauaggaa agagguggga ccu                                              23


<210> SEQ ID NO 476
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<400> SEQUENCE: 476

uagggauggg aggccaggau ga                                               22


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<400> SEQUENCE: 477

ucgaggacug guggaagggc cuu                                              23


<210> SEQ ID NO 478
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<400> SEQUENCE: 478

cuccuggggc ccgcacucuc gc                                               22


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<400> SEQUENCE: 479

agggagaagg gucggggcag ggagggcagg gcaggcucug ggguggggg ucugugaguc      60

agccacggcu cugcccacgu cucccc                                           86


<210> SEQ ID NO 480
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<212> TYPE: RNA
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<400> SEQUENCE: 480
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ccag                                                                  64


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uguggggagc gaaaugcaac                                                 80


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<400> SEQUENCE: 482

cugacuuuuu uagggaguag aagggugggg agcaugaaca auguuucuca cucccuaccc     60

cuccacuccc caaaaaaguc ag                                              82


<210> SEQ ID NO 483
<211> LENGTH: 84
<212> TYPE: RNA
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<400> SEQUENCE: 483

gaggcugggc ggggcgcggc cggaucgguc gagagcgucc uggcugauga cggucucccg     60

ugcccacgcc ccaaacgcag ucuc                                            84


<210> SEQ ID NO 484
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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 484

gugaggugug ggcccggccc caggagcggg gccugggcag ccccgugugu ugaggaagga     60

aggcagggcc cccgcucccc gggccugacc ccac                                 94


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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 485

aaaucucucu ccauaucuuu ccugcagccc ccaggugggg gggaagaaaa ggugggggaau    60

uagauuc                                                               67


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<212> TYPE: RNA
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<400> SEQUENCE: 486

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ag                                                                    62


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<211> LENGTH: 70
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gcaagggccg 70

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<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 488

cuuggucaau aggaaagagg ugggaccucc uggcuuuucc ucugcagcau ggcucggacc 60

uagugcaaug uuuaagcucc ccucucuuuc cuguucag 98

<210> SEQ ID NO 489
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<212> TYPE: RNA
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<400> SEQUENCE: 489

gggcuuaggg augggaggcc aggaugaaga uuaaucccua auccccaaca cuggccuugc 60

uauccccag 69

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<400> SEQUENCE: 490

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cuc 63

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<400> SEQUENCE: 495

ucugggcgag gggug 15

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ucggcucugg gucugugggg agc 23

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<400> SEQUENCE: 497

cggcucuggg ucugugg 17

<210> SEQ ID NO 498
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<400> SEQUENCE: 498

agggaguaga agggugggga gca 23

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uagggaguag aagggu 16

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gggcccccgc ucccc 15

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agcggggcug ggcgcgcg 18

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<400> SEQUENCE: 505

cggggcuggg cgcgc 15

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ucgaggacug guggaagggc cuuu 24

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The invention claimed is:

1. A method for detecting biliary tract cancer, comprising determining an expression level of hsa-miR-6836-3p in a sample comprising blood, serum, or plasma from a human subject using a kit comprising a nucleic acid(s), as a primer(s) for PCR, or a probe(s) for Northern blot, Southern blot, or in situ hybridization, capable of specifically binding to hsa-miR-6836-3p, wherein the determining comprises the following steps of:

(a) contacting hsa-miR-6836-3p in the sample or complementary polynucleotide(s) thereof prepared from hsa-miR-6836-3p with the nucleic acid(s);

(b) measuring an expression level of hsa-miR-6836-3p by quantitative RT-PCR using the nucleic acid(s) as the primer(s), or Northern blot, Southern blot, or in situ hybridization using the nucleic acids as the probe(s); and

(c) comparing the expression level of hsa-miR-6836-3p measured in step (b) with a control expression level of hsa-miR-6836-3p in a control sample of a healthy subject measured in the same way as in step (b),

wherein a higher expression level of hsa-miR-6836-3p in the sample of the subject as compared to the control expression level is detected and is indicative that the subject has biliary tract cancer; and

treating the subject for biliary tract cancer or performing a diagnostic procedure on the biliary tract of the subject, wherein the treatment comprises surgery, radiotherapy, chemotherapy or a combination thereof, and wherein the diagnostic procedure comprises a biochemical examination of hepatic dysfunction markers in a blood sample, detecting a concentration of a biliary tract tumor biomarker protein in a blood sample, or imaging the biliary tract of the subject.

2. A method for detecting biliary tract cancer, comprising determining an expression level of hsa-miR-6836-3p in a sample comprising blood, serum, or plasma from a human subject using a device comprising a nucleic acid(s), as a probe(s), capable of specifically binding to hsa-miR-6836-3p, wherein the determining comprises the following steps of:

(a) binding hsa-miR-6836-3p in the sample or cDNA thereof prepared from hsa-miR-6836-3p to the nucleic acid(s) to measure an expression level of hsa-miR-6836-3p by hybridization using the nucleic acid(s); and

(b) comparing the expression level of hsa-miR-6836-3p measured in step (a) with a control expression level of hsa-miR-6836-3p in a control sample of a healthy subject measured in the same way as in step (a),

wherein a higher expression level of hsa-miR-6836-3p in the sample of the subject as compared to the control expression level is detected and is indicative that the subject has biliary tract cancer; and

treating the subject for biliary tract cancer or performing a diagnostic procedure on the biliary tract of the subject, wherein the treatment comprises surgery, radiotherapy, chemotherapy or a combination thereof, and wherein the diagnostic procedure comprises a biochemical examination of hepatic dysfunction markers in a blood sample, detecting a concentration of a biliary tract tumor biomarker protein in a blood sample, or imaging the biliary tract of the subject.

3. The method according to claim **1**, wherein step (c) further comprises preparing a discriminant based on a formula.

4. The method according to claim **3**, wherein the discriminant is compared to a threshold.

5. The method according to claim **2**, wherein step (b) further comprises preparing a discriminant based on a formula.

6. The method according to claim **5**, wherein the discriminant is compared to a threshold.

* * * * *

专利名称(译)	胆道癌检测试剂盒或装置及检测方法		
公开(公告)号	US10633708	公开(公告)日	2020-04-28
申请号	US15/317846	申请日	2015-06-11
[标]申请(专利权)人(译)	东丽株式会社 NAT癌症CENT		
申请(专利权)人(译)	TORAY INDUSTRIES，INC. 国家癌症中心		
当前申请(专利权)人(译)	TORAY INDUSTRIES，INC. 国家癌症中心		
[标]发明人	KAWAUCHI JUNPEI NOBUMASA HITOSHI KOZONO SATOKO KONDOU SATOSHI SUDO HIROKO OCHIAI ATSUSHI KOJIMA MOTOHIRO		
发明人	KAWAUCHI, JUNPEI NOBUMASA, HITOSHI KOZONO, SATOKO KONDOU, SATOSHI SUDO, HIROKO OCHIAI, ATSUSHI KOJIMA, MOTOHIRO		
IPC分类号	C12Q1/68 C12Q1/6886 G01N33/53 G01N37/00 G01N33/566 C12N15/09 C12P19/34		
CPC分类号	G01N33/53 G01N33/566 G01N37/00 C12Q1/68 C12Q1/6886 C12N15/09 C12Q2600/178 C12Q2600/158 C12Q1/6834		
优先权	2014120884 2014-06-11 JP 2014185733 2014-09-11 JP		
其他公开文献	US20170107581A1		
外部链接	Espacenet		

摘要(译)

本发明提供了用于检测胆道癌的试剂盒或装置，以及用于检测胆道癌的方法。 本发明涉及一种用于检测胆道癌的试剂盒或装置，其包含能够与受试者的样品中的miRNA特异性结合的核酸，以及一种用于检测胆道癌的方法，其包括在体外测量miRNA。

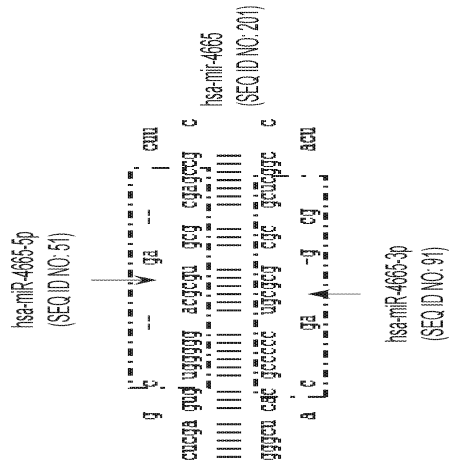

Fig. 1