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(12) EUROPEAN PATENT APPLICATION

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(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
01962813.0 / 1 294 950

(71) Applicant: **Epigenomics AG**
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(54) Diagnosis of diseases associated with development by means of assessing their methylation status

(57) The present invention relates to the chemically modified genomic sequences of genes associated with diseases associated with development, to oligonucleotides and/or PNA-oligomers for detecting the cytosine methylation state of genes associated with diseases associated with development which are directed against the sequence, as well as to a method for ascertaining genetic and/or epigenetic parameters of genes associated with diseases associated with development.

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European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 06 00 2091

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	SEMINA E V ET AL: "CLONING AND CHARACTERIZATION OF A NOVEL BICOID-RELATED HOMEOBOX TRANSCRIPTION FACTER GENE RIEG INVOLVED IN RIEGER SYNDROME" NATURE GENETICS, NEW YORK, NY, US, vol. 14, no. 4, December 1996 (1996-12), pages 392-399, XP002062612 ISSN: 1061-4036 * page 398, right-hand column, paragraph 2 * * figure 1 *	1,3	INV. C12Q1/68 B01J19/00 G01N33/483 C07K14/47
Y		4-31	
X	-& DATABASE GENBANK NCBI; 13 May 1998 (1998-05-13), SEMINA, E.V. ET AL.: "Homo sapiens solurshin (RGS) mRNA" XP002393422 retrieved from HTTP://WWW.NCBI.NLM.NIH.GOV Database accession no. U69961 * the whole document *	1,3	
Y		4-31	TECHNICAL FIELDS SEARCHED (IPC)
	----- -/--		C12Q B01J G01N

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

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Place of search	Date of completion of the search	Examiner
Munich	4 August 2006	Ulbrecht, Matthias

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 06 00 2091

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (IPC)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y,D	WO 99/28498 A (OLEK ALEXANDER ;WALTER JOERN (DE); EPIGENOMICS GMBH (DE); OLEK SVE) 10 June 1999 (1999-06-10) * the whole document * -----	4-31	
Y	DE 199 05 082 C (EPIGENOMICS GMBH) 18 May 2000 (2000-05-18) * the whole document * -----	4-31	
P,X	TOYOTA M ET AL: "Methylation profiling in acute myeloid leukemia" BLOOD, W.B.SAUNDERS COMPANY, ORLANDO, FL, US, vol. 97, no. 9, 1 May 2001 (2001-05-01), pages 2823-2829, XP002226261 ISSN: 0006-4971 * the whole document * -----	1,3-31	TECHNICAL FIELDS SEARCHED (IPC)
E	WO 01/92565 A (EPIGENOMICS AG; OLEK, ALEXANDER; PIEPENBROCK, CHRISTIAN; BERLIN, KURT) 6 December 2001 (2001-12-06) * the whole document * * sequences 127,128 * -----	1,3-31	
A	BENDER CM ET AL.: "Roles of cell division and gene transcription in the methylation of CpG islands." MOLECULAR AND CELLULAR BIOLOGY, vol. 19, no. 10, October 1999 (1999-10), pages 6690-6698, XP002185033 * page 6691, right-hand column, paragraph 3 - page 6692, left-hand column, paragraph 1 * -----	1	
	-/--		

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 06 00 2091

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (IPC)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	TOKUHARA M ET AL.: "Molecular cloning of the human frizzled-6" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 243, 1998, pages 622-627, XP002185034 * figure 1 *	1	
A	DATABASE EMBL [Online] EBI; 15 November 1999 (1999-11-15), WATERSTON RH: "The sequence of Homo sapiens clone"" XP002185035 retrieved from HTTP://WWW.EBI.AC.UK/CGI-BIN/EMBLFETCH Database accession no. AC013731 * the whole document *	1	TECHNICAL FIELDS SEARCHED (IPC)
A	DATABASE EMBL [Online] EBI; 2 May 2000 (2000-05-02), BOECKELMANN R ET AL.: "Gene expression in psoriatic skin." XP002185036 retrieved from HTTP://WWW.EBI.AC.UK/CGI-BIN/EMBLFETCH Database accession no. AF143346 * the whole document *	1	
A,D	US 5 744 305 A (FODOR STEPHEN P A ET AL) 28 April 1998 (1998-04-28) * column 6, line 5 * * claims 1,8,15,20,26 * * figure 14 *	9,11-15	
A	WO 99/29898 A (MAX PLANCK GESELLSCHAFT ;BERLIN KURT (DE); GUT IVO GLYNNE (DE); LE) 17 June 1999 (1999-06-17) * page 10, line 19 - page 15, line 21 *	24-27	

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European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 06 00 2091

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (IPC)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A,D	GRIGG G AND CLARK S: "Sequencing 5-methylcytosine residues in genomic DNA" BIOESSAYS, CAMBRIDGE, GB, vol. 16, no. 6, June 1994 (1994-06), pages 431-436, XP002106411 ISSN: 0265-9247 * the whole document *	1,3-31	
T	HAMPTON T.: "New markers may help predict prostate cancer relapse risk" JAMA THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, CHICAGO,IL, US, vol. 295, no. 19, 17 May 2006 (2006-05-17), pages 2234-2238, XP009070133 ISSN: 0098-7484 * the whole document *	1,3-31	TECHNICAL FIELDS SEARCHED (IPC)
T	MARKERT-HAHN C ET AL: "Validity of DNA-methylation marker PITX2 to predict risk of recurrence in lymph node-negative hormone receptor-positive breast cancer patients: a transfer study." BREAST CANCER RESEARCH AND TREATMENT, vol. 94, no. Suppl. 1, 2005, page S57, XP009070135 & 28TH ANNUAL SAN ANTONIO BREAST CANCER SYMPOSIUM; SAN ANTONIO, TX, USA; DECEMBER 08 -11, 2005 ISSN: 0167-6806	1,3-31	

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INCOMPLETE SEARCH SHEET C

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Although claim 30 is directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claim 31 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Reason for the limitation of the search:

Should the Applicant decide to have inventions covering claim 2 searched he should note the following: Claim 2 refers inter alia to DNA related to the genes designated by the acronyms: ACCPN, ADFN, AHO2, AMCD1, AMCD2B, AMCN, AMCX1, AMDM, ANOP1, ASMD, ATD, BDC, BDE, BDMR, CHH, GLI4, GSC, HNF4B, ORW2, and RIEG2. Said genes either cannot be found or a number of apparently unrelated sequences are contained in the GenBank database are linked with said acronyms. Furthermore, the description of the present application does not provide any information beyond the acronyms with regard to said genes. Therefore, subject-matter referring to said genes is unclear (Art. 84 EPC) and will not be searchable.

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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

1, 3-31 (partly)

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
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The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

Invention 1: claims 1, 3-31 (all part.)

A nucleic acid comprising a sequence at least 18 bases in length of a segment of the chemically pretreated DNA of a gene associated with development according to sequence SEQ ID NO. 1 or 2, oligonucleotides having a sequence of at least 9 nucleotides identical or hybridizing to said DNA; a set of said oligonucleotides; the use of said set for detecting SNPs or the methylation state of cytosines in said nucleic acid; an array or set of said oligonucleotides fixed to a carrier; a method of producing said array; a method for diagnosis and/or therapy of diseases or disease predispostion using said oligonucleotides by analysing cytosine methylations; a kit comprising said oligonucleotides and bisulfite; and the use of said nucleic acid, oligonucleotides, set of oligonucleotides, array or kit for the diagnosis or therapy of diseases associated with development genes.

Inventions 2-175: claims 1, 3-31 (all partially)

Idem as invention 1, but each of inventions 2-175 limited to one of two consequtive SEQ ID Nos. from SEQ ID Nos. 5-350.

Invention 176: claims 2-31 (all partially)

A nucleic acid comprising a sequence at least 18 bases in length of a segment of the chemically pretreated DNA of a gene associated with development ACCPN, oligonucleotides having a sequence of at least 9 nucleotides identical or hybridizing to said DNA; a set of said oligonucleotides; the use of said set for detecting SNPs or the methylation state of cytosines in said nucleic acid; an array or set of said oligonucleotides fixed to a carrier; a method of producing said array; a method for diagnosis and/or therapy of diseases or disease predispostion using said oligonucleotides by analysing cytosine methylations; a kit comprising said oligonucleotides and bisulfite; and the use of said nucleic acid, oligonucleotides, set of oligonucleotides, array or kit for the diagnosis or therapy of diseases associated with development genes.

Inventions 177-270: claims 2-31 (all partially)

idem as invention 176, but each of inventions 177-270 limited to one the genes referred to in calim 2 as designated either by an acronym alone or an acronym in combination with a single database accession no..

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 06 00 2091

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

04-08-2006

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9928498 A	10-06-1999	AT 217348 T	15-05-2002
		AU 753368 B2	17-10-2002
		AU 2408599 A	16-06-1999
		CA 2310384 A1	10-06-1999
		CN 1283235 A	07-02-2001
		CZ 20001934 A3	15-11-2000
		DE 19754482 A1	01-07-1999
		DK 1034309 T3	26-08-2002
		EP 1034309 A2	13-09-2000
		ES 2173669 T3	16-10-2002
		HK 1033473 A1	13-10-2006
		HU 0100424 A2	28-06-2001
		IL 136158 A	25-07-2004
		IS 5493 A	12-05-2000
		JP 2001525181 T	11-12-2001
		NZ 504586 A	25-10-2002
		PL 341681 A1	23-04-2001
		PT 1034309 T	31-10-2002
		RU 2223324 C2	10-02-2004
		US 6214556 B1	10-04-2001
DE 19905082 C	18-05-2000	AT 252159 T	15-11-2003
		AU 764683 B2	28-08-2003
		AU 3144700 A	18-08-2000
		CA 2359182 A1	03-08-2000
		WO 0044934 A2	03-08-2000
		DE 10080169 D2	24-01-2002
		EP 1147228 A2	24-10-2001
		ES 2208285 T3	16-06-2004
		JP 2002535011 T	22-10-2002
		US 6977146 B1	20-12-2005
WO 0192565 A	06-12-2001	AU 5478801 A	23-10-2001
		AU 5479401 A	23-10-2001
		AU 7566301 A	23-10-2001
		AU 7633001 A	23-10-2001
		AU 7633101 A	23-10-2001
		AU 7748701 A	23-10-2001
		AU 7842001 A	07-11-2001
		AU 8960001 A	11-12-2001
		WO 0177375 A2	18-10-2001
		WO 0177164 A2	18-10-2001
		WO 0177376 A2	18-10-2001
		WO 0177377 A2	18-10-2001
		WO 0181622 A2	01-11-2001
		WO 0177378 A2	18-10-2001

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 06 00 2091

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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04-08-2006

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0192565 A		WO 0176451 A2	18-10-2001
		EP 1268857 A2	02-01-2003
		EP 1272670 A2	08-01-2003
		EP 1278893 A2	29-01-2003
		EP 1274865 A2	15-01-2003
		EP 1274866 A2	15-01-2003
		EP 1360319 A2	12-11-2003
		EP 1370685 A2	17-12-2003
		EP 1268861 A2	02-01-2003
		JP 2004508807 T	25-03-2004
		JP 2003534780 T	25-11-2003
		JP 2003531589 T	28-10-2003
		US 2003082609 A1	01-05-2003
		US 2003162194 A1	28-08-2003
		US 2003148326 A1	07-08-2003
		US 2004067491 A1	08-04-2004
		US 2003148327 A1	07-08-2003
		US 2004076956 A1	22-04-2004
		US 2005282157 A1	22-12-2005
US 5744305 A	28-04-1998	NONE	
WO 9929898 A	17-06-1999	AT 217028 T	15-05-2002
		CA 2312052 A1	17-06-1999
		DE 59804008 D1	06-06-2002
		DK 1036202 T3	12-08-2002
		ES 2173670 T3	16-10-2002
		JP 2001526381 T	18-12-2001

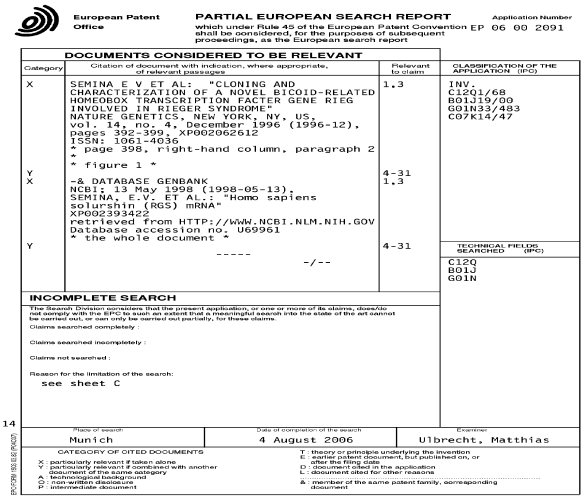
EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

专利名称(译)	通过评估甲基化状态诊断与发育相关的疾病		
公开(公告)号	EP1676927A3	公开(公告)日	2006-12-06
申请号	EP2006002091	申请日	2001-07-02
[标]申请(专利权)人(译)	埃皮吉諾米克斯股份公司		
申请(专利权)人(译)	AG EPIGENOMICS		
当前申请(专利权)人(译)	AG EPIGENOMICS		
[标]发明人	OLEK ALEXANDER PIEPENBROCK CHRISTIAN BERLIN KURT		
发明人	OLEK, ALEXANDER PIEPENBROCK, CHRISTIAN BERLIN, KURT		
IPC分类号	C12Q1/68 B01J19/00 G01N33/483 C07K14/47 G01N27/62 C07K14/82 C12M1/00 C12M1/34 C12N15/09 G01N33/53 G01N33/58 G01N37/00		
CPC分类号	C07K14/82 C07K14/4703 C12Q1/6883 C12Q1/6886 C12Q2523/125 C12Q2600/154 C12Q2600/156		
代理机构(译)	KRAUSS，JAN		
优先权	10032529 2000-06-30 DE 10043826 2000-09-01 DE		
其他公开文献	EP1676927A2		
外部链接	Espacenet		

摘要(译)

本发明涉及与发育相关的疾病相关的基因的化学修饰的基因组序列，寡核苷酸和/或PNA-寡聚体，用于检测与针对该序列的发育相关的疾病相关的基因的胞嘧啶甲基化状态，以及关于确定与发育相关的疾病相关基因的遗传和/或表观遗传参数的方法。



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Y		4-31	
X	-& DATABASE GENBANK NCBI; 13 May 1998 (1998-05-13), SEMINA, E.V. ET AL.: "Homo sapiens solursshin (RGS) mRNA" XP002393422 retrieved from HTTP://WWW.NCBI.NLM.NIH.GOV Database accession no. U69961 * the whole document *	1,3	
Y		4-31	

TECHNICAL FIELDS SEARCHED (IPC)

C12Q
B01J
G01N

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Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
Munich	4 August 2006	Ulbrecht, Matthias

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
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& : member of the same patent family, corresponding document

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