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(54)【発明の名称】　ヘリコバクター・フェリス・ワクチン

(57)【要約】　（修正有）

【課題】本発明は、ヘリコバクター・フェリス由来の抗原性ポリペプチドをコードするポリヌクレオチドを提供する。さらにヘリコバクター・フェリスに対するワクチン、その感染診断法なども提供する。

【解決手段】新規なヘリコバクター・フェリス・ウレアーゼ・サブユニット・ポリペプチド、これらのサブユニット・ポリペプチドをコードする核酸配列、これらのサブユニット・ポリペプチドをコードする核酸配列を含むＤＮＡ断片及び組換えＤＮＡ分子、組換え生キャリアー、並びにこれらのサブユニット・ポリペプチドをコードする核酸配列を含む宿主細胞に関する。また、本発明は、ワクチンにおいて使用するためのサブユニット・ポリペプチド、それらの製造における使用、該サブユニット・ポリペプチドを含むワクチン、及びそのようなワクチンの調製のための方法に関する。

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【特許請求の範囲】

【請求項１】　ヘリコバクター・フェリス（Ｈｅｌｉｃｏｂａｃｔｅｒ　ｆｅｌｉｓ）により発現されるようなウレアーゼ複合体の２つのサブユニット・ポリペプチドをコードし、かつ配列番号１と少なくとも８５％の相同性を有する核酸配列、又は該サブユニットのうちの一つの免疫原性断片を少なくともコードし、かつ少なくとも４０ヌクレオチド、好ましくは４５ヌクレオチド、より好ましくは５０ヌクレオチドの長さを有するその一部。

【請求項２】　ウレアーゼＸサブユニット・ポリペプチド又はウレアーゼＹサブユニット・ポリペプチドをコードすることを特徴とする、請求項１に記載の核酸配列。

【請求項３】　配列番号１と少なくとも９０％、好ましくは９４％、より好ましくは９７％の相同性を有することを特徴とする、請求項１又は２に記載の核酸配列。

【請求項４】　請求項１～３に記載の核酸配列を含むＤＮＡ断片。

【請求項５】　機能的に連結したプロモーターの調節下で、請求項１～３に記載の核酸配列又は請求項４に記載のＤＮＡ断片を含む組換えＤＮＡ分子。

【請求項６】　請求項５に記載の組換えＤＮＡ分子を含む組換え生キャリアー。

【請求項７】　請求項１～３に記載の核酸配列、請求項４に記載のＤＮＡ断片、請求項５に記載の組換えＤＮＡ分子、又は請求項６に記載の組換え生キャリアーを含む宿主細胞。

【請求項８】　配列番号２と少なくとも８５％相同なアミノ酸配列を有するヘリコバクター・フェリス・ウレアーゼＸサブユニット・ポリペプチド、又は少なくとも４０アミノ酸、好ましくは４５アミノ酸、より好ましくは５０アミノ酸の長さを有し、かつウレアーゼＸＹに対する免疫応答を誘導する能力を有する該ポリペプチドの免疫原性断片。

【請求項９】　配列番号２と少なくとも９０％、好ましくは９４％、より好ましくは９７％の配列相同性を有する、請求項８に記載のポリペプチド、又はウレアーゼＸＹに対する免疫応答を誘導する能力を有する該ポリペプチドの免疫原性断片。

【請求項１０】　配列番号３と少なくとも８５％相同なアミノ酸配列を有するヘリコバクター・フェリス・ウレアーゼＹサブユニット・ポリペプチド、又は少なくとも４０アミノ酸、好ましくは４５アミノ酸、より好ましくは５０アミノ酸の長さを有し、かつウレアーゼＸＹに対する免疫応答を誘導する能力を有する、該ポリペプチドの免疫原性断片。

【請求項１１】　配列番号３と少なくとも９０％、好ましくは９４％、より好ましくは９７％の配列相同性を有する、請求項１０に記載のポリペプチド、又はウレアーゼＸＹに対する免疫応答を誘導する能力を有する該ポリペプチドの免疫原性断片。

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【請求項１２】　ワクチンにおいて使用するための、請求項８～１１に記載のポリペプチド。

【請求項１３】　ヘリコバクター・フェリス感染に対抗するためのワクチンの製造における、請求項８～１１に記載のポリペプチドの使用。

【請求項１４】　請求項１～３に記載の核酸配列、請求項４に記載のＤＮＡ断片、請求項５に記載の組換えＤＮＡ分子、請求項６に記載の組換え生キャリアー、請求項７に記載の宿主細胞、又は請求項８～１１記載のポリペプチドと、薬学的に許容される担体とを含むことを特徴とする、ヘリコバクター・フェリス感染に対抗するためのワクチン。

【請求項１５】　アジュバントを含むことを特徴とする、請求項１４に記載のワクチン。

【請求項１６】　哺乳動物にとって病原性のウイルスもしくは微生物に由来する抗原、又は該抗原をコードする遺伝情報を、さらに含むことを特徴とする、請求項１４又は１５に記載のワクチン。

【請求項１７】　哺乳動物にとって病原性のウイルス又は微生物が、ネコ伝染性腹膜炎ウイルス（Ｆｅｌｉｎｅ　Ｉｎｆｅｃｔｉｏｕｓ　Ｐｅｒｉｔｏｎｉｔｉｓ　ｖｉｒｕｓ）、ネコ免疫不全ウイルス（Ｆｅｌｉｎｅ　Ｉｍｍｕｎｅｄｅｆｉｃｉｅｎｃｙ　ｖｉｒｕｓ）、イヌ及びネコのパルボウイルス（Ｃａｎｉｎｅ　ａｎｄ　Ｆｅｌｉｎｅ　Ｐａｒｖｏｖｉｒｕｓ）、ジステンパーウイルス（Ｄｉｓｔｅｍｐｅｒ　ｖｉｒｕｓ）、アデノウイルス（Ａｄｅｎｏｖｉｒｕｓ）、カリシウイルス（Ｃａｌｉｃｉｖｉｒｕｓ）、ボーデテラ・ブロンキセプチカ（Ｂｏｒｄｅｔｅｌｌａ　ｂｒｏｎｃｈｉｓｅｐｔｉｃａ）、ボレリア・ブルグドルフェリ（Ｂｏｒｒｅｌｉａ　ｂｕｒｇｄｏｒｆｅｒｉ）、レプトスピラ・インテロガンス（Ｌｅｐｔｏｓｐｉｒａ　ｉｎｔｅｒｒｏｇａｎｓ）、クラミジア（Ｃｈｌａｍｙｄｉａ）及びバートネラ・ヘンセリ（Ｂａｒｔｏｎｅｌｌａｈｅｎｓｅｌｉ）からなる群より選択されることを特徴とする、請求項１６に記載のワクチン。

【請求項１８】　請求項８～１１に記載のポリペプチドに対する抗体を含むことを特徴とする、ヘリコバクター・フェリス感染に対抗するためのワクチン。

【請求項１９】　請求項８～１１に記載のポリペプチドと薬学的に許容される担体とを混合することを含む、請求項１４～１７に記載のワクチンを調製する方法。

【請求項２０】　請求項１～３に記載の核酸配列又はその断片を含むことを特徴とする、ヘリコバクター・フェリス特異的ＤＮＡの検出のための診断テスト。

【請求項２１】　請求項８～１１に記載のポリペプチド又はその断片を含むことを特徴とする、ヘリコバクター・フェリスに対する抗体の検出のための診断テスト。

【請求項２２】　請求項８～１１に記載のポリペプチド又はその断片に対する抗体を含むことを特徴とする、ヘ

リコバクター・フェリスの抗原性物質の検出のための診断テスト。

【発明の詳細な説明】

【０００１】本発明は、新規なヘリコバクター（Ｈｅｌｉｃｏｂａｃｔｅｒ）ウレアーゼ・サブユニット・ポリペプチド、これらのポリペプチドをコードする核酸配列、ワクチンにおいて使用するためのポリペプチド、それらの製造における使用、該ポリペプチドを含むワクチン、及びそのようなワクチンの調製のための方法に関する。さらに、本発明は、核酸配列、ポリペプチド、及びポリペプチドに対する抗体の検出のための診断法に関する。

【０００２】いくつかのヘリコバクター種が、胃上皮の病因となる。ヘリコバクター・ピロリ（Ｈｅｌｉｃｏｂａｃｔｅｒ　ｐｉｒｏｌｉ）、そして程度は低いがH.ヘイルマンニ（ｈｅｉｌｍａｎｎｉ）が、ヒトにおける消化性潰瘍及び胃リンパ腫の発生における主要な要因である胃炎を引き起こすことが知られている。ヘリコバクター・フェリス（Ｈｅｌｉｃｏｂａｃｔｅｒ　ｆｅｌｉｓ）は、ネコ及びイヌの両方における胃感染の最も多い原因である。高度に酸性の胃環境で生存するため、ヘリコバクター科の細菌は、胃液中に存在する尿素を加水分解することができるウレアーゼを産生する。この加水分解は、細菌の環境を中和するために十分な量のNH_4OHを放出させる。ウレアーゼは、細菌のコロニー形成においても、その病原においても役割を果たすことが知られている。ウレアーゼをコードする遺伝子は、ヘリコバクター・ピロリ（Ｌａｂｉｇｎｅ　ｅｔ　ａｌ．，Ｊ．Ｂａｃｔｅｒｉｏｌ．１７３：１９２０－１９３１（１９９１））及びヘリコバクター・フェリス（Ｆｅｒｒｅｒｏ　ｅｔ　ａｌ．，Ｍｏｌｅｃ．Ｍｉｃｒｏｂｉｏｌ．９，３２３－３３３（１９９３））の両方について記載され、配列決定されている。ウレアーゼの発現及び分泌に関与している７つの遺伝子のうち、２つの遺伝子のみが、ウレアーゼ酵素の２つの構造サブユニット、ウレアーゼA及びＢ；ｕｒｅA及びｕｒｅＢをコードしている。これら２つのポリペプチドは、ウレアーゼ活性を有するポリペプチド複合体を形成する。

【０００３】H.ピロリ及びフェリスの両方により引き起こされる感染に対するワクチンが製造されており、特に、国際特許出願WO９４／０９８２３及びWO９６／３４６２４の主題となっている。H.フェリス感染からネコを防御するためのワクチン成分としてH.ピロリのウレアーゼを使用しようとする試みが、いくつかなされている。実際、ある程度の防御は得られるが、結果は、

望ましいであろう１００％防御にはほど遠い。これまでに発表された動物実験から、H.ピロリで予防接種された動物の相当数が、その後のH.フェリス接種から全く防御されないことは明らかである。H.フェリス又はピロリのいずれかから精製されたウレアーゼで予防接種されたネコの防御は、記載されていない。H.フェリス完全細胞溶解物によるネコの予防接種は、理論的には可能であるが、実用的には選択されていない。これは、改良のための多くの試みにも関わらず、H.フェリスを増殖させることが困難なためである。明らかに、同種成分に基づく有効なワクチンの必要性が存在しており、そして既知のH.フェリス・ウレアーゼが完全な防御を与えないことは明らかである。

【０００４】イヌ及びネコにおけるヘリコバクター・フェリス感染からの防御を誘導することができるH.フェリス・ウレアーゼを提供することが、特に、本発明の目的である。驚くべきことに、H.フェリスには第２のウレアーゼが存在し、その構造サブユニットをコードする遺伝子は、既知のH.フェリスのｕｒｅA及びＢ遺伝子と低い相同性しか有しないことが本発明において見出された。新規なウレアーゼは、既知のウレアーゼＡＢと区別するため、ウレアーゼＸＹと命名されている。新規に見出されたウレアーゼは、H.フェリスにおいて発見され、H.ピロリには存在しない。２つの構造ウレアーゼ・サブユニットＵｒｅX及びＵｒｅYをコードする遺伝子の全体的な遺伝子構造は、H.フェリス及びH.ピロリにおける既知のＵｒｅA及びＢのそれと比較可能である。しかしながら、配列相同性は、驚くほど低い。さらに驚くべきことに、ある単一のH.フェリス株におけるｕｒｅA及びB遺伝子と新規ｕｒｅX及びY遺伝子との間の相同性は、様々なヘリコバクター種由来の様々なｕｒｅA及びB遺伝子の間の相同性よりも顕著に低い。

【０００５】表１ａ、１ｂ、及び１ｃは、５つの異なるヘリコバクター・フェリス種に由来するｕｒｅX及びY遺伝子並びにそれらがコードするポリペプチドと、ヘリコバクター・フェリス、ピロリ及びヘイルマンニに由来するｕｒｅA及びB並びにポリペプチドとの比較を示している。

【０００６】既知のｕｒｅA及びB遺伝子並びにポリペプチド・サブユニットのものと比較した、新規な構造ウレアーゼ・サブユニットX及びYをコードする遺伝子並びにそれらがコードするポリペプチドの相同性のレベルを、表１ａ、ｂ及びｃに提示する。

【０００７】

【表１】

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参照分子:H.フェリス ureX CS1	アミノ酸	核酸
H.フェリス ureA	50%	57%
H.ピロリ ureA	52%	60%
H.ヘイルマンニ ureA	54%	62%
H.フェリス Kukka 株 ureX	100%	91%
H.フェリス Ds4 株 ureX	99%	91%
H.フェリス 2301 株 ureX	99%	91%
H.フェリス 390 株 ureX	99%	91%

表 1a：H.フェリス ureX と様々な ureA サブユニットとの間のアミノ酸及び核酸の相同性

【０００８】　　＊　＊【表２】

参照分子:H.フェリス ureY CS1	アミノ酸	核酸
H.フェリス ureB	73%	71%%
H.ピロリ ureB	73%	70%
H.ヘイルマンニ ureB	74%	71%
H.フェリス Kukka 株 ureY	99%	95%
H.フェリス Ds4 株 ureY	98%	94%
H.フェリス 2301 株 ureY	99%	95%

表 1b：H.フェリス ureY と様々な ureB サブユニットとの間のアミノ酸及び核酸の相同性

【０００９】　　【表３】

参照分子:H.フェリス ureXY CS1	核 酸
H.フェリス ureAB	67%
H.ピロリ ureAB	67%
H.ヘイルマンニ ureAB	68%
H.フェリス Kukka 株 ureXY	94%
H.フェリス Ds4 株 ureXY	94%
H.フェリス 2301 株 ureXY	94%

表 1c：H.フェリス ureXY 遺伝子と様々な ureAB 遺伝子との間の核酸相同性

【００１０】従って、本発明の一つの実施形態は、新規なウレアーゼＸ及びＹサブユニットをコードする核酸配列に関する。

【００１１】第一に、本発明のこの実施形態は、配列番号１と少なくとも８５％の相同性を有する、ヘリコバクター・フェリスにより発現されるようなウレアーゼ複合体の２つのサブユニットをコードする核酸配列、又は該サブユニットのうちの一つの免疫原性断片を少なくともコードする、少なくとも４０ヌクレオチド、好ましくは４５ヌクレオチド、より好ましくは５０ヌクレオチドの長さを有するその一部に関する。少なくとも５５核酸、６０核酸又は７０核酸の長さを有する、さらに長い断片は、その順にさらに好ましい。

【００１２】この実施形態の好ましい形態は、ウレアーゼＸサブユニット・ポリペプチドもしくはウレアーゼＹサブユニット・ポリペプチドをコードし、かつ配列番号１と少なくとも８５％の相同性を有する核酸配列、又はウレアーゼＸサブユニット・ポリペプチドもしくはウレアーゼＹサブユニット・ポリペプチドの免疫原性断片を少なくともコードする、少なくとも４０ヌクレオチド、好ましくは４５ヌクレオチド、より好ましくは５０ヌクレオチドの長さを有するそれらの一部に関する。単なる例として、ヘリコバクター・フェリスＣＳ１株のウレアーゼＸサブユニットをコードする核酸配列は、２０６／２０７／２０８位（ＧＴＧ）（図１ａ（１）参照）で開始し、８８４／８８５／８８６位（ＴＡＡ）で終止する。ヘリコバクター・フェリスＣＳ１株のウレアーゼＹサブユニットをコードする核酸配列は、８９７／８９８／８９９位（ＡＴＧ）で開始し、２６０１／２６０２／２６０３位（ＴＡＧ）で終止する。少なくとも５５核酸、６０核酸又は７０核酸の長さを有する、さらに長い断片は、その順にさらに好ましい。

【００１３】この実施形態のさらに好ましい形態は、配列番号１と少なくとも９０％、好ましくは９４％、より好ましくは９７％の相同性を有する核酸配列に関する。

【００１４】相同率の決定は、サイエンティフィックアンドエデュケーショナルソフトウェア（Ｓｃｉｅｎｔｉｆｉｃ　ａｎｄ　Ｅｄｕｃａｔｉｏｎａｌ　Ｓｏｆｔｗａｒｅ）（Ｐ．Ｏ．Ｂｏｘ７２０４５　Ｄｕｒｈａｍ，ＮＣ２７７２２－２０４５，ＵＳＡ）から入手可能なコンピュータプログラム、アラインプラスフォーウィンドウズ（登録商標）（Ａｌｉｇｎ　Ｐｌｕｓ　ｆｏｒ　Ｗｉｎｄｏｗｓ（登録商標））を用いて実施された。核酸比較に使用された設定は、図１ａ、１ｂ及び１ｃに示されている。

【００１５】本発明は、新規な構造ヘリコバクター・フェリス・ウレアーゼ・サブユニットをコードする核酸配列を開示しているため、そのようなポリペプチドを十分な量で入手することが初めて可能となった。これは、例えば、ＵｒｅＸ及びＵｒｅＹサブユニットをコードする遺伝子を発現させるため発現系を使用することにより実施されうる。従って、より好ましい実施形態において、本発明は、本発明に係る核酸配列を含むＤＮＡ断片に関する。そのようなＤＮＡ断片は、例えば、本発明に係る核酸がクローニングされているプラスミドでありうる。そのようなＤＮＡ断片は、例えば、下記のように、プローブとして使用するためＤＮＡの量を増強するために有用である。

【００１６】核酸配列の発現のための必須の要件は、核酸配列と機能的に連結した適切なプロモーターである。プロモーターの選択が、タンパク質発現のため宿主細胞として使用される細胞において遺伝子転写を指図することができる任意の真核生物、原核生物又はウイルスのプロモーターに及ぶことは、当業者には明らかである。従って、この実施形態のさらに好ましい形態は、機能的に連結したプロモーターの調節下に置かれた本発明に係るＤＮＡ断片又は核酸配列を含む組換えＤＮＡ分子に関する。これは、例えば標準的な分子生物学的技術により入手可能である。（Ｍａｎｉａｔｉｓ／Ｓａｍｂｒｏｏｋ（Ｓａｍｂｒｏｏｋ，Ｊ．Ｍｏｌｅｃｕｌａｒ　ｃｌｏｎｉｎｇ：ａ　ｌａｂｏｒａｔｏｒｙ　ｍａｎｕａｌ，１９８９．ＩＳＢＮ０－８７９６９－３０９－６）。

【００１７】機能的に連結したプロモーターとは、それらが連結している核酸配列の転写を調節することができるプロモーターである。宿主細胞が細菌である場合、使用されうる有用な発現調節配列には、Ｔｒｐプロモーター及びオペレーター（Ｇｏｅｄｄｅｌ，ｅｔ　ａｌ．，Ｎｕｃｌ．Ａｃｉｄｓ　Ｒｅｓ．，８，４０５７，１９８０）、ｌａｃプロモーター及びオペレーター（Ｃｈａｎｇ，ｅｔ　ａｌ．，Ｎａｔｕｒｅ，２７５，６１５，１９７８）、アウターメンブレンプロテイン・プロモーター（Ｎａｋａｍｕｒａ，Ｋ．，ａｎｄ　Ｉｎｏｕｅ，Ｍ．，ＥＭＢＯ　Ｊ．，１，７７１－７７５，１９８２）、バクテリオファージラムダ・プロモーター及びオペレーター（Ｒｅｍａｕｔ，Ｅ．ｅｔ　ａｌ．，Ｎｕｃｌ．Ａｃｉｄ　Ｒｅｓ．，１１，４６７７－４６８８，１９８３）、α－アミラーゼ（Ｂ．ズブチリス）プロモーター及びオペレーター、終結配列、並びに選択された宿主細胞と適合性のその他の発現増強調節配列が含まれる。宿主細胞が酵母である場合、有用な発現調節配列には、例えばα－接合因子が含まれる。昆虫細胞の場合、バキュロウイルスのポリヘドリン・プロモーター又はｐ１０プロモーターが使用されうる（Ｓｍｉｔｈ，Ｇ．Ｅ．ｅｔ　ａｌ．，Ｍｏｌ．Ｃｅｌｌ．Ｂｉｏｌ．３，２１５６－６５，１９８３）。宿主細胞が哺乳動物起源である場合、例示的な有用な発現調節配列には、ＳＶ－４０プロモーター（Ｂｅｒｍａｎ，Ｐ．Ｗ．ｅｔ　ａｌ．，Ｓｉｅｎｃｅ，２２２，５２４－５２７，１９８３）又はメタロチオネイン・プロモーター（Ｂｒｉｎｓｔｅｒ，Ｒ．Ｌ．，Ｎａｔｕｒｅ，２９６，３９－４２，１９８２）又は熱ショック・プロモーター（Ｖｏｅｌｌｍｙ　ｅｔ　ａｌ．，Ｐｒｏｃ．Ｎａｔｌ．Ａｃａｄ．Ｓｃｉ．ＵＳＡ，８２，４９４９－５３，１９８５）が含まれる。

【００１８】細菌、酵母、真菌、昆虫及び哺乳動物の細胞発現系は、極めて頻繁に使用されている系である。そのような系は、当分野において周知であり、一般的に、例えばクロンテックラボラトリーズ社（Ｃｌｏｎｔｅｃｈ　Ｌａｂｏｒａｔｏｒｉｅｓ，Ｉｎｃ．）（４０３０Ｆａｂｉａｎ　Ｗａｙ，Ｐａｌｏ　Ａｌｔｏ，Ｃａｌｉｆｏｒｎｉａ　９４３０３－４６０７，ＵＳＡ）から市販されている。これらの発現系の次に、寄生虫に基づく発現系が、極めて魅力的な発現系である。そのような系は、例えば、公開第２７１４０７４号のフランス特許出願及びＵＳＮＴＩＳ公開第０８／０４３１０９号（Ｈｏｆｆｍａｎ，Ｓ．ａｎｄ　Ｒｏｇｅｒｓ，Ｗ．：公開日１９９３年１２月１日）に記載されている。

【００１９】従って、本発明のこの実施形態のさらに好ましい形態は、本発明に係るＵｒｅＸもしくはＵｒｅＹポリペプチド又はそれらの免疫原性断片をコードする遺伝子を含む組換え生キャリアー（Ｌｉｖｅ　Ｒｅｃｏｍｂｉｎａｎｔ　Ｃａｒｒｉｅｒ）微生物（ＬＲＣ）に関する。そのような微生物は、例えば、細菌及びウイルスである。これらのＬＲＣ微生物は、付加的な遺伝情報、この場合には、本発明に係るＵｒｅＸもしくはＵｒｅＹポリペプチド又はそれらの免疫原性断片をコードする遺伝子がクローニングされている微生物である。そのようなＬＲＣに感染した動物は、ベクターの免疫原に対してのみならず、遺伝暗号、例えばＵｒｅＸ又はＹ遺伝子がＬＲＣにクローニングされている（一つ又は複数の）ポリペプチドの免疫原性部分に対しても免疫原性応答を生じるであろう。細菌ＬＲＣの例として、当分野において

既知の弱毒化サルモネラ株が、魅力的に使用されうる。組換え生キャリアー寄生虫は、特に、バーメウレン（Ｖｅｒｍｅｕｌｅｎ）Ａ．Ｎ．（Ｉｎｔ．Ｊｏｕｒｎ．Ｐａｒａｓｉｔｏｌ．２８：１１２１－１１３０（１９９８））により記載されている。また、ＬＲＣウイルスは、核酸配列を標的細胞に輸送するための手段として使用されうる。組換え生キャリアーウイルスは、ベクターウイルスとも呼ばれる。ＵｒｅＸ又はＹポリペプチドをコードする遺伝子の組み込み部位は、ウイルスにとって必須ではないウイルス遺伝子内の部位、又は遺伝子間領域内の部位でありうる。ベクターとしてしばしば使用されるウイルスは、ワクシニアウイルス（Ｅ．Ｐ．Ａ．０４７３２１０Ａ２）及びレトロウイルス（Ｖａｌｅｒｉｏ，Ｄ．ｅｔ　ａｌ：ｉｎ　Ｂａｕｍ，Ｓ．Ｊ．，Ｄｉｃｋｅ，Ｋ．Ａ．，Ｌｏｔｚｏｖａ，Ｅ．ａｎｄ　Ｐｌｕｚｎｉｋ，Ｄ．Ｈ．，Ｅｘｐｅｒｉｍｅｎｔａｌ　Ｈａｅｍａｔｏｌｏｇｙ　ｔｏｄａｙ－１９８８，Ｓｐｒｉｎｇｅｒ　Ｖｅｒｌａｇ，Ｎｅｗ　Ｙｏｒｋ：９２～９９頁（１９８９））である。

【００２０】挿入された本発明に係る核酸配列の宿主動物における発現を誘導することができる、選択された細菌、寄生虫又はウイルスのゲノムへ、組換え核酸配列を導入するためには、当分野において周知のインビボ相同的組換え技術が使用されうる。

【００２１】本発明のこの実施形態の最後のもう一つの形態は、本発明に係るポリペプチドをコードする核酸配列、そのような核酸配列を含むＤＮＡ断片、又は機能的に連結したプロモーターの調節下でそのような核酸配列を含む組換えＤＮＡ分子を含む宿主細胞に関する。この形態は、本発明に係るＵｒｅＸもしくはＹポリペプチド又はそれらの免疫原性断片をコードする核酸分子を含有する組換え生キャリアーを含有する宿主細胞にも関する。宿主細胞は、ｐＢＲ３２２のような細菌プラスミド又はｐＧＥＸのような細菌発現ベクター、又はバクテリオファージと組み合わせられた、細菌起源、例えば大腸菌、バチルス・ズブチリス（Ｂａｃｉｌｌｕｓ　ｓｕｂｔｉｌｉｓ）、及びラクトバチルス（Ｌａｃｔｏｂａｃｉｌｌｕｓ）種の細胞でありうる。宿主細胞は、真核生物起源のもの、例えば酵母特異的ベクター分子と組み合わせられた酵母細胞、又はベクターもしくは組換えバキュロウイルスと組み合わせられた昆虫細胞（Ｌｕｃｋｏｗ　ｅｔ　ａｌ；Ｂｉｏ－ｔｅｃｈｎｏｌｏｇｙ　６：４７－５５（１９８８））、例えばＴｉプラスミド型ベクターもしくは植物ウイルスベクター（Ｂａｒｔｏｎ，Ｋ．Ａ．ｅｔ　ａｌ；Ｃｅｌｌ　３２：１０３３（１９８３））と組み合わせられた植物細胞、やはり適切なベクターもしくは組換えウイルスと組み合わせられたＨｅｌａ細胞、チャイニーズハムスター卵巣細胞（ＣＨＯ）もしくはクランデル（Ｃｒａｎｄｅｌｌ）ネコ腎細胞のような哺乳動物細胞のような高等真核細胞であってもよい。

【００２２】本発明のもう一つの実施形態は、核酸配列によりコードされるポリペプチド、即ち、ウレアーゼＸサブユニット及びウレアーゼＹサブユニットに関し、そして本発明に係るそれらの免疫原性断片に関する。

【００２３】従って、本発明のこの実施形態は、配列番号２と少なくとも８５％相同なアミノ酸配列を有する、ヘリコバクター・フェリス・ウレアーゼＸポリペプチド、又はウレアーゼＸＹに対する免疫応答を誘導する能力を有する、少なくとも４０アミノ酸の長さを有する、該ポリペプチドの免疫原性断片に関する。好ましくは、該断片の長さは４０アミノ酸超であり、少なくとも４５アミノ酸、５０アミノ酸、５５アミノ酸、６０アミノ酸又は７０アミノ酸が、この順に、より好ましい。

【００２４】好ましくは、この実施形態は、配列番号２と少なくとも９０％、より好ましくは９４％、さらに好ましくは９７％の配列相同性を有するそのようなポリペプチド、又はウレアーゼＸＹに対する免疫応答を誘導する能力を有する、少なくとも４０アミノ酸、より好ましくは少なくとも４５アミノ酸、５０アミノ酸、５５アミノ酸、６０アミノ酸もしくは７０アミノ酸（この順に、より好ましい）の長さを有する、該ポリペプチドの免疫原性断片に関する。

【００２５】本発明のこの実施形態は、配列番号３と少なくとも８５％相同なアミノ酸配列を有する、ヘリコバクター・フェリス・ウレアーゼＹポリペプチド、又はウレアーゼＸＹに対する免疫応答を誘導する能力を有する、少なくとも４０アミノ酸の長さを有する、該ポリペプチドの免疫原性断片に関する。好ましくは、該断片の長さは４０アミノ酸超であり、少なくとも４５アミノ酸、５０アミノ酸、５５アミノ酸、６０アミノ酸又は７０アミノ酸が、この順に、より好ましい。

【００２６】好ましくは、この実施形態は、配列番号３と少なくとも９０％、より好ましくは９４％、さらに好ましくは９７％の配列相同性を有するそのようなポリペプチド、又はウレアーゼＸＹに対する免疫応答を誘導する能力を有する、少なくとも４０アミノ酸、より好ましくは少なくとも４５アミノ酸、５０アミノ酸、５５アミノ酸、６０アミノ酸もしくは７０アミノ酸（この順に、より好ましい）の長さを有する、該ポリペプチドの免疫原性断片に関する。

【００２７】ヌクレオチド配列比較の場合と同様に、サイエンティフィックアンドエデュケーショナルソフトウェア（Ｓｃｉｅｎｔｉｆｉｃ　ａｎｄ　Ｅｄｕｃａｔｉｏｎａｌ　Ｓｏｆｔｗａｒｅ）（Ｐ．Ｏ．Ｂｏｘ７２０４５　Ｄｕｒｈａｍ，ＮＣ２７７２２－２０４５，ＵＳＡ）から入手可能なアラインプラスフォーウィンドウズ（Ａｌｉｇｎ　Ｐｌｕｓ　ｆｏｒ　Ｗｉｎｄｏｗｓ）を使用して様々なアミノ酸配列間の比較を実施した。アミノ酸比較に使用された設定は、図１ａ、１ｂ及び１ｃに

示されている。

【００２８】本明細書に包含されている特定のポリペプチドについて、個々のヘリコバクター・フェリス株の間には天然の差異が存在しうることが理解されよう。これらの差異は、全体的な配列における（一つ又は複数の）アミノ酸の違い、又は該配列内の（一つ又は複数の）アミノ酸の欠失、置換、挿入、逆位もしくは付加により示されうる。生物学的活性及び免疫学的活性を本質的に改変しないアミノ酸置換は、例えば「タンパク質（ｔｈｅ　Ｐｒｏｔｅｉｎｓ）」Ａｃａｄｅｍｉｃ　Ｐｒｅｓｓ　Ｎｅｗ　Ｙｏｒｋ（１９７９）においてニューラス（Ｎｅｕｒａｔｈ）らにより記載されている。関連アミノ酸間のアミノ酸交換、又は進化において高頻度に起こっている交換は、特に、Ｓｅｒ／Ａｌａ、Ｓｅｒ／Ｇｌｙ、Ａｓｐ／Ｇｌｙ、Ａｓｐ／Ａｓｎ、Ｉｌｅ／Ｖａｌである（Ｄａｙｈｏｆ，Ｍ．Ｄ．，Ａｔｌａｓ　ｏｆ　ｐｒｏｔｅｉｎ　ｓｅｑｕｅｎｃｅ　ａｎｄ　ｓｔｒｕｃｔｕｒｅ，Ｎａｔ．Ｂｉｏｍｅｄ．Ｒｅｓ．Ｆｏｕｎｄ．，ＷａｓｈｉｎｇｔｏｎＤ．Ｃ．，１９７８年、第５巻増補３参照）。その他のアミノ酸置換には、Ａｓｐ／Ｇｌｕ、Ｔｈｒ／Ｓｅｒ、Ａｌａ／Ｇｌｙ、Ａｌａ／Ｔｈｒ、Ｓｅｒ／Ａｓｎ、Ａｌａ／Ｖａｌ、Ｔｈｒ／Ｐｈｅ、Ａｌａ／Ｐｒｏ、Ｌｙｓ／Ａｒｇ、Ｌｅｕ／Ｉｌｅ、Ｌｅｕ／Ｖａｌ及びＡｌａ／Ｇｌｕが含まれる。この情報に基づき、リップマン（Ｌｉｐｍａｎ）及びピアソン（Ｐｅａｒｓｏｎ）は、迅速かつ高感度にタンパク質を比較し（Ｓｃｉｅｎｃｅ，２２７，１４３５－１４４１，１９８５）、相同タンパク質間の機能的類似性を決定する方法を開発した。本発明の例示的な実施形態のそのようなアミノ酸置換も、欠失及び／又は挿入を有する差異も、得られたポリペプチドが免疫応答性を保持している限りにおいて、本発明の範囲に含まれる。従って、配列番号２又は３に示されたような野生型ポリペプチドと比較した場合の、ポリペプチドの免疫原性に本質的に影響を与えない差異は、本発明の範囲に包含されると見なされる。Ｈ．フェリス感染、又は少なくとも感染の臨床的発現に対する免疫応答を誘導する能力を有するポリペプチドを提供する、本発明に係るいくつかの構造サブユニットＸ又はＹのアミノ酸配列のこれらの差異は、「免疫原性に本質的に影響を与えない」と見なされる。

【００２９】例えばワクチン目的又は抗体の惹起のためポリペプチドを使用する場合、完全なポリペプチドを使用する必要はない。そのままで、又は例えばＫＬＨのような担体とカップリングして、ポリペプチドに対する免疫応答を有する能力を有するポリペプチドの断片、いわゆる免疫原性断片を使用することも可能である。「免疫原性断片」とは、宿主において免疫応答を誘導する能力を保持している、即ちＢ細胞エピトープ又はＴ細胞エピトープを含む、構造サブユニットＸ又はＹの全長ポリペプチドの断片と理解される。現時点で、抗原性断片（決定基）をコードするＤＮＡ断片を容易に同定するための多様な技術が利用可能である。ゲイセン（Ｇｅｙｓｅｎ）ら（特許出願ＷＯ８４／０３５６４、特許出願ＷＯ８６／０６４８７、米国特許第ＮＲ．４，８３３，０９２号、Ｐｒｏｃ．Ｎａｔｌ．Ａｃａｄ．Ｓｃｉ．ＵＳＡ，８１：３９９８－４００２（１９８４）、Ｊ．Ｉｍｍ．Ｍｅｔｈ．１０２，２５９－２７４（１９８７））により記載された方法、いわゆるＰＥＰＳＣＡＮ法は、エピトープ、ポリペプチドの免疫学的に重要な領域を検出するための、実施が容易で、迅速で、かつ十分に確立されている方法である。この方法は世界中で使用されており、当業者に自体周知である。この（経験的な）方法は、Ｂ細胞エピトープの検出に特に適している。また、任意のタンパク質をコードする遺伝子の配列が与えられれば、コンピュータアルゴリズムが、現在既知であるエピトープとの配列及び／又は構造の一致性に基づき、免疫学的に重要なエピトープとして特定のポリペプチド断片を指定することができる。これらの領域の決定は、ホップ（Ｈｏｐｐ）及びウッズ（Ｗｏｏｄｓ）（Ｐｒｏｃ．Ｎａｔｌ．Ａｃａｄ．Ｓｃｉ．ＵＳＡ，７８：３８２４８－３８２８（１９８１））による親水性基準と、チョウ（Ｃｈｏｕ）及びファスマン（Ｆａｓｍａｎ）（Ａｄｖａｎｃｅｓ　ｉｎ　Ｅｎｚｙｍｏｌｏｇｙ　４７：４５－１４８（１９８７）及び米国特許第４，５５４，１０１号）による二次構造面との組み合わせに基づいている。Ｔ細胞エピトープは、同様に、バーゾフスキー（Ｂｅｒｚｏｆｓｋｙ）の両親媒性基準（Ｓｃｉｅｎｃｅ　２３５，１０５９－１０６２（１９８７）及び米国特許出願ＮＴＩＳ　ＵＳ　０７／００５，８８５）を利用して、コンピュータにより配列から予測されうる。要約された概要が、一般原理についてはＳｈａｎ　Ｌｕ：Ｔｉｂｔｅｃｈ　９：２３８－２４２（１９９１）に、マラリア・エピトープについてはＧｏｏｄ　ｅｔ　ａｌ；Ｓｃｉｅｎｃｅ　２３５：１０５９－１０６２（１９８７）に、概説についてはＬｕ；Ｖａｃｃｉｎｅ　１０：３－７（１９９２）に、ＨＩＶエピトープについてはＢｅｒｚｏｗｓｋｙ；Ｔｈｅ　ＦＡＳＥＢ　Ｊｏｕｒｎａｌ　５：２４１２－２４１８（１９９１）に見出される。

【００３０】例えば、唯１つのウレアーゼを有するヘリコバクター・ピロリに対するワクチンが、前記のように、このウレアーゼに基づき製造されうる。しかしながら、ヘリコバクター・フェリスの特定の場合、既知のヘリコバクター・フェリス構造サブユニットｕｒｅＡ及びＢに基づくワクチンは、ヘリコバクター・フェリス感染に対する十分な防御を提供することができない。報告によると、構造サブユニットｕｒｅＡ及びＢに対する免疫は、新たに見出された異種構造サブユニットＵｒｅＸ及びＹのウレアーゼ活性を中和しない。

【００３１】従って、ヘリコバクター・フェリス感染からの動物の防御のためのワクチンは、少なくとも、新規なウレアーゼＸＹに対するものでなければならない。従って、本発明のさらにもう一つの実施形態の一つの形態は、本発明に係る構造サブユニットＸもしくはＹ、好ましくはＸ及びＹ、より好ましくはＸ、Ｙ、Ａ及びＢ、又はＸ及び／もしくはＹの免疫原性断片を、薬学的に許容される担体と共に含む、ヘリコバクター・フェリス感染からイヌ及びネコのような動物を防御することができるワクチンに関する。

【００３２】本発明のさらにもう一つの実施形態は、ワクチンにおいて使用するための本発明に係るポリペプチドに関する。

【００３３】さらにもう一つの実施形態は、ヘリコバクター・フェリス感染に対抗するためのワクチンの製造における本発明に係るポリペプチドの使用に関する。

【００３４】本発明に係るワクチンを製造する一つの方法は、ウレアーゼＸＹポリペプチド又はそのサブユニットの細菌培養物からの生化学的な精製による。これは、例えば、細菌の遠心分離、及びウレアーゼポリペプチド又はそのサブユニットの他の成分からの分離のためのゲル濾過カラムの使用により実施されうる。さらなる精製は、例えば、硫酸アンモニウムで選択的に沈殿させ、続いて遠心分離、ゲル電気泳動を行い、そして、所望により、ウレアーゼＡＢサブユニットからの分離を行い、そして適当な緩衝液にペレットを溶解させることにより実施されうる。しかしながら、これは、ヘリコバクター・フェリスを増殖させることが困難である場合には特に、多大の時間を要するワクチン製造法である。

【００３５】従って、本発明に係るウレアーゼＸ及びＹサブユニットをコードする遺伝子の発現産物をワクチンにおいて使用する方が、はるかに便利である。そのようなワクチンは、本発明に係るウレアーゼＸＹ又はＵｒｅＸもしくはＹサブユニット又はそれらの免疫原性断片と、下記のような薬学的に許容される担体とを混合することにより、容易に製造されうる。

【００３６】さらに、ワクチンは、本発明に係るウレアーゼＸＹ、ＵｒｅＸもしくはＵｒｅＹサブユニット、又はそれらの免疫原性断片を発現することができる、前記のような組換え生キャリアーを含んでいてもよい。例えば、胃上皮に感染するサルモネラキヤリアー又はウイルスキャリアーに基づく、そのようなワクチンは、天然のヘリコバクター・フェリス感染様式を、よりよく模倣するという、他のサブユニットワクチンより優れた利点を有する。さらに、それらの自己繁殖は、少量の組換えキャリアーのみが免疫感作に必要となるため、有利である。

【００３７】前記のワクチンは、全て、能動予防接種に寄与する、即ち宿主の免疫系が、これらのポリペプチドに対する抗体を作るよう、ＵｒｅＸ及び／もしくはＹポリペプチド、又はそれらの免疫原性断片により誘発される。又は、そのような抗体を、例えばウサギにおいて惹起させることもできるし、又は下記のような抗体産生細胞系から入手することもできる。次いで、そのような抗体は、宿主動物へ投与されうる。この予防接種法、受動予防接種は、動物が既に感染しており、天然の免疫応答が誘発されるのを待つ時間が存在しない場合に、選択される予防接種である。また、免疫不全動物を予防接種するための好ましい方法でもある。投与されたヘリコバクターＵｒｅＸ又はＵｒｅＹに対する抗体は、これらの場合、細菌により分泌されたウレアーゼと直接結合することができる。これは、ウレアーゼ活性が直接的に排除され、従って、環境が酸性化され、ヘリコバクター増殖が減少又は停止するという利点を有する。従って、本発明のこの実施形態のもう一つの形態は、配列番号２と少なくとも８５％相同なアミノ酸配列を有するヘリコバクター・フェリス・ウレアーゼＸポリペプチド、もしくはウレアーゼＸＹに対する免疫応答を誘導する能力を有する少なくとも４０アミノ酸長を有するポリペプチドの免疫原性断片に対する抗体、又は配列番号３と少なくとも８５％相同なアミノ酸配列を有するヘリコバクター・フェリス・ウレアーゼＹポリペプチド、もしくはウレアーゼＸＹに対する免疫応答を誘導する能力を有する少なくとも４０アミノ酸長を有するポリペプチドの免疫原性断片に対する抗体を含むワクチンに関する。

【００３８】ワクチンは、本発明に係るウレアーゼＸＹ、ＵｒｅＸもしくはＵｒｅＹサブユニット、又はそれらの免疫原性断片を含む、前記のような宿主細胞に基づいていてもよい。

【００３９】別の効率的な予防接種法は、関連抗原をコードするＤＮＡによる直接予防接種である。ポリペプチドをコードするＤＮＡによる直接予防接種は、多くの異なるポリペプチドについて成功している（例えば、Ｄｏｎｎｅｌｌｙ　ｅｔ　ａｌ．，Ｔｈｅ　Ｉｍｍｕｎｏｌｏｇｉｓｔ　２：２０－２６（１９９３）に概説されている）。この予防接種法は、ヘリコバクター・フェリス感染に対するネコ及びイヌ両方の予防接種にとって極めて魅力的である。従って、本発明のこの実施形態のさらに他の形態は、本発明に係るポリペプチド又は本発明に係るそれらの免疫原性断片をコードする核酸配列を含むワクチンに関し、そしてそのような核酸配列を含むＤＮＡ断片を含むワクチンに関する。この実施形態のさらに他の形態は、本発明に係る組換えＤＮＡ分子を含むワクチンに関する。ＤＮＡワクチンは、例えば針なしの注射器を使用して、経皮的適用により容易に投与されうる。この投与法は、予防接種すべき動物の細胞へＤＮＡを直接輸送する。１～１００μｇのマイクログラム範囲の量のＤＮＡが、極めて良好な結果を提供する。

【００４０】さらなる実施形態において、本発明に係るワクチンは、イヌもしくはネコにとって病原性の生物及

びウイルスに由来する抗原、又はそのような抗原をコードする遺伝情報を含んでいてもよい。そのような生物及びウイルスは、例えば、ネコ伝染性腹膜炎ウイルス（Ｆｅｌｉｎｅ Ｉｎｆｅｃｔｉｏｕｓ Ｐｅｒｉｔｏｎｉｔｉｓ ｖｉｒｕｓ）、ネコ免疫不全ウイルス（Ｆｅｌｉｎｅ Ｉｍｍｕｎｅｄｅｆｉｃｉｅｎｃｙ ｖｉｒｕｓ）、イヌ及びネコのパルボウイルス（Ｃａｎｉｎｅ ａｎｄ Ｆｅｌｉｎｅ Ｐａｒｖｏｖｉｒｕｓ）、ジステンパーウイルス（Ｄｉｓｔｅｍｐｅｒ ｖｉｒｕｓ）、アデノウイルス（Ａｄｅｎｏｖｉｒｕｓ）、カリシウイルス（Ｃａｌｉｃｉｖｉｒｕｓ）、ボーデテラ・ブロンキセプチカ（Ｂｏｒｄｅｔｅｌｌａ ｂｒｏｎｃｈｉｓｅｐｔｉｃａ）、ボレリア・ブルグドルフェリ（Ｂｏｒｒｅｌｉａ ｂｕｒｇｄｏｒｆｅｒｉ）、レプトスピラ・インテロガンス（Ｌｅｐｔｏｓｐｉｒａ ｉｎｔｅｒｒｏｇａｎｓ）、クラミジア（Ｃｈｌａｍｙｄｉａ）及びバートネラ・ヘンセリ（Ｂａｒｔｏｎｅｌｌａ ｈｅｎｓｅｌｉ）である。

【００４１】また、本発明は、ヘリコバクター・フェリス感染に対抗するためのワクチンの製造において使用するための、本発明に係るポリペプチドに関する。

【００４２】本発明に係るワクチンは、全て、薬学的に許容される担体を含む。薬学的に許容される担体は、例えば、無菌水又は無菌生理的塩溶液である。より複雑な形態において、担体は、例えば緩衝液であってもよい。

【００４３】本発明に係るワクチンは、好ましくは、アジュバントも含有していてもよい。アジュバントは、一般的に、非特異的に宿主の免疫応答を強化する物質を含む。多数の異なるアジュバントが、当分野において既知である。アジュバントの例は、フロイント完全アジュバント及び不完全アジュバント、ビタミンＥ、非イオン性ブロック重合体、ムラミルジペプチド、Ｑｕｉｌｌ Ａ（登録商標）、鉱油、例えばＢａｙｏｌ（登録商標）又はＭａｒｋｏｌ（登録商標）、植物油、及びＣａｒｂｏｐｏｌ（登録商標）（同種重合体）又はＤｉｌｕｖａｃ（登録商標）Ｆｏｒｔｅである。ワクチンは、いわゆる「媒体」を含んでいてもよい。媒体とは、ポリペプチドが、共有結合することなく接着する化合物である。しばしば使用される媒体化合物は、例えばアルミニウムの水酸化物、リン酸塩、又は酸化物、シリカ、カオリン及びベントナイトである。抗原が媒体に部分的に埋め込まれている特別な形態のそのような媒体は、いわゆるＩＳＣＯＭである（ＥＰ１０９，９４２、ＥＰ１８０，５６４、ＥＰ２４２，３８０）。さらに、ワクチンは、一つ又は複数の適当な界面活性化合物又は乳化剤、例えばスパン（Ｓｐａｎ）又はトウィーン（Ｔｗｅｅｎ）を含みうる。しばしば、ワクチンは、例えば分解傾向のあるポリペプチドを分解から防御するため、ワクチンの貯蔵寿命を増強するため、又は凍結乾燥効率を改善するため、安定化剤と混合される。有用な安定化剤は、特に、ＳＰＧＡ（Ｂｏｖａｒｎｉｋ ｅｔ ａｌ；Ｊ．Ｂａｃｔｅｒｉｏｌｏｇｙ ５９：５０９（１９５０））、炭水化物、例えばソルビトール、マンニトール、トレハロース、デンプン、ショ糖、デキストラン又はグルコース、アルブミンもしくはカゼインのようなタンパク質又はそれらの分解産物、並びにアルカリ金属リン酸塩のような緩衝剤である。さらに、生理学的に許容される希釈剤にワクチンを懸濁させてもよい。言及するまでもなく、アジュバントによる強化、媒体化合物又は希釈剤の添加、ポリペプチドの乳化又は安定化のその他の方法も、本発明に包含される。

【００４４】ＵｒｅＸ又はＵｒｅＹサブユニット・ポリペプチドを含む本発明に係るワクチンは、１～１００マイクログラムの範囲の量で、特に好適に投与されうるが、それより少ない用量も、原則的には使用されうる。１００マイクログラムを越える量は、免疫学的には極めて適当であるが、商業的な理由からは魅力的ではない。

【００４５】前記のＬＲＣウイルス及びＬＲＣ細菌のような生弱毒化組換えキャリアーに基づくワクチンは、感染中に自己複製するため、はるかに少ない用量で投与されうる。従って、極めて適当な量は、それぞれ細菌及びウイルスについて10^3～10^9ＣＦＵ／ＰＦＵの間であろう。

【００４６】多くの投与法が適用されうる。鼻腔内適用は、ワクチンを投与するための高頻度に使用されている方法である。感染はしばしば消化管上部に位置しているため、経口投与も魅力的な投与法である。経口投与の好ましい方法は、高度に酸性の胃環境においてのみ崩壊する、当分野において既知であり高頻度に使用されているカプセル内へのワクチンのパッケージングである。また、ワクチンを胃のｐＨを一時的に増強するための、当分野において既知の化合物と混合してもよい。例えば、ワクチンの筋肉内適用による全身適用も適当である。この経路による場合、全身適用のための当分野において既知の標準的な手法が、非常に適している。

【００４７】本発明のもう一つの実施形態は、Ｈ．フェリス感染の検出のための診断テストに関する。Ｈ．ビッゾゼロニー（ｂｉｚｚｏｚｅｒｏｎｉｉ）、Ｈ．フェリス及びＨ．サロモニス（ｓａｌｏｍｏｎｉｓ）のようないくつかのヘリコバクター種が、ネコ及びイヌの両方に感染する能力を有する。これらの３種のうち、Ｈ．ビッゾゼロニー及びＨ．サロモニスはしばしば数で勝るが、病理の大部分を引き起こしていると推測される種は、Ｈ．フェリスである。従って、ヘリコバクター・フェリスにより引き起こされたネコ及びイヌの両方における疾患の迅速かつ正確な診断は、重要である。しかしながら、これらの３種は極めて密接に関連しているため、区別することが極めて困難であった。従って、他のヘリコバクター種からＨ．フェリスを区別するために適した診断道具を提供することが、本発明のもう一つの目的であ

る。

【００４８】新規なウレアーゼポリペプチド及びウレアーゼポリペプチドをコードする遺伝子に基づき、ヘリコバクター科の他の細菌からH．フェリスを区別するために特に適した少なくとも３つの異なる診断テストが開発された。１）特異的なＵｒｅＸ及びＵｒｅＹ構造サブユニットをコードするＤＮＡの存在又は欠如に基づく診断テスト。２）特異的なＵｒｅＸ及びＵｒｅＹ構造サブユニットに対する抗体の検出に基づく診断テスト。３）特異的なＵｒｅＸ及びＵｒｅＹ構造サブユニットの抗原性物質の検出に基づく診断テスト。

【００４９】１）の診断テストは、例えば、試験すべき動物から単離された細菌ＤＮＡと、ｕｒｅＸ又はＹ遺伝子の配列に基づく特異的なプローブ又はＰＣＲプライマーとの反応に基づいている。H．フェリスＤＮＡが動物に存在する場合には、これは、例えばｕｒｅＸ又はＹ特異的ＰＣＲプライマーと特異的に結合し、その後、ＰＣＲ反応において増幅されるであろう。次いで、ＰＣＲ反応産物は、ＤＮＡゲル電気泳動において容易に検出されうる。ＤＮＡは、試験すべき動物の消化管上部のスワブ又は唾液に存在する微生物から最も容易に単離されうる。特異的プライマーは、ｕｒｅＡＢコーディング配列内の比較可能な領域とは配列が異なる、ｕｒｅＸ及びｕｒｅＹコーディング配列並びに非コーディング遺伝子間配列の多くの領域から容易に選択されうる。一般的な核酸相同性レベルの決定及びヌクレオチド配列の比較に適した多くのアルゴリズムのうちの一つは、「クラスタル（Ｃｌｕｓｔａｌ）Ｗ」として既知である。それは、Ｎｕｃｌｅｉｃ Ａｃｉｄ Ｒｅｓｅａｒｃｈ ２２：４６７３－４６８０（１９９４）にトンプソン（Ｔｈｏｍｐｓｏｎ）らにより記載されている。このプログラムは、インターネット上のいくつかのサイトに見出される。このプログラムのより最近の代替物は、例えば、サイエンティフィックアンドエデュケーショナルソフトウェア（Ｓｃｉｅｎｔｉｆｉｃ ａｎｄ Ｅｄｕｃａｔｉｏｎａｌ Ｓｏｆｔｗａｒｅ）（Ｐ．Ｏ．Ｂｏｘ７２０４５ Ｄｕｒｈａｍ，ＮＣ２７７２２－２０４５，ＵＳＡ）から入手可能なアラインプラスフォーウィンドウズ（Ａｌｉｇｎ Ｐｌｕｓ ｆｏｒ Ｗｉｎｄｏｗｓ）である。図１の通り、ｕｒｅＸ又はｕｒｅＹに特異的な可能性のあるＰＣＲプライマーを、極めて多数見出すことができる。極めて特異的なＰＣＲプローブ対は、例えば、５’に位置する配列ＣＡＴＧＣＡＣＴＴＴＴＴＧＡＡＡＡＡＧＡ（配列番号１６）及び３’に位置する配列ＴＡＴＧＧＴＧＧＴＣＴＴＣＴＣＴ（配列番号１７）である。当然、ｕｒｅＸもしくはＹ又は遺伝子間領域に特異的なその他の多くの配列が適している。標準的なＰＣＲ参考書は、ｕｒｅＸ又はｕｒｅＹとの選択的なＰＣＲ反応のためのプローブの妥当性を決定するための方法を与えている。ＰＣＲ技術は、（Ｄｉｅｆｆｅｎｂａｃｈ&Ｄｒｅｋｓｌｅｒ；ＰＣＲ ｐｒｉｍｅｒｓ，ａ ｌａｂｏｒａｔｏｒｙ ｍａｎｕａｌ，ＩＳＢＮ０－８７９６９－４４７－５（１９９５））に詳細に記載されている。

【００５０】もう一つのＤＮＡ型テストは、スワブから得られた細菌物質の増殖、それに続く古典的なＤＮＡ精製、それに続く放射性又は色素で標識されたｕｒｅＸＹ特異的ＤＮＡ断片との古典的ハイブリダイゼーションに基づく。H．フェリス及びその他のヘリコバクター種、両方のｕｒｅＸＹコーディング領域とｕｒｅＡＢコーディング領域との間の相同性は極めて低いため、ハイブリダイゼーションは、H．フェリスの存在又は欠如を明確に示す。ＰＣＲ反応及びハイブリダイゼーション反応は、いずれも、当分野において周知であり、特に、Ｍａｎｉａｔｉｓ／Ｓａｍｂｒｏｏｋ（Ｓａｍｂｒｏｏｋ，Ｊ．ｅｔ ａｌ．Ｍｏｌｅｃｕｌａｒ ｃｌｏｎｉｎｇ：ａ ｌａｂｏｒａｔｏｒｙ ｍａｎｕａｌ，ＩＳＢＮ０－８７９６９－３０９－６）に記載されている。ＰＣＲプライマーによる選択的検出又はｕｒｅＸＹ特異的ＤＮＡ断片との古典的ハイブリダイゼーションは、好ましくは短い断片を用いて実施されるが、実用的な理由から、好ましくは配列番号１の少なくとも１０連続ヌクレオチドのストレッチからなる断片を用いて実施されうる。ハイブリダイゼーション実験には、ヘリコバクターｕｒｅＡ又はｕｒｅＢサブユニットをコードする配列との相同性よりも、配列番号１との相同性の方が高いプローブを選択する必要がある。そのようなプローブは、前記のようなアラインプラスフォーウィンドウズ（Ａｌｉｇｎ Ｐｌｕｓ ｆｏｒ Ｗｉｎｄｏｗｓ）プログラム又はクラスタルＷプログラムを利用して、極めて容易に選択されうる。比較ハイブリダイゼーション実験において、診断すべきＤＮＡは、例えばH．ピロリＤＮＡの隣でテストされうる。ｕｒｅＡＢをコードする遺伝子との相同性よりも配列番号１との相同性の方が高い、本発明に係るプローブは、他のヘリコバクター種のＤＮＡよりも、H．フェリスＤＮＡ（試料中に存在する場合）と強く結合し、従って、テストすべき試料中のH．フェリスＤＮＡの存在を特異的に示すであろう。前記の配列番号１６又は１７の配列は、標識し、その後、記載されたようなH．フェリス特異的ハイブリダイゼーション・アッセイにおいて使用するために極めて適しているプローブの例にすぎない。

【００５１】従って、本発明の一つの実施形態は、特異的なヘリコバクターＵｒｅＸ及びＵｒｅＹサブユニット・ポリペプチドをコードするＤＮＡの検出のための診断テストに関する。そのようなテストは、ＵｒｅＸ及びＵｒｅＹをコードするＤＮＡ、又はＵｒｅＸとＵｒｅＹとの間の遺伝子間領域に特異的な、本発明に係る核酸配列又はそれらの断片を含む。そのＤＮＡに特異的な断片は、ＵｒｅＡ及びＵｒｅＢをコードするＤＮＡ、又はＵ

ｒｅＡとＵｒｅＢとの間の遺伝子間領域よりも、ＵｒｅＸ及びＵｒｅＹをコードするＤＮＡ、又はＵｒｅＸとＵｒｅＹとの間の遺伝子間領域と、強く結合する断片である。

【００５２】ヘリコバクター・フェリスＤＮＡの検出法は、テストすべきＤＮＡとＵｒｅＸ又はＹ　ＤＮＡとのハイブリダイゼーション、又はテストすべきＤＮＡのＵｒｅＸ又はＹ　ＤＮＡ特異的プローブによるＰＣＲ反応を含む。

【００５３】血清中のヘリコバクター・フェリス抗体の検出のための２）の診断テストは、例えば、精製された本発明に係るＵｒｅＸもしくはＵｒｅＹサブユニット・ポリペプチド又はそれらの抗原性断片を、ＥＬＩＳＡプレートのウェルの壁にコーティングする、単純なサンドイッチＥＬＩＳＡテストである。そのような抗体の検出のための方法は、例えば、精製されたＵｒｅＸ又はＹポリペプチドを、試験すべき哺乳動物由来の血清と共にインキュベートし、それに続き、例えば関連哺乳動物抗体に対する標識抗体と共にインキュベートする方法である。次いで、呈色反応により、ヘリコバクター・フェリスウレアーゼＸＹに対する抗体の存在又は欠如を明らかにすることができる。使用される標識抗体によっては、この系の選択性は、非ＸＹ特異的反応を回避するため、試験すべき血清をウレアーゼＡＢと共にプレインキュベートし、それに続き、沈殿物の遠心分離を行うことにより改善されうる。本発明に係るＵｒｅＸ又はＵｒｅＹ構造サブユニットの抗原性断片をコーティングに使用する場合には、プレインキュベーション工程を省略することができる。

【００５４】診断テスト系のもう一つの例は、例えば、本発明に係るＵｒｅＸもしくはＵｒｅＹポリペプチド又はそれらの抗原性断片を含むウェスタンブロットと、テストすべき哺乳動物の血清とのインキュベーション、それに続くブロットの分析である。ＥＬＩＳＡプレートのコーティング又はウェスタンブロッティングに適した、精製された本発明に係るＵｒｅＸもしくはＵｒｅＹ構造サブユニット又はそれらの抗原性断片は、ｕｒｅＡ及びＢについてフェレロ（Ｆｅｒｒｅｒｏ　ｅｔａｌ．，Ｍｏｌｅｃ．Ｍｉｃｒｏｂｉｏｌ．９，３２３－３３３（１９９３））が記載したような、ｕｒｅＸ及びｕｒｅＹ遺伝子の発現により容易に入手されうる。

【００５５】又、本発明は、血清と、本発明に係るＵｒｅＸもしくはＵｒｅＹポリペプチド又はそれらの抗原性断片とのインキュベーションを含む、ヘリコバクター・フェリス抗体に対する抗体の血清中の検出のための方法に関する。

【００５６】ヘリコバクター・フェリス抗原の特異的ＵｒｅＸ及びＵｒｅＹ構造サブユニットの抗原性物質の検出に基づいており、従って、ヘリコバクター・フェリス感染の検出に適した３）の診断テストは、標準的なＥＬＩＳＡテストでありうる。そのような試験の一つの例においては、ＥＬＩＳＡプレートのウェルの壁に、ヘリコバクター・フェリスの特異的ＵｒｅＸ及びＵｒｅＹ構造サブユニットに対する抗体をコーティングする。試験すべき抗原性物質は、必要に応じて、ＵｒｅＡ及びＢに対する抗体とプレインキュベートされうる。これにより、ＵｒｅＸ及びＹ特異的エピトープはカバーされず、従って、プレインキュベートされたヘリコバクター種は、ＵｒｅＸ又はＹを含む場合にのみ、即ち特異的にヘリコバクター・フェリスである場合にのみ、ＥＬＩＳＡプレートと結合するであろう。ＵｒｅＸ又はＹに特異的であり、ＵｒｅＡ又はＢとは反応しないモノクローナル抗体の使用は、プレインキュベーション工程を不要とするため、そのようなテストにおける好ましい抗体である。そのようなモノクローナル抗体は、当分野において既知の技術により、本発明に係るＵｒｅＸ又はＹの免疫感作断片で、近交系マウスを免疫感作することにより容易に得ることができる（下記Ｋｏｈｌｅｒ　ａｎｄＭｉｌｓｔｅｉｎ論文参照）。

【００５７】前記のようにして発現させた本発明に係るポリペプチド又はそれらの免疫原性断片は、ポリクローナルであっても、単一特異的もしくはモノクローナルであってもよい抗体（又はそれらの誘導体）を製造するために使用されうる。ポリクローナル抗体が望ましい場合、ポリクローナル血清を製造し、加工する技術は、当分野において周知である（例えば、Ｍａｙｅｒ　ａｎｄ　Ｗａｌｔｅｒ，Ｉｍｍｕｎｏｃｈｅｍｉｃａｌ　Ｍｅｔｈｏｄｓ　ｉｎ　Ｃｅｌｌ　ａｎｄ　Ｍｏｌｅｃｕｌａｒ　Ｂｉｏｌｏｇｙ，Ａｃａｄｅｍｉｃ　Ｐｒｅｓｓ，Ｌｏｎｄｏｎ，１９８７）。本発明に係るポリペプチド（又はそれらの異型又は断片）と反応する、本発明に係るモノクローナル抗体は、やはり当分野において既知の技術により近交系マウスを免疫感作することにより調製されうる（Ｋｏｈｌｅｒ　ａｎｄＭｉｌｓｔｅｉｎ，Ｎａｔｕｒｅ，２５６，４９５－４９７，１９７５）。

【００５８】最後に、本発明は、血清、組織又は体液を、本発明に係るＵｒｅＸもしくはＵｒｅＹポリペプチド又はそれらの断片に対する抗体と共にインキュベートすることを含む、ヘリコバクター・フェリス由来の抗原性物質の検出のための方法に関する。

【００５９】実施例１

ヘリコバクター・フェリスＣＳ１株のｕｒｅＸ及びｕｒｅＹ遺伝子：大腸菌におけるクローニング及び発現

以下のようにして、Ｈ．フェリスＣＳ１株のｕｒｅＸ及びｕｒｅＹ遺伝子を、大腸菌Ｔ７発現ベクターｐＥＴ３ａにオペロンとしてクローニングした。ｐＥＴ３ａ（Ｎｏｖａｇｅｎ、６０１　Ｓｃｉｅｎｃｅ　Ｄｒｉｖｅ，ＭａｄｉｓｏｎＷＩ，ＵＳＡ）におけるＵｒｅＸ及びＹタンパク質の適切な発現のため、遺伝子をＮｄｅＩ－Ｂ

ａｍＨＩ　ＤＮＡ断片として、このベクターのＮｄｅＩ－ＢａｍＨＩにクローニングした。ウレアーゼＸＹオペロンは、内部ＮｄｅＩ部位を含有しており、それに、２つのＰＣＲ断片のオーバーラップ伸長ＰＣＲにより突然変異を導入した。その目的のため、２つのＰＣＲ断片（５’及び３’産物）を、Ｈ．フェリスＣＳ１の染色体ＤＮＡを鋳型として使用して増幅した。５’ＰＣＲ産物は、完全なｕｒｅＸ遺伝子及びｕｒｅＹ遺伝子の最初の部分を含有していた。順向きプライマーは、ＮｄｅＩ制限部位及びｕｒｅＸの開始コドンを含有しており（ＧＧＡＧＴＡＡＣＡＴＡＴＧＡＡＡＣＴＣＡＣＡＣＣＣＡＡＡＧＡＧＣ）（配列番号１８）、逆向きプライマーは、点突然変異を含有している（ＣＡＣＡＣＣＣＡＣＧＡＣＣＡＴＧＴＧＡＧＧＧＣＴＴＡＣ）（配列番号１９）。第二の３’ＰＣＲ産物は、ｕｒｅＹ遺伝子の３’末からなっていた。この順向きプライマーは、第一ＰＣＲ産物の逆向きプライマーと相補的であり、同一の点突然変異も含有しており（ＧＴＡＡＧＣＣＣＴＣＡＣＡＴＧＧＴＣＧＴＧＧＧＴＧＴＧ）（配列番号２０）、逆向きプライマーは、ｕｒｅＹ遺伝子の終止コドンの直下流にＢａｍＨＩ制限部位を含有していた（ＣＧＡＡＴＴＣＧＧＡＴＣＣＴＡＧＡＡＧＡＡＡＧＴＧＴＡＧＣＧＣＴＧＧ）（配列番号２１）。ｕｒｅＹ内の内部ＮｄｅＩ部位を欠失させるための突然変異を、相補的プライマー内に作成し、それは、ＣＡＴＡＴＧ（Ｈｉｓ－Ｍｅｔ）をＣＡＣＡＴＧ（Ｈｉｓ－Ｍｅｔ）に交換した。両ＰＣＲ産物の増幅後、両ＰＣＲ産物を鋳型として使用した、ｕｒｅＸの順向きプライマー及びｕｒｅＹの逆向きプライマーによるオーバーラップ伸長ＰＣＲにより、完全なオペロンを得た。得られたＰＣＲ産物を、ＰＣＲ－ｂｌｕｎｔｌ－ＴＯＰＯ（Ｉｎｖｉｔｒｏｇｅｎ、Ｐ．Ｏ．Ｂｏｘ２３１２，９７０４ＣＨ　Ｇｒｏｎｉｎｇｅｎ，Ｔｈｅ　Ｎｅｔｈｅｒｌａｎｄ）へクローニングし、大腸菌ＴＯＰ１０Ｆ’細胞（Ｉｎｖｉｔｒｏｇｅｎ）へ形質転換した。陽性クローンを単離し、ウレアーゼＸＹ遺伝子をｐＥＴ３ａにＮｄｅＩ－ＢａｍＨＩを用いてサブクローニングした。得られたプラスミドをｐＵｒｅＸＹ－１と命名し、発現株ＨＭＳ１７４（ＤＥ３）／ｐＬｙｓＳ（Ｎｏｖａｇｅｎ）へと形質転換した。

【００６０】以下のようにして、ｐＵｒｅＸＹ－１のｕｒｅＸ遺伝子及びｕｒｅＹ遺伝子をＨＭＳ１７４（ＤＥ３）／ｐＬｙｓＳにおいて発現させた。一夜培養物をＴＢＡｍｐ^{100}Ｃａｍ^{25}で１／１００に希釈し、この培養物を３７℃で２００ｒｐｍで３時間インキュベートした。１ｍＭのＩＰＴＧを添加することにより培養物を誘導し、２００ｒｐｍで３７℃でさらに３時間インキュベートした。誘導を、小規模で１回、大規模で１回、計２回実施した。誘導した試料を、ＳＤＳ－ＰＡＧＥゲルで分析した（図２）。レーン９に明確に見られるように、誘導した場合のＵｒｅＸ及びＵｒｅＹの発現は、２つの構造サブユニットを、ＵｒｅＸサブユニットについては２５ｋＤａ、ＵｒｅＹサブユニットについては６２ｋＤａの分子量を有するポリペプチド・バンドとして提供する。

【００６１】

【配列表】

【００６２】

【化１】

SEQUENCE LISTING

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ttacttatat taaaaagtta ataaaaagta acgaaattag gactataatc ccattgcctt 180

taaaatttaa cacaaggagt aatag gtg aaa ctc aca ccc aaa gag caa gaa 232
Val Lys Leu Thr Pro Lys Glu Gln Glu
1 5

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aag ttc ttg tta tat tat gcg ggc gaa gtg gct aga aag cgc aaa gca   280
Lys Phe Leu Leu Tyr Tyr Ala Gly Glu Val Ala Arg Lys Arg Lys Ala
 10                  15                  20                  25

gag ggc tta aag ctc aac caa ccc gaa gcc att gct tac att agt gcc   328
Glu Gly Leu Lys Leu Asn Gln Pro Glu Ala Ile Ala Tyr Ile Ser Ala
                 30                  35                  40

cat att atg gac gaa gcg cgc cgt gga aaa aaa acc gtt gcc cag ctt   376
His Ile Met Asp Glu Ala Arg Arg Gly Lys Lys Thr Val Ala Gln Leu
             45                  50                  55

atg gaa gag tgc atg cac ttt ttg aaa aaa gat gaa gta atg ccc ggg   424
Met Glu Glu Cys Met His Phe Leu Lys Lys Asp Glu Val Met Pro Gly
         60                  65                  70

gtg ggt aat atg gtt ccc gat cta ggt gta gaa gcc acc ttt cct gat   472
Val Gly Asn Met Val Pro Asp Leu Gly Val Glu Ala Thr Phe Pro Asp
     75                  80                  85

ggt acg aaa ctt gta act gtg aat tgg ccc atc gaa cca gat gag cac   520
Gly Thr Lys Leu Val Thr Val Asn Trp Pro Ile Glu Pro Asp Glu His
 90                  95                 100                 105

ttc aaa gcg ggc gaa gtg aaa ttt ggt tgc gat aaa gac atc gag ctc   568
Phe Lys Ala Gly Glu Val Lys Phe Gly Cys Asp Lys Asp Ile Glu Leu
                110                 115                 120

aat gca ggc aaa gaa gta acc gaa ctt gag gtt act aat gaa ggg cct   616
Asn Ala Gly Lys Glu Val Thr Glu Leu Glu Val Thr Asn Glu Gly Pro
            125                 130                 135

aaa tcc ttg cat gtg ggt agc cat ttc cac ttc ttt gaa gct aac aag   664
Lys Ser Leu His Val Gly Ser His Phe His Phe Phe Glu Ala Asn Lys
        140                 145                 150

gca cta aaa ttc gat cgt gaa aaa gcc tat ggc aaa cgc cta gat att   712
```

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Ala Leu Lys Phe Asp Arg Glu Lys Ala Tyr Gly Lys Arg Leu Asp Ile
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ccc tct ggc aac acg cta cgc att ggg gca gga caa acc cgc aaa gtg   760
Pro Ser Gly Asn Thr Leu Arg Ile Gly Ala Gly Gln Thr Arg Lys Val
170                 175                 180                 185

cag ttg att cct ctt ggt ggc agt aaa aaa gtg att ggc atg aac ggg   808
Gln Leu Ile Pro Leu Gly Gly Ser Lys Lys Val Ile Gly Met Asn Gly
                190                 195                 200

ctt gtg aat aac atc gcg gat gaa cgc cat aaa cat aaa gcg ctt gac   856
Leu Val Asn Asn Ile Ala Asp Glu Arg His Lys His Lys Ala Leu Asp
            205                 210                 215

aag gcg aaa tct cac gga ttt atc aag taa ggagactccc atg aaa atg    905
Lys Ala Lys Ser His Gly Phe Ile Lys                 Met Lys Met
        220                 225                         230

aaa aaa caa gaa tat gta aat acc tac gga ccc acc aaa ggc gat aaa   953
Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly Pro Thr Lys Gly Asp Lys
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gtg cgc tta gga gat acc gat ctt tgg gca gaa gta gaa cat gac tat   1001
Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu His Asp Tyr
            250                 255                 260

acc acc tat ggc gaa gaa ctt aaa ttt ggc gcg ggt aaa act atc cgt   1049
Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys Thr Ile Arg
        265                 270                 275

gag ggt atg ggt cag agc aat agc cct gat gaa aac acc cta gat tta   1097
Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr Leu Asp Leu
    280                 285                 290

gtc atc act aac gcg atg att atc gac tac acc ggg att tac aaa gcc   1145
Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile Tyr Lys Ala
295                 300                 305                 310
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gac att ggg att aaa aac ggc aaa atc cat ggc att ggc aag gca gga   1193
Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly Lys Ala Gly
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aac aag gac atg caa gat ggc gta agc cct cat atg gtc gtg ggt gtg   1241
Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val Val Gly Val
            330                 335                 340

ggc aca gaa gca cta gca ggg gaa ggt atg att att acc gct ggg gga   1289
Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr Ala Gly Gly
        345                 350                 355

atc gat tca cac acc cac ttc ctt tct cca caa caa ttc cct acc gct   1337
Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe Pro Thr Ala
    360                 365                 370

cta gcc aat ggc gtt aca acc atg ttt gga ggc ggc aca ggt cct gta   1385
Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr Gly Pro Val
375                 380                 385                 390

gat ggc acg aat gcg act act atc act ccg ggc aaa tgg aac ttg cac   1433
Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp Asn Leu His
                395                 400                 405

cgc atg ttg cgc gca gca gaa gag tat tct atg aat gtg ggc ttt ttg   1481
Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val Gly Phe Leu
            410                 415                 420

ggc aaa ggc aat agc tct agc aaa aaa caa ctt gta gaa caa gta gaa   1529
Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu Gln Val Glu
        425                 430                 435

gcg ggc gcg att ggt ttt aaa ttg cat gaa gac tgg ggc aca aca cca   1577
Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly Thr Thr Pro
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agt gcg atc gat cac tgc ttg agc gtg gca gat gaa tac gat gtg caa   1625
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```
Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr Asp Val Gln
455                 460                 465                 470

gtt tgt atc cac acc gat aca gtc aat gag gca ggt tat gta gat gac  1673
Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr Val Asp Asp
                475                 480                 485

acc cta aat gca atg aac ggg cgc gcc atc cat gcc tac cac att gag  1721
Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr His Ile Glu
            490                 495                 500

gga gcg ggt gga gga cac tca cct gat gtt atc acc atg gca ggc gag  1769
Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met Ala Gly Glu
        505                 510                 515

ctc aat att cta ccc tcc tcc acc acc ccc act att ccc tat acc att  1817
Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro Tyr Thr Ile
    520                 525                 530

aat acg gtt gca gaa cac tta gac atg ctc atg aca tgc cac cac cta  1865
Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys His His Leu
535                 540                 545                 550

gac aaa cgc atc cgc gag gat tta caa ttt tct caa agc cgt atc cgc  1913
Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser Arg Ile Arg
                555                 560                 565

ccc ggc tct atc gcg gct gaa gat gtg ctc cat gat atg ggt gtg atc  1961
Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Met Gly Val Ile
            570                 575                 580

gcg atg aca agc tcg gat tcg caa gca atg ggg cgt gca ggc gaa gtg  2009
Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala Gly Glu Val
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att cct cga act tgg cag act gcg gat aag aat aaa aaa gaa ttt ggt  2057
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tac atc tcc aaa tac act atc aac ccc gct ttg acc cac ggc gtg agc   2153
Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His Gly Val Ser
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gag tat atc ggc tct gtg gaa gag ggc aag atc gcc gac ttg gtg gtg   2201
Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp Leu Val Val
            650                 655                 660

tgg aat cct gcc ttt ttt ggc gta aaa ccc aaa atc gtg atc aaa ggc   2249
Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val Ile Lys Gly
        665                 670                 675

ggt atg gtg gtc ttc tct gaa atg ggc gat tct aac gcg tct gtg ccc   2297
Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala Ser Val Pro
    680                 685                 690

act ccc caa ccg gtt tat tac cgc gaa atg ttt ggg cat cac ggc aag   2345
Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His His Gly Lys
695                 700                 705                 710

gcg aaa ttt gac acc agc atc act ttt gtt tcc aaa gtc gcc tat gaa   2393
Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val Ala Tyr Glu
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aat ggc gtg aaa gaa aag ctg ggc tta gag cgc caa gtt cta ccg gtc   2441
Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Gln Val Leu Pro Val
            730                 735                 740

aaa aac tgc cgt aac atc acc aag aaa gac ttc aag ttc aac gac aaa   2489
Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe Asn Asp Lys
        745                 750                 755

acg gca aaa atc acc gtc gat ccg aaa acc ttc gag gtc ttt gta gat   2537
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Thr Ala Lys Ile Thr Val Asp Pro Lys Thr Phe Glu Val Phe Val Asp
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ggc aaa ctc tgc acc tct aaa ccc acc tcg caa gtg cct cta gcc cag 2585
Gly Lys Leu Cys Thr Ser Lys Pro Thr Ser Gln Val Pro Leu Ala Gln
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cgc tac act ttc ttc tag gcacaatgcc ccctttgggg gcaggttatt 2633
Arg Tyr Thr Phe Phe
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Arg Gly Lys Lys Thr Val Ala Gln Leu Met Glu Glu Cys Met His Phe

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Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
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Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
85 90 95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
100 105 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
115 120 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
130 135 140

His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu
145 150 155 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
165 170 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
180 185 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
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Ile Lys
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            20                  25                  30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
        35                  40                  45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
    50                  55                  60

Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
65                  70                  75                  80

Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
                85                  90                  95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
            100                 105                 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
        115                 120                 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
    130                 135                 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
145                 150                 155                 160

Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
                165                 170                 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
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Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
225 230 235 240

Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
245 250 255

Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
260 265 270

His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
275 280 285

Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
290 295 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
305 310 315 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
325 330 335

Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Met
340 345 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
355 360 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
370 375 380

Glu Phe Gly Lys Leu Pro Glu Asp Gly Lys Asp Asn Asp Asn Phe Arg
385 390 395 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
405 410 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
420 425 430

Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
435 440 445

Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
450 455 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
465 470 475 480

His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val
485 490 495

Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Gln Val
500 505 510

Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe
515 520 525

Asn Asp Lys Thr Ala Lys Ile Thr Val Asp Pro Lys Thr Phe Glu Val
530 535 540

Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Thr Ser Gln Val Pro
545 550 555 560

Leu Ala Gln Arg Tyr Thr Phe Phe
565

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Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
  1               5                  10                  15

ggc gaa gtg gct aga aag cgc aaa gca gag ggc tta aag ctc aat caa   96
Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
             20                  25                  30

ccc gaa gcc att gcc tac att agt gcc cat att atg gac gag gcg cgc   144
Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
         35                  40                  45

cgt ggc aaa aaa acc gtt gct gaa ctt atg gaa gaa tgt atg cac ttt   192
Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
     50                  55                  60

ttg aaa aaa gat gag gtg atg ccc ggt gtg ggg aat atg gtc cct gat   240
Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65                  70                  75                  80

ttg ggc gta gaa gcc act ttc ccc gat ggc acc aaa ctc gta acc gtg   288
Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
                 85                  90                  95
```

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aat tgg ccc att gaa cct gat gaa cac ttt aaa gcc ggt gaa gtg aaa   336
Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
            100                 105                 110

ttt ggc tgt gat aaa gac att gag ctc aac gcg ggt aag gaa gtt acc   384
Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
        115                 120                 125

gag ctt gaa gtt acc aac gaa gga cct aaa tcc ttg cat gtg ggt agc   432
Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
    130                 135                 140

cat ttc cac ttc ttt gaa acc aac aag gca ttg aaa ttc gat cgg gaa   480
His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg Glu
145                 150                 155                 160

aaa gcc tat ggc aaa cgc cta gat att ccc tct ggc aac acg cta cgc   528
Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
                165                 170                 175

att ggg gca gga caa acc cgt aaa gtg cag tta atc cct ctt ggc ggt   576
Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
            180                 185                 190

agt aaa aaa gtg att ggc atg aac ggg ctt gtg aat aat att gcg gac   624
Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
        195                 200                 205

gaa cgc cat aaa cac aaa gca cta gac aag gca aaa tct cac gga ttc   672
Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
    210                 215                 220

atc aag taa ggagactccc atg aaa atg aaa aaa caa gag tat gta aac   721
Ile Lys                 Met Lys Met Lys Lys Gln Glu Tyr Val Asn
225                             230                 235

acc tac gga ccc acc aca ggc gat aaa gtg cgc tta gga gat acc gat   769
Thr Tyr Gly Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr Asp
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        240                 245                 250

ctt tgg gca gaa gta gaa cat gac tat acc act tat ggc gaa gag ctc   817
Leu Trp Ala Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu
    255                 260                 265

aaa ttt ggc gcg ggt aaa act atc cgt gag ggt atg ggt cag agc aat   865
Lys Phe Gly Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser Asn
270                 275                 280                 285

agc cca gat gaa aac acc tta gat tta gtg atc acc aac gcg atg att   913
Ser Pro Asp Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met Ile
                290                 295                 300

atc gac tac acc ggg att tat aaa gcc gac att ggt att aaa aat ggc   961
Ile Asp Tyr Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly
            305                 310                 315

aaa atc cat ggt att ggc aag gcg ggg aac aaa gac atg caa gat ggc  1009
Lys Ile His Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp Gly
        320                 325                 330

gta agc cct cat atg gtc gtg ggt gtg ggc aca gaa gca cta gca ggg  1057
Val Ser Pro His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala Gly
    335                 340                 345

gaa ggt atg att att acc gct ggg ggg atc gat tcg cac acc cac ttc  1105
Glu Gly Met Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His Phe
350                 355                 360                 365

ctc tct ccc caa caa ttc cct acc gct cta gcc aat ggt gtt aca acc  1153
Leu Ser Pro Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr Thr
                370                 375                 380

atg ttt gga ggt ggc aca ggt ccg gta gat ggc acg aat gcg acc acc  1201
Met Phe Gly Gly Gly Thr Gly Pro Val Asp Gly Thr Asn Ala Thr Thr
            385                 390                 395
```

```
atc act ccg ggc aaa tgg aac ttg cac cgc atg ttg cgc gca gct gaa   1249
Ile Thr Pro Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala Glu
        400                 405                 410

gag tat tct atg aat gtg ggc ttt ttg ggc aaa ggc aat agc tcc agt   1297
Glu Tyr Ser Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser
    415                 420                 425

aaa aaa caa ctc gta gaa caa gta gaa gcg ggc gcg att ggc ttt aaa   1345
Lys Lys Gln Leu Val Glu Gln Val Glu Ala Gly Ala Ile Gly Phe Lys
430                 435                 440                 445

ttg cat gaa gac tgg ggc aca aca cca agt gcg atc gat cac tgc ttg   1393
Leu His Glu Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys Leu
                450                 455                 460

agc gta gca gat gaa tac gat gtg caa gtt tgt atc cac acc gat acg   1441
Ser Val Ala Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp Thr
            465                 470                 475

gtc aat gag gca ggt tat gta gat gac acc cta aat gcg atg aac ggg   1489
Val Asn Glu Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn Gly
        480                 485                 490

cgc gcc atc cat gcc tac cac att gag gga gcg ggc gga gga cac tca   1537
Arg Ala Ile His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His Ser
    495                 500                 505

cct gat gtt atc acc atg gca ggc gag ctc aat att cta ccc tcc tcc   1585
Pro Asp Val Ile Thr Met Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser
510                 515                 520                 525

acc acc ccc act att ccc tat acc att aat acg gtt gca gaa cac tta   1633
Thr Thr Pro Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His Leu
                530                 535                 540

gac atg ctc atg acc tgc cac cac cta gac aaa cgc atc cgc gag gat   1681
Asp Met Leu Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu Asp
```

545 550 555

ctc cag ttt tcc caa agc cgt atc cgc ccc ggc tct att gcc gct gaa 1729
Leu Gln Phe Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu
560 565 570

gat gtg ctc cat gat att ggc gtg atc gcg atg aca agc tcg gat tcg 1777
Asp Val Leu His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp Ser
575 580 585

caa gca atg ggg cgc gct ggg gaa gtg att cct aga act tgg caa act 1825
Gln Ala Met Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln Thr
590 595 600 605

gca gac aag aat aaa aaa gaa ttt ggt aag ctt cct gaa gat ggt gca 1873
Ala Asp Lys Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala
610 615 620

gat aat gac aac ttc cgc atc aaa cgc tat atc tcc aaa tac acc att 1921
Asp Asn Asp Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile
625 630 635

aat ccc gct ttg acc cat ggc gtg agc gag tat atc ggc tct gtg gaa 1969
Asn Pro Ala Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val Glu
640 645 650

gag ggc aag atc gcc gac ttg gtg gtg tgg aat cct gct ttc ttt ggt 2017
Glu Gly Lys Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe Gly
655 660 665

gta aaa ccc aaa atc gtg atc aaa ggc ggt atg gtg gtg ttc tct gaa 2065
Val Lys Pro Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser Glu
670 675 680 685

atg ggc gat tct aac gcg tct gtg ccc aca cct cag ccg gtt tat tac 2113
Met Gly Asp Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr
690 695 700

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cgc gaa atg ttt ggg cat cac ggc aag gcg aaa ttt gac acc agc atc   2161
Arg Glu Met Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser Ile
            705                 710                 715

act ttt gtt tcc aaa gtc gcc tat gaa aat ggc gtg aaa gaa aaa cta   2209
Thr Phe Val Ser Lys Val Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu
        720                 725                 730

ggc tta gag cgc aag gtg cta ccc gtg aaa aac tgc cgc aac atc act   2257
Gly Leu Glu Arg Lys Val Leu Pro Val Lys Asn Cys Arg Asn Ile Thr
    735                 740                 745

aag aaa gac ttc aaa ttc aac aac aag acg gcg cat atc act gtc gat   2305
Lys Lys Asp Phe Lys Phe Asn Asn Lys Thr Ala His Ile Thr Val Asp
750                 755                 760                 765

cct aaa acc ttc gag gtc ttt gta gat ggc aaa ctc tgc acc tct aaa   2353
Pro Lys Thr Phe Glu Val Phe Val Asp Gly Lys Leu Cys Thr Ser Lys
                770                 775                 780

ccc gcc tct gaa gtg cct cta gcc caa cgc tac act ttc ttc tag       2398
Pro Ala Ser Glu Val Pro Leu Ala Gln Arg Tyr Thr Phe Phe
            785                 790                 795

gcacaat                                                          2405
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Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
  1               5                  10                  15

Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
             20                  25                  30
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Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
35 40 45

Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
50 55 60

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
65 70 75 80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
85 90 95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
100 105 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
115 120 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
130 135 140

His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg Glu
145 150 155 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
165 170 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
180 185 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
195 200 205

Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
210 215 220

Ile Lys

225

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<213> Helicobacter felis

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Met Lys Met Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly Pro Thr Thr
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Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu
             20                  25                  30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
         35                  40                  45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
     50                  55                  60

Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
 65                  70                  75                  80

Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
                 85                  90                  95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
            100                 105                 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
        115                 120                 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
    130                 135                 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
145                 150                 155                 160
```

```
Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
                165                 170                 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
            180                 185                 190

Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
        195                 200                 205

Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
    210                 215                 220

Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
225                 230                 235                 240

Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
                245                 250                 255

Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
            260                 265                 270

His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
        275                 280                 285

Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
    290                 295                 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
305                 310                 315                 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
                325                 330                 335

Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile
            340                 345                 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
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355 360 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
370 375 380

Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp Asn Phe Arg
385 390 395 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
405 410 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
420 425 430

Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
435 440 445

Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
450 455 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
465 470 475 480

His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val
485 490 495

Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Lys Val
500 505 510

Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe
515 520 525

Asn Asn Lys Thr Ala His Ile Thr Val Asp Pro Lys Thr Phe Glu Val
530 535 540

Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Ala Ser Glu Val Pro
545 550 555 560

Leu Ala Gln Arg Tyr Thr Phe Phe
565

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Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr
1 5 10 15

gcg ggc gaa gtg gct aga aag cgc aaa gca gag ggc tta aag ctc aat 95
Ala Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn
20 25 30

caa ccc gaa gcc att gcc tac att agt gcc cat att atg gac gag gcg 143
Gln Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala
35 40 45

cgc cgt ggc aaa aaa acc gtt gct gaa ctt atg gaa gaa tgt atg cac 191
Arg Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His
50 55 60

ttt ttg aaa aaa gat gag gtg atg ccc ggt gtg ggg aat atg gtc cct 239
Phe Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro
65 70 75

```
gat ttg ggc gta gaa gcc act ttc ccc gat ggc acc aaa ctc gta acc   287
Asp Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr
 80                  85                  90                  95

gtg aat tgg ccc att gaa cct gat gaa cac ttt aaa gcc ggt gaa gtg   335
Val Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val
                100                 105                 110

aaa ttt ggc tgt gat aaa gac att gag ctc aac gtg ggt aag gaa gtt   383
Lys Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Val Gly Lys Glu Val
            115                 120                 125

acc gag ctt gaa gtt acc aac gaa gga cct aaa tcc ttg cat gtg ggt   431
Thr Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly
        130                 135                 140

agc cat ttc cac ttc ttt gaa acc aac aag gca ttg aaa ttc gat cgg   479
Ser His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg
    145                 150                 155

gaa aaa gcc tat ggc aaa cgc cta gat att ccc tct ggc aac acg cta   527
Glu Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu
160                 165                 170                 175

cgc att ggg gca gga caa acc cgt aaa gtg cag tta atc cct ctt ggc   575
Arg Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly
                180                 185                 190

ggt agt aaa aaa gtg att ggc atg aac ggg ctt gtg aat aat att gcg   623
Gly Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala
            195                 200                 205

gac gaa cgc cat aaa cac aaa gca cta gac aag gca aaa tct cac gga   671
Asp Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly
        210                 215                 220

ttc atc aag taa ggagactccc atg aaa atg aaa aaa caa gag tat gta   720
```

```
Phe Ile Lys                 Met Lys Met Lys Lys Gln Glu Tyr Val
    225                             230                 235

aac acc tac gga ccc acc aca ggc gat aaa gtg cgc tta gga gat acc   768
Asn Thr Tyr Gly Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr
            240                 245                 250

gat ctt tgg gca gaa gta gaa cat gac tat acc act tat ggc gaa gag   816
Asp Leu Trp Ala Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu
        255                 260                 265

ctc aaa ttt ggc gcg ggt aaa act atc cgt gag ggt atg ggt cag agc   864
Leu Lys Phe Gly Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser
    270                 275                 280

aat agc cca gat gaa aac acc tta gat tta gtg atc acc aac gcg atg   912
Asn Ser Pro Asp Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met
285                 290                 295                 300

att atc gac tac acc ggg att tat aaa gcc gac att ggt att aaa aat   960
Ile Ile Asp Tyr Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn
                305                 310                 315

ggc aaa atc cat ggt att ggc aag gcg ggg aac aaa gac atg caa gat  1008
Gly Lys Ile His Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp
            320                 325                 330

ggc gta agc cct cat atg gtc gtg ggt gtg ggc aca gaa gca cta gca  1056
Gly Val Ser Pro His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala
        335                 340                 345

ggg gaa ggt atg att att acc gct ggg ggg atc gat tcg cac acc cac  1104
Gly Glu Gly Met Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His
    350                 355                 360

ttc ctc tct ccc caa caa ttc cct acc gct cta gcc aat ggt gtt aca  1152
Phe Leu Ser Pro Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr
365                 370                 375                 380
```

```
acc atg ttt gga ggt ggc aca ggt ccg gta gat ggc acg aat gcg acc   1200
Thr Met Phe Gly Gly Gly Thr Gly Pro Val Asp Gly Thr Asn Ala Thr
                385                 390                 395

acc atc act ccg ggc aaa tgg aac ttg cac cgc atg ttg cgc gca gct   1248
Thr Ile Thr Pro Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala
            400                 405                 410

gaa gag tat tct atg aat gta ggc ttt ttg ggc aaa ggc aat agt tct   1296
Glu Glu Tyr Ser Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser
        415                 420                 425

agc aaa aaa caa ctt gta gaa caa gta gaa gcg ggc gcg att ggc ttt   1344
Ser Lys Lys Gln Leu Val Glu Gln Val Glu Ala Gly Ala Ile Gly Phe
    430                 435                 440

aaa ttg cat gaa gac tgg ggc aca aca cca agt gcg atc gat cac tgc   1392
Lys Leu His Glu Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys
445                 450                 455                 460

ttg agc gtg gca gat gaa tac gat gtg caa gtt tgt atc cac acc gat   1440
Leu Ser Val Ala Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp
                465                 470                 475

acg gtc aat gag gca ggt tat gtg gat gac acc cta aat gca atg aac   1488
Thr Val Asn Glu Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn
            480                 485                 490

ggg cgc gcc atc cat gcc tac cac att gag gga gcg ggc gga gga cac   1536
Gly Arg Ala Ile His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His
        495                 500                 505

tca cct gat gtt atc acc atg gca ggc gag ctc aat att cta ccc tcc   1584
Ser Pro Asp Val Ile Thr Met Ala Gly Glu Leu Asn Ile Leu Pro Ser
    510                 515                 520

tcc acc acc ccc act att ccc tat acc att aat acg gtt gca gaa cac   1632
```

```
Ser Thr Thr Pro Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His
525                 530                 535                 540

tta gac atg ctc atg acc tgc cac cac cta gat aag cgc atc cgc gag   1680
Leu Asp Met Leu Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu
                545                 550                 555

gat tta caa ttt tct caa agc cgt atc cgc ccc gga tct att gcc gct   1728
Asp Leu Gln Phe Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala
            560                 565                 570

gag gat gtg ctc cat gat att ggc gtg atc gcg atg act agc tcc gat   1776
Glu Asp Val Leu His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp
        575                 580                 585

tcg caa gca atg ggg cgc gct ggg gaa gtg att cct aga act tgg caa   1824
Ser Gln Ala Met Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln
    590                 595                 600

act gca gat aag aat aaa aaa gaa ttt ggt aag ctt cct gaa gat ggt   1872
Thr Ala Asp Lys Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Gly
605                 610                 615                 620

gca gat aac gac aac ttc cgc atc aaa cgc tat atc tcc aaa tac acc   1920
Ala Asp Asn Asp Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr
                625                 630                 635

att aat ccc gct ttg acc cat ggc gtg agc gag tat atc ggc tct gtg   1968
Ile Asn Pro Ala Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val
            640                 645                 650

gaa gag ggc aag atc gcc gac ttg gtg gtg tgg aat cct gcc ttt ttt   2016
Glu Glu Gly Lys Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe
        655                 660                 665

ggc gtg aaa cct aag att gtg att aaa ggt ggc atg gtg gtc ttc tct   2064
Gly Val Lys Pro Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser
    670                 675                 680
```

```
gaa atg ggc gat tct aac gcg tcc gtg ccc acg cct cag ccg gtt tat   2112
Glu Met Gly Asp Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr
685                 690                 695                 700

tac cgc gaa atg ttt ggg cac cac ggc aag gcg aaa ttt gac acc agc   2160
Tyr Arg Glu Met Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser
                705                 710                 715

atc act ttt cgt gtc tca agc gg                                    2183
Ile Thr Phe Arg Val Ser Ser
            720
```

<210> 8
<211> 226
<212> PRT
<213> Helicobacter felis

<400> 8

```
Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
  1               5                  10                  15

Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
             20                  25                  30

Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
         35                  40                  45

Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
     50                  55                  60

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65                  70                  75                  80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
                 85                  90                  95
```

```
Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
            100                 105                 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Val Gly Lys Glu Val Thr
        115                 120                 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
    130                 135                 140

His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg Glu
145                 150                 155                 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
                165                 170                 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
            180                 185                 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
        195                 200                 205

Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
    210                 215                 220

Ile Lys
225
```

<210> 9
<211> 496
<212> PRT
<213> Helicobacter felis

<400> 9

```
Met Lys Met Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly Pro Thr Thr
  1               5                  10                  15

Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu
```

20 25 30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
35 40 45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
50 55 60

Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
65 70 75 80

Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
85 90 95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
100 105 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
115 120 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
130 135 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
145 150 155 160

Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
165 170 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
180 185 190

Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
195 200 205

Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
210 215 220

```
Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
225                 230                 235                 240

Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
                245                 250                 255

Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
            260                 265                 270

His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
        275                 280                 285

Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
    290                 295                 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
305                 310                 315                 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
                325                 330                 335

Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile
            340                 345                 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
        355                 360                 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
    370                 375                 380

Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp Asn Phe Arg
385                 390                 395                 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
                405                 410                 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
            420                 425                 430
```

```
Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
        435                 440                 445

Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
    450                 455                 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
465                 470                 475                 480

His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Arg Val Ser Ser
                485                 490                 495
```

<210> 10
<211> 2407
<212> DNA
<213> Helicobacter felis

<220>
<221> CDS
<222> (2)..(682)

<220>
<221> CDS
<222> (693)..(2399)

<400> 10

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c gtg aaa ctc aca ccc aaa gag caa gaa aag ttc ttg tta tat tat gcg 49
  Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
    1               5                  10                  15

ggc gaa gtg gct aga aag cgc aaa gcg gag ggc tta aag ctc aac caa   97
Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
            20                  25                  30

ccc gaa gcc att gcc tac att agt gcc cat att atg gac gag gcg cgc   145
```

```
Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
         35                  40                  45

cgt ggc aaa aag acc gtt gcg gaa ctt atg gaa gag tgt atg cac ttt   193
Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
     50                  55                  60

ttg aaa aaa gac gag gtg atg ccc ggt gtg ggg aat atg gtc cct gat   241
Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65                  70                  75                  80

tta ggc gtg gaa gct act ttt ccc gat ggc acc aaa ctc gta acc gtg   289
Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
                85                  90                  95

aat tgg ccc atc gaa ccc gat gaa cac ttc aaa gcg ggc gaa gtc aaa   337
Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
            100                 105                 110

ttt ggc tgt gat aaa gac att gaa ctc aac gca ggt aag gaa gtt acc   385
Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
        115                 120                 125

gaa cta gaa gtt acc aac gaa gga cct aaa tcc ttg cat gtg ggt agc   433
Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
    130                 135                 140

cat ttc cac ttc ttt gaa gcc aac aag gca ttg aaa ttc gat cgg gaa   481
His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu
145                 150                 155                 160

aaa gcc tat ggc aaa cgc cta gat att ccc tct ggc aac acg cta cgc   529
Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
                165                 170                 175

att ggg gca gga caa acc cgt aaa gtg cag tta atc cct ctt ggc ggc   577
Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
            180                 185                 190
```

```
agt aaa aaa gtg att ggc atg aac ggg ctt gtg aat aat att gca gat   625
Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
        195                 200                 205

gaa cgc cat aaa cac aaa gcg tta gaa aaa gca aaa tct cac gga ttt   673
Glu Arg His Lys His Lys Ala Leu Glu Lys Ala Lys Ser His Gly Phe
    210                 215                 220

atc aaa taa ggagactccc atg aaa atg aaa aaa caa gag tat gta aat    722
Ile Lys                 Met Lys Met Lys Lys Gln Glu Tyr Val Asn
225                             230                 235

acc tac gga cct acc aca ggc gac aaa gtg cgc tta gga gat acc gat   770
Thr Tyr Gly Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr Asp
        240                 245                 250

ctt tgg gca gaa gta gaa cat gac tat acc act tat ggc gaa gag ctc   818
Leu Trp Ala Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu
    255                 260                 265

aaa ttt ggc gcg ggt aaa act atc cgt gag ggc atg ggt cag agc aat   866
Lys Phe Gly Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser Asn
270                 275                 280                 285

agt cca gat gaa aac acc cta gat tta gtc atc acc aac gcg atg att   914
Ser Pro Asp Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met Ile
                290                 295                 300

att gac tac acc ggg att tac aaa gcc gac att ggc att aaa aat ggc   962
Ile Asp Tyr Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly
            305                 310                 315

aaa atc cat ggc att ggc aag gca gga aac aag gac atg caa gat ggc   1010
Lys Ile His Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp Gly
        320                 325                 330

gta agc cct cat atg gtc gtg ggt gtg ggc aca gaa gca tta gca ggg   1058
```

```
Val Ser Pro His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala Gly
    335                 340                 345

gaa ggt atg att att acc gct ggg ggg atc gat tca cac acc cac ttc   1106
Glu Gly Met Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His Phe
350                 355                 360                 365

ctc tct cca caa caa ttc cct acc gct cta gcc aat ggc gtt aca acc   1154
Leu Ser Pro Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr Thr
                370                 375                 380

atg ttt ggc ggt ggc aca ggt ccg gta gat ggc acg aat gcg act acc   1202
Met Phe Gly Gly Gly Thr Gly Pro Val Asp Gly Thr Asn Ala Thr Thr
            385                 390                 395

atc act ccg ggc aaa tgg aac ttg cac cgc atg ttg cgc gca gct gaa   1250
Ile Thr Pro Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala Glu
        400                 405                 410

gag tat tct atg aat gtg ggc ttt ttg ggc aaa ggc aat agc tcc agt   1298
Glu Tyr Ser Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser
    415                 420                 425

aaa aaa caa ctt gta gaa caa ata gaa gcg ggc gcg atc ggc ttt aaa   1346
Lys Lys Gln Leu Val Glu Gln Ile Glu Ala Gly Ala Ile Gly Phe Lys
430                 435                 440                 445

ttg cat gaa gac tgg ggc aca act cca agt gca atc gat cac tgc ttg   1394
Leu His Glu Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys Leu
                450                 455                 460

agc gta gca gat gaa tac gat gtg caa gtt tgt atc cac acc gat acg   1442
Ser Val Ala Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp Thr
            465                 470                 475

gtc aat gag gca ggt tat gta gat gac acc ctg aat gcg atg aac ggg   1490
Val Asn Glu Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn Gly
        480                 485                 490
```

```
cgc gcc atc cat gcc tac cac att gag gga gcg ggc gga gga cac tca   1538
Arg Ala Ile His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His Ser
    495                 500                 505

cct gat gtt atc acc atg gca ggc gag ctc aat att cta ccc tcc tcc   1586
Pro Asp Val Ile Thr Met Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser
510                 515                 520                 525

aca acc ccc act atc ccc tat acc att aat acg gtt gca gaa cac tta   1634
Thr Thr Pro Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His Leu
                530                 535                 540

gac atg ctc atg acc tgc cac cac cta gat aaa cgc atc cgc gag gat   1682
Asp Met Leu Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu Asp
            545                 550                 555

tta caa ttt tcc caa agc cgt atc cgc ccc ggc tct atc gcc gct gaa   1730
Leu Gln Phe Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu
        560                 565                 570

gat gtg ctc cat gat att ggc gtg atc gcg atg aca agc tcg gat tcg   1778
Asp Val Leu His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp Ser
    575                 580                 585

caa gca atg ggg cgc gct ggc gaa gtg att cct cga act tgg cag act   1826
Gln Ala Met Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln Thr
590                 595                 600                 605

gcg gat aag aat aaa aaa gaa ttt ggt aag ctt cct gaa gat agt gca   1874
Ala Asp Lys Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Ser Ala
                610                 615                 620

gat aac gac aac ttc cgt atc aaa cgc tac atc tcc aaa tac act att   1922
Asp Asn Asp Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile
            625                 630                 635

aac ccc gct cta acc cat ggg gta agc gag tat atc ggc tct gtg gaa   1970
```

```
Asn Pro Ala Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val Glu
        640                 645                 650

gag ggc aaa atc gct gat ttg gtg gtg tgg aat cct gcc ttt ttt ggt   2018
Glu Gly Lys Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe Gly
    655                 660                 665

gtg aaa cct aag att gtg atc aaa ggc ggt atg gtg gtc ttc tct gaa   2066
Val Lys Pro Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser Glu
670                 675                 680                 685

atg ggc gac tcc aac gcg tcc gtg cct aca cct cag ccg gtt tat tac   2114
Met Gly Asp Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr
                690                 695                 700

cgc gaa atg ttt ggg cat cac ggc aag gcg aaa ttt gac acc agc atc   2162
Arg Glu Met Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser Ile
            705                 710                 715

act ttt gtt tcc aaa gtc gcc tat gaa aat ggc gtg aaa gaa aaa cta   2210
Thr Phe Val Ser Lys Val Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu
        720                 725                 730

ggc tta gag cgc aag gtg cta ccc gtg aaa aac tgc cgc aac atc act   2258
Gly Leu Glu Arg Lys Val Leu Pro Val Lys Asn Cys Arg Asn Ile Thr
    735                 740                 745

aag aaa gac ttc aaa ttc aac aac aag acg gcg cat atc act gtc gat   2306
Lys Lys Asp Phe Lys Phe Asn Asn Lys Thr Ala His Ile Thr Val Asp
750                 755                 760                 765

cct aaa acc ttc gag gtc ttt gta gat ggc aaa ctc tgc acc tct aaa   2354
Pro Lys Thr Phe Glu Val Phe Val Asp Gly Lys Leu Cys Thr Ser Lys
                770                 775                 780

ccc gcc tct gaa gtg cct cta gcc cag cgc tac act ttc ttc tag       2399
Pro Ala Ser Glu Val Pro Leu Ala Gln Arg Tyr Thr Phe Phe
            785                 790                 795
```

gcncaatg 2407

<210> 11
<211> 226
<212> PRT
<213> Helicobacter felis

<400> 11

Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
1 5 10 15

Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
20 25 30

Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
35 40 45

Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
50 55 60

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
65 70 75 80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
85 90 95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
100 105 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
115 120 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
130 135 140

His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu

```
145                 150                 155                 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
                165                 170                 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
            180                 185                 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
        195                 200                 205

Glu Arg His Lys His Lys Ala Leu Glu Lys Ala Lys Ser His Gly Phe
    210                 215                 220

Ile Lys
225
```

<210> 12
<211> 568
<212> PRT
<213> Helicobacter felis

<400> 12

```
Met Lys Met Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly Pro Thr Thr
  1               5                  10                  15

Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu
             20                  25                  30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
         35                  40                  45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
     50                  55                  60

Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
 65                  70                  75                  80
```

```
Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
                 85                  90                  95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
            100                 105                 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
        115                 120                 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
    130                 135                 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
145                 150                 155                 160

Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
                165                 170                 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
            180                 185                 190

Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
        195                 200                 205

Gln Ile Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
    210                 215                 220

Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
225                 230                 235                 240

Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
                245                 250                 255

Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
            260                 265                 270

His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
```

275 280 285

Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
290 295 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
305 310 315 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
325 330 335

Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile
340 345 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
355 360 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
370 375 380

Glu Phe Gly Lys Leu Pro Glu Asp Ser Ala Asp Asn Asp Asn Phe Arg
385 390 395 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
405 410 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
420 425 430

Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
435 440 445

Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
450 455 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
465 470 475 480

```
His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val
                485                 490                 495

Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Lys Val
            500                 505                 510

Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe
        515                 520                 525

Asn Asn Lys Thr Ala His Ile Thr Val Asp Pro Lys Thr Phe Glu Val
    530                 535                 540

Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Ala Ser Glu Val Pro
545                 550                 555                 560

Leu Ala Gln Arg Tyr Thr Phe Phe
                565
```

<210> 13
<211> 2452
<212> DNA
<213> Helicobacter felis

<220>
<221> CDS
<222> (48)..(728)

<220>
<221> CDS
<222> (739)..(2445)

<400> 13

```
aggactataa tcccattgcc tttaaaattt aacacaagga gtaatag gtg aaa ctc   56
                                                    Val Lys Leu
                                                      1
```

```
aca ccc aaa gag caa gaa aag ttc ttg tta tat tat gcg ggc gaa gtg   104
Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala Gly Glu Val
      5                  10                  15

gct aga aag cgc aaa gca gag ggc tta aag ctc aac caa ccc gaa gcc   152
Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln Pro Glu Ala
 20                  25                  30                  35

att gcc tac att agt gcc cat att atg gac gag gcg cgt cgt ggc aaa   200
Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg Arg Gly Lys
                 40                  45                  50

aaa acc gtt gcg gaa ctt atg gaa gag tgt atg cac ttt ttg aaa aaa   248
Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe Leu Lys Lys
             55                  60                  65

gac gag gtg atg ccc ggg gtg ggg aat atg gtc cct gat ttg ggc gtg   296
Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp Leu Gly Val
         70                  75                  80

gaa gcc act ttc ccc gat ggc acc aaa ctc gta act gtg aat tgg ccc   344
Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val Asn Trp Pro
     85                  90                  95

atc gaa cct gat gaa cac ttt aag gcg ggt gaa gtg aaa ttt ggc tgt   392
Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys Phe Gly Cys
100                 105                 110                 115

gat aaa gac att gaa ctc aac gca ggt aag gaa gtt acc gaa cta gaa   440
Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr Glu Leu Glu
                120                 125                 130

gtt act aac gaa gga cct aaa tcc ttg cat gtg ggt agc cat ttc cac   488
Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser His Phe His
            135                 140                 145

ttc ttt gaa gcc aac aaa gca ttg aaa ttc gat cgg gaa aaa gcc tat   536
Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu Lys Ala Tyr
```

150 155 160

ggc aaa cgc cta gat att ccc tct ggc aac aca cta cgc att ggg gca 584
Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg Ile Gly Ala
165 170 175

gga caa acc cgt aaa gtg cag tta atc cct ctt ggc ggt agt aaa aaa 632
Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly Ser Lys Lys
180 185 190 195

gtg att ggc atg aac ggg ctt gtg aat aat att gcg gac gaa cgc cat 680
Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp Glu Arg His
200 205 210

aaa cac aaa gcg cta gac aaa gca aaa tct cac gga ttt atc aag taa 728
Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe Ile Lys
215 220 225

ggagactccc atg aaa atg aaa aaa caa gag tat gta aat acc tac gga 777
Met Lys Met Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly
230 235 240

ccc acc aca ggc gat aaa gtg cgc tta gga gat acc gat ctt tgg gca 825
Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala
245 250 255

gaa gta gaa cat gac tat acc acc tat ggc gaa gaa ctc aaa ttc ggt 873
Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly
260 265 270

gca ggt aaa act atc cgt gag ggt atg ggt cag agc aat agc cca gat 921
Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp
275 280 285

gaa aac acc tta gat tta gtg atc acc aac gcg atg att att gac tac 969
Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr
290 295 300

```
acc ggg att tac aaa gcc gac att ggc att aaa aat ggc aaa atc cat   1017
Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His
305                 310                 315                 320

ggc att ggc aag gca gga aac aag gac atg caa gat ggc gta agc cct   1065
Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro
                325                 330                 335

cat atg gtc gtg ggt gtg ggc aca gaa gca cta gca ggg gaa ggt atg   1113
His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met
            340                 345                 350

att att acc gct ggg ggg atc gat tca cac acc cac ttc ctc tct cca   1161
Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro
        355                 360                 365

caa caa ttc cct acc gct cta gcc aat ggc gtt aca aca atg ttt ggc   1209
Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly
    370                 375                 380

ggt ggc aca ggc ccc gta gat ggc acg aat gcg act acc atc act ccg   1257
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Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser
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atg aat gtg ggc ttt ttg ggc aaa ggc aat agc tct agt aaa aaa caa   1353
Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln
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Leu Val Glu Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu
        435                 440                 445

gac tgg ggc aca act cca agt gcg atc gat cac tgc ttg agc gta gca   1449
Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala
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gat gaa tac gat gtg caa gtt tgt ata cac acc gat acg gtc aat gag   1497
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gca ggt tat gta gat gac acc cta aat gca atg aac ggg cgc gcc atc   1545
Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile
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cat gcc tac cac att gag gga gcg ggt gga gga cac tca cct gat gtt   1593
His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val
            500                 505                 510

atc acc atg gca ggc gaa gtg aat att cta ccc tcc tcc aca acc cct   1641
Ile Thr Met Ala Gly Glu Val Asn Ile Leu Pro Ser Ser Thr Thr Pro
        515                 520                 525

act atc ccc tat acc att aat acg gtt gca gaa cac tta gac atg ctt   1689
Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu
    530                 535                 540

atg acc tgc cac cac cta gat aaa cgc atc cgc gag gat ctc caa ttt   1737
Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe
545                 550                 555                 560

tct caa agc cgt atc cgc ccc ggc tct atc gcc gct gaa gat gtg ctc   1785
Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu
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cat gat atc ggt gtg atc gcg atg aca agt tcc gat tcg caa gca atg   1833
His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met
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Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys
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atc gcc gac ttg gtg gtg tgg aat cct gcc ttt ttt ggc gta aaa ccc   2073
Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro
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aaa atc gtg atc aaa ggc ggt atg gtg gtg ttc tct gaa atg ggc gat   2121
Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp
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tct aat gcg tct gtg ccc act cct cag ccg gtt tat tac cgc gaa atg   2169
Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met
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Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val
705                 710                 715                 720

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Ser Lys Val Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu
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cgc aag gtg ctc ccc gtg aaa aac tgc cgt aac atc acc aag aag gac   2313
Arg Lys Val Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp
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Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
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Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
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Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65                  70                  75                  80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
                 85                  90                  95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
            100                 105                 110
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Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
        115                 120                 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
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His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu
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Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
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Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
            180                 185                 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
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Ile Lys
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His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
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Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
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Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
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Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
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Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
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Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
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Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
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His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
        275                 280                 285

Ala Gly Glu Val Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
    290                 295                 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
305                 310                 315                 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
                325                 330                 335

Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile
            340                 345                 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
        355                 360                 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
    370                 375                 380

Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp Asn Phe Arg
385                 390                 395                 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
                405                 410                 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
            420                 425                 430

Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
        435                 440                 445
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Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
450 455 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
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His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val
485 490 495

Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Lys Val
500 505 510

Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe
515 520 525

Asn Asp Lys Thr Ala Lys Ile Thr Val Asp Pro Lys Thr Phe Glu Val
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【図面の簡単な説明】
【図１ａ】図１ａ（１～４）：ヘリコバクター・フェリス種、ＣＳ１、Ｋｕｋｋａ、Ｄｓ４、２３０１及び３９０に由来する、２つのコーディング配列をつなぐ短い非コーディング領域を含むＵｒｅＸ及びＹをコードする核酸配列と、ヘリコバクター・フェリス、ピロリ及びヘイルマンニに由来する、２つのコーディング配列をつなぐ短い非コーディング領域を含むＵｒｅＡ及びＢをコードする核酸配列との比較を示す図である。
【図１ｂ】図１ｂ：ヘリコバクター・フェリス種、ＣＳ

１、Ｋｕｋｋａ、Ｄｓ４、２３０１及び３９０に由来するＵｒｅＸのアミノ酸配列と、ヘリコバクター・フェリス、ピロリ及びヘイルマンニに由来するＵｒｅＡをコードするアミノ酸配列との比較を示す図である。

【図１ｃ】図１ｃ（１～２）：ヘリコバクター・フェリス種、ＣＳ１、Ｋｕｋｋａ、Ｄｓ４、２３０１及び３９０に由来するＵｒｅＹのアミノ酸配列と、ヘリコバクター・フェリス、ピロリ及びヘイルマンニに由来するＵｒｅＢをコードするアミノ酸配列との比較を示す図である。

【図２】発現産物ＵｒｅＸ及びＵｒｅＹのポリアクリルアミドゲルを示す図である。レーン７：バイオラド（Ｂｉｏｒａｄ）広域マーカーレーン８：誘導前の完全細胞培養物（小規模培養物）レーン９：誘導後の完全細胞培養物（小規模培養物）レーン１０：誘導後の完全細胞培養物（大規模培養物）レーン１１：誘導後の上清（大規模培養物）レーン１２：バイオラドプレ染色マーカー

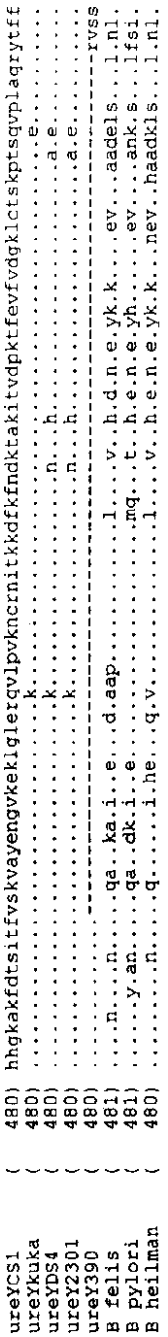

Figure 1c (2)

【図１ａ】

Figure 1a (1)

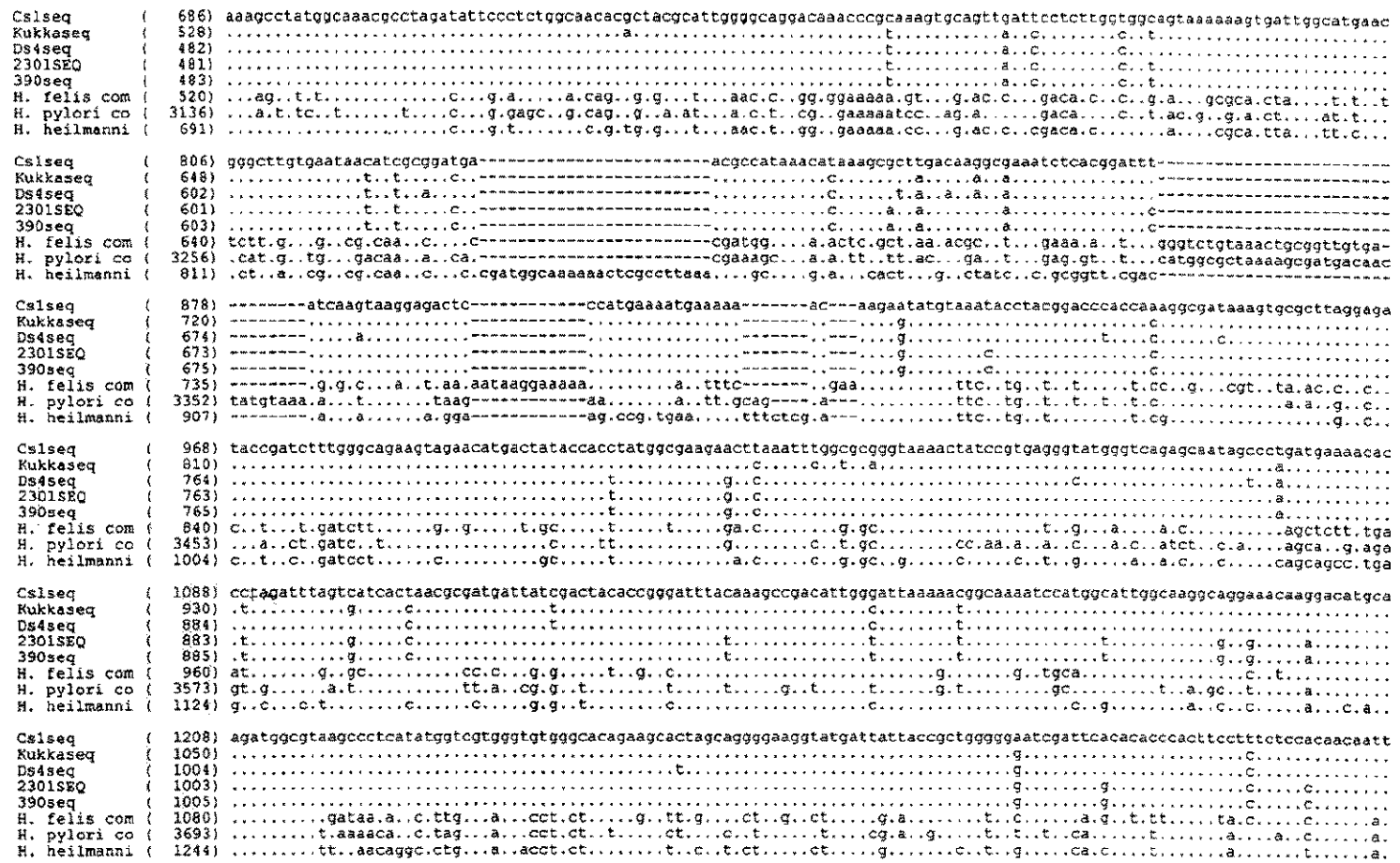

Figure 1a (2)

Figure 1a (3)

Figure 1a (4)

【図１ｂ】

11/15/99 ALIGNED SEQUENCES

Reference molecule:	ureXCS1	1 - 226 (226 aa)	Homology
Sequence 2:	ureXkuka	1 - 226 (226 aa)	100%
Sequence 3:	ureXDS4	1 - 226 (226 aa)	99%
Sequence 4:	ureX2301	1 - 226 (226 aa)	99%
Sequence 5:	ureX390	1 - 226 (226 aa)	99%
Sequence 6:	A felis	1 - 237 (237 aa)	50%
Sequence 7:	A pylori	1 - 238 (238 aa)	52%
Sequence 8:	A heilman	1 - 234 (234 aa)	54%

Alignment type: Global Protein
Parameters: Mismatch 2; Open Gap 4; Extend Gap 1; Conserv N

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ureXkuka     ( 1) ..........................................e.....................................................................
ureXDS4      ( 1) ..........................................e.....................................................................
ureX2301     ( 1) ?.........................................e.....................................................................
ureX390      ( 1) ..........................................e.....................iht.v.dngklap...-.lkne..t
A felis      ( 1) m.....ld.lm.h...rl.eeal.r.v...yc..v.l..grv.ek..d.n.s..d..q.grtw..en..d..as.ihev.i..n.....iht.v.dngklap...-.lkne..t
A pylori     ( 1) m.....ld.lm.h.....l.k...ek.i...yv..v.l.....e...a....a.e...q.grtl..p.d..d..as.ihev.i..m.....ht...angkvp..-.l.lkne..t
A heilman    ( 1) m.....ld.lm.h.....l.kq...k.i...yc..v.l.....v.e...a....s..d..q.grtl..a.d.....ah.ihev.i..g.....iht.v.agsdkl.pgevilkne..t

ureXCS1      ( 121) lnagkevtelevtnegpkslnvgshfhffeankalkfdrekaygkrldipsgntlrigagqtrkvqliplggskkvigmnglvvnniaderhkhkaldkakshgfi----------k
ureXkuka     ( 121) ..........................................a.....tav.fep.eeks.e..di..n.riy.f.s..drq..adg.klg.kr..ek..gsvncgceatkdk-q
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ureX390      ( 121) .v.....t...............v.i.d...a.sfc.....a..tav.fep.eeks.e..di..n.riy.f.s..drq..adg.klg.kr..ek..gsvncgceatkdk-q
A felis      ( 120) i...i.ais.k.k.k.drpvq.....v..i.d...a.sfc.....a..tav.fep.eeks.e..di..n.riy.f.s..drq..adg.klg.kr..ek..gsvncgceatkdk-q
A pylori     ( 120) i.e..kavsvk.k.v.drpvql.....v.rc.d.....tf.....a..tav.fep.eeks.e..di..nrrif.f.a..drq..nes.ki..hr..er..hgaksddnyvktike
A heilman    ( 121) .....havq.k.k.k.drpvq.....v..i.d.....a..tav.fep.eekt.e..di..n.riy.f.a..drq..hdg.kl..kr..ekh.gtincgcdn----.
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Figure 1b

【図１ｃ】

Figure 1c (1)

【図２】

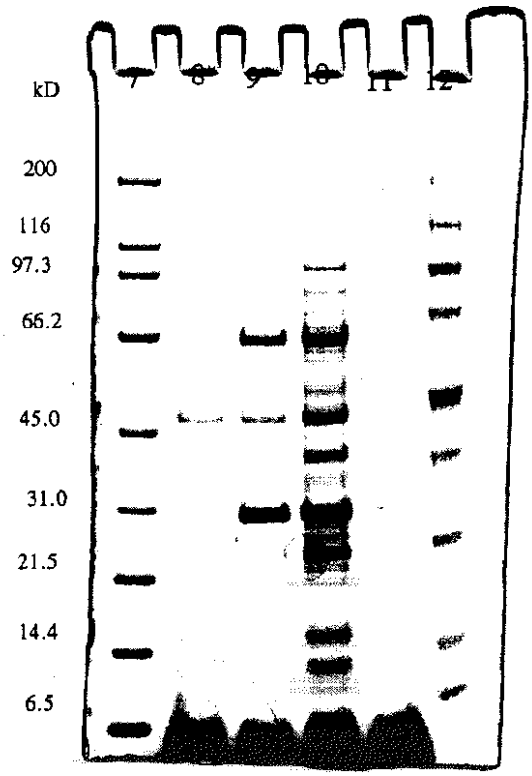

Figure 2

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(51)Int.Cl.[7]	識別記号	FI		ﾃｰﾏｺｰﾄﾞ(参考)
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	39/23		39/39	４Ｃ０８５
	39/235		39/395	D
	39/39	Ａ６１Ｐ	1/04	
	39/395		31/04	
Ａ６１Ｐ	1/04	Ｃ１２Ｎ	1/15	
	31/04		1/19	
Ｃ１２Ｎ	1/15		1/21	
	1/19		9/80	Z
	1/21	Ｃ１２Ｑ	1/68	A
	5/10	Ｇ０１Ｎ	33/15	Z
	9/80		33/50	Z
Ｃ１２Ｑ	1/68		33/53	D
Ｇ０１Ｎ	33/15			M
	33/50		33/566	
	33/53		33/569	B

	33/566	
	33/569	
//(Ｃ１２Ｎ	9/80	
Ｃ１２Ｒ	1:01)	
(Ｃ１２Ｑ	1/68	
Ｃ１２Ｒ	1:01)	
	Ｃ１２Ｒ	1:01
	Ｃ１２Ｎ	15/00　ＺＮＡＡ
		5/00　Ａ
	Ａ６１Ｋ	37/02

Ｆターム(参考)　2G045 AA40 BA11 BB50 DA12 DA13
DA36 FB02
4B024 AA01 AA13 BA14 BA31 CA04
DA02 DA05 DA12 EA04 FA02
GA11 HA12 HA15
4B050 CC03 DD02 LL01 LL03
4B063 QA19 QQ44 QR08 QR42 QR56
QS25 QS34 QX02
4B065 AA01X AA01Y AA26X AA57X
AA72X AA90X AB01 BA02
CA31 CA43 CA46
4C084 AA02 AA07 BA19 CA04 DC50
NA14 ZA68 ZB35
4C085 AA03 AA13 AA38 BA20 BA45
BA51 BA75 BA77 CC07 CC08
DD86 EE01 EE03 EE06

【外国語明細書】

1. Title of Invention

Helicobacter felis vaccine.

2. Claims

1) Nucleic acid sequence encoding two subunit polypeptides of a urease complex such as expressed by *Helicobacter felis*, said nucleic acid sequence having at least 85 % homology with SEQ ID NO: 1, or a part thereof encoding at least an immunogenic fragment of one of said subunits, said part having a length of at least 40, preferably 45, more preferably 50 nucleotides.

2) Nucleic acid sequence according to claim 1, characterised in that it encodes the urease X subunit polypeptide or the urease Y subunit polypeptide.

3) Nucleic acid sequence according to claim 1 or 2, characterised in that the sequence has at least 90 %, preferably 94 %, more preferably 97 % homology with SEQ ID NO: 1.

4) DNA fragment comprising a nucleic acid sequence according to claims 1-3

5) Recombinant DNA molecule comprising a nucleic acid sequence according to claims 1-3 or a DNA fragment according to claim 4, under the control of a functionally linked promoter.

6) Live recombinant carrier comprising a recombinant DNA molecule according to claim 5

7) Host cell comprising a nucleic acid sequence according to claims 1-3, a DNA fragment according to claim 4, a recombinant DNA molecule according to claim 5 or a live recombinant carrier according to claim 6.

8) *Helicobacter felis* urease X subunit polypeptide, said polypeptide having an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 2 or an immunogenic fragment of said polypeptide with a length of at least 40, preferably 45, more preferably 50 amino acids said immunogenic fragment being capable of inducing an immune response against ureaseXY.

9) Polypeptide according to claim 8, having a sequence homology of at least 90 %, preferably 94 %, more preferably 97 % homology to SEQ ID NO: 2, or an immunogenic fragment of said polypeptide capable of inducing an immune response against ureaseXY.

10) *Helicobacter felis* urease Y subunit polypeptide, said polypeptide having an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 3 or an immunogenic fragment of said polypeptide with a length of at least 40, preferably 45, more preferably 50 amino acids said immunogenic fragment being capable of inducing an immune response against ureaseXY.

11) Polypeptide according to claim 10, having a sequence homology of at least 90 %, preferably 94 %, more preferably 97 % homology to SEQ ID NO: 3, or an immunogenic fragment of said polypeptide capable of inducing an immune response

against ureaseXY.

12) Polypeptide according to claims 8-11 for use in a vaccine

13) Use of a polypeptide according to claims 8-11 in the manufacturing of a vaccine for combating *Helicobacter felis* infections.

14) Vaccine for combating *Helicobacter felis* infections, characterised in that it comprises a nucleic acid sequence according to claims 1-3, a DNA fragment according to claim 4, a recombinant DNA molecule according to claim 5, a live recombinant carrier according to claim 6, a host cell according to claim 7 or a polypeptide according to claims 8-11, and a pharmaceutically acceptable carrier.

15) Vaccine according to claim 14, characterised in that it comprises an adjuvant.

16) Vaccine according to claim 14 or 15, characterised in that it comprises an additional antigen derived from a virus or micro-organism pathogenic to mammals or genetic information encoding said antigen.

17) Vaccine according to claim 16, characterised in that said virus or micro-organism pathogenic to mammals is selected from the group of Feline Infectious Peritonitis virus, Feline Immune deficiency virus, Canine and Feline Parvovirus, Distemper virus, Adenovirus, Calicivirus, *Bordetella bronchiseptica, Borrelia burgdorferi, Leptospira interrogans, Chlamydia* and *Bartonella henseli.*

18) Vaccine for combating *Helicobacter felis* infections, characterised in that it comprises antibodies against a polypeptide according to claims 8-11.

19) Method for the preparation of a vaccine according to claims 14-17, said method comprising the admixing of a polypeptide according to claims 8-11 and a pharmaceutically acceptable carrier.

20) Diagnostic test for the detection of *Helicobacter felis* specific DNA characterised in that the test comprises a nucleic acid sequence according to claims 1-3, or a fragment thereof.

21) Diagnostic test for the detection of antibodies against *Helicobacter felis*, characterised in that said test comprises a polypeptide or a fragment thereof as described in claims 8-11.

22) Diagnostic test for the detection of antigenic material of *Helicobacter felis*, characterised in that said test comprises antibodies against a polypeptide or a fragment thereof as described in claims 8-11.

3. Detailed Description of Invention

The present invention relates to novel *Helicobacter* urease subunit polypeptides, nucleic acid sequences encoding these polypeptides, to the polypeptides for use in vaccines and to the use in the manufacturing thereof, to vaccines comprising said polypeptides and to methods for the preparation of such vaccines. Further, the invention relates to diagnostic methods for the detection of the nucleic acid sequences, the polypeptides and antibodies against the polypeptides.

Several *Helicobacter* spécies are the cause of pathogenesis of the gastric epithelium. *Helicobacter pylori*, and to a lesser extent *H. heilmannii* are known to cause gastritis, a major factor in the development of peptic ulcers and gastric lymphoma in humans. *Helicobacter felis* is most likely the cause of gastric infections in both cats and dogs. In order to survive the highly acidic environment of the stomach, members of the *Helicobacter* family produce an urease that is capable of hydrolysing the urea present in gastric juice. This hydrolysation sets free an amount of NH_4OH that suffices to neutralise the environment of the bacterium. It is known, that the urease plays a role in the colonisation of the bacterium as well as in its pathogenesis.
Genes encoding urease have been described and sequenced for both *Helicobacter pylori* (Labigne et al., J. Bacteriol. 173: 1920-1931 (1991)) and *Helicobacter felis* (Ferrero et al., Molec. Microbiol. 9, 323-333 (1993)). Of the seven genes involved in urease expression and secretion, only two genes encode the two structural subunits urease A en B of the urease enzyme; ureA and ureB. These two polypeptides form a polypeptide complex having urease activity.
Vaccines against infections caused by both *H. pylori* and *felis* have been made and have been the subject of i.a. International Patent Applications WO 94/09823 and WO 96/34624. Several attempt have been made, to use *H. pylori* urease as a vaccine component for the protection of cats against *H. felis* infection. Although indeed a certain level of protection can be obtained, the results are far from the 100 % protection that would be desirable. From animal experiments published so far it becomes clear that a significant number of animals vaccinated with *H. pylori* is not at all protected against subsequent challenge with *H. felis*. Protection of cats vaccinated with purified urease from either *H. felis* or *pylori* has not been described. Vaccinating cats with *H. felis* whole cell lysates might theoretically be feasible but is not a practical option. This is because in spite of many attempts for improvement, *H. felis* is difficult to grow.
There clearly is a need for an efficacious vaccine, based upon homologous components, and it is clear that the known *H. felis* urease does not confer full protection.

It is i.a. an object of the present invention to provide a *H. felis* urease which is able to induce protection against *Helicobacter felis* infection in dogs and cats. It was surprisingly found now, that in *H. felis* a second urease exists, of which the genes encoding the structural subunits share only low homology with the known *H. felis* ureA and B genes. The novel urease is named ureaseXY, in order to discriminate it from the known urease AB. The newly found urease has been discovered in *H. felis*, and is not present in *H. pylori*.
The overall genetic structure of the genes encoding the two structural urease subunits, UreX and UreY is comparable to that of the known UreA and B in *H. felis* and *H. pylori*. The sequence homology is however surprisingly low. It was even more surprisingly found, that the homology between the ureA and B genes and the novel ureX and Y genes in one single *H. felis* strain is even strikingly lower than the homology between the various ureA and B genes from the various *Helicobacter* species.

Table 1a, 1b and 1c show the comparison of the ureX and Y gene and the polypeptides they encode form five different *Helicobacter felis* species, with the ureA and B genes and polypeptides from *Helicobacter felis*, *pylori* and *heilmannii*.

The level of homology of the genes encoding the novel structural urease subunits X and Y and the polypeptides they encode as compared to that of known ureA and B genes and polypeptide subunits is presented in table 1a, b and c.

Reference molecule : *H. felis* ureX CS1	a.a.	n.a.
H. felis ureA	50 %	57 %
H. pylori ureA	52 %	60 %
H. heilmannii ureA	54 %	62 %
H. felis strain Kukka ureX	100 %	91 %
H. felis strain Ds4 ureX	99 %	91 %
H. felis strain 2301 ureX	99 %	91 %
H. felis strain 390 ureX	99 %	91 %

Table 1a: amino acid and nucleic acid homology between the *H. felis* ureX and various ureA subunits.

Reference molecule : *H. felis* ureY CS1	a.a.	n.a.
H. felis ureB	73 %	71 %
H. pylori ureB	73 %	70 %
H. heilmannii ureB	74 %	71 %
H. felis strain Kukka ureY	99 %	95 %
H. felis strain Ds4 ureY	98 %	94 %
H. felis strain 2301 ureY	99 %	95 %

Table 1b: amino acid and nucleic acid homology between the *H. felis* ureY and various ureB subunits.

Reference molecule: *H. felis* ureXY CSI	n.a.
H. felis ureAB	67 %
H. pylori ureAB	67 %
H. heilmannii ureAB	68 %
H. felis strain Kukka ureXY	94 %
H. felis strain Ds4 ureXY	94 %
H. felis strain 2301 ureXY	94 %

Table 1c: nucleic acid homology between *H. felis* ureXY and various ureAB genes.

One embodiment of the invention thus relates to nucleic acid sequences encoding the novel urease X and Y subunits.

First of all, this embodiment of the invention relates to nucleic acid sequences encoding two subunits of a urease complex such as expressed by *Helicobacter felis*, that have at least 85 % homology with SEQ ID NO: 1, or parts thereof with a length of at least 40, preferably 45, more preferably 50 nucleotides encoding at least an immunogenic fragment of one of the subunits. Still even longer fragments, with a length of at least 55, 60 or 70 nucleic acids are in that order even more preferred.

A preferred form of this embodiment relates to nucleic acid sequences that encode the urease X subunit polypeptide or the urease Y subunit polypeptide and that have at least 85 % homology with SEQ ID NO: 1, or parts thereof with a length of at least 40, preferably 45, more preferably 50 nucleotides encoding at least an immunogenic fragment of the urease X subunit polypeptide or the urease Y subunit polypeptide. Merely as an example: the nucleic acid sequence encoding the urease X subunit of *Helicobacter felis* strain CS1 starts at position 206/207/208 (GTG) (See figure 1a (1)) and stops at position 884/885/886 (TAA). the nucleic acid sequence encoding the urease Y subunit of *Helicobacter felis* strain CS1 starts at position 897/898/899 (ATG) and stops at position 2601/2602/2603 (TAG).
Still even longer fragments, with a length of at least 55, 60 or 70 nucleic acids are in that order even more preferred.

A more preferred form of this embodiment relates to nucleic acid sequences having at least 90 %, preferably 94 %, more preferably 97 % homology with SEQ ID NO: 1.

The determination of the homology percentages was done with the computer program Align Plus for Windows, available from Scientific and Educational Software, P.O.Box 72045 Durham, NC 27722-2045, USA. Settings used for the nucleic acid comparisons are indicated in figures 1a, 1b and 1c.

Since the present invention discloses nucleic acid sequences encoding novel structural *Helicobacter felis* urease subunits, it is now for the first time possible to obtain such polypeptides in sufficient quantities. This can e.g. be done by using expression systems to express the genes encoding the UreX and UreY subunits.
Therefore, in a more preferred embodiment, the invention relates to DNA fragments comprising a nucleic acid sequence according to the invention. Such DNA fragments can e.g. be plasmids, into which a nucleic acid sequence according to the invention is cloned. Such DNA fragments are useful e.g. for enhancing the amount of DNA for use as a probe, as described below.

An essential requirement for the expression of the nucleic acid sequence is an adequate promoter operably linked to the nucleic acid sequence. It is obvious to those skilled in the art that the choice of a promoter extends to any eukaryotic, prokaryotic or viral promoter capable of directing gene transcription in cells used as host cells for protein expression.
Therefore, an even more preferred form of this embodiment relates to a recombinant DNA molecule comprising a DNA fragment or a nucleic acid sequence according to the invention that is placed under the control of a functionally linked promotor. This can be obtained by means of e.g. standard molecular biology techniques. (Maniatis/Sambrook (Sambrook, J. Molecular cloning: a laboratory manual, 1989. ISBN 0-87969-309-6).

Functionally linked promotors are promotors that are capable of controlling the transcription of the nucleic acid sequences to which they are linked.
When the host cells are bacteria, useful expression control sequences which may be used include the Trp promoter and operator (Goeddel, et al., Nucl. Acids Res., 8, 4057, 1980); the lac promoter and operator (Chang, et al., Nature, 275, 615, 1978); the outer membrane protein promoter (Nakamura, K. and Inouge, M., EMBO J., 1, 771-775, 1982); the bacteriophage lambda promoters and operators (Remaut, E. et al., Nucl. Acids Res., 11, 4677-4688, 1983); the α-amylase (B. subtilis) promoter and operator, termination sequences and other expression enhancement and control sequences compatible with the selected host cell.
When the host cell is yeast, useful expression control sequences include, e.g., α-mating factor. For insect cells the polyhedrin or p10 promoters of baculoviruses can be used (Smith, G.E. et al., Mol. Cell. Biol. 3, 2156-65, 1983). When the host cell is of mammalian origin illustrative useful expression control sequences include the SV-40 promoter (Berman, P.W. et al., Science, 222, 524-527, 1983) or the metallothionein promoter (Brinster, R.L., Nature, 296, 39-42, 1982) or a heat shock promoter (Voellmy et al., Proc. Natl. Acad. Sci. USA, 82, 4949-53, 1985).

Bacterial, yeast, fungal, insect and mammalian cell expression systems are very frequently used systems. Such systems are well-known in the art and generally available, e.g. commercially through Clontech Laboratories, Inc. 4030 Fabian Way, Palo Alto, California 94303-4607, USA. Next to these expression systems, parasite-based expression systems are very attractive expression systems. Such systems are e.g. described in the French Patent Application with Publication number 2 714 074, and in US NTIS Publication No US 08/043109 (Hoffman, S. and Rogers, W.: Public. Date 1 December 1993).

Thus a still even more preferred form of this embodiment of the invention relates to Live Recombinant Carrier micro-organisms (LRCs) comprising a gene encoding the UreX or UreY polypeptide or an immunogenic fragment thereof according to the invention. Such micro-organisms are e.g. bacteria and viruses. These LRC micro-organisms are micro-organisms in which additional genetic information, in this case a gene encoding the UreX or UreY polypeptide or an immunogenic fragment thereof according to the invention has been cloned. Animals infected with such LRCs will produce an immunogenic response not only against the immunogens of the vector, but also against the immunogenic parts of the polypeptide(s) for which the genetic code is additionally cloned into the LRC, e.g. the ureX or Y gene.
As an example of bacterial LRCs, attenuated Salmonella strains known in the art can attractively be used.
Live recombinant carrier parasites have i.a. been described by Vermeulen, A. N. (Int. Journ. Parasitol. 28: 1121-1130 (1998))
Also, LRC viruses may be used as a way of transporting the nucleic acid sequence into a target cell. Live recombinant carrier viruses are also called vector viruses. The site of integration of the gene encoding a UreX or Y polypeptide may be a site in a viral gene that is not essential to the virus, or a site in an intergenic region. Viruses often used as vectors are Vaccinia viruses (Panicali et al; Proc. Natl. Acad. Sci. USA, 79: 4927 (1982), Herpesviruses (E.P.A. 0473210A2), and Retroviruses (Valerio, D. et al; in Baum, S.J., Dicke, K.A., Lotzova, E. and Pluznik, D.H. (Eds.), Experimental Haematology today - 1988. Springer Verlag, New York: pp. 92-99 (1989)).

The technique of *in vivo* homologous recombination, well-known in the art, can be used to introduce a recombinant nucleic acid sequence into the genome of a bacterium, parasite or virus of choice, capable of inducing expression of the inserted nucleic acid sequence according to the invention in the host animal.

Finally another form of this embodiment of the invention relates to a host cell comprising a nucleic acid sequence encoding a polypeptide according to the invention, a DNA fragment comprising such a nucleic acid sequence or a recombinant DNA molecule comprising such a nucleic acid sequence under the control of a functionally linked promotor. This form also relates to a host cell containing a live recombinant carrier containing a nucleic acid molecule encoding a UreX or Y polypeptide or an immunogenic fragment thereof according to the invention.
A host cell may be a cell of bacterial origin, e.g. Escherichia coli, Bacillus subtilus and Lactobacillus species, in combination with bacteria-based plasmids as pBR322, or bacterial expression vectors as pGEX, or with bacteriophages. The host cell may also be of eukaryotic origin, e.g. yeast-cells in combination with yeast-specific vector molecules, or higher eukaryotic cells like insect cells (Luckow et al; Bio-technology 6: 47-55 (1988)) in combination with vectors or recombinant baculoviruses, plant cells in combination with e.g. Ti-plasmid based vectors or plant viral vectors (Barton, K.A. et al; Cell 32: 1033 (1983), mammalian cells like Hela cells, Chinese Hamster Ovary cells (CHO) or Crandell Feline Kidney-cells, also with appropriate vectors or recombinant viruses.

Another embodiment of the invention relates to the polypeptides encoded by the nucleic acid sequences, i.e. the urease X subunit and the urease Y subunit and to immunogenic fragments thereof according to the invention.

Therefore, this embodiment of the invention relates to the *Helicobacter felis* urease X polypeptide, said polypeptide having an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 2 or an immunogenic fragment of that polypeptide with a length of at least 40 amino acids that is capable of inducing an immune response against ureaseXY. Preferably, the length of that fragment is more than 40 amino acids, more preferably at least 45, 50, 55, 60 or 70 amino acids in that order or preference.

Preferably this embodiment relates to such polypeptides having a sequence homology of at least 90 %, more preferably 94 %, even more preferably 97 % homology to SEQ ID NO: 2, or an immunogenic fragment of that polypeptide with a length of at least 40 amino acids, more preferably at least 45, 50, 55, 60 or 70 amino acids in that order or preference that is capable of inducing an immune response against ureaseXY.

This embodiment of the invention also relates to the *Helicobacter felis* urease Y polypeptide, said polypeptide having an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 3 or an immunogenic fragment of that polypeptide with a length of at least 40 amino acids that is capable of inducing an immune response against ureaseXY. Preferably, the length of that fragment is more than 40 amino acids, more preferably at least 45, 50, 55, 60 or 70 amino acids in that order or preference.

Preferably this embodiment relates to such polypeptides having a sequence homology of at least 90 %, more preferably 94 %, even more preferably 97 % homology to SEQ ID NO: 3, or an immunogenic fragment of that polypeptide with a length of at least 40 amino acids, more preferably at least 45, 50, 55, 60 or 70 amino acids in that order or preference that is capable of inducing an immune response against ureaseXY.

As for the nucleotide sequence comparison, the comparison between the various amino acid sequences was made using Align Plus for Windows, available from Scientific and Educational Software, P.O.Box 72045 Durham, NC 27722-2045, USA. Settings used for the amino acid comparisons are indicated in figures 1a, 1b and 1c.

It will be understood that, for the particular polypeptides embraced herein, natural variations can exist between individual *Helicobacter felis* strains. These variations may be demonstrated by (an) amino acid difference(s) in the overall sequence or by deletions, substitutions, insertions, inversions or additions of (an) amino acid(s) in said sequence. Amino acid substitutions which do not essentially alter biological and immunological activities, have been described, e.g. by Neurath et al in "The Proteins" Academic Press New York (1979). Amino acid replacements between related amino acids or replacements which have occurred frequently in evolution are, inter alia, Ser/Ala, Ser/Gly, Asp/Gly, Asp/Asn, Ile/Val (see Dayhof, M.D., Atlas of protein sequence and structure, Nat. Biomed. Res. Found., Washington D.C., 1978, vol. 5, suppl. 3). Other amino acid substitutions include Asp/Glu, Thr/Ser, Ala/Gly, Ala/Thr, Ser/Asn, Ala/Val, Thr/Phe, Ala/Pro, Lys/Arg, Leu/Ile, Leu/Val and Ala/Glu. Based on this information, Lipman and Pearson developed a method for rapid and sensitive protein comparison (Science,227, 1435-1441, 1985) and determining the functional similarity between homologous proteins. Such amino acid substitutions of the exemplary embodiments of this invention, as well as variations having deletions and/or insertions are within the scope of the invention as long as the resulting polypeptides retain their immunoreactivity. Thus, variations not essentially influencing the immunogenicity of the polypeptide compared to the wild type polypeptide as depicted in SEQ ID NO: 2 or 3 are considered to fall within the scope of the invention. Those variations in the amino acid sequence of a certain structural subunit X or Y according to the invention that still provide a polypeptide capable of inducing an immune response against infection with *H. felis* or at least against the clinical manifestations of the infection are considered as "not essentially influencing the immunogenicity".

When a polypeptide is used for e.g. vaccination purposes or for raising antibodies, it is however not necessary to use the whole polypeptide. It is also possible to use a fragment of that polypeptide that is capable, as such or coupled to a carrier such as e.g. KLH, of inducing an immune response against that polypeptide, a so-called immunogenic fragment. An "immunogenic fragment" is understood to be a fragment of the full-length polypeptide of the structural subunit X or Y, that still has retained its capability to induce an immune response in the host, i.e. comprises a B- or T-cell epitope. At this moment, a variety of techniques is available to easily identify DNA fragments encoding antigenic fragments (determinants). The method described by Geysen et al (Patent Application WO 84/03564, Patent Application WO 86/06487, US Patent NR. 4,833,092, Proc. Natl Acad. Sci. 81: 3998-4002 (1984), J. Imm. Meth. 102, 259-274 (1987), the so-called PEPSCAN method is an easy to perform, quick and well-established method for the detection of epitopes; the immunologically important regions of the polypeptide. The method is used world-wide and as such well-known to man skilled in the art. This (empirical) method is especially suitable for the detection of B-cell epitopes. Also, given the sequence of the gene encoding any protein, computer algorithms are able to designate specific polypeptide fragments as the immunologically important epitopes on the basis of their sequential and/or structural agreement with epitopes that are now known. The determination of these regions is based on a combination of the hydrophilicity criteria according to Hopp and Woods (Proc. Natl.

Acad. Sci. 78: 38248-3828 (1981)), and the secondary structure aspects according to Chou and Fasman (Advances in Enzymology 47: 45-148 (1987) and US Patent 4,554,101). T-cell epitopes can likewise be predicted from the sequence by computer with the aid of Berzofsky's amphiphilicity criterion (Science 235, 1059-1062 (1987) and US Patent application NTIS US 07/005,885). A condensed overview is found in: Shan Lu on common principles: Tibtech 9: 238-242 (1991), Good et al on Malaria epitopes; Science 235: 1059-1062 (1987), Lu for a review; Vaccine 10: 3-7 (1992), Berzowsky for HIV-epitopes; The FASEB Journal 5:2412-2418 (1991).

Vaccines against e.g. *Helicobacter pylori*, which has only one urease, can be made on the basis of this urease, as was described above. In the specific case of *Helicobacter felis* however a vaccine based upon the known *Helicobacter felis* structural subunits ureA and B is not capable of providing sufficient protection against *Helicobacter felis* infection: immunity against structural subunits ureA and B allegedly does not neutralise the urease activity of the newly found heterologous structural subunits UreX and Y.

Therefore, vaccines for the protection of animals against *Helicobacter felis* infection should at least be directed against the novel urease XY.
Therefore, one form of still another embodiment of the invention relates to vaccines capable of protecting mammals such as dogs and cats against *Helicobacter felis* infection, that comprise the structural subunit X or Y, preferably X and Y, more preferably X, Y, A and B, or an immunogenic fragment of X and/or Y according to the invention together with a pharmaceutically acceptable carrier.

Still another embodiment of the present invention relates to the polypeptides according to the invention for use in a vaccine.

Still another embodiment relates to the use of the polypeptide according to the invention in the manufacturing of a vaccine for combating *Helicobacter felis* infections.

One way of making a vaccine according to the invention is by biochemical purification of the ureaseXY polypeptide or its subunits from a bacterial culture. This can e.g. be done by centrifugation of the bacteria, and the use of gel-filtration columns for separation of the urease polypeptide or its subunits from other components. Further purification may e.g. be done by selective precipitation in ammonium-sulphate, followed by centrifugation, gel electrophoresis and, if desired, separation from the urease AB subunits and dissolving the pellet in a suitable buffer. This is however a time-consuming way of making the vaccine, especially where *Helicobacter felis* is difficult to grow.

It is therefore much more convenient to use the expression products of the genes encoding the urease X and Y subunits according to the invention in vaccines.
Such vaccines can easily be made by admixing ureaseXY or an UreX or Y subunit or an immunological fragment thereof according to the invention with a pharmaceutically acceptable carrier as described below.

Furthermore vaccines can comprise live recombinant carriers as described above, capable of expressing ureaseXY, an UreX or UreY subunit or immunogenic fragments thereof according to the invention. Such vaccines, e.g. based upon a Salmonella carrier or a viral carrier infecting the gastric epithelium have the advantage over subunit vaccines that they better mimic the natural way of infection of *Helicobacter felis*.

Moreover, their self-propagation is an advantage since only low amounts of the recombinant carrier are necessary for immunisation.

Vaccines described above all contribute to active vaccination, i.e. the host's immune system is triggered by the UreX and/or Y polypeptide or immunogenic fragments thereof, to make antibodies against these polypeptides.
Alternatively, such antibodies can be raised in e.g. rabbits or can be obtained from antibody-producing cell lines as described below. Such antibodies can then be administered to the host animal. This method of vaccination, passive vaccination, is the vaccination of choice when an animal is already infected, and there is no time to allow the natural immune response to be triggered. It is also the preferred method for vaccinating immune-compromised animals. Administered antibodies against *Helicobacter* UreX or UreY can in these cases bind directly to the urease excreted by the bacteria. This has the advantage that the urease activity is directly eliminated, thus resulting in acidification of the environment and decreased or stopped *Helicobacter* growth.
Therefore, one other form of this embodiment of the invention relates to vaccines comprising antibodies against *Helicobacter felis* urease X polypeptides that have an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 2 or immunogenic fragments of that polypeptide with a length of at least 40 amino acids that are capable of inducing an immune response against ureaseXY or antibodies against *Helicobacter felis* urease Y polypeptides that have an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 3 or immunogenic fragments of that polypeptide with a length of at least 40 amino acids that are capable of inducing an immune response against ureaseXY.

Vaccines can also be based upon host cells as described above, that comprise ureaseXY, an UreX or UreY subunit or immunogenic fragments thereof according to the invention.

An alternative and efficient way of vaccination is direct vaccination with DNA encoding the relevant antigen. Direct vaccination with DNA encoding polypeptides has been successful for many different polypeptides. (As reviewed in e.g. Donnelly et al., The Immunologist 2: 20-26 (1993)).
This way of vaccination is very attractive for the vaccination of both cats and dogs against *Helicobacter felis* infection.
Therefore, still other forms of this embodiment of the invention relate to vaccines comprising nucleic acid sequences encoding a polypeptide according to the invention or immunogenic fragments thereof according to the invention, and to vaccines comprising DNA fragments that comprise such nucleic acid sequences.
Still other forms of this embodiment relate to vaccines comprising recombinant DNA molecules according to the invention.
DNA vaccines can easily be administered through intradermal application e.g. using a needle-less injector. This way of administration delivers the DNA directly into the cells of the animal to be vaccinated. Amount of DNA in the microgram range between 1 and 100 μg provide very good results.

In a further embodiment, the vaccine according to the present invention also comprises antigens from other dog or cat pathogenic organisms and viruses, or genetic information encoding such antigens. Such organisms and viruses are e.g. Feline Infectious Peritonitis virus, Feline Immune deficiency virus, Canine and Feline Parvovirus,

Distemper virus, Adenovirus, Calicivirus, *Bordetella bronchiseptica, Borrelia burgdorferi, Leptospira interrogans, Chlamydia* and *Bartonella henseli.*

Also, the present invention relates to polypeptides according to the invention for use in the manufacturing of a vaccine for combating *Helicobacter felis* infections.

All vaccines according to the present invention comprise a pharmaceutically acceptable carrier. A pharmaceutically acceptable carrier can be e.g. sterile water or a sterile physiological salt solution. In a more complex form the carrier can e.g. be a buffer.

Vaccines according to the present invention may in a preferred presentation also contain an adjuvant. Adjuvants in general comprise substances that boost the immune response of the host in a non-specific manner. A number of different adjuvants are known in the art. Examples of adjuvants are Freunds Complete and Incomplete adjuvant, vitamin E, non-ionic block polymers, muramyldipeptides, Quill A(R), mineral oil e.g. Bayol(R) or Markol(R), vegetable oil, and Carbopol(R) (a homopolymer), or Diluvac(R) Forte.
The vaccine may also comprise a so-called "vehicle". A vehicle is a compound to which the polypeptide adheres, without being covalently bound to it. Often used vehicle compounds are e.g. aluminium hydroxide, -phosphate or -oxide, silica, Kaolin, and Bentonite.
A special form of such a vehicle, in which the antigen is partially embedded in the vehicle, is the so-called ISCOM (EP 109.942, EP 180.564, EP 242.380)
In addition, the vaccine may comprise one or more suitable surface-active compounds or emulsifiers, e.g. Span or Tween.
Often, the vaccine is mixed with stabilisers, e.g. to protect degradation-prone polypeptides from being degraded, to enhance the shelf-life of the vaccine, or to improve freeze-drying efficiency. Useful stabilisers are i.a. SPGA (Bovarnik et al; J. Bacteriology 59: 509 (1950)), carbohydrates e.g. sorbitol, mannitol, trehalose, starch, sucrose, dextran or glucose, proteins such as albumin or casein or degradation products thereof, and buffers, such as alkali metal phosphates.
In addition, the vaccine may be suspended in a physiologically acceptable diluent.
It goes without saying, that other ways of adjuvating, adding vehicle compounds or diluents, emulsifying or stabilising a polypeptide are also embodied in the present invention.

Vaccines according to the invention that comprise the UreX or UreY subunit polypeptide can very suitably be administered in amounts ranging between 1 and 100 micrograms, although smaller doses can in principle be used. A dose exceeding 100 micrograms will, although immunologically very suitable, be less attractive for commercial reasons.

Vaccines based upon live attenuated recombinant carriers, such as the LRC-viruses and bacteria described above can be administered in much lower doses, because they multiply themselves during the infection. Therefore, very suitable amounts would range between 10^3 and 10^9 CFU/PFU for respectively bacteria and viruses.

Many ways of administration can be applied. Intranasal application is a frequently used way of administrating a vaccine. Oral application is also an attractive way of administration, because the infection is often located in the upper digestive tract. A preferred way of oral administration is the packaging of the vaccine in capsules, known and frequently used in the art, that only disintegrate in the highly acidic environment of

the stomach. Also, the vaccine could be mixed with compounds known in the art for temporarily enhancing the pH of the stomach.
Systemic application is also suitable, e.g. by intramuscular application of the vaccine. If this route is followed, standard procedures known in the art for systemic application are well-suited.

Another embodiment of the invention relates to diagnostic tests for the detection of *H. felis* infection. It is known that several *Helicobacter* species such as *H. bizzozeronii, H. felis* and *H. salomonis* are capable of infecting both cats and dogs. Of these three, *H. felis* is the species suspected to cause most of the pathology, although it is often outnumbered by *H. bizzozeronii* and *H. salomonis*. Thus, a quick and correct diagnosis of disease, in both cats and dogs, caused by *Helicobacter felis* is important. It has however been very difficult to discriminate between these three species due to the fact that they are so very closely related.
Therefore it is another objective of this invention to provide such diagnostic tools suitable for discriminating *H. felis* from other *Helicobacter* species.

On the basis of the novel urease polypeptides and the genes encoding the urease polypeptides, at least three different diagnostic tests, specifically suitable for the discrimination of *H. felis* from other members of the *Helicobacter* family were developed:
1) a diagnostic test based upon the presence or absence of DNA encoding the specific UreX and UreY structural subunits
2) a diagnostic test based upon the detection of antibodies against the specific UreX and UreY structural subunits
3) a diagnostic test based upon the detection of antigenic material of the specific UreX and UreY structural subunits

A diagnostic test according to 1) is e.g. based upon the reaction of bacterial DNA isolated from the animal to be tested, with specific probes or PCR-primers based upon the sequence of ureX or Y genes. If *H. felis* DNA is present in the animal, this will e.g. specifically bind to ureX or Y specific PCR-primers and will subsequently become amplified in PCR-reaction. The PCR-reaction product can then easily be detected in DNA gel electrophoresis.
The DNA can most easily be isolated from the micro-organisms present in swabs of the upper digestive tract or in the saliva of the animal to be tested. Specific primers can easily be selected from the many regions of the ureX and ureY coding sequences and the non-coding intergenic sequence that differ in sequence from the comparable regions in the ureAB coding sequences. One of the many algorithms suitable for the determination of the level of nucleic acid homology and for comparison of nucleotide sequences in general is known as "Clustal W". It has been described by Thompson et al., in Nucleic Acid Research 22: 4673-4680 (1994). The program can be found at several sites on Internet. An more recent alternative for this program is e.g. Align Plus for Windows, available from Scientific and Educational Software, P.O.Box 72045 Durham, NC 27722-2045, USA.
As follows from figure 1, a large number of possible PCR-primers can be found that are specific for ureX or ureY. An extremely specific pair of PCR-probes is e.g. formed by the 5'-located sequence CATGCACTTTTTGAAAAAAGA (SEQ ID NO: 16) and the 3'-located sequence TATGGTGGTCTTCTCT (SEQ ID NO: 17). Of course many other sequences that are specific for ureX or Y or the intergenic region are suitable. Standard PCR-textbooks give methods for determining the suitability of the probes for selective PCR-reactions with ureX or ureY. PCR-techniques are extensively described in

(Dieffenbach & Dreksler; PCR primers, a laboratory manual. ISBN 0-87969-447-5 (1995)).

Another DNA-based test is based upon growth of bacterial material obtained from the swab, followed by classical DNA purification followed by classical hybridisation with radioactively or colour-labelled ureXY-specific DNA-fragments. Given the very low homology between the ureXY-coding regions and the ureAB coding regions of both *H. felis* and other *Helicobacter* species, hybridisation unambiguously indicates the presence or absence of *H. felis*. Both PCR-reactions and hybridisation reactions are well-known in the art and are i.a. described in Maniatis/Sambrook (Sambrook, J. *et al.* Molecular cloning: a laboratory manual. ISBN 0-87969-309-6).
Selective detection with PCR-primers or with classical hybridisation with ureXY-specific DNA-fragments can be done with fragments that preferably are short, but for practical reasons preferably consist of a stretch of at least 10 contiguous nucleotides of SEQ ID NO: 1. It is clear that for hybridisation experiments a probe needs to be selected that has a higher homology to SEQ ID NO: 1, than to sequences encoding the *Helicobacter* ureA or ureB subunit. Such a probe can very easily be selected with the help of the Align Plus for Windows program or the Clustal W program as discussed above. In a comparative hybridisation experiment the DNA to be diagnosed can be tested next to e.g. H. *pylori* DNA. The probe according to the invention, having a higher homology to SEQ ID NO: 1 than to a gene encoding ureAB, would bind better to *H. felis* DNA (if present in the sample) than to DNA of other *Helicobacter* species thus specifically revealing the presence of H. *felis* DNA in the sample to be tested. The sequences SEQ ID NO: 16 or 17 mentioned above are merely examples of probes very suitable for labelling and subsequent use in the *H. felis*-specific hybridisation assays as described.

Thus, one embodiment of the invention relates to a diagnostic test for the detection of DNA encoding the specific *Helicobacter* UreX and UreY subunit polypeptides. Such a test comprises a nucleic acid sequence according to the invention or a fragment thereof that is specific for the DNA encoding UreX and UreY or the intergenic region between UreX and UreY. A fragment that is specific for that DNA is a fragment that binds better to the DNA encoding UreX and UreY or the intergenic region between UreX and UreY than to the DNA encoding UreA and UreB or the intergenic region between UreA and UreB.

Methods for the detection of *Helicobacter felis* DNA comprise hybridisation of the DNA to be tested with UreX or Y DNA, or PCR-reaction of the DNA to be tested with UreX or Y DNA specific probes.

A diagnostic test according to 2) for the detection of *Helicobacter felis* antibodies in sera can be e.g. a simple sandwich-ELISA-test in which purified UreX or UreY subunit polypeptides or antigenic fragments thereof according to the invention are coated to the wall of the wells of an ELISA-plate. A method for the detection of such antibodies is e.g. Incubation of purified UreX or Y polypeptide with serum from mammals to be tested, followed by e.g. incubation with a labelled antibody against the relevant mammalian antibody. A colour reaction can then reveal the presence or absence of antibodies against *Helicobacter felis* urease XY. Depending on the labelled antibodies used, the selectivity of this system can be improved by pre-incubation of the serum to be tested with urease AB followed by spinning down the precipitate, in order to avoid non-XY-specific reactions.
If antigenic fragments of the UreX or UreY structural subunits according to the invention are used for coating, this pre-incubation step can be skipped.

Another example of a diagnostic test system is e.g. the incubation of a Western blot comprising UreX or UreY polypeptide or an antigenic fragment thereof according to the invention, with serum of mammals to be tested, followed by analysis of the blot.
The purified UreX and UreY structural subunits or antigenic fragments thereof according to the invention, suitable for the coating of ELISA plates or for Western blotting can easily be obtained by expression of the ureX and ureY gene as was described by Ferrero for ureA and B (Ferrero et al., Molec. Microbiol. 9, 323-333 (1993)).

Also, the invention relates to methods for the detection in serum of antibodies against *Helicobacter felis* antibodies in which the method comprises the incubation of serum with UreX or UreY polypeptide or an antigenic fragment thereof according to the invention.

A diagnostic test according to 3) based upon the detection of antigenic material of the specific UreX and UreY structural subunits of *Helicobacter felis* antigens and therefore suitable for the detection of *Helicobacter felis* infection can e.g. also be a standard ELISA test. In one example of such a test the walls of the wells of an ELISA plate are coated with antibodies directed against the specific UreX and UreY structural subunits of *Helicobacter felis*. The antigenic material to be tested can if necessary be pre-incubated with antibodies against UreA and B. This will leave the UreX and Y specific epitopes uncovered and therefore the pre-incubated *Helicobacter* species will bind to the ELISA plate only if it comprises UreX or Y, i.e. if it specifically is *Helicobacter felis*.
The use of monoclonal antibodies specific for UreX or Y and not reacting with UreA or B are the preferred antibodies in such tests, because they make the pre-incubation step superfluous. Such monoclonal antibodies can easily be obtained by immunising inbred mice with immunising fragments of UreX or Y according to the invention, by techniques also known in the art (See below: Kohler and Milstein).

The polypeptides or immunogenic fragments thereof according to the invention expressed as characterised above can be used to produce antibodies, which may be polyclonal, monospecific or monoclonal (or derivatives thereof). If polyclonal antibodies are desired, techniques for producing and processing polyclonal sera are well-known in the art (e.g. Mayer and Walter, eds. *Immunochemical Methods in Cell and Molecular Biology*, Academic Press, London, 1987).
Monoclonal antibodies, reactive against the polypeptide according to the invention (or variants or fragments thereof) according to the present invention, can be prepared by immunising inbred mice by techniques also known in the art (Kohler and Milstein, *Nature*, 256, 495-497, 1975).

Finally, the invention relates to methods for the detection of antigenic material from *Helicobacter felis* in which the method comprises the incubation of serum, tissue of body fluids with antibodies against UreX or UreY polypeptide or an antigenic fragment thereof according to the invention.

Example 1

The *ure*X and *ure*Y genes of *Helicobacter felis* strain CS1: cloning and expression in *Escherichia coli*.

The *ure*X and *ure*Y genes of *H. felis* strain CS1 were cloned as an operon into an *E. coli* T7 expression vector, pET3a, as follows:
For proper expression of the UreX and Y proteins in pET3a (Novagen, 601 Science Drive, Madison WI, USA) the genes were cloned as a *Nde*I-*Bam*HI DNA fragment into the *Nde*I-*Bam*HI sites of this vector. The *ureaseXY* operon contains an internal *Nde*I site that was mutated by overlap-extension PCR of 2 PCR fragments. For that purpose two PCR fragments (the 5' and the 3' products) were amplified using chromosomal DNA of H. *felis* CS1 as the template. The 5' PCR product contained the complete *ure*X gene and the first part of the *ure*Y gene. The forward primer contained a *Nde*I restriction site and the start codon of ureX (GGAGTAACATATGAAACTCACA CCCAAAGAGC) (SEQ ID NO: 18), and the reverse primer contains a point mutation (CACACCC ACGACCATGTGAGGGCTTAC) (SEQ ID NO: 19). The second, 3' PCR product consisted of the 3' end of the *ure*Y gene. This forward primer is complementary to the reverse primer of the first PCR product and also contained the same point mutation (GTAAGCC CTCACATGGTCGTGGGTGTG) (SEQ ID NO: 20), and the reverse primer contained a *Bam*HI restriction site just downstream of the stopcodon of the *ure*Y gene (CGAATT CGGATCCTAGAAGAAAGTGTAGCGCTGG) (SEQ ID NO: 21). The mutation in the complementary primers is made to delete the internal *Nde*I site in *ure*Y, it replaces the CATATG (His- Met) by CACATG (His-Met).
After amplification of both PCR products, the complete operon was obtained by overlap-extension-PCR with the forward primer of the *ure*X and the reverse primer of the *ure*Y using both PCR products as templates. The resulting PCR product was cloned into PCR-bluntII-TOPO (Invitrogen, P.O.Box 2312, 9704 CH Groningen, The Netherlands) and transformed into *E. coli* TOP10F' cells (Invitrogen). Positive clones were isolated and the *urease*XY genes were sub-cloned into pET3a with *Nde*I-*Bam*HI. The obtained plasmid was called pUreXY-1 and was transformed into the expression strain HMS174(DE3)/pLysS (Novagen).

The *ure*X and *ure*Y genes of pUreXY-1 were expressed in HMS174(DE3)/pLysS as follows: an overnight culture was diluted 1/100 into TB Amp^{100} Cam^{25}; this culture was incubated for 3 h at 37°C at 200 rpm; the culture was induced by adding 1 mM of IPTG and incubated for another 3 h at 37°C at 200 rpm. The induction was done twice, once in a small scale and once in a large scale.
The induced samples were analysed on a SDS-PAGE gel (fig. 2). As can be clearly seen from lane 9, expression of UreX and UreY, when induced provides the two structural subunits as polypeptide bands with a molecular weight of 25 kDa for the UreX subunit and 62 kDa for the UreY subunit.

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Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
    130                 135                 140

cat ttc cac ttc ttt gaa acc aac aag gca ttg aaa ttc gat cgg gaa   480
His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg Glu
145                 150                 155                 160

aaa gcc tat ggc aaa cgc cta gat att ccc tct ggc aac acg cta cgc   528
Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
                165                 170                 175

att ggg gca gga caa acc cgt aaa gtg cag tta atc cct ctt ggc ggt   576
Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
            180                 185                 190

agt aaa aaa gtg att ggc atg aac ggg ctt gtg aat aat att gcg gac   624
Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
        195                 200                 205

gaa cgc cat aaa cac aaa gca cta gac aag gca aaa tct cac gga ttc   672
Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
    210                 215                 220

atc aag taa ggagactccc atg aaa atg aaa aaa caa gag tat gta aac   721
Ile Lys                 Met Lys Met Lys Lys Gln Glu Tyr Val Asn
225                             230                 235

acc tac gga ccc acc aca ggc gat aaa gtg cgc tta gga gat acc gat   769
Thr Tyr Gly Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr Asp
```

240 245 250

ctt tgg gca gaa gta gaa cat gac tat acc act tat ggc gaa gag ctc 817
Leu Trp Ala Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu
255 260 265

aaa ttt ggc gcg ggt aaa act atc cgt gag ggt atg ggt cag agc aat 865
Lys Phe Gly Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser Asn
270 275 280 285

agc cca gat gaa aac acc tta gat tta gtg atc acc aac gcg atg att 913
Ser Pro Asp Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met Ile
290 295 300

atc gac tac acc ggg att tat aaa gcc gac att ggt att aaa aat ggc 961
Ile Asp Tyr Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly
305 310 315

aaa atc cat ggt att ggc aag gcg ggg aac aaa gac atg caa gat ggc 1009
Lys Ile His Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp Gly
320 325 330

gta agc cct cat atg gtc gtg ggt gtg ggc aca gaa gca cta gca ggg 1057
Val Ser Pro His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala Gly
335 340 345

gaa ggt atg att att acc gct ggg ggg atc gat tcg cac acc cac ttc 1105
Glu Gly Met Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His Phe
350 355 360 365

ctc tct ccc caa caa ttc cct acc gct cta gcc aat ggt gtt aca acc 1153
Leu Ser Pro Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr Thr
370 375 380

atg ttt gga ggt ggc aca ggt ccg gta gat ggc acg aat gcg acc acc 1201
Met Phe Gly Gly Gly Thr Gly Pro Val Asp Gly Thr Asn Ala Thr Thr
385 390 395

```
atc act ccg ggc aaa tgg aac ttg cac cgc atg ttg cgc gca gct gaa   1249
Ile Thr Pro Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala Glu
        400                 405                 410

gag tat tct atg aat gtg ggc ttt ttg ggc aaa ggc aat agc tcc agt   1297
Glu Tyr Ser Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser
    415                 420                 425

aaa aaa caa ctc gta gaa caa gta gaa gcg ggc gcg att ggc ttt aaa   1345
Lys Lys Gln Leu Val Glu Gln Val Glu Ala Gly Ala Ile Gly Phe Lys
430                 435                 440                 445

ttg cat gaa gac tgg ggc aca aca cca agt gcg atc gat cac tgc ttg   1393
Leu His Glu Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys Leu
                450                 455                 460

agc gta gca gat gaa tac gat gtg caa gtt tgt atc cac acc gat acg   1441
Ser Val Ala Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp Thr
            465                 470                 475

gtc aat gag gca ggt tat gta gat gac acc cta aat gcg atg aac ggg   1489
Val Asn Glu Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn Gly
        480                 485                 490

cgc gcc atc cat gcc tac cac att gag gga gcg ggc gga gga cac tca   1537
Arg Ala Ile His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His Ser
    495                 500                 505

cct gat gtt atc acc atg gca ggc gag ctc aat att cta ccc tcc tcc   1585
Pro Asp Val Ile Thr Met Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser
510                 515                 520                 525

acc acc ccc act att ccc tat acc att aat acg gtt gca gaa cac tta   1633
Thr Thr Pro Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His Leu
                530                 535                 540

gac atg ctc atg acc tgc cac cac cta gac aaa cgc atc cgc gag gat   1681
Asp Met Leu Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu Asp
```

545 550 555

ctc cag ttt tcc caa agc cgt atc cgc ccc ggc tct att gcc gct gaa 1729
Leu Gln Phe Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu
560 565 570

gat gtg ctc cat gat att ggc gtg atc gcg atg aca agc tcg gat tcg 1777
Asp Val Leu His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp Ser
575 580 585

caa gca atg ggg cgc gct ggg gaa gtg att cct aga act tgg caa act 1825
Gln Ala Met Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln Thr
590 595 600 605

gca gac aag aat aaa aaa gaa ttt ggt aag ctt cct gaa gat ggt gca 1873
Ala Asp Lys Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala
610 615 620

gat aat gac aac ttc cgc atc aaa cgc tat atc tcc aaa tac acc att 1921
Asp Asn Asp Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile
625 630 635

aat ccc gct ttg acc cat ggc gtg agc gag tat atc ggc tct gtg gaa 1969
Asn Pro Ala Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val Glu
640 645 650

gag ggc aag atc gcc gac ttg gtg gtg tgg aat cct gct ttc ttt ggt 2017
Glu Gly Lys Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe Gly
655 660 665

gta aaa ccc aaa atc gtg atc aaa ggc ggt atg gtg gtg ttc tct gaa 2065
Val Lys Pro Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser Glu
670 675 680 685

atg ggc gat tct aac gcg tct gtg ccc aca cct cag ccg gtt tat tac 2113
Met Gly Asp Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr
690 695 700

```
cgc gaa atg ttt ggg cat cac ggc aag gcg aaa ttt gac acc agc atc   2161
Arg Glu Met Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser Ile
            705                 710                 715

act ttt gtt tcc aaa gtc gcc tat gaa aat ggc gtg aaa gaa aaa cta   2209
Thr Phe Val Ser Lys Val Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu
        720                 725                 730

ggc tta gag cgc aag gtg cta ccc gtg aaa aac tgc cgc aac atc act   2257
Gly Leu Glu Arg Lys Val Leu Pro Val Lys Asn Cys Arg Asn Ile Thr
    735                 740                 745

aag aaa gac ttc aaa ttc aac aac aag acg gcg cat atc act gtc gat   2305
Lys Lys Asp Phe Lys Phe Asn Asn Lys Thr Ala His Ile Thr Val Asp
750                 755                 760                 765

cct aaa acc ttc gag gtc ttt gta gat ggc aaa ctc tgc acc tct aaa   2353
Pro Lys Thr Phe Glu Val Phe Val Asp Gly Lys Leu Cys Thr Ser Lys
                770                 775                 780

ccc gcc tct gaa gtg cct cta gcc caa cgc tac act ttc ttc tag       2398
Pro Ala Ser Glu Val Pro Leu Ala Gln Arg Tyr Thr Phe Phe
            785                 790                 795

gcacaat                                                          2405
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<210> 5
<211> 226
<212> PRT
<213> Helicobacter felis

<400> 5

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Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
  1               5                  10                  15

Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
            20                  25                  30
```

Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
35 40 45

Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
50 55 60

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
65 70 75 80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
85 90 95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
100 105 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
115 120 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
130 135 140

His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg Glu
145 150 155 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
165 170 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
180 185 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
195 200 205

Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
210 215 220

Ile Lys

225

<210> 6
<211> 568
<212> PRT
<213> Helicobacter felis

<400> 6

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Met Lys Met Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly Pro Thr Thr
  1               5                  10                  15

Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu
             20                  25                  30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
         35                  40                  45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
     50                  55                  60

Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
 65                  70                  75                  80

Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
                 85                  90                  95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
            100                 105                 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
        115                 120                 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
    130                 135                 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
145                 150                 155                 160
```

Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
165 170 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
180 185 190

Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
195 200 205

Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
210 215 220

Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
225 230 235 240

Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
245 250 255

Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
260 265 270

His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
275 280 285

Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
290 295 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
305 310 315 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
325 330 335

Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile
340 345 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala

355 360 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
370 375 380

Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp Asn Phe Arg
385 390 395 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
405 410 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
420 425 430

Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
435 440 445

Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
450 455 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
465 470 475 480

His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val
485 490 495

Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Lys Val
500 505 510

Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe
515 520 525

Asn Asn Lys Thr Ala His Ile Thr Val Asp Pro Lys Thr Phe Glu Val
530 535 540

Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Ala Ser Glu Val Pro
545 550 555 560

Leu Ala Gln Arg Tyr Thr Phe Phe
565

<210> 7
<211> 2183
<212> DNA
<213> Helicobacter felis

<220>
<221> CDS
<222> (3)..(683)

<220>
<221> CDS
<222> (694)..(2181)

<400> 7
tc gtg aaa ctc aca ccc aaa gag caa gaa aag ttc ttg tta tat tat 47
Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr
1 5 10 15

gcg ggc gaa gtg gct aga aag cgc aaa gca gag ggc tta aag ctc aat 95
Ala Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn
20 25 30

caa ccc gaa gcc att gcc tac att agt gcc cat att atg gac gag gcg 143
Gln Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala
35 40 45

cgc cgt ggc aaa aaa acc gtt gct gaa ctt atg gaa gaa tgt atg cac 191
Arg Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His
50 55 60

ttt ttg aaa aaa gat gag gtg atg ccc ggt gtg ggg aat atg gtc cct 239
Phe Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro
65 70 75

```
gat ttg ggc gta gaa gcc act ttc ccc gat ggc acc aaa ctc gta acc   287
Asp Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr
 80                  85                  90                  95

gtg aat tgg ccc att gaa cct gat gaa cac ttt aaa gcc ggt gaa gtg   335
Val Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val
                100                 105                 110

aaa ttt ggc tgt gat aaa gac att gag ctc aac gtg ggt aag gaa gtt   383
Lys Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Val Gly Lys Glu Val
            115                 120                 125

acc gag ctt gaa gtt acc aac gaa gga cct aaa tcc ttg cat gtg ggt   431
Thr Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly
        130                 135                 140

agc cat ttc cac ttc ttt gaa acc aac aag gca ttg aaa ttc gat cgg   479
Ser His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg
    145                 150                 155

gaa aaa gcc tat ggc aaa cgc cta gat att ccc tct ggc aac acg cta   527
Glu Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu
160                 165                 170                 175

cgc att ggg gca gga caa acc cgt aaa gtg cag tta atc cct ctt ggc   575
Arg Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly
                180                 185                 190

ggt agt aaa aaa gtg att ggc atg aac ggg ctt gtg aat aat att gcg   623
Gly Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala
            195                 200                 205

gac gaa cgc cat aaa cac aaa gca cta gac aag gca aaa tct cac gga   671
Asp Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly
        210                 215                 220

ttc atc aag taa ggagactccc atg aaa atg aaa aaa caa gag tat gta   720
```

```
Phe Ile Lys                 Met Lys Met Lys Lys Gln Glu Tyr Val
    225                             230                 235

aac acc tac gga ccc acc aca ggc gat aaa gtg cgc tta gga gat acc   768
Asn Thr Tyr Gly Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr
            240                 245                 250

gat ctt tgg gca gaa gta gaa cat gac tat acc act tat ggc gaa gag   816
Asp Leu Trp Ala Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu
        255                 260                 265

ctc aaa ttt ggc gcg ggt aaa act atc cgt gag ggt atg ggt cag agc   864
Leu Lys Phe Gly Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser
    270                 275                 280

aat agc cca gat gaa aac acc tta gat tta gtg atc acc aac gcg atg   912
Asn Ser Pro Asp Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met
285                 290                 295                 300

att atc gac tac acc ggg att tat aaa gcc gac att ggt att aaa aat   960
Ile Ile Asp Tyr Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn
                305                 310                 315

ggc aaa atc cat ggt att ggc aag gcg ggg aac aaa gac atg caa gat  1008
Gly Lys Ile His Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp
            320                 325                 330

ggc gta agc cct cat atg gtc gtg ggt gtg ggc aca gaa gca cta gca  1056
Gly Val Ser Pro His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala
        335                 340                 345

ggg gaa ggt atg att att acc gct ggg ggg atc gat tcg cac acc cac  1104
Gly Glu Gly Met Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His
    350                 355                 360

ttc ctc tct ccc caa caa ttc cct acc gct cta gcc aat ggt gtt aca  1152
Phe Leu Ser Pro Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr
365                 370                 375                 380
```

acc atg ttt gga ggt ggc aca ggt ccg gta gat ggc acg aat gcg acc 1200
Thr Met Phe Gly Gly Gly Thr Gly Pro Val Asp Gly Thr Asn Ala Thr
385 390 395

acc atc act ccg ggc aaa tgg aac ttg cac cgc atg ttg cgc gca gct 1248
Thr Ile Thr Pro Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala
400 405 410

gaa gag tat tct atg aat gta ggc ttt ttg ggc aaa ggc aat agt tct 1296
Glu Glu Tyr Ser Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser
415 420 425

agc aaa aaa caa ctt gta gaa caa gta gaa gcg ggc gcg att ggc ttt 1344
Ser Lys Lys Gln Leu Val Glu Gln Val Glu Ala Gly Ala Ile Gly Phe
430 435 440

aaa ttg cat gaa gac tgg ggc aca aca cca agt gcg atc gat cac tgc 1392
Lys Leu His Glu Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys
445 450 455 460

ttg agc gtg gca gat gaa tac gat gtg caa gtt tgt atc cac acc gat 1440
Leu Ser Val Ala Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp
465 470 475

acg gtc aat gag gca ggt tat gtg gat gac acc cta aat gca atg aac 1488
Thr Val Asn Glu Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn
480 485 490

ggg cgc gcc atc cat gcc tac cac att gag gga gcg ggc gga gga cac 1536
Gly Arg Ala Ile His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His
495 500 505

tca cct gat gtt atc acc atg gca ggc gag ctc aat att cta ccc tcc 1584
Ser Pro Asp Val Ile Thr Met Ala Gly Glu Leu Asn Ile Leu Pro Ser
510 515 520

tcc acc acc ccc act att ccc tat acc att aat acg gtt gca gaa cac 1632

```
Ser Thr Thr Pro Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His
525                 530                 535                 540

tta gac atg ctc atg acc tgc cac cac cta gat aag cgc atc cgc gag   1680
Leu Asp Met Leu Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu
                545                 550                 555

gat tta caa ttt tct caa agc cgt atc cgc ccc gga tct att gcc gct   1728
Asp Leu Gln Phe Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala
            560                 565                 570

gag gat gtg ctc cat gat att ggc gtg atc gcg atg act agc tcc gat   1776
Glu Asp Val Leu His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp
        575                 580                 585

tcg caa gca atg ggg cgc gct ggg gaa gtg att cct aga act tgg caa   1824
Ser Gln Ala Met Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln
    590                 595                 600

act gca gat aag aat aaa aaa gaa ttt ggt aag ctt cct gaa gat ggt   1872
Thr Ala Asp Lys Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Gly
605                 610                 615                 620

gca gat aac gac aac ttc cgc atc aaa cgc tat atc tcc aaa tac acc   1920
Ala Asp Asn Asp Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr
                625                 630                 635

att aat ccc gct ttg acc cat ggc gtg agc gag tat atc ggc tct gtg   1968
Ile Asn Pro Ala Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val
            640                 645                 650

gaa gag ggc aag atc gcc gac ttg gtg gtg tgg aat cct gcc ttt ttt   2016
Glu Glu Gly Lys Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe
        655                 660                 665

ggc gtg aaa cct aag att gtg att aaa ggt ggc atg gtg gtc ttc tct   2064
Gly Val Lys Pro Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser
    670                 675                 680
```

```
gaa atg ggc gat tct aac gcg tcc gtg ccc acg cct cag ccg gtt tat   2112
Glu Met Gly Asp Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr
685                 690                 695                 700

tac cgc gaa atg ttt ggg cac cac ggc aag gcg aaa ttt gac acc agc   2160
Tyr Arg Glu Met Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser
                705                 710                 715

atc act ttt cgt gtc tca agc gg                                    2183
Ile Thr Phe Arg Val Ser Ser
            720
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<210> 8
<211> 226
<212> PRT
<213> Helicobacter felis

<400> 8

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Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
  1               5                  10                  15

Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
             20                  25                  30

Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
         35                  40                  45

Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
     50                  55                  60

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65                  70                  75                  80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
                 85                  90                  95
```

```
Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
            100                 105                 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Val Gly Lys Glu Val Thr
        115                 120                 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
    130                 135                 140

His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg Glu
145                 150                 155                 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
                165                 170                 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
            180                 185                 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
        195                 200                 205

Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
    210                 215                 220

Ile Lys
225
```

<210> 9
<211> 496
<212> PRT
<213> Helicobacter felis

<400> 9

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Met Lys Met Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly Pro Thr Thr
  1               5                  10                  15

Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu
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20 25 30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
35 40 45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
50 55 60

Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
65 70 75 80

Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
85 90 95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
100 105 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
115 120 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
130 135 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
145 150 155 160

Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
165 170 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
180 185 190

Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
195 200 205

Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
210 215 220

```
Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
225                 230                 235                 240

Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
                245                 250                 255

Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
            260                 265                 270

His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
        275                 280                 285

Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
    290                 295                 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
305                 310                 315                 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
                325                 330                 335

Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile
            340                 345                 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
        355                 360                 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
    370                 375                 380

Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp Asn Phe Arg
385                 390                 395                 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
                405                 410                 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
            420                 425                 430
```

```
Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
        435                 440                 445

Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
    450                 455                 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
465                 470                 475                 480

His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Arg Val Ser Ser
                485                 490                 495
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<210> 10
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<213> Helicobacter felis

<220>
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<222> (2)..(682)

<220>
<221> CDS
<222> (693)..(2399)

<400> 10

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  Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
    1               5                  10                  15

ggc gaa gtg gct aga aag cgc aaa gcg gag ggc tta aag ctc aac caa   97
Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
            20                  25                  30

ccc gaa gcc att gcc tac att agt gcc cat att atg gac gag gcg cgc   145
```

```
Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
         35                  40                  45

cgt ggc aaa aag acc gtt gcg gaa ctt atg gaa gag tgt atg cac ttt   193
Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
     50                  55                  60

ttg aaa aaa gac gag gtg atg ccc ggt gtg ggg aat atg gtc cct gat   241
Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65                  70                  75                  80

tta ggc gtg gaa gct act ttt ccc gat ggc acc aaa ctc gta acc gtg   289
Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
                 85                  90                  95

aat tgg ccc atc gaa ccc gat gaa cac ttc aaa gcg ggc gaa gtc aaa   337
Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
            100                 105                 110

ttt ggc tgt gat aaa gac att gaa ctc aac gca ggt aag gaa gtt acc   385
Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
        115                 120                 125

gaa cta gaa gtt acc aac gaa gga cct aaa tcc ttg cat gtg ggt agc   433
Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
    130                 135                 140

cat ttc cac ttc ttt gaa gcc aac aag gca ttg aaa ttc gat cgg gaa   481
His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu
145                 150                 155                 160

aaa gcc tat ggc aaa cgc cta gat att ccc tct ggc aac acg cta cgc   529
Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
                165                 170                 175

att ggg gca gga caa acc cgt aaa gtg cag tta atc cct ctt ggc ggc   577
Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
            180                 185                 190
```

```
agt aaa aaa gtg att ggc atg aac ggg ctt gtg aat aat att gca gat   625
Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
        195                 200                 205

gaa cgc cat aaa cac aaa gcg tta gaa aaa gca aaa tct cac gga ttt   673
Glu Arg His Lys His Lys Ala Leu Glu Lys Ala Lys Ser His Gly Phe
    210                 215                 220

atc aaa taa ggagactccc atg aaa atg aaa aaa caa gag tat gta aat    722
Ile Lys                 Met Lys Met Lys Lys Gln Glu Tyr Val Asn
225                             230                 235

acc tac gga cct acc aca ggc gac aaa gtg cgc tta gga gat acc gat   770
Thr Tyr Gly Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr Asp
        240                 245                 250

ctt tgg gca gaa gta gaa cat gac tat acc act tat ggc gaa gag ctc   818
Leu Trp Ala Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu
    255                 260                 265

aaa ttt ggc gcg ggt aaa act atc cgt gag ggc atg ggt cag agc aat   866
Lys Phe Gly Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser Asn
270                 275                 280                 285

agt cca gat gaa aac acc cta gat tta gtc atc acc aac gcg atg att   914
Ser Pro Asp Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met Ile
                290                 295                 300

att gac tac acc ggg att tac aaa gcc gac att ggc att aaa aat ggc   962
Ile Asp Tyr Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly
            305                 310                 315

aaa atc cat ggc att ggc aag gca gga aac aag gac atg caa gat ggc   1010
Lys Ile His Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp Gly
        320                 325                 330

gta agc cct cat atg gtc gtg ggt gtg ggc aca gaa gca tta gca ggg   1058
```

```
Val Ser Pro His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala Gly
    335                 340                 345

gaa ggt atg att att acc gct ggg ggg atc gat tca cac acc cac ttc   1106
Glu Gly Met Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His Phe
350                 355                 360                 365

ctc tct cca caa caa ttc cct acc gct cta gcc aat ggc gtt aca acc   1154
Leu Ser Pro Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr Thr
                370                 375                 380

atg ttt ggc ggt ggc aca ggt ccg gta gat ggc acg aat gcg act acc   1202
Met Phe Gly Gly Gly Thr Gly Pro Val Asp Gly Thr Asn Ala Thr Thr
            385                 390                 395

atc act ccg ggc aaa tgg aac ttg cac cgc atg ttg cgc gca gct gaa   1250
Ile Thr Pro Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala Glu
        400                 405                 410

gag tat tct atg aat gtg ggc ttt ttg ggc aaa ggc aat agc tcc agt   1298
Glu Tyr Ser Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser
    415                 420                 425

aaa aaa caa ctt gta gaa caa ata gaa gcg ggc gcg atc ggc ttt aaa   1346
Lys Lys Gln Leu Val Glu Gln Ile Glu Ala Gly Ala Ile Gly Phe Lys
430                 435                 440                 445

ttg cat gaa gac tgg ggc aca act cca agt gca atc gat cac tgc ttg   1394
Leu His Glu Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys Leu
                450                 455                 460

agc gta gca gat gaa tac gat gtg caa gtt tgt atc cac acc gat acg   1442
Ser Val Ala Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp Thr
            465                 470                 475

gtc aat gag gca ggt tat gta gat gac acc ctg aat gcg atg aac ggg   1490
Val Asn Glu Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn Gly
        480                 485                 490
```

```
cgc gcc atc cat gcc tac cac att gag gga gcg ggc gga gga cac tca   1538
Arg Ala Ile His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His Ser
    495                 500                 505

cct gat gtt atc acc atg gca ggc gag ctc aat att cta ccc tcc tcc   1586
Pro Asp Val Ile Thr Met Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser
510                 515                 520                 525

aca acc ccc act atc ccc tat acc att aat acg gtt gca gaa cac tta   1634
Thr Thr Pro Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His Leu
                530                 535                 540

gac atg ctc atg acc tgc cac cac cta gat aaa cgc atc cgc gag gat   1682
Asp Met Leu Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu Asp
            545                 550                 555

tta caa ttt tcc caa agc cgt atc cgc ccc ggc tct atc gcc gct gaa   1730
Leu Gln Phe Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu
        560                 565                 570

gat gtg ctc cat gat att ggc gtg atc gcg atg aca agc tcg gat tcg   1778
Asp Val Leu His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp Ser
    575                 580                 585

caa gca atg ggg cgc gct ggc gaa gtg att cct cga act tgg cag act   1826
Gln Ala Met Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln Thr
590                 595                 600                 605

gcg gat aag aat aaa aaa gaa ttt ggt aag ctt cct gaa gat agt gca   1874
Ala Asp Lys Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Ser Ala
                610                 615                 620

gat aac gac aac ttc cgt atc aaa cgc tac atc tcc aaa tac act att   1922
Asp Asn Asp Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile
            625                 630                 635

aac ccc gct cta acc cat ggg gta agc gag tat atc ggc tct gtg gaa   1970
```

```
Asn Pro Ala Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val Glu
        640                 645                 650

gag ggc aaa atc gct gat ttg gtg gtg tgg aat cct gcc ttt ttt ggt   2018
Glu Gly Lys Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe Gly
    655                 660                 665

gtg aaa cct aag att gtg atc aaa ggc ggt atg gtg gtc ttc tct gaa   2066
Val Lys Pro Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser Glu
670                 675                 680                 685

atg ggc gac tcc aac gcg tcc gtg cct aca cct cag ccg gtt tat tac   2114
Met Gly Asp Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr
                690                 695                 700

cgc gaa atg ttt ggg cat cac ggc aag gcg aaa ttt gac acc agc atc   2162
Arg Glu Met Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser Ile
            705                 710                 715

act ttt gtt tcc aaa gtc gcc tat gaa aat ggc gtg aaa gaa aaa cta   2210
Thr Phe Val Ser Lys Val Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu
        720                 725                 730

ggc tta gag cgc aag gtg cta ccc gtg aaa aac tgc cgc aac atc act   2258
Gly Leu Glu Arg Lys Val Leu Pro Val Lys Asn Cys Arg Asn Ile Thr
    735                 740                 745

aag aaa gac ttc aaa ttc aac aac aag acg gcg cat atc act gtc gat   2306
Lys Lys Asp Phe Lys Phe Asn Asn Lys Thr Ala His Ile Thr Val Asp
750                 755                 760                 765

cct aaa acc ttc gag gtc ttt gta gat ggc aaa ctc tgc acc tct aaa   2354
Pro Lys Thr Phe Glu Val Phe Val Asp Gly Lys Leu Cys Thr Ser Lys
                770                 775                 780

ccc gcc tct gaa gtg cct cta gcc cag cgc tac act ttc ttc tag       2399
Pro Ala Ser Glu Val Pro Leu Ala Gln Arg Tyr Thr Phe Phe
            785                 790                 795
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gcncaatg 2407

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<211> 226
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<213> Helicobacter felis

<400> 11

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Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
  1               5                  10                  15

Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
             20                  25                  30

Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
         35                  40                  45

Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
     50                  55                  60

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65                  70                  75                  80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
                 85                  90                  95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
            100                 105                 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
        115                 120                 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
    130                 135                 140

His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu
```

145 150 155 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
165 170 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
180 185 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
195 200 205

Glu Arg His Lys His Lys Ala Leu Glu Lys Ala Lys Ser His Gly Phe
210 215 220

Ile Lys
225

<210> 12
<211> 568
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Met Lys Met Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly Pro Thr Thr
1 5 10 15

Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu
20 25 30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
35 40 45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
50 55 60

Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
65 70 75 80

```
Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
                 85                  90                  95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
            100                 105                 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
        115                 120                 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
    130                 135                 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
145                 150                 155                 160

Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
                165                 170                 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
            180                 185                 190

Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
        195                 200                 205

Gln Ile Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
    210                 215                 220

Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
225                 230                 235                 240

Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
                245                 250                 255

Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
            260                 265                 270

His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
```

275 280 285

Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
290 295 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
305 310 315 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
325 330 335

Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile
340 345 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
355 360 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
370 375 380

Glu Phe Gly Lys Leu Pro Glu Asp Ser Ala Asp Asn Asp Asn Phe Arg
385 390 395 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
405 410 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
420 425 430

Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
435 440 445

Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
450 455 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
465 470 475 480

```
His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val
                485                 490                 495

Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Lys Val
            500                 505                 510

Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe
        515                 520                 525

Asn Asn Lys Thr Ala His Ile Thr Val Asp Pro Lys Thr Phe Glu Val
    530                 535                 540

Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Ala Ser Glu Val Pro
545                 550                 555                 560

Leu Ala Gln Arg Tyr Thr Phe Phe
                565
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<220>
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<400> 13

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                                                    Val Lys Leu
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aca ccc aaa gag caa gaa aag ttc ttg tta tat tat gcg ggc gaa gtg   104
Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala Gly Glu Val
      5                  10                  15

gct aga aag cgc aaa gca gag ggc tta aag ctc aac caa ccc gaa gcc   152
Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln Pro Glu Ala
 20                  25                  30                  35

att gcc tac att agt gcc cat att atg gac gag gcg cgt cgt ggc aaa   200
Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg Arg Gly Lys
                 40                  45                  50

aaa acc gtt gcg gaa ctt atg gaa gag tgt atg cac ttt ttg aaa aaa   248
Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe Leu Lys Lys
             55                  60                  65

gac gag gtg atg ccc ggg gtg ggg aat atg gtc cct gat ttg ggc gtg   296
Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp Leu Gly Val
         70                  75                  80

gaa gcc act ttc ccc gat ggc acc aaa ctc gta act gtg aat tgg ccc   344
Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val Asn Trp Pro
     85                  90                  95

atc gaa cct gat gaa cac ttt aag gcg ggt gaa gtg aaa ttt ggc tgt   392
Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys Phe Gly Cys
100                 105                 110                 115

gat aaa gac att gaa ctc aac gca ggt aag gaa gtt acc gaa cta gaa   440
Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr Glu Leu Glu
                120                 125                 130

gtt act aac gaa gga cct aaa tcc ttg cat gtg ggt agc cat ttc cac   488
Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser His Phe His
            135                 140                 145

ttc ttt gaa gcc aac aaa gca ttg aaa ttc gat cgg gaa aaa gcc tat   536
Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu Lys Ala Tyr
```

150 155 160

ggc aaa cgc cta gat att ccc tct ggc aac aca cta cgc att ggg gca 584
Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg Ile Gly Ala
165 170 175

gga caa acc cgt aaa gtg cag tta atc cct ctt ggc ggt agt aaa aaa 632
Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly Ser Lys Lys
180 185 190 195

gtg att ggc atg aac ggg ctt gtg aat aat att gcg gac gaa cgc cat 680
Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp Glu Arg His
200 205 210

aaa cac aaa gcg cta gac aaa gca aaa tct cac gga ttt atc aag taa 728
Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe Ile Lys
215 220 225

ggagactccc atg aaa atg aaa aaa caa gag tat gta aat acc tac gga 777
Met Lys Met Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly
230 235 240

ccc acc aca ggc gat aaa gtg cgc tta gga gat acc gat ctt tgg gca 825
Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala
245 250 255

gaa gta gaa cat gac tat acc acc tat ggc gaa gaa ctc aaa ttc ggt 873
Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly
260 265 270

gca ggt aaa act atc cgt gag ggt atg ggt cag agc aat agc cca gat 921
Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp
275 280 285

gaa aac acc tta gat tta gtg atc acc aac gcg atg att att gac tac 969
Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr
290 295 300

```
acc ggg att tac aaa gcc gac att ggc att aaa aat ggc aaa atc cat   1017
Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His
305                 310                 315                 320

ggc att ggc aag gca gga aac aag gac atg caa gat ggc gta agc cct   1065
Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro
                325                 330                 335

cat atg gtc gtg ggt gtg ggc aca gaa gca cta gca ggg gaa ggt atg   1113
His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met
            340                 345                 350

att att acc gct ggg ggg atc gat tca cac acc cac ttc ctc tct cca   1161
Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro
        355                 360                 365

caa caa ttc cct acc gct cta gcc aat ggc gtt aca aca atg ttt ggc   1209
Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly
    370                 375                 380

ggt ggc aca ggc ccc gta gat ggc acg aat gcg act acc atc act ccg   1257
Gly Gly Thr Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro
385                 390                 395                 400

ggc aaa tgg aac ttg cac cgc atg ttg cgc gca gca gaa gag tat tct   1305
Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser
                405                 410                 415

atg aat gtg ggc ttt ttg ggc aaa ggc aat agc tct agt aaa aaa caa   1353
Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln
            420                 425                 430

ctt gta gaa caa gta gaa gcg ggc gcg att ggt ttt aaa ttg cat gaa   1401
Leu Val Glu Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu
        435                 440                 445

gac tgg ggc aca act cca agt gcg atc gat cac tgc ttg agc gta gca   1449
Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala
```

```
    450                 455                 460

gat gaa tac gat gtg caa gtt tgt ata cac acc gat acg gtc aat gag   1497
Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu
465                 470                 475                 480

gca ggt tat gta gat gac acc cta aat gca atg aac ggg cgc gcc atc   1545
Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile
                485                 490                 495

cat gcc tac cac att gag gga gcg ggt gga gga cac tca cct gat gtt   1593
His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val
            500                 505                 510

atc acc atg gca ggc gaa gtg aat att cta ccc tcc tcc aca acc cct   1641
Ile Thr Met Ala Gly Glu Val Asn Ile Leu Pro Ser Ser Thr Thr Pro
        515                 520                 525

act atc ccc tat acc att aat acg gtt gca gaa cac tta gac atg ctt   1689
Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu
    530                 535                 540

atg acc tgc cac cac cta gat aaa cgc atc cgc gag gat ctc caa ttt   1737
Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe
545                 550                 555                 560

tct caa agc cgt atc cgc ccc ggc tct atc gcc gct gaa gat gtg ctc   1785
Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu
                565                 570                 575

cat gat atc ggt gtg atc gcg atg aca agt tcc gat tcg caa gca atg   1833
His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met
            580                 585                 590

ggg cgc gct ggg gaa gtg att cct aga act tgg caa act gca gac aag   1881
Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys
        595                 600                 605
```

```
aat aaa aaa gaa ttt ggt aag ctt cct gaa gat ggt gca gat aat gac   1929
Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp
    610                 615                 620

aac ttc cgc atc aaa cgc tat atc tcc aaa tac acc att aat ccc gct   1977
Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala
625                 630                 635                 640

ttg acc cat ggc gtg agc gag tat atc ggc tct gtg gaa gag ggc aag   2025
Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys
                645                 650                 655

atc gcc gac ttg gtg gtg tgg aat cct gcc ttt ttt ggc gta aaa ccc   2073
Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro
            660                 665                 670

aaa atc gtg atc aaa ggc ggt atg gtg gtg ttc tct gaa atg ggc gat   2121
Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp
        675                 680                 685

tct aat gcg tct gtg ccc act cct cag ccg gtt tat tac cgc gaa atg   2169
Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met
    690                 695                 700

ttt ggg cat cac ggc aag gcg aaa ttt gac acc agc atc act ttt gtt   2217
Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val
705                 710                 715                 720

tcc aaa gtc gcc tat gaa aat ggt gtg aaa gaa aaa cta ggt tta gag   2265
Ser Lys Val Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu
                725                 730                 735

cgc aag gtg ctc ccc gtg aaa aac tgc cgt aac atc acc aag aag gac   2313
Arg Lys Val Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp
            740                 745                 750

ttc aag ttc aac gac aaa act gca aaa atc acc gtc gat ccg aaa acc   2361
Phe Lys Phe Asn Asp Lys Thr Ala Lys Ile Thr Val Asp Pro Lys Thr
```

755 760 765

ttc gag gtc ttt gta gat ggc aaa ctc tgc acc tct aaa ccc acc tct 2409
Phe Glu Val Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Thr Ser
770 775 780

gaa gtg cct cta gcc caa cgc tac act ttc ttc tag gcataat 2452
Glu Val Pro Leu Ala Gln Arg Tyr Thr Phe Phe
785 790 795

<210> 14
<211> 226
<212> PRT
<213> Helicobacter felis

<400> 14
Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
1 5 10 15

Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
20 25 30

Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
35 40 45

Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
50 55 60

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
65 70 75 80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
85 90 95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
100 105 110

```
Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
        115                 120                 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
    130                 135                 140

His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu
145                 150                 155                 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
                165                 170                 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
            180                 185                 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
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Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
    210                 215                 220

Ile Lys
225
```

<210> 15
<211> 568
<212> PRT
<213> Helicobacter felis

<400> 15

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  1               5                  10                  15

Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu
            20                  25                  30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
```

35 40 45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
50 55 60

Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
65 70 75 80

Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
85 90 95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
100 105 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
115 120 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
130 135 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
145 150 155 160

Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
165 170 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
180 185 190

Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
195 200 205

Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
210 215 220

Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
225 230 235 240

```
Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
                245                 250                 255

Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
            260                 265                 270

His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
        275                 280                 285

Ala Gly Glu Val Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
    290                 295                 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
305                 310                 315                 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
                325                 330                 335

Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile
            340                 345                 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
        355                 360                 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
    370                 375                 380

Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp Asn Phe Arg
385                 390                 395                 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
                405                 410                 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
            420                 425                 430

Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
        435                 440                 445
```

Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
450 455 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
465 470 475 480

His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val
485 490 495

Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Lys Val
500 505 510

Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe
515 520 525

Asn Asp Lys Thr Ala Lys Ile Thr Val Asp Pro Lys Thr Phe Glu Val
530 535 540

Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Thr Ser Glu Val Pro
545 550 555 560

Leu Ala Gln Arg Tyr Thr Phe Phe
565

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<213> Helicobacter felis

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catgcacttt ttgaaaaaag a 21

<210> 17
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<212> DNA
<213> Helicobacter felis

<400> 17
tatggtggtc ttctct 16

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<400> 18
ggagtaacat atgaaactca cacccaaaga gc 32

<210> 19
<211> 27
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<400> 19
cacacccacg accatgtgag ggcttac 27

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<400> 20
gtaagccctc acatggtcgt gggtgtg 27

<210> 21
<211> 34
<212> DNA
<213> Helicobacter felis

<400> 21
cgaattcgga tcctagaaga aagtgtagcg ctgg 34

4. Brief Description of the Drawings

(1～4)
Figure 1a: Comparison of the nucleic acid sequence encoding UreX and Y, including a short non-coding region bridging the two coding sequences, from *Helicobacter felis* species CS1, Kukka, Ds4, 2301 and 390 with the nucleic acid sequence encoding UreA and B, including a short non-coding region bridging the two coding sequences, from *Helicobacter felis*, *pylori* and *heilmannii*

Figure 1b: Comparison of the amino acid sequence of UreX from *Helicobacter felis* species CS1, Kukka, Ds4, 2301 and 390 with the amino acid sequence encoding UreA from *Helicobacter felis*, *pylori* and *heilmannii*

(1～2)
Figure 1c: Comparison of the amino acid sequence of UreY from *Helicobacter felis* species CS1, Kukka, Ds4, 2301 and 390 with the amino acid sequence encoding UreB from *Helicobacter felis*, *pylori* and *heilmannii*

Figure 2: Polyacrylamide gel of the expression products UreX and UreY

Lane 7 : Biorad broad range marker
Lane 8 : Complete cell culture before induction (small scale culture)
Lane 9 : Complete cell culture after induction (small scale culture)
Lane 10 : Complete cell culture after induction (large scale culture)
Lane 11 : Supernatant after induction (large scale culture).
Lane 12 : Biorad pre-stained marker

Ｆｉｇ．１ａ－１

Figure 1a (1)

Ｆｉｇ．１ａ－２

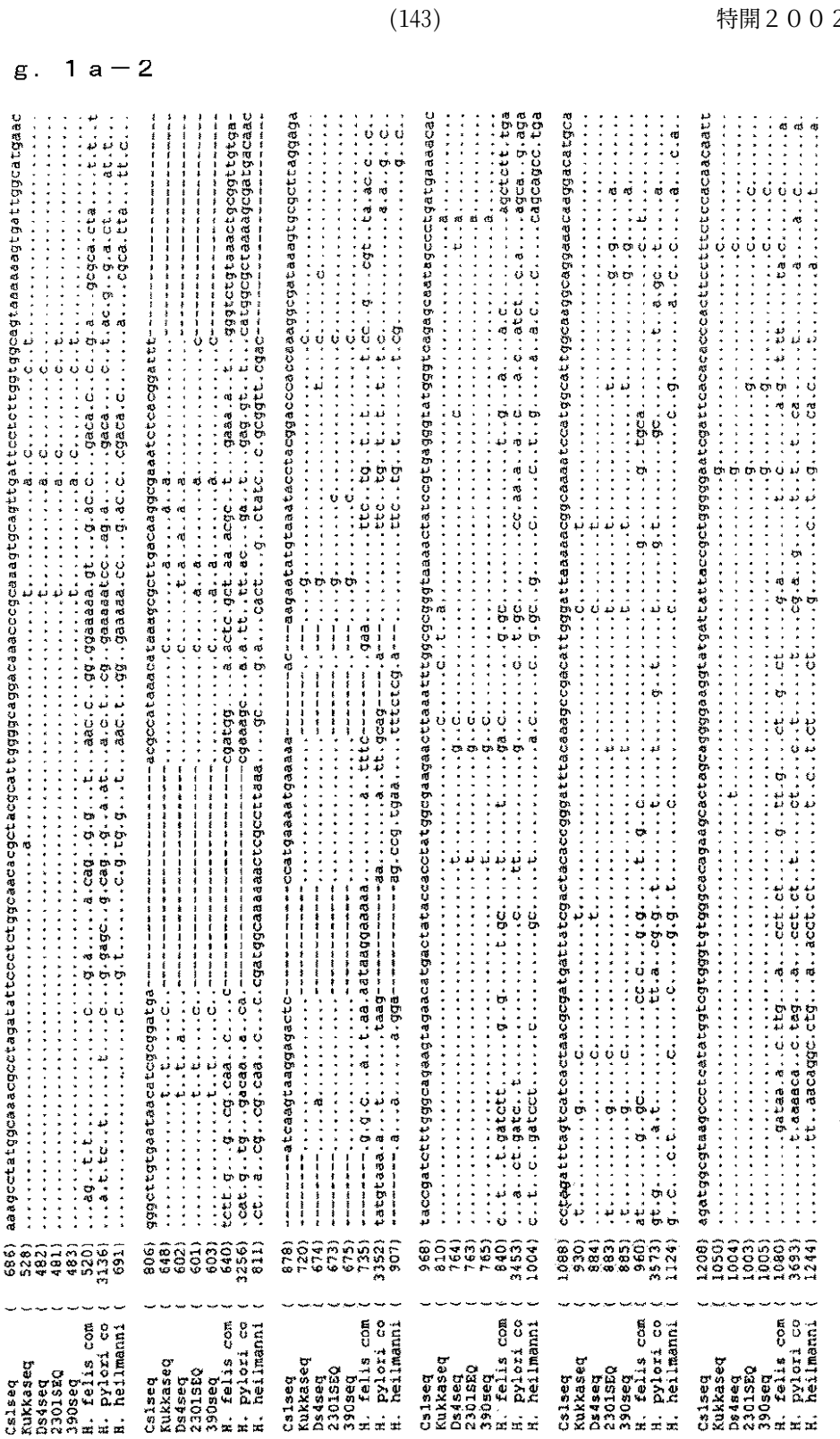

Figure 1a (2)

Ｆｉｇ．１ａ－３

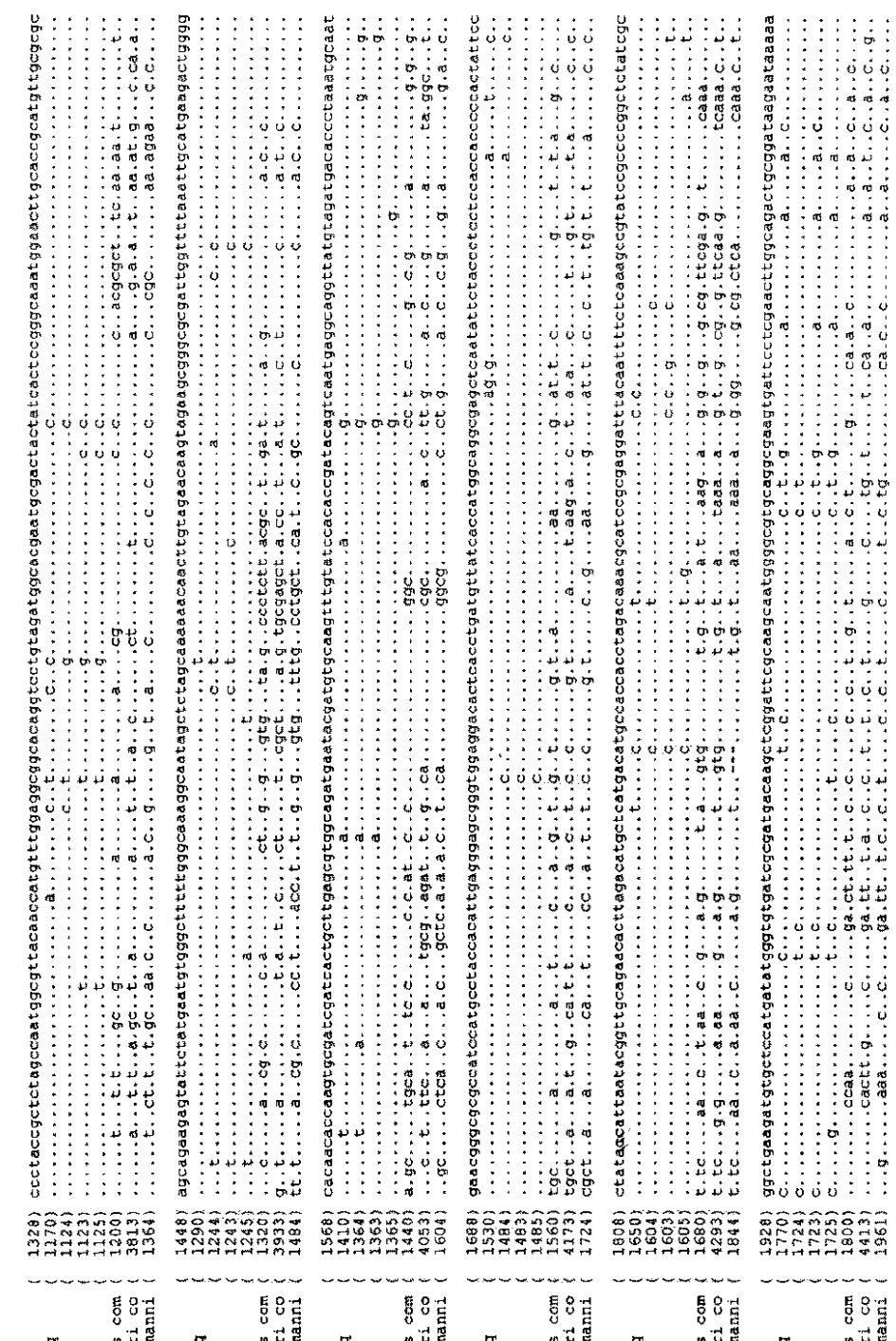

Figure 1a (3)

Ｆｉｇ．１ａ－４

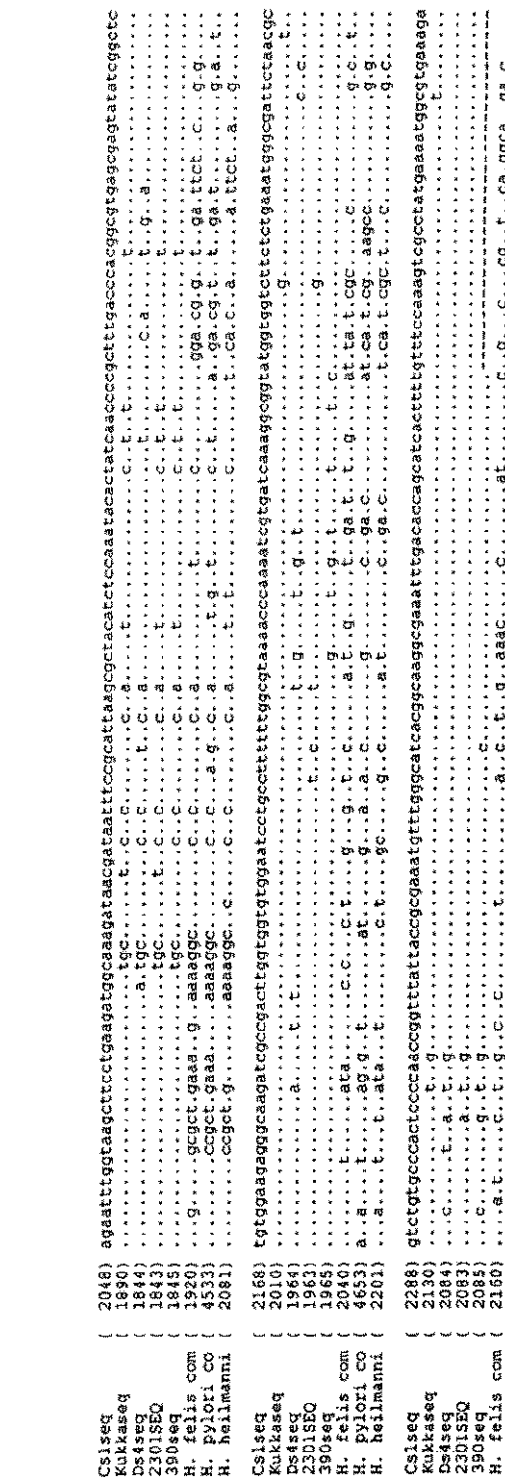

Figure 1a (4)

Ｆｉｇ．１ｂ

```
11/15/99          ALIGNED SEQUENCES

Reference molecule:  ureXCS1          1 -  226  (  226 aa)  Homology

     Sequence  2:  ureXkuka           1 -  226  (  226 aa)     100%
     Sequence  3:  ureXDS4            1 -  226  (  226 aa)      99%
     Sequence  4:  urex2301           1 -  226  (  226 aa)      99%
     Sequence  5:  urex390            1 -  226  (  226 aa)      99%
     Sequence  6:  A felis            1 -  237  (  237 aa)      50%
     Sequence  7:  A pylori           1 -  238  (  238 aa)      52%
     Sequence  8:  A heilman          1 -  234  (  234 aa)      54%

Alignment type:  Global Protein
Parameters:      Mismatch 2;  Open Gap 4;  Extend Gap 1;  Conserv N

ureXCS1          (    1) vklqpkeqekflyyageavarkrkaeglklnqpeaiayisahimdearrgkktvaqimeecmhflkkdevmpgvgnmvpdigveatfpdgtklvtvnwpiepdehfkagevkfgcdkdie
ureXkuka         (    1) ....................................e.....................................................................................
ureXDS4          (    1) ....................................e.....................................................................................
urex2301         (    1) ?...................................e.....................................................................................
urex390          (    1) ....................................e.....................................................................................
A felis          (    1) m.....ld.lm.h...rl.eeal.r.v...yt..v.l..grv.ek..d.n.s..d..q.grtl..p.d..d..as.ihev.i..m.....ht...angklvp..-l.lkne.t
A pylori         (    1) m.....ld.lm.h....l.k...ek.i...yv..v.l.....e...a....a.e..q.grtl..p.d..d..as.ihev.i..m.....ht...angklvp..-l.lkne.t
A heilman        (    1) m.....ld.lm.h....l.kq...k.i...yt..v.l....v.e...a....s..d..q.grtl..a.d.....ah.ihev.i..g.....iht.v.agsdkl.pgevilkne..t

ureXCS1          (  121) lnagkevtelevtnegpkslhvgshfhffeankalkfdrekaygkridipsgntlriqaqqtrkvqliplggskkvigmnglvmniaderhkhkaldkakshgfi----------k
ureXkuka         (  121) ..........................................................................e.....----------
ureXDS4          (  121) ..........................................................................e.....----------
urex2301         (  121) ..........................t.....................................................----------
urex390          (  120) i...s.ais.k.k.k.drpvq.....v..l.d...a.sfc.....a..tav.fep.eeks.e..di..n.riy.f.s..drq..adg.klg.kr..ek..gsvncgcatkdk-g
A felis          (  120) i.e..kavsvk.k.v.drpvqi.....v.rc.d.....tf.....a..tav.fep.eeks.e..di..nrrif.f.a..drq..nes.ki..hr..er..hgaksddnyvktike
A pylori         (  121) .....havq.k.k.k.drpvq.....v..l.d.....a..tav.fep.eekt.e..di..n.riy.f.a..drq..hdg.kl..kr..ekh.gtincgcdn-----.
A heilman        (  121) ..........................................................................e.....----------
```

Figure 1b

ALIGNED SEQUENCES

Reference molecule:	ureYCS1	1 -	568	(568 aa)	Homology	
Sequence 2:	ureYkuka	1 -	568	(568 aa)	99%	
Sequence 3:	ureYDS4	1 -	568	(568 aa)	98%	
Sequence 4:	ureY2301	1 -	568	(568 aa)	99%	
Sequence 5:	ureY390	1 -	496	(496 aa)	86%	
Sequence 6:	B felis	1 -	569	(569 aa)	73%	
Sequence 7:	B pylori	1 -	569	(569 aa)	73%	
Sequence 8:	B heilman	1 -	568	(568 aa)	74%	

Alignment type: Global Protein
Parameters: Mismatch 2; Open Gap 4; Extend Gap 1; Conserv N

```
ureYCS1      (    1) mkmkkq-eyvntygptkgdkvrlgdtdlwaevehdyttygeelkfgagktiregmgqsnspdentldlvitnamiidytgiykadigikngkihgigkagnkdmqdgvsphmvvgvgtea
ureYkuka     (    1) ......-.........t.....................................................................................................
ureYDS4      (    1) ......-.........t.....................................................................................................
ureY2301     (    1) ......-.........t.....................................................................................................
ureY390      (    1) ......-.........t.....................................................................................................
B felis      (    1) ..kisrk...sm....t..r.......il....c.....i...g.....d..s.t...ssye....l...l.v.............d...a.............dnnlc..pa...
B pylori     (    1) ..kisrk...sm....t..........i.......i.......g...l....s...n.skee...i....l.v.............d...a....g.........knnls..pa...
B heilman    (    1) ..kisrk...sm....t..........il....c.....i...g.....d....t...sshe.........l.v.....................l.....cnrlc..pa...

ureYCS1      (  120) lagegmiitaggidshthflspqqfptalangvttmfgggtgpvdgtnattitpgkwnlhrmlraaeeysmnvgflgkgnssskkqlveqveagaigfklhedwgttpsaidhclsvade
ureYkuka     (  120) ....................................................................................................i.....................
ureYDS4      (  120) ....................................................................................................i.....................
ureY2301     (  120) ....................................................................................................i.....................
ureY390      (  120) ....................................................................................................i.....................
B felis      (  121) ..a..l.v.....t.i..i....i...f.s.....i.....a..........ra..ks.........a..l...a...v.yeps.rd.i.........i.....s..a..h...n....
B pylori     (  121) ....l.v.....t.i..i....i...f.s.....i.....a..........rr..kw..........l...a...a.ndas.ad.i.........i...........n.a.d...k
B heilman    (  121) ..a..l.v.....t.i..i....i...f.s.i...i.....a..........r...ke....s...a..l.y.....v.fepa.id.l.........i.....s.....n.a.ni..k

ureYCS1      (  240) ydvqvcihtdtvneagyvddtlnamngraihayhiegagggghspdvitmagelnilpssttptipytintvaehldmlmtchhldkriredlqfsqsrirpgsiaaedvlhdmgviamts
ureYkuka     (  240) ..........................................v.....................................................i.....................
ureYDS4      (  240) ....................................................................................................i.....................
ureY2301     (  240) ....................................................................................................i.....................
ureY390      (  240) ....................................................................................................i.....................
B felis      (  241) ..a..a.....l....c.e...e.ia..t..tf.t.......a....k....f....a..n....f.k..e...m....v......s.k..v..ad.....qt.....q.....ifsi..
B pylori     (  241) ....a.....l....c.e..ma.ia..tm.tf.t.......a..i.kv...h....a..n....f.v..e...m....v......s.k..v..ad.....qt.....t.....ifsi..
B heilman    (  241) ....a.....l....c.e...e.ia..t..tf.t.......a....k....f....a..n....f.k..e...m....-......n.k..ve.ad.....qt.....k.....ifsi..

ureYCS1      (  360) sdsqamgrageviprtwqtadknkkefgklpedgkdndnfrikryiskytinpalthgvseyigsveegkiadlvvwnpaffgvkpkivikggmvvfsemgdsnasvptpqpvyyremfg
ureYkuka     (  360) ..................................a.....................................................................................
ureYDS4      (  360) ..................................sa....................................................................................
ureY2301     (  360) ..................................a.....................................................................................
ureY390      (  360) ..................................a.....................................................................................
B felis      (  361) ........v....t.............r.k.ekg.....................gia..i.d.v....v..y....l.s.....i..nmi....fial.q...a...i.............
B pylori     (  361) ........v....t.............r.k.ekg.....l.....ia..i...v....v..v....l.s.....nmi....fial.q...a...i.............a
B heilman    (  360) ........v....t.............r...ekg.....................i...i...v....v..y....l.s.....i..nmi....fial.q...a...i.............
```

Figure 1c (1)

Ｆｉｇ．１ｃ－２

```
ureYCS1     (  480) hhgkakfdtsitfvskvayengvkekiglerqvlpvkncrnitkkdfkfndktakitvdpktfevfvdgklctskptsqvplaqrytff
ureYkuka    (  480) ..........................k.....................................................e..........
ureYDS4     (  480) ..........................k.....................n...h.....................a.e..........
ureY2301    (  480) ..........................k.....................n...h.....................a.e..........
ureY390     (  480) ..........._______________________________________________________________________rvss
B felis     (  481) ....n....n......qa..ka.i..e...d.aap.....................l....v..h.d.n.e.yk.k....ev...aadels....i.nl.
B pylori    (  481) .......y.an.....qa..dk.i..e.....................mq...t..h.e.n.e.yh.....ev...ank.s....lfsi.
B heilman   (  480) .........n......q.....i.he...q.v.....................l....v..h.e.n.e.yk.k...nev..haadkls....l.nl.
```

Figure 1c (2)

Ｆｉｇ．２

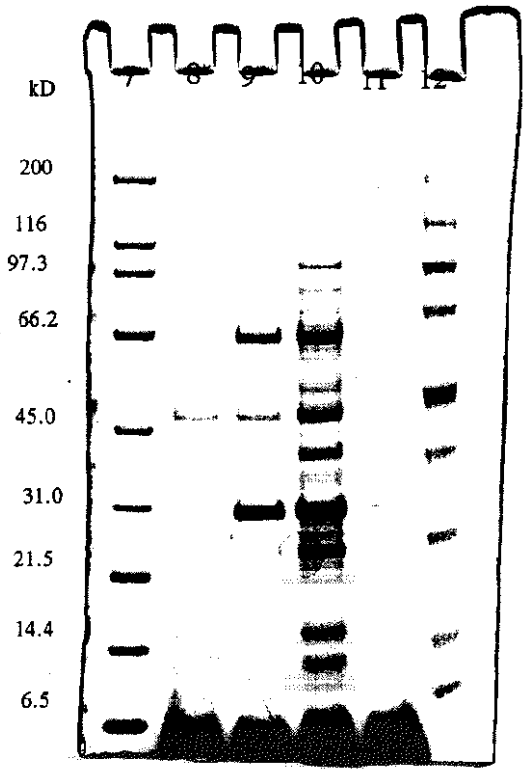

Figure 2

1．Ａｂｓｔｒａｃｔ

The present invention relates to novel *Helicobacter felis* urease subunit polypeptides and to nucleic acid sequences encoding these subunit polypeptides, to DNA fragments and recombinant DNA molecules comprising the nucleic acid sequences encoding these subunit polypeptides, to live recombinant carriers and to host cells comprising nucleic acid sequences encoding these subunit polypeptides. Also, the invention relates to the subunit polypeptides for úse in vaccines and the use in the manufacturing thereof, to vaccines comprising said subunit polypeptides and to methods for the preparation of such vaccines. Furthermore, the invention relates to diagnostic methods for the detection of *Helicobacter felis* specific nucleic acid sequences, *Helicobacter felis* antigenic material and to antibodies against *Helicobacter felis*.

专利名称(译)	Helicobacter felis疫苗		
公开(公告)号	JP2002355054A	公开(公告)日	2002-12-10
申请号	JP2001214711	申请日	2001-07-16
[标]申请(专利权)人(译)	阿克佐诺贝尔公司		
申请(专利权)人(译)	阿克苏诺贝尔的基础		
[标]发明人	ヨハネスヘラルドウスクステルス ジヨバンニカツトリ		
发明人	ヨハネス·ヘラルドウス·クステルス ジヨバンニ·カツトリ		
IPC分类号	G01N33/50 A61K38/00 A61K39/00 A61K39/106 A61K39/118 A61K39/12 A61K39/175 A61K39/23 A61K39/235 A61K39/39 A61K39/395 A61P1/04 A61P31/04 C07K14/205 C12N1/15 C12N1/19 C12N1/21 C12N5/10 C12N9/80 C12N15/09 C12Q1/68 C12R1/01 G01N33/15 G01N33/53 G01N33/566 G01N33/569		
CPC分类号	A61K39/00 A61P1/04 A61P9/10 A61P31/04 C07K14/205 C12N9/80		
FI分类号	A61K39/106 A61K39/118 A61K39/12 A61K39/175 A61K39/23 A61K39/235 A61K39/39 A61K39/395.D A61P1/04 A61P31/04 C12N1/15 C12N1/19 C12N1/21 C12N9/80.Z C12Q1/68.A G01N33/15.Z G01N33/50.Z G01N33/53.D G01N33/53.M G01N33/566 G01N33/569.B C12R1/01 C12N15/00.ZNA.A C12N5/00.A A61K37/02 A61K38/00 A61K38/16 C12N15/00.A C12N15/00.AZN.A C12N5/00.101 C12N5/10		
F-TERM分类号	2G045/AA40 2G045/BA11 2G045/BB50 2G045/DA12 2G045/DA13 2G045/DA36 2G045/FB02 4B024/AA01 4B024/AA13 4B024/BA14 4B024/BA31 4B024/CA04 4B024/DA02 4B024/DA05 4B024/DA12 4B024/EA04 4B024/FA02 4B024/GA11 4B024/HA12 4B024/HA15 4B050/CC03 4B050/DD02 4B050/LL01 4B050/LL03 4B063/QA19 4B063/QQ44 4B063/QR08 4B063/QR42 4B063/QR56 4B063/QS25 4B063/QS34 4B063/QX02 4B065/AA01X 4B065/AA01Y 4B065/AA26X 4B065/AA57X 4B065/AA72X 4B065/AA90X 4B065/AB01 4B065/BA02 4B065/CA31 4B065/CA43 4B065/CA46 4C084/AA02 4C084/AA07 4C084/BA19 4C084/CA04 4C084/DC50 4C084/NA14 4C084/ZA68 4C084/ZB35 4C085/AA03 4C085/AA13 4C085/AA38 4C085/BA20 4C085/BA45 4C085/BA51 4C085/BA75 4C085/BA77 4C085/CC07 4C085/CC08 4C085/DD86 4C085/EE01 4C085/EE03 4C085/EE06		
优先权	2000202565 2000-07-17 EP		
外部链接	Espacenet		

摘要(译)

要解决的问题：提供编码源自猫Helicobacter felis的抗原多肽的多核苷酸，并提供针对幽门螺杆菌的疫苗及其感染的诊断。解决方案：一种新型的幽门螺杆菌尿素酶亚基多肽;编码这些亚基多肽的核酸序列;编码这些亚基多肽的DNA片段和重组DNA分子;重组活菌载体和宿主细胞包括编码多肽的核酸序列。本发明还涉及用于疫苗的亚基多肽，其在其生产中的用途，包含亚基多肽的疫苗和制备这种疫苗的方法。

6

参照分子:H.フェリス ureX CS1	アミノ酸	核酸
H.フェリス ureA	50%	57%
H.ピロリ ureA	52%	60%
H.ヘイルマンニ ureA	54%	62%
H.フェリス Kukka 株 ureX	100%	91%
H.フェリス Ds4 株 ureX	99%	91%
H.フェリス 2301 株 ureX	99%	91%
H.フェリス 390 株 ureX	99%	91%