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(54) Title: TOOLS FOR DETECTING MORAXELLA CATARRHALIS.

(57) Abstract: The present invention provides compositions and methods useful for detecting Moraxella catarrhalis. The compositions are antibodies, proteins or nucleic acid sequences specific to Moraxella catarrhalis (M. catarrhalis). The method comprises the steps of obtaining a biological sample from an individual and detecting within the biological sample the presence of proteins, nucleic acid sequences and lipooligosaccharides (LOS) specific to Moraxella catarrhalis. Further, compositions and methods useful for distinguishing between M. catarrhalis serotypes are provided.

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TOOLS FOR DETECTING MORAXELLA CATARRHALIS

This application claims the priority of U.S. Provisional Application serial no. 60/470,022, filed on May 13, 2003, the disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates generally to the area of Moraxella catarrhalis infections and more particularly provides tools for specifically detecting Moraxella catarrhalis.

BACKGROUND OF THE INVENTION

Moraxella catarrhalis is a Gram-negative diplococcus that primarily infects young children where it is a major cause of bacteria-induced acute otitis media (AOM). Older adults with underlying lung disease such as chronic obstructive pulmonary disease (COPD) are also frequently affected. More than 3.5 million cases of AOM are recorded every year in the United States, and it is estimated that 80% of children have experienced at least one episode of otitis before reaching the age of 3 (Klein, J O (1994) Clin.Inf.Dis 19:823). Left untreated the disease may lead to hearing loss. Most cases of AOM are caused by one of three major pathogens, Streptococcus pneumoniae (S. pneumoniae) (30-40%), non-typeable Haemophilus influenzae (NTHi) (30%) and Moraxella catarrhalis (M. catarrhalis) (20%).

The treatment of the estimated 24 million cases of childhood AOM that occur each year in the United States is the single most prominent reason for prescribing antibiotics (Teele, et al 2001. Vaccine 19:S140-S143). In the past three decades, there has been a dramatic worldwide increase in antibiotic resistance in AOM pathogens which has resulted in a reduction of the number of effective antibiotics for this disease and has begun to pose a major public health threat. Accordingly, there is a need for reliable and rapid methods for identifying Moraxella catarrhalis infections in AOM. Further, there is a need for reliable and rapid methods by which Moraxella catarrhalis can be distinguished from other strains of Moraxella and other infectious organisms known to cause AOM., as M. catarrhalis induced AOM can not be diagnosed based on symptomology alone unlike other AOM pathogens.

SUMMARY OF THE INVENTION

The present invention provides compositions and methods useful for detecting Moraxella catarrhalis. The compositions are antibodies, proteins or nucleic acid sequences specific to Moraxella catarrhalis (M. catarrhalis).

The method comprises the steps of obtaining a biological sample from an individual and detecting within the biological sample the presence of proteins, nucleic acid sequences and lipooligosaccharides (LOS) specific to Moraxella catarrhalis. Further, compositions and methods useful for distinguishing between M. catarrhalis serotypes are provided.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1A and 1B are representations of an SDS PAGE gel and Western blot of the gel, respectively. Fig. 1B demonstrates reactivity of a monoclonal antibody (MAb) to all three M. catarrhalis serotypes. The lanes are:, a-25238 serotype A, b-CCUG 3292 serotype B, c-RS-10 serotype C, d-RS-26 serotype C, e-7169 (strain "B" from Buffalo (child), f-7431 isolate from Ohio (child), g-sk633 isolate from Buffalo (adult), h-O35E isolate from Houston (child), i-Tal 1 isolate from Philadelphia (adult), j-7482 isolate from Japan (child), k-7418 isolate from France (adult), l-7512 isolate from Belgium (child).

Figure 1B demonstrates that MAb 4G5 reacts all three the M. catarrhalis LOS A, B and C serotypes.

Figure 2 is a representation of a Western blot probed with a MAb that recognizes the LOS B serotype of M. catarrhalis. The antibody with which the Western was probed is Mab 3F7. Lane 1 demonstrates a lack of reactivity between MAb 3F7 and strain 25238 (serotype A). Lane 2 demonstrates MAb 3F7 reacting with strain CCUG3292 (serotype B). Lane 3 demonstrates MAb 3F7 reacting with strain 7169 (serotype B), and lane 4 demonstrates a lack of reactivity between MAb 3F7 and strain RS-10 (serotype C).

Figure 3A is a representation of an SDS PAGE analysis of whole cell lysates from a series of M. catarrhalis clinical isolates from various geographical locations.

Figure 3B is a Western blot of the gel depicted in Fig. 3A probed with a MAb specific to an external M. catarrhalis protein termed Mhua. The MAb with which the Western was probed is MAb 3F5-E5.

Figure 4A is a representation of an SDS PAGE analysis of outer membrane preparations from Moraxella catarrhalis strains 7169 (lanes 1, 3 and 5) and 7169::*mhuA* (lanes 2, 4, and 6) in which the mhuA gene is deleted.

Figure 4B is a representation of a Western blot performed on the SDS PAGE gel depicted in Fig. 4A using MAb 3F5-5E5 (an IgG2a) demonstrating the loss of the 107 KDa MhuA protein band in strain 7169::*mhu.*

Figure 5 is a representation of a Western blot of whole cell lysates from a series of M. catarrhalis clinical isolates from various geographical locations probed with a MAb specific to a M. catarrhalis internal protein termed Mcp67. The MAb with which the Western was probed is MAb 7C9 (an IgM). The strains shown are 7169, sk633, BC40 (Buffalo); Tal1 (Philadelphia); 7477 (Japan); 7512 (Belgium); 8063 (Germany); 10016 (Brazil); 10099 (Finland); 10113 (USA).

Figure 6 is a representation of an agarose gel showing PCR products amplified from chromosomal DNA isolated from M. catarrhalis strains. The PCR products in each lane were amplified using the primers 406/408. Lane 1 is a size ladder. Lane 2 is amplification of genomic DNA from strain 7169 and the resulting product is 3.3 Kb. Lane 3 is the negative control (no DNA in PCR reaction). Lanes 4, 5, 7, 8, 9, 11,12 and 13 contain an approximate 4.3 Kb are each serotype A or C. A 3.3 Kb band in lane 6 size was obtained by analyzing the only previously reported LOS serotype B strain, M. catarrhalis CCUG 3292, demonstrating strain 7169 as shown in Lane 2 is also serotype B. Lanes 6, 10 and 14 are other Moraxella isolates that were determined to be serotype B.

Figure 7 is a graphical representation of a PCR based scheme by which all three serotypes of M. catarrhalis can be distinguished from each other.

Figure 8 is a graphical representation of PCR primers and targets within the M. catarrhalis putative glycosyltransferase (pgt) gene cluster.

Fig. 9A is a graphical depiction of PCR amplifications of genomic DNA from various M. catarrhalis strains. The PCR amplifications in Figs. 9A and 9B were carried out with primers SEQ ID NO:3 and SEQ ID NO:4.

Fig. 9B is a graphical depiction of PCR amplifications of genomic DNA from M. catarrhalis in lane 1 and various other non M. catarrhalis organisms in the remaining lanes as indicated.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compositions and methods useful for detecting Moraxella catarrhalis. The compositions provided are antibodies, proteins or nucleic acid sequences unique to M. catarrhalis.

The method comprises the steps of obtaining a biological sample from an individual and detecting in the biological sample the presence of proteins, nucleic acid sequences, lipooligosaccharides (LOS) or antigens specific to Moraxella catarrhalis. The compositions and methods provided are therefore useful not only for detecting M. catarrhalis in a biological sample, but also for distinguishing M. catarrhalis from other organisms which may be present in the sample, and for further distinguishing between M. catarrhalis serotypes as will be described more fully below.

Biological Samples

A "biological sample" as used herein refers to a sample, such as tissue or fluid obtained from an individual, including without limitation urine, plasma, serum, lymph, tears, saliva, sputum, mucous, mucosal swabs, inner ear swabs and tissue sections.

Methods for obtaining biological samples are well known to those skilled in the art. For example, suitable biological samples can be obtained by swabbing mucosal surfaces such as the nasal cavity, oropharynx or throat area, inner ear swabs, sputum samples urine, blood and/or plasma samples using well known collection techniques.

Immunoassays

Once the biological sample is obtained, it can be prepared for immunological detection of M. catarrhalis by a wide variety of immunoassays using the MAbs of the

present invention which are specific for Moraxella catarrhalis. By describing proteins, nucleic acid sequences lipooligosaccharides and antigens (LOS) as "specific to Moraxella catarrhalis" it is meant that the particular feature so described is unique to Moraxella catarrhalis and is not found in other tested organisms.

Procedures for preparing biological samples for and performing Westerns blots, enzyme-linked immunosorbent assays (ELISA), radioimmunoassays (RIAs), capture assays and non-enzyme linked antibody binding assays are all well known.

In one embodiment, Western blots are performed with the MAbs of the present invention by separating whole cell lysates or outer membrane proteins by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), after which the proteins are transferred to a suitable substrate such as nitrocellulose membrane by application of an electric field in a transfer buffer. The substrate is then incubated with a blocking buffer which allows for blocking of nonspecific adsorption sites on the immobilizing substrate and thus reduces the background caused by non-specific binding of antibodies onto the surface. The blot is then incubated with a primary antibody to induce specific immunocomplex formation and washed in a suitable washing buffer. The primary antibody may be one or a combination of the MAbs provided herein. The occurrence and amount of immunocomplex formation may be determined by subjecting the immunocomplex to a secondary antibody having specificity for the primary antibody. To provide means for detection, the second antibody may have an associated activity such as an enzymatic activity that will generate, for example, a color development upon incubating with an appropriate chromogenic substrate. Quantification may then be achieved by measuring the degree of color generation using any suitable means, such as a spectrophotometer.

In another embodiment, the MAbs of the present invention are used in ELISA assays to detect M. catarrhalis from a biological sample. In general, such an ELISA assay (Coligan et al., Current Protocols in Immunology 1(2), Chapter 6, (1991)) initially comprises providing an antibody specific to an M. catarrhalis antigen, preferably a monoclonal antibody. In addition, a secondary antibody is prepared against the monoclonal antibody. To the secondary antibody is attached a detectable reagent such as radioactivity, fluorescence or colorimetric reagent such as horseradish peroxidase enzyme. The biological sample is prepared using standard techniques and

incubated on a solid support, e.g. a polystyrene dish, which binds the proteins in the sample. Any free protein binding sites on the dish are then covered by incubating with a non-specific protein, such as, bovine serum albumen.

Next, the monoclonal antibody is incubated in the dish during which time the monoclonal antibodies attach to any M. catarrhalis proteins attached to the polystyrene dish. All unbound monoclonal antibody is washed out with buffer. The secondary antibody linked to the detectable reagent is placed in the dish resulting in binding of the secondary antibody to any monoclonal antibody bound to M. catarrhalis proteins. Unattached secondary antibody is then washed out and any necessary reagents are then added to the dish and the amount of detectable reagent developed in a given time period is a measurement of the amount of M. catarrhalis protein present.

In another embodiment, the MAbs of the invention may be used in an immunochromatographic ("ICT") strip assay. A class of devices known as ICT devices uses immunoassay techniques in combination with a label that is conjugated with an antibody. Such devices are now commonly used for rapid, reliable field tests to determine the presence or absence of a particular analyte. The label, when attached to antibody/antigen molecules that are then amassed together in a specific, restricted area, becomes readily detectable by the naked human eye, or by a scanning device, depending on the type of label used. In general, the label can be a particle of latex, gold, or carbon, a radioactive particle, a magnetic particle, or have other physical or chemical properties that allow it to be fixed or attracted to a certain defined area. ICT devices that use the sandwich technique are particularly easy to use. With this technique, labeled antibody that binds with the specific antigen to be assayed is mixed with the sample that is suspected of containing the specific antigen. If the antigen is present in the sample, the labeled antibody binds with the antigen to form a label-antibody-antigen complex. A second antibody that is immovably fixed at a test zone and that also binds with the specific antigen binds the label-antibody-antigen complex at the test zone. A positive result is made visible by the accumulation of the label at the test zone. Such devices are economical and can be used by unskilled workers. Thus, a method that uses such an ICT device to determine, in a single assay, the presence or absence of multiple enteric pathogens, in particular, multiple enteric

pathogens, plus a general marker for an inflammatory condition of the intestines would provide valuable diagnostic information to a treating physician.

Several types of such ICT devices are known. Most are the "dipstick" type in which a test strip is encased in a hollow housing with a bibulous pad extending from one end. This pad is dipped into the liquid sample and draws the liquid by capillary ("wicking") action up onto a section of the test strip that contains a labeled antibody, i.e., a label conjugated to an antibody that will specifically bind with the antigen being assayed. The labeled antibody moves with the liquid that is being drawn by the capillary action further along the test strip and, if the specific antigen to which the antibody binds is present in the liquid sample, the labeled antibody will bind with the antigen, forming a labeled antibody-antigen complex. This complex continues to flow with the liquid along the test strip. Downstream from the area containing the conjugated antibody is a test zone. This test zone is typically a nitrocellulose pad into which a second binding partner, an antibody that binds to the same antigen as the labeled antibody, but to a second epitope of the antigen, has been immovably fixed. The fixed antibody will attach to the labeled antibody-antigen complex that flows onto the test zone and will bind the complex to the test zone. The presence of an antigen being assayed is then visible as a stripe across the test zone or otherwise readily detectable. The excess liquid continues to flow past the test zone across a control zone. There are a number of well-known means in the field of immunoassay of creating a control zone, such as embedding into the control zone a binding partner that binds non-specifically to one or more of the labeled antibodies contained on the conjugate section, or to a labeled analyte added to the liquid sample for the purpose of binding with the non-specific binding partner at the control zone. A properly completed test will always show a visible stripe across the control zone or, if a radioisotope or magnetic particle is used as a label, an otherwise readily detectable stripe. Typically, for those devices using a colored label, the housing of the ICT device has a window through which to view the test zone and the control zone. Devices of this type have been disclosed in May et al. (U.S. Pat. No. 5,622,871; issued Apr. 22, 1997) and Charlton et al. (U.S. Pat. No. 5,714,389; issued Feb. 3, 1998).

Further, U.S. Pat. No. 5,869,345, 5,877,028, and 6,727,073 disclose ICT

devices that are two-panel cards containing a test strip on one panel and a sample well on the other panel. These devices uses the sandwich technique described above with the dipstick devices, but have a particular advantage in that they allow the sample to be prepared for the test directly on the test card, rather than in a separate vessel. When the test card is closed, liquid from the sample well flows onto the test strip. As with the other devices, a window is provided through which to view the results.

Antibodies and Proteins

In various embodiments, the present invention provides antibodies that can bind surface and/or internal antigens specific to M. catarrhalis and are useful for detecting M. catarrhalis in the immunoassays as described above and as otherwise known in the art.

In one embodiment the present invention provides monoclonal antibodies (MAbs) to M. LOS antigens, which are the predominant, surface-exposed component of the M. catarrhalis outer membrane and have been implicated as a virulence factor in the pathogenesis of M. catarrhalis infections.

Three LOS serotypes (A, B and C) have been identified on the basis of structural and immunologic analyses of the LOS terminal oligosaccharide branch extensions. The A and B LOS serotypes of M. catarrhalis account for over 90%-95% of all M. catarrhalis isolates, and approximately 30% of isolates are serotype B.

In one embodiment of the invention, a MAb that can detect all three LOS serotypes is provided. In another embodiment, a MAb that is specific for a particular serotype is provided. For example, can discriminate the B serotype of M. catarrhalis is provided.

While providing MAbs to LOS antigens is useful for detection of M. catarrhalis, the present invention contemplates the use of combinations of antibodies to provide more complete detection of M. catarrhalis present in a biological sample. Accordingly, in yet another embodiment, the invention provides a novel MAb and novel M. catarrhalis surface protein to which the MAb is directed.

Further, detection of surface antigens may be combined with detection of internal antigens to improve detection of M. catarrhalis in a biological sample. The

present invention therefore provides in another embodiment a novel MAb and novel internal M. catarrhalis internal protein to which the MAb is directed to.

Nucleic Acids

Biological samples can be prepared for detection of unique M. catarrhalis nucleic acids by a wide variety of well known techniques. For example, genomic DNA can be isolated from a biological sample using any suitable technique such as by various kits and reagents for isolation of genomic DNA which are available commercially, for example, those provided by Qiagen (Valencia, Calif.). Alternatively, genomic DNA can be isolated by standard alkaline lysis procedures followed by equilibrium ultracentrifugation in cesium chloride gradients or ethanol precipitation.

The nucleic acid molecules of the invention can be used to detect M. catarrhalis using various techniques such as PCR amplification or hybridization technologies such as Northern blotting or microarrays.

In one embodiment, DNA isolated from a biological sample is analyzed using PCR to detect the presence of M. catarrhalis DNA. PCR reactions can be carried out according to methods well known to those skilled in the art. For examples of suitable PCR protocols see Sambrook et al, "Molecular Cloning: A Laboratory Manual" Cold Spring Harbor Laboratory Press; 3rd edition (2001). Briefly, PCR is performed by subjecting isolated nucleic acids the following steps: denaturation of the nucleic acids, annealing primers to the nucleic acids, extension of the primers with polymerase, and repeating the cycle for as many repetitions as desired, with a typical number of cycles being about thirty.

Accordingly, in one embodiment, the invention provides nucleic acid sequences, the detection of which definitively indicates the presence of M. catarrhalis in a biological sample.

In another embodiment, sets of PCR primers that are useful for detecting M. catarrhalis in biological samples are provided. Further, the invention provides sets of primers that can be used to determine the specific LOS serotype of M. catarrhalis in a biological sample.

The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific Examples. These Examples are described solely for purposes of illustration and are not intended to limit the scope of the invention. Changes in form and substitution of equivalents are contemplated as circumstances may suggest or render expedient. Although specific terms have been employed herein, such terms are intended in a descriptive sense and not for purposes of limitations.

EXAMPLE 1

This Example demonstrates a MAb that can recognize all three LOS serotypes of M. catarrhalis.

MAb 4G5 was developed by immunizing BALB/c mice using well known methods with iron-stressed whole bacteria of M. catarrhalis strain 25240. A fusion was performed after 28 days in which splenocytes from the immunized animals were fused to mouse myeloma cells. The resulting hybridomas were screened for the production of antibody by immunodot assay versus iron-stressed and iron-replete whole bacteria. All clones that were positive for the production of MAb to the crude antigen preparations were further tested in Western blots versus iron-stressed and iron-replete whole bacteria and subsequently against outer membrane proteins. This identified the target molecule as LOS for Mab 4G5.

Figure 1A and 1B are representations of an SDS PAGE gel and Western blot of the gel, respectively. Fig. 1B demonstrates reactivity of a monoclonal antibody (MAb) to all three M. catarrhalis serotypes. The lanes are:, a-25238 serotype A, b-CCUG 3292 serotype B, c-RS-10 serotype C, d-RS-26 serotype C, e-7169 (strain "B" from Buffalo (child), f-7431 isolate from Ohio (child), g-sk633 isolate from Buffalo (adult), h-O35E isolate from Houston (child), i-Tal 1 isolate from Philadelphia (adult), j-7482 isolate from Japan (child), k-7418 isolate from France (adult), l-7512 isolate from Belgium (child).

These data demonstrate that MAb 4G5 recognizes LOS conserved on a diversity of clinical isolates from different geographic regions, from both adults and children, and that MAb 4G5 recognizes the M. catarrhalis LOS A, B and C serotypes.

Further, additional Western blots assays with MAb 4G5 using proteinase K lysates from 8 strains of H. influenzae, 11 strains of N. meningitidis, 12 strains of N. gonorrhoeae, 2 strains of Neisseria lactamica, and 2 strains of Neisseria cinerea were performed, and none reacted with MAb 4G5. (Data not shown).

Thus, these data indicate that MAb 4G5 is specific for the LOS that is found on all three M. catarrhalis LOS serotypes. Further, these data demonstrate that MAb 4G5 distinguishes M. catarrhalis from pathogenic organisms that are found commensally with human biological mucus samples.

EXAMPLE 2

This Example demonstrates a MAb that can discriminate one of the three LOS serotypes.

MAb 3F7 (an IgM) is specific for M. catarrhalis LOS serotype B. Monoclonal antibodies 3F7 was developed essentially as described in Example 1 by immunizing mice with iron-stressed outer membranes proteins from M. catarrhalis strain 7169. Once reactivity was identified, further testing in Western blot versus iron-stressed and iron-replete whole bacteria was performed and subsequently outer membrane proteins which identified LOS B as the molecule targeted by Mab 3F7, as can be seen in Fig. 2.

Figure 2 is a representation of a Western blot probed with a MAb that recognizes the LOS B serotype of M. catarrhalis. The antibody with which the Western was probed is Mab 3F7. Lane 1 demonstrates a lack of reactivity between MAb 3F7 and strain 25238 (serotype A). Lane 2 demonstrates MAb 3F7 reacting with strain CCUG3292 (serotype B). Lane 3 demonstrates MAb 3F7 reacting with strain 7169 (serotype B), and lane 4 demonstrates a lack of reactivity between MAb 3F7 and strain RS-10 (serotype C). Thus, MAb 3F7 recognizes only LOS B in lanes 2 and 3, and can therefore discriminate the LOS B serotype.

Further, MAb 3F7 was tested against non M. catarrhalis strains including 4 Nontypable Haemophilus influenzae, 3 Neisseria gonorrhoeae and 4 Neisseria meningitidis, all of which were negative for interaction with MAb 3F7 as confirmed by Western blotting.

These results therefore demonstrate that MAb 3F7 can discriminate the B LOS serotype of M. catarrhalis and is specific for M. catarrhalis versus other organisms.

EXAMPLE 3

This Example demonstrates a MAb specific for a novel surface protein unique to M. catarrhalis.

MAb 3F5-5E5 was developed as described in Example 1. MAb 3F5-5E5 is specific for the MhuA surface protein of M. catarrhalis. MhuA is a novel putative hemoglobin (Hb)-binding protein homologue gene, and that the gene represented by SEQ ID NO:1 encodes the Mhua protein represented by SEQ ID NO:2 is disclosed herein. The wild type MhuA gene encodes a 961 amino acid polypeptide with a predicted molecular weight of 107 KDa. The mhuA gene sequence is deposited with GenBank under accession no. AY574198.

In order to characterize MhuA as a M. catarrhalis protein, strain 7169, a middle-ear isolate from a child with otitis media was used to construct a MhuA deficient mutant termed 7169::*mhuA* which does not express the MhuA protein. 7169::*mhuA* was constructed using standard molecular cloning methods. Clinical isolates of M. catarrhalis were obtained from Mark Achtman (Max Planck Institute, Germany) or from laboratory stocks. Routine culture of M. catarrhalis at 35°C in 5% CO_2 on brain heart infusion (BHI) or GC agar plates or at 37°C with rotary shaking at 225 rpm in the appropriate liquid medium was performed. The mutant strain 7169::*mhuA* was cultured in the presence of 20 μg kanamycin per ml.

For Western blot analysis of MhuA, M. catarrhalis strains 7169 and 7169::*mhuA* were cultured in 250 ml CDM broth containing 10 μM desferal plus 5 μM Hb, 8 μM Hm, 100 μM $Fe(NO_3)_3$, or no exogenous Hb. After 16 h, cultures were harvested and outer membrane proteins (OMPs) were isolated by standard Zwittergent extraction. Proteins were analyzed by sodium dodecyl sulfate-7% polyacrylamide gel electrophoresis (SDS-7% PAGE). Western blot analyses described below with MAb 3F5 were performed using standard methods.

Figure 3A is a representation of an SDS PAGE analysis of whole cell lysates from a series of M. catarrhalis clinical isolates from various geographical locations, while Fig. 3B is the gel from Fig. 3A probed with MAb 3F5 in a Western blot. Figs.

3A and 3B therefore demonstrate that the 107 KDa MhuA protein is present in each M. catarrhalis strain tested.

In order to confirm that MhuA is an OMP, OMPs from wild-type 7169 and 7169::*mhuA* were prepared. Analysis of OMP profiles are depicted in the Western blot shown in Fig. 4B. Fig. 4A represents an SDS PAGE gel of proteins isolated from 7169 (lanes 1, 3 and 5) and 7169::*mhuA* (lanes 2, 4 and 6). Fig. 4B is a Western blot of the gel of Fig. 4A and demonstrates the loss of a 107 KDa band seen in lanes 2, 4, and 6 as expected for strain 7169::*mhuA* while MhuA is expressed in 7169 (Fig. 4B, lanes 1, 3, and 5).

In order to determine the level of conservation exhibited by MhuA, whole bacterial samples were prepared from a series of M. catarrhalis clinical isolates from various geographical locations and analyzed by Western blots probed with MAb 3F5. This data is summarized in Table 1 and demonstrates that all of the isolates express MhuA. Table 1 further demonstrates that related species of Gram-negative bacteria do not express MhuA .

In addition, many of the M. catarrhalis strains in Table 1 were reactive in colony lift assays, which are indicative of surface exposed epitopes. Lift assays are performed by streaking out bacteria for single colonies on a solid media, placing a sheet of nitrocellulose over the colonies, allowing the colonies to "stick" to the sheet, lifting the sheet off and analyzing the sheet as if it was a Western blot.

Table 1

Strain	Reactivity to MAb 3F5
M. catarrhalis 7169	+
M. catarrhalis 7169::*mhuA*	-
M. catarrhalis isolates:	
CCUG 3292 (LOS serotype B)	+
O35E (Houston, TX, LOS serotype A)	+
7544 (Ethiopia, LOS serotype A)	+
RS10 (LOS serotype C)	+
genome strain	+
7477 (Japan)	+
7680 (United Kingdom)	+
7530 (Belgium)	+
7608 (Australia)	+

25240 (ATCC)	+
340535 (Buffalo, NY)	+
CCUG 26391 (LOS serotype C)	+
CCUG 26404 (LOS serotype C)	+
M. lacunata	-
M. bovis	-
H. ducreyi	-
H. influenzae A2	-
N. gonorrhoeae PID2	-
N. gonorrhoeae F62	-
N. cinerea	-
K. pneumoniae	-
P. aeruginosa	-
P. aeruginosa PSN	-

Thus, the present Example demonstrates the heretofore undisclosed characterization of the MhuA gene and its expression as surface-exposed, conserved protein among M. catarrhalis strains that is recognized by MAb 3F5, which is capable of detecting the novel M. catarrhalis MhuA protein against a background of other common pathogens, some of which share a common niche and cause disease of the respiratory mucosa.

EXAMPLE 4

This Example demonstrates a MAb specific for a novel internal protein unique to M. catarrhalis.

MAb 7C9 is specific for the Mcp67 internal protein of M. catarrhalis. MAb 7C9 was developed as described essentially as described in Example 2. As represented by the Western blot depicted in Fig. 5 and the data summarized in Table 2, the Mcp67 protein is conserved in every strain of M. catarrhalis tested. By using monoclonal antibody 7C9 in Western blots performed according to standard procedures, the Mcp67 protein (approximately 67 kilodaltons) has been detected in over 50 strains of Moraxella from around the world.

As can also be seen from Table 2, more than 25 various other gram negative strains have also been analyzed for reactivity with MAb 7C9 and all were negative. (The PCR results presented in Table 2 were generated using primers 537 (SEQ ID NO:3) and 538 (SEQ ID NO:4) as described more fully in Example 7 below).

Table 2

Strain	Reactivity to Mab 7C9	PCR Product		
M. cat 7169	+	+	MEF, Child	Buffalo, NY
M. cat ATCC 25238		+		
M. cat ATCC 43617		+	Transtracheal aspirate, Adult	
M. cat CCUG 3292		+		
M. cat Rs10		+		
M. cat Tal 1	+	+	Sputum, Adult	Philadelphia, PA
M. cat BC40	+	+	Sputum, Adult	Buffalo, NY
M. cat sk633	+	+	Sputum, Adult	Buffalo, NY
M. cat 7431		+	Clinical Isolate	Columbus, OH
M. cat 7482		+	Clinical Isolate	Japan
M. cat 7418		+	Clinical Isolate	France
M. cat 7488		+	Clinical Isolate	Germany
M. cat 7535		+	Clinical Isolate	Seattle, WA
M. cat 7544		+	Clinical Isolate	Ethiopia
M. cat 7591		+	Clinical Isolate	Spain
M. cat 7966		+	Clinical Isolate	Australia
M. cat 10105		+	Clinical Isolate	Finland
M. cat 10182		+	Clinical Isolate	Netherlands
M. cat 7550		+	Clinical Isolate	Ethiopia
M. cat 8150		+	Clinical Isolate	Houston, TX
M. cat 7608		+	Clinical Isolate	Australia
M. cat 7458		+	Clinical Isolate	Sweden
M. cat 7587		+	Clinical Isolate	Spain
M. cat 7477	+	+	Clinical Isolate	Japan
M. cat 7315		+	Clinical Isolate	Germany
M. cat 7574		+	Clinical Isolate	ChathamHospital,NC
M. cat 7512	+	+	Clinical Isolate	Belgium
M. cat 7565		+	Clinical Isolate	Yugoslavia
M. cat 7480		+	Clinical Isolate	Japan
M. cat 7680	+	+	Clinical Isolate	England
M. cat 7984		+	Clinical Isolate	Australia
M. cat 8063	+	+	Clinical Isolate	Germany
M. cat 10016	+	+	Clinical Isolate	Brazil
M. cat 10059		+	Clinical Isolate	Angola
M. cat 10099	+	+	Clinical Isolate	Finland
M. cat 10113	+	+	Clinical Isolate	USA
M. cat 10188		+	Clinical Isolate	Netherlands
M. cat 10218		+	Clinical Isolate	Africa
M. cat pw640	+		Sputum, Adult	England
M. cat Af218	+		Sputum, Adult	England
M. cat M10	+		Sputum, Adult	Houston, TX
M. cat O35E	+		MEF, child	Houson, TX

Additional tests have confirmed that c protein is not present on the surface of the bacteria and the protein has no significant homology with any other protein in the current data base. Further, as can be seen from Table 3, MAb 7C9 does not react to any other bacterial strains tested.

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Table 3

Bacterial Strain	Reactivity to Mab 7C9	PCR Product
H. influenzae 1479	–	–
Non-typeable H. influenzae 2019	–	–
Non-typeable H. influenzae 3198	–	–
H. ducreyi R3	–	–
H. ducreyi CIP 542	–	–
H. ducreyi HP35000	–	–
Psn	–	–
Psc	–	–
N. gonorrhoeae F62	–	–
N. gonorrhoeae PID2	–	–
N. gonorrhoeae FA19	–	–
M. bovis	–	–
M. nonliquifaciens	–	–
M. lacunata	–	–
M. osloensis	–	–
M. caviae	–	–
P. aeruginosa	–	–
N. cinerea	–	–
K. pneumoniae	–	–
E. aerogenes	–	–
N. gonorrhoeae 1	–	–
N. gonorrhoeae 2	–	–
N. gonorrhoeae 3	–	–
N. gonorrhoeae 4	–	–
N. gonorrhoeae 5	–	–
N. gonorrhoeae 6	–	–
N. gonorrhoeae 7	–	–
N. gonorrhoeae 8	–	–
N. gonorrhoeae 9	–	–
N. gonorrhoeae 10	–	–
H. parainfluenzae 7P10	–	–
H. parainfluenzae 9P20	–	–
H. parainfluenzae 6P30	–	–

H. parainfluenzae 15P0	–	–
H. influenzae 7502	–	–
H. influenzae 4971	–	–
K. oxytoca	–	–
P. mirabilis	–	–
E. coli	–	–
M. cuniculi	–	–

Thus, this Example demonstrates a MAb that can detect a novel protein unique to M. catarrhalis. That nucleotide sequence represented by SEQ ID NO:5 encodes the Mcp67 protein represented by SEQ ID NO:6 is disclosed herein.

EXAMPLE 5

This Example demonstrates DNA sequences that are unique to M. catarrhalis. The Example further describes a method for using PCR analysis of the DNA sequences to distinguish M. catarrhalis from other organisms and to distinguish between the three M. catarrhalis LOS serotypes.

M. catarrhalis chromosomal DNA was prepared using standard methods. All standard molecular biology reagents, including T4 ligase and restriction endonucleases, were purchased from either Promega (Madison, Wis.) or New England Biolabs, Inc. (Beverly, Mass.) and were utilized according to standard protocols. PCR amplification analyses were performed using genomic *M. catarrhalis* 7169 DNA with Platinum *Taq* High Fidelity Polymerase (Invitrogen Life Technologies Corp., Carlsbad, Calif.). All PCR products and plasmid constructs were purified using the MinElute kit and the QIAprep spin kit, respectively (Qiagen). DNA sequencing was performed (RPCI Biopolymer Facility, Roswell Park Cancer Institute, Buffalo, NY) and analyzed with MacVector software (version 7.2; Genetics Computer Group, Madison, Wis.).

Novel PCR primers were designed to amplify previously undisclosed differences in putative glycosyltransferase (pgt) genes unique to M. catarrhalis strains. Accordingly, using standard PCR protocols, combinations of the primers disclosed herein can be used to amplify regions of clustered genes from M. catarrhalis in a manner such that all three serotypes A, B and C can be distinguished from one another, and M. catarrhalis can be distinguished from other organisms.

The PCR primers used in this Example are summarized in Table 4. A flow chart for performing the steps of this identification strategy is presented in Fig. 7. Further, the genomic organization of the Moraxella catarrhalis LOS serotype defining pgt genes is depicted in Fig. 8.

The LOS gene cluster from 25238 (type A) as shown in Fig. 8 is represented by SEQ ID NO:15. With respect to SEQ ID NO:15, primer 406 binds from position 1-22, primer 408 binds from position 4292-4310, primer 649 binds from position 2379-2399 and primer 650 binds from position 2605-2624. Primers 750/751 do not bind to SEQ ID NO:15.

The LOS gene cluster from strain 7169 (type B) as shown in Fig. 8 is represented by SEQ ID NO:16. With respect to SEQ ID NO:16, primer 406 binds from position 1-22, primer 408 binds from position 3295-3313. Primers 649/650 and 750/751 do not bind to SEQ ID NO:16

The LOS gene cluster from RS-10 (type C) as shown in Fig. 8 is represented by SEQ ID NO:17. With respect to SEQ ID NO:17, primer 406 binds from position 1-22, primer 408 binds from position 4306-4324, primer 750 binds from position 822-840, and primer 751 binds from position 2239-2258. Primers 649/650 do not bind to SEQ ID NO:17.

Table 4

Pr 406 (SEQ ID NO:7)	CAAAAGAAGACAAACAAGCAGC
Pr 408 (SEQ ID NO:8)	CCCATTTAGTATCAGAAGATGACAC
Pr 649 (SEQ ID NO:9)	ATCCTGCTCCAACTGACTTTC
Pr 650 (SEQ ID NO:10)	GGTAACAGAACGCTCAACCC
Pr 750 (SEQ ID NO:11)	CCAAGGGGCTGATTTGACA
Pr 751 (SEQ ID NO:12)	ACTATCAGTAACCAGGTTTT

In LOS serotypes A and C primers 406 and 408 amplify an approximately 4.3 kB product,while in serotype B primers 406 and 408 amplify an approximately 3.3 kB product. This is demonstrated in Fig. 6 which is a representation of an agarose gel showing PCR products amplified from chromosomal DNA isolated from M. catarrhalis strains. The PCR products in each lane were amplified using the

primers 406/408. Lane 1 is a size ladder. Lane 2 is amplification of genomic DNA from strain 7169 and the resulting product is 3.3 Kb. Lane 3 is the negative control (no DNA in PCR reaction). A 3.3 Kb band in lane 6 size was obtained by analyzing the only previously reported LOS serotype B strain, M. catarrhalis CCUG 3292, demonstrating strain 7169 is also serotype B. Lanes 4, 5, 7, 8, 9, 11,12 and 13 contain an approximate 4.3 Kb are each serotype A or C. Lanes 6, 10 and 14 are other Moraxella isolates that were determined to be serotype B.

Using primers 649 and 650 results in amplification of a 246 bp fragment from LOS serotype A and no amplification in serotypes B and C. Further, using primers 750 and 751 results in amplification of a 1.44 kB product in serotype C, but no amplification in serotypes A and B. These results are summarized in Table 5.

Table 5.

	Pr 406/408	**Pr 649/650**	**Pr 750/751**
Serotype A	4.3 kb	245 bp	N/A
Serotype B	3.3 kb	N/A*	N/A
Serotype C	4.3 kb	N/A	1.44 kb

Thus, by performing PCR reactions using combinations of the primers disclosed herein, one can distinguish all three serotypes A, B and C from one another.

Primers 406 and 408 were tested on genomic DNA isolated from Neisseria meningitidis 121, Neisseria gonorrhoeae, Haemophilus influenzae (7 strains), Haemophilus ducreyi CIP542, Haemophilus ducreyi 35000, Haemophilus parainfluenzae, Klebsiella pneumoniae, Enterobacter aerogenes, Escherichia coli CP9, Psuedomonas aeruginosa, and Proteus mirabilis.

Thus, this Example demonstrates the identification of novel DNA sequences that can be used to detect M. catarrhalis in a biological sample and to discriminate between M. catarrhalis LOS serotypes. Further, the present examples illustrates primers and a PCR scheme for definitive identification of each M. catarrhalis LOS serotype.

EXAMPLE 6

This Example demonstrates DNA sequences encoding a novel surface protein unique to M. catarrhalis and methods for the identification of the DNA sequences.

M. catarrhalis chromosomal DNA was prepared and PCR reactions carried out essentially as described in Example 5 and the MhuA surface protein of M. catarrhalis was identified through BLAST searches based on homology to other TonB-dependent proteins in the National Center for Biotechnology Information (NCBI) data bank. PCR primers were designed for cloning *mhuA* based on its nucleotide sequence, accession number AX067431. PCR amplification of 75 bp upstream of the predicted 5' transcription start site and 197 bp upstream of the 3' predicted stop site was performed using primers 605 and 606 as depicted in Table 6.

Table 6

Pr 605 (SEQ ID NO:13)	TGATTGGTGATAAAAGTAGG
Pr 606 (SEQ ID NO:14)	TGTTGGCATCTAAGGGGTC

PCR analysis of primers 605 and 606 resulted in a 2782 bp product that was ligated into pGEM-T Easy (Promega), resulting in pTB6-AH. *E. coli* XL1-Blue were transformed with pTB6-AH using electroporation. PCR analysis, restriction digestion, and sequence analysis were performed using this plasmid to confirm the nucleotide organization of the 7169 *mhuA* as shown in SED ID NO:1.

As indicated in Table 7, PCR reactions performed on genomic DNA of various organisms using primers 605 and 606 results in amplification of genomic DNA in all M. catarrhalis strains tested and in no amplification in non-M. catarrhalis strains.

Table 7

Strain	PCR result (primers 605 and 606)
M. catarrhalis strains:	
7169	+
7169::*mhuA*	-
43617 (genome strain)	+
RS10	+
7680 (Mark Achtman)	+
7608 (MA)	+

7477 (MA)	+
7544 (MA)	+
Non-M. catarrhalis strains:	
M. bovis	-
Haemophilus influenzae *5657*	-
Neisseria cinerea 658	-
N. gonorrhoeae 3	-
Pseudomonas aeruginosa PSN	-
H. influenzae 2019	-
N. gonorrhoeae 4	-
Klebsiella pneumoniae	-

Further and as will be apparent to those skilled in the art, because the DNA sequence encoding MhuA has been shown to be unique to M. catarrhalis, amplification of any part of the sequence will specifically detect M. catarrhalis in a biological sample.

EXAMPLE 7

This Example demonstrates the detection of nucleic acid sequence encoding a novel internal protein unique to M. catarrhalis.

As demonstrated in Example 4 above using MAb 7C9, the Mcp67 protein is expressed in every strain of Moraxella tested to date. This Example provides a method for identifying the DNA sequences of the gene encoding the Mcp67 protein.

Using PCR analysis with the primers depicted in Table 8, over 50 strains of M. catarrhalis were tested and were positive for the Mcp67 gene DNA. The gene encoding the Mcp67 protein is represented by SEQ ID NO:5 and the Mcp67 amino acid sequence is represented by SEQ ID NO:6. These results are presented in Table 3 and are further demonstrated in Figs. 9A and 9B.

Table 8

Pr 537 (SEQ ID NO:3)	GCCAATGCTTTGCCTGATAATGAG
Pr 538 (SEQ ID NO:4)	TGGTGTTTTGACTGGGGTGGTAG

These primers are designed to the N-terminal internal portion of the gene that codes for the Mcp67 protein and amplify a product from nucleotide 566 to 994 of **SEQ ID NO:5.**

Figs. 9A and 9B depict PCR analysis using primers 537 and 538 demonstrating the presence of the Mcp67 gene in M. catarrhalis and the lack of amplification products in PCR analysis performed on a variety of other infectious bacterial species.

Further, Table 9 demonstrates results for both PCR analysis of the Mcp67 gene from clinical isolates from around the world in conjunction with antibody based detection of the Mcp67 protein using MAb 7C9.

Table 9.

Strain	**Reactivity to Mab 7C9**	PCR Product		
M. cat 7169	+	+	MEF, Child	Buffalo, NY
M. cat ATCC 25238	+	+		
M. cat ATCC 43617	+	+	Transtracheal aspirate, Adult	
M. cat CCUG 3292	+	+		
M. cat Rs10		+		
M. cat Tal 1	+	+	Sputum, Adult	Philadelphia, PA
M. cat BC40	+	+	Sputum, Adult	Buffalo, NY
M. cat sk633	+	+	Sputum, Adult	Buffalo, NY
M. cat 7431	+	+	Clinical Isolate	Columbus, OH
M. cat 7482	+	+	Clinical Isolate	Japan
M. cat 7418	+	+	Clinical Isolate	France
M. cat 7488	+	+	Clinical Isolate	Germany
M. cat 7535	+	+	Clinical Isolate	Seattle, WA
M. cat 7544	+	+	Clinical Isolate	Ethiopia
M. cat 7591	+	+	Clinical Isolate	Spain
M. cat 7966	+	+	Clinical Isolate	Australia
M. cat 10105	+	+	Clinical Isolate	Finland
M. cat 10182	+	+	Clinical Isolate	Netherlands
M. cat 7550	+	+	Clinical Isolate	Ethiopia
M. cat 8150	+	+	Clinical Isolate	Houston, TX
M. cat 7608	+	+	Clinical Isolate	Australia
M. cat 7458	+	+	Clinical Isolate	Sweden
M. cat 7587	+	+	Clinical Isolate	Spain
M. cat 7477	+	+	Clinical Isolate	Japan
M. cat 7315	+	+	Clinical Isolate	Germany
M. cat 7574	+	+	Clinical Isolate	ChathamHospital,NC
M. cat 7512	+	+	Clinical Isolate	Belgium

M. cat 7565	+	+	Clinical Isolate	Yugoslavia
M. cat 7480	+	+	Clinical Isolate	Japan
M. cat 7680	+	+	Clinical Isolate	England
M. cat 7984	+	+	Clinical Isolate	Australia
M. cat 8063	+	+	Clinical Isolate	Germany
M. cat 10016	+	+	Clinical Isolate	Brazil
M. cat 10059	+	+	Clinical Isolate	Angola
M. cat 10099	+	+	Clinical Isolate	Finland
M. cat 10113	+	+	Clinical Isolate	USA
M. cat 10188	+	+	Clinical Isolate	Netherlands
M. cat 10218	+	+	Clinical Isolate	Africa
M. cat pw640	+	+	Sputum, Adult	England
M. cat Af218	+	+	Sputum, Adult	England
M. cat M10	+	+	Sputum, Adult	Houston, TX
M. cat O35E	+	+	MEF, child	Houson, TX

Moreover, Table 10 demonstrates that a wide variety of organisms other M. catarrhalis are not detected by MAb 7C9 or PCR amplification.

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Table 10.

Bacterial Strain	**Reactivity to Mab 7C9**	**PCR Product**
H. influenzae 1479	–	–
Non-typeable H. influenzae 2019	–	–
Non-typeable H. influenzae 3198	–	–
H. ducreyi R3	–	–
H. ducreyi CIP 542	–	–
H. ducreyi HP35000	–	–
Psn	–	–
Psc	–	–
N. gonorrhoeae F62	–	–
N. gonorrhoeae PID2	–	–
N. gonorrhoeae FA19	–	–
M. bovis	–	–
M. nonliquifaciens	–	–
M. lacunata	–	–
M. osloensis	–	–
M. caviae	–	–
P. aeruginosa	–	–
N. cinerea	–	–
K. pneumoniae	–	–
E. aerogenes	–	–
N. gonorrhoeae 1	–	–
N. gonorrhoeae 2	–	–

N. gonorrhoeae 3	–	–
N. gonorrhoeae 4	–	–
N. gonorrhoeae 5	–	–
N. gonorrhoeae 6	–	–
N. gonorrhoeae 7	–	–
N. gonorrhoeae 8	–	–
N. gonorrhoeae 9	–	–
N. gonorrhoeae 10	–	–
H. parainfluenzae 7P10	–	–
H. parainfluenzae 9P20	–	–
H. parainfluenzae 6P30	–	–
H. parainfluenzae 15P0	-	–
H. influenzae 7502	-	–
H. influenzae 4971	–	–
K. oxytoca	–	–
P. mirabilis	–	–
E. coli	–	–
M. cuniculi	–	–

Thus, this Example demonstrates the detection of nucleic acid sequences encoding a novel internal protein unique to M. catarrhalis. Further and as will be apparent to those skilled in the art, because the DNA sequence encoding Mcp67 has been shown to be unique to M. catarrhalis, amplification of any part of the sequence will specifically detect M. catarrhalis in a biological sample.

Example 8

This Example demonstrates that using combinations of the antibodies of the present invention results in increased detection of M. catarrhalis proteins.

Table 11 summarizes data from a variety of ELISA assays using the MAbs indicated in the top row. The assays were performed as follows:

Approximately 10^6-10^7 M. catarrhalis 7169 whole bacteria were added to each well of a 96 well ELISA plate. The bacteria were allowed to coat the wells for 24 hours at 40C and the wells were washed and blocked for 1 hour with 2% milk in PBS. The wells were washed and 100 microliters of each antibody was added and than removed after 1 hour.

The data summarized in Table 11 demonstrates increased detection of M. catarrhalis by using combinations of the MAbs of the present invention. The positive

control was mouse sera from animals injected with M, catarrhalis strain 7169 and the negative control was normal mouse sera. Further, the data in the bottom row of Table 8 was obtained after adding a mild detergent to the bacteria in the wells and demonstrates enhanced detection, particularly when an antibody to the internal Mcp67 protein (i.e., MAb 7C9) is used.

Table 11.

Mab 4G5	**+Mab 3F7**	**+Mab 3F5**	**+Mab 7C9**	**Positive**	**Negative**
0.422	0.605	0.987	1.020	0.320	0.075
0.553	0.721	1.230	1.423	0.356	0.068

What is claimed is:

1. A method for detecting the presence of Moraxella catarrhalis in a biological sample comprising the steps of:

a) contacting the biological sample with at least two antibodies, wherein the epitope in Moraxella catarrhalis for each antibody is either internal or surface exposed; and

b) detecting binding of the antibodies to the biological sample, wherein said binding is indicative of the presence of Moraxella catarrhalis in the sample.

2. The method of claim 1, wherein the surface exposed epitope is part of Moraxella catarrhalis lipooligosaccharide (LOS) A, LOS B, LOS C, the protein of SEQ ID NO:2, or combinations thereof.

3. The method of claim 1, wherein the internal epitope is part of the protein of SEQ ID NO:6.

4. The method of claim 1, wherein the at least two antibodies are selected from the group consisting of 7C9, 4G5, 3F7 and 3F5.

5. The method of claim 1, wherein the binding of the antibodies is detected by a method selected from the group of Westerns blotting, enzyme-linked immunosorbent assay, radioimmunoassays, and immunochromatographic strip assay.

6. The method of claim 5, wherein the binding of the antibodies is detected by immunochromatographic strip assay.

7. A method of identifying Moraxella catarrhalis LOS serotypes in a biological sample comprising the step of:

contacting a first aliquot from the sample with a monoclonal antibody which recognizes Moraxella catarrhalis serotypes A, B and C, and contacting at least a second aliquot of the sample with a monoclonal antibody that is specific for the A, B or C serotypes, wherein a comparison of the binding of the monoclonal antibody

which recognizes Moraxella catarrhalis serotypes A, B and C to the monoclonal antibody that is specific for the A, B or C serotypes is indicative of the Moraxella catarrhalis LOS serotype in the sample.

8. The method of claim 7, wherein the monoclonal antibody that recognizes LOS serotypes A, B and C is 4G5.

9. The method of claim 7, wherein the monoclonal antibody that is specific for the A, B or C serotypes is monoclonal antibody 3F7.

10. The method of claim 7, wherein the binding of the monoclonal antibody which recognizes Moraxella catarrhalis serotypes A, B and C and the binding of a monoclonal antibody that is specific for the A, B or C serotypes is by measured by a method selected from the group of Westerns blotting, enzyme-linked immunosorbent assay, radioimmunoassays, and immunochromatographic strip assay.

11. The method of claim 10, wherein the binding of the monoclonal antibody which recognizes Moraxella catarrhalis serotypes A, B and C and the binding of a monoclonal antibody that is specific for the A, B or C serotypes is by measured by immunochromatographic strip assay.

12. A method for detecting the presence of Moraxella catarrhalis in a biological sample comprising the step of detecting a Moraxella catarrhalis gene in the biological sample wherein the detected gene is selected from the group consisting of:

a) a gene which encodes a protein that is unique to Moraxella catarrhalis and is exposed on the surface of Moraxella catarrhalis, wherein the gene encodes the protein of SEQ ID NO:2, and

b) a gene which encodes a protein that is unique to Moraxella catarrhalis and is not expressed on the surface of Moraxella catarrhalis, wherein the gene encodes a protein of SEQ ID NO:6.

13. The method of claim 12, wherein the gene of a) or b) is detected by amplifying a portion of the gene to obtain detectable amplification products and detecting the amplification products.

14. The method of claim 13, wherein the gene encoding of a) is detected by amplifying the gene by the polymerase chain reaction using the primers represented by SEQ ID NO:13 and SEQ ID NO:14.

15. The method of claim 13, wherein the gene of b) is detected by amplifying the gene by the polymerase chain reaction using the primers represented by SEQ ID NO:3 and SEQ ID NO:4.

16. A method for determining the LOS serotype of Moraxella catarrhalis in a biological sample, the method comprising the steps of:

a) amplifying Moraxella catarrhalis genomic DNA with primers represented by SEQ ID NO:7 and SEQ ID NO:8 wherein if the amplification product is 3.3 kilobases, the serotype is B and wherein if the amplification product is 4.3 kilobases, the serotype is either A or C; and

b) amplifying Moraxella catarrhalis genomic DNA with primers represented by SEQ ID NO:9 and SEQ ID NO:10 wherein if the amplification product is 245 nucleotides long the serotype is A; and

c) amplifying Moraxella catarrhalis genomic DNA with primers represented by SEQ ID NO:11 and SEQ ID NO:12, wherein if the amplification product is 144 kilobases the serotype is C.

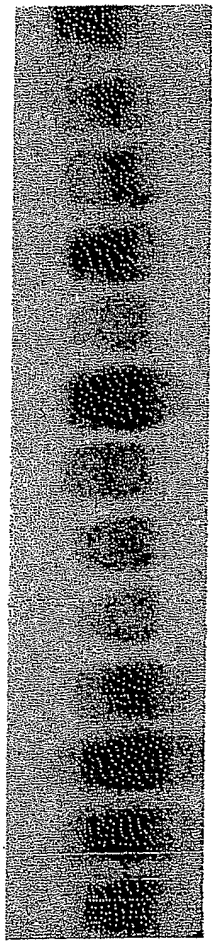


Fig. 1A

Fig. 1B

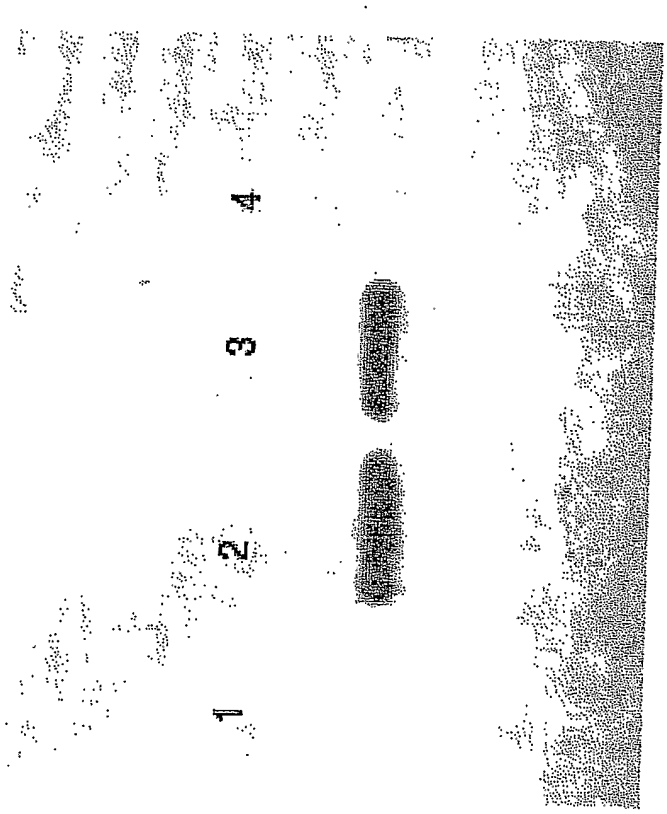


Fig. 2

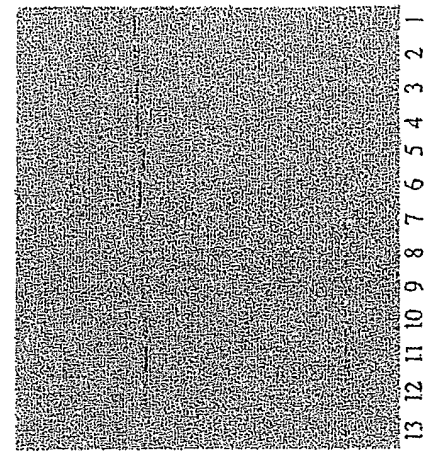


Fig. 3A

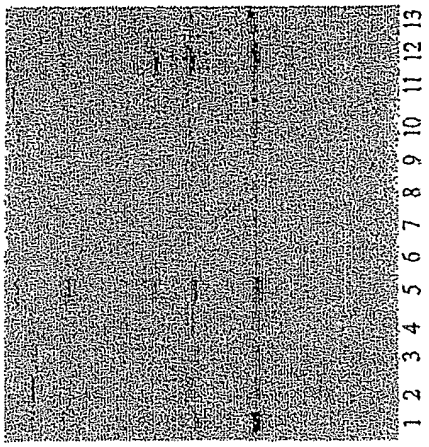


Fig. 3B

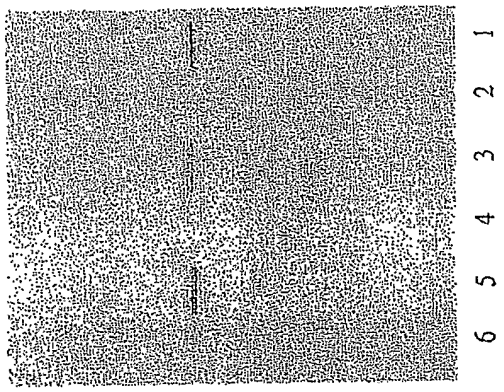


Fig. 4 B

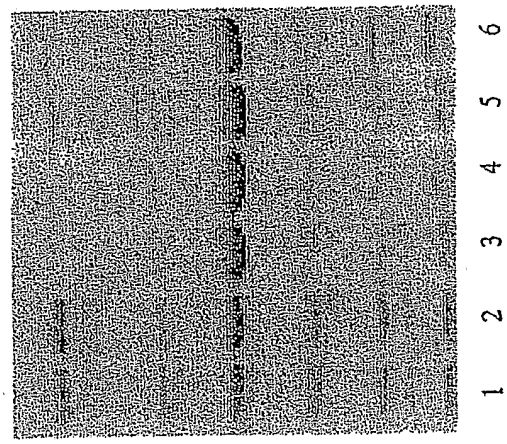


Fig. 4 A

Fig. 5

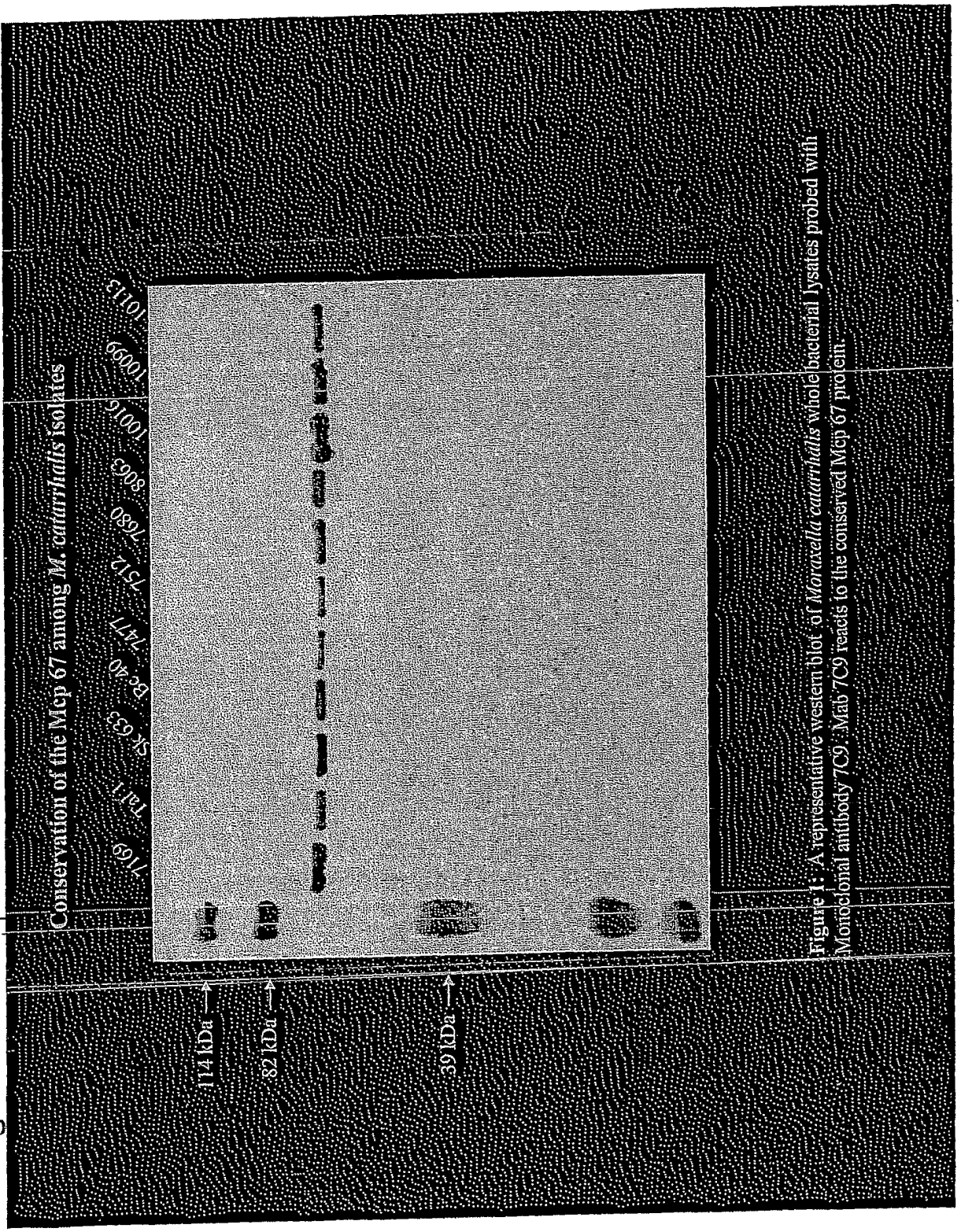
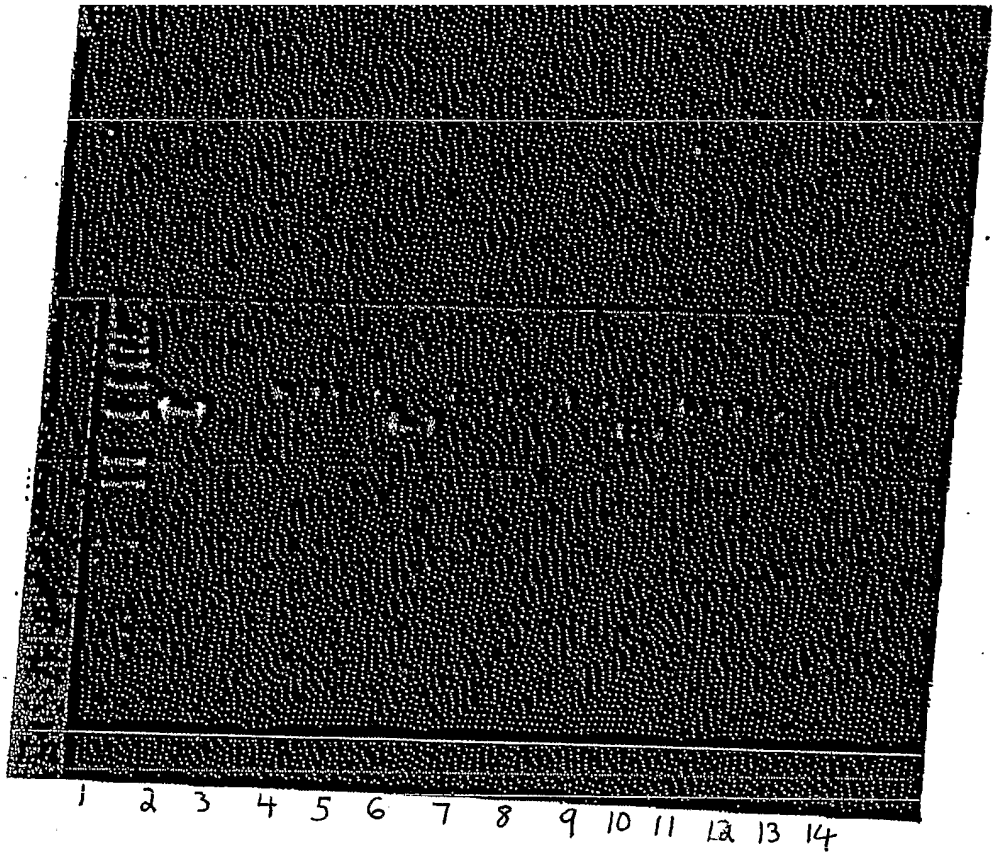


Figure 1: A representative western blot of *Moraxella catarrhalis* whole bacterial lysates probed with Monoclonal antibody 7C9. Mab 7C9 reacts to the conserved Mcp 67 protein.

Fig. 6



Flow Chart for LOS Serotype Analysis

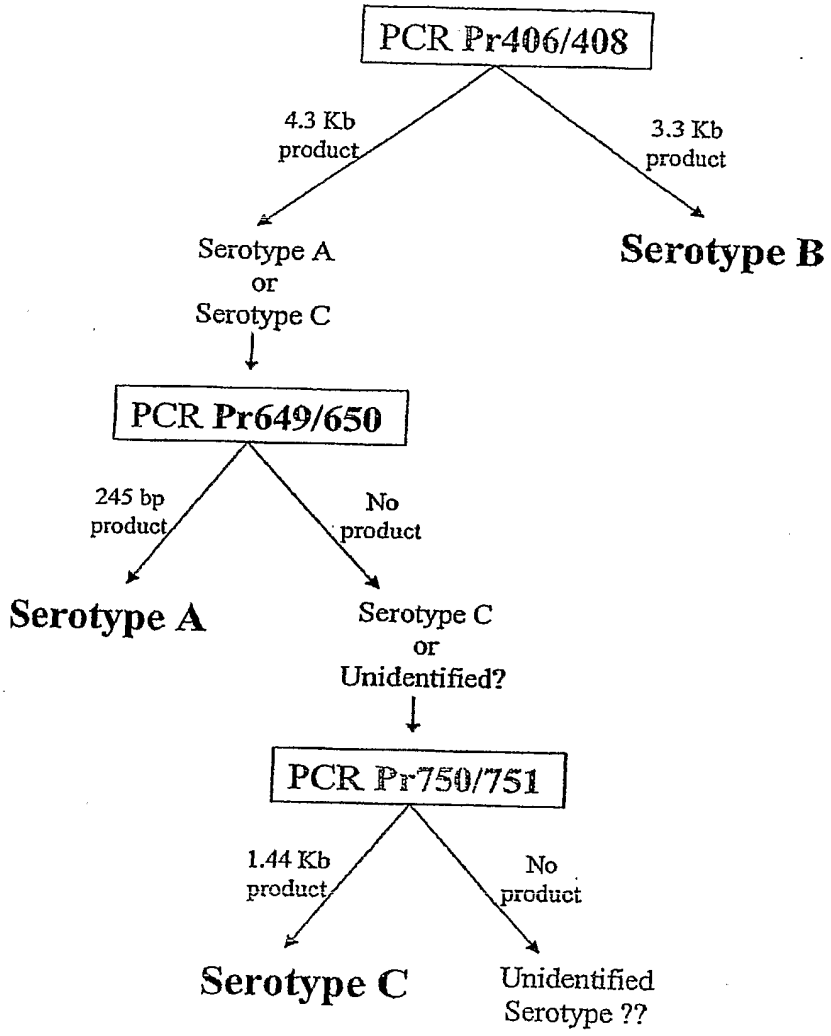
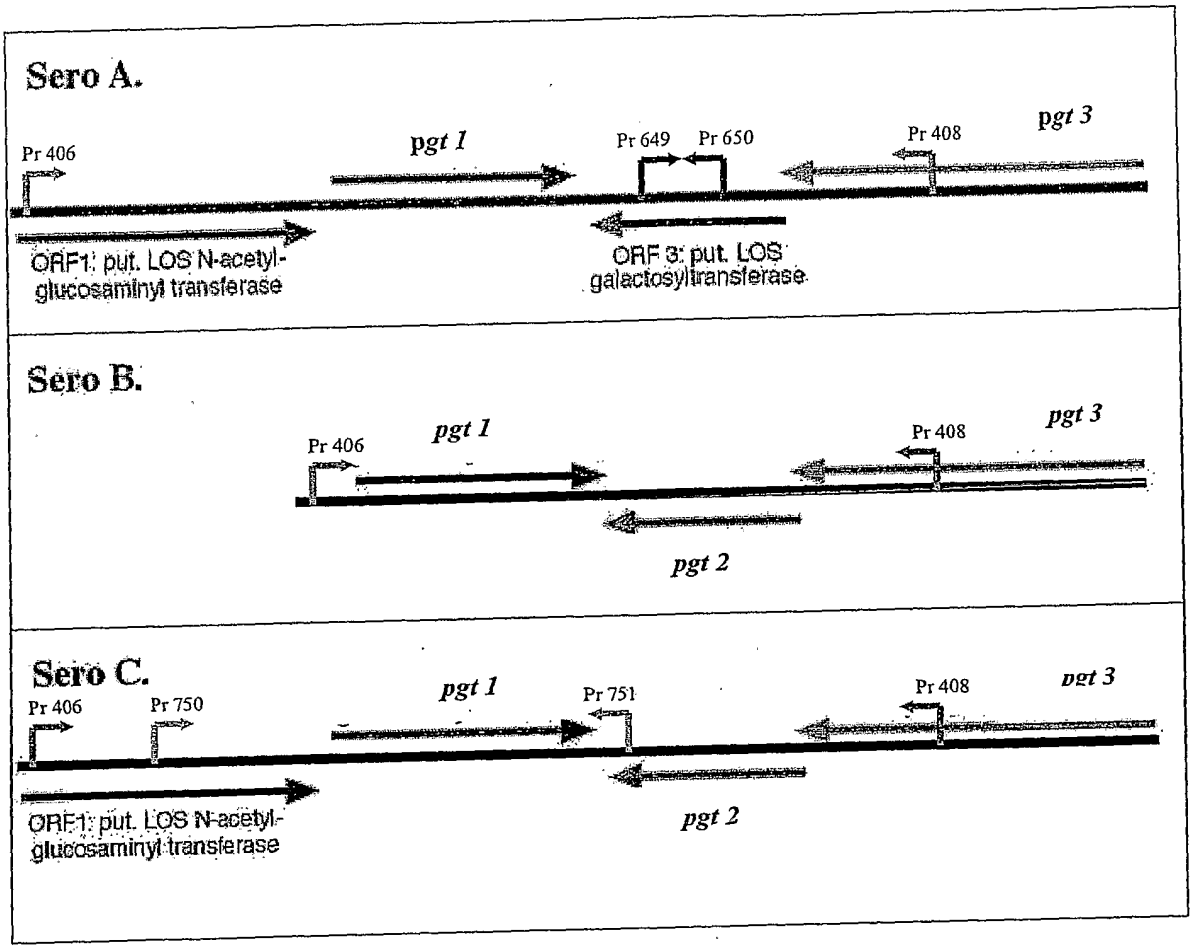


Figure 8.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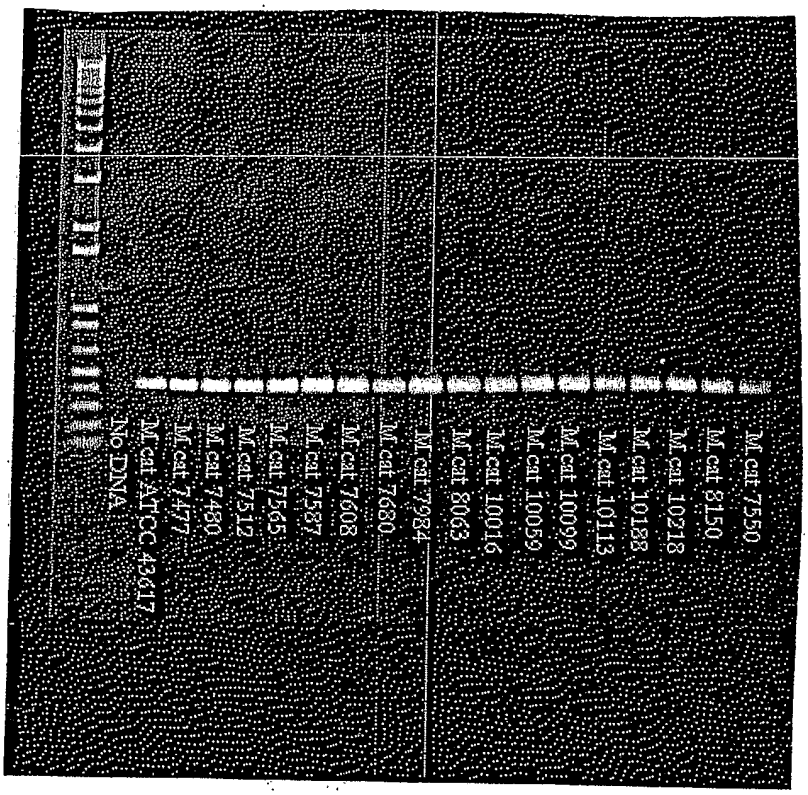
Pr 406
pgt 1
Pr 649
Pr 650
Pr 408
pgt 3
ORF1: put. LOS N-acetyl-glucosaminyl transferase
ORF 3: put. LOS galactosyltransferase
Sero B.
Pr 406
pgt 1
Pr 408
pgt 3
pgt 2
Sero C.
Pr 406
Pr 750
pgt 1
Pr 751
Pr 408
pgt 3
ORF1: put. LOS N-acetyl-glucosaminyl transferase
pgt 2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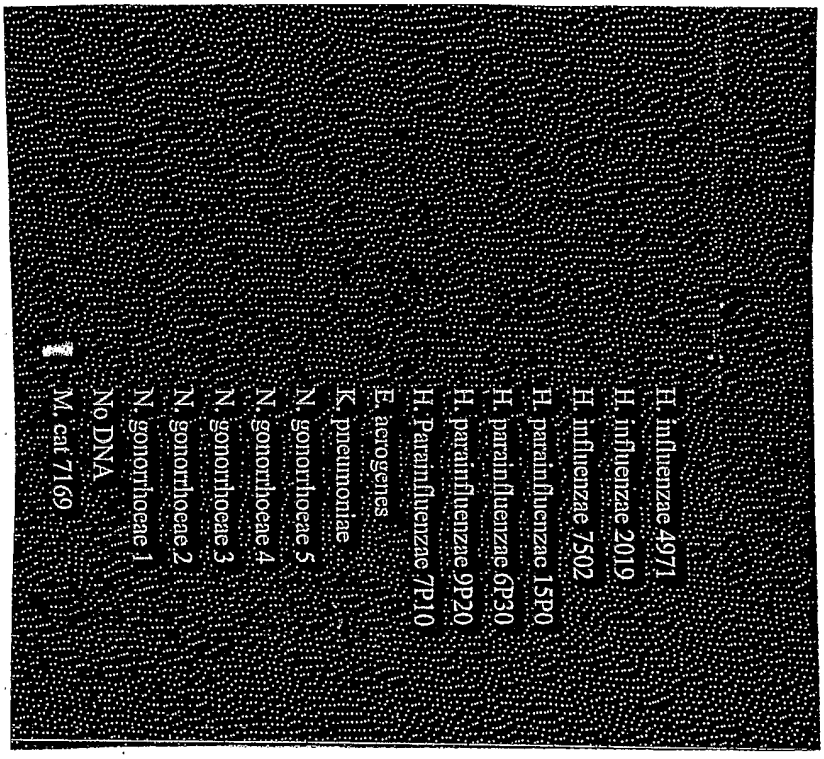
M.cat 8150
M.cat 10218
M.cat 10188
M.cat 10113
M.cat 10099
M.cat 10059
M.cat 10016
M.cat 8063
M.cat 7984
M.cat 7680
M.cat 7608
M.cat 7587
M.cat 7565
M.cat 7512
M.cat 7480
M.cat 7477
M.cat ATCC 43617
No DNA

Figure 9A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H. influenzae 2019
H. influenzae 7502
H. parainfluenzae 15P0
H. parainfluenzae 6P30
H. parainfluenzae 9P20
H. Parainfluenzae 7P10
E. acrogenes
K. pneumoniae
N. gonorrhoeae 5
N. gonorrhoeae 4
N. gonorrhoeae 3
N. gonorrhoeae 2
N. gonorrhoeae 1
No DNA
M. cat 7169

Figure 9B

Campagnari M.Cat sequences

<110> Campagnari, et al.

<120> TOOLS FOR DETECTING MORAXELLA CATARRHALIS

<130> 11520.0357

<140>
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<151> 2003-05-13

<160> 17

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<213> Moraxella catarrhalis

<220>

<222>
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acccaaactg ccatggcaga ggataccctt aaggatgtgc caaaagcaac ggatttttct 180
gtcatcttag atgaggttgt tgtaacggcg accaacggca ccaaaaaatc ccaaaaaccc 240
tttaccaaag catcggccac cagcgtgcga gaaaatgtat ttaatgccag tgagaatatt 300
gatgccattg tgcgcagtgt gccaggggcg tttactcagc aggataaatc ctctgggctg 360
gtatcattaa atgtacgagg cgatagtgga tttgggcgtg ccaatagcat ggttgatggt 420
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gatgatgtga ttaaagatga caaaaatttt ggcttcattg ccaagggttt gaccggtaaa 660
aatgcgacgg ataaaaattt tatgctggca gctggcggac gtggatggct tgataatggc 720
agtatcagtg ctttatatgc ttatagccac aaagacatta gccaaaatta taaagttggc 780
ggtggcggga cgcacattgg caatgttggt gatgatttgc tacttagtaa acaaaaacaa 840
gtttttgcca aagagcatgc actcacttac aatgaagcca gccgttcctg gcaaaaagat 900
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ggtaagtgct atgggctggg ctgtattgat acaaaagaga agtttgatga atatgttgct 1020
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atcaccgccc taaaccaaac ctcaaaaagc catttggcaa aaattcgtta caacaatgac 1140
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agcaatgata attatcaact tgatgctgct tacaacccaa atgagatcat tgatttaaaa 1260
gtgttggcag cccataatgt gggcgtacaa aaatacccca aaggttcaac ttttacaggc 1320
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actcacacct ttaatctgcc aaagcaaatg gatttgacca caaccgttgg gctgaacata 1440
ttgcataatg aatattcaaa aaatcgcttc ccagatgagc ttgggctatt ttataccaat 1500
gatttattat gtggcggcgg ttatgatgcc tgtggtggtc gttttcaggg gacaagcagc 1560
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tatttggaca catcattaca aaaagacaaa tatcagttag attatagcgt taatgccagt 1680
cagtaccgtt ttagtggtga gcatgccagt tattatagca gccaaaaaga gtttcaagat 1740
aagtttggtg aagattcgca aatttataaa cagcactgct cgccaagttg tgatgtgtat 1800
gagcctttgg taaccacttc tggtaaaaaa cacgccatca accattctgt tactttaagt 1860
gccaaatatg acacaggttt tatgcctttt gtcagctttg cacgcacgca cagaatgccc 1920
aacattcaag aaatgttctt ttctcaaatt ggtgatgttg gcgtcaatac tgcattaaaa 1980
ccagagcaag ccaatacata tcagttgggt tttaatgttt ttaaacgcaa tctattgaca 2040
gacaacgata ctttggggct aaaagtagtg ggttatcaaa gccgtattaa caattacatt 2100
cataatgttt atggtaaatg gtatgacaca aaaaatccac ccagttgggt gaccagtggt 2160
gcattaaaag gcgataccat acagcatcgc aattggcaaa tgcctgtgca taaacagggc 2220
ttagagcttg aaatcaacta tgatgctggg cggtatttta ccaatttgtc ttatgccaga 2280

Campagnari M.Cat sequences

caaaagaccg accagccaac caattatagc gatgccagcg agtccccacg aaatagctca 2340
aaagaagacc aattaaccca aggctatggg ctaagcaaag tgtcaatgtt gcccaaagat 2400
tatggtcgtt ttgaacttgg tgtgcgtggc tttgatgaca aactcaccat aggcagtgcg 2460
gtgcgttatt atggacaaag cccacgagcg accattgaac ccagatacat tgatggcacg 2520
catggtggca atacatcgca ttcagatgat aaaggtgctc atgtcatcaa gcaaattgag 2580
atgctaaaaa gacagccttt ggtgcatgat ttttatgttg cttatgagcc aataaaagat 2640
ttggtgatgc gtcttgatgt gcaaaatgcg tttgataaac tgtatattga ccccttagat 2700
gccaacaatg atgccgccac tcagcgttat tatcattcat attataatga tgcagacgaa 2760
ggcgcacctt gtgcagcggg gcagttgtgt aagcctgatg caaaatacgg cggtactact 2820
cgctcggtat tgaccaattt tgccaaaggg cgttctttat tatcttcaat gacttataag 2880
tggtag 2886

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<211> 961
<212> PRT
<213> Moraxella catarrhalis

<220>
<223> MhuA protein

<400> 2

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Thr	Gln	Thr	Lys	His	Thr	Asn	His	Thr	Lys	Lys	Val	Leu	Lys	Leu	
				20					25						30
Ser	Met	Leu	Ser	Leu	Cys	Leu	Leu	His	Ile	Thr	Gln	Thr	Ala	Met	
				35					40						45
Ala	Glu	Asp	Thr	Leu	Lys	Asp	Val	Pro	Lys	Ala	Thr	Asp	Phe	Ser	
				50					55						60
Val	Ile	Leu	Asp	Glu	Val	Val	Val	Thr	Ala	Thr	Asn	Gly	Thr	Lys	
				65					70						75
Lys	Ser	Gln	Lys	Pro	Phe	Thr	Lys	Ala	Ser	Ala	Thr	Ser	Val	Arg	
				80					85						90
Glu	Asn	Val	Phe	Asn	Ala	Ser	Glu	Asn	Ile	Asp	Ala	Ile	Val	Arg	
				95					100						105
Ser	Val	Pro	Gly	Ala	Phe	Thr	Gln	Gln	Asp	Lys	Ser	Ser	Gly	Leu	
				110					115						120
Val	Ser	Leu	Asn	Val	Arg	Gly	Asp	Ser	Gly	Phe	Gly	Arg	Ala	Asn	
				125					130						135
Ser	Met	Val	Asp	Gly	Val	Thr	Gln	Thr	Phe	Tyr	Ser	Thr	Ser	Thr	
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Asp	Ala	Gly	Arg	Gly	Gly	Gly	Thr	Ser	Gln	Phe	Gly	Ala	Val	Ile	
				155					160						165
Asp	Gln	Asn	Phe	Ile	Ala	Gly	Val	Glu	Leu	Asn	Lys	Gly	Ser	Phe	
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Asn	Gly	Lys	Gly	Gly	Leu	Asn	Thr	Leu	Thr	Gly	Ser	Ala	Asn	Phe	
				185					190						195
Arg	Thr	Leu	Asn	Ala	Asp	Asp	Val	Ile	Lys	Asp	Asp	Lys	Asn	Phe	
				200					205						210
Gly	Phe	Ile	Ala	Lys	Gly	Leu	Thr	Gly	Lys	Asn	Ala	Thr	Asp	Lys	
				215					220						225
Asn	Phe	Met	Leu	Ala	Ala	Gly	Gly	Arg	Gly	Trp	Leu	Asp	Asn	Gly	
				230					235						240
Ser	Ile	Ser	Ala	Leu	Tyr	Ala	Tyr	Ser	His	Lys	Asp	Ile	Ser	Gln	
				245					250						255
Asn	Tyr	Lys	Val	Gly	Gly	Gly	Gly	Thr	His	Ile	Gly	Asn	Val	Gly	
				260					265						270
Asp	Asp	Leu	Leu	Leu	Ser	Lys	Gln	Lys	Gln	Val	Phe	Ala	Lys	Glu	
				275					280						285
His	Ala	Leu	Thr	Tyr	Asn	Glu	Ala	Ser	Arg	Ser	Trp	Gln	Lys	Asp	
				290					295						300
Leu	Thr	Lys	Leu	Asp	Lys	Glu	Thr	Gly	Lys	Pro	Leu	Trp	Asp	Arg	

Campagnari M.Cat sequences

Lys Tyr Gln Phe Gly Gly Lys Cys Tyr Gly Leu Gly Cys Ile Asp
305 310 315
Thr Lys Glu Lys Phe Asp Glu Tyr Val Ala Asp Lys Gln Gln Gln
320 325 330
Trp Gln Lys His Gly Ala Lys Glu Tyr Ser Ile Thr Pro Ile Asp
335 340 345
Ile Thr Ala Leu Asn Gln Thr Ser Lys Ser His Leu Ala Lys Ile
350 355 360
Arg Tyr Asn Asn Asp Thr Ser Asp Val Gly Leu Gln Leu Arg Lys
365 370 375
Met Asp Thr Thr Ile Gly Ser Arg Arg Ile Ser Asn Asp Asn Tyr
380 385 390
Gln Leu Asp Ala Ala Tyr Asn Pro Asn Glu Ile Ile Asp Leu Lys
395 400 405
Val Leu Ala Ala His Asn Val Gly Val Gln Lys Tyr Pro Lys Gly
410 415 420
Ser Thr Phe Thr Gly Trp Lys Leu Asp Lys Asp Phe Glu Thr Lys
425 430 435
Asn Thr Ala Asn Leu Phe Asp Leu Asn Asn Thr His Thr Phe Asn
440 445 450
Leu Pro Lys Gln Met Asp Leu Thr Thr Thr Val Gly Leu Asn Ile
455 460 465
Leu His Asn Glu Tyr Ser Lys Asn Arg Phe Pro Asp Glu Leu Gly
470 475 480
Leu Phe Tyr Thr Asn Asp Leu Leu Cys Gly Gly Gly Tyr Asp Ala
485 490 495
Cys Gly Gly Arg Phe Gln Gly Thr Ser Ser Thr Leu Pro Lys Lys
500 505 510
Ser Val Ile Val Gln Pro Ser Gly Lys Gln Arg Phe His Ser Ile
515 520 525
Tyr Leu Asp Thr Ser Leu Gln Lys Asp Lys Tyr Gln Leu Asp Tyr
530 535 540
Ser Val Asn Ala Ser Gln Tyr Arg Phe Ser Gly Glu His Ala Ser
545 550 555
Tyr Tyr Ser Ser Gln Lys Glu Phe Gln Asp Lys Phe Gly Glu Asp
560 565 570
Ser Gln Ile Tyr Lys Gln His Cys Ser Pro Ser Cys Asp Val Tyr
575 580 585
Glu Pro Leu Val Thr Thr Ser Gly Lys Lys His Ala Ile Asn His
590 595 600
Ser Val Thr Leu Ser Ala Lys Tyr Asp Thr Gly Phe Met Pro Phe
605 610 615
Val Ser Phe Ala Arg Thr His Arg Met Pro Asn Ile Gln Glu Met
620 625 630
Phe Phe Ser Gln Ile Gly Asp Val Gly Val Asn Thr Ala Leu Lys
635 640 645
Pro Glu Gln Ala Asn Thr Tyr Gln Leu Gly Phe Asn Val Phe Lys
650 655 660
Arg Asn Leu Leu Thr Asp Asn Asp Thr Leu Gly Leu Lys Val Val
665 670 675
Gly Tyr Gln Ser Arg Ile Asn Asn Tyr Ile His Asn Val Tyr Gly
680 685 690
Lys Trp Tyr Asp Thr Lys Asn Pro Pro Ser Trp Val Thr Ser Gly
695 700 705
Ala Leu Lys Gly Asp Thr Ile Gln His Arg Asn Trp Gln Met Pro
710 715 720
Val His Lys Gln Gly Leu Glu Leu Glu Ile Asn Tyr Asp Ala Gly
725 730 735
Arg Tyr Phe Thr Asn Leu Ser Tyr Ala Arg Gln Lys Thr Asp Gln
740 745 750
Pro Thr Asn Tyr Ser Asp Ala Ser Glu Ser Pro Arg Asn Ser Ser
755 760 765
770 775 780

Campagnari M.Cat sequences

Lys Glu Asp Gln Leu Thr Gln Gly Tyr Gly Leu Ser Lys Val Ser
785 790 795
Met Leu Pro Lys Asp Tyr Gly Arg Phe Glu Leu Gly Val Arg Gly
800 805 810
Phe Asp Asp Lys Leu Thr Ile Gly Ser Ala Val Arg Tyr Tyr Gly
815 820 825
Gln Ser Pro Arg Ala Thr Ile Glu Pro Arg Tyr Ile Asp Gly Thr
830 835 840
His Gly Gly Asn Thr Ser His Ser Asp Asp Lys Gly Ala His Val
845 850 855
Ile Lys Gln Ile Glu Met Leu Lys Arg Gln Pro Leu Val His Asp
860 865 870
Phe Tyr Val Ala Tyr Glu Pro Ile Lys Asp Leu Val Met Arg Leu
875 880 885
Asp Val Gln Asn Ala Phe Asp Lys Leu Tyr Ile Asp Pro Leu Asp
890 895 900
Ala Asn Asn Asp Ala Ala Thr Gln Arg Tyr Tyr His Ser Tyr Tyr
905 910 915
Asn Asp Ala Asp Glu Gly Ala Pro Cys Ala Ala Gly Gln Leu Cys
920 925 930
Lys Pro Asp Ala Lys Tyr Gly Gly Thr Thr Arg Ser Val Leu Thr
935 940 945
Asn Phe Ala Lys Gly Arg Ser Leu Leu Ser Ser Met Thr Tyr Lys
950 955 960
Trp
961

<210> 3
<211> 24
<212> DNA
<213> Moraxella catarrhalis

<220>

<222>
<223> primer 537

<400> 3
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<210> 4
<211> 23
<212> DNA
<213> Moraxella catarrhalis

<220>

<222>
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tggtgttttg actggggtgg tag 23

<210> 5
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<213> Moraxella catarrhalis

<220>

<222>
<223> Mcp67 gene

Campagnari M.Cat sequences

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gcaggacgct tgagtaatga agatgtgtat cagcgtgcca atgctttgcc tgataatgag 180
cttgagcatg ggcatcatct gctcaatgtt gcttttagtg atgtttcaac tggtgaagat 240
cagattgctt ctttgagtaa tcaattagcc gatgaatatc atgtttcgcc agtaacggca 300
cgcaccgcaa tcgcaacggc agcacctttg gctttggcac gcattaaaga gcaagcaggt 360
gcattatctg taccgtcttt tattcgtact caattggcta aagaagaaaa ccgtttgcca 420
acttgggcgc atactttatt gccagcaggg ctatttgcaa ccgctgccac aaccaccgcc 480
gagcctgtaa cgacagcctc tgctgttgtg aaagagcctg tcaaaccaag tgttgtgaca 540
gaaccagttc atccagctgc ggctaccacc ccagtcaaaa caccaactgc ccagcattac 600
gaaaacaaag aaaaaagtcc ttttctaaaa acgattctac cgattattgg attgattatt 660
tttgcaggct tggcatggct tttgttaaga gcatgtcaag acaaaccaac acctgttgcg 720
gcacctgttg cgacagatac agcacctgtg gtagcggata atgctgtaca ggcagaccca 780
acacaaacag gtgttgccca agcacctgca acgcttagct tgtctgttga tgaaacgggt 840
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gctgaagatg caccaacacc tgttgcacaa aac 1653

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<213> Moraxella catarrhalis

<220>

<222>
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Leu Thr Ser Ile Lys Asn Gln Asp Gly Asp Asn Ala Asp Lys Ser
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Asn Leu Leu Thr Ala Phe Tyr Thr Ile Phe Ala Gly Arg Leu Ser
35 40 45
Asn Glu Asp Val Tyr Gln Arg Ala Asn Ala Leu Pro Asp Asn Glu
50 55 60
Leu Glu His Gly His His Leu Leu Asn Val Ala Phe Ser Asp Val
65 70 75
Ser Thr Gly Glu Asp Gln Ile Ala Ser Leu Ser Asn Gln Leu Ala
80 85 90
Asp Glu Tyr His Val Ser Pro Val Thr Ala Arg Thr Ala Ile Ala
95 100 105
Thr Ala Ala Pro Leu Ala Leu Ala Arg Ile Lys Glu Gln Ala Gly
110 115 120
Ala Leu Ser Val Pro Ser Phe Ile Arg Thr Gln Leu Ala Lys Glu
125 130 135
Glu Asn Arg Leu Pro Thr Trp Ala His Thr Leu Leu Pro Ala Gly
140 145 150

Campagnari M.Cat sequences

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Leu Phe Ala Thr Ala Ala Thr Thr Thr Ala Glu Pro Val Thr Thr
                155                 160                 165
Ala Ser Ala Val Val Lys Glu Pro Val Lys Pro Ser Val Val Thr
            170                 175                 180
Glu Pro Val His Pro Ala Ala Ala Thr Thr Pro Val Lys Thr Pro
        185                 190                 195
Thr Ala Gln His Tyr Glu Asn Lys Glu Lys Ser Pro Phe Leu Lys
    200                 205                 210
Thr Ile Leu Pro Ile Ile Gly Leu Ile Ile Phe Ala Gly Leu Ala
215                 220                 225
Trp Leu Leu Leu Arg Ala Cys Gln Asp Lys Pro Thr Pro Val Ala
            230                 235                 240
Ala Pro Val Ala Thr Asp Thr Ala Pro Val Val Ala Asp Asn Ala
        245                 250                 255
Val Gln Ala Asp Pro Thr Gln Thr Gly Val Ala Gln Ala Pro Ala
    260                 265                 270
Thr Leu Ser Leu Ser Val Asp Glu Thr Gly Gln Ala Leu Tyr Ser
275                 280                 285
His Arg Ala Gln Val Gly Ser Glu Glu Leu Ala Gly His Ile Arg
            290                 295                 300
Ala Ala Ile Ala Gln Val Phe Gly Val Gln Asp Leu Thr Ile Gln
        305                 310                 315
Asn Thr Asn Val His Thr Ala Thr Met Pro Ala Ala Glu Tyr Leu
    320                 325                 330
Pro Ala Ile Leu Gly Leu Met Lys Gly Val Pro Asn Ser Ser Val
335                 340                 345
Val Ile His Asp His Thr Val Arg Phe Asn Ala Thr Thr Pro Glu
            350                 355                 360
Asp Val Ala Lys Leu Val Glu Gly Ala Lys Asn Ile Leu Pro Ala
        365                 370                 375
Asp Phe Thr Val Glu Ala Glu Pro Glu Leu Asp Ile Asn Thr Ala
    380                 385                 390
Val Ala Asp Ser Ile Glu Thr Ala Arg Val Ala Ile Val Ala Leu
395                 400                 405
Gly Asp Thr Val Glu Glu Asn Glu Met Asp Ile Leu Ile Asn Ala
            410                 415                 420
Leu Asn Thr Gln Ile Ile Asn Phe Ala Leu Asp Ser Thr Glu Ile
        425                 430                 435
Pro Gln Glu Asn Lys Glu Ile Leu Asp Leu Ala Ala Glu Lys Leu
    440                 445                 450
Lys Ala Val Pro Glu Thr Thr Leu Arg Ile Ile Gly His Thr Asp
455                 460                 465
Thr Gln Gly Thr His Glu Tyr Asn Gln Asp Leu Ser Glu Ser Arg
            470                 475                 480
Ala Ala Ala Val Lys Glu Tyr Leu Val Ser Lys Gly Val Ala Ala
        485                 490                 495
Glu Arg Leu Asn Thr Gln Gly Ala Ser Phe Asp Tyr Pro Val Ala
    500                 505                 510
Ser Asn Ala Thr Glu Gln Gly Arg Phe Gln Asn Arg Arg Ile Glu
515                 520                 525
Phe Val Leu Phe Gln Glu Gly Glu Ala Ile Thr Gln Val Gly His
            530                 535                 540
Ala Glu Asp Ala Pro Thr Pro Val Ala Gln Asn
        545                 550 551
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<212> DNA
<213> Moraxella catarrhalis

<220>

<222>
<223> Pr 406

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<210> 8
<211> 25
<212> DNA
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<220>

<222>
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<400> 8
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<210> 9
<211> 21
<212> DNA
<213> Moraxella catarrhalis

<220>
<223> pr 649

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<211> 20
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<220>
<223> pr 650

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<210> 11
<211> 19
<212> DNA
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<220>
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<210> 12
<211> 20
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<220>

<223> pr 751

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<210> 13
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<212> DNA
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<210> 14
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tgttgagcta ttatttaaag ccaagtgatg atggtttgca agatgattga attgtttttt 180
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Campagnari M.Cat sequences

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Campagnari M.Cat sequences

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<211> 4583
<212> DNA
<213> Moraxella catarrhalis

<220>
<223> LOS gene cluster from strain 7169 (type B)

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Campagnari M.Cat sequences

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Campagnari M.Cat sequences

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Campagnari M.Cat sequences

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