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Pyeon et al.

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(45) **Date of Patent: Sep. 6, 2011**

(54) **BIOMARKERS FOR HUMAN PAPILLOMA VIRUS-ASSOCIATED CANCER**

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G01N 33/574 (2006.01)
C12Q 1/00 (2006.01)

(52) **U.S. Cl.** **435/4**; 435/235.1; 435/7.23

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

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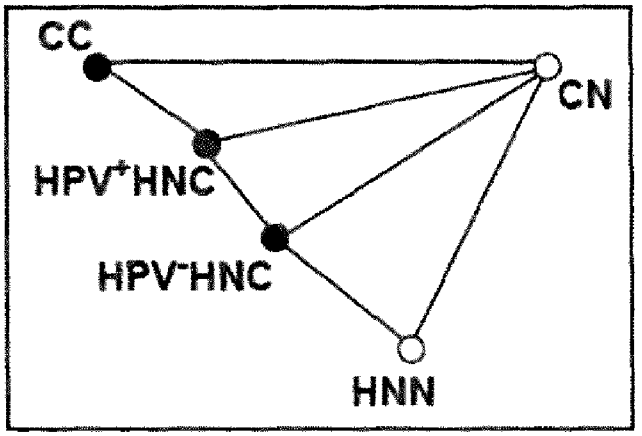
(57) **ABSTRACT**

Cervical cancer cells and HPV$^+$ head and neck cancer cells express three testis-specific genes not normally expressed in somatic cells: testicular cell adhesion molecule 1 (TCAM1), synaptonemal complex protein 2 (SYCP2) and stromal antigen 3 (STAG3). Among the three markers, TCAM1 and SYCP2 are early detection markers. Various methods for identifying a human or non-human animal as a candidate for further examination for cervical cancer, preneoplastic lesion for cervical cancer, head and neck cancer, or preneoplastic lesion for head and neck cancer are disclosed. Methods of detecting said cancers and preneoplastic lesions, methods of screening for drugs for treating said cancers and preneoplastic lesions, methods for monitoring the effectiveness of a treatment for said cancers, and methods of treating said cancers are also disclosed. Further disclosed are kits that can be used to practice the above methods.

11 Claims, 15 Drawing Sheets
(10 of 15 Drawing Sheet(s) Filed in Color)

A



	CC	HPV+HNC	HPV-HNC	HNN
HPV+HNC	0.21			
HPV-HNC	0.26	0.17		
HNN	0.38	0.29	0.25	
CN	0.53	0.44	0.39	0.30

FIG. 1

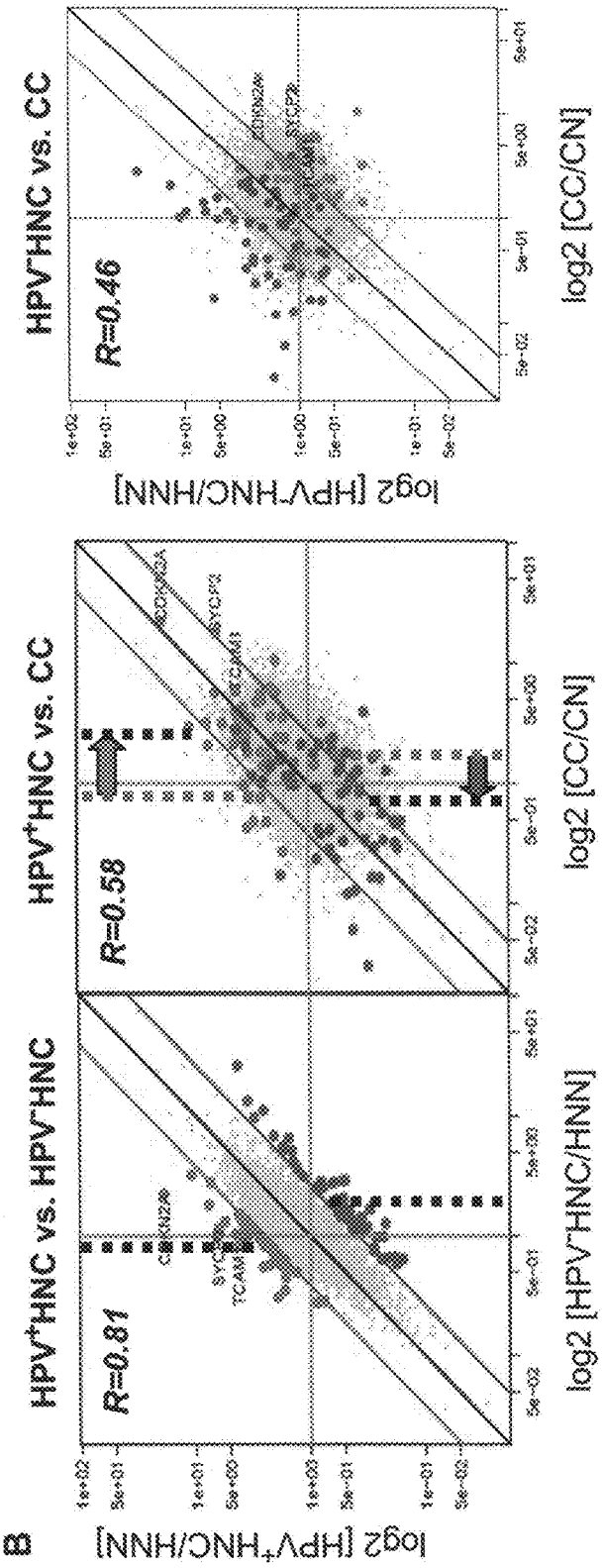

B
HPV+HNC vs. HPV-HNC
R=0.81
HPV+HNC vs. CC
R=0.58
HPV-HNC vs. CC
R=0.46
log2 [HPV+HNC/HNN]
log2 [HPV-HNC/HNN]
log2 [HPV-HNC/HNN]
log2 [CC/CN]
log2 [CC/CN]

FIG. 1

C

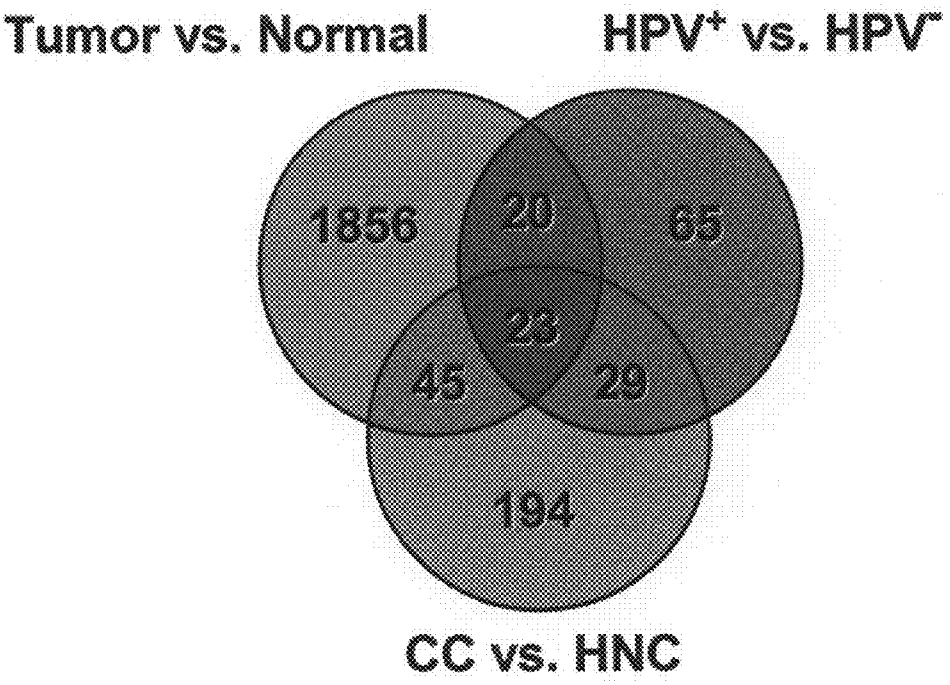


FIG. 1

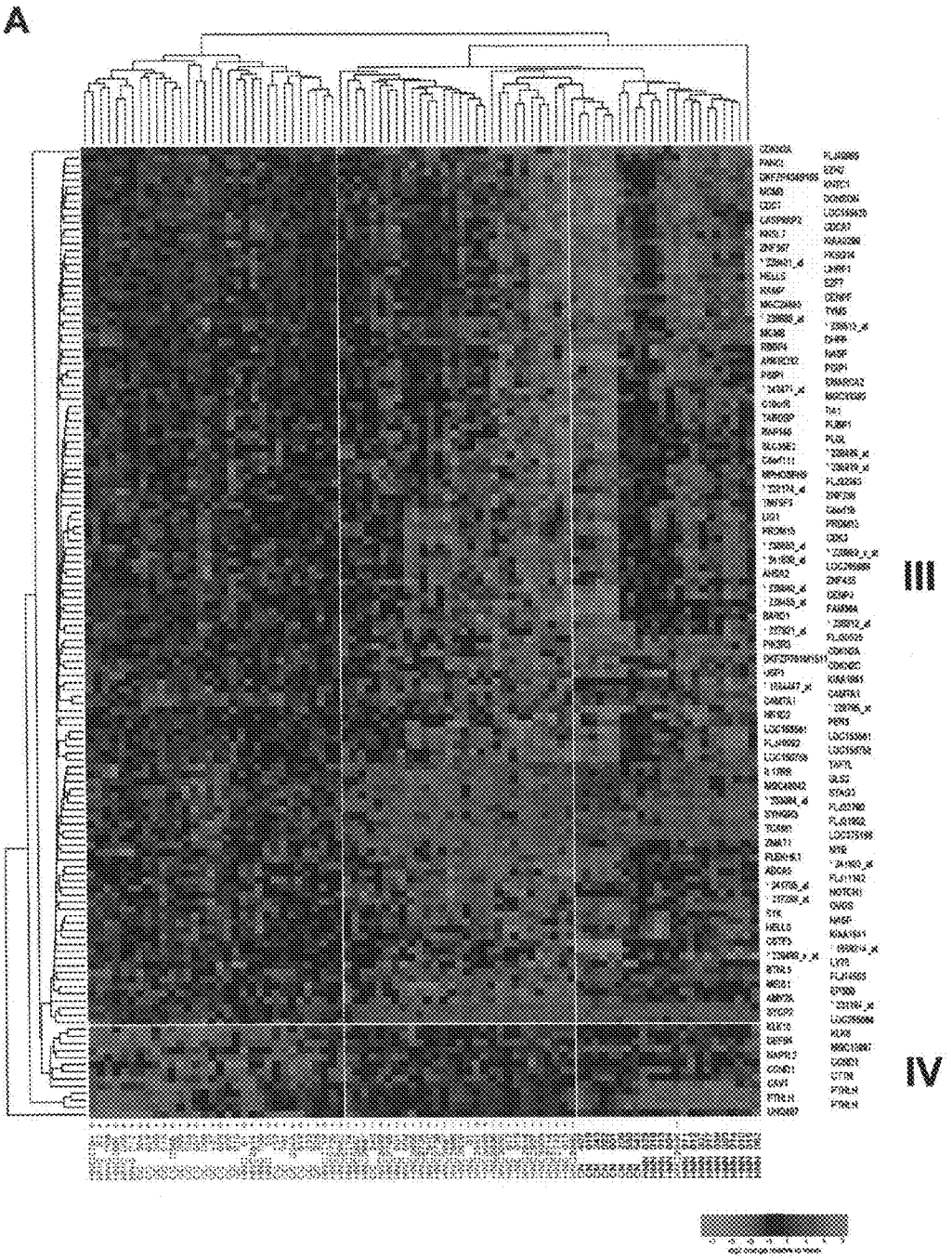


FIG. 2

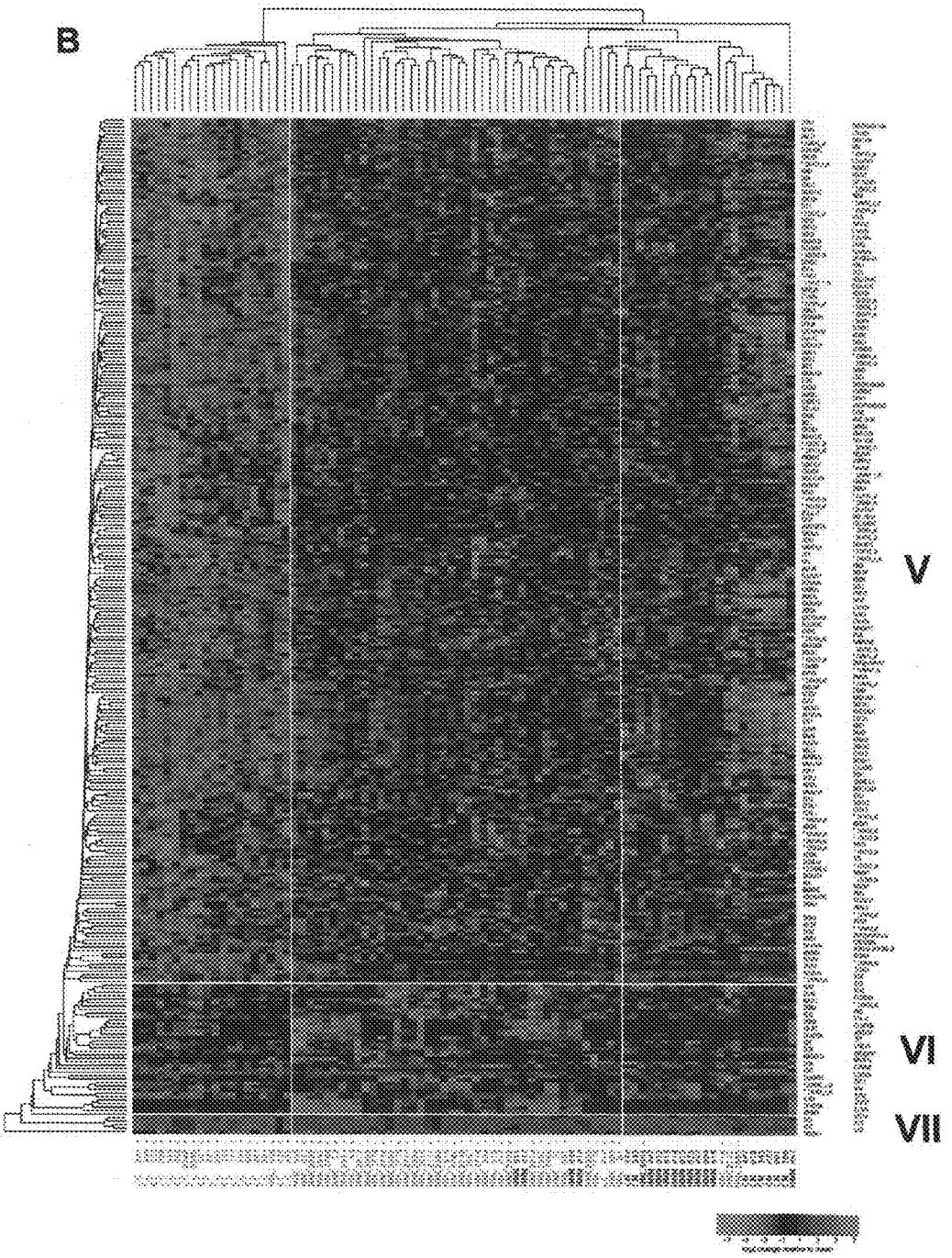


FIG. 2

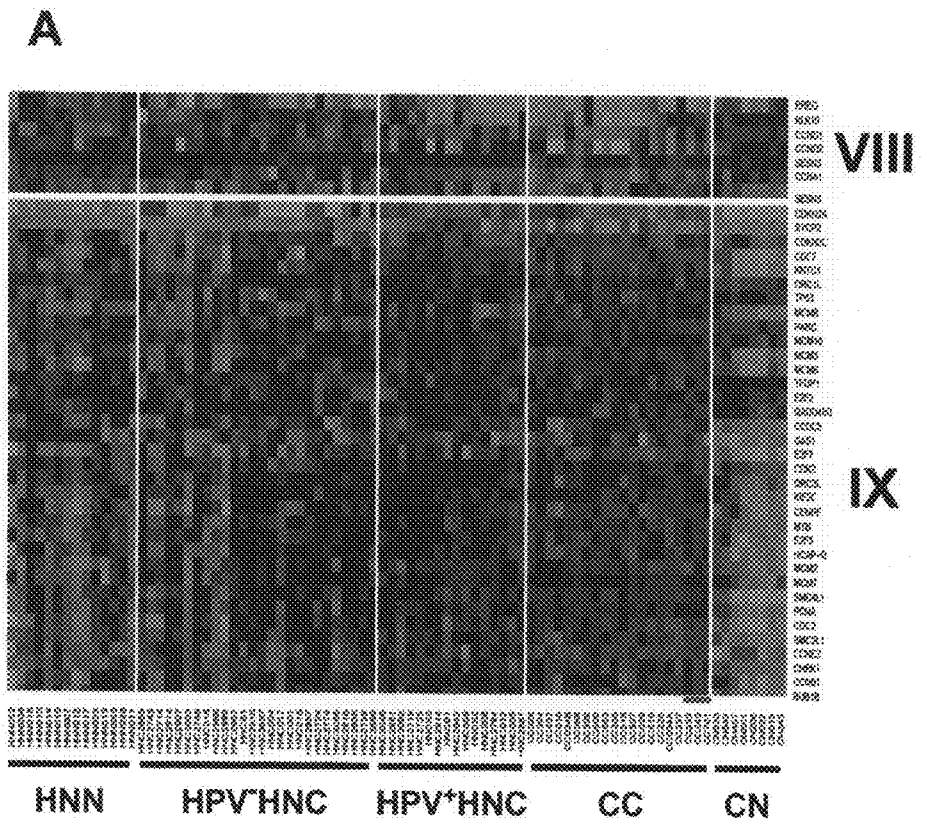


FIG. 3

B

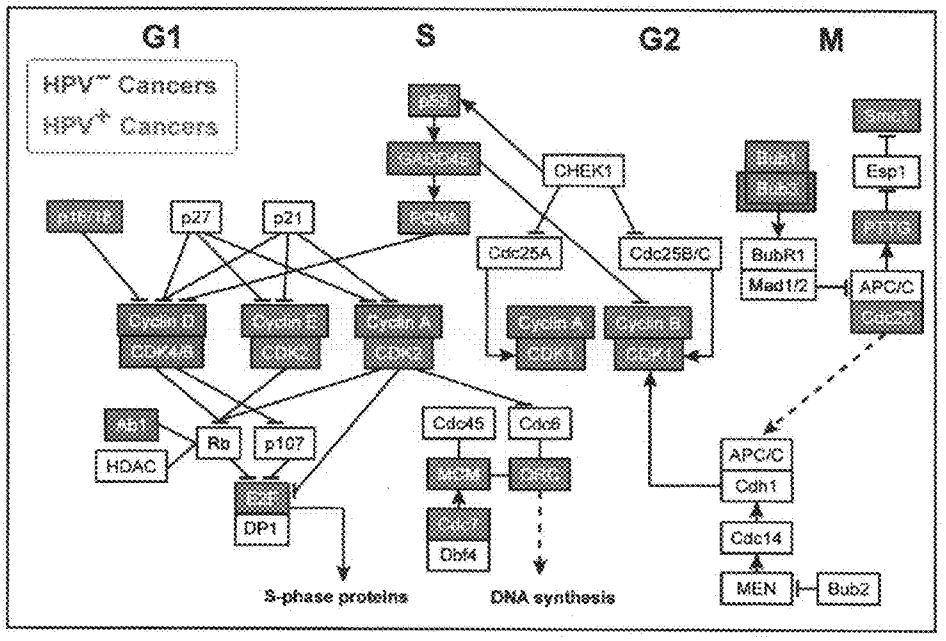

G1
S
G2
M
HPV⁻ Cancers
HPV⁺ Cancers
CHEK1
p27
p21
Cdc25A
Cdc25B/C
BubR1
Mad1/2
APC/C
Esp1
Rb
HDAC
p107
DP1
Cdc45
Cdc6
Orc2
Orc4
Obf1
Obf4
APC/C
Cdh1
Cdc14
MEN
Bub2
S-phase proteins
DNA synthesis

FIG. 3

C

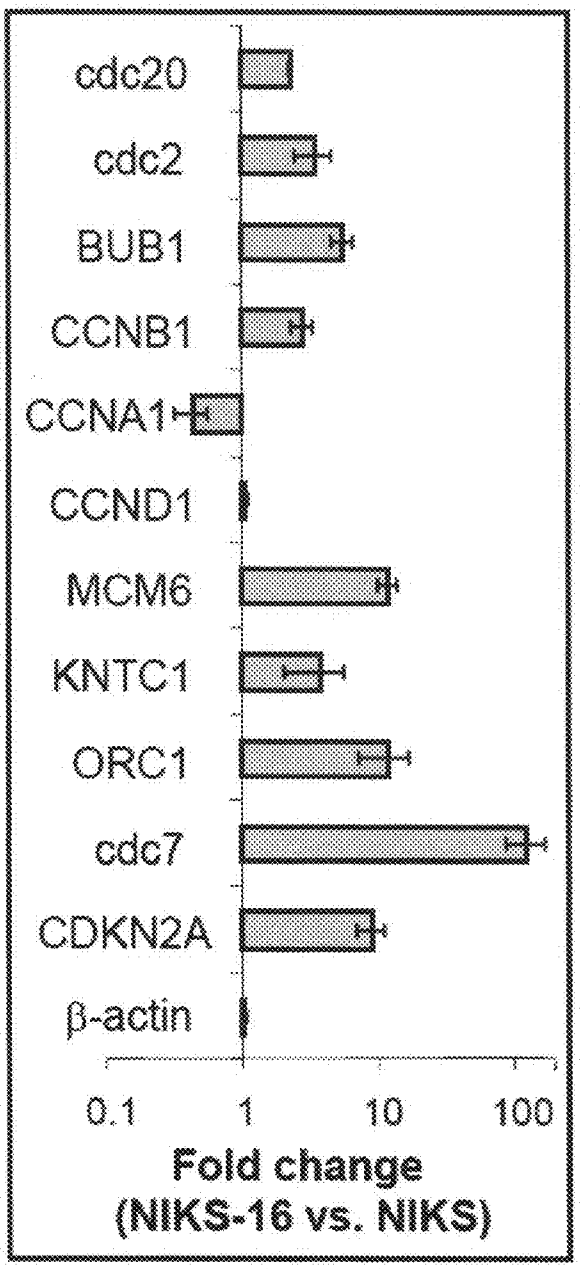

cdc20
cdc2
BUB1
CCNB1
CCNA1
CCND1
MCM6
KNTC1
ORC1
cdc7
CDKN2A
β-actin
0.1
1
10
100
Fold change
(NIKS-16 vs. NIKS)

FIG. 3

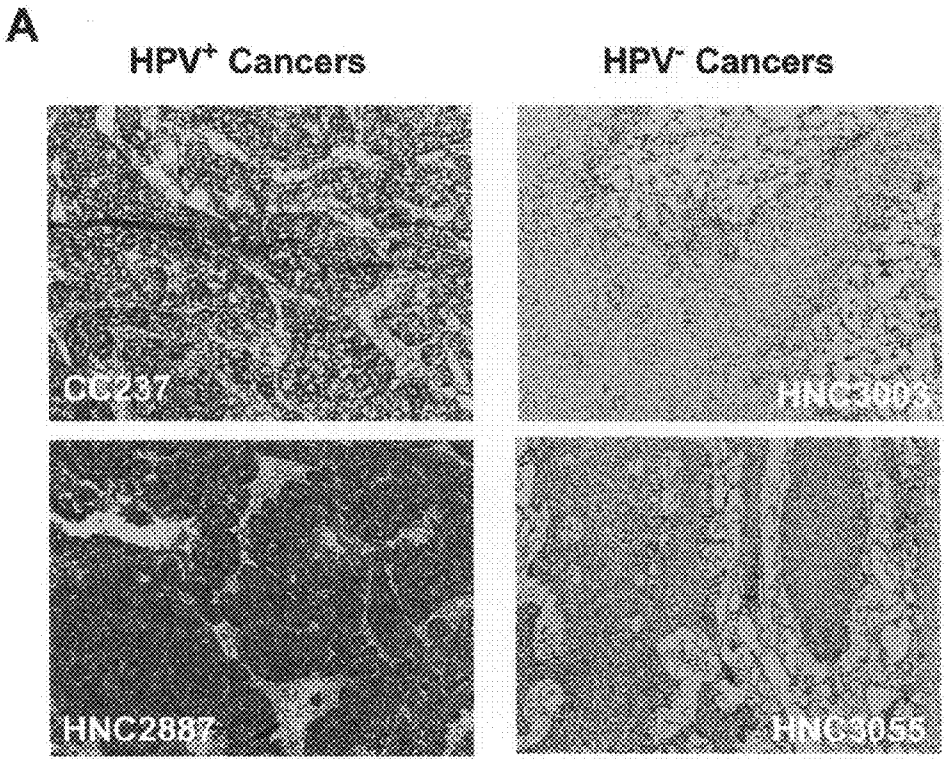


FIG. 4

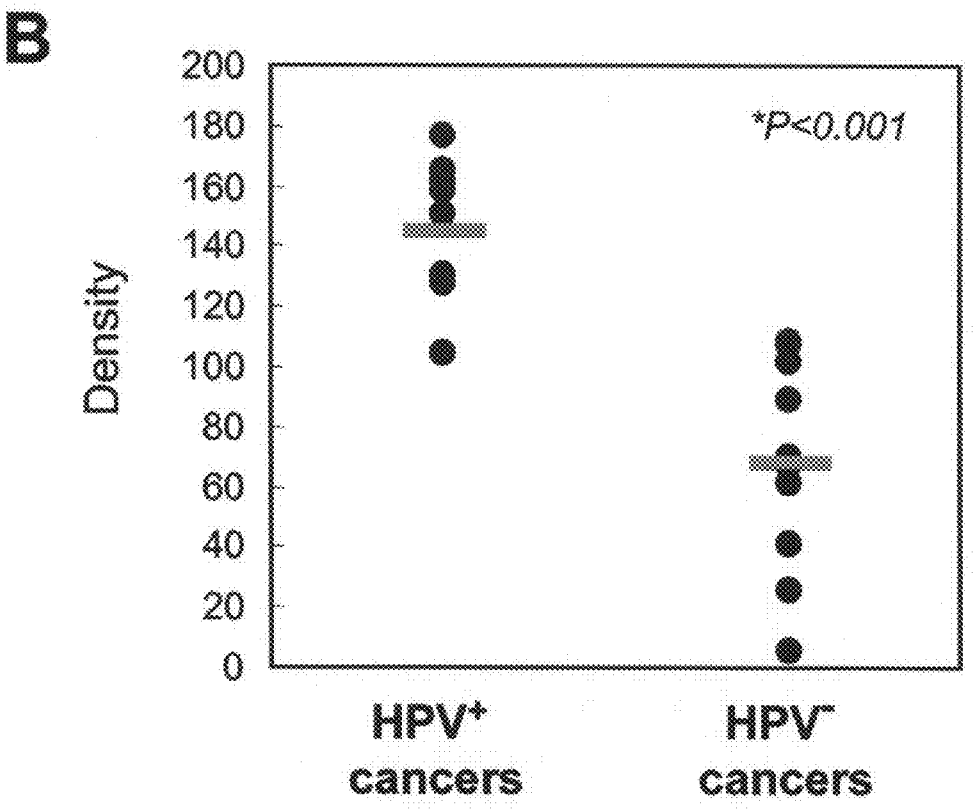

B
Density
200
180
160
140
120
100
80
60
40
20
0
*P<0.001
HPV+ cancers
HPV- cancers

FIG. 4

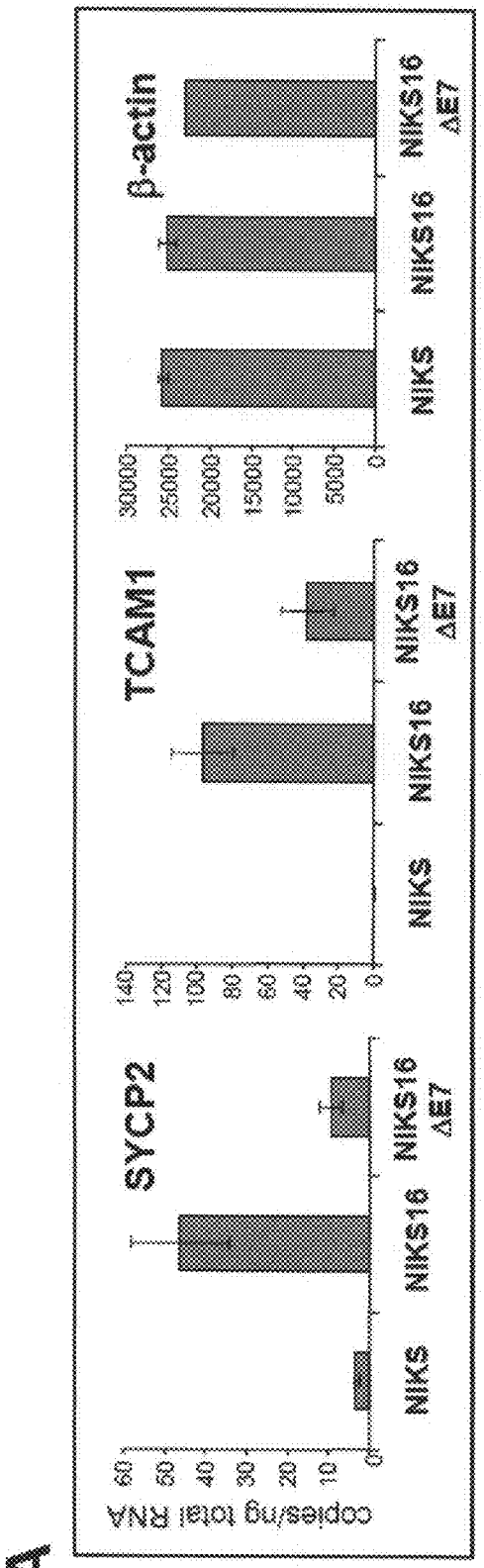
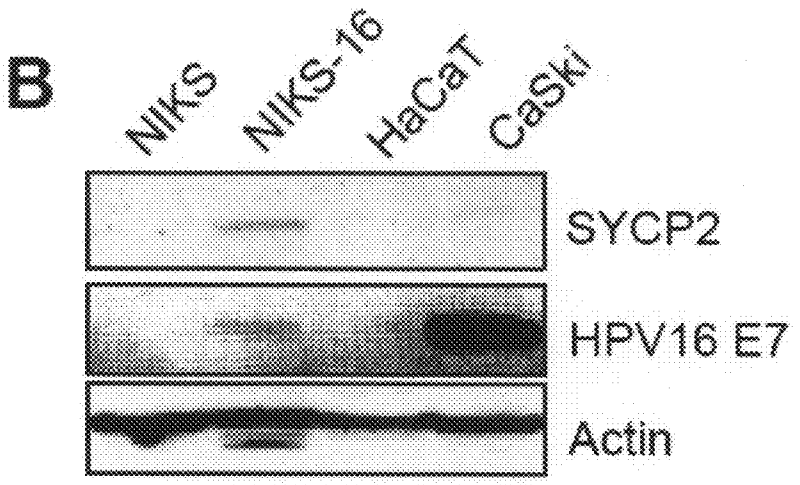

A
copies/ng total RNA
60
50
40
30
20
10
0
NIKS
NIKS16
NIKS16 ΔE7
SYCP2
140
120
100
80
60
40
20
0
TCAM1
30000
25000
20000
15000
10000
5000
0
β-actin

FIG. 5


B
NIKS
NIKS-16
HaCaT
CaSki
SYCP2
HPV16 E7
Actin

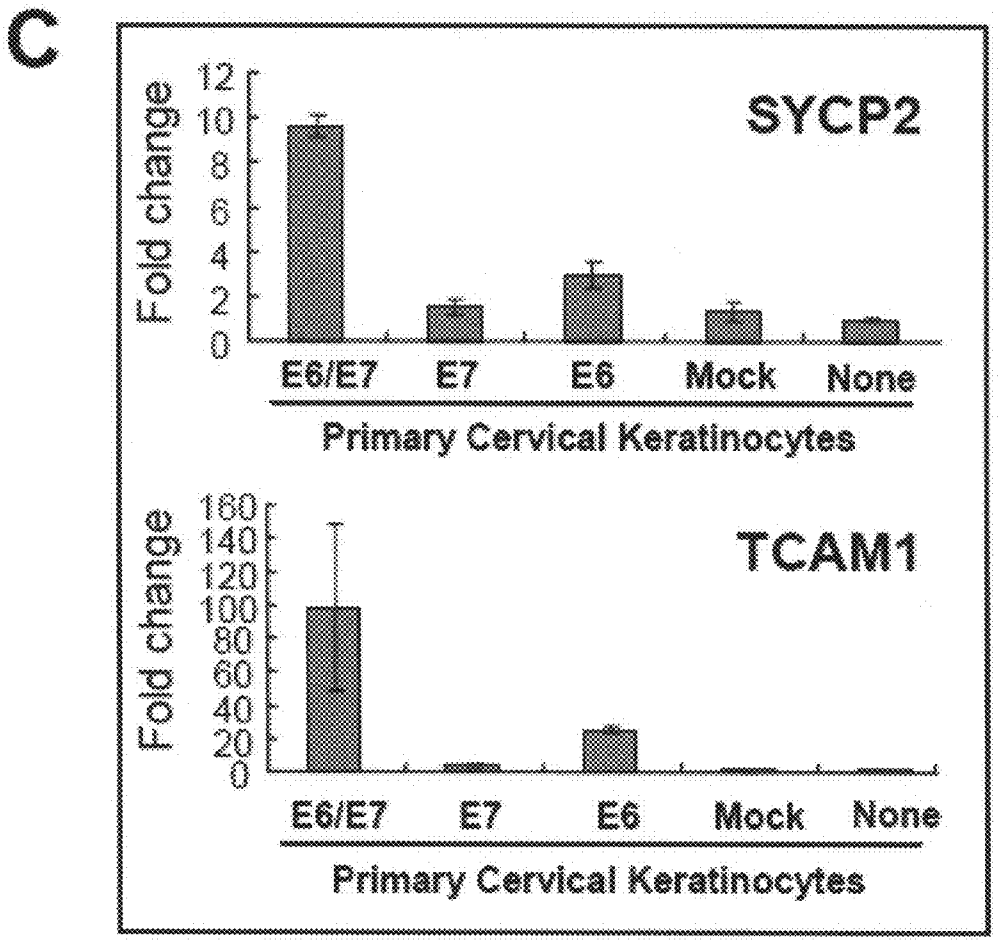

C
SYCP2
Fold change
12
10
8
6
4
2
0
E6/E7
E7
E6
Mock
None
Primary Cervical Keratinocytes
TCAM1
Fold change
160
140
120
100
80
60
40
20
0
E6/E7
E7
E6
Mock
None
Primary Cervical Keratinocytes

FIG. 5

D

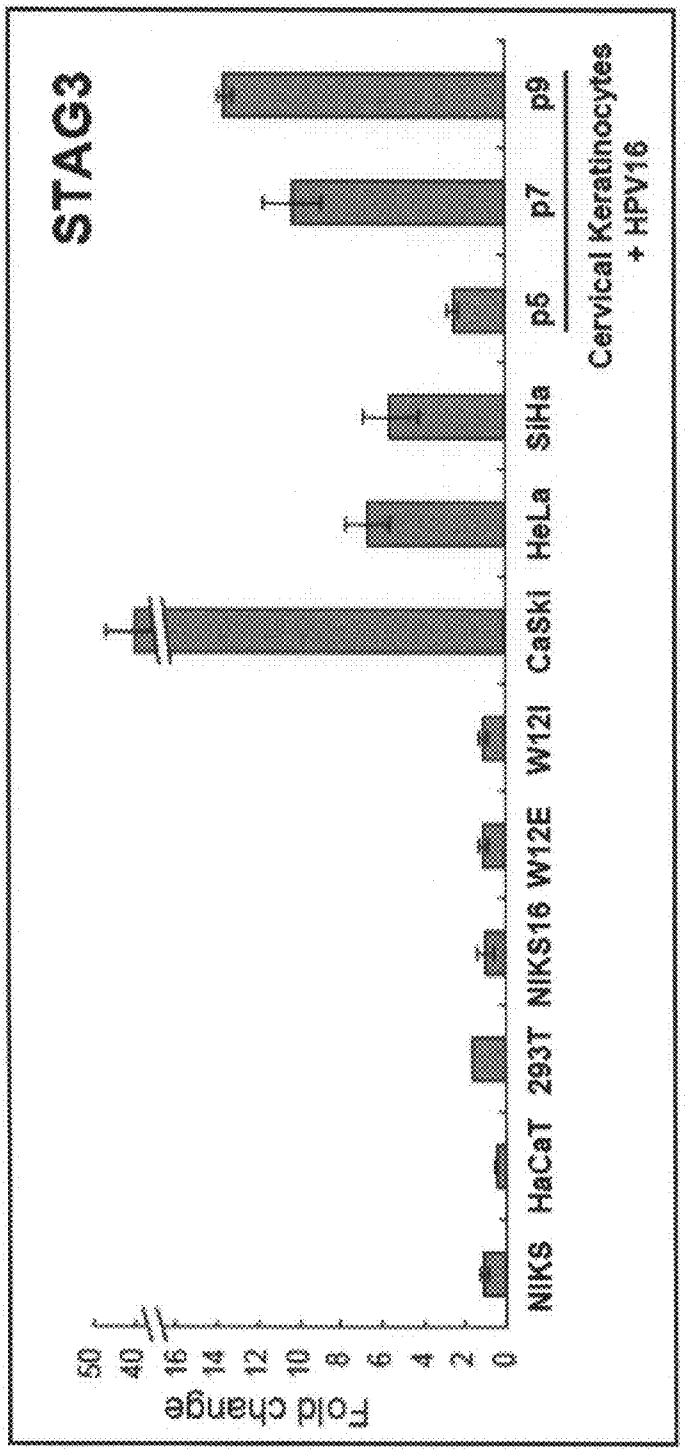

STAG3
Fold change
50
40
16
14
12
10
8
6
4
2
0
NIKS
HaCaT
293T
NIKS16
W12E
W12I
CaSki
HeLa
SiHa
p5
p7
p9
Cervical Keratinocytes
+ HPV16

FIG. 5

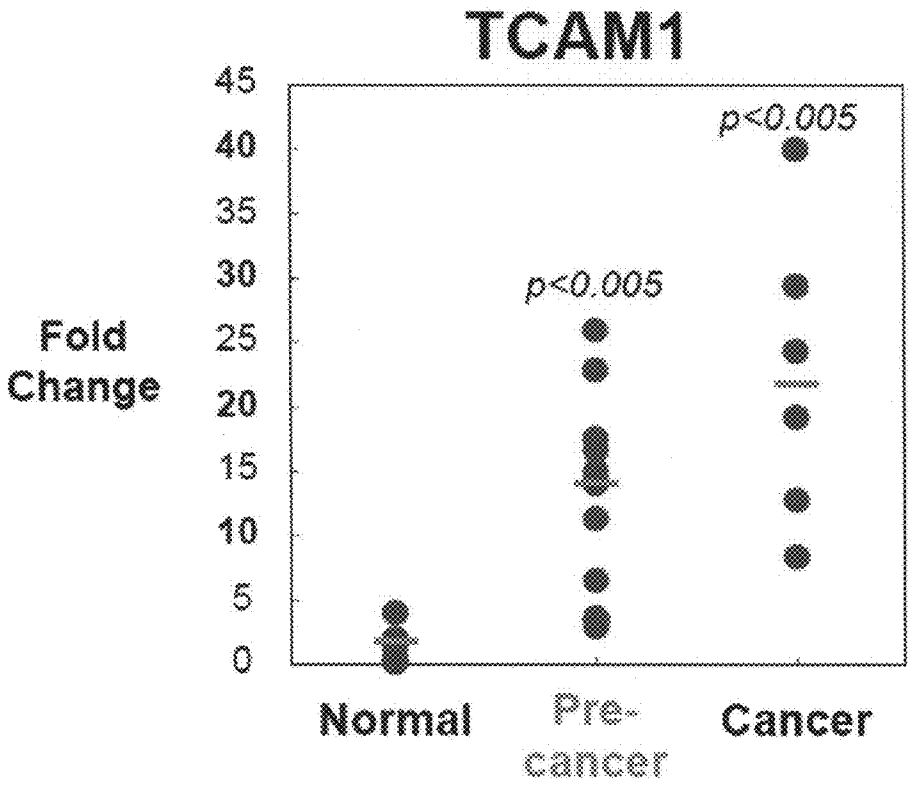

TCAM1
Fold Change
45
40
35
30
25
20
15
10
5
0
p<0.005
p<0.005
Normal
Pre-cancer
Cancer

FIG. 6

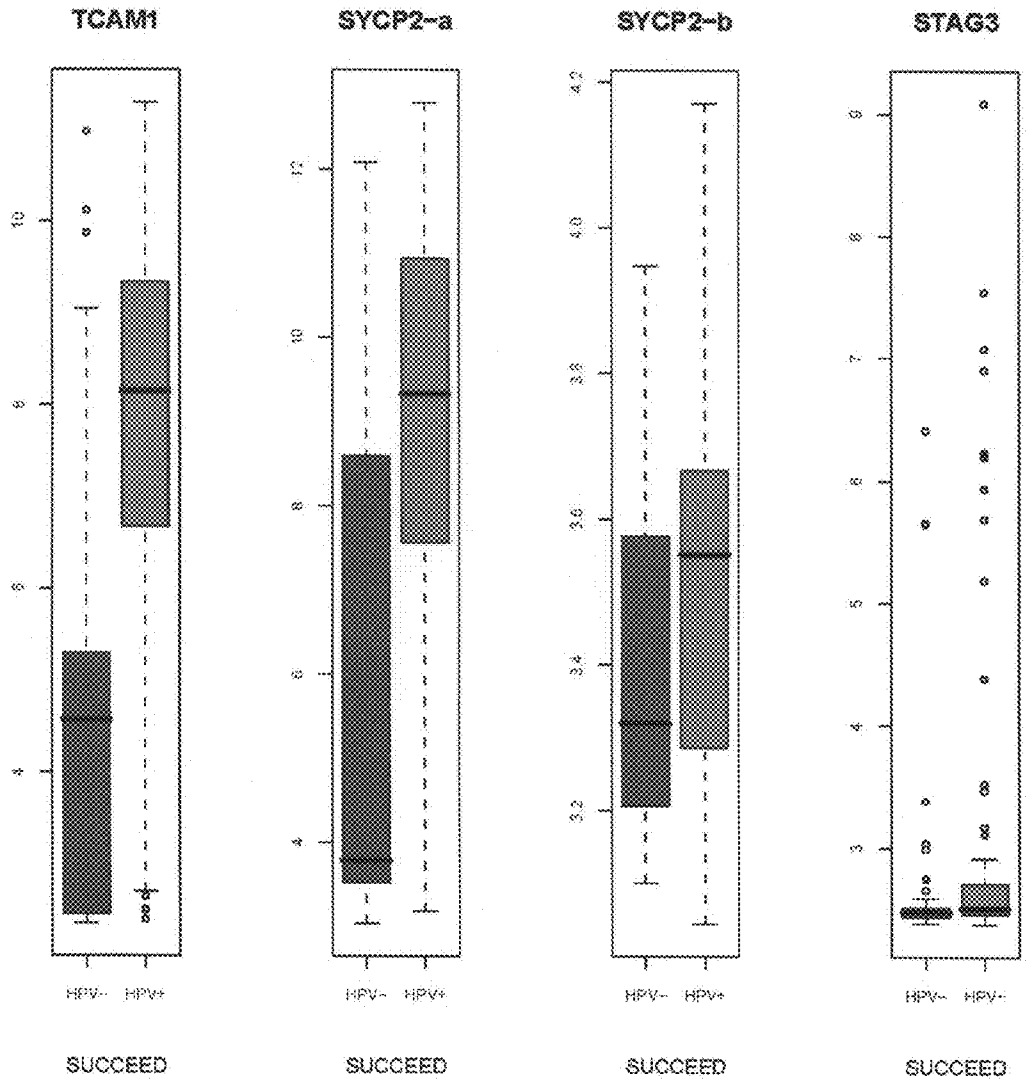


FIG. 7

BIOMARKERS FOR HUMAN PAPILLOMA VIRUS-ASSOCIATED CANCER

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Patent Application No. 60/961,774 filed Jul. 24, 2007, incorporated herein by reference as if set forth in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with United States government support awarded by the following agency: NIH CA097944 and CA022443 and CA064364. The United States has certain rights in this invention.

BACKGROUND OF THE INVENTION

Cervical cancer is the second most common malignancy in women worldwide and is a major cause of morbidity and mortality. Human papillomaviruses (HPV) are DNA viruses that infect and replicate in cutaneous and mucosal epithelia. High-risk mucosotropic HPV genotypes, including HPV16, HPV18 and HPV31, are associated with nearly all cervical cancers.

Head and neck cancer, which arises in mucosal epithelia lining various cavities in the head and neck region, such as the oral cavity and throat, is the sixth most common cancer in the United States with a survival rate of about 50%. 20-30% of head and neck cancers are associated with HPV; whereas the rest are linked to other risk factors, such as tobacco and alcohol.

The art, however, needs methods for predicting and diagnosing HPV, as well as diseases associated with HPV.

BRIEF SUMMARY

Cervical cancer (CC) cells and HPV$^+$ head and neck cancer (HNC) cells express three testis-specific genes not normally expressed in somatic cells: testicular cell adhesion molecule 1 (TCAM1), synaptonemal complex protein 2 (SYCP2) and stromal antigen 3 (STAG3). Among the three markers, TCAM1 and SYCP2 are early detection markers. Various methods for identifying a human or non-human animal as a candidate for further examination for CC, preneoplastic lesion for CC, HNC and preneoplastic lesion for HNC are disclosed. Methods of detecting CC and preneoplastic lesions thereof, methods of detecting HNC and preneoplastic lesions thereof, methods of screening for drugs for treating said cancers and preneoplastic lesions, methods for monitoring the effectiveness of a treatment for said cancers, and methods of treating said cancers are also disclosed. Further disclosed are kits that can be used to practice the above methods.

These and other features, objects and advantages of the present invention will become better understood from the description that follows. In the description, reference is made to the accompanying drawings, which form a part hereof and in which there is shown by way of illustration, not limitation, embodiments of the invention. The description of preferred embodiments is not intended to limit the invention to cover all modifications, equivalents and alternatives. Reference should therefore be made to the claims recited herein for interpreting the scope of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

FIG. **1**: Global gene expression analysis showed similarities and differences among HPV$^+$ HNC, HPV$^-$ HNC and CC. (A) Multidimensional scaling measurements between all indicated pairs of tumor and normal classes of the distances between class-averaged log 2 expression levels over all 54,675 Affymetrix probe sets. The relative distances between each class are approximated in the two-dimensional projection at the left and tabulated at below. (B) Pairwise comparisons of expression alterations from normal for three cancers are shown as scatter plots of average log 2 fold change from normal. Pearson correlations (R) measure global concordance in expression alterations between cancer pairs. Genes are highlighted that show differential expression between HPV$^+$ HNC and HPV$^-$ HNC; tracking into the HPV$^+$ HNC vs. HPV$^+$ CC comparison, these genes are predominantly equivalently expressed between these HPV$^+$ cancers. Dotted lines show median expression changes of red and blue genes, and red and blue arrows indicate the median shifted from HPV$^+$ HNC/HPV$^-$ HNC comparison to HPV$^+$ HNC/CC comparison. (C) Differential expression analysis revealed genes significantly altered between the respective tissue classes. The results of three pairwise comparisons are summarized in the Venn diagram and tabulated fully in Table 3 (HPV$^+$ vs. HPV−), Supplementary Table S5 (Tumor vs. Normal) and Supplementary Table S6 (HNC vs. CC).

FIG. **2**: Gene expression signatures for HPV$^+$ vs. HPV$^-$ cancers and HNC vs. CC cancers. (A) Normalized expression values are shown for all 84 samples and 137 probe sets that were significantly differentially expressed between the HPV$^+$ cancers and the HPV$^-$ cancers. As shown in the key at the bottom right, colors indicate high (red) and low (green) expression, corresponding to a +7.5 to −8.2 log 2 scale of fold change relative to each gene's average across all 84 microarrays. These genes were ordered by hierarchical clustering based on similarities in their expression changes across the samples (see, dendogram at left). Gene sets III and IV showed significantly up- or downregulated probe sets, respectively. HPV$^+$ cancer samples are indicated as red text and HPV$^-$ cancer samples are indicated as blue text on the bottom of a heat map. X axis is patient sample; Y axis is the probe sets, which are listed in order below in Table 2A. (B) Like (A), but using 291 probe sets that were significantly differentially expressed between CC and HNC. Again, X axis is patient sample; Y axis is the probe sets, which are listed in order below in Table 2B. Gene sets V and VII showed significantly upregulated probe sets in CC vs. HNC, while gene set VI showed significantly downregulated probe sets. CC samples are indicated as red text, and HNC samples are indicated as blue text on the bottom of the heat map. * indicates probe set ID that does not have annotated gene name. HPV status is shown as + and − on each sample ID.

FIG. **3**: Cell cycle-related genes were upregulated in HPV$^+$ cancers. X axis is patient sample; y axis is probe sets, which are listed in order below in Table 3A. Highly upregulated genes in HPV$^+$ cancers were analyzed by gene ontology grouping (A). Cell cycle-related genes were selected and plotted on a heat map. HPV$^-$ CCs are indicated with blue bars. Up- and downregulated genes were indicated in cell cycle pathway provided by the KEGG database (B). The red and blue boxes indicate upregulated genes in HPV$^+$ and HPV$^-$ cancers compared to corresponding normal tissue, respectively. A part of the cell cycle-related genes was analyzed using qRT-PCR (C). Fold changes of the gene expression in near-diploid immortalized keratinocytes (NIKS) relative to

gene expression in NIKS-16 are shown. Data are represented as mean+/−standard deviation.

FIG. **4**: Proliferating cell nuclear antigen (PCNA) protein expression was upregulated in HPV$^+$ cancers. Using anti-human PCNA antibody, immunohistochemistry (IHC) was performed with sections of 11 HPV$^+$ and 10 HPV$^-$ cancers. IHC images were analyzed and quantified as described previously (53; see, Supplementary Methods). Representative IHC images (A) and calculated density of all samples (B) are shown. Red bars indicate the mean values of each class. Tissue was also briefly counter-stained with hematoxylin.

FIG. **5**: Testis-specific genes SYCP2 and TCAM1 were induced by HPV16. Real time qRT-PCR was performed with total RNA extracted from NIKS cells with and without HPV16 (A). Also, total RNA from NIKS-16 cells without HPV16 E7 protein expression was used to show that testis-specific gene induction was partially by E7 protein. SYCP2 induction in HPV$^+$ cell lines was confirmed with Western blot analysis using anti-human SYCP2 antibody (B). Real time qRT-PCR was performed with total RNA extracted from primary cervical keratinocytes with either or both HPV16 E6 and E7 delivered by recombinant retrovirus. Retrovirus without HPV16 gene was used as mock control (C). STAG3 mRNA expression in various cell lines was quantified using qRT-PCR, and relative fold change to NIKS cells were plotted (D). Data are represented as mean+/−standard deviation.

FIG. **6**: TCAM1 expression was significantly induced in preneoplastic lesions of cervix (CIN).

FIG. **7**: TCAM1, SYCP2 and STAG2 were all significant induced in HPV+ samples compared to HPV− samples in a second, and larger, study. In the box plots, blue bars indicate HPV+; whereas red bars indicate HPV−; the bars range from 25th to 75th percentiles of each sample. Solid black lines indicate the median. The lines extending from the bars indicate the largest/smallest data point, and circles represent outliers.

While the present invention is susceptible to various modifications and alternative forms, exemplary embodiments thereof are shown by way of example in the drawings and are described herein in detail. It should be understood, however, that the description of exemplary embodiments is not intended to limit the invention to the particular forms disclosed, but on the contrary, the intention is to cover all modifications, equivalents and alternatives falling within the spirit and scope of the invention as defined by the appended claims.

DESCRIPTION OF EXEMPLARY EMBODIMENTS

The present invention is based, in part, on the inventors' observation that human primary tumors of CC cells and HPV$^+$ HNC cells expressed three testis-specific genes not normally expressed in somatic cells. These three testis-specific genes were TCAM1, SYCP2 STAG3. TCAM1 was also upregulated in preneoplastic lesions of cervical cells. Consistent with this finding, which suggests that TCAM1 upregulation is an early event in cancer development, TCAM1 expression was upregulated in early passages of NIKS (a spontaneously immortalized human keratinocyte cell line; see, 54) following HPV infection. A similar observation was made for SYCP2. Therefore, TCAM1 and SYCP2 can be detection markers not only for CC and HNC, but also for the corresponding preneoplastic lesions.

While not intending to be bound to any particular theory, the inventors believe that patients may develop an immune response to these three testis-specific antigens when they are overexpressed in preneoplastic and cancerous tissues; therefore, detecting or measuring the level of an antibody to one of these antigens in a body fluid, such as blood, provides a useful detection tool for CCs and HNCs as well as the corresponding preneoplastic lesions. In addition, TCAM1 resembles intracellular adhesion molecules in amino acid sequence and is expected to be located on cell surface. Accordingly, TCAM1 can be digested at a cell surface, and the extracellular domain part can be released into circulation. Cells containing TCAM1 also can be exfoliated and released into circulation. Either way, a body fluid can be used for detecting the upregulation of TCAM1 in cancer or preneoplastic cells.

The three testis-specific antigens are well known in the art. For example, the amino acid sequences for TCAM1 from mouse and rat can be found at NCBI GenBank Accession numbers CAM23792 (SEQ ID NO:1) and BAA75217 (SEQ ID NO:2), respectively; whereas the cDNA sequence for TCAM1 from human, mouse and rat can be found at NCBI GenBank Accession numbers NR_002947 (SEQ ID NO:3), NM_029467 (SEQ ID NO:4) and NM_021673 (SEQ ID NO:5), respectively.

Likewise, the amino acid sequences for SYCP2 from human, mouse, rat, pig, frog and chimpanzee can be found at NCBI GenBank Accession numbers CAM28338 (SEQ ID NO:6), NP_796165 (SEQ ID NO:7), NP_570091 (SEQ ID NO:8), CAN13245 (SEQ ID NO:9), NP_001072339 (SEQ ID NO:10) and XP_001141311 (SEQ ID NO:11), respectively; whereas the cDNA sequence for SYCP2 from human, mouse, rat, pig, frog and chimpanzee can be found at NCBI GenBank Accession numbers NM_014258 (SEQ ID NO:12), NM_177191 (SEQ ID NO:13), NM_130735 (SEQ ID NO:14), CR956363 (SEQ ID NO:15), NM_001078871 (SEQ ID NO:16) and XM_514753 (SEQ ID NO:17), respectively.

Furthermore, the amino acid sequences for STAG3 from human, mouse, rat, chimpanzee and duck-billed platypus can be found at NCBI GenBank Accession numbers CAB59367 (SEQ ID NO:18), NP_058660 (SEQ ID NO:19), NP_446182 (SEQ ID NO:20), XP_519253 (SEQ ID NO:21) and XP_001516109 (SEQ ID NO:22), respectively; whereas the cDNA sequence for STAG3 from human, mouse, rat, chimpanzee and duck-billed platypus can be found at NCBI GenBank Accession numbers NM_001025202 (SEQ ID NO:23), NM_016964 (SEQ ID NO:24), NM_053730 (SEQ ID NO:25), XM_519253 (SEQ ID NO:26) and XM_001516059 (SEQ ID NO:27), respectively.

As used herein, "cervical cancer" (CC) refers to carcinoma of the uterine cervix (e.g., carcinoma in situ, invasive carcinoma and metastatic carcinoma). CC is preceded with a well-recognized preneoplastic lesion, cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL) in the case of squamous cell carcinoma, and cervical glandular epithelial neoplasia in the case of adenocarcinoma.

As used herein, "head and neck cancer" (HNC) refers to cancer that arises in mucosal epithelia in the head or neck region, such as cancers in the nasal cavity, sinuses (e.g., paranasal sinuses), lip, mouth (e.g., oral cavity), salivary gland, throat (e.g., nasopharynx, oropharynx and hypopharynx), larynx, thyroid and parathyroid. One example of HNC is squamous cell carcinoma.

Although the examples below used samples from subjects with CC and HNC, the inventors contemplate that the methods can be used with any HPV-associated cancer including, but not limited to, anal cancer, CC, HNC, penile cancer, vaginal cancer and vulvar cancer.

In a first aspect, the present invention is summarized as a method for identifying a human or non-human animal as a candidate for further examination for CC. The method

includes the steps of obtaining a tissue sample from a region of the cervix of the human or non-human animal, measuring the expression of TCAM1, SYCP2 or STAG3 at the mRNA or protein level in the cells of the tissue sample, and comparing the expression level to a normal standard, wherein a higher than normal expression indicates that the human or non-human animal is a candidate for further examination for CC.

In one embodiment of the first aspect, the tissue sample can be a cervical smear such as a Papanicolaou (Pap) smear. In another embodiment of the first aspect, the tissue sample can be a fluid collected by vaginal rinsing.

In a second aspect, the present invention is summarized as a method for detecting CC in a human or non-human animal. The method includes the steps of obtaining a tissue sample from a region of the cervix of the human or non-human animal, measuring the expression of TCAM1, SYCP2 and/or STAG3 at the protein or mRNA level in the cells of the tissue sample, and comparing the expression level to a normal standard wherein a higher than normal expression indicates CC.

In one embodiment of the second aspect, the tissue sample can be a cervical smear such as a Pap smear or biopsy sample from the cervix. In another embodiment of the second aspect, the tissue sample can be a fluid collected by vaginal rinsing. Optionally, the method also includes the step of observing CC in the human or non-human animal, e.g., by standard pathological evaluation of a biopsy tissue specimen from the cervix (e.g., histopathological analysis). Known techniques such as radiographic imaging studies may be employed to evaluate for the presence of metastatic lesions.

In a third aspect, the present invention is summarized as a method for detecting preneoplastic lesion of the cervix in a human or non-human animal. The method includes the steps of obtaining a tissue sample from a region of the cervix of the human or non-human animal, measuring the expression of TCAM1 or SYCP2 at the protein and/or mRNA level in the cells of the tissue sample, and comparing the expression level to a normal standard wherein a higher than normal expression indicates a preneoplastic lesion in the cervix.

In one embodiment of the third aspect, the tissue sample can be a cervical smear, such as a Pap smear or a biopsy sample from the cervix. In another embodiment of the third aspect, the tissue sample can be a fluid collected by vaginal rinsing. Optionally, the method also includes the step of observing a preneoplastic lesion of the cervix in the human or non-human animal, e.g., by standard pathological evaluation of a biopsy tissue specimen from the cervix (e.g., histopathological analysis).

In a fourth aspect, the present invention is summarized as a method for identifying a human or non-human animal as a candidate for further examination for HNC. The method includes the steps of obtaining a tissue sample from a head or neck region of the human or non-human animal, measuring the expression of TCAM1 at the protein level, SYCP2 at the protein level, or STAG3 at the protein or mRNA level in the cells of the tissue sample, and comparing the expression level to a normal standard wherein a higher than normal expression indicates that the human or non-human animal is a candidate for further examination for HNC.

In one embodiment of the fourth aspect, the tissue sample can be a saliva specimen, preferably containing exfoliated epithelial cells, or mouth rinse, preferably containing exfoliated epithelial cells. In obtaining a mouth rinse sample, it is preferred that both the mouth and throat are rinsed. In another embodiment of the fourth aspect, the tissue sample can be a mouth swab sample.

In a fifth aspect, the present is summarized as a method for detecting HNC in a human or non-human animal. The method includes the steps of obtaining a tissue sample from a head or neck region of the human or non-human animal, measuring the expression of TCAM1 at the protein level, SYCP2 at the protein level, or STAG3 at the protein or mRNA level in the cells of the tissue sample, and comparing the expression level to a normal standard wherein a higher than normal expression indicates head and neck cancer.

In one embodiment of the fifth aspect, the tissue sample can be obtained from a head or neck region at least part of which is suspected of being cancerous or having preneoplastic development. In another embodiment of the fifth aspect, the tissue sample can be a saliva specimen, preferably containing exfoliated epithelial cells, or mouth rinse, preferably containing exfoliated epithelial cells. In obtaining a mouth rinse sample, it is preferred that both the mouth and throat are rinsed. In yet another embodiment of the fifth aspect, the tissue sample can be a mouth swab sample. Optionally, the method includes the step of observing HNC in the human or non-human animal, e.g., by standard pathological evaluation of a biopsy tissue specimen from the head and neck region (e.g., histopathological analysis). Known techniques such as radiographic imaging studies may be employed to evaluate for the presence of metastatic lesions.

In a sixth aspect, the present invention is summarized as a method for detecting preneoplastic lesion for HNC in a human or non-human animal. The method includes the steps of obtaining a tissue sample from a head or neck region of the human or non-human animal, measuring the expression of TCAM1 or SYCP2 at the protein or mRNA level in the cells of the tissue sample, and comparing the expression level to a normal standard wherein a higher than normal expression indicates a preneoplastic lesion in the head and neck region.

In one embodiment of the sixth aspect, the tissue sample can be obtained from a head or neck region at least part of which is suspected of being cancerous or having preneoplastic development. In another embodiment of the sixth aspect, the tissue sample can be a saliva specimen, preferably containing exfoliated epithelial cells, or mouth rinse, preferably containing exfoliated epithelial cells. In obtaining a mouth rinse sample, it is preferred that both the mouth and throat are rinsed. In yet another embodiment of the sixth aspect, the tissue sample can be a mouth swab sample. Optionally, the method includes the step of observing a preneoplastic lesion in the head and neck region of the human or non-human animal, e.g., by standard pathological evaluation of a biopsy tissue specimen from the head and neck region (e.g., histopathological analysis).

In a seventh aspect, the present invention is summarized as a method for identifying a human or non-human animal as a candidate for further examination for CC, preneoplastic lesion for CC, HNC, preneoplastic lesion for HNC or HPV infection. The method includes the steps of determining the level of TCAM1 in a body fluid from the human or non-human animal, comparing the level to a normal standard, and identifying the human or non-human animal as a candidate for further examination for CC, preneoplastic lesion for CC, HNC, preneoplastic lesion for HNC or HPV infection when the level exceeds the normal standard.

In one embodiment of the seventh aspect, the body fluid can be blood, plasma, serum, lymph, ascitic fluid, a gynecological fluid, urine, a fluid collected by vaginal rinsing, a saliva specimen or a fluid collected by mouth rinsing.

In an eighth aspect, the present invention is summarized as a method for identifying a human or non-human animal as a candidate for further examination for CC, preneoplastic lesion for CC, HNC, preneoplastic lesion for HNC or HPV infection. The method includes the steps of determining the

level of TCAM1 antibodies in a body fluid from the human or non-human animal, comparing the level to a normal standard, and identifying the human or non-human animal as a candidate for further examination for CC, preneoplastic lesion for CC, HNC, preneoplastic lesion for HNC or HPV infection when the level exceeds the normal standard.

In one embodiment of the eighth aspect, the body fluid can be blood, plasma, serum, lymph, ascitic fluid, a gynecological fluid, urine, a fluid collected by vaginal rinsing, a saliva specimen or a fluid collected by mouth rinsing.

In a ninth aspect, the present invention is summarized as a method for detecting HPV infection in a human or non-human animal. The method includes the steps of obtaining a tissue sample from the human or non-human animal, measuring the expression of TCAM1 and SYCP2 at the protein or mRNA level in the cells of the tissue sample, and comparing the expression level to a normal standard wherein a higher than normal expression indicates HPV infection.

A normal standard employed in any of the above methods can be readily established by one of ordinary skill in the art. For example, the expression level in HPV^- cells of the same human or non-human animal, preferably in the same type of cells from the same tissue during an HPV^- or cancer/preneoplastic lesion-free period, can be used as a normal standard. As another example, the expression level in HPV^- cells of a different human or non-human animal, preferably in the same type of cells from the same tissue during a HPV^- or cancer/preneoplastic lesion-free period, can be used as a normal standard. Given that testis-specific antigens are typically not expressed in somatic cells, any significant expression detected would represent a higher than normal expression. Similarly, TCAM1 protein level or TCAM1 antibody level in a body fluid from HPV^- or cancer/preneoplastic lesion-free individuals can likewise be used as a normal standard.

Any tissue sample used in the methods of the present invention can be subjected to a variety of well-known, post-collection preparative and storage techniques (e.g., nucleic acid and/or protein extraction, fixation, storage, freezing, ultrafiltration, concentration, centrifugation, etc.) prior to being used for detecting or measuring the expression of a marker provided herein.

When the mouth, throat or cervix area is rinsed to collect a tissue sample for detecting TCAM1, a suitable protease, such as trypsin, chymotrypsin or arginine carboxylase, that can cleave and release the entire or a substantial part of the extracellular domain of TCAM1 can be included in the rinsing fluid.

In a tenth aspect, the present invention is summarized as a method for identifying an agent as a candidate for treating CC or HNC. The method includes the steps of exposing CC cells or HNC cells expressing TCAM1, SYCP2 or STAG3 to a test agent, measuring the expression level of the marker, and comparing the expression level to that of control cells not exposed to the test agent, wherein a lower than control expression indicates that the agent is a candidate for treating CC or HNC. The cancer cells used can be either established cancer cell lines or cancer cells from one or more patients.

In an eleventh aspect, the present invention is summarized as a method for determining the effectiveness of a treatment for CC or HNC. The method includes the steps of measuring the expression of TCAM1, SYCP2 or STAG3 in a first sample from a CC or HNC patient prior to providing at least a portion of the treatment to the patient, measuring the expression of the marker in a second sample from the patient after said portion of the treatment is provided to the patient, and comparing the expression levels of the first sample and second sample, wherein a lower expression level in the second sample indicates that the treatment is effective.

In a twelfth aspect, the present invention is summarized as a method for treating or preventing CC, a preneoplastic lesion of CC, HNC, or a preneoplastic lesion of HNC in a human or non-human animal. The method includes the step of administering to the human or non-human animal having CC or HNC an active agent in an amount effective to treat CC or HNC, wherein the active agent contains a therapeutic agent (e.g., a chemotherapeutic agent) for CC, HNC or preneoplastic lesions thereof and a binding agent that can bind to TCAM1 (e.g., a ligand or antibody of TCAM1). The therapeutic agent and the binding agent are linked together. The therapeutic agent can be linked to the binding agent either covalently, through a linker or a chemical bond, or noncovalently, through ionic, van der Waals, electrostatic or hydrogen bonds. The therapeutic agent is typically a cytotoxic agent that can cause the death of a target cell. Similarly, an active agent can also contain a therapeutic agent and a targeting nucleic acid that can hybridize to a portion of the mRNA of TCAM1, SYCP2 or STAG3, wherein the therapeutic agent and the targeting nucleic acid are linked together.

As used herein, "antibody" includes an immunoglobulin molecule immunologically reactive with a particular antigen, and includes both polyclonal and monoclonal antibodies. The term also includes genetically engineered forms such as chimeric antibodies (e.g., humanized murine antibodies) and heteroconjugate antibodies (e.g., bispecific antibodies). For example, the term includes bivalent or bispecific molecules, diabodies, triabodies and tetrabodies. Bivalent and bispecific molecules are described in, e.g., Kostelny et al., J Immunol 148:1547 (1992); Pack & Pluckthun, Biochemistry 31:1579 (1992); Zhu et al., Protein Sci. 6:781 (1997); Hu et al., Cancer Res. 56:3055 (1996); Adams et al., Cancer Res. 53:4026 (1993); and McCartney et al., Protein Eng. 8:301 (1995). The term "antibody" also includes antigen binding forms of antibodies, including fragments with antigen-binding capability (e.g., Fab', $F(ab')_2$, Fab, Fv and rIgG). The term also refers to recombinant single chain Fv fragments (scFv). Preferably, antibodies employed to practice the present invention bind to its target protein with an affinity (association constant) of equal to or greater than 10^7 M^{-1}.

In a thirteenth aspect, the present invention is summarized as a kit for detecting the expression of TCAM1, SYCP2 or STAG3. The kit includes at least one of (i) an agent such as an antibody or a ligand that specifically binds to TCAM1, SYCP2 or STAG3 and (ii) a nucleic acid (e.g., a primer for PCR amplification or a probe for detection) that hybridizes to a polynucleotide containing a nucleotide sequence of TCAM1, SYCP2 or STAG3 cDNA or complements thereof. The kit also includes at least one control sample having a known amount of (i) a polypeptide containing an amino acid sequence of TCAM1, SYCP2 or STAG3 or (ii) a polynucleotide containing a nucleotide sequence of TCAM1, SYCP2 or STAG3 cDNA or complements thereof.

Examples of control samples include CC cells, preneoplastic cervical cells, normal cervical cells, HNC cells, preneoplastic head and neck cells, normal head and neck cells, an extract of any of the foregoing cells, a body fluid sample of a human or non-human animal having CC or HNC cancer, and a body fluid sample of a normal human or non-human animal.

In one embodiment of the thirteenth aspect, the control sample can be an isolated polypeptide containing an amino acid sequence of TCAM1, SYCP2 or STAG3. In another embodiment of the thirteenth aspect, the control sample can

be an isolated nucleic acid containing a nucleotide sequence of TCAM1, SYCP2 or STAG3 cDNA or complements thereof.

Expression of a marker provided herein may be assessed by any of a wide variety of well-known methods for detecting the expression of a gene at the protein or mRNA level. Non-limiting examples of such methods include immunological methods for detection of a target protein, protein purification methods, protein function or activity assays, nucleic acid hybridization methods, nucleic acid reverse transcription methods and nucleic acid amplification methods.

Preferably, expression of a marker can be assessed at the protein level using an antibody (e.g., a radio-labeled, chromophore-labeled, fluorophore-labeled or enzyme-labeled antibody) or an antibody derivative (e.g., an antibody conjugated with a substrate or with the protein or ligand of a protein-ligand pair (e.g., biotin-streptavidin)) that binds specifically to the marker protein or fragment thereof. For example, enzyme linked immunosorbent assays (ELISAs), Western blot analysis and in situ hybridizations can be employed for this purpose.

Alternatively, expression of a marker can be assessed at the mRNA level by preparing and detecting/measuring mRNA/cDNA from cells. For example, RT-PCR (e.g., quantitative RT-PCR), Southern blot analysis, Northern blot analysis, and in situ hybridizations can be used for this purpose. It is well within the capability of one of ordinary skill in the art to design primers and probes for assessing the expression of a marker at the mRNA level.

As for any cell surface protein, the expression of TCAM1 can be analyzed either qualitatively or quantitatively by flow cytometry. In addition, in vivo medical imaging can be used to detect or quantify the expression of TCAM1. For example, a suitable contrast agent can be linked to a TCAM1 binding agent (e.g., a TCAM1 ligand or antibody) and administered to an individual. Cells that express TCAM1 can be imaged as the contrast agent is retained by these cells due to the binding of the antibody to TCAM1 on the surface of the cells. Similarly, a suitable contrast agent can be linked to a targeting nucleic acid that can hybridize to TCAM1 mRNA and administered to an individual. Cells that express TCAM1 will retain the contrast agent as the targeting nucleic acid hybridizes to TCAM1 mRNA in these cells. As a result, cells that express TCAM1 can be imaged. Any suitable medical imaging techniques can be used. Examples of such techniques include ultrasound, computerized tomography (CT), magnetic resonance imaging (MRI) and nuclear medicine techniques such as gamma ray detection by a gamma ray detector (e.g., a gamma scintillation camera or a 3-dimensional imaging camera), positron emission tomography (PET) and single photon emission computed tomography (SPECT). One of ordinary skill in the art can readily link a contrast agent to a TCAM1 binding agent or TCAM1 mRNA targeting nucleic acid (e.g., covalently through a linker or a chemical bond). For example, for MRI detection, a superparamagnetic iron oxide nanoparticle (SPION) can be conjugated to a TCAM1 antibody or TCAM1 mRNA targeting nucleic acid for administration and MRI detection. For nuclear medicine detection, radionuclide-labeled TCAM1 antibody or radionuclide-labeled TCAM1 mRNA targeting nucleic acid can be administered and radiation emission from the nucleotide can be measured and an image thereof can be obtained. WO 2006/023888 describes linking a medical imaging contrast agent to a nucleic acid probe for imaging gene expression in various tissues by, e.g., MRI. WO 2006/023888 is herein incorporated by reference as if set forth in its entirety.

By way of example, but not limitation, examples of the present invention are described below.

EXAMPLES

Example 1

Differences in Gene Expression in Human Papillomavirus-Positive and -Negative Head/Neck and Cervical Cancers and Gene Expression in Preneoplastic Lesion of Cervical Cancer

Appendix I

Appendix I provides supplementary methods figures, and tables and is herein incorporated by reference in its entirety.

Materials and Methods

Tissue samples: 15 and 27 HNC samples were from the University of Iowa and Harvard School of Public Health, respectively. 5 and 9 HNN samples were from the University of Iowa and the National Disease Research Interchange (NDRI), respectively (Supplementary Table S1). CC and normal cervical samples were from the Gynecologic Oncology Group. Patient information is presented in Table 1A and Supplementary Table S1. All tissue samples were fresh frozen in liquid nitrogen and collected with patients' consent under approval of the Institutional Review Boards from all participating institutions. Also, all the tumor samples were primary resections collected before the initiation of chemotherapy radiotherapy. Each sample was processed, and RNA was prepared and labeled as described in Supplementary Methods.

Human and HPV microarrays: Human gene expression was profiled using Affymetrix U133 Plus 2.0 Arrays (Affymetrix; Santa Clara, Calif.). For HPV detection and genotyping, 70-mer oligonucleotide probes with a T_M of 80° C. (Supplementary Methods) were designed using Oligowiz 1.0 (16), were purchased from MWG-Biotech (High Point, N.C.) and were spotted in quadruplicate on epoxy glass slides (TeleChem International, Inc.; Sunnyvale, Calif.) with a BioRobotics MicroGrid II (Genomic Solutions; Ann Arbor, Mich.). HPV array hybridization was carefully optimized using RNA from known HPV^+ and HPV^- keratinocyte cell lines (Supplementary Methods). HPV arrays were hybridized with biotin-labeled cRNA, processed as in Supplementary Methods, and scanned using an Agilent DNA Microarray Scanner (Agilent; Palo Alto, Calif.). Images were analyzed using Axon GenePix Pro 5.1 Software (Molecular Devices; Sunnyvale, Calif.). 10 μg of cRNA was used for Affymetrix microarray hybridization and scanning at the University of Wisconsin Biotechnology Gene Expression Center (Madison, Wis.). To obtain statistically significant sample number in each group while minimizing unnecessary sample processing and microarray use, inventors selected HNC samples based in part on HPV status.

Statistical analysis: Tools in R (17) and Bioconductor (18) were adapted for statistical analysis. Probe set summary measures were computed by robust multiarray averaging (19) applied to the combined set of 84 microarrays. Average base-2 log expression was used to summarize each probeset's expression within a tissue class. Multidimensional scaling allowed global (i.e., averaged over the genome) comparisons between classes, and class-restricted nonparametric bootstrap sampling (20) was used to measure the significance of observed differences between global correlations computed on pairs of tumor classes. Permutation testing was used to confirm that each measured correlation was significantly

non-zero. The primary analysis of differential gene expression at the probe-set level was done in three pairwise comparisons: Tumor versus Normal, HPV^+ vs. HPV^-, and HNC vs. CC. Fold changes and t-statistics were used to identify differentially expressed probe sets; the latter were converted to q-values to control false discovery rate (21).

Enrichment of gene ontology (GO) categories for differentially expressed genes was measured using random-set testing methods (22, 23). Briefly, the proportion of significantly altered genes and the average log fold change for all genes in each of 2760 GO categories were compared, respectively, to their distributions on a random set of genes in order to obtain standardized enrichment Z scores. A category was considered significantly enriched for altered genes if both of these Z scores exceeded 4 (nominal p-value 3×10^{-5}). Calculations used version 1.0 of the R package allez, and the October 2005 build of Bioconductor package hgu133plus2. The same Z score standardization applied to class-averaged expression profiles (above) was used to compute GO profiles for each tissue class. These were correlated between classes to assess the similarity of tissue classes.

The inventors developed a parametric testing strategy (20) to evaluate the significance of apparent profile-defined tumor subgroups of the HPV^+HNC tumors (Supplementary FIG. S**4**A-C). Specifically, a multivariate normal distribution was fit to data from the 16 HPV^+ HNC arrays using n=100 genes most differentially expressed between HPV^+ cancers and HPV^- cancers (FIG. **2**A). The rationale was that such a unimodal Gaussian distribution represents a baseline null hypothesis of no actual subgrouping from which the significance of apparent subgroups could be gauged. Because the sample covariance matrix was rank deficient, inventors an empirical Bayes estimate of covariance (24) and repeatedly (104 times) sampled multivariate random n-vectors from a centered normal population with this covariance matrix. Using each bootstrap sample we divided the 16 tumors according to the subgrouping derived at the penultimate merge of a hierarchical cluster analysis. Each split was scored by the average of the squared t-statistics between the two subgroups, which is large if the subgroups are relatively well separated. The average squared t statistic on the subgroups identified by hierarchical clustering of the actual data was compared to the distribution of such scores derived, as above, on the null hypothesis that the profiles emerge from a single, multivariate normal, population, and a p-value was computed. To assess sensitivity, the inventors repeated the calculations at a range of gene set sizes n.

Tissue culture, quantitative reverse transcriptase-PCR, Western blot analysis and immunohistochemistry were performed as described in Supplementary Methods.

Results

Tissue samples, microarray profiling, and HPV status: Eighty four samples including 42 HNC, 14 head and neck normals (HNN), 20 CC and 8 cervical normals (CN) were cryosectioned, and selected sections were stained with hematoxylin and eosin, verified free of autolysis and freezing artifacts, and analyzed histopathologically. Relevant patient information is summarized in Table 1A and Supplementary Table S1. All tumor samples were collected prior to chemo- or radiotherapy. For all normal tissues and tumors with less than 90% cancer cells (61/84), laser microdissection was performed to capture normal epithelial or tumor cells, respectively (Supplementary FIG. S**1**). Complementary RNA (cRNA) was prepared and hybridized to Affymetrix U133 Plus 2.0 microarrays containing oligonucleotide probes for all known expressed human mRNAs. Normalization was performed as described in Experimental Procedures. Resulting microarray data were deposited to the NCBI Gene Expression Omnibus database under general accession number GSE6791 and sample accession numbers in Supplementary Table S1.

HPV status and genotype were determined by hybridization to custom-made 70-mer oligonucleotide microarrays containing probes for all 37 known mucosotropic HPV genotypes plus positive and negative control probes. These microarrays were sufficiently sensitive to detect HPV in cell lines harboring a few extrachromosomal copies or a single integrated copy of HPV DNA. No normal tissue showed any significant HPV signal but, consistent with prior findings (3), 16 of 42 HNCs harbored HPV (13 HPV16, two HPV33, and one HPV18; Table 1B). About half of CC were HPV16-positive, with lesser numbers carrying HPV genotypes 18, 31, 33, 35, 58 or 66 (Table 1B). Three of 20 CCs hybridized well to control cell mRNA probes but showed no detectable HPV signal. PCR with consensus HPV L1 primers MY09-MY11 (25) confirmed absence of detectable HPV DNA in these samples (Supplementary FIG. S**2**).

Since these samples shared some expression patterns with HPV^+ CC and HNCs (see, below), they may contain HPV, possibly with sequence variations inhibiting detection by these sequence-specific methods (26). However, varying the HPV status assigned to these three CCs had only minimal effects on the gene expression signature differentiating HPV^+ and HPV^- cancers. Comparisons of HPV^+ and HPV^- cancers with these samples included as HPV^- CC, as HPV^+ CC, or excluded all revealed HPV-specific expression signatures dominated by a robust common core of nearly 140 genes. The analysis below reports HPV^+ and HPV^- cancer comparisons based on the original HPV^- assignment of these CCs, since this yielded the best-conserved core expression signature (137 genes), while the alternate assumptions each added some additional genes whose differential expression levels were not as well conserved across the analyses.

Gene expression relationships among HPV^+ and HPV^- HNCs and CCs: Global pairwise comparisons of complete mRNA expression profiles between all tumor and normal sample classes were performed by multidimensional scaling (27). This analysis (FIG. **1**A) measures for each pair of tumor and normal classes the distances between class-averaged log 2 expression levels over all 54,675 Affymetrix probe sets. Not surprisingly, the most closely related classes were HPV^+ HNC and HPV^- HNC (average distance=0.17). Notably, next closest were the two HPV^+ cancers, HPV^+ HNC and HPV^+ CC, whose distance of 0.21 was closer than either to its corresponding normal (0.29, 0.53).

The global effect of virus-specific and tissue-specific factors is further illustrated in FIG. **1**B, which compares for paired tumor classes the log 2 average expression levels, relative to corresponding normals, of all probe sets. The indicated Pearson correlation coefficients confirm that the highest correlation is between HPV^+ HNC and HPV^- HNC (R=0.81). The substantial correlation between HPV^+ HNCs and HPV^+ CCs (R=0.58), well above HPV^+ CCs and HPV^- HNCs (R=0.46), again implies a substantial role for virus-dependent, tissue-independent factors in gene expression changes. HPV^+ HNC vs. HPV^+ CC correlation exceeds the HPV^- HNC vs. HPV^+ CC correlation in over 90% of bootstrap sampled data sets, and all correlations were significant by permutation analysis. Thus, both HPV status and tissue type contribute to the relatedness and distinction of HPV^+ HNCs, HPV^- HNCs and HPV^+ CCs.

To offset variation in probe set-level measurements, the inventors performed similar correlation analyses on fold changes averaged over Gene Ontology (GO) gene classes

rather than individual probe-sets, reinforcing the findings above (Supplementary FIG. S3A).

While HPV+ HNC and HPV− HNC exhibited generally high positive correlation in gene expression changes from normal, many genes had altered expression between these two classes. FIG. 1B highlights 47 genes selectively upregulated (red points) and 45 genes selectively downregulated (blue points) by >2.6 fold in HPV+ HNC relative to HPV− HNC (see also, Supplementary Table S3A and S3B). Notably, for genes that were highly upregulated in HPV+ HNC relative to HPV− HNC, parallel comparison of expression levels between HPV+ HNC and CC shifted their distribution in the plot dramatically rightward, revealing substantial correlated expression in these two HPV+ cancers (red arrow and points in FIG. 1B, middle panel).

Conversely, genes that were significantly downregulated in HPV+ HNC relative to HPV− HNC showed a substantial but opposite leftward shift into greater correlation in a comparison plot of expression levels between HPV+ HNC and CC (blue arrow and points in FIG. 1B, middle panel). Thus, the tumor-specific expression changes in these genes correlated much more strongly with the presence of HPV than the tissue site.

To further analyze gene expression changes based on tumor/normal, HPV+/HPV−, and HNC/CC differences, the inventors identified for each comparison differentially expressed genes with fold change >2 and t-test q-value <0.001. By these criteria, as shown in FIG. 1C, 1701 and 243 genes were up- and downregulated, respectively, in tumors relative to normals, while 124 and 13 genes were up- and downregulated in HPV+ relative to HPV− cancers, and 256 and 35 genes were up- and downregulated in CC relative to HNC.

More specifically, in tumor/normal comparisons (Supplementary FIG. S3B and Table S5), HPV+ HNC, HPV− HNC and CC all were upregulated relative to normals for a gene set I including keratins (KRT8, 17, 18), caveolin (CAV2), interferon α-inducible protein 6-16 (G1P3), matrix metallopeptidase 12 (MMP12), collagens (COL4A1, COL4A2) and phospholipid scramblase 1 (PLSCR1), and downregulated for another set II including other keratins (KRT4, 13, 15), programmed cell death 4 (PDCD4), protein tyrosine kinase 6 (PTK6), epithelial membrane protein 1 (EMP1), extracellular matrix protein 1 (ECM1), interleukin 1 receptor (IL1R2) and transglutaminase 3 (TGM3).

Relative to HPV− HNC (FIG. 2A, Table 2A), HPV+ HNC and CC showed significantly increased expression of gene set III, including PC4/SFRS1-interacting protein 1 (PSIP1), V-myb (MYB), synaptogyrin 3 (SYNGR3), SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin (SMARCA2), SYCP2, p16 (CDKN2A), lymphoid-specific helicase (HELLS) and TCAM1, while expression was decreased for gene set IV, including parathyroid hormone-like hormone (PTHLH), cortactin (CTTN), kallikreins (KLK8, 10), cyclin D1 (CCND1), caveolin 1 (CAV1) and defensin β4 (DEFB4). At the GO category level (Supplementary Table S4A), HPV+ cancers were upregulated relative to HPV− cancers for annotations related to DNA replication and cell cycle, and downregulated in genes involved in epidermal development and hormone activity.

In comparison between CC and HNC (FIG. 2B, Supplementary Table S6), CCs showed significantly upregulated expression of gene sets V and VII, including estrogen receptor 1 (ESR1), keratin 19 (KRT19), X (inactive)-specific transcript (XIST) and zinc finger protein 367 (ZNF367), while HNC showed increased expression of gene set VI (FIG. 2B, Supplementary Table S6), including dermatopontin (DPT), desmocollin 1 (DSC1), melanoma antigen A12 (MAGEA12) and chromosome Y open reading frame 15B (CY or f15B).

A distinct subgroup in HPV+ cancers: Hierarchical clustering of differentially expressed genes between HPV+ and HPV− cancers revealed two subgroups of HPV+ cancers (Supplementary FIGS. S4A and S4B). These subgroups (α and β) were not correlated with any identified sample characteristics including anatomical site, age, or clinical stage (Supplementary Table S1A) and were robustly preserved when the grouping was repeated using different agglomeration methods for clustering and varying numbers of differentially expressed genes.

The smaller subgroup, α showed high up-regulation of a set of B lymphocyte/lymphoma-related genes including baculoviral IAP repeat 3 (BIRC3), butyrophilin-like 9 (BTNL9), DKFZ P564O0823, homeobox C6 (HOXC6), and B-cell CLL/lymphoma 11A (BCL11A) (Supplementary FIG. S4C, Supplementary Table S7). B cell-related gene expression by this tumor subgroup was not due to tumor-infiltrating B cells, since there was no correlation between this subgroup and expression of CD19, CD20, and immunoglobulins, which are expressed in B cells throughout most or all circulating stages (28).

Subgroup α also was upregulated relative to other HPV+ cancers for genes expressed by endothelial cells, including vascular cell adhesion molecule 1 (VCAM1) and zinc finger protein 62 (ZNF62) and downregulated for genes, including several small proline-rich proteins (SPRR1A and SPRR2A), keratins (KRT6B and KRT16), and gap junction proteins (GJB2 and GJB6) (Supplementary FIG. S4C; Supplementary Table S7). Expression of synaptopodin (SYNPO2), an important regulator of cell migration (29), was increased >20-fold in this subgroup relative to other HPV+ cancers, suggesting potentially increased invasiveness.

Due to variations among microarray platforms and methods, reproducibility of expression profiling has been one of the biggest challenges in microarray studies of cancer (30). Chung et al. (5) recently reported dividing 60 HNCs into four subgroups by gene expression patterns. However, clustering of the inventors' samples based on the genes reported as differentially-expressed signatures of these four subgroups revealed little significant correlation. Possible causes for this lack of correlation include use of whole samples in the prior study vs. selectively microdissected samples here, differences in the microarray platforms used, or limitations in sample group sizes in these studies. Supplementary FIG. S5A shows the best association of our HNC samples into four groups based on the prior signature gene sets. Though weak, the B lymphocyte/lymphoma-related subset α identified in Supplementary FIG. S4 showed the most similarity for Chung et al.'s subgroup 2, in that most genes in Chung et al.'s set E were downregulated and, for two of the 6 relevant tumors (HNC005, HNC012), some genes in set F were upregulated, primarily including mesenchymal markers associated with poorer clinical outcomes (5, 31): syndecan, vimentin, and some collagens (Supplementary Table S8).

HPV+ and HPV− cancers are activated in different components of the cell cycle pathway: E7 oncoproteins of high risk HPVs induce DNA replication and mitosis by multiple mechanisms including interacting with pRb, HDACs and other factors to activate cell cycle-regulated transcription factors such as E2F (32-34). However, the extent of resulting gene expression changes, the full contributions of other HPV genes and additional genetic changes to oncogenesis, and the relation of these effects to those in HPV− HNC have not been determined. To test for differential expression in HPV+ versus HPV− cancers, we examined cell cycle-related genes based

on GO classification. A significant subset of cell cycle-regulated genes was differentially expressed in HPV$^+$ HNC and CC relative to HPV$^-$ HNC (FIG. **3**A, Table 2B). As shown in FIG. **3**B, HPV$^-$ HNCs upregulated, relative to HPV$^+$ cancers, a small set of cell cycle-specific genes including cyclin D1/D2 (CCND1 and CCND2) (G1-associated) and cyclin A1 (CCNA1) (FIGS. **3**A, set VIII, and **3**B).

By contrast, HPV$^+$ cancers upregulated, relative to HPV$^-$ HNC, a much larger set of cell cycle-specific genes such as cyclin E2 (CCNE2; G1-associated), cyclin B1 (CCNB1; G2-associated), and multiple MCMs (FIGS. **3**A, set IX, and **3**B). Among these, many genes that enhance DNA replication and cell mitosis including proliferating cell nuclear antigen (PCNA), E2Fs, cdc2, cdc7 and MCMs were significantly upregulated in HPV$^+$ HNC and CC relative to HPV$^-$ HNC, implying that the HPV$^+$ cancers were more active in cell division.

A subset of these genes were analyzed by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) with total RNA extracted from naturally immortalized human keratinocyte lines NIKS-16 and NIKS, which have and lack an extrachromosomal HPV16 genome, respectively (35). In keeping with the microarray results, p16, cdc7, origin recognition complex 1 (ORC1), kinetochore-associated protein (KNTC1), MCM6, cyclin B1 (CCNB1), BUB1, cdc2 and cdc20 were highly upregulated by HPV16, while cyclin A1 (CCNA1) was downregulated (FIG. **3**C). Since the NIKS-16 cells were only 5 to 6 passages after stable HPV16 transfection, these results indicate that HPV deregulates a subset of cell cycle-related genes soon after being acquired by cells. To eliminate possible effects of the prior spontaneous immortalization of NIKS cells, the inventors measured gene expression levels in normal (i.e., early passage) cervical epithelial cells transduced with HPV16 E6 and/or E7 oncogenes. The results confirmed NIKS data, showing an upregulation of CCNB1, cdc2, ORC1 and p16 by HPV16 E6 and E7 expression (Supplementary FIG. S**6**). Moreover, immunohistochemistry showed that tumor cells in HPV$^+$ cancers expressed significantly ($p<0.001$) higher levels of PCNA protein than HPV$^-$ tumor cells (FIG. **4**). In addition, PCNA protein levels were highly correlated with cell cycle-related gene expression levels (Supplementary Table S9). Together, these results indicate that HPV acts in HPV$^+$HNCs and CCs to deregulate the cell cycle pathway in shared ways that are markedly distinct from HPV$^-$HNCs.

Upregulation of Novel Testis antigens in HPV$^+$ cancers: Genes highly upregulated in HPV$^+$ cancers relative to HPV$^-$ HNC included two testis-specific genes not normally expressed in somatic cells—SYCP2 and TCAM1 (FIG. **2**A and Table 2A). qRT-PCR showed that SYCP2 and TCAM1 expression increased >15 and >100,000 fold, respectively, in HPV16$^+$ NIKS-16 relative to HPV16$^-$ NIKS cells (FIG. **5**A). SYCP2 also was detected at the protein level in NIKS-16 but not NIKS cells (FIG. **5**B). Comparative studies with NIKS16ΔE7 cells (FIG. **5**A) and in primary cervical keratinocytes with or without HPV16 E6 and/or E7 expression (FIG. **5**C), showed that SYCP2 and TCAM1 expression are synergistically upregulated by E6 and E7.

A third testis-specific gene upregulated in HPV$^+$ HNC and CC relative to HPV$^-$ HNC was STAG3 (Table 2A). Unlike SYCP2 and TCAM1, STAG3 mRNA was not upregulated in early passage NIKS-16 relative to NIKS cells nor in early passage HPV$^+$ W12 cells (FIG. **5**D). However, in three HPV$^+$ cervical carcinoma cell lines (i.e., CaSki, HeLa and SiHa), STAG3 expression was increased ~6-40-fold over NIKS. Additionally, the inventors observed a passage-dependent, increased expression of STAG3 in cervical epithelial cells harboring HPV16 (cervical keratinocytes +HPV16; FIG. **5**D). These data suggest that STAG3 induction was not an immediate effect of the virus, but rather a delayed response.

SYCP2 and TCAM1 were induced by HPV16 in human neonatal keratinocytes and cervical keratinocytes within a few cell passages, and this induction was dependent on E6 and E7 (FIGS. **5**A and **5**C). TCAM1 (52) in particular could be a useful biomarker and therapeutic target as it is expressed on the cell surface and thus is directly accessible.

TCAM1 expression in preneoplastic lesion of cervical cancer: TCAM1 expression in HPV+ preneoplastic lesions of cervix (CIN stages 1-3) was studied, and the inventors found that TCAM1 expression was induced significantly in preneoplastic lesions of cervix (see, pre-cancer in FIG. **6**).

TABLE 1A

Patient information.		
Head and Neck Cancers		
Cases and Controls	N = 54/56[A]	%
Case	40	74.1
Control	14	25.9
Age (mean = 59.9, ±15.2)		
≦55 years	19	35.2
>55 years	35	64.8
Gender		
Female	20	37.0
Male	34	63.0
Tumor Site		
Oral Cavity	32	59.3
Oropharynx	22	40.7
Normal Controls Only	N = 14	%
Age (mean = 58.0, ±23.6)		
≦55 years	6	42.9
>55 years	8	57.1
Gender		
Female	9	64.3
Male	5	35.7
Tumor Site		
Oral Cavity	9	64.3
Oropharynx	5	35.7
Cases Only	N = 40/42[A]	%
Age (mean = 60.0, ±11.3)		
≦55 years	13	32.5
>55 years	27	67.5
Gender		
Female	11	27.5
Male	29	72.5
Tumor Site		
Oral Cavity	23	57.5
Oropharynx	17	42.5
Stage		
I/II	6	15.0
III	8	20.0
IV	10	25.0
Unknown	16	40.0
Grade		
Poorly/undifferentiated	12	30.0
Well/moderately diff'd	28	70.0

TABLE 1A-continued

Patient information.		
Cervical Cancers		
Cases and Controls	N = 28	%
Case	20	71.4
Control	8	28.5
Age (mean = 43.9, ±10.4)		
≦45 years	18	64.3
>45 years	10	35.7
Normal Controls Only	N = 8	%
Age (mean = 58.0, ±23.6)		
≦45 years	3	37.5
>45 years	5	62.5
Cases Only	N = 20	%
Age (mean = 42.5, ±10.6)		
≦45 years	7	35.0
>45 years	13	67.0
Stage		
IB	16	80.0
II/III	3	15.0
IV	1	5.0

TABLE 1A-continued

Patient information.		
Grade		
Poorly/undifferentiated	12	60.0
Well/moderately diff'd	8	40.0

[A]Two patients have missing data.

TABLE 1B

HPV status in tumor samples.

	Head and Neck		Cervix	
Diagnosis	Cancer	Normal	Cancer	Normal
Total	42	14	20	8
HPV negative	26	14	3	8
HPV positive	16	—	17	—
HPV16	13	—	8	—
HPV18	1	—	3	—
HPV31	—	—	1	—
HPV33	2	—	1	—
HPV35	—	—	2	—
HPV58	—	—	1	—
HPV66	—	—	1	—

TABLE 2A

Differentially expressed genes in HPV$^+$ cancers vs. HPV$^-$ cancers.

Probeset ID*	Gene title	Gene symbol	t-statistic	Overlaps†
207039_at	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	CDKN2A	6.73	T/N, CC/HNC
228286_at	hypothetical protein FLJ40869	FLJ40869	5.45	CC/HNC
218397_at	Fanconi anemia, complementation group L	FANCL	5.63	CC/HNC
203358_s_at	enhancer of zeste homolog 2 (*Drosophila*)	EZH2	6.41	CC/HNC
218783_at	DKFZP434B168 protein	DKFZP434B168	6.00	CC/HNC
206316_s_at	kinetochore associated 1	KNTC1	6.26	T/N, CC/HNC
201555_at	MCM3 minichromosome maintenance deficient 3 (*S. cerevisiae*)	MCM3	5.88	T/N, CC/HNC
221677_s_at	downstream neighbor of SON	DONSON	6.08	T/N, CC/HNC
204510_at	CDC7 cell division cycle 7 (*S. cerevisiae*)	CDC7	6.42	T/N, CC/HNC
227255_at	casein kinase	LOC149420	5.59	CC/HNC
222201_s_at	CASP8 associated protein 2	CASP8AP2	5.09	T/N, CC/HNC
224428_s_at	cell division cycle associated 7	CDCA7	4.36	CC/HNC
219306_at	kinesin-like 7	KNSL7	5.45	CC/HNC
212621_at	KIAA0286 protein	KIAA0286	4.60	T/N
229551_x_at	zinc finger protein 367	ZNF367	6.29	T/N, CC/HNC
222848_at	leucine zipper protein FKSG14	FKSG14	4.37	T/N, CC/HNC
228401_at	—	—	4.49	T/N, CC/HNC
225655_at	ubiquitin-like, containing PHD and RING finger domains, 1	UHRF1	4.69	T/N, CC/HNC
227350_at	Helicase, lymphoid-specific	HELLS	5.13	T/N, CC/HNC
228033_at	E2F transcription factor 7	E2F7	4.36	T/N, CC/HNC
218585_s_at	RA-regulated nuclear matrix-associated protein	RAMP	4.99	T/N, CC/HNC
209172_s_at	centromere protein F, 350/400 ka (mitosin)	CENPF	4.51	T/N, CC/HNC
226456_at	hypothetical protein MGC24665	MGC24665	6.23	T/N
202589_at	thymidylate synthetase	TYMS	5.51	T/N
239680_at	—	—	5.19	CC/HNC
236513_at	—	—	4.85	CC/HNC
224320_s_at	MCM8 minichromosome maintenance deficient 8	MCM8	5.73	T/N
202532_s_at	dihydrofolate reductase	DHFR	5.24	None
210371_s_at	retinoblastoma binding protein 4	RBBP4	4.73	T/N, CC/HNC
201970_s_at	nuclear autoantigenic sperm protein (histone-binding)	NASP	6.42	T/N, CC/HNC
223542_at	ankyrin repeat domain 32	ANKRD32	4.40	T/N, CC/HNC
209337_at	PC4 and SFRS1 interacting protein 1	PSIP1	6.01	CC/HNC
205961_s_at	PC4 and SFRS1 interacting protein 1	PSIP1	5.59	CC/HNC
206542_s_at	SWI/SNF related, matrix associated, actin-dep chromatin regulator	SMARCA2	4.88	None
242471_at	—	—	4.97	None
229442_at	hypothetical protein MGC33382	MGC33382	4.45	T/N, CC/HNC
203482_at	chromosome 10 open reading frame 6	C10orf6	6.24	CC/HNC
201448_at	TIA1 cytotoxic granule-associated RNA binding protein	TIA1	5.60	None
221264_s_at	TAR DNA binding protein	TARDBP	5.57	None
214093_s_at	Far upstream element (FUSE) binding protein 1	FUBP1	4.78	None

TABLE 2A-continued

Differentially expressed genes in HPV+ cancers vs. HPV− cancers.

Probeset ID*	Gene title	Gene symbol	t-statistic	Overlaps†
209285_s_at	retinoblastoma-associated protein 140	RAP140	5.56	None
230120_s_at	plasminogen-like	PLGL	5.39	None
217122_s_at	solute carrier family 35, member E2	SLC35E2	7.47	None
228466_at	Clone IMAGE: 111714 mRNA sequence	—	5.59	None
212179_at	chromosome 6 open reading frame 111	C6orf111	5.31	None
235919_at	—	—	5.10	None
215731_s_at	M-phase phosphoprotein 9	MPHOSPH9	4.64	None
229886_at	FLJ32363 protein	FLJ32363	5.87	None
228174_at	—	—	6.44	None
212774_at	zinc finger protein 238	ZNF238	4.65	None
226478_at	Transmembrane 7 superfamily member 3	TM7SF3	4.64	None
42361_g_at	chromosome 6 open reading frame 18	C6orf18	5.76	CC/HNC
202726_at	ligase 1, DNA, ATP-dependent	LIG1	6.26	None
231931_at	PR domain containing 15	PRDM15	7.15	CC/HNC
230777_s_at	PR domain containing 15	PRDM15	6.54	CC/HNC
229468_at	cyclin-dependent kinase 3	CDK3	5.45	None
230653_at	—	—	5.15	None
220969_s_at	—	—	4.93	CC/HNC
241838_at	—	—	4.90	None
235231_at	hypothetical protein LOC285989	LOC285989	4.47	None
212980_at	AHA1, activator of heat shock 90 kDa protein ATPase homolog 2	AHSA2	4.47	None
219676_at	zinc finger protein 435	ZNF435	5.16	None
226040_at	Hypothetical protein LOC283585	—	4.43	None
223513_at	centromere protein J	CENPJ	5.41	T/N, CC/HNC
228455_at	CDNA FLJ43677 fis, clone SYNOV4009295	—	5.28	CC/HNC
225786_at	Family with sequence similarity 36, member A	FAM36A	4.56	CC/HNC
205345_at	BRCA1 associated RING domain 1	BARD1	5.04	CC/HNC
227921_at	—	—	4.97	None
230312_at	—	—	4.35	None
225841_at	hypothetical protein FLJ30525	FLJ30525	6.64	T/N
202743_at	phosphoinositide-3-kinase, regulatory subunit 3 (p55, gamma)	PIK3R3	5.96	None
209644_x_at	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	CDKN2A	6.39	T/N
225355_at	hypothetical protein DKFZP761M1511	DKFZP761M1511	5.05	None
204159_at	cyclin-dependent kinase inhibitor 2C (p18, inhibits CDK4)	CDKN2C	5.83	None
202412_s_at	ubiquitin specific protease 1	USP1	5.55	T/N
243539_at	KIAA1841 protein	KIAA1841	4.86	None
1554447_at	CDNA clone MGC: 32876 IMAGE: 4734912, complete cds	—	4.53	CC/HNC
213268_at	calmodulin binding transcription activator 1	CAMTA1	5.53	None
1555370_a_at	calmodulin binding transcription activator 1	CAMTA1	4.80	None
229795_at	—	—	4.27	T/N
225768_at	nuclear receptor subfamily 1, group D, member 2	NR1D2	4.51	CC/HNC
221045_s_at	period homolog 3 (*Drosophila*)	PER3	6.43	CC/HNC
232889_at	hypothetical protein LOC153561	LOC153561	4.97	None
213089_at	hypothetical protein LOC153561	LOC153561	4.58	None
213605_s_at	FLJ40092 protein	FLJ40092	5.95	None
221973_at	Hypothetical protein LOC150759	LOC150759	5.14	T/N, CC/HNC
213703_at	hypothetical protein LOC150759	LOC150759	5.46	None
220325_at	TAF7-like RNA polymerase II, TATA box binding protein-assoc factor	TAF7L	5.11	None
219255_x_at	interleukin 17 receptor B	IL17RB	5.67	None
205531_s_at	glutaminase 2 (liver, mitochondrial)	GLS2	4.44	None
230011_at	similar to mouse meiosis defective 1 gene	MGC40042	5.34	None
219753_at	stromal antigen 3	STAG3	6.09	None
233064_at	Hypothetical gene supported by AL365406; BC034005	—	7.85	None
1553611_s_at	hypothetical protein FLJ33790	FLJ33790	5.15	None
205691_at	synaptogyrin 3	SYNGR3	4.84	T/N
1558217_at	hypothetical protein FLJ31952	FLJ31952	4.64	None
233320_at	testicular cell adhesion molecule 1	TCAM1	7.07	T/N, CC/HNC
1556244_s_at	hypothetical protein LOC375196	LOC375196	7.56	None
226344_at	Zinc finger, matrin type 1	ZMAT1	5.47	None
204798_at	v-myb myeloblastosis viral oncogene homolog (avian)	MYB	5.12	None
230469_at	pleckstrin homology domain containing, family K member 1	PLEKHK1	6.22	None
241903_at	—	—	5.20	CC/HNC
213353_at	ATP-binding cassette, sub-family A (ABC1), member 5	ABCA5	4.35	CC/HNC
221103_s_at	hypothetical protein FLJ11142	FLJ11142	5.67	None
241705_at	—	—	4.63	None
218902_at	Notch homolog 1, translocation-associated (*Drosophila*)	NOTCH1	5.57	None
237269_at	—	—	4.92	CC/HNC
228245_s_at	ovostatin	OVOS	4.30	T/N
244023_at	Spleen tyrosine kinase	SYK	4.98	None
242918_at	Nuclear autoantigenic sperm protein (histone-binding)	NASP	4.60	None
242890_at	Helicase, lymphoid-specific	HELLS	4.45	T/N
220940_at	KIAA1641	KIAA1641	4.22	None
229666_s_at	cleavage stimulation factor, 3' pre-RNA, subunit 3, 77 kDa	CSTF3	4.44	None
1559214_at	—	—	4.52	T/N
229490_s_at	—	—	4.32	T/N
205668_at	lymphocyte antigen 75	LY75	4.26	None

TABLE 2A-continued

Differentially expressed genes in HPV+ cancers vs. HPV− cancers.

Probeset ID*	Gene title	Gene symbol	t-statistic	Overlaps†
228434_at	Butyrophilin-like 9	BTNL9	4.87	None
228262_at	hypothetical protein FLJ14503	FLJ14503	5.40	None
204069_at	Meis1, myeloid ecotropic viral integration site 1 homolog (mouse)	MEIS1	4.97	T/N, CC/HNC
1562921_at	E1A binding protein p300	EP300	4.28	CC/HNC
208498_s_at	amylase, alpha 2A; pancreatic	AMY2A	5.32	None
231164_at	Hypothetical gene supported by AK095200; BC042853	—	6.91	T/N
206546_at	synaptonemal complex protein 2	SYCP2	7.49	T/N, CC/HNC
1557570_a_at	hypothetical protein LOC285084	LOC285084	5.88	T/N
209792_s_at	kallikrein 10	KLK10	−4.32	None
206125_s_at	kallikrein 8 (neuropsin/ovasin)	KLK8	−5.68	CC/HNC
207356_at	defensin, beta 4	DEFB4	−4.28	CC/HNC
226448_at	hypothetical gene supported by BC009447	MGC15887	−4.40	T/N
219368_at	nucleosome assembly protein 1-like 2	NAP1L2	−5.63	None
208712_at	cyclin D1 (PRAD1: parathyroid adenomatosis 1)	CCND1	−4.50	None
208711_s_at	cyclin D1 (PRAD1: parathyroid adenomatosis 1)	CCND1	−5.27	None
214073_at	cortactin	CTTN	−5.10	None
203065_s_at	caveolin 1, caveolae protein, 22 kDa	CAV1	−4.58	T/N
210355_at	parathyroid hormone-like hormone	PTHLH	−4.45	T/N
1556773_at	Parathyroid hormone-like hormone	PTHLH	−4.43	T/N
211756_at	parathyroid hormone-like hormone	PTHLH	−4.46	T/N
230835_at	KIPV467	UNQ467	−4.37	CC/HNC

*In order as shown in FIG. 2A.

†Probe sets differentially expressed in other comparisons are indicated as T/N (tumor vs. normal) and CC/HNC (CC vs. HNC). Please see FIG. 1C.

TABLE 2B

Differentially expressed genes in cancers vs. normals.

Probeset ID*	Gene title	Gene symbol	t-statistic
212990_at	Synaptojanin 1	SYNJ1	5.238
227375_at	Hypothetical protein DKFZp566D1346	DKFZP566D1346	5.318
212061_at	U2-associated SR140 protein	SR140	5.115
225216_at	Chromosome X open reading frame 39	CXorf39	4.849
227471_at	HECT domain and ankyrin repeat containing, E3 ubiquitin protein ligase 1	HACE1	5.366
213387_at	KIAA1240 protein	KIAA1240	6.097
226894_at	—	—	6.056
209187_at	Down-regulator of transcription 1, TBP-binding (negative cofactor 2)	DR1	5.601
233898_s_at	FGFR1 oncogene partner 2	FGFR1OP2	4.697
229173_at	—	—	5.926
225539_at	Zinc finger protein 295	ZNF295	6.652
214820_at	Chromosome 21 open reading frame 107	C21orf107	5.467
230427_s_at	—	—	6.054
204727_at	WD repeat and HMG-box DNA binding protein 1	WDHD1	6.172
203689_s_at	Fragile X mental retardation 1	FMR1	5.614
212836_at	Polymerase (DNA-directed), delta 3, accessory subunit	POLD3	5.813
203347_s_at	Likely ortholog of mouse metal response element binding transcription factor 2	M96	5.724
234995_at	Hypothetical protein AY099107	LOC152185	6.488
202293_at	Stromal antigen 1	STAG1	7.607
229027_at	—	—	6.052
228334_x_at	KIAA1712	KIAA1712	5.785
204634_at	NIMA (never in mitosis gene a)-related kinase 4	NEK4	6.113
219171_s_at	Zinc finger protein 236	ZNF236	4.82
234997_x_at	—	—	4.747
226115_at	ELYS transcription factor-like protein TMBS62	ELYS	5.106
202294_at	—	—	8.547
229022_at	—	—	6.763
204835_at	Polymerase (DNA directed), alpha	POLA	6.672
203401_at	Phosphoribosyl pyrophosphate synthetase 2	PRPS2	6.139
225021_at	Zinc finger protein 532	ZNF532	5.759
220617_s_at	Zinc finger protein 532	ZNF532	6.463
203482_at	Chromosome 10 open reading frame 6	C10orf6	6.155
226730_s_at	Ubiquitin specific protease 37	USP37	6.055
218515_at	Chromosome 21 open reading frame 66	C21orf66	5.504
212943_at	KIAA0528 gene product	KIAA0528	5.973
218397_at	Fanconi anemia, complementation group L	FANCL	6.272
225017_at	Hypothetical protein FLJ12892	FLJ12892	5.375
228286_at	Hypothetical protein FLJ40869	FLJ40869	5.694
229303_at	—	—	5.471
232362_at	Sarcoma antigen NY-SAR-41	NY-SAR-41	5.009
225318_at	DDHD domain containing 2	DDHD2	4.732
214306_at	Optic atrophy 1 (autosomal dominant)	OPA1	5.141
222629_at	REV1-like (yeast)	REV1L	6.239

TABLE 2B-continued

Differentially expressed genes in cancers vs. normals.

Probeset ID*	Gene title	Gene symbol	t-statistic
224974_at	Likely ortholog of mouse Sds3	SDS3	6.108
213140_s_at	Synovial sarcoma translocation gene on chromosome 18-like 1	SS18L1	5.802
208798_x_at	Golgin-67	GOLGIN-67	5.185
210425_x_at	—	—	5.537
227199_at	Chromosome 21 open reading frame 106	C21orf106	6.379
236910_at	Mitochondrial ribosomal protein L39	MRPL39	6.352
228940_at	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15 kDa	NDUFB4	5.908
230516_at	Chromosome 7 open reading frame 30	C7orf30	5.057
243332_at	—	—	5.676
225595_at	MRNA; cDNA DKFZp566P1124 (from clone DKFZp566P1124)	—	4.672
225594_at	MRNA; cDNA DKFZp566P1124 (from clone DKFZp566P1124)	—	5.378
218793_s_at	Sex comb on midleg-like 1 (*Drosophila*)	SCML1	5.387
239577_at	—	—	4.466
222201_s_at	CASP8 associated protein 2	CASP8AP2	5.367
218979_at	Chromosome 9 open reading frame 76	C9orf76	5.468
218757_s_at	UPF3 regulator of nonsense transcripts homolog B (yeast)	UPF3B	7.293
202633_at	Topoisomerase (DNA) II binding protein 1	TOPBP1	7.354
227255_at	Casein kinase	LOC149420	4.722
201555_at	MCM3 minichromosome maintenance deficient 3 (*S. cerevisiae*)	MCM3	7.992
239413_at	KIAA0912 protein	Cep152	7.158
206316_s_at	Kinetochore associated 1	KNTC1	7.584
228859_at	Prematurely terminated mRNA decay factor-like	LOC91431	6.037
221677_s_at	Downstream neighbor of SON	DONSON	8.188
225655_at	Ubiquitin-like, containing PHD and RING finger domains, 1	UHRF1	8.055
228401_at	—	—	7.279
219306_at	Kinesin-like 7	KNSL7	6.072
235609_at	—	—	6.233
203209_at	Replication factor C (activator 1) 5, 36.5 kDa	RFC5	5.279
203432_at	Thymopoietin	TMPO	4.836
206102_at	KIAA0186 gene product	KIAA0186	5.766
204510_at	CDC7 cell division cycle 7 (*S. cerevisiae*)	CDC7	7.611
203358_s_at	Enhancer of zeste homolog 2 (*Drosophila*)	EZH2	6.571
218783_at	DKFZP434B168 protein	DKFZP434B168	5.005
224428_s_at	Cell division cycle associated 7	CDCA7	4.567
214804_at	FSH primary response (LRPR1 homolog, rat) 1	FSHPRH1	5.661
203744_at	High-mobility group box 3	HMGB3	6.469
212060_at	U2-associated SR140 protein	SR140	5.261
218304_s_at	Oxysterol binding protein-like 11	OSBPL11	5.936
228386_s_at	Hypothetical protein DKFZp564B1023	DKFZP564B1023	5.527
215009_s_at	SEC31-like 1 (*S. cerevisiae*)	SEC31L1	5.184
226350_at	Choroideremia-like (Rab escort protein 2)	CHML	6.435
1565951_s_at	Choroideremia-like (Rab escort protein 2)	CHML	5.487
242923_at	Hypothetical protein MGC15634	MGC15634	4.925
205296_at	Retinoblastoma-like 1 (p107)	RBL1	4.687
203276_at	Lamin B1	LMNB1	5.178
238756_at	Growth arrest-specific 2 like 3	GAS2L3	4.914
228577_x_at	KIAA1229 protein	KIAA1229	5.562
231909_x_at	KIAA1229 protein	KIAA1229	5.05
226164_x_at	KIAA1238 protein	KIAA1238	4.309
228397_at	—	—	4.259
239680_at	—	—	6.372
236513_at	—	—	5.773
231931_at	PR domain containing 15	PRDM15	6.115
230777_s_at	PR domain containing 15	PRDM15	5.542
208174_x_at	U2(RNU2) small nuclear RNA auxiliary factor 1-like 2	U2AF1L2	5.364
213876_x_at	U2(RNU2) small nuclear RNA auxiliary factor 1-like 2	U2AF1L2	5.517
42361_g_at	Chromosome 6 open reading frame 18	C6orf18	4.599
64408_s_at	Calmodulin-like 4	CALML4	4.377
220969_s_at	—	—	4.24
230209_at	Hypothetical protein MGC11349	MGC11349	4.501
203262_s_at	Family with sequence similarity 50, member A	FAM50A	6.106
213947_s_at	Nucleoporin 210	NUP210	5.367
230395_at	DORA reverse strand protein 1	DREV1	4.248
1562497_at	MKL/myocardin-like 2	MKL2	5.24
223797_at	—	—	4.519
244625_at	—	—	4.668
235646_at	—	—	5.002
242737_at	—	—	6.262
219280_at	Chromosome 21 open reading frame 107	C21orf107	7.491
222343_at	BCL2-like 11 (apoptosis facilitator)	BCL2L11	6.325
230534_at	Hypothetical protein MGC15634	MGC15634	5.384
238699_s_at	Calcium/calmodulin-dependent serine protein kinase (MAGUK family)	CASK	4.742
232370_at	Hypothetical protein LOC254057	LOC254057	4.482
204143_s_at	rTS beta protein	HSRTSBETA	4.634
237246_at	—	—	4.651
215623_x_at	SMC4 structural maintenance of chromosomes 4-like 1 (yeast)	SMC4L1	5.25

TABLE 2B-continued

Differentially expressed genes in cancers vs. normals.

Probeset ID*	Gene title	Gene symbol	t-statistic
241954_at	—	—	4.48
204224_s_at	GTP cyclohydrolase 1 (dopa-responsive dystonia)	GCH1	4.677
222603_at	KIAA1815	KIAA1815	5.974
223275_at	HMT1 hnRNP methyltransferase-like 6 (*S. cerevisiae*)	HRMT1L6	4.656
228778_at	—	—	6.636
203991_s_at	Ubiquitously transcribed tetratricopeptide repeat, X chromosome	UTX	6.092
214678_x_at	—	—	5.425
203992_s_at	Ubiquitously transcribed tetratricopeptide repeat, X chromosome	UTX	6.441
204061_at	Protein kinase, X-linked	PRKX	4.969
229305_at	MLF1 interacting protein	MLF1IP	4.709
218883_s_at	MLF1 interacting protein	MLF1IP	6.342
219990_at	FLJ23311 protein	FLJ23311	4.99
210371_s_at	Retinoblastoma binding protein 4	RBBP4	6.888
218733_at	Hypothetical protein FLJ10546	FLJ10546	5.501
233841_s_at	Likely ortholog of mouse Sds3	SDS3	5.987
221919_at	Heterogeneous nuclear ribonucleoprotein A1	HNRPA1	5.492
212515_s_at	DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, X-linked	DDX3X	4.514
220553_s_at	PRP39 pre-mRNA processing factor 39 homolog (yeast)	PRPF39	4.995
201970_s_at	Nuclear autoantigenic sperm protein (histone-binding)	NASP	5.843
212200_at	KIAA0692 protein	KIAA0692	5.66
215017_s_at	Chromosome 1 open reading frame 39	C1orf39	4.318
235142_at	Zinc finger and BTB domain containing 8	ZBTB8	4.617
219157_at	Kelch-like 2, Mayven (*Drosophila*)	KLHL2	6.137
236769_at	Hypothetical protein LOC158402	LOC158402	5.643
227133_at	Chromosome X open reading frame 39	CXorf39	4.437
220520_s_at	Hypothetical protein FLJ20130	FLJ20130	5.257
217936_at	Rho GTPase activating protein 5	ARHGAP5	5.74
223167_s_at	Ubiquitin specific protease 25	USP25	5.464
205281_s_at	Phosphatidylinositol glycan, class A (paroxysmal nocturnal hemoglobinuria)	PIGA	5.451
226302_at	—	—	4.823
213285_at	Transmembrane protein 30B	TMEM30B	4.978
228565_at	Mixed lineage kinase 4	KIAA1804	4.999
227356_at	CDNA: FLJ22198 fis, clone HRC01218	—	4.591
228201_at	ADP-ribosylation factor-like 2-like 1	ARL2L1	4.742
228812_at	—	—	4.625
225227_at	Homo sapiens, clone IMAGE: 5299642, mRNA	—	4.459
232398_at	Hypothetical protein DKFZp434P055	DKFZp434P055	5.822
233504_at	Chromosome 9 open reading frame 84	C9orf84	5.832
1554447_at	CDNA clone MGC: 32876 IMAGE: 4734912, complete cds	—	5.544
218966_at	Myosin VC	MYO5C	6.466
1556105_at	Par-3 partitioning defective 3 homolog (*C. elegans*)	PARD3	7.135
235635_at	—	—	4.637
228455_at	CDNA FLJ43677 fis, clone SYNOV4009295	—	5.957
225786_at	Family with sequence similarity 36. member A	FAM36A	4.716
223513_at	Centromere protein J	CENPJ	4.285
217894_at	Potassium channel tetramerisation domain containing 3	KCTD3	6.689
204146_at	RAD51 associated protein 1	RAD51AP1	4.219
203213_at	Cell division cycle 2, G1 to S and G2 to M	CDC2	5.255
201663_s_at	SMC4 structural maintenance of chromosomes 4-like 1 (yeast)	SMC4L1	4.65
201664_at	SMC4 structural maintenance of chromosomes 4-like 1 (yeast)	SMC4L1	6.127
225834_at	Similar to RIKEN cDNA 2700049P18 gene	MGC57827	7.226
228323_at	AF15q14 protein	AF15Q14	5.322
223381_at	Cell division cycle associated 1	CDCA1	4.969
228033_at	E2F transcription factor 7	E2F7	6.759
204641_at	NIMA (never in mitosis gene a)-related kinase 2	NEK2	4.905
209172_s_at	Centromere protein F, 350/400ka (mitosin)	CENPF	4.919
218585_s_at	RA-regulated nuclear matrix-associated protein	RAMP	5.95
222680_s_at	RA-regulated nuclear matrix-associated protein	RAMP	6.996
222740_at	ATPase family, AAA domain containing 2	ATAD2	5.314
222848_at	leucine zipper protein FKSG14	FKSG14	5.878
229551_x_at	Zinc finger protein 367	ZNF367	8.85
227350_at	Helicase, lymphoid-specific	HELLS	6.363
205034_at	Cyclin E2	CCNE2	7.033
223542_at	Ankyrin repeat domain 32	ANKRD32	7.339
216228_s_at	WD repeat and HMG-box DNA binding protein 1	WDHD1	4.689
226747_at	KIAA1344	KIAA1344	5.709
228597_at	Chromosome 21 open reading frame 45	C21orf45	5.181
209337_at	PC4 and SFRS1 interacting protein 1	PSIP1	5.364
205961_s_at	PC4 and SFRS1 interacting protein 1	PSIP1	4.401
226925_at	acid phosphatase-like 2	ACPL2	4.686
202983_at	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 3	SMARCA3	4.929
225768_at	Nuclear receptor subfamily 1, group D, member 2	NR1D2	5.387
229442_at	Hypothetical protein MGC33382	MGC33382	5.117
212840_at	KIAA0794 protein	KIAA0794	4.926
201329_s_at	v-ets erythroblastosis virus E26 oncogene homolog 2 (avian)	ETS2	6.218

TABLE 2B-continued

Differentially expressed genes in cancers vs. normals.

Probeset ID*	Gene title	Gene symbol	t-statistic
201328_at	v-ets erythroblastosis virus E26 oncogene homolog 2 (avian)	ETS2	4.879
208078_s_at	SNF1-like kinase \	SNF1LK	4.865
1555411_a_at	Cyclin L1	CCNL1	6.615
1555827_at	Cyclin L1	CCNL1	5.578
241495_at	Cyclin L1	CCNL1	4.355
241903_at	—	—	5.813
243030_at	—	—	5.475
205345_at	BRCA1 associated RING domain 1	BARD1	4.352
213353_at	ATP-binding cassette, sub-family A (ABC1), member 5	ABCA5	5.381
240452_at	—	—	4.398
230097_at	—	—	4.269
236322_at	—	—	4.201
242146_at	—	—	5.106
1559156_at	Protein inhibitor of activated STAT, 1	PIAS1	4.832
235926_at	—	—	4.262
244753_at	—	—	4.129
232058_at	Actinin, alpha 4	ACTN4	4.419
203767_s_at	Steroid sulfatase (microsomal), arylsulfatase C, isozyme S	STS	4.633
213150_at	Homeo box A10	HOXA10	4.669
235292_at	LOC441069	—	4.149
226374_at	—	—	4.552
204286_s_at	Phorbol-12-myristate-13-acetate-induced protein 1	PMAIP1	4.648
210540_s_at	UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 4	B4GALT4	4.992
237269_at	—	—	4.908
226420_at	Ecotropic viral integration site 1	EVI1	5.871
218901_at	Phospholipid scramblase 4	PLSCR4	6.1
235165_at	Par-6 partitioning defective 6 homolog beta (*C. elegans*)	PARD6B	4.241
221045_s_at	Period homolog 3 (*Drosophila*)	PER3	4.957
221973_at	Hypothetical protein LOC150759	LOC150759	4.445
238593_at	Hypothetical protein FLJ22531	FLJ22531	4.248
216248_s_at	Nuclear receptor subfamily 4, group A, member 2	NR4A2	4.868
204622_x_at	Nuclear receptor subfamily 4, group A, member 2	NR4A2	4.882
206698_at	Kell blood group precursor (McLeod phenotype)	XK	4.927
227492_at	—	—	6.648
1562921_at	E1A binding protein p300	EP300	4.238
235144_at	RAS and EF hand domain containing	RASEF	6.912
1553986_at	RAS and EF hand domain containing	RASEF	4.273
229842_at	—	—	4.773
209692_at	Eyes absent homolog 2 (*Drosophila*)	EYA2	6.153
219313_at	Hypothetical protein DKFZp434C0328	DKFZp434C0328	5.167
204069_at	Meis1, myeloid ecotropic viral integration site 1 homolog (mouse)	MEIS1	4.556
214464_at	CDC42 binding protein kinase alpha (DMPK-like)	CDC42BPA	4.303
214723_x_at	KIAA1641	KIAA1641	5.208
200800_s_at	Heat shock 70 kDa protein 1A /// heat shock 70 kDa protein 1B	HSPA1A /// HSPA1B	5.342
201169_s_at	Basic helix-loop-helix domain containing, class B, 2	BHLHB2	4.172
214651_s_at	Homeo box A9	HOXA9	7.526
209905_at	Homeo box A9	HOXA9	7.791
228904_at	—	—	5.333
206546_at	Synaptonemal complex protein 2	SYCP2	5.824
233320_at	Testicular cell adhesion molecule 1	TCAM1	4.918
229400_at	Homeo box D10	HOXD10	5.335
227671_at	X (inactive)-specific transcript	XIST	5.623
231592_at	—	—	4.565
224589_at	X (inactive)-specific transcript	XIST	4.966
205778_at	Kallikrein 7 (chymotryptic, stratum corneum)	KLK7	−4.171
206125_s_at	Kallikrein 8 (neuropsin/ovasin)	KLK8	−4.858
206192_at	Corneodesmosin	CDSN	−4.747
235514_at	Hypothetical protein FLJ25084	FLJ25084	−4.359
223582_at	Monogenic, audiogenic seizure susceptibility 1 homolog (mouse)	MASS1	−4.856
239352_at	—	—	−4.807
207356_at	Defensin, beta 4	DEFB4	−4.625
205054_at	Nebulin	NEB	−6.402
203562_at	Fasciculation and elongation protein zeta 1 (zygin I)	FEZ1	−4.482
221898_at	Lung type-I cell membrane-associated glycoprotein	T1A-2	−4.543
228492_at	Ubiquitin specific protease 9, Y-linked (fat facets-like, *Drosophila*)	USP9Y	−6.254
223646_s_at	Chromosome Y open reading frame 15B	CYorf15B	−7.48
204410_at	Eukaryotic translation initiation factor 1A, Y-linked	EIF1AY	−5.799
206700_s_at	Jumonji, AT rich interactive domain 1D (RBP2-like)	JARID1D	−8.832
223645_s_at	Chromosome Y open reading frame 15B	CYorf15B	−7.22
230760_at	Zinc finger protein, Y-linked	ZFY	−6.432
213068_at	Dermatopontin	DPT	−6.491
213909_at	Leucine rich repeat containing 15	LRRC15	−5.414
201893_x_at	Decorin	DCN	−4.228
223475_at	CocoaCrisp	LOC83690	−4.253
210467_x_at	Melanoma antigen, family A, 12	MAGEA12	−4.686

TABLE 2B-continued

Differentially expressed genes in cancers vs. normals.

Probeset ID*	Gene title	Gene symbol	t-statistic
232523_at	MEGF10 protein	MEGF10	−5.346
206584_at	Lymphocyte antigen 96	LY96	−4.524
236313_at	Cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4)	CDKN2B	4.437
205225_at	Estrogen receptor 1	ESR1	4.321
207039_at	Cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	CDKN2A	4.922
232170_at	S100 calcium binding protein A7-like 1	S100A7L1	−4.32
207324_s_at	Desmocollin 1	DSC1	−3.977
224646_x_at	—	—	−4.37
224997_x_at	H19, imprinted maternally expressed untranslated mRNA	H19	−4.791
224348_s_at	—	—	−4.566
205403_at	Interleukin 1 receptor, type II	IL1R2	−5.361
211372_s_at	Interleukin 1 receptor, type II	IL1R2	−4.172
205000_at	DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, Y-linked	DDX3Y	−8.052
214131_at	Chromosome Y open reading frame 15B	CYorf15B	−6.626
204409_s_at	Eukaryotic translation initiation factor 1A, Y-linked	EIF1AY	−5.951
201909_at	Ribosomal protein S4, Y-linked 1	RPS4Y1	−8.251
201650_at	Keratin 19	KRT19	4.223
224588_at	X (inactive)-specific transcript	XIST	9.351
224590_at	X (inactive)-specific transcript	XIST	8.602
214218_s_at	X (inactive)-specific transcript	XIST	9.127
221728_x_at	X (inactive)-specific transcript	XIST	9.808
230835_at	KIPV467	UNQ467	−4.315

*In order as shown in FIG. 2B.

TABLE 3A

Cell cycle genes up- or down-regulated in HPV^+ cancers vs. HPV^- cancers.

Probeset ID*	Gene title	Gene symbol	t-statistic
205767_at	Epiregulin	EREG	−3.47
209792_s_at	Kallikrein 10	KLK10	−4.25
208711_s_at	Cyclin D1	CCND1	−5.43
208712_at	Cyclin D2	CCND2	−4.48
1553869_at	Sestrin 3	SESN3	−3.39
205899_at	Cyclin A1	CCNA1	−4.06
235683_at	Sestrin 3	SESN3	−4.05
207039_at	Cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	CDKN2A	7.09
206546_at	Synaptonemal complex protein 2	SYCP2	7.36
204159_at	Cyclin-dependent kinase inhibitor 2C (p18, inhibits CDK4)	CDKN2C	5.73
204510_at	CDC7 cell division cycle 7	CDC7	6.51
206316_s_at	Kinetochore associated 1	KNTC1	6.28
205085_at	Origin recognition complex, subunit 1-like	ORC1L	4.96
201746_at	Tumor protein p53	TP53	3.57
224320_s_at	MCM8 minichromosome maintenance deficient 8	MCM8	5.61
213204_at	p53-associated parkin-like cytoplasmic protein	PARC	5.90
222962_s_at	MCM10 minichromosome maintenance deficient 10	MCM10	2.74
201555_at	MCM3 minichromosome maintenance deficient 3	MCM3	5.95
201930_at	MCM6 minichromosome maintenance deficient 6	MCM6	5.56
244550_at	Transcription factor Dp-1	TFDP1	3.00
228361_at	E2F transcription factor 2	E2F2	4.94
204121_at	Growth arrest and DNA-damage-inducible, gamma	GADD45G	2.16
225297_at	Coiled-coil domain containing 5 (spindle associated)	CCDC5	3.42
204457_s_at	Growth arrest-specific 1	GAS1	2.17
228033_at	E2F transcription factor 7	E2F7	4.39
204252_at	Cyclin-dependent kinase 2	CDK2	3.77
210028_s_at	Origin recognition complex, subunit 3-like (yeast)	ORC3L	4.12
209408_at	Kinesin family member 2C	KIF2C	5.52
209172_s_at	Centromere protein F, 350/400ka (mitosin)	CENPF	4.55
219588_s_at	Leucine zipper protein 5	LUZP5	4.86
203693_s_at	E2F transcription factor 3	E2F3	4.05
218663_at	Chromosome condensation protein G	HCAP-G	3.55
202107_s_at	MCM2 minichromosome maintenance deficient 2, mitotin	MCM2	4.37
208795_s_at	MCM7 minichromosome maintenance deficient 7	MCM7	4.06
201664_at	SMC4 structural maintenance of chromosomes 4-like 1	SMC4L1	4.44
201202_at	Proliferating cell nuclear antigen	PCNA	5.12
203213_at	Cell division cycle 2, G1 to S and G2 to M	CDC2	3.27
204240_s_at	SMC2 structural maintenance of chromosomes 2-like 1	SMC2L1	1.73
205034_at	Cyclin E2	CCNE2	3.59

TABLE 3A-continued

Cell cycle genes up- or down-regulated in HPV+ cancers vs. HPV− cancers.

Probeset ID*	Gene title	Gene symbol	t-statistic
205393_s_at	CHK1 checkpoint homolog	CHEK1	1.05
214710_s_at	Cyclin B1	CCNB1	1.20
203755_at	BUB1 budding uninhibited by benzimidazoles 1 homolog beta	BUB1B	2.77

*In order as shown in FIG. 3A.

Example 2

Confirmation of TCAM1, SYCP2 and STAG3 Expression in Human Papillomavirus-Positive Cancers

Materials and Methods

The above methods were repeated in a second, but larger, group of subjects. The group consisted of 128 samples collected. 79 were HPV+ and 47 were HPV−. Additional details on the subjects are shown below in Table 3.

TABLE 4

Patient information.

Cases and Controls	N = 128	100%
Normal Controls Only	N = 16	12.5%
Cases Only	N = 112	87.5%
Pathology		
CIN1	N = 14	10.9%
CIN2	N = 21	16.4%
CIN3	N = 41	32.0%
Cancer	N = 28	21.9%
Metaplasia	N = 7	5.5%
Adenocarcinoma in situ	N = 1	0.8%

Results

As shown in FIG. **7**, TCAM1, SYCP2 and STAG3 were significantly upregulated in HPV+ samples, confirming the result shown above in Example 1.

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Although the invention has been described in connection with specific embodiments, it is understood that the invention is not limited to such specific embodiments but encompasses all such modifications and variations apparent to a skilled artisan that fall within the scope of the appended claims.

SEQUENCE LISTING

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Thr Cys Pro Asp Pro Gly Pro Ser Gly Ile Glu Thr Phe Leu Lys Lys
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Thr Gln Leu Ser Lys Gly Ser Gln Trp Lys Glu Phe Leu Leu Glu Asp
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Ile Thr Glu Asp Leu Val Leu Gln Cys Phe Phe Ser Cys Ala Gly Glu
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Leu Thr Leu Leu Gln Gly Asp Gln Glu Leu His Arg Lys Asp Phe Leu
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Thr Arg Val Phe Pro Ala Gln Glu Ala Val Phe Arg Met Phe Leu Glu
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Ala Ser Ala Thr Ile Gln Ala Met Glu Thr Gly Asp Gln Glu Leu Thr
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Cys Leu Val Ser Leu Gly Pro Val Glu Gln Lys Thr Arg Lys Pro Val
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Tyr Val Tyr Ser Phe Pro Pro Pro Ile Leu Glu Ile Glu Asp Ala Tyr
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Pro Leu Ala Gly Thr Asp Val Asn Val Thr Cys Ser Gly His Val Leu
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Gln Ala Leu Val Glu Phe Gly His Ser Leu Thr Ile Asn Cys Ser Thr
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Thr Cys Pro Asp Pro Gly Pro Ser Gly Ile Glu Thr Phe Leu Lys Lys
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Thr Gln Leu Ser Lys Gly Ser Gln Trp Lys Glu Phe Leu Leu Glu Gly
65                  70                  75                  80

Ile Thr Glu Asn Ser Val Leu Gln Cys Phe Phe Ser Cys Ala Gly Val
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Gln Lys Asp Thr Ala Leu Asp Ile Thr Met Tyr Gln Pro Pro Glu Gln
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Val Ile Leu Asp Leu Gln Pro Glu Trp Val Ala Ile Asp Glu Ala Phe
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Ser Leu Ser Leu Val Ser Gln Arg Ala Glu Val Thr Val Asn Val Arg
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Lys Gln Leu Arg Ile Phe Glu Phe Ser Gln Asn Pro Gln Ile Leu Val
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Pro Ser Leu Leu Glu Val Gly Met Ala Glu Thr Met Ser Cys Glu Val
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Arg Leu Val Lys Thr Thr Lys Ile Gln Leu His Val Leu Tyr Lys Pro
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Arg Phe Gln Glu Ser Asp Cys Pro Gly Asn Gln Ile Trp Val Glu Gly
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Met Asp Gln Met Leu Ala Cys Ile Pro Glu Gly Asn Pro Ile Pro Ala
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Leu Val Cys Ile Trp Asn Gly Met Thr Phe Asp Leu Glu Val Pro Gln
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Cys Lys Arg Asn Gly Arg Lys Arg Thr His Arg Gln Lys Glu Gln Asn
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ttgtttcatg gcagctcagc caccaagcaa ctccggatct ttgaattctc tcagaatccc    660

cagatcttgg tgccttcact gctggaagtt gggatggccg agactatgag ctgtgaggtg    720

gttagggtgt tcccagccca ggaagctgtc ttccgaatgt ttctggaaga ccaggagctg    780

agccctttct cctcctggaa aggagatgca gcatgggcca gtgctaccat tcaggccatg    840

gagaccggtg accaggagct gacctgcctt gtgtctgtgg gtcctgtgga gcagaaagca    900

agaaaaccag tgcatgtcta cagtttccct ccaccagtcc tggagataga agatgcttac    960

ccacaggcag ggacagacgt taatgtgacc tgctcaggtc acgtgctaac atcgcccagc   1020

cctactcttc ggctccaggg atccctaaac ctctctgctc ccggggagcc tgcctggctt   1080

cggtttactg ccagggagga agatgatggc cggactctct cctgtgaggc ctctttggtg   1140

gtgcagggcc agcgactggt caaaaccacc aagatccagc ttcatgtgtt atacaagcca   1200

aggtttcagg aatccgactg ccctggcaac cagatatggg tagaagggat ggatcagatg   1260

cttgcctgca tcccagaggg aaaccccatc ccggctttgg tgtgtatctg gaatgggatg   1320

acctttgacc ttgaggtacc tcagaaggcc acccagaacc acacaggaac ttacagctgc   1380

acagccacca actccctagg ctctgtcagc aaagacatcg ctgtccttgt ccaaggcctg   1440

catgagggaa tcagctcgtc caccatcttc atcatcatca ttttcaccct cggcatggct   1500

gtgatcacca tagcattata tctgaactac cagccctgca aaagaaacgg taggaaacgg   1560

acgcacaggc agaaagagca gaacaaaggc ggggagagac agttctcgga tatacaagcc   1620

gaggagtgcc acgcgcacct ctgctga                                       1647
```

<210> SEQ ID NO 6
<211> LENGTH: 1023
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

```
Met Pro Ile Arg Pro Asp Leu Gln Gln Leu Glu Lys Cys Ile Asp Asp
1               5                   10                  15

Ala Leu Arg Lys Asn Asp Phe Lys Pro Leu Lys Thr Leu Leu Gln Ile
            20                  25                  30

Asp Ile Cys Glu Asp Val Lys Ile Lys Cys Ser Lys Gln Phe Phe His
        35                  40                  45

Lys Val Asp Asn Leu Ile Cys Arg Glu Leu Asn Lys Glu Asp Ile His
    50                  55                  60

Asn Val Ser Ala Ile Leu Val Ser Val Gly Arg Cys Gly Lys Asn Ile
65                  70                  75                  80

Ser Val Leu Gly Gln Ala Gly Leu Leu Thr Met Ile Lys Gln Gly Leu
                85                  90                  95

Ile Gln Lys Met Val Ala Trp Phe Glu Lys Ser Lys Asp Ile Ile Gln
            100                 105                 110

Ser Gln Gly Asn Ser Lys Asp Glu Ala Val Leu Asn Met Ile Glu Asp
        115                 120                 125

Leu Val Asp Leu Leu Leu Val Ile His Asp Val Ser Asp Glu Gly Lys
    130                 135                 140

Lys Gln Val Val Glu Ser Phe Val Pro Arg Ile Cys Ser Leu Val Ile
145                 150                 155                 160

Asp Ser Arg Val Asn Ile Cys Ile Gln Gln Glu Ile Ile Lys Lys Met
                165                 170                 175

Asn Ala Met Leu Asp Lys Met Pro Gln Asp Ala Arg Lys Ile Leu Ser
            180                 185                 190
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Asn Gln Glu Met Leu Ile Leu Met Ser Ser Met Gly Glu Arg Ile Leu
        195                 200                 205

Asp Ala Gly Asp Tyr Asp Leu Gln Val Gly Ile Val Glu Ala Leu Cys
    210                 215                 220

Arg Met Thr Thr Glu Lys Gln Arg Gln Glu Leu Ala His Gln Trp Phe
225                 230                 235                 240

Ser Met Asp Phe Ile Ala Lys Ala Phe Lys Arg Ile Lys Asp Ser Glu
                245                 250                 255

Phe Glu Thr Asp Cys Arg Ile Phe Leu Asn Leu Val Asn Gly Met Leu
            260                 265                 270

Gly Asp Lys Arg Arg Val Phe Thr Phe Pro Cys Leu Ser Ala Phe Leu
        275                 280                 285

Asp Lys Tyr Glu Leu Gln Ile Pro Ser Asp Glu Lys Leu Glu Glu Phe
    290                 295                 300

Trp Ile Asp Phe Asn Leu Gly Ser Gln Thr Leu Ser Phe Tyr Ile Ala
305                 310                 315                 320

Gly Asp Asn Asp Asp His Gln Trp Glu Ala Val Thr Val Pro Glu Glu
                325                 330                 335

Lys Val Gln Ile Tyr Ser Ile Glu Val Arg Glu Ser Lys Lys Leu Leu
            340                 345                 350

Thr Ile Ile Leu Lys Asn Thr Val Lys Ile Ser Lys Arg Glu Gly Lys
        355                 360                 365

Glu Leu Leu Leu Tyr Phe Asp Ala Ser Leu Glu Ile Thr Asn Val Thr
    370                 375                 380

Gln Lys Ile Phe Gly Ala Thr Lys His Arg Glu Ser Ile Arg Lys Gln
385                 390                 395                 400

Gly Ile Ser Val Ala Lys Thr Ser Leu His Ile Leu Phe Asp Ala Ser
                405                 410                 415

Gly Ser Gln Ile Leu Val Pro Glu Ser Gln Ile Ser Pro Val Gly Glu
            420                 425                 430

Glu Leu Val Ser Leu Lys Glu Lys Ser Lys Ser Pro Lys Glu Phe Ala
        435                 440                 445

Lys Pro Ser Lys Tyr Ile Lys Asn Ser Asp Lys Gly Asn Arg Asn Asn
    450                 455                 460

Ser Gln Leu Glu Lys Thr Thr Pro Ser Lys Arg Lys Met Ser Glu Ala
465                 470                 475                 480

Ser Met Ile Val Ser Gly Ala Asp Arg Tyr Thr Met Arg Ser Pro Val
                485                 490                 495

Leu Phe Ser Asn Thr Ser Ile Pro Pro Arg Arg Arg Arg Ile Lys Pro
            500                 505                 510

Pro Leu Gln Met Thr Ser Ser Ala Glu Lys Pro Ser Val Ser Gln Thr
        515                 520                 525

Ser Glu Asn Arg Val Asp Asn Ala Ala Ser Leu Lys Ser Arg Ser Ser
    530                 535                 540

Glu Gly Arg His Arg Arg Asp Asn Ile Asp Lys His Ile Lys Thr Ala
545                 550                 555                 560

Lys Cys Val Glu Asn Thr Glu Asn Lys Asn Val Glu Phe Pro Asn Gln
                565                 570                 575

Asn Phe Ser Glu Leu Gln Asp Val Ile Pro Asp Ser Gln Ala Ala Glu
            580                 585                 590

Lys Arg Asp His Thr Ile Leu Pro Gly Val Leu Asp Asn Ile Cys Gly
        595                 600                 605

Asn Lys Ile His Ser Lys Trp Ala Cys Trp Thr Pro Val Thr Asn Ile
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    610                 615                 620

Glu Leu Cys Asn Asn Gln Arg Ala Ser Thr Ser Ser Gly Asp Thr Leu
625                 630                 635                 640

Asn Gln Asp Ile Val Ile Asn Lys Lys Leu Thr Lys Gln Lys Ser Ser
                645                 650                 655

Ser Ser Ile Ser Asp His Asn Ser Glu Gly Thr Gly Lys Val Lys Tyr
            660                 665                 670

Lys Lys Glu Gln Thr Asp His Ile Lys Ile Asp Lys Ala Glu Val Glu
        675                 680                 685

Val Cys Lys Lys His Asn Gln Gln Gln Asn His Pro Lys Tyr Ser Gly
    690                 695                 700

Gln Lys Asn Thr Glu Asn Ala Lys Gln Ser Asp Trp Pro Val Glu Ser
705                 710                 715                 720

Glu Thr Thr Phe Lys Ser Val Leu Leu Asn Lys Thr Ile Glu Glu Ser
                725                 730                 735

Leu Ile Tyr Arg Lys Lys Tyr Ile Leu Ser Lys Asp Val Asn Thr Ala
            740                 745                 750

Thr Cys Asp Lys Asn Pro Ser Ala Ser Lys Asn Val Gln Ser His Arg
        755                 760                 765

Lys Ala Glu Lys Glu Leu Thr Ser Glu Leu Asn Ser Trp Asp Ser Lys
    770                 775                 780

Gln Lys Lys Met Arg Glu Lys Ser Lys Gly Lys Glu Phe Thr Asn Val
785                 790                 795                 800

Ala Glu Ser Leu Ile Ser Gln Ile Asn Lys Arg Tyr Lys Thr Lys Asp
                805                 810                 815

Asp Ile Lys Ser Thr Arg Lys Leu Lys Glu Ser Leu Ile Asn Ser Gly
            820                 825                 830

Phe Ser Asn Lys Pro Val Val Gln Leu Ser Lys Glu Lys Val Gln Lys
        835                 840                 845

Lys Ser Tyr Arg Lys Leu Lys Thr Thr Phe Val Asn Val Thr Ser Glu
    850                 855                 860

Cys Pro Val Asn Asp Val Tyr Asn Phe Asn Leu Asn Gly Ala Asp Asp
865                 870                 875                 880

Pro Ile Ile Lys Leu Gly Ile Gln Glu Phe Gln Ala Thr Ala Lys Glu
                885                 890                 895

Ala Cys Ala Asp Arg Ser Ile Arg Leu Val Gly Pro Arg Asn His Asp
            900                 905                 910

Glu Leu Lys Ser Ser Val Lys Thr Lys Asp Lys Lys Ile Ile Thr Asn
        915                 920                 925

His Gln Lys Lys Asn Leu Phe Ser Asp Thr Glu Thr Glu Tyr Arg Cys
    930                 935                 940

Asp Asp Ser Lys Thr Asp Ile Ser Trp Leu Arg Glu Pro Lys Ser Lys
945                 950                 955                 960

Pro Gln Leu Ile Asp Tyr Ser Arg Asn Lys Asn Val Lys Asn His Lys
                965                 970                 975

Ser Gly Lys Ser Arg Ser Ser Leu Glu Lys Gly Gln Pro Ser Ser Lys
            980                 985                 990

Met Thr Pro Ser Lys Asn Ile Thr  Lys Lys Met Asp Lys  Thr Ile Pro
        995                 1000                1005

Glu Gly  Arg Ile Arg Leu Pro  Arg Lys Ala Thr Lys  Thr Lys Lys
    1010                1015                1020


<210> SEQ ID NO 7
<211> LENGTH: 1500
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<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 7

Met Pro Val Arg Pro Asp Leu Gln Gln Leu Glu Lys Cys Ile Asp Asp
1 5 10 15

Ala Leu Arg Lys Asn Asp Phe Lys Pro Leu Leu Ala Leu Leu Gln Ile
20 25 30

Asp Ile Cys Glu Asp Val Lys Ile Lys Cys Ser Lys Gln Phe Leu Arg
35 40 45

Lys Leu Asp Asp Leu Ile Cys Arg Glu Leu Asn Lys Lys Asp Ile Gln
50 55 60

Thr Val Ser Ser Ile Leu Ile Ser Ile Gly Arg Cys Ser Lys Asn Ile
65 70 75 80

Phe Ile Leu Gly Gln Ala Gly Leu Gln Thr Met Ile Lys Gln Gly Leu
85 90 95

Val Gln Lys Met Val Ser Trp Phe Glu Asn Ser Lys Glu Ile Ile Leu
100 105 110

Asn Gln Gln Gln Ser Lys Asp Glu Ala Val Met Asn Met Ile Glu Asp
115 120 125

Leu Phe Asp Leu Leu Met Val Ile Tyr Asp Ile Ser Asp Glu Gly Lys
130 135 140

Asn Gln Val Leu Glu Ser Phe Ile Pro Gln Ile Cys Ala Leu Val Ile
145 150 155 160

Asp Ser Arg Val Asn Phe Cys Ile Gln Gln Glu Ala Leu Lys Lys Met
165 170 175

Asn Leu Met Leu Asp Arg Ile Pro Gln Asp Ala Asn Lys Ile Leu Ser
180 185 190

Asn Gln Glu Met Leu Thr Leu Met Ser Asn Met Gly Glu Arg Ile Leu
195 200 205

Asp Val Gly Asp Tyr Glu Leu Gln Val Gly Ile Val Glu Ala Leu Cys
210 215 220

Arg Met Thr Thr Glu Lys Arg Arg Gln Glu Leu Ala Tyr Glu Trp Phe
225 230 235 240

Ser Met Asp Phe Ile Ala Asn Ala Phe Lys Glu Ile Lys Asp Cys Glu
245 250 255

Phe Glu Thr Asp Cys Arg Ile Phe Leu Asn Leu Val Asn Gly Ile Leu
260 265 270

Gly Asp Lys Arg Arg Val Tyr Thr Phe Pro Cys Leu Ser Ala Phe Leu
275 280 285

Gly Lys Tyr Glu Leu Gln Ile Pro Ser Asp Glu Lys Leu Glu Glu Phe
290 295 300

Trp Ile Asp Phe Asn Leu Gly Ser His Thr Leu Ser Phe Tyr Ile Ala
305 310 315 320

Gly Asp Glu Glu Asp His Gln Trp Glu Ala Val Thr Val Pro Glu Glu
325 330 335

Lys Val Gln Met Tyr Asn Ile Glu Val Arg Glu Ser Lys Lys Leu Leu
340 345 350

Thr Leu Thr Leu Lys Asn Ile Val Lys Ile Ser Lys Lys Glu Gly Lys
355 360 365

Glu Leu Leu Phe Tyr Phe Asp Glu Ser Leu Glu Ile Thr Asn Val Thr
370 375 380

Lys Lys Val Phe Gly Gly Asn Lys Tyr Lys Glu Phe Thr Arg Lys Gln
385 390 395 400

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Gly Ile Ser Val Ala Lys Thr Ser Ile His Val Leu Phe Asp Ala Ser
                405                 410                 415

Gly Ser Gln Ile Leu Val Pro Glu Ser Gln Pro Ser Pro Val Lys Glu
            420                 425                 430

Asn Leu Ile His Leu Lys Glu Lys Ser Asp Ile Gln Lys Lys Leu Val
        435                 440                 445

Asn Pro Leu Glu Leu Gly Asn Ser Ser Ser Gln Asp Glu Ile Thr Thr
    450                 455                 460

Pro Ser Arg Lys Lys Met Ser Glu Ala Ser Met Ile Val Pro Asp Thr
465                 470                 475                 480

Asp Arg Tyr Thr Val Arg Ser Pro Ile Leu Leu Ile Asn Thr Ser Thr
                485                 490                 495

Pro Arg Arg Ser Arg Glu Pro Leu Gln Ala Ile Asn Ser Val Glu Lys
            500                 505                 510

Ala Val Ser Lys Thr Ser Glu Ser Gly Met Asp Tyr Ala Ala Ser Pro
        515                 520                 525

Lys Ser Arg Gln Ser Asp Gly Arg Lys Arg Trp Asn Asn Arg Ala Asn
    530                 535                 540

His Asn Lys Thr Thr Ala Val Ile Gln Asn Lys Gln Tyr Glu Asp Asn
545                 550                 555                 560

Glu Ser Pro Asp Gln Asn Phe Asn Glu Ile Glu Asp Thr Leu Ser Asn
                565                 570                 575

Val Ser Ser Ala Val Gly Lys Val Asp Lys Pro Val Leu Pro Gly Val
            580                 585                 590

Leu Asp Ile Ser Lys Asn Thr Thr His Ser Arg Trp Ala Cys Trp Thr
        595                 600                 605

Pro Val Thr Thr Ile Lys Leu Cys Asn Asn Gln Arg Ser Arg Ala Leu
    610                 615                 620

Pro Gly Asp Thr Cys Thr Gln Asp Thr Gly Val Asn Lys Lys Cys Thr
625                 630                 635                 640

Lys Gln Lys Ser Val Ser Asp Asp Asp Ser Glu Glu Thr Gln Lys Gly
                645                 650                 655

Lys Tyr Ser Lys Asp Val Ile Lys Cys Asn Lys Ser Asp Glu Ala Glu
            660                 665                 670

Phe Cys Glu Arg Asn Ile Gln Glu Gln Asn His Pro Lys Tyr Ser Gln
        675                 680                 685

Lys Lys Asn Thr Ala Asn Ala Lys Lys Ser Asp Trp His Ile Glu Ser
    690                 695                 700

Glu Thr Thr Tyr Lys Ser Val Leu Leu Asn Lys Thr Thr Glu Glu Ser
705                 710                 715                 720

Leu Ile Tyr Lys Lys Thr Cys Val Leu Ser Lys Asp Val Asn Thr Thr
                725                 730                 735

Ile Cys Asp Lys Ser Pro Ser Arg Lys Ser Lys Arg Asn His Thr Lys
            740                 745                 750

Ser Arg Lys Glu Leu Met Ser Glu Leu Thr Ser Cys Glu Leu Glu Glu
        755                 760                 765

Ile Pro Val Arg Glu Asn Ser Lys Gly Lys Arg Phe Thr Gly Ala Ser
    770                 775                 780

Glu Ser Leu Ile Asn Gln Ile Ser Arg Arg Tyr Asn Pro Ser Asp Ser
785                 790                 795                 800

Met Met Ser Thr Arg Lys Leu Lys Glu Pro Gln Asp Gly Ser Gly Phe
                805                 810                 815

Ser Lys Lys Pro Asp Leu Gln Phe Asn Lys Val Gln Arg Lys Ser Tyr
            820                 825                 830
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Arg Lys Leu Lys Ala Thr Val Val Asn Val Thr Ser Glu Cys Pro Leu
        835                 840                 845

Asp Asp Val Tyr Asn Phe Ser Leu Asn Gly Ala Asp Glu Pro Val Ile
    850                 855                 860

Lys Leu Gly Ile Gln Glu Phe Gln Ala Thr Thr Arg Glu Ala Ser Met
865                 870                 875                 880

Asp Asn Ser Leu Lys Leu Val Lys Asn His Asp Glu His Asp Pro Phe
                885                 890                 895

Leu Lys Thr Lys Asp Lys Arg Met Leu Ser Tyr Glu Lys Lys Thr Leu
            900                 905                 910

Leu Ser Asp Thr Glu Thr Glu Cys Gly Cys Asp Asp Ser Lys Thr Asp
        915                 920                 925

Ile Ser Trp Leu Lys Glu Pro Lys Thr Lys Arg Leu Met Asp Tyr Ser
    930                 935                 940

Arg Asn Lys Asn Thr Thr Lys Tyr Lys Ser Arg Lys Ser Arg Ser Ser
945                 950                 955                 960

Met Glu Lys Gly Gln Pro Arg Pro Thr Met Val Leu Asn Lys Asn Ser
                965                 970                 975

Met Lys Asn Asp Tyr Glu Val Val Val Asp Gly Arg Thr Arg Leu Pro
            980                 985                 990

Arg Arg Ala Thr Lys Thr Lys Lys  Asn Tyr Lys Asp Leu  Ser Thr Ser
        995                 1000                1005

Glu Ser  Glu Ser Glu Ser Glu  Lys Glu Cys Ser Tyr  Leu Phe Lys
    1010                1015                1020

Asp Lys  Leu Pro Thr Lys Glu  Glu Thr Ile His Ser  Arg Ala Gln
    1025                1030                1035

Thr Lys  Lys Leu Pro Glu Lys  Gln Gln Lys Val Phe  Asn Ser Glu
    1040                1045                1050

Ala Leu  Lys Gly Gln Pro Ser  Glu Glu Gln Lys Asn  Ser Ser Arg
    1055                1060                1065

Leu Arg  Glu Gly Arg Glu Asp  Ser Leu Cys Leu Ser  Ser Ala Ser
    1070                1075                1080

Val Ser  Arg Ser Ser Ser Ser  Val Glu Val Met Arg  Cys Thr Glu
    1085                1090                1095

Lys Ile  Thr Glu Arg Asp Phe  Thr Gln Asp Tyr Asp  Tyr Ile Thr
    1100                1105                1110

Lys Ser  Leu Ser Pro Tyr Pro  Lys Ala Pro Ser Pro  Glu Phe Leu
    1115                1120                1125

Asn Gly  Asn Asn Ser Val Val  Gly Arg Gly Gln Ser  Pro Arg Ile
    1130                1135                1140

Ser Glu  Thr Ser Ala Met Cys  Val Arg Lys Ser Tyr  Ser Pro Ala
    1145                1150                1155

Ser Gly  Pro Pro Phe Ser Pro  Arg His Thr Pro Thr  Lys Asn Asn
    1160                1165                1170

Ser Val  Val Asn Met Lys Lys  Ala Asn Ser Val Ile  Asn Asn Gln
    1175                1180                1185

Arg Thr  Gln His Cys Asn Ser  Tyr Ser Asp Val Ser  Ser Asn Ser
    1190                1195                1200

Ser Glu  Lys Leu Tyr Met Glu  Pro Glu Ser Pro Glu  Ser Cys Asp
    1205                1210                1215

Asn His  Met Gln Asn Lys Arg  Glu Gly Asn His Ala  Ala Ser Pro
    1220                1225                1230

Leu Ser  Leu Ser Ser Glu Lys  Ile Glu Lys Met Trp  Phe Asp Met
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    1235                1240                1245

Pro Ser  Glu Asn Thr His Val  Ser Gly Pro Ser Gln  Arg Gly Ser
    1250                1255                1260

Lys Arg  Arg Met Tyr Leu Glu  Asp Asp Glu Leu Ser  Asn Ser Asn
    1265                1270                1275

Glu Ala  Glu Val Glu Glu Ala  Glu Glu Arg Glu His  Leu Leu Ser
    1280                1285                1290

Lys Lys  Arg Cys Gln Trp Glu  Asn Ser Asp Gln His  Thr Phe Lys
    1295                1300                1305

Thr Ser  Leu Ser Thr Pro Asp  Phe Ser Val Pro Lys  Asp Trp Gln
    1310                1315                1320

Gln Glu  Leu Gln Gly Ala Gly  Met Phe Tyr Asp Asn  Ile Ser Ser
    1325                1330                1335

Asp Tyr  Lys Arg Lys Thr Asp  Ser Gln His Lys Ile  Met Asp Asp
    1340                1345                1350

Phe Thr  Thr Lys Thr Leu Lys  Leu Thr Gln Gln His  Leu Met Ala
    1355                1360                1365

Met Thr  Ser Gln Ala Gln Gly  Arg Arg Asp Glu Asn  Val Glu Lys
    1370                1375                1380

Phe Gln  Val Thr Leu Leu Asp  Glu Leu Glu Lys Val  Glu Lys Asp
    1385                1390                1395

Ser Gln  Thr Leu Arg Asp Leu  Glu Lys Glu Leu Val  Asp Ile Glu
    1400                1405                1410

Glu Lys  Leu Val Gln Lys Met  Arg Ala Tyr His Arg  Cys Glu Arg
    1415                1420                1425

Glu Arg  Phe Arg Val Leu Lys  Thr Ser Leu Asp Lys  Ser Phe Leu
    1430                1435                1440

Val Tyr  Asn Ser Val Tyr Glu  Glu Ser Val Phe Thr  Ser Glu Met
    1445                1450                1455

Cys Leu  Met Lys Ala Asn Met  Lys Met Leu Gln Asp  Lys Leu Leu
    1460                1465                1470

Lys Glu  Met His Glu Glu Glu  Val Leu Asn Ile Arg  Arg Gly Leu
    1475                1480                1485

Gln Ser  Leu Phe Lys Ala His  Glu Gly Asn Asp Ala
    1490                1495                1500


<210> SEQ ID NO 8
<211> LENGTH: 1505
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 8

Met Pro Val Arg Pro Asp Pro Gln Gln Leu Glu Lys Cys Ile Asp Asp
1               5                   10                  15

Ala Leu Arg Lys Asn Asp Phe Lys Pro Leu Val Thr Leu Leu Gln Ile
            20                  25                  30

Asp Ile Cys Glu Asp Val Lys Ile Lys Cys Ser Lys Gln Phe Leu Arg
        35                  40                  45

Lys Leu Asp Asp Leu Ile Cys Arg Glu Leu His Lys Lys Asp Ile Gln
    50                  55                  60

Thr Ile Ser Asn Ile Leu Ile Ser Ile Gly Arg Cys Ser Lys Asn Ile
65                  70                  75                  80

Phe Ile Leu Gly Gln Thr Gly Leu Gln Thr Met Ile Lys Gln Gly Leu
                85                  90                  95

Val Gln Lys Met Val Ser Trp Phe Glu Asn Ser Lys Glu Ile Ile Leu
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           100                 105                 110

Ser Gln Arg Gln Ser Lys Asp Glu Ala Val Met Asn Met Ile Glu Asp
        115                 120                 125

Leu Phe Asp Leu Leu Met Val Val Tyr Asp Val Asn Asp Glu Gly Lys
    130                 135                 140

Asn Gln Val Leu Glu Ser Phe Ile Pro His Ile Cys Ala Leu Val Ile
145                 150                 155                 160

Asp Ser Arg Val Asn Phe Cys Ile Gln Gln Glu Ala Leu Lys Lys Met
                165                 170                 175

Asn Leu Met Leu Asp Arg Ile Pro Gln Asp Ala Asn Lys Ile Leu Cys
            180                 185                 190

Asn Gln Glu Ile Leu Thr Leu Met Ser Asn Met Gly Glu Arg Ile Leu
        195                 200                 205

Asp Val Gly Asp Tyr Glu Leu Gln Val Gly Ile Val Glu Ala Leu Cys
    210                 215                 220

Arg Met Thr Thr Glu Lys Arg Arg Gln Glu Leu Ala Tyr Glu Trp Phe
225                 230                 235                 240

Ser Met Asp Phe Ile Ala Asn Ala Phe Lys Lys Ile Lys Asp Cys Glu
                245                 250                 255

Phe Glu Thr Asp Cys Arg Ile Phe Leu Asn Leu Val Asn Gly Met Leu
            260                 265                 270

Gly Asp Arg Arg Arg Val Phe Thr Phe Pro Cys Leu Ser Ala Phe Leu
        275                 280                 285

Gly Lys Tyr Glu Leu Gln Ile Pro Ser Asp Glu Lys Leu Glu Glu Phe
    290                 295                 300

Trp Ile Asp Phe Asn Leu Gly Ser His Thr Leu Ser Phe Tyr Ile Ala
305                 310                 315                 320

Gly Asp Asp Asp Asp His Gln Trp Glu Ala Val Thr Val Pro Glu Glu
                325                 330                 335

Lys Val Asp Met Tyr Asn Ile Glu Val Arg Glu Ser Lys Lys Leu Leu
            340                 345                 350

Thr Leu Thr Leu Lys Asn Ile Val Lys Ile Ser Lys Lys Glu Gly Lys
        355                 360                 365

Glu Leu Leu Leu Tyr Phe Asp Ala Ala Leu Glu Ile Thr Asn Val Thr
    370                 375                 380

Lys Lys Leu Phe Gly Gly Asn Lys Tyr Lys Glu Phe Thr Arg Lys Gln
385                 390                 395                 400

Asp Ile Ser Val Ala Lys Thr Ser Ile His Val Leu Phe Asp Ala Ser
                405                 410                 415

Gly Ser Gln Ile Leu Val Pro Glu Ser Gln Pro Ser Pro Val Lys Glu
            420                 425                 430

Asn Leu Ile His Leu Lys Glu Lys Ser Asn Leu Gln Lys Lys Leu Thr
        435                 440                 445

Asn Pro Leu Glu Pro Asp Asn Ser Ser Ser Gln Arg Asp Arg Lys Asn
    450                 455                 460

Ser Gln Asp Glu Ile Thr Thr Pro Ser Arg Lys Lys Met Ser Glu Ala
465                 470                 475                 480

Ser Met Ile Val Pro Asp Thr Asp Arg Tyr Thr Val Arg Ser Pro Ile
                485                 490                 495

Leu Leu Ile Asn Thr Ser Thr Pro Arg Arg Ser Arg Ala Pro Leu Gln
            500                 505                 510

Ala Ile His Ser Ala Glu Lys Ala Val Ser Lys Thr Ser Glu Ser Gly
        515                 520                 525
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Val Asp Tyr Ala Val Ser Leu Lys Ser Arg Gln Ser Asp Gly Arg Asn
    530                 535                 540

Arg Gly Asn Asn Arg Ala Asn His Asn Lys Thr Ala Thr Val Gln Asn
545                 550                 555                 560

Lys Gly His Glu His His Glu Ser Pro Asp Gln Thr Phe Asn Glu Ile
                565                 570                 575

Glu Glu Thr Leu Ser Asp Ala Tyr Ala Val Glu Lys Val Asp Lys Pro
            580                 585                 590

Val Leu Pro Gly Val Leu Asp Ile Ser Lys Asn Lys Ala His Ser Arg
        595                 600                 605

Trp Ala Cys Trp Thr Pro Val Thr Thr Ile Lys Leu Cys Asn Asn Gln
    610                 615                 620

Arg Ser Cys Ala Leu Pro Gly Asp Thr Phe Thr Gln Asp Thr Gly Val
625                 630                 635                 640

Asn Lys Lys Cys Thr Lys Gln Lys Ser Val Ser Asp Asp Asp Ser Glu
                645                 650                 655

Glu Thr Gln Arg Val Lys Tyr Ser Lys Asp Val Ile Lys Cys Asn Lys
            660                 665                 670

Ser Glu Glu Ala Glu Val Cys Glu Arg Asn Ile Gln Glu Gln Asn His
        675                 680                 685

Pro Lys Tyr Ser Gln Lys Lys Asn Thr Ala Asn Ala Lys Lys Asn Asp
    690                 695                 700

Trp His Ile Glu Ser Glu Thr Thr Tyr Lys Ser Val Leu Leu Asn Lys
705                 710                 715                 720

Thr Thr Glu Glu Ser Leu Ile Tyr Lys Lys Thr Cys Val Leu Ser Lys
                725                 730                 735

Asp Val Asn Thr Thr Ile Cys Asp Lys Ser Pro Ser Arg Lys Ser Met
            740                 745                 750

Arg Ser His Thr Lys Ser Arg Lys Glu Leu Met Ser Glu Val Thr Ser
        755                 760                 765

Cys Glu Leu Asp Glu Ile Pro Val Arg Glu Asn Ser Lys Gly Lys Arg
    770                 775                 780

Phe Thr Gly Thr Ala Glu Ser Leu Ile Asn Leu Ile Asn Lys Arg Tyr
785                 790                 795                 800

Asn Ser Ser Asp Asp Met Ile Ser Thr Arg Lys Leu Lys Glu Pro Arg
                805                 810                 815

Asp Gly Ser Gly Phe Ser Lys Lys Pro Glu Leu Gln Phe Asn Lys Val
            820                 825                 830

Gln Arg Lys Ser Tyr Arg Lys Leu Lys Thr Val Val Asn Val Thr Ser
        835                 840                 845

Glu Cys Pro Leu Asn Asp Val Tyr Asn Phe Ser Leu Asn Gly Ala Asp
    850                 855                 860

Glu Pro Val Ile Lys Leu Gly Ile Gln Glu Phe Gln Ala Thr Thr Arg
865                 870                 875                 880

Glu Ala Ser Met Asp Asn Ser Ile Lys Leu Val Asp Val Arg Asn Arg
                885                 890                 895

Asp Glu Arg Asp Leu Ser Leu Lys Thr Lys Asp Glu Arg Ile Leu Ser
            900                 905                 910

His Glu Arg Lys Thr Leu Phe Ser Asp Thr Glu Thr Glu Cys Gly Trp
        915                 920                 925

Asp Asp Ser Lys Thr Asp Ile Ser Trp Leu Arg Lys Pro Lys Ser Lys
    930                 935                 940

Arg Leu Met Asp Tyr Ser Arg Asn Lys Asn Thr Lys Lys Cys Lys Ser
945                 950                 955                 960
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```
Ile Lys Ser Arg Ser Ser Thr Glu Lys Gly Gln Pro Arg Ser Thr Val
               965                 970                 975

Val Leu Ser Lys Asn Ile Ala Lys Asn Asp Tyr Glu Val Ile Val Asp
           980                 985                 990

Gly Arg Thr Arg Leu Pro Arg Arg  Ala Thr Lys Thr Lys  Lys Asn Tyr
       995                1000                1005

Lys Asp  Leu Ser Thr Ser Gly  Ser Glu Ser Glu Ser  Glu Lys Glu
    1010                1015                1020

Ile Ser  Tyr Leu Phe Lys Asp  Lys Leu Pro Thr Lys  Glu Glu Thr
    1025                1030                1035

Val His  Ser Ser Ala Gln Thr  Lys Lys Leu Pro Lys  Lys Gln Gln
    1040                1045                1050

Lys Val  Phe Asn Thr Glu Ala  Leu Lys Gly Gln Pro  Ser Glu Glu
    1055                1060                1065

Gln Lys  Asn Ser Ser Thr Leu  Arg Asn Gly Arg Glu  Asp Ser Leu
    1070                1075                1080

Tyr Leu  Ser Ser Ala Ser Val  Ser Gly Ser Ser Ser  Ser Val Glu
    1085                1090                1095

Val Met  Arg Cys Thr Glu Lys  Ile Thr Glu Arg Asp  Phe Thr Gln
    1100                1105                1110

Asp Tyr  Asp Tyr Ile Thr Lys  Ser Leu Ser Pro Tyr  Pro Lys Ala
    1115                1120                1125

Ala Ser  Pro Glu Phe Leu Asn  Arg Ser Asn Arg Val  Val Gly His
    1130                1135                1140

Gly Lys  Ser Pro Arg Ile Ser  Glu Thr Ser Ala Val  Cys Val Arg
    1145                1150                1155

Lys Ser  Cys Ser Pro Ala Ser  Gly Leu Pro Phe Ser  Pro Arg His
    1160                1165                1170

Thr Thr  Lys Asn Asn Ser Val  Met Asn Ile Lys Asn  Thr Asn Ser
    1175                1180                1185

Val Ile  Asn Asn Gln Arg Thr  Gln His Cys Asn Ser  Tyr Ser Asp
    1190                1195                1200

Val Ser  Ser Asn Ser Ser Glu  Lys Leu Tyr Met Glu  Pro Glu Ser
    1205                1210                1215

Pro Asp  Ser Cys Glu Asn His  Val Gln Ser Lys Arg  Glu Glu Asn
    1220                1225                1230

His Ala  Ala Ser Pro Phe Ser  Leu Ser Ser Glu Lys  Ile Glu Lys
    1235                1240                1245

Ile Trp  Phe Asp Met Pro Asn  Asp Asn Thr His Val  Ser Gly Pro
    1250                1255                1260

Ser Gln  Arg Gly Ser Lys Arg  Arg Met Tyr Leu Glu  Glu Asp Glu
    1265                1270                1275

Leu Ser  Asn Pro Ser Glu Ala  Glu Val Gln Glu Ala  Glu Glu Arg
    1280                1285                1290

Glu His  Leu Val Ser Lys Lys  Leu Cys Gln Arg Glu  His Phe Asp
    1295                1300                1305

Gln His  Thr Ser Glu Thr Ser  Leu Ser Thr Pro Glu  Phe Ser Val
    1310                1315                1320

Pro Lys  Asp Trp Gln Gln Glu  Leu Gln Gly Ala Gly  Met Phe Tyr
    1325                1330                1335

Asp Asn  Ile Asn Ser Asp Tyr  Lys Arg Lys Thr Asp  Thr Gln His
    1340                1345                1350

Lys Ile  Met Asp Asp Phe Thr  Thr Lys Thr Leu Lys  Leu Thr Gln
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    1355                1360                1365

Gln His  Leu Leu Ala Met Ala  Cys Gln Ala Arg Gly  His Arg Asp
    1370                1375                1380

Glu Asn  Ile Asp Lys Phe Gln  Val Thr Leu Leu Asp  Glu Leu Glu
    1385                1390                1395

Lys Val  Glu Lys Asp Ser Gln  Thr Leu Arg Asp Leu  Glu Lys Glu
    1400                1405                1410

Phe Val  Asp Ile Glu Glu Lys  Ile Val His Lys Met  Arg Ala Phe
    1415                1420                1425

His Gln  Ser Glu Arg Glu Arg  Phe Arg Ala Leu Lys  Thr Ser Leu
    1430                1435                1440

Asp Lys  Ser Leu Leu Val Tyr  Asn Ser Val Tyr Glu  Glu Asn Val
    1445                1450                1455

Leu Thr  Ser Glu Met Cys Leu  Met Lys Ala Asn Met  Lys Met Leu
    1460                1465                1470

Gln Asp  Lys Leu Leu Lys Glu  Met His Glu Glu Glu  Leu Leu Asn
    1475                1480                1485

Ile Arg  Arg Gly Leu Glu Ser  Leu Phe Lys Asp His  Glu Gly Asn
    1490                1495                1500

Asn Ala
    1505


<210> SEQ ID NO 9
<211> LENGTH: 1079
<212> TYPE: PRT
<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 9

Val Ala Trp Phe Glu Lys Ser Lys Glu Ile Ile Leu Ser Gln Gly Ser
1               5                   10                  15

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

Leu Met Val Ile His Asp Ile Asp Asp Glu Gly Lys Arg Gln Val Val
        35                  40                  45

Glu Ser Phe Ile Pro Arg Ile Cys Ala Leu Val Ile Asp Ser Arg Val
    50                  55                  60

Asn Ile Cys Val Gln Gln Glu Thr Leu Lys Lys Met Asn Ala Met Leu
65                  70                  75                  80

Asp Lys Met Pro Gln Asp Ala Arg Lys Ile Leu Phe Asn Gln Glu Met
                85                  90                  95

Leu Ile Leu Met Ser Ser Met Gly Glu Arg Ile Leu Asp Ala Gly Asp
            100                 105                 110

Tyr Asp Leu Gln Val Gly Ile Val Glu Ala Leu Cys Arg Met Thr Thr
        115                 120                 125

Glu Lys Gln Arg Gln Glu Leu Ala Cys Gln Trp Phe Ser Met Asp Phe
    130                 135                 140

Val Ala Asn Ala Phe Lys Gly Ile Lys Asp Ser Glu Phe Glu Thr Asp
145                 150                 155                 160

Cys Arg Met Phe Leu Asn Leu Val Asn Gly Ile Leu Gly Asp Lys Arg
                165                 170                 175

Arg Val Phe Thr Phe Pro Cys Leu Ser Ala Phe Leu Asp Lys Tyr Glu
            180                 185                 190

Leu Gln Ile Pro Ser Asp Glu Lys Leu Glu Asp Phe Trp Ile Asp Phe
        195                 200                 205

Asn Leu Gly Ser Gln Thr Leu Ser Phe Tyr Ile Ala Gly Asp Asn Asp
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    210                 215                 220

Asp His Gln Trp Glu Ala Val Thr Val Pro Glu Glu Lys Val Gln Ile
225                 230                 235                 240

Tyr Ser Ile Glu Val Arg Asp Ser Lys Lys Leu Leu Thr Ile Ile Leu
                245                 250                 255

Lys Asp Thr Val Lys Ile Ser Lys Arg Lys Gly Lys Glu Leu Leu Leu
            260                 265                 270

Tyr Phe Asp Ala Ser Leu Glu Ile Thr Asn Val Thr Gln Lys Ile Phe
        275                 280                 285

Gly Ala Asn Lys Tyr Arg Glu Phe Ser Arg Lys Gln Gly Ile Ser Val
    290                 295                 300

Ala Lys Thr Ser Val His Ile Leu Phe Asp Ala Ser Gly Ser Gln Ile
305                 310                 315                 320

Leu Val Pro Glu Ser Gln Ile Ser Pro Val Glu Glu Leu Ser Thr Leu
                325                 330                 335

Lys Glu Lys Ala Asn Pro Gln Glu Glu Phe Val Lys Pro Pro Lys His
            340                 345                 350

Ile Lys Asn Ser Asn Lys Gly Asp Arg Lys His Gly Gln Pro Glu Ile
        355                 360                 365

Ile Thr Pro Ser Lys Arg Lys Met Ser Glu Ala Ser Met Ile Val Pro
    370                 375                 380

Gly Ala Glu Arg Tyr Thr Val Arg Ser Pro Ile Leu Leu Ile Asn Thr
385                 390                 395                 400

Ser Thr Pro Gln Arg Gly Arg Ile Lys Pro Pro Leu Gln Met Thr Ser
                405                 410                 415

Ser Met Glu Lys Pro Gly Phe Ser Lys Thr Ser Glu Asn Gly Val Asp
            420                 425                 430

Asn Ala Val Ser Leu Lys Ser Arg Pro Cys Glu Glu Arg Asn Arg Glu
        435                 440                 445

Asp Asn Thr Asp Lys His Ile Lys Thr Lys Val Ile Glu Lys Ala Glu
    450                 455                 460

Asn Lys Asp Ile Glu Tyr Pro Asn Gln Asn Phe Asn Glu Leu Gln Glu
465                 470                 475                 480

Ile Val Pro Asp Ser Gln Ala Val Gly Lys Ile Asp Lys Pro Val Leu
                485                 490                 495

Pro Gly Ile Leu Asp Asn Ile Cys Gly Asn Lys Met His Ser Lys Trp
            500                 505                 510

Ala Cys Trp Thr Pro Val Thr Asn Ile Lys Leu Cys Asn Asn Leu Arg
        515                 520                 525

Ala Ser Ser Ser Ser Glu Asp Thr Phe Asn Gln Asp Ile Ile Ile Asn
    530                 535                 540

Lys Asn Leu Thr Lys Lys Lys Ser Ser Ser Ser Met Ser Asp Asp Asn
545                 550                 555                 560

Ser Glu Glu Thr Ser Lys Val Gln Tyr Gly Lys Glu Leu Met Gln His
                565                 570                 575

Asn Lys Ile Asp Lys Ala Glu Ala Glu Ala Cys Lys Arg Asn Lys Gln
            580                 585                 590

Gln Gln Leu Asp His Ser Lys His Ser Glu Glu Lys Asn Thr Glu Asn
        595                 600                 605

Thr Lys Gln Asn Asp Trp Arg Ile Glu Ser Glu Thr Thr Phe Lys Ser
    610                 615                 620

Val Leu Leu Asn Lys Thr Val Glu Glu Ser Val Ile Tyr Arg Lys Lys
625                 630                 635                 640
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Tyr Thr Leu Ser Lys Asp Val Asn Thr Ala Ile Cys Asp Lys Ser Pro
                645                 650                 655

Ser Pro Arg Lys Asn Thr Lys Ser His Arg Lys Ser Gly Lys Arg Leu
            660                 665                 670

Thr Ser Glu Leu Asn Ser Trp Asp Leu Lys Gln Lys Glu Met Arg Glu
        675                 680                 685

Lys Ser Lys Gly Lys Gly Phe Asn Asp Ala Ala Glu Ser Leu Ile Ser
    690                 695                 700

Gln Ile Asn Lys Arg Tyr Lys Pro Lys Asp Gly Thr Lys Ser Thr Arg
705                 710                 715                 720

Lys Leu Lys Glu Ser Leu Ile Asp Ser Gly Phe Ser Asn Lys Ser Asp
                725                 730                 735

Leu Gln Leu Arg Lys Glu Lys Val Gln Lys Lys Ser Tyr Arg Gln Leu
            740                 745                 750

Lys Thr Thr Phe Val Asn Val Thr Ser Glu Cys Pro Leu Asn Asp Val
        755                 760                 765

Tyr Asn Phe Asn Leu Ser Gly Ala Asp Glu Pro Val Ile Lys Leu Gly
    770                 775                 780

Ile Gln Glu Phe Gln Ala Thr Ala Arg Glu Ala Cys Val Asp Ser Thr
785                 790                 795                 800

Ile Thr Leu Val Gly Leu Arg Asn His Asp Glu Leu Glu Thr Ser Leu
                805                 810                 815

Lys Thr Lys Asp Lys Arg Thr Val Thr Asn His Lys Lys Lys Thr Leu
            820                 825                 830

Phe Ser Asp Thr Asp Thr Glu Tyr Lys Cys Asp Asp Ser Lys Thr Asp
        835                 840                 845

Ile Ser Trp Leu Arg Glu Ser Lys Ser Lys Pro Gln Leu Ile Gly Tyr
    850                 855                 860

Ser Arg Asn Lys Asn Val Lys Lys His Lys Ser Gly Lys Ser Arg Ser
865                 870                 875                 880

Ser Leu Glu Arg Glu Gln Pro Arg Ser Lys Met Thr Pro Asp Lys Asn
                885                 890                 895

Ile Thr Lys Lys Val Asp Glu Thr Val Pro Asp Gly Arg Ile Arg Leu
            900                 905                 910

Pro Arg Arg Ala Ala Lys Thr Lys Lys Asn Tyr Lys Asp Leu Ser Asn
        915                 920                 925

Ser Glu Ser Glu Ser Glu Gln Glu Phe Ser His Ser Phe Lys Glu Lys
    930                 935                 940

Leu Leu Ile Lys Glu Asn Ile His Ser Arg Ser Lys Thr Met Lys Pro
945                 950                 955                 960

Pro Lys Lys Gln Asn Ser Phe Ser Ser Glu Met Gln Lys Asp Ile Ser
                965                 970                 975

Lys Glu Trp Lys Asn Ser Ser Leu Leu Lys Asp Thr Ile Arg Asp Asn
            980                 985                 990

Ser Leu Asp Lys Ser Pro Val Ser  Leu Ser Gly Ser Pro  Ser Ser Ile
        995                 1000                1005

Glu Val  Met Arg Cys Thr Glu  Lys Thr Thr Glu Arg  Asp Phe Thr
    1010                1015                1020

Gln Asp  Phe Asp Tyr Val Thr  Lys Ser Leu Ser Pro  Tyr Pro Lys
    1025                1030                1035

Thr Ser  Ser Pro Glu Ser Leu  Asn Ser Gly Val Glu  Ser Pro Ile
    1040                1045                1050

Asn Ser  Pro Asn Asn Ser Glu  Lys Asn Leu Leu Cys  Gly Gly Glu
    1055                1060                1065
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Ser Cys  Ser Pro Ile Pro Gln  Ser Gly Phe Leu
    1070                1075


<210> SEQ ID NO 10
<211> LENGTH: 919
<212> TYPE: PRT
<213> ORGANISM: Xenopus tropicalis

<400> SEQUENCE: 10

Met His Pro Lys Gln Glu Ser Lys Leu Glu Ala Asn Ile Asp His Gly
1               5                  10                  15

Leu Arg Thr Lys Gly His Asp Leu Arg Pro Leu Lys Ser Phe Leu Leu
            20                  25                  30

Thr Glu Ser Cys Ala Gly Thr Ser Ile Lys Cys Ser Lys Phe Leu Leu
        35                  40                  45

Gly Lys Leu Asp Lys Leu Ile Cys Met Glu Leu Asp Gln Arg Glu Val
    50                  55                  60

Lys Asn Ala Leu Leu Val Leu Asn Val Ile Leu Lys Phe Ala Ser Cys
65                  70                  75                  80

Met Thr Leu Asn Asn Glu Glu Trp Leu Thr Ala Ser Ile Lys Gln Gly
                85                  90                  95

Leu Val Gln Lys Met Ile Ile Trp Leu Glu Lys Ser Thr Tyr Phe Leu
            100                 105                 110

Ala Tyr Ser Glu Lys Gln Lys Asn Glu Thr Val Leu Asn Phe Ala Glu
        115                 120                 125

Asp Phe Phe Asp Ile Val Met Leu Val His Asp His Ser Ser Glu Gly
    130                 135                 140

Lys Met Gln Ile Leu Glu His Phe Leu Val Arg Ala Cys Ser Leu Val
145                 150                 155                 160

Ser Asn Ala Ala Thr Asn Ile Phe Val Lys Gln Glu Val Val Arg Arg
                165                 170                 175

Leu Asn Leu Met Leu Asn Thr Met Pro Leu Val Ala Arg Lys Lys Ile
            180                 185                 190

Leu Ser Thr Glu Glu Met Thr Ser Ala Met Ala Ser Met Ala Lys Arg
        195                 200                 205

Ile Leu Asp Ala Gly Asp Phe Asp Leu Gln Val Ala Ile Thr Glu Ala
    210                 215                 220

Leu Cys Arg Met Thr Ser Glu Ala Gln Arg Glu Leu Thr Ser Gln Trp
225                 230                 235                 240

Phe Pro Met Glu Phe Ile Ala Glu Ala Phe Lys Arg Ile Lys Asp Ser
                245                 250                 255

Glu Phe Glu Thr Asp Cys Arg Lys Phe Leu Asn Leu Ile Asn Gly Ile
            260                 265                 270

Leu Gly Gly Lys Lys Ser Val Val Thr Leu Pro Cys Leu Ser Ala Tyr
        275                 280                 285

Leu Asp Asn His Lys Phe Gln Met Pro Cys Asp Glu Lys Leu Glu Glu
    290                 295                 300

Phe Trp Ile Asp Phe Asn Thr Gly Thr Gln Ser Ile Ser Phe Tyr Ile
305                 310                 315                 320

Ser Ala Gly Ala Ala Glu Glu His Gln Trp Asp Thr Val Cys Val Lys
                325                 330                 335

Asp Ser Asp Val Ile Val Tyr Ser Ile Ala Glu Val Asp Asn Asn Lys
            340                 345                 350

Leu Leu Thr Val Asp Leu Lys Ala Pro Ile Ala Ala Gly Gln Tyr Glu
        355                 360                 365
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Gly Lys Gln Ile Arg Ile Tyr Phe Ser Cys Pro Leu Asp Ile Leu Ser
    370                 375                 380

Ala Ala Gln Arg Val Phe Ala Ala Gln Lys Asn Lys Asp Phe Ile Lys
385                 390                 395                 400

Lys Gln Thr Ala Ser Asp Ala Glu Thr Thr Val Arg Val Ile Phe Glu
                405                 410                 415

Glu Cys Arg Ser Gln Ile Leu Leu Ser Glu Ser Gln Gly Ser Asn Ser
            420                 425                 430

Ser Val Lys Pro Val Ala Glu Pro Asp Val Lys Asp Phe Ala Gly Lys
        435                 440                 445

Asn Gln Pro Pro Ser Ala Ala Ser Ser Leu Lys Gln Thr Thr Cys Asn
    450                 455                 460

His Glu His Asn Thr Asn Ser Leu Met Pro Thr Thr Pro Val Lys Val
465                 470                 475                 480

Lys Met Ser Glu Ser Ser Met Val Gly Ser Gly Leu Lys Ile Thr Asn
                485                 490                 495

Ile Ala Thr Asn Asn Pro Ala Ser Arg Arg Ile Arg Thr Lys Pro Pro
            500                 505                 510

Leu Glu Met Val Arg Pro Ala Glu Arg Asn Thr Val Pro Pro Asn Lys
        515                 520                 525

Ser Arg Gly Gly Ser Pro Cys Ser Asp Arg Thr Pro Gln Leu Pro Lys
    530                 535                 540

His Lys Ser Ser Thr Asp Ala Ala Cys Thr Phe Gln Tyr Val Asn Lys
545                 550                 555                 560

Ala Pro Lys Asp Glu Leu Asn Glu Ile Val Pro Asp Thr Gln Tyr Cys
                565                 570                 575

Ala Thr Lys Asp Ser Ser Leu Leu Pro Gly Leu Thr Lys Arg Ser Val
            580                 585                 590

Asn Gln His Glu Arg Asn Arg Lys Gln Glu Asn Ser Gly Gly Phe Gly
        595                 600                 605

Asn Lys Ile Ser Val Ser Ser Val Cys Ile Ala Asn Gln Gly Lys Ile
    610                 615                 620

Ser Ser His Leu Val Lys Gln His Ser Asn Glu Ile Ser Thr Thr Pro
625                 630                 635                 640

Thr Lys Glu Met Ser Ala Arg Ser Ser Glu Ser Ser Ile Gln Lys His
                645                 650                 655

Cys Glu Lys His Leu Lys Glu Lys Pro Lys Glu Leu Ile Gln Ala Thr
            660                 665                 670

Asp Leu Leu Val Glu Asn Ile Arg Arg Lys Tyr Ala Arg Leu Thr Glu
        675                 680                 685

Glu Asp Lys Arg Glu Glu Asn Thr Phe Glu Arg Lys Asn Val Asp Lys
    690                 695                 700

His Pro Leu His Thr Asn Lys Asp Lys Asn Arg Thr Arg Gly Phe Asn
705                 710                 715                 720

Gln His Ser Pro Lys Asp Phe Ser Thr Thr Thr Lys Lys Pro Trp Lys
                725                 730                 735

Asp Val Tyr Asp Phe Gln Phe Ser Ala Thr Asp Asn Pro Thr Ile Asn
            740                 745                 750

Leu Glu Val Ser Ala Pro Thr Val Ser Glu Arg Met Ser Ser Lys Ala
        755                 760                 765

Leu Ala Ile Gly Lys Lys Ser Thr Lys Asn Lys Gln Lys Gly Lys Thr
    770                 775                 780

Gly Thr Glu Ile Lys Thr Lys Ala His Gln Arg His Leu Phe Ser Asp
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785                 790                 795                 800

Thr Glu Ser Glu Arg Gly Gly Asp Asp Thr Lys Ser Asn Leu Ser Trp
                805                 810                 815

Leu Gln Glu Gln His Ser Lys Thr Lys Pro Pro Ile Ala Thr Tyr Arg
            820                 825                 830

Arg Gln Lys Ala Gln Lys Gln Gln Glu Gln Thr Met Pro Tyr Lys Met
        835                 840                 845

Arg His Ile Thr Thr Asn Asn Ser Pro Glu Pro Lys Thr Gly Lys Lys
    850                 855                 860

Ser Tyr Asn Arg Ser Gly Gly Asn Lys His Asn Lys Leu Lys Arg Pro
865                 870                 875                 880

Cys Arg Thr Ala Ala Lys Ser Thr Asn Tyr Lys Asp Leu Ser Asn Ser
                885                 890                 895

Glu Ser Asp Ala Glu Val Pro Phe Ser Pro Pro Lys Arg Glu Glu Pro
            900                 905                 910

Val Arg Arg Arg Cys Leu Lys
        915


<210> SEQ ID NO 11
<211> LENGTH: 1530
<212> TYPE: PRT
<213> ORGANISM: Pan troglodytes
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1456)..(1459)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 11

Met Pro Ile Arg Pro Asp Leu Gln Gln Leu Glu Lys Cys Ile Asp Asp
1               5                   10                  15

Ala Leu Arg Lys Asn Asp Phe Lys Pro Leu Lys Thr Leu Leu Gln Ile
            20                  25                  30

Asp Ile Cys Glu Asp Val Lys Ile Lys Cys Ser Lys Gln Phe Phe His
        35                  40                  45

Lys Val Asp Asn Leu Ile Cys Arg Glu Leu Asn Lys Glu Asp Ile His
    50                  55                  60

Asn Val Ser Ala Ile Leu Val Ser Val Gly Arg Cys Gly Lys Asn Ile
65                  70                  75                  80

Ser Val Leu Gly Gln Ala Gly Leu Leu Thr Met Ile Lys Gln Gly Leu
                85                  90                  95

Ile Gln Lys Met Val Ala Trp Phe Glu Lys Ser Lys Asp Ile Ile Gln
            100                 105                 110

Ser Gln Gly Asn Ser Lys Asp Glu Ala Val Leu Asn Met Ile Glu Asp
        115                 120                 125

Leu Val Asp Leu Leu Leu Val Ile His Asp Val Ser Asp Glu Gly Lys
    130                 135                 140

Lys Gln Val Val Glu Ser Phe Val Pro Arg Ile Cys Ser Leu Val Ile
145                 150                 155                 160

Asp Ser Arg Val Asn Ile Cys Ile Gln Gln Glu Ile Ile Lys Arg Met
                165                 170                 175

Asn Ala Met Leu Asp Lys Met Pro Gln Asp Ala Arg Lys Ile Leu Ser
            180                 185                 190

Asn Gln Glu Met Leu Ile Leu Met Ser Ser Met Gly Glu Arg Ile Leu
        195                 200                 205

Asp Ala Gly Asp Tyr Asp Leu Gln Val Gly Ile Val Glu Ala Leu Cys
    210                 215                 220
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Arg Met Thr Thr Glu Lys Gln Arg Gln Glu Leu Ala His Gln Trp Phe
225                 230                 235                 240

Ser Met Asp Phe Ile Ala Lys Ala Phe Lys Arg Ile Lys Asp Ser Glu
                245                 250                 255

Phe Glu Thr Asp Cys Arg Ile Phe Leu Asn Leu Val Asn Gly Met Leu
            260                 265                 270

Gly Asp Lys Arg Arg Val Phe Thr Phe Pro Cys Leu Ser Ala Phe Leu
        275                 280                 285

Asp Lys Tyr Glu Leu Gln Ile Pro Ser Asp Glu Lys Leu Glu Glu Phe
    290                 295                 300

Trp Ile Asp Phe Asn Leu Gly Ser Gln Thr Leu Ser Phe Tyr Ile Ala
305                 310                 315                 320

Gly Asp Asn Asp Asp His Gln Trp Glu Ala Val Thr Val Pro Glu Glu
                325                 330                 335

Lys Val Gln Ile Tyr Ser Ile Glu Val Arg Glu Ser Lys Lys Leu Leu
            340                 345                 350

Thr Ile Ile Leu Lys Asn Thr Val Lys Ile Ser Lys Arg Glu Gly Lys
        355                 360                 365

Glu Leu Leu Leu Tyr Phe Asp Ala Ser Leu Glu Ile Thr Asn Val Thr
    370                 375                 380

Gln Lys Ile Phe Gly Ala Asn Lys His Arg Glu Ser Ile Arg Lys Gln
385                 390                 395                 400

Gly Ile Ser Val Ala Lys Thr Ser Leu His Ile Leu Phe Asp Ala Ser
                405                 410                 415

Gly Ser Gln Ile Leu Val Pro Glu Ser Gln Ile Ser Pro Val Gly Glu
            420                 425                 430

Glu Leu Val Ser Leu Lys Glu Lys Ser Lys Ser Pro Lys Glu Phe Ala
        435                 440                 445

Lys Pro Ser Lys Tyr Ile Lys Asn Ser Asp Lys Gly Asn Arg Asn Asn
    450                 455                 460

Ser Gln Leu Glu Lys Ile Thr Pro Ser Lys Arg Lys Met Ser Glu Ala
465                 470                 475                 480

Ser Met Ile Val Ser Gly Ala Asp Arg Tyr Thr Met Arg Ser Pro Val
                485                 490                 495

Leu Phe Ser Asn Thr Ser Ile Pro Pro Arg Arg Arg Arg Ile Lys Pro
            500                 505                 510

Pro Leu Gln Met Met Ser Ser Ala Glu Lys Pro Ser Val Ser Gln Thr
        515                 520                 525

Ser Glu Asn Arg Val Asp Asn Ala Ala Ser Leu Lys Ser Arg Ser Ser
    530                 535                 540

Glu Glu Arg His Arg Arg Asp Asn Thr Asp Lys His Ile Lys Thr Ala
545                 550                 555                 560

Lys Cys Val Glu Asn Thr Glu Asn Lys Asn Val Glu Phe Pro Asn Gln
                565                 570                 575

Asn Phe Ser Glu Leu Gln Asp Val Ile Pro Asp Ser Gln Pro Val Glu
            580                 585                 590

Lys Arg Asp His Ala Ile Leu Pro Gly Val Leu Asp Asn Ile Cys Gly
        595                 600                 605

Asn Lys Ile His Ser Lys Trp Ala Cys Trp Thr Pro Val Thr Asn Ile
    610                 615                 620

Glu Leu Cys Asn Asn Gln Arg Ala Ser Thr Ser Ser Gly Asp Thr Leu
625                 630                 635                 640

Asn Gln Asp Ile Val Ile Asn Lys Lys Leu Thr Lys Gln Lys Ser Ser
                645                 650                 655
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Ser Ser Ile Ser Asp His Asn Ser Glu Gly Thr Gly Lys Val Lys Tyr
            660                 665                 670

Lys Lys Glu Gln Thr Asp His Ile Lys Ile Asp Lys Ala Glu Val Glu
        675                 680                 685

Val Cys Lys Lys His Asn Gln Gln Gln Asn His Pro Lys Tyr Ser Gly
    690                 695                 700

Gln Lys Asn Thr Glu Asn Ala Lys Gln Ser Asp Trp Pro Val Glu Ser
705                 710                 715                 720

Glu Thr Thr Phe Lys Ser Val Leu Leu Asn Lys Thr Ile Glu Glu Ser
                725                 730                 735

Leu Ile Tyr Lys Lys Lys Tyr Ile Leu Ser Lys Asp Val Asn Thr Ala
            740                 745                 750

Thr Cys Asp Lys Asn Pro Ser Ala Ser Lys Asn Val Gln Ser His Arg
        755                 760                 765

Lys Ala Glu Lys Glu Leu Thr Ser Glu Leu Asp Ser Trp Asp Leu Lys
    770                 775                 780

Gln Lys Lys Met Arg Glu Lys Ser Lys Gly Lys Glu Phe Thr Asp Val
785                 790                 795                 800

Ala Glu Ser Leu Ile Ser Gln Ile Asn Lys Arg Tyr Lys Thr Lys Asp
                805                 810                 815

Asp Ile Lys Ser Thr Arg Lys Leu Lys Glu Ser Leu Ile Asn Ser Asp
            820                 825                 830

Phe Ser Asn Lys Pro Val Val Gln Leu Ser Lys Glu Lys Val Gln Lys
        835                 840                 845

Lys Ser Tyr Arg Lys Leu Lys Thr Thr Phe Val Asn Val Thr Ser Glu
    850                 855                 860

Cys Pro Val Asn Asp Val Tyr Asn Phe Asn Leu Asn Gly Ala Asp Asp
865                 870                 875                 880

Pro Ile Ile Lys Leu Gly Ile Gln Glu Phe Gln Ala Thr Ala Lys Glu
                885                 890                 895

Ala Cys Ala Asp Arg Ser Ile Arg Leu Val Gly Pro Arg Asn His Asp
            900                 905                 910

Glu Leu Lys Ser Ser Val Lys Thr Lys Asp Lys Lys Ile Ile Thr Asn
        915                 920                 925

His Gln Lys Lys Asn Leu Phe Ser Asp Thr Glu Thr Glu Tyr Arg Cys
    930                 935                 940

Asp Asp Ser Lys Thr Asp Ile Ser Trp Leu Arg Glu Pro Lys Ser Lys
945                 950                 955                 960

Pro Gln Leu Ile Asp Tyr Ser Arg Asn Lys Asn Val Arg Asn His Lys
                965                 970                 975

Ser Gly Lys Ser Arg Ser Ser Leu Glu Lys Gly Gln Pro Ser Ser Lys
            980                 985                 990

Met Thr Pro Ser Lys Asn Ile Met  Lys Lys Thr Asp Lys  Thr Ile Pro
        995                 1000                1005

Glu Gly  Arg Ile Arg Leu Pro  Arg Lys Ala Thr Lys  Thr Lys Lys
    1010                1015                1020

Asn Tyr  Lys Asp Leu Ser Asn  Ser Glu Ser Glu Cys  Glu Gln Glu
    1025                1030                1035

Phe Ser  His Ser Phe Lys Glu  Asn Ile Pro Val Lys  Glu Glu Asn
    1040                1045                1050

Ile His  Ser Arg Met Lys Thr  Val Lys Leu Pro Lys  Lys Gln Gln
    1055                1060                1065

Lys Val  Phe Cys Ala Glu Thr  Glu Lys Glu Leu Ser  Lys Gln Cys
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    1070                1075                1080

Lys Asn  Ser Ser Leu Leu Lys  Asp Ala Ile Arg Asp  Asn Cys Leu
    1085                1090                1095

Asp Leu  Ser Pro Arg Ser Leu  Ser Gly Ser Pro Ser  Ser Ile Glu
    1100                1105                1110

Val Thr  Arg Cys Ile Glu Lys  Ile Thr Glu Lys Asp  Phe Thr Gln
    1115                1120                1125

Asp Tyr  Asp Cys Ile Thr Lys  Ser Ile Ser Pro Tyr  Pro Lys Thr
    1130                1135                1140

Ser Ser  Leu Glu Ser Leu Asn  Ser Asn Ser Gly Val  Gly Gly Thr
    1145                1150                1155

Ile Lys  Ser Pro Lys Asn Asn  Glu Lys Asn Phe Leu  Cys Ala Ser
    1160                1165                1170

Glu Ser  Cys Ser Pro Ile Pro  Arg Pro Leu Phe Leu  Pro Arg His
    1175                1180                1185

Thr Pro  Thr Lys Ser Asn Thr  Ile Val Asn Arg Lys  Lys Lys Ser
    1190                1195                1200

Ser Leu  Val Leu Thr Gln Glu  Thr Gln Asn Cys Asn  Ser Tyr Ser
    1205                1210                1215

Asp Val  Ser Ser Tyr Ser Ser  Glu Glu Arg Phe Met  Glu Ile Glu
    1220                1225                1230

Ser Pro  His Ile Asn Glu Asn  Tyr Ile Gln Ser Lys  Arg Glu Glu
    1235                1240                1245

Ser His  Leu Ala Ser Ser Leu  Ser Lys Ser Ser Glu  Gly Arg Glu
    1250                1255                1260

Lys Thr  Trp Phe Asp Met Pro  Cys Asp Ala Thr His  Val Ser Gly
    1265                1270                1275

Pro Thr  Gln His Leu Ser Arg  Lys Arg Ile Tyr Ile  Glu Asp Asn
    1280                1285                1290

Leu Ser  Asn Ser Asn Glu Val  Glu Met Glu Glu Lys  Gly Glu Arg
    1295                1300                1305

Arg Ala  Asn Leu Leu Pro Lys  Lys Leu Cys Lys Ile  Glu Asp Ala
    1310                1315                1320

Asp His  His Ile His Lys Met  Ser Glu Ser Val Ser  Ser Leu Ser
    1325                1330                1335

Thr Asn  Asp Phe Ser Ile Pro  Trp Glu Thr Trp Arg  Asn Glu Phe
    1340                1345                1350

Ala Gly  Ile Glu Met Thr Tyr  Glu Thr Tyr Glu Arg  Leu Asn Ser
    1355                1360                1365

Glu Phe  Lys Arg Arg Asn Asn  Ile Arg His Lys Met  Leu Ser Tyr
    1370                1375                1380

Phe Thr  Thr Gln Ser Trp Lys  Thr Ala Gln Gln His  Leu Arg Thr
    1385                1390                1395

Ile Asn  His Gln Ser Gln Asp  Ser Arg Ile Lys Lys  Leu Asp Lys
    1400                1405                1410

Phe Gln  Phe Ile Ile Ile Glu  Glu Leu Glu Asn Phe  Glu Lys Asp
    1415                1420                1425

Ser Gln  Ser Leu Lys Asp Leu  Glu Lys Glu Phe Val  Asp Phe Trp
    1430                1435                1440

Glu Lys  Ile Phe Gln Met Phe  Ser Ala Tyr Gln Lys  Xaa Xaa Xaa
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Xaa Arg  Leu His Leu Leu Lys  Thr Ser Leu Ala Lys  Ser Val Phe
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Asp Met  Leu Glu Glu Glu Leu  Leu Asn Val Arg Arg  Glu Leu Met
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Ser Val  Phe Met Ser His Glu  Arg Asn Ala Asn Val
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

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<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 13

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<211> LENGTH: 4771
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 14

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atatgagctg caaataccat cagatgaaaa acttgaggaa ttttggattg attttaatct 1140

tgggagtcag actctctcat tctacattgc tggagataat gatgatcatc aatgggaagc 1200

agttactgtg ccagaggaaa aagtacaaat atacagcatt gaagtgagag aatcaaagaa 1260

gctactgaca ataattctga aaaatacagt aaaaattagc aaaagagaag ggaaagaatt 1320

gcttttgtat tttgatgcat cactagaaat cactaatgta actcaaaaaa tttttggtgc 1380

aaataaacat agggaatcta tcagaaaaca aggtatttca gttgccaaaa cgtcgctgca 1440

tatacttttt gatgcaagtg gatcacagat tctagtgcca gaaagtcaaa tctcaccagt 1500

cggagaagag ctcgttagtt taaaggaaaa atcaaagtcc ccaaaggaat ttgctaaacc 1560

ttcaaaatat atcaaaaaca gtgacaaagg gaatagaaat aatagtcagc ttgagaaaat 1620

tactcctagc aaaagaaaaa tgtctgaagc atcaatgatt gtttctggtg cagatagata 1680

cactatgaga agtccagtac ttttcagcaa cacatcaata ccaccacgaa gaagaagaat 1740

taaaccacca ctgcaaatga tgagttctgc agagaaacct agtgtttctc aaacatcaga 1800

aaatagagtg gataatgctg catcactgaa atctagatca tcagaagaaa gacatagaag 1860

agataataca gacaaacata tcaaaactgc taagtgtgta gaaaacacag aaaataagaa 1920

tgttgaattc ccaaaccaaa attttagtga actccaggat gttataccag attcacagcc 1980

agtggaaaaa agagatcatg ctatattacc tggtgtttta gacaacatct gtggaaataa 2040

aatacacagc aaatgggcat gttggacacc tgtaacaaac attgaactat gtaataacca 2100

aagagcaagt acttcatcag gagacacatt gaatcaagat attgttataa ataaaaaact 2160

tactaaacaa aaatcatcct cttcaatatc tgatcataat tctgaaggaa caggaaaagt 2220

gaaatataag aaagaacaaa ccgaccatat caaaatagat aaagcagaag tagaagtttg 2280

caagaaacac aatcagcaac aaaatcatcc taaatattca gggcagaaaa atactgaaaa 2340

tgccaagcag agtgattggc ctgttgaatc tgaaactact tttaaatcgg ttctcctaaa 2400

taagacaatt gaagaatcgc tgatatataa gaagaaatac atattgtcaa aagatgtgaa 2460

tactgctact tgcgataaaa atccatctgc tagcaaaaat gtgcaaagtc atagaaaagc 2520

agagaaagaa ttgacttctg agcttgattc ctgggatttg aaacaaaaaa aaatgagaga 2580

aaagtcaaaa gggaaagaat ttaccgatgt agcagaatcc ttgataagcc aaatcaataa 2640

aagatacaaa acaaaagatg acatcaagtc tacaagaaaa ttaaaggagt ctttgattaa 2700

cagtgatttt tcaaacaaac ctgttgtaca actcagtaag gaaaaagttc agaaaaaaag 2760

ctacagaaaa ctgaagacta cctttgttaa tgttacttct gaatgcccag tgaatgatgt 2820

ttacaatttt aatttgaatg gagctgatga ccctatcata aaacttggaa tccaagagtt 2880

tcaagctaca gctaaagaag cttgtgcgga taggtcaatt agattggtag gtccaaggaa 2940

tcatgatgaa cttaaatctt ctgtcaaaac aaaagataaa aaaattataa caaatcatca 3000

aaagaaaaat ctgtttagtg atactgaaac agagtacaga tgtgatgaca gcaagactga 3060

tattagctgg ctaagagaac caaaatcaaa accacagcta atagactata gcagaaataa 3120

aaatgtgagg aatcataaaa gtggaaaatc aagatcatcc ttggaaaagg gacagccaag 3180

ctctaaaatg acacccagta aaaatatcat gaaaaagacg gacaagacaa ttccggaagg 3240

aagaatcaga cttccacgaa aagcaaccaa aacaaaaaaa aattataaag atctctcaaa 3300

ttcagaatca gagtgtgaac aagaattttc acattcattt aaagagaaca taccagtaaa 3360

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ggaggagaat atccattcca gaatgaaaac ggtaaagcta ccaaagaaac aacagaaagt 3420

cttctgtgct gaaacagaaa aggaactatc aaaacaatgc aaaaactcat ctctactaaa 3480

agatgctata cgagataatt gccttgactt atctcccaga tctttatctg gcagtccatc 3540

atctatagaa gtaacgagat gtatagagaa aataacagaa aaggatttta ctcaggatta 3600

tgactgcata acaaaatcta tatcacctta tccaaaaact tcatcacttg aatccttaaa 3660

tagtaacagt ggagttggag gtacaataaa gtcacccaaa aacaatgaga aaaacttcct 3720

gtgtgcaagt gaaagttgtt caccaattcc acgaccactg tttttgccca gacatactcc 3780

aactaagagt aatactattg taaatagaaa aaaaaaaagt tctctggtac ttacacaaga 3840

aacacaaaac tgtaacagct attcagatgt aagcagttat agttcagaag aacggtttat 3900

ggaaattgaa tctccacata tcaatgaaaa ttatatacaa agcaaaagag aggaaagtca 3960

tttagcatct tcattatcca agtctagtga aggaagagag aaaacgtggt ttgatatgcc 4020

ctgtgatgct actcatgtat caggccccac ccaacatctt agtcgcaaaa gaatatatat 4080

agaagataat ctaagtaatt ccaatgaagt agaaatggaa gagaaaggag aaaggagagc 4140

aaacttgctt cccaaaaaac tgtgtaaaat tgaagatgca gatcatcata tccacaaaat 4200

gtctgaaagt gtatcttcat tatcaacaaa tgacttttct attccttggg agacctggcg 4260

aaatgaattt gcaggtatag agatgactta tgagacttac gagaggctca attcagaatt 4320

taagagaagg aataatatcc gacataaaat gttgagttat tttactacgc agtcttggaa 4380

aacagctcag caacatctga gaacaataaa tcatcaaagt caggactcta ggattaaaaa 4440

acttgataaa ttccaattca ttatcataga ggagctggag aattttgaaa aagattcaca 4500

gtctttaaaa gatttggaaa aggaatttgt ggacttttgg gaaaagatat ttcagatgtt 4560

cagtgcatat caaaaaattt tacttcttag gcttcatctt ttgaaaactt cattggctaa 4620

aagtgtcttc tgtaatactg ataatgaaga aactgttttt acatccgaga tgtgtttgat 4680

gaaagaagat atgaaagtgc tgcaagacag gcttcttaag gacatgctag aagaggagct 4740

tcttaatgta cgcagagaac tgatgtcagt attcatgtct catgaaagaa atgctaatgt 4800

gtgaaatcta gtttttatca ccatacttta tctaattatt attctctgtg tataactgag 4860

gaaataagaa tagtcctaca aagagaaaaa tatacatgtc accgaagcaa gtgtaccctt 4920

tataggaacc ctcaaattaa aaaaaaatgt cttttaatgg atgagaggga accactataa 4980

catgagtcca agcccagaag acttctgtct atacaatatt tttttttact tttggagata 5040

gaagctttaa gaaacttttt tgagttaatt atactcataa aatgagtttc tttaataaat 5100

taaattttat tgtgtaaaat gtattattac ataaaatgtg tttttgaatc aatgcagttt 5160

ggggatgaat ataattaaaa tatgtttaat aacttagaat tcaactaata aaaatttagc 5220

cacacttaca agggggagga agtccctagt ttaaaatgta taactgagtg gtagatcagt 5280

actttcagca cactgttgga aacatttatt cagatatggc tctaatgtat taggaagcac 5340

taaatggcct aaaaaagcta ctacattgcc taaatatgtt aattcaatat agaagtccta 5400

tttcataagc aggctgtttg acaaatactt ttaatctagt agtcattgta atatcttgct 5460

agattaattt ataaaaatga gtatacattt gatttgcttt taatgaagtt gaaataaatg 5520

cttatgtcac ttgaataaat ataaatcatt atattccta 5559

<210> SEQ ID NO 18
<211> LENGTH: 1225
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 18

```
Met Ser Ser Pro Leu Gln Arg Ala Val Gly Asp Thr Lys Arg Ala Leu
1               5                  10                  15

Ser Ala Ser Ser Ser Ser Ser Ala Ser Leu Pro Phe Asp Asp Arg Asp
            20                  25                  30

Ser Asn His Thr Ser Glu Gly Asn Gly Asp Ser Leu Leu Ala Asp Glu
        35                  40                  45

Asp Thr Asp Phe Glu Asp Ser Leu Asn Arg Asn Val Lys Lys Arg Ala
    50                  55                  60

Ala Lys Arg Pro Pro Lys Thr Thr Pro Val Ala Lys His Pro Lys Lys
65                  70                  75                  80

Gly Ser Arg Val Val His Arg His Ser Arg Lys Gln Ser Glu Pro Pro
                85                  90                  95

Ala Asn Asp Leu Phe Asn Ala Val Lys Ala Ala Lys Ser Asp Met Gln
            100                 105                 110

Ser Leu Val Asp Glu Trp Leu Asp Ser Tyr Lys Gln Asp Gln Asp Ala
        115                 120                 125

Gly Phe Leu Glu Leu Val Asn Phe Phe Ile Gln Ser Cys Gly Cys Lys
    130                 135                 140

Gly Ile Val Thr Pro Glu Met Phe Lys Lys Met Ser Asn Ser Glu Ile
145                 150                 155                 160

Ile Gln His Leu Thr Glu Gln Phe Asn Glu Asp Ser Gly Asp Tyr Pro
                165                 170                 175

Leu Ile Ala Pro Gly Pro Ser Trp Lys Lys Phe Gln Gly Ser Phe Cys
            180                 185                 190

Glu Phe Val Arg Thr Leu Val Cys Gln Cys Gln Tyr Ser Leu Leu Tyr
        195                 200                 205

Asp Gly Phe Pro Met Asp Asp Leu Ile Ser Leu Leu Thr Gly Leu Ser
    210                 215                 220

Asp Ser Gln Val Arg Ala Phe Arg His Thr Ser Thr Leu Ala Ala Met
225                 230                 235                 240

Lys Leu Met Thr Ser Leu Val Lys Val Ala Leu Gln Leu Ser Val His
                245                 250                 255

Gln Asp Asn Asn Gln Arg Gln Tyr Glu Ala Glu Arg Asn Lys Gly Pro
            260                 265                 270

Gly Gln Arg Ala Pro Glu Arg Leu Glu Ser Leu Leu Glu Lys Arg Lys
        275                 280                 285

Glu Leu Gln Glu His Gln Glu Glu Ile Glu Gly Met Met Asn Ala Leu
    290                 295                 300

Phe Arg Gly Val Phe Val His Arg Tyr Arg Asp Val Leu Pro Glu Ile
305                 310                 315                 320

Arg Ala Ile Cys Ile Glu Glu Ile Gly Cys Trp Met Gln Ser Tyr Ser
                325                 330                 335

Thr Ser Phe Leu Thr Asp Ser Tyr Leu Lys Tyr Ile Gly Trp Thr Leu
            340                 345                 350

His Asp Lys His Arg Glu Val Arg Val Lys Cys Val Lys Ala Leu Lys
        355                 360                 365

Gly Leu Tyr Gly Asn Arg Asp Leu Thr Ala Arg Leu Glu Leu Phe Thr
    370                 375                 380

Ser Arg Phe Lys Asp Arg Met Val Ser Met Ile Met Asp Arg Glu Tyr
385                 390                 395                 400

Ser Val Ala Val Glu Ala Val Arg Leu Leu Ile Leu Ile Leu Lys Asn
                405                 410                 415
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Met Glu Gly Leu Leu Thr Asp Ala Asp Cys Glu Ser Val Tyr Pro Val
            420                 425                 430

Val Tyr Pro Ser Asn Arg Gly Leu Ala Ser Ala Ala Gly Glu Phe Leu
        435                 440                 445

Tyr Trp Lys Leu Phe Tyr Pro Glu Cys Glu Ile Arg Thr Met Gly Gly
    450                 455                 460

Arg Glu Gln Arg Gln Ser Pro Gly Ala Gln Arg Thr Phe Phe Gln Leu
465                 470                 475                 480

Leu Leu Ser Phe Phe Val Glu Ser Glu Leu His Asp His Ala Ala Tyr
                485                 490                 495

Leu Val Asp Ser Leu Trp Asp Cys Ala Gly Ala Arg Leu Lys Asp Trp
            500                 505                 510

Glu Gly Leu Thr Ser Leu Leu Leu Glu Lys Asp Gln Asn Leu Gly Asp
        515                 520                 525

Val Gln Glu Ser Thr Leu Ile Glu Ile Leu Val Ser Ser Ala Arg Gln
    530                 535                 540

Ala Ser Glu Gly His Pro Pro Val Gly Arg Val Thr Gly Arg Lys Gly
545                 550                 555                 560

Leu Thr Ser Lys Glu Arg Lys Thr Gln Ala Asp Asp Arg Val Lys Leu
                565                 570                 575

Thr Glu His Leu Ile Pro Leu Leu Pro Gln Leu Leu Ala Lys Phe Ser
            580                 585                 590

Ala Asp Ala Glu Lys Val Thr Pro Leu Leu Gln Leu Leu Ser Cys Phe
        595                 600                 605

Asp Leu His Ile Tyr Cys Thr Gly Arg Leu Glu Lys His Leu Glu Leu
    610                 615                 620

Phe Leu Gln Gln Leu Gln Glu Val Val Val Lys His Ala Glu Pro Ala
625                 630                 635                 640

Val Leu Glu Ala Gly Ala His Ala Leu Tyr Leu Leu Cys Asn Pro Glu
                645                 650                 655

Phe Thr Phe Phe Ser Arg Ala Asp Phe Ala Arg Ser Gln Leu Val Asp
            660                 665                 670

Leu Leu Thr Asp Arg Phe Gln Gln Glu Leu Glu Glu Leu Leu Gln Ser
        675                 680                 685

Ser Phe Leu Asp Glu Asp Glu Val Tyr Asn Leu Ala Ala Thr Leu Lys
    690                 695                 700

Arg Leu Ser Ala Phe Tyr Asn Thr His Asp Leu Thr Arg Trp Glu Leu
705                 710                 715                 720

Tyr Glu Pro Cys Cys Gln Leu Leu Gln Lys Ala Val Asp Thr Gly Glu
                725                 730                 735

Val Pro His Gln Val Ile Leu Pro Ala Leu Thr Leu Val Tyr Phe Ser
            740                 745                 750

Ile Leu Trp Thr Leu Thr His Ile Ser Lys Ser Asp Ala Ser Gln Lys
        755                 760                 765

Gln Leu Ser Ser Leu Arg Asp Arg Met Val Ala Phe Cys Glu Leu Cys
    770                 775                 780

Gln Ser Cys Leu Ser Asp Val Asp Thr Glu Ile Gln Glu Gln Ala Phe
785                 790                 795                 800

Val Leu Leu Ser Asp Leu Leu Leu Ile Phe Ser Pro Gln Met Ile Val
                805                 810                 815

Gly Gly Arg Asp Phe Leu Arg Pro Leu Val Phe Phe Pro Glu Ala Thr
            820                 825                 830

Leu Gln Ser Glu Leu Ala Ser Phe Leu Met Asp His Val Phe Ile Gln
        835                 840                 845
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Pro Gly Asp Leu Gly Ser Gly Asp Ser Gln Glu Asp His Leu Gln Ile
    850                 855                 860

Glu Arg Leu His Gln Arg Arg Arg Leu Leu Ala Gly Phe Cys Lys Leu
865                 870                 875                 880

Leu Leu Tyr Gly Val Leu Glu Met Asp Ala Ala Ser Asp Val Phe Lys
                885                 890                 895

His Tyr Asn Lys Phe Tyr Asn Asp Tyr Gly Asp Ile Ile Lys Glu Thr
            900                 905                 910

Leu Thr Arg Ala Arg Gln Ile Asp Arg Ser His Cys Ser Arg Ile Leu
        915                 920                 925

Leu Leu Ser Leu Lys Gln Leu Tyr Thr Glu Leu Leu Gln Glu His Gly
    930                 935                 940

Pro Gln Gly Leu Asn Glu Leu Pro Ala Phe Ile Glu Met Arg Asp Leu
945                 950                 955                 960

Ala Arg Arg Phe Ala Leu Ser Phe Gly Pro Gln Gln Leu Gln Asn Arg
                965                 970                 975

Asp Leu Val Val Met Leu His Lys Glu Gly Ile Gln Phe Ser Leu Ser
            980                 985                 990

Glu Leu Pro Pro Ala Gly Ser Ser  Asn Gln Pro Pro Asn  Leu Ala Phe
        995                 1000                1005

Leu Glu  Leu Leu Ser Glu Phe  Ser Pro Arg Leu Phe  His Gln Asp
    1010                1015                1020

Lys Gln  Leu Leu Leu Ser Tyr  Leu Glu Lys Cys Leu  Gln His Val
    1025                1030                1035

Ser Gln  Ala Pro Gly His Pro  Trp Gly Pro Val Thr  Thr Tyr Cys
    1040                1045                1050

His Ser  Leu Ser Pro Val Glu  Asn Thr Ala Glu Thr  Ser Pro Gln
    1055                1060                1065

Val Leu  Pro Ser Ser Lys Arg  Lys Arg Val Glu Gly  Pro Ala Lys
    1070                1075                1080

Pro Asn  Arg Glu Asp Val Ser  Ser Ser Gln Glu Glu  Ser Leu Gln
    1085                1090                1095

Leu Asn  Ser Ile Pro Pro Thr  Pro Thr Leu Thr Ser  Thr Ala Val
    1100                1105                1110

Lys Ser  Arg Gln Pro Leu Trp  Gly Leu Lys Glu Met  Glu Glu Glu
    1115                1120                1125

Asp Gly  Ser Glu Leu Asp Phe  Ala Gln Gly Gln Pro  Val Ala Gly
    1130                1135                1140

Thr Glu  Arg Ser Arg Phe Leu  Gly Pro Gln Tyr Phe  Gln Thr Pro
    1145                1150                1155

His Asn  Pro Ser Gly Pro Gly  Leu Gly Asn Gln Leu  Met Arg Leu
    1160                1165                1170

Ser Leu  Met Glu Glu Asp Glu  Glu Glu Glu Leu Glu  Ile Gln Asp
    1175                1180                1185

Glu Ser  Asn Glu Glu Arg Gln  Asp Thr Asp Met Gln  Ala Ser Ser
    1190                1195                1200

Tyr Ser  Ser Thr Ser Glu Arg  Gly Leu Asp Leu Leu  Asp Ser Thr
    1205                1210                1215

Glu Leu  Asp Ile Glu Asp Phe
    1220                1225


<210> SEQ ID NO 19
<211> LENGTH: 1240
<212> TYPE: PRT
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<213> ORGANISM: Mus musculus

<400> SEQUENCE: 19

```
Met Pro Thr Leu Trp Ser Pro Ser Thr Gln His His Gly Ser Ser Ser
1               5                   10                  15

Gly Ser Glu Ser Ser Pro Leu Gln Lys Ser Val Arg Arg Ala Gln Met
            20                  25                  30

Ala Leu Ser Pro Cys Ser Ser Ser Ile Leu Pro Cys Asp Asp Arg Asp
        35                  40                  45

Ser Gln Gly Thr Ala Glu Trp Asp Ser Pro Ser Thr Asn Glu Asp Ser
    50                  55                  60

Asp Phe Glu Asp Ser Leu Arg Arg Asn Val Lys Lys Arg Ala Ala Lys
65                  70                  75                  80

Gln Pro Pro Lys Ala Val Pro Ala Ala Lys His Arg Lys Lys Gln Ser
                85                  90                  95

Arg Ile Val Ser Ser Gly Asn Gly Lys Asn Glu Ser Val Pro Ser Thr
            100                 105                 110

Asn Tyr Leu Phe Asp Ala Val Lys Ala Ala Arg Ser Cys Met Gln Ser
        115                 120                 125

Leu Val Asp Glu Trp Leu Asp Asn Tyr Lys Gln Asp Glu Asn Ala Gly
    130                 135                 140

Phe Leu Glu Leu Ile Asn Phe Phe Ile Arg Ala Cys Gly Cys Lys Ser
145                 150                 155                 160

Thr Val Thr Pro Glu Met Phe Lys Thr Met Ser Asn Ser Glu Ile Ile
                165                 170                 175

Gln His Leu Thr Glu Glu Phe Asn Glu Asp Ser Gly Asp Tyr Pro Leu
            180                 185                 190

Thr Ala Pro Gly Pro Ser Trp Lys Lys Phe Gln Gly Ser Phe Cys Glu
        195                 200                 205

Phe Val Lys Thr Leu Val Tyr Gln Cys Gln Tyr Ser Leu Leu Tyr Asp
    210                 215                 220

Gly Phe Pro Met Asp Asp Leu Ile Ser Leu Leu Ile Gly Leu Ser Asp
225                 230                 235                 240

Ser Gln Val Arg Ala Phe Arg His Thr Ser Thr Leu Ala Ala Met Lys
                245                 250                 255

Leu Met Thr Ser Leu Val Lys Val Ala Leu Gln Leu Ser Leu His Lys
            260                 265                 270

Asp Asn Asn Gln Arg Gln Tyr Glu Ala Glu Arg Asn Lys Gly Pro Glu
        275                 280                 285

Gln Arg Ala Pro Glu Arg Leu Glu Ser Leu Leu Glu Lys Arg Lys Glu
    290                 295                 300

Phe Gln Glu Asn Gln Glu Asp Ile Glu Gly Met Met Asn Ala Ile Phe
305                 310                 315                 320

Arg Gly Val Phe Val His Arg Tyr Arg Asp Ile Leu Pro Glu Ile Arg
                325                 330                 335

Ala Ile Cys Ile Glu Glu Ile Gly Tyr Trp Met Gln Ser Tyr Ser Thr
            340                 345                 350

Ser Phe Leu Asn Asp Ser Tyr Leu Lys Tyr Ile Gly Trp Thr Leu His
        355                 360                 365

Asp Lys His Lys Glu Val Arg Leu Lys Cys Val Lys Ala Leu Ala Gly
    370                 375                 380

Leu Tyr Ser Asn Gln Glu Leu Ser Leu Arg Met Glu Leu Phe Thr Asn
385                 390                 395                 400

Arg Phe Lys Asp Arg Met Val Ser Met Val Met Asp Arg Glu Cys Glu
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               405                 410                 415

Val Ala Val Glu Ala Ile Arg Leu Leu Thr Leu Ile Leu Lys Asn Met
           420                 425                 430

Glu Gly Val Leu Thr Ser Ala Asp Cys Glu Lys Ile Tyr Ser Ile Val
       435                 440                 445

Tyr Ile Ser Asn Arg Ala Met Ala Ser Ser Ala Gly Glu Phe Val Tyr
   450                 455                 460

Trp Lys Ile Phe His Pro Glu Cys Gly Ala Lys Ala Val Ser Asp Arg
465                 470                 475                 480

Glu Arg Arg Arg Ser Pro Gln Ala Gln Lys Thr Phe Ile Tyr Leu Leu
               485                 490                 495

Leu Ala Phe Phe Met Glu Ser Glu His His Asn His Ala Ala Tyr Leu
           500                 505                 510

Val Asp Ser Leu Trp Asp Cys Ala Gly Ser Tyr Leu Lys Asp Trp Glu
       515                 520                 525

Ser Leu Thr Asn Leu Leu Leu Gln Lys Asp Gln Asn Leu Gly Asp Met
   530                 535                 540

Gln Glu Arg Met Leu Ile Glu Ile Leu Val Ser Ser Ala Arg Gln Ala
545                 550                 555                 560

Ala Glu Gly His Pro Pro Val Gly Arg Ile Thr Gly Lys Lys Ser Leu
               565                 570                 575

Thr Ala Lys Glu Arg Lys Leu Gln Ala Tyr Asp Lys Met Lys Leu Ala
           580                 585                 590

Glu His Leu Ile Pro Leu Leu Pro Gln Leu Leu Ala Lys Phe Ser Ala
       595                 600                 605

Asp Ala Glu Asn Val Ala Pro Leu Leu Gln Leu Leu Ser Tyr Phe Asp
   610                 615                 620

Leu Ser Ile Tyr Cys Thr Gln Arg Leu Glu Lys His Leu Glu Leu Leu
625                 630                 635                 640

Leu Gln Gln Leu Gln Glu Val Val Val Lys His Val Glu Pro Glu Val
               645                 650                 655

Leu Glu Ala Ala Ala His Ala Leu Tyr Leu Leu Cys Lys Pro Glu Phe
           660                 665                 670

Thr Phe Phe Ser Arg Val Asp Phe Ala Arg Ser Gln Leu Val Asp Phe
       675                 680                 685

Leu Thr Asp Arg Phe Gln Gln Glu Leu Asp Asp Leu Met Gln Ser Ser
   690                 695                 700

Phe Leu Asp Glu Asp Glu Val Tyr Ser Leu Thr Ala Thr Leu Lys Arg
705                 710                 715                 720

Leu Ser Ala Phe Tyr Asn Ala His Asp Leu Thr Arg Trp Glu Ile Ser
               725                 730                 735

Glu Pro Cys Ser Arg Leu Leu Arg Lys Ala Val Asp Thr Gly Glu Val
           740                 745                 750

Pro His Gln Val Ile Leu Pro Ala Leu Thr Leu Val Tyr Phe Ser Ile
       755                 760                 765

Leu Trp Thr Val Thr His Ile Ser Glu Ser Thr Ser His Lys Gln Leu
   770                 775                 780

Met Ser Leu Lys Lys Arg Met Val Ala Phe Cys Glu Leu Cys Gln Ser
785                 790                 795                 800

Cys Leu Ser Asp Val Asp Pro Glu Ile Gln Glu Gln Ala Phe Val Leu
               805                 810                 815

Leu Ser Asp Leu Leu Leu Ile Phe Ser Pro Gln Met Ile Val Gly Gly
           820                 825                 830
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Arg Asp Phe Leu Arg Pro Leu Val Phe Phe Pro Glu Ala Thr Leu Gln
        835                 840                 845

Ser Glu Leu Ala Ser Phe Leu Met Asp His Val Phe Leu Gln Pro Gly
    850                 855                 860

Glu Leu Gly Asn Gly Gln Ser Gln Glu Asp His Val Gln Ile Glu Leu
865                 870                 875                 880

Leu His Gln Arg Arg Arg Leu Leu Ala Gly Phe Cys Lys Leu Leu Leu
                885                 890                 895

Tyr Gly Val Leu Glu Leu Asp Ala Ala Ser Asp Val Phe Lys His Tyr
            900                 905                 910

Asn Lys Phe Tyr Glu Asp Tyr Gly Asp Ile Ile Lys Glu Thr Leu Thr
        915                 920                 925

Arg Ala Arg Gln Ile Asp Arg Cys Gln Cys Ser Arg Ile Leu Leu Leu
    930                 935                 940

Ser Leu Lys Gln Leu Tyr Thr Glu Leu Ile Gln Glu Gln Gly Pro Gln
945                 950                 955                 960

Gly Leu Thr Glu Leu Pro Ala Phe Ile Glu Met Arg Asp Leu Ala Arg
                965                 970                 975

Arg Phe Ala Leu Ser Phe Gly Pro Gln Gln Leu His Asn Arg Asp Leu
            980                 985                 990

Val Val Met Leu His Lys Glu Gly  Ile Lys Phe Ser Leu  Ser Glu Leu
        995                 1000                1005

Pro Pro  Ala Gly Ser Ser His  Glu Pro Pro Asn Leu  Ala Phe Leu
    1010                1015                1020

Glu Leu  Leu Ser Glu Phe Ser  Pro Arg Leu Phe His  Gln Asp Lys
    1025                1030                1035

Arg Leu  Leu Leu Ser Tyr Leu  Glu Lys Cys Leu Gln  Arg Val Ser
    1040                1045                1050

Lys Ala  Pro Asn His Pro Trp  Gly Pro Val Thr Thr  Tyr Cys His
    1055                1060                1065

Ser Leu  His Pro Leu Glu Ile  Thr Ala Glu Ala Ser  Pro Arg Gly
    1070                1075                1080

Pro Pro  His Ser Lys Lys Arg  Cys Val Glu Gly Pro  Cys Arg Pro
    1085                1090                1095

Gln Glu  Glu Glu Ser Ser Ser  Gln Glu Glu Ser Leu  Gln Leu Asn
    1100                1105                1110

Ser Gly  Pro Thr Thr Pro Thr  Leu Thr Ser Thr Ala  Val Lys Arg
    1115                1120                1125

Lys Gln  Ser Leu Arg Thr Val  Gly Lys Lys Gln Lys  Gly Arg Pro
    1130                1135                1140

Gly Pro  Gly Pro Gly Pro Gly  Pro Glu Leu Ile Cys  Ser Gln Gln
    1145                1150                1155

Leu Leu  Gly Thr Gln Arg Leu  Lys Met Ser Ser Ala  Pro Cys Phe
    1160                1165                1170

Gln Ile  Arg Cys Asp Pro Ser  Gly Ser Gly Leu Gly  Lys Gln Leu
    1175                1180                1185

Thr Arg  Leu Ser Leu Met Glu  Glu Asp Glu Glu Glu  Glu Leu Arg
    1190                1195                1200

Leu Leu  Asp Glu Glu Trp Gln  Arg Gly Asp Lys Met  Leu His Ser
    1205                1210                1215

Pro Ser  Ser Pro Ser Glu His  Gly Leu Asp Leu Leu  Asp Thr Thr
    1220                1225                1230

Glu Leu  Asn Met Glu Asp Phe
    1235                1240
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<210> SEQ ID NO 20
<211> LENGTH: 1256
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 20

Met Pro Thr Leu Trp Ser Pro Ser Thr Gln His His Gly Ser Ser Ser
1 5 10 15

Gly Ser Met Ser Ser Pro Leu Arg Lys Ser Val Arg Cys Ala Gln Met
20 25 30

Ala Leu Ser Pro Cys Ser Ser Asn Ile Gln Pro Cys Asp Asp Arg Asp
35 40 45

Ser Gln Gly Thr Ala Glu Trp Asp Ser Ser Ser Thr Ser Glu Asp Ser
50 55 60

Asp Phe Glu Asp Ser Leu Arg Arg Asn Val Arg Lys Arg Ala Ala Lys
65 70 75 80

Arg Pro Pro Lys Ala Ile Pro Val Ala Lys His Pro Lys Lys Gln Ser
85 90 95

His Ile Val Pro Gly Gly Asn Asp Lys Asn Lys Ser Val Pro Pro Thr
100 105 110

Ser Asp Leu Phe Asp Ala Val Lys Ala Ala Arg Ser Cys Ala Gln Ser
115 120 125

Leu Val Asp Glu Trp Leu Glu Asn Tyr Lys Gln Asp Glu Asn Ala Gly
130 135 140

Phe Leu Glu Leu Val Asn Phe Phe Ile Arg Ala Cys Gly Cys Lys Ser
145 150 155 160

Thr Val Thr Pro Glu Met Phe Lys Thr Met Ser Asn Ser Glu Ile Ile
165 170 175

Gln His Leu Thr Glu Glu Phe Asn Glu Asp Ser Gly Asp Tyr Pro Leu
180 185 190

Thr Ala Pro Gly Pro Ser Trp Lys Lys Phe Gln Gly Ser Phe Cys Glu
195 200 205

Phe Val Lys Thr Leu Val Cys Gln Cys Gln Tyr Ser Leu Leu Phe Asp
210 215 220

Gly Phe Pro Met Asp Asp Leu Ile Ser Leu Leu Ile Gly Leu Ser Asp
225 230 235 240

Ser Gln Val Arg Ala Phe Arg His Thr Ser Thr Leu Ala Ala Met Lys
245 250 255

Leu Met Thr Ser Leu Val Lys Val Ala Leu Gln Leu Ser Leu His Lys
260 265 270

Asp Asn Asn Gln Arg Gln Tyr Glu Ala Glu Arg Asn Lys Gly Pro Glu
275 280 285

Gln Arg Ala Pro Glu Arg Leu Glu Ser Leu Leu Glu Lys Arg Lys Glu
290 295 300

Phe Gln Glu Asn Gln Glu Glu Ile Glu Gly Met Met Asn Ala Ile Phe
305 310 315 320

Arg Gly Val Phe Val His Arg Tyr Arg Asp Ile Leu Pro Glu Ile Arg
325 330 335

Ala Val Cys Ile Glu Glu Ile Gly Cys Trp Met Gln Ser Tyr Ser Thr
340 345 350

Ser Phe Leu Asn Asp Ser Tyr Leu Lys Tyr Ile Gly Trp Thr Leu His
355 360 365

Asp Lys His Lys Glu Val Arg Leu Lys Cys Val Lys Ala Leu Ala Gly
370 375 380

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Leu Tyr Ser Asn Gln Glu Leu Ser Ser Arg Met Glu Leu Phe Thr Asn
385                 390                 395                 400

Arg Phe Lys Asp Arg Met Val Ser Met Val Met Asp Arg Glu Ser Glu
                405                 410                 415

Val Ala Val Glu Ala Ile Arg Leu Leu Thr Leu Ile Leu Lys Asn Met
            420                 425                 430

Glu Gly Val Leu Thr Ser Ala Asp Cys Glu Lys Ile Tyr Ser Ile Val
        435                 440                 445

Tyr Ile Ser Asn Arg Ala Met Ala Ser Ser Ala Gly Glu Phe Val Tyr
    450                 455                 460

Trp Lys Ile Phe His Pro Glu Cys Gly Ala Lys Ala Val Ser Gly Arg
465                 470                 475                 480

Glu Arg Arg Arg Ser Pro Gln Ala Gln Arg Thr Phe Ile Tyr Leu Leu
                485                 490                 495

Leu Ala Phe Phe Met Glu Ser Glu His His Asp His Ala Ala Tyr Leu
            500                 505                 510

Val Asp Ser Leu Trp Asp Cys Ala Gly Ser Tyr Leu Lys Asp Trp Glu
        515                 520                 525

Ser Leu Thr Ser Leu Leu Leu Gln Lys Asp Gln Asn Leu Gly Asp Met
    530                 535                 540

Gln Glu Arg Met Leu Ile Glu Ile Leu Val Ser Ser Ala Arg Gln Ala
545                 550                 555                 560

Ala Glu Gly His Pro Pro Val Gly Arg Ile Thr Gly Lys Lys Ser Leu
                565                 570                 575

Thr Ala Lys Glu Arg Lys Leu Gln Ala Tyr Asp Lys Val Lys Leu Ala
            580                 585                 590

Glu His Leu Ile Pro Leu Leu Pro Gln Leu Leu Ala Lys Phe Ser Ala
        595                 600                 605

Asp Ala Glu Asn Val Ala Pro Leu Leu Arg Leu Leu Ser Tyr Phe Asp
    610                 615                 620

Leu Asn Ile Tyr Cys Thr Gln Arg Leu Glu Lys His Leu Glu Leu Leu
625                 630                 635                 640

Leu Gln Gln Leu Gln Glu Val Val Val Lys His Val Glu Pro Glu Val
                645                 650                 655

Leu Glu Ala Ala Ala His Ala Leu Tyr Leu Leu Cys Lys Pro Glu Phe
            660                 665                 670

Thr Phe Phe Ser Arg Val Asp Phe Ala Arg Ser Gln Leu Val Asp Leu
        675                 680                 685

Leu Thr Asp Arg Phe Gln Gln Glu Leu Asp Asp Leu Met Gln Ser Ser
    690                 695                 700

Phe Leu Asp Glu Asp Glu Val Tyr Ser Leu Thr Ala Thr Leu Lys Arg
705                 710                 715                 720

Leu Ser Ala Phe Tyr Asn Ala His Asp Leu Thr Arg Trp Glu Ile Ser
                725                 730                 735

Glu Pro Cys Ser Arg Leu Leu Arg Lys Ala Val Asp Thr Gly Glu Val
            740                 745                 750

Pro His Gln Val Ile Leu Pro Ala Leu Thr Leu Val Tyr Phe Ser Ile
        755                 760                 765

Leu Trp Thr Val Thr His Ile Ser Glu Ser Thr Ser Gln Lys Gln Leu
    770                 775                 780

Met Ser Leu Lys Lys Arg Met Val Ala Phe Cys Glu Leu Cys Gln Ser
785                 790                 795                 800

Cys Leu Ser Asp Val Asp Pro Glu Ile Gln Glu Gln Ala Phe Val Leu
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               805                 810                 815

Leu Ser Asp Leu Leu Leu Ile Phe Ser Pro Gln Met Val Val Gly Gly
           820                 825                 830

Arg Asp Phe Leu Arg Pro Leu Val Phe Phe Pro Glu Ala Thr Leu Gln
       835                 840                 845

Ser Glu Leu Ala Ser Phe Leu Met Asp His Val Phe Leu Gln Pro Gly
   850                 855                 860

Glu Leu Gly Asn Gly Gln Ser Gln Glu Asp His Val Gln Ile Glu Leu
865                 870                 875                 880

Leu His Gln Arg Arg Arg Leu Leu Ala Gly Phe Cys Lys Leu Leu Leu
               885                 890                 895

Tyr Gly Val Leu Glu Leu Asp Ala Ala Ser Asp Val Phe Lys His Tyr
           900                 905                 910

Asn Lys Phe Tyr Glu Asp Tyr Gly Asp Ile Ile Lys Glu Thr Leu Thr
       915                 920                 925

Arg Ala Arg Gln Ile Asp Arg Cys Gln Cys Ser Arg Ile Leu Leu Leu
   930                 935                 940

Ser Leu Lys Gln Leu Tyr Thr Glu Leu Ile Gln Glu Gln Gly Pro Gln
945                 950                 955                 960

Asp Leu Thr Glu Leu Pro Ala Phe Ile Glu Met Arg Asp Leu Ala Arg
               965                 970                 975

Arg Phe Ala Leu Ser Phe Gly Pro Gln Gln Leu His Asn Arg Asp Leu
           980                 985                 990

Val Val Met Leu His Lys Glu Gly  Ile Lys Phe Ser Leu  Ser Glu Leu
       995                 1000                1005

Pro Pro  Ala Gly Ser Ser Arg  Glu Pro Pro Asn Ile  Ala Phe Leu
   1010                1015                1020

Glu Leu  Leu Ser Glu Phe Ser  Pro Arg Leu Phe His  Gln Asp Lys
   1025                1030                1035

Gln Leu  Leu Leu Ser Tyr Leu  Glu Lys Cys Leu Gln  Arg Val Ser
   1040                1045                1050

Met Ala  Pro Ser His Pro Trp  Gly Pro Val Thr Thr  Tyr Cys His
   1055                1060                1065

Ser Leu  His Leu Val Glu Asn  Thr Ala Glu Ala Ser  Ser Gln Gly
   1070                1075                1080

Pro Pro  His Ser Lys Lys Arg  Cys Ile Glu Val Pro  Arg Arg Leu
   1085                1090                1095

Gln Glu  Glu Glu Ser Ser Ser  Gln Gly Glu Ser Leu  Gln Leu Asn
   1100                1105                1110

Ser Gly  Pro Thr Thr Pro Thr  Leu Thr Ser Thr Ala  Val Lys Arg
   1115                1120                1125

Arg Gln  Ser Pro Arg Thr Val  Gly Lys Arg Gln Lys  Gly Gly Pro
   1130                1135                1140

Gly Pro  Gly Pro Gly Pro Gly  Pro Gly Pro Gly Pro  Gly Pro Gly
   1145                1150                1155

Pro Gly  Pro Gly Pro Gly Pro  Gly Pro Glu Leu Ile  Cys Ser Gln
   1160                1165                1170

Gln Leu  Ser Gly Thr Gln Arg  Leu Lys Met Ser Ser  Ala Pro Cys
   1175                1180                1185

Phe Gln  Ile Arg Cys Asp Pro  Ser Gly Ser Gly Leu  Gly Lys Gln
   1190                1195                1200

Met Thr  Arg Leu Ser Leu Met  Glu Glu Asp Glu Glu  Glu Glu Leu
   1205                1210                1215
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Arg Leu  Leu Asp Glu Glu Trp  Gln Cys Gly Asp Lys  Leu Leu His
    1220                 1225                 1230

Ser Pro  Ser Ser Pro Ser Glu  His Gly Leu Asp Leu  Leu Asp Thr
    1235                 1240                 1245

Thr Glu  Leu Asn Met Glu Asp  Phe
    1250                 1255


<210> SEQ ID NO 21
<211> LENGTH: 1226
<212> TYPE: PRT
<213> ORGANISM: Pan troglodytes

<400> SEQUENCE: 21

Met Ser Ser Pro Leu Gln Arg Ala Met Gly Asp Thr Lys Arg Ala Leu
1               5                   10                  15

Ser Ala Ser Ser Ser Ser Ser Ala Ser Leu Pro Phe Asp Asp Arg Asp
            20                  25                  30

Ser Asn His Thr Ser Glu Gly Asn Gly Asp Ser Leu Leu Ala Asp Glu
        35                  40                  45

Asp Thr Asp Phe Glu Asp Ser Leu Asn Arg Asn Val Lys Lys Arg Ala
    50                  55                  60

Ala Lys Arg Pro Pro Lys Thr Thr Pro Val Ala Lys His Pro Lys Lys
65                  70                  75                  80

Gly Ser Arg Val Val His Arg Tyr Ser Arg Lys Gln Ser Glu Pro Pro
                85                  90                  95

Ala Asn Asp Leu Phe Asn Ala Val Lys Ala Ala Lys Ser Asp Met Gln
            100                 105                 110

Ser Leu Val Asp Glu Trp Leu Asp Ser Tyr Lys Gln Asp Gln Asp Ala
        115                 120                 125

Gly Phe Leu Glu Leu Val Asn Phe Phe Ile Gln Ser Cys Gly Cys Lys
    130                 135                 140

Gly Ile Val Thr Pro Glu Met Phe Lys Lys Met Ser Asn Ser Glu Ile
145                 150                 155                 160

Ile Gln His Leu Thr Glu Gln Phe Asn Glu Asp Ser Gly Asp Tyr Pro
                165                 170                 175

Leu Ile Ala Pro Gly Pro Ser Trp Lys Lys Phe Gln Gly Ser Phe Cys
            180                 185                 190

Glu Phe Val Arg Thr Leu Val Cys Gln Cys Gln Tyr Ser Leu Leu Tyr
        195                 200                 205

Asp Gly Phe Pro Met Asp Asn Leu Ile Ser Leu Leu Thr Gly Leu Ser
    210                 215                 220

Asp Ser Gln Val Arg Ala Phe Arg His Thr Ser Thr Leu Ala Ala Met
225                 230                 235                 240

Lys Leu Met Thr Ser Leu Val Lys Val Ala Leu Gln Leu Ser Val His
                245                 250                 255

Gln Asp Asn Asn Gln Arg Gln Tyr Glu Ala Glu Arg Asn Lys Gly Pro
            260                 265                 270

Gly Gln Arg Ala Pro Glu Arg Leu Glu Ser Leu Leu Glu Lys Arg Lys
        275                 280                 285

Glu Leu Gln Glu His Gln Glu Glu Ile Glu Gly Met Met Asn Ala Leu
    290                 295                 300

Phe Arg Gly Val Phe Val His Arg Tyr Arg Asp Val Leu Pro Glu Ile
305                 310                 315                 320

Arg Ala Ile Cys Ile Glu Glu Ile Gly Cys Trp Met Gln Ser Tyr Ser
                325                 330                 335
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Thr Ser Phe Leu Thr Asp Ser Tyr Leu Lys Tyr Ile Gly Trp Thr Leu
            340                 345                 350

His Asp Lys His Arg Glu Val Arg Leu Lys Cys Val Lys Ala Leu Lys
        355                 360                 365

Gly Leu Tyr Gly Asn Arg Asp Leu Thr Thr Arg Leu Glu Leu Phe Thr
    370                 375                 380

Ser Arg Phe Lys Asp Arg Met Val Ser Met Val Met Asp Arg Glu Tyr
385                 390                 395                 400

Asp Val Ala Val Glu Ala Val Arg Leu Leu Ile Leu Ile Leu Lys Asn
                405                 410                 415

Met Glu Gly Val Leu Thr Asp Ala Asp Cys Glu Ser Val Tyr Pro Val
            420                 425                 430

Val Tyr Ala Ser His Arg Gly Leu Ala Ser Ala Ala Gly Glu Phe Leu
        435                 440                 445

Tyr Trp Lys Leu Phe Tyr Pro Glu Cys Glu Ile Arg Met Met Gly Gly
    450                 455                 460

Arg Glu Gln Arg Gln Ser Pro Gly Ala Gln Arg Thr Phe Phe Gln Leu
465                 470                 475                 480

Leu Leu Ser Phe Phe Val Glu Ser Glu Leu His Asp His Ala Ala Tyr
                485                 490                 495

Leu Val Asp Ser Leu Trp Asp Cys Ala Gly Ala Arg Leu Lys Asp Trp
            500                 505                 510

Glu Gly Leu Thr Ser Leu Leu Leu Glu Lys Asp Gln Asn Leu Gly Asp
        515                 520                 525

Val Gln Glu Ser Thr Leu Ile Glu Ile Leu Val Ser Ser Ala Arg Gln
    530                 535                 540

Ala Ser Glu Gly His Pro Pro Val Gly Arg Val Thr Gly Arg Lys Gly
545                 550                 555                 560

Leu Thr Ser Lys Glu Arg Lys Thr Gln Ala Asp Asp Arg Val Lys Leu
                565                 570                 575

Thr Glu His Leu Ile Pro Leu Leu Pro Gln Leu Leu Ala Lys Phe Ser
            580                 585                 590

Ala Asp Ala Glu Lys Val Thr Pro Leu Leu Gln Leu Leu Ser Cys Phe
        595                 600                 605

Asp Leu His Ile Tyr Cys Thr Gly Arg Leu Glu Lys His Leu Glu Leu
    610                 615                 620

Phe Leu Gln Gln Leu Gln Glu Val Val Val Lys His Ala Glu Pro Ala
625                 630                 635                 640

Val Leu Glu Ala Gly Ala His Ala Leu Tyr Leu Leu Cys Asn Pro Glu
                645                 650                 655

Phe Thr Phe Phe Ser Arg Ala Asp Phe Ala Arg Ser Gln Leu Val Asp
            660                 665                 670

Leu Leu Thr Asp Arg Phe Gln Gln Glu Leu Glu Glu Leu Leu Gln Ser
        675                 680                 685

Ser Phe Leu Asp Glu Asp Glu Val Tyr Asn Leu Ala Ala Thr Leu Lys
    690                 695                 700

Arg Leu Ser Ala Phe Tyr Asn Ala His Asp Leu Thr Arg Trp Glu Leu
705                 710                 715                 720

Tyr Glu Pro Cys Cys Gln Leu Leu Gln Lys Ala Val Asp Thr Gly Glu
                725                 730                 735

Val Pro His Gln Val Ile Leu Pro Ala Leu Thr Leu Val Tyr Phe Ser
            740                 745                 750

Ile Leu Trp Thr Leu Thr His Ile Ser Lys Ser Asp Ala Ser Gln Lys
        755                 760                 765
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```
Gln Leu Ser Ser Leu Arg Asp Arg Met Val Ala Phe Cys Glu Leu Cys
    770                 775                 780

Gln Ser Cys Leu Ser Asp Val Asp Thr Glu Ile Gln Glu Gln Ala Phe
785                 790                 795                 800

Val Leu Leu Ser Asp Leu Leu Leu Ile Phe Ser Pro Gln Met Ile Val
                805                 810                 815

Gly Gly Arg Asp Phe Leu Arg Pro Leu Val Phe Phe Pro Glu Ala Thr
            820                 825                 830

Leu Gln Ser Glu Leu Ala Ser Phe Leu Met Asp His Val Phe Ile Gln
        835                 840                 845

Pro Gly Asp Leu Gly Ser Gly Asp Ser Gln Glu Asp His Leu Gln Ile
    850                 855                 860

Glu Arg Leu His Gln Arg Arg Arg Leu Leu Ala Gly Phe Cys Lys Leu
865                 870                 875                 880

Leu Leu Tyr Gly Val Leu Glu Met Asp Ala Ala Ser Asp Val Phe Lys
                885                 890                 895

His Tyr Asn Lys Phe Tyr Asn Asp Tyr Gly Asp Ile Ile Lys Glu Thr
            900                 905                 910

Leu Thr Arg Ala Arg Gln Ile Asp Arg Ser His Cys Ser Arg Ile Leu
        915                 920                 925

Leu Leu Ser Leu Lys Gln Leu Tyr Thr Glu Leu Leu Gln Glu His Gly
    930                 935                 940

Pro Gln Gly Leu Asn Glu Leu Pro Ala Phe Ile Glu Met Arg Asp Leu
945                 950                 955                 960

Ala Arg Arg Phe Ala Leu Ser Phe Gly Pro Gln Gln Leu Gln Asn Arg
                965                 970                 975

Asp Leu Val Val Met Leu His Lys Glu Gly Ile Lys Phe Ser Leu Ser
            980                 985                 990

Glu Leu Pro Pro Ala Gly Ser Ser  Asn Gln Pro Pro Asn  Leu Ala Phe
        995                 1000                1005

Leu Glu  Leu Leu Ser Glu Phe  Ser Pro Arg Leu Phe  His Gln Asp
    1010                1015                1020

Lys Gln  Leu Leu Leu Ser Tyr  Leu Glu Lys Cys Leu  Gln His Val
    1025                1030                1035

Ser Gln  Ala Pro Gly Arg Pro  Trp Gly Pro Val Thr  Thr Tyr Cys
    1040                1045                1050

His Ser  Leu Ser Pro Val Glu  Asn Thr Ala Glu Thr  Ser Pro Gln
    1055                1060                1065

Val Leu  Pro Ser Ser Lys Arg  Arg Arg Val Glu Gly  Pro Ala Lys
    1070                1075                1080

Pro Asn  Arg Glu Asp Val Ser  Ser Ser Gln Glu Glu  Ser Leu Gln
    1085                1090                1095

Leu Asn  Ser Ile Pro Pro Thr  Pro Thr Leu Thr Ser  Thr Ala Val
    1100                1105                1110

Lys Ser  Arg Gln Pro Leu Trp  Gly Leu Lys Glu Met  Glu Glu Glu
    1115                1120                1125

Asp Gly  Ser Glu Leu Asp Phe  Ala Gln Gly Ser Gln  Pro Val Ala
    1130                1135                1140

Gly Thr  Glu Arg Ser Arg Phe  Leu Gly Pro Gln Tyr  Phe Gln Thr
    1145                1150                1155

Pro His  Asn Pro Ser Gly Pro  Gly Leu Gly Asn Gln  Leu Met Arg
    1160                1165                1170

Leu Ser  Leu Met Glu Glu Asp  Glu Glu Glu Glu Leu  Glu Ile Gln
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    1175                1180                1185

Asp Glu  Ser Asn Glu Glu Arg  Gln Asp Thr Asp Met  Gln Ala Ser
    1190                1195                1200

Ser Tyr  Cys Ser Thr Ser Glu  Arg Gly Leu Asp Leu  Leu Asp Ser
    1205                1210                1215

Thr Glu  Leu Asp Ile Glu Asp  Phe
    1220                1225


<210> SEQ ID NO 22
<211> LENGTH: 432
<212> TYPE: PRT
<213> ORGANISM: Ornithorhynchus anatinus

<400> SEQUENCE: 22

Met Ala Arg Arg Trp Gly Val Ala Cys Val Ser Lys Arg Val Gly Asp
1               5                   10                  15

Glu Asn Glu Ala Gln Arg Ala Gly Glu Val Asp Lys Asn Glu Gly Ile
            20                  25                  30

Glu Leu Gly Gly Ser Gly Arg Arg Leu Glu Arg Leu Asp Phe Trp Val
        35                  40                  45

Val Phe Cys Leu Ser Thr Pro Pro Gly Pro Ala Leu Gly Ser Glu Leu
    50                  55                  60

Val His Ser Pro Leu Ala Val Arg Glu Pro Val Arg Ser Pro Ser Ser
65                  70                  75                  80

Pro Pro Thr Arg Leu Ala Leu Leu Ala Gly Gly Ser Arg Asn Gly Pro
                85                  90                  95

Val Leu Pro Ile Phe Phe Thr Ile Leu Pro Pro Pro Ser Gly Thr Val
            100                 105                 110

Thr Leu Glu Met Phe Lys Thr Leu Gln Asn Ser Glu Ile Ile Gln Gln
        115                 120                 125

Met Thr Glu Lys Phe Asn Glu Asp Ser Val Glu Tyr Pro Leu Ser Ala
    130                 135                 140

Ser Gly Pro Thr Trp Lys Lys Phe Arg Gly Ser Phe Cys Glu Phe Val
145                 150                 155                 160

Ser Ser Leu Val His Gln Cys Arg Tyr Ser Phe Leu Tyr Asp Glu Phe
                165                 170                 175

Leu Met Asp Thr Leu Ile Ser Leu Leu Thr Gly Leu Ser Asp Ser Gln
            180                 185                 190

Val Arg Ala Phe Arg His Thr Ser Thr Leu Arg Arg Pro Ala Ser Phe
        195                 200                 205

Leu Gln Pro Arg Arg Asp Gly Gly Pro Ala Lys Thr Pro Pro Cys Cys
    210                 215                 220

Asp Ile Pro Pro Pro Phe Pro Asn Leu Leu Gln His Arg Pro Pro Leu
225                 230                 235                 240

Leu Ala Phe Pro Gln Ala Lys Pro Ala Gly Pro Ala Gly Pro Ala Arg
                245                 250                 255

Val Pro Gly Asp Gly Ala Ser Arg Leu Pro Val Ile Cys His Ala Lys
            260                 265                 270

Asp Thr Ser Gly Pro Phe Pro Phe Val Gln Val Ser Gly Arg Asp Pro
        275                 280                 285

Val Ala His Pro Pro Ala Lys Ala Glu Arg Glu Glu Lys Gly Leu Pro
    290                 295                 300

Pro Ser Ala Ile Pro Val Arg Ser Gln Gly Ala Glu Gly Leu Leu Ala
305                 310                 315                 320

Arg Ile His Ala Gly Gly Asp Arg Gly Gly Gly Gly Arg Thr Gly Leu
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               325                 330                 335

Pro Val Pro Cys Gln Thr Phe Pro Ala Cys His Arg Asn Gly Asp Leu
            340                 345                 350

Thr Gly Gly Tyr Arg Leu Gly Arg Ser Ala Ser Thr Ser Gly Val Arg
        355                 360                 365

Gln Ala Ala Leu His Thr Pro Arg Pro Cys Ser Gln Ala Arg Glu Ser
    370                 375                 380

Pro Ser Gln Val Arg Lys Ala Asp Gly Ser Leu Thr Gly Leu Leu Gly
385                 390                 395                 400

Leu Gly Leu Arg Glu Gly Gly Pro Glu Glu Pro Val Leu Glu Thr Arg
                405                 410                 415

Ala Gly Gly Gly Ala Ser Glu Gly Arg Glu Gly Trp Arg Pro Gly Arg
            420                 425                 430
```

<210> SEQ ID NO 23
<211> LENGTH: 1140
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

```
gcacaccgga ctgcgttttt tttccgaacg cccgcagcag ggtcagaagg gaggtggtcg     60

ccctccgtcg tggtctggcg tgtattccga gcgttggtgt ctggcggttt ccgagcgttg    120

gtgtctggcg gtttccgacc gttggtgtct ggcggtttcc gaccgttggt gtctggcacg    180

cgccaccctc tcttgctttg gttgcgccat gccgatgtac cagacaagaa gacaagaaaa    240

tgatttgagg acagcttcaa tcgcggtgtg aagaagaaag cagcaaaacg accactgaaa    300

acaacgccgg tggcaaaata tccaaagaaa gggtcccaag cggtacatcg tcatagccgg    360

aaacagtcag agccaccagc caatgatatt ttcaatgctg cgaaagctgc caaaagtgac    420

atgcagggat gtccttcctg agatccgtgc tatctgcatt gaggaaattg ggtgttggat    480

gcaaagctac agcacgtctt tcctcaccga cagctattta aaatatattg gttggactct    540

gcatgataag caccgagaag tccgcgtgaa gtgcgtgaag gctctgaaag ggctgtacgg    600

taaccgggac ctgaccgcac gcctggagct cttcactggc cgcttcaagg actggatggt    660

ttccatgatc gtggacagag agtacagtgt ggcagtggag gccgtcagat tactgatact    720

tatccttaag aacatggaag gggtgctgat ggacgtggac tgtgagagcg tctaccccat    780

tgtgtaggcc tctaattgag gcctggcctc tgctgtgggt gaatttctgt actggaaact    840

tttctaccct gagtgcgaga taagaacgat gggtggaaga gagcaacgcc agagcccagg    900

cgcccagagg actttcttcc agcttctgct gtccttcttt gtggagagca aggtgacata    960

cacagagaga actctggctg ttgtgcatag gacctacaag tgggctgggg ttggtggctc   1020

acgcctgtaa gcccagcact ttgggaggct gaggtgggag gatcctttga gcccaggagt   1080

ttgagaccag cttgggcaac atagtgagac cctgtctcta ccaaaaaaaa aaaaaaaaaa   1140
```

<210> SEQ ID NO 24
<211> LENGTH: 4246
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 24

```
ccgcgttttt ttctaaggct taaccgcccg ccaccagagg aagaagagca gctgcggcgg     60

gcgtctcgcg accgaggtgg gatgtccact gagacctgaa aggacctctg aggtggtgac    120

ctttcttcag ccgtgttcat ctaaagctgg attaacatgc ctactctgtg gtcaccttct    180
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acccagcacc atggctcttc ctcaggcagt gagtcttccc cacttcaaaa gtctgtgaga 240

cgtgcacaga tggccttgtc tccttgttcc tcctccatcc taccctgtga tgacagagac 300

tcacagggaa ctgcagagtg ggatagtccc tcaactaacg aagacagcga ctttgaagac 360

agcttaagac gaaatgtgaa gaagagagca gcaaagcaac cacccaaagc tgttccagca 420

gcaaaacatc ggaagaagca gtcccgaata gtatctagtg ggaatggcaa gaatgaatca 480

gtgccatcaa ccaattacct ttttgatgct gtgaaagctg ctagaagttg catgcagtct 540

ttggtggatg agtggctaga taactacaag caagatgaaa atgcaggatt cttggagctc 600

attaattttt tcatccgagc ctgtggatgt aaaagcactg tgactcctga gatgttcaag 660

acaatgtcca attcagagat catccaacac ctaacggaag agtttaatga ggactcgggg 720

gactatcccc tgacagctcc aggtccctcc tggaagaagt tccagggaag cttctgtgag 780

tttgtgaaga cattggtcta tcagtgccag tacagtctcc tctatgatgg ctttcctatg 840

gatgacctta tctccctgct cattggcctc tcagattccc aggtccgagc ctttcgtcat 900

actagtaccc tggctgccat gaagctaatg acttctctgg taaaagttgc actccagttg 960

agtctgcaca aagacaacaa tcaacgtcag tatgaggctg aacgaaacaa ggggccagag 1020

cagagagcac cggaacgact ggagagtctg ctggagaaac gaaaagagtt ccaagagaat 1080

caagaggaca tagaggggat gatgaatgcc atcttcagag gtgtctttgt ccatcggtac 1140

agggacatcc ttcctgagat ccgcgctatc tgcattgagg agattgggta ttggatgcaa 1200

agctacagca cctcctttct taatgacagc tacctaaaat acatcggctg gaccctgcat 1260

gataagcaca aggaagttcg cctgaagtgt gtgaaggctc tggcagggct gtacagcaac 1320

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tacatttcta atcgtgctat ggcctcttct gcaggggaat ttgtgtattg gaagatcttc 1560

catcctgaat gtggggcaaa agcagtgagt gatagagagc gacgccggag tccacaagcc 1620

cagaagactt tcatttatct tttactggcc ttctttatgg agagtgagca tcacaaccat 1680

gctgcttact tagtagacag cttgtgggac tgtgcggggt cttacctgaa ggactgggag 1740

agtctgacaa acctgttgct gcagaaagac cagaatctgg gtgatatgca agagagaatg 1800

ctgatagaaa tccttgtgtc tagtgcccgg caagctgcag agggtcaccc tccagtgggg 1860

cgcatcactg gaaagaagag tctgacggcc aaagaacgca agcttcaagc ctatgataag 1920

atgaagctgg ctgagcacct catccccctc ttgccccagc tccttgccaa gttctcagca 1980

gatgcagaga atgttgctcc cttgctccag ctgctcagtt actttgacct cagcatatat 2040

tgcactcagc gcttggaaaa gcacttggag ctgcttctgc aacaactcca ggaggtggtg 2100

gtgaagcatg tagagcctga ggtgcttgag gcagcagccc atgccctcta tctgctctgc 2160

aaaccagagt tcaccttctt cagcagagtg gactttgcca gaagccaatt agtagatttt 2220

ctgactgata gattccagca ggagcttgat gacctaatgc agtcatcctt cctagatgag 2280

gatgaggtat acagcctgac agccaccctg aagcgtctct ctgcctttta caatgctcat 2340

gacctgaccc gatgggagat ctctgaacca tgttctcgac tcctccggaa ggctgtagac 2400

acaggagaag ttcctcacca ggtgattttg ccagccttga ctctggtata tttttccatt 2460

ctctggacag taacccacat ttcagagtct acttctcata agcagctgat gagtctgaag 2520

aaaagaatgg tagccttctg tgagctttgc caaagctgcc tctcagacgt ggacccagag 2580

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We claim:

1. A method for identifying a human as a candidate for further examination for human papillomavirus (HPV) positive cervical cancer, the method comprising the steps of:

obtaining a tissue sample from a region of the cervix of the human;

measuring the expression of a member selected from testicular cell adhesion molecule 1 (TCAM1), synaptonemal complex protein 2 (SYCP2), and stromal antigen 3 (STAG3) in the cells of the tissue sample; and

comparing the expression level to a normal standard wherein a higher than normal expression indicates that the human is a candidate for further examination for cervical cancer.

2. The method of claim **1**, wherein the tissue sample is a cervical smear.

3. The method of claim **1**, wherein the tissue sample is a fluid collected by vaginal rinsing.

4. A method of screening for human papillomavirus (HPV) positive cervical cancer in a human comprising the steps of:

obtaining a tissue sample from a region of the cervix of the human;

measuring the expression of a member selected from TCAM1, SYCP2, and STAG3 in the cells of the tissue sample; and

comparing the expression level to a normal standard wherein a higher than normal expression indicates cervical cancer.

5. The method of claim **4**, wherein the tissue sample is a cervical smear.

6. The method of claim **4**, wherein the tissue sample is a fluid collected by vaginal rinsing.

7. The method of claim **4**, further comprising the step of observing cervical cancer in the human.

8. A method of screening for preneoplastic lesion for human papillomavirus (HPV) positive cervical cancer in a human, the method comprising the steps of:

obtaining a tissue sample from a region of the cervix of the human;

measuring the expression of a member selected from TCAM1 and SYCP2 in the cells of the tissue sample; and

comparing the expression level to a normal standard wherein a higher than normal expression indicates a preneoplastic lesion in the cervix.

9. The method of claim **8**, wherein the tissue sample is a cervical smear.

10. The method of claim **8**, wherein the tissue sample is a fluid collected by vaginal rinsing.

11. The method of claim **8**, further comprising the step of observing a preneoplastic lesion in a region of the cervix.

* * * * *