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(54) Title: METHODS FOR THE EARLY DIAGNOSIS OF VIRAL INFECTIONS AND INFLAMMATORY DISEASES OR A PREDISPOSITION OF A SUBJECT FOR PROLIFERATIVE DISORDERS OR HYPERPLASIA

(57) Abstract: The present invention provides a method for the identification of the predisposition of a subject for a proliferative disorder or a hyperplasia and a method for the early diagnosis of a viral infection or an inflammatory disease, comprising the step of analyzing the level of expression of an ether à go-go (EAG) potassium channel gene and/or an ether à go-go related gene (ERG) or the activity of a corresponding gene product in a sample of tissue or cells.

WO 2006/037611 A2

Methods for the early diagnosis of viral infections and inflammatory diseases or a predisposition of a subject for proliferative disorders or hyperplasia

The present invention relates to a method for the identification of the predisposition of a subject for a proliferative disorder or a hyperplasia and a method for the early diagnosis of a viral infection or an inflammatory disease, comprising the step of analyzing the level of expression of an ether à go-go (EAG) potassium channel gene and/or an ether à go-go related gene (ERG) or the activity of a corresponding gene product in a sample of tissue or cells.

Several documents are cited throughout the text of this specification. The disclosure content of each of the documents cited herein (including any manufacturer's specifications, instructions, etc.) is herewith incorporated by reference.

Viral infections, inflammatory diseases and proliferative diseases represent major groups of today's common diseases. At least some of said diseases are life-threatening, while others may result in long lasting or lifelong reduction of the quality of life. Furthermore, the treatment of said diseases requires a high portion of the public and private health budget. Accordingly, the improvement of strategies for the treatment or, even more desirable, the prevention of the manifestation of such diseases is of great importance in medical science.

Based on an increasing understanding of the heterogeneous nature of many pathological conditions, a principle aim of medical/pharmaceutical drug development is the establishment of individual or targeted therapies for the treatment of diseases "personalized medicine". Such specific therapies may e.g. comprise therapeutic antibodies, small molecule inhibitors, nucleic acid interference, an individual diet and the administration of an individually selected or dosed pharmaceutical composition.

dosed pharmaceutical composition.

In order for targeted therapy approaches to exert/elicit the most clinical benefit, it is of particular advantage to identify a person in the need of such therapy as early as possible. The same holds true for the treatment of diseases by conventional methods. Accordingly, there is a need of indicators for a predisposition of a subject for a disease and for an initiation of diseases. Candidates for such indicators are marker molecules.

Potassium channels play an important role in several cellular functions such as excitability, contraction, cell cycle progression and metabolism (1). In particular, some members of the *ether à go-go* (EAG) potassium channels family are modulated through the cell cycle (2-8) and have been suggested to be involved in tumorigenesis (9-17). Rat EAG channels expressed in frog oocytes display rectification induced by mitosis-promoting factor activation (2), and their conducting properties change during cell cycle (3). Retinoic acid down-regulates hEAG current in neuroblastoma cells (4). hEAG is transiently expressed before myoblasts fusion, which is a cell cycle-related event (5, 6). hEAG expression currently decreases during M phase and is modulated by cytoskeletal elements (7). Channel subunits of another member of the EAG channel family, the human *ether à go-go* related gene (hERG), are differentially expressed throughout the cell cycle (8).

One of the most intriguing aspect of hEAG and hERG channels is their relationship to cellular transformation. Cells transfected with EAG are able to grow in the absence of serum, lose contact inhibition, and induce aggressive tumors when injected into immune-depressed mice (9). EAG mRNA expression in normal tissues is mainly restricted to the brain. It is also expressed transiently in skeletal muscle and slightly expressed in placenta. On the other hand, EAG mRNA is expressed in several cancer cell lines including HeLa, MCF-7, SHSY-5Y, and IGR1 from carcinoma of the cervix, breast tumor, neuroblastoma, and melanoma, respectively (9, 10). Despite the major expression of EAG in normal brain (9), endogenous EAG-mediated currents have been reported only in myoblasts (6) and in the tumoral cell lines SHSY-5Y (4), MCF-7 (11), and IGR1 (10). EAG is expressed in the tumor cell

line HeLa (9); however, no EAG-mediated currents have been described in these cells.

Expression of EAG and EAG-mediated currents in transformed cells seems to be an important event for cell proliferation, because inhibition of EAG expression with antisense oligonucleotides reduces cell proliferation in some cancer cell lines (9). Similarly, EAG-mediated current inhibition by imipramine have been suggested to decrease cell proliferation in IGR1 cells (12). Furthermore, cells expressing nonconducting EAG channels fail to induce tumor formation when injected into immune-depressed mice. EAG mRNA has been described not only in tumor cell lines but also in several human tumors including mammary gland, liver, prostate, uterine cervix, ovary, endometrium, colon, and thyroid; a significant percentage of epithelial tumors show robust EAG expression (13), whereas hERG channels are expressed in several cancer cell lines from different histogenesis including leukemic cells (14-16) and frequently expressed in biopsies from endometrical cancer (17).

In WO 99/54463 is has been described that the analysis of EAG expression and activity can be used for the detection of an onset or progression (disease status) of cancer. However, in this case a patient is already affected by cancer.

In view of the above described high relevance of the recited diseases for the public health the technical problem underlying the present invention was to provide means and methods which enable a prevention or alleviation of said diseases or to detect a predisposition to develop a disease. In the latter case, this will allow taking actions prior to the outbreak or manifestation the diseases.

The solution to said technical problem is achieved by providing the embodiments characterized in the claims.

The present invention provides a method for the identification of the predisposition of a subject for a proliferative disorder or a hyperplasia, comprising the step of analyzing the level of expression of an ether à go-go (EAG) potassium channel

gene and/or an ether à go-go related gene (ERG) or the activity of a corresponding gene product in a sample of tissue or cells wherein

(a) a detection of expression or activity in said sample of tissue or cells which under physiological condition do not show an expression or activity of one or more of said genes is indicative for said predisposition; or

(b) a detection of an increased level of expression or activity in said sample of tissue or cells compared to a basal level characteristic for said samples of tissue or cells under physiological conditions of one or more of said genes is indicative for said predisposition.

Furthermore, the present invention provides in an alternative embodiment a method for the early diagnosis of a viral infection or an inflammatory disease, comprising the step of analyzing the level of expression of an ether à go-go (EAG) potassium channel gene and/or an ether à go-go related gene (ERG) or the activity of a corresponding gene product in a sample of tissue or cells wherein

(a) a detection of expression or activity in said sample of tissue or cells which under physiological condition do not show an expression or activity of one or more of said genes is indicative for said diagnosis; or

(b) a detection of an increased level of expression or activity in said sample of tissue or cells compared to a basal level characteristic for said samples of tissue or cells under physiological conditions of one or more of said genes is indicative for said diagnosis.

The term "predisposition for a disease" is understood to describe a status of a subject prior to the outbreak of said disease. Thus, the predisposition of a subject for such disease is analyzed prior to an early onset of the disease itself.

The term "early diagnosis of a disease" is understood in the context of the present invention to allow a diagnosis of the disease prior to the development of morphological alterations. Thus, the disease can be diagnosed prior to a manifestation of the disease in its early onset.

The term "sample" denotes in the context of the present invention body sample, such as samples of organs, tissues or cells of a subject/patient. Preferable the subject (patient) the sample is taken from is human.

Tissue samples explicitly comprise in the context of the present invention samples of dermal tissue material, such as epidemal detritus, mucosal swabs, such as, but

not limited to oral mucosal, tonsillar, rectal, genital or nasal swabs (e.g. pap smears), as well as samples obtained by surgical techniques including minimal invasive techniques such as biopsy as well as more invasive techniques. The preparation of the sample may comprise a cultivation of the obtained material (e.g. in tissue culture) prior to the detection of the expression of the recited genes or the activity of the encoded gene products.

The term "expression" of a gene characterizes the process of transcription of a gene into mRNA in a cell or in the cells of a tissue. Furthermore, in line with the present invention, said term also refers to the translation of said mRNA and, thus, the production to the encoded gene product in said cell or cell in a tissue.

As defined herein above the EAG as well ERG are transmembrane ion channels. Accordingly, the activity of the gene products encoded by the EAG or the ERG genes is to permit the flow of ions through the membrane of a cell.

The term "physiological condition" is understood in the context of the present invention to define a state of the body, an organ, a tissue or a cell, wherein their respective functions are non-phathological, i.e. the representative of a normal healthy individual according to established medical guidelines and practice. Thus, said organs, tissues and cells are in this state not effected by any changes that will result in the development of the above recited diseases.

It has been surprisingly found that the detection of an expression of an EAG gene or an ERG gene is an indicator for a predisposition of a subject for a proliferative disorder or a hyperplasia. Furthermore, it was observed that said expression is also an indicator helpful in the early diagnosis of a viral infection or an inflammatory disease. It has been found that prior to the outbreak of corresponding diseases the expression of said genes is primary initiated or significantly unregulated compared to a physiological basal level of expression. The same holds true for the activity of the encoded gene products. The question whether the predisposition is indicated by a primary initiation of the expression of the gene (undesired expression) or the enhancement of an basal expression (undesired overexpression) is dependent from the tissue/cells and the gene which is/are analyzed. For example a wide spread expression on a basal of ERG genes is observed in different tissues of the human body. In contrast it is known in the art that e.g. the Eag1 gene is only expressed

under physiological conditions on a basal level e.g. in tissues of the brain, nerves and kidney, whereas there is no significant basal expression of the gene in tissue of cervix uteri, liver, pancreas and prostate.

In the context of the present invention an increase of the expression (undesired overexpression) is understood as an at least 2 times overexpression compared to the basal level under physiological conditions, preferably 5 times, 10 times or 100 times.

As noted herein above, there is e.g. no significant expression for EAG genes, namely Eag1, in particular tissues. The detection of Eag1 expression in samples of such tissues is indicative for the predisposition of a subject from which said sample is derived from.

It is preferred for the methods of the invention that

(a) tissues and cells which under physiological condition do not show an expression of the EAG gene or activity of the corresponding gene product are selected from samples of a group consisting of samples of cervix uteri, liver, pancreas and prostate; and

(b) tissues and cells for which under physiological conditions a basal level for an expression of the EAG gene or activity of the corresponding gene product is characteristic are selected from samples of a group consisting of samples of brain, nerves and kidney.

In a preferred embodiment of the methods of the invention the nucleic acid sequence of the EAG gene comprises

(a) a nucleic acid molecule encoding the polypeptide having the amino acid sequence of SEQ ID: NO 2 or 4;

(b) a nucleic acid molecule having the DNA sequence of SEQ ID: NO 1 or 3;

(c) a nucleic acid molecule hybridizing to the complementary strand of a nucleic acid molecule of (a) or (b); or

(d) a nucleic acid molecule being degenerate to the sequence of the nucleic acid molecule of (c).

Furthermore, it is preferred for the methods of the invention that the nucleic acid sequence of the ERG gene comprises

(a) a nucleic acid molecule encoding the polypeptide having the amino acid sequence of SEQ ID: NO 6, 8 or 10;

(b) a nucleic acid molecule having the DNA sequence of SEQ ID: NO 5, 7 or 9;

(c) a nucleic acid molecule hybridizing to the complementary strand of a nucleic acid molecule of (a) or (b); or

(d) a nucleic acid molecule being degenerate to the sequence of the nucleic acid molecule of (c).

The term "hybridizing" as used herein refers to polynucleotides/nucleic acid sequences which are capable of hybridizing to the polynucleotides encoding the EAG or ERG proteins as defined herein. Therefore, said polynucleotides may be useful as probes in Northern or Southern Blot analysis of RNA or DNA preparations, respectively, or can be used as oligonucleotide primers in PCR analysis dependent on their respective size. Preferably, said hybridizing polynucleotides comprise at least 10, more preferably at least 15 nucleotides in length while a hybridizing polynucleotide of the present invention to be used as a probe preferably comprises at least 100, more preferably at least 200, or most preferably at least 500 nucleotides in length.

It is well known in the art how to perform hybridization experiments with nucleic acid molecules, i.e. the person skilled in the art knows what hybridization conditions she has to use in accordance with the present invention. Such hybridization conditions are referred to in standard text books such as Molecular Cloning A Laboratory Manual, Cold Spring Harbor Laboratory (2001) N.Y. Preferred in accordance with the present inventions are polynucleotides which are capable of hybridizing to the polynucleotides of the invention or parts thereof, under stringent hybridization conditions.

"Stringent hybridization conditions" refer, i.e. to an overnight incubation at 42°C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1 x SSC at about 65°C. Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide

concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH2PO4; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50°C with 1 X SSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC). It is of note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

The recited nucleic acid molecules may be, e.g., DNA, cDNA, RNA or synthetically produced DNA or RNA or a recombinantly produced chimeric nucleic acid molecule comprising any of those polynucleotides either alone or in combination.

In a more preferred embodiment of the methods of the invention the expression of an EAG gene and/or the expression of an ERG gene in a sample is determined on mRNA level or on protein level and/or the activity of said gene products is determined on an electrophysiological level.

Different methods for the determination of the expression of a gene on mRNA level or protein level are known in the art and described in several laboratory manuals; see e.g. Mülhardt, C. Der Experimentator: Molekularbiologe/Genomics; Spektrum Akademischer Verlag 2003; Rehm, H. Der Experimentator: Spektrum Akademischer Verlag; 2002; Lottspeich, F. and Zorbas, H. Bioanalytik Spektrum Akademischer Verlag 1998.

Moreover, different methods for the determination of the activity of a gene product on an electrophysiological level are known in the art; see e.g. Hamill OP et al., Pflügers Arch 1981.

It is further preferred that the expression of an EAG gene and/or the expression of

an ERG gene in a sample on a mRNA level is determined by RT-PCR, cDNA array or Northern Blot analysis. In the appended examples a possible RT-PCR approach is described in more detail.

Preferably, for the analysis of the expression of an EAG gene by RT-PCR a pair of sense and antisense primers is used selected from the sense primers having a nucleic acid sequence as shown in SEQ ID NO: 11 or 13 and from the antisense primers having a nucleic acid sequence as shown in SEQ ID NO: 12 or 14.

It is preferred in one embodiment of the invention that the detection of the translated protein of said EAG gene and/or ERG gene is effected by immunoblotting/Western blot analysis, immunohistochemical analysis, ELISA analysis, immunofluoresce analysis, FACS analysis or antibody array analysis.

Appropriate antibodies required for such analysis are known in the art and described e.g. in WO 99/54463 and a further application filed on October 1, 2004 by the present applicant. Protocols for said analysis are known to the person skilled in the art and represent standard techniques in biochemical laboratories.

In an alternatively preferred embodiment of the methods of the invention the activity of an EAG gene product and/or an ERG gene product in a sample on electrophysiological level is determined by patch clamp analysis.

The technique of patch clamp analysis is known in the art and described in Stühmer, W., 1992, *Methods in Enzymology* 207 and the appended examples.

According to a preferred embodiment of the methods of the invention the sample which is analyzed is a tissue culture of a tissue sample derived by biopsy from said subject. A corresponding approach is described in the appended examples.

It is preferred by the present invention that said viral infection, inflammatory disease, proliferative disorder or hyperplasia is a gynecological disease.

It is also preferred that the recited proliferative disorder is cancer. Preferably, said cancer is cervical cancer.

Furthermore, it is preferred that the recited hyperplasia is adenomatous hyperplasia or prostate hyperplasia.

Moreover, it is preferred that the recited viral infection is an infection with Human Papilloma Virus or Hepatitis C Virus (HCV).

In addition, it is preferred that the recited inflammatory disease is an pancreatitis.

In one alternative embodiment the recited inflammatory disease is a pancreatitis or hepatitis.

The figures show:

Figure 1: EAG expression in cancerous and normal cervix.

Southern blot analysis of 475-bp hEAG RT-PCR products is shown for RNAs obtained from primary cultures of cervical cancer biopsies (A, lanes 1–5), endocervical adenocarcinoma (A, lane 6), and control cervix (A, lanes 7–12). hEAG signals were detected in control cervixes (B) from patients whose samples were diagnosed as human papilloma virus infection (lane 14), atypical adenomatous hyperplasia of the endometrium (lane 15), and paratubaric serous cystadenoma without atypical cells (lane 16); in 1 case (lane 17) it was not possible to establish a detailed diagnosis, because the endometrium was reported as histologically lysed. hEAG-transfected CHO cells were used for positive control (lanes 13 and 18). Hybridization with a cyclophilin (Cyc) probe from the same RNAs is shown at the bottom of each gel.

Figure 2: Current to voltage relationships in cervical cancer cells.

Whole-cell patch-clamp experiments were performed, and ramp protocols from 80 to 120 mV were applied in isolated cells from cervical cancer primary cultures. Linear leak was subtracted after extrapolation of a linear fit to the current measured between 80 and 70 mV to the whole range. Four different I-V curves were found in different cells in every culture. In some cells, clear inward currents were followed by an outward current (A); other cells displayed very small inward currents followed by a slightly inactivating outward current (B); traces with the presence of small outward inactivating currents followed by non inactivating currents were also recorded (C); and finally, some cells showed only non inactivating outward currents (D) where

EAG activity was detected. Eh 80 mV.

Figure 3: Voltage- and magnesium- dependent activation of outward currents.
A, unsubtracted currents (*left traces*) elicited at 60 mV preceded by negative prepulses at different voltages indicated in the amplified extract (*right traces*).
B, outward currents elicited at 60 mV preceded by negative prepulses at 140 or 60 mV in magnesium-free solutions (*left traces*) or in solutions containing 10 mmol/L magnesium.
C, voltage-dependent activation (time to reach 80% of maximal amplitude, mean, *n* 6 for each condition; *bars*, SD,) at different external magnesium concentrations. Activation is strongly dependent on prepulse voltage and extracellular magnesium as expected for EAG channels.

Figure 4: Liver tissue sample stained for EAG1.
(a) shows a Interface hepatitis with inflammatory cells and Piecemeal necrosis
(b) a Nutritive-toxic hepatitis with fat droplets

Figure 5: EAG staining in pancreas tissue.
Immunhistochemistry demonstrates immunoreactivity for EAG1 in panreatitis but not in connective tissue (a). In addtion EAG1 expression was found in Mucinous metaplasia (b).

Figure 6:
shows no EAG 1 staining in (a) normal prostatic ducts whereas in (b) regions of benign prostate hyperplasia were immunoreactive

The invention is now described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of scope of the present invention.

Figure 7:
The figure shows the inhibition of cervix carcinoma cell proliferation by mouse anti-Eag1 antibody ImAb3 conjugated with the immunotoxin saporin.

The following examples illustrate the invention.

Example 1: quantitative RT-PCR

Total RNA was extracted from primary cultures of cervical cancer cells and directly from normal cervical tissue with Trizol reagent (Invitrogen). hEAG-transfected Chinese hamster ovary (CHO) cells were used as positive control. RNA was subjected to reverse transcription reaction, and PCR amplifications were performed with the following sense and antisense primers: 5 -GCTTTTGAGAACGTGGATGAG-3 (SEQ ID NO:11) and 5 -CGAAGATGGTGGCATAGAGAA-3 (SEQ ID NO: 12). These amplifications yielded a 475-bp hEAG1 product. The constitutive gene cyclophilin was also amplified as control, using the following sense and antisense primers: 5 -CCC CAC CGT GTT CTT CGACAT-3 and 5 -AGG TCC TTA CCG TTC TGG TCG-3 , respectively, which yielded a 453-bp product. Reverse transcription-PCR (RT-PCR) product identity was determined by nucleotide sequence in an automatic capillary genetic analyzer (ABI PRISM 3100, Applied Biosystems). The PCR products were separated in agarose gels, blotted onto nylon membranes, and hybridized with [^{32}P]dCTP-labeled nested probes. Probes were obtained with the following upper and lower primers: for the 228-bp hEAG1 probe, 5 -TGGTCCTGCTGGTGTGTG- 3 (SEQ ID NO:13) and 5 –ACAACGAGGAGATGTAGACA G-3 (SEQ ID NO: 14); and for the 187-bp cyclophilin probe, 5 -CACACGCCATAATGGCACTGGTGG-3 and 5 -AAAGACCACATGCTTGCCATC CAGC-3 . In all of the cases, filters were washed after 18-hour hybridization and exposed to X-ray films. Southern blot probes were also confirmed by sequence.

EAG expression was studied by RT-PCR and Southern blot analysis in 5 primary cultures from cervical cancer biopsies, in 1 fresh cervical cancer tissue, and in 12 noncancerous biopsies from normal cervixes. Fig. 1*A* shows EAG gene expression in 100% of the primary cultures from cervical cancer (Lanes 1–5). It is worth mentioning that in a patient who was submitted to hysterectomy without any previous evidence of cervical malignancy (negative pap smears), postsurgery pathological studies showed an unexpected endocervical adenocarcinoma expressing EAG. Hence, because this EAG expression was found in a cancerous

tissue, it was grouped together with the samples from primary cultures of cancer cells (Fig. 1*A*, lane 6). Studies of EAG expression in control cervical biopsies displayed samples either negative or positive for EAG, despite all of them coming from patients with negative pap smears. Southern blot experiments from control cervical tissue negative for EAG are also shown in Fig. 1*A* (Lanes 7–12); 8 of 12 samples were negative for EAG (only 6 are shown).

Eag expression was observed in 4 control biopsies of normal cervical tissue. Interestingly, 1 of these control EAG-positive samples (Fig. 1*B*, lane 14) came from a patient with human papilloma virus infection, the most important etiological factor associated with cervical cancer. Two other patients in whom EAG expression was found in normal cervix presented atypical adenomatous hyperplasia of the endometrium in 1 case and paratubaric serous cystadenoma without atypical cells in the other (Fig. 1*B*, lanes 15 and 16, respectively). In 1 patient of the EAG-positive control samples (Fig. 1*B*, lane 17) the endometrium was reported as histologically lysed, so a diagnosis could not be determined. hEAG-transfected CHO cells were used as positive control (Fig. 1, lanes 13 and 18).

RT-PCR product identity was determined by nucleotide sequence (data not shown). The amplified products were identical to the sequence reported for hEAG1. We determined that the cells from the cancerous biopsies studied herein express the two different mRNA spliced variants reported for hEAG1 gene.

Example 2: electrophysiology

Whole-cell recordings were acquired from isolated cells with the patchclamptechnique using an EPC-9 amplifier (HEKA Electronics, Germany)and analyzed with Igor Pro (WaveMetrics). Two to three M patch pipetteswere obtained by double-pulling Kimax capillaries. Internal solution contained(mmol/L) 140 KCl, 10 EGTA, and 10 HEPES/KOH (pH 7.2). Externalsolution contained (mmol/L) 115 NaCl, 2 CaCl2, 2 MgCl2, and 10 HEPES/NaOH (pH 7.2); in some experiments we used free-magnesium solutions or solutions containing 2, 5, or 10 mmol/L MgCl2. No capacitance compensation was performed. Holding potential was 80 mV, unless indicated. Experiments were performed at room temperature (20°C to 22°C).

Whole cell patch clamp experiments were performed in 5 primary cultures from cervical cancer cells. Before exploring EAG activity, we applied voltage ramp

protocols (from 80 mV to 120 mV) to study the current to voltage relationship. Four different shapes of I-V curves in every culture were found (Fig. 2). Some cells (Fig. 2*A*) displayed clear inward currents from 30 mV to 10 mV, probably mediated through sodium or calcium channels, followed by an outward non-inactivating current. Other cells showed a small outward current at very negative potentials (Fig. 2*B*) followed by a small inward current near 25 mV then followed by an inactivating or rectifying outward current. Fig. 4*C* shows an I-V curve with a very small inward current at 50 mV followed by outward current, and finally Fig. 2*D* displays exclusively non-inactivating outward currents. Cells showing such I-V curve had the highest current density and were the only cells where we detected EAG activity.

We looked for EAG activity in tumor cells by studying their voltage and magnesium dependent activation. Very negative prepulses have an especially strong effect on EAG activation; the more negative the prepulse potential, the slower the EAG activation (Cole-Moore shift, ref. 20);similarly, the higher the extracellular magnesium concentration, the slower the EAG activation. Fig. 3*A* shows the potential dependent activation of the outward currents recorded in cervical cancer cells. Unsubtracted traces of currents elicited at 60 mV preceded by pulses at different potentials are shown on the left. Prepulse values are indicated for each pulse in magnified traces on the right; the more negative the prepulse, the slower the channel activation. Magnesium-dependent activation is shown in Fig. 3*B*. Outward current elicited at 60 mV and preceded by a 140 or 60 mV prepulse were obtained either in the free-magnesium external solutions(left traces) or in solutions containing 10 mmol/L magnesium(right traces). As expected for EAG, activation is clearly delayed in the presence of magnesium, the effect being more pronounced by applying a very negative prepulse. Fig. 3*C* shows the required time to reach 80% of the maximum outward current amplitude at different prepulse voltages and extracellular magnesium concentrations. Time to 80% values is bigger at higher magnesium concentrations and very negative prepulses as described for EAG channels.

Example 3: identification of HPV16

Human Papilloma Virus 16. Expression of the E7 gene was studied. Genomic DNA was obtained with phenol-chloroform. PCR amplifications were performed with the

following sense and antisense specific primers:5 -GACAGCTCAGAGGAGGAGGATG-3 and 5 -GACTCTACGCTTCGGTTGTGC-3 . The product was separated in agarose gels. CaSki cells (American Type Culture Collection, Manassas, VA) were used as E7-positive control.

Example 4: Immunohistochemistry

Tissues from the tissue register Klinikum Kassel were analysed by immunohistochemistry in order to elucidate the role of EAG1 in non malignant disorders as for example inflammatory or hyperproliferative diseases as well as tissues affected by virus infection. The use of fixed tissue was approved by the review board of the Klinikum Kassel. Tissue was fixed for 16 to 20 hours in 4% neutral buffered formalin and then embedded in paraffin. With a microtome 2-4 µm thin sections of selected tissue blocks were cut, mounted on silanized glass slides (Sigma) and dried at 60°C for 30 min and at 38°C overnight.

Sections were deparaffinized by incubation in xylene bath for 5 minutes twice, in acetone for 5 minutes twice and finally in distilled water for 5 minutes. Heat pretreatment of the sections was done in 10 mM citrate buffer, pH 6.0 in a micowave oven for 30 minutes at 250W, followed by washing in distilled water. Endogenous peroxidase was blocked by incubation in a freshly prepared solution of 0.3% H_2O_2 in methanol for 20 minutes at room temperature followed by washing in distilled water for 5 minutes. Except for counterstaining with hematoxylin and mounting, the following steps were performed overnight using the Tecan-Immunostainer Genesis RSP 200 (Software: Gemini 3.40), which proceeds regarding manufacturer's EnVision+-staining procedure (DAKO Cytomation, ChemMate rabbit/mouse): Slides were rinsed twice in PBS/0.05% TWEEN pH 7.4 for 7 minutes and incubated with antibody eag-1 (provided by U3) for 4 hours (1:200 dilution in Antibody Diluent (DAKO)). The reaction was stopped with 100 µl PBS/0.05% TWEEN pH 7.4 per slide. After washing in 1400 µl PBS/0.05% TWEEN pH 7.4 for 7 minutes, the slides were incubated with secondary antibody/peroxidase- conjugate (30 minutes, 150 µl/slide, DAKO HRP/rabbit-mouse ChemMate). After washing as before the staining reaction was achieved with 120 µl/slide DAB solution (DAKO; 1:50 dilution in substrate buffer) for 10 minutes. The reaction was stopped with 100 µl PBS/0.05% TWEEN pH 7.4 for 20 min, followed

by washing with 1400 µl PBS/0.05% TWEEN pH 7.4 for 7 minutes and then slides were washed every two hours with PBS/0.05% TWEEN pH 7.4, totally three times. Finally the slides were rinsed in water, counterstained with Harris' hematoxylin and covered with a glass slide. To exclude unspecific binding of the IgG2b molecule, control sections were incubated with IgG2b negative control (DAKO) instead of eag-1 antibody.

As demonstrated in the drawings of the invention we were able to show that surprisingly EAG1 was expressed in prostate hyperplasia (fig 1), in pancreatitis (fig 2) and hepatitis (fig 3). These data emphasize a functional role for EAG in the course of non malignant disorders.

Example 5:

Inhibition of human cervix carcinoma cell proliferation by human anti-EAG1 antibody ImAb3 of the invention conjugated to the immunotoxin saporin

The effect of the saporin-conjugated anti-EAG1 antibody ImAb3-SAP on cervix carcinoma cell proliferation was tested. Conjugation of the anti-Eag1 antibody ImAb3 to saporin (ImAb3-SAP) via disulfide linkage and purification of the conjugated antibody ImAb3-SAP was performed by Advanced Targeting Systems (San Diego, CA, USA).

1000 cancer cells/well were seeded in 100 µl 10% FCS-containing culture medium on 96-well plates overnight. After 24h, cells were washed with PBS and incubated for 24h in 60 µl/well medium containing 10% FCS. Cells were treated in quadruplicates with 1µg/ml saporin-conjugated anti-Eag1 monoclonal antibody ImAb3-SAP or control IgG-SAP diluted in 40 µl/well. Cells were then incubated at 37°C in 5% CO_2 for 3 days. In order to assess proliferation and cell viability 20 µl/well CellTiter 96® AQ_{ueous} One Solution reagent (Promega) containing the tetrazolium salt MTS and the electron coupling reagent phenazine methosulfate (PMS) was added to each well and incubated at 37°C for various periods ranging from 10 min up to 3 hours. The quantity of the formazan product was measured by the amount of 590nm absorbance using an ELISA plate reader. The results shown in fig. 1 demonstrate that ImAb3-SAP inhibits cell proliferation of HeLa cells, a cervix adenocarcinoma cell line known to be HPV-18 positive. In addition it is shown that ImAb3-SAP significantly interferes with cell proliferation of three further cervix

carcinoma cell lines CERV-215, CERV-196 and CERV-186 (CLS) reported to be HPV-16 positive.

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Claims

1. A method for the identification of the predisposition of a subject for a proliferative disorder or a hyperplasia, comprising the step of analyzing the level of expression of an ether à go-go (EAG) potassium channel gene and/or an ether à go-go related gene (ERG) or the activity of a corresponding gene product in a sample of tissue or cells wherein
   (a) a detection of expression or activity in said sample of tissue or cells which under physiological condition do not show an expression or activity of one or more of said genes is indicative for said predisposition; or
   (b) a detection of an increased level of expression or activity in said sample of tissue or cells compared to a basal level characteristic for said samples of tissue or cells under physiological conditions of one or more of said genes is indicative for said predisposition.

2. A method for the identification of the early diagnosis of a viral infection or an inflammatory disease, comprising the step of analyzing the level of expression of an ether à go-go (EAG) potassium channel gene and/or an ether à go-go related gene (ERG) or the activity of a corresponding gene product in a sample of tissue or cells wherein
   (a) a detection of expression or activity in said sample of tissue or cells which under physiological condition do not show an expression or activity of one or more of said genes is indicative for said diagnosis; or
   (b) a detection of an increased level of expression or activity in said sample of tissue or cells compared to a basal level characteristic for said samples of tissue or cells under physiological conditions of one or more of said genes is indicative for said diagnosis.

3. The method according to claim 1 or 2, wherein the

(a) tissues and cells which under physiological condition do not show an expression of the EAG gene or activity of the corresponding gene product are selected from samples of a group consisting of samples of cervix uteri, liver, pancreas and prostate; and

(b) tissues and cells for which under physiological conditions a basal level for an expression of the EAG gene or activity of the corresponding gene product is characteristic are selected from samples of a group consisting of samples of brain, nerves and kidney.

4. The method according to anyone of claims 1 to 3, wherein the nucleic acid sequence of the EAG gene comprises

(a) a nucleic acid molecule encoding the polypeptide having the amino acid sequence of SEQ ID: NO 2 or 4;

(b) a nucleic acid molecule having the DNA sequence of SEQ ID: NO 1 or 3;

(c) a nucleic acid molecule hybridizing to the complementary strand of a nucleic acid molecule of (a) or (b); or

(d) a nucleic acid molecule being degenerate to the sequence of the nucleic acid molecule of (c).

5. The method according to anyone of claims 1 to 4, wherein the nucleic acid sequence of the ERG gene comprises

(a) a nucleic acid molecule encoding the polypeptide having the amino acid sequence of SEQ ID: NO 6, 8 or 10;

(b) a nucleic acid molecule having the DNA sequence of SEQ ID: NO 5, 7 or 9;

(c) a nucleic acid molecule hybridizing to the complementary strand of a nucleic acid molecule of (a) or (b); or

(d) a nucleic acid molecule being degenerate to the sequence of the nucleic acid molecule of (c).

6. The method of anyone of claims 1 to 5, wherein the expression of an EAG gene and/or the expression of an ERG gene in a sample is determined on mRNA level or on protein level and/or the activity of said gene products is determined on an electrophysiological level .

7. The method according to claim 6, wherein the expression of an EAG gene and/or the expression of an ERG gene in a sample on an mRNA level is determined by RT-PCR, cDNA array or Northern Blot analysis.

8. The method according to claim 7, wherein for the analysis of the expression of an EAG gene by RT-PCR a pair of sense and antisense primers is used selected from the sense primers having a nucleic acid sequence as shown in SEQ ID NO: 11 or 13 and from the antisense primers having a nucleic acid sequence as shown in SEQ ID NO: 12 or 14.

9. The method according to claim 6, wherein the detection of the translated protein of said EAG gene and/or ERG gene is effected by immuno-blotting/Western blot analysis, immunohistochemical analysis, ELISA analysis, immunofluoresce analysis, FACS analysis or antibody array analysis.

10. The method according to claim 6, wherein the activity of an EAG gene product and/or an ERG gene product in a sample on electrophysiological level is determined by patch clamp analysis.

11. The method of anyone of claims 1 to 10, wherein said sample is a tissue culture of a tissue sample derived by biopsy from said subject.

12. The method of anyone of claims 1 to 11, wherein said viral infection, inflammatory disease, proliferative disorder or hyperplasia is a gynecological disease.

13. The method of anyone of claims 1 to 12, wherein said proliferative disorder is cancer.

14. The method according to claim 13, wherein said cancer is cervical cancer.

15. The method of anyone of claims 1 to 12, wherein said hyperplasia is adenomatous hyperplasia or prostate hyperplasia.

16. The method of anyone of claims 1 to 12, wherein said viral infection is an infection with Human Papilloma Virus or Hepatitis C Virus (HCV).

17. The method of anyone of claims 1 to 11, wherein said inflammatory disease is a pancreatitis or a hepatitis.

Fig. 1

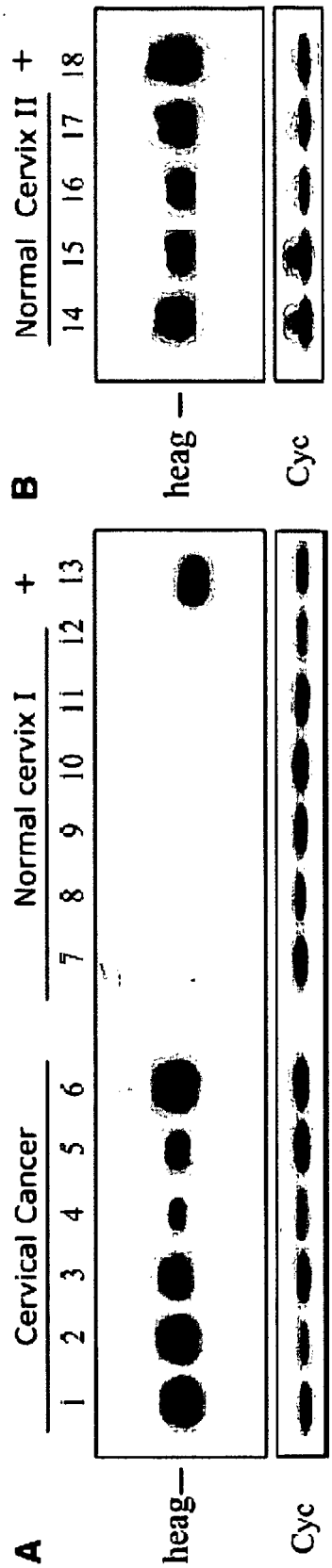
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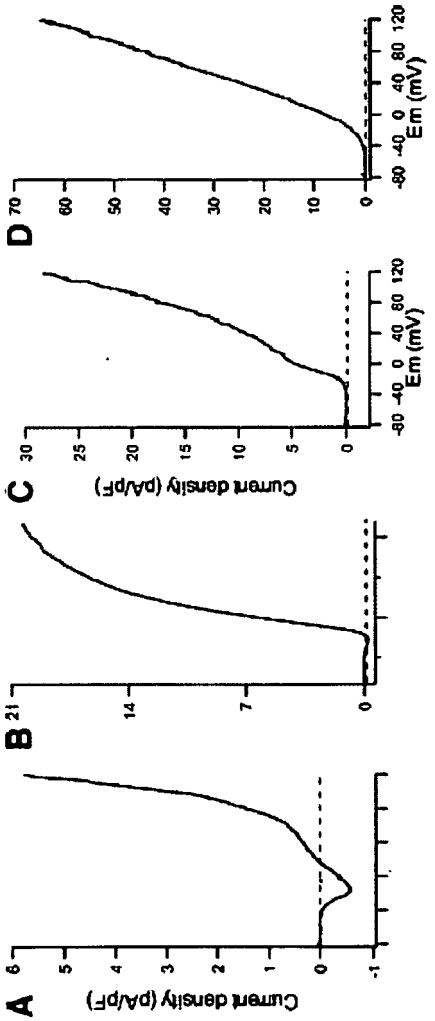
Fig. 2



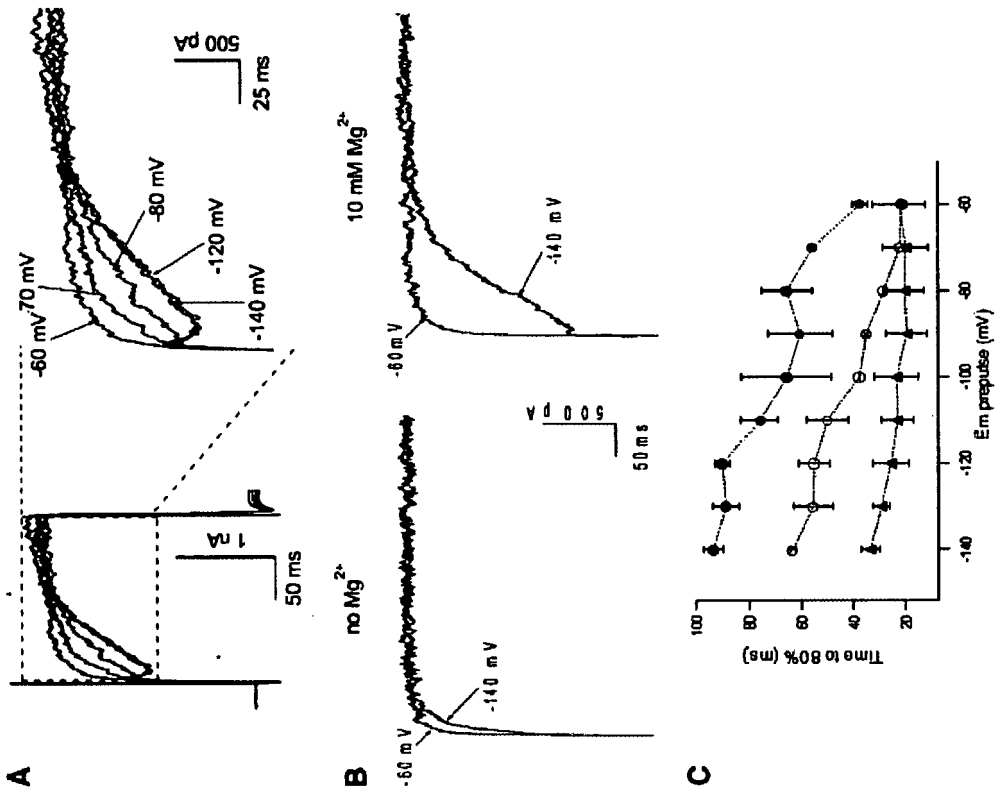

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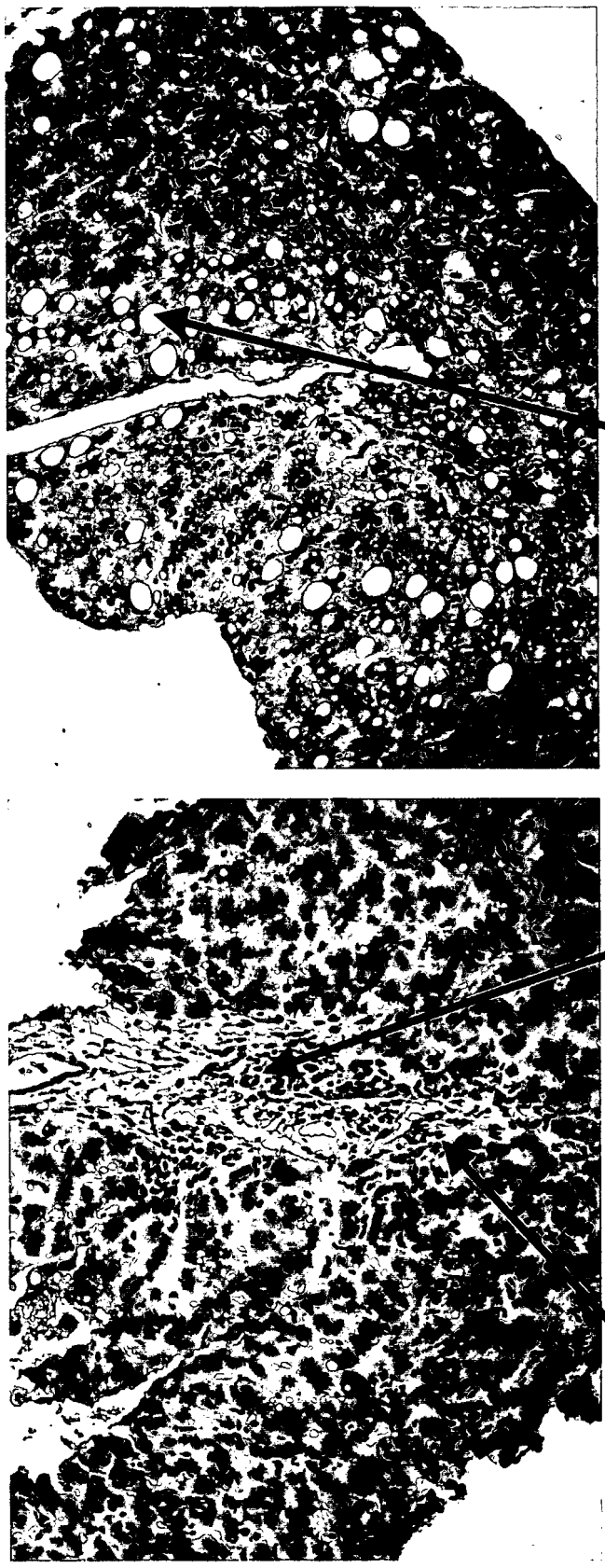
Fig. 3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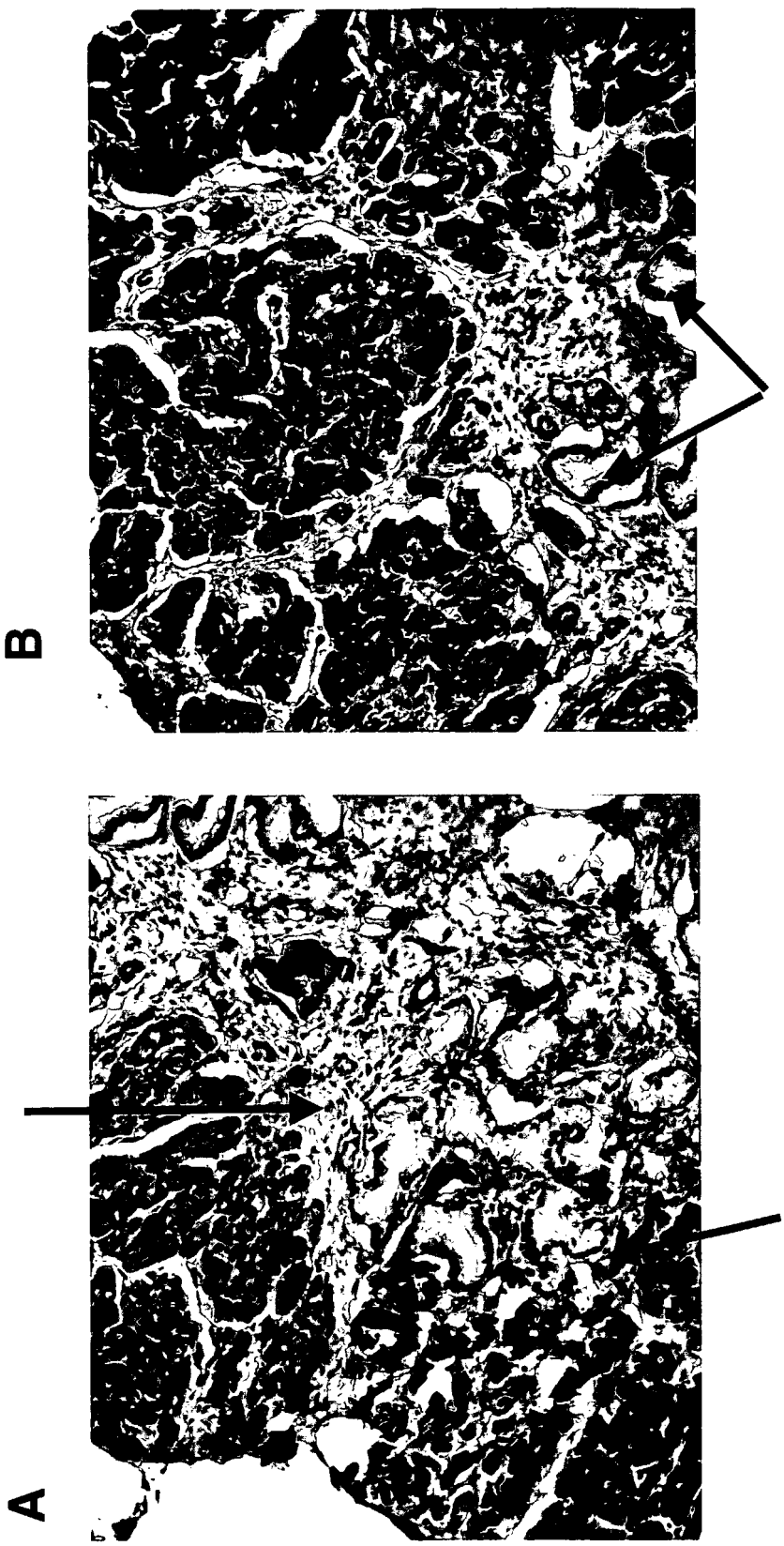
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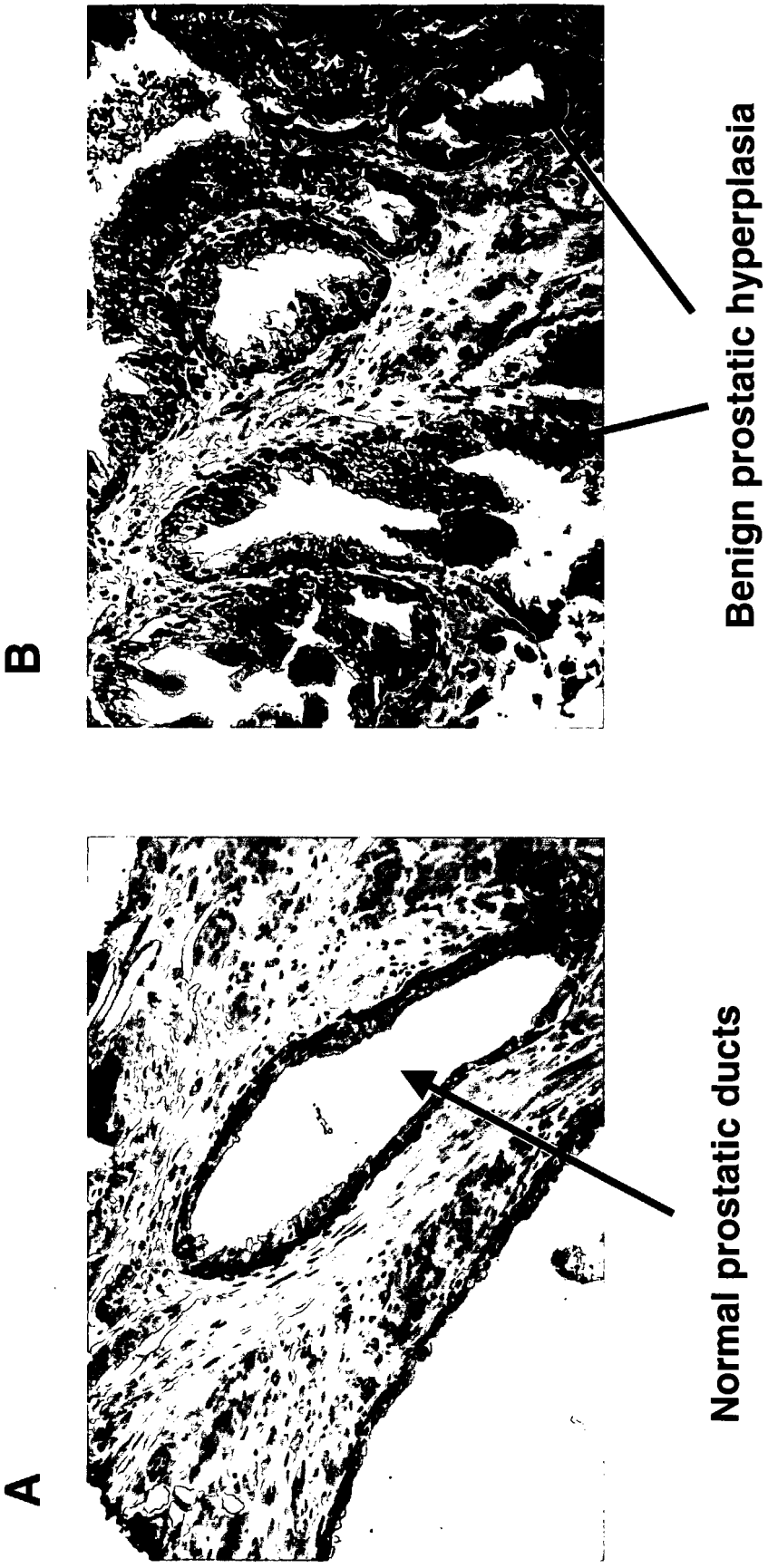
Fig. 5

Fig. 6



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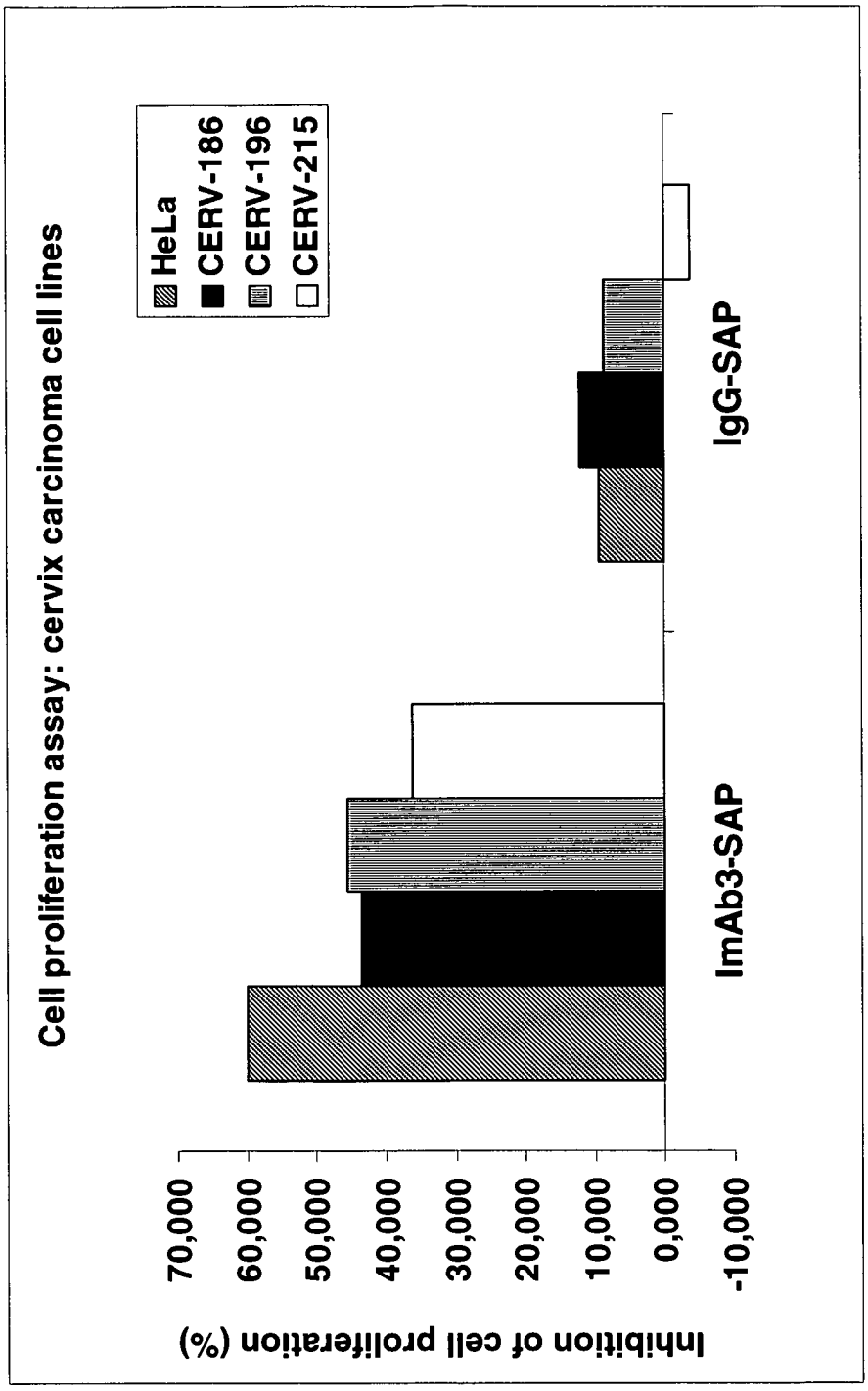
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tcgtaagaag ccgcgccagg acgcccgccg gaccccgagc tgctgggagg atgaccatgg 180

ctgggggcag gaggggacta gtggcccctc aaaacacgtt tctggagaat attgttcggc 240

ggtccaatga tactaatttt gtgttgggga atgctcagat agtggactgg cctattgtgt 300

acagcaatga tggattttgc aagctgtctg gctatcacag ggcagaagtg atgcaaaaaa 360

gcagcacctg cagttttatg tatggggagc tgactgataa agacacgatt gaaaaagtgc 420

ggcaaacatt tgagaactat gagatgaatt cctttgaaat tctgatgtac aagaagaaca 480

ggacacctgt gtggttcttt gtgaaaattg ctccaattcg aaacgaacag gataaagtgg 540

ttttatttct ttgcactttc agtgacataa cagctttcaa acagccaatt gaggatgatt 600

catgtaaagg ctgggggaag tttgctcggc tgacaagagc actgacaagc agcaggggtg 660

tcctgcagca gctggctcca agcgtgcaaa aaggcgagaa tgtccacaag cactcccgcc 720

tggcagaggt cctacagctg ggctcagaca tccttcccca gtacaagcaa gaggcaccaa 780

agactccccc tcacatcatc ttacattatt gtgtttttaa gaccacgtgg gattggatca 840

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Sequence listing K2636 PCT

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<210> 4

<211> 962

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<223> Homo sapiens potassium voltage-gated channel, subfamily H (eag-related), member 1 (KCNH1), transcript variant 2

<400> 4

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Phe Leu Glu Asn Ile Val Arg Arg Ser Asn Asp Thr Asn Phe Val Leu
20 25 30

Gly Asn Ala Gln Ile Val Asp Trp Pro Ile Val Tyr Ser Asn Asp Gly
35 40 45

Phe Cys Lys Leu Ser Gly Tyr His Arg Ala Glu Val Met Gln Lys Ser
50 55 60

Ser Thr Cys Ser Phe Met Tyr Gly Glu Leu Thr Asp Lys Asp Thr Ile
65 70 75 80

Glu Lys Val Arg Gln Thr Phe Glu Asn Tyr Glu Met Asn Ser Phe Glu
85 90 95

Ile Leu Met Tyr Lys Lys Asn Arg Thr Pro Val Trp Phe Phe Val Lys
100 105 110

Ile Ala Pro Ile Arg Asn Glu Gln Asp Lys Val Val Leu Phe Leu Cys
115 120 125

Thr Phe Ser Asp Ile Thr Ala Phe Lys Gln Pro Ile Glu Asp Asp Ser
130 135 140

Cys Lys Gly Trp Gly Lys Phe Ala Arg Leu Thr Arg Ala Leu Thr Ser

145 150 155 160

Ser Arg Gly Val Leu Gln Gln Leu Ala Pro Ser Val Gln Lys Gly Glu
165 170 175

Asn Val His Lys His Ser Arg Leu Ala Glu Val Leu Gln Leu Gly Ser
180 185 190

Asp Ile Leu Pro Gln Tyr Lys Gln Glu Ala Pro Lys Thr Pro Pro His
195 200 205

Ile Ile Leu His Tyr Cys Val Phe Lys Thr Thr Trp Asp Trp Ile Ile
210 215 220

Leu Ile Leu Thr Phe Tyr Thr Ala Ile Leu Val Pro Tyr Asn Val Ser
225 230 235 240

Phe Lys Thr Arg Gln Asn Asn Val Ala Trp Leu Val Val Asp Ser Ile
245 250 255

Val Asp Val Ile Phe Leu Val Asp Ile Val Leu Asn Phe His Thr Thr
260 265 270

Phe Val Gly Pro Ala Gly Glu Val Ile Ser Asp Pro Lys Leu Ile Arg
275 280 285

Met Asn Tyr Leu Lys Thr Trp Phe Val Ile Asp Leu Leu Ser Cys Leu
290 295 300

Pro Tyr Asp Val Ile Asn Ala Phe Glu Asn Val Asp Glu Gly Ile Ser
305 310 315 320

Ser Leu Phe Ser Ser Leu Lys Val Val Arg Leu Leu Arg Leu Gly Arg
325 330 335

Val Ala Arg Lys Leu Asp His Tyr Ile Glu Tyr Gly Ala Ala Val Leu
340 345 350

Val Leu Leu Val Cys Val Phe Gly Leu Ala Ala His Trp Met Ala Cys
355 360 365

Ile Trp Tyr Ser Ile Gly Asp Tyr Glu Ile Phe Asp Glu Asp Thr Lys
370 375 380

Thr Ile Arg Asn Asn Ser Trp Leu Tyr Gln Leu Ala Met Asp Ile Gly
385 390 395 400

Thr Pro Tyr Gln Phe Asn Gly Ser Gly Ser Gly Lys Trp Glu Gly Gly
405 410 415

Pro Ser Lys Asn Ser Val Tyr Ile Ser Ser Leu Tyr Phe Thr Met Thr

420 425 430

Ser Leu Thr Ser Val Gly Phe Gly Asn Ile Ala Pro Ser Thr Asp Ile
435 440 445

Glu Lys Ile Phe Ala Val Ala Ile Met Met Ile Gly Ser Leu Leu Tyr
450 455 460

Ala Thr Ile Phe Gly Asn Val Thr Thr Ile Phe Gln Gln Met Tyr Ala
465 470 475 480

Asn Thr Asn Arg Tyr His Glu Met Leu Asn Ser Val Arg Asp Phe Leu
485 490 495

Lys Leu Tyr Gln Val Pro Lys Gly Leu Ser Glu Arg Val Met Asp Tyr
500 505 510

Ile Val Ser Thr Trp Ser Met Ser Arg Gly Ile Asp Thr Glu Lys Val
515 520 525

Leu Gln Ile Cys Pro Lys Asp Met Arg Ala Asp Ile Cys Val His Leu
530 535 540

Asn Arg Lys Val Phe Lys Glu His Pro Ala Phe Arg Leu Ala Ser Asp
545 550 555 560

Gly Cys Leu Arg Ala Leu Ala Met Glu Phe Gln Thr Val His Cys Ala
565 570 575

Pro Gly Asp Leu Ile Tyr His Ala Gly Glu Ser Val Asp Ser Leu Cys
580 585 590

Phe Val Val Ser Gly Ser Leu Glu Val Ile Gln Asp Asp Glu Val Val
595 600 605

Ala Ile Leu Gly Lys Gly Asp Val Phe Gly Asp Val Phe Trp Lys Glu
610 615 620

Ala Thr Leu Ala Gln Ser Cys Ala Asn Val Arg Ala Leu Thr Tyr Cys
625 630 635 640

Asp Leu His Val Ile Lys Arg Asp Ala Leu Gln Lys Val Leu Glu Phe
645 650 655

Tyr Thr Ala Phe Ser His Ser Phe Ser Arg Asn Leu Ile Leu Thr Tyr
660 665 670

Asn Leu Arg Lys Arg Ile Val Phe Arg Lys Ile Ser Asp Val Lys Arg
675 680 685

Glu Glu Glu Glu Arg Met Lys Arg Lys Asn Glu Ala Pro Leu Ile Leu

690 695 700

Pro Pro Asp His Pro Val Arg Arg Leu Phe Gln Arg Phe Arg Gln Gln
705 710 715 720

Lys Glu Ala Arg Leu Ala Ala Glu Arg Gly Gly Arg Asp Leu Asp Asp
725 730 735

Leu Asp Val Glu Lys Gly Asn Val Leu Thr Glu His Ala Ser Ala Asn
740 745 750

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

Thr Pro Val Ser Phe Gln Ala Ala Ser Thr Ser Gly Val Pro Asp His
770 775 780

Ala Lys Leu Gln Ala Pro Gly Ser Glu Cys Leu Gly Pro Lys Gly Gly
785 790 795 800

Gly Gly Asp Cys Ala Lys Arg Lys Ser Trp Ala Arg Phe Lys Asp Ala
805 810 815

Cys Gly Lys Ser Glu Asp Trp Asn Lys Val Ser Lys Ala Glu Ser Met
820 825 830

Glu Thr Leu Pro Glu Arg Thr Lys Ala Ser Gly Glu Ala Thr Leu Lys
835 840 845

Lys Thr Asp Ser Cys Asp Ser Gly Ile Thr Lys Ser Asp Leu Arg Leu
850 855 860

Asp Asn Val Gly Glu Ala Arg Ser Pro Gln Asp Arg Ser Pro Ile Leu
865 870 875 880

Ala Glu Val Lys His Ser Phe Tyr Pro Ile Pro Glu Gln Thr Leu Gln
885 890 895

Ala Thr Val Leu Glu Val Arg His Glu Leu Lys Glu Asp Ile Lys Ala
900 905 910

Leu Asn Ala Lys Met Thr Asn Ile Glu Lys Gln Leu Ser Glu Ile Leu
915 920 925

Arg Ile Leu Thr Ser Arg Arg Ser Ser Gln Ser Pro Gln Glu Leu Phe
930 935 940

Glu Ile Ser Arg Pro Gln Ser Pro Glu Ser Glu Arg Asp Ile Phe Gly
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Sequence listing K2636 PCT

<210> 5

<211> 3191

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Homo sapiens potassium voltage-gated channel, subfamily H (eag-related), member 2 (KCNH2), transcript variant 3

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<211> 819

Sequence listing K2636 PCT

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<223> Homo sapiens potassium voltage-gated channel, subfamily H (eag-related), member 2 (KCNH2), transcript variant 3

<400> 6

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Arg Ala Gln Lys Gly Arg Val Arg Arg Ala Val Arg Ile Ser Ser Leu
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Val Ala Gln Glu Val Leu Ser Leu Gly Ala Asp Val Leu Pro Glu Tyr
        35                  40                  45

Lys Leu Gln Ala Pro Arg Ile His Arg Trp Thr Ile Leu His Tyr Ser
    50                  55                  60

Pro Phe Lys Ala Val Trp Asp Trp Leu Ile Leu Leu Leu Val Ile Tyr
65                  70                  75                  80

Thr Ala Val Phe Thr Pro Tyr Ser Ala Ala Phe Leu Leu Lys Glu Thr
                85                  90                  95

Glu Glu Gly Pro Pro Ala Thr Glu Cys Gly Tyr Ala Cys Gln Pro Leu
            100                 105                 110

Ala Val Val Asp Leu Ile Val Asp Ile Met Phe Ile Val Asp Ile Leu
        115                 120                 125

Ile Asn Phe Arg Thr Thr Tyr Val Asn Ala Asn Glu Glu Val Val Ser
    130                 135                 140

His Pro Gly Arg Ile Ala Val His Tyr Phe Lys Gly Trp Phe Leu Ile
145                 150                 155                 160

Asp Met Val Ala Ala Ile Pro Phe Asp Leu Leu Ile Phe Gly Ser Gly
                165                 170                 175

Ser Glu Glu Leu Ile Gly Leu Leu Lys Thr Ala Arg Leu Leu Arg Leu
            180                 185                 190

Val Arg Val Ala Arg Lys Leu Asp Arg Tyr Ser Glu Tyr Gly Ala Ala
        195                 200                 205
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Sequence listing K2636 PCT

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Val Leu Phe Leu Leu Met Cys Thr Phe Ala Leu Ile Ala His Trp Leu
    210                 215                 220

Ala Cys Ile Trp Tyr Ala Ile Gly Asn Met Glu Gln Pro His Met Asp
225                 230                 235                 240

Ser Arg Ile Gly Trp Leu His Asn Leu Gly Asp Gln Ile Gly Lys Pro
                245                 250                 255

Tyr Asn Ser Ser Gly Leu Gly Gly Pro Ser Ile Lys Asp Lys Tyr Val
            260                 265                 270

Thr Ala Leu Tyr Phe Thr Phe Ser Ser Leu Thr Ser Val Gly Phe Gly
        275                 280                 285

Asn Val Ser Pro Asn Thr Asn Ser Glu Lys Ile Phe Ser Ile Cys Val
    290                 295                 300

Met Leu Ile Gly Ser Leu Met Tyr Ala Ser Ile Phe Gly Asn Val Ser
305                 310                 315                 320

Ala Ile Ile Gln Arg Leu Tyr Ser Gly Thr Ala Arg Tyr His Thr Gln
                325                 330                 335

Met Leu Arg Val Arg Glu Phe Ile Arg Phe His Gln Ile Pro Asn Pro
            340                 345                 350

Leu Arg Gln Arg Leu Glu Glu Tyr Phe Gln His Ala Trp Ser Tyr Thr
        355                 360                 365

Asn Gly Ile Asp Met Asn Ala Val Leu Lys Gly Phe Pro Glu Cys Leu
    370                 375                 380

Gln Ala Asp Ile Cys Leu His Leu Asn Arg Ser Leu Leu Gln His Cys
385                 390                 395                 400

Lys Pro Phe Arg Gly Ala Thr Lys Gly Cys Leu Arg Ala Leu Ala Met
                405                 410                 415

Lys Phe Lys Thr Thr His Ala Pro Pro Gly Asp Thr Leu Val His Ala
            420                 425                 430

Gly Asp Leu Leu Thr Ala Leu Tyr Phe Ile Ser Arg Gly Ser Ile Glu
        435                 440                 445

Ile Leu Arg Gly Asp Val Val Val Ala Ile Leu Gly Lys Asn Asp Ile
    450                 455                 460

Phe Gly Glu Pro Leu Asn Leu Tyr Ala Arg Pro Gly Lys Ser Asn Gly
465                 470                 475                 480
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Sequence listing K2636 PCT

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Asp Val Arg Ala Leu Thr Tyr Cys Asp Leu His Lys Ile His Arg Asp
                485                 490                 495

Asp Leu Leu Glu Val Leu Asp Met Tyr Pro Glu Phe Ser Asp His Phe
            500                 505                 510

Trp Ser Ser Leu Glu Ile Thr Phe Asn Leu Arg Asp Thr Asn Met Ile
        515                 520                 525

Pro Gly Ser Pro Gly Ser Thr Glu Leu Glu Gly Gly Phe Ser Arg Gln
    530                 535                 540

Arg Lys Arg Lys Leu Ser Phe Arg Arg Arg Thr Asp Lys Asp Thr Glu
545                 550                 555                 560

Gln Pro Gly Glu Val Ser Ala Leu Gly Pro Gly Arg Ala Gly Ala Gly
                565                 570                 575

Pro Ser Ser Arg Gly Arg Pro Gly Gly Pro Trp Gly Glu Ser Pro Ser
            580                 585                 590

Ser Gly Pro Ser Ser Pro Glu Ser Ser Glu Asp Glu Gly Pro Gly Arg
        595                 600                 605

Ser Ser Ser Pro Leu Arg Leu Val Pro Phe Ser Ser Pro Arg Pro Pro
    610                 615                 620

Gly Glu Pro Pro Gly Gly Glu Pro Leu Met Glu Asp Cys Glu Lys Ser
625                 630                 635                 640

Ser Asp Thr Cys Asn Pro Leu Ser Gly Ala Phe Ser Gly Val Ser Asn
                645                 650                 655

Ile Phe Ser Phe Trp Gly Asp Ser Arg Gly Arg Gln Tyr Gln Glu Leu
            660                 665                 670

Pro Arg Cys Pro Ala Pro Thr Pro Ser Leu Leu Asn Ile Pro Leu Ser
        675                 680                 685

Ser Pro Gly Arg Arg Pro Arg Gly Asp Val Glu Ser Arg Leu Asp Ala
    690                 695                 700

Leu Gln Arg Gln Leu Asn Arg Leu Glu Thr Arg Leu Ser Ala Asp Met
705                 710                 715                 720

Ala Thr Val Leu Gln Leu Leu Gln Arg Gln Met Thr Leu Val Pro Pro
                725                 730                 735

Ala Tyr Ser Ala Val Thr Thr Pro Gly Pro Gly Pro Thr Ser Thr Ser
            740                 745                 750
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Sequence listing K2636 PCT

Pro Leu Leu Pro Val Ser Pro Leu Pro Thr Leu Thr Leu Asp Ser Leu
755 760 765

Ser Gln Val Ser Gln Phe Met Ala Cys Glu Glu Leu Pro Pro Gly Ala
770 775 780

Pro Glu Leu Pro Gln Glu Gly Pro Thr Arg Arg Leu Ser Leu Pro Gly
785 790 795 800

Gln Leu Gly Ala Leu Thr Ser Gln Pro Leu His Arg His Gly Ser Asp
805 810 815

Pro Gly Ser

<210> 7

<211> 3164

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Homo sapiens potassium voltage-gated channel, subfamily H (eag-related), member 2 (KCNH2), transcript variant 2

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ggagaactgc gccgtcatct actgcaacga cggcttctgc gagctgtgcg gctactcgcg 180

ggccgaggtg atgcagcgac cctgcacctg cgacttcctg cacgggccgc gcacgcagcg 240

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cgccttctac cggaaagatg ggagctgctt cctatgtctg gtggatgtgg tgcccgtgaa 360

gaacgaggat ggggctgtca tcatgttcat cctcaatttc gaggtggtga tggagaagga 420

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gctggtcatc tacacggctg tcttcacacc ctactcggct gccttcctgc tgaaggagac 1320

ggaagaaggc ccgcctgcta ccgagtgtgg ctacgcctgc cagccgctgg ctgtggtgga 1380

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tcagctctgt acaaacacaa atacacaccc ccacaaaact aaaatcaaag tttcactaca 3060

taacactggg ccttactgca tgtggttcat tctagcattt ctgttctgtg ctgtgctaag 3120

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<210> 8

<211> 888

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<223> Homo sapiens potassium voltage-gated channel, subfamily H (eag-related), member 2 (KCNH2), transcript variant 2

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Thr Ile Ile Arg Lys Phe Glu Gly Gln Ser Arg Lys Phe Ile Ile Ala
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Asn Ala Arg Val Glu Asn Cys Ala Val Ile Tyr Cys Asn Asp Gly Phe
35 40 45

Cys Glu Leu Cys Gly Tyr Ser Arg Ala Glu Val Met Gln Arg Pro Cys
50 55 60

Thr Cys Asp Phe Leu His Gly Pro Arg Thr Gln Arg Arg Ala Ala Ala
65 70 75 80

Gln Ile Ala Gln Ala Leu Leu Gly Ala Glu Glu Arg Lys Val Glu Ile
85 90 95

Ala Phe Tyr Arg Lys Asp Gly Ser Cys Phe Leu Cys Leu Val Asp Val
100 105 110

Val Pro Val Lys Asn Glu Asp Gly Ala Val Ile Met Phe Ile Leu Asn
115 120 125

Phe Glu Val Val Met Glu Lys Asp Met Val Gly Ser Pro Ala His Asp
130 135 140

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Thr Asn His Arg Gly Pro Pro Thr Ser Trp Leu Ala Pro Gly Arg Ala
145                 150                 155                 160

Lys Thr Phe Arg Leu Lys Leu Pro Ala Leu Leu Ala Leu Thr Ala Arg
                165                 170                 175

Glu Ser Ser Val Arg Ser Gly Gly Ala Gly Gly Ala Gly Ala Pro Gly
            180                 185                 190

Ala Val Val Val Asp Val Asp Leu Thr Pro Ala Ala Pro Ser Ser Glu
        195                 200                 205

Ser Leu Ala Leu Asp Glu Val Thr Ala Met Asp Asn His Val Ala Gly
    210                 215                 220

Leu Gly Pro Ala Glu Glu Arg Arg Ala Leu Val Gly Pro Gly Ser Pro
225                 230                 235                 240

Pro Arg Ser Ala Pro Gly Gln Leu Pro Ser Pro Arg Ala His Ser Leu
                245                 250                 255

Asn Pro Asp Ala Ser Gly Ser Ser Cys Ser Leu Ala Arg Thr Arg Ser
            260                 265                 270

Arg Glu Ser Cys Ala Ser Val Arg Arg Ala Ser Ser Ala Asp Asp Ile
        275                 280                 285

Glu Ala Met Arg Ala Gly Val Leu Pro Pro Pro Pro Arg His Ala Ser
    290                 295                 300

Thr Gly Ala Met His Pro Leu Arg Ser Gly Leu Leu Asn Ser Thr Ser
305                 310                 315                 320

Asp Ser Asp Leu Val Arg Tyr Arg Thr Ile Ser Lys Ile Pro Gln Ile
                325                 330                 335

Thr Leu Asn Phe Val Asp Leu Lys Gly Asp Pro Phe Leu Ala Ser Pro
            340                 345                 350

Thr Ser Asp Arg Glu Ile Ile Ala Pro Lys Ile Lys Glu Arg Thr His
        355                 360                 365

Asn Val Thr Glu Lys Val Thr Gln Val Leu Ser Leu Gly Ala Asp Val
    370                 375                 380

Leu Pro Glu Tyr Lys Leu Gln Ala Pro Arg Ile His Arg Trp Thr Ile
385                 390                 395                 400

Leu His Tyr Ser Pro Phe Lys Ala Val Trp Asp Trp Leu Ile Leu Leu
                405                 410                 415
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Sequence listing K2636 PCT

Leu Val Ile Tyr Thr Ala Val Phe Thr Pro Tyr Ser Ala Ala Phe Leu
420 425 430

Leu Lys Glu Thr Glu Glu Gly Pro Pro Ala Thr Glu Cys Gly Tyr Ala
435 440 445

Cys Gln Pro Leu Ala Val Val Asp Leu Ile Val Asp Ile Met Phe Ile
450 455 460

Val Asp Ile Leu Ile Asn Phe Arg Thr Thr Tyr Val Asn Ala Asn Glu
465 470 475 480

Glu Val Val Ser His Pro Gly Arg Ile Ala Val His Tyr Phe Lys Gly
485 490 495

Trp Phe Leu Ile Asp Met Val Ala Ala Ile Pro Phe Asp Leu Leu Ile
500 505 510

Phe Gly Ser Gly Ser Glu Glu Leu Ile Gly Leu Leu Lys Thr Ala Arg
515 520 525

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

Tyr Gly Ala Ala Val Leu Phe Leu Leu Met Cys Thr Phe Ala Leu Ile
545 550 555 560

Ala His Trp Leu Ala Cys Ile Trp Tyr Ala Ile Gly Asn Met Glu Gln
565 570 575

Pro His Met Asp Ser Arg Ile Gly Trp Leu His Asn Leu Gly Asp Gln
580 585 590

Ile Gly Lys Pro Tyr Asn Ser Ser Gly Leu Gly Gly Pro Ser Ile Lys
595 600 605

Asp Lys Tyr Val Thr Ala Leu Tyr Phe Thr Phe Ser Ser Leu Thr Ser
610 615 620

Val Gly Phe Gly Asn Val Ser Pro Asn Thr Asn Ser Glu Lys Ile Phe
625 630 635 640

Ser Ile Cys Val Met Leu Ile Gly Ser Leu Met Tyr Ala Ser Ile Phe
645 650 655

Gly Asn Val Ser Ala Ile Ile Gln Arg Leu Tyr Ser Gly Thr Ala Arg
660 665 670

Tyr His Thr Gln Met Leu Arg Val Arg Glu Phe Ile Arg Phe His Gln
675 680 685

Ile Pro Asn Pro Leu Arg Gln Arg Leu Glu Glu Tyr Phe Gln His Ala
690 695 700

Trp Ser Tyr Thr Asn Gly Ile Asp Met Asn Ala Val Leu Lys Gly Phe
705 710 715 720

Pro Glu Cys Leu Gln Ala Asp Ile Cys Leu His Leu Asn Arg Ser Leu
725 730 735

Leu Gln His Cys Lys Pro Phe Arg Gly Ala Thr Lys Gly Cys Leu Arg
740 745 750

Ala Leu Ala Met Lys Phe Lys Thr Thr His Ala Pro Pro Gly Asp Thr
755 760 765

Leu Val His Ala Gly Asp Leu Leu Thr Ala Leu Tyr Phe Ile Ser Arg
770 775 780

Gly Ser Ile Glu Ile Leu Arg Gly Asp Val Val Val Ala Ile Leu Gly
785 790 795 800

Met Gly Trp Gly Ala Gly Thr Gly Leu Glu Met Pro Ser Ala Ala Ser
805 810 815

Arg Gly Ala Ser Leu Leu Asn Met Gln Ser Leu Gly Leu Trp Thr Trp
820 825 830

Asp Cys Leu Gln Gly His Trp Ala Pro Leu Ile His Leu Asn Ser Gly
835 840 845

Pro Pro Ser Gly Ala Met Glu Arg Ser Pro Thr Trp Gly Glu Ala Ala
850 855 860

Glu Leu Trp Gly Ser His Ile Leu Leu Pro Phe Arg Ile Arg His Lys
865 870 875 880

Gln Thr Leu Phe Ala Ser Leu Lys
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<210> 9

<211> 3900

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Homo sapiens potassium voltage-gated channel, subfamily H (eag-re

Sequence listing K2636 PCT
lated), member 2 (KCNH2), transcript variant 1

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Sequence listing K2636 PCT

<210> 10

<211> 1159

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<223> Homo sapiens potassium voltage-gated channel, subfamily H (eag-related), member 2 (KCNH2), transcript variant 1

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Thr Ile Ile Arg Lys Phe Glu Gly Gln Ser Arg Lys Phe Ile Ile Ala
            20                  25                  30

Asn Ala Arg Val Glu Asn Cys Ala Val Ile Tyr Cys Asn Asp Gly Phe
        35                  40                  45

Cys Glu Leu Cys Gly Tyr Ser Arg Ala Glu Val Met Gln Arg Pro Cys
    50                  55                  60

Thr Cys Asp Phe Leu His Gly Pro Arg Thr Gln Arg Arg Ala Ala Ala
65                  70                  75                  80

Gln Ile Ala Gln Ala Leu Leu Gly Ala Glu Glu Arg Lys Val Glu Ile
                85                  90                  95

Ala Phe Tyr Arg Lys Asp Gly Ser Cys Phe Leu Cys Leu Val Asp Val
            100                 105                 110

Val Pro Val Lys Asn Glu Asp Gly Ala Val Ile Met Phe Ile Leu Asn
        115                 120                 125

Phe Glu Val Val Met Glu Lys Asp Met Val Gly Ser Pro Ala His Asp
    130                 135                 140

Thr Asn His Arg Gly Pro Pro Thr Ser Trp Leu Ala Pro Gly Arg Ala
145                 150                 155                 160

Lys Thr Phe Arg Leu Lys Leu Pro Ala Leu Leu Ala Leu Thr Ala Arg
                165                 170                 175

Glu Ser Ser Val Arg Ser Gly Gly Ala Gly Gly Ala Gly Ala Pro Gly
            180                 185                 190
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Sequence listing K2636 PCT

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Ser Leu Ala Leu Asp Glu Val Thr Ala Met Asp Asn His Val Ala Gly
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225 230 235 240

Pro Arg Ser Ala Pro Gly Gln Leu Pro Ser Pro Arg Ala His Ser Leu
245 250 255

Asn Pro Asp Ala Ser Gly Ser Ser Cys Ser Leu Ala Arg Thr Arg Ser
260 265 270

Arg Glu Ser Cys Ala Ser Val Arg Arg Ala Ser Ser Ala Asp Asp Ile
275 280 285

Glu Ala Met Arg Ala Gly Val Leu Pro Pro Pro Pro Arg His Ala Ser
290 295 300

Thr Gly Ala Met His Pro Leu Arg Ser Gly Leu Leu Asn Ser Thr Ser
305 310 315 320

Asp Ser Asp Leu Val Arg Tyr Arg Thr Ile Ser Lys Ile Pro Gln Ile
325 330 335

Thr Leu Asn Phe Val Asp Leu Lys Gly Asp Pro Phe Leu Ala Ser Pro
340 345 350

Thr Ser Asp Arg Glu Ile Ile Ala Pro Lys Ile Lys Glu Arg Thr His
355 360 365

Asn Val Thr Glu Lys Val Thr Gln Val Leu Ser Leu Gly Ala Asp Val
370 375 380

Leu Pro Glu Tyr Lys Leu Gln Ala Pro Arg Ile His Arg Trp Thr Ile
385 390 395 400

Leu His Tyr Ser Pro Phe Lys Ala Val Trp Asp Trp Leu Ile Leu Leu
405 410 415

Leu Val Ile Tyr Thr Ala Val Phe Thr Pro Tyr Ser Ala Ala Phe Leu
420 425 430

Leu Lys Glu Thr Glu Glu Gly Pro Pro Ala Thr Glu Cys Gly Tyr Ala
435 440 445

Cys Gln Pro Leu Ala Val Val Asp Leu Ile Val Asp Ile Met Phe Ile
450 455 460

Sequence listing K2636 PCT

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

Trp Phe Leu Ile Asp Met Val Ala Ala Ile Pro Phe Asp Leu Leu Ile
500 505 510

Phe Gly Ser Gly Ser Glu Glu Leu Ile Gly Leu Leu Lys Thr Ala Arg
515 520 525

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

Tyr Gly Ala Ala Val Leu Phe Leu Leu Met Cys Thr Phe Ala Leu Ile
545 550 555 560

Ala His Trp Leu Ala Cys Ile Trp Tyr Ala Ile Gly Asn Met Glu Gln
565 570 575

Pro His Met Asp Ser Arg Ile Gly Trp Leu His Asn Leu Gly Asp Gln
580 585 590

Ile Gly Lys Pro Tyr Asn Ser Ser Gly Leu Gly Gly Pro Ser Ile Lys
595 600 605

Asp Lys Tyr Val Thr Ala Leu Tyr Phe Thr Phe Ser Ser Leu Thr Ser
610 615 620

Val Gly Phe Gly Asn Val Ser Pro Asn Thr Asn Ser Glu Lys Ile Phe
625 630 635 640

Ser Ile Cys Val Met Leu Ile Gly Ser Leu Met Tyr Ala Ser Ile Phe
645 650 655

Gly Asn Val Ser Ala Ile Ile Gln Arg Leu Tyr Ser Gly Thr Ala Arg
660 665 670

Tyr His Thr Gln Met Leu Arg Val Arg Glu Phe Ile Arg Phe His Gln
675 680 685

Ile Pro Asn Pro Leu Arg Gln Arg Leu Glu Glu Tyr Phe Gln His Ala
690 695 700

Trp Ser Tyr Thr Asn Gly Ile Asp Met Asn Ala Val Leu Lys Gly Phe
705 710 715 720

Pro Glu Cys Leu Gln Ala Asp Ile Cys Leu His Leu Asn Arg Ser Leu
725 730 735

Leu Gln His Cys Lys Pro Phe Arg Gly Ala Thr Lys Gly Cys Leu Arg
740 745 750

Ala Leu Ala Met Lys Phe Lys Thr Thr His Ala Pro Pro Gly Asp Thr
755 760 765

Leu Val His Ala Gly Asp Leu Leu Thr Ala Leu Tyr Phe Ile Ser Arg
770 775 780

Gly Ser Ile Glu Ile Leu Arg Gly Asp Val Val Val Ala Ile Leu Gly
785 790 795 800

Lys Asn Asp Ile Phe Gly Glu Pro Leu Asn Leu Tyr Ala Arg Pro Gly
805 810 815

Lys Ser Asn Gly Asp Val Arg Ala Leu Thr Tyr Cys Asp Leu His Lys
820 825 830

Ile His Arg Asp Asp Leu Leu Glu Val Leu Asp Met Tyr Pro Glu Phe
835 840 845

Ser Asp His Phe Trp Ser Ser Leu Glu Ile Thr Phe Asn Leu Arg Asp
850 855 860

Thr Asn Met Ile Pro Gly Ser Pro Gly Ser Thr Glu Leu Glu Gly Gly
865 870 875 880

Phe Ser Arg Gln Arg Lys Arg Lys Leu Ser Phe Arg Arg Arg Thr Asp
885 890 895

Lys Asp Thr Glu Gln Pro Gly Glu Val Ser Ala Leu Gly Pro Gly Arg
900 905 910

Ala Gly Ala Gly Pro Ser Ser Arg Gly Arg Pro Gly Gly Pro Trp Gly
915 920 925

Glu Ser Pro Ser Ser Gly Pro Ser Ser Pro Glu Ser Ser Glu Asp Glu
930 935 940

Gly Pro Gly Arg Ser Ser Ser Pro Leu Arg Leu Val Pro Phe Ser Ser
945 950 955 960

Pro Arg Pro Pro Gly Glu Pro Pro Gly Gly Glu Pro Leu Met Glu Asp
965 970 975

Cys Glu Lys Ser Ser Asp Thr Cys Asn Pro Leu Ser Gly Ala Phe Ser
980 985 990

Gly Val Ser Asn Ile Phe Ser Phe Trp Gly Asp Ser Arg Gly Arg Gln
995 1000 1005

Tyr Gln Glu Leu Pro Arg Cys Pro Ala Pro Thr Pro Ser Leu Leu
1010 1015 1020

Asn Ile Pro Leu Ser Ser Pro Gly Arg Arg Pro Arg Gly Asp Val
1025 1030 1035

Glu Ser Arg Leu Asp Ala Leu Gln Arg Gln Leu Asn Arg Leu Glu
1040 1045 1050

Thr Arg Leu Ser Ala Asp Met Ala Thr Val Leu Gln Leu Leu Gln
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Arg Gln Met Thr Leu Val Pro Pro Ala Tyr Ser Ala Val Thr Thr
1070 1075 1080

Pro Gly Pro Gly Pro Thr Ser Thr Ser Pro Leu Leu Pro Val Ser
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Pro Leu Pro Thr Leu Thr Leu Asp Ser Leu Ser Gln Val Ser Gln
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Phe Met Ala Cys Glu Glu Leu Pro Pro Gly Ala Pro Glu Leu Pro
1115 1120 1125

Gln Glu Gly Pro Thr Arg Arg Leu Ser Leu Pro Gly Gln Leu Gly
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Ser

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<211> 21

<212> DNA

<213> Homo sapiens

<220>

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<223> RT-PCR primer for amplification of EAG1 fragments (sense)

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<210> 12

Sequence listing K2636 PCT

<211> 21

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<400> 13
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