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(54) **SINGLE NUCLEOTIDE POLYMORPHISMS OF HUMAN CHROMOSOME 4 IN THE INOSITOL POLYPHOSPHATE-4-PHOSPHATASE TYPE II GENE (INPP4B GENE) FOR THE DIAGNOSIS OR PRE-DIAGNOSIS OF MULTIPLE SCLEROSIS**

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(57) **ABSTRACT**

The invention relates to a single nucleotide polymorphism (SNP) of the nucleobase at base position 143470133 (rs13102150) of human chromosome 4 in the inositol polyphosphate 4-phosphatase type II gene (INPP4b gene) for the diagnosis or pre-diagnosis of multiple sclerosis or for determining the risk of contracting multiple sclerosis.

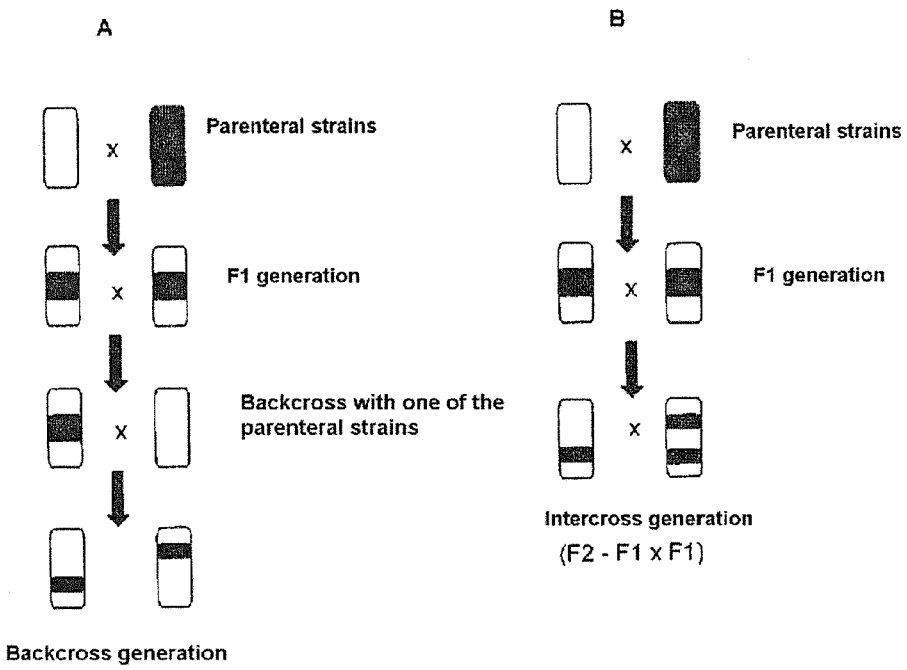
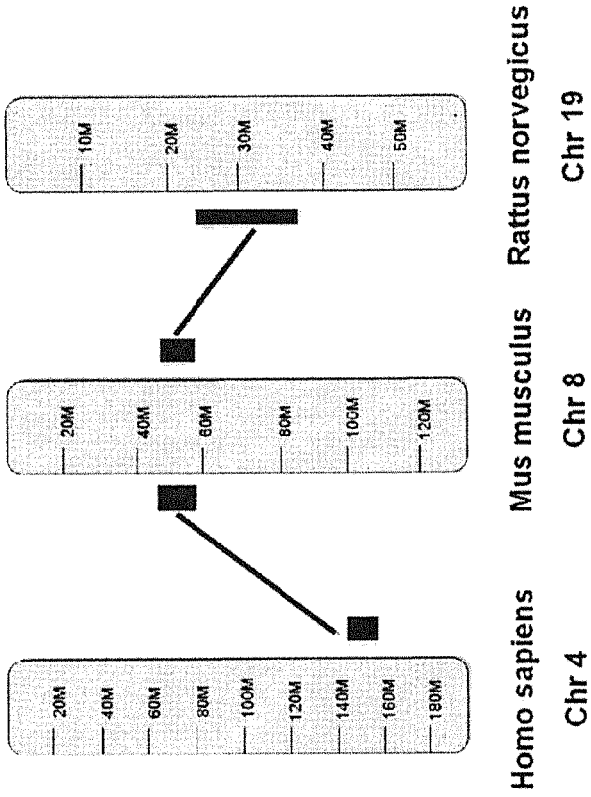

A
Parenteral strains
F1 generation
Backcross with one of the parenteral strains
Backcross generation
B
Parenteral strains
F1 generation
Intercross generation
(F2 - F1 x F1)

FIG. 1


Homo sapiens
Chr 4
20M
40M
60M
80M
100M
120M
140M
160M
180M
Mus musculus
Chr 8
20M
40M
60M
80M
100M
120M
Rattus norvegicus
Chr 19
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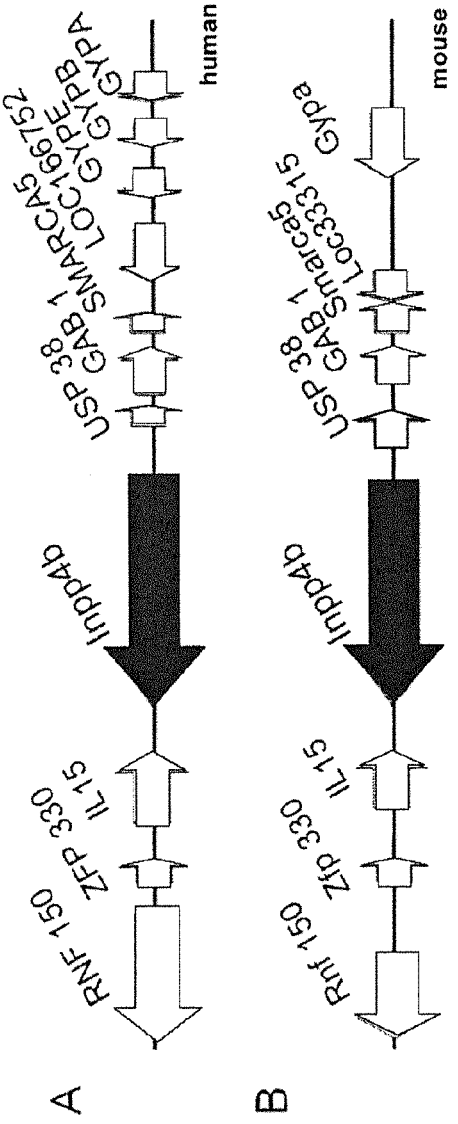
20M
30M
40M
50M

FIG. 2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USP38
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SMARCA5
LOC100652752
GYPA
GYPB
Inpp4b
RNF150
ZFP330
IL15
A
mouse
USP38
GABARAPL1
SMARCA5
LOC633315
GYPA
Inpp4b
Rnf150
Zfp330
IL15
B

FIG. 3

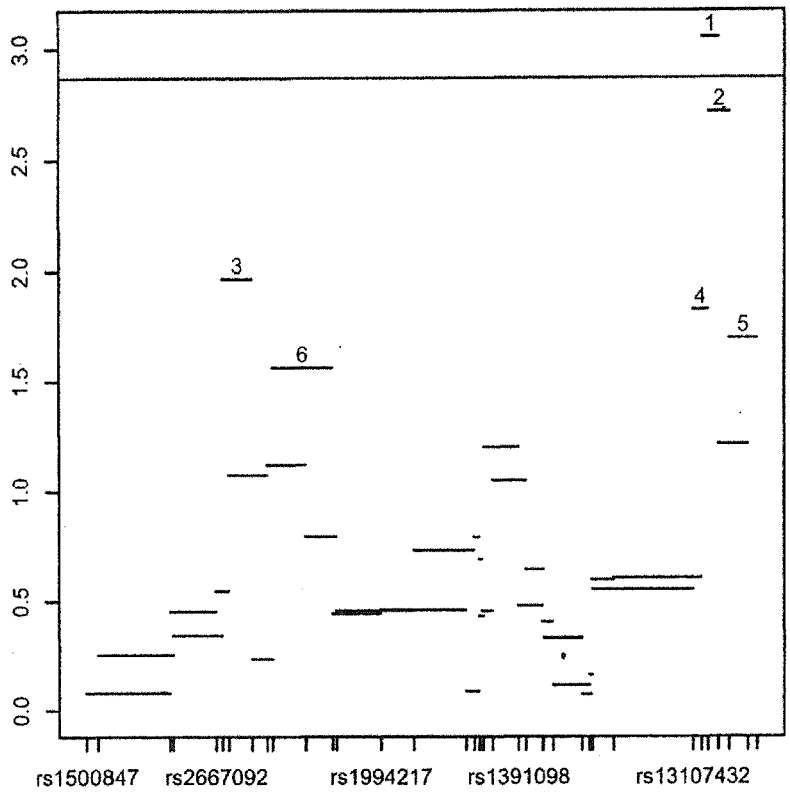
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1
2
3
4
5
6
rs1500847
rs2667092
rs1994217
rs1391098
rs13107432

FIG. 4

SINGLE NUCLEOTIDE POLYMORPHISMS OF HUMAN CHROMOSOME 4 IN THE INOSITOL POLYPHOSPHATE-4-PHOSPHATASE TYPE II GENE (INPP4B GENE) FOR THE DIAGNOSIS OR PRE-DIAGNOSIS OF MULTIPLE SCLEROSIS

[0001] The invention relates to a single nucleotide polymorphism (SNP) of the nucleobase at base position 143470133 (rs13102150) of human chromosome 4 in the inositol polyphosphate 4-phosphatase type II gene (INPP4b gene) for the diagnosis or pre-diagnosis of multiple sclerosis or for determining the risk of contracting multiple sclerosis.

[0002] Diseases which cause degeneration of the nerve tissue cover a wide range of different disorders in young and older people. Such diseases result in a decrease in functionally active neurons in the brain and/or bone marrow. Neurons can die off for various reasons: depositing of proteins or protein fragments, metabolic failure, toxins, inflammations, blood circulation disorders or head injuries. All these factors bring about a far-reaching loss of neurons and glia cells, for example in the event of a stroke. In other cases they cause a loss of specific groups of neurons and functional systems, in Parkinson's disease (PD) or amyotrophic lateral sclerosis (ALS) for instance.

[0003] Nevertheless, the clinical features and/or characteristics of the individual diseases are often almost indistinguishable. This causes difficulty when attempting to make a clear diagnosis. Furthermore, the course of different diseases varies greatly. Thus, in the case of some rare diseases the precise disease can often only be determined as part of an autopsy.

[0004] In the young population multiple sclerosis (MS) is the most frequently occurring of the neurodegenerative diseases. Multiple sclerosis is a chronic-inflammatory autoimmune disease of the central nervous system (CNS). It is characterised by the destruction of the myelin sheaths which surround the axons of the nerve cells. In the early stages of MS the patients often recover fully from the symptoms. However, the structural damage remains and with every further recurrence the probability of clinical damage increases. In most cases the damage is restricted to focal areas of the white matter. The structural changes give rise to various clinical symptoms, for example vision disorders, walking problems, ataxia, paraesthesia, muscle weakness and paresis, as well as speech and coordination problems, and also psychiatric difficulties. The cause of MS is still unknown.

[0005] In young adults the disease often already begins between the ages of 20 and 30 years, with considerably more women being affected. MS is an autoimmune disease which is structurally characterised by infiltration of peripheral inflammatory cells, which are usually T and B-lymphocytes. These cells are found in the white matter at local destruction points where they attack myelin sheaths. Destruction of the myelin affects the isolation of the axons. In the healthy state action potentials are transmitted by saltatory conduction at the Ranvier nodes. These nodes exhibit no or only slight myelination between two oligodendrocytes on one axon. Damaged isolation not only disrupts saltatory conduction, but due to the change in the ion concentration it also leads to metabolic problems.

[0006] With regard to the cause of MS there are only a few conjectures that a genetic predisposition or environmental influences could play a role in the course of the disease. An involvement of biological factors is also being discussed.

[0007] Particularly a genetic indicator for MS would be desirable as in this way a clear diagnosis would be possible. The approaches to date show that an increased risk of developing MS is associated with the presence of the human leukocyte antigen (HLA) DR2. HLA-DR2 is one of the definitive genetic indicators for MS in the HLA region. In addition to the HLA-DR2 haplotype other loci also modulate the susceptibility to MS in the HLA region, for example HLA-DR3. However, genomic studies show that further genetic factors also contribute to a susceptibility to MS. Endeavours are therefore being made to find other genetic factors.

[0008] The aim of the present invention was to find further genetic indictors which are associated with multiple sclerosis.

[0009] In humans this aim was achieved by a single nucleotide polymorphism (SNP) of the nucleobase at base position 143470133 (rs13102150) of human chromosome 4 in the inositol polyphosphate-4-phosphatase type II gene (INPP4b gene) which serves or is used to diagnose or pre-diagnose multiple sclerosis or to determine the risk of developing multiple sclerosis.

[0010] The search for genes which are involved in a polygenic disease such as MS is very complicated and extensive. A combination of mapping strategies was employed, whereby an animal model was initially used. Experimental autoimmune encephalomyelitis (EAE) is an animal model for MS. Thereby the disease can be induced in various species ranging from mice to higher primates. The animal model correlates with the human disease to a large extent, for example in terms of acute, chronic dysfunction with relapses and recovery phases as well as demyelination in the white matter of the CNS. In mice EAE can be induced in two different ways, i.e. by means of active or adaptive immunisation. The active inoculation includes immunisation with autoantigens of myelin proteins or with bone marrow homongenisates. Adaptive immunisation involves the transmission of lymph node cells from previously immunised mice or of stimulated antigen-specific T-cell lines.

[0011] For analysis evoked potentials (EPs) are used. An evoked potential is an electric potential which is recorded in a patient after a stimulus up to reaching the effector. Muscle contraction can be cited here as an example. EPs show whether lesions are present. For diagnosis various EPs can be used, for example visual evoked potentials (VEPs) or motor evoked potentials (MEPs). Here, for diagnosis the electrical stimulation of the brain was used to trigger motor evoked potentials (MEP) in the muscles of the extremities. Due to the damage to myelin sheaths temporary dispersal at neuronal conduction takes place which results in modified cortical evoked potentials. Cortical motor evoked potentials (cMEP) provide quantitative data on the physiological status and are therefore particularly suitable for a functional examination.

[0012] MS and EAE are complex diseases in which many gene loci are involved which could have an effect on the phenotype (quantitative trait loci, QTL). A QTL is a quantitative trait locus, i.e. a variable point on the genome with influences certain traits. Finding such points is very helpful in the search for genes in relation to diseases in which more than one gene is involved. As the trait is not formed by a single gene, each involved gene modifies the trait.

[0013] QTL mapping is used to identify potential genes for various traits. In mice inbred stains are used under controlled

environmental conditions for QTL mapping, for example C57BI/6, SJL, FVB and C57BU10.S.

[0014] For mapping genetic loci various markers are used, for example restriction fragment length polymorphisms (RLFPs), hypervariable RFLPs, mini-satellites, micro-satellites or single nucleotide polymorphisms (SNPs). QTL EAE 31 proved to be relevant.

[0015] As a single QTL can contain hundreds of genes, selecting individual potential genes for further examination was a demanding task. Additional fine mapping was therefore indispensable in order to identify the precise chromosomal locus. Used are the establishment of cogenic lines, recombinant selection and advanced incross lines. The first option for producing strains is the generation of backcross populations. The backcross strain implies the pairing of F1 individuals with one of the parent strains (cf. FIG. **1**B). Intercross generations are produced by pairing F1 generation siblings, which results in a mixed F2 population (cf. FIG. **1**B). It is possible to analyse a mixed population of two strains for various phenotypes. Software tools are used for mapping the QTL and the chromosomal locus.

[0016] The differences between various murine strains can be analysed by means of high-density markers or by the creation of strain distribution markers. In addition, single nucleotide polymorphisms (SNPs) can indicate phylogenetic relationships between inbred strains. Determining which fragment has the same or different ancestors is possible through comparing SNPs of various murine strains in the QTL region. By way of the SNPs strains can be subdivided into haplotype sub-groups. The SNPs help to combine this information with the phenotype data.

[0017] Another approach is comparative genomics. Through the genomic comparison of various species (for example rats, mice, humans, cf. FIG. **2**) common sequence fragments can be determined. Furthermore, the gene locus, highly preserved regions or the quantity of non-coding DNA can be determined. Highly preserved regions within pathogenic loci in various species can be determined by means of comparative genomics. This speeds up the isolation of likely pathogenic genes.

[0018] For the fine mapping of the QTL (EAE 31) haplotype analysis, intergenomic analysis and gene expression profiling were used, whereby the inositol polyphosphate 4-phosphatase type II gene (INPP4b gene) was determined as the best potential gene of chromosome 8 of mice (cf. FIG. **3**).

[0019] Inpp4b (protein) is an Mg^{2+}-independent phosphatase which catalyses the hydrolysis of the phosphate in the 4 position of phosphatidylinositol-3,4-biphosphate, inositol-1,3,4-triphosphate and inositol-3,4-biphosphate. The murine protein is 96% identical to human and 90% identical to the rat orthologue.

[0020] The Inpp4b gene, as the best potential gene, was sequenced in two mouse strains, the resistant strain C57BU10.S and the sensitive strain SJL, in order to find differences in the sequence. The resistant strain withstands EAE inducing, the sensitive strain reacts to inducing with EAE.

[0021] The sequence differences were compared to known polymorphisms which lead to amino acid variants in humans. The coding sequence of Inpp4b of SJL and of C57BL/10.S were cloned (Promega) in a pGEM-T easy vector and produced two SNP differences in the cDNA, which resulted in a displacement of amino acids (AA): c1434C/A (AA 478 S/R) and c1655A/C (AA 552 H/P).

[0022] In order to find out whether one or both SNPs are decisive for EAE susceptibility, DNA constructs were produced each containing one mutation (either serine->arginine or histidine->proline) or both mutations. Transgenic mice were produced by pronuclei injection. On inducing EAE it turned out that both SNPs are relevant.

[0023] The Inpp4b gene, which in mice is localised on chromosome 8 is on chromosome 4 in humans. The gene itself is known, with the sequence being described for example in Anderson et al., "The cDNA cloning and Characterization of Inositol Polyphosphatase 4-Phosphatase Typ II", J. Biolog. Chem. 1997, Vol. 272, no. 38, pages 23859-23864. The gene is also listed in the ENSEMBL database (chromosome 4: 142,949,186-143,383,906). Three splice variants are known, i.e. alpha, alpha short und beta. In the alpha short variant the exon 4 is missing.

[0024] All the following details about the individual SNPs relate to the definition and/or numbering in accordance with the Ensembl database (Ensembl release 56—Sept 2009; Homosapiens version 56.37a (GRCh37)). The Inpp4b gene and the individual bases respectively are read off in relation to the orientation of the codogen strand of chromosome 4.

[0025] In an association study MS patients were studied with 39 SNPs coming into consideration as markers. DNA was taken from body samples and the relevant sequence was identified in the area of the Inpp4b gene. The control group of the study included a total of 349 study participants who did not have MS, of whom 210 were women and 152 men. The group of patients with MS included 362 persons, 4 of whom had a clinically isolated syndrome, 8 were primary progressive, 3 progressive relapsing, 244 were in the recovery phase and 90 secondary progressive.

Tag SNP Selection

[0026] By way of the tagger algorithm in Haploview 39 tag SNPs were selected, which cover all usual haplotypes within the INPP4b gene (http://www/broad.mit.edu/mpg/tagger, www.hapmap.org). The algorithm is based on r^2. The use of a stringent r^2limit value (r^2>0.8) between the SNPs allows the selected tag SNPs to resolve most existing haplotypes (see Altshuler D, Brooks L D, Chakravarti A, Collins F S, Daly M J & Donnelly P 2005 International HapMap consortium a haplotype map of the human genome, Nature 437, 1299-1320; Barrett J C, Fry B, Maller J & Daly M J 2005 Haploview: analysis and visualization of LD and haplotype maps, Bioinformatics 21, 263-265). SNPs with minor allele frequencies (MAFs) of more than 0.05 were selected.

SNP Genotyping

[0027] Genomic DNA was extracted from peripheral blood leukocytes using the QIAamp DNA Blood Mini Kit (Qiagen, USA). The genotyping of all SNPs took place by means of a 5'-exonuclease assays (TaqMan assays on demand; Applied Biosystems, Inc., [ABI] Foster City, Calif.), whereby the primers provided by the manufacturer were used. The fluorescence signal of the sample was detected in accordance with the manufacturer's instructions (TaqMan Assay for Real-Time PCR, 7500 Real Time PCR System; ABI).

[0028] For each study participant the EDSS (Expanded Disability Status Scale), which is a measure of the severity of the disease, was determined. The Cochran-Armitage trend

test was used to test for association with susceptibility to the disease and with the EDSS value. The results for all examined SNPs are set out in Table 1.

[0029] The term "rsXXXXXXXX" stands for a designation in accordance with the Ensembl database, the base pair on human chromosome 4 affected by the SNP is shown in the second column, the P column shows the obtained potential values. Column A1 sets out the normal base, column A2 the SNP base. rs13102150 [4:143470133 (codogen strand, forward strand)], rs2059510 [4:143459907 (codogen strand, forward strand)] and rs17717651 [4:143453079 (codogen strand, forward strand)] exhibited significance, whereby rs13102150 was particularly relevant (Ensembl database entries of January 11, 2010).

TABLE 1

SNP	BP	A1	A2	P	OR	L95	U95
rs13102150	143470133	C	A	8.516E−03	0.729	0.576	0.923
rs2874870	143509994	C	T	1.189E−02	0.722	0.56	0.932
rs2636638	143230028	A	G	1.818E−02	0.741	0.577	0.951
rs4975311	143500223	G	A	5.062E−02	0.777	0.602	1
rs16998560	143481466	G	C	5.890E−02	0.783	0.607	1.01
rs2667092	142963604	C	G	7.155E−02	0.746	0.542	1.03
rs13107432	143444744	A	G	7.558E−02	0.811	0.644	1.02
rs336307	143020338	G	C	8.171E−02	0.808	0.635	1.03
rs1353624	143295246	T	C	1.310E−01	0.799	0.596	1.07
rs2636637	143081071	T	C	1.488E−01	1.22	0.93	1.61
rs1391098	143269745	A	T	1.875E−01	1.17	0.925	1.49
rs2667101	142976133	G	A	1.881E−01	0.849	0.664	1.08
rs2059510	143459907	T	C	1.998E−01	1.2	0.906	1.6
rs2667096	142969773	G	T	2.138E−01	0.857	0.671	1.09
rs336296	143014855	T	C	2.206E−01	0.849	0.654	1.1
rs1219275	143084950	T	C	2.383E−01	1.17	0.901	1.52
rs1391092	143341540	T	A	2.593E−01	0.869	0.681	1.11
rs1995960	142916958	A	G	2.618E−01	0.877	0.698	1.1
rs1907106	143229643	C	T	2.927E−01	1.13	0.898	1.43
rs1497389	143304592	C	A	3.370E−01	1.13	0.882	1.44
rs12499068	143343632	C	T	3.494E−01	0.894	0.706	1.13
rs6821787	142920229	G	T	3.797E−01	0.879	0.659	1.17
rs2635429	143243556	C	T	3.945E−01	1.11	0.876	1.4
rs1391095	143294023	A	T	4.270E−01	1.11	0.861	1.43
rs1817970	143364802	G	A	4.343E−01	0.872	0.619	1.23
rs17717651	143453079	C	A	4.609E−01	1.12	0.833	1.5
rs967003	142844783	A	T	5.069E−01	1.09	0.846	1.4
rs2627798	143163452	C	G	5.102E−01	0.921	0.722	1.18
rs1872292	143232882	G	T	5.507E−01	1.08	0.838	1.39
rs168059	142999991	T	G	5.837E−01	0.932	0.725	1.2
rs2636670	143234593	A	G	6.327E−01	1.06	0.837	1.34
rs3756125	143344473	T	C	6.820E−01	1.05	0.824	1.34
rs1994217	143130219	T	A	6.933E−01	0.953	0.748	1.21
rs2029990	143277467	C	T	7.027E−01	1.05	0.82	1.34
rs168061	143053786	C	T	7.221E−01	0.956	0.748	1.22
rs1500847	142833334	C	T	7.994E−01	1.03	0.817	1.3
rs3775707	143333792	A	G	8.607E−01	1.02	0.796	1.31
rs2636645	143216769	C	T	8.664E−01	0.979	0.761	1.26
rs3775692	143224971	C	T	9.781E−01	1	0.758	1.33

[0030] Accordingly the invention relates to a single nucleotide polymorphism (SNP) of the nucleobase at base position 143470133 (rs13102150) of human chromosome 4 in the inositol polyphosphate-4-phosphatase type II gene (INPP4b gene) for the diagnosis or pre-diagnosis of multiple sclerosis or for determining the risk of developing multiple sclerosis. Cytosine is normally found at this base position 143470133. In the case of an SNP this base is replaced with another base. In the entire text "another base" is taken to mean that the bases are generally the nucleobases adenine (A), guanine (G), cytosine (C) and thymine (T) and that the term "other bases" in each case covers the group of the three remaining bases, i.e. if a cytosine is normally present at base position 143470133 the other bases are adenine, guanine and thymine, one of which is then present instead of cytosine.

[0031] Particularly the invention relates to a single nucleotide polymorphism, which is a replacement of the base cytosine with adenine at base position 143470133 (rs13102150) of the human chromosome 4 in the inositol polyphosphate-4-phosphatase type II gene (INPP4b gene) for the diagnosis or pre-diagnosis of multiple sclerosis for determining the risk of developing multiple sclerosis.

[0032] In the event that at base position 143470133 another base, particularly adenine, is present instead of cytosine, the patient is diagnosed or pre-diagnosed with MS or is classified as being at increased risk of developing the disease.

[0033] The testing for association with EDSS was carried out by means of the Jonckheere-Terpstra test. Only MS patients were tested. As has already been stated above, the "Expanded Disability Status Score" (EDSS) is a performance scale which provides information about the severity of disability in multiple sclerosis patients. The scale starts with 0 and ends with 10, whereby the severity of the disease increases with increasing values. In determining the EDSS the doctor examines the patient's functional systems (FS). The results are set out in Table 2. Shown are the SNPs with $p<0.1$ from the MS association test or the Jonckhere-Terpstra test for association with EDSS. Here too rs13102150 turned out to be particularly relevant.

TABLE 2

SNP	pTrend	pJonckTerpstra
rs1391095	4.27E−01	3.60E−03
rs2029990	7.03E−01	5.50E−03
rs3775707	8.61E−01	6.70E−03
rs3756125	6.82E−01	1.51E−02
rs1872292	5.51E−01	1.63E−02
rs1497389	3.37E−01	6.52E−02
rs2635429	3.95E−01	6.92E−02
rs2636670	6.33E−01	6.99E−02
rs1391098	1.88E−01	8.21E−02
rs2059510	2.00E−01	8.97E−02
rs2874870	1.19E−02	9.64E−02
rs2667092	7.16E−02	1.27E−01
rs4975311	5.06E−02	2.23E−01
rs13107432	7.56E−02	2.94E−01
rs2636638	1.82E−02	3.25E−01
rs13102150	8.52E−03	4.70E−01
rs336307	8.17E−02	4.80E−01
rs16998560	5.89E−02	7.69E−01

[0034] The haplotype analysis for MS took place by way of a "sliding window approach", whereby the window size was set at 3. The result is shown in Table 3 and FIG. **4**. Of the haplotypes 1 to 6, haplotype 1, which has SNPs of the nucleobases at base position 143470133 (rs13102150), base position 143459907 (rs2059510) and base position 143453079 (rs17717651) of human chromosome 4 in the inositol polyphosphat-4-phosphatase type II gene (INPP4b gene), was shown to be significantly associated with MS.

TABLE 3

Haplotype	pHaploScore	snp1	snp2	snp3
1	8.92E−04	rs17717651	rs2059510	rs13102150
2	1.93E−03	rs2059510	rs13102150	rs16998560
3	1.08E−02	rs2667096	rs2667101	rs168059
4	1.49E−02	rs13107432	rs17717651	rs2059510
5	2.02E−02	rs16998560	rs4975311	rs2874870
6	2.74E−02	rs336307	rs168061	rs2636637

[0035] Accordingly one preferred form of embodiment of the invention is characterised in that a haplotype comprising single nucleotide polymorphisms (SNPs) of the nucleobases at base position 143470133 (rs13102150), base position 143459907 (rs2059510) and base position 143453079 (rs17717651) of human chromosome 4 in the inositol polyphosphat-4-phosphatase type II gene (INPP4b gene) is used for the diagnosis or pre-diagnosis of multiple sclerosis or for determining the risk of developing multiple sclerosis. Particularly preferably this haplotype is characterised in that the polymorphisms cover a replacement of the base cytosine with adenine at base position 143470133 (rs13102150), a replacement of the base thymine with cytosine at base position 143459907 (rs2059510) and a replacement of the base cytosine with adenine at base position 143453079 (rs17717651).

[0036] In other words in the case of a haplotype in which at base position 143470133 another base, particularly adenine, is present in place of cytosine, at base position 143459907 another base, particularly cytosine, is present in place of thymine and at base position 143453079 another base, particularly adenine is present in place of cytosine the patient is diagnosed or pre-diagnosed with MS or the patient is classified as being at increased risk of developing the disease.

[0037] In the method in accordance with the invention for diagnosing or pre-diagnosing MS or determining the risk of a study participant developing MS, at least the base at base position 143470133 (rs13102150) of human chromosome 4 in the inositol polyphosphate-4-phosphatase type II gene (INPP4b gene) is analysed, whereby if a base other than cytosine, more particularly an adenine, is present there instead of a cytosine, the proband is diagnosed with multiple sclerosis or the proband is classified as being at increased risk of developing the disease.

[0038] In a preferred form of embodiment of the method of diagnosing or pre-diagnosing multiple sclerosis or determining the risk of a proband of developing multiple sclerosis, at least the bases at base position 143470133 (rs13102150), base position 143459907 (rs2059510) and base position 143453079 (rs17717651) of human chromosome 4 in the inositol polyphosphate-4-phosphatase type II gene (INPP4b gene) are analysed, whereby if at base position 143470133 a base other than cytosine, particularly an adenine, is present in place of a cytosine and at base position143459907 a base other than thymine, particularly a cytosine, is present in place of a thymine and at base position 143453079 a base other than cytosine, particularly an adenine, is present in place of a cytosine, the proband is diagnosed with multiple sclerosis or the proband is classified as being at increased risk of developing the disease.

[0039] In the method in accordance with the invention, bodily material, preferable cell and/or tissue material, is taken from the proband. Particularly preferably blood samples are taken. From this DNA as the carrier of the genetic information is isolated and the sequence is then identified and compared with the reference sequence at the corresponding point of human chromosome 4 and the Inpp4b gene, respectively. There are many methods suitable and known to a person skilled in the art for identifying the sequence, which also include sequencing of the DNA. For methods requiring DNA replication the amplification of at least a part of the gene can be carried out with methods known to a person skilled in the art. Examples which can be mentioned here are PCR and/or LCR. Alternatively there are methods such as "self-sustained sequence replication", transcriptional amplification systems or Q-beta replicase.

[0040] As sequencing is very laborious, methods are preferably used for identification which do not require full sequencing. For this, methods such as pyrosequencing methods, which are, for example, provided by the company QIAGEN, specific methods of detecting DNA differences such as the Taqman® PCR (Real-Time PCR-Based Assays), offered for example by the company AB applied biosystems, or electrochemical approaches to DNA detection, such as GENSORIC® by the company Gensoric GmbH can be cited. Other methods used for identification are described in EP 1 388 589 A1 (paragraphs [0111] ff.).

DESCRIPTION OF THE FIGURES

[0041] FIG. **1** Shows two of the applied fine mapping strategies. In part A of the figure an F1 backcross with one parenteral strain (FO) is shown. In part B the F1 inter-crossing with a sibling is shown (F1).

[0042] FIG. **2** Shows the comparison of chromosomal fragments of human, mouse and rat. Shown is the location of the QTL EAE 31 in all three species.

[0043] FIG. **3** Shown schematically is the EAE 31 QTL in human (A) and in mouse (B). The fine mapping of the EAE 31 points to the gene Inpp4b.

[0044] FIG. **4** Shows the haplotype analysis, indicating the global p-values for sub-haplotypes based on table 3. The line between 2.5 and 3.0 shows the significance limit value after correction for multiple testing.

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tgtacttcta agtatgaaaa agttaacatg atgaacactg ctttcactgc ctactctggt 240

gagtactata gtctgtaaca tcaagtctct tctacaatta attctaaaat aattatagtt 300

aactgtacta gcaagcagac aaatgcaatt aggtaaaagc cattgagata tcttaaaact 360

gaaaattatg ttgttttaga tactgtaaaa tcttgaaaaa yaagaacaga caaaactcca 420

ccaaaaccag ctttatttaa attgcatttc caattttcaa tttatgaaga aggcaataca 480

aaaaaatcaa atgtcaagat cccatcctgg tctgcgttga atatttttga catacacact 540

ttcagtgcct tgtcttaaac aaatttcaag gttgcatcac ccatagcaaa aggaaaaaaa 600

caaactttaa aagtaatttt taaattatat ccaaagcaat atattaaaaa ttcttcaaaa 660

tttcctcaat caacattata cattggagac catggaatat ggtgttcagg gagaagaata 720

cgacgataac atatttttt cctgtttata ttttttaaa gacagcattc ataatttgat 780

ttcagaattt ccaaacaatt t 801

<210> SEQ ID NO 16
<211> LENGTH: 701
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (501)..(501)
<223> OTHER INFORMATION: SNP: T/C (code Y), maps to 4:143084950 (rs1219275)

<400> SEQUENCE: 16

tgcctcagat tgtctgggat ataaatcgcc cagtgtatcc gtgctgtata tgctactagc 60

ccactagtca cttaggtgcc atctgggtca ccagatcgac tgtcaggtta ttgcagtgct 120

catgttcaag tagccttgat gtggaagcct aacactacat cattcccctc actttatcta 180

atcacgtaga cattgtacca tctaacatca tcacaagaag acacgtgagt acagtacaag 240

aagatatttt gagagagacc acatttacat aactttcatt atagtatatt gttataattg 300

ttttgattat tagctcatgt tagtctctta ctgtgcctaa atttaaatta aattgtatca 360

tagctatgca tgtgtaggaa aaaaacagta tatacagggc ttggtactat caggggtttc 420

aggcatcccc tgggcgtctt ggaacatatc ctcgtggata agggggaact attgtattgc 480

tgttcttgca actgggacga yactaggaaa gttgaagtca tggaaaggat gtgaccatat 540

cactgagttg cctactgact gttctaaaaa acctttttct tttctcattt agcgtgaact 600

acattaaatg aaaaaagaaa gtctatctaa atgttatcat aagagtaggg caaacaattt 660

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atttaaaata tcagcttaat aatatcgtgt aaaaagaata a 701

<210> SEQ ID NO 17
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: A/T (code W), maps to 4:143341540
(rs1391092)

<400> SEQUENCE: 17

gcttcagtga ccaatgctct cagtaattag acaatggagg gagaaagtaa ttaggtaaac 60

cacaaagaag tagaaataaa ctgtatggga tatgttggtc atggatgaaa gacaaattaa 120

aaaaaagtat aaaggaaaca tctaggaaaa aataactaat aaataatttg cttaatccat 180

gttgaataat caatttaagc ctgtgaagtt aaacctgatt aaagatatcc cttaattaaa 240

aagttcctac aatgtattac ttagaaagaa acatgacaag aagaatagat ctattttatg 300

tcaacaacag ttcagttaaa tgatatagtc ctggcaagga gaagtgggag agaaaagttt 360

gaggtcttat atacttctca tttattaatt gatgtatcat wtctcatatc tgcggggtgc 420

accaaatgtg aatttaaacc agtgtcacta aaaacaggct acaatccaac tgcagaacat 480

gctaaatctt ggtcaccaga aaaccactac ccacccgaca gatgtgtaaa gaagctctaa 540

ttggttcatt ttctcttcct tcaattaaat aactatatca gaagtacaaa aacctcatgt 600

aggccttaga taacctttta ttgctgttct ctttcccatt cctgtacttt taatcataga 660

ccacaaagaa catggccttt ggaattaaaa tccagattgc tctacattct agatataggc 720

cttcacacaa gtgaatgaac ttgtctgtga aacataggta atgggaggca actgttgagc 780

ctgtaatagg aacaaaggag a 801

<210> SEQ ID NO 18
<211> LENGTH: 635
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (246)..(246)
<223> OTHER INFORMATION: SNP: G/A (code R), maps to 4:142916958
(rs1995960)

<400> SEQUENCE: 18

cagtaaattt gtgttatagg tggaaggaga ccagaccacg ttttctacag atggaaaatc 60

ctgaggtcaa gatgagtaga agtgagatag ttatacatac tgatttttct tcccaaatcc 120

attactcaaa tatatcactt ttccccctttg gggtaagttg ggggtagaga caaggaatgg 180

atatccttct agacccacag aaaaatagag aaaccctcct cccttcacag caacattcct 240

cagccrttgt cgtatttgcc cattcagttc aatcaataaa tccatagtca acctgtagga 300

agaaattagc aatctgtgag tttctgtttt cactttcctg aggctgttgt ccttaaaatc 360

accaaagttc ctttgagaat actactaata tcactgtatt gccaccacaa atcccttaaa 420

tgaggcagaa tagaatacca ataactccaa gcccctgtgt ttcattctcg ttttgttttt 480

taacaattag actcagcagc cttgtccaaa atagtatatt aaagtttctg taataagaat 540

aaatgataat gtaaaggtta gcctatataa aatgacaaca aatgaagatg cccaaattta 600

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tttccattat taaattctag aggatactta taacc 635

<210> SEQ ID NO 19
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: C/T (code Y), maps to 4:143229643
(rs1907106)

<400> SEQUENCE: 19

acgttggctt gtccatctcc tagctgagcc cagtgtctgg aacagagggc tgcactgtga 60

gtgcatacag tgtgccaaga acaatgccca tgagtcaggt ttatccatta taactgtcag 120

ccacttgctt gatctcaaag gataatgaaa atggtcacaa ataataaaat ctgttaaaaa 180

tcaatctgga taacgatggc atcataccat tacatttcgt aaacttgtca gacaagagga 240

gttattattt gggtaccaat gctatccttt ttttaatcct aaaaataact gtatatcagg 300

actgcatgtt gtataaacta cattaataaa atcaaaaaat gtgaggacaa ttgttttatg 360

ctgcaacaac aaacaatggg attgcctata catttacttt ygagctggtt tcttgttttc 420

ttcacctcag tataaataaa agaaggattc tctcaccctc aaagttagaa aataaatctt 480

ttatctatgt gaatactcac tgaacacatt gtaaaagaat gaatgagaag agtcttctct 540

atagcacatg atgctaatgt aaaagaataa tttaatataa agctattata tctttgctat 600

cactgtcatt ataattatat aatttaagat aatttattta attttttaat attttaaata 660

taattcaagg gacagtgttt tctgaatatc ctttggtgct gtttctatca ggggaaaata 720

aagacaaaaa agggaaagct tcactagagt tggagctcag aggtctgaag tgtggctcta 780

aatcagttat tctgtccaaa a 801

<210> SEQ ID NO 20
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: C/A (code M), maps to 4:143304592
(rs1497389)

<400> SEQUENCE: 20

gcctcttagc aatgagtttt ctcctttagt tattaacaaa atggattgtg ttgatagatg 60

tactgatatt aagccacttt tgctttcctg aattaaacat tacttggtcc gagtataatt 120

tttttcatag attaatccta ctgaacactg ttacatttat aatctttgca cctatgcttt 180

taattgaaat ttacttatag ctgttaaaaa aacattcatc aggttttagt attaaaccta 240

cctagtcctc ataaaatata ctttggaagc tttctttttt tcccaatata gtcacagtca 300

tactgcttat gtaccagtgt ttcaaatatt tctattacaa tacccataaa aggtgcttga 360

aagaataact gcttaccacc taggctatga ggttgtgggt maaacctaac tgcctaaatt 420

tctacttcct tatcatgagc ttcctaacat cttctgagca gacacccatc aaaacagagt 480

tatgtggaca tgtcaaaatt ccaatctgtg gacacaatag gctcaaagta gatctgcctt 540

gcaacttaac tcaaccactc ctctcaatag tatcccatga tgcttaaaaa tgaaactgct 600

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cactattcaa acactgataa gagaaaaaaa agtcatattt ttaccagaaa aaaaaatcta 660

ttgtttttgg acatgtgtag taatagttca gaaatataag cttcaaggat aatcattaat 720

attcacaaca gtggttgcac aggcaggagg gaaaggagag gagattgaga aggggatat 780

agaggacctt gactttattt a 801

<210> SEQ ID NO 21
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: T/C (code Y), maps to 4:143343632
(rs12499068)

<400> SEQUENCE: 21

tctgtccagt aatgataata tgggagagat attatagtat gaactcagac tcctgggttc 60

aaatcttagg ctcactactt taccagttta attctaagtt ttcttacata gaaatcaggg 120

atgataaaag agcaattact cataatgaaa tgataagaag taattaatat atgtaaatta 180

tttagaacag catatggcaa acaagtaagc aatcaataaa tgttagttac ttttaatatt 240

attatcctgt agagttgtgg tgagaaattc atgacatgct gtttgtaaag ttaagcccat 300

aatagatgct gaaaaaatgg tagttgttgc tgtgtcctcc tagggctttg aacaatgact 360

tgtcattaga aggcgcccag aaaatggtag ttcagggaaa ytcaatgttt tataagggat 420

gtgttacact ataagaagca agaaggctag gtgtggtggc tcatgcctgt actcccagca 480

ctttggaagg ctgaggtggt agattcactg gagcccaaga gttcaagacc aacctgggca 540

acatagtgag aacccccctct ctacaaaaaa taaaaatgaa aaaaactagc caggcatggt 600

catgtgcacc tgtggtccta gctacttggg aggctgctgg tggaaggatt gcttcagcct 660

aggagttgga ggctgcagtg agctatgatt atgccactgt gctctagtct gggtgaccga 720

gtgaaacctt atctaaaaag aaacaaacaa acaaaaaaca aaaaacagaa tcaagaaaat 780

ggatgtcaat caacttataa t 801

<210> SEQ ID NO 22
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: G/T (code K), maps to 4:142920229
(rs6821787)

<400> SEQUENCE: 22

aaaataaatc gaacaatttt caaaagccaa agcagtttat gaccttaaag catttagcaa 60

acctaatatc tgacctgcat aatctagaca aaatgtattt tatcaataat ctttaaagct 120

gttttttgag acagagtttc actcttgttg cccaggctgg agtgcaatgg catgatgttg 180

gctcactgca acctctacct ctagggttca cgtgattctc ctgcttcagc ctcccaagta 240

gctgggatta taggtgcctg ccattgacgc tcagctcacc tcagcctccc aagtggtggg 300

attacaggcg tgagccactg tgcccggctt ctaatgattt ttttgtgcag aaatacatag 360

tatcacaaga gtggagacat ggattttaaa attctgagct ktaagaaact tactcctcag 420

ataaacacat gcaaatgagt ccatgcattt atataactgg gagctctctg aattaacatt 480

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tatgtggtat atacaattta ttaaagcata accatgtttg agacattcac atatgtattt 540

acatgtaaca ctagtttatt ttttattgta caaatttcat tgaatatacc aagttttatt 600

ctactattga tggacttttg tgttatttac tattttgaaa tattatgaac gataaaaaat 660

cagaccatct tttattcttt tttctgtttt agttgttttg ttcaactctc taaatgcaag 720

gaacactcta atttccttca cccagggctt atttcttcca ccactccatt ctaggtatgc 780

cactgcctag gagtagaatt g 801

<210> SEQ ID NO 23
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: C/T (code Y), maps to 4:143243556
(rs2635429)

<400> SEQUENCE: 23

tatgattcag ccactattat aagcactggc aatctcagag agtaagagat taagaagaca 60

aggtatattt cgttgatacg caataacaat ggcatggtaa gagtcaaaca tctaataata 120

attgctaaga atcttcagct ttctaaaatc tatcagctag tcttagataa cggttttcta 180

gttgtttaat tttaatcttg catggagaaa atgatgcatg tacaaaccta aatgatttag 240

gtcacagaat cttagagatg caaggaatct ctcagttaat ctaaaaaaaa aactaggcaa 300

tatgaaaatt atatctgaaa tattcctggg aagtacattg aacatttctt cttcaacatt 360

tggaatttct agcttactat ctcacaaatc agtatcataa yggtagtgtt acaaactcac 420

atgcccacag gctccaggta ggtaaaatta atgaaaggag tggcctgggt gtttgagaca 480

ataggaattg gagaggactc tggcaaaatg gaatcacatt tctagtctat aagaagtgac 540

aactacccag cttcaacgga ttgaaaaaat tctgagaaat attccttcaa atattaacaa 600

tgggtaaata ttaattcttt tgaaagtggg ctattattac catatgctga tttttaccag 660

aaacatgctt tgtaactaag gtgagtgggc caaagcaagc ccactactat tttagtaaaa 720

ttagttttta aaatgtgcta ccctaaaaca gttgttatta accttgacaa cacagtagaa 780

tcgcctgtaa catgtttttg g 801

<210> SEQ ID NO 24
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: T/A (code W), maps to 4:143294023
(rs1391095)

<400> SEQUENCE: 24

tacacattct atgcctgtat caaaatatca catgtacccc ataaataagt acaatcatta 60

tatgcataga ggaaggtaaa aataaaagca gaaaatatca tatgcattgg gttctacaat 120

ggaaaagaca gagagggttg ggaagcattt caatgatggg cacatctctc ttcccaaggt 180

cttatttcat ttccagtacg acttctgaca gctggtagaa atgtgtgcct ctgacagagc 240

agtttcacac attctcaagt gcaaaaagta agattgacgg catcctttcc atttccatca 300

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tcagctgaag tgtctcctct ctaggaagga gtaattagct cagtcttcta gtactggaag 360

tcaaactaaa gcatcttgac tacactgact cctgctgcct wcctagtctc acaaatagga 420

attcatatga ttaagcacat tttacttcaa tctaggcctt gaaccaatga cctaccttct 480

ataactgcct acacaataca tacatacata cacacacagg ggcatgtagt gcacttctct 540

tctggacttg aaatacagat ggttttaaac tgaatcattt atattctatg ccagaataga 600

aatcagtctc aaatagctgc aggctctaac aatgactatt ttgaaaatcc aactccatat 660

tatgcagcat agtggaaaga gctctgattg aagagccaag tcctgtatgt gtcataaatt 720

ctatttttgc atctttattg aatagattgg tgccctttca taaagcagaa agtgtttgag 780

atgaatagag taacaacatt t 801

<210> SEQ ID NO 25
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: G/A (code R), maps to 4:143364802
(rs1817970)

<400> SEQUENCE: 25

tctttatgga cctcacccaa atgcccatga gaatgattgg aagcagagtg ggtgcctgga 60

gaaagtgtcc ctttgaggta catgcctgct gaaggggaac agcagtaatt gcaggaaaag 120

tacaaagacc cacttggatc ctctttccta cagaacaaaa atgacagacc ctgctgacct 180

taggtgaaga ctcattgaaa ttagaaaggg aggagcagta aatcttcctg ggatgacacc 240

actagagatc ctctgatcct ttattactat agagtgatcg gatcactgag aaagtcccac 300

cccaagaccc aagaacatcg ggcctgtcta caaccaagca tgaaagatga cgatagagaa 360

tgcctctgcc cccgccacca ggctgagaca ccaagaaaca rgtgacagaa ggctacctcc 420

caccagaggg ggcatgcaag cacaaataat gaacctctct caggtagaaa cttccaagaa 480

agcttaaagt agagagtgga gagtggagag cagtctccag gcatctaaac cgcactctaa 540

gcacaattta atattaaagt agaataaaga ggggaggaag aagagaagaa gataaaggag 600

agggagaaag aagaggaaga gaaggaaaag tggggcagaa gaggagaagg atgaaaaagt 660

gtcaaaagca aaagcaaaaa aataatatgt acatatatac caagagaccc agactcagat 720

attacccagg tattagaact aacagaaagg gaatatgcta aaaactctag tggaaaaagt 780

ggagaagttg catgaccaga t 801

<210> SEQ ID NO 26
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: A/C (code M), maps to 4: 143453079
(rs17717651)

<400> SEQUENCE: 26

tttgtgtcgt ctatgagaaa taatttctct tttctgagtc tatgttgatg atgtagcttt 60

cgacattatt ataacatgat ttattatata atccacactt tagtaaaatg acagttattc 120

tctgaatgga ataaaatttc ttttgagtag attttttttt taacaagcct gcgtgaaggt 180

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catatttgct gtcaattcca cagtctccga ctaaggggaa agaccctacc aaatatagta 240

aaatacaagt cagtggtaga ctatttctca acaaaggagc cagaatttgt taatgacatt 300

tacaaaggcc agttcttagt tgcttctcaa aatactaatt ttaaaatatt gactaagctg 360

aatataactg ataaatataa acattattga tttacttttt matatccaat ttcaccatgt 420

taattttatt ttctaattat tattaagaca tattgacttg tcctgttctt tgccaccacc 480

atcctggttc agataatcat ctgtagccca ggctgctgca atatttttca aattgatttc 540

tgcattcact tttatcctgc tctgcttttt ctcaacaaag tagtaggaag gatcctctta 600

gaaacgcaaa tcaggtaaca tttccctccg cttaaacact ttcaaaggat tccagttgtt 660

cctaagataa tgaaaaaacc acttgagggc ctgcatatgc ctgcagttgg cctctccatc 720

cacttcagca gcagcacccc ctgctctcat tattcttcac cttggccttt ccaggaatag 780

ccctgctccc tcccagtcga a 801

<210> SEQ ID NO 27
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: A/T (code W), maps to 4:142844783
(rs967003)

<400> SEQUENCE: 27

tgtgcctgtg tctgtggtga gaacacttaa gatctgctct cttagcaaat ttcaagtcta 60

caacacaata ttattaactg tatattatta ttaattatac tccatactat acattacctc 120

tccataactt acatcctgaa taactgagac tttgtattct ttgaaccaca tctccccttt 180

ggctccatcc ctatcccctg gcaatcacca ttctattctc tgcttttagg agtaacgttt 240

taagattccc tgtaaaaacg aggcaatgaa gtatttgcct ttctgtgcct gaattatttc 300

acttagcata atgtcctcca agtttatcca tgttgttgaa aatgtcagga tttccttctt 360

tttaaaggct gaatagtatt ccattgcata tatatacgcc wtattttctt tcttcatctg 420

ttgatagata ccgaagtagt ttgcgtattt tggctattgt gaatagtgga atgcacatgg 480

gcgtgcagat atctcttcaa gataatgact ttatttttctt tgaatatact ccagaagcag 540

tgtttctagt caatatggtg gccatatttt taatttttttg aggatcttcc atgttgtttt 600

taataatagc tgtactagtt tacatttcta ccaatagtat gtgtgagcat tccctttttct 660

tcacatcacg atgtttattt attcattgct aattactaca tgcaagcaga gtataacaaa 720

tgtcaataat aagctataaa cttctgaata ttctaaagtt cttaccatct gagatcagtt 780

ttataactcc cttatgctta a 801

<210> SEQ ID NO 28
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: G/C (code S), maps to 4:143163452
(rs2627798)

<400> SEQUENCE: 28

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ggcttcaggc agtacattca ttatttttact acactgcaga ttcttgtaga gaatctattc 120

attccatagt tttaattatg tagttgttta attaattatt cagctaaatg tatctatatt 180

gcctattctc caaaagctac attatacttt ctaaggataa gtctgtaatc caattagaca 240

ctgacacatc ctcatttgta tttgaagata tcttaaatac ataataaatg aaacttggct 300

cttttaaaga tcggatgagc actgagaaat ctaaacagaa attttacaaa aacactatcc 360

ttagcatggc ttcagaaaag tgagggtaag aaaaacatga saggagctca gaaaatacag 420

caaacagata ccctgaatgc agccaaaccc acaagctcct ggccaaaaat aagaaaaact 480

attgcagatg tcataataaa acacaaacgt attatttgtc tgcagttggt gacaattggt 540

gaatttcatc tgtagaattt ggatttgaga tcttgggtgg ttagaaaaag gattggcctt 600

agttctgttc attctgtttc agtgagtgaa ggatacaact tgtaaagcta gaagctagct 660

tctatttcat gctgaaaaaa ccaagacaac ccatactcta ttccactcat caagttgttt 720

cttgccagta tgcctctgat caaggcattc catgcaaatc acaggaaccc cccactttcc 780

taaccacatg taatcatcct a 801

<210> SEQ ID NO 29
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: G/T (code K), maps to 4:143232882
(rs1872292)

<400> SEQUENCE: 29

gcttgaactt tagttctgaa atcttacctg ccattttgag ttctgatggg tcacaaaatt 60

tgttagattt tctactgtat tattacagta atttctagaa tcccccaccc atttatttct 120

ggtggttcta ataatacata aaatggttgg caaaataaaa tcatggtgtg ctttttgatt 180

tattcaatac atagttcata gatttgctag cttccaagca caaagccagg aatattagaa 240

atagagactt tgctctcatg gagtacatct agcaggagtg tggagacatg actgattgcc 300

tatctaactc actttctgcc ctttcttcat tactaatagc acctcagttt tgtttaaatg 360

agaattgtac ccagattctc ttctagctaa ggacttaggc kctccccaat actatgtaag 420

tgacagtata caaaatgaaa tttcccagga aattattgtt ttccagaatt gaagggatag 480

gccagctgag ctttttgccc ttgatttttc actcaaccca gaatgtgcta cctggggtac 540

catggccagt ttgtgcaatt ctctaagaaa gaaggaccag gaagatggat agagtctggt 600

tgcttcaagt cacttttgag tagctgaagc cctggacaat tttcccaaga cttctataac 660

atgagaaaaa caaacccatt cattagtttt aagccagttt gtcacgttac ttgccttagg 720

gtacgttcct aattgcaaaa ataggcatgt cacaggatac caattgagat ttctctttta 780

gtccaggaat tatagccgag t 801

<210> SEQ ID NO 30
<211> LENGTH: 701
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (201)..(201)

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<223> OTHER INFORMATION: SNP: G/T (code K), maps to 4:142999991
(rs168059)

<400> SEQUENCE: 30

atttatatac ctttgctcat cgtaaataat ttgaaactgc tacagagata agcacaatac 60

aatagaaaat acttaatata gataaggaca aaataaaact aaataaagag tgatatgata 120

accttggcga actttatttt tcccttgagt ttttatgatg aagaaacctt ggtgaatttt 180

taagaaatcc agagaaaata kcctggaagg tgattggagt aattcaaagg taaaataaac 240

tgcaactgat gttaaataaa attaaaagtt gcagtaaatt caaaaacata caaatcaaat 300

tcctttaaaa cactgatttt taaaaatcca gagttgttcc ccagaatgtc tgtaaagttc 360

ttaaaaaatt aaatcctggg acccacctca gatcttctca attataatcc atgtgaggtc 420

taaacatatg tattgcgttt tagtatagga catgttgttt tattataaaa ttgaacccaa 480

gatgatgata acttaaacta catcttgata cattttttaaa aatagattta aggggtacag 540

gtgcatcttt gttacatgga catactgcat agtgctgaag tctgggcttt cagtgtaaac 600

gtcacctgaa tagtgtacat tatacccaac aggtagtttc tcatccctcc ctcccttctc 660

atccttccac cttttaacac accaatcaaa catatgtatt t 701

<210> SEQ ID NO 31
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: A/G (code R), maps to 4:143234593
(rs2636670)

<400> SEQUENCE: 31

ggcttcctcc ccactgcacg ttgctagagt cacagaaagt ctagcccgta gggggaaatg 60

gtgggaggag gtagaagaaa ataaaatcag aaaagagact caaggtttaa aataattaag 120

atggattccc aagaacatga gtgagagaaa aaaattggag aaatctacac gactgggcca 180

aaatatcatt aaagcttcaa gcaaggggga ttcaacacaa gagcagtggt ggagtggggt 240

cggggcaggc agtgaacaca ggagaaaaaa attaaaccag ctaagcttcc ttgaaccttg 300

ataaataaat ggaacacctt gatagaataa tgtattcccc atattaatac tttaaaaagt 360

ctcacatttt atgaagcagt gccaggggtg tgatgagagt rtgcatttag gatggagggt 420

ccagttggaa gcagggcccc agggtggtac tagtggaaac atgtgagctg agccctgagc 480

tgtggaaggg agccctctcc ccatgaagtg cagcagccca ggctgacaga ggtccatctg 540

cctgtgtctg tggaggtctg aagctgggga gaactttctg gatgcactgg aggaagtaaa 600

tgaaggtttg tgtagtcagc acagagattg gtagtagaag tgaatggcac aagaggttga 660

aggcagaaaa actgcaagga ctccctcaag tcaaagcagt tactcaacta gtcccaagga 720

agagatgaga ggcttgtgtt aggcatgaga aagcaagaca tcgccctttt ccctctgctt 780

tttcactaac agctgcagag a 801

<210> SEQ ID NO 32
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature

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<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: T/C (code Y), maps to 4:143344473 (rs3756125)

<400> SEQUENCE: 32

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atagaataaa tgcaaaaata tacctctgtg cttggtattc ccttcagcta gcatgccatg 120

taaaaggcaa aaatactaaa gaagatatcc taaaaccctc cattctccca ctggagtttt 180

aaaaaagtca gagctctata atcatttata gaacacagac cagcaagaga gtaggattgt 240

gaacatagaa gataattcat aagttgggcc tcttatgatt tttcctttta gaaaaacata 300

taaaacaatg cctgatttat agcaattcat aaagtatgaa tggacctgac attcaggtta 360

atgaaggccc ttgcaagttg taaatgctgt gtctgtaaag ygatgagaca ttttcttgtg 420

cagattgtca gttggggcac atttctatac atttttaaat gccgagcaca gaaaactgat 480

cacatgattt tatctttttt ttcccctaaa tgggctacta aaatacagta cctgcatata 540

taaaatccaa aatcagttca cattatttaa tacatgacct aacagacaaa gtatttagaa 600

tcagctctct cctggacaaa gccttaacca ccaaagagga taagcactcc ttatttatag 660

ccacgataat atttgaatta acctacctaa ggacctcttg tcattgtacc agtacatatt 720

gttgtgaaaa aactgaattt taatcattaa actctaggac ggtacacatc atttacctgg 780

tacagatgta tactgaattg c 801

<210> SEQ ID NO 33
<211> LENGTH: 634
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (204)..(204)
<223> OTHER INFORMATION: SNP: T/A (code W), maps to 4:143130219 (rs1994217)

<400> SEQUENCE: 33

cactttgagt aagtagagta attgcttcca cacctgtttc cttgctaagt tctgtcagaa 60

tgtcttggta catattcacc atttgatcac agtgagtaag gacatttttt cgcagattgt 120

cccaatgtgg agaaagctca ccaagttctt ttatctcctg gtttctgtta agagtggaag 180

agaagagaaa ctttatttttt atcwtaaatc cataaacgca taacccttag tcagagttgt 240

caagataata agaaattatt tcatcctaat tcccaggaaa gttctatgag cttattagct 300

taaatatttt ttaaaaatta ttttagcaca aaaaaatatg aatagcttaa ccacacaaat 360

aaaaacatta tgtcaaaggg caaaaaatta gaaatgttaa attccctgat aaatttttca 420

caaagatggc agacttccta ttcttatata catagggaag acatttagtt aaaaagcaaa 480

ttgtaaaacc tctatgtaaa gatggctaag tttttaagtt tcaactgtac aaaatcaaag 540

aatgtggaaa gggctacctg accatgttgg aagcaaacat gagatactta gtcaattcag 600

tttatatata atatagttac aaatattttt ttaa 634

<210> SEQ ID NO 34
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)

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<223> OTHER INFORMATION: SNP: C/T (code Y), maps to 4:143277467
(rs2029990)

<400> SEQUENCE: 34

tcttttctta acctcaagag aaatgaacag aattcaataa gattacctat ttttaaaatg 60

ccacatactc caatagatac tactggggct acaaaaaatt agaactatgt agttttatcc 120

tccccaaatc tttcatattg ataagggcaa aaaataggat gacacaattg gtttacaatg 180

tataaaatga taaagtgctg gacagaaggt acaaattaca atacaagttc aaaagagaaa 240

gattatatta gttaatctag aaaatgtaca aaggaggtga tattggcaga atacctttaa 300

agatggggta aaacttttgc caggggagaa aggcattcta gataaaaggg agagaggaga 360

gcagtgagtg ttgatttgaa aataagaaag ggtaattcaa ytgtgtaaga atgagaatgt 420

acagagatgt gtggcctact tttctcagag acaggggtca agtaagggag aaatctaaat 480

cttatataaa tgtttgaaat gatatgagaa ggaaatgtga ggaaagcttg gatagctttc 540

catccagaac tcaagggttg gggatcctgg ttagcaggag agcaaagacc aggacctgca 600

ggagtgatga ggagctggga ggataaaagg ttgctcttga gttagtaagg tttcagttgt 660

gaagtagtac aaataacata tttggtttct gctcttagtt cctggcacag aaccctaaaa 720

cctttgtaat ttcctgagtg atagaagtgt taggtgcatc ttttgtcctt ttatttggtc 780

tttggcctca gttcctgaca t 801

<210> SEQ ID NO 35
<211> LENGTH: 937
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (437)..(437)
<223> OTHER INFORMATION: SNP: C/T (code Y), maps to 4:143053786
(rs168061)

<400> SEQUENCE: 35

gcctgaaaca actcaacatt ttgttaaaag ggtgctagtg aatatgtttg tagagaataa 60

gattggagaa ggtttttttt tttcttggag agagcagagg caatgcatca tagactctaa 120

gagggcaggc tctggagcca gaccaccagg gttagaaccc aggctgtgca caggtcacta 180

caactctcta cttcttcatc ctttaatttt gtagaattaa ttctacagtg ttgtaagaat 240

taaatgagtt aacgcagtca atatttttttt ttaccacata tcaagtaatc cataaatatg 300

agcttctatg ttaaaacaat tcaaataaac aaagtaattt ctacatgata ctttgcactc 360

gccctcctac cagcattgat tctttatgct cttccttctg tcctatttct gaggatgaac 420

tgttgtctag ctcagaycat ctcctctgtt ggtacaccag atctcatcct ctctcaccta 480

cttaagagtg tcactctagc aattctctcc cttcctccca cattatcaat atttcctttt 540

taactggatc attcttgtca gaaaacaaac atgctattat ctcctcatct tgaaacaaat 600

atcactgttt tgaccctaat tccctttaca gctcctatac tttatttctc catttccttt 660

cacaatgaaa gttctcaaaa gagttgtcta tacaggttgt ctctacttcc tttacttcct 720

ctttctttta acccactcta cttaattcct acccactcta gtaaggctac tctcgtcatc 780

aaagacatcc gtactgctaa atccaaagcc atctcttagt cctcatttta tttgacctat 840

tttctaaccc cggctttcag gatagcatat tctctttgta ttcctcctac ctcactggcc 900

gtctcttgcc caactttgtt gctggttcct tcactta 937

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<210> SEQ ID NO 36
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: C/T (code Y), maps to 4:142833334
(rs1500847)

<400> SEQUENCE: 36

gtatgtcaag caagggaccc agaggtgcca gtgtgcctat tgagagggca gagtggtgct 60

tgaatctagg tgaagtgacc atggcgggca aggatgtaga aaccagtggc aaatggccag 120

aattgaggac tccagtgaag ggtgccagca tgtcaagctt aaattgctaa aggggactca 180

atcatagtga gaagtcaccc gtcctgggaa tcaatagccc agctactccg cagtgaagac 240

aagaggatcc tgagaggtca ggtcaatctg aggaccccag cctctccagt gctctatgat 300

cataggaaat ggagatggta gagagcacag aaaggaaaat ggcctgtgag gatcagagga 360

tttgcaggtt aaataagggg cttgcaatct cttcttatac ygtaacatga gcaaatttct 420

ggcctaactc caggtgttgc ctatctgtat atttctaaaa actgaagcat tctcctggaa 480

agtgaatcac tgagggtgtg gagtccggga tagacccttt aggattatgt tctcacttct 540

tttctcatct atcccttctt ttttacatat ctcttgttca agaagcaaag acctttccat 600

tctgtttgcc gtatcttctt gtgctatggc cataagcctc ttggattcgt tctcttttca 660

gaggggagat tctctccaaa gtctattaaa taaacacttt ttctacatcc tccaggtata 720

cctctctaac tgggagctgt ggtatgacat ggaagtagaa acctctgagg atgaaaatta 780

tttgctattc tatcttctaa a 801

<210> SEQ ID NO 37
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: G/A (code R), maps to 4:143333792
(rs3775707)

<400> SEQUENCE: 37

catacattaa aagatatata gagcacttaa aaagcctaat agcccctcta attactttat 60

tagtataata tgcttttcta tttttaatct cctttgcctt tttttgtttt ttattcttcc 120

ttcccctcaa gaattttaag acagcaattt tctgaagcct aggatgtcaa cctctccagc 180

tcagatctcc tgagtacatt cagaagagga tgcttcctag gctcagtgca ctacaatcca 240

tgataattca attatatata gtaaaatgac agaatgtaca gtgtccctgc ctatactaat 300

atccacacaa tgagaattgc acaagcagtt ggaaatactc tcttcactac tatctgttta 360

tggttatttc ttagaagaat atgtctctat atcatgctga rttgatttat ggccatgaat 420

atatatcctc ccatctttct tctgtattct ctgtaaaatc tttgagtctt taattcattg 480

agagtagctc tcatcttgtc cttcctctca ttttagctta ttttcaatcg ggcaagcctg 540

ctttttataa ttttcctttg acattattct ttttttcttct cttctctgcc atctcatatt 600

tcctctccaa catatgtgtt actctcatca ctctgaaaga cgaggttatc aaagtcacca 660

-continued

ctcatatatt ttataagact tgggactcta ggagtcaagc acacactgct cttaacaaac 720

cacagcttct cccctcagtt cactggtttt aaagtcttta tagaaacaaa acaaaaatgt 780

gttatgttct ccttaacttt t 801

<210> SEQ ID NO 38
<211> LENGTH: 601
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (301)..(301)
<223> OTHER INFORMATION: SNP: C/T (code Y), maps to 4:143216769
(rs2636645)

<400> SEQUENCE: 38

gccacaggtc tgtcaatgac tgtggatggg ggtatagcac ctgcatgtgg atggaggcat 60

gatgtgtggg gaattggggg gtgagtgttc atttgggtga ggatcacatg cctgcctatg 120

gatgtgtgtg ttacagaata tgcttatggc agaaaataca catagacaac cactcacaca 180

tttctttgaa aaatacattt ttgttgttct tctaaatcag cattttctga ataacatgac 240

tatgtttctt ggaacatagt gtctaataag ctgttgataa gtattccatg atgaaagctt 300

yttgcattca aattaattta agaaaagctg caggcgacac gtgtcctctg agcatcttcg 360

agggccttga aaggctactg aaggctctga gatgtcctac aggaaagaaa ttcactttcc 420

ctttttttt tcttttcttt ttttttaga ggactttcaa acttatttgg ccacagaatt 480

cctttattca aaaaacatgt attaataacc aaagggatac cggttttaca aaacaacact 540

ggaaaaagca gatataaatg tgtccagtga agcagaaaca cagtgataat aatgaaactg 600

a 601

<210> SEQ ID NO 39
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP: T/C (code Y), maps to 4:143224971
(rs3775692)

<400> SEQUENCE: 39

ataaaagtca gaaataatca gtgcaaagga atattttaaa atacaacaca aaacaaaaat 60

gcttcttaag gctgacctaa ggctcttcta actcaatact taagagacag aatcagtgga 120

aagaaaataa attacatcag aatttttaaa aaagccatct accagaaatc aagaggctac 180

gataaatcta taatctgtct ggttcatagg gagagaaaac cacaaatttg gcaaagcaca 240

aaactgggaa aaataataac ctagccattt cagaattggt tttctaacat tatttttttct 300

agaaaagtca attcttcgtt gttgaatttg ttttatataa tcaagatcaa atgactagga 360

atcaggggta ttaaaatcaa aagtgaagaa atttgtcttg ytttcatcta aatatgaaat 420

ttatgtattt ctttttctctt tcaagggtaa taccctaaac ttgacccttc ggttcttgtc 480

ctctctctaa ggtactgtgt gttcactaat tttaatttta ctaagaactg cttgtcccct 540

gatttctgtt tcaaaccaat gtctaaatgt tgcactagtg tgtagtatgc tcctgatgtt 600

aatgactgtt atgttataat gaatactggg gcttgtgagt cagtaagatg aagaagaaca 660

tgctatgcat ctgatctaga aaacatgtgg actgctagta gtcctaaggc aactcaatgt 720

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ttgacatctc atgttatgaa tccaggggca tatgggtcac attcaatagt caggctagaa 780

tgatgatatt ttctaggtta t 801

<210> SEQ ID NO 40
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP-1 invention: A/G/T (code D), maps to 4:143470133, inventive variation 1 (rs13102150)

<400> SEQUENCE: 40

actggtaaac acctcagtat gaaacagtca ttttgctcaa ttgttttgta gatacaatag 60

agcttcactc tacagaatcc ttgaaatgtg agtcattaaa gatgacatgt cttcagaata 120

acagaggggt tacctattta agtaccaaat atagtgcata cagatgtgtc tgtgtgtgtg 180

tgtgtgtgtg tgtgtgtata catatatata tattaattta acgttttgac agaaaatcat 240

tctaaaatgt attaaatttt ataaggcttc cttaaaagca cattaaacat aatgcaattt 300

tctttgatgg cccaaagtca ccattgtgaa tattaattat tatactgtgc tataataaaa 360

ttatgtctgt gaggccctca aaaatgggta cgctctattg dctctagaat tacacaatgt 420

cagaatgaaa tgggacctga gagcttgtcc agcattccca attacagatg ggacactaac 480

atcaagagaa gagtgatgtg atttaattaa gcggacacaa cagttatcta ccccaggtct 540

cccaacttct tatccagagt cctttcactt aacccgcact gcacagcatc atcacctatg 600

ctttcatttg ttcttctgct gccttttgaa gtttttttct cttctccctg gttagggtct 660

atgttcaccc ccatcactgt tgttggtgat gaaatctcat cctcccatac tgtgcactgt 720

aatgataggt ggggtagttc tggaatgtgg gagggcacgg gagcccatga ccatcagacg 780

gtaatgacta gatgtcagtt t 801

<210> SEQ ID NO 41
<211> LENGTH: 554
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (54)..(54)
<223> OTHER INFORMATION: SNP-2 invention: A/G/C (code V), maps to 4:143459907, inventive variation 2 (rs2059510)

<400> SEQUENCE: 41

tattttgaat ataagtagtg ggtatttaca tgttcatatt gcaggcatgg atgvgaaggt 60

taaggaaagt aaaaatattt ttcccaaaat tgttttaaca aaacatgtgt cctattgaaa 120

taagacttcc ctcaacttat aattatgaac catgcatttt cttgccaatg cggtaaaaaa 180

gagagaatcc atttaaaaaa agaaagagag agattaaaat tagtgacaat ggtgaggctg 240

gaaatttttat caattatacc tcaaaaaaga taaaagtaaa cctcaaatat ttgtacaaga 300

caatgaaaaa aattgtttag acttgatcct ggccctttttc aggccttttt ttgtgattat 360

atataattac aaaattgtta ttttatatat atatatataa acaatttagg attttatttc 420

cctctaagta gcaaatttttt ttctttgaga taataaaata tatatatata tatactgcca 480

gatacctgag tgtctgagaa agtcaaaaac agtcagatgg catttatttt gcatatcaac 540

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atgacaatat aaca 554

<210> SEQ ID NO 42
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (401)..(401)
<223> OTHER INFORMATION: SNP-3 invention: A/G/T (code D), maps to 4:143453079, inventive variation 3 (rs17717651)

<400> SEQUENCE: 42

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cgacattatt ataacatgat ttattatata atccacactt tagtaaaatg acagttattc 120

tctgaatgga ataaaatttc ttttgagtag attttttttt taacaagcct gcgtgaaggt 180

catatttgct gtcaattcca cagtctccga ctaaggggaa agaccctacc aaatatagta 240

aaatacaagt cagtggtaga ctatttctca acaaaggagc cagaatttgt taatgacatt 300

tacaaaggcc agttcttagt tgcttctcaa aatactaatt ttaaaatatt gactaagctg 360

aatataactg ataaatataa acattattga tttacttttt datatccaat ttcaccatgt 420

taattttatt ttctaattat tattaagaca tattgacttg tcctgttctt tgccaccacc 480

atcctggttc agataatcat ctgtagccca ggctgctgca atatttttca aattgatttc 540

tgcattcact tttatcctgc tctgcttttt ctcaacaaag tagtaggaag gatcctctta 600

gaaacgcaaa tcaggtaaca tttccctccg cttaaacact ttcaaaggat tccagttgtt 660

cctaagataa tgaaaaaacc acttgagggc ctgcatatgc ctgcagttgg cctctccatc 720

cacttcagca gcagcacccc ctgctctcat tattcttcac cttggccttt ccaggaatag 780

ccctgctccc tcccagtcga a 801

1-4. (canceled)

5. A method of diagnosing or pre-diagnosing MS or determining the risk of a proband developing MS characterised in that at least the base at base position 143470133 of human chromosome 4 in the inositol polyphosphate-4-phosphatase type II gene is analysed, whereby if another base is present there in place of a cytosine, the proband is diagnosed with multiple sclerosis or the proband is classified as being at increased risk of developing the disease.

6. The method of diagnosing or pre-diagnosing MS or determining the risk of a proband of developing MS in accordance with claim **5** characterised in that if at base position 143470133 (rs13102150) of human chromosome 4 in the inositol polyphosphate-4-phosphatase type II gene an adenine is present instead of a cytosine the proband is diagnosed with multiple sclerosis or the proband is classified as being at increased risk of developing the disease.

7. The method of diagnosing or pre-diagnosing multiple sclerosis or determining the risk of a proband developing multiple sclerosis characterised in that at least the bases at base position 143470133, base position 143459907 and base position 143453079 of human chromosome 4 in the inositol polyphosphate-4-phosphatase type II gene (INPP4b gene) are analysed whereby if at base position 143470133 another base is present in place of a cytosine and

at base position 143459907 another base is present in place of a thymine and

at base position 143453079 another base is present in place of a cytosine the proband is diagnosed with multiple sclerosis or the proband is classified as being at increased risk of developing the disease.

8. The method of diagnosing or pre-diagnosing multiple sclerosis or determining the risk of a proband of developing multiple sclerosis in accordance with claim **7** characterised in that if

at base position 143470133 an adenine is present in place of a cytosine and

at base position 143459907 a cytosine is present in place of a thymine and

at base position 143453079 an adenine is present in place of a cytosine, the proband is diagnosed with multiple sclerosis or the proband is classified as being at increased risk of developing the disease.

9. The method in accordance with claim **5** or **8** characterised in that bodily material is taken from the proband.

10. The method in accordance with claim **9** characterised in that blood samples are taken from the proband.

11. The method in accordance with claim **9** characterised in that the DNA to be analysed is isolated from the bodily material, and the sequence is then identified.

12. The method in accordance with claim **9** characterised in that bodily material comprises cell and/or tissue material.

13. The method in accordance with claim **11** characterised in that the bodily material comprises cell and/or tissue material.

14. The method in accordance with claim **13** wherein said cell and/or tissue material comprises blood samples.

* * * * *