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(54) Title: HAPLOTYPES OF THE IMPDH2 GENE

(57) Abstract: Novel single nucleotide polymorphisms in the human IMP dehydrogenase 2 (IMPDH2) gene are described. In addition, various genotypes, haplotypes and haplotype pairs for the IMPDH2 gene that exist in the population are described. Compositions and methods for haplotyping and/or genotyping the IMPDH2 gene in an individual are also disclosed. Polynucleotides containing one or more of the IMPDH2 polymorphisms disclosed herein are also described.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/11851

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C12Q 1/68; C12P 19/34

US CL :435/6, 91.1, 91.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 91.1, 91.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, caplus, medline, EAST, Genbank, NCBI, SNP database
search terms: IMP, type II IMP dehydrogenase, gene, IMPDH2, SNP, polymorphism, mutation, gene, haplotype

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GLESNE. D.A. et al. Cloning and Sequence of the Human Type II IMP Dehydrogenase Gene. Biochemical and Biophysical Research Communications. November 1994. Vol 205. pages 537-544, see whole document.	1-3
X	LIGHTFOOT. T. et al. Gene amplification and dual point mutations of mouse IMP dehydrogenase associated with cellular resistance to mycophenolic acid. Biochemica et Biophysica Acta. 1994. Vol 1217. pages 156-162, see especially p. 156.	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEHANNE SOUAYA Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/11851

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-3

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/11851

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Groups 1-24, claim(s) 1-3 in part, drawn to methods for haplotyping IMPDH2 comprising determining whether the individual has one of the IMPDH2 haplotypes shown in Table 4 or one of the haplotype pairs shown in Table 3. It is noted that Groups 1-24 correspond to the haplotypes of Table 4 and the haplotype pairs of Table 3, respectively. Therefore, the first mentioned invention is the methods of claims 1-3 to the extent that they apply to haplotype 1. Group 1, the first mentioned invention, is the invention which will be searched in accordance with PCT Article 17(3)(a). Additional groups may be elected. For example, if Group 2 is elected, and the proper fees are paid, then claims 1-3 will be examined to the extent that they apply to methods of haplotyping comprising a step of determining whether the individual has the second haplotype of Table 4 of the IMPDH2 gene. Upon election of an invention to be searched in addition to group 1, please identify the number of the haplotype or haplotype pair to be searched.

Groups 25-37, claim(s) 4-6, in part drawn to a method for genotyping the IMPDH2 gene It is noted that Groups correspond to polymorphic sites PS1-PS13, respectively. For example, if Group 25 is elected, claims will be examined to the extent that they apply to methods of genotyping comprising a step of identifying the nucleotide pair at PS1

Groups 38-115, claim(s) 7-8 in part drawn to a method for haplotyping the IMPDH2 gene by identifying a IMPDH2 genotype for the individual at two or more polymorphic sites PS1-PS13. It is noted that the claims encompass methods requiring identification of 78 possible combinations of two of the recited polymorphic sites, and that Groups 38-115 each correspond to one of these possible pairs, in the order recited in the claim. For example, if Group 38 is selected, then claim 7 will be examined to the extent that it applies to a combination of PS1 and PS2. If Group 115 is selected, then claim 7 will be examined to the extent that it applies to a combination of PS12 and PS13. If applicants elect any of these groups, please specify the two sites to be examined in the method for predicting a haplotype pair.

Groups 116-193, claim(s) 9-10, in part drawn to a method for predicting a haplotype pair for the IMPDH2 gene by identifying a IMPDH2 genotype for the individual at two or more polymorphic sites PS1-PS13. It is noted that the claims encompass methods requiring identification of 78 possible combinations of two of the recited polymorphic sites, and that Groups 116-193 each correspond to one of these possible pairs, in the order recited in the claim. For example, if Group 116 is selected, then claim 9 will be examined to the extent that it applies to a combination of PS1 and PS2. If Group 193 is selected, then claim 9 will be examined to the extent that it applies to a combination of PS12 and PS13. If applicants elect any of these groups, please specify the two sites to be examined in the method for predicting a haplotype pair.

Groups 194-217, claim(s) 11-12, in part drawn to a method for identifying an association between a trait and a haplotype between one of the 12 haplotypes and 12 haplotype pairs of the IMPDH2 gene. Groups 194-217 each correspond to one of the 24 particular combinations of the polymorphic sites, haplotypes, and the haplotype pairs encompassed by the claims (i.e., the 12 different haplotypes, as well as the 12 different haplotype pairs). For example if Group 194 is selected, the claims will be examined to the extent that they apply to the first haplotype.

Groups 218-230, claim(s) 13-17, in part, drawn to a composition comprising at least one genotyping oligonucleotide for detecting a polymorphism in the IMPDH2 gene.

Group 231, claim 18, drawn to a kit comprising a set of oligonucleotides designed to genotype each of the polymorphic sites.

Groups 232-256, claims 19-20 and 23-24, in part, drawn to a polynucleotide which is a polymorphic variant of a reference sequence for the IMPDH2 gene or a fragment thereof. Claims 19-20 and 23-24 recite 12 different isogenes and 13 fragments comprising polymorphisms.

Groups 257-281, claim(s) 21-22 and 25-26, in part drawn to recombinant nonhuman organisms comprising a polynucleotide which is a polymorphic variant of a reference sequence for the IMPDH2 gene or a fragment thereof.

Group 282, claim(s) 27, drawn to a computer system comprising polymorphism data wherein the data comprises the haplotypes and haplotype pairs listed in the claims.

Groups 283-294, claim(s) 28, in part,drawn to genome anthologies comprising IMPDH2 isogenes having any one of the

haploytpes of Table 4. It is noted that Groups 283-294 correspond to anthologies comprising one of the haplotypes 1-12 of Table 4 in the order shown in Table 4. For example, Group 283 is drawn to an anthology comprising haplotype 1 of Table 4.

The inventions listed as Groups 1-294 do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The first claimed inventions, claims 1-3 (groups 1-24) lack unity because they represent methods which have different results depending on the nucleic acid present in the sample. That is, depending on the nucleic acid present in the sample, the special technical feature of each part of the invention would be the haplotype listed in the table. Since these methods result in different outcomes, they lack unity with one another.

The haplotyping methods of claims 1-3 comprises haplotyping the IMPDH2 gene to determine the presence of haplotype 1. Haplotype 1 is the reference or "wild type." Methods for "haplotyping" encompass methods in which the gene in question is sequenced, since during such a sequencing the nucleotide present at each position in the gene is determined. Since haplotype 1 is the reference type, group 1 merely reads on sequencing the reference type gene. This method does not provide a special technical feature over the art, since the gene was known in the art, as were methods for sequencing the gene, as is admitted by the specification. Thus, there is no special technical feature linking the recited groups, as would be necessary to fulfill the requirement for unity of invention.

Further the products claimed in Claims 13-17, 19-20 include fragments of variant sequences, and the claims do not require, e.g., that the recited polymorphic sites be included in said fragments. Accordingly, the claims are sufficiently broad so as to encompass nucleic acid fragments taught in the art (see, e.g., Teaching the sequence of the human IMPDH2 gene and fragments thereof). As these products do not represent a contribution over the prior art, the claims lack a special technical feature that is the same as or that corresponds to a special technical feature of the other claimed inventions. Thus, there is no special technical feature linking the recited Groups, as would be necessary to fulfill the requirement for unity of invention

Each polymorphic site and each molecule containing said polymorphic site is structurally and functionally distinct from and has a different special technical feature than each other polymorphic site and molecules containing said site The chemical structure of each polymorphism and of each molecule containing the same differ from each other. For example, a polynucleotide comprising PS1 is chemically, structurally, and functionally different from a molecule comprising PS4. As the products and methods encompassed by the claims do not share a special technical feature, the distinct products and methods may not properly be presented in the alternative. Accordingly, the claims have been separated into a number of groups corresponding to the number of different inventions encompassed by the claims, and the claims will be examined only as they read upon the invention of the elected group. For the same reasons, the remainder of the claims have been separated in a number of groups corresponding to the number of different inventions encompassed thereby.

The haplotypes and genotypes encompassed by the instantly recited method claims are also distinct from each other and from the single polymorphisms recited in e.g., claims 4-6. For example, a molecule of haplotype 1, comprising a particular combination of polymorphisms, differs chemically, structurally, and functionally from a molecule of haplotype 2 and from a molecule comprising a single polymorphism (e.g., PS1). The special technical feature of each haplotype or genotype is the combination of polymorphisms contained therein, which feature is lacking from and not shared with each other haplotype or genotype or with, e.g., a molecule comprising any single polymorphism set forth in the claims. Similarly, with respect to the pairs of polymorphisms of Claims 7-8, each combination of polymorphisms differs from each other combination and from each of the other combinations discussed above (i.e., haplotypes, genotypes, and single polymorphic sites). Thus, the claims have been separated into a number of groups corresponding to the number of different inventions encompassed thereby, and the claims will be examined only as they read upon the invention of the elected group.

Further, the different methods have different objectives and require different process steps. The haplotyping methods require steps of identifying haplotypes and haplotype pairs to achieve the objectives of haplotyping. The methods of genotyping require steps of identifying a single nucleotide on one gene copy to achieve the objective of genotyping. The methods of predicting a haplotype pair require steps of identifying two polymorphisms in a gene to achieve the objective of "predicting a haplotype pair". The methods of identifying an association requires steps of comparing frequencies of haplotypes in a population to achieve the objective of "identifying an association between a trait" and a haplotype. The methods of assaying for binding activity require steps of assaying for binding activity for candidate agents. In addition to differences in objectives, effects, and method steps, it is again noted that the claims of the

present Groups are not directed to the detection or identification of molecules having the same or common special technical feature, for the reasons discussed above.

The groups comprising polynucleotides, kits, recombinant organisms, computer systems and genome anthologies are additionally drawn to multiple, distinct products lacking the same or corresponding special technical features. The nucleic acids are composed of nucleotides and function in, e.g., methods of nucleic acid hybridization or amplification. These groups are directed to different combinations of nucleic acids which are different from one another and may be employed in different methods. The recombinant organisms are complex organisms that are employed in, e.g. animal research methods. Such organisms cannot be employed as, e.g., probes or primers and they differ in both structure and function from the nucleic acids. Further the computer systems are composed of, e.g., a CPU, a display device, an input device, etc., as recited in Claim 27, and function in, e.g., methods of electronic sequence comparison. Accordingly, the products differ structurally and functionally from one another. As products of different sets of Groups differ from each other in structure, function, and effect, they do not belong to a recognized class of chemical compound, or have both a "common property or activity" and a common structure as would be required to show that the inventions are "of a similar nature".