Abstract:

Seven protective alleles for IgA nephropathy have been discovered that can be identified by analyzing a DNA sample for seven respective SNPs. A method is provided for identifying and treating subjects at risk of developing IgA neuropathy based on a new seven-SNP genetic risk score. Also provided are screening methods to identify compounds that bind to and reduce the expression or biological activity of a either CFHRI or CFHR3.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68 (2012.01)
USPC - 435/6. 11
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)
USPC- 435/6.1 1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 435/6.12

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(PGPB,USPT,USOC,EPAB,JPAB); Google, Google Scholar: IgA nephritis, IgAN, Berger's disease, Berger's syndrome, synpharyngitic glomerulonephritis, IgA nephropathy, rs6677604, risk, score, allele, protective, allele, kidney, steroid, CFHL, CFHL1, CFH1P, CFHR1P, Complement factor H-related protein 1, FHR1 atypical hemolytic uremic syndrome

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

Further documents are listed in the continuation of Box C.

+ Special categories of cited documents:
  - A” document defining the general state of the art which is not considered to be of particular relevance
  - E” earlier application or patent but published on or after the international filing date
  - 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)
  - 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

- 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
- 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
- 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
- Z” document member of the same patent family

Date of the actual completion of the international search
17 July 2012 (17.07.2012)

Date of mailing of the international search report
24 SEP 2012

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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Facsimile No. 571-272-3201

Authorized officer:
Lee W. Young
PCT Handle: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/2 10 (second sheet) (July 2009)
<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)</td>
<td></td>
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<tr>
<td>----------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>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:</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>This International Searching Authority found multiple inventions in this international application, as follows:</td>
</tr>
<tr>
<td>Group I: claims 1-4, drawn to a method, comprising... c. determining whether the sample has one or more SNPs, wherein each of the SNPs indicates a respective protective allele, and d. determining that the subject has a reduced risk of developing IgA nephropathy if the subject has at least one protective allele. The first invention is restricted to rs6677604. Should an additional fee(s) be paid, Applicant is invited to elect an additional SNP(s) to be searched.</td>
</tr>
</tbody>
</table>

After the above, see Supplemental Sheet to continue. |

| 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 additional fees, this Authority did not invite payment of additional fees. |
| 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.: |
| 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.: 1-4, restricted to rs6677604 |

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

Form PCT/ISA/2 10 (continuation of first sheet (2)) (July 2009)
Box III. Observations where unity of invention is lacking:

Group II: claims 5-7, drawn to a method, comprising
(a) providing a library of candidate compounds to screen for binding to a target protein that is selected from the group comprising CFHRI and CFHRS;
(b) providing the target protein;...
(d) screening the library of candidate compounds for a compound that has high affinity binding to the target protein;
(e) if a compound binds to the target protein with high affinity, then determining if binding of the compound to the target protein reduces the biological activity of the target protein, and
(f) selecting the compound if it binds with high affinity to the target protein and thereby reduces the biological activity of the target protein.

Group III: claims 8-9, drawn to a method for treating or preventing IgAN in a subject by reducing the expression of CFHRI or CFHRS, or both comprising administering therapeutically effective amounts of inhibitory oligonucleotides that reduce the expression of CFHRI or CFHRS, or both.

Group IV: claims 10-11, drawn to a micro array comprising two or more oligonucleotides bound to a support that are complementary to and hybridize to one or more respective target oligonucleotide.

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

The inventions of Groups I through III do not include the inventive concept of a method comprising (a) providing a library of candidate compounds to screen for binding to a target protein that is selected from the group comprising CFHRI and CFHRS; (d) screening the library of candidate compounds for a compound that has high affinity binding to the target protein, as required by Group II.

The inventions of Group I through III do not include the inventive concept of a method, comprising (a) providing a library of candidate compounds to screen for binding to a target protein that is selected from the group comprising CFHRI and CFHRS; (d) screening the library of candidate compounds for a compound that has high affinity binding to the target protein, as required by Group II.

The inventions of Group I do not include the inventive concept of a method for treating or preventing IgAN in a subject by reducing the expression of CFHRI or CFHRS, or both comprising administering therapeutically effective amounts of inhibitory oligonucleotides that reduce the expression of CFHRI or CFHRS, or both, as required by Group III.

The inventions of Group III do not include the inventive concept of a method, comprising c. determining whether the sample has one or more SNPs, wherein each of the SNPs indicates a respective protective allele, and d. determining that the subject has a reduced risk of developing IgA nephropathy if the subject has at least one protective allele, as required by Group I.

The inventions of Group I share the technical feature of a method, comprising a. obtaining a DNA sample from a subject, b. analyzing the DNA sample to detect the presence of one or more SNPs, c. determining whether the sample has one or more SNPs, wherein each of the SNPs indicates a respective protective allele, and d. determining that the subject has a reduced risk of developing IgA nephropathy if the subject has at least one protective allele. However, this shared technical feature does not represent a contribution over prior art as being anticipated by an article titled "Uteroglobin gene polymorphisms affect the progression of immunoglobulin A nephropathy by modulating, the level of uteroglobin expression" by Kim et al. (Pharmacogenetics. 2001, 11(4):299-305) (hereinafter "Kim") that discloses a method, comprising:

a. obtaining a DNA sample from a subject (pg 2, col 2, "Extraction of genomic DNA and genotype determination. Genomic DNA was extracted from peripheral blood lymphocytes by standard methods using a commercially available kit");
b. analyzing the DNA sample to detect the presence of one or more SNPs (pg 2, col 2, "The A to G polymorphism in the 59 UTR of exon 1 of the uteroglobin gene was determined according to the method of Laing et al. (1998)");
c. wherein each of the SNPs indicates a respective protective allele (Abstract, G in the position 38), and
(d) determining that the subject has a reduced risk of developing IgA nephropathy if the subject has at least one protective allele (Abstract, G in the position 38, "Uteroglobin (UG) is an anti-inflammatory/immunomodulatory protein. Targeted disruption of UG rendered mouse glomerulonephritis resembling immunoglobulin (Ig)A nephropathy (IgAN). Sequence analysis on exon 1 of UG showed several putative binding sites for transcription factors, and polymorphisms in this site might influence the expression level of UG as a competitive protein. We speculated that the single nucleotide polymorphism at the 38th nucleotide (A to G) from the transcription initiation site of UG exon 1 would impact the progression of IgA nephropathy (IgAN)... An excess of A genotype was found in one patient having progressive disease (P = 0.03) and the risk for the disease progression increased as the number of A alleles increased (P for trend = 0.03) after follow-up for 116 months. The odds ratio for progression with the AA genotype was 4.9 (95% CI = 1.0-23.9) compared to patients having the GG genotype. Significant interactive effects of hypertension and genetic polymorphisms of UG on the disease progression were observed (P for interaction = 0.001). In the luciferase assay, the gene construct with G at the 38th site showed a decreased activity of 74 +/- 8.4% compared to that showed by G gene construct. Our results suggest that polymorphism at the 5' UTR region of UG exon 1 is an important marker for the progression of IgAN and may modulate the level of protein expression"). As said method was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another special technical feature of the inventions listed as Group I is the specific SNP(s) recited therein. The inventions do not share a special technical feature, because 1) no significant structural similarities can readily be ascertained among the SNPs, and 2) rs6677604 was known in the art at the time of the invention, as evidenced by the article titled "Association of factor H autoantibodies with deletions of CFHRI, CFHRS, CFH4, and with mutations in CFH, CFI, CD46, and C3 in patients with atypical hemolytic uremic syndrome" by Moore, et al. (Blood ePub 27 October 2009, 115(2):379-387) (pg 387, col 2, "In the study undertaken by Spencer et al, all deletion homozygotes were homozygous for alleles GCGAAG at ... rs6677604..."). Without a shared special technical feature, the inventions lack unity with one another.

Groups I through IV therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.