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(US).
- (81) Designated States (*unless otherwise indicated, for every  
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BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,  
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,  
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR,  
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,  
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,  
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MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,  
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20 February 2014



WO 2014/005076 A3

(54) Title: METHODS AND BIOMARKERS FOR DETECTION OF KIDNEY DISORDERS

(57) Abstract: Provided herein are compositions, kits, methods and biomarkers for detection and characterization and diagnosis of kidney disorders (e.g., one or more of nephronophthisis-related ciliopathies (NPHP-RC), congenital abnormalities of the kidney and urinary tract (CAKUT)), and karyomegalic interstitial nephritis (KIN)) in biological samples (e.g., tissue samples, blood samples, plasma samples, cell samples, serum samples).

INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2013/048688

<p>A. CLASSIFICATION OF SUBJECT MATTER INV. C12Q1/68 ADD.</p> <p>According to International Patent Classification (IPC) or to both national classification and IPC</p>														
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) C12Q</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, BIOSIS, EMBASE</p>														
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <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>X</td> <td>HILDEBRANDT F: "Exome resequencing identifies novel NPHP genes, implicating DNA damage response signaling in the pathogenesis of ciliopathies", CILIA, BIOMED CENTRAL LTD, LONDON, UK, vol. 1, no. Suppl 1, 18 May 2012 (2012-05-18), page 02, XP021123118, ISSN: 2046-2530, DOI: 10.1186/2046-2530-1-S1-02 the whole document</td> <td>1-43</td> </tr> <tr> <td>A</td> <td>US 2008/044831 A1 (HILDEBRANDT FRIEDHELM [US] ET AL) 21 February 2008 (2008-02-21) claims 1-15</td> <td>1-43</td> </tr> <tr> <td></td> <td style="text-align: center;">----- -/--</td> <td></td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	HILDEBRANDT F: "Exome resequencing identifies novel NPHP genes, implicating DNA damage response signaling in the pathogenesis of ciliopathies", CILIA, BIOMED CENTRAL LTD, LONDON, UK, vol. 1, no. Suppl 1, 18 May 2012 (2012-05-18), page 02, XP021123118, ISSN: 2046-2530, DOI: 10.1186/2046-2530-1-S1-02 the whole document	1-43	A	US 2008/044831 A1 (HILDEBRANDT FRIEDHELM [US] ET AL) 21 February 2008 (2008-02-21) claims 1-15	1-43		----- -/--	
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<p><input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.      <input checked="" type="checkbox"/> See patent family annex.</p>														
<p>* Special categories of cited documents :</p> <table border="0"> <tr> <td style="vertical-align: top;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="vertical-align: top;"> <p>"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</p> <p>"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</p> <p>"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</p> <p>"&amp;" document member of the same patent family</p> </td> </tr> </table>			<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&amp;" document member of the same patent family</p>										
<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&amp;" document member of the same patent family</p>													
<p>Date of the actual completion of the international search</p> <p style="text-align: center;">1 October 2013</p>		<p>Date of mailing of the international search report</p> <p style="text-align: center;">11/12/2013</p>												
<p>Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016</p>		<p>Authorized officer</p> <p style="text-align: center;">Schmitt, Anja</p>												

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2013/048688

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EDGAR A. OTTO ET AL: "Mutation analysis in nephronophthisis using a combined approach of homozygosity mapping, CEL I endonuclease cleavage, and direct sequencing", HUMAN MUTATION, vol. 29, no. 3, 1 March 2008 (2008-03-01), pages 418-426, XP055080938, ISSN: 1059-7794, DOI: 10.1002/humu.20669 the whole document	1-43
A	----- TOBY W HURD ET AL: "Mechanisms of Nephronophthisis and Related Ciliopathies", EXPERIMENTAL NEPHROLOGY, vol. 118, 11 November 2010 (2010-11-11), pages e9-e18, XP055081039, table 1 the whole document	1-43
A	----- MOUMITA CHAKI ET AL: "Genotype-phenotype correlation in 440 patients with NPHP-related ciliopathies", KIDNEY INTERNATIONAL, vol. 80, no. 11, 24 August 2011 (2011-08-24), pages 1239-1245, XP055080820, ISSN: 0085-2538, DOI: 10.1038/ki.2011.284 the whole document	143
A	----- HILDEBRANDT FRIEDHELM ET AL: "Ciliopathies.", THE NEW ENGLAND JOURNAL OF MEDICINE 21 APR 2011, vol. 364, no. 16, 21 April 2011 (2011-04-21), pages 1533-1543, XP009172886, ISSN: 1533-4406 the whole document	1-43
A	----- SIVASUBRAMANIAM SUDHAKAR ET AL: "Cep164 is a mediator protein required for the maintenance of genomic stability through modulation of MDC1, RPA, and CHK1", GENES AND DEVELOPMENT, COLD SPRING HARBOR LABORATORY PRESS, PLAINVIEW, NY, US, vol. 22, no. 5, 1 March 2008 (2008-03-01), pages 587-600, XP002577482, ISSN: 0890-9369, DOI: 10.1101/GAD.1627708 [retrieved on 2008-02-18] the whole document	1-43
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INTERNATIONAL SEARCH REPORT

International application No  
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X,P	<p>MOUMITA CHAKI ET AL: "Exome Capture Reveals ZNF423 and CEP164 Mutations, Linking Renal Ciliopathies to DNA Damage Response Signaling", CELL, vol. 150, no. 3, 1 August 2012 (2012-08-01), pages 533-548, XP055080695, ISSN: 0092-8674, DOI: 10.1016/j.cell.2012.06.028 the whole document -----</p>	1-43

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2013/048688

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search 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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional 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 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.:

1-43

### 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.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-43

Methods and kits for detecting gene variants associated with nephronophthisis-related ciliopathies (NPHP-RC) comprising identification of one or more variants in a first and a second gene selected from the group consisting of MRE11, ZNF423, CEP164.

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2. claims: 44-91

Methods and kits for detecting gene variants associated with congenital abnormalities of the kidney and urinary tract (CAKUT) comprising identification of one or more variants in a first and in a second gene selected from the group consisting of FRAS1, FREM1, RET, and BMP4.

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3. claims: 92-144

Methods and kits for detecting gene variants associated with karyomegalic interstitial nephritis (KIN) comprising identification at least one or at least two variants or mutations in a KAN or KAN1 gene.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2013/048688

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2008044831	A1	NONE	21-02-2008
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