



- (51) International Patent Classification:
C12Q 1/68 (2006.01) *G06F 19/22* (2011.01)
- (21) International Application Number:
PCT/US2014/039389
- (22) International Filing Date:
23 May 2014 (23.05.2014)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
61/827,385 24 May 2013 (24.05.2013) US
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,

[Continued on next page]

(54) Title: METHODS AND PROCESSES FOR NON-INVASIVE ASSESSMENT OF GENETIC VARIATIONS

FIG. 1

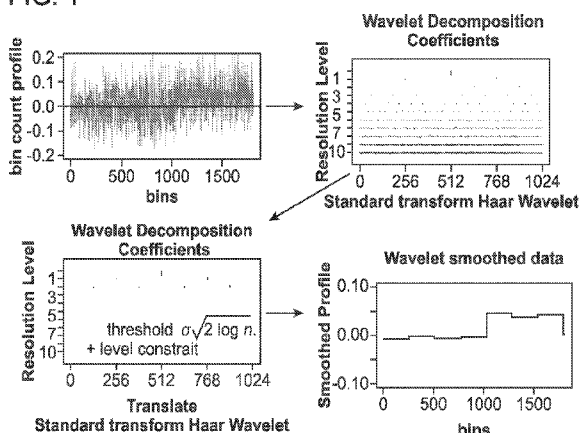
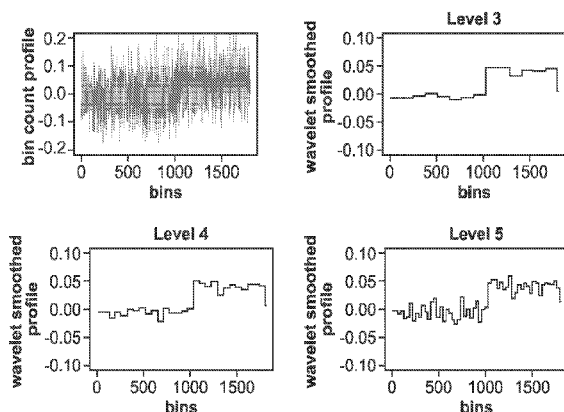


FIG. 2



(57) Abstract: Provided herein are methods for non-invasive assessment of genetic variations. The methods are based on mapped sequence reads and make use of decision analyses. The decision analyses sometimes include segmentation analyses and/or odds ratio analyses.



DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, 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, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,

LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(88) Date of publication of the international search report:

26 February 2015

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2014/039389

A. CLASSIFICATION OF SUBJECT MATTER

INV. C12Q1/68 G06F19/22
ADD.

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)

C12Q G06F

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)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHENGPEI CHEN ET AL: "A method for noninvasive detection of fetal large deletions/duplications by low coverage massively parallel sequencing", PRENATAL DIAGNOSIS, vol. 33, no. 6, 17 May 2013 (2013-05-17), pages 584-590, XP055136781, ISSN: 0197-3851, DOI: 10.1002/pd.4110	1-10, 21-74
Y	page 586, right-hand column, paragraph 4 Supplementary Material & Shangpei Chen ET AL: "Supplementary", Prenatal Diagnosis, 14 May 2013 (2013-05-14), pages 1-6, XP055137133, Retrieved from the Internet: URL: http://onlinelibrary.wiley.com/doi/10.1002/pd.4110/supinfo [retrieved on 2014-08-28] ----- -/-	11-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* 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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search

28 August 2014

Date of mailing of the international search report

17/12/2014

Name and mailing address of the ISA/

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METHODS AND PROCESSES FOR NON-INVASIVE ASSESSMENT OF GENETIC VARIATIONS

Provided herein are methods for non-invasive assessment of genetic variations. The methods are based on mapped sequence reads and make use of decision analyses. The decision analyses sometimes include segmentation analyses and/or odds ratio analyses.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/039389

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.:

1-74

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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/039389

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2013/052913 A2 (SEQUENOM INC [US]) 11 April 2013 (2013-04-11) claims 1,29 -----	11-14
Y	KIM K Y ET AL: "Identification of significant regional genetic variations using continuous CNV values in aCGH data", GENOMICS, ACADEMIC PRESS, SAN DIEGO, US, vol. 94, no. 5, 1 November 2009 (2009-11-01), pages 317-323, XP026691331, ISSN: 0888-7543, DOI: 10.1016/J.YGENO.2009.08.006 [retrieved on 2009-08-19] page 320, right-hand column, lines 17-19 -----	15-20
Y	OH M ET AL: "CAM: A web tool for combining array CGH and microarray gene expression data from multiple samples", COMPUTERS IN BIOLOGY AND MEDICINE, NEW YORK, NY, US, vol. 40, no. 9, 1 September 2010 (2010-09-01), pages 781-785, XP027274293, ISSN: 0010-4825 [retrieved on 2010-08-21] page 782, right-hand column, lines 38-41 -----	15-20
A	ERIC Z. CHEN ET AL: "Noninvasive Prenatal Diagnosis of Fetal Trisomy 18 and Trisomy 13 by Maternal Plasma DNA Sequencing", PLOS ONE, vol. 6, no. 7, 6 July 2011 (2011-07-06), page e21791, XP055024137, DOI: 10.1371/journal.pone.0021791 abstract -----	1
A	FANG-HAN HSU ET AL: "A model-based circular binary segmentation algorithm for the analysis of array CGH data", BMC RESEARCH NOTES, BIOMED CENTRAL LTD, GB, vol. 4, no. 1, 10 October 2011 (2011-10-10), page 394, XP021114635, ISSN: 1756-0500, DOI: 10.1186/1756-0500-4-394 abstract ----- -/--	3

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2014/039389

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NHA NGUYEN ET AL: "Denoising of Array-Based DNA Copy Number Data Using The Dual-tree Complex Wavelet Transform", BIOINFORMATICS AND BIOENGINEERING, 2007. BIBE 2007. PROCEEDINGS OF THE 7TH IEEE INTERNATIONAL CONFERENCE ON, IEEE, PISCATAWAY, NJ, USA, 1 October 2007 (2007-10-01), pages 137-144, XP031156780, ISBN: 978-1-4244-1509-0 abstract	3
A	----- WO 02/42496 A2 (UNIV CALIFORNIA [US]; HAUSSLER DAVID [US]; WINTERS HILT STEPHEN [US];) 30 May 2002 (2002-05-30) page 20, paragraph 2	15
A,P	----- WO 2013/177086 A1 (SEQUENOM INC [US]) 28 November 2013 (2013-11-28) page 78, paragraph 2 -----	1-74

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/039389

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013052913 A2	11-04-2013	AU 2012318371 A1 CA 2850781 A1 EP 2764459 A2 WO 2013052913 A2	17-04-2014 11-04-2013 13-08-2014 11-04-2013
WO 0242496 A2	30-05-2002	AU 3928402 A US 2003099951 A1 WO 0242496 A2	03-06-2002 29-05-2003 30-05-2002
WO 2013177086 A1	28-11-2013	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-74

Method of non-invasively determining the presence of a chromosomal aneuploidy, deletion or duplication by mapping sequence reads from a cell-free sample taken from a pregnant female carrying a fetus, and normalising and segmenting (wavelet decomposition or binary segmentation) the reads.

2. claims: 75-101

Method for determining a chromosomal aneuploidy by mapping sequence reads from a cell-free sample from a pregnant female bearing a fetus, determining a fetal fraction of the reads and calculating a log odds ratio of an aneuploidy by multiplying a conditional probability and a prior probability.
