(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 September 2003 (12.09.2003)

PCT

(10) International Publication Number
WO 03/074734 A2

(51) International Patent Classification[7]: C12Q 1/68

(21) International Application Number: PCT/GB03/00941

(22) International Filing Date: 5 March 2003 (05.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0205153.0 5 March 2002 (05.03.2002) GB
60/362,023 5 March 2002 (05.03.2002) US

(71) Applicant *(for all designated States except US)*: **MANTEIA S.A.** [CH/CH]; Zone Industrielle, Case postale 18, CH-1267 Coinsins (CH).

(71) Applicant *(for MN only)*: **LEE, Nicholas, John** [GB/GB]; Kilburn & Strode, 20 Red Lion Street, London WC1R 4PJ (GB).

(72) Inventors; and

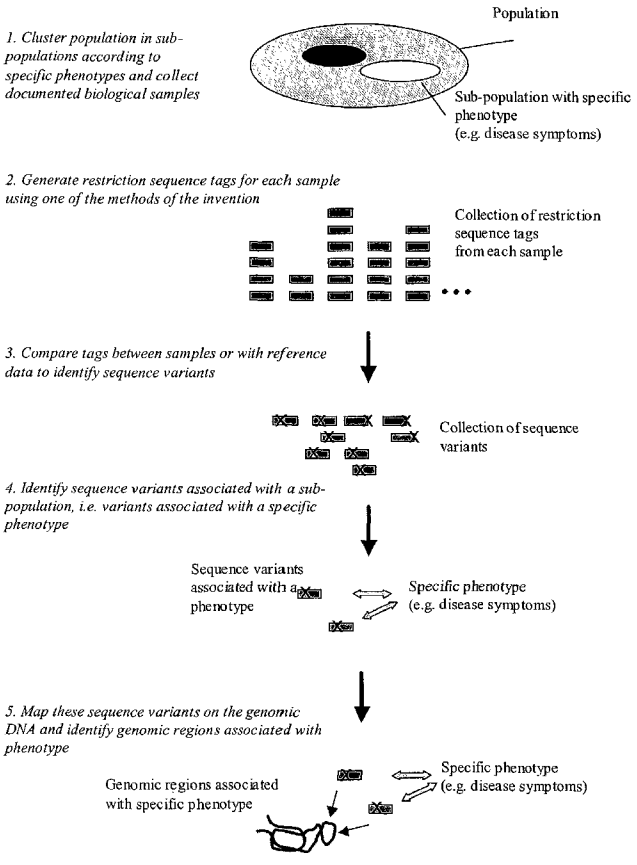
(75) Inventors/Applicants *(for US only)*: **MAYER, Pascal** [FR/FR]; Residence les Closets, Chemin de Ney, F-01200 Eloise (FR). **LEVIEV, Ilia** [RU/CH]; 33 route de Yens, CH-1143 Apples (CH). **OSTERAS, Magne** [NO/CH]; 32, route de Cite-Ouest, CH-1196 Gland (CH). **FARINELLI, Laurent** [CH/CH]; 55 Chemin du Grand-Puits, CH-1217 Meyrin (CH).

(74) Agents: **FORD, Timothy, James** et al.; Kilburn & Strode, 20 Red Lion Street, London WC1R 4PJ (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

[Continued on next page]

(54) Title: METHODS FOR DETECTING GENOME-WIDE SEQUENCE VARIATIONS ASSOCIATED WITH A PHENOTYPE



(57) Abstract: The invention provides methods for determining genome-wide sequence variations associated with phenotype of a species in a hypothesis-free manner. In the methods of the invention, a set of restriction fragments for each of a sub-population of individuals having the phenotype are generated by digesting nucleic acids from the individual using one or more different restriction enzymes. A set of restriction sequence tags for the individual is then determined from the set of restriction fragments. The restriction sequence tags for the sub-population of organisms are compared and grouped into one or more groups, each of which comprising restriction sequence tags that comprise homologous sequences. The obtained one or more groups of restriction sequence tags identify the sequence variations associated with the phenotype. The methods of the invention can be used for, *e.g.*, analysis of large numbers of sequence variants in many patient samples to identify subtle genetic risk factors.

WO 03/074734 A2

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.