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(51) International Patent Classification ⁶ : C12N 15/12, C12Q 1/68, C07K 14/47, 16/18, G01N 33/574, 33/577		A3	(11) International Publication Number: WO 97/24974 (43) International Publication Date: 17 July 1997 (17.07.97)	
(21) International Application Number: PCT/CA97/00006 (22) International Filing Date: 6 January 1997 (06.01.97) (30) Priority Data: 08/583,289 5 January 1996 (05.01.96) US 08/699,628 19 August 1996 (19.08.96) US (60) Parent Applications or Grants (63) Related by Continuation US 08/583,289 (CIP) Filed on 5 January 1996 (05.01.96) US 08/699,628 (CIP) Filed on 19 August 1996 (19.08.96) (71) Applicant (for all designated States except US): VISIBLE GENETICS INC. [CA/CA]; 700 Bay Street, Box 333, Toronto, Ontario M5G 1Z6 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): HUI, May [CA/CA]; 24 Wellesley Street, Toronto, Ontario M4Y 1G1 (CA). DUNN, James, M. [CA/CA]; 117 Citadel Drive, Scarborough, Ontario M1K 2S8 (CA). STEVENS, John, K. [CA/CA]; 540 Huron Street, Toronto, Ontario M5R 2R7 (CA). CAPATOS,			Denis [ZA/CA]; 646 Monarch Place, Waterloo, Ontario N2V 1X2 (CA). MATTHEWS, David, E. [CA/CA]; 774 Belmont Avenue West, Kitchener, Ontario N2M 1P4 (CA). (74) Agent: DEETH WILLIAMS WALL; Suite 400, 150 York Street, Toronto, Ontario M5H 3S5 (CA). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 27 November 1997 (27.11.97)	
(54) Title: COMPOSITIONS AND METHODS FOR DIAGNOSIS OF MUTATION IN THE VON HIPPEL-LINDAU TUMOR SUPPRESSOR GENE (57) Abstract The instant invention relates to methods and products for the diagnosis of mutations in the von Hippel-Lindau tumor suppressor gene. More specifically, the products are DNA oligonucleotides for use in amplifying and sequencing genomic DNA and kits including these oligonucleotides. The method of the invention relates to a hierarchical system for cost-effective diagnosis of von Hippel-Lindau tumor suppressor disease-associated mutations.				

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INTERNATIONAL SEARCH REPORT

Intern. Appl. No.

PCT/CA 97/00006

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C12Q1/68 C07K14/47 C07K16/18 G01N33/574
G01N33/577

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)

IPC 6 C12Q C07K

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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 26894 A (US HEALTH) 24 November 1994	13
A	cited in the application	14-29
	see the whole document	

Y	CHEN F ET AL: "Germline mutations in Von Hippel-Lindau disease tumor suppressor gene: Correlations with phenotype" HUMAN MUTATION, vol. 5, no. 1, 1995, pages 66-75, XP000677115 whole document, especially page 68, lns 7 & 8.	1-5, 13-29

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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *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

7 October 1997

Date of mailing of the international search report

22. 10. 97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 apo nl,
Fax: (+31-70) 340-3016

Authorized officer

Osborne, H

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 97/00006

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SUN Y ET AL: "The Von Hippel-Lindau (VHL) disease tumor -suppressor gene is not mutated in Nasopharyngeal carcinomas" INTERNATIONAL JOURNAL OF CANCER, vol. 60, May 1995, pages 437-38, XP000677121 see the whole document ---	1-5, 13-29
Y	DECKER H ET AL: "Molecular and cytogenetic studies on sporadic and familial forms of renal cell carcinomas: Detection of homozygous loss of the Von Hippel-Lindau tumor suppressor gene by cytogenetics, PCR-SSCP, FISH with 3P YAC probes and CGH" CANCER GENET. CYTOGENET, vol. 84, no. 2, February 1995, page 130 XP000677164 see the whole document ---	1-5, 13-29
P,X	WO 96 01909 A (VISIBLE GENETICS INC ;DIAMANDIS ELEFThERIOS (CA); DUNN JAMES M (CA) 25 January 1996 see page 8 -----	6-11

INTERNATIONAL SEARCH REPORT

... international application No.

PCT/CA 97/ 00006

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 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 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:

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 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.:
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/CA 97 00006

FURTHER INFORMATION CONTINUED FROM PCT/ISA210

- Subject 1: Claims 1-5,13-29: Nucleic acid based detection of mutations in the Von Hippel-Lindau tumor suppressor gene and oligonucleotides therefore
- Subject 2: Claims 6-12 : Hierarchical system of methods for testing a plurality of patients for a disease associated mutation in the Von Hippel-Lindau tumor suppressor gene

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/CA 97/00006

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9426894 A	24-11-94	US 5654138 A AU 6833794 A EP 0698093 A JP 8511158 T	05-08-97 12-12-94 28-02-96 26-11-96
WO 9601909 A	25-01-96	US 5545527 A US 5552283 A AU 3094895 A AU 4321696 A EP 0770145 A EP 0760011 A WO 9607761 A	13-08-96 03-09-96 09-02-96 27-03-96 02-05-97 05-03-97 14-03-96