



US005612179C1

(12) **EX PARTE REEXAMINATION CERTIFICATE** (7478th)
United States Patent
Simons
(10) **Number:** **US 5,612,179 C1**
(45) **Certificate Issued:** **May 4, 2010**

(54) **INTRON SEQUENCE ANALYSIS METHOD
FOR DETECTION OF ADJACENT AND
REMOTE LOCUS ALLELES AS
HAPLOTYPES**

(75) **Inventor:** **Malcolm J. Simons, Fryerstown (NZ)**

(73) **Assignee:** **Genetic Technologies Limited, Fitzroy,
Victoria (AU)**

Reexamination Request:
No. 90/010,318, Oct. 15, 2008

Reexamination Certificate for:
Patent No.: **5,612,179**
Issued: **Mar. 18, 1997**
Appl. No.: **07/949,652**
Filed: **Sep. 23, 1992**

FOREIGN PATENT DOCUMENTS

AU	16727/88	12/1988
AU	36908/89	12/1989
AU	45565/89	5/1990
DE	69029018	5/1997
EP	0237362	9/1987
EP	0256630	2/1988
EP	0269260	6/1988
EP	0364255	4/1990
EP	0370719	5/1990
EP	0414469	2/1991
EP	0443748	8/1991
WO	WO 89/12697	12/1969
WO	WO 89/04168	5/1989
WO	WO 89/04875	6/1989
WO	WO 89/11547	11/1989
WO	WO 90/02818	3/1990
WO	WO 90/12891	11/1990

OTHER PUBLICATIONS

Funke et al., "Detection of a New MSP I Restriction Fragment Length Polymorphism in the Apolipoprotein A-I Gene," J. Clin. Chem. Clin. Biochem., 25(3): 131-134, 1987.*

Geisel et al., "A New Aa L1 Restriction Fragment Length Polymorphism in the Low Density Lipoprotein Receptor Gene," J. Clin. Chem. Clin. Biochem., 26(7): 429-434, 1988.*

Koller et al., "Cloning and Complete Sequence of an HLA-A2 Gene: Analysis of Two HLA-A Alleles at the Nucleotide Level," J. Immunology, 134(4): 2727-2733, Apr., 1985.*

Koller et al., "Comparison of Multiple HLA-A Alleles at the DNA Level by Using Southern Blotting and HLA-A-Specific Probes," J. of Immunology, 135(6): 4229-4234, Dec. 1985.*

N'Guyen et al., "The HLA-AW24 Gene: Sequence, Surrounding and Comparison with HLA-A2 and HLA-A3 Genes," Immunogenetics, 21, 479, 1985.*

(Continued)

Related U.S. Application Data

(63) Continuation of application No. 07/551,239, filed on Jul. 11, 1990, now Pat. No. 5,192,659, which is a continuation-in-part of application No. 07/465,863, filed on Jan. 16, 1990, now abandoned, which is a continuation-in-part of application No. 07/405,499, filed on Sep. 11, 1989, now abandoned, which is a continuation-in-part of application No. 07/398,217, filed on Aug. 25, 1989, now abandoned.

(51) **Int. Cl.**
C12Q 1/68 (2006.01)
C12P 19/34 (2006.01)
C07H 21/04 (2006.01)
C12N 15/00 (2006.01)

(52) **U.S. Cl.** **435/6; 435/91.1; 435/91.2;
536/23.1; 536/24.3; 536/24.31; 536/24.33**

(58) **Field of Classification Search** None
See application file for complete search history.

References Cited**U.S. PATENT DOCUMENTS**

4,302,204 A	11/1981	Wahl et al.
4,458,066 A	7/1984	Caruthers et al.
4,582,788 A	4/1986	Erllich
4,683,194 A	7/1987	Saiki et al.
4,683,195 A	7/1987	Mullis et al.
4,683,202 A	7/1987	Mullis
4,772,549 A	9/1988	Frossard
4,835,098 A	5/1989	Orr et al.
4,994,370 A	2/1991	Silver et al.
5,075,217 A	12/1991	Weber
5,192,659 A	3/1993	Simons
5,200,313 A	4/1993	Carrico
5,310,893 A	5/1994	Erllich et al.
5,364,759 A	11/1994	Caskey et al.
5,612,179 A	3/1997	Simons
5,789,568 A	8/1998	Simons
5,851,762 A	12/1998	Simons
6,194,147 B1	2/2001	Baxter-Lowe et al.
6,503,707 B1	1/2003	Baxter-Lowe
2002/0197613 A1	12/2002	Canck et al.
2003/0119003 A1	6/2003	Simons
2004/0197775 A1	10/2004	Simons et al.

Primary Examiner—Gary L. Kunz

(57) ABSTRACT

The present invention provides a method for detection of at least one allele of a genetic locus and can be used to provide direct determination of the haplotype. The method comprises amplifying genomic DNA with a primer pair that spans an intron sequence and defines a DNA sequence in genetic linkage with an allele to be detected. The primer-defined DNA sequence contains a sufficient number of intron sequence nucleotides to characterize the allele. Genomic DNA is amplified to produce an amplified DNA sequence characteristic of the allele. The amplified DNA sequence is analyzed to detect the presence of a genetic variation in the amplified DNA sequence such as a change in the length of the sequence, gain or loss of a restriction site or substitution of a nucleotide. The variation is characteristic of the allele to be detected and can be used to detect remote alleles. Kits comprising one or more of the reagents used in the method are also described.

US 5,612,179 C1

Page 2

OTHER PUBLICATIONS

- Stetler et al., "Polymorphic restriction endonucleases sites linked to the HLA-DRa gene: Localization and use as genetic markers of insulin-dependent diabetes," *Proc. Natl. Acad. Sci.* 82: 8100-8104, Dec., 1985.*
- Koller et al., "Cloning and Complete Sequence of an HLA-A2 Gene: Analysis of Two HLA-A A1 at the Nucleotide Level," *J. Immunol.* 133: 2727, 1985.*
- N'Guyen et al., "The HLA-AW24 Gene: Sequence, Surroundings and Comparison with the HLA-A2 and HLA-A3 Genes," *Immunogenetics* 21: 479, 1985.*
- Stetler et al., "Polymorphic restriction endonuclease sites linked to the HLA-DRalpha gene: Localization and use as genetic markers of insulin-dependent diabetes," *Proc. Natl. Acad. Sci.* 82: 8100-8104, 1985.*
- Götze, et al., "The Major Histocompatibility Complex", *Fundamentals of Immunology*, Springer Verlag, 1981 (ed. Bier, da Silva, Götze, Mota).
- "Conserved Sequences at Exon-Intron Boundaries in Pre-mRNA," *Molecular Biology of the Gene*, 4th Edition, California, 1987, Chapter 20, pp. 639-640.
- Molecular Biology of The Cell*, 2nd Edition, New York, 1989, Chapter 9: "RNA Synthesis and RNA Processing" and Chapter 10: Control of Gene Expression, pp. 523-612.
- Royer-Pokora, et al., "Cloning the Gene for the Inherited Disorder Chronic Granulomatous Disease on the Basis of Its Chromosomal Location" *Cold Sp. Harbor Symp. LI:177-183* (1986).
- Lebo, et al., "Flow-sorting Analysis of Normal and Abnormal Human Genomes" *Cold Sp. Harbor Symp. LI:169-176* (1986).
- U.S. Appl. No. 07/398,217, filed Aug. 25, 1989, Simons.
- U.S. Appl. No. 07/405,499, filed Sep. 11, 1989, Simons.
- U.S. Appl. No. 07/465,863, filed Jan. 16, 1990, Simons.
- U.S. Appl. No. 07/550,939, filed Jul. 11, 1990, Simons.
- U.S. Appl. No. 07/907,721, filed Nov. 8, 1991, Simons.
- U.S. Appl. No. 07/971,856, filed Mar. 9, 1993, Simons.
- U.S. Appl. No. 09/070,497, filed Apr. 30, 1998, Simons.
- A.S.E.A.T.T.A. "Donor Reactive Alloantibodies Auto-Antibodies Revisited Aseatta Quality Control Transplantation in Thailand", vol. 20, No. 2, 1995, Newsletter, 15 pages.
- Adams, et al *Sci.* 252:1651-1656 (1991).
- Amselem, et al., "Determination of the Spectrum of β -Thalassemia Genes in Spain by Use of Dot-Blot Analysis of Amplified β -Globin DNA," *Am. J. Hum. Genet.* 43:095-100, 1988.
- Arnheim et al., "Use of Pooled DNA Samples To Detect Linkage Disequilibrium of Polymorphic Restriction Fragments and Human Disease: Studies of the HLA Class II Loci," *Proc. Natl. Acad. Sci. USA* 82:6970-6974 (Oct. 1985).
- Baird, et al. A Nucleotide Change At A Spice Junction In The Human B-Globin Gene is Associated With B-Thalassemia. *Jul. 1981. pp. 4218-4221. vol. 78 No. 7. Proc. Natl. Acad. Sci. USA.*
- Boehnke et al., "Fine-Structure Genetic Mapping of Human Chromosomes Using the Polymerase Chain Reaction on Single Sperm: Experimental Design Considerations," *The American Journal of Human Genetics*, vol. 45, No. 1, Jul. 1989, pp. 21-32.
- Boerwinkle et al, *PNAS*, 86:212-216 (1989).
- Brinster, et al. *Proc. Natl. Acad. Sci.* (1988) 85: 836-840.
- Brooks, et al., "Association of the Widespread A149P Hereditary Fructose Intolerance Mutation with Newly Identified Sequence Polymorphisms in the Aldolase B Gene," *Am. J. of Hum. Genet.*, 52:835-840 (1993).
- Bugawan et al., "The Use of Non-Radioactive Oligonucleotide Probes to Analyze Enzymatically Amplified DNA for Prenatal Diagnosis and Forensic HLA Typing", *Biotechnology* 6:943-947 (1988).
- Bugawan et al., *J. Immunol.* vol. 141, No. 12, pp. 4024-4030, 1988.
- C.K. Hurley, et al. "Large-Scale DNA-Based Typing of HLA-A and HLA-B At Low Resolution Is Highly Accurate Specific and Reliable", *Tissue Antigens* 55: 352-358, 2000.
- Cavalli-Sforza, L. *Am. J. Hum. Genet.* 46:649-651 (1990).
- Cereb, Nezh, et al., "Locus-Specific Conservation of the HLA Class Introns by Intra-Locus Homogenization," (1997) *Immunogenetics*, 47: 30-36.
- Certified Translation of Inoko (1989) "DNA Typing of HLA Antigen," *Nihon Rinsho*, 47, 550-576.
- Chien et al. *J. Bacteriol.*, 127:1550-1557 (1976).
- Clark, "Interference of Haplotypes from PCR-amplified Samples of Diploid Populations", *Mol. Biol. Evol.*, vol. 7, No. 2, 1990, pp. 111-112.
- Coleman. et al. "Polymorphisms in The Apolipoprotein AIOCI Gene Complex." 1986. pp. 213-228. *Mol. Biol. Med.* (1986) 3, 1986 Academic Press Inc. (London) Ltd.
- Coleman. et al. *Chemical Abstracts*. Sep. 15, 1986. pp. 175-176. vol. 105 No. 11. *Chemical Abstracts Service-The American Chemical Society*.
- Collins et al., "Variations on a Theme: Cataloging Human DNA Sequence Variation" *Science Nov. 28, 1997: vol. 278. No. 5343, pp. 1580-1581.*
- Caruthers, *Science* 230:281-285 (1985).
- Degli-Esposti, et al., "Updated Characterization Of The Fourth Ancestral Haplotypes Using Asia-Oceania Histocompatibility Workshop Panel", *Human Immunology* 44, 12-18 (1995).
- Den Dunnen et al, *Am. J. Hum. Genet.* 45(6):835-847 (1989).
- Deng, "A sensitive non-radioactive PCR-RFLP analysis for detecting point mutations at 12th condon oncogene c-Ha-ras in DNAs of gastric cancer," *Nucleic Acids Research*, vol. 16. No. 13, 1988, p. 6231.
- Di Marzo, et al., "The Spectrum of β -Thalassaemia Mutations in Sicily," *British Journal of Haematology*, 69, 393-397, 1988.
- Dicker, et al., "Sequence Analysis of a Human Gene Responsible for Drug Resistance: A Rapid Method for Manual and Automated Direct Sequencing of Products Generated by the Polymerase Chain Reaction," *BioTechniques*, vol. 7, No. 8, 1989, pp. 830-837.
- Diethard Tauiz, "Hypervariability of Simple Sequences As A General Source For Polymorphic DNA Markers", vol. 17, No. 16, 1989.
- DiLella, et al., "Tight linkage between a splicing mutation and a specific DNA haplotype in phenylketonuria," *Nature*, vol. 322, No. 28, Aug. 1986, pp. 799-803.
- Duyk, et al. *Proc. Natl. Acad. Sci.* (1990) 87:8995-8999.
- Eisses, et al., "Analysis of the Gene Encoding the Multifunctional Alcohol Dehydrogenase Allozyme ADH-71k of *Drosophila Melanogaster*," *Mol. Biol. Evol.*, 7:459-469 (1990).
- Erlich et al., *Biotechnology* 4:975-981 (1986).

US 5,612,179 C1

Page 3

- Feder et al., "A Novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis", *Nature Genetics*, vol. 13, Aug. 199, pp. 399-408.
- Funke et al., *Biosis* No. 84025050 Abstract.
- Funke, et al., "Pst I RFLP close to the LDL receptor gene—Synthetic 45 Base Oligodeoxynucleotide Representing A Sequence From the 18th Exon of The LDL Receptor Gene," p. 7820, vol. 14 No. 19, IRL Press United, Oxford, England, Nov. 19, 1986.
- Gavrilidis, A., et al., "HLA DRB1 Locus Sequence Typing", *Genotype*, Melbourne, Victoria, date unknown, pp. 1-2.
- Geisel et al., *Abstract Biosis* No. 87082065.
- Gitschier et al., "Genetic mapping and diagnosis of haemophilia A achieved through a BclI polymorphism in the factor VIII gene", *Nature*, 1985 Apr. 25-May 1;314(6013):pp. 738-740.
- Goldman et al., *Electrophoresis*, 3:24-26 (1982).
- Graham et al., "Application of Molecular Genetics to Prenatal Diagnosis and Carrier Detection in the Hemophilias: Some Limitations," *Blood*, vol. 66, No. 4, Oct. 1985, pp. 759-764.
- Green et al., "Chromosomal Region of the Cystic Fibrosis Gene in Yeast Artificial Chromosomes: A Model for Human Genome Mapping" *Science*, vol. 250, pp. 94-98.
- Grimm et al., *Am. J. Hum. Genet.* 45(3):368-372 (1989).
- Guardiola, John et al., "Molecular Genotyping of the HLA-DQalpha Gene Region," (1988) *Immunogenetics*, 27: 12-18.
- Gyllensten et al., *Proc. Natl. Acad. Sci. USA*, vol. 85, pp. 7652-7656, 1988.
- H. J. Noreen et al., "Validation Of DNA-Based HLA-A and HLA-B Testing Of Volunteers For A Bone Marrow Registry Through Parallel Testing With Serology", *Tissue Antigens* 57: 221-229, 2001.
- Harano et al., "Hemoglobin Abnormalities In A Black Family With HB S, Hereditary Persistence Of HB F, and A Y Chain Variant; A Reevaluation Through Gene Mapping", *Hemoglobin*, vol. 8(6), pp. 549-568, (1984).
- Horn et al., "Characterization and Rapid Diagnostic Analysis of DNA Polymorphisms Closely Linked to the Cystic Fibrosis Locus," *Clin. Chem.* 36: 1614-1619 (1990).
- Hyldig-Nielsen et al., *Proc. Natl. Acad. Sci. USA* 84:1644-1648 (1987).
- Inoko (1989) "DNA Typing of HLA Antigen," *Nihon Rinsho*, 47, 550-576.
- Iwahana, et al., "A New RFLP in Intron 1 of the Human c-Ha-ras1 Gene and its Close Relationship with the Variable Tandem Repeats in the Region 3' to the Gene," *Oncogene*, 5:1049-53, 1990.
- Jeffreys et al., "Amplification of human minisatellites by the polymerase chain reaction: towards DNA fingerprinting of single cells", *Nucleic Acid Research* 16:10953-10971 (1988).
- Jeffreys et al., *Nature*, 314 (1985), pp. 67-73.
- Kan et al., *N. Engl. J. Med.* 297: 1081-1084 (1977).
- Kazazian, Jr., Haig H. et al., "Molecular Basis and Prenatal Diagnosis of P-Thalassemia," (1988) *The Journal of The American Society of Hematology*, vol. 72, No. 4, pp. 1107-1116.
- Kerem et al., "Identification of the Cystic Fibrosis Gene: Genetic Analysis", *Science*, vol. 245, 1989, pp. 1073-1080.
- Kogan et al., "An Improved Method for Prenatal Diagnosis of Genetic Diseases by Analysis of Amplified DNA Sequences—Application to Hemophilia A," *The New England Journal of Medicine*, vol. 317, No. 16, Oct. 15, 1987, pp. 985-990.
- Kotsch, K. et al., "Sequencing of HLA Class I Genes Based on the Conserved Diversity of the Noncoding Regions: Sequencing-Based Typing of the HLA-A Gene," (1997) *Tissue Antigens*, 50: 178-191.
- Lander et al., "Homozygosity mapping: A way to map human recessive traits with the DNA of inbred children", *Science* 236: 1567-1570, Jun. 1987.
- Lawrence, et al., "Neonatal Lupus In Twins", *Southern Medical Journal*, vol. 82, No. 5, 1989, pp. 657-660.
- Liebhauer, et al., "Compensatory Increase in α 1-Globin Gene Expression in Individuals Heterozygous for the α -Thalassemia-2 Deletion," *J. Clin Invest*, Sep. 1985, 76(3): 1057-1064.
- Limm et al., "HLA-DQAI Allele and Suballele Typing Using Noncoding Sequence Polymorphisms Application to 4A0HW Cell Panel Typing", *Human Immunology* 38, 57-68 (1993).
- Little et al., "Nature", 285: 144-147, 1980.
- Maeda et al., *Tissue Antigens*, (1989), 34:290-298.
- Mariapia A. Degli-Esposti, et al., Characterization of 4A0HW Cell Line Panel Including New Data For The 10IHW Panel, *Hum. Immunol.* 1993,38: 3-16.
- Marshall, *Electrophoresis*, 4:269-272 (1983).
- Marx, "Dissecting the Complex Diseases," *Science*, vol. 247, Mar. 30, 1990, pp. 1540-1542.
- McGinnis et al., Ancient, Highly Polymorphic Human Major Histocompatibility Complex DQAI Intron Sequences, *American Journal of Medical Genetics*, 52:438-444 (1994) © 1994 Wiley-Liss, Inc.
- Messer, et al., "Polymorphic Structure of the Tumor Necrosis Factor (TNF) Locus: An NcoI Polymorphism in the First Intron of the Human TNF- α Gene Correlates with Variant Amino Acid in Position 26 and a Reduced Level of TNF α Production," *J. Exp. Med.*, 173: 209-219 (1991).
- Myerowitz, "Splice Junction Mutation in Some Ashkenazi Jews with Tay-Sachs Disease Evidence Against a Single Defect Within this Ethnic Group," *Proc. Natl. Acad. Sci. USA*, Jun. 1988 85(11): 3955-59.
- Nakamura, et al. *Science* (1987) 235: 1616-1620.
- Nakatsuji, et al., "Fetal Hemoglobin Variants Identified in Adults Through Restriction Endonuclease Gene Mapping Methodology", *Blood*, vol. 66, No. 4, 1985, pp. 803-807.
- Nathans et al., *Annual Review of Biochemistry* 44:273-293 (1975).
- Naughton et al., DPBI Locus PCR-RFLP Typing Of The Fourth Asia-Oceania Histocompatibility Workshop Cell Panel Reveals A Novel OPBI Allele, *European Journal Of Immunogenetics* (1994), 21, 351-364.
- Nickerson et al., "Identification of Clusters of Biallelic Polymorphic Sequence-Tagged sites (pSTSs) That Generate Highly Informative and Automatable Markers for Genetic Linkage Mapping", *Genomics* 12, 377-387, 1992.
- Ochman et al., "Genetic Applications of an Inverse Polymerase Chain Reaction", *Genetics* 120: 621-623 (1988).
- Olson et al, *Science* 245: 1434-1435 (1989).
- Orkin, et al., "Nonsense And Frameshift Mutations in β -Thalassemia Detected in Cloned β -Globin Genes." Oct. 10, 1981. pp. 9782-9784, vol. 256. No. 19. *The Journal Of Biological Chemistry USA*.

US 5,612,179 C1

Page 4

- Paul, et al, "DNA Polymorphic Patterns and Haplotype Arrangements of the apo A-I, apo C-ID, apc A-IV Gene Cluster in Different Ethnic Groups," *Hum Genet* (1987) 75: 264-268.
- R. V. Lebo, et al *Am. J. Hum. Genet* 47:583-590 (1990).
- Ricketts, et al, "Defective Splicing of Thyroglobulin Gene Transcripts in the Congenital Goitre of the Afrikaner Cattle," *The EMBO Journal*, vol. 4, No.3, pp. 731-737, 1985.
- Rieß, et al., "Hypervariability of intronic simple (gt).sub.n (ga).sub.m repeats in HLA-DRB genes," *Immunogenetics*, vol. 32, No. 2, Aug. 1990, pp. 110-116.
- Rigby et al. *J. Mol. Biol.*, 113: 237 (1977).
- Riordan et al., "Identification of the Cystic Fibrosis Gene: Cloning and Characterization of Complementary DNA," *Science*, vol. 245, 1989, pp. 1066-1073.
- Roger L. Dawkins, "Conclusions And Proposals For Future Workshops", *Human Immunology*, vol. 38, pp. 83-85, (1993).
- Rommens et al., "Identification of the Cystic Fibrosis Gene: Chromosome Walking and Jumping," *Science*, vol. 245, 1989, pp. 1059-1065.
- Ruano et al, "Direct haplotyping of chromosomal segments from multiple heterozygotes via allele-Specific PCR amplification," *Nucl. Acids. Res.* 17:8392 (1989).
- Ruano. et al., "Haplotype Of Multiple Polymorphisms Resolved By Enzymatic Amplification Of Single DNA Molecules," *Aug. 1990. pp. 6296-300. vol. 87. Proc. Natl. Acad. Sci USA.*
- Saiki et al., "Enzymatic Amplification of .beta.-Globin Genomic Sequences and Restriction Site Analysis for Diagnosis of Sickle Cell Anemia," *Science*, vol. 230, 1985, pp. 1350-1354.
- Saiki, Gyllensten and Erlich, *The Polymerase Chain Reaction in Genome Analysis: A Practical Approach*, ed. Davies pp. 141-152, (1988) I.R.L. Press, Oxford.
- Sallee et al., *Am. J. Human Genet.*, 45(4): A216, 1989.
- Sargent et al *EMBO* 8:2305-2312 (1989).
- Scharf et al., *Science*, Sep. 5, 1986, 233(4768), pp. 1076-1078.
- Scheffer et al, *Am. J. Hum. Genet.* 45(2):252-260 (1989).
- Schwartz et al., "Ordered Restriction Maps of Saccharomyces cerevisiae Chromosomes Constructed by Optical Mapping", *Science*, vol. 262, Oct. 1, 1993, pp. 110-114.
- Simons, et al., "HLA Haplotyping Using Non-Coding Polymorphisms", 4th Chromosome 6 Workshop, (1999), 4 pages.
- Simons, et al., "Strategy For Definition Of Drug Haplotypes In The 4AOHW Cell Panel Using Noncoding Sequence Polymorphisms", *Human Immunology*, vol. 38, pp. 69-74 (1993).
- Singer et al., "Genes & Genomes", 1991, pp. 698-699, 873, 929.
- Skolnick et al (1989) "Simultaneous analysis of multiple polymorphic loci, using amplified sequence polymorphisms (ASPo)," *Genomics* 2:273-279.
- Smeets et al., Use Of Variable Simple Sequence Motifs As Genetic Markers: Application To Study Of Myotonic Dystrophy, *Hum Genet* (1989) 83: 245-251.
- Stephens et al., "Theoretical Underpinning of the Single-Molecule-Dilution (SMD) Method of Direct Haplotype Resolution," *Am. J. Hum. Genet*, vol. 46, 1990, pp. 1149-1155.
- Taylor et al, *Nature* 251:392-393 (1974).
- Tegelstrom, *Electrophoresis*, 7:226-229 (1986).
- The Journal of the Japan Medical Association, vol. 97 (1987), pp. 637-640.
- Traver, et al. *Proc. Natl. Acad. Sci.* (1989) 86: 5898-5902.
- Varney, A. Gavrilidis, B.D. Tait, "Polymorphism In The Regulatory Regions Of HLA-DPB1" Tissue Laboratory, Department Of Pathology, The Royal Melbourne Hospital, Grattan Street, Parkville 3050, Australia., date unknown, 1 page.
- Wahl, et al. *PNAS* 6:3683-3687 (1979).
- Waikan et al. *P.N.A.S. U.S.A.*, vol. 75, No. 11, pp. 5631-5635, Nov. 1978.
- Wallace, et al *Sci.* 249:181-186 (1990).
- Weber et al. (1989) "Abundant class of human DNA polymorphisms which can be typed using polymerase Chain Reaction," *Am. J. Hum. Gen.* 44: 388-396.
- White, et al, "The Polymerase Chain Reaction," *TIG*, Jun. 1989, vol. 5, No. 6, pp. 185-189.
- Wong, Corrine et al., "Characterization of β -thalassaemia Mutations Using Direct Genomic Sequencing of Amplified Single Copy DNA," (1987) *Nature*, vol. 330, pp. 384-386.
- Zeng, et al., "Hereditary Persistence Of Fetal Hemoglobin Or ($\delta\beta$)^o-Thalassemia: Three Types Observed In South-Chinese Families", *Blood*, vol. 66, No. 6, 1985, pp. 1430-1435.
- Geisel, J. *Clin. Chem. Clin. Biochem.*, 26(7), 1988, 429-434.
- Aseatta, 1996 Annual Scientific Meeting, M.J. Simons, Genotype P/L. Fitzroy, Victoria, 3065.
- David Botstein. et al., Construction Of A Genetic Linkage Map in Man Using Restriction Fragment Length Polymorphisms, 1980. pp. 314-331. *Am J. Hum Genet* 32. 1980 American Society of Human Genetics.
- Elsevier, "Human Immunology", Fourth Asia-Oceania Histocompatibilityworkshop, Apr. 22-29, 1993, Perth, Western Australia, 1993HUIMDQ 38(1), 1993, pp.1, 2, 57-85.
- Simons, et al., "Donor Reactive Alloantibodies Auto-Antibodies Revisted Aseatta Quality Control Transplantation In Thailand", vol. 20, No.2 (1995).
- Basic & Clinical Immunology, 3rd Ed (1980) Lange Medical Publications, pp. 181-190.
- Abraham, et al., "Sequence differences between HLA-B and TNF distinguish different MHC ancestral haplotypes," *Tissue Antigens*, vol. 39, No. 3, Mar. 1992, pp. 117-121.
- Akerman, et al., "Identification of Deletion and Triple α -Globin Gene Haplotypes in the Montreal β -Thalassemia Screening Program: Implications for Genetic Medicine," *Am. J. Med. Genet.*, 36:76-84 (1990).
- Allen et al., *Biotechniques*, vol. 7, No. 7, pp. 736-744 (1989).
- Blasczyk et al., "Sequence analysis of the 2nd intron revealed common sequence motifs providing the means for a unique sequencing based typing protocol of the HLA-A locus," *Tissue Antigens*. 1996 Feb; 47(2):102-10.
- Brown et al, *Meth. Enzymol.*, 68:109-151 (1979).
- Burnside, et al, *Endocrinology* (1991) 128: 3183-3191.
- Carmi et al., "Use of a DNA pooling strategy to identify a human obesity syndrome locus on chromosome 15", *Human Molec. Genet.* 4: 9-13, 1995.
- Compton *Nature* 350:91 [1991].
- Cremer, et al. *Hum. Genet.* (1988) 80: 235-246.
- DiLella, et al., "Screening for Phenylketonuria Mutations by DNA Amplification with the Polymerase Chain Reaction," *The Lancet*, Mar. 5, 1988, pp. 497-499.

US 5,612,179 C1

Page 5

- Erlich et al., "Reliability of the HLA-DQ.alpha. PCR-Based Oligonucleotide Typing System," *Journal of Forensic Sciences*, Sep. 1990, pp. 1017-1018.
- Fries, et al., "The Bovine Genome Contains Polymorphic Microsatellites," *Genomics*, Oct. 1990; 8(2):403-6.
- Goto et al., "Genetic linkage of Werner's syndrome to five markers on chromosome 8", *Nature* 355: 735-738, Feb. 20, 1992.
- Honig, et al., "Human Hemoglobin Genetics," 1986, Springer-Verlag, pp. 227-249.
- Mardis et al., "Automated Methods for Single-Stranded DNA Isolation and Dideoxynucleotide DNA Sequencing Reactions on a Robotic Workstation," *BioTechniques*, vol. 7, No. 8, 1989, pp. 840-850.
- Monaco, et al. *Nature* 323:656-650 (1986).
- Nrang, et al, *Meth. Enzymol.*, 68:90-98 (1979).
- O'Hara et al. (1988) "The human factor VII gene is polymorphic due to variation in repeat copy number in a minisatellite," *Gene* 66: 147-158.
- Padgett et al., "Splicing of Messenger RNA Precursors," *Ann. Rev. Biochem.*, 55:1119-1150 (1986).
- Wyngaarden, *Human Gene Therapy* 1:73-92 (1990).
- S. H. Orkin, et al *Ann. Rev. Genet* 18:131-171 (1984).
- Saiki et al., *Nature*, vol. 324, pp. 163-166, 1986.
- Schreuder et al., *Human Immunology*, Nov. 1999, vol. 60, pp. 1157-1181.
- Schreuder et al., *Tissue Antigens*, Aug. 2001, vol. 58, pp. 109-140.
- Sheng-Jing Lu, et al., "Linkage Of A Nasopharyngeal Carcinoma Susceptibility Locus To The HLA Regions", *Letters To Nature*, *Nature* 346,470-471 (1990).
- Southern, *J. Mol. Biol.*, 98:503-517 (1975).
- Zhang et al. (1987) Structure of the mouse Adh-1 gene etc. *Gene* 57: 27-36.
- Jeffreys "DNA Sequence Variants in the Gy-, Ay-, Oy- and β-Globin Genes of Man" *Cell*, vol. 18, pp. 1-10, Sep. 1979.
- Bröcker-Vriends et al., "Carrier Detection of Haemophilia B by Using Intragenic Restriction-Fragment Length Polymorphism", *Thrombosis and Haemostasis*, 54(2), pp. 506-509, 1985.
- Connor et al., "Application of three intragenic DNA polymorphisms for carrier detection in haemophilia B", *Journal of Medical Genetics* 1986, vol. 23, pp. 300-309.
- Rees et al., "Haplotypes identified by DNA polymorphisms at the apolipoprotein A-I and CIII loci and hypertriglyceridaemia", *Hum. Genet* (1986), vol. 72, pp. 168-171.
- Moodie et al., "Carrier detection in 50 haemophilia A kindred by means of three intragenic and two extragenic restriction fragment length polymorphisms", *British Journal of Haematology*, 1988, vol. 70, pp. 77-84.
- "Linkage disequilibrium", copy from Wikipedia, printed Jan. 9, 2008, pp. 1-4.
- Strobeck, *Genetics* 103, pp. 545-555 (1983).
- Casula et al., *Blood*, vol. 75, No. 3, p. 662-670 (1990).
- Beaucage et al, *Tetrahedron letters*, 22:1859-1862 (1981).
- Maniatis et al. "Molecular Cloning A Laboratory Manual", 1982, p. 437.
- Simons and Erlich, pp. 952-959 In: *Immunology of HLA*, vol. 1: Springer-Verlag, New York (1989).
- Simons et al., pp. 959-1023 In: *Immunology of HLA*, vol. 1: Springer-Verlag, New York (1989).
- New England BioLabs 1988-1989 Catalog, p. 62, 1988.
- Search Report for nucleotide residue sequence "CTCTCAG-GCCTTGTT", Dec. 1996.
- Genetic Technologies Limited vs. Applera Corporation*, "Reply of Genetic Technologies Limited To Counterclaims of Applera Corporation" Sep. 25, 2003.
- Genetic Technologies Limited vs. Covance, Inc., And Variagenics Inc. Now Known As Nuvelo Inc., And Nuvelo, Inc.*, "Answer And Counterclaims By Covance, Inc., and Nuvelo, Inc., To Plaintiffs Complaint For Patient Infringement Demand For Jury Trial" Aug. 26, 2003.
- Genetic Technologies Ltd., v. Applera Corporation*, "Claim Construction Order", dated Sep. 15, 2004, pp. 1-13.
- Genetic Technologies Ltd., v. Applera Corporation*, "Answer and Counterclaims of Defendant Applera Corporation", dated Sep. 5, 2003, pp. 1-16.
- Genetic Technologies Limited vs. Applera Corporation*, "Complaint For Patent Infringement" Mar. 26, 2003.
- "Nullification Action of Bioscientia Institute for Medical Diagnostics" against EP-B1 0 414 469 (German patent 690 29 018), Jun. 21, 2007, 860 pages.
- Translation of Opposition dated Jul. 15, 2007 against the nullity complaint, 136 pages.
- Translation of Reply to the brief of the patent proprietor dated Dec. 13, 2007 supplying grounds for its objection, pp. 1-28.
- Schlieben, et al., "Genotyping of Bovine Kappa-Casein (Kappa-CAN, Kappa-CNB, Kappa-CNC, Kappa-CNE) Following DNA Sequence Amplification and Direct Sequencing of Kappa-CNE PCR Product," *Anim. Genet.* 1991; 22(4):333-42.
- Seilhamer et al., *DNA*, vol. 3, No. 4, 309-317 (1984).

* cited by examiner

US 5,612,179 C1

1
EX PARTE
REEXAMINATION CERTIFICATE
ISSUED UNDER 35 U.S.C. 307

NO AMENDMENTS HAVE BEEN MADE TO
THE PATENT

2
AS A RESULT OF REEXAMINATION, IT HAS BEEN
DETERMINED THAT:

5 The patentability of claims **26-32** is confirmed.
Claims **1-25** and **33-36** were not reexamined.

* * * * *