UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

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ASSOCIATION FOR MOLECULAR PATHOLOGY; AMERICAN COLLEGE OF MEDICAL GENETICS; AMERICAN SOCIETY FOR CLINICAL PATHOLOGY; COLLEGE OF AMERICAN PATHOLOGISTS; HAIG KAZAZIAN, MD; ARUPA GANGULY, PhD; WENDY CHUNG, MD, PhD; HARRY OSTRER, MD; DAVID LEDBETTER, PhD; STEPHEN WARREN, PhD; ELLEN MATLOFF, M.S.; ELSA REICH, M.S.; BREAST CANCER ACTION; BOSTON WOMEN'S HEALTH BOOK COLLECTIVE; LISBETH CERIANI; RUNI LIMARY; GENAE GIRARD; PATRICE FORTUNE; VICKY THOMASON; KATHLEEN RAKER,

Plaintiffs,

v.

UNITED STATES PATENT AND TRADEMARK OFFICE; MYRIAD GENETICS; LORRIS BETZ, ROGER BOYER, JACK BRITTAIN, ARNOLD B. COMBE, RAYMOND GESTELAND, JAMES U. JENSEN, JOHN KENDALL MORRIS, THOMAS PARKS, DAVID W. PERSHING, and MICHAEL K. YOUNG, in their official capacity as Directors of the University of Utah Research Foundation,

Defendants.

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09 Civ. 4515 (RWS)

ECF Case

DECLARATION OF CHRISTOPHER E. MASON

I, Christopher E. Mason, declare under penalty of perjury:

1. I am a post-doctoral associate in the Program on Neurogentics at Yale University. I am also the Visiting Fellow in Genomics, Ethics and Law of the Information Society Project at Yale Law School and a lecturer at the Law School.

2. I received a BS from the University of Wisconsin in 2001, a Masters degree from Yale in 2003, and a PhD from Yale in 2006. In each case, my area of study has been genetics.

3. I have written widely on the subject of genetics, publishing approximately 20 papers. For many of those papers, I was principal author. All were published in peer-reviewed journals such as Science, Genome Research, American Journal of Medical Genetics, Neurogenetics, and Human Mutation. I have also lectured all over the world on the subject of genetics. A copy of my curriculum vitae is attached.

4. The human genome is a three billion letter recipe for the creation of a human being, from a single-celled embryo to the 10 trillion cells of an adult. The genome of each human being is contained within almost every cell in the body. It defines obvious traits such as skin tone, eye color, and sex, but also directs the manifestation of very complex traits such as obesity, diabetes, Alzheimer's, or bipolar disorder.

5. Within the nucleus of human cells, the genome is found in tightly wound strands of DNA that merge with multiple proteins to form 46 chromosomes (23 inherited from mother and 23 inherited from father). This is the double-helix structure made famous by Watson and Crick.

6. The genome is composed of proteins and DNA. The DNA is the information content of the genome. DNA is made from four different nucleic acids: Adenosine (A), Cytosine (C), Guanine (G), and Thymine (T). Thus, each of the DNA strands consists essentially of a long string of these nucleic acids, represented by the four letters.

7. Smaller pieces of the DNA on each chromosome have been shown to create the proteins that the body uses for many of its functions. These smaller pieces are called genes. They are represented by certain combinations of these letters (A, C, G, and T) and are the specific instructions and actions of the genome.

8. The concept of a gene has existed since the 19th century. Gregor Mendel, in his experiments with pea plants,showed that certain traits are passed on as discrete entities, and do not appear blended in offspring. Mendel hypothesized that it was the assortment of these factors –called the genotype – that determined the appearance of the plants – the phenotype.

9. In 1909, Mendel's hidden unit of inheritance was called the "gene." Yet, the gene remained an abstract concept until 1915, when it was shown that genes corresponded to physical spans of chromosomal material. In 1941, George Beadle and Edward Tatum proposed the 'one gene, one enzyme' hypothesis. This hypothesis stated that each individual gene gives rise to a single protein which in turn carries out a distinct biochemical function in the cell. A subsequent series of experiments revealed that the genes on chromosomes were made of DNA. In 1953, James Watson and Francis Crick discovered the double-helix structure of the DNA molecule.

10. Francis Crick continued decrypting the genetic code and proposed "the central dogma" of molecular biology: (1) information is encoded in DNA, (2) expressed as a copy called RNA, then (3) translated to eventually create a functional protein. In this scheme, a gene is a defined span of chromosomal DNA. In this central dogma, an active gene undergoes transcription and translation.

11. In transcription, DNA strands are unwound inside the body and the region that is the gene creates a temporary copy of itself called a messenger RNA (mRNA). This mRNA is initially very long and contains regions that need to be spliced out (introns) and regions that remain as part of the transcript (exons). The spliced mRNA is then finished by adding a cap on the beginning (5' G Cap) and a protective tail at the end (polyA tail). All of these process are done by the body and the order and actions are dictated by nature. The introns are removed by

the body as a natural process because they will not be necessary for creation of a protein. The body ensures that the exons remain because they will be necessary for creation of a protein.

12. Translation is the process of converting the processed mRNA into a protein. This occurs at the ribosome of the cell. The ribosome converts tri-nucleotide segments (codons) into amino acids, which create the poly-peptide (protein). In other words, the DNA represented by three letters (called a tri-nucleotide or a codon) create a single amino acid. The amino acids, when linked together, create a protein and the protein does the work of the body.

13. Genes are represented by letters corresponding to nucleic acids. This is referred to as the gene sequence. A gene sequence is generally hundreds or thousands of letters long and looks like GATCGCATG.... The process by which scientists or clinicians identify the sequence of a particular gene is called gene sequencing and is described below.

14. Except for identical twins, no two humans are genetically the same. Variation in the human genome is very common, and each person is estimated to be 99.5% similar, or to have five differences every 1000 base pairs (bp). The longest form of the BRCA gene is approximately 80,000bp, meaning that each person possesses at least 400 points of genetic variation in this gene.

15. Large scale variation can occur in the genome, such as the addition or deletion of substantial chromosomal regions. Thus, a particular gene may omit several hundred letters at one point or may add several hundred letters where they do not normally exist.

16. Small scale variation can also occur, manifested as slight sequence differences between the same genes in different individuals. Thus, for example, a sequence of a gene represented by ...GACTCG... might contain a variation that omits the first C (GATCG) or that

adds an extra C at that point (GACCTCG) or that reverses the order of two of the letters (CCATCG).

17. Scientists often refer to the "wild-type" or "normal" gene, which is the gene without variations. However, the notion that there exists a gene without variations is increasingly misleading. Newfound recognition of the high frequency of variation between individuals has implications for the definition (and patenting) of genes: such variation reinforces the emerging idea that no single DNA sequence can adequately capture either the human genome or a single gene, both of which occur naturally in a variety of forms.

18. Molecular characterization of genomes has already revealed substantial variation between normal human individuals in the form of chromosomal abnormalities. These structural variants are now believed to cover as much as 12% of the human genome. Thus, in any given individual, some tens of millions of nucleotides can be missing or duplicated with respect to the publicly available reference (or "wild-type") sequence. These extra copies or missing copies of the genome that are larger than 1000bp are called copy number variants (CNVs).

19. Some variants appear to have little or no effect on the body's processes. There are also variants whose significance is currently unknown. Other variants appear to correlate with an increased risk of particular diseases. These variants are called mutations. If a mutation exists in enough people (>5% of the population), they are called polymorphisms.

20. For example, certain mutations in the genes at issue in this case have been correlated with an increased risk of breast and/or ovarian cancer. These mutations were created by nature. The correlations between the mutations and the increased risk of disease are created by nature.

21. Because nature dictates that certain mutations increase the risk of disease, it is informative to sequence an individual's gene and determine if the mutation exists in one or both alleles, and if the person is carrying a mutant allele.

22. Labs and scientists sequence genes on a daily basis all over the world. Thousands of people have the technical knowledge and skill to sequence a gene, and now there are dozens of companies offering whole genome sequencing.

23. Once a gene has been sequenced, the result is the string of letters (bp). The letters are then examined to see if the mutation exists. In other words, the process of sequencing is designed simply to illuminate the information that nature has dictated in that person's genome. In that respect, sequencing is essentially no different than looking at something through a microscope. It takes something created by nature but too small to be seen and makes it visible.

24. There are a number of ways to sequence a gene. The first complete human genome was sequenced by the Human Genome Project. The main method of the Human Genome Project and the main method for most scientists still, is PCR (Polymerase Chain Reaction)-based amplification.

25. To sequence a gene, there are two main methods. PCR-amplification of the targeted gene or molecular cloning of a transformed eukaryotic host cell. Most scientists today use PCR-based methods to examine heritable (germline) genetic alterations and the germline sequence. However, these same methods can be used to examine non-heritable (somatic) changes; the source of DNA is what determines the difference.

26. For PCR-based amplification of a gene, primers are designed that flank the sequence of the gene, and a template DNA is required (for example, from a human patient). For this reaction to occur, the gene must first be taken out of the body and the DNA strands isolated.

This is done by lysing (breaking open) the cells through sonication, removal of membranes by adding a detergent, removing proteins with a digestive enzyme, and then precipitating (condensing) the DNA in alcohol.

27. Another way to extract the DNA from a sample is by reverse transcription. In this process, the mRNA from cells are isolated and converted back into DNA for subsequent sequencing.

28. Reverse transcription of RNA depends upon having processed mRNAs. Mature mRNAs lack all the introns (have been spliced). They also have a long poly-adenosine (polyA) tail, and so the transcripts can be bound and isolated by pushing them through a column packed with complementary polyT sequences. Once isolated, the single-stranded mRNAs serve as a template in a reaction to create the complementary sequence, using an enzyme called reverse transcriptase. This creates the complementary DNA (cDNA) of the RNA, which can then be sequenced on machines that sequence DNA.

29. cDNA does not exist in the body in the resultant form. However, cDNA is simply a mirror of the RNA which does exist in the body. In other words, as with the RNA, introns have been removed. The letter order is no longer that of the RNA but of its mirror. In other words, in the body, certain of the nucleotides, represented by the letters, always bind or attach to certain other nucleotides or letters. G always links to C and A always links to T. If the RNA in the body is a G, then the cDNA in the lab is a C. Knowing that the cDNA is a C tells you without exception that the RNA was a G. An alternative way of looking at this is to compare the cDNA with the original DNA. In this case, because the RNA was a mirror of the DNA, the cDNA is again identical to the DNA. The only difference is the introns have been removed. Thus, the functional sequence of the cDNA is identical to the functional sequence of the DNA.

30. To sequence DNA, researchers usually use dye-terminator methods, where a single-stranded DNA template is annealed to an oligonucleotide primer, extended using DNA polymerase, and then monitored by cameras. Each of the four bases (A,C,G,T) has a specific fluorescent dye that absorbs and emits light as the bases are integrated into the new strand of DNA, producing a chromatogram that indicates the sequence present in the template.

31. I have personally sequenced genes.

32. Regardless of the technique used to sequence the gene, the resultant string of letters is useful only insofar as it illuminates the sequence found in the body. The informational and functional content of the sequence produced as a result of any of these techniques is identical to the sequence in the body. Thus, even though the structure of cDNA does not exist in precisely the same form in the body, for literally all practical and information-based purposes it is identical to that in the body. In addition, the sequence even of the cDNA is dictated not by scientists but by nature. And, as noted, the significance of that sequence, including its relationship to any disease, is dictated by nature.

33. As a product of nature, the DNA should never have been awarded patent protection. As the cDNA is essentially equivalent to the DNA, and was found using established methods, patents claims of the cDNA should also be rejected.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

Executed 08/20, 2009

Christopher Mason