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(54) **Title:** SYSTEM AND METHOD FOR THE COMPUTATIONAL PREDICTION OF EXPRESSION OF SINGLE-GENE PHENOTYPES

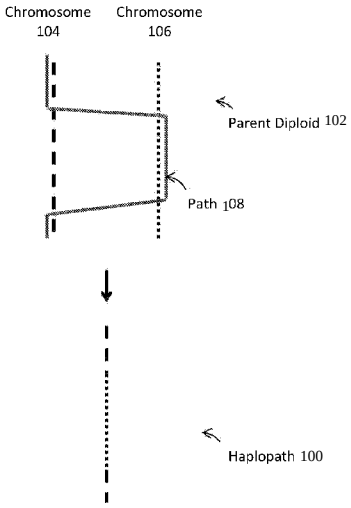

Fig. 4

(57) **Abstract:** In accordance with an embodiment of the invention, a system and method is provided for determining a probability of a progeny having one or more phenotypes Phj each associated with a single gene Qj. A score sip may be assigned to each allele hip at a plurality of genetic loci (i) in a haploid genome profile Hp of a parent (p). A plurality (Nj) of the alleles hkp (k=l,...,Nj) associated with the gene Q may be identified. The scores sip may be mapped or indexed to gene- specific scores sj,kp associated with gene Q_j for the plurality of (Nj) alleles hkp. A probability may be computed for alter - ing the gene product from gene Q_j in a progeny of the parent (p) to be a func - tion of the gene- specific scores sj,kp.

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SYSTEM AND METHOD FOR THE COMPUTATIONAL PREDICTION OF EXPRESSION OF SINGLE-GENE PHENOTYPES

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit of prior U.S. Provisional Application Serial No. 61/733,600, filed December 5, 2012, which is incorporated herein by reference in its entirety.

FIELD OF EMBODIMENTS OF THE INVENTION

[002] Embodiments of the present invention relate generally to the field of genetics. In particular, embodiments of the present invention relate to predicting expression of single gene phenotypes in virtual or potential progeny or to predicting a future emergence of expression of single gene phenotypes in living organisms.

BACKGROUND OF EMBODIMENTS OF THE INVENTION

[003] Carrier testing is currently the most highly resolving method for determining the risk of recessive disease in a potential child of two prospective parents. A carrier test determines whether or not a potential parent has one gene copy containing a mutation associated with an autosomal recessive Mendelian disease caused by mutations in both copies of the gene. DNA-based carrier tests for over one thousand disease-genes have been defined, for example, at Genetic Testing Registry (GTR) at the National Center for Biotechnology Information (NCBI).

[004] A "carrier" of a recessive disease mutation does not exhibit disease symptoms because that person also carries a "normal" allele of the gene that produces a sufficient amount of the protein. But when two individuals are both carriers for a recessive mutation in the same gene, the likelihood of having a child with the disease is 25%.

[005] Carrier tests are designed and scored based on the simple Mendelian assumption that every variant of a gene is either "pathogenic" (mutant) or "non-pathogenic" (normal). As a consequence, carrier test results are restricted to one of three possible outcomes: a "positive" diagnosis means the variant is known empirically to be pathogenic; a "negative" diagnosis means the variant is known to be non-pathogenic; and "VUS" refers to a variant of unknown significance which means that a diagnosis cannot be made because of the lack of sufficient prior data. Still, the assumption is that VUS is a temporary classification and that with sufficient data, the variant will be classifiable as either positive (pathogenic) or negative (non-pathogenic).

[006] Reference is made to Fig. **1**, which is a diagram of traditional carrier testing results for (n=4) variants of the ACYL-CoA Dehydrogenase Medium-Chain (ACADM) gene associated

with the genetic disease MCADD. The table in Fig. **1** charts the (n^2=16) possible combinations of such variants in a potential progeny of maternal and paternal parents. Tests are positive for MCADD expression in the potential progeny when the combined proportional reduction in function of the maternal and paternal parents is above a threshold and negative when the combined proportional reduction in function is below a threshold. The simple positive/negative results do not distinguish between mild and severe forms of the disease. The carrier test also provides a number of inaccurate diagnoses in the form of false positives and false negatives as compared to the validated clinical outcome results empirically observed that are shown in Fig. **2.**

[007] Carrier testing is unique among diagnostic tests in that disease is typically only observed in persons other than those being tested. This is problematic for several reasons. First, a positive diagnosis has no disease relevance to a person who chooses not to reproduce. Second, even for cystic fibrosis (CF: the most prevalent serious recessive disease among children born to people of European descent), the risk of disease for a child of a diagnosed carrier is only 1%. (In northern European populations, the carrier frequency for pathogenic mutations in the cystic fibrosis-associated CFTR gene is 0.04, which represents the probability (4%) that a diagnosed carrier will, by chance, marry another carrier. The probability that a child of two carriers will inherit the disease is 25%. Thus, the next-generation risk to a single person who is a CF carrier is 0.04 X 0.25 = 0.01 or 1%.) Nevertheless, if the simple Mendelian model of disease causation were true and two prospective parents both tested positive, the result would be sufficient to predict a 25% risk of disease in their child.

[008] However, the Mendelian model is not correct in many cases, for example, because a gene may harbor variants at any DNA base across its coding region. Different non-synonymous variants may correspond to different amino acid changes at different locations in the gene product with different effects on protein function. Whether a child expresses a phenotype such as disease, and how severely, may depend on the particular pair of variants present in a genotype. In particular, the same variant may cause severe disease in genotypic combination with some variants but not others. In such cases, simple categorization of a variant as pathogenic or non-pathogenic is meaningless, as is the notion of carrier status.

[009] Carrier tests are typically categorized as medical diagnostic tests and, as such, typically undergo the same process of validation as other diagnostic tests. Reference is made to Fig. **2,** which is a diagram of validated clinical outcome results for the variants of the ACADM gene shown in Fig. **1.** Validation requires a demonstrated association between test results and clinical disease. This means that a particular DNA variant cannot be considered pathogenic unless it is found in a child with disease. In the pre-personal genomics era (prior to 2007), pathogenic

variants were routinely discovered through DNA sequencing of children expressing disease. However, with whole exome sequencing of tens of thousands of healthy individuals, numerous supposedly pathogenic DNA variants have been discovered in known disease genes without having been observed in subjects.

[0010] The lack of forward association is not unexpected since the incidence of a recessive disease is typically orders of magnitude lower than the frequency of corresponding disease alleles. As an example, a genetic disease with an incidence of one in 40,000 is associated with a carrier frequency of 1% (according to a Hardy-Weinberg calculation). In the absence of disease association, a particular damaging DNA variant may not be incorporated into a "diagnostic" carrier test, even if disease likelihood may be estimated on theoretical grounds. As a consequence of large-scale sequencing efforts, unvalidated but potentially deleterious DNA variants (in the VUS class) now outnumber validated disease variants in nearly every established recessive disease gene. Thus, the {+ / - / VUS } result choice used in diagnostic testing is even less accurate in predicting gene expression in virtual progeny since there may be no clinical validation of a simulated organism.

SUMMARY OF EMBODIMENTS OF THE INVENTION

[001 1] There is now provided according to embodiments of the invention an improved system and method for effectively overcoming the aforementioned difficulties inherent in the fields of carrier testing and clinical validation.

[0012] In accordance with an embodiment of the invention, a system and method is provided for determining a probability of a progeny having one or more phenotypes *Phj* each associated with a single gene *Qj* . A haplopath $H^p = [hf, hf, \ldots, h^p_N\}$ may be generated including a single allele hf £ (1,2) at each of a plurality of loci *(i=\ ,…, N)* from a genome profile of a potential parent *(p).* A variance score sf may be assigned to each of a plurality of the alleles hf in the haplopath. Each of the variance scores sf may indicate a probability that the allele hf results in altering the gene product from gene *Qj.* Each variant allele hf^1, which has a variance score sf indicating a non-zero probability, may be associated with a corresponding one of a plurality of *(k=l, …,Nj)* variant alleles hf known to alter the gene product from gene *Qj.* For each gene *Qj,* a gene-specific penetrance score $\hat{s}^p_{j,k}$ may be assigned to each of the *(Nj)* variant alleles hf associated with the gene *Qj.* For each gene *Qj* , a probability of altering the gene product from gene *Qj* in the virtual progeny of the parent *(p)* may be determined based on the gene-specific penetrance scores $\hat{s}^p_{j,k}$ of the plurality of *(Nj)* variant alleles *hf.* For each gene *Qj,* the probability of

expression of the phenotype ***Phj*** or a derivation of the probability of altering the gene product or a derivation of the probability of altering the gene product, for example, displayed or further processed.

[0013] In accordance with an embodiment of the invention, a system and method is provided for determining a probability of a progeny having one or more phenotypes ***Phj*** each associated with a single gene ***Qj***. A score ***sf*** may be assigned to each allele h_i^p at a plurality of genetic loci ***(i)*** in a haploid genome profile H^p of a parent ***(p)***. A plurality ***(Nj)*** of the alleles h_k^p ***(k=l, …,Nj)*** associated with the gene ***Qj*** may be identified. The scores ***sf*** may be mapped or indexed to gene-specific scores $\hat{s}_{j,k}^p$ associated with gene ***Qj*** for the plurality of ***(Nj)*** alleles hi_k^p. A a probability of altering gene product from gene ***Qj*** in a progeny of the parent ***(p)*** may be computed to be a function of the gene-specific scores $\hat{s}_{j,k}^p$.

[0014] In accordance with an embodiment of the invention, a system and method is provided for determining a probability of having a phenotype in a virtual progeny. A virtual progeny genome sampling ***G*** may be generated, wherein at each of a plurality of genetic loci ***i = 1, … , N*** the sampling comprises one allele h_i^{p1} from a first genome profile of a first potential parent ***(pi)*** and one allele h_i^{p2} from a second genome profile of a second potential parent ***(p2)***. Genotypes of said virtual progeny genome sampling ***G*** may be compared to one or more databases of genotype-phenotype associations to determine a phenotype associated with database genotypes matching genotypes of said virtual progeny genome sampling ***G***. Each genotype-phenotype association may also be associated with a penetrance value. A random number may be generated to determine if the virtual progeny is predicted to express the phenotype. If the virtual progeny is predicted to express the phenotype, the penetrance value may be associated with a degree of expressivity of the phenotype in the virtual progeny.

[0015] In contrast to current methods that consider only a positive/negative (or unknown, VUS) carrier status for individual persons, embodiments of the invention provide a scale of the degree or severity of expression in actual or simulated genomes. In contrast to current methods that assume a 100% correlation between genotype and phenotype, embodiments of the invention generate a random number to randomize the correlation between genotype and phenotype that mimics the randomized correlation in nature. In contrast to current methods that score phenotypic expression for each allele individually, embodiments of the invention combining gene-specific scores for a plurality of alleles associated with a gene, thereby incorporating all possible gene-specific effects.

BRIEF DESCRIPTION OF THE DRAWINGS

[001] The subject matter regarded as the invention is particularly pointed out and distinctly claimed in the concluding portion of the specification. The invention, however, both as to organization and method of operation, together with objects, features, and advantages thereof, may best be understood by reference to the following detailed description when read with the accompanying drawings in which:

[002] Fig. **1** is a diagram of traditional carrier testing results for variants of the ACYL-CoA Dehydrogenase Medium-Chain (ACADM) gene associated with the genetic disease MCAD deficiency;

[003] Fig. **2** is a diagram of validated clinical outcome results for the variants of the ACADM gene shown in Fig. **1**;

[004] Fig. **3** is a diagram of results of testing for expression of the MCAD deficiency due to any of four known mutations of the ACADM gene in accordance with embodiments of the invention;

[005] Fig. **4** is a schematic illustration of a haplopath or virtual gamete generated from a potential parent diploid genome profile according to an embodiment of the invention;

[006] Fig. **5** is a schematic illustration of a system according to an embodiment of the invention;

[007] Fig. **6** is a flowchart of a matching method for predicting the expression of phenotypes in progeny according to embodiments of the invention;

[008] Fig. **7** is a flowchart of a scoring method for predicting the expression of phenotypes in progeny according to embodiments of the invention; and

[009] Fig. **8** lists genes and their associated diseases, which may be used for computer-generated diagnosis according to embodiments of the invention.

[0010] It will be appreciated that for simplicity and clarity of illustration, elements shown in the figures have not necessarily been drawn to scale. For example, the dimensions of some of the elements may be exaggerated relative to other elements for clarity. Further, where considered appropriate, reference numerals may be repeated among the figures to indicate corresponding or analogous elements.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

[001] In the following description, various aspects of the present invention will be described. For purposes of explanation, specific configurations and details are set forth in order to provide a thorough understanding of the present invention. However, it will also be apparent to one skilled

in the art that the present invention may be practiced without the specific details presented herein. Furthermore, well known features may be omitted or simplified in order not to obscure the present invention.

[002] Unless specifically stated otherwise, as apparent from the following discussions, it is appreciated that throughout the specification discussions utilizing terms such as "processing," "computing," "calculating," "determining," or the like, refer to the action and/or processes of a computer or computing system, or similar electronic computing device, that manipulates and/or transforms data represented as physical, such as electronic, quantities within the computing system's registers and/or memories into other data similarly represented as physical quantities within the computing system's memories, registers or other such information storage, transmission or display devices.

[0011] In accordance with embodiments of the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

[0012] As used herein, "haploid cell" refers to a cell with a haploid number (n) of chromosomes.

[0013] "Gametes", as used herein, are specialized haploid cells (e.g., spermatozoa and oocytes) produced through the process of meiosis and involved in sexual reproduction.

[0014] As used herein, "gametotype" refers to single genome copies with one allele of each of one or more loci in the haploid genome of a single gamete.

[0015] As used herein, an "autosome" is any chromosome exclusive of the X and Y sex chromosomes.

[0016] As used herein, "diploid cell" has a homologous pair of each of its autosomal chromosomes, and has two copies (2n) of each autosomal genetic locus.

[0017] The term "chromosome", as used herein, refers to a molecule of DNA with a sequence of base pairs that corresponds closely to a defined chromosome reference sequence of the organism in question.

[0018] The term "gene", as used herein, refers to a DNA sequence in a chromosome that codes for a product (either RNA or its translation product, a polypeptide) or otherwise plays a role in the expression of said product. A gene contains a DNA sequence with biological function. The biological function may be contained within the structure of the RNA product or a coding region for a polypeptide. The coding region includes a plurality of coding segments ("exons") and intervening non-coding sequences ("introns") between individual coding segments and non-coding regions preceding and following the first and last coding regions respectively.

[0019] The term "gene product", as used herein, refers to a product (either RNA or its translation product, a polypeptide) that is encoded by a gene and that has biological function.

[0020] As used herein, "locus" refers to any segment of DNA sequence defined by chromosomal coordinates in a reference genome known to the art, irrespective of biological function. A DNA locus may contain multiple genes or no genes; it may be a single base pair or millions of base pairs.

[0021] As used herein, a "polymorphic locus" is a genomic locus at which two or more alleles have been identified.

[0022] As used herein, an "allele" is one of two or more existing genetic variants of a specific polymorphic genomic locus.

[0023] As used herein, a "single nucleotide polymorphism" or "SNP" is a particular base position in the genome where alternative bases are known to distinguish one individual from another. Most categories of more complex genetic variants may be reduced for analytical purposes to one or a few defining SNPs.

[0024] As used herein, a "copy number variant" or "CNV" is a deletion or duplication of a large block of genetic material that exists in a population at a frequency less than 1%.

[0025] As used herein, a "copy number polymorphism" or "CNP" is a deletion or duplication of a large block of genetic material that exists in a population at a frequency of greater than 1%. Since a CNV in one population may be a CNP in a second population, the two terms may be used interchangeably.

[0026] As used herein, "genotype" refers to the diploid combination of alleles at a given genetic locus, or set of related loci, in a given cell or organism. A homozygous subject carries two copies of the same allele and a heterozygous subject carries two distinct alleles. In the simplest case of a locus with two alleles "A" and "a", three genotypes may be formed: A/A, A/a, and a/a.

[0027] As used herein, "genotyping" refers to any experimental, computational, or observational protocol for distinguishing an individual's genotype at one or more well-defined loci.

[0028] As used herein, a "haplotype" is a unique set of alleles at separate loci that are normally grouped closely together on the same DNA molecule, and are observed to be inherited as a group. A haplotype may be defined by a set of specific alleles at each defined polymorphic locus within a haploblock.

[0029] As used herein, a "haploblock" refers to a genomic region that maintains genetic integrity over multiple generations and is recognized by linkage disequilibrium within a population. Haploblocks are defined empirically for a given population of individuals.

[0030] As used herein, "linkage disequilibrium" is the non-random association of alleles at two or more loci within a particular population. Linkage disequilibrium is measured as a departure

from the null hypothesis of linkage equilibrium, where each allele at one locus associates randomly with each allele at a second locus in a population of individual genomes.

[0031] As used herein, a "genome" is the total genetic information carried by an individual organism or cell, represented by the complete DNA sequences of its chromosomes.

[0032] As used herein, a "genome profile" is a representative subset of the total information contained within a genome. A genome profile contains genotypes at a particular set of polymorphic loci.

[0033] As used herein, a "personal genome profile", abbreviated PGP, is the genome profile of a particular individual person.

[0034] As used herein, a genetic "trait" is a distinguishing attribute of an individual, whose expression is fully or partially influenced by an individual's genetic constitution.

[0035] As used herein, "disease" refers to a trait that is at least partially heritable and causes a reduction in the quality of life of an individual person.

[0036] As used herein, a "phenotype" includes alternative traits which may be discrete or continuous. Phenotypes may include both traits and diseases.

[0037] As used herein, a "haplopath" is a haploid path laid out along a defined region of a diploid genome by a single iteration of a Monte Carlo simulation or a single chain generated through a Markov process. A haplopath is generated through the application of formal rules of genetics that describe the reduction of the diploid genome into haploid genomes through the natural process of meiosis. It may be formed by starting at one end of a personal chromosome or genome and walking from locus to locus, choosing a single allele at each step based on available linkage disequilibrium information, inter-locus allele association coefficients, and formal rules of genetics that describe the natural process of gamete production in a sexually reproducing organism.

[0038] A Virtual Gamete is a single haplopath that extends across an entire genome.

[0039] As used herein, a "Virtual Progeny genome sampling" is the discrete genetic product of two Virtual Gametes.

[0040] As used herein, a "Virtual Progeny genome" is a collection of discrete Virtual Progeny genome samplings, each generated by combining two uniquely-derived (e.g. random or partially random) Virtual Gametes. In some instances, a Virtual Progeny genome is represented as a probability mass function over a sample space of all discrete genome states. In some instances, a Virtual Progeny genome is an informed simulation of a child or children that might result as a consequence of sexual reproduction between two individuals.

[0041] As used herein, a "Virtual Progeny phenome" is a multi-dimensional likelihood function representing the likelihood and/or likely degree of expression of a set of one or more phenotypes from a complete Virtual Progeny genome. In some instances, a Virtual Progeny phenome is represented as a probability mass function over a sample space of discrete or continuous phenotypic states. In some instances, a Virtual Progeny phenome is an informed simulation of a child or children that might result as a consequence of sexual reproduction between two individuals.

[0042] As used herein, "partner" includes a marriage partner, sexual or reproductive partner, domestic partner, opposite-sex partner, and same-sex partner.

[0043] The methods and compositions disclosed herein relate to assessing the genotypes of individuals and the phenotypes associated with particular genotypes of potential progeny from such individuals. Generally, genome profiles from two individuals are used to determine the probabilities that potential progeny from such individuals will express certain traits, such as an increased risk of disease. Such methods are referred to herein as "Virtual Progeny assessment."

[0044] As used herein, "NCBI" refers to the National Center for Biotechnology Information which is a division of the National Library of Medicine at the U.S. National Institutes of Health. The NCBI operates under a Congressional mandate to develop, maintain and distribute databases and software to the research and medical communities.

[0045] As used herein, a "variant" is a particular allele at a locus where at least two alleles have been identified.

[0046] As used herein, a "mutation" has the same meaning as a "mutant allele" which is a variant that causes a gene to function abnormally.

[0047] As used herein, a "single gene phenotype" is a phenotype that may be caused by the expression of a genotype of a single gene.

[0048] As used herein, a "single gene disease" is a disease that may be caused by a mutation or mutations in a single gene

[0049] As used herein, a "recessive phenotype" is a single gene phenotype whose expression is restricted to individuals who inherit a genotype with two copies of a particular gene.

[0050] As used herein, a "dominant phenotype" is a single gene phenotype whose expression is restricted to individuals who inherit a genotype with at least one copy of a particular gene.

[0051] As used herein, "disease risk" refers to the likelihood that an existing person or virtual progeny will express a specified disease based on an interpretation of genetic data which is informed by empirical data or bioinformatic modeling.

[0052] As used herein, a "non-synonymous variant" is a DNA variant that alters the coding sequence of a gene, thereby altering the amino acid sequence of the protein product of the gene.

[0053] As used herein, "altering the gene product" (and grammatical variations thereof and the like) from a gene, refers to a change of the wild-type or normal biological function of the gene and that is caused by mutations of the gene. Alteration of the gene product from a gene includes alterations to transcription of the gene, alterations to translation of the gene, and alterations to the gene product itself.

[0054] It may be appreciated by persons of skill in the art that the discussion herein of disease, mutations, variants and other defective or negative functions are only examples of phenotypes and that such embodiments relate to any phenotype having negative, positive or neutral function.

[0055] Embodiments of the invention may provide a system and method for testing for a probability of future emergence of phenotypes in living organisms (real progeny that do not currently express the phenotypes) or for testing for a probability of phenotypic expression in virtual progeny (simulated progeny or genetic information for a hypothetical organism that does not currently exist). Although a virtual progeny is not a living organism, its genetic information is derived or extracted from real genetic material of living organisms - the virtual progeny's living potential parents. (Living organisms may include organisms that were living at any time including those that are now dead.)

[0056] In contrast to a living organism that has known or empirically observable genetic information, the genetic information of a virtual progeny is unknown. To predict a virtual progeny genome sampling, a virtual haploid (e.g. a virtual sperm or egg) may be simulated from the real diploid genetic material of each potential parent. In nature, haploids are generated from diploids by genetic recombination in which two copies of a chromosome from a single parent are crossed or combined into one, e.g., at least partially at random.

[0057] Reference is made to Fig. **4,** which schematically illustrates a haplopath **100** generated from a potential parent diploid genome profile **102** in accordance with an embodiment of the invention. Haplopath **100** $H^p = \{h_1, h_2, \ldots, h_N\}$ may be a virtual gamete such as a virtual egg or virtual sperm (or genetic information therefrom) including a single allele h_i £ (1,2) of a genotype at each of a plurality of loci *i*=\,. .., N from a diploid genome profile **102** of a potential parent *(p).* Generating the haplopath may simulate genetic recombination of the two chromosomes **104** and **106** from the parent's diploid genome profile **102** (having two alleles at each genetic locus) to generate one haploid or haplopath (having one allele per genetic locus). A haplopath may be generated by progressing locus-by-locus through the first parent's diploid genome and selecting one of the two alleles at each genetic locus (either the allele in

chromosome 104 or the allele in chromosome 106). The process of selecting alleles locus-by-locus may resemble a path 108 moving or progressing back and forth between chromosomes 104 and 106. The selection of one allele per locus —a "haploid" progressing along that "path" 108 - forms a virtual haploid referred to as a "haplopath" 100. Haplopath 100 may mimic virtual recombination of the genetic material in the two chromosomes 104 and 106 to form a discrete haploid genome, e.g., as a sperm or egg. This process may be repeated for each potential parent to generate two haplopaths 100 H^{p1} and H^{p2} (e.g. sperm and egg). The first and second haplopaths 100 may be combined to simulate the mating of the first and second potential parents resulting in a virtual progeny genome sampling $G = \{[h_i^{p1}, h_i^{p2}]; i = 1, \ldots, N\}$ (a discrete genome of a child potentially to be conceived).

[0058] However, this mating is just one of the many possible genetic combinations of the first and second potential parents. To generate a statistically reliable result, this process is repeated multiple (M) times (e.g., a thousand or ten thousand times) to generate a virtual progeny genome G including a plurality of the virtual progeny genome samplings $G^{vp} = \{G_1, G_2, \ldots, G_M\}$, where each iteration may use a different genetic recombination path 108, to see other recombination possibilities of mating the first and second potential parents.

[0059] Phenotypic analysis may be executed for each individual virtual progeny sample G_x and the results for all (or a subset) of the samplings in the virtual progeny G^{Vp} may be combined to generate an average probability, probability distribution or virtual progeny phenome (a multi-dimensional likelihood function) to indicate, for multiple possible simulated matings, the overall likelihood of phenotypic expression in a potential progeny.

[0060] Current carrier testing determines the probability of expression of a phenotype based each parent's allele at only a single genetic locus, one locus at a time (e.g. see the 16 individual +/- results for 16 individual mutant combinations for the two parents in Fig. 1). However, each phenotype Phj and its corresponding gene Qj may be associated with multiple (Nj) genetic loci (e.g. tens, hundreds or thousands). Any one (or combination of more than one) of the (Nj) gene-specific loci may activate (or damage) gene Qj and trigger the expression of the corresponding phenotype Phj , and different combinations of the (Nj) gene-specific loci may trigger different degrees or likelihoods of expression. To take the multiple, gene-specific loci into account, embodiments of the invention may determine the probability of expression of phenotype Phj by analyzing the impact of the combination of alleles at the plurality of the (Nj) associated gene-specific loci. Embodiments of the invention may test phenotype expression using a matching method and/or a scoring method.

[0061] In the matching method, genotypes from a virtual or real progeny genome sampling are compared and matched to one or more databases of genotype-phenotype associations. If database genotypes match the genotypes of the virtual progeny genome sampling at one, multiple or all of the *(Nj)* gene-specific loci, the progeny may have a non-zero probability of altering the gene product of gene *Qj*. A random number may be generated and compared to one or more thresholds to predict if the virtual or living progeny will have the phenotype associated with the matched gene (e.g. an above-threshold random number indicating expression and a below-threshold random number indicating no expression). Determining phenotypic expression based on a random number may simulate the at least partially random correlation between genotype and phenotype expression in nature. If the phenotype is predicted to express, the degree or likelihood of expression may be defined as an expressivity or penetrance value (or a function thereof) associated with the matching genotype in the database. A match for a dominant gene may include a match of one of the two alleles for each genotype, while a match for a recessive gene may include only matches of both alleles for each genotype. When analyzing a living organism for recessive genotypes, each allele may be associated with its originating parent, for example, to detect if both parents carry an allele to express a recessive genotype.

[0062] In the scoring method, scores may be assigned to alleles at a plurality of genetic loci of each parent diploid genome profile. The scores may define a degree or likelihood of altering a gene product. The scores may be gene-specific, for example, representing an empirically observed or statistically predicted probability that alleles at the associated gene-specific genetic loci in the parents result in alteration of the gene product in a progeny of those parents, such as an autosomal recessive disease. In one example, there may be a mutation in which a damage score may indicate that an allele causes a loss of function of the gene product (e.g., alters the amino acid sequence known to damage the protein product of the gene causing a diseased phenotype). Scores for all (or a subset) of alleles at the *(Nj)* gene-specific genetic loci may be combined to determine an overall probability *Pj* of altering the gene product from gene *Qj*. For example, the probability *Pj* of altering the gene product from gene *Qj* associated with each individual parent *(p)* may be $(1 - \prod_{k=1}^{Nj} [1 - \hat{s}_{j,k}^{p}])$, where $\hat{s}_{j,k}^{p}$ is the gene-(/) specific score assigned to the allele located at the *k*th genetic locus *(k* runs from a first *(k=\)* to a last *(k= Nj)* of the *(Nj)* gene-specific loci). Since $\hat{s}_{j,k}^{p}$ represents the probability of expression or expressivity associated with an allele at the *k*th locus, $(1 - \hat{s}_{j,k}^{p})$ may represent the probability of alteration of the gene product (e.g., loss of function of the gene product) associated with the allele at the Mi locus, $\prod_{k=1}^{Nj}[1 - \hat{s}_{j,k}^{p}]$ may represent the combined probability that the gene product associated

with alleles at all *Nj* gene-(Qj) loci is not altered, and $(1 - \prod_{k=1}^{Nj}[1 - \hat{s}_{j,k}^{p}])$ may represent the combined probability of alteration of the gene product associated with alleles at all *Nj* gene-(<2/) loci. For a recessive phenotype, the probability *Pj* of having the gene-(<2/) phenotype *Phj* in a progeny of two potential parents *(pi)* and *(p2)* may be the product of the probabilities associated with each individual parent, e.g. $p_j^{p1,p2} = (1 - \prod_{k=1}^{Nj}[1 - \hat{s}_{j,k}^{p1}])(1 - \prod_{k=1}^{Nj}[1 - \hat{s}_{j,k}^{p2}])$. For a dominant phenotype, the probability *Pj* of having the gene-(Q/) phenotype *Phj* in a progeny of two potential parents *(pi)* and *(p2)* may be the sum of the probabilities associated with each individual parent, e.g., $P_j^{p1,p2} = (1 - \Pi¾ \quad 1 - ¾¾ + (1 - \prod_{k=1}^{Nj}[1 - \hat{s}_{j,k}^{p2}])$. Other probabilities or derivations or modifications of the aforementioned probabilities may be used.

[0063] The probability of expression *Pj* (e.g. generated by either the matching or scoring methods) may be used to determine a phenotype outcome for each living or virtual progeny. A continuous range of outcomes (e.g. such as a percentage) or a plurality of discrete outcomes (e.g., no expression, mild, moderate, severe or complete expression, or any other categories) may be used to define a degree or likelihood of phenotype expression. Discrete outcomes may be determined by comparing the probability *Pj* (or a derivation thereof) to one or more threshold ranges each associated with a different outcome category and selecting the outcome category associated with the threshold range satisfied by the probability.

[0064] In embodiments in which scores define a degree of alteration of a gene product, the degree of alteration may be equated with the probability *Pj* (or a derivation thereof). In embodiments in which scores define likelihoods of complete expression, a random number may be used to determine if the phenotype completely expresses or not, and if the phenotype is determined to completely express, the likelihood of complete expression may be equated with the probability *Pj* (or a derivation thereof). The random number may be used to simulate the indeterminate nature of phenotype expression.

[0065] The genetic information for a living organism is unique. Accordingly, a single iteration of the scoring or matching process may be executed to generate a single probability of expression *Pj* for the living organism. However, for a virtual organism, the genetic information is not known but predicted, and thus a plurality (e.g. thousands) of virtual progeny genome samplings G_i may be generated in a virtual progeny genome G^{vp}. Accordingly, the aforementioned processes may be repeated for each of the plurality of virtual progeny genome samplings G_i and the resulting probabilities and/or outcomes may be combined, for example, to produce an average, median or mode single outcome or a statistical distribution of outcomes.

[0066] The aforementioned processes may generate the probability P_j of degree or likelihood of expression for a phenotype associated with a single gene Qj. Such processes may be repeated for each of a plurality of genes $(j=\ ,\ldots,J)$.

[0067] The following discussion of diseases or mutations is provided as an example and these embodiments may relate to any phenotype. Embodiments of the invention may use genetic information, such as, established disease genotypes (e.g. for the matching method) and variant risk of impact on gene product (e.g. for the scoring method).

[0068] The established disease genotypes database may include information representing diploid genotypes found previously in individual persons together with empirically derived values for expressivity and penetrance. Resources for the derivation of this table include the genotype-phenotype correlations section of each disease record in Gene Reviews at the NCBI, the Allelic Variants section of the OMIM database, and other databases maintained by NCBI or other organizations. Genotypes may be single locus or multi-locus.

[0069] The variant risk of impact on gene product may include information representing known and/or postulated DNA variant alleles in each recessive gene together with computationally derived scores. The scores may describe the likely impact on the gene product of a gene copy containing the variant. Scores may range in value between, for example, zero and one (or indicating probabilities in a range from zero to one). Scores may be generated through the integration of data obtained from computational tools such as PolyPhen, which evaluates the likelihood that a specific amino acid substitution will damage protein function, and Provean, which implements a damage potential algorithm based on natural selection, for example, by detecting changes in amino acids and determining if such change is tolerated in other species. Provean and PolyPhen may be used to predict loss-of-function and gain-of-function mutations.

[0070] In one example, a score of 0.0 may indicate that an allele that has no impact on gene function and a score of 1.0 may indicate that an allele is likely to eliminate 100% of gene function with 100% probability, and scores between 0.0 and 1.0 represent corresponding intermediate degrees or likelihoods of gene damage, although any other scores may be used. The score may be interpreted as a likelihood of the loss of function of the gene product (e.g., protein inactivation or as a relative reduction in protein activity).

[0071] Virtual gametes from hypothetical or maternal (M) and paternal (P) potential parents may be constructed, e.g. as described herein and/or in US Patent Application Publication No. 2011/0124515, which is hereby incorporated by reference in its entirety. Two virtual gametes are combined (MxP) to produce a discrete virtual progeny genome (G). Virtual progeny genome (G) may be represented, for example, as an (Nx2) dimensional data structure such as a table, matrix,

or sequence, defining alleles h_i^m and h_i^p at the *N* genome loci of each of the maternal *(H™)* and paternal *(Hp)* haplopaths, for example, as follow.

$$\mathbf{G}^{\mathrm{M\times P}} = \left\{ \left[\mathrm{h}_i^m , \mathrm{h}_i^p \right]; i = 1,\ldots,N \right\}$$

[0072] In accordance with the matching method, the two alleles at each individual locus of the virtual progeny genome *G* may be combined into a third set of genotypes. Embodiments of the invention may interrogate or search for this set of genotypes in the established disease genotype database. If a match is detected, a random number may be used to determine whether the specific virtual progeny under investigation is affected. If affected, the severity of the disease may be defined as the expressivity value (or a function thereof).

[0073] In accordance with the scoring method, alleles h_i™ and h_i^p in each haplopath *(H'n)* and *{HP)* of the virtual progeny genome *G* may be mapped by a one-to-one mapping to corresponding scores s_i™ and s_i^p, for example, as follows.

$$\left[\mathrm{h}_i^m , \mathrm{h}_i^p \right] \rightarrow \left[\mathrm{S}_i^m , \mathrm{S}_i^p \right]$$

In various embodiments, every allele in *G* may be assigned a score, or only a subset of alleles may be assigned scores, e.g., only alleles at the *(Nj)* gene-specific loci. Normal (non-mutant) alleles may have scores of zero, which may (or may not) be recorded along with non-zero scores for other alleles.

[0074] The following describes scoring method steps executed for a maternal haplopath. A parallel process may be executed for the paternal haplopath.

[0075] Haplopaths may be divided into subsets of SNPs or other alleles associated with each gene or complementation group *Q* under investigation. Genes *Qj* may be indexed on *j*. Gene-specific loci associated with a disease gene may be indexed on *k*. A gene-specific score may be distinguished from a general penetrance or expressivity score s by the variable symbol ŝ. The gene index *j* may be indicated as a first subscript value and the second subscript may indicate the gene-specific locus *k* Every gene *Qj* may have a defined rule set of the following form (indicated for the maternal haplopath).

$$Q_j^m : \left\{ \mathrm{s}_i^m \rightarrow \hat{\mathrm{s}}_{j,k}^m ; k = 1,\ldots,N_j \right\}$$

[0076] For example, disease gene *Q3* may encompass alleles indexed at genetic loci *i=5, i=9, i=25,* and *i*=30 on a master virtual progeny genome. Scores for alleles indexed at the gene *Q3*-specific loci *i* may be mapped to sequential *k*-values, e.g. beginning with *i*=\, according to a *Q3*

mapping rule associated with gene *Qj*. The mapping rule, which is a re-indexing, may be represented as follows:

$$Q_3^m : \left\{ s_5^m \rightarrow \hat{s}_{3,1}^m ; s_9^m \rightarrow \hat{s}_{3,2}^m ; s_{25}^m \rightarrow \hat{s}_{3,3}^m ; s_{30}^m \rightarrow \hat{s}_{3,4}^m \right\}$$

[0077] Alteration of gene function (e.g., protein damage) may be caused by any of multiple variants within each gene *Qj*. The probability of alteration of the gene product (e.g., damage or inactivity of the protein product) may be computed individually for each copy of gene *Qj*, for example, as follows.

$$P_j^m = \left(1 - \prod_{k=1}^{N_j} \left[1 - \hat{s}_{j,k}^m \right] \right)$$

[0078] For example, when the gene product is a protein, the probability of a functional protein is the joint probability that none of the gene's allele variants cause inactivation. In other words, the probability of a functional protein is the product of the terms (1-damage score) for each variant as shown in the right-most term of the equation above. The probability of damage is calculated by subtracting the product term from 1.

[0079] For a recessive disease or phenotype, based on the penetrance or expressivity model, the likelihood of disease in a virtual progeny may be the joint probability that both parents' gene copies are defective. This genome probability is the product of the maternal and paternal probabilities, for example:

$$\left(1 - \prod_{k=1}^{N_j} \left[1 - \hat{s}_{j,k}^m \right] \right) \left(1 - \prod_{k=1}^{N_j} \left[1 - \hat{s}_{j,k}^p \right] \right)$$

[0080] For a dominant incompletely penetrant disease or phenotype, the likelihood of disease in a virtual progeny may be the probability that either parent' s gene copy is defective. This genome probability is the sum of the maternal and paternal probabilities, for example, since the inactivity of either one is sufficient to cause disease in the progeny.

$$\left(1 - \prod_{k=1}^{N_j} \left[1 - \hat{s}_{j,k}^m \right] \right) + \left(1 - \prod_{k=1}^{N_j} \left[1 - \hat{s}_{j,k}^p \right] \right)$$

[0081] In some embodiments, scores may define likelihoods of complete protein inactivation. In such cases, a random number generator may be used to determine whether or not the associated phenotype *Phj* is expressed, for example, such that the particular gene copy produces a dysfunctional protein or not. For phenotype *Phj* , the probability *Pj* may define a penetrance or expressivity factor or likelihoods of expression associated with each copy of each gene *Qj*.

[0082] In some embodiments, scores may define a relative reduction in protein activity or degree of expressivity rather than a probability of complete inactivation. In such embodiments, the probability P_j may be interpreted as an indication of functional protein level and one or more thresholds defining different severities of disease may be applied to the probability to determine the severity of expression (e.g., no expression, mild, moderate, severe or complete expression).

[0083] Reference is made to Fig. **3,** which is a diagram of results of testing for expression of the MCAD deficiency due to any of four known mutations of the ACADM gene in accordance with embodiments of the invention.

[0084] The following table lists four mutations of the ACADM gene responsible for the recessive disease MCAD deficiency. Each mutation is identified by a decimal number assignment from the OMIM database at NCBI and a identification code including a three letter code identifying the amino acid in the normal protein, followed by a number indicating the position of the amino acid in the protein, followed by a three letter code identifying a replacement amino acid caused by the mutation. The second column provides a probability P_j^p of protein damage associated with each of the second listed amino acids for each parent. In this example, the first amino acid of each row may be assumed to be "normal" and has a damage score of zero (not shown), although in some cases, a "normal" or non-variant allele may have a non-zero score.

0.0001 LYS304GLU	0.70
0.0009 GLY170ARG	1.00
0.0011 TYR42HIS	0.35
0.0013 ARG256THR	0.20

[0085] Since MCAD deficiency is a recessive disease, the probability $P_j^{p1,p2}$ of protein damage for each combination of mutations in the progeny of the two parents *(pi)* and *(p2)* is the product of the probabilities associated with each individual parent $P_j^{p_i}$. For example, each of the 16 row-column entries defines a total probability for a different one of the 16 possible mutant combinations.

[0086] In the example of Fig. **3,** the probabilities of protein damage may be equated with the severity of protein dysfunction. The probabilities may be compared to one or more threshold ranges each associated with a different outcome of the severity of protein dysfunction. Threshold ranges of, for example, 0%-13%, 13%-14.$\bar{9}$%, 15%-34.$\bar{9}$%, and 35%-99.$\bar{9}$% are associated with

outcomes, such as, asymptomatic, mild disease, moderate disease, severe disease and severe disease with no survival, respectively.

[0087] The probabilities for multiple mutation pairs may be combined into a single probability and/or outcome for each real genome or set of virtual progeny genomes generated for a single pairing of potential parents (e.g. referred to as a "virtual progeny"). For a virtual progeny having a plurality of genome samplings G_i, the resulting probabilities and/or outcomes may be combined, for example, to produce an average, median or mode single outcome or a statistical distribution of outcomes.

[0088] Fig. **5** is a schematic illustration of a system **500** according to an embodiment of the invention. Methods disclosed herein may be performed using the system of Fig. **5.**

[0089] System **500** may include a genetic sequencing module **502** that accepts genetic material or DNA samples from each of a plurality of living donors and generates a genome or genome profile for each donor. Genetic sequencing module **502** may include a processor **504** for generating each donor' s genome profile and a memory **506** for storing each donor' s genome profile.

[0090] Computing device **508** may include, for example, any suitable processing system, computing system, computing device, processing device, computer, processor, or the like, and may be implemented using any suitable combination of hardware and/or software. Computing device **508** may include for example one or more processor(s) **512,** memory **514** and software **516.** Data generated by genetic sequencing module **502,** such as each donor' s genome profile, may be transferred, for example, to computing device **508.** The data may be stored in the memory **514** as for example digital information and transferred to computing device **508** by uploading, copying or transmitting the digital information. Processor **504** may communicate with computing device **508** via wired or wireless command and execution signals.

[0091] Computing device **508** may use each donor's genome information to generate a virtual gamete or haplopath for the donor. Computing device **508** may combine the virtual gametes from pairs of donors to generate a virtual progeny genome sampling to simulate the mating of one donor with another individual donor or with each of a pool of potential donors. Computing device **508** may repeat the process to generate a virtual progeny genome for each pair of potential parents. Computing device **508** may analyze the virtual progeny genome of the potential parents to predict whether a virtual progeny potentially to be conceived will have phenotypes Phj associated with a single gene Qj by those potential parents as described herein.

[0092] In some embodiments using a matching method, computing device **508** may compare genotypes in the virtual progeny genome to genotypes in a genotype-phenotype association

database 510 to detect any genotype-phenotype matches. Genotype-phenotype association database 510 may connect to computing device 508 via a wired or wireless connection.

[0093] In some embodiments using a scoring method, computing device 508 may compute scores associated with genotypes in the virtual progeny genome or retrieve scores from an external score database.

[0094] Memory 506 and 514 and database 510 may include cache memory, long term memory such as a hard drive, and/or external memory, for example, including random access memory (RAM), read only memory (ROM), dynamic RAM (DRAM), synchronous DRAM (SD-RAM), flash memory, volatile memory, non-volatile memory, cache memory, buffer, short term memory unit, long term memory unit, or other suitable memory units or storage units. Memory 506 and 514 and database 510 may store instructions (e.g., software 516) and data to execute embodiments of the aforementioned methods, steps and functionality (e.g., in long term memory, such as a hard drive).

[0095] Computing device 508 may include a computing module having machine-executable instructions. The instructions may include, for example, a data processing mechanism (including, for example, embodiments of methods described herein) and a modeling mechanism. These instructions may be used to cause processor 512 using associated software 516 modules programmed with the instructions to perform the operations described. Alternatively, the operations may be performed by specific hardware that may contain hardwired logic for performing the operations, or by any combination of programmed computer components and custom hardware components.

[0096] Embodiments of the invention may include an article such as a computer or processor readable medium, or a computer or processor storage medium, such as for example a memory, a disk drive, or a USB flash memory, encoding, including or storing instructions, e.g., computer-executable instructions, which when executed by a processor or controller, carry out methods disclosed herein.

[0097] Processor 512 may perform various methods described herein. For example, processor 512 may execute methods 600 and 700 of Figs. 6 and 7.

[0098] Display 518 may display results and/or intermediate data such as outcomes, probabilities, virtual progeny phenomes, for example, as shown in the diagram of Fig. 3. Display 518 may include a monitor or screen, such as an organic light emitting diode (LED) screen, liquid crystal display (LCD) screen, thin film transistor display, or the like. In one embodiment, the user may interact with display 580 using input device(s) 520.

[0099] Input device(s) **520** may include a keyboard, pointing device (e.g., mouse, trackball, pen,), a touch screen or cursor direction keys, communicating information and command selections to processor **514.** Input device **520** may communicate user direction information and command selections to the processor **514.** For example, a user may use input device **520** to select donors for testing, define genes and/or phenotypes to be under investigation, set thresholds or phenotype categories, set margins of error or certainty of calculations, etc.

[00100] Processor **504** and **514** may include, for example, one or more processors, controllers, central processing units ("CPUs"), or graphical processing units ("GPUs"). Software **516** may be stored, for example, in memory **514.**

[00101] Reference is made to Fig. **6,** which is a flowchart of a matching method **600** for predicting the expression of phenotypes in progeny according to embodiments of the invention. Method **600** may be implemented by a computer processor (e.g. processor **514** of Fig. **5)** executing program instructions (e.g. in software **516** of Fig. **5).**

[00102] In operation **610,** a processor (e.g. processor **514** of Fig. **5)** may be adapted to generate a virtual progeny genome sampling $G = \{[h_i^{p1}, h_i^{p2}]; i = 1, \ldots, N\}$ for a virtual progeny. The virtual progeny genome sampling G may include, at each of a plurality of genetic loci $i = 1, \ldots, N$, one allele h_i^{p1} from a first genome profile of a first potential parent ***(pi)*** and one allele h_i^{p2} from a second genome profile of a second potential parent ***(p2).*** In one embodiment, the set of alleles $\{h_i^p, i = 1, \ldots, N\}$ for each potential parent ***p=(pl, p2)*** is a haplopath H^p generated by selecting one of the two alleles $h_i^p G(1,2)$ at each genetic locus along a path of the genome profile of the potential parent. The two haplopaths H^{p1} and H^{p2} may form two virtual gametes from respective parents ***(pi)*** and ***(p2),*** which may be combined to generate the virtual progeny genome sampling ***G.***

[00103] In operation **620,** the processor may be adapted to compare genotypes for a gene Q_j of the virtual progeny genome sampling G to one or more databases of genotype-phenotype associations (e.g. genotype-phenotype association database **510** of Fig. **5)** to determine a phenotype associated with database genotypes matching genotypes of said virtual progeny genome sampling ***G.*** Each genotype-phenotype may be associated with a penetrance or expressivity value indicating the empirically observed likelihood that a phenotype will be expressed in a progeny having the associated genotype.

[00104] In operation **630,** the processor may be adapted to generate a random number to determine if the virtual progeny is predicted to express the phenotype. For example, the random number may oscillate randomly between 0 (no expression) and 1 (expression), or on a scale e.g. 1-10 and may be compared to a threshold e.g. of 5, for an equal probability of expression and

non-expression. In some examples, a phenotype may be biased to express or non-express with a non-equal probability, in which case the random number may be weighted by a bias factor or the threshold may be shifted to bias the outcome to either express or non-express according to a predefined bias ratio. In the absence of such randomization, genotypes and phenotypes are exactly correlated, which does not generally occur in nature and thus, provides less accurate results than embodiments of the invention using the random number to determine expression. If the virtual progeny is predicted to express the phenotype, a process or processor may proceed to operation 640. Otherwise, a process or processor may proceed to operation 650.

[00105] In operation 640, the processor may be adapted to predict positive expression of the phenotype in the virtual progeny with a degree of expression equal the penetrance or expressivity value (or a derivation thereof). If the phenotype is a disease, the degree of expression may define the severity of the disease (e.g. as shown in Fig. 3).

[00106] In operation 650, the processor may be adapted to predict a negative expression of the phenotype in the virtual progeny.

[00107] After operation 640 or 650, a process or processor may repeat operations 610-650 for a plurality of different virtual progeny genome samplings $G^{vp} = \{G_1, G_2, \ldots, G_M\}$, where each sampling may differ from each other sampling by at least one or more alleles.

[00108] After operation 640 or 650, a process or processor may repeat operations 620-650 to determine phenotypic expression for another genotype match for another gene Qj_{+1} in the virtual progeny genome profile.

[00109] In operation 660, the processor may be adapted to output or display (e.g. on display 518 of Fig. 5) the probability of expression of the phenotype Phj or a derivation thereof for one or more genes Qj.

[001 10] Other operations or orders of operations may be used. In various embodiments, operations 610-650 may be repeated before, after, or in parallel (simultaneously to) repeating operations 620-650. In one example, a single, multiple or multi-core processor may execute operations 610-650 for a plurality of the virtual progeny genome sampling G_i in parallel for predicting the expression of a phenotype associated with a single gene Qj, and in each consecutive series of operations the processor may predict for the samplings G_i the expression of a phenotype associated with a sequential gene Qj_{+1}, for example, until matching genotypes for all $j = 1,\ldots,J$ genes are analyzed.

[001 11] Fig. 7 is a flowchart of a scoring method for predicting whether progeny will one or more phenotypes Phj each associated with a single gene Qj according to embodiments of the

invention. Method **700** may be implemented by a computer processor (e.g. processor **514** of Fig. **5)** executing program instructions (e.g. in software **516** of Fig. **5).**

[001 12] In operation **710,** a processor (e.g. processor **514** of Fig. **5)** may be adapted to generate a haplopath $H^p = \{h_1^p, h_2^p, \ldots, hf_i\}$ including a single allele h_i^p **£ (1,2)** at each of a plurality of loci ***(i=\, …, N)*** from a genome profile of a potential parent ***(p).***

[001 13] In operation **720,** the processor may be adapted to assign a score ***sf*** to each allele h_i^p at a plurality of genetic loci ***(i)*** in a haploid genome profile H^p of a parent ***(p).*** Scores ***sf*** may indicate a probability that the allele ***hf*** results in expression of a variant trait or genotype in progeny, a probability that the variant allele h_i^p indicating an amino acid substitution at the locus (0 will damage protein function, and/or a probability that the variant allele h_i^p indicating a change in one or more amino acids will occur randomly based on natural selection.

[001 14] In operation **720,** the processor may be adapted to identify a plurality ***(Nj)*** of the alleles h_k^p ***(k=l, …,Nj)*** associated with the gene ***Qj.***

[001 15] In operation **730,** the processor may be adapted to map the scores ***sf*** to gene-specific scores $\hat{s}_{j,k}^p$ associated with gene ***Qj*** for the plurality of ***(Nj)*** alleles h_k^{γ}.

[001 16] In operation **740,** the processor may be adapted to compute a probability of having the phenotype ***Phj*** associated with gene ***Qj*** in a progeny of the parent ***(p)*** to be a function of the gene-specific scores $\hat{s}_{j,k}^p$. In one embodiment, the scores or probability may indicate a likelihood of expression of the phenotype ***Phj*** in the virtual progeny, a random number generator (e.g. executed by processor **514)** may generate a random number to predict if the phenotype ***Phj*** will express in the progeny (e.g. as described in reference to operations **630-650** of Fig. **6).** In one embodiment, the scores or probability may indicate a degree of expressivity of the phenotype ***Phj*** in the progeny. The probability may be compared to one or more thresholds to determine a category of severity of the expression of the phenotype ***Phj*** .

[001 17] Operation **710-740** may be repeated for a plurality of different virtual progeny genome samplings $G^{vp} = \{G_1, G_2, \ldots, G_M\}$ and/or operations **720-740** may be repeated for a plurality of different genes ***Qj, j=\, …,J,*** for example, as described in reference to Fig. **6.**

[001 18] In operation **750,** the processor may be adapted to output or display (e.g. on display **518** of Fig. **5)** the probability of expression of the phenotype ***Phj*** or a derivation thereof for one or more genes ***Qj.***

[001 19] Other operations or orders of operations may be used.

[00120] The aforementioned block diagrams illustrate the architecture, functionality, and operation of possible implementations of systems and methods according to various

embodiments of the present invention. In this regard, each block in the flowchart or block diagrams may represent a module, segment, or portion of code, which comprises one or more executable instructions for implementing the specified logical function(s). It should also be noted that, in some alternative implementations, the functions noted in the block may occur out of the order noted in the figures. For example, two blocks shown in succession may, in fact, be executed substantially concurrently, or the blocks may sometimes be executed in the reverse order, depending upon the functionality involved. It will also be noted that each block of the block diagrams and/or flowchart illustration, and combinations of blocks in the block diagrams and/or flowchart illustration, can be implemented by special purpose hardware-based systems that perform the specified functions or acts, or combinations of special purpose hardware and computer instructions.

[00121] Nonlimiting examples of phenotypes that may be assessed using the methods described herein include or relate to ability to roll the tongue, ability to taste PTC, acute inflammation, adaptive immunity, addiction(s), adipose tissue, adrenal gland, age, aggression, amino acid level, amyloidosis, anogenital distance, antigen presenting cells, auditory system, autonomic nervous system, avoidance learning, axial defects or lack thereof, B cell deficiency, B cells, B lymphocytes (e.g., antigen presentation), basophils, bladder size/shape, blinking, blood chemistry, blood circulation, blood glucose level, blood physiology, blood pressure, body mass index, body weight, bone density, bone marrow formation/structure, bone strength, bone/skeletal physiology, breast size/shape, bursae, cancellous bone, cardiac arrest, cardiac muscle contractility, cardiac output, cardiac stroke volume, cardiomyopathy, cardiovascular system/disease, carpal bone, catalepsy, cell abnormalities, cell death, cell differentiation, cell morphology, cell number, cell-mediated immunity, central nervous system, central nervous system physiology, chemotactic factors, chondrodystrophy, chromosomal instability, chronic inflammation, circadian rhythm, circulatory system, cleft chin, clonal anergy, clonal deletion, T and B cell deficiencies, conditioned emotional response, congenital skeletal deformities, contextual conditioning, cortical bone thickness, craniofacial bones, craniofacial defects, crypts of Lieberkuhn, cued conditioning, cytokines, delayed bone ossification, dendritic cells (e.g., antigen presentation), Di George syndrome, digestive function, digestive system, digit dysmorphology, dimples, discrimination learning, drinking behavior, drug abuse, drug response, ear size/shape including ear lobe attachment, eating behavior, ejaculation function, embryogenesis, embryonic death, embryonic growth/weight/body size, emotional affect, enzyme/coenzyme level, eosinophils, epilepsy, epiphysis, esophagus, excretion physiology, extremities, eye blink conditioning, eye color/shape, eye physiology, eyebrows shape, eyelash

length, face shape, facial cleft, femur, fertility/fecundity, fibula, finger length/shape, fluid regulation, fontanels, foregut, fragile skeleton, freckles, gall bladder, gametogenesis, gastrointestinal hemorrhage, germ cells (e.g., morphology, depletion), gland dysmorphology, gland function, glucagon level, glucose homeostasis, glucose tolerance, glycogen catabolism, granulocytes, granulocytes (e.g., bactericidal activity, chemotaxis), grip strength, grooming behavior, hair color, hair follicle structure/orientation, hair growth, hair on mid joints, hair texture, handedness, harderian glands, head, hearing function, heart, heart rate, heartbeat (e.g., rate, irregularity), height, hemarthrosis, hemolymphoid system, hepatic system, hitchhiker's thumb, homeostasis, humerus, humoral immune response, hypoplastic axial skeleton, hypothalamus, immune cell, immune system (e.g., hypersensitivity), immune system response/function, immune tolerance, immunodeficiency, inability to urinate, increased sensitivity to gamma-irradiation, inflammatory mediators, inflammatory response, innate immunity, inner ear, innervation, insulin level, insulin resistance, intestinal bleeding, intestine, ion homeostasis, jaw, kidney hemorrhage, kidney stones, kidney/renal system, kyphoscoliosis, kyphosis, lacrimal glands, larynx, learning/memory, leukocyte, ligaments, limb dysmorphology, limb grasping, lipid chemistry, lipid homeostasis, lips size/shape, liver (e.g., development/function), liver/hepatic system, locomotor activity, lordosis, lung, lung development, lymph organ development, macrophages (e.g., antigen presentation), mammary glands, maternal/paternal behavior, mating patterns, meiosis, mental acuity, mental stability, mental state, metabolism of xenobiotics, metaphysis, middle ear, middle ear bone, morbidity and mortality, motor coordination/balance, motor learning, mouth, movement, muscle, muscle contractility, muscle degeneration, muscle development, muscle physiology, muscle regeneration, muscle spasms, muscle twitching, musculature, myelination, myogenesis, nervous system, neurocranium, neuroendocrine glands, neutrophils, NK cells, nociception, nose, nutrients/absorption, object recognition memory, ocular reflex, odor preference, olfactory system, oogenesis, operant or "target response", orbit, osteogenesis, osteogenesis/developmental, osteomyelitis, osteoporosis, outer ear, oxygen consumption, palate, pancreas, paralysis, parathyroid glands, pelvis girdle, penile erection function, perinatal death, peripheral nervous system, phalanxes, pharynx, photosensitivity, piloerection, pinna reflex, pituitary gland, PNS glia, postnatal death, postnatal growth/weight/body size, posture, premature death, preneoplasia, propensity to cross the right arm over the left of vice versa, propensity to cross the right thumb over the left thumb when clasping hands or vise versa, pulmonary circulation, pupillary reflex, radius, reflexes, reproductive condition, reproductive system, resistance to fatty liver development, resistance to hyperlipidemia, respiration (e.g., rate, shallowness), respiratory

distress or failure, respiratory mucosa, respiratory muscle, respiratory system, response to infection, response to injury, response to new environment (transfer arousal), ribs, salivary glands, scoliosis, sebaceous glands, secondary bone resorption, seizures, self tolerance, senility, sensory capabilities, sensory system physiology/response, sex, sex glands, shoulder, skin, skin color, skin texture/condition, skull, skull abnormalities, sleep pattern, social intelligence, somatic nervous system, spatial learning, sperm count, sperm motility, spermatogenesis, startle reflex, sternum defect, stomach, suture closure, sweat glands, T cell deficiency, T cells (e.g., count), tarsus, taste response, teeth, temperature regulation, temporal memory, tendons, thyroid glands, tibia, touch/nociception, trachea, tremors, trunk curl, tumor incidence, tumorigenesis, ulna, urinary system, urination pattern, urine chemistry, urogenital condition, urogenital system, vasculature, vasoactive mediators, vertebrae, vesicoureteral reflux, vibrissae, vibrissae reflex, viscerocranium, visual system, weakness, widows peak or lack thereof, etc.

[00122] Other nonlimiting phenotypes include cognitive ability (Ruano et al., Am. J. Hum. Genet. 86:113 (2010)); Familial Osteochondritis Dissecans (Stattin et al., Am. J. Hum. Genet. 86:126 (2010)); hearing impairment (Schraders et al., Am. J. Hum. Genet. 86:138 (2010)); mental retardation associated with autism, epilepsy, or macrocephaly (Giannandrea et al., Am. J. Hum. Genet. 86:185 (2010)); muscular dystrophies (Bolduc et al., Am. J. Hum. Genet. 86:213 (2010)); Diamond-Blackfan anemia (Doherty et al., Am. J. Hum. Genet. 86:222 (2010)); osteoporotic fractures (Kung et al., Am. J. Hum. Genet. 86:229 (2010)); familial exudative vitreoretinopathy (Poulter et al., Am. J. Hum. Genet. 86:248 (2010)); skeletal dysplasia, eye, and cardiac abnormalities (Iqbal et al., Am. J. Hum. Genet. 86:254 (2010)); Warsaw breakage syndrome (van der Lilij et al., Am. J. Hum. Genet. 86:262 (2010)); arterial calcification of infancy (Lorenz-Depiereux et al., Am. J. Hum. Genet. 86:267 (2010)); hypophosphatemic rickets (Lorenz-Depiereux et al., Am. J. Hum. Genet. 86:267 (2010); Levy-Litan et al., Am. J. Hum. Genet. 86:273 (2010)); rhabdoid tumor predisposition syndrome (Schneppenheim et al., Am. J. Hum. Genet. 86:279 (2010)); and multiple sclerosis (Jakkula et al., Am. J. Hum. Genet. 86:285 (2010)).

[00123] Yet other nonlimiting phenotypes include 21-Hydroxylase Deficiency, ABCC8-Related Hyperinsulinism, ARSACS, Achondroplasia, Achromatopsia, Adenosine Monophosphate Deaminase 1, Agenesis of Corpus Callosum with Neuronopathy, Alkaptonuria, Alpha-1-Antitrypsin Deficiency, Alpha-Mannosidosis, Alpha-Sarcoglycanopathy, Alpha-Thalassemia, Alzheimers, Angiotensin II Receptor, Type I, Apolipoprotein E Genotyping, Argininosuccinicaciduria, Aspartylglycosaminuria, Ataxia with Vitamin E Deficiency, Ataxia-Telangiectasia, Autoimmune Polyendocrinopathy Syndrome Type 1, BRCAl Hereditary

Breast/Ovarian Cancer, BRCA2 Hereditary Breast/Ovarian Cancer, Bardet-Biedl Syndrome, Best Vitelliform Macular Dystrophy, Beta-Sarcoglycanopathy, Beta-Thalassemia, Biotinidase Deficiency, Blau Syndrome, Bloom Syndrome, CFTR-Related Disorders, CLN3-Related Neuronal Ceroid-Lipofuscinosis, CLN5-Related Neuronal Ceroid-Lipofuscinosis, CLN8-Related Neuronal Ceroid-Lipofuscinosis, Canavan Disease, Carnitine Palmitoyltransferase IA Deficiency, Carnitine Palmitoyltransferase II Deficiency, Cartilage-Hair Hypoplasia, Cerebral Cavernous Malformation, Choroideremia, Cohen Syndrome, Congenital Cataracts, Facial Dysmorphism, and Neuropathy, Congenital Disorder of Glycosylationla, Congenital Disorder of Glycosylation lb, Congenital Finnish Nephrosis, Crohn Disease, Cystinosis, DFNA 9 (COCH), Diabetes and Hearing Loss, Early-Onset Primary Dystonia (DYTI), Epidermolysis Bullosa Junctional, Herlitz-Pearson Type, FANCC-Related Fanconi Anemia, FGFRl-Related Craniosynostosis, FGFR2-Related Craniosynostosis, FGFR3-Related Craniosynostosis, Factor V Leiden Thrombophilia, Factor V R2 Mutation Thrombophilia, Factor XI Deficiency, Factor XIII Deficiency, Familial Adenomatous Polyposis, Familial Dysautonomia, Familial Hypercholesterolemia Type B, Familial Mediterranean Fever, Free Sialic Acid Storage Disorders, Frontotemporal Dementia with Parkinsonism-17, Fumarase deficiency, GJB2-Related DFNA 3 Nonsyndromic Hearing Loss and Deafness, GJB2-Related DFNB 1 Nonsyndromic Hearing Loss and Deafness, GNE-Related Myopathies, Galactosemia, Gaucher Disease, Glucose-6-Phosphate Dehydrogenase Deficiency, Glutaricacidemia Type 1, Glycogen Storage Disease Type la, Glycogen Storage Disease Type lb, Glycogen Storage Disease Type II, Glycogen Storage Disease Type III, Glycogen Storage Disease Type V, Gracile Syndrome, HFE-Associated Hereditary Hemochromatosis, Haider AIMs, Hemoglobin S Beta-Thalassemia, Hereditary Fructose Intolerance, Hereditary Pancreatitis, Hereditary Thymine-Uraciluria, Hexosaminidase A Deficiency, Hidrotic Ectodermal Dysplasia 2, Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency, Hyperkalemic Periodic Paralysis Type 1, Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome, Hyperoxaluria, Primary, Type 1, Hyperoxaluria, Primary, Type 2, Hypochondroplasia, Hypokalemic Periodic Paralysis Type 1, Hypokalemic Periodic Paralysis Type 2, Hypophosphatasia, Infantile Myopathy and Lactic Acidosis (Fatal and Non-Fatal Forms), Isovaleric Acidemias, Krabbe Disease, LGMD2I, Leber Hereditary Optic Neuropathy, Leigh Syndrome, French-Canadian Type, Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency, MELAS, MERRF, MTHFR Deficiency, MTHFR Thermolabile Variant, MTRNR1-Related Hearing Loss and Deafness, MTTSl-Related Hearing Loss and Deafness, MYH-Associated Polyposis, Maple Syrup Urine Disease Type 1A, Maple Syrup Urine Disease Type IB, McCune-Albright Syndrome, Medium Chain Acyl-Coenzyme A

Dehydrogenase Deficiency, Megalencephalic Leukoencephalopathy with Subcortical Cysts, Metachromatic Leukodystrophy, Mitochondrial Cardiomyopathy, Mitochondrial DNA-Associated Leigh Syndrome and NARP, Mucolipidosis IV, Mucopolysaccharidosis Type I, Mucopolysaccharidosis Type IIIA, Mucopolysaccharidosis Type VII, Multiple Endocrine Neoplasia Type 2, Muscle-Eye-Brain Disease, Nemaline Myopathy, Neurological phenotype, Niemann-Pick Disease Due to Sphingomyelinase Deficiency, Niemann-Pick Disease Type CI, Nijmegen Breakage Syndrome, PPTl-Related Neuronal Ceroid-Lipofuscinosis, PROPl-related pituitary hormome deficiency, Pallister-Hall Syndrome, Paramyotonia Congenita, Pendred Syndrome, Peroxisomal Bifunctional Enzyme Deficiency, Pervasive Developmental Disorders, Phenylalanine Hydroxylase Deficiency, Plasminogen Activator Inhibitor I, Polycystic Kidney Disease, Autosomal Recessive, Prothrombin G20210A Thrombophilia, Pseudovitamin D Deficiency Rickets, Pycnodysostosis, Retinitis Pigmentosa, Autosomal Recessive, Bothnia Type, Rett Syndrome, Rhizomelic Chondrodysplasia Punctata Type 1, Short Chain Acyl-CoA Dehydrogenase Deficiency, Shwachman-Diamond Syndrome, Sjogren-Larsson Syndrome, Smith-Lemli-Opitz Syndrome, Spastic Paraplegia 13, Sulfate Transporter-Related Osteochondrodysplasia, TFR2-Related Hereditary Hemochromatosis, TPPl-Related Neuronal Ceroid-Lipofuscinosis, Thanatophoric Dysplasia, Transthyretin Amyloidosis, Trifunctional Protein Deficiency, Tyrosine Hydroxylase-Deficient DRD, Tyrosinemia Type I, Wilson Disease, X-Linked Juvenile Retinoschisis, and Zellweger Syndrome Spectrum.

[00124] Reference is made to Fig. 8, which lists genes and their associated diseases, which may be used for computer-generated diagnosis of the disease(s) in virtual progeny or the future emergence of the disease(s) in a living organism, according to embodiments of the invention. The gene-disease associations may be stored in one or more databases (e.g. database **510** of Fig. **5)** for comparison with the virtual progeny or living organism genotypes for those genes.

[00125] The methods of assessing the probability that progeny will express certain phenotypes, as described herein, may be implemented into systems, programs, and/or services, which may be authorized by, referred by, and/or performed by, e.g., agencies, public or private companies, genetic counseling centers, dating or match-making services, sperm banks, egg providers, reproductive service providers, fertility clinics, or specialty laboratories.

[00126] Virtual Progeny Assessment and Genetic Counseling Referral System

[00127] In one example, the methods described herein are integrated into a testing service that may provide information to a couple on the probability that the couple's offspring will express one or more phenotypes described herein, such as risk of a disease. In addition to the results of

the Virtual Progeny assessment, referrals to genetic counselors and/or other relevant medical professionals may be provided in order to provide for follow up testing and consultation.

[00128] In certain embodiments, a Virtual Progeny assessment begins with a customer order, and the customer may pay a service provider a fee in exchange for the assessment. A customer may be two potential parents, e.g., partners. Alternatively, a customer may be a physician, a genetic counselor, a medical center, an insurance company, a website, a dating service, a matchmaking service, a pharmaceutical company, or a laboratory testing service provider, who places an order on behalf of two potential parents. For example, a customer may be two prospective parents who seek to learn whether their offspring will be at risk for developing disease. After a customer places an order, DNA collection kits may be sent to the prospective parents, who may deposit a biological sample described herein into the collection kits. The collection kits may then be returned to the company for sending to a specialty lab or may be returned directly to the specialty lab for performing the assessment. A specialty lab, either internal within the company, contracted to work with the company, or external from the company, may isolate the potential parents' DNA from the provided samples for genome scanning from which Virtual Progeny may be generated, as described herein. After analysis of the Virtual Progeny, the results may be provided to the potential parents. The results may inform the potential parents of the chances that their future offspring will express one or more phenotypes, such as phenotypes described herein. In certain instances, the potential parents may also receive, for example, direct phone consultation with a genetic counselor employed by the company, or contact information for genetic counselors and/or other medical professionals who may provide the potential parents with follow up testing and consultation.

[00129] Virtual Progeny Assessment and Dating/Marriage Services

[00130] In other instances, the methods described herein may be used to allow for the evaluation of potential partners in connection with a matchmaking service. In one example, a Virtual Progeny assessment may be offered to a customer in connection with a matchmaking service, for example, through a single company or a co-marketing or partnership relationship. A user of a matchmaking service may order an assessment of Virtual Progeny described herein to determine the probability that an offspring resulting from the potential match between the user and a candidate partner will express one or more phenotypes described herein. The user may then use this information to aid in evaluating the candidate partner for a potential match. The matchmaking service may be an on-line service, such as Shaadi.com, eHarmony.com and Match.com.

[00131] In a particular application, assessment of Virtual Progeny begins with a customer order, where the customer pays a fee in exchange for the assessment. For example, a customer may be a user of a matchmaking service who is interested in evaluating another user for a suitable match. Such a customer may use an assessment of Virtual Progeny described herein to learn whether the potential offspring of a match between such customer and a candidate partner will express one or more phenotypes or traits, such as risk of disease. After selecting a candidate partner to evaluate, a customer may pay for both the customer's and the candidate partner's initial genomic scans with the candidate partner's consent. In other instances, the customer and the candidate partner may also pay separately for the initial genomic scans. After a customer places an order, DNA collection kits may be sent to the customer and the candidate partner, and the customer and the candidate partner may each deposit a biological sample into the collection kit. The collection kits may then be returned to the company for sending to a specialty lab or may be returned directly to the specialty lab for processing according to the methods described herein. A specialty lab, either internal within the company, contracted to work with the company, or external from the company, may perform genomic scans on the customer's and candidate partner's DNA from the provided sample and perform an assessment of Virtual Progeny using the methods described herein. The results of the assessment may then be provided to the customer and/or the candidate partner, and the customer and/or the candidate partner may use the results of the assessment in determining whether the other party is a suitable match.

[00132] Virtual Progeny Assessment and Sperm Donors/Egg Donors

[00133] In other applications, a female client seeking to have a child may have a Virtual Progeny assessment performed with one or more sperm donors to aid in selecting a donor. In one exemplary method, potential sperm donors are first recruited by a sperm bank. Donors who complete the screening process and are considered qualified by the sperm bank then provide a biological sample (such as a buccal swab) that may be processed to obtain whole DNA sequence, SNP genotypes, CNV genotypes or any other digital genetic information.

[00134] A female client also provides a biological sample, such as a buccal swab, which is used to generate a genome profile for the female client. The female client genome is then recombined computationally with each donor genome to generate a series of independent Virtual Progeny genomes, as described herein, representing each potential donor-client combination. Each Virtual Progeny genome may then be assessed for the probability of exhibiting one or more phenotypes, such as increased risk of disease. In certain instances, incompatible donor-client combinations are subtracted from the total donor pool to obtain a client-specific filtered donor pool, which may be used, e.g., as a starting point for further selection by the client. In other

instances, a client may be given information on the probability of the incidence of one or more phenotypes from donor-client combinations, such as phenotypes preselected by the client, for further sperm donor selection by the client.

[00135] In other applications, a male client seeking to have a child may have a Virtual Progeny assessment performed with one or more egg donors to aid in selecting a donor. Egg donors may provide a biological sample (such as a buccal swab) to generate a genome profile for the egg donor, as described herein. The male client also provides a biological sample, such as a buccal swab, which is used to generate a genome profile for the male client. The male client genome is then recombined computationally with each egg donor genome to generate a series of independent Virtual Progeny genomes, as described herein, representing each potential donor-client combination. Each Virtual Progeny genome may then be assessed for the probability of exhibiting one or more phenotypes or traits, such as increased risk of disease. In certain instances, incompatible donor-client combinations are subtracted from the total donor pool to obtain a client-specific filtered donor pool, which may be used, e.g., as a starting point for further selection by the client. In other instances, a client may be given information on the probability of the incidence of one or more phenotypes from donor-client combinations, such as phenotypes preselected by the client, for further egg donor selection by the client.

[00136] In yet other applications, a heterosexual couple seeking to use a sperm or egg donor to have a child may use Virtual Progeny assessments to screen potential donors. For example, the couple may seek a sperm donor, and the female partner will be the genetic parent of offspring with the sperm donor. Alternatively, the couple may seek an egg donor, and the male partner will be the genetic parent of offspring with the egg donor. In such instances, two rounds of Virtual Progeny assessments may be performed. A first round of Virtual Progeny assessment is performed using biological samples from the heterosexual couple. A second round of Virtual Progeny assessment is performed between the genetic parent and one or more potential donors. The results of the first round of Virtual Progeny assessment may then be compared with the results of the second round, and a donor may be chosen whose Virtual Progeny exhibits an acceptable amount of matching in one or more phenotypes with the Virtual Progeny from the heterosexual couple.

[00137] In still other applications, a female homosexual couple seeking to use a sperm donor to have a child may use Virtual Progeny assessments to screen potential sperm donors. Only one of the female partners will be the genetic parent of offspring with the sperm donor. A first round of Virtual Progeny assessment is performed using biological samples from the homosexual couple. A second round of Virtual Progeny assessment is performed between the genetic female parent

and one or more potential sperm donors. The results of the first round of Virtual Progeny assessment may then be compared with the results of the second round, and a sperm donor may be chosen whose Virtual Progeny exhibits an acceptable amount of matching in one or more phenotypes with the Virtual Progeny from the homosexual couple. In some situations, a Virtual Progeny assessment is also performed with the second female partner and one or more potential sperm donors, and a donor is selected whose Virtual Progeny exhibits an acceptable amount of matching in one or more phenotypes with the Virtual Progeny from the homosexual couple.

[00138] In yet other applications, a male homosexual couple seeking to use an egg donor to have a child may use Virtual Progeny assessments to screen potential egg donors. Only one of the male partners will be the genetic parent of offspring with the egg donor. A first round of Virtual Progeny assessment is performed using biological samples from the homosexual couple. A second round of Virtual Progeny assessment is performed between the genetic male parent and one or more potential egg donors. The results of the first round of Virtual Progeny assessment may then be compared with the results of the second round, and an egg donor may be chosen whose Virtual Progeny exhibits an acceptable amount of matching in one or more phenotypes with the Virtual Progeny from the homosexual couple. In some situations, a Virtual Progeny assessment is also performed with the second male partner and one or more potential egg donors, and a donor is selected whose Virtual Progeny exhibits an acceptable amount of matching in one or more phenotypes with the Virtual Progeny from the homosexual couple.

[00139] In further applications of the methods disclosed herein, the risk of disease in a potential progeny may be assessed, as well as the likelihood of expressing a genetically influenced trait or phenotype. As with the other methods disclosed, a first genomic DNA sample is obtained from a first potential parent and a second genomic DNA sample from a second potential parent. The presence or absence of one or more nucleotide variants are identified at one or more loci of at least one pair of chromosomes of the first and the second genomic DNA samples and these identified nucleotide variants for the first and second genomic DNA samples are compared to a plurality of predetermined genomic sequences of haplotypes having predetermined frequencies at predetermined loci to identify haplotypes present in the first and second genomic DNA samples. A first diploid genome profile for the first potential parent is constructed. The first genome profile comprises the identified haplotypes in the first genomic DNA sample and a linkage probability determined by the frequencies of the identified haplotypes in the plurality of predetermined genomic sequences. A second diploid genome profile for the second potential parent is constructed. The second genome profile comprises the identified haplotypes in the second genomic DNA sample and a linkage probability determined by the frequencies of the

identified haplotypes in the plurality of predetermined genomic sequences. A first library is constructed that comprises potential haploid gamete genomes from the first diploid genome profile by generating a combination of the haplotypes identified in the first genomic DNA sample using the linkage probability for each combination of the identified haplotypes, while a second library is constructed that comprises potential haploid gamete genomes from the second diploid genome profile by generating a combination of the haplotypes identified in the second genomic DNA sample using the linkage probability for each combination of the identified haplotypes. The method also entails combining a first haploid gamete genome from the first library with a second haploid gamete genome from the second library to form a diploid progeny genome. The diploid progeny genome is compared to a database of genomes relating to disease-associated or genetically influenced phenotypes, thereby assessing the risk of disease or the likelihood of expressing a genetically influenced phenotypes of the potential progeny.

[00140] Computer Systems/Processors (the following computer systems/processors may be used in combination with, or as an alternative to, computer systems/processors described in reference to Fig. **5).**

[00141] The methods and systems described herein may be used in combination with one or more processors, having either single or multiple cores. The processor may be operatively connected to a memory. For instance, the memory may be solid state, flash, or nanoparticle based. The processor and/or memory may be operatively connected to a network via a network adapter. The network may be digital, analog, or a combination of the two. The processor may be operatively connected to the memory to execute computer program instructions to perform one or more steps described herein. Any computer language known to those skilled in the art may be used.

[00142] Input/output circuitry may be included to provide the capability to input data to, or output data from, the processor and/or memory. For example, input/output circuitry may include input devices, such as keyboards, mice, touch pads, trackballs, scanners, and the like, output devices, such as video adapters, monitors, printers, and the like, and input/output devices, such as, modems and the like.

[00143] The memory may store program instructions that are executed by, and data that are used and processed by, CPUs to perform various functions. The memory may include electronic memory devices, such as random-access memory (RAM), read-only memory (ROM), programmable read-only memory (PROM), electrically erasable programmable read-only memory (EEPROM), and flash memory, and electro-mechanical memory, such as magnetic disk drives, tape drives, and optical disk drives, which may be used as an integrated drive electronics

(IDE) interface, or a variation or enhancement thereof, such as enhanced IDE (EIDE) or ultra direct memory access (UDMA), or a small computer system interface (SCSI) based interface, or a variation or enhancement thereof, such as fast-SCSI, wide-SCSI, fast and wide-SCSI, etc, or a fiber channel-arbitrated loop (FC-AL) interface.

[00144] The systems described herein may also include an operating system that runs on the processor, including UNIX®, OS/2®, and WINDOWS®, each of which may be configured to run many tasks at the same time, e.g., a multitasking operating systems. In one aspect, the methods are utilized with a wireless communication and/or computation device, such as a mobile phone, personal digital assistant, personal computer, and the like. Moreover, the computing system may be operable to wirelessly transmit data to wireless or wired communication devices using a data network, such as the Internet, or a local area network (LAN), wide-area network (WAN), cellular network, or other wireless networks known to those skilled in the art.

[00145] In one embodiment, a graphical user interface may be included to allow human interaction with the computing system. The graphical user interface may comprise a screen, such as an organic light emitting diode screen, liquid crystal display screen, thin film transistor display, and the like. The graphical user interface may generate a wide range of colors, or a black and white screen may be used.

[00146] In certain instances, the graphical user interface may be touch sensitive, and it may use any technology known to skilled artisans including, but not limited to, resistive, surface acoustic wave, capacitive, infrared, strain gauge, optical imaging, dispersive signal technology, acoustic pulse recognition, frustrated total internal reflection, and diffused laser imaging.

[00147] The methods and compositions disclosed herein are further illustrated by the following examples. The examples are provided for illustrative purposes only. They are not to be construed as limiting the scope or content of the invention in any way.

[00148] EXAMPLES

[00149] Generation of Virtual Progeny Genome

[00150] In this particular example, the generation of a Virtual Progeny genome is a four step process. One of ordinary skill in the art will understand that other steps may be added, combined, or deleted as desired.

[00151] Step 1 - Genome Scans

[00152] Processing is accomplished with the use of DNA microarrays, DNA sequencing protocols, or other DNA reading technologies. In the present example, a DNA microarray is used to generate information relating to loci of interest. This information is utilized to produce genome scans that include genotype information from the plurality of loci of interest, which are

defined by single base polymorphisms ("SNPs or CNPs"), DNA sequence reads, copy number, or other forms of personal genetic information. In the present example, Jane Doe and John Smith provided samples, which have such information provided for loci 0 1 through N.

[00153] Step 2 - Expansion of Genome Scans to Generate Genome Profiles

[00154] Existing population datasets, genome scans of family members, and a variety of computational tools and algorithms, known to those skilled in the art, may be used in combination with each person's genome scan to distinguish haplotypes, impute genotypes at additional loci, and establish long-range genetic phasing. The derived genome profile preferably incorporates phasing information in the form of stochastic matrices between haplotypes.

[00155] With genome scans performed on two or more related persons, phasing information is extended. In an example of genome analysis, the UCSC genome browser is used to display phasing over large maternally-inherited chromosomal segments that comprise 100 million base pairs or more. A Monte Carlo simulation or Markov process as described above is used to generate haplopaths through a genome, where haplotypes are transmitted intact, and stochastic matrices are used to move from one haplotype or locus to the next one. In the example, John Smith's genome is converted into a series of haplopaths by means of a Monte Carlo simulation.

[00156] Each individual genome profile is used to generate a pool of VirtualGametes.

[00157] Step 4 - Virtual Progeny Permutations from Random Virtual Gametes from Each Individual

[00158] Single Virtual Gametes from each person is chosen randomly and combined to produce one permutation of a Virtual Progeny genome. The process of Virtual Gamete choice and reproductive combination to produce a diploid genome is iterated a sufficient number of times such that the normalized sum of Virtual Progeny permutations provides a stable estimate of the Virtual Progeny genome probability distribution. For instance, the number of iterations may be between about 10 and about 100. More preferably, the number of iterations may be between about 100 and about 1000. Most preferably, the number of iterations may be between about 1000 and about 100,000. In another aspect, the number of iterations may be about 50 or greater. More preferably, the number of iterations may be about 150 or greater. Most preferably, the number of iterations may be about 3000 or greater.

[00159] In the above description, an embodiment is an example or implementation of the inventions. The various appearances of "one embodiment," "an embodiment" or "some embodiments" do not necessarily all refer to the same embodiments.

[00160] Although various features of the invention may be described in the context of a single embodiment, the features may also be provided separately or in any suitable combination.

Conversely, although the invention may be described herein in the context of separate embodiments for clarity, the invention may also be implemented in a single embodiment.

[00161] Reference in the specification to "some embodiments", "an embodiment", "one embodiment" or "other embodiments" means that a particular feature, structure, or characteristic described in connection with the embodiments is included in at least some embodiments, but not necessarily all embodiments, of the inventions.

[00162] It is to be understood that the phraseology and terminology employed herein is not to be construed as limiting and are for descriptive purpose only.

[00163] The principles and uses of the teachings of the present invention may be better understood with reference to the accompanying description, figures and examples.

[00164] It is to be understood that the details set forth herein do not construe a limitation to an application of the invention.

[00165] Furthermore, it is to be understood that the invention can be carried out or practiced in various ways and that the invention can be implemented in embodiments other than the ones outlined in the description above.

[00166] It is to be understood that the terms "including", "comprising", "consisting" and grammatical variants thereof do not preclude the addition of one or more components, features, steps, or integers or groups thereof and that the terms are to be construed as specifying components, features, steps or integers.

[00167] If the specification or claims refer to "an additional" element, that does not preclude there being more than one of the additional element.

[00168] It is to be understood that where the claims or specification refer to "a" or "an" element, such reference is not be construed that there is only one of that element.

[00169] It is to be understood that where the specification states that a component, feature, structure, or characteristic "may", "might", "can" or "could" be included, that particular component, feature, structure, or characteristic is not required to be included.

[00170] Where applicable, although state diagrams, flow diagrams or both may be used to describe embodiments, the invention is not limited to those diagrams or to the corresponding descriptions. For example, flow need not move through each illustrated box or state, or in exactly the same order as illustrated and described.

[00171] Methods of the present invention may be implemented by performing or completing manually, automatically, or a combination thereof, selected steps or tasks.

[00172] The term "method" may refer to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and

procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the art to which the invention belongs.

[00173] The descriptions, examples, methods and materials presented in the claims and the specification are not to be construed as limiting but rather as illustrative only.

[00174] Meanings of technical and scientific terms used herein are to be commonly understood as by one of ordinary skill in the art to which the invention belongs, unless otherwise defined.

[00175] The present invention may be implemented in the testing or practice with methods and materials equivalent or similar to those described herein.

[00176] While the invention has been described with respect to a limited number of embodiments, these should not be construed as limitations on the scope of the invention, but rather as exemplifications of some of the preferred embodiments. Other possible variations, modifications, and applications are also within the scope of the invention. Accordingly, the scope of the invention should not be limited by what has thus far been described, but by the appended claims and their legal equivalents.

CLAIMS

What is claimed is:

1. A method of determining a probability of a progeny having one or more phenotypes *Phj* each associated with a single gene *Qj,* the method implemented by a computer processor executing program instructions, the method comprising the steps of:
   a. assigning a score *sf* to each allele h_i^p at a plurality of genetic loci *(i)* in a haploid virtual gamete profile H^p of a parent *(p)*;
   b. identifying a plurality *(Nj)* of the alleles h_k^p *(k=1,...,Nj)* associated with the gene Q_j;
   c. mapping the scores *sf* to gene-specific scores $\hat{s}_{j,k}^p$ associated with gene *Qj* for the plurality of *(Nj)* alleles h_k^p; and
   d. computing a probability of altering gene product from gene *Qj* in a progeny of the parent *(p)* to be a function of the gene-specific scores $\hat{s}_{j,k}^p$.
2. A method of determining a probability of a virtual progeny having one or more phenotypes *Phj* each associated with a single gene *Qj,* the method implemented by a computer processor executing program instructions, the method comprising the steps of:
   a. generating a haplopath $H^p = \{h_1^p, h_2^p, \ldots, h_N^p\}$ including a single allele *hf* £ (1,2) at each of a plurality of loci *(i=1,..., N)* from a genome profile of a potential parent *(p)*;
   b. assigning a variance score *sf* to each of a plurality of the alleles h_i^p in the haplopath, each of the variance scores *sf* indicating a probability that the allele h_i^p results in altering gene product from gene *Qj* in the progeny;
   c. associating each variant allele h_i^{p1}, which has a variance score *sf* indicating a non-zero probability, with a corresponding one of a plurality of *(k=1,...,Nj)* variant alleles h_k^v known to alter the gene product from gene *Qj;*
   d. for each gene *Qj,* assigning a gene-specific penetrance score $\hat{s}_{j,k}^p$ to each of the *(Nj)* variant alleles h_k^p associated with the gene *Qj;*
   e. for each gene *Qj,* determining a probability of altering the gene product from gene *Qj* in the virtual progeny of the parent *(p)* based on the gene-specific penetrance scores $\hat{s}_{j,k}^p$ of the plurality of *(Nj)* variant alleles h_k^v; and

f. for each gene Q_j, outputting the probability of altering the gene product or a derivation of the probability of altering the gene product.

3. The method of claim 1 or 2, wherein the probability of having the phenotype Ph_j in the progeny of the parent *(p)* is $P_j^p = 1 - \prod_{k=1}^{Nj}[1 - \hat{s}_{j,k}^p]$, or a derivation thereof.

4. The method of claim 1 comprising:

repeating steps (a)-(d) for each of two parents *p=(pl, p2)* using two respective genome profiles thereof; and

combining the probabilities for each parent to determine the probability of having the phenotype Ph_j associated with each gene Q_j in a progeny of the two parents *(pi)* and *(p2).*

5. The method of claim 4, wherein the probability of having a recessive phenotype (Ph_j) in the progeny of the two parents *(pi)* and *(p2)* is $p_j^{p1,p2} = (1 - \prod_{k=1}^{Nj}[1 - \hat{s}_{j,k}^{p1}])(1 - \prod_{k=1}^{Nj}[1 - \hat{s}_{j,k}^{p2}])$, or a derivation thereof.

6. The method of claim 4, wherein the probability of having a dominant phenotype Ph_j in the progeny of the two parents *(pi)* and *(p2)* is $p_j^{p1,v2} = (1 - \prod_{k=1}^{Nj}[1 - \hat{s}_{j,k}^{p1}]) + (1 - \prod_{k=1}^{Nj}[1 - \hat{s}_{j,k}^{p2}])$, or a derivation thereof.

7. The method of claim 1 comprising:

e. repeating steps (a)-(d) for a plurality of different haploid genome profiles or Haplopaths H^p of the genome profile of the parent *(p),* each pair of progeny genome samplings differing from each other by at least one allele hf; and

f. determining a probability or probability distribution of having the phenotype Ph_j by combining the probabilities of expression determined for each of the plurality of progeny genome samplings.

8. The method of any of the preceding claims, wherein each of the scores sf defines a likelihood that the variant allele h_i^p is an amino acid substitution at the locus *(i)* that will damage protein function.

9. The method of any of claims 1-7, wherein each of the scores sf defines the probability that for a change in one or more amino acids that the change will occur randomly based on natural selection.

10. The method of any of the preceding claims, wherein the progeny is a virtual progeny including virtual alleles h_i^p analyzed to predict phenotypes ***Phj*** in a potential progeny.

11. The method of any of claims 1-9, wherein the progeny is a living organism including real alleles h_i^p analyzed to predict a future emergence of phenotypes ***Phj*** in the living progeny.

12. The method of any of the preceding claims, wherein when the probability indicates a likelihood of having the phenotype ***Phj*** in the virtual progeny, further comprising generating a random number to determine if the progeny will have the phenotype ***Phj*** .

13. The method of any of claims 1-11, wherein the probability indicates a degree of expressivity of the phenotype ***Phj*** in the progeny.

14. The method of any of the preceding claims comprising comparing the probability to one or more thresholds to determine a category of expressivity of the phenotype ***Phj*** .

15. The method of any of the preceding claims, wherein the genotype of the gene ***Qj*** alters an amino acid sequence known to damage a protein product of the gene causing a disease phenotype.

16. The method of any of the preceding claims, wherein the probability of a progeny having one or more phenotypes ***Phj*** is a probability of protein damage in one or more gene products, each associated with a single gene ***Qj.***

17. A method of determining a probability of having a phenotype in a virtual progeny, the method implemented by a computer processor executing program instructions, the method comprising the steps of:

a. generating a virtual progeny genome sampling ***G***, wherein at each of a plurality of genetic loci $i = 1, \ldots, N$ the sampling comprises one allele h_i^{p1} from a first genome profile of a first potential parent ***(pi)*** and one allele h_i^{p2} from a second genome profile of a second potential parent ***(p 2)***;

b. using the processor, comparing genotypes of said virtual progeny genome sampling ***G*** to one or more databases of genotype-phenotype associations to determine a phenotype associated with database genotypes matching genotypes of said virtual progeny genome sampling ***G***, wherein the phenotype is associated with a penetrance value;

c. using the processor, generating a random number to determine if the virtual progeny is predicted to have the phenotype;

d. wherein if the virtual progeny is predicted to have the phenotype, using the processor, associating the penetrance value with a degree of expressivity of the phenotype in the virtual progeny.

18. The method of claim 17 comprising:

e. repeating steps (a)-(c) for a plurality of different virtual progeny genome samplings $G^{vp} = \{G_1, G_2, \ldots, G_M\}$ each sampling differing from each other sampling by at least one allele; and

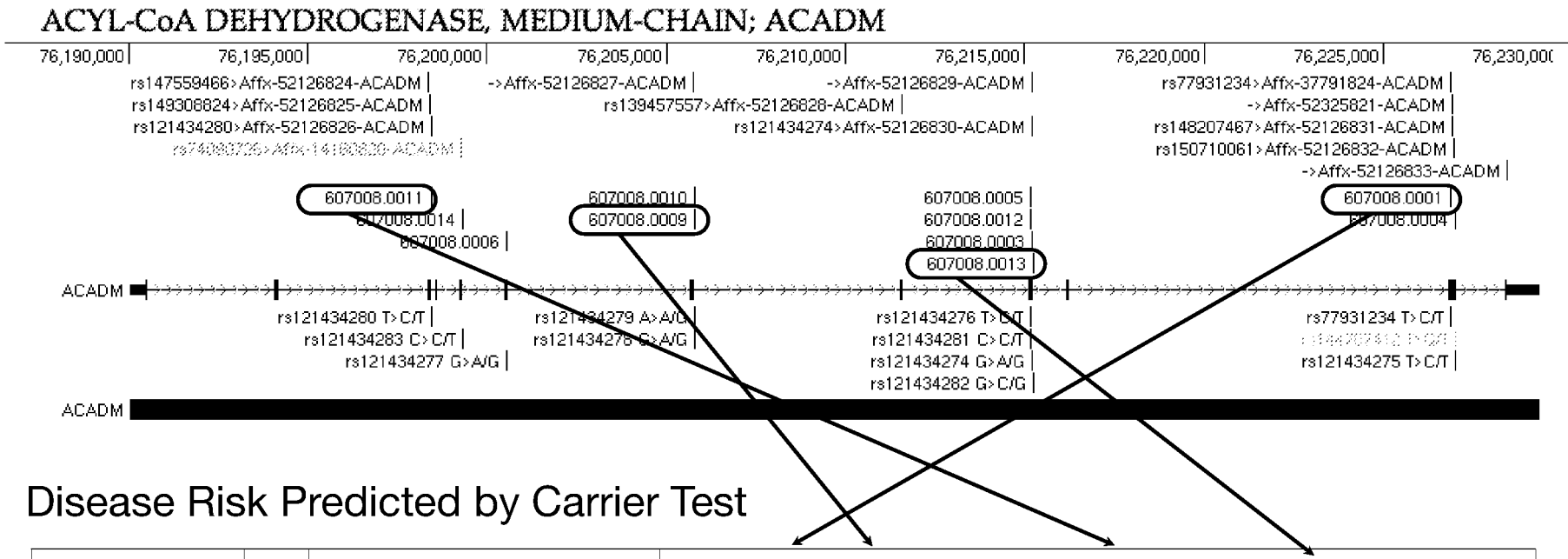
f. outputting the predicted expression of the phenotype in the virtual progeny if said determination of step (c) converges to the same result in multiple iterations.

19. The method of claim 17 or 18 comprising repeating steps (b)-(d) for each of a plurality of genotype-phenotype associations.

20. The method of any of claims 17- 19, wherein the set of alleles $\{h_i^p, i = 1, \ldots, N\}$ for each potential parent $p=(pl, p2)$ is a haplopath H^p generated by selecting one of the two alleles h_i^p £ (1,2) at each genetic locus along a path of the genome profile of the potential parent.

21. A system comprising a processor configured to implement the steps of the method of any preceding claim.

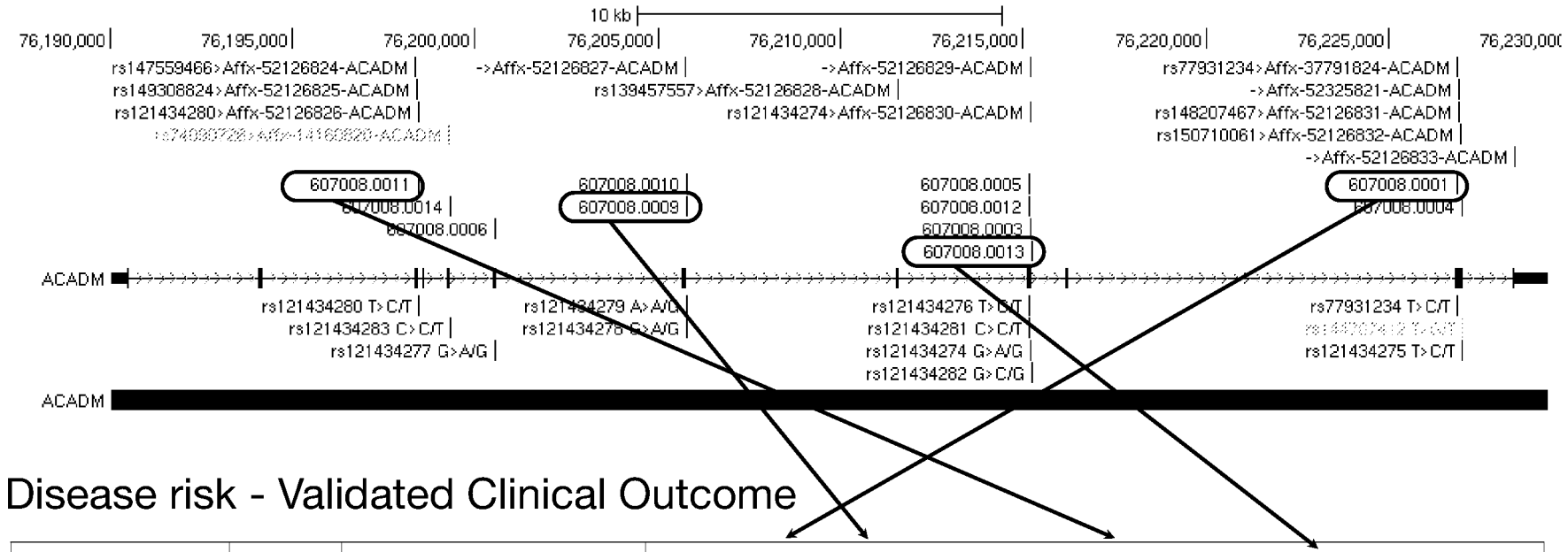
22. A system comprising a processor configured to implement the steps of the method of any of claims 15-18, wherein the processor is operatively connected to one or more databases of genotype-phenotype with which to comparing database genotypes with genotypes of said virtual progeny genome sampling G.



Disease Risk Predicted by Carrier Test

			Male parent			
MCAD mutations			0.0001 LYS304GLU	0.0009 GLY170ARG	0.0011 TYR42HIS	0.0013 ARG256THR
		Proportion reduction in function	0.70	1.00	0.35	0.20
0.0001 LYS304GLU	Female parent	0.70	Positive	Positive	Positive	**Negative
0.0009 GLY170ARG		1.00	Positive	Positive	Positive	**Negative
0.0011 TYR42HIS		0.35	Positive	Positive	*Positive	Negative
0.0013 ARG256THR		0.20	**Negative	**Negative	Negative	Negative

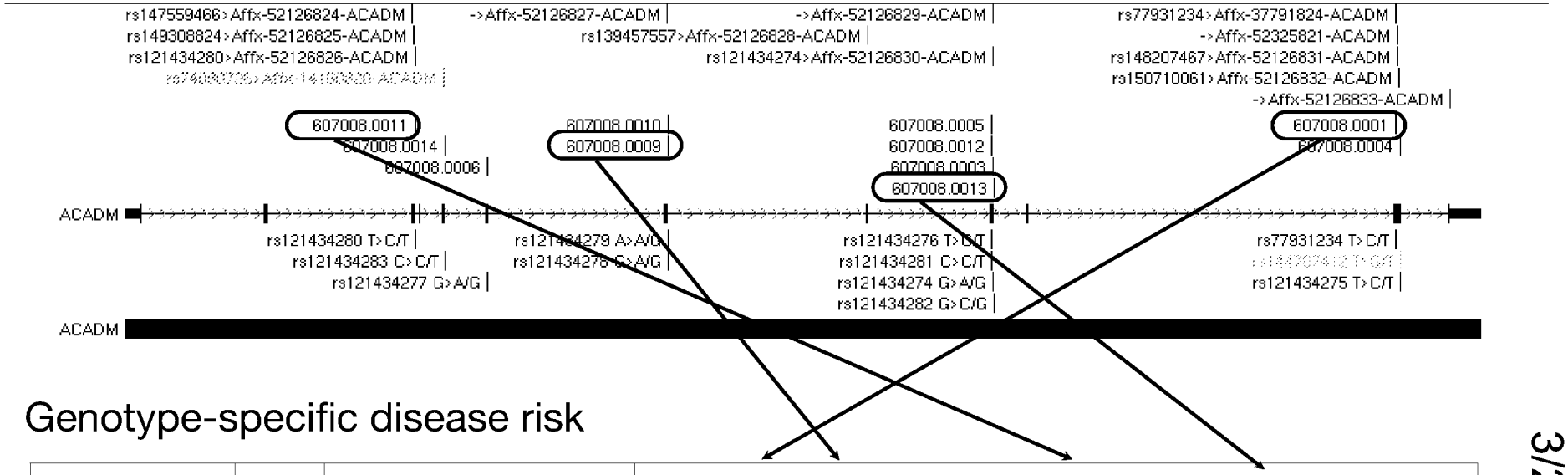
Fig. 1



Disease risk - Validated Clinical Outcome

			Male parent			
MCAD mutations			0.0001 LYS304GLU	0.0009 GLY170ARG	0.0011 TYR42HIS	0.0013 ARG256THR
		Proportion reduction in function	0.70	1.00	0.35	0.20
0.0001 LYS304GLU	Female parent	0.70	Second year of life: liver failure, coma, and death	neonatal death	partial penetrance in older children	mild or benign
0.0009 GLY170ARG		1.00	neonatal death	no live births	No Data	No Data
0.0011 TYR42HIS		0.35	partial penetrance in older children	No Data	Common variant, no symptoms	No Data
0.0013 ARG256THR		0.20	mild or benign	No Data	No Data	No Data

Fig. 2



Genotype-specific disease risk

			Male Parent			
MCAD mutations			0.0001 LYS304GLU	0.0009 GLY170ARG	0.0011 TYR42HIS	0.0013 ARG256THR
		Proportion reduction in function	0.70	1.00	0.35	0.20
0.0001 LYS304GLU	Female parent	0.70	49%	70%	24.5%	14%
0.0009 GLY170ARG		1.00	70%	100%	35%	20%
0.0011 TYR42HIS		0.35	24.5%	35%	12.25%	7%
0.0013 ARG256THR		0.20	14%	20%	7%	4%

Threshold	Outcome
100%	Severe Disease, No Survival
35% - 99%	Severe Disease
15% - 34%	Moderate Disease
13% - 14%	Mild Disease
<13%	Asymptomatic

Fig. 3

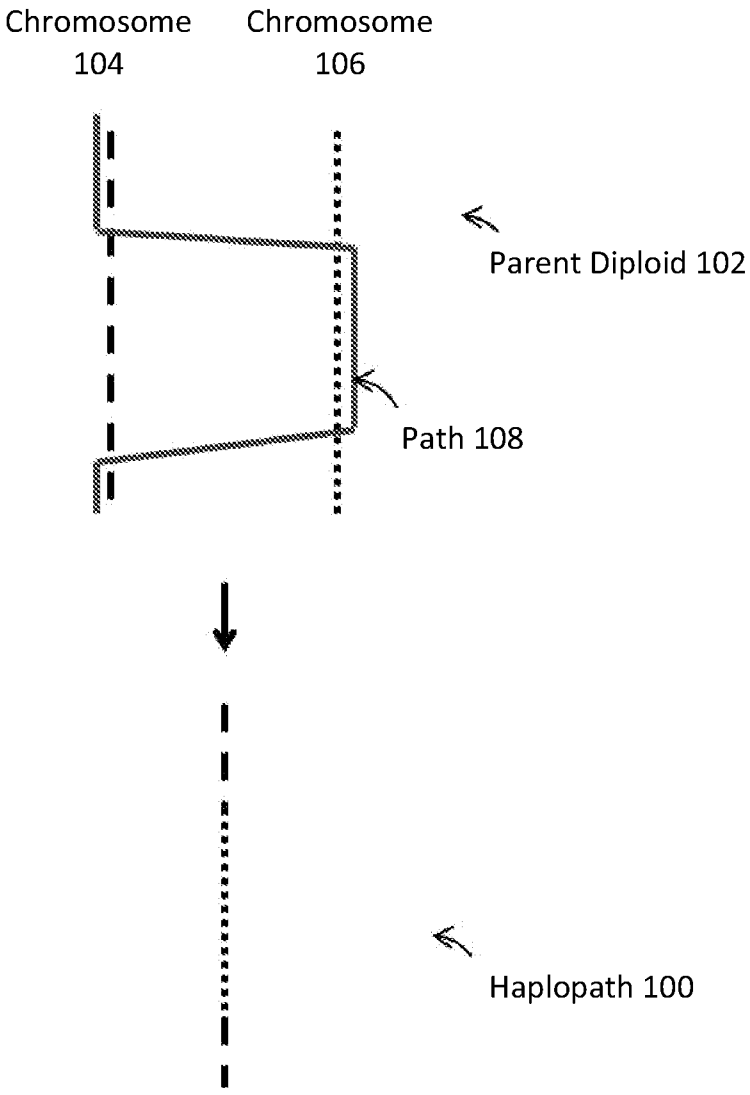

Chromosome 104
Chromosome 106
Parent Diploid 102
Path 108
Haplopath 100

Fig. 4

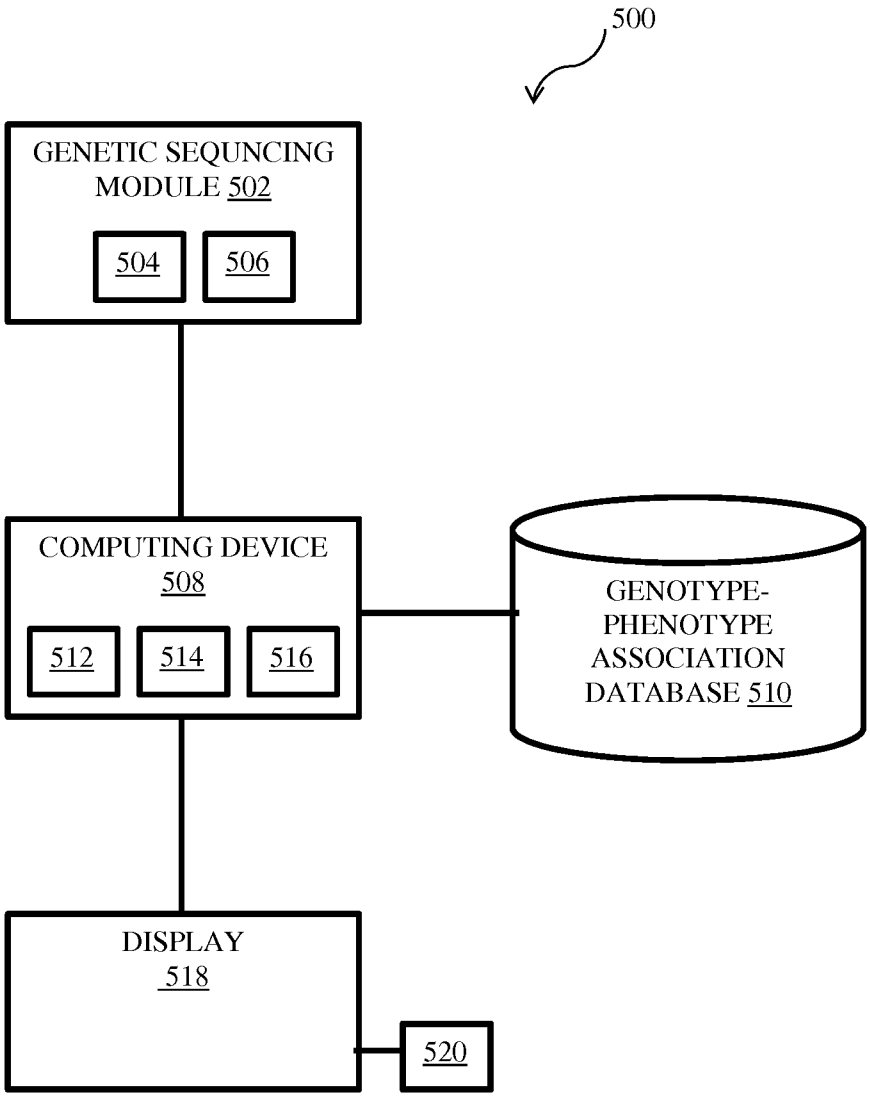

500
GENETIC SEQUNCING MODULE 502
504
506
COMPUTING DEVICE 508
512
514
516
GENOTYPE-PHENOTYPE ASSOCIATION DATABASE 510
DISPLAY 518
520

Fig. 5

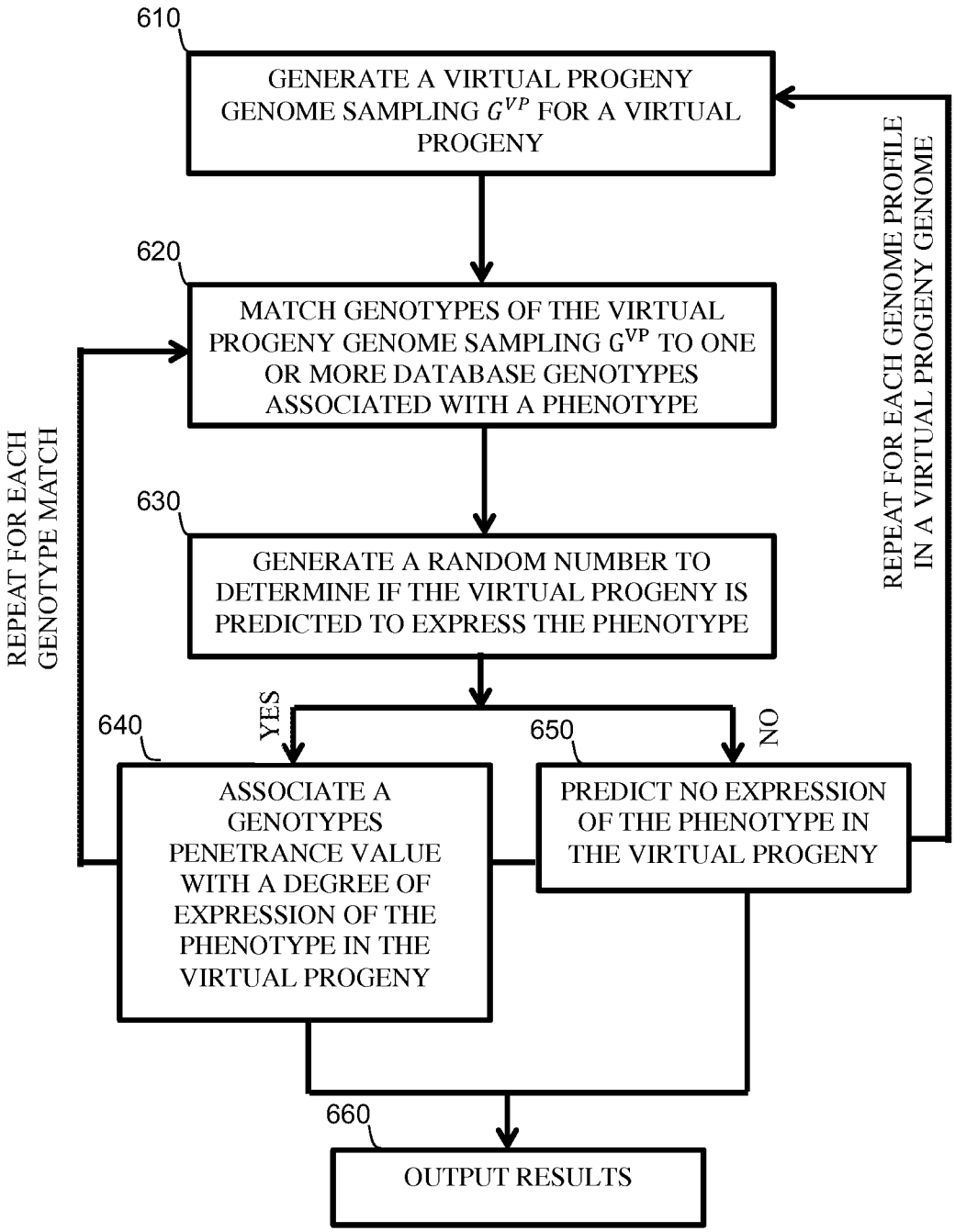

610
GENERATE A VIRTUAL PROGENY GENOME SAMPLING G^{VP} FOR A VIRTUAL PROGENY
620
MATCH GENOTYPES OF THE VIRTUAL PROGENY GENOME SAMPLING G^{VP} TO ONE OR MORE DATABASE GENOTYPES ASSOCIATED WITH A PHENOTYPE
630
GENERATE A RANDOM NUMBER TO DETERMINE IF THE VIRTUAL PROGENY IS PREDICTED TO EXPRESS THE PHENOTYPE
YES
NO
640
ASSOCIATE A GENOTYPES PENETRANCE VALUE WITH A DEGREE OF EXPRESSION OF THE PHENOTYPE IN THE VIRTUAL PROGENY
650
PREDICT NO EXPRESSION OF THE PHENOTYPE IN THE VIRTUAL PROGENY
660
OUTPUT RESULTS
REPEAT FOR EACH GENOTYPE MATCH
REPEAT FOR EACH GENOME PROFILE IN A VIRTUAL PROGENY GENOME

Fig. 6

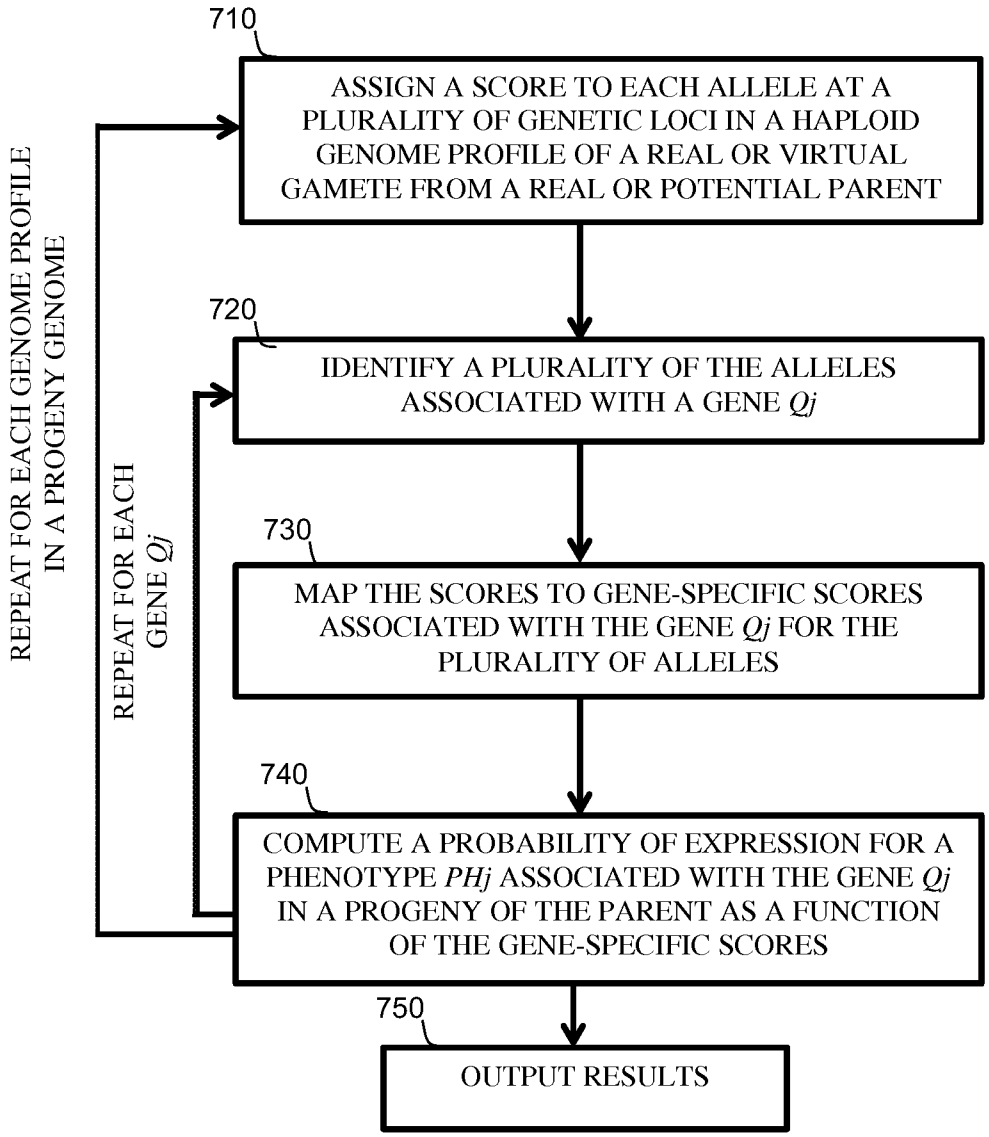

710
ASSIGN A SCORE TO EACH ALLELE AT A PLURALITY OF GENETIC LOCI IN A HAPLOID GENOME PROFILE OF A REAL OR VIRTUAL GAMETE FROM A REAL OR POTENTIAL PARENT
720
IDENTIFY A PLURALITY OF THE ALLELES ASSOCIATED WITH A GENE Qj
730
MAP THE SCORES TO GENE-SPECIFIC SCORES ASSOCIATED WITH THE GENE Qj FOR THE PLURALITY OF ALLELES
740
COMPUTE A PROBABILITY OF EXPRESSION FOR A PHENOTYPE PHj ASSOCIATED WITH THE GENE Qj IN A PROGENY OF THE PARENT AS A FUNCTION OF THE GENE-SPECIFIC SCORES
750
OUTPUT RESULTS
REPEAT FOR EACH GENOME PROFILE IN A PROGENY GENOME
REPEAT FOR EACH GENE Qj

Fig. 7

DISEASE	GENE	OMIM#
SEVERE COMBINED IMMUNODEFICIENCY, AR, T CELL-NEGATIVE,	ADA	102700
MYOADENYLATE DEAMINASE DEFICIENCY, MYOPATHY DUE TO	AMPD1	102770
ANGELMAN SYNDROME AS	MECP2	105830
PROTEASE INHIBITOR 1; PI	SERPINA1	107400
MITOCHONDRIAL COMPLEX III DEFICIENCY	BCS1L	124000
MITOCHONDRIAL COMPLEX III DEFICIENCY	UQCRB	124000
MITOCHONDRIAL COMPLEX III DEFICIENCY	UQCRQ	124000
COCKAYNE SYNDROME, B; CSB	ERCC6	133540
HEMOGLOBIN--ALPHA LOCUS 1; HBA1	HBA1	141800
HEMOGLOBIN--BETA LOCUS; HBB	HBB	141900
HYPERTROPHIC NEUROPATHY OF DEJERINE-SOTTAS. CMT3, CMT4F	EGR2	145900
HYPERTROPHIC NEUROPATHY OF DEJERINE-SOTTAS. CMT3, CMT4F	MPZ	145900
HYPERTROPHIC NEUROPATHY OF DEJERINE-SOTTAS. CMT3, CMT4F	PMP22	145900
HYPERTROPHIC NEUROPATHY OF DEJERINE-SOTTAS. CMT3, CMT4F	PRX	145900
THROMBOPHILIA DUE TO ACTIVATED PROTEIN C RESISTANCE	F5	188055
DOWN SYNDROME	GATA1	190685
ABETALIPOPROTEINEMIA; ABL	MTTP	200100
ACROCALLOSAL SYNDROME; ACLS	GLI3	200990
CARPENTER SYNDROME	RAB23	201000
ACYL-CoA DEHYDROGENASE, MEDIUM-CHAIN, DEFICIENCY OF	ACADM	201450
ACYL-CoA DEHYDROGENASE, LONG-CHAIN, DEFICIENCY OF	ACADL	201460
ACYL-CoA DEHYDROGENASE, SHORT-CHAIN, DEFICIENCY OF	ACADS	201470
ACYL-CoA DEHYDROGENASE, VERY LONG-CHAIN, DEFICIENCY OF	ACADVL	201475
LIPOID CONGENITAL ADRENAL HYPERPLASIA	CYP11A1	201710
LIPOID CONGENITAL ADRENAL HYPERPLASIA	STAR	201710
CONGENITAL ADRENAL HYPERPLASIA, 21-HYDROXYLASE DEFICIENCY	CYP21A2	201910
AFIBRINOGENEMIA, CONGENITAL	FGA	202400
AFIBRINOGENEMIA, CONGENITAL	FGB	202400
AFIBRINOGENEMIA, CONGENITAL	FGG	202400
ALKAPTONURIA	HGD	203500
ALPERS DIFFUSE CEREBRAL DEGENERATION WITH HEPATIC CIRRHOSIS	POLG	203700
ALPORT SYNDROME, AR	COL4A3	203780
ALPORT SYNDROME, AR	COL4A4	203780
ALSTROM SYNDROME; ALMS	ALMS1	203800
CEROID LIPOFUSCINOSIS, NEURONAL, 3; CLN3	CLN3	204200

Fig. 8

DISEASE	GENE	OMIM#
CEROID LIPOFUSCINOSIS, NEURONAL, 2; CLN2	TPP1	204500
AMYOTROPHIC LATERAL SCLEROSIS 2, JUVENILE; ALS2	ALS2	205100
ANIRIDIA, CEREBELLAR ATAXIA, AND MENTAL DEFICIENCY	PAX6	206700
ANTLEY-BIXLER SYNDROME; ABS	FGFR2	207410
ARGININOSUCCINIC ACIDURIA	ASL	207900
ARTERIAL CALCIFICATION, GENERALIZED, OF INFANCY; GACI	ENPP1	208000
ARTHROGRYPOSIS, RENAL DYSFUNCTION, AND CHOLESTASIS	VPS33B	208085
FETAL AKINESIA DEATION SEQUENCE; FADS	RAPSN	208150
ASPARTYLGLUCOSAMINURIA	AGA	208400
RENAL-HEPATIC-PANCREATIC DYSPLASIA; RHPD	NPHP3	208540
ATAXIA-TELANGIECTASIA; AT	ATM	208900
EARLY-ONSET ATAXIA WITH OCULOMOTOR APRAXIA AND HYPOALBUMINEMIA	APTX	208920
3-METHYLCROTONYL-CoA CARBOXYLASE 2 DEFICIENCY	MCCC2	210210
SECKEL SYNDROME 1	ATR	210600
BLOOM SYNDROME; BLM	BLM	210900
CHOLESTASIS, PROGRESSIVE FAMILIAL INTRAHEPATIC 1; PFIC1	ATP8B1	211600
C SYNDROME	CD96	211750
CONGENITAL DISORDER OF GLYCOSYLATION, Ia; CDG1A	PMM2	212065
CONGENITAL DISORDER OF GLYCOSYLATION, IIa; CDG2A	MGAT2	212066
MARTSOLF SYNDROME	RAB3GAP2	212720
CEREBROTENDINOUS XANTHOMATOSIS	CYP27A1	213700
CEREBROOCULOFACIOSKELETAL SYNDROME 1; COFS1	ERCC6	214150
GRISCELLI SYNDROME, 1; GS1	MYO5A	214450
CHEDIAK-HIGASHI SYNDROME; CHS	LYST	214500
BILE ACID SYNTHESIS DEFECT, CONGENITAL, 4	AMACR	214950
CHONDRODYSPLASIA, BLOMSTRAND ; BOCD	PTH1R	215045
RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, 1; RCDP1	PEX7	215100
HYDROPS-ECTOPIC CALCIFICATION-MOTH-EATEN SKELETAL DYSPLASIA	LBR	215140
OTOSPONDYLOMEGAEPIPHYSEAL DYSPLASIA; OSMED	COL11A2	215150
OTOSPONDYLOMEGAEPIPHYSEAL DYSPLASIA; OSMED	COL2A1	215150
CIRRHOSIS, FAMILIAL	KRT18	215600
CIRRHOSIS, FAMILIAL	KRT8	215600
CITRULLINEMIA, CLASSIC	ASS1	215700
COCKAYNE SYNDROME, A; CSA	ERCC8	216400
COHEN SYNDROME; COH1	VPS13B	216550
PLASMINOGEN DEFICIENCY, I	PLG	217090
CORNEAL DYSTROPHY AND PERCEPTIVE DEAFNESS	SLC4A11	217400
AGENESIS OF THE CORPUS CALLOSUM WITH PERIPHERAL NEUROPATHY; ACCPN	SLC12A6	218000
FRASER SYNDROME	FRAS1	219000
FRASER SYNDROME	FREM2	219000
CUTIS LAXA, AR, I	EFEMP2	219100
CUTIS LAXA, AR, I	FBLN5	219100

Fig. 8 cont.

DISEASE	GENE	OMIM#
CUTIS LAXA, AR, II	ATP6V0A2	219200
CYSTIC FIBROSIS; CF	CFTR	219700
CYSTINOSIS, ADULT NONNEPHROPATHIC	CTNS	219750
CYSTINOSIS, NEPHROPATHIC; CTNS	CTNS	219800
CYSTINOSIS, LATE-ONSET JUVENILE OR ADOLESCENT NEPHROPATHIC	CTNS	219900
LEIGH SYNDROME, FRENCH-CANADIAN ; LSFC	LRPPRC	220111
DEAFNESS, AR 1A	GJB2	220290
JERVELL AND LANGE-NIELSEN SYNDROME 1; JLNS1	KCNQ1	220400
DONNAI-BARROW SYNDROME	LRP2	222448
DIASTROPHIC DYSPLASIA	SLC26A2	222600
NEUROPATHY, HEREDITARY SENSORY AND AUTONOMIC, III; HSAN3	IKBKAP	223900
CEREBELLAR HYPOPLASIA AND MENTAL RETARDATION	VLDLR	224050
DYSSEGMENTAL DYSPLASIA, SILVERMAN-HANDMAKER ; DDSH	HSPG2	224410
EHLERS-DANLOS SYNDROME, AR, CARDIAC VALVULAR	COL1A2	225320
EHLERS-DANLOS SYNDROME, VII, AR	ADAMTS2	225410
AICARDI-GOUTIERES SYNDROME 1; AGS1	TREX1	225750
PONTOCEREBELLAR HYPOPLASIA 4; PCH4	TSEN54	225753
EPIDERMOLYSIS BULLOSA DYSTROPHICA, AR; RDEB	COL7A1	226600
EPIDERMOLYSIS BULLOSA, JUNCTIONAL, NON-HERLITZ	COL17A1	226650
EPIDERMOLYSIS BULLOSA, JUNCTIONAL, NON-HERLITZ	ITGB4	226650
EPIDERMOLYSIS BULLOSA, JUNCTIONAL, NON-HERLITZ	LAMA3	226650
EPIDERMOLYSIS BULLOSA, JUNCTIONAL, NON-HERLITZ	LAMB3	226650
EPIDERMOLYSIS BULLOSA, JUNCTIONAL, NON-HERLITZ	LAMC2	226650
EPIDERMOLYSIS BULLOSA SIMPLEX WITH MUSCULAR DYSTROPHY	PLEC1	226670
EPIDERMOLYSIS BULLOSA, JUNCTIONAL, HERLITZ	LAMA3	226700
EPIDERMOLYSIS BULLOSA, JUNCTIONAL, HERLITZ	LAMB3	226700
EPIDERMOLYSIS BULLOSA, JUNCTIONAL, HERLITZ	LAMC2	226700
EPIDERMOLYSIS BULLOSA JUNCTIONALIS WITH PYLORIC ATRESIA	ITGA6	226730
EPIDERMOLYSIS BULLOSA JUNCTIONALIS WITH PYLORIC ATRESIA	ITGB4	226730
EPIPHYSEAL DYSPLASIA, MULTIPLE, WITH EARLY-ONSET DIABETES MELLITUS	EIF2AK3	226980
FIBROMATOSIS, JUVENILE HYALINE	ANTXR2	228600
FIBULAR APLASIA OR HYPOPLASIA	WNT7A	228930
BRITTLE CORNEA SYNDROME; BCS	ZNF469	229200
FRUCTOSE INTOLERANCE, HEREDITARY	ALDOB	229600
FUCOSIDOSIS	FUCA1	230000
GALACTOSEMIA	GALT	230400
GM1-GANGLIOSIDOSIS, I	GLB1	230500
GM1-GANGLIOSIDOSIS, II	GLB1	230600
GAUCHER DISEASE, I	GBA	230800
GAUCHER DISEASE, II	GBA	230900
GAUCHER DISEASE, III	GBA	231000
GELEOPHYSIC DYSPLASIA	ADAMTSL2	231050

Fig. 8 cont.

DISEASE	GENE	OMIM#
3-HYDROXYACYL-CoA DEHYDROGENASE DEFICIENCY	HADH	231530
ACHALASIA-ADDISONIANISM-ALACRIMA SYNDROME; AAA	AAAS	231550
GLUTARIC ACIDEMIA I	GCDH	231670
MULTIPLE ACYL-CoA DEHYDROGENASE DEFICIENCY; MADD	ETFA	231680
MULTIPLE ACYL-CoA DEHYDROGENASE DEFICIENCY; MADD	ETFB	231680
MULTIPLE ACYL-CoA DEHYDROGENASE DEFICIENCY; MADD	ETFDH	231680
GLYCOGEN STORAGE DISEASE I	G6PC3	232200
GLYCOGEN STORAGE DISEASE Ib	SLC37A4	232220
GLYCOGEN STORAGE DISEASE Ic	SLC37A4	232240
GLYCOGEN STORAGE DISEASE II	GAA	232300
GLYCOGEN STORAGE DISEASE III	AGL	232400
GLYCOGEN STORAGE DISEASE IV	GBE1	232500
HEMOCHROMATOSIS; HFE	HFE	235200
HEMOCHROMATOSIS; HFE	HFE2	235200
HEPATIC VENOOCCLUSIVE DISEASE WITH IMMUNODEFICIENCY; VODI	SP110	235550
HOMOCYSTINURIA	CBS	236200
HOMOCYSTINURIA DUE TO DEFICIENCY OF METHYLENETETRAHYDROFOLATE	MTHFR	236250
HYALINOSIS, INFANTILE SYSTEMIC	ANTXR2	236490
WALKER-WARBURG SYNDROME; WWS	POMT1	236670
WALKER-WARBURG SYNDROME; WWS	POMT2	236670
HYDROLETHALUS SYNDROME 1	HYLS1	236680
CARBAMOYL PHOSPHATE SYNTHETASE I DEFICIENCY, HYPERAMMONEMIA	CPS1	237300
N-ACETYLGLUTAMATE SYNTHASE DEFICIENCY	NAGS	237310
HYPERORNITHINEMIA-HYPERAMMONEMIA-HOMOCITRULLINURIA SYNDROME	SLC25A15	238970
PAGET DISEASE, JUVENILE	TNFRSF11B	239000
AUTOIMMUNE POLYENDOCRINE SYNDROME, I; APS1	AIRE	240300
BARTTER SYNDROME, ANTENATAL, 2	KCNJ1	241200
HYPOPARATHYROIDISM-RETARDATION-DYSMORPHISM SYNDROME; HRD	TBCE	241410
HYPOPHOSPHATASIA, CHILDHOOD	ALPL	241510
HYPOPHOSPHATEMIC RICKETS, AR	DMP1	241520
HYPOPLASTIC LEFT HEART SYNDROME	GJA1	241550
ICHTHYOSIS, LAMELLAR, 1; LI1	TGM1	242300
ICHTHYOSIS CONGENITA, HARLEQUIN FETUS	ABCA12	242500
IMMUNODEFICIENCY-CENTROMERIC INSTABILITY-FACIAL ANOMALIES SYNDROME	DNMT3B	242860
ISOVALERIC ACIDEMIA; IVA	IVD	243500
JOHANSON-BLIZZARD SYNDROME; JBS	UBR1	243800
KENNY-CAFFEY SYNDROME, 1; KCS	TBCE	244460
KRABBE DISEASE	GALC	245200
PYRUVATE DEHYDROGENASE E3-BINDING PROTEIN DEFICIENCY	PDHX	245349

Fig. 8 cont.

DISEASE	GENE	OMIM#
LACTIC ACIDOSIS, FATAL INFANTILE	SUCLG1	245400
LARYNGOONYCHOCUTANEOUS SYNDROME; LOCS	LAMA3	245660
DONOHUE SYNDROME	INSR	246200
3-HYDROXY-3-METHYLGLUTARYL-CoA LYASE DEFICIENCY	HMGCL	246450
HYPOMAGNESEMIA, RENAL, WITH OCULAR INVOLVEMENT	CLDN19	248190
MANNOSIDOSIS, ALPHA B, LYSOSOMAL	MAN2B1	248500
MAPLE SYRUP URINE DISEASE Ia	BCKDHA	248600
MAPLE SYRUP URINE DISEASE, CLASSIC, IB	BCKDHB	248600
MAPLE SYRUP URINE DISEASE III	DLD	248600
Marinesco-Sjogren Syndrome	SIL1	248800
MECKEL SYNDROME, 1; MKS1	MKS1	249000
FAMILIAL MEDITERRANEAN FEVER; FMF	MEFV	249100
METACHROMATIC LEUKODYSTROPHY DUE TO SAPOSIN B DEFICIENCY	PSAP	249900
METACHROMATIC LEUKODYSTROPHY	ARSA	250100
CARTILAGE-HAIR HYPOPLASIA; CHH	RMRP	250250
BETA-HYDROXYISOBUTYRYL CoA DEACYLASE, DEFICIENCY OF	HIBCH	250620
3-METHYLGLUTACONIC ACIDURIA, I	AUH	250950
METHYLMALONIC ACIDURIA DUE TO METHYLMALONYL-CoA MUTASE DEFICIENCY	MUT	251000
METHYLMALONIC ACIDURIA, cblB	MMAB	251110
NIJMEGEN BREAKAGE SYNDROME	NBN	251260
MITOCHONDRIAL DNA DEPLETION SYNDROME, HEPATOCEREBRAL	C10ORF2	251880
MITOCHONDRIAL DNA DEPLETION SYNDROME, HEPATOCEREBRAL	DGUOK	251880
MITOCHONDRIAL DNA DEPLETION SYNDROME, HEPATOCEREBRAL	MPV17	251880
MOLYBDENUM COFACTOR DEFICIENCY	MOCS1	252150
MOLYBDENUM COFACTOR DEFICIENCY	MOCS2	252150
MUCOLIPIDOSIS II ALPHA/BETA	GNPTAB	252500
MUCOLIPIDOSIS III ALPHA/BETA	GNPTAB	252600
MUCOLIPIDOSIS IV	MCOLN1	252650
MUCOPOLYSACCHARIDOSIS IIIA	SGSH	252900
MUCOPOLYSACCHARIDOSIS IIIC	HGSNAT	252930
MUCOPOLYSACCHARIDOSIS VI	ARSB	253200
MUCOPOLYSACCHARIDOSIS VII	GUSB	253220
MUCOPOLYSACCHARIDOSIS VIII	GNS	253230
MULIBREY NANISM	TRIM37	253250
BIOTINIDASE DEFICIENCY	BTD	253260
MUSCLE-EYE-BRAIN DISEASE; MEB	FKRP	253280
MUSCLE-EYE-BRAIN DISEASE; MEB	POMGNT1	253280
MULTIPLE PTERYGIUM SYNDROME, LETHAL	CHRNA1	253290
MULTIPLE PTERYGIUM SYNDROME, LETHAL	CHRND	253290
MULTIPLE PTERYGIUM SYNDROME, LETHAL	CHRNG	253290
SPINAL MUSCULAR ATROPHY, I; SMA1	SMN1	253300
LETHAL CONGENITAL CONTRACTURE SYNDROME 1; LCCS1	GLE1	253310
SPINAL MUSCULAR ATROPHY, III; SMA3	SMN1	253400

Fig. 8 cont.

DISEASE	GENE	OMIM#
SPINAL MUSCULAR ATROPHY, II; SMA2	SMN1	253550
FUKUYAMA CONGENITAL MUSCULAR DYSTROPHY; FCMD	FKTN	253800
MYOCLONIC EPILEPSY OF LAFORA	EPM2A	254780
MYOCLONIC EPILEPSY OF LAFORA	NHLRC1	254780
MYOCLONIC EPILEPSY OF UNVERRICHT AND LUNDBORG	CSTB	254800
CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY, LATE-ONSET	CPT2	255110
CARNITINE PALMITOYLTRANSFERASE I DEFICIENCY	CPT1A	255120
MYXOMA, INTRACARDIAC	PRKAR1A	255960
NEMALINE MYOPATHY 2; NEM2	NEB	256030
ATELOSTEOGENESIS, II; AOII	SLC26A2	256050
NEPHRONOPHTHISIS 1; NPHP1	NPHP1	256100
NEPHROSIS 1, CONGENITAL, FINNISH ; NPHS1	NPHS1	256300
NEPHROTIC SYNDROME, EARLY-ONSET, WITH DIFFUSE MESANGIAL SCLEROSIS	WT1	256370
NEURAMINIDASE DEFICIENCY	NEU1	256550
NEUROAXONAL DYSTROPHY, INFANTILE; INAD1	PLA2G6	256600
ELEJALDE DISEASE	MYO5A	256710
CEROID LIPOFUSCINOSIS, NEURONAL, 1; CLN1	PPT1	256730
CEROID LIPOFUSCINOSIS, NEURONAL, 5; CLN5	CLN5	256731
INSENSITIVITY TO PAIN, CONGENITAL, WITH ANHIDROSIS; CIPA	NTRK1	256800
NAVAJO NEUROHEPATOPATHY; NN	MPV17	256810
NIEMANN-PICK DISEASE, A	SMPD1	257200
NIEMANN-PICK DISEASE, C1; NPC1	NPC1	257220
LISSENCEPHALY 2; LIS2	RELN	257320
ODONTOONYCHODERMAL DYSPLASIA; OODD	WNT10A	257980
3-METHYLGLUTACONIC ACIDURIA, III	OPA3	258501
OSTEOPETROSIS, AR 1; OPTB1	TCIRG1	259700
OSTEOPETROSIS, AR 5; OPTB5	OSTM1	259720
OSTEOPETROSIS, AR 3; OPTB3	CA2	259730
OSTEOPOROSIS-PSEUDOGLIOMA SYNDROME; OPPG	LRP5	259770
RAINE SYNDROME; RNS	FAM20C	259775
HYPEROXALURIA, PRIMARY, I	AGXT	259900
HYPEROXALURIA, PRIMARY, II	GRHPR	260000
SHWACHMAN-DIAMOND SYNDROME; SDS	SBDS	260400
D-BIFUNCTIONAL PROTEIN DEFICIENCY	HSD17B4	261515
PHENYLKETONURIA; PKU	PAH	261600
GLYCOGEN STORAGE DISEASE OF HEART, LETHAL CONGENITAL	PRKAG2	261740
ACHROMATOPSIA 3; ACHM3	CNGB3	262300
PITUITARY DWARFISM III	HESX1	262600
PITUITARY DWARFISM III	LHX3	262600
PITUITARY DWARFISM III	POU1F1	262600
PITUITARY DWARFISM III	PROP1	262600
POLYCYSTIC KIDNEY DISEASE, AR; ARPKD	PKHD1	263200
PORPHYRIA, CONGENITAL ERYTHROPOIETIC	UROS	263700
PSEUDOHYPOALDOSTERONISM, I, AR; PHA1	SCNN1A	264350
PSEUDOHYPOALDOSTERONISM, I, AR; PHA1	SCNN1B	264350

Fig. 8 cont.

DISEASE	GENE	OMIM#
PSEUDOHYPOALDOSTERONISM, I, AR; PHA1	SCNN1G	264350
PEROXISOMAL ACYL-CoA OXIDASE DEFICIENCY	ACOX1	264470
VITAMIN D-DEPENDENT RICKETS, I	CYP27B1	264700
MULTIPLE PTERYGIUM SYNDROME, ESCOBAR	CHRNG	265000
PULMONARY ALVEOLAR MICROLITHIASIS	SLC34A2	265100
SURFACTANT METABOLISM DYSFUNCTION, PULMONARY, 1; SMDP1	SFTPB	265120
NEWBORN PULMONARY HYPERTENSION, FAMILIAL PERSISTENT	CPS1	265380
PULMONARY VENOOCCLUSIVE DISEASE; PVOD	BMPR2	265450
PYCNODYSOSTOSIS	CTSK	265800
GLUTATHIONE SYNTHETASE DEFICIENCY	GSS	266130
PYRUVATE CARBOXYLASE DEFICIENCY	PC	266150
PYRUVATE KINASE DEFICIENCY OF RED CELLS	PKLR	266200
CONGENITAL DISORDER OF GLYCOSYLATION, IIc; CDG2C	SLC35C1	266265
SENIOR-LOKEN SYNDROME 1; SLSN1	NPHP1	266900
RENAL TUBULAR DYSGENESIS; RTD	ACE	267430
RENAL TUBULAR DYSGENESIS; RTD	AGT	267430
RENAL TUBULAR DYSGENESIS; RTD	AGTR1	267430
RENAL TUBULAR DYSGENESIS; RTD	REN	267430
RESPIRATORY DISTRESS SYNDROME IN PREMATURE INFANTS	SFTPA1	267450
RESPIRATORY DISTRESS SYNDROME IN PREMATURE INFANTS	SFTPB	267450
RESPIRATORY DISTRESS SYNDROME IN PREMATURE INFANTS	SFTPC	267450
ROBERTS SYNDROME; RBS	ESCO2	268300
SANDHOFF DISEASE	HEXB	268800
SCHNECKENBECKEN DYSPLASIA	SLC35D1	269250
INFANTILE SIALIC ACID STORAGE DISORDER	SLC17A5	269920
SJOGREN-LARSSON SYNDROME; SLS	ALDH3A2	270200
SMITH-LEMLI-OPITZ SYNDROME; SLOS	DHCR7	270400
INSULIN-LIKE GROWTH FACTOR I, RESISTANCE TO	IGF1	270450
SPASTIC ATAXIA, CHARLEVOIX-SAGUENAY ; SACS	SACS	270550
INFANTILE-ONSET SPINOCEREBELLAR ATAXIA; IOSCA	C10ORF2	271245
CANAVAN DISEASE	ASPA	271900
STRIATONIGRAL DEGENERATION, INFANTILE; SNDI	NUP62	271930
SUCCINIC SEMIALDEHYDE DEHYDROGENASE DEFICIENCY	ALDH5A1	271980
SULFOCYSTEINURIA	SUOX	272300
TAY-SACHS DISEASE; TSD	HEXA	272800
TETRA-AMELIA, AR	WNT3	273395
THROMBOTIC THROMBOCYTOPENIC PURPURA, CONGENITAL; TTP	ADAMTS13	274150
DIHYDROPYRIMIDINE DEHYDROGENASE; DPYD	DPYD	274270
PENDRED SYNDROME; PDS	SLC26A4	274600
HYPOTHYROIDISM, CONGENITAL, NONGOITROUS, 4; CHNG4	TSHB	275100
TIGHT SKIN CONTRACTURE SYNDROME, LETHAL	LMNA	275210
TIGHT SKIN CONTRACTURE SYNDROME, LETHAL	ZMPSTE24	275210

Fig. 8 cont.

DISEASE	GENE	OMIM#
TYROSINEMIA, I	FAH	276700
ULNA AND FIBULA, ABSENCE OF	WNT7A	276820
USHER SYNDROME, I	MYO7A	276900
USHER SYNDROME, IIA; USH2A	USH2A	276901
USHER SYNDROME, III; USH3	CLRN1	276902
USHER SYNDROME, IC; USH1C	USH1C	276904
SPONDYLOCOSTAL DYSOSTOSIS, AR 1; SCDO1	DLL3	277300
METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblC	MMACHC	277400
VITAMIN D-DEPENDENT RICKETS, II	VDR	277440
VITAMIN E, FAMILIAL ISOLATED DEFICIENCY OF; VED	TTPA	277460
PONTOCEREBELLAR HYPOPLASIA 2A; PCH2A	TSEN54	277470
WAARDENBURG-SHAH SYNDROME	EDN3	277580
WAARDENBURG-SHAH SYNDROME	EDNRB	277580
WAARDENBURG-SHAH SYNDROME	SOX10	277580
WILSON DISEASE	ATP7B	277900
XERODERMA PIGMENTOSUM, COMPLEMENTATION GROUP A; XPA	XPA	278700
XERODERMA PIGMENTOSUM, COMPLEMENTATION GROUP D; XPD	ERCC2	278730
XERODERMA PIGMENTOSUM, COMPLEMENTATION GROUP E	DDB2	278740
XERODERMA PIGMENTOSUM, COMPLEMENTATION GROUP F; XPF	ERCC4	278760
XERODERMA PIGMENTOSUM, COMPLEMENTATION GROUP G; XPG	ERCC5	278780
DE SANCTIS-CACCHIONE SYNDROME	ERCC6	278800
DE SANCTIS-CACCHIONE SYNDROME	XPA	278800
CORPUS CALLOSUM, AGENESIS OF, WITH ABNORMAL GENITALIA	ARX	300004
DOSAGE-SENSITIVE SEX REVERSAL; DSS	NR0B1	300018
INTESTINAL PSEUDOOBSTRUCTION, NEURONAL, CHRONIC IDIOPATHIC, XLR	FLNA	300048
LISSENCEPHALY, XLR, 1; LISX1	DCX	300067
CARDIOMYOPATHY, DILATED, 3A; CMD3A	TAZ	300069
ADRENOLEUKODYSTROPHY; ALD	ABCD1	300100
SIMPSON-GOLABI-BEHMEL SYNDROME, 2	OFD1	300209
LISSENCEPHALY, XLR, 2 LISX2	ARX	300215
MENTAL RETARDATION, XLR, SYNDROMIC 10; MRXS10	HSD17B10	300220
HOYERAAL-HREIDARSSON SYNDROME; HHS	DKC1	300240
MENTAL RETARDATION, XLR, SYNDROMIC, CHRISTIANSON	SLC9A6	300243
ECTODERMAL DYSPLASIA, HYPOHIDROTIC, WITH IMMUNE DEFICIENCY	IKBKG	300291
OSTEOPETROSIS, LYMPHEDEMA, ECTODERMAL DYSPLASIA, ANHIDROSIS, IMMUNODEFICIENCY	IKBKG	300301
LESCH-NYHAN SYNDROME; LNS	HPRT1	300322
CREATINE DEFICIENCY SYNDROME, XLR	SLC6A8	300352
SEVERE COMBINED IMMUNODEFICIENCY, XLR; SCIDX1	IL2RG	300400
AGENESIS OF CORPUS CALLOSUM WITH MENTAL RETARDATION, OCULAR COLOBOMA	IGBP1	300472

Fig. 8 cont.

DISEASE	GENE	OMIM#
ALLAN-HERNDON-DUDLEY SYNDROME AHDS	SLC16A2	300523
EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 2	CDKL5	300672
ENCEPHALOPATHY, NEONATAL SEVERE, DUE TO MECP2 MUTATIONS	MECP2	300673
AGAMMAGLOBULINEMIA, XLR XLA	BTK	300755
WISKOTT-ALDRICH SYNDROME; WAS	WAS	301000
α-THALASSEMIA/MENTAL RETARDATION SYNDROME,NONDELETION , XLR ATRX	ATRX	301040
FABRY DISEASE	GLA	301500
SPINAL MUSCULAR ATROPHY, XLR 2; SMAX2	UBA1	301830
ARTS SYNDROME; ARTS	PRPS1	301835
CARDIOMYOPATHY, DILATED, 3B; CMD3B	DMD	302045
BARTH SYNDROME; BTHS	TAZ	302060
CHONDRODYSPLASIA PUNCTATA 1, XLR RECESSIVE; CDPX1	ARSE	302950
CHOROIDEREMIA; CHM	CHM	303100
MASA SYNDROME	L1CAM	303350
CORPUS CALLOSUM, PARTIAL AGENESIS OF, XLR	L1CAM	304100
IMMUNODYSREGULATION, POLYENDOCRINOPATHY, AND ENTEROPATHY, XLR	FOXP3	304790
ECTODERMAL DYSPLASIA, HYPOHIDROTIC, XLR; XHED	EDA	305100
GLUCOSE-6-PHOSPHATE DEHYDROGENASE; G6PD	G6PD	305900
HETEROTAXY, VISCERAL, 1, XLR; HTX1	ZIC3	306955
HYDROCEPHALUS DUE TO CONGENITAL STENOSIS OF AQUEDUCT OF SYLVIUS; HSAS	L1CAM	307000
IMMUNODEFICIENCY WITH HYPER-IgM, 1; HIGM1	CD40LG	308230
LYMPHOPROLIFERATIVE SYNDROME, XLR, 1; XLP1	SH2D1A	308240
EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 1	ARX	308350
INFERTILE MALE SYNDROME	AR	308370
LEIGH SYNDROME, XLR	PDHA1	308930
LOWE OCULOCEREBRORENAL SYNDROME; OCRL	OCRL	309000
MENKES DISEASE	ATP7A	309400
RENPENNING SYNDROME 1; RENS1	PQBP1	309500
LUJAN-FRYNS SYNDROME	MED12	309520
MUSCULAR DYSTROPHY, DUCHENNE ; DMD	DMD	310200
MYOTUBULAR MYOPATHY 1; MTM1	MTM1	310400
NORRIE DISEASE; ND	NDP	310600
OPTICOACOUSTIC NERVE ATROPHY WITH DEMENTIA	TIMM8A	311150
ORNITHINE TRANSCARBAMYLASE DEFICIENCY, HYPERAMMONEMIA DUE TO	OTC	311250
PROPERDIN DEFICIENCY, XLR	CFP	312060
PELIZAEUS-MERZBACHER DISEASE; PMD	PLP1	312080
RETINOSCHISIS 1, XLR, JUVENILE; RS1	RS1	312700
RETT SYNDROME; RTT	MECP2	312750
COMBINED IMMUNODEFICIENCY, XLR; CIDX	IL2RG	312863
SPASTIC PARAPLEGIA 2, XLR; SPG2	PLP1	312920
VACTERL ASSOCIATION WITH HYDROCEPHALUS, XLR	FANCB	314390
DEAFNESS, NEUROSENSORY, AR 2; DFNB2	MYO7A	600060
WARBURG MICRO SYNDROME; WARBM	RAB3GAP1	600118

Fig. 8 cont.

DISEASE	GENE	OMIM#
RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, 3; RCDP3	AGPS	600121
CEROID LIPOFUSCINOSIS, NEURONAL, 8; CLN8	CLN8	600143
ABCD SYNDROME	EDNRB	600501
CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY, INFANTILE	CPT2	600649
D-2-HYDROXYGLUTARIC ACIDURIA	D2HGDH	600721
INCLUSION BODY MYOPATHY 2, AR; IBM2	GNE	600737
SEVERE COMBINED IMMUNODEFICIENCY, AR, T CELL- B CELL+, NK CELL-	JAK3	600802
ACHONDROGENESIS, IB; ACG1B	SLC26A2	600972
USHER SYNDROME, ID; USH1D	CDH23	601067
MICROPHTHALMIA, SYNDROMIC 9; MCOPS9	STRA6	601186
CRISPONI SYNDROME	CRLF1	601378
NEVO SYNDROME	PLOD1	601451
SEVERE COMBINED IMMUNODEFICIENCY, AR, T CELL-NEGATIVE,	RAG1	601457
SEVERE COMBINED IMMUNODEFICIENCY, AR, T CELL-NEGATIVE,	RAG2	601457
STUVE-WIEDEMANN SYNDROME	LIFR	601559
TRICHOTHIODYSTROPHY, PHOTOSENSITIVE; TTDP	ERCC2	601675
TRICHOTHIODYSTROPHY, PHOTOSENSITIVE; TTDP	ERCC3	601675
TRICHOTHIODYSTROPHY, PHOTOSENSITIVE; TTDP	GTF2H5	601675
BARTTER SYNDROME, ANTENATAL, 1	SLC12A1	601678
T-CELL IMMUNODEFICIENCY, CONGENITAL ALOPECIA, AND NAIL DYSTROPHY	FOXN1	601705
YEMENITE DEAF-BLIND HYPOPIGMENTATION SYNDROME	SOX10	601706
CEROID LIPOFUSCINOSIS, NEURONAL, 6; CLN6	CLN6	601780
CHOLESTASIS, PROGRESSIVE FAMILIAL INTRAHEPATIC 2; PFIC2	ABCB11	601847
USHER SYNDROME, IF; USH1F	PCDH15	602083
NEPHRONOPHTHISIS 2; NPHP2	INVS	602088
HEMOCHROMATOSIS, JUVENILE; JH	HAMP	602390
HEMOCHROMATOSIS, JUVENILE; JH	HFE2	602390
DESMOSTEROLOSIS	DHCR24	602398
ENCEPHALOPATHY, ETHYLMALONIC	ETHE1	602473
CONGENITAL DISORDER OF GLYCOSYLATION, Ib; CDG1B	MPI	602579
RIGID SPINE MUSCULAR DYSTROPHY 1; RSMD1	SEPN1	602771
CONGENITAL DISORDER OF GLYCOSYLATION, Ic; CDG1C	ALG6	603147
GRACILE SYNDROME	BCS1L	603358
OMENN SYNDROME	DCLRE1C	603554
OMENN SYNDROME	RAG1	603554
OMENN SYNDROME	RAG2	603554
CONGENITAL DISORDER OF GLYCOSYLATION, IIf; CDG2F	SLC35A1	603585
SICKLE CELL ANEMIA	HBB	603903
MEGALENCEPHALIC LEUKOENCEPHALOPATHY WITH SUBCORTICAL CYSTS; MLC	MLC1	604004
HEMOCHROMATOSIS, 3	TFR2	604250
SPINAL MUSCULAR ATROPHY, DISTAL, AR, 1; DSMA1	IGHMBP2	604320
SIALURIA, FINNISH	SLC17A5	604369

Fig. 8 cont.

DISEASE	GENE	OMIM#
CARDIOENCEPHALOMYOPATHY, FATAL INFANTILE, DUE TO CYTOCHROME c OXIDASE	SCO2	604377
AMEGAKARYOCYTIC THROMBOCYTOPENIA, CONGENITAL; CAMT	MPL	604498
C-LIKE SYNDROME	CD96	605039
NEUROPATHY, HYPOMYELINATING/CHARCOT-MARIE-TOOTH DISEASE, 4E	EGR2	605253
NEUROPATHY, HYPOMYELINATING/CHARCOT-MARIE-TOOTH DISEASE, 4E	MPZ	605253
NEMALINE MYOPATHY 5; NEM5	TNNT1	605355
SEGAWA SYNDROME, AR	TH	605407
USHER SYNDROME, IIC; USH2C	GPR98	605472
GLYCINE ENCEPHALOPATHY; GCE	AMT	605899
GLYCINE ENCEPHALOPATHY; GCE	GCSH	605899
GLYCINE ENCEPHALOPATHY; GCE	GLDC	605899
CONGENITAL DISORDER OF GLYCOSYLATION, IIb; CDG2B	MOGS	606056
PRIMARY LATERAL SCLEROSIS, JUVENILE; PLSJ	ALS2	606353
EPILEPTIC ENCEPHALOPATHY, LENNOX-GASTAUT	MAPK10	606369
HYPOTONIA-CYSTINURIA SYNDROME	PREPL	606407
HYPOTONIA-CYSTINURIA SYNDROME	SLC3A1	606407
MUSCULAR DYSTROPHY, CONGENITAL, 1C; MDC1C	FKRP	606612
FUMARASE DEFICIENCY	FH	606812
USHER SYNDROME, IG; USH1G	USH1G	606943
NEPHRONOPHTHISIS 4; NPHP4	NPHP4	606966
HURLER SYNDROME	IDUA	607014
CONGENITAL DISORDER OF GLYCOSYLATION, IId; CDG2D	B4GALT1	607091
ANAUXETIC DYSPLASIA	RMRP	607095
LATHOSTEROLOSIS	SC5DL	607330
COENZYME Q10 DEFICIENCY	APTX	607426
COENZYME Q10 DEFICIENCY	CABC1	607426
COENZYME Q10 DEFICIENCY	COQ2	607426
COENZYME Q10 DEFICIENCY	PDSS1	607426
COENZYME Q10 DEFICIENCY	PDSS2	607426
ICOS DEFICIENCY; LCCS2	ERBB3	607598
NIEMANN-PICK DISEASE, B	SMPD1	607616
GRISCELLI SYNDROME, 2; GS2	RAB27A	607624
NIEMANN-PICK DISEASE, C2	NPC2	607625
ICHTHYOSIS, LEUKOCYTE VACUOLES, ALOPECIA, AND SCLEROSING CHOLANGITIS	CLDN1	607626
SKIN FRAGILITY-WOOLLY HAIR SYNDROME	DSP	607655
MUSCULAR DYSTROPHY, CONGENITAL MEROSIN-DEFICIENT, 1A; MDC1A	LAMA2	607855
GAUCHER DISEASE, PERINATAL LETHAL	GBA	608013
CONGENITAL DISORDER OF GLYCOSYLATION, Ij; CDG1J	DPAGT1	608093
MUSCULAR DYSTROPHY, LIMB-GIRDLE, 2D; LGMD2D	SGCA	608099
COLORECTAL ADENOMATOUS POLYPOSIS, AR	MUTYH	608456
CONGENITAL DISORDER OF GLYCOSYLATION, Ik; CDG1K	ALG1	608540
MANDIBULOACRAL DYSPLASIA WITH B LIPODYSTROPHY; MADB	ZMPSTE24	608612

Fig. 8 cont.

DISEASE	GENE	OMIM#
JOUBERT SYNDROME 3; JBTS3	AHI1	608629
AROMATIC L-AMINO ACID DECARBOXYLASE DEFICIENCY	DDC	608643
AICAR TRANSYLASE/IMP CYCLOHYDROLASE, DEFICIENCY OF	ATIC	608688
PYRUVATE DEHYDROGENASE PHOSPHATASE DEFICIENCY	PDP1	608782
CONGENITAL DISORDER OF GLYCOSYLATION, Ie; CDG1E	DPM1	608799
SUDDEN INFANT DEATH WITH DYSGENESIS OF THE TESTES SYNDROME; SIDDT	TSPYL1	608800
LEUKODYSTROPHY, HYPOMYELINATING, 2	GJC2	608804
CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY, LETHAL NEONATAL	CPT2	608836
MUSCULAR DYSTROPHY, CONGENITAL, 1D	LARGE	608840
TRIFUNCTIONAL PROTEIN DEFICIENCY	HADHA	609015
TRIFUNCTIONAL PROTEIN DEFICIENCY	HADHB	609015
LONG-CHAIN 3-HYDROXYACYL-CoA DEHYDROGENASE DEFICIENCY	HADHA	609016
PIERSON SYNDROME	LAMB2	609049
AMISH INFANTILE EPILEPSY SYNDROME	ST3GAL5	609056
COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 1; COXPD1	GFM1	609060
SCHINDLER DISEASE, I	NAGA	609241
SENIOR-LOKEN SYNDROME 5; SLSN5	IQCB1	609254
EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 3	SLC25A22	609304
CHARCOT-MARIE-TOOTH DISEASE, 4H; CMT4H	FGD4	609311
CEREBRAL DYSGENESIS, NEUROPATHY, ICHTHYOSIS, PALMOPLANTAR KERATODERMA	SNAP29	609528
MITOCHONDRIAL DNA DEPLETION SYNDROME, MYOPATHIC	TK2	609560
JOUBERT SYNDROME 4; JBTS4	NPHP1	609583
EPIDERMOLYSIS BULLOSA, LETHAL ACANTHOLYTIC	DSP	609638
CEROID LIPOFUSCINOSIS, NEURONAL, 8, NORTHERN EPILEPSY	CLN8	610003
2-METHYLBUTYRYL-CoA DEHYDROGENASE DEFICIENCY	ACADSB	610006
PYRIDOXAMINE 5-PRIME-PHOSPHATE OXIDASE DEFICIENCY	PNPO	610090
CEROID LIPOFUSCINOSIS, NEURONAL, 10; CLN10	CTSD	610127
JOUBERT SYNDROME 5; JBTS5	CEP290	610188
3-METHYLGLUTACONIC ACIDURIA, V	DNAJC19	610198
DIARRHEA 4, MALABSORPTIVE, CONGENITAL	NEUROG3	610370
MEVALONIC ACIDURIA	MVK	610377
COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 2; COXPD2	MRPS16	610498
COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 3; COXPD3	TSFM	610505
LEUKODYSTROPHY, HYPOMYELINATING, 5	FAM126A	610532
XERODERMA PIGMENTOSUM, COMPLEMENTATION GROUP B; XPB	ERCC3	610651
JOUBERT SYNDROME 6; JBTS6	TMEM67	610688
NEPHROTIC SYNDROME, 3; NPHS3	PLCE1	610725

Fig. 8 cont.

DISEASE	GENE	OMIM#
CONGENITAL DISORDER OF GLYCOSYLATION, Im; CDG1M	DOLK	610768
OSTEOGENESIS IMPERFECTA, IIB	CRTAP	610854
OSTEOGENESIS IMPERFECTA, VIII	LEPRE1	610915
CEROID LIPOFUSCINOSIS, NEURONAL, 7; CLN7	MFSD8	610951
PHOSPHOSERINE AMINOTRANSFERASE DEFICIENCY	PSAT1	610992
SPINAL MUSCULAR ATROPHY, DISTAL, AR, 4; DSMA4	PLEKHG5	611067
ACYL-CoA DEHYDROGENASE FAMILY, MEMBER 9, DEFICIENCY OF	ACAD9	611126
MECKEL SYNDROME, 5; MKS5	RPGRIP1L	611561
MYOPATHY, EARLY-ONSET, WITH FATAL CARDIOMYOPATHY	TTN	611705
COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 5; COXPD5	MRPS22	611719
COMBINED SAPOSIN DEFICIENCY	PSAP	611721
KRABBE DISEASE, ATYPICAL, DUE TO SAPOSIN A DEFICIENCY	PSAP	611722
EPILEPSY, PROGRESSIVE MYOCLONIC 3; EPM3	KCTD7	611726
EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 4	STXBP1	612164
THROMBOPHILIA, HEREDITARY, DUE TO PROTEIN C DEFICIENCY, AUTOSOMAL	PROC	612304
FACTOR XI DEFICIENCY	F11	612416

Fig. 8 cont.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/73415

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C40B 50/04, G01N 33/50, G06F 19/00, G06G 7/58 (2013.01)
USPC - 506/25, 700/92, 700/93, 702/19, 702/181, 703/11
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(8)- C40B 50/04, G01N 33/50, G06F 19/00, G06G 07/58 (2013.01)
USPC- 506/25, 700/92, 700/93, 702/19, 702/181, 703/1 1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 706/46, 706/54, 506/2, 506/5, 506/6, 702/19, 700/1, 700/93

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Pub West (US EP JP WO), Pat Base (AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO), Google Patent, Google Scholar, Free Patents Online; search terms: probability, phenotype, score, rank, map, allele, haplotype, haplopath, genomic, gene, progeny, paret, inherit, gamete, profile, iterate, recursive, penetrance, converge...

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	'Relevant to claim No.
X -- Y	US 2009/0099789 A1 (STEPHAN, et al.) 16 April 2009 (16.04.2009) para [0009], [0012], [0027], [0030], [0039], [0049]-[0053], [0077]-[0082], [0087], [0088], [0095], [0107], [01 15], [0132], [0137], [0146], [0150]-[0157]	1, 3/(1) ---------- 2, 3/(2), 4-7, 17-19
Y	WO 2004/031912 A2 (ZHAO) 15 April 2004 (15.04.2004), pg 4, In 4-22; pg 33, In 20-31; pg 36, In 9-17; pg 52, In 14 to pg 13, In 10; pg 58, In 8-16; pg 58, In 29 to pg 61, In 7; pg 62, In 28-32	2, 3/(2), 4-7, 17-19
A	US 2012/0215458 A1 (MARCOTTE, et al.) 23 August 2012 (23.08.2012) para [0004]-[0106]	1-7, 17-19
A	WO 2012/034030 A1 (REESE, et al.) 15 March 2012 (15.03.2012) para [0005]-I00210]	1-7, 17-19
A	US 201 1/0312534 A1 (KAYSER, et al.) 22 December 201 1 (22.12.201 1) para [0009]-[0235]	1-7, 17-19
A	US 2007/0185656 A1 (SCHADT) 09 August 2007 (09.08.2007) para [0021]-[0438]	1-7, 17-19
A	US 2004/0197797 A1 (INOKO, et al.) 07 October 2004 (07.10.2004) para [0016]-[0306]	1-7, 17-19
A	US 2003/0059808 A1 (LIU, et al.) 27 March 2003 (27.03.2003) para [0014]-[01 12]	1-7, 17-19
A	US 2002/0123058 A1 (Threadgill, et al.) 05 September 2002 (05.09.2002) para [0012]- [0143]	1-7, 17-19
A	WO 2002/35442 A2 (ZAYKIN) 02 May 2002 (02.05.2002) pg 3, In 30 to pg 42, In 21	1-7, 17-19
A	WO 2001/49104 A2 (JANSEN, et al.) 12 July 2001 (12.07.2001) pg 3, In 1 to pg 48, In 30	1-7, 17-19
A	WO 1992/01066 A1 (SIMONS) 23 January 1992 (23.01 .1992) pg 13, In 21 to pg 67, In 50	1-7, 17-19

☐ Further documents are listed in the continuation of Box C.

* 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	Date of mailing of the international search report
19 January 2014 (19.01 .2014)	19 FEB 2014

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/73415

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.: 8-16.20-22
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. Ill 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:

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 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.:

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.