1998;339:1734-8; Saito H et al., *Lancet* 2000;356:1170; Chiu RW et al., *Lancet* 2002;360:998-1000).

[0004] However, the detection of certain paternally-inherited mutant alleles can be difficult, e.g., gene deletion, inversion, mutations in repetitive elements, and homologous genes, even with excessive depths of sequencing. Further, it can be difficult to detect maternally-inherited mutations, particularly if no genetic information is available from the father.

SUMMARY

[0004a] In one aspect, the present invention provides a method of determining a portion of a fetal genome of a fetus inherited from a pregnant mother using a biological sample obtained from the pregnant mother, the pregnant mother having a maternal genome with a first maternal haplotype and a second maternal haplotype in a chromosomal region, where the biological sample comprises a mixture of maternal and fetal DNA fragments, the method comprising:

based on an analysis of DNA in one or more other samples:

determining the first maternal haplotype to have first alleles at a plurality of loci in the chromosomal region, the maternal genome being heterozygous at the plurality of loci, and

determining the second maternal haplotype to have second alleles at the plurality of loci in the chromosomal region, the second alleles being different than the first alleles;

selecting a set of the plurality of loci, wherein selecting the set of loci does not use any measurements of a paternal allele;

analyzing a plurality of cell-free DNA fragments from the biological sample obtained from the pregnant mother, wherein analyzing a DNA fragment includes:

identifying a location of the DNA fragment in a reference genome; and

determining an allele of the DNA fragment;

identifying a first group of DNA fragments in the biological sample as having one of the first alleles at one of the set of loci based on the identified locations and the determined alleles for the first group of DNA fragments;

identifying a second group of DNA fragments in the biological sample as having one of the second alleles at one of the set of loci based on the identified locations and the determined alleles for the second group of DNA fragments;

calculating, by a computer system, a first value of the first group of DNA fragments, the first value defining a property of the DNA fragments of the first group;

calculating, by the computer system, a second value of the second group of DNA fragments, the second value defining a property of the DNA fragments of the second group;

computing a separation value between the first value and the second value;

determining that the fetus inherited the first maternal haplotype when the separation value is greater than a first threshold; and

determining that the fetus inherited the second maternal haplotype when the separation value is less than a second threshold.

[0004b] In another aspect, the present invention provides a method for detecting a mutation in a fetal genome in a fetal genome of a fetus inherited from a pregnant mother using a biological sample obtained from the pregnant mother, the pregnant mother having a maternal genome with a first maternal haplotype and a second maternal haplotype in a chromosomal region, wherein the biological sample contains a mixture of maternal and fetal DNA fragments, the method comprising:

sequencing DNA molecules that overlap with the chromosomal region and that are at least 1 kb long in a cellular maternal sample to obtain long sequence reads from both chromosomal copies in the chromosomal region;

constructing the first maternal haplotype using a first set of long sequence reads that share alleles at a plurality of loci in the chromosomal region, the first maternal haplotype having first alleles at the plurality of loci;

constructing the second maternal haplotype using a second set of long sequence reads that share alleles at the plurality of loci in the chromosomal region, the second maternal haplotype having second alleles at the plurality of loci;

identifying a mutation at a first location in the first maternal haplotype in the chromosomal region;

analyzing a plurality of cell-free DNA fragments from the biological sample obtained from the pregnant mother, wherein analyzing a DNA fragment includes:

identifying a location of the DNA fragment in a reference genome; and

determining an allele of the DNA fragment;

selecting a set of the plurality of loci based on the first location of the mutation;

determining paternal alleles inherited by the fetus from a father at the set of loci, wherein the paternal alleles correspond to the first alleles or the second alleles, and wherein the set of loci is further selected based on locations that the paternal alleles are determined;

identifying a first group of DNA fragments in the biological sample as having one of the first alleles at one of the set of loci based on the identified locations and the determined alleles for the first group of DNA fragments;

identifying a second group of DNA fragments in the biological sample as having one of the second alleles at one of the set of loci based on the identified locations and the determined alleles for the second group of DNA fragments;

calculating, by a computer system, a first value of the first group of DNA fragments, the first value defining a property of the DNA fragments of the first group;

calculating, by the computer system, a second value of the second group of DNA fragments, the second value defining a property of the DNA fragments of the second group;

computing a separation value between the first value and the second value; and

determining whether the fetus inherited the mutation on the first maternal haplotype based on a comparison of the separation value to a cutoff value and based on whether the paternal alleles correspond to the first alleles or the second alleles.

[0004c] In yet another aspect, the present invention provides a method for detecting a mutation in a fetal genome of a fetus inherited from a father using a biological sample obtained from a pregnant mother of the fetus, the father having a paternal genome with a first paternal haplotype and a second paternal haplotype in a chromosomal region, wherein the biological sample contains a mixture of maternal and fetal DNA fragments, the method comprising:

sequencing DNA molecules that overlap with the chromosomal region and that are at least 1 kb long in a cellular paternal sample to obtain long sequence reads from both chromosomal copies in the chromosomal region, the long sequence reads being at least 1 kb long;

constructing the first paternal haplotype using a first set of long sequence reads that share alleles at a plurality of loci in the chromosomal region, the first paternal haplotype having first alleles at the plurality of loci;

constructing the second paternal haplotype using a second set of long sequence reads that share alleles at the plurality of loci in the chromosomal region, the second paternal haplotype having first alleles at the plurality of loci;

identifying the mutation at a first location in the first paternal haplotype in the chromosomal region;

analyzing a plurality of cell-free DNA fragments from the biological sample obtained from the pregnant mother, wherein analyzing a DNA fragment includes:

identifying a location of the DNA fragment in a reference genome; and

determining an allele of the DNA fragment;

selecting a set of the plurality of loci based on the first location of the mutation and based on a maternal genome of the pregnant mother being homozygous at the set of loci, wherein the maternal genome is homozygous for the first alleles at a first subset of the set of loci, and wherein the maternal genome is homozygous for the second alleles at a second subset of the set of loci;

identifying a first group of DNA fragments in the biological sample as having one of the first alleles at one of the first subset of loci based on the identified locations and the determined alleles for the first group of DNA fragments;

identifying a second group of DNA fragments in the biological sample as having one of the second alleles at one of the second subset of loci based on the identified locations and the determined alleles for the second group of DNA fragments;

calculating, by a computer system, a first amount of the first group of DNA fragments;

calculating, by the computer system, a second amount of the second group of DNA fragments;

computing a separation value between the first amount and the second amount; and

determining whether the fetus inherited the mutation on the first paternal haplotype based on a comparison of the separation value to a cutoff value.

[0004d] In yet another aspect, the present invention provides a computer product comprising a computer readable medium storing a plurality of instructions for controlling a computer system to perform operations of any of the methods as disclosed herein.

[0004e] In yet another aspect, the present invention provides a system comprising: the computer product as disclosed herein; and one or more processors for executing instructions stored on the computer readable medium.

[0004f] In yet another aspect, the present invention provides a system comprising means for performing any of the methods as disclosed herein.

[0004g] In yet another aspect, the present invention provides a system configured to perform any of the methods as disclosed herein.

[0004h] In yet another aspect, the present invention provides a comprising modules that respectively perform the steps of any of the methods as disclosed herein.

[0005] Embodiments can provide efficient and accurate techniques for measuring genomic properties of a fetus without invasively taking a sample directly from the fetus, which would otherwise carry a significant risk to the fetus. Instead, embodiments can analyze a cell-free mixture of fetal and maternal DNA fragments (e.g., plasma, serum, urine, and the like) obtained from the mother. The analysis can be performed in a particular manner to determine inheritance of a parental haplotype, which may include a mutation. Such techniques can be valuable to determine whether the fetus has inherited a mutation from a parent, where genetic treatment can be performed when the fetus has inherited the mutation.

[0006] Some embodiments can advantageously reduce the number of samples to be analyzed and/or a number of loci analyzed in the cell-free mixture. For example, the testing of samples from a father to obtain paternal genetic information can be avoided (e.g., to address situations where such information is not available), while still allowing a determination of an inheritance of a maternal haplotype from the mother in a given chromosomal region. In some implementations, to provide the technical ability to perform such a measurement without paternal genetic information, a property of each maternal haplotype can be measured in the cell-free mixture (e.g., counts or sizes of sequence reads having different alleles at loci in the chromosomal region). A separation value (e.g., a difference or ratio) between values of the property for the two maternal haplotypes can be compared to thresholds to determine which haplotype is inherited. As

measurements of a paternal allele may not be available, embodiments can measure the property at some loci where the fetus is homozygous and some loci where the fetus is heterozygous, but account for such loci where the fetus is heterozygous in the selection of a threshold for determining inheritance of a maternal haplotype.