

including cell-free DNA from the fetus and from the female subject, the method comprising:

receiving one or more sequence tags for each of a plurality of DNA fragments in the biological sample;

5 determining genomic positions for the sequence tags;
for each of a plurality of genomic regions:
determining, with a computer system, a respective amount of DNA fragments within the genomic region from sequence tags having genomic positions within the genomic region;

10 normalizing the respective amount to obtain a respective density; and
comparing the respective density to a reference density to identify whether the respective density is statistically different from the reference density, wherein the plurality of genomic regions are non-overlapping;
determining whether any of the genomic regions identified to have a

15 respective density statistically different from the reference density is consecutive with another genomic region identified to have a respective density statistically different from the reference density, wherein each genomic region of the plurality of genomic regions is 10 Mb or less;
when at least N first genomic regions identified to have respective

20 densities statistically higher than the reference density are consecutive, identifying the first-consecutive first genomic regions as a microamplification, N being an integer equal to or greater than two; and
when at least N second genomic regions identified to have respective densities statistically lower than the reference densities are consecutive, identifying the ~~second~~

25 consecutive second genomic regions as a microdeletion.

[0006b] In another aspect, the present invention provides a computer product comprising a non-transitory computer readable medium storing a plurality of instructions that when executed perform an operation as described herein. ~~control a computer system to identify~~

30 ~~microamplifications or microdeletions in a genome of a fetus by analyzing a biological sample obtained from a female subject pregnant with the fetus, the biological sample~~

including cell-free DNA from the fetus and from the female subject, the method comprising:

receiving one or more sequence tags for each of a plurality of DNA fragments in a biological sample;

5 determining genomic positions for the sequence tags;

for each of a plurality of genomic regions:

determining a respective amount of DNA fragments within the genomic region from sequence tags having genomic positions within the genomic region;

normalizing the respective amount to obtain a respective density; and

10 comparing the respective density to a reference density to identify whether the respective density is statistically different from the reference density;

determining whether any of the genomic regions identified to have a respective density statistically different from the reference density is consecutive with another genomic region identified to have a respective density statistically different from

15 the reference density;

when at least N first genomic regions identified to have respective densities statistically higher than the reference density are consecutive, identifying the first consecutive genomic regions as a microamplification, N being an integer equal to or greater than two;

20 when at least N second genomic regions identified to have respective densities statistically lower than the reference densities are consecutive, identifying the second consecutive genomic regions as a microdeletion.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] FIG 1 is a flowchart showing a method of identifying microamplifications or

25 microdeletions in a genome of a fetus.

CLAIMS:

- 1 1. A method of identifying microamplifications or microdeletions in a
2 genome of a fetus by analyzing a biological sample obtained from a female subject
3 pregnant with the fetus, the biological sample including cell-free DNA from the fetus and
4 from the female subject, the method comprising:
5 receiving one or more sequence tags for each of a plurality of DNA
6 fragments in the biological sample;
7 determining genomic positions for the sequence tags;
8 for each of a plurality of genomic regions:
9 determining, with a computer system, a respective amount of DNA
10 fragments within the genomic region from sequence tags having genomic positions
11 within the genomic region;
12 normalizing the respective amount to obtain a respective density;
13 and
14 comparing the respective density to a reference density to identify
15 whether the respective density is statistically different from the reference density;
16 determining whether any of the genomic regions identified to have a
17 respective density statistically different from the reference density is consecutive with
18 another genomic region identified to have a respective density statistically different from
19 the reference density;
20 when at least N first genomic regions identified to have respective
21 densities statistically higher than the reference density are consecutive, identifying the
22 first consecutive genomic regions as a microamplification, N being an integer equal to or
23 greater than two;
24 when at least N second genomic regions identified to have respective
25 densities statistically lower than the reference densities are consecutive, identifying the
26 second consecutive genomic regions as a microdeletion.
- 1 2. The method of claim 1, wherein the biological sample is maternal
2 blood, plasma, serum, urine, or saliva.

1 3. The method of claim 1, wherein the sequence tags are obtained by
2 massively parallel sequencing.

1 4. The method of claim 1, wherein N is 3.

1 5. The method of claim 1, wherein the genomic regions are non-
2 overlapping.

1 6. The method of claim 1, wherein the genomic regions are
2 contiguous.

1 7. The method of claim 1, wherein the genomic regions are of equal
2 size.

1 8. The method of claim 7, wherein the size of each genomic region is
2 about 1 Mb.

1 9. The method of claim 1, wherein the respective density for a
2 genomic region is obtained by dividing the respective amount of DNA fragments for the
3 genomic region by the total amount of DNA fragments for multiple genomic regions.

1 10. The method of claim 1, wherein the respective density for a
2 genomic region equals the respective amount of DNA fragments for the genomic region.

1 11. The method of claim 1, wherein the reference density for a
2 genomic region is a mean or median of a plurality of respective densities determined
3 from one or more other biological samples not exhibiting microamplifications or
4 microdeletions in the genomic region.

1 12. The method of claim 1, wherein the reference density for a
2 genomic region is the mean or median of a plurality of respective densities obtained for
3 other genomic regions.

1 13. The method of claim 1, further comprising the step of determining
2 whether a microamplification or microdeletion is maternally inherited.

1 14. The method of claim 13, wherein a microamplification or
2 microdeletion is determined to be maternally inherited if, for each of the consecutive
3 genomic regions corresponding to the microamplification or microdeletion, the difference
4 between the respective density and reference density exceeds a particular cutoff, the
5 particular cutoff being larger than a cutoff used to determine whether the respective
6 density and reference density are statistically different.

1 15. A computer product comprising a non-transitory computer
2 readable medium storing a plurality of instructions that when executed control a
3 computer system to identify microamplifications or microdeletions in a genome of a fetus
4 by analyzing a biological sample obtained from a female subject pregnant with the fetus,
5 the biological sample including cell-free DNA from the fetus and from the female
6 subject, the method comprising:
7 receiving one or more sequence tags for each of a plurality of DNA
8 fragments in a biological sample;
9 determining genomic positions for the sequence tags;
10 for each of a plurality of genomic regions:
11 determining a respective amount of DNA fragments within the
12 genomic region from sequence tags having genomic positions within the genomic region;
13 normalizing the respective amount to obtain a respective density;
14 and
15 comparing the respective density to a reference density to identify
16 whether the respective density is statistically different from the reference density;
17 determining whether any of the genomic regions identified to have a
18 respective density statistically different from the reference density is consecutive with
19 another genomic region identified to have a respective density statistically different from
20 the reference density;
21 when at least N first genomic regions identified to have respective
22 densities statistically higher than the reference density are consecutive, identifying the
23 first consecutive genomic regions as a microamplification, N being an integer equal to or
24 greater than two;

25 when at least N second genomic regions identified to have respective
26 densities statistically lower than the reference densities are consecutive, identifying the
27 second consecutive genomic regions as a microdeletion.

1 16. The computer product of claim 15, wherein N is 3.

1 17. The computer product of claim 15, wherein the genomic regions
2 are non-overlapping.

1 18. The computer product of claim 15, wherein the genomic regions
2 are contiguous.

1 19. The computer product of claim 15, wherein the genomic regions
2 are of equal size.

1 20. The computer product of claim 15, wherein the respective density
2 for a genomic region is obtained by dividing the respective amount of DNA fragments for
3 the genomic region by the total amount of DNA fragments for multiple genomic regions.

WHAT IS CLAIMED IS:

1. A method of identifying microamplifications or microdeletions in a genome of a fetus by analyzing a biological sample obtained from a female subject pregnant with the fetus, the biological sample including cell-free DNA from the fetus and from the female subject, the method comprising:

receiving one or more sequence tags for each of a plurality of DNA fragments in the biological sample;

determining genomic positions for the sequence tags;

for each of a plurality of genomic regions:

determining, with a computer system, a respective amount of DNA fragments within the genomic region from sequence tags having genomic positions within the genomic region;

normalizing the respective amount to obtain a respective density;

and

comparing the respective density to a reference density to identify whether the respective density is statistically different from the reference density, wherein the plurality of genomic regions are non-overlapping;

determining whether any of the genomic regions identified to have a respective density statistically different from the reference density is consecutive with another genomic region identified to have a respective density statistically different from the reference density, wherein each genomic region of the plurality of genomic regions is 10 Mb or less;

when at least N first genomic regions identified to have respective densities statistically higher than the reference density are consecutive, identifying the consecutive first genomic regions as a microamplification, N being an integer equal to or greater than two; and

when at least N second genomic regions identified to have respective densities statistically lower than the reference density are consecutive, identifying the consecutive second genomic regions as a microdeletion.

2. The method of claim 1, wherein the biological sample is maternal blood, plasma, serum, urine, or saliva.
3. The method of claim 1, wherein the sequence tags are obtained by massively parallel sequencing.
4. The method of claim 1, wherein N is 3.
5. The method of claim 1, wherein the genomic regions are contiguous.
6. The method of claim 1, wherein the genomic regions are of equal size.
7. The method of claim 6, wherein the size of each genomic region is about 1 Mb.
8. The method of claim 1, wherein the respective density for a genomic region is obtained by dividing the respective amount of DNA fragments for the genomic region by the total amount of DNA fragments for multiple genomic regions.
9. The method of claim 1, wherein the respective density for a genomic region equals the respective amount of DNA fragments for the genomic region.
10. The method of claim 1, wherein the reference density for a genomic region is a mean or median of a plurality of respective densities determined from one or more other biological samples not exhibiting microamplifications or microdeletions in the genomic region.
11. The method of claim 1, wherein the reference density for a genomic region is the mean or median of a plurality of respective densities obtained for other genomic regions.
12. The method of claim 1, further comprising the step of determining whether a microamplification or microdeletion is maternally inherited.

13. The method of claim 12, wherein the microamplification or microdeletion is determined to be maternally inherited if, for each of the consecutive genomic regions corresponding to the microamplification or microdeletion, the difference between the respective density and reference density exceeds a particular cutoff, the particular cutoff being larger than a cutoff used to determine whether the respective density and reference density are statistically different.

14. A computer product comprising a non-transitory computer readable medium storing a plurality of instructions that when executed perform an operation of any of the methods of claims 1 to 13.