CLAIMS

1. A method for obtaining a nucleic acid derived from a fetus, comprising:

a. specifically labeling white blood cells (WBCs) and cell nuclei in a fraction A, the fraction A being a fraction which is obtained from a maternal blood sample by fractionizing blood cells in the maternal blood sample based on either or both of their volumetric mass densities and their sizes, and in which nucleated red blood cells (NRBCs) are concentrated in a population of whole blood cells;

b. obtaining a fraction B containing NRBCs of maternal origin and NRBCs derived from a fetus by sorting out the labeled blood cells in the fraction A by at least cell sorting, in which the sorting-out is performed so that blood cells labeled by a WBCs specific label are removed and blood cells labeled by a label specific to the cell nuclei are collected;

c. obtaining fractions C by separating each of blood cells in the fraction B at a single-cell level irrespective of whether or not the blood cell is a nucleated red blood cell (NRBC), and performing a process for extracting a nucleic acid for each of the blood cells separated at the single-cell level irrespective of whether or not the blood cell is an NRBC, each of the fractions C containing a nucleic acid distinguishable at the single-cell level; and

d. selecting a fraction D containing a nucleic acid derived from a fetus distinguishable at a single-cell level from a group of the fractions C by performing a molecular biological analysis for each of the fractions C.

2. The method according to Claim 1, wherein, if it is determined in step d. that the nucleic acid contained in the fraction D is derived from a fetus, the nucleic acid is presumed to originate from an NRBC separated at a single-cell level in the step c, on the basis that the fraction C is obtained by a method in which it is not determined whether or not a blood cell was derived from an NRBC.

3. The method according to Claim 1 or 2, wherein

the maternal blood sample is maternal blood itself or a non-concentrated sample in which the concentration of NRBCs in relation to a population of whole blood cells is not increased as compared to the maternal blood, and

the fraction A is a fraction obtained from the maternal blood sample by fractionating blood cells in the maternal blood sample based on their sizes and removing at least some of non-nucleated RBCs from the blood cells in the maternal blood sample.

4. The method according to Claim 3, wherein

blood cells of the maternal blood sample are fractionated based on their sizes by processing the maternal blood sample by using a blood-cell separation chip,

the blood-cell separation chip comprises a main channel, a sub channel connected to a side of the main channel, and a removal channel connected to a side of the main channel downstream from the sub channel, the side of the main channel to which the removal channel is connected being opposite to the side to which the sub channel is connected, wherein

the maternal blood sample is flowed through the main channel,

a liquid is flowed out from the sub channel to push blood cells flowing through the main channel from the side of the main channel toward the removal channel,

non-nucleated RBCs are removed from the maternal blood sample at the removal channel and NRBCs are collected from the maternal blood sample in a place in the main channel downstream from a connection point of the removal channel, so that the fraction A is obtained, and

an inscribed diameter of the removal channel is 12 to 19 μm.

5. The method according to Claim 4, wherein

the blood-cell separation chip further comprises a recovery channel connected to a side of the main channel downstream from the removal channel, the side of the main channel to which the recovery channel is connected being opposite to the side to which the sub channel is connected, wherein

a liquid is flowed out from the sub channel to further push blood cells flowing through the main channel from the side of the main channel toward the recovery channel,

NRBCs are collected from the maternal blood sample at the recovery channel, so that the fraction A is obtained from the recovery channel, and

an inscribed diameter of the recovery channel is 20 to 30 μm.

6. The method described in any one of 1 to 5, wherein in the step c, fractions E are obtained by fractionizing the fraction B by a limited dilution method and the fraction C is obtained by performing the process for extracting the nucleic acid for each of the fractions E, each of the fractions E containing a blood cell separated at a single-cell level.

7. The method according to Claim 6, wherein

the cell sorting comprises successively sorting out small amounts of fluids containing blood cells, and

dispensing the fluids into separate containers without collecting the fluids into one container again so that each container contains one blood cell.

8. The method according to Claim 7, wherein

the fluids are dispensed into the separate containers with an apparatus that discharges a droplet containing a granular substance.

9. The method according to Claim 6, further comprising:

obtaining a fraction F by sorting blood cells from the fraction B irrespective of whether or not the blood cells are NRBCs,

photographing the fraction F; and

determining whether or not the fraction F is obtained as the fraction E by checking that a blood cell separated at a single-cell level is contained in the fraction F by using an image of the fraction F, while it is not determining whether or not the blood cell separated at the single-cell level is an NRBC from the image of the fraction F.

10. The method described in any one of 1 to 5, wherein

in the step c, the fraction C is obtained by using a fluid device comprising a channel, a plurality of trapping structures successively arranged along the channel and connected to the channel, and reaction structures provided for respective trapping structures, and

separating blood cells contained in the fraction B from each other at a single-cell level by distributing the blood cells to respective trapping structures through the channel, and after trapping the blood cells in the respective trapping structures, obtaining the

fraction C in the reaction structures by dissolving the trapped cells and washing out the dissolved substance from the trapping structures toward the reaction structures.

11. The method described in any one of 1 to 10, wherein

in the step a, the labeling for at least the nucleic acid is performed by using fluorescent labeling, and

in the step b, blood cells that have been specifically fluorescent-labeled for at least the nucleic acid in the fraction A are sorted out by cell sorting based on a fluorescence activated cell sorting method.

12. The method described in any one of claims 1 to 11, wherein, before the step of specifically labeling white blood cells (WBCs) and cell nuclei, the method further comprises a step of removing WBCs from the fraction by immunological removal, and

in the step of specifically labeling white blood cells (WBCs) and cell nuclei, specifically labeling remaining white blood cells.

13. The method described in any one of 1 to 12, wherein

in the step c, the nucleic acid contained in the fraction C is chromosomal DNA,

in the step d, the whole genome of the chromosomal DNA or a partial area in the genome is amplified in order to perform a molecular biological analysis, and

the fraction D containing DNA is sorted out as the nucleic acid derived from a fetus, the DNA being an amplification product.

14. The method described in any one of 1 to 12, wherein

in the step c, the nucleic acid contained in the fraction C is RNA,

the RNA is either or both of an mRNA and a non-coding RNA,

in the step d, reverse transcription of the RNA is performed in order to perform a molecular biological analysis, and

the fraction D containing a cDNA is sorted out as the nucleic acid derived from a fetus, the cDNA being a reverse-transcription product.

15. The method according to Claim 14 wherein

in the step c, fractions W associated with respective fractions C are further obtained by extracting chromosomal DNA from each blood cell at the same time when the RNA is extracted, and

obtaining a fraction Z associated with the fraction D from a group of the fractions W as a fraction containing chromosomal DNA derived from a fetus distinguishable at a single-cell level.

16. A method comprising:

analyzing a sequence of the nucleic acid in the fraction D obtained by a method according to any one of 1 to 15 by a micro-array or a sequencing method; and

obtaining data used for a diagnosis in noninvasive prenatal genetic testing from a result of the analysis.

17. A method for obtaining chromosomal DNA of fetal cell origin, comprising:

a. specifically labeling red blood cells (RBCs) including NRBCs and nucleic acids in a fraction A, the fraction A being a fraction which is obtained from a maternal blood sample and in which NRBCs are concentrated in a population of whole blood cells, wherein nucleic acids are labeled at least by using fluorescent labeling when;

b. obtaining a fraction B having an increased purity of NRBCs by sorting out at least the labeled blood cells in the fraction A by cell sorting, in which blood cells in the fraction A which have been specifically fluorescent-labeled for at least nucleic acids are sorted out by cell sorting based on a fluorescence activated cell sorting method;

c. obtaining fractions C by indiscriminately separating each of blood cells in the fraction B at a single-cell level and indiscriminately and independently performing a process for extracting chromosomal DNA for each of the separated blood cells, each of the fractions C containing chromosomal DNA distinguishable at a single-cell level; and

d. selecting a fraction D containing chromosomal DNA derived from a fetus distinguishable at a single-cell level from a group of the fractions C by performing a molecular biological analysis for each of the fractions C, wherein,

if it is determined in step d. that the chromosomal DNA contained in the fraction D is derived from a fetus, the chromosomal DNA is presumed to originate from an NRBC separated at a single-cell level, on the basis that the fraction C is indiscriminately

obtained,

the fraction A is obtained by fractionizing blood cells in a maternal blood sample according to either their volumetric mass densities or their sizes,

in the step c, fractions E are obtained by fractionizing the fraction B by a limited dilution method, each of the fractions E containing a blood cell separated at a single-cell level, and the fraction C is obtained by performing the process for extracting the chromosomal DNA for each of the fractions E, and

NRBCs of maternal origin and NRBCs derived from a fetus are contained in the fraction B.

18. The method according to Claim 17, wherein

in the step a, WBCs in the fraction A are specifically labeled in an additional manner, and

in the step b, the fraction B is obtained by sorting out blood cells from the labeled blood cells in the fraction A by cell sorting, the fraction B being a fraction from which blood cells labeled by a WBCs specific label are removed.

19. The method according to Claim 17 or 18, wherein

in the step a, the labeling for RBCs is performed by magnetic labeling,

in the step b, blood cells in the fraction A which have been specifically magnetic-labeled for RBCs are sorted out by cell sorting based on a cell sorting method using magnetic labeling before or after the cell sorting based on the fluorescence activated cell sorting method, or

in the step a, the labeling for RBCs is performed by using fluorescent labeling, and

in the step b, blood cells in the fraction A which have been specifically fluorescent-labeled for nucleic acids and RBCs are sorted out by cell sorting based on the fluorescence activated cell sorting method.

20. A method for obtaining a nucleic acid derived from a fetus, comprising:

a. specifically labeling red blood cells (RBCs) including NRBCs and cell nuclei in a fraction A, the fraction A being a fraction which is obtained from a maternal blood

sample by fractionizing blood cells in the maternal blood sample based on either or both of their volumetric mass densities and their sizes, and in which nucleated red blood cells (NRBCs) are concentrated in a population of whole blood cells;

b. obtaining a fraction B containing NRBCs of maternal origin and NRBCs derived from a fetus by sorting out the labeled blood cells in the fraction A by at least cell sorting, in which the sorting-out is performed so that blood cells labeled by a RBCs specific label and a label specific to the cell nuclei are collected;

c. obtaining fractions C by separating each of blood cells in the fraction B at a single-cell level irrespective of whether or not the blood cell is a nucleated red blood cell (NRBC), and performing a process for extracting a nucleic acid for each of the blood cells separated at the single-cell level irrespective of whether or not the blood cell is an NRBC, each of the fractions C containing a nucleic acid distinguishable at the single-cell level; and

d. selecting a fraction D containing a nucleic acid derived from a fetus distinguishable at a single-cell level from a group of the fractions C by performing a molecular biological analysis for each of the fractions C.

21. The method described in Claim 20, wherein

in the step c, the nucleic acid contained in the fraction C is RNA,

the RNA is either or both of an mRNA and a non-coding RNA,

in the step d, reverse transcription of the RNA is performed in order to perform a molecular biological analysis, and

the fraction D containing a cDNA is sorted out as the nucleic acid derived from a fetus, the cDNA being a reverse-transcription product.

22. The method according to Claim 21 wherein

in the step c, fractions W associated with respective fractions C are further obtained by extracting chromosomal DNA from each blood cell at the same time when the RNA is extracted, and

obtaining a fraction Z associated with the fraction D from a group of the fractions W as a fraction containing chromosomal DNA derived from a fetus distinguishable at a single-cell level.