WHAT IS CLAIMED IS:

1.A method of detecting a fetal chromosomal abnormality, comprising:

(1) obtaining sequencing data of cell-free nucleic acid fragments and clinical phenotypic feature data from a pregnant woman to be detected, wherein the sequencing data comprise a plurality of read segments, and the clinical phenotypic feature data of the pregnant woman to be detected form a phenotypic feature vector of the pregnant woman;

(2) performing window division on at least part of a chromosome sequence of a reference genome to obtain sliding windows, counting the read segments falling within the sliding windows, and generating a sequence feature matrix of the chromosome sequence;

(3) inputting the sequence feature matrix into a trained machine learning model to extract a sequence feature vector of the chromosome sequence;

(4) combining the sequence feature vector and the phenotypic feature vector of the pregnant woman to form a combined feature vector, and inputting the combined feature vector into a classification detection model to obtain the fetal chromosomal abnormality state of the pregnant woman to be detected.

2.The method of Claim 1, in (1), the cell-free nucleic acid fragments are derived from the peripheral blood, liver, and/or placenta of the pregnant woman.

3.The method of Claim 1 or 2, in (1), the cell-free nucleic acid fragments are cell-free DNA.

4.The method of any one of Claims 1-3, in (1), the sequencing data are derived from ultra-low depth sequencing; preferably, the sequencing depth of the ultra-low depth sequencing is 1×, 0.1×, or 0.01×.

5.The method of any one of Claims 1-4, in (1), the read segments are aligned to the reference genome to obtain the unique mapping reads (preferably, GC content correction is performed); preferably, the subsequent steps are carried out with the unique mapping reads (preferably, the read segments are corrected by GC content), ~~,~~

~~6.The method of Claim 5~~preferably, the GC content correction is performed as follows:

a. firstly, m fragments of length ℓ are randomly selected from a chromosome of the human reference genome;

b. the number of fragments with GC content of i, N_i, is calculated by:

$$N_i = \sum_{k=1}^{m} \mathbb{I}_i(f(k))$$

wherein $\mathbb{I}_i(f(k)) = \begin{cases} 1, & f(k) = i \\ 0, & other \end{cases}$, $f(k)$ is GC content of fragment k, and i represents GC content ($i = 0\%, 1\%, \ldots, 100\%$);

c. the number of sequencing read segments with GC content of i, F_i, is calculated by:

$$F_i = \sum_{k=1}^{m} c_k \cdot \mathbb{I}_i(f(k))$$

wherein $c_k \cdot \mathbb{I}_i(f(k))$ represents GC content of fragment k, and F_i represents the number of sequencing read segments with GC content of i and start site same as that of the fragment.

d. Observation-expectation ratio of GC content λ_i is calculated by:

$$\lambda_i = \begin{cases} r \cdot \dfrac{F_i}{N_i}, & F_i > 0 \ \ and \ \ N_i > 0 \\ 1, & other \end{cases}$$

wherein r is the global scaling factor, which is defined as:

$$r = \frac{\sum_i N_i}{\sum_i F_i}$$

e. the number of sequencing read segments is corrected by:

$$R_i = \frac{1}{\lambda_i}$$

wherein R_i represents the expected number of sequencing read segments with a correcte GC content of i.

~~7~~6.The method of any one of Claims 1-~~6~~5, in (1), the phenotypic feature data of the pregnant woman are selected from one or combination of more of: age, gestational week, height, weight, BMI, biochemical test results of prenatal examination, ultrasonic diagnosis results, and cell-free fetal DNA concentration in plasma.

~~8~~7.The method of any one of Claims 1-~~7~~6, in (1), the phenotypic feature data of the pregnant woman are subjected to outlier processing, missing value processing and/or

null value processing. -

~~9.The method of Claim 8, in (1)~~preferably, the phenotypic data of the pregnant woman sample will be judged as outliers if the following records appear:

a. $x_{age} < 10$ or $x_{age} > 80$;

b. $x_{GW} < 5$ or $x_{GW} > 50$;

c. $x_{height} < 40$ or $x_{height} > 300$;

d. $x_{weight} < 10$ or $x_{weight} > 200$;

and these outliers are set as null values, and preferably, the missing values and null values are padded by missForest algorithm.

~~10.The method of Claim 8 or 9, the missing values and null values are padded by missForest algorithm.~~

~~11.The method of any one of Claims 1-10, in (2), the chromosome is chromosome 21, chromosome 18, chromosome 13 and/or a sex chromosome.~~

~~12~~8.The method of any one of Claims 1-~~11~~7, (2) comprises: (2.1) using the window with length b to overlap and slide the chromosome sequence with length L of the reference genome at step size of t to obtain sliding windows, wherein b is a positive integer and b=[10000,10000000], t is any positive integer, L is a positive integer and L≥b; (2.2) counting the read segments falling within each of the sliding windows, and generating a sequence feature matrix of the chromosome sequence.

~~13~~9.The method of any one of Claims 1-~~12~~8, in (2), the sequence feature matrix includes the number, the base quality and the mapping quality of read segments within the sliding windows.

~~14.The method of Claim 13, the base quality includes the mean, the standard deviation, the skewness, and/or the kurtosis of the base quality.~~

~~15.The method of Claim 13, the mapping quality includes the mean, the standard deviation, the skewness and/or the kurtosis of the mapping quality.~~

~~16~~10.The method of any one of Claims 1-~~15~~9, in (2), the sequence feature matrix is:

$$\boldsymbol{X} = (x_{ij})_{h \times w}$$

wherein h represents the number of sliding windows, w represents the number

of sequence features within a single sliding window, and $\boldsymbol{x}_{ij}$ represents the jth sequence eigenvalue in the ith sliding window.

~~17~~11.The method of any one of Claims 1-~~16~~10, in (3), the sequence feature matrix is normalized, ~~.~~

~~18.The method of Claim 17~~preferably, in (3), the sequence feature matrix is normalized by using formula (I):

$$\boldsymbol{Z}_{i,j}^{(k)} = \frac{\boldsymbol{X}_{i,j}^{(k)} - \mu_{i,j}}{\sigma_{i,j}}$$

(I)

wherein $\boldsymbol{Z}_{i,j}^{(k)}$ is the normalized sequence feature matrix of sample k, $\boldsymbol{X}_{i,j}^{(k)}$ represents the jth sequence eigenvalue in the ith sliding window of sample k, and $\mu_{i,j}$ and $\sigma_{i,j}$ represent the mean and standard deviation of the jth sequence eigenvalue in the ith sliding window of all samples, respectively.

~~19~~12.The method of any one of Claims 1-~~18~~11, in (3), the trained machine learning model is a neural network model or an AutoEncoder model; preferably, the neural network model is a deep neural network model, and more preferably, the neural network model is a deep neural network model based on 1D convolution, ~~.~~

~~20.The method of any one of Claims 1-19~~preferably, the structure of the deep neural network model includes:

an input layer, for receiving the sequence feature matrix;

a pre-module, being connected with the input layer, for performing the first convolution and activation operation of the sequence feature matrix from the input layer, to obtain a feature map;

a core module, being connected with the pre-module, for further abstraction and feature extraction of the feature map from the pre-module, and strengthening the expression ability of the neural network by effectively increasing the depth of the neural network model;

a post-module, being connected with the core module, for the feature abstraction representation of the feature map from the core module;

a first global average pooling layer, being connected with the post-module, for vectorizing the feature map of the feature abstraction representation and outputting the sequence feature vector of the chromosome sequence.

~~21~~13.The method of Claim ~~20~~12, the pre-module includes:

(I) a 1D convolution layer;

(II) a batch normalization layer, being connected with the 1D convolution layer described in (I);

(III) ReLU activation layer, being connected with the batch normalization layer described in (II).

~~22~~14.The method of Claim ~~20~~12 or ~~21~~13, the core module consists of one or more residual submodules with the same structure, wherein the output of each residual module is the input of the next residual module, ~~.~~

~~23.The method of any one of Claims 20-22~~preferably, the residual submodule includes:

(A) a pre-submodule of the core module, each of which includes a 1D convolution layer, a Dropout layer connected with the 1D convolution layer, a batch normalization layer connected with the Dropout layer, and a ReLU activation layer connected with the batch normalization layer;

(B) a first 1D average pooling layer, being connected with the pre-submodule of the core module described in (A);

(C) a Squeeze-Excite module, and/or a Spatial Squeeze-Excite module, being connected with the first 1D average pooling layer described in (B);

(D) a first Addition layer, being connected with the Squeeze-Excite module and/or Spatial Squeeze-Excite module described in (C);

(E) a second 1D average pooling layer, being connected with the ReLU activation layer in the pre-module;

(F) a second Addition layer, being connected with the first Addition layer described in (D) and the second 1D average pooling layer described in (E).

~~24~~15.The method of Claim ~~23~~14, the Squeeze-Excite module includes:

(a) a second global average pooling layer, being connected with the first 1D

average pooling layer in (B) of the residual submodule;

(b) a Reshape layer, being connected with the second global average pooling layer described in (a), and the size of the output feature map of the Reshape layer is $1 \times f$, wherein f is the number of 1D convolution kernels;

(c) a first fully connected layer, being connected with the Reshape layer described in (b), and the number of output neurons of the first fully connected layer is $\frac{f}{r_{SE}}$, wherein f is the number of 1D convolution kernels, and r_{SE} is the decline speed of the Squeez-Excite module;

(d) a second fully connected layer, being connected with the first fully connected layer described in (c), and the number of output neurons of the second fully connected layer is f, wherein f is the number of 1D convolution kernels;

(e) a Multiply layer, being connected with the second fully connected layer described in (d) and the first 1D average pooling layer in (B) of the residual submodule.

~~25~~16.The method of Claim ~~23~~14 or ~~24~~15, the Spatial Squeeze-Excite module includes:

a. a 1×1 1D convolution layer, being connected with the first 1D average pooling layer in (B), which uses sigmoid function as the activation function;

b. a Multiply layer, being connected with the first 1D average pooling layer in (B) and the 1×1 1D convolution layer in a.

~~26~~17.The method of any one of Claims 1-~~25~~16, in (4), the combined feature vector is obtained by combining the sequence feature vector and the phenotypic feature vector of the pregnant woman. ~~.~~

~~27.The method of any one of Claims 1-26~~preferably, in (4), the combined feature vector x is normalized by:

$$x_i' = \frac{x_i - \mu_i}{\sigma_i}$$

wherein x_i' is the ith sequence eigenvalue of the normalized combined feature vector x, x_i is the ith sequence eigenvalue of the combined feature vector, μ_i is the mean of the ith sequence eigenvalues of the combined feature vector x, and σ_i is the standard

deviation of the ith sequence eigenvalues of the combined feature vector.

~~28~~18.The method of any one of Claims 1-~~27~~17, in (4), the classification detection model is an ensemble learning model, ~~.~~

~~29.The method of Claim 28~~preferably, the ensemble learning model is an ensemble learning model based on Stacking or Majority Voting; preferably, the ensemble learning model is one or more of: support vector machine model, naive Bayes classifier, random forest classifier, XGBoost and logistic regression.

~~30~~19.The method of Claim 1, the chromosomal abnormality includes at least one or more of: trisomy 21 syndrome, trisomy 18 syndrome, trisomy 13 syndrome, 5p-syndrome, chromosomal microdeletion and chromosomal microduplication.

~~31~~20.A method of constructing a classification detection model for detecting a fetal chromosomal abnormality, comprising:

(1) obtaining sequencing data of cell-free nucleic acid fragments and clinical phenotypic feature data from a plurality of pregnant women, wherein the sequencing data comprise a plurality of read segments, and the fetal chromosomal state of each of the pregnant women is known, and the clinical phenotypic feature data of each of the pregnant women form a phenotypic feature vector of the pregnant woman;

(2) for each of the pregnant women, performing window division on at least part of a chromosome sequence of a reference genome to obtain sliding windows, counting the read segments falling within the sliding windows, and generating a sequence feature matrix of the chromosome sequence;

(3) for each of the pregnant women, constructing the training data set using the sequence feature matrix and the fetal chromosomal state, and training the machine learning model to extract a sequence feature vector of the chromosome sequence;

(4) combining the sequence feature vector and the phenotypic feature vector of each of the pregnant women to form a combined feature vector, and training the classification model with the combined feature vectors and the fetal chromosomal states of the pregnant women to obtain a trained classification detection model.

~~32~~21.The method of Claim ~~31~~20, the fetal chromosomal state of each of the pregnant women is one or more of: normal diploid, chromosomal aneuploid, partial monosomy

syndrome, chromosomal microdeletion and chromosomal microduplication; preferably, the chromosomal aneuploidy includes at least one or more of: trisomy 21 syndrome, trisomy 18 syndrome and trisomy 13 syndrome; preferably, the partial monosomy syndrome includes 5p-syndrome.

~~33~~22.The method of Claim ~~32~~20 or ~~33~~21, the number of the pregnant women is greater than 10, and the ratio of the number of fetuses with normal diploid to that of fetuses with chromosomal aneuploidy is ½ to 2.

~~34~~23.The method of any one of Claims ~~31~~20-~~33~~22, in (3), the training data set is represented as:

$$D_{seq} = \{\boldsymbol{Z}_{i,j}^{(k)}, y^{(k)}\}_{k=1}^{N}$$

$$y^{(k)} = \begin{cases} 1, abnormal\ \ fetal\ \ chromosomes\ \ of\ \ sample\ \ k \\ 0, normal\ \ fetal\ \ chromosomes\ \ of\ \ sample\ \ k \end{cases}$$

wherein N represents the number of training samples, and N is an integer≥ 1; $\boldsymbol{Z}_{i,j}^{(k)}$ is the normalized sequence feature matrix of training sample k, and k∈[1,N], wherein i is an integer≥ 1 and j is an integer≥ 1;

the chromosomal abnormality includes at least one or more of: trisomy 21 syndrome, trisomy 18 syndrome, trisomy 13 syndrome, 5p-syndrome, chromosomal microdeletion and chromosomal microduplication.

~~35~~24.A system of detecting a fetal chromosomal abnormality, comprising:

a data acquisition module, for obtaining sequencing data of cell-free nucleic acid fragments and clinical phenotypic feature data from a pregnant woman sample to be detected, wherein the sequencing data comprise a plurality of read segments, and the clinical phenotypic feature data of the pregnant woman sample to be detected form a phenotypic feature vector of the pregnant woman;

a sequence feature matrix generation module, for performing window division on at least part of a chromosome sequence of a reference genome to obtain sliding windows, counting the read segments falling within the sliding windows, and generating a sequence feature matrix of the chromosome sequence;

a sequence feature vector extraction module, for inputting the sequence feature matrix into a trained machine learning model to extract a sequence feature vector of the chromosome sequence;

a classification detection module, for combining the sequence feature vector and the phenotypic feature vector of the pregnant woman to form a combined feature vector, and inputting the combined feature vector into a classification detection model to obtain the fetal chromosomal abnormality state of the pregnant woman to be detected.

3625.The system of Claim 3524, the system further includes an alignment module, for aligning the reads of the sequencing data to a reference genome to obtain the unique mapping reads.

37.The system of Claim 35 or 36, in the data acquisition module, the cell-free nucleic acid fragments are derived from the peripheral blood, liver, and/or placenta of the pregnant woman.

38.The system of any one of Claims 35-37, in the data acquisition module, the cell-free nucleic acid fragments are cell-free DNA.

39.The system of any one of Claims 35-38, in the data acquisition module, the sequencing data are derived from ultra-low depth sequencing; preferably, the sequencing depth of the ultra-low depth sequencing is 1×, 0.1×, or 0.01×.

40.The system of any one of Claims 35-39, in the data acquisition module, the read segments are aligned to the reference genome to obtain the unique mapping reads (preferably, GC content correction is performed); preferably, the subsequent steps are carried out with the unique mapping reads (preferably, the read segments are corrected by GC content).

4126.The system of any one of Claims 24 or 2535-40, in the data acquisition module, the phenotypic feature data of the pregnant woman are selected from one or combination of more of: age, gestational week, height, weight, BMI, biochemical test results of prenatal examination, ultrasonic diagnosis results, and cell-free fetal DNA concentration in plasma, .

42.The system of any one of Claims 35-40, in the data acquisition modulepreferably,

the phenotypic feature data of the pregnant woman are subjected to outlier processing, missing value processing and/or null value processing.

~~43.The system of any one of Claims 35-42, in the data acquisition module, the phenotypic data of the pregnant woman sample will be judged as outliers if the following records appear:~~

~~a. $x_{age} < 10$ or $x_{age} > 80$;~~

~~b. $x_{GW} < 5$ or $x_{GW} > 50$;~~

~~c. $x_{height} < 40$ or $x_{height} > 300$;~~

~~d. $x_{weight} < 10$ or $x_{weight} > 200$;~~

~~and these outliers are set as a null value.~~

~~44.The system of Claim 42 or 43, the missing values and null values are padded by missForest algorithm.~~

~~45.The system of any one of Claims 35-44, in the sequence feature matrix generation module, the chromosome is chromosome 21, chromosome 18, chromosome 13 and/or a sex chromosome.~~

~~46~~27.The system of any one of Claims ~~35~~24-~~45~~26, the following steps are performed in the sequence feature matrix generation module: (2.1) using the window with length b to overlap and slide the chromosome sequence with length L of the reference genome at step size of t to obtain sliding windows, wherein b is a positive integer and b=[10000,10000000], t is any positive integer, L is a positive integer and L≥b; (2.2) counting the read segments falling within each of the sliding windows, and generating a sequence feature matrix of the chromosome sequence.

~~47.The system of any one of Claims 35-46, in the sequence feature matrix generation module, the sequence feature matrix includes the number, the base quality and the mapping quality of read segments within the sliding windows.~~

~~48.The system of Claim 47, the base quality includes the mean, the standard deviation, the skewness, and/or the kurtosis of the base quality.~~

~~49.The system of Claim 47, the mapping quality includes the mean, the standard deviation, the skewness and/or the kurtosis of the mapping quality.~~

50.The system of any one of Claims 35-49, in the sequence feature matrix generation module, the sequence feature matrix is:

$$\boldsymbol{X} = \left(x_{ij}\right)_{h \times w}$$

wherein h represents the number of sliding windows, w represents the number of sequence features within a single sliding window, and x_{ij} represents the jth sequence eigenvalue in the ith sliding window.

51.The system of any one of Claims 35-50, in the sequence feature vector extraction module, the sequence feature matrix is normalized.

52.The system of any one of Claims 35-51, in the sequence feature vector extraction module, the sequence feature matrix is normalized by using formula (I):

$$\boldsymbol{Z}_{ij}^{(k)} = \frac{\boldsymbol{X}_{ij}^{(k)} - \mu_{ij}}{\sigma_{ij}}$$

(I)

wherein $\boldsymbol{Z}_{ij}^{(k)}$ is the normalized sequence feature matrix of sample k, $\boldsymbol{X}_{ij}^{(k)}$ represents the jth sequence eigenvalue in the ith sliding window of sample k, and μ_{ij} and σ_{ij} represent the mean and standard deviation of the jth sequence eigenvalue in the ith sliding window of all samples, respectively.

53.The system of any one of Claims 35-52, in the sequence feature vector extraction module, the trained machine learning model is a neural network model or an AutoEncoder model; preferably, the neural network model is a deep neural network model, and more preferably, the neural network model is a deep neural network model based on 1D convolution.

54.The system of any one of Claims 35-53, in the classification detection module, the combined feature vector is obtained by combining the sequence feature vector and the phenotypic feature vector of the pregnant woman.

55.The system of any one of Claims 35-54, in the classification detection module, the combined feature vector x is normalized by:

$$x_i^* = \frac{x_i - \mu_i}{\sigma_i}$$

wherein x_i^* is the ith sequence eigenvalue of the normalized combined feature

vector x, x_i is the ith sequence eigenvalue of the combined feature vector x, μ_i is the mean of the ith sequence eigenvalues of the combined feature vector x, and σ_i is the standard deviation of the ith sequence eigenvalues of the combined feature vector.

56.The system of any one of Claims 35-55, in the classification detection module, the classification detection model is an ensemble learning model.

57.The system of Claim 56, the ensemble learning model is an ensemble learning model based on Stacking or Majority Voting; preferably, the ensemble learning model is one or more of: support vector machine model, naive Bayes classifier, random forest classifier, XGBoost and logistic regression.

58.A system of constructing a classification detection model for detecting a fetal chromosomal abnormality, comprising:

a data acquisition module, for obtaining sequencing data of cell-free nucleic acid fragments and clinical phenotypic feature data from of a pregnant woman, wherein the sequencing data comprise a plurality of read segments, and the fetal chromosomal state of the pregnant woman is known, and the clinical phenotypic feature data of the pregnant woman form a phenotypic feature vector of the pregnant woman;

a sequence feature matrix generation module, for performing window division on at least part of a chromosome sequence of a reference genome to obtain sliding windows, counting the read segments falling within the sliding windows, and generating a sequence feature matrix of the chromosome sequence;

a sequence feature vector extraction module, for constructing the training data set using the sequence feature matrix and the fetal chromosomal state, and training the machine learning model to extract a sequence feature vector of the chromosome sequence;

a classification detection module, for combining the sequence feature vector and the phenotypic feature vector of a pregnant woman to form a combined feature vector, and training the classification model with the combined feature vectors and the fetal chromosomal states of a plurality of pregnant women to obtain a trained classification detection model.

59.The system of Claim 58, the system further includes an alignment module, for

~~aligning the read segments of the sequencing data to a reference genome to obtain the unique mapping reads.~~