Diagnostic accuracy and value of chromosomal microarray analysis for chromosomal abnormalities in prenatal detection: a prospective clinical study

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Abstract

Background

Chromosomal microarray analysis (CMA) has emerged as a primary diagnostic tool for the evaluation of developmental delay and structural malformations in children. The aim of this study was to compare the accuracy and diagnostic value of CMA and karyotyping on chromosomal abnormalities in Fujian province of South China.

Methods

In the study, 410 samples were obtained from pregnant women between March 2015 and December 2016, including 3 villus (0.73%, 3/410), 296 amniotic fluid (72.20%, 296/410), and 111 umbilical cord blood (27.07%, 111/410). Each sample was screening for chromosomal abnormalities by both using CMA and karyotyping.

Results

The success rates of CMA and karyotyping were 100% (410/410) and 99.27% (407/410), respectively. 61 (14.88%, 61/410) samples were presented with chromosomal abnormalities using CMA, whereas 47 (11.46%, 47/410) samples were shown with chromosomal abnormalities using karyotyping. 31 (7.56%, 31/410) samples with normal karyotypes were found to have chromosomal abnormalities using CMA. Receiver operating characteristic (ROC) analysis showed that the area under the curve (AUC) of CMA on the diagnosis of chromosomal abnormalities was 0.93, with 90.68% sensitivity and 94.40% specificity. The AUC of karyotyping on the diagnosis of chromosomal abnormalities was 0.90, with 87.56% sensitivity and 91.22% specificity.

Conclusions

Our data demonstrated that CMA has a better diagnostic value for screening chromosomal abnormalities, especially for pregnant women with normal karyotypes.

Introduction

Chromosomal abnormalities has focused commonly on detection of the aneuploidy in human trisomy 21 and 18 in prenatal diagnosis (PND) [1, 2]. Currently, the mainly means of PND are to apply a combination of diagnostic procedures in the one and two-trimester based on concentrations of serum analytes, genetic history, maternal age, and ultrasound-detected data from pregnant women [3–5]. Karyotyping is commonly technique in screen chromosome abnormalities from individuals with congenital malformations, including chromosome deletion, inversion, duplication, translocation, aneuploidy, and

polyploidy [6]. Because karyotyping is reliably method for the detection of chromosome aneuploidies and large rearrangements, which has been the preferred method for prenatal diagnosis of chromosomal abnormalities for a long time in the past. However, karyotyping has considerable limitations, especially for the lack of detection of many unbalanced structural abnormalities from submicroscopic chromosomal aberrations. In recent years, molecular cytogenetic methods, including multiplex ligation-dependent probe amplification (MLPA), quantitative fluorescence polymerase chain reaction (QF-PCR), and fluorescence in situ hybridization (FISH), are gradually applied to evaluate submicroscopic chromosomal aberrations [7, 8]. However, these techniques are not feasible to detect all possible chromosome deletion and duplication.

Chromosomal microarray analysis (CMA) is known as array-based comparative genomic hybridization (array CGH) [9, 10]. At present, the advantages of CMA in PND are gradually presented with the rapid development of chip technology. CMA has the ability to disclose a wide range of chromosomal abnormalities with length from 50 kb to 100 kb, which produces 100 times better resolution than karyotyping [11]. More and more evidence has indicated that CMA can improve the diagnostic accuracy by approximately 15–20% over that of karyotyping when applied for the evaluation of fetuses with unexplained developmental delay, mental retardation, and autism [12]. CMA raises the diagnostic rates from 0.5–16% for screening commonly chromosomal abnormalities in PND [13]. In addition, CMA also obviously increases the success rates for diagnosing fetuses with chromosomal structural anomalies compared with karyotyping [14, 15]. Up to now, there is still no systematic study on the diagnostic accuracy of CMA for chromosomal abnormalities in PND in Fujian province of South China.

Here, our study aimed to compare the diagnostic accuracy of CMA and karyotyping for screening chromosomal abnormalities in PND, and to analyze theirs diagnostic values. Firstly, we collected 410 samples were obtained from pregnant women. Second, the CMA and karyotyping were performed to determine the rate of chromosomal abnormalities from all samples. Finally, the sensitivity and specificity of CMA and karyotyping in the diagnosis of chromosomal abnormalities was calculated and compared using ROC analysis. Our data confirmed that CMA is efficient to improve the diagnostic accuracy of chromosomal abnormalities in PND. CMA has a better diagnostic value than karyotyping, especially for pregnant women with normal karyotypes.

Materials And Methods

Patient samples collection

This research was a prospective clinical study conducted in Fujian Provincial Maternity and Children's Hospital (Fujian, China). A total of 410 samples were obtained from pregnant women between March 2015 and December 2016 in Fujian province of South China. Inclusion criteria: normal pregnant women. Exclusion criteria: history of chronic diseases and family history of genetic diseases. The accurately clinicopathological parameters of each pregnant women were presented in Table 1. Ethics approval (No.00157) was acquired from the Medical Research Ethics Committee of Fujian Provincial Maternity and

Children's Hospital, and written informed consent was provided by each patients in compliance with ethics of the World Medical Association (version 1991) Declaration of Helsinki.

Table 1
The general clinical information of 410 pregnant women

Variables	Number of cases	Percentage (/n, %)
High age	69	69/410, 16.83%
Abnormal ultrasound	182	182/410, 44.39%
High risk of serological screening in early or middle pregnancy	25	25/410, 6.10%
Fetuses with abnormal karyotypes	13	13/410, 3.17%
Patients with abnormal karyotypes	12	12/410, 2.93%
Adverse pregnancy history	23	23/410, 5.61%
High risk of NIPT	5	5/410, 1.22%
Two kinds of abnormal indications	70	70/410, 17.07%
Three kinds of abnormal indications	3	3/410, 0.73%
Others	8	8/410, 1.95%
NIPT: non-invasive prenatal testing.		

Karyotyping Analysis

Karyotyping was performed using G-banding analysis as previous literatures [16, 17]. G-banding was conducted according to the manufacturer operational protocols. Each samples were digested mechanically with collagenase II (TIANGEN, Beijing, China) at 37 °C for 20 min. After that, the metaphases were tretaed with the CytoVision computer assisted karyotyping system version 2.7 (Santa Clara, CA, USA). Karyotyping was then observed based on the criterion of the International System for Human Cytogenetics Nomenclature in 1995 (ISCN). Five metaphase cells were detailed examined by two experienced diagnostic specialists to determine chromosomal structural abnormalities, and at least fifteen metaphase cells were used to define chromosomal numerical abnormalities.

Chromosomal Microarray Analysis (CMA)

CMA test was carried out as previous literatures [18, 19]. Briefly, genomic DNA from each samples was isolated using a commonly DNA extraction kit (Qiagen, Hilden, Germany), according to the manufacturer's procedures. Then the isolated DNA was quantified using a NanoDrop 2000 Spectrophotometer (Thermo

Fisher Scientific, MA, USA). When the concentration of DNA from sample was > 100 ng/μl and optical densities were 1.8-2.0 at 260/280 nm, the DNA was selected and stored at -20˚C. Finally, the DNA was loaded with Affymetrix CytoScan HD/750 k array (Affymetrix, CA, USA), hybridized, and scanned with DNA MicroArray SureScan scanner (Affymetrix, CA, USA), according to the manufacturer's procedures. Data were dealt with the Affymetrix Chromosome Analysis Suite software (ChAS v.1.1, Affymetrix, CA, USA). All chromosomal abnormalities were checked and compared with the well-known databases, including the DECIPHER v9.30 (https://decipher.sanger.ac.uk/), the Online Mendelian Inheritance in Man (OMIM; http://omim.org/), and the Database of Genomic Variants (http://dgv.tcag.ca/dgv/app/home/). According to the deletion and duplication in chromosome location, the clinical significances of each abnormalities were evaluated. Chromosomal abnormalities were defined as five types of properties, including pathogenicity, possible pathogenicity, benign, possible benign, and unclear.

Statistical analysis

The statistical analyses were conducted with the SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Data were shown as mean ± SD (standard deviation) from three independent assays with each measured in triplicate. Differences among the groups were estimated using Chi-square test. Receiver operating characteristic (ROC) curves were drawn, and the area under curve (AUC) was analyzed to determine the specificity and sensitivity of CMA and karyotyping. A value of $P < 0.05$ was considered to be a statistically significant difference.

Results

General clinical information

A total number of 410 samples of pregnant women was recruited in this study, including 3 villus (0.73%, 3/410), 296 amniotic fluid (72.20%, 296/410), and 111 umbilical cord blood (27.07%, 111/410). The age of pregnant women varied from 19 to 42 years (mean at 24.33 ± 2.74 years), and gestational ages from 11 to 31 weeks (mean at 17.54 ± 3.17 weeks). The gestational ages in villus, amniotic fluid, and umbilical cord blood groups were 11^{+}-13^{+}, 18^{+}-24^{+}, and 24^{+}-31^{+} weeks, respectively. As shown in Table 1, the prenatal samples are classified into ten subgroups according to clinical indications, including high age group (16.83%, 69/410), abnormal ultrasound group (44.39%, 182/410), high risk of serological screening in early or middle pregnancy group (6.10%, 25/410), fetuses with abnormal karyotypes group (3.17%, 13/410), patients with abnormal karyotypes group (2.93%, 12/410), adverse pregnancy history group (5.61%, 23/410), high risk of non-invasive prenatal testing (NIPT) group (1.22%, 5/410), two kinds of abnormal indications group (17.07%, 70/410), three kinds of abnormal indications group (0.73%, 3/410), and others group (1.95%, 8/410).

Diagnostic Efficacy Of Karyotyping For Chromosomal Abnormalities

In the 410 samples, the success rate of karyotyping was 99.27% (407/410). Only 3 cases of samples were not successful detected with karyotyping, including one villus, one amniotic fluid, and one umbilical cord blood. 47 samples (11.46%, 47/410) were shown with chromosomal abnormalities, including 13 cases of chromosomal numerical abnormalities (27.66%, 13/47), 26 cases of chromosomal structural abnormalities (55.32%, 26/47), and 8 cases of chimeras (17.02%, 8/47). The representative karyotyping of chromosomal numerical abnormality, structural abnormality and chimera were presented in Fig. 1–3, respectively. Among the 13 cases of chromosomal numerical abnormalities, including 5 cases of trisomy 21 (38.46%, 5/13), 2 cases of trisomy 18 (15.38%, 2/13), one case of 47, XYY (7.69%, 1/13), 4 cases of extra small marker chromosome (30.77%, 4/13), and one case of triploid (7.69%, 1/13).

Diagnostic Efficacy Of Cma For Chromosomal Abnormalities

In the 410 samples, the success rate of CMA was 100% (407/410). 61 (14.88%, 61/410) samples were found to have chromosomal abnormalities, including 10 cases of copy number variations (CNVs) (16.39%, 10/61), 9 cases of large fragment abnormality (≥ 10 Mb) (14.75%, 9/61), 38 cases of small fragment abnormality (< 10 Mb) (62.30%, 38/61) and 4 cases of heterozygous abnormality (6.56%, 4/61). Among the 9 cases of large fragment abnormality, including 4 cases of deletion (44.44%, 4/9), 3 cases of duplication (33.33%, 3/9), and 2 cases of deletion and duplication (22.22%, 2/9). Among the 38 cases of small fragment abnormality, including 14 cases of microdeletion (36.84%, 14/38) and 24 cases of microduplication (63.16%, 24/38). In addition, 31 (31/410, 7.56%) samples with normal karyotypes were found to have chromosomal abnormalities by CMA.

Diagnostic Values Of CMA And Karyotyping For Chromosomal Abnormalities

To investigate the potential diagnostic value of CMA and karyotyping for chromosomal abnormalities in PND, ROC curves were plotted on data from 410 samples. As presented in Fig. 4, representation of the data revealed the AUC of CMA was 0.93 (95% CI: 0.90 to 0.95), the sensitivity and specificity was 90.68% and 94.40%, respectively. The AUC of karyotyping was 0.90 (95% CI: 0.87 to 0.93) with 87.56% sensitivity and 91.22% specificity. Compared with karyotyping, the diagnostic value of CMA was remarkable for chromosomal abnormalities in PND.

Analysis of the relationships between the chromosomal abnormalities and clinical indications

As shown in Table 2, the rates of chromosomal abnormalities by karyotyping in high age group was 5.8%, in abnormal ultrasound group was 8.24%, in fetuses with abnormal karyotypes group was 76.92%, in patients with abnormal karyotypes group was 41.67%, in adverse pregnancy history group was 8.70%, in high risk of NIPT group was 20%, in two kinds of abnormal indications group was 11.43%, and in three

kinds of abnormal indications group was 66.67%. The rates of chromosomal abnormalities by CMA in high age group was 1.45%, in abnormal ultrasound group was 14.84%, in high risk of serological screening in early or middle pregnancy group was 8.00%, in fetuses with abnormal karyotypes group was 61.54%, in patients with abnormal karyotypes group was 16.67%, in adverse pregnancy history group was 17.39%, in high risk of NIPT group was 20%, and in two kinds of abnormal indications group was 14.29%, in three kinds of abnormal indications group was 66.67%, and in others groups was 50.00%. There were no significant differences in chromosomal abnormalities of clinical indication groups by CMA and karyotyping.

Table 2
Analysis of the relationships between chromosomal abnormalities and clinical indications

Variables	Karyotyping (/n, %)	CMA (/n, %)	*P*
High age	4 (4/69, 5.80%)	1 (1/69, 1.45%)	0.37
Abnormal ultrasound	15 (15/182, 8.24%)	27 (27/182, 14.84%)	0.07
High risk of serological screening in early or middle pregnancy	0 (0/25, 0.00%)	2 (2/25, 8.00%)	0.49
Fetuses with abnormal karyotypes	10 (10/13, 76.92%)	8 (8/13, 61.54%)	0.67
Patients with abnormal karyotypes	5 (5/12, 41.67%)	2 (2/12, 16.67%)	0.37
Adverse pregnancy history	2 (2/23, 8.70%)	4 (4/23, 17.39%)	0.67
High risk of NIPT	1 (1/5, 20.00%)	1 (1/5, 20.00%)	1.00
Two kinds of abnormal indications	8 (8/70, 11.43%)	10 (10/70, 14.29%)	0.80
Three kinds of abnormal indications	2 (2/3, 66.67%)	2 (2/3, 66.67%)	1.00
Others	0 (0/8, 0.00%)	4 (4/8, 50.00%)	0.08
CMA: chromosomal microarray analysis.			

Discussion

CMA uses various array techniques, including oligonucleotide arrays, bacterial artificial chromosome (BAC) arrays, and single nucleotide polymorphism (SNP) arrays to determine molecular karyotype [20, 21]. Recently, a mostly proportion of chromosomal abnormalities has be confirmed with the promotion of CMA in PND, in addition to some balanced rearrangements, triploidies, and uniparental disomy [22, 23]. The resolution of detectable chromosomal abnormalities has heightened from 10 Mb or larger-sized

rearrangements to a few kb in size, thus significantly improves the diagnostic accuracy of abnormalities in PND.

Here, the purpose of our study was to assess the diagnostic accuracy of CMA and karyotyping on chromosomal abnormalities, and to analyze the diagnostic value of CMA as a routine inspection for chromosomal abnormalities in PND. The 410 cases of villus, amniotic fluid, and umbilical cord blood samples were obtained and cultured, and karyotyping and CMA were conducted in all samples in parallel. In the 410 samples, the success rate of CMA was 100%. 61 samples were found to show chromosomal abnormalities by CMA. Furthermore, 31 samples with normal karyotypes were presented with chromosomal abnormalities using CMA. The overall abnormal rate of chromosomal abnormalities by CMA (14.88%) in this study was higher than several reports at recent studies (2-7.1%) [24, 25]. The causes mainly focused on larger proportion of women with high risk of serological screening in early or middle pregnancy accounted for 6.10% of our cohort.

Further, 47 samples were shown with chromosomal abnormalities by karyotyping, including 13 cases of numerical abnormalities, 26 cases of structural abnormalities, and 8 cases of chimeras. 61 samples were presented with chromosomal abnormalities by CMA, including 10 cases of CNVs, 9 cases of large fragment abnormality, 38 cases of small fragment abnormality, and 4 cases of heterozygous abnormality. The overall abnormal rate of chromosomal abnormalities by CMA was 14.88%, which reflected 14 more cases than identified by karyotyping (11.46%), for an additional diagnostic yield of 3.42%. The samples with chromosomal abnormalities by CMA were exhibited as small fragment abnormality, deletion, and duplication. These results were consistent with a recent meta-analysis (3-5.2%) by Hillman et al [26]. Moreover, our data indicated that CMA have a high diagnostic value for chromosomal abnormalities in PND. The ROC curve of CMA showed 90.68% sensitivity and 94.40% specificity. The AUC of CMA was significantly larger than that of karyotyping, indicating that CMA may have excellent diagnostic value for chromosomal abnormalities in PND.

Besides, we also analyzed the relationships between chromosomal abnormalities and clinical indications. In terms of single clinical indication, the rates of chromosomal abnormalities had not obviously differences by CMA and karyotyping in simple high age, abnormal ultrasound, fetuses and patients with abnormal karyotypes, adverse pregnancy history, and high risk of NIPT groups. However, the rates of chromosomal abnormalities by CMA had an increased tendency in high risk of serological screening in early or middle pregnancy group. The diagnostic yield of CMA is related to the particular population, clinical indications, fetuses from selective terminations, and spontaneous miscarriages [27, 28].

Conclusions

Our study demonstrated that CMA is efficient to improve diagnostic accuracy of chromosomal abnormalities in PND. CMA has a higher diagnostic value for chromosomal abnormalities, especially for pregnant women with normal karyotypes. The limitation of this study is that clinical samples were relative small. Further researches with larger population should be conducted.

Abbreviations

CMA: chromosomal microarray analysis; ROC: receiver operating characteristic; AUC: area under the curve; PND: prenatal diagnosis; BAC: bacterial artificial chromosome; SNP: single nucleotide polymorphism; NIPT: non-invasive prenatal testing.

Declarations

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethics approval (No.00157) was acquired from the Medical Research Ethics Committee of Fujian Provincial Maternity and Children's Hospital in compliance with ethics of the World Medical Association (version 1991) Declaration of Helsinki.

Consent for publication

Informed written consent was provided was obtained from parents for publication.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HH and LX conceived and designed the study. HH, YW, MZ, NL and GA conducted the experiments. DH, MC and LC collected the experimental data and completed data analyses. HH wrote the first version of the manuscript. LX revised the manuscript and finalized the manuscript. All authors read and approved the final version of the manuscript.

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Figures

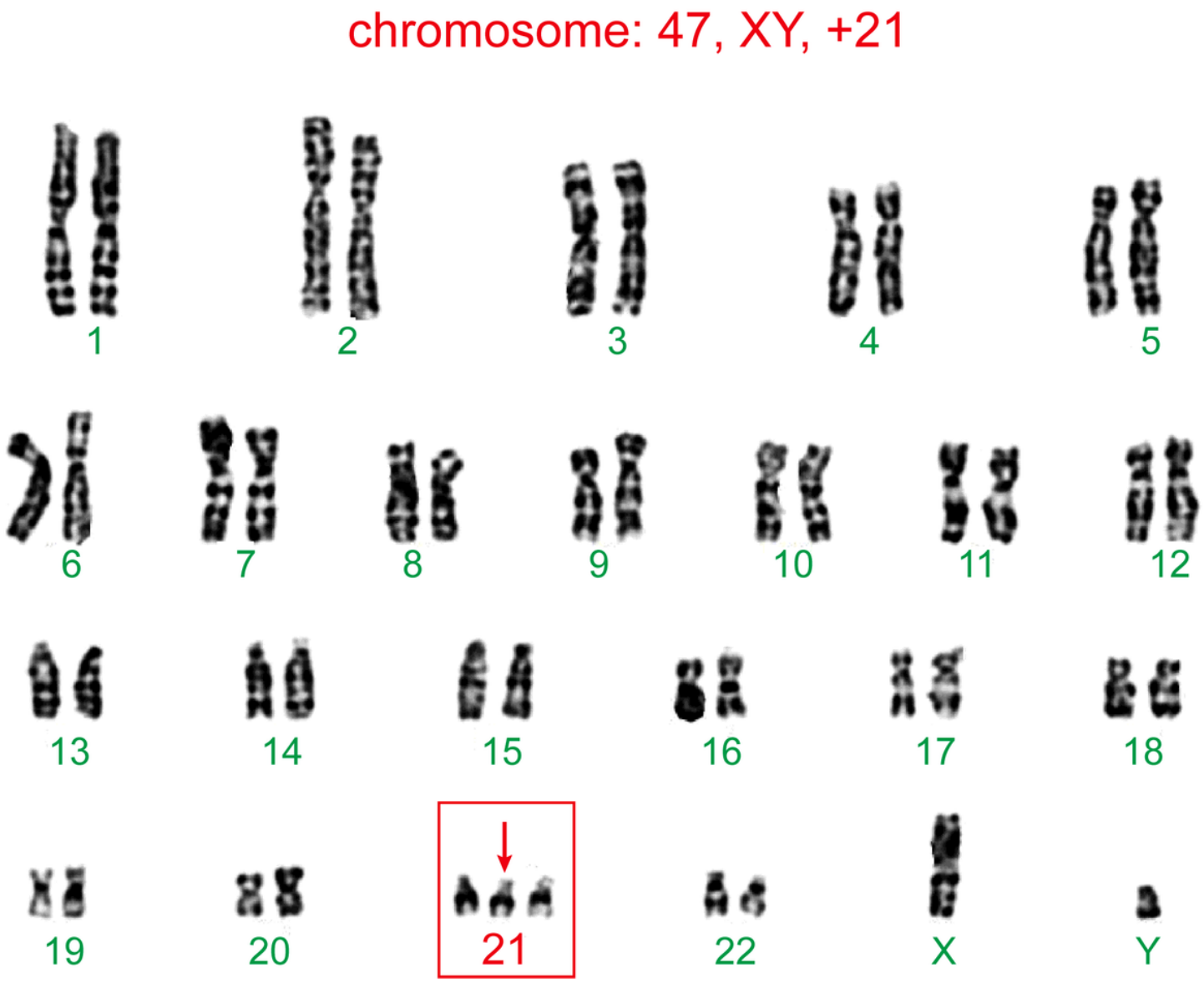

Figure 1

The representative karyotyping of chromosomal numerical abnormality. The karyotypes of a sample with 47, XY, +21 were shown.

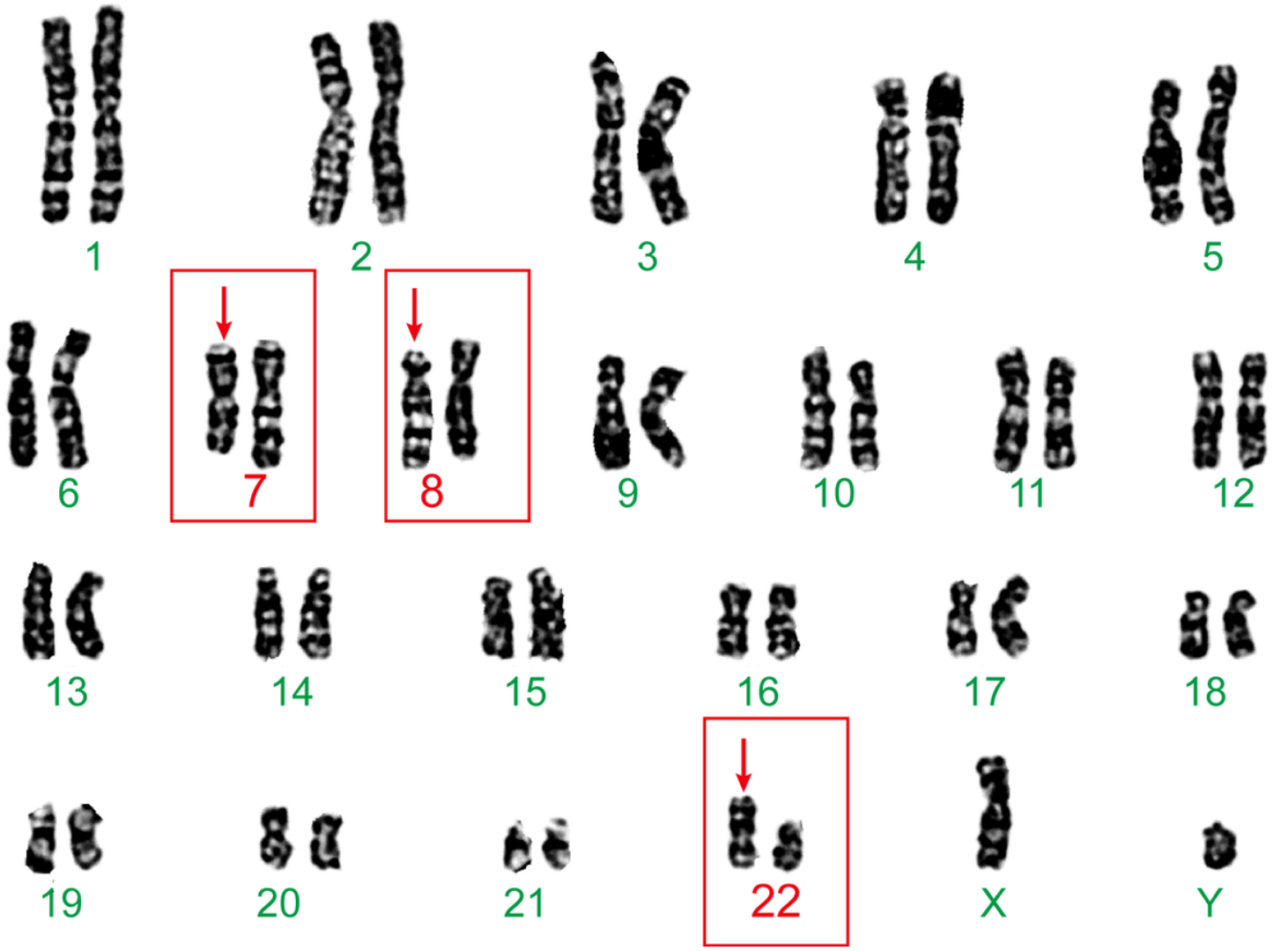

Figure 2

The representative karyotyping of chromosomal structural abnormality. The karyotypes of a sample with 46, XY, t(7; 8) (q22; q22), t(8; 22) (p12; p12) were shown.

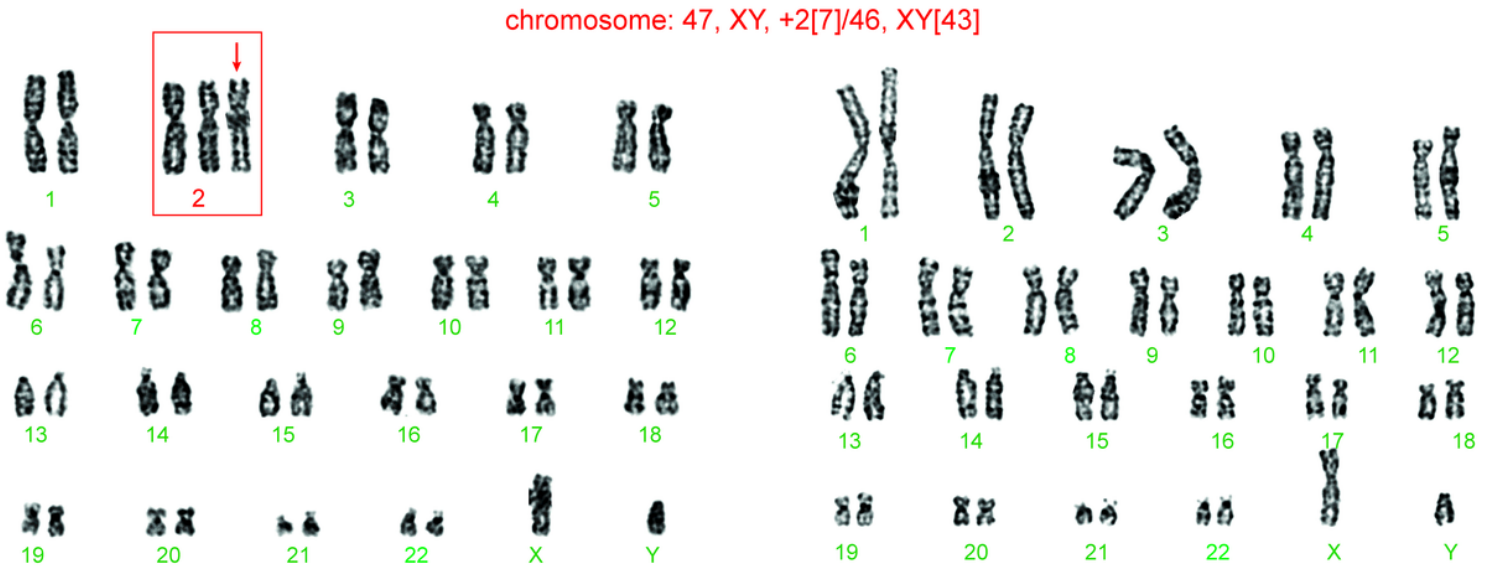

Figure 3

The representative karyotyping of chimera. The karyotypes of a sample with 47, XY, +2[7]/46, XY[43] were shown.

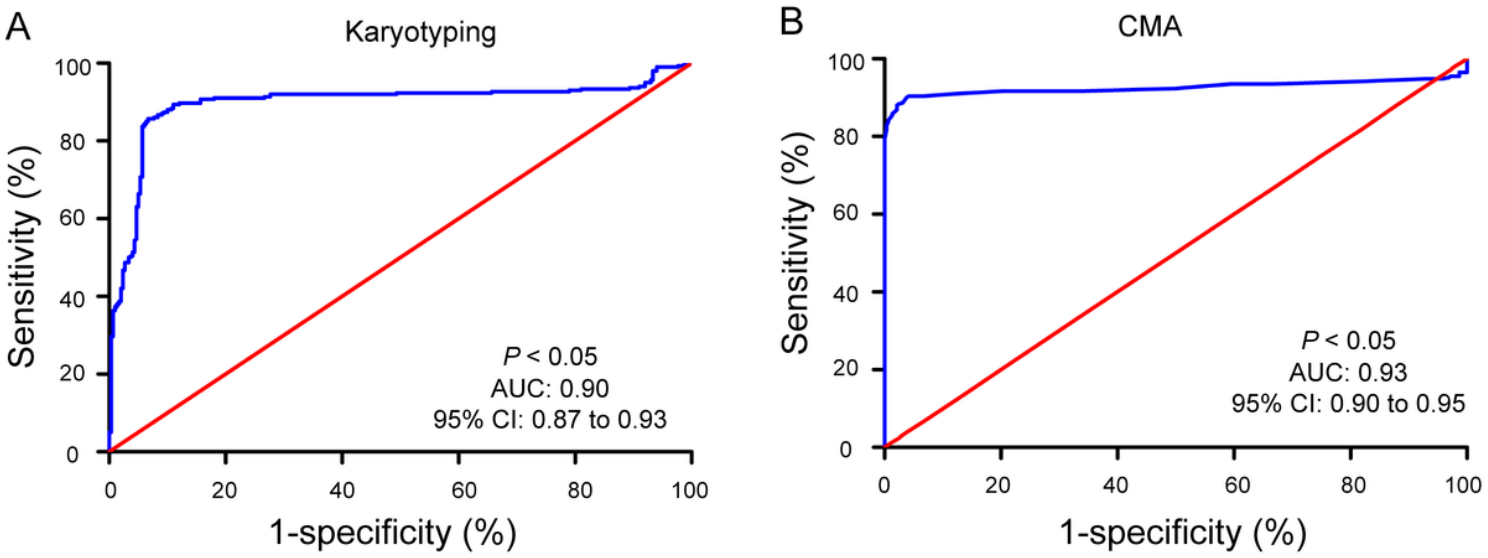

Figure 4

The ROC curves of karyotyping and CMA for screening chromosomal abnormalities. (A) The AUC of karyotyping was 0.90 (95% CI: 0.87 to 0.93), the sensitivity and specificity was 87.56% and 91.22%, respectively. (B) The AUC of CMA was 0.93 (95% CI: 0.90 to 0.95), with 90.68% sensitivity and 94.40% specificity. ROC, receiver operating characteristic; CMA, chromosomal microarray analysis; AUC, area under curve; CI, confidence interval.