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Original Article

The application of chromosome microarray analysis in fetuses with ultrasound-detected cardiac anomalies

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Abstract: Objective: To investigate the value of chromosome microarray analysis (CMA) in fetuses with ultrasound-detected cardiac anomalies. Methods: CMA and chromosome karyotype analysis (CKA) examinations were performed on 316 single-pregnancy women showing fetal cardiac anomalies in ultrasound examinations. The results were analyzed and the two methods were compared. Results: The chromosome abnormality detection rate of CMA (31.65%) was higher than the rate of CKA (16.77%) ($P<0.001$). Based on their ages, the pregnant women were classified into the advanced maternal age group (age ≥35) and the normal maternal age group (age <35). Based on whether they had other combined malformations, the fetuses were divided into two categories: fetuses having isolated congenital heart disease (CHD), and those having CHD combined with other malformations. The occurrence rate of the normal copy number variant (CNV) in the advanced maternal age group was lower than it was in the normal maternal age group; in contrast, the occurrence rate of pathogenic or possibly pathogenic CNV in the advanced maternal age group was higher than it was in the normal maternal age group ($P<0.05$). The occurrence rate of normal CNV isolated CHD was higher than it was in CHD with other combined malformations; in contrast, the occurrence rate of pathogenic or possibly pathogenic CNV in isolated CHD was lower than it was in CHD with other combined malformations ($P<0.05$). The occurrence rate of isolated CHD in the advanced maternal age group was lower than it was in the normal maternal age group; in contrast, the occurrence rate of CHD with other combined malformations in the advanced maternal age group was higher than it was in the normal maternal age group ($P<0.05$). The investigators detected 72 cases of pathogenic or possibly pathogenic chromosome variations using CMA, 34 (47.22%) of which fell within the scope of numerical abnormalities of chromosomes, and 38 (53.78%) of which fell within the scope of structural abnormalities. Among different cardiac anomalies, the main ones detected by CMA were ventricular septal defect, Tetralogy of Fallot, atrial septal defect, single-ventricle, and single-atrium lesion/malformation. Conclusion: Relative to CKA, CMA has a higher detection rate of chromosome abnormalities for fetuses with ultrasound-detected cardiac anomalies; considering the high occurrence rate of chromosome abnormalities in elderly pregnancy and in CHD with other combined malformations, CMA is better at diagnosing CHD.

Keywords: Chromosome microarray analysis, congenital heart disease, copy number variants, diagnostic value

Introduction

Congenital heart disease (CHD) is one of the most common defects in fetuses in clinical practice and is a primary cause of death for newborns with noninfectious diseases [1]. Studies have shown that the incidence of CHD is rising year by year, reaching about 0.7%-1.1% [2]. CHD has many causes. In about 25% of children with CHD, the onset of CHD is correlated with genetic factors and associated with chromosomal abnormalities [3, 4]. With the development of ultrasound, it is now possible to detect abnormalities in cardiac structures, blood vessels, and functions in the embryonic period. As for fetuses with structural abnormalities found in ultrasound, chromosome microarray analysis (CMA) is recommended for further detection [5, 6]. CMA is a molecular detection technique that can realize a full coverage of gene expression profiles and can detect chromosome abnormalities in structure, number, chimera, homozygous region, and so forth, without a need for cell cultures. It is more convenient than chromosome karyotype analysis (CKA) [7]. CMA can be used to detect chromo-

somally imbalanced CNV. By virtue of its high resolution, high pass, and high automation, it has been extensively applied in clinical practice for the early diagnosis of spontaneous abortion, congenital malformations, developmental retardation, mental retardation, autism, and other diseases with unknown causes. CMA is also available for scanning at the genome-wide level, and detecting imbalanced CNV longer than 1 kb and undetectable the at chromosome level; in particular, it enjoys great advantages when it comes to detecting genome microdeletion, microduplication, and other imbalanced rearrangements. Studies have found that CMA has a higher accuracy rate than CKA [8], and that, in the case of normal results in CKA, further CMA examination can still detect about 1%-1.7% of clinically significant chromosome abnormalities [9, 10]. According to existing studies, CHD is correlated with genetic factors in 25% of the cases, 9% of which are identified in prenatal diagnoses and 16% in postnatal diagnoses [3, 4]. Cardiac surgery on children having CHD after birth can greatly improve their quality of life; however, the efficacy of cardiac surgery in children having CHD with combined genetic abnormalities after birth is not ideal, and it also affects their quality of life [11]. For this reason, it is of vital importance to provide prenatal diagnosis for fetuses having CHD correlated with genetic factors as early as possible. On that account, this study performed further CMA and CKA on children with ultrasound-detected cardiac anomalies to investigate the diagnostic value of CMA in fetuses with CHD.

Materials and methods

Clinical data

This study was approved by the Ethics Committee of Zhangzhou Affiliated Hospital of FuJian Medical University and obtained the patients' informed consent. This study enrolled 316 single-pregnancy women showing ultrasound-detected fetal cardiac anomalies and admitted to Zhangzhou Affiliated Hospital of FuJian Medical University between September 2017 and September 2019. The pregnant women were 18-50 years old (31.3±7.3 years old on average), and the cardiac anomalies were detected in the gestational period of 18-28 weeks (22.3±3.6 weeks on average).

Inclusion criteria

Only subjects meeting all of the following criteria were enrolled: (1) Compliance with the criteria in *Prenatal Ultrasound Diagnostics of Fetal Malformations* on abnormalities in fetal ultrasound diagnosis [12]; (2) Single pregnancy; (3) High risk revealed in the screening for Down syndrome; (4) Normal chromosomes in both parents in the CKA; (5) Amniocentesis or cordocentesis performed to collect amniotic fluid or umbilical cord blood specimens.

Exclusion criteria

Those meeting any of the following criteria were excluded: (1) History of adverse pregnancy, such as habitual abortion, embryo damage, fetal malformations, or chromosome abnormalities; (2) Bad addictions, exposure to toxicants or radioactive substances, or the use of drugs; (3) Family history of related genetic diseases; (4) Double pregnancy or multiple pregnancy.

Specimen collection and grouping

The Metasystems automatic chromosome scanning and analysis system was used for the slide scanning and karyotype analysis.

The subjects received CMA in the gestational period of 18-28 weeks, and amniocentesis or cordocentesis was performed to collect amniotic fluid or umbilical cord blood specimens. Based on their ages, the pregnant women were classified into the advanced maternal age group (age ≥35) with 119 cases, or the normal maternal age group (age <35) with 197 cases. Based on whether they had other combined ultrasound-detected malformations, the fetuses were divided into two categories: 202 fetuses with isolated CHD and 114 with CHD with other combined malformations.

Methods

CMA detection: The collected amniotic fluid or umbilical cord blood specimens were subjected to genome-wide CMA analysis; the DNA genes were extracted from the specimens using a DNA extraction kit (Guangzhou Dingguo Biotechnology Co., Ltd., China) according to its operation flow; the detection chips used Cyto Scan HD chips (Affymetrix, America), and they were scanned with a Gene Chip 3000

Table 1. Comparison of the CMA and CKA examination results

Group	Normal CNV	Pathogenic or possibly pathogenic CNV	VOUS	Total detection rate
CKA	83.23% (263/316)	16.46% (52/316)	0.32% (1/316)	16.77% (53/316)
CMA	68.35% (216/316)	22.78% (72/316)	8.86% (28/316)	31.65% (100/316)
χ^2				19.05
P				<0.001

Note: Total detection rate = (Pathogenic or possibly pathogenic CNV + VOUS)/Total number of cases * 100%; CMA: chromosome microarray analysis; CKA: chromosome karyotype analysis; CNV: copy number variant; VOUS: variant of unknown significance.

Table 2. Comparison of the CMA detection results in the different age groups

Group	Normal CNV	Pathogenic or possibly pathogenic CNV	VOUS
Advanced maternal age group (n=119)	73 (61.35%)	37 (31.09%)	9 (7.56%)
Normal maternal age group (n=197)	145 (73.60%)	33 (16.75%)	19 (9.64%)
χ^2	5.212	8.848	0.398
P	0.022	0.003	0.528

Note: CMA: chromosome microarray analysis; CNV: copy number variant; VOUS: variant of unknown significance.

Scanner with a 7G upgrade. The results of the detection were interpreted with reference to international genome and phenotype public databases and were classified into three types, i.e., a normal copy number variant (CNV), a pathogenic or possibly pathogenic CNV, or a variant of unknown significance (VOUS).

Pregnancy outcomes

In the cases of confirmed pathogenic CNV, each pregnant woman was notified of the result, so that she could decide whether to continue the pregnancy or not. Should she decide to terminate the pregnancy, it was suggested that a pathological examination be conducted to identify the type of cardiac anomalies; should she decide to continue the pregnancy, follow-up cardiac color ultrasound would be conducted after the delivery to identify the type of cardiac anomalies.

Statistical methods

SPSS 19.0 statistical software was used for the statistical analysis, this study expressed continuous variables in the form of mean ± standard deviation ($\bar{x}$ ± sd). In the case of compliance with a normal distribution and homogeneity of variance, independent t tests were performed, as represented by t; in the cases of incompliance with a normal distribution and homogeneity of variance, rank sum tests were performed as represented by Z. P<0.05 is considered a statistically significant difference.

Results

Comparison of the CMA and CKA examination results

In terms of the chromosome abnormality detection rate, the chromosome abnormality detection rate of CMA (31.65%) was higher than the rate of CKA (16.77%) (P<0.001), as shown in **Table 1**.

Comparison of the CMA detection results in the different age groups

The occurrence rate of normal CNV in the advanced maternal age group was lower than it was in the normal maternal age group; in contrast, the occurrence rate of pathogenic or possibly pathogenic CNV in the advanced maternal age group was higher than it was in the normal maternal age group (P<0.05), as shown in **Table 2**.

Comparison of CMA detection results in the different categories of cardiac anomalies

The occurrence rate of normal CNV in the category of isolated CHD was higher than it was in the category of CHD with other combined malformations; however, the occurrence rate of pathogenic or possibly pathogenic CNV in the

Table 3. Comparison of the CMA detection results in the different categories of cardiac anomalies

Group	Normal CNV	Pathogenic or possibly pathogenic CNV	VOUS
Isolated CHD (n=202)	149 (73.76%)	36 (17.82%)	17 (8.42%)
Merge other malformed CHD group (n=114)	67 (58.77%)	36 (31.58%)	11 (9.65%)
χ^2	7.57	7.839	0.137
P	0.006	0.005	0.711

Note: CMA: chromosome microarray analysis; CNV: copy number variant; VOUS: variant of unknown significance; CHD: congenital heart disease.

Table 4. Comparison of the occurrence of cardiac anomalies in the different age groups

Group	Isolated CHD	Merge other malformed CHD
Advanced maternal age group (n=119)	60 (50.42%)	59 (49.58%)
Normal maternal age group (n=197)	142 (72.08%)	55 (27.92%)
χ^2	15.094	
P	<0.001	

Note: CHD: congenital heart disease.

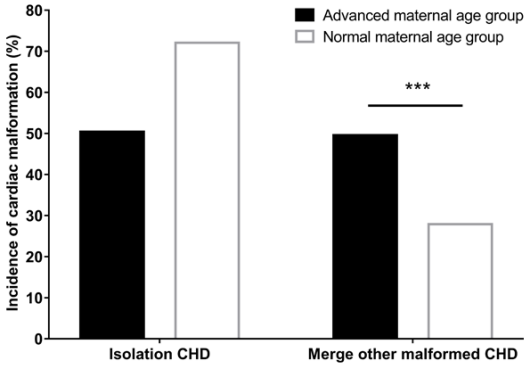

Figure 1. Comparison of the incidence of cardiac malformations in pregnant women of different ages. Compared with merge other malformed CHD group in advanced and non-elderly pregnancy women, ***P<0.001.

category of isolated CHD was lower than it was in the category of CHD with other combined malformations (P<0.05), as shown in **Table 3**.

Comparison of the occurrence of cardiac anomalies in the different age groups

The occurrence rate of isolated CHD in the advanced maternal age group was lower than it was in the normal maternal age group; however, the occurrence rate of CHD with other combined malformations in the advanced maternal age group was higher than it was in the normal maternal age group, with a statistically significant difference (P<0.05), as shown in **Table 4** and **Figure 1**.

Distribution of pathogenic or possibly pathogenic chromosome variations in CMA detection

The investigators detected 72 cases of pathogenic or possibly pathogenic chromosome variations using CMA, 34 (47.22%) of which fell within the scope of numerical abnormalities of chromosomes, and 38 (53.78%) of which fell within the scope of structural abnormalities, as shown in **Table 5**.

Comparison of the CMA examination results of different cardiac anomalies

Among the different cardiac anomalies, the main ones detected by CMA were ventricular septal defect, Tetralogy of Fallot, atrial septal defect, single-ventricle, and single-atrium lesion/malformation, as shown in **Table 6**.

Discussion

This study used two detection methods to examine fetuses with ultrasound-detected cardiac anomalies. In terms of the chromosome abnormality detection rate, the chromosome abnormality detection rate of CMA (31.65%) was higher than that of CKA (16.77%), which confirmed the higher detection rate of CMA relative to CKA. In a previous study [13], CMA and CKA were performed on 575 pregnant women showing high risks in serum screening; according to the study results, the anomaly detection rate of CKA (6.8%, 39 cases) was lower than

Table 5. Distribution of the pathogenic or possibly pathogenic chromosome variations in CMA detection

Group	Case	Ratio
Chromosomes numerical abnormalities (n=34)		
21-trisomy syndrome	12	35.29
18-trisomy syndrome	11	32.35
13-trisomy syndrome	3	8.82
Turner syndrome	3	8.82
Turner syndrome chimerism	1	2.94
47, XYY	1	2.94
45, X	1	2.94
47, XXY	1	2.94
47, XN, +I (18) (p10)	1	2.94
Chromosomes structural abnormalities (n=38)		
Interchromosomal unbalanced translocations	10	26.32
22q11.2 microdeletion syndrome	10	26.32
Williams-Beuren syndrome (7q11, 23 microdeletion)	5	13.16
Jacobsen syndrome	1	2.63
Chromosomes microdeletion	10	26.32
Chromosomes microduplication	2	5.26

Note: CMA: chromosome microarray analysis.

Table 6. Comparison of the CMA examination results of the different cardiac anomalies

Type of CHD	Normal CNV (n=216)	Pathogenic or possibly pathogenic CNV (n=72)	VOUS (n=28)
Atrioventricular septum defect (n=17)	12 (5.56%)	4 (5.56%)	1 (3.57%)
Ventricular septal defect (n=69)	44 (20.37%)	18 (25.00%)	7 (25.00%)
Atrial septal defect (n=43)	32 (14.81%)	7 (9.72%)	4 (14.29%)
Tetralogy of Fallot (n=62)	40 (18.52%)	16 (22.22%)	6 (21.43%)
Right-position aortic arch (n=9)	5 (2.31%)	3 (4.17%)	1 (3.57%)
Single-ventricle (n=19)	13 (6.02%)	4 (5.56%)	2 (7.14%)
Single-atrium (n=17)	11 (5.09%)	4 (5.56%)	2 (7.14%)
Aortic stenosis (n=12)	9 (4.17%)	2 (2.78%)	1 (3.57%)
Pulmonary artery stenosis (n=18)	14 (6.48%)	3 (4.17%)	1 (3.57%)
Transposition of great arteries (n=17)	15 (6.94%)	2 (2.78%)	0 (0)
Left ventricular dystrophy (n=16)	14 (6.48%)	1 (1.39%)	1 (3.57%)
Double outlet of right ventricle (n=3)	2 (0.93%)	1 (1.39%)	0 (0.00%)
Stenosis of the isthmus of the aorta (n=4)	2 (0.93%)	1 (1.39%)	1 (3.57%)
Persistent left superior vena cava (n=3)	0 (0)	2 (2.78%)	1 (3.57%)
Absence of aortic valve (n=2)	1 (0.46%)	1 (1.39%)	0 (0)
Pulmonary valve defect (n=3)	1 (0.46%)	2 (2.78%)	0 (0)
Mitral tricuspid regurgitation (n=2)	1 (0.46%)	1 (1.39%)	0 (0)

Note: CMA: chromosome microarray analysis; CNV: copy number variant; VOUS: variant of unknown significance; CHD: congenital heart disease.

the rate of CMA (8.9%, 51 cases), and was consistent with the results of our study. In another study examining CHD cases using CMA detection, it was found that, after excluding non-integral multiple chromosome abnormalities, pathogenic CNV could be detected in another 12% of the cases [14]. The consistency between the above study results and the results of this

study suggests that CMA has a higher detection rate of chromosome abnormalities for fetuses having CHD, and a higher diagnostic value.

Further research on pregnant women in different age groups found that, when CMA was performed on elderly pregnant women, the occurrence rate of pathogenic or possibly pathogenic CNV was higher. This is possibly because, with age, both the ova and spindles also begin to age and degrade, making it easier for chromosome segregation to occur during pregnancy in this case; under the combined action of environmental factors and other factors, elderly pregnant women are more likely to experience fetal chromosome abnormalities [15]. In a foreign large-sample meta-study on 10,614 elderly pregnant women [16], the detection rate of pathogenic CNV by CMA was 0.84%. This is consistent with the results of this study and confirms that elderly pregnant women are more likely to experience fetal chromosome abnormalities. Based on whether they have other combined malformations, fetuses having CHD can be divided into two categories: fetuses having isolated congenital heart disease (CHD) and those having CHD with other combined malformations. In this study, we found that the occurrence rate of pathogenic or possibly pathogenic CNV by CMA detection was higher in fetuses having CHD with other combined malformations. According to a previous study [17], when CMA was used to examine fetuses having CHD, 4.3%-9.3% of the isolated CHD cases had combined pathogenic or possibly pathogenic CNV, lower than the detection rate in the case of non-isolated CHD cases. Another study found that [18] when CMA was used to examine fetuses having CHD with other combined malformations, the detection rate of pathogenic CNV rose significantly. The consistency between the above study results and the results of this study suggests that chromosome abnormalities, besides causing cardiac anomalies, may also give rise to malformations at other sites. In this study, it was found that the occurrence rate of CHD with other combined malformations in fetuses in the advanced maternal age group was higher than it was in the normal maternal age group. This is possibly because elderly pregnancy is susceptible to chromosome abnormalities, and chromosome abnormalities are usually associated with a higher occurrence rate of CHD with other combined malformations in fetuses.

It was found in this study that, of the 72 cases of pathogenic or possibly pathogenic CNV detected, 34 fell within the scope of numerical abnormalities of chromosomes, and 38 fell within the scope of structural abnormalities. Previous studies have reported that about 5%-6% of fetuses having CHD have combined chromosome variations, manifesting as non-integral multiple changes of chromosomes [4]. The most common ones with such changes are 21-trisomy syndrome and 18-trisomy syndrome, consistent with the results of this study. As regards patients with structural abnormalities of chromosomes, previous studies have identified the microdeletion or microduplication of chromosomes as the primary pathogenic factor [19]. The most common example is 22q11.2 microdeletion syndrome. In about 60%-81% of cases, 22q11.2 microdeletion appears as CHD, with diversified manifestations of cardiac anomalies, such as atrial septal defect, aortic arch anomalies, and coronary artery origin anomalies [20-22]. Another common example is Williams-Beuren syndrome, which, in 90% of cases, is associated with CHD, as well as changes in facial features and intellectual and physical dysplasia. This disease is mainly caused by the 7q11, 23 microdeletion [23, 24]. In this study, interchromosomal unbalanced translocations also had a high occurrence rate. This disease occurs mainly because there are carriers of balanced translocations in the chromosomes of one parent; it may be associated with the occurrence of multiple malformations, including cardiac anomalies [25, 26]. Different chromosome abnormalities can be manifested as different cardiac anomalies [27-29]. This study found that, among all cardiac anomalies, the main ones detected by CMA were ventricular septal defect, Tetralogy of Fallot, atrial septal defect, single-ventricle, and single-atrium lesion/malformation. This suggests that, as regards the diversified manifestations of CHD caused by chromosome lesions, the early diagnosis of chromosome abnormalities can be made using CMA, and that early interventions are of vital significance for the prognosis of children [30].

Considering that this study was based on a small sample from a single center, multi-center

studies can be conducted to further clarify the role and significance of CMA examination. In addition, this study did not follow up the progression of the diseases in the fetuses after pregnancy, so efforts can be made in this regard in the future as well.

To sum up, CMA has a higher detection rate of chromosome abnormalities in fetuses with ultrasound-detected cardiac anomalies; considering the high occurrence rate of chromosome abnormalities in elderly pregnancy and in CHD with other combined malformations, CMA has a higher value in the diagnosis of CHD.

Disclosure of conflict of interest

None.

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