Clinical Application of Chromosomal Microarray Analysis in Fetuses with Congenital Heart Disease

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Research Article

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Abstract

Background: Congenital heart disease (CHD) is an important birth defect, but its mechanism is still unclear. In recent years, genetic causes including chromosomal abnormalities are associated with the occurrence of congenital heart disease. In this study, CMA technology is applied to explore the genetic causes of congenital heart disease, so as to further clarify the correlation between genotype and phenotype and prepare for late pregnancy intervention and postnatal diagnosis and treatment.

Objective: To explore the chromosomal abnormalities and copy number variation (CNVs) of fetuses with CHD by CMA technology, and to clarify the clinical application value of CMA technology as a detection method of first-tier antenatal CHD.

Methods: Amniotic fluid sample from 155 pregnant women diagnosed with fetus CHD by prenatal ultrasound from 2018 to 2021 are collected for SNP-array detection and karyotype analysis. According to the detected CNVs results, FISH, CMA or karyotype analysis are further selected for parental verification.

Results: Among the 155 fetuses with CHD, a total of 32 (20.6%) cases of chromosomal abnormalities are detected, of which 31.3% are chromosome number abnormalities. CNVs of likely pathogenicity and unknown significance are 2.5% and 5.2% respectively. The detection rate of chromosomal abnormalities in CHD of different subtypes is different, among which the high detection rate is complex CHD (31.2%), right ventricular outflow tract obstruction (30.7%) and conotruncal defects (25%). The detection rate of chromosomal abnormalities in CHD with extracardiac structural abnormalities is significantly higher than that in isolated CHD (52.4% vs 11.3%, $p < 0.05$). In addition, the detection rate of CHD with abnormal extracardiac structure is significantly higher than that of CHD with soft markers (52.4% vs 17.8%, $p < 0.05$), which is statistically significant. There is no significant difference in detection rate between CHD with soft markers and isolated CHD (17.8% vs 11.3%). Of the 155 pregnant women with fetus CHD, 59 chose to terminate their pregnancies, some of which were terminated according to the results of SNP-array, and some of which were terminated according to the severity of CHD.

Conclusion: SNP-array technology can be used to detect chromosomal abnormalities of first-tier antenatal CHD fetuses, with high resolution, short reporting period and high efficiency. Meanwhile, pregnancy intervention can be taken according to the results.

Introduction

CHD is the most common birth defect and is one of the most common causes of morbidity in infants and young children worldwide, accounting for 0.8-1.3% of live births [1]. The etiology is complicated, including genetic and environmental factors[2, 3] and genetic etiology includes chromosome number abnormality, copy number variation (CNVs), single-gene disease, etc., in which chromosome abnormality accounts for about 20%[4]. At present, prenatal CHD is mainly diagnosed by echocardiography, but it is difficult to overall evaluate the fetus with CHD by prenatal echocardiography. In addition, most infants with CHD need postnatal surgery and multidisciplinary intervention. After surgical treatment, most infants with CHD can restore cardiac function. However, when accompanied by chromosomal abnormalities, it is often associated with extracardiac structural abnormalities or neurodevelopmental retardation, mental retardation, etc., so it is necessary to carry out prenatal diagnosis of fetus CHD, in order to determine the prognosis and genetic counseling.

With the development of genetic techniques, prenatal diagnostic techniques are also developing from Chromosomal karyotype analysis and fluorescence in situ hybridization (FISH) to Chromosomal microarray analysis (CMA). Compared with the above two techniques, CMA can detect chromosome number and submicroscopic abnormalities at the whole genome level. And the single nucleotide polymorphism array (SNP-array) we apply can also detect the uniparental disomic and heterozygous deletion.

In 2013, the American Congress of Obstetricians and Gynecologists recommended replacing karyotype analysis with CMA technology in the prenatal diagnosis of fetus structural abnormalities[5]. Therefore, this study applies CMA technology to the prenatal diagnosis of fetus CHD, to explore the genetic causes of CHD and to further clarify the correlation between genotype and phenotype, as well as the intervention of late pregnancy, diagnosis and treatment after birth, and the assessment of recurrence risk.

In this study, we apply CMA technology to prenatal diagnosis of 155 fetuses with CHD and evaluate its clinical value as a prenatal diagnostic tool. We assess the detection rates of chromosomal abnormalities in fetuses with different subtypes of CHD. We then compare the chromosomal abnormalities in isolated CHD, CHD with soft indicators, and CHD with structural abnormalities.

Materials And Methods

Subjects

Retrospective analysis is performed on 155 pregnant women who were admitted to the prenatal diagnosis center of Zhejiang Jiaxing maternal and child health care hospital from January 2018 to May 2021, they were diagnosed as fetus CHD by fetus echocardiography. Samples were collected by amniocentesis and amniotic fluid was extracted, then SNP-array and chromosome karyotype analysis were conducted at the same time.

Before surgery, fetus medicine physicians and genetic counselors signed informed consent forms with pregnant women and their families to inform them of the risks of prenatal diagnosis and the advantages and potential risks of SNP-array testing, such as the possible detection of clinically ambiguous mutations, non-paternal diseases and adult diseases. The average age of the pregnant women is 28.6 years old (range, 20-42 years), and the average gestational age of the fetus for invasive prenatal diagnosis is 26.1 weeks (range, 22-30 weeks).

Of the 155 fetuses diagnosed with CHD, 106 are isolated CHD, and 49 are associated with sonographic abnormalities, including 21 cases with structural abnormalities and 28 cases with soft markers. The classification of CHD is carried out by referring to the classification method of Fengqun Dong et al. 2011. The work is discussed and approved by the ethics committee of Jiaxing maternal and child health care hospital. (2020-Prenatal ethics-1)

Chromosomal microarray analysis

10-ml amniotic fluid sample was taken from each pregnant woman, and QIAamp DNA mini kit (Qiagen, Germany) is applied to extract genomic DNA. Affymetrix CytoScan 750K Array technology platform (Santa Clara, CA, USA) is applied to detect the microarray. The microarray contains 550,000 CNV probes and 200,000 SNP probes, which are distributed throughout the human genome at a density of about 1 probe per 4kb on average.

SNP array experimental operation, referring to protocol, data Analysis using Chromosome Analysis Suite V4.0 software (Affymetrix Inc, USA). The microarray analyses the data at a resolution level of 25 SNP probes per 50kb and 50 CNV probes per 200kb, with a set report range of copy number variations (CNVs) of more than 200kb for

deletion and more than 500kb for duplication. The threshold range of loss of heterozygosity (LOH) is more than 10Mb.

The Allele Difference and smooth signal tracks can be used to assess mosaicism[5], which can detect over 30% mosaicism. For Maternal cell contamination (MCC) of amniotic fluid sample, STR genotyping based on capillary electrophoresis is applied [6]. The detected CNVs is reported according to GRCh37 (hg19). CNVs is further classified according to fragment size: when CNVs<10M, it is defined as microdeletion/microduplication. If CNVs>10M, defined as partial aneuploidy.

The detected CNVs should be evaluated in combination with public databases and literatures. The public databases referred to are as follows:

DGV, Decipher, ClinGen, OMIM. As for the interpretation of CNV, referred to the standard and guide of ACMGG, which classifies the microdeletion and microduplication of chromosomes into five categories: pathogenic CNVs, possible pathogenic CNVs, variants of uncertain significance (VOUS), possible benign CNVs, benign CNVs. In our study, CNVs of normal polymorphism are not reported in genome chromosomes.

Conventional cytogenetic analysis

20-ml of amniotic fluid is collected, and the amniotic fluid cell culture and G-banded karyotype analysis (550 banded resolution) are performed according to the standard operation procedure. The karyotypes are described using the International System for Human Cytogenetics Nomenclature (ISCN 2016).

Parents verification

For CNVs detected in amniotic fluid samples, karyotype analysis, FISH and SNP-array a selected according to the results of fetus SNP-array, and 2-ml of each maternal and parental peripheral blood is extracted for verification. Conventional G-banding karyotype analysis performed according to the standard method. FISH test must use specific commercial probe following the manufacturer's standard operating procedures (VYSIS Ins, Downers Grove, IL).

Obstetrical outcomes

We further track the late pregnancy outcomes of fetuses diagnosed with CHD prenatally in this study, and further analyze the causes of early pregnancy termination.

Statistical analysis

In this study, chi-square test is used to compare the differences between the two groups, and p value <0.05 is considered to be statistically significant.

Results

The diagnostic rate of fetus with CHD detection by SNP-array

We use SNP-array to detect a total of 155 fetus samples of CHD and identified maternal source contamination, and the results show no contamination of maternal cells. The overall diagnostic rate of SNP-array of CHD fetuses is 18.1% (28/155), while the detection rate is 20.6 % (32/155) when the possible pathogenicity of CNVs is considered.

A total of 8 cases of VOUS (8/155) are detected (supplementary table 1). The detection rate of pathogenicity of SNP-array in the CHD types and the fetuses with CHD in different groups can be seen: Figure1, Table1, Table2.

In this study, chromosome number abnormality is detected in 10 cases (6.4%, 10/155), including 5 cases of 18-trisomy, 3 cases of 21-trisomy, and 2 case of X trisomy. A total of 6 cases of partial aneuploidy are detected (3.9%, 6/155) (supplementary table 2), some of which are new and some of which are caused by unbalanced translocation. 16 (10.3%, 16/155) cases of pathological microdeletion/microduplication are found, among which 5 cases are 22q11.2 (DiGeorge syndrome),3 cases are 7q11.23 (Williams-Beuren Syndrome), two cases are 1q21.1q21.2 microduplication. Cases of pathological microdeletion/microduplication are shown in supplementary table 3.

Analysis of detection results of different subtypes CHD

We have classified fetus CHD into seven subtypes, the first of which is Septal defects, which are the most common cardiac defects, with 58 cases (37.4%,58/155); Conotruncal defects followed, in 28 cases (18.1%, 28/155). The pathogenicity of different subtypes CHD is shown in Table1. The detection rate of pathogenic chromosomal abnormalities is high in complex CHD (31.2%), right ventricular outflow tract obstruction (30.7%) and conotruncal defects (25%), which is shown in Table 3, Figure2.

The diagnostic rates comparison of SNP-array in isolated CHD and nonisolated CHD

The incidence of pathogenic chromosomal abnormalities in isolated CHD, CHD accompanied by soft markers, and CHD accompanied by additional structural abnormalities are (11.3%, 12/106), (17.8%, 5/28), (52.4%, 11/21), respectively. The distribution of chromosomal abnormalities in each group is shown in Table4.

Compared with isolated CHD (11.3% vs 52.4%, $p<0.05$), the detection rate of pathogenic chromosome abnormality in CHD with additional structural abnormalities is significantly higher. If likely pathogenic CNVs are included, the group of CHD with additional structural abnormalities is still statistically significant compared with the group of isolated CHD (15.1% vs 52.4%, $p<0.05$).The detection rate of CHD with abnormal extra structure is significantly higher than that of CHD with soft markers (52.4% vs 17.8%, $p<0.05$). Compared with isolated CHD (15.1% vs 17.8%), there is no significant difference in CHD with soft markers. The incidence rates of pathological microdeletion/microduplication in isolated CHD, CHD with soft markers, and CHD with structural abnormalities are 6.6% (7/106), 0% (0/28), and 23.8% (5/21), respectively.

A total of 28 CHD fetuses are united with soft markers, 25 of which are single soft marker and 3 of which are multiple soft markers. There is clear distinction between single soft markers and multiple soft markers (16% vs33.3%), while due to the sample size of multiple soft marker, this conclusion needs further exploration. The detection rate of CHD with soft markers is summarized in Table 5.

A total of 21 fetuses are united with structural abnormalities, 18 of which are single structural abnormalities and 3 of which are multiple structural abnormalities. The incidence of pathogenic chromosomal abnormalities in single structural abnormalities is (55.5%, 10/18), and that in multiple structural abnormalities is (33.3%, 1/3). The detection rate of CHD with structural abnormalities is shown in Table 6.

Analysis results of routine G-banding karyotype of 155 CHD fetuses

The amniotic fluid cells samples of 155 CHD fetuses are cultured, one case of which is not successfully cultured due to intrauterine death, only SNP-array detection is conducted, and G-banded karyotype analysis is performed for the rest. Among the 154 samples, aneuploidy is detected in ten cases, 47,XX,+mar in two cases, 47,XY,+mar in two cases, and the molecular karyotype is further confirmed by SNP-array. One case of partial deletion of 4p16 chromosome. Chromosome aneuploidy includes three cases of 21-trisomy, five cases of 18-trisomy, and two cases of X-trisomy. In another case where amniotic fluid cells are not cultured successfully, partial deletion and duplication of the short arm of chromosome 4 are detected by SNP-array, as shown in supplementary table 4.

Obstetrical outcomes

We subsequently followed up the pregnancy outcomes of 155 pregnant women with CHD fetuses. 61.9% (96/155) of the pregnant women continued their pregnancy, 38.1% (59/155) of the pregnant women terminated their pregnancy early, and one case of fetus intrauterine death, and the results of SNP-array detection shows partial deletion and duplication of the short arm of chromosome 4. We further analyze the causes of 59 cases of early termination of pregnancy, including 10 cases with abnormal chromosome number, 18 cases with pathogenic CNV, 5 cases with VOUS, and 28 cases with normal SNP-array detection results. Of the 28 cases, 6 cases are nonisolated CHD with structural abnormalities or soft markers. 22 cases are serious CHD, such as single atrium, single ventricle, endocardial cushion defect, hypoplastic left heart syndrome, tetralogy of Fallot, etc.

Discussion

We use SNP-array technique combined with karyotype analysis to detect chromosomal abnormalities in 155 CHD fetuses. Based on the above results, we clearly describe the types and distribution frequencies of chromosomal abnormalities in different CHD subtypes. Meanwhile, we compare the chromosomal abnormalities in isolated CHD and nonisolated CHD. The overall detection rate of pathological chromosomal abnormalities is 18.1%, among which 6.4% are chromosome number abnormalities. The likely pathogenicity of CNVs and VOUS is 2.5% and 5.2% respectively. In comparison with previous studies, we have reported slightly different rates of pathological chromosomal abnormalities and VOUS detection [7, 8].

In the past few years, chromosomal microdeletion and microduplication have been an important cause of CHD. Karyotype analysis combined with FISH technique is used for detection of 22q11[9]. However, karyotype analysis can only detect aneuploidy, and FISH technique has its limitations, which can only detect specific sites. Our study finds that compared with the karyotype, the detection rate of pathological CNVs increases by 10.3% (16/155) by SNP-array technique, which is consistent with the original study[10]. Karyotype analysis can be used to detect >10Mb chromosomal abnormalities, but the location and size of chromosome duplication or deletion cannot be determined based on karyotype. For pathological CNVs <10Mb, only SNP-array can be used for detection.

In clinical application, we find high pathological findings in complex CHD (31.2%), right ventricular outflow tract obstruction (30.7%), and conotruncal defects (25%). In addition, our results show that the incidence of chromosomal submicroscopic abnormalities in conotruncal defects is (25%, 7/28), among which 4 cases are all identified as tetralogy of Fallot, and the SNP-array results are all microdeletion of 22q11.21. Compared with the previous study, the detection rate of submicroscopic abnormalities in tetralogy of Fallot is 23.1% and that of ventricular septal defect is 5.8%, while our study show the ventricular septal defect is 15.5%, slightly different from the original report[11], which is mainly due to the difference in sample size between the two groups of studies and the inconsistent sample types.

It has been reported that the incidence of chromosomal abnormalities would increase when CHD is accompanied by additional structural abnormalities[12], which is consistent with our study. According to our results, the overall detection rate of CHD with extracardiac structural abnormalities is 52.4%. CHD with abnormal nervous system, abnormal urinary system and cleft lip were detected. This suggests that when CHD is accompanied by additional structural abnormalities, SNP-array detection is necessary to exclude chromosomal abnormalities.

In recent years, the correlation between prenatal ultrasound soft markers and CNVs has also been reported[13, 14]. We find that there is no significant difference in the overall detection rate of chromosomal abnormalities between CHD with soft indicators and isolated CHD. However, in our study, when accompanied by mild ventricular dilatation and choroid cyst, the detection rate of chromosomal abnormalities is slightly higher, and most of them are aneuploidy and >10Mb chromosomal abnormalities. Mild ventricular dilatation has been reported in the literature, which significantly increases the risk of chromosomal abnormalities, especially submicroscopic chromosomal abnormalities[15].

In this study, we observe that 28 patients with severe fetus CHD or accompanied by abnormal extracardiac ultrasound have early termination of pregnancy, but no chromosomal abnormality detected by SNP-array. This suggests that there are many other factors contributing to CHD, and we can conduct in-depth genetic studies, such as whole-exon sequence or whole-genome sequence[16].

This study analyzes the chromosomal abnormalities in different subtypes of CHD, and analyzes the differences of chromosomal abnormalities in isolated CHD, CHD with soft indicators, and CHD with extracardiac structural abnormalities. This has special clinical application value for genetic counseling and later invasive prenatal diagnosis. In addition, the SNP-array technique is used to analyze chromosomal abnormalities, which greatly reduces the reporting period compared with karyotype analysis. The limitation of this study is that the number of samples is still small, only 155 samples are detected. In later studies, the sample size needs to be further expanded to make the types of CHD more extensive, more comprehensive and more representative. In addition, the SNP-array technique cannot detect balanced translocations, inversion, and low-rate mosaicism, so patients should be informed of these limitations during genetic counseling.

In conclusion, our study confirms that SNP-array technology has a high resolution, short reporting cycle and reliable method for first-tier diagnosis of antenatal CHD fetuses.

Declarations

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Women and Children's Hospital Affiliated to Jiaxing University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Yuxia Jin and Huaxiang Shen conceived the study, participated to its design and coordination, and wrote the manuscript. Suping Li and Meidi Ni carried out the assays and participated to designing the study. Xiaodan Liu, Li Yang, Huling Jiang and Yue Hu carried out laboratory tests. Ping Tang, Jie Chen, Jing Yang and Qinqin Zhou prepared the figures and tables. All authors read and approved the final manuscript.

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Tables

Table 1 Chromosomal abnormalities in isolated CHD and nonisolated CHD

	Isolated CHD				Nonisolated CHD			
	Chromosomal abnormalities				Chromosomal abnormalities			
CHD classification	n	NCA	pCNV>10Mb	pCNV<10Mb	n	NCA	pCNV>10Mb	pCNV<10Mb
septal defects	34	2	0	2	24	3	1	1
Conotruncal defects	25	1	0	3	3	0	1	2
LVOTO	12	0	0	0	4	2	0	0
RVOTO	8	1	0	1	5	0	1	1
Valve incompetence	10	0	1	1	5	0	0	0
Complex CHD	11	0	0	2	5	0	2	1
Other CHD	6	0	0	2	3	1	0	0
Total	106	4	1	11	49	6	5	5

CHD,congenital heart disease;LVOTO,left ventricular outflow tract obstruction;RVOTO,right ventricular outflow tract obstruction;pCNV,pathogenic copy number variation;VI,Valve incompetence;DR,detection rate;NCA,numerical chromosomal abnormalities.

Table2 Chromosomal abnormalities in CHD with additional structural anomalies and CHD with soft markers

CHD with additional structural anomalies					CHD with soft markers			
CHD classification	Chromosomal abnormalities				Chromosomal abnormalities			
	n	NCA	pCNV>10Mb	pCNV<10Mb	n	NCA	pCNV>10Mb	pCNV<10Mb
Septal defects	8	1	1	1	16	2	0	0
Conotruncal defects	3	0	1	2	0	0	0	0
LVOTO	2	1	0	0	2	1	0	0
RVOTO	3	0	0	1	3	0	1	0
Valve incompetence	1	0	0	0	4	0	0	0
Complex CHD	4	0	2	1	1	0	0	0
Other CHD	0	0	0	0	2	1	0	0
Total	21	2	4	5	28	4	1	0

CHD,congenital heart disease;LVOTO,Left ventricular outflow tract obstruction;RVOTO,Right ventricular outflow tract obstruction;pCNV,pathogenic copy number variation;

Table 3 Chromosomal abnormalities in different Subgroups of CHD

Subgroups of CHD	n	Chromosomal abnormalities (%)
Septal defects	58	9 (15.5%)
Conotruncal defects	28	7 (25.0%)
Left ventricular outflow tract obstruction	16	2 (12.5%)
Right ventricular outflow tract obstruction	13	4 (30.7%)
Valve incompetence	15	2 (13.3%)
Complex CHD	16	5 (31.2%)
Other CHD	9	3 (33.3%)
Total	155	32 (20.6%)

CHD=congenital heart disease

Table4 The distribution of chromosomal abnormalities in isolated CHD and nonisolated CHD

CHD	n	Aneuploidy	pCNV>10Mb	pCNV<10Mb	Likely pathogenic CNVs	Known pathogenic findings	known pathogenic and likely pathogenic findings
Isolated CHD	106	4	1	11	4	12	16
CHD with soft markers	28	4	1	0	0	5	5
CHD with additional structural anomalies	21	2	4	5	0	11	11

Table5 Chromosomal abnormalities in CHD with soft markers

				Chromosomal	abnormalities
CHD with nonstructural anomalies	n	Total	Aneuploidy	pCNV>10Mb	pCNV<10Mb
CHD with single soft marker	25	5	4	1	0
Single umbilical artery	8	0	0	0	0
Mild ventriculomegaly	2	1	1	0	0
Echogenic bowel	1	0	0	0	0
Persistent right umbilical vein	3	0	0	0	0
Increased nuchal translucency	3	0	0	0	0
Choroid plexus cysts	6	3	2	1	0
echogenic intrahepatic	2	0	0	0	0
CHD with multiple soft markers	3	1	1	0	0

CHD,congenital disease ; pCNV,pathogenic copy number variation.

Table6 Chromosomal abnormalities in CHD with structural anomalies

				Chromosomal	abnormalities
CHD with additional structural anomalies	n	Total	Aneuploidy	pCNV>10Mb	pCNV<10Mb
CHD with single additional structural anomaly	18	10	2	3	5
Central nervous system	3	2	0	2	0
Urinary tract system	5	3	0	0	3
cleft lip and pallate	3	2	1	1	0
Gastrointestinal system	1	0	0	0	0
Skeletal system	2	0	0	0	0
Respiratory system	2	2	0	0	2
seroperitoneum	1	0	0	0	0
cyst cord	1	1	1	0	0
CHD with multiple additional structural anomalies	3	1	0	1	0

CHD,congenital disease ; pCNV,pathogenic copy number variation.

Figures

Figure 1

The detection rate of pathogenicity of SNP-array in the CHD types and the fetuses with CHD in different groups.

Figure 2

The detection rate of pathogenic chromosomal abnormalities is high in complex CHD (31.2%), right ventricular outflow tract obstruction (30.7%) and conotruncal defects (25%).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [1ThecasesofVOUS.xls](#)
- [2casesofpartialaneuploidy.xls](#)
- [3Casesofpathologicalmicrodeletionmicroduplication.xls](#)
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