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Chromosomal microarray analysis for the detection of chromosome abnormalities in fetuses with echogenic intracardiac focus in women without high-risk factors

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Abstract

To investigate the association between pathogenic copy number variants (p-CNVs) and abnormal karyotypes detected by chromosomal microarray analysis (CMA) and echogenic intracardiac focus (EIF).

This was a retrospective study of fetuses with EIF with CMA data at the Prenatal Diagnosis Center of the West China Second University Hospital of Sichuan University between September 2014 and May 2017. Fetuses were assigned to the isolated EIF and non-isolated EIF groups according to the presence of other ultrasound abnormalities.

Among 244 pregnant women, there were 143 cases of isolated EIF and 101 of non-isolated EIF. CMA revealed chromosome abnormality (n = 9 (3.7%): trisomy 21, n = 4; sexual trisomy, n = 2; and p-CNV, n = 3), variants of unknown significance (VOUS, n = 19), and benign CNV (b-CNV, n = 216). Among the fetuses with isolated EIF, 5 had chromosomal abnormalities (3.5%). Among the fetuses with non-isolated EIF, four had chromosomal abnormalities (4.0%). All fetuses with trisomy 21 were in the non-isolated group. The frequency of labor induction was 66.7% (6/9) among the fetuses with chromosome abnormality and 21.1% (4/19) among those with VOUS. Among those with chromosomal abnormalities, one (11.1%) had congenital heart disease.

In pregnant women without high-risk factors for chromosomal abnormalities, ultrasound abnormalities, including EIF, could be an indication for CMA. Ultrasound abnormalities (including EIF) and chromosome abnormality could indicate a high risk of CHD. The presence of EIF and at least another ultrasound abnormality could indicate a high risk of trisomy 21.

Abbreviations: xxxx.

Keywords: chromosomal micro-array analysis, copy number variant, echogenic intracardiac focus, karyotype, prenatal ultrasound

1. Introduction

Congenital disorders are conditions present at birth, regardless of the cause.[1,2] They may result in physical, intellectual, or developmental disabilities, ranging from mild to severe.[1,2] Birth defects can be divided into two main types: structural and functional.[1,2] In the United States, congenital abnormalities resulted in 632,000 infant deaths in 2013, of which the most common cause of death (n = 323,000) was congenital heart diseases (CHD).[3,4] Since birth defects may result in fetal death or fetuses developing secondary congenital diseases, prenatal diagnosis and screening are extremely important. Structural heart defects can be detected by prenatal ultrasound. The ultrasound at 11 to 14 weeks of gestation allows the early detection of major structural abnormalities and aneuploidy screening.[5]

Many structural birth defects are attributable to copy number variants (CNVs),[6] which are defined as the repetition or deletion of sections of the genome involving a considerable number of base pairs.[7] Although many CNVs are non-pathogenic and are part of the healthy genome, the others are associated with a variety of disorders, mainly through the copy number-dependent expression of specific proteins.[6] CNVs are thought to be involved in the pathogenesis of CHDs.[6,8–10]

At present, the common prenatal diagnosis techniques include karyotype analysis, chromosomal microarray analysis (CMA), and fluorescence in situ hybridization (FISH). Historically,

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karyotype has been the main method for the diagnosis of chromosomal abnormalities, but karyotype analysis requires viable amniocytes obtained invasively and cell culture, and its sensitivity is low for CNVs because of its maximal resolution of 5 Mbp.[11,12] CMA has a higher resolution than karyotyping, does not require cell culture, and the results are available faster.[12] Therefore, CMA is a useful tool for the prenatal diagnosis of chromosomal aberrations and CNVs.[12–14] Nevertheless, the variants of unknown significance (VOUSs) represent an ethical issue.[13,14]

An echogenic intracardiac focus (EIF) is a bright spot in the heart seen on fetal ultrasound due to calcium deposition in the heart muscle.[15] EIFs are found in 3% to 5% of normal pregnancies and cause by themselves no health problems.[16,17] They are more common in Asians.[16] It has been suggested that the presence of an EIF raises the risk of chromosomal abnormality in the fetus, most commonly trisomy 21.[18,19] EIF should be used to identify, rather than exclude, fetuses at high risk of trisomy 21,[17] indicating that further testing has to be done to confirm the presence of a chromosomal abnormality. The need for invasive prenatal diagnosis in the presence of an EIF is unknown.

Invasive prenatal diagnosis carries some risks for the pregnancy,[20] and the karyotype analysis is not sensible to small DNA changes.[21] In addition, the association between EIFs and chromosomal abnormalities is uncertain,[22,23] and CMA has many advantages over karyotyping.[12] Therefore, the objective of the present study was to investigate whether EIFs and maybe other ultrasound abnormalities are associated with an increased risk of chromosomal abnormalities pathogenic CNVs (p-CNVs) and abnormal karyotypes using CMA in women without high-risk factors. The results could provide support for whether further invasive diagnosis should be performed in the prenatal consultation.

2. Patients and methods

2.1. Study design and patients

This was a retrospective observational study of pregnant women with confirmed EIF and who underwent CMA at the Prenatal Diagnosis Center of the West China Second University Hospital of Sichuan University between September 2014 and May 2017. The study was approved by the Ethics Committee of West China Second University Hospital of Sichuan University (approval No. [2016] 29). Informed consent was waived because of the retrospective nature of the study.

The inclusion criteria were:

1) single birth (to ensure the accuracy of the sample);
2) the EIF, with or without other abnormalities, was observed by prenatal ultrasound (as per study objective, only women with fetuses with EIF were included); and
3) available CMA results (as per study objective, CMA results must be available for analysis).

The exclusion criteria were:

1) positive result of serum screening (fetus is at high risk for Down's syndrome, 18-triploidy and open neural tube defect by maternal serum prenatal screening at 16–20 weeks);
2) age ≥35 years;
3) history of frequent abortion and stillbirth with unknown reasons or delivery of babies with congenital defects;
4) history of congenital malformations; or
5) unable to complete the serum test for the parents.

2.2. Ultrasound

All women underwent prenatal ultrasound examination, performed by sonologists with a certificate in maternal and infant care and qualification for prenatal diagnosis. The examination standards were implemented in accordance with the guidelines for fetal ultrasound by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG).[24,25] When EIFs were observed, their number and location were recorded; scans of the fetal cardiac structure, other organ systems, placenta, umbilical cord, and amniotic fluid were performed to observe whether it was complicated by other ultrasound abnormalities. All fetuses with EIFs were assigned to the isolated EIF and non-isolated EIF groups, based on the presence or not of other US abnormalities. All examinations were performed using a Philips IU22, IU elite, or IE33 system (Philips, Best, The Netherlands), or a GE E8 or G9 system (GE Healthcare, Waukesha, WI), with the appropriate abdominal convex array probes with a frequency of 3.5 to 5 MHz.

2.3. Genetic examination

Routine genetic counseling was conducted in pregnant women and family members when a fetus was diagnosed with EIF. All patients included in this study freely consented to CMA. The CytoScan 750k chip (Affymetrix, Santa Clara, CA) was used for CMA, according to the manufacturer's instructions. The results were interpreted in relation to international public databases (DGV, Decipher, OMIM, ISCA, and PubMed). For the preliminarily identified VOUSs, further detection and comparison were performed in the parents.

2.4. Follow-up

All pregnant women with fetuses that tested positive for p-CNV or VOUS by CMA were routinely followed by outpatient visits or telephone calls. For the children, the development of body, movement, language, and intelligence were followed based on the evaluation from the pediatricians during their regular checkups after birth.

2.5. Statistical analysis

SPSS 16.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. Continuous variables were tested with the Kolmogorov-Smirnov test to determine their distribution. Normally distributed continuous variables are expressed as means ± standard deviation. Non-normally distributed continuous variables are expressed as medians (range). Categorical data are presented as frequencies and were analyzed using the Fisher exact test. P values $<.05$ were considered statistically significant.

3. Results

3.1. Characteristics of the women

During the study period, 45,793 pregnant women underwent ultrasound examination at our center; 1355 had ultrasound abnormalities and underwent CMA. Among them, 244 pregnant women had fetuses diagnosed with EIF and were included. Their

Table 1

Distribution of the chromosomal abnormalities in the fetuses.

	Abnormal karyotype	p-CNV	VOUS	b-CNV	*P*
All (n=244)	6 (2.5%)	3 (1.2%)	19 (7.9%)	216 (88.5%)	.276
Isolated EIF (n=143)	2 (1.4%)	3 (2.0%)	12 (8.4%)	126 (88.1%)	
Non-isolated EIF (n=101)	4 (4.0%)	0 (0%)	7 (6.9%)	90 (89.1%)	

EIF=echogenic intracardiac focus, p-CNV=pathologic copy number variant, VOUS=variant of undetermined significance.

mean age was 27.3 (range, 18–34) years. Their mean gestational age at ultrasound examination was 24.5 (range, 17–36) weeks.

3.2. Genetic screening

There were 6 fetuses (2.5%) with abnormal karyotypes, three (1.2%) with p-CNV, 19 with VOUS (7.9%), and 216 (88.5%) with benign CNV (b-CNV) (Table 1). The total frequency of chromosomal abnormality was 3.7% (9/244).

3.3. Association between EIF and EIF complicated with other abnormalities

The isolated EIF group included 143 fetuses, and the non-isolated EIF group included 101 fetuses (including 71 complicated by other ultrasound soft markers and 30 with structural abnormalities). There was no difference in the proportion of CMA results between the two groups ($P=.65$) (Table 1). Among the fetuses with isolated EIF, five had chromosomal abnormalities (3.5%). Among the fetuses with non-isolated EIF, four had chromosomal abnormalities (4.0%).

3.4. Characteristics of the fetuses with isolated EIF

Table 2 shows the distributions of the CNVs according to sex and location and the number of EIF. The distribution of the CNVs was not associated with fetus sex, location of EIF, and number of EIF (all $P>.05$).

3.5. Characteristics of the fetuses with p-CNV and abnormal karyotypes

The clinical data of the 9 fetuses with p-CNV and abnormal karyotypes are presented in Table 3. Among them, the frequency of labor induction was 66.7% (6/9). Four infants (44.4%) had trisomy 21, and 2 infants (22.2%) had sexual chromosome trisomy (XXY and XYY, respectively). The other 3 fetuses displayed various CNVs (Table 3). All fetuses with trisomy 21 had left heart EIF and at least another ultrasound marker or abnormality. Among the 9 fetuses with EIF and chromosome abnormality, one (11.1%) had CHD.

3.6. Characteristics of the fetuses with VOUS

The clinical data of the 19 fetuses with VOUS are presented in Table 4. Among them, the frequency of labor induction was 21.1% (4/19). Two infants showed a slight delay in language development.

4. Discussion

EIF should not be considered alone, and their exact clinical significance probably depends upon the presence of other factors. It has been suggested that EIF in fetuses at low risk of aneuploidy is not an indication for invasive procedures, and even in high-risk fetuses, the decision of an invasive procedure should be based on the calculated risk.[26] Studies suggested that EIFs, if found alone, do not indicate an increased risk of trisomy,[27,28] but that the presence of other ultrasound abnormalities or older maternal age could indicate a higher risk of trisomy.[18,28] Therefore, the aim of the present study was to investigate the association between p-CNVs and abnormal karyotypes detected by CMA and ultrasound abnormalities, including EIF. The results suggest that fetuses with ultrasound abnormalities, including EIF, could be a candidate for CMA. In pregnant women without high-risk factors for chromosomal abnormalities, ultrasound abnormalities, including EIF, could be an indication for CMA. Ultrasound abnormalities (including EIF) and chromosome abnormality could indicate a high risk of CHD. The presence of EIF and at least another ultrasound abnormality could indicate a high risk of trisomy 21.

In the present study, pregnant women with high-risk factors for chromosomal aberrations were excluded since they already had

Table 2

Distribution of the CNVs in the fetuses with isolated EIF.

	Abnormal karyotype	p-CNV	VOUS	b-CNV	*P*
Sex					
Male (n=81)	2 (2.5%)	0 (0%)	8 (9.9%)	71 (87.7%)	.096
Female (n=62)	0	3 (4.8%)	4 (6.5%)	55 (88.7%)	
EIF location					
Left ventricle (n=98)	2 (2.0%)	2 (2.0%)	6 (6.1%)	88 (89.8%)	.531
Right ventricle (n=6)	0	0	1 (16.7%)	5 (83.3%)	
Both ventricles (n=39)	0	1 (2.6%)	5 (12.8%)	33 (84.6%)	
Number of EIF					
1 (n=43)	2 (4.7%)	1 (2.3%)	4 (9.3%)	36 (83.7%)	.103
2 (n=56)	0	2 (3.6%)	7 (12.5%)	47 (83.9%)	
≥3 (n=44)	0	0	1 (2.3%)	43 (97.7%)	

EIF=echogenic intracardiac focus, p-CNV=pathologic copy number variant, VOUS=variant of undetermined significance.

Table 3

Clinical data of pediatric patients with p-CNV and abnormal karyotype.

Patient No.	Gender	Ultrasound	Other ultrasound soft marker	Other structural abnormalities	Results of CMA	Clinical outcomes
Isolated EIF						
1	F	One EIF at left ventricle	–	–	arr [hg19] 1q21.3(151515327-152652691) x3 (1137kb)	Full-term normal delivery, the height was in the normal lower limit
2	F	Two EIFs at left ventricle	–	–	arr [hg19] 7q11.23 (72697461-74154209)x1(1457kb) (WBS)	Labor induction
3	F	One EIF at each of left and right ventricle	–	–	arr [hg19] Xp22.31 (6455151-8152978) x1 (1698kb)	Full-term cesarean delivery
4	M	One EIF at left ventricle	–	–	XXY	Labor induction
5	M	One EIF at left ventricle	–	–	XYY	Loss to follow-up
Non-isolated EIF						
1	M	Two EIFs at left ventricle	Widening of posterior cranial fossa	–	Trisomy 21 (mosaic) (51%)	Labor induction
2	M	One EIF at left ventricle	Thickening of nuchal fold Long bone dysplasias Hypoplasia of nasal bone	–	Trisomy 21	Labor induction
3	M	Two EIFs at left ventricle	Hypoplasia of nasal bone	–	Trisomy 21	Labor induction
4	M	Multiple EIFs at left ventricle	Absence of nasal bone	Ventricular septal defect	Trisomy 21	Labor induction

CMA = chromosomal micro-array analysis, EIF = echogenic intracardiac focus, F = female, M = male, p-CNV = pathological copy number variant.

indications for invasive prenatal diagnosis.[29] For the women without high-risk factors but fetuses with ultrasound abnormalities, including EIF, whether further invasive examinations should be performed is unclear. The present study investigated the value of CMA in detecting fetal chromosome abnormalities among these pregnant women, thereby providing data to support prenatal consultation.

CMA can detect CNV and VOUS, which cannot be discovered by karyotype analysis. Regarding the 9 fetuses detected with chromosome abnormality and the 19 fetuses with VOUS, 6

Table 4

Clinical data of pediatric patients with VOUS.

No.	Gender	Ultrasound	Other ultrasound soft marker	Other structural abnormalities	Clinical outcomes
Isolated EIF					
1	M	One EIF at each of left and right ventricle	–	–	Full-term normal delivery
2	M	Two EIFs at left ventricle	–	–	Loss to follow-up
3	M	One EIF at right ventricle	–	–	Full-term normal delivery
4	M	One EIF at left ventricle Two EIFs at right ventricle	–	–	42 week+1 day cesarean delivery
5	M	One EIF at each of left and right ventricle	–	–	Full-term cesarean delivery
6	F	Two EIFs at left ventricle	–	–	Labor induction
7	F	One EIF at each of left and right ventricle	–	–	Full-term cesarean delivery
8	F	One EIF at left ventricle	–	–	Full-term cesarean delivery
9	F	One EIF at left ventricle			Full-term cesarean delivery, the language development showed slight delay
10	M	Two EIFs at left ventricle			Labor induction
11	M	One EIF at each of left and right ventricle			Full-term normal delivery
12	M	One EIF at left ventricle			Full-term cesarean delivery, the development of language and teeth showed slight delay
Non-isolated EIF					
1	F	One EIF at left ventricle	Tricuspid regurgitation	–	29 week+1 day fetal development stopped, labor induction
2	M	One EIF at left ventricle	Absence of nasal bone	–	Labor induction
3	M	One EIF at each of left and right ventricle	Separation of right renal pelvis	–	Full-term normal delivery
4	M	One EIF at left ventricle	Separation of bilateral renal pelvises	–	Full-term normal delivery
5	F	Two EIFs at left ventricle	Widening of posterior cranial fossa	–	Full-term cesarean delivery
6	M	One EIF at each of left and right ventricle	Tricuspid regurgitation	Ventricular septal defect	Full-term cesarean delivery
7	M	One EIF at left ventricle		Residual of left upper cavity	Full-term normal delivery

EIF = echogenic intracardiac focus, F = female, M = male.

(66.7%) and 4 (21.1%) women chose labor induction, respectively. Two infants with VOUS (10.5%) showed a slight delay in language development. The present study showed that the distribution of the CNVs was not associated with fetus sex, location of EIF, or number of EIF. Hence, these factors cannot be used to guide or refine the decision to perform invasive prenatal diagnosis or not, at least based on the present study. Additional research is necessary to improve the indications for invasive prenatal diagnosis.

Many ultrasound abnormalities, such as nuchal translucency and developmental defects, are considered as indications for prenatal screening.[30–32] EIF is considered as a soft ultrasound marker because it is an incidental finding in 3% to 5% of normal pregnancies, and is benign in most cases.[16,17] Of significance, 6 fetuses among the 244 (2.5%) with EIF were found to be with trisomy (four with trisomy 21 and 2 with sexual trisomy). Previous studies suggested that the presence of an EIF raises the risk of chromosomal abnormality in the fetus, most commonly trisomy 21.[18,19] On the other hand, the studies by Shanks et al,[23] Coco et al,[33] Mirza et al,[22] and Rochon et al[34] indicated that the presence of EIF does not increase the risk of trisomy 21 in fetuses without high-risk factors. Lorente et al[17] showed that EIF should be used to identify, rather than exclude, fetuses at high risk of trisomy 21, indicating that in the presence of EIF, further testing has to be done to confirm the presence of a chromosomal abnormality. In the present study, there was no difference in chromosomal abnormalities between fetuses with isolated EIF and those with EIF with another ultrasound abnormality. On the other hand, all fetuses with trisomy 21 had EIF and at least another ultrasound abnormality. Nevertheless, the conflicting results suggest that EIF cannot be used as an indication for prenatal screening, but the presence of EIF with another ultrasound abnormality could suggest prenatal screening. Future studies could examine novel ultrasound techniques[35,36] to describe those lesions in better ways that could perhaps reveal new or more refined associations between EIF and chromosomal abnormalities.

Accordingly, Dagklis et al[37] showed that EIF combined with other signs such as hyperechogenic bowel and hydronephrosis could play a role in trisomy 21 screening. In a study of 2647 fetuses with EIF, all cases of aneuploidy had left heart EIF,[38] as observed in the present study. Coco et al[33] also suggested that the presence of another abnormality along EIF should prompt amniocentesis. Additional studies are necessary to determine the diagnostic value of these signs.

The present study has limitations. First, the pregnant women included in this study were the patients who visited the outpatient department of our hospital because many of them were referred from other hospitals. This is a retrospective study in which the subjects are not as strictly selected and examined as in a prospective study. Many patients chose the CMA examination without karyotype analysis due to economic reasons and their own wills, introducing some bias. Second, as this was a retrospective study, no sample size calculation was performed, and all eligible patients during the study period were included. The number of cases was small, precluding any firm conclusion on the diagnostic value of EIF, p-CNV on CMA, and ultrasound abnormalities. Third, gestational age was 17 to 36 weeks, which is over the window for standard prenatal screening for many women. Because of the retrospective nature of the study, the exact reason for screening cannot be found in the charts of many women. Nevertheless, the reasons that could be found in some cases included the psychological comfort of the women or the physician willing to be conservative and to confirm suspicions. Multicenter studies with large numbers of patients are necessary to confirm these results. Finally, follow-up data was mostly lacking because many children were followed at local hospitals. Those data could not be formally analyzed and only the general comments in the pediatricians' consultations were available, preventing the observation of the long-term impact of EIF and CNVs on the development and health of the infants.

5. Conclusion

In pregnant women without high-risk factors for chromosomal abnormalities, ultrasound abnormalities, including EIF, could be an indication for CMA. Ultrasound abnormalities (including EIF) and chromosome abnormality could indicate a high risk of CHD. The presence of EIF and at least another ultrasound abnormality could indicate a high risk of trisomy 21.

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Author contributions

Min He, first author, is responsible for study design, fetal ultrasound examination and interpretation of image, collecting and analyzing the materials of the participants, article writing and revision. Zhu Zhang, is responsible for genetic examination and interpretation of results. Ting Hu, is responsible for genetic examination and interpretation of results. Shanling Liu, corresponding author, is responsible for overall design and quality control of study and article review.

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