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Evaluation of genetic variants using chromosomal microarray analysis for fetuses with polyhydramnios

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Abstract

Background: Polyhydramnios, the excessive accumulation of amniotic fluid, is associated with an elevated risk of abnormal karyotype, particularly aneuploidy. Studies focusing on chromosomal microarray analysis (CMA) in pregnancies with polyhydramnios are limited. The aim of this study is to evaluate the implications of pregnancy with polyhydramnios by CMA testing and routine karyotyping.

Methods: Data from 131 singleton and 17 twin pregnancies that underwent prenatal CMA testing due to polyhydramnios between May 2017 and May 2021 were reviewed. Enrolled cases were grouped into isolated polyhydramnios (N = 39) and non-isolated polyhydramnios (N = 111). Non-isolated group was further categorized as subgroup of soft markers (n = 59) and non-soft markers (n = 52).

Results: CMA revealed an additional 10 (6.7%) chromosomal aberrations with clinical significance in 9 fetuses from singleton pregnancies and 1 from a twin pregnancy. Six microdeletion/microduplication syndromes were observed, of which 4 were located on chromosome 17. The incremental yields of clinically significant CMA findings in non-isolated polyhydramnios was 8.1%, and the values in fetuses along with soft markers and non-soft markers were 5.1% and 11.5% ($p > 0.05$), respectively. Only one incidental finding related to neuropathy with liability to pressure palsies was detected from 39 fetuses with isolated polyhydramnios.

Conclusions: Non-isolated polyhydramnios is associated with several microdeletion/microduplication syndromes, regardless of singleton or twin pregnancies. Our results suggest insufficient evidence to recommend CMA in pregnancies with isolated polyhydramnios.

Background

Amniotic fluid is derived from the dialysate of maternal serum that enters the amniotic cavity through the fetal membranes, the exudate of fetal lungs, umbilical cord, Wharton's jelly and fetal skin, as well as fetal urine. In general, amniotic volume increases gradually with the gestation, increasing to about 1000 ml at 36 weeks of gestation and gradually decreasing thereafter. Appropriate amount of amniotic fluid can protect the fetus and the mother. Polyhydramnios refers to the situation that the amniotic fluid volume is more than 2000 mL during pregnancy, with an incidence of between 1–2% [1, 2]. The maximum depth of amniotic fluid (maximum vertical pocket depth, MVP) and amniotic fluid index (AFI) are used for ultrasonic assessment of amniotic fluid volume.

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The generally accepted definition of polyhydramnios is AFI above 24 cm or MVP above 8 cm [3, 4].

Polyhydramnios could be isolated or accompanied with other ultrasound anomalies. The etiology for polyhydramnios is complicated, with about 60% of them being idiopathic polyhydramnios of unexplained origin, 30% being caused by fetal disease, and the rest being caused by maternal disease and other factors [2]. Polyhydramnios was considered to be related to increased risk of chromosomal aberration mainly in the form of aneuploidy [5, 6]. Thus invasive prenatal testing is routinely recommended for abnormal karyotypes evaluation in many countries. The most frequently detected abnormalities were trisomy 21 and trisomy 18. However, the association between the risk of chromosomal aberrations and isolated polyhydramnios is controversial regarding routine karyotype testing. In last few years, chromosomal microarray analysis (CMA) has been widely applied in the field of prenatal diagnosis, especially for pregnancies with ultrasound anomalies [7–9]. However, studies focusing on the CMA results in pregnancies with polyhydramnios is limited [10, 11]. Therefore, we conducted a retrospective study based on the results of CMA testing and routine karyotyping in pregnancies with polyhydramnios, in order to evaluate the implication value of CMA in pregnancy with polyhydramnios.

Material and method

Patients and samples

The retrospective study reviewed 131 singleton pregnancies and 17 twin pregnancies that underwent prenatal CMA testing due to polyhydramnios, accompanied with or without other ultrasound abnormalities between May 2017 and May 2021 at the Medical Genetic Diagnosis and Therapy center of Fujian Maternal and Child Health Hospital, China. All the enrolled pregnant women did not have pregnancies of polyhydramnios before. Polyhydramnios was defined as amniotic fluid index above 24 cm or maximal vertical pocket above 8 cm. Pregnancies with maternal diabetes, isoimmunization, fetal infection, and twin pregnancies with twin-to-twin transfusion syndrome were not included in the study. Among the 17 twin pregnancies, 2 pregnancies showed polyhydramnios in both the twins, and in other 15 pregnancies, polyhydramnios occurred only in one of the twins. As a results, a total of 150 specimens including 81 cases of amniotic fluid and 69 cases of umbilical cord blood were sampled. According to the ultrasound findings, the enrolled 150 fetuses were classified into groups of isolated (N = 39) and non-isolated polyhydramnios (N = 111). Cases with non-isolated polyhydramnios were subgrouped into polyhydramnios associated with soft markers and structural abnormalities. The soft markers included thickened nuchal translucency, thickened nuchal fold, echogenic intracardiac focus, mild ventriculomegaly, choroid plexus cysts, echogenic bowel, mild hydronephrosis, mild tricuspid regurgitation, short femur length, aberrant right subclavian artery, absent or hypoplastic nasal bone, renal pelvis dilatation and single umbilical artery. The mean maternal age was 31 ± 4.7 years old, and the mean gestational age at the diagnosis of polyhydramnios was 27.4 ± 1.9 weeks. Demographic characters were presented in Table 1. The study was approved by the local Ethics Committee of Fujian Maternity and Child Health Hospital. Written informed consent to participate in the study was obtained from each patient.

DNA extraction and CMA platforms

Genomic DNA was extracted from uncultured amniotic fluid, fetal cord blood using a QIAGEN kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Single nucleotide polymorphism array (SNP array) was performed using Affymetrix CytoScan 750 K array (Affymetrix Inc., Santa Clara, CA, UA), which includes 200,000 probes for single nucleotide polymorphisms and 550,000 probes for copy number variations (CNVs) distributed across the entire human genome. Chromosome Analysis Suite software (Affymetrix) and human genome version GRCh37 (hg19) were used. A resolution was generally applied: gains or losses of ≥ 400 kb

Table 1 Demographic characters for 150 pregnancies with polyhydramnios

	Total (n = 150)	Isolated polyhydramnios (N = 39)	Non-isolated polyhydramnios (N = 119)
Maternal age (y): mean ± SD	30.5 ± 4.9	31.2 ± 5.2	30.2 ± 4.7
Gestation age at invasive testing (wk): mean ± SD	27.5 ± 3.6	26.3 ± 3.1	27.9 ± 3.7
Specimen			
AF n (%)	81 (54.0%)	31 (79.5%)	50 (45.1%)
CB n (%)	69 (46.0%)	8 (20.5%)	61 (54.9%)

AF, amniotic fluid; CB, cord blood

and regions of homozygosity (ROH) ≥ 10 Mb. Quality control was conducted by using the Median Absolute Pairwise Difference (MAPD) and SNP-QC score for copy number and SNP probes, respectively. Samples with MAPD > 0.25 and SNPQC < 15 for SNP array were excluded from the cohort. All CNVs were analyzed at the resolution of 100 kb of 50 markers and compared with in-house and national public CNV databases as follows: Database of Genomic Variants (DGV), Database of Chromosome Imbalance and Phenotype in Humans Using Ensemble Resources (DECIPHER), International Standards for Cytogenomic Arrays Consortium, and Online Mendelian Inheritance in Man (OMIM).

CMA data interpretation

The CNVs were classified into five groups according to the American College of Medical Genetics (ACMG) definitions [12] and local database: pathogenic, benign, likely pathogenic, likely benign, and variants of uncertain significance (VOUS). Pathogenic/likely pathogenic CNVs were considered clinically significant findings. Parental CMA was recommended to determine the inheritance of CNVs.

Routine karyotyping

Routine karyotyping consisted of cell culture and G-banded karyotyping was performed currently on cultured amniotic fluid and fetal cord blood according to the standard protocols in our laboratory. The karyotype was determined at a resolution of 320–500 bands level.

Statistical analysis

The data were analyzed using SPSS software v26.0 (SPSS Inc., Chicago, IL, USA). Statistical comparisons were performed using the chi-square test, and $p < 0.05$ was considered statistically significant.

Results

Among the 150 pregnancies with polyhydramnios, chromosomal aberrations were detected in 22 (14.7%) cases, including 3 cases of trisomy 21, 3 cases of trisomy 18, 9 cases of clinically significant CNVs, 3 cases of VOUS, 1 case of likely benign CNVs, and 3 cases of ROH with one of them being pathogenic. Therefore, the overall detection rate of clinically significant findings was 10.7% (16/150).

The distribution of clinically significant findings in isolated and non-isolated polyhydramnios pregnancies is summarized in Table 2, and the detailed results detected by CMA only are presented in Table 3.

In the isolated polyhydramnios group, one (2.6%) additional aberration by CMA was revealed. The only case showed a maternal 1.3 Mb deletion in the region of 17p12 (case 1, Table 2), which is related to neuropathy with liability to pressure palsies (HNPP) (#162500). The mother was prone to sprained ankles since the age of 35, and the child showed a normal phenotype before 4 years of age.

Table 2 Distribution of clinically significant CMA findings in fetuses with isolated and non-isolated polyhydramnios

	Karyotype-detectable		CMA-detectable only		Total (%)
	T21 (%)	T18 (%)	CNVs (P + LP) (%)	LOH (%)	
Isolated (N = 39)	0, 0.0	0, 0.0	1, 2.6	0, 0.0	1, 2.6
Non-isolated(N = 111)	3, 2.7	3, 2.7	8, 7.2	1, 0.9	15, 13.5
soft markers (n = 59)	1, 1.7	0, 0.0	3, 5.1	0, 0.0	4, 6.8
Non-soft markers (n = 52)	2, 3.8	2, 3.8	5, 9.6	1, 1.9	10, 19.2
Total	3, 2.0	3, 2.0	9, 6.0	1, 0.7	16, 6.7

T21, trisomy 21; T18, trisomy 18; CNVs, copy number variants; P, pathogenic; LP, likely pathogenic; LOH, loss of heterozygosity

In the non-isolated group, the overall rate of clinically significant findings was 13.5% (15/111), which was not significantly higher than that in the isolated group ($p > 0.05$). The incremental yields of clinically significant results by CMA was 8.1% (9/111), including 8 cases of CNVs and 1 case of ROH. As shown in Table 3, 8 cases of CNVs (case 2–9) sized from 994 kb to 10.4 Mb, were detected in the non-isolated group, of which 5 were related to clinical syndromes: Smith-Magenis syndrome (#182290, case 3), Miller-Dieker syndrome (#247200, case 5), DiGeorge syndrome (#611867, case 6), 17q12 microdeletion syndrome (#614527, case 8), and Potocki–Lupski syndrome (#610883, case 9). In addition to CNVs, CMA yielded 1 case (case 10) of uniparental disomy (UPD). The case harbored a ROH of 19.2 Mb in region 15q14q21.3, which was finally confirmed to be composed of segmental UPiD and UPhD using the UPDtool. As a result, maternal UPD (15) related to Prader–Willi syndrome (PWS, #176270) was diagnosed, and the pregnancy was terminated. In this group, the incremental yields of clinically significant findings in pregnancies with soft markers and non-soft markers were 5.1% and 11.5%, respectively ($p > 0.05$).

Among the 19 fetuses with polyhydramnios from 17 twin pregnancies, 1 fetus demonstrated pathogenic CNVs (duplication on 17p12p11.2), which was related to Potocki–Lupski syndrome (case 9, Table 3). In addition to polyhydramnios, the fetus had aberrant right subclavian artery, and talipes; the other fetus of the twins had a normal ultrasound and normal CMA results. At the

Table 3 Clinically significant CMA findings and ultrasound details in pregnancies with polyhydramnios and normal karyotype

Case Number	Gestational age (weeks)	Ultrasound findings	CMA results	Size	Inheritance	Pathogenicity category	Associated syndrome	Outcome
1	23+	Polyhydramnios	arr[GRCh37] 17p12(14,099,504–15,491,533) × 1	1.3 Mb	mat	Pathogenic	Hereditary Neuropathy With Liability to Pressure Palsies	Normal phenotype at 4-year-old follow-up
2	32+	Polyhydramnios, umbilical artery atresia	arr[GRCh37] 2q13(111,397,949–113,142,794) × 1	1.7 Mb	dn	Likely pathogenic	NV	Live birth with normal phenotype
3	34+	Polyhydramnios, ventricular septal defects, persistent left superior vena cava, nasal bone dysplasia	arr[GRCh37] 17p11.2(16,727,4900–20,433,723) × 1	3 Mb	dn	Pathogenic	Smith-Magenis Syndrome	TOP
4	19+	Polyhydramnios, pulmonary stenosis, strawberry like head, nuchal cystic lymphangioma	arr[GRCh37] 1p32 .1p31.1(60,575,608–71,024,736) × 3	10.4 Mb	dn	Pathogenic	NV	TOP
5	26+	Polyhydramnios, bilateral ventriculomegaly, talipes	arr[GRCh37] 17p13.3p13.2(525–5,768,789) × 1	5.7 Mb	nd	Pathogenic	Miller-Dieker Syndrome	TOP
6	31+	Polyhydramnios, aberrant right subclavian artery	arr[GRCh37] 22q11.21(18,916,842–21,800,471) × 1	3.1 Mb	dn	Likely pathogenic	DiGeorge Syndrome	TOP
7	24+	Polyhydramnios, nasal bone dysplasia	arr[GRCh37] 16p12.2(21,816,542–22,710,614) × 1	994 Kb	dn	Likely pathogenic	NV	Live birth with normal phenotype
8	28+	Polyhydramnios, Hyperechogenic kidneys	arr[GRCh37] 17q12(34,822,465–36,404,555) × 1	1.58 Mb	dn	Likely pathogenic	17q12 Microdeletion Syndrome	Normal development at 3-year-old follow-up
9	25+	Twin pregnancy, polyhydramnios, right foot varusaberrant right subclavian artery	arr[GRCh37] 17p12p11.2(15,759,453–20,547,625) × 3	4.7 Mb	nd	Pathogenic	Potocki-Lupski Syndrome	ADHD, language disability at 3-year-old follow-up
10	32+	Polyhydramnios, FGR,VSD	arr[GRCh37] 15q14q21.3(35,077,111–54,347,324) hmz	19.2 Mb	mat upd	Pathogenic	Prader-Willi Syndrome	TOP

dn, de novo; nd, not detected; NV, not available; TOP, termination of pregnancy; FGR, fetal growth restriction; ADHD, attention deficit hyperactivity disorder; VSD, ventricular septal defect

3-year-old follow-up, the parents of the child with pathogenic CNVs mentioned that the child has attention deficit hyperactivity disorder (ADHD) and language disability.

Discussion

In the past few years, CMA testing has been widely applied during prenatal development, especially for pregnancies with abnormal ultrasound findings [8, 13, 14]. In fetuses with ultrasound anomalies, CMA can detect an additional 5.2–10% of clinically significant aberrations compared to that by conventional karyotyping [14–16]. However, to the best of our knowledge, few studies have examined the association between polyhydramnios and genetic anomalies according to CMA analysis. Previous studies exploring the relationship between polyhydramnios and conventional karyotyping showed a 2.8% ± 3.7% pooled prevalence of chromosomal aberrations in pregnancies with idiopathic polyhydramnios, associated mainly with trisomy 21 and trisomy 18 [5, 6]. In our study, trisomy 21 and trisomy 18 were the only 2 chromosomal abnormalities detected by traditional karyotyping in non-isolated polyhydramnios pregnancies, and their overall incidence was 2.0%. These were detected in all fetuses of polyhydramnios, together with additional ultrasound abnormalities, especially structural abnormalities. Thus, aneuploidy was more likely to be detected when polyhydramnios was found in combination with additional ultrasound. A recent study with a large cohort of pregnancies with polyhydramnios undergoing CMA testing showed an additional 2.7% clinically significant abnormalities by CMA compared to that by conventional karyotyping [10]. In our present study, the incremental yield by CMA in isolated polyhydramnios group was 2.6%, similar to the 8.1% in the non-isolated group. With regard to the frequency of additional clinically significant findings within the non-isolated group, pregnancies with structural abnormalities were higher than pregnancies with soft markers, although not statistically significant. Therefore, CMA testing plays an important role in the etiological analysis of polyhydramnios, regardless of the presence of other ultrasound abnormalities.

Among the 10 additional clinically significant anomalies detected by CMA, 5 cases of CNVs were found on chromosome 17, including 17p12, 17p11.2, 17p13.3p13.2, and 17q12 deletions and 17p12p11.2 duplication, and they were related to HNPP, Smith–Magenis syndrome, Miller–Dieker syndrome, 17q12 microdeletion syndrome, and Potocki–Lupski syndrome, respectively. Among them, 17q12 microdeletion was more frequently reported in pregnancies with polyhydramnios [17–19]. Inefficient expression of *HNF1B* in the region of 17q12 is known to be a predominant factor leading to renal disease, which may result in fetal polyuria and polyhydramnios. The most common ultrasound finding in fetuses with 17q12 deletion was hyperechogenic kidneys [20], which was also present in our case. Thus, a view has been proposed when hyperechogenic kidney and polyhydramnios were observed prenatally, a possible diagnosis of 17q12 deletion should be considered [18, 19]. The 17q12 deletion is thought to be one of the most common microdeletions found in children with unexplained developmental delay [21] and may be associated with learning difficulties and autism [22, 23]. The child in our study manifested a normal phenotype at the 3-year-old follow-up, but long-term follow-up is still needed to accurately assess the prognosis. In addition to CNVs, a ROH of 15q14q21.3 detected in a polyhydramnios fetus with FGR was confirmed to be maternal UPD (15), which would result in PWS. Gross et al. [24] reported polyhydramnios in 43% of PWS pregnancies and a combination of polyhydramnios and FGR in 34% of PWS pregnancies. Geysenbergh et al. reported prenatal data of 11 children who were diagnosed with PWS and suggested that the combination of severe growth restriction and polyhydramnios can prompt clinicians to perform invasive tests for PWS diagnosis [25]. The only aberration detected in fetuses with isolated polyhydramnios was a maternal 1.3 Mb deletion on 17p12, which is a well-known pathogenic aberration related to HNPP. HNPP generally manifested as nerve disease after the second or third decade [26], and it has never been reported in previous reports of polyhydramnios. Therefore, the deletion was not a causative but an incidental finding.

Of note, most previous studies did not include twin pregnancies because of potentially confounding factors. In the present study, one or two fetuses with polyhydramnios from twin pregnancies without apparent twin-to-twin transfusion syndrome were included. In a pair of twins, one fetus with polyhydramnios developed an aberrant right subclavian artery and talipes and was revealed to have a duplication of 17p12p11.2 related to Potocki–Lupski syndrome, while the other fetus had normal ultrasound and CMA results. Potocki–Lupski syndrome is known to be associated with multiple congenital abnormalities, including developmental delays, autistic features, and certain structural anomalies, with cardiovascular being the most common [27, 28]. Both aberrant right subclavian artery and talipes have been previously reported in cases of PTLS [29–31], but polyhydramnios has not been reported before. The abnormal phenotype of ADHD and language disability after birth confirmed the diagnosis of Potocki–Lupski syndrome.

We acknowledged the following limitations of this study. First, the sample size was small, especially in the isolated group. Second, owing to missing data regarding the AFI/MVP, we could not perform an analysis

on the risk of clinically significant CMA aberrations according to different degrees of polyhydramnios.

In conclusion, non-isolated polyhydramnios is associated with several genetic syndromes involving aneuploidy syndrome, microduplication syndrome, and microdeletion syndrome. CMA testing should be recommended in pregnancies with non-isolated polyhydramnios regardless of singleton or twin pregnancies. Our limited results suggest insufficient evidence to recommend CMA in pregnancies with isolated polyhydramnios.

Abbreviations

CMA: Chromosomal microarray analysis; MVP: Maximum vertical pocket depth; AFI: Amniotic fluid index; CNVs: Copy number variations; DGV: Database of Genomic Variants; VOUS: Variants of uncertain significance; ROH: Loss-of heterozygosity; UPD: Uniparental disomy; TOP: Termination of pregnancy; FGR: Fetal growth restriction; ADHD: Attention deficit hyperactivity disorder; VSD: Ventricular septal defect.

Supplementary Information

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Additional file 1. Details of all 150 pregnancies with polyhydramnios.

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Author contributions

XW, YL and LS prepared the original draft; BL, MC, XX and NL prepared the experiment; DG and QS conducted data analysis and prepared Tables 1, 2, 3. LX and HH revised the manuscript. All authors have reviewed and approved the final article.

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Availability of data and materials

All data generated or analysed during this study are included in this published article and its Additional file 1.

Declarations

Ethics approval and consent to participate

All experiments were performed in accordance with relevant guidelines and regulations.

The present study was approved by the Protection of Human Ethics Committee of Fujian Provincial Maternity and Children's Hospital, affiliated Hospital of Fujian Medical University. Written informed consent was obtained from individual or guardian participants.

Consent for publication

All participants provided informed consent and they agreed to publish their clinical data.

Competing interests

The authors declare no competing interests.

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