Archives of Gynecology and Obstetrics (2019) 300:633–639
https://doi.org/10.1007/s00404-019-05235-4

MATERNAL-FETAL MEDICINE

Subchromosomal anomalies in small for gestational-age fetuses and newborns

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Received: 9 January 2019 / Accepted: 27 June 2019 / Published online: 4 July 2019

Abstract

Purpose To analyze copy number variants (CNVs) in subjects with small for gestational age (SGA) in China.

Methods A total of 85 cases with estimated fetal weight (EFW) or birth weight below the 10th percentile for gestational age were recruited, including SGA associated with structural anomalies (Group A, $n=20$) and isolated SGA (Group B, $n=65$). In all cases, cytogenetic karyotyping and infection screening were normal. We examined DNA from fetuses (amniocentesis or cordocentesis) and newborns (cord blood) to detect CNVs using a single nucleotide polymorphism (SNP, $n=75$) array or low-pass whole-genome sequencing (WGS, $n=10$).

Results Of 85 total cases, 3 (4%) carried pathogenic chromosomal abnormalities, including 2 cases with pathological CNVs and 1 case with upd(22)pat. In Group A, the mean gestational age at the time of diagnosis was 26.8 (SD 4.1) weeks and mean EFW/birth weight was 907.2 (SD 567.8) g. In Group B, the mean gestational age at the time of diagnosis was 34.1 (SD 5.8) weeks. Mean EFW/birth weight was 1879.2 (SD 714.5) g. The pathologic detection rate was 10% (2/20) in Group A and 2% (1/65) in Group B. It was inclined that the lower the EFW percentile, the more frequent the occurrence of CNVs.

Conclusions Pathological subchromosomal anomalies were detected by CMA or low-pass WGS in 10% and 2% of SGA subjects with and without malformation, respectively. SGA fetuses with structural anomalies presented with higher pathological subchromosomal anomalies. The molecular genetic analysis is not recommended for isolated SGA pregnancies without other abnormal findings.

Keywords Copy number variations · Small for gestational age · Single-nucleotide polymorphism array · Whole-genome sequencing

Introduction

The association of small-for-gestational-age (SGA) fetuses with chromosomal abnormalities, especially trisomy 18 is well established [1, 2]. However, there is still an ongoing debate regarding whether copy number variants (CNVs) detected by molecular genetic tests such as chromosomal microarray analysis (CMA) are more common in fetuses with SGA. Biron-Shental et al. [3] used single-nucleotide polymorphism (SNP) arrays to detect CNVs in placentas from small fetuses with normal anomaly scans and karyotypes and healthy neonates. The authors identified significantly more genomic alterations in small fetal group and a significant correlation between the size of the CNVs and the severity of growth restriction [3]. Borrell et al. [4] examined fetuses with isolated fetal growth below the 3rd centile and with a normal cytogenetic karyotype, pathological

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genomic imbalances were found in 4% of the cases. This rate was increased to 10% in those small fetuses' cases with additional defects [4]. A multicenter study revealed that after exclusion of aneuploides, in fetuses with early growth retardation (estimated fetal weight below the 3rd percentile before 32 weeks of pregnancy), pathogenic CNVs were detected in 4.8%, 10%, and 10.5% of subjects having isolated SGA, SGA with minor congenital anomalies and SGA with major congenital anomalies, respectively [5].

Ongoing research is focused on the extension of molecular genetic testing to whole-exome and -genome sequencing. To date, experience with these methods is still limited, but in approximately 23–50% of cases with normal cytogenetic and CMA results, whole-exome sequencing revealed a chromosomal abnormality [6, 7]. Others have reported a 16% incremental CNVs yield by genome-wide screening in infants with prenatal and postnatal growth retardation associated with dysmorphic features and/or developmental delay [8]. However, the high cost of WES and WGS limits their wide use in clinical practice. CNVs is still one of screening methods with reasonable cost-effect.

In this study, we examined the proportion of pathogenic subchromosomal anomalies in pregnancies with SGA fetuses with and without structural defects, to investigate clinical value of CNVs screening in both groups of SGA fetuses.

Methods

Patients

Outpatient and inpatient singleton pregnant women treated at Beijing Obstetrics and Gynecology Hospital of Capital Medical University between 2014 and 2016 were selected for this study. Gestational age (GA) was assessed according to the last menstrual period and the crown-rump length at 11–13 + 6 weeks. All these cases underwent a detailed ultrasound examination according to the practice guidelines of the International Society of Ultrasound in Obstetrics and Gynecology to detect structural anomalies. Fetal weight was estimated (EFW) according to the Hadlock II formula [9]. An EFW or birth weight below the 10th percentile for GA was defined as SGA [10, 11]. An assessment of the maternal infection status (standard TORCH serology including Parvo virus B19) was performed in all cases. Furthermore, invasive testing including cytogenetic karyotyping and CNVs detection was recommended prenatally. In cases the parents opted against invasive testing, above genetic examinations were carried out after birth if requested. CNVs was detected using CMA from 2014 to 2015, whereas in 2016 they were identified by new generation sequencing (NGS), named low-pass whole genome sequencing(WGS).

Maternal and pregnancy characteristics and the results of the antenatal examinations are entered into a digital database (Excel 2007, Microsoft, Richmond, USA). Data of pregnancy outcome were followed up and were added after delivery.

The study cohort includes women with SGA pregnancies between 2014 and 2016 where first, cytogenetic karyotyping and infection screening were uneventful, second, where a CMA or a low-pass WGS was done and third, who agreed to participate in the study.

Molecular genetic follow-up examinations

From 2014 to 2015, CMA technology was used. To detect CNVs the CytoScan™ 750D array (Affymetrix Inc., Santa Clara, CA, USA) was used in combination with the CytoScan™ 750D Reagent Kit. One array was used for each sample. The results were analyzed with Chromosome Analysis Suite (ChAS) software (Affymetrix, USA) using annotations of the genome version GRCH37 (hg19). The array detects the sample at the resolution level of 50 kb/50 marker deletion and 100 kb/50 marker repeat.

In cases in which CNVs were detected in fetal or neonatal DNA, DNA from the parents (peripheral blood) was examined using the same CytoScan™ 750D array to detect CNVs and establish whether the CNVs were de novo or inherited.

In 2016, CNVs were detected by NGS technique, named low-pass whole genome sequencing (WGS). The DNA library was prepared and subjected to deep sequencing using a NextSeq CN500 high-throughput sequencer. The detection sensitivity of low-pass WGS is 100 kb.

If Uniparental disomy (UPD) was detected, then linkage analysis by polymerase chain reaction (PCR)-based Sequence-Tagged Site (STS) marker showed which one the segmental isodisomy was of parental origin.

The URLs for data presented herein are as follows:

- Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER), https://decipher.sanger.ac.uk/application/.
- Database of Genomic Variants (DGV), https://projects.tcag.ca/variation/.
- Database of Genotype and Phenotype, dbGaP, https://www.ncbi.nlm.nih.gov/gap.
- Database of Structural Variation, dbVAR, https://www.ncbi.nlm.nih.gov/dbvar/.
- International Standard Cytogenomic Array Consortium, https://isca.genetics.emory.edu.
- Online Mendelian Inheritance in Man (OMIM), https://www.ncbi.nlm.nih.gov/Omim.

All analysis results of CNVs and genes in this study were interpreted by professionally certified clinical

molecular geneticists or genetic experts. Pathological CNVs were assessed if they met the following criteria: gene content, overlap with genomic coordinates for a known genomic imbalance syndrome, and overlap with a CNVs previously identified in FGR or short stature subjects.

CNVs were classified according to the recommendation of the American College of Medical Genetics Laboratory Quality Assurance Committee (REF) as: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign [12], and variants of uncertain clinical significance (VOUS). This study did not include benign CNVs, pathogenic and likely pathogenic were considered as an abnormal result.

Statistical methods

The SGA pregnancies were grouped according to the presence (Group A) or absence of fetal defects (Group B). Continuous variables are expressed as the mean [standard deviation (SD)]. Categorical variables were represented as n (proportion). In each group, we calculated the proportion of chromosomal defects identified by CMA or by low pass WGS. Significant differences are identified by comparing confidence intervals using the Clopper–Pearson method. Data analysis was performed using SPSS 22.0 software (IBM) for Windows (IBM Corp., Armonk, NY, USA).

Results

Clinical features

The study enrolled 85 pregnancies. There were 20 cases with a fetal defect (Group A) whereas in 65 cases, there was isolated SGA (Group B). All families were of nonconsanguineous marriages, and the women had no history of infection or exposure to adverse environments. The parents of the enrolled subjects were all of the Han ethnicity, and their phenotypes were normal. Table 1 summarizes the maternal and pregnancy characteristics of the two study groups.

Diagnostic yield

Of all cases (Group A and Group B), 13 (15%) cases had CNVs less than 10 Mb, and CNVs > 500 kb were detected in 7 (8%) cases. In 2 cases, the results showed pathological or likely pathological CNVs (1 case in each group), whereas 11 fetuses carried VOUS (9 cases in Group A and 2 cases in Group B). Moreover, 1 case with upd(22)pat was identified in Group B.

In Group A, 2 (10%) fetuses had a pathological chromosomal abnormality. In one case, a pathological microdeletion syndrome (4p16.3) was found that causes Wolf–Hirschhorn Syndrome, whereas in the other case, UPD on chromosome 22 [upd(22)pat] in 1 fetus associated with Dandy–Walker malformation was detected (CNVs are

Table 1 The maternal and pregnancy characteristics of the two study populations

Statistical indicators	Group A (SGA with fetal defects, $n=20$)	Group B (SGA without defects, $n=65$)
Age	26–38 years old, 32.00 ± 4.34 years old	21–42 years old, 31.46 ± 4.34 years old
Pregnancy outcome		
Induced labor	13 cases (65%)	0 case (0%)
Fetal death	1 case (5%)	2 case (3%)
Newborns got	6 case (30%)	63 cases (97%)
Delivery gestational weeks	24–41 weeks, 33.00 ± 6.37 weeks	29–41 weeks, 37.16 ± 2.38 weeks
Birth weight	440–2575 g, 1570.56 ± 770.04 g	1000–2720 g, 2211.13 ± 416.05 g
Prenatal testing		
Serological examination for Down syndrome screening	Low-risk, 2 cases, (10%) High-risk, 0 case, (0%)	Low-risk, 50 cases (77%) High-risk, 3 case (5%)
NIPT	Low-risk, 5 cases (25%)	Low-risk, 10 cases (15%)
Prenatal diagnosis		
Amniocentesis	6 cases (30%)	9 cases (14%)
Cordocentesis	7 case (35%)	1 case (2%)
Pregnancy complications		
Uterine fibroids	1 cases (5%)	4 cases (6%)
Pregnancy hypertensive disorder	3 cases (15%)	18 cases (28%)
GDM or DM	2 cases (10%)	11 cases (17%)
Hypothyroidism	7 cases (35%)	7 cases (11%)

Table 2 CNVs in SGA with malformation (Group A)

No	Ultrasound	Test results (hg19)	CNV and size	Verification
1	Kidney dysplasia Single umbilical artery	4p16.3 (68,345–3,328,887)×1	Del 3.2 Mb	Pathogenic WHS (de novo)
2	Increased NF	8q13.3 (72,210,736–72,220,009)×1	Del 9.2 Kb	VOUS
3	Dandy–Walker	Upd(22)		Upd(22)pat
4	Increased NT Fetal edema hydramnios	Xp21.1 (31,691,101–31,844,706)×1	Del 153 Kb	VOUS
5	Short limbs, fetal edema, hydrothorax and ascites	Normal		
6	Fallot	Normal		
7	Hyperechoic right ventricle (myxoma?)	Normal		
8	Small chest, coarctation of the aorta, short limbs	Normal		
9	Ventricular deficiency	Normal		
10	Short limbs	Normal		
11	Cerebellar vermis deletion	Normal		
12	Duodenal atresia	Normal		
13	Single umbilical artery, single kidney?	Normal		
14	Ventricular deficiency, double kidney enlargement	Normal		
15	Cryptorchism	Normal		
16	Hypospadias	Normal		
17	Hypospadias	Normal		
18	Hypospadias	Normal		
19	Accessory auricle	Normal		
20	Right foot syndactylia	Normal		

shown in Table 2). And in Group A, the mean GA at the time of diagnosis was 26.8(SD 4.1) weeks and mean EFW/birth weight was 907.2 (SD 567.8) g. In 17 cases, a CMA analysis was carried out and in 2 cases, the result was pathological or likely pathological. In the remaining cases, the molecular genetic analysis involved low-pass WGS and in none of the cases, the result was abnormal. In summary, in this group, molecular genetic testing was abnormal in 2 of 20 cases [10.0% (95% 1.2–31.7%)]. Figure 1 gives the

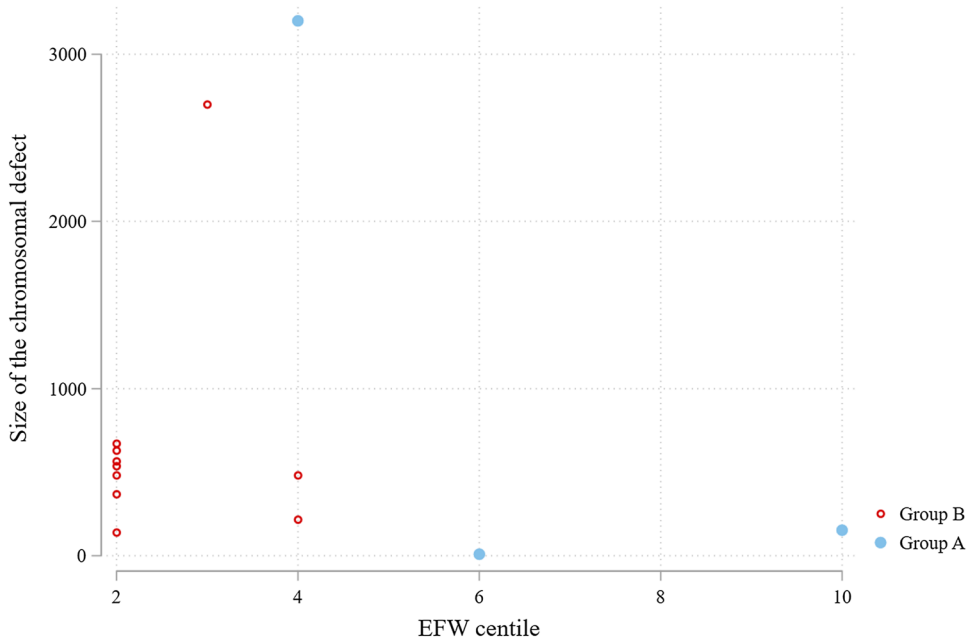

Fig. 1 EFW centile on the *x* axis, size of the chromosomal defect on the *y*-axis. Group A and B were shown in the graph with blue and red colors, respectively

situation of the chromosomal defect (abnormal CNVs and VOUS) and the EFW/ birth weight centile.

In Group B, 10 (15%) cases presented 11 CNVs, ranging from 217.0 kb to 2.7 Mb. 1 (2%) fetus with birth weight below the 3rd percentile and postnatal developmental delay showed a pathogenic CNVs. Microdeletions found in this fetus overlapped with a known pathological CNVs (9q34.3), and these subjects were diagnosed with Kleefstra syndrome (CNVs are shown in Table 3). And in Group B, the mean GA at the time of diagnosis was 34.1 (SD 5.8) weeks. Mean EFW/ birth weight was 1879.2 (SD 714.5) g. In 58 (89%) and 7 (11%) pregnancies, the molecular genetic analysis involved CMA and Low-pass WGS, respectively. The analysis classified as pathological or likely pathological in the former was 1 case (2%) and 0 case in the latter, respectively. Thus, the overall proportion of abnormal test results was 2.0% (95% CI 0.2–10.5%). Figure 1 demonstrates the situation of the chromosomal defect (abnormal CNVs and VOUS) and the EFW/birth weight centile.

Discussion

The American College of Obstetricians and Gynecologists guidelines were published in 2013, in which CMA is allowed to replace a G-banded karyotyping when fetal ultrasound

Table 3 Situation of CNV of isolated SGA (Group B)

No. test results	CNV	Involved genes	Verification
21			
9q34.3 (140,388,330−141,018,648)×1	Del 630.3 Kb	PNPLA7, MRPL41, DPH7, ZMYND19, EHMT1, CACNA1B	Pathogenic Kleefstra (de novo)
22			
2q22.1 (137,860,001−138,000,000)×1	Del 140 Kb	THSD7B	VOUS (de novo)
23			
Xp22.11 (24,332,336−24,898,275)×3	Dup 565.9 Kb	PDK3, PCYT1B, POLA1	Likely benign (heredity-mat)
24			
8q22.2 (99,991,771−100,360,830)×1	Del 369.0 Kb	VPS13B gene fragment, span 1–19 exons	VOUS
25			
1q21.2 (147,277,333−147,814,497)×3	Dup 537.1 Kb	GJA8, GPR89B, NBPF11, NBPF8	Likely benign (heredity-mat)
26			
2q13 (110,498,141−110,980,295)×3	Dup 482.1 Kb	NPHP1, RGPD6, MALL	VOUS (heredity-mat)
27			
Yq11.23 (27,007,371−27,224,389)×0	Del 217.0 Kb	DAZ3, DAZ2	Likely benign (heredity-pat)
28			
2q13 (110,498,141−110,980,295)×3	Dup 482.1 Kb	NPHP1, RGPD6, MALL	VOUS
29			
3q13.13q13.2 (110,890,975−111,563,344)×3	Dup 672.3 Kb	NECTIN3, CD96, ZBED2, PLCXD2, PHLDB2,	Likely benign (heredity-mat)
8q13.3 (72,210,734−72,220,009)×0	Del 9.2 Kb	EYA1 gene fragment	Benign (heredity-mat)
30			
8p23.2 (3,685,300−5,935,671)×3	Dup 2.2 Mb	CSMD1	Likely benign (heredity-mat)
19p13.2 (10,467,488−13,218,411)×1	Del 2.7 Mb	TYK2, CDC37, PDE4A, KEAP1, S1PR5, ATG4D, CDKN2D, AP1M2, SLC44A2), ILF3, QTRT1, DNM2, MIR199A1, TMED1, CARM1, SMARCA4, LDLR, SPC24, KANK2, DOCK6, RAB3D, TMEM205, SWSAP1, EPOR, PRKCSH, ELAVL3, ZNF653, ECSIT), CNN1, ACP5, ZNF627, ZNF69, ZNF20, ZNF136, ZNF44, ZNF443, MAN2B1, DHPS, FBXW9, TNPO2, ASNA1, BEST2, HOOK2, JUNB, PRDX2, RNASEH2A, RTBDN, MAST1, DNASE2, KLF1, GCDH, SYCE2, FARSA, CALR, RAD23A, GADD45GIP1, DAND5, NFIX, LYL1, TRMT1, EYA1 gene fragment, span exons 8 and 9	VOUS

anomalies are detected [13]. Pathogenic or likely pathogenic CNVs were detected in 6–7% of fetuses with normal karyotyping but with structural abnormalities found by ultrasound [14, 15]. Subjects with more abnormal structural findings had a greater rate of detection of chromosomal anomalies [16]. In the case associated with small fetal weight, an incremental yield of 6.1% over karyotyping was detected by CMA [17]. In our study of SGA cases with structural malformation, the detection rate of pathological chromosomal abnormalities was 10%, which is consistent with the previous report in similar population [4, 5], and higher than fetuses with structural anomalies [14, 15]. Therefore, for a fetus or neonate presenting with SGA with structural anomalies, even when karyotyping is normal, additional genetic testing is recommended.

Callaway et al. [15] reviewed studies on prenatal cases subjected to CMA for various reasons after a normal karyotyping, and found clinically significant CNVs in 2.4% of these cases. In the cases without abnormal finding in both karyotyping analysis and ultrasound screening, 1.0–1.7% of fetuses with increased maternal age or abnormal serum screening result presented pathogenic or likely pathogenic CNVs [14, 15]. It was also reported that no pathogenic CNVs were detected in isolated small fetuses group [17]. Our results suggest that abnormal subchromosomal results were found in 2% of isolated SGA. Due to these relatively low detection rate, the molecular genetic analysis is not recommended for isolated SGA pregnancies not complicated by other abnormal finding.

In addition, population studies suggest that many variants exist in diverse populations, > 99% of all benign CNVs are inherited, and most inherited CNVs are much smaller than 500 kb [18]. In general, many CNVs that are less than ~ 400 kb in size are frequently observed in normal individuals, and larger CNVs sizes are correlated with lower population frequencies [19, 20]. In our study, 8% of CNVs were > 500 kb among all subjects, which is similar to reports on normal individuals [18, 19]. As shown in Fig. 1, the lower the EFW percentile, the more frequent the occurrence of CNVs. A significant correlation between the size of the CNVs and the severity of SGA was reported [3]. The effects of VOUS on human development and function are still unknown, and further studies are needed.

UPD of certain chromosomes has been associated with disruption of intrauterine growth and small fetus due to genetic disorders [21–23]. Our study detected UPD on chromosome 22 [upd(22)pat] in 1 fetus with SGA associated with Dandy–Walker malformation (Table 2, case 3), which is consistent with previously mentioned studies [21–23].

Our results showed that most CNVs were detected in different chromosomal regions, but a 482.1 kb microduplication on 2q13 was found in 2 isolated SGA cases (Table 3, cases 26 and 28). Yu et al. [24] reported five patients with CNVs on 2q13 and concluded that CNVs on 2q13 caused DD and structural abnormalities. Since these two cases showed a surprisingly consistent microduplication, we speculated that these CNVs on 2q13 are likely associated with SGA.

This study strengthens that 10% of those SGA fetuses with structural abnormalities had a pathological subchromosomal abnormalities, whereas only 2% of isolated SGA cases with normal karyotyping showed abnormal results. Small fetus with structural abnormalities presenting much higher risk of subchromosomal abnormalities was confirmed in this study. Limitations of this study are relatively small sample size and no stratification of early SGA and late SGA.

In summary, SGA fetuses with structural anomalies presented with higher subchromosomal abnormalities' occurrence after exclusion of aneuploides. The molecular genetic analysis is not recommended for isolated SGA pregnancies without other abnormal findings.

Author contributions Protocol/project development and study design: YM, CY and QW; drafting of the study and revision for important intellectual content: KOK, YJ, CY and LL; data collection: YM, YP and XL; data analysis and interpretation: YM and JW; manuscript writing/editing: YM; KOK; substantial contributions to the study conception: QW; final approval of the version to be published: YM and QW.

Funding This study was supported by the National Key Research and Development Program of China (Grant No. 2016YFC1000104 and 2016YFC1000101), Beijing Municipal Administration of Hospitals' Ascent Plan (Grant No. DFL20151302), and National Science and Technology Infrastructure Program (Grant No. 2014BAI06B05).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Ethics Committee of Beijing Obstetrics and Gynecology Hospital and was in accordance with the 1964 Helsinki Declaration and its later amendments.

Informed consent Each participant in this study signed an informed consent form.

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