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Prenatal findings of 2q13 Duplication and Deletion: Further Evidence for Lack of Phenotypic-Genotype Correlation

Lu Li[1,2], Xiuzhu Huang[1,2], Mei Ye[2], Jieping Chen[2], Zhipeng Zeng[2], Hui Guo[2], Qiuyan Liao[2], Wenlong Hu[*2], Donge Tang[*2], Yong Dai[*2]

Abstract

Objective: In previous studies, 2q13 CNV was associated with various diseases, with a lack of consensus. This study aimed to analyze the prenatal diagnosis and clinical presentation of fetuses with different deletions or duplications of 2q13.

Materials and methods: Detailed prenatal screening and laboratory examinations, including prenatal ultrasound diagnosis and amniocentesis, were performed, and genetic analysis was performed using multiplex ligation-dependent probe amplification (MLPA) and chromosome microarray analysis (CMA).

Results: CMA analysis showed that four fetuses had deletion in the proximal region of 2q13, one had duplication, and one had duplication in the distal region of 2q13. Four fetuses had inherited copy number variation (CNV) from their parents; however, they had variable outcomes.

Conclusion: Individuals with the same CNV of 2q13 may have different phenotypes or are unaffected; multiple individuals with the same deletion or duplication need to be evaluated to capture feature sets associated with that CNV. Genetic counseling and follow-up to the fetus's mother and family are essential. Genomic diseases' characteristics should be explained in detail when providing prenatal genetic counseling to mothers and their families.

Keywords: chromosome 2q13; copy number variation; prenatal diagnosis; chromosomal microarray analysis

Introduction

Copy number variation (CNV) is the gain or loss of genomic material greater than 1 KB in the genome [1]. Although CNV is common in normal people, in some cases, due to chromosomal rearrangement, it can affect certain genes' expression, leading to disease development [2, 3]. Deletion or duplication of the long arm of chromosome 2 have been reported to be associated with a variety of phenotypes, including orofacial clefting, developmental delay (DD), failure to thrive and dysmorphism [4, 5]. Not all CNVs have a pathogenic phenotype, and 2q13 CNVs have unknown clinical significance.

Compared with karyotype analysis, the chromosome microarray analysis (CMA) technique can detect small deletions and duplicates, effectively improving the detection rate of chromosomal abnormalities [6]. It has rapidly replaced the standard G-band karyotype and has become an important

Affiliation:

[1]MOE Key Laboratory of Tumor Molecular Biology and Key Laboratory of Functional Protein Research of Guangdong Higher Education Institutes, Institute of Life and Health Engineering, College of Life Science and Technology, Jinan University, Guangzhou, Guangdong 510632, P.R. China

[2]Clinical Medical Research Center, The Second Clinical Medical College of Jinan University, The First Affiliated Hospital of Southern University of Science and Technology, Shenzhen People's Hospital, Shenzhen, Guangdong 518020, P.R. China

***Corresponding author:**

1. Yong Dai, MD, PhD. Clinical Medical Research Center. The Second Clinical Medical College of Jinan University, The First Affiliated Hospital of Southern University of Science and Technology, Shenzhen People's Hospital, Shenzhen, Guangdong 518020, P.R. China.
2. Donge Tang, PhD, Clinical Medical Research Center, The Second Clinical Medical College of Jinan University, The First Affiliated Hospital of Southern University of Science and Technology, Shenzhen People's Hospital, Shenzhen, Guangdong 518020, P.R. China.
3. Wenlong Hu, Clinical Medical Research Center, The Second Clinical Medical College of Jinan University, The First Affiliated Hospital of Southern University of Science and Technology, Shenzhen People's Hospital, Shenzhen, Guangdong 518020, P.R. China.

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diagnostic method for detecting chromosomal abnormalities in pregnancy products [7]. Here, six new cases have been identified through the CMA with a 2q13 genomic imbalance and each with similar or different outcomes at prenatal diagnosis. Nevertheless, it may help identify these features early in the prenatal period for reference by parents and healthcare providers and monitor the condition or intervene promptly.

Materials and Methodology

The six probands with 2q13 duplication or deletion were seen in the Antenatal Diagnosis Center of Shenzhen People's Hospital. We collected clinical information on these cases. The following data were collected through medical record reviews: age, sex, gestational age and growth parameters at birth, parameters of obstetric examination during pregnancy, the risk of multiple genetic diseases and diagnostic CMA analysis, and multiplex ligation-dependent probe amplification (MLPA) assays were performed as part of their clinical evaluations.

Samples were taken from fetal exfoliated cells in amniotic fluid and lymphocytes of cord blood or parent peripheral blood. CMA was performed for each sample using a Cytoscan HD array (Affymetrix Inc., Santa Clara, CA, USA), and DNA was extracted according to the manufacturer's instructions. The annotation of the results was conducted in accordance with the Human Feb.2009 (GRCh37/hg19) Assembly.

Results

Table 1 summarizes detailed clinical information for each fetus. The mothers ranged in age from 29 to 43, and the average gestational age at the time of testing was about 21 weeks. Three fetuses were at high risk for Down syndrome. Three women had a history of spontaneous abortion, and two had a history of induced abortion. The mother of fetus 1 had two sons, one who died of neuroblastoma at age three and the other who died of intracranial hemorrhage at age 2. The maternal and fetal outcomes of pregnancy were followed up (Table 2). All six cases were delivered successfully, with four fetuses delivered to term and one premature. All the fetuses were in the normal range of height and weight. Among them, the baby boy in case 4 was born with congenital hydrocephalus and congenital pulmonary cystadenomatous.

The UCSC database shows duplication or deletion regions and their involved genes in six fetuses (Figure1).

Table 1: Clinical data.

Fetus	1	2	3	4	5	6
Mother's age	29	29	31	29	43	30
Sample type	Cord blood	Cord blood	Cord blood	Amniotic fluid	Cord blood	Amniotic fluid
Gestational weeks	18+	22+	25+	19+	22+	20+
MLPA	duplication of exon 8 of the SMN1; heterozygous deletions of exon 8 of the SMN2	N	heterozygous deletions of exon 7 and exon 8 of the SMN2; duplication of terminal subtelomeres of PAR region of Xp22	N	N	duplication of exon 7 and exon 8 of the SMN1; heterozygous deletions of exon 7 and exon 8 of the SMN2
AFP(MoM)	2.01	1.23	0.77	0.58	0.89	0.67
Free β-hCG (MoM)	7.16	2.46	0.9	2.63	2.177	2.87
uE3 (MoM)	0.47	1.14	0.732	0.64	1.443	0.26
Ds risk	1/10000	Jan-68	1/473	1/250	Jan-65	1/204
NTD	Low risk	Low risk	Low risk	U	U	Low risk
Clinical diagnosis	FGR	bowel strong echo and left ventricular strong echo	N	left ventricle punctate strong echo	Elderly couple, two renal pelvis dissection in the fetus	N
Abnormal pregnancy-labor history of mother	gave birth to two boys who died in infancy	one spontaneous abortion	one induced labor due to "cleft lip and cleft palate" and one spontaneous abortion due to fetal termination	N	two induced abortions	N

Abbreviations: MPLA, multiplex ligation-dependent probe amplification; AFP, alpha-fetoprotein (Normal range: 0.61-2.49); Free β-hCG, free beta-human chorionic gonadotropin (0.41-2.39); uE3, unconjugated estriol (>0.73); MoM, multiple of median; DS, Down syndrome (Normal range: < 1/1000); NTD, neural tube defects; FGR, fetal growth restriction; U, unknown; N, normal.

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Table 2: Pregnancy outcome

Case	1	2	3	4	5	6
Gestational weeks	40	39	36	39	38	38
Delivery situation	Caesarean section	Normal delivery	Caesarean section	Caesarean section	Caesarean section	Normal delivery
Sex of the baby	Girl	Girl	Boy	Boy	Girl	Boy
Weight (g)	3000	3130	2800	3450	3500	3000
Height (cm)	50	49	49	50	50	50

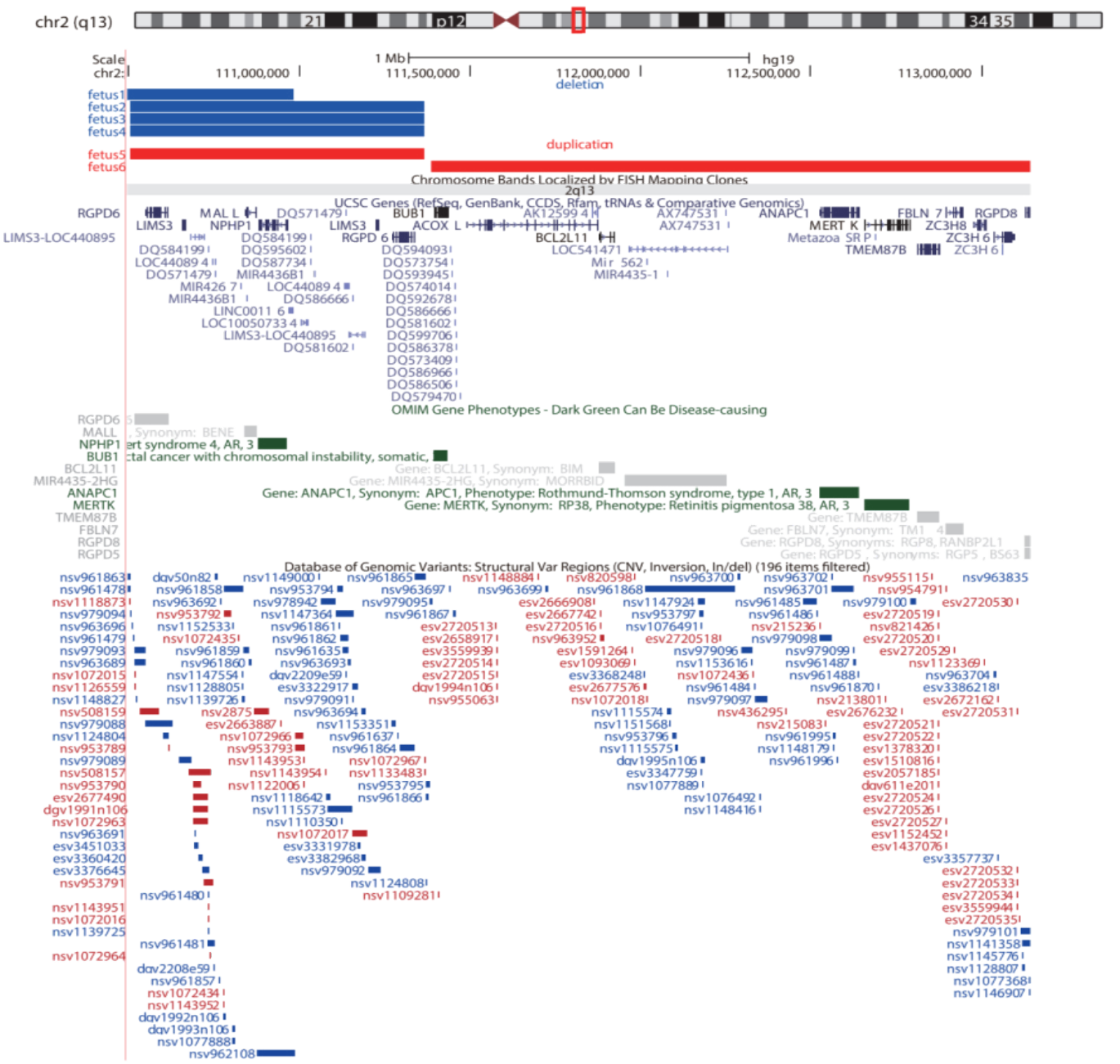

Figure 1: UCSC Genome Browser (http://genome.ucsc.edu/) view of 2q13. The top panel shows the deletion or duplication reported here. UCSC genes, OMIM genes and Database of Genomic Variants (DGV) cases are shown below the custom track.

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Five fetuses had deletions or duplications in the proximal or distal regions of 2q13. Among them, four were deletions in the proximal region of 2q13, and one was duplication. A search of the Decipher database (https://decipher.sanger.ac.uk/) revealed that this region contained ten genes, of which 4 were OMIM genes: NPHP1 (OMIM: 607100), RGPD5 (OMIM: 612708), MALL (OMIM: 602022), RGPD6 (OMIM: 612709), and 1 was Morbid genes: NPHP1. Another fetus had a duplication of the distal region of 2q13, which the Decipher database showed contained 27 genes, including 8 OMIM genes: BUB1 (OMIM: 602452), ANAPC1 (OMIM: 608473), MERTK (OMIM: 604705), MIR4435-2HG (OMIM: 617144), BCL2L11 (OMIM: 603827), TMEM87B (OMIM: 617203), FBLN7 (OMIM: 611551), RGPD8 (OMIM: 602752), and 3 Morbid genes: BUB1, ANAPC1, MERTK. Figure 2 shows the chromosomal locations of duplication and deletion in six fetuses.

Discussion

The deletion of the proximal region of 2q13.

One of the genes located in 2q13, NPHP1, has been reported to be closely associated with human disease. Nephronophthisis (NPHP) is a tubulo-interstitial, autosomal recessive cystic kidney disease, which is one of the most frequent genetic diseases causing end-stage renal disease (ESRD) in children and adolescents [8]. At first, Hildebrandt et al. found homozygous deletion of Mall and NPHP1 genes in 16 out of 22 families with nephropathy, suggesting a relationship between nephronophthisis and 2q13 [9]. This could be explained by interchromosomal or intrachromosomal mispairing of the genome inverted repeat, followed by an interchromosomal unequal crossover event [10]. In addition to NPHP, Cogan-type congenital ocular motor apraxia (COMA), retinitis pigmentosa (Senior-Loken syndrome), and Joubert syndrome were also found in patients with a deletion of the NPHP1 gene [11-13].

However, deletion of the proximal region of 2q13 involving RGPD5, RGPD6, and LIMS3 genes has not been reported. Ciccarelli et al. found that genomic rearrangement

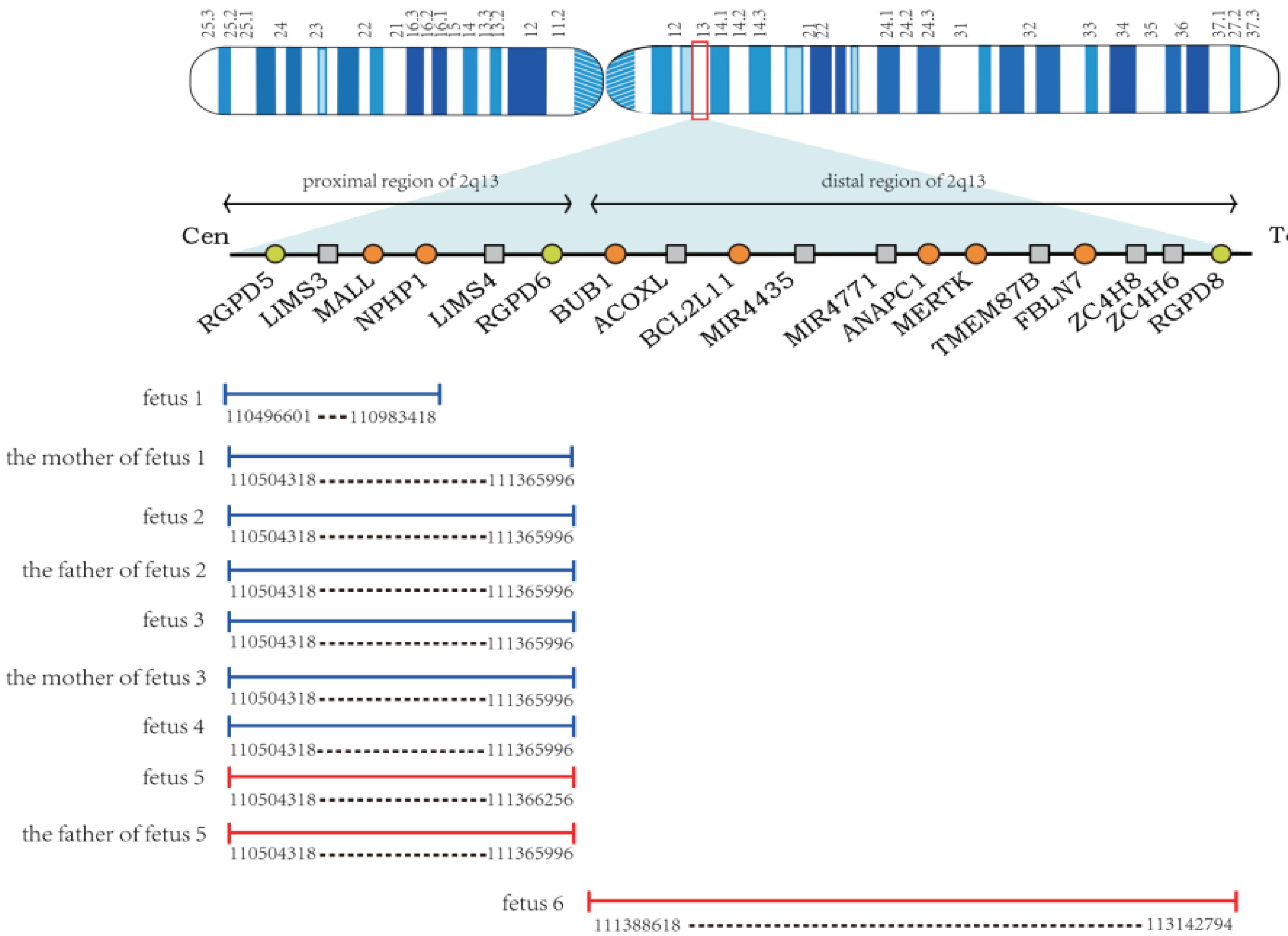

Figure 2: Schematic maps of human chromosome 2q13. Circles are OMIM genes. The proximal and distal region of 2q13 is shown with locations of the deletion and duplication reported here. Deletion of the fetus and the parents is depicted in blue, and duplication is shown in red.

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of RANBP2 and GCC2 genes on chromosome 2 of primates produced 8 RGPD genes, including RGPD5, RGPD6, and RGPD8 [14]. LIMS3 encodes a conserved protein containing the LIM domain, which plays a role in cell-cell and cell-matrix adhesion in the formation of multi-protein complexes. MALL is a member of the MyD88 adapter-like (Mal) family, which functions in a variety of tumors [15].

The duplication of the proximal region of 2q13

Previous studies have shown that duplication of the 2q13 proximal region is commonly associated with autism spectrum disorder (ASD). Baris et al. reported a single-copy gain in the NPHP1 gene in patients with speech delay, global developmental delay, attention hyperactivity disorder (AHDH), and veformities of varying degrees. [16]. Previous reports also found some cases of 2q13 duplication associated with ASD, DD, and mental retardation (ID)[17, 18]. Similarly, two brothers with ASD were reported. Both brothers had 2q13 duplication, including MALL, NPHP1, RGPD6, and BUB1 genes, and both suffer from ID and liver disorder [19]. It is clear that duplication of the 2q13 proximal region increases the risk of ASD.

The duplication of the distal region of 2q13

Although the penetrance of duplication is lower than that of deletion [4]. Duplications at the distal region of 2q13 are increasingly accepted as risk factors for developmental delay, autism, adult neuropsychiatric expression, and deformities [20-22].

Rudd et al. reported that two patients with patrilineal 2q13 had dental crowding [22], while FBLN7 plays a crucial role in odontoblast differentiation and maintenance, as well as in dentine formation [23]. Another gene in the region, BUB1, belongs to a family of genes that encodes proteins that bind to the kinetochore, and BUB1 is a vital component of the spindle checkpoint. Tang et al. also demonstrated the role of hBUB1 in centromeric cohesion during mitosis in mammalian cells [24]. There are three isoforms of BCL2L11, which sense apoptotic stimuli and initiate apoptosis by activating BAK, BAX, and other multi-domain pro-apoptotic proteins [25, 26]. ANAPC1 is the largest subunit of anaphase-promoting complex/cyclosome (APC/C) and ANAPC1 deficiency is the cause of Rothmund-Thomson syndrome type 1 [27]. Homozygous mutations in MERTK, a tyrosine kinase, are associated with retinal dystrophy and retinitis pigmentosa [28].

Cases

Six fetuses in our study showed deletion or duplication at a different region of 2q13 on the CMA results. Fetus 1-5 was a deletion or duplication of the proximal region of 2q13, and fetus 6 was a duplication of the distal region of 2q13. Among them, four fetuses had the same breakpoint, which could be considered a 2q13 recurrent breakpoint. The deletions of fetuses 1 and 3 were inherited from their mother. The deletion of fetus 3 was identical to that of his mother, while the deletion of fetus 1 was smaller than that of her mother. Both the deletion of fetus 2 and the duplication of fetus 5 are inherited from the father. The deletion of fetus 2 is identical to her father, and the termination site of fetus 5 is slightly different from her father.

Although, almost all pathogenic CNVs have two characteristics: variable expression and incomplete penetrance, which implies a series of phenotypic outcomes and unaffected family members carrying the same CNV [29, 30]. To date, many 2q13 deletions and duplications have been hereditary, but parental phenotypes have been poorly described. Half of the six fetuses were at high risk for Down syndrome, and four mothers in this study had a history of abnormal pregnancy-labor. Fetus 1 was accompanied by fetal growth restriction (FGR), and the mother had given birth to two boys who both died of neuroblastoma or intracranial hemorrhage. The mother of fetus 2 had a spontaneous abortion due to the termination of the embryo. Fetus 2 was found to have strong echoes in the left ventricle and bowel. LISM3 is involved in cell-cell and cell-matrix adhesion processes and is involved in cytoskeleton regulation. However, molecules that regulate cell migration and cell adhesion are thought to be involved in congenital heart defect (CHD) [31]. The deletion of fetus 3 is inherited from the mother. The mother of fetus 3 had three pregnancies, including one induced labor due to "cleft lip and cleft palate" and one spontaneous abortion due to fetal termination, while fetus 3 was accompanied by Xp22 subtelomere microduplication. It is widely accepted that subtelomere chromosome rearrangement may be a common cause of idiopathic mental retardation (MR) [32]. The genotypes of aborted fetuses cannot be determined, but chromosomal abnormalities may play a role in early pregnancy loss. Deletion of 2q13 also occurs in fetus 4; congenital hydrocephalus and congenital pulmonary cystadenomatous were found after birth. Fetus 5 was born to elderly parents. It is believed that elderly parturient women have a higher incidence of chromosomal abnormalities than younger mothers [33]. Furthermore, MLPA results showed an abnormal copy number of the SMN gene in fetal 1, 3, and 6, which is the primary pathogenic gene of spinal muscular atrophy (SMA) [34].

Conclusion

The presence of a chromosomal-specific low-copy repeat sequence (LCR) increases the risk of chromosomal rearrangement and makes chromosome 2 susceptible to many unbalanced structural variants, including deletions and duplications. These CNVs can be developed de novo or inherited from parents with similar deletions or duplications. However, almost all CNVs have two characteristics of

variable expression and incomplete penetrance, and patients with the same CNV may have different phenotypes or be unaffected [29, 30], and the penetrance of duplication is lower than that of deletion [4] . Therefore, it is necessary to evaluate multiple individuals with the same CNV to capture characteristic sets associated with genomic diseases.

Of the six fetuses reported here, four had deletions or duplicates inherited from their parents, and they had different phenotypes. The characteristics of variable expression and incomplete penetrance of genomic diseases pose challenges for prenatal diagnosis and genetic counseling. These two characteristics should be explained in detail when providing prenatal genetic counseling to mothers and their families.

Authorship

The corresponding authors are responsible for the study design and revision of the paper. Lu Li and Xiuzhu Huang worked together on analyzing the genetic data and drafted the present manuscript. Mei Ye, Jieping Chen and Zhipeng Zeng collected clinical information and provided genetic counseling. Hui Guo and Qiuyan Liao contributed to the data analysis and interpretation. All authors have read and approved the final manuscript.

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Declaration of competing interest

The authors declare no conflicts of interest.

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