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Prenatal diagnosis and molecular cytogenetic analyses of a rare 15q21.3 and 16p11.2 microduplication family

Fei Zhang[1†], Gaoqi Liao[2†], Xin Wen[2†] and Chengcheng Zhang[2*]

Abstract

Background Copy number variants (CNVs) are an important source of normal and pathogenic genome variations. Microduplication of 15q21.3 is rare and is associated with an increased risk of developmental retardation, corpus callosum hypoplasia, microcephaly, cardiomyopathy, optic nerve hypoplasia and so on. Microduplication of 16p11.2 is associated with 16p11.2 microduplication syndrome (OMIM: 614671). The main clinical manifestations are low birth weight, microcephaly, mental retardation, language retardation, abnormal behavior, attention deficit, schizophrenia, affective disorder, loneliness spectrum disorder and so on. Individuals who carry these two microduplications are even more rare.

Materials and methods In this research, a 32-year-old woman (gravida 1, para 0) underwent amniocentesis at 20 weeks' gestation because the results of ultrasound showed that one of the twins was smaller than the other.

Results Copy number variation sequencing (CNV-seq) from this family revealed two types of microduplication (420 kb microduplication on chromosome 15q21.3 and 560 kb microduplication on chromosome 16p11.2) in both fetuses. Trio whole-exome sequencing (WES) showed that the two types of microduplication both originated from the father. After genetic counselling and being informed of the unfavourable prognosis, the parents decided to continue the pregnancy.

Conclusion We provide a detailed description of the phenotype in a rare family with 15q21.3 and 16p11.2 microduplication. Combination of karyotype analysis, CNV-seq, WES, prenatal ultrasound and genetic counselling is helpful for the prenatal diagnosis of chromosomal microdeletions/microduplications.

Clinical trial number Not applicable.

Keywords Copy number variations, 15q21.3 microduplication, 16p11.2 microduplication, Copy number variation sequencing, Whole-exome sequencing, Prenatal ultrasound

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Introduction

Copy number variations (CNVs) in chromosome 16p11.2 involves 16p11.2 recurrent region (proximal, BP4-BP5) and is related to 16p11.2 microduplication syndrome (OMIM: 614671). The main clinical manifestations of chromosome 16p11.2 microduplication syndrome (OMIM 614671) are low birth weight, microcephaly, mental retardation, language retardation, abnormal behavior, attention deficit, schizophrenia, affective disorder and loneliness spectrum disorder [1–4]. These microduplications are pathogenic variants with incomplete penetrance and variable expressivity [4].

The microduplication of 15q21.3 is generally considered to be a copy number variation with uncertain clinical significance, and there are few related reports. The reported clinical symptoms mainly include: overall developmental retardation, corpus callosum hypoplasia, microcephaly, cardiomyopathy and optic nerve hypoplasia [5].

Here, we provide a detailed description of the phenotype and mechanisms of a rare family with microduplication on chromosome 15q21.3 and 16p11.2.

Methods

Patients and samples

A 32-year-old woman (gravida 1, para 0) underwent amniocentesis at 20 weeks' gestation because the results of ultrasound showed that one of the twins was smaller than the other. The pregnant woman conceived naturally, and the ultrasound indicated a twin pregnancy with monochorionic diamniotic. Fetus B is smaller and is accompanied by a single umbilical artery as well as a smaller right lung. She and her 35-year-old husband were normal, healthy and non-consanguineous. There was no family history of birth defects or genetic diseases. In the context of the comprehensive normal results obtained from the family members' evaluations, the following is a detailed description:

Detailed neuropsychological assessment results

All family members have undergone rigorous neuropsychological assessments, which have revealed normal cognitive functioning, including memory, attention, executive functions, and problem-solving abilities. There are no indications of neuropsychological impairments or deviations from the norm in any of the participants. Additionally, their emotional well-being and mental health status have been assessed as within normal ranges, with no signs of depression, anxiety, or other neuropsychiatric disorders.

Developmental milestone history

A thorough review of the developmental milestone history for all family members has confirmed that they have all achieved age-appropriate milestones in their respective life stages. This includes normal progress in motor skills, language acquisition, social skills, and cognitive development. There are no reported delays or deviations in their developmental trajectories.

Comprehensive family history investigation

An extensive family history investigation has been conducted, encompassing multiple generations and including detailed inquiries about potential subtle manifestations in other family members. The results indicate that there is no history of genetic disorders, neurological diseases, or other conditions that could impact neuropsychological functioning. Furthermore, no subtle or mild symptoms have been reported among family members that could suggest a predisposition to the conditions under investigation.

Any potentially overlooked subclinical features

A meticulous review of medical records and past health evaluations has been conducted to identify any potentially overlooked subclinical features. The results confirm that there are no subclinical manifestations or subtle signs that could indicate underlying neuropsychological or medical conditions. Additionally, direct interviews with family members have not revealed any previously unreported symptoms or experiences that could suggest the presence of subclinical features.

In summary, the comprehensive evaluations of the family members have yielded normal results across all assessed domains, including neuropsychology, developmental milestones, family history, and subclinical features. These findings provide reassurance that the family members do not exhibit any abnormalities or deviations from the expected norm in these areas.

G-banding karyotype analysis was performed on cultured amniocytes and parental blood samples. Copy number variation sequencing (CNV-seq) on uncultured amniocytes and parental blood samples was performed. DNA was extracted using a DNA extraction kit (Axygen) according to the manufacturer's instructions. DNA concentration was measured using the Qubit® DNA Assay Kit in Qubit® 3.0 Fluorometer (Life Technologies, CA, USA). The chromosome CNV detection kit (Hangzhou Berry Genomics Diagnostic Technology Co., Ltd.) was utilized according to the instructions: 50 ng of whole genome DNA was randomly digested into fragments of approximately 200 bp, and the ends of the broken DNA fragments were supplemented and connected through an enzyme reaction. Fragment selection and purification were conducted using the magnetic bead purification method to remove the interference of primer dimers in the reaction system, thereby obtaining the DNA library. CNV sequencing was performed on the NextSeq CN500

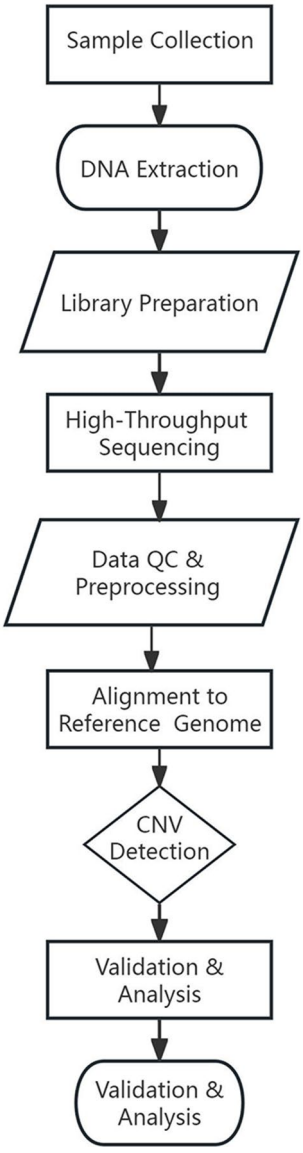

Fig. 1 Brief workflow diagram of CNV-seq

platform (Illumina). The platform can detect whole-chromosome aneuploidies, large-scale deletions and duplications, as well as genome-wide copy number variations (CNVs). The platform can typically identify copy number variations (CNVs) ranging from 100 kb to several megabases (Mb), with a sequencing depth of 0.05×. Sequencing data were analyzed using the chromosome copy number variation detection software (version V3, Hangzhou Berry Genomics Diagnostic Technology Co., Ltd.), to obtain chromosome copy number detection results. Candidate CNVs were annotated by analyzing the genes contained within the CNVs and the CNV intervals themselves using the databases Decipher, ClinVar, ClinGen, and OMIM. The candidate CNVs were then filtered against normal frequency databases DGV and ISCA. The interpretation of constitutional CNVs was undertaken based on annotation information and frequency databases according to the standards and guidelines of the American College of Medical Genetics (Fig. 1). The CNVs were categorized into five levels as follows: Level 1: Report indicates a clearly pathogenic CNV; Level 2: Report indicates a possibly pathogenic CNV; Level 3: Report indicates a CNV of unknown clinical significance (conflicting pathogenicity across databases); Level 4: Report indicates a possibly benign CNV; Level 5: All databases indicate benign, or frequency databases show a frequency greater than 0.5% (Table 1). If abnormal CNV changes with unknown clinical significance were found in the amniotic fluid sample, the parents' samples were tested for these abnormalities. The platform is capable of covering whole-chromosome aneuploidies, large-scale deletions/duplications, and genome-wide CNVs [6–7]. We performed Trio whole-exome sequencing (WES) on the family. The Novaseq6000 platform (Illumina, San Diego, USA), with 150 bp pair-end sequencing mode, was used for sequencing the genomic DNA of the family. The sequencing reads were aligned to the human reference genome (hg38/GRCh38) using the Burrows-Wheeler Aligner tool [8].

Table 1 Technical standards for CNV interpretation. The CNVs were categorized into five levels as follows

Score	variant classification	Evaluation Criteria
Score≥0.99	Pathogenic（P）	Report indicates a clearly pathogenic CNV
0.90≤Score≤0.98	Likely Pathogenic（LP）	Report indicates a possibly pathogenic CNV
-0.89≤Score≤0.89	Variant of Uncertain Significance（VUS）	Report indicates a CNV of unknown clinical significance (conflicting pathogenicity across databases)
-0.98≤Score≤-0.90	Variant of Uncertain Significance（VUS）	Report indicates a possibly benign CNV
Score≤-0.99	Benign（B）	All databases indicate benign, or frequency databases show a frequency greater than 0.5%

Genetic counselling

To effectively communicate the significance of the identified rare variants to the family, we employed several tailored strategies:

Visual Aids and Educational Materials: We utilized visual aids such as diagrams, flowcharts, and informational brochures that clearly depict the genetic architecture, the location of the rare variants, and their potential impact on the twins' health. These materials were designed to be easy-to-understand, ensuring that complex genetic information was presented in a user-friendly manner.

Analogies and Real-Life Examples: To facilitate comprehension, we drew analogies between genetic variants and everyday scenarios, such as comparing a gene to a recipe and a variant to a minor ingredient change that might alter the final product. Real-life examples of other families' experiences with similar variants were also shared, providing context and empathy.

Interactive Sessions and Open Discussions: We conducted interactive sessions where family members could ask questions freely. These discussions were facilitated by a genetic counselor with expertise in rare variant interpretation, ensuring accurate and comprehensive information dissemination.

Risk assessment for future pregnancies

To address concerns about future pregnancies, we conducted a thorough risk assessment:

Family History Analysis: A detailed analysis of the family history was conducted to identify any patterns or recurrences of rare variants. This helped in understanding the likelihood of the variants being passed down to future generations.

Genetic Counselling and Reproductive Options: The family was provided with genetic counselling sessions focusing on reproductive choices. Options such as natural conception, preimplantation genetic diagnosis (PGD), and adoption were discussed, along with their respective risks and benefits.

Psychological Support: Recognizing the emotional weight of such decisions, we referred the family to a psychological counselor who specialized in reproductive genetics to provide ongoing support and guidance.

Long-term follow-up planning for the twins

A comprehensive long-term follow-up plan was established for the twins:

Specialized Medical Care: The twins were enrolled in a specialized medical care program involving multidisciplinary teams, including pediatricians, geneticists, cardiologists, and neurologists, to monitor their health closely.

Regular Screenings and Monitoring: Regular screenings and monitoring protocols were put in place to detect any early signs of potential health issues related to the rare variants.

Family Education and Support: The family was provided with educational resources and support groups to help them navigate the challenges associated with rare variants and to foster a sense of community and shared experience.

Decision-making process Documentation

To ensure transparency and accountability, the decision-making process was meticulously documented:

Consultation Notes: Detailed notes were taken during all genetic counselling sessions, capturing the discussions, recommendations, and decisions made.

Consent Forms and Acknowledgments: Family members were required to sign consent forms acknowledging the receipt of genetic information and their understanding of the associated risks and benefits of various management options.

Review and Audit Trails: Regular reviews of the documentation were conducted to ensure accuracy and completeness. Audit trails were maintained to track any changes or updates made to the records.

Results

Chromosomal G-banding on cultured amniocytes revealed that the karyotypes of both fetuses were 46, XX. CNV-seq on uncultured amniocytes revealed a 420 kb chromosomal microduplication at 15q21.3 (seq[hg19]dup(15)(q21.3)chr15:g.55520000_55940000)(Fig. 2) and a 560 kb microduplication at 16p11.2 (seq[hg19]dup(16)(p11.2)chr16:g.29700000_30200000)(Fig. 3) in both fetuses. Then we performed both CNV-seq and chromosomal G-banding using the samples from the parents' peripheral blood. Their karyotypes were normal. The CNV-seq results showed the father had the same chromosomal microduplications as the fetuses.

We performed a comprehensive physical examination of the parents and failed to identify anything abnormal. Trio-WES on the family showed no pathogenic SNV and InDel variants were detected in the sample of the subjects, but 15q21.3 and 16p11.2 microduplication were detected in fetal and paternal samples (Fig. 4).

The microduplications of the fetuses are 420 kb in the region of 15q21.3 (variant of uncertain significance) and 560 kb in the region of 16p11.2 (pathogenic), the microduplications of the father are same size in the same regions of 15q21.3 and 16p11.2.

Ultrasound examination showed that fetus B was smaller than fetus A. Fetus B has a single umbilical artery and a smaller right lung.

After genetic counselling and being informed of the possible unfavourable prognosis, the parents decided to continue the pregnancy. At 37 weeks of gestation, the

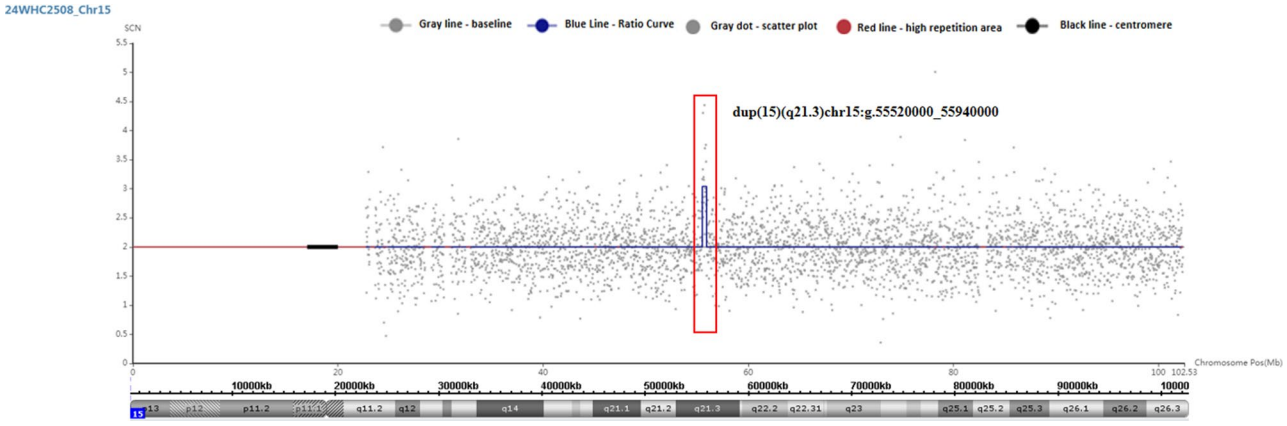

Fig. 2 CNV-seq detected a 420 kb chromosomal microduplication in the region of 15q21.3(seq[hg19]dup(15)(q21.3)chr15:g.55520000_55940000)

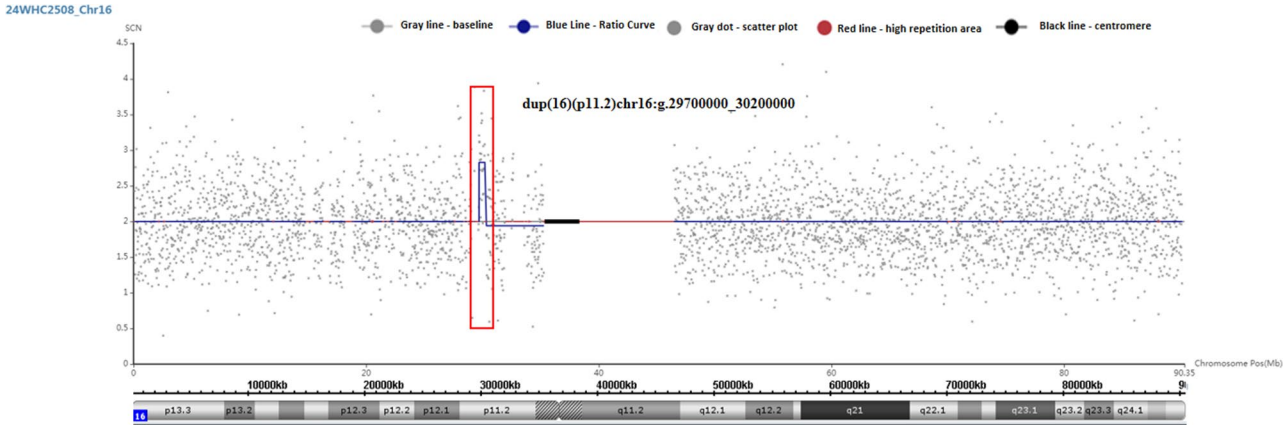

Fig. 3 CNV-seq detected a 560 kb chromosomal microduplication in the region of 16p11.2 (seq[hg19]dup(16)(p11.2)chr16:g.29700000_30200000)

expectant mother delivered twin female babies through cesarean section. The growth parameters at birth of baby A were in the normal ranges. Baby A received a complete physical examination and the results were normal. Baby B was transferred to the neonatology department for treatment due to her low birth weight (1.9 kg) combined with right lung hypoplasia. The phenotypic features were systematically compared between the father and the twin pair (Table 2). We will continue to monitor the twins' growth and development.

Discussion

CNV-seq revealed a 420 kb microduplication on chromosome 15q21.3 and a 560 kb microduplication on chromosome 16p11.2 in this family. The 15q21.3 microduplication encompasses eight protein-coding genes, including *RAB27A*, *PIGBOS1*, *PIGB*, *CCPG1*, *PIERCE2*, *DNAAF4*, *PYGO1*, and *PRTG* (Fig. 5). According to current literature, none of these genes have been clearly identified as triplosensitivity genes, and the pathogenicity of this microduplication remains uncertain. In contrast, the 16p11.2 microduplication is well-documented and associated with 16p11.2 microduplication syndrome (OMIM: 614671), which is characterized by a wide range of neurodevelopmental and psychiatric disorders, including low birth weight, microcephaly, intellectual disability, and autism spectrum disorder [1–4].

To better understand the phenotypic variability associated with these microduplications, we compared our findings with previously reported cases. The 16p11.2 microduplication syndrome has been extensively studied, with a reported incidence of approximately 3/10,000 and a penetrance rate of 27.2% [9–11]. Phenotypic variability is a hallmark of this syndrome, with some individuals exhibiting severe neurodevelopmental disorders, while others remain asymptomatic. In our case, the father carried the same 16p11.2 microduplication but displayed no obvious clinical symptoms, consistent with the incomplete penetrance and variable expressivity reported in the literature [9–11]. In contrast, the 15q21.3 microduplication is less well-characterized, with only a few reported cases. These cases have described a range of phenotypes, including developmental delay, corpus callosum hypoplasia, and microcephaly [5]. However, the lack of clear triplosensitivity genes in this region makes it challenging to establish a definitive genotype-phenotype correlation.

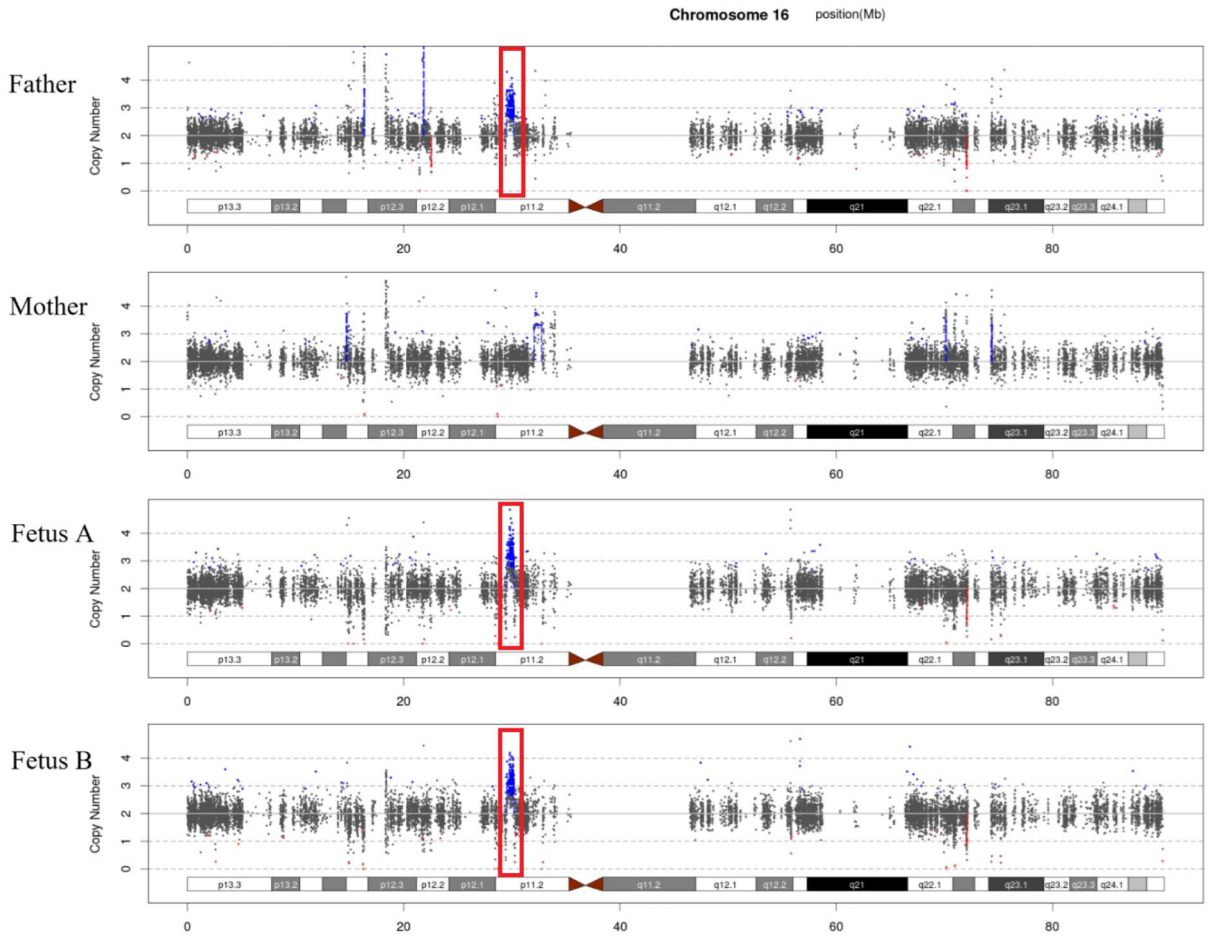

Fig. 4 Trio-WES showed a 0.64-Mb chromosomal microduplication in the region of 16p11.2 of the fetuses and the same chromosome segment microduplication of the father

Table 2 Comparison of phenotypic features between the father and both twins

Phenotypic Features	Father	Fetus A	Fetus B
Single Umbilical Artery	No	No	Yes
Pulmonary Dysplasia	No	No	Yes
Fetal Growth Restriction	No	No	Yes
Low Birth Weight	No	No	Yes
Microcephaly	No	No	No
Corpus Callosum Hypoplasia	No	No	No
Cardiomyopathy	No	No	No
Optic Nerve Hypoplasia	No	No	No
Mental or Language Retardation	No	Unknown	Unknown
Abnormal Behavior	No	Unknown	Unknown
Schizophrenia or Affective Disorder	No	Unknown	Unknown

The phenotypic differences observed in this family may be attributed to several molecular mechanisms. First, the incomplete penetrance and variable expressivity of the 16p11.2 microduplication could be influenced by genetic modifiers or epigenetic factors. For example, variations in the expression levels of genes within the duplicated region, such as *KCTD13* and *TAOK2*, have been implicated in neurodevelopmental disorders [9, 10]. Second, the 15q21.3 microduplication, although of uncertain significance, may interact with the 16p11.2

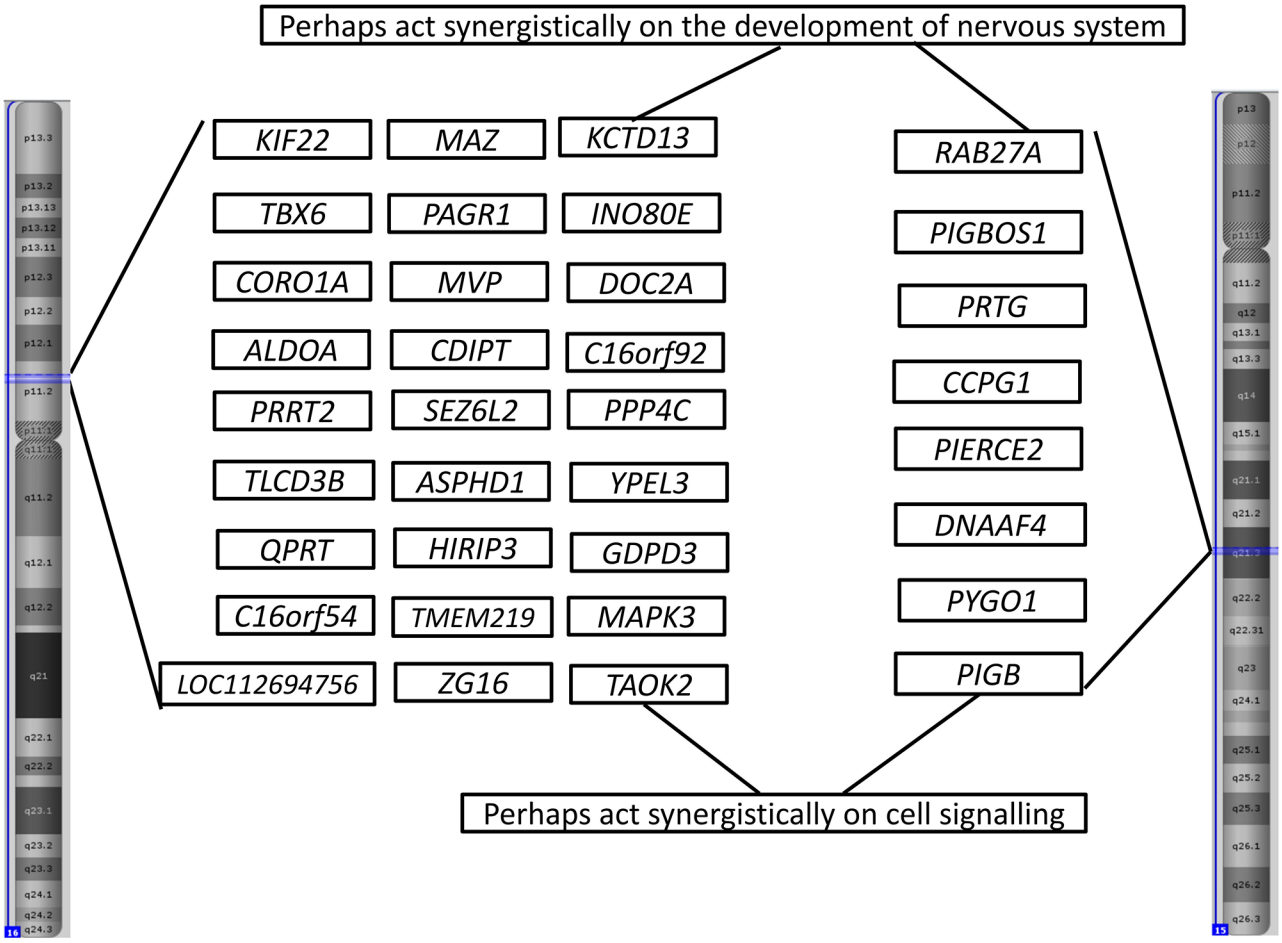

Fig. 5 Key genes on 15q21.3 and 16p11.2 and the potential interactions between these genes

microduplication to modulate the overall phenotype. The combined effect of these microduplications could lead to additive or synergistic impacts on gene dosage, potentially disrupting developmental pathways.

The co-occurrence of 15q21.3 and 16p11.2 microduplications in this family raises questions about their combined effect on fetal development. While the 16p11.2 microduplication is known to be pathogenic, the contribution of the 15q21.3 microduplication remains unclear. It is possible that the 15q21.3 microduplication exacerbates the phenotypic severity of the 16p11.2 microduplication.

While the individual effects of 15q21.3 and 16p11.2 microduplications are partially understood, their combined impact likely involves synergistic gene dosage effects and epigenetic interactions. For instance, genes in the 16p11.2 region (e.g., *KCTD13* and *TAOK2*) are critical for neuronal development [9, 10], while 15q21.3 contains genes like *RAB27A* involved in vesicular trafficking [5]. Our hypothetical model (Fig. 5) suggests that the co-occurrence of these duplications may potentially exacerbating phenotypic severity. Further functional studies are needed to validate these interactions.

Trio-WES on the family showed no pathogenic SNV and InDel variants were detected in the sample of the subjects. After genetic counselling again and being informed of the possible unfavourable prognosis, the parents decided to continue the pregnancy.

Microdeletion and microduplication of chromosome have shown considerable variability in clinical manifestations. The prenatal identification of the CNVs enables discussions with the prospective parents about possible future health risks of the affected individuals. However, the incomplete penetrance and variable expressivity especially involving possible neurodevelopmental phenotypes pose challenges for prenatal counselling.

For prenatal diagnosis, traditional karyotyping is still considered the gold standard, however, studies have indicated that for fetuses with abnormal ultrasonographic finding, CNV-seq detection has a significant advantage over karyotyping and has a higher detection rate for chromosomal abnormalities [12–13]. The wide use of CNV-seq makes it possible to find pathogenic CNVs

prenatally, leading early evaluation and clinical management of possible problems.

WES is a method that utilizes sequence capture technology or probe hybridization technology to capture and enrich the DNA sequences of all exon regions in the entire genome, followed by high-throughput sequencing. Therefore, WES has become the preferred method for studying genetic variations related to human diseases. WES can be used to study single nucleotide polymorphism sites, insertion-deletion sites, and other variations in known genes, which helps identify candidate genes and mutations associated with diseases. It has been widely applied in research on various complex diseases, genetic diseases, prenatal diagnosis and cancers, providing important genetic information for the prevention, diagnosis, and treatment of diseases [14–16].

Microduplications of 15q21.3 and 16p11.2 are associated with variable phenotypes. Genetic counselling of the microduplications remains a challenge for obstetricians as well as parents, genetic counselors, and clinicians.

In this research, we provide a detailed description of a rare 15q21.3 and 16p11.2 microduplication family. In this family, the microduplications of the fetuses is in the region of 15q21.3 and 16p11.2, the microduplications of the father is same size in the same region. The fetus B has abnormal phenotype (low birth weight combined with right lung hypoplasia), but the father and fetus A have normal phenotype. We think the reason maybe the incomplete penetrance and variable expressivity of 16p11.2 or 15q21.3 microduplications.

While this study provides valuable insights into the phenotypic variability and potential interactions of 15q21.3 and 16p11.2 microduplications, several limitations should be acknowledged. First, the small sample size of this family limits the generalizability of the findings. Larger cohorts with similar microduplications are needed to establish more robust genotype-phenotype correlations and to better understand the combined effects of these CNVs. Second, as this study primarily focuses on the clinical application of prenatal diagnosis, the investigation into the pathogenic mechanisms of chromosomal microdeletions and microduplications, the potential interactions between the duplicated regions, and the molecular mechanisms underlying the phenotypic differences in the twins remains insufficient. Deeper mechanistic studies, such as functional assays or transcriptomic analyses, are needed to elucidate these aspects. Third, while trio-WES was performed, it did not identify any pathogenic SNVs or InDels, but the potential role of non-coding variants or structural variations outside the exonic regions cannot be ruled out. Additionally, epigenetic modifications and environmental factors, which may influence the expressivity and penetrance of these microduplications, were not explored in this study. Finally, the long-term follow-up of the affected individuals, particularly fetus B, is necessary to fully understand the developmental and clinical outcomes associated with these microduplications.

Conclusion

In conclusion, we provide a detailed description of a rare 15q21.3 and 16p11.2 microduplication family. Combined use of conventional karyotyping, CNV-seq, Trio-WES, prenatal ultrasound and genetic counselling is helpful for the prenatal diagnosis of chromosomal microdeletions/microduplications.

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Author contributions
Fei Zhang and Xin Wen are responsible for clinical diagnosis and treatment. Chengcheng Zhang is responsible for pathological examination. Fei Zhang is responsible for genetic testing and thesis writing. Gaoqi Liao is responsible for drawing figures and tables.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The research was approved by the Ethics Committee of Maternal and Child Health Hospital of Hubei Province. All patient guardians gave informed consent to the study.

Consent for publication
All patient guardians gave informed consent to the publication of this study.

Competing interests
The authors declare no competing interests.

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