Molecular Cytogenetics

RESEARCH

Open Access

Prenatal diagnosis of fetuses with 15q11.2 BP1-BP2 microdeletion in the Chinese population: a seven-year single-center retrospective study

Jianlong Zhuang[1*†], Na Zhang[1†], Wanyu Fu[1], Yuying Jiang[1], Yu'e Chen[2*] and Chunnuan Chen[3*]

Abstract

Background The 15q11.2 BP1-BP2 microdeletion syndrome is associated with developmental delays, language impairments, neurobehavioral disorders, and psychiatric complications. The aim of the present study was to provide prenatal and postnatal clinical data for 16 additional fetuses diagnosed with the 15q11.2 BP1-BP2 microdeletion syndrome in the Chinese population.

Methods A total of 5,789 pregnancy women that underwent amniocentesis were enrolled in the present study. Both karyotype analysis and chromosomal microarray analysis (CMA) were conducted on these subjects to detect chromosomal abnormalities and copy number variants (CNVs). Whole exome sequencing (WES) was performed to investigate sequence variants in subjects with clinical abnormalities after birth.

Results Sixteen fetuses with 15q11.2 BP1-BP2 microdeletion were identified in the present study, with a detection rate of 0.28% (16/5,789). The 15q11.2 BP1-BP2 microdeletion fragments ranged from 311.8 kb to 849.7 kb, encompassing the *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5* genes. The follow-up results regarding pregnancy outcomes showed that five cases opted for pregnancy termination, while the remaining cases continued with their pregnancies. Subsequent postnatal follow-up indicated that only one case with the 15q11.2 BP1-BP2 microdeletion displayed neurodevelopmental disorders, demonstrating an incomplete penetrance rate of 9.09% (1/11).

Conclusion The majority of fetuses with the 15q11.2 microdeletion exhibit typical features during early childhood, indicating a low penetrance and mild impact. Nonetheless, pregnancies involving fetuses with the 15q11.2

†Jianlong Zhuang, Na Zhang these authors contribute equally to this work.

*Correspondence:
Jianlong Zhuang
415913261@qq.com
Yu'e Chen
26608708@qq.com
Chunnuan Chen
chenchunnuan1983@aliyun.com

Full list of author information is available at the end of the article

microdeletion require thorough prenatal counseling. Additionally, enhanced supervision and extended postnatal monitoring are warranted for those who choose to proceed with their pregnancies.

Keywords 15q11.2 BP1-BP2 microdeletion, Chromosomal microarray analysis, Karyotype analysis, Prenatal diagnosis, Whole exome sequencing

Introduction

Chromosome 15q11-q13 represents as one of the most genetically volatile regions in the genome. It features five frequently occurring breakpoints (BP1-BP5) that facilitate non-allelic homologous recombination, leading to the occurrence of chromosome microdeletions and duplications [1]. As is well known, deletions between BP1 and BP3 are associated with Prader Willi syndrome and Angelman syndrome [2–4]. The 15q11.2 BP1-BP2 microdeletion encompasses the ~500 kb region, located between breakpoints BP1 and BP2, containing four OMIM genes including *NIPA1*, *NIPA2*, *CYFIP1* and *TUBGCP5* [5–7]. Previous studies have indicated that individuals with 15q11.2 BP1-BP2 microdeletion commonly present with a wide range of neurodevelopmental disorders. These may encompass intellectual disability, delays in language development, neurobehavioral disorders, and/or mild physical deformities [1, 7–9]. However, the effect of 15q11.2 BP1-BP2 microdeletion is not significant, often displaying incomplete penetrance and phenotypic variability. Penetrance can vary considerably, ranging from 0.10 to 0.83, indicating that not all individuals with the deletion will exhibit the associated phenotypic traits [10, 11].

All the *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5* genes are expressed in the central nervous system, involved in axonal growth and neural connectivity [12]. The *NIPA1* gene contains 5 exons and spans 38.8 kb, is highly expressed in neuronal tissues and encodes a putative membrane transporter or receptor. This gene has been linked to a neurodegenerative disorder known as spastic paraplegia 6 [13]. A previous study conducted by Jiang et al. [14] indicated that haploinsufficiency of the *NIPA2* gene might serve as a susceptibility factor for childhood absence epilepsy in Chinese patients. However, another study indicated that *NIPA2* gene variants were not associated with generalized epilepsy in the Caucasian population [15]. Moreover, the *CYFIP1* gene has been found to encode a protein that interacts with the Fragile X Mental Retardation Protein (FMRP) associated with Fragile X syndrome [16]. In addition, the *TUBGCP5* gene has been found to be highly expressed in the subthalamic nuclei of the brain, which was associated with attention-deficit hyperactivity disorder (ADHD) and compulsions [17].

In the present study, 16 cases with 15q11.2 BP1-BP2 microdeletion were retrospectively reviewed. The primary objective was to offer additional clinical insights spanning the prenatal and postnatal periods.

Materials and methods

Subjects

A cohort comprising 5,789 pregnant women, exhibiting various high-risk factors such as advanced maternal age (>35 years), abnormal ultrasound findings, elevated results in serological screening, and other relevant risk factors, underwent amniocentesis between July 2017 and December 2023. Karyotype analysis and chromosomal microarray analysis were performed to detect chromosomal abnormalities. Among them, 16 cases with recurrent 15q11.2 BP1-BP2 microdeletion were retrospectively reviewed. Whole exome sequencing was employed to identify additional sequence variants in fetuses exhibiting clinical abnormalities following birth. All enrolled subjects provided written informed consent prior to participation in the study. Ethics Committee approval was obtained from the Institutional Ethics Committee of Quanzhou Women's and Children's Hospital prior to the commencement of the study (2020No.31).

Karyotype analysis

Approximately 30 ml of amniotic fluid was collected, with 20 ml allocated for karyotype analysis and 10 ml designated for chromosomal microarray analysis. The amniotic fluid cells were harvested using a Sinochrome-ChromprepII automatic chromosome harvesting system according to the standard protocol (Shanghai Lechen Biotechnology Co., Ltd.). After staining with Giemsa stain, twenty karyotypes were counted and analyzed, with five of them undergoing detailed examination. Nomenclature and diagnosis of the karyotypes were conducted according to the International System for Human Cytogenomic Nomenclature (ISCN 2020).

Genomics DNA extraction and chromosomal microarray analysis (CMA)

About 10 ml of amniotic fluid from the fetuses and 2 ml of peripheral blood from the parents were collected for CMA and parental CMA verification. Genomic DNA was extracted from enrolled subjects using the QIAamp DNA Blood Kit (QIAGEN, Germany) according to the manufacturer's protocol (www.qiagen.com) [18].

Chromosomal microarray analysis was performed using a single-nucleotide polymorphism based Affymetrix Cytoscan 750 K chip (Life Technologies, American) [18]. The detected copy number variants (CNVs) were subjected to further assessment utilizing various databases including the Database of Genomic Variants

(DGV), Online Mendelian Inheritance in Man (OMIM), DECIPHER, PubMed, and other relevant databases [18]. A joint consensus of the American College of Medical Genetics (ACMG) and the Clinical Genome Resource (ClinGen) standards and guidelines was used for interpretation of the CNV pathogenicity [19].

Whole exome sequencing and data analysis

About 2 ml of peripheral blood from each patient was collected for whole exome sequencing (WES) [20]. The genomic DNA extracted from each patient was subjected to WES analysis. DNA quantification was conducted using the Qubit dsDNA HS Assay (Invitrogen, Carlsbad, CA, USA). The approximate mean fragment length of 150–200 bp was sheared using the Covaris LE220 (Covaris, Woburn, MA, USA). Then, the sheared DNA was used for library preparation of targeted regions by means of the SureSelect whole-exome capture kit (Agilent). The Illumina DNA Standards and Primer Premix Kit (Kapa Biosystems, Boston, MA, USA) were used for the sequencing libraries quantification. Subsequently, sequencing was performed using the Illumina HiSeq 2500 platform (Illumina, San Diego, CA, USA) [20].

Data analysis was conducted following the process described in Zhuang et al.'s research [20]. Firstly, data analysis was conducted, encompassing variant calling, annotation, and variant screening processes. The dbSNP, 1000 Genomes Project, Exome Aggregation Consortium and Exome Variant Server databases were used for searching the minor allele frequencies (MAF < 0.1%) of all known variants. The OMIM, ClinVar, Human Gene Mutation Database and SwissVar databases were used to determine the harmfulness and pathogenicity of the detected variants. According to the ACMG guidelines, variants were classified as pathogenic, likely pathogenic, variants of unknown significance (VOUS), likely benign and benign [21].

Results

Subject information

In the present study, a total of 5,789 pregnant women who underwent amniocentesis were included. Among them, 16 fetuses were diagnosed with 15q11.2 BP1-BP2 microdeletion using CMA, resulting in a detection rate of 0.28% (16/5,789). In addition, all of the 16 cases exhibited a normal karyotype. As demonstrated in Table 1, the deletion fragments in these cases ranged from 311.8 kb to 849.7 kb, while all of the deletions encompassed four OMIM genes, including *NIPA1*, *NIPA2*, *CYFIP1* and *TUBGCP5.* According to information from the ClinGen database, all of these genes are associated with the syndrome of 15q11.2 recurrent region (BP1-BP2), which includes NIPA1. This suggests haploinsufficiency, with a sufficiency haploinsufficiency score of 3. According to the ACMG and ClinGen standards and guidelines, the recurrent 15q11.2 BP1-BP2 microdeletion was interpreted as a pathogenic variant.

In the enrolled 16 cases with 15q11.2 BP1-BP2 microdeletion, nine of them underwent parental CMA verification. The results elicited that one of them was *de novo*, three of them were inherited from the mother and five of them were transmitted from the father (Table 1).

Ultrasound results of fetuses with recurrent 15q11.2 BP1-BP2 microdeletion

Among the 16 cases enrolled in the study, ultrasound examination results were available for 15 fetuses. As outlined in Table 1, two fetuses presented structural ultrasound anomalies, specifically whole visceral inversion, spinal bifida with spinal meningocele, and umbilical protrusion. Additionally, two fetuses exhibited isolated ultrasound soft indicators, while four fetuses demonstrated normal ultrasound examination findings. Notably, seven fetuses exhibited increased NT, with the detected value ranging from 2.6 mm to 4.1 mm. This anomaly was the most frequently observed ultrasound finding in the study. Among them, four fetuses had isolated increased NT and the other three fetuses also had abnormal ultrasound soft indicators.

Pregnancy outcome follow up

As shown in Table 1, the pregnancy outcome follow up results demonstrated that five cases with 15q11.2 BP1-BP2 microdeletions chose to terminate their pregnancies. This decision was influenced by concerns regarding the potential effects of the 15q11.2 BP1-BP2 microdeletion and the presence of abnormal ultrasound findings in the fetuses. Notably, two of these cases involved fetuses with structural ultrasound anomalies. The other 11 cases continued their pregnancies and had full term deliveries with normal APGAR scores ranging from 9 to 10. The follow up results showed that 10 cases exhibited normal clinical features in early childhood. Further, among the eight parents who also harbored the 15q11.2 BP1-BP2 microdeletion, normal developmental milestones were observed during early childhood. However, one male pediatric patient exhibited abnormal clinical phenotypes, including motor and language developmental delays, and autism spectrum disorder (ASD). Notably, he also displayed soliloquizing behavior and an exaggerated response to noise, indicating a low penetrance rate of 9.09% (1 out of 11) in the present study.

The patient was subjected to a further pedigree investigation. The parental CMA verification indicated that the 15q11.2 BP1-BP2 microdeletion was inherited from his mother who had normal clinical features. In addition, results from pedigree analysis indicated that the proband's 15-year-old cousin also exhibited abnormal

Table 1 The chromosomal microarray analysis results of the enrolled cases

Cases	CMA results	Sizes (kb)	Pathogenicity	Origin	Prenatal ultrasound examination results	Pregnancy outcome and follow up	Follow up years
1	arr[hg19] 15q11.2(22770421_23620192)x1	849.7	P	*De novo*	Nasal bone dysplasia, bilateral choroid plexus cyst	Normal	5
2	arr[hg19] 15q11.2(22770421_23282798)x1	512.3	P	/	Increased NT, enhanced intestinal echogenicity	Normal	5
3	arr[hg19] 15q11.2(22770421_23082237)x1	311.8	P	/	Double renal pelvis separation	Normal	4
4	arr[hg19] 15q11.2(22770421_23276833)x1	506.4	P	Paternal	Normal	Normal	4
5	arr[hg19]15q11.2(22770421_23282798)x1	512.3	P	Paternal	Increased NT (3.6 mm)	Normal	3
6	arr[hg19]15q11.2(22770421_23282798)x1	512.3	P	/	/	Normal	3
7	arr[hg19]15q11.2(22770421_23277436)x1	507	P	Maternal	Increased NT (3.6 mm)	Normal	2
8	arr[hg19]15q11.2(22770422_23277436)x1	507	P	Paternal	Increased NT (4.1 mm)	TOP	/
9	arr[hg19]15q11.2(22770422_23214655)x1	444.2	P	Maternal	Increased NT (3.0 mm), enhanced intestinal echogenicity	Normal	2
10	arr[hg19]15q11.2(22770422_23277436)x1	507	P	/	Spinal bifida with spinal meningocele, umbilical protrusion	TOP	/
11	arr[hg19]15q11.2(22770422_23277436)x1	507	P	/	Increased NT, bilateral choroid plexus cyst	TOP	/
12	arr[hg19]15q11.2(22770421_23288350)x1	517.9	P	Maternal	Normal	Autism spectrum disorder, motor and language developmental delay, soliloquize and overreaction to noise	9
13	arr[hg19]15q11.2(22770422_23282798)x1	512.3	P	/	Increased NT (2.6 mm)	Normal	1
14	arr[hg19]15q11.2(22770422_23214655)x1	444.2	P	Paternal	Normal	Normal	1
15	arr[hg19]15q11.2(22770422_23276833)x1	506.4	P	Paternal	Normal	TOP	/
16	arr[hg19]15q11.2(22770422_23082237)x1	311.8Kb	P	/	Whole visceral inversion, middle hepatic vein widened; right lateral ventricle dilated	TOP	/

P: Pathogenic, TOP: Terminate of pregnancy

clinical features, notably severe autism spectrum disorder and severe language developmental delay (Fig. 1). Unfortunately, the proband's cousin declined to undergo further genetic analysis.

Additional variants detected in the patient

In the present study, whole exome sequencing was further conducted to investigate the additional sequence variants in the proband, with the aim of exploring the phenotypical diversity observed in the family. Clinical signs were converted into Human Phenotype Ontology (HPO) terminology, and a phenotypic scoring algorithm called Phrank, which relies on HPO terminology, was employed to aid in prioritizing changes. Subsequently, inheritance mode, allele frequency, and silico prediction were used to filter variants. However, none of the filtered sequence variants sufficiently accounted for the patient's clinical features. Although a likely pathogenic variant in the *TBC1D24* gene was detected in the patient, the *TBC1D24* gene is associated with autosomal recessive disorders (Table 2). Unfortunately, the parents of the patient refused to undergo further Sanger sequencing to verify the origin of the variants.

Discussion

The 15q11.2 BP1-BP2 microdeletion exhibits incomplete penetrance and phenotypic variability, presenting challenges for adequate clinical consultation during the prenatal period. Additionally, there is ongoing debate among researchers regarding the pathogenicity of the 15q11.2 BP1-BP2 microdeletion. In the present study, 16 additional cases of 15q11.2 BP1-BP2 microdeletion were reported with the aim of offering more comprehensive clinical information spanning the prenatal and postnatal periods.

The prevalence of 15q11.2 BP1-BP2 microdeletions in the population was reported to be 0.5–1% [22–24]. In the present study, the frequency of 15q11.2 BP1-BP2

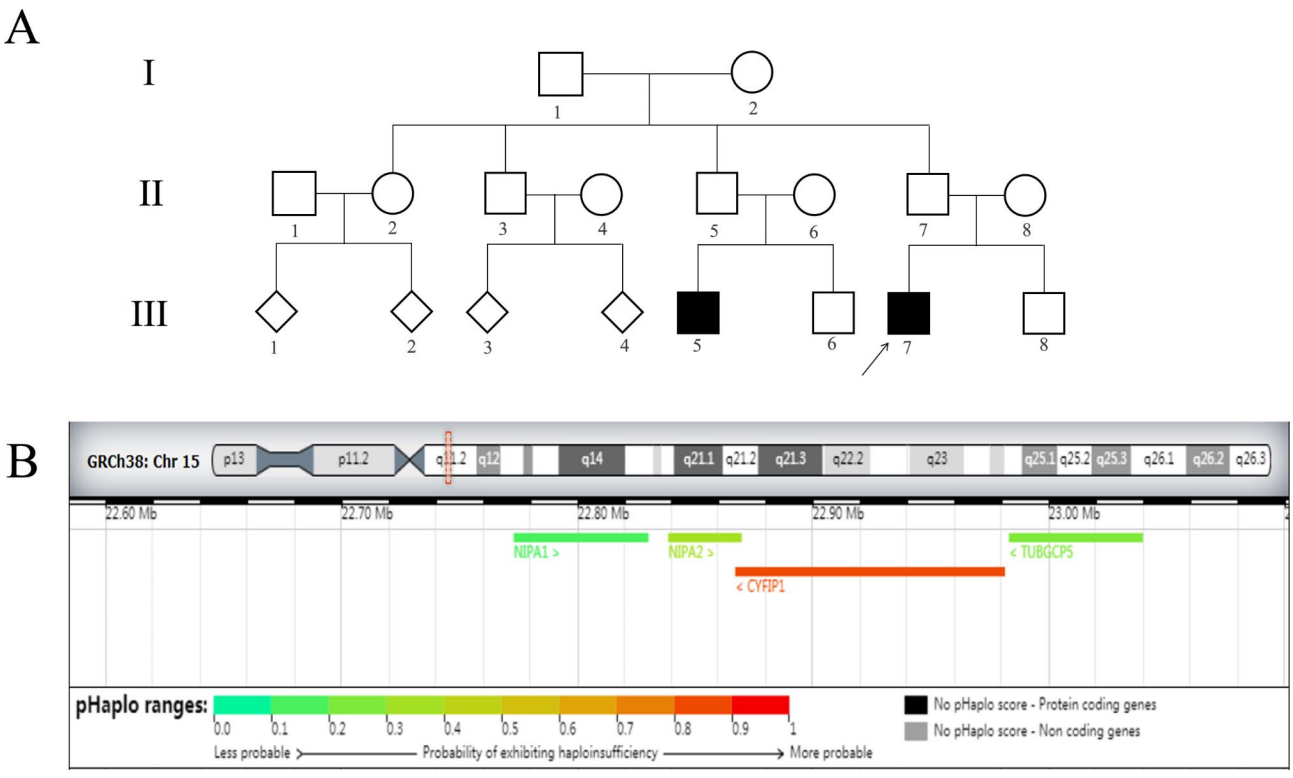

Fig. 1 The pedigree information and chromosomal microarray analysis results of the enrolled family
The pedigree analysis results indicated two pediatric patients with neurodevelopmental disorder. The arrow indicates the proband. II8 indicates the proband's mother who also had the 15q11.2 BP1-BP2 microdeletion
A 517.9Kb deletion was observed in the proband using chromosomal microarray analysis (arr[hg19]15q11.2(22,770,421 – 23,288,350)x1), containing four OMIM genes (*NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5*)

Table 2 The whole exome sequencing results of the patient

Genes	RefGene	Variants	Genotype	Mode of inheritance	Original	East Asian Frequency	ACMG classification
MEF2C	NM_002397	c.403–3 C > A	Heterozygote	AD	/	/	VOUS (PM2_supporting, PP3)
CDON	NM_016952	c.1295 C > T	Heterozygote	AD	/	/	VOUS (PM2_supporting)
TBC1D24	NM_001199107	c.1499 C > T	Heterozygote	AR	/	0.0003	LP (PM3_verystrong, PM2_supporting)
TRAPPC6B	NM_001079537	c.97 A > G	Heterozygote	AR	/	/	VOUS (PM2_supporting)
GALNT2	NM_004481	c.179 A > G	Heterozygote	AR	/	0.000054	VOUS (PM2_supporting)
CARS2	NM_024537	c.340 A > C	Heterozygote	AR	/	0.0002	VOUS (PM2_supporting)

LP: Likely pathogenic, VOUS: Variants of unknown significance, AD: autosomal dominant, AR: autosomal recessive

microdeletion was 0.28%, which is slightly lower than in previous reports. Similar to the present report, a previous study indicated that the frequency of prenatal diagnosis of 15q11.2 microdeletion was 0.21% (31/15,051) [25]. Individuals with 15q11.2 BP1-BP2 microdeletion typically present with a broad array of clinical features that lack specificity. Nonetheless, this deletion is strongly associated with various neurodevelopmental disorders, including but not limited to intellectual disability, language developmental delays, neurodevelopmental behavioral disorders, epilepsy, autism spectrum disorder (ASD), and/or mild deformities [1, 7–9]. A previous study indicated that the penetrance of 15q11.2 BP1-BP2 microdeletion was 10.4% [10]. Consistent with previous research, the present study also manifested a low penetrance of 15q11.2 BP1-BP2 microdeletions (9.09%).

A previous study conducted by Vanlerberghe et al. [26] recruited 34 families of 15q11.2 BP1-BP2 microdeletion, which similarly demonstrated incomplete penetrance and variable expressivity. Moreover, their parental verification results indicated that 18.8% were *de novo*, and 81.2% were parental inherited. In the present study, the findings indicated 11.11% (1/9) were *de novo*, and 88.89% (8/9) were inherited from their parents. In fact, the validation

of parental sources with 15q11.2 microdeletion had minimal predictive effect on clinical phenotypes after birth. In addition, a prior study identified decreased expression levels of *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5* genes in both affected patients and transmitting parents who exhibited normal phenotypes [12]. Hence, the observed phenotypic heterogeneity associated with this deletion may be linked to epigenetic mechanisms, warranting further investigation. A previous meta-analyses conducted by Jønch et al. [27] analyzed new data from 241 individuals and previously published data from 150 individuals with 15q11.2 BP1-BP2 deletion. This analysis revealed that the 15q11.2 BP1-BP2 deletion was associated with a decrease in IQ by 4.3 points, and assumed a 4% risk for intellectual disability compared to 2% in the general population. The estimated ORs and respective frequencies in deletion carriers for intellectual disabilities, schizophrenia, and epilepsy were 1.7 (3.4%), 1.5 (2%), and 3.1 (2.1%), respectively.

Nevertheless, the analysis did not indicate an increased risk for heart malformations or autism associated with the 15q11.2 BP1-BP2 deletion [27]. Further, a recent study [28] further supported the association of 15q11.2 microdeletions with intellectual disability, schizophrenia and epilepsy. In the present study, one case of 15q11.2 BP1-BP2 microdeletion exhibited motor and language developmental delay and autism spectrum disorder, which is consistent with previous reports.

Because of the incomplete penetrance observed with 15q11.2 BP1-BP2 microdeletion, prenatal consultation poses challenges. Additionally, these deletions are not frequently associated with structural abnormalities in the fetus. Moreover, neurodevelopmental disorders are not effectively detectable during the fetal period. In a previous study, prenatal diagnosis was conducted in a fetus with 15q11.2 BP1-BP2 microdeletion, which revealed abnormal ultrasound anomalies such as intrauterine growth restriction and pulmonary vein dislocation [29]. Another study enrolled 31 fetuses with 15q11.2 BP1-BP2 microdeletion, among them, 12 cases exhibited abnormal prenatal ultrasound results, including fetal malformations, increased NT, and oligohydramnios, but none of them exhibited developmental delay after birth [25]. In contrast, a previous study conducted by Chen et al. [30] reported that two patients with chromosome 15q11.2 BP1-BP2 microdeletion exhibited motor, developmental, and speech delays, without notable prenatal ultrasound findings. Meanwhile, some structural ultrasound anomalies observed in the present study may not be directly related to the 15q11.2 BP1-BP2 microdeletion. The pediatric patient in the present study, who had motor and language developmental delay and ASD, exhibited a normal prenatal ultrasound result. In the present study, increased NT was commonly observed in the fetuses with 15q11.2 BP1-BP2 microdeletion. In addition, a previous study involving a series of 21 cases with 15q11.2 microdeletion similarly reported a high incidence of increased NT during the prenatal period [28]. Despite increased NT being a non-specific manifestation, it did not show a strong predictive effect for 15q11.2 microdeletion after birth in the present study. A previous study conducted by Jønch et al. [27] indicated that 15q11.2 BP1-BP2 microdeletion should be classified as a "pathogenic of mild effect size" and may not warrant extensive discussion in developmental clinics or prenatal settings. In a recent study [31] outlining guidelines for the application of chromosomal microarray analysis in prenatal diagnosis in China, it was suggested that CNVs with incomplete penetrance below 10% would not be reported back to clinicians. Given that the 15q11.2 BP1-BP2 microdeletion demonstrates a borderline incomplete penetrance of 10%, the decision to report this deletion during the prenatal period requires further data analysis and careful discussion.

Whole exome sequencing (WES) technology has also been increasingly used for revealing the phenotypical variability of CNVs detected using CMA [32–34]. In the present study, WES was also utilized to explore additional sequence variants in a patient with 15q11.2 BP1-BP2 microdeletion who exhibited abnormal clinical phenotypes. However, none of the detected variants sufficiently accounted for the patient's clinical features. Thus, it is plausible that other mechanisms, such as epigenetic modifications or genetic variations not captured by WES, may be responsible for the variable clinical phenotypes observed in patients with 15q11.2 BP1-BP2 microdeletion.

In conclusion, the present study provides prenatal clinical information and postnatal follow-up data for an additional 16 cases with 15q11.2 BP1-BP2 microdeletions. In the present study, most of the fetuses were born without obvious developmental delay or neurological disorders in early childhood. The present findings further support the notion of the low penetrance of 15q11.2 BP1-BP2 microdeletion, corroborating the mild effect associated with this deletion. However, despite its mild effect, 15q11.2 BP1-BP2 microdeletion has been implicated in susceptibility to various neurodevelopmental disorders, such as intellectual disability, schizophrenia and epilepsy. Despite the fact that most individuals with 15q11.2 BP1-BP2 microdeletion present with normal clinical features, pregnancies involving this deletion necessitate careful prenatal consultation. Strengthened supervision and extended follow-up should be implemented if women opt to continue their pregnancies.

Acknowledgements
We extend our sincere appreciation to the patient and all other subjects who participated in this study. Additionally, we would like to express our gratitude

to the Fujian Provincial Health Commission and Quanzhou Science and Technology Bureau for funding this research.

Author contributions
JZ and NZ wrote the article; WF and YJ recruited the participants and analyzed the data; CC, JZ and YC revised and polished the paper. All authors have approved the final article.

Funding
This research was supported by Fujian Provincial Science and Technology Project (2020QNB045) and Quanzhou Science and Technology Program of China (2023NS068).

Data availability
The datasets used and analyzed in the current study were obtained from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethics Committee approval was obtained from the Institutional Ethics Committee of Quanzhou Women's and Children's Hospital prior to the commencement of this study (2020No.31). We received informed consent from the study participants, and they agreed to the publication of a report on the study. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication
We confirm that written informed consent was signed by the patient's parents for publishing their own and their children's genetic data and relevant information, and the written informed consent is available on request.

Competing interests
The authors declare that they have no conflict of interest.

Author details
[1]Prenatal diagnosis center, Quanzhou Women's and Children's Hospital, Quanzhou 362000, Fujian Province, China
[2]Department of Ultrasound, Quanzhou Women's and Children's Hospital, Quanzhou 362000, Fujian Province, China
[3]Department of Neurology, Second Affiliated Hospital of Fujian Medical University, Quanzhou 362000, Fujian Province, China

Received: 29 December 2023 / Accepted: 25 August 2024
Published online: 02 September 2024

References

1. Burnside RD, Pasion R, Mikhail FM, et al. Microdeletion/microduplication of proximal 15q11.2 between BP1 and BP2: a susceptibility region for neurological dysfunction including developmental and language delay. Hum Genet. 2011;130(4):517–28.
2. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Genet Med. 2012;14(1):10–26.
3. Butler MG, Kimonis V, Dykens E, et al. Prader-Willi syndrome and early-onset morbid obesity NIH rare disease consortium: a review of natural history study. Am J Med Genet A. 2018;176(2):368–75.
4. Williams CA, Driscoll DJ, Dagli AI. Clinical and genetic aspects of Angelman syndrome. Genet Med. 2010;12(7):385–95.
5. Chai JH, Locke DP, Greally JM, et al. Identification of four highly conserved genes between breakpoint hotspots BP1 and BP2 of the Prader-Willi/Angelman syndromes deletion region that have undergone evolutionary transposition mediated by flanking duplicons. Am J Hum Genet. 2003;73(4):898–925.
6. Bittel DC, Butler MG. Prader-Willi syndrome: clinical genetics, cytogenetics and molecular biology. Expert Rev Mol Med. 2005;7(14):1–20.
7. Cox DM, Butler MG. The 15q11.2 BP1-BP2 microdeletion syndrome: a review. Int J Mol Sci. 2015;16(2):4068–82.
8. Abdelmoity AT, LePichon JB, Nyp SS, Soden SE, Daniel CA, Yu S. 15q11.2 proximal imbalances associated with a diverse array of neuropsychiatric disorders and mild dysmorphic features. J Dev Behav Pediatr. 2012;33(7):570–6.
9. Cafferkey M, Ahn JW, Flinter F, Ogilvie C. Phenotypic features in patients with 15q11.2(BP1-BP2) deletion: further delineation of an emerging syndrome. Am J Med Genet A. 2014;164A(8):1916–22.
10. Rosenfeld JA, Coe BP, Eichler EE, Cuckle H, Shaffer LG. Estimates of penetrance for recurrent pathogenic copy-number variations. Genet Med. 2013;15(6):478–81.
11. Cooper GM, Coe BP, Girirajan S et al. A copy number variation morbidity map of developmental delay [published correction appears in Nat Genet. 2014;46(9):1040]. Nat Genet. 2011;43(9):838–846.
12. Picinelli C, Lintas C, Piras IS, et al. Recurrent 15q11.2 BP1-BP2 microdeletions and microduplications in the etiology of neurodevelopmental disorders. Am J Med Genet B Neuropsychiatr Genet. 2016;171(8):1088–98.
13. Rainier S, Chai JH, Tokarz D, Nicholls RD, Fink JK. NIPA1 gene mutations cause autosomal dominant hereditary spastic paraplegia (SPG6). Am J Hum Genet. 2003;73(4):967–71.
14. Jiang Y, Zhang Y, Zhang P, et al. NIPA2 located in 15q11.2 is mutated in patients with childhood absence epilepsy. Hum Genet. 2012;131(7):1217–24.
15. Hildebrand MS, Damiano JA, Mullen SA, Bellows ST, Scheffer IE, Berkovic SF. Does variation in NIPA2 contribute to genetic generalized epilepsy? Hum Genet. 2014;133(5):673–4.
16. Woo YJ, Wang T, Guadalupe T, et al. A common CYFIP1 variant at the 15q11.2 Disease Locus is Associated with Structural Variation at the Language-Related Left Supramarginal Gyrus. PLoS ONE. 2016;11(6):e0158036.
17. Butler MG. Prader-Willi Syndrome and chromosome 15q11.2 BP1-BP2 region: a review. Int J Mol Sci. 2023;24(5):4271.
18. Zhuang J, Zhang N, Fu W, et al. Cytogenetic and molecular analysis of distal 4q duplication with distinctive phenotype using single-nucleotide polymorphism array. Mol Cytogenet. 2021;14(1):46.
19. Riggs ER, Andersen EF, Cherry AM et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen) [published correction appears in Genet Med. 2021;23(11):2230]. Genet Med. 2020;22(2):245–257.
20. Zhuang J, Chen C, Chen Y, et al. Identification of a rare variant of c.1777G > A (p.G593S) in the COL1A1 gene as the etiology of recurrent Osteogenesis Imperfecta by whole-exome sequencing. Front Pediatr. 2022;10:816090.
21. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–24.
22. Stefansson H, Meyer-Lindenberg A, Steinberg S, et al. CNVs conferring risk of autism or schizophrenia affect cognition in controls. Nature. 2014;505(7483):361–6.
23. Crawford K, Bracher-Smith M, Owen D, et al. Medical consequences of pathogenic CNVs in adults: analysis of the UK Biobank. J Med Genet. 2019;56(3):131–8.
24. Hashemi B, Bassett A, Chitayat D, et al. Deletion of 15q11.2(BP1-BP2) region: further evidence for lack of phenotypic specificity in a pediatric population. Am J Med Genet A. 2015;167A(9):2098–102.
25. Kang J, Lee CN, Su YN, et al. The prenatal diagnosis and clinical outcomes of fetuses with 15q11.2 Copy Number variants: a Case Series of 36 patients. Front Med (Lausanne). 2021;8:754521.
26. Vanlerberghe C, Petit F, Malan V, et al. 15q11.2 microdeletion (BP1-BP2) and developmental delay, behaviour issues, epilepsy and congenital heart disease: a series of 52 patients. Eur J Med Genet. 2015;58(3):140–7.
27. Jønch AE, Douard E, Moreau C, et al. Estimating the effect size of the 15Q11.2 BP1-BP2 deletion and its contribution to neurodevelopmental symptoms: recommendations for practice. J Med Genet. 2019;56(10):701–10.
28. Jiang XL, Liang B, Zhao WT, et al. Prenatal diagnosis of 15q11.2 microdeletion fetuses in Eastern China: 21 case series and literature review. J Matern Fetal Neonatal Med. 2023;36(2):2262700.
29. Tang W, Chen G, Xia J, Zhang Y. Prenatal diagnosis and genetic counseling of a paternally inherited chromosome 15q11.2 microdeletion in a Chinese family. Mol Cytogenet. 2022;15(1):28.
30. Chen CP, Lin SP, Lee CL, et al. Familial transmission of recurrent 15q11.2 (BP1-BP2) microdeletion encompassing NIPA1, NIPA2, CYFIP1, and TUBGCP5 associated with phenotypic variability in developmental, speech, and motor delay. Taiwan J Obstet Gynecol. 2017;56(1):93–7.

31. Prenatal Screening And Diagnosis Group Birth Defect Prevention And Control Professional Committee Chinese Preventive Medical Association, Prenatal Diagnosis Group Society Of Medical Genetics Chinese Medical Association, Liu J. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2023;40(9):1051–61.
32. Dastan J, Chijiwa C, Tang F, et al. Exome sequencing identifies pathogenic variants of VPS13B in a patient with familial 16p11.2 duplication. BMC Med Genet. 2016;17(1):78.
33. Zhuang J, Chen C, Wang Y, et al. Case Report: prenatal whole-exome sequencing identified a Novel nonsense mutation of the *KCNH2* gene in a Fetus with familial 2q14.2 duplication. Front Genet. 2022;13:924573.
34. Zhuang J, Xie M, Yao J, et al. A de novo PAK1 likely pathogenic variant and a de novo terminal 1q microdeletion in a Chinese girl with global developmental delay, severe intellectual disability, and seizures. BMC Med Genomics. 2023;16(1):3.

Publisher's note