**INTRODUCTION**

Chromosomal microarray analysis (CMA) is a molecular technique for detecting copy number variations (CNVs). It can detect microduplication or microdeletion of DNA within the genome at a resolution of 10 KB, which is not available by karyotype analysis. In addition, in some cases, phenotypes are influenced not only by CNVs but also by the sex of the carrier and other genetic variations and environmental factors. Therefore, CNVs do not imply abnormal or pathogenic phenotype (Levy & Wapner, 2018). Nevertheless, CMA has underlying limitations, among which the most notable disadvantages are its deficiency in recognizing variants of undiscovered and variants of unknown significance (VOUS) and
the resulting difficulties it may bring to clinical treatments (Dhillon et al., 2014).

The 15q region is reported to be involved in many structural variations, microdeletions, and microduplications, which mainly occur in the 15q11-q13 region (Isles et al., 2016). The proximal long arm of chromosome 15 has five common breakpoints: from breakpoint 1 to breakpoint 5 (BP1-BP5). 15q11-q13 can be broken down into BP1, BP2, and BP3. 15q11-q13 is prone to copy number variation caused by low copy repeats (LCRs), which are considered to increase the risk of chromosome rearrangement through nonallelic homologous recombination (Cox & Butler, 2015). The common diseases involved in the 15q11-q13 regional deletion are Prader-Willi syndrome (PWS; OMIM 176270) and Angelman syndrome (AS; OMIM 105830). 15q11-q13 BP1-BP3 deletion (type I) and BP2-BP3 (type II) deletion are often classified (Figure 1) (Sahoo et al., 2007). It has been reported that the source of the missing 15q11-q13 region is related to the parent (Christian et al., 1999). Since the clinical phenotypes of 15q11-q13 may not be different, not all microdeletions or microduplications of 15q11-q13 will be clinically detected.

The purpose of this paper is to provide genetic counseling for patients with 15q11-q13 microdeletion or microduplication through CMA research and an analysis of the screening of seven fetuses in the middle period of pregnancy to promote advantages and mitigate disadvantages for them.

## METHODS

### 2.1 Cases

From 2018 to June 2020, seven fetuses with 15q11-q13 abnormalities were found in the Antenatal Diagnosis Center of Shenzhen People’s Hospital. This study is expected to identify the characteristics of genetic abnormalities in seven fetuses during prenatal screening. Fetuses ranged in gestational age from 15 to 27 weeks at the time of assessment. CMA was performed in high-risk pregnancies with indications for testing and abnormal anatomical fetal scans: increased risk for Down syndrome (advanced maternal age and abnormal biochemical screening), high level of alpha-fetoprotein (AFP), microdeletion of chromosome 15 in multiple connected
probe amplification (MLPA), and maternal request for invasive testing (in vitro fertilization-embryo transfer or other reason). Fetal exfoliated cells in amniotic fluid, cord blood lymphocytes, and parent peripheral blood lymphocytes were used for karyotyping and CMA. Informed consent was obtained from the mothers and their family members. This study was conducted in strict accordance with the approval and supervision of the Committee of Shenzhen People’s Hospital. All participants provided written informed consent for sample collection and subsequent analyses.

2.2 | Cytogenetic analysis

Among the cases, we collected two amniotic fluid samples and five cord blood samples. Chromosomal analyses of the fetuses and parents were performed by conventional G-bandning techniques according to the standard protocol. The results were described with reference to the International System for Human Cytogenetic Nomenclature (ISCN 2013).

2.2.1 | Chromosomal microarray analysis and statistical analysis

The CMA of each sample was carried out using A CytoScan HD/750 K array (Affymetrix Inc, Santa Clara, CA, USA). In addition, a QIAamp DNA Mini Kit (Qiagen Inc., Valencia, CA) was used to extract the DNA according to the manufacturer’s instructions. The results were annotated based on the Human Feb.2009 (GRCh37/hg19) Assembly. The following public databases were used to interpret the data:
- Database of Chromosomal Imbalance and Phenotype in Humans Ensembl Resources (DECIPHER; https://decipher.sanger.ac.uk/).
- Online Mendelian Inheritance in Man (OMIM; http://www.omim.org).
- University of California Santa Cruz (UCSC; http://genome.ucsc.edu/).
- The Clinical Genome Resource (ClinGen; https://www.clinicalgenome.org/).
- Database of Genomic Variants (DGV; http://dgv.tcag.ca/dgv/app/home).

3 | RESULTS

3.1 | Case report

Detailed clinical data of each fetus are summarized in Table 1. We followed up on the maternal and fetal outcome of pregnancy. Case 1 declined to be involved in our investigation, and cases 3 and 4 were both pregnant and had not delivered their babies.

In case 2, a baby girl was born at 38 weeks gestation, weighing approximately 3,000× g and measuring 50 cm. In case 5, a baby girl was delivered by cesarean section at 36 weeks of gestation, weighing 3,450× g and measuring approximately 51 cm, and the baby girl was diagnosed with congenital heart disease. In cases 6 and 7, labor was induced.

3.2 | 15q11.2 BP1-BP2 microdeletion and microduplication

The CMA analysis of seven fetuses showed that five fetuses had microduplications or microdeletions of BP1-BP2 in 15q11.2 and that two fetuses had microdeletions of BP2-BP3 in 15q11-q13 (Figure 1). Fetuses 1-4 had a microdeletion, and fetus 5 has a microduplication of 15q11.2. In fetus 4, 16p13.11 was also absent. The microdeletion of fetus 3 and microduplication of fetus 5 were of paternal inheritance. The origins of the microdeletions and microduplications of the remaining three fetuses are unknown. Table 2 shows the chromosomal locations of microduplication and microdeletion in five fetuses. We searched the DECIPHER database and found that the five fetuses of 15q11.2 microduplication and microdeletion contained four OMIM genes: CYFIP1 (OMIM: 606322), NIPA1 (OMIM: 608145), NIPA2 (OMIM: 608146), and TUBGCP5 (OMIM: 608147), and one of them was the Morbid gene: NIPA1. Table 3 shows the details of the Morbid gene. According to the ClinGen database, the microduplications and microdeletions in all five fetuses overlap with the 15q11-q13 recurrent (PWS/AS) region (Class 1) between BP1 and BP3 (chr15:22,832,519-28,379,874) and contain the 15q11.2 recurrent region between BP1 and BP2 (chr15:22,832,519-23,090,897). UCSC showed the genes involved in microduplication or microdeletion regions in five fetuses and other cases in their locations in the DGV database (Figure 2).

3.3 | 15q11-q13 BP2-BP3 microdeletion

Two fetuses reported having a 15q11-q13 microdeletion (4.93 Mb in size), and the two microduplications largely overlapped. Table 2 shows the chromosomal locations of microdeletions in the two fetuses. Data mining of the related genes between BP2 and BP3 through DECIPHER revealed that the microdeletion comprises 17 OMIM genes, including eight Morbid genes: GABRA5 (OMIM: 137142), GABRB3 (OMIM: 137192), MAGEL2 (OMIM: 605283), MKRN3 (OMIM: 603856), NDN (OMIM: 602117), OCA2 (OMIM: 611409), SNRPN (OMIM: 182279), and UBE3A (OMIM: 601623). Table 3 shows the details of the genes. We searched the ClinGen database and found that the abnormal regions of chromosome 15 of fetus 6 and fetus 7 overlap with the 15q11-q13...
| Fetus | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|-------|---|---|---|---|---|---|---|
| Mother's age | 33 | 28 | 32 | 33 | 43 | 29 | 23 |
| Sample type | Cord blood | Cord blood | Amniotic fluid | Cord blood | Amniotic fluid | Cord blood | Cord blood |
| Gestational weeks | 23+ | 21+ | 19+ | 25+ | 15+ | 17+ | 27+ |
| Karyotype | N | N | N | N | N | N | N |
| MLPA | N | N | N | 15q11.2 microdeletion | N | 15q11.2 microdeletion | 15q11.2 microdeletion |
| AFP (MoM) | 1.03 | U | 3.11 | 0.7 | 1.01 | 0.90 | 1.61 |
| Free β-hCG (MoM) | 2.94 | U | 1.87 | 1.61 | 0.93 | 1.48 | 3.47 |
| uE3 (MoM) | 0.79 | U | 0.92 | 1.12 | 0.64 | 1.22 | U |
| Ds risk | High | U | High | N | High | N | U |
| NTD | U | U | High | U | Low | Low | Low |

**Clinical diagnosis**

- Pregnancy with chronic hepatitis B
- Birth history of deaf children, The couple suffered from thalassemia
- IVF-ET, 16p13.11 microdeletion
- FGR and CSP are slightly narrower
- Spontaneous abortion three times, elderly couple
- IVF, Primary infertility
- Microdeletion of chromosome 15 by NIPT

**Delivery situation**

- Cesarean
- Gestation
- Cesarean
- Induced labor
- Induced labor

*Abbreviations: AFP, alpha-fetoprotein (normal range: 0.61–2.49); DS, down syndrome; free β-hCG, free beta-human chorionic gonadotropin (0.41–2.39); MoM, multiple of median; MLPA, multiplex ligation-dependent probe amplification; NTD, neural tube defects; U, unknown; uE3, unconjugated estriol (>0.73).*
TABLE 2  Cytogenetic characterization and parental transmission for each patient.

| Fetus | ISCN 2016 description (hg19/GrCh37) | Duplication or deletion size (Mb) | Inheritance | Other CNVs >200 kb |
|-------|-----------------------------------|---------------------------------|-------------|------------------|
| 1     | 15q11.2(22,770,421-23,082,328) x1  | 0.31                            | U           |                  |
| 2     | 15q11.2(22,770,421-23,283,811) x1 | 0.51                            | U           |                  |
| 3     | 15q11.2(22,770,421-23,282,799) x1| 0.51                            | Paternal    | 16p13.11(16,309,164-16,519,971) x1 |
| 4     | 15q11.2(22,770,421-23,290,819) x1 | 0.52                            | U           |                  |
| 5     | 15q11.2(22,770,421-23,288,350) x3| 0.52                            | Paternal    |                  |
| 6     | 15q11.2q13.1(23,290,786-28,545,355) x1 | 5.25                        | U           |                  |
| 7     | 15q11.2q13.1(23,615,768-28,545,355) x1 | 4.93                        | U           |                  |

TABLE 3  Morbid genes in the region of 15q11.2-q13 and the associated phenotype

| Gene | location | OMIM   | Explanation | Phenotype | Inheritance |
|------|----------|--------|-------------|-----------|-------------|
| NIPA1 | 15q11.2  | 608145 | NIPA magnesium transporter 1 | Spastic paraplegia 6, autosomal dominant | Autosomal dominant |
| MKRN3 | 15q11.2  | 603856 | makorin ring finger protein 3 | Precocious puberty, central, 2 | Autosomal dominant |
| MAGEL2 | 15q11.2  | 605283 | MAGE family member L2 | Schaaf-Yang syndrome | Autosomal dominant |
| NDN   | 15q11.2  | 602117 | necdin, MAGE family member | Prader-Willi syndrome | Autosomal dominant |
| SNRPN | 15q11.2  | 182279 | small nuclear ribonucleoprotein polypeptide N | Prader-Willi syndrome | Autosomal dominant |
| UBE3A | 15q11.2  | 601623 | ubiquitin protein ligase E3A | Angelman syndrome | Autosomal dominant |
| GABRB3 | 15q12   | 137192 | gamma-aminobutyric acid type A receptor subunit beta3 | Epileptic encephalopathy, early infantile, 43, Epilepsy, childhood absence, susceptibility to, 5 | Autosomal dominant |
| GABRA5 | 15q12   | 137142 | gamma-aminobutyric acid type A receptor subunit alpha5 | Epileptic encephalopathy, early infantile, 79 | Autosomal dominant |
| OCA2  | 15q12-15q13.1 | 611409 | OCA2 melanosomal transmembrane protein | Albinism, brown oculocutaneous, Albinism, oculocutaneous, type II, Skin/hair/eye pigmentation 1, blond/brown hair, Skin/hair/eye pigmentation 1, blue/nonblue eyes | Autosomal recessive |

recurring (PWS/AS) region (Class 1) between BP1 and BP3 (chr15:22,832,519-28,379,874) and contain the 15q11-q13 recurrent (PWS/AS) region (Class 2) between BP2 and BP3 (chr15:23,747,996-28,379,874). UCSC shows the location of the genes involved in the microdeletion of two fetuses (Figure 3). After the prenatal screening, we informed these couples of the diagnosis of 15q11-q13 microdeletion or microduplication in the fetus. Next, we will provide genetic counseling for these couples.

4 | DISCUSSION

Chromosome 15 imprinting disorders are classified into three categories, namely PWS, AS, and 15q duplication. There are two common microdeletion types in PWS/AS patients, namely PWS/AS deletion type I (BP1-BP3 deletion) and PWS/AS deletion type II (BP2-BP3 deletion) (Amos-Landgraf et al., 1999; Buiting et al., 1999). According to previous studies, PWS/AS’s pathogenesis appears to be related to genes and transcripts in the 15q11-q13 region. The imprinting nature of genes and genetic and epigenetic errors may all be contributing factors.

BP1-BP3 of the 15q11-q13 region contains genes and transcripts including ATP10A (OMIM: 605855), GABRA5, GABRB3, GABRG3 (OMIM: 600233), HERC2 (OMIM: 605837), MAGEL2, MRKN3, NDN, NIPA1, NIPA2, OCA2, SNRPN, TUBGCP5, UBE3A, and noncoding RNAs. Each of these genes has a behavioral finding associated with the pathogenic variation. For example, TUBGCP5 is highly expressed in the most differentiated tissues in the heart and skeletal muscle but moderately expressed in the brain. Attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) are associated with...
TUBGCP5 expression. CYFIP1, a protein that encodes and regulates cytoskeletal dynamics and protein translation, plays a key role in the neuron cytoskeleton's remodeling. CYFIP1 is a common gene involved in PWS/AS, and may be associated with autism and is more common in tumors. NIPA1 encodes a magnesium transporter that is widely expressed at high levels in neuronal tissues. The deletion of NIPA1 results in slowness, weakness, and spasms of the lower extremities. Finally, NIPA2, also a member of the NIPA family, is mutated, causing absence epilepsy in children and may play a role in the phenotype of 15q11.2 BP1-BP2 deficiency syndrome. Another gene associated with epileptic encephalopathy (EEs) is GABRB3. The GABRB3 gene encodes gamma-aminobutyric acid type A receptor subunit beta3, which is a member of the ligand-gated ionic channel family. In the case reported, the proband carried a de novo likely pathogenic GABRB3 mutation, which suggested that GABRB3 was a Dravet syndrome candidate gene (Pavone et al., 2020). However, imprinted MAGEL2, MRKN3, NDN, and SNURF-SNRPN genes are expressed in paternal lines (Bittel & Butler, 2005; Butler et al., 2015; Hassan & Butler, 2016).

Prader-Willi syndrome was the first genomic imprinting disease discovered in humans. Most cases of PWS are episodic, with an incidence of 1/15,000–1/30,000 (Cassidy & Driscoll, 2009). A total of 65%–75% of cases were caused by paternal microdeletion in 15q11, 20%–30% were caused by uniparental disomy (UPD) in the 15q11 region, and only 1%–3% were caused by a single gene defect (Angulo et al., 2015). The syndrome is characterized by low blood pressure in infancy, poor sucking with eating problems and hypoplasia, hypogonadism, and reduced growth hormone production, resulting in short stature, short feet, stunted growth, and mild facial deformities. During pregnancy involving PWS, the onset is significantly delayed, and fetal activity is reduced. Prenatal cytogenetic tests also produce normal results when fetal activity is reduced, so an alert obstetrician should refer to the data from pregnant women with low fetal activity for a molecular diagnosis of the syndrome (Schinzel, 1986). However, PWS patients have different stages due to individual growth. According to the report, the SNORD116 gene was identified as the smallest gene in the patient with the PWS phenotype (Salles et al., 2020). So far, PWS patients and mouse models have been reported, suggesting that the loss of SNORD116 may be associated with diseases such as overeating, obesity, and neurobehavioral disorders (Bieth et al., 2015; Polex-Wolf et al., 2018).

Angelman syndrome (OMIM: 105830) is a neurogenetic imprinting disorder with an estimated incidence of 1 in 10,000–24,000 births. (Keute et al., 2020; Thibert et al., 2013). AS is caused by the loss or mutation of regional
imprinting and maternal genes especially influences on the \textit{UBE3A} gene. \textit{UBE3A} is the only gene in 15q11-q13 that shows maternal allele preference (Butler & Duis, 2020; Gu et al., 2019). Microdeletion of 15q11 causes 70% to 90% of cases, UPD causes 3% to 7% of cases, and single-gene defects cause only 2% to 4% of cases (Neubert et al., 2013). Through clinical studies, the pathogenesis of AS is characterized by cognitive impairment, dyskinesia, speech disorder, hyperactivity, and frequency of occurrence. Unfortunately, there is no cure for AS.

The seven fetuses in our study were associated with microdeletion or microduplication of 15q11-q13. Among them, the 15q11.2 microdeletion of fetus 3 was inherited from the father and accompanied by a 16p13.11 microdeletion. Mutations on chromosome 15 of fetus 5 were also inherited from the father, but 15q11.2 was a microduplication. At the same time, we found that fetus 1, fetus 3, and fetus 5 had a high risk of Down syndrome. However, the sources of the 15q11.2 microdeletions of fetus 1, fetus 2, and fetus 4 are unknown, requiring further follow-up studies. According to existing research reports, the most common clinical manifestations of the 15q11-q13 microdeletion are mental delay, autism spectrum disorders, and other related behaviors (Butler, 2017; Farrell et al., 2020). The size of the lost region of fetus 6 and fetus 7 at 15q11-q13 was approximately 4-5 MB and contained the 15q11-q13 recurrence PWS/AS region (BP2-BP3). It has been reported that the abnormal BP1-BP3 or BP2-BP3 in 15q11-q13 regions is recognized as a risk factor for developmental delay (DD) and autism spectrum disorder (ASD) (Girirajan et al., 2012; Sanders et al., 2011).

5 | CONCLUSIONS

As previously discussed, microdeletion and microduplication in the 15q11-q13 region may lead to disease. However, there are no comprehensive treatment guidelines for fetuses with 15q11-q13 microdeletions and microduplications. More significantly, not all 15q11-q13 microdeletions and microduplications have a clinical phenotype, and not all fetuses carrying this abnormality are clinically affected; thus, there are no formal diagnostic criteria at this stage. Obstetricians usually cannot detect fetal abnormalities on ultrasound. The 15q11-q13 microdeletion and microduplication have probabilistic rather than deterministic risks. Therefore, clinicians should refer to pregnant women’s multiple data points to avoid misjudging etiology, diagnosis, and clinical importance. The parents’ psychological stress and consequences during later pregnancy should not be underestimated when loss in the 15q11-q13 region and microduplication in the fetus are reported to them. The majority of children with 15q11-q13 microdeletion and microduplication survive birth but develop more or less abnormally on a physical or mental level.
In summary, all seven fetuses in our study had varied-size copy number variations in 15q11-q13. Therefore, we should carefully consider whether to report these copy number changes to couples in the future. If the patient is truthfully informed of the status of the pregnancy check-ups and potential risks, then the follow-up should provide genetic counseling, implement humanistic care and analysis of the pros and cons of the patients, and strive to provide effective and practical help for patients with 15q11-q13 microdeletion and microduplication.

ACKNOWLEDGMENTS
We sincerely thank the seven families for supporting our research.

CONFLICT OF INTEREST
The author solemnly states that there is no conflict of interest to be disclosed.

AUTHOR CONTRIBUTIONS
XZH and LL worked together on analyzing the genetic data and drafted the present manuscript. WLH, JPC and MY collected patient data and track pregnancy. HYH, HG and QYL contributed to the data analysis and interpretation. DET and YD were responsible for the conception and revision of the paper, and made significant contributions to the manuscript. All authors have read and approved the final manuscript.

ETHICS STATEMENT
This study was conducted in strict accordance with the approval and supervision of the Committee of Shenzhen People’s Hospital. All participants provided written informed consent for sample collection and subsequent analyses.

DATA AVAILABILITY STATEMENT
Data for this study can be obtained from the author of the reply upon reasonable request.

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**How to cite this article:** Huang X, Chen J, Hu W, et al. A report on seven fetal cases associated with 15q11-q13 microdeletion and microduplication. *Mol Genet Genomic Med*. 2021;9:e1605. https://doi.org/10.1002/mgg3.1605