Han *et al. J Transl Genet Genom.* 2025;9:114-129
DOI: 10.20517/jtgg.2025.15

Journal of Translational Genetics and Genomics

Original Article

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Pregnancy outcomes and short-term follow-up of fetuses with recurrent microdeletion-microduplication syndromes featuring variable penetrance in prenatal diagnosis

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How to cite this article: Han C, Zhang Y, Xue J, Liu Y, An Y, Li H. Pregnancy outcomes and short-term follow-up of fetuses with recurrent microdeletion-microduplication syndromes featuring variable penetrance in prenatal diagnosis. *J Transl Genet Genom.* 2025;9:114-129. https://dx.doi.org/10.20517/jtgg.2025.15

Received: 8 Feb 2025 **First Decision:** 15 Apr 2025 **Revised:** 5 May 2025 **Accepted:** 28 May 2025 **Published:** 30 May 2025

Academic Editor: Saumya Shekhar Jamuar **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Objective: To retrospectively determine the incidence of recurrent microdeletion/microduplication syndromes in a prenatal cohort from Ningbo, China, and to evaluate pregnancy outcomes and live births in women carrying recurrent copy number variations (CNVs), this study aims to provide more clinical insights for assessing the variable penetrance of recurrent CNVs.

Method: A retrospective analysis was conducted on 7,645 pregnant women who underwent testing between 2019 and 2022 to investigate the incidence of locally recurrent microdeletion/microduplication syndromes and associated pregnancy outcomes. Chromosomal microarray analysis (CMA) identified 162 cases of recurrent CNVs. These cases were followed up to assess pregnancy outcomes, focusing on the implications of variable penetrance. The 162 patients were divided into two groups: Group 1 (n = 34), pregnancies with suspected genetic disease; Group 2 (n = 128), pregnancies with no apparent fetal abnormalities detected by ultrasonography. The study

compared CNV pathogenicity and the rate of abnormal live births between the two groups.

Results: Among the 7,645 microarray tests, 162 cases of recurrent CNVs were identified across 34 distinct recurrent regions, yielding an incidence rate of 2.1%. The highest proportion was observed in pregnancies of advanced maternal age (45/162, 28%), followed by cases with high-risk serological screening results (40/162, 25%) and abnormal non-invasive prenatal testing (NIPT) results (38/162, 23%). CMA revealed that the most frequently involved chromosomes were chromosome 16, chromosome 22, and the sex chromosomes (X and Y): 3 recurrent regions on chromosome 16 affected 37 fetuses; 2 recurrent regions on chromosome 22 affected 28 fetuses; and 4 recurrent regions on sex chromosomes (X and Y) affected 47 fetuses. Follow-up analysis showed a pregnancy termination rate of 36.97% among the 162 cases. In Group 1, 37% (13/34) of women continued their pregnancies, and 3 of the live births exhibited postnatal congenital cardiac anomalies; the remaining had no reported anomalies. In Group 2, 41% (54/128) continued the pregnancy, with postnatal anomalies identified in 11 cases. A chi-square (χ^2) test showed no statistically significant difference in the proportion of abnormal live births between the two groups ($P > 0.001$).

Conclusion: CMA enabled detection and analysis of recurrent CNVs in prenatal samples, offering insight into their clinical manifestations and associated pregnancy outcomes, particularly in cases with variable penetrance. Our findings enhance understanding of the clinical phenotypes of recurrent CNVs and provide additional data support for genetic counseling. Importantly, we found that fetuses carrying CNVs, despite the absence of structural anomalies, may face risks comparable to those with visible malformations. Therefore, we strongly recommend invasive prenatal diagnostic procedures when NIPT or serologic screening indicates abnormalities, as CMA-detected pathogenic CNVs can significantly impact prognosis and clinical decision making.

Keywords: Chromosomal microarray analysis (CMA), prenatal diagnosis, clinical phenotype, recurrent region

INTRODUCTION

Recurrent copy number variants (rCNVs), caused by genomic duplications and deletions, are a major contributor to genomic disorders. A key mechanism for these disorders is non-allelic homologous recombination (NAHR), which involves low copy repeats (LCRs) at specific genomic loci. Enhanced technologies have facilitated the characterization of the population prevalence and clinical features of rCNVs, which are increasingly recognized as important genetic factors in neurodevelopmental disorders (NDDs) and psychiatric conditions[1]. Several large population cohort studies have investigated the prevalence and inheritance patterns of rCNVs[2,3]. However, little research has been conducted on the association between rCNVs and congenital abnormalities or pregnancy outcomes.

The clinical significance of rCNVs has also been explored, particularly in terms of their roles in diagnosis, prognosis, and genetic underpinnings and biological pathways. Nevertheless, interpreting the clinical outcomes of rCNVs is highly complex due to their wide phenotypic spectrum, variable expressivity, and reduced penetrance - factors that complicate genetic counseling and clinical decision making. Additionally, the interpretation of CNV data raises ethical concerns, especially regarding how to counsel patients about uncertain prognoses and the potential psychological impact of genetic findings. Follow-up studies examining pregnancy outcomes in cases with rCNVs could provide valuable insights into the genotype-phenotype correlations of these associated prenatal disorders.

In this study, we performed a comprehensive analysis of 7,645 cases from a local prenatal amniocentesis cohort, incorporating detailed clinical data and chromosomal microarray analysis (CMA) findings, with particular emphasis on recurrent genomic regions identified through the DECIPHER database. We assessed the pathogenicity of identified variants according to the American College of Medical Genetics and

Genomics (ACMG) guidelines[4], and we conducted follow-up evaluations of pregnancy outcomes to better understand the clinical implications of recurrent microdeletion/microduplication syndromes. This study aims to systematically evaluate the various prenatal and postnatal clinical phenotypes associated with rCNVs of variable penetrance, thereby providing additional insights into their genetic interpretation.

MATERIALS AND METHODS

Between January 2019 and August 2022, 7,645 prenatal samples were collected from pregnant women who visited our hospital and underwent chromosomal microarray analysis, of which 7,518 were amniotic fluid samples and 127 were chorionic villi samples. A total of 162 recurrent microdeletions/microduplications were detected and included in this retrospective analysis. This investigation was approved by the Institutional Review Board of NingBo Women's and Children's Hospital.

Indications for CMA

Prenatal CMA was recommended based on the following indications: abnormal fetal free DNA results from maternal peripheral blood, high-risk serological screening outcomes, fetal structural abnormalities on ultrasound, soft ultrasound markers, fetal growth restriction, advanced maternal age, and a history of abnormal pregnancies.

Data collection

Clinical data were collected during pregnancy and after birth, including prenatal ultrasound findings, serological screening results, genetic testing results, pregnancy outcomes, and postnatal child development. Postnatal follow-up was conducted via telephone to assess the health status of each child. Relevant clinical and family history, including pedigree information, was also obtained.

Sample collection

Amniotic fluid samples were obtained via ultrasound-guided amniocentesis performed between 19 and 24^{+6} weeks of gestation. Three 15 mL samples were collected in sterile tubes: two for cell culture and karyotyping, and one for whole-genome DNA extraction. Additionally, 5 mL of peripheral blood was collected from each parent for parental verification.

Transabdominal chorionic villus sampling (CVS) was performed between 10 and 13 weeks of gestation under continuous transvaginal ultrasound guidance. Prior to the procedure, fetal crown-rump length (CRL) was measured to confirm gestational age, placental position was assessed, fetal heart rate was documented, and the needle path was planned. Following local anesthesia, an introducer needle was inserted into the placenta under ultrasound guidance. The stylet was then removed, and a biopsy needle was used to collect 8-10 mg of chorionic villus tissue in 1-2 passes. The sample was immediately preserved in a sterile 15 mL centrifuge tube containing saline. Peripheral blood (5 mL) was collected from both parents for further analysis.

CMA

All samples were analyzed using the CytoScan 750K Array (Affymetrix Inc., Santa Clara, CA, USA), which includes 750,000 probes - 550,000 non-polymorphic (NP) probes and 200,000 single nucleotide polymorphism (SNP) probes, offering a resolution of 0.1 Mb. Interpretation of copy number variations (CNVs) was based on the joint consensus recommendations of the ACMG and Clinical Genome Resources (ClinGen), as published in *Genetics in Medicine*, November 2019.

Genetic analysis

Each sample was interpreted by a clinical genetics laboratory. Chromosomal CNV regions were classified as benign, likely benign, pathogenic, likely pathogenic, or variants of uncertain significance.

Grouping criteria

Group 1: Pregnant women with strong clinical suspicion of a genetic disorder, such as increased nuchal transparency at 11-14 weeks, structural anomalies on ultrasound, or sonographic findings suggestive of increased genetic risk (e.g., intrauterine growth restriction (IUGR), polyhydramnios, or fluid buildup/neck edema). Group 2: Pregnancies without notable ultrasound abnormalities but with other risk indicators (e.g., abnormal NIPT or serologic screening results, advanced maternal age).

Statistical analysis

Data were processed using Microsoft Excel 2016 and analyzed with SPSS version 20.0. Frequencies and percentages (%) were compared using the chi-square (χ^2) test. A P value < 0.05 was considered statistically significant.

RESULTS

Specimen characteristics

In this study, the term "recurrent CNV" refers to CNVs listed in the DECIPHER database (https://www.deciphergenomics.org/disorders/syndromes/list), which includes a curated list of microdeletion and microduplication syndromes related to developmental disorders. The detected microdeletions/microduplications in our cohort were compared with those listed in the DECIPHER database. Cases with complete or partial overlap with CNVs in the DECIPHER list were further analyzed to explore their genetic characteristics. We analyzed CMA data from local amniotic fluid samples collected between 2019 and 2022. Thirty-four recurrent CNV regions were identified in our local database. CNVs detected in abortive tissue or peripheral blood samples were excluded from the current analysis.

A total of 7,645 prenatal cases were initially included in this study, comprising 7,518 amniotic fluid samples and 127 chorionic villi samples. Among these, 162 cases showed CNVs detected by microarray analysis, of which 34 involved recurrent regions - yielding an overall incidence rate of 2.1%. Maternal age distribution was as follows: < 30 years in 70 cases (43%), 30-34 years in 47 cases (29%), 35-39 years in 31 cases (19%), and ≥ 40 years in 14 cases (9%) [Figure 1A]. Clinical phenotype data (ultrasound findings), partial follow-up information, and inheritance patterns were available for the included cases. Among the 162 cases with recurrent CNVs, advanced maternal age (≥ 35 years at expected delivery) was the most common indication (45/162, 28%), followed by high-risk results from maternal serum screening (40/162, 25%) and abnormal findings from non-invasive prenatal testing (NIPT) (38/162, 23%). The distribution of other clinical indications, including abnormalities in the digestive, skeletal, and urinary systems, as well as soft ultrasound markers, is shown in Figure 1B.

Among the 162 CNV-positive cases, 24 also showed abnormal karyotypes in amniotic fluid samples. None of these abnormalities were detected in parental samples. Of these 24 cases, six pregnancies were continued, resulting in live births without obvious abnormalities. The detection rate of CNVs was 12% in amniotic fluid samples and 39% in chorionic villus samples, resulting in an overall prenatal diagnostic yield of 13%. A summary of copy number abnormalities identified in prenatal samples is shown in Figure 2.

Chromosomal abnormalities detected by CMA

Among the 162 cases analyzed, deletions accounted for 66% (109/162) and duplications for 32% (53/162) [Figure 3A]. CNVs were interpreted according to the joint consensus recommendations of the ACMG and

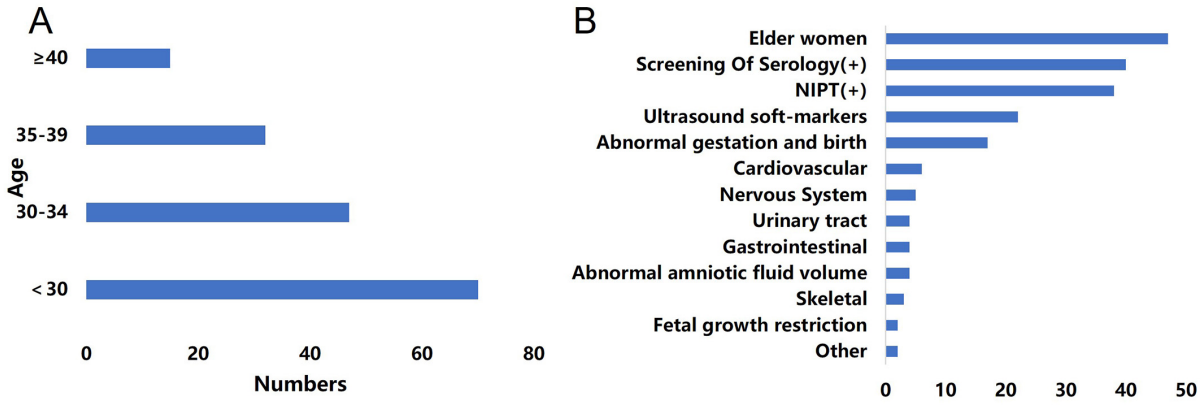

Figure 1. Age and clinical characteristics of the study population. (A) Age distribution of pregnant women. (B) Clinical phenotypes observed in pregnant women and fetuses.

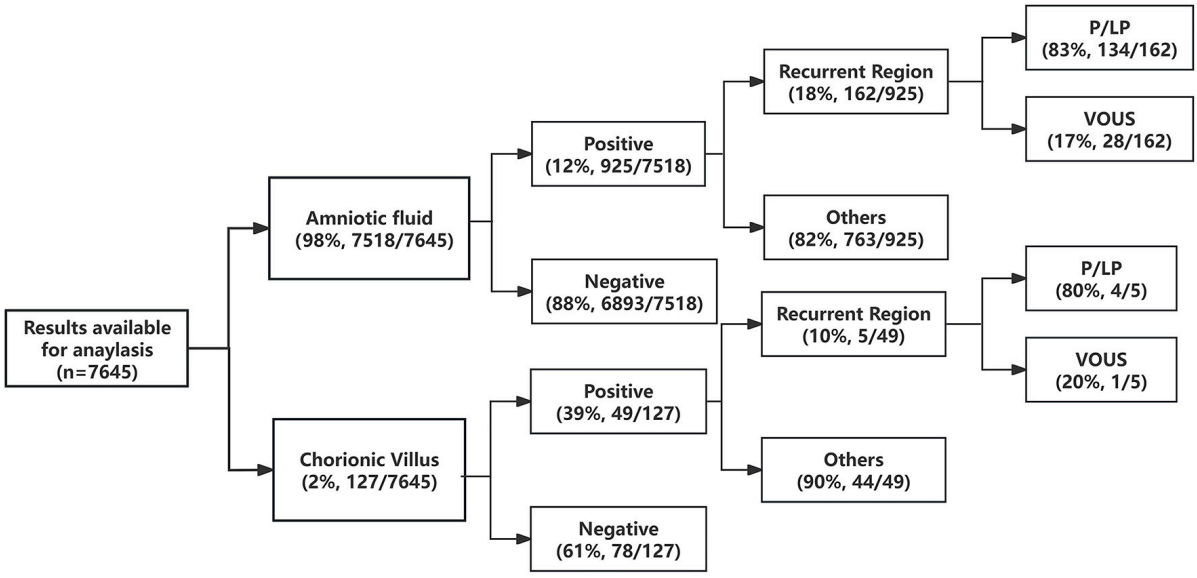

Figure 2. Summary and characterization of CNVs in prenatal samples. Resolution based on traditional G-banded karyotyping (> 10 Mb). Positive: CNV detected; Negative: no CNV detected; VOUS: variant of uncertain significance; P: pathogenic; LP: likely pathogenic; CNVs: copy number abnormalities.

the ClinGen, published in *Genetics in Medicine*, November 2019. Based on these guidelines, 134 cases (83%) were classified as pathogenic or likely pathogenic, while 28 cases (17%) were classified as VOUS [Figure 3B]. Additionally, 4 cases (2%) involved unverified regions of loss of heterozygosity (LOH) located in imprinted genomic regions. Of the 162 CNV cases, 26% (42/162) underwent parental origin verification, with 18% inherited from a parent and 8% identified as *de novo* [Figure 3C]. The samples were further categorized by maternal age into two groups: ≥ 35 years (n = 45) and ≤ 35 years (n = 117). Statistical analysis showed no significant relationship between CNV pathogenicity and maternal age ($\chi^2 = 0.058$, $P = 0.80 > 0.001$).

Analysis of recurrent regions revealed that chromosomes 16, 22, and the sex chromosomes (X and Y) were most frequently involved. Specifically: Chromosome 16 was associated with 3 recurrent regions, affecting 37 fetuses. Chromosome 22 was associated with 2 recurrent regions, affecting 28 fetuses. Sex chromosomes

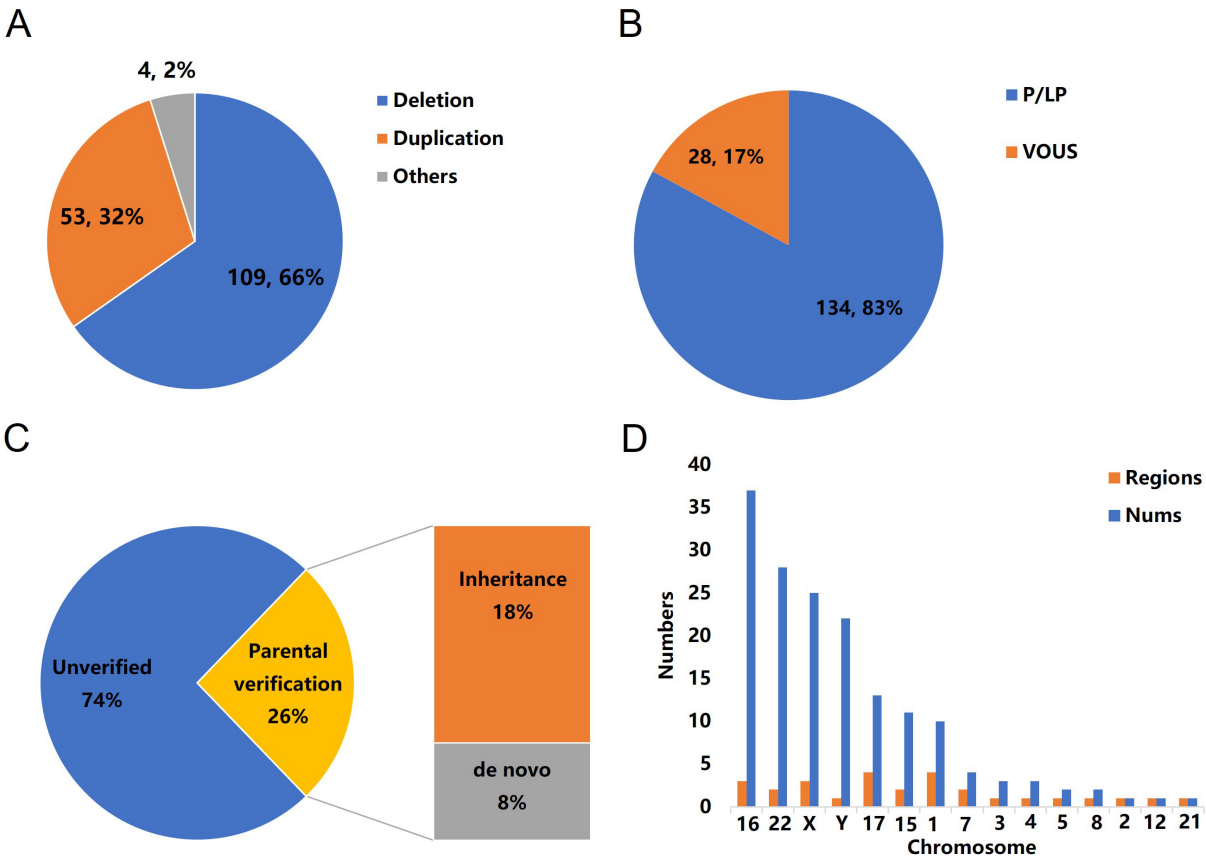

Figure 3. CMA results from 162 patients with recurrent CNVs. (A) Classification of CNV types. (B) Pathogenicity assessment results. (C) Parental origin verification outcomes. (D) Chromosomal distribution of recurrent CNVs.

(X and Y) were involved in 4 recurrent regions, affecting 47 fetuses [Figure 3D]. Among these, chromosome 16 showed the highest frequency of involvement in recurrent regions and affected the greatest number of fetuses. The pregnancy termination rate after follow-up was 36.97%.

The most frequently observed recurrent regions in our study included: 16p13.11 duplications (14/162, 8.6%), 16p11.2deletions (8/165, 5.0%), 22q11deletions (11/162, 6.8%), 22q11duplications (13/162, 8.0%), Xp22.33 deletions (Leri-Weill dyschondrosteosis) (10/162, 6.1%), Xp22.31 deletions (Steroid sulphatase deficiency) (14/162, 8.6%), and *AZFb+AZFc* (14/162, 8.6%). A summary of the recurrent regional incidence is shown in Table 1. Detailed information on the specific CNVs and corresponding pregnancy outcomes can be found in Supplementary Table 1.

The analysis of 162 CMA results and the pathogenicity classifications for different risk groups are summarized in Figure 4. Group 1: Pregnant women with a high clinical suspicion of a genetic disorder, indicated by one or more of the following findings: increased nuchal transparency at 11-14 weeks, structural abnormalities on fetal ultrasound, or ultrasound features suggestive of genetic disorders such as IUGR, polyhydramnios, or fluid buildup/neck edema. Group 2: 128 pregnancies without notable structural abnormalities on fetal ultrasound, but with other risk indicators such as abnormal NIPT, abnormal serologic screening, or advanced maternal age. In Group 1, 29 out of 34 cases (85%) had pathogenic or likely pathogenic (P/LP) variants *vs.* 105 out of 128 cases (82%) in Group 2 [Figure 4]. Among the Group 1 pregnancies, 37% (13/34) were continued, and 3 of these fetuses were found to have postnatal anomalies, all

Table 1. Incidence of recurrent CNVs in the study cohort

Region (gene)	CNV type	Coordinates (GRCh37/hg19)	Frequency	*De novo* frequency	Inherited frequency	Termination frequency	Size range (Kb)
1q21.1(BP3-BP4)(GJA5)	Deletion	chr1:146533376-147883376	2/162(1.21%)	N/A	N/A	2/2	1935-2048
1q21.1(BP3-BP4)(GJA5)	Duplication	chr1:146533376-147883376	5/162(3.05%)	1/5	1/5	2/5	838-3409
1q21.1 (TAR syndrome)(BP2-BP3)(RBM8A)	Deletion	chr1:145386506-145748067	1/162(0.61%)	N/A	1/1	0/2	548
1p36	Deletion	chr1:10001-12840259	2/162(1.21%)	1/2	N/A	2/2	2590-9397
2q37	Deletion	chr2:239969863-240322643	1/162(0.61%)	N/A	N/A	1/1	952
3q29(DLG1)	Deletion	chr3:195726835-197344663	2/162(1.21%)	N/A	1/2	2/2	802-1650
3q29(DLG1)	Duplication	chr3:195726835-197344663	1/162(0.61%)	N/A	1/1	1/1	1667
Wolf-Hirschhorn syndrome	Deletion	chr4:1569197-2110236	3/162(1.83%)	N/A	N/A	3/3	9446-23261
Cri du chat syndrome (5p deletion)	Deletion	chr5:10001-12533304	2/162(1.21%)	1/2	N/A	2/2	9868-16272
7q11.23(Williams-Beuren syndrome)(ELN)	Deletion	chr7:72744455-74142672	3/162(1.83%)	1/3	N/A	2/3	1560-3545
7q11.23	Duplication	chr:72744455-74142672	1/162(0.61%)	N/A	N/A	1/1	1548
8p23.1(GATA4)	Duplication	chr8:8100055-11764629	2/162(1.21%)	N/A	1/2	1/2	2156
12q14	Deletion	chr12:65071919-68645525	1/162(0.61%)	N/A	N/A	0	2215
15q13.3(BP4-BP5)(CHTNA7)	Deletion	chr15:30910306-32445407	1/162(0.61%)	N/A	1/1	0	444
Angelman syndrome&Prader-Willi Syndrome	Deletion	chr15:23619912-28438266	8/162(4.88%)	N/A	N/A	2/4	5488-79579
15q26 overgrowth syndrome	Duplication	chr15:99357970-102521392	3/162(1.83%)	N/A	N/A	1/3	778-1401
16p11.2-p12.2	Deletion	chr16:21512062-30199854	8/162(4.88%)	3/8	2/8	3/8	585-761
16p11.2(BP4-BP5)(TBX6)	Duplication	chr16:29606852-30199855	6/162(3.66%)	1/6	N/A	3/6	561-610
16p12.2(EEF2R, CDR2)	Deletion	chr16:21946524-22467284	2/162(1.21%)	N/A	1/2	0/2	601
16p13.11(BP2-BP3)(MYH11)	Deletion	chr16:14986684-16286684	7/162(4.27%)	1/7	3/7	1/7	852-1965
16p13.11(BP2-BP3)(MYH11)	Duplication	chr16:14986684-16286684	14/162(8.54%)	1/14	3/14	1/14	796-2918
17p12 (CMT1A, Charcot-Marie-Tooth disease)(PMP22)	Duplication	chr17:14097915-15470903	1/162(0.61%)	1/1	N/A	1/1	1343
17p12 (HNPP, Hereditary neuropathy with liability to pressure	Deletion	chr17:14097915-15470903	5/162(3.05%)	N/A	1/5	1/5	1383-1424

palsies)(PMP22)							
Miller-Dieker syndrome(17p13.3)	Deletion	chr17:1-2588909	5/162(3.05%)	N/A	1/5	2/5	472-1856
17q12 (RCAD syndrome)(HNF1B)	Deletion	chr17:34815072-36215917	2/162(1.21%)	N/A	1/2	2/2	1421-1927
21q21.2 (Early-onset Alzheimer's disease with cerebral amyloid angiopathy)	Duplication	chr21:27252860-27543446	1/162(0.61%)	N/A	N/A	0	10517
22q13(Phelan-Mcdermid syndrome)	Deletion	chr22:51045516-51187844	4/162(2.44%)	N/A	N/A	4/4	69-8996
22q11(TBX1,CRKL,SMARCB1)	Deletion	chr22:19009792-21452445	11/162(6.70%)	3/11	5/11	10/11	312-2884
	Duplication	chr22:19009792-21452445	13/162(7.93%)	1/13	2/13	12/13	653-3152
Leri-Weill dyschondrosteosis(*SHOX*)	Deletion	chrX:460558-867875	10/162(6.10%)	N/A	1/10	9/10	1066-58358
Xp22.31 (Steroid sulphatase deficiency)(STS)	Deletion	chrX:6455812-8124954	14/162(8.54%)	N/A	5/14	2/14	869-1688
Xq28(MECP2)	Duplication	chrX:153287263-153363188	1/162(0.61%)	N/A	N/A	0	7087
AZFb+AZFc	Deletion	chrY:19964826-27793830	14/162(8.54%)	N/A	1/14	3/14	1196-10318
AZFc	Deletion	chrY: 24977425-28033929	8/162(4.27%)	N/A	N/A	0	1734-34390

involving congenital cardiac anomalies; the remainder showed no anomalies. In Group 2, 42% (54/128) of the pregnancies were continued, and 11 fetuses were found to have postnatal anomalies. Postnatal anomalies were slightly more frequent in Group 1 than in Group 2 (23% *vs.* 20%). The 95% confidence interval for this difference is [-22.6%, +28.0%], which includes the possibility of "no difference" or even a "reverse difference". This suggests that the difference is not statistically significant, and the current sample size is insufficient to draw definitive clinical conclusions. The correlation between CNV pathogenicity and prenatal risk factors was evaluated using the χ^2 test. The difference in the detection rate of pathogenic CNVs between the two groups was not statistically significant ($P = 0.827$).

We also calculated the incidence of CNVs involving neuro-susceptibility genes among high-risk pregnancies. A total of 59 CNVs associated with neurodevelopmental disorders were identified (1q21.1, 3q29, 7q11.23, 15q11.2-q13.1, 15q13.3, 16p11.2 distal and proximal, 17p13.3, 17p11.2, 17q12, 17q21.31, 22q11.2 distal and proximal). Of these, 26 cases resulted in live births, 17 of which presented with congenital heart disease. To date, no clinical phenotypes related to the nervous system have been observed in these infants. The estimated incidence of CNVs associated with neurodevelopmental disorders among high-risk pregnancies is approximately 0.7% (59/7645) - equivalent to one deletion or duplication in every 150 high-risk pregnancies. For comparison, Smajlagić *et al.* reported an estimated incidence of 0.48% (1 in 200) for NDD-related CNVs in live-born infants from the general population. Given that our study cohort consisted of high-risk pregnancies, a slightly higher incidence rate is expected and reasonable[1].

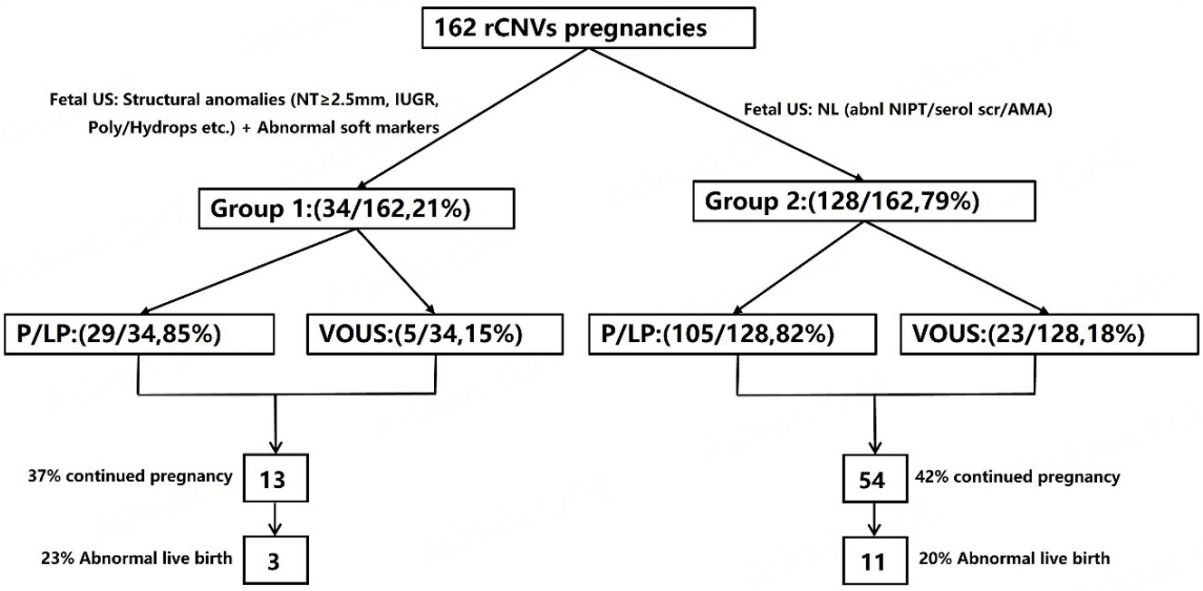

Figure 4. Overview of early-onset severe genetic disorders in different risk groups. NT: Nuchal translucency; Fetal US: fetal ultrasound; IUGR: intrauterine growth restriction; Poly/Hydrops: polyhydramnios/hydrops; abnl: abnormal; serol scr: serologic screening; AMA: advanced maternal age.

DISCUSSION

In the present study, we analyzed 162 recurrent CNVs, with a detection rate of 2.1%. The most common clinical indication was advanced maternal age, accounting for 28% (45/162) of the cases. However, statistical analysis revealed no significant differences in the pathogenicity or prognosis of CNVS between the advanced and non-advanced maternal age groups. While advanced age is a well-established risk factor for aneuploidies (e.g., Down syndrome) and *de novo* mutations[5], its association with microdeletions and microduplications remains unclear. Notably, each additional year of maternal age is associated with an average increase of 0.37 *de novo* mutations in offspring, whereas paternal age contributes to a greater increase of 1.51 mutations per year. Furthermore, high-risk results from serologic screening and cell-free fetal DNA screening were linked to a higher proportion of recurrent CNV regions. Huang *et al.* reported a CNV detection rate of approximately 3% among pregnant women with high serological risk[6]. In our intergroup analysis, no significant differences were found between groups, supporting the recommendation for invasive prenatal diagnostic procedures when non-invasive tests indicate serological abnormalities. These findings highlight the clinical relevance of CNV testing, as CNVs may have pathogenicity and prognostic outcomes comparable to those observed in fetuses with structural abnormalities, even in the absence of overt prenatal clinical features.

In our study, we utilized CMA of prenatal samples to assess the incidence of rCNVs on chromosomes 16, 22, X, Y, and others. We also examined the association between rCNVs and structural abnormalities detected by prenatal ultrasound. In addition, we followed up on all live births to better characterize the clinical phenotypes of rCNVs and investigated the occurrence of early-onset severe genetic disorders in different high-risk populations.

Chromosome 16

Genomic disorders are often caused by NAHR between segmental duplications. Chromosome 16 is among the most gene-rich chromosomes in the human genome, with approximately 10% of its sequence

comprising segmental duplications. This high density of duplicated regions renders it particularly unstable and prone to rearrangements via NAHR. In our study, we identified 37 CNVs on chromosome 16 through CMA analysis of amniotic fluid samples from 7,645 cases. Specially, three recurrent CNV regions were detected on chromosomes 16: 16p13.11 in 21 patients (7 deletions, 14 duplications), 16p11.2 in 14 patients (8 deletions, 6 duplications), and 16p12.1 in 2 patients (both deletions). These findings underscore the significant contribution of CNVs on chromosome 16 to genomic instability and their association with various disorders.

A large population-based cohort study found that individuals carrying the 16p13.11 duplication performed worse on cognitive function tests than non-carriers[7], although the effect size was modest. The clinical features associated with 16p13.11 duplication are relatively nonspecific and include developmental delay, intellectual disability/learning difficulties, behavioral abnormalities (e.g., ASD and ADHD), and various dysmorphic features. Most affected individuals inherit this duplication from unaffected parents[7-9]. Approximately 90% of pregnant women carrying a fetus with 16p13.11 duplication chose to continue the pregnancy. Follow-up data revealed that only one fetus (Case 14) exhibited postnatal abnormalities: a preauricular tag, a small left ear, and an abnormally shaped right auricle (Case 14). A similar variant reported in DECIPHER (287444), classified as of uncertain clinical significance, showed overlapping phenotypes, including external ear abnormalities, hearing impairment, and scalp dysplasia. No abnormalities were found in the remaining live births. Notably, the 16p13.11 region exhibits incomplete penetrance, and the limited prenatal indicators pose challenges in accurately evaluating the pathogenic potential, especially in relation to sex differences. We plan to follow up on relevant cases regularly to further elucidate this issue. The clinical phenotype associated with 16p13.11 syndrome mainly includes abnormal mental development, delayed speech, intellectual disability, epilepsy, and autism. Currently, these neurodevelopmental disorders cannot be reliably assessed during prenatal diagnosis, and our findings may differ from previous studies due to the pleiotropic nature and variable penetrance of the region.

We identified eight fetuses with 16p11.2 deletions, two of which exhibited prenatal ultrasound abnormalities - namely a single umbilical artery and abnormal skeletal development - both previously reported[10]. Among six fetuses with 16p11.2 duplications, one (Case 24) presented with megacystis on ultrasound. This is the first reported case of bladder dysplasia associated with 16p11.2 duplication syndrome. Although bladder dysplasia has not been reported in earlier studies, Rosenfeld *et al.* have reported 45 cases of 16p11.2 microdeletions and 32 microduplications, where three deletion cases involved urinary anomalies such as hydronephrosis and polycystic kidney disease. Four duplication cases involved renal anomalies such as vesicoureteral reflux and horseshoe kidney[11]. Other urinary abnormalities have been reported in deletion carriers[12-14]. Unfortunately, pregnancy was terminated in Case 24, and the amount of prenatal specimen was insufficient for further testing, so no additional genetic testing (e.g., for single-gene variants) was performed. We speculate that the fetus may have had structural or functional abnormalities in the urinary system that would have become more evident in mid-to-late gestation.

Ultimately, 50% of pregnancies with 16p11.2 CNVs were electively terminated. Among the continuing pregnancies, one child (Case25) carrying a *de novo* deletion was born with a diagnosis of atrial septal defect and patent foramen ovale. At age two, the child exhibited delayed language development. No significant abnormalities were observed in the remaining live births.

In our cohort, we identified a fetus (Case 36) with a 16p12.2 deletion inherited from an asymptomatic mother. Prenatal ultrasound revealed lateral ventriculomegaly and a persistent right superior vena cava. Genetic studies indicate that most 16p12.2 deletions are inherited (22/23; 95.7%) and that carrier parents are

more likely to exhibit neurological or psychiatric symptoms (e.g., learning disabilities, depression, bipolar disorder) than non-carrier parents, whose symptoms may include affective disorders and seizures. Typically, parental phenotypes are milder than those of the proband[15]. Therefore, in the absence of severe structural abnormalities, CNVs inherited from asymptomatic parents may be considered less pathogenic. Both fetuses with 16p12.2 deletions (Cases 36 and 37) were born without abnormalities.

Microdeletions and microduplications of chromosome 16 are primarily associated with cognitive and developmental delays, speech impairments, behavioral abnormalities, and other neurodevelopmental disorders. Based on CMA analysis of prenatal amniotic fluid samples, we estimated that the incidence of recurrent deletions on chromosome 16 was 22.42%. By summarizing follow-up data on live births with recurrent CNVs in chromosome 16, we enriched the clinical phenotypic spectrum of these regions and provided additional evidence to support clinical genetic counseling.

Chromosome 22

We identified a total of 24 CNVs in two recurrent regions on chromosome 22. Specifically, 22q11 alterations were found in 24 patients (11 deletions and 13 duplications), while deletions in 22q13 were detected in 4 patients.

According to the ClinGen dosage sensitivity curation and clinical overview of 22q11.2 rCNVs, individuals with 22q11.2 microdeletion/microduplication syndrome present with a wide range of phenotypes involving multiple organ systems. The most frequently observed congenital abnormalities are congenital heart defects and craniofacial dysmorphisms. However, data on the penetrance of these rCNVs remain limited. Some patients individuals carrying the same genotype appear phenotypically normal, while others exhibit mild to severe abnormalities[16-18]. After genetic counseling, over 90% of pregnant women continued their pregnancies. Among the fetuses with a 22q11 deletion, 72% (8/11) developed congenital heart disease. In the duplication group, 23% (3/13) developed neonatal jaundice and congenital heart defects after birth. Across the 22q11.2 microdeletion cases, congenital cardiovascular defects were the most common feature (observed in 45%) and included conditions such as tetralogy of Fallot, ventricular septal defect, and patent foramen ovale. In line with ClinGen's triplosensitivity phenotype annotations, 22q11.2 microduplications are associated with a broad range of variable phenotypes. Among the amniotic fluid samples affected by these CNVs, 46% of the pregnant women underwent CMA testing primarily due to high-risk results for trisomy 21 on maternal serological screening. B-mode ultrasound examinations revealed a variety of anomalies, including ventricular septal defect, absent right kidney, fetal cerebral ventriculomegaly, gallbladder fissure, and a small, poorly visualized cavum septi pellucidi. In our cohort, the penetrance of the recurrent 22q11 region reached 41% (10/24), slightly higher than previously reported. This difference may be attributed to the sample type, as all women who underwent amniocentesis did so due to high-risk factors[19].

In the present study, all four pregnancies involving a 22q13 deletion were electively terminated. The region includes two major pathogenic genes: *SHANK3* (606230) and *TCF20* (603107). Ultrasound findings included a small fetal cerebellum, persistent superior vena cava, and increased echogenicity in the intestine (Case 118). Alston *et al.* reported associations between cerebellar hypoplasia, progressive white matter lesions, and cortical atrophy in MC1DN33 disease[20]. Ferreira and Gahl[21] found that Schindler disease is characterized by white matter abnormalities and atrophy in many brain structures. Tahata *et al.* reported that ALG12-CDG manifests with gyrus hypertrophy, cerebellar vermis hypoplasia, enlarged cisterna magna, and corpus callosum hypoplasia[22]. The 22q13 region contains two key genes: *SHANK3* and *TCF20*. Mutations in *TCF20* are linked to an autosomal dominant disorder (MIM: 618430) characterized by developmental delay, variable intellectual disability, and behavioral abnormalities. Most affected individuals

have impaired intellectual development and speech difficulties, with many exhibiting features such as autism spectrum disorder and attention-deficit/hyperactivity disorder[23-25].

X chromosome

Xp22.33

Deletion of the pathogenic *SHOX* gene located at Xp22.33 can lead to Langer mesomelic dysplasia (LWD; MIM: 249700) and Leri-Weill dyschondrosteosis (LWD; MIM:127300). In our study, we identified 10 genetic variants in this region and conducted a 21-month follow-up on a live-born female infant (Case 74) who inherited the variants maternally. No growth retardation was observed during the follow-up period. The child continues to be closely monitored for developmental progress. The biological mother has a height of approximately 152 cm (5 feet) and shows no other notable phenotypic abnormalities within the family history. In contrast, all 8 other cases with large deletions and abnormal karyotypes all decided to terminate the pregnancy. Additionally, loss-of-function mutations in the *ARSE* gene cause X-linked recessive chondrodysplasia punctata (MIM:302950), which is characterized by short stature, microcephaly, hearing loss, cataracts, nasal bone dysplasia, and developmental delay (PMIDs: 993917, 9719382). According to previous literature, families with Xp22.3 deletions involving *SHOX* and *ARSE* genes often exhibit short stature, skeletal abnormalities, and attention-deficit/hyperactivity disorder[26]. In cases of idiopathic familial short stature (MIM: 300582), the height typically falls below the 3rd percentile for age or is more than 2 standard deviations (SD) below the national height standard[27].

Xp22.31

We report a total of 14 cases involving recurrent deletion in the Xp22.31 segment. In 5 of these cases, the deletion was clearly inherited from the mother, while the inheritance pattern in the remaining cases was undetermined. The sex ratio of affected fetuses was 1 male to 1.3 females, and 85% of pregnancies were continued. Postnatal follow-up revealed mild dry skin in female infants. All four affected male infants exhibited varying degrees of skin abnormalities. One male infant (Case 75), who inherited the deletion from an asymptomatic mother, manifested with severe scaly black patches on the legs and dry skin on the abdomen and back. Another male (Case 77) developed cryptorchidism. Previous reports indicate that female carriers may also display mild symptoms, such as corneal opacity and subtle skin abnormalities[27,28]. X-linked ichthyosis (XLI), most commonly observed in males, typically manifests after birth or during infancy. It is characterized by large, scaly, reddish-brown to dark patches, often covering much of the body. Affected areas may include the scalp, ears, neck, armpits, and cubital fossa, with the abdomen generally more severely involved than the back. Follicular keratosis is usually absent. Additional features may include corneal opacity (typically not affecting vision) and an increased risk of cryptorchidism[29].

Y chromosome

In the present study, 14 cases involved deletions in the AZFb+c regions and 7 cases in the AZFc region. Three fetuses with abnormal karyotypes (Cases 91, 102, and 108) resulted in elective pregnancy termination. No significant abnormalities were observed in the live births during follow-up. Y chromosome deletions are a known cause of male infertility, although affected individuals typically exhibit no obvious symptoms. Some infertile males with Y chromosome deletions may present with short stature and micropenis[30].

The Y chromosome primarily carries genes related to sexual development and fertility, including the sex-determining region. The SRY (sex-determining region Y) gene is located on the short arm of the Y chromosome at position Yp11.2. Clinically significant deletions often occur on the long arm of the Y chromosome, where one or more azoospermia factor (AZF) regions - classified as AZFa, AZFb, and AZFc - are partially or completely deleted. Overlap between the AZFb and AZFc regions was also observed[31,32].

Interstitial or terminal deletions involving the *AZFb* and/or *AZFb+c* regions (hereafter referred to as *AZFb/c*) are typically caused by recombination events between palindromic repeats, such as P5/proxP1, P5/distP1, or P4/distP1. These deletions are relatively rare and usually lead to severe azoospermia[33]. In contrast, deletions involving only the *AZFc* region are more common and are mediated by recombination between the b2/b4 palindromic repeats. These deletions result in a variable infertility phenotype, ranging from azoospermia and Sertoli cell-only (SCO) syndrome to severe or mild oligozoospermia[31,32].

Other findings

We also identified three cases of Williams-Beuren syndrome. Among them, two women chose to terminate the pregnancy, while the only live birth (Case 111) presented with a ventricular septal defect. The deleted chromosomal segment includes the region associated with Williams-Beuren syndrome, which is characterized by cardiovascular abnormalities, distinctive facial features, and connective tissue defects. The estimated prevalence is approximately 1 in 10,000 newborns[34,35]. Most individuals with this syndrome exhibit some degree of intellectual disability, ranging from mild to severe, along with specific cognitive impairments, growth abnormalities, and endocrine disorders. The majority of cases are caused by *de novo* mutations[36].

In the present study, we observed seven cases involving recurrent copy number variations in the 1q21.1 region (2 deletions, 5 duplications), all located in the recurrent distal region (BP3-BP4), which includes the GJA5 gene. These CNVs are associated with autosomal dominant congenital heart disease. Prenatal ultrasonography revealed hyperechogenic bowel in one fetus, which was inherited from an asymptomatic mother (Case 116). Thus far, only three cases of prenatal 1q21.1 duplications have been reported in the literature, including one case of duodenal atresia and two cases of absent nasal bone[37]. This syndrome exhibits strong clinical heterogeneity, with variable penetrance and a broad phenotypic spectrum ranging from asymptomatic to severe developmental delay and multiple congenital malformations. Common clinical features include mild to moderate developmental delay, microcephaly, subtle facial dysmorphism, and ocular anomalies[5,38,39]. Following genetic counseling, 42% (3 out of 7) of the pregnant women opted to continue the pregnancy. Among these three cases, one was inherited from a father with normal cognitive function; the child was followed up until 3 years old and showed no significant abnormalities (Case 122). Another case with an unverified mode of inheritance also showed no obvious abnormalities (Case 117). One *de novo* case mutation presented with postnatal cardiac abnormalities, including ventricular and atrial defects, as well as patent ductus arteriosus (Case 119). These findings suggest that some carriers of 1q21.1 microduplications may be phenotypically normal, implying incomplete penetrance or the presence of modifying factors at this locus[5].

Nonetheless, this study has certain limitations. The sample size was insufficient to systematically evaluate disorders with low penetrance or low incidence. Additionally, group analyses were performed only on recurrent CNV regions, which may have introduced bias. Therefore, larger cohort studies are required to validate the clinical significance of the CNVs identified in this study. In conclusion, our findings underscore the importance of advanced molecular techniques in prenatal diagnostics, which can improve diagnostic accuracy in both low- and high-risk pregnancies. We offer a clinical overview aligned with ClinGen recommendations and provide supporting clinical data for ACMG-based evaluation of pathogenicity in recurrent CNV deletions and duplications. However, further evidence is needed to clarify genotype-phenotype correlations across different recurrent regions.

Our research contributes to a deeper understanding of the clinical phenotypes associated with rCNVs and provides valuable data to support genetic counseling. The results suggest that fetuses with CNVs but no

structural abnormalities may carry risks comparable to those with structural defects. Therefore, in cases of abnormal prenatal screening, invasive prenatal testing is recommended. Pathogenic CNVs detected via chromosomal microarray analysis (CMA) are crucial for accurate prognostic assessment and clinical decision making.

DECLARATIONS

Acknowledgment

The authors would like to thank the participating families for their interest and involvement in this study.

Authors' contributions

Designed the study and wrote the manuscript: Han C
Helped with clinical information: Xue J
Writing - review & editing: Zhang Y
Critically revised the manuscript: An Y, Li H
All authors read and approved the final manuscript.

Availability of data and materials

All data presented in the study are included in this published article and its Supplementary Materials. Other raw data that support the findings of this study are available from the corresponding author upon reasonable request.

Financial support and sponsorship

This publication was funded by Ningbo Top Medical and Health Research Program (2022020405), Ningbo Science and Technology Project (2023Z178), Key Technology Breakthrough Program of 'Ningbo Sci-Tech Innovation YONGJIANG 2035'(2024Z221), Municipal Public Welfare Project (2022S035), and Ningbo Medical Brand Discipline Project (PPXK2024-06).

Conflicts of interest

Li H is a Junior Editorial Board member of *Journal of Translational Genetics and Genomics*. Li H was not involved in any steps of the editorial process, including reviewer selection, manuscript handling, or decision making, while the other authors have declared that they have no conflicts of interest.

Ethical approval and consent to participate

This study was approved by the Ethics Committee of The Affiliated Women and Children's Hospital of Ningbo University (EC2020-048). All the participants and the legal guardians/parents of minors gave written informed consent for their personal to be published in this study.

Consent for publication

Not applicable.

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