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ORIGINAL ARTICLE

Prenatal Genetic Diagnosis of Williams-Beuren Syndrome with Atypical and Complex Phenotypes

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SUMMARY

Background: **Williams-Beuren syndrome (WBS) is a severe congenital disorder that presents challenges in prenatal diagnosis due to the atypical or incomplete phenotypes exhibited by affected fetuses. This study investigated the relationship between genotype and complex phenotype in WBS fetuses using ultrasound, SNP array, and whole exome sequencing.**

Methods: **Chromosomal microarray analysis (CMA) and whole genome sequencing (WES) were conducted on pregnant women undergoing prenatal diagnosis. We analyzed genome-wide copy number variants (CNVs), regions of homozygosity (ROH), single nucleotide variants (SNVs), small insertions and deletions, and splice sites.**

Results: **A deletion at 7q11.23 was identified in 7 out of 6,718 prenatal diagnostic samples (1 in 960). Ultrasound findings varied: two fetuses exhibited cardiovascular anomalies; one presented with persistent left superior vena cava and intrauterine growth retardation (IUGR), while two others displayed polycystic kidney dysplasia, one accompanied by mild tricuspid regurgitation, and the remaining two fetuses showed no apparent ultrasound abnormalities. Genetic analysis revealed CNVs ranging in size from 1.43 to 1.66 megabase pairs (Mb), affecting 34 to 41 genes. On average, one additional CNV larger than 100 kilobase pairs (Kb) of unknown significance and 0.43 ROH larger than 5 Mb were identified in these cases. Although pathogenic or likely pathogenic SNV or splice sites related to renal development and cardiovascular development were found, none correlated with the fetal phenotype observed.**

Conclusions: **The phenotypes of WBS fetuses are often atypical and complex. Future research should focus on integrating advanced genetic technologies and improved imaging modalities to enhance our understanding of the intricate genotype-phenotype relationships associated with WBS.**

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KEYWORDS

Williams-Beuren syndrome, prenatal diagnosis, phenotype, chromosome microarray analysis, whole exome sequencing

LIST OF ABBREVIATIONS

WBS - Williams-Beuren syndrome
CMA - chromosomal microarray analysis
CNVs - copy number variants
ROH - regions of homozygosity
WES - whole exome sequencing
IUGR - intrauterine growth retardation
LSVC - left superior vena cava
DA - duct arterial
AA - aortic arch
RSVC - right superior vena cava
T - trachea
ARSA - aberrant right subclavian artery
P - pathogenic
VUS - variants of unknown significance

INTRODUCTION

Williams-Beuren syndrome (WBS), also known as Williams syndrome (WS; MIM 194050), is a rare neurodevelopmental disorder with an estimated prevalence of 1 in 7,500 to 1 in 20,000 live births [1,2]. WBS is characterized by a distinctive constellation of clinical features, including cardiovascular conditions such as coarctation of the aorta, peripheral pulmonary stenosis, and hypertension; mild to moderate intellectual disability; developmental delays; growth retardation; distinctive facial features; and endocrine and neurocognitive abnormalities [3,4].

The genetic basis of WBS is typically identified through a heterozygous microdeletion in the WBS critical region (WBSCR) on chromosome 7q11.23. This deletion typically spans 1.55 to 1.83 megabase pairs (Mb) [2,3]. Significant deletions in this region can lead to various clinical phenotypes [5-7]. The critical pathogenic region associated with WBS includes 31 known genes, with several such as *ELN*, *FZD9*, *BAZ1B*, *STX1A*, *LIMK1*, *CLIP2*, and *GTF2I* believed to contribute to the syndrome's complex phenotypic expression [3,8]. However, no single gene has been definitively linked as the sole cause of WBS, and understanding the contribution of these genes to the overall WBS phenotype remains an area of active research.

Currently, most WBS cases are diagnosed postnatally [9]. The ultrasound anomalies primarily drive prenatal diagnosis. Nevertheless, fetuses with WBS often not exhibit characteristic features of the syndrome during pregnancy. Instead, they may present with non-specific signs, such as increased amniotic fluid, intrauterine growth retardation (IUGR), short fetal femur length, and polycystic kidney dysplasia [10,11]. The relationship between these prenatal phenotypes and the 7q11.23 deletion is not fully understood and warrants further investigation.

With the increasing use of chromosomal microarray analysis (CMA) as a primary technique for prenatal diagnosis, more cases of WBS are being identified before birth. Although approximately 100 prenatal cases of WBS with various atypical phenotypes have been reported in the literature, these studies often focus on the 7q11.23 deletion, with less attention given to other genetic variants. This study aimed to integrate evidence from CMA, whole exome sequencing (WES), and imaging data to explore the correlation between complex phenotypes and genotypes in fetuses with WBS.

MATERIALS AND METHODS

Subject

This retrospective study analyzed the CMA results of 6,718 pregnant women who prenatally underwent diagnosis at our hospital and the Third Affiliated Hospital of Guangzhou Medical University between January 2019 and August 2023. The women were aged between 20 to 45 years, with gestational ages ranging from 11^{+2} to 35^{+4} weeks. The study received approval from the Medical Ethics Committee of Longgang District Maternal and Child Health Hospital (approval no. LGFYYXLLQF-2022-003). Written informed consent was obtained from all participants prior to amniocentesis.

Ultrasound examination

Each participant underwent a routine ultrasound examination, with a median gestational age of 24 weeks (11 - 35 weeks). Ultrasound examinations were performed using the Voluson E10 system (GE Medical Systems), with a 1 to 5 MHz scanning frequency. A comprehensive level III fetal anatomic scan was conducted for each case, and any detected abnormalities were documented and recorded.

Amniotic fluid sampling and DNA extraction

Amniotic fluid sample (5 mL) was collected following standard protocols and used for DNA extraction using the QIAamp DNA Blood Mini Kit (no. 51106, Qiagen, Germany). Additionally, 5 ml of peripheral blood were obtained from the pregnant woman to test for maternal contamination.

CMA analysis

CMA was conducted using the Affymetrix Cytoscan 750K chip (Thermo Fisher, USA). The extracted DNA underwent digestion, ligation, PCR amplification, purification, fragmentation, and labeling according to the manufacturer's instructions. The prepared chip was then washed, stained, and scanned. Data were collected and analyzed using Chromosome Analysis Suite (ChAS 4.3) software. The analysis focused on detecting aneuploidy,

Table 1. CNVs recognized with CMA and genes involved.

Case no.	Microarray nomenclature	Size (kbp)	Number of genes (protein-coding genes)	Genes involved	Classification
1	7q11.23 (72692113_74154209) x 1	1,462	37 (25)	*GTF2IRD2P1, POM121B, NSUN5, TRIM50, RPL7AP77, FKBP6, RNU6-1080P, FZD9, BAZ1B, RNU6-1198P, BCL7B, TBL2, MLXIPL, VPS37D, DNAJC30, BUD23, STX1A. MIR4284, RN7SL265P, BICDL3P, ABHD11, CLDN3, CLDN4, METTL27, TMEM270, ELN, ELN-AS1, LIMK1, EIF4H, MIR590, LAT2, RFC2, CLIP2, GTF2IRD1, RNA5SP233, GTF2I, GTF2I-AS1*	P
2	2q37.1 (233917755_234137480) x 3	220	1 (1)	*INPP5D*	VUS
	7q11.23 (72624167_74288694) x 1	1,665	41 (27)	*NCF1B*,...(same as case 1)....*PHB1P15, NCF1,GTF2IRD2*	P
	8q21.13(82088743_82229807) x 3	141	1 (1)	*FABP5*	VUS
3	7q11.23 (72669481_74154209) x 1	1,485	37 (25)	Same as case 1	P
4	7q11.23 (72664089_74154209) x 1	1,490	37 (25)	Same as case 1	P
	18p11.32 (283770_462315) x 3	179	1 (1)	*COLEC12*	VUS
5	7q11.23 (72669481_74146927) x 1	1,477	37 (25)	Same as case 1	P
6	6q14.2 (84606383_84776946) x 3	171	2 (2)	*CYB5R4, MRAP2*	VUS
	7q11.23 (72723371_74154209) x 1	1,431	34 (24)	*TRIM50*, ..(same as case 1).. *GTF2I-AS1*	P
	9p21.1 (30587632_30697418) x 1	110	0	/	VUS
	Xq28(148128198_148571167) x 2	443	1(1)	*IDS*	VUS
7	7q11.23 (72669481_74154209) x 1	1,485	37 (25)	Same as case 1	P
	6q21(110802069_110934453) x 3	132	1 (1)	*CDK19*	VUS

P - pathogenic, VUS - variants of unknown significance.
Genes marked with an underscore are protein-coding genes.

Table 2. ROH detection in WBS fetal samples.

Case	ROH	Size (Mb)	Number of genes included (number of protein-coding genes)
1	/	/	/
2	17q11.1q11.2 (25309337_30511274) x 2 hmz	5.2	148(70)
3	11p11.2p11.12 (45546761_51550787) x 2 hmz	6.0	117 (57)
4	/	/	/
5	/	/	/
6	/	/	/
7	3p21.31p21.1(46700713_52738165) x 2 hmz	6.0	222 (141)

Table 3. Fetal ultrasound findings or prenatal indications in 7 cases of WBS.

Case	Maternal age	Gestational week	Ultrasound phenotype or indication for prenatal diagnosis
1	37	23^{+2}	Enlarged right fetal heart, permanent left superior vena cava, left aortic arch with right clavicle; inferior arterial vagus, aortic isthmus distortion.
2	27	28^{+0}	Left polycystic dysplastic kidney; left heart slightly smaller, mild tricuspid regurgitation
3	36	18^{+3}	NIPT high risk for CNV in 7q11.23, strong light spot in left heart
4	22	23^{+2}	NIPT high risk for CNV in 7q11.23
5	29	32^{+2}	Pulmonary Artery Anomalies
6	44	31^{+1}	Intrauterine growth retardation, permanent left superior vena cava
7	30	32^{+6}	Left polycystic dysplastic kidney

Figure 1. 7q11.23 deletions identified in 7 fetuses.

The CMA results indicated that seven fetuses had heterozygous deletions in the 7q11.23 region, with all deletions involving the ELN gene. There were differences in the size of the deletion fragments and the genes involved in different samples (the lower black square columns represent OMIM-causing genes, and the gray square columns represent OMIM genes).

copy number variation (CNV), and region of homozygosity (ROH), with CNVs filtered at a threshold of 100 kilobase pairs (Kb) and ROH at 5 Mb. The interpretation of CNVs followed established guidelines [12].

Whole exome sequence analysis

Whole exome sequencing (WES) was performed on prenatal WBS cases. DNA extraction and purification were carried out using the TIANamp Genomic DNA Kit (DP705, China). Library construction was completed according to the manufacturer's instructions (ND617, Vazyme, China), and sequencing was conducted on a GenoLab M sequencer (Genemind, China), using pair-end reads with a length of 150 bp and an average sequencing depth of at least 20-fold.

The raw sequencing reads were processed using the BWA-GATK pipeline along with ClinSV for bioinformatics analysis. Single nucleotide polymorphisms (SNPs) and insertions/deletions (INDELs) were annotated using ANNOVAR software, and structural vari-

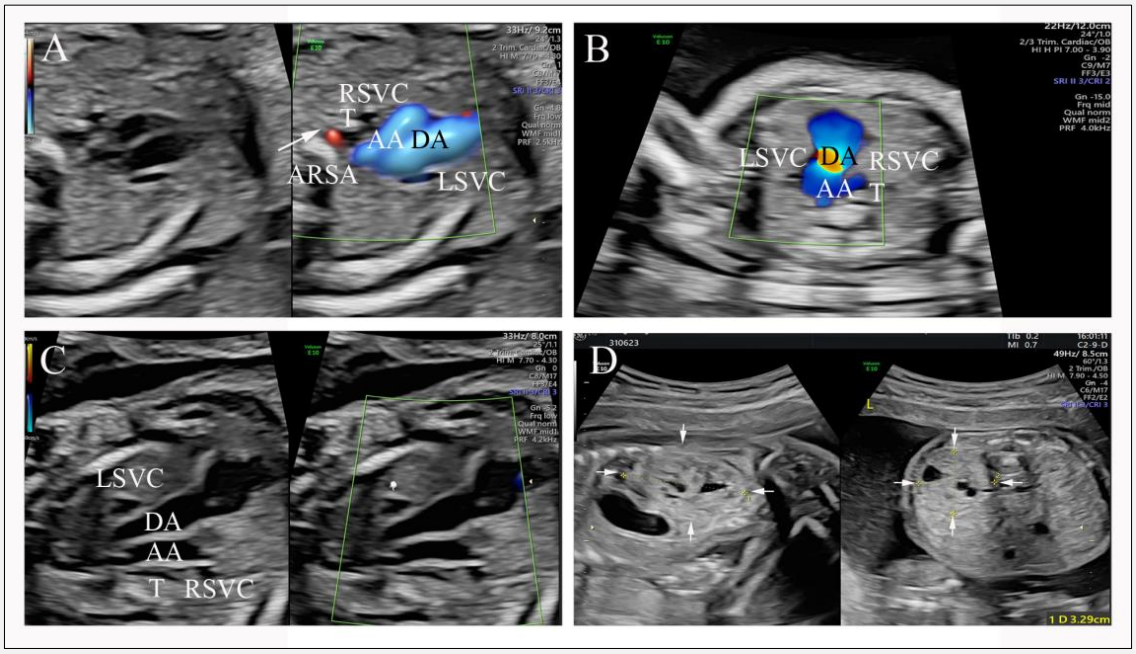

Figure 2. Ultrasound findings on WS fetuses.

Case 1: Ultrasound findings include: (A) in the three-vessel tracheal section (3VT section), the persistent left superior vena cava (LSVC) is observed on the left side of the arterial duct (DA). The right subclavian artery (ARSA) is seen anteriorly on the right side of the spine, originating from the descending aorta and looping behind the trachea to the right side.
(B) and (C) show a persistent left superior vena cava (LSVC) on the left side of the ductus arteriosus (DA) in both cases 1 and 6.
(D) In case 2, the fetal left kidney is enlarged with increased echogenicity, and multiple cysts are visible within the left kidney.
LSVC - left superior vena cava, DA - arterial duct, AA - aortic arch, RSVC - right superior vena cava, T - trachea, ARSA - aberrant right subclavian artery.

ants were annotated using AnnotSV software.

RESULTS

CNV analysis of the 7q11.23 region

Heterozygous deletions within the 7q11.23 region were identified in seven cases, with deletion sizes ranging from 1.43 Mb to 1.66 Mb. These deletions affected between 34 and 41 genes (Figure 1, Table 1). The specific genes involved in the deletions were consistent across five of the seven cases, emphasizing the recurrent nature of these deletions in WBS.

CNV detections outside the 7q11.23 region

In addition to the deletions in the 7q11.23 region, we identified six duplications and one additional deletion outside this region across the seven cases analyzed. Following the guidelines for CNV interpretation, these additional CNVs were classified as variants of uncertain clinical significance. Specifically, cases 2, 4, 6, and 7 exhibited two, one, two, and one additional duplicated CNVs, respectively. Case 6 also presented one additional deletion (Table 1).

ROH analysis

ROH analysis, utilizing a threshold of 5 Mb and a minimum of 50 markers, revealed the presence of ROHs in cases 2, 3, and 7. No ROHs were detected in the remaining cases, suggesting variable genomic stability among the affected individuals (Table 2).

Ultrasound findings

Cardiac or cardiovascular anomalies were documented in four out of the seven WBS cases (57.14%). Specific ultrasound findings included significant abnormalities such as an enlarged right heart with a thin aortic isthmus in case 1, pulmonary artery anomalies in case 5, and a slightly smaller left heart with a small amount of tricuspid regurgitation in case 2. Case 6 presented with a persistent left superior vena cava and intrauterine growth retardation (IUGR). Additionally, polycystic renal dysplasia was suggested by ultrasound in cases 2 and 7 (28.57%). The other two fetuses (cases 3 and 4) did not

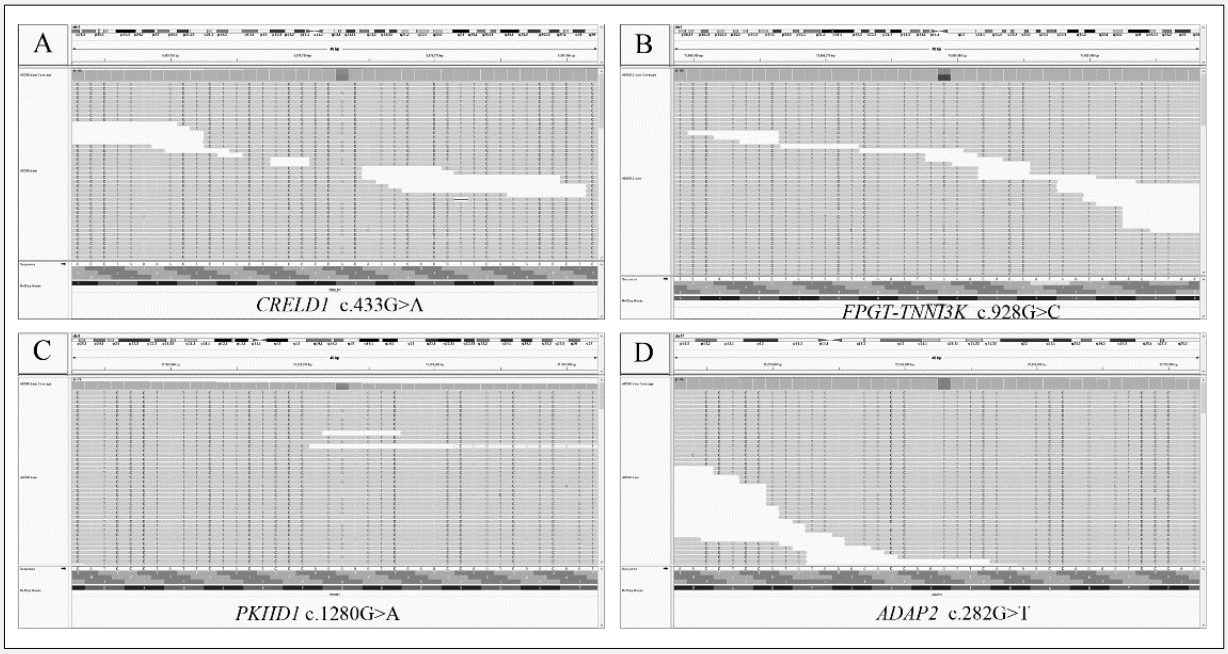

Figure 3. Whole exome sequencing.

A heterozygous variant was observed in case 1; the mutation in the *CRELD1* gene was associated with an atrioventricular septal defect. (B) A probable pathogenic variant in the *FPGT-TNNI3K* gene was identified in case 2, associated with cardiac conduction disease. (C) A VUS variant in the *PKHD1* gene was found in case 2, who had multiple cysts on ultrasound. A homozygous variant in the *ADAP2* gene was identified in the ROH region of case 2.

show significant cardiovascular abnormalities, although case 3 presented with intense echogenicity in the left heart. Detailed ultrasound findings are summarized in Table 3 and illustrated in Figure 2.

Whole exome sequencing

Due to insufficient DNA quality and quantity, only four out of the seven samples underwent WES. No homozygous variants were identified within the 7q11.23 region, where one allele was deleted. A single homozygous variant of uncertain significance was found in the ROH region of case 2. Although variants associated with atrioventricular septal defects or congenital heart defects were identified in cases 1, 2, and 3, none of these genetic findings correlated directly with the observed complex phenotypes (Figure 3, Supplementary Table).

DISCUSSION

WBS is primarily characterized by a spectrum of clinical phenotypes that complicate prenatal diagnosis. Despite advances in prenatal diagnostic techniques, only a limited number of WBS have been identified prenatally before birth [10,11,13-16]. This challenge comes primarily from the atypical or incomplete manifestation of the syndrome's phenotypes during fetal development, often leading to missed diagnoses. For instance, although cardiovascular abnormalities are a hallmark of WBS, only 42.9% to 58.82% of affected fetuses exhibit detectable ultrasound abnormalities [10,11]. Conversely, non-specific phenotypes, such as IUGR, abnormal fetal placental Doppler indices, thickened nuchal translucency (NT) or nuchal fold (NF), polyhydramnios, are more frequently observed [10,11,14]. Our study provides crucial insights into the prenatal genetic diagnosis of WBS, particularly in cases presenting with atypical and complex phenotypes.

The identification of heterozygous deletions in the 7q11.23 region in seven out of 6,718 prenatal diagnostic samples highlights the importance of using CMA as a primary diagnostic tool. Consistent with previous reports [17,18], the deletion sizes in our cases were variable, affecting between 34 and 41 genes. This variability may contribute to the observed clinical heterogeneity, suggesting that larger or smaller deletions within the WBS critical region may lead to differing pheno-

typic outcomes. Intriguingly, while five of the seven cases shared the same deleted genes, cases 1, 3, 4, 5, and 7 exhibited different phenotypes. This discrepancy may be due to limited prenatal evaluation, inherent clinical heterogeneity among individuals with WBS, or the influence of other undiscovered genetic variants.

The observation that some fetuses had cardiovascular anomalies while others had no detectable abnormalities despite having similar deletions highlights the need to better understand the relationship between specific CNVs and their phenotypic manifestations. In addition to the 7q11.23 deletion, our study identified other CNVs, including duplications and deletions classified as variants of unknown clinical significance. For instance, case 7 had a duplicated CNV on chromosome 6, encompassing the *CDK19* gene, associated with mental retardation and epileptic encephalopathy [19,20], but this condition is unrelated to the duplication. Similarly, case 4 had an additional deletion CNV on chromosome 18 involving the *COLEC12* gene, which is part of a class of c-type lectins [21], but its disease relevance is currently unknown. The clinical implications of these CNVs, particularly their role in the complex phenotypes associated with WBS, remain unclear and warrant further investigation.

Our study also examined the presence of regions of homozygosity (ROH). Although ROHs were identified in three cases, they were not localized to disease-causing regions. The absence of pathogenic variants in these regions suggests that ROH is unlikely to significantly influence the phenotypic complexity of WBS. Thus, the phenotypic variability observed in WBS is more closely related to the size and specific gene content of CNVs rather than ROHs.

Furthermore, the limited correlation between identified pathogenic or likely pathogenic variants and the observed complex phenotypes suggests that more extensive genome-wide analyses, such as WES, may not improve our understanding of genotype-phenotype correlations in our prenatally diagnosed WBS cases. In case 1, characterized by cardiovascular abnormalities, a *CRELD1* variant was found. Although *CRELD1* variants are known to cause atrial septal defects [22] and are associated with bicuspid aortic valve anomalies [23], the clinical significance of the variant identified in our study remains unknown. Similarly, a heterozygous variant in the *PKHD1* gene was found in case 2 with polycystic dysplastic renal phenotype. However, only homozygous or compound heterozygous mutations in *PKHD* cause polycystic kidney disease [24]. Thus, the complexity of the WBS phenotype in these fetuses does not appear to correlate with the variants identified by WES. It is essential to recognize that while WES provides valuable insights into the genetic landscape, the nuances of phenotypic expression may not always align with the detected genetic variations.

In conclusion, this study highlights the multifaceted nature of prenatal phenotypes in WBS and emphasizes that ultrasound findings often do not reliably predict genetic outcomes. Future research should focus on the integration of advanced genetic technologies and improved imaging modalities to improve our understanding of the intricate genotype-phenotype relationships associated with WBS.

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Declaration of Interest:

The authors declare that they have no competing financial interests.

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