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Phenotypic spectrum of 11p15.5 duplications: parent-of-origin and copy number variant size shape outcomes from Silver-Russell to Beckwith-Wiedemann syndromes

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Abstract

Background Genomic imprinting at the 11p15.5 region is critically involved in fetal growth regulation. Disturbances in this region are primarily associated with two opposing growth disorders: Silver-Russell syndrome (SRS, growth restriction) and Beckwith-Wiedemann syndrome (BWS, overgrowth). While epigenetic alterations are well-characterized in SRS and BWS, copy number variants (CNVs) rearrangements remain incompletely understood, particularly in terms of how duplication size and parental origin shape the phenotypic spectrum.

Methods We present a case series of three prenatally identified fetuses with 11p15.5 duplications, characterized by chromosomal microarray analysis and Methylation-Specific Multiplex Ligation-dependent Probe Amplification (MS-MLPA). Parental origin was determined by segregation analysis.

Results *Case A*: A focal duplication of the maternally inherited allele encompassing only the ICR2/*CDKN1C* domain presented with severe isolated intrauterine growth restriction (IUGR), consistent with a SRS phenotype. *Case B*: A large duplication of the maternally inherited allele spanning both the ICR1/*H19/IGF2* and ICR2/*CDKN1C* domains resulted in a complex phenotype of IUGR (SRS-like) with omphalocele (a BWS-associated anomaly), demonstrating a mixed and paradoxical presentation. *Case C*: A large duplication of the paternally inherited allele of the entire 11p15.5 region was associated with a BWS phenotype, presenting with macrosomia and other features, consistent with the predominant effect of paternal inheritance.

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Conclusion Our findings support a model in which parental origin shows a strong tendency to determine the direction of growth dysregulation (maternal allele duplications predominantly associate with SRS-like restriction; paternal allele duplications with BWS-like overgrowth), while duplication size contributes to phenotypic complexity, with larger rearrangements involving both ICRs more frequently associated with severe or blended features. However, exceptions to this generalization exist in the literature, highlighting that 11p15.5 duplication disorders exhibit variable penetrance and expressivity.

Keywords 11p15.5 duplications, Parent-origin, Copy number variant, Silver-Russell, Beckwith-Wiedemann syndromes

Introduction

Genomic imprinting, an epigenetic phenomenon, results in monoallelic expression of a subset of genes in a parent-of-origin-specific manner [1]. This process is vital for coordinating fetal growth and placental resource acquisition. The 11p15.5 region involves several intricately imprinted loci that play a critical role in regulating human growth both prenatally and postnatally [2]. Disruption of the fine-tuned regulatory mechanisms within this region underlies two contrasting syndromes characterized by growth disorders: Beckwith-Wiedemann syndrome (BWS) [3] and Silver-Russell syndrome (SRS) [4, 5].

The 11p15.5 domain is organized into two independently regulated imprinting control regions (ICRs). The telomeric ICR1, also known as the H19/IGF2 intergenic differentially methylated region (IG-DMR) [6], is paternally methylated. This methylation silences the maternal allele of the long non-coding RNA H19 and allows the enhancers to access the paternal allele of *IGF2*, a potent paternally expressed fetal growth factor. Centromeric to ICR1 lies ICR2, or the *KCNQ1OT1* transcription start site DMR, which is maternally methylated. The methylation on the maternal allele suppresses the expression of the *KCNQ1OT1* lncRNA, thereby permitting the expression of several maternally expressed genes, most notably *CDKN1C*, a key cyclin-dependent kinase inhibitor that functions as a potent growth suppressor [7]. The harmonious opposition between the growth-promoting *IGF2* and the growth-restraining *CDKN1C*, governed by their respective ICRs, is fundamental to achieving normal fetal growth equilibrium (Fig. 1).

An imbalance in this region underlies two clinically antithetical growth syndromes. SRS is primarily characterized by severe prenatal and postnatal growth restriction, relative macrocephaly, body asymmetry, and feeding difficulties. The most common molecular cause (in ~ 50% of cases) is hypomethylation of ICR1 on the paternal allele, which leads to a loss of *IGF2* expression and biallelic expression of H19 [8]. Conversely, Beckwith-Wiedemann syndrome (BWS) is an overgrowth disorder featuring macrosomia, macroglossia, abdominal wall defects (e.g., omphalocele), and a predisposition to embryonal tumors [9]. The predominant mechanism (in ~ 50–60% of cases) is loss of methylation at ICR2 on the maternal allele [10], resulting in silencing of *CDKN1C* and biallelic expression of *KCNQ1OT1* [11, 12] .

While epigenetic alterations account for the majority of SRS and BWS cases, copy number variations (CNVs) affecting the 11p15.5 region represent a rare but informative etiology. Current research and clinical diagnostics have largely focused on methylation defects, creating a knowledge gap regarding the precise role of CNVs. The phenotypic consequences of these CNVs are complex and not fully predictable from CNV type alone. For instance, duplications of maternal origin are typically associated with growth restriction, while duplications of the paternally inherited allele tend to associate with overgrowth. However, cases with overlapping or mixed phenotypes challenge this general pattern, highlighting the need for a deeper understanding of how CNV size, genomic context, and other modifiers influence clinical outcomes.

In this study, we present a characterized series of three prenatal cases with 11p15.5 duplications that exemplify the phenotypic spectrum from isolated growth restriction to overgrowth. Through CNV mapping, methylation analysis, and determination of parental origin, we illustrate how duplication size and parental origin interact to influence phenotypic presentation. Our findings provide a contribute to the evolving understanding of genotype-phenotype correlations in 11p15.5 duplication syndromes, and underscore the importance of integrating molecular findings with cautious, family-specific counseling.

Materials and methods

Study subjects and clinical data collection

This was a retrospective case series of three pregnant women whose fetuses were diagnosed with 11p15.5 duplications through prenatal genetic testing at our institution. The study was approved by the Medical Ethics Committee of Henan Provincial People's Hospital (No.134 of 2019). Informed consent was obtained from all participating families.

Clinical indications for testing included abnormal prenatal ultrasound findings (e.g., growth restriction, omphalocele) and/or a high-risk result from maternal serum screening for aneuploidy. Clinical data, including maternal age, prenatal ultrasound reports, serum

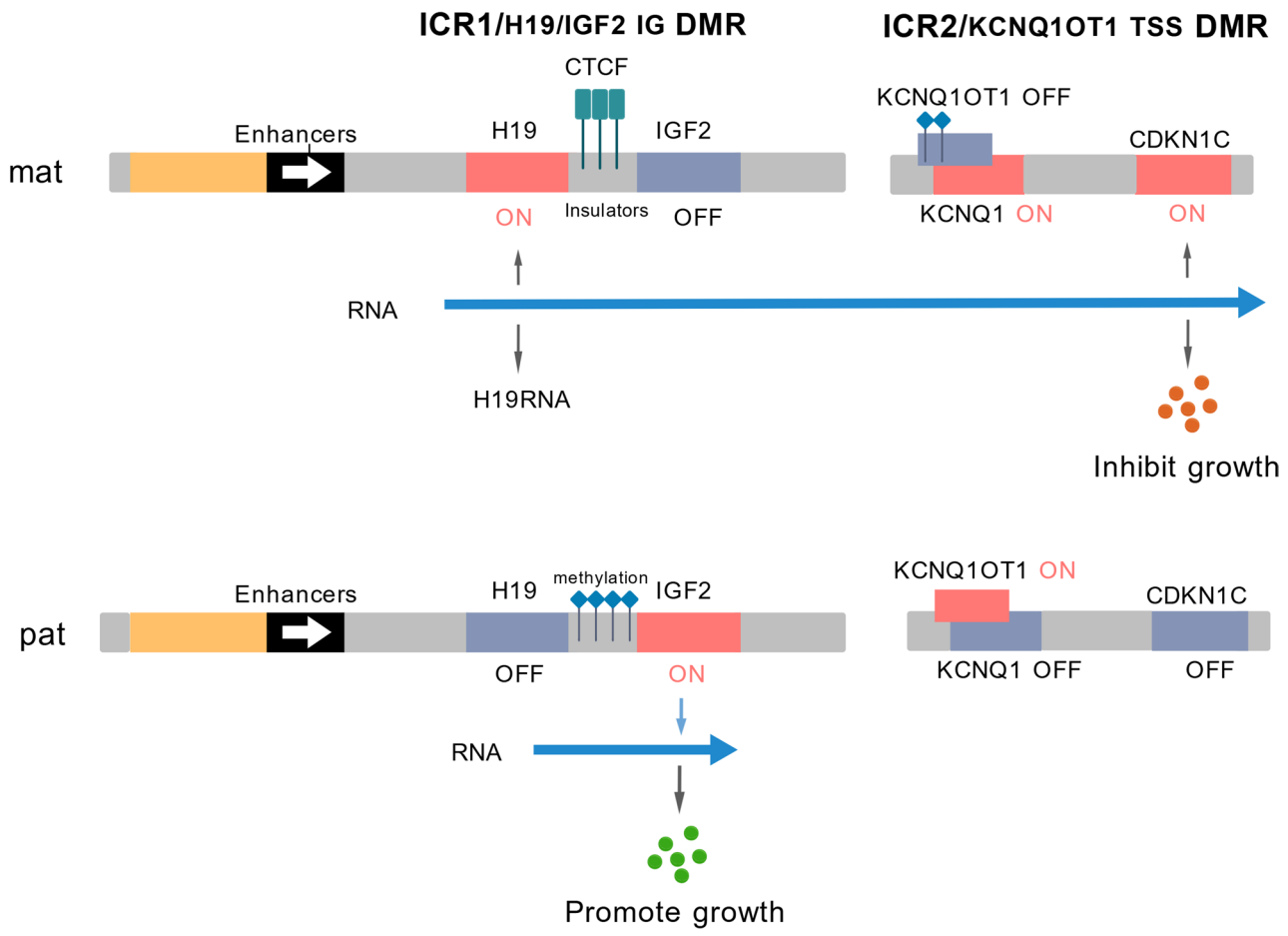

Fig. 1 This diagram illustrates the imprinted gene clusters at human 11p15.5, comprising two domains regulated by parent-specific DNA methylation. In the telomeric domain, differential methylation of ICR1 dictates allele-specific expression. On the maternal allele, unmethylated ICR1 binds the insulator protein CTCF, blocking enhancer access to the *IGF2* promoter and restricting expression to *H19*. On the paternal allele, ICR1 methylation prevents CTCF binding, allowing enhancer-driven *IGF2* expression and silencing *H19*. In the centromeric domain, reciprocal methylation of ICR2 controls a long non-coding RNA. The unmethylated paternal ICR2 permits *KCNQ1OT1* transcription, which silences neighboring genes (*CDKN1C*, *KCNQ1*) in cis. On the maternal allele, ICR2 methylation represses *KCNQ1OT1*, enabling expression of *CDKN1C* and *KCNQ1*

screening results, and pregnancy outcomes, were collected from electronic medical records.

Cytogenetic and molecular genetic analyses

Karyotyping

G-banding karyotype analysis was performed on cultured amniotic fluid or umbilical cord blood cells according to standard protocols. At least 20 metaphases were analyzed for each case, and the results were reported according to the International System for Human Cytogenomic Nomenclature (ISCN 2020).

Array-comparative genomic hybridization (aCGH)

Genomic DNA samples meeting quality control standards were analyzed using SurePrint G3 Human CGH 8 × 60 K microarrays (Agilent Technologies). The experimental procedure was performed according to the manufacturer's protocol, which included DNA labeling, hybridization, and washing. Slides were scanned using an Agilent microarray scanner, and CNVs were called based on three consecutive probes with a log2 ratio > 0.25 or <-0.25, providing a reliable detection resolution of approximately 200 kb. All genomic coordinates are based on the GRCh37/hg19 reference sequence.

Copy number variation sequencing (CNV-seq)

CNV-seq libraries were constructed using a commercial high-throughput sequencing kit (BerryGenomics) following the manufacturer's instructions. The process included DNA fragmentation, adapter ligation, and sample barcoding. Pooled libraries were sequenced on the NextSeq CN500 platform to achieve a minimum 1× genome coverage, enabling the detection of CNVs at a 100 kb resolution. Sequencing reads were aligned to the GRCh37/hg19 reference genome, and quality metrics including read depth and coverage uniformity were assessed to ensure data reliability.

Methylation analysis

The methylation status of the ICR1 (H19 DMR) and ICR2 (KCNQ1OT1 TSS-DMR) was analyzed using Methylation-Specific Multiplex Ligation-dependent Probe Amplification (MS-MLPA) with the SALSA MS-MLPA Probemix ME030 BWS/RSS (MRC Holland, Amsterdam, The Netherlands). Genomic DNA was subjected to sodium bisulfite conversion. Specific probes designed for methylated and unmethylated sequences within the ICR1 and ICR2 regions were hybridized to the DNA, followed by ligation and PCR amplification. The amplified products were separated and quantified by capillary electrophoresis. Methylation ratios were analyzed using Coffalyser.Net software (MRC Holland), allowing simultaneous assessment of both copy number and methylation status at these imprinted loci.

Determination of parental origin

The parental origin of the identified duplications was determined by segregation analysis using STR markers Short Tandem Repeat (STR) markers within and flanking the duplicated 11p15.5 region were analyzed in the proband and both parents using fluorescently labeled primers and capillary electrophoresis. The haplotype phase was constructed to determine which parental chromosome carried the duplication.

Results

Clinical presentation and molecular findings in three prenatal cases with 11p15.5 duplications

We present a series of three prenatal cases with 11p15.5 duplications, illustrating a broad spectrum of clinical phenotypes observed in association with different duplication sizes and parental origins. The molecular characteristics and clinical summaries of all three cases are detailed in Table 1.

Case 1: isolated growth restriction associated with a maternal allele duplication spanning the ICR2 domain

A fetus was referred for prenatal genetic testing following the sonographic identification of severe, proportionate growth restriction, with both head circumference (HC) and abdominal circumference (AC) measuring below the 3rd percentile according to NICHD standards. The family history was significant, as the mother's first pregnancy had resulted in a term small-for-gestational-age (SGA) infant who succumbed at one month of age, raising suspicion of an inherited genetic condition.

Conventional karyotyping of the proband was normal (46, XN). Subsequent CNV-seq analysis identified a ~ 810 kb duplication at 11p15.5p15.4 (arr[hg19] chr11:g (2155190–2966876)dup) (Fig. 2A). Segregation analysis confirmed that this variant was inherited from the phenotypically normal mother, establishing its maternal origin. The duplicated segment is located telomeric to the ICR1 domain and encompasses the entire *KCNQ1* gene and the *CDKN1C* gene within the ICR2 domain. Consistent with a duplication of the maternally inherited allele of this locus, methylation analysis of the *KCNQ1OT1*/ICR2 domain revealed an average methylation level of approximately 70%, significantly elevated from the expected 50% (Fig. 3). In contrast, the H19/ICR1 domain displayed a normal methylation pattern, and the H19 copy number was two.

Case 2: a complex phenotype of growth restriction with omphalocele associated with a large maternal allele duplication involving both ICR1 and ICR2

A second fetus presented with both intrauterine growth restriction (IUGR) and an omphalocele. CNV-seq analysis revealed a larger ~ 3.6 Mb duplication at 11p15.5p15.4 (arr[hg19] chr11:g.(86591-3,680506)dup) (Fig. 2B). The mother was found to carry the same duplication, confirming the maternal origin. This large duplication encompasses the entire critical 11p15.5 imprinting region, including both the telomeric ICR1 (*H19*/*IGF2*) and the centromeric ICR2 (*KCNQ1OT1/CDKN1C*)

Table 1 Summary of clinical and molecular characteristics of the three prenatal cases with 11p15.5 duplications

Case	Prenatal indication	Karyotype	CNV (hg19) & size	Parental origin	Key implicated genes	Predominant phenotypic assignment
1	Isolated growth restriction	46, XX	arr[GRCh37] 11p15.5p15.4(2155190_2966876)×3 (~ 810 kb)	Maternal	*CDKN1C*: 3 copies (2 expressed maternal alleles)	Silver-Russell syndrome (SRS)
2	Growth restriction, omphalocele	46, XY	arr[GRCh37] 11p15.5p15.4(86591_3680506)×3 (~ 3.6 Mb)	Maternal	*IGF2*: Loss of Imprinting (LOI); *CDKN1C: 3* copies (2 expressed maternal alleles)	Mixed/Atypical BWS-SRS phenotype
3	High-risk T21 screen, macrosomia	46, XX	arr[GRCh37] 11p15.5p15.5(440000_2460000)×3 (~ 2.02 Mb)	Paternal	*IGF2*: 3 copies (2 expressed paternal alleles; overexpression); *CDKN1C*: 3 copies (1 expressed maternal allele; relative under-expression)	Beckwith-Wiedemann syndrome (BWS)

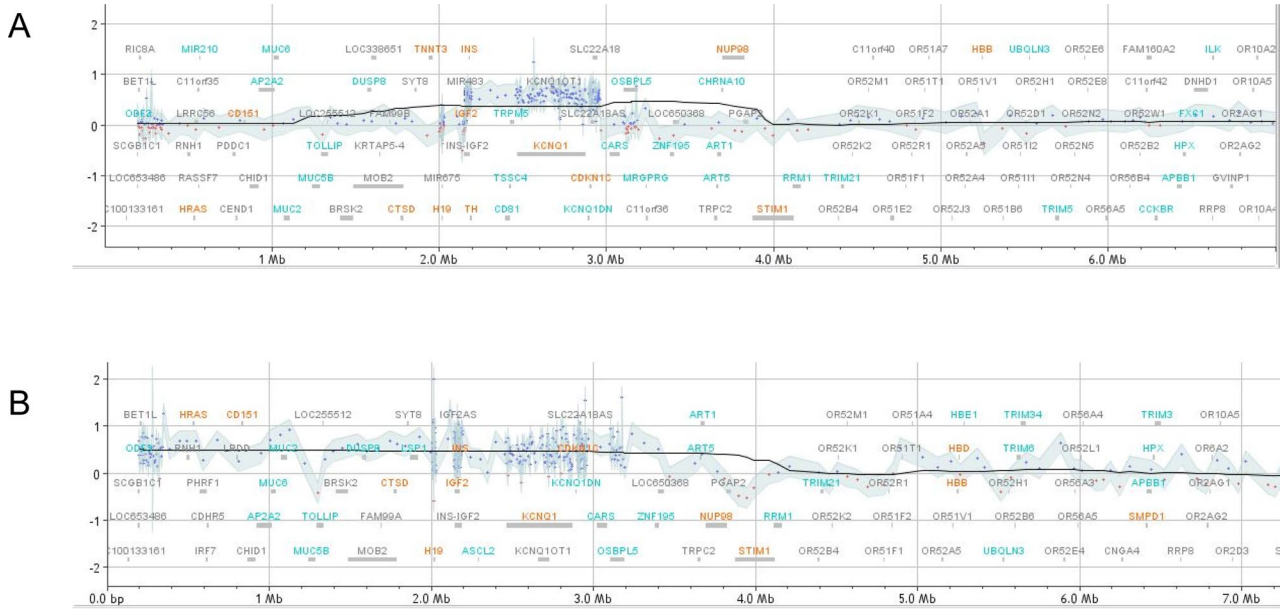

Fig. 2 Schematic representation of the 11p15.5 duplications in the three prenatal cases. Zoomed-in views of the 11p15.5 region are shown for **A** Case 1 and **B** Case 2. Analysis was performed using array-comparative genomic hybridization (aCGH) for Cases (**A** and **B**)

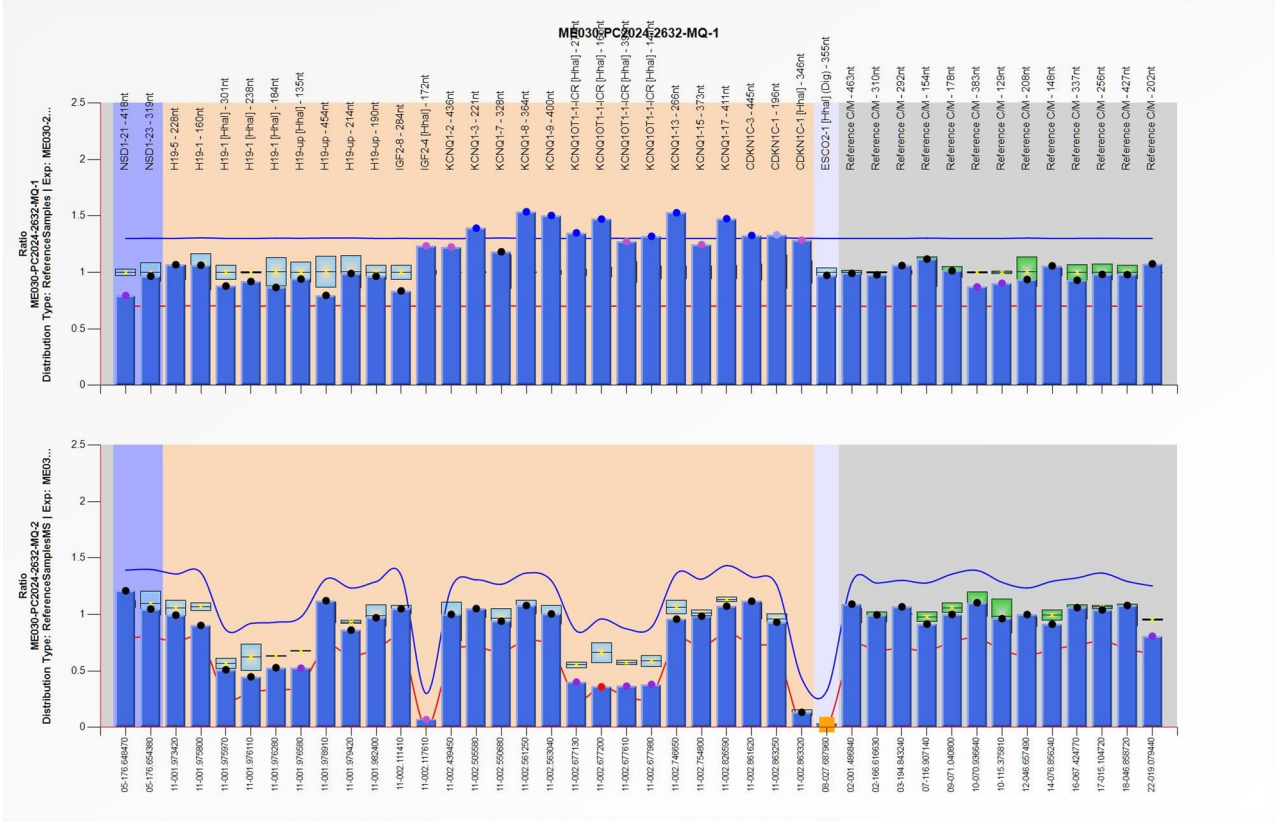

Fig. 3 Methylation analysis of the ICR2 (KCNQ1OT1 TSS-DMR) by Multiplex Ligation-dependent Probe Amplification (MS-MLPA). Case 1, demonstrating a hypermethylation pattern (~ 70%) at the ICR2 region, consistent with a maternal allele duplication of this domain. Data were analyzed using Coffalyser. Net software (MRC Holland)

domains. The pregnancy was terminated, and a male fetus was delivered.

Case 3: Beckwith-Wiedemann syndrome (BWS) phenotype associated with a paternal allele duplication of the 11p15.5 critical region

The third case involved a fetus with a high-risk result (1 in 45) for trisomy 21 from first-trimester maternal serum screening. Subsequent ultrasonography revealed macrosomia, with biometry measurements estimating a fetal size greater than two weeks ahead of the gestational age. Additionally, an omphalocele was identified. Karyotyping from amniotic fluid was normal (46, XN), ruling out classic aneuploidy.

CNV-seq analysis identified a ~ 2.02 Mb tandem duplication at 11p15.5 (arr[hg19] chr11:g. (440000-2460,000) dup) (Fig. 2C). Crucially, segregation analysis determined that this duplication was of paternal origin. This large duplication spans the entire genomic interval containing both the ICR1 (*H19/IGF2*) and ICR2 (*KCNQ1OT1/CDKN1C*) imprinting control regions.

The combination of a duplication of the paternally inherited allele encompassing the entire BWS critical region and the prenatal findings of macrosomia and omphalocele is highly suggestive of Beckwith-Wiedemann syndrome. The positive first-trimester aneuploidy screen may be attributed to alterations in placental function or specific analyte profiles (e.g., elevated hCG) secondary to the overgrowth syndrome and dysregulated imprinted gene expression. The pregnancy was subsequently terminated.

Discussion

This case series of three prenatal subjects with 11p15.5 duplications illustrates a continuous but variable phenotypic spectrum associated with these duplications, spanning from SRS-like restriction to BWS-like overgrowth, with an intermediate case of blended features. By integrating precise CNV mapping with parental origin studies, we observe a pattern of interaction between genetic architecture and clinical outcome in these rare genomic disorders.

Comparison with prior studies

Our findings are consistent with and extend the foundational observations of Begemann et al. [13] and Heide et al. [3], who established that parental origin and CNV size jointly influence phenotypic outcomes in 11p15.5 duplication syndromes. While their studies delineated key genotype–phenotype correlations across postnatal and mixed cohorts, our work translates these principles into a prenatal diagnostic context. By presenting three consecutive prenatal cases that span the SRS–BWS spectrum, we provide a clear, clinically applicable model in which Parental origin is a major determinant of growth direction and CNV size contributes substantially to phenotypic complexity. This prenatal focus—coupled with integrated methylation and segregation analysis—enhances the mechanistic understanding and may inform prenatal counseling, while acknowledging the need for further cohort studies to refine predictions.

Toward a probabilistic framework for phenotypic interpretation

Our findings support a conceptual framework wherein the phenotypic manifestation of 11p15.5 duplications is governed by two principal determinants. The first is the parental origin, which acts as the master switch for the direction of growth dysregulation. As established in the literature and confirmed here, duplications of the maternally inherited allele predispose to growth restriction pathways, whereas duplications of the paternally inherited allele drive overgrowth [14, 15] The second, and more nuanced, determinant is the genomic size of the CNV, which functions as a modulator of phenotypic complexity[16]. Focal duplications affecting a single ICR are frequently—but not invariably—associated with a more restricted phenotypic spectrum, as seen in Case 1. In contrast, larger duplications encompassing both ICR1 and ICR2 disrupt the entire imprinted domain, creating competing signals from growth-promoting (*IGF2*) and growth-suppressing (*CDKN1C*) pathways. The net effect of this imbalance results in complex or mixed phenotypes, exemplified by Case 2.

However, this association is not invariant. Reports have documented duplications of the maternally inherited allele restricted to ICR2 presenting without growth restriction, as well as duplications of the paternally inherited allele involving both ICRs associated with only mild or atypical BWS features [16]. These exceptions underscore that duplication size and parental origin are not sufficient to fully predict clinical expression, and that other modifiers—epigenetic, placental, or environmental—likely modulate the final phenotype. Thus, we propose that 11p15.5 duplications operate within a probabilistic phenotypic spectrum, where the two variables identified here shift the probability toward certain presentations, but do not exclude alternative outcomes.

Dissecting the molecular mechanisms

The molecular findings in our series offer compelling insights into the dosage sensitivity of the 11p15.5 region [17]. The case1 overall molecular profile—a maternally inherited duplication confined to the ICR2 domain, leading to a double dosage of the growth suppressor *CDKN1C*—is a well-established mechanism for SRS, which aligns well with the observed severe and proportionate fetal growth restriction. Furthermore, this finding

provides a plausible molecular explanation for the previous neonatal loss of a SGA sibling, highlighting the critical importance of family history and parental testing in the diagnosis of inherited imprinting disorders.

The comparison between large duplications of opposite parental origin is instructive. This case 2 demonstrates a mixed phenotype, where the maternal origin of the duplication is expected to lead to a dosage gain of the growth suppressor *CDKN1C* (causing growth restriction), while the physical disruption of the ICR1 domain on the maternal allele can predispose to a loss-of-imprinting and aberrant activation of the normally silenced paternal allele of *IGF2*, contributing to localized overgrowth manifestations such as omphalocele. This conflict manifests as a mixed phenotype of overall growth restriction with specific overgrowth-related malformations.

Conversely, a large duplication of the paternally inherited allele (Case 3) had the opposite effect, the molecular pathogenesis is twofold: firstly, the presence of two paternal alleles leads to a direct dosage gain of the paternally expressed growth promoter *IGF2*. Secondly, the duplication likely causes a relative haploinsufficiency of the maternally expressed growth suppressor *CDKN1C*, as two copies of the gene are present on the duplicated paternal allele, where they are inherently silenced by the ICR2 imprint. This potent combination of increased growth promotion and diminished growth suppression is considered a major driver of the BWS overgrowth phenotype [18]. This juxtaposition illustrates how opposing gene dosage effects within the imprinted network can contribute to markedly different clinical outcomes [19].

Our framework may help contextualize previously reported, yet seemingly paradoxical, cases in the literature. For instance, reports of patients with 11p15.5 duplications presenting with both SRS and BWS features [17, 20, 21], which were difficult to reconcile with a simple parent-of-origin model, can now be understood through the lens of CNV size. Our work suggests that moving beyond a parental-origin-only paradigm to include CNV size as a key modifier may refine genotype–phenotype correlations for 11p15.5 duplication syndromes. However, given the documented exceptions, this framework should be viewed as a probabilistic guide rather than a deterministic predictor.

Clinical implications, limitations, and future directions

The implications for clinical practice are notable. First, our data underscore the necessity of moving beyond the mere detection of an 11p15.5 CNV Determining the parental origin and performing precise breakpoint mapping should be considered standard of care in the diagnostic workflow, as this information is critical for informing recurrence risk and for contextualizing the likelihood of specific phenotypic outcomes. Second, this understanding can support genetic counseling. Families can be informed that the risk of recurrence and the phenotypic spectrum in offspring may be influenced by duplication size and parental origin, although variable expressivity and incomplete penetrance are well-recognized.

We acknowledge several limitations. First, this is a small case series ($n = 3$), which precludes robust statistical generalization. Second, phenotypic descriptions were limited to prenatal findings; postnatal follow-up was unavailable due to pregnancy termination, restricting our ability to assess long-term expressivity. Third, while we emphasize the existence of phenotypic exceptions, our cohort did not itself contain such cases; therefore, the model we propose is derived from integration of our data with previously published observations, rather than from internal contradictory cases. Despite these limitations, this series adds valuable prenatal cases to the literature and reinforces the need for humility in interpreting 11p15.5 CNVs, particularly in the absence of larger cohort-based penetrance estimates.

For future research, it would be highly informative to utilize advanced techniques [22, 23] to investigate how these structural rearrangements disrupt the three-dimensional chromatin topology and higher-order regulatory interactions within the 11p15.5 region, which may reveal further layers of gene regulation.

Conclusion

In summary, this prenatal case series provides further evidence that parental origin and CNV size are two interacting factors contributing the phenotypic outcomes of 11p15.5 duplications. Maternal allele duplications frequently lead to growth restriction phenotypes, whereas paternal allele duplications typically result in overgrowth; however, atypical and mixed presentations have been reported.

Abbreviations

SRS	Silver-Russell syndrome
BWS	Beckwith-Wiedemann syndrome
CNVs	Copy number variants
PCR	Polymerase chain reaction
ICR1	Imprinting control region 1
ICR2	Imprinting control region 2
IUGR	Intrauterine growth restriction
IG-DMR	Intergenic differentially methylated region
MS-MLPA	Multiplex ligation-dependent probe amplification
STR	Short tandem repeat
HC	Head circumference
AC	Abdominal circumference
NICHD	National institute of child health and human development

Author contributions

CYW, HYZ and MYW contributed to the study design, data analysis, and manuscript drafting. JG, YBL, and JMH conducted the literature review and participated in manuscript revision. SXP, DW, BK, QFH, and SXL were responsible for verifying the authenticity of all raw data, conceiving the

study, and overseeing its design and coordination. All authors have read and approved the final manuscript.

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Data availability
The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The presented study was performed in accordance with the Declaration of Helsinki and approved by The study was approved by the Medical Ethics Committee of Henan Provincial People's Hospital (No.134 of 2019) Informed consent was obtained from all participating families.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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