Clinical Epigenetics

BRIEF REPORT

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Thirteen cases support the clinical significance of imprinting center 1 (IC1) microdeletions in Beckwith–Wiedemann syndrome

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Abstract

Most Beckwith–Wiedemann syndrome (BWS) cases are sporadic; nonetheless, imprinting center 1 (IC1) microdeletions have been suggested as a rare cause of familial BWS, with ~ 20 reported cases. We report 13 cases from nine families with IC1 microdeletions. Recurrent 1.4-kb, 1.8-kb, and 2.2-kb deletions were observed. IC1 hypermethylation was identified in all families, and we established a statistically significant relationship between IC1 microdeletions and hypermethylation (OR: 108.17, $p = 2.76e\text{-}13$). This study confirms IC1 microdeletions as a cause of familial BWS, expands the understanding of their molecular mechanisms, and supports a Likely Pathogenic clinical classification for IC1 microdeletions.

Keywords Beckwith–Wiedemann syndrome, BWS, Familial BWS, Imprinting center 1, IC1 microdeletion, IC1 hypermethylation, Imprinting disorder, MS-MLPA

Introduction

Beckwith–Wiedemann syndrome (BWS) is an imprinting overgrowth disorder commonly associated with macroglossia, macrosomia, hemihyperplasia, abdominal wall defects, and/or increased risk for malignancies such as Wilms tumor [1]. The BWS locus is located at chromosome 11p15.5 and contains two differentially methylated imprinting centers [2]. Imprinting center 1 (IC1) regulates the expression of *IGF2* and *H19*, while imprinting center 2 (IC2) regulates the expression of *CDKN1C*, *KCNQ1*, and *KCNQ1OT1*. The methylation status of these centers depends on the parent-of-origin. On the paternally inherited allele, IC1 is methylated and IC2 is unmethylated, resulting in *IGF2* expression and *CDKN1C* silencing. Conversely, IC1 is unmethylated and IC2 is methylated on the maternally inherited allele, resulting in *CDKN1C* expression and *IGF2* silencing [3, 4].

The most prevalent molecular mechanism of BWS, found in approximately 50% of the patients, involves the loss of IC2 methylation on the maternal allele. Other common mechanisms include paternal uniparental disomy (UPD) of 11p15.5, IC1 gain-of-methylation on the maternal allele, and pathogenic variants in the *CDKN1C* gene on the maternal allele. Additionally, 11p15 duplications have been implicated in BWS patients [5]. Although the majority of these abnormalities are caused by primary epimutations and are thus sporadic, maternally inherited *CDKN1C* pathogenic

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variants are frequently observed in familial/inherited BWS cases. In addition, microdeletions in the IC1 region of the maternal allele have also been reported in approximately 20 instances of familial BWS [5–12] (summarized in Table S1). To date, three types of recurring IC1 microdeletions (1.4 kb, 1.8 kb, and 2.2 kb in size) have been described, and are thought to result from non-homologous allelic recombination of low-copy repeat blocks located between *H19* and *IGF2* [10, 13]. The pathophysiology of these is typically associated with the loss and/or spatial rearrangement of transcription factor (e.g., CTCF, OCT4, ZFP57, etc.) binding sites, resulting in hampered CTCF binding, and ultimately contribute to IC1 gain-of-methylation [10].

In this study, we conducted a retrospective review of copy number and methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) results from 8,878 cases tested for BWS or Russell–Silver syndrome (RSS) at the Mayo Clinic Genomics Laboratory between June 2015 and June 2024. Among these, 13 individuals from nine families were found to have IC1 microdeletions, one of which was de novo. IC1 hypermethylation was observed in all families. PCR, followed by gel electrophoresis and Sanger sequencing were used to further characterize these deletions and revealed 1.4-kb deletions in two families, 1.8-kb deletions in four families, and 2.2-kb deletions in three families. This study represents one of the largest cohorts of IC1 microdeletions reported to date, contributing valuable insights into this rare cause of familial BWS.

Methods

The individuals included in this investigation were retrospectively identified from patients with suspected BWS/RSS and their relatives that were tested in our laboratory using a clinically validated MS-MLPA assay (Supplementary Methods). We searched for cases with deletions affecting copy-number probes within the previously described IC1 microdeletions (10,588-L11143 and 10,586-L11141), while leaving the adjacent probes intact (see Fig. 1C for an example). The Human Genome Variation Society (HGVS) nomenclature for these cases is as follows (GRCh37/hg19): NC_000011.9:g.(2020007_2022376)_(2022833_2025882)del. To characterize the sizes and breakpoints of the IC1 microdeletions, we performed PCR, followed by gel electrophoresis and Sanger sequencing (Supplementary Methods). Breakpoints of the IC1 microdeletions were determined using the HGVS 3' rule (Figure S1). Statistical analyses were performed using R version 4.3.1.

Results

A retrospective review of 8,878 cases tested between 2015 and 2024 revealed 13 individuals with IC1 microdeletions (Table 1). Deletions of similar genomic content were absent in population databases, including gnomAD SV (v2.1) and the Database of Genomic Variants (Gold Standard variants, February 2020 release). Among these 13 individuals, four belonged to a three-generation family (Family 1, Table 1; Fig. 1A). The proband (III-1) was referred to our laboratory for BWS testing shortly after birth due evidence of increased birth weight, macroglossia, and umbilical hernia. MS-MLPA testing of the proband revealed an IC1 microdeletion and hypermethylation of all four IC1 methylation-specific probes (Fig. 1B). Subsequent familial testing confirmed the presence of the IC1 microdeletion in the proband's mother (II-2, Fig. 1C), maternal uncle (II-3), as well as maternal grandmother (I-2). Further characterization revealed a 1.8-kb microdeletion (GRCh37/hg19, 11:2,022,152–2,023,984; Figs. 1D and S2), with breakpoints similar but not identical to those in previous reports [13]. The maternal grandmother (I-2) had normal IC1 methylation (Fig. 1E), suggesting that the microdeletion likely resided on her paternally inherited allele, and in this scenario, may not lead to aberrant methylation and phenotypes. Interestingly, when inherited maternally, this 1.8-kb IC1 microdeletion exhibited variable expressivity within the family as evident by the varying methylation status and contrasting clinical phenotypes of the maternal uncle and mother of the proband. MS-MLPA revealed clear IC1 hypermethylation in the proband's maternal uncle (II-3; Fig. 1F), who had previously been diagnosed with BWS and Wilms tumors. In contrast, MS-MLPA only showed borderline IC1 hypermethylation in the mother of the proband (II-2; Fig. 1G), who had increased birth weight but was otherwise phenotypically unremarkable.

Furthermore, our cohort includes two two-generation families (Families 2 and 3; Table 1). In Family 2, confirmatory molecular testing was performed for the proband following a clinical diagnosis of BWS. MS-MLPA analysis identified an IC1 microdeletion accompanied by hypermethylation of IC1. Subsequent familial testing revealed the presence of the microdeletion in the proband's mother, who had normal IC1 methylation; this suggests that the microdeletion is likely located on her paternal allele. Additionally, a maternal half-sibling of the proband was tested and found to be negative for both the IC1 microdeletion and hypermethylation. In Family 3, the proband was tested due to macrosomia, organomegaly, and hypoglycemia. MS-MLPA also detected an IC1 microdeletion and hypermethylation in this patient. It was further reported that the mother and sister of this proband tested positive for IC1 microdeletion at an external institution. However, their clinical evaluations

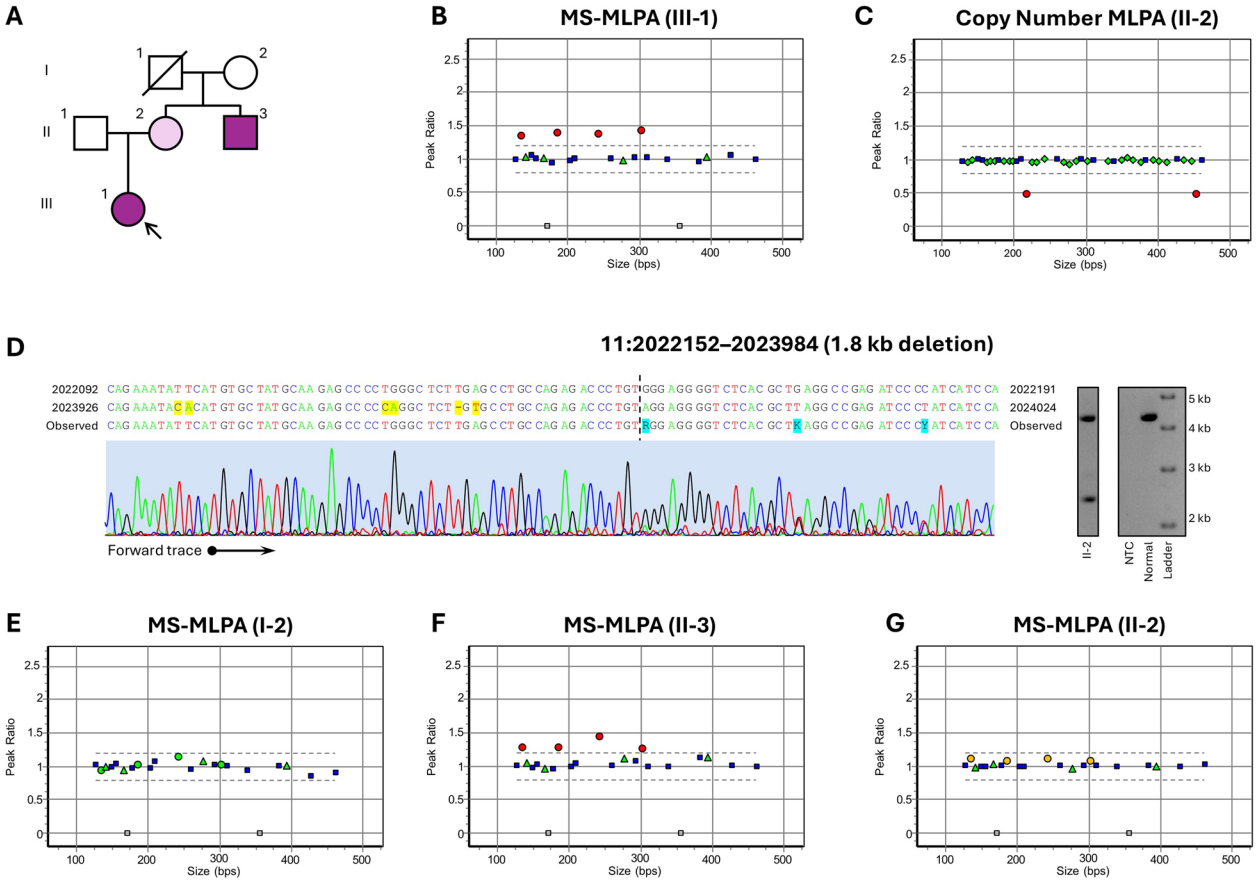

Fig. 1 Molecular genetic findings for Family 1. **A** Pedigree of Family 1. Dark purple (II-3, III-1): affected by BWS. Light purple (II-2): increased birth weight, but no additional features of BWS. **B**, **E**–**G** MS-MLPA results for members of Family 1. Each point in the plot represents a MLPA probe (circles and triangles: MS-MLPA probes for IC1 and IC2, respectively; squares: control probes). The Y-axis is the normalized peak ratio, with a normal range of 0.8–1.2 (dashed horizontal lines). MS-MLPA probes demonstrate hypermethylation (red), borderline hypermethylation (yellow), or normal methylation (green). Borderline hypermethylation is referred to as all four MS-MLPA probes of the same IC consistently trending up (i.e., peak ratio above 1.0) but not exceeding the cutoff of hypermethylation. The X-axis denotes fragment sizes of the MLPA probes. **C** Copy-number MLPA results for II-2. Each point in the plot represents a MLPA probe (circles: the two copy-number probes within the IC1 microdeletion; diamonds: other copy-number probes for IC1 and IC2; squares: control probes). The two circles are at 51.0% and 51.5%, consistent with a heterozygous deletion spanning these probes. **D** Gel electrophoresis and Sanger sequencing revealed a 1.8-kb IC1 microdeletion. Following PCR using the primer set 1 (see Methods), two bands, approximately 4.2 kb and 2.4 kb in size, were observed for II-2 (Individual 2 in Table 1) by gel electrophoresis. In contrast, only the 4.2-kb band was observed for the normal control. The genomic sequences (GRCh37/hg19) flanking the deletion are shown above the Sanger trace, with the dashed vertical line denoting the breakpoints according to the HGVS 3′ rule. The yellow-shaded nucleotides denote mismatches with the Sanger trace, while the cyan-shaded nucleotides denote heterozygous sites in the Sanger trace. The deletion breakpoints were determined based on the cyan-shaded nucleotides, where they first appear in the Sanger trace (see Figure S1 for details)

and genetic testing were conducted elsewhere, thus we did not have access to their IC1 methylation status or detailed clinical information. PCR, followed by gel electrophoresis and Sanger sequencing uncovered a 1.8-kb deletion in both families, although the breakpoints differ slightly (Figures S3A, S3B, S4 and S5).

This study also includes one family with a de novo IC1 microdeletion in the proband (Family 4, Table 1), in whom IC1 hypermethylation was detected. Sanger sequencing and gel electrophoresis revealed a 1.4-kb deletion (Figure S6A). Both parents of the proband tested negative for IC1 microdeletions by MS-MLPA.

The five remaining cases in our cohort were singletons, with age ranged from 0 days to 70 years (Figures S3, S6 and S7; Table 1). IC1 hypermethylation was identified in all five cases with one case being borderline hypermethylated (Figure S8). Further characterization revealed one case with a 1.4-kb deletion (Figure S6B), another with a 1.8-kb deletion (Figure S3C), and three cases with 2.2-kb deletions (Figure S7). The breakpoints of these were generally similar but not identical among patients and compared with the previous reports [13], consistent with independent mutagenesis events with the same underlying mechanism (i.e., non-allelic homologous recombination).

Table 1 Clinical features and molecular findings of the 13 individuals with IC1 microdeletions in our cohort

Individual	Family	Age	IC1 Methylation	Parent-of-origin of the Allele Harboring Deletion	Deletion Type	Breakpoints[1] (Fused Repeat Blocks)	Clinical Information
1	1	5 w	Hypermethylation	Maternal	1.8-kb	11:2,022,152–2,023,984 (B6/B3)	Increased birth weight, macroglossia, umbilical hernia
2		36 y	Borderline hypermethylation	Maternal			Mother of Patient 1; increased birth weight, no additional features of BWS
3		31 y	Hypermethylation	Maternal			Maternal uncle of Patient 1; clinical diagnosis of BWS, Wilms tumors
4		64 y	Normal	Unknown[2]			Maternal grandmother of Patient 1; unaffected
5	2	15 m	Hypermethylation	Maternal	1.8-kb	11:2,022,100–2,023,933 (B6/B3)	Clinical diagnosis of BWS
6		29 y	Normal	Unknown[2]			Mother of Patient 5; no clinical information provided
7	3	0 d	Hypermethylation	Maternal	1.8-kb	11:2,022,337–2,024,168 (B7/B3)[3]	Macrosomia, organomegaly (kidneys), hypoglycemia; patient has a family history of BWS (mother and sister reportedly tested positive for IC1 microdeletion at an external institution; however, no clinical information or IC1 methylation status were provided)
8	4	7 m	Hypermethylation	Unknown (de novo)	1.4-kb	11:2,022,160–2,023,591 (B5/B3)	Testing ordered by a pediatric oncologist; de novo (both parents tested negative for IC1 microdeletion)
9	5	10 m	Hypermethylation	Unknown[2]	2.2-kb	11:2,021,975–2,024,214 (B7/B3)	Early excess growth, macrosomia, organomegaly (kidneys, liver), facial dysmorphism, macroglossia
10	6	70 y	Hypermethylation	Unknown[2]	2.2-kb	11:2,021,616–2,023,855 (B6/B2)	Macroglossia, ear creases, rule out organomegaly
11	7	0 d	Hypermethylation	Unknown[2]	1.8-kb	11:2,022,337–2,024,168 (B7/B3)[3]	No clinical information provided
12	8	41 y	Hypermethylation	Unknown[2]	1.4-kb	11:2,021,940–2,023,372 (B5/B3)	Clinical diagnosis of BWS, lower limb asymmetry, macroglossia, omphalocele, overgrowth, history of tumors/masses
13	9	4 y	Borderline hypermethylation	Unknown[2]	2.2-kb	11:2,021,718–2,023,957 (B6/B2)	Increased birth weight, hypotonia since birth, protruding tongue, large multi-focal left-sided renal mass, right upper lobe pulmonary nodule

d days, *w* weeks, *m* months, *y* years

[1] Coordinates are in GRCh37/hg19; repeat block information from[18]

[2] The parent-of-origin and inheritance status were unknown due to the lack of parental samples

[3] The 5′-breakpoint of this deletion was between repeat blocks B3 and B4

Altogether, within a cohort of 8,878 cases that underwent MS-MLPA testing for suspected BWS/RSS, IC1 microdeletions were significantly more prevalent in individuals with IC1 hypermethylation, compared to those without IC1 hypermethylation ($p = 2.76 \times 10^{-13}$, odds ratio: 108.17 [95% confidence interval: 23.48–997.39], Fisher's exact test). Eleven of the 429 cases with IC1 hypermethylation had IC1 microdeletions. In contrast, only 2 of the 8,449 cases without IC1 hypermethylation had IC1 microdeletions, both being unaffected relatives of BWS patients (Individuals 4 and 6, Table 1). No RSS patients were found to have IC1 microdeletions.

We implemented the ACMG/ClinGen guidelines for copy-number variant interpretation to evaluate the IC1 microdeletions [14]. The de novo 1.4-kb deletion in our study, along with a previously reported de novo 1.8-kb deletion [8], supported applying code 4A (0.75 points; for a "highly specific and relatively unique" phenotype). Code 4F (0.15 points) was applied based on co-segregation in Family 1, considering the parent-of-origin requirements for imprinting conditions. We also applied code 4L (0.45 points) based on the statistical significance established in this study, for a "specific, well-defined" phenotype. Taken together, a total of 1.35 points supports a *Pathogenic* classification. Nonetheless, on a clinical basis, we opted to downgrade to *Likely Pathogenic* due to the variability in breakpoints of IC1 microdeletions among patients.

Discussion

Here, we present a cohort of 13 individuals with IC1 microdeletions at the BWS locus (11p15.5). Initially detected by MS-MLPA, we further characterized the sizes and breakpoints of these microdeletions, identifying 1.4-kb, 1.8-kb, and 2.2-kb deletions in these cases.

Table S2 summarizes the frequency of the main clinical features, outlined by the international consensus guidelines for BWS [1], in our 13 cases and literature reports [5–12, 15]. Clinical correlations by fused repeat blocks and deletion sizes are in Tables S3 and S4, respectively. The reported frequencies of clinical features in these tables are likely underestimations, as these features may not have been consistently documented in the literature or by ordering clinicians.

In this case series, we identified two individuals (2 and 13) who had borderline hypermethylation of IC1, despite their IC1 microdeletions appeared heterozygous (instead of mosaic). For Individual 2, the variant is most certainly heterozygous, as it was maternally inherited. For Individual 13, the signals of the two copy-number probes overlapping the deletion were 51.7% and 50.1% of the normal, respectively. These values were consistent with a heterozygous deletion; however, high-level mosaicism could not be fully ruled out. The mechanism for borderline IC1 hypermethylation in individuals with heterozygous IC1 microdeletion remains unclear. One potential explanation involves the spatial arrangement of transcription factor binding sites that remain after the deletion. CTCF binding site rearrangements that result in similar spacing to the wild-type complement are associated with stochastic DNA methylation and reduced penetrance, while more significant disruptions are associated with prominent IC1 hypermethylation and full penetrance [10]. However, because our study included only two individuals with borderline IC1 hypermethylation, we were unable to test this hypothesis. Future studies involving additional individuals with IC1 microdeletion and borderline IC1 hypermethylation would be helpful to clarify the mechanism.

In addition, previous studies on familial BWS caused by pathogenic single-nucleotide variants in IC1 have reported methylation anticipation, where IC1 hypermethylation progressively increases in successive generations [16, 17]. In Family 1, II-2 had borderline hypermethylation and only increased birth weight, while her offspring, III-1, had full hypermethylation and additional BWS features. This pattern may reflect methylation anticipation; however, with only one instance, it is challenging to draw definitive conclusions. Future studies involving additional families with IC1 microdeletions would be helpful to study this issue.

This study has several limitations. We do not have complete clinical information for all patients in our cohort. As a national reference laboratory, many patients were referred to our institution for genetic testing without providing detailed description of clinical phenotype. This limitation affected our ability to compare phenotypes among patients. As awareness of this rare cause of BWS increases, we are hopeful that future studies will fill this important gap with more comprehensive clinical information. This limitation also prevented us from determining which of the 8,878 cases had BWS-like clinical presentations. Therefore, we were unable to assess the prevalence of IC1 microdeletions among patients with BWS-like phenotypes. To evaluate the statistical significance that the genetic variant (i.e., IC1 microdeletion) is enriched among affected individuals, we opted to define them by a molecular phenotype found in a subset of BWS patients, i.e., IC1 hypermethylation, rather than clinical presentation. Moreover, smaller deletions that fall within the two MLPA probes may remain undetected due to technical limitations; nonetheless, this also does not affect the conclusions of our study.

To conclude, this study reports 13 individuals with IC1 microdeletions at the BWS locus. This is not only one of the largest IC1 microdeletion cohorts documented to date, but also one of the first to demonstrate a statistically

significant relationship between these deletions and IC1 hypermethylation, providing vital insights into the genetic underpinnings of familial BWS.

Abbreviations

BWS	Beckwith–Wiedemann syndrome
CNV	Copy-number variants
HGVS	Human genome variation society
IC	Imprinting center
MS-MLPA	Methylation-specific multiplex ligation-dependent probe amplification
NTC	No-template control
RSS	Russell–Silver syndrome
UPD	Uniparental disomy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13148-025-01873-5.

Additional file1 (DOCX 4729 KB)

Additional file2 (XLSX 31 KB)

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Author contributions
Conceptualization: Q.D., Z.S., L.H., K.M.R., and W.S.; Investigation: Q.D., Z.S., B.J.E., E.S.S., J.C.D., N.V.F., L.H., K.M.R., and W.S.; Writing – Original Draft Preparation: Q.D. and Z.S.; Writing – Review & Editing: Q.D., Z.S., E.S.S., J.C.D., and W.S. All authors reviewed the manuscript.

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Availability of data and materials
All data generated during this study are included in this published article.

Declarations

Ethics approval and consent to participate
This study was reviewed by the Mayo Clinic Institutional Review Board (IRB) and determined to be exempt from the requirement for IRB approval. The Mayo Clinic IRB has approved a waiver of informed consent (IRB Application #: 24–008513).

Consent for publication
The Mayo Clinic IRB has approved a waiver for consent for publication.

Competing interests
The authors declare no competing interests.

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