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Challenges and Pitfalls in Diagnosing Twins With Discordant BWS Phenotype

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To the Editors,

Beckwith–Wiedemann syndrome (BWS) the most common cause of genetic overgrowth, and it is caused by genetic and epigenetic alterations on chromosome 11p15.5, including abnormal methylation of imprinting centers, paternal uniparental disomy, and mutations in the CDKN1C gene [1]. BWS is characterized by a wide phenotypic variability, from isolated hemihypertrophy to abdominal wall abnormalities, macroglossia, neonatal hypoglycemia, and predisposition to embryonal cancers, especially Wilms' tumor [1].

Even though a clinical score is available to stratify patients for molecular diagnosis, the concept of Beckwith-Wiedemann spectrum has been recently introduced, with molecular confirmation in roughly 70% of the cases [1, 2].

BWS phenotypic variability has been reported in monozygotic twins sharing the same molecular anomaly but discordant clinical features [3].

Here we report two females, spontaneous monochorionic-diamniotic twins with the same hypomethylation pattern of the KvDMR/IC2 region but different phenotypes. Parents' consent was acquired according to the ethical standards of the institutional committee.

The twins were born prematurely after urgent cesarean section at 32 weeks and 5 days of gestation due to maternal pre-eclampsia. The proband, the first-born twin, was initially suspected of Silver-Russell Syndrome due to pre- and postnatal growth restriction, hypoglycemia, and oral-feeding difficulties. During her hospitalization, she was treated for respiratory distress, anemia, urinary tract infection, and underwent surgical repair of bilateral inguinal hernia at 3 months old. Unexpectedly, multiple ligation-dependent probe amplification (MS-MLPA) analysis revealed hypomethylation of the KvDMR/IC2 region, associated with BWS. The result was confirmed upon test repetition, and microsatellite testing showed a biparental origin of the haplotype. Array-CGH analysis was normal, and multilocus imprinting disorder was excluded. Oncological recommended screening for BWS comorbidities was started, resulting negative until the last follow-up at 4 years old. MS-MLPA analysis of the twin sister, who displayed normal growth, revealed the same IC2 hypomethylation as her sister.

During subsequent assessments, in addition to a slight psychomotor delay, the proband showed lower limb asymmetric growth consistent with a mild BWS phenotype. Conversely, the sister had appropriate psychomotor development and growth without any related clinical issues.

Phenotype discordance and atypical presentation of BWS have been documented in monozygotic twins, who were mostly females, exhibiting IC2-LOM on 11p15.5, with one of the twins being unaffected or just mildly symptomatic [4]. The methylation defect is thought to act as an initial trigger for the twinning event, thus explaining the higher incidence of monozygosity in BWS patients compared to the general population (2.5% vs. 0.3%–0.4%) [5]. This is believed to result from BWS mosaicism and the asymmetric migration of affected cells during early gestational stages [3].

Genomic medicine's rise is expected to bring more unpredictable genetic findings.

Given the higher risk of embryonic malignancies in atypical BWS, which ranges between 4% and 21%, in case of a negative test performed on peripheral blood, mosaicism should be ruled out by performing further molecular investigations on other tissues [1]. Once the diagnosis is reached, oncological screening needs to be tailored according to the specific genetic defect [1].

However, no data on oncological risk in twins with discordant BWS phenotypes are currently available, and adopting the standard surveillance protocol might be debated. Some authors suggest a clinical monitoring in line with patients' phenotype and parents' compliance [3]. In our case, we applied for both girls the international clinical and oncological BWS protocol, as the procedures are neither costly nor invasive [3].

Further studies are required to elucidate the molecular mechanisms underlying "diffused mosaicism", which could help predict the phenotypic severity in BWS twins [3]. Interestingly, prenatal auxological gradient has been observed in BWS IC2-LoM patients displaying an excess of preterm births [5].

Considering multiple pregnancy, growth and overgrowth assessment might be particularly challenging. This complex evaluation is further complicated by growth differences between fetuses, often influenced by pregnancy-specific factors, such as chorionicity, zygosity, vascular connections, or shift of affected hematopoietic cells from the yolk-sac [5].

Therefore, given the association of twinning zygosity and pregnancies resulting from assisted reproductive technologies (ART) with BWS, their inclusion as supporting criteria might be discussed in the context of future international consensus guidelines [5].

To conclude, our report aims to support clinicians facing challenges and pitfalls in diagnosing and managing BWS in twins with discordant phenotype (Figure 1). While waiting for a shared diagnostic algorithm, based on a scoring system, to deal with unexpected results and define appropriate surveillance, we recommend always testing both twins and exercising caution in data interpretation [3].

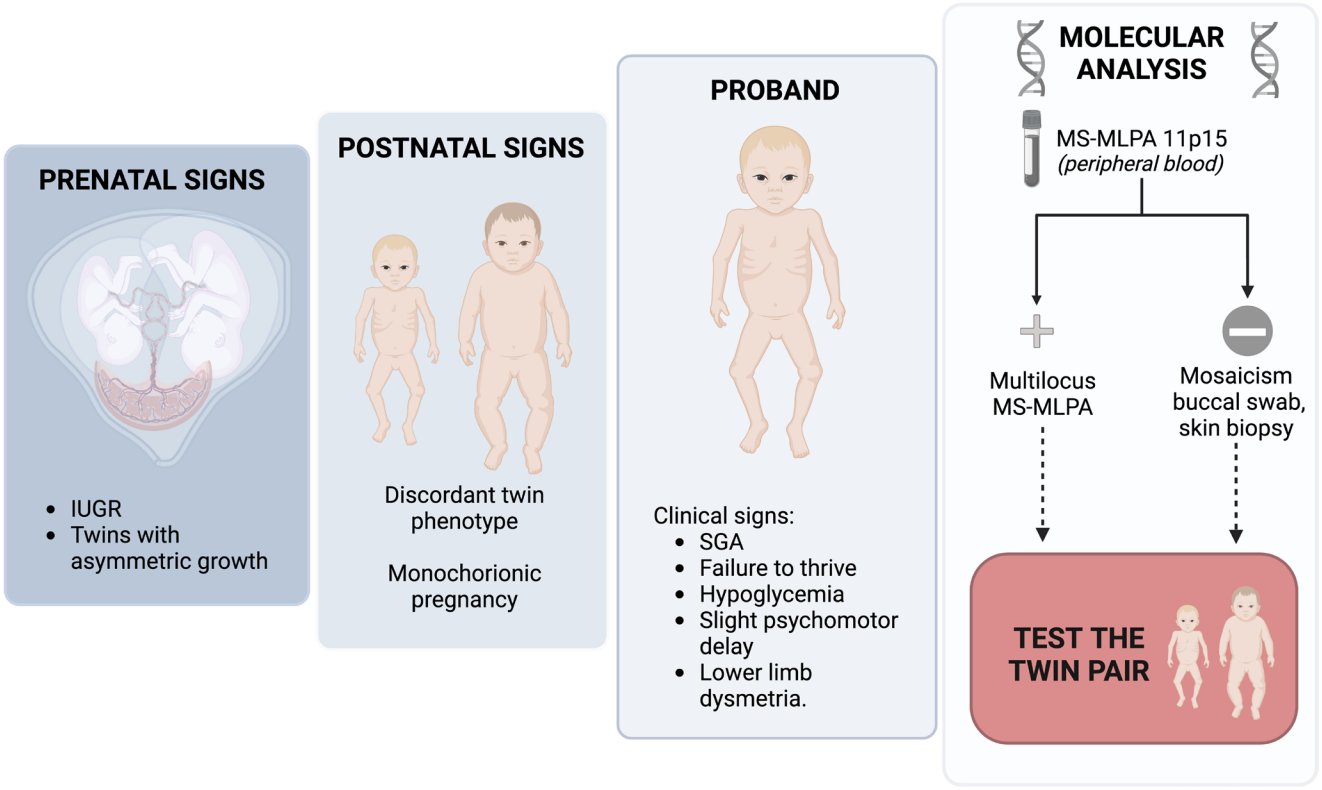

FIGURE 1 | Diagnostic approach suggested in case of BWS twins with discordant phenotype. [Colour figure can be viewed at wileyonlinelibrary.com]

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Image created with BioRender. Nero, C. (2025). https://BioRender.com/z76j880.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/cge.70022.

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