Beckwith-Wiedemann and Russell-Silver Syndromes

Beckwith-Weidemann syndrome (BWS) is a congenital overgrowth condition associated with neonatal hypoglycemia, macroglossia, macrosomia, hemihypertrophy and increased risk for embryonal tumors. Russell-Silver syndrome (RSS) is a congenital condition characterized by stunted growth, limb length asymmetry, and developmental delay. Testing can confirm a suspected clinical diagnosis of BWS or RSS.

**DISEASE OVERVIEW**

- **Incidence**
  - BWS: ~1/10,000-13,700 newborns
  - RSS: ~1/100,000 newborns

- **Symptoms**
  - **BWS (Major Findings)**
    - Macrosomia
    - Visceromegaly
    - Hemihyperplasia
    - Embryonal tumors in childhood (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma)
    - Macroglossia
    - Omphalocele
    - Renal abnormalities
    - Ear creases or pits
  - **RSS**
    - Pre- and postnatal growth deficiency
    - Proportionate short stature
    - Limb length asymmetry
    - Developmental delay and/or learning disabilities
    - Triangular facies, broad forehead, narrow chin

**GENETICS**

- **Etiology**
  - **Causes of BWS**
    - 50% have loss of maternal methylation on chromosome 15q11 imprinting center (IC)2
    - 20% have paternal uniparental disomy (UPD) for chromosome 11p15
    - 5% have gain of methylation in maternal IC1
    - Pathogenic sequence variants in **CDKN1C**
      - 5-10% of nonfamilial cases
      - ~40% of familial cases
    - <1% cytogenetic abnormalities involving 11p15
  - **Causes of RSS**
    - 35-50% have hypomethylation of paternal IC1
    - 10% have maternal UPD of chromosome 7
    - ~40% have an unknown genetic mechanism

- **Inheritance**
  - Sporadic in 85% of BWS cases and 60% of RSS cases
  - Autosomal dominant in 15% of BWS cases due to parent-of-origin transmission
Penetrance
- Complete for RSS
- Incomplete for BWS due to methylation (eg, individuals with a paternally inherited CDKN1C pathogenic variant will not show features of BWS)

TEST INTERPRETATION

Clinical sensitivity/specificity: 75% for BWS; 35-50% for RSS
Analytical sensitivity/specificity: 99%

Results

<table>
<thead>
<tr>
<th>Result</th>
<th>BWS</th>
<th>RSS</th>
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</thead>
<tbody>
<tr>
<td>Positive</td>
<td>IC2 hypomethylation AND normal IC1 methylation</td>
<td>IC1 hypomethylation</td>
</tr>
<tr>
<td></td>
<td>IC1 hypermethylation AND hypomethylation of IC2</td>
<td></td>
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<tr>
<td></td>
<td>IC1 hypermethylation AND normal methylation of IC2</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Normal methylation patterns:</td>
<td>Normal methylation patterns:</td>
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<tr>
<td></td>
<td>• Risk reduced but not excluded</td>
<td>• Risk reduced but not excluded</td>
</tr>
<tr>
<td></td>
<td>• Consider CDKN1C gene sequencing and deletion/duplication</td>
<td>• Consider UPD analysis of chromosome 7</td>
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<td>• Consider chromosome analysis</td>
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Limitations
Molecular mechanisms causing BWS or RSS that do not affecting methylation patterns are not assessed, including:
- Maternal UPD of chromosome 7
- Chromosomal translocations, inversions, deletions, or duplications
- Pathogenic CDKN1C sequence variants, deletions/duplications
Diagnostic errors can occur due to rare sequence variations.