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 grow, limb length asymmetry, and developmental delay. Testing can confirm a suspected clinical diagnosis of BWS or RSS.

Tests to Consider

Beckwith-Wiedemann Syndrome (BWS) and Russell-Silver Syndrome (RSS) by Methylation-Specific MLPA 3001635

Method: Multiplex Ligation-dependent Probe Amplification

Confirm diagnosis of BWS or RSS in individuals with a suspected clinical diagnosis

Disease Overview

Incidence

BWS: ~1/10,000-13,700 newborns

RSS: ~1/100,000 newborns

Symptoms

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

Genetics

Etiology

Causes of BWS

- 50% have loss of maternal methylation on chromosome 11p15 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

Result	BWS	RSS
Positive	IC2 hypomethylation AND normal IC1 methylation	IC1 hypomethylation
	IC1 hypermethylation AND hypomethylation of IC2	
	IC1 hypermethylation AND normal methylation of IC2	
Negative	Normal methylation patterns: • Risk reduced but not excluded • Consider *CDKN1C* gene sequencing and deletion/duplication • Consider chromosome analysis	Normal methylation patterns: • Risk reduced but not excluded • Consider UPD analysis of chromosome 7

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.

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