Beckwith-Wiedemann and Russell-Silver Syndromes

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Beckwith-Weidemann syndrome (BWS) is a congenital overgrowth condition associated with neonatal hypoglycemia, macroglossia, macrosomia, hemihypertrophy, and an increased risk for embryonal tumors.[1] Russell-Silver syndrome (RSS) is a congenital condition characterized by pre- and postnatal growth deficiency, limb length asymmetry, relative macrocephaly at birth, feeding difficulties, and developmental delay.[2] Laboratory testing can confirm a suspected clinical diagnosis of BWS or RSS.

Featured ARUP Testing

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

Method: Qualitative Methylation-Specific Multiplex Ligation-Dependent Probe Amplification (MS-MLPA)

Disease Overview

Incidence

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

RSS: ~1/30,000-100,000 newborns[2]

Symptoms

BWS (Major Findings)	RSS
Macrosomia	Pre- and postnatal growth deficiency
Visceromegaly	Proportionate short stature
Hemihyperplasia	Limb length asymmetry
Embryonal tumors in childhood (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma)	Relative macrocephaly at birth
Macroglossia	Feeding difficulties
Omphalocele	Developmental delay and/or learning disabilities
Renal abnormalities (cytomegaly of the adrenal cortex is considered pathognomonic)	Triangular facies, broad forehead, narrow chin
Ear creases or pits	

Sources: Shuman, 2023[1]; Saal, 2025[2]

Genetics

Etiology

Causes of BWS

- 50% have loss of maternal methylation on chromosome 11p15 imprinting center (IC)2[1]
- 20% have paternal uniparental disomy (UPD) for chromosome 11p15[1]
- 5% have gain of methylation in maternal IC1[1]
- Pathogenic sequence variants in *CDKN1C*
  - 5% of nonfamilial cases[1]
  - Approximately 40% of familial cases[1]
- <1% cytogenetic abnormalities involving 11p15[1]

Causes of RSS

- 35-67% have hypomethylation of paternal IC1[2]
- 7-10% have maternal UPD of chromosome 7[2]
- Approximately 40% have an unknown genetic mechanism[2]

Inheritance

- 85% of BWS cases are sporadic.[3]
- 15% of BWS cases are inherited.
- Most cases of molecularly confirmed RSS are sporadic.[2]

Penetrance

- Complete for RSS[2]
- Incomplete for BWS due to methylation (e.g., individuals with a paternally inherited *CDKN1C* pathogenic variant will not show features of BWS)[1]

Test Interpretation

Clinical sensitivity/specificity: 75% for BWS; 35-67% for RSS

Analytic sensitivity/specificity: 99%

Results

Result	BWS	RSS
Positive	IC2 hypomethylation AND normal IC1 methylation IC1 hypermethylation AND hypomethylation of IC2 IC1 hypermethylation AND normal methylation of IC2	IC1 hypomethylation
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, and low-level mosaicism may not be identified.

References

1. Shuman C, Kalish JM, Weksberg R. Beckwith-Wiedemann syndrome. In: Adam MP, Bick S, Mirzaa GM, et al, eds. *GeneReviews*. University of Washington, Seattle. Updated Sep 2023; accessed Jun 2026.

2. Saal HM, Harbison MD, Netchine I. Silver-Russell syndrome. In: Adam MP, Bick S, Mirzaa GM, et al, eds. *GeneReviews*. University of Washington, Seattle. Updated Jan 2025; accessed Jun 2026.

3. Romanelli V, Meneses HN, Fernández L, et al. Beckwith-Wiedemann syndrome and uniparental disomy 11p: fine mapping of the recombination breakpoints and evaluation of several techniques. *Eur J Hum Genet*. 2011;19(4):416-421.

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology.
500 Chipeta Way, Salt Lake City, UT 84108
Phone: 801-583-2787
Toll-Free Phone: 800-522-2787

aruplab.com | arupconsult.com

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