
Lab Dept: Anatomic Pathology

Test Name: BECKWITH-WIEDEMANN SYNDROME /RUSSELL-SILVERY SYNDROME METHYLATION, BLOOD

General Information

Lab Order Codes: BWS

Synonyms: BWS Genetic Analysis; Beckwith-Wiedeman Syndrome (BWS)/Russell-Silver Syndrome (RSS) Molecular Analysis

CPT Codes: 81401 x2– Molecular Pathology procedure, Level 2 (H19 and KCNQ1OT1)

Test Includes: Methylation-sensitive multiple ligation-dependent probe amplification is utilized to test for the presence of large deletions, duplications and methylation defects in the imprinting center 1 (IC1) (H19) and IC2 (LIT1) critical region on chromosome 11p15 (unpublished Mayo method).

Logistics

Test Indications: Beckwith-Wiedemann syndrome (BWS) is a disorder characterized by prenatal and /or postnatal overgrowth, neonatal hypoglycemia, congenital malformations, and an increased risk for embryonal tumors. Physical findings are variable and can include abdominal wall defects, macroglossia, and hemihyperplasia. The predisposition for tumor development is associated with specific tumor types such as adrenal carcinoma, nephroblastoma (Wilms tumor), hepatoblastoma, and rhabdomyosarcoma. In infancy, BWS has a mortality rate of approximately 20%.

Current data suggest that the etiology of BWS is due to the dysregulation of imprinted genes in the 11p15 region of chromosome 11, including H19 (maternally expressed), LIT1 (official symbol KCNQ1OT1; paternally expressed). Expression of these genes is controlled by 2 imprinting centers (IC).

Approximately 85% of BWS cases appear to be sporadic, while 15% of cases are associated with an autosomal dominant inheritance pattern. When a family history is present, the etiology is often due to inherited point mutation in the CDKN1C or an unknown cause. The etiology of sporadic cases includes:

- Hypomethylation of imprinting center 2 (IC2) (LIT1) approximately 50-60%
- Paternal uniparental of imprinting disomy of chromosome 11: approximately 10-20%
- Hypermethylation of imprinting center 1 (IC1) (H19): approximately 2-7%
- Unknown: approximately 10-20%
- Point mutation in CDKN1C: approximately 5-10%
- Cytogenetic abnormality: approximately 1-2%
- Differentially methylated region 1 (DMR1) or DMR2 microdeletion: rare

The clinical presentation of BWS is dependent on which gene in the 11p15 region is involved. The risk for cancer has been shown to be significantly higher in patients with abnormal methylation of IC1 (H19) vs IC2 (LIT1). In patients with abnormal methylation of IC2 (LIT1), abdominal wall defects and overgrowth are seen at a higher frequency.

Russell-Silver syndrome (RSS) is a rare genetic condition with incidence of approximately 1 in 100,000. RSS is characterized by pre- and postnatal growth retardation with normal head circumference, characteristic facies, fifth finger clinodactyly, and asymmetry of the face, body, and/or limbs. Less commonly observed clinical features include café au lait spots, genitourinary anomalies, motor, speech, cognitive delays, and hypoglycemia. Although clinical diagnostic criteria have been developed, it has been demonstrated that many patients with molecularly confirmed RSS do not meet strict clinical diagnostic criteria for RSS. Therefore, most groups recommend a relatively low threshold for considering molecular testing in suspected cases of RSS.

RSS is a genetically heterogeneous condition that is associated with genetic and epigenetic alterations at chromosome 7 and the chromosome 11p15.5 region. The majority of cases of RSS are sporadic, although familial cases have been reported. The etiology of sporadic cases of RSS includes:

- Hypomethylation of IC1 (H19): approximately 30-50%
- Maternal uniparental disomy (UPD) of chromosome 7: approx. 5-10%
- 11p15.5 duplications: rare
- Chromosome 7 duplications: rare

Note: This test does not detect chromosome 7 UPD.

The clinical phenotype of RSS has been associated with the specific underlying molecular etiology. Patients with hypomethylation of IC1 (H19) are more likely to exhibit "classic" RSS phenotype (ie, severe intrauterine growth retardation, postnatal growth retardation, and asymmetry), while patients with maternal UPD7 often show a milder clinical phenotype. Despite these general genotype-phenotype correlations, many exceptions have been reported.

Methylation abnormalities of IC1 (H19) and IC2 (LIT1) can be detected by methylation-sensitive multiple ligation-dependant probe amplification. While testing can determine methylation status, it does not identify the mechanism responsible for the methylation defect (such as paternal uniparental disomy or cytogenetic abnormalities). Hypomethylation of IC2 (LIT1) is hypothesized to silence the expression of a number of maternally expressed genes, including CDKN1C. Hypermethylation of IC1 is hypothesized to silence the expression of H19, while also resulting in overexpression of IGF2. Absence of CDKN1C and H19 expression, in addition to overexpression of IGF2, is postulated to contribute to the clinical phenotype of BWS. Hypomethylation of IC1 is hypothesized to result in overexpression of H19 and underexpression of IGF2, which is thought to contribute to the clinical phenotype of RSS.

Lab Testing Sections: Anatomic Pathology - Sendouts

Referred to: Mayo Medical Laboratories (MML: BWRS)

Phone Numbers: MIN Lab: 612-813-6280
STP Lab: 651-220-6550

Test Availability: Daily, 24 hours

Turnaround Time: 2 weeks

Special Instructions: Specimen must arrive within 96 hours of collection. Please include Mayo's Molecular Genetics-Congenital Inherited Diseases Patient Information Sheet (Supply T521). The information sheet is available from the lab.

Specimen

Specimen Type: Whole blood

Container: Lavender top (EDTA) tube
Alternate tube: Yellow top (ACD) tube

Draw Volume: 3 mL (Minimum: 1 mL) blood

Processed Volume: Same as Draw Volume

Collection: Routine venipuncture, mix specimen by gentle inversion

Special Processing: Lab Staff: **Do Not** centrifuge. Specimen should be sent in original collection container. Send at room temperature and include the Molecular Genetics-Congenital Inherited Diseases Patient Information Sheet (Supply T521). Specimen must be received within 96 hours of collection at the reference lab. Forward promptly.

Patient Preparation: None

Sample Rejection: Mislabeled or unlabeled specimen

Interpretive

Reference Range: An interpretive report will be provided

Critical Values: N/A

Limitations:

In addition to disease-related probes, the multiple ligation-dependent probe amplification technique utilizes probes localized to other chromosomal regions as internal controls. In certain circumstances, these control probes may detect other diseases or conditions for which this test was not specifically intended. Results of the control probes are not normally reported. However, in cases where clinically relevant information is identified, the ordering physician will be informed of the result and provided with recommendations for any appropriate follow-up testing.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete.

Methylation status cannot be assessed on chorionic villus specimens.

A previous bone marrow transplant from an allogenic donor will interfere with testing. Call Mayo Medical Laboratories for instructions for testing patients who have received a bone marrow transplant.

This assay does not detect mutations in the maternal uniparental disomy of chromosome 7, or cytogenetic abnormalities such as translocations, inversions, or duplications.

Methodology:

Methylation-Sensitive Multiplex Ligation-Dependent Probe Amplification (MPLA)

References:

[Mayo Medical Laboratories Web Page](#) (August 2015)
Phone: 1-800-533-1710

Updates:

10/6/2011: Moved from Barnes Jewish Molecular Diagnostic Laboratory, St. Louis, MO to Mayo Medical Laboratories.
11/6/2012: Updated procedure testing new chromosome segments and added info regarding RSS.
1/30/13: CPT 2013 update
8/2/15: CPT update