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Beaumont Laboratory

Laboratory Bulletin

Prader-Willi/Angelman Syndrome Methylation Molecular Analysis

Effective Date: November 6, 2018

Effective November 6, 2018, Beaumont Laboratory Cytogenetics Laboratory, Royal Oak, will offer testing on Prader-Willi/Angelman Syndrome Methylation Molecular Analysis.

Prader-Willi (PWS) and Angelman (AS) syndromes are clinically distinct neurodevelopmental genetic diseases with multiple distinct phenotypic manifestations that have, in common, a molecular abnormality in the proximal portion of chromosome 15q. PWS is characterized loss of one or more paternally-inherited transcripts at the imprinted 15q11-q13 locus. In approximately 70% of patients, this loss is due to a large interstitial deletion of ~5 megabases on the paternally-derived chromosome 15. An additional 25% of patients have maternal uniparental disomy for chromosome 15, and 1% to 2% of cases have a mutation in the imprinting control center gene within the PWS/AS critical region. Candidate genes for the disorder have included SNURF and SNRPN which are transcribed from the paternal unmethylated allele only and are silenced in the methylated maternal allele. Loss of gene expression from the paternally-inherited chromosome leads to PWS. Angelman syndrome is also caused by disruption of gene expression in the PWS/AS critical region. It is characterized by absence of gene expression from the maternally-inherited allele. Large interstitial deletions and paternal uniparental disomy account for 80% of AS cases. Mutation of the maternally-inherited UBE3A gene, located within the critical region, is found in 5% to 11% cases of AS, indicating that loss of expression of this single gene is responsible for the phenotype.

This test involves distinguishing paternal and maternal copies of the PWS/AS critical region by DNA methylation analysis of the SNRPN gene. Methylation-sensitive PCR uses DNA modified by sodium bisulfite to detect the methylated and unmethylated alleles. Multiplex PCR using two sets of allele-specific primer pairs (methylated and unmethylated allele-specific primer pairs) is performed. Amplicons are detected by simple agarose gel electrophoresis. The absence of the band corresponding to the paternal unmethylated allele is indicative of a diagnosis of PWS while the lack of the maternal methylated allele is consistent with an AS diagnosis.

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Instructions	Transport 5 ml of peripheral blood. If the specimen will not be received at the testing laboratory within 48 hours of collection, transport refrigerated. Do not freeze the specimen. Read our complete shipping instructions.
Specimen Collection Criteria	Peripheral blood in an EDTA tube. (Min: 5.0 mL) A copy of the requisition must be sent with the specimen.
Physician Office/Draw Site Specimen Preparation	Do not freeze specimen. Maintain specimens at room temperature (20-25°C or 68-77°F) prior to courier pickup. For delays in transport (greater than 48 from the time of collection), refrigerate (2-8°C or 36-46°F) the specimen.
Specimen Preparation for Courier Transport	Transport peripheral blood at room temperature (20-26°C or 68-78.8°F) or refrigerated (2-8°C or 36-46°F).
Rejection Criteria	• Specimens arriving in the laboratory 4 days or more following the original collection date. • Frozen specimens.
Performed	Once a week Results available within 10-14 days of receipt in the Laboratory
Reference Range	Positive for Prader-Willi Syndrome or Angelman syndrome/Normal chromosome 15q11q13 methylation pattern. An interpretative report will be provided.
Test Methodology	Methylation-sensitive PCR analysis of the SNRPN gene.
Interpretation	Abnormal chromosome 15q11q13 (SNRPN gene) methylation pattern consistent with either Prader-Willi or Angelman syndrome.
CPT Code	81331: SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide and ubiquitin protein ligase E3A) Prader-Willi-syndrome and/or Angelman syndrome methylation analysis

If you have questions, please contact Client Services (1-800-551-0488, option 5).

Laboratory Test Directory: http://beaumontlaboratory.com/test-lab-directory.

Date submitted: October 19, 2018

Submitted by: Mark Micale, PhD, Medical Director, Cytogenetics, Royal Oak