Russell-Silver Syndrome: \textit{H19} Methylation and UPD7 Panel

\textbf{Test Code:} NZ  
\textbf{Turnaround time:} 3 weeks  
\textbf{CPT Codes:} 81401 x1, 81402 x1

\section*{Condition Description}
Russell-Silver syndrome (RSS) is a disorder of growth characterized by intrauterine growth retardation with postnatal growth deficiency. Many patients have diminished subcutaneous fat and may experience hypoglycemia during infancy. Short stature typically presents between 2 and 10 years and is proportional. Bone age may be delayed. Serum growth hormone levels are typically normal and patients generally have normal growth velocity. Limb length asymmetry is common, and isolated relative hemiasymmetry, due to underdevelopment of the affected side, is reported. Children may be at risk for motor delays and learning disabilities, however typically do not have mental retardation.

Other symptoms include gastrointestinal and genitourinary dysfunction. Gastroesophageal reflux is most common; however, esophagitis and food aversions are also reported. Many patients are considered failure to thrive. Congenital genitourinary disorders have been reported. Additional features include fifth finger clinodactyly, brachydactyly, and multiple cafe au lait spots. Suggested criteria for diagnosis include the following:

- IUGR with a birth weight >2 SD below the mean.
- Postnatal growth >2 SD below the mean for length.
- Proportional short stature with preservation of occipitofrontal head circumference.
- Facial features include prominent forehead, small triangular face & narrow chin.
- Limb, body, or facial asymmetry.
- Additional features that can be diagnostically helpful include fifth finger clinodactyly, brachydactyly, cafe au lat spots, and arm span less than height.

RSS is a heterogenous disorder that may represent a clinical spectrum rather than a discrete clinical entity. The occurrence of RSS is thought to be sporadic in most cases, and is seen in all racial and ethnic groups.

Defects in gene expression are associated with RSS. It is estimated that between 20-35\% of RSS are due to hypomethylation of the differentially methylated region (DMR1) at the H19 gene (located on chromosome 11p15). The recurrence risk of RSS due to hypomethylation of H19 is estimated to be very low. Approximately 10\% of RSS is due to maternal uniparental disomy (UPD) for chromosome 7. Some forms of RSS are inherited in autosomal dominant or autosomal recessive patterns, for which genes have not been identified. No single explanation can account for the phenotypic heterogeneity seen in patients with RSS.

References:

\section*{Genes}
\textit{H19}

\section*{Indications}
This test is indicated for:

- Individuals with a clinical diagnosis of RSS.
- Individuals with limb asymmetry combined with prenatal and postnatal growth delay.

\section*{Methodology}
Methylation-specific MLPA (MS-MLPA) is used to test for hypomethylation of DMR1 at 11p15 for RSS. One advantage of MS-MLPA is that it not only detects DNA methylation abnormalities (epimutations), similar to Southern blot and quantitative methylation sensitive PCR, but it will also detect deletions and duplications (CNVs) of the 11p15 region. The presence of a CNV can increase the recurrence risk from that of the general population up to a 50\% risk. Both methylation and CNVs will be reported from this analysis.

\section*{Detection}
Hypomethylation of H19 is expected to detect up to 35\% of individuals with a clinical diagnosis of SRS. Maternal uniparental disomy (UPD) for
chromosome 7 will be detected in an additional 10% of patients with a clinical diagnosis, for a total detection of up to 45%.

Reference Range

Normal methylation range of H19 was determined by quantifying DNA methylation in a cohort of normal individuals (see Coffee et al. Genet Med. 8:628-634 2006). The mean methylation index (MI; the amount of methylated DMR1 DNA divided by methylated and unmethylated DMR1 DNA) was 0.49 with a standard deviation of 0.08, resulting in normal MI range of 0.33-0.65 (mean 2 standard deviations).

Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

Related Tests

- Standard Blood Chromosome Analysis (Test Codes: CA, CB) and EmArray Cyto (Test Code: VA) are available for children with growth and developmental delay.