Coffin-Lowry Syndrome: **RPS6KA3 Gene Sequencing**

**Test Code:** SPS6K  
**Turnaround time:** 6 weeks  
**CPT Codes:** 81479 x1

### Condition Description

Intellectual disability (ID) is a nonprogressive cognitive impairment affecting 1-3% of the Western population. It is estimated that up to 50% of moderate-severe cases have genetic causes and approximately 10% are due to X-linked intellectual disability disorders (XLID). XLID can be syndromic or nonsyndromic and is observed in all ethnic groups. More than 100 XLID syndromes have been described in the literature to date. Fragile X is the most common XLID syndrome (~1 in 4000 males) while others can be quite rare with only a few patients reported in the literature. Males can have moderate to severe intellectual disability depending on the syndrome, and carrier females can also be affected, but typically have milder clinical symptoms.

Coffin-Lowry syndrome (CLS) is an X-linked condition characterized in males by mild to profound ID, dysmorphic facies and extremities. The facial features include prominent forehead, hypertelorism, large mouth, and prominent ears. The extremity features include fingers that taper, short, soft, fleshy hands with hyper-extensible fingers, and full, fleshy forearms. Females can range from asymptomatic carriers to fully affected.

Mutations in the **RPS6KA3** gene (Xp22.2-p22.1), also known as **RSK2**, cause CLS. It is the only gene known to be associated with CLS. 90-95% of mutations can be identified in individuals clinically diagnosed with CLS. 70-80% of individuals with CLS have no family history of CLS. Additionally, missense mutations in the **RPS6KA2** gene have been demonstrated to cause XLMR 19.

For patients with suspected CLS, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

### References:

- GeneReviews
- **OMIM #300075**: RPS6KA3 gene  
- **OMIM #303600**: Coffin-Lowry syndrome  
- **OMIM #300844**: XLMR 19

### Genes

**RPS6KA3**

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of Coffin-Lowry syndrome.  
- Carrier testing in adults with a family history of Coffin-Lowry syndrome.

### Methodology

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

### Detection

**Clinical Sensitivity:** Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be
detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient’s clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%

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<th>Specimen Requirements</th>
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<td>Submit only 1 of the following specimen types</td>
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<td>* Preferred specimen type: Whole Blood</td>
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**Type: Whole Blood**

Specimen Requirements:

- In EDTA (purple top) or ACD (yellow 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.

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<th>Special Instructions</th>
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<tr>
<td>Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.</td>
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<th>Related Tests</th>
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<td>• Deletion/duplication analysis of the RPS6KA3 gene by CGH array is available for those individuals in whom sequence analysis is negative.</td>
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<td>• Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.</td>
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<td>• Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.</td>
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<td>• X-Linked Intellectual Disability panels are available for 30, 60, and 90 genes.</td>
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