Lowe Syndrome: **OCRL Gene Sequencing**

**Condition Description**

Lowe syndrome (oculocerebrorenal syndrome) is an X-linked intellectual disability condition characterized by:

- hydrophthalmia
- dense congenital cataracts (found in all affected boys)
- infantile glaucoma (in approximately 50% of affected boys)
- intellectual disability
- vitamin D-resistant rickets
- amino aciduria
- reduced ammonia production by the kidney

Generalized hypotonia is noted at birth which may slowly improve by age. Affected males are delayed in their motor milestones. Approximately 95% of carrier females over age 15 years have characteristic findings in the lens of the eye when the lens is evaluated by slit-lamp examination. Most carrier females show numerous irregular, punctate, smooth, off-white (white to gray) opacities, present in the lens cortex, more in the anterior cortex than the posterior cortex and wrapping around the lens equator.

The **OCRL** gene (Xq26.1) encodes the protein inositol polyphosphate 5-phosphatase OCRL-1, an enzyme that is present in the trans-Golgi network and the endosomal compartment of a variety of cell types, including brain, skeletal muscle, heart and kidney. The loss of inositol polyphosphate 5-phosphatase OCRL-1 causes a defect in intracellular protein trafficking. Affected males have less than 10% normal activity of the enzyme in cultured skin fibroblasts. Peripheral blood samples cannot be used for enzyme analysis because the enzyme is not present in lymphocytes. Measurement of enzyme activity is not accurate for carrier detection in females because of a wide range of "normal" activity due to random X-chromosome inactivation.

New mutations have been reported in 32% of affected males with Lowe syndrome. A high risk of germline mosaicism (4.5%) has been identified. Sequence analysis of the **OCRL** gene identifies mutations in approximately 95% of males with Lowe syndrome. There are no common mutations. Although a few mutations have been noted in more than one affected individual, most mutations are unique to a family. Penetrance is complete, with similar phenotype in affected males within any given family. Lowe syndrome is an uncommon, pan-ethnic disorder with the prevalence of only a few individuals per 100,000 births.

For patients with suspected Lowe syndrome, 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.

Please [click here](#) for the GeneReviews summary on this condition.

**Genes**

**OCRL**

**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of Lowe syndrome.
- Carrier testing in adult females with a family history of Lowe 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:
Sequence analysis of the **OCRL** gene identifies mutations in approximately 95% of males with Lowe syndrome. Mutations in the promoter region, some mutations in the introns, other regulatory element mutations, and large deletions cannot be detected by this analysis.

Analytical Sensitivity: ~99%.

Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

**Specimen Requirements**
Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**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.

**Special Instructions**

Please submit copies of diagnostic biochemical test results along with the sample, if appropriate. Contact the laboratory if further information is needed. 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.

**Related Tests**

- Deletion/Duplication Assay is available separately for individuals where mutations are not identified by sequence analysis.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.