OCRL Gene Analysis in Lowe Syndrome (Oculocerebrorenal syndrome of Lowe)

Clinical Features:
Lowe syndrome is a rare X-linked disorder caused by the deficiency of a phosphatidylinositol 4,5 bisphosphate (PIP2) 5-phosphatase. The disorder is characterized by bilateral congenital cataracts, a form of renal Fanconi syndrome, with proteinuria, albuminuria, aminoaciduria and phosphaturia, and neurologic deficits including developmental delay/mental retardation, seizures and behavioral stereotypies. Additional findings include hypotonia, a characteristic facies, postnatal growth retardation and corneal keloids.[1]

Variants in the OCRL gene also cause a form of Dent disease, known as Dent disease 2 (OMIM 300555). Although the most common cause of Dent disease is variants in the CLCN5 gene, approximately 16-23% of Dent disease cases are due to pathogenic variants in the OCRL gene. Dent disease is a rare X-linked disorder characterized by renal Fanconi syndrome, without the cataracts and neurologic deficits that occur in Lowe syndrome.[2]

Lowe syndrome is a rare X-lined disorder due to the deficiency of a PIP2 5-phosphatase that catalyzes the hydrolysis of the lipid second messenger, PIP2. The ocrl1 enzyme is expressed in most tissues, except for hematapoeitic tissues.[3] Therefore the enzyme activity can be measured in fibroblasts, but not in lymphocytes. OCRL sequence analysis or deletion testing is necessary for carrier testing since due to random X inactivation in females, carrier testing is not accurate by enzyme assay. The OCRL gene is located on the X chromosome Xq26.1 and has 24 exons. The incidence of Lowe syndrome is approximately 1 in 1,000,000 worldwide.

Inheritance Pattern/Genetics:
X-linked Recessive

Test Methods:
Variant analysis of the OCRL gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of exons 1-23 (including the alternatively spliced exon, 18a),[4] and the corresponding intron/exon boundaries. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

For carrier testing it is strongly recommended that the variant be identified first in blood or tissue from the affected male. Then, targeted testing of adult female relatives can be performed more reliably and at a much lower cost. For carrier testing, if a sample from an affected male is not available for testing and no variant is found by sequencing, targeted array

CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons of this gene.

Test Sensitivity:

Variant analysis is expected to identify a sequence variant in greater than 95% of patients with Lowe syndrome. Variants can occur throughout the gene, and some patients have been found with large deletions of the OCRL gene that would not be detectable by sequencing in females. Variants in the promoter regions or deep within introns would not be detectable by this analysis, but these have not been reported.

Dent disease, another X-linked disorder is most commonly due to variants in the CLCN5 gene (testing available at GeneDx). However variants in the OCRL gene are responsible for the disease in approximately 16-23% of patients and in approximately 40% of patients with Dent disease who have no variant in the CLCN5 gene.[2,5]

References:

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