CLCN5 Gene Analysis in Dent Disease

Disorder also known as: X-linked Hypercalciuria Nephrolithiasis; X-linked Recessive Nephrolithiasis; Nephrolithiasis 2 (NPHL2); X-linked Recessive Hypophosphatemic Rickets; Low Molecular Weight Protienuria

Clinical Features:
Dent disease is characterized by renal Fanconi syndrome with low molecular weight proteinuria, hypercalciuria, nephrolithiasis (kidney stones), nephrocalcinosis (calcification of renal tissue) and progressive renal failure. Hypophosphatemic rickets in the first years of life can be a presenting feature. Renal tubular dysfunction may be evident even in the neonatal period. Variants in the CLCN5 gene have been observed in patients with Dent disease but not in patients with isolated nephrolithiasis.[1] Genetic heterogeneity in Dent Disease exists as pathogenic variants in the OCRL1 gene, encoding a phosphatidylinositol 4,5-bisphosphate (PIP2) 5-phosphatase, have been found in approximately 40% of families with the isolated renal phenotype of Dent disease who did not have pathogenic variants in CLCN5. These patients also lacked the classic findings of cataract, renal tubular acidosis and neurological abnormalities characteristic of Lowe syndrome.[2]

Genetics:
Dent disease has an X-linked recessive pattern of inheritance.

Test Methods:
Using genomic DNA obtained from the submitted biological material, the 11 coding exons and their intron/exon boundaries of the CLCN5 gene are screened by bi-directional sequence analysis. In addition, if no variant is found by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available in females to evaluate for a deletion or duplication of one or more exons of this gene. 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.

Test Sensitivity:
Pathogenic variants in the CLCN5 gene detectable by sequence analysis are reportedly found in 60-87% of patients with the clinical diagnosis of Dent disease.[2,3,4] Sensitivity of sequencing may be lower in female index cases due to the rare occurrence of large deletions in the gene.

Variant Spectrum:
The majority of reported variants in CLCN5 are missense and nonsense, although splicing and small deletion and insertion variants have been observed. Less common are gross deletions,

insertions and rearrangements of the CLCN5 gene. Variants are distributed throughout the gene.

References:

1. Rebelo et al., (2005) An Acad Bras Cienc 77(1):95-101;
2. Hoopes et al., (2005) Am J Hum Genet 76:260-267;
3. Ludwig et al., (2005) Hum Genet 117:228-237;
4. Tosetto et al., (2006) Nephrol Dial Transplant 21:2452-2463