Distal Renal Tubular Acidosis Panel

Panel Gene List (6 genes): ATP6V0A4, ATP6V1B1, CA2, HNF4A, SLC34A1, SLC4A1

Clinical Features and Genetics:
Renal tubular acidosis (RTA) is a disorder that involves the acidification of blood and metabolic acidosis due to the kidney’s inability to excrete acids in urine. It is broadly classified into three major types: distal, proximal and hyperkalemic. Distal RTA (dRTA) is characterized by defects of the distal portion of the nephron tubule and is usually diagnosed in childhood. Features of dRTA include vomiting, dehydration, lethargy, short stature, rickets in children and osteomalacia/osteopenia in adults, weakness, failure to thrive and nephrolithiasis. Hearing loss and hypokalemia have been reported in some cases. Pathogenic variants in the ATP6V1B1, ATP6V0A4 and CA2 genes cause autosomal recessive dRTA, and variants in the SLC4A1 gene cause autosomal dominant, and rarely autosomal recessive, RTA. Heterozygous carriers of variants in ATP6V0A4 or ATP6V1B1 may have an increased risk of nephrolithiasis and nephrocalcinosis in adulthood. Proximal RTA is similarly diagnosed in childhood with short stature, lethargy and/or vomiting and respiratory distress in severe cases. However, proximal RTA often resolves after a few years, unlike the lifetime symptoms caused by dRTA. Proximal RTA may also present as part of renal Fanconi syndrome, a broader excretory disease that presents with heightened urine levels of multiple substances such as glucose, phosphates and amino acids, and can present with hypokalemia in some cases. Genetic defects in genes such as HNF4A and SLC34A1 are associated with renal Fanconi syndrome. Finally, hyperkalemic RTA is related to low aldosterone. Patients are often clinically asymptomatic, although they may present with lethargy or postural hypotension. It usually appears in adulthood and the majority of cases are acquired.

Test Methods:
Genomic DNA is extracted from the submitted specimen. For skin punch biopsies, fibroblasts are cultured and used for DNA extraction. The DNA is enriched for the complete coding regions and splice site junctions of the genes on this panel using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CN维). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons at the exon-level; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely
pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

**Technical Test Sensitivity:**
The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events, but less for deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test identify most deletions and duplications involving coding exons but are less reliable for detecting copy number variants of less than 500 base pairs. Assessment of copy number events also depends on the inherent sequence properties of the targeted regions, including shared homology and exon size. Mosaicism detection is limited and balanced chromosome aberrations cannot be identified.

**Clinical Test Sensitivity:**
Previous reports collectively suggest a clinical sensitivity for dRTA of approximately 72%, based on testing of SLC4A1, ATP6V0A4 and ATP6V1B1. The additional genes on this panel provide additional sensitivity for dRTA or similar presentations. Additional information about the general clinical sensitivity of each gene is included in the table below.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance</th>
<th>Disease association</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP6V0A4</td>
<td>ATPase H+ transporting V0 subunit a4</td>
<td>AR</td>
<td>dRTA</td>
<td>34% of dRTA patients3</td>
</tr>
<tr>
<td>ATP6V1B1</td>
<td>ATPase H+ transporting V1 subunit B1</td>
<td>AR</td>
<td>dRTA with deafness</td>
<td>28% of dRTA patients3</td>
</tr>
<tr>
<td>CA2</td>
<td>Carbonic anhydrase II</td>
<td>AR</td>
<td>CA II deficiency</td>
<td>100% of patients with CA II deficiency4</td>
</tr>
<tr>
<td>HNF4A</td>
<td>Hepatocyte nuclear factor 4 alpha</td>
<td>AD</td>
<td>One variant (R63W) reported in association with renal Fanconi syndrome, hyperinsulinism and macrosomia; MODY</td>
<td>Rare in renal Fanconi syndrome,5 ~5% of MODY6</td>
</tr>
<tr>
<td>SLC34A1</td>
<td>Solute carrier family 34 member 1</td>
<td>AD/AR</td>
<td>Renal Fanconi syndrome, IIH</td>
<td>Rare in renal Fanconi,7 14/126 (11%) IIH patients without CYP24A1 variants6</td>
</tr>
<tr>
<td>SLC4A1</td>
<td>Solute carrier family 4 member 1</td>
<td>AD/AR</td>
<td>dRTA</td>
<td>10% of dRTA patients3</td>
</tr>
</tbody>
</table>
Abbreviations:
AD – Autosomal dominant
AR – Autosomal recessive
dRTA – distal renal tubular acidosis
IIH – idiopathic infantile hypercalcemia
MODY – Maturity-onset diabetes of the young
XL – X-linked

References: