Bartter Syndrome Panel

**Panel Gene List (12 genes):** AP2S1, BSND, CASR, CLCNKA, CLCNKB, CLDN16, CLDN19, GNA11, HSD11B2, KCNJ1, MAGED2, SLC12A1

**Clinical Features and Genetics:**
Bartter syndrome is an autosomal recessive disorder that presents with hypokalemic metabolic alkalosis, hypercalciuria, nephrocalcinosis and renal salt wasting. It is sub-categorized as types I-IV. Types I, II and IV are caused by pathogenic variants in the SLC12A1, KCNJ1 and BSND genes, respectively, and typically present with polyhydramnios in the antenatal period. The other previously-listed features are most often present in infancy and childhood. In addition to the features above, Bartter syndrome type IV also results in congenital hearing loss. Type III, caused by pathogenic variants in the CLCNKB gene, often does not involve polyhydramnios, presents in the neonatal period or childhood with a classic but occasionally less severe Bartter syndrome phenotype and lacks nephrocalcinosis. A handful of patients have been reported to have digenic variants in both the CLCNKA and CLCNKB genes; however, more studies are needed to establish the relationship of the CLCNKA gene with Bartter syndrome. In addition to these, the MAGED2 gene has been implicated in a transient antenatal form of Bartter syndrome that presents with a later onset of polyhydramnios, slight prematurity, more severe metabolic alkalosis and a higher birth weight and plasma chloride level when compared to other forms of Bartter syndrome. One particular study showed patients with MAGED2 variants comprised 9% of cases of antenatal Bartter syndrome; however, symptoms resolved between 2-18 months of age in those that survived the perinatal period.

Other genes previously reported to be associated with features present in Bartter syndrome that are included in this panel to aid in differentials are AP2S1, CASR, CLDN16, CLDN19, GNA11 and HSD11B2.

**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-CNv). 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. For the
CLCNKA, HSD11B2 and MAGED2 genes, sequencing but no copy number testing is performed. 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:
An overall sensitivity for Bartter syndrome is not available due to the lack of comprehensive studies. Information about the general clinical sensitivity of each gene on this panel 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>AP2S1</td>
<td>Sigma subunit of adaptor related protein complex 2</td>
<td>AD</td>
<td>FHH type II</td>
<td>14-22% FHH patients without CASR variants⁶,⁹</td>
</tr>
<tr>
<td>BSND</td>
<td>Barttin (CLCNK type accessory beta subunit)</td>
<td>AR</td>
<td>Bartter syndrome</td>
<td>Unknown; 2/5 of Bartter syndrome with hearing loss¹⁰</td>
</tr>
<tr>
<td>CASR</td>
<td>Calcium sensing receptor</td>
<td>AD/AR</td>
<td>Disorders of calcium homeostasis</td>
<td>84% of FHH,¹¹ 42% of ADH,¹² 14-18% of FIH¹³,¹⁴</td>
</tr>
<tr>
<td>CLCNKA</td>
<td>Chloride voltage-gated channel Ka</td>
<td>AR</td>
<td>Bartter syndrome (possibly digenic)</td>
<td>Rare, possibly digenic with CLCNKB⁵,⁶</td>
</tr>
<tr>
<td>CLCNKB</td>
<td>Chloride voltage-gated channel Kb</td>
<td>AR</td>
<td>Bartter syndrome, Gitelman syndrome</td>
<td>Rare in Bartter,⁴,¹⁵ ~3% in Gitelman¹⁶</td>
</tr>
<tr>
<td>CLDN16</td>
<td>Claudin 16</td>
<td>AR</td>
<td>Familial hypomagnesemia with hypercalciuria and nephrocalcinosis</td>
<td>23/25 (92%) families with FHHNC¹⁷</td>
</tr>
</tbody>
</table>
**Test Information Sheet**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLDN19</td>
<td>Claudin 19</td>
<td>AR</td>
<td>Familial hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement</td>
<td>26/27 (91%)</td>
</tr>
<tr>
<td>GNA11</td>
<td>G protein subunit alpha 11</td>
<td>AD</td>
<td>Hyper- and hypocalcemia</td>
<td>2/10 (20%)</td>
</tr>
<tr>
<td>HSD11B2</td>
<td>Hydroxysteroid 11-beta dehydrogenase 2</td>
<td>AR</td>
<td>AME</td>
<td>Rare</td>
</tr>
<tr>
<td>KCNJ1</td>
<td>Potassium voltage-gated channel subfamily J member 1</td>
<td>AR</td>
<td>Bartter syndrome type II</td>
<td>8/14 (57%)</td>
</tr>
<tr>
<td>MAGED2</td>
<td>MAGE family member D2</td>
<td>XL</td>
<td>Transient antenatal Bartter syndrome</td>
<td>9%</td>
</tr>
<tr>
<td>SLC12A1</td>
<td>Solute carrier family 12 member 1</td>
<td>AR</td>
<td>Bartter syndrome type 1</td>
<td>9/13 (69%)</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- AD – Autosomal dominant
- ADH – autosomal dominant hypocalcemia
- AME – apparent mineralocorticoid excess
- AR – Autosomal recessive
- FHH – familial hypocalciuric hypercalcemia
- FIH – familial isolated hyperparathyroidism
- XL – X-linked

**References:**