SLC26A4 Gene Analysis in Pendred Syndrome / DFNB4
Nonsyndromic Hearing Loss and Deafness

Clinical Features:
Variants in the SLC26A4 gene have been associated with two autosomal recessive disorders, Pendred syndrome and DFNB4 non-syndromic hearing loss. Pendred syndrome is the most common form of syndromic deafness, accounting for approximately 5-10% of hereditary hearing loss. The Pendred syndrome phenotype includes bilateral sensorineural hearing loss, which is usually severe to profound at birth, temporal bone abnormalities, vestibular abnormalities, and thyroid dysfunction, which usually leads to goiter formation in late childhood to early adulthood. The degree of hearing loss and thyroid disease is highly variable within families with Pendred syndrome. DFNB4 non-syndromic hearing loss is characterized by enlarged vestibular aqueduct and temporal bone abnormalities, without the thyroid disease. Pendred syndrome is caused by variants of the SLC26A4 gene, which encodes the protein pendrin. Pendrin is a transmembrane protein that regulates flux of chloride, bicarbonate and iodine into cells of the inner ear and thyroid gland.

Genetics:
Pendred syndrome and DFNB4 nonsyndromic hearing loss due to pathogenic variants in the SLC26A4 gene both have an autosomal recessive pattern of inheritance.

Test Sensitivity:
In patients with Pendred syndrome or DFNB4 sensorineural hearing loss, variants in the SLC26A4 gene are identified in approximately 50% of affected individuals, although some studies report a test sensitivity of up to 90%. However, within this 50%, only 27-39% of patients are found to be homozygous or compound heterozygous. A novel variant in the promoter region of the SLC26A4 gene, c.-103 T>C, has been identified in 2% of patients who were negative or heterozygous for a single variant by gene sequencing of the coding region of SLC26A4. A single report identified variants in the FOXI1 gene in patients with Pendred syndrome/DFNB4, including a double-heterozygous individual who carried a single variant in the FOXI1 gene and a single variant in the SLC26A4 gene. To our knowledge, genetic testing for the FOXI1 gene is currently only offered on a research basis.

Variant Spectrum:
More than 200 distinct variants have been identified in SLC26A4, including splice site, frame shift, and nonsense variants; however the majority are missense variants. In addition, a relatively common variant, c.-103 T>C, has been described in a regulatory element of the promoter region of the SLC26A4 gene. There have also been rare cases of large deletions observed in the SLC26A4 gene. Variants are distributed throughout the SLC26A4 gene,
although several variants have been reported more than once, and some are more common in persons of certain ethnic heritages.

**Test Methods:**
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. A region of the promoter containing a known variant (c.-103 T>C) is also included. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. 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.

**References:**