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.[1] The degree of hearing loss and thyroid disease is highly variable within families with Pendred syndrome.[2] DFNB4 non-syndromic hearing loss is characterized by enlarged vestibular aqueduct and temporal bone abnormalities, without the thyroid disease.[1] Pendred syndrome is caused by variants of the SLC26A4 gene, which encodes the protein pendrin.[3] 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 non-syndromic hearing loss produced by variants in the SLC26A4 gene both have an autosomal recessive pattern of inheritance.

Test Methods:
Variant analysis of the SLC26A4 gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of all coding exons, the corresponding intron/exon boundaries, as well as variant detection of a known variant in the promoter region of the gene (c.-103 T>C). If sequencing identifies a variant on only one allele of the SLC26A4 gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/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:
In patients with Pendred syndrome or DFNB4 sensorineural hearing loss, variants in the SLC26A4 gene are identified in approximately 50% of affected individuals,[6] although some studies report a test sensitivity of up to 90%.[7] However, within this 50%, only 27-39% of patients are found to be homozygous or compound heterozygous.[4-7] 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.[4] 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.[4] 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.[3] 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.[4] Additionally, there have been rare cases of large deletions observed in the SLC26A4 gene.[3,5] 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.

References:

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