Pendred Syndrome and DFNB4 Panel

Genes Tested

SLC26A4	*FOXI1*	*KCNJ10*

Disorder: Approximately one-third of all children with sensorineural hearing loss have an abnormality in their temporal bones. Mutations in the *SLC26A4* gene, which encodes for the pendrin protein, are identified in approximately 25-50% of children with temporal bone abnormalities and/or enlarged vestibular aqueducts.

Biallelic mutations in *SLC26A4* results in one of two phenotypes: Pendred syndrome (hearing loss in association with cochlear abnormalities, enlarged vestibular aqueducts and euthyroid goiter) or DFNB4 (hearing loss and enlarged vestibular aqueducts with or without cochlear defects). Two mutations are identified in 80-90% of patients with a family history of PDS, while only a single mutation is identified in approximately 30% of patients with no family history of PDS. Digenic inheritance is postulated in these patients.

Heterozygous mutations in two other genes, *FOXI1* and *KCNJ10,* have been reported in associated with DFNB4 in a few individuals in which only a single *SLC26A4* mutation was identified, thus supporting digenic inheritance as a rare cause of this condition. Of note, biallelic inheritance of two mutations in *KCNJ10* causes SeSAME/EAST syndrome which is characterized by seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance.

Indications: Hearing loss of unknown etiology in association with enlargement of the ventricular aqueducts with or without a cochlear defect.

Specimen: At least 5 mLs whole blood in a lavender (EDTA) tube. Label each tube with patient's name, birth date, and date of collection

Testing Methodology: This test is performed by enrichment of the exons, flanking intronic and un-translated regions (5' and 3') of the genes specified above using microdroplet PCR technology followed by next-generation sequencing with > 20 fold coverage at every target base. All pathogenic and novel variants, as well as variants of unknown (indeterminate) significance, as determined bioinformatically, are confirmed by Sanger sequencing.

If the Pendred Syndrome Panel test result is normal, reanalysis of the remaining genes on the **OtoSeq® Hearing Loss Panel** may be requested. Alternately, you may opt to order the **OtoSeq® Hearing Loss Panel**, which detects mutations in these genes as well as 20 other genes which cause hearing loss, in lieu of the Pendred Syndrome Panel.

Test Sensitivity: Next-generation sequencing detects >90% of the reported mutations in the *SLC26A4* gene. The mutation detection rates in *KCJN10* and *FOXI1* are not known. Large multiexon deletions have been reported in patients with Pendred syndrome, but are rare. Mutations in *SLC26A4* account for approximately 8% of congenital sensorineural hearing loss overall and for approximately 25% of congenital

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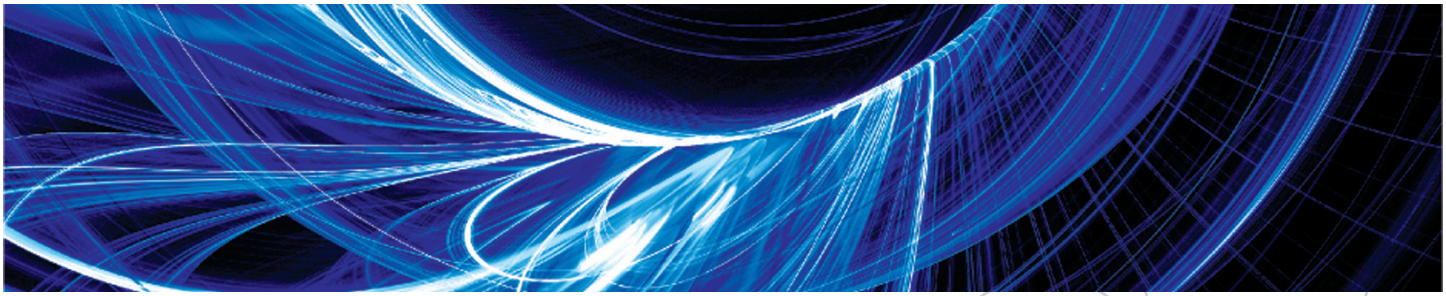


hearing loss associated with temporal bone abnormalities. Mutations in the *FOXI1* and *KCNJ10* genes are identified in less than 1% of patients with PDS/DFNB4.

The sensitivity of next- generation sequencing is over 99% for the detection of nucleotide base changes and small deletions and insertions (<10 bases) in the regions analyzed. Larger deletions, insertions and other complex genetic events are not identified using this test methodology. Rare primer site variants may lead to erroneous results.

Note: Single gene sequencing is available for all genes in the panel.

Turn-Around Time:

- 56 days for NGS of the panel
- Up to 42 days for analysis of any gene on the panel by Sanger sequencing
- Additional 42 days for reanalysis of remaining genes on the **OtoSeq® Hearing Loss Panel** (if requested).

Cost: Please call 1-866-450-4198 for current pricing, insurance precertification, or with any billing questions.

CPT Codes:

- **Pendred Syndrome Panel by NGS**: 81404, 81406, 81479
- Single gene sequencing of *KCNJ10* 81404
- Single gene sequencing of *SLC26A4* 81406
- Single gene sequencing of *FOXI1* 81479
- **OtoSeq® reanalysis (if requested)** 81479

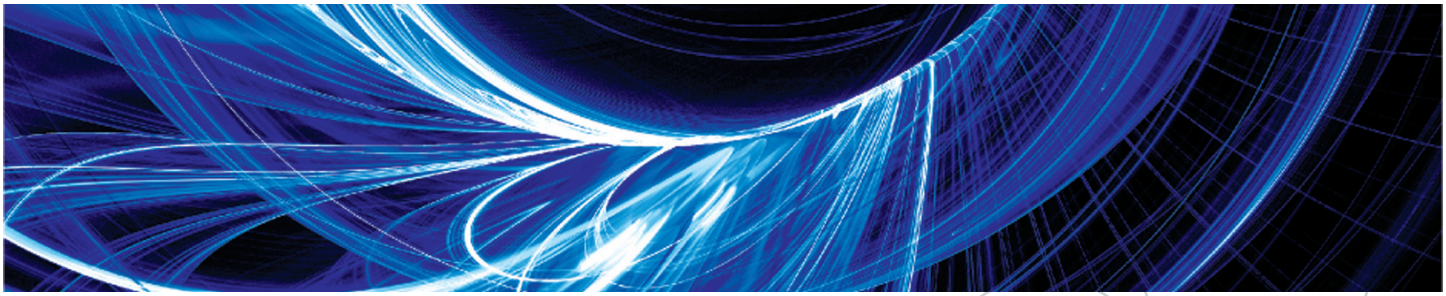
Results: Each test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

Shipping Instructions

Please enclose a completed **test requisition, audiogram and MRI/CT report, if available** with the sample. **All information must be completed before the sample can be processed.** Place samples in Styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:

Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474



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Additional information and test requisitions are available at: **www.cchmc.org/hearing-loss**

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