Usher syndrome type 1 and non-syndromic hearing loss secondary to *CDH23* (cadherin) mutations

Disorder: Hearing loss affects about 1 in 500 newborns and a genetic etiology is suspected in two thirds of these patients. Hearing loss can be caused by mutations in many different genes which can be inherited in an autosomal dominant, autosomal recessive, X-linked or mitochondrial (maternal inheritance) manner.

Biallelic mutations in the *CDH23* gene, which encodes for the cadherin protein, cause between 10-30% of cases of Usher syndrome type 1. Usher syndrome type 1 is characterized by severe to profound congenital sensorineural hearing loss, balance disturbances with poor coordination, and retinitis pigmentosa with onset in childhood. Biallelic mutations in the *CDH23* gene also account for approximately 3-6% of all early onset non-syndromic sensorineural hearing loss. This autosomal recessive form of non-syndromic hearing loss is known as DFNB12.

Indications:

- Usher syndrome type 1
- Non-syndromic hearing loss of unknown etiology
- Carrier testing in relative of patient with proven *CDH23* mutation(s).

Specimen: At least 3 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 may be performed either by PCR and bidirectional sequence analysis of the coding regions and exon/intron boundaries of the *CDH23* gene or by enrichment of the exons, flanking intronic and untranslated regions (5' and 3') of the genes specified above using microdroplet PCR technology followed by next-generation sequencing with > 40 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.

CDH23 sequencing is also available as part of our **Usher Syndrome** and **OtoSeq® Hearing Loss Panels** which detects mutations in *CDH23*, as well as in other genes which cause Usher syndrome and/or nonsyndromic hearing loss. Please see our web site for details.

Cincinnati Children's®

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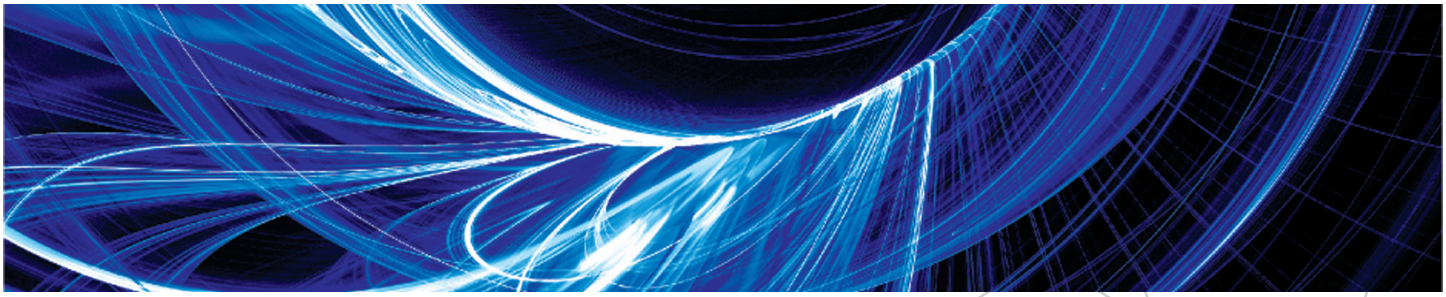

Test Sensitivity:

This test detects an estimated 90% of the reported mutations in *CDH23*. Mutations in *CDH23* account for approximately 3-6% of nonsyndromic sensorineural hearing loss and approximately 10%-30% of Usher syndrome type 1.

The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed. Mutations in regulatory regions or other untranslated regions are not detected by this test. Large deletions involving entire single exons or multiple exons, large insertions and other complex genetic events have been reported in *CDH23* and will not be identified using this test methodology. Rare primer site variants may lead to erroneous results.

Turn-Around Time:

***CDH23* full gene sequence analysis:** 42 days

Family specific mutation analysis: 28 days

Cost:

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

CPT Codes:

***CDH23* full gene sequence analysis**	81408
Family specific mutation analysis	81403

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.

References:

Astuto, L. M., J. M. Bork, et al. (2002). "CDH23 mutation and phenotype heterogeneity: a profile of 107 diverse families with Usher syndrome and nonsyndromic deafness." Am J Hum Genet 71(2): 262-275.

Bork, J. M., L. M. Peters, et al. (2001). "Usher syndrome 1D and onsyndromic autosomal recessive deafness DFNB12 are caused by allelic mutations of the novel cadherin-like gene CDH23." Am J Hum Genet 68(1): 26-37.

Le Quesne Stabej, P., Z. Saihan, et al. (2012). "Comprehensive sequence analysis of nine Usher syndrome genes in the UK National Collaborative Usher Study." J Med Genet 49(1): 27-36

Millan, J. M., E. Aller, et al. (2011). "An update on the genetics of usher syndrome." J Ophthalmol 2011: 417217.

Oshima, A., T. Jaijo, et al. (2008). "Mutation profile of the CDH23 gene in 56 probands with Usher syndrome type I." Hum Mutat 29(6): E37-46.

Pennings, R. J., V. Topsakal, et al. (2004). "Variable clinical features in patients with CDH23 mutations (USH1D-DFNB12)." Otol Neurotol 25(5): 699-706.

Roux, A. F., V. Faugere, et al. (2006). "Survey of the frequency of USH1 gene mutations in a cohort of Usher patients shows the importance of cadherin 23 and protocadherin 15 genes and establishes a detection rate of above 90%." J Med Genet 43(9): 763-768.

Schultz, J. M., R. Bhatti, et al. (2011). "Allelic hierarchy of CDH23 mutations causing non-syndromic deafness DFNB12 or Usher syndrome USH1D in compound heterozygotes." J Med Genet 48(11): 767-775.

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

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
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513-636-4474