

Usher Syndrome Panel

Genes Tested

<i>ADGVR1</i>	<i>CDH23</i>	<i>CLRN1</i>
<i>MYO7A</i>	<i>PCDH15</i>	<i>USH1C</i>
<i>USH1G</i>	<i>USH2A</i>	<i>WHRN</i>

Disorder: Usher syndrome is characterized by sensorineural hearing loss in association with retinitis pigmentosa. It is estimated that upwards of 10% of patients with early onset sensorineural hearing loss have Usher syndrome. The prevalence of Usher syndrome in the general population is approximately 4 per 100,000 and the carrier frequency is estimated at 1-in-70. Usher syndrome is inherited as an autosomal recessive disorder. Genetic testing improves classification of individual patients and allows for better prognostic information for patients and their physicians. Usher syndrome is often divided into subtypes based on severity of symptoms and age at onset of retinitis pigmentosa.

Usher syndrome type 1 (USH1) is characterized by severe to profound congenital sensorineural hearing loss, balance disturbances with poor coordination, and retinitis pigmentosa with onset in childhood. Variant(s) in one of five genes (*CDH23*, *MYO7A*, *PCDH15*, *USH1C* and *USH1G*) account for USH1 in 80-90% of affected individuals.

Usher syndrome type 2 (USH2) is associated with congenital, bilateral sensorineural hearing loss which is quite variable and tends to affect higher frequencies, in addition to retinitis pigmentosa with onset in adolescence to adulthood. Variant(s) in one of three genes (*USH2A*, *GPR98* and *WHRN*) are identified in approximately 80% of USH2 patients.

Usher syndrome type 3 (USH3) is characterized by post-lingual, progressive sensorineural hearing loss, late-onset retinitis pigmentosa, and variable degrees of

balance disturbance and poor coordination. *CLRN1* is the only gene associated with USH3 to date.

Indications:

Symptoms of Usher syndrome (type 1,2, or 3)

Specimen: At least 3 mLs whole blood in a lavender top (EDTA) tube or at least 2 mLs of saliva in an Oragene saliva collection kit. To request saliva kits, please call (513) 636-4474. Label each tube with patient's name, birth date, and date of collection.

Testing Methodology: This test is performed by enrichment of the coding exons, flanking intronic and un-translated regions (5' and 3') of the genes specified above using oligonucleotide probe hybridization followed by next-generation sequencing with > 50 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 Usher 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 variants in these genes as well as 14 other genes which cause hearing loss, in lieu of the Usher Syndrome Panel.



Human Genetics

Laboratory of Genetics and Genomics

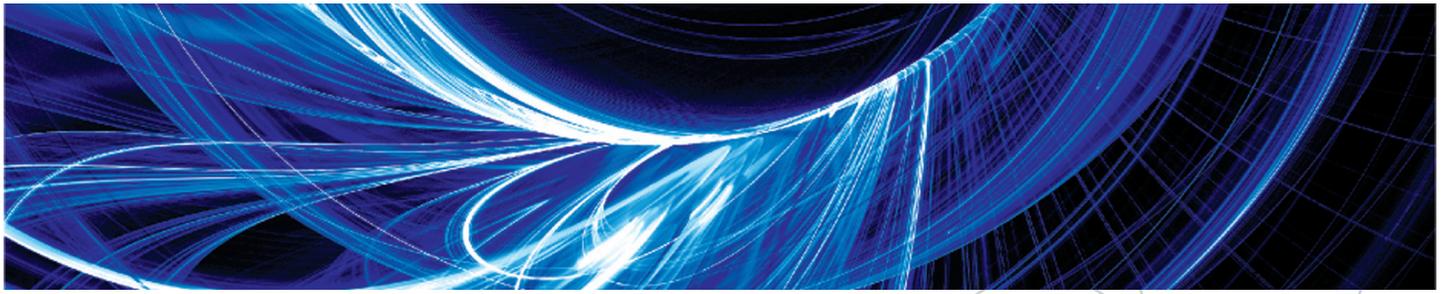
CLIA#: 36D0656333

Phone: (513) 636-4474

Fax: (513) 636-4373

Email: LabGeneticCounselors@cchmc.org

www.cchmc.org/hearing-loss



Test Sensitivity: Sequencing detects 60-99% of the reported variants in in these genes using this testing methodology. Large exonic deletions have been reported in *MYO7A*, *UCH1C*, *PCDH15*, and *GPR98*. Deletion/duplication analysis may be indicated as a follow-up test in patients with a single variant identified in one of these genes.

The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed. Variants 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 these genes and will not be 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. Deletion/duplication analysis is available for all genes on the panel except *WHRN*.

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:

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| • Usher Syndrome Panel | 81407 |
| • Single gene sequencing of <i>USH1G</i> , <i>CLRN1</i> | 81404 |
| • Single gene sequencing of <i>MYO7A</i> ,
<i>PCDH15</i> , <i>USH1C</i> | 81407 |
| • Single gene sequencing of <i>CDH23</i> , <i>USH2A</i> | 81408 |
| • Single gene sequencing of <i>GPR98</i> , <i>WHRN</i> | 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.

References:

- Abadie, C., C. Blanchet, et al. (2011). "Audiological findings in 100 *USH2* patients." *Clin Genet*.
- Ahmed, Z. M., S. Riazuddin, et al. (2003). "The molecular genetics of Usher syndrome." *Clin Genet* 63(6): 431-444.
- Keats, B. J. B. and J. Lentz (1999). *Usher Syndrome Type I*. *GeneReviews*. R. A. Pagon, T. D. Bird, C. R. Dolan, K. Stephens and M. P. Adam. Seattle (WA).
- Keats, B. J. B. and J. Lentz (1993). *Usher Syndrome Type II*. *GeneReviews*. R. A. Pagon, T. D. Bird, C. R. Dolan, K. Stephens and M. P. Adam. Seattle (WA).

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.

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
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474