

Usher Syndrome Test

Panel Gene List: ADGRV1 (GPR98), CDH23, CLRN1, DFNB31 (WHRN), MYO7A, PCDH15, USH1C, USH1G, USH2A and PDZD7

Clinical Features:

Usher syndrome is a group of autosomal recessive disorders involving progressive degeneration of the retina that leads to severe visual impairment, deafness, and variable degrees of vestibular dysfunction. These disorders are divided into three clinical classes and are differentiated by the severity and progression of both the hearing loss and visual impairment and by the absence or presence of vestibular symptoms.¹⁻³

Usher syndrome type 1: It is characterized by profound congenital deafness, pre-pubertal onset of retinitis pigmentosa, and vestibular dysfunction.¹⁻³

Usher syndrome type 2: It is characterized by congenital moderate to severe deafness, early onset of retinitis pigmentosa in the first to second decade of life, and no vestibular dysfunction.¹⁻³

Usher syndrome type 3: It is characterized by variable onset of deafness and of retinitis pigmentosa, and variable impairment of vestibular function.¹⁻³

Inheritance Pattern/Genetics:

Autosomal recessive

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. 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.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Test Sensitivity:

ADGRV1 (GPR98) gene: AdhesionG protein-coupled receptor V1

Approximately 3%-7% of patients with Usher syndrome type II have a variant in this gene.³ A homozygous partial gene deletion of the GPR98 gene was reported in one family.^{3,8,15}

CDH23 gene: Cadherin 23

Approximately 19%-35% of patients with Usher syndrome type 1 have a variant in this gene.³

CLRN1 gene: Clarin 1

All variants thus far identified in patients diagnosed with Usher syndrome type III have been in the CLRN1 (USH3A) gene.³

DFNB31 (WHRN) gene: Whirlin

Variants in the WHRN gene appear to be a rare cause of Usher syndrome type II.^{3,15}

MYO7A gene: Myosin VIIA

Approximately 29%-63% of patients with Usher syndrome type 1 have a variant in this gene.^{3,7,14} Partial and entire gene deletions of the MYO7A gene are estimated to account for approximately 7% of the variants.¹⁴

PCDH15 gene: Protocadherin 15

Approximately 11%-19% of patients with Usher syndrome type 1 have a variant in this gene.³ Large rearrangements of the PCDH15 gene are estimated to account for up to 37% of the variants.¹⁴

USH1C gene: Harmonin

Approximately 4.5%-7% of patients with Usher syndrome type 1 have a variant in this gene.^{3,14} A contiguous deletion which included a portion of the USH1C gene was identified in two families with an unusual phenotype which included severe hyperinsulinism, profound congenital sensorineural deafness, renal tubular dysfunction, and enteropathy.⁵

USH1G gene: Scaffold protein containing Ankyrin repeats and SAM domain

Approximately 7% of patients with Usher syndrome type 1 have a variant in this gene.³

USH2A gene: Usherin

Among Usher syndrome type II patients the USH2A gene accounts for 74%-90% of cases¹⁰⁻¹¹. In a study of 118 unrelated Scandinavian patients with Usher syndrome type II, variant analysis of the USH2A gene revealed that 2 patients carry homozygous large deletions including more than one exon¹².

PDZD7 gene: PDZ Domain-Containing 7

The true sensitivity of PDZD7 gene analysis is unknown. The PDZD7 gene appears to be either a modifier that could result in a more severe phenotype or a gene involved in digenic inheritance when a single pathogenic variant is present in another Usher syndrome gene. In a cohort of 188 Usher patients, 4 individuals were found to harbor loss-of-function variants in PDZD7. The presence of a PDZD7 variant either correlated with a more severe phenotype (when pathogenic variants were present on both USH2A alleles) or in an Usher syndrome phenotype (when only 1 pathogenic variant was identified in ADGRV1).¹⁶ Functional studies and animal models were used to support these findings.¹⁶

| Gene | Protein | Inheritance | Disease Associations |
|-----------------------------------|--|-------------|--|
| <i>ADGRV1</i> (<i>GPR98</i>) | Adhesion G protein-coupled receptor V1 | AR | Usher syndrome, type 2C (ADGRV1/PDZD7 digenic); ?febrile seizures, familial, 4 |
| <i>CDH23</i> | Cadherin 23 | AR | Usher syndrome, type 1D; Usher syndrome, type 1D/F digenic; Deafness, autosomal recessive 12 |
| <i>CLRN1</i> | Clarin 1 | AR | Usher syndrome, type 3A; Retinitis pigmentosa 61 |
| <i>DFNB31</i> (<i>WHRN</i>) | Whirlin | AR | Usher syndrome, type 2D; deafness, autosomal recessive 31 |
| <i>MYO7A</i> | Myosin VIIA | AR | Usher syndrome, type 1B; deafness, autosomal recessive 2; deafness, autosomal dominant 11 |
| <i>PCDH15</i> | Protocadherin 15 | AR | Usher syndrome, type 1F; Usher syndrome, type 1D/F digenic; Deafness, autosomal recessive 23 |
| <i>USH1C</i> | Harmonin | AR | Usher syndrome, type 1C; deafness, autosomal recessive 18A |
| <i>USH1G</i> | Scaffold protein containing Ankyrin repeats and SAM domain | AR | Usher syndrome, type 1G |
| <i>USH2A</i> | Usherin | AR | Usher syndrome, type 2A; Retinitis pigmentosa 39 |
| <i>PDZD7</i> | PDZ Domain-Containing 7 | AR | Usher syndrome, type 2C digenic; Usher syndrome, type 2A modifier of retinal disease |

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