Usher Syndrome Panel

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

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:
The coding regions and splice junctions of the 9 genes of this panel are enriched using a proprietary targeted capture system developed by GeneDx. The targeted regions are sequenced simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequence is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 19 reads are achieved by NextGen sequencing.

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 cases.\(^10,11\)

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 exon.\(^12\)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance</th>
<th>Disease Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADGRV1 (GPR98)</td>
<td>Adhesion G protein-coupled receptor V1</td>
<td>AR</td>
<td>Usher syndrome, type 2C (ADGRV1/PDZD7 digenic); febrile seizures, familial, 4</td>
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<tr>
<td>CDH23</td>
<td>Cadherin 23</td>
<td>AR</td>
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<tr>
<td>CLRN1</td>
<td>Clarin 1</td>
<td>AR</td>
<td>Usher syndrome, type 3A; Retinitis pigmentosa 61</td>
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<tr>
<td>DFNB31 (WHRN)</td>
<td>Whirlin</td>
<td>AR</td>
<td>Usher syndrome, type 2D; deafness, autosomal recessive 31</td>
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<tr>
<td>MYO7A</td>
<td>Myosin VIIA</td>
<td>AR</td>
<td>Usher syndrome, type 1B; deafness, autosomal recessive 2; deafness, autosomal dominant 11</td>
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</tbody>
</table>
**Test Information Sheet**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>Mode of Inheritance</th>
<th>Phenotype</th>
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</thead>
<tbody>
<tr>
<td>PCDH15</td>
<td>Protocadherin 15</td>
<td>AR</td>
<td>Usher syndrome, type 1F; Usher syndrome, type 1D/F digenic; Deafness, autosomal recessive 23</td>
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<tr>
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<td>Harmonin</td>
<td>AR</td>
<td>Usher syndrome, type 1C; deafness, autosomal recessive 18A</td>
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<td>USH1G</td>
<td>Scaffold protein containing Ankyrin repeats and SAM domain</td>
<td>AR</td>
<td>Usher syndrome, type 1G</td>
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<tr>
<td>USH2A</td>
<td>Usherin</td>
<td>AR</td>
<td>Usher syndrome, type 2A; Retinitis pigmentosa 39</td>
</tr>
</tbody>
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**References:**