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Usher Syndrome Type II

Synonym: USH2

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Summary

Clinical characteristics

Usher syndrome type II (USH2) is characterized by the following:

- Congenital, bilateral sensorineural hearing loss that is mild to moderate in the low frequencies and severe to profound in the higher frequencies
- Intact or variable vestibular responses
- Retinitis pigmentosa (RP); progressive, bilateral, symmetric retinal degeneration that begins with night blindness and constricted visual fields (tunnel vision) and eventually includes decreased central visual acuity; the rate and degree of vision loss vary within and among families.

Diagnosis/testing

The diagnosis of USH2 is established in a proband using electrophysiologic and subjective tests of hearing and retinal function. Identification of biallelic pathogenic variants in one of three genes – *ADGRV1*, *USH2A*, or *WHRN* – establishes the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Early fitting of hearing aids and speech training. Children with incomplete speech and sentence rehabilitation with hearing aids and older individuals with severe-to-profound hearing loss should be considered for cochlear implantation. Standard treatments for retinitis pigmentosa; vestibular rehabilitation.

Surveillance: Annual audiometry and tympanometry with hearing aids or cochlear implant to assure adequate auditory stimulation. Annual ophthalmologic evaluation from age 20 years to detect potentially treatable complications such as cataracts, refractive errors, and cystoid macular edema. Annual fundus photography,

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visual acuity, visual field, electroretinography, optical coherence tomography, and fundus autofluorescence from age ten years.

Agents/circumstances to avoid: Tunnel vision and night blindness can increase the likelihood of accidental injury. Competition in sports requiring a full range of vision may be difficult and possibly dangerous. Progressive loss of peripheral vision impairs the ability to safely drive a car.

Evaluation of relatives at risk: The hearing of at-risk sibs should be assessed as soon after birth as possible to allow early diagnosis and treatment of hearing loss.

Genetic counseling

USH2 is inherited in an autosomal recessive manner. Each subsequent pregnancy of a couple who have had a child with Usher syndrome type II has a 25% chance of resulting in an affected child, a 50% chance of resulting in an unaffected child who is a carrier, and a 25% chance of resulting in an unaffected child who is not a carrier. Prenatal testing and preimplantation genetic testing are possible for pregnancies at increased risk if the pathogenic variants have been identified in the family.

Diagnosis

Suggestive Findings

Usher syndrome type II (USH2) **should be suspected** in individuals with:

- Congenital (i.e., prelingual) sensorineural hearing loss that is mild to moderate in the low frequencies and severe to profound in the higher frequencies (see Hereditary Hearing Loss and Deafness Overview);
- Intact or variable vestibular responses;
- Retinitis pigmentosa (RP);
- Normal general health and intellect; otherwise normal physical examination;
- A family history consistent with autosomal recessive inheritance.

Establishing the Diagnosis

The diagnosis of USH2 **is established** in a proband with the above clinical features and family history. Identification of biallelic pathogenic (or likely pathogenic) variants in one of the genes listed in Table 1 establishes the diagnosis if clinical features are inconclusive.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic variants of uncertain significance (or of one known pathogenic variant and one variant of uncertain significance) in one of the genes listed in Table 1 does not establish or rule out the diagnosis.

The phenotype of USH2 is often indistinguishable from many other inherited disorders associated with hearing loss and/or RP, therefore the recommended molecular testing approaches can include use of **a multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing is rarely useful and typically NOT recommended.

- An **Usher syndrome multigene panel** or a more comprehensive multigene panel (e.g., **inherited retinal dystrophy panel**, **hereditary hearing loss panel**) that includes the genes listed in Table 1 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while

limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  Note: Unlike exome sequencing, genome sequencing can identify variants outside of the coding region. Although most confirmed pathogenic variants identified by genome sequencing are within exons [Taylor et al 2015], several pathogenic variants have been detected in the noncoding region of *USH2A* [Daich Varela et al 2023].

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Usher Syndrome Type II (USH2)

Gene [1, 2]	USH2 Subtype	Proportion of USH2 Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detected by Method	
			Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
ADGRV1	USH2C	6.6%-19% [6]	>90% [7]	3/49 individuals [8]
USH2A	USH2A	57%-79% [6]	>90% [7, 9]	6%-9% [10, 11]
WHRN	USH2D	0%-9.5% [6]	>95% [7]	None reported [7]

Table 1. continued from previous page.

Gene [1, 2]	USH2 Subtype	Proportion of USH2 Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detected by Method	
			Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
Unknown [12, 13]			NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Bonnet et al [2011], Le Quesne Stabej et al [2012], García-García et al [2013]
7. LOVD Usher Syndrome Database
8. Hilgert et al [2009], Besnard et al [2012], Aparisi et al [2014]
9. Several deep intronic variants outside of the exon and splice junction regions typically included in standard sequencing have been observed, especially in *USH2A* [Vaché et al 2012, Liquori et al 2016, Baux et al 2017, Mansard et al 2021, Daich Varela et al 2023].
10. Bernal et al [2005], Dreyer et al [2008], Steele-Stallard et al [2013], Aparisi et al [2014], Baux et al [2014], Krawitz et al [2014], Sodi et al [2014], Dad et al [2015]
11. By screening for duplications/deletions, Steele-Stallard et al [2013] found a second *USH2A* pathogenic variant in 26% (6/23) of individuals for whom only one disease-causing allele had been found by sequencing.
12. A fourth locus associated with Usher syndrome type II has been provisionally mapped to 15q in a consanguineous Tunisian family [Ben Rebeh et al 2008].
13. To date, *PDZD7* pathogenic variants have not been shown to cause Usher syndrome but may act as modifiers of the retinal phenotype in individuals with *USH2A*-related USH2 [Ebermann et al 2010]. Additionally, an individual with USH2 and compound heterozygous pathogenic variants in *USH2A* and *PDZD7* and another affected individual with compound heterozygous variants in *ADGRV1* and *PDZD7* were reported, leading to the suggestion of digenic inheritance [Ebermann et al 2010].

Clinical Characteristics

Clinical Description

Usher syndrome type II (USH2) is characterized by moderate-to-severe sensorineural hearing loss at birth and retinitis pigmentosa (RP) that begins in late adolescence or early adulthood. Some individuals also have vestibular loss [Yang et al 2012, Blanco-Kelly et al 2015, Magliulo et al 2017].

Table 2. Select Features of Usher Syndrome Type II

Feature	% of Persons w/Feature	Comment
Hearing loss	100%	High-frequency loss which is usually stable
RP	100%	Variable age of onset & rate of progression
Vestibular loss	40%-80%	Usually asymptomatic but identifiable on specialized testing [1]

RP = retinitis pigmentosa
1. Magliulo et al [2017]

Hearing Loss

The hearing loss in USH2 is typically congenital and bilateral, occurring predominantly in the higher frequencies and ranging from moderate to severe. The degree of hearing loss varies within and among families; however, the "sloping" audiogram is characteristic of USH2. The hearing loss may be perceived by the affected individual as progressing over time because speech perception decreases, possibly as a result of diminished vision that

interferes with subconscious lip reading. Hearing aids are usually adequate in individuals with USH2. Cochlear implants are highly effective if speech and sentence testing indicates inadequate response with hearing aids.

Clinical variability of the hearing phenotype has been observed. In particular, a few individuals with USH2 have a mild but definite progression of hearing loss that is unrelated to presbycusis. A cross-sectional study of 27 persons with *USH2A*-USH2 confirmed by linkage analysis compared hearing threshold against age; significant progression of hearing impairment was observed but at a much slower rate than reported for Usher syndrome type III (USH3) [Pennings et al 2003]. In contrast, in a large study of 125 individuals with USH2, Reisser et al [2002] found no clinically relevant progression of hearing loss over a span of up to 17 years.

Visual Loss

Children with USH2 are often misdiagnosed as having nonsyndromic hearing impairment until tunnel vision and night blindness (early signs of RP) become severe enough to be noticeable, either by parents and teachers or by the individual. The onset of RP in individuals with USH2 is variable but typically starts in late adolescence or early adulthood and occasionally can start much earlier. RP is progressive, bilateral, symmetric photoreceptor degeneration of the retina that initiates in the mid-periphery; rods (photoreceptors active in the dark-adapted state) are mainly affected first, causing night blindness and constricted visual fields (tunnel vision). Cones (photoreceptors active in the light-adapted state) are affected second and eventually die and cause central blindness. Contrast sensitivities, color vision, and mobility may become severely affected as the retinal degeneration progresses.

Visual fields become progressively constricted with time. The rate and degree of visual field loss show intra- and interfamilial variability. A visual field of 5-10 degrees ("severe tunnel") is common for a person with USH2 at age 30-40 years. Visual impairment worsens significantly each year [Iannaccone et al 2004, Pennings et al 2004]. Individuals with USH2 may become completely blind. Cataracts and/or cystoid macular edema sometimes reduce central vision. These two associated conditions are treatable.

Vestibular Loss

Vestibular loss has been identified in 40%-80% of individuals with USH2 in a small study of specialized vestibular testing [Magliulo et al 2017]. However, these individuals were found to be asymptomatic suggesting that they compensate for the loss of vestibular function.

Heterozygotes

Heterozygotes are asymptomatic; however, they may exhibit audiogram anomalies that are not sensitive or specific enough for carrier detection.

Phenotype Correlations by Gene

Sadeghi et al [2004] compared serial audiograms of individuals with USH2 who had pathogenic variants in *USH2A* (group 1) with those of individuals diagnosed with USH2 who did not have pathogenic variants in *USH2A* (group 2). They found significantly worse thresholds in group 1 than in group 2 after the second decade. These results suggested that the *USH2A*-USH2 auditory phenotype may be different from that of other subtypes of USH2. Abadie et al [2012], however, did not find any significant differences between the audiograms from 88 individuals with pathogenic variants in *USH2A* and ten individuals with pathogenic variants in *ADGRV1*.

Schwartz et al [2005] did not observe any genotype-phenotype correlations between individuals with pathogenic variants in *USH2A* and those with variants in *ADGRV1*; however, only three sibs with pathogenic variants in *ADGRV1* were evaluated. They found a wide spectrum of photoreceptor disease with more rod than cone dysfunction, and both intra- and interfamilial variation for *USH2A*-USH2.

Frenzel et al [2012] performed two measures of touch sensation (tactile sensation and vibrational detection threshold) on two cohorts of individuals with USH2 from Germany and Spain. *USH2A* variants were associated with poor touch acuity as well as congenital hearing loss and adult-onset RP.

Genotype-Phenotype Correlations

***USH2A*.** Deleterious null (e.g., nonsense, frameshift, splicing) variants are associated with USH2, whereas homozygous missense variants that generate partially functional proteins typically cause nonsyndromic RP [Lenassi et al 2015b, Hartel et al 2016, Jung 2020]. The visual phenotype in individuals with *USH2A*-USH2 pathogenic variants is associated with more severe RP compared with nonsyndromic *USH2A*-RP [Pierrache et al 2016, Sengillo et al 2017, Gao et al 2021]. The hearing phenotype in individuals with *USH2A*-USH2 is more severe and progressive in individuals with one or more deleterious *USH2A* variants [Hartel et al 2016, Jung 2020].

Lenassi et al [2015b] designated retinal disease-specific pathogenic variants in *USH2A* that cause RP with preservation of normal hearing. While these individuals did not report hearing loss, audiometric testing found variable hearing loss in a substantial number. A correlation between severity of hearing loss and severity of RP was not found.

Individuals of Swedish or Dutch origin with biallelic *USH2A* truncating variants (including homozygous c.2299delG variants) developed significantly more severe and progressive hearing loss than individuals with one truncating *USH2A* variant combined with one nontruncating variant and individuals with two nontruncating variants. Similar findings were also reported in individuals of Korean ancestry [Hartel et al 2016, Jung 2020].

Penetrance

Penetrance is 100% in USH2.

Nomenclature

The numbering system used in Usher syndrome classification (USH1, USH2, and USH3) corresponds with the associated severity of the clinical presentation (i.e., degree of hearing impairment, the presence or absence of vestibular areflexia, and the age of onset of retinitis pigmentosa). The letter following USH2 indicates the molecular subtype caused by biallelic variants in one of the related genes listed in Table 1.

Prevalence

The prevalence of Usher syndrome in the general US population has been conservatively estimated at 4.4:100,000. However, a study of children with hearing loss in Oregon found that 11% had pathogenic variants in genes associated with Usher syndrome and estimated that the prevalence may be as high as 1:6,000 [Kimberling et al 2010].

Usher syndrome has been estimated to be responsible for 3%-6% of all childhood deafness and approximately 50% of all deaf-blindness. These estimates were made prior to 1989, when Möller et al [1989] subdivided Usher syndrome into USH1 and USH2, and USH3 had not yet been recognized. The specialized educational requirements of the congenitally deaf have historically rendered the population with USH1 more accessible for study by researchers. Persons with USH2 or USH3 communicate orally and are mainstreamed into regular schools; thus, the prevalence of USH2 and USH3 in the general population cannot be estimated as accurately as that of USH1. Often, persons with USH2 are not diagnosed until early adulthood, when progressive RP becomes debilitating.

The prevalence of Usher syndrome in Heidelberg, Germany and its suburbs has been calculated to be 6.2:100,000 [Spandau & Rohrschneider 2002]. In that study, the ratio of USH1 to USH2 was 1:3.

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *ADGRV1*, *USH2A*, and *WHRN* are summarized in Table 3.

Table 3. Allelic Disorders

Gene	Disorder	MOI	Comment
ADGRV1	Familial febrile seizures (OMIM 604352)	AD	A pathogenic nonsense variant was found in 1 of 48 families w/febrile seizures.
USH2A	Nonsyndromic retinitis pigmentosa [1]	AR	Common cause of nonsyndromic AR retinitis pigmentosa
WHRN	Nonsyndromic hearing loss (DFNB31) (See Hereditary Hearing Loss and Deafness Overview.)	AR	

AD = autosomal dominant; AR = autosomal recessive; DFNB = nonsyndromic deafness, autosomal recessive; MOI = mode of inheritance

1. Lenassi et al [2015b]

Differential Diagnosis

Often, a family with more than one affected sib is thought to have nonsyndromic hearing loss (NSHL) (see Hereditary Hearing Loss and Deafness Overview) until the oldest is diagnosed with retinitis pigmentosa (RP). Subsequent visual evaluation often reveals the presymptomatic early stages of RP in younger affected sibs.

Pathogenic variants associated with NSHL and RP can be inherited independently by a single individual whose symptoms mimic those of Usher syndrome [Fakin et al 2012]. Larger families lessen the statistical probability of this occurrence because at least one sib is likely to inherit one pathogenic variant without the other. NSHL and RP are both relatively common, with frequencies of 1:1,000 and 1:4,000, respectively, and are characterized by extreme genetic heterogeneity (to date, >110 genes have been associated with NSHL and >80 genes have been associated with RP).

Hereditary disorders characterized by both sensorineural hearing impairment and decreased visual acuity to consider in the differential diagnosis of Usher syndrome type II (USH2) are summarized in Table 4.

Table 4. Genes of Interest in the Differential Diagnosis of Usher Syndrome Type II

Gene(s)	Disorder	MOI	Clinical Characteristics	Comment
CDH23 *CIB2* *MYO7A* *PCDH15* *USH1C* *USH1G*	USH1	AR	Congenital bilateral profound SNHL, vestibular areflexia, adolescent-onset RP	Children w/USH1 are usually do not walk until age 18 mos to 2 yrs due to vestibular involvement (those w/USH2 usually walk at age ~1 yr).
CLRN1 *HARS1*	USH3 (OMIM 276902, 614504)	AR	Postlingual progressive SNHL, late-onset RP, variable impairment of vestibular function	Some persons w/USH3 may have profound HL & vestibular disturbance & thus be clinically misdiagnosed w/USH1 or USH2. [1]

Table 4. continued from previous page.

Gene(s)	Disorder		MOI	Clinical Characteristics	Comment
PEX1 *PEX6* *PEX12* (13 genes) [2]	Zellweger spectrum disorder (ZSD) [3]	Intermediate/ milder ZSD	AR (AD) [4]	Mainly sensory deficits &/or mild developmental delay; intellect may be normal.	Milder ZSD & USH2 can both have SNHL & retinal pigmentary abnormalities, but visual impairment in milder ZSD is more variable. Also, those w/milder ZSD typically develop ameliogenesis imperfecta of secondary teeth.
		Severe ZSD	AR	Severe neurologic dysfunction, craniofacial abnormalities, liver disfunction, absent peroxisomes	Infants w/severe ZSD are significantly impaired & usually die during 1st yr of life, usually having made no developmental progress.
PEX7 *PHYH*	Refsum disease		AR	RP, HL, anosmia, polyneuropathy, ataxia	RP is nearly always 1st noticeable feature; anosmia, polyneuropathy, & then mild-to-moderate HL follow.
ABHD12	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, & cataract (PHARC) (OMIM 612674)		AR	Polyneuropathy, HL, ataxia, RP, cataract	Persons w/PHARC typically develop polyneuropathy & ataxia in teens or early adulthood; & RP typically later in adulthood.
TIMM8A [5]	Deafness-dystonia-optic neuronopathy syndrome (DDON)		XL	Males: pre- or postlingual SNHL in early childhood; optic atrophy → slowly progressive ↓ visual acuity from age ~20 yrs; dementia from age ~40 yrs; slowly progressive dystonia or ataxia in the teens [6] Females: mild hearing impairment & focal dystonia	In DDON, appearance of the retina, night vision, & ERG are usually normal; in USH, impaired vision results from retinal dystrophy that first manifests as impaired dark adaptation. [7]

AD = autosomal dominant; AR = autosomal recessive; HL = hearing loss; MOI = mode of inheritance; RP = retinitis pigmentosa; SNHL = sensorineural hearing loss; USH = Usher syndrome; XL = X-linked

1. Pennings et al [2003]

2. 60.5% of Zellweger spectrum disorder (ZSD) is associated with biallelic pathogenic variants in *PEX1*, 14.5% with pathogenic variants in *PEX6*, and 7.6% with pathogenic variants in *PEX12*. In total, 13 genes are known to be associated with ZSD.

3. The term "Zellweger spectrum disorder" refers to all individuals with a defect in one of the ZSD-PEX genes regardless of phenotype.

4. One *PEX6* variant, p.Arg860Trp, has been associated with ZSD in the heterozygous state due to allelic expression imbalance dependent on allelic background.

5. DDON syndrome is caused by either (1) a hemizygous *TIMM8A* pathogenic variant in a male proband or a heterozygous *TIMM8A* pathogenic variant in a female proband or (2) a contiguous gene deletion of Xp22.1 involving *TIMM8A*.

6. In DDON syndrome, hearing impairment appears to be constant in age of onset and progression, whereas the neurologic, visual, and neuropsychiatric signs (e.g., personality change and paranoia) vary in degree of severity and rate of progression.

7. Sadeghi et al [2004]

Other. Viral infections, diabetic neuropathy, and syndromes involving mitochondrial defects (see Mitochondrial Disorders Overview) can all produce concurrent symptoms of hearing loss and retinal pigmentary changes that suggest Usher syndrome.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Usher syndrome type II (USH2), the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Usher Syndrome Type II

System/Concern	Evaluation	Comment
Audiology	Otoscopy, puretone audiometry, assessment of speech perception	Consider auditory brain stem response (ABR), electrocochleography (ECOG), and distortion product otoacoustic emission (DPOAE). Speech and sentence tests with hearing aids will determine if cochlear implantation offers better rehabilitation than hearing aids.
Vestibular function	Rotary chair, calorics, electronystagmography, ocular & cervical myogenic evoked potentials, video head impulse testing, computerized posturography	Persons describing imbalance or dizziness should undergo comprehensive vestibular testing to guide rehabilitation.
Ophthalmology	Fundus photography, VA, VF (Goldmann perimetry, Humphrey perimetry, Dark adapted rod perimetry), ERG, OCT, FAF	Fundus photography documents extent of pigmentation & RPE atrophy; VA is often maintained until late in disease; VF maps extent of functional peripheral vision, retinal sensitivities, & functional rod & cone responses. ERG is often nondetectable at presentation; OCT allows determination of "live" photoreceptors (measuring the ellipsoid zone); FAF can measure the perifoveal hyperfluorescent ring lipofuscin disturbance.
Genetic counseling	By genetics professionals [1]	To inform affected individuals & families re nature, MOI, & implications of USH2 in order to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support.	

ERG = electroretinography; FAF = fundus autofluorescence; OCT = optical coherence tomography; RPE = retinal pigment epithelium; VA = visual acuity; VF = visual field; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with Usher Syndrome Type II

Manifestation/ Concern	Treatment	Considerations/Other
Hearing loss	Hearing aids	Young children benefit from early fitting of hearing aids & speech training.
	Cochlear implantation	Children w/incomplete speech & sentence rehabilitation w/hearing aids & older persons w/severe-to-profound hearing loss: consider for cochlear implantation.

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Retinitis pigmentosa	• See Retinitis Pigmentosa Overview, Management. • Argus II prosthesis [1]	Tunnel vision & night blindness can ↑ likelihood of accidental injury.
Imbalance	Vestibular rehab	Neurologically active medications or sedatives can aggravate mild vestibular dysfunction.

1. Nadal & Iglesias [2018] describe the visual outcomes and rehabilitation of a one individual with USH2 that underwent Argus II prosthesis surgery.

Surveillance

Table 7. Recommended Surveillance for Individuals with Usher Syndrome Type II

System/Concern	Evaluation	Frequency
Hearing loss	Audiometry & tympanometry w/hearing aids or cochlear implant to assure adequate auditory stimulation	Annually, incl testing w/hearing aids in place
Cataracts	Ophthalmologic eval	Annually from age 20 yrs or age of diagnosis
Cystoid macular edema	Ophthalmologic eval	
Retinitis pigmentosa	Fundus photography, VA, VF (Goldmann perimetry, Humphrey perimetry, dark adapted rod perimetry), ERG, OCT, FAF	Annually from age 10 yrs or age of diagnosis

ERG = electroretinography; FAF = fundus autofluorescence; OCT = optical coherence tomography; VA = visual acuity; VF = visual field

Agents/Circumstances to Avoid

Competition in various sports requiring a full range of vision may be difficult and possibly dangerous.

Progressive loss of peripheral vision impairs the ability to safely drive a car. An Esterman visual field test (automated Humphrey, static visual field analyzer) with both eyes open during testing is a helpful measure to assess degrees of peripheral vision along the midline. Night driving is impaired very early.

Evaluation of Relatives at Risk

It is appropriate to evaluate all sibs at risk for USH2 as soon after birth as possible to allow early support and management of the child and the family. Evaluations include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Auditory brain stem response (ABR) and distortion product otoacoustic emission (DPOAE) if the pathogenic variants in the family are not known.

See Genetic Counseling for issues related to evaluation of at-risk relatives for genetic counseling purposes.

Pregnancy Management

High-dose vitamin A supplementation should not be used by affected pregnant women, as large doses of vitamin A (doses above the RDA for pregnant or lactating women) may be teratogenic to the developing fetus (see Other).

Therapies Under Investigation

QR-421 antisense treatment. Study to Evaluate Safety and Tolerability of QR-421a in Subjects with RP Due to Mutations in Exon 13 of the *USH2A* Gene (Stellar). This is an interventional, Phase I/II clinical trial to evaluate the safety of an antisense oligonucleotide (ASO) therapy to treat RP in individuals with USH2 due to specific *USH2A* pathogenic variants. This study is active and recruiting (see ClinicalTrials.gov).

C-18-04 antioxidant treatment. Safety and Efficacy of NPI-001 Tablets for Retinitis Pigmentosa Associated with Usher Syndrome (SLO RP). This is an interventional, two-year, Phase I/II clinical trial to evaluate the safety and efficacy of NPI-001 tablets in individuals with RP associated with Usher syndrome. This trial is active and recruiting (see ClinicalTrials.gov).

CL-17-01 antioxidant treatment. Phase I, Single- and Multiple-Ascending Dose Study of the Safety and Tolerability of NPI-001 Solution in Healthy Subjects. This clinical trial established that NPI-001 was generally well tolerated in all but the highest dose and determined key pharmacokinetic parameters of the NPI-001 solution (search on ACTRN12617000911392 at www.anzctr.org.au).

Search ClinicalTrials.gov in the US, EU Clinical Trials Register in Europe, and ANZCTR Trial Search in Australia and New Zealand for access to information on clinical studies for a wide range of diseases and conditions.

Other

Vitamin A supplements. Vitamin A plays an essential role in the visual (retinoid) cycle as the photosensitive intermediate 11 cis retinal. Although treatment with vitamin A palmitate may limit the progression of RP in persons with isolated RP and USH2, no studies have evaluated the effectiveness of vitamin A palmitate in individuals with USH2. Vitamin A is fat soluble and not excreted in the urine. Therefore, high-dose vitamin A dietary supplements should be used only under the direction of a physician because of the need to monitor for harmful side effects such as hepatotoxicity [Sibulesky et al 1999]. Of note, the studies by Berson et al [1993] were performed on individuals older than age 18 years because of the unknown effects of high-dose vitamin A on children. High-dose vitamin A supplementation should not be used by affected pregnant women, as large doses of vitamin A (i.e., above the recommended daily allowance for pregnant or lactating women) may be teratogenic to the developing fetus.

Lutein supplements may enhance retinal macular pigment. Lutein, zeaxanthin, meso-zeaxanthin, and their oxidative metabolites accumulate in the human fovea and macula as the macular pigment (MP). They are obtained through dietary sources (green leafy vegetables, yellow and/or orange fruits and vegetables). Inherited retinal dystrophies may cause or be associated with loss of MP [Aleman et al 2001]. Oral administration of lutein (20 mg/d) for seven months had no effect on central vision [Aleman et al 2001]. However, Berson et al [2010] showed that lutein supplementation of 12 mg/d slowed loss of midperipheral visual field among nonsmoking adults with RP taking vitamin A.

Omega 3 supplements (e.g., docosahexaenoic acid [DHA]) may replenish membranes of the photoreceptor outer segments, which are largely composed of polyunsaturated fatty acids. Supplementation of DHA significantly elevated blood DHA levels and reduced the rate of progression in final dark-adapted thresholds and visual field sensitivity [Hoffman et al 2015].

N-acetyl-cysteine (NAC) supplements. NAC is a safe oral antioxidant used to treat liver toxicity due to acetaminophen overdose. NAC reduces oxidative damage and increases cone function and survival in animal models of RP [Lee et al 2011]. In a Phase l study, 600 mg, 1200 mg, or 1800 mg were safe in individuals with RP and significant improvements were found in cone function, including visual acuity [Campochiaro et al 2020].

Blueberry extract supplements. Blueberry fruits contain anthocyanins, members of the flavonoid group of phytochemicals, which are powerful antioxidants. No studies have been done on individuals with RP or USH2. Because of their natural occurrence, they are probably safe and may be efficacious.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Usher syndrome type II (USH2) is inherited in an autosomal recessive manner.

Digenic inheritance and/or disease-modifier genes

- Multiple affected individuals have been found with two pathogenic variants in one USH1-related gene and another pathogenic variant in a second gene associated with Usher syndrome, which may modify the retinal phenotype [Zheng et al 2005, Bonnet et al 2011, Vozzi et al 2011, Yoshimura et al 2014].
- Although digenic inheritance has been proposed in Usher syndrome, particularly involving *PDZD7* (see Molecular Genetics), only two studies have reported evidence of digenic inheritance: Ebermann et al [2010] described an individual with USH2 with heterozygous pathogenic variants in both *ADGRV1* and *PDZD7*; Yoshimura et al [2014] described an individual with USH1 with heterozygous pathogenic variants in both *MYO7A* and *PCDH15*. Large meta-analysis of the genetics of Usher syndrome by Jouret et al [2019] concluded that data "do not support the existence of digenic inheritance in Usher syndrome" and suggest that the affected individuals in the above-referenced studies may have had genetic variants undetectable by the genetic testing capabilities available at the time.

Risk to Family Members (Autosomal Recessive Inheritance)

Parents of a proband

- The unaffected parents of an individual with USH2 are obligate heterozygotes (i.e., presumed to be carriers of one *ADGRV1*, *USH2A*, or *WHRN* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an USH2-causing pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an USH2-causing variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Considerable variability in the degree of hearing loss and the rate and degree of vision loss may be observed among affected sibs.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Unless an affected individual's reproductive partner also has USH2 or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in an USH2-related gene.
- The carrier frequency of pathogenic variants in *USH2A* is estimated at approximately 1:70 as an average across most ethnic populations. Importantly, many pathogenic variants in *USH2A* are associated with retinitis pigmentosa (RP) in the absence of hearing loss ("retinal disease-specific variants"). As a result, families segregating a retinal disease-specific *USH2A* variant and an *USH2A* pathogenic variant not specific to retinal disease only may have multiple affected individuals, with some developing USH2 and others with nonsyndromic RP [Lenassi et al 2015a].
- Thus, for each pregnancy of a couple in which one partner has USH2 and the other partner has normal vision and no family history of USH2 or RP, the probability of a child having USH2 or RP due to biallelic pathogenic variants in *USH2A* is approximately 1:140.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a pathogenic variant in an USH2-related gene.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the USH2-causing pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA and/or cellular banking is the storage of DNA (typically extracted from white blood cells) or cells for possible future use in research to improve our understanding of Usher syndrome and to develop new therapies. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA and/or cells of affected individuals. For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the USH2-causing pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **CUREUsher**

United Kingdom

Email: contact@cureusher.org

www.cureusher.org

- **MedlinePlus**

  Usher syndrome

- **Usher Syndrome Coalition**

  Phone: 978-637-2625; 617-951-9542

  Email: k.vasi@usher-syndrome.org; m.dunning@lek.com

  www.usher-syndrome.org

- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**

  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)

  Fax: 202-337-8314

  Email: info@agbell.org

  Listening and Spoken Language Knowledge Center

- **American Society for Deaf Children**

  Phone: 800-942-2732 (ASDC)

  Email: info@deafchildren.org

  deafchildren.org

- **BabyHearing.org**

  This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.

  www.babyhearing.org

- **Ciliopathy Alliance**

  United Kingdom

  ciliopathyalliance.org

- **Foundation Fighting Blindness**

  7168 Columbia Gateway Drive

  Suite 100

  Columbia MD 21046

  Phone: 800-683-5555 (toll-free); 800-683-5551 (toll-free TDD); 410-423-0600

  Email: info@fightblindness.org

  www.fightingblindness.org

- **Medical Home Portal**

  Hearing Loss and Deafness

- **National Association of the Deaf**

  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)

Fax: 301-587-1791

Email: nad.info@nad.org

nad.org

- **SENSE**
  101 Pentonville Road
  London N1 9LG
  United Kingdom
  Phone: 0845 127 0060 (voice); 0845 127 0062 (textphone)
  Fax: 0845 127 0061
  Email: info@sense.org.uk
  www.sense.org
- **Usher Syndrome Registry**
  Usher Syndrome Coalition
  Phone: 978-637-2625
  Email: k.vasi@usher-syndrome.org
  www.usher-registry.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Usher Syndrome Type II: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ADGRV1	5q14.3	Adhesion G-protein coupled receptor V1	GPR98 @ USHbases CCHMC - Human Genetics Mutation Database (GPR98)	ADGRV1	ADGRV1
USH2A	1q41	Usherin	USH2A @ LOVD CCHMC - Human Genetics Mutation Database (USH2A)	USH2A	USH2A
WHRN	9q32	Whirlin	WHRN @ USHbases (DFNB31) CCHMC - Human Genetics Mutation Database (DFNB31)	WHRN	WHRN

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Usher Syndrome Type II (View All in OMIM)

276901	USHER SYNDROME, TYPE IIA; USH2A
602851	ADHESION G PROTEIN-COUPLED RECEPTOR V1; ADGRV1
605472	USHER SYNDROME, TYPE IIC; USH2C
607928	WHIRLIN; WHRN

Table B. continued from previous page.

608400	USHERIN; USH2A
611383	USHER SYNDROME, TYPE IID; USH2D

Molecular Pathogenesis

The proteins associated with Usher syndrome type I (USH1) and Usher syndrome type II (USH2) interact with one another in the "Usher interactome." When one of these proteins is nonfunctional or absent, sensorineural degeneration occurs in the inner ear and the retina [Bonnet & El-Amraoui 2012, Mathur & Yang 2015, Géléoc & El-Amraoui 2020]. The USH2-related proteins include the following.

ADGRV1, encoded by *ADGRV1*

- Member of subgroup of the large N-terminal family B seven-transmembrane receptors
- Contains pentaxin (PTX) domains, similar to USH2A; may share binding partners
- Contains cadherin domains similar to USH1 proteins CDH23 and PCDH15
- Expressed as multiple variants that comprise isoforms a, b, and c [Reiners et al 2006]

Usherin, encoded by *USH2A*

- Expressed as two alternatively spliced isoforms that comprise a short "isoform a" (21 exons, 1546 amino acids) and a longer "isoform b" (72 exons, 5202 amino acids)
- Isoform a is a secreted protein that contains 1 laminin N-terminal (LN), 10 laminin epidermal growth factor (LE), and 4 fibronectin III (FN3) domains [Weston et al 2000].
- Isoform b is a transmembrane protein. The extracellular N-terminal end contains 1 laminin globular-like (LGL), 1 laminin N-terminal (LN), 10 laminin epidermal growth factor (LE), 2 laminin globular (LG), and 32 firbronectin III (FN3) domains. The intracellular C-terminal end contains a PDZ-binding domain (PBD) that interacts with other USH and deafness proteins in retinal photoreceptors and inner ear hair cells [van Wijk et al 2004, van Wijk et al 2006, Michalski et al 2007, Yang et al 2010, Zou et al 2011, Yu et al 2020].
- Usherin colocalizes with and binds to the extracellular basement membrane protein, type IV collagen, with a relatively broad tissue distribution [Bhattacharya et al 2002, Pearsall et al 2002, Bhattacharya et al 2004].

Whirlin, encoded by *WRHN*

- Expressed as multiple transcripts with two predicted promotor regions and alternative splicing that encode full-length (FL)-, N-, and C-terminal whirlin proteins [Mathur & Yang 2019]
- FL-whirlin has two harmonin N-like (HNL), three PDZ, one proline-rich (PR), and one PDZ-binding domain (PBD) [Mathur & Yang 2019].
- Whirlin interacts *in vivo* with usherin and ADGRV1, suggesting that these three proteins function as a multiprotein complex in both the stereocilia of the cochlear hair cells and the periciliary membrane complex of the retinal photoreceptor cells [Yang et al 2010].

Another PDZ domain-containing protein, PDZD7, was identified as a result of a study of a child with nonsyndromic sensorineural hearing loss and a homozygous reciprocal translocation; protein-protein interaction studies indicated that PDZD7 is a part of the Usher protein network [Schneider et al 2009]. Pathogenic variants in *PDZD7* have not yet been shown to cause Usher syndrome, but it has been suggested that *PDZD7* pathogenic variants may act as modifiers of the retinal phenotype in individuals with *USH2A*-USH2.

Mechanism of disease causation. Pathogenic variants in USH2-causing genes result in defects in cochlear hair cell development and photoreceptor cell maintenance. The autosomal recessive inheritance of USH2 strongly suggests a loss-of-function mechanism.

Table 8. Usher Syndrome Type II: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
ADGRV1	Small & large deletions reported
USH2A	• Multiple deep intronic pathogenic variants, which would not be detected by standard exome sequencing, are known to occur in *USH2A* [Liquori et al 2016, Baux et al 2017, Mansard et al 2021, Daich Varela et al 2023]. • Large single- & multiexon pathogenic variants have also been identified.

1. Genes from Table 1 in alphabetic order

Table 9. Usher Syndrome Type II: *USH2A* Notable Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_206933.2 NP_996816.2	c.2276G>T	p.Cys759Phe	Common pathogenic variant w/ reported allele frequency of 5%-10%
	c.2299delG	p.Glu767SerfsTer21	Common pathogenic variant w/ reported allele frequency of >20%
	c.4338_4339delCT	p.Cys1447GlnfsTer29	Founder variant in French-Canadians [Ebermann et al 2009]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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- 23 March 2023 (aa/gm) Revision: references (Baux et al [2017], Mansard et al [2021], Daich Varela et al [2023]) and information about likely pathogenic variants in noncoding regions detected by genome sequencing added to Establishing the Diagnosis and Molecular Genetics
- 22 October 2020 (sw) Comprehensive update posted live
- 21 July 2016 (sw) Comprehensive update posted live
- 29 August 2013 (me) Comprehensive update posted live
- 29 December 2011 (cd) Revision: deletion/duplication analysis available for *GPR98* and *DFNB31*
- 23 December 2010 (me) Comprehensive update posted live
- 14 April 2009 (me) Comprehensive update posted live
- 5 November 2007 (cd) Revision: prenatal diagnosis for Usher syndrome type 2A available
- 14 November 2006 (me) Comprehensive update posted live
- 20 October 2004 (wk) Revision: sequencing of entire coding region available
- 13 January 2004 (wk) Revision: change in test availability
- 20 November 2003 (me) Comprehensive update posted live
- 10 December 1999 (me) Review posted live
- 19 February 1999 (wk) Original submission

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