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Usher Syndrome Type I

Synonyms: USH1, Usher 1

Robert K Koenekoop, MD, PhD, FACS,[1] Moises A Arriaga, MD, MBA, FACS,[2] Karmen M Trzupek, MS, CGC,[3] and Jennifer J Lentz, PhD[4]

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Summary

Clinical characteristics

Usher syndrome type I (USH1) is characterized by congenital, bilateral, profound sensorineural hearing loss, vestibular areflexia, and adolescent-onset retinitis pigmentosa (RP). Unless fitted with a cochlear implant, individuals do not typically develop speech. RP, a progressive, bilateral, symmetric degeneration of rod and cone functions of the retina, develops in adolescence, resulting in progressively constricted visual fields and impaired visual acuity.

Diagnosis/testing

The diagnosis of USH1 is established in a proband using electrophysiologic and subjective tests of hearing and retinal function. Identification of biallelic pathogenic variants in one of six genes – *MYO7A*, *USH1C*, *CDH23*, *PCDH15*, *USH1G*, and *CIB2* – establishes the diagnosis if clinical features are inconclusive. Possible digenic inheritance has been reported in a few families.

Management

Treatment of manifestations: In infants: an initial trial of hearing aids to stimulate residual hearing and accustom the infant to auditory stimulation. Cochlear implantation should be considered as young as medically feasible. Sign language and tactile signs (once visual loss occurs) for families who choose non-auditory communication. Specialized training from educators of the hearing impaired. Vestibular compensation therapy for children with residual balance function and sensory substitution therapy for individuals with complete absence of vestibular function. Standard treatments for retinitis pigmentosa.

Surveillance: Annual audiometry and tympanometry in those with cochlear implant or hearing aids to assure adequate auditory stimulation. Annual otoscopic exam with tympanometry in children with profound loss to

Author Affiliations: 1 Pediatric Surgery, Human Genetics, and Adult Ophthalmology, McGill University Health Center, Montreal, Quebec, Canada; Email: robert.koenekoop@mcgill.ca. 2 Otolaryngology and Neurosurgery, Louisiana State University Health Sciences Center, New Orleans, Louisiana; Email: maa@neurotologic.com. 3 Ocular & Rare Disease Genetics Services InformedDNA, St Petersburg, Florida; Email: ktrzupek@informeddna.com. 4 Neuroscience Center of Excellence, Louisiana State University Health Sciences Center, New Orleans, Louisiana; Email: jlentz@lsuhsc.edu.

evaluate for chronic otitis media. Annual ophthalmologic evaluation, fundus photography, visual acuity, visual field testing, electroretinography, optical coherence tomography, and fundus autofluorescence from age 20 years.

Agents/circumstances to avoid: Competition in sports requiring acute vision and/or good balance may be difficult and possibly dangerous. Because of the high risk for disorientation when submerged in water, swimming needs to be undertaken with caution. 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

USH1 is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has 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. Once the USH1-causing pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal diagnosis for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Usher syndrome type I (USH1) **should be suspected** in individuals with:

- Congenital (i.e., prelingual) severe-to-profound bilateral sensorineural hearing loss (see Hereditary Hearing Loss and Deafness Overview);
- No significant or delayed vestibular responses;
- Retinitis pigmentosa (RP);
- Normal general health and intellect and otherwise normal physical examination;
- A family history consistent with autosomal recessive inheritance.

Establishing the Diagnosis

The diagnosis of USH1 **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 USH1 is often indistinguishable from many other inherited disorders associated with hearing loss and/or RP; therefore, the recommended molecular genetic testing approaches 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.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 I (USH1)

Gene [1]	USH1 Subtype	Proportion of USH1 Attributed to Pathogenic Variants [2] in Gene [3]	Proportion of Pathogenic Variants [2] Detected by Method	
			Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
MYO7A	USH1B	53%-70%	~98% [6]	<2% [7]
USH1C	USH1C	6%-15% [8]	>98%	2 reported [9, 10]
CDH23	USH1D	10%-20%	~85% [11]	<15% [12]
PCDH15	USH1F	7%-12% [13]	~75%	~25% [14, 15]
USH1G	USH1G	Rare (0%-4%)	>85%	2 reported [15]
CIB2	USH1J	Unknown	1 reported [16]	None reported [16]

Table 1. continued from previous page.

Gene [1]	USH1 Subtype	Proportion of USH1 Attributed to Pathogenic Variants [2] in Gene [3]	Proportion of Pathogenic Variants [2] Detected by Method	
			Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
Unknown [17]		10%-15% [18]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Jouret et al [2019]
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. Maubaret et al [2005], Jaijo et al [2007], Bonnet et al [2011], Roux et al [2011], Le Quesne Stabej et al [2012]
7. The majority of reported pathogenic variants are detectable by sequence analysis; however, intragenic multiexon deletions have been reported [Adato et al 1997, Baux et al 2008, Roux et al 2011, Bonnet et al 2016].
8. Almost all Usher syndrome type I in the Acadian population is caused by *USH1C* pathogenic variants. Five pathogenic variants in *USH1C* have been identified in 53 Acadian individuals with USH1 from Louisiana and Canada [Lentz et al, ongoing Natural History Study, unpublished]. Of these, c.216G>A is the most common variant (95/106 alleles, 90%), followed by c.238dupC (6/106 alleles, 6%).
9. Sun et al [2018]
10. Homozygous 11p15-p14 deletion syndrome (see Genetically Related Disorders) is caused by a contiguous gene deletion that includes *USH1C* and *ABCC8* and has been observed in families from Saudi Arabia and Kuwait [Bitner-Glindzicz et al 2000, Al Mutair et al 2013].
11. Bonnet et al [2011], Roux et al [2011], Le Quesne Stabej et al [2012]
12. The majority of reported pathogenic variants are detectable by sequence analysis; however, intragenic deletions and duplications have been reported [Nakanishi et al 2010, Roux et al 2011, Aparisi et al 2014, Bonnet et al 2016].
13. p.Arg245Ter (c.733C>T) is detected in a large percentage of Ashkenazi Jewish individuals with *PCDH15*-Usher syndrome type I.
14. Roux et al [2011]
15. Bonnet et al [2016]
16. Riazuddin et al [2012]. Note: Booth et al [2018] suggest that *CIB2* pathogenic variants cause DFNB48 and not USH1J.
17. USH1E has been mapped to 21q21; USH1H has been mapped to 15q22-q23 [Ahmed et al 2009]; USH1K has been mapped to 10p11.21-q21.1 [Jaworek et al 2012].
18. Bonnet et al [2011], Roux et al [2011], Le Quesne Stabej et al [2012], Yoshimura et al [2014], and personal communication with Kerry Goetz at eyeGENE.

Clinical Characteristics

Clinical Description

Hearing loss. The hearing loss in Usher syndrome type I (USH1) is congenital (i.e., present at birth), bilateral, severe-to-profound sensorineural hearing impairment (SNHI). While congenital SNHI should be identified through universal hearing screening at birth, occasionally false negative screening or missed screening before discharge to home results in delayed diagnosis until speech delay is obvious. Affected individuals do not develop speech unless fitted with cochlear implants. Hearing aids are usually inadequate in individuals with USH1 because of the severity of the hearing loss. Alternatively, sign language and tactile signs (once visual loss occurs) are communication options for families who choose nonauditory communication.

Imbalance. The imbalance in individuals with USH1 is associated with the deafness and is a defining feature of this disorder. While the timing and extent of "vestibular areflexia" is not fully understood, children with USH1 typically walk later than usual, at approximately age 18 months to two years. Older children may seem "clumsy" and experience frequent accidental injuries or have difficulty with activities requiring balance, such as riding a bicycle or playing sports.

Visual loss. Children with USH1 are often misdiagnosed as having nonsyndromic hearing impairment until delayed walking or tunnel vision and night blindness – early signs of retinitis pigmentosa (RP) – become severe enough to be noticeable, either by parents and teachers or by the individual. The onset of RP in individuals with USH1 is variable but can start in early infancy or childhood. RP is progressive, bilateral, symmetric photoreceptor degeneration of the retina that initiates in the midperiphery; 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, resulting in 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 USH1 age 30-40 years. Visual impairment worsens significantly each year [Pennings et al 2004]. Individuals with USH1 may become completely blind. Cataracts and/or cystoid macular edema sometimes reduce central vision. These two associated conditions are treatable.

Heterozygotes. Heterozygotes are asymptomatic.

Genotype-Phenotype Correlations

A genotype-phenotype correlation has been reported for pathogenic variants in the genes associated with USH1. Homozygous null (e.g., nonsense, frameshift, splicing) variants are associated with USH1, whereas homozygous missense variants that generate partially functional proteins typically cause nonsyndromic hearing impairment or atypical Usher syndrome. This genotype-phenotype correlation suggests that deaf children found to be homozygous for hypomorphic variants in an USH1 gene are unlikely to develop vision loss.

USH1C

- **c.1220delG.** Audiometric screening of ten individuals of Yemenite Jewish ancestry revealed that individuals younger than age 40 years had normal hearing while older individuals showed mild-to-severe high-frequency hearing loss. This is the first report of individuals with USH1 and adult-onset hearing loss rather than congenital hearing loss [Khateb et al 2012].
- **c.667G>T (p.Gly223Cys).** Heterozygous variant reported in individuals with autosomal dominant nonsyndromic hearing impairment from a Korean cohort [Song et al 2020]

CDH23. A reduced frequency of null (e.g., nonsense, frameshift, splice) variants in *CDH23* was observed in individuals with less severe phenotypes, with approximately 88%, 67%, and 0% of null variants found in persons with typical Usher type I (USH1D), atypical Usher syndrome, and nonsyndromic deafness type 12 (DFNB12), respectively [Bolz et al 2001, Bork et al 2001, Liu et al 2001, Astuto et al 2002, Bork et al 2002, Valero et al 2019].

PCDH15. Hypomorphic variants were associated with nonsyndromic hearing impairment indicating that residual function with some missense variants are sufficient for normal vision but not hearing, while more severe pathogenic variants result in USH1 [Ahmed et al 2001, Alagramam et al 2001, Ahmed et al 2003, Doucette et al 2009].

CIB2. To date all known pathogenic variants (copy number variants, splicing, indels, and missense) identified in *CIB2* are associated with DFNB48, except one variant, c.192G>C (p.Glu64Asp), identified in four individuals from a single consanguineous Pakistani family with USH1J [Riazuddin et al 2012]. Booth et al [2018], however, reported three different loss-of-function variants in three families from diverse origins that cause DFNB48 (autosomal recessive nonsyndromic hearing loss) and not USH1.

Penetrance

Penetrance is complete in Usher syndrome type I.

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, presence or absence of vestibular areflexia, and age at onset of retinitis pigmentosa). The letters (e.g., USH1C, USH1B) indicate the molecular subtype with biallelic pathogenic variants in one of the related genes listed in Table 1.

Note: Gerber et al [2006] provide evidence that the USH1A locus does not exist; six of the nine families from the Bressuire region of France originally reported to map to this locus have been found to have pathogenic variants in *MYO7A* (USH1B).

Prevalence

In older publications the prevalence of Usher syndrome has been reported to range from 3.2 to 6.2 per 100,000. Usher syndrome was estimated to be responsible for 3%-6% of all childhood deafness and approximately 50% of all deaf-blindness. Many of these estimates were made prior to 1989, when Möller et al [1989] subdivided Usher syndrome into Usher syndromes type I and II, and before the recognition of Usher syndrome type III. The specialized educational requirements of the congenitally deaf have historically rendered the population with Usher syndrome type I more accessible for study by researchers. Persons with Usher syndrome type II or Usher syndrome type III, who communicate orally and who are mainstreamed into regular schools, are not well represented in these estimates. It has been argued that the prevalence of Usher syndrome in the general population may therefore be substantially greater than estimated.

A recent study of children with hearing loss in Oregon found pathogenic variants in Usher syndrome-associated genes in 11% and estimated that the prevalence may be as high as one in 6,000 [Kimberling et al 2010].

Genetically Related (Allelic) Disorders

Table 2. Allelic Disorders

Gene	Disorder	MOI	Associated Pathogenic Variant(s) / Comments
MY07A	DFNA11 [1]	AD	A unique putative dominant-negative variant in the coiled-coil domain necessary for myosin VIIa homodimer formation [2]
	DFNB2 [1]	AR	Note: A reanalysis of the phenotype in 1 large DFNB2 pedigree revealed presence of RP, indicating that the affected persons have USH1B (not DFNB2) & reinforcing the need for a multidisciplinary approach in making an accurate diagnosis of USH. [3]
USH1C	Homozygous 11p15-p14 deletion syndrome (OMIM 606528)	AR	A contiguous gene deletion incl *USH1C* causes infantile hyperinsulinism, enteropathy, & deafness.
	DFNB18 [1]	AR	Less deleterious variants in *USH1C* may be assoc w/deafness w/o RP. [4]
	Nonsyndromic hearing loss	AD	Sensorineural hearing impairment w/o RP [5]
	USH3	AR	RP w/late-onset high-frequency hearing loss [6]
CDH23	DFNB12 [1]	AR	
	USH2, atypical USH	AR	A wide range of auditory & retinal phenotypes have been found in persons w/biallelic *CDH23* pathogenic variants, some more consistent w/ USH2 than w/USH1. [7]

Table 2. continued from previous page.

Gene	Disorder	MOI	Associated Pathogenic Variant(s) / Comments
PCHD15	DFNB23 [1]	AR	Missense variants have been found to cause DFNB23, [8] while more severe variants (splicing, frameshift, nonsense, large deletions) cause USH1.
USH1G	USH2, atypical USH	AR	Some pathogenic variants in *USH1G* have been shown to cause a relatively mild form of USH, more consistent w/USH2 than w/USH1. [9]

AD = autosomal dominant; AR = autosomal recessive; DFNA = nonsyndromic deafness, autosomal dominant; DFNB = nonsyndromic deafness, autosomal recessive; MOI = mode of inheritance; RP = retinitis pigmentosa; USH = Usher syndrome; USH1 = Usher syndrome type I; USH2 = Usher syndrome type II

1. See Hereditary Hearing Loss and Deafness Overview.
2. Tamagawa et al [2002]
3. Zina et al [2001]
4. Ahmed et al [2002], Ouyang et al [2002]
5. Song et al [2020]
6. Khateb et al [2012]
7. Astuto et al [2002]
8. Ahmed et al [2008], Doucette et al [2009]
9. Bashir et al [2010]

Differential Diagnosis

Nonsyndromic hearing loss (NSHL). Often, a family with more than one affected sib is thought to have NSHL (see Hereditary Hearing Loss and Deafness Overview) until the oldest affected sib manifests signs of retinal degeneration (e.g., night blindness, dark adaptation impairment, contrast vision difficulties, visual acuity changes, and visual field narrowing) and is diagnosed with retinitis pigmentosa (RP). Subsequent visual evaluation often reveals the presymptomatic signs of RP in younger affected sibs.

While the timing and extent of vestibulopathy related to Usher syndrome is not fully defined, vestibular symptoms in young children thought to have NSHL may also prompt visual evaluation and subsequent genetic testing.

Coinheritance of NSHL and RP. Pathogenic variants associated with separate NSHL and RP (e.g., *OTOA*-NSHL and *NR2E3*-RP [Neuhaus et al 2017]) can be inherited independently by a single individual whose symptoms can then 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 (or inherited retinal degeneration) are both relatively common, with frequencies of 1:1,000 and 1:3,000, respectively, and are both characterized by extreme genetic heterogeneity (to date, >110 genes have been associated with NSHL, >60 genes have been associated with RP, and >172 genes have been associated with inherited retinal degeneration) [Pagon 1988]. See also Hereditary Hearing Loss and Deafness Overview and RetNet™: Retinal Information Network.

Hereditary disorders characterized by both sensorineural hearing impairment (SNHI) and decreased visual acuity to consider in the differential diagnosis of Usher syndrome type I (USH1) are summarized in Table 3.

Table 3. Genes of Interest in the Differential Diagnosis of Usher Syndrome Type I

Gene(s)	Disorder	MOI	Clinical Characteristics	Comment
ADGRV1 *PDZD7* *USH2A* *WHRN*	USH2	AR Digenic [1]	• Congenital bilateral SNHL (predominantly in the higher frequencies); ranges from mild to severe • Adolescent- to adult-onset RP • Normal vestibular function	Children w/USH1 are usually delayed in walking until age 18 mos to 2 yrs because of vestibular involvement, whereas children w/ USH2 usually begin walking at ~1 yr.
ALMS1	Alström syndrome	AR	• SNHI • Progressive cone-rod dystrophy leading to blindness • Childhood obesity associated w/ hyperinsulinemia, & type 2 diabetes	• Cardiomyopathy occurs in ~70% of affected persons in infancy or adolescence. • Kidney failure & pulmonary, hepatic, & urologic dysfunction are frequent. • Systemic fibrosis develops w/age.
CEP250	Cone-rod dystrophy and hearing loss 2 (OMIM 618358)	AR	• Variable onset & severity of hearing loss • Variable onset & severity of visual loss	Can be diagnosed as atypical USH1 [2]
CEP78	Cone-rod dystrophy & hearing loss 1 (OMIM 617236)	AR	• Late-onset hearing loss • Late-onset visual loss	Can be diagnosed as atypical USH2 [3]
CISD2 *WFS1*	Wolfram syndrome (DIDMOAD) (See *WFS1* Spectrum Disorder.)	AR	Severe neurodegenerative disease w/diabetes insipidus, diabetes mellitus, OA, & deafness	Affected persons may also have kidney abnormalities, ataxia, dementia, or ID & diverse psychiatric illnesses.
CLRN1 *HARS1*	USH3 (OMIM 276902, 614504)	AR	• Postlingual progressive SNHL • Late-onset RP • Variable impairment of vestibular function	Some persons w/USH3 have profound hearing loss & vestibular disturbance & thus may be clinically misdiagnosed as having USH1 or USH2.
COL4A3 *COL4A4* *COL4A5*	Alport syndrome	XL AR AD Digenic	• Variable SNHL • Variable ocular anomalies • Progressive deterioration of glomerular basement membranes resulting in progressive kidney failure	Both Alport syndrome & USH1 have hearing & visual loss, but Alport syndrome also has progressive kidney disease. Urinalysis abnormalities in Alport are clinically distinctive.
PEX1 *PEX6*	Heimler syndrome (OMIM 234580, 616617)	AR	• SNHL • Retinal degeneration • Enamel dysplasia & nail abnormalities	Both Heimler syndrome & USH1 have hearing & visual loss, but Heimler syndrome also has a defect of the teeth in which the enamel is hypoplastic.
PEX1 *PEX6* *PEX10* (13 genes) [4]	Zellweger spectrum disorder	AR	Severe neurologic dysfunction, craniofacial abnormalities, liver dysfunction, & absent peroxisomes	Persons w/Zellweger syndrome typically die in the 1st yr of life.
PEX6	Peroxisome biogenesis disorder 4B (OMIM 614863)	AD AR	• SNHL • RP • Hypotonia	Overlapping phenotype w/ neonatal adrenoleukodystrophy, infantile Refsum disease, & Zellweger spectrum disorder

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Characteristics	Comment
PRPS1	*PRPS1* hereditary motor & sensory neuropathy (CMTX5) (See Phosphoribosylpyrophosphate Synthetase Deficiency.)	XL	• Deafness • OA • Polyneuropathy	Males tend to be severely affected.
PRPS1	Arts syndrome (See Phosphoribosylpyrophosphate Synthetase Deficiency.)	XL	• Hearing impairment • OA • ID, early-onset hypotonia, ataxia, delayed motor development	Both Arts syndrome & USH1 have hearing & visual loss, but Arts syndrome also has neurologic & immune system deficits.
RPGR	RPGR nonsyndromic RP (See Nonsyndromic Retinitis Pigmentosa Overview.)	XL	Progressive RP	2% of persons w/RPGR nonsyndromic RP also have ciliary dyskinesia & hearing loss. [5]
TIMM8A	Deafness-dystonia-optic neuronopathy syndrome (DDON)	XL	• Males: prelingual or postlingual SNHL in early childhood; slowly progressive ↓ visual acuity from OA beginning at age ~20 yrs; dementia beginning at age ~40 yrs; slowly progressive dystonia or ataxia in the teens • 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, which first manifests as impaired dark adaptation.

AR = autosomal recessive; CMTX5 = Charcot-Marie-Tooth neuropathy X type 5; DIDMOAD = diabetes insipidus, diabetes mellitus, optic atrophy, and deafness; ID = intellectual disability; MOI = mode of inheritance; OA = optic atrophy; RP = retinitis pigmentosa; SNHI = sensorineural hearing impairment; SNHL = sensorineural hearing loss; USH = Usher syndrome; XL = X-linked; USH1 = Usher syndrome type I; USH2 = Usher syndrome type II; USH3 = Usher syndrome type III

1. Digenic USH2 is caused by pathogenic variants in *ADGRV1* and *PDZD7*.

2. Khateb et al [2014], Fuster-García et al [2018]

3. Nikopoulos et at [2016], Fu et al [2017]

4. 60.5% of Zellweger spectrum disorder (ZSD) is associated with biallelic pathogenic variants in *PEX1*, 14.5% with pathogenic variant in *PEX6*, and 7.6% with pathogenic variants in *PEX12*. In total, 13 genes are known to be associated with ZSD.

5. Shu et al [2007]

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 I (USH1), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Usher Syndrome Type I

System/Concern	Evaluation	Comment
Audiology	Otoscopy, pure tone audiometry, assessment of speech perception	Consider ABR, ECOG, & DPOAE.
Vestibular function	Rotary chair, VNG incl calorics, & computerized posturography	Consider VHIT, vestibular evoked myogenic potentials (cVEMP & oVEMP).
Ophthalmology	Fundus photography, VA, VF (Goldmann perimetry, Humphrey perimetry, dark-adapted rod perimetry), ERG, OCT, & FAF	• Fundus photography documents the extent of pigmentation & retinal/RPE atrophy. • VA is often maintained until late in the disease. • VF maps the extent of functional peripheral vision, retinal sensitivities, & functional rod & cone responses. • ERG is often nondetectable at presentation. • OCT allows the determination of "live" photoreceptors (measuring the ellipsoid zone). • FAF can measure the perifoveal hyperfluorescent ring, & lipofuscin disturbance.
Other	Consultation w/clinical geneticist &/or genetic counselor	

ABR = auditory brain stem response; DPOAE = distortion product otoacoustic emission; ECOG = electrocochleography; ERG = electroretinography; FAF = fundus autofluorescence; OCT = optical coherence tomography; RPE = retinal pigment epithelium; VA = visual acuity; VF = visual field; VHIT = vestibular head impulse testing; VNG = videonystagmography

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Usher Syndrome Type I

Manifestation/ Concern	Treatment	Considerations/Other
Hearing loss	• An initial trial of hearing aids even w/profound loss stimulates any residual hearing & accustoms the infant to auditory stimulation for auditory/ oral language development. • Cochlear implantation should be considered as early as is medically feasible. [1]	Hearing aids are usually inadequate in severe-to-profound hearing loss. Sign language such as American Sign Language and tactile signs (once visual loss occurs) are communication options for families who choose nonauditory communication.
	Specialized training from educators of the hearing impaired	Recommended for affected children & all family members to improve communication skills
Balance difficulties & ↑ risk of accidental injury	Vestibular compensation therapy for children w/ residual balance function & sensory substitution therapy for individuals w/complete absence of vestibular function	Well-supervised sports activities may help develop somatosensory component of the balance system.
Vision loss	See Nonsyndromic Retinitis Pigmentosa Overview, Management.	Adults w/USH1 age >20 yrs use sign language & lip reading for communication. As vision loss progresses, these methods become increasingly difficult & tactile signing may ultimately be required.

1. Damen et al [2006], Pennings et al [2006], Liu et al [2008]

Surveillance

Table 6. Recommended Surveillance for Individuals with Usher Syndrome Type I

System/Concern	Evaluation	Frequency
Hearing loss	Audiometry & tympanometry w/ cochlear implant or hearing aids to assure adequate auditory stimulation	• For persons w/o profound loss, annual testing allows appropriate hearing aid adjustment. • For cochlear implant recipients, annual follow up is necessary to assure appropriate implant function & programming. • Children w/profound loss & cochlear implants can still develop fluid & chronic ear infection issues, which are less evident to the child because of hearing loss. Annual otoscopic exam w/ tympanometry avoids potential serious complications of chronic otitis media.
Cataracts	Ophthalmologic eval	Annually from age 20 yrs or from age at diagnosis
Cystoid macular edema		
Retinitis pigmentosa	Fundus photography, VA, VF (Goldmann perimetry, Humphrey perimetry, dark-adapted rod perimetry), ERG, OCT, & FAF	

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

Agents/Circumstances to Avoid

Competition in sports requiring acute vision and/or good balance may be difficult and possibly dangerous.

Persons with USH1 often become disoriented when submerged in water because they lack the sense of where "up" is; they should therefore exercise caution while swimming. Similarly, the vestibular dysfunction increases the risk of falls when walking on sloped or uneven surfaces.

Progressive loss of peripheral vision may eventually impair 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 the hearing of all sibs at risk for USH1 as soon after birth as possible to allow early diagnosis and treatment of hearing impairment.

Additional 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 testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

UshStat® gene replacement of *MYO7A* – A Study to Determine the Long-Term Safety, Tolerability and Biological Activity of UshStat® in Patients with Usher Syndrome Type 1B. This is an interventional, Phase I/II

clinical trial to evaluate the safety and activity of retinal gene therapy to treat RP in individuals with *MYO7A*-USH1. This trial is active but not recruiting. (See NCT02065011.)

QR-421 antisense treatment – A 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. (See NCT03780257.)

C-18-04 antioxidant treatment – Safety and Efficacy of NPI-001 Tablets versus Placebo for Treatment of Retinitis Pigmentosa Associated with Usher Syndrome. 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 NCT04355689.)

CL-17-01 antioxidant treatment – A 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. (See ACTRN12617000911392.)

Search ClinicalTrials.gov in the US, EU Clinical Trials Register in Europe, and ANZCTR 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 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 USH1. 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/day) 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/day 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. Blueberries contain anthocyanins, members of the flavonoid group of phytochemicals, which are powerful antioxidants. No studies have been done on individuals with RP or USH1. Because of their natural source, blueberry extract supplements 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 I (USH1) is typically 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*, 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 USH1 are obligate heterozygotes (i.e., presumed to be carriers of one USH1-causing 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 a USH1-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 a USH1-causing pathogenic 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.
- 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 USH1 or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in an USH1-related gene.

- Assuming that: (1) the prevalence of Usher syndrome is one in 20,000, (2) 30% of individuals with Usher syndrome have type I, and (3) 60% of individuals with USH1 have biallelic pathogenic variants in *MYO7A*; the population carrier frequency is approximately one in 165 for an *MYO7A* pathogenic variant. Thus, for each pregnancy of a couple in which one partner has USH1 and the other partner has normal hearing and no family history of Usher syndrome, the probability of a child having Usher syndrome due to biallelic pathogenic variants in *MYO7A* is approximately one in 330. When similar calculations are done for the other molecular etiologies of USH1, the total probability of this couple having a child with USH1 is approximately one in 300. (Note that this probability would not be correct if both parents are of Acadian or Ashkenazi Jewish ancestry.)

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a pathogenic variant in a USH1-related gene.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the USH1-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 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 USH1-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, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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.
  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 I: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CDH23	10q22.1	Cadherin-23	CDH23 @ USHbases Hereditary Hearing Loss Homepage (CDH23) CCHMC - Human Genetics Mutation Database (CDH23)	CDH23	CDH23
CIB2	15q25.1	Calcium and integrin-binding family member 2		CIB2	CIB2
MYO7A	11q13.5	Unconventional myosin-VIIa	MYO7A @ LOVD Hereditary Hearing Loss Homepage (MYO7A) CCHMC - Human Genetics Mutation Database (MYO7A)	MYO7A	MYO7A
PCDH15	10q21.1	Protocadherin-15	PCDH15 @ LOVD CCHMC - Human Genetics Mutation Database (PCDH15)	PCDH15	PCDH15
USH1C	11p15.1	Harmonin	USH1C @ USHbases CCHMC - Human Genetics Mutation Database (USH1C)	USH1C	USH1C

Table A. continued from previous page.

USH1G	17q25.1	pre-mRNA splicing regulator USH1G	USH1G @ LOVD CCHMC - Human Genetics Mutation Database (USH1G) RetNet: Genes and Mapped Loci Causing Retinal Diseases (USH1G)	USH1G	USH1G

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 I (View All in OMIM)

276900	USHER SYNDROME, TYPE I; USH1
276903	MYOSIN VIIA; MYO7A
276904	USHER SYNDROME, TYPE IC; USH1C
601067	USHER SYNDROME, TYPE ID; USH1D
602083	USHER SYNDROME, TYPE IF; USH1F
602097	USHER SYNDROME, TYPE IE; USH1E
605242	USH1 PROTEIN NETWORK COMPONENT HARMONIN; USH1C
605514	PROTOCADHERIN 15; PCDH15
605516	CADHERIN 23; CDH23
605564	CALCIUM- AND INTEGRIN-BINDING PROTEIN 2; CIB2
606943	USHER SYNDROME, TYPE IG; USH1G
607696	USH1 PROTEIN NETWORK COMPONENT SANS; USH1G
612632	USHER SYNDROME, TYPE IH; USH1H
614869	USHER SYNDROME, TYPE IJ; USH1J
614990	USHER SYNDROME, TYPE IK; USH1K

Molecular Pathogenesis

Usher syndrome is the most frequent genetic cause of concurrent deaf-blindness. It is clinically and genetically heterogeneous. Currently, three clinical types and ten different genes (subtypes) are associated with Usher syndrome. The proteins encoded by the six known Usher syndrome type I (USH1) genes are hypothesized to interact with one another. These proteins are expressed in the eye and ear during and after development, forming a critical macromolecular complex necessary for the development of cilia structure and function. If any one protein in this "Usher interactome" 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].

- *MYO7A* encodes myosin VII (USH1B).
- *USH1C* encodes are harmonin (USH1C).
- *CDH23* encodes cadherin-23 (USH1D).
- *PDCH5* encodes protocadherin 15 (USH1F).
- *USH1G* encodes sans (USH1G).
- *CIB2* encodes CIB2 (USH1J).

Note: A comprehensive set of databases (UMD-USHbases) provides information about pathogenic variants responsible for Usher syndrome [Baux et al 2008].

Mechanism of disease causation. Pathogenic variants in USH1 genes result in defects in cochlear hair cell development and photoreceptor maintenance. The autosomal recessive inheritance of USH1 strongly suggests a loss-of-function mechanism.

Table 7. Usher Syndrome Type I: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
CIB2	NM_006383.3 NP_006374.1	c.192G>C	p.Glu64Asp	Variant found in 1 Pakistani family [Riazuddin et al 2012]
PCDH15	NM_033056.3 NP_149045.3	c.733C>T	p.Arg245Ter	Ashkenazi Jewish founder variant [Ben-Yosef et al 2003]
USH1C	NM_005709.3 NP_005700.2	c.216G>A	See footnote 2.	Acadian founder variant [Ouyang et al 2002, Lentz et al 2005]
	NM_005709.3	c.238dupC	--	Common variant found across populations [Bitner-Glindzicz et al 2000, Verpy et al 2000, Zwaenepoel et al 2001, Ahmed et al 2002, Blaydon et al 2003, Ouyang et al 2003]
		c.1220delG	--	Causes RP w/late-onset high-frequency HL [Khateb et al 2012]

HL = hearing loss; RP = retinitis pigmentosa
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.
1. Genes from Table 1 in alphabetic order.
2. Although this variant is predicted to result in a p.Val72Glu missense change, it is known to cause abnormal splicing.

Chapter Notes

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Edward Cohn, MD, Department of Otolaryngology, Boys Town National Research Hospital

Janos Sumegi, PhD, Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha

Claes Möller, MD, PhD, Department of Otorhinolaryngology, Sahlgrenska University Hospital, Göteborg, Sweden

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Author History

Moises A Arriaga, MD, MBA, FACS (2020-present)
Bronya Keats, PhD; Louisiana State University Health Sciences Center (2006-2020)
William J Kimberling, PhD, FACMG; Boys Town National Research Hospital (1999-2006)
Robert K Koenekoop, MD, PhD, FACS (2020-present)
Jennifer J Lentz, PhD (2006-present)
Sandra Pieke-Dahl, PhD; Ohio State University (1999-2006)
Karmen M Trzupek, MS, CGC (2020-present)
Michael D Weston, MA; Boys Town National Research Hospital (1999-2006)

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- 8 October 2020 (jjl) Revision: C-18-04 antioxidant treatment clinical trial now active (Therapies Under Investigation)
- 25 June 2020 (sw) Comprehensive update posted live
- 19 May 2016 (sw) Comprehensive update posted live
- 20 June 2013 (me) Comprehensive update posted live
- 28 October 2010 (me) Comprehensive update posted live
- 29 June 2010 (cd) Revision: sequence analysis and prenatal testing available for *USH1G*; USHIH locus added
- 28 May 2009 (me) Comprehensive update posted live
- 14 May 2008 (cd) Revision: prenatal testing available for *CDH23*
- 10 December 2007 (cd) Revision: sequence analysis of exon 3 of *USH1C* available clinically
- 5 November 2007 (cd) Revision: sequence analysis of the entire coding regions of *PCDH15* (USH1F) and *CDH23* (USH1D) available clinically
- 7 November 2006 (me) Comprehensive update posted live
- 6 February 2004 (cd) Revision: change in gene name (*SANS* to *USH1G*)
- 13 January 2004 (wk) Author revisions
- 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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