

Usher syndrome

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Abstract

Usher syndrome is defined as a genetically heterogeneous condition comprising 12 independent loci with nine known genes, and at least three clinical entities, USH1, USH2, USH3 associating retinitis pigmentosa (RP) and deafness with varying age of onset. Although differences in auditory and vestibular function are the distinguishing features between the different types of Usher syndrome, RP is the main ophthalmic manifestation shared by all three types. Patients with USH1 are congenitally affected with profound sensorineural hearing loss and absent vestibular function, and usually do not show any manifestation of RP at birth, although the electroretinogram (ERG) is strongly altered and ophthalmoscopy shows retinal pigmentary degenerations. USH2 is distinguished from USH1 by a less severe but still congenital hearing loss with preserved vestibular function. The onset of RP overlaps with that of USH1. USH3 distinguishes from type 1 and 2 by a later onset of both deafness and RP. Usher syndrome shows a prevalence of 3-4/100,000 in European based populations.

Keywords

microcornea, cataract, syndrome, USH

Included diseases

Usher syndrome type 1A: USH1A

Usher syndrome type 1B: USH1B

Usher syndrome type 1C: USH1C

Usher syndrome type 1D: USH1D

Usher syndrome type 1E: USH1E

Usher syndrome type 1F: USH1F

Usher syndrome type 1G: USH1G

Usher syndrome type 2A: USH2A

Usher syndrome type 2B: USH2B

Usher syndrome type 2C: USH2C

Usher syndrome type 3: USH3

Sensorineural Deafness with RP

Excluded diseases

The following disorders, which are also associated with deafness and retinal signs, must be differentiated from the Usher syndromes:

- Mohr-Tranebjaerg syndrome
- [Duane retraction syndrome](#)
- [Wolfram syndrome](#)
- Wolfram syndrome, mitochondrial form
- [Albinism-deafness syndrome](#)
- Albinism, ocular, with sensorineural deafness

History

In 1858, von Graefe gave probably one of the earliest description of Usher syndrome by reporting the case of a deaf and dumb male patient who presented with retinal pigment degeneration and who had two equally affected brothers (58). Such observations were again reported in 1861 by Liebreich who screened the population of Berlin for syndromes including Retinitis pigmentosa (RP)(36). He emphasized the recessive nature of the disease by commenting on the combination of deaf-mutism with RP in several siblings from either consanguineous marriages (5/14 index cases) or families with several members affected in different generations. In addition, his observations were the first to provide evidence for the coinheritance of RP and deafness, since they pointed towards the absence of isolated RP cases in the pedigrees segregating deafness. Finally the disease combining deafness and RP was named after Charles Usher, a British ophthalmologist who also described the hereditary nature of this disorder (56).

Definition

Several authors defined Usher syndrome as a genetically heterogeneous condition comprising 12 independent loci with nine known genes, and at least three clinical entities, USH1, USH2, USH3 associating RP and deafness with varying age of onset. Several of these genes have been found to be involved in disorders of isolated deafness or retinal degenerative diseases also. Table 1 in Annex summarizes the genetic data on Usher syndrome

Frequency of the various Usher syndromes

Usher syndrome shows a prevalence of 3-4/100,000 in European based populations (12, 23).

Although some authors have reported that USH1 and USH2 are about equally frequent, two population-based studies have found that USH2 is about twice and three times more frequent than USH1, respectively (46, 51).

Ophthalmological features in USH1 and USH2

Although differences in auditory and vestibular function are the distinguishing features between the different types of Usher syndrome, RP is the main ophthalmic manifestation shared by all three types. In comparison to patients with USH2, patients with USH1 have frequently been reported to present with more severely impaired visual acuity and visual fields, and a higher prevalence of macular lesions (14, 18, 19, 31, 43). However, in a recent study of 66 patients no significant differences between USH1 and USH2 were found with regard to visual acuity, visual field area, electroretinographic amplitude, incidence of cataract and macular lesions (55). However, the ages when night blindness was perceived and RP was diagnosed differed significantly between the two types. Mean age of perceived night blindness was 10 years (standard deviation SD 6.6.y) in USH1, and 15 years (SD 6.9 y) in USH2. Mean age of diagnosis of RP was 17 years (SD 9.2 y) in USH1, and 24 years (SD 10.3 y) in USH2. The authors emphasize that some of the differences may be due to ascertainment bias. This is supported by the fact that the ophthalmoscopic findings as well as the levels of visual impairment were not significantly different in the two types.

Usher Syndrome Type 1 (USH1)

Clinical description

Patients with USH1 are congenitally affected with profound sensorineural hearing loss and absent vestibular function. This indicates defects in the generation of the nerve impulse in the vestibulum and cochlear hair cells, which affect development of walking and speaking as an early indication. USH1 patients usually do not show subjective manifestation of RP at birth, although the electroretinogram (ERG) is strongly altered and ophthalmoscopy shows retinal pigmentary degenerations. Several different entities of USH1 have been identified, but they cannot be currently differentiated on a clinical basis.

Etiology

- *USH1B*

75% of USH1 patients are affected with mutations in the unconventional *myosin VIIa* gene ([MyoVIIa](#)), which is one of the five genes identified among the 7 loci known in type 1 of Usher syndrome. [MyoVIIa](#) is responsible for USH1B (49, 51).

[MyoVIIa](#) is a member of the family of unconventional myosins, which do not assemble into filaments like conventional myosins (40). [MyoVIIa](#) has been localized to connecting cilium

in photoreceptors and the apical processes of the retinal pigment epithelium (RPE). In the ear it is found in vestibular neuroepithelium and embryonic cochlear cells (37, 63). Wherever [MyoVIIa](#) is found, it always co-localizes with cilia, thus indicating a role in maintaining the axonemal structures or function (67). An defect in axonemal transport of rhodopsin has been suggested as a reason for RP (37).

A natural mouse model of USH1B is the [shaker 1 \(sh-1\)](#) mouse. These mice show preserved disk length but reduced disk turnover including accumulation of rhodopsin in the axoneme. The development of the organ of Corti is delayed and sensory hair cells degenerate immediately after birth. Pigment in the RPE shows an aberrant distribution but no signs of retinal degeneration can be seen (38, 52). The absence of retinal degenerations in the [sh-1](#) mouse might be attributed to the different expression of [MyoVIIa](#) in human and mouse RPE and photoreceptors. [MyoVIIa](#) is not expressed in mice photoreceptor cells, but it is expressed in human photoreceptors cells, and only during adulthood. This suggests that RP of USH1B results from a primary rod defect (18).

- **USH1C**

The second gene known for type 1 Usher syndrome is [Harmonin](#), which underlies USH1C, also known as Acadian Usher syndrome since this disease entity was first described in the French-Acadian population of southwest Louisiana (33, 57). [Harmonin](#) is present in several splice forms in mice and contains PDZ domains involved in organizing multiprotein complexes in specific subcellular domains such as synaptic junctions. The function of [Harmonin](#) is not yet known, but PDZ domains have been found in receptors, channels, and proteins, suggesting a role in transmitting the nerve impulse by establishing contact between the receptor and the ganglion cell. In mice [Harmonin](#) is localized in the sensory hair cells of the organ of Corti and the sensory regions of the vestibulum (57).

- **USH1D**

USH1D is the third disease locus for which the underlying gene is known. This form of Usher syndrome is caused by mutations in the gene *CDH23*, which encodes otocadherin, a member of the cadherin family. Otocadherin is present in several human tissues including brain, kidney, skeletal muscle and blood (9). This protein contains 27 cadherin repeats. Cadherins are components of adherens junctions, and are necessary for cell adhesion, migration, and compaction during embryogenesis and

organogenesis, and play important roles in the inner ear of mice (9).

- **USH1C (Harmonin)**

Harmonin contains a PDZ domain frequently found in proteins involved in multi-subunit complexes. Studies in mice showed Harmonin expression in precursors of the labyrinth of mice (57). It is variably spliced and the smaller splice form is expressed in both eye and ear (8).

- **USH1D**

Mutations in *CDH23* have been identified in humans with USH1D (10) and studied in a mouse model of USH1D, the [Waltzer](#) mouse (*v*). Waltzer mice present with disorganized stereocilia of the inner hair cells while the kinocilium of the outer hair cells is displaced and the cells completely lack stereocilia (16). This observation agrees with the proposed function of *CDH23*, a Ca²⁺-binding protein involved in the organization of stereocilia of the inner ear and outer hair cells (42).

- **USH1F**

A further protein known to be involved in USH1 is related to [Otocadherin](#), and like all the other USH1 genes, the encoding gene is expressed in the retina and hair cells. This gene is named [Protocadherin 15 \(PCDH15\)](#) and is underlying USH1F. In addition to its localization in retina and cochlea, *PCDH15* is expressed in brain, kidney, lung, and spleen, but mutations in *PCDH15* do not cause additional dysfunctions despite RP and deafness. Protocadherins are required for neural development and synapse formation. The function of *PCDH15* in the mammalian inner ear is yet unsolved, but a role in the formation of stereocilia from microvilli has been suggested (4).

The mouse model of USH1F is called the [Ames Waltzer](#) mouse (*av*). Like [sh-1](#) mice, [Ames Waltzer](#) mice do not exhibit an ocular phenotype, indicating a different retinal function of [PCDH15](#) between men and mice (3).

- **USH1G**

USH1G is caused by mutations in *SANS*. This protein, like Harmonin, contains a PDZ domain and additionally two ankyrin motifs. Investigations in Jackson Shaker mice showed disorganization of the hair bundles of inner ear sensory cells. *SANS* binds to Harmonin, *CDH23* and *MyoVIIa* indicating a functional network built up by these proteins (64).

In conclusion, USH1 has to be considered as a disease entity caused by impaired development of structural components of cilia in the receptors of the visual, the auditory, and the balance

system. This impairs the production of the nerve impulse and causes early deafness and progressing retinal degeneration.

Usher syndrome Type 2 (USH2)

Clinical description

USH2 is distinguished from USH1 by a less severe but still congenital hearing loss with preserved vestibular function. The onset of RP overlaps with that of USH1 and does not enable the differentiation between these two entities, although an ERG can be useful since only USH2 patients present with a recordable a-wave (indicative of the generation of nerve impulse) (49, 54).

Etiology

Three loci are known for USH2 (Table 1) and two underlying genes, [Usherin](#) (USH2a) and [VLGR1](#) (USH2c), have been identified.

[Usherin](#) contains domains commonly found in extracellular matrix and cell surface receptor proteins (7, 65). It is expressed in fetal human cochlear and eye, as well as in adult human retina. In the retina, Bruch's membrane and the interphotoreceptor matrix (IPM) are rich in proteins of this kind (20). [Usherin](#) could be found in all of the capillary and structural basement membranes of the human and mouse retina. Additionally, it is present in the murine inner ear, in spleen, testis, oviduct, epididymis, submaxillary gland, and large and small intestines (7). The definite function of [Usherin](#) has not yet been elucidated.

[VLGR1](#) is the largest cell surface receptor and is present in 3 splice forms in fetal retina and cochlear cells. Its motif architecture is similar to the cadherins (PCDH15 and CDH23). The C-terminus contains a PDZ domain involved in binding class I PDZ-binding interfaces on SANS, PCDH15, CDH23, and Harmonin, thus establishing a functional connection of the products of *USH1* and *USH2* genes, forming a macromolar complex necessary to shape the stereocilia. The phenotype caused by *VLGR1* mutations is reported to be markedly similar to *Usherin* mutations (66).

Usher syndrome Type 3 (USH3)

Clinical description

USH3 distinguishes from type 1 and 2 by a later onset of both deafness and RP. Deafness starts postlingually and is progressive. Progressive RP has its onset in the 2nd decade of life.

Etiology

The underlying [Clarín-1](#) gene codes for a protein of unknown function, which contains two transmembrane domains and an endoplasmic

reticulum retention signal in the C-terminus, and is expressed ubiquitously. The gene was identified in the Finnish population, which showed a founder mutation. In addition, Italian families have also been associated with mutations in the [Clarín-1](#) gene (28). Histological studies showed expression of [Clarín-1](#) in cochlear hair cells and spiral ganglion and a role in hair cell and photoreceptors cell synapses is suggested (2).

Sensorineural Deafness with RP

A large Irish kindred that segregates progressive sensorineural hearing loss and RP has been reported (39). The disease resembles the features of USH3, but muscle biopsy revealed that patients had additional subclinical abnormalities. Interestingly the inheritance pattern pointed towards dominant, X-linked dominant, or maternal inheritance. Autosomal loci failed to show linkage, but mutation analysis in the mitochondrial genome identified a mutation in the second mitochondrial serine tRNA (MTTS2).

Diagnosis methods

Molecular diagnosis is available.

Management including treatment

- Cochlear implant for USH1. Although some patients benefit from powerful modern devices and cochlear implants, traditional hearing aids are not well accepted (49).
- No treatment is available for RP.

Genetic counseling

Increasing knowledge of the genes involved in the various forms of Usher syndrome and detailed genotype-phenotype correlations may allow to better correlate the ophthalmic signs and symptoms with a given genotype in the future.

Unresolved questions

Some families with Usher syndrome could not be linked to any chromosomal locus and, therefore they may be candidates for mutations in mitochondrial genes, in a way similar to the Irish kindred mentioned in the section on "Sensorineural Deafness with RP".

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Annex

Table 1: Compilation of genetic data on Usher syndrome

Locus	Locus MIM	Assignment	Gene	Gene MIM	Linked Marker	References
USH1A	276900	14q32			D14S51- D14S78- D14S13-- D14S260, D14S250, D14S292	(21) (27) (4) (1) (16) (32)
USH1B	276903	11q13.5	MyoVIIa	600060	D11S527	(46) (58) (57) (15) (4) D11S861- D11S899 (5) D11S419 (12)
USH1C	276904	11p14.3	Harmonin	605242	D11S861- D11S419-(D1S397- D11S902- D11S921- D11S1890- (23) D11S1888(<680 kb))- D11S1310- (28) D11S899- D11S928 (46) (53)	
USH1D	601067	10q21-22	Otocadherin	605516	D10S529- [D10S535- D10S1737]- D10S188- [D10S1432, 152N13aat]- (21) D10S218- [D10S1694- D10S1650]- (55) D10S195- D10S202- D10S69- D10S219- (8) D10S201- D10S551- D10S573 [15]	
USH1E	602097	21q21			D21S1905- D21S1922- D21S1884- D21S1257- D21S1914- D21S265- D21S1896- D21S1258- D21S1916- (10) D21S1913 [15]	
USH1F	602083	10q11.2-21	PCDH15	605514	D10S199- D10S596 [15], D10S193, (3) D10S1791, D10S220, D10S1790 (4) (56)	
USH1G	606943	17q24-25	SANS	607696	D17S949- D17S1350- DFNA26- [D17S1351- D17S1831- D17S1352- (38) D17S1807- D17S1839- D17S1603- (5) D17S785- D17S1806 23]-DFNA20- D17S1830- D17S928	
USH2A	276901	1q41	Usherin	608400	D1S2646/D1S2629- DS2827- (11) AFM268ZD1, cen- D1S505- D1S425- (17) D1S217- D1S556- D1S237-[1 D1S474- (29) EB1-EB2-KB6- AFM144XF2]-KB1-KB4- (44) D1S229- D1S490- D1S227-TGFb2- (49) D1S439-tel	
USH2B	276905	3p24.2-23			[D3S1766- D3S400- D3S1289- [D3S1613, D3S1582, D3S1578]- (41) D3S3647- D3S1767- D3S658- D3S1298- (22) D3S1619- D3S1266 14cM]	
USH2C	605472	5q14.3-21.3	VLGR1	602851	D5S617, D5S484, D5S505, D5S485 (40) (6)	
USH3	276902	3q21-25	CLARIN-1	606397	D3S1299-[1] TW250376- 25B8CA2- (26) 25B8CA1- USH3- 107G19CA7- RSNP2- (24) TSNP1- D3S3625- D3S1594- D3S1279- (43) D3S1308 [5], D3S555, D3S1279, (25) D3S1280	
Sensorineural Deafness with RP		mtDNA position 12258	MTTS2	590085		(36)