Usher syndrome

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Usher syndrome (sometimes referred to as "Usher's syndrome") is a relatively rare genetic disorder that is a leading cause of deafblindness and that is associated with a mutation in one of 10 genes. Other names for Usher syndrome include Hallgren syndrome, Usher-Hallgren syndrome, rpdysacusis syndrome and dystrophia retinae dysacusis syndrome. Usher syndrome is incurable at present; however, using gene therapy to replace the missing gene, researchers have succeeded in reversing one form of the disease in knockout mice.

This syndrome is characterized by deafness and a gradual vision loss. The hearing loss is associated with a defective inner ear, whereas the vision loss is associated with retinitis pigmentosa (RP), a degeneration of the retinal cells. Usually, the rod cells of the retina are affected first, leading to early night blindness and the gradual loss of peripheral vision. In other cases, there is early degeneration of the cone cells in the macula, leading to a loss of central acuity. In some cases, the foveal vision is spared, leading to "doughnut vision"; central and peripheral vision are intact, but there is an annulus around the central region in which vision is impaired.

Usher syndrome has three clinical subtypes, denoted as I, II and III in decreasing order of severity. People with Usher I are born profoundly deaf, and begin to lose their vision in the first decade of life. They also exhibit balance difficulties and learn to walk slowly as children, due to problems in their vestibular system. People with Usher II are also born deaf, but do not seem to have noticeable problems with balance; they also begin to lose their vision later (in the second decade of life) and may preserve some vision even into middle age. People with Usher syndrome III are not born deaf, but experience a gradual loss of their hearing and vision; they may or may not have balance difficulties.

Usher syndrome is a variable condition; the degree of severity is not tightly linked to whether it is Usher 1, 2 or 3. For example, someone with Type 3 may be unaffected in childhood but go on to develop a profound hearing loss and a very significant loss of sight by early to mid-adulthood. Similarly, someone with Type 1, who is therefore profoundly deaf from birth, may keep good central vision until the sixth decade of life, or even beyond. People with Type 3, who have useful hearing with a hearing aid, can experience a wide range of severity of the RP. Some may maintain good reading vision into their sixties, while others cannot see to read while still in their forties.

Usher syndrome I and II are associated with a mutation in any one of six or three different genes, respectively, whereas only one mutation has been linked with Usher III. Since Usher syndrome is inherited in an autosomal recessive pattern, both males and females are equally likely to inherit Usher syndrome. Consanguinity of the parents is a risk factor. Children of parents who both are carriers of the same mutation have a one fourth chance of inheriting the condition and children of such parents who are unaffected have a two thirds chance of being carriers. Children of parents where only one parent is a carrier have a no chance of having the disease but have a one half chance of being a carrier. First recognized in the 19th century, Usher syndrome was the first condition to demonstrate that phenotypes could be inherited in tandem; deafness and blindness are inherited together, but not separately. Animal models of this human disease (such as knockout mice and zebrafish) have been developed recently to study the effects of these gene mutations and to test potential cures for Usher syndrome.

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History

Usher syndrome is named after the British ophthalmologist Charles Usher, who examined the pathology and transmission of this illness in 1914 on the basis of 69 cases. However, it was first described in 1858 by Albrecht von Graefe, a pioneer of modern ophthalmology. He reported the case of a deaf patient with retinitis pigmentosa, who had two brothers with the same symptoms. Three years later, one of his students, Richard Liebreich, examined the population of Berlin for disease pattern of deafness with retinitis pigmentosa. Liebreich noted that Usher syndrome is recessive, since the cases of blind-deafness combinations occurred particularly in the siblings of blood-related marriages or in families with patients in different generations. His observations supplied the first proofs for the coupled transmission of blindness and deafness, since no isolated cases of either could be found in the family trees.

Symptoms and subtypes

Usher syndrome is responsible for the majority of deaf-blindness. The word syndrome means that multiple symptoms occur together, in this case, deafness and blindness. It occurs in roughly 1 person in 23,000 in the United States, 1 in 28,000 in Norway and 1 in 12,500 in Germany. People with Usher syndrome represent roughly one-sixth of people with retinitis pigmentosa.

Usher syndrome is inherited in an autosomal recessive pattern. "Recessive" means that both parents must contribute an appropriate gene for the syndrome to appear, and "autosomal" means that the gene is not carried on one of the sex chromosomes (X or Y), but rather on one of the 22 other pairs. (See the article on human genetics for more details.)

The progressive blindness of Usher syndrome results from retinitis pigmentosa. The photoreceptors usually start to degenerate from the outer periphery to the center of the retina including the macula. The degeneration is usually first noticed as night blindness (nyctalopia); peripheral vision is gradually lost, restricting the visual field (tunnel vision), which generally progresses to complete blindness. The qualifier pigmentosa reflects the fact that clumps of pigment may be visible by an ophthalmoscope in advanced stages of degeneration.

Although Usher syndrome has been classified clinically in several ways, the prevailing approach is to classify it into three clinical sub-types called Usher I, II and III in order of decreasing severity of deafness.

Usher I and II are the more common forms; the fraction of people with Usher III is significant only in a few specific areas, such as Finland and Birmingham. As described below, these clinical subtypes may be further subdivided by the particular gene mutated; people with Usher I and II may have any one of six and three genes mutated, respectively, whereas only one gene has been associated with Usher III. The function of these genes is poorly understood as of yet. The hearing impairment associated with Usher syndrome is better understood: damaged hair cells in the cochlea of the inner ear inhibit electrical impulses from reaching the brain.

Usher syndrome I

People with Usher I are usually born deaf and often have difficulties in maintaining their balance owing to

problems in the vestibular system. Babies with Usher I are usually slow to develop motor skills such as walking. Worldwide, the estimated prevalence of Usher syndrome type I is 3 to 6 per 100,000 people in the general population.

Usher syndrome type I can be caused by mutations in any one of several different genes: CDH23, MYO7A, PCDH15, USH1C, and USH1G. These genes function in the development and maintenance of inner ear structures such as hair cells (stereocilia), which transmit sound and motion signals to the brain. Alterations in these genes can cause an inability to maintain balance (vestibular dysfunction) and hearing loss. The genes also play a role in the development and stability of the retina by influencing the structure and function of both the rod photoreceptor cells and supporting cells called the retinal pigment epithelium. Mutations that affect the normal function of these genes can result in retinitis pigmentosa and vision loss.

Type I has been found to be more common in people of Ashkenazi Jewish ancestry (central and eastern European) and in the French-Acadian populations (Louisiana).

Usher syndrome II

People with Usher II are generally hard-of-hearing rather than deaf, and their hearing does not degrade over time; moreover, they generally have a normal vestibular system. Usher syndrome type II occurs at least as frequently as type I, but because type II may be underdiagnosed or more difficult to detect, it could be up to three times as common as type I.

Usher syndrome type II may be caused by mutations in any of three different genes: USH2A, GPR98 and DFNB31. The protein encoded by the USH2A gene, usherin, is located in the supportive tissue in the inner ear and retina. Usherin is critical for the proper development and maintenance of these structures, which may help explain its role in hearing and vision loss. The location and function of the other two proteins are not yet known.

Usher syndrome III

By contrast, people with Usher III experience a progressive loss of hearing and roughly half half have vestibular dysfunction. The frequency of Usher syndrome type III is highest in the Finnish population, but it has been noted rarely in a few other ethnic groups.

Mutations in only one gene, the CLRN1 gene, have been linked to Usher syndrome type III. The CLRN1 gene encodes Clarin-1, a protein that is important for the development and maintenance of the inner ear and retina. However, the protein’s function in these structures, and how its mutation causes hearing and vision loss, is poorly understood as yet.

Differential diagnosis

Since Usher syndrome is incurable at present, it is helpful to diagnose children well before they develop the characteristic night blindness. Some preliminary studies have suggested that as many as 10% of congenitally deaf children may have Usher syndrome.\(^{1}\) However, a mis-diagnosis can have bad consequences.

The simplest approach to diagnosing Usher syndrome is to test for the characteristic chromosomal mutations. An alternative approach is electroretinography (ERG), although this is often disfavored for children, since its discomfort can also make the results unreliable.\(^{1}\) Parental consanguinity is a significant factor in diagnosis. Usher syndrome I may be indicated if the child is profoundly deaf from birth and especially slow in walking.

Thirteen other syndromes may exhibit signs similar to Usher syndrome, including Alport syndrome, Alström syndrome, Bardet-Biedl syndrome, Cockayne syndrome, spondyloepiphysial dysplasia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hurler syndrome (MPS-1), Kearns-Sayre syndrome (CPEO), Norrie syndrome, osteopetrosis (Albers-Schonberg disease), Refsum’s disease (phytanic acid storage disease), and Zellweger syndrome (cerebro-hepato-renal syndrome).

Genes associated with Usher syndrome

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trip to Brighton pier.[26] Other people with Usher syndrome have posted videos about their lives and condition on YouTube, most notably Ginny Paja-Nyholm.[27] In October 2007, Candice, a mom living in Texas, began blogging about her two daughters, Jasmine and Rebecca; Rebecca has Usher syndrome I.[28]

Catherine Fischer has written a well-received autobiography of growing up with Usher syndrome in Louisiana, entitled *Orchid of the Bayou*.[29] Similarly, Vendon Wright has written two books describing his life with Usher syndrome, *I was blind but now I can see*.[30] and *Through my eyes*.[31] Louise Boardman has also written a short book called *My son has Usher's Syndrome*.[32]

Christian Markovic, an artist living with Usher syndrome, runs a company, Fuzzy Wuzzy Designs.[33]

Spencer Tracy’s son John was a well-known person with Usher syndrome who lived a full life.[34] The John Tracy Clinic was founded in 1942 by his mother Louise to offer free help to parents of hearing-impaired infants and preschool children.[35]

Jacob Desormeaux, son of horse-racing jockey Kent Desormeaux, suffers from Usher syndrome. Jacob was born deaf and is progressively going blind. Kent dedicated his race in the Belmont Stakes, which would give him and his horse Big Brown the Triple Crown, to his son Jacob. The family has started an organization to raise funds and awareness of the disease. Usher syndrome is disproportionately common among the Cajuns of south Louisiana, such as Desormeaux and Fischer, because of a genetic mutation among early French Acadian settlers in Nova Scotia.

DNA helix co-discoverer and Nobel laureate James D. Watson has had homozygous USH1B mutations, according to his published genome.[35] It is not clear why he did not develop the syndrome. This lack of genetic penetrance argues that expression of the phenotype of Usher syndrome may be more complex than originally assumed.

References

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