

RETINA

Planning for Usher's-Related Vision Loss

BY LINDA ROACH, CONTRIBUTING WRITER

Blindness from Usher's syndrome currently cannot be prevented, but there is a new emphasis on diagnosing this hereditary disease as early as possible—years before children develop one of the syndrome's landmarks: retinitis pigmentosa (RP). Early diagnosis can assure that Usher's children, who are already hearing-impaired or deaf, will receive the help they need to communicate before their vision fails. It also will help researchers assess Usher's wide variety of clinical features as they design RP gene-based treatment trials, said William J. Kimberling, PhD, a medical geneticist, Usher's specialist and visiting professor of ophthalmology and otolaryngology at the University of Iowa in Iowa City.

The Origins of Usher's

Usher's syndrome, which affects 45,000 Americans, is an autosomal recessive disease responsible not only for RP but for sensorineural hearing loss. About half of all deaf and blind adults have Usher's syndrome, according to the National Institute on Deafness and Other Communication Disorders. In its most severe form, Usher's syndrome causes profound deafness at birth, with the onset of RP as early as age 10 and functional blindness by 20.

Molecular biologists have identified nine genes in which more than 400 mutations have been associated with Usher's syndrome. These mutations produce faulty proteins that cause hearing loss and RP by a mechanism that is

only partly understood. Rods are the first photoreceptors to die. In the late stages, cone photoreceptors and retinal pigment epithelial cells also fail.

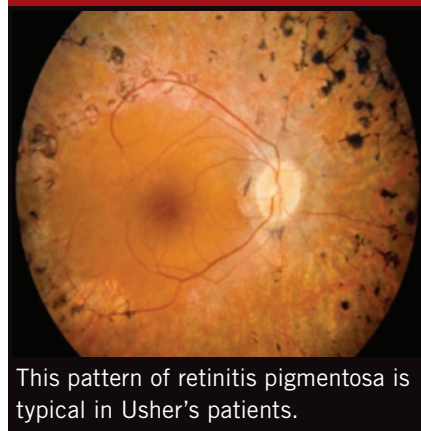
As genetic studies have revealed more about Usher's syndrome, it also has become apparent that different mutations in the same gene can give rise to wide range of disease severity, even within families. The signs of Usher's range across three categories:

- **Type 1** is characterized by profound deafness at birth, balance problems and the progressive narrowing of the visual field between the ages of 10 and 20. Because of the vestibular problems, these children learn to walk late (18 months to 2 years) and can become disoriented in water. Hearing aids usually do not help them, and cochlear implants are recommended in early childhood to aid language development while vision is still good.
- **Type 2** children lose vision more slowly than type 1 patients do, beginning around age 20. They have a mild-to-severe hearing loss at birth, which is helped by hearing aids, and they do not display problems with balance.
- **Type 3** children are born with normal hearing but have a progressive hearing loss after the time of language development. Vision loss begins in the first or second decade of life. They present like type 2 as children but are more like type 1 as adults.

First Signs of Sensory Loss

In the past it was common for an ophthalmologist to be the first physician

An Usher's Retina



This pattern of retinitis pigmentosa is typical in Usher's patients.

to suggest the diagnosis of Usher's syndrome, usually after problems with night or peripheral vision had already begun in late childhood or the early teen years.

"Usher's syndrome always has been underreported and overlooked because it takes putting together both the hearing and visual phenotypes to come up with the diagnosis," Dr. Kimberling said.

Any child who has signs of RP in combination with any level of hearing loss should be presumed to have Usher's syndrome unless another cause for the combined sensorineural losses can be found, Dr. Kimberling said. (See "Deaf and Blind Kids.")

Timelier diagnosis now possible.

Recent advances in knowledge about hereditary retinal diseases—including a newly available, low-cost screening test for Usher's syndrome at Iowa's Carver Nonprofit Genetic Testing

Laboratory are likely to reduce ophthalmologists' chances of being the first to diagnose a child with Usher's syndrome. However, ophthalmologists can expect to receive more referrals from otolaryngologists who already have used a genetic test to make the diagnosis, Dr. Kimberling predicted. Usher's patients in ophthalmic exam chairs will be younger, will have hearing losses of varying severity, might have cochlear implants already in place, might lack early signs of RP and will be accompanied by more savvy parents, he said.

"With early referrals from otolaryngologists, now the ophthalmologist will know before they even look at the child's retina that there will eventually be problems," Dr. Kimberling said.

Based on his experiences counseling parents of hearing-impaired children in Omaha at Boys Town National Research Hospital, Dr. Kimberling said ophthalmologists can expect parents of these children to be well-informed, assertive advocates for their offspring. "Twenty years ago, I never saw children with Usher's syndrome until they already had extensive retinal disease. Now we're seeing them earlier and earlier. The parents of young hearing-impaired children will come in saying, 'I want to know if my child has Usher's syndrome.'"

How and When to Test

Concern for their children can cause these parents to insist on diagnostic tests such as electroretinography (ERG), which can identify abnormalities in photoreceptor function in children as young as 2 years of age. "We recently had a case of a 2-year-old with parents who were pushing for an ERG, which many ophthalmologists don't like to do in very young children because it often requires sedation," Dr. Kimberling said. "In a child that young, it would be much better to initially confirm the Usher's diagnosis with a genetic test and then move on to more functional tests like the ERG to determine the extent of the RP and to have a baseline to help in following progression."

Genetic screening. The Carver Lab's new two-stage genetic test for Usher's syndrome was submitted for federal certification this year, after being validated in more than 350 people. It will allow pediatricians and otolaryngologists to find out in a matter of weeks if children who have failed hearing screening tests have Usher's syndrome, Dr. Kimberling said.

The test's first stage, called SNPlex, will screen for the 94 most common single nucleotide mutations reported in Usher's patients worldwide. These include the genetic variation commonly found in Usher's cases among Ashkenazi Jews, among Acadian communities in Canada and Louisiana and among Scandinavians. Because many Usher's patients do not have known mutations, the lab then will confirm or expand the results by individually sequencing the sections of the patient's DNA at the known Usher's genes.

Therapies on the Horizon?

The genetic tests could clarify which patients might benefit from the gene therapy trials that are expected to begin in the next few years.

Among the researchers who hope to make these trials possible is David S. Williams, PhD, professor of ophthalmology and neurobiology at the University of California, Los Angeles. He is collaborating with University of Pennsylvania researchers who reported in 2001 on a therapy with the RPE65 gene that recovered vision for dogs suffering from a canine version of Leber's congenital amaurosis (LCA). Dr. Williams and colleagues hope to be ready to launch human trials of gene therapy for Usher's-related RP by around 2013. "After we have settled on a vector to deliver the gene, the only real hurdle to getting this beyond a phase 1 clinical trial is determining how we would measure efficacy," Dr. Williams said.

Dr. Kimberling remains optimistic about the prospects because, ironically, congenital hearing impairment in Usher's syndrome identifies a pool of young patients in whom the photoreceptors are still healthy.

Preparation for life. For now, Dr.

Deaf and Blind Kids

There were 10,174 deaf-blind children in the United States in 2007, according to the National Consortium on Deaf-Blindness. Because Usher's syndrome often does not cause severe visual loss until adulthood, most of this childhood dual sensory loss had other causes, listed below.

CAUSE	PREVALENCE
Unknown etiology	2,012
Hereditary disorders	1,339
that were not Usher's	
Complications of prematurity . . .	1,194
Pre- and perinatal complications	551
Postnatal complications440
Cytomegalovirus346
Asphyxia283
Meningitis271
Down syndrome (trisomy 21) . .	.236
Congenital rubella.115
Encephalitis099
Leber's congenital amaurosis . .	.049
Fetal alcohol syndrome047
Norrie's disease.032
Refsum's disease029
Aicardi's syndrome028
Alström syndrome.027
Bardet-Biedl syndrome015
Alport's syndrome.003

Kimberling's personal goal is more modest than total prevention of RP. "I would like for us to be able to give children with Usher's syndrome at least 20 years of additional useful vision," he said. "If we could give this to type 1 Usher's patients, then instead of having a visual field of only 5 to 20 degrees at age 21 they could spend their 20s getting established in the world. We would be giving them time to find work and develop interpersonal connections that would help carry them if they did develop severe symptoms later in life."

1 Cideciyan, A. V. et al. *Proc Natl Acad Sci USA* 2008;105(39):15112-15117.