Clinical and Molecular Genetics of Usher Syndrome

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Abstract

Usher syndrome is an autosomal-recessive disorder manifested by hearing impairment, retinitis pigmentosa (RP), and variable vestibular deficit. Recent progress in the characterization of the genetics of Usher syndrome has shown that this disorder is phenotypically and genetically complex. This progress impacts the approach of the clinicians in the study of patients who may potentially have Usher syndrome. There are three major phenotypic classes: Usher I, II, and III. Usher I is distinguished from Usher II by having a more severe audiologic involvement and by the presence of vestibular areflexia. Usher III has a progressive hearing loss with variable vestibular involvement. A minimum of three genes have been identified as being responsible for Usher I; two have been identified as being responsible for Usher II. It is not yet clear whether other manifestations such as progressive hearing loss, associated mental retardation, or other physical anomalies are associated with the known Usher genes or whether they represent as yet undiscovered genetic disorders. As progress towards the identification of the Usher genes is made, the clinician will gradually gain new and effective diagnostic procedures for the identification and delineation of the Usher syndromes.

Key words: Deafness, molecular genetics, portional cloning, retinitis pigmentosa (RP), Usher syndrome

Usher syndrome is an autosomal recessive disorder characterized by deafness and retinitis pigmentosa (RP). The coincidence of hearing loss with RP was first recognized by Von Graefe (1858). Later, Usher (1914, 1935) collected a large series of patients and emphasized its hereditary nature.

The prevalence of Usher syndrome has been estimated at 3.0/100,000 in Scandinavia (Hallgren, 1959; Nuutila, 1970) and at 4.4/100,000 in the United States (Boughman et al, 1983). The prevalence of Usher syndrome among deaf individuals has been reported to range from 0.6 to 28 percent (Vernon, 1969) and is generally accepted to average at a rate of about 5 percent of the childhood deaf population. Thus, Usher syndrome is the single, most common, identifiable cause of hereditary deafness among children who are profoundly deaf, and, as a consequence, the clinician must consider it as a possible diagnosis with every deaf child.

Bell (1933) was one of the first to note the clinical heterogeneity characteristic of Usher syndrome. Hallgren (1959), however, who conducted the first large study on Usher syndrome, pointed out that at least two distinct clinical types of Usher syndrome existed, hypothesizing that they might be due to different genes. Only recently has this hypothesis been proven to be true. Different genes are responsible for types I and II Usher syndrome. In fact, recent research suggests that the genetic heterogeneity of Usher syndrome is more extensive than previously thought and that at least five different Usher genes exist: three for type I and two for type II (Kimberling et al, 1990, 1992; Smith et al, 1992; Pieke Dahl et al, 1993). One of the more immediate clinical consequences of the current surge of molecular research is to improve the prospects for accurate and early diagnosis of Usher syndrome. Once the genes are cloned, diagnosis of Usher syndrome,
by type and subtype, will be possible well before
the child enters school (see Table 1). In fact, the
diagnosis can be made at or before birth.

The value of early diagnosis for Usher syn-
drome might be questioned by some. Why should
a child be saddled early in life with the burden
of a diagnosis that carries such a poor prognosis
for visual abilities? Certainly one should be symp-
athetic to the psychological health of the patient,
and the value of an accurate diagnosis must be
weighed against its potential negative impact on
a patient's self-image. With that in mind, there
are, nonetheless, several cogent reasons why an
early diagnosis is preferred. First, Usher syn-
drome is an inherited disease, and the burden of
a life of combined sensory deficit is perceived by
many as far greater than that of either hearing
or visual handicap alone. Normal hearing/seeing
parents might well view the burden of having a
child with Usher syndrome differently from that
of having a deaf child. It is a different perspec-
tive that would understandably influence their
attitudes about family planning. If diagnosis is
delayed, the parents may elect to continue with
their family, only to learn later that their deaf
children are not just deaf but will “go blind” as
well. Early diagnosis is key to accurate genetic
counseling. Once the correct diagnosis is made,
parents can make an informed decision that
takes into account both the risk of having a child
with a heritable disorder and the burden of that
disorder to the child and family.

A second reason for early diagnosis concerns
the safety of the child. Night blindness is usually
the first visual manifestation of RP. It impairs a
child's mobility at night and in any area where
there is automobile traffic or other dangers, a
night-blind child is at risk. Early diagnosis can
alert parents and teachers to this potential prob-
lem.

Early diagnosis may also be helpful to edu-
cators of children with Usher syndrome. As an
adult, a person with Usher has limited ability to
use visual cues to augment communication.
Knowing about the visual handicap may influ-
ence decisions about modes of communication.
Also, it may be easier for a person with Usher syn-
drome to learn tactile communication as a child
rather than waiting until it becomes a necessity
as a young adult. Knowledge about the diagno-
sis of Usher syndrome is important for career
planning since a person with Usher syndrome
may want to plan a career that can continue
even after vision has been significantly compro-
mised.

In summary, early diagnosis of Usher syn-
drome has several benefits to both patient and
family. A full appreciation of the molecular and
clinical characteristics of this disorder will help
the clinician in achieving this goal.

**AUDIOLOGIC CHARACTERISTICS
OF USHER SYNDROME**

Clinically, Usher type I is distinguishable
from Usher type II on the basis of the severity
of hearing loss and the extent of vestibular
involvement. Type I patients are profoundly deaf,
while type II patients are “hard of hearing” and
have a sloping audiogram going from mild to
severe in the low frequencies to profound impair-
ment in the higher frequencies (Möller et al,
1989). The audiograms are so characteristic that
significant deviation away from their expected
patterns, without documentable reason, is
grounds to question the diagnosis of typical
Usher syndrome types I or II. A comparison of the
audiologic profiles characteristic of each Usher
type is given in Figure 1. Type I patients are
almost always profoundly deaf (there is no doc-
umented case of a proven type I with any resid-
ual hearing). Any history to the contrary should
alert the clinician to the possibility that the diag-
nosis is in error. Hearing aids have seldom been
helpful to type I patients. On the other hand,
some type I patients have had successful cochlear
implants (Hinderink et al, 1994).

Usher type II patients have residual hear-
ing and amplification is often a benefit. The
audiogram is almost always sloping, as shown
in Figure 1. Any deviations from this pattern

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Location</th>
<th>Hearing Loss</th>
<th>Vestibular Areflexia</th>
<th>Retinitis Pigmentosa</th>
</tr>
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<td>Usher II</td>
<td>USH2a</td>
<td>1q41</td>
<td>Sloping</td>
<td>No</td>
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<td></td>
<td>Not known</td>
<td>Progressive</td>
<td>?</td>
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</tbody>
</table>
Figure 1 Typical audiograms for Usher syndrome types I and II. The top three audiograms are from three independent cases with Usher type I, all showing a profound hearing loss. The bottom three audiograms are from three independent Usher type II cases and show a sloping loss with greater severity at the higher frequencies, a configuration characteristic of Usher type II. While there is some variation in hearing acuity with type II cases, most have quite similar audiograms. The audiometric profile is an important consideration in the diagnosis of the different types of Usher syndrome.

Many type II patients are quite oral. Several have phoned our office wanting to participate in the Usher syndrome research project. Our first reaction was to discount these calls, but we learned that the hearing ability of type II patients was sometimes so good that it was difficult for an untrained listener to be aware of the loss. It is this difference in hearing abilities that defines how Usher type I and II patients see themselves. Type I patients see themselves as deaf people who are going blind while the type II patients see themselves as RP patients who have hearing problems. Indeed, types I and II are two distinctly different disorders, and the clinician should be aware of the differences and not ascribe the symptoms of one to those expected in the other.

The hearing loss in Usher type I is definitely prelingual and believed to be congenital. However, whether onset is prenatal, congenital, or early in infancy has not been established. This is an important distinction. RP is defined as an abiotrophy that affects the retina progressively. However, there is no apparent progressive com-
component for the hearing loss. Both the retina and cochlea are peripheral, neurosensory systems, and it would be reasonable to expect the gene to affect both in a similar way. Since it does not, there is a minor paradox. One explanation is that there might be two genes, adjacent to one another on the same chromosome, one for a progressive cochlear component and another for a congenital cochlear defect. The two genes could have unrelated functions but both would be inactivated by any deletion that spanned the two genes. If each Usher syndrome locus was just a single gene coding for similar functions in both the retina and cochlea, we could reasonably expect the cochlear component to also be progressive. Perhaps this is true, but the cochlear damage has a very early onset with more rapid loss of function. This is a critical distinction because, if the hearing loss is progressive and not developmental, then there is a greater possibility of being able to interfere with the natural history of the disease and to prevent or ameliorate the hearing loss.

A third type of Usher syndrome has been proposed. It is characterized by a progressive hearing loss (Karjalainen et al, 1989). This type has rarely been described outside of Finland and may represent a disorder common in the Finnish population but extremely rare elsewhere. Whether or not Usher type II patients have a progressive loss remains to be established. There is good evidence that the hearing loss is present early in childhood, if not at the time of birth. However, type II patients often perceive that their hearing is not as good as when they were younger. The question is whether the loss of hearing is due to the Usher gene or whether it is due to the natural process of aging. Progression of hearing loss is uncommon enough that when present, it indicates the possibility of an alternative diagnosis.

We have had some examples of progressive hearing losses among our patients but none have fit comfortably into the type III category. Most have remained puzzles, with no resolution of the cause of the progression. For example, patient P phoned our study to ask if he could participate. He stated that his hearing had progressively worsened over the past several years. His sister was similarly affected and had also complained of a progressive loss. The preliminary history of both suggested normal vestibular responses compatible with a preliminary diagnosis of Usher type II. Both were well-educated professionals, which gave weight to this anamnestic data. So, because of the possibility of being able to confirm a progressive loss in Usher syndrome, both patient P and his sister were brought to Boys Town National Research Hospital (BTNRH) for evaluation, and we began to collect audiograms that had been taken over the past several years. Two audiometric profiles separated by 10 years on patient P are presented in Figure 2. As can be seen, over that period of years, the maximal loss is 10 to 20 dB over all frequencies. This is only somewhat more than expected for aging. Note also that the left ear worsened more rapidly than the right; the left ear received more amplification. We felt that amplification in addition to aging could explain his progressive loss.

People with Usher syndrome can be affected with the same problems as anyone else. Patient P's sister is a good example. She had a loss whose magnitude and shape was not within expectation (see also Fig. 2). She had a history of vertigo, tinnitus, and episodic worsening of her hearing ability. It was found that she had Meniere's disease in addition to Usher syndrome. The audiogram of Usher type II is remarkably consistent, even across families. Deviation from the expected configuration should be investigated thoroughly, and one should not assume that such deviation is simply an alternative phenotypic manifestation of the Usher gene.

Many type II patients report a progressive hearing loss but repeated audiologic evaluations show that their hearing level has stayed stable or minimally decreased over decades. Why would progressive loss be such a common complaint? Our explanation is that their listening ability is, in fact, diminishing. Most Usher II patients are oral and rely on visual cues to supplement understanding in conversation. RP is progressive, and the patient's visual fields are gradually constricted. This reduces their understanding of the spoken word but does not impact hearing per se. Thus, patients note a gradual loss of their ability to communicate, which is due primarily to the loss of vision.

VESTIBULAR DYSFUNCTION

In Hallgren's original monograph (1959), he referred to the unsteady gait in some Usher syndrome patients as a vestibulocerebellar ataxia. Although it was clear that he meant that the abnormality was of vestibular origin, the term has sometimes been misconstrued to mean that Usher patients also have some cerebellar component to their ataxia. There is no evidence for any cerebellar symptom in either Usher types I or II (Möller et al, 1989). The
balance problems in Usher type I are completely of vestibular origin.

Vestibular function is a reliable and consistent discriminator between Usher types I and II since most, if not all, type I patients lack vestibular function (Nuutila, 1970; Kumar et al, 1984; Möller et al, 1989). The consistency of the association between vestibular involvement and the severity of hearing loss is remarkable. Profoundly deaf persons have virtually no vestibular function, while those who are merely hearing impaired have normal vestibular reflexes. Unexplained deviations from this rule would bring the diagnosis into question.

Vestibular testing is always an important part of the evaluation of the deaf child and is absolutely essential if Usher syndrome has not yet been ruled out as a possible diagnosis. Vestibular testing can be used to rule out Usher syndrome early in the life of a profoundly deaf child without having to perform ophthalmologic testing, especially the electroretinogram (ERG), on young children. A normal vestibular test rules out the diagnosis of Usher type I, and since a normal ERG in a young child does not rule out the diagnosis of RP in the Usher homozygote, a normal vestibular test can be reassuring to parents of profoundly deaf children.

The vestibular deficit appears to be congenital, or at least occurs at a very early age, since children with Usher type I are late to sit and walk. None of the patients (Möller et al, 1989) in one large, well-studied series walked before the age of 18 months. In fact, walking age is a good predictor of the US subtype, since few children with type II are delayed in walking for as long as those with type I. One should be especially suspicious of an Usher type I diagnosis in a child who walked earlier than 18 months.

The postural system in humans relies on input from three sources: vestibular, visual, and somatosensory. While patients with Usher syndrome type I have compensated well for the vestibular deficit, postural stability is aggravated because of the progressive vision loss due to RP. The result is that Usher I patients are more posturally unstable than expected when compared with other patients who have hearing or visual loss alone. Patients with Usher type II, however, are essentially normal with regard to the vestibular system. Although there have been some reports of mild vestibular abnormalities,
such as hypo- or hyperactivity, it is unclear whether these findings are within the normal range. Thus, the presence of vestibular deficit in Usher type II remains to be proven.

Sophisticated vestibular studies (including rotary chair, bithermal caloric, dynamic, and posturography) are often necessary to confirm that the "ataxia" of Usher type I is vestibular in origin and to determine the degree to which the visual loss is affecting postural control. Visual impairment complicates, but does not invalidate, the otoneurologic examination. Since RP affects the corneoretinal potential, the basis of electronystagmography, one must sometimes increase the gain of the response and perform the test in the dark since even dim light will decrease the signals. If the ataxia is not due to a labyrinthine defect, then the diagnosis of Usher syndrome type I should be questioned. The vestibular phenotype is highly correlated with the severity of hearing loss, and the finding of normal vestibular responses with profound deafness or absent vestibular responses with a sloping type II audiometric profile should alert the researcher that the diagnosis is not certain.

**RETINITIS PIGMENTOSA**

RP is a term that applies to a large and heterogeneous group of disorders that affect the retina. The clinical hallmarks of RP are progressively restricted visual fields and night blindness. Night blindness is frequently the first symptom noted by the patient. As mentioned above, the RP exacerbates the effect of the vestibular deficit. For young children with Usher syndrome, this is particularly noticeable at night since they temporarily lose the visual component to balance function in darkness. Thus, parents often note that their child is particularly clumsy at night or doesn't like to sleep with the light off.

RP is the *sine qua non* of Usher syndrome. Without it, the diagnosis is always in doubt. Electrophysiologic studies provide the earliest and most reliable diagnosis of RP. Several studies have shown that the ERG is subnormal as early as 2½ to 3 years of age, before abnormalities can be seen functionally or on fundoscopic examination (De Haas et al, 1970; Merin et al, 1974; Abraham et al, 1977). ERG responses distinguish totally as the degeneration progresses. The earliest age at which the RP in Usher syndrome can be detected has not been determined. Furthermore, there must be an age at which the absence of RP contraindicates a diagnosis of Usher syndrome; unfortunately, that age is not known. This is important, because one would like to know the likelihood, for example, that a 10-year-old deaf child with a normal ERG has Usher syndrome. How old must the child be for the clinician to be comfortable in ruling out the diagnosis of Usher syndrome based on a negative ERG? There is no answer to this question, and it is unlikely that it will ever be answered before the application of molecular diagnostics makes it a moot point.

The age at onset/diagnosis of RP, although more consistent within sibships than between, nonetheless overlaps all types of Usher syndrome (Piazza et al, 1986). Because the hearing and vestibular defects are more severe in type I, our bias would be to think that the RP in type I Usher syndrome would also be more severe. However, this has not been proven.

**ASSOCIATED SYMPTOMS**

Congenital anomalies are supposedly not part of Usher syndrome. Occasionally, congenital anomalies have been noted in association with Usher syndrome; however, no clear pattern of dysmorphology has emerged. It seems likely that whenever major or minor anomalies are found in conjunction with Usher syndrome, they either occur by random chance or they indicate a different diagnosis. One might expect to find a few legitimate cases of Usher syndrome with anomalies and/or mental impairment as the result of a contiguous deletion of the Usher gene and its neighbors. One such possibility occurred in case S and his sister P (see Fig. 4). Both children were profoundly and congenitally deaf. Both also had minor anomalies of the hands and feet, notably broad and/or bifid great toes and thumbs. Patient S also had a history of seizures. This family failed to show linkage with either 1q, 11q, 11p, or 14q markers, indicating that none of the known Usher genes were involved. Interestingly, both children walked well before 18 months and had normal vestibular responses on testing, further suggesting that the "Usher" gene in this family is different from that in typical Usher families. The recessive nature of the disorder in the family is supported by the consanguinity between the parents of the two children. The occurrence of minor anomalies in children with hearing loss and RP should alert the clinician to the possibility that there may be a different syndrome present in the case.

Psychiatric disturbances and mental retardation have been associated with Usher syndrome. Hallgren (1959) originally noted a high
frequency of mental deficiency (24%) in his series. However, this association has not been noted by most other investigators (Nuutila, 1970; Fishman et al, 1983; Möller et al, 1989). Merin et al (1974) designated Usher patients with mental retardation as type IV, but the existence of a type IV has not been verified. Although the literature is confusing with regard to the nosology of type IV/Hallgren syndrome, there is little doubt that retardation is an uncommon aspect of all types of Usher syndrome.

Various psychiatric disorders have been associated with Usher syndrome. This includes schizophrenia-like disorder, atypical psychosis, and recurrent depression (Usher, 1914; Hallgren, 1959; Vernon, 1969; Nuutila, 1970). Hallgren (1959) observed the highest frequency of mental disturbance (> 20%), but subsequent studies did not confirm such a high prevalence. Two different etiologies have been hypothesized as the cause of this association. One is that it is part of the syndrome and reflects a pleiotropic effect of the Usher gene. The pleiotropic theory would be more reasonable had the putative association between mental deficiency and Usher syndrome been upheld by subsequent studies. The second, more likely, hypothesis is that the psychiatric dysfunction is due to stress and is a reaction to the loss of both of the two major senses. This premise is supported by the finding that patients who have gone blind or deaf have often been reported to experience temporary reactive psychosis. Furthermore, the schizophrenia-like symptoms seen in Usher syndrome are also temporary, a feature not seen in true schizophrenia. Thus, they contribute nothing to the differential diagnosis of Usher syndrome.

**PATTERN OF INHERITANCE**

All types of Usher syndrome are inherited as autosomal recessive. At one time, an X-linked recessive mode of inheritance was proposed, based on a single observation of four brothers affected with type II (Davenport and Ommen, 1977). This family was later studied by linkage and found to be linked to markers on chromosome 1q41, thus establishing them as type IIa. There is no evidence suggesting an X-linked pattern of inheritance for Usher syndrome.

We have observed one family in which RP with hearing impairment was inherited in an autosomal dominant manner. Family members presented with hearing loss much milder than expected with Usher syndrome. The RP also had a later onset, as would be expected with dominantly inherited RP. Here, the question is not so much whether a dominant Usher syndrome exists but rather to what extent hearing loss occurs in dominant RP. Epidemiologic data indicate that hearing problems may occur in over 50 percent of all persons with RP. These individuals cannot all have Usher syndrome, and a reasonable conclusion is that what we think of a typical RP may often be associated with a mild hearing impairment. As discussed above, unless the configuration of the audiogram conforms to that observed for well-studied Usher type II cases, the diagnosis of Usher syndrome should be doubted. When this is coupled with a family history suggesting dominance, then the clinician should be doubly cautious.

Sometimes family history gives strong clues either supporting or contraindicating the diagnosis. One such instance is presented here. Patient M is a 12-year-old male whose hearing loss had been diagnosed in the first year of school. The diagnosis of RP was just recently made, and the diagnosis of Usher syndrome was made. The pedigree of patient M is presented in Figure 3 alongside the audiogram of the affected young man. Based on the moderate hearing loss, the diagnosis of Usher type II seemed a reasonable presumption; however, the audiogram was flat across all frequencies and thus not typical of Usher II. Furthermore, his first cousin was reported to be affected with RP. This diagnosis was confirmed and normal hearing was verified audiometrically. The possibility that patient M was affected with two different problems (hearing loss due to an unidentified cause, RP due to a recessive gene), rather than a syndrome, became an appealing hypothesis. This became even more likely once it was found that patient M and his cousin were actually double first cousins (brothers married sisters) and shared more genes than expected for regular first cousins.

There is little variability in expression within sibships for type I patients for the obvious reason that it is so severe that there is little left to vary. Greater variation between sibships than within for both hearing and visual involvement has been observed for type II families (Hallgren, 1959; Fishman, 1979). The reason for this phenomenon has not been rigorously investigated. Certainly, one might expect some of the variation to be due to the different genes known to be involved. On the other hand, some variation might be due to different types of mutations within any of the type II genes.

The extensive heterogeneity has importance in genetic counseling. When two persons with
Figure 3  This figure presents a family that was initially diagnosed with Usher syndrome (patient M). The audiogram is atypical with milder loss in the higher frequencies. The family history revealed that a double first cousin had RP and normal hearing, suggesting that the concurrence of hearing loss with RP in patient M was due to chance and not the pleiotropic effect of a single gene.

Usher syndrome marry, the risk they have for offspring with Usher syndrome depends upon the type and subtype of their diagnosis. We recently had one case where both parents were type I Usher. The father was from the Louisiana Acadian community and most likely had Usher type Ic, which is almost exclusively found in that population. The mother was not French Acadian and her Usher diagnosis was likely to be of a different subtype. The mother’s blood, along with her sibling’s, was typed for DNA markers, and the linkage was compatible with a subtype diagnosis of type Ib. Unfortunately, her fiancé was an only child and her family was not informative for linkage, but since the family was French Acadian, it was deemed likely that his Usher syndrome was type Ic. Since Ib and Ic are different loci, the likelihood that the couple would have a child with Usher syndrome is low.

MOLECULAR GENETICS

At least five loci are now identified as being associated with Usher syndrome. Two of these are responsible for the milder Usher type II while three are coding for Usher type I.

The Usher syndrome type I gene was first localized to chromosome 14q by a linkage with marker D14S13 in 15 families (Gerber et al, 1992). A statistical test for genetic heterogeneity was significant, suggesting the possibility that the linkage was being obscured by virtue of two or more different genes being involved. Further investigation showed only some families with linkage to the appropriate 14q markers. Most of the linked came from the same region known as Poitou-Charentes in France. The gene has since been designated USH1a. In an analysis of Usher consortium data, Keats et al (1992) were unable to find families with linkage to 14q, suggesting that this gene might be uncommon outside the Poitou-Charentes region. However, a recent analysis (unpublished data) of our families revealed that a significant fraction (> 10%) were indeed linked to that region.

It was subsequently discovered that other Usher families linked to two different regions on
The gene linked to 11q has been designated USH1b and the one to 11p has been called USH1c. Recent results (unpublished data) localize the USH1b gene to a small region probably between the markers OMP (olfactory marker protein) and D11S911. This is a very small region estimated to be no more than 1 megabase.

The linkage of USH1c has been refined and flanking markers have been described (Keats et al, 1994). Families with USH1c have so far been found only within the French Acadian community of southern Louisiana. The French Acadians migrated to the bayous of Louisiana from Quebec over 100 years ago and had, until the Second World War, remained genetically isolated. Presumably because of founder effect, Usher syndrome has been found to be of a high frequency in that population. In fact, southern Louisiana may have the highest frequency of Usher syndrome in the US, perhaps even the world. The Acadians were originally from the Normandy area in France, and there is no evidence that they share ancestry with the families from Poitou-Charentes showing linkage to 14q. The fact that there are at least three different genes for Usher type I complicates the problem of molecular diagnosis, since it will be uncommon to find an Usher family of sufficient size so that linkage could be used to definitively prove diagnosis. A more feasible approach to diagnosis will have to await the cloning of the Usher I genes.

Usher syndrome type II was localized to chromosome 1q32 (Kimberling, 1990; Lewis, 1990). The gene has subsequently been shown to be flanked by the anonymous markers, D1S237 and D1S229. One family with Usher type II was observed not to be linked to the 1q32 region (Pieke Dahl et al, 1993). Nor does the Usher syndrome in the family show linkage to markers on chromosomes 11q, 11p, or 14. This establishes the fact that a second locus for Usher type II exists that is not located on 1q32-42 and that the gene is not an allele at any of the other three Usher type I loci. This new gene has been given the designation USH2b, leaving USH2a to refer to the original 1q locus. The frequency of Usher IIb relative to IIa is not known.

While types I and II are clearly different with no clinical overlap, the subtypes within each group are indistinguishable. This fact underlines our need to further investigate the clinical variation of Usher syndrome types I and II. Questions now arise as to whether any of the clinical variation previously ascribed to other putative types actually represent one or more of the five different loci.

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**Figure 4** This shows a pedigree of two siblings with hearing impairment, RP, and mild anomalies. The observation of consanguinity suggests that a single gene is involved. However, the family failed to show linkage to any of the known Usher gene regions. The presence of minor or major anomalies in a patient with hearing impairment and RP should alert the clinician to the possibility of atypical Usher diagnosis.
Considerable progress has been made towards the identification and cloning of the Usher genes. Unfortunately, this progress cannot yet be translated into a meaningful test for the diagnosis of Usher syndrome and its subtypes. Linkage has very limited use when dealing with a recessive trait, especially one as heterogeneous as Usher syndrome. Once the genes are cloned, however, we will have rapid and accurate means of testing for Usher syndrome homozygotes and heterozygote carriers. One important consequence of this progress will be the ability to screen the deaf population for Usher syndrome and thus provide an early diagnosis without the expense and potential false negatives associated with a visual screening examination. Also, diagnosis of the appropriate subtype will help in genetic counseling by identifying carriers of the same subtype gene.

REFERENCES


