Visual Prognosis in USH2A-Associated Retinitis Pigmentosa Is Worse for Patients with Usher Syndrome Type IIa Than for Those with Nonsyndromic Retinitis Pigmentosa

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Purpose: USH2A mutations are an important cause of retinitis pigmentosa (RP) with or without congenital sensorineural hearing impairment. We studied genotype–phenotype correlations and compared visual prognosis in Usher syndrome type IIa and nonsyndromic RP.

Design: Clinic-based, longitudinal, multicenter study.

Participants: Consecutive patients with Usher syndrome type IIa (n = 152) and nonsyndromic RP (n = 73) resulting from USH2A mutations from ophthalmogenetic clinics in the Netherlands and Belgium.

Methods: Data on clinical characteristics, visual acuity, visual field measurements, retinal imaging, and electrophysiologic features were extracted from medical charts over a mean follow-up of 9 years. Cumulative lifetime risks of low vision and blindness were estimated using Kaplan-Meier survival analysis.

Main Outcome Measures: Low vision and blindness.

Results: Participant groups had similar distributions of gender (48% vs. 45% males in Usher syndrome type IIa vs. nonsyndromic RP; \( P = 0.8 \)), ethnicity (97% vs. 99% European; \( P = 0.3 \)), and median follow-up time (6.5 years vs. 3 years; \( P = 0.3 \)). Usher syndrome type IIa patients demonstrated symptoms at a younger age (median age, 15 years vs. 25 years; \( P < 0.001 \)), were diagnosed earlier (median age, 26 years vs. 36.5 years; \( P < 0.001 \)), and became visually impaired 13 years earlier (median age, 41 years vs. 54 years; \( P < 0.001 \)) based on VF and 18 years earlier based on VA (median age, 54 years vs. 72 years; \( P < 0.001 \)) than nonsyndromic RP patients. The presence of 2 truncating mutations in USH2A was associated mostly with the syndromic phenotype, whereas other combinations were present in both groups. We found novel variants in Usher syndrome type IIa (25%) and nonsyndromic RP (19%): 29 missense mutations, 10 indels, 14 nonsense mutations, 9 frameshift mutations, and 5 splice-site mutations.

Conclusions: Most patients with USH2A-associated RP have severe visual impairment by age 50. However, those with Usher syndrome type IIa have an earlier decline of visual function and a higher cumulative risk of visual impairment than those without nonsyndromic RP. Complete loss of function of the USH2A protein predisposes to Usher syndrome type IIa, but remnant protein function can lead to RP with or without hearing loss. Ophthalmology 2016;123:1151-1160 © 2016 by the American Academy of Ophthalmology.

Supplemental material is available at www.aaojournal.org.
Approximately 50% to 75% of Usher syndrome patients and 12% to 25% of nonsyndromic RP patients carry mutations in USH2A, making it one of the most important mutated genes in these populations. Generally, patients with Usher syndrome type IIa can be identified early because of their congenital hearing impairment. At this young age, most photoreceptors are still viable and would be amenable targets for gene replacement therapy. USH2A is a challenge for developers of gene therapy because the size of the gene largely exceeds the capacity of adeno-associated virus and lentivirus vectors. Other strategies such as antisense oligonucleotide-based therapy and cell replacement therapy with induced pluripotent stem cells seem promising. As treatment options for USH2A mutations become apparent, it is important to identify individuals who have the greatest chance to benefit from these therapies. Therefore, being able to predict the course of the disease early in the process is highly desirable.

Thus far, genotype–phenotype correlations have not been very distinct in patients with USH2A mutations. Certain mutations in USH2A, such as p.(Glu767Serfs*21), have been associated mainly with the syndromic phenotype. Others seem to have a predilection for nonsyndromic RP, such as p.(Cys759Phe). It remains unknown why some mutations in USH2A lead to Usher syndrome type IIa and others to nonsyndromic RP. A great number of mutations are missense mutations and are private, which means that they are observed only in 1 family. In addition, most patients are compound heterozygotes because they carry different mutations on the maternal and paternal allele. This makes it even more difficult to predict the effect of each of these mutations on the phenotype and complicates assessing a possible allelic hierarchy. Affected siblings are prone to having the same phenotype, but differences in severity occur. This suggests that each phenotype may be caused by a distinct set of genotypes.

The aim of this study was to investigate the visual prognosis in a large series of patients with retinal degenerations resulting from USH2A mutations. We compared the course of disease in patients with Usher syndrome type IIa with that of patients with nonsyndromic RP and aimed to investigate whether their genetic constitutions can predict the progression of visual function loss.

Methods

Study Population

We ascertained 225 consecutive subjects with RP resulting from mutations in USH2A from 5 ophthalmogenetic clinics in the Netherlands and Belgium. Of these, 152 had a diagnosis of congenital hearing impairment based on audiologic test results and all procedures were reviewed by the Medical Ethics Committee of Erasmus Medical Center and the Medical Ethics Committee of the University Hospital of Ghent. Participants provided a written informed consent to retrieve data from medical records.

Clinical Examination

We strived to establish a database with virtually complete longitudinal data. Participants were queried for all ophthalmologists and otolaryngologists they had consulted during their lifetimes, and medical records were retrieved. We gathered longitudinal data from 171 patients and examined 54 patients cross-sectionally. Eye examinations were performed in accordance with good clinical practice at regular intervals by a small number of ophthalmologists (n = 6) with expertise in ophthalmogenetics and included best-corrected Snellen visual acuity (VA), Goldmann VFs, electrotoretinography (full-field electrotetinography according to the standards of the International Society for Clinical Electrophysiology of Vision; available at www.iscerv.org), color vision testing, slit-lamp examination, and ophthalmoscopy. Not all of these examinations had been performed at each visit, and not all participants had undergone all examinations. We digitized VF retinal area of the V4 target using a method described by Dagnelie.

Genetic Analysis

To provide the molecular diagnosis, different molecular testing approaches were used over the course of 20 years (1996–2015). In the initial years, participants were analyzed with polymerase chain reaction amplification and subsequent Sanger sequencing. From 2006 through 2013, participants were analyzed with an Usher syndrome APEX (arrayed primer extension) genotyping microarray or an autosomal recessive RP APEX genotyping microarray. Sanger direct sequencing was performed subsequently to confirm the identified mutation(s). When only 1 heterozygous mutation in USH2A was found, the entire USH2A gene was sequenced to screen for a second pathogenic mutation. From 2014 onward, ophthalmogenetic laboratories used targeted next-generation sequencing of 160 genes associated with hereditary blindness or whole-exome sequencing to identify mutations for RP. Pathogenicity of mutations was scored using Combined Annotation Dependent Depletion (CADD).
Statistical Analysis

Differences in age at onset and age at diagnosis were compared using a Wilcoxon–Mann–Whitney test. To compare differences in gender ratio, ethnicity, and refractive error, we used a chi-square test. Outcome variables were low vision and blindness. These functional stages were based on VA and VF and were in accordance with World Health Organization standards. Visual impairment was defined as either low vision (0.05 ≤ VA < 0.3, 10° ≤ VF < 20° central VF diameter, or both) or blindness (VA < 0.05, central VF diameter < 10°, or both). Lifetime cumulative risk of the outcome variables was estimated using Kaplan-Meier product-limit survival analysis. The log-rank test was used to determine the statistical significance of risk differences. Analyses were stratified for clinical diagnosis and the number of truncating variants present, because these variants are predicted to lead to nonsense-mediated decay, significant truncation of the protein, or both if translated. Progression of VF loss was evaluated with mixed-model analysis.

Results

Clinical Characteristics

The average follow-up time did not differ significantly between the groups (Table 1) and was 9 years on average with a maximum of 43 years. Participants with Usher syndrome type IIa in our cohort were younger than participants with nonsyndromic RP, but did not differ in gender. The vast majority of participants in both groups were of European descent. All participants had at least 2 RP hallmarks on fundus examination, that is, the presence of a waxy optic disc, narrow blood vessels, midperipheral and peripheral bone spicules, and atrophy of the retinal pigment epithelium. There were no differences in refractive error between the patient groups (Table 1). Subcapsular cataract was common (overall median age, 48 years), and 46 patients (21%) had undergone cataract extraction. Participants with Usher syndrome type IIa underwent cataract extraction approximately 10 years earlier than participants with nonsyndromic RP (Table 1).

Visual Function

Subjects with Usher syndrome type IIa were younger at age of onset of symptoms, that is, night blindness and VF constriction, and were diagnosed with RP at a younger age (Table 2). The VF constriction preceded VA loss in all but 1 patient who had irreversible central visual loss resulting from longstanding cystoid macular edema. Participants with Usher syndrome type IIa became visually impaired approximately 13 years earlier based on VF constriction criteria (VF < 20°; P < 0.001) and 18 years earlier based on VA criteria (VA < 0.3; P < 0.001) than subjects with nonsyndromic RP (Table 2; Figs 2 and 3). At 50 years of age, 83% of participants with syndromic RP had VF constriction versus only 40% of participants with nonsyndromic RP. These numbers were 46% versus 6% for VA. Exclusion of relatives did not alter these risk estimates significantly (data not shown). To validate our findings, we repeated the analyses and excluded subjects with a single USH2A mutation. This exclusion did not alter our estimates (Table 3, available at www.aaojournal.org). Progression of VF loss was evaluated with mixed-model analysis. At baseline (intercept), there was no difference between subjects with Usher syndrome type IIa and nonsyndromic RP (P = 0.3), but with aging, the difference in progression became statistically significant (P < 0.01; Fig 4).

Genotype

Pathogenic mutations on both alleles were found in 160 participants (71%), among whom 31 (19%) were homozygous and 129 (81%) were compound heterozygous. In 53 patients (24%), only 1 pathogenic mutation was detected, and in 12 participants (5%), multiple mutations (≥3) in USH2A were found (Fig 1). One hundred twenty-eight different mutations were recorded, of which 65 were missense mutations, 10 were insertions or deletions, 30 were nonsense mutations, 16 were frame-shift mutations, and 7 were splice-site mutations. Sixty-eight of these variants were newly identified, because they were not present in the Leiden Open Variant Database (accessed July 17, 2015): 29 missense mutations, 10 insertions or deletions, 14 nonsense mutations, 9 frame-shift mutations, and 5 splice-site mutations (Table 4, available at www.aaojournal.org). The most common mutations in syndromic participants were p.(Glu767Serfs*21) (65 of 250 observed USH2A variants), p.(Cys419Phe) (29 of 250 observed USH2A variants), and p.(Cys536Arg) (15 of 250 observed USH2A variants). The most frequent mutations in nonsyndromic RP participants were p.(Cys759Phe) (33 of 130 observed USH2A variants), p.(Glu767Serfs*21) (13 of 130 observed USH2A variants), and p.(Arg4115Cys) (8 of 130 observed USH2A variants; Table 4, available at www.aaojournal.org). Twenty-one of the 225 participants (9%) resulted from a consanguineous marriage, and in only 10 of them did we find a homozygous mutation. In the remaining participants carrying homozygous mutations, p.(Glu767Serfs*21) was the most frequently observed mutation (n = 12). Figure 5 shows the protein structure of USH2A and the locations of mutations in the protein per phenotype. Strikingly, participants with 2 mutations in the N-terminal laminin domain always had the Usher syndrome type IIa phenotype at presentation, independent of the effect on the protein (Table 5, available at www.aaojournal.org).

We stratified all variants into 2 groups: truncating variants (also referred to as inactivating or null variants) and nontruncating variants. Participants carrying 2 nontruncating variants or 1 nontruncating and 1 truncating variant had both phenotypes at presentation. All but 1 participant carrying truncating variants on both alleles had Usher syndrome type IIa. The number of truncating variants present seems to be associated with an earlier decline in visual function (Table 6). As the number of truncating variants increases, participants become visually impaired earlier in life. More detailed analysis of pathogenicity was performed using CADD scores. Most variants exceeded a CADD score of 15, the cutoff score suggested by the authors to identify potentially pathogenic variants. No significant correlations between the score and age at diagnosis or age at visual impairment were found (data not shown). The CADD score can be used to predict whether a variant is deleterious in diagnostics, but we could not use it as a proxy for remaining protein function.

Discussion

In this study, we compared the visual course between subjects with Usher syndrome and nonsyndromic RP resulting from mutations in USH2A. We found that Usher syndrome type IIa patients demonstrated visual symptoms at an earlier age, had an earlier onset of disease, and became visually impaired at a younger age than participants with nonsyndromic RP. We observed several genotype–phenotype correlations: the presence of 2 truncating mutations was restricted to the Usher syndrome phenotype, as was the presence of 2 missense variants in the N-terminal laminin of USH2A.
Table 1. Distribution of Clinical Characteristics in Patients with USH2A Mutations

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Usher Syndrome Type IIa (n = 152)</th>
<th>Nonsyndromic Retinitis Pigmentosa (n = 73)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD, yrs</td>
<td>48±2.5</td>
<td>55±3.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Male gender, no. (%)</td>
<td>73 (48)</td>
<td>33 (45)</td>
<td>0.8*</td>
</tr>
<tr>
<td>Median follow-up (range), yrs</td>
<td>6.5 (0–43)</td>
<td>3 (0–37)</td>
<td>0.3*</td>
</tr>
<tr>
<td>European ethnicity, no. (%)</td>
<td>148 (97)</td>
<td>72 (99)</td>
<td>0.3*</td>
</tr>
<tr>
<td>Median refractive error (SE; n = 189), D</td>
<td>−1.50 (−16 to +5)</td>
<td>−0.75 (−14 to +4)</td>
<td>0.2*</td>
</tr>
<tr>
<td>Cataract extraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right eye, no.</td>
<td>30</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Median age (range), yrs (n = 46)</td>
<td>45 (27–64)</td>
<td>56 (31–73)</td>
<td>0.002†</td>
</tr>
<tr>
<td>Left eye, no.</td>
<td>32</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Median age (range), yrs (n = 46)</td>
<td>43 (28–64)</td>
<td>57 (32–78)</td>
<td>0.003†</td>
</tr>
<tr>
<td>Electroretinography results (n = 142), no. (%)</td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Reduced rods and cones</td>
<td>1 (1)</td>
<td>18 (35)</td>
<td></td>
</tr>
<tr>
<td>Rods extinguished, reduced cones</td>
<td>9 (9)</td>
<td>9 (17)</td>
<td></td>
</tr>
<tr>
<td>Rods and cones extinguished</td>
<td>86 (90)</td>
<td>26 (48)</td>
<td></td>
</tr>
</tbody>
</table>

D = diopter; SD = standard deviation; SE = spherical equivalent.
*Student t test.
†Chi-square test.
‡Wilcoxon–Mann–Whitney test.

the gene. The presence of at least 1 truncating mutation was associated with a earlier visual decline, regardless of the phenotype.

Our study has benefits and drawbacks. Among the benefits is our establishment of the largest cohort of USH2A patients with genetic and longitudinal follow-up data to date. The 225 Dutch and Belgian participants had been examined by a small number of ophthalmologists and had been followed up for a relatively long period. Finally, our analysis focused on the lifetime course of disease and used end points, which are considered gold standards for functional vision. The drawbacks include the lack of power for detailed subgroup analysis and the incomplete genotyping in a proportion of the patients. There may have been selection bias because patients with hearing loss are more sensitive to visual decline than nonsyndromic RP patients because they rely more on visual cues in daily life. These patients may have been referred for ophthalmologic screening at a younger age, and thereby may have received an earlier diagnosis of RP. We do not think that the raised alertness explains the difference in visual decline, because this was registered by severe outcome measures using standardized criteria. We believe these differences to be genuine.

Others studied disease progression of Usher syndrome type IIa or nonsyndromic RP in smaller groups of patients. Fishman et al examined the course of visual function in 58 subjects with Usher syndrome type IIa by examining change in VF over 3 years. They found that the progression rate did not depend on initial localization of the VF defect. Blanco-Kelly et al compared 276 subjects with Usher syndrome type IIa with 93 subjects with Usher syndrome type I cross-sectionally using historical data and found an earlier onset for Usher syndrome type I. For subjects with Usher syndrome type IIa in this study, the age at onset of symptoms (18.1 years vs. 15 years) and diagnosis (26.8 years vs. 26 years) was similar to our findings. Another large study by Sandberg et al investigated 125 RP patients with mutations in USH2A with and without hearing loss and calculated rates of decline in electroretinography results, VA, and VF. Annual decline of cone electroretinography amplitudes was 13.2%, which was a rate faster than that of patients with mutations in retinitis pigmentosa GTPase regulator (RPGR) or rhodopsin (RH0). The estimated decline of VA and VF in this study occurred earlier than in our study. At 65 years of age, 50% were legally blind based on VA or VF in the study of Sandberg et al, whereas these proportions were 22% and 49% at 65 years of age in our study for both phenotypes combined. Their

<table>
<thead>
<tr>
<th>Median Age Time Point (yrs)</th>
<th>Usher Syndrome Type IIa (n = 152)</th>
<th>Nonsyndromic Retinitis Pigmentosa (n = 73)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of symptoms</td>
<td>15 (0–46)</td>
<td>25 (0–68)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>26 (8–56)</td>
<td>36.5 (12–74)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Low vision based on VF (n = 176)</td>
<td>41 (15–67)</td>
<td>54 (32–78)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Low vision based on VA (n = 225)</td>
<td>54 (20–74)</td>
<td>72 (15–72)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Legal blindness based on VF (n = 176)</td>
<td>54 (19–58)</td>
<td>80 (34–80)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Legal blindness based on VA (n = 225)</td>
<td>74 (32–74)</td>
<td>77 (49–77)</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

VA = visual acuity; VF = visual field.
Data are median (range) unless otherwise indicated.
*Wilcoxon–Mann–Whitney test.
†Log-rank test.
‡P > 0.008, after Bonferroni correction.
Figure 2. Graphs showing cumulative incidence (%) of low vision based on (A) visual acuity of less than 0.3 and (B) GVF of less than 20 as a function of age stratified for Usher syndrome type IIa and nonsyndromic retinitis pigmentosa (RP). The cumulative incidence of low vision at 0, 20, 40, 60, and 80 years of age is indicated in the grey box below the graph. Red = Usher syndrome type IIa; black = nonsyndromic RP.
Figure 3. Graphs showing cumulative incidence (%) of legal blindness based on (A) visual acuity of less than 0.05 and (B) GVF of less than 10 as a function of age stratified for Usher syndrome type IIa and nonsyndromic retinitis pigmentosa (RP). The cumulative incidence of legal blindness at 0, 20, 40, 60, and 80 years of age is indicated in the grey box below the graph. Red line = Usher syndrome type IIa; black = nonsyndromic RP.
risk estimates were derived from a fitted model based on only a small number of observations in the higher age range, whereas our estimates were based on actual data and included a larger number of data points. Therefore, we believe our estimates may be more realistic. Note that the rate of VF loss, expressed as remaining retinal area capable of detecting the target, follows the same time course in both subgroups, with a plateau before onset in the nonsyndromic group and a slowing at older age in the syndromic group. The mixed-model analysis we used does not test for the concept of a critical age as postulated by Massof.19

We studied the distribution of USH2A genotypes and found that less than 19% of mutations were homozygous and that most mutations were private (69%). This indicates that the heterogeneity is very large and that de novo mutations may occur frequently. We found 2 pathogenic USH2A mutations in 72%, 3 mutations in 5%, and only 1 pathogenic mutation in 23% of our study population. The most frequently occurring mutation in the Usher syndrome type IIa group was p.(Glu767Serfs*21), but this was also the second most common variant in the nonsyndromic group. This mutation was found in 7 of 16 homozygous subjects. Carrier frequency of this allele is 0.08% in the general population according to the Exome Aggregation Consortium data set (accessed July 17, 2015). This mutation was found in control populations of European, African, and Latin descent, but seems to be of European ancestral origin.20 In the 25% (n = 52) of patients in whom we detected only 1 USH2A mutation using APEX microarray we did not find a second mutation with Sanger sequencing. This may be the result of deep intronic variants that affect splicing, intronic or intergenic variants that affect transcription or deletions, or duplications that escaped detection. The disease may also be the result of mutations in other genes that mimic this phenotype.

Variants were distributed all over the gene for both phenotypes (Fig 5). We observed only 1 distinct hotspot; this was located in the N-terminal laminin domain, which was associated with the Usher syndrome type IIa phenotype. Subjects in our cohort with biallelic variants in this domain always had impaired hearing, implying that this protein domain is essential for normal cochlear development (Table 5, available at www.aaojournal.org). Although Baux et al21 found a high density of pathogenic variants in this domain, they did not report a relationship with function. There were no other apparent genotype–phenotype relationships; however, all 21 sibling pairs with USH2A mutations shared the same phenotype. Most of the unrelated patients with identical genotypes (13/15) also shared the same phenotype. Therefore, the combination of mutations seems to predispose individuals to a certain phenotype.

Approximately half (49.2%) of the mutations were truncating, leading to a shortened or absent protein resulting from nonsense-mediated mRNA decay. These were twice as frequent in Usher syndrome type IIa (60.33% vs. 25.00%), and we confirmed that 2 truncating variants always caused congenital hearing loss, but not congenital blindness.3 However, we observed that biallelic missense mutations also caused congenital hearing loss in 19 patients (Table 5, available at www.aaojournal.org; and Table 6). Patients with 2 truncating mutations have an earlier onset of RP and a earlier progression to visual impairment than
Figure 5. Schematic representation of the usherin protein and localization of mutations. Mutations in the first column were found only in participants with Usher syndrome type IIa. Mutations in the last column were found only in nonsyndromic retinitis pigmentosa (RP) participants. Mutations in the middle column were present in both phenotype groups.
those with residual protein function (Table 6). It seems that at least 1 functional allele is needed for normal cochlear development, but not for retinal development. In the retina, the function of the USH2A protein usherin is maintenance of photoreceptor cells.22 Zebrashots have shown that the long isoform of the protein is located at the connecting cilium and photoreceptor synapse and that knockdown of the gene causes photoreceptor degeneration.23 In the cochlea, both isoforms are present transiently during development, and functional studies in mice have shown that knockout of the gene leads to nonprogressive sensory hearing loss.22 The protein in the ear seems to function in the ankle link complex that organizes stereocilia in a V-shaped pattern in the developmental phase. It does not seem to have a role in maintenance of the cochlea. The dissipative roles of the protein in the eye and the ear clarify the difference in age of onset and clinical course.

Our data do not support the allelic hierarchy theory proposed by Lenassi et al.10 which stratifies disease-causing variants in retinal-disease specific alleles and Usher syndrome type IIa-specific alleles. Retinal disease-specific alleles had to be present in more than 1 patient with nonsyndromic RP and did not occur in Usher syndrome type IIa. The authors proposed that 1 or more retinal disease-specific alleles were associated with preserved hearing. In our cohort, 6 patients with Usher syndrome type IIa were heterozygous for the c.2276G→T allele, which they attributed to the retinal disease-specific group.21 In the Leiden Open Variant Database (accessed July 17, 2015), 31 patients with Usher syndrome type IIa also carried the c.2276G→T variant.12,16,18,21,24–31

We suggest that the effect of this variant on usherin is not confined to the retina, but also can affect cochlear development. The c.2276G→T variant causes a change in amino acid residue from cysteine to phenylalanine. Cysteine is crucial for the formation of 1 of the 4 disulphide bonds required for proper protein folding in the epidermal growth factor (EGF) domain. Another variant, c.11156G→A, which Lenassi et al.10 proposed to be retina specific, also was present in the Leiden Open Variant Database in an Usher syndrome type IIa patient.32 Therefore, we do not support this allelic hierarchy theory, but suggest that normal cochlear development depends on the presence of at least 1 functional copy of the USH2A protein.

In conclusion, we studied the progression of visual function in a large cohort (n = 225) of patients with RP resulting from mutations in USH2A. Participants with Usher syndrome type IIa had a worse visual prognosis than patients with nonsyndromic RP. Hence, variants causing Usher syndrome type IIa seem to have a more deleterious effect on the protein in the retina. Our data aid in patient counselling by clinicians and geneticists and can provide valuable information for researchers developing therapy for this debilitating disease.

References


Table 6. Mutations in Usher Syndrome Type IIa and Nonsyndromic Retinitis Pigmentosa

<table>
<thead>
<tr>
<th>Usher syndrome type IIa, no. (%)</th>
<th>Nontruncating</th>
<th>Truncating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontruncating RP, no. (%)</td>
<td>19 (16)</td>
<td>14 (36)</td>
</tr>
<tr>
<td>Median age at low vision by VA, yrs (n = 160)</td>
<td>59</td>
<td>57</td>
</tr>
<tr>
<td>Median age at low vision by GVF, yrs (n = 124)</td>
<td>45</td>
<td>48</td>
</tr>
</tbody>
</table>

GVF = Goldmann Visual Field; RP = retinitis pigmentosa; VA = visual acuity.

* Chi-square test.

* Log-rank test.
Footnotes and Financial Disclosures

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Data collection: Pierrache, Hartel, Meester-Smoor, F. P. M. Cremers, de Baere, de Zaeytijd, van Schoonevelt, C. W. R. J. Cremers, Hooying, Bergen, Leroy, Pennings, van den Born, Klaver

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Abbreviations and Acronyms:
APEX = arrayed primer extension; CADD = Combined Annotation Dependent Depletion; RP = retinitis pigmentosa; USH2A = Usher syndrome type 2A; VA = visual acuity; VF = visual field.

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