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Disease Course in Patients with Autosomal Recessive Retinitis Pigmentosa due to the *USH2A* Gene

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Abstract

Purpose—To estimate the mean rates of ocular function loss in patients with autosomal recessive retinitis pigmentosa due to *USH2A* mutations.

Methods—In 125 patients with *USH2A* mutations, we used longitudinal regression to estimate mean rates of change of Snellen visual acuity, Goldmann visual field area (V4e white test light), and 30 Hz (cone) full-field electroretinogram amplitude. We compared these rates to those of previously studied cohorts with dominant retinitis pigmentosa due to *RHO* mutations and with X-linked retinitis pigmentosa due to *RPGR* mutations. We also compared rates of change in patients with the Cys759Phe mutation, the *USH2A* mutation associated with nonsyndromic disease, with rates of change in patients with the Glu767fs mutation, the most common *USH2A* mutation associated with Usher syndrome, type II (i.e., retinitis pigmentosa and hearing loss).

Results—Mean annual exponential rates of decline for the *USH2A* patients were 2.6% for visual acuity, 7.0% for visual field area, and 13.2% for electroretinogram amplitude. The rate of acuity loss fell between the corresponding rates for the *RHO* and *RPGR* patients, while the rates for field and ERG amplitude loss were faster than those for the *RHO* and *RPGR* patients. No significant differences were found for patients with the Cys759Phe mutation versus patients with the Glu767fs mutation.

Conclusions—On average, *USH2A* patients lose visual acuity faster than *RHO* patients and slower than *RPGR* patients. *USH2A* patients lose visual field and cone electroretinogram amplitude faster than *RHO* patients and *RPGR* patients. Patients with a nonsyndromic *USH2A* mutation have the same retinal disease course as patients with syndromic *USH2A* disease.

Introduction

Mutations in the genes encoding rhodopsin (*RHO*), retinitis pigmentosa GTPase regulator (*RPGR*), and usherin (*USH2A*) are the most common causes of retinitis pigmentosa, each gene accounting for about 10% of cases in North America.^{1–3} We previously reported differences in the mean rates of loss of visual acuity, visual field, and ERG amplitude between patients with *RHO* mutations and patients with *RPGR* mutations.⁴ The present study was done to determine the rates of progression for patients with *USH2A* mutations and compare them to those previously reported for the other two common forms of retinitis pigmentosa.

In 1998 mutations in the *USH2A* gene were first reported as a cause for Usher syndrome, type II, an autosomal recessive form of retinitis pigmentosa with mild-to-moderate congenital hearing loss and normal vestibular function,⁵ based on analysis of the 21 exons found to encode an *USH2A* transcript.⁶ A longer transcript consisting of 51 additional 3' exons was more recently identified, and mutations causing Usher syndrome, type II were also found in these exons.⁷ Most *USH2A* mutations individually account for a only few percent of cases of Usher syndrome, type II. An exception is the mutation c.2299delG (Glu767fs) in exon 13 which is geographically widespread and found to have been derived from a common ancestor.⁸ In addition, another common mutation in this gene—Cys759Phe, also in exon 13—has been reported to cause 4% to 5% of autosomal recessive retinitis pigmentosa without hearing loss.^{9,10} Because in many cases this mutation in one allele does not cause hearing loss even when combined with a pathogenic *USH2A* mutation in the second allele,^{9,10} we hypothesized that a patient with at least one allele carrying the Cys759Phe mutation might have a less severe ocular disease course than patients with other *USH2A* mutations. To test this hypothesis, we also compared mean rates of decline of patients with the Cys759Phe mutation to those of patients with the Glu767fs mutation. We restricted this comparison to patients who carried the one mutation without carrying the other mutation.

Methods

Patients

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Boards of the Massachusetts Eye and Ear Infirmary and Harvard Medical School. Our *USH2A* longitudinal dataset comprised 125 patients with pathogenic mutations (see Table 2). This cohort (mean age at baseline: 31.6 years, age range at baseline: 6 to 59 years) had 3 to 27 years of follow-up from 1975 to 2005 utilizing the same test conditions with a mean follow-up of 10.4 years and an average of 7.4 ocular examinations/patient. All patients had parents with no history of retinitis pigmentosa, and, therefore, we presumed that the condition in these patients was autosomal recessive. The *RHO* and *RPGR* longitudinal datasets, derived from a previous study,² were also limited to patients with at least 3 years of follow-up. They yielded a sample of 134 *RHO* patients (mean age at baseline: 36.0 years, age range at baseline: 8 to 66 years) who had been followed for 3 to 24 years with an average follow-up of 8.9 years based on an average of 6.2 examinations/patient and 113 *RPGR* patients (mean age at baseline: 26.1 years, age range at baseline: 5 to 61 years) who had been followed for 3 to 28 years with an average follow-up of 9.8 years based on an average of 7.2 examinations/patient. The mean age at baseline of the patients varied significantly by group ($p < 0.001$).

Clinical evaluation

All of the patients underwent identical ocular examinations and quantification of data as described in detail previously.⁴ We recorded best-corrected Snellen visual acuities and coded them as decimals. Kinetic visual fields were measured to the V4e white test light against the standard background of 31.5 apostilbs. Fields were plotted with a digitizing tablet or scanned by custom software and converted to areas in deg². We placed a contact lens electrode on the topically anesthetized cornea and elicited full-field cone ERGs with 10 μ s, 30 Hz flashes of white light (0.2 cd-s/m²) after pupillary dilation and 45 minutes of dark adaptation; digital filtering and signal averaging were used to quantify responses $< 10 \mu$ V in amplitude. As part of another research project,¹¹ we had recorded optical coherence tomograms (OCTs) from 4 of the patients with the Glu767fs mutation (ages, 43 to 54 years) who had visual acuities spanning 20/20 to 20/70. We evaluated these tomograms to try to reveal the morphological basis for visual acuity loss in this disease.

Statistical analyses

We censored visual acuities, visual field areas, and ERG amplitudes from selected visits to minimize ceiling and floor effects, converted these measures to natural logarithms, and performed analyses as described previously.⁴ In addition, we excluded *USH2A* patients from visual field analyses if they showed marked inconsistency over the course of follow-up, possibly due to an impaired ability to hear the examiner's prompts. Specifically, we eliminated patients if their root mean square error from the regression of $\log_e$ visual field area on time exceeded 4 standard deviations from the grand mean. Altogether, we excluded 23 patients from the analysis of visual acuity change, 16 patients from the analysis of visual field change, and 56 patients from the analysis of ERG change.

We used repeated-measures longitudinal regression with PROC MIXED of SAS, version 9 (SAS Institute, Cary, NC) to estimate the mean rate of change for each outcome measure based on the average $\log_e$ value for one or both eyes at each visit and compared mean slopes for patients by genotype. We used PROC LIFEREG of SAS to fit a Weibull function to survival data to compare the age distribution for legal blindness (i.e., a visual acuity of 20/200 or worse or a visual field diameter of 20° or less in each eye) in patients by genotype. This procedure accounts for left censoring (i.e., patients who were legally blind at their baseline visit), right censoring (i.e., patients who had not become legally blind by their last follow-up visit), and interval censoring (i.e., patients who became legally-blind between two follow-up visits).

Results

USH2A Mutations

Table 1 lists the nucleotide change and protein change for each of the 38 mutations identified in the patients included in this study. Many of these mutations were reported previously as the result of a screen of the short isoform of *USH2A*.³ Subsequently, we screened additional patients including the exons for the long isoform and found 18 novel mutations (indicated in bold).

Table 2 lists the identified mutations by patient. Not all patients were screened for mutations in the entire gene, and some patients carried a rare *USH2A* missense change that was not demonstrably pathogenic; these factors likely account for the high prevalence of patients with only one detected pathogenic mutation in our series. The table shows that 41 patients (33%) had the Cys759Phe mutation, associated with nonsyndromic retinitis pigmentosa, and not the Glu767fs mutation, associated with hearing loss. Conversely, 43 patients (34%) had the Glu767fs mutation and not the Cys759Phe mutation.

Baseline ocular function

Table 2 also reveals that at a mean age of 32 years our *USH2A* patients had mean visual acuities that were reduced 1 to 2 lines, mean visual fields that were reduced about 40% below normal, and cone ERG amplitudes that were reduced nearly 90% below normal.

Mean rates of change

Table 3 lists the mean annual $\log_e$ rates of change for patients with *USH2A* mutations with standard errors and significance levels. The mean $\log_e$ values correspond to mean annual exponential rates of decline of 2.6% for Snellen visual acuity, 7.0% for visual field area to the V4e test light, and 13.2% for cone ERG amplitude to 30 Hz flashes. In comparison, the *RHO* patients and *RPGR* patients, respectively, had mean annual exponential rates of decline of 1.6% and 4.0% for visual acuity, 2.9% and 4.7% for visual field area, and 7.7% and 7.1% for cone ERG amplitude. The mean rate of visual acuity loss for the *USH2A* patients was significantly faster than that for the *RHO* patients ($p = 0.005$) but significantly slower than that

for the *RPGR* patients ($p < 0.001$). On the other hand, the mean rate of visual field loss and the mean rate of ERG amplitude loss for the *USH2A* patients were significantly faster than the corresponding rates for the *RHO* patients and for the *RPGR* patients ($p < 0.001$ in all cases).

We then compared mean rates of change for *USH2A* patients with the Cys759Phe mutation (and not the Glu767fs mutation) to the mean rates for *USH2A* patients with the Glu767fs mutation (and not the Cys759Phe mutation). Mean rates of annual decline were, respectively, 2.9% versus 2.1% for visual acuity, 6.9% versus 7.7% for visual field area, and 13.1% versus 12.9% for ERG amplitude. None of these differences was statistically significant.

Distributions of rate of change

Figures 1 to 3 show the distributions of annual rate of change by ocular function and genotype. The x-axes are all spaced in intervals of 0.1 log_e-unit (i.e., ~10%) and, for a given measure of ocular function, span the same range. The modal values provide a gauge of the variation in rate of change and represent 60.6% to 61.8% of cases for visual acuity, 47.6% to 54.7% of cases for visual field area, and 33.3% to 40.4% of cases for cone ERG amplitude. Even though these modal values, on average, represent only about half of each group of change scores, it is still possible to discern differences in these distributions that parallel the mean differences cited above. With the location of the mode on the x-axis for the *USH2A* patients as reference, the cumulative percentage of cases to the left of this value (i.e., associated with faster progression) for visual acuity is 9.9% for *USH2A* patients, 6.7% for *RHO* patients, and 19.5% for *RPGR* patients. The cumulative percentage of cases to the left of the *USH2A* mode for visual field area is 31.2% for *USH2A* patients, 11% for *RHO* patients, and 19.5% for *RPGR* patients. The cumulative percentage of cases to the left of the *USH2A* mode for cone ERG amplitude is 37.6% for *USH2A* patients, 12.3% for *RHO* patients, and 15.1% for *RPGR* patients. Thus, the visual acuity distribution for the *USH2A* patients tends to lie between those of the *RHO* patients and *RPGR* patients, while the visual field and ERG distributions for the *USH2A* patients tend to lie to the left of the corresponding distributions for the *RHO* patients and *RPGR* patients — similar to what was observed for mean rates of change.

Median age to reach legal blindness

We found a significant effect of genotype on the age distribution for legal blindness ($p < 0.001$). Our patients with *USH2A* mutations reached legal blindness, based on loss of acuity or field, at a median age of 58 years (Fig 4); this age lies between those previously reported for the patients with *RPGR* mutations (45 years) and for the patients with *RHO* mutations (77 years).⁴ When visual acuity and visual field survival were considered separately, patients with *USH2A* mutations failed at a median age of 65 years for both measures of ocular function (Fig 4).

OCTs in patients with the Glu767fs mutation

Figure 5 illustrates tomograms recorded from a normal control and 4 patients with the *USH2A* Glu767fs mutation. In contrast to the normal tomogram, all 4 patients show a loss of the outer nuclear layer (ONL) outside of the fovea. In addition, the thickness of the outer nuclear layer in the foveal center is smaller for eyes with lower visual acuity in this sample, and the patient with a visual acuity of 20/50 has small off-center cysts.

Discussion

The present study shows that patients with retinitis pigmentosa due to *USH2A* mutations, on average, lost Snellen visual acuity more quickly (i.e., 2.6%/year or ~0.6 letter/year) than patients with *RHO* mutations (i.e., 1.6%/year or ~0.4 letter/year) but more slowly than patients with *RPGR* mutations (i.e., 4.0%/year or ~0.9 letter/year). On the other hand, the *USH2A*

patients lost visual field area and full-field cone ERG amplitude, which reflect predominantly extrafoveal function, more rapidly than the other two groups. These differences in mean rates of change could be detected even though patients within a given genotype and for a particular measure of ocular function showed some variation in their rates of change. These results provide a framework for planning clinical trials aimed at stabilizing or slowing the course of this condition.

Two previous studies also evaluated rates of loss of ocular function in patients with *USH2A* mutations. One of these studies followed Snellen visual acuity in 6 patients and Goldmann visual field in 4 patients but quantified results in “functional” value units that cannot readily be compared to the standard measurements used in the present study.¹² The second study followed visual field area in 8 patients with the Glu767fs mutation, censoring areas above their lower limit of normal and data “... that deviated from both preceding and succeeding field areas by 50% or more ...” regardless of the intervening time interval.¹³ These patients had an average rate of decline to the V4e stimulus of 12.1%/year, faster than what we observed in our patients with this mutation (7.7%/year), possibly due to methodological differences. Contrary to our initial hypothesis, we found that patients with nonsyndromic disease (i.e., due to the Cys759Phe mutation) did not have a significantly slower course of disease than patients with retinitis pigmentosa and hearing loss (i.e., due to the Glu767fs mutation).

Our data also revealed that patients with *USH2A* mutations become legally blind due to loss of visual acuity or visual field at a median age that is older than that of patients with *RPGR* mutations and younger than that of patients with *RHO* mutations. Loss of visual acuity and loss of visual field equally contributed to our *USH2A* patients becoming legally blind. This distinguishes them from *RPGR* patients, who generally become legally blind due to loss of visual acuity, and *RHO* patients, who generally become legally blind due to loss of visual field.⁴

The tomograms recorded from patients with the *USH2A* Glu767fs mutation showed thinning and loss of the outer nuclear layer with increasing eccentricity consistent with central visual field constriction, thinning of the outer nuclear layer in the center in parallel with decreased visual acuity, and macular cysts in one case. These changes are typical of those that have been described in patients with different forms of retinitis pigmentosa.^{4,11,14}

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Distributions of Rate of Change of Visual Acuity in Patients with Retinitis Pigmentosa

Figure 1.

Distributions of rate of change of visual acuity by genotype. Represented are 102 patients with *USH2A* mutations, 89 patients with *RHO* mutations, and 93 patients with *RPGR* mutations.

Distributions of Rate of Change of Visual Field in Patients with Retinitis Pigmentosa

Figure 2.

Distributions of rate of change of visual field area by genotype. Represented are 109 patients with *USH2A* mutations, 128 patients with *RHO* mutations, and 103 patients with *RPGR* mutations.

Distributions of Rate of Change of ERG Amplitude in Patients with Retinitis Pigmentosa

Figure 3.

Distributions of rate of change of cone ERG amplitude by genotype. Represented are 69 patients with *USH2A* mutations, 89 patients with *RHO* mutations, and 66 patients with *RPGR* mutations.

Figure 4. Weibull plot survival analysis for age to legal blindness (i.e., visual acuity $\leq 20/200$ or visual field equivalent diameter $\leq 20^\circ$), to visual acuity $\leq 20/200$, and to visual field equivalent diameter $\leq 20^\circ$ among patients with *USH2A* mutations. The vertical dashed lines designate the median ages for legal blindness.

OCTs of RP Patients with the USH2A Glu767fs Mutation

Figure 5.

Tomograms from a normal subject and from 4 patients (ages 54, 45, 43, and 52 years from top to bottom) with retinitis pigmentosa (RP) due to the Glu767fs mutation. Images span 6 mm horizontally. The arrow designates the low-reflectance outer nuclear layer (ONL) visible over the full 6 mm in the normal tomogram.

Table 1*USH2A* Mutations in DNA and Protein Format

Exon/Intron	Nucleotide change	Protein change
3	c.545_546delAA	Lys182fs
6	c.920_923dupGCCA	His308fs
6	c.1026_29delCTCT	Ser343fs*
6	c.1110_1111delTA	Ile371fs
7	c.1214delA	Asn405fs
7	c.1256G>T	Cys419Phe
Intron 10	c.1841-2A>G	Alters splice site IVS10-2A>G
11	c.1876C>T	Arg626X
12	c.2073C>A	Cys691X
12	c.2100delG	Thr701fs*
Intron 12	c.2168-1G>C	Alters splice site IVS12-1G>C
13	c.2276G>T	Cys759Phe
13	c.2299delG	Glu767fs
13	c.2761delC	Leu921fs
16	c.3187_3188delCA	Gln1063fs
20	c.4314delG	Ile1439fs
20	c.4338_39delCT	Cys1447fs
21	c.4510_4511insA	Arg1504fs
22	c.4645C>T	Arg1549X
26	c.5191_5192delAT	Met1731fs
Intron 28	c.5775+1G>A	Alters splice site IVS28+1G>A
Intron 29	c.5857+1G>C	Alters splice site IVS29+1G>C
Intron 29	c.5857+2T>C	Alters splice site IVS29+2T>C
30	c.5933_5940delCTGTTGTC	Pro1978fs
32	c.6169C>T	Gln2057X
40	c.7493delG	Ser2498fs
41	c.8167C>T	Arg2723X
42	c.8557A>T	Arg2853X
44	c.8834G>A	Trp2945X
48	c.9424G>T	Gly3142X
52	c.10190_10191delAA	Lys3397fs
59	c.11533C>T	Gln3845X
61	c.11864G>A	Trp3955X
Intron 61	c.12067-2A>G	Alters splice site IVS61-2A>G
64	c.14010_14062del	Glu4671fs
64	c.14131C>T	Gln4711X
68	c.14803C>T	Arg4935X
68	c.14879_c.14880delAAins45	Gln4960fs

Mutations in bold are novel.

* Mutation nomenclature in original publication³ was incorrect.

Table 2

Baseline Ocular Function of Patients with *USH2A* Mutations

ID	Mutation (Exon)	Mutation (Exon)	Age	VA OD *	VA OS *	VF OD †	VF OS †	ERG OD ‡	ERG OS ‡
19238	Lys182fs (3)	Glu767fs (13)	24	20/100	20/70	6438	5205	0.61	0.48
22085	His308fs (6)	Trp3955X (61)	59	20/200	20/200	152	213	0.30	0.15
19083	His308fs (6)		15	20/30	20/30	10451	8768	1.89	1.82
06863	Ser343fs (6)		34	20/50	20/60	384	279	0.30	0.30
02933	Ile371fs (6)		31	20/30	20/40	1073	585	NA	NA
19824	Asn405fs (7)		26	20/30	20/30	3795	3457	0.73	0.61
06236	Cys419Phe (7)		28	20/40	20/40	14349	15336	3.04	3.72
19477	Cys419Phe (7)	IVS10-2A>G (110)	44	20/40	20/40	410	545	0.08	0.31
00304	Cys419Phe (7)		35	20/25	20/25	10716	10322	6.00	6.00
07018	Cys419Phe (7)		30	20/30	20/30	16134	15672	2.86	2.62
13287	Arg626X (11)	Arg626X (11)	32	20/25	20/25	3700	3610	0.23	0.09
15597	Arg626X (11)	Cys1447fs (20)	20	20/30	20/30	NA	NA	2.31	1.75
13574	Cys691X (12)	Glu767fs (13)	25	20/20	20/20	8157	7770	0.90	0.90
14419	Thr701fs (12)	Gly3142X (48)	17	20/20	20/30	6926	4379	0.45	0.37
01376	IVS12-1G>C (112)		53	20/30	20/40	NA	NA	NA	NA
05831	Cys759Phe (13)		43	20/40	20/50	1576	1646	0.26	0.24
13445	Cys759Phe (13)	Trp3955X (61)	28	20/30	20/30	NA	NA	29.40	29.40
15657	Cys759Phe (13)	Cys759Phe (13)	36	20/25	20/50	10920	9497	9.24	4.20
11572	Cys759Phe (13)	Cys759Phe (13)	15	20/30	20/30	7711	9867	0.41	0.55
05014	Cys759Phe (13)	Cys759Phe (13)	35	20/40	20/30	9132	8980	22.00	22.00
06705	Cys759Phe (13)	Glu767fs (13)	28	20/25	20/25	21176	23087	13.74	12.71
05918	Cys759Phe (13)	Glu767fs (13)	40	20/30	20/30	8367	8174	7.48	9.13
06475	Cys759Phe (13)	Glu767fs (13)	32	20/40	20/40	1556	1117	2.07	1.83
06792	Cys759Phe (13)	Cys1447fs (20)	33	20/20	20/20	4288	3258	3.19	2.36
07889	Cys759Phe (13)	Cys1447fs (20)	27	20/20	20/20	8243	7725	29.40	52.94
11439	Cys759Phe (13)	Cys1447fs (20)	28	20/20	20/20	10077	11732	10.64	14.00
14338	Cys759Phe (13)	Pro1978fs (30)	36	20/20	20/25	7600	7944	0.20	0.11
14436	Cys759Phe (13)	IVS29+2T>C (129)	43	20/20	20/40	12170	12186	23.50	20.60
14483	Cys759Phe (13)		38	20/20	20/20	6934	6403	29.40	23.50
06966	Cys759Phe (13)		44	20/30	20/30	4245	4077	11.69	8.06
05666	Cys759Phe (13)		44	20/20	20/20	9554	9787	1.20	1.90
03458	Cys759Phe (13)	Glu4671fs (64)	34	20/25	20/25	4703	4488	NA	NA
15221	Cys759Phe (13)		34	20/20	20/20	8843	8927	7.79	11.40
19431	Cys759Phe (13)		21	20/30	20/30	15970	16092	19.6	18.2
06191	Cys759Phe (13)		33	20/30	20/30	2751	3039	0.09	0.21
05917	Cys759Phe (13)		38	20/20	20/25	17802	20246	5.08	4.99
05907	Cys759Phe (13)		35	20/25	20/25	5312	4899	1.89	1.32
07008	Cys759Phe (13)		43	20/60	20/100	196	231	0.16	0.13
06898	Cys759Phe (13)		40	20/30	20/30	9763	9364	1.13	2.62
05967	Cys759Phe (13)		33	20/20	20/20	402	583	1.21	0.77
03753	Cys759Phe (13)		33	20/30	20/50	12960	10952	59.0	59.0
02874	Cys759Phe (13)		33	20/25	20/25	10191	10172	6.00	6.00
07065	Cys759Phe (13)		45	20/30	20/30	16342	17005	6.25	6.12
00220	Cys759Phe (13)		40	20/25	20/20	10102	9972	NA	NA
05377	Cys759Phe (13)		41	20/25	20/30	8560	9000	14.0	8.40
06144	Cys759Phe (13)		38	20/30	20/25	1572	490	0.33	0.18
06210	Cys759Phe (13)		37	20/50	20/60	2555	1449	1.80	2.08
06732	Cys759Phe (13)		32	20/30	20/30	175	227	3.41	2.54
07879	Cys759Phe (13)		45	20/40	20/30	3148	3377	23.5	11.00
13613	Cys759Phe (13)		26	20/25	20/25	98	733	1.30	2.50
11259	Cys759Phe (13)		28	20/20	20/20	6154	8217	1.40	5.04
11505	Cys759Phe (13)		25	20/25	20/25	8759	7407	1.50	0.52
05011	Cys759Phe (13)		33	20/20	20/20	11992	10804	11.00	21.0

ID	Mutation (Exon)	Mutation (Exon)	Age	VA OD*	VA OS*	VF OD [†]	VF OS [†]	ERG OD [‡]	ERG OS [‡]
13115	Cys759Phe (13)		44	20/20	20/20	8155	9740	1.20	1.90
14027	Cys759Phe (13)		32	20/25	20/20	13887	12868	23.50	23.50
02726	Cys759Phe (13)		55	20/30	20/30	7391	6701	11.00	11.00
02943	Cys759Phe (13)		23	20/30	20/25	9294	8715	NA	NA
02954	Cys759Phe (13)		45	20/20	20/20	1001	1460	NA	12.0
00994	Cys759Phe (13)		36	20/40	20/50	366	264	NA	NA
15169	Glu767fs (13)		17	20/25	20/25	7686	8028	0.35	0.21
11451	Glu767fs (13)		27	20/20	20/20	9997	10274	1.19	1.40
22045	Glu767fs (13)		27	20/50	20/50	6141	4992	1.87	NA
02265	Glu767fs (13)	Gln4960fs (68)	17	20/25	20/50	5415	5654	NA	NA
02267	Glu767fs (13)	Cys1447fs (20)	16	20/25	20/30	7430	7106	NA	NA
02266	Glu767fs (13)	Cys1447fs (20)	15	20/20	20/20	10467	9806	62.0	NA
19249	Glu767fs (13)	Arg1549X (22)	22	20/20	20/20	3802	2508	0.80	0.53
15499	Glu767fs (13)	Arg2853X (42)	24	20/30	20/30	6201	7648	0.80	0.88
05958	Glu767fs (13)		37	20/30	20/30	12011	12341	8.00	8.00
11300	Glu767fs (13)	IVS29+1G>C (129)	45	20/40	20/40	290	523	0.20	0.20
19281	Glu767fs (13)	IVS61+2A>G (161)	44	20/25	20/20	3329	1618	2.35	1.91
06991	Glu767fs (13)		40	20/25	20/30	9672	12803	0.96	0.93
06724	Glu767fs (13)		31	20/40	20/40	12591	11592	1.10	0.92
05148	Glu767fs (13)		40	20/30	20/200	8558	7642	2.72	1.79
15297	Glu767fs (13)		45	20/60	20/25	11342	10503	5.87	4.56
15375	Glu767fs (13)		47	20/25	20/25	11456	11815	1.98	1.44
06704	Glu767fs (13)		24	20/30	20/40	10999	7670	35.9	34.2
06750	Glu767fs (13)		32	20/30	20/40	3447	2591	4.32	4.02
06178	Glu767fs (13)		36	20/40	20/25	650	881	0.56	0.48
06226	Glu767fs (13)		26	20/30	20/30	8477	9762	1.25	1.42
06256	Glu767fs (13)	Arg1549X (22)	27	20/25	20/30	3900	4100	0.31	0.33
06650	Glu767fs (13)		33	20/20	20/25	13164	11544	1.62	1.81
06666	Glu767fs (13)		23	20/25	20/25	944	888	0.51	0.85
05751	Glu767fs (13)		23	20/30	20/20	5306	5518	0.32	0.47
06017	Glu767fs (13)		31	20/25	20/25	4705	3610	5.37	4.65
05916	Glu767fs (13)		39	20/30	20/30	4140	5787	1.96	1.96
03960	Glu767fs (13)		17	20/40	20/30	11182	10842	1.04	0.77
06798	Glu767fs (13)		32	20/25	20/25	14005	15158	2.05	1.38
05556	Glu767fs (13)		19	20/25	20/25	11028	15047	0.35	0.35
05213	Glu767fs (13)		15	20/20	20/20	7774	8778	1.05	1.08
02130	Glu767fs (13)		21	20/20	20/25	3122	3561	0.94	0.94
07031	Glu767fs (13)		26	20/30	20/40	14551	13448	1.15	0.77
02510	Glu767fs (13)		26	20/30	20/25	565	2407	6.00	6.00
03193	Glu767fs (13)		28	20/20	20/20	638	690	NA	NA
05800	Glu767fs (13)		42	20/50	20/50	1798	2151	0.22	0.34
05785	Glu767fs (13)		27	20/30	20/25	14130	17982	3.52	3.07
07401	Glu767fs (13)		39	20/40	20/30	283	332	0.16	0.16
05252	Glu767fs (13)	Arg4935X (68)	42	NA	NA	9897	9504	NA	NA
14015	Glu767fs (13)		25	20/20	20/20	9755	10317	17.60	20.60
01445	Glu767fs (13)		54	20/30	20/30	10561	10759	0.25	0.67
15938	Glu767fs (13)		29	20/30	20/40	7220	7556	0.74	0.60
15579	Glu767fs (13)		31	20/25	20/25	8868	6637	1.12	0.87
19822	Glu767fs (13)		52	20/40	20/60	168	138	0.14	0.11
05766	Leu921fs (13)		30	20/25	20/20	973	1400	0.49	0.68
15285	Gln1063fs (16)		22	20/25	NA	6457	4376	NA	NA
05960	Gln1408X (19)	Cys1447fs (20)	33	20/25	20/25	3974	5820	NA	NA
07916	Ile1439fs (20)	Trp2945X (44)	30	20/20	20/20	NA	NA	0.50	0.70
04129	Cys1447fs (20)		6	20/40	20/30	10261	11787	NA	NA
04032	Cys1447fs (20)		7	20/40	20/30	4839	4754	NA	NA
03482	Cys1447fs (20)		19	20/30	20/30	10576	11651	NA	NA

ID	Mutation (Exon)	Mutation (Exon)	Age	VA OD*	VA OS*	VF OD†	VF OS‡	ERG OD‡	ERG OS‡
06241	Cys1447fs (20)		36	20/30	20/30	13131	7372	11.96	12.59
07607	Cys1447fs (20)	Arg4935X (68)	15	20/20	20/20	10117	10547	NA	1.40
11719	Cys1447fs (20)	Cys1447fs (20)	27	20/25	20/25	9121	9317	1.10	1.10
06019	Cys1447fs (20)		40	20/50	20/50	489	421	0.10	0.12
06088	Arg1504fs (21)		20	20/25	20/25	1572	1410	0.20	0.30
03811	Arg1549X (22)		31	20/30	20/40	2925	3961	NA	NA
05857	Met1731fs (26)		39	20/70	20/100	14753	14331	3.14	2.50
07278	Gln2057X (32)		22	20/20	20/30	8943	10503	0.60	0.20
05558	Ser2498fs (40)		34	20/25	20/30	11524	10354	3.02	2.42
14888	Arg2723X (41)	Arg2723X (41)	43	20/400	20/80	186	172	0.10	NA
00943	Arg2723X (41)		36	20/50	HM	234	198	0.17	0.10
03541	Gly3142X (48)		29	20/30	20/25	434	347	NA	NA
04132	Lys3397fs (52)	IVS28+1G>A (128)	30	HM	20/50	NA	8261	NA	NA
14402	Gln3845X (59)	Gln3845X (59)	18	20/30	20/25	4605	3266	0.23	0.16
05765	Trp3955X (61)		24	20/30	20/50	110	129	0.29	0.33
14518	Gln4711X (64)		22	20/20	20/25	12843	13452	4.90	3.60
		Arithmetic mean	31.6	20/28	20/29	7003	6987	5.91	5.50
		Number of patients with values	125	124	123	120	121	105	104

Parentheses enclosing an “T” designate “intron”.

* Measured with a projected Snellen chart.

† Visual field area in deg² to the V4e white stimulus of the Goldmann perimeter (normal ≥ 11310 deg²).

‡ ERG amplitude in μV to 30 Hz white full-field stimulation (normal ≥ 50 μV).

“NA” = not available.

Table 3Annual Rates of Change in Patients with *USH2A* Mutations

Ocular Function	N*	Mean $\pm$ SEM (geometric mean) [†]	P-value [†]
Log _e Visual Acuity	102	-0.026 $\pm$ 0.002 (-2.6%)	< 0.001
Log _e Visual Field Area	109	-0.074 $\pm$ 0.003 (-7.0%)	< 0.001
Log _e ERG Amplitude	69	-0.141 $\pm$ 0.005 (-13.2%)	< 0.001

* After censoring data to minimize ceiling and floor effects and preserve a follow-up $\geq$ 3 years (see Methods for details).

[†] Calculated by longitudinal regression using PROC MIXED of SAS.