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Visual Acuity, Full-field Stimulus Thresholds, and Electroretinography for 4 Years in The Rate of Progression of USH2A-related Retinal Degeneration (RUSH2A) Study

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Purpose: To describe progression of best-corrected visual acuity (BCVA), full-field stimulus thresholds (FST), and electroretinography (ERG) over 4 years in the *USH2A*-related Retinal Degeneration study and to assess their suitability as clinical trial endpoints.

Design: Prospective natural history study.

Participants: Participants (n = 105) with biallelic disease-causing sequence variants in USH2A and BCVA letter scores of ≥54 were included.

Methods: BCVA, FST, fundus-guided microperimetry, static perimetry, and spectral domain OCT were performed annually and ERG at baseline and 4 years only. Mixed effects models were used to estimate annual rates of change with 95% confidence intervals. Associations of change from baseline to 4 years between BCVA, FST, ERG, and other metrics were assessed with Spearman correlation coefficients (r_s).

Main Outcome Measures: Best-corrected visual acuity, FST, and ERG.

Results: The annual rate of decline in BCVA was 0.83 (95% confidence interval: 0.65−1.02) letters/year. For FST, the change was 0.09 (0.07−0.11) log cd.s/m^2/year for white threshold, 0.10 (0.08−0.12) log cd.s/m^2/year for blue threshold, and 0.05 (0.04−0.06) log cd.s/m^2/year for red threshold. Changes were 22.6 (17.4−28.2)%/year for white threshold, 26.0 (20.3−32.1)%/year for blue threshold, and 12.3 (8.7−16.0)%/year for red threshold. The high percentage of eyes with undetectable ERGs at baseline limited assessment of change.

Conclusions: Best-corrected visual acuity was not a sensitive measure of progression over 4 years. Full-field stimulus threshold was a more sensitive measure; however, additional information on the clinical relevance of changes in FST is needed before this test can be adopted as an endpoint for clinical trials.

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Supplemental material available at www.ophthalmologyscience.org.

Variants in the *USH2A* gene are among the most common causes of inherited retinal degenerations.[1−3] They are the most common variants found in patients with Usher syndrome type 2, and among patients with nonsyndromic autosomal recessive retinitis pigmentosa (ARRP), 12% to 19% have one or more likely pathogenic sequence variants in *USH2A*.[4,5] The Rate of Progression of *USH2A*-related Retinal Degeneration (RUSH2A) Study was a multicenter, international, longitudinal, observational study to monitor disease progression by collecting data from multiple visual functional and structural measures over 4 years.[6]

Three of these measures are of particular interest due to their widespread use in current gene therapy trials for retinitis pigmentosa (RP) and other retinal dystrophies. Impaired visual acuity (VA) is consistently associated with decreased quality of life, including reduced ability to perform activities of daily living, work, and drive safely, as well as increased risk of falls and other unintentional injuries.[7−11] The full-field stimulus threshold (FST) reflects the response of photoreceptors with the greatest dark-adapted (DA) sensitivity, and FST chromatic threshold measures can identify the receptor type mediating visual

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perception.[12,13] Although the range of light detection thresholds among patients covers a range of up to 7 log units,[14] the test-retest repeatability has been reported to range from 0.28 to 0.4 log cd.s/m^2.[12,15–18] In patients with *RPE65*-related Leber congenital amaurosis treated with voretigene neparvovec-rzyl, FST thresholds showed an improvement of up to 4.0 log units.[19,20] Full-field stimulus threshold thresholds have also been shown to be correlated with ellipsoid band width and with hyperautofluorescent ring diameter in RP.[21] The full-field electroretinogram (ERG) is commonly used in the assessment of patients with inherited retinal degenerations. However, previous studies in patients with *USH2A*-associated RP have found undetectable rod responses and greatly reduced cone responses by young adulthood.[22,23] Here, we analyze the data collected over the 4-year RUSH2A study to describe the progression of visual acuity, FST, and ERG over time.

Methods

Study Design

The RUSH2A study design has been described previously (NCT03146078).[6] Briefly, 127 participants were enrolled between August 2017 and December 2018 at 16 clinical sites in Europe and North America. The study adhered to the tenets of the Declaration of Helsinki and was approved by the ethics boards or institutional review boards associated with each participating site. Informed consent was obtained from all participants before enrollment.

Participants were ≥8 years old with a clinical diagnosis of rod-cone degeneration associated with ≥2 disease-causing *USH2A* sequence variants in trans. A committee reviewed all genetic reports to confirm the variants as pathogenic or likely pathogenic. An audiologist assessed the history of hearing loss and baseline audiology tests to determine a clinical diagnosis of either Usher syndrome type 2 (USH2) or nonsyndromic ARRP. Most of the testing was performed in the "study" eye, defined as the eye with better baseline BCVA. The primary cohort included 105 participants with a baseline ETDRS[24] letter score of 54 or greater (20/80 or better) in the better eye, central visual field ≥10 degrees diameter, and stable fixation. A secondary cohort of 22 participants with worse visual function was enrolled to complete a baseline visit only. The primary cohort was scheduled to be tested annually for 4 years after the baseline visit.[25]

Outcome Measures

Best-corrected visual acuity was measured in each eye once per visit by study-certified personnel using standard protocols for refraction and test administration.[26] The ETDRS eye charts or the electronic visual acuity, shown to be equivalent to the charts[27] were used, with results recorded as the ETDRS letter score.

Full-field stimulus thresholds were determined using the Espion E^3 system (Diagnosys LCC).[28] Only participants enrolled at sites with that equipment had the test done. White, blue, and red stimuli were used for FST testing in a Ganzfeld dome, with the value of 0 decibels (dB) set as 0.1 cd.s/m^2 (−1.0 log cd.s/m^2). Thus, FST thresholds reported in log cd.s/m^2 were converted from dB using this formula: log cd.s/m^2 = dB/10−1.0. Thresholds were measured in triplicate for each color at each visit, and the averaged result from the 3 tests was used for each color to determine the photoreceptor type mediating threshold. No children were disqualified because of not being able to do FST in the RUSH2A study; the youngest participant enrolled (age 14 years) completed the FST testing. The type of photoreceptor mediation was classified using 2 sets of criteria. The first was based on the lower limit for cone mediation of the white stimulus, which was −4.0 log cd.s/m^2.[28] That is, any threshold below −4.0 log cd.s/m^2 [equivalent to a threshold of −30 dB in the previous paper[28]] was considered to be mediated by rods. The second was based on the difference in FST blue threshold and red threshold (blue-red threshold) indicating rod-mediated (difference >2.0 log cd.s/m^2), mixed (difference between 1.0 and 2.0 log cd.s/m^2), or cone-mediated (difference <1.0 log cd.s/m^2) sensitivity.[12,28]

Full-field ERG was performed at study baseline and 4 years following the International Society for Clinical Electrophysiology of Vision protocol.[28] The ERG measures in the current analyses included the amplitudes of the b-wave from the DA dim-flash 0.01 cd.s/m^2 ERG response (DA 0.01 ERG), the amplitudes of the b-wave from the DA standard flash 3.0 cd.s/m^2 ERG response (DA 3.0 ERG), and the trough-to-peak amplitude of the light-adapted (LA) 30 Hz flicker (3.0 flicker ERG).[6] If the site investigators determined that the ERG responses were undetectable or too low at baseline, ERG was not performed at the year 4 visit. For this report, undetectable ERGs were defined as b-wave amplitude <1.0 μV for DA 0.01 ERG and DA 3.0 ERG, and <0.3 μV for LA 3.0 flicker ERG.

Additional Testing in RUSH2A

Fundus-guided mesopic microperimetry (MP) was performed with a custom 89-point grid using the Macular Integrity Assessment (MAIA-2) unit (iCare) and summarized by mean sensitivity.[29] The ellipsoid zone (EZ) area and central subfield thickness were derived from spectral domain OCT volume scans using a Heidelberg Spectralis HRA + OCT unit (Heidelberg Engineering GmbH). Ellipsoid zone area was provided by a reading center after manually correcting individual segmented B-scans to determine EZ width on each of 121 scans.[29] Static perimetry (SP) was performed using the Octopus 900 (Haag-Streit).[6]

Statistical Methods

The analysis cohort for this report is defined as the study eyes that have test results for ≥2 of the 5 time points (baseline and 1−4 years). One hundred three study eyes of the 105 participants in the primary cohort met the above criterion for BCVA. Because FST was measured in only selected clinical centers, 77 study eyes were included in the FST analyses. Although ERG testing was performed in all clinical centers, only 45 study eyes were included in the ERG analyses because testing was not performed at the year 4 visit for 48 eyes of the 93 participants who completed a year 4 visit. Electroretinogram testing was not required if no detectable ERG was found on a prior visit.

The distributions of BCVA, FST, and ERG measures at each visit were summarized using means, standard deviations (SDs), medians, interquartile ranges (IQRs), and ranges. Mixed effects regression models with a random intercept were used to estimate the annual rates of change with 95% confidence intervals. Time was calculated as the number of days from baseline divided by 365.25.

A model that down-weighted outlier rates of change was also used. For the outlier down-weighted model, first the rate of decline for each participant was calculated from a simple linear regression model, then a robust regression model using M-estimation with a Huber weighting function[30,31] was used to calculate the weight to be applied in the mixed effect model for each eye (Figs S1A and B, available at www.ophthalmologyscience.org). Absolute rates of

change from random intercept models were converted into percentage rates of change using the following equations.

For visual acuity,

$$\%change\ in\ MAR = 100 \times \left(10^{-0.02\delta} - 1\right)$$

where MAR is minimum angle of resolution and δ = estimated annual change in BCVA letter score.

For FST,

$$\%change\ in\ cd.s/m^2 = 100 \times (10^{\Delta} - 1)$$

where Δ = estimated annual change in log cd.s/m^2. Seven baseline factors (BCVA, clinical diagnosis, age, duration of disease, sex, smoking history, and use of dietary supplements) were assessed for their effect on rate of change by including an interaction term between each baseline factor and time from baseline visit in the models (equal weight per eye) in addition to the main effects of baseline factor and time, with adjustment for baseline level of the outcome and interaction between baseline level of the outcome and time. The coefficient of repeatability (CoR) for each FST measure was calculated using the baseline FST data, and the proportion of study eyes that had changed exceeding the corresponding CoR from baseline to 4 years was reported.[32]

The correlation between change in BCVA, FST, and ERG measures and with change in other measures (OCT, MP, and SP) from baseline to 4 years was assessed with Spearman correlation coefficients. To assess disease symmetry, correlation between the study eye and the nonstudy eye of each participant was assessed by change in BCVA letter scores using Spearman correlation coefficients (r_s).

All analyses were conducted using SAS version 9.4 (SAS Institute), and reported *P* values are 2-sided.

Results

Study Population

Among the 103 participants with BCVA data, the clinical diagnosis was Usher syndrome type 2 (USH2) for 64 (62%) participants and ARRP for 39 (38%) participants. The mean age was 37 years (SD, 12), and 58 (56%) were female. For age of enrollment, 35% were <35 years, 35% were between 35 and 45 years, and 30% were ≥45. For duration of disease, 29% were <10 years, 37% were 10 to 19 years, and 34% were ≥20 years. Median duration of disease at enrollment was 12 years (IQR, 7−20).[25] Demographic characteristics were similar in the FST participants (N = 77). For ERG group (N = 46), the clinical diagnosis was USH2 for 25 (54%) participants and ARRP for 21 (46%) participants; age and duration of disease distribution were similar to the BCVA group, and 23 (50%) were female. Two of the 105 primary cohort participants died during the follow-up period. Visit completion rates for living participants were 102/104 (98%) at 1 year, 88/104 (85%) at 2 years, 99/104 (95%) at 3 years, and 95/103 (92%) at 4 years. Many of the missed visits at 2 years were attributable to the suspension of clinical research studies during the coronavirus disease 2019 pandemic.

BCVA Outcome

Figure 2A provides a trajectory plot of BCVA values for each study eye vs. the duration of disease at each visit, showing an overall downward trend over time but with some eyes showing increases (improvements up to 16 letters) between adjacent measurements. The average BCVA for study eyes was 81 (SD, 7) letters at baseline, 79 (SD, 8) letters at year 1, 80 (SD, 7) letters at year 2, 78 (SD, 9) letters at year 3, and 78 (SD, 8) letters at year 4 (Table 1). For nonstudy eyes (the worse-seeing eyes), the average BCVA was stable at approximately 76 letters over the 4-year follow-up period. The Snellen equivalent of visual acuity letter scores from 74 to 83 is 20/32−20/25.

The estimated annual rates of change in BCVA in the study eye based on mixed models are shown in Table 2. The average decline of BCVA score [N = 103] was 0.83 (95% confidence interval, 0.65, 1.02) letters/year, which is equivalent to a 3.9 (3.1, 4.8)%/year increase (worsening) in minimal angle of resolution, based on a model with equal weight for each participant. The estimated decline of visual acuity based on a model with down-weighted outliers was slightly less than the equally weighted model, with a decline of 0.80 (0.62, 0.97) letters/year, or 3.7 (2.9, 4.6)%/year increase in minimal angle of resolution. The annual rate of change for BCVA was significantly associated with disease duration at baseline: for every 10 years of increase in disease duration, the rate of decline increased by 0.22 letters/year (P = 0.02) (Table S3, available at www.ophthalmologyscience.org).

Among the 95 study eyes of participants who had BCVA data at both baseline and the year 4 visit, BCVA letter score increased by ≥5 (one line) letters in 2 (2%), remained stable (change between −4 and +4 letters) in 57 (60%) and decreased by ≥5 letters in 36 (37%). Best-corrected visual acuity changes from study and nonstudy eyes are contrasted in Table 4 and Figure 3. The mean (SD) change in BCVA from baseline to 4 years was −3.6 (4.3) letters in study eyes versus −0.8 (5.5) letters in nonstudy eyes. There was a moderate correlation in BCVA change between the study and nonstudy eyes, with a Spearman correlation coefficient of 0.57 (P < 0.001) (Fig 3). Less than one line (5 letters) of change (increase or decrease) was present in 57 (60%) of study eyes versus 61 (64%) of nonstudy eyes, and <2 lines of change was present in 87 (91%) of study eyes versus 90 (95%) of nonstudy eyes (Table 4).

Change in BCVA letter score from baseline to 4 years was not correlated with change in FST, ERG, other functional metrics (MP mean retinal sensitivity, SP visual fields, and mean sensitivity), or with structural measures based on OCT (EZ area and central subfield thickness), with r_s ranging from −0.30 to 0.04 (P values ranging from 0.08 to 1.0).

FST Outcomes

Figure 2B provides a trajectory plot of FST white threshold for each study eye versus the duration of disease at each visit, showing an overall upward (worsening) trend over time; however, some eyes had decreases (improvement up to 1.30 log cd.s/m^2) between adjacent measurements. The average FST white threshold was −4.29 (SD, 1.24) log cd.s/m^2 at study baseline, −4.15 (SD, 1.21) log cd.s/m^2 at

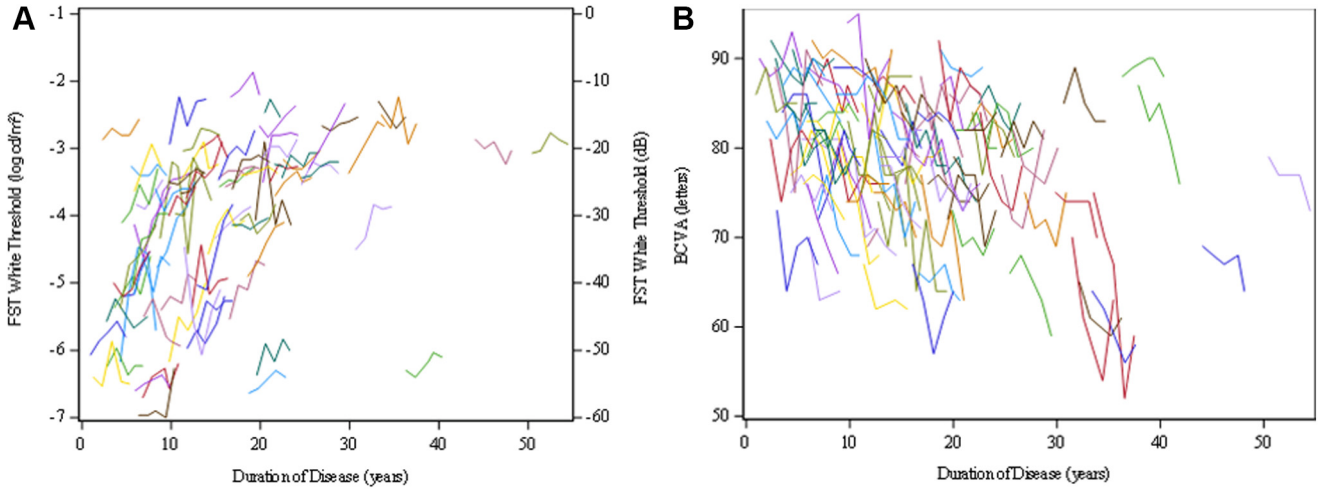

Figure 2. BCVA (A) and FST (B) measures by duration of disease for study eyes of individual patients. BCVA = best-corrected visual acuity; FST = full-field stimulus threshold.

year 1, −3.98 (SD, 1.21) log cd.s/m^2 at year 2, −4.04 (SD, 1.20) log cd.s/m^2 at year 3, and −4.04 (SD, 1.22) log cd.s/m^2 at year 4. The average blue threshold was −4.76 (SD, 1.39) log cd.s/m^2 at study baseline, −4.64 (SD, 1.39) log cd.s/m^2 at year 1, −4.46 (SD, 1.38) log cd.s/m^2 at year 2, −4.47 (SD, 1.38) log cd.s/m^2 at year 3, and −4.50 (SD, 1.39) log cd.s/m^2 at year 4. The average red threshold was −3.58 (SD, 0.61) log cd.s/m^2 at study baseline, −3.52 (SD, 0.65) log cd.s/m^2 at year 1, −3.43 (SD, 0.60) log cd.s/m^2 at year 2, −3.43 (SD, 0.61) log cd.s/m^2 at year 3, and −3.43 (SD, 0.61) log cd.s/m^2 at year 4 (Table 1).

For FST measures (N = 77), the average annual rate of change was 0.09 (0.07−0.11) log cd.s/m^2/year for white threshold, 0.10 (0.08−0.12) log cd.s/m^2/year for blue threshold, and 0.05 (0.04−0.06) log cd.s/m^2/year for red threshold. On the linear scale (cd.s/m^2), the annual percentage rate of change was 22.7 (17.4−28.2)%/year for white threshold, 26.0 (20.3−32.1)%/year for blue threshold, and 12.3 (8.7−16.0)%/year for red threshold based on the equally weighted models. Compared with models that had equal weights for each participant, models that down-weighted outliers yielded nearly identical rates

Table 1. BCVA and FST Measures at Each Visit

Outcomes	Baseline	Year 1	Year 2	Year 3	Year 4
BCVA (study eye, letters)					
N	103	102	88	99	95
Mean ± SD	81 ± 7	79 ± 8	80 ± 7	78 ± 9	77 ± 8
Range	64 to 94	61 to 95	57 to 91	52 to 93	58 to 91
BCVA (nonstudy eye, letters)					
N	103	102	88	99	95
Mean ± SD	76 ± 8	77 ± 9	78 ± 7	76 ± 10	76 ± 9
Range	55 to 92	51 to 96	54 to 91	32 to 91	54 to 96
FST (study eye, log cd/m2)					
White Stimulus					
N	77	73	69	73	66
Mean ± SD	−4.29 ± 1.24	−4.15 ± 1.21	−3.98 ± 1.21	−4.04 ± 1.20	−4.04 ± 1.22
Range	−6.97 to −2.23	−6.97 to −2.13	−6.90 to −1.87	−7.00 to −2.20	−6.57 to −2.27
Blue Stimulus					
N	77	73	69	73	66
Mean ± SD	−4.76 ± 1.39	−4.64 ± 1.39	−4.46 ± 1.38	−4.47 ± 1.38	−4.50 ± 1.39
Range	−7.53 to −2.43	−7.53 to −2.47	−7.60 to −2.07	−7.67 to −2.23	−7.33 to −2.27
Red Stimulus					
N	77	72	69	73	66
Mean ± SD	−3.58 ± 0.61	−3.52 ± 0.65	−3.43 ± 0.60	−3.43 ± 0.61	−3.43 ± 0.61
Range	−5.23 to −2.13	−5.20 to −2.10	−5.07 to −2.10	−5.27 to −2.17	−5.17 to −2.20

BCVA = best-corrected visual acuity; FST = full-field stimulus threshold; SD = standard deviation.

Table 2. Estimated Annual Rates of Change in BCVA and FST Based on Random Intercept Models

	Change		%Change	
	Equally Weighted Model	*Outliers Down-Weighted**	*Equally Weighted Model*	*Outliers Down-Weighted**
BCVA (N = 103)	Change in letter score		%Change in MAR	
Slope estimate†	−0.83	−0.80	3.9	3.7
95% CI	(−1.02 to −0.65)	(−0.97 to −0.62)	(3.1 to 4.8)	(2.9 to 4.6)
FST (N = 77)	**Change in log cd/m^2**		**%Change in cd/m^2**	
White stimulus				
Slope estimate†	0.09	0.09	22.6	22.3
95% CI	(0.07 to 0.11)	(0.07 to 0.11)	(17.4 to 28.2)	(17.3 to 27.4)
Blue stimulus				
Slope estimate†	0.10	0.09	26.0	24.3
95% CI	(0.08 to 0.12)	(0.08 to 0.11)	(20.3 to 32.1)	(19.4 to 29.5)
Red stimulus				
Slope estimate†	0.05	0.05	12.3	11.6
95% CI	(0.04 to 0.06)	(0.03 to 0.06)	(8.7 to 16.0)	(8.3 to 15.0)

BCVA = best-corrected visual acuity; CI = confidence interval; FST = full-field stimulus threshold; MAR = minimal angle of resolution.
*Outliers were down-weighted in weighted mixed-effects model, weights were computed from robust regression modeling of the estimated rate of decline from each participant.
†All *P* values for testing the slope estimates against zero were < 0.001.

of change in log cd.s/m^2 and slightly lower rates for the percentage change in cd.s/m^2 (Table 2).

When baseline characteristics were examined for their association with the annual rates of change for FST measures, 3 characteristics were identified. The eyes with the worst FST baseline values had the smallest rate of change for both blue ($P = 0.004$) and red ($P = 0.02$) thresholds (Table S3, available at www.ophthalmologyscience.org). Greater rates of worsening were associated with younger enrollment age for white ($P = 0.02$) and blue ($P = 0.001$) thresholds (Table S3, available at www.ophthalmologyscience.org). The annual rate of change for FST white threshold was 0.11 log cd.s/m^2/year among rod-mediated eyes at baseline (mediation determined by white stimulus criteria) and was 0.07 log cd.s/m^2/year among cone-mediated eyes at baseline ($P < 0.001$).

Changes in the 3 FST measures from baseline to 4 years were correlated with each other (r_s between 0.40 and 0.74; all $P \leq 0.01$). Change in FST white threshold ($r_s = 0.64$, $P = 0.002$) and FST blue threshold ($r_s = 0.43$, $P = 0.06$) were correlated with change in DA 3.0 ERG b-wave amplitude. Change in FST blue threshold was significantly correlated with change in MP mean sensitivity ($r_s = -0.37$, $P = 0.006$) and change in LA 3.0 flicker ERG b-wave amplitude ($r_s = 0.50$; $P = 0.02$). Changes in FST measures were not significantly correlated with changes in other functional metrics (BCVA, SP mean sensitivity) or structural measures based on OCT (EZ area and central subfield thickness), with r_s ranging from −0.30 to 0.43 (*P* values ranging from 0.05 to 0.86).

There were 66 eyes that had FST testing at both the baseline and year 4 visits. When classified based on the white stimulus criteria, 10 (27%) of the 37 eyes that had rod-mediated thresholds at baseline progressed to cone mediation at year 4, and all 29 that were cone-mediated at baseline remained cone-mediated (Table S5A, available at www.ophthalmologyscience.org). When classified based on the blue-red threshold difference (Table S5B, available at www.ophthalmologyscience.org), 5 (20%) of 25 eyes that were rod-mediated at baseline became mixed, and 1 (4%) became cone-mediated; 6 (43%) of 14 eyes that were mixed at baseline became cone-mediated; and all 27 with cone-mediated responses at baseline remained cone-

Table 4. Change from Baseline to 4 Years in Best-Corrected Visual Acuity for Study and Nonstudy Eyes

		Nonstudy Eye Change in Letters					
Study Eye Change in Letters	**Decrease ≥15**	*Decrease 10−14*	*Decrease 5−9*	*Change <5*	*Increase 5−9*	*Increase ≥15*	*Total*
Decrease ≥15	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)
Decrease 10−14	1 (1%)	3 (3%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)	6 (6%)
Decrease 5−9	0 (0%)	1 (1%)	12 (13%)	15 (16%)	0 (0%)	0 (0%)	28 (29%)
Change <5	0 (0%)	0 (0%)	3 (3%)	44 (46%)	9 (9%)	1 (1%)	57 (60%)
Increase 5−9	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	2 (2%)
Total	1 (1%)	4 (4%)	17 (18%)	61 (64%)	11 (12%)	1 (1%)	95 (100%)

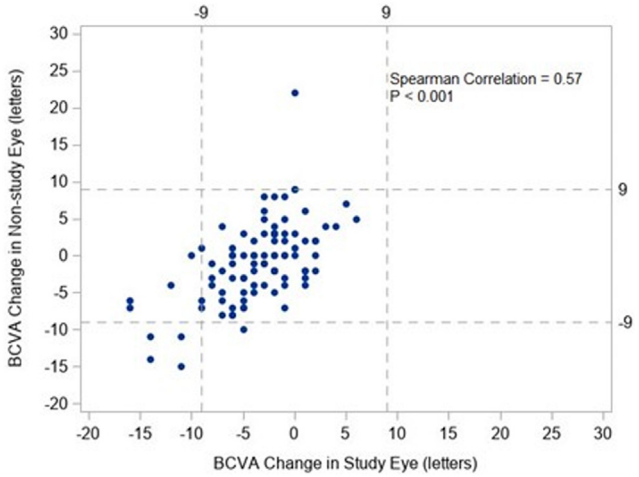

Figure 3. Scatter plot for changes in BCVA measures from baseline to 4 years among nonstudy eyes vs. study eyes. BCVA = best-corrected visual acuity.

mediated. Full-field stimulus threshold white and blue thresholds had a similar CoR of 0.39 to 0.40 log cd.s/m^2. For FST white, 31 (47%) study eyes had threshold increase (worsening) from baseline to year 4 exceeding the CoR of 0.39 log cd.s/m^2, and 2 (3%) had threshold decrease (improvement) exceeding the CoR. For FST blue, similar proportions of study eyes as for FST white had threshold change in each direction exceeding the CoR of 0.40 log cd.s/m^2. For FST red, 17 (26%) of study eyes had threshold worsening from baseline to year 4 exceeding the CoR of 0.34 log cd.s/m^2, and 1 (2%) had threshold improving exceeding the CoR (Table 6).

Participants with mixed rod and cone mediation defined by the difference in red and blue FST thresholds at baseline were more likely to be classified as rod-mediated by the white stimulus at baseline (13 participants rod-mediated vs. 2 participants cone-mediated). As sensitivity decreased by year 4, participants with mixed mediation based on red and blue FST thresholds were increasingly classified as cone mediated by the white stimulus (7 rod-mediated vs. 6 cone-mediated).

ERG Outcomes

Among the 95 eyes with an in-clinic visit at year 4, 22 had an undetectable ERG for all 3 tests at baseline and did not have ERG testing at year 4. An additional 20 did not have ERG testing due to investigator discretion or clinic error, and 6 did not have testing due to equipment or certified staff being unavailable. Among the 46 study eyes that had ERG testing at both baseline and year 4, 14 (30%) had undetectable DA 0.01 ERG at baseline, which increased to 17 (37%) at year 4. The number of eyes with undetectable DA 3.0 ERG increased from 3 (7%) at baseline to 9 (20%) at year 4, and, for LA 3.0 flicker ERG, the number increased from 2 (4%) at baseline to 6 (13%) at year 4 (Table 7). Among those eyes with detectable ERGs, the median (IQR) b-wave amplitude for DA 0.01 ERG was 16.8 (5.8−38.1) μV at baseline and 11.0 (5.8−26.3) μV at year 4. The median (IQR) b-wave amplitude for DA 3.0 ERG was 16.0 (5.8−65.0) μV at baseline and 14.7 (4.2−46.0) μV at year 4, with an increase in undetectable signals from 7% to 20%.The median (IQR) b-wave amplitude for LA 3.0 flicker ERG was 9.6 (2.6−22.7) μV at baseline and 6.7 (3.0−16.8) μV at year 4. Over the 4 years of study, median (IQR) change in b-wave amplitude was −12.2 (−17.0 to −0.3) μV for DA 0.01 ERG, −11.2 (−27.6 to −0.6) for DA 3.0 ERG, and −1.9 (−8.0 to 1.0) μV for LA 3.0 flicker ERG. The median implicit time was 99 to 97 msec for DA 0.01 ERG, 58 to 59 msec for DA 3.0 ERG, and 36 to 35 msec for LA 3.0 flicker ERG at study baseline and 4 years. DA 3.0 ERG b-wave amplitude was significantly correlated with FST white threshold ($r_s = 0.64$; $P = 0.002$).

Discussion

Best-corrected visual acuity tends to decrease slowly in most patients with USH2 and ARRP.[33,34] Therefore, reduced BCVA is often considered an indicator of advanced disease. The BCVA results presented here from participants with *USH2A* variants are consistent with the previous studies. Best-corrected visual acuity averaged 81 letters (20/25) at baseline. Because the average change in acuity in these participants was <1 letter/year, BCVA is not a sensitive measure of progression in these participants over a 4-year period. Best-corrected visual acuity values were stable from year to year and across eyes, with 92% of study eyes having <10 letters (2 lines) change in 4 years. The BCVA test has a CoR of 9 letters if VA is 20/100 or better or 13 letters if VA is worse than 20/100,[26,35] and in our cohort, none of the study eyes had BCVA improvement from baseline to Year 4 exceeding the CoR. Thus, an improvement in BCVA exceeding the CoR might be a useful measure for detecting a beneficial treatment effect for a treatment intended to restore or enhance function since no such improvement was observed with no treatment. However, improvement may have been unlikely in the study eyes, given that BCVA was better than 20/20 in 33% and better than 20/25 in 59% of participants at baseline.[28] Thus, the changes over 4 years might be different in *USH2A* populations with later stages of disease than were included in the RUSH2A study.

We found that approximately 50% of RUSH2A had unmeasurable rod-mediated ERG responses at baseline. This is similar to previous reports of few patients with measurable responses beyond early adulthood.[22,23] Thus, ERG may not be a suitable measure for following patients with intermediate RP. Full-field stimulus threshold demonstrated better potential as a reliable measure of rod function.[28] The FST was measurable in all participants, correlated to rod ERG amplitude, and sensitive in detecting progression, with an average yearly worsening of the threshold of 22.7% in linear scale (cd.s/m^2) to a full-field white stimulus. The rate of change to the blue stimulus was similar to that of the white stimulus, consistent with many of these participants

Table 6. CoR for FST Measures

	FST White	FST Blue	FST Red
CoR (log cd/m^2)	0.39	0.40	0.34
Participants with FST increase greater than CoR at 4 years, *n* (%)	31 (47%)	27 (41%)	17 (26%)
Participants with FST decline greater than CoR at 4 years, *n* (%)	2 (3%)	1 (2%)	1 (2%)

CoR = coefficient of repeatability; FST = full-field stimulus threshold.

retaining some rod function when fully DA. The average yearly worsening of the threshold for the red stimulus was smaller at 12.3%, consistent with predominantly cone-mediation. The greater changes observed in response to blue and white stimuli compared to red stimuli suggest that rod function changed more over 4 years than cone-mediated function and support the use of measures that can delineate rod function, such as FST, to monitor disease progression over 4 years in patients with *USH2A*-related retinal degeneration.

The 95% confidence intervals for the FST slope estimates were fairly narrow, suggesting that changes in FST were relatively consistent across eyes and that participants were able to perform this test with low variability. This is consistent with a CoR of 0.28-0.4 log cd.s/m^2 for test-retest measures.[12,14–18] For the FST white threshold, 31 (47%) study eyes had change from baseline to year 4 exceeding the CoR of 0.39 log cd.s/m^2. This proportion is much higher than that from BCVA, suggesting that FST is a more sensitive outcome measure compared to BCVA. Reasons for inter-visit stability could include a constant pupil size, a short (approximately 30 min after dark adaptation) test duration, and a salient full-field stimulus. Full-field stimulus threshold testing is easier for patients than other tests like MP. It was originally developed to determine visual function in low-vision children with conditions like Leber congenital amaurosis. Fixation is not required, and the full-field stimulus can be readily distinguished from the entoptic phenomena patients frequently perceive.

The utility of the test is also evidenced by the fact that no eyes reverted from cone photoreceptor mediation to rod mediation, while some eyes progressed toward cone mediation. The disadvantage of the FST is that it measures the threshold of the most sensitive region of the retina and is thus nonlocalizable.[13] Dark-adapted visual fields are arguably necessary for a more comprehensive, topographical assessment of rod function.[13]

The inclusion criteria for the primary cohort of the RUSH2A study included BCVA of 20/80 or better and a visual field diameter of 10 degrees or more in every meridian of the central field, resulting in a population of participants with syndromic (USH2) and nonsyndromic (ARRP) intermediate stage disease. In other cohorts, such as the patients with *RPE65*-related retinopathy, which initially predominantly affects rods, the FST has proven to be a valid indicator of treatment efficacy.[20,36] Mobility task thresholds across a cohort of Leber congenital amaurosis patients with substantial differences in disease severity showed a linear relationship to FST thresholds (slope = 0.92, r^2 = 0.87) but not to visual acuity.[37] Mobility task assessments have been shown to reflect real-world performance under various illumination levels.[8] Given that multi-luminance mobility tests can take several hours to perform, it is useful to know that FST is associated with functional vision performance in low illumination settings, at least in patients with *RPE65*-related retinal degeneration. Although the *USH2A* gene impacts both cones and rods, understanding FST changes in this cohort is potentially important.

Four years is a relatively short period for studying a disease process that progresses slowly over many decades of life. Longer-term follow-up of the RUSH2A study participants is planned. Longer follow-up will provide more precise assessments of change over time and will allow more precise investigation of differences in progression among subgroups based on such factors as age, duration, or genetic mutation. Additionally, longer follow-up may be helpful to assess the possible association of the observed FST changes with eventual functional vision changes.

Table 7. Full-Field ERG Measures at Baseline and 4 Years

Outcomes	Baseline (N = 46)	Year 4 (N = 46)
DA 0.01 ERG		
Undetectable, n (%)	14 (30%)	17 (37%)
B-wave amplitude (μV)	N = 32	N = 29
Median (IQR)	16.8 (5.8–38.1)	11.0 (5.8–26.3)
Range	1.2–163.6	1.2–133.4
Implicit time (msec)	N = 32	N = 29
Median (IQR)	99 (84–108)	97 (86–104)
Range	58–122	71–122
DA 3.0 ERG		
Undetectable, n (%)	3 (7%)	9 (20%)
B-wave amplitude (μV)	N = 43	N = 37
Median (IQR)	16.0 (5.8–65.0)	14.7 (4.2–46.0)
Range	1.2–189.1	1.3–168.2
Implicit time (msec)	N = 43	N = 37
Median (IQR)	58 (51–64)	59 (50–63)
Range	37–76	31–71
LA 3.0 Flicker ERG		
Undetectable, n (%)	2 (4%)	6 (13%)
B-wave amplitude (μV)	N = 44	N = 40
Median (IQR)	9.6 (2.6–22.7)	6.7 (3.0–16.8)
Range	0.6–82.2	1.2–48.4
Implicit time (msec)	N = 44	N = 40
Median (IQR)	36 (32–40)	35 (31–42)
Range	25–45	27–49

DA = dark-adapted; ERG = electroretinography; IQR = interquartile range; LA = light-adapted.

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Abbreviations and Acronyms:
ARRP = autosomal recessive retinitis pigmentosa; **BCVA** = best-corrected visual acuity; **CoR** = coefficient of repeatability; **DA** = dark-adapted; **dB** = decibels; **ERG** = electroretinography; **EZ** = ellipsoid zone; **FST** = full-field stimulus threshold; **IQR** = interquartile range; **LA** = light-adapted; **MP** = microperimetry; **RP** = retinitis pigmentosa; **RUSH2A** = Rate of Progression of USH2A-related Retinal Degeneration (RUSH2A) Study; **SD** = standard deviation; **SP** = static perimetry; **VA** = visual acuity.

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