Self-Reported Functional Vision in *USH2A*-Associated Retinal Degeneration as Measured by the Michigan Retinal Degeneration Questionnaire

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Purpose. The purpose of this study was to evaluate self-reported functional vision (FV) and the impact of vision loss in patients with *USH2A*-associated retinal degeneration using a patient-reported outcome (PRO) measure, the Michigan Retinal Degeneration Questionnaire (MRDQ), to correlate MRDQ scores with well-established visual function measurements.

Design. An observational cross-sectional study ($n = 93$) of participants who had Usher Syndrome Type 2 (USH2, $n = 55$) or autosomal recessive non-syndromic retinitis pigmentosa (ARRP; $n = 38$) associated with biallelic variants in the *USH2A* gene.

Methods. The study protocol was approved by all ethics boards and informed consent was obtained from each participant. Participants completed the MRDQ at the 48-month study follow-up visit. Disease duration was self-reported by participants. One-way ANOVA was used to compare subgroups (clinical diagnosis, age, disease duration, and full-field stimulus threshold [FST] Blue-Red mediation) on mean scores per domain. Spearman correlation coefficients were used to assess associations between MRDQ domains and visual/retinal function assessments.

Results. Of the study sample, 58% were female participants and the median disease duration was 13 years. MRDQ domains were sensitive to differences between subgroups of clinical diagnosis, age, disease duration, and FST Blue-Red mediation. MRDQ domains correlated with static perimetry, microperimetry, full-field stimulus testing, and best-corrected visual acuity (BCVA).

Conclusions. Self-reported FV measured by the MRDQ, when applied to USH2 and ARRP participants, had good distributional characteristics and correlated well with visual function tests. MRDQ adds a new dimension of understanding on vision-related functioning and establishes this PRO tool as an informative measure in evaluating *USH2A* outcomes.

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Keywords: *USH2A*, autosomal recessive retinitis pigmentosa (ARRP), Michigan retinal degeneration questionnaire (MRDQ), patient-reported outcome (PRO) tool, functional vision (FV)

Inherited retinal diseases (IRDs) are chronic eye conditions that can have a profound impact on self-reported functional vision (FV), especially as vision progressively and irreversibly declines.[1] According to the Global Retinal Inherited Disease (GRID) dataset, the *USH2A* gene is the second most common pathogenic variant in IRDs at 14.6%, following only behind ABCA4 (24.8%).[2,3] Pathogenic variants in the *USH2A* gene can cause Usher Syndrome Type 2 (USH2) and non-syndromic autosomal recessive retinitis pigmentosa (ARRP), both of which involve progressive rod photoreceptor loss and subsequent cone degeneration.[3,4] Although patients with USH2-associated auditory deficits may benefit from hearing aids or, in exceptional cases with profound deafness, cochlear implants, there are currently no US Food and Drug Administration (FDA)-approved treatments available for the associated retinopathy, leaving these patients with severe lifelong visual impairment.[3,5] To help assess the efficacy of current and future therapies, as well as to investigate the natural course of disease in a manner relevant to patient functioning, patient-reported outcomes (PROs) from reliable and validated questionnaires can be utilized to measure changes in FV.[6–8]

There have been several efforts to create vision-specific PRO instruments. One of the earliest PRO measures used in the study of eye diseases is the National Eye Institute Visual Function Questionnaire (NEI-VFQ); later, subsequent PRO measures became available including the Activity Inventory (AI), Daily Living Tasks Dependent on Vision (DLTV), and the Veterans Affairs Low-Vision Visual Functioning Questionnaire (VA LV VFQ).[8–11] However, in contrast to other more prevalent eye diseases, patients with IRDs have greater phenotypic variability as well as unique FV limitations. For example, PRO measures used in age-related macular degeneration or diabetic retinopathy do not have domains relevant to photosensitivity, peripheral vision loss, or color vision problems seen in those with retinal dystrophies.[7,9–11] Documenting these domains requires PRO tools specifically designed for and tested in target populations to capture the unique difficulties and patients' self-perceived feelings regarding their health and FV in these diseases.[1,8] The Michigan Retinal Degeneration Questionnaire (MRDQ) is a validated and psychometrically calibrated PRO instrument designed using the FDA guidelines to measure vision functioning in patients with rod-cone dystrophy, cone/cone-rod dystrophy, or macular dystrophy.[7] Patients being treated may perceive improvement in FV, making this PRO tool attractive for use in capturing self-reported patient functioning validly and reliably.[12,13] Conversely, a patient with possible changes in objective function and structural vision tests may not report FV changes using the PRO tool. The MRDQ helps evaluate patients' self-assessments of their FV and can provide an efficacy signal with respect to outcome measures in gene therapy clinical trials, something that has been lacking in recent trials that failed to meet primary end points.[6] Although the MRDQ does not have a composite score, it has domains of FV that segregate according to retinal function (e.g. color, contrast, and photopic peripheral) unlike other PRO instruments that segregate into social function domains (e.g. visual motor or visual processing).[7,14] In the MRDQ, each domain produces a level of disability ranging from −3 to +3 theta, with a higher score indicating greater disability, that is, severity in difficulties and limitations.[7]

In this study, we used the MRDQ to evaluate self-reported FV and the impact of vision loss in a cohort of patients with *USH2A*-associated retinal degeneration using the MRDQ. Additionally, we sought to correlate MRDQ scores with visual functional measures, such as best-corrected visual acuity (BCVA), full-field stimulus testing (FST), and visual fields (from static perimetry and microperimetry), and structural measures such as spectral domain optical coherence tomography (SD-OCT)-derived ellipsoid zone (EZ) area and central subfield thickness (CST) data.

Methods

Study Design

The Rate of Progression in *USH2A*-related Retinal Degeneration (RUSH2A) is registered on www.clinicaltrials.gov (NCT03146078) and the study methods have been described in previous publications.[15] The protocol and informed consent adhered to the tenets of the Declaration of Helsinki and were approved by the ethics boards of each participating institution. Participants were at least 8 years old, and had either pathogenic homozygous or compound heterozygous *USH2A* variants inherited in trans. The history of hearing loss and baseline audiology examinations of participants were reviewed by an audiologist, and a clinical diagnosis of either USH2 or ARRP was assigned accordingly.[15]

Patient Cohorts

The primary cohort ($n = 105$) included participants having at least one eye with baseline Early Treatment of Diabetic Retinopathy Study (ETDRS) BCVA letter score of 54 or more, stable fixation, and clinically determined kinetic visual field III4e diameter 10 degrees or greater in every meridian of the central field. The study eye was defined as the eye having better BCVA at baseline. They were tested annually for 4 years after the baseline visit. A secondary cohort of 22 participants with worse visual function was enrolled to complete a baseline visit only. For this report, only data at the 48-month visits were analyzed.

Outcomes

The 59-item MRDQ was verbally administered to participants in RUSH2A ≥ 18 years at the 48-month visit by site staff. It was completed in person or remotely any time within the 48-month visit window (208 ± 4 weeks). MRDQ domains and 59-items are listed in the initial publication.[7]

Clinical assessments of visual function and structure were made by study-certified personnel following standard protocols. Details of testing have been described in Supplementary Table S1 and prior publications.[16,17] In brief, BCVA was measured after refraction with the ETDRS charts or the electronic version of the test, static perimetry was performed with the Octopus 900 automated perimeter (Haag-Streit, Mason, OH, USA) using a 185-point grid, mesopic microperimetry was performed with the Macular

Integrity Assessment (MAIA-2) unit (iCare, Raleigh, NC, USA) using a 89-point grid, FST was performed with the Espion E3 device (Diagnosys LLC, Lowell, MA, USA), and OCT was performed with the Heidelberg Spectralis HRA + OCT unit (Heidelberg Engineering GmbH).

Statistical Analyses

A graded response model[7] was used to estimate FV scores for each participant within seven domains: central vision (questions = 11), color vision (questions = 4), contrast (questions = 7), scotopic (questions = 12), photopic peripheral (questions = 9), mesopic peripheral (questions = 9), and photosensitivity (questions = 7). The R score MRDQ package (R Foundation for Statistical Computing, Vienna, Austria) was used to calculate FV scores (θ) that quantified participant disability, where higher scores indicate greater disability.

FV score distributions were summarized using means, standard deviations (SDs), medians, interquartile ranges (IQRs), and ranges. The distribution of FV scores by clinical diagnosis and rod-cone mediation were summarized using box plots. Associations between age and disease duration with FV scores were tested using linear regression. One-way ANOVA was used to compare the mean scores by subgroup (clinical diagnosis and rod-cone mediation) in each domain. Tukey-Kramer methods were used to adjust for multiple pairwise comparisons. Association of FV scores with visual function measures at the 48-month visit were assessed with Spearman correlation coefficients.

All analyses (except calculating FV scores using a graded response model), were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Study Population

Ninety-eight participants completed the MRDQ questionnaire at the 48-month follow-up visit, but 3 participants were excluded from the analysis due to participation in treatment trials in the non-study eye, leaving 95 participants in the analysis cohort (Fig. 1). Mean age at enrollment of the analysis cohort was 38 years (SD = 13), median disease duration at enrollment was 13 years (IQR = 7 to 20 years), 55 were female participants (58%), and 84 (88%) reported their race as White. Clinical diagnosis was USH2 in 57 participants and ARRP in 38 participants (Table 1).

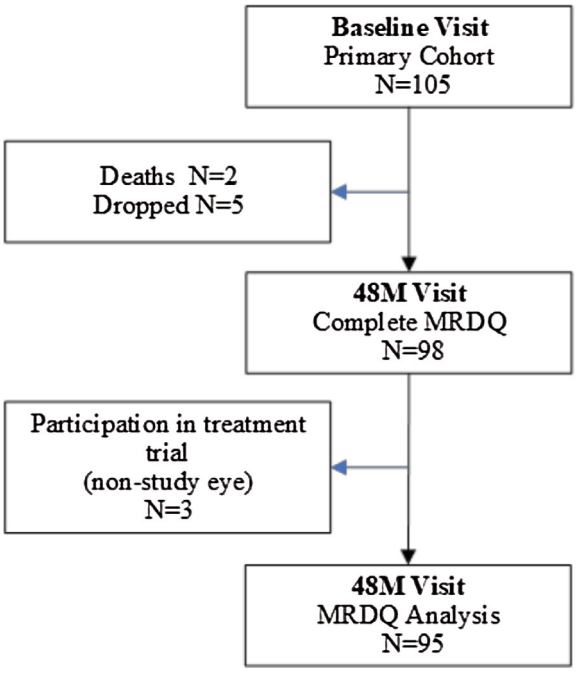

Figure 1. Flowchart of participants.

Table 1. Participant Characteristics at Baseline for the Analysis Cohort ($N = 95$)

	N (%)
Clinical diagnosis	
USH2	57 (60%)
ARRP	38 (40%)
Gender	
F	55 (58%)
M	40 (42%)
Race/ethnicity	
White	84 (88%)
Hispanic or Latino	8 (8%)
Asian	3 (3%)
Daily smoker ever	
Yes	25 (26%)
No	70 (74%)
Duration of disease at enrollment, y*	
<10	33 (35%)
10 to <20	37 (39%)
≥20	24 (25%)
Mean (SD)	15 (10)
Median (IQR)	13 (7 to 20)
Age at enrollment, y	
<35	37 (39%)
35 to <45	34 (36%)
≥45	24 (25%)
Mean (SD)	38 (13)
Median (IQR)	38 (28 to 45)
BCVA	
Mean (SD)	81 (7)
Median (IQR)	82 (76 to 86)
SP mean sensitivity	
Mean (SD)	12.6 (5.4)
Median (IQR)	12.1 (7.7 to 16.3)

*One participant was missing age of onset (a participant-reported field based on their awareness of visual symptoms) and duration of disease (computed based on age of onset and date of enrollment).

Distribution of FV Scores in MRDQ Domains

Supplementary Table S2 and Figures 2A and 2B summarize the FV score range (and overall possible FV score range) and distributions by domain across the analysis cohort and by subgroup according to gender, clinical diagnosis, disease duration at enrollment, age at enrollment, and rod-cone mediation. Mean theta values ranged from -0.5 for central vision to 0.6 to 0.7 for mesopic and scotopic domains (Supplementary Table S1). USH2 and ARRP groups had similar score distributions over all MRDQ domains (see Fig. 2). All MRDQ domains had a positive association with age and disease duration (Table 2). The color vision, scotopic, photopic peripheral, and mesopic peripheral domains showed a statistically significant difference in mean FV scores between individuals with rod versus cone mediated responses. Participants in the rod mediated group[16] had lower scores, indicating less disability, compared to those in the cone mediated group (Fig. 3).

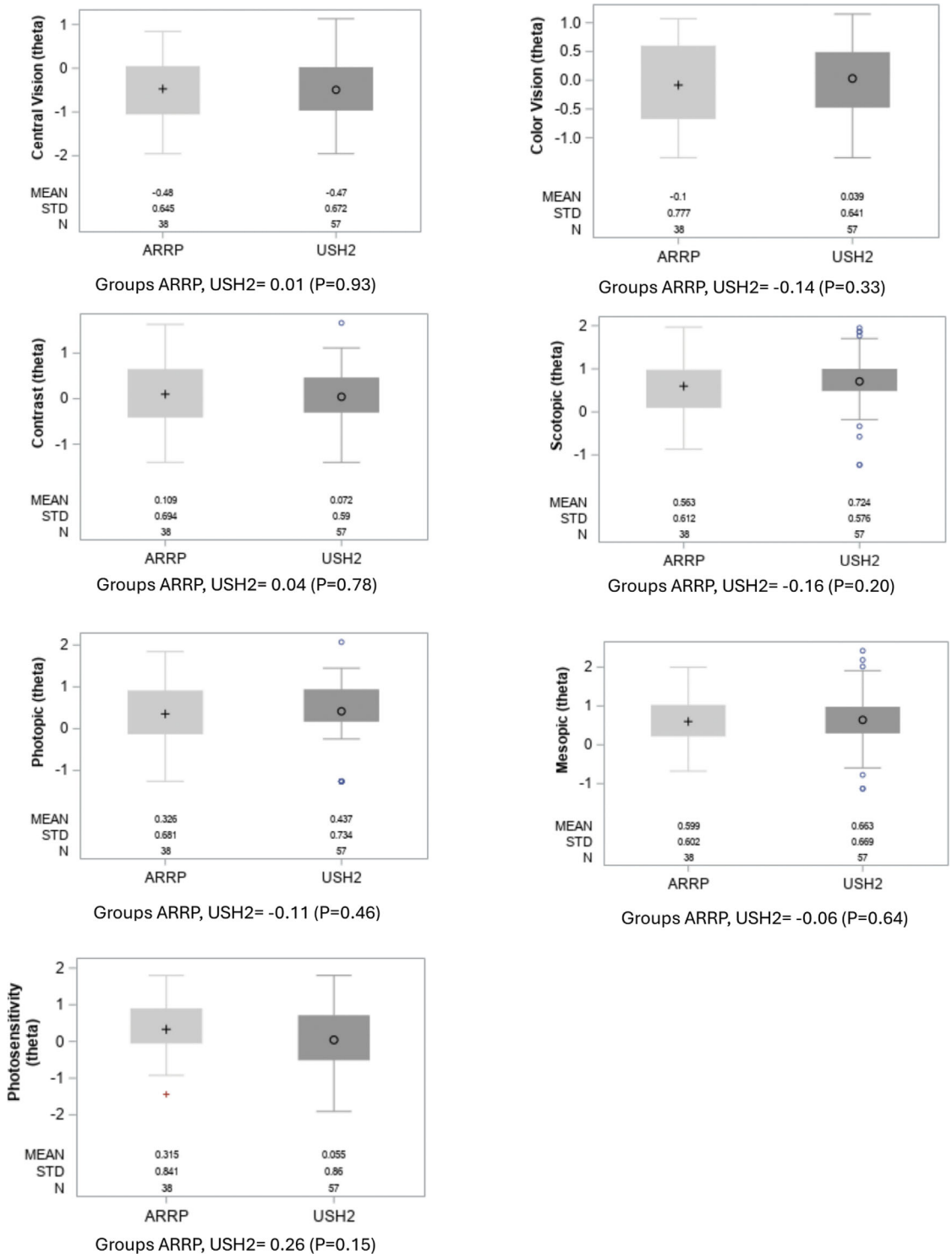

Figure 2. Distribution of MRDQ scores by clinical diagnosis groups (USH2 $n = 57$ and ARRP $n = 38$).

Correlation with Visual Function Measures at the 48-Month Visit

FV scores in all domains were moderately correlated with BCVA, with a Spearman correlation coefficient (r) ranging from −0.33 to −0.49. FST mediation (white, blue, and red) had a moderate correlation with scores for color vision, scotopic, and mesopic peripheral domains ($r = 0.31$ to 0.49). The EZ area moderately correlated with central vision ($r = -0.48$) and contrast ($r = -0.44$) domains. CST had a moderate correlation with scores in all MRDQ domains (range $r = -0.27$ to -0.55). Microperimetry mean sensitivity (MP MS) had a moderate correlation with scores in all MRDQ domains (range $r = -0.39$ to -0.52). All static perimetry

Table 2. Regression Analysis for FV Scores With Age and Disease Duration

		Functional Vision Score (FV)						
		Central Vision	Color Vision	Contrast	Scotopic	Photopic Peripheral	Mesopic Peripheral	Photosensitivity
Age at enrollment	Slope	0.02	0.01	0.01	0.01	0.01	0.01	0.02
($N = 93$)	*P* value	<0.001	0.06	0.006	0.16	0.02	0.05	0.004
Disease duration	Slope	0.02	0.02	0.01	0.01	0.01	0.01	0.01
($N = 92$)	*P* value	0.01	0.01	0.26	0.03	0.10	0.04	0.28

(SP) measures (V_{TOT}, V_{30}, and MS) were moderately correlated with all MRDQ domains (range $r = -0.26$ to $r = -0.68$; Table 3).

Discussion

In our study, we found that self-reported FV as measured by the MRDQ, when applied to participants with *USH2A*-associated retinal degeneration, had good distribution characteristics with no ceiling or floor effects, and correlated well with several visual function and structural tests. The overall FV scores for MRDQ suggest that, on average, participants had the least difficulty with central vision, affected by cone dysfunction, and the most difficulty with scotopic and mesopic vision, affected by rod dysfunction.

To correlate MRDQ domain scores with visual function tests, we evaluated four measures: BCVA, FST, static perimetry, and microperimetry. Lower BCVA values correlated with worse MRDQ FV scores across all domains, including central, color, and contrast vision. This finding is consistent with the natural disease progression of a rod-cone dystrophy, such as *USH2A*-associated retinal degeneration, in which patients often present with peripheral visual field loss earlier due to degeneration of peripheral cones secondary to rod degeneration.[18,19] This is followed by loss of central visual acuity, contrast sensitivity, and color vision later in the disease course, as central cones eventually undergo degeneration.[18,19] Therefore, early in the disease process, patients with good FV in all domains of the MRDQ will perform better in visual function tests, such as BCVA, and, as the disease progresses, they will perform worse in MRDQ domains as well as tests of visual function.

Although this study did not compare the magnitude of correlations among MRDQ domains, MRDQ central, color, contrast, and scotopic domains had high correlations with BCVA, indicating their sensitivity/affinity with cone-driven visual function. Furthermore, MRDQ color and contrast domains had lower FV scores compared to the central vision domain as indicated by the distribution of MRDQ scores. This may indicate that either patients are more impacted by contrast and color dysfunctions and/or these functions are affected earlier in the disease process.

FST is used to evaluate function of the surviving photoreceptors, and a higher threshold value indicates greater disability.[16,20] Higher thresholds imply a brighter light stimulus is required for visual perception. In this study, we found that higher FST values were moderately correlated with greater impairment in the MRDQ color, scotopic, and peripheral (mesopic and photopic) domains. When interpreting FST values, it is important to note that lower values represent a rod-mediated response (e.g. light perceived even at low intensity).[21] However, as rod function diminishes, the response becomes more cone-mediated, resulting in a higher FST value (e.g. high intensity light required for perception).[20] With a cone-mediated FST response, we would expect debilitated rod function, which could manifest as poor scotopic, photopic peripheral, and mesopic peripheral vision.[14,21] Therefore, the loss of rod function and subsequently cone function in this rod-cone dystrophy, as measured by thresholds/sensitivities discovered on FST, correlate significantly with functional vision impairments in domains of color vision, scotopic function, and peripheral vision (photopic and mesopic).

Our findings also demonstrate correlations of higher magnitude among perimetry, measured by visual field testing, and photopic and mesopic peripheral vision scores on the MRDQ, suggesting alignment with peripheral functional visual capabilities. Importantly, all perimetry values – "V_{TOT}" (total hill of vision), "V_{30}" (central 30° hill of vision), "V_{PERIPH}" (peripheral hill of vision) – show a high correlation (all absolute *r* values above 0.65) with photopic peripheral field impairments, and, to a lesser extent, with mesopic and scotopic functions. Furthermore, preserved photopic peripheral vision function implies better ability to navigate and avoid obstacles in well-lit environments. This aligns with the observation that patients with progressive loss in the peripheral visual field often experience difficulties during daylight hours.[22]

Furthermore, FV scores across MRDQ domains overall correlated better with perimetry assessments than with FST. Both tests assess visual function, visual fields related to localized space dimension, and FST related to light perception in the most sensitive retinal location. Although both tests assess retinal sensitivity, the spatial information provided by perimetry may have greater relevance to an individual's visual function and activities than the luminance sensitivity captured by FST. When an FST signal is cone mediated (as calculated by FST Blue-Red mediation), this indicates poor to no rod function, and therefore we see worse scotopic FV and worse mesopic peripheral FV.

To correlate FV scores in different MRDQ domains with structural assessments, we evaluated EZ area and CST. We found that larger EZ areas are correlated with better central and contrast vision. In contrast, larger CST measurements are highly correlated with better scores on the peripheral FV domains. Although the correlations with EZ area are not surprising, the magnitude of association of CST with peripheral retinal function domains is an interesting finding. Additional analysis is needed to understand how change in central retinal thickness corresponds to loss of peripheral vision and indeed, whether it is predictive or an indirect effect.

Given promising correlations with functional and structural ophthalmic testing, the MRDQ could possibly be used to distinguish among IRD phenotypes, as patients with cone-dominated as opposed to rod-dominated dystrophies

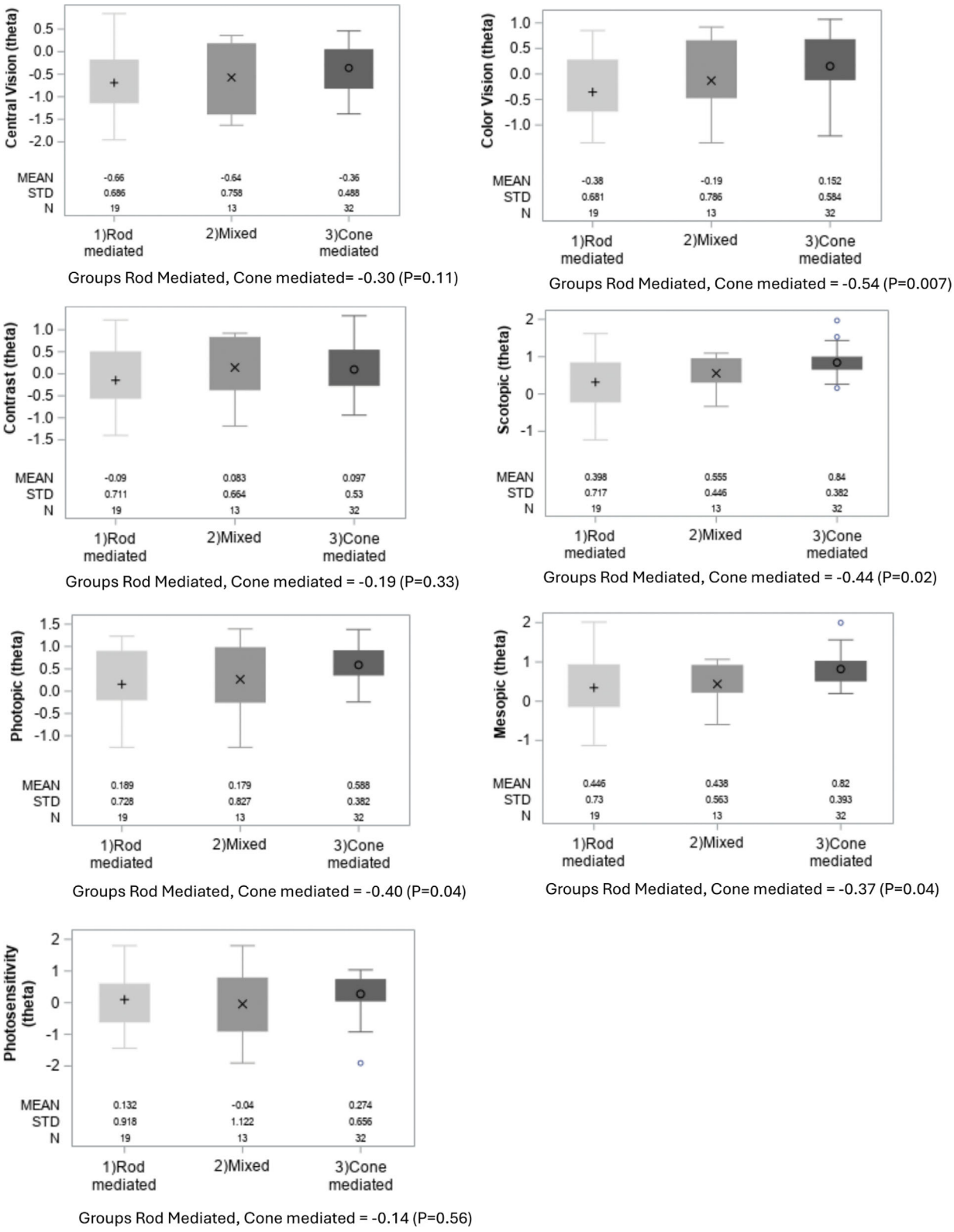

Figure 3. Distribution of MRDQ scores by FST Blue-Red mediated groups (Rod $n = 19$, Mixed $n = 13$, and Cone $n = 32$).

can present with different symptoms. For example, patients with a cone-dominated dystrophy may exhibit deficits in contrast sensitivity, central vision, photosensitivity, and color vision, whereas those with rod-dominated dystrophy have reduced peripheral vision in evening (mesopic) lighting, in addition to low ambient light (scotopic) visual function.[14] In this cohort, patients with central FV deficits had concurrent peripheral vision loss as well. Importantly, all

Table 3. Spearman Correlation Coefficients and 95% CI for Domain Scores (MRDQ) at 48M Visit with Key Participant Characteristics at 48M Visit

	Functional Vision Score (FV)*						
	Central Vision	**Color Vision**	**Contrast**	**Scotopic**	**Photopic Peripheral**	**Mesopic Peripheral**	**Photosensitivity**
Age at Enrollment (*N* = 95)	**0.31**† (0.12, 0.48)	0.20 (0.00, 0.39)	**0.24** (0.04, 0.42)	0.17 (−0.03, 0.36)	**0.20** (0.00, 0.39)	**0.22** (0.01, 0.40)	**0.27**† (0.07, 0.45)
Disease Duration (*N* = 94)	**0.25** (0.05, 0.43)	**0.31**† (0.11, 0.48)	0.14 (−0.06, 0.34)	**0.27**† (0.07, 0.44)	**0.22** (0.02, 0.40)	**0.24** (0.04, 0.42)	0.16 (−0.05, 0.35)
Visual Acuity (*N* = 92)	**−0.42**‡ (−0.57, −0.23)	**−0.49**‡ (−0.63, −0.31)	**−0.39**‡ (−0.55, −0.20)	**−0.40**‡ (−0.55, −0.21)	**−0.39**‡ (−0.55, −0.20)	**−0.34**† (−0.50, −0.14)	**−0.33**† (−0.50, −0.13)
FST White (*N* = 68)	**0.29** (0.06, 0.49)	**0.49**‡ (0.28, 0.65)	**0.26** (0.02, 0.47)	**0.46**‡ (0.25, 0.63)	**0.29** (0.06, 0.49)	**0.41**† (0.18, 0.59)	0.18 (−0.06, 0.41)
FST Blue (*N* = 64)	**0.29** (0.06, 0.49)	**0.48**‡ (0.27, 0.64)	**0.27** (0.04, 0.48)	**0.46**‡ (0.24, 0.63)	**0.32** (0.08, 0.51)	**0.39**† (0.16, 0.57)	0.19 (−0.05, 0.41)
FST Red (*N* = 64)	0.21 (−0.03, 0.43)	**0.39**† (0.17, 0.57)	0.22 (−0.02, 0.44)	**0.37**† (0.14, 0.56)	0.16 (−0.08, 0.39)	**0.31**† (0.08, 0.51)	0.07 (−0.17, 0.30)
FST Blue - Red (*N* = 64)	**0.26** (0.02, 0.47)	**0.32**† (0.09, 0.52)	0.23 (−0.01, 0.44)	**0.34** (0.11, 0.53)	**0.31**† (0.08, 0.51)	**0.28** (0.05, 0.49)	0.14 (−0.10, 0.37)
Ellipsoid Zone Area (*N* = 31)	**−0.48**† (−0.71, −0.14)	−0.17 (−0.49, 0.20)	**−0.44** (−0.68, −0.09)	−0.23 (−0.54, 0.14)	−0.33 (−0.61, 0.04)	−0.23 (−0.54, 0.14)	−0.003 (−0.36, 0.35)
Central Subfield Thickness (*N* = 57)	**−0.28** (−0.50, −0.02)	**−0.35**† (−0.56, −0.09)	**−0.27** (−0.50, −0.01)	**−0.50**‡ (−0.67, −0.27)	**−0.32** (−0.53, −0.06)	**−0.55**‡ (−0.70, −0.33)	**−0.29** (−0.51, −0.03)
Microperimetry Mean Sensitivity (*N* = 75)	**−0.42**† (−0.59, −0.22)	**−0.39**† (−0.57, −0.18)	**−0.52**‡ (−0.66, −0.32)	**−0.45**‡ (−0.61, −0.25)	**−0.53**‡ (−0.68, −0.34)	**−0.52**‡ (−0.66, −0.32)	**−0.42**† (−0.59, −0.21)
V_{TOT} (*N* = 79)	**−0.36**† (−0.54, −0.15)	**−0.29**† (−0.48, −0.08)	**−0.36**† (−0.53, −0.15)	**−0.49**‡ (−0.64, −0.29)	**−0.66**‡ (−0.76, −0.51)	**−0.56**‡ (−0.69, −0.38)	**−0.30**† (−0.49, −0.09)
V_{30} (*N* = 78)	**−0.41** (−0.58, −0.21)	**−0.32**† (−0.50, −0.10)	**−0.50**‡ (−0.65, −0.30)	**−0.52**‡ (−0.66, −0.33)	**−0.68**‡ (−0.79, −0.54)	**−0.58**‡ (−0.71, −0.41)	**−0.38**† (−0.55, −0.17)
V_{PERIPH} (*N* = 68)	**−0.36** (−0.55, −0.13)	**−0.26** (−0.47, −0.03)	**−0.37**† (−0.56, −0.14)	**−0.51**‡ (−0.67, −0.31)	**−0.65**‡ (−0.77, −0.48)	**−0.57**‡ (−0.71, −0.38)	**−0.29** (−0.50, −0.06)
Static Perimetry Mean Sensitivity (*N* = 80)	**−0.44**‡ (−0.60, −0.24)	**−0.36**† (−0.54, −0.16)	**−0.52**‡ (−0.66, −0.34)	**−0.54**‡ (−0.68, −0.36)	**−0.73**‡ (−0.82, −0.60)	**−0.62**‡ (−0.74, −0.46)	**−0.39**† (−0.56, −0.18)
Central Vision (*N* = 95)	1.00	**0.63**‡ (0.49, 0.73)	**0.66**‡ (0.53, 0.76)	**0.47**‡ (0.29, 0.61)	**0.62**‡ (0.47, 0.73)	**0.48**‡ (0.31, 0.62)	**0.52**‡ (0.38, 0.67)
Color Vision (*N* = 95)		1.00	**0.61**‡ (0.49, 0.72)	**0.56**‡ (0.40, 0.68)	**0.52**‡ (0.35, 0.65)	**0.42**‡ (0.23, 0.57)	**0.43**‡ (0.25, 0.58)
Contrast (*N* = 95)			1.00	**0.60** (0.45, 0.71)	**0.73**‡ (0.62, 0.81)	**0.56**‡ (0.40, 0.68)	**0.59**‡ (0.44, 0.71)
Scotopic (*N* = 95)				1.00	**0.73**‡ (0.61, 0.81)	**0.83**‡ (0.75, 0.88)	**0.42**‡ (0.23, 0.57)
Photopic Peripheral (*N* = 95)					1.00	**0.77**‡ (0.68, 0.84)	**0.60**‡ (0.45, 0.71)
Mesopic Peripheral (*N* = 95)						1.00	**0.44**‡ (0.26, 0.59)
Photosensitivity (*N* = 95)							1.00

* Correlation coefficients with *P* value < 0.05 are bolded.
† Correlation coefficients with *P* values < 0.01.
‡ Correlation coefficients with *P* values < 0.001.

the correlations identified in this study illustrate a consistent pattern: worse self-reported FV on the MRDQ corresponds to a higher degree of peripheral, and central vision loss as assessed by visual function assessments, visual field parameters, and structural characteristics. The severity of peripheral vision loss also relates to the extent of central vision loss, highlighting the mutual relationship between these two types of MRDQ domains in disease progression. In other words, as peripheral vision loss increases in severity, there is subsequent loss of central vision and a worsening of self-reported FV for both peripheral and central vision in this disease form. In addition, given that cone-driven MRDQ domains (day-light vision, color, and contrast) and rod-driven domains (scotopic and mesopic peripheral) were affected differently within themselves and correlated differently with corresponding visual tests, the MRDQ may be an exploratory tool to identify meaningful and sensitive outcome measures for clinical trials.

This study has limitations. Due to the local demographics of the study sites' catchment areas, our study population was not racially representative of the global diversity of patients. Additionally, our results show a weak correlation (r = 0.2–0.3) between self-reported FV across all MRDQ domains with age and disease duration. This is only moderately in accordance with our initial hypothesis that older individuals would exhibit more advanced disease and worse functioning. However, it is important to consider that this weak association for disability distribution may be due to enforcement of the study's inclusion criteria (visual acuity of 20/80 or better and visual field diameter greater than 10 degrees in each meridian), which selected a group of patients that were more homogenous and relatively less advanced in their phenotypic expression and severity. This could also explain why median MRDQ values between patients with syndromic (USH2) and non-syndromic (ARRP) forms of *USH2A*-associated disease were equivalent. Previous publications have found, however, that the natural progression of ARRP when compared to those with USH2 may represent a milder form of retinal degeneration.[16] The protocol-forced selection of a homogenous patient sample to meet inclusion criteria could have obscured differences in natural disease progression between USH2 and ARRP. An alternative explanation could be that patients with longer duration of disease have accommodated to their visual deficits. Further assessment of the MRDQ with longitudinal data has the potential to demonstrate whether MRDQ is sensitive to deterioration in visual function over time.

Ultimately, the MRDQ is a tool specifically developed to measure PROs for patients with IRDs and is reliable, with low test-retest variability, and valid, correlating well with other measurements of vision, including functional, and structural assessments.[7,14] These characteristics provide the MRDQ with substantial advantages over a less disease-specific PRO questionnaire in the IRD patient populations with rod-cone dystrophy (retinitis pigmentosa), such as *USH2A*-related retinal degeneration.[7] The utility of the MRDQ FV measure is of important note, including its application as an efficacy outcome measure in low vision rehabilitation, the current standard clinical management for patients with IRD.[14] Most promising, however, is its use in measuring patients' self-reported FV improvement to document treatment efficacy for interventions, including gene therapies, undergoing clinical trial investigation.[7,13,14]

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