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Relationship between the full-field stimulus test and self-reported visual function in patients with retinitis pigmentosa: REPEAT Study report No. 3

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Abstract

Purpose: To determine the relationship between the full-field stimulus test (FST) and self-reported visual function using the Michigan Retinal Degeneration Questionnaire (MRDQ) in patients with retinitis pigmentosa (RP).

Methods: In this cross-sectional study, patients with clinically diagnosed RP ($n=31$) performed FST to determine retinal sensitivity thresholds for blue, red and white stimuli. The difference between the blue and red thresholds was used to identify photoreceptor mediation type. Patients completed the MRDQ from which disability (Θ) scores were derived across seven visual function domains. Correlations between the FST thresholds and MRDQ domain Θ-scores were analysed using Spearman's rank correlation.

Results: The median age was 38.0 years, and photoreceptor mediation was rod-based in 11 patients (35.5%), cone-based in seven patients (22.6%) and mixed in 13 patients (41.9%). The highest disability scores were reported in the domains of '*mesopic peripheral function*' and '*scotopic function*'. Significant correlations were found between all chromatic stimuli thresholds and the MRDQ domains of '*scotopic function*', '*mesopic peripheral function*' and '*photopic peripheral function*'. The strongest correlations of these domains were observed with the blue FST ($p<0.001$). The threshold on blue stimulus FST and age were significant predictors of the domain scores on '*scotopic function*' ($p<0.001$), '*mesopic peripheral function*' ($p<0.001$) and '*photopic peripheral function*' ($p<0.001$).

Conclusions: Strong correlations between MRDQ domains related to rod function and FST were found in patients with RP. These findings confirm that FST can be used as an informative and clinically relevant endpoint in RP trials when evaluating therapeutic interventions.

KEYWORDS
full-field stimulus threshold testing, inherited retinal degeneration, Michigan retinal degeneration questionnaire, patient-reported outcome, quality of life, retinal sensitivity, rod-cone dystrophy

1 | INTRODUCTION

Retinitis pigmentosa (RP) is a clinically and genetically heterogeneous inherited retinal degeneration (IRD) that affects 1 in 3000–5000 individuals globally (Nguyen et al., 2023; Verbakel et al., 2018). RP is characterized by the sequential degeneration of rod and cone photoreceptors, resulting in the progressive loss of various visual functions (Verbakel et al., 2018). Initial symptoms typically include night blindness due to rod receptor degeneration. As the condition progresses and cone receptors are affected, the peripheral visual field constricts and central visual functions, such as visual acuity and colour vision, become impaired. The diversity of symptoms and the chronic progressive nature can have a profound impact on the vision-related quality of life and self-reported visual function of patients (Gouveia et al., 2024; Marques et al., 2023).

The approval of the first successful gene-based therapy, voretigene neparvovec, has marked a significant advancement in treating IRDs, and sparked a surge in research on genetic therapies, leading to an increase in the number of interventional clinical trials for IRDs that were previously considered untreatable (Georgiou et al., 2024; Talib & Boon, 2020). To demonstrate treatment efficacy in clinical trials for RP, it is essential to use validated and reliable clinical endpoints. In addition, regulatory agencies favour clinical endpoints that have proven correlations with patients' quality of life and daily experiences (Varma, 2010; Stingl et al., 2023). Until recently, clinical trials for RP were limited, and it became necessary to develop clinical endpoints that were specifically relevant and appropriate for patients with RP. One of these endpoints is the full-field stimulus test (FST), a psychophysical measurement that evaluates the threshold of dark-adapted retinal sensitivity across the entire visual field using a light stimulus flicker of different wavelengths. FST can roughly discriminate between rod- and cone-mediated vision, based on the difference between blue and red stimuli (Roman et al., 2022). FST was used as a secondary endpoint in the first clinical trials that tested the efficacy of voretigene neparvovec (Hauswirth et al., 2008; Maguire et al., 2019, 2021; Russell et al., 2017). Following the success of these trials, FST is now increasingly adopted as a clinical endpoint in other IRD studies, as it is especially useful for the evaluation of residual visual function in patients with profound vision loss. In addition, its independence from fixation requirements is advantageous for individuals with poor fixation or nystagmus, which is often seen in RP (Jolly et al., 2024; Shi et al., 2024).

Despite its practical value, it is unclear to what extent FST measurements accurately reflect the patient's perspective and quality of life, and little research has thus far been dedicated to this topic. Patient-reported outcome measures (PROMs) assess the impact of a disease or treatment on daily life, often through self-reported questionnaires. The Michigan Retinal Degeneration Questionnaire (MRDQ) was developed specifically for patients with an IRD, to capture subjective changes in visual function in real-life situations (Lacy et al., 2020, 2021). The MRDQ was validated in patients with an IRD, and fulfils the criteria set by some of the regulatory agencies (Varma, 2010; Jayasundera et al., 2023; Lacy et al., 2021). In a recent study, we have described a strong relation between self-reported visual function using the MRDQ, and several psychophysical visual function measures including best-corrected visual acuity (BCVA), low-luminance visual acuity and mesopic microperimetry in patients with RP (Karuntu et al., 2024).

Here, we investigate the relationship between the different chromatic FST measurements and self-reported visual function as assessed by the MRDQ. This study provides compelling evidence for using the FST as a measure for rod-based vision-related quality of life, in addition to its practical value as a psychophysical measure of objective efficacy.

2 | METHODS

2.1 | Study design and participants

This cross-sectional study is part of the 'test–REtest reliability in Patients with inhErited retinAl dysTrophies' (REPEAT) study, which is described in further detail elsewhere (Karuntu et al., 2024). All measurements were performed by a single research physician (JSK) to minimize interobserver bias. The study was approved by the Medical Ethics Committee of Leiden University Medical Center (NL79646.058.21/P21.121) and adhered to the Tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants and, if applicable, their care-takers.

Included participants originated from the Leiden University Medical Center and the Amsterdam University Medical Center, had a BCVA of ≤20/32 Snellen (≥0.20 logMAR), and a clinical diagnosis of typical RP based on the findings on full-field electroretinography, ocular examination, retinal imaging, medical and family history. Exclusion criteria included: age under 16 years, a BCVA of light perception or less in the best eye, history of (non-) ocular conditions affecting measurements (e.g. amblyopia), known allergy to ocular drops used in the study or concurrent participation in other ocular drug trials. BCVA was measured for both eyes as part of the screening for the REPEAT study, and as per study protocol, the left eye was appointed as the study eye for the FST unless it did not meet the inclusion criteria. However, self-reported visual function is mainly dependent on the BCVA of the better-seeing eye. Due to the high interocular similarity seen in RP, we investigated the FST of the eye with the higher or same BCVA in 25/31 patients (Bellingrath et al., 2017; Mathijssen et al., 2017). In two cases, the better-seeing eye had visually disturbing cataract in the central visual axis, and in two other cases the better-seeing eye had cystoid macular oedema that was either moderate or had not been stable for over a year. The mean difference between the better-seeing eye and the worse-seeing eye was 0.8 logMAR ($p=0.016$).

2.2 | Clinical examination

Refraction and BCVA were measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter charts (Precision Vision, Bloomington, IL, USA) and established protocols. If BCVA was too low to measure on these letter charts, the Berkley Rudimentary Vision Test (BRVT) was used to accurately quantify visual acuity in logMAR (Bailey et al., 2012). Slit lamp biomicroscopy and ophthalmoscopy were performed to detect cataract and to exclude other ocular abnormalities besides RP. Spectral-domain optical coherence tomography (SD-OCT; Spectralis, Heidelberg Engineering, Heidelberg, Germany) was performed to evaluate the presence and extent of cystoid macular oedema. Pupil dilation was achieved with topical application of phenylephrine 2.5% and tropicamide 0.5%. Fixation stability was determined using the bivariate contour ellipse area encompassing

95% of the fixation points (BCEA95) on microperimetry as reported earlier (Karuntu et al., 2024). The BCEA95 value was then compared to the fixation stability of healthy controls, previously reported as 2.40 deg^2 (Morales et al., 2016), and to the reliability criterion established by Josan et al. for rod-cone dystrophies (Josan et al., 2023).

2.3 | Full-field stimulus (FST) protocol

FST was performed using the Espion ColorDome™ LED full-field stimulator, software version V6.59.2 (Diagnosys LLC, Lowell, MA, USA). Prior to the FST measurement, patients underwent dark adaptation for 45 minutes with both eyes patched (Jolly et al., 2024). Patients first performed a practice session to reduce learning effects.

Blue (448 nm) and red (627 nm) stimuli were used to estimate responses as rod-mediated (blue–red difference ≤−1.93 log units), cone-mediated (blue–red difference ≥−0.36 log units), or mixed rod- and cone-mediated (blue–red difference between −0.36 and −1.93 log units) (Roman et al., 2022). An achromatic stimulus (white; 6500 K) was used to determine the threshold of general retinal sensitivity. The reference luminance of 0 dB was set at 0.1 cd·s·m^{-2}, with stimulus luminance ranging from −8.5 log units (dimmest) to +2.5 log units (brightest). Each stimulus was presented for 4 ms. Patients indicated stimulus perception using a textured two-button box (yes/no). The stimulus luminance was increased by 0.4 log units until the first response reversal, then decreased by 0.2 log units until a second reversal. The luminance of the last seen stimulus was recorded as the starting point for a second sample, following the same procedure. The final threshold was determined as the midpoint of the frequency-of-seeing curve, generated using a two-parameter Weibull function (Figure S1). This function accounts for false positives or 'error blanks' (EB), and false negatives or 'error max' (EM). Results were manually reviewed if patient responses were inadequate to determine response reversals. Unreliable results were excluded from the analysis, defined as having more than 20% EB or EM and/or an unfit Weibull function curve. Final sensitivity thresholds were determined by averaging three individual threshold measurements for each chromatic stimulus, the FST measurements were all within the expected test–retest variability of the FST (manuscript in submission).

2.4 | Michigan retinal degeneration questionnaire (MRDQ)

The Dutch translation of the MRDQ was used which consists of 59 items that investigate several visual domains relevant for patients with an IRD: '*central vision*', '*colour vision*', '*contrast sensitivity*', '*scotopic function*', '*photopic peripheral function*', '*mesopic peripheral function*' and '*photosensitivity*' (Karuntu et al., 2024; Lacy et al., 2021). Response options regarding the degree of difficulty included: 'A little difficulty: I notice a problem, but I do not struggle', 'Moderate difficulty: I struggle, but I can still do this', 'Extreme difficulty: I struggle a lot, and sometimes I cannot do this' and 'N/A for non-vision reasons: I do not do this'. Likewise, response options for frequency include 'Never', 'Sometimes', 'Frequently', 'Always', 'Does not help' and 'N/A for non-vision reasons'. A graded response model was used to produce a theta score (Θ) reflecting functional disability within each visual domain, standardized around the average trait level of the patient population (Lacy et al., 2021). Extreme Θ-values of −3 and +3 denote the lowest and highest levels of visual disability, respectively. The MRDQ was completed by all patients during the dark-adaptation period prior to the FST measurement. All questionnaires were administered in person by a single research physician (JSK) to maintain consistency.

2.5 | Statistical analysis

MRDQ patient responses were analysed using the graded response model with Cai's Metropolis-Hastings Robbins-Monro algorithm from the original authors' R package in Rstudio software version 4.3.3 (Lacy et al., 2021; R Core Team, 2023). Data distribution was checked for normality with histograms and the Shapiro–Wilk test; normal distributed data are reported as mean ± standard deviation (SD), whilst non-normal distributed data are reported as median and interquartile range (IQR). Since some MRDQ domains scores had a non-normal distribution, both the median and mean domain scores are reported and shown in a boxplot, respectively, to facilitate comparison of scores. Correlations between Θ-scores and FST thresholds were analysed with Spearman's rank correlation (ρ), and Pearson correlation coefficients (r) were used to check for multicollinearity prior to multivariate regression analysis. Generally, p-values of ≤0.05 were considered statistically significant, and Bonferroni adjustments were applied to correct for multiple testing across the MRDQ domains.

3 | RESULTS

3.1 | Study population

Initially, 34 patients were included for this study, but two patients were unable to complete the FST due to temporary device malfunctioning. Additionally, one patient was excluded from the final analysis due to unreliable performances for all chromatic stimuli based on too many false negative errors. Consequently, we included the FST and MRDQ measurements of 31 patients for the final analysis (Table 1). The median BCVA of the study eye was 20/155 Snellen, equivalent to 0.89 logMAR (IQR: 0.62–1.22). Twenty-one patients had a BCEA95 greater than 2.40 deg^2, indicating poorer fixation compared to the healthy population (Morales et al., 2016). Furthermore, 15 patients had a BCEA95 greater than 23.1 deg^2, which would classify them as having unreliable microperimetry assessments (Josan et al., 2023). The median age at enrolment was 38.0 years (IQR: 22–57 years). Eleven patients (36%) were pseudophakic, nine patients

(29%) had mild cataract that was not in the visual axis, and one patient (3%) had mild cystoid macular oedema that had been stable for over a year. The underlying genetic cause of RP was known in the majority of the patients (90%), two patients had inconclusive genetic test results and one patient declined genetic testing (Figure 1). There was an enrichment of patients with underlying pathogenic variants in *CRB1* (35%), of which four patients (13%) were homozygous for c.3122T>C (p.(Met1041Thr)) variant, and who have been described earlier (Mathijssen et al., 2017; Talib et al., 2021).

TABLE 1 Patient characteristics.

Age in years, median (IQR)	38.0 (22–57)
Gender, *n* (%)	
Female	13 (41.9%)
Male	18 (58.1%)
BCVA in logMAR, median (IQR)	0.89 (0.62–1.22)
Fixation stability according to BCEA95	
Poor fixation[a], *n* (%)	21 (67.7%)
Unreliable measurement on microperimetry[b], *n* (%)	15 (48.4%)
Ethnicity, *n* (%)	
Caucasian	27 (87.1%)
Middle-Eastern	3 (9.7%)
Asian	1 (3.2%)
Presence of cataract[c], *n* (%)	9 (29%)
Nuclear cataract	3 (33.3%)
Posterior subcapsular cataract	6 (66.7%)
Pseudophakia, *n* (%)	11 (35.5%)
FST blue–red difference in log cd·s·m^{-2}, median (IQR)	−0.7 (−2.1–−0.2)
Rod mediation (≤−1.93 log units), *n* (%)	11 (35.5%)
Mixed mediation (−0.36–−1.93 log units), *n* (%)	7 (22.6%)
Cone mediation (≥−0.36 log units), *n* (%)	13 (41.9%)

Abbreviations: BCEA95, bivariate contour ellipse area of 95% of the fixation points; BCVA, best-corrected visual acuity; IQR, interquartile range; logMAR, Logarithm of the Minimum Angle of Resolution; FST, full-field stimulus test.

[a](Morales et al., 2016).

[b]According to Josan et al. (Josan et al., 2023).

[c]Cataract was considered "not vision-impairing".

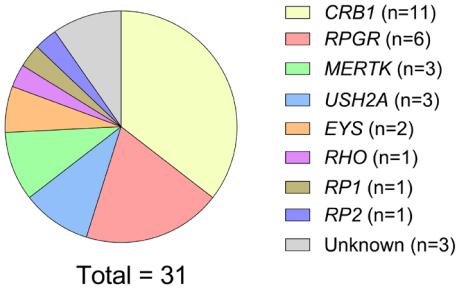

FIGURE 1 Pie chart of the distribution of the affected genes causing RP in this study cohort. The category 'Unknown' refers to patients who have had inconclusive results following genetic testing (*n* = 2) or who declined genetic testing (*n* = 1).

3.2 | Full-field stimulus test (FST)

The white stimulus on FST, a general indicator of retinal sensitivity irrespective of photoreceptor mediation, showed a range of 4.92 log units. The blue and red stimuli reflect rod and cone function, respectively, and the difference between these stimuli can be used to estimate the dominant type of photoreceptor mediation (Roman et al., 2022). The blue threshold values on the FST displayed the widest range of 5.85 log units, effectively revealing the varying levels of rod dysfunction (Figure 2). In comparison, the red threshold had a narrower range of 3.38 log units, suggesting less variability in cone function. The difference between the blue and red thresholds was used to estimate the type of photoreceptor mediation, and ranged from −2.60 to +0.04 log units. Based on the blue–red difference and the pre-defined criteria from Roman et al., 11 patients were estimated to have predominantly rod mediation, seven patients with mixed mediation, and 13 patients presented with primarily cone mediation (Roman et al., 2022).

3.3 | Michigan retinal degeneration questionnaire domain scores

All patients completed the MRDQ (Figure 3). Median MRDQ Θ-scores (IQR) were highest in the rod function-related domains of '*mesopic peripheral function*' (1.09; IQR: 0.51–1.55) and '*scotopic function*' 0.86 (IQR: 0.34–1.23), indicating more perceived disability. The median domain scores for the cone function-related domains '*photopic peripheral function*', '*contrast sensitivity*' and '*central vision*' were 0.78 (IQR: 0.41–1.08), 0.60 (IQR: 0.36–1.19), and 0.56 (IQR: 0.15–1.32), respectively. The lowest median scores were found in the domains of '*photosensitivity*' (0.27; IQR: −0.02–0.59) and '*colour vision*' (0.55; IQR: 0.33–0.89).

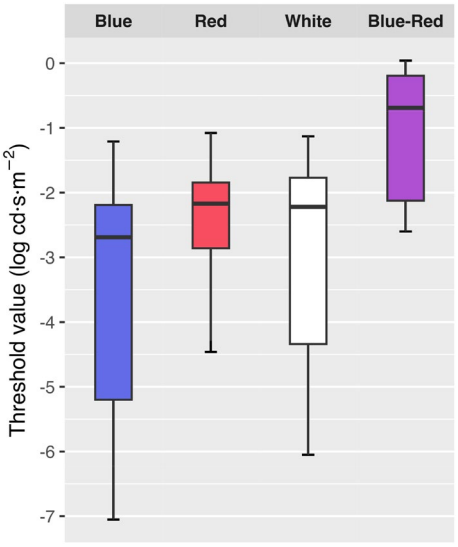

FIGURE 2 Boxplots of the full-field stimulus test (FST) threshold values for each chromatic measurements. Blue–red denotes the difference between the values measured with the blue and red stimuli, and was used to determine the type of photoreceptor mediation: Rod mediation (≤−1.93 log units), cone (≥−0.36 log units), or mixed rod and cone mediation (between −1.93 log units and −0.36 log units). Data represent 31 patients with retinitis pigmentosa (RP).

3.4 | FST parameters correlate with three MRDQ domains

To investigate potential correlations between FST parameters and self-reported visual function, Spearman's rank correlation coefficients (ρ) were determined between the chromatic threshold values and the difference between the blue and red thresholds, and the Θ-scores of the various MRDQ domains (Table 2). All FST parameters, that is, blue, red and white thresholds, as well as the difference between the blue and red thresholds, were strongly and significantly correlated to the MRDQ domain scores of '*scotopic function*', '*mesopic peripheral function*' and '*photopic peripheral function*' (Table 2 and Figures S2–S5). These domains reflect the earlier symptoms of RP. The ability to distinguish objects from different backgrounds is often affected in later stages of the disease, and is reflected in the domain score of '*contrast sensitivity*'. This domain score was initially significantly correlated to the FST parameters as well, but this correlation was no longer significant after correction for multiple testing. However, this trend does suggest that FST parameters may be a measure for tracking progression based on the MRDQ.

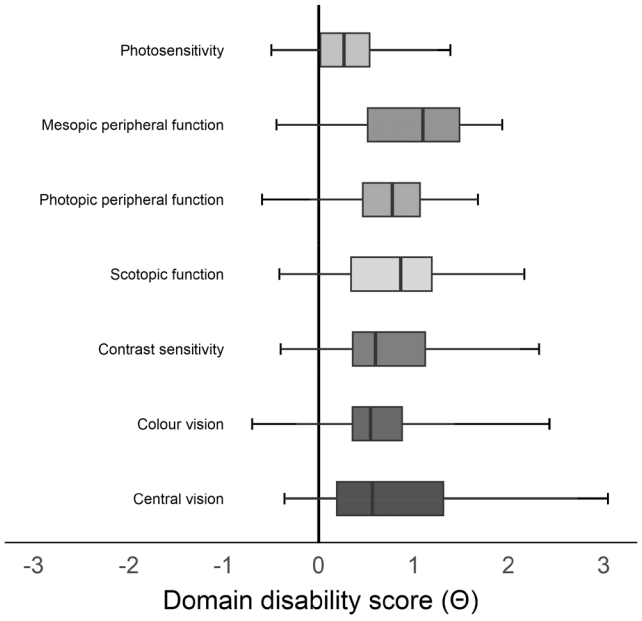

FIGURE 3 Boxplot of Michigan Retinal Degeneration Questionnaire (MRDQ) disability (*Θ*) scores. The scores are calculated for each MRDQ domain separately. The MRDQ scores range from −3 (lowest experienced disability) to +3 (highest experienced disability). Data represent 31 patients with retinitis pigmentosa (RP).

3.5 | Effects of age, cataract and FST on MRDQ scores

Using an exploratory regression analysis, we investigated whether the thresholds on FST, cataract presence and age were significant predictors of the MRDQ domain scores of '*scotopic function*', '*mesopic peripheral function*' and '*photopic peripheral function*'. Initially, we aimed at investigating the effect of all FST parameters. However, one key condition for conducting a multivariable regression analysis, is the absence of multicollinearity, meaning that the variables should not be highly correlated. We found a high correlation between the white threshold on FST and both chromatic thresholds on FST (data not shown), which was expected as white FST responses are a combination of the chromatic

TABLE 2 Spearman's rank correlation coefficient (*ρ*) analyses between different chromatic FST values (log cd·s·m^{-2}) and disability scores *Θ* for each domain of the Michigan Retinal Degeneration Questionnaire (MRDQ).

	Domain score of the Michigan retinal degeneration questionnaire						
	Central vision	**Colour vision**	**Contrast sensitivity**	**Scotopic function**	**Photopic peripheral function**	**Mesopic peripheral function**	**Photo-sensitivity**
FST Blue							
ρ	0.301	0.218	0.451	0.720	0.569	0.609	0.179
p value	0.100	0.239	0.011	**<0.001**	**<0.001**	**<0.001**	0.335
FST Red							
ρ	0.158	0.165	0.438	0.572	0.488	0.484	−0.009
p value	0.394	0.376	0.014	**<0.001**	**0.005**	**0.006**	0.962
FST White							
ρ	0.245	0.232	0.407	0.670	0.522	0.553	0.127
p value	0.183	0.209	0.023	**<0.001**	**0.003**	**0.001**	0.495
FST Blue–red							
ρ	0.208	0.082	0.322	0.672	0.492	0.519	0.244
p value	0.262	0.661	0.078	**<0.001**	**0.005**	**0.003**	0.187

Note: Following Bonferroni correction for multiple testing, the significance threshold was adjusted to $p<0.0071$; statistically significant correlations are marked in bold.

Abbreviations: FST, full-field stimulus test.

stimuli responses. As a result, the white threshold on FST was excluded from this analysis.

The MRDQ domains of '*scotopic function*', '*mesopic peripheral function*' and '*photopic peripheral function*' were highly correlated with the FST responses, and pertain to relatively 'early-stage' symptoms of RP, such as night blindness and visual field constriction. Since RP is primarily a degeneration of rod photoreceptors, it is thus more appropriate to focus on the rod-driven blue FST responses, rather than the cone-driven red FST responses.

For the regression analysis, we focus on the impact of the blue FST threshold on the MRDQ Θ-scores of '*scotopic function*', '*mesopic peripheral function*' and '*photopic peripheral function*', and demonstrate that both age and the threshold value of the blue FST were statistically significant predictors for these MRDQ Θ-scores (Table S1, models 1B, 2B, 3B). Specifically, the threshold on blue stimulus FST had a significant impact on the domain scores of '*scotopic function*' ($p<0.001$), '*mesopic peripheral function*' ($p=0.008$) and '*photopic peripheral function*' ($p=0.014$). Similarly, age was a significant predictor of the domain score of '*scotopic function*' ($p=0.031$), '*mesopic peripheral function*' ($p=0.013$) and '*photopic peripheral function*' ($p=0.005$). In contrast, the presence of cataract did not significantly impact the domain scores of '*scotopic function*' ($p=0.616$), '*mesopic peripheral function*' ($p=0.856$) or '*photopic peripheral function*' ($p=0.829$) (Table S1; models 1C, 2C, and 3C).

4 | DISCUSSION

In RP, few studies have been published thus far on patient-perceived quality of life, and its correlation with visual function parameters. Recently, we described the correlation between the self-reported visual function on the MRDQ, and visual acuity parameters and microperimetry in a comparable cohort of RP patients (Karuntu et al., 2024). Similarly, another study identified correlations between MRDQ domains and structural markers on OCT in 49 patients with biallelic *EYS* mutations (Marques et al., 2023). However, despite the successful use of FST as a functional clinical endpoint in the clinical trials on voretigene neparvovec treatment in *RPE65*-associated IRD and other clinical trials for IRDs, (Roman et al., 2022) little is known on the potential relation between FST and self-reported visual function in patients with RP. In the current study, we found a strong correlation between the FST parameters and the MRDQ domains related to early symptoms of RP, such as night blindness and loss of peripheral vision. All chromatic FST thresholds correlated with the domain scores of '*scotopic function*', '*photopic peripheral function*' and '*mesopic peripheral function*'. The strongest correlations were observed for blue thresholds on FST, which reflects rod function, followed by the white threshold, blue–red difference, and red threshold respectively (Roman et al., 2005). Among the MRDQ domains, the strongest correlation was found in the scotopic domain, followed by mesopic and photopic peripheral functions. Given that rod photoreceptors are (1) primarily impaired in patients with RP, (2) are most sensitive to wavelengths corresponding to blue light and (3) are responsible for night vision, it is thus no surprise that the strongest correlations are found between the blue FST and domains concerning low-light situations in this patient cohort (Alexander & Fishman, 1984). This provides a rationale for using FST parameters as a measure of functional vision as well as self-reported visual function. In a recent report, Parekh et al. also explored the correlation between FST measurements and MRDQ scores in a cohort of patients with biallelic pathogenic *USH2A* variants (Parekh et al., 2024). In line with our findings, the domains '*mesopic peripheral function*' and '*scotopic function*' on the MRDQ also showed the strongest correlations with FST. In contrast to the study of Parekh et al., who found that the domain score of '*colour vision*' correlated most strongly with all FST parameters, our study did not demonstrate any significant correlation with this domain. This discrepancy may stem from the difference in median BCVA (0.08 logMAR vs. 0.89 logMAR in this study), suggesting different disease stages. FST is generally more appropriate in patients with more advanced RP, where central visual function is significantly impaired, as observed in this study (Roman et al., 2022). The patients in the study of Parekh et al. still had measurable electroretinography (ERG) responses and a relatively high BCVA, indicating a relatively preserved central and peripheral retinal function (Birch et al., 2020; Parekh et al., 2024). Discrepancies between the studies may also stem from differences in sample sizes ($n=64$ in their study vs. $n=32$ in ours), as well as the fact that their data focuses exclusively on *USH2A*-associated IRDs, whereas our cohort included a spectrum of genotypes.

In addition to the confirmation of the correlation between the FST and the MRDQ, in this study we further investigated the exact nature of the relationship between these endpoints. Following a linear trend, an increase in threshold value of the blue FST, indicating worse visual function, was associated with an increase in experienced disability across the domains of scotopic, mesopic peripheral and photopic peripheral function on the MRDQ. Furthermore, we explored the effect of potential predictors and confounders by including age and the presence of cataract. Parekh et al. reported recently that age is a predictor of experienced disability in patients with biallelic pathogenic *USH2A* variants (Parekh et al., 2024). However, the addition of FST thresholds to a model with only age led to a substantial improvement of model fit, suggesting that the combination of both variables is better at predicting experienced disability than either variable alone. We found that cataract was not a confounder in the current study, but this may have been the result of selection bias, as patients with visually disturbing cataract were excluded in our study.

Strengths of this prospective study include the use of a standardized testing protocol, consistent administration of all tests by a single investigator, and incorporating a training test to minimize learning effects. There are also several limitations to consider. First, FST data were collected before the recent publication of the International Society for Clinical Electrophysiology of Vision (ISCEV) guideline, which

recommends measuring pupil sizes to account for the differences in illuminated retinal surface area (Jolly et al., 2024). However, the impact of pupil size on the FST thresholds is expected to be minimal in our study, as all patients were administered topical pupil dilation according to a standardized protocol prior to testing, and most patients had relatively late-staged RP where the effect of pupil dilation appears less relevant due to visual field constriction (Reith et al., 2024). In addition, although we found strong correlations between the MRDQ and FST parameters, this study is limited by its relatively small sample size. This restricted psychometrical validation of the Dutch MRDQ, and prevented the conduction of sub-analyses on the effects of genetic origin and fixation ability. Given the orphan nature of RP, recruiting large numbers of patients is challenging, and clinical trials for RP are likely to face similar limitations. The current study population also included a broad range of genetic origins of RP, as well as a variability in BCVA, age, and presence of cataract. While this diversity can be regarded as a limitation, it also serves as an advantage, allowing for a broader generalization of patients with RP as a clinical group with similar phenotypes, mimicking a real-world scenario of clinical trial inclusion. Finally, volunteer bias may be a potential limitation, as patients who choose to participate in this study might experience lower levels of disability compared to those who opted not to participate.

In conclusion, this prospective cohort study is the first to correlate the FST with self-reported visual function, using the MRDQ in a broad cohort of patients with RP. The established correlations with related domains of the MRDQ further underscore the clinical relevance and utility of FST measurements for monitoring disease progression and evaluating treatment efficacy in RP. These findings strengthen the use of FST-based endpoints in both natural history studies and treatment trials involving patients with RP.

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ETHICS STATEMENT

This study includes human participants and was approved by the ethics committee of the Leiden University Medical Center (NL79646.058.21/P21.121). Before participating in the study, the participants were informed in detail and provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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