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Longitudinal Changes in Scotopic and Mesopic Macular Function as Assessed with Microperimetry in Patients with Stargardt Disease: SMART Study Report No. 2

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Short Title:
Scotopic and Mesopic Macular Functions in Stargardt Disease

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Abstract

Purpose: To estimate and compare cross-sectional scotopic versus mesopic macular sensitivity losses measured by microperimetry, and to report and compare the longitudinal rates of scotopic and mesopic macular sensitivity losses in *ABCA4* gene associated Stargardt Disease (STGD1).

Design: Multicenter prospective cohort study.

Methods: Participants: 127 molecular confirmed STGD1 patients enrolled from 6 centers in the USA and Europe and followed every 6 months for up to 2 years.

Observation Procedures: The Nidek MP-1S device was used to measure macular sensitivities of the central 20° under mesopic and scotopic conditions. The mean deviations (MD) from normal for mesopic macular sensitivity for the fovea (within 2° eccentricity) and extrafovea (4°-10° eccentricity), and the MD for scotopic sensitivity for the extrafovea were calculated. Linear mixed effects models were used to estimate mesopic and scotopic changes.

Main Outcome Measures: Baseline mesopic mean deviation (mMD) and scotopic MD (sMD) and rates of longitudinal changes in the mMDs and sMD.

Results: At baseline, all eyes had larger sMD, and the difference between extrafoveal sMD and mMD was 10.7 dB (p<.001). Longitudinally, all eyes showed a statistically significant worsening trend: the rates of foveal mMD and extrafoveal mMD and sMD changes were 0.72 (95%CI: 0.37 to 1.07), 0.86 (95%CI: 0.58 to 1.14) and 1.12 (95%CI: 0.66 to 1.57) dB/year, respectively.

Conclusions: In STGD1, in extrafovea, loss of scotopic macular function preceded and was faster than the loss of mesopic macular function. Scotopic and mesopic

macular sensitivities using microperimetry provide alternative visual function outcomes for STGD1 treatment trials.

Introduction

Stargardt disease type 1 (STGD1) is the most prevalent juvenile macular dystrophy with an estimated population prevalence of 1/6,500 in the US, and can affect both children and adults[1-4]. It is caused by variants in the *ABCA4* gene, and primarily inherited as an autosomal recessive trait[3]. The disease exhibits great genotypic and phenotypic heterogeneity, but the typical pathology involves atrophy of the para-foveal and/or foveal regions of the macula, with expansion to the peripheral retina over time[3]. Clinically, patients experience a gradual loss of central vision, and may reach legal blindness over decades[5,6].

The *ABCA4* gene is expressed in both rod and cone photoreceptors[7-9], and both cone and rod functions are affected in STGD1 as a consequence of pathogenic variants in *ABCA4*. A study at the photoreceptor level using Adaptive Optics Scanning Light Ophthalmoscopy (AOSLO) technology suggested that at the early stage loss of cone photoreceptors focused in the fovea whereas peripheral loss focused on rod photoreceptors[10]. Understanding clinically the temporal and spatial loss of different photoreceptor types will facilitate a better understanding of disease pathophysiology and can inform choices of clinical measurements based on the specific pathways targeted by therapeutic interventions.

Microperimetry (MP), an automated fundus perimetry with live eye tracking, has become a useful clinical tool to monitor retinal disease progression [11]. The quantitative

macular sensitivity measurements generated from MP also provide potential visual function outcome measures for STGD1 treatment trials. A few studies have reported macular sensitivity loss in STGD1 under mesopic conditions using cross-sectional and longitudinal MP data[12-19], but there is little available data describing scotopic macular function loss in STGD1[20 21].

The prospective ñProgression of Atrophy Secondary to Stargardt Diseaseò (ProgStar) study (ClinicalTrials.gov ID: NCT01977846) is a multicenter natural history study designed to assess visual function and retinal morphological changes in STGD1 and to help identify appropriate outcome measures for STGD1 treatment trials[22]. Its ancillary study, the ñScotopic Microperimetric Assessment of Rod Function in Stargardt Diseaseò(SMART) study, focused on assessing macular function loss under scotopic conditions in STGD1[23].

To better understand macular function loss in STGD1 natural history and to assess the potential of macular sensitivity measurements as primary outcome measures for STGD1 trials, the current analysis used the longitudinal data of ProgStar participants enrolled in the SMART study and aimed to compare cross-sectional scotopic versus mesopic macular sensitivity loss, to report the longitudinal rate of scotopic macular sensitivity loss and to compare it to the rate of mesopic macular sensitivity loss.

Methods

The study designs of the ProgStar and the SMART studies were reported previously[22,23]. In brief, the international ProgStar study enrolled 259 STGD1 patients from 9 clinical centers in the US, United Kingdom, France and Germany during 2014-

15. Eligibility of participants and inclusion criteria of study eyes particularly relevant here included: ageÓ6 years and having 2 pathogenic mutations in the ABCA4 gene, or having 1 pathogenic mutation in the ABCA4 gene together with a typical STGD1 phenotype; and eyes having a best corrected visual acuity (BCVA) of 20 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters (i.e., 20/400 Snellen equivalent or better), and having at least 1 well-demarcated area of atrophy on fundus autofluorescence (FAF) imaging with a diameter of 300 ε m or more and the sum of all lesions of 12 mm^2 or less (further inclusion/exclusion criteria are described in ProgStar report no. 1 22). All participants provided written informed consent before enrollment in the study. ProgStar participants were followed every 6 months for 2 years. At each study visit, participants underwent a detailed ophthalmic exam, BCVA testing using the ETDRS protocol 24, and mesopic MP testing. FAF and spectral domain ocular coherence tomography (SD-OCT) images were also obtained.

After the ProgStar study started enrollment, the SMART study was initiated and 6 ProgStar sites participated. Informed consents were obtained for ProgStar participants to undergo scotopic MP testing during their remaining ProgStar visits. Only one eye was selected to undergo scotopic testing. The selection was determined by the site principal investigators and they were recommended by the study protocol to select the eye with the smaller lesion from FAF imaging, better BCVA, and/or better fixation23. Mesopic and scotopic MP tests were repeated at each subsequent available ProgStar follow-up visit using the follow-up function of the MP device.

Nidek MP-1S (Nidek Technologies, Inc., Gamagori, Japan) and the associated NAVIS Software (v.1.7.7 or higher) (Nidek Technologies S.R.L.) were used for both

mesopic and scotopic MP testing. Procedures for the mesopic testing and fixation assessment were described previously [19,25]. Briefly, under dim room lighting, mesopic macular sensitivity was tested at 68 retinal locations using a pattern comparable to the Humphrey 10-2 protocol (**Error! Reference source not found.** Left). A white stimulus (0.43 degree diameter; comparable to Goldmann III) was used with a duration of 200 ms and on a dim white background (1.27 candela (cd)/m^2). Both cones and rods should contribute to the sensitivity response under such testing conditions. The maximum stimulus luminance in MP-1S was 127 cd/m^2 [26].

Under the SMART study protocol, testing under scotopic conditions was added where macular response was predominantly driven by rod photoreceptors in normal eyes. The scotopic testing was performed in a fully darkened room. Sensitivity was tested at 40 retinal locations distributed in a region that extended 4-10 degrees from the foveal center in a custom pattern shown in **Error! Reference source not found.** Right. Before scotopic testing, the eye selected for SMART was occluded for dark adaptation using a double pad and eye patch for at least 30 minutes. To maintain the dark-adapted state, the test background was changed to dim red, and a short-pass (<500 nm, blue) filter (NT52532, Edmund Optics, Barrington, NJ) was inserted into the light path. The dynamic range of the test stimuli was tuned to the typical range of the rod threshold by inserting neutral density (ND) filters. Considering the already impaired visual functions in STGD1 patients, the SMART protocol requested a 1.0-log unit ND filter (1.0ND) which attenuated the luminance of the test stimuli by a factor of 10, although the commonly used 2.0ND filter was also provided. The ND filter used was recorded in the data collection form.

In both the scotopic and the mesopic tests, the SD-OCT image was used to center the test pattern on the anatomical fovea as accurately as possible by the photographer. The sensitivity at each retinal location was determined using the 4-2 threshold strategy. A sensitivity value of 0 dB corresponded to the brightest stimulus applied and a 20 dB value corresponded to the dimmest stimulus. To ensure optimal tracking of the fundus during the testing, participants were instructed to fixate on a fixation target throughout testing (a red cross for the mesopic test and a ñwhiteò circle that appeared blue due to the inserted blue filter for the scotopic test). All examinations were performed monocularly with the contralateral eye patched. The mesopic test always preceded the scotopic test for SMART study eyes, and both MP tests always preceded FAF imaging.

The pattern placement on the fovea was categorized as ñadequateò, ñfairò, ñpoorò, or ñcannot gradeò by the study central reading center. When the center of the grid was Ò1Áfrom the anatomical fovea this was graded as ñadequateò. Distances from 1Áto less than 2Áwere ñfairò. ñPooròpattern placement meant that the grid was improperly placed at a distance Ó2Áand these test results were excluded from subsequent analyses.

Macular Sensitivity

The dB output from the MP-1 is a unit relative to the maximum luminance of the MP test which was different between mesopic and scotopic conditions. The thresholds under mesopic and scotopic conditions in normal eyes are also different. Therefore, direct comparison of the numerical output from the above mesopic and scotopic MP tests would not be meaningful. For mesopic response, the dB output from the MP-1 (denoted as X_m) was converted to the mean deviation (MD) from the maximum

measurable normal mesopic sensitivity, that is, the mesopic MD was calculated as (20-X_m) 27. For scotopic response, the dB value (denoted as X_s) was converted to the MD from the maximum measurable normal scotopic mean sensitivity under the scotopic testing condition using the 2ND filter (i.e. 20dB)28, that is, the scotopic MD was calculated as (20- X_s) for eyes where the 2ND filter was used and as [20-(X_s-10)] for eyes where the 1ND filter was used.

The scotopic MP test pattern covered the extrafoveal region extending 4°-10° eccentricity. To compare mesopic and scotopic macular function losses in this same region (Figure 1 Left), the mesopic MD (mMD) of the 64 test loci in this region was calculated (Figure 1 Right), and the scotopic MD (sMD) was calculated from the 40 test loci. Fovea mMD was also calculated using the 4 loci within 2° eccentricity from the mesopic MP test.

Statistical Analyses

At the first visit for the SMART study, participantsô corresponding mesopic MP test results were abstracted from the ProgStar study database. Paired t-test was used to compare the extrafoveal mMD and sMD, and Pearson correlation coefficient was estimated for the extrafoveal mMD and sMD. A linear regression model was also used to assess whether the difference between extrafoveal mMD and sMD was associated with the level of scotopic function loss (i.e. sMD). In addition, the foveal mMD and extrafoveal sMDs were estimated for the subgroups of eyes that had ñapproximately normalò extrafoveal mesopic sensitivity and of eyes that had ñapproximately normalò foveal mesopic sensitivity (operationally defined as mesopic mean sensitivity from MP1-S Ó12dB, i.e. mMD<8 dB 29).

Longitudinally, the rate of change of each MP parameter was estimated using a linear mixed effect model (LMEM), where the mean of the parameter was modeled as a linear function of time since the first visit, with the intercept and slope parameter assumed to be random effects following normal distributions. Such modeling implicitly accounted for the correlation from repeated measurements. To compare between the rates of changes of extrafoveal sMD and mMD, the LMEM was extended to include an indicator of MP test type and its interaction with time. The coefficient of the interaction term quantifies the difference in the rates of changes of extrafoveal MDs between the scotopic MP and mesopic MP tests.

All analyses were conducted in SAS 9.4, and two-sided p-values from Wald-tests were reported. The model fit for LMEMs was inspected visually and based on plots of scaled residuals [30].

Results

Participants Disposition and Demographics

The SMART study enrolled 130 participants (eyes) and scotopic MP was tested for a total of 497 eye-visits. Among these eye-visits, 4 scotopic tests (0.8%) and 6 mesopic MP tests (1.2%) were deemed ungradable by the reading center, and 41 scotopic tests (8.3%) and 60 mesopic tests (12.1%) had poor pattern placement. Among the 442 eye-visits with scotopic MP of adequate or fair pattern placement, 401 eye-visits had mesopic MP tests of adequate or fair pattern placement. These 401 eye-visits were from 127 of the SMART participants (97.7%), and their baseline data (i.e., their first SMART visit) were used to compare between mesopic and scotopic sensitivity impairments cross-sectionally. There were 116 participants for whom data for at least 2

visits were available for the longitudinal data analysis. Seventy-three eyes contributed data at the 6-months follow-up, 89, 83, and 29 eyes contributed data at the 12, 18 and 24-months follow-ups, respectively.

Table 1 summarizes the baseline characteristics for the 127 SMART participants: 52% were female, 83% were white, mean age was 34.5 (standard deviation [SD]=15.1) years, and mean BCVA was 52 ETDRS letters (20/91 Snellen equivalent) (SD=19 letters). The mean age at symptom onset was 24.7 (SD=14.5) years and the mean duration of symptoms was 10.1 years (SD=7.0); with 41.7% of the cohort reporting symptom onset at an age Ò18 years (Table 1).

Mean Deviations (MD) at the Baseline Visit

At SMART baseline (Table 1), the median mesopic MD (mMD) of the overall central 20° test field was 8.4 dB (interquartile range [IQR] 4.8 to 10.8). The median mMD for the foveal region was 16.8 (IQR 15.0 to 20.0) dB. The median mMD and scotopic MD (sMD) for the extrafoveal region was 7.9 dB (IQR 4.2 to 10.3) and 18.6 dB (IQR 14.9 to 21.8), respectively. Figure 2A shows the cross-sectional distribution of sMD and mMD for the extrafovea. The mean difference between extrofoveal sMD and mMD was 10.7 dB (95%CI 10.1 to 11.3, p<.001) (positive [sMD-mMD] value indicates larger scotopic impairment). The correlation coefficient between extrafoveal sMD and mMD was 0.82 (p<.001). All eyes had mMD smaller than sMD, indicating larger impairment of scotopic sensitivity in the extrafoveal region. Figure 2B is the scatterplot showing the difference between extrafoveal scotopic and mesopic MDs as a function of extrafoveal sMD: the positive linear trend had a slope of 0.32 (95%CI: 0.20 to 0.43, p<.001), suggesting that every 1dB larger scotopic sensitivity loss was significantly

associated with 0.32 dB greater difference between mesopic and scotopic sensitivity impairments.

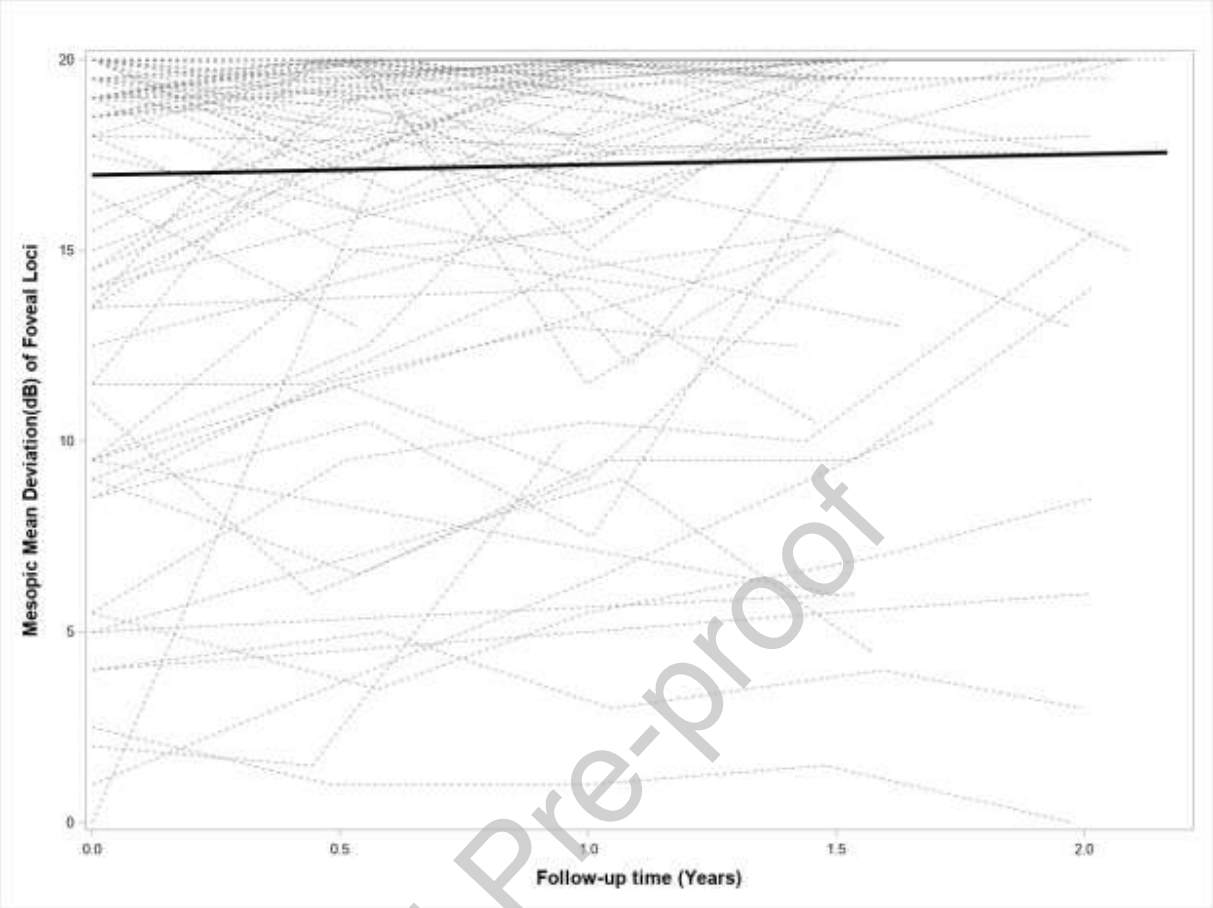
At baseline, there were 81 eyes that had ñapproximately normalò extrafoveal mMP (MD<8dB). Among these eyes, the median foveal mMD was 19.0 (IQR 11.5 to 20; range 0 to 20) dB; and the median extrafoveal sMD was 15.6 (IQR 13.7 to 17.8, and range 0.6 to 29.1) dB (Table 1).

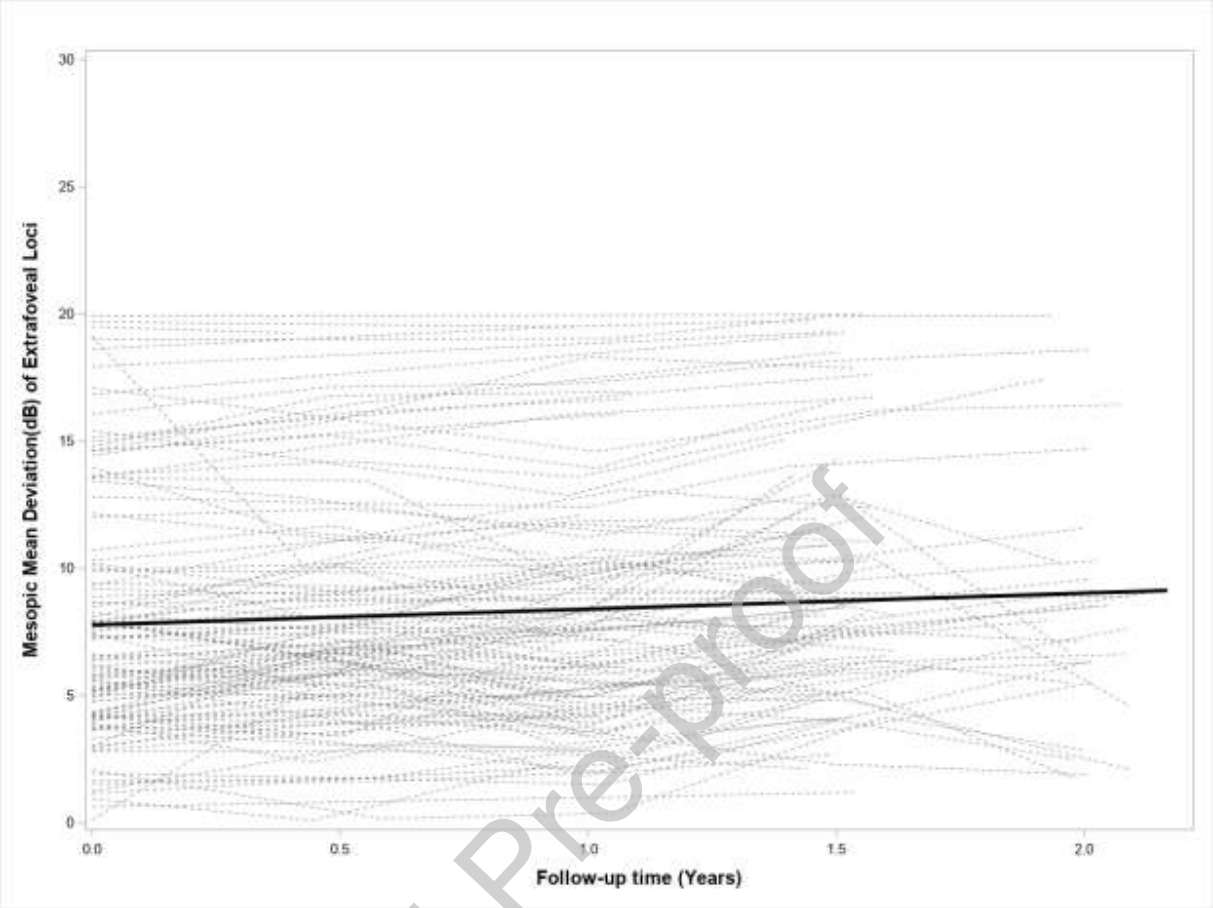
There were 11 eyes that had ñapproximately normalò foveal mMP (i.e. sensitivity Ó12dB) (Supplemental table 1). Among these eyes, the median extrafoveal mMD was 1.7 dB (IQR 0.6 to 3.7, range 0 to 9.3); the median extrafoveal sMD was 12.6 dB (IQR 10.4 to 15. 6, range 0.6 to 25.7); and the median difference between extrafoveal sMD and mMD was 11.6 dB (IQR 6.7 to 12.6, range 0.5 to 17.6) dB (sMD-mMD positive indicates larger scotopic impairment).

Longitudinal Changes in Mean Deviations (MD)

Figure 3 shows the longitudinal data of foveal mMD and extrafoveal mMD and sMD of individual eyes. Large within-eye variability across visits for foveal mMD was observed for some eyes (Figure 3A). Nevertheless, the average of all eyes showed a statistically significant worsening trend and the rate of foveal mMD change was 0.72 (95%CI: 0.37 to 1.07) dB/year (Table 2). The rates of extrafoveal mMD and sMD changes were 0.86 (95%CI: 0.58 to 1.14) dB/year and 1.12 (95%CI: 0.66 to 1.57) dB/year (Figure 3 B-C) (Table 2), respectively.

Comparing between the rates of mesopic and scotopic changes, the model using both extrafoveal mMD and sMD data estimated that the difference in the rate of change





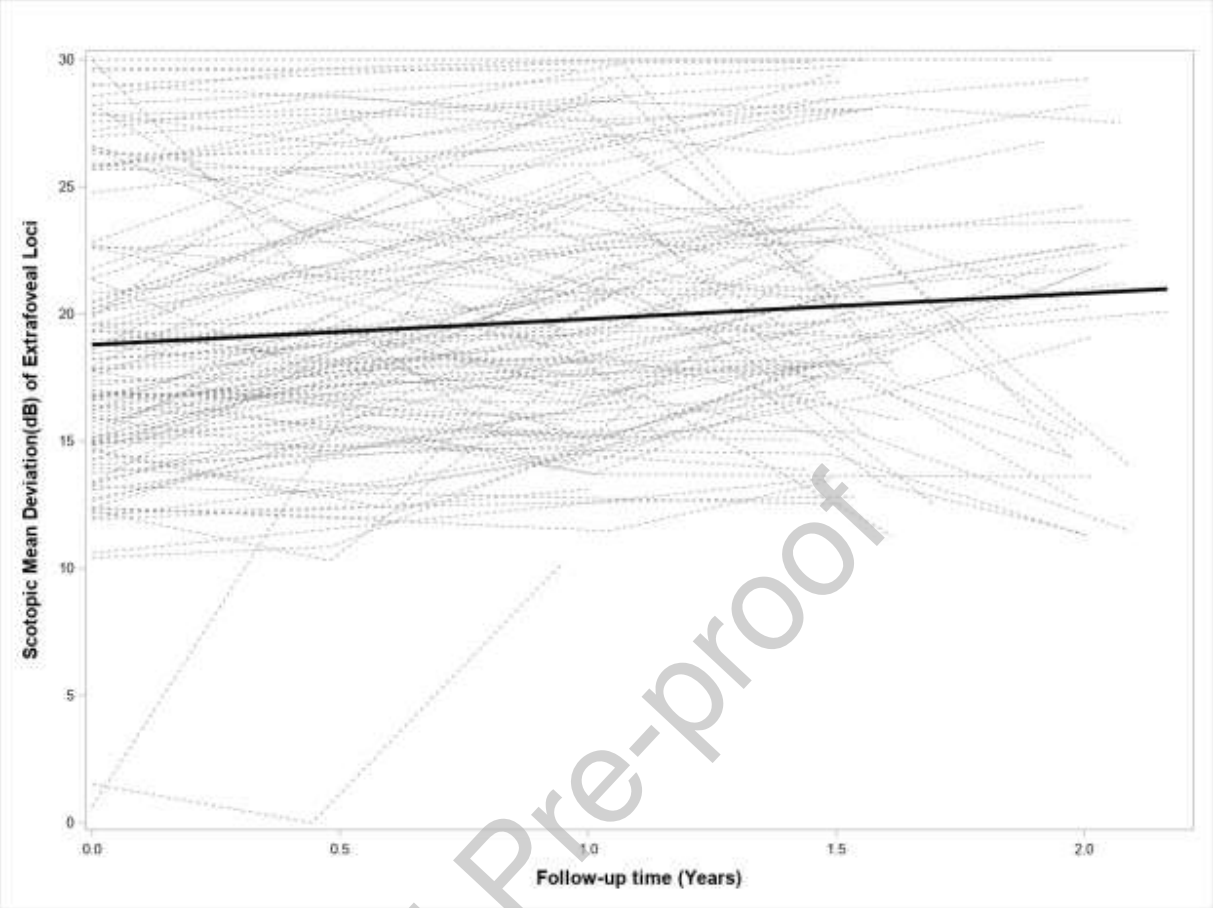


Figure 3. Spaghetti plots showing the longitudinal trajectories of mean deviations (MD) during the follow-up. Each dotted line shows observed data for one eye. The real line is the trend of average MD over time estimated using linear mixed effects model.

A. Mesopic MD of the fovea loci. The slope estimate is 0.72 (95%CI: 0.37 to 1.07) dB/year.

B. Mesopic MD of the extrafoveal loci. The slope estimate is 0.86 (95%CI: 0.58 to 1.14) dB/year.

C. Scotopic MD of the extrafoveal loci. The slope estimate is 1.12 (95%CI: 0.66 to 1.57) dB/year.

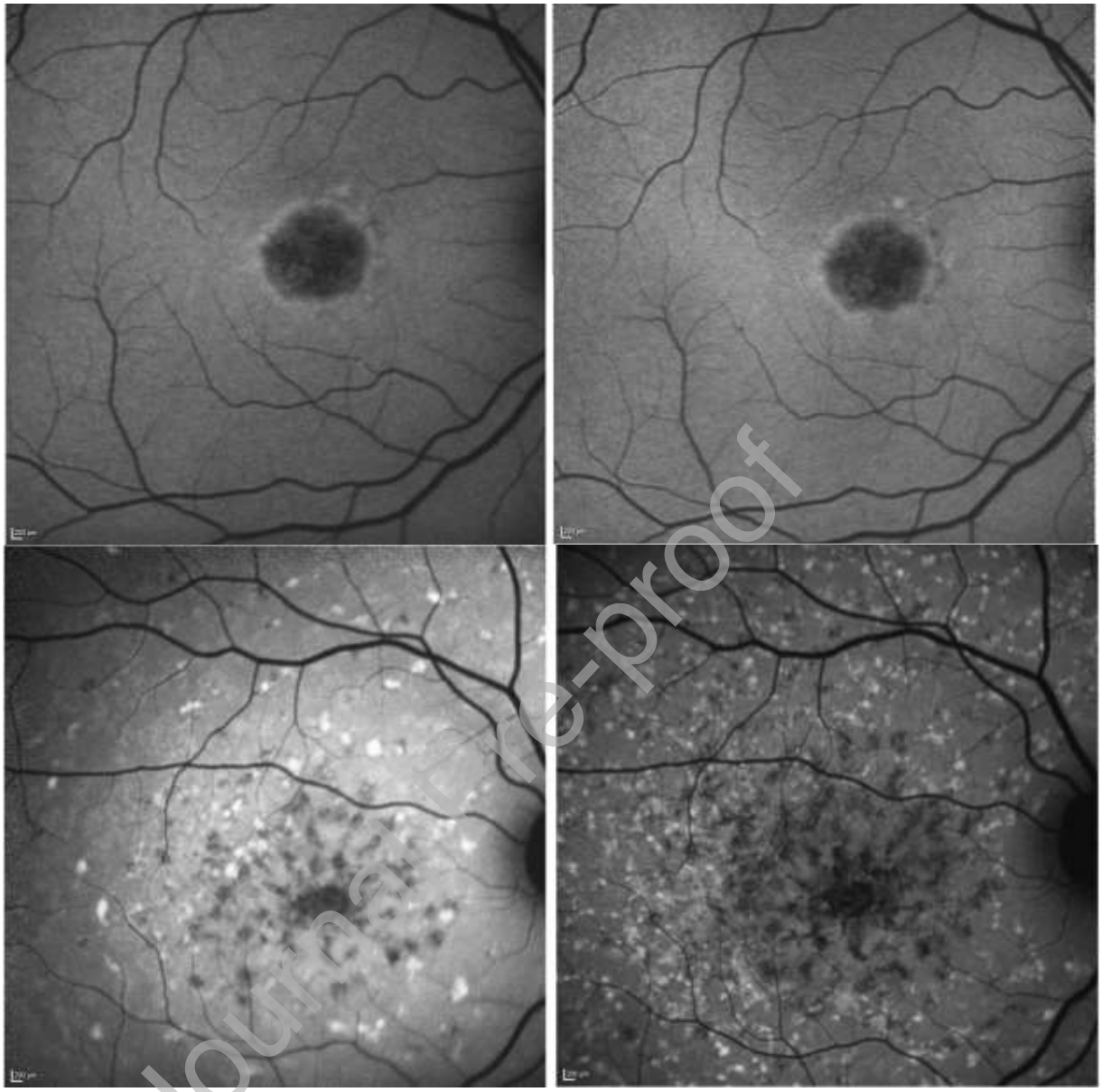


Figure 4. Fundus autofluorescence (FAF) images of the 2 eyes that had normal extrafoveal mesopic and scotopic sensitivity responses at SMART baseline.

A. FAF image of Eye 1 in Table 3 acquired at the SMART baseline visit (left) and the image acquired approximate 12-months after the SMART baseline visit (right).
B. FAF image of Eye 2 in Table 3 acquired at the SMART baseline visit (left) and image acquired at approximate 18-months after the SMART baseline visit (right).

Table 1. Baseline demographics and clinical characteristics of participants enrolled in the SMART study.

		Number *(n=127)*	%		
Gender					
Female		66	52.0		
Race					
White/Caucasian		105	82.7		
Black/African American		12	9.5		
Asian		7	5.5		
Unknown		3	1.6		
Age at onset					
Ò18		53	41.7		
>18		68	53.5		
unknown		6	4.7		
	Mean	**SD**	**Median**	**IQR**	Range
Age at Baseline (years)	34.5	15.1	33.0	22.0-45.0	11.0-70.0
Duration of symptoms (years)	10.1	7.0	8.5	5.5-13.5	0-30.0
Age at onset among known (years)	24.7	14.5	21.0	13.0-36.0	4.0-64.0
Best corrected visual acuity (ETDRS Letters) (Snellen equivalent)	52.0 (20/91)	18.6	45.0 (20/126)	39.0-70.0 (20/166-20/40)	19.0-93.0 (20/417 to 20/14)
Mean Deviations (MD) (dB) in all eyes (N=127)					
Overal Mesopic MD (central 20°)	8.36	4.79	7.20	4.80 to 10.80	0 to 19.90
Mesopic MD in the fovea (loci of 2° eccentricity)	16.78	5.32	19.50	15.00 to 20.00	0 to 20.00
Mesopic MD Extrafovea (loci of 4-10° eccentricity)	7.91	4.90	6.59	4.22 to 10.31	0 to 19.94
Scotopic MD Extrafovea (loci of 4-10° eccentricity)	18.59	5.60	17.40	14.90 to 21.78	0.63 to 30.00
Extrafovea Difference*: Scotopic MD-Mesopic MD	10.68	3.53	10.69	9.09 to 12.21	-0.03 to 24.93
Mean Deviations (MD) in eyes with approximately normal extrafovea mMD at baseline (N=81)					
Mesopic MD in the fovea	15.74	6.00	19.0	11.5 to 20.0	0 to 20

Scotopic MD Extrafovea	15.72	4.07	15.55	13.73 to 17.75	0.63 to 29.05
Mean Deviations (MD) in eyes with approximately normal fovea mMD at baseline (N=11)					
Mesopic MD in the extrafovea	2.67	2.89	1.66	0.63 to 3.69	0-9.34
Scotopic MD Extrafovea	12.67	7.06	12.58	10.43 to 15.56	0.63 to 25.68

IQR= interquartile range, SD = standard deviation. MD=Mean deviation from maximally measurable normal under Nidek MP-1S

*: Positive difference between scotopic and mesopic MDs means larger impairment in sMD.

Table 2. Rates of declines in foveal mesopic and extrafoveal mesopic and scotopic mean deviations. mMD: mesopic mean deviation. sMD: scotopic mean deviation. CI: confidence interval.

	Rates		
	Foveal mMD (dB/year) (95%CI)	**Extrafovea mMD (dB) (95%CI)**	**Extrafovea sMD (dB) (95%CI)**
Among all eyes (N=127)	0.72 (0.37 to 1.07)	0.86 (0.58 to 1.14)	1.12 (0.66 to 1.57)
Among the eyes with approximately normal extrafovea mMD at baseline (N=81)	0.96 (0.47 to 1.46)	0.96 (0.61 to 1.32)	1.31 (0.74 to 1.89)
Among the eyes with approximately normal fovea mMD at baseline (N=11)	2.98 (-0.21, 6.18)	1.20 (-0.06 to 2.46)	1.58 (-0.84 to 4.00)

Table 3. Detailed data for the 2 eyes that had both scotopic and mesopic extrafoveal sensitivity above average normal at the baseline.

		Foveal mMD (dB)	**Extrafovea mMD (dB)**	**Extrafovea sMD (dB)**	**Atrophic lesion size in FAF (mm^2)***	**BCVA(ETDRS Letters)** (Snellen equivalent)
Eye 1	First visit	2.0	0.94	1.53	2.19	48 (20/110)
	Last visit (12-months follow-up)	10	2.41	10.20	2.25	49 (20/100)
Eye 2	First visit	0	0.13	0.63	0.57	45 (20/126)
	Last visit (18-months follow-up)	20.0	4.41	11.28	1.59	43 (20/138)

mMD: mesopic mean deviation.
sMD: scotopic mean diviation.
*: Atrophic lesion size was measured as the area of decreased autofluoresence
FAF: fundus autofluorescence
BCVA: best corrected visual acuity
ETDRS: Early Treatment Diabetic Retinopathy Study