Subretinal Drusenoid Deposits and the Loss of Rod Function in Intermediate Age-Related Macular Degeneration

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Numerous psychophysical studies have reported that rod function is affected in the early stages of AMD.1–5 However, these early studies1–5 have been limited by two important considerations. First, when these studies were performed, AMD status was graded using only color fundus photographs. Multimodal imaging (MMI) was not available at the time to further phenotype the participants with newly described changes that contribute to risk of vision loss, such as the presence of subretinal drusenoid deposits (SDD), also referred to as reticular pseudodrusen.6 Second, the ability to test rod function in earlier studies (primarily by determining the rod intercept time) was in large part limited to one location within the macula. Thus, rod functional topography and the structure–function relationship within the macula could not be obtained in previous studies.1–5 These two limitations have now been addressed with the recent development of the Macular Integrity Assessment (S-MAIA; CenterVue, Padova, Italy) microperimeter,16,17 designed to allow static rod-mediated function to be assessed at multiple locations within the macula in the one testing session.

To date however, data on rod function throughout the macula, in eyes with early stages of AMD, remains limited because many scotopic perimeters do not have sufficient dynamic range to allow detection of the earliest rod abnormalities without coming up against the floor and ceiling effects.16,18 The issues associated with limited dynamic range have now been addressed with the recent development of the Medmont dark-adapted chromatic perimeter (DACP; Medmont Pty Ltd International, Nunawading, Victoria, Australia), which has a large dynamic range covering the entire range of dark-adapted rod-mediated function.18 As both static and dynamic rod function can be assessed at multiple retinal locations using a DACP,19 the relationship between rod function and new anatomic features now discernable with MMI can be investigated.
In recent years, several studies have used a scotopic perimeter to assess static and dynamic rod function at multiple retinal locations in eyes with AMD.\(^1\)\(^6\)\(^-\)\(^8\) In these studies, rod function was assessed after a period of dark-adaptation either with or without preceding photobleach. Given that there is increased interest in using a scotopic perimeter for monitoring AMD progression in clinical studies and drug trials it is important to determine which perimetric testing method is superior in detecting rod abnormality and functionally characterizing the disease phenotype in eyes with AMD. Thus, the aim of this study was to compare dark-adapted rod-mediated function obtained without photobleach to that obtained with a preceding photobleach in healthy control participants and those with intermediate AMD in the presence and absence of SDD.

Methods

This was a cross-sectional study, which was approved by the Human Ethics Committee of the Royal Victorian Eye and Ear Hospital. Written informed consent conforming to the tenets of the Declaration of Helsinki was acquired from all participants.

Subjects

Participants were recruited from existing research cohorts in the Macular Research Unit at the Centre for Eye Research Australia. Participant’s eligibility criteria included age 50 years and older with best-corrected visual acuity (BCVA) of 20/60 or better. Inclusion criteria required AMD cases to have drusen greater than 125 μm with or without any AMD pigmentary abnormalities in both eyes (a subset of intermediate AMD as classified by the Beckman classification).\(^2\) Subjects with evidence of current or past neovascular AMD, or GA in either eye were excluded. Control participants were recruited from spouses, friends, or relatives of the AMD participants or were staff members. Control participants were defined as having no apparent aging changes, with no drusen nor AMD pigmentary abnormalities as defined by the Beckman classification.\(^2\) Exclusion criteria for both groups included people with cataract grade greater than 2 (World Health Organization grading system)\(^5\) and other significant ocular media opacity that could obscure fundus examination or multimodal imaging examination, diabetic retinopathy, glaucoma, refractive error of greater than 6 diopters, severe neck and spinal problems preventing the performance of the perimetry tests, or having medications that might affect the retinal function.

Procedures

Upon arrival at the clinic, the subjects were seated in an examination room with a standardized lighting condition. The nature of the study was explained to the subjects and informed consent was obtained. Best-corrected and low-luminance logMAR visual acuity (LLVA) was measured at a distance of 4 m. LLVA was assessed immediately after BCVA with a 2.0-log unit neutral density filter. We chose one eye, the one with the better BCVA as the study eye. When both eyes had the same BCVA, the right eye was chosen as the study eye. After visual acuities were measured, the pupils were dilated with a drop of tropicamide 0.5% in each eye (Mydriacyl; Alcon Laboratories (Australia) Pty Ltd, Frenchs Forest, New South Wales, Australia). The study eye was then dark-adapted for scotopic perimetric examinations. The commencement of dark-adaptation was approximately 30 minutes after the subjects arrived at the clinic. During dark adaptation, participants were interviewed with a standardized questionnaire including history of systemic and eye diseases, medications, vitamins, and supplements being taken to rule out any systemic or eye condition that may affect vision. Scotopic perimetric examinations were performed when the eye had been dark-adapted for 30 minutes. Multimodal imaging was performed after all psychophysics testing was completed to prevent additional bleaching of the retina prior to measurement of rod-mediated function.

Dark-Adapted Chromatic Perimeter (DACP) Examination

Rod-mediated function was assessed using a Medmont dark-adapted chromatic perimeter. The DACP has two color stimuli, one at 505 nm (dynamic range, 0–75 dB) and the other at 625 nm (dynamic range, 0–50 dB); thus, a two-color perimetry technique can be used to determine rod function at multiple retinal locations.\(^1\) Spherocylindrical lens correction was inserted into a lens holder with the refractive correction set-up for a viewing distance of 30 cm. A stimulus size of 1.73° (Goldmann size V) was used and the stimuli were presented with durations of 200 ms. Retinal sensitivities were determined using a 4-2 staircase threshold strategy.

We performed two scotopic perimetric examinations on each participant to compare the rod function obtained without (first examination) and with a preceding photobleach (second examination). Sensitivity of both the 505- and 625-nm stimuli was measured for each perimetric examination.

For the first scotopic perimetric examination, the stimulus grid for the 505-nm stimulus consisted of 28 test points located within the central 24° of the retina and distributed at 4°, 6°, 8°, 12°, 17°, and 24° eccentricity from the fovea. Test points for the 625-nm stimulus were distributed at 2°, 4°, 6°, 8°, 12°, 17°, and 24° eccentricity from the fovea. Retinal sensitivity for the 505-nm stimulus was obtained first, followed by the 625-nm stimulus. Retinal sensitivity measurement for the 505-nm stimulus was performed after the eye had been dark-adapted for 30 minutes without a preceding photobleach. At the completion of the measurement for the 505-nm stimulus a short break was provided before the commencement of the measurement for the 625-nm stimulus. This was to avoid fatigue and to ensure an accurate time frame for the 625-nm measurement. Retinal sensitivity measurement for each stimulus took approximately 3 to 4 minutes.

After the first scotopic perimetric examination, participants had a short break (~1–2 minutes) in the dark, then the study eye was bleached approximately 20% with a customized Ganzfeld flash. The details of the photobleach device have been described in our previous publications.\(^1\)\(^9\) In brief, the device was constructed in our laboratory comprising a tube with a translucent dome positioned inside the tube at the observer’s end and a light source positioned at the other end. The light source was a photographic flash (Mecablitz 45 CL-4; Metz-Werke GmbH & Co., Zirndorf, Germany). Only one flash was applied to the study eye and it bleached approximately 20% of rod photopigment with an 8-mm pupil. After a photobleach, the eye was dark-adapted for 30 minutes. During these 30 minutes, recovery of retinal sensitivity was assessed at a regular interval (data not presented). The scotopic perimetric data obtained at 30 minutes after dark-adaptation were used to compare with those obtained in the first scotopic perimetry examination. As we were recording the recovery of retinal sensitivity following bleaching, we limited the number of test points to reduce the testing time. For the 505-nm stimulus, 14 test points were distributed at 4°, 6°, 8°, and 12° eccentricity rings and for the 625-nm stimulus, there were 18 test points located in 2°, 4°, 6°, 8° to 12° eccentricity rings.
Digital color fundus photographs with 50 RPE.24,25 To ensure we recruited certain patient phenotypes, membra or outer plexiform layers and retinal pigment epithelium shaped subretinal deposits between external limiting mem-

gird). On SD-OCT, SDD were defined as clear-round or cone-absence of SD-OCT findings (including outside the SD-OCT more than one B-scan and in at least one en-face modality (CFP , SW-FAF, and NIR images. A senior grader using a Heidelberg Eye Explorer software (Heidelberg Engineering). The NIR was exported into Tagged Image File Format and the sensitivity plot was then superimposed onto the NIR image based on their subtended visual angle.

We also evaluated the SD-OCT for presence of other AMD-related changes, which have been reported as being associated with risk of progression to vision loss, such as hyperreflective foci,11,13 and nGA.14 Hyperreflective foci (HF) were defined as hyperreflective material above the RPE and on the top of drusen.12 We defined the presence of hyperreflective foci if there were five or more focal hyperreflectivity material in more than one SD-OCT B-scan. Nascent geographic atrophy is defined on SD-OCT by evidence of photoreceptor loss, such as the subsidence of the inner retinal layers (outer plexiform layer and inner plexiform layer) or a hyperreflective wedge-shaped band within the limits of the outer plexiform layer, in a region of RPE disruption and signal hypertransmission at the level of the choroid.14,15

Multimodal Imaging

Multimodal imaging was performed on both eyes after the DACP testing was complete. All participants underwent NIR, short-wavelength FAF (SW-FAF), OCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany), and color fundus photography (Canon CR6-45NM; Canon, Saitama, Japan). For the SD-OCT imaging, we obtained 49 B-scans within the central 20° × 20° of the retina in high-resolution mode and averaged 25 frames for every single OCT scan. Digital color fundus photographs with 50° field centered on the fovea were taken.

Clinical Grading

AMD was graded using color fundus photographs and SDD status was confirmed with a combination of color fundus photographs, OCT, SW-FAF, and NIR images. A senior grader graded AMD characteristics, however, both a senior grader and a senior medical retina specialist (RHG) graded the SDD status. If disagreement occurred they met to reach a consensus. Both graders were masked to the perimetric examinations. The AMD grading was based on the Beckman Classification and Grading System.22 We included individuals with no apparent aging changes (no drusen and no AMD pigmentary abnormalities), and no SDD in the control group. Cases with intermediate AMD (drusen >125 μm with or without any AMD pigmentary abnormalities) were divided into those with SDD and those without. SDD was graded into three categories of definitely present, questionable, or absent. Definitely present category was defined as the presence of five or more SDD on SD-OCT in more than one B-scan and in at least one en-face modality (CFP, FAF, NIR) or SDD present on two en-face modalities in the absence of SD-OCT findings (including outside the SD-OCT grid). On SD-OCT, SDD were defined as clear-round or cone-shaped subretinal deposits between external limiting mem-

brane or outer plexiform layers and retinal pigment epithelium (RPE).21,25 To ensure we recruited certain patient phenotypes, only subjects with definite bilateral SDD or definitely no SDD in either eye were included in the study. Subjects with questionable SDD were excluded. To examine the relationship between rod function and the presence of SDD or drusen, the areas of SDD and drusen were marked on an NIR image by a single examiner using a Heidelberg Eye Explorer software (Heidelberg Engineering). The NIR was exported into Tagged

Statistical Analysis

We analyzed the data with our participants divided into the following three groups based upon their clinical characteristics: control participants, intermediate (i)AMD without SDD, and iAMD with SDD in both eyes. ANOVA and a post hoc analysis using Bonferroni correction were used to compare the age, BCVA, LLVA, and low-luminance deficit (LLD) in between the study groups. We performed a χ² test to determine whether the characteristics in the AMD phenotypes were different between no SDD and SDD groups. To determine the rod function at each test point, the sensitivity difference between the 505- and 625-nm stimuli (Fig. 1) were calculated for locations where both stimuli were tested. The average point-wise sensitivity difference (PWSD) was compared among the study groups. The smaller the sensitivity difference (ΔS) indicated the worse rod function as depicted in Figure 1. The average point-wise sensitivities (PWS) for the 505- and 625-nm stimuli as well as the PWSD obtained after either without or with a photobleach were compared among the study groups using linear mixed-effects model, with the study groups as the fixed effect and test points nested within an eye as a random effect, and age as a covariate. To examine the extent of rod dysfunction as a function of eccentricity, the average PWSD for each concentric ring and each test point were calculated and compared among the study groups. Rod function was also compared between areas with and without SDD or drusen, and between the presence or absence of hyperreflective foci and/ or nGA. All statistical analyses were performed using SPSS software (IBM SPSS Statistics, software version 21; IBM/SPSS, Inc., Chicago, IL, USA), and the significance level was set at 0.05.

Results

A total of 66 eyes of 66 subjects, 29 control and 37 iAMD subjects, were included in this study. Twenty participants in the iAMD group did not have SDD in either eye, while 17 study participants had SDD in both eyes. None of the subjects had questionable SDD. The Table provides a summary of the clinical characteristics of the study subjects. Both the iAMD with and without SDD groups were older and had worse LLVA (but not LLD) compared with the control group. There was no significant difference in age, BCVA, LLVA, LLD, and AMD characteristics between the iAMD without SDD and the iAMD with SDD groups (P ≥ 0.46).

The average PWSD for 505- and 625-nm stimuli as well as the PWSD of the two wavelengths obtained without and with preceding photobleach are shown in Figure 2. The average
PWSs for the 505- and 625-nm stimuli measured without photobleach were significantly lower in both the SDD and no SDD groups compared with the control group (Fig. 2A). The rod-mediated function, as demonstrated by the average PWSD, was significantly reduced in the iAMD with SDD group (19.7 ± 0.3 dB) compared with both the control (P < 0.001) and the iAMD without SDD group (21.3 ± 0.2 dB, P < 0.001). No significant difference in the average PWSD was found between the iAMD without SDD and control group (P = 0.79).

The average PWS and the PWSD obtained with a preceding photobleach are presented in Figure 2B. The average PWS for the 505- and 625-nm stimuli as well as the PWSD were significantly reduced in both the iAMD with and without SDD groups compared with that of the control group; however, the greatest reduction in sensitivity was observed in the SDD group. Note that the smallest PWSD, implying worst rod-mediated dysfunction, was seen in iAMD eyes with SDD, and that scotopic perimetric examination with a preceding photobleach (Fig. 2B) demonstrated a greater rod dysfunction.

### TABLE. Characteristics of Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n = 29)</th>
<th>iAMD Without SDD (n = 20)</th>
<th>iAMD With SDD (n = 17)</th>
<th>Control vs. No SDD</th>
<th>Control vs. SDD</th>
<th>No SDD vs. SDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>64.2 ± 8.7</td>
<td>70.5 ± 7.9</td>
<td>74.1 ± 5.3</td>
<td>P = 0.02*</td>
<td>P &lt; 0.001*</td>
<td>P = 0.48*</td>
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<td>BCVA (mean ± SD, letters)</td>
<td>90.0 ± 4.6</td>
<td>81.2 ± 20.1</td>
<td>82.4 ± 4.7</td>
<td>P = 0.04*</td>
<td>P = 0.11*</td>
<td>P = 1.00*</td>
</tr>
<tr>
<td>LLVA (mean ± SD, letters)</td>
<td>79.3 ± 6.4</td>
<td>72.2 ± 10.6</td>
<td>69.4 ± 8.1</td>
<td>P = 0.02*</td>
<td>P &lt; 0.001*</td>
<td>P = 0.91*</td>
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<tr>
<td>LLD (mean ± SD, letters)</td>
<td>10.7 ± 3.0</td>
<td>12.6 ± 7.0</td>
<td>13.0 ± 5.0</td>
<td>P = 0.60*</td>
<td>P = 0.42*</td>
<td>P = 1.00*</td>
</tr>
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</table>

**AMD characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n = 29)</th>
<th>iAMD Without SDD (n = 20)</th>
<th>iAMD With SDD (n = 17)</th>
<th>Control vs. No SDD</th>
<th>Control vs. SDD</th>
<th>No SDD vs. SDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigmentary abnormalities, n (%)</td>
<td>0</td>
<td>7 (35%)</td>
<td>8 (47.1%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hyperreflective foci and/or nGA, n (%)</td>
<td>0</td>
<td>10 (50%)</td>
<td>7 (41.2%)</td>
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* Obtained by Bonferroni post-hoc test after 1-way ANOVA.
† Obtained by χ².

**FIGURE 2.** Average PWS and the average PWS difference (PWSD, 505–625 nm) of the study groups. (A) Rod function obtained without photobleach. The SDD group had a significant lower retinal sensitivity compared with the no SDD group for the 505-nm stimuli but not for the 625-nm stimuli. The average PWSD was significantly reduced in the iAMD with SDD group compared with both the control (P < 0.001) and the iAMD without SDD group (P < 0.001), however, no significant difference in the average PWSD was observed between the iAMD without SDD and control group. (B) Rod function obtained with a preceding photobleach. The average PWS for the 505- and 625-nm stimuli as well as the average PWSD were significantly reduced in both the iAMD groups compared with the control group (P < 0.001); however, eyes with SDD had a much greater reduction. Note that a greater rod dysfunction, as demonstrated by a smaller PWSD value, was observed when tested with a preceding photobleach compared with without photobleach. Error bars represent 95% CI.
The average PWSD was significantly smaller, but only within the central 8°, compared with that measured without a preceding photobleach (Fig. 2A).

**Topographic Sensitivity**

To determine if rod function varied with retinal location, we analyzed the results by ring of eccentricities (Fig. 3). When tested without photobleach, the average PWSD of eyes with SDD was significantly smaller within the central 8°, with the lowest sensitivity difference found at the 4° ring when compared with the control and the iAMD group without SDD groups. The average PWSD at test points greater than 8° was similar among all the study groups.

A similar finding was found when tested with a preceding photobleach, however the bleach accentuated the difference between the SDD group and the other two groups. A significant difference in PWSD was also noted at 12° ring but only between the iAMD with SDD and the control group (P = 0.03). No significant difference in PWSD was observed between the control and iAMD without SDD groups at any ring of concentricity tested.

The average PWSD at every test point is presented topographically in Figure 4. The smallest sensitivity difference was again observed at test points within the central 8° in the iAMD group with SDD.

We did not observe a correlation between the location of the SDD and the reduced function nor any correlation between the presence of normal drusen with loss of function in the AMD eyes. SDD were often identified outside the central 8°, particularly in the superior retina and yet the marked reduction in rod function was only within 8° of the central macula. Similarly the presence of large drusen within the central 8° in those without SDD did not contribute to a greater loss of function. Representative cases are shown in Figure 5.

We also evaluated rod function in a subset of the iAMD groups determined by the presence or absence of other identified anatomic changes considered to be high-risk features for progression to vision loss, hyperreflective foci, and/or nGA. The average PWSD did not differ in eyes with or without these high-risk features in groups either without SDD (21.6 ± 0.3 dB with the features and 21.3 ± 0.3 dB without the features, P = 0.60) nor with SDD (19.4 ± 0.4 vs. 20.3 ± 0.4 dB, P = 0.12).

**DISCUSSION**

In this study, we took advantage of MMI to phenotype our AMD cohort so that we could compare static rod function between healthy control participants and a homogeneous population of iAMD eyes that differed by the presence or absence of SDD and other high-risk features of progression. Using a Medmont DACP to perform two-color perimetry, we were able to not only isolate pure rod function but also to obtain rod function at multiple retinal locations to examine correlations between function and AMD phenotypic changes.

We found that the presence of SDD drove the association of reduced rod function, as determined by the PSWD, in eyes with iAMD. Although this study examined static rod function, our findings are in agreement with those reported in previous studies where rod recovery was assessed.19,26,27 In addition, we have further shown that static rod function of iAMD cases without SDD was indistinguishable from control cases when tested without photobleach. A difference in static rod function between iAMD without SDD and control group was only observed when tested with preceding photobleach. Our study highlights the importance of determining the presence of SDD in rod functional testing. Also determining rod function after bleaching may be necessary as it provides greater ability to differentiate disease severity when using scotopic perimetry.

This new finding is significant because many current clinical and drug trials in AMD do not bleach the retina prior to performing scotopic perimetric examination, and do not differentiate the presence or absence of SDD.

Another important finding in this study was the apparent lack of association between the functional deficit and the anatomic location of drusen or SDD. The greatest loss in rod function we detected was seen centrally within 8° in eyes where SDD were far more widely distributed. Conversely the
centrally located typical large drusen in cases without SDD, failed to be associated with poor function. Outside the parafoveal area, rod function of iAMD eyes with or without SDD was similar to healthy control participants, despite both drusen and SDD being present outside the central 8°. Similarly, other high-risk features for progression, such as HF or nGA also failed to be associated with worse rod function in either iAMD group. Recently, Lains et al. 27 reported a somewhat similar finding that abnormal rod function was associated with the presence of SDD anywhere in the macula. However, in the Lains et al. study, 27 the rod intercept time was used to determine rod recovery function and it was tested only at one retinal location 5° superior to the fovea.

It is still not well understood as to why the presence of SDD is strongly associated with defective rod function. There are several hypotheses. First, studies using histologic samples and adaptive optics imaging technique have suggested a potential direct mechanical influence or physical barrier, which affects transport between the RPE and the photoreceptor outer segment.6,28 However, this mechanism does not explain the lack of structure–function correlation in eyes with SDD. Second, decreased retinoid availability associated with choroidal thinning has also been hypothesized as a mechanism for abnormal rod function. Although, many studies have shown a significant decrease in choroidal thickness in eyes with SDD it remains unclear whether choroidal changes precede the development of SDD are sequelae.29–31 Furthermore, previous studies on choroidal thickness in eyes with SDD did not adequately adjust for variables known to influence choroidal thickness, such as age and refractive error. Once these factors are adjusted, we were unable to find any evidence of an association between the presence of SDD and choroidal thickness.32 Third, it has been shown that phagocytosis of outer segment by the RPE is an important contributor to retinoid recycling.33,34 As such it is possible that anomalies in photoreceptor outer segment phagocytosis by the RPE in eyes with SDD could explain rod dysfunction observed.

The strength of this study lies in having an AMD cohort, that are well phenotyped using MMI, and which have a uniform AMD stage; all having drusen greater than 125 μm in both eyes, a subset of iAMD. Additionally, we evaluated the spatial, topographic scotopic function using the novel DACP, a perimeter that has a very large dynamic range of test luminance to measure subtle deficits in sensitivity and two wavelengths stimuli, which allowed rod-mediated function to be measured. We also included cases with HF and/or nGA in our study, which represents a new appreciation of OCT defined signs that are thought to portent the development of GA and have not been considered in any similar study before. Finally, the level of bleach used in our study (20%) is less than the level used in other studies (>80%),1,2,26 which allowed for a more rapid delineation between the iAMD with SDD compared with those...
without SDD. This highlights the potential influence of different bleach level on the detection of rod dysfunction in iAMD eyes.

The limitations associated with the study included smaller AMD numbers once we divided into the two subgroups, and the study subjects were not aged-matched in the two AMD groups, with the SDD group being as expected, older. However, we controlled for the age difference in the statistical analysis to reduce the bias of age when comparing the retinal sensitivity between study groups. There was only one grader grading the AMD status, however, the grader was masked from the rod function assessment. The arduous nature of the perimetric tests means that we had to curtail the testing time to 30 minutes of adaptation, whereas a longer adaptation time would have allowed continued adaptation to occur. It would be interesting to know if rod sensitivity, in those with SDD can return to normal levels if given enough time to DA. These data will provide some clues as to whether impairment of rod function in eyes with SDD is a result of a total loss of rod function or merely a very prolonged rod functional recovery. Another limitation was that only subjects with BCVA of 20/60 or better were included in the study. Thus, our results are generalizable only to those with iAMD who have relatively good vision.

In conclusion, using a two-color perimetry technique offered in the Medmont DACP, we found that static rod-mediated function within the central 8° was preferentially affected in iAMD eyes with SDD regardless of whether tests were performed with or without preceding phobleach. Bleaching yielded a greater rod dysfunction compared with no bleaching. As SDD is considered a potential risk factor for late AMD, better understanding of their pathophysiology and how changes in rod function are associated with the progression of AMD warrant further investigation.

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