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Persons with age-related maculopathy risk genotypes and clinically normal eyes have reduced mesopic vision

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ABSTRACT

PURPOSE: To determine if participants with normal visual acuity, no ophthalmoscopically signs of age-related maculopathy (ARM) in both eyes and who are carriers of the $CFH$, $LOC387715$ and $HRTA1$ high-risk genotypes (“gene-positive”) have impaired rod- and cone-mediated mesopic visual function compared to persons who do not carry the risk genotypes (“gene-negative”).

METHODS: Fifty-three Caucasian study participants (mean 55.8 ± 6.1) were genotyped for $CFH$, $LOC387715/ARMS2$ and $HRTA1$ polymorphisms. We genotyped single nucleotide polymorphisms (SNPs) in the $CFH$ (rs380390), $LOC387715/ARMS2$ (rs10490924) and $HTRA1$ (rs11200638) genes using Applied Biosystems optimised TaqMan assays. We determined the critical fusion frequency (CFF) mediated by cones alone (Long, Middle and Short wavelength sensitive cones; LMS) and by the combined activities of cones and rods (LMSR). The stimuli were generated using a 4-primary photostimulator that provides independent control of the photoreceptor excitation under mesopic light levels. Visual function was further assessed using standard clinical tests, flicker perimetry and microperimetry.

RESULTS: The mesopic CFF mediated by rods and cones (LMSR) was significantly reduced in gene-positive compared to gene-negative participants after correction for age ($p=0.03$). Cone-mediated CFF (LMS) was not significantly different between gene-positive and -negative participants. There were no significant associations between flicker perimetry and microperimetry and genotype.

CONCLUSIONS: This is the first study to relate ARM risk genotypes with mesopic visual function in clinically normal persons. These preliminary results could become of clinical
importance as mesopic vision may be used to document sub-clinical retinal changes in persons with risk genotypes and to determine whether those persons progress into manifest disease.
The pathomechanisms of ARM involve complex relationships between genetics, oxidative stress and cardiovascular environmental risk factors. The genetic contribution to age-related maculopathy susceptibility (risk) is well known and a number of risk genotypes have been identified to associate with ARM and its progression. Potential ARM risk genes involve single nucleotide polymorphisms (SNPs) and although gene carrier status can be used to determine risk, it doesn’t determine whether a person will progress to disease. However, in clinical practice genetic status is not currently used as a marker to predict the need to undertake functional vision assessments in ophthalmoscopically normal eyes and visual function is quantitatively monitored only after patients show clinical signs of eye disease. Indeed, it is not known how sub-clinical changes in visual function can be detected in persons with healthy eyes who are genetically at risk of ARM, nor how those with high-risk genes differ in visual function from age-similar healthy persons who do not carry the gene.

In this study, we detect coding variants in the complement factor H region at chromosome 1q32 (CFH rs380390) and at 10q26 (LOC387715/ARMS2 rs10490924 and HTRA1 rs11200638) and relate genetic results to mesopic visual function. Mesopic vision occurs under dim light levels where the rod and cone photoreceptors of the human retina simultaneously convey visual information, spanning approximately 3-4 log units in natural viewing environments. It is known that mesopic vision testing can be sensitive to the early signs of retinal disease. Our experimental approach uses a 4-primary photostimulator to independently control the excitation of the rod and cone photoreceptor classes and determines flicker thresholds under mesopic lighting conditions. The advantage of this approach for the detection of sub-clinical signs of ARM is that flicker stimulation increases metabolic demand to the neuroretina by inducing higher blood flow and mesopic light conditions increase the activity of all photoreceptor types (rods and cones) thereby increasing oxygen demand. Taken together, these conditions could promote hypoxia/ischaemia in
a healthy retina that is susceptible to disease. Losses in flicker sensitivity are highly predictive of early ARM\textsuperscript{12} and the development of neovascular AMD\textsuperscript{13} which is thought to be promoted by ischaemia and VEGF release.\textsuperscript{14} We determine whether persons with ophthalmoscopically normal eyes and normal visual acuity who carry the risk genotypes have poorer mesopic visual function compared to persons who do not carry the ARM risk genotypes.

**METHODS**

**Participants**

Written informed consents were obtained from all participants and the study was conducted in accordance with the requirements of the Queensland University of Technology Human Research Ethics Committee and the tenets of the Declaration of Helsinki. Fifty-three healthy volunteers (28 female and 25 male) were enrolled through advertisement in University and community newspapers. Participants (mean age: 55.8 ± 6.1 years; range: 46 – 68 years) had no history of ocular or systemic disease and underwent a complete eye examination by an ophthalmologist (BF) according to the inclusion and exclusion criteria (Table 1). Participants had visual acuity ≥ 20/20, normal colour and contrast vision and no retinal anatomical abnormalities as measured with optical coherence tomography (OCT) and with ophthalmoscopy. Crystalline lens and fundus grading was performed according to the AREDS templates and participants were excluded with any posterior subcapsular cataract, cortical or nuclear opacities higher than grade 1 or signs of early ARM (level 1).\textsuperscript{15-16} Perimetry and mesopic vision testing was performed with the right eyes and practice trials were conducted to familiarise participants with the protocols.

**Genotyping**

Saliva samples were collected using OraGene DNA Self-Collection kits (OraGene, Canada). DNA was manually extracted from the participants sample using the OraGene protocol and genotyped for
selected polymorphisms using optimised TaqMan assays (Applied Biosystems, Foster City, CA) on the ABI 7300 real-time PCR machine. DNA was screened for the SNPs in CFH (rs 380390) of the complement factor H gene on chromosome 1q32, LOC387715 (A69S, rs10490924) also known as age-related maculopathy susceptibility 2 gene (ARMS2) and in the high temperature requirement factor A1, HTRA1 (rs11200638) gene in the region of chromosome 10q26. Gene loci 1q32 and 10q26 have been repeatedly linked to age-related maculopathy. There is controversy as to which SNPs on chromosome 10q26 confers risk for ARM and strong linkage disequilibrium has been demonstrated across this region; we therefore genotyped both SNPs in the ARMS2 and HTRA1 genes.

In total, 53 participants were genotyped and examined ophthalmologically. Ten participants were excluded from mesopic vision and perimetry testing after ophthalmological examination revealed a cataract >AREDS grade 1 (n=1), early ARM (n=5), congenital disc disorder (n=1), protanopia (n=1), macular gliosis (n=1) and intraocular lens extraction after cataract (n=1). Of the remaining 43 participants, 28 carried one or more of the risk genotypes (“gene-positive”) and 15 had no gene variants (“gene-negative”). Genotyping confirmed the strong linkage disequilibrium across the 10q26 by showing complete disequilibrium between the LOC387715 and HTRA1. The investigator (BF) was masked to the genetic results as genotyping was performed after the vision testing.

Clinical testing

Flicker perimetry was assessed with the Medmont Perimeter M700 (Medmont International Pty Ltd, Vermont, Australia) using the standard M700 flicker protocol. The flicker stimuli (800 ms duration) are equivalent to a Goldman size III (0.43°). Landers et al. describe formulae to convert between M700 and Humphrey visual field indices.
Standard automated perimetry was evaluated with the MP-1 Microperimeter (Nidek Technologies, Italy) using the MP1 Humphrey 10-2 program for equivalence to the standard Humphrey field test. The microperimeter allows visualization of the retinal location of the threshold measurement and an autotracking system corrects the stimulus projection every 40 ms to compensate for eye movements. Standard perimetric indices (mean sensitivity and pattern defect) were used for statistical analysis of all visual field data.

Optical coherence tomography (OCT) (Stratus III, Zeiss, Germany) imaging was performed in both eyes using 6 diagonal fast, low-density 6-mm scans (128 A scans /diagonal) and 6 diagonal slow, high-density 6-mm scans (512 A scans /diagonal) at 30° angles. Visual acuity (Bailey-Lovie charts), contrast vision (Pelli–Robson) and colour vision (Lanthony desaturated) was assessed in both eyes in accordance with standard procedures.

Mesopic vision testing with the 4-primary photostimulator

The photostimulator is a 2-channel, Maxwellian view optical system with four narrow bandwidth primary lights for each channel derived from light emitting diode – interference filter combinations with dominant wavelengths of 459 nm (blue), 516 nm (greenish-yellow), 561 nm (green) and 658 nm (red). The design and control of the photostimulator is described in detail elsewhere. Independent control of the excitation of the four photoreceptor types in the human eye is achieved using the method of silent substitution.

To evaluate long-, middle-, and short-wavelength-sensitive cone (L-, M-, S-cone) and Rod (R) activity under mesopic light levels, we investigated two types of luminance stimuli, one mediated by cones alone (LMS) and the other mediated by the combined activities of rod and cones (LMSR). The LMS stimulus modulates cone luminance signals to the postreceptoral magnocellular (MC)
pathway and rod excitations remain steady. Since S-cones do not contribute to luminance, modulating cone luminance (L+M) requires a proportional change in S-cone excitation to prevent a change in chromaticity. The LMSR stimuli measured combined LMS-cone and rod inputs to the post-receptoral MC pathway.

The stimulus was a 2° circular field set within a 13° surround and positioned at 7.5° temporal eccentricity, the approximate locus of equal rod and cone density. Any difference in sensitivity to the two stimulus types reflects local rod-cone interactions (within the stimulus area) in the inferred MC-pathway. This configuration is important for studying persons at risk of ARM because we can evaluate both rod and cone function in the same retinal area; the first photoreceptor losses occur parafoveally in ARM. The time-averaged retinal illuminance was 33 photopic Troland (Td) with a chromaticity metameric to the equal-energy-spectrum [L/(L+M) = 0.667, S/(L+M) = 1.0]. Participants were dark adapted for 10 minutes as pilot studies indicate this was sufficient to study mesopic vision under our experimental conditions. Testing was performed with natural pupils through a 2 mm artificial pupil; refractive correction was placed on the instrument side of the artificial pupil if required. The critical fusion frequency (CFF) was measured for the two postreceptoral stimulus types modulated at 15% Michelson contrast (LMS and LMSR) using a paradigm developed by the co-authors. The stimulus was presented in a 1 s raised cosine envelope and alternated with a 1 s steady field. On each trial, the initial frequency was randomly set between 5 Hz and 30 Hz and the observer altered the stimulus frequency using a method of adjustment to determine the critical fusion frequency (CFF), that is, the transitional frequency between seeing flicker and no-flicker (steady). Six repeats were performed for each stimulus type.
**Statistical analysis**

We first examined the distributions of the variables that did not show major deviations from normality. Therefore, we used parametric tests that allowed for controlling age, an important factor for studying age-related maculopathy. We performed Pearson’s correlation to determine the relationship between mesopic critical fusion frequency (CFF), mean sensitivity (MS) and pattern defect (PD) (microperimetry and flicker perimetry), retinal thickness (OCT) and age. ANOVA was performed to evaluate the difference between the CFF measurements, flicker perimetry, microperimetry and the odds ratio (OR) of the three SNPs, with age controlled. The following odds ratios were assigned to each genotype according to previously published values$^{2,3}$: *CFH* rs380390$^2$, GG OR = 7.4, CC+CG OR = 1; *LOC387715/ARMS2* rs10490920$^3$, TT OR = 6.09, GT OR = 1.35, GG OR = 1; *HTRA1* rs11200638$^3$, AA OR = 6.56, AG OR = 1.85, GG OR = 1.

**RESULTS**

The genotype frequencies of all tested SNPs were in Hardy-Weinberg (HWE) equilibrium as assessed using the HWE program.$^{31}$ Data screening was performed and seven outliers were identified due to repeated fixation losses on the 4-primary photostimulator or because only the 5 Hz adjustment step was used to set CFF. The outliers were removed from subsequent statistical analysis. Of the remaining 36 participants, 11 were classified as normal (low risk homozygous, gene-negative) and 25 gene-positive (hetero- or homozygous carriers of either one, or more than one gene variant tested). Table 2 shows the individual gene variant distributions (e.g. all persons who were heterozygous for the *LOC* gene variant and not accounting for other co-existing gene variations in these persons). The mean values (± standard deviation) of the CFF for LMSR and LMS for each genotype are given in Tables 3 and 4. Note that *LOC* and *HTRA1* CFF values are the same due to the linkage disequilibrium. Data demonstrate that LMSR CFF decreases in gene-
positive compared to gene-negative participants, with the exception of the high risk homozygote CFH.

Mean sensitivities and pattern defects were determined for microperimetry and flicker perimetry with four and five exclusions, respectively due to increased false positive responses. The mean sensitivities (MS) and pattern defects (PD) ± standard deviations for the microperimeter (n=32) were 17.8 dB (±0.93 SD) and -1.6 dB (±0.96 SD), respectively. The mean MS and PD for flicker perimetry (n=31) were 25.08 dB (±0.7) and 0.9 dB (±0.6), respectively. The values for both flicker and microperimetry were within normal ranges.\(^{22, 32}\) Mean central retinal thickness as measured with the OCT (228.6 μ m ±19.6) was within normal limits in all participants.\(^{33}\) Microperimetry mean sensitivity and pattern defect were significantly correlated with age (r=-0.39, p≤0.03) and LMSR (r=0.42, p<0.02) (Figure 1). Figure 1 shows that lower LMSR CFF was associated with lower MS on the microperimeter. A significant correlation between central retinal thickness (OCT) age (r=-0.4, p=0.02) was found as demonstrated previously.\(^{34}\)

ANOVA demonstrates a significant reduction of LMSR CFF in gene-positive compared to gene-negative participants without correction for age (F\(_{1,35}=4.16, p=0.05\)) and after correction for age (F\(_{1,35}=5.18, p=0.03\)) (Figure 2). There was no significant difference between gene-positive and gene-negative participants in the other clinical tests (flicker perimetry, microperimetry) as well as in mean retinal thickness (OCT).

We conducted a sub-analysis of the individual gene variant combinations and divided those into five groups according to each persons’ genetic combination; group 1 included all gene-negative participants (n=11), group 2 consisted of all participants who were only heterozygous for LOC/HTRA1 (n=13), group 3 consisted of participants with only the CFH homo/heterozygous
variant and heterozygous for LOC/HTRA1 (n=6), group 4 included all participants with only the homo/heterozygous CFH variant (n=4) and group 5 consisted of persons only homozygous for the LOC/HTRA1 variant (n=2) (Table 5). Table 5 demonstrates the CFF results for both LMS and LMSR for each group and shows a trend of lower LMSR values in all groups with the risk genes compared to the gene-negative group. A two-sample t-test with equal variances revealed a significant difference for group 2 with lower LMSR CFF in participants heterozygous for the LOC/HTRA1 compared to group 1 (gene-negative) (p=0.01). Groups 3-5 and in particular homozygotes, were not significantly different compared to group 1, most likely due to small sample sizes in these remaining sub-groups.

**DISCUSSION**

This is the first demonstration that in a randomly chosen sample with normal visual acuity and central visual fields and no clinical signs of ARM in both eyes, persons with ARM risk genotypes have on average, lower mesopic visual function after correction for age compared to those who do not carry the risk genotype (“gene-negative”). The reduction in rod-and cone mediated (LMSR) and not cone-mediated only (LMS) mesopic vision is consistent with rod dysfunction, or selective rod loss as demonstrated histologically, psychophysically and electrophysiologically in early ARM and ageing. Previous studies demonstrate reduced rod-mediated neuroretinal function in early ARM sufferers that exceeds those changes associated with normal ageing. Delayed dark-adaptation as well as reduced scotopic sensitivity are evident in early ARM. Foveal critical fusion frequency is reduced under photopic light levels in advanced ARM, but is not sensitive as a diagnostic tool, consistent with our observation that there were no differences in the cone mediated (LMS) CFF in gene-positive and gene-negative participants. These preliminary results in persons with no signs of ARM signify rod-mediated mesopic visual function testing as important
for the evaluation of older persons with ARM risk genotypes, and that it may become a functional marker for disease.

We further report a novel relationship between microperimetry and the 4-primary photostimulator where lower MS and PD are significantly correlated with lower LMSR CFF. Although the microperimeter background light level is in upper mesopic range and the achromatic test stimuli estimate visual sensitivity mediated by rods and cone in different states of relative sensitivity, its inbuilt fixation tracking system may improve the detection of functional vision changes over that of other conventional ophthalmic tests we performed under photopic illuminations (e.g. colour vision, flicker perimetry). While microperimetry results were not significantly reduced in gene-positive compared to gene-negative participants in this cohort, future studies in a larger cohort of older gene-positive participants may have increased statistical power to detect sub-clinical deficits.

The SNPs identified in this study have been all related to neovascular AMD. Ischaemia due to underlying cardiovascular conditions has been suggested to be a major factor in the development of ARM and in neovascular AMD. Moreover, a recent study has identified three other gene variants on chromosomes 15, 16 and 22 with an increased risk of AMD that are related to the cholesterol metabolism and thus cardiovascular risk factors. A person with these gene variants may be predisposed to functional deficits due to ischaemic insults. Thus a test that increases the oxygen demand by both, increased photoreceptor activity (during mesopic conditions) and increased blood flow (during flicker stimulation) as used in our experiment, may facilitate the early detection of the first functional deficits.

The demonstrated relationship between a risk genotype and impaired mesopic visual function in persons with clinically normal eyes is important because visual function may be responsive to
appropriate environmental manipulation such dietary and lifestyle changes.\textsuperscript{44} Persons with ARM risk genotypes who smoke or have a poor diet have an approximate doubling of the risk of ARM progression, compared with those who are gene-positive but do not have such environmental exposures.\textsuperscript{45} Moreover, late stages of ARM may be preventable as recent studies indicate that a healthy lifestyle including a healthy diet, physical activity, adequate vitamin D intake and no smoking can decrease the risk for developing intermediate age-related macular degeneration by about two-fold.\textsuperscript{46} These findings support our approach that the application of sensitive tests for the early detection and appropriate monitoring of disease is vital because risk is modifiable. Monitoring visual function with a quantitative test will further enable the evaluation of the effect of lifestyle changes on a person’s health (such as change in a person’s environmental exposures), and reduce the economic costs associated with the most common cause of blindness in the western world. The study findings may have future applications in the verification of sub-clinical ARM without genetic assessment.

Assessing mesopic vision as an early detector of sub-clinical ARM may have potential significant implications in determining the pathomechanisms of the subtypes of neovascular ARM such as occult, classic, polypoidal choroidal vasculopathy (PCV) or retinal angiomatous proliferations (RAP) that are poorly understood. It has been demonstrated that different gene variants promote subtypes of ARM.\textsuperscript{47-48} Further longitudinal clinical investigation is required to study persons with significantly reduced mesopic vision and gene-positive carrier status to determine whether visual function deteriorates faster than those in the low-risk (gene-negative) group and to understand the relationship between genotype and phenotype by quantitatively measuring visual function related to genotypes to determine progression to ARM.
Acknowledgement

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References


**Figure Legends**

**Figure 1.** Rod and cone mediated (LMSR) critical fusion frequency (CFF) as a function of microperimetry (MP-1) mean sensitivity (MS). There is a significant correlation between LMSR CFF and MS.

**Figure 2.** Mean LMSR CFF values for participants who were heterozygous and homozygous for high-risk CFH, LOC and HRTA1 SNPs are significantly lower compared to the gene-negative participants (asterisk). Box-and whiskers plot show the median (50\textsuperscript{th} percentile), inter-quartile range (25\textsuperscript{th} - 75\textsuperscript{th} percentile) and highest and lowest values.
Figure 1

Figure 2
Table 1. Eligibility and ineligibility criteria

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
<th>Ineligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Age between 45 and 68 years</td>
<td>- Aphakia or pseudophakia</td>
</tr>
<tr>
<td>- Visual acuity ≥ 20/20 in both eyes</td>
<td>- Cataract &gt; grade 1 (AREDS)</td>
</tr>
<tr>
<td>- Normal colour vision both eyes (Lanthony)</td>
<td>- Glaucoma and/or IOP &gt;22 mmHg</td>
</tr>
<tr>
<td>- Normal contrast vision (Pelli Robson)</td>
<td>- Diabetes and diabetic retinopathy</td>
</tr>
<tr>
<td>- No ARM in both eyes (according to AREDS)</td>
<td>- No venous/arterial occlusion</td>
</tr>
<tr>
<td>- Normal OCT in both eyes</td>
<td>- Uncontrolled hypertension</td>
</tr>
<tr>
<td>- Normal peripheral fundus</td>
<td>- Recent myocardial infarct/stroke</td>
</tr>
<tr>
<td></td>
<td>- Uncontrolled hypercholesterinaemia</td>
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<td>- Major illness with chronic medication</td>
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Table 2. The distribution of genotypes

<table>
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<tr>
<th>Gene variant</th>
<th>Low risk Homozygotes (n)</th>
<th>Heterozygotes (n)</th>
<th>High risk Homozygotes (n)</th>
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<tr>
<td>LOC rs10490924</td>
<td>n=15 (GG)</td>
<td>n=19 (GT)</td>
<td>n=2 (TT)</td>
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<tr>
<td>HRTA1 rs1120038</td>
<td>n=15 (GG)</td>
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<td>CFH rs380390</td>
<td>n= 5 (GG)</td>
<td>n=21 (CG)</td>
<td>n=10 (CC)</td>
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Table 3. Mean (±SD) LMSR Critical Flicker Frequency (CFF) for each of the gene variants

<table>
<thead>
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<th>High risk Homozygotes</th>
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<td>LOC rs10490924</td>
<td>15.3 (±1.25)</td>
<td>14.4 (±0.96)</td>
<td>14.9 (±0.95)</td>
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<tr>
<td>HRTA1 rs1120038</td>
<td>15.3 (±1.25)</td>
<td>14.4 (±0.96)</td>
<td>14.9 (±0.95)</td>
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<tr>
<td>CFH rs380390</td>
<td></td>
<td>14.8 (±1.19)</td>
<td>14.9 (±1.08)</td>
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</table>

Table 4. Mean (±SD) LMS Critical Flicker Frequency (CFF) for each of the gene variants

<table>
<thead>
<tr>
<th>Gene variant</th>
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<th>Heterozygotes</th>
<th>High risk Homozygotes</th>
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</thead>
<tbody>
<tr>
<td>LOC rs10490924</td>
<td>19.8 (±1.07)</td>
<td>19.4 (±1.43)</td>
<td>19.7 (±1.27)</td>
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<td>HRTA1 rs1120038</td>
<td>19.8 (±1.07)</td>
<td>19.5 (±1.40)</td>
<td>19.7 (±1.27)</td>
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<td>CFH rs380390</td>
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<td>19.4 (±1.17)</td>
<td>20.1 (±1.45)</td>
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Table 5. The LMSR and LMS CFF for each of the gene combinations

<table>
<thead>
<tr>
<th>Gene combinations (n=36)</th>
<th>LMSR CFF</th>
<th>LMS CFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (gene-negative) (n=11)</td>
<td>15.4 ±1.38</td>
<td>19.8 ±1.13</td>
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<tr>
<td>Group 2 (LOC/HTRA1 heterozygous) (n=13)</td>
<td>*14.22 ±0.78</td>
<td>19.1 ±1.19</td>
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<tr>
<td>Group 3 (CFH, LOC/HTRA1 heterozygous) (n=6)</td>
<td>14.85 ±1.25</td>
<td>20.1 ±1.78</td>
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<tr>
<td>Group 4 (CFH only) (n=4)</td>
<td>15.1 ±0.92</td>
<td>20.2 ±0.96</td>
</tr>
<tr>
<td>Group 5 (LOC/HTRA1 homozygous) (n=2)</td>
<td>14.9 ±0.95</td>
<td>19.7 ±1.27</td>
</tr>
</tbody>
</table>

*p=0.01 compared with gene-negative participants (group 1)