Polygenic Risk Score Impact on Visual Function in Older Individuals with Healthy Macula: The Northern Ireland Sensory Ageing Study

Fangyao Tang, PhD[1]; Ruth E. Hogg, PhD[2]; Bethany E. Higgins, PhD[3], David M. Wright, PhD[2]; Laura Smyth, PhD[2]; Sobha Sivaprasad, DM[1,4]

1. Institute of Ophthalmology, University College London, London, United Kingdom
2. Centre for Public Health, Queen's University Belfast, Belfast, United Kingdom
3. Optometry and Vision Sciences, City, University of London, London, United Kingdom
4. National Institute for Health Research Biomedical Research Centre, Moorfields Eye Hospital National Health Service Foundation Trust, London, United Kingdom.

Correspondence

Sobha Sivaprasad

National Institute for Health Research Biomedical Research Centre, Moorfields Eye Hospital National Health Service Foundation Trust, London, United Kingdom.

Tel: (44) 7817886759 Email: sobha.sivaprasad@nhs.net

Date of revision: 3 October 2024.

20 **Word counts**

21 abstract: 245 words; text: 3548 words. References: 28; tables: 3; figures: 2.

Abstract

Background/objectives: Although polygenic risk scores (PRSs) have been developed for age-related macular degeneration (AMD), it is not known whether these scores are associated with impairment of visual functions in older individuals with healthy macula. We evaluated age-related changes in visual function in people aged 55 years or above with healthy macula, and determined the associations of age-related visual function changes with AMD PRS in people with healthy macula.

Subjects/Methods: Participants aged 55 years or above with healthy macula and a comparative group of people with early or intermediate AMD from the Northern Ireland Sensory Ageing study were included. 45 SNPs were included for PRS calculation.

Results: A total of 470 participants with healthy macula were included (Beckman grade 0 or 1). The comparator group consisted of participants with early AMD (n = 87) or intermediate AMD (n = 48). All visual functions except metrics of central visual field assessment showed significant decline with age in adjusted linear regression models. Rod intercept time (RIT) was the only visual function significantly associated with PRS with Beta = 0.12 (95% confidence interval: 0.01 to 0.23), P = 0.03. A PRS integrated model achieved the highest area under the receiver operating characteristic curve (AUC) of 0.803 (0.732 to 0.874) to distinguish between normal or

increased RIT.

Conclusions and relevance: We observed a significant decline in multiple visual functions with increasing age. However, PRS was significantly associated with RIT only, highlighting the genetic association of age-related decline in rod function.

Introduction

Age-related macular degeneration (AMD) is a complex disease with genetic susceptibility and remains a leading cause of vision loss in older individuals especially in the White population.(1) Most older individuals with healthy macula have good visual acuity (VA) and are visually asymptomatic, while some report difficulties in performing daily activities under dim light conditions such as night driving and reading in a dim environment, and sub-optimal performance in visual function tests.(2, 3) Previous reports have highlighted numerous factors associated with decline in both mesopic and scotopic visual functions with increasing age, and some of these factors increase risk of AMD. However, most patients with early or intermediate AMD are also asymptomatic and have good visual acuity.(2, 3) We hypothesised that both older individuals with apparently healthy macula and people with early to intermediate AMD who suffer from visual function losses may share biological mechanisms that regulate these ocular traits.

A possible link may be the genetic risk for AMD. The heritability of AMD is estimated at over 50%.(4-6) In a genome-wide association study (GWAS), Fritsche et al. identified 52 common and rare variants distributed across 34 loci associated with AMD. These include genes involved in the complement pathway, lipid metabolism

and extracellular matrix remodelling, all of which are implicated in the pathology of AMD.(7) Despite the identification of genetic variants associated with AMD, each variant only confers a modest effect and has limited predictive power individually. Polygenic risk score (PRS) examines the aggregate genetic effect by combining these separate genetic variants into a single measure. Currently, there is limited data on whether PRS derived from AMD-associated single nucleotide polymorphisms (SNPs) is associated with visual function losses in AMD.(8) A previous study observed a progressive non-linear deterioration of visual function over 24 months and moderate correlation with the genetic burden score and rod intercept time (RIT) in early and intermediate AMD.(9) The study provided a proof of principle of a possible genetic link with visual function. However, the genetic burden score was generated from only nine SNPs in nine genes and may not have captured sufficient predictive power of the included variants. Furthermore, the visual function tests were evaluated in a small cohort (n = 101), 33 with early AMD, 47 with intermediate AMD, and 21 with apparently healthy macula.(9) A larger cohort is required to understand the relation of AMD PRS with age-related visual function losses.

Therefore, our aim was to conduct a more comprehensive evaluation of both mesopic and scotopic visual functions in older individuals with apparently healthy macula and

determine whether any changes observed are associated with AMD PRS. If so, we aimed to explore whether a risk model that incorporates AMD PRS can accurately discriminate people with visual function losses in a population-based study. Additionally, we examined whether the presence of AMD could be identified in those with with visual function losses.

Methods

Study Cohort

We used prospectively collected data from a case-control, cross sectional study, the Northern Ireland Sensory Ageing study, which was part of the long-term, ongoing epidemiologic Northern Ireland Cohort of Longitudinal Study of Ageing (NICOLA) study conducted at Queen's University, Belfast. The NICOLA study is a population-based, nationally representative ageing cohort study that was established in 2012. The study recruited adults aged 50 years or over of European ancestry and residing in Northern Ireland. The primary aim was to identify factors affecting health and social outcomes in an ageing population. Detailed descriptions of the sampling procedures and study design of the NICOLA Study have been provided elsewhere.(10) The Northern Ireland Sensory Ageing study adhered to the tenets of the Declaration of Helsinki, with ethical approval from the School of Medicine, Dentistry and

Biomedical Sciences Ethics Committee, Queens University, Belfast (Ref. 14.25v4). Participants provided written informed consent before enrollment.

Inclusion criteria for the current study comprised of adults aged 55 years or above with (a) apparently healthy fundus; and (b) with early or intermediate AMD. The better seeing eye of each eligible participant was included. If the monocular VA scores were found to be equal, an eye was either chosen randomly or according to the participant preference at the point of consent. Exclusion criteria comprised: (1) participants with diabetes; (2) eyes with advanced AMD (neovascular AMD and/or geographic atrophy); (3) eyes with glaucoma; (4) eyes with a refractive error of greater than −6.0 diopters (D); (5) other eye pathologies that interfere with imaging and visual function examinations (e.g., dense cataract and corneal opacities).

Data collection

Details on image acquisition, image grading,(11) collections of demographic, systemic and ocular factors, genotyping methods, and PRS calculation(7, 12) have been reported elsewhere. A total of 45 variants met the following criteria and were included for PRS calculation: (1) minor allele count > 5; (2) info-Score (quality) for imputation (R^2) > 0.3; (3) not a monomorphic variant. PRS was calculated as per

Colijn et al.(8) A detailed description of the visual function tests and retinal structure evaluations can be found in **Supplementary Information 1**. Briefly, best-corrected distance VA by Early Treatment Diabetic Retinopathy Study chart (ETDRS, Precision Vision, USA) and the Moorfields Acuity Chart, low-luminance visual acuity (LLVA), low luminance deficit (LLD), near visual acuity by Bailey-Lovie reading charts and Smith-Kettlewell Institute Low Luminance (SKILL) card, contrast sensitivity, reading index, central visual field, macular sensitivity, and RIT were measured. The Beckman Initiative for Macular Research Classification was used to define the severity of AMD on colour photographs. The apparently healthy fundus group consisted of eyes with Beckman grade 0 or 1. Eyes with Beckman grade 2 or 3 were classified as early or intermediate AMD group. Macular thickness was measured by Spectralis optical coherence tomography (OCT) (Heidelberg Engineering GmbH, Heidelberg, Germany) with volumetric scan protocol.

Statistical analysis

All statistical analysis was conducted using R V.4.3.0. Normality of all continuous variables was examined using Shapiro-Wilk tests and histograms. Continuous and ordinal demographic data were analysed using independent t-tests and chi-square test, respectively. Continuous variables were normalised using Z-score normalisation for

140 further analyses.

141

142 Linear regression analyses were performed to determine the associations between
143 visual functions with age and PRS. Univariable models were firstly used to determine
144 the associations between each visual function with age, ocular, systemic and
145 demographic factors. The associations with visual function were compared between
146 Beckman grade 1,2, and 3 versus grade 0. Since age, sex and SDD have been reported
147 to be associated with prevalence of AMD,(13, 14) they were incorporated in further
148 analyses. Finally, we examined the association of PRS with visual functions using
149 multivariable linear models adjusted for age, sex, presence of SDD, and factors with P
150 ≤ 0.05 in the univariable models for confounding controlling. Sensitivity analysis was
151 performed to further validate the robustness of the associations between PRS and
152 visual functions in participants aged over 60 years.

153

154 Logistic regression models were applied to investigate the association between PRS
155 and risk of visual function losses. Receiver operating characteristic (ROC) curve
156 analyses were conducted and the area under the curve (AUC) were calculated to
157 examine those with delayed dark adaptation (defined as RIT > 12.5 minutes)(15)
158 versus the rest of the cohort, and for distinguishing participants with AMD within the

group with delayed dark adaptation. DeLong tests were also performed to compare the AUCs between models.(16) A P-value $\leqslant 0.05$ was considered as a level of statistical significance. The sample size was determined for a linear regression with an effect size of 0.3 and an alpha level of 0.05. A total of 54 eyes were required to achieve 80% power.

Results

Table 1 presents the demographics and clinical characteristics of the eligible participants included in this study. The mean age (SD) of the group of 470 participants with apparently healthy macula (Beckman grade 0 or 1) was 66.34 (7.55) years and the age-range was 55 to 94 years and 237 (50%) were males. The AMD group consisted of 135 participants had a diagnosis of early AMD (n = 87) or intermediate AMD (n = 48), with mean age (SD) of 68.84 (8.49) years, the age-range was 52 to 90, and 56 (41%) were males. SDD was present in 90 (20%) participants with Beckman grade 1, which is classed as otherwise apparently healthy macula.

Figure 1 shows the distribution of the PRS in the group with apparently healthy macula (n = 470) and those with AMD phenotypes (early AMD, n = 87, and intermediate AMD, n = 48). In the group with apparently healthy macula, the mean (SD) of PRS was 0.42 (1.14) ranged from -2.48 to 3.84 and showed a normal

distribution (P = 0.70). The mean (SD) of PRS in AMD was 0.82 (1.28) ranged from -2.19 to 3.72 and demonstrated a normal distribution (P = 0.50). There was statistically higher PRS in the AMD cohort compared to the group with apparently healthy macula (P < 0.01).

Evaluation of age-related visual function changes in the group with apparently healthy macula

ETable 1 shows the univariable linear regression analyses between visual functions and possible risk factors in the group with apparently healthy macula. The differences in visual function between Beckman grade 0 or 1 are also shown. Age, sex, and other factors with P ≤ 0.05 were entered into a full linear regression model. **Table 2** presents the results of associations between age and visual functions in fully adjusted multivariable model. All visual functions except for metrics of FDT showed significant decline with age after adjustment for sex and variables significantly associated in univariable linear regression. Of note, mean visual acuity and macular sensitivity were decreased in eyes with Beckman grade 1 versus 0 within this group.

The relation of age-related visual function changes and AMD PRS

Table 3 displays the multivariable linear regression results between visual functions

and PRS in all participants, adjusted for age, sex, and other associated factors shown in **eTable 2**. RIT was the only visual function that was significantly associated with PRS, with Beta = 0.12 (95% confidence interval: 0.01 to 0.23), P = 0.03. Other functions such as decreasing VA measured by ETDRS chart, Moorfields chart, and SKILL card (light), poorer LLVA, mean deviation of FDT, and contrast sensitivity were associated with female sex and higher baseline Beckman grade of AMD. Average macular sensitivity was lower in eyes with Beckman grade 1 versus 0. Multivariable analyses showed that the association of RIT and PRS in the whole cohort was driven by the group with apparently healthy macula (n = 470), with Beta = 0.15 (0.05 to 0.25), P = 0.01 (**Table 2**) but not AMD (n=135, **eTable 3**). Sensitivity analyses in the group with apparently healthy macula with age over 60 years (n = 386) further confirmed the significant association between RIT and PRS (**eTable 4**). In the group with healthy macula, RIT was also significantly associated with history of anti-hypertension medicine with Beta = 0.26 (0.03 to 0.48), P = 0.03 (**Table 2**).

A risk model that incorporates AMD PRS can accurately discriminate people with increased RIT

We then estimated the accuracy of a model that could discriminate participants with increased RIT (n = 56) versus the rest (n = 396). **Figure 2** presents the discriminatory

power. Baseline Beckman grade, age, sex, presence or absence of SDD, and history of using anti-hypertension medicine were entered into model 1, with AUC = 0.798 (0.730 to 0.865). Model 2 involved PRS only, with AUC = 0.612 (0.525 to 0.699). Model 3 combined PRS with baseline Beckman grade, age, sex, presence of SDD, and history of using anti-hypertension showed the highest AUC = 0.803 (0.732 to 0.874). DeLong tests were also performed to compare the AUCs between models, with $P = 0.002$ for model 1 vs. model 2, $P < 0.001$ for model 2 vs. model 3, and $P = 0.144$ for model 3 vs. model 1. Accuracy of the risk model was further estimated in participants with apparently healthy fundus (**eFigure 1**), with 34 eyes with increased RIT and 326 eyes with normal RIT. Again, model 3 with PRS, baseline Beckman grade 0 or 1, age, sex, presence of SDD and history of using anti-hypertension showed the highest AUC = 0.776 (0.679 to 0.873), compared to AUC = 0.763 (0.670 to 0.875) for model 1 (Baseline Beckman grade 0 or 1, age, sex, presence or absence of SDD, and history of using anti-hypertension medicine), and AUC = 0.588 (0.476 to 0.701) for model 2 (PRS only), respectively. A model integrating PRS showed the highest AUC = 0.690 (0.528 to 0.851) in differentiating the presence (n = 22) or absence of AMD (n = 34) among participants with increased RIT (**eFigure 2**).

Discussion

The key findings of our study include an age-related decline in all photopic and scotopic visual functions except FDT in those with apparently healthy macula; the only visual function decline that was associated with AMD PRS was delayed dark adaptation (an increase in RIT); an AMD PRS integrated model consisting of Beckman AMD classification (grade 0-3), age, sex, and history of using anti-hypertension medications could discriminate people with increased RIT across the entire study cohort; the model could not discriminate participants with AMD (Beckman grade 2 or 3) from those with healthy macula (Beckman grade 0 or 1) in people with increased RIT. To our knowledge, this study is the first to report the association of a PRS developed from 45 AMD variants and RIT in a population aged 55 years or over and its use in a risk score to detect age-related increase in RIT in people with apparently healthy macula.

Our finding that most visual function tests decline with ageing in participants with apparently healthy macula is consistent with previous reports that older age is associated with poorer VA measured under photopic and mesopic conditions.(17) However, only prolonged dark adaptation (increased RIT) was associated with higher AMD PRS.[18] These observations suggest that increased RIT is indeed driven by local factors in the outer retina and choroid that impact rods directly or indirectly. In contrast, decline in other visual functions seems to be unrelated to the same

mechanisms of increased RIT and may be related to changes in any part of the visual pathway from the photoreceptors to the cortex that are not associated with AMD PRS score.

When we consider local factors, an increase in RIT may indicate an exaggerated age-related decline in numbers or function of rod photoreceptors or alterations in phagocytosis by the RPE or a disturbed retinoid cycle.(19) Although most individuals can adapt to the declining numbers of rods with age, it may be that those with high AMD PRS do not have that plasticity and consequently manifest functional losses.(20) Structurally, an increase in RIT may be explained by a decrease in inner segment outer segment-retinal pigment epithelium (ISOS-RPE) and RPE-BM thickness in normal macula of adults with AMD risk SNPs.(21) Although, OCT evidence of thinning of ISOS-RPE may be a pre-morbid marker of AMD, our findings indicate that there may be other factors such as oxidative stress and inflammation that are required to trigger AMD.(22) We observed that although Grade 0 and 1 of Beckman grade are usually grouped together as ‘healthy ageing’.(23) Our study showed that Beckman grade 1 had more functional losses than Beckman grade 0 and this may be explained by SDD being included in Beckman grade 1. Increased RIT and other visual functions, thinning of the choroid and loss of choriocapillaris are

established associations of SDD.(24) *ARMS2* risk alleles and higher PRS including 6 SNPs are associated with the presence of SDD in the Age-Related Eye Disease Study 2 (AREDS2) trial and these genotypes within our AMD PRS may contribute to increased RIT in eyes with SDD.(25) Another local structural change that may be associated with increased RIT may be age-related lipid laden thickening of the Bruch's membrane (BM) that may slow rhodopsin regeneration. Increased AMD PRS score is also associated with thickening of the RPE-BM thickening but thinning of the photoreceptor layer occurs decades below RPE-BM thickening.(26)

Overall, all three local effects that may explain the link between increased RIT and AMD PRS may be interlinked at some stage although some changes may precede others as demonstrated mathematically by Curcio et al.(27) It was interesting to note that while the rods declined by 36% with age, there was a similar decline of choriocapillaris density by 35% and choroidal thickness, which included the choriocapillaris, by 24%.(27) Histochemical analysis revealed a 15-fold increase in esterified cholesterol in BM with normal aging, while BM thickness doubled in the same eyes.(28) The interplay of these age-related cellular decline in the outer retina and choroid may be exaggerated in people with high AMD PRS and may explain our finding of the association with increased RIT.

Indeed, there seems to be a complex relation of SDD, choroid and outer retinal thinning and increased RIT. SDD is thought to be associated with cardiovascular disease, which can further explain the association of increased RIT with anti-hypertensive medications and male gender.(29) These point towards the need for lifestyle changes in people with increased RIT especially if associated with high AMD PRS.

When we consider the link of higher AMD PRS with increased RIT, both high-risk *ARMS2* and *CFH* genotypes are associated with delayed RIT.(18) While the PRS was significantly higher in our AMD group compared to the group with apparently healthy macula, only 39% of the patients with delayed RIT had early or intermediate AMD. We also observed that people with AMD could not be distinguished within a cohort with increased RIT, indicating that other triggers are required for the development of AMD, or that delayed RIT may precede the development of AMD by a considerable period. It also explained why our previous report revealed that PRS were highly significantly associated with presence or absence of AMD in fully adjusted multivariable logistic regression model in the NICOLA study.(12) This model included advanced AMD and previous AMD studies have demonstrated that RIT

311 increases with the increasing severity of disease.(30) Indeed it has been shown to be a
312 predictor of vision loss in geographic atrophy.[21]
313
314 Other mechanisms also need to be considered to explain the association of PRS and
315 RIT. The strongest genetic associations for AMD are polymorphisms at chromosome
316 1 and chromosome 10. *ARMS2* A69S is more closely associated with the SDD
317 phenotype than is *CFH* Y402H.(31) Although the exact patho-mechanism of *ARMS2*
318 genotype is unclear, it is worth noting that among the 45 AMD SNPs included in this
319 PRS calculation, there were 7 rare variants with larger effect size, and all of them are
320 located in or near genes that are related to complement system. These components of
321 the PRS are also linked to lipid and extracellular matrix pathways in AMD.[15] Together
322 with the association with high cardiovascular risk profile, our findings emphasized the
323 link of RIT to these pathways too. Although smoking is the strongest modifiable risk
324 factor for AMD, it was not associated with a decline in visual function in the
325 population with apparently normal macula. Smoking increases oxidative stress and
326 hypoxia due to decrease in choroidal blood flow and may affect the macula
327 independent of the AMD PRS.
328
329 The strengths of this study include the PRS consisting of nearly all AMD associated

SNPs identified to date. Also, rare variants which may have larger effect were included in this PRS construction. Secondly, comprehensive scotopic and photopic visual function examinations were performed. There are three limitations, however. First, PRS was constructed using SNPs collected from single ethnicity (i.e., Whites) and may reduce the generalisability of its associations with RIT. Second, the small sample size of AMD participants may make it difficult to detect significant associations of PRS and visual functions in people with early or intermediate AMD. Further studies for replicating these findings are needed. Third, our study excluded seven SNPs that did not meet the quality control criteria for imputation. Six of them have low to moderate effect size with ORs ranged from 0.57 to 2.79, and a rare variant in the *CFH*, namely rs121913059, have a strong effect on AMD risk (OR = 47.62).(7) While the number of excluded SNPs was relatively small, it is possible that their exclusion could have slightly underestimated the true genetic contribution to decline in dark adaptation. It should be noted that, including genotypes with lower quality may introduce noise into the analysis and weaken the predictability of PRS. Although excluding the SNPs might have resulted in a slightly weaker PRS performance, maintaining data quality is essential for a robust analysis. In future studies, using proxy SNPs derived from linkage disequilibrium database to replace the excluded SNPs could potentially address the limitation. Fourth, the apparently higher proportion of eyes with AMD in our study

cohort (22.3%) than the general population may result in a bias result of the risk model for differentiating eyes with or without increased RIT. Further validation in a population-based study.

In summary, we observed a significant decline in photopic and scotopic visual functions with increasing age in a cross-sectional sample with apparently healthy macula recruited from a population-based study. Furthermore, PRS composed of 45 reported AMD-associated SNPs were significantly associated with RIT in this population. Our study extends the promise of applying PRS as a population-based risk stratification tool to identify individuals with increased RIT and normal macula that could benefit from strategies to improve lifestyle, especially to control cardiovascular risk factors.

Contributions

SS, REH: research design. FYT: data analysis, interpretation, REH, BEH, DMW, LS: research execution. All authors contributed towards the preparation of the manuscript and approved the final submitted version. The corresponding author is solely responsible for managing communication between co-authors; that all authors are included in the author list; order has been agreed by all authors; and that all authors are aware that the paper was submitted.

Conflict of Interest Disclosures: None.

Funding

Atlantic Philanthropies, the Economic and Social Research Council, the UKCRC Centre of Excellence for Public Health Northern Ireland, the Centre for Ageing Research and Development in Ireland, the Office of the First Minister and Deputy First Minister, the Health and Social Care Research and Development Division of the Public Health Agency, the Wellcome Trust/Wolfson Foundation, Fight for Sight (Ref No.: 1906), and Queen's University Belfast provide core financial support for the Northern Ireland Cohort of Longitudinal Study of Ageing study. The authors alone are responsible for the interpretation of the data, and any views or opinions presented are solely those of the authors and do not necessarily represent those of the Northern Ireland Cohort of Longitudinal Study of Ageing study team. The Northern Ireland Sensory Ageing study was funded by grants from the College of Optometrists, Diabetes UK, Macular Society, RNIB, Guide Dogs for the Blind, Thomas Pocklington Trust and the Belfast Association for the Blind. Role of the Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit

the manuscript for publication.

Data availability: The data collected for the current study, including individual patient data and a data dictionary defining each field in the data set, will not be made available to others.

References:

1. Klein R, Klein BE, Knudtson MD, Wong TY, Cotch MF, Liu K, et al. Prevalence of age-related macular degeneration in 4 racial/ethnic groups in the multi-ethnic study of atherosclerosis. Ophthalmology. 2006;113(3):373-80.

2. Owsley C, McGwin G, Jr., Scilley K, Kallies K. Development of a questionnaire to assess vision problems under low luminance in age-related maculopathy. Invest Ophthalmol Vis Sci. 2006;47(2):528-35.

3. Mangione CM, Berry S, Spritzer K, Janz NK, Klein R, Owsley C, et al. Identifying the content area for the 51-item National Eye Institute Visual Function Questionnaire: results from focus groups with visually impaired persons. Arch Ophthalmol. 1998;116(2):227-33.

4. DeAngelis MM, Owen LA, Morrison MA, Morgan DJ, Li M, Shakoor A, et al. Genetics of age-related macular degeneration (AMD). Hum Mol Genet. 2017;26(R1):R45-r50.

5. Jabbarpoor Bonyadi MH, Yaseri M, Bonyadi M, Soheilian M, Karimi S. Association of Combined Complement Factor H Y402H and ARMS/LOC387715 A69S Polymorphisms with Age-related Macular Degeneration: A Meta-analysis. Curr Eye Res. 2016;41(12):1519-25.

6. Ulańczyk Z, Grabowicz A, Mozolewska-Piotrowska K, Safranow K, Kawa MP,

412 Pałucha A, et al. Genetic factors associated with age-related macular degeneration:
413 identification of a novel PRPH2 single nucleotide polymorphism associated with
414 increased risk of the disease. Acta Ophthalmol. 2021;99(7):739-49.
415 7. Fritsche LG, Igl W, Bailey JN, Grassmann F, Sengupta S, Bragg-Gresham JL,
416 et al. A large genome-wide association study of age-related macular degeneration
417 highlights contributions of rare and common variants. Nat Genet. 2016;48(2):134-43.
418 8. Colijn JM, Meester-Smoor M, Verzijden T, de Breuk A, Silva R, Merle BMJ, et
419 al. Genetic Risk, Lifestyle, and Age-Related Macular Degeneration in Europe: The
420 EYE-RISK Consortium. Ophthalmology. 2021;128(7):1039-49.
421 9. Lad EM, Fang V, Tessier M, Rautanen A, Gayan J, Stinnett SS, et al.
422 Longitudinal Evaluation of Visual Function Impairments in Early and Intermediate
423 Age-Related Macular Degeneration Patients. Ophthalmol Sci. 2022;2(3):100173.
424 10. Neville CE, Young IS, Kee F, Hogg RE, Scott A, Burns F, et al. Northern Ireland
425 Cohort for the Longitudinal Study of Ageing (NICOLA): health assessment protocol,
426 participant profile and patterns of participation. BMC Public Health. 2023;23(1):466.
427 11. Higgins BE, Montesano G, Crabb DP, Naskas TT, Graham KW, Chakravarthy
428 U, et al. Assessment of the Classification of Age-Related Macular Degeneration
429 Severity from the Northern Ireland Sensory Ageing Study Using a Measure of Dark
430 Adaptation. Ophthalmol Sci. 2022;2(4):100204.

12. Hogg RE, Wright DM, Quinn NB, Muldrew KA, Hamill B, Smyth L, et al. Prevalence and risk factors for age-related macular degeneration in a population-based cohort study of older adults in Northern Ireland using multimodal imaging: NICOLA Study. Br J Ophthalmol. 2023;107(12):1873-9.

13. Rudnicka AR, Jarrar Z, Wormald R, Cook DG, Fletcher A, Owen CG. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. Ophthalmology. 2012;119(3):571-80.

14. Flamendorf J, Agrón E, Wong WT, Thompson D, Wiley HE, Doss EL, et al. Impairments in Dark Adaptation Are Associated with Age-Related Macular Degeneration Severity and Reticular Pseudodrusen. Ophthalmology. 2015;122(10):2053-62.

15. Jackson GR, Edwards JG. A short-duration dark adaptation protocol for assessment of age-related maculopathy. J Ocul Biol Dis Infor. 2008;1(1):7-11.

16. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837-45.

17. Rubin GS, West SK, Muñoz B, Bandeen-Roche K, Zeger S, Schein O, et al. A comprehensive assessment of visual impairment in a population of older Americans. The SEE Study. Salisbury Eye Evaluation Project. Invest Ophthalmol Vis Sci.

1997;38(3):557-68.

18. Mullins RF, McGwin G, Jr., Searcey K, Clark ME, Kennedy EL, Curcio CA, et al. The ARMS2 A69S Polymorphism Is Associated with Delayed Rod-Mediated Dark Adaptation in Eyes at Risk for Incident Age-Related Macular Degeneration. Ophthalmology. 2019;126(4):591-600.

19. Curcio CA, Medeiros NE, Millican CL. Photoreceptor loss in age-related macular degeneration. Invest Ophthalmol Vis Sci. 1996;37(7):1236-49.

20. Goodman C, Podolsky RH, Childers KL, Roberts R, Katz R, Waseem R, et al. Do multiple physiological OCT biomarkers indicate age-related decline in rod mitochondrial function in C57BL/6J mice? Front Neurosci. 2023;17:1280453.

21. Kaye RA, Patasova K, Patel PJ, Hysi P, Lotery AJ. Macular thickness varies with age-related macular degeneration genetic risk variants in the UK Biobank cohort. Sci Rep. 2021;11(1):23255.

22. Kamoshita M, Ozawa Y, Kubota S, Miyake S, Tsuda C, Nagai N, et al. AMPK-NF-κB axis in the photoreceptor disorder during retinal inflammation. PLoS One. 2014;9(7):e103013.

23. Ferris FL, 3rd, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, et al. Clinical classification of age-related macular degeneration. Ophthalmology. 2013;120(4):844-51.

469 24. Grewal MK, Chandra S, Gurudas S, Rasheed R, Sen P, Menon D, et al.
470 Functional clinical endpoints and their correlations in eyes with AMD with and without
471 subretinal drusenoid deposits-a pilot study. Eye (Lond). 2022;36(2):398-406.
472 25. Domalpally A, Agrón E, Pak JW, Keenan TD, Ferris FL, 3rd, Clemons TE, et
473 al. Prevalence, Risk, and Genetic Association of Reticular Pseudodrusen in Age-related
474 Macular Degeneration: Age-Related Eye Disease Study 2 Report 21. Ophthalmology.
475 2019;126(12):1659-66.
476 26. Zekavat SM, Sekimitsu S, Ye Y, Raghu V, Zhao H, Elze T, et al. Photoreceptor
477 Layer Thinning Is an Early Biomarker for Age-Related Macular Degeneration:
478 Epidemiologic and Genetic Evidence from UK Biobank OCT Data. Ophthalmology.
479 2022;129(6):694-707.
480 27. Curcio CA, Kar D, Owsley C, Sloan KR, Ach T. Age-Related Macular
481 Degeneration, a Mathematically Tractable Disease. Invest Ophthalmol Vis Sci.
482 2024;65(3):4.
483 28. Curcio CA, Millican CL, Bailey T, Kruth HS. Accumulation of cholesterol with
484 age in human Bruch's membrane. Invest Ophthalmol Vis Sci. 2001;42(1):265-74.
485 29. Smith RT, Olsen TW, Chong V, Kim J, Hammer M, Lema G, et al. Subretinal
486 drusenoid deposits, age-related macular degeneration, and cardiovascular disease. Asia
487 Pac J Ophthalmol (Phila). 2024;13(1):100036.

30. Owsley C, Swain TA, McGwin G, Jr., Clark ME, Kar D, Crosson JN, et al. How Vision Is Impaired From Aging to Early and Intermediate Age-Related Macular Degeneration: Insights From ALSTAR2 Baseline. Transl Vis Sci Technol. 2022;11(7):17.

31. Lin LY, Zhou Q, Hagstrom S, Maguire MG, Daniel E, Grunwald JE, et al. Association of Single-Nucleotide Polymorphisms in Age-Related Macular Degeneration With Pseudodrusen: Secondary Analysis of Data From the Comparison of AMD Treatments Trials. JAMA Ophthalmol. 2018;136(6):682-8.

Figure legends

Figure 1: Bar graph shows (A) distributions of the total AMD PRS in apparently healthy macula, and (B) participants with early or intermediate AMD.

Figure 2: Baseline Beckman grade, age, sex, presence or absence of SDD, and history of using anti-hypertension medicine were entered into model 1. Model 2 involved PRS only. Model 3 combined PRS with baseline Beckman grade, age, sex, presence of SDD, and history of using anti-hypertension. DeLong tests were also performed to compare the AUCs between models.