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1 **Polygenic Risk Score Impact on Visual Function in Older Individuals with Healthy**

2 **Macula: The Northern Ireland Sensory Ageing Study**

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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

41   increased RIT.

42   **Conclusions and relevance:** We observed a significant decline in multiple visual

43   functions with increasing age. However, PRS was significantly associated with RIT

44   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

64 and extracellular matrix remodelling, all of which are implicated in the pathology of

65 AMD.(7) Despite the identification of genetic variants associated with AMD, each

66 variant only confers a modest effect and has limited predictive power individually.

67 Polygenic risk score (PRS) examines the aggregate genetic effect by combining these

68 separate genetic variants into a single measure. Currently, there is limited data on

69 whether PRS derived from AMD-associated single nucleotide polymorphisms (SNPs)

70 is associated with visual function losses in AMD.(8) A previous study observed a

71 progressive non-linear deterioration of visual function over 24 months and moderate

72 correlation with the genetic burden score and rod intercept time (RIT) in early and

73 intermediate AMD.(9) The study provided a proof of principle of a possible genetic

74 link with visual function. However, the genetic burden score was generated from only

75 nine SNPs in nine genes and may not have captured sufficient predictive power of the

76 included variants. Furthermore, the visual function tests were evaluated in a small

77 cohort (n = 101), 33 with early AMD, 47 with intermediate AMD, and 21 with

78 apparently healthy macula.(9) A larger cohort is required to understand the relation of

79 AMD PRS with age-related visual function losses.

80

81 Therefore, our aim was to conduct a more comprehensive evaluation of both mesopic

82 and scotopic visual functions in older individuals with apparently healthy macula and

83   determine whether any changes observed are associated with AMD PRS. If so, we

84   aimed to explore whether a risk model that incorporates AMD PRS can accurately

85   discriminate people with visual function losses in a population-based study.

86   Additionally, we examined whether the presence of AMD could be identified in those

87   with with visual function losses.

88

89   **Methods**

90   **Study Cohort**

91   We used prospectively collected data from a case-control, cross sectional study, the

92   Northern Ireland Sensory Ageing study, which was part of the long-term, ongoing

93   epidemiologic Northern Ireland Cohort of Longitudinal Study of Ageing (NICOLA)

94   study conducted at Queen's University, Belfast. The NICOLA study is a population-

95   based, nationally representative ageing cohort study that was established in 2012. The

96   study recruited adults aged 50 years or over of European ancestry and residing in

97   Northern Ireland. The primary aim was to identify factors affecting health and social

98   outcomes in an ageing population. Detailed descriptions of the sampling procedures

99   and study design of the NICOLA Study have been provided elsewhere.(10) The

100   Northern Ireland Sensory Ageing study adhered to the tenets of the Declaration of

101   Helsinki, with ethical approval from the School of Medicine, Dentistry and

102   Biomedical Sciences Ethics Committee, Queens University, Belfast (Ref. 14.25v4).

103   Participants provided written informed consent before enrollment.

104

105   Inclusion criteria for the current study comprised of adults aged 55 years or above

106   with (a) apparently healthy fundus; and (b) with early or intermediate AMD. The

107   better seeing eye of each eligible participant was included. If the monocular VA scores

108   were found to be equal, an eye was either chosen randomly or according to the

109   participant preference at the point of consent. Exclusion criteria comprised: (1)

110   participants with diabetes; (2) eyes with advanced AMD (neovascular AMD and/or

111   geographic atrophy); (3) eyes with glaucoma; (4) eyes with a refractive error of

112   greater than −6.0 diopters (D); (5) other eye pathologies that interfere with imaging

113   and visual function examinations (e.g., dense cataract and corneal opacities).

114

115   **Data collection**

116   Details on image acquisition, image grading,(11) collections of demographic,

117   systemic and ocular factors, genotyping methods, and PRS calculation(7, 12) have

118   been reported elsewhere. A total of 45 variants met the following criteria and were

119   included for PRS calculation: (1) minor allele count > 5; (2) info-Score (quality) for

120   imputation (R^2) > 0.3; (3) not a monomorphic variant. PRS was calculated as per

121   Colijn et al.(8) A detailed description of the visual function tests and retinal structure

122   evaluations can be found in **Supplementary Information 1**. Briefly, best-corrected

123   distance VA by Early Treatment Diabetic Retinopathy Study chart (ETDRS, Precision

124   Vision, USA) and the Moorfields Acuity Chart, low-luminance visual acuity (LLVA),

125   low luminance deficit (LLD), near visual acuity by Bailey-Lovie reading charts and

126   Smith-Kettlewell Institute Low Luminance (SKILL) card, contrast sensitivity, reading

127   index, central visual field, macular sensitivity, and RIT were measured. The Beckman

128   Initiative for Macular Research Classification was used to define the severity of AMD

129   on colour photographs. The apparently healthy fundus group consisted of eyes with

130   Beckman grade 0 or 1. Eyes with Beckman grade 2 or 3 were classified as early or

131   intermediate AMD group. Macular thickness was measured by Spectralis optical

132   coherence tomography (OCT) (Heidelberg Engineering GmbH, Heidelberg,

133   Germany) with volumetric scan protocol.

134

135   Statistical analysis

136   All statistical analysis was conducted using R V.4.3.0. Normality of all continuous

137   variables was examined using Shapiro-Wilk tests and histograms. Continuous and

138   ordinal demographic data were analysed using independent t-tests and chi-square test,

139   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

159 group with delayed dark adaptation. DeLong tests were also performed to compare

160 the AUCs between models.(16) A P-value $\leqslant$ 0.05 was considered as a level of

161 statistical significance. The sample size was determined for a linear regression with an

162 effect size of 0.3 and an alpha level of 0.05. A total of 54 eyes were required to

163 achieve 80% power.

164 **Results**

165 **Table 1** presents the demographics and clinical characteristics of the eligible

166 participants included in this study. The mean age (SD) of the group of 470 participants

167 with apparently healthy macula (Beckman grade 0 or 1) was 66.34 (7.55) years and

168 the age-range was 55 to 94 years and 237 (50%) were males. The AMD group

169 consisted of 135 participants had a diagnosis of early AMD (n = 87) or intermediate

170 AMD (n = 48), with mean age (SD) of 68.84 (8.49) years, the age-range was 52 to 90,

171 and 56 (41%) were males. SDD was present in 90 (20%) participants with Beckman

172 grade 1, which is classed as otherwise apparently healthy macula.

173

174 **Figure 1** shows the distribution of the PRS in the group with apparently healthy

175 macula (n = 470) and those with AMD phenotypes (early AMD, n = 87, and

176 intermediate AMD, n = 48). In the group with apparently healthy macula, the mean

177 (SD) of PRS was 0.42 (1.14) ranged from -2.48 to 3.84 and showed a normal

178 distribution (P = 0.70). The mean (SD) of PRS in AMD was 0.82 (1.28) ranged from -

179 2.19 to 3.72 and demonstrated a normal distribution (P = 0.50). There was statistically

180 higher PRS in the AMD cohort compared to the group with apparently healthy macula

181 (P < 0.01).

182

183 **Evaluation of age-related visual function changes in the group with apparently**

184 **healthy macula**

185 **ETable 1** shows the univariable linear regression analyses between visual functions

186 and possible risk factors in the group with apparently healthy macula. The differences

187 in visual function between Beckman grade 0 or 1 are also shown. Age, sex, and other

188 factors with P ≤ 0.05 were entered into a full linear regression model. **Table 2** presents

189 the results of associations between age and visual functions in fully adjusted

190 multivariable model. All visual functions except for metrics of FDT showed

191 significant decline with age after adjustment for sex and variables significantly

192 associated in univariable linear regression. Of note, mean visual acuity and macular

193 sensitivity were decreased in eyes with Beckman grade 1 versus 0 within this group.

194

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

196 **Table 3** displays the multivariable linear regression results between visual functions

197 and PRS in all participants, adjusted for age, sex, and other associated factors shown

198 in **eTable 2**. RIT was the only visual function that was significantly associated with

199 PRS, with Beta = 0.12 (95% confidence interval: 0.01 to 0.23), P = 0.03. Other

200 functions such as decreasing VA measured by ETDRS chart, Moorfields chart, and

201 SKILL card (light), poorer LLVA, mean deviation of FDT, and contrast sensitivity

202 were associated with female sex and higher baseline Beckman grade of AMD.

203 Average macular sensitivity was lower in eyes with Beckman grade 1 versus 0.

204 Multivariable analyses showed that the association of RIT and PRS in the whole

205 cohort was driven by the group with apparently healthy macula (n = 470), with Beta =

206 0.15 (0.05 to 0.25), P = 0.01 (**Table 2**) but not AMD (n=135, **eTable 3**). Sensitivity

207 analyses in the group with apparently healthy macula with age over 60 years (n = 386)

208 further confirmed the significant association between RIT and PRS (**eTable 4**). In the

209 group with healthy macula, RIT was also significantly associated with history of anti-

210 hypertension medicine with Beta = 0.26 (0.03 to 0.48), P = 0.03 (**Table 2**).

211

212 **A risk model that incorporates AMD PRS can accurately discriminate people**

213 **with increased RIT**

214 We then estimated the accuracy of a model that could discriminate participants with

215 increased RIT (n = 56) versus the rest (n = 396). **Figure 2** presents the discriminatory

216   power. Baseline Beckman grade, age, sex, presence or absence of SDD, and history of

217   using anti-hypertension medicine were entered into model 1, with AUC = 0.798

218   (0.730 to 0.865). Model 2 involved PRS only, with AUC = 0.612 (0.525 to 0.699).

219   Model 3 combined PRS with baseline Beckman grade, age, sex, presence of SDD,

220   and history of using anti-hypertension showed the highest AUC = 0.803 (0.732 to

221   0.874). DeLong tests were also performed to compare the AUCs between models,

222   with P = 0.002 for model 1 vs. model 2, P < 0.001 for model 2 vs. model 3, and P =

223   0.144 for model 3 vs. model 1. Accuracy of the risk model was further estimated in

224   participants with apparently healthy fundus (**eFigure 1**), with 34 eyes with increased

225   RIT and 326 eyes with normal RIT. Again, model 3 with PRS, baseline Beckman

226   grade 0 or 1, age, sex, presence of SDD and history of using anti-hypertension

227   showed the highest AUC = 0.776 (0.679 to 0.873), compared to AUC = 0.763 (0.670

228   to 0.875) for model 1 (Baseline Beckman grade 0 or 1, age, sex, presence or absence

229   of SDD, and history of using anti-hypertension medicine), and AUC = 0.588 (0.476 to

230   0.701) for model 2 (PRS only), respectively. A model integrating PRS showed the

231   highest AUC = 0.690 (0.528 to 0.851) in differentiating the presence (n = 22) or

232   absence of AMD (n = 34) among participants with increased RIT (**eFigure 2**).

233

234   **Discussion**

235   The key findings of our study include an age-related decline in all photopic and scotopic

236   visual functions except FDT in those with apparently healthy macula; the only visual

237   function decline that was associated with AMD PRS was delayed dark adaptation (an

238   increase in RIT); an AMD PRS integrated model consisting of Beckman AMD

239   classification (grade 0-3), age, sex, and history of using anti-hypertension medications

240   could discriminate people with increased RIT across the entire study cohort; the model

241   could not discriminate participants with AMD (Beckman grade 2 or 3) from those with

242   healthy macula (Beckman grade 0 or 1) in people with increased RIT. To our knowledge,

243   this study is the first to report the association of a PRS developed from 45 AMD variants

244   and RIT in a population aged 55 years or over and its use in a risk score to detect age-

245   related increase in RIT in people with apparently healthy macula.

246

247   Our finding that most visual function tests decline with ageing in participants with

248   apparently healthy macula is consistent with previous reports that older age is

249   associated with poorer VA measured under photopic and mesopic conditions.(17)

250   However, only prolonged dark adaptation (increased RIT) was associated with higher

251   AMD PRS.[18] These observations suggest that increased RIT is indeed driven by local

252   factors in the outer retina and choroid that impact rods directly or indirectly. In

253   contrast, decline in other visual functions seems to be unrelated to the same

254   mechanisms of increased RIT and may be related to changes in any part of the visual

255   pathway from the photoreceptors to the cortex that are not associated with AMD PRS

256   score.

257

258   When we consider local factors, an increase in RIT may indicate an exaggerated age-

259   related decline in numbers or function of rod photoreceptors or alterations in

260   phagocytosis by the RPE or a disturbed retinoid cycle.(19) Although most individuals

261   can adapt to the declining numbers of rods with age, it may be that those with high

262   AMD PRS do not have that plasticity and consequently manifest functional

263   losses.(20) Structurally, an increase in RIT may be explained by a decrease in inner

264   segment outer segment-retinal pigment epithelium (ISOS-RPE) and RPE-BM

265   thickness in normal macula of adults with AMD risk SNPs.(21) Although, OCT

266   evidence of thinning of ISOS-RPE may be a pre-morbid marker of AMD, our findings

267   indicate that there may be other factors such as oxidative stress and inflammation that

268   are required to trigger AMD.(22) We observed that although Grade 0 and 1 of

269   Beckman grade are usually grouped together as 'healthy ageing'.(23) Our study

270   showed that Beckman grade 1 had more functional losses than Beckman grade 0 and

271   this may be explained by SDD being included in Beckman grade 1. Increased RIT and

272   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.

292

293 Indeed, there seems to be a complex relation of SDD, choroid and outer retinal

294 thinning and increased RIT. SDD is thought to be associated with cardiovascular

295 disease, which can further explain the association of increased RIT with anti-

296 hypertensive medications and male gender.(29) These point towards the need for

297 lifestyle changes in people with increased RIT especially if associated with high AMD

298 PRS.

299

300 When we consider the link of higher AMD PRS with increased RIT, both high-risk

301 *ARMS2* and *CFH* genotypes are associated with delayed RIT.(18) While the PRS was

302 significantly higher in our AMD group compared to the group with apparently healthy

303 macula, only 39% of the patients with delayed RIT had early or intermediate AMD.

304 We also observed that people with AMD could not be distinguished within a cohort

305 with increased RIT, indicating that other triggers are required for the development of

306 AMD, or that delayed RIT may precede the development of AMD by a considerable

307 period. It also explained why our previous report revealed that PRS were highly

308 significantly associated with presence or absence of AMD in fully adjusted

309 multivariable logistic regression model in the NICOLA study.(12) This model

310 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

330   SNPs identified to date. Also, rare variants which may have larger effect were included

331   in this PRS construction. Secondly, comprehensive scotopic and photopic visual

332   function examinations were performed. There are three limitations, however. First, PRS

333   was constructed using SNPs collected from single ethnicity (i.e., Whites) and may

334   reduce the generalisability of its associations with RIT. Second, the small sample size

335   of AMD participants may make it difficult to detect significant associations of PRS and

336   visual functions in people with early or intermediate AMD. Further studies for

337   replicating these findings are needed. Third, our study excluded seven SNPs that did

338   not meet the quality control criteria for imputation. Six of them have low to moderate

339   effect size with ORs ranged from 0.57 to 2.79, and a rare variant in the *CFH*, namely

340   rs121913059, have a strong effect on AMD risk (OR = 47.62).(7) While the number of

341   excluded SNPs was relatively small, it is possible that their exclusion could have

342   slightly underestimated the true genetic contribution to decline in dark adaptation. It

343   should be noted that, including genotypes with lower quality may introduce noise into

344   the analysis and weaken the predictability of PRS. Although excluding the SNPs might

345   have resulted in a slightly weaker PRS performance, maintaining data quality is

346   essential for a robust analysis. In future studies, using proxy SNPs derived from linkage

347   disequilibrium database to replace the excluded SNPs could potentially address the

348   limitation. Fourth, the apparently higher proportion of eyes with AMD in our study

349 cohort (22.3%) than the general population may result in a bias result of the risk model

350 for differentiating eyes with or without increased RIT. Further validation in a

351 population-based study.

352

353 In summary, we observed a significant decline in photopic and scotopic visual functions

354 with increasing age in a cross-sectional sample with apparently healthy macula

355 recruited from a population-based study. Furthermore, PRS composed of 45 reported

356 AMD-associated SNPs were significantly associated with RIT in this population. Our

357 study extends the promise of applying PRS as a population-based risk stratification tool

358 to identify individuals with increased RIT and normal macula that could benefit from

359 strategies to improve lifestyle, especially to control cardiovascular risk factors.

360

361 **Contributions**

362 SS, REH: research design. FYT: data analysis, interpretation, REH, BEH, DMW, LS:

363 research execution. All authors contributed towards the preparation of the manuscript

364 and approved the final submitted version. The corresponding author is solely

365 responsible for managing communication between co-authors; that all authors are

366 included in the author list; order has been agreed by all authors; and that all authors are

367 aware that the paper was submitted.

387   the manuscript for publication.

388

389   **Data availability:** The data collected for the current study, including individual patient

390   data and a data dictionary defining each field in the data set, will not be made available

391   to others.

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496

497 **Figure legends**

498 Figure 1: Bar graph shows (A) distributions of the total AMD PRS in apparently healthy

499 macula, and (B) participants with early or intermediate AMD.

500 Figure 2: Baseline Beckman grade, age, sex, presence or absence of SDD, and history

501 of using anti-hypertension medicine were entered into model 1. Model 2 involved PRS

502 only. Model 3 combined PRS with baseline Beckman grade, age, sex, presence of SDD,

503 and history of using anti-hypertension. DeLong tests were also performed to compare

504 the AUCs between models.

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