Journal of Statistics on Health Decision

EXTENDED ABSTRACT

A9 Genetic risk variants for Age-related Macular Degeneration in a Portuguese population - the Coimbra Eye Study

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Introduction

Age-related macular degeneration (AMD) is a progressive degenerative disease of the central area of the retina, the macula, which is responsible for central vision. It is a multifactorial disease, strongly influenced by a combination of environmental factors (such as age, smoking, lifestyle, diet) and genetic factors. In 2016, the largest genome-wide association study (GWAS) in AMD was published and 52 common and rare genetic variants distributed across 34 loci were associated with increased risk of disease development and progression [1].

We propose to investigate the contribution of 52 previously identified genetic variants to the risk of AMD development in a Portuguese population from a central region of Portugal (Mira).

Methods

The Coimbra Eye Study (CES) is an epidemiologic study for the estimation of prevalence and 6.5-year incidence of AMD in central Portugal (NCT01298674, NCT02748824) [2,3].

A total of 948 DNA samples were genotyped under the collaboration with the European Eye Epidemiology Consortium (E3) [4]. After quality control, 69 single nucleotide polymorphism (SNPs) were genotyped successfully.

A case-control analysis was performed for the 52 independently associated variants from the International Age-related IAMDGC GWAS [1]. Cases were considered participants if staged 2, 3 or 4 (Rotterdam Classification) and controls were participants staged 0 or 1 (above 60years-old) or 1 (above 70years-old).

A logistic regression analysis was performed to assess allelic odds ratio (ORs) at 95% CI (confidence interval) for each single variant, adjusted for age and sex, and significance level was set to 0.05. All variants with a P-value <0.05 form the univariable analysis where combined in a multivariable logistic regression model.

To assess individual genetic risk, a genetic risk score (GRS) was calculated for each individual [4]. The GRS was considered missing if at least one genotype of the major risk variants (*CFH* rs570618, *CFH* rs10922109, *C2/CFB/SKIV2L* rs429608, *ARMS2* rs3750846 or *C3* rs2230199) was missing.

Results

A total of 829 samples (607 controls and 222 cases) and 52 variants were analyzed, according to the flow chart of the study participants (Fig. 1). The mean age was 72.6 ± 6.8 years, and the percentage of females was 57.4 %.

To test for variants associated with AMD, a single variant logistic regression analysis, adjusted for age and sex, was performed for the 52 variants.

We have identified 4 variants associated with the increased risk of AMD presence in our study population: *ARMS2/HTRA*1 rs3750846 (OR 1.460; CI 95% 1.098 -1.930, P =0.009), *SLC16A8* rs8135665 (OR 1.440; CI 95% 1.056 -1.960, P =0.020), *CFH* rs35292876 (OR 2.690; CI 95% 1.145 -6.220, P =0.020) and , *TGFBR1* rs1626340 (OR 1.320; CI 95% 1.008 -1.730, P =0.042) (Table 1).

Moreover, we have also identified 4 variants which suggest a potential protective effect: *C2/CFB/SKIV2L* rs429608 (OR 0.509; CI 95% 0.339 -0.743, P=0.001), *CFH* rs10922109 (OR 0.697; CI 95% 0.555 -0.872 P=0.002), *CETP* rs5817082 (OR 0.688; CI 95% 0.525 -0.896, P =0.006), and *CNN2* rs10422209(OR 0.667; CI 95% 0.471 -0.929, P =0.019).

Keywords:
Age-related Macular Degeneration (AMD), Genetics, Epidemiology, Risk score.

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Clinical study registration number: NCT02748824

Conflict of interest:
Rufino Silva is consultant for: Alimera, Abbvie, Alcon, Bayer, Novonordisk, Novartis and THEA

First published: 22JUN2021

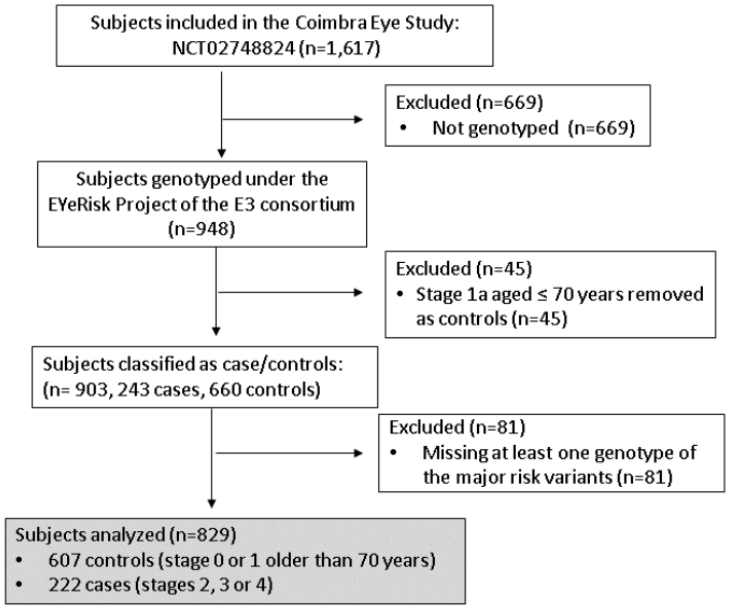

Figure 2 - Distribution of the genetic risk score in cases and controls

Table 1 - Univariate logistic regression analysis for AMD asssociation (adjusted for age and sex)

Gene	Rs number	Major/ Minor allele	MAF controls CES	MAF cases CES	OR CES	P-value CES	OR IAMDGC primary analysis [4]	P-value IAMDGC primary analysis [4]
C2/CFB/SKIV2L	rs429608	G/A	0.143	0.079	0.509 [0.339 -0.743]	0.001	0.57	1.2e–103
CFH	rs10922109	C/A	0.441	0.351	0.697 [0.555 - 0.872]	0.002	0.38	9.6e–618
CETP	rs5817082	C/CA	0.293	0.229	0.688 [0.525 - 0.896]	0.006	0.84	3.6e–19
ARMS2/HTRA1	rs3750846	T/C	0.140	0.198	1.46 [1.098 - 1.93]	0.009	2.81	6.5e–735
CNN2	rs10422209	C/G	0.228	0.167	0.667 [0.471 - 0.929]	0.019	0.90	2.6e–8
SLC16A8	rs8135665	C/T	0.152	0.206	1.44 [1.056 - 1.96]	0.020	1.14	5.5e–11
CFH	rs35292876	C/T	0.011	0.025	2.69 [1.145 - 6.22]	0.020	2.42	8.2e–37
TGFBR1	rs1626340	G/A	0.183	0.221	1.32 [1.008 - 1.73]	0.042	0.88	3.8e–10

MAF = Minor allele frequency, OR=Odds-ratio. To distinguish from protective variants, risk variants are highlighted in grey.

Table 2 - Multivariate logistic regression analysis for AMD asssociation (adjusted for age and sex)

Variables	Odds Ratio	95% CI	P- value CES
age	1.064	1.039-1.089	2.77e-07
C2/CFB/SKIV2L_ rs429608	0.526	0.349-0.771	1.45e-03
CFH_rs10922109	0.690	0.546-0.868	1.71e-03
ARMS2/HTRA1_rs3750846	1.511	1.128-2.017	5.32e-03
CFH_rs35292876	2.187	0.906-5.185	7.56e-02
CETP_rs5817082	0.800	0.617-1.013	8.02e-02
Sex (male)	0.749	0.536-1.041	8.73e-02
CNN2_rs10422209	0.986	0.942-1.031	5.46e-01
SLC16A8_rs8135665	0.991	0.937-1.046	7.40e-01
TGFBR1_rs1626340	1.026	0.833	7.93e-01

All 8 variants with a p-value<0.05 from the univariate analysis were combined in a multivariate analysis (Table 2), adjusted for age and sex. Age, and variants *C2/CFB/SKIV2L* rs429608, *CFH* rs10922109 and *ARMS2/HTRA1* rs3750846 were statistically significant.

To assess individual genetic risk, the GRS was calculated for the 829 subjects (Fig. 2). Despite the significant differences between cases and controls (0.794 ±1.151 vs 1.302 ± 1.229, p<0.001), there is a substantial overlap between cases and controls in our study and therefore we cannot distinguish them based on the GRS alone.

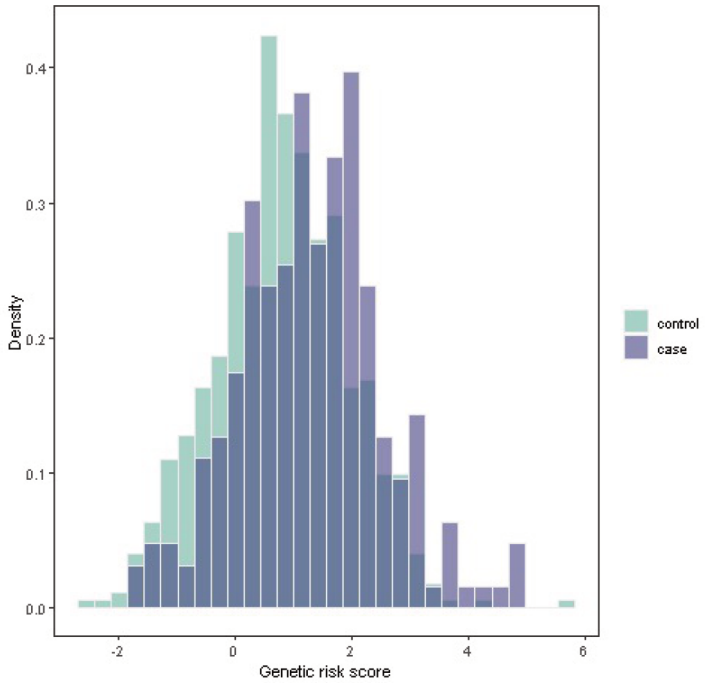

Figure 2 - Distribution of the genetic risk score in cases and controls

Discussion

Focusing on the 52 independently associated variants identified in the largest GWAS study in the European population, our results are generally in agreement with previously published major reports, despite the limited number of CES .

Variants associated with AMD in our multivariable analysis are mainly associated with the complement system (*CFH, C2/CFB/SKIV2L*) and ARMS2/HTRA1 genes, highlighting the polygenic nature of the disease

Our data also support the role of genetic risk profiling in the identification of individuals at high risk of AMD development and that can benefit from a healthy diet, lifestyle changes and ophthalmological monitoring.

This was the first genetic study in a Portuguese population with AMD, and opened avenues for future studies that should explore the correlation between genetics, phenotypic and environmental features in risk and progression assessment.

Ethics committee and informed consent

The current research was approved by an independent ethics committee and subjects gave their informed consent before they were enrolled in the study.

Acknowledgements

The authors gratefully acknowledge the financing from Novartis Pharma AG that made this study possible and the collaboration and dedication from the personnel of primary healthcare unit of Mira.

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