

The Bridlington Eye Assessment Project Age-related Macular Degeneration Study (BEAP-AMD2): Characterising Phenotype-Genotype Associations in a UK Population Cohort

Winfried Amoaku

Winfried.Amoaku@nottingham.ac.uk

Queen's Medical Centre, Nottingham University Hospital <https://orcid.org/0000-0001-5028-7984>

Christian Pappas

University of Utah

Richard Gale

York District Hospital

Vittorio Silvestri

Laura Cushley

Institute of Clinical Sciences, Queen's University of Belfast

Jill Hageman

Reuben Amoaku

Rukhsar Akhtar

Rochelle Amoaku

Rajnikant Mehta

William Hubbard

University of Utah

Stephen Vernon

Gianni Virgili

Azienda Ospedaliero-Universitaria Careggi <https://orcid.org/0000-0002-9960-2989>

Gregory Hageman

Giuliana Silvestri

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Abstract

Background/Objectives:

Data on UK population prevalence of age-related macular degeneration (AMD) genetic-risk and retinal thickness (RT) and choroidal thickness (CT) is limited. This study investigates RT and CT, and associations of chromosome 1 (Chr1) and 10 (Chr10) AMD-associated gene variants in a UK population aged ≥ 55 years.

Subjects/Methods:

Prospective cross-sectional population study in Bridlington, UK. Participants completed a health questionnaire, had logMAR visual acuities, intraocular pressures, colour fundus photographs, optical coherence tomography, and angiography recorded. Extracted DNA were genotyped for single-nucleotide variants at three major AMD loci. Relative AMD-risk based on the Utah AMD Genetic Risk classification was investigated. RT and CT in the 'No-AMD' group were compared with late AMD.

Results

Total of 1364 participants were recruited; 83.9% had no AMD. Rotterdam Grade 1b-2, Grade 3, Grade 4a-4c comprised 11.4%, 3.2%, and 4.7% respectively. The commonest Bridlington haplotype: C allele at rs1061170, was associated with increased AMD-risk. Protective haplotypes at rs800292 or rs12144939 had reduced AMD-risk. Diplotypes G1 and G2 occurred in one-third of late AMD. RT and CT reduction were significantly progressive across AMD grades but not genetic risk. Smoking was associated with RT thinning. Multivariate analyses showed a trend towards RT and CT thinning with moderate and high genetic risk.

Conclusions

AMD genetic risk in this UK cohort parallels other Caucasian populations. The Bridlington control set haplotype structure is closely similar to that in other EU cohorts. Diplotype distribution with G1 and G2, commonest in late AMD cases, is consistent with the Utah data.

Introduction

Age-related macular degeneration (AMD) is the most common cause of irreversible visual loss in the western world.^{1,2} Susceptibility to AMD results from an interplay of aging, environmental factors and genetics.³ We have previously reported the prevalence of AMD and reticular pseudodrusen (RPD) in persons aged 65 years and older in Bridlington, a well-defined Caucasian UK population.^{4,5} Dysregulation of the alternative complement pathway at the ocular retinal pigment epithelium (RPE)-choroid interface - mediated by variants in complement factor H (*CFH*) and complement factor H-related genes (*CFHRs*) on Chr1⁶⁻¹⁰, complement factor I (*CFI*) on Chr4¹¹⁻¹³, complement factor B (*CFB*)¹⁴⁻¹⁵ and complement component 2 (*C2*) genes on Chr6 (Gold et al, 2006)¹⁴, and complement component 3 (*C3*) gene on Chr19^{16,17} - plays a major role in the development of AMD. In addition, variants in the non-complement pathway *ARMS2* and *HTRA1* genes on Chr10 are strongly associated with AMD risk¹⁸⁻²⁰ although the specific biological pathways mediating Chr10-directed disease are poorly understood. Recently, Williams et al (2021)²¹ reported that reduced levels of HTRA1 in the retinal pigment epithelium (RPE) may drive Chr10 related AMD. Collectively, these loci account for approximately 90% of AMD risk in the US population. Importantly, highly 'protective' polymorphisms and haplotypes within the *CFH-CFHR* locus exist.^{22,23}

Findings from our group suggest that AMD is multiple, distinct biological diseases - one directed by Chr1 and another by Chr10 - that exhibit significant overlap in populations.²³⁻²⁵ Furthermore, genetic variations may determine AMD disease progression, and that treatment outcomes in eyes with neovascular AMD (nAMD) with anti-vascular endothelial growth factor (VEGF) agents

vary dramatically.^{26–28} As such, it is important to determine the relative occurrence of the different genetic associations of AMD, particularly at the Chr1 and Chr10 loci in different populations, including the UK population.

It is also important to accurately characterise the disease phenotype. Although colour fundus photography (CFP) has been the gold standard tool in population-based AMD studies, it has the limitations of inter-patient variability of fundus pigmentation, media opacities, the variability of drusen appearance, the presence of small satellites of atrophic patches and the impossibility of detecting three-dimensional information of choroido-retinal abnormalities.²⁹ In particular, as CFP does not provide appropriate information about the depth resolution and cross-sectional view of retinal/subretinal pathology or outer retinal/RPE integrity, other imaging modalities that are non-invasive but enhance our ability to determine depth resolution are welcome. The diagnostic accuracy of CFP has been improved by the recent introduction of Optical Coherence Tomography (OCT)³⁰, OCT angiography (OCT-A)^{31–34}, and other imaging modalities. OCT demonstrates CNV in nAMD.³⁵ Spectral domain (SD) OCT allow better sub-phenotypic classification and is reported to have a high sensitivity 98–100% and a specificity of approximately 75% in diagnosing late stages of AMD.³⁶ Similarly, the earlier stages of AMD are well-characterised by SD-OCT.³⁶ The swept-source OCT (SS-OCT) has improved the simultaneous detailed visualisation of the choroid, retina and vitreous. OCT-A is the most recent technology development and has even better characterisation and higher resolution of different types of AMD.³⁴ The Topcon SS DRI Triton plus OCT system provides multimodal imaging: CFP, fundus autofluorescence (FAF), OCT and OCT-A imaging with single scan capture of comprehensive data for the retina and choroid, and importantly provides more detailed imaging of the choroid compared to other OCT systems, including the SD-OCT.

Several studies have reported OCT changes in the different ETDRS sectors of the retina in the normal population as well as at different stages of AMD.^{37–42} Although OCT thickness changes in the choroid have been described in different populations, these thickness measurements are based on single line scans of the subfoveal choroid.^{43–57} As such, OCT thickness changes in the different ETDRS sectors have not been widely reported. This study will address the deficiency in the literature.

The aims/objectives of this study were to i) determine the prevalence of different stages of AMD in a Bridlington population aged 55 years and older (representative of UK Caucasian population), ii) evaluate retinal and choroidal thickness in different AMD grades, and iii) determine association of haplotypes and diplotypes in AMD-associated gene variants on Chr1 and Chr10 with AMD grades.

Methods

This study was a prospective cross-sectional study carried out in Bridlington, England, UK. The study protocol was approved by the NHS Health Research Authority East Midlands-Nottingham 2 Research Ethics Committee (REC) (ref 17/EM/0085; IRAS Project ID: 215114).

Study population and Recruitment. All Bridlington residents aged > 55 years at Feb 1, 2019 were invited to participate in this study. Exclusion criteria were i) persons unwilling to participate, ii) persons too ill or unable to attend, or unwilling to give samples for analyses. Recruitment was conducted through postal adverts and information sent to persons falling within the recruitment age range. Advertisements were also posted around the Bridlington area.

Study procedures. All participants were given a participant information leaflet and signed consents at their visits. Participants completed a questionnaire including demographic details, whether they participated in the original Bridlington Eye Study, history of diabetes, hypertension, previous stroke, previous optometric assessment, and whether they were registered as visually impaired. They were also asked about previous ophthalmic operations, diabetic retinopathy, macular degeneration, and medications, especially the use of statins. Cheek swab samples were then taken for genetic analyses. Participants had 45-degree fundus photographs (fields 1 [centred on macula] and 2 [centred on the optic disc]) and OCT images taken with a SS-OCT: Topcon Triton Plus Camera OCT, with or without pupillary dilatation as necessary.

Data & Analyses. All data were entered into a FileMaker-based clinical study database developed by the Steele Center for Translational Medicine (SCTM; GSH) by trained assistants. The entries were checked for accuracy by the Research Manager

through a random selection of 10% of the data aiming for an error rate of < 0.1%. The biological samples were processed and analysed in the Steele Center for Translational Medicine (SCTM) laboratories, University of Utah under the supervision of GSH.

All fundus images were graded independently by JLH at the University of Utah and WMA at University of Nottingham. Any differences were discussed to arrive at a consensus. Automated reports were generated for OCT images. Retinal and choroidal thickness, and other characteristics on the SS-OCT in the 'No-AMD' group were compared with that in late AMD eyes. We investigated whether retinal and choroidal thickness differed by AMD grade across ETDRS sectors (Temporal [T], Superior [S], Nasal [N], and inferior [I]) and circles (Inner vs Outer).

Genotyping and Genetic Analyses. DNA derived from cells in cheek swab samples from participants were processed and analysed in the SCTM under the supervision of GSH.

Genotyping. We genotyped single-nucleotide variants (SNPs) at three major AMD loci, *CFH-CFH5*, *ARMS2/HTRA1* and *C3*. We then analysed the association of SNPs and haplotypes with AMD grade. Total genomic DNA was extracted from buccal cells, using the Isohelix BFP-50 Plus DNA Isolation Kit (Cell Projects Ltd. Harrietsham, Kent, UK). Genotypes were determined using Taqman assays (Applied Biosystems [ABI], Waltham, MA, USA) under the manufacturer's recommended conditions.²² Six putative AMD variants were genotyped, including *CFH* variants rs800292, rs1061170, rs1410996 and rs12144939, *ARMS2/HTRA1* variant rs10490924, and *C3* variant rs2230199. All SNP assays were predesigned or made using ABI's Custom TaqMan Assay Design Tool. Samples were amplified using a PTC-225 Thermal Cycler (Madison James Research, Asheboro, NC, USA). Thermal cycling consisted of an initial hold at 95°C for 10 minutes, followed by 40 cycles of a 15-second 95°C denaturation step and a 1-minute 60°C annealing and extension step. Samples were analyzed in the 7900HT Fast Real-Time PCR System (Applied Biosystems).

AMD risk assessment

Relative risk assessment was conducted using variants from the most highly associated AMD loci, those within *CFH*, *ARMS2/HTRA1*, and *C3*. Specifically, rs800292 (*CFH* I62V), rs1061170 (*CFH* Y402H), rs12144939 (proxy for *CFHR3/CFHR1* deletion), rs10490924 (*ARMS2* A69S), and rs2230199 (*C3*) were assessed. Risk, neutral and protective *CFH* haplotypes were identified as previously described by Hageman et al (2006a, 2006b) and Pappas et al, (2021)^{22,23} and combined with *ARMS2/HTRA1* risk allele number to establish each individual's genetic group. The genotype groups represent diplotypes combinations at the two most prominent AMD-associated loci, *CFH-CFH5* and *ARMS2/HTRA1*. Samples were stratified into AMD risk categories (high, intermediate, low) based on the Utah AMD Genetic Risk classification scheme (Supplementary Table S1).²³

Outcomes

Our primary outcomes were the prevalence of different AMD grades, and retinal and choroidal thicknesses. Retinal and choroidal thickness, and other characteristics on the SS-OCT in the 'No-AMD' group (and specific diplotypes without AMD) were compared with that in late AMD eyes, and related to the genetic data. Other outcomes were retinal and choroidal thickness, and the frequency of participants with Chr1 and Chr10 in the late AMD group compared to 'No AMD'. Analyses were conducted using Stata 18.1 software (StataCorp, College Station, TX).

Statistics

Sample size estimation. The UK Census data Office for National Statistics (<https://www.ons.gov.uk/census/2011census> and <https://www.ons.gov.uk/peoplepopulationandcommunity>) accessed 3/9/14 and 2/9/16 was used to plan the study. The original sample size estimation was based on a population of ≥ 60 years. The population of Bridlington in 2011 aged ≥ 60 years was 10,166. The estimated population in 2015 was 10,949. An estimated 80% uptake of the population would result in approximately 8,000 to 8,200 participants (the overall study sample size). To determine a difference in frequency of participants with Chr 1 and Chr10 variants with 'No AMD' (AREDS/Rotterdam Grade 0,1) (and 'Late AMD' (AREDS/Rotterdam Grade 4) a sample size of 140 for each AMD grade. As AMD Grade 3 has the least prevalence of 111 in the 4368 sample in the

Chakravarthy et al (2013)⁵⁸ study, and 97 of 3475 in the Wilde et al (2017)⁵ study, a sample size of 5016 was required in this study to provide a 5% significance level and 90% power. With the onset of Covid-19, the recruitment target was reduced to 1200, and the participant inclusion age reduced to ≥ 55 years with approval of the Ethics Committee.

Statistical analyses. The frequency of different grades of AMD in this population was measured, and the difference in frequency of participants with pure Chr1 or Chr10 with 'No AMD' compared to those people at Late AMD Stage 4 with 5% significance level and 90% power were determined. Retinal and choroidal thickness are presented in boxplots using the full Rotterdam AMD classification. For statistical analyses, we used structural equation modelling (SEM) as an overarching regression framework, adjusting for correlated data within subject, with the 3-grade AMD classification (None, Intermediate, Late).

Since the original intended sample size was not achieved, we performed a post-hoc power calculation regarding the hypotheses made in each of three main objectives, given the sample size of 1364 individuals. We considered choroidal measures as more relevant than retinal measures, which are well known.

Regarding objective 1, our sample size had 90% power to detect an overall AMD prevalence of 12.75%, when the null hypotheses was 10%. Therefore, we had 100% power to detect an almost 20% prevalence as we found, as compared to a 10% prevalence. We used linear regression to investigate the association of retinal and choroidal thickness with genetic risk score, AMD status, as well as with age, and sex in univariate and multivariate models. We considered average retinal (ART) and choroidal (ACT) thickness the primary dependent variable and used Pearson correlation to select other OCT variables, provided the correlation with average thickness, was < 0.5 , meaning the two variables may be partly independent.

For objective 2, we found the precision of the 95% CI for overall choroidal thickness was 8.7 micron considering the observed standard deviation (SD) (80 micron), which we consider to be sufficiently precise.

Objective 3 consisted in associations between genotype and phenotype. We verified that, given the observed overall choroidal SD (80 microns), the sample size of 1364 could have had 90% power to detect a difference in choroidal thickness by 18 microns vs. control with a 20% prevalence of the trait; a difference of 25 microns would be detected if the prevalence were 10%. In regression models, the correlation between eyes of an individual was accounted for clustering on the subject with a robust Huber-White variance estimator. Cardiovascular risk factors were assessed in univariate analyses, and only those with a significant association with ART or ACT were considered in multivariate models.

We used SEM to jointly model the association of ART and ACT with AMD grade and genetic risk, adjusting for age. This type of modelling also allowed testing for overall subgroup analyses. Again, robust variance estimation clustering on subjects was used to account for correlation between eyes,

Results

The initial recruitment in the population study opened on 25th Feb 2019 and yielded 440 participants. Recruitment re-opened (after Covid-19) in April 2022, and the final recruitment wave was completed on 9th June 2023. A total of 1641 participants were recruited. This includes 274 participants who attended twice either at 6 or 24–36 months from first attendance; 116 re-attended twice, 19 re-attended three times. Gradable images were available in 1364 population participants.

AMD Phenotype count. Based upon the Rotterdam grading schema, the Bridlington Study cohort shows that the majority of individuals (83.9%) included in this study population showed no signs of AMD (grades 0-1a). Individuals with early AMD (1b-3) comprise 11.4% of the cohort, while late AMD (4a-4c) was observed in 4.7% of participants. The prevalence of Grades 4a, 4b, and 4c were 2.1, 2.3 and 0.4% respectively. A simple count of AMD grades based on the worst eye phenotype in the Bridlington study are summarised in Supplementary Table 2 (Table S2).

AMD Genotypes. Single-Marker associations. Table 1 provides a summary of single genetic marker associations of key AMD SNPs vs all AMD, early AMD, and late AMD. All variants tested exhibit significant associations with AMD when comparing all cases to all controls. The associations are in a direction consistent with previous AMD studies. Except for C3 variant rs2230199 (R102G), all risk or non-protective variants are more prevalent in advanced AMD cases than in cases of early AMD.

Table 1
Association analyses of key AMD SNPs (single marker associations) vs All AMD, early and late AMD.

0,1a vs 1b-4c	Assoc Allele	Case,Control Ratio Counts	Case,Control Frequencies	Chi square	P value
rs800292	G	328:58, 1236:396	0.850, 0.757	15.282	9.26E-05
rs1061170	C	183:209, 601:1023	0.467, 0.370	12.441	4.00E-04
rs1410996	G	289:103, 929:703	0.737, 0.569	37.229	1.05E-09
rs12144939	G	340:54, 1295:337	0.863, 0.794	9.826	0.0017
rs10490924	T	127:265, 308:1340	0.324, 0.187	35.473	2.59E-09
rs2230199	G	96:298, 319:1307	0.244, 0.196	4.378	0.0364
0,1a vs 1b-3	Assoc Allele	Case,Control Ratio Counts	Case,Control Frequencies	Chi square	P value
rs800292	G	227:41, 1236:396	0.847, 0.757	10.45	0.0012
rs1061170	C	113:157, 601:1023	0.419, 0.370	2.313	0.1283
rs1410996	G	190:80, 929:703	0.704, 0.569	17.295	3.20E-05
rs12144939	G	225:47, 1295:337	0.827, 0.794	1.645	0.1997
rs10490924	T	82:190, 308:1340	0.301, 0.187	18.935	1.35E-05
rs2230199	G	68:204, 319:1307	0.250, 0.196	4.157	0.0415
0,1a vs 4a-4c	Assoc Allele	Case,Control Ratio Counts	Case,Control Frequencies	Chi square	P value
rs800292	G	101:17, 1236:396	0.856, 0.757	5.931	0.0149
rs1061170	C	70:52, 601:1023	0.574, 0.370	19.899	8.17E-06
rs1410996	G	99:23, 929:703	0.811, 0.569	27.457	1.61E-07
rs12144939	G	115:7, 1295:337	0.943, 0.794	16.01	6.30E-05
rs10490924	T	45:75, 308:1340	0.375, 0.187	24.768	6.46E-07
rs2230199	G	28:94, 319:1307	0.230, 0.196	0.792	0.3735
Individuals Age < 65 analyzed as NG					

Chr1 Haplotype Structure Comparison. The Chr1 haplotype structure was compared to that in the 1G Genome/EUR Studies. The four most common haplotypes make up 97.2% of all control haplotypes. As is the case in most Caucasian chromosomes, the risk allele at rs1061170 rarely co-occurs on the same chromosome with either the protective allele from rs800292 or the *CFHR3/1* deletion. Table 2 summarises the haplotype structure comparison.

Table 2
Chr1 Haplotype Structure Composition

Haplotype	rs800292	rs1061170	rs1410996	rs12144939	Bridlington Control Frequency	1K Genomes EUR Freq
GCGG	G	C	G	G	0.370	0.3539
GTGG	G	T	G	G	0.183	0.1988
ATAG	A	T	A	G	0.219	0.2276
GTAT	G	T	A	T	0.200	0.1759
ATGG	A	T	G	G	0.017	0.0139
ATAT	A	T	A	T	0.007	0.0109
GTAG	G	T	A	G	0.005	0.0109
ACAG	A	C	A	G	0.001	NP

Chr1 Haplotype Associations. The most common Bridlington haplotype, containing a C allele at rs1061170, is associated with increased risk of developing AMD. The common haplotypes containing a protective allele at either rs800292 or rs12144939 (associated with a reduced risk for developing AMD) were observed. The GTGG haplotype is skewed toward cases in the Bridlington cohort, reaching significance in the early AMD cases but not in the later AMD stages. Rare haplotypes do not occur frequently enough to reach significance. (See Table 3).

Table 3
Chr1 Haplotype associations

0,1a vs 1b-4c									
Haplotype	rs800292	rs1061170	rs1410996	rs12144939	Freq.	Case, Control Ratio Counts	Case,Control Freqs	Chi Square	P Value
GCGG	G	C	G	G	0.381	185.5 : 212.5, 609.5 : 1038.5	0.466, 0.370	12.489	4.00E-04
GTGG	G	T	G	G	0.205	100.9 : 297.1, 300.8 : 1347.2	0.254, 0.183	10.262	0.0014
ATAG	A	T	A	G	0.198	51.6 : 346.4, 361.1 : 1286.9	0.130, 0.219	15.895	6.70E-05
GTAT	G	T	A	T	0.187	52.5 : 345.5, 329.6 : 1318.4	0.132, 0.200	9.822	0.0017
ATGG	A	T	G	G	0.017	5.7 : 392.3, 28.1 : 1619.9	0.014, 0.017	0.146	0.7028
ATAT	A	T	A	T	0.006	1.6 : 396.4, 10.9 : 1637.1	0.004, 0.007	0.323	0.5697
GTAG	G	T	A	G	0.005	0.1 : 397.9, 7.4 : 1640.6	0.000, 0.005	1.69	0.1936
ACAG	A	C	A	G	0.001	0.1 : 397.9, 0.6 : 1647.4	0.000, 0.000	0.018	0.8945
0,1a vs 1b-3									
Haplotype	rs800292	rs1061170	rs1410996	rs12144939	Freq.	Case, Control Ratio Counts	Case,Control Freqs	Chi Square	P Value
GCGG	G	C	G	G	0.381	115.5 : 160.5, 609.5 : 1038.5	0.419, 0.370	2.387	0.1223
GTGG	G	T	G	G	0.205	72.9 : 203.1, 300.8 : 1347.2	0.264, 0.183	10.066	0.0015
ATAG	A	T	A	G	0.198	35.7 : 240.3,	0.129, 0.219	11.661	6.00E-04

0,1a vs 1b-4c									
						361.1 : 1286.9			
GTAT	G	T	A	T	0.187	45.5 : 230.5, 329.6 : 1318.4	0.165, 0.200	1.878	0.1705
ATGG	A	T	G	G	0.017	4.7 : 271.3, 28.1 : 1619.9	0.017, 0.017	0	0.9982
ATAT	A	T	A	T	0.006	1.6 : 274.4, 10.9 : 1637.1	0.006, 0.007	0.016	0.9004
GTAG	G	T	A	G	0.005	0.0 : 276.0, 7.4 : 1640.6	0.000, 0.005	1.154	0.2826
ACAG	A	C	A	G	0.001	0.1 : 275.9, 0.6 : 1647.4	0.000, 0.000	0.013	0.9076
0,1a vs 4a-4c									
Haplotype	rs800292	rs1061170	rs1410996	rs12144939					
GCGG	G	C	G	G	0.381	70.0 : 52.0, 609.5 : 1038.5	0.574, 0.370	19.925	8.05E-06
GTGG	G	T	G	G	0.205	28.0 : 94.0, 300.8 : 1347.2	0.230, 0.183	1.672	0.196
ATAG	A	T	A	G	0.198	16.0 : 106.0, 361.1 : 1286.9	0.131, 0.219	5.273	0.0217
GTAT	G	T	A	T	0.187	7.0 : 115.0, 329.6 : 1318.4	0.057, 0.200	15.007	1.00E-04
ATGG	A	T	G	G	0.017	1.0 : 121.0, 28.1 : 1619.9	0.008, 0.017	0.546	0.4599
ATAT	A	T	A	T	0.006	0.0 : 122.0, 10.9 : 1637.1	0.000, 0.007	0.809	0.3683
GTAG	G	T	A	G	0.005	0.0 : 122.0, 7.4 : 1640.6	0.000, 0.005	0.541	0.4622

0,1a vs 1b-4c									
ACAG	A	C	A	G	0.001	0.0 : 122.0, 0.6 : 1647.4	0.000, 0.000	0.005	0.9428
Individuals Age < 65 analyzed as NG									

Diplotype Group Associations. Among Bridlington late AMD cases, the largest diplotypes are G1 and G2, which carry at least one risk allele at rs1061170 without risk from Chr10 or protection from rs800292 or the *CFHR3/1* deletion. G1 and G2 combine for nearly one-third of the late AMD cases. The same Chr1 combinations with one risk allele at rs10490924 on Chr10, G11 and G12, or two risk alleles at rs10490924, G21 and G22, make up another 18% and 11.5% of late AMD cases, respectively. Less than 15% of late AMD cases have genetic risk originating solely from rs10490924. Diplotypes with Chr10 risk (G24, G25, G26) combined with Chr1 protection resulted in significant risk reduction for late AMD. Table 4 provides a summary of number and percentage of each genotype groups within controls, early AMD and late AMD.

Table 4
Genetic Group breakdown

Genetic Group	Chromosome 1	Chromosome 10	Controls (0,1a)	As % of Controls	Early AMD (1b-3)	As % of Early AMD	Late AMD (4a-4c)	As % of Late AMD
G1	Risk/Risk	No Risk	88	8.6%	10	7.5%	12	19.7%
G2	Risk/Neut	No Risk	108	10.6%	19	14.2%	8	13.1%
G3	Risk/I62	No Risk	112	11.0%	6	4.5%	5	8.2%
G4	Risk/3,1 del	No Risk	96	9.4%	6	4.5%	2	3.3%
G5	Neut/Neut	No Risk	31	3.0%	4	3.0%	0	0.0%
G6	Neut/I62	No Risk	53	5.2%	3	2.2%	2	3.3%
G7	Neut/3,1 del	No Risk	57	5.6%	4	3.0%	0	0.0%
G8	I62/I62	No Risk	39	3.8%	1	0.7%	0	0.0%
G9	I62/3,1 del	No Risk	55	5.4%	6	4.5%	0	0.0%
G10	3,1 del/3,1 del	No Risk	30	2.9%	3	2.2%	0	0.0%
G11	Risk/Risk	Het Risk	37	3.6%	9	6.7%	4	6.6%
G12	Risk/Neut	Het Risk	46	4.5%	14	10.4%	7	11.5%
G13	Risk/I62	Het Risk	57	5.6%	10	7.5%	1	1.6%
G14	Risk/3,1 del	Het Risk	54	5.3%	7	5.2%	2	3.3%
G15	Neut/Neut	Het Risk	20	2.0%	3	2.2%	1	1.6%
G16	Neut/I62	Het Risk	24	2.3%	5	3.7%	0	0.0%
G17	Neut/3,1 del	Het Risk	17	1.7%	5	3.7%	1	1.6%
G18	I62/I62	Het Risk	19	1.9%	2	1.5%	3	4.9%
G19	I62/3,1 del	Het Risk	33	3.2%	5	3.7%	0	0.0%
G20	3,1 del/3,1 del	Het Risk	12	1.2%	3	2.2%	0	0.0%
G21	Risk/Risk	Homo Risk	3	0.3%	2	1.5%	2	3.3%
G22	Risk/Neut	Homo Risk	3	0.3%	3	2.2%	5	8.2%
G23	Risk/I62	Homo Risk	9	0.9%	1	0.7%	2	3.3%
G24	Risk/3,1 del	Homo Risk	6	0.6%	1	0.7%	0	0.0%
G25	Neut/Neut	Homo Risk	3	0.3%	2	1.5%	1	1.6%
G26	Neut/I62	Homo Risk	4	0.4%	0	0.0%	1	1.6%
G27	Neut/3,1 del	Homo Risk	1	0.1%	0	0.0%	1	1.6%
G28	I62/I62	Homo Risk	2	0.2%	0	0.0%	0	0.0%
G29	I62/3,1 del	Homo Risk	2	0.2%	0	0.0%	0	0.0%
G30	3,1 del/3,1 del	Homo Risk	1	0.1%	0	0.0%	1	1.6%

OCT Analyses of AMD Grade and Genotype correlations

The raw values of retinal and choroidal measures for the different AMD grades are shown in Table 6. The corresponding values for AMD genetic risk are also presented in Table 5. Both retinal and choroidal thinning were progressive and significant across AMD grades, but this was less apparent, or not significant, for genetic risk, particularly for the choroid. There is considerably more thickness variability for late than for no/intermediate AMD, as expected, particularly for retinal thickness (Table 5, and Fig. 1).

Table 5

Raw values of retinal and choroidal measures across subgroups with different AMD grade and genetic risk score. P-values for overall differences among covariate subgroups, as derived from linear regression models with clustering on individuals, are shown at the bottom of each subgroup values.

AMD grade	Retina			Choroid		
	Average thickness (ART)	Central thickness (CRT)	Total volume (RV)	Average thickness (ACT)	Central thickness (CCT)	Total volume (CV)
None	267.1 (0.5)	203.6 (0.83)	7.55 (0.01)	191.1 (2.0)	215.1 (3.1)	5.40 (0.06)
Intermediate	266.6 (1.2)	204.2 (2.25)	7.50 (0.3)	174.1 (4.9)	197.9 (5.8)	4.92 (0.14)
Late	252.3 (3.6)	176.1 (7.28)	7.13 (0.10)	170.4 (9.4)	177.6 (11)	4.82 (0.27)
Genetic risk	p < 0.001	p < 0.001	p < 0.001	p = 0.001	P < 0.001	P = 0.001
Low	266.6 (0.6)	202.9 (1.1)	7.54 (0.02)	190.4 (2.6)	215.1 (3.1)	5.40 (0.07)
Medium	265.8 (1.0)	198.3 (2.1)	7.51 (0.03)	183.5 (4.5)	207.1 (5.0)	5.19 (0.13)
High	265.7 (1.6)	204.9 (2.8)	7.50 (0.04)	185.4 (6.0)	206.3 (7.0)	5.23 (0.17)
	p = 0.740	p = 0.004	p = 0.057	p = 0.363	p = 0.269	p = 0.358

When assessing correlation between OCT measures, the average retinal thickness (ART) was perfectly correlated with retinal volume (RV) (Pearson rho = 1.00) but weakly correlated with central field retinal thickness (CRT) (rho = 0.39) and moderately with centre point thickness (0.59). Given their relative independence, both ART and CRT were used in analyses. The average choroidal thickness (ACT) was perfectly correlated with choroidal volume (CV) (Pearson rho = 1.00) and highly correlated with centre field choroidal thickness (CCT) (rho = 0.92) and centre point choroidal thickness (0.94), thus ACT was used in analyses as the only variable.

Univariate and multivariate associations of OCT parameters with different variables are included in Supplementary Table 3 (Table S3). Retinal and choroidal thinning were progressive and significant across AMD grades, without significant genetic risk association. In univariate regression analysis, age showed a borderline association with retinal thinning, as was intermediate AMD. Retinal (ART) thinning became highly significant for late AMD (both vs. 'No AMD'). No systemic factor was associated with ART, apart from current smoking, which was associated with slightly thinner retina (vs. non-smokers). Late AMD was also associated with CRT thinning. There was no definite association of age with central choroidal thickness, whereas male sex was associated with minimal choroidal thickening in multivariable models. Multivariate models substantially confirmed these univariate associations, when age, sex, AMD grade and genetic risk were simultaneously tested. The direction of the effect was towards retinal and choroidal thinning with moderate and high genetic risk (vs Low); however, the differences were borderline or not statistically significant (Table S3).

OCT measurements of retinal and choroidal thickness in ETDRS sectors

At graphical inspection, retinal thickness was lower in the outer vs. the inner ETDRS circles, with a similar profile according to AMD grades. This was confirmed in SEM models, which found a difference between inner and outer circle by -40, -37, and -16 micron for AMD grades: none, intermediate and late, respectively ($p < 0.001$), with a significant interaction between circle differences and AMD grade (Fig. 1). Retinal thickness was similar across AMD grades and different sectors ($p > 0.500$ for the interaction between AMD grade and each sector vs temporal or thinner sector) (Fig S2a and b).

Choroidal thickness was also slightly lower in the outer vs. the inner circle, with a similar profile according AMD grades (Fig. 1). This was also confirmed in SEM models, which found a difference by -21, -19, and -13 microns in the outer vs. inner circle (p -value respectively < 0.001 , < 0.001 and $= 0.063$), but no interaction with AMD grades: None, Intermediate, Late. Although choroidal thickness was lower in the nasal vs. temporal sectors, no significant interaction between AMD grade and sector was recorded (p -values between 0.260 and 0.997) (see Fig S3a-c).

Discussion

The occurrence of AMD in the BEAP-AMD study is not different from that previously reported from the same population.⁵ An increase in the prevalence of AMD was anticipated on account of the changing demographics (increasing ageing of the population). This absence of an increase in AMD prevalence in the population may be due to the lower inclusion age of 55 years compared to 65 years in the original BEAP study. Interestingly, the proportion of grade 4c CNV of 8.5% in this study is comparable to that of 7.0% previously reported from our BEAP AMD study.⁵⁹ The attendance of previous participants in the original BEAP Study was significantly less than anticipated. A potential explanation for this phenomenon could be that the advanced age prevented the older participants from attending. It is also possible that a significant number of the original participants had passed away. Post-hoc power estimations showed that the number of participants recruited was enough to provide the answer the original research questions.

Nevertheless, this study has provided significant information on the distribution of AMD risk genes in a large UK population study. The SNP distribution and association with different AMD grades are similar to that previously reported in European AMD population studies.^{23,60} The frequencies of key AMD-associated variants in Bridlington controls are similar to those of other Caucasian cohorts, suggesting that the Bridlington Study population is genetically consistent with these other cohorts. Compared to advanced AMD cases from the largest AMD GWAS study⁶¹, as well as cohorts from Iowa, Utah²³ (Pappas et al, 2021) and Melbourne²³, the Bridlington AMD cases exhibit a similar frequency of effect alleles at all key AMD loci tested, except for risk at rs10490924, where Bridlington samples showed a modest decreased frequency. This difference in allele frequency is likely due to the low number of AMD cases in the Bridlington set. This is despite the *ARMS2/HTRA1* risk variant showing the highest penetrance for AMD.

This study confirms that haplotype combinations (diplotypes) that include the presence of Chr1 protective haplotypes decreased risk of late AMD in individuals with Chr10 risk allele, as previously reported by Pappas et al (2021).²³ Among Bridlington late AMD cases, the largest diplotypes are G1 and G2, which carry at least one risk allele at rs1061170 without risk from Chr10 or protection from rs800292 or the *CFHR3/1* deletion. Haplotype structure in the Bridlington control set is closely similar to that of the EUR cohort. The four most common haplotypes make up 97.2% of all control haplotypes (versus 95.6% in the EUR cohort).

Progressive retinal and choroidal thinning was observed with progression of AMD grades. However, this phenomenon was less apparent (or not significant) for genetic risk, particularly for the choroidal thickness. It is known that macular thickness increases with age in persons up to 60 years, when it starts decreasing.⁶² This phenomenon may confound studies with small sample sizes. A significant association of smoking with retinal and choroidal thinning is reported in this study. Although smoking is a well described risk for AMD, previous reports have suggested no association of smoking with retinal or choroidal thickness⁶³, as summarised in the review by Yang et al (2019).⁶⁴ Subsequently, studies from Africa⁶⁵ and the USA⁶⁶ have, however, reported decreased choroidal thickness with smoking in particular populations. No such association was found in European studies to date. Yang et al (2019)⁶⁴, however, suggested that the RNFL and GCL thickness may be affected by

smoking. The Zouache study (2020)⁴² clearly showed that eyes with Chr10 risk with early and intermediate AMD had thinner retina compared to those with Chr1 risk. Smoking did not have any detectable effect on retinal thickness in that study (Zouache et al, 2020).⁴² Our finding of thinned retina in smokers is therefore interesting. The slight choroid thinning noted in the inner and outer ETDRS sectors in this study is consistent with that described in normal eyes by Manjunath et al (2010)⁴⁵, Shin et al (2012),^{53,54} Gehl et al (2014)⁶⁷, and Ruiz-Medrano et al (2014)⁶⁸. This finding was statistically significant, and seems to correspond to the retinal thickness changes from central to outer sectors. No statistically significant interaction between AMD grade and choroidal thickness in the different sectors was observed. Shin et al (2012)^{53,54} described age changes of choroidal thickness in normal eyes, and reported that the nasal outer macula choroid was thinner than any other ETDRS sector. Gupta et al (2015)⁶⁹ using an automated software showed that automated choroidal segmentation software provided reliable and objective measurements of the choroid in population-based studies, and that choroidal thickness was highest under the fovea followed by the temporal, and thinnest on the nasal macula. On the contrary, Cai et al (2022)⁷⁰ reported from a Chinese population that the inner superior ETDRS sector choroid was thickest followed by the foveal centre. Lu et al (2016)⁷¹, in their retrospective cross-sectional study in Shanghai reported that (in AMD) the subfoveal choroidal thickness was greater in early AMD compared to intermediate AMD. Ryoo et al (2018)⁷² reported thinned subfoveal choroidal thickness in association with *CHF* rs1061170.

Multivariate models substantially confirmed these univariate associations, when age, sex, AMD grade and genetic risk were simultaneously tested. Although the direction of the effect was towards retinal and choroidal thinning with moderate and high genetic risk (vs Low), the differences were borderline or not statistically significant.

The strength of this project is that it represents the first population study of AMD that used multimodal imaging technology and complements our earlier BEAP study.⁵ It provides information on retinal and choroidal thicknesses in the population. In addition, it is the first to provide significant information on the distribution of AMD risk genes in a large UK population study rather than hospitals cohorts.

Limitations

A larger number of participants was planned for and expected in this study. However, the Covid-19 pandemic led to significant disruption of the research programme. Nevertheless, our post-hoc power estimates confirmed that the number of participants recruited were adequate to fulfil the study objectives. We did not segment the individual retinal layers on OCT in this report. As such, we are unable to comment on any changes in the different retinal layers with AMD grade and or genetic associations.

Conclusions: The prevalence of AMD in this study is consistent with our previous report (Wilde et al, 2017). The haplotype structure in the Bridlington control set is closely similar to that reported in other EU cohorts, and the diplotype distribution in the late AMD cases is consistent with the Utah data, with G1 and G2 occurring in nearly one-third of late AMD cases. The AMD genetic risk distribution is similar to that reported from other Caucasian populations. Retinal and choroidal thinning are associated with increasing AMD severity.

SUMMARY

What was known before

- AMD is the commonest cause of irreversible vision loss in the western world.
- Prevalence of late AMD in the UK is 4.6% in persons aged ≥ 65 years (2.5% for GA, 1.8% for neovascular AMD (nAMD), and in 0.3% for peripapillary CNV) (Wilde et al, 2017).
- Genetic associations of AMD are described. However, there is limited data on UK population prevalence of genetic risk and retinal and choroidal thickness in age-related macular degeneration (AMD).

What this study adds

- AMD prevalence is similar to that reported in our earlier report (Wilde et al, 2017).
- AMD genetic risk in this UK cohort parallels other Caucasian populations. The Bridlington control set haplotype structure is closely similar to that in other EU cohorts.
- The commonest Bridlington haplotype: C allele at rs1061170, was associated with increased AMD risk. Protective haplotypes at rs800292 or rs12144939 had reduced AMD risk. Risk originating solely from rs10490924 occurred in < 15% of late AMD cases.
- Diplotypes G1 and G2 (with > 1 risk allele at rs1061170 without risk from Chr10, protection from rs800292 or CFHR3/1 deletion), occurred in one-third of late AMD cases. Diplotype distribution with G1 and G2 commonest in late AMD cases is consistent with the Utah data.
- Retinal and choroidal thinning were significantly progressive across AMD grades but not genetic risk.
- Smoking was associated with retinal thinning.

Declarations

BEAP Population Study Group members

Amie Manjang, Nottingham

Deanna Gardner, Nottingham

Helen Jacques, Nottingham

Susan Williams, Nottingham

Susan Paley-Kemp, Nottingham

Rosemarie Frier, Nottingham

Natalia Wojtowicz, Nottingham

Jaiamee Jeeavo, Nottingham

Mary McKeating, Nottingham

Tracy Williams, Nottingham

Natalia Chinyerere, Nottingham

Rachel Punshon, Nottingham

Kate Howard, York

Tania Neale, York

Sally Gilroy, York

Luminata Ioana Dutia, Nottingham

Louise Bell, York & Hull

Laura Barman, York

Jennifer Baker, York

Janine Mallinson, Scarborough

Rachel Harrison, York

Hannah Sharratt, Nottingham

Emily Hogan, Nottingham

Ben Taylor-Day, Nottingham

Flor Davies, York

Dana Groom, Scarborough

Caroline Duncan, York

Claire Brookes, York

Alison, Turnbull, Scarborough

Mandy Barret, Nottingham

Laura Pigula, Topcon

Danielle Lee, Topcon

Stephen Connell, Sheffield

Rachel Scholes, Topcon

Samantha Mejor, Topcon

Beverly Proctor, York

Lou Bell, York

Lydia Harris, Head R&D, York

Kate Howard, York

Hilary Campbell, York

Alison Frice-Holt, York

Laura Burgess, York

Carol Sarginson, York

Simon Dyer, Bridlington

Kelly Hird, York

Richard Pilbery, York

Jane Sherwan, Wakefield

Mark Aldous, York

Stacie Matthews, Utah, US

Mark Kunz, Bridlington

Barbara Birkin, Bridlington

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Ethics statement: This research was approved by the UK NHS Health Research Authority East Midlands-Nottingham 2 Research Ethics Committee (REC) (ref 17/EM/0085; IRAS Project ID: 215114).

The BEAP AMD Study Research Team members included Winfried Amoaku (Nottingham) CI, Gregory Hageman (Utah) Co-CI, Giuliana Silvestri (Belfast), Richard Gale (York), Sushma Dhar-Munshi (King's Mill Centre), Vittorio Silvestri (Belfast). The initial study statistician was Rajnikant Mehta (ex-Nottingham), and subsequently replaced by Gianni Virgli (Belfast and Florence).

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Figures

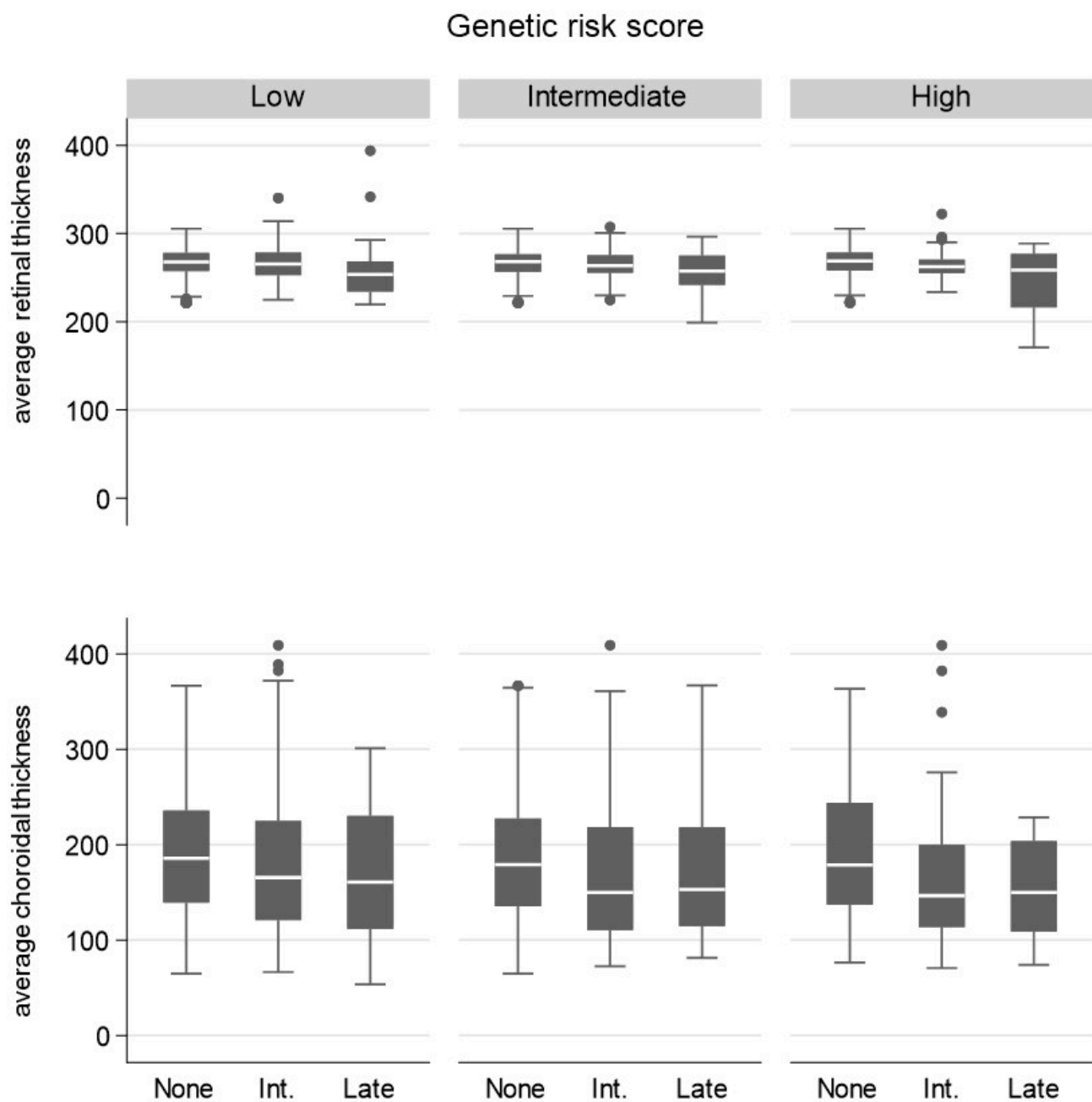


Figure 1

Average retinal (top) and choroidal (bottom) thickness by genetic risk score and AMD grade (none, intermediate, late).

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