

Genetic analysis of age-related macular degeneration highlights precision therapy opportunities for patients with high polygenic risk

Jonathan S. Packer

Foresite Labs

Alice Zheng

Massachusetts General Hospital

Travis Mize

Icahn School of Medicine at Mount Sinai

Kathleen D. Ferar

Icahn School of Medicine at Mount Sinai

Lisa Bedford

Foresite Labs

Eimear E. Kenny

Icahn School of Medicine at Mount Sinai

Krishna G. Aragam

Massachusetts General Hospital

Mary Helen Black

mhblack@foresitelabs.com

Foresite Labs

Article

Keywords:

Posted Date: March 19th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-8863554/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: Competing interest reported. JSP, LB, and MHB were employees of Foresite Labs during the data collection, analysis, and writing of the manuscript. KGA reported research funding

from Sarepta Therapeutics and Bayer AG during the conduct of the study.

Abstract

Importance: In the past two decades, genetic studies have elucidated the contributions of key biological pathways to the pathogenesis of age-related macular degeneration (AMD), including the predominant role of complement. Yet, clinical treatment of AMD with complement inhibitors has met with limited success.

Objectives: To examine whether genetic heterogeneity in complement pathway activity, as represented by a polygenic risk score (PRS), may account for genetically predicted differential response to therapy with complement inhibitors in AMD. We additionally explored this effect on quantitative biomarkers of disease derived from optical coherence tomography (OCT).

Subjects: Participants were ascertained from four large-scale cohorts (UK Biobank, eMERGE, International Age-related Macular Degeneration Genomics Consortium (IAMDGC), Mass General Brigham Biobank) spanning 30,251 AMD cases and 438,016 AMD controls.

Methods: Using the available genomic data, we identified functional variants in *C3* and *CFB* to serve as proxies for complement inhibitor drug effects, generated a pharmacomimetic score for each drug target, and tested each score for interaction with genome-wide and complement pathway-specific AMD polygenic risk scores (PRS). In each cohort, subjects were divided into low, medium, and high AMD risk groups based on quantiles of the PRS, such that each risk group included one-third of the cohort's AMD cases. Drug target variant associations with AMD were evaluated in each risk group, as well as in all-comers. Quantitative biomarker analysis leveraging retinal phenotypes derived from optical coherence tomography (OCT) data was also performed.

Main Outcome Measures: AMD case status and OCT-derived measures of retinal thickness

Results: Among AMD cases, mean age at diagnosis ranged 76-80 years and 40-48% were male across the four cohorts. Functional genetic variants serving as proxies for C3 and CFB inhibition had an effect on AMD risk that was 1.6 to 2.3 times higher in the high complement pathway-specific PRS group compared to all-comers. Interactions between pharmacomimetic scores and the PRS were statistically significant, with replication across cohorts. Statistical support was strongest in three cohorts for C3 and across all four cohorts for CFB. Examining retinal thickness phenotypes (eg. ISOS-RPE), genetic drug proxy by PRS interaction was nominally significant for CFB, and directionally consistent for C3. Our results point to a continuous relationship between genetic complement activation/inhibition and AMD risk, across disease stages, without threshold effects.

Conclusions: Our findings suggest that patient heterogeneity due to genetically-influenced complement activation may explain the limited efficacy of AMD treatment with complement inhibitors to date. Prospective studies are warranted to assess whether precision therapy with complement inhibitors may be achieved by enrichment of patients with high PRS in future trials.

Introduction

The first genome-wide association study (GWAS) published in 2005 identified a complement factor H (*CFH*) missense variant association with risk of age-related macular degeneration (AMD).¹ Subsequent GWAS confirmed that variants contributing to dysregulation of the complement system — specifically, the alternative complement pathway — dominate AMD's genetic architecture.^{2,3} These genes include complement components (*C3*, *C5*, *C9*); complement factors (*CFB*, *CFD*, *CFH*, *CFHR1*, *CFI*); *CD46*, a cofactor of *CFI* and negative regulator of complement activation^{4–6}; vitronectin (*VTN*), an extracellular matrix component that inhibits formation of the membrane attack complex^{7,8}; and *HTRA1*, a protease that cleaves vitronectin and fibromodulin and triggers inflammation.^{9–11} Later GWAS also highlighted non-complement loci, including *e.g.* genes involved in cholesterol and lipoprotein metabolism (*APOE*, *LIPC*, *CETP*), extracellular matrix maintenance (*TIMP3*), and angiogenesis (*VEGFA*).¹²

Wet AMD, or choroidal neovascularization (CNV), is characterized by abnormal blood vessels penetrating the barrier between the choroid and retina, leading to fluid leakage, cell damage, and vision loss. Advanced dry AMD, or geographic atrophy (GA), features retinal pigment epithelium (RPE) and photoreceptor cell death in the absence of neovascularization. Earlier stages of dry AMD can progress to either CNV or GA. “Early”/“intermediate” AMD is typically defined by the size and abundance of drusen — deposits filled with proteins, lipids, and cellular debris that form under the retina — and other retinal characteristics. Per-variant GWAS effect sizes for CNV, GA, intermediate AMD, and early AMD are highly correlated.^{2,13}

While wet AMD is effectively treated with vascular endothelial growth factor antagonists, GA is treated with complement inhibitors, which are only modestly effective at slowing disease progression. Pegcetacoplan, an intravitreally-delivered peptide C3 inhibitor, and avacincaptad pegol, and intravitreal RNA aptamer C5 inhibitor, slow GA progression by ~20% over 1-2 years of follow-up.^{14–16} They were approved for GA in 2023 after previous failures in the indication, *e.g.* eculizumab, an intravenous C5 antibody, and lampalizumab, an intravitreal CFD antibody. Additional clinical trials of complement inhibitors are ongoing, *e.g.* iptacopan, an oral small molecule CFB inhibitor (NCT05230537); vonaprumant, an intravitreal C1q antibody fragment (NCT06510816); and pozelimab + cemdisiran, a combination of subcutaneous C5 antibody and subcutaneous liver-targeted C5 siRNA (NCT06541704).

Given the overwhelming genetic evidence for the centrality of the complement system in AMD pathogenesis, the underwhelming performance of complement inhibitors in GA is perplexing. It is possible that partial complement inhibition is insufficient to halt GA, although variants in/near complement genes have relatively large effects, even in a heterozygous state. It is also possible that earlier intervention is necessary for complement inhibitors to be effective in preventing disease progression. However, variants in complement pathway genes are associated with disease risk at every stage and their effect sizes across GA and CNV subtypes are remarkably correlated^{2,13}. Moreover, for any given variant, studies report greater effect size in advanced vs. intermediate AMD. Thus, these

variants affect both risk of progression from early to intermediate and intermediate to advanced disease. Consistent with the genetic evidence, terminal complement activation (*i.e.* membrane attack complex formation and deposition) has been observed in the choroid and Bruch's membrane of healthy subjects as young as 5 years, and increases with age and AMD stage.¹⁷ In this setting, complement activation in the retina may help clear cellular debris produced when RPE phagocytoses and lyses photoreceptor outer segments.^{17, 18} Lastly, it is possible that variable response to treatment with complement inhibitors is largely explained by patient heterogeneity. We hypothesize that AMD pathogenesis is a spectrum ranging from disease driven by genetically-influenced complement hyperactivation to disease driven by complement-independent, non-heritable environmental factors. Biomarker data supports this hypothesis; while markers of complement activation are significantly elevated in AMD cases vs. controls, case-control distributions overlap considerably.^{19,20}

We sought to investigate the heterogeneity hypothesis from a genetic perspective, using pharmacomimetic (*i.e.* drug-mimicking) variants in *C3* and *CFB*. Specifically, we tested whether the effect of these variants on AMD risk is modified by background genetic predisposition to complement hyperactivation, as modeled by a complement pathway polygenic risk score (PRS).

Methods

Cohorts

Our study included data from UK Biobank (UKB), Electronic Medical Records and Genomics Network (eMERGE) III, Mass General Brigham Biobank (MGBB), and the International AMD Genetics Consortium (IAMDGC). UKB is a population-based biobank that broadly sampled ~500,000 participants in the United Kingdom. eMERGE and MGBB employed hospital-based ascertainment of participants in the United States. IAMDGC is a case-control cohort in which participants were recruited from ophthalmology clinics across the United States, Europe, Australia, and Israel.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All study participants provided written, informed consent to participate in UKB, eMERGE, MGBB, and IAMDGC through institution-specific protocols. Institutional Review Board (IRB) approval was obtained for secondary analysis of eMERGE (WCG IRB, protocol 20226241) and MGBB (IRB protocol 2023P002617) data for the purposes of this study, in accordance with the terms of participant consent; additional IRB approval was not required for other data used in this study. Further details are provided in the Data Availability section.

Outcomes

In UKB, MGBB, and eMERGE, we defined AMD cases as subjects with ≥ 1 ICD-10 H35.3 ("Degeneration of macula and posterior pole"), ICD-9 362.5, OPCS-4 C82 ("Destruction of lesion of retina") or X93.1 ("Subfoveal choroidal neovascularisation drugs"), and/or who self-reported AMD at enrollment (data field 20002 code 1528). Cases had no instances of ICD-10 H35.5 ("Hereditary retinal dystrophy"), H36.0

("Diabetic retinopathy") or ICD-9 362.0, 362.70-362.73, 362.75, 372.79. Across all cohorts, controls were defined as subjects who were not cases, and did not have any instances of ICD-10 E10.3, E11.3, E12.3, E13.3, E14.3 ("Diabetes with ophthalmic complications"), H35 ("Other retinal disorders"), H36.0 ("Diabetic retinopathy"), H54.0 ("Blindness, binocular"), H54.1 ("Severe visual impairment, binocular"), H54.4 ("Blindness, monocular"), or ICD-9 362.0, 362.5, 362.70-73, 362.75, 362.79, 369.0-1, 369.6. For UKB, controls with any OPCS-4 C79, C80, C81, C82, C83, C84, C85, X93 (ocular procedures and drug administration) procedure code, or self-reported diabetic eye disease, retinitis pigmentosa, or macular degeneration (data field 20002 codes 1276, 1527, 1528; data field 6148 codes 1, 5) were also excluded.

In UKB, we defined CNV cases as subjects with ≥ 1 OPCS-4 C82 or X93.1, and dry AMD cases as those with AMD who were not CNV cases. Analyses compared these cases to the AMD control set described above.

In IAMDGC, subjects were clinically assessed for CNV, GA, and intermediate AMD. Intermediate AMD was defined as the presence of pigmentary changes in the RPE or more than five macular drusen greater than 63 μm , with age at first diagnosis ≥ 50 years, in the absence of CNV or GA.

Quantitative biomarker analysis was conducted in UKB using retinal thickness measurements (category 100079, "Advanced boundary segmentation [TABS]"). Measures were previously derived from optical coherence tomography (OCT) imaging performed in a subset of UKB subjects.^{21,22} Prior to statistical analysis, we excluded subjects who were <60 years at the time of the OCT imaging, computed the average measurements from the left and right eyes, and applied a rank-based inverse normal transformation.

Pharmacomimetic variants

We examined two pharmacomimetic missense variants in *C3*: 1) GRCh38-19-6718376-G-C (rs2230199) = *C3* R102G, which is also in strong linkage disequilibrium with *C3* P314L. 2) GRCh37-19-6718135-T-G (rs147859257) = *C3* K155Q.

C3 K155Q results in resistance to C3 inactivation by *CFI* and *CFH*.²³ While to our knowledge, *C3* R102G has not yet undergone experimental characterization, data from proteomics analyses suggests a consistent association of R102G with reduced C3b and increased C3d levels, suggesting that R102G increases the rate of C3b to C3d conversion.²⁴⁻²⁶ Thus, both variants were considered to increase complement activation.

We examined four pharmacomimetic non-coding variants at the *CFB* locus: 1) GRCh38-6-31962685-G-A (rs429608), 2) GRCh38-6-31979015-G-A (rs2746394), 3) GRCh38-6-32187804-A-G (rs204993), and 4) GRCh38-6-31979250-G-T (rs181705462). These variants have conditionally independent, genome-wide significant associations with AMD.² While conclusive evidence for variant effects on *CFB* expression or function is lacking, GWAS associations of *C3*, *CFH*, and *CFI* with AMD implicate the alternative complement pathway in AMD pathogenesis; outside of the *CFB-C2-C4A-C4B* locus, there are no other

loci that implicate the classical pathway. Second, *CFB* R74H, a rare coding variant, has been reported to have a strong protective effect against AMD.²⁷ While *CFB* R74H is most often linked to *C2* P37L, a rare haplotype with *CFB* 74H (minor allele) but *C2* 37P (major allele) is protective for AMD, indicating that *CFB* 74H has an independent effect. Third, *CFB* R32Q, in modest LD in Europeans with the AMD GWAS variant rs429608, has been reported to reduce C3 to C3b conversion.²⁸ Lastly, a Ph2 clinical trial of iptacopan is underway in AMD (NCT05230537, study registration date 2022-02-09), following success in trials of IgA nephropathy, pointing to AMD as an alternate indication benefitting from CFB inhibition.

Pharmacomimetic scores

We aggregated the effects of the two *C3* variants into a *C3* pharmacomimetic score. This score was defined as the weighted sum of the alternate allele dosages for each variant, where the weights were taken as variant-specific GWAS effect sizes from the Fritsche *et al.* IAMDGC joint model of 52 variants². We aggregated four *CFB* variants into a *CFB* score in similar fashion.

Polygenic risk scores

We used the same weighted-sum method described in the previous section to define a complement pathway-specific AMD polygenic risk score (PRS). This PRS included 18 variants at the following loci: *C3*, *C9*, *CFB*, *CFH*, *CFI*, *VTN*, *HTRA1*.

For comparison, we also defined a genome-wide AMD PRS using 48 out of 52 variants reported by the Fritsche *et al.* IAMDGC study.² We excluded 4 variants: rs3138141, rs121913059, and rs142450006 were not present in the UKB genotype data; rs191281603 was not significant in the IAMDGC joint model.

Due to overlap between individual-level IAMDGC data used for PRS training and a subset of interaction analyses presented, we re-weighted the variants using an inverse variance weighted meta-analysis of: 1) a joint model in UKB of the PRS variants' association with AMD, and 2) GWAS effect sizes for each variant in the FinnGen r9 AMD GWAS.²⁹ The meta-analysis weights were highly correlated with the original IAMDGC weights ($R^2 = 0.87$).

PRS variants and weights included in the present analyses are listed in Table S1.

We also compared PRS to single-gene scores for *CFH* and *HTRA1*. These were constructed using the method described above, with variants annotated as residing in/near the *CFH* or *HTRA1* loci in Fritsche *et al.*²

Statistical analysis of individual-level data

We restricted all analyses to unrelated subjects of genetically-defined European ancestry. Sample sizes for non-European subjects were insufficient (Table S2, *e.g.* <550 cases of African ancestry) for genetic interaction analyses that are the central focus of our study. Interaction tests require larger sample sizes

compared to single-variant association tests. In individuals of African ancestry, AMD GWAS effect sizes at complement gene loci are attenuated, further reducing statistical power.³

We used logistic regression models to assess the association of the pharmacomimetic (PM) scores, the AMD PRS, and the PM scores in interaction with the PRS with risk of AMD. In each model, we included covariates: age, age squared, sex, age*sex, age²*sex, and cohort-specific principal components of genetic ancestry. We defined “age” as “age at right censoring”, *i.e.* a subject’s age on the date of the most recent phenotypic data in their cohort (considering all subjects in the cohort), or the subject’s age at death, whichever came first.

Before fitting any regression model that included an interaction term for a PM score and an AMD PRS, we first adjusted the PRS by linear regression to remove the contribution of the variants in the PM score to the PRS. We confirmed that this *post-hoc* adjustment of the PRS gave identical results to entirely re-constructing the PRS excluding the PM variants.

AMD cases and controls in each cohort were stratified into three bins, corresponding to low, medium, and high AMD risk, based on values of the AMD complement pathway PRS. PRS cut-offs were selected within each cohort such that each bin captured one-third of the AMD cases. In several analyses, we evaluated the ratio of the model coefficient representing a PM score’s effect on AMD risk in subjects in the high PRS bin, to the model coefficient representing that PM score’s effect on AMD risk in the full cohort.

Imaging biomarker analyses were performed using the quantitative retinal thickness measures described above with linear regression models adjusted for the same covariates.

Meta-analysis of AMD GWAS summary statistics

To provide further context on the 18 variants in the AMD complement pathway PRS, we compared the associations of each variant with overall AMD risk in a GWAS meta-analysis to the corresponding associations of each variant in analyses of stage-specific AMD phenotypes.

We used METAL³⁰ to perform an inverse variance weighted meta-analysis of European-ancestry AMD GWAS summary statistics from UKB, FinnGen r11²⁹, MVP³¹, and GERA.³² For UKB, we performed GWAS using REGENIE³³ to test variant association with AMD, as described above, adjusted for the same covariates. For all other studies, published GWAS summary statistics were used without further processing. We assessed variant associations with early AMD using GWAS summary statistics from Winkler *et al.*¹³. We assessed variant associations with intermediate AMD, advanced AMD, and “advanced AMD conditional on intermediate AMD” by applying logistic regression models to individual-level IAMDGC data.

Results

Altogether, our study included 30,251 AMD cases and 438,016 AMD controls (Table 1, Table S3). In each cohort, the *C3* and *CFB* pharmacomimetic scores, the 18-variant AMD complement pathway PRS, and the 48-variant AMD genomewide PRS were predictive of AMD case-control status (Table 2). Complement pathway PRS effect sizes were similar to those of the genomewide PRS.

Cohort	Cohort type	AMD cases	AMD controls	AMD subtypes available for analysis
UK Biobank	Population-based biobank	9,638	331,639	Dry, CNV
IAMDGC	Clinical cohort	14,075	12,054	Intermediate, GA, CNV
eMERGE	Hospital biobanks	4,117	56,328	(none)
MGBB	Hospital biobank	2,421	37,995	(none)

Table 1. Cohorts included in the analysis. “AMD subtypes” column refers to which disease subtypes could be characterized in a given cohort using the available phenotype information. CNV = choroidal neovascularization, GA = geographic atrophy. In the UK Biobank, Dry AMD was defined as any AMD that could not be determined to be CNV.

Genetic instrument	UKB	IAMDGC	eMERGE	MGBB
<i>C3</i> PM score	OR = 1.09 $p = 1.8 \times 10^{-18}$	OR = 1.26 $p = 2.9 \times 10^{-62}$	OR = 1.07 $p = 2.8 \times 10^{-4}$	OR = 1.05 $p = 3.4 \times 10^{-2}$
<i>CFB</i> PM score	OR = 1.08 $p = 1.3 \times 10^{-11}$	OR = 1.29 $p = 9.1 \times 10^{-82}$	OR = 1.11 $p = 7.6 \times 10^{-8}$	OR = 1.10 $p = 5.0 \times 10^{-5}$
AMD complement PRS	OR = 1.39 $p = 7.1 \times 10^{-226}$	OR = 2.43 $p < 10^{-300}$	OR = 1.39 $p = 6.3 \times 10^{-66}$	OR = 1.32 $p = 2.9 \times 10^{-38}$
AMD genomewide PRS	OR = 1.41 $p = 4.4 \times 10^{-236}$	OR = 2.58 $p < 10^{-300}$	OR = 1.41 $p = 1.6 \times 10^{-73}$	OR = 1.33 $p = 2.8 \times 10^{-39}$

Table 2. Associations of the genetic instruments used in the analysis with AMD case-control status, in each cohort. PM = pharmacomimetic. PRS = polygenic risk score. OR = adjusted odds ratio. IAMDGC associations are based on AMD definition under clinical diagnostic criteria, while associations in other datasets were based on AMD identified from ICD-9/10 codes.

In individuals with high complement pathway PRS, *C3* and *CFB* scores were substantially more predictive of AMD case-control status than in those with medium or low PRS (Fig 1A). This pattern was consistent across each cohort evaluated (*C3* score x PRS model $p_{\text{interaction}} = 2.9 \times 10^{-12}$ in UKB, 1.5×10^{-5} in IAMDGC,

1.5×10^{-5} in eMERGE, 0.17 in MGBB; *CFB* score x PRS model $p_{\text{interaction}} = 8.3 \times 10^{-7}, 3.7 \times 10^{-8}, 0.036, 0.009$). The ratio of the *C3* and *CFB* score effects in the high PRS group vs. all-comers was also similar across cohorts, ranging from 1.6 to 2.3 (ratios for *C3* score: 1.84 in UKB, 1.56 in IAMDG, 2.31 in eMERGE, 1.82 in MGBB; ratios for *CFB* score: 1.92, 1.57, 1.83, 1.86). The pattern of PRS stratification of *C3* and *CFB* score effects was similar when dry AMD was modeled as the disease outcome instead of overall AMD, in cohorts for which dry and wet subtypes were discernible (Fig 1B).

Two loci, *CFH* and *HTRA1*, account for a disproportionately large share of the variance in AMD liability that is explained by common genetic variants.² We evaluated digenic models, in which the pharmacomimetic scores for *C3* and *CFB* were tested for interaction with single-gene risk scores for *CFH* and *HTRA1*, and compared them to our previous polygenic model (Table S4). There was strong evidence for a digenic *CFB-CFH* interaction ($p < 0.05$ in all 4 cohorts) and *C3-CFH* interaction ($p < 0.05$ in 3 cohorts). The ratio of the *CFB-CFH* interaction effect size to the *CFB*-PRS interaction effect size was 70% in UKB, 82% in IAMDG, and >100% in eMERGE and MGBB. For *C3*, the corresponding statistics were 70%, 67%, 80%, and 19%. Taken together, our findings suggest complement pathway-based PRS is a more effective stratifier of *C3*- and *CFB*-specific effects, and therefore response to treatment with complement inhibition.

C3 and *CFB* score interactions with AMD complement pathway PRS were recapitulated in retina OCT data from ~45,000 UKB subjects. We tested each OCT-derived measure for association with dry AMD case-control status (Table S5). ISOS-RPE thickness in the central subfield, *i.e.* the thickness of the retina as measured from the junction of the inner and outer photoreceptor segments to the RPE, yielded the strongest association. Reduced central subfield ISOS-RPE thickness was correlated with increased risk of dry AMD (Fig 2A). Correspondingly, the AMD risk-increasing *C3* and *CFB* scores correlated with reduced ISOS-RPE thickness, and the magnitude of this correlation was amplified in subjects with high PRS (Fig 2B).

Our results are consistent with the hypothesis that there is substantial heterogeneity across AMD patients represented by the extent to which the complement pathway is driving disease progression. We represent this heterogeneity by low, medium, and high PRS (*cf.* Fig 1, Fig 2), but we note that the relationship between the complement pathway PRS and log odds of AMD is approximately linear and continuous (Fig 3A). This indicates that 1) the distribution of common genetic variants results in a continuous spectrum in which individuals can have a low, medium, or high level of predisposition to complement hyperactivation; 2) an individual's location on this spectrum is physiologically relevant to AMD; and 3) there is no genetic evidence for the existence of a critical complement inhibition threshold, within this physiologically-relevant range. Lastly, the observed effects of genetic variants on risk of AMD are highly correlated with those at particular disease stages, *i.e.* early, intermediate, or advanced AMD, and with their effects on the likelihood of a patient having advanced AMD conditional on that patient having intermediate AMD (Fig 3B). This suggests that the contribution of genetically-regulated complement dysregulation to AMD is continuous throughout the disease course.

Discussion

Given the underwhelming success of complement inhibition in the treatment of AMD despite the strength of genetic evidence for the role of complement activation in disease pathogenesis, we hypothesized genetic heterogeneity to account for this disparity and conducted analyses of four large-scale human cohorts spanning nearly 470,000 individuals to test this hypothesis. Our findings indicate that polygenic predisposition to complement hyperactivation in AMD, represented by a novel complement pathway-specific PRS, modifies the magnitude of genetically inferred C3/CFB effects on AMD risk, supporting the hypothesis that complement inhibition may yield larger benefit in genetically high-risk individuals.

Considering the modest performance of complement inhibitors in GA patients to date, the large number of poorly differentiated complement inhibitors currently in preclinical and clinical stages of development, and the persistently high unmet clinical need in this stage of AMD, these findings warrant further clinical investigation. Yet to our knowledge, only one emerging biopharma company (Character Bio, Series B announced March 2025)³⁴ has publicly disclosed plans to develop a proprietary complement pathway PRS for use in phase 2 trials of CTX114, a novel complement inhibitor designed to delay or prevent retinal cell death and vision loss in patients with GA.³⁵

Past clinical trials of complement inhibitors in GA have used change in square-root transformed lesion area as a primary endpoint, quantified by fundus autofluorescence (FAF). This endpoint is challenging, and affected by parameters that can be difficult to model, such as pre-treatment lesion size and growth rate. Accordingly, OCT-derived measures have been investigated as potential endpoints.³⁶ Our analysis of UKB data demonstrates that genetic validation of AMD drug targets and patient stratification approaches can be recapitulated in OCT data, further supporting arguments for using OCT in clinical development, especially for high-risk intermediate AMD.

Early-stage research into approaches for patient stratification has greatly outpaced clinical implementation, particularly for indications outside of oncology. We note one example of an FDA-approved therapy with a precision approach: the use of eosinophil count as a patient stratifier in the development of dupilumab, an IL4R antibody used to suppress Th2-driven/eosinophil-mediated inflammation. In the United States, dupilumab is approved for asthma and chronic obstructive pulmonary disease characterized by high eosinophils (eg. ≥ 300 cells/ μ L). We propose that the mechanistic link between eosinophil activity and dupilumab efficacy is analogous to that between our proposed stratifier (a PRS representing complement pathway activity) and the therapies to which it would be relevant (complement inhibitors).

A limitation of our study was that we were precluded from assessing statistical genetic interactions in individuals of non-European ancestry, as we had insufficient individual-level data available (e.g. <550 African ancestry AMD cases). Further investigation in diverse cohorts such as Million Veteran's Program (MVP) and AllOfUs is warranted, particularly given the attenuation of complement variant associations

with AMD in individuals with local African ancestry at complement gene loci.³ We also acknowledge that our analyses and insights are based on genetic proxies for drug effects, rather than treated trial participants. As such, they do not directly estimate drug efficacy and should be interpreted as hypothesis-generating for PRS-guided trial design.

In conclusion, our findings suggest that patient heterogeneity with respect to genetically- influenced complement activation may explain the limited efficacy of complement inhibitors in the treatment of AMD. Specifically, we observed substantially stronger genetic effects corresponding to complement inhibition among individuals with high complement pathway PRS, and this was true regardless of AMD subtype or disease stage. Prospective studies are needed to assess whether precision therapy targeting patients most likely to benefit from complement inhibitor treatment may be achieved by enrichment of high PRS patients in future clinical trials.

Declarations

Competing Interests

JSP, LB, and MHB were employees of Foresite Labs during the data collection, analysis, and writing of the manuscript. KGA reported research funding from Sarepta Therapeutics and Bayer AG during the conduct of the study.

Research Funding

Eimear E. Kenny and Krishna G. Aragam received funding from Foresite Labs.

Author Contribution

JSP and MHB wrote the manuscript text. JSP, AZ, TM, and KDF collected data and performed analyses. JSP generated all tables and figures. LB, EEK, KGA, and MHB reviewed drafts of the manuscript and edited the text. All authors participated in the discussion of data and analytical results and reviewed the manuscript.

Data Availability

Foresite Labs analysis of UK Biobank data was conducted under approved application #44424. Access to these data can be requested from UK Biobank (<https://ams.ukbiobank.ac.uk/ams/>). eMERGE and IAMDGc data can be accessed via the dbGaP repository (<https://dbgap.ncbi.nlm.nih.gov/home/>). Foresite Labs analysis of eMERGE data (phs001584.v2.p2) was conducted under approved dbGaP project #33440, with review and ethical approval for this work from WIRB-Copernicus Group Institutional

Review Board (WCG IRB, protocol 20226241). Foresite Labs analysis of IAMDGC data (phs001039.v1.p1) was conducted under approved dbGaP project #32415. The Mass General Brigham Institutional Review Board approved the use of Mass General Brigham Biobank data for research (IRB protocol 2023P002617). All MGB Biobank participants provided written informed consent for Biobank participation and genetic research. Analyses were conducted on de-identified data in accordance with applicable institutional and regulatory requirements. Analysis of summary statistics from other cohorts described in this manuscript were publicly available.

References

1. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. *Science*. 2005;308(5720):385–389.
2. Fritsche LG, Igl W, Bailey JNC, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat Genet*. 2016;48(2):134–143.
3. Gorman BR, Voloudakis G, Igo RP Jr, et al. Genome-wide association analyses identify distinct genetic architectures for age-related macular degeneration across ancestries. *Nat Genet*. 2024;56(12):2659–2671.
4. Oglesby TJ, Allen CJ, Liszewski MK, White DJ, Atkinson JP. Membrane cofactor protein (CD46) protects cells from complement-mediated attack by an intrinsic mechanism. *J Exp Med*. 1992;175(6):1547–1551.
5. Kojima A, Iwata K, Seya T, et al. Membrane cofactor protein (CD46) protects cells predominantly from alternative complement pathway-mediated C3-fragment deposition and cytolysis. *J Immunol*. 1993;151(3):1519–1527.
6. Barilla-LaBarca ML, Liszewski MK, Lambris JD, Hourcade D, Atkinson JP. Role of membrane cofactor protein (CD46) in regulation of C4b and C3b deposited on cells. *J Immunol*. 2002;168(12):6298–6304.
7. Milis L, Morris CA, Sheehan MC, Charlesworth JA, Pussell BA. Vitronectin-mediated inhibition of complement: evidence for different binding sites for C5b-7 and C9. *Clin Exp Immunol*. 1993;92(1):114–119.
8. Sheehan M, Morris CA, Pussell BA, Charlesworth JA. Complement inhibition by human vitronectin involves non-heparin binding domains. *Clin Exp Immunol*. 1995;101(1):136–141.
9. An E, Sen S, Park SK, Gordish-Dressman H, Hathout Y. Identification of novel substrates for the serine protease HTRA1 in the human RPE secretome. *Invest Ophthalmol Vis Sci*. 2010;51(7):3379–3386.
10. Papp A, Papp K, Uzonyi B, et al. Complement factor H-related proteins FHR1 and FHR5 interact with extracellular matrix ligands, reduce factor H regulatory activity and enhance complement activation. *Front Immunol*. 2022;13:845953.

11. Kumar S, Nakashizuka H, Jones A, et al. Proteolytic degradation and inflammation play critical roles in polypoidal choroidal vasculopathy. *Am J Pathol*. 2017;187(12):2841–2857.
12. Black JRM, Clark SJ. Age-related macular degeneration: genome-wide association studies to translation. *Genet Med*. 2016;18(4):283–289.
13. Winkler TW, Grassmann F, Brandl C, et al. Genome-wide association meta-analysis for early age-related macular degeneration highlights novel loci and insights for advanced disease. *BMC Med Genomics*. 2020;13(1):120.
14. Heier JS, Lad EM, Holz FG, et al. Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials. *Lancet*. 2023;402(10411):1434–1448.
15. Patel SS, Lally DR, Hsu J, et al. Avacincaptad pegol for geographic atrophy secondary to age-related macular degeneration: 18-month findings from the GATHER1 trial. *EYE*. 2023;37(17):3551–3557.
16. Khanani AM, Patel SS, Staurengi G, et al. Efficacy and safety of avacincaptad pegol in patients with geographic atrophy (GATHER2): 12-month results from a randomised, double-masked, phase 3 trial. *Lancet*. 2023;402(10411):1449–1458.
17. Mullins RF, Schoo DP, Sohn EH, et al. The membrane attack complex in aging human choriocapillaris: relationship to macular degeneration and choroidal thinning. *Am J Pathol*. 2014;184(11):3142–3153.
18. Snodderly DM, Sandstrom MM, Leung IYF, Zucker CL, Neuringer M. Retinal pigment epithelial cell distribution in central retina of rhesus monkeys. *Invest Ophthalmol Vis Sci*. 2002;43(9):2815–2818.
19. Smailhodzic D, Klaver CCW, Klevering BJ, et al. Risk alleles in CFH and ARMS2 are independently associated with systemic complement activation in age-related macular degeneration. *Ophthalmology*. 2012;119(2):339–346.
20. Heesterbeek TJ, Lechanteur YTE, Lorés-Motta L, et al. Complement activation levels are related to disease stage in AMD. *Invest Ophthalmol Vis Sci*. 2020;61(3):18.
21. Patel PJ, Foster PJ, Grossi CM, et al. Spectral-domain optical coherence tomography imaging in 67 321 adults: Associations with macular thickness in the UK Biobank study. *Ophthalmology*. 2016;123(4):829–840.
22. Ko F, Foster PJ, Strouthidis NG, et al. Associations with retinal pigment epithelium thickness measures in a large cohort: Results from the UK biobank. *Ophthalmology*. 2017;124(1):105–117.
23. Seddon JM, Yu Y, Miller EC, et al. Rare variants in CFI, C3 and C9 are associated with high risk of advanced age-related macular degeneration. *Nat Genet*. 2013;45(11):1366–1370.
24. Ferkingstad E, Sulem P, Atlason BA, et al. Large-scale integration of the plasma proteome with genetics and disease. *Nat Genet*. 2021;53(12):1712–1721.
25. Zhang J, Dutta D, Köttgen A, et al. Plasma proteome analyses in individuals of European and African ancestry identify cis-pQTLs and models for proteome-wide association studies. *Nat Genet*. 2022;54(5):593–602.

26. Gudjonsson A, Gudmundsdottir V, Axelsson GT, et al. A genome-wide association study of serum proteins reveals shared loci with common diseases. *Nat Commun*. 2022;13(1):480.
27. Momozawa Y, Akiyama M, Kamatani Y, et al. Low-frequency coding variants in CETP and CFB are associated with susceptibility of exudative age-related macular degeneration in the Japanese population. *Hum Mol Genet*. 2016;25(22):5027–5034.
28. Pilotti C, Greenwood J, Moss SE. Functional evaluation of AMD-associated risk variants of complement factor B. *Invest Ophthalmol Vis Sci*. 2020;61(5):19.
29. Kurki MI, Karjalainen J, Palta P, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature*. 2023;613(7944):508–518.
30. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*. 2010;26(17):2190–2191.
31. Verma A, Huffman JE, Rodriguez A, et al. Diversity and scale: Genetic architecture of 2068 traits in the VA Million Veteran Program. *Science*. 2024;385(6706):eadj1182.
32. Guindo-Martínez M, Amela R, Bonàs-Guarch S, et al. The impact of non-additive genetic associations on age-related complex diseases. *Nat Commun*. 2021;12(1):2436.
33. Mbatchou J, Barnard L, Backman J, et al. Computationally efficient whole-genome regression for quantitative and binary traits. *Nat Genet*. 2021;53(7):1097–1103.
34. Character Bio. Accessed December 18, 2025. <https://www.characterbio.com/>
35. Avrutsky M, Nadkarni T, Adem S, Carter LL, van der Brug M, Karrer EE. CTX114, a novel complement inhibitor for the treatment of AMD, has enhanced SCR7-mediated ligand binding and complement regulatory activity. *Invest Ophthalmol Vis Sci*. 2024;65(7):6110–6110.
36. Sadda SR, Chakravarthy U, Birch DG, Staurengi G, Henry EC, Brittain C. Clinical endpoints for the study of geographic atrophy secondary to age-related macular degeneration. *Retina*. 2016;36(10):1806–1822.

Figures

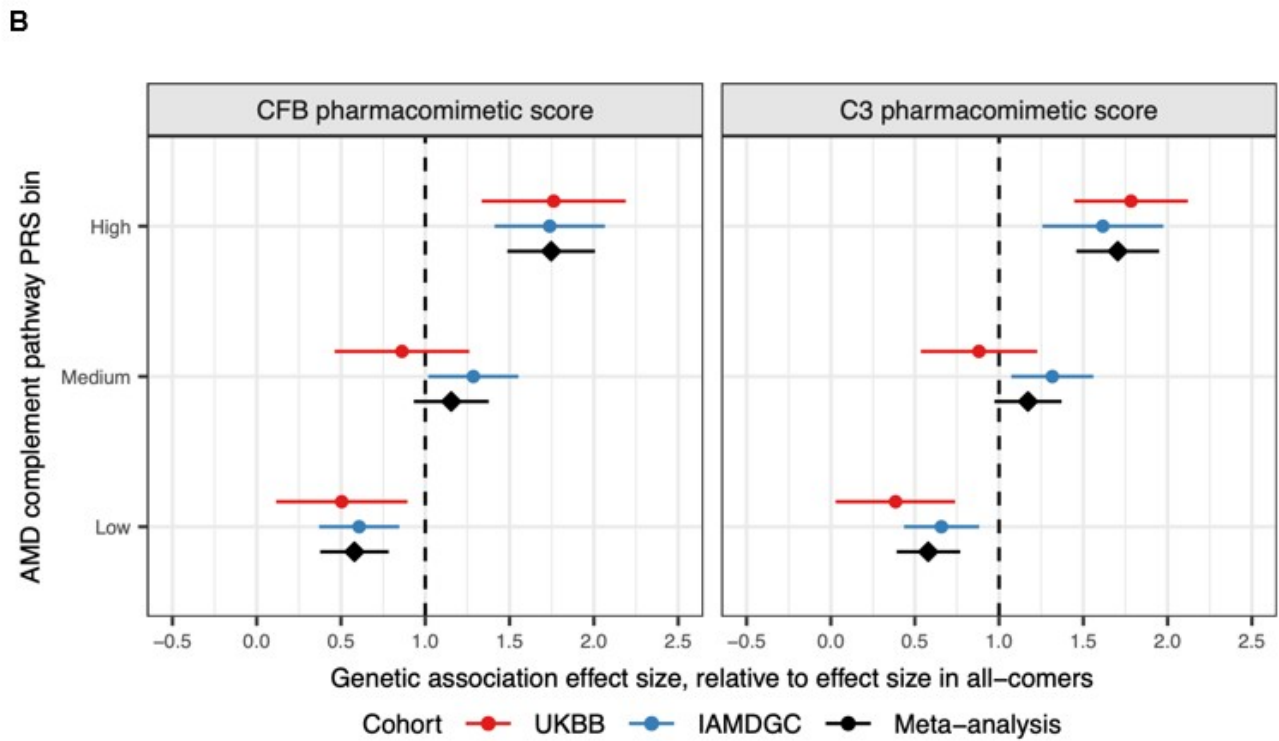
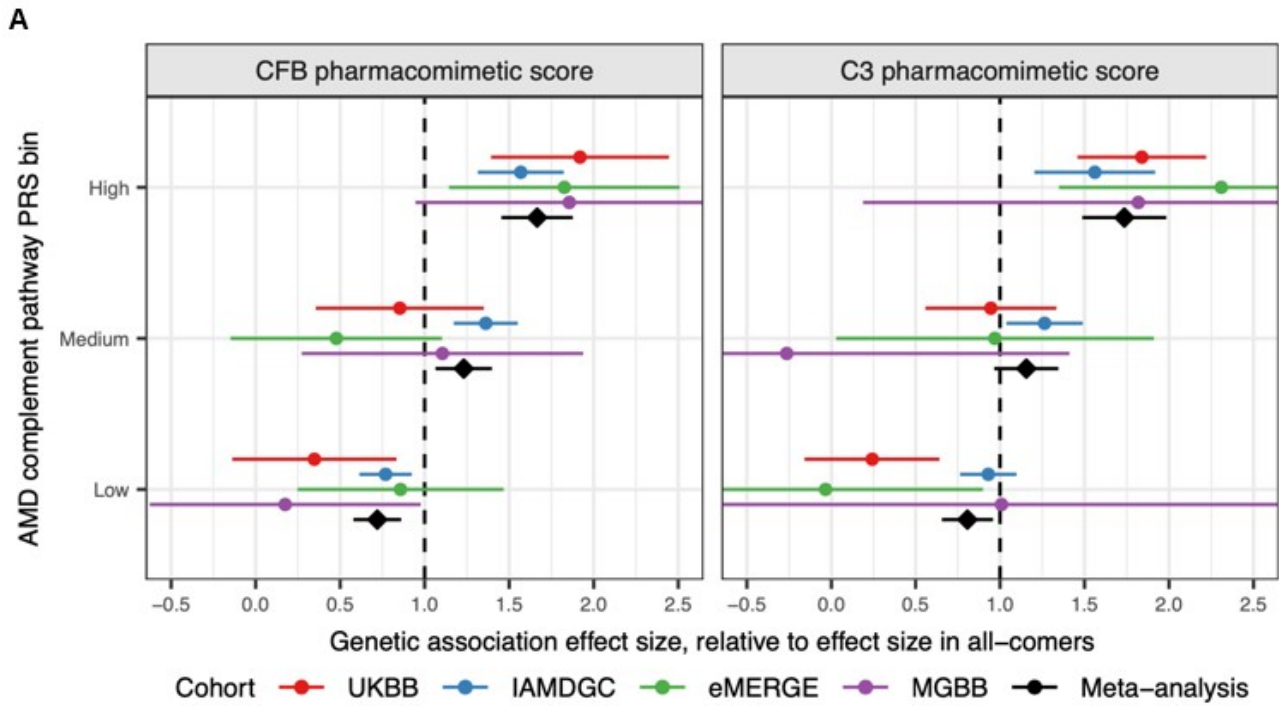


Figure 1

Effects of the *CFB* and *C3* pharmacomimetic scores (units = standard deviations) on risk of any AMD and dry AMD, respectively.

A. Effects of the *CFB* and *C3* pharmacomimetic scores (units = standard deviations) on risk of any AMD, in individuals defined as having low, medium, or high AMD complement pathway PRS. The PRS cut-offs

for the three subgroups were selected such that each subgroup represents exactly one-third of the AMD cases within a given cohort. **B.** As panel A, but with dry AMD assessed as the outcome.

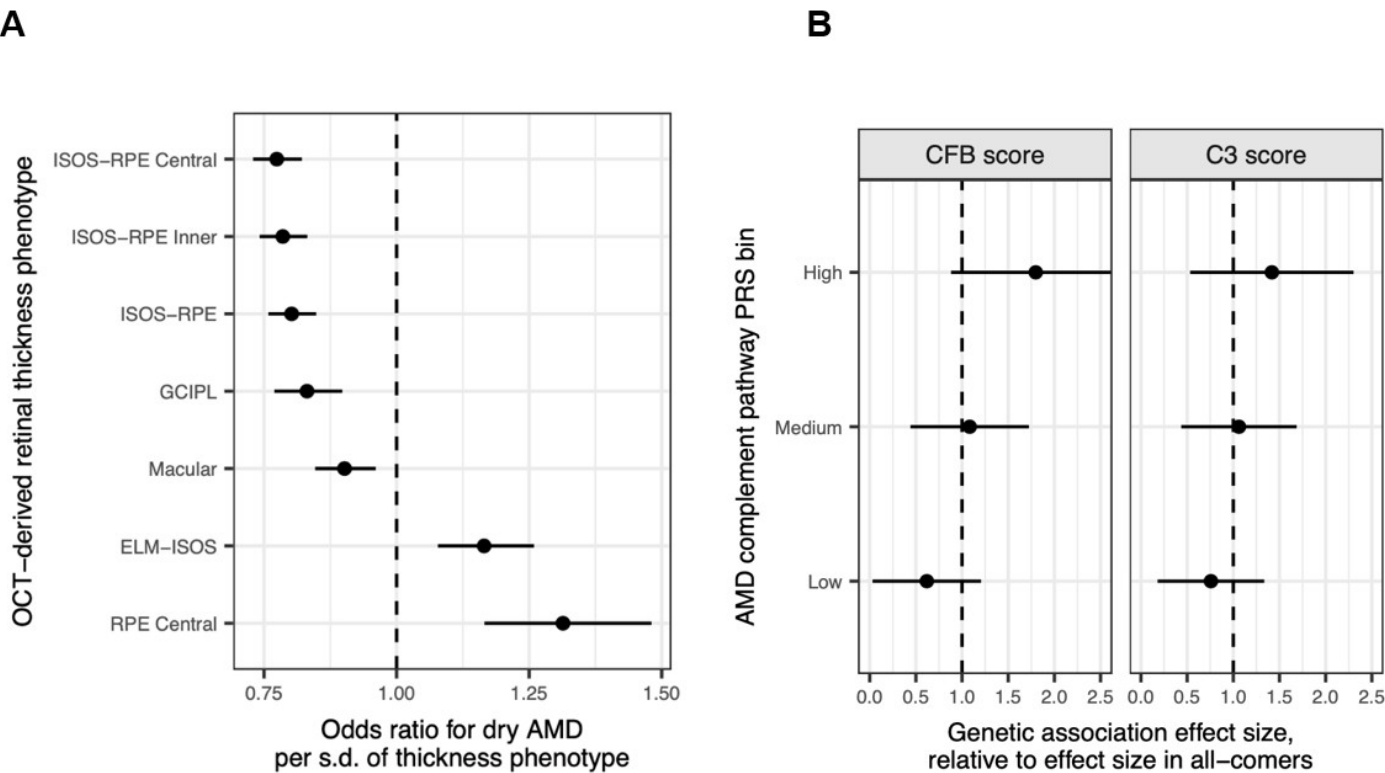
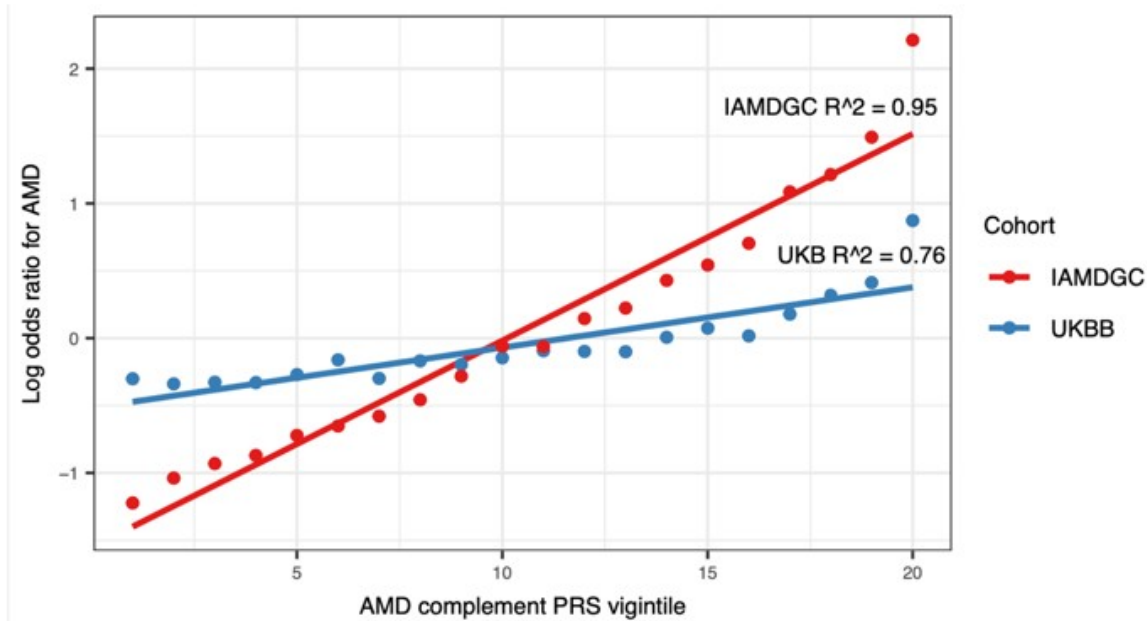
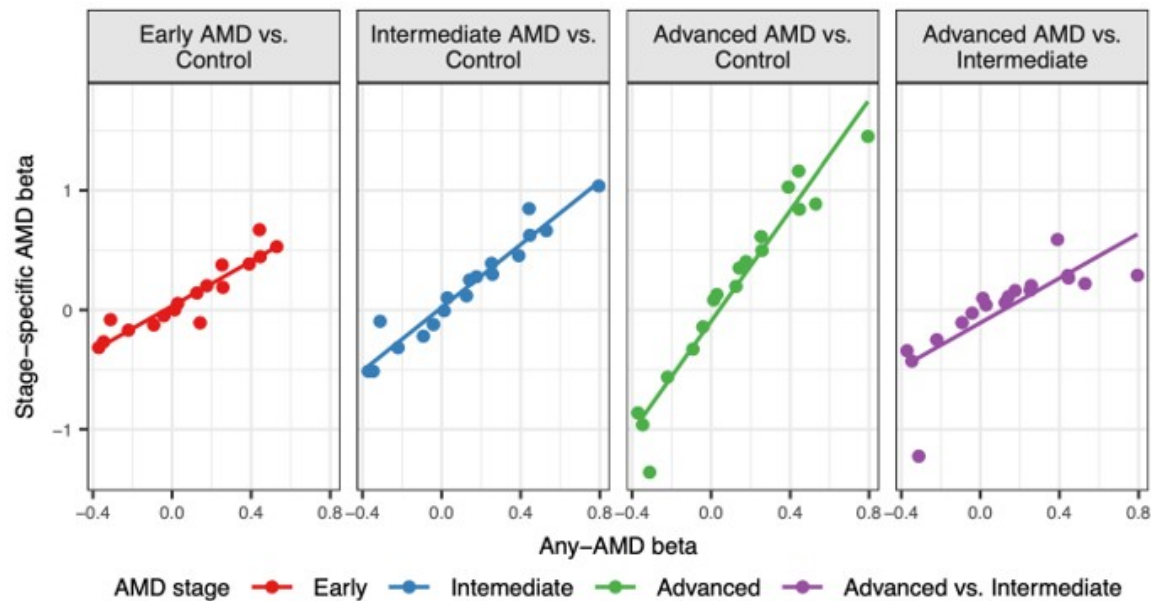


Figure 2

Association of selected retinal thickness phenotypes with dry AMD, and effects of the *CFB* and *C3* pharmacomimetic scores on ISOS-RPE thickness in the central subfield stratified by complement pathway PRS, respectively.

A. Association of selected retinal thickness phenotypes with dry AMD. The phenotypes were derived from UKB optical coherence tomography (OCT) data. Subjects with age <60 at time of OCT measurement were excluded. **B.** Effects of the *CFB* and *C3* pharmacomimetic scores on ISOS-RPE thickness in the central subfield, in groups of subjects defined as having low, medium, or high AMD complement pathway PRS. *CFB* score x PRS interaction is nominally significant ($p = 0.014$); *C3* score x PRS interaction is directionally consistent ($p = 0.25$).

A**B****Figure 3**

Associations of the AMD complement pathway PRS with any AMD, and associations with stage-specific AMD phenotypes, respectively.

A. Correlation of AMD complement pathway PRS vigintiles (5%-iles) with the log odds of a subject having AMD, relative to all-comers in each respective cohort. Specifically, the log odds of a subject having AMD

was computed for each PRS vigintile and divided by the log odds of a subject having AMD among those in the cohort (all-comers), irrespective of PRS. Correlation between the log odds ratio statistics and PRS vigintile number (1 to 20) was computed. The association of the PRS with AMD is stronger (*i.e.* slope is greater) in IAMDGC vs. UKB. This may be attributed to IAMDGC having clinically-assessed AMD, which is likely more accurate than the ICD-9/10 code-derived AMD extracted from UKB, especially in distinguishing *bona fide* controls for subjects with asymptomatic early / intermediate AMD. **B.** Associations of the 18 variants of the AMD complement pathway PRS with any AMD, compared to associations with stage-specific AMD phenotypes. Associations are presented as “betas”, *i.e.* the coefficient for the variant in a logistic regression model associating variant genotype with AMD phenotype. “Any AMD” associations were computed in a European-ancestry AMD GWAS meta-analysis (see Methods). Stage-specific AMD association statistics were retrieved from IAMDGC studies.^{2,13} The linear regression R^2 statistics for the comparisons of the any-AMD betas to the stage-specific betas are as follows: 0.86 (early), 0.94 (intermediate), 0.94 (advanced), 0.60 (advanced vs. intermediate). The outlier variant in the advanced vs. intermediate analysis (right-most panel) is *CFH* rs148553336. Excluding this variant, the R^2 is 0.76. One variant, *CFI* rs141853578, was missing from the early AMD GWAS¹³ and was thus excluded from the early AMD analysis (left-most panel).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [AMDPaperSuppTablesTableS1PRSVariants.pdf](#)
- [AMDPaperSuppTablesTableS2SampleSizebyAncestry.pdf](#)
- [AMDPaperSuppTablesTableS3AddCohortChars.pdf](#)
- [AMDPaperSuppTablesTableS4InteractionTests.pdf](#)
- [AMDPaperSuppTablesTableS5UKBOCTMeasures.pdf](#)