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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No custom software was used for data collection.
Data analysis	The following software was used for data analysis: PLINK (versions 1.9, 1.07, 2.0), REGENIE (versions 1.6.7, 2.0.2, and 2.2.4), LDSC 1.01, FINEMAP 1.4, eCAVIAR 2.2, HIBAG 1.22.0, PheWAS R package 0.12, TwoSampleMR 0.5.6, SMR 1.03, GCTA 1.94.0beta, VerifyBamID V1.1.3. TWAS-based methods: Michigan Imputation Server (HRC reference panel), R >= 3.6, Python 2.7, PrediXcan v1 (model training), EpiXcan v1 (model training), S-PrediXcan v0.6.5.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Clinical and genetic data in MVP were collected as previously described (PMID: 26441289, 31258967, 32005911, and 32243820).

The full summary level association data from the individual population association analyses in MVP and the ancestry-stratified and multi-ancestry meta-analyses are available via dbGaP (accession number phs001672). Polygenic scores based on European-ancestry and African-ancestry GWAS are deposited in the PGS Catalog (https://www.pgscatalog.org/) with accessions PGS004606 and PGS004607.

TWAS-based methods: Data were collected through the online portals and/or websites as described in the manuscript. STARNET EpiXcan models are available at: https://zhangw17.u.hpc.mssm.edu/epixcan/about.php#dl and https://predictdb.org/post/2019/08/23/epixcan-models-integrated-epigenetics/. GTEx reference datasets: http://www.gtexportal.org/. MSigDB: http://software.broadinstitute.org/gsea/msigdb. REMC: https://egg2.wustl.edu/roadmap/web_portal/. Gene expression data for retina data from Ratnapriya et al. (PMID 30742112): https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE115828
Genotype data for retina from Ratnapriya et al. (PMID 30742112) was acquired via data transfer agreement.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	All analyses were performed using sex assessed using genetic markers, and the term "sex" is used throughout the manuscript.
Population characteristics	Supplementary Table 1 summarizes participant numbers relevant to each cohort as well as their age and sex distribution. Supplementary Table 2 describes characteristics of the MVP cohort.
Recruitment	Subjects were recruited from VA Medical Centers participating in the Million Veteran Program. Veterans were identified from VA databases and recruited via invitational and appointment mailings. In addition, Veterans were recruited at selected VA Medical Centers. More details on recruitment are previously provided in PMID 26441289. Genentech GA and Genentech CNV participants were recruited in the course of their participation in clinical trials. IAMDGC data was obtained from a prior GWAS analysis of AMD (PMID 23455636, 26691988) GERA and UKBiobank recruitment has been previously described (PMID 26176866, 29662168).
Ethics oversight	The VA Office of Research and Development Central IRB approved the MVP005 and MVP024 study protocols. Genentech, IAMDGC, GERA and UKBiobank participants provided written informed consent in IRB approved protocols.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	After quality control, all samples of three ancestries (European, African, Hispanic) for whom genetic data were available were used for analysis. Participants were included if they met our phenotype definition for AMD case or control. Data from UKBiobank, GERA, Genentech CNV, and Genentech GA studies were meta-analyzed with the MVP.
Data exclusions	Subjects that did not meet the criteria of our phenotyping algorithm (PMID 31258967) for AMD case or control were excluded.
Replication	We performed a meta-analysis across 5 independent cohorts. We examined directions of effect and effect sizes for consistency across cohorts (Supplementary Tables 5, 6, 14). We report only those loci that were significant after meta-analysis.
Randomization	Randomization is not relevant for this GWAS study which is a retrospective analysis of AMD cases and controls.
Blinding	Blinding is not relevant for this GWAS study which is a retrospective analysis of AMD cases and controls.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging