JAMA Ophthalmology | Original Investigation

Overlap of Genetic Loci for Central Serous Chorioretinopathy With Age-Related Macular Degeneration

Joel T. Rämö, MD, PhD; Erik Abner, PhD; Elon H. C. van Dijk, MD, PhD; Xin Wang, MD; Joost Brinks, MD; Tiit Nikopensius, PhD; Margit Nõukas, MSc; Heidi Marjonen, PhD; Kaisa Silander, PhD; Sakari Jukarainen, MD, PhD; Tuomo Kiiskinen, MD; Seung Hoan Choi, PhD; Risto Kajanne, PhD; Juha Mehtonen, MSc; Priit Palta, PhD; Steven A. Lubitz, MD, PhD; Kai Kaarniranta, MD, PhD; Lucia Sobrin, MD, MPH; Mitja Kurki, PhD; Suzanne Yzer, MD, PhD; Patrick T. Ellinor, MD, PhD; Tõnu Esko, PhD; Mark J. Daly, PhD; Anneke I. den Hollander, PhD; Aarno Palotie, MD, PhD; Joni A. Turunen, MD, PhD; Camiel J. F. Boon, MD, PhD, FEBO; Elizabeth J. Rossin, MD, PhD; for the FinnGen Study; for the Estonian Biobank Research Team

IMPORTANCE Central serous chorioretinopathy (CSC) is a serous maculopathy of unknown etiology. Two of 3 previously reported CSC genetic risk loci are also associated with AMD. Improved understanding of CSC genetics may broaden our understanding of this genetic overlap and unveil mechanisms in both diseases.

OBJECTIVE To identify novel genetic risk factors for CSC and compare genetic risk factors for CSC and AMD.

DESIGN, SETTING, AND PARTICIPANTS Using *International Classification of Diseases, Ninth* (*ICD-9*) and *Tenth* (*ICD-10*) *Revision* code-based inclusion and exclusion criteria, patients with CSC and controls were identified in both the FinnGen study and the Estonian Biobank (EstBB). Also included in a meta-analysis were previously reported patients with chronic CSC and controls. Data were analyzed from March 1 to September 31, 2022.

MAIN OUTCOMES AND MEASURES Genome-wide association studies (GWASs) were performed in the biobank-based cohorts followed by a meta-analysis of all cohorts. The expression of genes prioritized by the polygenic priority score and nearest-gene methods were assessed in cultured choroidal endothelial cells and public ocular single-cell RNA sequencing data sets. The predictive utility of polygenic scores (PGSs) for CSC and AMD were evaluated in the FinnGen study.

RESULTS A total of 1176 patients with CSC and 526 787 controls (312 162 female [59.3%]) were included in this analysis: 552 patients with CSC and 343 461 controls were identified in the FinnGen study, 103 patients with CSC and 178 573 controls were identified in the EstBB, and 521 patients with chronic CSC and 3577 controls were included in a meta-analysis. Two previously reported CSC risk loci were replicated (near *CFH* and *GATA5*) and 3 novel loci were identified (near *CD34/46*, *NOTCH4*, and *PREX1*). The *CFH* and *NOTCH4* loci were associated with AMD but in the opposite direction. Prioritized genes showed increased expression in cultured choroidal endothelial cells compared with other genes in the loci (median [IQR] of log 2 [counts per million], 7.3 [0.6] vs 4.7 [3.7]; $P = .004$) and were differentially expressed in choroidal vascular endothelial cells in single-cell RNA sequencing data (mean [SD] fold change, 2.05 [0.38] compared with other cell types; $P < 7.1 \times 10^{-20}$). A PGS for AMD was predictive of reduced CSC risk (odds ratio, 0.76; 95% CI, 0.70-0.83 per +1 SD in AMD-PGS; $P = 7.4 \times 10^{-10}$). This association may have been mediated by loci containing complement genes.

CONCLUSIONS AND RELEVANCE In this 3-cohort genetic association study, 5 genetic risk loci for CSC were identified, highlighting a likely role for genes involved in choroidal vascular function and complement regulation. Results suggest that polygenic AMD risk was associated with reduced risk of CSC and that this genetic overlap was largely due to loci containing complement genes.

Invited Commentary page 457

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the FinnGen Study and the Estonian Biobank Research Team appear in Supplement 3.

Corresponding Author: Elizabeth J. Rossin, MD, PhD, Harvard Medical School Department of Ophthalmology, Massachusetts Eye and Ear, 243 Charles St, Boston, MA 02114 (elizabeth_rossin@meei.harvard.edu).

JAMA Ophthalmol. 2023;141(5):449-457. doi:10.1001/jamaophthalmol.2023.0706
Published online April 20, 2023.

Central serous chorioretinopathy (CSC) is a maculopathy seen commonly by retina specialists, yet it is poorly understood. A better understanding of CSC pathophysiology is an exciting avenue to shed light on underrecognized pathways in retinal and choroidal disease.

The hallmark of CSC is the accumulation of subretinal fluid (SRF), often involving the fovea, with associated retinal pigment epithelium (RPE) detachments (PEDs) in 1 or both eyes.[1] The disease manifests with decreased visual acuity and metamorphopsia between the ages of 30 and 50 years,[2] and CSC is more common in men (male:female ratio, 3-5:1),[2,3] though the etiology behind this sex disparity is not understood.[4,5] Reported risk factors include type A personality, obstructive sleep apnea, exogenous or endogenous corticosteroids, pregnancy, sildenafil, MAPK/ERK (also known as Ras-Raf-MEK-ERK) pathway inhibitors, and caffeine use.[5-9] On optical coherence tomography scanning, patients with CSC often have a thick choroid[10-12] and SRF associated with a PED, and eyes with previously active CSR show RPE elevations with overlying outer nuclear layer thinning. Fluorescein angiography (FA) may reveal characteristic leakage when the disease is active,[13,14] indocyanine green angiography shows hyperfluorescent changes with an indistinct border,[15,16] and fundus autofluorescence may reveal a hyperautofluorescent gravitational guttering pattern[11] indicative of prior or active SRF. Although the SRF in acute CSC is usually self-limiting,[17] SRF can become recurrent or persistent in 20% to 30% of patients, and a subset develop choroidal neovascularization (CNV).[18-21]

Genetics is an avenue to understanding underlying pathophysiologic mechanisms, and CSC has been noted to cluster in families.[22-24] The lack of clearly segregating variants in sequencing analyses suggests that CSC is a genetically complex disorder.[25] A 2018 genome-wide association study (GWAS) in 521 European patients with chronic CSC (cCSC) identified a susceptibility locus near *CFH*,[26] whereas a later study including 1025 Japanese patients with CSC identified susceptibility loci near *GATA5* and *TNFRSF10A*.[27]

Interestingly, 2 of 3 reported CSC GWAS loci (*CFH* and *TNFRSF10A*) were also found to be associated with AMD in recent European or Japanese GWASs.[22-24] Further characterization of the overlap of associated genetic variation between CSC and AMD is warranted but has been limited by the small number of identified genetic CSC loci.

Here we performed a meta-analysis of 2 national biobank-based GWASs (FinnGen and Estonian Biobank, [EstBB]) together with the previously reported European cohort of patients with cCSC. We replicate 2 known genetic loci and report 3 novel loci for CSC.

Key Points

Question What are the genetic risk factors for central serous chorioretinopathy (CSC) and to what extent do they overlap with age-related macular degeneration (AMD)?

Finding In this 3-cohort genetic association study, 5 genetic loci were associated with CSC and highlighted genes regulating the complement system and choroidal vascular function or development. Genetic overlap between CSC and AMD was largely due to complement-containing loci.

Meaning These findings support a role for choroidal vascular dysfunction in CSC pathogenesis and delineate the genetic overlap between CSC and AMD.

Methods

Study Design

FinnGen Data Freeze 9 has data for 377 777 individuals and is a collection of prospective Finnish epidemiological and disease-based cohorts and hospital biobank samples linked to electronic health records.[28] EstBB is a population-based biobank with over 200 000 biological samples linked to electronic health record data (eMethods in Supplement 1).[25] Based on genetic information, only individuals of Finnish ancestry were included in the FinnGen analysis, and only individuals of European ancestry were included in the EstBB analysis. This 3-cohort genetic association study followed the Strengthening the Reporting of Genetic Association Studies (STREGA) reporting guidelines.

In both biobanks, patients with CSC were identified based on the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) code H35.7; other study participants were used as controls. We excluded potential patients and controls with AMD, hereditary retinal dystrophies, ophthalmic complications of diabetes, chorioretinal inflammation and other choroidal disorders, retinal detachments, and degenerative myopia (eTable 1 in Supplement 2).

Details for the European cCSC cohort have been reported previously.[26] European patients were recruited from the outpatient clinics of the Radboud University Medical Center (Nijmegen, the Netherlands), University Hospital of Cologne (Cologne, Germany), and Leiden University Medical Center (Leiden, the Netherlands). Controls from the Nijmegen Biomedical Study were also included. The patients with cCSC had SRF in at least 1 eye, RPE irregularities with characteristic leakage on FA, and corresponding hyperfluorescence on indocyanine green angiography.

For analyses involving AMD, we identified patients and controls with prevalent AMD (either wet or dry) in the FinnGen study based on the *ICD-10* codes H35.30 and H35.31 and *Ninth Revision* (*ICD-9*) codes 3625A and 3625B. All patients with AMD were required to have at least 1 corresponding diagnosis code at age 50 or older.

Ethics Statement

Patients and control participants in the FinnGen study provided verbal or written informed consent for biobank research based on the Finnish Biobank Act or separate research cohort protocols. The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa statement number for the FinnGen study is Nr HUS/990/2017.

The activities of the EstBB are regulated by the Human Genes Research Act, and patients provided written or verbal consent. Individual level data in EstBB was analyzed under ethical approval 1.1-12/624 from the Estonian Committee on Bioethics and Human Research (Estonian Ministry of Social Affairs), using data according to release application 3-10/GI/21273 from the EstBB. No stipends were given to FinnGen or EstBB study participants.

Genotyping and Imputation

The FinnGen study samples were genotyped using Illumina arrays (Illumina Inc) and Affymetrix arrays (Thermo Fisher Scientific) as detailed previously (eMethods in Supplement 1).[26] Genotype imputation was performed using a population-specific SISu, version 4 imputation reference panel comprising 8557 whole genomes. Based on principal component (PC) analysis, study participants who were not of Finnish ancestry and who were twins or duplicates of included samples were removed similarly to the method described by Kurki et al.[26]

All EstBB participants have been genotyped at the Core Genotyping Lab of the Institute of Genomics, University of Tartu, Tartu, Estonia, using Illumina Global Screening Array, version 3.0_EST (Illumina Inc). Genotype quality control is detailed in the eMethods in Supplement 1. A population-specific reference panel consisting of 2297 whole genome–sequencing samples was used for imputation.[29] Based on PC analysis, participants who were not of European ancestry and who were twins or duplicates were removed. Sample ascertainment, genotyping, imputation and GWAS for the European cCSC data set has been described previously.[26] Details regarding gene prioritization, single-cell expression analysis and polygenic score analysis methodologies are detailed in the eMethods in Supplement 1.

GWASs and Meta-analysis

Genome-wide association analysis in the FinnGen study was performed for all variants with an imputation information (INFO) score greater than 0.7 using the additive model as implemented in regenie, version 2.2.4 (Regeneron Genetics Center).[30] In addition, imputed sex, age at death or end of follow-up, first 10 PCs, genotyping array, and genotyping batch were used as fixed-effect covariates.

Association analysis in EstBB was carried out for all variants with an INFO score greater than 0.7 using the additive model as implemented in Scalable and Accurate Implementation of Generalized mixed model (SAIGE, version 1.0.7 [Lee lab for Statistical Genetics and Data Science]),[31] with a saddlepoint approximation to calibrate unbalanced case-control ratios. Logistic regression was carried out with the LOCO = TRUE setting and was adjusted for current age, current age squared, sex, and 10 PCs as covariates, analyzing only variants with a minimum minor allele count of 2.

Statistical Analysis

For the meta-analysis, we used inverse-variance weighted fixed-effect meta-analysis implemented in GWAMA, version 2.2.2 (Estonian Genome Center).[32] We included 12 522 976 variants that were present in at least 2 cohorts at a cross-cohort allele frequency of 0.1% or greater. A 2-sided *P* value threshold of 5×10^{-8} was used to establish genome-wide significance accounting for multiple comparisons. Data were analyzed from March 1 to September 31, 2022.

Results

GWAS of CSC in 2 Biobank-Based Studies

We first conducted cohort-specific GWASs in FinnGen and EstBB separately. After filtering (Methods; eTable 1 in Supplement 2), 552 patients with CSC and 343 461 controls in FinnGen and 103 patients with CSC and 178 573 controls in EstBB were included (total patients with CSC: 434 male [66.3%]; 221 female [33.7%]; total controls: 212 141 male [40.6%]; 309 893 female [59.4%]) (eTable 2 in Supplement 2).

We observed 1 genome-wide significant locus (Bonferroni-adjusted, $P < 5 \times 10^{-8}$) in FinnGen in the previously reported region near the *CFH* gene (lead variant rs1329428, AF = 0.40; odds ratio [OR], 1.54 for CSC; $P = 7.9 \times 10^{-14}$) (eFigure 1 in Supplement 1). The effect was concordant but not significant in EstBB (OR = 1.23; AF = 0.41; *P* = .14). One locus reached genome-wide significance in EstBB (eFigure 2 in Supplement 1), marked by the rare intronic variant rs941444936 (12: 891646 A>T) in *WNK1* (OR, 4229.98; AF = 0.0064; $P = 1.9 \times 10^{-8}$); however, this signal was not observed in FinnGen (OR, 0.95; AF 0.0070; *P* = .89).

To evaluate genetic similarity of the biobank CSC case definition with a clinical case definition, we constructed a polygenic score (PGS) for cCSC based on summary statistics from the previous European cCSC GWAS. The cCSC-PGS was predictive of the *ICD* code–based CSC case definition in FinnGen (OR, 1.17 per +1 SD in cCSC-PGS; *P* < .001) (eTable 3 in Supplement 2). Motivated by the lack of novel findings in individual cohorts and the need for an expanded sample size, we proceeded with a meta-analysis.

Meta-analysis of Biobank-Based Studies and cCSC Cohort

We performed a meta-analysis of the results from the 2 biobank-based studies and the published European study for a total of 1176 cases and 526 787 controls. Five loci reached genome-wide significance (**Table**; **Figure 1**). Unadjusted genomic control coefficient and linkage disequilibrium (LD) score regression intercept were 1.028 and 1.024, respectively, suggesting insignificant genomic inflation (eTable 4 in Supplement 2 and eFigure 3 in Supplement 1); we adjusted test statistics and *P* values for the LD score regression intercept, which did not affect the number of significant loci. The significant loci included 2 previously reported loci near *CFH* and *GATA5* and 3 novel loci near the *NOTCH4*, *PREX1*, and *CD34/CD46* genes (eFigure 4A and E in Supplement 1). Although we did not replicate the third previously reported susceptibility locus near *TNFRSF10A*, we observed a comparable effect size (OR, 1.25; $P = 3.2 \times 10^{-7}$) (eFigure 4F in Supplement 1). Effect estimates were concordant across the 3 cohorts (Figure 1C) without significant heterogeneity (*P* > .05 for all tests using Cochran *Q* statistic) (eTable 5 in Supplement 2). Effect estimates were similar in repeat analyses in FinnGen with age cutoffs of 50, 60, and 70 years, and additional sensitivity analyses revealed no significant source of bias (eResults and eFigures 5-7 in Supplement 1 and eTable 6 in Supplement 2). There were no significant differences in effect estimates between male and female participants for the 5 lead variants in either biobank (*P* > .05 for all tests of heterogeneity using Cochran *Q* statistic) (eTable 5 in Supplement 2).

The *NOTCH4* locus contains the *C4B* gene, and copy number variation at this gene has been associated with CSC.[33] We did not find evidence for an association between a structural variation in *C4B* and CSC given that only 2 of 103

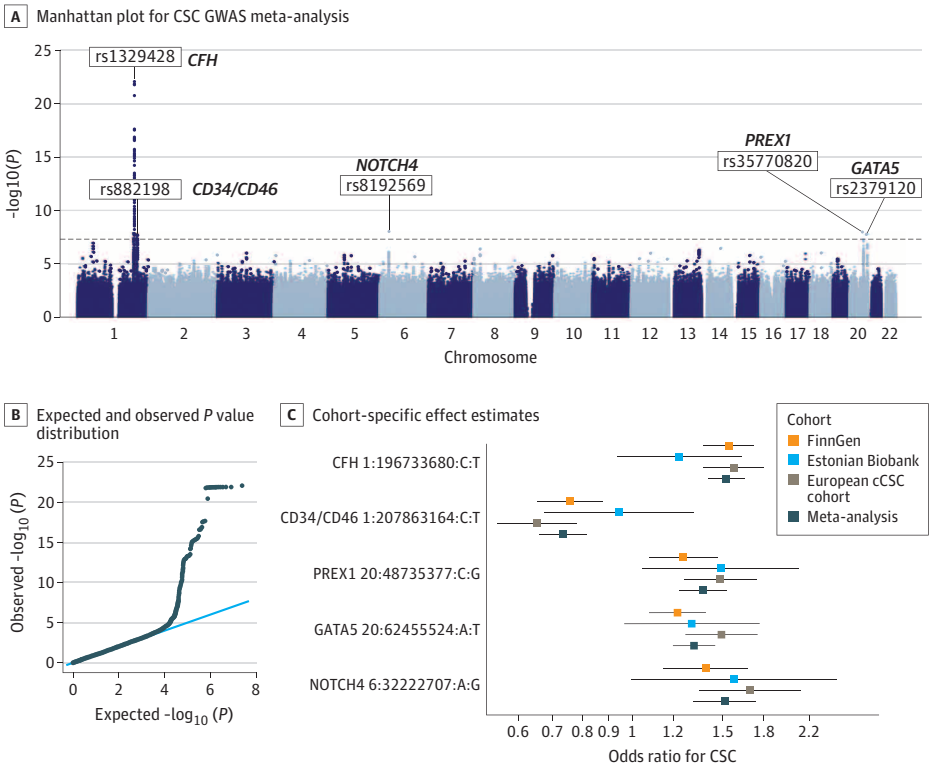
Table. Lead Variants in the Genome-Wide Association Study Meta-analysis[a]

rsID	Nearest gene(s)	Chromosome	Position	Consequence	NEA	EA	OR (95% CI)	EAF		P value
								Cases	Controls	
rs1329428	*CFH*	1	196 733 680	Intronic	C	T	1.52 (1.4-1.65)	0.52	0.41	2.71×10^{-23}
rs882198	*CD34/CD46*	1	207 863 164	Intronic	C	T	0.73 (0.66-0.82)	0.18	0.23	1.43×10^{-8}
rs8192569	*NOTCH4*	6	32 222 707	Synonymous	G	A	1.51 (1.32-1.74)	0.12	0.08	5.76×10^{-9}
rs35770820	*PREX1*	20	48 735 377	Intronic	G	C	1.37 (1.23-1.52)	0.22	0.17	5.91×10^{-9}
rs2379120	*GATA5*	20	62 455 524	Intergenic	A	T	1.32 (1.2-1.45)	0.75	0.69	1.28×10^{-8}

Abbreviations: CD, cluster of differentiation; CFH, complement factor H; CSC, central serous chorioretinopathy; EA, effect allele; EAF, effect allele frequency; GATA5, GATA-binding protein 5; NEA, noneffect allele; NOTCH4, notch receptor 4; OR, odds ratio; PREX1, phosphatidylinositol-3,4,5-trisphosphate–dependent Rac exchange factor 1; rsID, reference single nucleotide variation cluster identification.

[a] A total of 1176 patients with CSC and 526 787 controls from the FinnGen study, Estonian Biobank, and a previously reported European clinical CSC cohort were included in the meta-analysis. A Bonferroni-corrected 2-sided genome-wide *P* value threshold of 5×10^{-8} was used to establish significance, accounting for multiple comparisons. For all loci, the nearest protein-coding gene is shown.

Figure 1. Significant Loci in the Genome-Wide Association Study (GWAS) Meta-analysis



A, Manhattan plot for the central serous chorioretinopathy (CSC) genome-wide association study meta-analysis. A total of 1176 patients with CSC and 526 787 controls from the FinnGen study, Estonian Biobank, and a previously reported European clinical chronic CSC (cCSC) cohort were included in the meta-analysis. Each data point corresponds to a single genetic variant. A Bonferroni-corrected 2-sided genome-wide *P* value threshold of 5×10^{-8} (dashed line) was used to establish significance accounting for multiple comparisons. Each locus is annotated with the name(s) of the nearest protein coding gene(s).
B, Expected and observed *P* value distributions are represented in a quantile-quantile plot.
C, Cohort-specific effect estimates are shown for the meta-analysis and separately for the FinnGen study (552 patients with CSC and 343 461 controls), Estonian Biobank (103 patients with CSC and 178 573 controls), and a previously reported European CCSC cohort (521 patients with CSC and 3577 controls). Squares and lines correspond to odds ratios and 95% CIs, respectively.

patients with CSC (1.94%) carried homozygous deletions spanning the *C4B* gene compared with 3387 participants (1.90%) in the whole EstBB. Additional results are presented in the eResults in Supplement 1 and eTable 7 in Supplement 2.

Gene Set Enrichment Analysis and Gene Prioritization

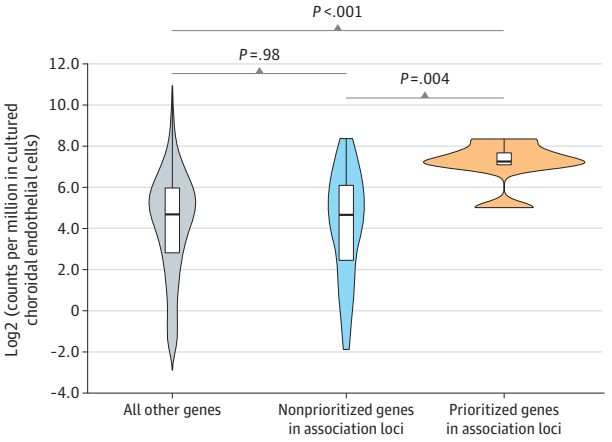
To highlight associated molecular pathways, we performed gene-based tests using MAGMA (CTG Lab, Amsterdam University Medical Center) to assign each gene a score (eTable 8 in Supplement 2) followed by GO-based gene set enrichment analysis while controlling for local LD structure. We identified significant enrichment of genes in the alternative complement activation pathway (linear regression β coefficient [SE], 1.17 [0.25]; $P = 1.6 \times 10^{-6}$). No other pathway reached significance (eTables 9-10 in Supplement 2 and eFigure 8 in Supplement 1).

To prioritize genes in associated multigene loci, we used the gene-level polygenic priority score (PoPS) method that incorporates information on gene expression, biological pathways, and protein-protein interactions.[34] This analysis prioritized the genes *CFH*, *CD34*, *NOTCH4*, *PREX1*, and *LAMA5* most strongly in their respective loci, although discriminative performance was worse in the latter 2 loci (eFigure 9 in Supplement 1). In 4 of 5 loci, the PoPS-prioritized genes were nearest to the lead variants (*CFH*, *CD34*, *NOTCH4*, and *PREX1*).

Expression of Prioritized Genes in the Associated Loci in Choroidal Vascular Endothelial Cells

We queried the expression levels of the genes prioritized by PoPS or the nearest gene approach (7 total: *CFH*, *CD34*, *CD46*, *NOTCH4*, *PREX1, LAMA5*, and *GATA5*) using publicly available ocular single-cell sequencing data sets.[35-38] We observed expression of 6 of 7 prioritized genes in the endothelial cells of arteries, veins, and capillaries (eFigure 10A in Supplement 1) based on an integrated data set of retinal, RPE, and choroidal cells, and replicated this finding in a data set focusing on RPE/choroid lysates (eFigure 11A in Supplement 1). Specifically, we found increased expression in vascular cells when compared with all other cells (mean [SD] per-gene fold change, 2.05 [0.38]; unadjusted *P* values $<7.1 \times 10^{-20}$ for all 6 genes), with rods and cones (mean [SD] fold change, 2.64 [1.19]; *P* values $<3.8 \times 10^{-23}$), with RPE (mean [SD] fold change, 2.27 [0.50]; *P* values $<2.9 \times 10^{-4}$), and with T cells, B cells, and macrophages (mean [SD] fold change, 2.52 [1.11]; *P* values $<1.3 \times 10^{-12}$) (eTable 11 in Supplement 2). We did not observe similar consistent enrichment for the second-nearest genes in the association loci (*KCNT2*, *CR1L*, *GPSM3*, *ARFGEF2*, and *RBBP8NL*) analyzed as negative controls (mean [SD] fold change, 0.93 [0.30]) (eFigure 10B, 11B, and eTable 12 in Supplement 2). We replicated these findings in 2 independent single-cell data sets (eMethods, eResults, and eFigures 12 and 13 in Supplement 1 and eTable 13 in Supplement 2). Furthermore, in an independent data set of cultured choroidal endothelial cells from cadaveric human donors,[5] basal expression levels of the 6 lead genes were higher on average compared with 54 nonprioritized genes in the association loci (median [IQR] of log 2 [counts per million], 7.3 [0.6] vs 4.7 [3.7]; Wilcoxon rank sum *P* = .004) and compared with all other 13 128 genes (median [IQR] of log 2 [counts per million] 7.3 [0.6] vs 4.7 [3.2], *P* = .002) (**Figure 2**, eFigure 14 in Supplement 1, and eTable 14 in Supplement 2).

Figure 2. Expression of Prioritized and Nonprioritized Genes in Human Primary Cultured Choroidal Endothelial Cells



Basal gene expression levels were quantitated in cultured choroidal endothelial cells from 10 human cadaveric donors (5 males and 5 females) using RNA sequencing. Expression is shown separately for 6 genes in the association loci that were prioritized by the polygenic priority score or nearest-gene method (*CFH*, *CD34*, *CD46*, *NOTCH4*, *PREX1*, and *LAMA5*), 54 nonprioritized genes in the association loci, and all other 13 128 quantifiable genes. Genes were designated as belonging to the association loci if they were located within ±500 kilobases from the genome-wide association meta-analysis lead variants. The 25%, 50%, and 75% percentiles and 1.5 × IQRs for each group are represented by box and whisker plots. *P* values were calculated with the Wilcoxon rank sum test. Exact expression levels for genes in the association loci are additionally presented in eTable 14 in Supplement 2. No measurable expression was observed for the nearest protein-coding gene *GATA5*.

Selective Overlap Between Genetic Risk Loci for CSC and AMD

Following the observation of shared loci between CSC and AMD, we first evaluated the coassociations of the CSC lead variants with AMD based on a custom GWAS of AMD in FinnGen (8913 patients with AMD and 348 936 controls) and a previously reported AMD GWAS by the International AMD Genomics Consortium (IAMDGC) (eTable 15 in Supplement 2, **Figure 3**A, and eFigure 15 in Supplement 1).[39] We observed significant coassociations for CSC and AMD for 2 lead variants (in the *CFH* and *NOTCH4* genes) with opposite effect directions.

Next, we evaluated whether any of 32 lead variants from the previous IAMDGC meta-analysis were nominally associated with CSC, even if not genome-wide significant.[39] The effect estimates were generally lower for CSC but showed an overall inverse directional correlation ($R = -0.60$; $P < .001$) (Figure 3B and eTable 16 in Supplement 2), though a subset of loci showed concordant effect directions (eg, *TNFRSF10A*) or near-null effects for CSC (eg, *APOE*).

Lower Associated Risk of CSC With Higher Polygenic Score for AMD

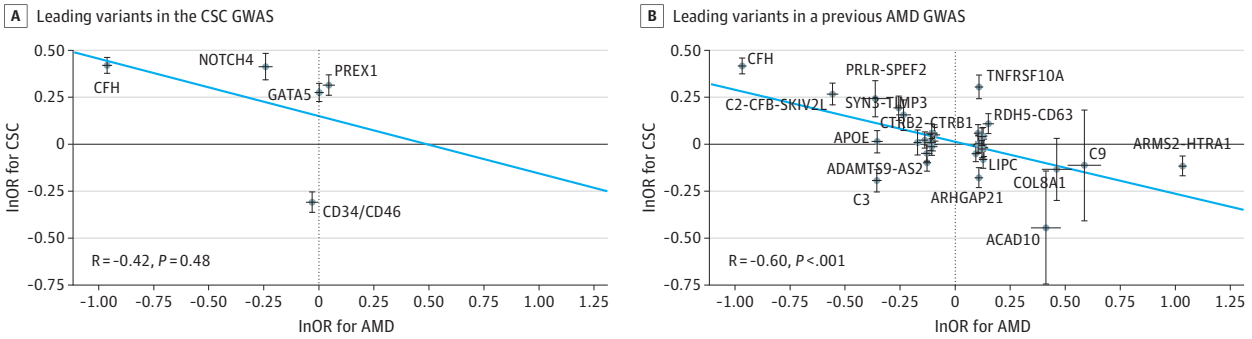
To contrast individual-level genetic risk for AMD and CSC, we constructed genome-wide polygenic scores for AMD in FinnGen using PRS-CS based on summary statistics from the most recent IAMDGC meta-analysis, incorporating information from a total of 1 077 835 variants. The AMD-PGS was associated with increased risk of AMD in FinnGen (OR, 2.0; 95% CI, 1.96-2.05 per +1 SD in AMD-PGS, $P < 1 \times 10^{-32}$) and notably with decreased risk of CSC (OR, 0.76; 95% CI, 0.70-0.83; $P = 7.4 \times 10^{-10}$) (**Figure 4** and eTable 2 in Supplement 2).[2]

To evaluate the contribution of complement-annotated loci, we constructed versions of the AMD-PGS excluding first the *CFH* locus and then all 6 complement-annotated loci (Figure 4 and eTable 2 in Supplement 2).[2] The association of the AMD-PGS with CSC was markedly reduced when removing the *CFH* locus (OR, 0.89; 95% CI, 0.81-0.97; $P = .006$) and was further attenuated when removing all 6 complement-annotated loci (OR, 0.93; 95% CI, 0.85-1.01; $P = .09$), whereas the parsed AMD-PGS was still strongly associated with AMD (OR, 1.60; 95% CI, 1.57-1.64; $P < 1 \times 10^{-32}$). Due to limitations in data availability, we were not able to conduct this same analysis in the patients from Estonia.

Discussion

In this 3-cohort GWAS and meta-analysis, we replicated 2 previously reported CSC loci and identified 3 novel loci near the genes *CD34/CD46*, *NOTCH4*, and *GATA5*. We were encouraged that the genetic signals based on *ICD*-defined CSC cases showed little heterogeneity across biobanks, and although the

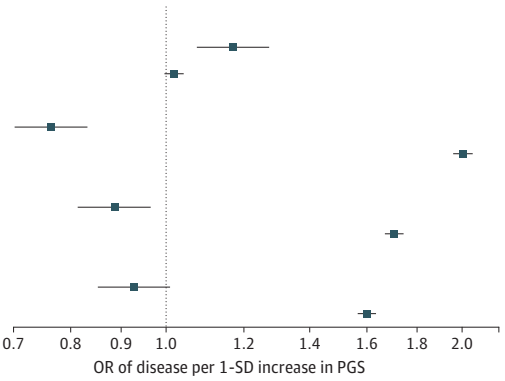
Figure 3. Comparison of Effect Estimates Between Central Serous Chorioretinopathy (CSC) and Age-Related Macular Degeneration (AMD)



Effect estimates (natural logarithms of odds ratios [ORs]) for CSC (y-axis) and AMD (x-axis) are contrasted for 5 lead variants from the genome-wide association study (GWAS) meta-analysis of CSC (A), and 32 lead variants that were reported in a previous GWAS of AMD (B).[39] Pearson correlation coefficients and best-fit lines based on linear regression are shown.

Figure 4. Predictive Utility of Polygenic Scores (PGS) for Central Serous Chorioretinopathy (CSC) and Age-Related Macular Degeneration (AMD)

	OR (95% CI)
cCSC-PGS	
CSC	1.17 (1.07-1.27)
AMD	1.02 (1.00-1.04)
AMD-PGS	
CSC	0.76 (0.70-0.83)
AMD	2.01 (1.96-2.05)
AMD-PGS (excluding CFH locus)	
CSC	0.89 (0.81-0.97)
AMD	1.71 (1.67-1.75)
AMD-PGS (excluding 6 complement loci)	
CSC	0.93 (0.85-1.01)
AMD	1.60 (1.57-1.64)



PGSs were used to predict prevalent CSC (552 patients with CSC and 343 461 controls) and AMD (8913 patients with AMD and 348 936 controls) in the FinnGen study. PGSs were constructed based on previously reported genome-wide association studies of chronic CSC (cCSC) and AMD. Additional versions of the PGS for AMD were calculated after removing variants in the *CFH* locus and all 6 loci previously annotated as complement associated (*CFH*, *CFI*, *C9*, *C2-CFB-SKIV*, *C3*, and *TMEM97-VTN* loci). In each logistic regression model, a PGS, age at end of follow-up or death, age at end of follow-up or death squared, sex, first 5 genomic principal components, genotyping batch, and genotyping array were used as covariates. OR indicates odds ratio.

biobank-based diagnosis of CSC cannot be confirmed with imaging, the consistent genetic signal suggests homogeneity.

Prioritized genes in the loci (*CFH*, *CD34*, *CD46*, *NOTCH4*, *PREX1*, and *LAMA5*) are particularly expressed in choroidal vascular endothelial cells compared with retina and RPE, which corroborates a role for choroidal vascular dysfunction in CSC pathogenesis.[35] In fact, the first novel locus is marked by an intronic variant in *PREX1*, which codes for a protein implicated in vascular hyperpermeability.[40]

The 2 other novel CSC loci near *NOTCH4* and *CD34*/*CD46* have potential links to both vascular and immune function. Transmembrane Notch receptors are required for vascular development[41,42] and Notch4 protein regulates arteriovenous malformation and choroidal neovascularization.[43,44] We note that the *NOTCH4* locus also contains several complement genes (*C2*, *CFB*, *C4A*, and *C4B*),[39] the relevance of which is not clear. The last novel locus points to *CD34* and *CD46*, which are both expressed in choroidal vasculature.[35] *CD46* codes for MCP/CD46 which has a canonical role as a complement inhibitor via the proteolytic cleavage and inactivation of C3b and C4b[45] and regulates RPE adhesion through its interaction with β1 integrin.[46] CD34 is strongly expressed in early hematopoietic cells and vascular endothelial cells at different stages of development[47] and has been implicated in AMD.[48] Together with *CFH*, these 3 loci suggest that genetic variation in the complement cascade may be associated with CSC, but this hypothesis is purely speculative given lack of confirmation that complement is expressed in CSC eyes.

Three of 6 total-reported lead variants including all published studies are also associated with AMD,[27] but the direction of effect is opposite in the *CFH* and *NOTCH4* loci and concordant in the *TNFRSF10A* locus.[39] The benefit of GWAS is that it is truly unaffected by previous hypotheses (as compared with a candidate gene approach), and we controlled for major confounders including population stratification, age, and sex. The opposite genetic risk between CSC and AMD is not likely an artifact of misdiagnosed or underdiagnosed AMD given that (1) the discordant effect sizes in some loci do not fit a pattern

of systematic misdiagnosis of AMD as CSC, (2) AMD was excluded symmetrically from cases and controls in the biobank-based cohorts, and (3) undiagnosed AMD in the controls should manifest in reverse associations with CSC in all AMD loci, which we did not observe. Further study is needed to understand the implications of this association.

Strengths and Limitations

This study has several strengths. It was the first, to our knowledge, CSC GWAS meta-analysis to date, increasing sample size beyond 2 previous discovery GWASs. It encompassed an earlier European cohort, and although the case counts are comparable to previous Japanese cohorts,[22,23] the meta-analysis design and expansion of controls (526 787 compared with 13 029) were likely reasons for the discovery of 5 loci compared with 1 to 2 loci in previous GWASs.

This study has important limitations. Most importantly, in the FinnGen study and EstBB, patients with CSC were identified based on *ICD* codes; review of medical records or imaging was not possible. However, genetic similarity between case definitions is supported by cross-cohort homogeneity and lack of age of onset dependency in lead variant effect estimates. Second, sample sizes and statistical power differ in GWAS and PGS analyses of AMD and CSC, which limits interpretation. Finally, the study samples were of European origin; more work is needed to generalize these results.

Conclusions

In conclusion, in this 3-cohort meta-analysis, we combined 3 CSC cohorts and reported 5 associated loci—3 of which are novel. Three of the 5 loci contain complement genes, and prioritized genes overall are expressed in choroidal tissue specimens compared with others.

ARTICLE INFORMATION

Accepted for Publication: February 12, 2023.

Published Online: April 20, 2023. doi:10.1001/jamaophthalmol.2023.0706

Author Affiliations: Institute for Molecular Medicine Finland (FIMM), Helsinki Institute of Life Science (HiLIFE), University of Helsinki, Helsinki, Finland (Rämö, Jukarainen, Kiiskinen, Kajanne, Mehtonen, Palta, Kurki, Daly, Palotie); Massachusetts Eye and Ear, Boston (Rämö); Cardiovascular Disease Initiative, Broad Institute of MIT and Harvard, Cambridge, Massachusetts (Rämö, Wang, Choi, Lubitz, Ellinor); Cardiovascular Research Center, Massachusetts General Hospital, Boston (Rämö); Department of Ophthalmology, Leiden University Medical Center, Leiden, the Netherlands (Abner, Brinks, Palta, Esko); Estonian Genome Center, University of Tartu, Tartu, Estonia (van Dijk, Nikopensius, Nõukas, Boon); Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia (Nõukas, Esko); Finnish Institute for Health and Welfare, Helsinki, Finland (Marjonen, Silander); Department of Biostatistics, Boston University, Boston, Massachusetts (Choi); Cardiovascular Research Center, Massachusetts General Hospital, Harvard Medical School, Boston (Lubitz, Ellinor); Department of Ophthalmology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland (Kaarniranta); Harvard Medical School Department of Ophthalmology, Massachusetts Eye and Ear, Boston (Sobrin, Rossin); Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, Massachusetts (Kurki); Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston (Kurki, Palotie); Department of Ophthalmology, Radboud University Medical Center, Nijmegen, the Netherlands (Yzer, den Hollander); Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands (Yzer); Analytic and Translational Genetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston (Daly); Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts (Daly, Palotie); Genomics Research Center, AbbVie, Cambridge, Massachusetts (den Hollander); Department of Neurology, Massachusetts General Hospital, Boston (Palotie); Analytic and Translational Genetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston (Palotie); Folkhälsan Research Center, Biomedicum, Helsinki, Finland (Turunen); Department of Ophthalmology, University of Helsinki, Helsinki, Finland (Turunen); Department of Ophthalmology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands (Boon); Broad Institute of MIT and Harvard, Cambridge, Massachusetts (Rossin).

Author Contributions: Drs Rossin and Rämö had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Rämö, van Dijk, Kiiskinen, Kajanne, Kaarniranta, Sobrin, den Hollander, Palotie, Turunen, Rossin.
Acquisition, analysis, or interpretation of data: Rämö, Abner, van Dijk, Wang, Brinks, Nikopensius, Marjonen-Lindblad, Silander, Jukarainen, Choi, Mehtonen, Palta, Sobrin, Kurki, Yzer, Ellinor, Esko, Daly, Turunen, Boon, Rossin.
Drafting of the manuscript: Rämö, Nikopensius, Kajanne, Kaarniranta, den Hollander, Rossin.
Critical revision of the manuscript for important intellectual content: Rämö, Abner, van Dijk, Wang, Brinks, Marjonen-Lindblad, Silander, Jukarainen, Kiiskinen, Choi, Mehtonen, Palta, Sobrin, Kurki, Yzer, Ellinor, Esko, Daly, den Hollander, Palotie, Turunen, Boon, Rossin.
Statistical analysis: Rämö, Abner, Wang, Marjonen-Lindblad, Jukarainen, Choi, Kurki, Esko, Rossin.
Obtained funding: Rämö, Abner, Ellinor, Palotie, Boon, Rossin.
Administrative, technical, or material support: Abner, Brinks, Silander, Kiiskinen, Kajanne, Palta, Daly, Boon, Rossin.
Supervision: Palta, Sobrin, Ellinor, den Hollander, Palotie, Turunen, Boon, Rossin.

Conflict of Interest Disclosures: Dr Rämö reported receiving a personal research grant from The Mary and Georg C. Ehrnrooth Foundation during the conduct of the study. Dr Abner reported receiving grants from the European Commission Horizon 2020 Framework Programme and the European Commission European Regional Development Fund during the conduct of the study. Dr Lubitz reported receiving grants from Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, Fitbit, IBM, Medtronic, and Premier; personal fees from Blackstone Life Sciences, Invitae, Bristol Myers Squibb, Bayer, and Pfizer; and being a full-time employee of Novartis outside the submitted work. Dr Ellinor reported receiving sponsored research support from Bayer AG, IBM Health, Bristol Myers Squibb and Pfizer; and serving on advisory boards or consulting for Bayer AG, MyoKardia, and Novartis. Dr Daly reported being a founder of Maze Therapeutics outside the submitted work. Dr den Hollander reported receiving personal fees from and being a full-time employee of AbbVie outside the submitted work. Dr Palotie reported receiving grants from Academy of Finland, the FinnGen project, 13 pharma partners, and Business Finland during the conduct of the study. No other disclosures were reported.

Funding/Support: This work was supported in part by a research fellowship from the Mary and Georg C. Ehrnrooth Foundation (Dr Rämö); grant K12EY016335 from the National Institutes of Health and the Massachusetts Lions Eye Research Fund (Dr Rossin); grants 312074 and 336824 from the Academy of Finland Centre of Excellence in Complex Disease Genetics (Dr Palotie); grant 333302 from the Academy of Finland (Dr Kaarniranta); grant 341747 from the Academy of Finland (Dr Jukarainen); grants 1RO1HL092577, 1RO1HL157635, and 5RO1HL139731 from the National Institutes of Health, grant 18SFRN34110082 from the American Heart Association Strategically Focused Research Networks, and grant MAESTRIA 965286 from the European Union (Dr Ellinor); Stichting Ooglijders (Rotterdam, the Netherlands), Stichting Macula Fonds, Retina Nederland Onderzoek Fonds, Stichting Blinden-Penning, Algemene Nederlandse Vereniging ter Voorkoming van Blindheid, Landelijke Stichting voor Blinden en Slechtzienden (which contributed through UitZicht), Rotterdamse Stichting Blindenbelangen (Rotterdam, the Netherlands), and Stichting Leids Oogheelkundig Ondersteuningsfonds (Leiden, the Netherlands);

the Gisela Thier Fellowship of Leiden University (Dr Boon); the Netherlands Organization for Scientific Research (Dr Boon); grants HUS 4685/31/2016 and UH 4386/31/2016 from Business Finland and the following industry partners: AbbVie Inc, AstraZeneca UK Ltd, Biogen MA Inc, Bristol Myers Squibb (and Celgene Corporation & Celgene International II Sàrl), Genentech Inc, Merck Sharp & Dohme LCC, Pfizer Inc, GlaxoSmithKline Intellectual Property Development Ltd, Sanofi US Services Inc, Maze Therapeutics Inc, Janssen Biotech Inc, Novartis AG, and Boehringer Ingelheim International GmbH; grants 810645 and 894987 from the European Union through Horizon 2020 Research and Innovation Program; grants 2014-2020.4.01.15-0012 from Genomics and Translational Medicine; grant MOBEC008 from the Centre for Genomics, Evolution and Medicine; and grant PRG1291 from the Estonian Research Council.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The members of the FinnGen Study and the Estonian Biobank Research Team appear in Supplement 3.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We thank the participants and investigators of the FinnGen study and Estonian Biobank for their contributions; the team at Core Facility of Genomics and the Biobank Lab of the Estonian Biobank; and the following biobanks for delivering biobank samples to FinnGen: Arctic Biobank, Auria Biobank, THL Biobank, Helsinki Biobank, Biobank Borealis of Northern Finland, Finnish Clinical Biobank Tampere, Biobank of Eastern Finland, Central Finland Biobank, Finnish Red Cross Blood Service Biobank, Terveystalo Biobank, and The Finnish Hematology Registry and Clinical Biobank. No one received financial compensation for these contributions.

REFERENCES

1. Spaide RF, Campeas L, Haas A, et al. Central serous chorioretinopathy in younger and older adults. *Ophthalmology*. 1996;103(12):2070-2079. doi:10.1016/S0161-6420(96)30386-2

2. Kitzmann AS, Pulido JS, Diehl NN, Hodge DO, Burke JP. The incidence of central serous chorioretinopathy in Olmsted County, Minnesota, 1980-2002. *Ophthalmology*. 2008;115(1):169-173. doi:10.1016/j.ophtha.2007.02.032

3. Brinks J, van Dijk EHC, Tsonaka R, Meijer OC, Boon CJF. Sex hormones in males and females with active central serous chorioretinopathy. *Ophthalmologica*. 2022;245(6):555-562. doi:10.1159/000526052

4. Brinks J, van Dijk EHC, Kiełbasa SM, et al. The cortisol response of male and female choroidal endothelial cells: implications for central serous chorioretinopathy. *J Clin Endocrinol Metab*. 2022;107(2):512-524. doi:10.1210/clinem/dgab670

5. Yannuzzi LA. Type-A behavior and central serous chorioretinopathy. *Retina*. 1987;7(2):111-131. doi:10.1097/00006982-198700720-00009

6. Chatziralli I, Kabanarou SA, Parikakis E, Chatzirallis A, Xirou T, Mitropoulos P. Risk factors for central serous chorioretinopathy: multivariate approach in a case-control study. *Curr Eye Res*. 2017;42(7):1069-1073. doi:10.1080/02713683.2016.1276196

7. Francis JH, Habib LA, Abramson DH, et al. Clinical and morphologic characteristics of MEK inhibitor–associated retinopathy: differences from central serous chorioretinopathy. *Ophthalmology*. 2017;124(12):1788-1798. doi:10.1016/j.ophtha.2017.05.038

8. Lee LC, Wu TJ, Huang KH, et al. Increased risk for central serous chorioretinopathy in nephrotic syndrome patients: a population-based cohort study. *J Chin Med Assoc*. 2021;84(11):1060-1069. doi:10.1097/JCMA.0000000000000591

9. Mylona I, Dermenoudi M, Tsinopoulos I, Floros G. Personality of patients with central serous chorioretinopathy. *Eur J Ophthalmol*. 2022;32(1):497-500. doi:10.1177/1120672120968763

10. Gajdzik-Gajdecka U, Dorecka M, Nita E, Michalska A, Miniewicz-Kurowska J, Romaniuk W. Indocyanine green angiography in chronic central serous chorioretinopathy. *Med Sci Monit*. 2012;18(2):CR51-CR57. doi:10.12659/MSM.882455

11. Lee WJ, Lee JH, Lee BR. Fundus autofluorescence imaging patterns in central serous chorioretinopathy according to chronicity. *Eye (Lond)*. 2016;30(10):1336-1342. doi:10.1038/eye.2016.113

12. Baran NV, Gürlü VP, Esgin H. Long-term macular function in eyes with central serous chorioretinopathy. *Clin Exp Ophthalmol*. 2005;33(4):369-372. doi:10.1111/j.1442-9071.2005.01027.x

13. Imamura Y, Fujiwara T, Margolis R, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. *Retina*. 2009;29(10):1469-1473. doi:10.1097/IAE.0b013e3181be0a83

14. Spaide RF, Gemmy Cheung CM, Matsumoto H, et al. Venous overload choroidopathy: a hypothetical framework for central serous chorioretinopathy and allied disorders. *Prog Retin Eye Res*. 2022;86:100973. doi:10.1016/j.preteyeres.2021.100973

15. Brinks J, van Dijk EHC, Meijer OC, Schlingemann RO, Boon CJF. Choroidal arteriovenous anastomoses: a hypothesis for the pathogenesis of central serous chorioretinopathy and other pachychoroid disease spectrum abnormalities. *Acta Ophthalmol*. 2022;100(8):946-959. doi:10.1111/aos.15112

16. Montero JA, Ruiz-Moreno JM. Optical coherence tomography characterisation of idiopathic central serous chorioretinopathy. *Br J Ophthalmol*. 2005;89(5):562-564. doi:10.1136/bjo.2004.049403

17. Nicholson B, Noble J, Forooghian F, Meyerle C. Central serous chorioretinopathy: update on pathophysiology and treatment. *Surv Ophthalmol*. 2013;58(2):103-126. doi:10.1016/j.survophthal.2012.07.004

18. Weenink AC, Borsje RA, Oosterhuis JA. Familial chronic central serous chorioretinopathy. *Ophthalmologica*. 2001;215(3):183-187. doi:10.1159/000050855

19. van Dijk EHC, Schellevis RL, Breukink MB, et al. Familial central serous chorioretinopathy. *Retina*. 2019;39(2):398-407. doi:10.1097/IAE.0000000000001966

20. Lehmann M, Bousquet E, Beydoun T, Behar-Cohen F. Pachychoroid: an inherited condition? *Retina*. 2015;35(1):10-16. doi:10.1097/IAE.0000000000000287

21. Schellevis RL, van Dijk EHC, Breukink MB, et al. Exome sequencing in families with chronic central serous chorioretinopathy. *Mol Genet Genomic Med*. 2019;7(4):e00576. doi:10.1002/mgg3.576

22. Schellevis RL, van Dijk EHC, Breukink MB, et al. Role of the complement system in chronic central serous chorioretinopathy: a genome-wide association study. *JAMA Ophthalmol*. 2018;136(10):1128-1136. doi:10.1001/jamaophthalmol.2018.3190

23. Hosoda Y, Miyake M, Schellevis RL, et al. Genome-wide association analyses identify 2 susceptibility loci for pachychoroid disease central serous chorioretinopathy. *Commun Biol*. 2019;2:468. doi:10.1038/s42003-019-0712-z

24. Akiyama M, Miyake M, Momozawa Y, et al. Genome-wide association study of age-related macular degeneration reveals 2 new loci implying shared genetic components with central serous chorioretinopathy. *Ophthalmology*. 2022;S0161-6420(22)00900-9. doi:10.1016/j.ophtha.2022.10.034

25. Leitsalu L, Haller T, Esko T, et al. Cohort profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. *Int J Epidemiol*. 2015;44(4):1137-1147. doi:10.1093/ije/dyt268

26. Kurki MI, Karjalainen J, Palta P, et al. FinnGen: unique genetic insights from combining isolated population and national health register data. *bioRxiv*. Preprint posted online March 6, 2022. doi:10.1101/2022.03.03.22271360

27. Mitt M, Kals M, Pärn K, et al. Improved imputation accuracy of rare and low-frequency variants using population-specific high-coverage WGS-based imputation reference panel. *Eur J Hum Genet*. 2017;25(7):869-876. doi:10.1038/ejhg.2017.51

28. FinnGen. FinnGen home page. Accessed October 26, 2022. https://www.finngen.fi/en

29. Kurki MI, Karjalainen J, Palta P, et al; FinnGen. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature*. 2023;613(7944):508-518. doi:10.1038/s41586-022-05473-8

30. 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. doi:10.1038/s41588-021-00870-7

31. Zhou W, Nielsen JB, Fritsche LG, et al. Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. *Nat Genet*. 2018;50(9):1335-1341. doi:10.1038/s41588-018-0184-y

32. Mägi R, Morris AP. GWAMA: software for genome-wide association meta-analysis. *BMC Bioinformatics*. 2010;11:288. doi:10.1186/1471-2105-11-288

33. Breukink MB, Schellevis RL, Boon CJF, et al. Genomic Copy Number Variations of the Complement Component C4B Gene Are Associated With Chronic Central Serous Chorioretinopathy. *Invest Ophthalmol Vis Sci*. 2015;56(9):5608-5613. doi:10.1167/iovs.15-17343

34. Weeks EM, Ulirsch JC, Cheng NY, et al. Leveraging polygenic enrichments of gene features to predict genes underlying complex traits and

diseases. *bioRxiv*. Preprint posted online September 10, 2020. doi:10.1101/2020.09.08.20190561

35. Voigt AP, Whitmore SS, Mulfaul K, et al. Bulk and single-cell gene expression analyses reveal aging human choriocapillaris has proinflammatory phenotype. *Microvasc Res*. 2020;131:104031. doi:10.1016/j.mvr.2020.104031

36. Voigt AP, Mulfaul K, Mullin NK, et al. Single-cell transcriptomics of the human retinal pigment epithelium and choroid in health and macular degeneration. *Proc Natl Acad Sci U S A*. 2019;116(48):24100-24107. doi:10.1073/pnas.1914143116

37. Voigt AP, Binkley E, Flamme-Wiese MJ, et al. Single-cell RNA sequencing in human retinal degeneration reveals distinct glial cell populations. *Cells*. 2020;9(2):438. doi:10.3390/cells9020438

38. Voigt AP, Whitmore SS, Flamme-Wiese MJ, et al. Molecular characterization of foveal vs peripheral human retina by single-cell RNA sequencing. *Exp Eye Res*. 2019;184:234-242. doi:10.1016/j.exer.2019.05.001

39. 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. doi:10.1038/ng.3448

40. Naikawadi RP, Cheng N, Vogel SM, et al. A critical role for phosphatidylinositol (3,4,5)-trisphosphate-dependent Rac exchanger 1 in endothelial junction disruption and vascular hyperpermeability. *Circ Res*. 2012;111(12):1517-1527. doi:10.1161/CIRCRESAHA.112.273078

41. Robey E. Regulation of T cell fate by notch. *Annu Rev Immunol*. 1999;17:283-295. doi:10.1146/annurev.immunol.17.1.283

42. Lawson ND, Scheer N, Pham VN, et al. Notch signaling is required for arterial-venous differentiation during embryonic vascular development. *Development*. 2001;128(19):3675-3683. doi:10.1242/dev.128.19.3675

43. Carlson TR, Yan Y, Wu X, et al. Endothelial expression of constitutively active Notch4 elicits reversible arteriovenous malformations in adult mice. *Proc Natl Acad Sci U S A*. 2005;102(28):9884-9889. doi:10.1073/pnas.0504391102

44. Camelo S, Raoul W, Lavalette S, et al. Delta-like 4 inhibits choroidal neovascularization despite opposing effects on vascular endothelium and macrophages. *Angiogenesis*. 2012;15(4):609-622. doi:10.1007/s10456-012-9290-0

45. Yamamoto H, Fara AF, Dasgupta P, Kemper C. CD46: the 'multitasker' of complement proteins. *Int J Biochem Cell Biol*. 2013;45(12):2808-2820. doi:10.1016/j.biocel.2013.09.016

46. McLaughlin BJ, Fan W, Zheng JJ, et al. Novel role for a complement regulatory protein (CD46) in retinal pigment epithelial adhesion. *Invest Ophthalmol Vis Sci*. 2003;44(8):3669-3674. doi:10.1167/iovs.02-0813

47. Lin G, Finger E, Gutierrez-Ramos JC. Expression of CD34 in endothelial cells, hematopoietic progenitors, and nervous cells in fetal and adult mouse tissues. *Eur J Immunol*. 1995;25(6):1508-1516. doi:10.1002/eji.1830250606

48. Sohn EH, Flamme-Wiese MJ, Whitmore SS, Wang K, Tucker BA, Mullins RF. Loss of CD34 expression in aging human choriocapillaris endothelial cells. *PLoS One*. 2014;9(1):e86538. doi:10.1371/journal.pone.0086538

Invited Commentary

What Can We Learn From the Surprising Insight Into the Genetic Background of Age-Related Macular Degeneration and Central Serous Chorioretinopathy?

Samer Khateb, MD, PhD; Itay Chowers, MD; Michelle Grunin, PhD

Important insights into the pathophysiology and underlying genetic causes of central serous chorioretinopathy (CSC) were provided in recent years, but comprehensive understanding of the disease and its genetics are still lacking. Although mendelian inheritance is unlikely in this case, a multifactorial etiology involving acquired environmental risk factors together with genetic susceptibility factors may consist of the pathological basis of CSC. The meta-analysis by Rämö and his colleagues[1] replicated 2 previously reported risk loci (near *CFH* and *GATA5*) and identified an additional 3 novel risk alleles (near *CD34/46*, *NOTCH4*, and *PREX1*) in a total of 1176 patients with CSC compared with 526 787 controls, using a genome-wide association study (GWAS). Polygenic priority score (PPS) and nearest-gene methods were used to assess prioritized genes in the associated loci in publicly available cultured choroidal endothelial cells and ocular single-cell RNA sequencing data sets. Two of the 5 reported loci (*CFH* and some of the genes in the *NOTCH4* locus) were oppositely associated with AMD in this analysis.[1]

Related article page 449

The clinical presentation of CSC and AMD share some similarities such as retinal pigment epithelium (RPE) abnormalities, presence of pigment epithelial detachment (PED), serous detachment, and choroidal neovascularization (CNV). In addition, both AMD and CSC are considered complex diseases associated with environmental factors and clustering in families. However, there are also many dissimilarities between CSC and AMD, including different age at onset and gender propensity, unalike risk factors (eg, corticosteroids for CSC but not for AMD), distinguishable histopathological characteristics (ie, basal linear deposits and drusen for AMD), and different alteration patterns of the choroidal blood flow. Characteristic patterns for AMD and CSC are also present in imaging modalities such as fundus autofluorescence, fluorescein angiography, indocyanine green angiography, and optical coherence tomography.

Two previous larger GWASs on CSC have been reported, one on a subset including 521 European patients from the current study[2] and another on 1546 Japanese patients with CSC.[3] In the European population, a susceptibility locus near *CFH* was found, whereas in the Japanese study, susceptibility loci were detected near *GATA5* and *TNFRSF10A* as well as other AMD loci like *CFH*, *C2/FB*, and *ARMS2*. These findings of the involvement of the complement system genes and the overlap between AMD and CSC were found in other smaller studies as well. Both *CFH* and *TNFRSF10A* loci were previously associated with AMD.[4] However, the *TNFRSF10A* locus was not identified in the study by Rämö et al.[1] In a cohort from Japan, a *CFH* allele that is associated with high risk for AMD was also associated with increased choroidal thickness among patients with CSC. However, this locus was inversely associated in the CSC cohort with both choroidal thickness and with development of CSC. This indicates that there are important clinical features in both diseases directly associated with genetic findings and some that can potentially be used to differentiate