Central serous chorioretinopathy (CSC) is a common disease affecting younger people and may lead to vision loss. CSC shares phenotypic overlap with age-related macular degeneration (AMD). As recent studies have revealed a characteristic increase of choroidal thickness in CSC, we conducted a genome-wide association study on choroidal thickness in 3,418 individuals followed by TaqMan assays in 2,692 subjects, and we identified two susceptibility loci: *CFH* rs800292, an established AMD susceptibility polymorphism, and *VIPR2* rs3793217 (P = 2.05 × 10−10 and 6.75 × 10−8, respectively). Case-control studies using patients with CSC confirmed associations between both polymorphisms and CSC (P = 5.27 × 10−5 and 5.14 × 10−5, respectively). The *CFH* rs800292 G allele is reportedly a risk allele for AMD, whereas the A allele conferred risk for thicker choroid and CSC development. This study not only shows that susceptibility genes for CSC could be discovered using choroidal thickness as a defining variable but also, deepens the understanding of differences between CSC and AMD pathophysiology.

GWAS | choroidal thickness | CFH | VIPR2 | central serous chorioretinopathy

Central serous chorioretinopathy (CSC) constitutes a common eye disease characterized by serous detachment of the central retina (1). The incidence of CSC is reportedly around 10 per 100,000 in men and 2 per 100,000 in women (2). CSC can spontaneously resolve, but 30–50% of cases become chronic and/or recurrent, which results in severe retinal tissue damage and permanent vision loss (3–5). Recent studies suggest that eyes with CSC may be at higher risk of developing age-related macular degeneration (AMD) or its subtype of polypoidal choroidal vasculopathy (PCV) even after spontaneous resolution of CSC or that the development of CSC and AMD/PCV may share a common background (6, 7).

Although the precise pathogenesis of CSC has not yet been elucidated, genetic factors may contribute to CSC occurrence. Familial clustering of CSC has been reported (8–10), and the prevalence of CSC varies in different populations, being high in Caucasians and Hispanics, with the highest prevalence reported in Asians and an extremely low prevalence found in African Americans; these differences may also reflect genetic predisposition (11). To date, genome-wide association studies (GWAs) have not reported any susceptibility genes for CSC. However, three candidate gene studies have evaluated the established AMD susceptibility gene *CFH* as a putative gene in CSC (12–14). Notably, all reported that the *CFH* risk alleles associated with AMD appeared as protective alleles for CSC, although these two diseases might share pathophysiological overlap. There is no clear explanation of why these alleles in *CFH* confer opposite effects in the development of AMD and CSC. Other than *CFH*, no other susceptibility gene for CSC has been identified, although some candidate gene studies reported possible genes of interest (15–17).

**Significance**

Although central serous chorioretinopathy (CSC) presumptively shares pathophysiological basis with age-related macular degeneration (AMD), the *CFH* risk alleles for AMD are reportedly protective against CSC development. Our finding, that the *CFH* risk allele for AMD is protective against choroidal thickening in a Japanese cohort, indicates that *CFH* affects CSC development through its choroid-thickening effects rather than its association with AMD, highlighting the need for a new AMD classification, with CSC/pachychoroid-associated choroidal neovascularization as a distinct disease. Furthermore, our genome-wide association study (GWAS) addressing choroidal thickness successfully discovered a susceptibility gene for CSC: *VIPR2*. Future GWASs on choroidal thickness will likely discover additional CSC susceptibility genes and provide key molecules to elucidate the pathophysiological difference between CSC and AMD.
Recent progress in imaging technology for use in the diagnosis and monitoring of eye diseases has revealed that the choroid, from where fluid leaks into the subretinal space to cause retinal detachment in CSC, is thicker in eyes with CSC than in normal eyes (18). This finding is in accordance with a previous suggestion of choroidal vessel hyperpermeability in the pathogenesis of CSC and that increased choroidal thickness is considered the start of CSC development. Increased choroidal thickness is also reported to be inherited (19). In this study, we performed GWAS on choroidal thickness in a Japanese community-based cohort to discover putative candidate genes, and using case–control studies, we further evaluated whether there was an association between these discovered genes and CSC development. We found robust evidence of association of two susceptibility loci, rs800292 in CFH and rs3793217 in VIPR2, with choroidal thickness and CSC development.

Results

Two-Stage GWAS for Choroidal Thickness. To investigate and identify genetic loci associated with choroidal thickness, subfoveal choroidal thickness in the right eye was used as the dependent variable for genome-wide quantitative trait loci (QTL) analyses in 6,110 participants from the Nagahama Prospective Cohort for Comprehensive Human Bioscience (the Nagahama Study) (SI Appendix, Table S1). We included age, sex, axial length, and the first principal component as covariates. A genome inflation factor lambda of 0.9991 indicated excellent control of the study population substructure (SI Appendix, Fig. S1).

For this two-stage GWAS, experiment-wide significance was set at 5.0 × 10−8; additionally, we also tested SNPs with P values less than 5.0 × 10−7 in the replication stage as findings indicative of association. During the discovery stage using 4,710,779 SNPs from 3,418 participants, we identified genome-wide significant association near the CFH locus with rs7535394 (P = 2.44 × 10−8) (Fig. 1 and Table 1) and indicative evidence of association at VIPR2 with rs7782658 (P = 4.03 × 10−7). The respective SNP association plots for the CFH and VIPR2 regions are shown in Figs. 2 and 3, respectively. CFH rs7535394 was in moderate linkage disequilibrium with rs800292, which is a widely known susceptibility SNP for AMD (R2 = 0.721 in the discovery set). Because rs800292 also showed strong association with choroidal thickness (P = 8.43 × 10−8) in the discovery stage, we chose rs800292 as a candidate SNP to be analyzed in the replication stage.

Conversely, for another putative susceptibility SNP, rs7782658 at the VIPR2 locus, a commercially designed TaqMan probe was not available. Thus, to facilitate replication studies by other groups, we sought SNPs in commercially available microarrays. Among the VIPR2 SNPs found in both Illumina and Affymetrix microarrays, rs3793217 had the strongest association with choroidal thickness (P = 1.28 × 10−6) (Fig. 3). Because rs3793217 was in moderate linkage disequilibrium with rs7782658 (R2 = 0.605 in the discovery set), we analyzed rs3793217 in the replication stage (Fig. 3).

In the replication stage with 2,692 participants, both CFH rs800292 and VIPR2 rs3793217 showed significant association with choroidal thickness (P = 4.37 × 10−8 and P = 7.58 × 10−7, respectively). Meta-analysis of the discovery and replication sets further confirmed robust association of CFH rs800292 and VIPR2 rs3793217 with choroidal thickness (P = 2.05 × 10−10 and P = 6.75 × 10−8, respectively).

Association of CFH and VIPR2 with CSC. Next, the two SNPs identified during the GWAS for choroidal thickness, rs800292 in CFH and rs3793217 in VIPR2, were evaluated to determine whether they were associated with CSC in a Japanese case–control study. We collected 701 DNA samples of patients with CSC from five facilities in Japan, among which most of the samples from Kobe University Hospital had already been tested for an association between rs800292 and CSC (12). Thus, we used 539 CSC cases from the four remaining facilities for the case–control study of rs800292 by comparing its genotype distribution with that of the entire Nagahama cohort as a control group. The genotype distribution of rs800292 did not significantly deviate from Hardy–Weinberg equilibrium (HWE) in either our cohort of patients with CSC or Nagahama controls (both P > 0.05). In our test cohort, CFH rs800292 was associated with CSC development (P = 5.27 × 10−5) (Table 2).

To test for association between VIPR2 and CSC, we used all 701 CSC DNA samples. We found that rs3793217 was in HWE in both our CSC cohort and the Nagahama control cohort (P > 0.05) and that rs3793217 also showed significant association with CSC development in the Japanese (P = 4.59 × 10−4) (Table 3).

Although the association between CFH and CSC has been evaluated in other ethnicities (13, 14), an association between VIPR2 and CSC had not been investigated. Therefore, we conducted further replication analyses to test for evidence of an association between rs3793217 and CSC in a Korean population. In a case–control study using 425 patients with CSC and 1,643 controls, we found that rs3793217 showed significant association, with an odds ratio similar to that found in the Japanese analysis (P = 0.038). In addition, a meta-analysis using data from both
Association Between CFH and VIPR2 with Axial Length. Because choroidal thickness becomes thinner in eyeballs with a longer axial length (20), we next evaluated whether there was an association between rs800292 and rs3793217 with axial length in the right eye using the entire Nagahama cohort. In our cohort of 6,110 participants, we found no association between either rs800292 or rs3793217 with axial length (P = 0.074 and P = 0.30, respectively) on linear regression analysis.

Table 1. Discovery stage to identify SNPs associated with choroidal thickness

| SNP      | CHR | Position | Effect allele | EAF | Nearby genes | Discovery stage | Replication stage | Meta-analysis |
|----------|-----|----------|---------------|-----|--------------|-----------------|------------------|---------------|
| rs3753934 | 1   | 196620917| C             | 0.487| CFH (nearby) | 3,418 11.84 2.44 × 10⁻⁸ | —               | —             |
| rs800292  | 1   | 196642233| A             | 0.406| CFH (in gene)| 3,418 11.55 8.43 × 10⁻⁸ | 2,692 8.61 4.37 × 10⁻⁴ | 6,110 10.27 2.05 × 10⁻¹0 |
| rs7782658 | 7   | 158858007| A             | 0.307| VIPR2 (in gene) | 3,418 11.59 4.03 × 10⁻⁷ | —               | —             |
| rs3793217 | 7   | 158848821| G             | 0.213| VIPR2 (in gene)| 3,418 12.46 1.28 × 10⁻⁶ | 2,692 7.69 7.58 × 10⁻₃ | 6,110 10.34 6.75 × 10⁻₈ |

CHR, chromosome; EAF, effect allele frequency in the discovery stage.

ethnicity groups revealed additional support for an association between VIPR2 rs3793217 and CSC (P = 5.14 × 10⁻⁵).

Association of Previously Reported Putative CSC Susceptibility Genes with Choroidal Thickness and CSC in a Japanese Population. Of the SNPs analyzed in the discovery stage, no SNPs in the 4B region were associated with choroidal thickness (P > 0.05), although significant associations between 4B genomic copy numbers and CSC were previously reported (16). Within the regions of NR3C2 and CDH5, which are two previously reported putative susceptibility genes for CSC (15, 17), rs10519952 in NR3C2 (P = 0.030) showed nominally significant association with choroidal thickness in our GWAS discovery stage (SI Appendix, Figs. S2 and S3 and Table S2). However, no association was found for the SNP with CSC development in our case–control study using 250 Japanese CSC samples genotyped with the HumanExome chip and genome-wide genotyping data of 3,418 controls from the Nagahama cohort (SI Appendix, Table S3).

Discussion

Our GWAS using a Japanese cohort identified two genes significantly associated with choroidal thickness, CFH and VIPR2; moreover, these genes were also significantly associated with the occurrence of CSC in a Japanese case–control study. Although CFH constitutes an established susceptibility gene for AMD and three previous studies also reported an association between CFH and CSC (12–14), no prior GWAS has investigated CFH in relation to choroidal thickness. Furthermore, the conflicting report that the CFH risk alleles for AMD were protective for CSC, two diseases with a possible shared pathophysiological basis, has not been clearly explained. Our GWAS discovery of a significant association between CFH and choroidal thickness suggested that CFH affects the occurrence of CSC via its effects on choroidal thickness rather than via the previously suspected pathophysiological overlap between CSC and AMD. In turn, our findings regarding VIPR2 were supported by the replication of its association with CSC in a Korean cohort. Considering that the minor allele frequency of VIPR2 rs3793217 is low in many ethnicities, haplotype-tagged SNP analysis may be needed for further replication studies in other populations, which is warranted to determine whether VIPR2 represents a common susceptibility gene for CSC or is specific to Asian populations.

Using choroidal thickness in GWAS to discover susceptibility genes for CSC is demonstrably warranted, because hyperpermeability of choroidal vessels has been considered a strong candidate as the main cause of CSC for over 50 y (21). Choroidal hyperpermeability is predicted to result in a thicker choroid; accordingly, recent progress in eye imaging technology has enabled us to confirm a thick choroid in the eyes of most patients with CSC (18). Although some patients with CSC have a thinner choroid than normal and not all eyes with a thicker choroid will develop CSC, the discovery of two potential susceptibility genes for CSC via GWAS for choroidal thickness supports the premise that a thick choroid makes up at least one of the major contributing factors in the development of CSC. Because recent population-based cohort studies often included optical coherence tomography (OCT) examination as part of their assessment, meta-analysis of GWASs for choroidal thickness measured by OCT may discover additional susceptibility genes for CSC. The fact that not all eyes with a thicker choroid develop CSC likely indicates that CSC develops via a multistep process. The first step is increased choroidal thickness, which may confer greater susceptibility to CSC, with a second step that may include a trigger to cause CSC in those eyes with a thick choroid. Further studies using CSC cohorts subgrouped by genes associated with choroidal thickness may identify the genes associated with the next step of CSC development as representing the trigger causing CSC in eyes with a thicker choroid. Furthermore, as choroidal structure is complex, GWASs for choroidal vessel thickening/dilation, choroidal hyperpermeability, choroidal vascularity index, and choroidal thickness change in each individual might be able to specify more genes associated with choroidal thickness and CSC.

The discovery of genes associated with choroidal thickness and CSC occurrence signifies that treatment strategies for CSC may be developed by focusing on the mechanisms that underlie thicker choroid. It is well-known that CFH is expressed in choroidal vessels (22) and that VIPR2 is expressed in the retina and choroid (23, 24). Pathways including CFH or VIPR2 may serve as promising targets to treat CSC by controlling choroidal thickness.

Fig. 2. Regional association plots for genotyped SNPs in CFH regions. Plots show the −log10(P values) obtained from the first-stage GWAS. Each P value was calculated by age-, sex-, axial length-, and first principal component-adjusted QTL analysis.
have minor roles in myopia development. Both (23, 30). However, there were no previous re-
washed was not included as 1 of 51 major myopia-related
and MAF
and Regional association plots for genotyped SNPs in
and axial length/myopia by evaluating other
and gene copy number variations in
values) obtained from the first-stage GWAS. Each
CFH
may thus directly influence CSC occurrence by af-
factors in various vascular tissues (27–29). Further studies on
CFH
and VIPR2 pathways are warranted to identify new treat-
mets for CSC.

An important factor in the interpretation of associations be-
tween CFH and VIPR2 with choroidal thickness and CSC is the
size of the eyeball as determined by axial length. A longer axial
length results in myopia (nearsightedness). Because choroidal
thickness is thinner in myopic eyeballs with a longer axial length
(20), we included axial length as an adjustment factor in our
GWAS on choroidal thickness. In fact, in addition to its associ-
ation with choroidal thickness and CSC occurrence, rs800292
showed indicative, but not significant, association with axial
length in our Japanese cohort (P = 0.073). Although VIPR2
did not show significant association with axial length, two previous
studies in Chinese populations showed a significant association
between VIPR2 and axial length/myopia by evaluating other
SNPs in VIPR2 (23, 30). However, there were no previous re-
ports regarding the association of CFH with axial length/myopia,
and VIPR2 was not included as 1 of 51 major myopia-related
genes reported in large-scale GWASs for myopia using more
than 45,000 samples (31, 32), an omission that suggests that CFH
and VIPR2 have minor roles in myopia development. Both CFH
and VIPR2 may thus directly influence CSC occurrence by af-
fecring choroidal thickness rather than through their effect on
axial length.

In this study, we generated robust evidence that CFH constitu-
tes a susceptibility gene for CSC. Notably, CFH is also an
established susceptibility gene for AMD (22). Our previous study
showed that the G allele of rs800292 in CFH was a risk allele for
AMD with an odds ratio of 2.12 in the Japanese (33). In com-
parsion, the rs800292 A allele was a risk allele for CSC with an
odds ratio of 1.30 in this study, with previous studies also
reporting the A allele as a risk allele for CSC with odds ratios of
1.66 and 1.50 in Japanese (12) and Caucasians (13), respectively.
We posit that the recent findings of choroidal thickness being
thinner in AMD and thicker in CSC (34) can be accounted for by
the effects of the rs800292 G allele toward reducing choroidal
thickness in AMD and the A allele toward promoting thicker
choroid in CSC.

The possibility of a pathophysiological overlap between CSC
and AMD has facilitated analyses toward identifying associations
between CSC and AMD (6) or between CSC and AMD susceptibility
genes (13). However, an overlap between the path-
physiology of these diseases cannot explain the opposing effects
conferred by the same genetic polymorphisms in the respective
development of CSC and AMD. Recently, another theory was
proposed that a thick choroid, termed pachychoroid from the
ancient Greek, serves as a common background of CSC and an
AMD-like disorder that should be distinguished from AMD
named pachychoroid neovasculopathy (PCN) (35). Thus, the
seemingly contrasting findings between CFH and AMD vs. CFH
and CSC/thick choroid in our study would support the need to
distinguish pachychoroid and PCN from AMD in clinical settings,
with the premise that PCN and AMD have different underlying
pathophysiologicals. Currently, a clear definition to differentiate
PCN from AMD has not yet been established, because PCN
shares many clinical characteristics with AMD. Further genetic
studies using choroidal thickness, CSC, PCN, and AMD may
reveal the detailed underlying relationships of these three dis-
ases and enable tailored treatment strategies in the future.

Candidate gene studies previously reported that SNPs in
CDH5 and NR3C2 and gene copy number variations in C4B, but
not SNPs, were significantly associated with CSC development
(15–17). In our GWAS discovery cohort, we found that no SNPs
or indels in C4B and CDH5 showed significant association
with choroidal thickness. Although an SNP in NR3C2 (P = 0.030)
showed nominally significant associations with choroidal thick-
ness, it was not significantly associated with CSC development.
Furthermore, because the allele effects were opposite from those
found in the original report, we concluded that CDH5 and
NR3C2 do not make up susceptibility genes for CSC in our
Japanese population.

In conclusion, using GWAS, we identified significant associ-
ations between CFH and VIPR2 with choroidal thickness and
robustly showed significant associations of CFH and VIPR2 with
the development of CSC. Based on our findings, we propose that
CFH and VIPR2 contribute to the pathogenesis of CSC via their
effects on choroidal thickness. Our findings also indicate that the
reveal in choroidal thickness found between CSC and AMD,
where CSC has a thicker choroid and AMD has a thinner
choroid, may be accounted for by genetic differences between
the two diseases. Our genetic study thus provides the basis for un-
derstanding the roles of choroidal thickness in CSC and AMD.

Methods

Study Participants for the Choroidal Thickness GWAS. The study population
consisted of healthy Japanese volunteers enrolled in the Nagahama Study. Participants
were recruited between 2008 and 2010 from the general population of
Nagahama in Japan (36, 37). Community residents living independently

| Table 2. Association between CFH rs800292 and CSC in the Japanese |
|-----------------------------|-----------------|------------|-----------------|-----------------|
| Ethnicity      | Major/minor allele | N  | MAF  | N  | MAF  | Odds ratio (95% CI) | P*         |
| Japanese       | G/A             | 6110| 0.401| 539| 0.464| 1.29 (1.14–1.47)   | 5.27 × 10⁻⁵ |

MAF, minor allele frequency.
*P values derived using χ² test.
and without physical impairment or dysfunction were eligible. Blood sampling was performed at the time of enrollment. Of the 9,804 recruited participants, 14 withdrew consent to participate, and 26 were excluded, because genetic analysis indicated an ethnic background other than Japanese. Participants were offered physical and ophthalmic evaluation 5 y after the baseline evaluation from 2013 to 2015, and 8,289 of the original 9,764 cohort members, ages between 34 and 80 y old, participated.

In the follow-up assessment, all subjects underwent ophthalmic examinations, including an objective determination of the refractive error and corneal curvature using an Autorefractor ARK-530 (Nidek), axial length measurements by partial coherence interferometry with an IOL Master (Carl Zeiss Meditec, Inc.), color fundus imaging using a CD-DG10 (Canon), and a cross-line scan of spectral domain OCT examination using an RS-3000 Advance (Nidek) with an enhanced depth imaging (EDI) technique.

In this study, we used a dataset of the follow-up measurements. Study subjects consisted of individuals with available DNA samples as well as age, sex, axial length, fundus imaging, and OCT data. Exclusion criteria included prior intraocular surgery (except for cataract surgery), laser photocoagulation, and the presence of other macular-involving diseases that may affect choroidal thickness, such as active CSC, neovascular AMD, dry AMD with geographic atrophy, retinal vein occlusion, retinoschisis, macular hole, focal choroidal excavation, drusen, retinal pigment epithelium (RPE) damage, pigment epithelium detachment, or macular edema. Subjects with poor-quality images of fundus OCT were excluded. Highly myopic samples with axial length longer than 26 mm were also excluded from the analysis.

The Kyoto University Graduate School and Faculty of Medicine Ethics Committee and the Nagahama Municipal Review Board of Personal Information Protection approved the study protocol and procedures used to obtain informed consent. All study procedures adhered to the tenets of the Declaration of Helsinki. All participants were fully informed regarding the purpose and procedures of the study, and written consent was obtained from each subject. Patient records and information were anonymized before analysis.

**Evaluation of Choroidal Thickness.** Images of the foveal line EDI OCT scans centered on the fovea in right eyes were used to measure choroidal thickness. The choroidal–scleral interface was defined manually as the hyperreflective line behind the large choroidal vessel layers, and choroidal thickness was automatically measured between the RPE line and the choroidal–scleral interface at 1,024 points along the horizontal and vertical scans. The average thickness of points 512 and 513 on both scans was defined as the subfoveal choroidal thickness.

**Genome-Wide SNP Genotyping and Statistical Analysis.** Genome-wide QTL analysis was performed using subfoveal choroidal thickness in the discovery set of the Nagahama cohort. For every SNP that passed quality control, we evaluated whether there was an association between genotype and subfoveal choroidal thickness using a multivariable linear regression, assuming an additive model. This regression framework allowed us to adjust for covariates, such as age, sex, axial length, and the first principal component. Genome-wide SNP genotyping was performed on samples from 5,324 participants who joined the Nagahama cohort from 2008 to 2009. A series of BeadChip DNA arrays (Illumina), namely HumanHap610 Quad (1,833 samples), HumanOmni2.5–4 (1,611 samples), HumanOmni2.5–8 (375 samples), HumanOmni2.5s (670 samples), CoreExome24 (1,727 samples), and HumanExome (670 samples), were used for the analysis. SNPs with a call rate <99%, a minor allele frequency <1%, or significant deviation ($P < 1.0 \times 10^{-9}$) from HWE were excluded from further statistical analysis. Samples with a call rate <95% were also excluded from the analysis. Subjects estimated to have an inactive CSC, fundus autofluorescence (FAF), fluorescence angiography (FA), and indocyanin green angiography (ICGA). CSC was defined as divided on the basis of subretinal fluid at the macular region on OCT together with a leakage on FA and choroidal vascular hyperpermeability on ICGA.

**Replication Genotyping for the Association Study on Choroidal Thickness.** In the replication stage, we used the remaining samples from the Nagahama cohort, rs800292 and rs3793217 were genotyped using TaqMan allelic discrimination probes (Applied Biosystems) with an ABI PRISM 7700 system (Applied Biosystems). Deviations in genotype distributions from HWE were assessed with the $\chi^2$ test. To determine whether there was an association between rs800292 and rs3793217 with choroidal thickness, the subfoveal choroidal thickness in the right eye was used as the dependent variable for multi-variable linear regression analysis, including age, sex, and axial length as covariates.

To replicate our findings from the GWAS of choroidal thickness, we used 2,692 samples from the remaining 3,314 individuals of the Nagahama Study; two samples with withdrawn consent, 94 samples without sufficient quality EDI OCT images, 44 samples with macular-involved diseases, 83 samples lacking the data of axial length, 135 samples with intraocular surgery or laser photocoagulation, and 264 samples with axial length >26 mm were excluded. A P value <0.05 was considered statistically significant.

**Diagnosis of Patients with CSC.** We recruited 701 unrelated Japanese patients with acute, chronic, or steroid-induced CSC from the Kyoto University Hospital, the Kobe University Hospital, the Yamanashi University Hospital, the Fukushima Medical University Hospital, and the Kagawa University Hospital. All procedures adhered to the tenets of the Declaration of Helsinki. The institutional review boards of the ethics committees of the participating institutions approved the study protocols. All patients were fully informed of the purpose and procedures of the study, and written consent was received from each patient before their participation in the study.

All of the patients underwent a comprehensive ophthalmic examination, including dilated funduscopy, color fundus photography, OCT examination including EDI, fundus autofluorescence (FAF), fluorescent angiography (FA), and indocyanin green angiography (ICGA). CSC was diagnosed as an eye with subretinal fluid at the macular region on OCT together with a leakage on FA and choroidal vascular hyperpermeability on ICGA.

*Table 3. Association between VIPR2 rs3793217 and CSC*

| Ethnicity | Major/minor allele | N | MAF | Odds ratio (95% CI) | P* |
|----------|-------------------|---|-----|-------------------|---|
| Japanese | A/G               | 6,110 | 0.213 | 701 0.254 | 1.26 (1.11–1.43) | 4.59 × 10^{-4} |
| Korean   | A/G               | 1,643 | 0.201 | 425 0.234 | 1.21 (1.01–1.45) | 0.038 |
| Meta     | —                 | 7,753 | 1,126 | 1.24 (1.12–1.38) | 5.14 × 10^{-5} |

MAF, minor allele frequency. *P values derived using $\chi^2$ test.
assessed in the CSC cohort with the χ² test. The χ² test for trend or its exact counterpart was used to compare the genotype distributions between two groups. A P value ≤ 0.05 was considered statistically significant.

Replication Study for Association of VIPR2 rs3793217 with CSC in Koreans.
We recruited 425 unrelated Korean patients with acute or chronic CSC at the Seoul National University Bundang Hospital (SNUBH) retina clinic. Control samples consisted of subjects recruited from visitors to the SNUBH healthcare center for regular medical checkups or from patients undergoing cataract surgery at the SNUBH retina clinic (n = 310). Control subjects were also participants of the Korean Longitudinal Study on Health and Aging (KLoSHA; n = 233) (44) and were from the Korean Reference Genome database (n = 1,100; available at 152.99.75.168/KRGDB). All procedures adhered to the tenets of the Declaration of Helsinki. The institutional review boards and the organizations Zeroji Club for help in conducting the Nagahama Study. This study was supported by a University Grant from Kyoto University; a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science & Technology in Japan; the Center of Innovation Program and the Global University Project from Japan Science and Technology Agency; the Practical Research Project for Rare/Intractable Diseases and the Comprehensive Research on Aging and Health Science Research Grants for Dementia R&D from Japan Agency for Medical Research and Development; and a research grant from the Takeda Science Foundation.

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Title: 
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