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^{-9}, 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

**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 $5.0 \times 10^{-8}$; additionally, we also tested SNPs with $P$ values less than $5.0 \times 10^{-7}$ 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 rs3753394 ($P = 2.44 \times 10^{-8}$) (Fig. 1 and Table 1) and indicative evidence of association at VIPR2 with rs7782658 ($P = 4.03 \times 10^{-7}$). The respective SNP association plots for the CFH and VIPR2 regions are shown in Figs. 2 and 3, respectively. CFH rs3753394 was in moderate linkage disequilibrium with rs800292, which is a widely known susceptibility SNP for AMD ($R^2 = 0.721$ in the discovery set). Because rs800292 also showed strong association with choroidal thickness ($P = 8.43 \times 10^{-8}$) 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 ($P = 1.28 \times 10^{-6}$) (Fig. 3). Because rs3793217 was in moderate linkage disequilibrium with rs7782658 ($R^2 = 0.605$ 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 ($P = 4.37 \times 10^{-4}$ and $P = 7.58 \times 10^{-4}$, respectively). Meta-analysis of the discovery and replication sets further confirmed robust association of CFH rs800292 and VIPR2 rs3793217 with choroidal thickness ($P = 2.05 \times 10^{-10}$ and $P = 6.75 \times 10^{-8}$, 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 ($P = 5.27 \times 10^{-5}$) (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 ($P = 4.59 \times 10^{-5}$) (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

![Fig. 1. Manhatten plots of the discovery-stage GWAS for subfoveal choroidal thickness. Each plot shows $-\log_{10}$(transformed $P$ values) for all SNPs. The upper horizontal line represents the genome-wide significance threshold of $5.0 \times 10^{-8}$, and the lower horizontal line represents the indicative threshold of $5.0 \times 10^{-7}$.](image-url)
VIPR2 risk alleles for AMD were protective for CSC, two × (0.030) and choroidal thickness suggested that × 2,692 8.61 4.37 affects the occurrence of CSC via its effects on choroidal and VIPR2; Regional association plots for genotyped SNPs in PN is expressed in the retina and × 10 region 2,692 7.69 7.58 values) obtained from the first-stage GWAS. Each = represents a common susceptibility gene constitutes an established susceptibility gene for AMD and × 10 genomic copy numbers and × 10 0.30, | rs3793217 and CSC (× 0.05), although no prior GWAS has investigated × CFH as promising targets to treat CSC by c × choroid (23, 24). Pathways including CFH or VIPR2 may serve × choroidal thickness may identify the genes associated with the × 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 × 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.

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

**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.

**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 C4B region were associated with choroidal thickness (P > 0.05), although significant associations between C4B 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.

<table>
<thead>
<tr>
<th>SNP</th>
<th>CHR</th>
<th>Position</th>
<th>Effect allele</th>
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<th>Nearby genes</th>
<th>Discovery stage</th>
<th>Replication stage</th>
<th>Meta-analysis</th>
</tr>
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<td>rs3753394</td>
<td>1</td>
<td>196620917</td>
<td>C</td>
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<td>2.44 × 10^{-8}</td>
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<td>CFH (in gene)</td>
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<td>9.15</td>
<td>8.43 × 10^{-8}</td>
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<td>A</td>
<td>0.307</td>
<td>VIPR2 (in gene)</td>
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<td>11.59</td>
<td>4.03 × 10^{-7}</td>
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<td>rs3793217</td>
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<td>G</td>
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<td>VIPR2 (in gene)</td>
<td>3,418</td>
<td>12.46</td>
<td>1.28 × 10^{-6}</td>
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CHR, chromosome; EAF, effect allele frequency in the discovery stage.
In addition, VIPR2 expression is up-regulated by Helicobacter pylori infection, a known risk factor of CSC development (25, 26). Notably, the VIPR2 agonist vasoactive intestinal peptide can control corticosteroid secretion in addition to its vasodilatory effects in various vascular tissues (27–29). Further studies on CFH and VIPR2 pathways are warranted to identify new treatments for CSC.

An important factor in the interpretation of associations between 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 association 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 reports 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 affecting choroidal thickness rather than through their effect on axial length.

In this study, we generated robust evidence that CFH constitutes 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 comparison, 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 pathophysiology 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 neovascularopathy (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 diseases 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 PASH1 are risk factors for CSC (36, 37). Community residents living independently of Nagahama in Japan (36, 37). Community residents living independently of Nagahama in Japan (36, 37). 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>
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<th>Ethnicity</th>
<th>Major/minor allele</th>
<th>N</th>
<th>MAF</th>
<th>Odds ratio (95% CI)</th>
<th>539</th>
<th>0.464</th>
<th>1.29 (1.14–1.47)</th>
<th>5.27 × 10⁻⁵</th>
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<tbody>
<tr>
<td>Japanese</td>
<td>G/A</td>
<td>6,110</td>
<td>0.401</td>
<td>539</td>
<td>0.464</td>
<td>1.29 (1.14–1.47)</td>
<td>5.27 × 10⁻⁵</td>
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</tbody>
</table>

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 using a cross-line scan of spectral domain OCT examination using an RS-3000 Advance (Nidek) with an enhanced depth imaging (EDI) technique. 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-involving 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), fluorescein 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. Eyes with AMD or PCV were excluded. Eyes with RPE damage or atrophic dependent tracks on FA or FAF and choroidal vascular hyperpermeability on ICGA were included as eyes with “inactive CSC,” despite an absence of documented subretinal fluid (38–41).

### Replication Genotyping for the Association Study on Choroidal Thickness
In the replication stage using 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 χ² 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 multivariable linear regression analysis, including age, sex, and axial length as between analyses.

### Table 3. Association between VIPR2 rs3793217 and CSC

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Major/minor allele</th>
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<th>N</th>
<th>MAF</th>
<th>N</th>
<th>MAF</th>
<th>Odds ratio (95% CI)</th>
<th>P*</th>
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<td>701</td>
<td>0.254</td>
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<td>1,126</td>
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<td>1.24 (1.12–1.38)</td>
<td>5.14 × 10⁻⁵</td>
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**MAF, minor allele frequency.** *P* values derived using χ² 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 VIPPR2 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 ethics committees of the institutions approved the study protocols. All participants were fully informed of the purpose and procedures of the study, and written consent was received from each participant. Patients with CSC were genotyped using the TaqMan SNP assay (Applied Biosystems), and controls from the SNUBH and the KLoSHA were genotyped with the OmniExpress array (Illumina). The genotypes of rs3793217 were directly determined from the chip.

Acknowledgments. We thank Ms. Hatsue Hamaoka for her assistance in genotyping. We also thank the Nagahama City Office and the nonprofit organization 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.