



# Natural Course of Pachychoroid Pigment Epitheliopathy

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**Purpose:** To investigate the natural course of pachychoroid pigment epitheliopathy (PPE).

**Design:** A retrospective cohort study.

**Subjects:** From the Kyoto central serous chorioretinopathy (CSC) cohort consisting of 548 patients with CSC as of September 2020, we included consecutive unilateral patients with acute or chronic CSC between January 2013 and December 2016.

**Methods:** All patients underwent complete ophthalmic examination, including multimodal imaging such as fundus autofluorescence, spectral-domain optical coherence tomography, and fluorescein angiography/indocyanine green angiography and/or optimal coherence tomography angiography. The fellow eyes of eyes diagnosed with CSC were screened for PPE, and their natural course was evaluated. We also evaluated the association of *ARMS2* rs10490924, *CFH* rs800292, *TNFRSF10A* rs13278062, and *GATA5* rs6061548 genotypes with the natural course.

**Main Outcome Measures:** Incidence of CSC, pachychoroid neovascularopathy, and pachychoroid geographic atrophy (GA).

**Results:** In total, 165 patients with unilateral CSC (mean age, 55.7 ± 12.6 years; female, 22.4%) were included from the Kyoto CSC cohort. Among them, 148 (89.7%) were diagnosed as having PPE in their non-CSC eye. Survival analysis revealed that 16.8% of PPE eyes developed CSC during the 6-year follow up, whereas non-PPE eyes did not. Although genetic factors did not have significant association with CSC development ( $P > 0.05$ , log-rank test), choroidal vascular hyperpermeability (CVH) and subfoveal choroidal thickness (SFCT) were significantly associated with CSC incidence ( $P = 0.001$ , log-rank test). Survival analysis showed that eyes without CVH and eyes with SFCT < 300 μm did not develop CSC during the 6-year follow-up. Pachychoroid neovascularopathy developed in only 1 eye with PPE during a follow-up of 46.4 months. Pachychoroid GA did not develop in any of the studied eyes.

**Conclusions:** This study revealed a natural history of PPE in a relatively large Japanese cohort. Choroidal vascular hyperpermeability and SFCT were significant risk factors for the development of CSC in PPE eyes. Although the current results cannot be generalized for all eyes with PPE, these findings present an important clinical implication. *Ophthalmology Science* 2022;2:100201 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Pachychoroid pigment epitheliopathy (PPE) is a relatively new disease concept first introduced by Freund et al in 2013.<sup>1</sup> It is characterized by pachychoroid features, such as choroidal vascular hyperpermeability (CVH), dilatation of choroidal vessels, and increased choroidal thickness, that are associated with retinal pigment epithelium abnormalities.<sup>1</sup> As PPE cannot present subretinal fluid by its definition, the disease is considered to be a “forme fruste” of central serous chorioretinopathy (CSC).

After the recognition of pachychoroid neovascularopathy (PNV) as an important subtype of macular neovascularization (MNV),<sup>2–6</sup> pachychoroid spectrum diseases, including CSC, PNV,<sup>7</sup> pachychoroid geographic atrophy (GA),<sup>8</sup> and PPE,<sup>1</sup> have received much attention, especially in Asian countries where pachychoroid is relatively

common.<sup>9–11</sup> However, the pathogenesis of pachychoroid is not yet fully understood. Some studies have suggested that choroidal congestion may play a role in pachychoroid development.<sup>12–14</sup> We have also reported the involvement of genetic factors by conducting a 2-staged genome-wide association study of 1546 CSC cases and 13 029 controls from Asian and Caucasian participants.<sup>15,16</sup> Pachychoroid neovascularopathy reportedly shows a lower VEGF level in their aqueous humor,<sup>17,18</sup> and the presence of pachychoroid features is associated with good outcomes after anti-VEGF therapy.<sup>2,3</sup> Nevertheless, there are few existing studies on PPE.<sup>19</sup> One reason for this paucity of information is the fact that PPE is usually asymptomatic; therefore, patients with PPE alone do not visit an ophthalmology clinic. In addition, multimodal imaging is

required to diagnose PPE; hence, it is difficult to identify PPE even in a cohort study.

The only study that has evaluated the natural course of PPE was reported by Karacorlu et al in 2018.<sup>19</sup> They investigated 46 eyes of 44 Turkish patients and showed that 17.6% of PPE developed CSC, whereas none of the studied eyes developed PNV. We therefore need to further accumulate fundamental data on PPE, which is the underlying condition of pachychoroid spectrum diseases, to comprehend the pathogenesis of pachychoroid. In the current study, we evaluated the natural course of 165 PPE eyes among Asian patients. In addition, the involvement of genetic factors on CSC development from PPE was evaluated for the first time.

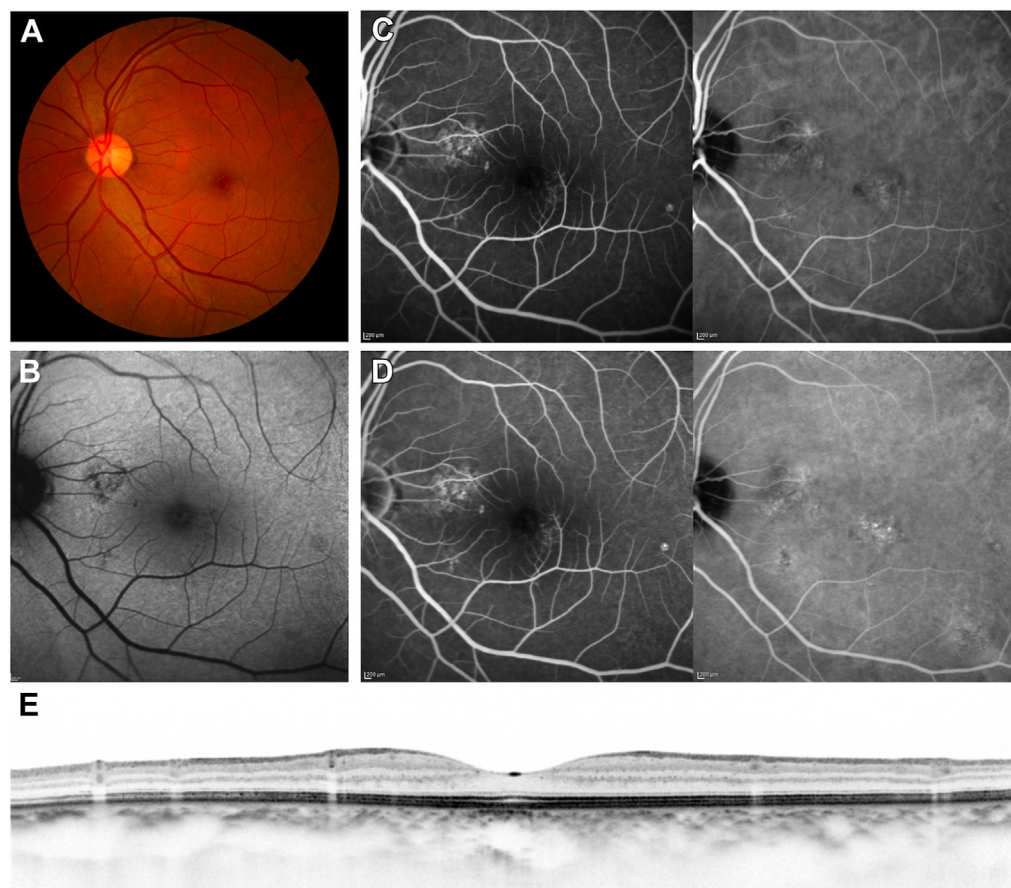
## Methods

This retrospective cohort study followed the tenets of the Declaration of Helsinki. This study was also approved by the ethics committee of the Kyoto University Graduate School of Medicine (G566). Written informed consent was obtained from all participants.

## Participants and Data Collection

In the current study, we screened the fellow eyes of eyes diagnosed with CSC to identify PPE. For that, we retrospectively reviewed the medical records of patients belonging to the Kyoto CSC cohort, which consisted of 548 patients with CSC as of September 2020.<sup>15</sup> We included consecutive patients (1) who had visited the macular clinic at the Kyoto University Hospital between January 2013 and December 2016 and agreed to participate in the genetic study (the participation rate was  $\geq 99\%$ ) and (2) who were diagnosed with unilateral acute or chronic CSC. All patients underwent a complete ophthalmic examination, including best-corrected visual acuity (BCVA), noncontact intraocular pressure, indirect ophthalmoscopy, slit-lamp biomicroscopy with a noncontact lens, color fundus photography, axial length measurement, fundus autofluorescence, spectral-domain OCT, fluorescein angiography/indocyanine green angiography (FA/ICGA), and/or OCT angiography.

Color fundus images were acquired through a Topcon TRC NW6S (Topcon) after medical dilatation of the pupil using phenylephrine 0.5% and tropicamide 0.5%. The axial length was measured by partial coherence interferometry (IOL Master, Carl Zeiss). Fundus autofluorescence and FA/ICGA images were obtained using HRA II (Heidelberg Engineering). Fundus



**Figure 1.** A representative case of pachychoroid pigment epitheliopathy. A 51-year-old female visited the macular clinic at Kyoto University Hospital with a diagnosis of central serous chorioretinopathy in her right eye. Her left eye was diagnosed with pachychoroid pigment epitheliopathy (PPE). The baseline visual acuity of the PPE eye was 20/15. Color fundus photography (A), fundus autofluorescence (B), early phase fluorescein and indocyanine green angiography (FA/ICGA) images and late phase FA/ICGA images (C, D, respectively), and spectral-domain-OCT (E) are shown. The multimodal imaging showed retinal pigment epithelium alteration (B) accompanied by choroidal vascular hyperpermeability on ICGA (C, D). Serous retinal detachment was not observed in spectral domain-OCT (E).

Table 1. Background Characteristics of the Study Participants

	All	Eyes with PPE	Eyes without PPE*	P Value
N	165	148 (89.7%)	17 (10.3%)	
Age [years] (mean [SD])	55.7 (12.6)	55.2 (12.5)	59.4 (13.1)	0.20
Sex, female (%)	37 (22.4)	33 (22.3)	4 (23.5)	1
Axial length [mm] (mean [SD])	24.02 (1.28)	23.97 (1.25)	24.54 (1.51)	0.098
CVH (%)	84 (51.5)	81 (55.5)	3 (17.6)	0.007
Follow-up period [months] (mean [SD])	40.0 (28.2)	39.5 (28.9)	44.9 (21.2)	0.51
SFCT [ $\mu$ m] (mean [SD])	350.0 (105.3)	360.6 (99.7)	264.0 (114.0)	< 0.001
logMAR (mean [SD])	-0.12 (0.09)	-0.12 (0.09)	-0.12 (0.06)	0.90
CFH, rs800292 (%)				0.24
AA	32 (19.8)	28 (19.3)	4 (23.5)	
AG	78 (48.1)	73 (50.3)	5 (29.4)	
GG	52 (32.1)	44 (30.3)	8 (47.1)	
TNFRSF10A, rs13278062 (%)				0.88
GG	65 (40.1)	59 (40.7)	6 (35.3)	
TG	67 (41.4)	59 (40.7)	8 (47.1)	
TT	30 (18.5)	27 (18.6)	3 (17.6)	
ARMS2, rs10490924 (%)				0.66
GG	63 (38.9)	58 (40.0)	5 (29.4)	
TG	79 (48.8)	69 (47.6)	10 (58.8)	
TT	20 (12.3)	18 (12.4)	2 (11.8)	
GATA5, rs6061548 (%)				0.44
CC	112 (69.1)	98 (67.6)	14 (82.4)	
TC	48 (29.6)	45 (31.0)	3 (17.6)	
TT	2 (1.2)	2 (1.4)	0 (0.0)	

CVH = choroidal vascular hyperpermeability; logMAR = logarithm of the minimum angle of resolution; PPE = pachychoroid pigment epitheliopathy; SD = standard deviation; SFCT = subfoveal choroidal thickness.

\*Including 1 pachychoroid neovasculopathy.

autofluorescence images ( $30^\circ \times 30^\circ$  centered on the macula) were acquired using an excitation light of 488 nm and a barrier filter beginning at 500 nm. Spectral-domain OCT was conducted using a Spectralis HRA + OCT (Heidelberg Engineering). Cross and raster scans centered on the fovea (angle of  $30^\circ$ ) were obtained, as well as cross scans through the enhanced depth imaging technique. OCT angiography imaging of the macula covering a  $6 \times 6$ -mm area was acquired using swept-source OCT (PLEX Elite 9000, Carl Zeiss Meditec).

## Diagnosis and Phenotyping

Referencing previous reports,<sup>1–3,8,19</sup> PPE was diagnosed in this study when all of the following conditions were present: (1) retinal pigment epithelium abnormality on the fundus autofluorescence image without preceding MNV, GA, or

subretinal fluid; (2) pachychoroid phenotype such as reduced fundus tessellation on color fundus photographs, pathologically dilated outer choroidal vessels on OCT and ICGA images, and regional CVH on ICGA images; and (3) no drusen except for nonextensive (total area, 125 mm) hard drusen (63 mm) (Age-Related Eye Disease Study level 1, no age-related macular degeneration). The existence of “type B drusen” or “type C drusen” following the definition of Spaide on color fundus photographs (i.e., pachydrusen) was allowed.<sup>20</sup>

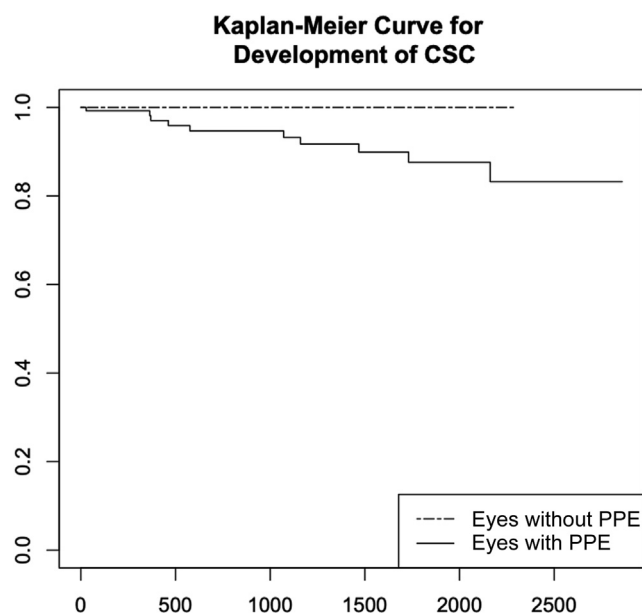
Subfoveal choroidal thickness (SFCT) was manually measured on horizontal enhanced depth imaging–OCT images and was defined as the vertical distance between Bruch’s membrane and the choriocleral interface at the fovea. Choroidal vascular hyperpermeability was determined by investigating the presence of multifocal hyperfluorescent areas with blurred margins that expanded during the late ICGA phase (i.e., 10–15 minutes after

Table 2. Development of Pachychoroid-Related Diseases During Long-term Follow-up

	Eyes with PPE		Eyes without PPE	
	N	Months	N	Months
All	148	-	17	-
Occurrence of central serous chorioretinopathy	10	31.3 $\pm$ 23.1 (0.9–72.1)	0	NA
Occurrence of pachychoroid neovasculopathy	1	46.4	0	NA
Occurrence of pachychoroid geographic atrophy	0	NA	0	NA

PPE = pachychoroid pigment epitheliopathy.

Mean  $\pm$  standard deviation (range) is presented (months).



**Figure 2.** The Kaplan–Meier curve for central serous chorioretinopathy (CSC) development stratified by the presence of pachychoroid pigment epitheliopathy (PPE) is shown. The number of non-PPE eyes was relatively small ( $n = 10$ , 7.8%), and non-PPE eyes did not develop CSC during the 6-year follow-up period. By contrast, the cumulative CSC incidence in PPE eyes was 16.8% in 6 years. This difference was not statistically significant because of the small number of non-PPE eyes ( $P = 0.30$ , log-rank test).

dye injection), according to the previous studies.<sup>21,22</sup> Pachychoroid neovascularopathy was confirmed through multimodal imaging, which included OCT, OCT angiography, and FA/ICGA.

These phenotypes and diagnoses were determined by 2 of 3 macular specialists (M.Y., Y.H., and M.M.). Discrepancies were discussed face to face to arrive at a consensus. The representative case of PPE is presented in [Figure 1](#).

### Genotyping and Single-Nucleotide Polymorphism Selection

Genotyping was performed as previously described.<sup>15</sup> Briefly, genomic DNA was extracted from peripheral blood samples according to standard laboratory procedures. All samples were genotyped using a series of BeadChip DNA arrays (Illumina), namely, OmniExpress and Asian Screening Array. Genotype imputation was performed using the Michigan imputation server (<https://imputationserver.sph.umich.edu/index.html#!pages/home>) with the 1000 Genome data set (phase III, version 5, release) of East Asians as a reference panel for each data set. In each data set, single nucleotide polymorphisms (SNPs) with a call rate < 90% or a minor allele frequency < 1% were excluded before genotype imputation. We extracted representative age-related macular degeneration susceptibility SNPs<sup>23,24</sup> *ARMS2* rs10490924 and *CFH* rs800292 and representative CSC susceptibility SNPs<sup>15,25,26</sup> *TNFRSF10A* rs13278062 and *GATA5* rs6061548.

### Statistical Analyses

Fisher exact test was employed to evaluate  $2 \times 2$  or  $2 \times 3$  tables. An unpaired *t* test was used to compare continuous variables. Differences in genotype distribution were evaluated using the chi-square test for trends. Survival analysis on the development of

subretinal fluid was conducted using the Kaplan–Meier method. Differences in the Kaplan–Meier curves between genotypes were evaluated using the log-rank test. A *P* value < 0.05 was considered statistically significant. These statistical analyses were conducted using R software, version 4.05 (<http://www.r-project.org/>). The CRAN package “survival” was used for survival analysis.

## Results

A total of 165 patients met the criteria for the current study. The demographics of the study subjects are summarized in [Table 1](#). The mean age was 55.7 years (standard deviation [SD], 12.6 years), and 22.4% of the patients were females. Patients were followed up for an average of 40.0 months (SD, 28.2 months; standard error, 2.2 months; range, 1–95.3 months). Among the 165 participants, 148 (89.7%) had PPE in the fellow eye of the CSC eye. Although there were no significant differences in age, sex, axial length, and BCVA between PPE and non-PPE eyes, PPE eyes showed a significantly higher rate of CVH (55.5% vs. 17.6%,  $P = 0.007$ ) and significantly thicker choroid ( $360.6 \pm 99.7 \mu\text{m}$  vs.  $264.0 \pm 114.0 \mu\text{m}$ ,  $P < 0.001$ ) than non-PPE eyes. There were no significant differences in genotype distributions. None of the participants used spirinolactone or eplerenone.

The occurrence of events is shown in [Table 2](#). We evaluated PPE eyes with at least 1 follow-up such that 129 PPE eyes were included for the subsequent analysis. Although 10 PPE eyes developed CSC during the mean follow-up duration of 31.3 months (SD, 23.1 months; standard error, 7.3 months; range, 0.9–72.1 months), the same did not occur in non-PPE eyes. Similarly, 1 PPE eye developed PNV during a follow-up duration of 46.4 months, but the same did not occur in non-PPE eyes. Pachychoroid GA was observed neither in PPE eyes nor in non-PPE eyes. [Figure 2](#) is a Kaplan–Meier curve for CSC development comparing PPE and non-PPE eyes. According to this Kaplan–Meier curve, the 1-, 2-, 4-, and 6-year survival rates in PPE eyes were 98.1% (95% confidence interval [CI], 95.5%–100%), 94.7% (95% CI, 90.2%–99.4%), 91.7% (95% CI, 85.9%–97.9%), and 83.2% (95% CI, 72.6%–95.3%), respectively.

The association between baseline parameters and the development of CSC in PPE eyes is shown in [Table 3](#). Age, sex, axial length, and BCVA were not significantly associated with CSC development. By contrast, CVH (100% vs. 52.1%,  $P = 0.009$ ) and SCFT ( $456.4 \pm 102.4 \mu\text{m}$  vs.  $349.8 \pm 97.9 \mu\text{m}$ ,  $P = 0.001$ ) exhibited significant associations with the development of CSC. Again, genotype distribution was not significantly different between eyes that developed CSC and those that did not. The Kaplan–Meier curve for CSC development in PPE eyes is shown in [Figure 3](#). During the 6-year follow-up, 32.5% of PPE eyes with CVH developed CSC, whereas PPE eyes without CVH did not ( $P = 0.001$ ). Among several cutoff values for SFCT, 350  $\mu\text{m}$  was determined as the most discriminative cutoff ( $P = 0.001$ ) compared with 400  $\mu\text{m}$  ( $P = 0.002$ ) and 300  $\mu\text{m}$  ( $P = 0.03$ ). Eyes with the SFCT of < 300  $\mu\text{m}$  did not develop CSC.

Table 3. Factors Associated with the Occurrence of CSC during the Follow-up Period

	Eyes with PPE That Developed CSC	Eyes with PPE That Did Not Develop CSC	P Value
N	10 (7.8%)	119 (92.2%)	-
Age [years] (mean [SD])	55.2 (14.7)	56.1 (12.1)	0.82
Sex, female (%)	1 (10.0)	29 (24.4)	0.52
Axial length [mm] (mean [SD])	23.81 (1.10)	23.96 (1.30)	0.71
CVH (%)	10 (100.0)	61 (52.1)	0.009
Follow-up period [months] (mean [SD])	59.5 (23.8)	37.8 (28.7)	0.022
SFCT [ $\mu\text{m}$ ] (mean [SD])	456.4 (102.4)	349.8 (97.9)	0.001
logMAR (mean [SD])	-0.08 (0.13)	-0.12 (0.09)	0.19
CFH, rs800292 (%)			0.66
AA	1 (10.0)	24 (20.7)	
AG	5 (50.0)	57 (49.1)	
GG	4 (40.0)	35 (30.2)	
TNFRSF10A, rs13278062 (%)			0.16
GG	2 (20.0)	46 (39.7)	
TG	7 (70.0)	45 (38.8)	
TT	1 (10.0)	25 (21.6)	
ARMS2, rs10490924 (%)			0.87
GG	5 (50.0)	48 (41.4)	
TG	4 (40.0)	54 (46.6)	
TT	1 (10.0)	14 (12.1)	
GATA5, rs6061548 (%)			0.87
CC	7 (70.0)	74 (63.8)	
TC	3 (30.0)	40 (34.5)	
TT	0 (0.0)	2 ( 1.7)	

CSC = central serous chorioretinopathy; CVH = choroidal vascular hyperpermeability; logMAR = logarithm of the minimum angle of resolution; PPE = pachychoroid pigment epitheliopathy; SD = standard deviation; SFCT = subfoveal choroidal thickness.

## Discussion

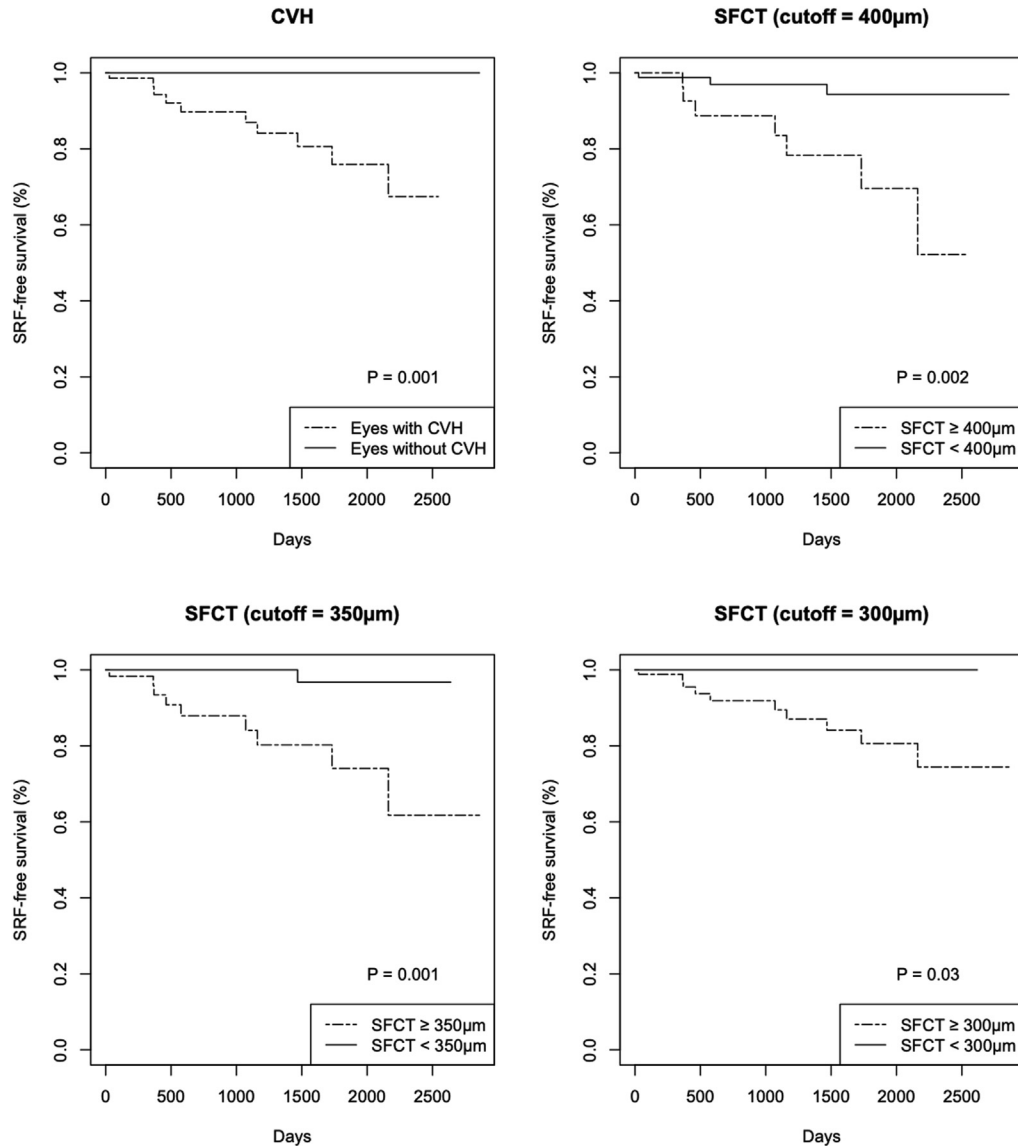
To the best of our knowledge, this is the largest study to describe the natural course of PPE eyes. Choroidal vascular hyperpermeability and SFCT were demonstrated to have a strong association with CSC development, whereas genetic factors did not. Interestingly, the survival analysis showed that eyes without CVH and eyes with the SFCT of  $< 300 \mu\text{m}$  did not develop CSC during the 6-year follow-up. Although the current result cannot be generalized for all eyes with PPE, we believe that our results have an important clinical implication.

Currently, we have continued the studies that focused on pachychoroid diseases including CSC,<sup>15,16,27</sup> PNV,<sup>2,3,28</sup> pachydrusen,<sup>29</sup> pachychoroid GA,<sup>8</sup> and focal choroidal excavation.<sup>30</sup> For instance, we were the first to propose the definition of PNV worldwide in 2015, which was updated in 2020 by applying the deep phenotype unsupervised machine learning method.<sup>2,3</sup> We also performed large genome-wide association studies and identified novel CSC susceptibility SNPs in 2019<sup>15</sup> and have reported 2 epidemiological studies: one was the epidemiology of CSC using Japan's National Insurance Claims Database, and the other was the normative data of choroidal parameters using the community-based cohort study in 2021.<sup>9,10</sup> Because pachychoroid spectrum diseases receive much attention as a novel underlying pathology of drusen, MNV, and GA, accumulation of the fundamental

data is expected. Nevertheless, there is only 1 other report about the natural history of PPE, which is a study from Turkey.<sup>19</sup>

The report from Turkey<sup>19</sup> involved 46 eyes of 44 Turkish patients, with a mean follow-up of  $1901 \pm 700$  days (5.2 years). All but 2 eyes came from the fellow eye of eyes with CSC or PNV, and the diagnosis was made without performing FA/ICGA.<sup>19</sup> Their reported CSC incidence of 8 of 46 (17.3%) PPE eyes during their follow-up period is similar to our results: a 6-year cumulative CSC incidence of 16.8%. Their results showed that eyes developing CSC had thicker choroid than those that did not; however, the association was not statistically significant ( $420.5 \mu\text{m}$  vs.  $375.5 \mu\text{m}$ ,  $P = 0.72$ ). Our study successfully identified SFCT as a strong predictive factor of CSC development in PPE eyes. According to our survival analysis (Figure 3), PPE eyes with the SFCT of  $< 300 \mu\text{m}$  at the baseline did not develop CSC within the follow-up period. The PPE eyes in the current study have a higher risk of CSC than general PPE eyes because CSC was already present in the fellow eyes.<sup>31</sup> Thus, we suggest that general PPE with the SFCT of  $< 300 \mu\text{m}$  is far less likely to develop CSC, at least during a 6-year period.

Another important risk factor for developing CSC was CVH,<sup>22,32</sup> which is a characteristic of pachychoroid diseases, in addition to choroidal filling delay and dilation of choroidal vessels. We have previously screened CVH in 438 consecutive patients who visited the Macular Service at the Kyoto University Hospital and who underwent FA/ICGA,



**Figure 3.** The Kaplan–Meier curves for central serous chorioretinopathy (CSC) development in pachychoroid pigment epitheliopathy (PPE) eyes stratified by the presence of choroidal vascular hyperpermeability (CVH) (top left), subfoveal choroidal thickness (SFCT) of  $\geq 400\ \mu\text{m}$  (top right), SFCT of  $\geq 350\ \mu\text{m}$  (bottom left), and SFCT of  $\geq 300\ \mu\text{m}$  (bottom right) are shown. Pachychoroid pigment epitheliopathy eyes without CVH did not develop CVH during the 6-year follow-up period, whereas PPE eyes with CVH had a cumulative CSC incidence of 32.5% in 6 years ( $P = 0.001$ ). Among all SFCT cutoff values, the most discriminating cutoff was  $350\ \mu\text{m}$  ( $P = 0.001$ ). Pachychoroid pigment epitheliopathy eyes with the SFCT of  $< 300\ \mu\text{m}$  did not develop CSC during the 6-year follow-up period. SRF = subretinal fluid.

which revealed that, in Japan, 26.1% of eyes with macular diseases had CVH.<sup>22</sup> By contrast, some previous studies have reported that the same is observed in 90% to 100% of eyes with CSC.<sup>33–35</sup> Because CVH is thought to represent choroidal congestion, which is a hypothetical pathology of pachychoroid diseases, the current result is plausible. Because all PPE eyes that developed CSC had CVH at their baseline in the current study, PPE eyes without CVH would also be less likely to develop CSC. Nevertheless, we need to standardize the definition of CVH to further understand the condition and the prediction of CSC.

Genetics is generally thought to be an important risk factor for CSC development;<sup>15,16,25,26</sup> however, the current study did not observe the statistically significant contribution of genetics on CSC development in PPE eyes. One possible reason is a lack of statistical power; we may have needed more samples to detect the contribution of genetics. However, because genotype distribution is similar between PPE eyes that developed CSC and those that did not, we think that the lack of association could be a true negative. At least, we can say we did not observe a clinically significant contribution.

The lack of association might also be because all of the current eyes came from fellow eyes of eyes with CSC such that they were already genetically susceptible to CSC. If we included general PPE eyes, genetics might have been able to predict CSC development from PPE.

The current study has strengths in its relatively large sample size, detailed multimodal imaging, and genetic association analysis. However, the current study also has certain limitations. First, the PPE eyes in the current study were recruited from the fellow eye of eyes with CSC. Thus, the PPE eyes in the current study might be different from general eyes with PPE. Because PPE is asymptomatic and requires multimodal imaging for its diagnosis, it is difficult to identify PPE in a hospital-based study or in a cohort study. A prospective PPE registry study is therefore needed to comprehend the natural history of general PPE. Second, we employed the date when PPE was identified through multimodal imaging as the date of PPE incidence because the accurate incidence date is unknown because of the abovementioned reasons. If we observed cases of very recently developed PPE, CSC development may take longer than that reported in our results. Third, although we excluded the eyes with suspected prior subretinal fluid based on the interview and the presence of apparent fundus autofluorescence change (such as descending tract), we cannot eliminate the possibility that the included eyes had

asymptomatic subretinal fluid previously, which led to an overestimation of PPE. Lastly, our study was retrospective; hence, the follow-up period was variable. In addition, survivorship bias could have been present. Nevertheless, our use of the survival analysis has minimized such potential bias. Because a prospective design requires considerable effort, we believe that a well-conducted retrospective study is a reasonable alternative in estimating the natural course of CSC.

In summary, the current study revealed the natural course of PPE in a relatively large cohort. The survival analysis showed that 16.8% of PPE eyes developed CSC within the 6-year follow-up period. Choroidal vascular hyperpermeability and SFCT were significant predictive factors for the development of CSC in PPE eyes but not genetic factors. Eyes without CVH and eyes with the SFCT of  $< 300 \mu\text{m}$  did not develop CSC during the 6-year follow-up. Although we cannot simply generalize the current results for all general eyes with PPE, our findings have an important clinical implication. Further studies on pachychoroid spectrum diseases are warranted.

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## Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. This retrospective cohort study followed the tenets of the Declaration of Helsinki. This study was also approved by the ethics committee of the Kyoto University Graduate School of Medicine. Written informed consent was obtained from all participants.

No animal subjects were included in this study.

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Dr Miyake had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors meet the criteria for authorship.

#### Abbreviations and Acronyms:

**BCVA** = best-corrected visual acuity; **CI** = confidence interval; **CSC** = central serous chorioretinopathy; **CVH** = choroidal vascular hyperpermeability; **FA** = fluorescein angiography; **GA** = geographic atrophy; **ICGA** = indocyanine green angiography; **MNV** = macular neovascularization; **PNV** = pachychoroid neovascularopathy; **PPE** = pachychoroid pigment epitheliopathy; **SD** = standard deviation;

**SFCT** = Subfoveal choroidal thickness; **SNPs** = single nucleotide polymorphisms.

#### Keywords:

central serous chorioretinopathy, pachychoroid, pachychoroid pigment epitheliopathy.

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