Different impact of high-density lipoprotein-related genetic variants on polypoidal choroidal vasculopathy and neovascular age-related macular degeneration in a Chinese Han population

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A B S T R A C T

Neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) are both major serosanguinous maculopathies among the Asian elderly. They are similar in phenotype. Genetic variants in high-density lipoprotein (HDL) pathway were discovered to be associated with AMD in two genome-wide association studies. In this study with a Chinese Han cohort, we investigated the impacts of these genetic variants on nAMD and PCV separately. The missense coding variants and previously identified variants at LIPC, ABCA1, CETP, LPL and FADS1 loci were genotyped in 157 nAMD patients, 250 PCV patients and 204 controls without any macular abnormality. The known variants in CFH, ARMS2 and near HTRA1 were also genotyped. Fasting serum cholesterol levels were determined. The variants in CFH, ARMS2 and near HTRA1 were strongly associated with both PCV (P < 10⁻⁶, 10⁻⁶ and 10⁻⁷ respectively) and nAMD (P < 10⁻⁶, 10⁻¹⁰ and 10⁻¹⁰ respectively). None of the studied HDL-related variants were significantly associated with nAMD. A missense variant in CETP, rs5882, was significantly associated with PCV (P = 2.73 × 10⁻³). The rs5882 GG genotype had a 3.53-fold (95% CI: 1.93–6.45) increased risk for PCV, and conferred a significantly lower serum HDL-cholesterol level for PCV patients than the AA genotype (P = 0.048). These results suggest the need to separate PCV from nAMD in association studies especially with Asian cohorts, and that the HDL pathway may involve in the pathogenesis of PCV and nAMD differently.

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1. Introduction

Polypoidal choroidal vasculopathy (PCV) and neovascular age-related macular degeneration (nAMD) are both the leading cause of irreversible vision impairment among Asian elderly (Byeon et al., 2008; Liu et al., 2007; Maruko et al., 2007; Wen et al., 2004). They are similar in clinical manifestation (Imamura et al., 2010; Laude et al., 2010). Indocyanine green angiography (ICGA) can be used to differentiate these two serosanguineous maculopathies morphologically. Although there is still some debate on the nature of PCV (Imamura et al., 2010), an increasing understanding of PCV and the widespread availability of ICGA has helped us to recognize PCV as a clinical entity, possibly distinct from nAMD. However, the differences between the pathogenesis of PCV and nAMD are mostly unknown. Genome-wide association studies (GWAS) for AMD have led to substantial discoveries, finding the risk loci such as the CFH and HTRA1/ARMS2 (Peter and Seddon, 2010). However, in those cohorts, PCV is not identified using ICGA and investigated separately. Several genetic association studies (Laude et al., 2010) that were designed to compare these two entities aimed to discover if these two different phenotypes can be attributed to genetic differences that may reveal different underlying pathogenic mechanisms. The genes complement factor 2 (C2) and complement factor B (CFB) (Lee et al., 2008) were found to be associated with nAMD, but not with PCV. Recently, we showed that a risk variant for intracranial aneurysm and coronary artery disease on chromosome 9p21 was associated with PCV, but not with nAMD (Zhang et al., 2011). In this study with an extended cohort, we investigated the serum cholesterol levels and the high-density lipoprotein (HDL)-related genetic variants, which were newly identified to be associated with AMD by two GWAS (Chen et al., 2010; Neale et al., 2010), and demonstrated the differential impacts of each on the risk of PCV and nAMD.

2. Patients and methods

2.1. Study population

This study was performed in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the
institutional review board at the Zhongshan Ophthalmic Center of Sun Yat-sen University. Written informed consent was obtained from all subjects for providing medical information and a blood sample.

All study subjects were unrelated Chinese Han individuals that were recruited from the Zhongshan Ophthalmic Center from June 2008 to July 2011. They were asked about their smoking status and alcohol consumption and were asked to provide a detailed medical history. All PCV and nAMD patients were newly diagnosed and treatment-naïve. They all underwent bilateral ophthalmic examinations including visual acuity measurements, slit-lamp biomicroscopy, ophthalmoscopy, color fundus photography, fluorescein angiography and ICGA. Diagnosis was based on the worst eye, but cases with comorbidity of any other retinal or choroidal disease in one or both eyes were excluded. The diagnosis of PCV was based on the identification of characteristic polypoidal choroidal vascular dilations with branching inner choroidal vascular network within the first 5 min after the injection of ICGA. Cases that were difficult to distinguish from nAMD and retinal angiomatous proliferation were excluded. The diagnosis of nAMD was based on the identification of typical choroidal neovascularization with both fluorescein angiography and ICGA. Patients with other neovascularized maculopathies, such as pathologic myopia, angioid streaks, multifocal choroiditis and punctate inner choroidopathy were excluded. All control subjects were aged ≥50 years and underwent ophthalmic examinations including visual acuity measurements, slit-lamp biomicroscopy, ophthalmoscopy and 50° color fundus photography. Those with macular degeneration of any cause, macular changes (such as drusen or pigment abnormalities), or media opacities preventing the clear visualization of the macula were excluded from the study.

2.2. Single nucleotide polymorphism (SNP) selection

Previously reported AMD-associated SNPs at HDL metabolism loci, as identified by GWAS (Chen et al., 2010; Neale et al., 2010), were selected. Meanwhile, to narrow down the candidate SNPs, only the missense coding SNPs, which would be more likely to influence the protein function, across the genes hepatic lipase (LIPC), ATP-binding cassette sub-family A member 1 (ABCA1), cholesteryl ester transfer protein (CETP), lipoprotein lipase (LPL) and fatty acid desaturase 1 (FADS1), with a minor allele frequency above 1% in HAPMAP-HCB (Han Chinese in Beijing, China, in the International HapMap project), were selected from the NCBI Entrez SNP database (http://www.ncbi.nlm.nih.gov/SNP/). The SNPs repeatedly confirmed to be associated with PCV and nAMD in complement factor H (CFH) (rs800292), age-related maculopathy susceptibility 2 (ARMS2) (rs10490924) and near HtrA serine peptidase 1 (HTRA1) (rs11200638) (Hayashi et al., 2010; Lee et al., 2008; Lima et al., 2010) were also included to confirm their association in the cohorts studied. Thus, a total of 17 candidate SNPs were selected and are listed in Supplementary Table 1.

2.3. Genotyping

The collection of a peripheral blood sample and the extraction of genomic DNA were performed as previously described (Li et al., 2010). The SNPs were genotyped using a Multiplex SNPShot system with an ABI 3730XL genetic analyzer (Applied Biosystems, Foster City, CA). The genotypes of the SNPs were determined using Genemapper software v4.1 (Applied Biosystems, Foster City, CA). The sequences of the primers used for each SNP are provided in Supplementary Table 1. To confirm the accuracy of the Multiplex SNPShot method, randomly selected subjects (10% of all samples) were analyzed by direct sequencing (Generay Biotech Co., Ltd., Shanghai, China). The primers that were used for the direct sequencing are available on request.

2.4. Serum analysis

Fasting serum samples were collected on the same day as the ophthalmic examinations and were analyzed for total cholesterol, HDL-cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c), as measured on a Hitachi 7170A automatic analyzer (Hitachi Ltd., Tokyo, Japan) using the Cholesterol (CHO) Assay kit (Hunan GmbH, Wiesbaden, Germany), the Cholestest-N HDL kit and the Cholestest-LDL kit (Sekisui Medical Co., Ltd., Tokyo, Japan), respectively.

2.5. Covariates

Clinical information and family histories were collected from medical records and interviews. A smoker was defined as having smoked at least 1 cigarette per day for at least 6 months. An alcohol drinker was defined as having at least 1 drink of beer, wine, or liquor per week for at least 6 months. A person with hypertension was diagnosed by having a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or because they were being treated with anti-hypertensive medication. Coronary artery disease was defined by a physician's diagnosis. Body weight and height were measured on the same day as the ophthalmic examinations. The body mass index was calculated as weight (kilograms) divided by height (meters) squared.

2.6. Statistical analysis

Differences in the demographic characteristics between cases and controls were assessed using unpaired Student’s t-tests for means and chi-squared tests for proportions using SPSS 13.0 software for Windows (SPSS Inc., Chicago, IL). Genetic association analyses were performed using the PLINK software package v1.07 (http://pngu.mgh.harvard.edu/~purcell/plink/index.shtml). Deviations from the Hardy–Weinberg equilibrium and allele frequencies between cases and controls were evaluated for each SNP using the exact test and the chi-square test in PLINK, respectively. The minor allele frequency was calculated based on all the case and control subjects. A Bonferroni correction was used to correct the P values obtained from the allele frequencies analysis. For the genotypeic additive model we used the logistic option in PLINK, which provided a test based on logistic regression; for the dominant and recessive model we used the model option in PLINK, which provided a chi-square test. Power calculation of single association was performed using PGA (Power for Genetic Association Analyses) software (Menashe et al., 2008), based on minor allele frequency and sample size, with relative risks at 1.8, disease prevalence of 0.56% for nAMD (Kawasaki et al., 2010) and 0.14% for PCV (Kawasaki et al., 2010; Liu et al., 2007), respectively, effective degrees of freedom of 17, and a false positive rate of 5%, under a co-dominant model (heterozygous vs. all homozygotes) with two degrees of freedom. Linkage disequilibrium patterns and haplotype association analyses were performed with the Haploview software package (Barrett et al., 2005) v4.2 (http://www.broadinstitute.org/haploview). Logistic regression analysis was used to estimate the adjusted odds ratio and 95% confidence intervals (CI) with the controlling factors known to be associated with the diseases. Model A was adjusted for gender, age, body mass index, smoking status, alcohol consumption and history of hypertension and coronary artery disease. Model B was adjusted for the same covariates as in model A plus the genotypes of rs800292 in FH (CC, CT, TT), rs10490924 in ARMS2 (TT, CT, CC) and rs11200638 near HTRA1 (AA, AG, GG). The Cochran–Armitage trend test was used to estimate the trend of proportions. A value of P < 0.05 was considered to be statistically significant.
3. Results

A total of 611 subjects were enrolled in this study including 250 patients with PCV, 157 patients with nAMD and 204 control individuals. The characteristics of the study population including gender, age, body mass index, smoking status, alcohol consumption and history of hypertension and coronary artery disease are summarized in Table 1. Nine patients with PCV (3.6%) and 1 patient with nAMD (0.6%) were under the age of 50. The mean age of the PCV patients was significantly lower than that of the control individuals (P < 0.001). The nAMD patients tended to have a higher incidence for hypertension (P = 0.025) and coronary artery disease (P = 0.003).

The genotypes were successfully determined using the SNPshot method for all 17 SNPs of all the subjects, and the randomly selected samples were completely verified using direct sequencing in the replicate samples. The results of Hardy–Weinberg equilibrium (HWE) analysis are summarized in Supplementary Table 2. The genotype distributions of the SNPs in ARMS2 (rs10490924), near HTRA1 (rs11200638) and near LPL (rs12678919) were in Hardy–Weinberg equilibrium (HWE) in the control group but not in the PCV or the nAMD groups. The genotype distribution of the rs3764261 near CETP was in HWE in the control and the nAMD groups, but not in the PCV group. The genotype distributions of the other SNPs that were studied in each group were all in HWE. The analysis results of the minor allele frequencies for the candidate SNPs in each group are summarized in Table 2. The following SNPs, rs800292 in CFH, rs10490924 in ARMS2 and rs11200638 near HTRA1, were strongly associated with PCV and nAMD. The associations with the CFH rs800292 were similar for PCV (P = 2.66 × 10⁻⁷) and nAMD (P = 9.01 × 10⁻⁷). The associations with the rs10490924 in ARMS2 and the rs11200638 near HTRA1 were weaker for PCV (P = 1.78 × 10⁻⁸ and 1.09 × 10⁻⁸, respectively) than for nAMD (P = 4.96 × 10⁻¹⁷ and 1.65 × 10⁻¹⁸, respectively). Among the HDL-related candidate SNPs, rs1883025 in ABCA1, rs3764261 near CETP and rs5882 in CETP exhibited evidence for association. However, we did not find any significant associations for the candidate SNPs near or in the LIPC, LPL or FADS1 genes. The ABCA1 rs1883025 was significantly associated with both PCV (P = 0.007) and nAMD (P = 0.016). The rs3764261 near CETP and the rs5882 in CETP were significantly associated with PCV (P = 0.003 and 2.73 × 10⁻⁴, respectively) but not with nAMD, although they remained significantly associated with the total case group (P = 0.018 and 0.003, respectively). The statistical powers to detect the associations of rs1883025, rs3764261 and rs5882 with PCV of this cohort were 79.8%, 84.0%, 89.7% and with nAMD were 68.0%, 63.5%, 81.1% respectively. After Bonferroni correction, only the association between CETP rs5882 and PCV remained significant (P = 2.73 × 10⁻⁴ × 3 = 1.03 × 10⁻⁹). The linkage disequilibrium structure across the genotyped SNPs in or near ABCA1 and CETP, based on the data of the control individuals, is shown in Supplementary Fig. 1. A single haplotype block (rs2066718 and rs1883025 for ABCA1 and rs5882 and rs2303790 for CETP) was outlined for each gene region according to the 4-gamete rule. A haplotype analysis based on each block revealed associations that were similar to the allele analysis of rs1883025 and rs5882, respectively, and did not find any associations that were stronger than the single SNP associations (Supplementary Table 3).

The genotype-specific effect of the CETP rs5882 on the risk of PCV is summarized in Table 3. The SNP rs5882 was significantly associated with PCV in all three genetic models. The association in the recessive (OR, 2.31; 95% CI, 1.46–3.65; P = 3.00 × 10⁻⁷) genetic model was stronger than that in the additive (OR, 1.62; 95% CI, 1.24–2.11; P = 3.93 × 10⁻⁶) or dominant (OR, 1.62; 95% CI, 1.07–2.45; P = 0.022) genetic models. After adjustment, a homozygous carrier of the risk allele G had a 3.35-fold (95% CI, 1.80–6.24) and a 3.53-fold (95% CI, 1.93–6.45) increased risk of PCV in models A and B, respectively, when compared with a homozygous carrier of the protective allele A. There was a trend of a greater risk for PCV with an increasing number of G alleles (P = 1.26 × 10⁻⁴ in model A and P = 5.10 × 10⁻⁵ in model B).

Serum samples were available for 312 subjects, including 124 patients with PCV, 80 patients with nAMD and 108 control individuals. The serum levels of HDL-c, LDL-c and total cholesterol for each group are shown in Table 4. The serum HDL-c levels were significantly lower in the patients with PCV (1.36 vs. 1.07 mmol/L, P = 0.015) and in the patients with nAMD (1.32 vs. 1.33 mmol/L, P = 0.006) than in the control individuals (1.46 vs. 1.37 mmol/L), but this finding did not remain significant after adjusting using model A. No significant differences were found for serum LDL-c or total cholesterol levels between the cases and controls. According to the quartile of serum HDL-c levels, no effects were found on the risk of PCV or nAMD (Supplementary Table 4).

The PCV patients with the risk GG genotype had significantly lower serum HDL-c levels than did those with the AA genotype (1.26 ± 0.22 mmol/L vs. 1.43 ± 0.35 mmol/L, P = 0.027). After adjustment, the GG genotype still had an effect on the serum HDL-c level for the PCV patients (P = 0.048 in model A and P = 0.046 in model B, Table 5). However, the rs5882 genotype was not associated with the serum HDL-c levels for the control individuals or the nAMD patients. No associations were found between the rs5882 genotype and the serum levels for LDL-c or total cholesterol in each group (Supplementary Table 5). We also investigated the associations of the genotypes of the rs1883025 in ABCA1 and the rs3764261 near CETP with serum cholesterol levels for each group and found no significant results.

4. Discussion

In the current study, we first found a significant association between PCV and the CETP rs5882 variant in a Chinese Han population, and this association was attributed to a phenotypic correlation to serum HDL-c. Before the Bonferroni correction, we also observed a significant association between PCV and the rs3764261 variant near CETP. This variant was previously reported to be associated with AMD in two GWAS (Chen et al., 2010; Neale et al., 2010) whose cohorts included the cases with large drusen, geographic atrophy and nAMD. However, we found no evidence of association for any CETP variants with nAMD in our cohort.
GWAS for AMD achieved significant success, but those study cohorts were primarily Caucasian and did not utilize the angiographic subtype classification. Based on the GWAS finding, the subsequent studies (Hayashi et al., 2010; Lee et al., 2008; Lima et al., 2010) that focused on different ancestry and distinct AMD angiographic subtypes added new information. Our results strongly indicate that it would be necessary to treat PCV and nAMD separately to help rectify the misclassification bias of association results, especially in Asian cohorts due to the higher proportion of PCV. In the GWAS by Chen et al. (Chen et al., 2010), a Japanese replication sample was included for the rs3764261 variant near CETP and confirmed a significant association, whereas the other seven Caucasian replication samples failed to confirm this association. A recent study (Yu et al., 2011) in Caucasians also could not replicate the association between the rs3764261 variant near CETP and nAMD. In our current study, the association of the rs3764261 variant near CETP was still significant even when PCV and nAMD patients were included together as one group. The Japanese sample in the GWAS by Chen et al. (Chen et al., 2010) was of nAMD patients without the angiographic classification. Because 54.7% of Japanese nAMD patients are reported to be PCV actually by ICGA (Maruko et al., 2007), the association of rs3764261 with this Japanese nAMD sample might be due to a real association with PCV.

The associations of the SNPs in CFH (rs800292), ARMS2 (rs10490924) and near HTRA1 (rs11200638) with PCV and nAMD were once again confirmed by our cohort. These results confirmed our sample set and were used to adjust our other results to avoid producing false positives. Consistent with the previous studies (Hayashi et al., 2010; Lima et al., 2010), we showed a similar distribution of the CFH variant, but different distributions of the ARMS2/HTRA1 variants between PCV and nAMD. Combined with the genetic differences in the complement component genes (Lee et al., 2008), the chromosome 9p21 risk interval (Zhang et al., 2011) mentioned above and the CETP shown in the current study, the possibility exists that PCV is genetically distinct from nAMD, which accounts for the distinct phenotypes of these two clinical entities and suggests some differences in their pathogenesis.

CETP mediates the transfer of cholesteryl esters from HDL to triglyceride-rich lipoproteins and thereby influences the concentration, apolipoprotein content, and size of the HDL particles (Bruce et al., 1998). CETP rs5882 is a common variant with an A-to-G transition in exon 14, which leads to a missense mutation with the substitution of valine for isoleucine at codon 405. The minor G-allele of this variant has been consistently associated with decreased CETP mass and activity (Bruce et al., 1998; Thompson et al., 2008), but its subsequent influence on the serum HDL-C level is not always upward and can be reversed by dietary fatty acid consumption (Darabi et al., 2009). The GG homozygote of the CETP rs5882 variant is reported to be associated with exceptional longevity (Atzmon et al., 2005; Barzilai et al., 2003), coronary artery

### Table 2

Association of minor allele frequency of the candidate SNPs with PCV and nAMD.

<table>
<thead>
<tr>
<th>Gene region</th>
<th>SNP</th>
<th>Minor/major allele</th>
<th>MAF in controls (n = 204)</th>
<th>PCV + nAMD (n = 407)</th>
<th>PCV (n = 250)</th>
<th>nAMD (n = 157)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MAF</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P allele</td>
<td>P allele</td>
<td>P allele</td>
</tr>
<tr>
<td>CFH</td>
<td>rs800292</td>
<td>T/C</td>
<td>42.4%</td>
<td>26.2% (0.36–0.60)</td>
<td>0.68</td>
<td>0.70</td>
</tr>
<tr>
<td>ARMS2</td>
<td>rs10490924</td>
<td>G/T</td>
<td>74.7%</td>
<td>23.2% (0.36–0.60)</td>
<td>0.52</td>
<td>0.60</td>
</tr>
<tr>
<td>HTRA1</td>
<td>rs11200638</td>
<td>G/A</td>
<td>57.8%</td>
<td>0.38</td>
<td>0.38 (0.29–0.47)</td>
<td>0.47 (0.35–0.60)</td>
</tr>
<tr>
<td>LIPC</td>
<td>rs10468107</td>
<td>T/C</td>
<td>20.0%</td>
<td>25.1% (0.36–0.60)</td>
<td>0.52</td>
<td>0.60</td>
</tr>
<tr>
<td>CETP</td>
<td>rs3764261</td>
<td>T/G</td>
<td>16.5%</td>
<td>1.45</td>
<td>1.08</td>
<td>0.86</td>
</tr>
<tr>
<td>ABCA1</td>
<td>rs2230808</td>
<td>A/G</td>
<td>44.6%</td>
<td>0.77</td>
<td>0.77 (0.58–1.03)</td>
<td>0.77 (0.58–1.03)</td>
</tr>
<tr>
<td>CETP</td>
<td>rs3764261</td>
<td>T/G</td>
<td>16.5%</td>
<td>0.77</td>
<td>0.77 (0.58–1.03)</td>
<td>0.77 (0.58–1.03)</td>
</tr>
<tr>
<td>CETP</td>
<td>rs5882</td>
<td>A/G</td>
<td>41.7%</td>
<td>0.77</td>
<td>0.77 (0.58–1.03)</td>
<td>0.77 (0.58–1.03)</td>
</tr>
<tr>
<td>CETP</td>
<td>rs2303790</td>
<td>G/A</td>
<td>3.7%</td>
<td>1.32 (0.72–2.42)</td>
<td>0.371</td>
<td>0.371</td>
</tr>
<tr>
<td>LPL</td>
<td>rs12678919</td>
<td>G/A</td>
<td>5.5%</td>
<td>1.61</td>
<td>1.61 (0.75–1.60)</td>
<td>1.61 (0.75–1.60)</td>
</tr>
<tr>
<td>FADS1</td>
<td>rs174574</td>
<td>T/C</td>
<td>38.2%</td>
<td>0.827</td>
<td>0.827</td>
<td>0.827</td>
</tr>
</tbody>
</table>

SNP = single nucleotide polymorphism; PCV = polychoroidal choroidal vasculopathy; nAMD = neovascular age-related macular degeneration; CFH = complement factor H; ARMS2 = age-related maculopathy susceptibility 2; HTRA1 = HtrA serine peptidase 1; LPL = lipoprotein lipase; ABCA1 = ATP-binding cassette sub-family A member 1; FADS1 = fatty acid desaturase 1; LIPC = hepatic lipase; CETP = cholesteryl ester transfer protein; MAF = minor allele frequency; OR = odds ratio; 95% CI = 95% confidence intervals.

- Minor/major allele were calculated based on the all cases and control subjects.
- Statistically significant values are marked in bold.

### Table 3

Risk of PCV according to the CETP rs5882 genotype.

<table>
<thead>
<tr>
<th>Genetic model</th>
<th>OR (95% CI)</th>
<th>P genotype</th>
<th>Genotype</th>
<th>Frequency in controls</th>
<th>Frequency in PCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant</td>
<td>1.62</td>
<td>1.07–2.45</td>
<td>rs5882</td>
<td>32.9%</td>
<td>23.2%</td>
</tr>
<tr>
<td>Additive</td>
<td>1.62</td>
<td>1.24–2.41</td>
<td>rs5882</td>
<td>51.6%</td>
<td>46.0%</td>
</tr>
<tr>
<td>Recessive</td>
<td>2.31</td>
<td>1.46–3.65</td>
<td>rs5882</td>
<td>11.0%</td>
<td>30.8%</td>
</tr>
</tbody>
</table>

PCV = polychoroidal choroidal vasculopathy; CETP = cholesteryl ester transfer protein; OR = odds ratio; 95% CI = 95% confidence intervals.

- Adjusted for gender, age, body mass index, smoking status, alcohol consumption, history of hypertension and coronary artery disease.
- Adjusted for same variables in model A plus: CFH rs800292 (CC, CT, TT), ARMS2 rs10490924 (TT, GT, GG), rs11200638 near HTRA1 (AA, AG, GG).
- Trend test.
**Table 4**

<table>
<thead>
<tr>
<th>Serum cholesterol</th>
<th>Control (n = 108)</th>
<th>PCV (n = 124)</th>
<th>nAMD (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD, mmol/L</td>
<td>Mean ± SD, mmol/L</td>
<td>P value</td>
</tr>
<tr>
<td>HDL-c</td>
<td>1.46 ± 0.37</td>
<td>1.36 ± 0.27</td>
<td>0.015</td>
</tr>
<tr>
<td>LDL-c</td>
<td>3.46 ± 0.73</td>
<td>3.42 ± 0.86</td>
<td>0.694</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.15 ± 0.78</td>
<td>5.20 ± 0.88</td>
<td>0.672</td>
</tr>
</tbody>
</table>

HDL-c = high density lipoprotein-cholesterol; LDL-c = low density lipoprotein-cholesterol; SD = standard deviation; PCV = polypoidal choroidal vasculopathy; nAMD = neovascular age-related macular degeneration.

a Adjusted for gender, age, body mass index, smoking status, alcohol consumption, history of hypertension and coronary artery disease.

**Table 5**

<table>
<thead>
<tr>
<th>rs5882 genotype</th>
<th>Controls (n = 108)</th>
<th>PCV (n = 124)</th>
<th>nAMD (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD, mmol/L</td>
<td>Mean ± SD, mmol/L</td>
<td>P value</td>
</tr>
<tr>
<td>rs5882 genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>1.53 ± 0.55</td>
<td>1.43 ± 0.35</td>
<td>0.143</td>
</tr>
<tr>
<td>GA</td>
<td>1.43 ± 0.36</td>
<td>0.539</td>
<td>0.624</td>
</tr>
<tr>
<td>GG</td>
<td>1.40 ± 0.32</td>
<td>0.499</td>
<td>0.560</td>
</tr>
</tbody>
</table>

CETP – cholesteryl ester transfer protein; PCV – polypoidal choroidal vasculopathy; HDL-c – high density lipoprotein-cholesterol.

a Adjusted for gender, age, body mass index, smoking status, alcohol consumption, history of hypertension and coronary artery disease.

b Adjusted for same variables in model A plus: CHS rs800292 (CC, CT, TT), ARMS2 rs10490924 (TT, GT, GG), rs11200638 near HTRA1 (AA, AG, GG).
shared by nAMD to lead to the same HDL-c profile. Collectively, it suggests that different aspects of the HDL pathway are involved in the mechanism of PCV and nAMD.

In our cohort, the genotype distributions of the rs10490924 in ARMS2, rs11200638 near HTRA1 and rs12678919 near LPL in PCV and nAMD patients, and the rs3764261 near CETP in PCV patients showed a deviation from HWE, despite the fact that they were all in HWE in the controls. The deviations might suggest a selection bias for the rs12678919 near LPL and the presence of a susceptibility variant (Nielsen et al., 1998) for the rs10490924 in ARMS2, rs11200638 near HTRA1 and rs3764261 near CETP.

In conclusion, we investigated HDL-related genetic variants and serum cholesterol levels in Chinese Han patients with nAMD and PCV. None of them was significantly associated with nAMD. A significant association between the rs5882 variant in CETP and PCV was discovered, and this association was reversely correlated to serum HDL-c levels. These results suggest the need to separate PCV from nAMD especially in Asian cohorts, and provide biological clues about the different underlying HDL pathways involved in the pathogenesis of PCV and nAMD. Though interpretations of the findings are challenged by relatively small sample sizes, this study does provide grounds for further research. Additional resources will be required to verify our association findings with independent cohorts and to explain the different impacts of HDL-related genetic variants on the risk of PCV and nAMD.

Conflict of interest

The authors have no financial or conflicting interests to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.exer.2012.12.005.

References


