Gender specific association of a complement component 3 polymorphism with polypoidal choroidal vasculopathy

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Neovascular age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV) are leading causes of irreversible blindness in developed countries. In this study, we investigated the associations of haplotype-tagging single nucleotide polymorphisms (SNPs) in the complement component 3 (C3) gene with both neovascular AMD and PCV, and potential epistatic effects on C3. Eight tagging SNPs in C3 were genotyped in 708 unrelated study subjects: 200 neovascular AMD patients, 233 PCV patients and 275 controls. Among the eight C3 SNPs, rs17030 was associated with PCV after adjusted for gender and SNP-gender interaction (P = 0.008, OR = 2.94; 95% CI: 1.32-6.52). Moreover, an interaction between rs17030 and gender was identified in PCV (P = 0.02). After stratification by gender, the rs17030 G allele was found to confer an increased risk for PCV in male (P = 0.010, OR = 1.56) but not in female. The haplotype AG defined by the major alleles of rs17030 and rs344555 was also associated with PCV in male (P = 0.010, OR = 0.64). In contrast to PCV, none of the eight SNPs was significantly associated with neovascular AMD. This study shows an association of C3 rs17030 with PCV in male, indicating that C3 may have an epistatic effect with gender in the pathogenesis of PCV.

A ge-related macular degeneration (AMD) is a degenerative disease at the central region of the retina – the macula. AMD is a leading cause of irreversible blindness among the elderly. Age, genetic susceptibility and environmental factors are the major risk factors. Advanced AMD is associated with poor central vision, and can be subdivided into geographic atrophy (GA) and neovascular AMD. In the Chinese population, GA is relatively rare while neovascular AMD is the main cause of vision loss. Polypoidal choroidal vasculopathy (PCV) is characterized by inner choroidal vascular networks ending in polypoidal lesions diagnosed by indocyanine green angiography (ICGA). The incidence of PCV in neovascular AMD is high in Asian populations, ranging from 24.5% to 54.7%. Moreover, PCV is more common in male than females in Asians, with a male to female ratio of about 3:2. Clinically, it remains debatable whether PCV is a subtype of neovascular AMD or a distinct disease entity, and whether it represents inner choroidal vascular abnormalities or a variant of choroidal neovascularization (CNV). Genetically, diversities also exist between AMD and PCV. The complement factor H gene (CFH) and the ARMS2-HTRA1 locus have been associated with AMD and PCV in different populations, but their effect sizes were different between the two diseases. Recently, we also found that the association profiles of the superkiller viralicidic activity 2-like (SKIV2L) and cholesteryl ester transfer protein (CETP) genes are different between AMD and PCV. Moreover, we identified a significant interaction between CFH and CETP in both AMD and PCV, suggesting epistasis could have played a role in their disease mechanisms. In the study, we found that the CFH rs800292 G allele conferred a significantly increased risk of the diseases only in individuals carrying the risk allele T of CETP rs3764261, suggesting CETP may exert an epistatic effect on CFH in the genetic mechanisms of AMD and PCV.

Apart from CFH, other components in the complement pathway have also been suggested to play a role in AMD pathogenesis, such as involvement in drusen formation, retinal pigment epithelium deterioration, photoreceptor degeneration, and CNV progression. The complement component 3 (C3) is the central component of the complement cascade. A nonsynonymous single-nucleotide polymorphism (SNP) in C3, rs2220399 (R102G), was found to be strongly associated with AMD. However, this association was not identified in Chinese. In Japanese, instead of rs2231099, a more common SNP rs2241394 was reported to be associated with AMD and PCV. Therefore, the reported association profiles of C3 with AMD and PCV are inconsistent among popula-
tions. Recently, a rare missense variant (K155Q) in C3 was identified to confer a strong risk toward AMD. Therefore, C3 could play an important role in AMD genetics, while having ethnic diversities in allelic distributions. So far however, little is known about the genetic profile of C3 in PCV.

In this study, we investigated the associations of the C3 gene with both neovascular AMD and PCV by using haplotype-tagging SNP analysis in a Han Chinese population. Also, we explored potential epistatic effects between different factors and C3 in the both diseases.

**Results**

A total of 708 unrelated study subjects were included, consisting of 200 patients with neovascular AMD, 233 patients with PCV, and 275 controls (Table 1). Notably, gender was not matched between the both disease groups and control group; therefore gender was adjusted in the association analysis using logistic regression. The mean age of the control individuals was significantly greater than that of the PCV patients \((P<0.05)\). This is because we purposely recruited subjects older than 60 years as controls, with a view to reduce the confounding effects from younger subjects; thus age was not adjusted in association analysis.

According to the International HapMap Project for the Chinese Han population, the 8 tagging SNPs evaluated in this study captured 96% of alleles in the C3 locus with minor allele frequencies greater than 0.1 and a mean \(r^2\) of 0.97. All of the tested SNPs followed HWE in the control group \((P>0.05)\). In single marker analyses, none of the 8 SNPs showed a significant allelic association with neovascular AMD or PCV (Table 2). Also, no SNP showed a significant association with the diseases in the dominant or recessive genetic models \((P>0.05)\). Moreover, no SNP showed a significant difference between neovascular AMD and PCV (Table 2).

In the epistatic analysis, no SNP-SNP interaction was detected between each C3 SNP and CFH rs800292, HTRA1 rs11200638, or CETP rs3764261 \((P>0.05)\). However, logistic regression analyses revealed that C3 rs17030 was significantly associated with PCV after adjusted for gender and SNP-gender interaction \((P=0.008, \text{OR}=2.94, 95\% \text{CI}: 1.32–6.52)\), and there was a significant interaction between rs17030 and gender in PCV \((P=0.02, \text{Table 3})\). In contrast, gender independently was not associated with PCV \((P=0.06)\). Stratification by gender revealed that rs17030 was significantly associated with PCV in male but not in female \((P=0.02)\). The minor allele G of rs17030 showed a risk effect toward PCV in male \((P=0.010, \text{OR}=1.56, 95\% \text{CI}: 1.11–2.20)\). This gender difference was further confirmed by the homogeneity test of the ORs between men and women \((P=0.0005, \text{and} 0.027, \text{respectively})\). However, the \(P\) values could not withstand the Bonferroni correction \((P=0.025)\). In female, this SNP was not associated with PCV in any models. Breslow-Day test showed a statistically significant difference in the ORs between male and female in the recessive model \((P=0.014)\) but not the dominant model \((P=0.15\); Table 4\). Such gender difference was not observed in neovascular AMD \((P>0.05)\). The other C3 SNPs were not associated with neovascular AMD or PCV after adjusted by gender and SNP-gender interaction \((data not shown)\).

Linkage disequilibrium (LD) analysis revealed two haplotype blocks in neovascular AMD \((\text{Block 1 involves SNPs rs17030 and rs344555, Block 2 involves SNPs rs428453 and rs11672613})\) and one in PCV \((\text{involves SNPs rs17030 and rs344555})\) \((Figure 1)\). No haplotype was significantly associated with either disease. Since rs17030 showed an association with PCV in male, haplotype analyses were performed in different genders. The LD structure across C3 in male PCV patients was similar to that in all PCV patients, with rs17030 and rs344555 being in the same LD block \((Figure 1)\). A haplotype AG, defined by the major alleles of the two SNPs, showed a significant protection for PCV in male \((P=0.010, \text{permutation} P=0.030; \text{OR}=0.64, 95\% \text{CI}: 0.45–0.90)\). This haplotype was present in 53.7% of male patients and 64.5% of male controls. No significant haplotype association between C3 and PCV was detected in female.

**Discussion**

In this study, we have, for the first time, reported a haplotype tagging SNP analysis of the C3 gene concurrently in neovascular AMD and PCV. The 8 tagging SNPs capture the majority of common genetic variations in C3. Our results capture that none of the tagging SNPs was associated with neovascular AMD, whereas rs17030 was associated with PCV after adjusted for gender and SNP-gender interaction. These findings suggest that in the Chinese population C3 may play a relatively more important role in PCV. Moreover, the male-specific association and SNP-gender interaction between rs17030 and PCV suggest additional risk factors should be required for C3 to exert its effect in the pathogenesis of PCV, likely through an epistatic function.

Results of this study enrich our knowledge of the genetic diversities of C3 in AMD and PCV. The nonsynonymous variant rs2230199 (R102G) in C3 was consistently associated with AMD in Caucasians, but not in Asian populations. This is likely due to the difference in the frequencies of the risk allele of rs2230199 between Caucasians and Asians. The risk allele frequency of rs2230199 is relatively high in Caucasians (0.2), while being absent in Japanese and Koreans \((P=0.005)\). In contrast, SNP rs2241394, which has a minor allele frequency \((MAF)\) of 0.11 in Japanese, was significantly associated with neovascular AMD \((OR=0.48)\). However, the MAF of rs2241394 is less than 0.05 in Chinese \((P=0.005)\). Therefore, the statistical power to detect a significant association in our study would be less than 30%. Thus, this SNP was not included in the present study. Notably, another SNP rs2250656 was reported to be associated with neovascular AMD in a Chinese cohort, with the minor allele showing a

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**Table 1** Characteristics of the Study Subjects

|                | AMD \(n=200\) | PCV \(n=233\) | Control \(n=275\) | Comparison |
|----------------|-------------|-------------|-----------------|------------|
| **Gender**     |             |             |                 |            |
| Male/Female    | 110/90      | 162/71      | 121/154         | \(P=0.02\) |
| **Mean age ± SD (years)** |             |             |                 |            |
| Male           | 73.9 ± 7.4  | 69.2 ± 8.8  | 73.6 ± 7.1      | \(P=0.05\) |
| Female         | 77.0 ± 7.7  | 67.6 ± 9.6  | 74.8 ± 7.9      | \(P=0.05\) |
| **Age range (years)** |             |             |                 |            |
| Male           | 50–94       | 43–90       | 60–94           | NA         |
| Female         | 56–94       | 43–85       | 60–94           | NA         |

AMD: age related macular degeneration; NA: not applicable; PCV: polypoidal choroidal vasculopathy; SD: standard deviation.
Plasma concentrations of the des Arg form of complement C3a, a product of C3 cleavage, are found to be significant mostly in women.18 Similarly, in the study of Wiggs et al., associations of CFH (184G) were found as a genetic risk marker for primary open angle glaucoma with several CAV1/CAV2 SNPs were found to be significant mostly in women.19 In the study of Yang et al., the rs17030 G allele showed a trend of protection in female carriers. By stratification, the association of rs17030 with PCV was significant in male, in agreement with the gender differences by using logistic regression, which, in return, suggested that gender was not a significant confounding factor in AMD.

Table 2 | Allelic association of SNPs in C3 region with neovascular AMD and PCV

| SNP       | Location (residue change) | Minor allele | AMD (n=200) | PCV (n=233) | Control (n=275) | Minor allele frequency | P | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) |
|-----------|---------------------------|--------------|-------------|-------------|-----------------|-----------------------|---|-------------|---|-------------|---|-------------|
| rs2250656 | Intron 2                   | G            | 0.28        | 0.27        | 0.24            | 0.11                  | 1.27          | (0.95–1.71) | 0.24 | 1.19       | (0.89–1.58) | 0.64 | 0.93       | (0.69–1.26)          |
| rs2230205 | Exon 14 [T612T] A          |              | 0.39        | 0.42        | 0.42            | 0.26                  | 0.86          | (0.66–1.12) | 0.94 | 0.99       | (0.77–1.27) | 0.31 | 1.15       | (0.88–1.51)          |
| rs11672613| Intron 17                  | G            | 0.42        | 0.44        | 0.43            | 0.67                  | 0.95          | (0.73–1.23) | 0.68 | 1.05       | (0.82–1.35) | 0.43 | 1.12       | (0.85–1.46)          |
| rs428453  | Exon 19 [V807V] C          |              | 0.20        | 0.17        | 0.16            | 0.11                  | 1.32          | (0.94–1.84) | 0.67 | 1.07       | (0.77–1.50) | 0.25 | 0.82       | (0.58–1.15)          |
| rs2241392 | Intron 29                  | G            | 0.31        | 0.33        | 0.31            | 0.99                  | 1.00          | (0.76–1.32) | 0.45 | 1.11       | (0.85–1.44) | 0.49 | 1.11       | (0.83–1.47)          |
| rs2241393 | Intron 29                  | G            | 0.36        | 0.36        | 0.34            | 0.72                  | 1.05          | (0.80–1.38) | 0.53 | 1.09       | (0.84–1.41) | 0.81 | 1.03       | (0.78–1.37)          |
| rs344555  | Intron 37                  | A            | 0.28        | 0.26        | 0.25            | 0.40                  | 1.13          | (0.85–1.52) | 0.64 | 1.07       | (0.81–1.42) | 0.71 | 0.95       | (0.70–1.28)          |
| rs17030   | Exon 41 [P1632P] G         |              | 0.43        | 0.45        | 0.41            | 0.69                  | 1.06          | (0.81–1.37) | 0.28 | 1.15       | (0.90–1.47) | 0.53 | 1.09       | (0.83–1.43)          |

*The allelic association was adjusted for gender imbalance but not for SNP-gender interaction.

AMD: age related macular degeneration; C3: complement component 3; CI: confidence interval; OR: odds ratio; PCV: polypoidal choroidal vasculopathy; SNP: single nucleotide polymorphism.

Table 3 | Logistic regression analysis of C3 rs17030, gender and C3 rs17030gender interaction

| Variable      | P Value | OR (95% CI)       | P Value | OR (95% CI)       |
|---------------|---------|-------------------|---------|-------------------|
| C3 rs17030 G  | 0.46    | 1.37 (0.60–3.12)  | 0.008   | 2.94 (1.32–6.52)  |
| Gender, female| 0.25    | 0.71 (0.40–1.26)  | 0.06    | 0.58 (0.33–1.02)  |
| C3 rs17030 gender | 0.58 | 0.87 (0.52–1.45)  | 0.02    | 0.54 (0.32–0.90)  |

AMD: age related macular degeneration; C3: complement component 3; CI: confidence interval; OR: odds ratio; PCV: polypoidal choroidal vasculopathy.
Thus, the male-specific association between rs17030 and PCV should not be artifact due to gender imbalance in this study. Meanwhile, although significant association between rs17030 and PCV was identified in male after Bonferroni correction ($P_{\text{corr}} = 0.025$), the protective association of the haplotype AG defined by rs17030 and rs344555 with PCV in male maintained significant after correction by permutation ($P_{\text{perm}} = 0.034$), the significance in allelic association would have disappeared if a more stringent Bonferroni correction as adopted, such as adjusting the $P$ values by the number of SNPs divided by the number of strata (i.e., 8 divided by 2 equals 4). This is likely due to the relatively small sample size in our study. Therefore, the role of rs17030 in PCV should be verified in larger study cohorts with matched gender and exhaustive information of smoking status. Also, whether the gender-specific association of C3 with PCV exists in other ethnic groups remains to be investigated.

In summary, this present study shows that no SNP in C3 was significantly associated with neovascular AMD, whereas rs17030 was associated with PCV in male but not female. These findings reveal a gender-susceptibility pattern in the genetic association of C3 with PCV, suggesting an epistatic effect between C3 and gender in the pathogenesis of PCV. Further studies in larger cohorts and in other populations are warranted to confirm these new findings.

**Methods**

**Study participants.** All study subjects were Han Chinese recruited at the Hong Kong Eye Hospital and the Eye Centre of the Prince of Wales Hospital, Hong Kong. The study protocol was approved by the Ethics Committee on Human Research, the Chinese University of Hong Kong. Written informed consent was obtained from every subject. The study procedures were performed in accordance with the tenets of the Declaration of Helsinki.

The patients were given complete ophthalmic examinations, including ocular tonometry, best-corrected visual acuity measurement, slit-lamp biomicroscopy, color fundus photographs, fluorescein angiography, and ICGA. All AMD patients had neovascular AMD in at least one eye. PCV was diagnosed using ICGA. Patients with any eye with other causes of CNV, such as myopic maculopathy, or with both CNV and PCV lesions in the same or fellow eye, were excluded. Unrelated control subjects were recruited from people who attended the clinic for eye examinations. After complete ophthalmic examinations they were included on the following criteria: (1) age $\geq 60$ years; (2) no age-related maculopathy or macular degeneration of any cause; and (3) no any other major eye diseases, except for mild senile cataracts and mild refractive errors (Table 1).

**SNP selection and genotyping.** Haplotype tagging SNPs across the C3 region were obtained from the International HapMap Project (http://hapmap.ncbi.nlm.nih.gov/).
HapMap Genome Browser release #27, accessed Jun 20, 2012) for the Han Chinese in Beijing (CHB) population. Eight SNPs were selected by the tagger-pairwise method with R square and MAF values greater than 0.8 and 0.10 respectively. Genomic DNA was extracted from whole blood using a QiAamp Blood Kit (Qiagen, Hilden, Germany) according to the protocol from the manufacturer. The 8 candidate SNPs were genotyped using TaqMan genotyping assays (Applied Biosystems [ABI], Foster City, CA) on a Roche LightCycler® 480 Real-Time PCR System (Roche, Switzerland) according to the manufacturer’s instructions.

Statistical analysis. Hardy-Weinberg Equilibrium (HWE) of individual SNP in the control group was tested using the exact test implemented in the software package PLINK v1.07 (http://pngu.mgh.harvard.edu/purcell/plink/)26. Allelic or genotype association of each SNP was evaluated using the chi-square test or Fisher’s exact test in PLINK. The odds ratio (OR) and corresponding 95% confidence interval (CI) were estimated with the major allele as reference. Pairwise linkage disequilibrium and haplotype associations were assessed using the Haploview software27. HaploType blocks were determined using the confidence interval method in Haploview. Logistic regression was performed with gender and SNP-gender interaction to adjust the effect of gender on SNPs, referring to previously reported28. We stratified the study subjects according to gender and performed association analysis of the SNP in each gender stratum, and used the Breslow-Day test to examine the homogeneity of the OR in different gender strata. The SPSS software (ver.20.0, SPSS Inc., Chicago, IL) was used. Also, the epistasis algorithm in PLINK was applied to detect gene-gene interaction between the 33 SNPs and three major gene variants for AMD, C3R rs800292, HTRA1 rs11200638 and CFT rs5764261. Genotype data of the latter two SNPs were obtained from our previous studies29,30. For the significance threshold of P values, as no C3 SNP was found of significant association with overall AMD or PCV, correction for multiple testing was not required. In the interaction analysis, all items (either SNP*SNP or SNP*gender) with P<0.05 will be subjected to further stratification analysis. In the stratification analysis, the Bonferroni correction was applied to adjust the P values by the number of strata. In particular, since the SNP rs17030 was analyzed separately in males and females, a P value of less than 0.025 (<0.5/2) was considered statistically significant.

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Author contributions
K.L., C.P.P. and L.J.C. designed the experiments. K.L., S.C. and P.T. performed the experiments. K.L. performed the analysis and wrote the paper. T.L., V.C. and A.Y. contributed the clinical samples. C.P.P. and L.J.C. revised the paper. All authors contributed to the editing of the paper and to scientific discussions.

Additional information
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