Difference between age-related macular degeneration and polypoidal choroidal vasculopathy in the hereditary contribution of the A69S variant of the age-related maculopathy susceptibility 2 gene (ARMS2)

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Purpose: To investigate whether the A69S variant of the age-related maculopathy susceptibility 2 gene (ARMS2) has a different hereditary contribution in neovascular age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV).

Methods: We initially conducted a comparative genetic analysis of neovascular AMD and PCV, genotyping the ARMS2 A69S variant in 181 subjects with neovascular AMD, 198 subjects with PCV, and 203 controls in a Japanese population. Genotyping was conducted using TaqMan technology. Results were then integrated into a meta-analysis of previous studies representing an assessment of the association between the ARMS2 A69S variant and neovascular AMD and/or PCV, comprising a total of 3,828 subjects of Asian descent. The Q-statistic test was used to assess between-study heterogeneity. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using a fixed effects model.

Results: The genetic effect of the A69S variant was stronger in neovascular AMD (allelic summary OR=3.09 [95% CI, 2.71–3.51], fixed effects p<0.001) than in PCV (allelic summary OR=2.13 [95% CI, 1.91–2.38], fixed effects p<0.001). The pooled risk allele frequency was significantly higher in neovascular AMD (64.7%) than in PCV (55.6%). The population attributable risks for the variant allele were estimated to be 43.9% (95% CI, 39.0%–48.4%) and 29.7% (95% CI, 25.4%–34.0%) for neovascular AMD and PCV, respectively. No significant between-study heterogeneity was observed in any statistical analysis in this meta-analysis.

Conclusions: Our meta-analysis provides substantial evidence that the ARMS2 A69S variant confers a significantly higher risk of neovascular AMD than PCV. Furthermore, there is compelling evidence that the risk attributable to the A69S variant differs between geographic atrophy and neovascular AMD. Together with defining the molecular basis of susceptibility, understanding the relationships between this genomic region and disease subtypes will yield important insights, elucidating the biologic architecture of this phenotypically heterogeneous disorder.
AMD [17]. The meta-analysis showed that the missense allele encoding A69S (rs10490924) in ARMS2 confers the strongest disease risk, among others [17].

Polypoidal choroidal vasculopathy (PCV), characterized by inner choroidal vascular networks ending in polypoidal lesions [18], is now clinically classified as a specific type of AMD [19]. PCV is particularly prevalent in Asian populations, accounting for 54.7% of patients with the neovascular form of AMD in the Japanese population [20] and 24.5% in the Chinese population [21], but only 8% to 13% in Caucasians [22]. PCV shares many similarities with neovascular AMD, including demography [20], pathology [23,24], and manifestation [20]; however, important differences have been noted in histopathology [25], clinical behavior [22], and response to therapy [18,26]. These similarities and differences have been a subject of much interest and debate regarding whether the vascular abnormality in PCV represents neovascularization or a phenotype distinct from CNV [23-25,27].

We have previously shown that the ARMS2 A69S variant is strongly associated with neovascular AMD and PCV, with a stronger association in neovascular AMD than in PCV [28]; however, the difference was not statistically significant, probably owing to a limitation in statistical power. Subsequent A69S association studies have consistently reported a trend toward stronger evidence for association in neovascular AMD than in PCV [29-31]. Interestingly, a significant difference in genetic susceptibility between geographic atrophy and neovascular AMD has been repeatedly observed at this locus [17,32]. Sub-phenotype associations are currently being actively researched in complex diseases, such as inflammatory bowel disease [33], rheumatoid arthritis [34], and various cancers [35-37]. Genotype–phenotype correlations between risk alleles and disease subtypes may provide an insight into the underlying etiologic pathways of complex diseases.

To date, some meta-analyses have been published regarding the association between AMD and the ARMS2/HTRA1 region [38-40], but none of these studies focused on PCV. Here we conducted a comparative genetic analysis of neovascular AMD and PCV in our original sample set of Japanese ancestry, genotyping the ARMS2 A69S variant in 181 subjects with neovascular AMD, 198 subjects with PCV, and 203 controls. Results were then integrated into a meta-analysis of previous studies representing an assessment of the association between the ARMS2 A69S variant and neovascular AMD and/or PCV, comprising a total of 3,828 subjects of Asian descent, to more reliably compare the genetic effect of ARMS2 A69S between neovascular AMD and PCV.

**METHODS**

New data set: Study participants: The study protocol was approved by the Institutional Review Board at Kobe University Graduate School of Medicine and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects before participation in this study. All cases and controls included in our original sample set were Japanese individuals recruited from the Department of Ophthalmology at Kobe University Hospital in Kobe, Japan. This cohort is an extension of one previously published for an association with the ARMS2 A69S variant [28]. A portion of the subjects in the present study had participated in our previous studies in which phenotyping criteria were fully described [28,41,42]. In brief, all our subjects with neovascular AMD and PCV underwent a comprehensive ophthalmic examination including indocyanine green angiography, and were defined as having angiographically well defined lesions of CNV or PCV. The controls were not related to the cases and were defined as individuals without macular degeneration and changes such as drusen or pigment abnormalities, and were thus categorized as having clinical age-related maculopathy staging system stage 1 [43]. The demographic details of the study subjects are listed in Table 1.

**Genotyping:** Genomic DNA was extracted from peripheral blood using a standard methodology. Genotyping was performed using a pre-developed TaqMan SNP Genotyping Assay (Assay ID: C_29934973_20; Applied Biosystems, Foster City, CA) on a StepOnePlus™ Real-Time PCR System (Applied Biosystems) in accordance with the manufacturer’s recommendations.

**Statistical analysis:** Allelic associations were evaluated for the ARMS2 A69S variant with chi-square tests on 2 × 2 contingency tables using the software package PLINK v1.07. Deviations from the Hardy–Weinberg equilibrium

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**Table 1. Characteristics of the Study Population**

| Groups          | Neovascular AMD | PCV  | Control |
|-----------------|-----------------|------|---------|
| Number of subjects | 181             | 198  | 203     |
| Gender (male/female) | 139/42          | 157/41 | 120/83 |
| Mean age ± SD (years) | 75±7.4          | 73±7.3 | 72±6.0  |
| Age range (years) | 55–94           | 54–93 | 56–95   |

Abbreviations: AMD, age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; SD, standard deviation.
(HWE) were tested using the exact test [44] implemented in PLINK. The odds ratio (OR) and corresponding 95% confidence interval (CI) were calculated relative to the major allele. Genotype-specific ORs were estimated for the heterozygous (GT) and risk homozygous (TT) genotypes, with the common homozygous (GG) genotype the baseline category with unconditional logistic regression using the JMP software (version 6.0.3; SAS Institute, Cary, NC). To test for heterogeneity between ORs for neovascular AMD and PCV, we conducted a logistic regression analysis of the cases (case-only analysis) using R project, where the subtypes were used as the outcome and the A69S genotype as the explanatory variable [45].

**Meta-analysis: Identification and eligibility of relevant studies:** We performed a systematic PubMed literature search (up to May 2011) using the following search terms in different combinations: “HtrA serine peptidase 1” or “HTRA1,” “age-related maculopathy susceptibility 2,” “ARMS2,” or “LOC387715,” and “age-related macular degeneration” or “polypoidal choroidal vasculopathy.” The literature search was performed in duplicate by two authors (S.Y. and N.K.).

Studies included in the meta-analysis had to fulfill the following criteria: (1) The study must be unrelated case-control or population-based representing an assessment of the association between the ARMS2 A69S variant and neovascular AMD and/or PCV in East Asian populations. (2) The study must distinguish PCV from the neovascular form of AMD based on findings of indocyanine green angiography, and must look at PCV and/or neovascular AMD (CNV) as specific outcomes. (3) The study must present available data on allele and genotype distributions for cases and controls. (4) The study must be written in English and published in peer-reviewed journals. For duplicate publications, the largest data set was chosen for meta-analysis.

**Data extraction:** The following variables were extracted from each study: the name of the first author, the year of publication, ethnicity, and allele and genotype distributions in cases and controls.

**Statistical analyses:** For each study, deviations from the HWE in controls were tested using the exact test [44]. Pooled allele and genotype frequencies of the A69S variant were estimated with the fixed effects model [46] if heterogeneity among studies was absent, or with the random effects model [47] if heterogeneity was present. We estimated summary ORs and 95% CIs according to the Mantel–Haenszel fixed effects model [46] if heterogeneity among studies was absent or the DerSimonian–Laird random effects model [47] if there was evidence of between-study heterogeneity. The population attribute risk was calculated to demonstrate the number of cases in the total population that could be attributed to the risk genotype, as described previously [48].

Between-study heterogeneity was assessed using the Q-statistic test and $I^2$ statistic [49,50]. A $p$ value of <0.1 was considered statistically significant for the Q-statistic test. $I^2$ ranges between 0% and 100% (where a value of 0% represents no heterogeneity), and larger values represent increasing heterogeneity.

All meta-analyses were conducted using the Stata software (version 11.0; Stata Corporation, College Station, TX). All tests were two tailed. A $p$ value of <0.05 was considered statistically significant except for the test of between-study heterogeneity.

**RESULTS**

**Comparative genetic analysis in our original sample set:** We initially conducted a comparative genetic analysis of neovascular AMD and PCV, genotyping the ARMS2 A69S variant (rs10490924) in our original sample set. Genotype distributions for this variant are given in Table 2, along with those of other studies included in the subsequent meta-analysis. No departure from the HWE was observed at this variant among the controls ($p=0.88$). As expected, the ARMS2 A69S variant showed strong evidence of association with neovascular AMD and PCV. ORs for the risk allele T were 2.82 (95% CI, 2.10–3.78, $p=2.4\times10^{-12}$) and 2.39 (95% CI, 1.80–3.17, $p=1.3\times10^{-6}$) for neovascular AMD and PCV, respectively. For heterozygous and homozygous carriers of the risk allele, the genotype-specific OR was 2.62 (95% CI, 1.55–4.52) and 7.49 (95% CI, 4.11–14.07) for neovascular AMD and 1.56 (95% CI, 0.97–2.53) and 5.02 (95% CI, 2.89–8.90) for PCV, respectively. Similar to previous findings of ARMS2 A69S association studies [29-31], the variant showed a trend toward stronger effect in neovascular AMD than in PCV. However, a case-only heterogeneity test with logistic regression analysis showed a nonsignificant value in our original sample set (heterogeneity $p=0.31$), possibly reflecting inadequate statistical power in this single study. Our own data were then combined with those from previously published studies in the subsequent meta-analysis.

**Meta-analysis: Eligibility of studies:** Our search identified five studies that met our inclusion criteria [29-31,51,52]. Data from these five studies and our original study were combined for the meta-analysis. Table 2 lists the studies included in the meta-analysis. The combined sample size for this meta-analysis was 3,828.

**Allele and genotype frequency:** None of the five previously published studies demonstrated significant deviation from the HWE among controls (Table 2). To estimate the pooled frequency of the A69S variant in Asian populations, we used allele data from controls. The pooled frequency for the risk allele T was 37.4% (95% CI, 35.9–38.8), and individuals carrying at least one copy of the risk allele (GT + TT) accounted for 60.8% (95% CI, 58.7–62.9) of the control populations. No evidence of heterogeneity in these frequencies was observed among controls across the six studies (allele frequency, $Q=8.50$, 5 degrees of freedom [d.f.],
Quantitative synthesis: We conducted a meta-analysis based on an allele contrast model. The A69S variant showed a significant summary OR of 3.09 (95% CI, 2.71–3.51), fixed effects p<0.001; Figure 1) for neovascular AMD and 2.13 (95% CI, 1.91–2.38), fixed effects p<0.001; Figure 2) for PCV. The Q-statistic test showed no significant between-study heterogeneity in association tests for neovascular AMD or PCV (p=0.11, I^2=44.5%). This result, coupled with the finding that the 95% CIs for allelic summary ORs for neovascular AMD did not overlap with those for PCV, indicates that the genetic effect of the ARMS2 A69S variant is significantly stronger in neovascular AMD than in PCV.

DISCUSSION
Several studies have reported that the ARMS2 A69S variant is strongly associated with neovascular AMD and PCV, with a stronger association in neovascular AMD than in PCV [29-31]. However, the differences between the two were not statistically significant in most studies, probably owing to a limitation in the statistical power. Our meta-analysis has revealed that the ARMS2 A69S variant confers a significantly greater risk of neovascular AMD than of PCV. The pooled risk allele frequency was significantly higher in neovascular AMD than in PCV (64.7% versus 55.6%; p<0.001), without heterogeneity across studies (Q=5.38, 3 d.f., p=0.15, I^2=44.3%). This result, coupled with the finding that the 95% CIs for allelic summary ORs for neovascular AMD did not overlap with those for PCV, indicates that the genetic effect of the ARMS2 A69S variant is significantly stronger in neovascular AMD than in PCV.

Table 2. Allele and Genotype Distributions of the ARMS2 A69S Variant of Case-Control Studies Contributing to the Meta-Analysis

| Study        | Year | Ethnicity | Neovascular AMD | PCV | Control | Neovascular AMD | PCV | Control | PHWE* |
|--------------|------|-----------|-----------------|-----|---------|-----------------|-----|---------|-------|
| [51]         | 2008 | Japanese  | NA              | 15/49/45 | 39/32/14 | NA              | 0.64 | 0.35    | 0.10  |
| [52]         | 2008 | Chinese   | 18/30/52        | 17/30/25 | 33/48/12 | 18/50/32        | 0.67 | 0.37    | 0.11  |
| [29]         | 2009 | Japanese  | 67/155/183      | 122/216/171 | 502/638/196 | 132/216/171 | 0.64 | 0.57    | 1.0   |
| [30]         | 2010 | Japanese  | 6/20/24         | 22/20/18 | 64/58/16 | 6/20/24         | 0.68 | 0.47    | 0.70  |
| [31]         | 2011 | Japanese  | 26/81/74        | 42/77/79 | 79/94/30 | 26/81/74        | 0.63 | 0.59    | 0.88  |

Abbreviations: ARMS2, age-related maculopathy susceptibility 2; AMD, age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; HWE, Hardy–Weinberg equilibrium; NA, not available. *p values generated by the exact test for Hardy–Weinberg equilibrium.
risk allele frequency was significantly higher in neovascular AMD (64.7%) compared with PCV (55.6%). The meta-analysis estimated the attributable risks for the variant allele were 43.9% and 29.7% for neovascular AMD and PCV, respectively. In the control populations, the pooled frequency for the risk allele T of the A69S variant was estimated to be 37.4%, and individuals carrying at least one copy of the risk allele accounted for 60.8%, indicating its population-wide epidemiological consequence in Asian populations owing to the high frequency of the risk allele. No significant between-study heterogeneity was observed in any statistical analysis in this meta-analysis of Asian populations.

There is increasing evidence that ethnicity influences disease via genetic background [53]. Risk allele frequencies of A69S diverge greatly between European and Asian populations from the HapMap sample, with almost 40% risk allele frequencies in Asian populations compared to 20% in individuals of European descent. The distributions of the neovascular subtype of AMD differ markedly between European and Asian populations, and parallel the risk allele frequencies of this variant, with Asians having a much higher rate of the neovascular subtype than Europeans [2-5], suggesting that this locus may contribute to ethnic heterogeneity in the manifestation of AMD subtypes.

Currently, how the ARMS2/HTRA1 region on 10q26 is a source of genetic risk for AMD is unclear. Much effort has been made to localize variant(s) causally related to AMD in this region and to understand the molecular basis of the susceptibility [10,11,54-58]. However, there is high linkage disequilibrium (LD) across the ARMS2/HTRA1 region, adding to the difficulty in identifying true causal variant(s) by association mapping alone [55]. The association signal at 10q26 converges on a region of an extensive LD block spanning ARMS2 and HTRA1 [54,55]. This LD block harbors multiple susceptibility alleles of which the ARMS2 A69S variant has been reported to show the strongest evidence for association [54]. Two variants within this LD block that were correlated with A69S through strong LD—SNP rs11200638 in the promoter of HTRA1 [10,11] and the insertion/deletion polymorphism (c.(*)372_815del443ins54) in the 3′-UTR region of ARMS2 [55]—have recently been proposed as causal variants based on mechanistic functional evidence, but there is no agreement across studies [10,11,54-58]. Thus, the molecular basis of the susceptibility remains obscure.

In conclusion, our meta-analysis has identified a difference in the hereditary contribution of the ARMS2 A69S variant between neovascular AMD and PCV. In addition, a significant difference has been reported between geographic atrophy and neovascular AMD with respect to genetic susceptibility at this locus [17,32]. This fact, coupled with our findings, indicates that the risk attributable to the A69S variant differs among AMD subtypes. Given the importance of the ARMS2/HTRA1 region on 10q26 in AMD susceptibility, defining molecular mechanisms through which the genomic variants influence disease risk and understanding the relationships between this region and disease subtypes will yield important insights, elucidating the biologic architecture of this phenotypically heterogeneous disorder.
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