Meta-analysis of the relationship between the LOC387715/ARMS2 polymorphism and polypoidal choroidal vasculopathy

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ABSTRACT. We investigated the association between the LOC387715/ ARMS2 polymorphism (rs10490924 G>T) and susceptibility to polypoidal choroidal vasculopathy (PCV) through a meta-analysis of 1446 cases and 3255 controls from eight case-control studies. The genetic effect of the LOC387715/ARMS2 rs10490924 G>T polymorphism on PCV was assessed by calculating pooled odds ratios (ORs) with 95% confidence intervals (95%CIs). We found that elevated PCV risk was significantly associated with the GG genotype (GG *vs* TT, OR = 4.23, 95%CI = 3.53-5.06), and heterozygous genotype TG appeared to have a minor effect on PCV risk (TG *vs* TT, OR = 1.47, 95%CI = 1.26-1.71). Patients with the T allele were 2.09 times more likely to have PCV than those with the G allele (95%CI = 1.906-2.288). A further subgroup analysis by ages also showed that the genetic effect of the LOC387715/ARMS2 rs10490924 G>T polymorphism on PCV

is stronger among patients with mean age <73 years. Our meta-analysis strengthened the evidence that the LOC387715/ARMS2 rs10490924 G>T polymorphism plays an important role in PCV susceptibility.

Key words: Polypoidal choroidal vasculopathy; LOC387715/ARMS2; Gene polymorphism; Meta-analysis

INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is a macular disease associated with an irreversible reduction of vision and is commonly found in the elderly population. The characteristic lesion of PCV is inner branching choroidal networks with orange polyp-like aneurismal dilation, which can be clearly demonstrated by indocyanine green angiography. Although some similarities with age-related macular degeneration (AMD), PCV has been described as a separate clinical entity differing from AMD and other macular diseases associated with subretinal neovascularization (Yannuzzi et al., 1999; Ciardella et al., 2004; Laude et al., 2010). PCV can occur in any gender or race, but it is more commonly seen in non-white patients and its incidence in the Asian population with AMD is as high as 20 to 55% (Sho et al., 2003; Maruko et al., 2007).

Previous studies on the genetic basis of PCV have recognized it as a complex disease resulting from the actions and interactions of multiple genes and environmental factors. Many candidate genes have been chosen based on their prior close connection with AMD or an entire genome analysis to investigate the risk regions of PCV. Age-related maculopathy susceptibility 2 (LOC387715/ARMS2) is one of the most focused candidate genes, and various single nucleotide polymorphisms have been identified within it. Polymorphisms in LOC387715/ARMS2 were reported to decrease the stability of ARMS2 mRNA (Fritsche et al., 2008).

Empirical studies have shown positive correlations between AMD and the G>T polymorphism in the LOC387715/ARMS2 gene on chromosome 10q26 (Jakobsdottir et al., 2005; Dewan et al., 2006; Kondo et al., 2007). Recent studies have revealed that this polymorphism also contributes to the risk of PCV. However, those studies were either based on small sample size or lacked evaluation of the biological model of genetic effect. Therefore, a focused meta-analysis of current results published in the literature is greatly needed. In this paper, we combined information from eight significant publications and tried to extract powerful pieces of evidence on the correlation between the LOC387715/ARMS2 rs10490924 G>T polymorphism and susceptibility to PCV.

MATERIAL AND METHODS

Search strategy

We searched Medline, PubMed, Embase, Web of Science, and Chinese National Knowledge Infrastructure (CNKI) database using the following search terms: "age-related maculopathy susceptibility 2" or "ARMS2" or "LOC387715" or " rs10490924" or "A69s" and "genetic variant" or "polymorphism" and "polypoidal choroidal vasculopathy" or "PCV". All searched articles were manually checked to exclude any clearly irrelevant studies, and

the remaining articles were further reviewed based on their suitability for our meta-analysis. References of the retrieved articles or preceding reviews on this topic were also screened to find additional eligible publications. For overlapping studies, only the articles with the largest sample size were included. All the search results were assessed independently by two of the authors (Jiang JJ and Wu X).

Eligibility study and data extraction

The eligibility criteria were: a) evaluations of the polymorphisms in the ARMS2 gene and PCV risks; b) original data of retrospective case-control or prospective cohort publications; c) the alleles and genotypes of the LOC387715/ARMS2 polymorphism (rs10490924), respectively, were G and T and GG, GT, and TT; d) sufficiency of available data for each allele or genotype in both PCV and control groups; e) fulfilling Hardy-Weinberg equilibrium (HWE) in the control group (P > 0.01 was eligible). Any study with inconsistent data was excluded.

The following information was extracted from selected studies: surname of the first author, publication year, country or origin, ethnicity of the studied population, characteristics of the cases and controls, number of individuals with genotypes GG, GT and TT in both cases and controls, and the methods used for genotyping. All information was carefully extracted from eligible publications independently and in duplicate by the two authors who used recommended guidelines to report on meta-analyses. Any disagreement was adjudicated by a third author.

Statistical analysis

For each study, the odds ratio (OR) with 95% confidence interval (95%CI) were calculated to assess the strength of association between the LOC387715/ARMS2 rs10490924 G>T polymorphism and PCV risk. HWE was assessed in the control group by using the χ^2 goodness-of-fit test. Gene effect on PCV was estimated by a logistic regression approach proposed for molecular association studies. The pooled OR was calculated by the fixed effects model or the random effects model according to the heterogeneity. Heterogeneity assumption was tested by the Q-test and a P value greater than 0.10 indicates the lack of heterogeneity among studies. If no heterogeneity (P > 0.10) was observed, the fixed effects model was used to calculate the pooled OR. Otherwise, the random effects model was employed. Three different types of OR were calculated: i) allele comparison (T allele versus G allele in the LOC387715/ARMS2 rs10490924 G>T polymorphism); ii) comparison between risk-variant homozygotes and wild homozygotes (TT genotype versus GG genotype in the LOC387715/ARMS2 rs10490924 G>T polymorphism); iii) comparison between risk-variant heterozygotes and wild homozygotes (TG genotype versus GG genotype in the LOC387715/ARMS2 rs10490924 G>T polymorphism). Population attributable risk of the risk allele was calculated according to the method described by Chang et al. (2007). The potential publication bias was assessed visually in a funnel plot of log (OR) against its standard error, and the degree of asymmetry was evaluated using the Egger test (P < 0.05 was considered to be statistically significant). Sensitivity analyses were carried out by including or excluding studies not in HWE, but a deviation from HWE in mixed control population was allowed (Wittke-Thompson et al., 2005). All statistical analyses were carried out with Stata/SE version 10.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Study characteristics

There were 14 published articles investigating the association between the LOC387715/ARMS2 rs10490924 G>T polymorphism and PCV risk. Two of them were kind of overlapping, and only the one with larger sample was included (Gotoh et al., 2009, 2010), four publications did not involve a case-control design (Sakurada et al., 2010, 2011; Bessho et al., 2011; Tsujikawa et al., 2011), and one was a sibling-based study (Machida et al., 2010). All remaining publications were verified for being suitable for meta-analysis. Thus, data from eight publications (Kondo et al., 2007; Lee et al., 2008; Sakurada et al., 2008; Hayashi et al., 2010; Lima et al., 2010; Nakanishi et al., 2010; Gotoh et al., 2010; Fuse et al., 2011) were included in the following analysis, to investigate the modifying effect of the rs10490924 G>T polymorphism on PCV risk. Table 1 demonstrates the characteristics of these studies.

The sum of sample sizes of the eight studies was 4701, which included 1446 cases and 3255 controls. The average ages ranged from 63.8 to 75.1 in case groups and 46.6 to 73.2 in control groups. The gender ratio (M/F) in the two groups varied from 0.75 (40/53) to 4 (48/12) across the eight studies. All studies were of case-control design, with seven conducted among Asians and one in Caucasians. Cases were recruited from hospital patients and controls had mainly healthy characteristics with regard to vision and unrelated to the cases. The genotyping methods used in these studies included polymerase chain reaction, TaqMan assay, sequencing, and denaturing high-performance liquid chromatography. The HWE tests performed on controls showed that all studies fulfilled HWE (see Table 2).

Allele comparison

The frequency of the risk allele T in the LOC387715/ARMS2 rs10490924 G>T polymorphism in controls across all studies ranged from 0.22 to 0.39, while the variation among Asians was smaller, ranging from 0.33 to 0.39 (Table 2). The mean T allele frequency in Asians was significantly higher than in Caucasians (0.37 versus 0.22).

The association between the LOC387715/ARMS2 rs10490924 G>T polymorphism and PCV was evaluated in the eight studies included. The heterogeneity test of the T allele versus the G allele (OR) showed no statistical significance (Q = 9.32, P = 0.231, I^2 = 24.9%); therefore, pooled OR were estimated based on the fixed effects model. As shown in Figure 1A, individuals with the T allele were 2.09 times more likely to have PCV than individuals with the G allele (95%CI = 1.906-2.288). The cumulative meta-analysis results remained significant and were consistent over time (Figure 1B). No individual study affected dominantly the overall OR in further conducted influence analysis (OR = 2.09, 95%CI = 1.903-2.285). Moreover, a funnel plot and the Egger test were used to detect publication bias. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (Figure 1C), and the Egger test also suggested an absence of publication bias in the model (t = 0.84, P = 0.435).

Table 1. General characteristics of case-control studies included in the meta-analysis.

Ref	Author	Country	Ethnicity	Study design	No. of eligible subjects		Mean age (years)		Gender ratio (male/female)		Genotyping methods
					Cases	Controls	Cases	Controls	Cases	Controls	
1	Kondo et al., 2007	Japan	East Asian	Case-control	76	94	73.6	71.2	62/14	63/31	TaqMan
2	Lee et al., 2008	Singapore	Chinese	Case-control	72	96	63.8	67.2	46/26	40/53	TaqMan
3	Sakurada, 2008	Japan	Japanese	Case-control	109	85	70.6	73.2	80/29	62/23	Multiplex PCR
4	Hayashi et al., 2010	Japan	Japanese	Case-control	518	1351	75.1	51.2	381/137	722/629	TaqMan
5	Lima et al., 2010	USA	Caucasian	Case-control	55	368	73.0	NR	32/23	NR	TaqMan
6	Nakanishi et al., 2010	Japan	Japanese	Case-control	375	847	73.1	65.5	269/106	418/429	TaqMan
7	Fuse et al., 2011	Japan	Japanese	Case-control	60	138	70.3	68.6	48/12	101/37	Sequencing
8	Gotoh et al., 2010	Japan	Japanese	Case-control	181	276	73.0	46.6	130/51	NR	TaqMan

NR = not reported; PCR = polymerase chain reaction.

Table 2. Number of alleles and genotypes in case and control groups of studies in a meta-analysis of the association between the LOC387715 gene polymorphism and polypoidal choroidal vasculopathy.

Ref.	Author	Cases/controls	T allele frequency		Genotype frequencies						HWE P
			Cases	Controls	Cases			Controls			
					TT	TG	GG	TT	TG	GG	
1	Kondo	76/94	0.64	0.38	33	31	12	15	41	38	0.783
2	Lee	72/93	0.56	0.39	25	30	17	12	48	33	0.699
3	Sakurada	109/85	0.64	0.35	45	49	15	14	32	39	0.269
4	Hayashi	509/1336	0.55	0.39	171	216	122	196	638	502	0.959
5	Lima	55/368	0.32	0.22	6	23	26	14	136	218	0.439
6	Nakanishi	375/847	0.56	0.37	133	152	90	113	401	333	0.903
7	Fuse	60/138	0.47	0.33	18	20	22	16	58	64	0.876
8	Gotoh	181/276	0.57	0.38	65	77	39	33	142	101	0.283

HWE = Hardy-Weinberg equilibrium.

Subgroup analysis was conducted by median (73 years) of mean ages of case groups, where a stronger effect was noted for mean age <73 years (OR = 2.29, 95%CI = 1.79-2.94) compared to mean age ≥73 years (OR = 2.06, 95%CI = 1.87-2.27) (see Table 3).

Genotype comparison

The genotype frequency of the LOC387715/ARMS2 rs10490924 G>T polymorphism between the case and control groups is presented in Table 2. The heterogeneity test of both TT genotype versus GG genotype (OR_1) and TG genotype versus GG genotype (OR_2) showed no statistical significance (Q = 5.90, P = 0.55, I^2 = 0.0%; Q = 10.04, P = 0.19, I^2 = 30.3%); therefore, pooled OR were estimated based on the fixed effects model. Overall meta-analysis indicated that the individuals who had the homozygous variant TT genotype and the heterozygous variant TG genotype had 4.23- and 1.47-fold increased risk of PCV, respectively, compared to the individuals with the wild homozygote GG genotype [OR_1 (TT *vs* GG) = 4.23, 95%CI = 3.53-5.06; OR_2 (TG *vs* GG) = 1.47, 95%CI = 1.26-1.71] (see Figures 2 and 3). The cumulative meta-analysis results remained significant and were consistent over time. No individual study affected the overall OR dominantly in further conducted influence analysis (OR_1 = 4.21, 95%CI = 3.51-5.04; OR_2 = 1.46, 95%CI = 1.25-1.71). Publication bias was detected by both a funnel plot and the Egger test. The shape of the funnel plot did not reveal any evidence of obvious asymmetry, and the Egger test suggested an absence of publication bias in the model (t = 1.32, P = 0.235; t = 0.97, P = 0.71).

Moreover, we performed subgroup analysis by median (73 years) of the mean ages of case groups, where a stronger effect was found for both homozygous variant TT genotype and heterozygous variant TG genotype for mean age <73 years (OR_1 = 4.85, 95%CI = 2.97-7.91; OR_2 = 1.68, 95%CI = 1.11-2.53) compared to mean age ≥73 years (OR_1 = 4.13, 95%CI = 3.40-5.02; OR_2 = 1.43, 95%CI = 1.21-1.69) (see Table 3).
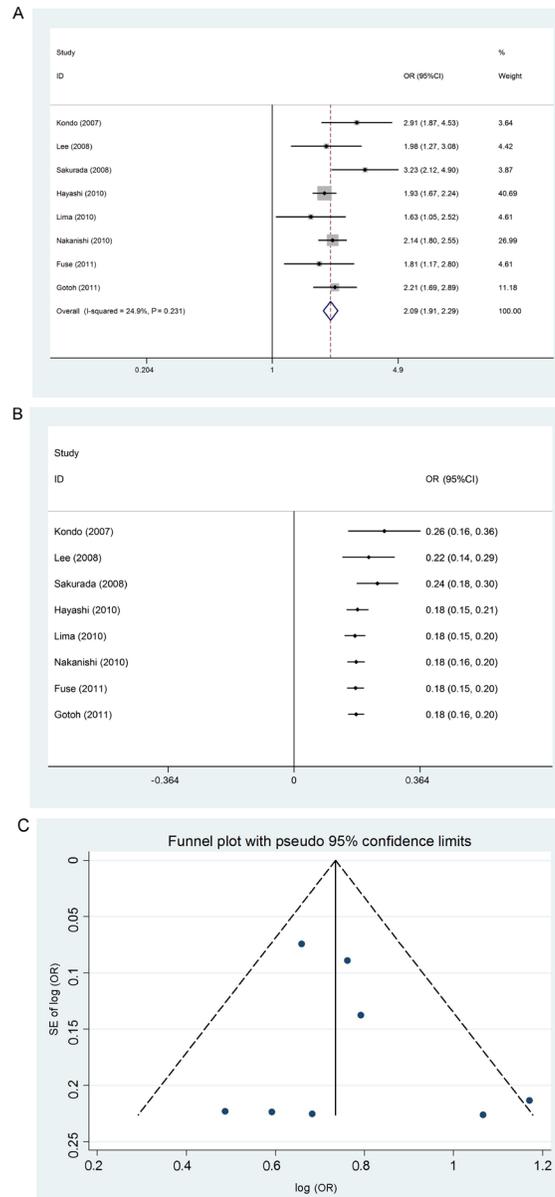
Figure 1. Forest plot, cumulative random-effects meta-analysis, and publication bias plot for meta-analysis of allele (T versus G) of the LOC387715/ARMS2 rs10490924 G>T polymorphism and polypoidal choroidal vasculopathy. **A.** Shows the forest plot of meta-analysis. Each study is shown by the point estimate of the odds ratio (OR) (the size of the square is proportional to the weight of each study) and 95% confidence interval (95%CI) for the OR (extending lines). **B.** Shows cumulative random-effects meta-analysis. The point indicate the OR and horizontal lines indicate 95%CI. **C.** Shows the Begg funnel plot of studies included in the meta-analysis. The horizontal axis represents log (OR) and the vertical axis means the standard error (SE) of log (OR). Vertical line and sloping lines in the funnel plot represent random effect summary OR and expected 95%CI for a given SE, respectively. Each circle area represents the contribution of each study to the pooled OR.

Table 3. Subgroup analysis of the LOC387715 gene polymorphism and polypoidal choroidal vasculopathy.

	Studies	Cases	Controls	T vs G				TT vs GG				T G vs GG			
				OR	95%CI	Q*	P*	OR	95%CI	Q*	P*	OR	95%CI	Q	P
All studies	8	1446	3255	2.088	1.906~2.288	9.32	0.231	4.225	3.526~5.063	5.9	0.551	1.465	1.256~1.709	10.04	0.186
Mean age															
<73 years	3	241	319	2.292	1.788~2.938	4.11	0.128	4.85	2.974~7.911	2.61	0.271	1.677	1.112~2.527	7.98	0.018
≥73 years	5	1205	2936	2.058	1.866~2.270	4.6	0.331	4.132	3.401~5.021	2.96	0.564	1.434	1.214~1.693	1.66	0.798
Ethnicity															
Asian	7	1391	2887	2.111	1.923~2.317	8.02	0.236	4.241	3.530~5.097	5.81	0.445	1.469	1.252~1.723	10.03	0.123
Non-Asian	1	55	368	1.625	1.051~2.520	-	-	3.593	1.271~10.159	-	-	1.418	0.778~2.585	-	-

95%CI = 95% confidence interval; OR = odds ratio. *Test for heterogeneity.
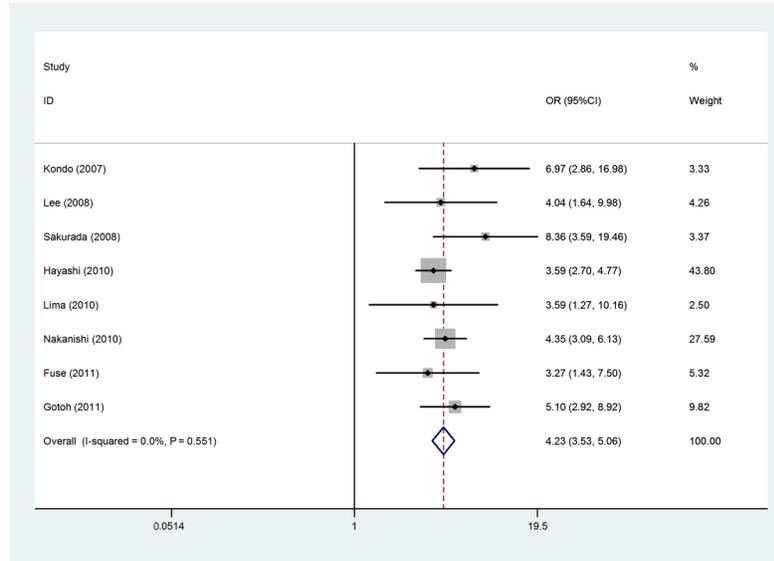
Figure 2. Random-effects meta-analysis of homozygous (TT versus GG) genotypes of the LOC387715/ARMS2 rs10490924 G>T polymorphism and polypoidal choroidal vasculopathy. Squares indicate study-specific odds ratio (OR) (size of square reflects the study-statistical weight, i.e., inverse of variance); horizontal lines indicate 95% confidence interval (95%CI); diamond indicates summary OR with its corresponding 95%CI.
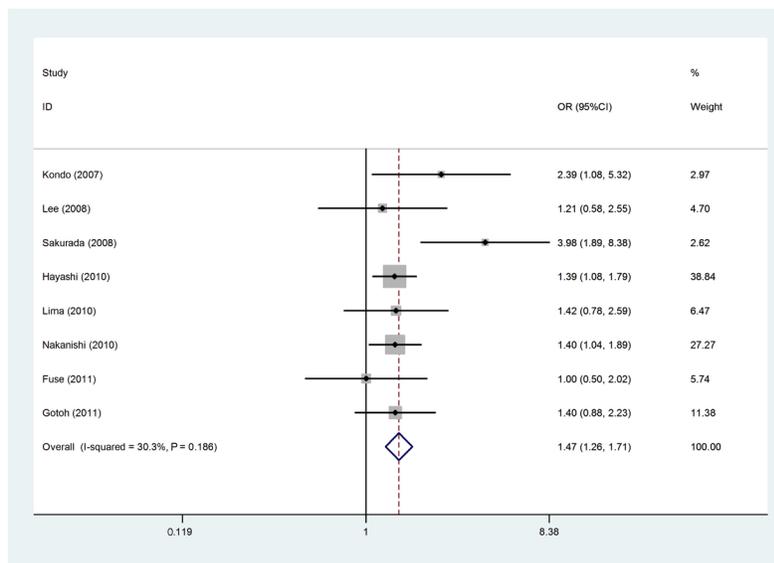
Figure 3. Random-effects meta-analysis of heterozygous (TG versus GG) genotypes of the LOC387715/ARMS2 rs10490924 G>T polymorphism and polypoidal choroidal vasculopathy. Squares indicate study-specific odds ratio (OR) (size of square reflects the study-statistical weight, i.e., inverse of variance); horizontal lines indicate 95% confidence interval (95%CI); diamond indicates summary OR with its corresponding 95%CI.

DISCUSSION

A single nucleotide polymorphism in LOC387715/ARMS2 rs10490924 has been suggested as a possible modifier of PCV risk in a few studies. The present study for the first time looks into this issue using meta-analysis. Our study showed a strong genetic effect of the LOC387715/ARMS2 rs10490924 G>T polymorphism on PCV and indicated a moderate co-dominant mode of action.

It is widely accepted that the LOC387715/ARMS2 gene polymorphisms are significantly associated with the phenotype and progression of AMD (Rivera et al., 2005; Dewan et al., 2006; Yoshida et al., 2007). PCV is usually clinically categorized as a subtype of neo-vascular AMD because it has been determined that PCV and AMD have considerable overlaps in molecular gene determinants, genetic background, pathophysiological characteristics, clinical manifestations, and environmental risk factors (Ciardella et al., 2004; Maruko et al., 2007; Laude et al., 2010). Our primary analysis indicated that, for the LOC387715/ARMS2 rs10490924 G>T polymorphism, homozygosity and heterozygosity for the at-risk allele genotype (TT and TG) increased the likelihood for PCV 4.2- and 1.5-fold, respectively, compared to the wild-type genotype. This finding confirmed the remarkable genetic effect of the LOC387715/ARMS2 gene polymorphism and provided additional evidence of the common genetic background shared between PCV and AMD.

The LOC387715/ARMS2 gene has been shown to be expressed in the mitochondria of retina photoreceptors and may be associated with RPE dysfunction (Fritsche et al., 2008). The lesion of RPE may subsequently lead to abnormal choroidal vasculopathy, which results in PCV. In addition, chromosome 10q26 has been reported to harbor three important AMD susceptible genes, including Pleckstrin homology domain-containing protein family A member 1, age-related maculopathy susceptibility 2 (LOC387715/ARMS2), and high-temperature requirement factor A 1 (HTRA1/PRSS11) (Jakobsdottir et al., 2005; Rivera et al., 2005). Previous studies have shown the distinct association between the HTRA1 polymorphism and PCV (Kondo et al., 2007; Lee et al., 2008; Gotoh et al., 2010) and proved the strong linkage disequilibrium (LD) across the ARMS2/HTRA1 region (Laude et al., 2010). Therefore, the T allele is possibly in LD with the causative allele, which may further contribute to the significant effect of the LOC387715/ARMS2 rs10490924 G>T polymorphism on PCV.

The present meta-analysis shows that the genetic effect of the LOC387715/ARMS2 rs10490924 G>T polymorphism on PCV was more significant among patients of mean age <73 years than among patients of mean age ≥73 years. This conclusion is inconsistent with previous studies, which have shown that the older age subgroup has a stronger effect of the HTRA1 polymorphism on AMD (Leske et al., 2006; Tang et al., 2009). Although age is an acceptable environmental risk factor for PCV (Yannuzzi et al., 1999; Ciardella et al., 2004), a few studies indicated that PCV was most commonly diagnosed among the patients with ages between 60 and 70 years (Ciardella et al., 2004; Imamura et al., 2010). It is also possible that PCV does not have a steep slope for age-specific increase in incidence, which is different from AMD. Our analysis confirms that environmental factors can also play an important role in PCV development. Seven of eight publications were based on Asian populations, which may be explained by the asymmetry incidence of PCV in different ethnicities. According to previous research, PCV tends to occur more frequently in dark-pigmented individuals, such as black patients and Asians (Sho et al., 2003), and the incidence of PCV seems to be remark-

ably high in Japanese (Maruko et al., 2007). Thus, our meta-analysis results reinforced the conclusion that the effect of the LOC387715/ARMS2 rs10490924 G>T polymorphism on susceptibility to PCV is particularly important for Asians.

Some limitations of our meta-analysis should be acknowledged. First, the numbers of non-Asian patients included from the selected studies in our meta-analysis were relatively small to perform reliable subgroup analysis by ethnicity. Second, the unavailability of more detailed information of target patients prevented a more elaborative evaluation over adjusted OR by age, gender, environmental factors, and other potentially suspected factors (DeAngelis et al., 2007). Third, further explorations of gene-gene or gene-environment interactions and gene-subtype PCV associations were limited due to the lack of original data.

In summary, our meta-analysis provided evidence that the LOC387715/ARMS2 rs10490924 G>T polymorphism is strongly associated with a PCV risk. The genetic effect on PCV was more significant among individuals of mean age <73 years and particularly played a more important role among Asians. Further well-designed studies with larger sample size, less ethnic bias and better control of suspected factors are necessary to fully evaluate the genetic contributions and confirm these findings.

ACKNOWLEDGMENTS

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