8 Differential Genotypes in Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy: A Updated Meta-Analysis

Haoyu Chen, Li Ma, Xulong Liao, Li Jia Chen, and Chi Pui Pang

Abstract

Neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) have some shared risk factors and clinical manifestation, but there are also some different features. Genetic variants are an important risk factor for both conditions. In this chapter, we reported an updated meta-analysis comparing the genetic variants between PCV and nAMD. Totally 57 SNPs in 20 genes were investigated. Among them, 11 SNPs in AR*MS2-HTRA1* and rs77466370 in *FGD6* showed significant differences between PCV and nAMD, but the other SNPs had similar distribution between PCV and nAMD, including variants in *CFH, VEGF, C2, CFB*. These results suggest that PCV and nAMD shares the majority of genetic components, but the variants that distribute differently between these two conditions may explain the pathogenic and clinical difference of PCV and nAMD.

Keywords

Age-related macular degeneration
Polypoidal choroidal vasculopathy · Meta-analysis · Single nucleotide polymorphism
Genetic association

8.1 Introduction

Age-related macular degeneration (AMD) is a leading cause of blindness and central vision impairment and blindness in elderly patients [1]. There are two types of AMD, dry and wet (exudative or neovascular) AMD (nAMD), which is characterized by atrophy of retinal pigment epithelium (RPE) and choroidal neovascularization respectively. The clinical manifestations of nAMD include choroidal neovascularia-

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tion, subretinal fluid, hemorrhage, exudation, and fibrosis. Polypoidal choroidal vasculopathy (PCV) is characterized by the branching vascular network of the choroid and polyp-like aneurysmal dilations of its terminals [2]. Clinically, PCV is manifested as serosanguineous detachments of the pigmented epithelium and exudative changes that can recur in several episodes.

It is still controversy whether PCV presents a subtype of nAMD or a distinct disease. PCV and nAMD have some shared characters but there are also some different features, including risk factors, clinical manifestations, natural course, and response to treatment.

Both PCV and nAMD are commonly seen in elderly patients. However, PCV presents a younger age than nAMD [3, 4]. Although both PCV and nAMD occur in any race, PCV is known to be more prevalent in pigmented ethnicity while nAMD has a high prevalence in European than in Asian [5]. Smoking is a proven risk factors for both PCV and nAMD, while female gender is a protective factor for both conditions [3, 6]. Diabetes was found to be more prevalent in nAMD than in PCV patients [4].

Clinically, Both PCV and nAMD present as exudation or hemorrhage at the macular region. But there are also different characters between them. nAMD is predominantly located at the fovea or parafoveal region, while PCV may involve perifoveal, peripapillary, or even peripheral retina. The histological feature of PCV is majorly polypoidal enlargement of the terminal of the choroidal vessel. nAMD is characterized by choroidal neovascularization above or underneath the RPE. The choroidal thickness of nAMD is usually thin but that of PCV is usually thick. The natural history of PCV is multiple, recurrent episodes while nAMD is a progressive disease. Although both disorders can be treated using photodynamic therapy or anti-vascular endothelial growth factor (VEGF) antibody, nAMD responses better to anti-VEGF therapy and PCV responses better to photodynamic therapy [7].

Genetic studies of AMD have identified susceptibility single-nucleotide polymorphisms (SNPs) in multiple genes, including rs1061170 in *complement factor H (CFH)*, rs10490924 in *age-related maculopathy susceptibility* 2 (*ARMS2*), and rs11200638 in *high-temperature requirement factor H* (*HTRA1*) [8, 9]. In 2016, the International AMD Genomics Consortium reported 34 loci associated with AMD [10]. Due to the similarities between nAMD and PCV, major gene SNPs for nAMD have also been evaluated in PCV. The *CFH* SNP rs1061170 was not found to be associated with PCV [11], while an adjacent SNP rs800292 was significantly associated [11–13]. Both rs10490924 and rs11200638 at the *ARMS2-HTRA1* locus were associated with PCV [11, 12, 14, 15]. In 2012, we published a meta-analysis investigating genetic associations of PCV with SNPs in the *ARMS2*, *HTRA1*, *CFH*, and *complement component 2* (*C2*) genes. The results also showed that one SNP, rs10490924, in *ARMS2* showed a significant difference between PCV and AMD [16]. In 2015, we reported the updated meta-analysis of the association of genetic variants with PCV, which found 31 polymorphisms in 10 genes/loci (including ARMS2, HTRA1, CFH, C2, CFB, RDBP, SKIV2L, CETP, 8p21, and 4q12) were significantly associated with PCV. Twelve polymorphisms at the ARMS2-HTRA1 locus showed significant differences between PCV and nAMD. There are many new articles investigating these topics since the publication of the latest meta-analysis. In this chapter, we further updated our meta-analysis comparing the genetic association profiles between PCV and nAMD.

8.2 Methods of Meta-Analysis

A systematic literature search was performed using EMBASE, PubMed, Web of Science, and Chinese Biomedical Literature Database. The search used the terms (polypoidal choroidal vasculopathy or PCV) and (gene or genetic or polymorphism or variant or SNP or DNA). We retrieved all related records published from February 1, 2015, and September 27, 2018, and then added the articles published before Feb 2015 that were included in our previous meta-analysis. The reference lists of all eligible studies, reviews, and meta-analyses were also screened to prevent that any relevant studies were omitted.

The retried records were reviewed by two independent reviewers (L.M. and X. L.) and any inconsistency was resolved by discussion with another reviewer (H.C.). The following criteria were used when assessing the records [1]. case-control studies, cohort studies, or population-based studies that evaluated the difference of gene variants between PCV and nAMD; and [2] allele or genotype counts and/or frequencies being presented or able to be calculated from the data in the study. For those reports published by the same study group on the same gene markers, only the latest study was included. Case reports, animal studies, reviews, conference abstracts, comments, articles without sufficient data, or published in language other than English were excluded.

The data from included studies were extracted by the two independent reviewers (L.M. and Z.L.) and any inconsistency was resolved by discussion with another reviewer (H.C.). If there were several cohorts in the same article, they were treated as independent study. The following information from each record was extracted: first author, year of publication, the ethnicity of study subjects, study design, genotyping method, and sample size, demographics, allele, and genotype distribution in PCV and nAMD.

The distribution of genetic variants between PCV and nAMD from all included studies were pooled. Three genetic models were used, including allelic, dominant, and recessive models. The effect size was assessed using a summary odds ratio (OR) and its 95% confidence intervals (CIs) of each SNP. The software, Review Manager software (RevMan, version 5.3.5, The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis. The I^2 statistic was adopted to assess the heterogeneity among the studies. The I^2 values correspond with no (<25%), low (25%–50%), moderate (50%–75%), and high heterogeneity (≥75%). If the I^2 value was ≥50%, the fixed effects model was used in the meta-analysis, otherwise, the random effects model was used. A summary P value <0.05 was considered statistically significant. We performed a sensitivity analysis by omitting one study at a time and calculating the pooled ORs for the remaining studies. Funnel plots were constructed to assess potential publication bias.

8.3 Results of Updated Meta-Analysis

Our literature search yielded a total of 1315 reports published between February 1, 2015, and September 27, 2018, from EMBASE, PubMed, Web of Science and Chinese Biomedical Literature Database. Out of these, 502 articles were excluded due to duplicates. After assessing the titles and abstracts, a further 606 reports with unrelated topics were omitted. For the remaining 107 studies, the full-texts were retrieved and reviewed. Another 89 reports were excluded, among which 62 studies were on AMD but not PCV, 2 were reviews, 23 were non-genetic studies, and 1 was a case report. Finally, 18 articles were eligible for the meta-analysis. A further 66 studies published before 2015 that were used in our previous meta-analysis were added. However, 19 of these studies were excluded because they only studied in PCV patients. Thus, a total of 65 studies were included in the meta-analysis. Figure 8.1 shows the flowchart of literature inclusion and exclusion with the specification of reasons and Table 8.1 shows the characters of the included studies.

In these 65 studies, both PCV and nAMD were assessed for associations with a total of 57 SNPs in 20 genes or loci (i.e., *ARMS2*, *HTRA1*, *CFH*, *VEGF-A*, *C2*, *CFB*, *SKIV2L*, *CETP*, 8p21, 4q12, *ELN*, *LIPC*, *LPL*, *FGD6*, *ABCA1*, *ABCG1*, *PGF*, *TLR3*, *LOXL1*, and *PEDF*; Table 8.1). In total, 11 SNPs at the *ARMS2-HTRA1* locus and 1 in *FGD6* showed significant differences between PCV and nAMD (Tables 8.2 and 8.3). There was no significant difference between PCV and nAMD in the remaining 45 SNPs (Table 8.4).

There are 12 studies tested the most-investigated SNP, *ARMS2* rs10490924, involving 2361 PCV and 2138 nAMD patients (Table 8.2) [3, 12, 15, 22, 26, 27, 35, 36, 38, 43, 44, 78]. The frequency of the T allele was significantly lower in PCV than in nAMD (summary OR 0.69; 95% CI 0.63–0.75; $P = 5.50 \times 10^{-16}$;

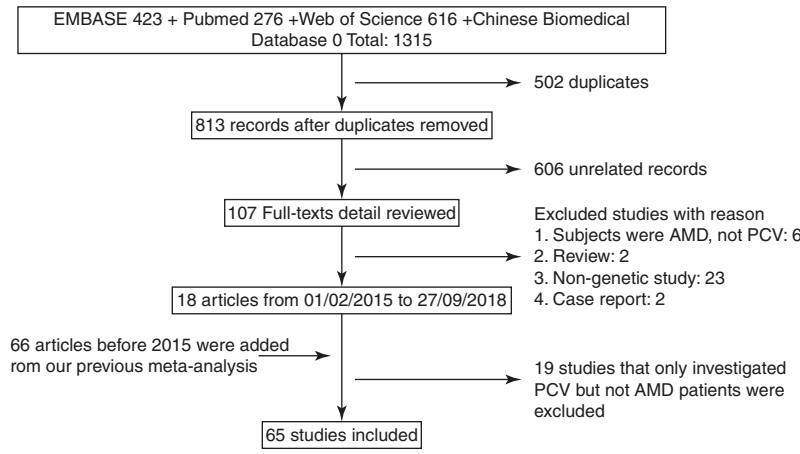

Fig. 8.1 Flow chart of literature screen

Table 8.2 and Fig. 8.2). The association was also statistically significant in both dominant and recessive models (OR = 0.64, $P = 8.80 \times 10^{-8}$ and OR = 0.62, $P = 1.47 \times 10^{-13}$ respectively; Table 8.3 and Fig. 8.2). The results of the sensitivity analysis found that the association remains significant after omitting any single included cohorts (data not shown). And there was no asymmetry on the funnel plots (Fig. 8.5). There are 8 other SNPs in *ARMS2*, namely rs3750848, rs36212731, rs36212732, rs36212733, rs3750846, rs10664316, c.372_815del443ins54 and rs2672587, were evaluated in 2 to 3 cohorts, and also showed significant differences between PCV and nAMD (ORs values between 0.48 and 0.71, P values between 7.19×10^{-9} and 0.05; Table 8.2).

There are seven studies tested the *HTRA1* SNP rs11200638 in 1362 PCV and 1364 nAMD patients [3, 14, 18, 43, 44, 57, 73]. The A allele frequency was lower in PCV compared to nAMD, with a summary OR of 0.75 (95% CI, 0.67–0.84; $P = 2.14 \times 10^{-5}$; Table 8.2 and Fig. 8.3). The association was also statistically significant in both dominant and recessive models (OR = 0.67, P = 0.006 and OR = 0.70, $P = 9.87 \times 10^{-6}$ respectively, Table 8.3 and Fig. 8.3). The results of the sensitivity analysis found that the association remain significant after omitting any single included cohorts (data not shown). And there was no asymmetry on the funnel plots (Fig. 8.5). Another *HTRA1* SNP, rs2672587, was also evaluated in two cohorts, and showed significant differences between PCV and nAMD (G allele; OR, 1.41; 95% CI, 1.07–1.85; $P = 0.01$; Table 8.2).

The SNP rs77466370 in *FGD6* was studied in 3318 PCV and 2457 nAMD patients from five cohorts. The summary OR for the T allele was 1.86 (95% CI, 1.48–2.35; $P = 1.29 \times 10^{-7}$; Table 8.2 and Fig. 8.4). The association was statistically significant in the dominant model but no in the recessive model (OR = 1.89, $P = 1.52 \times 10^{-7}$ and OR = 2.19, $P = 0.27$ respectively; Table 8.3 and Fig. 8.4). The results of the sensitivity analysis found that the association remain significant after omitting any single included cohorts (data not shown). And there was no asymmetry on the funnel plots (Fig. 8.5).

8.4 Discussion

Genetic variants are important risk factors for both nAMD and PCV. This updated systematic review and meta-analysis compared the distribution of genetic variants between nAMD and PCV. The results showed that 57 SNPs in 20 genes had been investigated in both PCV and nAMD in the same cohorts. The pooled outcomes showed 11 SNPs at the *ARMS2-HTRA1* locus and 1 SNP in *FGD6* had significant differences between PCV and nAMD. The results are robust because the sensitivity test found consistency when omitting any included studies. There was no publication bias found on the funnel plots. There was no significant difference between PCV and nAMD in

Table 8.1 Characteristics of the included studies in the meta-analysis

First author and reference	Year	Ethnicity	Study design	Genotyping method	HWE reported	PCV			AMD			Gene/loci investigated
						N	Male ratio	Mean age ± SD (years)	*N*	Male ratio	Mean age ± SD (years)	
						N	Male ratio	Mean age ± SD (years)	N	Male ratio	Mean age ± SD (years)	
Gotoh N [17]	2004	Japanese	1	PCR	Yes	58	0.76	71.6 ± 6.2	85	0.81	70.9 ± 7.9	*APOE*
Kondo N[a] [18]	2007	Japanese	1	TaqMan	Yes	76	0.82	73.6 ± 7.4	73	0.79	75.7 ± 7.3	*ARMS2*, *HTRA1*
Gotoh N[a] [19]	2008	Japanese	1	TaqMan	NA	204	0.72	73.1 ± 7.7	116	0.74	76.1 ± 8.3	*CFH*, *HTRA1*
Kondo N[a] [20]	2008	Japanese	2	TaqMan	Yes	103	0.81	74 ± 6.6	78	0.78	76 ± 7.4	*ELN*
Bessho H[a] [21]	2009	Japanese	2	TaqMan	Yes	140	0.77	73 ± 6.9	116	0.78	75 ± 7.2	*PEDF*
Goto A[a] [22]	2009	Japanese	2	TaqMan	Yes	100	0.81	72.7 ± 8.3	100	0.73	74.6 ± 8.8	*ARMS2*, *CFH*, *C3*
Gotoh N[a] [23]	2009	Japanese	2	PCR	Yes	55	0.82	72.9 ± 7.3	56	0.64	76.2 ± 9.1	*ARMS2*
Kondo N [24]	2009 a	Japanese	2	TaqMan	Yes	140	0.77	73 ± 6.9	116	0.78	75 ± 7.2	*SOD2*
Gotoh N[a] [14]	2010	Japanese	2	TaqMan	Yes	181	0.72	73.0 ± 7.83	84	0.74	76.2 ± 8.58	*ARMS2*, *HTRA1*
Hayashi H[a] [25]	2010	Japanese	2	TaqMan	Yes	518	0.73	75.0 ± 7.8	408	0.72	77.4 ± 8.4	*ARMS2*, *CFH*
Lima LH[a] [15]	2010	Caucasian	2	PCR & TaqMan	NA	55	0.58	73 ± 8.2	368	–	–	*ARMS2*, *CFH*, *CFB*, *C2*
Bessho H[a] [26]	2011	Japanese	3	TaqMan	NA	119	0.81	73 ± 8.0	68	0.78	76 ± 7.0	*ARMS2*
Fuse N[a] [27]	2011	Japanese	2	PCR	Yes	60	0.80	70.3 ± 9.2	50	0.80	71.3 ± 8.2	*ARMS2*, *LOXL1*
Lima LH[a] [28]	2011	Caucasian	2	TaqMan	NA	56	0.59	72 ± 8.3	368	–	71.3 ± 8.9	*ELN*
Nakata I [29]	2011 b	Japanese	2	TaqMan	Yes	510	0.73	77.4 ± 8.4	401	0.72	75.0 ± 7.8	*SERPING1*
Sng CCA[a] [30]	2011	Chinese	1	PCR	Yes	120	0.64	68.8 ± 7.9	126	0.67	73.0 ± 8.6	*TLR3*
Yamashiro K[a] [31]	2011	Japanese (Kyoto)	2	TaqMan	NA	518	0.74	75.1 ± 8.5	408	0.72	77.7 ± 8.4	*ELN*
		Japanese (Saitama)	2	TaqMan	NA	154	0.79	71.8 ± 7.8	216	0.73	72.7 ± 8.7	*ELN*
Zhang X [32]	2011	Chinese	2	PCR	Yes	177	0.66	65 ± 8.45	131	0.64	67 ± 9.46	9q21

(continued)

Table 8.1 (continued)

First author and reference	Year	Ethnicity	Study design	Genotyping method	HWE reported	PCV			AMD			Gene/loci investigated
						N	Male ratio	Mean age ± SD (years)	*N*	Male ratio	Mean age ± SD (years)	
Wu K[a] [33]	2012	Chinese	2	PCR	Yes	177	0.66	65 ± 8.45	131	0.64	67 ± 9.46	*PEDF*
Arakawa S[a] [10]	2011	Japanese	2	BeadChip & PCR	NA	480	–	–	298	–	–	8p21, 4q12
Sakurada Y[a] [34]	2011	Japanese	2	PCR	Yes	135	–	–	89	–	–	*LOXL1*
Tanaka K[a] [35]	2011	Japanese	2	TaqMan	Yes	381	0.71	69.9 ± 9.1	253	0.74	73.7 ± 7.5	*CFH*, *ARMS2*, *ELN*, *MTHFR*
Yanagisawa S[a] [36]	2011	Japanese	2	TaqMan	Yes	198	0.79	73 ± 7.3	181	0.77	75 ± 7.4	*ARMS2*
Bessho H [37]	2012	Japanese	2	TaqMan	Yes	210	0.79	73.8 ± 7.5	139	0.78	75.3 ± 7.3	*CD36*
Liang XY[a] [38]	2012	Chinese	2	PCR	Yes	164	0.69	67.5 ± 9.0	156	0.53	75.9 ± 7.4	*ARMS2*, *HTRA1*
Nakata I[a] [39]	2012 a	Japanese (Kyoto)	2	TaqMan & Beadchip	Yes	720	–	–	664	–	–	8p21, 4q12
		Japanese (Yamanashi)	2	TaqMan	Yes	211	–	–	112	–	–	8p21, 4q12
		Chinese (Singapore)	2	Beadchip	Yes	118	–	–	122	–	–	8p21, 4q12
		Chinese (Hong Kong)	2	TaqMan	Yes	200	–	–	233	–	–	8p21, 4q12
Nakata I[a] [40]	2012 b	Japanese	2	TaqMan	Yes	581	0.72	72.59 ± 8.13	455	0.73	75.59 ± 8.60	*C2/CFB*
Nishiguchi KM [41]	2012	Japanese	2	PCR	Yes	105	0.85	70.2 ± 6.7	198	0.72	73.1 ± 8.0	*C9*
Zeng R [42]	2012	Chinese	2	PCR	Yes	195	0.67	64 ± 8.75	136	0.63	67 ± 9.29	*TIMP3*
Zuo C [43]	2012	Chinese	2	PCR	Yes	195	0.67	64 ± 8.75	136	0.63	67 ± 9.29	*COL1A2*
Cheng Y[a] [44]	2013	Chinese	2	PCR	Yes	92	0.52	69.5 ± 9.4	96	0.65	70.3 ± 8.8	*ARMS2*, *HTRA1*
Guo J [45]	2013	Chinese	2	PCR	Yes	300	0.63	66.8 ± 9.7	300	0.63	69.4 ± 8.9	*TOMM40*
Liu K[a] [46]	2013	Chinese	2	TaqMan	Yes	233	0.70	68.5 ± 9.0	200	0.55	75.3 ± 7.7	*C2-CFB-RDBP-SKIV2L*, *CFH*, *HTRA1*
Su Y [47]	2013	Chinese	2	PCR	Yes	251	0.67	65 ± 8.61	157	0.64	67 ± 9.21	*VEGF-A*

Sun Y[a] [48]	2013	Chinese	2	PCR	Yes	300	0.63	66.8 ± 9.7	300	0.63	69.4 ± 8.9	8p21, 4q12
Zhang X[a] [49]	2013	Chinese	2	PCR	Yes	250	0.66	65 ± 8.60	157	0.64	67 ± 9.21	*LIPC*, *ABCA1*, *CETP*, *LPL*, *FADS1*, *CFH*, *ARMS2*, and near *HTRA1*
Cheng Y[a] [50]	2014	Chinese	2	PCR	NA	92	0.52	69.5 ± 9.4	96	0.65	70.3 ± 8.8	*TLR3*
Huang L[a] [51]	2014a	Chinese	2	PCR	Yes	368	0.61	66.6 ± 9.6	344	0.64	69.2 ± 8.7	*CFH*
Huang L[a] [52]	2014b	Chinese	2	PCR	Yes	300	0.63	66.8 ± 9.6	300	0.63	69.4 ± 8.9	*FEK/COL10A1*, *VEGF-A*
Hata M [53]	2014	Japanese	3	TaqMan	NA	70	0.81	72.2 ± 8.8	58	0.71	76.4 ± 8.2	*CFH*, *ARMS2*
Ji Y[a] [54]	2014	Chinese	2	PCR	Yes	251	0.67	65 ± 8.6	157	0.64	67 ± 9.2	*GDF6*
Li F[a] [55]	2014	Chinese	2	PCR	Yes	298	0.62	66.8 ± 9.7	300	0.63	69.4 ± 8.9	*ABCA1*
Liang XY[a] [56]	2014	Chinese	2	PCR	Yes	179	0.71	67.9 ± 9.0	155	0.55	75.6 ± 7.5	*FPR1*
Liu K[a] [57]	2014a	Chinese	2	TaqMan	Yes	233	0.70	68.5 ± 9.0	200	0.55	75.3 ± 7.7	*ABCA1*, *LIPC*, *CETP*, *LCAT*, *PLTP*, *ABCG1*, *CFH*, *HTRA1*
Liu K[a] [58]	2014b	Chinese	2	TaqMan	Yes	233	0.70	68.5 ± 9.0	200	0.55	75.3 ± 7.7	*C3*, *CFH*, *HTRA1*
Park DH[a] [59]	2014	Korean	2	PCR	NA	62	0.79	70.3 ± 6.9	42	0.71	70.9 ± 7.2	*ARMS2*
Tanaka K[a] [60]	2014	Japanese	2	TaqMan	Yes	376	0.71	70.0 ± 8.9	250	0.75	73.6 ± 7.5	*C2*, *CFB*
Yang F [61]	2014	Chinese	2	PCR	Yes	300	0.63	66.8 ± 9.6	300	0.63	69.4 ± 8.9	*CFI*
Yoneyama S[a] [62]	2014 a	Japanese	1	TaqMan	Yes	250	0.76	73.1 ± 8.2	132	0.72	76.9 ± 7.7	*CFH*, *ARMS2*
Yoneyama S[a] [63]	2014 b	Japanese	1	TaqMan	Yes	333	0.76	73.1 ± 8.2	157	0.73	75.6 ± 8.4	*CFH*, *ARMS2*, *SKIV2L*
Zeng R [64]	2014	Chinese	2	PCR	Yes	251	0.67	66 ± 9.44	157	0.64	67 ± 9.17	*MMP9*
Huang L [65]	2015	Chinese	2	MALDI-TOF-MS	Yes	300	0.63	66.8 ± 9.7	300	63%	69.4 ± 8.9	*CFH, ARMS2/HTRA1*
Chen LJ [66]	2015	Chinese	2	TaqMan	Yes	236	0.69	68.5 ± 9.0	214	0.57	75.2 ± 7.6	*PGF, VEGF-A, VEGFB*
Jin E [67]	2015	Chinese	2	PCR	Yes	174	0.54	64.52 ± 6.78	453	0.56	67.12 ± 6.81	*HERPUD1*
Meng Q [68]	2015	Chinese	2	MALDI-TOF-MS	Yes	291	0.60	66.6 ± 9.6	230	0.63	69.3 ± 8.8	*CETP, LIPC*
Woo S [3]	2015	Korean	2	PCR	Yes	111	0.55	67.35 ± 7.34	154	0.56	72.56 ± 8.10	*31 candidate genes*
Yu Y [69]	2015	Chinese	2	MALDI-TOF-MS	Yes	300	0.63	66.8 ± 9.7	300	0.63	69.4 ± 8.9	*COL8A1*
Huang L [70]	2016	Chinese, Japanese, and Korean	2	Exome sequencing	Yes	3318	–	–	2457	–	–	

(continued)

Table 8.1 (continued)

First author and reference	Year	Ethnicity	Study design	Genotyping method	HWE reported	PCV			AMD			Gene/loci investigated
						N	Male ratio	Mean age ± SD (years)	*N*	Male ratio	Mean age ± SD (years)	
Ma L [71]	2016	Hong Kong Chinese	2	TaqMan	Yes	236	0.69	68.5 ± 9.0	235	0.55	75.3 ± 7.6	*ABCG1*
		Shantou Chinese	2	TaqMan	Yes	187	0.72	63.1 ± 10.5	189	0.69	67.3 ± 10.1	*ABCG1*
		Japanese	2	TaqMan	Yes	204	0.77	72.2 ± 8.0	192	0.67	74.3 ± 7.3	*ABCG1*
Ng TK [72]	2016	Chinese	2	PCR	Yes	188	–	–	195	–	–	*HTRA1*
Ye Z [73]	2016	Chinese	2	SNaPshot	Yes	419	0.70	64.8 ± 9.7	490	0.62	67.5 ± 9.6	*6p21.3, CFH, HTRA1*
Zuo C [74]	2016	Chinese	2	SNaPshot	Yes	250	0.66	65 ± 8.60	157	0.64	67 ± 9.21	*ENOS*
Fan Q [75]	2017	East Asian	2	Beadchips	Yes	1157	–	–	1062	–	–	*34 known AMD loci*
Ma L [76]	2017	Hong Kong Chinese	2	TaqMan	Yes	236	0.69	68.5 ± 9.0	214	0.57	75.2 ± 7.6	*ANGPT2, CFH*
		Shantou Chinese	2	TaqMan	Yes	187	0.72	63.1 ± 10.5	189	0.69	67.3 ± 10.1	*ANGPT2, CFH*
		Japanese	2	TaqMan	Yes	204	0.77	72.2 ± 8.0	192	0.67	74.3 ± 7.3	*ANGPT2, CFH*
Wen X [77]	2018	Chinese		Whole-exome and Sequenom MassARRAY	Yes	180	–	–	166	–	–	

Study design: 1 = cross-sectional study; 2 = case-control study; 3 = cohort study

[a]Indicates the study included both PCV and nAMD; "-" indicates there was no data for the ascertainment of controls; *NA* not mentioned in original studies

nAMD neovascular age-related macular degeneration; *PCR* polymerase chain reaction; *PCV* polypoidal choroidal vasculopathy

Table 8.2 Polymorphisms with significant differences between PCV and neovascular AMD

Region	Gene	Polymorphism	Ethnicity	Associated vs. reference allele	No. of cohorts	PCV vs. nAMD (sample size)	OR (95% CI)	*P*	I^2 (%)
10q26	*ARMS2*	rs10490924	All ancestries	T vs. G	12	2361 vs. 2138	0.69 (0.63–0.75)	5.50E−16	29
10q26	*ARMS2*	rs3750848	Asian	G vs. T	3	316 vs. 304	0.60 (0.47–0.76)	2.14E−05	0
10q26	*ARMS2*	rs36212731	Asian	T vs. G	3	1279 vs. 1364	0.71 (0.63–0.79)	2.23E−09	48
10q26	*ARMS2*	rs36212732	Asian	G vs. A	2	217 vs. 207	0.57 (0.42–0.76)	0.0001	0
10q26	*ARMS2*	rs36212733	Asian	C vs. T	2	217 vs. 204	0.57 (0.42–0.76)	0.0001	0
10q26	*ARMS2*	rs3750846	Asian	C vs. T	2	216 vs. 204	0.57 (0.42–0.76)	0.0001	0
10q26	*ARMS2*	rs10664316	Asian	I vs. N[a]	2	218 vs. 208	0.48 (0.33–0.69)	8.49E−05	45
10q26	*ARMS2*	c.372_815del443ins54	Asian	D vs. N†	2	219 vs. 209	0.55 (0.41–0.73)	4.50E−05	0
10q26	*ARMS2*	rs2014307	Asian	G vs. T	2	216 vs. 212	0.52 (0.27–1.00)	0.05	64
10q26	*HTRA1*	rs11200638	Asian	A vs. G	7	1362 vs. 1251	0.75 (0.67–0.84)	8.65E−07	32
10q26	*HTRA1*	rs2672587	Asian	G vs. C	2	276 vs. 182	1.41 (1.07–1.85)	0.01	9
12q22	FGD6	rs77466370	Asian	T vs. C	5	3318 vs. 2457	1.86 (1.48–2.35)	1.29E−07	0

Gene symbols: *ARMS2 = age-related maculopathy susceptibility 2*; *HTRA1 = HtrA serine peptidase 1*
[a]insAT vs. wide type; † del443ins54 vs. wide type
AMD age-related macular degeneration; *CI* confidence interval; *OR* odds ratio; *PCV* polypoidal choroidal vasculopathy; *Ref* reference

Table 8.3 Gene SNPs with significant differences between PCV and nAMD in dominant, recessive, homozygous and heterozygous models

Region	Gene	Polymorphism	Ethnicity	Associated vs. reference genotype	No. of cohorts	PCV vs. nAMD (sample size)	OR (95% CI)	*P*	I^2 (%)
10q26	*ARMS2*	rs10490924	All ancestries	TT + TG vs. GG	12	2361 vs. 2138	0.64 (0.54–0.75)	8.80E−08	0
				TT vs. TG + GG			0.62 (0.55–0.71)	1.47E−13	49
10q26	*ARMS2*	rs3750848	Asian	GG + GT vs. TT	3	316 vs. 304	0.78 (0.50–1.22)	0.28	0
				GG vs. GT + TT			0.44 (0.32–0.61)	6.70E−07	0
10q26	*ARMS2*	rs36212731	Asian	TT + TG vs. GG	2	1279vs. 1364	0.64 (0.55–0.75)	0.0001	0
				TT vs. TG + GG			0.64 (0.55–0.75)	2.70E−08	67
10q26	*ARMS2*	rs36212732	Asian	GG + GA vs. AA	2	219 vs. 212	0.84 (0.50–1.41)	0.51	0
				GG vs. GA + AA			0.47 (0.32–0.70)	0.0002	0
10q26	*ARMS2*	rs36212733	Asian	CC + CT vs. TT	2	217 vs. 204	0.84 (0.50–1.41)	0.51	0
				CC vs. CT + TT			0.47 (0.32–0.70)	0.0002	16
10q26	*ARMS2*	rs3750846	Asian	CC + CT vs. TT	2	216 vs. 204	0.65 (0.37–1.15)	0.14	0
				CC vs. CT + TT			0.44 (0.30–0.66)	4.70E−05	0
10q26	*ARMS2*	rs10664316	Asian	II + IN vs. NN[a]	2	218 vs. 208	0.35 (0.12–0.99)	0.05	0
				II vs. IN+NN[a]			0.50 (0.24–1.00)	0.05	57
10q26	*ARMS2*	c.372_815del443ins54	Asian	DD + DN vs. NN†	2	219 vs. 209	0.56 (0.32–0.98)	0.04	0
				DD vs. DN + NN†			0.45 (0.31–0.66)	5.58E−05	0
10q26	*ARMS2*	rs2014307	Asian	GG + GT vs. TT	2	216 vs. 212	0.37 (0.13–1.06)	0.06	0
				GG vs. GT + TT			0.49 (0.22–1.13)	0.09	68
10q26	*HTRA1*	rs11200638	Asian	AA+AG vs. GG	7	1362 vs. 1251	0.67 (0.53–0.84)	0.0006	13
				AA vs. AG + GG			0.70 (0.60–0.82)	9.87E−06	35
10q26	*HTRA1*	rs2672587	Asian	GG + GC vs. CC	2	276 vs. 182	1.74 (0.89–3.43)	0.11	64
				GG vs. GC + CC			1.32 (0.80–2.18)	0.28	0
12q22	FGD6	rs77466370	Asian	TT + TC vs. CC	5	3318 vs. 2457	1.89 (1.49–2.40)	1.52E−07	0
				TT vs. TC + CC			NA	NA	NA

Gene symbols: *ARMS2* age-related maculopathy susceptibility 2; *HTRA1* HtrA serine peptidase 1

[a]I vs. N = insAT vs. wide type; † D vs. N = del443ins54 vs. wide type

CI confidence interval; *nAMD* neovascular AMD; *OR* odds ratio; *PCV* polypoidal choroidal vasculopathy

Table 8.4 Gene variants not significantly different between PCV and neovascular AMD

Region	Gene	Polymorphism	Ethnicity	Associated vs. reference genotype	No. of cohorts	PCV vs. nAMD (sample size)	OR (95% CI)	*P*	I^2 (%)
1q32	*CFH*	rs800292	Asian	A vs. G	12	3344 vs. 2803	0.98 (0.90–1.06)	0.57	24
				AA+AG vs. GG			0.99 (0.90–1.10)	0.91	9
				AA vs. AG + GG			1.01 (0.84–1.23)	0.88	0
1q32	*CFH*	rs1061170	All ancestries	C vs. T	3	1127 vs. 1268	0.86 (0.72–1.03)	0.11	0
				CC + CT vs. TT			0.87 (0.71–1.08)	0.20	0
				CC vs. CT + TT			0.71 (0.42–1.19)	0.19	0
1q32	*CFH*	rs1410996	All ancestries	T vs. C	3	617 vs. 867	0.99 (0.73–1.80)	0.94	64
				TT + TC vs. CC			0.96 (0.68–1.34)	0.81	49
				TT vs. TC + CC			0.89 (0.61–1.31)	0.56	6
1q32	*CFH*	rs529825	All ancestries	A vs. G	2	423 vs. 712	0.98 (0.48–2.00)	0.96	85
				AA+AG vs. GG			0.98 (0.43–2.22)	0.96	84
				AA vs. AG + GG			0.66 (0.38–1.13)	0.13	35
1q32	*CFH*	rs3766404	Asian	C vs. T	2	249 vs. 523	1.14 (0.74–1.75)	0.55	0
				CC + CT vs. TT			1.10 (0.70–1.75)	0.68	0
				CC vs. CT + TT			1.39 (0.22–8.64)	0.72	0
4q12		rs1713985	Asian	G vs. T	6	2062 vs. 1611	0.99 (0.90–1.10)	0.86	0
				GG + GT vs. TT			0.99 (0.87–1.13)	0.93	0
				GG vs. GT + TT			0.97 (0.77–1.22)	0.79	0
4q35.1	TLR3	rs3775291	Chinese	T vs. C	2	201 vs. 172	1.25 (0.92–1.70)	0.15	0
				TT + TC vs. CC			1.47 (0.95–2.26)	0.08	0
				TT vs. TC + CC			1.15 (0.61–2.17)	0.66	0
6p21	*C2*	rs547154	Asian	T vs. G	5	1439 vs. 1428	1.08 (0.84–1.40)	0.55	16
				TT + TG vs. GG			1.09 (0.83–1.42)	0.54	19
				TT vs. TG + GG			1.16 (0.29–4.62)	0.83	0
6p21	*CFB*	rs4151667	All ancestries	A vs. T	4	858 vs. 973	1.19 (0.70–2.04)	0.53	0

(continued)

Table 8.4 (continued)

Region	Gene	Polymorphism	Ethnicity	Associated vs. reference genotype	No. of cohorts	PCV vs. nAMD (sample size)	OR (95% CI)	*P*	I^2 (%)
				AA+AT vs. TT			1.11 (0.63–1.96)	0.72	0
				AA vs. AT+TT			NA	NA	NA
6p21	*CFB*	rs2072633	Asian	G vs. A	3	1190 vs. 905	1.02 (0.90–1.15)	0.75	22
				GG + GA vs. AA			1.01 (0.82–1.23)	0.94	0
				GG vs. GA + AA			1.04 (0.85–1.27)	0.71	0
6p21	*SKIV2L*	rs429608	Asian	A vs. G	3	985 vs. 847	1.77 (1.12–2.81)	0.01	47
				AA+AG vs. GG			1.79 (1.12–2.85)	0.02	45
				AA vs. AG + GG			NA	NA	NA
6p21	*SKIV2L*	rs401775	Chinese	C vs. T	2	1295 vs. 1357	1.01 (0.84–1.22)	0.90	0
				CC + CT vs. TT			1.02 (0.83–1.24)	0.88	0
				CC vs. CT + TT			1.06 (0.49–2.30)	0.88	0
6p21.1	*VEGF-A*	rs833069	Asian	G vs. T	2	362 vs. 327	1.61 (0.82–3.17)	0.17	88
				GG + GT vs. TT			1.67 (0.81–3.44)	0.16	79
				GG vs. GT + TT			2.22 (0.64–7.76)	0.21	84
6p21.1	*VEGF-A*	rs833069	Asian	G vs. T	3	681 vs. 526	1.05 (0.89–1.24)	0.59	28
				GG + GT vs. TT			1.00 (0.79–1.26)	0.98	33
				GG vs. GT + TT			1.19 (0.87–1.63)	0.28	0
6p21.1	*VEGF-A*	rs943080	Asian	C vs. T	2	487 vs. 371	0.87 (0.69–1.10)	0.25	0
				CC + CT vs. TT			0.85 (0.64–1.12)	0.24	41
				CC vs. CT + TT			0.91 (0.47–1.73)	0.76	0
7q11	*ELN*	rs884843	Asian	G vs. A	3	760 vs. 665	0.94 (0.81–1.09)	0.41	43
				GG + GA vs. AA			0.93 (0.74–1.16)	0.52	31
				GG vs. GA + AA			0.91 (0.70–1.19)	0.49	15
7q11	*ELN*	rs13239907	Asian	G vs. A	3	766 vs. 683	0.97 (0.83–1.13)	0.70	0

Table 8.4 (continued)

Region	Gene	Polymorphism	Ethnicity	Associated vs. reference genotype	No. of cohorts	PCV vs. nAMD (sample size)	OR (95% CI)	*P*	I^2 (%)
				GG + GA vs. AA			0.91 (0.66–1.25)	0.56	0
				GG vs. GA + AA			0.99 (0.80–1.22)	0.89	0
7q11	*ELN*	rs2856728	Asian	C vs. T	3	758 vs. 670	1.05 (0.63–1.75) 0.90 (0.76–1.06)	0.84 0.22	85
				CC + CT vs. TT			1.09 (0.64–1.87)	0.75	80
				CC vs. CT + TT			0.83 (0.34–2.03)	0.68	69
7q11	*ELN*	rs868005	Asian	C vs. T	3	650 vs. 539	1.06 (0.87–1.29)	0.54	26
				CC + CT vs. TT			1.13 (0.89–1.42)	0.32	16
				CT vs. TT			1.15 (0.79–1.67)	0.46	32
7q11	*ELN*	rs2301995	All ancestries	A vs. G	5	1203 vs. 1305	1.09 (0.74–1.59)	0.67	80
				AA+AG vs. GG			1.14 (0.70–1.86)	0.59	80
				AA vs. AG + GG			0.77 (0.53–1.12)	0.17	14
8p21.3	LPL	rs12678919	Asian	G vs. A	2	827 vs. 997	0.99 (0.81–1.20)	0.89	0
				GG + GA vs. AA			1.02 (0.82–1.27)	0.83	0
				GG vs. GA + AA			0.54 (0.23–1.31)	0.17	28
				CC vs. CT + TT			3.42 (0.59–19.64)	0.17	0
8p21.3	*LPL*	rs12678919	Asian	G vs. A	2	541 vs. 387	1.16 (0.86–1.57)	0.32	0
				GG + GA vs. AA			1.18 (0.85–1.64)	0.32	0
				GG vs. GA + AA			1.20 (0.35–4.17)	0.77	0
8p21		rs13278062	Asian	T vs. G	6	2062 vs. 1611	1.00 (0.91–1.10)	0.96	0
				TT + TG vs. GG			1.01 (0.88–1.15)	0.94	0
				TT vs. TG + GG			1.01 (0.83–1.22)	0.94	0
				AA vs. AC + CC			1.86 (0.65–5.37)	0.25	43
8p23.1	*ANGPT2*	rs2515487	Asian	A vs. C	3	627 vs. 595	1.05 (0.88–1.25)	0.62	18
				AA+AC vs. CC			1.05 (0.84–1.32)	0.66	0

(continued)

Table 8.4 (continued)

Region	Gene	Polymorphism	Ethnicity	Associated vs. reference genotype	No. of cohorts	PCV vs. nAMD (sample size)	OR (95% CI)	*P*	I^2 (%)
				AA vs. AC + CC			1.11 (0.73–1.68)	0.63	0
8p23.1	*ANGPT2*	rs2922869	Asian	T vs. C	3	627 vs. 595	1.15 (0.96–1.37)	0.12	0
				TT + TC vs. CC			1.25 (0.81–1.91))	0.31	0
				TT vs. TC + CC			1.18 (0.94–1.47)	0.16	0
8p23.1	*ANGPT2*	rs13255574	Asian	C vs. T	3	627 vs. 595	0.99 (0.80–1.22)	0.91	2
				CC + CT vs. TT			0.99 (0.51–1.90)	0.97	0
				CC vs. CT + TT			0.98 (0.77–1.25)	0.86	0
8p23.1	*ANGPT2*	rs4455855	Asian	G vs. A	3	627 vs. 595	0.93 (0.79–1.10)	0.41	30
				GG + GA vs. AA			0.90 (0.66–1.22)	0.50	0
				GG vs. GA + AA			0.92 (0.73–1.17)	0.50	0
8p23.1	*ANGPT2*	rs11775442	Asian	A vs. G	3	627 vs. 595	0.92 (0.75–1.13)	0.42	0
				AA+AG vs. GG			0.86 (0.46–1.60)	0.64	0
				AA vs. AG + GG			0.92 (0.73–1.17)	0.49	0
9q31.1	*ABCA1*	rs1883025	Chinese	T vs. C	3	779 vs. 657	0.98 (0.82–1.17)	0.82	0
				TT + TC vs. CC			0.98 (0.79–1.21)	0.84	0
				TT vs. TC + CC			0.96 (0.61–1.53)	0.88	0
				TT vs. TC + CC			2.83 (0.59–13.45)	0.19	0
10q26	*ARMS2*	rs2736912	Asian	T vs. C	2	229 vs. 212	1.17 (0.45–3.04)	0.74	78
				TT + TC vs. CC			1.10 (0.37–3.28)	0.86	80
				TT vs. TC + CC			3.42 (0.56–21.04)	0.19	0
10q26	*ARMS2*	rs3750847	Asian	T vs. C	2	519 vs. 505	0.84 (0.69–1.01)	0.06	86
				TT + TC vs. CC			0.97 (0.67–1.41)	0.88	53
				TT vs. TC + CC			0.44 (0.30–0.66)	4.91E −05	0
10q26	*HTRA1*	rs11200644	Asian	C vs. T	2	281 vs. 182	1.40 (0.94–2.09)	0.10	0
				CC + CT vs. TT			1.35 (0.87–2.11)	0.18	0

Table 8.4 (continued)

Region	Gene	Polymorphism	Ethnicity	Associated vs. reference genotype	No. of cohorts	PCV vs. nAMD (sample size)	OR (95% CI)	*P*	I^2 (%)
				CC vs. CT + TT			3.42 (0.59–19.64)	0.17	0
10q26	*HTRA1*	rs7093894	Japanese	A vs. C	2	281 vs. 184	1.41 (0.99–2.01)	0.06	0
				AA+AC vs. CC			1.43 (0.95–2.16)	0.08	0
				AA vs. AC + CC			1.86 (0.65–5.37)	0.25	43
10q26	*HTRA1*	rs3793917	Asian	C vs. G	2	481 vs. 384	1.15 (0.95–1.40)	0.16	73
				CC + CG vs. GG			1.34 (0.96–1.88)	0.08	46
				CC vs. CG + GG			1.09 (0.82–1.45)	0.56	64
11q12.1	*SERPING1*	rs2511989	Asian	A vs. G	2	628 vs. 1643	0.90 (1.75–1.09)	0.30	22
				AA+AG vs. GG			0.93 (0.75–1.15)	0.50	0
				AA vs. AG + GG			0.82 (0.12–5.46)	0.84	61
14q24.3	*PGF*	rs2268615	Asian	G vs. C	2	423 vs. 403	0.74 (0.58–0.93)	0.01	0
				GG + GC vs. CC			0.60 (0.32–1.13)	0.11	0
				GG vs. GC + CC			0.70 (0.53–0.93)	0.01	0
14q24.3	*PGF*	rs2268614	Asian	G vs. C	2	423 vs. 403	0.75 (0.59–0.95)	0.02	0
				GG + GC vs. CC			0.58 (0.30–1.11)	0.10	0
				GG vs. GC + CC			0.74 (0.56–0.98)	0.03	0
15q21.3	LIPC	rs493258	Chinese	G vs. T	2	483 vs. 357	1.12 (0.90–1.41)	0.31	0
				GG + GT vs. TT			1.15 (0.87–1.52)	0.33	0
				GG vs. GT + TT			1.23 (0.70–2.19)	0.47	0
15q21.3	LIPC	rs10468017	Chinese	T vs. C	3	804 vs. 587	1.02 (0.83–1.26)	0.83	0
				TT + TC vs. CC			1.03 (0.82–1.31)	0.79	0
				TT vs. TC + CC			0.97 (0.49–1.91)	0.92	0
15q24.1	*LOXL1*	rs1048661	Japanese	T vs. G	2	195 vs. 139	0.80 (0.58–1.09)	0.15	0
				TT + TG vs. GG			0.77 (0.45–1.32)	0.35	0
				TT vs. TG + GG			0.73 (0.46–1.16)	0.18	0

(continued)

Table 8.4 (continued)

Region	Gene	Polymorphism	Ethnicity	Associated vs. reference genotype	No. of cohorts	PCV vs. nAMD (sample size)	OR (95% CI)	*P*	I^2 (%)
16q13	CETP	rs3764261	Chinese	T vs. C	3	774 vs. 587	1.09 (0.91–1.31)	0.34	0
				TT + TC vs. CC			1.11 (0.89–1.38)	0.37	0
				TT vs. TC + CC			1.12 (0.68–1.85)	0.66	0
16q13	CETP	rs2303790	Chinese	G vs. A	2	170 vs. 143	1.21 (0.96–1.51)	0.11	80
				GG + GA vs. AA			1.20 (0.95–1.52)	0.13	78
				GG vs. GA + AA			NA	NA	NA
17p13.3	*PEDF*	rs1136278	Asian	T vs. G	2	317 vs. 247	1.07 (0.72–1.61)	0.73	65
				TT + TG vs. GG			1.29 (0.64–2.58)	0.47	70
				TT vs. TG + GG			0.91 (0.62–1.34)	0.64	0
21q22.3	*ABCG1*	rs57137919	Asian	A vs. G	3	627 vs. 616	1.16 (0.97–1.39)	0.11	0
				AA+AG vs.GG			1.18 (0.94–1.47)	0.16	0
				AA vs. AG + GG			1.29 (0.82–2.04)	0.27	0
21q22.3	*ABCG1*	rs225396	Asian	T vs. C	3	627 vs. 616	1.12 (0.95–1.32)	0.19	0
				TT + TC vs. CC			1.14 (0.91–1.44)	0.24	0
				TT vs. TC + CC			1.19 (0.86–1.65)	0.30	0

Gene symbols: *ABCA1* ATP-binding cassette-sub-family A (ABC1)-member 1; *ARMS2* age-related maculopathy susceptibility 2; C2 complement component 2; *C4orf14* nitric oxide associated 1; *CETP* cholesteryl ester transfer protein-plasma; *CFB* complement factor B; *CFH* complement factor H; *ELN* elastin; *HTRA1* HtrA serine peptidase 1; *IGFBP7* insulin-like growth factor binding protein 7; *LIPC* lipase-hepatic; *LOC389641* uncharacterized LOC389641; *LOXL1* lysyl oxidase-like 1; *PEDF* pigment epithelium derived factor; *POLR2B* polymerase (RNA) II (DNA directed) polypeptide B; *REST* RE1-silencing transcription factor; *SKIV2L* superkiller viralicidic activity 2-like; *TLR3* toll-like receptor 3; *TNFRSF10A* tumor necrosis factor receptor superfamily-member 10a

CI confidence interval; *nAMD* neovascular age-related macular degeneration; *OR* odds ratio; *PCV* polypoidal choroidal vasculopathy

the remaining 45 SNPs in CFH, VEGF, *C2*, *CFB*, *SKIV2L*, *CETP,* 8p21, 4q12, *ELN*, *LIPC*, *LPL*, *FGD6*, *ABCA1*, *ABCG1*, *PGF*, *TLR3*, *LOXL1,* and *PEDF.*

The similarity and difference of PCV and nAMD attracted the interest in investigating the genetic susceptibility between them. There was a large sample size study investigated the genetic variants of 34 AMD loci for PCV and nAMD in East Asians [75]. The results showed that PCV and tAMD were highly correlated (r_g = 0.69, $P = 4.68 \times 10^{-3}$) in genetic variants. Weaker association for PCV compared to nAMD was found at *ARMS2-HTRA1* and *KMT2E-SRPK2*. The different association

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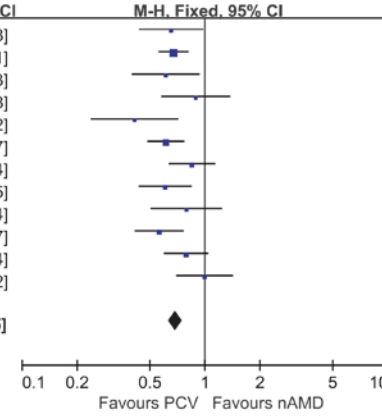
Study or Subgroup	PCV Events	PCV Total	nAMD Events	nAMD Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Goto 2009 JPN	114	200	134	200	5.0%	0.65 [0.43, 0.98]
Hayashi 2010 JPN	558	1018	521	810	22.7%	0.67 [0.56, 0.81]
Lima 2010 Caucasian	35	110	319	736	4.9%	0.61 [0.40, 0.93]
Bessho 2011 JPN	144	238	86	136	3.7%	0.89 [0.58, 1.38]
Fuse 2011 JPN	56	120	68	100	3.4%	0.41 [0.24, 0.72]
Tanaka 2011 JPN	412	762	333	506	15.9%	0.61 [0.48, 0.77]
Yanagisawa 2011 JPN	235	396	229	362	8.4%	0.85 [0.63, 1.14]
Liang 2012 Chinese	199	324	226	312	7.7%	0.61 [0.43, 0.85]
Cheng 2013 Chinese	110	166	134	188	3.7%	0.79 [0.50, 1.24]
Zhang 2013 Chinese	307	500	232	314	9.5%	0.56 [0.41, 0.77]
Yoneyama 2014 b JPN	400	666	206	314	9.7%	0.79 [0.60, 1.04]
Woo 2015 Japanese	141	222	196	308	5.2%	0.99 [0.69, 1.42]
Total (95% CI)		**4722**		**4286**	**100.0%**	**0.69 [0.63, 0.75]**
Total events	2711		2684			

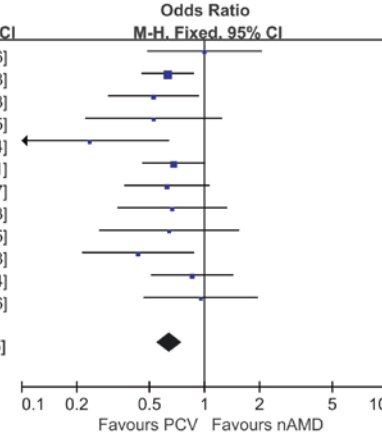
Heterogeneity: Chi² = 15.56, df = 11 (P = 0.16); I² = 29%
Test for overall effect: Z = 8.10 (P < 0.00001)



b

Study or Subgroup	PCV Events	PCV Total	nAMD Events	nAMD Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Goto 2009 JPN	82	100	82	100	4.0%	1.00 [0.49, 2.06]
Hayashi 2010 JPN	387	509	338	405	24.4%	0.63 [0.45, 0.88]
Lima 2010 Caucasian	29	55	250	368	8.3%	0.53 [0.30, 0.93]
Bessho 2011 JPN	95	119	60	68	4.2%	0.53 [0.22, 1.25]
Fuse 2011 JPN	38	60	44	50	4.8%	0.24 [0.09, 0.64]
Tanaka 2011 JPN	287	381	207	253	16.6%	0.68 [0.46, 1.01]
Yanagisawa 2011 JPN	156	198	155	181	9.3%	0.62 [0.36, 1.07]
Liang 2012 Chinese	139	162	136	151	5.4%	0.67 [0.33, 1.33]
Cheng 2013 Chinese	70	83	84	94	3.3%	0.64 [0.27, 1.55]
Zhang 2013 Chinese	213	250	146	157	7.2%	0.43 [0.21, 0.88]
Yoneyama 2014 b JPN	275	333	133	157	8.5%	0.86 [0.51, 1.44]
Woo 2015 Japanese	96	111	134	154	4.1%	0.96 [0.47, 1.96]
Total (95% CI)		**2361**		**2138**	**100.0%**	**0.64 [0.54, 0.75]**
Total events	1867		1769			

Heterogeneity: Chi² = 9.61, df = 11 (P = 0.57); I² = 0%
Test for overall effect: Z = 5.35 (P < 0.00001)



c

Study or Subgroup	PCV Events	PCV Total	nAMD Events	nAMD Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Goto 2009 JPN	32	100	52	100	5.8%	0.43 [0.24, 0.77]
Hayashi 2010 JPN	171	509	183	405	22.0%	0.61 [0.47, 0.80]
Lima 2010 Caucasian	6	55	69	368	2.6%	0.53 [0.22, 1.29]
Bessho 2011 JPN	49	119	26	68	3.2%	1.13 [0.61, 2.08]
Fuse 2011 JPN	18	60	24	50	3.0%	0.46 [0.21, 1.02]
Tanaka 2011 JPN	125	381	126	253	16.6%	0.49 [0.36, 0.68]
Yanagisawa 2011 JPN	79	198	74	181	7.6%	0.96 [0.64, 1.45]
Liang 2012 Chinese	60	162	90	151	9.5%	0.40 [0.25, 0.63]
Cheng 2013 Chinese	40	83	50	94	4.0%	0.82 [0.45, 1.48]
Zhang 2013 Chinese	94	250	86	157	10.7%	0.50 [0.33, 0.75]
Yoneyama 2014 b JPN	125	333	73	157	10.1%	0.69 [0.47, 1.02]
Woo 2015 Japanese	45	111	62	154	5.0%	1.01 [0.62, 1.66]
Total (95% CI)		**2361**		**2138**	**100.0%**	**0.62 [0.55, 0.71]**
Total events	844		915			

Heterogeneity: Chi² = 21.75, df = 11 (P = 0.03); I² = 49%
Test for overall effect: Z = 7.39 (P < 0.00001)

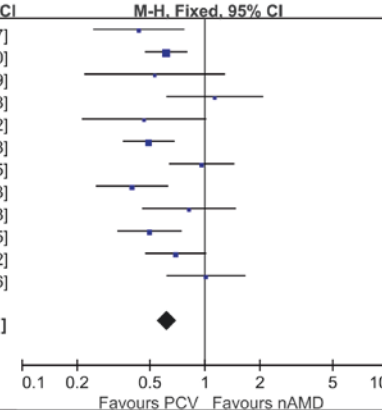


Fig. 8.2 Forest plots of meta-analysis comparing the SNP rs10490924 at *ARMS2* between PCV and nAMD. (**a**) allele frequencies; (**b**) dominant model; (**c**) recessive model

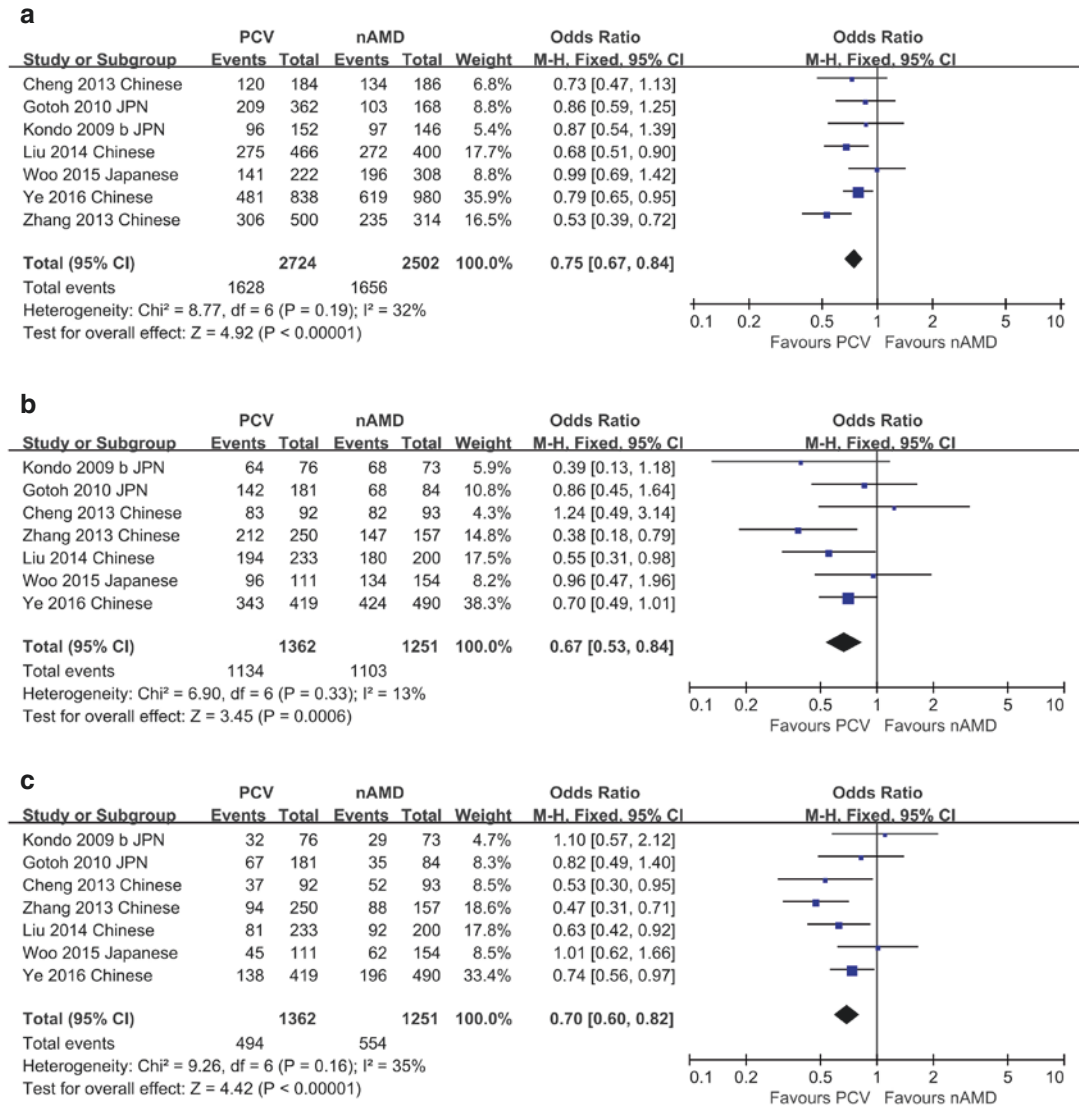


Fig. 8.3 Forest plots of meta-analysis comparing the SNP rs11200638 at *HTRA1* between PCV and nAMD. (**a**) allele frequencies; (**b**) dominant model; (**c**) recessive model

of *ARMS2-HTRA1* variants between PCV and nAMD was confirmed in this meta-analysis. But *KMT2E-SRPK2* was investigated in only one study and therefore no meta-analysis was performed. In 2016, an article using exome sequencing identified a rare variant, rs77466370, in *FGD6* was significantly associated with PCV (OR = 2.12) but not with CNV (OR = 1.13) [70]. Our meta-analysis confirmed that most genetic polymorphisms were distributed similarly between nAMD and PCV, But also some polymorphisms had a statistically significant difference between PCV and nAMD. These results suggest that PCV and nAMD have shared the majority of genetic background, while the differences of *ARMS2-HTRA1* locus and *FGD6* variants may be correlated with the differences in the pathologic and clinical manifestations of PCV and nAMD. The molecular mechanisms underlying their differences in pathogenesis remain to be further investigated.

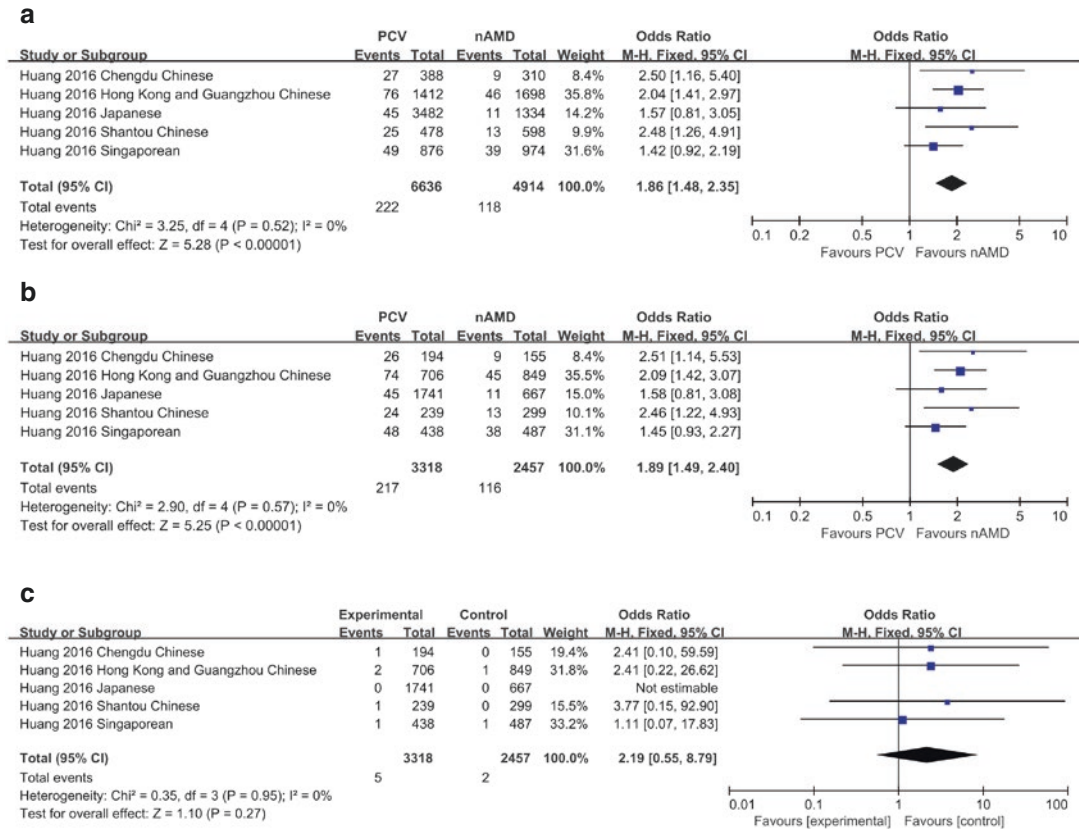


Fig. 8.4 Forest plots of meta-analysis comparing the SNP rs77466370 at *FGD6* between PCV and nAMD. (**a**) allele frequencies; (**b**) dominant model; (**c**) recessive model

ARMS2-HTRA1 locus located at chromosome 10q26. It was one of the most strong associated locus with AMD [79, 80]. There are many SNPs in this locus and they are in strong linkage disequilibrium. ARMS2 was expressed in the mitochondria of the outer segment of photoreceptors [81]. The function of *ARMS2* was suggested to be associated with loss of function of RPE [81]. HTRA1 can inhibit transforming growth factor-βin chronic inflammation [82]. In the *HTRA1* transgenic mice model, retinal pigment epithelium atrophy, photoreceptor degeneration, and grape-cluster structure in choroidal vasculature were reported, which is similar to the PCV phenotype [83]. However, our meta-analysis found that the effect size of *ARMS2-HTRA1* locus was weaker in PCV compared to nAMD. Further functional studies are needed to elucidate the role of *ARMS2-HTRA1* locus in PCV/nAMD.

FGD6 located at chromosome 12q22. FGD6 expresses in all human tissue but has a higher level of expression in retina and choroid, especially in retinal microvascular endothelial cells. Rs77466370, c.986A > G (p.Lys329Arg), is a rare variant with the minor allele frequency of 0.02–0.03 in normal subjects. FGD6-Arg329 has a different pattern of intracellular localization from FGD6-Lys329. In vitro, FGD6 could promote endothelial cells tube formation, furthermore, FGD6-Arg329 promoted more abnormal vessel development in the mouse retina than FGD6-Lys329 [70]. These functional studies support the role of FGD6 in the pathogenesis of PCV.

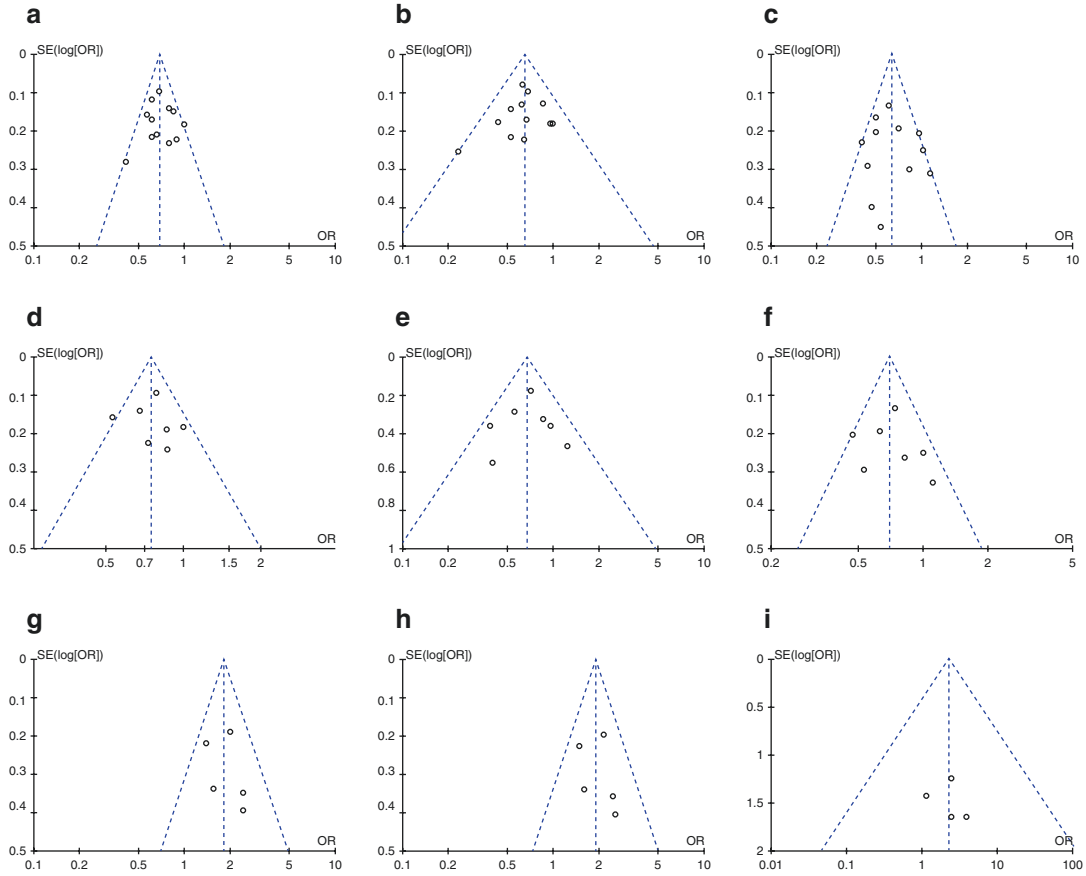


Fig. 8.5 Funnel plots of the meta-analysis comparing rs10490924 (**a**–**c**), rs11200638 (**d**–**f**) and rs77466370 (**g**–**i**) between PCV and nAMD. (**a**, **d**, **g**) Allele frequencies; (**b**, **e**, **h**) dominant model; C, F, I. recessive model

8.5 Summary

In summary, we pooled the results 57 SNPs in 20 genes that had been investigated in both PCV and nAMD in the same studies. Among them, 11 SNPs at the *ARMS2-HTRA1* locus and rs77466370 in *FGD6* showed significant differences between PCV and nAMD, but the other SNPs had similar distribution between PCV and nAMD. Our results suggest that PCV and nAMD have shared the majority of genetic components, but the variants distributed differently between these two conditions may explain the pathogenic and clinical differences of PCV and nAMD.

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