·Meta-Analysis·

Association between complement factor I gene polymorphisms and the risk of age-related macular degeneration: a Meta-analysis of literature

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Received: 2015-04-12 Accepted: 2015-05-27

Abstract

• AIM: To systematically review the association between complement factors I (CFI) polymorphisms and age-related macular degeneration (AMD) and to explore whether CFI polymorphisms are associated with AMD.

• METHODS: Meta-analysis of articles published from 1995 to January 2015 of articles involved with AMD and polymorphisms of the CFI gene. Eligible data were pooled in a Meta-analysis, analyzing using STATA software (version 12.0), Review Manager (version 5.2) and different models based on the heterogeneity of effect sizes. Egger´s test, Begg´s rank correlation methods were used to evaluate for publication bias.

• RESULTS: Thirteen articles were eligible, describing two loci polymorphisms of the CFI gene (of which 12 articles focus on rs10033900T>C and 3 articles focus on rs2285714C>T). For rs10033900T>C, the results of our study revealed that having a mutant allele C, TC, CC and TC+CC was associated with a decreased risk of AMD in all population groups studied (C versus T models, OR=0.84, 95% CI: 0.72-0.99, *P*=0.04; TC versus TT models OR=0.89, 95% CI: 0.88-0.99, *P*=0.04; CC versus TT models, OR=0.76, 95% CI: 0.60-0.98, *P*=0.03; TC+CC versus TT models, OR=0.81, 95% CI:0.65-0.99, *P*=0.04). We found that C allele were related to lower AMD risk in the Caucasian population by subgroup analysis, but there was no association with AMD under the allele and genotypes comparison in Asian studies. For rs2285714 C>T, the TC, TT genotypes contributed to a higher risk of AMD, compared with the CC carriers and CT+CC (OR=1.34, 95%CI: 1.09-1.63, *P*=0.004; OR=1.50, 95%CI: 1.25-1.80, *P*<0.0001).

• CONCLUSION: This Meta-analysis suggests that CFI rs10033900T>C and rs2285714C>T polymorphisms may contribute to AMD.

• KEYWORDS: complement factors I; age-related macular degeneration; age-related maculopathy; single-nucleotide polymorphisms; Meta-analysis
DOI:10.18240/ijo.2016.02.23

Wang Q, Zhao HS, Li L. Association between complement factor I gene polymorphisms and the risk of age-related macular degeneration: a Meta-analysis of literature. *Int J Ophthalmol* 2016;9(2):298-305

INTRODUCTION

Age-related macular degeneration (AMD) is one of the most important diseases that cause vision loss among older patients. The prevalence of early AMD is more common in Chinese and Indians than in Malays, but there were no racial variations in the prevalence of late AMD[1], and prevalence of AMD was similar in the 3 major ethnic groups in Asia and comparable with white populations. Myopic refractive error was associated with reduced risk of AMD in Chinese men [2]. The prevalence of any AMD in the 2005-2008 National Health and Nutrition Examination Survey of USA was 6.5%[3]. The characteristic features of AMD include the loss of retinal pigment epithelium and photoreceptors, geographic atrophy (GA), neovascularization (NV) and exudative changes [4]. AMD is known to be a poly-factorial disease and numerous studies have demonstrated strong evidence of a genetic contribution in the etiology of AMD. Genome-wide association studies (GWAS) and candidate association studies have corroborated risk loci for AMD in the alternative pathway of complement. Complement factor I (CFI) is an important component of the complement system, which is expressed by hepatocytes, macrophages, lymphocytes, endothelial cells and fibroblasts, and encodes factor I, a regulatory protein for the three complement pathways. By cleaving C3b and C4b under the

regulation of complement facrot H (CFH), factor I reduces the formation of the C3 and C5 convertase enzymes [5]. The association between CFI single-nucleotide polymorphisms (SNPs) and AMD was first reported by Fagerness *et al*[6], after which a number of studies suggesting an association between CFI SNPs and the risk of AMD were published[7-23]. The SNPs of interest included rs10033900T>C and rs2285714C>T, among others. Due to the relatively small sample size of each study, the results of the individual studies remain inconclusive and controversial. Furthermore, there is no conclusion for racial differences. Therefore a Meta-analysis to assess the putative association between CFI polymorphisms (rs10033900T>C and rs2285714C>T) and AMD risk is carried out.

MATERIALS AND METHODS

Information Sources and Search Strategy Articles were identified through a systematic computerized search in MEDLINE, Embase, and the Cochrane database up to 1st January 2015. The search terms used were "age-related macular degeneration" or "AMD", "complement factor I" or "CFI" and "single-nucleotide polymorphism" or "SNPs". The references of the retrieved studies were also checked to see if any additional published articles could be included. For overlapping studies, only the latest published study was selected for inclusion in the Meta-analysis. No further limitations were used, except for language, which was restricted to English, Dutch, French, German, and Spanish. Two independent investigators (Wang Q and Li L) conducted the search process.

Literature Inclusion and Exclusion Criteria The retrieved records were assessed independently by two investigators (Wang Q and Li L) to determine which studies should be included. Eligible studies were 1) population-based association studies, regardless of the sample size or ethnicity of the patient pool, or 2) case-control studies that assessed the association of CFI genetic variants and/or phenotypes with AMD risk, and each had to have 3) sufficient data to evaluate an odds ratio (OR) with a 95% confidence interval (CI). Where the eligible studies provided insufficient information, we contacted the authors to request additional information. 4) Hardy-Weinberg equilibrium (HWE) tests also had to be performed on the control group of each study. 5) The studies had to assess and grade AMD (*e.g.* large drusen, intermediate AMD, geographic atrophy, and neovascularization), and these grades were summed up for the AMD group. Studies were excluded when 1) there were repetitive publications or multiple publications from the same study group (in this case, the most complete and recent publications were used); 2) the article type was inappropriate for analysis (*e.g.* a review, case report, or editorial comment); 3) the control group did not conform to the HWE; 4) the article provided insufficient information and the authors did not provide additional data after being contacted.

Data Extraction Data were extracted from eligible studies by two reviewers (Wang Q and Zhao HS) independently using a standard template. Operationalization of the quality items was achieved by consensus meetings of 3 researchers (Wang Q, Zhao HS and Li L), before the process of data abstraction began. The results were discussed between the 3 researchers. The following information was extracted from each study: the surname of the first author, the sample sizes of cases and controls, the year of publication, the country of origin or ethnicity of the subjects, the mean subject age, the gender of subjects, the types of cases and controls, and the HWE of the control subjects.

Quality Score Assessment The Newcastle-Ottawa Scale (NOS) was independently applied by two reviewers (Wang Q and Zhao HS) to assess the quality of the studies [20]. Briefly, the criteria include 3 broad perspectives: selection, comparability, and exposure. Scores range from 0 stars (worst) to 9 stars (best), with scores of 5 or higher indicating a moderate to high methodological quality.

Statistical Analysis For each study, Chi-squared analysis was applied to test for departures from the HWE for the CFI genetic polymorphisms in the control group. $P<0.05$ was considered significant. ORs and 95% CIs were used to estimate the associations between the CFI polymorphisms and AMD risk. If the wild-type allele was set as C and the mutant allele as T, the C and T allele frequencies were first compared in the case and control groups. Then, Meta-analyses were performed for different genetic models, including recessive (TT versus CC+CT), dominant (TT+CT versus CC) and co-dominant (CT versus CC and TT versus CC) models. The Z test was used to determine the statistical significance of the summary OR of the genetic models, for which $P<0.05$ was considered statistically significant. Heterogeneity across studies was estimated using a Q test, and quantification of the heterogeneity was completed using the I^2 metric. If heterogeneity was detected ($P<0.05$ or $I^2>50\%$), a random effects model was used to analyze the data, while if the $P>0.05$ or $I^2<50\%$, a fixed-effects model was instead used. Sensitivity analysis was performed by changing the effects model. For studies for which a fixed effects model was previously used, a random effects model was used. Potential publication bias among individual studies was assessed by using the Egger's weighted regression method, the Begg's rank correlation method (with contour-enhanced funnel plots). Statistical calculations were all performed using STATA software (version 12.0) and Review Manager (version 5.2).

RESULTS

Search Results and Study Characteristics A total of 78 potentially relevant research articles were retrieved from MEDLINE, Embase, and the Cochrane database. Of these, 65 papers were excluded based on the selection criteria

Table 1 Baseline characteristics and main conclusion per articles

References	Country (ethnicity)	Cases/controls	Mean age (a)	Male (%)	Type of cases	Type of controls	HWE	Polymorphisms of CFI gene	NOS score
Wu *et al*[17]	Chinese	339/140	68.7±8.3	33.0	Early AMD and NV	Non AMD	Yes	rs10033900, rs2285714, rs13117504	7
Reynolds *et al*[13]	American	102/60	82.0±6.9	50.0	GA and NV	CARMS (grade 1)	Yes	rs10033900	8
Reynolds *et al*[14]	Caucasian	318/140	81.0±7.0	57.0	NV and GA	CARMS (grade 1 and 2)	Not mentioned	rs10033900	8
Yu *et al*[19]	Caucasian	2830/221	75.8±6.0	43.0	Druse (>63 μm) NV and GA	CARMS (grade 1)	Yes	rs10033900	8
Kondo *et al*[9]	Japanese	116/189	75.0±7.2	78.0	NV	Non AMD	Yes	rs10033900	6
Losonczy *et al*[10]	Hungarian	276/106	75.0±12.0	44.0	Dry and exudative AMD	Non AMD	Yes	rs10033900	9
Chen *et al*[21]	American	2155/1150	78.6	38.2	Large drusen, GA, and NV	Non AMD	Yes	rs2285714	8
Seddon *et al*[15]	European ancestry	545/265	-	42.0	GA and NV	Non AMD	Yes	rs10033900	8
Smailhodzic *et al*[22]	Unrelated Caucasian	192/140	-	39.0	NV	Non AMD	Not mentioned	rs10033900	8
Peter *et al*[11]	European ancestry	146/1260	-	0.0	Intermediate and late AMD	Non AMD	Yes	rs10033900	7
Cipriani *et al*[7]	English and Scottish	1026/744	-	42.0	GA and CNV	Non AMD	Yes	rs10033900	6
Yang *et al*[18]	Chinese	598/299	-	63.0	NV and PCV	Non AMD	Yes	rs10033900, rs2285714	7
Qian *et al*[12]	Chinese	288/384	75.1±7.0	49.4	GA and CNV	Non AMD	Yes	rs10033900	6

CD: Cuticular drusen; PCV: Polypoidal choroidal vasculopathy; NV: Neovascularization; GA: Geographic atrophy; CNV: Classic neovascularization.

described above. We identified 13 cross-sectional studies that examined the association between CFI polymorphisms and AMD risk [7,9-15,17-19,21-22]. The procedure for selecting and identifying the studies is shown in Figure 1. The baseline characteristics of the studies included in the Meta-analysis are listed in Table 1. These studies focused on 2 polymorphisms of the CFI gene polymorphisms and AMD risk: rs10033900 and rs2285714. Data from at least three published studies were available for 2 CFI polymorphisms (rs10033900 and rs2285714). For rs10033900, 12 articles were available (8 of Caucasian populations and 4 of Asian populations). Similarly, 3 articles were available for rs2285714. In one study on the rs2285714 polymorphism[17], the distribution of genotypes in the control subjects did not conform to the HWE. The lists of genotypes and allelic frequencies of these 2 CFI polymorphisms in the eligible studies are provided in Table 2.

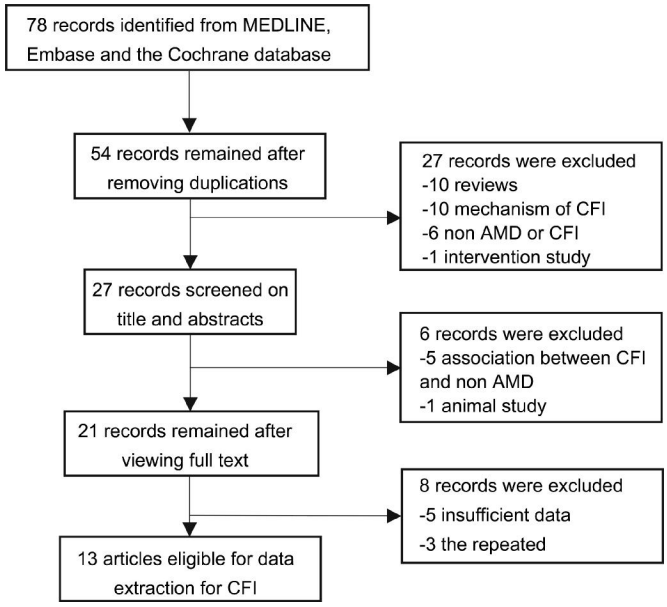

Figure 1 Search strategy used in the selection of articles.

Meta-analysis Results

CFI rs10033900T >C The rs10033900 polymorphism is located 2781 bp upstream of the 3'UTR of the CFI gene and has been investigated in association with AMD by Fagerness *et al* [6] in 2009. Replicated observations of their work appeared in subsequent studies [9,11-14,17-19]. However, some studies [7-8,10,21] reported no correlation between the rs10033900 polymorphism of the CFI gene and AMD.

In this Meta-analysis, the genetic models of rs10033900 in all populations were first estimated, including 6776 AMD cases and 3943 controls. The estimate for the association between the CFI rs10033900 polymorphism and AMD risk is shown in Table 3. A decreased AMD risk was found in the C versus the T (OR=0.84, 95%CI: 0.72-0.99, P=0.04), TC versus TT (OR=0.89, 95% CI: 0.80-0.99, P=0.04), CC versus TT (OR=0.76, 95%CI: 0.60-0.98, P=0.03), TC+CC versus TT (OR=0.81, 95%CI: 0.65-0.99, P=0.04) models. However, the CC genotype carriers showed no association with AMD in comparison with TC+TT (OR=0.84, 95%CI: 0.69-1.03, P=0.09). The forest figure of the CC versus TT models is presented in Figure 2A.

In the subgroup analysis, 8 studies [7,10-11,13-15,19,22] analyzed Caucasian populations and 4 studies [9,12,17-18] analyzed Asian populations. In the Caucasian, the comparison of the allele models (C versus T), the pooled OR was 0.86 (95% CI: 0.79-0.93, P=0.0001), indicating that the C allele confers a protective effect against AMD development. The OR for the

Table 2 The allele and genotype distribution of the CFI polymorphisms used in this study

Polymorphism	[1]Ref	Country (ethnicity)	Cases/controls	Genotype		Allele		[2]*P* value for HWE
				Case	Control	Case	Control	
rs 10033900				TT/TC/CC		T/C		
	10	Hungarian	276/106	73/142/61	31/56/19	288/264	118/94	0.470
	15	European ancestry individuals	545/265	147/278/120	54/134/87	572/518	242/308	0.980
	22	Unrelated Caucasian individuals	192/140	52/92/48	35/80/25	196/188	150/138	0.400
	13	American	102/60	23/50/29	7/28/20	96/108	42/68	0.840
	14	Caucasian	318/140	92/153/73	30/73/37	337/299	133/147	0.870
	17	Chinese	339/140	154/68/13	70/58/12	376/94	198/82	1.000
	9	Japanese	116/189	51/59/6	73/85/31	161/71	231/147	0.760
	19	Caucasian	2830/216	740/1387/703	44/107/65	2867/2793	195/237	1.000
	11	European ancestry	146/1260	44/68/34	289/623/346	156/132	1201/1315	0.950
	7	English and Scottish	1026/744	258/537/231	179/384/181	1053/999	742/746	0.380
	18	Chinese	598/299	254/283/61	126/138/35	791/405	390/208	0.760
	12	Chinese	288/384	113/127/48	184/152/48	353/223	520/248	0.080
rs2285714				CC/CT/TT		C/T		
	17	Chinese	339/140	124/111/4	68/71/1	359/119	207/73	0.001
	21	American	2155/1150	825/1082/468	421/550/179	2332/2002	1392/909	0.980
	18	Chinese	598/299	367/202/31	167/121/11	936/264	455/143	0.052

[1]References; [2]Hardy-Weinberg equilibrium.

Table 3 Results of Meta-analysis of the association between rs10033900 polymorphism of CFI gene and AMD risk

Genotype contrast	[1]*n*	Cases/controls	Heterogeneity			[2]Genotype effect			[3]Genotype effect		
			Q	I^2 (%)	*P*	*Z*	*P*	OR (95%CI)	*Z*	*P*	OR (95%CI)
All populations	12	6776/3943									
C versus T			54.08	80	<0.0001	2.10	0.04	0.84 [0.72, 0.99]	3.84	0.0001	0.88 [0.82, 0.94]
TC versus TT			18.02	39	0.08	2.09	0.04	0.89 [0.80, 0.99]	1.9	0.06	0.87 [0.75, 1.00]
CC versus TT			28.81	62	0.02	2.16	0.03	0.76 [0.60, 0.98]	3.43	0.0006	0.89 [0.67, 1.16]
(TC+CC) versus TT			40.47	73	<0.0001	2.21	0.04	0.81 [0.65, 0.99]	3.21	0.001	0.84 [0.76, 0.94]
CC versus (TC+TT)			26.60	59	0.005	1.71	0.09	0.84 [0.69, 1.03]	2.88	0.004	0.84 [0.75, 0.95]
Caucasian	8	5435/2931									
C versus T			13.84	49	0.05	3.81	0.0001	0.86 [0.79, 0.93]	2.6	0.009	0.85 [0.76, 0.96]
TC versus TT			4.96	0	0.66	2.57	0.01	0.83 [0.73, 0.96]	2.55	0.01	0.83 [0.73, 0.96]
CC versus TT			12.95	46	0.07	3.54	0.0001	0.75 [0.64, 0.88]	2.44	0.01	0.74 [0.59, 0.94]
(TC+CC) versus TT			5.71	0	0.57	2.72	0.007	0.84 [0.73, 0.95]	2.71	0.007	0.84 [0.73, 0.95]
CC versus (TC+TT)			12.64	45	0.08	2.52	0.01	0.85 [0.75, 0.96]	1.58	0.11	0.86 [0.71, 1.04]
Asian	4	1341/1012									
C versus T			36.6	92	<0.001	1.05	0.29	0.78 [0.48, 1.25]	1.64	0.1	0.90 [0.79, 1.02]
TC versus TT			10.82	72	0.01	0.31	0.76	0.95 [0.66, 1.36]	0.05	0.96	1.00 [0.83, 1.20]
CC versus TT			14.28	79	0.003	0.91	0.36	0.73 [0.37, 1.44]	0.69	0.49	0.90 [0.68, 1.20]
(TC+CC) versus TT			33.79	91	<0.001	0.81	0.42	0.78 [0.43, 1.42]	1.4	0.16	0.88 [0.75, 1.05]
CC versus (TC+TT)			13.75	78	0.003	1.19	0.23	0.68 [0.36, 1.29]	1.23	0.22	0.84 [0.65, 1.11]

[1]Number of studies. [2]The Meta-analysis results after a effects model was selected according to the between-study heterogeneity. [3] The result of sensitivity analysis after changing effects models.

recessive models (CC versus TC+TT) was 0.85 with a 95% CI: 0.75-0.96 and *P*=0.01, suggesting that the CC genotype of the rs10033900 polymorphism is associated with resistance to AMD. We also performed comparisons for the co-dominant (CC versus TT: OR=0.75, 95%CI: 0.64-0.88, *P*=0.0001; TC versus TT: OR=0.83, 95%CI: 0.73-0.96, *P*= 0.01) and the dominant (TC+CC versus TT: OR=0.84, 95% CI: 0.73-0.95, *P*=0.007) models (Table 3). However, In the studies on Asian populations, there were not associations between the rs10033900 polymorphism and risk of AMD [C versus T (OR=0.78, 95%CI: 0.48-1.25, *P*=0.29), TC versus TT (OR=0.95, 95%CI: 0.66-1.36, *P*=0.76), CC versus TT (OR=0.73 ,95%CI: 0.37-1.44, *P*=0.36), TC+CC versus TT (OR=0.78, 95% CI: 0.43-1.42, *P*=0.42) and CC versus

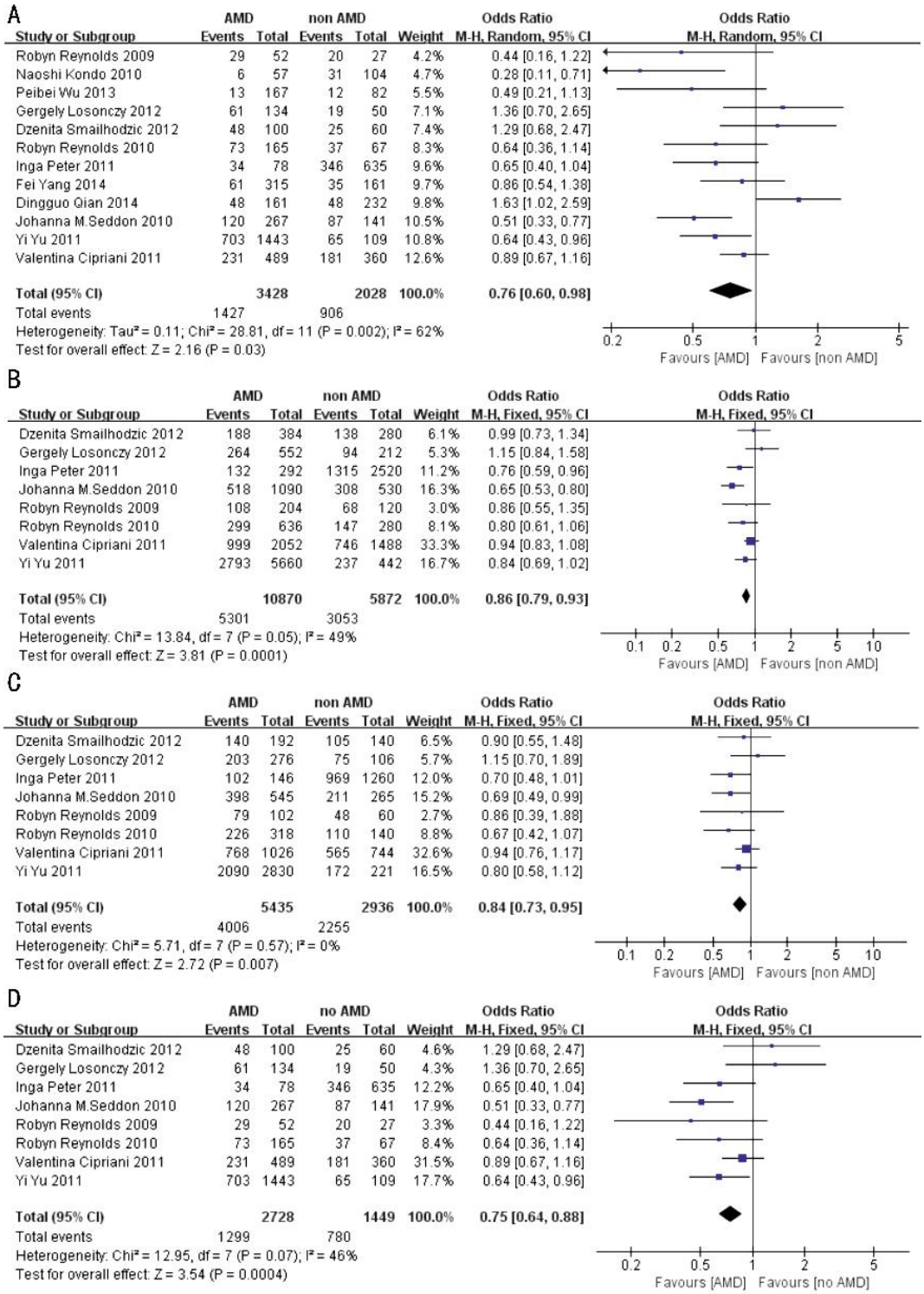

Figure 2 Forest plots for the association between the CFI rs10033900T>C polymorphisms and AMD risk A: The forest figure of the CC versus TT models in all populations; B: The forest figure of the C versus T in the Caucasian populations; C: The forest figure of the TC+CC versus TT models in the Caucasian populations; D: The forest figure of the CC versus TT models in the Caucasian populations.

TC+TT (OR=0.68, 95% CI: 0.36-1.29, P=0.23) models]. The forest figure of the C versus T, TC+CC versus TT and CC versus TT in the Caucasian populations is presented in Figure 2B, 2C, 2D.

Obvious heterogeneity among studies was found in most of the comparisons; the I^2 rose from 39% (Q=18.02; P=0.08) to 80% (Q=54.08; P<0.0001). We tried to explore the heterogeneity through subgroup analyses by ethnicity. We found there was no evidence of heterogeneity be in the between individual study comparison of Caucasian populations and obvious heterogeneity in the comparison of Asian populations. Thus, ethnicity may be the main source of heterogeneity.

A sensitivity analysis was performed by changing the effects model (change the random-effect model into fixed-effect model or versus versa) and sequential removal of individual

Table 4 Results of Meta-analysis of the association between rs2285714 polymorphism of CFI gene and AMD risk

Genotype contrast	[1]*n*	Cases/controls	Heterogeneity			[2]Genotype effect			[3]Genotype effect		
			Q	I^2 (%)	*P*	*Z*	*P*	OR (95%CI)	*Z*	*P*	OR (95%CI)
All populations	3	3092/1589									
T versus C			25.7	92	<0.001	0.39	0.7	0.92 [0.59, 1.42]	3.62	0.0001	1.18 [1.08, 1.29]
CT versus CC			2.93	32	0.23	1.01	0.31	0.93 [0.82, 1.07]	1.06	0.29	0.91 [0.76, 1.09]
TT versus CC			0.21	0	0.9	2.85	0.004	1.34 [1.09, 1.63]	2.85	0.004	1.34 [1.09, 1.63]
(CT+TT) versus CC			34.12	94	<0.001	0.50	0.62	0.85 [0.45, 1.60]	2.32	0.02	1.16 [1.02, 1.32]
TT versus (CT+CC)			0.03	0	0.99	4.35	<0.0001	1.50 [1.25, 1.80]	4.35	<0.0001	1.50 [1.25, 1.80]

[1]Number of studies; [2]The Meta-analysis results after a effects model was selected according to the between-study heterogeneity; [3]The result of sensitivity analysis after changing effects models.

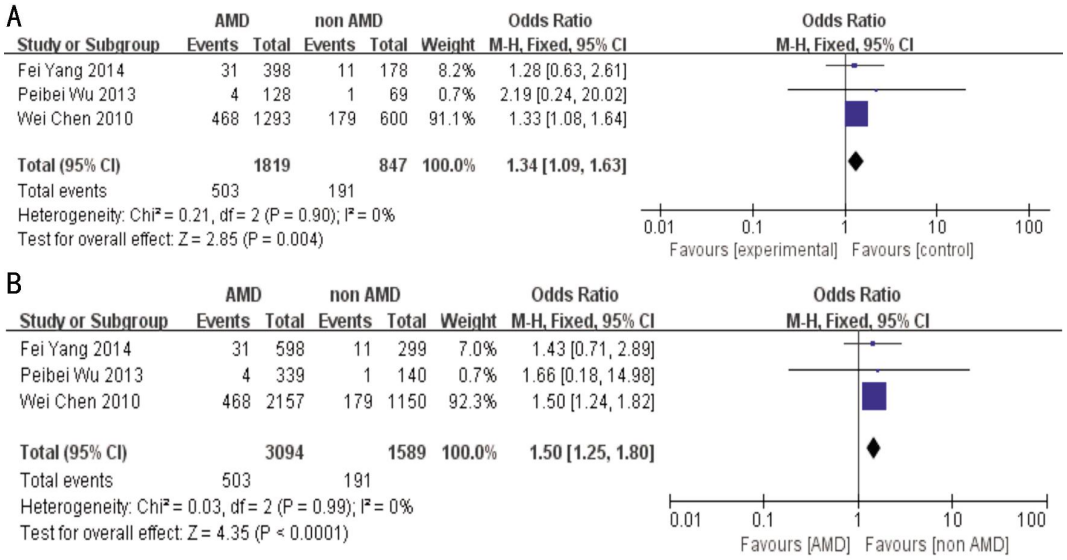

Figure 3 Forest plots for the association between the CFI rs2285714T>C polymorphisms and AMD risk A: The forest figure of the TT versus CC models in all populations; B: The forest figure of the TT versus CT+CC models in all populations.

studies at one time. The corresponding pooled ORs were not altered (Table 3) in all comparison except for CC versus (TC+TT) models in Caucasian, indicating that our results are statistically stable and convincing.

In addition, when we excluded the study by Qian *et al*[12] from the Meta-analysis, we discovered that the heterogeneity decreased. Thus, this study would have been the main source of heterogeneity.

CFI rs2285714C >T The rs2285714 polymorphism is located upstream of the CFI gene. Fagerness *et al* [6] first detected this gene locus in 2009. Subsequently, Chen *et al* [21] found that it has a significant correlation with AMD (OR= 1.31, 95%CI: 1.18-1.45). In this Meta-analysis, the effects of the genetic models in the AMD cases and non-AMD controls were determined in 3 studies (of 3092 AMD cases and 1589 controls). High between-study heterogeneity was found in T versus C (I^2=92; *P*<0.001) and TC+TT versus CC (I^2= 94; *P*<0.001) model, so a random effects model was used. In the fixed effects model, the pooled OR for the genotypes TT versus CC was 1.34 (95%CI: 1.09-1.63, *P*=0.004), pooled OR for TT versus TC+CC was 1.50 (95%CI: 1.25-1.80, *P*< 0.0001) (Table 4 and Figure 3A, 3B).

When we excluded the study by Chen *et al* [21] from the Meta-analysis, we discovered that the heterogeneity decreased. Thus ethnicity may be the main source of heterogeneity. When a sensitivity analysis was conducted after excluding and adjusting one study [17,23] that deviated from the HWE, the results did not change (data not shown). As shown in Table 4, after changing the effects model; this altered the pattern of the results. The small number of studies, small sample size, and high level of between-study heterogeneity may have been the main causes of this alteration.

Publication Bias As shown in Tables 5 and 6, Begg's rank correlation method and Egger's test were conducted to assess for possible publication bias among the studies. These tests demonstrated the absence of a publication bias in these polymorphisms.

DISCUSSION

The CFI gene is located on chromosome 4q25. It spans 63 kb and contains 13 exons. The first 8 exons encode the heavy chain, and the last 5 exons encode the light chain, which contains a serine protease domain. Under the regulation of CFH, the serine protease domain can cleave and inactivate C4b and C3b. It is a negative regulator of the complement system [22]. CFI polymorphisms that can alter CFI expression

Table 5 Assessment for publication bias in the reported CFI rs10033900 gene polymorphisms

Genotype contrast	[1]*n*	Egger's		Begg's
		P>|*t*|	95%CI	P_r>|*z*|
All populations	12			
C versus T		0.304	[-25.53723, 8.921145]	0.276
TC versus TT		0.479	[-4.575586, 2.305361]	0.837
CC versus TT		0.148	[-34.61434, 5.999052]	0.016
(TC+CC) versus TT		0.526	[-5.838634, 3.181772]	0.537
CC versus (TC+TT)		0.070	[-87.22298, 4.200584]	0.062
Caucasian populations	8			
C versus T		0.978	[-1.417191,1.450019]	0.764
TC versus TT		0.145	[-1.151035, 2162161]	0.536
CC versus TT		0.743	[-1.01868, 7680381]	0.536
(TC+CC) versus TT		0.656	[-1.097826, 7454658]	0.711
CC versus (TC+TT)		0.749	[-15.73909, 11.94231]	0.266
Asian populations	4			
C versus T		0.367	[-117.545, 67.78446]	0.734
TC versus TT		0.471	[-33.74927, 22.26781]	0.497
CC versus TT		0.363	[-115.1454, 65.97659]	0.174
(TC+CC) versus TT		0.459	[-32.38015, 49.77209]	0.734
CC versus (TC+TT)		0.437	[-247.2637, 156.8288]	0.734

[1]Number of studies.

Table 6 Assessment for publication bias in the reported CFI rs2285714 gene polymorphisms

Genotype contrast	[1]*n*	Egger's		Begg's
		P>|*t*|	(95%CI)	P_r>|*z*|
All populations	3			
T versus C		0.170	[-193.8548, 107.0692]	1.000
CT versus CC		0.544	[-94.27381, 82.19215]	1.000
TT versus CC		0.136	[-736.7271, 344.0816]	0.296
(CT+TT) versus CC		0.222	[-64.60554, 41.63955]	1.000
TT versus (CT+CC)		0.212	[-2536.353, 1596.484]	0.296

[1]Number of studies.

and protein production may increase the risk of AMD. A number of published studies have been performed in recent years to evaluate the association CFI SNPs in terms of their effect on AMD risk, but their results remain inconclusive. An earlier Meta-analysis with very limited number of studies included failed to result in a positive finding [7]. Recently, there was a Meta-analyses included much fewer numbers of studies than ours, yielded similar findings to ours. In truth, this paper has larger number of AMD cases for the rs10033900 analysis, there are 6776 AMD cases and 3943 controls compared to 3752 AMD cases and 3163 controls in the study by Yang *et al* [18].

A total of 13 articles were included: 12 for rs10033900 and 3 for rs2285714. In addition, we conducted subgroup analysis in CFI rs10033900, the result which is much more convincing and reliable. Fagerness *et al* [6] found SNP (rs10033900) remained the associated with a *P*-value of 6.46×10^{-8} (OR=0.7056 referring to lower-risk C allele) with AMD, which was replicated by Ennis *et al* [8]. But there was no association with AMD on the study of Chinese in recent articles [18]. Our result revealed that C allele, and genotype CC, TC and TC+CC carriers were related to lower AMD risk in all populations. In the Caucasian, the comparison of the allele models (C versus T), recessive models (CC versus TC+TT), co-dominant (CC versus TT, TC versus TT) and the dominant (TC+CC versus TT) models revealed that C allele were related to lower AMD risk. However, in Asian studies, we didn't observe the association of rs10033900 with AMD under the allele and genotypes comparison.

In terms of analysis for SNP rs2285714, the combined results indicated that individuals with the rs2285714 genotype TT had a 34 percent higher risk of AMD compared with individuals with the rs2285714 CC genotype, and carriers of the TT genotype had a 50 percent higher risk of AMD compared with those with the (CT+CC) genotype, supporting the rs2285714 may play a potential role in the pathogenesis of AMD, which was consistent with previously published research[21]. More studies are needed to verify this evaluation and evaluate the differences between ethnicity.

There some limitations in the present study. First, the number of study was not large enough for stratified analyses by ethnicity, gender, age and disease phenotypes (especially for rs2285714). Second, obvious between-study heterogeneity was found in some comparisons. Chinese Studies may be the main source of heterogeneity by stratified analyses by ethnicity in rs10033900. Third, the included studies only investigated the associations between these 2 SNPs and AMD, without evaluating the gene-gene and gene-environment interactions. Fourth, the Meta-analysis probably should be done by AMD types, since the association of CFI with AMD can vary with AMD type, but this analysis was not performed in this paper due to the small number of cases in each late AMD types. In summary, despite the above-mentioned limitations, there was sufficient evidence to demonstrate a significant association between CFI polymorphisms and AMD in this Meta-analysis. That is, having a mutant allele C, TC, CC and TC+CC was associated with a decreased risk of AMD in all population and carrying the C allele for CFI rs10033900 may contribute to lower risk of AMD development in the Caucasian, but not in Asian subjects. Additionally, carrying TT genotype of rs2285714 polymorphisms are associated with a increased risk of AMD. For future studies, it will be necessary to carry out further large sample studies to confirm these associations from our Meta-analysis. At the same time, the biological implications and interactions between gene and environment should be further investigated and clarified.

ACKNOWLEDGEMENTS

Foundation: Supported by the Scientific Research Project of Traditional Chinese Medicine of Health and Family Planning Commission of Chongqing (ZY20150243).

Conflicts of Interest: Wang Q, None; **Zhao HS,** None; **Li L,** None.

REFERENCES

1 Cheung CM, Li X, Cheng CY, Zheng Y, Mitchell P, Wang JJ, Wong TY. Prevalence, racial variations, and risk factors of age-related macular degeneration in singaporean chinese, indians, and malays. *Ophthalmology* 2014;121(8)1598-1603.

2 Cheung CM, Tai ES, Kawasaki R, Tay WT, Lee JL, Hamzah H, Wong TY. Prevalence of and risk factors for age-related macular degeneration in a multiethnic Asian cohort. *Arch Ophthalmol* 2012;130(4):480-486.

3 Klein R, Chou CF, Klein BE, Zhang X, Meuer SM, Saaddine JB. Prevalence of age-related macular degeneration in the US population. *Arch Ophthalmol* 2011;129(1):75-80.

4 Ding X, Patel M, Chan CC. Molecular pathology of age-related macular degeneration. *Prog Retin Eye Res* 2009;28(1):1-18.

5 Fraczek LA, Martin BK. Transcriptional control of genes for soluble complement cascade regulatory proteins. *Mol Immunol* 2010;48 (1-3): 9-13.

6 Fagerness JA, Maller JB, Neale BM, Reynolds RC, Daly MJ, Seddon JM. Variation near complement factor I is associated with risk of advanced AMD. *Eur J Hum Genet* 2009;17(1):100-104.

7 Cipriani V, Matharu BK, Khan JC, Shahid H, Hayward C, Wright AF, Armbrecht AM, Dhillon B, Harding SP, Bishop PN, Bunce C, Clayton DG, Moore AT, Yates JR. No evidence of association between complement factor I genetic variant rs10033900 and age-related macular degeneration. *Eur J Hum Genet* 2012; 20(1):1-2.

8 Ennis S, Gibson J, Cree AJ, Collins A, Lotery AJ. Support for the involvement of complement factor I in age-related macular degeneration. *Eur J Hum Genet* 2010;18(1):15-16.

9 Kondo N, Bessho H, Honda S, Negi A. Additional evidence to support the role of a common variant near the complement factor I gene in susceptibility to age-related macular degeneration. *Eur J Hum Genet* 2010;18 (6): 634-635.

10 Losonczy G, Vajas A, Takacs L, Dzsudzsák E, Fekete A, Márhoffer E, Kardos L, Ajzner E, Hurtado B, de Frutos PG, Berta A, Balogh I. Effect of the Gas6 c.834+7G>A polymorphism and the interaction of known risk factors on AMD pathogenesis in Hungarian patients. *PLoS One* 2012; 7 (11):e50181.

11 Peter I, Huggins GS, Ordovas JM, Haan M, Seddon JM. Evaluation of new and established age-related macular degeneration susceptibility genes in the Women's Health Initiative Sight Exam (WHI-SE) Study. *Am J Ophthalmol* 2011;152(6):1005-1013.

12 Qian D, Kan M, Weng X, Huang Y, Zhou C, Yu G, Wang T, Zhou D, Zhang Z, Zhang D, Tang W, Liu Y. Common variant rs10033900 near the complement factor I gene is associated with age-related macular degeneration risk in Han Chinese population. *Eur J Hum Genet* 2014;22 (12):1417-1419.

13 Reynolds R, Hartnett ME, Atkinson JP, Huang Y, Zhou C, Yu G, Wang T, Zhou D, Zhang Z, Zhang D, Tang W, Liu Y. Plasma complement components and activation fragments: associations with age-related macular degeneration genotypes and phenotypes. *Invest Ophthalmol Vis Sci* 2009;50(12):5818-5827.

14 Reynolds R, Rosner B, Seddon JM. Serum lipid biomarkers and hepatic lipase gene associations with age-related macular degeneration. *Ophthalmology* 2010;117(10):1989-1995.

15 Seddon JM, Reynolds R, Rosner B. Associations of smoking, body mass index, dietary lutein, and the LIPC gene variant rs10468017 with advanced age-related macular degeneration. *Mol Vis* 2010;16:2412-2424.

16 Seddon JM, Yu Y, Miller EC, Reynolds R, Tan PL, Gowrisankar S, Goldstein JI, Triebwasser M, Anderson HE, Zerbib J, Kavanagh D, Souied E, Katsanis N, Daly MJ, Atkinson JP, Raychaudhuri S. Rare variants in CFI, C3 and C9 are associated with high risk of advanced age-related macular degeneration. *Nat Genet* 2013;45(11):1366-1370.

17 Wu PB, Gu H, Yang XF, Liu NP. Association of single nucleotide polymorphism in complement factor I gene with age-related macular degeneration. *Zhonghua Yan Ke Za Zhi* 2013;49(4):350-356.

18 Yang F, Sun Y, Jin Z, Cheng Y, Li S, Bai Y, Huang L, Li X. Complement factor I polymorphism is not associated with neovascular age-related macular degeneration and polypoidal choroidal vasculopathy in a Chinese population. *Ophthalmologica* 2014;232(1):37-45.

19 Yu Y, Reynolds R, Fagerness J, Rosner B, Daly MJ, Seddon JM. Association of variants in the LIPC and ABCA1 genes with intermediate and large drusen and advanced age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2011;52(7):4663-4670.

20 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25(9):603-605.

21 Chen W, Stambolian D, Edwards AO, *et al*. Genetic variants near TIMP3 and high-density lipoprotein-associated loci influence susceptibility to age-related macular degeneration. *Proc Natl Acad Sci U S A* 2010; 107(16):7401-7406.

22 Smailhodzic D, Klaver CC, Klevering BJ, Boon CJ, Groenewoud JM, Kirchhof B, Daha MR, den Hollander AI, Hoyng CB. Risk alleles in CFH and ARMS2 are independently associated with systemic complement activation in age-related macular degeneration. *Ophthalmology* 2012;119 (2):339-346.

23 Cipriani V, Leung HT, Plagnol V, *et al*. Genome-wide association study of age-related macular degeneration identifies associated variants in the TNXB-FKBPL-NOTCH4 region of chromosome 6p21.3. *Hum Mol Genet* 2012;21(18):4138-4150.