Roles of Three Common *VEGF* Polymorphisms in the Risk of Age-Related Macular Degeneration

Yuqing Liu, Siqing Hou, Weihua Lang, Dongshu Dai, Zhixue Wang, Xiangning Ji,
Kun Li, Xi Zhang, Yuanyuan Zou, and Jingxian Wang

Associations between vascular endothelial growth factor (*VEGF*) polymorphisms (rs833061, rs1413711, and rs3025039) and risk of age-related macular degeneration (AMD) have been extensively studied, but the currently available results are contentious rather than conclusive. Therefore, we performed the present meta-analysis to further assess the associations. Literature search in PubMed, Embase, and Web of Science databases was conducted until April 2013. The strength of the associations between *VEGF* polymorphisms and AMD risk was estimated by pooled odds ratios (ORs) and 95% confidence intervals (CIs). Both models of fixed effects and random effects were performed to summarize the pooled ORs. All data were analyzed by Stata software 12.0. The meta-analysis results based on nine case-control studies with 2427 cases and 2037 controls showed that rs833061 had protective effects on AMD risk (TT vs. CT+CC: OR=0.58, 95% CI=0.41–0.81), whereas rs1413711 (TT vs. CT+CC: OR=1.46, 95% CI=1.10–1.93) and rs3025039 (TT vs. CC: OR=1.87, 95% CI=1.15–3.02; TT vs. CT+CC: OR=2.09, 95% CI=1.30–3.37) represented as risk factors for AMD. Subgroup analysis by ethnicity suggested significantly reduced risk in Caucasians (TT vs. CT+CC: OR=0.60, 95% CI=0.36–0.99; T vs. C: OR=0.89, 95% CI=0.78–1.00) and Asians (TT+CT vs. CC: OR=0.57, 95% CI=0.34–0.96; TT vs. CT+CC: OR=0.54, 95% CI=0.33–0.90) for rs833061, yet elevated risk in Caucasians (TT vs. CT+CC: OR=2.05, 95% CI=1.24–3.38) for rs1413711 and in Asians (TT vs. CC: OR=2.06, 95% CI=1.24–3.43; TT vs. CC: OR=2.34, 95% CI=1.42–3.89) for rs3025039. In stratified analysis by type of AMD, rs833061 was observed to decrease wet AMD risk, while rs1413711 and rs3025039 were found to increase the risk of wet AMD. Based on the currently available data, this meta-analysis suggests that the *VEGF* polymorphisms may be associated with risk of AMD, particularly wet AMD.

Introduction

AGE-RELATED MACULAR DEGENERATION (AMD), a degenerative disease of the retina leading to progressive impairment of central vision, is the major cause of irreversible vision loss among older populations in developed countries (Jager *et al.*, 2008). There are two subtypes of AMD: nonexudative (dry or atrophic) AMD and exudative (wet or neovascular). Exudative AMD is characterized by geographic atrophy or the development of choroidal neovascularization, where abnormal blood vessels grow from the choroid underneath the retina and leak, thus causing rapid deterioration in central vision (Ferris *et al.*, 2005). AMD is a complex disorder known to result from environmental and genetic factors (Seddon *et al.*, 2011). While an array of genes have been identified as susceptibility factors to the disease (Ting *et al.*, 2009; Yachimski *et al.*, 2009), the mechanism of AMD progression has not been well understood.

Tumor growth progresses from the formation of blood vessels, a process known as angiogenesis (Folkman, 1971). Vascular endothelial growth factor (*VEGF*) is a fundamental mediator of angiogenesis, vasculogenesis, and lymphangiogenesis in normal and pathological cells (Ferrara, 1999). *VEGF* is essential for retinal health due to its involvement in vascular development, survival of nascent retinal vessels, and maintenance of stable mature vessels (Penn *et al.*, 2008). Many retinal diseases, including the highly prevalent AMD, have been reported to be correlated with elevated expression of *VEGF* (Penn *et al.*, 2008).

The human *VEGF* gene, located on chromosome 6p21.3, is comprised of eight exons and seven introns, with the coding region spanning ~14 kb (Vincenti *et al.*, 1996; Ferrara *et al.*, 2003; Goncalves *et al.*, 2010). Polymorphisms of the *VEGF* gene have been substantially investigated in AMD, yet the data obtained from the investigations remain contentious and ambiguous. For example, a study containing seven

single-nucleotide polymorphisms (SNPs) of the *VEGF* gene conducted in an Anglo-Celtic subpopulation demonstrated no associations between the studied SNPs and AMD (Richardson *et al.*, 2007). However, a subsequent study of a Chinese population indicated *VEGF* gene is relevant to wet AMD (Lin *et al.*, 2008). The similar conflicting results were also presented in recently published meta-analyses (Lu *et al.*, 2012; Huang *et al.*, 2013).

Based on the importance of *VEGF* in AMD pathogenesis and contradictory data on the role of *VEGF* SNPs in AMD risk, we sought to derive compelling evidence for the association through a meta-analysis of all eligible case-control studies concerning the associations between three common SNPs (rs833061, rs1413711, and rs3025039) and the risk of AMD.

Materials and Methods

Search strategy

We carried out a literature search in PubMed (www.ncbi.nlm.nih.gov/pubmed), Embase (http://202.106.73.6:8080/medlib/s/com/embase/www/G.http/home), and Web of Science (www.thomsonscientific.com.cn/productsservices/webofscience/), covering all articles addressing the associations between the three polymorphisms of *VEGF* gene and AMD risk (up to April 2013). The search strategy used a combination of the following terms: vascular endothelial growth factor or *VEGF*; rs833061, rs1413711, and rs3025039 or -460T/C, +674C/T, and +936C/T; age-related macular degeneration or AMD. Besides the database search, the reference lists of the retrieved articles were also screened for other potential articles.

We defined the following criteria for inclusion: (1) used a case-control study design; (2) evaluated one of the three polymorphisms of *VEGF* gene and AMD risk; (3) contained enough genotype data to estimate odds ratios (ORs) and 95% confidence intervals (CIs). The major reasons for exclusion were (1) case-only study; (2) overlapping data; (3) insufficient information on genotype frequency; (4) review articles and comment letters.

Data extraction

Data were independently retrieved in duplicate by two authors according to the defined inclusion criteria to ensure the accuracy of the data. For each study, the following information was recorded: first author, publication year, country of origin, sources of AMD cases and controls, study type, ethnicity, numbers of cases and controls, and genotype frequencies of cases and controls.

Statistical analysis

The associations between *VEGF* polymorphisms and AMD risk were estimated by calculating pooled ORs and 95% CIs under homozygote model TT versus CC, dominant model TT+CT versus CC, recessive model TT versus CT+CC, allele model T versus C and heterozygote model CT versus CC. The significance of the summary ORs was checked by Z test ($p < 0.10$ was deemed significant). The χ^2 -based Q statistic and I^2 -based Q statistic test (Higgins *et al.*, 2003) were performed to evaluate variations due to heterogeneity rather than chance. Heterogeneity was considered statistically significant when $p < 0.10$ or $I^2 > 50\%$. A random-effects model (DerSimonian-Laird method) (DerSimonian and Laird, 1986) was used if obvious heterogeneity was indicated, or the fixed-effects model (Mantel-Haenszel method) (Mantel and Haenszel, 1959) was applied to calculate pooled effect estimates. Stratified analyses were also performed by types of AMD and ethnicity. A χ^2 test was performed to determine the Hardy-Weinberg equilibrium (HWE) of the control subjects and $p < 0.10$ suggested representative of deviation from HWE. Publication bias was detected by Begg's funnel plots and Egger's test (Egger *et al.*, 1997). Asymmetry of the funnel plot or $p < 0.10$ indicated a potential publication bias across the included studies. The leave-one-out sensitivity analysis by repeated meta-analyses of excluding each study was conducted to reflect the influence of the excluded study to the overall summary ORs. All data were done with Stata software (version 12.0; Stata Corp LP, College Station, TX).

FIG. 1. Studies identified with criteria for inclusion and exclusion.

TABLE 1. CHARACTERISTICS OF STUDIES INCLUDED IN THE META-ANALYSIS

First author, year	Type	Ethnicity	Source	SNP	Cases					Controls					HWE		
					Study size	CC	CT	TT	C	T	Study size	CC	CT	TT		C	T
Richardson, 2007 ^a	Total	Caucasian	PB	rs833061	566	153	259	154	565	567	157	39	78	40	156	158	0.937
Richardson, 2007 ^a	Dry	Caucasian	PB	rs833061	100	30	43	27	103	97	157	39	78	40	156	158	0.937
Richardson, 2007 ^a	Wet	Caucasian	PB	rs833061	336	86	158	92	330	342	157	39	78	40	156	158	0.937
Lin, 2008 ^a	Total	Asian	HB	rs833061	190	8	66	116	82	298	80	4	60	116	68	92	<0.001
Lin, 2008 ^a	Dry	Asian	HB	rs833061	104	6	38	60	50	158	80	4	60	116	68	92	<0.001
Lin, 2008 ^a	Wet	Asian	HB	rs833061	86	2	28	56	32	140	80	4	60	116	68	92	<0.001
Janik-Papis, 2009 ^a	Total	Caucasian	HB	rs833061	265	26	191	48	243	287	134	11	63	60	85	183	0.323
Janik-Papis, 2009 ^a	Dry	Caucasian	HB	rs833061	88	8	67	13	83	93	134	11	63	60	85	183	0.323
Janik-Papis, 2009 ^a	Wet	Caucasian	HB	rs833061	177	18	124	35	160	194	134	11	63	60	85	183	0.323
Szaflik, 2009	Wet	Caucasian	HB	rs833061	100	8	78	14	94	106	104	11	56	37	78	130	0.129
Qu, 2011	Wet	Asian	HB	rs833061	159	20	58	81	98	220	140	9	50	81	68	212	0.733
Churchill, 2006	Wet	Caucasian	PB	rs1413711	45	17	18	10	52	38	94	19	54	21	92	96	0.147
Lin, 2008 ^a	Total	Asian	HB	rs1413711	190	57	80	53	194	186	180	50	85	45	185	175	0.462
Lin, 2008 ^a	Dry	Asian	HB	rs1413711	104	29	46	29	104	104	180	50	85	45	185	175	0.462
Lin, 2008 ^a	Wet	Asian	HB	rs1413711	86	28	34	24	90	82	180	50	85	45	185	175	0.462
Qu, 2011	Wet	Asian	HB	rs1413711	159	81	58	20	220	98	140	81	50	9	212	68	0.733
Almeida, 2012 ^a	Total	Caucasian	HB	rs1413711	160	65	66	29	196	124	140	67	65	8	199	81	0.127
Almeida, 2012 ^a	Dry	Caucasian	HB	rs1413711	36	14	14	8	42	30	140	67	65	8	199	81	0.127
Almeida, 2012 ^a	Wet	Caucasian	HB	rs1413711	124	51	52	21	154	94	140	67	65	8	199	81	0.127
Lin, 2008 ^a	Total	Asian	HB	rs3025039	190	120	58	12	298	82	280	134	42	4	410	150	<0.001
Lin, 2008 ^a	Dry	Asian	HB	rs3025039	114	75	27	12	177	51	280	134	42	4	410	150	<0.001
Lin, 2008 ^a	Wet	Asian	HB	rs3025039	86	45	31	10	121	51	280	134	42	4	410	150	<0.001
Galan, 2010	Total	Caucasian	HB	rs3025039	226	175	48	3	398	54	248	190	54	4	434	62	0.942
Qu, 2011	Wet	Asian	HB	rs3025039	159	114	33	12	261	57	140	92	40	8	224	56	0.249
Jiang, 2013 ^a	Total	Asian	HB	rs3025039	200	132	50	18	314	86	200	138	55	7	331	69	0.603
Jiang, 2013 ^a	Dry	Asian	HB	rs3025039	49	32	13	4	77	21	200	138	55	7	331	69	0.603
Jiang, 2013 ^a	Wet	Asian	HB	rs3025039	99	66	25	8	157	41	200	138	55	7	331	69	0.603

^aOne study included several single-nucleotide polymorphisms (SNPs).
HWE, Hardy-Weinberg equilibrium; PB, population-based; HB, hospital-based.

Results

Characteristics of studies

Two hundred sixteen potentially relevant studies were recovered by literature search in PubMed, Embase, and Web of Science. All retrieved articles were examined by reading titles, abstracts, and full texts to check the eligibility for this meta-analysis. After careful screening, nine case-control studies (Churchill *et al.*, 2006; Richardson *et al.*, 2007; Lin *et al.*, 2008; Janik-Papis *et al.*, 2009; Szaflik *et al.*, 2009; Galan *et al.*, 2010; Qu *et al.*, 2011; Almeida *et al.*, 2012; Jiang *et al.*, 2013) with 2427 cases and 2037 controls were finally included in the meta-analysis (Fig. 1). Among them, five studies were (1150 cases and 615 controls) for rs833061 SNP, four studies (554 cases and 554 controls) for rs1413711 SNP, and four studies (723 cases and 868 controls) for rs3025039 SNP (two studies contained three SNPs). Main characteristics of the included studies are summarized in Table 1.

Quantitative synthesis

Table 2 shows the results of the meta-analysis on the associations between *VEGF* polymorphisms and risk of AMD. For rs833061, a reduced AMD risk associated with the recessive model (TT vs. CT+CC: OR=0.58, 95% CI=0.41–0.81) (Fig. 2) was observed in the general analysis. In the stratified analysis based on ethnicity, we found a decreased risk of AMD in Asians under the dominant model (TT + CT vs. CC: OR=0.57, 95% CI=0.34–0.96) and the recessive model (TT vs. CT+CC: OR=0.54, 95% CI=0.33–0.99). However, a borderline association was indicated in Caucasians under the recessive model (TT vs. CT+CC: OR=0.60, 95% CI=0.36–0.99) and the allele model (T vs. C: OR=0.89, 95% CI=0.78–1.00). Stratifying the overall population by type of AMD showed that the recessive model (TT vs. CT+CC: OR=0.61, 95% CI=0.41–0.91) reduced risk of wet AMD. But none of the genetic models were found to be associated with dry AMD.

For rs1413711, overall, we found that the recessive model (TT vs. CT+CC: OR=1.46, 95% CI=1.10–1.93) (Fig. 3) was significantly associated with an increased AMD risk. Similarly, stratified analyses showed the TT genotype conferred 2.05-fold risk to AMD susceptibility in Caucasians and 1.49-fold risk to wet AMD, compared to the CT+CC genotypes (OR=2.05, 95% CI=1.24–3.38; OR=1.49, 95% CI=1.04–2.12, respectively), but not in Asians or dry AMD (Table 2).

For rs3025039, statistical evidence for significant association between this polymorphism and AMD risk was indicated in overall population under the homozygote model (TT vs. CC: OR=1.87, 95% CI=1.15–3.02) (Fig. 4) and the recessive model (TT vs. CT+CC: OR=2.09, 95% CI=1.30–3.37) (Fig. 5). The two genetic models also showed significantly elevated risk in Asians (TT vs. CC: OR=2.06, 95% CI=1.24–3.43; TT vs. CC: OR=2.34, 95% CI=1.42–3.89) and in wet AMD (TT vs. CC: OR=2.24, 95% CI=1.24–4.05; TT vs. CC: OR=2.50, 95% CI=1.39–4.49) (Table 2).

Test of heterogeneity and sensitivity analysis

The Q-test and I^2 statistics were used to test heterogeneity among the studies. Significant heterogeneity was observed in the dominant model, recessive model, and allele model for rs833061; weak heterogeneity was indicated in the homozygote model for rs1413711; and obvious between-study

TABLE 2. META-ANALYSIS OF *VEGF* POLYMORPHISMS (RS833061, RS1413711, AND RS3025039) AND RISK OF AGE-RELATED MACULAR DEGENERATION

Variables	TT vs. CC			TT+CT vs. CC			TT vs. CT+CC			Allele T vs. Allele C			CT vs. CC		
	OR (95% CI)	Ph	I^2	OR (95% CI)	Ph	I^2	OR (95% CI)	Ph	I^2	OR (95% CI)	Ph	I^2	OR (95% CI)	Ph	I^2
rs833061															
Caucasian	0.88 (0.68–1.15)	0.929	0.0%	0.98 (0.84–1.15)	0.998	0.0%	0.60 (0.36–0.99)	0.002	77.1%	0.89 (0.78–1.00)	0.575	0.0%	1.00 (0.83–1.21)	0.977	0.0%
Asian	0.94 (0.73–1.21)	0.936	0.0%	0.57 (0.34–0.96)	0.002	83.5%	0.54 (0.33–0.90)	0.012	77.3%	1.17 (0.88–1.56)	0.068	62.8%	0.92 (0.67–1.27)	0.954	0.0%
Dry	0.90 (0.65–1.24)	0.848	0.0%	0.73 (0.43–1.25)	0.003	82.4%	0.52 (0.26–1.04)	0.007	79.6%	0.99 (0.74–1.34)	0.069	62.5%	0.95 (0.71–1.27)	0.872	0.0%
Wet	0.92 (0.74–1.15)	0.943	0.0%	0.85 (0.64–1.12)	0.011	69.2%	0.61 (0.41–0.92)	0.004	74.0%	0.96 (0.81–1.14)	0.099	48.7%	0.99 (0.81–1.21)	0.982	0.0%
All	0.91 (0.76–1.10)	0.993	0.0%	0.80 (0.63–1.03)	0.000	73.1%	0.58 (0.41–0.81)	0.000	74.1%	0.97 (0.84–1.12)	0.067	47.0%	0.98 (0.83–1.15)	0.998	0.0%
rs1413711															
Caucasian	1.83 (0.69–4.88)	0.041	68.6%	1.03 (0.77–1.38)	0.517	0.0%	2.05 (1.24–3.38)	0.080	60.5%	1.17 (0.92–1.49)	0.186	40.6%	0.93 (0.67–1.29)	0.616	0.0%
Asian	1.16 (0.80–1.68)	0.368	0.1%	1.03 (0.82–1.29)	0.741	0.0%	1.24 (0.88–1.75)	0.476	0.0%	1.07 (0.89–1.29)	0.529	0.0%	0.98 (0.75–1.29)	0.801	0.0%
Dry	1.72 (0.55–5.36)	0.061	71.4%	1.04 (0.76–1.43)	0.657	0.0%	1.40 (0.88–2.23)	0.036	77.2%	1.12 (0.87–1.45)	0.251	24.1%	0.99 (0.67–1.45)	0.923	0.0%
Wet	1.36 (0.76–2.42)	0.093	53.2%	1.02 (0.82–1.27)	0.635	0.0%	1.49 (1.04–2.12)	0.181	38.5%	1.10 (0.92–1.32)	0.299	18.3%	0.95 (0.47–1.22)	0.695	0.0%
All	1.42 (0.91–2.23)	0.077	49.6%	1.03 (0.86–1.23)	0.860	0.0%	1.46 (1.10–1.93)	0.100	45.9%	1.11 (0.96–1.28)	0.415	0.1%	0.96 (0.78–1.18)	0.916	0.0%
rs3025039															
Caucasian	0.82 (0.18–3.70)	—	—	0.96 (0.64–1.46)	—	—	0.82 (0.18–3.72)	—	—	0.96 (0.65–1.41)	—	—	0.97 (0.63–1.49)	—	—
Asian	2.06 (1.24–3.43)	0.232	28.4%	1.38 (0.87–2.17)	0.003	74.6%	2.34 (1.42–3.89)	0.190	34.8%	0.93 (0.78–1.13)	0.056	56.6%	1.06 (0.83–1.36)	0.282	20.9%
Dry	1.58 (0.57–4.39)	0.387	0.0%	1.43 (0.96–2.14)	0.312	2.2%	1.89 (0.68–5.23)	0.613	0.0%	0.73 (0.53–1.02)	0.020	81.4%	1.07 (0.70–1.64)	0.840	0.0%
Wet	2.24 (1.24–4.05)	0.101	56.4%	1.37 (0.65–2.90)	0.001	86.4%	2.50 (1.39–4.49)	0.059	64.8%	1.06 (0.84–1.33)	0.589	0.0%	1.05 (0.78–1.43)	0.082	60.1%
All	1.87 (1.15–3.02)	0.230	27.2%	1.29 (0.88–1.89)	0.003	72.1%	2.09 (1.30–3.37)	0.168	35.9%	0.94 (0.79–1.11)	0.101	45.8%	1.04 (0.84–1.28)	0.395	3.4%

P_h , p -value of heterogeneity test; CI, confidence interval; OR, odds ratio; VEGF, vascular endothelial growth factor.

FIG. 2. Meta-analysis of the association between rs833061 and AMD risk stratified by ethnicity under TT versus CT + CC. Squares represent the point estimate of effect for each study, and horizontal lines through the squares represent 95% CIs. The area of each square reflects the weight assigned to that study. The center of the diamond represents the summary point estimate of effect, and the width of the diamond represents the 95% CI of the summary point estimate of effect. *Represents an independent population in a single article. AMD, age-related macular degeneration; CIs, confidence intervals.

FIG. 3. Meta-analysis of the association between rs1413711 and AMD risk stratified by ethnicity under TT versus CT + CC. Squares represent the point estimate of effect for each study, and horizontal lines through the squares represent 95% CIs. The area of each square reflects the weight assigned to that study. The center of the diamond represents the summary point estimate of effect, and the width of the diamond represents the 95% CI of the summary point estimate of effect. *Represents an independent population in a single article.

FIG. 4. Meta-analysis of the association between rs3025039 and AMD risk stratified by ethnicity under TT versus CC. Squares represent the point estimate of effect for each study, and horizontal lines through the squares represent 95% CIs. The area of each square reflects the weight assigned to that study. The center of the diamond represents the summary point estimate of effect, and the width of the diamond represents the 95% CI of the summary point estimate of effect. *Represents an independent population in a single article.

FIG. 5. Meta-analysis of the association between rs3025039 and AMD risk stratified by ethnicity under TT versus CT+CC. Squares represent the point estimate of effect for each study, and horizontal lines through the squares represent 95% CIs. The area of each square reflects the weight assigned to that study. The center of the diamond represents the summary point estimate of effect, and the width of the diamond represents the 95% CI of the summary point estimate of effect. *Represents an independent population in a single article.

FIG. 6. Begg's funnel plot for publication bias test (TT vs. CC for rs833061). Each point represents a separate study for the indicated association. Log OR natural logarithm of OR. Horizontal line mean effect size. OR, odds ratio.

heterogeneity in the dominant model for rs3025039 ($p < 0.10$ or $I^2 > 50\%$). The subsequent sensitivity analysis identified Lin *et al.* (2008) and Almeida *et al.* (2012) were potential sources of heterogeneity. The corresponding ORs were not altered quantitatively by excluding the two studies, suggesting our results were statistically stable and reliable.

Publication bias

The Begg's funnel plot and Egger's test were performed to determine the publication bias in the reports included in this meta-analysis. The symmetrical shape of funnel plots and the p -values of Egger's test showed no evidence of significant publication bias (TT vs. CC: $p = 0.523$ for rs833061; TT + CT vs. CC: $p = 0.303$ for rs1413711; TT vs. CC: $p = 0.201$ for rs3025039) (Figs. 6–8).

Discussion

Based on all available published studies to date, we performed a meta-analysis with an objective to examine the associations between *VEGF* polymorphisms and susceptibility to AMD. The results based on the pooled data by both fixed

FIG. 7. Begg's funnel plot for publication bias test (TT+CT vs. CC for rs1413711). Each point represents a separate study for the indicated association. Log OR natural logarithm of OR. Horizontal line mean effect size.

FIG. 8. Begg's funnel plot for publication bias test (TT vs. CC for rs3025039). Each point represents a separate study for the indicated association. Log OR natural logarithm of OR. Horizontal line mean effect size.

and random effects models suggested different overall effects of the *VEGF* polymorphisms on risk of AMD. Significantly lowered risk was indicated in rs833061, while rs1413711 and rs3025039 showed an obviously increased risk. In addition, the predisposition to AMD related to the three polymorphisms greatly differed in the studied ethnic groups. For rs833061, both Caucasians and Asians were found to be relevant to reduced risk of AMD, whereas rs1413711 showed significantly elevated risk in Caucasians rather than Asians and rs3025039 implicated an association in Asians, but not in Caucasians. In stratified analysis by type of AMD, all of the *VEGF* polymorphisms showed significant associations in wet AMD only.

Genetic factors play important roles in the pathogenesis of AMD. Recently, a number of investigators take great interest in the associations between *VEGF* polymorphisms and AMD susceptibility. However, the associations are conflicting rather than conclusive. *VEGF* polymorphisms were reported to be positively relevant (Almeida *et al.*, 2012), inversely relevant (Janik-Papis *et al.*, 2009), or irrelevant (Richardson *et al.*, 2007) to the risk of AMD in diverse ethnic populations. This might be because of the different ethnic origin of cases and controls, limited sample sizes, and/or limited number of polymorphisms analyzed to ensure a statistically valid conclusion.

Previously, Lu *et al.* demonstrated no significant associations between *VEGF* polymorphisms (rs833061, rs1413711, and rs2010963) and the risk of AMD (Lu *et al.*, 2012). However, different observation was indicated in the study by Huang *et al.* (2013), suggesting the *VEGF* rs1413711 and rs833061 polymorphisms may contribute to AMD susceptibility. Inconsistent results also implicated different associations between *VEGF* polymorphisms and various cancers, such as oral squamous cell carcinoma (Supic *et al.*, 2012), colorectal cancer (Jang *et al.*, 2013), gastric cancer (Liu *et al.*, 2011), breast cancer (Wang *et al.*, 2011), and lung cancer (Sun *et al.*, 2013). The controversial data may be due to the disparities in study design and the limited articles included in these analyses. Moreover, the pathogenesis of diseases is complicated and a variety of factors including gene-to-gene and gene-to-environment interactions may be involved in such a progression. Thus, future studies with these interactions considered are required to ascertain the uncertain relationship of *VEGF* polymorphisms and AMD risk.

Meta-analysis is considered as a powerful tool to identify the associations between polymorphisms and diseases. However, some potential limitations should be acknowledged. First, meta-analysis of pooled data indicated significant heterogeneity across the studies, which may be interpreted by the subjects of various ethnicities and basic methodological differences among the studies. Second, it is impossible to completely rule out the selection bias, because all of the included studies were observational, and confounders of age and gender might have effects on the results. Finally, gene–gene and gene–environment interactions were not addressed in our meta-analysis. Some polymorphisms themselves do not modify disease risks, but the modification would be indicated when interacting with other polymorphisms.

In conclusion, despite the above-mentioned limitations, our results suggest that the *VEGF* polymorphisms are associated with increased or decreased risk of AMD. In addition, stratified analyses indicate significantly statistical evidence for modified wet AMD risk associated with the TT genotype of the studied polymorphisms. Future large-scale studies are needed to validate the current conclusions.

Author Disclosure Statement

The authors have declared that no competing interests exist.

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Address correspondence to:
 Yuqing Liu, MD
 Department of Ophthalmology
 Cangzhou Central Hospital
 Hebei Medical University
 16 Xinhua West Road
 Cangzhou 061001
 Hebei Province
 China
 E-mail: waterlyq@sohu.com