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Vascular endothelial growth factor gene polymorphisms and psoriasis susceptibility: a meta-analysis

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ABSTRACT. The aim of this study was to explore whether vascular endothelial growth factor (*VEGF*) polymorphisms confer susceptibility to psoriasis. Meta-analyses were conducted to examine the associations between the +405 C/G, -460 C/T, -1154 A/G, and -2578 A/C polymorphisms of *VEGF* and psoriasis using allele contrast and recessive, dominant, and additive models. Seven studies on *VEGF* polymorphisms and psoriasis involving 1956 subjects (psoriasis patients 665, controls 1291) were included in this meta-analysis. We observed no association between psoriasis and the *VEGF* +405 C allele in all study subjects (odds ratio = 0.984, 95% confidence interval = 0.754-1.285, P = 0.906), but stratification by ethnicity indicated a significant association between the *VEGF* +405 C allele and psoriasis in Asians (odds ratio = 0.762, 95% confidence interval = 0.628-0.923, P = 0.005). In addition, we observed a significant association between the *VEGF* -460 C allele and psoriasis in Europeans (odds ratio = 0.807, 95% confidence interval = 0.672-0.968, P = 0.021). Meta-analyses of the -1154 A/G polymorphism also revealed a significant association with psoriasis in Europeans. However, the *VEGF* -2578 A/C polymorphism showed no

association in all subjects or in Europeans or Asians. This meta-analysis suggests the *VEGF* +405 C/G polymorphism confers susceptibility to psoriasis in Asians, and that the -460 C/T and -1154 A/G polymorphisms confer susceptibility to psoriasis in Europeans.

Key words: Meta-analysis; Polymorphism; Psoriasis; Vascular endothelial growth factor

INTRODUCTION

Psoriasis is a chronic inflammatory skin disorder characterized by keratinocyte hyperproliferation and increased blood flow induced by the stimulation of tissue-resident immune cells by markedly altered cutaneous cytokine profiles (Bhalerao and Bowcock, 1998; Lee et al., 2010). Psoriasis is the most common autoimmune disorder, affecting 0.5-3% of the general population. Although its etiology is not fully understood, it has been established that psoriasis has a genetic component, and the most powerful genetic factors identified include human leukocyte antigen loci (Nair et al., 2006). However, increasing evidence suggests that non-human leukocyte antigen genes also contribute to psoriasis (Zhang et al., 2009).

Neovascularization plays a key role in the pathogenesis of psoriasis, and vascular endothelial grow factor (VEGF) is considered to be the main angiogenic genetic contributor to this disorder. It has been well-established that VEGF expression is elevated in psoriatic skin (Bhushan et al., 1999), and transgenic mice overexpressing VEGF in the skin develop chronic inflammatory lesions resembling those of psoriasis (Xia et al., 2003). Furthermore, VEGF plasma levels are directly correlated with disease activity (Bhushan et al., 1999).

The *VEGF* gene is located on chromosome 6p21, which is close to a major psoriasis susceptibility locus; some polymorphisms in the *VEGF* gene have been shown to influence cytokine production (Vincenti et al., 1996). In addition, the +405 C/G (rs2010963), -460 C/T (rs833601), -1154 A/G (rs1570360), and -2578 A/C (rs699947) polymorphisms of *VEFG* reportedly have functional consequences (Koukourakis et al., 2004). Particularly, the +405 C/G polymorphism in the 5'-untranslated region and 3 polymorphisms in the promoter region (-460 C/T, -1154 A/G, and -2578 A/C) have been associated with VEGF production (Young et al., 2006). Previous studies showed that these polymorphisms are associated with several autoimmune diseases, including psoriasis, while other reports found no such associations (Young et al., 2004; Barile et al., 2006; Butt et al., 2007; Wang et al., 2008; Wongpiyabovorn et al., 2008; Wu et al., 2010; Zablotna et al., 2013). The reasons for these disparities may be small sample sizes, low statistical power, and/or clinical heterogeneity. Therefore, to overcome the limitations of individual studies, resolve inconsistencies, and reduce the likelihood that random errors were responsible for false-positive or false-negative associations, we conducted a meta-analysis (Lee et al., 2006a,b, 2007). In this present study, we used meta-analysis to examine whether the +405 C/G, -460 C/T, -1154 A/G, and -2578 A/C polymorphisms of *VEGF* confer susceptibility to psoriasis.

MATERIAL AND METHODS

Identification of eligible studies and data extraction

We performed a search for studies that examined the associations between *VEGF*

polymorphisms and psoriasis. The literature was searched using the MEDLINE citation database to identify available articles in which *VEGF* polymorphisms were analyzed in psoriasis patients. Combinations of keywords, such as, 'vascular endothelial growth factor', 'VEGF', 'polymorphism', and 'psoriasis' were entered as Medical Subject Headings (MeSH) or text words. References in identified studies were also investigated to identify additional studies not indexed by MEDLINE. Genetic association studies that determined the distributions of the +405 C/G, -460 C/T, -1154 A/G, and -2578 A/C genotypes of *VEGF* in psoriasis and normal controls were also eligible for inclusion. The following information was extracted from each study: author, year of publication, ethnicity of the study population, demographics, and numbers of cases and controls for each of the +405 C/G, -460 C/T, -1154 A/G, and -2578 A/C genotypes of VEGF. Frequencies of alleles were calculated from corresponding genotype distributions.

Evaluation of publication bias

Funnel plots can be used to detect publication bias. However, because of the limitations of funnel plotting, which requires a range of studies of varying sizes involving subjective judgments, we evaluated publication bias using the Egger linear regression test (Egger et al., 1997a), which measures funnel plot asymmetry using a natural logarithm scale of odds ratios (ORs).

Evaluations of statistical associations

We performed meta-analyses using; 1) the allelic contrast and 2) homozygote contrast techniques and the 3) recessive and 4) dominant models. Point estimates of risk, ORs, and 95% confidence intervals (CIs) were estimated for each study. In addition, within- and between-study variations or heterogeneities were assessed using Cochran's Q-statistic. This heterogeneity test assesses the null hypothesis that all studies evaluated the same effect. The effect of heterogeneity was quantified using I^2, which ranges from 0-100% and represents the proportion of between-study variability that can be attributed to heterogeneity rather than to chance (Higgins and Thompson, 2002). I^2 values of 25, 50, and 75% were nominally assigned as low, moderate, and high estimates. The fixed-effect model assumes that genetic factors have similar effects on psoriasis susceptibility across all studies investigated, and that observed variations between studies are caused by chance alone (Egger et al., 1997b). The random-effect model assumes that different studies show substantial diversity and assesses both within-study sampling error and between-study variance (DerSimonian and Laird, 1986). When study groups are homogeneous, the fixed- and random-effect models produce similar results, and when this is not the case, the random-effect model typically provides wider CIs than the fixed-effect model. Thus, the random-effect model is used when significant between-study heterogeneity is present (DerSimonian and Laird, 1986). Statistical manipulations were conducted using a Comprehensive Meta-Analysis computer program (Biosta, Englewood, NJ, USA). The power of each study was computed as the probability of detecting an association between the *VEGF* polymorphisms and psoriasis at a level of significance of 0.05, assuming an OR of 1.5 (small effect size). Power analysis was performed using the G*Power statistical program (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower).

RESULTS

Studies included in the meta-analysis

Ten studies were identified by electronic and manual searching and all 10 were selected for full-text review based on title and abstract details (Young et al., 2004, 2006; Barile et al., 2006; Butt et al., 2007; Lee et al., 2008; Stefanaki et al., 2008; Wang et al., 2008; Wongpiyabovorn et al., 2008; Wu et al., 2010; Zablotna et al., 2013). However, 3 of the 10 were excluded because they had no control group or did not contain genotype data (Young et al., 2006; Lee et al., 2008; Stefanaki et al., 2008). Thus, 7 studies met the study inclusion criteria, and these studies included a total 1956 subjects (psoriasis 665, controls 1291) and consisted of European and Asian populations (Young et al., 2004; Barile et al., 2006; Butt et al., 2007; Wang et al., 2008; Wongpiyabovorn et al., 2008; Wu et al., 2010; Zablotna et al., 2013) (Table 1).

Five studies examined the +405 C/G polymorphism, 5 the -460 C/T polymorphism, 3 the -1154 A/G polymorphism, and 3 the -2578 A/C polymorphism. Selected characteristics of these studies with respect to associations between *VEGF* polymorphisms and psoriasis are summarized in Table 1. Meta-analysis was performed to examine the association between these 4 VEGF polymorphisms and psoriasis. In addition, ethnicity-specific meta-analysis was performed in European and Asian populations.

Table 1. Characteristics of the studies included in this meta-analysis.

Reference	Ethnicity	Polymorphism	Numbers		Case			Control			Association P value	Power (%)[a]
			Case	Control	GG	GC	CC	GG	GC	CC		
Zablotna, 2013	European	+405 C/G	189	214	94	81	14	121	86	7	0.077	51.8
Wu, 2010	Asian	+405 C/G	257	258	100	111	46	73	133	52	0.037	62.1
Wongpiyabovorn, 2008	Asian	+405 C/G	154	234	69	74	11	87	118	29	0.066	50.3
Barile, 2006	European	+405 C/G	117	215	53	50	14	88	99	28	0.484	44.5
Young, 2004	European	+405 C/G	137	102	50	67	20	47	48	7	0.051	33.9
			Case	Control	TT	TC	CC	TT	TC	CC		
Zablotna, 2013	European	-460 C/T	189	215	67	90	32	59	119	37	0.235	51.9
Wongpiyabovorn, 2008	Asian	-460 C/T	154	234	75	73	6	117	97	20	0.613	50.3
Wang, 2008	Asian	-460 C/T	101	101	44	51	6	49	47	5	0.514	29.5
Barile, 2006	European	-460 C/T	117	215	33	51	33	39	117	59	0.252	44.5
Young, 2004	European	-460 C/T	137	101	42	74	21	20	60	21	0.078	33.8
			Case	Control	GG	GA	AA	GG	GA	AA		
Zablotna, 2011	European	-1154 A/G	189	215	80	89	20	75	103	37	0.040	51.9
Wang, 2008	Asian	-1154 A/G	100	103	80	18	2	75	27	1	0.351	29.6
Butt, 2007	European	-1154 A/G	257	147	69	121	67	35	69	43	0.395	51.9
			Case	Control	CC	CA	AA	CC	CA	AA		
Wongpiyabovorn, 2008	Asian	-2578 A/C	154	234	77	70	7	114	105	15	0.634	50.3
Wang, 2008	Asian	-2578 A/C	101	117	57	44	0	64	53	0	0.828	31.4
Butt, 2007	European	-2578 A/C	257	150	68	124	65	45	70	35	0.449	52.2

[a]Assuming an odds ratio of 1.5 (small effect size) at a level of significance of 0.05.

Heterogeneity and publication bias

The distributions of genotypes of the 4 *VEGF* polymorphisms in the control groups were consistent with the Hardy-Weinberg equilibrium, except for 1 study (Wang et al., 2008), implying bias in terms of control selection or genotyping errors. However, when

we excluded this study, overall results were not substantially affected. No between-study heterogeneity was observed during the meta-analyses of the -460 C/T, -1154 A/G, and -2578 A/C polymorphisms, but some heterogeneity was found in the meta-analyses of the +405 C/G polymorphism for all studies. It was difficult to correlate the funnel plot, which is typically used to detect publication bias, as the number of studies included in the analysis was relatively small. However, the Egger regression test showed no evidence of publication bias (Egger regression test P values >0.1).

Meta-analysis of relationship between +405 C/G, -460 C/T, -1154 A/G, and -2578 A/C polymorphisms and psoriasis

A summary of meta-analyses findings regarding the associations between the 4 polymorphisms and psoriasis is shown in Table 2. In all study subjects, we found no association between psoriasis and the *VEGF* +405 C allele (OR = 0.984, 95%CI = 0.754-1.285, P = 0.906) (Table 2). However, stratification by ethnicity revealed a significant association between the *VEGF* +405 C allele and psoriasis in Asians but not in Europeans (OR = 0.762, 95%CI = 0.628-0.923, P = 0.005; OR = 1.186, 95%CI = 0.974-1.445, P = 0.090) (Table 2 and Figure 1). We found no association between psoriasis and the *VEGR* +405 C/G polymorphism using the recessive model, but the dominant and additive models showed that this polymorphism, similarly to the +405 C allele, was associated with psoriasis in Europeans but not in Asians (Table 2).

Table 2. Meta-analysis of the associations between the *VEGF* +405 C/G and -460 C/T polymorphisms and psoriasis.

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95%CI	P value	Model	P value	I^2
+405 C *vs* G	Overall	5	0.984	0.754-1.285	0.906	R	0.006	72.4
	European	3	1.186	0.974-1.445	0.090	F	0.103	56.0
	Asian	2	0.762	0.628-0.923	0.005	F	0.911	0
CC *vs* CG + GG (recessive)	Overall	5	1.093	0.666-1.793	0.724	R	0.043	59.3
	European	3	1.498	0.936-2.398	0.092	F	0.143	48.5
	Asian	2	0.763	0.523-1.111	0.158	F	0.286	12.2
CC + CG *vs* GG (dominant)	Overall	5	0.925	0.664-1.290	0.269	R	0.016	67.0
	European	3	1.171	0.904-1.516	0.231	F	0.198	38.2
	Asian	2	0.666	0.606-0.877	0.004	F	0.565	65.0
CC *vs* GG	Overall	5	1.044	0.555-1.964	0.894	R	0.007	71.8
	European	3	1.702	0.756-3.833	0.199	F	0.073	61.7
	Asian	2	0.590	0.389-0.896	0.013	F	0.518	0
-460 C *vs* T	Overall	5	0.867	0.747-1.005	0.059	F	0.566	0
	European	3	0.807	0.672-0.968	0.021	F	0.777	0
	Asian	2	0.998	0.773-1.289	0.989	F	0.409	0
CC *vs* CT + TT (recessive)	Overall	5	0.874	0.653-1.171	0.367	F	0.470	0
	European	3	0.927	0.675-1.273	0.639	F	0.608	0
	Asian	2	0.635	0.302-1.334	0.231	F	0.190	41.7
CC + CT *vs* TT (dominant)	Overall	5	0.800	0.643-0.994	0.044	F	0.113	46.4
	European	3	0.699	0.463-0.827	0.001	F	0.790	0
	Asian	2	1.109	0.799-1.540	0.536	F	0.674	0
CC *vs* TT	Overall	5	0.659	0.469-0.925	0.016	F	0.633	0
	European	3	0.652	0.446-0.953	0.027	F	0.653	0
	Asian	2	0.688	0.322-1.474	0.336	F	0.193	41.1

OR = odds ratio; CI = confidence interval; R = random-effect model; F = fixed-effect model.

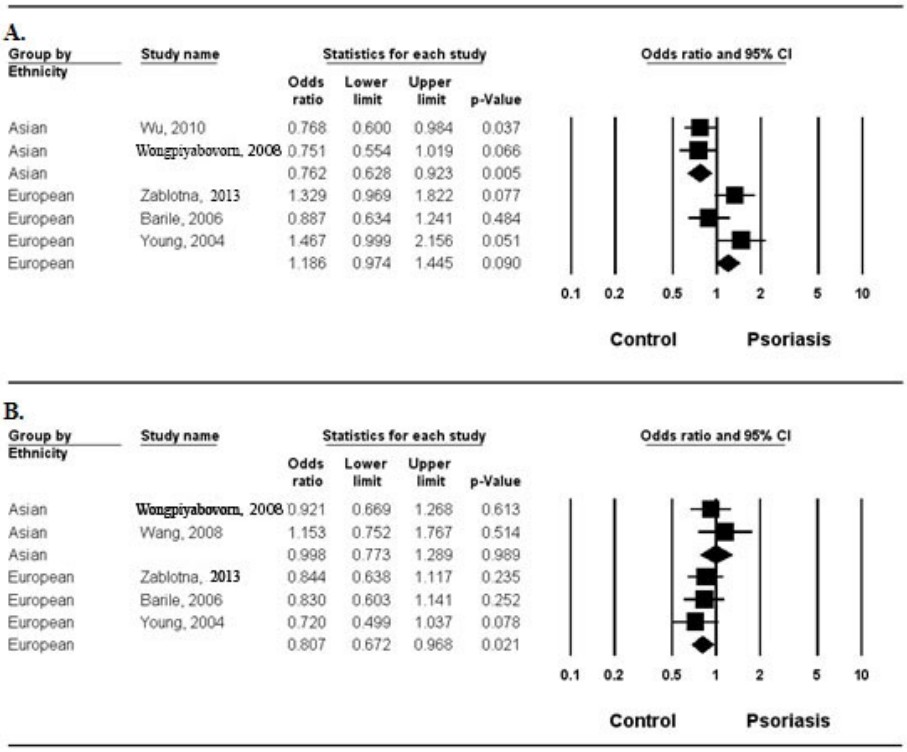

Figure 1. Odds ratios (ORs) and 95% confidence intervals (CIs) of individual studies and pooled data for allele associations between the *VEGF* +405 C/G (**A**) and -460 C/T (**B**) polymorphisms and psoriasis in each ethnic group.

We observed no association between psoriasis and the *VEGF* -460 C allele (OR = 0.867, 95%CI = 0.747-1.005, P = 0.059) (Table 2). However, stratification by ethnicity indicated a significant association between the *VEGF* -460 C allele and psoriasis in Europeans but not in Asians (OR = 0.807, 95%CI = 0.672-0.968, P = 0.021; OR = 0.998, 95%CI = 0.773-1.289, P = 0.989) (Table 2 and Figure 1). We found no association between psoriasis and the *VEGR* -460 C/T polymorphism using the recessive model, but the dominant and the additive models showed the same pattern as the results for the -460 C allele, which showed a significant association in Europeans but not in Asians (Table 2).

In all study subjects, meta-analysis showed a significant association between psoriasis and the *VEGF* -1154 A allele (OR = 0.803, 95%CI = 0.663-0.972, P = 0.025) (Table 3). Stratification by ethnicity revealed a significant association between the *VEGF* -1154 A allele and psoriasis in Europeans but not in Asians (OR = 0.808, 95%CI = 0.660-0.990, P = 0.040; OR = 0.754, 95%CI = 0.417-1.363, P = 0.351) (Table 3 and Figure 2). We found no association between psoriasis and the VEGR -1154 A/G polymorphism using the recessive or dominant models, but meta-analyses using the additive model showed the same pattern as the meta-analysis of the -1154 A allele, showing a significant association in Europeans but not in Asians (Table 3). We found no association between psoriasis and the *VEGF* -2578 A/C polymorphism using the allelic contrast, recessive, dominant, or additive models in all study subjects or in Europeans or Asians (Table 3).

Table 3. Meta-analysis of the associations between the *VEGF* -1154 A/G and -2578 A/C polymorphisms and psoriasis.

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95%CI	P value	Model	P value	I^2
-1154 A *vs* G	Overall	3	0.803	0.663-0.972	0.025	F	0.680	0
	European	2	0.808	0.660-0.990	0.040	F	0.395	0
	Asian	1	0.754	0.417-1.363	0.351	NA	NA	NA
AA *vs* AG + GG (recessive)	Overall	3	0.750	0.527-1.067	0.110	F	0.396	
	European	2	0.732	0.513-1.048	0.088	F	0.283	13.2
	Asian	1	2.082	0.186-23.32	0.552	NA	NA	NA
AA + AG *vs* GG (dominant)	Overall	3	0.758	0.575-1.000	0.050	F	0.816	0
	European	2	0.779	0.574-1.057	0.109	F	0.625	0
	Asian	1	0.670	0.348-1.289	0.230	NA	NA	NA
AA *vs* GG	Overall	3	0.670	0.444-1.011	0.056	F	0.409	0
	European	2	0.650	0.428-0.986	0.043	F	0.300	6.80
	Asian	1	1.875	0.167-21.10	0.611	NA	NA	NA
-2578 A *vs* C	Overall	3	1.013	0.835-1.229	0.894	F	0.660	0
	European	1	1.116	0.839-1.485	0.449	NA	NA	NA
	Asian	2	0.934	0.719-1.213	0.607	F	0.922	0
AA *vs* AC + CC (recessive)	Overall	2	1.009	0.663-1.535	0.967	F	0.373	0
	European	1	1.112	0.694-1.782	0.658	NA	NA	NA
	Asian	1	0.695	0.227-1.747	0.439	NA	NA	NA
AA + AC *vs* CC (dominant)	Overall	3	1.023	0.787-1.329	0.867	F	0.708	0
	European	1	1.191	0.763-1.860	0.442	NA	NA	NA
	Asian	2	0.943	0.682-1.304	0.725	F	0.956	0
AA *vs* Cc	Overall	2	1.059	0.655-1.710	0.816	F	0.303	5.89
	European	1	1.229	0.704-2.146	0.468	NA	NA	NA
	Asian	1	0.691	0.269-1.773	0.442	NA	NA	NA

OR = odds ratio; CI = confidence interval; R = random-effect model; F = fixed-effect model; NA = not available.

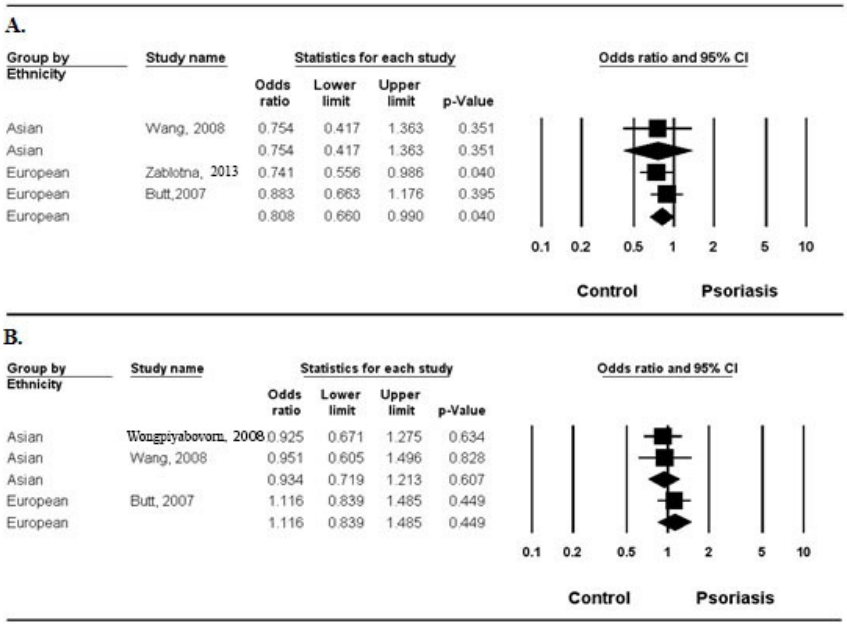

Figure 2. Odds ratios (ORs) and 95% confidence intervals (CIs) of individual studies and pooled data for allele associations between the *VEGF* -1154 A/G (**A**) and -2578 A/C (**B**) polymorphisms and psoriasis in each ethnic group.

DISCUSSION

Although association studies are excellent for identifying genetic factors that confer susceptibility to common diseases such as psoriasis, most of the reported association studies are underpowered in terms of detecting modest genetic effects that underlie susceptibilities to common diseases (Lohmueller et al., 2003). This results in inconsistent findings because of false-positive, false-negative, or true association variability in different populations. Meta-analysis integrates previous research and increases the statistical power and resolution by pooling the results of independent analyses (Lee et al., 2006a, 2007), providing a powerful means of overcoming the small sample size problem and the often inadequate statistical powers of genetic studies of complex traits.

Although the multifactorial nature of psoriasis is well known, genetic factors are considered to be strong determinants of these diseases, and thus studies have been encouraged to search for the genes responsible. Several genes have been studied for this reason, and the *VEGF* gene is one such gene in the context of psoriasis (Vincenti et al., 1996). VEGF plays a key role in angiogenesis and contributes to immune system regulation. Given the potential link between VEGF and autoimmune diseases, *VEGF* polymorphisms, which may influence VEGF expression, have been studied as potential causes of autoimmune diseases (Watson et al., 2000). VEGF acts as a potent mediator of angiogenesis and inflammation and is known to be overexpressed in the psoriatic epidermis (Schön, 1999). Furthermore, VEGF is thought to participate in the pathogenesis of psoriasis. For example, transgenic mice over-expressing VEGF in the epidermis developed skin lesions with psoriatic features; retinoids, which are widely used to treat psoriasis, have shown to inhibit VEGF-induced angiogenesis (Xia et al., 2003; Young et al., 2006). Furthermore, VEGF levels in the blood have been correlated with psoriasis activity (Bhushan et al., 1999). VEGF expression is affected by genetic factors, and the +405 C/G, -460 C/T, -1154 A/G, and -2578 A/C polymorphisms have been reported to influence VEGF production and to be associated with other inflammatory diseases. Particularly, +405 has been reported to be a myeloid zinc finger protein (MZF1)-binding site, and it has been suggested that its C allele decreases *VEGF* gene transcription and protein production (Lip and Chung, 2005). Young et al. (2004) showed that the +405 CC and -460 TT genotypes are associated with early-onset psoriasis and high VEGF expression in peripheral blood mononuclear cells. Furthermore, the -2578 A/C polymorphism is thought to be a GATA-2 binding site, and the -2578 A and -460 T alleles were reported to be associated with high VEGF expression in the plasma (Lip and Chung, 2005). Finally, the -1154 A/G polymorphism is associated with VEGF production by stimulated peripheral mononuclear cells (Zablotna et al., 2013).

In this meta-analysis, we combined data from published studies to evaluate genetic associations between psoriasis and the most commonly studied polymorphisms of the *VEGF* gene, including +405 C/G, -460 C/T, -1154 A/G, and -2578 A/C. Our meta-analysis of the VEGF -2578 A/C polymorphism revealed no association with psoriasis in all study subjects or in Europeans or Asians. However, a significant association between the *VEGF* +405 C allele and psoriasis was observed in Asians but not in Europeans, suggesting that the C allele is a protective factor with an OR of 0.762 (95%CI = 0.628-0.923, P = 0.005). We also found a significant association between the 460 C allele and psoriasis in Europeans but not in Asians (OR = 0.807, 95%CI = 0.672-0.968, P = 0.021; OR = 0.998, 95%CI = 0.773-1.289, P = 0.989). Furthermore, the -1154 A/G polymorphism showed a significant association with psoriasis in Europeans and Asians, suggesting that the -460 C and -1154 A alleles are protective factors

with ORs of 0.807 (95%CI = 0.672-0.968, P = 0.021) and 0.803 (95%CI = 0.663-0.972, P = 0.025), respectively.

There were some limitations to this study. First, heterogeneity and confounding factors may have distorted the analysis. Furthermore, publication bias may have adversely affected the analysis, as studies that produced negative results may not have been published or may have been missed; although the Egger regression test was used, the possibility of bias cannot be eliminated. Second, ethnicity-specific analysis was performed using European and Asian data, and thus our results are only applicable to these ethnic groups. Third, haplotype analysis may have provided more information and would have been more powerful than single polymorphism analysis. For example, Wongpiyabovorn et al. (2008) showed that the -2578 C/-460T/+405G haplotype is a marker for susceptibility to psoriasis. Furthermore, the +405 C/G and -460 C/T polymorphisms were found to be in linkage disequilibrium. However, unfortunately, no meta-analysis of haplotypes was possible because of inadequate haplotype data. Fourth, the *VEGF* polymorphisms examined may be associated with psoriasis severity, but the small amount of data available did not allow us to investigate these associations.

In conclusion, this meta-analysis showed that the *VEGF* +405 C/G confers susceptibility to psoriasis in Asians. Furthermore, the -460 C/T and -1154 A/G polymorphisms were found to confer susceptibility to psoriasis in Europeans. These findings prompt further investigation of the associations between *VEGF* polymorphisms and psoriasis susceptibility. Particularly, larger scale studies in populations with different ethnicities are necessary to explore the roles of *VEGF* polymorphisms in the pathogenesis of psoriasis.

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