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META-ANALYSIS

DOI: 10.12659/MSM.896552 Received: 2015.11.05 **Association Between Gene Polymorphisms on** Accepted: 2015.12.09 Published: 2016.06.27 Chromosome 1 and Susceptibility to **Pre-Eclampsia: An Updated Meta-Analysis** Guixin Zhang Authors' Contribution: F The Hospital of Maternal and Child Health of Tangshan, Tangshan, Hebei, Study Design A PR China Е Jinheng Zhao Data Collection B **Jianping Yi** CDG Statistical Analysis C ACG Yuanyuan Luan Data Interpretation D Manuscript Preparation E AB **Qian Wang** Literature Search E Funds Collection G **Corresponding Author:** Qian Wang, e-mail: gianwdr@126.com Source of support: Departmental sources Background: This meta-analysis enabled us to obtain a precise estimation of the association between gene polymorphisms on chromosome 1 (MTHFR, AGT, F5, IL-10, LEPR) and the susceptibility to pre-eclampsia (PE) in order to reach a uniform conclusion. Material/Methods: Web of Science, PubMed, EMBASE, Cochran Library (CENTRAL), and Chinese databases (Chinese National Knowledge Infrastructure-CNKI and Wan Fang) were electronically searched to select relevant studies for this meta-analysis. We selected 95 case-control studies investigating 5 genes (MTHFR, AGT, F5, IL-10, and LEPR) with 8 SNPs. Odds ratios (OR) with their 95% confidence intervals (CI) were used for estimating the association. **Results:** A total of 16 646 PE patients and 28 901 normal-pregnancy patients were included in this meta-analysis. The overall results suggested that rs1801133 of MTHFR (OR=1.17, 95% CI: 1.05–1.13) and rs6025 of F5 (OR=1.53, 95%CI: 1.07-2.20) are significantly associated with PE, whereas rs1801131 of MTHFR, rs699 and rs4762 of AGT, rs1800896 and rs1800871 of *IL*-10, and rs1137101 of *LEPR* have no significant association with PE. Subgroup analysis by ethnicity revealed that, except for MTHFR rs1801133 and F5 rs6025 in Caucasians, which were significantly associated with an increased risk of PE, none of these SNPs were significantly associated with PE. As suggested by a symmetric funnel plot in conjunction with the Egger's test, there was no significant publication bias in MTHFR rs1801133 (P=0.318) and rs1801131 (P=0.204), F5 rs6025 (P=0.511), LEPR rs1137101 (P=0.511), AGT rs4762 (P=0.215) and rs699 (P=0.482), IL-10 rs1800871 (P=0.955), and rs1800896 (P=0.144). **Conclusions:** This meta-analysis provides evidence that MTHFR rs1801133 and F5 rs6025 are associated with an increased risk of PE, especially in Caucasians. However, we do not have sufficient evidence to conclude there is a significant association between other gene polymorphisms and PE. **MeSH Keywords:** Meta-Analysis as Topic • Polymorphism, Genetic • Pre-Eclampsia Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/896552 1 1 **1**1 ₪ 11 **2** 64 2 2721



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Background

Pre-eclampsia (PE) has a cluster of symptoms, including hypertension and albuminuria, which usually appear together after 20 weeks of pregnancy. PE has an incidence rate of 2-8% in pregnant females and it is associated with lesions of the vascular (high blood pressure) and renal (albuminuria) systems [1,2]. Furthermore, PE is thought to be associated with eclampsia, HELLP syndrome (characterized by hemolysis, upregulated liver enzymes, and low levels of platelets), kidney failure, lung edema, and hemorrhagic stroke; therefore, it poses enormous threats to the health of mothers and infants [3]. Although the etiology of PE is still unclear, it is suspected that various genetic and environmental factors are associated with the susceptibility to PE [2,4]. It has been observed that females who were born from a mother with PE have an increased risk of PE during their own gestation period. In addition, females with fathers who were born of mothers with PE have an increased risk of PE. Therefore, numerous investigations have been undertaken to clarify the role of genetic factors with significant effects on the prevalence of PE [5]. As suggested by previous reports, genetic polymorphisms of interleukin (IL)-10, methylenetetrahydrofolate reductase (MTHFR), angiotensinogen (AGT), leptin receptor (LEPR), and factor V (FV) might explain the potential role of genetic factors that affect the development of PE [6-10].

There are 2 procedures which are critical to the maintenance of pregnancy: one is the inhibition of T-helper 1 (Th1) lymphocytes and the other is the stimulation of Th2 lymphocytes [11–13]. IL-10 is believed to be involved in the etiology of PE due to its role in the reduction of inflammation-mediated vascular dysfunction and the regulation of trophoblastic infiltration [6].

Hyperhomocysteinemia has been confirmed to be involved in the pathogenesis of PE [14,15]. Furthermore, a high level of serum homocysteine is likely to be followed by endothelial disorders such as coronary artery disease [16] and atherosclerosis [17]. As a key enzyme for homocysteine and folate metabolism, MTHFR transforms 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is a methyl donor in the transformation from homocysteine to methionine, and this implies a relatively negative correlation between homocysteine and folate [7,18].

AGT is converted into angiotensin II by angiotensin-converting enzyme and is a major component of the renin-angiotensin system (RAS) [19]. The RAS is also a strong regulating system that greatly affects blood pressure and water-salt balance, indicating its critical role in the development of PE [20]. Additionally, leptin, which is well known to regulate body weight, tends to be an important cytokine for the regulation of arterial blood pressure [21]. Elevated circulating leptin levels, along with the reduced soluble LEPR concentrations, are reported to be associated with susceptibility to PE [22]. The activated FV (FVa) accompanied by activated factor X (FXa) converts prothrombin into thrombin, and a connection between hypercoagulability and PE has been proposed [4].

The *IL-10* gene, *MTHFR* gene, *AGT* gene, *LEPR* gene, and *FV* gene map to 1q31-q32, 1p36.3, 1q42.2, 1p31, and 1q23, respectively. We have noticed that inconsistent conclusions still exist among meta-analyses investigating the *IL-10* gene [6,23–25]. Few studies have examined the relationship between the *LEPR* gene and PE risk, and there is no published meta-analysis focusing on the association between the *LEPR* gene and susceptibility to PE. Therefore, this study was designed to assess the association between multiple genetic polymorphisms and PE susceptibility in order to address the issue of contradictory findings resulting from heterogeneity.

Material and Methods

Search strategy

Initially, a computer-based search of the online databases Web of Science, PubMed, EMBASE, Cochran Library (CENTRAL), and Chinese databases (Chinese National Knowledge Infrastructure-CNKI and Wan Fang) was conducted with no language constraint (up to September 2015) and the following searching terms were used: ("preeclampsia" OR "pre-eclampsia") AND ("polymorphism" OR "single nucleotide polymorphism" OR "SNP" OR "variant") AND ("factor V" OR "thrombophilia" OR "MTHFR" OR "methylenetetrahydrofolate reductase" OR "homocysteine" OR "interleukin-10" OR "IL-10" OR "angiotensinogen" OR "AGT" OR "leptin receptor" OR "LEPR"). References in the included articles containing meta-analyses were manually searched to identify additional related papers.

Inclusion criteria

Case-control studies investigating the association between genetic polymorphisms on chromosome 1 and PE susceptibility were considered. Females with new-onset high blood pressure (>140/90 mm Hg) and albuminuria (\geq 300 mg/24 h) at or after 20 weeks of pregnancy were diagnosed as having PE [26]. Females with a previous twin pregnancy and history of hormone therapy were excluded. Studies with genotype frequencies or adequate original data in the case and control groups were included, and genotyping was carried out using recognized methods. All included studies were done in humans. Publications with duplicate data were selected based on the sample size. Meta-analyses, editorials, or other articles irrelevant to the research subjects were excluded.



Quality assessment

The methodological quality of the eligible studies was assessed by 2 independent researchers using the Newcastle-Ottawa Quality Assessment Scale (NOS) and any discrepancies between them were solved by discussion. The score system of NOS was based on 3 perspectives: selection, comparability, and exposure. A score of 6 or more out of 8 stars represents good quality [27].

Data extraction

Relevant information was independently obtained from all included studies by 2 researchers and any inconsistencies between them were reviewed by a third researcher. The following information was selected: name of first author, publication date, country and ethnicity, method for genotyping, and the number of cases and controls for each genotype.

Statistical analysis

The chi-squared goodness-of-fit test was used to assess whether the observed genotype frequency in the control group complied with Hardy-Weinberg equilibrium (HWE), and a *P* value of less than 0.05 suggests significant deviation from HWE. If the genotype distribution did not comply with HWE, then the corresponding study was eliminated. The strength of association between genetic polymorphisms on chromosome 1 and PE susceptibility was measured by odds ratios (ORs) along with their corresponding 95% confidence intervals (CIs). Moreover, the pooled ORs were calculated under the allele model, and the Z-test with a significance level of 0.05 was used to determine whether a significant association existed between each SNP and PE susceptibility. Study heterogeneity was measured by using the l^2 statistic and *Cochran's Q* [28,29]. The randomeffects model was used to summarize the ORs if $l^2 > 50\%$ and *P* value <0.1 [30]; whereas the fixed-effects model was used if there was no significant heterogeneity [28]. Potential publication bias was evaluated by a funnel plot, with a significance level of 0.05 [31]. The above analyses were all performed using R (version 3.2.1) statistical software.

Results

Literature selection

A total of 386 articles were discovered after the initial search strategy performed in Web of Science, PubMed, EMBASE, Cochran Library (CENTRAL), and Chinese databases (Chinese National Knowledge Infrastructure-CNKI and Wan Fang). By reviewing the abstracts and titles, 218 articles were excluded as not relevant to the research subject. After the exclusion of meta-analyses, reviews, studies without sufficient data, and studies with duplicate data, 95 articles with 150 eligible studies were selected (Figure 1). The methodological quality of these studies was systematically evaluated by 2 independent reviewers in accordance with the Newcastle-Ottawa Quality Assessment Scale (NOS). The NOS involves 3 main areas: study selection, comparability, and exposure. Each study was scored with answers to 8 questions, with a maximum score of 8. A total of 16 646 PE patients and 28 901 healthy mothers were included in the meta-analysis. The characteristics of the 150 included studies are summarized in Supplementary Figures 1, 2: 28 case-control studies involving F5 polymorphisms (rs6025); 23 case-control studies involving AGT polymorphisms (rs699,

tudv	Exper Events	imental Total	Co Events	ntrol Total	Odds ratio	OR	95% (I	W(fixed)	W(random)
	Events	lotal	Events			on	5570 Cl	(incu)	W(rundom)
Ethnicitv=African					Ĺ				
Groten 2014 Ghana	147	162	240	262	E	0.90	[0.45, 1.79]	2.0%	3.9%
Jenkins 2008 USA	32	36	319	404		- 2.13	[0.73, 6.19]	0.8%	2.2%
Hillerman 2005 South Africa	82	98	74	90	<u>á</u>	1.11	[0.52, 2.37]	1.6%	3.5%
Fixed effect model		296		756	_	1.14	[0.72, 1.81]	4.5%	
Radnom effects model						1.14	[0.72, 1.81]		9.6%
Heterogeneity: I ² =0.0%, tau	² =0.0, <i>P</i> =	0.4088			í.		[]		
Ethnicitv=Asian					í í				
Dissanayake 2012 Sri Lanka	209	348	209	342	_ 	0.96	[0.71, 1.30]	10.2%	6.6%
Kim 2004 South Africa	107	174	102	176		1.16	[0.76, 1.78]	5.2%	5.7%
Choi 2004 Korea	142	200	155	200	<u>_</u>	0.71	[0.45, 1.12]	4.7%	5.5%
Roberts 2004 Brazil	499	542	622	676		1.01	[0.66, 1.53]	5.4%	5.7%
Kobashi 2001 Japan	102	116	251	328	<u> </u>	2.24	[1.21, 4.13]	2.5%	4.3%
Guo 1997 China	51	82	71	94	L	0.53	[0.28, 1.02]	2.3%	4 1%
Fixed effect model	5.	1462		1816	- 5	0.98	[0.82, 1.17]	30.2%	
Radnom effects model					<u> </u>	0.99	[0.73, 1.33]		31.9%
Heterogeneity: <i>I</i> ² =61.2%, ta	u ² =0.0817	7, P =0.024	4		Tí í		[]		
Ethnicity=Caucasian					Ĺ				
Groten 2014 Germany	61	148	153	350	<u></u>	0.90	[0.61, 1.33]	6.2%	6.0%
Coral-Vazguez 2013 Mexico	366	460	542	704		1.16	[0.87,1.55]	11.5%	6.7%
Jenkins 2008 USA	137	304	197	476	<u>F</u>	1.16	[0.87, 1.55]	11.2%	6.7%
Knyrim 2008 Germany	61	134	82	200		1.20	[0.77, 1.87]	4.9%	5.5%
Bendetto 2007 Italy	105	240	100	206	<u>_</u>	0.82	[0.57, 1.20]	6.8%	6.1%
Wang 2006 USA	30	242	294	2002		0.82	[0.55, 1.23]	5.9%	5.9%
Tempfer 2004 Austria	24	48	19	48		1.53	[0.68, 3,43]	1.4%	3.2%
Bouba 2003 Greece	48	82	82	204		2.10	[1.25, 3.54]	3.5%	5.0%
Zhang 2003 USA	76	120	288	800	í	3.07	[2.06, 4.57]	6.0%	5.9%
Procopciuc 2002 Romania	11	26	4	12	(,	1.47	[0.35, 6,13]	0.5%	1.4%
Curnow 2000 USA	86	142	902	1288		0.66	[0 46, 0 94]	7.4%	6.2%
Fixed effect model	00	1946		6290		1.13	[1.00, 1.28]	65.3%	
Radnom effects model					L.	1.19	[0.90, 1.56]		58.6%
Heterogeneity: <i>I</i> ² =78.1%, ta	u²=0.153,	<i>P</i> <0.0001			T.		[0.50, 1.50]		50.070
Fixed effect model		3704		8862	í o	1.08	[0.98, 1.20]	100.0%	
Radnom effects model					ž.	1.12	[0.92, 1.35]		100.0%
	.2 0 1 1 4	7 8 -0 000	1		Y		[0.72, 1.33]		

Supplementary Figure 1. Forest plot by ethnicity for rs699 in *AGT* gene.

	Experir	mental	Co	ontrol					
Study	Events	Total	Event	s Total	Odds ratio	OR	95% CI	W(fixed)	W(random)
					ć				
Ethnicity=African	10	240	122	1050	č	1.07	[0.(2, 1.04]	22 50/	24.00/
Wang 2006 USA	16	240	122	1952		1.07	[0.62, 1.84]	33.5%	34.0%
Pixed effect model		240		1952	í.	1.07	[0.62, 1.84]	33.3%	24.00/
Heterogeneity: <i>I</i> ² =0.0%, tau	² =0.0, <i>P</i> =0	.4088				1.07	[0.02, 1.04]		54.0%
Fthnicity=Asian					ĉ				
Dissanavake 2012 Sri Lanka	36	350	47	340	(0.71	[0 45, 1 13]	45.6%	42.4%
Choi 2004 Korea	21	200	16	200	<u> </u>	1.35	[0.68, 2.67]	20.9%	23.5%
Fixed effect model		550		540		0.87	[0.60, 1.28]	66.5%	
Radnom effects model						0.93	[0.50, 1.72]		66.0%
Heterogeneity: P=61.2%, ta	u ² =0.0817,	P=0.024	4						
					L C	0.93	[0.68, 1.28]	100.0%	
Fixed effect model		790		2492	č	0.95	[0.66, 1.37]		100.0%
Radnom effects model					\sim				
Heterogeneity: P=69.5%, ta	u²=0.1147,	<i>P</i> <0.000	1						

Supplementary Figure 2. Forest plot by ethnicity for rs4762 in AGT gene.

Gana	CND	Genetic	OR [95%	D	Tou?	12	D		Ethnicity		P _{publication}
Gene	SNP	model	CI]	odds ratio	iau-	F	heterogeneity	Caucasians	Asian	African	bias
F5	rs6025	A <i>vs</i> . G	1.53 [1.07,2.20]	0.024	0.659	74.02%	0.000	1.54 [1.01,2.36]	1.35 [0.92,1.99]	-	0.511
ACT	rs699	G <i>vs</i> . A	1.12 [0.92,1.35]	0.266	0.129	71.97%	0.000	1.19 [0.90,1.56]	0.99 [0.73,1.33]	1.14 [0.72,1.81]	0.482
AGI ···	rs4762	T <i>vs</i> . C	0.93 [0.68,1.28]	0.673	0.029	26.65%	0.266	-	0.93 [0.50,1.72]	1.07 [0.62.1.84]	0.215
MTHED	rs1801131	T <i>vs</i> . C	1.14 [0.93,1.40]	0.196	0.054	59.61%	0.012	1.17 [0.86,1.59]	1.25 [0.98,2.18]	0.91 [0.64,1.29]	0.204
MINK.	rs1801133	C <i>vs</i> . A	1.17 [1.05,1.31]	0.002	0.073	67.26%	0.000	1.16 [1.02,1.32]	1.21 [0.95,1.54]	1.20 [0.77,1.88]	0.318
	rs1800896	G <i>vs</i> . A	0.91 [0.75,1.11]	0.366	0.063	72.77%	0.000	0.99 [0.90,1.10]	0.98 [0.45,2.14]	0.20 [0.07,0.58]	0.144
IL-10 ·	rs1800871	T <i>vs</i> . C	0.79 [0.58,1.07]	0.655	0.166	82.99%	0.000	0.94 [0.69,1.27]	0.65 [0.41,1.03]	-	0.694
LEPR	rs1137101	G <i>vs</i> . A	1.41 [0.93,2.12]	0.114	0.126	69.59%	0.024	1.44 [1.05,1.98]	1.28 [0.46,3.55]	-	0.486

Table 1. Meta analysis of eight polymorphisms and PE susceptibility.

¹ Pooled odds ratios and 95% confidence intervals.

rs4762); 58 case-control studies involving *MTHFR* polymorphisms (rs1801131, rs1801133); 13 studies involving *IL-10* polymorphisms (rs1800896, rs1800971); and 4 studies involving *LEPR* polymorphism (rs1137101).

Association between chromosome 1 polymorphisms and PE

In this meta-analysis, we identified 8 polymorphisms on chromosome 1 that may be associated with PE susceptibility (Table 1). The random-effects model was used to synthesize evidence for studies involving rs6025, rs699, rs1801131, rs1801133, rs1800896, rs1800871, and rs1137101, whereas the fixed-effects model was used for rs4762 (l^2 =26.65%, P=0.266) (Table 1). Results of the meta-analysis showed that polymorphism of rs1801133 (6 678 cases/11 756 controls) was significantly associated with a 17% increase in risk of PE under the allelic model (OR=1.17, 95%CI: 1.05-1.13, P=0.002, Figure 2). Subgroup analysis by ethnicity revealed that this association was significant in Caucasians under the allelic model (OR=1.16, 95%CI: 1.02-1.32, Figure 2), but this association under the allelic model was not significant in Asians (OR=1.21, 95%CI: 0.95-1.54) or Africans (OR=1.20, 95%CI: 0.77-1.88, Figure 2). For rs6025 (4105 cases/4917 controls), the pooled result demonstrated that rs6025 was also significantly associated with a 53% increase in the risk of PE under the allelic model (OR=1.53, 95%CI: 1.07-2.20, P=0.024, Figure 3). Subgroup analysis by ethnicity suggested that this association was significant in Caucasians (OR = 1.54, 95% CI: 1.01-2.36, Figure 3) but not in Asians (OR=1.35, 95%CI: 0.92-1.99, Figure 3).

As shown in Supplementary Figures 1–6, none of the polymorphisms of rs699 (1852 cases/4431 controls), rs4762 (395 cases/1246 controls), rs1800896 (1510 cases/3393 controls), rs1800871 (489 cases/1087 controls), rs1137101 (149 cases/499 controls), or rs1801131 (1390 cases/1818 controls) were significantly associated with PE susceptibility under the allelic model (all P values >0.05). Results of subgroup analysis by ethnicity were consistent with those of the overall analysis.

Publication bias

Potential publication bias of the included studies was assessed by the funnel plot, which revealed no significant publication bias in 8 SNPs under the allelic model (all P values >0.05): rs1801133, P=0.318 (Figure 4A); rs6025, P=0.511 (Figure 4B); rs1801131, P=0.204; rs1137101, P=0.511; rs4762, P=0.215; rs699, P=0.482; rs1800871, P=0.955; and rs1800896, P=0.144 (Supplementary Figure 7A–7F).

Discussion

Pre-eclampsia (PE) is a complex disease with great phenotypic diversity. It is a serious threat to the health of females during gestation. Although the pathogenesis of preeclampsia is extremely complex, previous studies showed that thrombophilia genes are associated with hypercoagulable state [32,33], which may partly explain the development of PE. In recent years, great attention has been paid to the role of SNPs in

tudy	Experies	rimental 5 Total	Event	ontroi ts Total	Odds ratio 0)R	95% CI	W(fixed)	W(random)
<u>.</u>									
Ethnicitv=African									
Pegarora 2004 South Africa	40	542	42	676	1.2	20	[0.77, 1.88]	1.4%	2.0%
Fixed effect model		542		676		20	[0.77, 1.88]	1.4%	
Radnom effects model					1.2	20	[0.77, 1.88]		2.0%
Heterogeneity: not applicable	for a sig	nle study			i		. ,		
Fthnicity—Asian					1 1				
Salimi 2015 Iran	76	384	60	302	11	16	[0.80, 1.66]	2 1%	2 30%
Diccanavako 2012 Sri Lanka	/0	350	31	3/2	1.1	27	[0.80, 1.00]	1 10%	2.3%
Aggarwal 2012 Ji Laina	42	100	7/	J4Z 400	i	50	[0.04, 2.23]	1.170	7 70
Pracmusinto 2002 Indonesian	۲ <i>۲</i>	82	/4	400	0.5) <i>5</i>)6	[0.40, 0.07]	0.2%	0.7%
Watanahe 2001 Janan	127	266	167	1/18		5/	[1 13 2 00]	2 9%	2 50%
Kobachi 2000 Janan	127	200	165	440	1)4)E	[1.13, 2.07]	2.0%	2.5%
Li 2000 China	109	11/	201	430)) ()	[0.77, 1.45]	2.970	2.370
Chikosi 1000 South Africa	20	210	12	40	1.0 1.0	0Z 20	[0.02, 3.20]	0.070	1.470
Chikosi 1999 South Anita Sobda 1007 Janan	20	124	13	106))0 :1	[0.01, 5.40]	1 /0/2	2.004
Sound 1777 Japall	04	134	/1	190	j E 1.0	0	[1.03 2.32]	1.4%	2.0%
nixeu ellett illudel Dadnam offacts madal		2210		2000		17	[1.05, 1.5/]	13.4%	16 904
naunum enecis mudei	-0 071	6 D_0 017	0			. 1	[0.95, 1.54]		10.0%
neterogeneity: 1 ² =58.8%, tau	=0.071	o, r=0.012	0		1				
Ethnicity=Caucasian					1				
Coral-Vazquez 2013 Mexico	275	460	396	704	- <mark>-</mark>				
Lykke 2012 Denmark	180	524	1079	3684	「品 1.1	16	[0.91, 1.47]	4.8%	2.7%
Mislanova 2011 Austria	21	56	21	80	1.2	26	[1.04, 1.53]	7.3%	2.8%
Rojas 2010 Mexico	31	546	39	82	i 1.6	59	[0.81, 3.52]	0.5%	1.3%
Hitunen 2009 Finland	112	496	327	1350	<u></u> _ر 1.3	37	[0.69, 2.70]	0.6%	1.4%
Kahn 2009 Canada	60	226	337	886	_ ; 0.9	91	[0.71, 1.17]	4.6%	2.6%
Stiefel 2009 Spain	141	368	106	268	0.5	59	[0.43, 0.81]	2.6%	2.4%
Canto 2008 Mexico	112	250	295	548	i 0.9	95	[0.69, 1.31]	2.6%	2.4%
Dusse 2007 Brazil	16	60	43	166	0.7	70	[0.52, 0.94]	3.0%	2.5%
Stonek 2007 Austria	18	50	883	2794	1.0)4	[0.53, 2.03]	0.6%	1.4%
lvanov 2007 Bulgaria	27	50	34	98	1.2	22	[0.68, 2.18]	0.8%	1.7%
Nagy 2007 Hungary	61	202	47	146	2.2	21	[1.10, 4.43]	0.6%	1.4%
Jaaskelainen 2006 Finland	67	266	54	224	0.9	91	[0.58, 1.44]	1.3%	2.0%
Demir 2006 Germany	45	112	71	204	1.0)6	[0.70, 1.60]	1.6%	2.1%
Dalmaz 2006 Brazil	61	150	87	290	1.2	26	[0.78, 2.02]	1.2%	2.0%
Driul 2005 Italy	28	78	42	128	1.6	50	[1.06, 2.41]	1.6%	2.1%
Mello 2005 Italy	505	1616	220	1616		15	[0.63, 2.07]	0.8%	1.6%
Also-Rallo 2005 Spain	40	86	111	244	L ¹ ^{±±} 2.8	38	[2.42, 3.44]	8.8%	2.8%
Yilmaz 2004 Turkey	42	128	29	94	1.0)4	[0.64, 1.71]	1.1%	1.9%
Perez-Mutul 2004 Mexico	164	296	202	354	1.0)9	[0.62, 1.94]	0.8%	1.7%
Williams 2004 Peru	112	250	147	358	- 0.9	93	[0.68, 1.28]	2.8%	2.5%
De Maat 2004 Netherlands	99	314	113	314		16	[0.84, 1.61]	2.6%	2.4%
Prochazka 2003 Czech	16	76	10	100		32	[0.59, 1.14]	2.5%	2.4%
Fabbro 2003 Italy	41	104	62	160	2.4	10	[1.02, 5.64]	0.4%	1.1%
D'Elia 2002 Italy	37	116	52	148	1.0)3	[0.62, 1.71]	1.1%	1.9%
Prassmusinto 2002 Germanv	25	80	54	144		36	[0.52, 1.45]	1.0%	1.8%
Morrison 2002 England	277	808	100	328		76	[0.42, 1.35]	0.8%	1.7%
Raijmakers 2001 Scotland	116	334	234	806		19	[0.90, 1.57]	3.6%	2.6%
achmeijer 2001 Netherlands	29	94	73	240	1.3	30	[0.99, 1.71]	3.7%	2.6%
Alfirevic 2001 UK	42	126	19	88)2	[0.61, 1.71]	1.0%	1.8%
Livingston 2001 USA	54	220	42	194	1.8	32	[0.97, 3.40]	0.7%	1.5%
Kim 2001 USA	183	562	234	720		18	[0.74, 1.86]	1.3%	2.0%
Rajkovic 2000 USA	30	342	32	366		00	[0.79, 1.27]	4.9%	2.7%
Kupferminc 2000 Israel	61	126	78	252		00	[0.60, 1.69]	1.0%	1.8%
Zusterzeel 2000 Netherlands	116	334	234	806) 20)9	[1,35, 3 25]	1.4%	2.1%
Laivouri 2000 Finland	53	226	54	206		30	[0.99, 1 71]	3.7%	2.6%
O'Shaughnessy 1999 UK	176	566	61	200		36	[0.56, 1 34]	1 4%	2.1%
Powers 1999 USA	79	198	74	228)3	[0.72, 1 46]	2.2%	2.3%
Grandone 1997 Italv	104	192	111	258	1.0 1.0	38	[0.93, 2.06]	1 7%	2.2%
Fixed effect model	101	10598		19876)	57	[1 07 2 28]	1.9%	2.2%
Radnom effects model		10570		17070	1	 91	[1 14 1 28]	85 7%	2.3/0
Heterogeneity: <i>I</i> ² =77.9%, tau	e=0.117	5, P <0.000)1		۰ خ	6	[1.02, 1.32]		81.1%
					Į.		,		
Fixed effect model		13356		23082	i i				
Radnom effects model					o 1.2	21	[1.15, 1.27]	100.0%	
Heterogeneity: P=75%, tau ² =	0.1062,	P<0.0001			ا . ا	7	[1.05, 1.31]		100.0%

Figure 2. Forest plot by ethnicity for rs18001133 in MTHFR gene.

					Forest plot by ethnicity for rs6025 in F5 gene							
Study	Experi Events	mental Total	Cor Events	ntrol Total	Odds ratio	OR	95% Cl	W(fixed)	W(random)			
					1							
Ethnicity=Asian)							
Salimi 2015 Iran	20	384	22	392	- 	0.92	[0.50, 1.72]	8.0%	4.8%			
Dissanayake 2012 Sri Lanka	7	350	2	342		3.47	[0.72, 16.82]	1.2%	2.7%			
Aggarwal 2011 India	30	400	15	400	- 3 -	2.08	[1.10, 3.93]	7.7%	4.8%			
Malek-Khosravi 2012 Iran	15	396	8	202	— ————————————————————————————————————	0.95	[0.40, 2.29]	4.1%	4.2%			
Fixed effect model		1530		1336	\$	1.35	[0.92, 1.99]	21.0%				
Radnom effects model					\$	1.39	[0.81, 2.38]		16.4%			
Heterogeneity: <i>P</i> =42.1%, tau ² =	0.1234	, P =0.159	2		1							
Ethnicity=Caucasian					į							
Seremak-Mrozikiewicz 2010 Polish	n 11	218	14	800		2.98	[1.33, 6.67]	4.8%	4.4%			
Kahn 2009 Canada	6	226	22	886	— ————————————————————————————————————	1.07	[0.43, 2.67]	3.7%	4.1%			
Hiltunen 2008 Finland	10	496	16	1358	- .	1.73	[0.78, 3.83]	4.9%	4.4%			
Ivanov 2007 Bulgaria	0	50	3	98	<u>;</u>	0.27	[0.01, 5.33]	0.3%	1.2%			
Dalmáz 2006 Brazil	2	150	1	290	<u>,</u>	3.91	[0.35, 43.42]	0.5%	1.6%			
Mello 2005 Italy	71	812	15	812	li D	5.09	[2.89, 8.97]	9.7%	4.9%			
Tempfer 2004 Austria	6	96	4	96		1.53	[0.42, 5.62]	1.8%	3.2%			
Prassmusinto 2004 Germany	4	80	1	144		7.53	[0.83, 68, 53]	0.6%	1.8%			
Faisel 2004 Finland	39	532	14	448) []	2.45	[1.31, 4.58]	8.0%	4.8%			
Lévesque 2004 Canada	8	350	11	34		0.05	[0.02, 0.13]	3.1%	3.9%			
Currie 2002 Austria	4	96	6	96		0.65	[0.18, 2.39]	1.8%	3.2%			
Benedetto 2002 Denmark	8	222	5	222	<u>- à</u>	1.62	[0.52, 5.04]	2.4%	3.6%			
Morrison 2002 England	17	788	8	326	- <mark></mark>	0.88	[0.37, 2.05]	4.3%	4.3%			
Peternoster 2002 Italy	3	94	2	70		1.12	[0.18, 6.89]	0.9%	2.3%			
Alfirevic 2001 IIK	1	126	3	88		0.23		0.6%	1.7%			
Kim 2001 USA	15	500	12	506		1 27	[0.59 2.22]	5.3%	4.4%			
Livingston 2001 USA	6	220	3	194	<u>_</u>	1.27	[0.44 7 74]	1.6%	3.0%			
von Tempelhoff 2000 Germany	6	58	3	127	<u>)</u>	4 58	[1 10 10 01]	1.0%	3.0%			
Kunferminc 1999 Germany	9	68	7	220	·	4 64	[1.66, 12, 99]	2.9%	3.8%			
0'Shaughnessy 1999 LIK	15	566	6	200		0.88	[0 34 2 30]	3.4%	4.0%			
De Groot 1999 Netherlands	16	326	15	326	- Fa r	1.07	[0.57, 2.50]	6.0%	4.6%			
Grandone 1997 Italy	10	190	2	256	<u></u>	4.60	[0.32, 2.20]	1 20%	3 70%			
Lindoff 1997 Sweden	13	100	5	100		7.05	[0.07.8.20]	7.0%	3.2%			
Dizon-Townson 1006 USA	1/	316	17	806		2.04	[0.97, 0.29]	6.0%	J.7 70			
Fived effect model	14	6680	17	8498	8	1 71	[1.05, 4.42]	70 004	4.070			
Radnom effects model		0000		0470	Ġ	1.71	[1.40, 2.09]	/ 7.0%	83 60%			
Heterogeneity: $l^2 = 74.7\%$, tau ² =	0.7454	, P <0.000)1		1	1.34	[1.01, 2.30]		03.070			
Fixed effect model		8210		0851	ì	1.62	[1 37 1 05]	100 004				
Radnom effects model		0210		7034	\$	1.05	[1.37, 1.93]	100.070	100 0%			
Hotorogonaity: P-72 20% +2112-	-0 6022	P-0 000	1		3	1.72	[1.07, 2.20]		100.070			
neteroyeneity. 1 - 12.3%, ldu=	-0.0023	, r < 0.000										
					0.1 0.511 2 10							

Figure 3. Forest plot by ethnicity for rs6025 in F5 gene.

disease pathology; most of the published studies focused on the association between several SNPs and the susceptibility to PE, including *AGT*[34,35], *ACE*[36–39], *F5*[4,40–44], *MTHFR* [7,18,45–49], and *TNF-alpha* [23,24,50,51]. The present study enabled us not only to explore the relationship between gene polymorphisms on chromosome 1 (*MTHFR*, *AGT*, *F5*, *IL-10*, *LEPR*) and susceptibility to PE, but also to assess potential heterogeneity among studies.

The methylenetetrahydrofolate reductase (*MTHFR*) gene encodes the enzyme 50, 100-methylenetetrahydrofolate reductase, located on chromosomal region 1p36.3. Many studies have indicated an association between *MTHFR* SNPs and risk of PE. However, the results were inconclusive due to significant

heterogeneity resulting from differences in study population, ethnicity, and genotypes. Our meta-analysis provides evidence that *MTHFR* rs1801133 is significantly associated with increased risk of PE in Caucasians under the allelic model, but this association was not significant in Asians or Africans. In contrast, a study by Wu et al. concluded that there was a significant association between SNP of rs1801133 and PE susceptibility in Asians [7]. This inconsistency may be explained by 2 factors. Firstly, the current meta-analysis had a smaller sample size for Asians, which may have restricted its ability to detect any significant association. Secondly, only the allelic genetic model was incorporated in the meta-analysis, which may lead to a biased estimation of the association. Therefore, it is necessary to design studies with large sample sizes, particularly for

					Forest plot by ethnicity for rs1800896 in <i>IL-10</i> g	jene			
Study	Experir	nental	Cor	ntrol Total	Odds ratio	OP	05% (I	W(fixed)	W(random)
Study	LVEIILS	IUtai	LVEIIIS	IUtai	OddsTatio	011	9570 CI	w(lixeu)	w(laliuolli)
					1				
Ethnicity=African									
Elhawary 2012 Egypt	16	40	23	30		0.20	[0.07, 0.58]	0.8%	2.9%
Fixed effect model		40		30		0.20	[0.07, 0.58]	0.8%	
Radnom effects model						0.20	[0.07, 0.58]		2.9%
Heterogeneity: not applicable	for a sing	le study							
Féhnisian Asian									
Ethnicity=Asian Vural 2010 Turkov	71	202	96	100		0.66	[0 44 0 09]	E 60/	10 10/
Kamali Sarvostani 2006 Iran	05	202	00	210		1 45	[0.44, 0.96]	5.0% 7.404	10.1%
Fixed effect model	95	446	51	508		1.45	[0 79 1 35]	13.0%	11.470
Radnom effects model		110		500	× ·	0.98	[0.45 2.14]		21 5%
Heterogeneity: /2=88.2%, tau2	=0.2792.	P=0.003	7			0.20	[0:13/2:11]		211370
	,								
Ethnicity=Caucasian						1.12	[0.76, 1.66]	6.0	10.5%
Pinheiro 2015 Brazil	83	232	71	214		1.03	[0.83, 1.28]	19.7	14.7%
Valencia Villalvazo 2012 Mexico	177	822	257	1226	<u>+</u>	0.73	[0.46, 1.15]	4.5	9.2%
Lima 2009 Brazil	46	176	62	190		1.15	[0.98, 1.35]	34.2	15.9%
Stonek 2009 Austria	328	722	1234	2938		0.71	[0.50, 0.99]	7.8	11.6%
Daher 2006 Brazil	/6	284	122	358	- 	0.90	[0./0, 1.1/]	14.0	13.7%
Haggerty 2005 USA	121	298	569	1322	- -	1.01	[0.91, 1.12]	86.2%	
Pixed effect model		2534		0248	\$	0.96	[0.83, 1.13]		/5.0%
Heterogeneity: P=47.9% tau ²	=0 017	P=0 0877			\$				
neterogenery. n = 11.570, au	0.01771	010077				1.00	[0.91, 1.10]	100.0%	
Fixed effect model		3020		3786		0.91	[0.75, 1.11]		100.0%
Radnom effects model					Å		- / -		
Heterogeneity: <i>I</i> ² =70.2%, tau ²	=0.0559,	P=0.000	7		Y .				
					0.1 0.5 1 2 10				

Supplementary Figure 3. Forest plot by ethnicity for rs1800896 in *IL-10* gene.

					Forest plot by ethnicity for rs1800871 in <i>IL-1</i>	0 gene			
Study	Experir	nental Total	COI Events	ntrol Total	Odds ratio	OP	05% (1	W(fixed)	W(random)
Study	LVEIILS	IULAI	LVCIILS	IULAI	Ouusiallo	UN	9070 CI	W(IIXeu)	w(lalluolli)
Ethnicity=Asian Sowmya 2014 India Kamali-Sarvestani 2006 Iran Fixed effect model Radnom effects model Heterogeneity: I ² =69.8%, tau ² :	92 72 = 0.0785 ,	240 262 502	132 102 38	240 322 562		0.51 0.82 0.65 0.65	[0.35, 0.73] [0.57, 1.17] [0.50, 0.84] [0.41, 1.03]	23.1% 23.7% 46.8%	24.8% 25.0% 49.8%
Ethnicity—Caucasian									
Lima 2009 Brazil	62	176	61	190		1.15	[0.75, 1.78]	16.2%	21.5%
Haggerty 2005 USA	75	300	377	1322		0.84	[0.63, 1.11]	37.0%	28.6%
Fixed effect model		476		1512		0.92	[0.72, 1.17]	53.2%	
Radnom effects model		170		1912		0.94	[0.69, 1.27]		50.2%
Heterogeneity: <i>I</i> ² =30.9%, tau ²	=0.0158,	<i>P</i> =0.228	39		{				
Fixed effect model Radnom effects model Heterogeneity: J²=65.4%, tau²:	=0.0619,	978 <i>P</i> =0.034	11	2074		0.78 0.79	[0.66, 0.93] [0.58, 1.07]	100.0% 	 100.0%
					r1				

Supplementary Figure 4. Forest plot by ethnicity for rs1800871 in *IL-10* gene.

Asians and Africans. For rs1801131, the overall analysis and the subgroup analysis did not provide sufficient evidence to suggest a significant association. As of September 2015, 3 other

meta-analyses had suggested that there is no significant association between rs1801131 and PE [7,18,49]. Compared to the large number of cases and controls for rs1801133, we only

					Forest plot by ethnicity for rs1137101 in LEA	PR gene			
Study	Experin Events	nental Total	Cor Events	ntrol Total	Odds ratio	OR	95% Cl	W(fixed)	W(random)
Ethnicity=Asian					;				
Salimi 2015 Iran	20	384	22	392	-+++;	0.92	[0.50, 1.72]	8.0%	4.8%
Dissanayake 2012 Sri Lanka	7	350	2	342	<u>+_</u>	3.47	[0.72, 16.82]	1.2%	2.7%
Aggarwal 2011 India	30	400	15	400		2.08	[1.10, 3.93]	7.7%	4.8%
Malek-Khosravi 2012 Iran	15	396	8	202	- 	0.95	[0.40, 2.29]	4.1%	4.2%
Fixed effect model		1530		1336	\$	1.35	[0.92, 1.99]	21.0 %	
Radnom effects model						1.39	[0.81, 2.38]		16.4%
Heterogeneity: <i>I</i> ² =42.1%, tau ² =	=0.1234,	P =0.159	2		1 1				
Ethnicity=Caucasian					3				
Seremak-Mrozikiewicz 2010 Polis	h 11	218	14	800	; ⊡-	2.98	[1.33, 6.67]	4.8%	4.4%
Kahn 2009 Canada	6	226	22	886	- 	1.07	[0.43, 2.67]	3.7%	4.1%
Hiltunen 2008 Finland	10	496	16	1358		1.73	[0.78, 3.83]	4.9%	4.4%
Ivanov 2007 Bulgaria	0	50	3	98		0.27	[0.01, 5.33]	0.3%	1.2%
Dalmáz 2006 Brazil	2	150	1	290		- 3.91	[0.35, 43.42]	0.5%	1.6%
Mello 2005 Italy	71	812	15	812		5.09	[2.89, 8.97]	9.7%	4.9%
Tempfer 2004 Austria	6	96	4	96		1.53	[0.42, 5.62]	1.8%	3.2%
Prassmusinto 2004 Germany	4	80	1	144		7.53	[0.83, 68.53]	0.6%	1.8%
Faisel 2004 Finland	39	532	14	448		2.45	[1.31, 4.58]	8.0%	4.8%
Lévesque 2004 Canada	8	350	11	34	— — —	0.05	[0.02, 0.13]	3.1%	3.9%
Currie 2002 Austria	4	96	6	96		0.65	[0.18, 2.39]	1.8%	3.2%
Benedetto 2002 Denmark	8	222	5	222		1.62	[0.52, 5.04]	2.4%	3.6%
Morrison 2002 England	17	788	8	326	- 	0.88	[0.37, 2.05]	4.3%	4.3%
Peternoster 2002 Italy	3	94	2	70	<mark>=</mark>	1.12	[0.18, 6.89]	0.9%	2.3%
Alfirevic 2001 UK	1	126	3	88	i	0.23	[0.02, 2.22]	0.6%	1.7%
Kim 2001 USA	15	500	12	506	— <mark>—</mark> ——	1.27	[0.59, 2.75]	5.3%	4.4%
Livingston 2001 USA	6	220	3	194	— <u>b</u> —	1.79	[0.44, 7, 24]	1.6%	3.0%
von Tempelhoff 2000 Germany	6	58	3	122		4.58	[1 10 19 01]	1.5%	3.0%
Kunferminc 1999 Germany	9	68	7	220	; B	4 64	[1.66, 12, 99]	2.9%	3.8%
0'Shaughnessy 1999 UK	15	566	6	200	— <mark>@ ></mark>	0.88	[0 34 2 30]	3.4%	4.0%
De Groot 1999 Netherlands	16	326	15	326	- 	1 07	[0.52, 2.20]	6.0%	4.6%
Grandone 1997 Italy	10	190	3	256	<u>, </u>	4 69	[1 27 17 27]	1.8%	3.2%
Lindoff 1997 Sweden	13	100	5	100	<mark> ;⊞</mark> —	2 84	[0.97 8 29]	2.7%	3.7%
Dizon-Townson 1996 USA	14	316	17	806		2.04		6.0%	4.6%
Fixed effect model	17	6680	17	8498	\	1 71	[1 40 2 00]	79.0%	
Radnom effects model				0.00	♦	1 54	[1 1 2 36]		83.6%
Heterogeneity: <i>l</i> ² =74.7%, tau ² =	=0.7454,	<i>P</i> <0.000	1		L L	1.54	[1.1, 2.50]		55.070
Fixed offect model		8210		0024) 👌	1.63	[1.37, 1.95]	100 004	
Padnom offects model		0210		7034	Ġ	1.00	[1.07, 2.20]	100.0%	100.00/
Nautorogonaity: $R_{-72} = 70\%$ to: r^2	-0 6022	D ~ 0 000	1		ž				100.0%
neterogeneity: r=r2.2%, tau=	-0.0023,	r<0.000							
					0.2 0.5 1 2 5				

Supplementary Figure 5. Forest plot by ethnicity for rs1137101 in LEPR gene.

have 1390 cases/1818 controls for rs1801131, which may significantly reduce the statistical power of a meta-analysis to detect a significant association. Therefore, further studies with large sample sizes should be carried out to increase the credibility of this conclusion. Overall, we concluded that *MTHFR* rs1801133 might be an effective marker for use in PE diagnosis.

F5 is considered to be a potential genetic factor for PE because it encodes an essential cofactor of the blood coagulation cascade. *F5* has also been widely studied due to its common thrombophilic mutation [52,53]. Although the overall results suggested a significant association between polymorphism of *F5* (rs6025) and PE, other studies have not provided sufficient evidence to conclude there is a significant association [53]. Our meta-analysis indicates that *F5* rs6025 is associated with an increased risk of PE, which is contrary to the results of some other studies. This may be explained by the typical publication bias and time-lag bias inherent in smaller studies [54,55]. In addition, these smaller studies may also have failed to comply with strict standards. For example, some terms must be carefully defined, including *paternity* [56] and *gravidity* [57], because they may interact with genetic factors to affect PE susceptibility. Moreover, results from subgroup analysis may not be applicable to other ethnicities such as Africans because the included study did not involve African subjects. Thus, studies that incorporate different ethnicities, particularly Africans, should be designed to confirm the association between *F5* (rs6025) and the susceptibility to PE.

					Forest plot by ethnicity for rs18001131 in MTHFR gene							
Study	Experii Events	nental Total	Cor Events	ntrol Total	Odds ratio	OR	95% CI	W(fixed)	W(random)			
Ethnicitv=African					L L L							
Pegoraro 2004 South Africa	61	542	83	676		0.91	[0.64, 1.29]	12.1%	12.7%			
Fixed effect model		542		676		0.91	[0.64, 1.29]	12.1%				
Radnom effects model					\diamond	0.91	[0.64, 1.29]		12.7%			
Heterogeneity: not applicable	for a sing	le study			L Ĺ							
Fthnicity=Asian					ç							
Salimi 2015 Iran	78	384	57	392	L 4 (1)	1.50	[1.03, 2.18]	10.6%	12.1%			
Dissanayake 2012 Sri Lanka	115	346	107	342		1.09	[0.79, 1.51]	14.6%	13.6%			
Fixed effect model		730		734		1.25	[0.98, 1.59]	25.2%				
Radnom effects model						1.26	[0.93, 1.71]		25.7%			
Heterogeneity: P=36.2%, tau	² =0.018, <i>I</i>	P=0.2105			Ľ.							
Ethnisity_Courseion					L L							
Chedraui 2014 Ecuador	73	300	41	300	í.	2.03	[1 33 3 10]	8 4%	10.9%			
Klai 2011 Tunisia	8	88	7	200	· — —	2.76	[0.97, 7.86]	1.4%	3.2%			
Also-Rallo 2005 Spain	19	86	63	244	_ 1	0.81	[0.45, 1.46]	4.4%	7.6%			
Lachmeijer 2001 Netherlands	36	94	86	240	<u> </u>	1.11	[0.68, 1.82]	6.2%	9.3%			
Kaiser 2000 Australia	214	588	154	436		1.05	[0.81, 1.36]	22.4%	15.4%			
Zusterzeel 2000 Netherlands	102	352	262	806		0.85	[0.64, 1.11]	20.0%	15.0%			
Fixed effect model		1508		2226	Т <u>Г</u>	1.08	[0.93, 1.26]	62.7%				
Radnom effects model					Ľ.	1.17	[0.86, 1.59]		61.5%			
Heterogeneity: <i>P</i> =68.1%, tau	=0.0899,	P=0.007	8		í.							
Fixed effect model		2780		3636	C C	1.10	[0.97, 1.24]	100.0%				
Radnom effects model		_,			•	1.14	[0.93, 1.40]		100.0%			
Heterogeneity: <i>I</i> ² =59.2%, tau	² =0.0527,	P=0.012	4		\$							

Supplementary Figure 6. Forest plot by ethnicity for rs18001131 in MTHFR gene.



Figure 4. Publication bias for rs1801133 and rs6025.



Supplementary Figure 7. Publication bias of non-significant SNPs.

AGT is a key effector in regulating the blood pressure, and the level of AGT among hypertensive patients is related to the SNPs of the AGT gene [58]. The expression of AGT rs699 was elevated in decidual spiral arteries, which play a vital role in developing several events that may trigger PE [59,60]. Lin et al. indicated that AGT rs699 was significantly associated with PE, whereas there was no significant association between AGT rs4762 and PE [8]. Similar results were also found in studies conducted by Ni et al. and Zhu et al. [35,39]. On the other hand, the present meta-analysis discovered that there was no significant association between AGT polymorphism (rs699, rs4762) and PE. This inconsistency may be attributable to the limited number of studies investigating AGT polymorphisms. Although ethnicity has been taken into consideration to explain the potential source of heterogeneity, the lack of information on gene-environment interaction or the interaction between several genes could have a substantial effect on the overall conclusion.

Interleukin 10 (IL-10) is located on the chromosome of 1g21-32 and it is an immune-regulatory cytokine associated with different biological functions [61]. Furthermore, IL-10 exerts regulatory effects on the balance of Th1/ Th2 and it is a crucial cytokine for females during gestation [13,62]. This study enabled us to investigate the association between IL-10 polymorphisms (rs1800896, rs1800871) and PE. The results suggest that rs1800896 or rs1800871 is not significantly associated with PE susceptibility. Results from subgroup analysis by ethnicity were consistent with those from the overall analysis. However, we should interpret these results with great caution since all of the included studies came from different regions, which may be considered as a confounding factor that influences the conclusion. Apart from that, other confounding factors, including gestational age at the sample collection time, body mass index, and assay sensitivity, should be taken into account in order to further investigate the association between IL-10 polymorphisms and PE susceptibility.

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It has been suggested that the expression of leptin receptor (*LEPR*) significantly increases when inflammation occurs and that it plays an important role in immune responses [63]. Immune response is a factor for PE [63,64] and mutations in this gene have been shown to be associated with PE. For instance, a study by Fong et al. revealed that LEPR rs1137101 was significantly associated with PE, which is contrary to the results obtained from our meta-analysis. This discrepancy may also come from our small sample size, which significantly reduces the statistical power of the present meta-analysis to detect any significant association.

Conclusions

We conclude that rs1801133 of *MTHFR* and rs6025 of *F*5 are significantly associated with PE, whereas rs1801131 of *MTHFR*, rs699 and rs4762 of *AGT*, rs1800896 and rs1800871 of *IL*-10, and rs1137101 of *LEPR* have no significant association with PE. Studies with large sample sizes adjusting for various confounding factors should be designed to confirm the above conclusion. Nevertheless, our meta-analysis provides some evidence to help explain the mechanism of susceptibility to PE, which can be critical to the health of females during gestation.

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Disclosure of conflict of interest

None.

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