CHAPTER II

GENETIC VARIANTS IN PREECLAMPSIA: A META-ANALYSIS

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Abstract

BACKGROUND Preeclampsia has a clear familial component, suggesting that the condition may be partly attributable to genetic susceptibility. The search for susceptibility genes has led to a drastic increase in the number of published studies associating genetic factors with preeclampsia. However, attempts to replicate these findings have yielded inconsistent results. This meta-analysis assessed the pooled effect of each genetic variant that is reproducibly associated with preeclampsia.

METHODS Studies that assessed the association between genes and preeclampsia were searched in PubMed, Embase and Web of Science. We selected all genetic variants that were significantly associated with preeclampsia in an initial study and were subsequently independently reproduced in at least one additional study. All studies that assessed these reproduced variants were then included. The association between genetic variants and preeclampsia was calculated at the allele level, and the main measure of effect was a pooled odds ratio in a random-effects model.

RESULTS The literature search yielded 2965 articles, of which 542 investigated genetic associations in preeclampsia. We identified 22 replicated genetic variants, of which seven remained significantly associated with preeclampsia following meta-analysis. These variants were in or near the following genes: ACE, CTLA4, F2, FV, LPL and SERPINE1.

CONCLUSIONS This meta-analysis identified seven genetic variants associated with preeclampsia. Importantly, many of these variants are also risk factors for developing cardiovascular disease, revealing that preeclampsia and cardiovascular disease have shared genetic risk factors. The contribution of the identified genetic variants in the pathogenesis of preeclampsia should be the focus of future studies.

Introduction

Preeclampsia is a severe pregnancy complication characterized by hypertension and proteinuria after 20 weeks of gestation. Globally, preeclampsia affects 5-8% of pregnancies and contributes significantly to maternal and fetal morbidity and mortality.[1] Furthermore, women with preeclampsia have an increased risk of developing cardiovascular disease later in life.[2] Because the precise etiology of preeclampsia remains unknown, accurate prediction and prevention of the condition are at present difficult.

Preeclampsia is believed to result from a complex interplay between genetic components and environmental factors. Evidence for a genetic component comes from family studies, which have shown that preeclampsia is relatively common among daughters and sisters of preeclamptic women.[3-8] Furthermore, the prevalence of preeclampsia differs between various ethnic groups.[1] However, the underlying genetics are complex, and it is currently unclear what genes are involved and how individual genetic variants contribute to preeclampsia.

Numerous genetic association studies have been performed to elucidate the genetic background of preeclampsia. An overview of candidate genes investigated in the setting of preeclampsia indicates a sharp increase in the number of published studies regarding genetic associations in preeclampsia, with three published studies in 1996 in contrast to 30 published studies in 2004.[9] However, attempts to replicate these studies have yielded inconsistent results. Although this lack of reproducibility can be due simply to population diversity, it is often the result of small sample sizes or false-positive results.[10] Because the prior probabilities of genetic associations are low, the number of false-positive associations that are generated by chance alone is high. The likelihood of finding false-positive associations increases when low prior probabilities are not accounted for in the statistical analysis.

Therefore, independently replicating an association is essential for identifying true genetic associations among the large number of false-positives.

The aim of this study was to compile an overview of the genetic variants that are truly associated with preeclampsia. Therefore, we performed a meta-analysis to assess the pooled effect of genetic variants that have been reproducibly associated with preeclampsia.

Methods

LITERATURE SEARCH The databases PubMed, Embase and Web of Science were searched through February 2012 for studies that evaluated genetic variants in preeclampsia. A comprehensive search strategy was developed in collaboration with a trained librarian. The search terms that were used in the search strategy included: "Preeclampsia" and "Polymorphisms" or "Genes". For these terms, all relevant keyword variants were included. The names of specific genes and polymorphisms that were yielded in the first search were added to the search strategy in subsequent searches. The search strategy was optimized for each database (see Supplementary data). Aside from limiting the searches to studies published in English, no other limits or filters were applied in the searches. In addition, references of other narrative and systematic reviews were checked for relevant articles.

ELIGIBILITY CRITERIA We searched for case-control studies that compared genetic variants between patients with preeclampsia and healthy women with uncomplicated pregnancies. We only included studies that defined preeclampsia as elevated blood pressure (with clear cut-off values for systolic and diastolic blood pressure) accompanied with proteinuria measured in at least a semi-quantitative way, in line with the ISSHP (International Society for the Study of Hypertension in Pregnancy) criteria.[11] For inclusion,

the study had to involve unrelated women. Studies in which the case group contained women with gestational hypertension were excluded, as were studies in which the control group contained subjects who had never been pregnant. All titles and abstracts were reviewed by two observers (A.B. and R.T.), who independently assessed whether the study investigated the relationship between preeclampsia and at least one genetic variant. Genetic association studies were screened for whether they contained a positive or negative association between an individual genetic variant and preeclampsia (based on the reported p-values, with association defined as significant when $p < 0.05$). When a genetic variant was found to be significantly associated with preeclampsia (either at the allelic or genotypic level, including the recessive and dominant model) in at least two independent studies, that variant was considered to be reproduced. For these reproduced genetic variants, all other genetic studies—irrespective of their p-values—were identified to estimate the pooled effect of the variant on preeclampsia in a meta-analysis.

DATA EXTRACTION Allele frequencies were extracted and entered into separate databases by two authors independently. These two databases were then compared, and disparities were resolved by consensus. Multiple studies published by the same author(s) were checked for overlapping (i.e. redundant) participant groups, and in cases in which the studies overlapped the study with the smaller dataset was excluded. When insufficient data was provided to calculate an odds ratio, at least two attempts were made to contact the corresponding author. When neither the published report nor the corresponding author provided sufficient data to calculate an odds ratio at the allele level, the study was excluded.

STATISTICAL ANALYSIS The main outcome of the meta-analysis was the pooled odds ratio (calculated at the allele level) for the association between reproduced genetic variants and preeclampsia.

The frequency of the minor allele was compared between women with preeclampsia and healthy control subjects who had an uncomplicated pregnancy. The data were pooled using a random-effects model to account for between-study heterogeneity. To estimate heterogeneity, we used I^2, which reflects the percentage of total variation across studies that is due to heterogeneity rather than due to chance.[12] Bias due to small study size was tested using a stratified analysis for study size as described previously.[13] This analysis was performed only for genetic variants that were significantly associated with preeclampsia after the meta-analysis and for which the number of studies that investigated the genetic variant was higher than ten. Publication bias was assessed using the Begg and Egger tests. In addition, we generated funnel plots of all reproduced genetic variants. All analyses were performed using STATA (StataCorp. 2011. Stata Statistical Software, Release 10. College Station, TX; StataC).

Results

The initial literature search yielded 2965 articles, 542 of which were genetic association studies regarding preeclampsia (Figure 1). We identified 22 polymorphisms in 15 genes that were reproducibly associated with preeclampsia. Associations between these 22 variants and preeclampsia were described in 163 articles, representing 283 studies. These articles were published from 1993 through 2012. The number of studies per genetic variant ranged from 2 to 45, and the number of cases included in these studies ranged from 7 to 808.

In a random-effects meta-analysis, seven genetic variants in or near six genes were significantly associated with preeclampsia (Figure 2a). The remaining 15 reproduced variants were not associated with preeclampsia following meta-analysis (Figure 2b). The odds ratios of the significant associations with preeclampsia ranged from 1.20 to 2.42. The genes with the largest effect had wider confidence intervals, indicating less certainty in the effect estimates. No

significant protective effect was found for any gene. Table I provides an overview of the analyses of all reproduced genetic variants as well as the location and the functional consequences of these genetic variants, and Table II provides the references of the included studies per genetic variant. The characteristics of all included studies, as well as forest plots of the individual reproduced genetic variants, funnel plots for assessment of publication bias and stratified analysis for study size are provided in Supplementary data. The cut-off values for hypertension and proteinuria in Table II of the Online Supplement show that some studies only included women with severe preeclampsia.

GENETIC VARIANTS INVOLVED IN COAGULATION AND FIBRINOLYSIS Five genetic variants in four genes that are related to coagulation and fibrinolysis were associated reproducibly with preeclampsia. Of these five variants, four were still associated with preeclampsia after the meta-analysis. Two variants in coagulation factor V (FV), rs6025 and rs6020, remained associated with preeclampsia in the meta-analysis. The rs6025 variant, which is also known as Factor V Leiden, was a frequently studied polymorphism in preeclampsia, with 40 studies resulting in a pooled odds ratio of 1.94 (95% CI 1.56-2.45). In a sensitivity analysis, the pooled odds ratio decreased slightly with increasing study size, decreasing from 1.99 in studies with <100 cases to 1.71 in studies with ≥200 cases. The rs6020 variant was reported in only two studies, resulting in a pooled odds ratio of 1.94 (95% CI 1.05-3.60). A variant in methylenetetrahydrofolate reductase (MTHFR), rs1801133, was reported in 45 studies, resulting in a pooled odds ratio of 1.06 (95% CI 0.97-1.16). The rs1799963 variant of the coagulation factor II (F2) gene (also known as prothrombin) was investigated in 30 studies and was associated with preeclampsia with an odds ratio of 1.95 (95% CI 1.43-2.66). In a sensitivity analysis, the studies with the largest number of cases yielded the largest effect estimate, with an odds ratio of 3.84 (95% CI 2.18-6.78). The rs1799889 variant in

serpin peptidase inhibitor (SERPINE1, also known as plasminogen activator inhibitor type 1) was associated with preeclampsia in the meta-analysis with an odds ratio of 1.17 (95% CI 1.03-1.33). When subdividing the studies based on study size, the effect estimate diminished slightly from 1.21 in studies with < 100 cases to 1.17 in studies with 100-200 cases and 1.14 in studies with ≥ 200 cases.

GENETIC VARIANTS INVOLVED IN THE RENIN-ANGIOTENSIN SYSTEM The angiotensin I converting enzyme (ACE) rs4646994 variant has been studied frequently in preeclampsia, with 20 studies yielding a pooled odds ratio of 1.20 (95% CI 1.08-1.34). A stratified analysis revealed a diminishing effect as study size increased, with a pooled odds ratio of 1.45 (95% CI 1.21-1.73) for studies with <100 cases, which is in contrast with a pooled OR of 1.05 (95% CI 0.90-1.23) for pooled studies with ≥200 cases. The rs699 and rs4762 variants in angiotensinogen (AGT) were studied in 21 and five studies, respectively. The rs699 variant was not associated with preeclampsia after meta-analysis, with a pooled odds ratio of 1.23 (95% CI 0.98-1.54). The rs4762 variant was also not associated with preeclampsia, with an odds ratio of 1.25 (95% CI 0.67-2.30). Another variant in the renin-angiotensin system, rs5186 of angiotensin II receptor type 1 (AT1R), was investigated in nine studies and was not associated with preeclampsia after meta-analysis.

GENETIC VARIANTS INVOLVED IN OXIDATIVE STRESS Three variants in the nitric oxide synthase 3 (NOS3) gene were reproducibly associated with preeclampsia, but none was still associated with preeclampsia following the meta-analysis. The 27 bp-VNTR in intron 4 yielded a pooled odds ratio of 1.14 (95% CI 0.90-1.43), and the rs2070744 and rs1799983 variants yielded pooled odds ratios of 1.08 (95% CI 0.95-1.23) and 1.19 (95% CI 1.00-1.42), respectively.

GENETIC VARIANTS INVOLVED IN INFLAMMATION

The cytotoxic T-lymphocyte-associated protein 4 (CTLA4) rs231775 variant was reported in four studies. The meta-analysis revealed an association with preeclampsia with a pooled odds ratio of 1.24 (95% CI 1.01-1.52). The rs1800896 variant of interleukin 10 (IL-10) was not associated with preeclampsia in the meta-analysis (OR 0.91, 95% CI 0.74-1.12). Two variants in the tumor necrosis factor alpha (TNF-alpha) gene (rs1800629 and rs1799724) were reproduced in preeclampsia but were not associated with preeclampsia after the meta-analysis, with odds ratios of 1.17 (95% CI 0.91-1.49) and 0.66 (95% CI 0.33-1.31), respectively.

GENETIC VARIANTS INVOLVED IN LIPID METABOLISM

The rs1800590 and rs268 variants in the lipoprotein lipase (LPL) gene were reproduced in preeclampsia, but only rs268 remained associated with preeclampsia following the meta-analysis (OR 2.42, 95% CI 1.25-4.68). The combined rs429358 and rs7412 polymorphisms (E2 allele) in the apolipoprotein E (APOE) gene was reported in eight studies, yielding a pooled odds ratio of 0.86 (95% CI 0.66-1.13).

GENETIC VARIANTS INVOLVED IN OTHER PATHWAYS

Two variants in the toll-like receptor 4 (TLR4) gene, rs4986790 and rs4986791, were reported in four and three studies, respectively. Neither variant remained associated with preeclampsia following the meta-analysis. The rs3025039 variant in the vascular endothelial growth factor (VEGF) gene was reproduced in preeclampsia, although the meta-analysis did not reveal a statistically significant association (OR 1.36, 95% CI 0.64-2.91).

Discussion

In this meta-analysis, seven genetic variants were found to be associated with preeclampsia. Meta-analysis for several individual genetic variants in the setting of preeclampsia has been performed previously. However, the present study provides the first complete and comprehensive overview of all genetic variants that are reproducibly associated with preeclampsia. These data may shed light on the pathogenesis of preeclampsia and thereby reveal molecular pathways that can be targeted in the management of this condition. Genetic variants in or near the ACE, CTLA4, F2, FV (two variants), LPL and SERPINE1 genes were associated with preeclampsia. The results of this meta-analysis suggest that the following systems may play a role in the pathogenesis of preeclampsia: the renin-angiotensin system, coagulation and fibrinolysis, lipid metabolism, and inflammation. Functional studies are needed to elucidate the contribution of these variants and pathways to the pathogenesis of preeclampsia.

One genetic variant involved in the renin-angiotensin system remained associated with preeclampsia following the meta-analysis; the D (deletion) allele of ACE rs4646994. This finding is in line with a previous meta-analysis, which also revealed evidence of small study bias.[13] The ACE rs4646994 variant is known to be associated with increased activity of the angiotensin-converting enzyme[14], which could increase the conversion of angiotensin I into angiotensin II, thus affecting the regulation of blood pressure and blood volume.

Preeclampsia is associated with an exaggerated maternal inflammatory response. Therefore, various candidate genes involved in inflammation have been studied in the setting of preeclampsia; only one genetic variant in CTLA-4 remained associated with preeclampsia after our meta-analysis. No previous meta-analysis of this variant in the setting of preeclampsia has been published to date. CTLA-4 plays an important role in the negative regulation of T-cell proliferation and activation. The G allele of CTLA4

rs231775 is associated with reduced surface expression of CTLA-4, possibly leading to increased T-cell proliferation and activation.[15-16] Carrying the G allele of CTLA-4 could contribute to the maternal inflammatory response, thereby increasing the risk of developing preeclampsia.

With respect to genes involved in lipid metabolism, one variant in LPL remained associated with preeclampsia following the meta-analysis. No previous meta-analysis of this variant in the setting of preeclampsia has been published to date. The G allele of LPL rs268 is associated with reduced LPL activity and dyslipidemia.[17] Because dyslipidemia can contribute to endothelial cell dysfunction, carriers of the G allele may have an increased risk for developing preeclampsia.[18]

After meta-analysis, several factors involved in coagulation and fibrinolysis remained associated with preeclampsia, which is largely in line with previous meta-analyses.[19-20] Normal pregnancy is associated with the development of a hypercoagulable, hypofibrinolytic state, which is exaggerated in preeclampsia. Thrombophilias can increase the risk of developing preeclampsia via placental thrombosis and effects on both trophoblast growth and differentiation.[21] The A allele of F2 rs1799963 is associated with both higher prothrombin levels and an increased risk of thrombosis.[22-23] Two variants in FV are associated with preeclampsia. FV rs6025 causes activated protein C resistance and subsequent thrombophilic events. The A allele of FV rs6020 is also associated with a weak response to activated protein C[24] and can therefore cause a predisposition to thrombotic events. The SERPINE1 gene encodes the plasminogen activator inhibitor 1 (PAI-1) protein, which is an important inhibitor of fibrinolysis. The 4G allele of SERPINE1 rs1799889 is associated with elevated plasma levels of PAI-1.[25] By increasing the inhibition of fibrinolysis, this genetic variant may contribute to the exaggerated hypercoagulable state that characterizes women with preeclampsia.

In accordance to previous meta-analyses, many genetic variants did not remain associated with preeclampsia following meta-

analysis.[26-29] Perhaps this is due to the clinical variety of the cases that were included in the studies. Some studies, for instance, only included women with severe preeclampsia. It is, however, also likely that there is a true lack of association between preeclampsia and these genetic variants. Illustratively, publication bias can lead to the early publication of extreme, promising results, while subsequent (larger) studies often contradict these initial findings.[30-31]

It is important to note that epidemiological studies have revealed a relationship between preeclampsia and cardiovascular morbidity and mortality later in life.[32-36] Women who have had preeclampsia are more likely to develop cardiovascular disease, and preeclampsia and cardiovascular disease share various risk factors, including obesity, hypertension and diabetes.[1] Several of the variants that were associated with preeclampsia in this meta-analysis are also identified risk factors for developing cardiovascular disease. For example, the SERPINE1 rs1799889 variant, the FV rs6025 and the F2 rs1799963 variant are all associated with coronary disease.[37] In addition, carriers of select LPL alleles have an increased risk for developing coronary disease, and the rs268 variant of LPL is associated with adverse lipid profiles.[38] Thus, preeclampsia and cardiovascular disease have shared genetic risk factors as well as overlapping environmental risk factors. The presence of genetic variants may contribute to the increased risk of cardiovascular disease among women who have a history of preeclampsia. It would be interesting to investigate whether a combination of environmental and genetic risk factors can predict what women with preeclampsia will be more likely to develop cardiovascular disease later in life. In this way, preventive strategies that are tailored to the individual patient could be developed.

Our meta-analysis included only genetic variants that were associated with preeclampsia and for which independent replication was available. This approach has been described previously[39] and aims to reduce the likelihood of reporting false-positive associations. However, by selecting only the genetic variants that are reproducibly associated with preeclampsia, genetic variants with smaller effect

sizes might have been overlooked. For example, when variants were described in small studies that individually lacked sufficient power to detect modest effects, pooling these studies may have resulted in a significant association. Publication bias is an issue for concern in all meta-analyses. Studies yielding negative results are less likely to be published; as a result, authors might only report those associations that reach statistical significance, thereby omitting non-significant genetic associations. Together, these publication biases could result in an overrepresentation of significant effects. Therefore, the effect estimates that are reported in this study should be interpreted with caution, particularly when associations were based on a small number of studies and/or relatively small groups of participants. In addition, small study bias may have affected the outcomes of this meta-analysis. Small-study bias is a form of bias in which small studies regarding gene-disease associations report genetic effects that are not found—or are found at a much smaller magnitude—in larger studies. In addition to preeclampsia[13], evidence for small-study bias has previously been reported with respect to both neurological and cardiovascular diseases.[30;40] When many small studies that report false-positive associations are pooled in a meta-analysis, conclusions drawn from that meta-analysis are likely to be unreliable. Therefore, results that are drawn from meta-analyses in which there is evidence of small-study bias should be interpreted with caution. To investigate whether small-study bias played a role in our analyses, we subdivided the studies based on the number of cases and performed a stratified analysis. We found that the ACE rs4646994 variant appeared to be subject to small-study bias. The rs6020 variant in FV was reported in only two studies; therefore, no study size-based analysis was performed for this variant. For the remaining variants, no change—or only a slight change—in effect estimates was observed with increasing study size. Moreover, it is important to note that in this study, the genes with the largest effects were generally associated with wider confidence intervals, suggesting greater uncertainty in their effect estimates.

Because the precise etiology of preeclampsia remains unknown, effective strategies for preventing and treating preeclampsia are currently lacking. The identification of genetic variants associated with preeclampsia susceptibility can lead to novel biological insights[41] and result in new targets for the prevention and treatment of preeclampsia. However, in order to prevent (small-study) bias, genetic association studies should preferably be performed using large (multi-center) cohorts. Furthermore, most genes that were studied in the setting of preeclampsia were investigated because they were previously shown to be involved in hypertension or cardiovascular disease. An alternate method for identifying new susceptibility genes is to use a hypothesis-free approach such as genome-wide association studies. In addition, next-generation sequencing—which allows the sequencing of DNA at unprecedented speeds—may identify rare causal variants that are associated with preeclampsia. Aside from searching for novel susceptibility genes, future studies should also focus on assessing the relevance of previously detected and reproduced genetic variants.

In summary, this meta-analysis identified seven genetic variants in or near six different genes that are associated with preeclampsia. These genetic variants are likely to represent true associations. Moreover, this is the first study to report that preeclampsia and cardiovascular disease have genetic risk factors in common. Further studies investigating the relative contribution of these variants and the mechanisms by which they affect the risk of developing preeclampsia are warranted.

FIG 1 STUDY SELECTION PROCESS

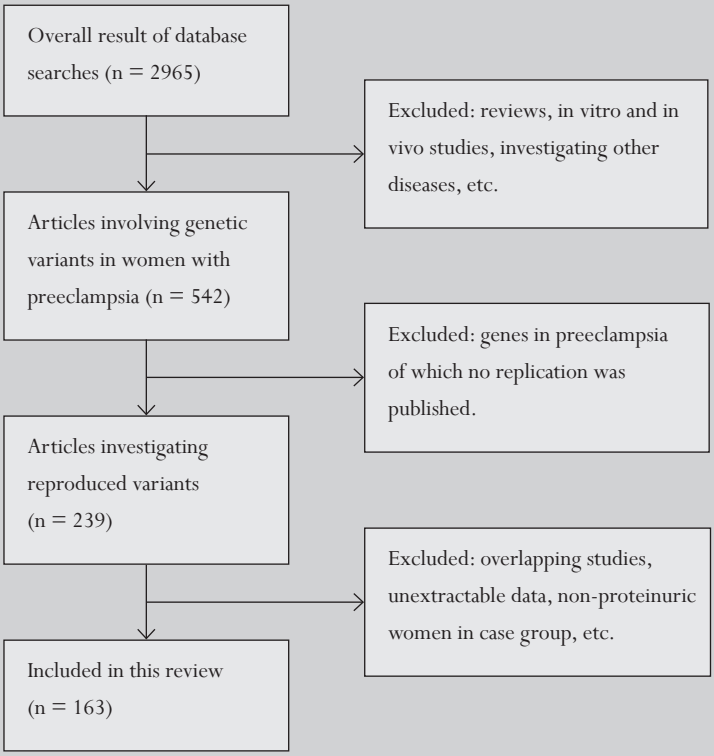

Figure 1: Flow chart illustrating how the studies were selected for the meta-analysis.

ODDS RATIOS FOR THE GENETIC VARIANTS THAT WERE REPRODUCIBLY ASSOCIATED WITH PREECLAMPSIA

FIG 2A

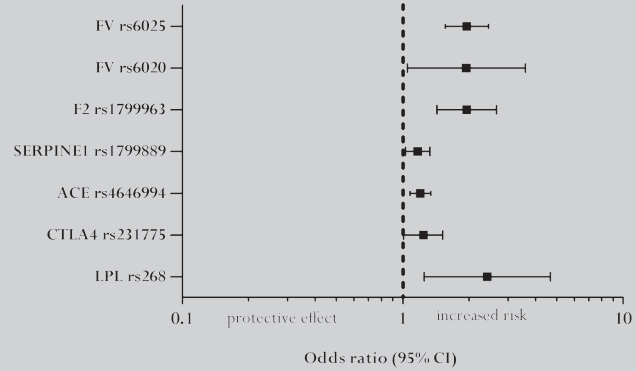

FIG 2B

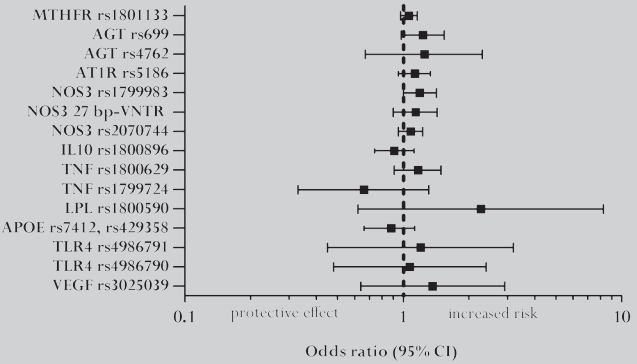

Figure 2 odds ratios (with 95% confidence intervals) for the genetic variants that were reproducibly associated with preeclampsia.

Figure 2A shows all the genetic variants that were reproduced in an independent study and significantly associated with preeclampsia following the meta-analysis.

Figure 2B shows all the genetic variants that were reproduced in an independent study, but were not significantly associated with preeclampsia following the meta-analysis.

TABLE 1 RANDOM-EFFECTS META-ANALYSIS OF REPRODUCED VARIANTS

VARIANT BY GENE	MINOR ALLELE	STUDIES (N)	CASES (N)	CONTROLS (N)	OR (95% CI)
ACE					
rs4646994	Deletion	20	2855	4582	1.20 (1.08-1.34)
AGT					
rs699	C	21	2104	4530	1.23 (0.98-1.54)
rs4762	T	5	497	1395	1.25 (0.67-2.30)
APOE					
rs429358, rs7412	E2	7	554	712	0.86 (0.66-1.13)
AT1R					
rs5186	C	9	886	1230	1.13 (0.95-1.33)
CTLA4					
rs231775	G	4	353	536	1.24 (1.01-1.52)
F2					
rs1799963	A	30	3329	4878	1.95 (1.43-2.66)
FV					
rs6020	A	2	266	336	1.94 (1.05-3.60)
rs6025	A	40	4373	6446	1.95 (1.56-2.45)
IL-10					
rs1800896	G	8	1075	1360	0.91 (0.74-1.12)
LPL					
rs1800590	G	3	395	579	2.27 (0.62-8.24)
rs268	G	4	530	933	2.42 (1.25-4.68)
MTHFR					
rs1801133	T	45	5418	7271	1.06 (0.97-1.16)
NOS3					
27 bp-VNTR in intron 4	4a	14	1593	2239	1.14 (0.90-1.43)
rs2070744	C	11	1571	2202	1.08 (0.95-1.23)
rs1799983	T	24	2825	4048	1.19 (1.00-1.42)
SERPINE1					
rs1799889	4G	11	1283	1661	1.17 (1.03-1.33)

FOR PREECLAMPSIA

I^2 (%)	P VALUE FOR FUNNEL PLOT ASYMMETRY*	LOCATION	FUNCTION/ CONSEQUENCE
47	0.044	in an intron	higher serum ACE levels [14]
81	0.116	in the gene	higher plasma angiotensinogen levels [42]
80	0.327	in the gene	conflicting data [42 43]
2	0.881	in the gene	hyperlipoproteinemia [44]
0	0.022	in the 3' untrans-lated region	increased response to angiotensin II [45]
3	1	in the gene	higher T-cell activation and proliferation rates [16]
8	0.133	in the 3'-untrans-lated region	elevated prothrombin levels [46]
60	0.317	in the gene	poor response to activated protein C [24]
34	0.456	in the gene	poor response to activated protein C [47]
64	0.621	in the promoter region	lower serum IL-10 levels [48]
72	0.602	in the 5' untrans-lated region	no changes in lipid profiles [38]
21	1	in the gene	adverse lipid profiles [38]
45	0.531	in the gene	elevated plasma homocysteine levels [49]
63	0.071	in an intron	altered nitrite and nitrate levels [50]
28	0.484	in the promoter region	reduced eNOS gene promoter activity [51]
68	0.960	in the gene	reduced nitrate, nitrite and nitric oxide production [52 53]
10	0.102	in the promoter region	higher PAI-1 levels [25 54 55]

TABLE 1 *CONTINUED*

VARIANT BY GENE	MINOR ALLELE	STUDIES (N)	CASES (N)	CONTROLS (N)	OR (95% CI)
TLR4					
rs4986790	G	4	723	614	1.07 (0.48-2.40)
rs4986791	T	3	614	461	1.20 (0.45-3.20)
TNF-alpha					
rs1800629	A	12	1592	1837	1.17 (0.91-1.49)
*rs*1799724	T	3	390	385	0.66 (0.33-1.31)
VEGF					
rs3025039	T	3	377	514	1.36 (0.64-2.91)

* Begg test for funnel plot asymmetry, which is suggestive of publication bias

ACE: angiotensin converting enzyme
AGT: angiotensinogen
APOE: apolipoprotein E
AT1R: angiotensin II receptor type 1
CTLA: cytotoxic T-lymphocyte-associated protein 4
F2: factor 2
FV: factor V
IL10: interleukin 10
LPL: lipoprotein lipase
MTHFR: methylenetetrahydrofolate reductase
NOS3: nitric oxide synthase 3
SERPINE: serine peptidase inhibitor
TLR: toll like receptor
TNF: tumor necrosis factor
VEGF: vascular endothelial growth factor

I^2 (%)	P VALUE FOR FUNNEL PLOT ASYMMETRY*	LOCATION	FUNCTION / CONSEQUENCE
78	0.497	in the gene	dampened inflammatory response [56]
79	0.602	in the gene	dampened inflammatory response [56]
55	0.237	in the gene	higher TNF-alpha gene expression [57]
85	0.602	near the gene	higher TNF-alpha serum levels [58]
88	0.602	in the gene	lower VEGF levels [59 60]

TABLE 2 REFERENCES OF INCLUDED ARTICLES, PER GENETIC VARIANT

VARIANT BY GENE	REFERENCES
ACE	
rs4646994	61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 13 13 78 79
AGT	
rs699	61 62 80 63 64 65 81 82** 83 84 85 86 75 76 87 79 88 89 90
rs4762	65 81 84 75 79
APOE	
rs429358, rs7412	91 92 93 94 95 96 97
AT1R	
rs5186	98 63 64 71 99 100 75 77 101
CTLA4	
rs231775	102 103 104 105
F2	106 107 108 109 110 111 112 113 114 115 116 117 118 119
rs1799963	120 121 122 123 124 † 125 126 127 128 129 130 131 132 133 87 134
FV	
rs6020	135 136
rs6025	62 106 107 108 109 137 110 138 111 112 139 113 115 135 116 117 119 120 121 122 140 141 126 142 127 128 143 129 130 131 144 95 145 146 147 148 133 87 149 134
IL-10	
rs1800896	150 151 152 153 154 155 156 157
LPL	
rs1800590	158 159 160
rs268	92 158 159 161
MTHFR	62 162 163 164 110 138 165 112 113 114 115 116 117 166
rs1801133	119 167 120 168 121 141 169 170 171 126 127 130 131 144 172 146 173 174 175 176*** 177 178 148 179 97 136 180 181 89
NOS3	
27 bp-VNTR in intron 4	61 80 63 182 183 184 185 186 187 188 189 190 191 192
rs2070744	61 183 184 193 187 188 189 194 190 87 192
rs1799983	61 195 182 183 184 196 197 193 198 199 200 186 160 188 189 190 201 202 87 203 204 205 206 192
SERPINE1	
rs1799889	110 165 115 116 196 121 126 131 207 87 208

CONTINUED

VARIANT BY GENE	REFERENCES
TLR4	
rs4986790	209 210 211 212
rs4986791	210 211 212
TNF-alpha	
rs1800629	213 214 150 152 215 216 153 217 218 155 219 220 221 222 157
*rs*1799724	213 223 220
VEGF	
rs3025039	193 224 225

** Two datasets

*** Three datasets

† Similar control group to another article (Kupferminc et al., 2000); this and the subsequent citation (Kupferminc et al., 2000) are considered to be one dataset.

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