Endothelial pathology in preeclampsia

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Chapter 2

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 pre-eclampsia. We identified 22 replicated genetic variants, of which 7 remained significantly associated with pre-eclampsia 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 pre-eclampsia. Importantly, many of these variants are also risk factors for developing cardiovascular disease, revealing that pre-eclampsia and cardiovascular disease have shared genetic risk factors. The contribution of the identified genetic variants in the pathogenesis of pre-eclampsia 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 (Steegers *et al.*, 2010). Furthermore, women with preeclampsia have an increased risk of developing cardiovascular disease later in life (Bellamy *et al.*, 2007). 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 (Arngrimsson *et al.*, 1990, Chesley *et al.*, 1986, Cincotta *et al.*, 1998, Esplin *et al.*, 2001, Nilsson *et al.*, 2004, Sutherland *et al.*, 1981). Furthermore, the prevalence of preeclampsia differs between various ethnic groups (Steegers *et al.*, 2010). However, the underlying genetics are complex, and it is currently unclear which 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 (Chappell and Morgan, 2006). 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 (Ioannidis *et al.*, 2001). 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 (Brown et al., 2001). 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 (AB and RT)

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 (Higgins *et al.*, 2003). Bias due to small study size was tested using a stratified analysis for study size as described previously (Serrano *et al.*, 2006). 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 pre-eclampsia (Fig. 1). We identified 22 polymorphisms in 15 genes that were reproducibly associated with pre-eclampsia. 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 pre-eclampsia (Fig. 2a). The remaining 15 reproduced variants were not associated with preeclampsia following meta-analysis (Fig. 2b). The odds ratios of the significant associations with pre-eclampsia 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 Supplementary data, Table II show that some studies included only women with severe pre-eclampsia.

Genetic variants involved in coagulation and fibrinolysis

Five genetic variants in four genes that are related to coagulation and fibrinolysis were associated reproducibly with pre-eclampsia. Of these five variants, four were still associated with pre-eclampsia after the meta-

analysis. Two variants in coagulation factor V (FV), rs6025 and rs6020, remained associated with pre-eclampsia in the meta-analysis. The variant rs6025, which is also known as Factor V Leiden, was a frequently studied polymorphism in pre-eclampsia, 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 variant rs6020 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 variant rs1799963 of the coagulation factor II (F2) gene (also known as prothrombin) was investigated in 30 studies and was associated with pre-eclampsia 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 variant rs1799889 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 the 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 pre-eclampsia, 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. Both rs699 and rs4762 variants in angiotensinogen (AGT) were studied in 21 and 5 studies, respectively. The variant rs699 was not associated with pre-eclampsia after meta-analysis, with a pooled odds ratio of 1.23 (95% CI 0.98–1.54). The variant rs4762 was also not associated with pre-eclampsia, 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 pre-eclampsia after meta-analysis.

Genetic variants involved in oxidative stress

Three variants in the nitric oxide synthase 3 (NOS3) gene were reproducibly associated with pre-eclampsia, but none was still associated with pre-eclampsia 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 pre-eclampsia 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 pre-eclampsia 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 pre-eclampsia but were not associated with pre-eclampsia 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 variants rs1800590 and rs268 in the lipoprotein lipase (LPL) gene were reproduced in pre-eclampsia, but only rs268 remained associated with pre-eclampsia 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 pre-eclampsia following the meta-analysis. The rs3025039 variant in the vascular endothelial growth factor (VEGF) gene was reproduced in pre-eclampsia, 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 pre-eclampsia. Meta-analysis for several individual genetic variants in the setting of pre-eclampsia has been performed previously. However, the present study provides the first complete and comprehensive overview of all genetic variants that are reproducibly associated with pre-eclampsia. These data may shed light on the pathogenesis of pre-eclampsia 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 pre-eclampsia. The results of this meta-analysis suggest that the following systems may play a role in the pathogenesis of pre-eclampsia: 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 pre-eclampsia.

One genetic variant involved in the renin–angiotensin system remained associated with pre-eclampsia 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 (Serrano et al., 2006). The ACE rs4646994 variant is known to be associated with increased activity of the angiotensinconverting enzyme (Sayed-Tabatabaei et al., 2006), which could increase the conversion of angiotensin I into angiotensin II, thus affecting the regulation of blood pressure and blood volume.

Pre-eclampsia is associated with an exaggerated maternal inflammatory response. Therefore, various candidate genes involved in inflammation have been studied in the setting of pre-eclampsia; only one genetic variant in CTLA-4 remained associated with pre-eclampsia after our meta-analysis. No previous meta-analysis of this variant in the setting of pre-eclampsia 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 (Teft et al., 2006; Sun et al., 2008). Carrying the G allele of CTLA-4 could contribute to the maternal

inflammatory response, thereby increasing the risk of developing pre-eclampsia.

With respect to genes involved in lipid metabolism, one variant in LPL remained associated with pre-eclampsia following the meta-analysis. No previous meta-analysis of this variant in the setting of pre-eclampsia has been published to date. The G allele of LPL rs268 is associated with reduced LPL activity and dyslipidemia (Fisher et al., 1997). Because dyslipidemia can contribute to endothelial cell dysfunction, carriers of the G allele may have an increased risk for developing pre-eclampsia (Mayret-Mesquiti et al., 2007).

After meta-analysis, several factors involved in coagulation and fibrinolysis remained associated with pre-eclampsia, which is largely in line with previous meta-analyses (Lin and August, 2005; Dudding et al., 2008). Normal pregnancy is associated with the development of a hypercoagulable, hypofibrinolytic state, which is exaggerated in pre-eclampsia. Thrombophilias can increase the risk of developing pre-eclampsia via placental thrombosis and effects on both trophoblast growth and differentiation (Isermann et al., 2003). The A allele of F2 rs1799963 is associated with both higher prothrombin levels and an increased risk of thrombosis (Kyrle et al., 1998; Ceelie et al., 2004). Two variants in FV are associated with pre-eclampsia. 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 (Le et al., 2000) 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 (Ye et al., 1995). By increasing the inhibition of fibrinolysis, this genetic variant may contribute to the exaggerated hypercoagulable state that characterizes women with pre-eclampsia.

In accordance to previous meta-analyses, many genetic variants did not remain associated with pre-eclampsia following meta-analysis (Medica et al., 2007; Bombell and McGuire, 2008; Molvarec et al., 2008a, b, c; Xie et al., 2011). Perhaps this is due to the clinical variety of the cases that were included in the studies. Some studies, for instance, included only women with severe

pre-eclampsia. It is, however, also likely that there is a true lack of association between pre-eclampsia 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 (Ioannidis and Trikalinos, 2005; Healy et al., 2006).

It is important to note that epidemiological studies have revealed a relationship between pre-eclampsia and cardiovascular morbidity and mortality later in life (Jonsdottir et al., 1995; Hannaford et al., 1997; Irgens et al., 2001; Smith et al., 2001; Rodie et al., 2004). Women who have had pre-eclampsia are more likely to develop cardiovascular disease, and pre-eclampsia and cardiovascular disease share various risk factors, including obesity, hypertension and diabetes (Steegers et al., 2010). 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 variants are all associated with coronary disease (Ye et al., 2006). 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 (Sagoo et al., 2008). Thus, pre-eclampsia 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 pre-eclampsia. It would be interesting to investigate whether a combination of environmental and genetic risk factors can predict what women with pre-eclampsia 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 pre-eclampsia and for which independent replication was available. This approach has been described previously (Mooyaartetal.,2011)and aims to reduce the likelihood of reporting false-positive associations. However, by selecting only the genetic variants that are reproducibly associated with pre-eclampsia, 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 pre-eclampsia (Serrano et al., 2006), evidence for small-study bias has previously been reported with respect to both neurological and cardiovascular diseases (Keavney et al., 2000; Healy et al., 2006). 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 (McCarthy *et al.*, 2008) 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. 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.

SUPPLEMENTARY DATA

Supplementary data are available *at http://humupd.oxfordjournals.org/.*

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TABLES

Table I. Random-effects meta-analysis of reproduced variants for preeclampsia

Variant by gene	Minor allele	Studies (n)	Cases (n)	Control subjects (n)	OR (95% CI)	I^2 (%)	p value for funnel plot asymmetry*	Location	Function/ consequence
ACE									
rs4646994	Deletion	20	2855	4582	1.20 (1.08-1.34)	47	0.044	In an intron	Higher serum ACE levels (Sayed-Tabatabaei et al., 2006)
AGT									
rs699	C	21	2104	4530	1.23 (0.98-1.54)	81	0.116	In the gene	Higher plasma angiotensinogen levels (Jeunemaitre et al.,1992)
rs4762	T	5	497	1395	1.25 (0.67-2.30)	80	0.327	In the gene	Conflicting data(Balam-Ortiz et al.,2011 ; Jeunemaitre et al., 1992)
APOE									
rs429358 rs7412	E2	7	554	712	0.86 (0.66-1.13)	2	0.881	In the gene	Hyperlipoproteinemia (Utermann,1987)
AT1R									
rs5186	C	9	886	1230	1.13 (0.95-1.33)	0	0.022	In the 3' untranslated region	Increased response to angiotensin II (van Geel et al., 2000)

Variant by gene	Minor allele	Studies (n)	Cases (n)	Control subjects (n)	OR (95% CI)	I^2 (%)	p value for funnel plot asymmetry*	Location	Function/ consequence
CTLA4									
rs231775	G	4	353	536	1.24 (1.01-1.52)	3	1	In the gene	Higher T-cell activation and proliferation rates (Sun et al., 2008)
F2									
rs1799963	A	30	3329	4878	1.95 (1.43-2.66)	8	0.133	In the 3' untranslated region	Elevated prothrombin levels (Poort et al.,1996)
FV									
rs6020	A	2	266	336	1.94 (1.05-3.60)	60	0.317	In the gene	Poor response to activated protein C (Le et al, 2000)
rs6025	A	40	4373	6446	1.95 (1.56-2.45)	34	0.456	In the gene	Poor response to activated protein C (Bertina et al.,1994)

Variant by gene	Minor allele	Studies (n)	Cases (n)	Control subjects (n)	OR (95% CI)	I^2 (%)	p value for funnel plot asymmetry*	Location	Function/ consequence
IL-10									
rs1800896	G	8	1075	1360	0.91 (0.74-1.12)	64	0.621	In the promotor region	Lower serum IL-10 levels (Wang et al, 2011)
LPL									
rs1800590	G	3	395	579	2.27 (0.62-8.24)	72	0.602	In the 5' untranslated region	No changes in lipid profiles (Sagoo et al, 2008)
rs268	G	4	530	933	2.42 (1.25-4.68)	21	1	In the gene	Adverse lipid profiles (Sagoo et al, 2008)
MTHFR									
rs1801133	T	45	5418	7271	1.06 (0.97-1.16)	45	0.531	In the gene	Elevated plasma homocysteine levels (Frosst et al, 1995)

Variant by gene	Minor allele	Studies (n)	Cases (n)	Control subjects (n)	OR (95% CI)	I^2 (%)	p value for funnel plot asymmetry*	Location	Function/ consequence
NOS3									
27bp repeat	4a	14	1593	2239	1.14 (0.90-1.43)	63	0.071	In an intron	Altered nitrite and nitrate levels (Wang and Wang, 2000)
rs2070744	C	11	1571	2202	1.08 (0.95-1.23)	28	0.484	In the promotor region	Reduced eNOS gene promotor activity (Nakayama et al., 1999)
rs1799983	T	24	2825	4048	1.19 (1.00-1.42)	68	0.960	In the gene	Reduced nitrate, nitrite and nitric oxide production (Sofowora et al, 2001; Veldman et al, 2002)
SERPINE1									
rs1799889	4G	11	1283	1661	1.17 (1.03-1.33)	10	0.102	In the promotor region	Higher PAI-1 levels (Lin et al, 2009; Rallidis et al, 2010; Ye et al, 1995)

Variant by gene	Minor allele	Studies (n)	Cases (n)	Control subjects (n)	OR (95% CI)	I^2 (%)	p value for funnel plot asymmetry*	Location	Function/ consequence
TLR4									
rs4986790	G	4	723	614	1.07 (0.48-2.40)	78	0.497	In the gene	Dampened inflammatory response (Kiechi et al, 2002)
rs4986791	T	3	614	461	1.20 (0.45-3.20)	79	0.602	In the gene	Dampened inflammatory response (Kiechi et al, 2002)
TNF-alpha									
rs1800629	A	12	1592	1837	1.17 (0.91-1.49)	55	0.237	In the gene	Higher TNF-alpha gene expression (Kroeger et al, 1997)
rs1799724	T	3	390	385	0.66 (0.33-1.31)	85	0.602	Near the gene	Higher TNF-alpha serum levels (Puthotu et al, 2009)
VEGF									
rs3025039	T	3	377	514	1.36 (0.64-2.91)	88	0.602	In the gene	Lower VEGF levels (Al-Habboubi et al, 2011; Ruggiero et al, 2011)

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

Table II. References of the included articles, per genetic variant

Variant by gene	
ACE	
rs4646994	Aggarwal et al., (2010) Aggarwal et al., (2011) Benedetto et al., (2007) Bouba et al., (2003) Choi et al., (2004) Galao et al., (2004) Gurdol et al., (2004) Heiskanen et al., (2001) Kaur et al., (2005) Kobashi et al., (2005) Li et al., (2007) Mando et al., (2009) Miskovic et al., (2008) Morgan et al., (1999) Procopciuc et al., (2009) Roberts et al., (2004) Salimi et al., (2011) Serrano et al., (2006)2006 Serrano et al., (2006), Uma et al., (2010) Wang et al., (2006)
AGT	
rs699	Aggarwal et al., (2010) Aggarwal et al., (2011) Bashford et al., (2001) Benedetto et al., (2007) Bouba et al., (2003) Choi et al., (2004) Dissanayake et al., (2009) Guo et al., (1997)** Jenkins et al., (2008) Knyrim et al., (2008) Kobashi et al., (1999) Morgan et al., (1999) Procopciuc et al., (2009) Roberts et al., (2004) Tempfer et al., (2004) Wang et al., (2006) Ward et al., (1993) Yoshida et al., (2008) Zhang et al., (2003)
rs4762	Choi et al., (2004) Dissanayake et al., (2009) Knyrim et al., (2008) Procopciuc et al., (2009) Wang et al., (2006)
APOE	
rs429358, rs7412	Belo et al., (2004) Bernard et al., (2007) Chikosi et al., (2000) Francoual et al., (2002) Nagy et al., (1998) Procopciuc et al., (2011) Stiefel et al., (2009)
AT1R	
rs5186	Akbar et al., (2009) Benedetto et al., (2007) Bouba et al., (2003) Li et al., (2007) Morgan et al., (1998) Plummer et al., (2004) Procopciuc et al., (2009) Salimi et al., (2011) Seremak-Mrozikiewicz et al., (2005)
CTLA4	
rs231775	Best et al., (2011) Jaaskelainen et al., (2008) Pendeloski et al., (2011) Samsami et al., (2005)

Variant by gene	
F2	
rs1799963	Agorastos et al., (2002) Alfirevic et al., (2001) Benedetto et al., (2002) Best et al., (2009) Dalmaz et al., (2006) de Groot et al., (1999) Demir et al., (2006) Dogan et al., (2011) Dusse et al., (2007) Fabbro et al., (2003) Gerhardt et al., (2005) Grandone et al., (1999) Higgins et al., (2000) Hiltunen et al., (2009) Jarvenpaa et al., (2006) Kankova et al., (2000) Karakantza et al., (2008) Kupferminc et al., (1999) Kupferminc et al., (2000) † Kupferminc et al., (2000) Larciprete et al., (2007) Livingston et al., (2001) Malek-Khosravi et al., (2011) Mello et al., (2005) Mendilcioglu et al., (2011) Morrison et al., (2002) O'Shaughnessy et al., (2001)2001 Seremak-Mrozikiewicz et al., (2010) Tempfer et al., (2004) Yalinkaya et al., (2006)
FV	
rs6020	Faisel et al., (2004) Watanabe et al., (2001)
rs6025	Aggarwal et al., (2011) Agorastos et al., (2002) Alfirevic et al., (2001) Benedetto et al., (2002) Best et al., (2009) Currie et al., (2002) Dalmaz et al., (2006) Davalos et al., (2005) de Groot et al., (1999) Demir et al., (2006) Dizon-Townson et al., (1996) Dogan et al., (2011) Fabbro et al., (2003) Faisel et al., (2004) Gerhardt et al., (2005) Grandone et al., (1999) Hiltunen et al., (2009) Jarvenpaa et al., (2006) Kankova et al., (2000) Karakantza et al., (2008) Karimi et al., (2012 Kim et al., (2001) Larciprete et al., (2007) Lindoff et al., (1997) Livingston et al., (2001) Malek-Khosravi et al., (2011) Mello et al., (1999) Mello et al., (2005) Mendilcioglu et al., (2011) Morrison et al., (2002) Murphy et al., (2000) Nagy et al., (1998) Omar et al., (2008) O'Shaughnessy et al., (1999) Prasmusinto et al., (2004) Rigo et al., (2000) Seremak-Mrozikiewicz et al., (2010) Tempfer et al., (2004) von Tempelhoff et al., (2000) Yalinkaya et al., (2006)
IL-10	
rs1800896	Daher et al., (2006) de Groot et al., (2004) de Lima et al., (2009) Haggerty et al., (2005) Kamali-Sarvestani et al., (2006) Mirahmadian et al., (2008) Stonek et al., (2008) Vural et al., (2010)

Variant by gene	
LPL	
rs1800590	Hubel et al., (1999) Kim et al., (2001) Pappa et al., (2011)
rs268	Bernard et al., (2007) Hubel et al., (1999) Kim et al., (2001) Zhang et al., (2006)
MTHFR	
rs1801133	Aggarwal et al. (2011), Also-Rallo et al. (2005), Canto et al. (2008), Chikosi et al. (1999), Dalmaz et al. (2006), Davalos et al. (2005), De Maat et al. (2004), Demir et al. (2006), Dogan et al. (2011), Dusse et al. (2007), Fabbro et al. (2003), Gerhardt et al. (2005), Grandone et al. (1999), Hill et al. (2011), Hiltunen et al. (2009), Jaaskelainen et al. (2006), Jarvenpaa et al. (2006), Kaiseret al. (2001), Kankova et al. (2000), Kim et al. (2001), Klai et al. (2011), Kobashi et al. (2000), Laivuori et al. (2000), Larciprete et al. (2007), Livingston et al.(2001), Mendilcioglu et al.(2011), Morrison et al. (2002), Murphy et al. (2000), Nagy et al. (2007) ,O'Shaughnessy et al. (1999), Pegoraro et al. (2004), Perez-Mutul et al. (2004), Powers et al. (1999), Prasmusinto et al. (2002)***, Procopciuc et al. (2010), Rajkovic et al. (2000), Rigo et al. (2000), Sohda et al. (1997), Stiefel et al. (2009), Watanabe et al. (2001), Williams et al.(2004),Yilmaz et al. (2004), Yoshida et al. (2008).
NOS3	
27bp repeat	Aggarwal et al., (2010) Bashford et al., (2001) Benedetto et al., (2007) Chen et al., (2007) Diaz-Olguin et al., (2011) Fatini et al., (2006) Grandone et al., (2003) Ozturk et al., (2011) Salimi et al., (2011) Sandrim et al., (2008) Sandrim et al., (2010) Serrano et al., (2004) Tempfer et al., (2001) Zdoukopoulos et al., (2011)
rs2070744	Aggarwal et al., (2010) Diaz-Olguin et al., (2011) Fatini et al., (2006) Kim et al., (2008) Salimi et al., (2011) Sandrim et al., (2008) Sandrim et al., (2010) Seremak-Mrozikiewicz et al., (2011) Serrano et al., (2004) Tempfer et al., (2004) Zdoukopoulos et al., (2011)

Variant by gene	
rs1799983	Aggarwal et al., (2010) Best et al., (2010) Chen et al., (2007) Diaz-Olguin et al., (2011) Fatini et al., (2006) Hakli et al., (2003) Kim et al., (2006) Kim et al., (2008) Kobashi et al., (2001) Landau et al., (2004) Nishizawa et al., (2009) Ozturk et al., (2011) Pappa et al., (2011) Sandrim et al., (2008) Sandrim et al., (2010) Serrano et al., (2004) Sharma et al., (2011) Singh et al., (2010) Tempfer et al., (2004) Turan et al., (2010) Yaghmaei et al., (2011) Yoshimura et al., (2000) Yoshimura et al., (2003) Zdoukopoulos et al., (2011)
SERPINE1	
rs1799889	Dalmaz et al., (2006) De Maat et al., (2004) Fabbro et al., (2003) Gerhardt et al., (2005) Hakli et al., (2003) Kankova et al., (2000) Larciprete et al., (2007) Morrison et al., (2002) Pegoraro et al., (2003) Tempfer et al., (2004) Yamada et al., (2000)
TLR4	
rs4986790	Franchim et al., (2011) Molvarec et al., (2008) van Rijn et al., (2008) Xie et al., (2010)
rs4986791	Molvarec et al., (2008) van Rijn et al., (2008) Xie et al., (2010)
TNF-alpha	
rs1800629	Canto-Cetina et al., (2007) Chen et al., (1996) Daher et al., (2006) de Lima et al., (2009) Dizon-Townson et al., (1998) Freeman et al., (2004) Haggerty et al., (2005) Kaiser et al., (2004) Levesque et al., (2004) Mirahmadian et al., (2008) Molvarec et al., (2008) Pazarbasi et al., (2007) Saarela et al., (2005) Stonek et al., (2008) Vural et al., (2010)
rs1799724	Canto-Cetina et al., (2007) Heiskanen et al., (2002) Pazarbasi et al., (2007)
VEGF	
rs3025039	Kim et al., (2008) Papazoglou et al., (2004) Shim et al., (2007)

** 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

FIGURES & LEGENDS

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

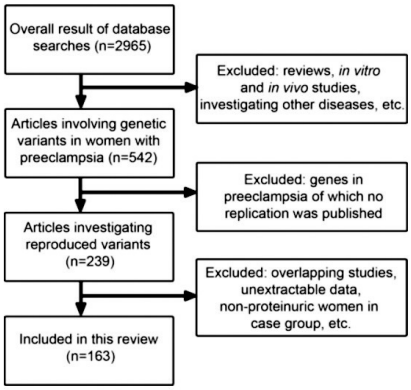
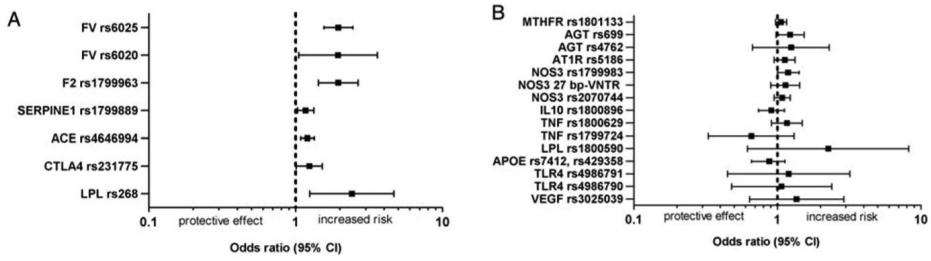


Figure 2. Odds ratios (with 95% confidence intervals) for the genetic variants that were reproducibly associated with preeclampsia.



A. All genetic variants that were reproduced in an independent study and significantly associated with preeclampsia following the meta-analysis.
B. All genetic variants that were reproduced in an independent study, but were not significantly associated with preeclampsia following the meta-analysis.