

# The role of genetics in pre-eclampsia and potential pharmacogenomic interventions

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**Abstract:** The pregnancy-specific condition pre-eclampsia not only affects the health of mother and baby during pregnancy but also has long-term consequences, increasing the chances of cardiovascular disease in later life. It is accepted that pre-eclampsia has a placental origin, but the pathogenic mechanisms leading to the systemic endothelial dysfunction characteristic of the disorder remain to be determined. In this review we discuss some key factors regarded as important in the development of pre-eclampsia, including immune maladaptation, inadequate placentation, oxidative stress, and thrombosis. Genetic factors influence all of these proposed pathophysiological mechanisms. The inherited nature of pre-eclampsia has been known for many years, and extensive genetic studies have been undertaken in this area. Genetic research offers an attractive strategy for studying the pathogenesis of pre-eclampsia as it avoids the ethical and practical difficulties of conducting basic science research during the preclinical phase of pre-eclampsia when the underlying pathological changes occur. Although pharmacogenomic studies have not yet been conducted in pre-eclampsia, a number of studies investigating treatment for essential hypertension are of relevance to therapies used in pre-eclampsia. The pharmacogenomics of antiplatelet agents, alpha and beta blockers, calcium channel blockers, and magnesium sulfate are discussed in relation to the treatment and prevention of pre-eclampsia. Pharmacogenomics offers the prospect of individualized patient treatment, ensuring swift introduction of optimal treatment whilst minimizing the use of inappropriate or ineffective drugs, thereby reducing the risk of harmful effects to both mother and baby.

**Keywords:** pre-eclampsia, pharmacogenetics, placenta, trophoblast, genetics

## Introduction

One of the major aims of the human genome project and subsequent disease initiatives was the discovery of new pharmaceutical targets. With the current advances in our understanding of genetics and the ever-improving sequencing technologies available we are now at an exciting time not just for research, but also for the translation of research results into potential health benefits due to the evolution of pharmacogenomics and the development of personalized medicine. The focus of this review is to provide a comprehensive overview of the genetic and pharmacogenetic aspects of pre-eclampsia. An in-depth review of the pathophysiology of the disorder is outside the scope of this review.<sup>1</sup>

Genetic involvement in the pregnancy-specific condition pre-eclampsia has long been recognized but determining the mode of inheritance and the genes involved has not been straightforward. Research is continuing to unravel the genetic component of pre-eclampsia, aiding understanding of the pathophysiological changes that

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occur in this disorder. The importance of these findings in understanding the pathogenesis of pre-eclampsia cannot be overstated. The trigger for pre-eclampsia arises in the placental bed early in pregnancy, at a time and location that precludes basic science research for ethical and practical reasons. Molecular genetics research can therefore provide clues to the primary causes of pre-eclampsia that are unavailable by other methods. Potential opportunities for pharmacogenomic interventions are considered in the light of evidence from other related diseases.

## The impact of pre-eclampsia

Pre-eclampsia is a leading cause of maternal and perinatal morbidity and mortality, affecting between 0.4% and 2.8% of all pregnancies in developed countries and many more in developing countries, leading to over 8 million cases worldwide per year.<sup>2</sup> Although the definition of pre-eclampsia focuses on the occurrence of hypertension and proteinuria, this is a multisystem disorder that may affect the brain, lungs, kidney, and liver. Not only does pre-eclampsia impact on maternal health but the growth and development of the fetus are frequently compromised, and pre-eclampsia has long-term impacts on the health of both the mother and offspring.<sup>3-5</sup> A two-stage model for pre-eclampsia has been proposed.<sup>6</sup> The first stage is reduced placental perfusion, secondary to abnormal implantation and development of placental vasculature. The second stage is the maternal response to this condition, characterized by widespread inflammation and maternal endothelial cell dysfunction.<sup>7</sup> A number of pregnant women have pre-existing risk factors that make them more susceptible to the development of pre-eclampsia and the other hypertensive disorders of pregnancy (see Table 1).

Studies examining plasma and tissue samples following the onset of pre-eclampsia have confirmed the presence of oxidative stress, and the release of endothelial proteins and pro-inflammatory cytokines,<sup>8</sup> but discriminating between causal factors and secondary responses presents significant challenges. In this regard, genetic studies of pre-eclampsia offer an advantage in that genotype remains constant and is not affected by the disease process.

## Genetic basis of pre-eclampsia

Genetic studies of pre-eclampsia have been confounded by the problem that there is currently no universally accepted definition of the disorder, with several internationally recognized definitions available.<sup>9</sup> The general consensus diagnosis of pre-eclampsia is a blood pressure of  $\geq 140/90$  mmHg

**Table 1** Risk factors for pre-eclampsia

Risk factors for pre-eclampsia	
Immunological	Nulliparity Primipaternity Donor sperm/oocyte
Obstetric	In vitro fertilization treatment Multiple pregnancy Previous adverse obstetric history – gestational hypertension, pre-eclampsia, fetal growth restriction, abruption placentae, perinatal death
Pre-existing conditions	Chronic hypertension Renal disease Type 2 diabetes Thrombophilia syndromes Autoimmune disorder
Abnormal uterine Doppler	Resistance index 0.58 Presence of diastolic notch
Maternal factors	Extremes of maternal age Black ethnicity Obesity

measured on at least two occasions separated by 6 hours after the twentieth week of pregnancy in a previously normotensive woman, accompanied by significant proteinuria (300 mg/L or 500 mg/24 hours) in the absence of a urinary tract infection.<sup>9</sup> In pre-eclampsia the elevated blood pressure returns to normal 6 to 12 weeks following delivery. Pre-eclampsia can progress rapidly, at times without warning, to the life-threatening convulsive condition eclampsia. Development of pre-eclampsia begins with a loss of vascular refractoriness to vasoactive agents followed by vasoconstriction, resulting in a decrease in intravascular volume. Fluid is then passed across the “leaky” capillaries to the extravascular space. Pre-eclampsia is subsequently characterized by a generalized dysfunction of the maternal endothelium<sup>10</sup> with impairment of endothelium-dependent relaxation in maternal resistance arteries.<sup>11</sup>

A genetic component for pre-eclampsia has been indicated since the observation in the nineteenth century of a clustering of cases within families.<sup>12</sup> Challenges to defining this genetic involvement include the fact that the phenotype is expressed only in parous females, and also the need to evaluate the genotypes of both the mother and her fetus.

## Pre-eclampsia is a complex genetic disorder

It is now accepted that pre-eclampsia is a complex genetic disorder, occurring as the result of variants at different loci, which individually have small effects but collectively contribute to an individual’s susceptibility to disease. It is

probable that no single gene or variant will be identified that is responsible for all cases of pre-eclampsia, although different variants may prove to be associated with subsets of disease, such as early onset pre-eclampsia with fetal growth restriction. In agreement with this is the recent study that identifies three separate subgroups of pre-eclampsia based on expression of plasma membrane proteins involved in angiogenesis (group 1), mitogen-activated protein kinase signaling (group 2), and hormone biosynthesis and metabolism (group 3).<sup>13</sup> Environmental factors, such as psychological stress<sup>14</sup> and vitamin D deficiency,<sup>15</sup> also modify an individual's risk of developing pre-eclampsia, determining whether variants with low penetrance result in phenotypic manifestation of the disease.

## Deciphering the relative contribution of fetal and maternal genes

Investigation of both fetal and maternal genotypes is essential to better our understanding of the genetics of pre-eclampsia. An undisputable role of the placenta in the primary pathogenesis of pre-eclampsia is clear, indicating a fetal contribution to susceptibility to the disorder.<sup>16</sup> Placental development in pre-eclampsia is superficial. Normal placental development is characterized by invasion of cytotrophoblast cells into the maternal decidua and inner third of the myometrium. Cytotrophoblast invasion serves to anchor the placenta to the wall of the uterus and also to gain access to the maternal vasculature. Endovascular trophoblast invasion enables the onset of placental circulation. The endovascular trophoblast cells also serve to trigger the process of physiologic conversion which is characterized by a loss of elastic fibers and smooth muscle cells due to proteolytic activity of the invasive endovascular trophoblast cells. Furthermore, spiral artery walls are replaced by intramural fibrin and fibrinoid, which is produced by the trophoblast cells, resulting in a considerable increase in the luminal diameter. These changes serve to transform the originally flexible vessels into rigid high-capacitance vessels which are incapable of constricting. Both extravillous and endovascular cytotrophoblast invasion is deficient in pre-eclampsia resulting in spiral arteries retaining their original architecture which precludes an adequate vascular response to the demands from the fetus for increased blood flow.<sup>17</sup> Decreased expression of laminin receptor 1 by cytotrophoblasts and syncytiotrophoblasts has been found in pre-eclampsia which may have a role in the shallow trophoblastic invasion in pre-eclampsia.<sup>18</sup> A role for paternally inherited fetal genes in the determination of clinical phenotype is evident from reports of higher rates of

pre-eclampsia in pregnancies fathered by men who were born of a pre-eclamptic pregnancy.<sup>16,19</sup>

It has been suggested that an excessive or atypical maternal immune response to invading trophoblast may be the cause of the placental stage of pre-eclampsia, resulting in impaired decidualization and placentation. Thus, pre-eclampsia can be considered a disease of failed interaction between two genetically different organisms. The genetic conflict hypothesis states that the fetal genetic component comprised of paternal genes functions to enhance the growth and development of the fetus by maximizing nutrient transfer to the fetus. In conflict with this, the maternal genes function to limit transfer to the fetus to ensure that no compromise is made to maternal health.<sup>20</sup> Fetal genes are predicted to raise maternal blood pressure in order to enhance uteroplacental blood flow, whereas maternal genes act to oppose this. Endothelial dysfunction in pre-eclamptic mothers could, therefore, be interpreted as a fetal attempt to compensate for an inadequate uteroplacental nutrient supply by increasing maternal blood pressure. The Genetics of Pre-eclampsia consortium highlighted the need for examination of both maternal and fetal genotypes performing transmission of disequilibrium testing in both maternal and fetal triads.<sup>21</sup> Interpreting the relative contribution and interactive effects of both maternal and fetal genes on pre-eclampsia has not been straightforward, but statistical methods are now becoming available.<sup>22</sup> Unraveling the maternal and fetal genetic contributions to pre-eclampsia will require very large sample sizes, with the development of new statistical algorithms to aid with data analysis, including a multinomial modeling approach that allows the estimation of such genetic effects using either case/mother duos or case/parent trios.<sup>23</sup>

## Candidate gene studies of pre-eclampsia

Over 70 candidate genes selected on the basis of prior biological knowledge of the pathological changes in pre-eclampsia have been investigated. Candidate genes studied to date can be separated into groups based on their suggested pathophysiological mechanisms: vasoactive proteins, thrombophilia and hypofibrinolysis, oxidative stress and lipid metabolism, endothelial injury, and immunogenetics (see Table 2).<sup>24</sup> In spite of the large research effort, no candidate gene has been universally accepted as a causal gene for pre-eclampsia. Whilst this may be due in part to ethnic variations within study populations and inconsistency in the definition of pre-eclampsia, the major reason is the fact that the majority of candidate gene studies have been

**Table 2** Candidate genes and predominant polymorphisms implicated in the pathogenesis of pre-eclampsia

Proposed mechanism	Gene name	Gene symbol	Polymorphism
Vasoactive proteins	Angiotensinogen	<i>AGT</i>	235Met > Thr
	Angiotensin converting enzyme	<i>ACE</i>	I/D intron 16
Thrombophilia and hypofibrinolysis	Factor V Leiden	<i>F5</i>	506Gln > Arg
	Methylenetetrahydrofolate reductase	<i>MTHFR</i>	C667T
	Prothrombin	<i>F2</i>	G20210A
	Plasminogen activator factor-I	<i>SERPINE1</i>	Promoter insertion/deletion
	Integrin glycoprotein IIIa	<i>GPIIIA</i>	C98T
Oxidative stress and lipid metabolism	Apolipoprotein E	<i>APOE</i>	C886T
	Microsomal epoxide hydrolase	<i>EPHX</i>	113Tyr > His
	Glutathione-S-transferase	<i>GST</i>	A313G
Endothelial function	Endothelial nitric oxide synthase 3	<i>eNOS3</i>	298Glu > Asp
	Vascular endothelial growth factor receptor 1	<i>VEGFR1</i>	TG repeat
	Vascular endothelial growth factor	<i>VEGF</i>	C936T
Immunogenetics	Tumour necrosis factor $\alpha$	<i>TNF</i>	G-308A
	Interleukin 10	<i>IL10</i>	G1082A

grossly underpowered to detect variants with small effects. It is only in recent years that the small effect size of causal variants has become appreciated in the study of complex genetic disorders, with the majority of variants increasing disease risk by <50%. Candidate gene studies are further limited by their reliance on our incomplete understanding of the pathogenic processes that occur in pre-eclampsia, which therefore restricts the genes that are evaluated.

## Clotting cascade abnormalities

The occurrence of thrombophilias is well documented in women with pre-eclampsia.<sup>25</sup> Establishment of the utero-placental circulation is crucial in determining the success of pregnancy. Thrombophilias are believed to heighten the risk of placental insufficiency due to the formation of placental thrombi, in addition to having direct effects on trophoblast growth and differentiation.<sup>26</sup> Whether the procoagulant state which characterizes pre-eclampsia is present before a pre-eclamptic pregnancy or whether it is rather a result of damage initiated during placentation remains unclear. The thrombophilic factors methylenetetrahydrofolate reductase, factor V Leiden variant, and prothrombin have been investigated in numerous candidate gene studies. These have yielded conflicting results with the majority of studies showing no association with pre-eclampsia,<sup>24,27,28</sup> which have been further confirmed by two large meta-analyses.<sup>29,30</sup>

## Regulation of endothelial function and hemodynamics

Due to the role of the renin-angiotensin system in regulating the renal and cardiovascular changes that occur during pregnancy this system has been implicated in the

pathophysiology of pre-eclampsia. A number of candidate gene studies, concentrating mainly on angiotensin converting enzyme (ACE), angiotensin II type 1 and type 2 receptor, and angiotensinogen, have yielded inconclusive results. Meta-analyses have implicated the T allele of angiotensinogen M235T and the deletion allele of the ACE I/D polymorphism.<sup>31,32</sup>

Endothelial nitric oxide synthase 3 has decreased activity in pre-eclampsia.<sup>33</sup> This enzyme is important for the production of nitric oxide (NO), an important regulator of vasodilatation and vascular remodeling. Genetic association studies of endothelial nitric oxide synthase 3 variants in different ethnic populations have produced conflicting results, and a recent meta-analysis has shown no association with pre-eclampsia.<sup>31</sup>

Vascular endothelial growth factor (VEGF) has also been implicated in the pathophysiological changes of pre-eclampsia due to its role in regulating endothelial cell function and vascular permeability. Two small studies have suggested that the *VEGF* 405G > C and 936C > T alleles are associated with pre-eclampsia; results await confirmation in larger studies.<sup>34</sup> The soluble fms-like tyrosine kinase 1 (sFLT1) located on 13q12, binds VEGF with high affinity thus preventing VEGF from interacting with its receptor VEGFR1, resulting in decreased bioavailability of VEGF. The incidence of trisomy 13 is 2.3 in 10,000 births in pregnancies with pre-eclampsia in comparison with 0.5 in 10,000 births in pregnancies without pre-eclampsia.<sup>35</sup> It is suggested that the extra copy of chromosome 13 in trisomy 13 results in increased levels of sFLT1, explaining the increased incidence of pre-eclampsia in women carrying trisomy 13 conceptuses.<sup>36</sup>

## Oxidative stress and lipid metabolism

Oxidative stress is central to the pathogenesis of pre-eclampsia.<sup>37</sup> During the first trimester of pregnancy placental development is in relatively hypoxic conditions, thereby protecting fetal DNA from the harmful effects of damaging free radicals.<sup>38</sup> Between gestational weeks 8 and 12 extravillous trophoblast plugs are released allowing maternal perfusion of the placenta.<sup>39</sup> This leads to a sudden burst of oxidative stress. In normal pregnancy oxidative damage is prevented by the expression of antioxidant enzymes including glutathione peroxidase, catalase, and various forms of superoxide dismutase.<sup>40,41</sup> Expression of these antioxidant enzymes is reduced in the pre-eclamptic placenta leading to a cascade of events which result in impaired placental development. The reduced antioxidant protection in pre-eclampsia culminates in inadequate inactivation of harmful reactive oxygen species (ROS) which cause endothelial dysfunction through lipid peroxidation.<sup>42</sup> Only a small number of genes involved in regulating oxidative stress have been examined in pre-eclampsia, including epoxide hydrolase and glutathione-S-transferase, and none has been clearly shown to increase susceptibility.<sup>43-45</sup>

Abnormal lipid profiles are a characteristic feature of pre-eclampsia, including the increase in lipid peroxidation brought about by increased oxidative stress. Two major regulators of lipid metabolism, lipoprotein lipase (LPL) and apolipoprotein, are abundantly expressed in the placenta and have been investigated as candidate genes for pre-eclampsia.<sup>46-48</sup> The Asn291Ser mis-sense mutation in *LPL* has been associated with lowered plasma LPL activity and increased dyslipidemia in pre-eclampsia,<sup>47</sup> but other researchers have failed to confirm these findings.<sup>49</sup>

## Immune system involvement in pre-eclampsia

The fetus is hemiallogeneic with respect to its mother, and the maternal immune response is a key factor in determining pregnancy outcome. The increased risk of pre-eclampsia in first pregnancies suggests immune system involvement in its pathogenesis. A lengthy period of exposure to paternal semen prior to pregnancy appears to be protective, which may explain in part the three-fold increase in risk of developing pre-eclampsia following use of donor sperm or oocytes.<sup>50,51</sup>

## Killer immunoglobulin-like receptors and the human leucocyte antigen

Expression of major histocompatibility complex molecules by invading extravillous cytotrophoblast cells is limited to

the invariant Class 1b molecules, human leucocyte antigen (HLA)-E, HLA-F, and HLA-G, and the moderately polymorphic Class Ia antigen HLA-C. Interactions between trophoblast HLA-C and maternal killer-cell immunoglobulin-like receptors (KIR) expressed by uterine natural killer cells are important for regulating trophoblast invasion and are crucial for successful placentation.<sup>52</sup> The two basic KIR haplotypes, A and B, differ in that the B haplotype is more potent in activating uterine natural killer cells, and stimulating the secretion of cytokines essential for trophoblast invasion. Fetal HLA-C antigens are also represented by two groups, HLA-C1 and HLA-C2, which have differing affinities for KIR haplotypes. There is evidence that certain maternal KIR/fetal HLA-C combinations increase the risk of inefficient placentation leading to pre-eclampsia.<sup>53</sup>

## TNF $\alpha$

Excessive release of tumor necrosis factor alpha (TNF $\alpha$ ) is associated with endothelial activation, and plasma levels of TNF $\alpha$  are significantly higher in women with pre-eclampsia.<sup>54</sup> Furthermore, treatment of pregnant rats with TNF $\alpha$  induces hypertension.<sup>55</sup> TNF $\alpha$  is also involved in the production of ROS and oxidant-mediated endothelial damage. The most frequently studied polymorphism in the TNF $\alpha$  gene is the 308G > A transition in the promoter region, which is associated with increased production of TNF $\alpha$ . This variant has been associated with an increased risk of pre-eclampsia and pre-eclampsia linked disorders, including type 2 diabetes, coronary artery disease, and dyslipidemia.<sup>56,57</sup> However, a large-scale meta-analysis of this polymorphism failed to demonstrate significant association with pre-eclampsia.<sup>58</sup>

## Interleukin 10 (IL-10)

Trophoblast invasion and spiral artery remodeling are also regulated by IL-10<sup>59</sup> which is expressed at lower levels in pre-eclamptic placentae compared to matched controls.<sup>60</sup> Large-scale studies examining genetic variants of *IL-10* have failed to demonstrate a significant association with pre-eclampsia.<sup>61,62</sup>

## Animal models of pre-eclampsia

Due to the differences in placental development between humans and other mammals, specifically deep trophoblast invasion, animal models have been of only limited significance in the help to elucidate factors involved in the pathophysiology of pre-eclampsia.<sup>63</sup> However, recently the murine catechol-O-methyltransferase (COMT) knockout model has been useful in unraveling the significance of

decreased placental COMT expression in pre-eclampsia. Estradiol is metabolized by cytochrome P450 generating 17-hydroxyestradiol which is a substrate for COMT, which converts 17-hydroxyestradiol into 2-methoxyestradiol (2-ME). 2-ME inhibits HIF-1 $\alpha$  by possibly destabilizing microtubules in trophoblasts.<sup>64</sup> During pregnancy the concentration of maternal circulatory 2-ME immediately increases and peaks at term.<sup>64,65</sup> The plasma concentration of 2-ME is decreased in pre-eclampsia.<sup>64</sup> COMT-deficient mice (COMT<sup>-/-</sup>) display a pre-eclampsia-like phenotype, including pregnancy-induced hypertension with proteinuria.<sup>64</sup> Administration of exogenous 2-ME ameliorates the hypertension, proteinuria, placental defects, acute atherosclerosis, and glomerular and placental endothelial damage present in pregnant COMT<sup>-/-</sup> mice. It is thought that the pre-eclampsia like symptoms present in COMT<sup>-/-</sup> mice is due to placental accumulation of HIF-1 $\alpha$ . In the presence of COMT, 2-ME suppresses HIF-1 $\alpha$  accumulation and production of sFLT1. In COMT<sup>-/-</sup> mice, however, HIF-1 $\alpha$  accumulation is associated with an increased inflammatory response and endothelial damage.

The rs4680 polymorphism in the coding sequence of *COMT* produces a G to A nucleotide substitution leading to a valine to methionine amino acid substitution at amino acid position 158.<sup>66</sup> The *COMT*<sup>Met158</sup> variant has a lower stability and shows a lower enzymatic activity, with this variant present in around 30% of the population. This polymorphism has been found to be associated with fetal growth restriction and abnormalities.<sup>66</sup> Pre-eclampsia may therefore be associated with such polymorphisms within the *COMT* gene, however, robust genetic studies are still needed to confirm or dispute such an association.

## Genome-wide screening

Genome-wide screening provides an unbiased approach to the search for susceptibility genes for pre-eclampsia, unlimited by current understanding of the underlying pathophysiological changes. It therefore offers an opportunity to elucidate previously unsuspected pathogenic pathways, and identify novel interventional targets.

## Genome-wide linkage screens (GWLS)

GWLS have been very successful in identifying highly penetrant variants in monogenic disorders, but this method is inadequately powered for detecting the causal variants with small effect size typical of complex genetic disorders. A number of GWLS have been performed in pre-eclampsia,

assessing the segregation of microsatellite alleles in affected siblings. This method can only identify relatively large regions of the genome, typically tens of centimorgan in size, and containing hundreds of genes, many of which may be biologically plausible. Significant linkage with pre-eclampsia on chromosomes 2p13,<sup>67</sup> 2p25,<sup>68</sup> and 9p13<sup>68</sup> has been reported. Suggestive linkage has also been described at different loci on chromosomes 2q, 9p, 10q, 11q, and 22q.<sup>69,70</sup> Disappointingly, none of these loci have been independently replicated in another GWLS. Limited statistical power is a major factor in the failure to replicate these GWLS in studies of complex genetic disorders. Meta-analysis of the five GWLS performed in pre-eclampsia produced modest evidence for linkage at several loci, but cautioned that insufficient data were available for conclusive results.<sup>71</sup>

## Positional candidate genes

Activin A receptor type IIA (*ACVR2A*) has been identified as a strong positional candidate on the 2q22-23 locus. As a key receptor for the cell-signaling protein activin A, an important regulator of human pregnancy, *ACVR2A* represents a biologically plausible candidate. Activin A has also been investigated as a potential biomarker for pre-eclampsia as circulating levels are increased in pre-eclamptic pregnancies.<sup>72</sup> In a large study of over 1100 pre-eclamptic women and 2200 normotensive controls, four single nucleotide polymorphisms (SNPs) in *ACVR2A* were significantly associated with pre-eclampsia,<sup>73</sup> and the influence of these variants on the expression and function of *ACVR2A* is currently being investigated. However, in a study of 74 affected families from Australia/New Zealand the *ACVR2A* association was not replicated.<sup>74</sup> This gene still remains an interesting target due to its strong biological involvement in the establishment and maintenance of pregnancy.

Within the pre-eclampsia linkage peak on chromosome 2p25 lies the *ROCK2* gene. This gene encodes rho-associated coiled-coil protein kinase 2 and, interestingly, has been implicated in essential hypertension.<sup>68</sup> *ROCK2* is widely expressed in smooth muscle cells and animal models have indicated a role in vasoconstriction.<sup>75,76</sup> It has also been shown that syncytiotrophoblast cells of the placenta express *ROCK2* and expression is up regulated in pre-eclampsia.<sup>77</sup> A study examining ten polymorphisms within *ROCK2* failed to detect any association with pre-eclampsia.<sup>78</sup> This study was powered only to detect a genetic effect of 1.6, and a larger study is warranted to investigate both *ROCK2* and other genes at the 2p25 locus.

## Genome-wide association screening (GWAS)

GWAS is a second unbiased approach to the identification of susceptibility genes for pre-eclampsia. Rather than sequencing the entire genome GWAS makes use of the abundant SNPs scattered throughout the human genome. Due to the lack of independence between the alleles of SNPs in close proximity, a phenomenon known as linkage disequilibrium, a number of representative tagSNPs can be used to infer the genotype of adjacent SNPs. Genotyping of between 300,000 and 1 million carefully selected tagSNPs enables the majority of variation in the human genome to be captured. A SNP that is associated with disease may be causal, or may be acting as a marker for another functional SNP in linkage disequilibrium. Deep resequencing is often required to identify all the polymorphisms present at the susceptibility locus.

GWAS has identified over 2000 genetic variants associated with common diseases, including essential hypertension, coronary artery disease, and type 2 diabetes<sup>79</sup> conditions which carry an increased risk of pre-eclampsia. Although many of these loci have been independently confirmed, further functional studies are frequently required in order to elucidate the exact pathophysiological mechanisms involved in these disease processes. GWAS to identify susceptibility genes for pre-eclampsia are currently underway; the results are eagerly awaited.

## Treatment and prevention of pre-eclampsia

Prevention, early identification, and individualized treatments may become feasible if reliable early biomarkers can be developed. A recent microarray study has found dysregulation of gene expression in early placenta in women 6 months before development of pre-eclampsia,<sup>80</sup> confirming placental involvement in this disorder, and also offering the prospect of early prediction of those women at highest risk. It is hoped that completion of GWAS studies and subsequent deep resequencing will help suggest additional biomarkers and improve our understanding of the pathophysiological changes that occur in this disorder.

A number of interventions are available to help treat and prevent pre-eclampsia, including antiplatelet agents, beta blockers, alpha blockers, diuretics, vasodilators (NO agents), and calcium channel blockers.<sup>81</sup>

## The benefits of pharmacogenomics

The aim of pharmacogenomics is to individualize treatments in a rational and directed manner, thereby removing

the element of trial and error from current clinical practice. This will in turn reduce morbidity and mortality at the same time as maximizing the benefit to patients and significantly reducing costs. In the UK, around 6.5% of hospitalizations are due to adverse drug reactions.<sup>82</sup> The benefits of personalization and rationalization of treatment by pharmacogenomic approaches are therefore clear. They would be of particular benefit for treatment of pre-eclampsia, a condition in which patients can deteriorate rapidly and therefore need treatments that are immediately effective.

Oncology is the current leading example for personalized medicine with pharmacogenomics being used to identify new targets influencing drug absorption, distribution, metabolism and excretion, drug safety, and drug efficacy. The ability to segregate patients into drug responders and nonresponders is the cornerstone of personalized medicine and is now becoming standard practice in the use of oncology medication. Genetic prediction of adverse effects is one of the major successes of pharmacogenomics, for example, prediction of hypersensitivity to the antiretroviral drug abacavir used to treat patients infected with human immunodeficiency virus.<sup>83,84</sup>

A clear message coming from researchers interested in pharmacogenomics and personalized medicine is that translation of this research into clinical benefit demands access to large, well-characterized sample bio banks. This will require large-scale international collaborations, exemplified by the International Warfarin Pharmacogenetics Consortium which has identified a model comprising environmental factors (age, height, weight, and amiodarone use) and genotype at rs9923231 (VKORC1), rs1799853 and rs1057910 (CYP2C9\*2 and \*3), rs2108622 (CYP4F2), and rs6042 (F7), which accounts for over 50% of warfarin stable dose variance.<sup>85</sup> Sharing of knowledge has been facilitated by the development of databases, such as the Pharmacogenomics Knowledge Base (PharmGkb),<sup>86</sup> to act as worldwide resources.

The ever-increasing level of data being generated about our genomes and health and disease is leading the way for so-called proactive P4 (prediction, personalization, prevention, participation) medicine. P4 medicine is important for future health as it will enable the prediction of individual health risk and also allow the development of personalized treatment based on an individual's genetic variation. Furthermore, P4 medicine will lead to the prevention of more disease by the design of new therapeutic drugs. However, for P4 medicine to be fully beneficial patients, doctors and the medical community must all understand and participate.<sup>87</sup>

## Drug metabolism is the key to pharmacogenomics

The challenge within pharmacogenomics is to define the physiological pathways that are involved in drug metabolism; pathways which involve multiple interacting proteins. Each of these proteins may contain a polymorphism, transcription of these proteins is in turn regulated by proteins, which again may contain polymorphisms in their genetic coding. Further complexity is added as these biochemical pathways can interact amongst themselves in complex ways which are as yet undefined. This can make determining the actual cause of a change to a response to a drug very difficult. Such complexity has led to two generic streams for pharmacogenomic research: studies based on the pathophysiological pathways involved in disease and studies based on genome-wide association screening.

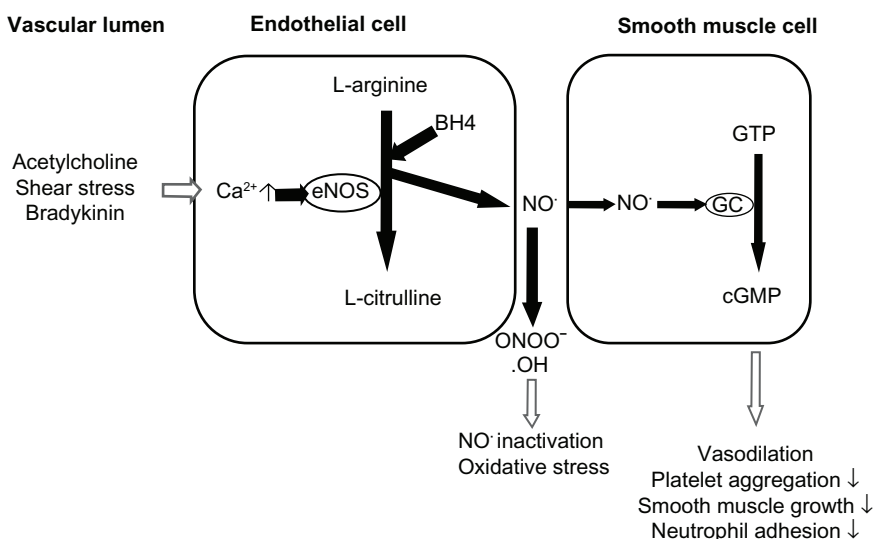
## Nitric oxide synthase as a potential target for therapy for pre-eclampsia

Endothelial dysfunction is characteristic of pre-eclampsia, being associated with the hypertension and proteinuria that are symptomatic of this disorder. Among several mediators released by the endothelium, NO plays an important role in regulating endothelial function (see Figure 1). NO produced by the endothelium targets the vascular smooth muscle, and activates soluble guanylate cyclase by interacting with its heme group. This enzyme synthesizes cyclic guanosine monophosphate from guanosine triphosphate, leading to an accumulation of cyclic guanosine monophosphate. This activates intracellular signaling pathways that decrease

the degree of vascular smooth muscle contraction leading to vessel relaxation.<sup>88</sup> In addition to functioning as an endogenous vasodilator, NO also serves as a platelet inhibitor, antioxidant, and regulator of vascular endothelium by sustaining its anticoagulant and antithrombogenic properties,<sup>89</sup> all of which are perturbed in pre-eclampsia. Within the cardiovascular system it is the endothelial isoform of nitric oxide synthase (eNOS) which is responsible for NO synthesis.<sup>90</sup> Reduced expression of eNOS consequently results in reduced NO bioavailability which plays a significant role in the endothelial dysfunction associated with pre-eclampsia.<sup>91</sup> eNOS represents an interesting pharmacogenomic target, but the multiple interdependent control mechanisms and signaling pathways that act throughout the various stages of the enzyme's life history make this a difficult challenge.

Pre-eclampsia is also associated with an increase in oxidative stress. The ROS superoxide anion is able to react with NO resulting in the formation of the highly damaging peroxynitrite, and further reducing the bioavailability of NO.<sup>92</sup> ROS can also cause oxidation of the tetrahydrobiopterin cofactor of eNOS, resulting in uncoupling of this enzyme and further production of superoxide anion in favor of NO,<sup>93</sup> a vicious cycle that further increases oxidative stress.

The *eNOS* gene, located on 7q35-7q36, is approximately 21 to 22 Kb and consists of 26 exons and 25 introns.<sup>94,95</sup> Since its characterization in the 1990s, a large number of polymorphic sites have been identified in the *eNOS* gene, including variable number tandem repeats, dinucleotide repeats (CA)<sub>n</sub>, and SNPs. Several polymorphisms have been associated with pre-eclampsia and other cardiovascular



**Figure 1** The importance of nitric oxide (NO) in the regulation of endothelial function.

**Abbreviations:** eNOS, endothelial nitric oxide synthase; BH4, tetrahydrobiopterin; GC, guanylate cyclase; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; ONOO<sup>-</sup>, peroxynitrite; OH, hydroxide.



and hypertensive disorders.<sup>96–98</sup> A relationship between eNOS polymorphisms and differential responses to several classes of cardiovascular drugs has been shown,<sup>99</sup> some of which are used for the treatment of pre-eclampsia.

In animal models statins have been shown to be beneficial in ameliorating pre-eclampsia<sup>100</sup> and currently the StAmP (Trial of proveraStatin to Ameliorate early onset Pre-eclampsia) trial is underway to assess the use of statins in pregnancy as a therapeutic intervention to prolong pre-eclamptic pregnancies, thereby reducing the incidence of prematurity associated with the disorder.<sup>101</sup> Recent evidence suggests genetic polymorphisms of *eNOS* modulate the effects of statins. Statin treatment induced a greater increase in eNOS mRNA levels in cultured endothelial cells with the CC genotype at the  $-786T > C$  polymorphism compared to cells with the TT genotype.<sup>102</sup> These findings have been confirmed in a clinical study showing that atorvastatin increases the bioavailability of NO and decreases oxidative stress in CC homozygotes.<sup>103</sup> The same polymorphism in the *eNOS* gene modulates the anti-inflammatory effect of atorvastatin, resulting in significant reductions in the inflammatory cytokines CD40L, VCAM-1, P-Selectin, and MMP-9 in individuals with the CC genotype but not the TT genotype.<sup>104</sup> These findings suggest that statins might be more useful for the treatment of pre-eclampsia in women with the CC genotype than in those with the TT genotype.

A further polymorphism in intron 4 (4a/b) of the *eNOS* gene is also associated with modulation of the response to statins. In a study evaluating coronary vasodilatation induced by adenosine after 6-months' treatment with pravastatin, individuals carrying an A allele showed significant improvement of vasodilatation compared to homozygous bb individuals, possibly due to increased endothelial production of NO.<sup>105</sup>

## Prevention of pre-eclampsia

### Labetalol

Labetalol is a mixed alpha- and beta-blocker that is used for controlling high blood pressure during pregnancy. Although no studies have been performed examining pharmacogenomic effects on labetalol, a number of studies have been performed assessing other beta-blockers in patients with hypertension which may be of relevance to the use of labetalol in pre-eclampsia. Using a technique similar to GWAS, polymorphisms in *eNOS* have been shown to be associated with variations in pharmacological responses to the beta-blocker atenolol. In hypertensive patients, allele G of the A2996G polymorphism in *eNOS* is associated with a

greater decrease in blood pressure following treatment with atenolol compared with patients with the A allele.<sup>106</sup> Allele A of the G498A polymorphism in the *eNOS* gene is also associated with a better response to atenolol treatment.<sup>106</sup> The presence of a 2996G allele and a 498A allele may therefore be beneficial for patients treated with beta-blockers. These promising results need to be confirmed in a higher number of patients from different populations but may be important when considering pharmacogenomic approaches to the treatment of pre-eclampsia.

### Hydralazine (HDZ)

HDZ is commonly used in pre-eclampsia as an intravenous treatment for quickly lowering severely high blood pressure during pregnancy.<sup>107</sup> Hypotension is a frequent adverse effect of HDZ treatment.<sup>107</sup> HDZ is biotransformed by the enzyme N-acetyltransferase (NAT) forming acetyl HDA, which spontaneously converts to the stable product 3-methyl-S-triazolo-[3,4-a]-phthalazine.<sup>108</sup> Two isoforms of NAT are encoded by *NAT1* and *NAT2*. Several polymorphisms in *NAT1* and *NAT2* have functional consequences including truncation of the proteins, which leads to reduced enzyme activity. This affects the rates of inactivation of many drugs, including HDZ.<sup>109</sup>

As previously mentioned, COMT deficiency is implicated in the pathogenesis of pre-eclampsia. Importantly, HDZ has also been shown to inhibit placental COMT activity.<sup>110</sup> Therefore, HDZ mediated suppression of COMT/2-ME needs to be carefully evaluated for its connection with possible drug-exacerbated pre-eclampsia.

However, it is questionable whether pretreatment NAT genotyping would be clinically justified, as the benefits of HDZ therapy in severe pre-eclampsia outweigh the risk of adverse drug reactions.

### Aspirin

Aspirin reduces the risk of pre-eclampsia<sup>111</sup> through its antithrombotic action. A recent Cochrane review showed that aspirin at doses of between 50 and 150 mg/day reduces the risk of pre-eclampsia by 17% (relative risk 0.83; 95% confidence interval 0.77–0.89).<sup>112</sup> Current guidelines from the National Institute for Health and Clinical Excellence<sup>81</sup> recommend that women at high risk of pre-eclampsia should take aspirin 75 mg daily from 12 weeks of pregnancy until the birth of the baby. Low-dose aspirin functions as an antiplatelet agent through its ability to irreversibly acetylate and thus inhibit the enzyme cyclo-oxygenase-1 (COX-1). This suppresses the synthesis of thromboxane A<sub>2</sub>, a potent

vasoconstrictor and activator of platelet aggregation.<sup>112</sup> Therefore, low-dose aspirin may enhance uterine blood flow and tissue perfusion, and promote optimal uterine hemodynamics.

There is interindividual variation in the antiplatelet effects of aspirin giving rise to the concept of antiplatelet drug resistance.<sup>113</sup> A number of laboratory assays are available to test for aspirin resistance which include light transmission aggregometry, platelet function analyser-100, VerifyNow® Aspirin system (Accumetrics, San Diego, CA), thromboelastography, or measurements of serum levels of thromboxane B<sub>2</sub> or the urinary metabolite 11-dehydro-thromboxane B<sub>2</sub>. The definition of antiplatelet drug resistance is controversial and therefore the reported prevalence varies widely, between 5% and 60%, depending on the laboratory methods used and the population studied.<sup>114–116</sup> However, it is important to note that poor compliance by patients has been identified as a primary cause of resistance.<sup>117</sup> In addition to COX-1-specific effects, aspirin also has COX-1 independent effects, which may be subject to more interindividual variability and may explain the adverse outcomes among patients with high platelet reactivity.<sup>114,118</sup>

A number of mechanisms may be related to aspirin resistance.<sup>119</sup> Clinical factors including poor patient compliance, drug-absorption abnormalities, or drug–drug interactions play a role.<sup>120</sup> Cellular factors have also been proposed to influence aspirin efficacy, such as inadequate suppression of platelet COX-1 due to increased platelet turnover, over expression of COX-2 mRNA, erythrocyte-platelet interaction, catecholamine levels, or the generation of 8-iso-PGF<sub>2</sub>.<sup>121</sup> Polymorphisms in both the *COX-1* and *COX-2* genes may have roles in aspirin resistance.<sup>122</sup> The *COX-1* C50T and *COX-2* (G-765C) polymorphisms have both been associated with the efficiency of reduction of thromboxane B<sub>2</sub> levels after aspirin treatment.<sup>118,123</sup>

A number of polymorphisms have been identified as being associated with aspirin drug resistance (see Table 3).<sup>121,124</sup> However, these studies have often been underpowered and inconclusive. This is perhaps not surprising given the different methods used to assess resistance and the lack of assessment of compliance. A comprehensive systematic review and meta-analysis of pharmacogenomics of aspirin resistance has been performed identifying 50 polymorphisms in eleven genes in the aspirin pathway.<sup>125</sup> A subgroup analysis in healthy individuals identified a statistically significant genetic association between aspirin resistance and a polymorphism in the glycoprotein (GP) IIb/IIIa platelet receptor gene. The platelet GPIIb/IIIa receptor is essential for platelet activation and aggregation by binding fibrinogen and von Willebrand factor. This receptor complex is the main pharmaceutical target for aspirin and other antiplatelet therapies. The GP IIb/IIIa complex is highly polymorphic. Healthy carriers of the PI<sup>A2</sup> allele, which is responsible for a Pro33 Leu amino acid change, are 2.36 times more likely to display resistance to aspirin<sup>126</sup> and therefore require a greater dose of aspirin to experience the same antiaggregant effect as do subjects with a PI<sup>A1</sup> homozygous genotype.<sup>127</sup> However, no studies have been undertaken in pregnant women on aspirin to determine whether there is genetic variability in response to aspirin, and certainly this has never been related to clinical outcomes.

A second complex which may also regulate patient response to aspirin and other antiplatelet agents is the GP Ia/IIa complex, a high-affinity receptor for collagen which plays a key role in platelet adhesion. Polymorphisms that alter the structure and density of the GP Ia/IIa receptor complex on the platelet surface include C807T (Phe 224), a silent polymorphism affecting the Ia subunit. The 807T allele is associated with up to ten times higher expression of the receptor on the platelet surface and may modify the effect of antiplatelet drugs.<sup>128</sup>

**Table 3** Summary of pharmacogenomic studies on antiplatelet agents

Protein	Polymorphism	Patient numbers studied	Functional effects	Clinical effects
GP IIb/IIIa	PI <sup>A</sup> (Pro33Leu)	>5000	Individuals with PI <sup>A2</sup> allele require higher dose of aspirin to achieve comparable anti-aggregant effect as wild-type homozygotes	Increased risk of thrombosis
GPIa	C807T	1170	Associated with collagen-receptor density on the platelet membrane surface and greater platelet reactivity	Conflicting data
COX-1	C50T	563	Associated with higher levels of thromboxane B <sub>2</sub>	No clinical data
COX-2	G-765C	24	Associated with a higher reduction of thromboxane B <sub>2</sub> levels after aspirin treatment	No clinical data
ADP subtype receptor	P2Y <sub>12</sub>	980	Associated with reduced platelet aggregation after aspirin intake	No clinical data

**Abbreviations:** ADP, adenosine diphosphate; COX, cyclooxygenase; GP, glycoprotein.

## Magnesium sulfate

Magnesium sulfate is used therapeutically to prevent eclamptic convulsions in women with pre-eclampsia. The pharmacological actions of magnesium include cerebral vasodilatation thereby reducing cerebral ischemia,<sup>129</sup> or blocking of neuronal damage associated with ischemia.<sup>130</sup> However, magnesium sulfate also has side effects for the mother.<sup>131</sup> An increase in postpartum hemorrhage has been reported following magnesium sulfate treatment,<sup>132</sup> although its incidence was not increased in the Magpie trial.<sup>133</sup> Importantly, magnesium is able to cross the placenta and hypermagnesemia in the neonate is associated with flaccidity, hyporeflexia, and respiratory depression.<sup>134</sup> To the best of the authors' knowledge, no pharmacogenomic studies have been performed with magnesium sulfate.

## Calcium channel blockers

The calcium channel blockers nifedipine, verapamil, and nifedipine are also recommended to treat hypertension in pre-eclampsia.<sup>135</sup> Calcium channel blockers function by blocking voltage-gated calcium channels in the heart and vasculature, thereby reducing intracellular calcium. In the heart, this results in decreased cardiac contractility and reduced cardiac output; in the blood vessels, this leads to decreased smooth muscle contraction and peripheral resistance. Although no pharmacogenomic studies have been performed in pre-eclampsia, over recent years, a number of studies have examined calcium channel blockers in the treatment of hypertension. Three SNPs in *CACNA1A* (rs2239050, rs2238032, and rs2239128) have been associated with success of treatment in a study of blood pressure lowering with calcium channel blockers,<sup>136</sup> however, Beitelshees et al<sup>137</sup> failed to replicate this finding. A recent study has also shown that individuals with rs1051375 A/A benefit from treatment with a calcium channel blocker, whereas those with the G/G genotype would benefit from treatment with a beta blocker, and in those individuals that are heterozygous it does not matter which treatment is chosen.<sup>137</sup> Suggestive associations between CYP3A5\*3 and CYP3A5\*6 variants and verapamil treatment for blood pressure and hypertension risk outcomes in black and Hispanic populations have also been observed.<sup>138</sup> The Glu65 Lys and Val110Leu variants of *KCNMB1* have also been studied with regard to systolic blood pressure regulation by verapamil. Although blood pressure response did not vary by genotype, Lys65 carriers achieved earlier blood pressure control and required fewer additional treatments. Leu110 carriers were found to have a reduced risk of death, myocardial infarction, or stroke.<sup>139</sup>

Higher mortality rates have also been reported for individuals with the Ser49-Arg389 variant of *ADRB1* following treatment with verapamil.<sup>140</sup> Additionally, individuals homozygous for the T allele of *NPPA* T2238C had more favorable clinical outcomes when treated with a calcium channel blocker whereas C carriers responded better to a diuretic.<sup>141</sup>

## Conclusion

The need for collaboration within the field of genetics of pre-eclampsia, as with all other complex genetic disorders, is now accepted by researchers. Only large-scale collaborations can achieve sufficient sample sizes to perform adequately powered studies. Whilst a role for pharmacogenomics is accepted in the field of cancer treatment, further research is needed before pharmacogenomic approaches can be considered appropriate for pre-eclampsia. Due to concerns about possible teratogenic/harmful effects on the fetus only minimal medication is given to a woman during pregnancy. A recent Confidential Enquiry into Maternal and Child Health report, attributes the occurrence of fatal intracranial hemorrhages to inadequate treatment of severe systolic hypertension (>160 mmHg) in women with pre-eclampsia, recommending urgent and effective treatment for such cases.<sup>142</sup> Pharmacogenomics could help reduce the incidence of such fatal hemorrhages by helping to ensure that women received the optimal treatment regimen for them. Such accurate prediction of which women will respond well to a particular treatment will be further beneficial in the management of pre-eclampsia by preventing unnecessary exposure of the fetus to ineffective drugs. Progress in understanding the genetic component of pre-eclampsia will aid development of novel pharmaceutical treatments; personalized medicine informed by pharmacogenomics will target the treatments for this devastating disorder of pregnancy at those most likely to benefit.

## Disclosure

The authors report no conflicts of interest in this work.

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