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PREECLAMPSIA (VD GAROVIC, SECTION EDITOR)

Candidate Gene, Genome-Wide Association and Bioinformatic Studies in Pre-eclampsia: a Review

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Abstract

Purpose of Review Regardless of the familial linkage reported in pre-eclampsia development, understanding the polymorphic genes associated with pre-eclampsia remains limited. Hence, this review aims to outline the main genetic factors that have been investigated in respect to pre-eclampsia development.

Recent Findings It is apparent that different genes show significance in varying populations. Notably, it is reported that apolipoprotein-1 gene polymorphisms are associated with pre-eclampsia development in an African-American population, which may be worthwhile to investigate in a Black South African cohort.

Summary Despite the research attention that is focused on this surreptitious syndrome, a definitive cause eludes scientists and physicians, alike. Genetic studies can fulfil a dual purpose of suggesting novel hypotheses through genome-wide screening and testing these hypotheses via candidate gene studies. However, publications to date have only presented inconsistent and conflicting results regarding candidate gene analysis.

Keywords Pre-eclampsia · Candidate gene studies · Genome-wide association studies · Bioinformatic studies
Apol-1 gene polymorphisms

Introduction

Pre-eclampsia (PE) is a disorder specific to human pregnancies, characterised by hypertension and proteinuria occurring for the first time after the 20th week of gestation [1••, 2, 3]. The diagnosis of PE can be made in the absence of proteinuria, if there is laboratory evidence of target organ damage as demonstrated by either thrombocytopenia, renal insufficiency, impaired liver function tests and pulmonary oedema [1••, 2, 3]. Pre-eclampsia/eclampsia accounts for 50,000–60,000 deaths per annum moreover, World Health Organization (WHO) indicates that the incidence of PE is seven times greater in low-middle income countries (LMIC) compared to high-income countries [4]. Furthermore, PE is associated with an elevated risk of both the mother and baby developing cardiovascular and metabolic complications in later life [2, 5, 6]. More importantly, PE is the major cause of maternal mortality in LMIC, accounting for 14.8% of all maternal deaths in South Africa [7•]. There are a variety of reasons for this, the main being that the exact aetiology is unknown, therefore both detection and the timing of delivery remain a contentious clinical dilemma.

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Diagnosis of Pre-eclampsia

Understanding factors that are involved in the pathogenesis of PE will aid in the early identification of women at risk thereby reducing morbidity and mortality. Currently, predictive tests for PE diagnosis have optimum performance after the first trimester of pregnancy [8]. Unfortunately, this is a period reported to be too late to reverse PE development. Moreover, symptoms exist in the presence of the placenta and they regress shortly after its delivery [8].

Current Theories on the Aetiology

Pre-eclampsia is considered a two-stage disorder [9]. The first preclinical stage involves poor placentation [9]. Early in normal pregnancy, cytotrophoblast cells permeate the uterine spiral arteries where they replace the endothelial cell layer and the muscular media is replaced by a fibrinoid-type material. This transformation of the spiral arteries into large bore conduits of low resistance, allows for a high volume of blood to meet the growing demands of the foetus [10, 11]. However, in PE, maternal uterine spiral artery wall remodelling is limited to the decidua. This results in narrow vessels of high resistance with resultant decreased blood supply that creates an ischaemic microenvironment [11]. The initial trigger leading to the impaired placentation remains unknown.

The resultant hypoxic milieu releases placental factors into the systemic circulation, bringing about the second stage of PE [12]. Some of these factors include soluble endoglin, soluble fms-like tyrosine kinase-1 (sFlt-1) and pro-inflammatory cytokines, which contribute to oxidative stress and systemic inflammation. The aforementioned causes the clinical symptoms, i.e. hypertension and proteinuria, of PE [13]. In women that develop PE, the pre-existing metabolic conditions such as diabetes, chronic hypertension as well as hyperlipidaemia exacerbates endothelial damage [11].

Early Onset Pre-eclampsia vs Late Onset Pre-eclampsia

Two subtypes of PE have been categorised based on gestational age [14]. In early onset pre-eclampsia (EOPE), clinical signs are evident prior to 33 weeks ±6 days of gestation. In EOPE, impaired spiral artery transformation results in reduced placental perfusion. This causes an increased production of oxidative free radicals and hence, pro-inflammatory cytokines in the maternal circulation inducing the characteristic endothelial dysfunction [14]. Furthermore, the ischaemic placenta also leads to foetal growth restriction [2]. Notably, EOPE is associated with high maternal and perinatal morbidity and mortality rates [2].

In late onset pre-eclampsia (LOPE), clinical signs appear after 34 weeks of gestation and occur as a consequence of pre-existing metabolic and cardiovascular conditions [14]. The production of oxidative free radicals is also apparent in LOPE albeit towards the end of gestation [14]. There is no foetal growth restriction because spiral artery transformation is unaffected [2, 14].

Familial Association of Pre-eclampsia

A variety of genetic components, of both maternal and foetal origin, are role players in the aetiology of PE development. The risk of developing PE in a first pregnancy is calculated to be ≥ 3% and elevates marginally with increasing maternal age [15]. In second pregnancies, the risk is 1.7% if fathered by the same partner whilst it is 1.9% if the partner differs from the first pregnancy [15]. Additionally, men born from pregnancies complicated by PE are likely to father such pregnancies [8], justified by the fact that as per genomic imprinting, paternal genes are involved in placental growth. Overall, studies investigating a family history of PE have concluded that despite genetic factors contributing to more than 50% of PE development, it is still influenced by racial, geographical and socio-economic factors [8]. In a large Swedish cohort, foetal genes contributed to 20% of the variability that could result in PE development [16].

Genetic Factors Contributing to the Susceptibility of Pre-eclampsia Development

With strong familial associations being reported, it is of no surprise that numerous candidate gene and genome-wide linkage studies have been implicated in PE development. Ideally, these studies would better identify women at risk for PE development even before they fall pregnant. Also, the inheritability of specific genes that play a role in the clinical signs of PE has been assessed. The aim of this review article outlines various genetic factors that have been investigated with regard to classification, aetiology and significance of PE development.

Candidate Gene Studies

With the strong genetic association evident in PE, it is no surprise that numerous candidate gene studies have been carried out. This approach simply compares the frequency of genetic variation between PE and normotensive pregnancies [17]. Investigations may include analysis of single-nucleotide polymorphisms in one candidate gene or even many polymorphisms in one or several genes [17]. This review explores the main candidate genes and SNPs involved in the pathogenesis of PE and is summarised in Table 1.

Interleukin-10

Interleukin-10 (IL-10) is an anti-inflammatory cytokine that inhibits cytotrophoblast invasion [45]. A decrease in IL-10 in pre-eclamptic placentas has been demonstrated [45]. Furthermore, gene polymorphisms of the promoter region of IL-10-1082G/A, IL-10-819 C/T and IL-10-592 C/A correlate with its transcription and hence production. Nonetheless, these polymorphisms are reported to be unlikely genetic factors that increase the susceptibility to PE development [21, 46–48]. In contrast, the IL-10-1082G allele frequency is

Table 1 Candidate genes associated with the susceptibility to pre-eclampsia development discussed in this review

Author and year	Gene associated with PE development	Country
Uteroplacental pathology		
Daher et al. 2006 [18]	IL-10-1082G	Brazil
Kamali-Sarvestani et al. 2006 [19]		Iran
Vural et al. 2010 [20]		Turkey
Pinheiro et al. 2015 [21]	IFN-γ–+874T/T	Brazil
Chen et al. 1996 [22]	TNF1	UK
Mohajertehran et al. 2012 [23]	TNFα-G308A	Iran
Shao et al. 2017 [24]	CYP24A1 rs2209314	China
Endothelial dysfunction		
Luizon et al. 2012 [25]	MMP-9-1562CC and VEGF-634CC MMP9-1562CT and VEGF-634CC	Brazil
	MMP9-1562CT and VEGF-634GG	
Sun et al. 2016 [26]	MMP9-1562CT	China
Srinivas et al. 2010 [27]	Flt-1 rs12584067 Flt-1 rs7335588	USA
	VEGF-C rs1485766	
	VEGF-C rs6838834	
Bouba et al. 2003 [28]	Angiotensinogen 235T	Greece
Aung et al. 2017 [29]	Angiotensinogen 235T	South Africa
Rahini et al. 2014 [30]	AT2R 1332G and AT1R C ACE D & MMP-9T	Iran
Bhatnagar et al. 2007 [31]	iNOS G300A iNOS G274T	India
Chen et al. 2005 [32]	Apolipoprotein J 866CT	China
Maternal immune maladaptation		
Tan et al. 2008 [33]	HLA-G 0106G	Singapore
Quach et al. 2014 [34]	HLA-G + 3027C/C and +3187G/G	Canada
Rousseau et al. 2003 [35]	HLA-G 010102	France
O'Brien et al. 2001 [36]	HLA-G3	France
Inflammation and oxidative stresS		
Chen et al. 2016 [37]	IL-27 rs151785370	China
Liu et al. 2016 [38]	IL-27 rs153109 C/C	China
Zhang et al. 2017 [39]	IL-4 C-5907T	China
Fraser et al. 2008 [40]	IL-4590 C/T	UK
Salimi et al. 2014 [41]	IL-4 VNTR RP2	Iran
Andraweera et al. 2015 [42]	IL-1α rs17561 IL-1α rs1800587	Sri Lanka
Pontillo et al. 2015 [43]	NLPR1 L155H	Brazil
Wang et al. 2015 [44]	CARD8 rs2043211	China

significantly elevated in Iranian pre-eclamptic women, suggesting its role in PE predisposition [18–20].

Uric Acid

Pre-eclampsia is also associated with hyperuricemia in that circulating uric acid increase prior to clinical manifestations of the condition [49]. This increase may be associated with renal dysfunction in the form of fractional excretion or reduced urate clearance, increased production of uric acid, acidosis and/or tissue ischaemia [50]. Hawkins et al. (2012) concluded that in women with a pregnancy complicated by hypertension, increased uric acid levels are linked with PE development. Mulla et al. (2010) demonstrated that uric acid activates trophoblast inflammasomes resulting in IL-1β production, providing an explanation for the exacerbated inflammation of PE. Similarly, Matias et al. (2015) described uric acid crystals or monosodium urate activating inflammasomes that contribute to the hyper-inflamed milieu. An inflammasome is defined as a multiprotein oligomer

responsible for the activation of inflammatory responses. A higher gene expression of inflammasomes, NLRP1 and NLRP3 as well as caspase-1, are all pro-inflammatory [51]. Pontillo et al. (2015) reported an association between the NLRP1 variant rs12150220 (L155H) and PE development [43]. Also, the CARD8 gene contains the code for proteins that may be a component of the inflammasome. Wang et al. (2015) discovered that the presence of the rs2043211 CARD8 polymorphism increases the susceptibility for PE in the Chinese Han population [44].

Tumour Necrosis Factor-Alpha

Tumour necrosis factor-α (TNF-α) is a pro-inflammatory cytokine with a vital role in reproduction. Its functions include gamete and embryo development, placental differentiation and parturition [52]. During the first trimester, cells of trophoblastic lineage, namely syncytiotrophoblasts, proliferating trophoblasts and extravillous trophoblasts (EVT), all express TNF-α mRNA [52]. It is believed that macrophage derived placental TNF-α facilitates trophoblast differentiation. PE is considered a state of exaggerated inflammation, where high levels of Th1 cytokines like TNF-α is expressed [52]. In the first trimester, the combination of TNF-α and IFN-γ inhibit extravillous trophoblast invasion due to decreased proliferation of EVTs, increased apoptosis as well as a reduction in pro-MMP-2 secretion [52]. This increased expression of TNF-α contributes to the abnormal placentation in pre-eclampsia [53]. In contrast, Hayashi et al. reported no significant difference in placental TNF-α levels in pre-eclamptic compared to normotensive pregnancies albeit with an increased serum TNF-α concentration being evident [54].

Genetic studies on TNF-α were performed as early as 1996 by Chen and colleagues who observed an increased TNF-α expression association with the increased frequency of TNF1 allele in pre-eclamptic patients [22]. Mohajertehran et al. corroborated the association of TNF-α gene polymorphisms with elevated levels of TNF-α in PE [23]. However, de Lima et al. 2009 reported a lack of association between the polymorphic gene of TNF-α and PE development. Interestingly, a study in Finland found that the T allele of the TNF-α gene may provide a protective effect, reducing the risk of PE development [55].

Human Leukocyte Antigen-G

At the maternal-foetal interface, human leukocyte antigen-G (HLA-G) is expressed by foetal trophoblast cells [33]. It is possible that, due to the presence of HLA-G maternal NK cells do not lyse the invading semi-allogenic cytotrophoblasts. Another role of HLA-G is inhibition of transendothelial migration of maternal NK cells across the placenta. In doing so, maternal tolerance to the growing foetus is augmented. Additionally, HLA-G may also reduce activated populations of CD4+ and CD8+ T cells bringing about maternal tolerance to paternal alloantigen's [33].

It is proposed that maternal maladaptation to foetal antigens during pregnancy contributes to the pathogenesis of PE. The foreign foetal antigens are of paternal origin and this may induce the release of cytokines causing endothelial cell damage [56]. Numerous studies have reported reduced expression of HLA-G in PE [33, 56–58].

Tan and co-workers [33] reported a significant link between HLA-G-G*0106 present in the foetus and PE development. Furthermore, it was observed that there is maternal-foetal HLA-G genotype mismatch in PE. It may be surmised that foreign HLA-G variants results in histo-incompatibility between the mother and foetus, thereby eliciting a HLA-G antibody response contributing to the pathogenesis of PE [33]. Studies done by Quach et al.; Rousseau et al. and O'Brien et al. corroborated these findings [34–36]. However, contrary to the above, many studies found no significant difference between HLA-G polymorphisms and PE development, eliminating it as a probable candidate gene [59–61].

The findings of the protective nature of prolonged sperm exposure prior to pregnancy, the effect of a change in father and the "dangerous" partner theory are all consistent with the maternal immune maladaptation concept. It is uncertain if the paternal HLA is carried in the seminal plasma or the spermatozoa itself, yet it is certain that prior exposure reduces the risk of PE development. Soluble HLA induces apoptosis in human cytotoxic T cells, thereby inducing maternal tolerance to paternal antigens [62].

Macrophages and dendritic cells are cells of the innate immune system. They are major antigen presenting cells in the uterus, facilitating the adaptation of the maternal immune response to the growing foetus. An elevated concentration of chemokines, which are macrophage and dendritic cell recruiters, are evident in pre-eclamptic placentas [63]. An investigation carried out by Mellembakken et al. demonstrated an increased expression of monocytes and adhesion molecules on neutrophils in neonates born from PE [64]. A significant finding of this study was the heightened plasma levels of interleukin-8 (IL-8) and growth related oncogene-α (GRO-α). These CXC chemokines are compelling chemoattractants for neutrophils and they activate monocytes and T cells. Additionally, they attract leukocytes to inflammation sites inducing reactive oxygen species expression and secretion of matrix-degrading enzymes [64]. CXC chemokines that contain the ELR motif are unique in their ability in regulating angiogenesis. However, those lacking the ELR motif are potent antiangiogenic factors inhibiting neovascularization [65]. CXCL10 is expressed in placental vascular smooth muscle and endothelial cells of blood vessels where it alters their motility and differentiation, thus mitigating spiral artery reshaping, whilst CXCL12 attenuates trophoblast invasion. Higher concentrations of CXCL10 and

CXCL12 have being reported in pre-eclamptic than in healthy pregnancies [65].

Interleukin-27

Two IL-27 SNPs, rs17855750 and rs153109, influence PE development [37]. Rs17855750 is a missense polymorphism, where the conversion of a T allele to a G allele results in a serine alanine alteration, whilst Rs153109 is a SNP located on the promoter region of the IL-27 gene, mediating transcription and protein expression. It was established that the SNP rs17855750 is associated with PE, whilst the rs153109 SNP exhibited a protective effect against PE development. Hence, they may be used as potential genetic markers for the susceptibility to PE [37, 38].

Interleukin-4

Interleukin-4 (IL-4), secreted by activated Th2 cells, basophils, mast cells and B-lymphocytes, is vital in the regulation of Th2-type immunity. This pleiotropic cytokine plays a role in antagonising the Th-1 immune response and promoting humoral immunity. Zhang et al. (2017) did a study with 162 pre-eclamptic pregnant women and 266 healthy controls [39]. Their study reported no significant association with the IL-4 C + 33T polymorphism and PE, yet found that an IL-4 C-590T polymorphism contributes to the development of PE, suggesting its role as a candidate gene [39]. Fraser and co-workers conveyed similar findings [40]. On the other hand, Salimi et al. considered the 70 bp variable number of tandem repeat (VNTR) polymorphism on the IL-4 gene and established that the presence of the IL-4 VNTR RP2 allele is associated with PE susceptibility [41].

Interleukin-1

Another prominent cytokine mediating the inflamed milieu exhibited in PE is interleukin-1 (IL-1). This family of cytokines consist of two pro-inflammatory mediators, IL-1alpha (IL-1α) and IL-1beta (IL-1β). They are secreted by monocytes, macrophages and epithelial cells and possess a host of functions, of which induction of a pro-inflammatory cascade is included [66]. The IL-1α gene polymorphisms rs17561 and rs1800587 were demonstrated to be associated with PE development in a cohort of Sri Lankan women [42]. Also, the IL-1α rs17561 TT and GT genotypes induce a higher plasma level of C-reactive protein in its carriers, inferring a pro-inflammatory phenotype as exhibited in PE [42].

Vitamin D

Vitamin D is involved in the control of phosphorus and calcium homeostasis, apoptosis, cell differentiation and regulation of the maternal immune system all of which are crucial to implantation [67]. A deficiency in vitamin D has been associated with unfavourable pregnancy outcomes such as PE [68, 69]. The placenta was identified as the major site for the circulating form of vitamin D, 25(OH) D, to be converted to the active form, 1.25(OH)2D3, by enzyme action of 1α-hydroxylase (CY27B1) [70]. 1.25(OH)2D3 binds to the vitamin D receptor (VDR) which regulates genes that are involved in trophoblast functioning and implantation [67]. This suggests an autocrine pathway of vitamin D in trophoblast cells [71]. Additionally, it is reported that 1.25(OH)2D3 promotes anti-inflammatory responses in both the maternal decidua and foetal trophoblast cells. Importantly, 25(OH) D is a potent suppressor of placental inflammation; hence, it is plausible to assume that a deficiency in vitamin D results in the hyperimmune activity evident in PE [70]. The expression of the different metabolic components of placental vitamin D have being demonstrated where vitamin D-binding protein, VDR and CYP2R1 expressions were decreased whilst CYP24A1 and CYP27B1 expressions were increased in pre-eclamptic compared to normotensive placentae [71]. Furthermore, a significant association was found between the CYP24A1 risk variant rs2209314 and vitamin D deficiency in pregnant women in Southeast China [24].

Interferon-Gamma

Interferon-gamma (IFN-γ) is commonly assayed in pregnancy related research to determine deviations from healthy gestations. It has a dynamic role in a variety of cellular processes such as inhibition of cell proliferation and induction of apoptosis as well as a role in immune-surveillance of tumours and pathogens [72]. IFN-γ is involved in vascular remodelling and maintaining the decidual layer of the uterus in normal pregnancy [73]. Studies have shown that uterine natural killer cell secrete IFN-γ which inhibits trophoblast cell invasion in the first trimester of human gestation [72]. In pre-eclamptic pregnancies, concentrations of IFN-γ are heightened in plasma and decidual tissue, proposing this elevation to be the hallmark of impaired vascularisation which occurs in PE [72, 73]. Pinheiro and colleagues (2015) investigated the association of the IFN-γ polymorphic gene and concluded that the + 874T/T genotype of IFN-γ is associated with severe PE development, proposing that it may be a candidate gene for the syndrome. In contrast, other studies have reported no association with IFN-γ gene polymorphisms in PE [19, 74].

Transforming Growth Factor-Beta

Transforming growth factor-β (TGF-β) has many biological functions that include extracellular matrix formation, mediation of cell proliferation, differentiation and migration as well as regulation of immune responses. Endoglin (Eng) or CD

105, is a cell surface co-receptor of TFG-β1 and TGF-β3. This antiangiogenic factor is also a critical component in endothelial cells and syncytiotrophoblasts [75]. In addition to sFlt-1, soluble endoglin (sEng) is reported to be elevated in pre-eclamptic women [9, 76–78]. Interestingly, Govender et al. [76] carried out a novel study demonstrating an increase of sEng and sFlt-1 in PE compared to normotensive pregnancies, the levels of these antiangiogenic factors increased only marginally in the HIV positive pre-eclamptic cohort as compared to the HIV negative pre-eclamptic women. This suggests that there may be a neutralisation of the immune hyperactivity associated with PE, by infection [76]; however, HAART may also influence these results.

sVEFGR-1

Both vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) work synergistically to mediate angiogenesis [9]. Alternatively known as sVEGFR-1, soluble fms-like tyrosine kinase-1 (sFlt-1) is a shortened spliced variant of Flt-1. This antiangiogenic factor acts as an antagonist to VEGF and PlGF by binding to and inhibiting their interaction with endothelial receptors. The placenta is the major source of sFlt-1 during pregnancy in response to hypoxia, as elevated circulating levels regress after delivery of the placenta [9, 79, 80].

An equilibrium of pro-angiogenic medium is desired for optimum angiogenesis hence, is a pre-requisite for placentation. In PE, there is an increase in the antiangiogenic factor sFlt-1, with concomitant decrease in serum VEGF and PlGF (angiogenic factors) [10, 76, 79–81]. In contrast to normal pregnancy, VEGF has a higher binding affinity to sFlt-1 than Flt-1, diminishing the circulating levels of VEGF [25]. Simultaneously, there is a degradation of the extracellular domain of VEGFR-2 by MMP-9 [25]. This leads to a reduced bioavailability of nitric oxide due to impaired phosphorylation of endothelial nitric oxide synthase by Akt culminating in endothelial dysfunction and impaired angiogenesis [25].

The inherited vulnerability of PE in women is probably associated with the heredity of endothelial function via the endothelial dysfunction theory [13]. Luizon and colleagues [25] hypothesised that single polymorphisms interacting with each other can warrant the development of PE. Hence, epistasis is proposed to be an important component in increasing the vulnerability and liability to PE development. Combinations of MMP-9-1562CC with VEGF-634CC and MMP-9-1562CT with VEGF-634CC or-634GG occur more frequently in pre-eclamptic than normotensive pregnant women. Thus, it is understood that combinations of specific genotypes of MMP-9 and VEGF increases the susceptibility to PE development [25]. Sun et al. had also reported an association of MMP-9 polymorphisms with PE [26]. Srinivas et al. [27] investigated the link between allelic variations in angiogenesis and PE, in a cohort of 606 Black and White women. The Flt-1 rs12584067 and rs7335588 and VEGF-C rs1485766 and rs6838834 single-nucleotide polymorphisms (SNPs) were associated with PE in Black women. However, in White women, Flt-1 rs722503 and VEGF-C rs7664413 SNPs were associated with PE [27].

Endothelial Nitric Oxide Synthase

In addition to TFG- β, Eng also impacts on endothelial nitric oxide synthase (eNOS) activity in regulating vascular tone. Endothelium-derived nitric oxide is a formidable vasorelaxant that is involved in the regulation of systemic blood pressure, angiogenesis and vascular permeability. Nitric oxide dependant vasodilation is disparate in the presence of sFlt-1 and sEng [9, 75]. Singh et al. found no significant association between Glu298Asp eNOS gene polymorphism and PE [82]. Whilst TNF-α is implicated in the structural and functional changes in endothelial cells resulting in the placental shortcomings exhibited in PE, its activity involving inducible nitric oxide synthase (iNOS) impacts vascular reactivity and directly induces oxidative damage. Single-nucleotide polymorphisms of iNOS have been evaluated in an Indian population of pre-eclamptic women where the candidate genes viz., G300A exon 8 and G274T exon 16 of iNOS show a significant association with PE development [31]. In healthy normotensive gestation, iNOS mRNA is expressed, regulating myometrial tone; however, low concentrations of iNOS mRNA are evident in PE [31].

Renin-Angiotensin System

During pregnancy, the physiological remodelling of spiral arteries is influenced by the renin-angiotensin system (RAS) [83]. In women with uncomplicated normotensive pregnancies, oestrogen induces an elevation in circulating and tissue levels of angiotensinogen, subsequently causing an overexpression of the RAS. Additionally, their prorenin, renin and angiotensin II levels increase in correlation with a rise in angiotensinogen [84]. In PE, plasma angiotensinogen levels remain unchanged when compared to normotensive pregnancies, whilst their plasma renin and aldosterone levels are normal or reduced [84]. Mello et al. [83] made a novel discovery regarding angiotensin converting enzyme (ACE) I/D polymorphisms and the recurrence of unfavourable obstetric outcomes in women with previous PE. Although the ACE DD genotype, at present, is not a good risk indicator for PE development, it could be used as a counselling tool in women with a history of PE for subsequent pregnancies [83]. Bouba et al. and Aung et al. demonstrated an association with angiotensinogen 235T gene polymorphism and PE [28, 29]. Also, Rahini et al. demonstrated that epistatic combinations of the G allele of the angiotensin type 2 receptor (AT2R) and the C allele of the angiotensin type 1 receptor (AT1R), D allele of the ACE and T allele of the MMP-9 genes respectively, were

associated with the risk of PE development [30]. In contrast, Roberts et al. and Li et al. found no association between RAS polymorphisms and PE development [85, 86].

Apolipoprotein

Hyperlipidaemia can result in endothelial dysfunction and may contribute to atherosclerosis and PE development [87]. It has been reported that atherosclerosis in decidual vessels is caused by an increased triglyceride and low-density lipoprotein levels with concurrent deceased high-density lipoprotein-cholesterol and apolipoprotein A1 concentrations [87]. Apolipoprotein E is a vital role player in atherosclerosis, by altering inflammatory responses. Individuals that carry the apolipoprotein E polymorphism containing the E2+ allele is associated with lower cholesterol levels, whilst those with the E4+ allele is associated with higher cholesterol levels; however, neither polymorphisms are linked with PE development [88, 89]. Apolipoprotein J is responsible for stabilising cell membranes at the fluid-tissue interface thereby protecting the vascular endothelium from attack by certain plasma factors such as complement complexes. Chen et al. concluded that the 866C → T apolipoprotein J polymorphism is associated with PE and essential hypertension in a Chinese population and hence, may play a role in PE predisposition [32].

Genome-Wide Association and Linkage Studies

Studies published have largely focused on SNPs; however, this approach is limiting in the overall inheritability associated with complex disorders [90]. Hence, an opening for genome-wide association studies (GWAS) was created (summarised in Table 2), as this approach is not bound by current functional biological knowledge that is used in candidate gene evaluation [97].

The first GWAS in PE analysed copy-number variants (CNVs) and identified three rare deletions in PE, of which the most interesting deletion involved the pregnancy-specific glycoprotein 11 (PSG11) gene located on chromosome 19 [90]. Pregnancy-specific glycoproteins are produced by placental syncytiotrophoblasts and possess immunomodulatory functions. In particular, PSG11 induces the secretion of anti-inflammatory cytokines that are required to maintain a successful pregnancy [90]. PSG11 is also reported to have a low density of CNVs and a high frequency of segmental duplications, predisposing the affected region to recurrent chromosomal rearrangements [90]. Through inspection of the whole PSG gene family, deletions in the 48.461 to 48.476 Mb region was shown to be augmented in PE [90]. Despite no replication of the CNVs identified by Zhao et al. (2012), several novel potential CNVs found on chromosome 1, 2, 3, 5, 6, 7, 9, 12 and 22 were identified [91]. The variance in the results attained from the two studies was attributed to differences in microarray coverage and geographical location of the study populations [91].

Despite the HLA gene been identified as a candidate gene predisposing a mother to PE development [33–36], there are conflicting findings through genome-wide linkage studies [98–100]. Hence, it is plausible that the maternally expressed gene responsible for the susceptibility to PE does not lie near the HLA region [99]. Interestingly, genome-wide linkage scans of Finland (2p25) [92], Icelandic (2p13) [93], Australian (2q14.2) [94] and New Zealand (2q23) [95] populations concluded that similar positions on chromosome 2 predisposes these populations to PE; therefore, it should be designated the "PREG11" (pre-eclampsia, eclampsia gene 1) locus [95]. In addition, a study carried out in 2009 by Johnson et al. [96] focused on identifying genes susceptible to PE on chromosome 5q. They reported a significant genetic linkage for the endoplasmic reticulum aminopeptidase 2 (ERAP2) gene and PE development [96].

Bioinformatic Studies

Since PE is expressed phenotypically only in pregnancy, challenges surrounding study of its aetiology are pronounced. Obtaining tissue from first trimester placenta is not possible, whilst animal models present with their own set of criticisms [101]. Hence, Rabaglino et al. [101] used a bioinformatics approach by way of surplus chorionic villous tissue sampling.

Table 2 Genome-wide association/linkage studies in pre-eclampsia discussed in this review

Author and year	Chromosomes/genes identified to be associated with PE	Study population
Zhao et al. 2012 [90]	PSG11	American (Iowa)
Zhao et al. 2013 [91]	Chromosome 1, 2, 3, 5, 6, 7, 9, 12 and 22	Afro-Caribbean, European ancestry, Hispanic and Thai
Laivuori et al. 2003 [92]	Chromosome 2 (2p25)	Finland
Arngrı'msson et al. 1999 [93]	Chromosome 2 (2p13)	Icelandic
Johnson et al. 2012 [94]	Chromosome 2 (2q14.2)	Australian
Moses et al. 2000 [95]	Chromosome 2 (2q23)	Australian and New Zealand
Johnson et al. 2009 [96]	ERAP2	Australian and Norwegian

Table 3 Bioinformatic studies in pre-eclampsia discussed in this review

Author and Year	Gene associated with PE
Tejera et al. 2012 [102]	FLT1, TNF, VEGFA and PGF, SH2B2, MEN1, SAT1, DNM1, IQGAP1, LYN, TBK1, NDRG1 and PDIA3
Tejera et al. 2013 [103]	FLT1, ENG, INHA, LEP, FSTL3, XBP1, MMP1, PROCR, FLNR, BCL6, INHBA, QSOX1, LYN, NDRG1 and TPBG
Song et al. 2015 [104]	CRN, LHB, VTN, FN1, miRNA 200b/c, miRNA 154 and miRNA 27 a/b
Ching et al. 2015 [105]	IL12B, PIK31, FAS and IGF1

Their results suggest that there is impaired or insufficient endometrium and decidual natural killer cell maturation during the secretory phase and early pregnancy prior to PE development hence, pre-decidualization and decidualization is defective.

Tejera et al. [102] also applied bioinformatic tools to create a wide-ranging database of genes reported to be associated with PE. They detected some known PE genes like FLT1, TNF, VEGFA and PGF [102]. In addition, other genes such as SH2B2, MEN1, SAT1, DNM1, IQGAP1, LYN, TBK1, NDRG1 and PDIA3 also reported high scores but have been poorly explored regarding PE pathophysiology [102]. Analysis of genetic algorithms and gene co-expression have identified the FLT1, ENG, INHA, LEP, FSTL3, XBP1, MMP1 and PROCR genes pertinent to PE [103]. However, they have also identified the FLNR, BCL6, INHBA, QSOX1, LYN, NDRG1 and TPBG genes that require more laboratory research to explore its probable role in PE [103].

Abnormally expressed CRN, LHB, VTN and FN1 genes were revealed in early onset PE and are believed to be causal in some of the associated pathologies such as angiogenesis, hypoxia-ischaemia, inflammation and autoimmunity [104]. Furthermore, miRNA 200b/c, miRNA 154 and miRNA 27 a/b were notable in the analysis of microRNAs from early onset pre-eclamptic placentas through bioinformatic techniques and may play a role in the expression of differentially expressed genes [104].

Given the established risk of preterm birth and adulthood disease onset, Ching and colleagues identified significant DNA methylation alterations on IL12B, PIK31, FAS and IGF1 genes signifying an association between lipid dysregulation and inflammation in new-borns of early onset pre-eclamptic patients, which may predispose them to an increased lifelong risk of cardiovascular disease [105]. Table 3 provides a synopsis of pertinent genes discovered through bioinformatic studies.

Why Certain Genes in African Population May Be Important?

Worldwide, both PE and HIV infection contribute significantly to adverse perinatal and maternal outcomes [106]. This is especially true for South Africa, a low- to middle-income country in which the incidence of both conditions is high and is major contributors to maternal morbidity and mortality [10]. Maharaj et al. reported that although the rudimentary immunological fluctuations exhibited in HIV and PE is incompletely understood, inflammation seems to be a commonality in both conditions [107].

MicroRNAs (miRNAs) are small non-coding RNAs that are responsible for gene expression. MiRNA-146a represents an overstimulation of the inflammatory response by acting on its target genes, TRAF-6 and IRAK-1; hence, a dysfunctional miRNA-146a results in a pro-inflammatory milieu [106]. A downregulated presence of miRNA-146a has been reported in pre-eclamptic compared to normotensive placentas, suggesting a probable role of this miRNA in the pathogenesis of PE [108]. A study carried out on Zulu ethnic South African women concluded that the miRNA-146a rs2910164 polymorphism is not associated with PE susceptibility; however, the miRNA-146a GC/CC genotype may reduce the susceptibility of severe PE, which might be further influenced by HIV infection [106].

Genotypes of renin, angiotensin II receptor 1 and 2 as well as angiotensin converting enzyme gene polymorphisms showed no association with PE development in the cohort of South African women [29, 109]. Despite the report confirming that the presence of the TT allele on the cytochrome P450 gene exerted a protective effect against PE development it highlights that the T allele of the angiotensinogen gene may be a role player in PE pathogenesis [29, 109].

Also, apolipoprotein-L1 (Apol-L1) confers resistance to parasites of the *Trypanosomida* family, which can be found in high frequencies in sub-Saharan Africa [110]. With the evolution of subspecies of trypanosomes, the Apol-L1 gene also underwent a positive selection to continuously provide protection against the parasite [110]. Kasembeli et al. have reported an extremely strong link between the presence of the Apol-1 gene polymorphism and kidney disease in HIV positive Black South African women [111••]. Pre-eclampsia is associated with kidney disease [112]. It is reported in an African-American population, mothers of children with Apol-1 two risk alleles are at an increased risk of developing PE, thus it is plausible that Apol-1 gene polymorphisms involving the G1 and G2 risk alleles will be implicated in its aetiology [113].

Future Considerations

Regardless of the familial linkage reported and the associated risks, understanding of the polymorphic genes remains

limited. Moreover, over a third of possible candidate genes have been shown to be not associated or even present in pre-eclamptic placentae [114]. Conversely, bioinformatic studies have identified an array of possible genes that may play a role in the pathogenesis of PE, although they still require laboratory validation [102, 103]. With respect to GWAS/GWLS, the smaller sample size and accompanying low odds ratio and statistical power serves as a limitation in identifying single SNPs causing complex disorders like PE [97].

Scientists are aware of the growing need for large DNA sample collections and the formation of bio-sample banks [97]. In the future, studies could involve more diverse populations, which would be possible through collaborations [97]. Additionally, the cohort could include samples taken from the baby, mother and father to get a complete understanding of the roles of the genes. Studies could also look at genes in various combinations to determine if the presence of two or more genes working synergistically, results in PE. Furthermore, the effect of environmental factors affecting the liable gene/s will also assist in understanding and identifying at risk women [97].

Summary

Despite the research attention that is focused on this surreptitious syndrome, a definitive cause eludes scientists and physicians, alike. Genetic studies can fulfil a dual purpose of suggesting novel hypotheses through genome-wide screening and testing these hypotheses via candidate gene studies. However, publications to date have only presented inconsistent and conflicting results regarding candidate gene analysis. Hence, this leaves an abundance of unidentified knowledge, with the need to re-examine current findings to better perceive the significance of genes in PE.

Compliance with Ethics Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major Importance

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