Genes for Preeclampsia
An Opportunity for Blood Pressure Genomics

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Preeclampsia is a special case of hypertension with proteinuria, complicating 3% to 8% of pregnancies[1]: It is induced by pregnancy and always vanishes with the delivery of the placenta. The dreaded complications are progression to eclampsia, a life-threatening condition in which grand mal seizures occur in a woman with preeclampsia, or hemolysis, elevated liver enzymes, low platelets syndrome that might be considered a severe form of preeclampsia. Overall, there is significant mortality because of preeclampsia with ≈1 death per 100 000 pregnancies, even in high-income settings.

Although preeclampsia likely follows a separate pathophysiology, analogies can be drawn to primary hypertension as risk factors partly overlap: older women, women with chronic kidney disease, and women with higher body mass index are at increased risk; preeclampsia is rigorously monitored and followed because of the dreaded consequences, as is primary hypertension, but mild preeclampsia is most often asymptomatic and does not always progress to target organ damage; the incidence of preeclampsia is on the rise and induces important societal costs[2]; the root origin of preeclampsia remains obscure, similar to primary hypertension: endothelial causes have been of major interest,[3] and evidence for similar origins exists in primary hypertension.[4]

There is a distinct role of genes in the pathogenesis of preeclampsia as suggested by heritability studies, and this is best illustrated by the observation that women who have a first-degree relative with preeclampsia have ≈2-fold risk of developing preeclampsia themselves.[5]

One important difference between primary hypertension and preeclampsia is the presence of fetal tissue, illustrated by the regression of preeclampsia with the delivery of the placenta. In turn, the fetus may also be effected by eclampsia with particular risks of intrauterine growth restriction, prematurity, and stillbirth. This makes the genomics more rich and complex: similar to oncology (and infectious disease), there are >1 genome to analyze that are similar, but distinctly different: there are possible genetic contributions by the mother and the fetus.

Both types of genetic contributions, of the mother and the fetus, have now been assessed using unbiased genome-wide association study (GWAS) approaches (Table), a technique that greatly helps to better understand complex genetic cardiovascular traits.

A variant near *FLT1* has been identified in a GWAS on fetal DNA from pregnancies with preeclampsia[8] and gene with possible involvement points toward a role of angiogenesis in the pathophysiology of preeclampsia.

Gray et al[6] now report a large maternal DNA GWAS, and they identify 1 variant as experiment-wide significant, near the *PLEKHG1* gene.

It is interesting to see that the locus identified by Gray et al[6] overlaps with previous blood pressure GWAS results (Table) and also several other phenotypes ranging from coronary artery disease to substance abuse. The other maternal DNA GWAS finding published[7] does not overlap with blood pressure GWAS findings. Does this indicate that the pathophysiology of hypertension in the general population and preeclampsia are different? The number of GWAS findings to date is too small to answer the question. Both of the currently published genome-wide findings on preeclampsia using maternal DNA are not yet replicated in an independent study and therefore have an increased chance of being false-positive findings.

Table. Summary of Current Genome-Wide Significant Loci by Preeclampsia GWAS, Both Using Maternal and Offspring DNA (Type of Analysis)

Type of Analysis	Sentinel SNP	Effect Size (OR)	Nearby Gene	Locus Known for GWAS BP Signal	*P* Value in SBP GWAS	Ref
Maternal						
	rs9478812*	1.18	*PLEKHG1*	Yes	0.278	6
	rs7579169*	1.57	*INHBB*	No	0.837	7
Offspring						
	rs4769613	1.44	*FLT1*	No	0.975	8

The sentinel single nucleotide polymorphism (SNP) designates the genetic variant (effect size given as OR) that was genome-wide significant, the nearby gene highlighted by the respective authors is indicated. If the locus is overlapping (<1 Mbp) with a known BP locus, this is indicated in the column Locus known for GWAS BP signal based on www.bloodpressuregenetics.org. *P* value in SBP GWAS indicates a lookup of the preeclampsia SNP in a large SBP GWAS of the general population that is publicly available.[9] BP indicates blood pressure; GWAS, genome-wide association study; OR, odds ratio; and SBP, systolic BP.

*Without independent replication. rs9478812 was assessed by the proxy rs1494311 (r2 0.945 in 1000G).

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In summary, these findings are encouraging—preeclampsia is a phenotype that is difficult to analyze with large-scale genomic studies because it does not occur frequently in the population, and therefore the initial approaches of GWAS by large population-based studies can only be of limited help. Large studies based on electronic health records will bring additional cases. But building on several studies without genome-wide significant findings,[10,11] there are now first results, and the continuation of this journey can help to better understand the deadly disease preeclampsia.

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Disclosures

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