

Genetic aspects of preeclampsia

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Does preeclampsia have a genetic basis?
 - 3.1. Family studies
 - 3.2. Twin studies
 - 3.3. Genetic aberration in the fetus
 - 3.4. Contribution of the paternal genotype
 - 3.5. Change in paternity-Interpregnancy interval
4. Molecular genetics of preeclampsia
 - 4.1. Candidate gene studies
 - 4.2. Genome-wide scans
 - 4.3. Gene expression studies
5. Perspective
6. Acknowledgements
7. References

1. ABSTRACT

Preeclampsia has a familial component suggesting that one or more common alleles may act as susceptibility genes. Some families may have "private" predisposing mutations. The central role of the placenta in the pathogenesis of preeclampsia implies that fetal genes contribute to the disease process. Twin studies support the role of maternal and fetal gene interaction. Candidate gene studies have not yielded consistent results. Genome-wide linkage studies provide powerful means to study disease susceptibility genes, and several loci have been mapped. Parent-of-origin effect of the *STOX1* gene has been suggested on chromosome 10q22 locus in the Dutch population. Maternally inherited missense mutations in the *STOX1* gene of the fetus have been shown to co-segregate with the maternal preeclamptic phenotype. Up-regulation of placental leptin expression has been found in several studies and might be of importance in the pathogenesis of preeclampsia. DNA microarray is ideal tool for screening gene expression in preeclamptic tissues, but critical attitude is needed when interpreting the results. The placental DNA and mRNA in maternal plasma hold great promise as novel biomarkers for the prediction of preeclampsia. Finding genes predisposing to preeclampsia will enhance our understanding of the disease mechanism, and might allow identification of prognostic and therapeutic subgroups.

2. INTRODUCTION

Preeclampsia is common (3-5% of pregnancies), and it is one of the major causes of maternal and perinatal morbidity and mortality worldwide. If undiagnosed, or without intervention, preeclampsia is potentially a life-threatening disease. It places great demands for prenatal care because the onset and clinical course is unpredictable, and there are currently no predictive tests or prophylaxis available. Placenta is vital for the disease process. The current therapy is delivery, which often causes iatrogenic prematurity. If preeclampsia could be prevented or fully treated 50 000 maternal deaths could be avoided every year.

Although the etiology of preeclampsia is still unknown, there has been considerably progress to understand the pathophysiology of the disorder, especially during the past two decades when the attention has been directed at the entire syndrome and not just at the increased blood pressure (1). Preeclampsia is considered secondary to the interactions of reduced placental perfusion with diverse maternal factors that alter endothelial function, and the pathological process is present already in the first half of the pregnancy long before the clinical syndrome becomes apparent (2). Preeclampsia is more than reduced placental perfusion, because placental biopsies examined

Genetic aspects of preeclampsia

with conventional histological techniques indicate similar reduced vascular remodeling and abnormal implantation not only in preeclampsia, but also in pregnancies with intrauterine growth restriction without maternal syndrome, and in pregnancies with preterm births that are not associated with infection (3, 4). Some maternal risk factors for preeclampsia, such as hypertension, diabetes mellitus, obesity (5-7) and insulin resistance (8) are identical to those for atherosclerosis. The balance between placental and maternal factors predisposing to preeclampsia is likely to be different in different pregnancies. It is possible that preeclampsia is not a single entity, but a final common pathway by which the woman reacts to pathological pregnancy (9). Research and recognition of genes and thereby biochemical components critical for complex interactions between mother and fetal/placental unit will highlight known biochemical pathways or reveal entirely new pathways for the pathogenetic process. It would be highly desirable to refine the diagnostics of preeclampsia based on tests of genetic variants that might allow identification of prognostic and therapeutic subgroups.

Not only the complex interactions between mother and fetal/placental unit makes the genetic approach to preeclampsia difficult. First, multiplex families (with several patients) are more difficult to find in preeclampsia than in disorders in which both genders are affected. Moreover, in preeclampsia not only status of all men is unknown, but also of those women who are not reproduced. Second, the mode of inheritance is unknown. Third, the definition of preeclamptic phenotype for genetic analysis is not always easy especially in circumstances where antenatal care is inadequate. Preeclampsia is easily confused with other hypertensive disorders of pregnancy (10). There are currently several classifications. Davey and McGillivray's definition of pregnancy hypertension (11) and Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (12) are commonly cited. These two definitions stipulate normotension before 20 weeks of gestation, new onset hypertension, and proteinuria. The unambiguous phenotype is essential for the genetic studies. It has been recommended that the disease should be defined for research purposes only in primigravidae since women with recurrent preeclampsia often have other underlying conditions such as renal disease or hypertension (9). Fourth, preeclampsia affects internal organs, and as a consequence does not provide easy access to target tissues for the researchers. Preeclamptic placenta is not available in the first half of the pregnancy when the pathological process has its roots. Glomerular endotheliosis in the preeclamptic kidney is a lesion, which has been used to characterize the clinical-pathological correlation of the disease (13). The use of renal biopsies is not ethical any more because the interpretation does not influence management or timing of delivery. However, the renal biopsies have demonstrated how difficult it can be to distinguish by clinical criteria alone between preeclampsia, essential or secondary hypertension, renal disease, or combination of these entities (13). Last, attempts has been made to produce animal models for preeclampsia, but most are incomplete compared to the full spectrum of the human

disease (14). However, some or most clinical signs can be produced in laboratory animals by uteroplacental hypoperfusion, dietary manipulation, alterations in endothelial function (nitric oxide synthesis inhibition, low-dose endotoxin infusion) and gene manipulation (14, 15). Administration of sFlt1 (soluble fms-like tyrosine kinase 1) to pregnant rats induces hypertension, proteinuria, and glomerular endotheliosis, the classic lesion of preeclampsia (16).

Genetic factors contribute to virtually every human disease, and understanding the role played by genetic factors in disease is also expected to increase the understanding of non-genetic, environmental contributions (17). Despite the obstacles placed to the genetic research of preeclampsia by the nature of this condition, there has been a considerable progress in the field. The first part of this review asks: Does preeclampsia have a genetic basis? To this end family studies, twin studies, the effect of genetic aberration in the fetus, the contribution of paternal genotype, and change in paternity and the interpregnancy interval as risk factors will be presented. The second part concentrates on the molecular genetic studies of preeclampsia. Last, the intriguing perspectives such as the use of placental nucleic acids in maternal plasma as biomarkers for the prediction of preeclampsia in the presymptomatic stage will be discussed.

3. DOES PREECLAMPSIA HAVE A GENETIC BASIS?

3.1. Family studies

Preeclampsia has clearly a familial component. Women who were born of a pregnancy complicated by preeclampsia are three times as likely to have preeclampsia as women born from pregnancy without such complication (18). Dr. Leon Chesley is due to collect credit for the "flagship" family study. He started a study of women with eclampsia in 1935 and continued it until 1974. He collected data on pregnancies of 147 sisters, 248 daughters, 74 granddaughters, and 131 daughters-in-laws of eclamptic women delivered in the Margaret Hague Maternity Hospital in New Jersey between 1931 and 1951 (19, 20). This study and other family studies from the United States (21, 22), Scotland (23-26), and Iceland (27) have been summarized in Table 1. Dr. Chesley has emphasized that multiparous preeclamptic or eclamptic women are different and should be analyzed separately (28). Indeed, in the majority of family studies only first viable pregnancies have been included into the analyses.

Chesley's data fit closely with the single gene model with the frequency of the putative gene being 0.25 (20). Arngrimsson *et al.* tested four inheritance models for the combined family data, and the major maternal dominant gene model with reduced penetrance or multifactorial model fit best (29). There are basically two alternatives. (i) It is possible that one or more common genetic variants may contribute to the risk of preeclampsia. A common predisposing variant might allow predictive testing or suggest a treatment widely applicable (30). (ii) It is also likely that many of the aberrant genes will be "private"

Genetic aspects of preeclampsia

Table 1. Family studies of preeclampsia and eclampsia

Result	Comment	Reference
Preeclampsia in 28% of the mothers of preeclamptic women Preeclampsia in 13% the mothers of women with normal pregnancies	All pregnancies of mothers analysed	21
Preeclampsia in 13.8% of the sisters of preeclamptic women Preeclampsia in 4.5% of the sisters of women with normotensive pregnancies	First pregnancies of sisters analysed	23
Preeclampsia or eclampsia in 36.7% of sisters, 26.2% of daughters, 6.1% of daughters-in-law, 16.2% of granddaughters of eclamptic women	First viable pregnancies of relatives analysed Population: Caucasian	19,20
Preeclampsia in 22.9% of mothers of preeclamptic women Preeclampsia in 6.4% of mothers of women with normal pregnancies Preeclampsia in 18.2% of sisters of preeclamptic women Preeclampsia in 8.6% of sisters of women with normal pregnancies	Index women: primiparous First pregnancies of relatives analysed	24
Preeclampsia in 15.9% of mothers of preeclamptic women Preeclampsia in 3.1% of mothers of women with normal pregnancies Preeclampsia in 4.4% of mothers-in-law of preeclamptic women Preeclampsia in 5.3% of mothers-in-law of women with normal pregnancies	Index women: primiparous analysed separately First pregnancies of relatives analysed	25
Preeclampsia or eclampsia in 38.1% of daughters of eclamptic women	Index women: primiparous First pregnancies analysed Population: African-American, Caucasian	22
Preeclampsia in 11.3% of sisters of preeclamptic women	Index women: multiparous included First pregnancies analysed	26
Preeclampsia or eclampsia in 25.8% of daughters of preeclamptic or eclamptic women Preeclampsia or eclampsia in 10.6% of the daughters-in-law of preeclamptic or eclamptic women	Index women: multiparous included	27

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mutations, affecting only a handful of women (30). Family studies support the major role of maternal genes in the etiology of preeclampsia.

3.2. Twin studies

Twin studies have been used to estimate the heritability of the disease. Monozygotic (MZ) twins are genetically identical (except somatic cell mutations, numbers of mitochondrial DNA molecules, and pattern of x-inactivation in females), whereas dizygotic (DZ) twins share on average half of their genes (same as sibs). Two case reports on MZ twin pairs concordant for preeclampsia has been published (31, 32), but three large twin studies did not find a single twin pair concordant for preeclampsia (33-35). However, one study which included 917 MZ and 1199 DZ female twin pairs found that 25% of the women with a MZ twin sister who had had preeclampsia will develop the same disease (36). Among DZ twin sisters, the corresponding proportion was 6%. According to the heritability estimates of that study, environmental effects are of about equal importance as genetic effects in the etiology of preeclampsia (36). Twin studies support the role of maternal and fetal gene interaction more maternal genes alone in the etiology of preeclampsia. In other words, increased risk of preeclampsia may be associated with a specific combination of maternal and fetal alleles. Such a combination could consist of alleles of the same or different genes. Good example comes from transgenic mice model for preeclampsia in which female mice carrying human angiotensinogen (*AGT*) gene were mated with male mice carrying human renin gene (37). Paternal human renin gene expression in the placenta resulted in preeclampsia-like syndrome with hypertension and proteinuria in the female mice carrying human *AGT* gene, but not in the wild type mice (37).

Twin studies cannot separate the effects of maternal and fetal genetic factors from environmental factors. To this end, Cnattingius and coworkers analyzed in a large database study pregnancy outcomes from families

joint by full siblings (38). According to their analyses, genetic factors accounted more than half of the liability to preeclampsia, and maternal genes contributed more (variance 0.35) than the fetal genes (variance 0.20). Maternal and paternal components were equal to fetal genetics effects. They also find strong couple effect (environmental contribution and interaction between maternal and paternal genes) on the liability for preeclampsia (variance 0.13).

3.3. Genetic aberration in the fetus

An association between preeclampsia and fetal trisomy 13 (39-42), or partial trisomy for 13q (43) suggests the dose effect of some fetal genes encoded on chromosome 13. Excess secretion of a naturally occurring anti-angiogenic molecule of placental origin, sFlt-1, the gene of which is located on chromosome 13q12, may contribute to the pathogenesis of the maternal syndrome in preeclampsia (16, 44). Preeclampsia, usually of early-onset, has also been associated with pregnancies complicated by molar placental changes (45, 46). Complete hydatidiform moles have 46 chromosomes and contain solely paternal contribution to the genome (47). Partial hydatidiform moles have 69 chromosomes (triploidy), including 23 of maternal origin and 46 of paternal origin, whereas triploidy that involves 23 paternal chromosomes and 46 maternal chromosomes is not associated with molar placental changes (48). The report on 70 second trimester pregnancies with triploidy, placental molar changes were noted in 28.3% (49). Preeclampsia was diagnosed in 4.3% of all triploid pregnancies, but in 15% of subgroup presenting placental molar changes (49).

Both paternal and maternal contributions to the trophoblastic genome are necessary for maintaining a balanced development of both embryonic and extraembryonic tissues (47). There are several possible explanations for suggested predisposition to preeclampsia in hydatidiform moles. (i) Increase in gene load, and changes in imprinting (determination of the expression of a gene by its parental origin) disrupt the normal development of the conceptus. (ii)

Genetic aspects of preeclampsia

Amount of the genome of the conceptus foreign to the mother increases, being completely foreign in pregnancies with complete hydatiform moles. The incidence of preeclampsia is also increased in ovum donation pregnancies, another situation where the whole genome of the conceptus is foreign to the mother (50). (iii) Reduced perfusion in enlarged, cystic placenta predisposes to preeclampsia. Studies on genetic aberration in the fetus support the major role of fetal genes in the etiology of preeclampsia.

3.4. Contribution of paternal genotype

The central role of the placenta in preeclampsia may imply that also paternal genes through the fetus contribute to the disease process. According to the population based data from Norway, mothers who were pregnant by a partner who had fathered a preeclamptic pregnancy in another woman had nearly twice the risk in their own pregnancies (51). These data were supported by the results from the Utah Population Database. A child of a man, whose own mother had had preeclampsia had twice the risk to be born of a pregnancy complicated by preeclampsia than a child of a man, whose own mother's pregnancy was not complicated by preeclampsia (18). The Norwegian investigators studied the preeclampsia in the second generation by analyzing information of 438 597 mother and baby pairs and 286 945 father and baby pairs obtained from Norwegian Birth Registry (52). Men born after pregnancy complicated by preeclampsia had 1.5-fold increased risk of fathering a preeclamptic pregnancy (52). The contribution of paternal genotype to preeclampsia is supported by large database studies.

3.5. Change in paternity-Interpregnancy interval

Preeclampsia has been hypothesized to have a immunebased or immunogenetic etiology (53). Preeclampsia is predominantly a disease of first pregnancy (1). The incidence of preeclampsia after a previous normal pregnancy is half of the incidence of the first pregnancy (51). Also women with a history of abortion who conceived again with the same partner nearly half the risk of preeclampsia (54). The change of partner has been shown to increase the risk of preeclampsia in women with no history of preeclampsia (51, 54-55), or unreported previous pregnancy outcome (56), and decrease the risk in women with previous preeclampsia (50, 55). However, these studies have been recently challenged by the four epidemiological studies from Scandinavia, which suggest that after adjustment of interpregnancy (38, 58,) or interbirth (59, 60) interval, a change of partner is not associated with the increased risk of preeclampsia in women without history of preeclampsia. These recent findings question the change in paternity as a risk factor for pre-eclampsia. However, potential confounders such as smoking, have not always been included in the analyses (59, 60). The association between change in paternity and preeclampsia is still being debated. Whether birth interval should be controlled as a confounder in the analysis is an unsettled question.

4. MOLECULAR GENETICS OF PREECLAMPSIA

4.1. Candidate gene studies

In genetic association studies educated guess is made of candidate genes relevant to the pathophysiology of preeclampsia. Blood samples are collected from patients

and matched controls. After isolation of DNA, the prevalence of genetic polymorphism in candidate gene is compared in the two groups. Genetic polymorphism is a variation in DNA sequence that occurs at least once in every 100 copies, and occurs throughout the human genome on average once every 500-1000 base pairs (61). Therefore, it should usually be possible to choose a functionally significant polymorphism for studying the gene of interest (61). The number of publications of genetic association studies of preeclampsia has exponentially increased in the last decade, but these studies have failed to identify universally accepted susceptibility genes. Candidate genes studies have been reviewed by Lachmeijer *et al* 2002. (62), Wilson *et al.* 2003 (63), and most recently Chappell & Morgan 2006 (64). Eight candidate genes involving thrombophilia (e.g. factor V Leiden (*F5*), methylenetetrahydrofolate reductase (*MTHFR*), prothrombin (*F2*), hemodynamics (e.g., angiotensin converting enzyme (*ACE*), angiotensin II type 1 and type 2 receptors (*AGTR1*, *AGTR2*), angiotensinogen (*AGT*), endothelial function (e.g. endothelial nitric oxide synthase (*NOS3*), and cytokines (e.g. tumor necrosis factor alpha (*TNF*), have been studied extensively with inconsistent results (70% of published candidate gene studies in preeclampsia) (64). Several explanations can be proposed for inconsistent outcome of candidate gene association studies. (i) The selection of the study population. If an allele is more frequent in one population than another, and if the disease frequency also differs between these populations, this is likely to create a false positive association unless the analysis is carefully stratified with regard to these populations. (ii) Definition of the preeclamptic phenotype is not straightforward. Several classifications have been used (11, 12), and medical records are not always complete. None of current definitions necessarily reflect the different pathogenetic mechanisms behind the disease. (iii) Different environmental factors may interact with genetic factors and modify liability to preeclampsia. (iv) In majority of the candidate studies single nucleotide polymorphisms (SNPs) has been analysed. In multifactorial diseases like preeclampsia, haplotype analysis is likely to provide additional power in detecting or excluding association. (v) In association studies statistical correction of multiple testing is necessary, but may lead to too conservative level of statistical significance.

Majority of the candidate gene studies have addressed the role of maternal genotype. Recently, The GOPEC (The Genetics of Pre-eclampsia) Consortium addressed the contribution of maternal and fetal genes in a large multicenter study (65). They studied seven candidate genes implicated in preeclampsia: *AGT* (66), *AGTR2* (67, 68), *TNF* (69), *NOS3* (70), *MTHFR* (71), and *F5* (72). Six hundred fifty-seven women affected by preeclampsia and their families were genotyped, and transmission/disequilibrium testing (TDT) (73) was used to distinguish between maternal- and fetal-gene effects. No genotype risk ratios associated with maternal or fetal genotypes achieved statistical significance (65). This study excludes major risks associated with number of single nucleotide polymorphisms in candidate genes that have dominated studies of the genetics of preeclampsia (65).

Genetic aspects of preeclampsia

Table 2. Genome-wide scans for preeclampsia

Country	Model	Criteria S=Strict G=General	Number of Markers	Number of Families	Chromosome with nominal or suggestive linkage	Chromosome with significant linkage	Reference
Scotland	AR	S	43	35	3, 9		82
Australia	AR, AD	S, G	90	15	4q34 (G)		85
Iceland	Non-parametric	S, G	440	124	2q23 ¹ (G)	2p13 (G)	86
Australia, New Zealand	Non-parametric	S, G	400	34	2q23 (S), 11q23 (G)		87
Netherlands	Non-parametric	S, HELLP	293	67	10q, 22q (S), 12q(HELLP)		88
Finland	Non-parametric	S, G	435	15	4q32 (G)	2p25 (G), 9p13 (G)	89

AR=autosomal recessive, AD=autosomal dominant, Strict criteria marks only women with new onset hypertension and proteinuria, or eclampsia as affected, General criteria marks also women with the non-proteinuric new onset hypertension as affected, HELLP= hemolysis, elevated liver enzymes, low platelets, ¹ Without the two large families contributing to the significant linkage at 2p13. Adapted with permission from 124.

The guidelines for genetic association studies have been recently suggested: large number of patients, control subjects matched for ethnic background, age and gender, adjustments for multiple comparisons, the polymorphism with a functional change in physiology, replication of the results in an independent group of subjects, and the publication of the high quality association studies with negative results (74). Association studies are not functional studies, but provide new hypothetical approaches for developing future translational and clinical research investigations (75). The systematic reviews of various candidate genes with detailed information of population studied, definition of the patients, sampling, number of patients and controls, and results would be helpful for the readers, such as the recently published reviews of prothrombotic genotypes and preeclampsia (76, 77). In preeclampsia candidate gene studies are probably best directed towards genes involved in the maternal fetal interaction (78). The number of studies that have investigated the fetal genes and interaction of the maternal and fetal genotype is small, and currently no susceptibility genes have been confirmed. Following the example set by the GOPEC Consortium, collection of triads (preeclamptic woman, her partner and baby) will enable testing of fetal genes independently of maternal genes (64, 65). It is likely that no single major gene will be found to be associated with preeclampsia but rather multiple associations will be uncovered (79). Appropriately conducted association studies have great potential to stimulate research and perhaps bring into attention unconventional biochemical pathways related to preeclampsia.

4.2. Genome-wide scans

Positional cloning of a disease gene begins with the identification of chromosomal region that is transmitted within families along with the disease of interest (genetic linkage) (80). In genome-wide scan evenly spaced microsatellites (small runs of tandem repeats of very simple DNA sequence) are used throughout the genome to identify such chromosomal regions. Genome-wide scan provides powerful means to study disease susceptibility genes. The mode of inheritance can be unknown, because data can be analyzed using nonparametric methods. On the other hand, this method is expensive and time consuming. Big effort is needed to assemble the family and medical records and collect the blood samples. An accurate diagnosis is a requirement.

The genome-wide scans for preeclampsia are summarized in Table 2. The strict criteria marks only women with new onset hypertension and proteinuria, or eclampsia as affected, whereas the general criteria marks also women with the non-proteinuric new onset hypertension as affected. It is likely, but not certain, that a woman who meets a general criteria in a preeclampsia family shares the same genetic risk factors for preeclampsia with her affected relatives who meet strict criteria. Even if the strict criteria are used exclusively, there is always a possibility of phenocopies (a mimic phenotype with a different genetic background). The threshold for genome-wide significant linkage is determined by according to the principles set forth by Lander and Kruglyak (81). Significance levels are expressed as LOD (Logarithm of Odds) scores, and LOD score >3.6 (P<0.00002) verifies significant linkage.

In the first genome-wide scan for preeclampsia, published in 1992, a fully penetrant recessive model of inheritance and strict criteria were used for analysis (82). No evidence was found to the linkage of HLA region, which was at that time the scope of some linkage studies focused on candidate regions (83, 84). The second genome-wide scan found a candidate region on chromosome 4q (85). The researchers used two models of inheritance: a recessive gene with high penetrance or a dominant gene with a low penetrance, and both strict and general criteria (85). Two next genome-wide scans found a maternal susceptibility locus for preeclampsia on chromosome 2. Using general criteria, a significant locus at 2p13 was detected in the Icelandic study but this finding was mostly supported by two large families (86). After exclusion of these two families they found with general criteria another locus at 2q23 (86). With similar criteria, a second genome scan of families from Australia and New Zealand showed a suggestive linkage to 2q23 (87). With this extended family panel the researchers were not able to verify their previously reported candidate region on 4q. Although the distance between the most significant loci from the Islandic scan (2p13) and the second Australian scan (2q32) is approximately 50 cM, the investigators concluded that it is likely that both studies have detected the same locus, and the locus has been designated PREG1/PEE1 for preeclampsia, eclampsia gene-1. On the other hand, the next genome-wide scan of Dutch affected sib-pair families failed to detect linkage to chromosome 2 (88). This is the only genome-wide scan that has used the

Genetic aspects of preeclampsia

HELLP (hemolysis, elevated liver enzymes, low platelets)-syndrome criteria. The suggestive linkage to 12q appeared to be associated with the HELLP-syndrome, whereas the suggestive linkage to 10q and 22q were found in the non-HELLP families (88). The most recent genome-wide scan was published from Finland (89). Using general criteria the significant linkage was found to chromosome 2p25 (PEE2) and 9p13 (PEE3), and suggestive linkage to chromosome 4q32. In this study the susceptibility locus on chromosome 2p25 was clearly different compared to the 2p13 in the Icelandic study and 2q23 in the Australia/New Zealand study. The locus at 9p13 has been shown to be a candidate region to type 2 diabetes in two recently-published genome-wide scans from China and Finland (90, 91). The locus at 4q32 is near the candidate region found in the first genome-wide scan from Australia (85). None of the genome-wide scans were able to confirm previously suggested linkage to 7q36, the endothelial isoform of nitric oxide synthase gene region (92, 93).

Linkage analysis has been a method of choice in monogenic disorders, but it has been less effective at identifying common variants with modest effects typical for complex traits. The positional cloning based on whole-genome scans in multifactorial diseases has proved more difficult than originally had been envisioned (80). Although several loci in preeclampsia have been mapped using genome-wide scan, only one candidate gene has been assessed so far. The Dutch researchers identified a parent-of-origin effect with matrilineal transmission on chromosome 10q22 in a subgroup of their sib-pair families suggestive of imprinting (94). Imprinted genes represent a small number of genes in the mammalian genome whose expression or repression depends on whether they come from mother or father (95). The evolution and maintenance of imprinting has been linked to the balance between the allocation of maternal resources to the developing fetus and the mother's well being (96, 97). Interestingly, pregnant mice carrying heterozygous deletions for maternally expressed imprinted gene *p57^{Kip2}* (*Cdkn1c*) develop glomerular endotheliosis and trophoblastic hyperplasia, and show preeclampsia-like symptoms and signs (hypertension, proteinuria, thrombocytopenia, decreased antithrombin III activity and increased endothelin levels) (98). The Dutch researchers explored the presence of maternally expressed imprinted genes on chromosome 10q22 that function in the early placenta, and tested these genes for reduced or absent expression in androgenetic placentas (complete hydatiform moles) (94). They identified *STOX1* (also called *C10orf24*) gene, which contained five different missense mutations identical between affected sisters, co-segregating with the preeclamptic phenotype and following matrilineal inheritance (99). The *STOX1* dysfunction in the placenta predisposes to preeclampsia possibly by interfering with differentiation of the trophoblast cells (99). They suggest that mutations might exist in paralogous genes in other loci linked to preeclampsia in different populations (94, 99).

4.3. Gene expression studies

Microarray analysis is a powerful tool, which identifies genes that are differentially expressed in specific tissues obtained from patients and controls. The expression

of thousands of genes can be assayed simultaneously. However, microarray should be considered a screening method, and more specific methods are necessary to verify the results (100). The results were only partly overlapping in two recently published studies, which used the same microarray platform to find differentially expressed genes between leiomyoma and normal myometrial tissue (101-103). Moreover, several results were different in the second microarray performed by the same researchers (100). Confirmation of hundreds of differentially expressed genes is expensive and labour intensive. First, reverse transcriptase-polymerase chain reaction (RT-PCR) and real-time RT-PCR can be used to confirm differences in mRNA expression; second, protein analysis confirms that differing mRNA levels actually translate to differing protein levels, and last, functional studies (cell culture, animal models) confirms that the gene is involved with the disease in question (103).

Placenta has been the target tissue for transcriptional profiling in established preeclampsia in the second half of the pregnancy. The first microarray study was performed to compare the expression levels of 5600 full-length human cDNAs in preterm (29-32 weeks of gestation) preeclamptic placentas and preterm (25-32 weeks of gestation) placentas from normotensive women (104). One of the most up-regulated genes was leptin (42.6-fold). It has been suggested that placental production of leptin is augmented in preeclampsia because of placental hypoxia, which is a consequence of reduced placental perfusion (105). However, the results indicating that placental leptin gene expression is not increased in placentas from pregnancies with intrauterine growth restriction that are also presumably hypoxic compared to controls suggest that there are likely additional contributing factors to placental leptin expression (Laivuori *et al.* unpublished results). In subsequent microarray studies different expression of placental glycogen phosphorylase (106), acid phosphatase 5, calmodulin 2, v-rel reticuloendotheliosis viral oncogene homolog A (107), as well as cytokine-associated (108), trophoblast-invasion associated (109), metabolism-related (110), and apoptosis related genes (111) have been reported.

Microarray has a great potential as a screening tool to identify relevant genes in the pathogenesis of preeclampsia. Critical attitude is needed when interpreting the results. Data analysis is lagging behind and more specific methods are necessary to verify the results. Transcriptional profiling might become less important in the future, because RNA might be too volatile to be used for diagnostic purposes and too far removed from the actual cellular effectors for identifying therapeutic approaches (112).

5. PERSPECTIVE

Finding several genes of small effect in liability to preeclampsia is possible. Data from family, twin and epidemiological studies encourage studying maternal and fetal genes and their interaction. Multiple large study populations with detailed phenotypes are necessary.

Genetic aspects of preeclampsia

Collection of triads (preeclamptic woman, her partner and baby) will enable testing of fetal genes independently of maternal genes. Consensus is needed on diagnostic criteria and recruitment protocols. Multidisciplinary national and international collaboration, including obstetricians, clinical and molecular geneticists, epidemiologists and bioinformaticians, is vital.

Genome-wide linkage studies have already provided several promising chromosomal loci to study further. The availability of ultra-high-volume genotyping chip technology makes the genome-wide association studies a real possibility in various diseases, including preeclampsia, but there is little consensus how to design and analyze those studies (113). Using the the International Haplotype Mapping (HapMap) Project database (www.hapmap.org), it is possible to select tag SNPs that capture a substantial portion of common human genetic variability, and get a good coverage to genome-wide association studies (114).

Candidate gene studies have so far provided inconsistent results. Rigorous study design in combination with haplotype analysis is likely to provide additional power in detecting or excluding association with preeclampsia. Common haplotypes in the desired region can be identified by genotyping only a small subset of carefully chosen SNPs.

Proteome analysis is a promising method to screen and characterize proteins for the presymptomatic detection of preeclampsia (115). Another interesting research area is cell free nucleic acids. Syncytiotrophoblast microparticles are shed into the maternal circulation in higher amounts in preeclampsia compared to normal pregnancy and intrauterine growth restriction without maternal preeclampsia (116, 117). These particles contains cell-free nucleic acids (DNA and mRNA), which are readily detectable in maternal plasma (118-120). Moreover, analysis of epigenetic modifications, such as differential DNA methylation between fetus and mother is feasible (121, 122). The placental DNA and mRNA in maternal plasma hold great promise as novel biomarkers for the presymptomatic detection in preeclampsia (123). Using gene expression databases Dutch researchers have identified genes with expression restricted to or predominant in the placenta (123). Sixty-nine genes with high expression (at or above 7000 arbitrary units) including insulin-like growth factor binding proteins (*IGFBP1* and *IGFBP3*) and imprinted genes (*H19*, *IGF2*, *DLK1*, *CDKN1C*,) can be potentially detected reliably in the maternal plasma, and thus may qualify for such novel biomarkers (123). However, a biomarker has to have a very high sensitivity, specificity, and positive predictive value. It remains to be determined how well cell free DNA or mRNA meet these criteria.

The identification of genes predisposing for preeclampsia has many ramifications for both clinical and theoretical sciences. First, it would be highly desirable to refine the diagnostics of preeclampsia based on tests of genetic variants that might allow the refining of therapeutic

or prognostic subgroups. Second, any new gene discovery will highlight a known pathway or reveal an entirely new biochemical pathway for the pathogenetic process. Third, preeclampsia involves complex and important functions in maternal metabolism and regulation of vascular function. Thus, research and recognition of genes and thereby biochemical components critical for such functions will open up new paths for the study of physiology and evolution.

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