REFERENCES

Paternal contribution to the risk for pre-eclampsia

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Pre-eclampsia is a major cause of fetal and maternal morbidity and mortality with a still obscure aetiology. A major feature in pre-eclampsia is placental maladaptation, probably because of inadequate invasion of fetal trophoblast cells in the myometrium and spirular arteries that might be related to local oxidative stress. Reactive Oxygen species (ROS), lipid peroxides, and other toxic compounds are metabolised by biotransformation enzymes in scavenging and detoxifying processes. Increasing evidence suggests an important function of antioxidants and detoxification enzymes in pre-eclampsia. We recently proposed that the 105Ile→Val polymorphisms in the glutathione S-transferase P1 gene (GSTP1), associated with lower enzyme detoxification capacity, enhanced maternal susceptibility to pre-eclampsia.1 Glutathione S-transferase P1-1 (GSTP1-1) is an important detoxification enzyme and is the main GST isoform in placenta and decidua.2 The GSTP1-1 level was found to be lower in placental and decidual tissue of pre-eclamptic women as compared with corresponding tissues of normal pregnant women.3 Since placental fetal origin and therefore characterised by both maternal and paternal contribution, the risk for pre-eclampsia might be modified by maternal as well as paternal genetic variations in detoxification activities. We therefore studied GSTP1 polymorphisms in a cohort of 113 pre-eclampsia trios (mother, father, baby) in which the mothers had suffered pre-eclampsia and 317 Dutch, population based, healthy controls, recruited by advertisement (149 men, 168 women).

METHODS
The mothers in the study group consisted of Dutch women who had previously been admitted to the antenatal wards of the University Medical Centre, Nijmegen for pre-eclampsia. Pre-eclampsia was defined as the occurrence after 20 weeks’ gestation of a diastolic blood pressure greater than 90 mm Hg and concordant proteinuria (urinary protein greater than 0.3 g/l in a 24 hour collection period or a protein/creatinine ratio greater than 0.3 g/10 mmol). The local ethical committee on human experimentation approved the study protocol. Genomic DNA from mothers and fathers was extracted from blood samples collected by venepuncture using the Wizard® genomic DNA purification kit, according to the instructions of the manufacturer (Promega, Madison, WI, USA). DNA from offspring was collected from buccal cell samples collected on sterile swabs as described by Richards et al.4 After extraction, DNA was further purified by phenol/chloroform extraction. Subsequently, the 105 Ile→Val polymorphism in GSTP1 was assessed by polymerase chain reaction as described previously.5 Chi-square analyses and relative risks approximated by odds ratios were used for statistical evaluation of differences in polymorphic rates and allele frequencies. A p value of 0.05 represents statistical significance. Association analysis was also performed using the transmission disequilibrium test (TDT) described by Spielman et al.6 The TDT test evaluates the observed number of parent-offspring transmissions of alleles, compared with the number of transmissions expected by chance. Only parents heterozygous for the polymorphism tested are informative for the test. Association was tested using chi-square statistics. A p value <0.05 was considered significant.

RESULTS
No significant sex differences in the frequency of the Val105 allele could be shown in the population based control group. The distribution of polymorphic variants in the GSTP1 gene in pre-eclampsia trios and controls is shown in table 1. The
GSTP1 Val105/Val105 genotype was found significantly more often in mothers, fathers, and offspring of pre-eclamptic pregnancies than in controls (p=0.005, p=0.0001, and p=0.0006, respectively). Also, the Val105 allele was present significantly more often in mothers (0.32), fathers (0.37), and offspring (0.38) of pre-eclamptic pregnancies compared with the frequency in controls (0.22). Comparisons of GSTP1 genotypes and allele frequencies between pre-eclampsia mothers, fathers, and offspring showed no statistically significant differences.

The TDT test applied to the parents heterozygous for the Val105 allele was found to be positive (χ² TDT=4.24, p< 0.05), confirming linkage disequilibrium of pre-eclampsia with this allele.

**DISCUSSION**

Epidemiological studies show that pre-eclampsia has hereditary characteristics. Both the mother and the fetus may contribute to the risk of pre-eclampsia, the contribution of the fetus and trophoblastic factors also being affected by paternal genes. Strong support for a paternal role in pre-eclampsia comes from a study showing an association between paternal factors and trophoblastic factors also being affected by paternal genes. Furthermore, we were able to confirm linkage disequilibrium of pre-eclampsia with the Val105 allele, again strongly suggesting that the GSTP1 polymorphism is indeed associated with the disease. This is also in accordance with the recent findings of Esplin et al. who reported that both men and women who were the product of a pregnancy complicated by pre-eclampsia were significantly more likely than control men and women to have a child who was also the product of a pregnancy complicated by pre-eclampsia.

To our knowledge, this is the first polymorphism in the paternal genome related to pre-eclampsia. Higher frequencies of the Val105 allele in pre-eclampsia might result in a lower detoxification capacity in the trophoblast and inadequate coping with local oxidative stress, resulting in a higher susceptibility to pre-eclampsia.

**REFERENCES**