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ABSTRACT

Preeclampsia (PE) is a pregnancy-specific hypertensive and proteinuric disorder that complicates 3-5% of pregnancies worldwide. It is one of the major causes of maternal and fetal morbidity and mortality. PE occurs typically in the third trimester of pregnancy by symptoms like elevated blood pressure, proteinuria and edema. The etiology of PE is unknown.

Placental ischemia due to abnormal placentation, oxidative stress, endothelial cell dysfunction, defects in the immune system and abnormal coagulation together with genetic susceptibility have been suggested to be involved in the pathogenesis of PE. The main aim of the present thesis was to evaluate candidate genes proposed to be important in the pathogenesis of PE including genes related to hemodynamics, the immune system, coagulation and detoxification. Furthermore, one possible PE-associated locus was investigated on chromosome region 2p13-p12.

The main study population consisted of 133 PE patients and 115 control women who all gave birth at the Kuopio University Hospital between January 1994 and December 1999. The study population was collected retrospectively. In the candidate gene association studies the polymorphisms of the genes for angiotensin-converting enzyme (ACE), tumor necrosis factor- α (TNF- α), β -fibrinogen, coagulation factor VII and microsomal epoxide hydrolase (EPHX) were screened. Population-based association screening was conducted with the seven microsatellite markers at the region 2p13-p12.

We found the polymorphism C-850T (the T allele) at the promoter of the TNF- α gene and the high-activity haplotype T-A (Tyr113-His139) of the EPHX gene to be associated with PE. In addition, allele 6 of the marker D2S286 on chromosome 2 was associated with PE. Furthermore, haplotype analysis was found to be more informative than multiple single-locus tests in this kind of candidate gene-testing study. We did not find an association of the gene polymorphisms for ACE, β -fibrinogen and coagulation factor VII with PE, indicating that they are unlikely to substantially contribute to the risk of PE in the Finnish population.

The clinical importance of the T allele of the TNF- α gene is obscure. However, we suggest that the T allele is a protective factor against PE, because it was over-represented in the women who had healthy pregnancies. The high-activity haplotype T-A of the EPHX gene may produce toxic intermediates through fast hydrolysis of oxides. These toxic intermediates may cause endothelial cell dysfunction and damage and result in PE. We suggest that the high-activity haplotype T-A of the EPHX gene contributes to the increased risk of PE in Finnish population. The risk locus for PE found on chromosome 2 needs to be further studied to uncover the functional mechanisms behind it.

National Library of Medicine Classification: WQ 215, QZ 50

Medical Subject Headings: pre-eclampsia/genetics; genetic predisposition to disease; pregnancy; chromosomes, human; polymorphism (genetics); alleles; haplotypes; genotype; tumor necrosis factor; fibrinogen; blood coagulation factors; factor VII; epoxide hydrolases; endopeptidases; microsatellite repeats; polymerase chain reaction; female; Finland