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Genotyping analysis for the 46 C/T polymorphism of coagulation factor XII and the involvement of factor XII activity in patients with recurrent pregnancy loss

Background: Established causes of recurrent pregnancy loss (RPL) include antiphospholipid syndrome, uterine anomalies, parental chromosomal abnormalities, particularly translocations and abnormal embryonic karyotype. A systematic review concluded that coagulation factor XII (FXII) deficiency was associated with RPL. However, it could not be established whether the 46 C/T SNP of FXII or low activity of FXII was a risk factor for RPL, because of the small sample size.

Methods: We conducted a cross-sectional and cohort study in 279 patients with two or more unexplained consecutive pregnancy losses and 100 fertile women. The association between the lupus anticoagulant (LA) activity and FXII activity was examined. The frequency of the CC, CT and TT genotypes and the FXII activity were also compared between the patients and controls. Subsequent miscarriage rates among the CC, CT, TT genotypes and according to the FXII activity was examined.

Results: LA was associated with reduced FXII activity. The CT, but not the TT, genotype was confirmed to be a risk factor for RPL in the cross-sectional study using multivariate logistic regression analysis (OR, 2.8; 95% CI, 1.37-5.85). The plasma FXII activity in the patients was similar to that in the controls. Neither low FXII activity nor the CT genotype predicted the subsequent pregnancy outcome in the cohort study. On the other hand, and intermediate FXII activity level of 85-101% was predictive of subsequent miscarriage.

Conclusions: Low FXII activity was not associated with RPL. The FXII gene was found to be one of the significant susceptibility genes for RPL. However, the clinical influence of the CT genotype might be relatively small, because the presence/absence of this genotype did not have any predictive value for the subsequent pregnancy outcome. This was the first study indicating the influence of *FXII 46C/T* on further pregnancy outcomes.