ASSOCIATION OF STAT4, IRF5 AND BLK POLYMORPHISMS WITH SEVERITY AND OUTCOME IN LUPUS NEPHRITIS

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Background and objectives Lupus nephritis (LN) is a cause of significant morbidity and mortality and occurs in 15–50% of patients with SLE. Proliferative nephritis is most severe and 10% of LN patients develop end stage renal disease (ESRD). Several susceptibility genes for SLE have been identified where an association with LN has been shown for SNPs in STAT4 and ITGAM. The aim of this investigation was to analyse the genetic data from a previous study1 for association with LN, in particular proliferative nephritis and ESRD.

Materials and methods The authors included 567 Swedish Caucasian patients with SLE and 512 matched controls. All samples had been genotyped on a custom array 12K chip1. A total of 195 (34.4%) patients had a history of LN. Renal biopsies were available from 153 patients where 92 (60.1%) showed a proliferative nephritis. During follow-up (median 14 years, range 0–46), 11.1% reached ESRD. Case-control association analyses were performed for patients with LN, in particular proliferative nephritis and ESRD.

Results The authors detected strong signals of association between SNPs in STAT4 (OR 2.2, 95% CI 1.7 to 2.8), IRF5 (OR 2.0, 95% CI 1.5 to 2.7) and a marker for HLA-DR3 (OR 1.95, 95% CI 1.4 to 2.6), in the analysis of LN patients versus controls (all p<0.0001). In addition, six genes showed an association with LN with OR 1.5-2.2, p<0.001 (PMS2, TNIP1, CARD11, ITGAM, BLK and IRAK1). When analysing only the patients with proliferative nephritis versus controls the OR for association increased for STAT4, IRF5 and BLK to 2.4, 2.2 and 1.7 respectively (all p<0.01). For patients in ESRD the OR for STAT4, IRF5 and BLK increased further to 2.9, 3.1 and 2.1 whereas the OR for association with the HLA-DR3 marker was decreased to 1.7. The association between the risk alleles in IRF5, STAT4 and BLK and LN phenotypes was stronger than the association to SLE per se.

Conclusions Risk alleles in STAT4, IRF5 and BLK are associated with an increased risk for LN. The association with proliferative nephritis was particularly strong and the risk of developing ESRD was even more striking. On the contrary, the HLA-DR3 marker did not display a strong association with LN. The authors conclude that variations in genes in immunological pathways predispose to LN severity and renal outcome.

REFERENCE