A80 GENETIC VARIATION AT THE IRF7/PHRF1 LOCUS IS ASSOCIATED WITH AUTOANTIBODY PROFILE AND SERUM INTERFERON α ACTIVITY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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10.1136/ard.2010.129619n

Objective Interferon α (IFN α) is a heritable risk factor for systemic lupus erythematosus (SLE). Genetic variation near IFN regulatory factor 7 (IRF7) is implicated in SLE susceptibility. SLE-associated autoantibodies can stimulate IFN α production through the Toll-like receptor/IRF7 pathway. The authors hypothesised that variants of IRF7 may cause risk of SLE by increasing IFN α production, and that autoantibodies may be important in this phenomenon.

Methods 492 patients with SLE were studied (236 African American, 162 European American and 94 Hispanic American

subjects). Serum IFN α was measured using a reporter cell assay and SNPs in the IRF7/PHRF1 locus were genotyped.

Results In European American and Hispanic American subjects, rs702966C was associated with anti-dsDNA antibodies (OR 83, $p=0.0069$ in joint analysis). The rs702966 CC genotype was only associated with higher serum IFN α levels in European American and Hispanic American patients with anti-dsDNA antibodies (joint analysis $p=1\times 10^{-5}$ in anti-dsDNA positive vs 0.99 in anti-dsDNA negative patients). In African American subjects, anti-Sm antibodies were associated with the rs4963128 SNP near IRF7 (OR 95, $p=0.0017$). rs4963128 CT and TT genotypes were associated with higher serum levels of IFN α only in African American patients with anti-Sm antibodies ($p=0.0012$). In African American patients lacking anti-Sm antibodies, the anti-dsDNA/rs702966C interaction upon serum IFN α was observed, similar to the other ancestral backgrounds (overall joint analysis $p=0\times 10^{-6}$). In European American and Hispanic American patients, the IRF5 SLE-risk haplotype showed an additive effect with rs702966C upon IFN α in anti-dsDNA positive patients.

Conclusions IRF7/PHRF1 variants cooperate with SLE-associated autoantibodies to result in higher serum IFN α , providing a biological relevance for this locus at the protein level in human SLE in vivo.