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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Objective Interferon α (IFNα) 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 IFNα production through the Toll-like receptor/IRF7 pathway. The authors hypothesised that variants of IRF7 may cause risk of SLE by increasing IFNα 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 IFNα 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 IFNα levels in European American and Hispanic American patients with anti-dsDNA antibodies (joint analysis p=1×10^-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 IFNα 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 IFNα was observed, similar to the other ancestral backgrounds (overall joint analysis p=0×10^-6). In European American and Hispanic American patients, the IRF5 SLE-risk haplotype showed an additive effect with rs702966C upon IFNα in anti-dsDNA positive patients.

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