A10 IRF8 ALLELE ASSOCIATED WITH SUSCEPTIBILITY TO MULTIPLE SCLEROSIS IS ASSOCIATED WITH SERUM INTERFERON α AND SEROLOGIC PROFILE IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective Alleles of IRF8 have been associated with susceptibility to both systemic lupus erythematosus (SLE) and multiple sclerosis (MS). While interferon α (IFN-α) is thought to be causal in SLE, recombinant human IFN-α is used as a therapy in MS. We investigated whether the IRF8 alleles associated with these two diseases were associated with differences in serum IFN-α or serologic profile in a multi-ancestral cohort of SLE patients.

Methods The rs12444486 and rs17445836 single nucleotide polymorphisms (SNPs) in IRF8 (associated with SLE and MS respectively) were genotyped with Taqman primer-probe sets. We studied 548 SLE patients (258 African-American, 147 European-American, and 143 Cretan) and 526 matched controls (298 African-American, 117 European-American, and 111 Cretan). All patients had serum IFN-α and serology data available, and had been previously genotyped at SLE-risk SNPs in the IRF5 and IRF7 loci. Data from each ancestral background

was analysed separately initially, and combined in meta-analysis when associations were not significantly heterogeneous between ancestral backgrounds. Principal component analysis was used to control for proportional ancestry at the individual level in logistic regressions.

Results In case-control meta-analysis, we observed a stronger and more consistent cross-ancestral background association between IRF8 and SLE at the MS-associated rs17445836 SNP than at the previously reported SLE-associated rs1244486 SNP (OR=0.66, $p=2.7\times10^{-3}$, Cochran's Q=0.80). The MS-associated rs17445836 G allele was associated with the presence of anti-dsDNA autoantibodies in SLE patients of both ancestral backgrounds (meta-analysis OR=2.01 (1.09–3.68), p=0.024). The same allele was also associated with increased serum IFN-α activity in both ancestral backgrounds (meta-analysis p=0.017). There was no evidence for statistical interaction between rs17445836 G and SNPs in IRF5 and IRF7 which have been previously associated with anti-dsDNA in SLE patients. No significant associations were observed between the SLE-associated rs12444486 SNP and serum IFN-α or serologic profile.

Conclusions The rs17445836 G allele associated with susceptibility to MS was associated with SLE, and with anti-dsDNA antibodies and serum IFN-α in SLE patients of both African-American and European ancestry. This is interesting, given the therapeutic effect of IFN-α in MS patients, and the pathogenic effect of this same cytokine in SLE. Further exploration of the impact of the IRF8 locus upon in vivo IFN-α levels should provide insight into both diseases.