Admixture mapping in lupus identifies multiple functional variants within IFIH1 associated with apoptosis, inflammation, and autoantibody production.

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Abstract
Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease with a strong genetic component. African-Americans (AA) are at increased risk of SLE, but the genetic basis of this risk is largely unknown. To identify causal variants in SLE loci in AA, we performed admixture mapping followed by fine mapping in AA and European-Americans (EA). Through genome-wide admixture mapping in AA, we identified a strong SLE susceptibility locus at 2q22-24 (LOD=6.28), and the admixture signal is associated with the European ancestry (ancestry risk ratio ~1.5). Large-scale genotypic analysis on 19,726 individuals of African and European ancestry revealed three independently associated variants in the IFIH1 gene: an intronic variant, rs13023380 [P(meta) = 5.20×10(-14); odds ratio, 95% confidence interval = 0.82 (0.78-0.87)], and two missense variants, rs1990760 (Ala946Thr) [P(meta) = 3.08×10(-7); 0.88 (0.84-0.93)] and
rs10930046 (Arg460His) \( P(\text{dom}) = 1.16 \times 10^{-8}; \\
0.70 (0.62-0.79) \). Both missense variants 
promoted dramatic phenotypic changes in 
apoptosis and inflammation-related gene 
expression. We experimentally validated function 
of the intronic SNP by DNA electrophoresis, 
protein identification, and in vitro protein binding 
assays. DNA carrying the intronic risk allele 
rs13023380 showed reduced binding efficiency to 
a cellular protein complex including nucleolin and 
lupus autoantigen Ku70/80, and showed reduced 
transcriptional activity in vivo. Thus, in SLE 
patients, genetic susceptibility could create a 
biochemical imbalance that dysregulates 
nucleolin, Ku70/80, or other nucleic acid 
regulatory proteins. This could promote antibody 
hypermation and auto-antibody generation, 
further destabilizing the cellular network. 
Together with molecular modeling, our results 
establish a distinct role for IFIH1 in apoptosis, 
inflammation, and autoantibody production, and 
explain the molecular basis of these three risk 
alleles for SLE pathogenesis.
Admixture mapping in lupus identifies multiple functional variants within IFIH1 associated with apoptosis, inflammation, and autoantibody production.