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Admixture mapping and its application to lupus gene identification in African-Americans

Swapan K. Nath
Oklahoma Medical Research Foundation, USA

African-Americans (AA) are at increased risk of systemic lupus erythematosus (SLE or lupus), an inflammatory autoimmune disease with strong genetic component, but the genetic basis of this risk increase is largely unknown. To identify causal variants in SLE, 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 peak is associated with the European ancestry that contributes ancestry risk ratio of ~1.5. Large-scale genotypic analysis on 19,726 individuals of African and European ancestry revealed three independently associated variants, including the previously known variant, within the IFIH1gene: an intronic variant, rs13023380 [P_{meta}=5.20x10^{-14}; odds ratio, 95% confidence interval = 0.82 (0.78-0.87)], and two missense variants, rs1990760 (Ala946Thr) [P_{meta}=3.08x10^{-7}; 0.88 (0.84-0.93)] and rs10930046 (Arg460His) [P_{dom}=1.16x10^{-8}; 0.70 (0.62-0.79)]. We showed distinct functions of two coding SNPs including changes in gene expression and assigned function of the intronic SNP by EMSA, protein identification and *in vitro* protein binding assays. Both missense variants produced dramatic phenotypes changes in apoptosis and gene expression leading to inflammation. DNA carrying intronic risk allele of rs13023380 showed reduced binding efficiency to a cellular protein complex including NCL and Ku70/80, and showed reduced transcriptional activity *in vivo*. Thus in SLE patients, genetic susceptibility could create a biochemical imbalance that dysregulates NCL, Ku 70/80, or other nucleic acid regulatory proteins. This could promote antibody hypermutation and auto-antibody generation, further destabilizing the cellular network. SLE is commonly identified with an up-regulation of the interferon pathway. Together with molecular modeling, our results establish a distinct role for *IFIH1* in apoptosis, inflammation and autoantibody interaction, and explain the molecular basis of these three risk alleles for SLE pathogenesis.

Biography

Swapan K Nath completed his M.Sc. from University of Calcutta, India in 1989 and later on did his Doctoral & Post doctoral studies at Indian Statistical Institute, Calcutta, India, 1995 and Case Western Reserve University, Cleveland, OH from 1995-2000 respectively. He is the recipient of many Honors and Awards as distinguished scientist as well as a researcher and the Ad hoc reviewer for 6 international Scientific Journals & a member of 3-4 scientific societies. Currently he is the Member, Arthritis & Clinical Immunology Research Program and Adjunct Associate Professor, Department of Pediatrics and Department of Pathology, University of Oklahoma Health Sciences Center, USA.

naths@lupus.omrf.org