A MISSENSE MUTATION IN NEUTROPHIL CYTOSOLIC FACTOR 1 (WCF1) IS ASSOCIATED WITH SUSCEPTIBILITY TO MULTIPLE AUTOIMMUNE DISEASES

**Background** Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease with a strong genetic component. Dozens of SLE-associated loci have been identified by genome-wide associated studies (GWAS) and included in the ImmunoChip for fine-mapping.

**Materials and methods** Using ImmunoChip, we assessed case-control subjects including Chinese, European Americans (EA) and African Americans (AA) for association with SLE. Subsequently, we carried out trans-ancestral mapping and resequenced the complex: GTF2IRD1-GTF2I-NCFI region on 7q11.23 rather than SLE-associated GWAS loci. This association was confirmed in EA (OR = 1.37, \( P = 2.5 \times 10^{-5} \)) but not in AA. By trans-ancestral mapping and sequencing, we identified R90H of NCF1, a neighbouring gene of GTF2I encoding the p47phox subunit of NADPH oxidase, as a highly plausible causal variant. R90H was associated with SLE in East Asians (OR = 3.47, \( P_{\text{meta}} = 3.0 \times 10^{-16} \)), EA (OR = 2.11, \( P_{\text{meta}} = 7.0 \times 10^{-8} \)) and AA (OR = 1.91, \( P = 7.2 \times 10^{-3} \)), and in conditional test R90H eliminated SLE-associated signals within the GTF2IRD1-GTF2I region including rs73366469. Furthermore, R90H was dose-dependently associated with early age of onset in Korean (\( P = 0.011 \)) and EA (\( P = 0.012 \)) patients with SLE. In addition to SLE, R90H was associated with seropositive rheumatoid arthritis (RA) in Koreans (OR = 1.66, \( P = 1.2 \times 10^{-3} \)) and primary Sjögren’s syndrome (SS) in EA (OR = 1.72, \( P = 5.8 \times 10^{-3} \)). The conserved arginine 90 to histidine substitution located in the PX-binding domain of p47phox is predicted deleterious, which is supported by a report showing R90H results in reduced reactive oxygen species (ROS) production.

**Conclusions** We identified R90H of NCF1 as a novel risk variant for multiple autoimmune diseases, highlighting the pathogenic role of reduced ROS production in developing autoimmune diseases.
chromatin accessibility “peaks” were identified with MACS2. For each cell type, we identified the consensus set of epigenetically active peaks across all 14 subjects. We conducted enrichment tests of identified loci using the GREAT tool and performed differential accessibility analysis using the edgeR package in R. Transcription factor binding motif enrichment and overlaps with known SLE risk haplotypes were also determined.

Results Chromatin accessibility profiles among the three cell types shared common features as well as peaks specific to each cell-type profile. The peaks unique to each profile were enriched in genomic loci specific to their cellular function as well as their known immunologic molecular signatures in SLE. Quantitative analysis of differential chromatin accessibility loci which discriminate between individuals with SLE and healthy controls patients with high versus low disease activity. Motif analysis revealed that many consensus peaks occupy binding sites of cohesin complex subunits, suggesting that long-range chromatin interactions may mediate immune responses that drive SLE progression. In addition, 320 SLE risk SNPs were located within an open chromatin peak suggesting these as SNPs candidates for functional impact.

Conclusions Our analysis suggests that chromatin profiling may have power to differentiate patients from controls as well varying extremes of disease activity and can pinpoint putative functional SNPs. Additional insight will be gained from further refinement of immune cell compartments. Future studies will focus on long-range interactions driving differences in chromatin accessibility and integrating these data with transcriptome data. We expect this approach to expound our knowledge of how regulatory networks in specific cells and cell states drive SLE progression.

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GG-07 SLE RISK HAPLOTYPES ARE ASSOCIATED WITH DEVELOPMENT OF SEROLOGIC AUTOIMMUNITY IN HEALTHY INDIVIDUALS

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Background Approximately 60 loci are associated with SLE in genotyping studies. These loci impact several pathways in the immune response. ANA are one of the earliest features of lupus, preceding the onset of clinical symptoms by many years. The genetic risk factors that underlie the development of serological autoimmunity are unknown. A genome-wide association study was undertaken to understand the genetics of ANA development.

Materials and methods Serum and DNA were collected from 2,635 healthy individuals with no personal history of autoimmunity. Antibodies were detected using an ELISA to human nuclear extract (NOVA). Sera from 724 individuals (ANA-, ANA+, and SLE) were assayed by protein microarray quantifying IgM and IgG responses to 96 human autoantigens. A nested cohort of 1,969 subjects consisting of all the ANA+ Caucasian individuals and age/gender matched ANA- controls were genotyped using the ImmuNoChip SNP array.

Results In 2,635 healthy individuals, 16.2% had moderate and 8.0% had high levels of IgG antinuclear antibodies. High titer ANA was almost exclusively seen in female subjects (OR (CI): = 1.6 (1.1–2.1), p = 0.003). Age was not associated with the presence or titer of ANA. On the autoantigen microarray, ANA+ healthy individuals had a high prevalence of antibodies to non-nuclear and cytoplasmic antigens, while subjects with SLE predictably produced antibodies to a variety of nuclear antigens. A quantitative genetic association test with ANA identified genomc loci associated with high ANA phenotype. HLA was second strongest signal (p = 6.2 × 10^{-8}). The frequencies of the SLE risk haplotypes at STAT4, TNFAIP3, BLK, BANK1, NCF2, and MNAT2 were also significantly (p<0.05) increased in the ANA high positive group compared to ANA negative healthy subjects. On the other hand, SLE risk haplotypes in ITGAM, UBE2L3, IRF5-TNPO3 loci were only high in the SLE group, suggesting their main role in a transition to clinical disease.