

locus has powerful common variant associations with SLE risk with odds ratio = 1.5 and $p < 10^{-20}$ in all human ancestries and also has an association, though not necessarily identical to SLE, with rheumatoid arthritis, primary biliary cirrhosis, Behcet's Disease, Sjögren's syndrome, progressive systemic sclerosis, and type I diabetes.

Methods Genome wide association studies of SLE, Bayesian and frequentist fine mapping methods, DNA affinity purification assays, and electrophoretic mobility shift assays.

Results We are attempting to identify the causal variants and determine the mechanism for SLE disease risk at this locus. Our data suggest that the risk haplotype alters the expression of mRNA from both *STAT1* and *STAT4*. Application of frequentist and Bayesian methods restrict the plausibly causal variants to four possibilities in introns 4 and 5 of *STAT4* under the assumption that the association observed across human ancestries is being driven by the same causal variants. Three of these four polymorphisms are predicted to alter the binding of a specific transcription factor, leading to the hypothesis that the same transcription factor is operating at multiple sites in a risk haplotype. We have data suggesting differential and allele preferential binding of the transcription factor at one variant with evaluation of the others in process. This may possibly be the first discovered example of the phenomenon of multiple transcription factor binding on multiple variants of a risk haplotype.

Conclusion In general, genome wide association studies (GWASs) provide powerful evidence of the presence of a genetic variation altering phenotype risk without revealing what the specific responsible variant is among those in a statistical dead heat for causation, in which cell type(s) or stage(s) of differentiation in which the risk difference is relevant, or what the molecular mechanism might be. We have work underway to reveal these details for lupus loci, initially concentrating on *IRF5*, *STAT1-STAT4*, and *ETS1*. The *STAT1-STAT4* association with SLE can be isolated to involve only a few variants, which are predicted to have curiously similar transcription factor binding behaviour.

GG-04

A MISSENSE MUTATION IN NEUTROPHIL CYTOSOLIC FACTOR 1 (*NCF1*) IS ASSOCIATED WITH SUSCEPTIBILITY TO MULTIPLE AUTOIMMUNE DISEASES

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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-NCF1* region on 7q11.23 to identify underlying causal variant.

Results The strongest association signal in Chinese was unexpectedly detected at rs73366469 (OR = 2.88, $P = 3.6 \times 10^{-29}$) within the *GTF2IRD1-GTF2I* intergenic region on 7q11.23 rather than SLE-associated GWAS loci. This association was confirmed in EA (OR = 1.37, $P = 2.5 \times 10^{-3}$) 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, $P_{\text{meta}} = 3.0 \times 10^{-105}$), 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, $P = 1.2 \times 10^{-8}$) 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.

GG-05

ATAC-SEQ PROFILING REVEALS CELL-TYPE SPECIFIC EPIGENETIC FEATURES OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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Background Genetics studies have now identified over 80 SLE risk loci that influence predisposition to SLE with the majority of risk variants altering regulatory elements that govern gene expression. Precise understanding of how risk variants in regulatory elements influence gene expression in different cell types and cell states is critical for defining the molecular networks leading to autoimmunity. To begin to address this issue, we profiled the chromatin accessibility landscape of three distinct, albeit heterogeneous, compartments of the immune system across three clinical states.

Materials and methods Primary B and T lymphocytes and monocytes from 5 SLE subjects with high disease activity (SLEDAI ≥ 3) and 4 SLE subjects with low disease activity (SLEDAI ≤ 2) and 5 healthy controls were collected and processed for high-throughput open chromatin profiling by ATAC-seq. Reads were aligned to the hg19 genome and regions of enriched