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 transcriptional data. We expect this approach to expand 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. Antinuclear 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+ Caucasion 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 (Cl): = 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 genomic loci associated with high ANA phenotype. HLA was second strongest signal (p = 6.2 × 10–6). 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, IRF3-TNPO3 loci were only high in the SLE group, suggesting their main role in a transition to clinical disease.
Conclusions As has been seen in previous cohorts, a quarter of healthy individuals in this study made antinuclear antibodies, often at high titers. ANA testing, however, underestimates the repertoire of autoantibodies in these individuals. Healthy individuals who react in ANA testing produce antibodies against both non-nuclear and cytoplasmic antigens while SLE patients react to the classical RNA and DNA associated proteins. There is genetic risk for the development of ANA that includes many of the previously documented SLE risk haplotypes. However, other genetic associations are specific for SLE, suggesting distinct risk factors for ANA and for lupus.

**GG-08 TRANSANCESTRAL MAPPING AND GENETIC LOAD IN SYSTEMIC LUPUS ERYTHEMATOSUS**

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Background Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organs, and disproportionately affects women and individuals of non-European ancestry. Here, we report the results of genotyping individuals of European Ancestry (EA), African American (AA), and Hispanic (Amerindian) American ancestry (HA) on the Immunochip (196,524 polymorphisms: 718 small insertion deletions, 195,806 SNPs).

Methods Genotype calling was completed in multiancestral batches (AA: 2,970 cases, 2,452 controls; EA: 6,748 cases, 11,516 controls; HA: 1,872 cases and 2,016 controls). Admixture estimates were computed using the program ADMIXTURE. To test for an association between a SNP and case/control status within an ancestry, a logistic regression analysis was computed adjusting for admixture factors as covariates. Transancestral meta-analysis was computed using the inverse normal method, weighted by sample size. The EA SLE-risk allele genetic load was computed as the weighted (log of the odds ratio (OR)) and unweighted sum of the number of EA risk alleles. The genetic load was computed in an independent set of EA 2000 cases and 2000 controls, and AA and HA samples. Individuals whose genetic load (risk allele count) was in the lower 10% of the count distribution were the reference group.

Results In total, 9, 58, and 6 distinct non-HLA regions had P < 1x10E-6 (Bonferroni threshold) for the AA, EA, and HA cohorts, respectively. The three-ancestry meta-analysis was particularly informative for 22 additional SLE-associated regions that met P < 5x10E-8: 11 novel regions, 3 published regions now established, a complex multigenic region identified by adjusting for HLA alleles, and 7 established regions more sharply genome-significance, a complex multigenic region identified by adjusting for admixture factors as covariates. Transancestral meta-analysis was computed using the inverse normal method, weighted by sample size. The EA SLE-risk allele genetic load was computed as the weighted (log of the odds ratio (OR)) and unweighted sum of the number of EA risk alleles. The genetic load was computed in an independent set of EA 2000 cases and 2000 controls, and AA and HA samples. Individuals whose genetic load (risk allele count) was in the lower 10% of the count distribution were the reference group.

Results More than 300 arrays from lupus patients and appropriate controls were analysed to determine differentially expressed (DE) genes [8279 discoid lupus skin, 5465 synovial lupus arthritis, 6381 glomerulus (G) lupus nephritis, 5587 tubulointerstitial (TI) lupus nephritis]. Notably, the majority of lupus affected tissue DE genes were detected in more than one tissue and 439 were differentially expressed in all tissues. Tissue lymphocyte infiltration was documented by cell markers as well as by published unique gene expression signatures (BIG-C®). Common up-regulated transcripts in affected tissues displayed a variety of functions including pattern recognition receptors, p38/MAPK14 activation, endothelial endocytosis, and TLR activation. Unique targets of intervention were discovered when up-regulated transcripts in all lupus tissues were cross-referenced to molecular pathway and drug interaction databases. Canonical signalling pathways, published to be important for lupus pathogenesis, such as CD40L-CD40, IL-6, and IL-12/23 were visualised in IPA. Both MS®-scoring and IPA®-UR analysis predicted that signalling mediated by CD40 and IL12R occur in lupus skin, synovium and kidney glomeruli. LINCS connectivity analysed the effect of in vitro knockdown of ligand-receptor pairs and compared the genes affected with lupus tissue DE lists. Lupus nephritis (LN) kidney glomeruli received a LINCS connectivity score of −77 for CD40, implying that DE genes in this tissue have a high likelihood of being regulated by CD40-induced signalling. Skin and lupus nephritis kidney glomeruli received LINCS connectivity scores of −73 and −97, respectively, for the key signalling molecule required for IL6 signalling, IL6ST/pgp130. All lupus-affected tissues had negative connectivity scores (skin, −98; synovium, −89; LN glomeruli, −91 and LN TI, −87) for IL12a. Examination of curated functional groups from the STRING output of