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 genome-significance, a complex multigenic region identified by adjusting for HLA alleles, and 7 established regions more sharply localised by transancestral mapping or novel to these ancestries

Genetic load was strongly predictive of SLE status in the 2000 EA cases/controls that were independent from the discovery set ($OR_{unweighted} > 30$ and $OR_{weighted} > 100$). There was a greater than additive effect in the log(OR) (i.e., β parameter denoting slope) for the highest quarter of the genetic load range, suggesting the cumulative effect is greater than the sum of the individual effects (cumulative hit hypothesis). HA and AA showed markedly smaller ORs (between 3 and 10), reflecting a reduced predictive ability of EA-identified SLE risk loci in non-EA populations and the lack of capturing non-EA SLE risk loci on the Immunochip.

Conclusion The multiancestral analysis of the Immunochip data identified numerous novel SNP associations. The genetic load leads us to posit a cumulative hit hypothesis, where the cumulative effect is greater than the sum of the individual alleles' effects.

GG-09 COMPARATIVE ANALYSIS OF GENE EXPRESSION IN LUPUS-AFFECTED TISSUES REVEALS COMMON AND DISPARATE PATHWAYS OF INFLAMMATION

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Background Immunologic mechanisms causing tissue damage in autoimmune diseases such as SLE are not fully understood. The hypothesis to be tested is that gene expression analysis of lupus-affected tissues will generate novel insights into targets of immunological intervention.

Materials and methods To gain additional insight, gene expression profiles obtained from lupus affected skin, synovium and kidney were obtained, compared to meta-analysed data obtained from active lupus B, T and myeloid cells, and cross-referenced to various pathway analytic tools including Molecular Signature (MS©)-Scoring, Ingenuity Pathway Analysis© Upstream Regulator (IPA©-UR) analysis, and Library of Integrated Network of Cellular Signatures (LINCS).

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 tubulointerstitum (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/gp130. All lupus-affected tissues had negative connectivity scores (skin, −98; synovium, −89; LN glomeruli, −91 and LN TI, −87) for IL12α. Examination of curated functional groups from the STRING output of