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

common up-regulated transcripts in lupus tissue using IPA's Bio-Profiler© function predicted therapeutic targets and drugs for all three ligand-receptor pairs examined by MS©-scoring, IPA©-UR and LINCS.

Conclusions This approach demonstrated that there are pathways common to all lupus tissue, and there are pathways involved in inflammatory response of some but not all tissues. Further analysis should generate a model of lupus immunopathogenesis and could identify therapies that may be useful in all lupus patients versus those with involvement of specific tissues.

GG-10 IMAGINE SLE: INTERNATIONAL MULTI-SITE ASSESSMENT OF GENETICS AND INFLAMMATION IN EARLY ONSET AND FAMILIAL SYSTEMIC LUPUS ERYTHEMATOSUS

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Background Systemic Lupus Erythematosus (SLE) is a severe, multisystem autoimmune disease. Twin and sibling studies indicate a strong genetic contribution (44–69%) to SLE. Although numerous recent GWAS studies have identified gene variants, few have been linked to causal polymorphisms in SLE. It may be that few, rare variants could have large impact on SLE risk. Paediatric SLE patients have earlier onset of disease, suffer aggressive course of illness, and may have a stronger genetic risk than adults. Studying aggressive disease in paediatrics has led to myriad breakthroughs in disease pathogenesis, as demonstrated by familial hypercholesterolemia and atherosclerosis, and fever syndromes and autoinflammation. Whole exome sequencing (WES) is a powerful tool to identify rare coding variants for complex phenotypes such as that of SLE. We have established a multisite international paediatric SLE collaboration at four sites: USA, Canada, South Africa, and Mexico. We will use WES to investigate the genetic variants which may give insight into molecular pathways contributing to SLE.

Materials and methods Paediatric SLE patients at sites in the USA, Canada, South Africa and Mexico will be consented. Whole exome capture/sequencing will be performed on patients with paediatric-onset SLE age ≤10 years and/or SLE with strong familial aggregation, defined as ≥ one first degree relative or two second degree relatives with SLE. Patient and parent samples will be processed and analysed as trios.

We will collect standard information on all cohorts, including demographic information, clinical history, family history, medications, exam findings, laboratory values, SLEDAI and SLICC-DI. Organ damage will be defined as end stage renal disease or SLICC-DI>0.

Raw data will be processed by Whole Exome Sequencing using Illumina HiSeq2500. Bioinformatic analysis will be performed at NIH. We will develop an SLE specific bioinformatics pipeline to process data and analyse variants. Results will be filtered against known variants and parental samples.

Results We currently have access to 50 pSLE patients in the US, 75 pSLE patients in SA, 200 pSLE patients in Mexico, and 500 pSLE patients in Canada from which to recruit patients.

We anticipate analysis of 160 samples (20 patient/parent trios at NIH, 50 in Canada) to be complete at the time of presentation. We expect to recruit 30 SA trios, 135 Mexican trios, 40 US trios, and 200 Canadian trios during the total course of the study. Novel rare variants identified will be reviewed.

Conclusions Novel rare variants identified will be reviewed.

GG-11 SYSTEMICLUPUS ERYTHEMATOSUS (SLE) SUSCEPTIBILITY LOCI IN ASSOCIATION WITH AGE OF SLE DIAGNOSIS AND SUBPHENOTYPES OF SLE IN AN ANCESTRALLY COMPLEX CHILDHOOD-ONSET SLE LONGITUDINAL COHORT

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Background Recent large scale meta-genome-wide association studies (GWAS) of systemic lupus erythematosus (SLE) in Europeans have confirmed and identified new loci (Bentham *et al*. Nat Gen 2015). Up to 20% of those affected with SLE are diagnosed in childhood (cSLE). There is evidence for a higher burden of SLE susceptibility loci in those diagnosed in childhood compared to those diagnosed as adults. However, few studies have investigated how known susceptibility loci influence the timing of disease onset and sub-phenotype manifestations in cSLE across different ancestral groups.

Materials and methods We will examine SLE-susceptibility single nucleotide polymorphisms (SNPs) individually and in a weighted genetic risk score (GRS), for association with age of SLE diagnosis and sub-phenotype (eg: lupus nephritis (LN), dsDNA, CNS disease). We used a population of children diagnosed and followed for cSLE at the Hospital for Sick Children, Toronto (≥4/11 ACR classification criteria and/or ≥4/11 SLICC classification criteria) between 1982–2014. Participants were genotyped on the Illumina Immunochip. We examined ancestry by comparing with the 1000 genomes data using population stratification and ADMIXTURE. We will use additive genetic models to test the association of each SLE SNP with age of SLE diagnosis (linear regression), and the presence of subphenotypes (logistic regression) in the total cohort, and stratified by ancestral group.

Results In our cohort of 342 cSLE patients, the median age of SLE diagnosis was 13 (interquartile range: 10–15) years and the median duration of follow-up was 4.1 (IQR 2.7, 6.1) years. 44% of participants were of a single Ancestry (>95% of the genome from a single ancestral group: 16% European, 23% East Asian, 4% African), and 56% were admixed (genome comprised of more than one ancestral group).

Conclusions Our findings will provide insight into the generalizability of a SLE susceptibility GRS across ancestral groups, as it relates to age of diagnosis and subphenotypes of SLE in a cSLE population. Replication and meta-analyses in independent cohorts are planned.