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, 5,081 controls; HA: 1,689 cases, 1,314 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 < 1×10⁻⁶ (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 < 5×10⁻⁸: 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 transancestral 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.
Background Systemic Lupus Erythematosus (SLE) is a severe, multisystem autoimmune disease. Twin and sibling studies indicate a strong genetic component (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 a large impact on SLE risk. Paediatric SLE patients have earlier onset of disease, suffer more aggressive course of illness, and may have a stronger genetic risk than adults. Studies of disease pathogenesis, as demonstrated by familial aggregation, defined as familial hypercholesterolemia and atherosclerosis, and fever syndromes 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.