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 SLE 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** TRANSCANCESTRAL MAPPING AND GENETIC LOAD IN SYSTEMIC LUPUS ERYTHEMATOSUS

1Carl D Langefield*, 2Robert G Graham, 3Patrick M Gaffney, 4Timothy J Vye. 1Center for Public Health Genomics and Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA; 2Human Genetics, Genentech Inc, South San Francisco, California, USA; 3Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA; 4Divisions of Genetics and Molecular Medicine and Immunology, Infection and Inflammatory Diseases, King’s College London, Guy’s Hospital, London, SE1 9RT, UK

**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, 6,151 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 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.

Conclusions 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

1Amrie Grammer*, 1Sarah Heuer, 1Robert Robl, 1Prathyusha Bachali, 1Sushma Madamanchi, 1Matthew Kretzler, 2Celine Berthier, 2Benjamin Chong, 3Laurie Davis, 4Bernard Lauvreyns, 5Nicole Catalina, 6Peter Lipsky, 7RUTE and AMPLE Solutions, U. of Virginia Research Park, Charlottesville, VA; 8Molecular Nephropathy Research Lab, U. of Michigan; 9Depts. Dermatology and Internal Medicine, UTSW Med. Ctr., Dallas, TX; 10U. Catholique de Louvain, Brussels

**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 tubulointerstitium (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 upregulated 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 analysis 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.

**Abstracts**

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

1Laura B Lewandowski*, 1Christian Scott, 1Diana Gómez-Martin, 1Earl D Silverman, 1Ivana Aksentijevich, 1Zuximing Deng, 1Richard M Siegel, 1Lisa G Rider, 1Saifuraz Hashi, 1Mariana J Kaplan. 1Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD; 2Paediatric Rheumatology, Red Cross War Memorial Children’s Hospital and University of Cape Town, Cape Town, South Africa; 3Institucio Nacional de Ciencies Médicas y Nutrición Salvador Zubirán, Mexico; 4Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada; 5National Human Genome Research Institute, NIH, Bethesda, Maryland; 6Office of the Clinical Director National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD; 7Environmental Autoimmunity Group, National Institute of Environmental Health Sciences, NIH, HHS, Bethesda, MD 10.1136/lupus-2016-00179.62

**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.

**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.

**Conclusions** Novel rare variants identified will be reviewed.

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

1Chen Di Liao, 1Shazia Ali, 2,3Deborah Levy, 2,3Earl D Silverman, 2,3Linda T Hiraki*. 1Genetics and Genome Biology, Research Institute, the Hospital for Sick Children, Toronto, Canada; 2Division of Rheumatology, the Hospital for Sick Children, Toronto, Canada; 3Child Health Evaluative Sciences, Research Institute, the Hospital for Sick Children, Toronto, Canada; 4Department of Paediatrics, University of Toronto, Toronto, Canada; 5Physiology and Experimental Medicine, Research Institute, the Hospital for Sick Children, Toronto, Canada 10.1136/lupus-2016-00179.63

**Background** Recent large scale meta-genome-wide association studies (GWAS) of systemic lupus erythematosus (SLE) in Europeans have confirmed and identified new loci (Kentham 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 (e.g: 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 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.