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

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Background Immune 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 glomerulos (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©-CT). 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 analysis presented 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/IGP130. 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 BioProfiler® 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: I INTERNATIONAL MULTI-SITE ASSESSMENT OF GENETICS AND INFLAMMATION IN EARLY ONSET AND FAMILIAL SYSTEMIC LUPUS ERYTHEMATOSUS

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Materials and methods Paediatric SLE patients at sites in the 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.

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** 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


Background We examined 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 10,000 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.

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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.