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.

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GG-12 ALTERED EXPRESSION OF LONG NONCODING RNA IS ASSOCIATED WITH A LUPUS-ASSOCIATED VARIANT IN COMPLEMENT RECEPTOR 2

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Background Systemic lupus erythematosus is a multisystemic autoimmune disease characterised by the production of autoantibodies to nuclear antigens. We have identified a variant in intron 1 of complement receptor 2 (*CR2/CD21*) that is associated with decreased risk of lupus (rs1876453; $P_{meta} = 4.2 \times 10^{-4}$, OR = 0.85). Its effect is strongest in subjects with anti-dsDNA antibodies (case-control $P_{meta} = 7.6 \times 10^{-7}$, OR = 0.71; case-only $P_{meta}1.9 \times 10^{-4}$, OR = 0.75), suggesting a preferential association with this endophenotype. rs1876453, located 97 nucleotides from the 5' end of *CR2* intron 1, alters the binding of multiple protein complexes, including one containing CTCF, and is associated with increased B cell-specific expression of the adjacent gene, complement receptor 1 (*CR1/CD35)*. The transcriptional mechanism connecting these observations remains unclear, and we hypothesised that long noncoding RNA (lncRNA) play a role.

Materials and methods cDNA was generated by reverse transcription from RNA purified from the Raji B cell line as well as from human tonsil and spleen, peripheral blood mononuclear cells, and purified primary B cells. PCR was performed using 5' and 3' primers that targeted spliced exons from known lncRNA sequences in the intergenic region 5' of *CR2,* in the *CR2* gene, and in *CR1* intron 1. Quantitative PCR of primary B cell transcripts was performed using cDNA transcribed using random primers and MultiScribe reverse transcriptase (Applied Biosystems), customised lncRNA primers and probe that targeted spliced exons, Taqman assays for *U6 snRNA* and *b-actin* mRNA, and the Applied Biosystems 7500 Real-Time PCR System. Relative expression levels of lncRNA, normalised to either *U6 snRNA* (A) or *b-actin* (B), were calculated using the comparative C_T method. P values were determined using a two-tailed Student t test and a p value of <0.05 was considered significant.

Results We confirmed the presence of annotated lncRNAs in the *CR2-CR1* genomic region in various cell types. One annotated lncRNA located downstream of rs1876453 in *CR2* intron 1 was readily detected in B cells. We determined the allele-specific expression of this lncRNA by quantitative RT-PCR and found that it was ~3-fold increase in individuals with the minor protective allele at rs1876453 ($p = 0.0025$ normalised to *U6 snRNA* and $p = 0.0054$ normalised to *beta-actin*).

Conclusions Our data suggest that the generation of pathogenic autoantibodies associated with early, active, and severe lupus is modified by expression of a *CR2* lncRNA that appears to have long-range effects. Examination of its mechanism and effects may therefore reveal a novel target for the treatment of lupus.

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GG-13 PATHOGENESIS OF LUPUS PROLIFERATIVE GLOMERULONEPHRITIS (LPGN): PODOCYTES AS TARGETS AND RESPONDERS PROVIDE EVIDENCE FOR THE IMPORTANCE OF LOCAL FACTORS CONTROLLING END ORGAN DAMAGE

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Background LPGN is the prototypic immune-complex (IC) mediated disease. The current dogma that IC deposition with complement (C') activation inevitably leads to renal damage is neither sufficient nor comprehensive to account for the pathogenesis of LPGN. Our genetic studies support the thesis that acute GN (aGN) with IC deposition with C' activation and cell infiltration and mesangial proliferation is a distinct phenotype from chronic GN (cGN) that is characterised by glomerulosclerosis, tubular dilatation and interstitial fibrosis with severe proteinuria and premature mortality. Furthermore, circulating ANA and anti-dsDNA Abs are not required for LPGN.

Materials and methods Female mice of NZM2328 and its intrachromosomal recombinant congenic line NZM2328.Lc1R27 (R27) were used. Anti-GBM induced GN was used as a model for IC mediated LPGN. Immunofluorescence was used to identify cell populations that made cytokines and complement components.

Results R27 developed aGN and mild proteinuria without progression to cGN, end stage renal failure and early mortality. The kidneys of aged R27 had IC deposition and cellular infiltration, not distinguishable from that of aGN in NZM2328. Multiple approaches showed that the lack of progression from aGN to cGN in R27 was due to podocyte resistance to IC-mediated damage, a phenotype controlled by the allelic *Cgnz1* gene.

With a novel method to study intra-glomerular cytokine production, NZM podocytes were shown to be the major cell population that makes IL-1β in cGN, infiltrating CD11b+ macrophages make TNFα and the mesangial cells make IL-6. R27 mice do not show this compartmentalization of cytokine production. Preliminary data showed that the podocytes in Class III and IV lupus GN make IL-1β.

Podocytes at the early and late cGN were shown to make C1q and C3. The expression of these complement components is less evident in R27 kidneys. C1q and C3 were present in some podocytes in biopsies of class III and IV lupus nephritis. Urinary podocytes making C1q were detected by us in of four patients with LPGN but not in normal individuals.

Conclusions Our studies of lupus GN in both mouse and in man have provided significant information and insight regarding the role of podocytes as targets and as responders to IC mediated injuries. Our results suggest that the pathogenesis of LPGN should be revisited with focus on the local factors that may be of