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 path-
ways 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 immunopatho-
genesis and could identify therapies that may be useful in all
lupus patients versus those with involvement of specific tissues.

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 famil-
ial aggregation, defined as ≥ one first degree relative or two sec-
ond 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, medica-
tions, exam findings, laboratory values, SLEDAI and SLICC-DL.
Organ damage will be defined as end stage renal disease or
SLICC-DL>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 presenta-
tion. 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.

Abstracts

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

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Background Systemic Lupus Erythematosus (SLE) is a severe,
multisystem autoimmune disease. Twin and sibling studies indi-
cate 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 break-
throughs 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 phenos-
types such as that of SLE. We have established a multisite interna-
tional 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 famil-
ial aggregation, defined as ≥ one first degree relative or two sec-
ond 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, medica-
tions, exam findings, laboratory values, SLEDAI and SLICC-DL.
Organ damage will be defined as end stage renal disease or
SLICC-DL>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 presenta-
tion. 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

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Canada; Department of Paediatrics, University of Toronto, Toronto, Canada; Physiology
and Experimental Medicine, Research Institute, the Hospital for Sick Children, Toronto,
Canada

Background Recent large scale meta-genome-wide association
studies (GWAS) of systemic lupus erythematosus (SLE) in Euro-
peans have confirmed and identified new loci (Bentham et al.
Nat Gen 2015). Up to 20% of those affected with SLE are diag-
osed in childhood (cSLE). There is evidence for a higher burden
of SLE susceptibility loci in those diagnosed in childhood com-
pared 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 diagno-
sis and sub-phenotype (eg: lupus nephritis (LN), dsDNA, CNS
disease). We used a population of children diagnosed and fol-
lowed 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 Immonochip. 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 regres-
sion), and the presence of subphenotypes (logistic regres-
sion) 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 generaliz-
ability 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.
ALTERED EXPRESSION OF LONG NONCODING RNA IS ASSOCIATED WITH A LUPUS-ASSOCIATED VARIANT IN COMPLEMENT RECEPTOR 2

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10.1136/lupus-2016-000179.64

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; \( P_{\text{meta}} = 4.2 \times 10^{-4}, \) OR = 0.85). Its effect is strongest in subjects with anti-dsDNA antibodies (case-control \( P_{\text{meta}} = 7.6 \times 10^{-7}, \) OR = 0.71; case-only \( P_{\text{meta}} = 1.9 \times 10^{-4}, \) 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 to target 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 \( \Delta \Delta C_T \) 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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