autoimmunity for several years prior to the onset of clinical disease. Measuring anti-nuclear antibodies (ANA) is a common test for humoral autoimmunity. It is sensitive (95+%) for SLE, but not specific as up to 25% of healthy controls (HC) will have a measurable ANA. While very few of the ANA +HC will develop SLE, they represent a group at higher risk of the disease. Understanding the risks for ANA positivity provides essential knowledge about the development of SLE.

Methods Serum and DNA were collected from 2903 healthy individuals with no personal history of autoimmunity. Antinuclear antibodies were detected using Inova QuantaLite ELISA. Sera from subset (n=724) individuals (ANA– HC, ANA+ HC, and SLE) were assayed by protein microarray quantifying IgM and IgG responses to 89 previously known human autoantigens. A nested cohort consisting of all the ANA +Caucasian individuals and age/gender matched ANA– controls were genotyped using the ImmunoChipv.1 SNP array.

Results In HC, 16% had moderate and 10% had high levels of IgG ANA. Autoantigen microarray data showed that ANA+ HC had a high prevalence of antibodies to non-nuclear and cytoplasmic antigens while subjects with SLE predictably produced antibodies to a variety of nuclear antigens as well. A quantitative genetic association test with ANA identified the locus *c11orf30* or *EMSY*, associated with high ANA phenotype in the healthy population (see figure 1). This locus codes for a negative transcriptional regulator. A haplotype comprised of many potentially regulatory polymorphisms at *EMSY* contributed to strong risk for ANA in healthy individuals [(p=3.83E-04, OR=2.6)]. eQTL data suggests that the ANA-associated *EMSY* haplotype leads to reduced expression of *EMSY* protein in human macrophages and EBV cell lines. Autoantibody profiles of serum samples from healthy individuals with the *EMSY* risk genotype exhibited high titers of anti-IgG and IgA antibodies targeted to multiple autoantigens as well as food and environmental allergens.

Conclusions *EMSY*, a locus previously linked with atopy, psoriasis and inflammatory bowel disease was associated with ANA in healthy individuals. The *EMSY* protein is a BRCA2-associated transcriptional repressor. Individuals with risk haplotypes in *EMSY* make a wide variety of disease-associated antibodies, suggesting an early common pathway for autoimmune and allergic conditions.

GG-08 IMMUNE REPERTOIRE AND GENETIC RISK ALLELES IN HEALTHY PEDIATRIC POPULATIONS WITH AUTOIMMUNE INDICATORS

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Background The antibody specificities of an infant progressively form in response to infections, environmental exposures, and vaccinations. While many adults develop antibodies to self-antigens, it remains unknown if these are present in infants and toddlers.

Methods Serum, peripheral blood, and clinical data have been collected from 102 healthy children (1–2 year of age). ANA titers were measured by QuantiaLite ELISA (Inova) and reactivity to 125 diverse autoantigens tested by autoantibody array. Targeted sequencing was performed in 60 children to capture HLA alleles and potentially pathogenic genetic variations in 100 plus loci that are implicated in various autoimmune, rheumatic and immune system related diseases. Sequencing libraries were made using KAPA Biosystems kits. Custom target oligos were synthesized from Nimblegen. Deep sequencing was performed using Illumina HiSeq 4000 platform. Sequencing reads were aligned to reference genome and variants were called using GATK Pipeline. Secondary data analysis is done using Metlab, GraphPad Prism, Haploview and Golden Helix programs.

Results Approximately 28% of very young children have moderate to high-titer autoantibodies, similar to adults, however, no female gender bias was observed. Significant differences between the child and adult immune repertoires were seen. Some samples demonstrated strong signatures of non-nuclear antigens reactivities. Interestingly, the ANA positive group of children exhibited significantly high titers of anti-alpha fodrin IgG (p=0.01), an autoantibody reported in juvenile Sjogren's syndrome. Analysis of sequencing data identified regulatory polymorphisms in HLA class II and III regions that were associated with ANA positivity. About 8% of the ANA positive children also carried autoimmune disease associated HLA-DR-DQ alleles. HLA alleles and regulatory haplotypes were analyzed in relation to various clinical features in children. Serum C4 level measured in subset of ANA positive children identified few with reduced expression.

Conclusions While the immune repertoire of very young children is typically thought of as naïve and self-tolerant, a significant fraction of very young children makes autoantibodies as detected by commercial ANA ELISA and autoantigen arrays. This supports the conclusion that ANA and other autoantibodies are consequences of general body development and immune upregulation and not markers of pathology. One of the major genetic determinants of 'pre-clinical' autoimmunity as measured by ANA is the human major histocompatibility locus, *HLA*. Within *HLA*, several 'endophenotypes' emerge, including expression of a complement protein involved in immune complex removal, as well as multiple proteins associated with antigen presentation, including MHC class II. These findings support the idea that there is quantifiable genetic risk for the development of autoimmunity that can be measured in very young individuals.

GG-09 A ROLE FOR EBNA2 IN MECHANISMS THAT ARE RESPONSIBLE FOR LUPUS AND OTHER AUTOIMMUNE DISEASES

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Background Explaining the genetics of many diseases is challenging because most associations localize to incompletely understood regulatory regions.

Methods We show that transcription factors (TFs) occupy multiple loci of individual complex genetic disorders much more than expected by chance using novel computational methods.

Results Application to 213 phenotypes and 1,544 TF binding datasets identifies 2,264 relationships between hundreds of TFs and 94 phenotypes, including AR in prostate cancer and GATA3 in breast cancer. Strikingly, nearly half of the systemic lupus erythematosus risk loci are occupied by the Epstein-Barr virus (EBV) Nuclear Antigen 2 (EBNA2) protein (OR=6, $P < 10E-24$ after Bonferroni correction), which co-clusters with a sub-set (<60) human TFs, revealing gene-environment interaction, and identifying the EBV transformed B cell as a putative site for some of the genetic mechanisms altering disease risk. Analogous EBNA2-anchored associations exist in multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, juvenile idiopathic arthritis, and celiac disease. Instances of allele-dependent DNA binding with downstream effects on gene expression at plausibly causal variants are consistent with EBNA2 dependent genetic mechanisms.

Conclusions Our results nominate mechanisms that operate across risk loci within disease phenotypes; they suggest new paradigms for disease origin and strongly support a role for Epstein-Barr virus in the generation of systemic lupus erythematosus, as well as of particular other autoimmune diseases, apparently related to lupus by the genomic mechanisms that produce them.

GG-10 FEASIBILITY OF CONDUCTING EPIGENETIC ANALYSIS IN PEDIATRIC LUPUS B CELLS

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Background Bennett et al identified the presence of interferon gene expression signatures in peripheral blood of children with systemic lupus erythematosus (pSLE). Here, we aim to identify how B cells contribute to those signatures. We hypothesize that disordered transcription in pSLE will be prominent in B cells and attributed to disease-specific epigenetic alterations. Thus we will not only identify important disease mechanisms in SLE, we will shed light on the genetics of SLE. Our previously published work demonstrated that most of the genetic risk for SLE located within non-coding regions of the genome appears to also contain higher than baseline epigenetic modifications of DNA and transcription factor binding sites that regulate and coordinate transcription.

Methods Our specific aim is to assess regions of open chromatin in untreated pSLE and compare findings with healthy children. We propose to use assays of transposase-accessible chromatin with sequencing (ATACseq) to broadly survey open regions of chromatin and clarify the functional epigenome. In this pilot study, we propose to determine feasibility of performing this assay and developing methods for data analysis using 5 pediatric lupus patients and 5 healthy children.

Anticipated results and conclusions Our long-term goal is to gain a mechanistic understanding of the aberrant transcriptional signatures in untreated SLE. The data generated by this pilot study will provide the basis for a rigorous power analysis, and firmly establish the working relationship between the

Buffalo and Cohen Children's Medical Center groups, both of which will be essential for a competitive application to NIH. Our preliminary findings from this pilot study will also allow us to begin the exciting process of linking the genetics and epigenetics of pSLE to the well-established transcriptional aberration.

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GG-11 IDENTIFYING GENETIC VARIANTS FOR MONOGENIC LUPUS AND MACROPHAGE ACTIVATION SYNDROME (MAS) IN CHILDHOOD ONSET SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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Background There is strong evidence that genetics plays an important role in the pathogenesis of systemic lupus erythematosus (SLE). Genome wide association studies (GWAS) have identified >90 loci associated with SLE risk, which suggests SLE is a complex trait. Yet collectively these genes explain a small fraction of SLE heritability. Within the broad category of SLE, there are genetically distinct Mendelian/monogenic diseases, presenting with lupus features. Macrophage activation syndrome (MAS) is an increasing recognized complication of SLE. It shares similarities with familial hemophagocytic lymphohistiocytosis (HLH), a Mendelian disease. We hypothesize that whole exome (WES) and whole genome sequencing (WGS) of SLE patients suspected of carrying rare genetic variants with large effects, will identify variants and genes associated with SLE risk and MAS. This information has implication for therapy, screening as well as providing insights into the pathogenesis of SLE and MAS broadly.

Methods WGS on 8 cSLE patients with one of: (i) age diagnosis <10 y, (ii) from families with multiple affected members with SLE; or (iii) evidence of consanguinity, and WES on 11 cSLE with MAS was completed at TCAG. Paired end sequencing completed using HiSeq X (WGS, read depth 37–40X) and Illumina HiSeq 2500 (WES, 70–118X) platforms. GATK and HAS were used for variant calling and ANNOVAR for functional annotation, with TCAG Small Variant annotation pipeline, v26.2, v26.5. We initially focused on rare (minor allele frequency <0.01) gene coding regions from 36 known monogenic lupus, and 14 HLH genes.

Results WGS of cSLE patients revealed potential disease causing monogenic variants in known genes including *SLC7A7* and *DNASE1*. All MAS-SLE patients heterozygous for ≥1 rare variant in HLH gene, with 5/14 heterozygous for exonic non-synonymous variants in *PRF1*, *LYST*, *ITK* and *AP3B1*.

Conclusions We identified candidate variants leading to monogenic lupus and MAS in SLE. Additional validation studies are planned to confirm our findings and elucidate the precise pathogenic mechanism leading to disease. These variants have the potential for prognostication, secondary screening