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, (i) 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, v.26.5. 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