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, \( P<10^{-24} \) 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-11 IDENTIFYING GENETIC VARIANTS FOR MONOGENIC LUPUS AND MACROPHAGE ACTIVATION SYNDROME (MAS) IN CHILDHOOD ONSET SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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, 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 DNAE1. All MAS-SLE patients heterozygous for ≥1 rare variant in HLH gene, with 3/14 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.