(rs145588689) is present in 0.2% of the world population and in 0.3~04% of non-Finnish Europeans. It seems likely that the variant underwent selection during the period of urbanization during the Middle Ages. The increased interferon responses may have enhanced survival against pandemic viruses. Whether P193A increases risk of systemic lupus erythematosus is unknown.

1506 A HUMAN SLE VARIANT NCF1-R90H PROMOTES KIDNEY DAMAGE AND MURINE LUPUS THROUGH ENHANCED TFH2 RESPONSES INDUCED BY DEFECTIVE EFFEROCYTOSIS OF MACROPHAGES

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Background We previously identified a p.Arg90His (p.R90H) hypomorphic variant of neutrophil cytosolic factor 1 (*NCF1*, a regulatory subunit of phagocyte NADPH oxidase 2 complex, NOX2) predisposes to multiple autoimmune diseases including systemic lupus erythematosus (SLE). We established a C57BL/6 (B6) mouse model with a knock-in (KI) H90 variant in the *Ncf1* locus by CRISPR/Cas9 editing to study how this common *NCF1* variant promotes the development of lupus manifestations.

Materials and Methods Wild type (WT) and KI littermates were assessed either for spontaneously-developed or pristane-induced immune profiles and lupus-like features. Efferocytosis was assessed using irradiated WT thymocytes or Jurkat cells as apoptotic cells (AC) to co-culture with murine bone marrow-derived macrophages or human circulating monocyte-derived macrophages, respectively. Disease activity and renal damage of SLE patients were assessed by SLEDAI and renal items of SLICC, respectively.

Results Compared to WT littermates, 5-week-old homozygous KI mice had reduced oxidative burst, splenomegaly, elevated type I interferon (IFN-I) scores, increased ratios of splenic follicular T helper 2 (Tfh2) to either T follicular regulatory (Tfr) or Tfh1 cell numbers, increased ANA^+ follicular, germinal center B cells and plasma cells, but no spontaneous kidney disease up to one-year of age. Pristane treatment induced kidney disease development in 36-week-old H90 KI B6 female mice, exhibiting increased Tfh2 coupled with decreased Tfr and Tfh1 proportions, robust germinal center formation and IgG autoantibody production. Decreased efferocytosis of macrophages derived from KI mice and homozygous H90 SLE patients promoted elevated ratios of Tfh2/Tfr and Tfh2/Tfh1 as well as dysregulated humoral responses due to reduced Hv1-dependent acidification of phagosome pH to neutralize the decreased electrogenic effect of the H90 variant, resulting in impaired maturation and proteolysis of phagosome. SLE patients carrying homozygous H90 genotype had elevated circulating Tfh2/Tfr and Tfh2/Tfh1 ratios, positive correlations of circulating Tfh2 percentage with plasmablast frequency and disease activity, deposition of IgG and complement C3 in kidney biopsies, and increased kidney damage in multiple ethnic populations.

Conclusion The same links between the NCF1 H90 hypofunctional genotype to lupus-like phenotype in a mouse model and SLE patients demonstrates it is the causal variant in the NCF1 locus associated with SLE.

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1507 THE RELATIONSHIP BETWEEN DNA METHYLATION PATTERNS AND DISEASE ACTIVITY IN A LONGITUDINAL MULTI-ANCESTRAL COHORT OF LUPUS PATIENTS

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Background Epigenetic dysregulation is implicated in the pathogenesis of lupus. We performed a longitudinal analysis of DNA methylation in lupus patients and assessed epigenetic changes over time and across disease activity status. Combining genetic and epigenetic analyses, we also examined ancestry-specific DNA methylation and DNA methylation changes influenced by genetic variants across the genome.

Methods A total of 54 female lupus patients, including 32 European-American and 22 African-American, were followed for up to 4 years. Blood samples were obtained at routine follow up visits and during disease flares, with a total of 229 samples collected. Disease activity at each blood draw was determined by SLEDAI. Granulocytes were isolated and DNA extracted. Genotyping was performed using the Infinium Global Screening Array v2.0, and genome-wide DNA methylation was assessed at each time-point using the Infinium MethylationEPIC array. Ancestry-specific DNA methylation changes and methylation quantitative trait loci (meQTL) were identified. A linear mixed effects model was implemented to identify DNA methylation alterations that vary with disease activity and the development of lupus nephritis during follow up.

Results We identified 487 hypomethylated and 420 hypermethylated CpG sites in African-American compared to European-American lupus patients, annotated to 391 and 316 unique genes, respectively. Differentially methylated genes include type I interferon-response genes such as *IRF7* and *IFI44,* and genes related to the NFkB pathway. After adjusting for age, medications, and genetic background, DNA methylation levels in 142 (15.7%) differentially methylated sites were found to be allele-specific and influenced by at least one genetic variant located within 1kb. *TREML4*, which plays a vital role in toll-like receptor signaling, was hypomethylated in African-American patients and demonstrated a strong *cis*-meQTL association (R^2=0.91). The associated genetic variant (rs9369265) significantly differs in allele frequencies between

African-American and European-Americans, and is located within an active enhancer region in neutrophils and modifies *TREML4* expression. *In vitro* patch methylation experiments confirmed the regulatory effects of *TREML4* methylation upon gene expression. Experiments to assess the functional effects of TREML4 overexpression in human neutrophils are underway in our laboratory. Interestingly, the DNA methylome was highly stable across disease activity levels and over time. Two sites cg26104306 (*SNX18*; FDR-adjusted P-value = 3.38 x 10^{-2}) and cg06708913 (FDR-adjusted P-value = 3.43 x 10^{-2}) were associated with changing disease activity levels in African-American patients. Demethylation of a CpG site located within *GALNT18* was associated with the development of active lupus nephritis.

Conclusion Lupus granulocytes demonstrate significant differences in DNA methylation patterns between African-American and European-American patients. DNA methylation profiles in lupus patients are influenced by ancestry-specific genetic variants and are highly stable over time independent of disease activity levels. Progressive demethylation in *SNX18* was observed with increasing disease activity in granulocytes from African-American lupus patients, and demethylation in *GALNT18* was associated with the development of lupus nephritis in our cohort during follow up.

1508 SINGLE-CELL EPIGENETIC PROFILING HIGHLIGHTS GENETIC IMPACT ON CHROMATIN ACCESSIBILITY IN SLE

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Background Chromatin accessibility (CA) is a critical epigenetic feature identifying genomic loci that actively participate in gene-regulating functions, such as transcription and DNA repair. In turn, genetic polymorphisms within these loci can affect the magnitude of CA, i.e. a chromatin accessibility quantitative trait locus (caQTL). Changes in CA have been implicated in inflammatory disease, and previous genetic research has identified several risk haplotypes for systemic lupus erythematosus (SLE). However, it remains unclear how CA may interact with genetic risk factors in SLE pathogenesis. To better understand how CA in SLE may be driven by genetic variation, we performed single-cell assay for transposase accessible chromatin (sciATAC-seq) on peripheral blood mononuclear cells (PBMCs). SciATAC-seq is an efficient, scalable and sensitive assay that allows the epigenetic profiling of thousands of cells from an individual. By combining these profiles with genotypic data, we can search for caQTLs as evidence of genetic-epigenetic interaction specific to SLE.

Methods PBMCs were isolated from 45 SLE patients and 50 healthy controls. Each PBMC sample underwent both genotyping and sci-ATAC sequencing. DNA was then sequenced by Illumina Next-seq. Cell-specific ATAC reads were demultiplexed and quantified by custom software developed by the BROAD Institute (Cambridge, MA). Genotyping data was phased and imputed using the IMPUTE2 tool suite. Cell type-specific caQTL analysis was performed by RASQUAL.

Results An average of 980 cells were sequenced per sample, with a total of 745,697 CA sites measured. We identified a total of 153,716 caQTL relationships across 17 distinct immune cell types, involving 59,715 unique variants; 59% of which are also reported as expression QTLs in whole blood. The majority of caQTLs already implicated in autoimmune disease risk haplotypes occurred predominantly in B cells and plasmacytoid dendritic cells. CA profiles exhibit cell type-specific cluster orientation highly correlated with caQTL genotype. Genotypes at variant rs1131665, previously associated with an SLE risk haplotype in IRF7 and here as a caQTL, distinguished subpopulations of B cells and monocytes on the basis of global CA profiles. Increases of CA at the variant were present in SLE individuals compared to controls, suggesting caQTL variants contribute to a genome-wide epigenetic phenotype for SLE risk.

Conclusion Using advances in single-cell epigenetic profiling, we were able to identify thousands of genetic variants which influence epigenetic functions, in a cell type-specific way, through their association to CA. Understanding the molecular mechanisms for how caQTLs alter cell type-specific chromatin accessibility will provide new insights into the role of epigenetic regulation in SLE pathogenesis.

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1509 DIFFERENCES IN CHROMATIN ARCHITECTURE PRE- AND POST-INDUCTION THERAPY IN PEDIATRIC LUPUS PATIENTS

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Background Systemic lupus erythematosus (SLE) may be triggered by gene-environment interactions. Data remain scarce on how epigenetic variance contributes to disease risk in pediatric SLE (pSLE). Our objectives were to identify differences in chromatin architecture in treatment-naïve pSLE compared to healthy children (HC) and pSLE patients after induction therapy.

Methods We used assays for transposase-accessible chromatin-sequencing (ATACseq) in 8 pSLE patients pre- and post-induction therapy and 5 HC to investigate whether regions of open chromatin unique to pSLE patients demonstrate enrichment for transcriptional regulators, using standard computational approaches and a false discovery rate of <0.05.

Results The mean age of onset was 13.75 (range 7-17) years in pSLE, and mean SLEDAI was 12.8 (range 6-24). We