

(rs145588689) is present in 0.2% of the world population and in 0.3~0.4% 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