
COMMITTEE IN CHARGE: Patrick M. Gaffney, M.D., Christopher J. Lessard, PhD., A. Darise Farris, PhD., Scott M. Plafker, PhD., Priyabrata Mukherjee, PhD., Zhizhuang Joe Zhao, PhD.

ABSTRACT: Systemic Lupus Erythematosus (SLE) is a debilitating autoimmune disease characterized by innate and adaptive immune dysfunctions. Genome-wide association studies (GWAS) have identified genetic polymorphisms in ubiquitin-conjugating enzyme E2 L3 (UBE2L3) and Tumor Necrosis Factor Alpha-Induced Protein 3 (TNFAIP3) to be associated with SLE susceptibility. The presence of the UBE2L3 risk haplotype results in increased UBE2L3-encoded UbcH7 protein expression whereas the TNFAIP3 risk haplotype results in reduced TNFAIP3-encoded A20 protein expression. Both UbcH7 and A20 are involved in the ubiquitin signaling pathway, and their dysregulated expression leads to increased NFκB activation, inflammatory...
responses and susceptibility to SLE. Despite the usefulness of GWAS in identifying SLE susceptibility loci spanning UBE2L3 and TNFAIP3, the precise causal variants responsible for these statistically significant associations remain unexplored. Our study is aimed at the identification and functional characterization of causal variants among the single nucleotide polymorphisms (SNPs) residing in the UBE2L3 and TNFAIP3 risk haplotypes. We systematically evaluated seven risk variants in the UBE2L3 haplotype to identify four variants in the UBE2L3 and YDJC promoters as plausible causal variants. The risk variants were found to drive hypermorphic UBE2L3 expression by strengthening a YY1-mediated long-range interaction between the UBE2L3 and YDJC promoter elements. In the TNFAIP3 risk haplotype, we characterized a RelA/p65-dependent enhancer element upstream of TNFAIP3 that exhibited CEBPB-dependent allele-specific enhancer activation. The risk alleles of rs10499197 and rs9494868 were identified to be responsible for modulating this upstream enhancer function. Overall, this dissertation provides mechanistic insights on how SLE risk haplotypes modulate UBE2L3 or TNFAIP3 expression, focusing the critical role of causal variants in SLE pathogenesis.