AUTOIMMUNE CONNECTIVE TISSUE DISEASES

THE POLYMORPHISM RS13259960 IN A LONG NONCODING GENE, SLEAR, PREDISPOSES TO SYSTEMIC LUPUS ERYTHEMATOSUS

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Introduction: Genome-wide association studies have been performed to identify numerous susceptibility loci in SLE. However, they in total cannot fully explain SLE heritability, suggesting many genetic variants to be discovered yet. In order to determine the presence of novel susceptibility Long noncoding RNAs (lncRNAs) for systemic lupus erythematosus (SLE), we used data from our previously published genome-wide association studies (GWAS) in Han Chinese population to generate candidate association signals and performed experiments to discover the mechanism of this gene implicated in SLE.

Methods: In this study, we carried out a genome-wide survey of SLE risk variants in long noncoding gene loci in Han Chinese, and identified a new susceptibility locus in an lncRNA gene which we named SLEAR(rs13259960). We performed 5' and 3' RACE combined northern blotting to determine the full-length of the lncRNA. We further studied the connection between the SNP rs13259960 and SLEAR by eQTL, motif analysis, ChIP-qPCR and allele-specific ChIP-qPCR. We investigated the function of SLEAR by RNA pull-down, RNA immunoprecipitation, immunoprecipitation, Western blotting, and ChIRP-Seq.

Results: We identified a new susceptibility locus in a lncRNA gene which we named SLEAR (rs13259960, Pcombined = 1.03×10-11, OR = 1.35). The A>G variation at rs13259960, located in an intronic enhancer, impairs STAT1 recruitment to the enhancer that loops to SLEAR promoter, resulting in decreased SLEAR level. Moreover, SLEAR interacts with ILF2, hnRNP F and TAF15 to form a complex for transcription activations of the downstream anti-apoptotic genes. SLEAR regulates apoptosis in vitro and its expression level is correlated with cell death in SLE patients.

Conclusion: Our results suggest a mechanism that the risk variant at rs13259960 modulates SLEAR expression and predispose to SLE.