A 3'-untranslated region variant is associated with impaired expression of CD226 in T and natural killer T cells and is associated with susceptibility to systemic lupus erythematosus.

Costimulatory receptor CD226 plays an important role in T cell activation, differentiation, and cytotoxicity. This study was undertaken to investigate the genetic association of CD226 with susceptibility to systemic lupus erythematosus (SLE) and to assess the functional implications of this association. Twelve tag single-nucleotide polymorphisms (SNPs) in CD226 were typed in 1,163 SLE patients and 1,482 healthy control subjects from Europe or of European ancestry. Analyses of association were performed by single-marker Cochran-Mantel-Haenszel meta-analysis, followed by haplotype analysis. Gene expression was analyzed by quantitative real-time polymerase chain reaction analyses of RNA from peripheral blood mononuclear cells, and by fluorescence-activated cell sorter analysis. To study the functional impact of the associated variants, luciferase reporter constructs containing different portions of the 3'-untranslated region (3'-UTR) of the gene were prepared and used in transfection experiments. A 3-variant haplotype, rs763361; rs34794968;
rs727088 (ATC), in the last exon of CD226 was associated with SLE (P = 1.3 × 10(-4), odds ratio 1.24, 95% confidence interval 1.11-1.38). This risk haplotype correlated with low CD226 transcript expression and low CD226 protein levels on the surface of CD4+ and CD8+ T cells and natural killer T (NKT) cells. NK cells expressed high levels of CD226, but this expression was independent of the haplotype. Reporter assays with deletion constructs indicated that only the presence of rs727088 could account for the differences in the levels of luciferase transcripts. This study identified an association of CD226 with SLE in individuals of European ancestry. These data support the importance of the 3'-UTR SNP rs727088 in the regulation of CD226 transcription both in T cells and in NKT cells.