The Genetics Behind Systemic Lupus Erythematosus: An in silico Analysis on the HLA-DRB1 Gene to Identify High-Risk Variants

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Systemic Lupus Erythematosus (SLE) is a complex chronic autoimmune disease characterized by widespread inflammation and tissue damage. Its multifactorial etiology, involving a variety of environmental, hormonal, and genetic factors, complicates diagnosis and in turn, limits treatment options. This research investigates the genetic basis of SLE by leveraging in-silico bioinformatics tools to examine how variations in the HLA-DRB1 gene influence susceptibility to the disease. HLA-DRB1 gene variants were retrieved from the NCBI SNP database and mapped onto the GRCh38 genome assembly via the NCBI Variation Viewer. Variants were categorized into nsSNVs (missense and nonsense) and indels, and evolutionary conservation was assessed using the ConSurf server. Variants with a maximum scaled CADD score of at least 30 were deemed high-risk. High-risk missense variants were analyzed with the HOPE server to predict protein impacts, while high-risk nonsense and indel variants were evaluated using the Variant Effect Predictor and SIFT tools, respectively, and then validated using pyMOL and AlphaFold. The research found that 4 missense, 12 nonsense, and 5 indel variants were predicted to be high-impact/damaging to the protein structure by their respective In-silico tools, suggesting their potential role in the development of SLE. These findings enhance understanding of the genetic contributors to SLE, offering insights that could improve diagnostic times and open up possibility for new treatments. Future research could focus on functional validation of these variants and explore their role in immune dysregulation pathways. Such efforts may lead to the development of personalized treatment strategies and novel therapeutic interventions, ultimately improving outcomes for SLE patients.

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