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Linking genetic variation with epigenetic profiles in Sjögren's syndrome

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ABSTRACT

DNA methylation represents an important regulatory event governing gene expression that is dysregulated in Sjögren's syndrome (SjS) and a number of autoimmune/inflammatory diseases. As disease-associated single-nucleotide polymorphisms (SNPs) have relevance in controlling DNA methylation, 94 non-HLA SjS-SNPs were investigated, among them 57 (60.6%) with widespread effects on 197 individual DNA methylation quantitative trait loci (meQTL) were selected. Typically, these SNPs are intronic, possess an active promoter histone mark, and control *cis*-meQTLs located around transcription start sites. Interplay is independent of the physical distance between SNPs and meQTLs. Using epigenome-wide association study datasets, SjS-meQTLs were characterized (41 genes and 13 DNA methylation CpG motifs) and for the most part map to a pro-inflammatory cytokine pathway, which is important for the control of DNA methylation in autoimmune diseases. In conclusion, exploring meQTLs represents a valuable tool to predict and investigate downstream effects of genetic factors in complex diseases such as SjS.

1. Introduction

Primary Sjögren's syndrome (SjS) is a systemic autoimmune disease with female predominance. It is characterized by epithelitis that affects exocrine glands, mainly lachrymal and salivary glands, and results in progressive loss of secretory function[43,50,51]. Clinical manifestations include xerophthalmia and xerostomia, but also systemic manifestations. Patients have a 20- to 40-fold increased risk of developing lymphoma[14,46,50,51,64]. Histological evaluation shows focal and peri-epithelial T and B cell infiltration in exocrine glands together with characteristic circulating autoantibodies, including anti-sicca syndrome type A (SSA/Ro) and type B (SSB/La) antibodies [4,9,14,46,64].

Approximately 120 million single nucleotide polymorphisms (SNPs) have been reported in the human genome, and among them approximately one hundred can increase the risk of developing SjS [23,55]. The pathophysiological contribution of genetic factors in SjS is estimated to be around 35% according to the familial clustering analyses[6,54]. However, the genetic impact of individual risk alleles is usually modest (Odds ratios < 2). Exceptions are variants in the human leucocyte antigen (HLA) cluster that result in moderately increased Odds ratios of 2–3[17,34]. Another key challenge in understanding the impact is that up to 90% of genetic risk variants map to non-coding regions of the human genome, and only a subset co-localize with regulatory regions[23,34]. These “regulatory SNPs” can control gene expression through direct or indirect effects on the recruitment and/or assembly of the transcriptional machinery. Direct effects are mediated when SNPs are present within proximal gene regulatory regions close to the transcription start site (TSS) where they control transcription factor

Abbreviations: SjS, Sjögren's syndrome; GWAS, Genome wide association studies; QTL, Quantitative trait loci; HLA, Human leucocyte antigen; SNPs, Single nucleotide polymorphisms; IFN, Interferon; EWAS, Epigenome wide association studies; SGECs, Salivary gland epithelial cells; IRF5, IFN-regulatory factor 5; STAT4, Signal transducer and activation of transcription 4; PBMCs, Peripheral blood mononuclear cells; SGECs, Salivary gland epithelial cells; DMCs, Differentially methylated CpGs; eQTL, Expression quantitative trait loci; meQTL, Methylation quantitative trait loci; BRD1, Bromodomain 1; RAR, heumatoid arthritis

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