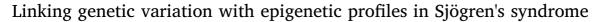
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ABSTRACT

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

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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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