**Supplementary text.**

## PATIENTS AND METHODS

### Sample preparation

Genomic DNA from whole blood was isolated using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). CD19+ B cells were fractionated from buffy coats applying Ficoll-Hypaque density-gradient centrifugation (GE Healthcare, Little Chalfont, UK) for PBMC isolation followed by positive selection with a cell type specific antibody (Miltenyi Biotec, Bergisch Gladbach, Germany). For DNA and RNA preparation from B cells the AllPrep DNA/RNA Mini Kit or the AllPrep DNA/RNA/miRNA Universal Kit (Qiagen) were used. Minor salivary gland biopsies were homogenized prior to DNA preparation using the Qiagen DNeasy Blood and Tissue kit (Qiagen).

### Genome-wide methylation analysis

DNA methylation levels of 485,577 CpG sites were determined on the HM450K BeadChip (Illumina Inc., San Diego, CA, USA). Bisulfite treatment was performed with 500 ng of DNA using the EZ DNA Methylation-Gold Kit (Zymo Research, Irvine, CA, USA). Samples were randomized on the BeadChip to avoid any batch effects. Arrays were scanned on an iScan SQ instrument (Illumina), and signal intensities were exported as intensity data files and parsed into the Minfi R package for quality control (QC) and Subset-quantile Within Array Normalization (SWAN).[1-3] Methylation beta-values were calculated as the fraction of the signal intensity from the methylated CpG sites over the total intensity (range 0-1, corresponding to 0-100% methylation). Only CpG sites with complete data across all samples, signal detection $p>0.01$, unambiguously mapping to autosomes, containing no SNPs in the 10 bp at the 3'-end of the probe (1000 genomes CEU populations, release 3) [4] and not overlapping any known copy number variant were kept for further analysis. The post-QC dataset comprised 388,971 CpG sites.

### Epigenome-wide association and pathway analysis

Differential cell counts for each whole blood sample were estimated using publicly available reference DNA methylation signatures of flow sorted blood cells types.[5 6] To determine differential methylation between pSS patients and controls a linear regression model containing cell count estimates, age and sex as covariates was fitted, predicting methylation

at each CpG site as a function of disease. Differentially methylated CpG sites (DMCs) with a Bonferroni-adjusted threshold of $p<1.3\times10^{-7}$ were considered significant. Sex-chromosomal data were analyzed separately for female and male individuals applying the same significance threshold. Functional gene-set enrichment analysis was performed using the Ingenuity Pathway Analysis (IPA) software (Qiagen) for the 500 most significantly associated DMCs exhibiting a gene name annotation. Classification of IFN regulated genes was conducted using the Interferome v2.01 analysis tool.[7]

**Functional genomic annotation**

Probe mapping and annotation in relation to CpG island information and to gene regions was performed as previously described.[8] The regional distribution of probes that passed the filtering was compared to the distribution of associated CpGs using the $X^2$-test, where $p<0.005$ was regarded as significant (Bonferroni corrected). Publicly available chromatin modification datasets from primary CD3+ T cells and CD19+ B cells were obtained from the NIH Roadmaps Epigenomics Project for the histone modification marks H3K4me1, H3K4me3, H3K27ac, H3K36me3, H3K9me3, H3K27me3 and DNase I hypersensitive sites (DHS).[9] Chromatin mark peaks from the reference cells were analyzed for overlap with the genomic coordinates of pSS associated CpG sites applying a Bonferroni corrected $X^2$-test.

**Gene expression profiling of CD19+ B cells**

Sequencing libraries were prepared from 1 µg of total RNA from CD19+ B cells (n=16 patients, n=23 controls), applying the TruSeq stranded mRNA sample preparation kit including poly-A selection (Illumina), followed by paired-end RNA-sequencing (50bp read length) on a HiSeq2500 instrument (Illumina). QC was conducted using RNA-seQC.[10] Reads were mapped to the human reference genome (GRCh37) with Tophat2 and analysis of differential gene expression was performed using the Cufflinks pipeline.[11 12]

**Methylation quantitative trait loci (metQTL) analysis**

Methylation levels were tested in PLINK for genotype association at loci that have previously shown an association with pSS with genome-wide significance.[13 14] Genotype data generated on the Infinium ImmunoChip (Illumina) containing 196,524 probes were available for 382 of the healthy control individuals in our study. Genotype QC at the sample level was performed as previously described.[15] SNP probes fulfilling ≥98% call rate, a Hardy-

Weinberg equilibrium test $p>1x10^{-4}$ and a minor allele frequency (MAF) of ≥1% were included. After filtering 135,503 probes remained for analysis. All CpG sites within a gene locus plus 100 kb flanking regions were tested against all genotypes within the same region (in total 404,000 association tests). A Bonferroni corrected $p<1.24x10^{-7}$ was considered significant.

**REFERENCES**


1. R Core Development Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2011.
2. Aryee MJ, Jaffe AE, Corrada-Bravo H, et al. Minfi: a flexible and comprehensive Bioconductor package for the analysis of Infinium DNA methylation microarrays. Bioinformatics 2014;**30**(10):1363-9 doi: 10.1093/bioinformatics/btu049.
3. Maksimovic J, Gordon L, Oshlack A. SWAN: Subset-quantile within array normalization for illumina infinium HumanMethylation450 BeadChips. Genome biology 2012;**13**(6):R44 doi: 10.1186/gb-2012-13-6-r44.
4. 1000 Genomes Project Consortium, Abecasis GR, Auton A, et al. An integrated map of genetic variation from 1,092 human genomes. Nature 2012;**491**(7422):56-65 doi: 10.1038/nature11632.
5. Houseman EA, Accomando WP, Koestler DC, et al. DNA methylation arrays as surrogate measures of cell mixture distribution. BMC bioinformatics 2012;**13**:86 doi: 10.1186/1471-2105-13-86.
6. Reinius LE, Acevedo N, Joerink M, et al. Differential DNA methylation in purified human blood cells: implications for cell lineage and studies on disease susceptibility. PloS one 2012;**7**(7):e41361 doi: 10.1371/journal.pone.0041361.
7. Rusinova I, Forster S, Yu S, et al. Interferome v2.0: an updated database of annotated interferon-regulated genes. Nucleic acids research 2013;**41**(Database issue):D1040-6 doi: 10.1093/nar/gks1215.
8. Grundberg E, Meduri E, Sandling JK, et al. Global analysis of DNA methylation variation in adipose tissue from twins reveals links to disease-associated variants in distal regulatory elements. American journal of human genetics 2013;**93**(5):876-90 doi: 10.1016/j.ajhg.2013.10.004.
9. Bernstein BE, Stamatoyannopoulos JA, Costello JF, et al. The NIH Roadmap Epigenomics Mapping Consortium. Nature biotechnology 2010;**28**(10):1045-8 doi: 10.1038/nbt1010-1045.
10. DeLuca DS, Levin JZ, Sivachenko A, et al. RNA-SeQC: RNA-seq metrics for quality control and process optimization. Bioinformatics 2012;**28**(11):1530-2 doi: 10.1093/bioinformatics/bts196.
11. Trapnell C, Roberts A, Goff L, et al. Differential gene and transcript expression analysis of RNA-seq experiments with TopHat and Cufflinks. Nature protocols 2012;**7**(3):562-78 doi: 10.1038/nprot.2012.016.
12. Kim D, Pertea G, Trapnell C, Pimentel H, Kelley R, Salzberg SL. TopHat2: accurate alignment of transcriptomes in the presence of insertions, deletions and gene fusions. Genome biology 2013;**14**(4):R36 doi: 10.1186/gb-2013-14-4-r36.
13. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. American journal of human genetics 2007;**81**(3):559-75 doi: 10.1086/519795.

14. Lessard CJ, Li H, Adrianto I, et al. Variants at multiple loci implicated in both innate and adaptive immune responses are associated with Sjogren's syndrome. Nature genetics 2013;**45**(11):1284-92 doi: 10.1038/ng.2792.
15. Berggren O, Alexsson A, Morris DL, et al. IFN-alpha production by plasmacytoid dendritic cell associations with polymorphisms in gene loci related to autoimmune and inflammatory diseases. Human molecular genetics 2015 doi: 10.1093/hmg/ddv095.