# Genetic Determinants of Fatigue in Primary Sjögren`s Syndrome – a Genome Wide Association Study

## Abstract #182

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**Background/Purpose:**
Fatigue is common in primary Sjögren`s syndrome (pSS), but the mechanisms that lead to fatigue are not fully understood. We hypothesized that there is a genetic basis for fatigue, and that specific gene-variants (single nucleotide polymorphisms – SNPs) influence the severity of fatigue. To investigate this further we performed a genome wide association study (GWAS) of 367 Scandinavian pSS patients.

**Methods:**
PSS patients from 4 sites in Norway and Sweden were collected through the Scandinavian Sjögren's syndrome network. Genotyping was performed at the SNP&SEQ platform, Uppsala University, Sweden using the Illumina Human OmniExpressExome array. All included cases fulfilled the American-European Classification Criteria for pSS. Fatigue was assessed using the fatigue Visual Analogue Scale or the European Sjøgren`s Syndrome Patient Reported Index. Imputation was performed using SHAPEIT2 and IMPUTE2. After genotype and sample quality control and imputation a total of 365 samples and 4 966 159 SNPs remained for analysis. A linear regression analysis of fatigue scores versus minor alleles was performed.

**Results:**
The pSS patients were 92% females, mean age 57 years with a median fatigue score of 66 (range 0-100). Our analysis revealed five SNPs exceeding the genome wide significance (GWS) threshold of p=5E-8 with a beta coefficient of 12.8. All five SNPs were in linkage disequilibrium and two of the SNPs, rs7626469 and rs73182503, were in the gene Receptor Transporter Protein 4 (RTP4), in which the minor allele was associated with less fatigue. RTP4 encodes a Golgi chaperone, involved in the cell surface expression of opioid receptors. In addition, 58 SNPs in 4 genes (Endoplasmatic Reticulum to Nucleus Signaling 1 (ERN1), Long intergenic non-protein coding RNA 1553 (LINC01553), Long intergenic non-protein coding RNA 1184 (LINC01184) and (RP11-15I11.2) reached a suggestive significance level (p<1E-5).

**Conclusion:**
We identified genetic variants in RTP4 exceeding the GWS level for association with fatigue. Notably, this gene encodes a protein involved in pain processing. Pain is known to influence fatigue, and this finding could point to a possible molecular explanation. The present study is the largest GWAS of fatigue in autoimmune disease, and adds further evidence to a genetic regulation of fatigue.

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