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712 - Additive Effects of the Major Risk Alleles of IRF5 and STAT4 in Primary Sjögren's Syndrome

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Purpose: To investigate the association with primary Sjögren's syndrome (pSS) of the two major *IRF5* polymorphisms, the CGGGG indel and the SNP rs10488631 and the *STAT4* SNP rs7582694 and determine the joint effect of these three polymorphisms on the risk of developing pSS.
Methods: A total of 368 patients with pSS fulfilling the American-European consensus criteria and 711 controls from Sweden and Norway were included. The SNPs in all patients and the Norwegian controls were genotyped using a homogenous minisequencing assay with fluorescence polarization detection and the Swedish controls were genotyped using the Golden Gate assay from Illumina. In all samples the CGGGG indel was PCR amplified and separated on high resolution agarose gels.
Results: We observed strong signals for association between all three polymorphisms and pSS. The risk allele frequencies for cases/controls were for the *IRF5* CGGGG (4x=risk) 0.56/0.46, p=2.1E-06, OR 1.55, for SNP rs10488631 (C=risk), 0.21/0.14, p=2.01E-05, OR 1.67 and for the *STAT4* SNP rs7582694 (C=risk) 0.29/0.23, p=8.0E-04, OR 1.42. The joint effect of the number of these strongly associated risk alleles and the risk for pSS was investigated. We found that 14% of pSS patients carried 4-5 risk alleles compared with 6% of controls whereas 52% of controls carried only 0-1 risk alleles compared with 35% of pSS patients. No individual carried all 6 risk alleles. The significance for the overall differences in the number of risk allele counts between patients and controls was very high with a one-sided p-value of 8.4E-11. The OR for the risk of developing pSS increases in a multiplicative manner with a 1.62-fold increase in OR for each additional risk allele using individuals with 0-1 risk alleles as a reference. For carriers of 2 risk alleles the OR for pSS is 1.54 while carriers of 5 risk alleles have an OR of 7.17. There was no correlation between the presence of ANA, anti SS-A or anti-SS-B antibodies and any of the polymorphisms or the number of risk alleles.
Conclusions: Here we show for the first time an association with the *IRF5* 3' end SNP rs10488631 or its proxies, with another autoimmune disease apart from SLE and add pSS to the list of autoimmune diseases (SLE, IBD, and MS) associated with the *IRF5* promoter CGGGG indel. We confirm the association between *STAT4* SNP rs7582694 which is a perfect proxy of the previously published SNP rs7574865, and pSS, and describe for the first time an additive effect of these three polymorphisms and the risk for pSS.