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Genetic association between methyl-CpG-binding protein 2 (MECP2) and primary Sjögren's syndrome

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Primary Sjögren's syndrome (pSS) is a complex autoimmune disease that is incompletely understood. The principal manifestations of pSS are dry eyes and dry mouth due to lymphocytic infiltration of the salivary and lacrimal glands. Like lupus, women are affected by pSS more than 9 times compared to men. Association of HLA loci with pSS and other autoimmune diseases is well documented.[1–3]

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A genetic association of the Methyl-CpG-binding protein 2 (MECP2) gene with lupus has been reported and confirmed in multiple independent cohorts.[4,5] Herein, we examine the genetic association between MECP2 and pSS in a large cohort of pSS patients and healthy controls.

We studied a cohort of 460 European-derived independent pSS patients (423 women and 37 men) and 1828 ethnically-matched normal healthy controls (1279 women and 549 men). All patients fulfilled the American-European Consensus Group classification criteria for pSS.[6] Our study protocols were approved by the institutional review boards or ethics committees in our institutions and a written informed consent was obtained from each patient.

We genotyped one SNP in the MECP2 gene (rs17435) in the pSS cases and controls. We have previously established and replicated the genetic association between rs17435 and the susceptibility to lupus, and these findings were subsequently independently replicated by others.[7] This SNP showed the most significant association in lupus and tags the lupus-risk haplotype. Genotyping was performed using a TaqMan SNP Genotyping Assay or an Illumina Infinium Genotyping Assay. Genotyping success rate was 98.9% in the cases and 99.8% in the controls. The SNP rs17435 was within Hardy-Weinberg (HW) equilibrium in cases and controls (HW P value= 0.39). Allele frequencies and odds ratios were determined. P values were calculated using a χ^2 test. Genotype frequency analysis was only performed in female patients and controls since MECP2 is located on the X chromosome.

We found evidence for a genetic association between rs17435 within the MECP2 gene and pSS. Our results indicate that allele “T” in rs17435 is the disease risk allele in pSS, similar to lupus patients. The “T” allele in rs17435 is present in 24.5% of pSS patients compared to 19.5% in controls (odds ratio= 1.33, P= 0.0016) (Table 1). In addition, the homozygous risk genotype “TT” is more frequent in patients with pSS compared to controls (odds ratio= 2.17, P= 0.0024, Table 1).

To investigate the effect of the pSS-associated MECP2 polymorphism upon the presence of anti-Ro and anti-La autoantibodies, we determined the frequency of anti-Ro and anti-La in female pSS patients with the homozygous risk genotype “TT” compared to the homozygous protective genotype “AA”. The MECP2 genotype did not significantly influence the frequency of neither anti-Ro nor anti-La autoantibodies. Anti-Ro was present in 69.2% and 72.8% of patients with the “TT” and “AA” MECP2 genotype, respectively (p= 0.70). Similarly, anti-La was detected in 61.5% and 52.3% of patients with the “TT” and “AA” genotype, respectively (p= 0.37). Further, the association with MECP2 in pSS is not dependent upon the presence of anti-Ro or anti-La, as subset analysis revealed genetic association with rs17435 in patients with and without anti-Ro, and in patients with and without anti-La (data not shown).

We report the first genetic association between pSS and a gene on the X chromosome. Replication studies in non-Caucasian populations are warranted. MECP2 is critically involved in DNA methylation-induced transcriptional silencing, and its genetic association with lupus susceptibility has been previously established.[4,5] The predominance of both lupus and pSS in females, and the presence of common clinical and serological features in lupus and pSS suggests that the genetic association with MECP2 in both diseases might explain a common pathogenic pathway. Indeed, the genetic association between MECP2 and lupus suggests a role for genetic-epigenetic interaction in the pathogenesis of the disease, as defective T cell DNA methylation plays an important role in the pathogenesis of lupus.[8–10] Whether abnormal DNA methylation is also involved in the pathogenesis of pSS remains to be studied.

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Allele and genotype frequencies in rs17435 within the MECP2 gene in a cohort of 460 European-derived primary Sjögren's syndrome (pSS) patients and 1828 ethnically-matched normal healthy controls.

Table 1

	Cases (n,%)	Controls (n,%)	OR (95%CI)	X ²	P value
Allele frequencies					
T	212 (24.4)	604 (19.5)	1.33 (1.12–1.59)	10.01	0.0016
A	658 (75.6)	2499 (80.5)			
Genotype frequencies*					
TT	26 (6.2)	39 (3.1)	2.17 (1.30–3.62)**	9.21**	0.0024**
TA	145 (34.8)	421 (32.9)			
AA	246 (59.0)	819 (64.0)			

* Only female patients and controls were used to calculate genotype frequencies

** TT versus TA+AA

n, number; OR, odds ratio; CI, confidence interval