Letter

CTLA-4 polymorphism and primary Sjögren's syndrome: authors' response

Corinne Miceli-Richard, Jacques-Eric Gottenberg and Xavier Mariette

Rhumatologie, Institut Pour la Santé et la Recherche Médicale (INSERM) U802, Université Paris-Sud 11, Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris (AP-HP), Le Kremlin Bicêtre, France

Corresponding author: Xavier Mariette, xavier.mariette@bct.aphp.fr

Published: 5 June 2007
This article is online at http://arthritis-research.com/content/9/3/402

Arthritis Research & Therapy 2007, **9:**402 (doi:10.1186/ar2199)

See related research article by Gottenberg *et al*., http://arthritis-research.com/content/9/2/R24, and related letter by Lester *et al*., http://arthritis-research.com/content/9/3/401

We thank Dr Lester and colleagues [1] for their interest in our recent article [2] and for their comments.

As underlined by Lester and colleagues [1], replication cohorts are of primary importance in genetic association studies. With regard to primary Sjögren's syndrome (pSS), however, it is difficult to collect a very large group of patients and our cohort of pSS patients, even though it comprised 281 patients, remains somehow of moderate size when compared with other cohorts of patients with closely related auto-immune diseases such as lupus. This observation leads us all to be very careful with the reported findings from pSS genetic association studies. The objective of our discussion was not to suggest that our results could be interpreted meaningfully against those of Downie-Doyle and colleagues [3], but to highlight the fact that contradictory results could be observed if small populations of patients and controls are analyzed.

As discussed in our manuscript [2], the at-risk allele found in our first cohort of patients (CTLA-4 +49A/G*A) has been reported to be protective in various auto-immune diseases. These results naturally prompted us to confirm the findings in a second cohort of patients. The results in this second cohort were opposite to those in the first cohort and, overall, there was no association. Our study was not restricted to individual single nucleotide polymorphism analysis but also included haplotypic analyses that showed an overrepresentation of *CTLA-4* +49A:CT60A and *CTLA-4* +49A:CT60G haplotypes among patients ($P = 0.03$, odds ratio 1.41, 95% confidence interval [1.02 to 1.95]) in the first cohort, as observed by Downie-Doyle and colleagues [3]. As those haplotypes carry *CTLA-4* CT60*G and *CTLA-4* CT60*A alleles, respectively, each of them having opposite functional effects on CTLA-4 mRNA expression, we just wondered in the discussion how such an association could be functionally explained. In fact, the positive association reported in lupus by Torres and colleagues [4] involved only the CTLA-4 +49A:CT60G haplotype (and not CTLA-4 +49A:CT60A, which had a neutral effect on lupus susceptibility), which has been demonstrated to lead to a lower level of soluble CTLA-4 at the mRNA level in unstimulated CD4 T cells. Such a haplotype could, therefore, also be rationally considered as an at-risk haplotype at a functional level.

Therefore, we are convinced that definite conclusions can not be drawn on the role of CLTA-4 polymorphisms and haplotypes in pSS disease susceptibility. For this purpose, other replication studies have to be performed in Caucasian patients, ideally in populations with large sample sizes, in order to be confident that they are involved in pSS pathogeny.

Competing interests

The authors declare that they have no competing interests.

References

1. Lester S, Downie-Doyle S, Rischmueller: **CTLA4 polymorphism and primary Sjögren's syndrome.** *Arthritis Res Ther* 2007, **9:** 401.
2. Gottenberg JE, Loiseau P, Azarian M, Chen C, Cagnard N, Hachulla E, Puechal X, Sibilia J, Charron D, Mariette X, Miceli-Richard C: ***CTLA-4* +49A/G and CT60 gene polymorphisms in primary Sjögren syndrome.** *Arthritis Res Ther* 2007, **9:**R24.
3. Downie-Doyle S, Bayat N, Rischmueller M, Lester S: **Influence of CTLA4 haplotypes on susceptibility and some extraglandular manifestations in primary Sjogren's syndrome.** *Arthritis Rheum* 2006, **54:**2434-2440.
4. Torres B, Aguilar F, Franco E, Sanchez E, Sanchez-Roman J, Jimenez Alonso J, Nunez-Roldan A, Martin J, Gonzalez-Escribano MF: **Association of the CT60 marker of the CTLA4 gene with systemic lupus erythematosus.** *Arthritis Rheum* 2004, **50:** 2211-2215.

pSS = primary Sjögren's syndrome.