LETTER

REPLY TO LIU ET AL.:

Translation of rat congenic data to humans on a conserved MHC-III haplotype associated with rheumatoid arthritis

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Major histocompatibility complex (MHC)-related phenotype/genotype correlations are important in study of autoimmune disorders. We previously identified a conserved 33-kb haplotype comprising five genes, *lymphotoxin-α* (*Lta*), *Tnf*, *lymphotoxin-β* (*Ltb*), *leukocyte-specific transcript 1* (*Lst1*), and *natural cytotoxicity-triggering receptor 3* (*Ncr3*), in the MHC class-III region regulating arthritis in rats (1). In our study, higher *Ltb* and *Ncr3* expression and lower *Lst1* expression correlate with reduced arthritis severity in rats (1). Following these findings, we compared expression of these genes in a cohort of patients with rheumatoid arthritis (RA) and healthy controls and found that the expression of *LTB*, *LST1*, and *NCR3* was higher in RA cases, but patients with mild RA showed higher *NCR3* expression and lower *LST1* expression than patients with severe RA (1).

To address genetic variability in the locus, Liu et al. (2) investigate this genetic variability further by analyzing the expression quantitative trait loci (eQTL) dataset from patients with RA in combination with RA genome-wide association studies (GWAS) data. They concluded that increased *LST1* and *NCR3* were associated with reduced RA susceptibility (2), which could differ from our findings (1) and the findings of another group (3) that *LST1* and *NCR3* expression was increased in RA cases versus controls (Fig. 1). We believe that this conclusion is not supported by experimental data for several reasons.

First, healthy controls were not investigated in this study, and data from patients with RA could not be interpreted in terms of susceptibility.

Second, a cohort of patients with RA in this study consists of only nonresponders to methotrexate (MTX) therapy (2, 4), whereas we included patients with a broader spectrum of treatments and disease activity (1). Because gene expression profiles differ between patients responding and not responding to MTX (5), it is not surprising that findings from two different cohorts could not be cross-replicated. It is also not optimal to make generalized conclusions on RA risk by integration of the eQTL dataset from nonresponding to MTX patients with severe RA with the GWAS dataset, which gives information on disease risk.

Third, Liu et al. (2) do not state if they have controlled for the effect of the *DRB1* gene, which is in strong linkage disequilibrium with *LST1* and *NCR3* (6–8), when selecting eQTLs. We performed association analysis using Immunochip data for SNPs from the study by Liu et al. (2) in our EIRA (Epidemiological Investigation of Rheumatoid Arthritis) cohort (9), which was, in fact, part of the dataset used by Liu et al. (2). In this cohort of 2,762 RA cases and 1,940 controls, we found that after stratification by RA-associated alleles (total for *DRB1*01*, *DRB1*04*, and *DRB1*10*), there is no longer any significant association with RA in *LST1-NCR3* after Bonferroni correction (Table 1).

Therefore, we believe that the findings by Liu et al. (2) on *LST1* and *NCR3* should be reevaluated. This discussion again highlights the advantage of using congenic animals to study complex diseases, in which qualitative conclusions can be made and the isolated loci studied experimentally (1, 10).

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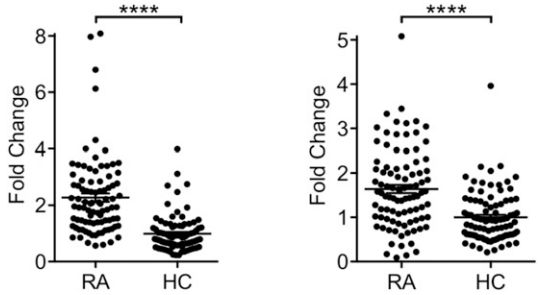

Fig. 1. Expression of *LST1* (*Left*) and *NCR3* (*Right*) in patients with RA ($n = 91$) and healthy controls (HC; $n = 92$). ****$P < 0.0001$.

Table 1. Association results for SNPs in the *LST1-NCR3* region in the EIRA study

					2,762 cases/1,940 controls			708 SE negative cases/878 SE negative controls		
SNP	Chr	Position (hg19)	A1	A2	*P* value*	*P* value$_{BONF}$	OR (95% CI)	*P* value*	*P* value$_{BONF}$	OR (95% CI)
rs2071596	6	31506691	A	G	0.01608	0.1447	1.13 (1.02–1.25)	0.6206	1	0.95 (0.79–1.15)
rs2523500	6	31518354	G	A	0.008165	0.07348	0.89 (0.81–0.97)	0.5025	1	0.95 (0.82–1.10)
rs6929796	6	31522669	A	G	0.01526	0.1373	1.13 (1.02–1.25)	0.5065	1	0.94 (0.78–1.13)
rs2256974	6	31555392	A	C	0.05241	0.4717	1.11 (1.00–1.22)	0.6696	1	0.96 (0.80–1.16)
rs2844479	6	31572956	C	A	8.576E-07	7.72E-06	1.24 (1.14–1.35)	0.594	1	1.05 (0.89–1.23)
rs2736176	6	31587561	C	G	5.002E-10	4.502E-09	1.32 (1.21–1.44)	0.2806	1	1.10 (0.93–1.30)
rs755714	6	31609813	A	G	9.458E-10	8.512E-09	1.32 (1.20–1.44)	0.3052	1	1.09 (0.92–1.30)
rs805297	6	31622606	A	C	6.164E-10	5.548E-09	1.32 (1.21–1.44)	0.2967	1	1.10 (0.92–1.30)
rs707919	6	31641139	G	A	7.716E-10	6.944E-09	1.32 (1.21–1.44)	0.2967	1	1.10 (0.92–1.30)

*All *P* values have been calculated for the allelic model. Chr, chromosome; CI, confidence interval; OR, odds ratio; *P* value$_{BONF}$, *P* value after Bonferroni correction; SE, shared epitope.

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