

Cis-eQTLs regulate reduced *LST1* gene and *NCR3* gene expression and contribute to increased autoimmune disease risk

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In PNAS, Yau et al. (1) identify a conserved 33-kb haplotype *Ltab-Ncr3* across five genes, lymphotoxin- α (*Lta*), *Tnf*, lymphotoxin- β (*Ltb*), leukocyte-specific transcript 1 (*Lst1*), and natural cytotoxicity-triggering receptor 3 (*Ncr3*) in the MHC-III region in wild rats. The higher *Ltb* and *Ncr3* expression, the lower *Lst1* expression, and the expression of a shorter splice variant of *Lst1* were associated with reduced arthritis severity in rats (1). Yau et al. (1) further analyzed the expression levels of *LTB*, *LST1*, and *NCR3* using whole-blood samples from 32 patients with rheumatoid arthritis (RA) and 92 healthy controls (1). They identify significantly increased expression of these three genes in RA cases (1). The mild RA cases also showed lower expression of *LST1* and higher expression of *NCR3* than the severe RA cases (1).

Although these results are interesting, there are still two concerns to be mentioned. First, Yau et al. (1) report increased *LST1* and *NCR3* expression in RA cases. However, they did not investigate whether SNPs in *LST1* and *NCR3* genes could regulate the expression of both genes in RA cases. Second, Yau et al. (1) selected 13 SNPs and identified the *Ltab-Ncr3* haplotype regulating arthritis severity in rats. However, they did not evaluate whether the SNPs in *LST1* and *NCR3* genes could regulate arthritis severity or susceptibility in humans. Thus, both of these concerns have prompted us to investigate these findings further.

Evidence shows that genetic variants modify gene expression and cause disease risk (2, 3). Here, we used a whole-genome expression quantitative trait loci (eQTL) dataset in whole blood to evaluate whether these eQTLs could regulate *LST1* and *NCR3* expression in 377 RA cases (4). We got the summary results about the *cis*-eQTL with a false discovery rate (FDR) of <5% in the original study (4). Interestingly, we identified 1,012 significant associations between

578 *cis*-eQTL and *NCR3* expression, and 69 significant associations between 35 *cis*-eQTL and *LST1* expression with an FDR of <5%.

We further investigated the potential association of these *cis*-eQTL with RA susceptibility using a large-scale RA genome-wide association studies (GWAS) dataset (19,234 RA cases and 61,565 controls) (5). We found that 415 of the 578 *cis*-eQTL and 34 of the 35 *cis*-eQTL were available in the RA GWAS dataset. Three hundred ninety-seven of these 415 *cis*-eQTL and 32 of these 34 *cis*-eQTL were significantly associated with RA susceptibility ($P < 0.05$). We further compared the findings from the RA GWAS and RA eQTL datasets. We found that the alleles of *cis*-eQTL significantly regulating increased *LST1* and *NCR3* expression were significantly associated with reduced RA susceptibility. In contrast, the alleles of *cis*-eQTL significantly regulating reduced *LST1* and *NCR3* expression were significantly associated with increased RA risk (28–35% for *NCR3* and 6–19% for *LST1*). We list the top 10 significant association signals in Table 1.

Taken together, we analyzed a large-scale eQTL dataset from 377 RA patients and RA GWAS from 19,234 RA cases. We found that SNPs in *LST1* and *NCR3* could regulate the expression of both genes in RA cases and that the increased *LST1* and *NCR3* expression was significantly associated with reduced RA susceptibility. We believe that our findings provide important supplementary information about the role of *LST1* and *NCR3* in human RA.

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Table 1. Top 10 significant association signals in RA eQTLs dataset and RA GWAS dataset

SNP	Chr	Position (hg19)	A1	A2	RA eQTL dataset				RA GWAS dataset	
					Probe ID	Gene	Beta (A1)	P value	OR (A1)	P value
rs812561	6	31676641	T	C	211583_x_at	NCR3	-0.32	5.26E-06	1.35	1.20E-106
rs5872	6	31637734	T	A	211583_x_at	NCR3	-0.33	4.99E-06	1.33	2.80E-101
rs707919	6	31641139	G	A	211583_x_at	NCR3	-0.33	4.99E-06	1.33	4.40E-101
rs805299	6	31619652	A	T	211583_x_at	NCR3	-0.33	4.99E-06	1.34	7.10E-101
rs2736176	6	31587561	C	G	211583_x_at	NCR3	-0.33	3.45E-06	1.33	1.00E-100
rs755714	6	31609813	T	C	211583_x_at	NCR3	-0.33	4.99E-06	1.34	1.00E-100
rs805297	6	31622606	A	C	211583_x_at	NCR3	-0.33	2.51E-06	1.34	1.10E-100
rs2857698	6	31585084	T	C	211583_x_at	NCR3	-0.33	3.45E-06	1.34	1.10E-100
rs2844479	6	31572956	C	A	210763_x_at	NCR3	-0.38	1.07E-07	1.30	1.10E-82
rs2736178	6	31585821	C	A	211583_x_at	NCR3	-0.32	8.30E-06	1.28	3.20E-80
rs915654	6	31538497	A	T	210629_x_at	LST1	-0.37	3.19E-07	1.19	5.30E-39
rs73396237	6	31532490	G	C	210629_x_at	LST1	-0.41	5.47E-06	1.16	8.50E-20
rs9380261	6	31505784	C	G	210629_x_at	LST1	-0.41	6.29E-06	1.15	5.00E-19
rs6929796	6	31522669	A	G	210629_x_at	LST1	-0.43	1.26E-06	1.11	7.60E-11
rs2071596	6	31506691	A	G	210629_x_at	LST1	-0.43	1.26E-06	1.11	1.90E-10
rs2516493	6	31482714	C	T	210629_x_at	LST1	-0.37	4.99E-07	1.09	1.30E-08
rs2256974	6	31555392	A	C	210629_x_at	LST1	-0.44	1.03E-06	1.08	2.70E-07
rs2523500	6	31518354	A	G	210629_x_at	LST1	-0.34	1.11E-06	1.06	1.80E-05
rs2071590	6	31539768	G	A	210629_x_at	LST1	-0.35	7.79E-07	1.06	4.20E-05
rs2516492	6	31482727	A	G	210629_x_at	LST1	0.37	3.72E-07	1.06	5.30E-05

Chr, chromosome; ID, identification number; OR, odds ratio.

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