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

Guiyou Liu[a], Yang Hu[a], Shuilin Jin[b], Fang Zhang[c], Qinghua Jiang[a,1], and Junwei Hao[c,1]

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.

[a]School of Life Science and Technology, Harbin Institute of Technology, Harbin 150001, China; [b]Department of Mathematics, Harbin Institute of Technology, Harbin 150001, China; and [c]Department of Neurology and Tianjin Neurological Institute, Tianjin Medical University General Hospital, Tianjin 300052, China

Author contributions: G.L., Q.J., and J.H. designed research; Q.J. performed research; G.L., Y.H., S.J., and F.Z. analyzed data; and G.L., Q.J., and J.H. wrote the paper.

The authors declare no conflict of interest.

[1]To whom correspondence may be addressed. Email: hjw@tmu.edu.cn or qhjiang@hit.edu.cn.

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.

1 Yau ACY, et al. (2016) Conserved 33-kb haplotype in the MHC class III region regulates chronic arthritis. *Proc Natl Acad Sci USA* 113(26):E3716–E3724.
2 Zou F, et al.; Alzheimer's Disease Genetics Consortium (2012) Brain expression genome-wide association study (eGWAS) identifies human disease-associated variants. *PLoS Genet* 8(6):e1002707.
3 Liu G, Bao X, Wang R (2015) Expression quantitative trait loci regulate HNF4A and PTBP1 expression in human brains. *Proc Natl Acad Sci USA* 112(30):E3975.
4 Walsh AM, et al. (2016) Integrative genomic deconvolution of rheumatoid arthritis GWAS loci into gene and cell type associations. *Genome Biol* 17:79.
5 Okada Y, et al.; RACI consortium; GARNET consortium (2014) Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature* 506(7488): 376–381.