

Genetic Interactions Between *BANK1* and *BLK* in Chinese Patients with Systemic Lupus Erythematosus

To the Editor:

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with strong genetic components, with over 40 susceptibility loci identified at present. These SLE susceptibility loci are predominantly common variants that have been confirmed among multiple ancestries, suggesting shared mechanisms in disease etiology¹. However, genetic heterogeneity was also suggested, as some genetic polymorphisms are restricted to specific ethnic populations. Recent descriptions of gene–gene interactions, or epistasis, may explain some of the genetic heterogeneity and missing heritability in SLE. We previously reported potential epistasis between *BLK* and *TNFSF4* in both Chinese and white populations, suggesting that unbalanced functions of B cell and T cell signaling may be involved synergistically in the pathogenesis of SLE². Another large-scale association study confirmed the genetic interactions between *BANK1* and *BLK* in Europeans, indicating B cell activity and a B cell-specific pathway were crucial in lupus pathogenesis³. No further replications were conducted in Chinese subjects or other populations with independent sets of cases and controls. Of note, remarkably different frequency distributions of risk alleles of *BANK1* and *BLK* were observed in Chinese and Europeans: for example, the risk alleles of *BLK* were minor alleles in Europeans but major alleles in Chinese². We thus aimed to determine whether the genetic epistatic interaction between *BANK1* and *BLK* polymorphisms could be confirmed in a Chinese population.

A total of 1000 Chinese with Han ethnicity living in Beijing were enrolled, including 500 patients with SLE (mean age 31.9 ± 11.2 yrs, female/male ratio 6:1) and 500 ethnically and geographically matched healthy blood donor controls (mean age 40.0 ± 8.6 yrs). All the patients met the revised SLE criteria of the American College of Rheumatology without selection⁴. The study was approved by the medical ethics committee of Peking University; all patients gave informed consent. The reported single-nucleotide polymorphisms (SNP) with top association signals of interactions were selected without optional discrimination³. Genotyping was undertaken as reported². Genetic associations were determined by chi-square test. Genetic interactions were determined using a classical 2 × 2 factorial design². For replications, no further corrections were applied.

Statistical analyses were performed with SPSS 12.0 (SPSS Inc.). A 2-tailed *p* value < 0.05 was considered statistically significant.

The call rates for rs10516487 and rs2736340 were both 99.7%. *BLK* rs2736340 T showed a significant association with susceptibility to SLE (*p* = 3.27 × 10⁻³, OR 1.36, 95% CI 1.11–1.67; Table 1), whereas *BANK1* rs10516487 G showed a marginal association (*p* = 0.06). The risk allele frequency was high in this Chinese population, similar to that previously reported⁵. In the gene interaction analysis, because few homozygous protective genotypes were observed, genotypes were grouped under recessive models. An epistatic interaction between *BLK* rs2736340 T and *BANK1* rs10516487 G was detected. Only individuals carrying both the *BANK1* rs10516487 GG genotype and the *BLK* rs2736340 TT genotype were susceptible to SLE (*p* = 1.21 × 10⁻³, OR 2.13, 95% CI 1.34–3.38), whereas individuals carrying 1 or no risk genotype factor did not show such an association (Table 2). However, because of possible underpowering of our sample size to detect associations of subphenotypes, we did not observe any correlations between genotype combinations and subphenotypes of SLE.

A recent study observed similar epistasis in rheumatoid arthritis^{6,7}. The proteins of these 2 genes interact physically and work in concert during B cell signaling. And a more recent work suggested that the kinase activity of BLK enhanced BANK1-PLCγ2 (phospholipase Cγ2) binding, further supporting the role of these 2 genes in basic B cell physiology and immune-related diseases⁸. Previous genetic studies also revealed *BLK* rs2736340 has an expression quantitative trait loci (eQTL) effect⁹; and the nonsynonymous SNP rs10516487 (G>A; R61H) showed a dual nature by influencing mRNA splicing and consequently the quantity of protein, and by producing a risk variant-containing protein isoform with increased potential for multimerization¹⁰. However, future functional analysis focusing on combination effects of these 2 SNP are needed.

Our study confirms evidence for epistasis between *BLK* and *BANK1* in SLE from a Chinese population for the first time. The data illustrate that the genetic interaction of B cell SLE-associated genes may represent a shared common pathway among different ethnic populations.

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Table 1. Replications of association between *BANK1* and *BLK* polymorphisms with systemic lupus erythematosus.

Gene	Chromosome	SNP	Risk Allele	Frequency (%)		<i>p</i>	OR (95% CI)
				Case	Control		
<i>BANK1</i>	4	rs10516487	G	89.56	86.87	0.06	1.30 (0.99–1.71)
<i>BLK</i>	8	rs2736340	T	78.31	72.65	3.27 × 10 ⁻³	1.36 (1.11–1.67)

SNP: single-nucleotide polymorphism.

Table 2. Genetic interaction analysis between *BANK1* and *BLK* polymorphisms with systemic lupus erythematosus. The attributable proportion due to interaction (AP) was 0.36; and the relative excess risk due to interaction (RERI) was 0.17.

<i>BANK1</i>		<i>BLK</i>	
rs10516487 AA+AG		rs2736340 CC+CT	rs2736340 TT
No. cases/controls		35/56	61/67
<i>p</i>		—	0.18
OR (95% CI)		1.0 (reference)	1.46 (0.84–2.52)
rs10516487 GG			
No. cases/controls		156/191	246/185
<i>p</i>		0.27	1.21 × 10 ⁻³
OR (95% CI)		1.31 (0.82–2.10)	2.13 (1.34–3.38)

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