be considered in the differential diagnosis so that patients can receive immediate treatment.

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Gene-Gene Interaction between *LCE* and *CLEC16A* Increases the Risk of Psoriasis in a Chinese Population

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Dear Editor:

Psoriasis is a common cutaneous disease characterized by inflammation and abnormal epidermal proliferation. Currently, some inflammatory cells, such as dendritic cells, macrophages, neutrophils, and keratinocytes, and several cytokines are believed to play important roles in the pathogenesis of psoriasis[1]. Our previous genome-wide association study (GWAS) provided convincing evidence for the *LCE* gene cluster being a susceptibility factor for psoriasis and showed that *CLEC16A* was significantly associated with development of psoriasis (SNP rs193756, odds ratio [OR] = 0.8, $p = 0.0004$)[2], although $P_{rs193756}$ was found to be $>10^{-8}$. Moreover, *CLEC16A* has previously been found to be linked to multiple sclerosis, and patients with this gene were at a higher risk of developing psoriasis[3]. The *LCE* gene cluster encodes epidermal barrier proteins, and perturbation of expression of these genes is associated with psoriasis[4]. Bergboer et al.[5] found that the expression of *LCE* proteins was regulated by a combination of pro-inflammatory cytokines. In fact, *CLEC16A* is shown to be highly expressed in inflammatory cells such as dendritic cells, macrophages, B-lymphocytes, and natural killer cells[6]. In addition, the interaction between *LCE* and *HLA-C* and among the *MHC* locus, *LCE*, and *IL12B* have also been studied in large samples of diverse ethnic populations[7,8]. Therefore, the postulated common pathway of *LCE* and *CLEC16A* between inflammatory response and epidermal barrier prompted us to examine the combined contribu-

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Table 1. Disease association analysis of *LCE* and *CLEC16A* and their interaction

Genotype		Genotype count and frequency		Association analysis	
		Psoriasis cases	Controls	OR (95% CI)	*p*-value
rs4112788 (*LCE*)					
T/T		575 (11.5)	1,072 (17.8)	1.00 (reference)	N/A
T/C		2,472 (49.4)	2,883 (47.9)	1.60 (1.22～2.08)	0.001
C/C		1,958 (39.1)	2,064 (34.3)	1.76 (1.34～2.33)	5.90E-05
rs193756 (*CLEC16A*)					
A/A		463 (9.6)	544 (9.7)	1.00 (reference)	N/A
A/G		1,247 (25.8)	1,724 (30.9)	0.84 (0.61～1.17)	0.317
G/G		3,120 (64.6)	3,318 (59.4)	1.10 (0.81～1.49)	0.588
LCE-CLEC16A interaction					
LCE C/C	*CLEC16A* A/G or G/G			Interaction $p=0.1169$	
−	−	299 (6.3)	357 (6.4)	1.00 (reference)	
−	+	2,593 (54.3)	3,308 (59.6)	0.93 (0.64～1.34)	
+	−	161 (3.4)	185 (3.3)	1.05 (0.58～1.89)	
+	+	1,725 (36.1)	1,701 (30.6)	1.20 (0.82～1.75)	
LCE C/C	*CLEC16A* G/G			Interaction $p=0.0053$	
−	−	1,078 (22.6)	1,476 (26.6)	1.00 (reference)	
−	+	1,814 (38.0)	2,189 (39.4)	1.14 (0.91～1.42)	
+	−	621 (13.0)	780 (14.1)	1.09 (0.81～1.46)	
+	+	1,265 (26.5)	1,106 (19.9)	1.57 (1.21～2.02)	
LCE T/C or C/C	*CLEC16A* A/G or G/G			Interaction $p=0.2837$	
−	−	60 (1.3)	93 (1.7)	1.00 (reference)	
−	+	489 (10.2)	890 (16.0)	0.83 (0.38～1.79)	
+	−	400 (8.4)	449 (8.1)	1.36 (0.62～2.97)	
+	+	3,829 (80.1)	4,119 (74.2)	1.41 (0.68～2.93)	
LCE T/C or C/C	*CLEC16A* G/G			Interaction $p=0.0605$	
−	−	213 (4.5)	387 (7.0)	1.00 (reference)	
−	+	336 (7.0)	596 (10.7)	1.02 (0.63～1.65)	
+	−	1,486 (31.1)	1,869 (33.7)	1.44 (0.96～2.15)	
+	+	2,743 (57.4)	2,699 (48.6)	1.84 (1.24～2.72)	

OR: odds ratio, CI: confidence interval, N/A: not availble.

tion of both these genes to susceptibility to psoriasis.

The study subjects (5,101 psoriasis patients and 6,183 healthy controls) were the same as those in our previous GWAS[2]. Diagnosis, clinical assessment, and recruitment of subjects have previously been described[2]. Cases and controls were matched on age and gender. Collection of blood samples and information were carried out after obtaining written informed consent from the participants. The study was approved by the ethics committee of Anhui Medical University and was conducted according to the principles of the Declaration of Helsinki. Our previous GWAS identified four novel SNPs (rs4112788, rs4845454, rs4085613, and rs1886734) within the *LCE* gene cluster for psoriasis, and all four SNPs are located within the same linkage disequilibrium (LD) block and in almost complete LD (pairwise $r^2>0.95$). Furthermore de Cid et al.[9] found LCE3C_LCE3B-del was tagged by rs4112788 ($r^2=0.93$), which was also strongly associated with psoriasis. Thus, we selected SNP rs4112788 for this study. Genotyping data of *LCE* rs4112788 and *CLEC16A* rs193756 were directly extracted from the previous study[2]. For quality control, we excluded the samples with no call for rs4112788 and rs193756. The association between dichotomous variables was determined based on the OR, and 95% confidence intervals were estimated by the Cornfield method or the exact method. *p*-values were estimated by chi-square or Fisher exact tests. Interrelations were analyzed by multiple logistic regression analysis. All statistical analyses were performed using the SPSS 12.0 (SPSS Inc., Chicago, IL, USA).

Associations of psoriasis with *LCE* rs4112788 and *CLEC16A* rs193756 and the interaction between these two SNPs are shown in Table 1 for the combined series. As expected, *LCE* rs4112788-CC patients were at an increased risk to develop psoriasis (OR=1.76, $p=5.90\times10^{-5}$); however, the presence of *CLEC16A* rs193756 was not significantly

associated with psoriasis ($p>0.05$). Furthermore, under four different interactive models of *LCE* and *CLEC16A*, we observed that the subjects carrying the *LCE* rs4112788-CC and the *CLEC16A* rs193756-GG had a significant higher possibility of development of psoriasis (OR=1.57, $p=0.0053$), suggesting the existence of a gene-gene interaction between these two genes.

We discovered the association with prompt significance ($P_{rs}193756=0.0004>10^{-8}$) between *CLEC16A* and psoriasis in our previous GWAS; however, the presence of *CLEC16A* rs193756 did not show a significant association with psoriasis in this study. Moreover, we observed that the subjects carrying the *LCE* rs4112788-CC and the *CLEC16A* rs193756-GG had a significantly higher chance of development of psoriasis. *CLEC16A* maybe a minor gene associated with psoriasis development, triggering psoriasis through interaction with *LCE*.

A reconstructed skin model showed that a combination of the psoriasis-associated proinflammatory cytokines induced the expression of *LCE* proteins, and the *LCE* proteins may play a vital role in repairing the epidermal barrier in response to skin injury[4]. *LCE* rs4112788-CC may be associated with reduced *LCE* expression. Todd et al.[10] have suggested that *CLEC16A* may be a functional element involved in maintaining immune homeostasis by the immunoreceptor tyrosine-based activation motif, and the *CLEC16A* protein is shown to be highly expressed on inflammatory cells. *CLEC16A* rs193756-GG may be linked to enhanced expression of *CLEC16A* which enhances inflammatory reaction. We speculated that *CLEC16A* rs193756-GG first altered inflammatory cells and responses in the injured skin via several proinflammatory cytokines, some of which in turn induced the expression of *LCE* proteins. On the other hand, *LCE* rs4112788-CC resulted in defective *LCE* proteins, because of which the epidermal barrier could not be repaired. In addition, it may be that defective *LCE* first rendered the injured epidermal barrier unrepairable and then *CLEC16A* acted to induce a more aggressive inflammatory response. In short, the combined actions of *LCE* and *CLEC16A* may lead to development of psoriasis or may aggravate the disease. It was perhaps not surprising that *LCE* would interact with *CLEC16A* between repairing epidermal barrier and inducing an inflammatory response in the development of psoriasis.

Our findings provide a new way to search for new susceptibility genes and suggest that the interaction between the epidermal barrier and the inflammatory response system may be involved in the pathogenesis of psoriasis, although further studies are needed to confirm this.

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