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Letter to the Editor

Association analysis of allergic sensitization susceptibility loci with atopic dermatitis in Chinese population

Keywords
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Atopic dermatitis is a chronically recurrent disorder involving disturbed skin barrier functions with inflammatory hypersensitivity. It was often accompanied with other atopic manifestations, elevated serum immunoglobulin E [1]. The prevalence was about 10–20% in children and 1–3% in adults [2]. The etiology has not been fully elucidated which combined with genetic and environmental factors. Previous genetic studies had identified amount of susceptibility genes/loci that associated with AD [3]. However, these findings did not fully explain the risk of AD, suggesting additional genetic factors remain need to be discovered. Recent meta-analysis had established several susceptibility loci for allergic sensitization [4]. Due to the similar features between allergic sensitization and AD, they may share common genetic components in the etiology of these two diseases. In order to identify the overlapping susceptibility loci and enhance understanding their relationship, we performed the association analysis of allergic sensitization related loci with AD in Chinese population.

A total of 2205 cases (1359 men and 846 women, mean age of 4.10 ± 1.41) and 2208 controls (1162 men and 1046 women, mean age of 25.01 ± 15.23) were enrolled. The diagnosis of AD according to standard criteria [5], demographic and clinical information, such as accompanying symptoms, serum IgE level, age of onset, SCORAD and family history were collected. The study was approved by the Ethical Committee and was conducted according to Declaration of Helsinki principles. We selected 8 SNPs (Table 1) in non-HLA region which reached the genome-wide significance threshold of $P \leq 5 \times 10^{-8}$ [4], and genotyped by Sequenom Mass Array system. P-values, ORs and 95% CIs were estimated using PLINK 1.07 software. The level of associated significance was assigned at $P < 0.006$ (0.05/8) after Bonferroni correction. The genetic statistical power for SNPs was estimated using CaTS-Power Calculator.

We only found rs10056340 ($P = 0.003$, OR = 1.19) and rs2155219 ($P = 0.004$, OR = 0.88) significantly associated with AD (Table 1). For rs10056340, risk allele G was the minor allele in Han population, which was higher in AD than controls (16.6% vs. 14.4%). Compared to the additive model ($P = 0.006$, OR = 1.12), the dominant model provided best fit for rs10056340 associated with AD in genetic model analysis ($P = 0.002$, OR = 1.24) (Table A.1). OR of the G allele for rs2155219 was 0.88 (95% CI: 0.81–0.96), which suggested a protective effect relative to the T allele with regards to susceptibility to AD. Genetic model analysis showed

Abbreviations: AD, atopic dermatitis; GWAS, genome-wide association study; OR, odds ratio; CI, confidence interval; SCORAD, scoring of atopic dermatitis; C11orf30, chromosome 11 open reading frame 30; SLC25A46, solute carrier family 25 member 46.

Table 1
The results of 8 SNPs replicated in Han Chinese AD cases and controls.

SNP	Chr	Alleles	Nearest gene	MAF		*P* value	OR (95% CI)	Statistical power
				Controls	Case			
rs10056340	5q22.1	G/T	*SLC25A46*	0.144	0.166	3.00E-03	1.188 (1.058-1.335)	89%
rs2155219	11q13.5	G/T	*C11orf30*	0.44	0.409	4.00E-03	0.884 (0.812-0.962)	79%
rs17454584	4q27	G/A	*IL2/ADAD1*	0.12	0.131	1.08E-01	1.110 (0.978-1.260)	27%
rs9865818	3q28	G/A	*LPP*	0.297	0.311	1.56E-01	1.068 (0.975-1.170)	17%
rs4410871	8q24.21	T/C	*MYC/PVT1*	0.343	0.356	2.29E-01	1.055 (0.967-1.152)	11%
rs1059513	12q13.3	G/A	*STAT6*	0.074	0.07	4.67E-01	0.941 (0.800-1.108)	3%
rs17616434	4p14	T/C	*TLR1/6/10*	0.353	0.359	6.14E-01	1.023 (0.937-1.116)	2%
rs3771175	2q12.1	A/T	*IL1RL1/IL18R1*	0.086	0.087	9.61E-01	0.996 (0.859-1.156)	1%

rs2155219 was suited to the additive model ($P = 0.004$) compared to the recessive and dominant model (Table A.1) in AD. When TT genotype was used as reference, the combined genotype GG + GT were associated with a higher risk of AD (Table A.1). The other 6 SNPs did not reached the statistical significance, which might result from low statistical power (1 ~ 27%) (Table 1).

We also performed a stratified analysis to determine which subtype of AD was associated with these two SNPs. For rs10056340, there was no significant results for each of the subtype of AD in case-only analysis, except for the genotype test showed a marginally association with age onset ($P = 0.057$) (Table A.2). The risk allele of rs10056340 SNP was significantly associated with early age onset of disease, high SCORAD and with xeroderma syndrome (Table A.2). However, as for the rs2155219, there was a potential difference between the high and low IgE level in the case only analysis ($P = 0.035$) (Table 2). Besides, SNP rs2155219 was significantly associated with high and low level of IgE phenotypes in sub-phenotype-control analyses.

The main effort is to reveal shared susceptibility loci between these two diseases in Chinese population, an alternative approach is to take susceptibility loci of closely related physiological mechanism phenotype to replicate in AD. Through this method, we confirmed that rs2155219 at 11q13.5 and rs10056340 at 5q22.1 were the overlapping susceptibility loci in AD and allergic sensitization. Both of these two SNPs were not contained in our GWAS data of AD. Although the 11q13.5 locus has been identified in allergic sensitization and atopic disease [6,7], it was first confirmed in Chinese population. In previous study [8], we identified SNP rs7936562 at 11q13.5 (Pcombined $= 2.98 \times 10^{-4}$, OR = 0.91) only with suggestive evidence. The SNP rs2155219 ($P = 0.004$ after correction) showed moderate correlated with rs7936562 ($D' = 0.86$, $r^2 = 0.58$), which further support the role of 11q13.5 in AD. In 5q22.1 region, although SNP rs10056340 was only weakly correlated with the 4 SNPs in Chinese population ($D' = 0.69$, $r^2 = 0.30$ for rs7701890; $D' = 0.70$, $r^2 = 0.28$ for rs10067777; $D' = 0.73$, $r^2 = 0.34$ for rs13360927; $D' = 0.73$, $r^2 = 0.34$ for rs13361382 based

Table 2
Associations between rs2155219 and AD in subphenotype control- and case-only analyses.

	Genotype			$P_{genotype}$ value	Allele		$P_{subgroup}$ vs controls	Combined genotypes		$P_{combined}$ value	OR (95% CI)
	TT	GT	GG		T	G		TT	GG+GT		
Age at onset											
≤1 years	655(34.6)	933(49.2)	307(16.2)	4.22E-01	2243(59.2)	1547(40.8)	5.00E-03	655(34.6)	1240(65.4)	6.70E-01	0.95(0.73-1.23)
>1 years	104(35.9)	132(45.5)	54(18.6)		340(58.6)	240(41.4)	2.50E-01	104(35.9)	186(64.1)		
AD with diseases											
Yes	323(36.0)	426(47.4)	149(16.6)	5.98E-01	1072(59.7)	724(40.3)	8.00E-03	323(36.0)	575(64.0)	3.70E-01	1.09(0.98-1.30)
No	423(34.1)	615(49.6)	203(16.4)		1461(58.9)	1021(41.1)	2.50E-02	423(34.1)	818(65.9)		
IgE level											
High	115(40.1)	137(47.7)	35(12.2)	3.50E-02	367(63.9)	207(36.1)	1.00E-04	115(40.1)	172(59.9)	4.00E-02	1.31(1.01-1.68)
Low	635(33.9)	915(48.8)	324(17.3)		2185(58.3)	1563(41.7)	3.00E-02	635(33.9)	1239(66.1)		
AD with xeroderma											
Yes	550(34.3)	780(48.7)	273(17.0)	7.20E-01	1880(58.2)	1348(41.8)	2.60E-02	550(34.3)	1053(65.7)	5.70E-01	0.94(0.77-1.16)
No	189(35.7)	258(48.7)	83(15.7)		636(60.0)	424(40.0)	1.00E-02	189(35.7)	341(64.3)		
SCORAD											
<25	149(32.8)	224(49.3)	81(17.8)	2.70E-01	522(57.5)	386(42.5)	5.80E-01	149(32.8)	305(67.2)	3.00E-01	0.89(0.71-1.11)
≥25	581(35.4)	794(48.4)	264(16.1)		1956(59.7)	1322(40.3)	1.60E-03	581(35.4)	1058(64.6)		
Familial history											
Positive	87(32.8)	128(48.3)	50(18.9)	4.67E-01	302(57.0)	228(43.0)	6.40E-01	87(32.8)	178(67.2)	6.20E-01	0.93(0.71-1.23)
Negative	672(34.4)	973(49.7)	311(15.9)		2317(59.2)	1595(40.8)	2.40E-03	672(34.4)	1284(65.6)		
AD with Keratosis pilaris											
Yes	111(38.7)	133(46.3)	43(15.0)	2.95E-01	355(61.8)	219(38.2)	7.30E-03	111(38.7)	176(61.3)	1.30E-01	1.22(0.94-1.58)
No	620(34.1)	890(48.9)	309(17.0)		2130(58.5)	1508(41.5)	2.60E-02	620(34.1)	1199(65.9)		
AD with ichthyosis											
Yes	97(30.7)	164(51.9)	55(17.4)	2.57E-01	358(56.6)	274(43.4)	7.50E-01	97(30.7)	219(69.3)	1.00E-01	0.81(0.62-1.04)
No	635(35.5)	859(48.0)	297(16.6)		2129(59.4)	1453(40.6)	2.60E-03	635(35.5)	1156(64.5)		
AD with Palm disease											
Yes	171(38.4)	204(45.8)	70(15.7)	1.84E-01	546(61.3)	344(38.7)	3.30E-03	171(38.4)	274(61.6)	6.60E-02	1.22(0.99-1.52)
No	561(33.8)	819(49.3)	282(17.0)		1941(58.4)	1383(41.6)	4.30E-02	561(33.8)	1101(66.2)		