

Four genetic variants interact to confer susceptibility to atopic dermatitis in Chinese Han population

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Abstract Atopic dermatitis is a chronic inflammatory skin disease and is affected by environmental and genetic factors. Gene–gene/environment interactions are strongly believed to contribute to the genetic risk of common diseases. A number of gene–environment interactions of atopic dermatitis were performed. However, there are few comprehensive investigations on the gene–gene (or genetic variants) interactions for atopic dermatitis. We explored the association model of 6 single nucleotide polymorphisms (SNPs) which were most significant ($P < 10E-05$) in our previous genome wide association study (GWAS) for atopic dermatitis, and search for the possible genetic variant interactions based on the previous GWAS data using Generalized Multifactor Dimensionality Reduction and Plink 1.07 in the combined sample of 4,636 cases and 13,559 controls. The most significant associated evidence was observed under dominant model for SNPs rs3126085, rs12085366,

and rs7701890, recessive model for SNP rs17173197, and additive model for SNPs rs2393903 and rs6010620. Three significant pair–way interactions were observed, including *PRKAG2* and *FLG* SNPs (rs17173197 $\times$ rs3126085, $P_{\text{combined}} = 1.11E-15$), *PRKAG2* and *TMEM232-SLC25A46* SNPs (rs17173197 $\times$ rs7701890, $P_{\text{combined}} = 2.22E-15$), *PRKAG2* and *TNFRSF6B-ZGPAT* SNPs (rs17173197 $\times$ rs6010620, $P_{\text{combined}} = 6.66E-16$). Besides, a three-way significant interaction among *PRKAG2*, *TMEM232-SLC25A46* and *TNFRSF6B-ZGPAT* SNPs (rs17173197 $\times$ rs7701890 $\times$ rs6010620, $P_{\text{combined}} = 5.99E-15$) was observed in this study. These four genetic variant interactions confer susceptibility to atopic dermatitis, and highlight the genetic variant interactions in the etiology of atopic dermatitis in Chinese Han population.

Keywords Atopic dermatitis · Interactions · Genome-wide association study · Multifactor dimensionality reduction

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Introduction

Atopic dermatitis (MIM603165) is a common complex skin disease with chronically relapsing skin inflammation, which often co-occurs with asthma and allergic rhinitis (Willis-Owen et al. 2007). Atopic dermatitis affects 1–20 % populations worldwide (DaVeiga 2012). There are substantial evidences suggesting that genetic factors play an important role in the development of atopic dermatitis (Brown and McLean 2009). Linkage analysis and candidate gene studies have identified a number of genes or loci predisposing to atopic dermatitis (Barnes 2010). Recent genome-wide association studies (GWASs) for atopic dermatitis in diverse populations have identified approximately 20 susceptibility genes or loci, including two susceptibility loci at 5q22.1 (*TMEM232-SLC25A46*, rs7701890) and 20q13.33 (*TNFRSF6B-ZGPAT*, rs6010620) in Chinese Han population (Sun et al. 2011; Tamari and Hirota 2014). However, these genetic factors only explain collectively a small fraction of variation of heritability to atopic dermatitis (Ellinghaus et al. 2013); this phenomenon has been termed as “missing heritability” (Manolio et al. 2009). Therefore, additional genetic factors still remain to be discovered. We conducted a genetic variant interaction study based on our previous GWAS data of atopic dermatitis in Chinese Han population (Sun et al. 2011). In this study, we aim to search for possible genetic variant interactions which may affect the susceptibility to atopic dermatitis and to explain part of the pathogenesis for atopic dermatitis.

Materials and methods

Patients and controls

In total, we included 4,636 cases (2,766 men and 1,870 women, with the mean age of 5.45 years) and 13,559 unrelated controls (7,159 men and 6,400 women, with the mean age of 28.01 years) in this study (Table 1). All the atopic dermatitis cases and healthy controls enrolled in this study were recruited from multiple hospitals of China, and the patients were diagnosed by at least two experienced dermatologists. The controls were healthy individuals without

atopic dermatitis, other atopic diseases, systemic disorders or family history of atopic dermatitis (including first-, second- and third-degree relatives). All the cases and controls were collected using uniform criteria, and their clinical information was collected using the structured questionnaire. The written informed consent was obtained from each of the participants. This study was approved by the Institutional Ethic Committee of each hospital and was conducted according to Declaration of Helsinki principles.

Selection of SNPs and genotyping data

In our previous GWAS study for atopic dermatitis, there are 19 most promising SNPs that showed supportive association evidence in multiple stages (Sun et al. 2011). We selected 6 most significant SNPs (rs3126085, rs12085366, rs7701890, rs17173197, rs2393903, and rs6010620, all SNPs with $P < 10E-05$) from the 19 SNPs to conduct an interaction study and search for the possible genetic variant interactions for atopic dermatitis. For the SNPs in *FLG* and *TMEM232-SLC25A46*, all these SNPs in the same LD block with $r^2 > 0.80$, we selected the most significant SNPs.

Genotype data of the 6 SNPs in this study were extracted from our previous GWAS for atopic dermatitis, including 1,012 cases and 1,362 controls from Illumina Human610-Quad BeadChips and 3,624 cases and 12,197 controls from Sequenom MASSArray (Sequenom, Inc., San Diego, CA, USA) at the State Key Laboratory Incubation of Dermatology, Ministry of Science and Technology, Hefei, Anhui, China. The concordance between genotypes from both platforms was >99 %, suggesting that there is no heterogeneity between the two platforms (Sun et al. 2011).

Statistical analyses

The genotype frequencies of 6 SNPs were tested for Hardy–Weinberg equilibrium in controls. The association P value, odds ratio (OR) and 95 % confidence intervals (95 % CIs) were calculated using PLINK 1.07 (<http://pngu.mgh.harvard.edu/purcell/plink/>). Comparisons of allele frequencies were performed using the Pearson’s Chi square test. Fisher’s exact test was used when the expected count was <5.

Table 1 Demographical characteristics of the cases and controls

Stages	Initial		Replication		Combined	
	Cases	Controls	Cases	Controls	Cases	Controls
Number	1,012	1,362	3,624	12,197	4,636	13,599
Male/female	588/424	755/607	2,178/1,446	6,404/5,793	2,776/1,870	7,159/6,440
Mean age (SD)	5.01 (7.63)	33.10 (13.60)	5.57 (7.62)	27.53 (12.53)	5.45 (7.62)	28.01 (12.60)
Mean age of onset (SD)	1.37 (4.68)		1.60 (3.76)		1.55 (4.80)	

We considered atopic dermatitis as a dependent binary variable. It is a non-condition logistic regression model in Random Forest in R package (<http://www.r-project.org/>), which was used in the multivariate analyses to adjust for potential confounding factors, including age and sex. ORs and 95 % CIs were calculated as estimates of the relative risk for variables. The statistically significant level is a two-sided value of 0.05 for all tests.

We applied multifactor dimensionality reduction (MDR) algorithm to evaluate genetic variant interactions (Ritchie et al. 2001). Models are evaluated based on the testing balanced accuracy (TBA) statistic (Velez et al. 2007), the cross-validation consistency (CVC) (Cherkassky and Ma 2009) and the statistical significance of the model. The TBA measures how often individuals are correctly classified with respect to their case/control status, and the CVC evaluates the consistency with which individuals are classified. Heuristically, a satisfactory TBA score is above 0.55. We explored the association model of 6 SNPs, and assuming an additive, dominant, or recessive model for each SNP. The model with strongest association significance (determined through comparing the *P* value) was assigned as the best-fit model for that SNP. To avoid the disturbance by age and gender, these data were also analyzed using an extension of the MDR algorithm (Generalized Multifactor Dimensionality Reduction, GMDR, V0.7 software package) that includes adjustment for covariates (sex and age).

Results

The best-fit association model for 6 SNPs

We tested the best-fit association models (dominant, recessive, or additive) for the 6 SNPs in the combined sample size with 4,636 cases and 13,559 controls controlled for the effect of sex and age. Our results shown in Table 2 that dominant model was best to describe the association of 3 SNPs (rs3126085, rs12085366, rs7701890), the most significant associated evidence was observed under recessive model for SNP rs17173197, and additive model for 2 SNPs (rs2393903 and rs6010620).

Genetic variant interactions analysis

We observed three pairwise interactions including *PRKAG2* and *FLG* SNPs (rs17173197 × rs3126085, $P_{\text{combined}} = 1.11\text{E-}15$), *PRKAG2* and *TMEM232-SLC25A46* SNPs (rs17173197 × rs7701890, $P_{\text{combined}} = 2.22\text{E-}15$), *PRKAG2* and *TNFRSF6B-ZGPAT* SNPs (rs17173197 × rs6010620, $P_{\text{combined}} = 6.66\text{E-}16$), and a three-way interaction among *PRKAG2* × *TMEM232-SLC25A46* × *TNFRSF6B-ZGPAT* SNPs (rs17173197 × rs7

701890 × rs6010620, $P_{\text{combined}} = 5.99\text{E-}16$). Table 3 shows these significant interactions and maintains the consistent significant evidence among the initial, replication and combined stages.

Discussion

Gene–gene (or genetic variants) interaction is strongly believed to contribute to the genetic risk of common diseases (Cordell 2009). Several genetic variant interactions for autoimmune diseases have been reported (Yin et al. 2013; Zuo et al. 2014). Environmental factors interact with susceptibility genes of atopic dermatitis which were performed in some studies (Li et al. 2012). There were few comprehensive investigations on the genetic variant interactions for atopic dermatitis. We investigated the genetic variant interactions among 6 SNPs using MDR/GMDR with the genotyping data of 4,636 atopic dermatitis patients and 13,559 normal controls. There are four genetic variant interactions among 4 SNPs in *FLG*, *TNFRSF6B-ZGPAT*, *PRKAG2*, and *TMEM232-SLC25A46* that showed significant in statistics and confer susceptibility to atopic dermatitis. These associated genes were identified susceptibility to atopic dermatitis at genome-wide level of significance ($P < 5\text{E-}08$) in previous GWASs, and with different functions, involved in different pathways, and the genetic variant interactions affect the development of atopic dermatitis (Sun et al. 2011; Hirota et al. 2012; Ellinghaus et al. 2013).

The *FLG* gene is located in the “epidermal differentiation complex” on chromosome 1q21. *FLG* (encoding filaggrin) has been identified as a major locus causing skin barrier deficiency (Palmer et al. 2006) and with the most robust known genetic risk factor for atopic dermatitis (van den Oord et al. 2009). *PRKAG2* encodes AMP-activated protein kinase (AMPK), an important energy-sensing enzyme, which monitors cellular energy status and functions. Within 20q13.33, *TNFRSF6B* belongs to the tumor necrosis factor receptor superfamily, and plays an important role in adaptive immune responses. Research has shown that mRNA expression of serum *TNFRSF6B* in individuals with atopic dermatitis increased compared with healthy individuals and control subjects with non-atopic inflammatory disease (Chen et al. 2004). *ZGPAT* is a transcription repressor and negatively regulates the expression of epidermal growth factor receptor (EGFR) (Chan et al. 2006). *EGFR* pathway has a major impact on the inflammatory/immune reactions of the skin, enhancing innate immune defense while opposing over activation of keratinocyte pro-inflammatory functions (Pastore et al. 2008). In addition, *EGFR* is overexpressed in the lesional skin of atopic dermatitis individuals, and the blocking *EGFR* enhances skin inflammation (Mascia et al. 2003).

Table 2 The association model of 6 SNPs

SNPs (SNPs type)	Locus	Nearest gene	Model	A1	A2	Case (11/12/22) ^a	Sum ^b	Control (11/12/22)	Sum	het-OR (95 % CI)	hom-OR (95 % CI)	P	OR (95 % CI)
rs3126085	1q21.3	FLG	Additive	A	G	1,688/2,033/684	4,405	4,243/6,252/2,298	12,793	0.81 (0.75–0.88)	0.75 (0.68–0.83)	2.38E-09	0.86 (0.81–0.90)
Intron			Recessive			1,688/2,717		4,243/8,850				1.58E-04	0.84 (0.76–0.92)
rs12085366	1q31.3	ATP6V1G3	Dominant			3,721/684		10,495/2,298				3.21E-12	0.78 (0.72–0.83)
Intergenic			Additive	C	T	473/2,037/2,058	4,568	1,265/5,605/6,153	13,023	0.97 (0.86–1.09)	0.89 (0.80–1.01)	5.94E-03	1.09 (1.02–1.15)
			Recessive			473/4,095		1,265/11,758				5.27E-02	1.12 (1.00–1.25)
rs7701890	5q22.1	TMEM232	Dominant			2,510/2,058		6,870/6,153				5.27E-04	1.13 (1.05–1.21)
Intron		SLC2A46	Additive	A	G	3,247/1,169/96	4,512	9,748/2,940/231	12,919	1.19 (1.10–1.29)	1.25 (0.98–1.59)	9.39E-02	1.11 (0.98–1.25)
		<i>7SLP</i>	Recessive			3,247/1,265		9,748/3,171				2.07E-01	1.17 (0.92–1.49)
rs17173197	7q36.1	PRKAG2	Dominant			4,416/96		12,688/231				9.23E-08	1.23 (1.14–1.33)
Intron			Additive	C	T	1,300/1,964/1,182	4,446	3,660/6,054/2,586	12,300	0.91 (0.84–0.99)	1.29 (1.17–1.41)	2.30E-09	1.15 (1.10–1.21)
			Recessive			1,300/3,146		3,660/8,640				4.39E-20	1.45 (1.34–1.57)
rs2393903	10.21.2	ZNF365	Dominant			3,264/1,182		9,714/2,586				9.45E-01	1.00 (0.93–1.08)
Intron			Additive	A	G	1,138/2,252/1,056	4,446	2,448/4,179/1,764	8,391	1.16 (1.06–1.26)	1.28 (1.16–1.43)	1.10E-09	1.17 (1.12–1.24)
			Recessive			1,138/3,308		2,448/5,943				1.12E-06	1.24 (1.14–1.35)
rs6010620	20q13.33	TNFRSF6B	Dominant			390/1,056		6,627/1,764				3.48E-07	1.24 (1.14–1.34)
Intron		ZGPAT	Additive	A	G	2,294/1,861/422	4,577	7,135/5,032/920	13,087	1.15 (1.07–1.23)	1.43 (1.26–1.62)	2.24E-07	1.18 (1.11–1.26)
			Recessive			2,294/2,283		7,135/5,952				1.24E-05	1.31 (1.16–1.48)
			Dominant			4,155/422		12,167/920				5.59E-07	1.19 (1.11–1.27)

The best-fit association models for the 6 SNPs are presented in bold

^a “1” stands for the minor allele and “2” stands for the major allele

^b Sample size among these 6 SNPs was not exactly the same due to genotyping missing

Table 3 Results of genetic variants interactions for atopic dermatitis in Chinese Han population

Interacting SNPs (related genes)	Covariates	GWAS (1,012 cases vs 1,362 controls)			Replication (3,624 cases vs 12,197 controls)			Combined (4,646 cases vs 13,559 controls)		
		CVC ^a	TBA ^b	P value	CVC	TBA	P value	CVC	TBA	P value
rs17173197 × rs3126085 (<i>PRKAG2</i> × <i>FLG</i>)	Sex, age	10/10	0.6138	6.35E-06	10/10	0.5971	4.70E-06	10/10	0.5987	1.11E-15
rs17173197 × rs7701890 (<i>PRKAG2</i> × <i>TMEM232</i> - <i>SLC25A46</i>)	Sex, age	10/10	0.5971	1.44E-12	10/10	0.6254	9.46E-08	10/10	0.6045	2.22E-15
rs17173197 × rs6010620 (<i>PRKAG2</i> × <i>TNFRSF6B</i> - <i>ZGPAT</i>)	Sex, age	10/10	0.6085	1.47E-05	10/10	0.6157	6.50E-10	10/10	0.6058	6.66E-16
rs17173197 × rs7701890 × rs6010620 (<i>PRKAG2</i> × <i>TMEM232</i> - <i>SLC25A46</i> × <i>TNFRSF6B</i> - <i>ZGPAT</i>)	Sex, age	10/10	0.5962	1.31E-06	10/10	0.6052	5.20E-12	10/10	0.5988	5.99E-15

^a Cross-validation consistency^b Testing balanced accuracy

At 5q22.1, several SNPs have been identified to be associated with atopic dermatitis in various populations. Several genes were observed in the association interval (Sun et al. 2011; Hirota et al. 2012). Of these genes, *SLC25A46* is a member of the solute carrier 25 (SLC25) family, which encodes mitochondrial carrier proteins and functions as transporters of a large variety of molecules (Palmieri 2004). Previous study has shown that *SLC25A46* is up-regulated after IL-2 deprivation in both primary and immortalized cells (Chechlinska et al. 2009). *TMEM232* encodes a transmembrane protein 232, belonging to the functional class of tetraspan transmembrane proteins. Notably, *TSLP* primes dendritic cells to promote the Th2 inflammatory response, and plays a potentially important role in the pathogenesis of inflammatory diseases such as atopic dermatitis (Fang et al. 2010).

Significant interaction between *FLG* and *PRKAG2* SNPs was identified. *PRKAG2* as an energy-sensing gene may monitor the energy status and functions of filaggrin during the process of epidermal differentiation and maintaining barrier function. There is a pair-way interaction between *PRKAG2* and *TNFRSF6B*-*ZGPAT* SNPs. We speculate that this interaction may prompt the inflammatory progress and regulate the innate-adaptive immune response. For the interaction between *PRKAG2* and *SLC25A46*-*TMEM232*, *PRKAG2* may provide energy for the progress of protein transport and inflammatory response in the development of atopic dermatitis. We observed that *PRKAG2* interacts with *TNFRSF6B*-*ZGPAT* and *SLC25A46*-*TMEM232*, respectively. Interestingly, we observed that the three SNPs of *PRKAG2*, *TNFRSF6B*-*ZGPAT* and *TMEM232*-*SLC25A46* constitute a three-way interaction. Taken together, our study indicates that the interactions among these loci may play an important role in the innate-adaptive immune response, regulatory T cells, cellular energy, and protein transport, to make a systematic effect on the pathogenesis of atopic dermatitis.

In this study, we evaluated genetic variant interactions using MDR/GMDR, which is genetically model free, non-parametric and directly applicable to case-control and discordant-sib-pair studies. The false-positive results are minimized due to multiple testing. However, the results of MDR/GMDR are difficult to interpret, and the prediction ability is limited for independent data sets when the dimensionality of the best model is relatively high and the sample is relatively small (Ritchie et al. 2001). In view of these aspects, some other more effective interaction methods need to be developed.

In conclusion, we provided evidence for interactions in the susceptibility of atopic dermatitis. These findings will expand our understanding of the contribution of complex genetic effects to the pathogenesis of atopic dermatitis, and highlight the important role of the epistatic effect in the etiology of atopic dermatitis. Further pathway and functional studies of these genetic variant interactions with atopic dermatitis need to be conducted in more depth and identified by other new methods in the future.

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Conflict of interest None declared.

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