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Association analyses identify two susceptibility loci 5q31 and 5q22.1 for atopic dermatitis in Chinese Han population

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Abstract

Background: Atopic dermatitis (AD) and other atopic diseases often share some common genetic and pathogenic bases. Recent genome-wide association studies (GWAS) have identified several loci associated with atopic diseases, allergic sensitization and asthma in different populations. The aim of this study was to investigate whether these susceptibility loci were related to AD in Chinese Han population.

Methods: Eight single nucleotide polymorphisms (SNPs) from recent atopic diseases and allergic sensitization GWAS were genotyped in 3,013 AD patients and 5,483 healthy controls in Chinese Han population using Sequenom MassArray system. Data was analyzed with PLINK 1.07 software.

Results: We identified that the susceptibility loci at 5q31 (*RAD50/IL13*, rs2158177, $P = 1.08\times10^{-3}$, OR = 1.15) and 5q22.1 (*TSLP*, rs1837253, $P = 2.66\times10^{-3}$, OR = 0.91) were significantly associated with AD. Genotype-based association testing revealed that the dominant model provided the best fit for both rs2158177 ($P = 3.75\times10^{-3}$) and rs1837253 ($P = 5.30\times10^{-3}$). Pathway analysis conformed that both loci were associated with the JAK-STAT signaling pathway.

Conclusions: We identified two susceptibility loci 5q31 and 5q22.1 for AD that might bear candidate genes conferring susceptibility to AD.

Keywords: *Atopic dermatitis*, *Allergic sensitization*, *Single nucleotide polymorphisms*, *Susceptibility loci*, *Pathway analysis*

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Introduction

Atopic dermatitis (AD) is a common chronic relapsing, pruritic and inflammatory skin disease caused by the combined interaction between genetic and environmental factors.[1] AD has become a global health problem with prevalence ranging from 3.0% to 17.0% in the general population worldwide[2] and from 8.3%[3] to 11.8%[4] in China. AD, allergic rhinitis (AR) and asthma belong to atopic diseases and often coexist. Globally, the co-morbidity rate of these three diseases were 5.1-13.6% in asthma patients, 4.3-21.2% in rhinoconjunctivitis patients and 8.6-19.1% in eczema patients.[2] A number of genetic factors had been observed in patients with atopic diseases, which suggested that common predisposing genetic factors might be involved in these diseases.[5]

Our previous genome-wide association studies (GWAS) of AD have identified 2 loci relate to AD.[6] Allergic sensitization is a multifactorial process that is influenced by the allergen and its biological function per se as well as other small molecular compounds.[7] It is an important risk factor for the development of atopic disease[8] and has an estimated heritability of 0.40–0.85.[9] Many susceptibility loci of allergic sensitization have been reported. Hinds et al.[10] performed a genome-wide association studies (GWAS) meta-analysis of allergic sensitization susceptibility loci in European population with self-reported cat, dust-mite and pollen allergies. They identified 16

susceptibility loci ($P < 5 \times 10^{-8}$), including 8 loci previously associated with asthma, as well as 8 novel loci. A similar study identified ten single nucleotide polymorphisms (SNPs) with allergic sensitization in European descent population.[9]

In present study, we selected eight SNPs from recent AD, asthma and allergic sensitization GWAS in different populations to investigate whether these genetic variants are associated with AD in Chinese Han population. Consequently, we found that genetic variants in 5q31 and 5q22.1 were significantly associated with AD in Chinese Han population. Moreover, bioinformatics analysis conformed that both loci were associated with the JAK-STAT signaling pathway which plays an important role in the pathogenesis of AD.

Methods

Study Subjects

A total of 3,013 AD patients including of 1824 (60.54%) males and 1189 (39.46%) females with the mean age of 5.51±7.93 years and 5,483 controls including of 2742 (50.01%) males and 2741 (49.99%) females with the mean age of 28.41±13.70 years were enrolled in this study. All DNA samples were from Chinese Han population. The patients fulfilled the Hannifin -Rajka criteria[11] and the controls were healthy individuals without AD, other atopic diseases, systemic disorders or family history of AD (including first-, second- and third-degree relatives). Informed consent was obtained from all individual participants included in the study. The study was approved by the Institutional Ethical Committee of Anhui Medical University and was conducted according to the Declaration of Helsinki principles.

SNP selection

After excluding the SNPs evaluated in the previously replications in Chinese population, eight SNPs were selected for analysis in this study (**Table 1**), including five SNPs (rs2101521 at 4p14, rs1438673 at 5q22.1, rs7720838 at 5p13.1, rs6021270 at 20q13.2, rs3771175 at 2q12.1) associated with allergic sensitizationin in Americans and Europeans,[9,10] two SNPs (rs1469621 at 2q22 and rs2158177 at 5q31)related to AD with athsma in an AD-GWAS of Europeans,[12] and one SNP (rs1837253 at 5q22.1) associated with athsma in adult and allergic rhinitis with asthma in children.[13,14]

Genotyping and quality controls

Genomic DNA was extracted using QIAamp DNA Blood KIT (Qiagen, Valencia, CA, USA). SNPs were genotyped using the Sequenom MassArray system. The DNA of each sample was amplified by multiplex polymerase chain reaction (PCR) reactions, and PCR products were used for locus -specific single-base extension reactions. Then, the reactions products were desalted and transferred to a 384-element Spectro-CHIP array, alleles detection was performed using MALDI-TOF MS. The mass spectrograms were analyzed by MassARRAYTyper software (Sequenom). Exclusion criteria for the genotyped SNPs were call rate <95%, minor allele frequency(MAF) <0.05, and deviation from Hardy-Weinberg equilibrium (HWE, $P < 0.05$) in the controls.

Statistical Analysis

The possible associations of the eight SNPs with AD and its subphenotypes were assessed by using Plink 1.07 software.[15] The strength of association was estimated by calculating the odds ratio (OR) with a 95% confidence interval (95%CI). The association model (dominant, recessive, additive) of each allele was tested using the Pearson's chi-square test. Conservatively accounting for the multiple comparisons by the Bonferroni correction, the threshold for statistical significance was $P < 6.3\times10^{-3}$ (0.05/8). The genetic statistical power for all genotyped SNPs was estimated using the CaTS-Power Calculator.

Table 1. Summary of SNP selection

SNP	Chr	Gene	Population	Allele	P value	Disease
rs3771175	2q12.1	IL1RL1-IL18R1	European American[9]	A/T	4.9×10^{-11}	allergic sensitization
rs1469621	2q22	THSD7B	European[12]	A/G	3.9×10^{-9}	AD with asthma and psoriasis
rs2101521	4p14	TLR1–TLR6	European American[10]	A/G	5.3×10^{-21}	allergic sensitization
rs7720838	5p13.1	PTGER4	European American[10]	G/T	8.2×10^{-11}	allergic sensitization
rs1438673	5q22.1	WDR36–CAMK4	European American Australian[10]	T/C	2.3×10^{-20}	allergic sensitization asthma
rs1837253	5q22.1	TSLP	Japanese[13] North American[14]	T/C	1.2×10^{-16} 1.5×10^{-14}	asthma
rs2158177	5q31	RAD50/IL13	European[12]	A/G	5.9×10^{-11}	AD with asthma and psoriasis
rs6021270	20q13.2	NFATC2	European American[10]	C/T	6.9×10^{-9}	allergic sensitization

SNP single nucleotide polymorphism, Chr chromosome.

Results

Association between AD and SNPs

All the SNPs passed the quality control. The association analysis for the eight SNPs between cases and controls was shown in **Table 2**. The SNP rs2158177 ($P = 1.08\times10^{-3}$, OR = 1.15, 95%CI = 1.06-1.24) at 5q31 and rs1837253 ($P = 2.66\times10^{-3}$, OR = 0.91, 95%CI = 0.85-0.97) at 5q22.1 were significantly associated with AD after correcting for multiple testing ($P_{Bonferroni} < 6.3\times10^{-3}$). There was no significant association between AD cases and controls for any other SNPs. Genotype-based association analysis revealed that the dominant model provided the best fit for both rs2158177 ($P = 3.75\times10^{-3}$) and rs1837253 ($P = 5.30\times10^{-3}$) (**Table 3**).

Bioinformatics analysis of validated SNPs for putative pathways

The two SNPs which were validated in the Chinese Han population were analyzed for their positions relative to nearby genes using the LocusZoom.[16] Interestingly, the rs2158177 falls in the *RAD50/IL13* region (**Figure 1**) and the rs1837253 is located 5.7 kb upstream of the transcription initiation

Table 2. Associations for 8 SNPs between cases and controls

SNP	CHR	Gene	Allele	MAF		*P*	OR(95%CI)	P_{HWE}	Callrate	statistical power
				Cases	Controls					
rs2158177	5q31	RAD50/IL13	G/A	0.19	0.17	**1.08E-03**	1.15(1.06-1.24)	0.74	0.98	100%
rs1837253	5q22.1	TSLP	C/T	0.39	0.41	**2.66E-03**	0.91(0.85-0.97)	0.59	0.98	100%
rs7720838	5p13.1	PTGER4	T/G	0.23	0.24	9.30E-02	0.94(0.87-1.01)	0.21	0.98	91%
rs1438673	5q22.1	WDR36-CAMK4	G/A	0.44	0.43	9.54E-02	1.06(0.99-1.13)	0.68	0.98	92%
rs2101521	4p14	TLR1-TLR10	G/A	0.38	0.37	1.62E-01	1.05(0.98-1.12)	0.70	0.98	86%
rs6021270	20q13.2	NFATC2	C/T	0.06	0.06	6.95E-01	1.03(0.90-1.17)	0.05	0.98	40%
rs3771175	2q12.1	IL1RL1-IL18R1	A/T	0.09	0.09	8.46E-01	0.99(0.88-1.11)	0.61	0.98	27%
rs1469621	2q22	THSD7B	C/T	0.17	0.17	9.44E-01	1.00(0.92-1.08)	0.30	0.98	22%

[a]SNP single nucleotide polymorphism, CHR chromosome, MAF minor allele frequency,OR odds ratio,CI confidence interval,HWE Hardy-Weinberg equilibrium

Table 3. Distribution of genotypes and genetic model analysis for rs2158177 and rs1837253 in AD patients and controls

SNP ID	Genotype	Cases(%)	Controls(%)	*P*	OR(95%CI)
rs2158177	GG	118(4.00%)	163(3.05%)	—	1
	GA	902(30.61%)	1521(28.44%)	1.19E-01	1.22(0.95-1.57)
	AA	1927(65.39%)	3663(68.51%)	9.82E-03	1.38(1.08-1.76)
	Recessive model GG/(GA+AA)	118(4.00%)/2829(96.00%)	163(3.05%)/5148(96.95%)	2.13E-02	1.33(1.04-1.69)
	Dominant model (GG+GA)/AA	1020(34.61%)/1927(65.39%)	1684(31.49%)/3663(68.51%)	**3.75E-03**	1.15(1.05-1.27)
	Additive model GG/GA/AA	118(4.00%)/902(30.61%)/1927(65.39%)	163(3.05%)/1521(28.44%)/3663(68.51%)	**4.30E-03**	
rs1837253	CC	450(15.23%)	907(16.96%)	—	1
	CT	1405(47.57%)	2614(48.89%)	2.28E-01	0.92(0.81-1.05)
	TT	1099(37.20%)	1826(34.15%)	**5.19E-03**	0.82(0.72-0.94)
	Recessive model CC/(CT+TT)	459(15.23%)/2504(84.77%)	907(16.96%)/4440(83.04%)	4.14E-02	0.88(0.78-1.00)
	Dominant model (CC+CT)/TT	1855(62.80%)/1099(37.20%)	3521(65.85%)/1826(34.15%)	**5.30E-03**	0.88(0.80-0.96)
	Additive model CC/CT/TT	450(15.23%)/1405(47.57%)/1099(37.20%)	907(16.96%)/2614(48.89%)/1826(34.15%)	1.00E-02	

[a] SNP single nucleotide polymorphism,OR odds ratio,CI confidence interval
[b] Genotyping of 59 cases for rs2158177, 66 cases for rs1837253 and 136 controls failed

Table 4. Pathway identification result annotation for *IL13* and *TSLP* by KOBAS

Gene	Term	Database	ID	*P*-Value
IL13	Gata3 participate in activating the th2 cytokine genes expression	BioCarta	100157	4.51E-03
	IL12 signaling mediated by *STAT4*	PID	Il12 stat4 pathway	7.50E-03
	Asthma	KEGG PATHWAY	Hsa05310	8.09E-03
	Inflammatory bowel disease(IBD)	KEGG PATHWAY	Hsa05321	1.67E-02
	Fc epsilon RI signaling pathway	KEGG PATHWAY	hsa04664	1.73E-02
	Interleukin signaling pathway	PANTHER	P00036	1.97E-02
	Glucocorticoid receptor regulatory network	PID	Req qr pathway	2.02E-02
	Measles	KEGG PATHWAY	hsa05162	3.28E-02
	Jak-STAT signaling pathway	KEGG PATHWAY	hsa04630	3.80E-02
TSLP	Jak-STAT signaling pathway	KEGG PATHWAY	hsa04630	2.35E-02
	Cytokine-cytokine receptor interaction	KEGG PATHWAY	hsa04060	2.17E-02

[a] Databases: BioCarta, Gene Ontology, GAD, FunDO, KEGG PATHWAY, OMIM, PID, PANTHER, Reactome, BioCyc, NHGRI GWAS Catalog, KEGG DISEASE.
[b] Statistical test method: hypergeometric test / Fisher's exact test.

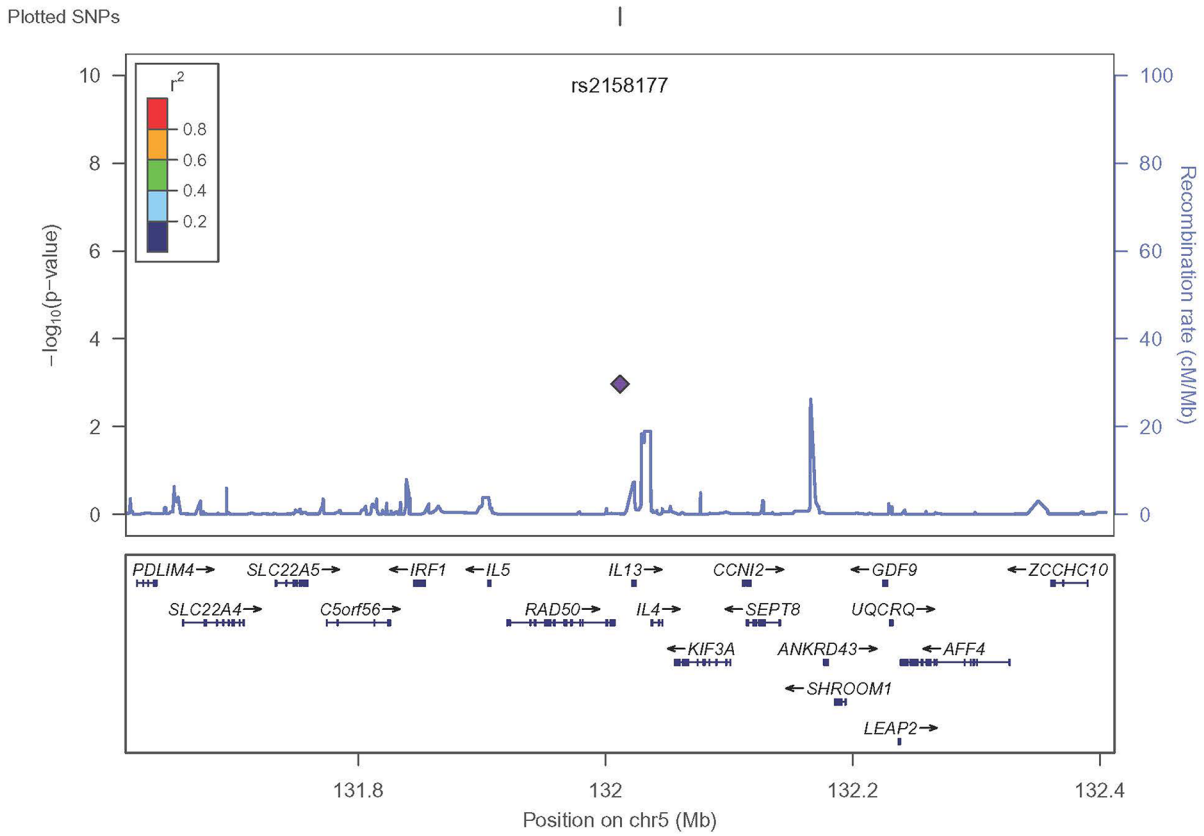

Figure 1. Regional plots for associated SNP rs2158177 ($P_{Bonferroni}$ = 1.08E-03) at 5q31. The log P values (y axis) of the rs2158177 is presented according to its chromosomal positions (x axis), The color of rs2158177 reflects its r^2. Estimated recombination rates (based on the combined CHB and JPT samples from the HapMap project) are plotted in light blue. Gene annotations were adapted from the University of California, Santa Cruz Genome Browser (http://genome.ucsc.edu/)

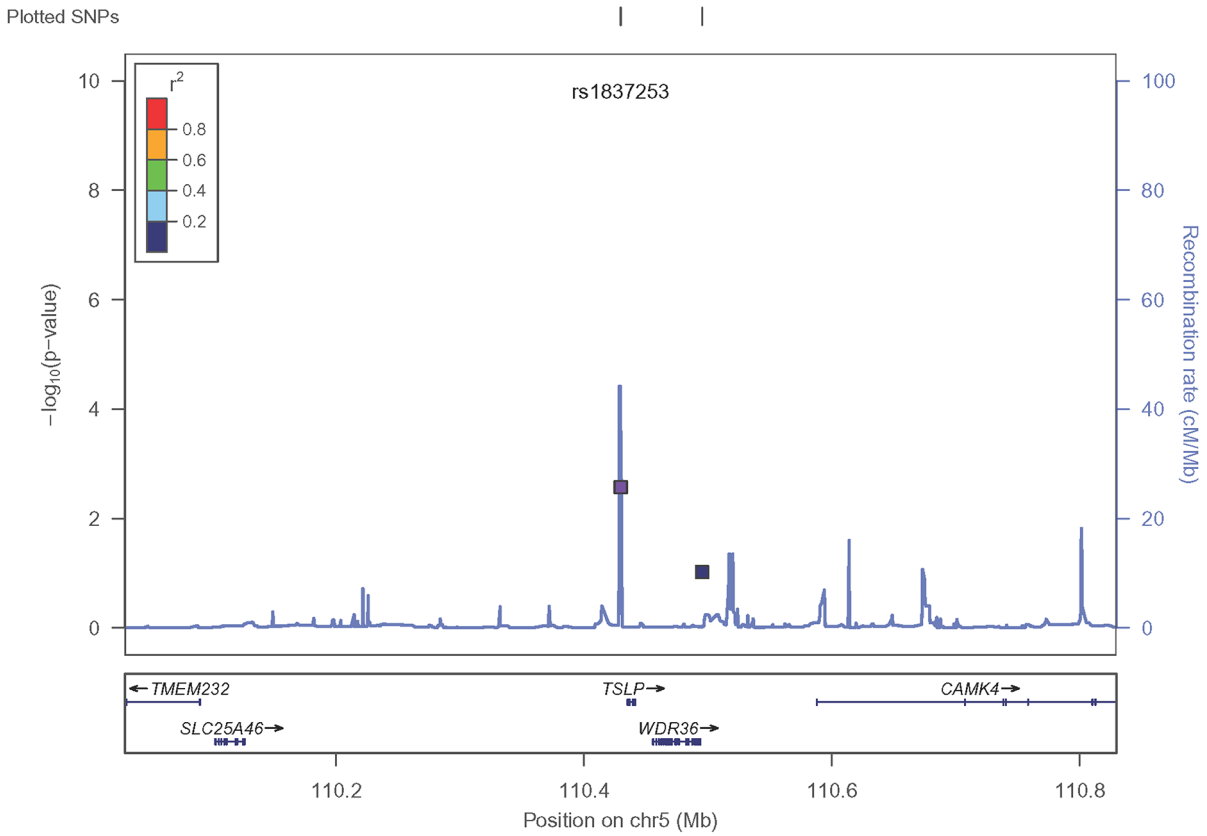

Figure 2. Regional plots for associated SNP rs1837253 ($P_{Bonferroni}$ = 2.66E-03) at 5q22.1. The log *P* values (y axis) of the rs1837253 is presented according to its chromosomal positions (x axis), The color of rs1837253 reflects its r^2. Estimated recombination rates (based on the combined CHB and JPT samples from the HapMap project) are plotted in light blue. Gene annotations were adapted from the University of California, Santa Cruz Genome Browser (http://genome.ucsc.edu/).

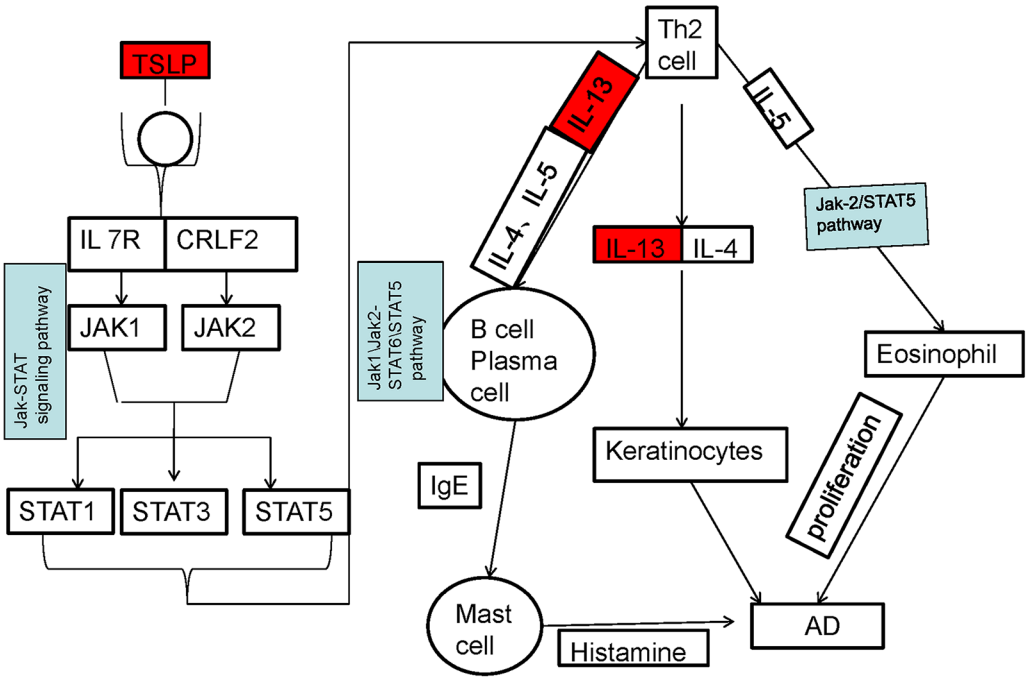

Figure 3. Proposed mechanism of JAK-STAT involvement in atopic dermatitis (AD) development. The *TSLP* promotes the differentiation of Th2 cells through JAK-STAT pathway. Th2 cells play a significant role in AD. By their abilities to provide *IL4*, *IL5* and *IL13* stimulation via the JAK-STAT pathway, immature B cells could be differentiated into mature B cell and plasma cells would undergo antibody heavy chain switching to IgE class. The subsequent binding of IgE to skin mast cells could lead to release of histamine, which is known to exacerbate AD. Similarly, this hyper Th2 immune milieu, particularly *IL4* and *IL13*, could trigger epidermal cells to produce and release various chemokines, pro-inflammatory cytokines, and angiogenic factors, leading to AD pathophysiology. Moreover, *IL5* released from this hyper Th2 milieu could, through JAK-STAT pathway, activate eosinophils and worsening the AD condition.

region of *TSLP* (**Figure 2**). The KOBAS 2.0 computer program (http://kobas.cbi.pku.edu.cn/home.do.) was applied to identify biological pathways that these genes may be involved and their relations to AD. We found that *IL13* was associated with nine signaling pathways. In addition, both *IL13* and *TSLP* were strongly associated with JAK-STAT signaling pathway, but no pathway was related to *RAD50*. Information about the potential pathways to these genes has been summarized in **Table 4**.

Discussion

AD is a complex genetic disease, which often develops with asthma, allergic rhinitis and other allergic diseases.[17] Although the atopic march was generally accepted, it is still debated whether it is due to their sharing common genetic factors.[18] Therefore, understanding the genetic relationships between AD and other allergic states might help to further elucidating the pathogenesis of AD. Here we investigated eight SNPs located in different genes, which were susceptibility loci for atopic diseases, allergic sensitization and asthma in European, American and Japanese populations and analyzed their association with AD in Chinese Han population. Interestingly, 2 SNPs in 5q31 and 5q22.1 showed significant differences between AD patients and controls.

Chromosome 5q31-32 is considered a critical region for several allergic and atopic diseases, including asthma. rs17690965 at 5q31.1 is a susceptibility loci for atopic march.[19] Functional polymorphism C-159Tof the CD14 promoter region might play a role in the pathogenesis of nasal polyposis and in the incidence of asthma.[20] rs2158177 in the 5q31 falls in the *RAD50/IL13* region. The protein encoded by *RAD50* forms a complex with MRE11 and NBS1, and is important for DNA double-strand break repair, cell cycle checkpoint activation, telomere maintenance, and meiotic recombination.[21] However, it has no known function directly related to AD. On the contrary, *IL13* encodes an immunoregulatory cytokine produced primarily by activated Th2 cells. *IL13* is critical to the pathogenesis of both atopy and asthma.[22,23] The SNP rs1837253 at 5q22.1, which was not in the same LD with rs7701890 ($P_{combined} = 3.15 \times 10^{-9}$, OR=1.24) reported by our previous GWAS[6] ($r^2 < 0.01$) through Haploview 4.2, is located 5.7 kb upstream of the transcription initiation region of TSLP. It is a susceptibility gene for allergic diseases and plays an important role in these diseases.[24] Tang et al[25] in our study group also detected one significant risk haplotype GGGA from 4 SNPs (rs10067777, rs7701890, rs13360927 and rs13361382) at 5q22.1 in AD cases and the haplotype was suggestive of risk in asthma cases, which suggested that 5q22.1 might be shared by AD and asthma in Chinese Han population.

A recent study indicated that *IL13* induces AD and atopic march via a *TSLP* dependent mechanism.[26] Interestingly, through pathway annotation analysis using KOBAS 2.0, we found that both *IL13* and *TSLP* are strongly associated with JAK-STAT signaling pathway. The JAK-STAT pathway is a classical signal transduction pathway for numerous cytokines and growth factors. The *TSLP* is high expressed in acute and chronic lesions of AD patients[27] and plays an important role in stimulating neurons and provoking itch in AD patients.[28] The human *TSLP* receptor activates STAT1, STAT3, STAT5/JAK1, JAK2 and promotes the differentiation of Th2 cells.[29,30] Then, Th2 cells produce IL4, IL-5, and IL13, which activate eosinophils, affect B cell maturation and plays an essential role in the dysregulation of immune responses in AD(**Figure 3**).[31] In contrast to the therapeutic applications existing for haematology and rheumatology, there are no licensed dermatological indications for JAK or STAT inhibitors.[32] Through our analysis, JAK-STAT signaling pathway may be a potential therapeutic target for the treatment of AD. *IL13* can suppress human cathelicidin LL-37 through STAT6 in eczema vaccinatum of AD patients.[33] Loricrin and involucrin are two important factors for skin barrier function and downregulated by *IL4* and *IL13* in keratinocytes.[34]

Here we found that two SNPs in 5q31 and 5q22.1 showed significantly differences between AD patients and controls while the other six SNPs were not related to AD. That might be caused by racial differences. Furthermore, in these six SNPs we noticed that the statistical power of three SNPs in 20q13.2, 2q12.1 and 2q22 were less than 80%, which might be the reason why these three SNPs were not associated with AD in our study and called for more subjects in further study to confirm these findings from independent cohorts.

In summary, this study indicates that 5q31(*RAD50/IL13*) and 5q22.1(*TSLP*) are associated with AD and confer susceptibility to AD. Pathway analysis reveals that both *IL13* and *TSLP* are associated with JAK-STAT signaling pathway which plays an influential role in the pathogenesis of AD. To further analyze the true susceptibility gene for AD within these loci, fine mapping and functional studies is needed.

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Conflict of interest

None declared

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