# Association of the chromosome 11p13.5 variant and atopic dermatitis with a family history of atopy in the Chinese Han population

Fang Cheng,[1-3#] Jin-Hua Zhao,[1-3#] Xian-Fa Tang,[1-3] Hui Cheng,[1-3] Yu-Jun Sheng,[1-3] Xiao-Yun Jiang,[1-3] Ling Fang,[1-3] Xiao-Guang Zhang,[1-3] Xian-Bo Zuo,[2-3] Xiao-Dong Zheng,[2-3] Fu-Sheng Zhou,[2-3] Hua-Yang Tang,[1-3] Sen Yang,[1-3] Feng-Li Xiao[1-3] and Xue-Jun Zhang[1-3]

## Summary

***Background:*** **Recent genome-wide association studies (GWAS) and a meta-analysis of GWAS for atopic dermatitis (AD) have identified some AD genetic loci in European and Japanese populations.**

***Objective:*** **To investigate whether some novel susceptibility loci are associated with AD in the Chinese Han population.**

***Methods:*** **We first selected eight novel susceptibility loci to replicate in 2,205 AD patients and 2,116 healthy controls using the Sequenom platform. Data were analyzed with PLINK 1.07 software.**

***Results:*** **We found that rs12634229 (3q13.2), rs7927894 (11p13.5) and rs878860 (11p15.4) showed a slight association with AD (*P* = 0.012, *P* = 0.033, *P* = 0.020, respectively); rs6780220 (3p21.33) was preferentially related to AD with keratosis pilaris, but did not reach the threshold of significance after correction. The frequency of rs7927894 allele T was significantly different between AD patients with a positive and negative family history of atopy.**

***Conclusion:*** **The loci rs7927894 (11p13.5) are related to AD with a positive family history of atopy in Chinese Han population, providing novel insight into the genetic pathogenesis of AD.** ***(Asian Pac J Allergy Immunol 2016;34:109-14)***

***Keywords:*** *atopic dermatitis, chromosome 11q13.5, rs7927894, single nucleotide polymorphism, family history*

From 1. Institute of Dermatology and Department of Dermatology, No.1 Hospital, Anhui Medical University, Hefei, Anhui, China.

2. Key Laboratory of Dermatology, Anhui Medical University, Ministry of Education, China, Hefei, Anhui, China.

3. State key Laboratory Incubation Base of Dermatology, Anhui Medical University, Hefei, Anhui, China.

#These authors contributed equally to this work.

Corresponding author: Feng-Li Xiao

E-mail: xiaofengli@126.com

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## Introduction

Atopic dermatitis (AD) is a chronic, pruritic inflammatory dermatosis that affects up to 25% of children and 2% to 3% of adults.[1] Its clinical phenotype is complex, and is often accompanied with other clinical atopic manifestations, such as bronchial asthma (BA), allergic rhinitis (AR) and the elevated total and/or allergen-specific serum IgE levels. Although the exact mechanism of AD is poorly clarified, epithelial barrier defects as well as immune response dysfunction with a strong genetic basis are thought to have important roles in disease development.[2]

Many susceptibility loci/genes predisposing to AD have been identified through linkage and candidate gene association studies as well as genome-wide association studies (GWAS).[2-6] However, only a few of genes, such as filaggrin (*FLG*), have been consistently replicated in multiple studies.[2] The first GWAS of AD in a European population found an association of a new genetic locus, rs7927894 at 11q13.5 downstream of C11orf30, with AD development.[3] A subsequent GWAS identified two new susceptibility loci in a Chinese Han cohort, rs7701890 at 5q22.1 (TMEM232/SLC25A46) and rs6010620 at 20q13.33 (TNFRSF6B/ZGPAT), and the latter also showed evidence for an association in a German cohort.[4] A meta-analysis of GWAS performed in European cohorts indicated that three new loci are associated with the development of AD, including rs479844

upstream of OVOL1 and rs2164983 near ACTL9, both of which are near genes that have been implicated in epidermal proliferation and differentiation, as well as rs2897442 in KIF3A within the cytokine cluster at 5q31.1.[5] Hirota et al.[6] identified eight new susceptibility loci for AD with genome-wide significance in the Japanese population: rs13015714 at 2q12(IL1RL1/IL18R1/IL18RAP), rs12634229 at 3q13.2(CCDC80), rs6780220 at 3p21.33 (GLB1), rs176095 at 6p21.3(GPSM3), rs4722404 at 7p22 (CARD11), rs10995251 at 10q21.2 (ZNF365), rs878860 at 11p15.4 (OR10A3/ NLRP10) and rs16999165 at 20q13 (CYP24A1/ PFDN4). They also validated the seven previously reported loci associated with AD, including two susceptibility loci first reported in the Chinese Han population.[4] To date, it is unclear whether these novel susceptibility loci previously reported in European and Japanese populations are also associated with AD in Chinese Han patients.

In this study, we aimed to investigate the association of eight single nucleotide polymorphisms (SNPs), including six confirmed and two suggestive AD susceptibility loci reported by two GWAS for AD and a meta-analysis of GWAS, with AD and AD phenotypes in a large Chinese Han cohort.

## Methods

### *Research Subjects*

AD cases and controls in this study were recruited from multiple hospitals in China. In total, 2,205 cases and 2,116 controls were involved in the replication study (Table 1). All objects provided detailed clinical information in terms of gender, age, age of onset, family history, concomitant diseases, and disease severity determined by Severity Scoring of Atopic Dermatitis (SCORAD) index.[7]

All cases were diagnosed using the AD criteria of Hanifin and Rajka.[8] The demographic and clinical information was collected from both cases and controls through a structured questionnaire and a full clinical checkup by specialist physicians. All controls were healthy individuals without AD, other atopic diseases, systemic disorders or a family history of AD (including first-, second- and third-degree relatives). The written informed consent was obtained from all participants or the children's guardians. The study was approved by the Institutional Ethical Committee of each hospital and was conducted according to the principles of the Declaration of Helsinki.

**Table 1.** Demographic characteristic of AD cases and controls

| Characteristics | AD cases(2205) | Controls(2116) |
|---|---|---|
| Gender, Male/Female | 1359/846 | 1107/1009 |
| Average age (years, mean ± SD) | 5.40±7.7 | 27.50±12.6 |
| Age of onset (years, mean ± SD) | 1.5±5.0 | |
| Family history of atopy | | |
| AD positive/AD negative | 709/1441 | |
| Disease severity (Objective SCORAD) | | |
| Mild (0-25) | 467 | |
| Moderate (25-50) | 1224 | |
| Severity (>50) | 426 | |
| AD with/without keratosis pilaris | 289/1835 | |

Patients were categorized according to: (1) family history of atopy (positive: at least one relative of proband suffered from AD or BA or AR, including first-, second- and third-degree relatives; negative: otherwise), (2) concomitant keratosis pilaris: AD with keratosis pilaris, AD without keratosis pilaris, (3) the severity of AD (SCORAD less than 25 as mild, 25~49 as moderate, and more than 50 as severe).

### *SNP selection and genotyping*

On the basis of previous AD GWAS in Japanese and European populations, we first selected eight confirmed and suggestive AD susceptibility loci for genotyping in all samples using the Sequenom MassArray system (Table 2).

### *Statistical analysis*

The quality control for the analyzed SNP was required a call rate >95%, Hardy–Weinberg equilibrium (HWE) ($P_{HWE}$ >0.05) in the controls. The genetic statistical power for all genotyped SNPs was estimated using CaTS-Power Calculator software. *P*-values, odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using PLINK 1.07 software. The statistical significance was defined as $P$ <0.006 after the Bonferroni Multiple Testing correction (0.05/8).

## Results

### *Distribution of eight SNPs in patients and controls*

The eight SNPs were eligible for the validation analysis. As shown in Table 2, the minor allele frequency (MAF) of rs12634229, rs7927894 and

**Table 2.** The distribution of 8 SNPs allele in AD patients and controls

| SNP | Chromosome | Genes in or near regions of association | Minor Allele | MAF | | P | OR(95% CI) | *p*-hwe | call-rate | power |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Case | Control | | | | | |
| **rs12634229** | **3q13.2** | CCDC80 | **C** | **0.309** | **0.284** | **0.012** | **1.126(1.025-1.236)** | **0.625** | **0.981** | **100** |
| rs6780220 | 3p22.3 | GLB1 | A | 0.428 | 0.442 | 0.176 | 0.943(0.865-1.027) | 0.475 | 0.986 | 99 |
| rs4722404 | 7p22.2 | CARD11 | C | 0.356 | 0.346 | 0.337 | 1.045(0.956-1.142) | 0.243 | 0.987 | 98 |
| rs7000782 | 8q21.13 | ZBTB10 | T | 0.322 | 0.333 | 0.275 | 0.951(0.869-1.041) | 0.766 | 0.988 | 93 |
| rs7024096 | *9p21.3* | CDKN2B/ DMRTA1 | C | 0.174 | 0.177 | 0.689 | 0.978(0.874-1.093) | 0.650 | 0.988 | 87 |
| **rs7927894** | **11q13.5** | C11orf30 | **T** | **0.185** | **0.168** | **0.033** | **1.129(1.009-1.262)** | **0.237** | **0.988** | **100** |
| **rs878860** | **11p15.4** | OR10A3-NLRP10 | **T** | **0.381** | **0.406** | **0.020** | **0.902(0.827-0.984)** | **0.409** | **0.981** | **100** |
| rs2164983 | 19p13.2 | ACTL9 | A | 0.119 | 0.126 | 0.347 | 0.940(0.826-1.070) | 0.764 | 0.988 | 96 |

MAF, minor allele frequency; CI, confidence interval

rs878860 ($P$ = 0.012, 0.033, 0.020, respectively) was slightly different between AD cases and controls, but none were statistically significant after the Bonferroni correction.

### *Subphenotype stratification analyses*

We further performed a stratified analysis according to AD-associated phenotypes, including family history of atopy, AD with concomitant keratosis pilaris, and the severity of disease.

The distribution of rs7927894 variant T was significantly different between patients with a positive family history of atopy and controls (19.4% vs. 16.8%, $P$ = 0.004, OR = 1.196), and in patients with and without a positive family history of atopy (19.4% vs. 16.7%, $P$ =0.032, OR = 1.201). Its frequency in AD patients without a positive family history of atopy and controls was not different ($P$ =0.960) (Table 3).

The A allele of rs6780220 was preferentially lower in patients with keratosis pilaris than those without keratosis pilaris (38.6% vs. 43.6%, $P$ = 0.024, OR = 0.813) and controls (38.6% vs. 44.2%, $P$ = 0.010, OR = 0.792), respectively, but these differences were not significant after the Bonferroni correction (Table 4).

Furthermore, no significant association was observed between these SNPs and the severity of AD ($P$ > 0.05, data not shown).

## Discussion

AD is a chronic inflammatory skin disorder with an increasing prevalence in industrialized countries.[9] A genetic basis for AD has long been recognized.[2] Recent 2 GWAS for AD and a meta-analysis of GWAS have identified some genetic loci that predispose carriers to AD in European and Japanese populations.[3,5,6] We first attempted to replicate the association of eight SNPs with AD in a Chinese Han population.

In this study, we found that three of SNPS, i.e. rs12634229, rs7927894 and rs878860, were close to the threshold of significance ($P$ = 0.012, 0.033, 0.020, respectively), although none of them reached a significant correlation with AD.

The SNPs rs12634229 and rs878860 were first found to be related to AD in a Japanese cohort.[6] The SNP rs12634229 is in the 3q13.2 region including coiled-coil domain containing 80 (CCDC80), which encodes for a protein involved in the induction of C/EBPα and peroxisome proliferator-activated receptor γ (PPARγ).[10] C/EBPα and C/EBPβ are coexpressed in basal keratinocytes and are upregulated when keratinocytes exit the basal layer and undergo terminal differentiation.[11] PPARγ acts as a negative regulator in immune cells, and a PPARγ agonist markedly suppresses both the expression of thymic stromal lymphopoietin (TSLP) in the skin and the maturation and migration of dendritic cells in a mouse model of atopic dermatitis.[12]

**Table 3.** Distribution of 8 SNPs in different subphenotype of AD patients with atopic family history and controls

| SNP | Minor Allele | MAF | | | Ca1 vs. Control | | Ca2 vs. Control | | Ca1 vs. Ca2 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Ca1 | Ca2 | Control | P | OR(95% CI) | P | OR(95% CI) | P | OR(95% CI) |
| rs12634229 | C | 0.309 | 0.304 | 0.284 | 0.022 | 1.130 (1.018-1.254) | 0.143 | 1.104 (0.967-1.260) | 0.745 | 1.023 (0.891-1.175) |
| rs6780220 | A | 0.424 | 0.434 | 0.442 | 0.134 | 0.929 (0.844-1.023) | 0.596 | 0.968 (0.857-1.093) | 0.537 | 0.960 (0.844-1.092) |
| rs4722404 | C | 0.355 | 0.348 | 0.346 | 0.403 | 1.043 (0.944-1.153) | 0.874 | 1.010 (0.890-1.147) | 0.635 | 1.033 (0.904-1.180) |
| rs7000782 | T | 0.325 | 0.322 | 0.333 | 0.509 | 0.966 (0.873-1.069) | 0.457 | 0.952 (0.837-1.083) | 0.831 | 1.015 (0.886-1.163) |
| rs7024096 | C | 0.171 | 0.172 | 0.177 | 0.425 | 0.959 (0.866-1.062) | 0.584 | 0.964 (0.845-1.1) | 0.949 | 0.995 (0.864-1.147) |
| rs7927894 | **T** | 0.194 | 0.167 | 0.168 | **0.004** | 1.196 (1.058-1.353) | **0.960** | 0.996 (0.847-1.171) | **0.032** | 1.201 (1.016-1.420) |
| rs878860 | T | 0.384 | 0.378 | 0.406 | 0.061 | 0.911 (0.826-1.004) | 0.061 | 0.888 (0.784-1.005) | 0.702 | 1.026 (0.900-1.170) |
| rs2164983 | A | 0.118 | 0.118 | 0.126 | 0.33 | 0.930 (0.804-1.076) | 0.453 | 0.931 (0.773-1.121) | 0.99 | 0.999 (0.820-1.216) |

MAF, minor allele frequency; Ca1, AD with a positive family of atopy ; Ca2, AD with no family history of atopy; CI, confidence interval.

The SNP rs878860 on 11p15.4 includes the OR10A3-NLRP10 gene. OR10A3 is an olfactory receptor family gene, and NLRP10 encodes for a protein that belongs to the NALP protein family but lacks the leucine-rich repeat region. NLRP10 is a NOD-like receptor essential to initiating adaptive immunity by dendritic cells[13] and has an anti-inflammatory role through negative regulatory effects on caspase-1–dependent IL-1β secretion and apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC)-mediated nuclear factor (NF)-κB activation.[14]

The SNP rs7927894 was identified as a susceptibility factor for AD in European population by a GWAS and a meta-analysis of GWAS.[3,5] It was first reported to be related to Crohn's disease.[15] This SNP is on chromosome 11q13.5, located 38 kb downstream of C11orf30. C11orf30 may be involved in DNA damage repair, genomic instability and chromatin remolding, and it is related to the development of breast, ovarian, prostate and pancreatic cancers derived from the epithelium.[16] The potential involvement of C11orf30 in multiple inflammatory and malignant epithelial diseases (atopic dermatitis, Crohn's disease and adenocarcinoma) strongly suggests a role for C11orf30 in epithelial immunity, growth and/or differentiation.[3] Furthermore, the association between rs7927894 and atopic eczema was also replicated in Irish pediatric cases.[17] The rs7927894 variant also showed a statistically Significant association with AD, but not with other disease-related phenotypes in Austrian patients.[18] Simultaneously, we found that it was a suggestive locus in Chinese Han AD cases.

We performed a subgroup analysis, and found that the rs7927894 T allele was significantly related to AD with a family history of atopy. Marenholz et al.[19] replicated the effects of rs7927894[T] on eczema-associated asthma and hay fever independently in German genetic studies of nuclear families with atopic dermatitis, and showed a significantly effect that that observed with eczema. These authors suggested that rs7927894 affects a common atopy phenotype.

The rs6780220 was first found to be related to AD in the Japanese population.[6] It is in the 3p21.33 region within GLB1 encoding β-galactosidase-1. Its associated region is adjacent to the *CCR4* gene, which is expressed by Th2 and regulatory T cells and directs their migration along gradients of the chemokines CCL17 and CCL22. Both chemokines and the receptor are upregulated in allergic disease, making CCR4 a therapeutic target for the treatment of allergy.[20] We also found that rs6780220 was

**Table 4.** Distribution of 8 SNPs in different subphenotype of AD patients with keratosis pilaris and controls

| SNP | Minor Allele | MAF | | | AD with KP vs. Control | | AD without KP vs. Control | | AD with KP vs. AD without KP | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | AD with KP | AD without KP | Control | P | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) |
| rs12634229 | C | 0.333 | 0.307 | 0.284 | 0.014 | 1.261 (1.047-1.519) | 0.027 | 1.117 (1.013-1.231) | 0.202 | 1.129 (0.937-1.362) |
| **rs6780220** | A | 0.386 | 0.436 | 0.442 | **0.010** | 0.792 (0.663-0.947) | 0.566 | 0.974 (0.891-1.065) | **0.024** | 0.813 (0.680-0.973) |
| rs4722404 | C | 0.367 | 0.352 | 0.346 | 0.318 | 1.097 (0.915-1.314) | 0.587 | 1.026 (0.935-1.127) | 0.475 | 1.069 (0.891-1.282) |
| rs7000782 | T | 0.321 | 0.323 | 0.333 | 0.580 | 0.949 (0.787-1.143) | 0.38 | 0.959 (0.872-1.054) | 0.915 | 0.990 (0.820-1.195) |
| rs7024096 | C | 0.166 | 0.171 | 0.177 | 0.383 | 0.929 (0.788-1.096) | 0.44 | 0.963 (0.873-1.061) | 0.685 | 0.965 (0.814-1.144) |
| rs7927894 | T | 0.197 | 0.184 | 0.168 | 0.078 | 1.219 (0.978-1.520) | 0.06 | 1.119 (0.995-1.257) | 0.446 | 1.090 (0.874-1.360) |
| rs878860 | T | 0.374 | 0.382 | 0.406 | 0.140 | 0.874 (0.730-1.046) | 0.03 | 0.904 (0.825-0.991) | 0.711 | 0.966 (0.806-1.158) |
| rs2164983 | A | 0.114 | 0.118 | 0.126 | 0.431 | 0.896 (0.683-1.177) | 0.315 | 0.933 (0.814-1.069) | 0.778 | 0.961 (0.730-1.266) |

MAF, minor allele frequency; KP, keratosis pilaris; CI, confidence interval.

preferentially related to AD with keratosis pilaris, but did not reach significance after correction.

We did not find any of the other five SNPs to be associated with AD, and no SNP was related to the severity of AD disease. One possible reason may be genetic heterogeneity, primarily in terms of racial and regional differences. In addition, the differences in the main clinical characteristics of the patients could explain the lack of association in our study. Compared to others, our study included a lower proportion of positive family history patients (12.3%) and a higher proportion of infant AD patients (85.3%). In this way, the effect of the allele on AD risk could be greater in juvenile and adult AD cases with familial disease, which could have led to a different result among our cases.

In conclusion, we replicated previous studies on some AD susceptibility loci in European and Japanese populations in the Chinese Han population. Our study indicates that rs7927894 (11p13.5) significantly affects the disease phenotype of AD with a family history of atopy. This study may provide novel insight into the genetic pathogenesis of AD and help us to gain a better understanding of disease pathogenesis and clinical evaluation.

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## Conflict of interest

None declared.

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