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ORIGINAL RESEARCH

# Genetic Loci in Phospholipase C-Like 1 (*PLCL1*) are Protective Factors for Allergic Rhinitis in Han Population of Northern Shaanxi, China

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**Background:** Allergic rhinitis (AR) is a common allergic disease in otolaryngology. Its pathogenesis is still unclear. *PLC1* plays a key role in calcium homeostasis and immune response, which is potentially related to AR. We aimed to explore the association between *PLCL1* genetic loci and susceptibility to AR.

**Methods:** We recruited 1975 volunteers to perform an association analysis through SNPStats online software. False-positive report probability (FPRP) analysis was used to detect whether the positive findings were worth noting. Linkage disequilibrium and haplotype analysis were completed through Haploview and SNPStats. The influence of SNP-SNP interaction on AR susceptibility was evaluated through multifactor dimensionality reduction (MDR).

**Results:** The results showed that four genetic loci in *PLCL1* (rs2139049, rs212164068, rs2228135, and rs6738825) are associated with AR susceptibility under multiple genetic models. Allele "A" of *PLCL1*-rs2139049 (OR = 0.85, $p$ = 0.031) or of -rs212164068 (OR = 0.85, $p$ = 0.030), and allele "G" of *PLCL1*-rs6738825 (OR = 0.84, $p$ = 0.022) are significantly associated with reduced AR risk. *PLCL1*-rs2228135 is associated with an increased risk of AR in males or participants older than 43 years of age. FPRP analysis showed that most of positive results are noteworthy findings. Three loci model composed of rs2139049, rs2164068, and rs2228135 is the best model for predicting AR risk ($p$ = 0.0022). In addition, the haplotype "$G_{rs2139049}A_{rs6738825}A_{rs2164068}A_{rs2228135}$" (OR = 0.50, $p$ = 0.033) can reduce the AR risk.

**Conclusion:** Allele "A" of *PLCL1*-rs2139049, allele "A" of -rs212164068, and allele "G" of *PLCL1*-rs6738825 are protective factors of AR in Han population from northern Shaanxi, China.

**Keywords:** allergic rhinitis, *PLCL1*, genetic loci, association analysis

## Introduction

Allergic rhinitis (AR) is a mucosal inflammatory response mediated by specific IgE after nasal mucosal contact with allergens, which leads to a series of clinical symptoms such as nasal exhaustion, sneezing, rhinorrhea and nasal congestion.[1] In various diseases caused by allergic inflammation (allergic rhinitis, specific dermatitis, etc), various immune cells are involved in complex pathological processes (mast cells, T cells, and B cells).[2] Studies have shown that $Ca^{2+}$ mobilization caused by IgE binding to high-affinity receptors on mast cells is the core of immune allergy.[3] At present, the etiology of AR is not completely clear, but the interaction between genetics and environment is involved in the complex pathogenesis of AR.[4,5]

Single nucleotide polymorphisms (SNP) are the widest genetic variation in human genome, which reflect the most basic form of individual DNA sequence variation in the population. More than 90% of human DNA variation is related to SNP.[6] In an AR study with the largest sample size at present, Waage et al identified 41 genetic loci related to AR risk through genome-wide association analysis.[7] In addition, several SNPs have also been found to be associated with susceptibility to AR.[8–10] Nevertheless, the etiology of AR has not been fully understood. Phospholipase c-like 1 (*PLCL1*)

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is a homologous protein of PLC family, which is expressed in various embryos and mature individual organs such as brain, lung and kidney.[11] PLCs play a key role in calcium homeostasis and immune response.[12] Other studies have reported PLCL1 gene polymorphism associated with allergic diseases.[13] According to the above, we suspected *PLCL1* may play an important role in the occurrence and development of AR, and it is expected to become a new biomarker for predicting or diagnosing of AR. No research has been reported on the relationship between allergic rhinitis and *PLCL1* SNPs.

Due to the differences in environmental factors, climate factors and economic levels in different regions of China, the prevalence of AR may be different. Therefore, it is necessary to identify AR susceptible genetic loci for specific populations. Accordingly, this study aimed to conduct a case–control study in the Han population from northern Shaanxi to explore the susceptible genetic loci of *PLCL1* in AR. This study will lay a scientific foundation for the early diagnosis and screening of AR in clinics and provide valuable reference for finding scientific and effective individual prevention and treatment strategies for AR.

# Materials and Methods

## Sample Source

### Experimental Group

We recruited 978 AR patients in the outpatient Department of Otolaryngology Head and Neck Surgery of Shenmu Hospital. The patients mainly came from Han population in Shenmu downtown or surrounding counties (Shenmu Town: 387; Jinjie Town: 109; Daliuta Town: 254; Langanbao Town: 78; Hejiachuan Town: 57; Yingbin Road Street: 93). These patients were tested for allergen-specific IgE and the results were positive. The diagnostic criteria for AR refer to the internationally accepted ARIA guidelines:[14] AR patients include at least two of the clinical symptoms such as nasal congestion, rhinorrhea, sneezing and nasal itching; AR patients present with pale and edema of the nasal mucosa.

### Control Group

During the same period, we recruited 997 healthy Han people in the health examination center of the same hospital (Shenmu Town: 326; Jinjie Town: 110; Daliuta Town: 270; Langanbao Town: 48; Hejiachuan Town: 66; Yingbin Road Street: 177). The inclusion criteria are as follows: no symptoms, signs and family history of AR; no asthma, skin allergies, food allergies and other allergic diseases; no chronic sinusitis, no other inflammations of the nose, tumors, and no history of respiratory tract infection within the past month; No history of drug use in the past month; no history of serious heart, liver, lung, kidney and other diseases and tumors.

After the two groups of volunteers were recruited, we obtained the epidemiological data (name, age, gender, height, weight, region, etc) of all volunteers by referring to medical records and questionnaire survey. The study was conducted after obtaining the approval of the Medical Ethics Committee of Shenmu City Hospital. After the two groups of volunteers were recruited, we obtained the epidemiological data (name, age, sex, height, weight, region, etc) of all volunteers by referring to medical records and questionnaire survey. The follow-up study was conducted after obtaining approval from the Medical Ethics Committee of Shenmu City Hospital. Before blood collection, the staff will fully inform the volunteers of the purpose and significance of the experiment, and the possible bodily injury and accident in the blood collection process, and ensure that the relevant information of the volunteers is strictly confidential. After informed consent of the volunteers, 2–4mL peripheral venous blood was collected and stored in a −80°C ultra-low temperature refrigerator for use.

## Selection of SNPs

First, the physical position of the *PLCL1* was obtained through online tool (e!GRCh37: http://asia.ensembl.org/Homo_sapiens/Info/Index), and it was on the Chromosome 2: 197804593–198572581. Then, files related to *PLCL1* gene variants in CHB and CHS populations were downloaded using the online conversion window (VCF to PED: http://grch37.ensembl.org/Homo_sapiens/Tools/VcftoPed). Finally, we selected rs2139049, rs6738825, rs2164068, and rs2228135 of *PLCL1* as the candidate genetic loci over Haploview software. The software-specific setting conditions are as follows:Tagger $r^2$> 0.8, Min Genotype >75%, MAF>0.05 and HWE>0.01.

## DNA Extraction, Primer Design and Genotyping

We used the kit (GoldMag Co. Ltd. Xi'an, China) to extract and purify whole-genome DNA from serum samples. All primers of candidate genetic loci were designed by MassARRAY Assay Design software. Primer details for all candidate genetic loci are summarized in Supplemental Table 1. rs2139049, rs6738825, rs2164068, and rs2228135 were genotyped using MassARRAY®-IPLEX SNP genotyping technique.

## Statistical Analysis of Data

We used HaploReg v4.1 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) to predict the potential function of candidate genetic loci. The information about candidate genetic loci can be obtained from dbSNP online database (https://www.ncbi.nlm.nih.gov/snp/). SPSS 22.0 software (SPSS Inc., Chicago, IL, USA) was used to complete statistical analysis. In this study, the association between AR susceptibility and candidate genetic loci was completed by SNPStats (https://www.snpstats.net/start.htm?q=snpstats/start.htm). Impact of candidate genetic loci on AR risk can be evaluated over odds ratios (OR) and 95% confidence intervals (CI). In addition, all the results were adjusted by the confounding factors (age, gender or BMI) to avoid the influence of confounding factors on the accuracy of results. In addition, we also used false-positive report probability (FPRP) analysis to detect whether all positive results are noteworthy at a prior probability level of 0.25 and FPRP threshold of 0.2. Haploview 4.2 software and SNPStats online software were used to perform the haplotype analysis of candidate SNPs and evaluation of linkage disequilibrium (LD). Finally, the interaction of candidate SNPs in LC risk was evaluated by multifactor dimensionality reduction (MDR). The $p < 0.05$ indicated statistically significant.

# Results

The average ages of subjects in case and control groups were 42.60 ± 10.38 and 43.80 ± 8.19 years, respectively. There are 377 (38.5%) males and 601 (61.5%) females in the case group, and 345 (34.6%) males and 652 (65.4%) females in the control group. The average BMI of subjects in case and control groups were 24.80 ± 3.62 and 24.88 ± 3.65, respectively. In addition, 270 (27.1%) AR patients came from Blown-Sand region and 727 (72.9%) from Hilly Loess; 254 (26.0%) healthy participants came from Blown-Sand region and 724 (74.0%) from Hilly Loess. The basic information of the participants can be found in Table 1.

## Genotyping and Information About Candidate SNPs

Genotyping for the four *PLCL1* candidate genetic loci (rs2139049, rs6738825, rs2164068, and rs2228135) have been successfully completed. The HaploReg showed that the rs2139049, rs6738825, rs2164068 were all intronic variants in *PLCL1* and rs2228135 was synonymous variants in *PLCL1*. Candidate genetic loci all met with Hardy–Weinberg

**Table 1** Characteristics of Patients with AR and Healthy Individuals

| Characteristics | | Cases | Control | *p* |
|---|---|---|---|---|
| | | n = 978 | n = 997 | |
| Age (years) | Mean ± SD | 42.60 ± 10.38 | 43.80 ± 8.19 | 0.004[a] |
| | ≤43 | 491 (50.2%) | 424 (42.5%) | |
| | >43 | 487 (49.8%) | 573 (57.5%) | |
| Gender | Male | 377 (38.5%) | 345 (34.6%) | 0.076[b] |
| | Female | 601 (61.5%) | 652 (65.4%) | |
| BMI (kg/m$^2$) | Mean ± SD | 24.80 ± 3.62 | 24.88 ± 3.65 | 0.631[a] |
| | ≤24 | 483 (49.4%) | 470 (47.1%) | |
| | >24 | 495 (50.6%) | 527 (52.9%) | |
| Area | Blown-sand region | 270 (27.1%) | 254 (26.0%) | 0.610[b] |
| | Hilly loess | 727 (72.9%) | 724 (74.0%) | |

**Note**: [a]Represents the p value calculated by the *t*-test; [b]represents the p value calculated by the chi-square test.
**Abbreviation**: AR, allergic rhinitis.

**Table 2** The Basic Information and HWE About the Candidate SNPs of *PLCL1*

| SNP ID | Function | Chr: Position | Alleles (A/B) | MAF | | HWE (*P* value) | Haploreg 4.1 |
|---|---|---|---|---|---|---|---|
| | | | | Cases | Controls | | |
| rs2139049 | Intronic | 2: 198022936 | A/G | 0.21 | 0.24 | 0.100 | Motifs changed; Selected eQTL hits |
| rs6738825 | Intronic | 2: 198032171 | G/A | 0.21 | 0.24 | 0.084 | Enhancer histone marks; Motifs changed; NHGRI/EBI GWAS hits; Selected eQTL hits |
| rs2164068 | Intronic | 2: 198079128 | A/T | 0.22 | 0.25 | 0.050 | Motifs changed; GRASP QTL Hits; Selected eQTL hits |
| rs2228135 | Synonymous | 2: 198085305 | G/A | 0.34 | 0.32 | 0.380 | SiPhy cons; GRASP QTL Hits; Selected eQTL hits |

**Note**: *P* > 0.05 indicates that the genotypes were in Hard–Weinberg Equilibrium; "-" indicates data missing.
**Abbreviations**: A, minor allele; B, wild-type allele; HWE, Hardy–Weinberg equilibrium; SNP, Single nucleotide polymorphisms; MAF, minor allele frequency.

equilibrium (HWE $p$>5%). We also used HaploReg online software to predict the potential functions of genetic loci and found that candidate genetic loci in *PLCL1* may be regulated by a variety of factors (Table 2).

## *PLCL1* Genetic Loci and Susceptibility to AR (Overall Analysis)

### Overall Analysis

The association analysis showed that three candidate genetic loci in *PLCL1* (rs2139049, rs6738825, and rs2164068) are associated with susceptibility to AR (Table 3). Specifically, compared with "G" or "GG", allele "A" or homozygous genotype "AA" of *PLCL1*-rs2139049can significantly reduce AR risk (A: OR (95% CI) = 0.85 (0.73–0.98), $p$ = 0.031; AA: OR (95% CI) = 0.44 (0.26–0.74), $p$ = 0.002). And *PLCL1*-rs2139049is significantly associated with susceptibility to AR under multiple genetic models (recessive: OR (95% CI) = 0.46 (0.27–0.76), $p$ = 0.002; log-additive: OR (95% CI) = 0.83 (0.71–0.97), $p$ = 0.021).

**Table 3** Genetic Variants in *PLCL1* Associated with Susceptibility of AR

| SNP ID | Model | Genotype | Control | Case | OR (95% CI) | *p* |
|---|---|---|---|---|---|---|
| rs2139049 | Allele | G | 1513 (75.9%) | 1539 (78.8%) | 1 | |
| | | A | 481 (24.1%) | 415 (21.2%) | 0.85 (0.73–0.98) | **0.031** |
| | Codominant | GG | 564 (56.6%) | 584 (59.8%) | 1 | |
| | | AG | 385 (38.6%) | 371 (38%) | 0.93 (0.77–1.11) | 0.413 |
| | | AA | 48 (4.8%) | 22 (2.2%) | 0.44 (0.26–0.74) | **0.002** |
| | Dominant | GG | 564 (56.6%) | 584 (59.8%) | 1 | 0.140 |
| | | AG-AA | 433 (43.4%) | 393 (40.2%) | 0.87 (0.73–1.04) | |
| | Recessive | GG-AG | 949 (95.2%) | 955 (97.8%) | 1 | **0.002** |
| | | AA | 48 (4.8%) | 22 (2.2%) | 0.46 (0.27–0.76) | |
| | Overdominant | GG-AA | 612 (61.4%) | 606 (62%) | 1 | 0.730 |
| | | AG | 385 (38.6%) | 371 (38%) | 0.97 (0.81–1.16) | |
| | Log-additive | — | — | — | 0.83 (0.71–0.97) | **0.021** |
| rs6738825 | Allele | A | 1501 (75.7%) | 1535 (78.6%) | 1 | |
| | | G | 481 (24.3%) | 417 (21.4%) | 0.84 (0.73–0.98) | **0.022** |
| | Codominant | AA | 558 (56.3%) | 581 (59.5%) | 1 | |
| | | GA | 385 (38.9%) | 373 (38.2%) | 0.93 (0.77–1.12) | 0.428 |
| | | GG | 48 (4.8%) | 22 (2.2%) | 0.44 (0.26–0.74) | **0.002** |
| | Dominant | AA | 558 (56.3%) | 581 (59.5%) | 1 | 0.140 |
| | | GA-GG | 433 (43.7%) | 395 (40.5%) | 0.87 (0.73–1.05) | |
| | Recessive | AA-GA | 943 (95.2%) | 954 (97.8%) | 1 | **0.002** |
| | | GG | 48 (4.8%) | 22 (2.2%) | 0.46 (0.27–0.76) | |
| | Overdominant | AA-GG | 606 (61.1%) | 603 (61.8%) | 1 | 0.750 |
| | | GA | 385 (38.9%) | 373 (38.2%) | 0.97 (0.81–1.17) | |
| | Log-additive | — | — | — | 0.83 (0.71–0.97) | **0.023** |

(*Continued*)

**Table 3** (Continued).

| SNP ID | Model | Genotype | Control | Case | OR (95% CI) | *p* |
|---|---|---|---|---|---|---|
| rs2164068 | Allele | T | 1499 (75.3%) | 1529 (78.3%) | 1 | |
| | | A | 493 (24.7%) | 423 (21.7%) | 0.85 (0.73–0.98) | **0.030** |
| | Codominant | TT | 552 (55.4%) | 577 (59.1%) | 1 | |
| | | TA | 395 (39.7%) | 375 (38.4%) | 0.91 (0.75–1.09) | 0.292 |
| | | AA | 49 (4.9%) | 24 (2.5%) | 0.46 (0.28–0.77) | **0.003** |
| | Dominant | TT | 552 (55.4%) | 577 (59.1%) | 1 | 0.092 |
| | | TA-AA | 444 (44.6%) | 399 (40.9%) | 0.86 (0.72–1.03) | |
| | Recessive | TT-TA | 947 (95.1%) | 952 (97.5%) | 1 | **0.003** |
| | | AA | 49 (4.9%) | 24 (2.5%) | 0.48 (0.29–0.80) | |
| | Overdominant | TT-AA | 601 (60.3%) | 601 (61.6%) | 1 | 0.560 |
| | | TA | 395 (39.7%) | 375 (38.4%) | 0.95 (0.79–1.14) | |
| | Log-additive | — | — | — | 0.82 (0.70–0.96) | **0.015** |
| rs2228135 | Allele | A | 1356 68.2(%) | 1281 (65.6%) | 1 | |
| | | G | 632 (31.8%) | 671 (34.4%) | 1.12 (0.98–1.28) | 0.085 |
| | Codominant | AA | 456 (45.9%) | 414 (42.4%) | 1 | |
| | | GA | 444 (44.7%) | 453 (46.4%) | 1.12 (0.93–1.36) | 0.221 |
| | | GG | 94 (9.5%) | 109 (11.2%) | 1.27 (0.93–1.73) | 0.126 |
| | Dominant | AA | 456 (45.9%) | 414 (42.4%) | 1 | 0.130 |
| | | GA-GG | 538 (54.1%) | 562 (57.6%) | 1.15 (0.96–1.37) | |
| | Recessive | AA-GA | 900 (90.5%) | 867 (88.8%) | 1 | 0.230 |
| | | GG | 94 (9.5%) | 109 (11.2%) | 1.20 (0.89–1.60) | |
| | Overdominant | AA-GG | 550 (55.3%) | 523 (53.6%) | 1 | 0.430 |
| | | GA | 444 (44.7%) | 453 (46.4%) | 1.07 (0.90–1.28) | |
| | Log-additive | — | — | — | 1.13 (0.98–1.29) | 0.085 |

**Notes**: "-" indicates Log-additive model. "p < 0.05" and bold text represent statistical significance.
**Abbreviations**: AR, allergic rhinitis; SNP, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

Compared with "A" or "AA", allele "G" or homozygous genotype "GG" of *PLCL1*-rs6738825 can significantly reduce AR risk (G: OR (95% CI) = 0.84 (0.73–0.98), $p = 0.022$; GG: OR (95% CI) = 0.44 (0.26–0.74), $p = 0.002$). And *PLCL1*-rs6738825 is significantly associated with susceptibility to AR under log-additive model (OR (95% CI) = 0.83 (0.71–0.97), $p = 0.023$). Compared with "T" or "TT", allele "A" or homozygous genotype "AA" of *PLCL1*-rs2164068 can significantly reduce AR risk (A: OR (95% CI) = 0.85 (0.73–0.98), $p = 0.030$; AA: OR (95% CI) = 0.46 (0.28–0.77), $p = 0.003$). And *PLCL1*-rs2164068 is significantly associated with susceptibility to AR under multiple genetic models (recessive: OR (95% CI) = 0.48 (0.29–0.80), $p = 0.003$; log-additive: OR (95% CI) = 0.82 (0.70–0.96), $p = 0.015$).

In addition, we found no evidence that *PLCL1*-rs2228135 have association with susceptibility to AR in overall analysis.

## *PLCL1* Genetic Loci and Susceptibility to AR (Subgroup Analysis)

### Age (>43 Years)

The association analysis showed that three candidate genetic loci in *PLCL1* are associated with reducing risk of AR among participants older than 43 years old (Table 4). Specifically, allele "A" or homozygous genotype "AA" of *PLCL1*-rs2139049 can significantly reduce AR risk (A: OR (95% CI) = 0.74 (0.61–0.92), $p = 0.005$; AA: OR (95% CI) = 0.21 (0.08–0.52), $p = 0.001$). And *PLCL1*-rs2139049 is significantly associated with susceptibility to AR under multiple genetic models (recessive: OR (95% CI) = 0.22 (0.09–0.54), $p = 0.0002$; log-additive: OR (95% CI) = 0.73 (0.58–0.91), $p = 0.005$). Compared with "A" or "AA", allele "G" or homozygous genotype "GG" of *PLCL1*-rs6738825 can significantly reduce AR risk (G: OR (95% CI) = 0.76 (0.62–0.93), $p = 0.008$; GG: OR (95% CI) = 0.25 (0.11–0.59), $p = 0.002$). And *PLCL1*-rs6738825 is significantly associated with susceptibility to AR under recessive (OR (95% CI) = 0.27 (0.11–0.62), $p = 0.001$) and log-additive model (OR (95% CI) = 0.74 (0.59–0.93), $p = 0.009$). The allele "A" or

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**Table 4** Genetic Variants in *PLCL1* Associated with Susceptibility of AR in the Subgroup Analysis (Age and Gender)

| SNP ID | Model | GenoType | ≤43 Years Old | | >43 Years Old | | Female | | Male | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* |
| rs2139049 | Allele | G | 1 | | 1 | | 1 | | 1 | |
| | | A | 0.98 (0.79–1.22) | 0.868 | 0.74 (0.61–0.92) | **0.005** | 0.86 (0.72–1.04) | 0.118 | 0.83 (0.65–1.07) | 0.152 |
| | Codominant | GG | 1 | | 1 | | 1 | | 1 | |
| | | AG | 1.03 (0.78–1.36) | 0.825 | 0.87 (0.67–1.12) | 0.277 | 0.87 (0.69–1.10) | 0.254 | 1.02 (0.76–1.39) | 0.881 |
| | | AA | 0.74 (0.36–1.51) | 0.403 | 0.21 (0.08–0.52) | **0.001** | 0.66 (0.37–1.15) | 0.141 | / | / |
| | Dominant | GG | 1 | 0.990 | 1 | 0.065 | 1 | 0.160 | 1 | 0.580 |
| | | AG-AA | 1.00 (0.76–1.31) | | 0.79 (0.61–1.01) | | 0.85 (0.68–1.07) | | 0.92 (0.68–1.24) | |
| | Recessive | GG-AG | 1 | 0.380 | 1 | **0.0002** | 1 | 0.190 | 1 | / |
| | | AA | 0.73 (0.36–1.48) | | 0.22 (0.09–0.54) | | 0.70 (0.40–1.21) | | / | |
| | Overdominant | GG-AA | 1 | 0.730 | 1 | 0.590 | 1 | 0.380 | 1 | 0.530 |
| | | AG | 1.05 (0.80–1.38) | | 0.93 (0.72–1.20) | | 0.90 (0.72–1.13) | | 1.10 (0.81–1.49) | |
| | Log-additive | — | 0.97 (0.76–1.22) | 0.780 | 0.73 (0.58–0.91) | **0.005** | 0.85 (0.70–1.03) | 0.099 | 0.80 (0.61–1.05) | 0.110 |
| rs6738825 | Allele | A | 1 | | 1 | | 1 | | 1 | |
| | | G | 0.97 (0.78–1.21) | 0.767 | 0.76 (0.62–0.93) | **0.008** | 0.88 (0.73–1.05) | 0.160 | 0.81 (0.63–1.04) | 0.102 |
| | Codominant | AA | 1 | | 1 | | 1 | | 1 | |
| | | GA | 1.03 (0.78–1.36) | 0.838 | 0.87 (0.67–1.13) | 0.295 | 0.89 (0.71–1.13) | 0.347 | 0.99 (0.73–1.34) | 0.949 |
| | | GG | 0.68 (0.33–1.41) | 0.299 | 0.25 (0.11–0.59) | **0.002** | 0.67 (0.38–1.17) | 0.156 | / | / |
| | Dominant | AA | 1 | 0.960 | 1 | 0.081 | 1 | 0.230 | 1 | 0.440 |
| | | GA-GG | 0.99 (0.76–1.30) | | 0.80 (0.62–1.03) | | 0.87 (0.70–1.09) | | 0.89 (0.66–1.20) | |
| | Recessive | AA-GA | 1 | 0.280 | 1 | **0.001** | 1 | 0.200 | 1 | / |
| | | GG | 0.67 (0.33–1.38) | | 0.27 (0.11–0.62) | | 0.70 (0.40–1.21) | | / | |
| | Overdominant | AA-GG | 1 | 0.720 | 1 | 0.590 | 1 | 0.500 | 1 | 0.670 |
| | | GA | 1.05 (0.80–1.39) | | 0.93 (0.72–1.21) | | 0.92 (0.73–1.16) | | 1.07 (0.79–1.44) | |
| | Log-additive | — | 0.95 (0.75–1.21) | 0.690 | 0.74 (0.59–0.93) | **0.009** | 0.87 (0.71–1.05) | 0.140 | 0.78 (0.59–1.02) | 0.071 |
| rs2164068 | Allele | T | 1 | | 1 | | 1 | | 1 | |
| | | A | 0.96 (0.77–1.19) | 0.715 | 0.74 (0.60–0.91) | **0.004** | 0.84 (0.70–1.01) | 0.068 | 0.85 (0.66–1.09) | 0.199 |
| | Codominant | TT | 1 | | 1 | | 1 | 0.150 | 1 | |
| | | TA | 1.01 (0.76–1.33) | 0.951 | 0.84 (0.65–1.09) | 0.179 | 0.83 (0.66–1.05) | | 1.05 (0.78–1.43) | 0.739 |
| | | AA | 0.70 (0.35–1.4) | 0.310 | 0.25 (0.11–0.59) | **0.002** | 0.66 (0.38–1.16) | | 0.11 (0.02–0.46) | **0.003** |
| | Dominant | TT | 1 | 0.850 | 1 | **0.044** | 1 | 0.075 | 1 | 0.690 |
| | | TA-AA | 0.97 (0.74–1.28) | | 0.77 (0.60–0.99) | | 0.82 (0.65–1.02) | | 0.94 (0.70–1.27) | |
| | Recessive | TT-TA | 1 | 0.300 | 1 | **0.001** | 1 | 0.230 | 1 | **0.0001** |
| | | AA | 0.70 (0.35–1.38) | | 0.27 (0.12–0.63) | | 0.71 (0.41–1.24) | | 0.10 (0.02–0.46) | |
| | Overdominant | TT-AA | 1 | 0.820 | 1 | 0.400 | 1 | 0.190 | 1 | 0.420 |
| | | TA | 1.03 (0.78–1.36) | | 0.90 (0.69–1.16) | | 0.86 (0.68–1.08) | | 1.13 (0.84–1.53) | |
| | Log-additive | — | 0.94 (0.74–1.19) | 0.600 | 0.73 (0.58–0.91) | **0.005** | 0.83 (0.68–1.00) | 0.051 | 0.82 (0.63–1.08) | 0.150 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| rs2228135 | Allele | A | 1 | | 1 | | 1 | | 1 | |
| | | G | 1.01 (0.83–1.23) | 0.890 | 1.22 (1.02–1.47) | **0.031** | 1.08 (0.92–1.28) | 0.348 | 1.2 (0.96–1.50) | 0.105 |
| | Codominant | AA | 1 | | 1 | | 1 | | 1 | |
| | | GA | 1.00 (0.75–1.32) | 0.981 | 1.29 (0.99–1.68) | 0.055 | 0.83 (0.66–1.05) | 0.118 | 1.41 (1.03–1.92) | **0.031** |
| | | GG | 1.11 (0.71–1.73) | 0.659 | 1.43 (0.92–2.23) | 0.114 | 0.66 (0.37–1.16) | 0.148 | 1.20 (0.72–2.00) | 0.479 |
| | Dominant | AA | 1 | 0.900 | 1 | **0.032** | 1 | 0.730 | 1 | **0.035** |
| | | GA-GG | 1.02 (0.78–1.33) | | 1.32 (1.02–1.69) | | 1.04 (0.83–1.30) | | 1.37 (1.02–1.85) | |
| | Recessive | AA-GA | 1 | 0.630 | 1 | 0.290 | 1 | 0.140 | 1 | 0.930 |
| | | GG | 1.11 (0.73–1.69) | | 1.25 (0.82–1.91) | | 1.32 (0.92–1.90) | | 1.02 (0.63–1.66) | |
| | Overdominant | AA-GG | 1 | 0.860 | 1 | 0.130 | 1 | | 1 | **0.040** |
| | | GA | 0.98 (0.75–1.28) | | 1.21 (0.94–1.56) | | 0.99 (0.78–1.25) | 0.922 | 1.36 (1.01–1.83) | |
| | Log-additive | — | 1.03 (0.85–1.26) | 0.750 | 1.23 (1.02–1.49) | **0.034** | 1.31 (0.89–1.93) | 0.167 | 1.21 (0.96–1.51) | 0.100 |

**Notes**: "-" indicates Log-additive model; "/" indicates that the data are missing. "$p < 0.05$" and bold text represent statistical significance.
**Abbreviations**: AR, allergic rhinitis; SNP, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.


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homozygous genotype "AA" of *PLCL1*-rs2164068 can significantly reduce AR risk (A: OR (95% CI) = 0.74 (0.60–0.91), $p = 0.004$; AA: OR (95% CI) = 0.25 (0.11–0.59), $p = 0.002$). And *PLCL1*-rs2164068 is significantly associated with susceptibility to AR under multiple genetic models (dominant: OR (95% CI) = 0.77 (0.60–0.99), $p = 0.044$; recessive: OR (95% CI) = 0.27 (0.12–0.63), $p = 0.001$; log-additive: OR (95% CI) = 0.73 (0.58–0.91), $p = 0.005$).

In addition, *PLCL1*-rs2228135 is significant associated with increasing risk of AR (G: OR (95% CI) = 1.22 (1.02–1.47), $p = 0.031$; dominant genetic model: OR (95% CI) = 1.32 (1.02–1.69), $p = 0.032$; log-additive genetic model: OR (95% CI) = 1.23 (1.02–1.49), $p = 0.034$).

### Age (≤43 Years)

The results showed that no candidate genetic locus has association with susceptibility to AR among participants ≤43 years old.

### Gender (Male)

Among male participants, we have found (Table 4) that *PLCL1*-rs2164068 is significantly associated with susceptibility to AR (AA: OR (95% CI) = 0.11 (0.02–0.46), $p = 0.003$; recessive genetic model: OR (95% CI) = 0.10 (0.02–0.46), $p = 0.0001$). *PLCL1*-rs2228135 is significant associated with increasing risk of AR (GA: OR (95% CI) = 1.41 (1.03–1.92), $p = 0.031$; dominant genetic model: OR (95% CI) =1.37 (1.02–1.85), $p = 0.035$; overdominant genetic model: OR (95% CI) = 1.36 (1.01–1.83), $p = 0.040$).

In addition, *PLCL1*-rs2139049 and -rs6738825 are not associated with susceptibility to AR among male participants.

### Gender (Female)

The results showed that no candidate genetic locus has association with susceptibility to AR among female participants.

### BMI (≤24 kg/m$^2$)

Among participants with BMI ≤ 24 kg/m$^2$ (Table 5), *PLCL1*-rs2139049 is significantly associated with reducing risk of AR (allele "A": OR (95% CI) = 0.76 (0.61–0.94), $p = 0.012$; genotype "AA": OR (95% CI) = 0.39 (0.19–0.80), $p = 0.010$; dominant genetic model: OR (95% CI) = 0.77 (0.59–0.99), $p = 0.043$; recessive genetic model: OR (95% CI) = 0.43 (0.21–0.86), $p = 0.013$; log-additive genetic model: OR (95% CI) = 0.75 (0.60–0.93), $p = 0.010$). *PLCL1*-rs6738825 is significantly associated with reducing risk of AR (allele "G": OR (95% CI) = 0.75 (0.61–0.93), $p = 0.010$; genotype "GG": OR (95% CI) = 0.36 (0.17–0.74), $p = 0.006$; dominant genetic model: OR (95% CI) = 0.77 (0.59–0.99), $p = 0.043$; recessive genetic model: OR (95% CI) = 0.39 (0.19–0.79), $p = 0.007$; log-additive genetic model: OR (95% CI) = 0.74 (0.59–0.92), $p = 0.008$). *PLCL1*-rs2164068 is significantly associated with reducing risk of AR (allele "A": OR (95% CI) = 0.76 (0.61–0.94), $p = 0.011$; genotype "AA": OR (95% CI) = 0.34 (0.16–0.69), $p = 0.003$; recessive genetic model: OR (95% CI) = 0.36 (0.18–0.73), $p = 0.003$; log-additive genetic model: OR (95% CI) = 0.74 (0.59–0.93), $p = 0.009$).

In addition, *PLCL1*-rs2228135 is not associated with susceptibility to AR among participants with BMI ≤24 kg/m$^2$.

### BMI (>24 kg/m$^2$)

The results showed (Table 5) that no candidate genetic loci has association with susceptibility to AR among participants with BMI >24 kg/m$^2$.

### Region (Blown-Sand Region)

We also performed stratified analysis by dividing participants according to their region. Among the participants from Blown-Sand region (Table 5), *PLCL1*-rs2139049 is significantly associated with reducing risk of AR (allele "A": OR (95% CI) = 0.65 (0.48–0.86), $p = 0.003$; genotype "AA": OR (95% CI) = 0.06 (0.01–0.43), $p = 0.006$; dominant genetic model: OR (95% CI) = 0.66 (0.46–0.93), $p = 0.019$; recessive genetic model: OR (95% CI) = 0.06 (0.01–0.49), $p = 0.0001$; log-additive genetic model: OR (95% CI) = 0.60 (0.43–0.82), $p = 0.001$). *PLCL1*-rs6738825 is significantly associated with reducing risk of AR (allele "G": OR (95% CI) = 0.67 (0.50–0.90), $p = 0.007$; genotype "GG": OR (95% CI) = 0.06 (0.01–0.45), $p = 0.006$; recessive genetic model: OR (95% CI) = 0.06 (0.01–0.49), $p = 0.0001$; log-additive genetic model: OR (95% CI) = 0.64 (0.46–0.87), $p = 0.005$). We also have found evidence that *PLCL1*-rs2164068 is

**Table 5** Genetic Variants in *PLCL1* Associated with Susceptibility of AR in the Subgroup Analysis (BMI and Region)

| SNP ID | Model | Genotype | BMI ≤24 kg/m$^2$ | | BMI >24 kg/m$^2$ | | Blown-Sand Region | | Hilly Loess | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* |
| rs2139049 | Allele | G | 1 | | 1 | | 1 | | 1 | |
| | | A | 0.76 (0.61–0.94) | **0.012** | 0.94 (0.76–1.16) | 0.552 | 0.65 (0.48–0.86) | **0.003** | 0.94 (0.79–1.12) | 0.471 |
| | Codominant | GG | 1 | | 1 | | 1 | | 1 | |
| | | AG | 0.82 (0.63–1.07) | 0.140 | 1.03 (0.80–1.34) | 0.801 | 0.74 (0.52–1.06) | 0.098 | 1.00 (0.80–1.24) | 0.991 |
| | | AA | 0.39 (0.19–0.80) | **0.010** | 0.5 (0.23–1.08) | 0.078 | 0.06 (0.01–0.43) | **0.006** | 0.63 (0.36–1.11) | 0.112 |
| | Dominant | GG | 1 | **0.043** | 1 | 0.880 | 1 | **0.019** | 1 | 0.740 |
| | | AG-AA | 0.77 (0.59–0.99) | | 0.98 (0.76–1.26) | | 0.66 (0.46–0.93) | | 0.96 (0.78–1.19) | |
| | Recessive | GG-AG | 1 | **0.013** | 1 | 0.061 | 1 | **0.0001** | 1 | 0.110 |
| | | AA | 0.43 (0.21–0.86) | | 0.49 (0.23–1.06) | | 0.06 (0.01–0.49) | | 0.63 (0.36–1.11) | |
| | Overdominant | GG-AA | 1 | 0.290 | 1 | 0.610 | 1 | 0.270 | 1 | 0.780 |
| | | AG | 0.87 (0.67–1.13) | | 1.07 (0.83–1.38) | | 0.82 (0.57–1.17) | | 1.03 (0.83–1.28) | |
| | Log-additive | — | 0.75 (0.60–0.93) | **0.010** | 0.92 (0.74–1.15) | 0.480 | 0.60 (0.43–0.82) | **0.001** | 0.93 (0.77–1.11) | 0.410 |
| rs6738825 | Allele | A | 1 | | 1 | | 1 | | 1 | |
| | | G | 0.75 (0.61–0.93) | **0.010** | 0.95 (0.77–1.16) | 0.597 | 0.67 (0.50–0.90) | **0.007** | 0.92 (0.78–1.1) | 0.373 |
| | Codominant | AA | 1 | | 1 | | 1 | | 1 | |
| | | GA | 0.82 (0.63–1.07) | 0.152 | 1.03 (0.80–1.33) | 0.811 | 0.80 (0.56–1.14) | 0.217 | 0.98 (0.79–1.21) | 0.842 |
| | | GG | 0.36 (0.17–0.74) | **0.006** | 0.55 (0.26–1.17) | 0.119 | 0.06 (0.01–0.45) | **0.006** | 0.62 (0.35–1.10) | 0.102 |
| | Dominant | AA | 1 | **0.043** | 1 | 0.910 | 1 | 0.053 | 1 | 0.600 |
| | | GA-GG | 0.77 (0.59–0.99) | | 0.99 (0.77–1.27) | | 0.71 (0.50–1.01) | | 0.95 (0.77–1.17) | |
| | Recessive | AA-GA | 1 | **0.007** | 1 | 0.100 | 1 | **0.0001** | 1 | 0.110 |
| | | GG | 0.39 (0.19–0.79) | | 0.55 (0.26–1.14) | | 0.06 (0.01–0.49) | | 0.63 (0.36–1.11) | |
| | Overdominant | AA-GG | 1 | 0.320 | 1 | 0.640 | 1 | 0.490 | 1 | 0.920 |
| | | GA | 0.88 (0.67–1.14) | | 1.06 (0.82–1.37) | | 0.88 (0.62–1.26) | | 1.01 (0.82–1.25) | |
| | Log-additive | — | 0.74 (0.59–0.92) | **0.008** | 0.93 (0.75–1.16) | 0.540 | 0.64 (0.46–0.87) | **0.005** | 0.91 (0.76–1.10) | 0.320 |
| rs2164068 | Allele | T | 1 | | 1 | | 1 | | 1 | |
| | | A | 0.76 (0.61–0.94) | **0.011** | 0.93 (0.76–1.14) | 0.475 | 0.65 (0.48–0.87) | **0.003** | 0.92 (0.78–1.10) | 0.355 |
| | Codominant | TT | 1 | | 1 | | 1 | | 1 | |
| | | TA | 0.85 (0.65–1.11) | 0.231 | 0.96 (0.74–1.23) | 0.733 | 0.76 (0.53–1.08) | 0.128 | 0.96 (0.78–1.19) | 0.726 |
| | | AA | 0.34 (0.16–0.69) | **0.003** | 0.65 (0.32–1.33) | 0.242 | / | / | 0.67 (0.39–1.15) | 0.145 |
| | Dominant | TT | 1 | 0.061 | 1 | 0.570 | 1 | 0.026 | 1 | 0.520 |
| | | TA-AA | 0.78 (0.60–1.01) | | 0.93 (0.72–1.19) | | 0.67 (0.47–0.95) | | 0.93 (0.76–1.15) | |
| | Recessive | TT-TA | 1 | **0.003** | 1 | 0.250 | 1 | / | 1 | 0.160 |
| | | AA | 0.36 (0.18–0.73) | | 0.67 (0.33–1.35) | | / | | 0.68 (0.40–1.16) | |
| | Overdominant | TT-AA | 1 | 0.480 | 1 | 0.870 | 1 | 0.320 | 1 | 0.940 |
| | | TA | 0.91 (0.70–1.18) | | 0.98 (0.76–1.26) | | 0.84 (0.59–1.19) | | 0.99 (0.80–1.23) | |
| | Log-additive | — | 0.74 (0.59–0.93) | **0.009** | 0.91 (0.73–1.13) | 0.380 | 0.60 (0.43–0.83) | **0.002** | 0.91 (0.76–1.09) | 0.300 |

(*Continued*)

**Table 5** (Continued).

| SNP ID | Model | Genotype | BMI ≤24 kg/m$^2$ | | BMI >24 kg/m$^2$ | | Blown-Sand Region | | Hilly Loess | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* |
| rs2228135 | Allele | A | 1 | | 1 | | 1 | | 1 | |
| | | G | 1.10 (0.91–1.33) | 0.323 | 1.14 (0.95–1.38) | 0.162 | 1.15 (0.89–1.48) | 0.294 | 1.12 (0.96–1.31) | 0.156 |
| | Codominant | AA | 1 | | 1 | | 1 | | 1 | |
| | | GA | 1.05 (0.80–1.37) | 0.753 | 1.20 (0.92–1.55) | 0.177 | 1.07 (0.74–1.56) | 0.726 | 1.16 (0.93–1.44) | 0.187 |
| | | GG | 1.27 (0.82–1.96) | 0.278 | 1.26 (0.81–1.96) | 0.298 | 1.44 (0.82–2.54) | 0.207 | 1.22 (0.85–1.77) | 0.285 |
| | Dominant | AA | 1 | 0.540 | 1 | 0.140 | 1 | 0.480 | 1 | 0.140 |
| | | GA-GG | 1.08 (0.84–1.40) | | 1.21 (0.94–1.55) | | 1.14 (0.80–1.62) | | 1.17 (0.95–1.44) | |
| | Recessive | AA-GA | 1 | 0.300 | 1 | 0.500 | 1 | 0.220 | 1 | 0.470 |
| | | GG | 1.24 (0.82–1.87) | | 1.15 (0.76–1.76) | | 1.39 (0.82–2.36) | | 1.14 (0.80–1.62) | |
| | Overdominant | AA-GG | 1 | 0.970 | 1 | 0.270 | 1 | 0.910 | 1 | 0.290 |
| | | GA | 0.99 (0.77–1.29) | | 1.15 (0.90–1.47) | | 0.98 (0.69–1.39) | | 1.12 (0.91–1.38) | |
| | Log-additive | — | 1.10 (0.91–1.33) | 0.340 | 1.15 (0.95–1.39) | 0.150 | 1.16 (0.89–1.51) | 0.260 | 1.13 (0.96–1.32) | 0.140 |

**Notes**: "-" indicates Log-additive model; "/" indicates that the data are missing. "$p < 0.05$" and bold text represent statistical significance.
**Abbreviations**: AR, allergic rhinitis; SNP, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

significantly associated with reducing risk of AR (allele "A": OR (95% CI) = 0.65 (0.48–0.87), $p = 0.003$; log-additive genetic model: OR (95% CI) = 0.60 (0.43–0.83), $p = 0.002$).

In addition, *PLCL1*-rs2228135 is not associated with susceptibility to AR among participants from Blown-Sand region.

### Region (Hilly Loess)

We have not found any evidence that four candidate genetic loci are associated with participants from Hilly Loess (Table 5).

## FPRP Analysis

At the prior probability level of 0.25 and FPRP threshold of 0.2, most of the positive results in this study are noteworthy findings (Supplemental Table 2).

Specifically, our results showed that *PLCL1*-rs2164068 may be potentially associated with the AR risk among male participants (genotype AA: prior probability = 0.282; recessive: prior probability = 0.328); *PLCL1*-rs2139049 (genotype AA: prior probability = 0.468; recessive: prior probability = 0.520) and *PLCL1*-rs6738825 (genotype GG: prior probability = 0.487; recessive: prior probability = 0.520) may be potentially associated with the AR risk among participants from Blown-Sand region. However, FPRP analysis suggested the above positive results may not be worth noting. Therefore, the conclusions directly concluded from the above results should need further experimental verification to be trustworthy. In addition to the above, other positive results are found worthy of attention.

## SNP-SNP Interaction and AR Risk

As shown in Figure 1, the dendrogram has described the interaction between the four candidate SNPs. The color of the lines in the dendrogram represents the level of redundancy or synergy. The closer the lines are to red the stronger the synergy between genetic loci, the closer they are to blue the more redundant they are. It follows that, interaction between the four candidate genetic loci is redundant. The MDR results showed (Table 6) that three loci model composed of rs2139049, rs2164068, and rs2228135, which can be chosen as the best model for predicting AR risk ($p = 0.0022$), with the best test accuracy of 0.528 and a perfect CVC = 10/10.

## Haplotype Analysis

The result of linkage disequilibrium showed that (Figure 2) the four candidate genetic loci in *PLCL1* (rs2139049, rs6738825, rs2164068, and rs2228135) composed one LD block. And the results of haplotype analysis showed that the haplotype "$G_{rs2139049}A_{rs6738825}A_{rs2164068}A_{rs2228135}$" (OR = 0.50, CI = 0.27–0.95, $p = 0.033$) can reduce the susceptibility to AR (Table 7).

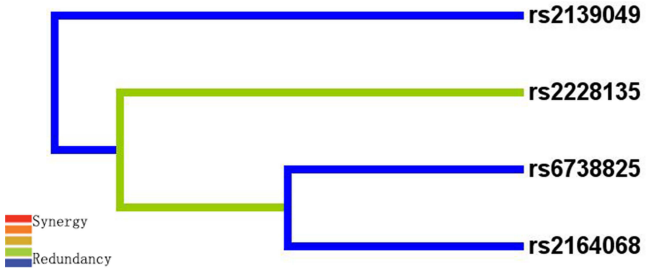


**Figure 1** Multifactor dimensionality reduction (MDR) analysis of interaction between the candidate genetic loci of *PLCL1* (rs2139049, rs6738825, rs2164068, and rs2228135). The color represents the degree of redundancy or synergy between SNP-SNP; the closer the color is to red, the more synergy, and the closer to blue, the more redundancy.

**Table 6** *PLCL1* SNP-SNP Interaction Models Analyzed by the MDR Method

| Model | Training Bal. Acc | Testing Bal. Acc | OR (95% CI) | *p*-value | CVC |
|---|---|---|---|---|---|
| rs2228135 | 0.521 | 0.505 | 1.18 (0.98–1.41) | 0.0759 | 6/10 |
| rs2164068, rs2228135 | 0.526 | 0.506 | 1.31 (1.07–1.61) | **0.0092** | 6/10 |
| rs2139049, rs2164068, rs2228135 | 0.531 | 0.528 | 1.37 (1.12–1.67) | **0.0022** | 10/10 |
| rs2139049, rs6738825, rs2164068, rs2228135 | 0.532 | 0.521 | 1.39 (1.14–1.70) | **0.0013** | 10/10 |

**Note**: *p* values were calculated using $\chi^2$ tests; "p-value < 0.05" and bold text represent statistical significance.
**Abbreviations**: MDR, multifactor dimensionality reduction; Bal. Acc., balanced accuracy; CVC, cross-validation consistency; OR, odds ratio; 95% CI, 95% confidence interval.

## Discussion

The geographical complexity of China leads to differences between different regions in many aspects (geographical characteristics, climatic conditions, economic conditions and living habits, etc.). A number of AR epidemiological studies have found that there are significant regional differences in the prevalence of AR in China, such as Beijing (8.7%),[15] northern grassland (32.4%)[16] and Xilinhot, Inner Mongolia (52.9%).[16] The above studies indicate that there are significant regional differences in the prevalence of AR, so it is of great significance to identify the genetic locus of AR susceptibility in specific populations. In this study, the association between *PLCL1* genetic loci and AR susceptibility was studied in 1975 participants. Association analysis and FPRP results showed that *PLCL1*-rs2139049, -rs6738825, and -rs2164068 were significantly associated with AR risk reduction. In addition, in the subgroup analysis, we also found evidence that *PLCL1*-rs2228135 was significantly associated with the increase in AR risk of Han population of northern Shaanxi. The overall analysis showed that the allele "A" and genotype "AA" of *PLCL1*-rs2139049 or -rs212164068, the allele "G" and genotype "GG" of *PLCL1*-rs6738825 can significantly reduce the risk of AR in Han population of Northern Shaanxi. As we know, this study is the first to study the association between *PLCL1* genetic loci and AR susceptibility, and found valuable positive results.

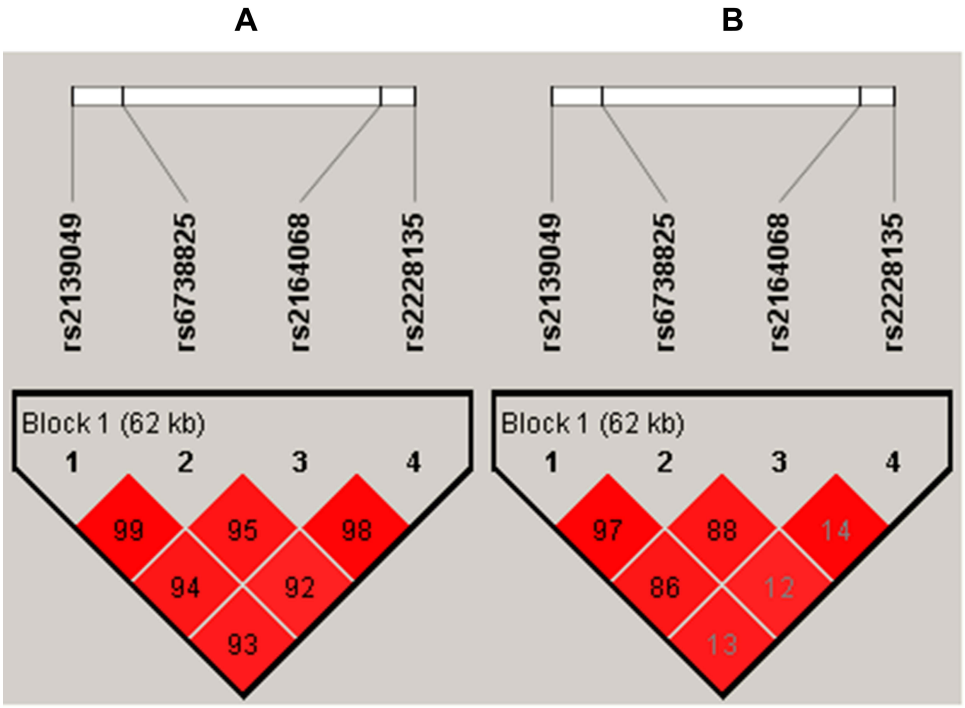


**Figure 2** Haplotype block map for the *PLCL1* genetic loci (rs2139049, rs6738825, rs2164068, and rs2228135). (**A**) The numbers inside the diamonds indicate the D' for pairwise analyses. (**B**) The numbers inside the diamonds indicate the $r^2$ for pairwise analyses. The colors represent the degree of linkage disequilibrium: the redder the color, the stronger the linkage disequilibrium.

**Table 7** Haplotype Analysis of Candidate *PLCL1* Genetic Polymorphisms with AR Risk

| SNP | Haplotype | Freq (Case) | Freq (Control) | Crude Analysis | | Adjusted by Gender, Age, BMI | |
|---|---|---|---|---|---|---|---|
| | | | | OR (95% CI) | *p* | OR (95% CI) | *p* |
| rs2139049\|rs6738825\|rs2164068\|rs2228135 | GATA | 0.436 | 0.428 | 1 | | 1 | |
| rs2139049\|rs6738825\|rs2164068\|rs2228135 | GATG | 0.341 | 0.313 | 1.08 (0.93–1.25) | 0.320 | 1.07 (0.93–1.24) | 0.340 |
| rs2139049\|rs6738825\|rs2164068\|rs2228135 | AGAA | 0.207 | 0.230 | 0.86 (0.73–1.02) | 0.092 | 0.86 (0.72–1.02) | 0.088 |
| rs2139049\|rs6738825\|rs2164068\|rs2228135 | GAAA | 0.007 | 0.014 | 0.51 (0.27–0.96) | **0.037** | 0.50 (0.27–0.95) | **0.033** |
| Rare | **** | 0.015 | 0.010 | 0.68 (0.31–1.47) | 0.330 | 0.67 (0.31–1.47) | 0.320 |

**Note**: "p < 0.05" and bold text represent statistical significance.
**Abbreviations**: AR, allergic rhinitis; SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Researchers have found that age can cause a variety of changes, including immunity, inflammatory patterns and susceptibility to allergic rhinitis.[17,18] Based on this, we grouped the subjects according to age and conducted stratified analysis. The results showed that allele "A" and genotype "AA" of *PLCL1*-rs2139049 or -rs212164068, the allele "G" and genotype "GG" of *PLCL1*-rs6738825 can significantly reduce the risk of AR among participants older than 43 years old. Previous studies have reported that allergic rhinitis symptoms decrease with age.[19] Elderly AR patients have milder symptoms, lower IgE production, and less sensitization than adult AR patients.[20] Based on previous studies and the results of our study, we conjectured that *PLCL1*-rs2139049, -rs212164068, and -rs6738825 played an indispensable role in the low risk of AR in the Han population older than 43 years in northern Shaanxi. In addition, we found evidence that *PLCL1*-rs2228135 was associated with an increased risk of AR in subgroups older than 43 years. Although no evidence was found for the remaining susceptibility to AR in the overall analysis, the FPRP analysis suggested that *PLCL1*-rs2228135 was associated with an increased risk of AR in the subgroup as a noteworthy positive finding. More importantly, we observed that although *PLCL1*-rs2228135 was not associated with AR susceptibility in subgroups less than 43 years, the risk of AR showed an increasing trend (OR > 1 or the value of OR is approaching 1). Based on this, we conjectured that allele "G" of *PLCL1*-rs2228135 is a risk factor for AR in the subgroup older than 43 years, and this genetic factor may be not affected by age. The above are just speculations, further verification of the test is very necessary.

In addition, obesity has an impact on a variety of allergic diseases, including allergic rhinitis, obesity/overweight is identified as a risk factor for AR in children.[21] It is necessary to control the BMI of allergic patients within the normal range.[22] Green et al reported that people who had been diagnosed with allergic rhinitis were exposed to a deteriorating environment for a long time, and the symptoms became worse.[23] According to the influence of the above factors on the susceptibility to AR, we also divided the research objects according to BMI and regional environmental conditions, and conducted stratified analysis. The association results were similar in the subgroups with BMI ≤24 kg/m$^2$ or participants from Blown-Sand region as in the subgroup older than 43 years. *PLCL1*-rs2139049, -rs212164068, -rs6738825 were significantly associated with the reduction of AR risk in study subjects with BMI ≤24 kg/m$^2$ or from Blown-Sand region.

Combined with previous studies and results of our study, it can be further demonstrated that AR is the result of the joint action of environment and genetics. To the best of our knowledge, *PLCL1*-rs2139049, -rs212164068, -rs2228135, and -rs6738825 have not been reported to be associated with susceptibility to AR. The candidate *PLCL1* genetic polymorphism in this study may be expected to be a new target for individualized prevention and treatment of AR among Han population in northern Shaanxi.

*PLCL1* is a homologous protein of PLC family. PLC mainly encodes an IP3-binding protein, competitively binding to IP3, thereby inhibiting IP3R-mediated $Ca^{2+}$ signal transduction, resulting in reduced $Ca^{2+}$ release.[24] $Ca^{2+}$ plays a complex role in initiating and coordinating various cellular processes in human body (including cell necrosis, apoptosis and cell survival).[25,26] A recent study has shown that $Ca^{2+}$ inhibitors can effectively alleviate AR symptoms in mice. Based on the above results, we further speculated that *PLCL1*-rs2139049, -rs212164068, and-rs6738825 might protect

AR by promoting *PLCL1* activity and inhibiting $Ca^{2+}$ release. However, the above is only a speculation, and further molecular mechanism research is necessary to explore how the candidate *PLCL1* loci affect the AR susceptibility of Han population of northern Shaanxi through affecting *PLCL1* activity.

In any case, this study provides a theoretical basis for further research on the pathogenesis of AR. At the same time, it provides a new idea for AR risk assessment and clinical individualized prevention and treatment of Han population of northern Shaanxi province. However, this study has some shortcomings: in order to ensure the reliability and repeatability of the results, a large sample size validation study is necessary. In addition, it is of great interest to conduct larger studies in different regions of the country, which will help to verify the association between *PLCL1* loci and susceptibility to AR in population with other genetic backgrounds. In any case, this study is the first to explore the association between *PLCL1* genetic loci and susceptibility to AR. Positive results were found, that is, *PLCL1*-rs2139049, -rs212164068, -rs2228135, and -rs6738825 are associated with susceptibility to AR among Han population of northern Shaanxi.

## Conclusion

In summary, four genetic loci in *PLCL1* (rs2139049, rs212164068, rs2228135, and rs6738825) are associated with susceptibility to AR. Especially for allele "A" of *PLCL1*-rs2139049 or *PLCL1*-rs212164068, and allele "G" of *PLCL1*-rs6738825 are protective factors for AR in Han population of northern Shaanxi. This study provides a new research idea and lays a reliable theoretical foundation for the early diagnosis and individualized treatment of allergic rhinitis.

## Data Sharing Statement

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

This study complies with the Declaration of Helsinki. The study was conducted under the standard approved by the ethics committee of the Shenmu Hospital. All participants signed informed consent forms before participating in this study.

## Consent for Publication

All authors agreed to publish the manuscript.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no conflicts of interest in this work.

## References


1. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(Suppl 86):8–160. doi:10.1111/j.1398-9995.2007.01620.x
2. Nam JH, Kim WK. The role of TRP channels in allergic inflammation and its clinical relevance. *Curr Med Chem*. 2020;27(9):1446–1468. doi:10.2174/0929867326666181126113015
3. Holowka D, Wilkes M, Stefan C, Baird B. Roles for Ca2+ mobilization and its regulation in mast cell functions: recent progress. *Biochem Soc Trans*. 2016;44(2):505–509. doi:10.1042/BST20150273
4. Li Y, Chen J, Rui X, Li N, Jiang F, Shen J. The association between sixteen genome-wide association studies-related allergic diseases loci and childhood allergic rhinitis in a Chinese Han population. *Cytokine*. 2018;111:162–170. doi:10.1016/j.cyto.2018.08.022
5. Choi BY, Han M, Kwak JW, Kim TH. Genetics and epigenetics in allergic rhinitis. *Genes*. 2021;12(12):2004. doi:10.3390/genes12122004
6. van Veen EM, Brentnall AR, Byers H, et al. Use of single-nucleotide polymorphisms and mammographic density plus classic risk factors for breast cancer risk prediction. *JAMA Oncol*. 2018;4(4):476–482. doi:10.1001/jamaoncol.2017.4881
7. Waage J, Standl M, Curtin JA, et al. Genome-wide association and HLA fine-mapping studies identify risk loci and genetic pathways underlying allergic rhinitis. *Nat Genet*. 2018;50(8):1072–1080. doi:10.1038/s41588-018-0157-1
8. Jiang F, Yan A. IL-4 rs2243250 polymorphism associated with susceptibility to allergic rhinitis: a meta-analysis. *Biosci Rep*. 2021;41(4). doi:10.1042/BSR20210522
9. Joob B, Wiwanitkit V. IL33 rs1342326 gene variation and allergic rhinitis. *Acta paediatrica*. 2020;109(10):2117. doi:10.1111/apa.15227
10. Song Y, Yan Z. Exploring of the molecular mechanism of rhinitis via bioinformatics methods. *Mol Med Rep*. 2018;17(2):3014–3020. doi:10.3892/mmr.2017.8213
11. Wang Q, Chen S, Li Y, et al. Positive association of genetic variations in the phospholipase C-like 1 gene with dermatomyositis in Chinese Han. *Immunol Res*. 2016;64(1):204–212. doi:10.1007/s12026-015-8738-x
12. Ramezanpour N, Nasiri M, Akbarpour OR. Association of rs4618210A>G variant in PLCL2 gene with myocardial infarction: a case-control study in Iran. *J Cardiovasc Thorac Res*. 2020;12(4):303–306. doi:10.34172/jcvtr.2020.49
13. Hinds DA, McMahon G, Kiefer AK, et al. A genome-wide association meta-analysis of self-reported allergy identifies shared and allergy-specific susceptibility loci. *Nat Genet*. 2013;45(8):907–911. doi:10.1038/ng.2686
14. Pawankar R, Bunnag C, Khaltaev N, Bousquet J. Allergic rhinitis and its impact on asthma in Asia Pacific and the ARIA update 2008. *World Allergy Organization J*. 2012;5(Suppl 3):S212–7. doi:10.1186/1939-4551-5-S3-S212
15. Zhang L, Han D, Huang D, et al. Prevalence of self-reported allergic rhinitis in eleven major cities in China. *Int Arch Allergy Immunol*. 2009;149(1):47–57. doi:10.1159/000176306
16. Wang XY, Ma TT, Wang XY, et al. Prevalence of pollen-induced allergic rhinitis with high pollen exposure in grasslands of northern China. *Allergy*. 2018;73(6):1232–1243. doi:10.1111/all.13388
17. Roditi RE, Shin JJ. The influence of age on the relationship between allergic rhinitis and otitis media. *Curr Allergy Asthma Rep*. 2018;18(12):68. doi:10.1007/s11882-018-0826-2
18. Roditi RE, Veling M, Shin JJ. Age: an effect modifier of the association between allergic rhinitis and Otitis media with effusion. *Laryngoscope*. 2016;126(7):1687–1692. doi:10.1002/lary.25682
19. Schoenwetter WF. Allergic rhinitis: epidemiology and natural history. *Allergy Asthma Proc*. 2000;21(1):1–6. doi:10.2500/108854100778248971
20. Ciprandi G, Comite P, Ferrero F, Fontana V, Bruzzone M, Mussap M. Serum allergen-specific IgE, allergic rhinitis severity, and age. *Rhinology*. 2016;54(3):231–238. doi:10.4193/Rhino15.300
21. Han MW, Kim SH, Oh I, Kim YH, Lee J. Obesity can contribute to severe persistent allergic rhinitis in children through leptin and interleukin-1β. *Int Arch Allergy Immunol*. 2021;182(6):546–552. doi:10.1159/000512920
22. Tajima H, Pawankar R. Obesity and adiposity indicators in asthma and allergic rhinitis in children. *Curr Opin Allergy Clin Immunol*. 2019;19(1):7–11. doi:10.1097/ACI.0000000000000504
23. Green RJ, Van Niekerk A, McDonald M, et al. Acute allergic rhinitis. *South African Family Pract*. 2020;62(1):e1–e6. doi:10.4102/safp.v62i1.5154
24. Tsukamoto A, Hayashida Y, Furukawa KS, Ushida T. Spatio-temporal PLC activation in parallel with intracellular Ca2+ wave propagation in mechanically stimulated single MDCK cells. *Cell Calcium*. 2010;47(3):253–263. doi:10.1016/j.ceca.2009.12.008
25. Kania E, Roest G, Vervliet T, Parys JB, Bultynck G. IP(3) receptor-mediated calcium signaling and its role in autophagy in cancer. *Front Oncol*. 2017;7:140. doi:10.3389/fonc.2017.00140
26. Santulli G, Nakashima R, Yuan Q, Marks AR. Intracellular calcium release channels: an update. *J Physiol*. 2017;595(10):3041–3051. doi:10.1113/JP272781