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Genetic Variant rs4982958 at 14q11.2 Is Associated With Allergic Rhinitis in a Chinese Han Population
Running title: 14q11.2 Is a Susceptibility Locus for Allergic Rhinitis

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Abstract

Background: Allergic rhinitis (AR) is one of the most common diseases caused by the combined effects of intrinsic factors (susceptibility genes and immunological status) and the external environment. Analyses of ascendant family history of atopic disease suggest that AR and atopic dermatitis might share a similar genetic background.
Objective: To conduct a case-control study in a Chinese Han population to evaluate the potential influence of single nucleotide polymorphisms (SNPs) at *FLG*, 5q22.1, 11q13.5, 14q11.2 and 20q13.33 on AR.
Methods: Ten SNPs—rs11204971 and rs3126085 at *FLG*, rs10067777, rs7701890, rs13360927, and rs13361382 at 5q22.1, rs6010620 at 20q13.33, rs7936562 and rs7124842 at 11q13.5, and rs4982958 at 14q11.2 were genotyped in 363 cases and 668 controls using the Sequenom MassArray system. Data were analyzed with PLINK 1.07 software.
Results: The T allele of rs4982958 at 14q11.2 was observed to be significantly associated with AR (P=.002, OR=0.73, $P_{Bonferroni}$=.02). Genotype-based association testing revealed that the recessive model might provide the best fit for rs4982958 ($P_{Bonferroni}$=.01). In subphenotype analyses, the rs4982958 T allele was also significantly associated with persistent AR (P=.01) and more than 2 positive skin prick tests (P=.038).
Conclusion: We identified a novel susceptibility locus 14q11.2 for AR that might bear candidate genes conferring susceptibility to AR and affecting disease phenotypes.

Key words: Allergic rhinitis. Genetic. Susceptibility. 14q11.2. Polymorphism.

Resumen

Antecedentes: La rinitis alérgica (RA) es una de las enfermedades más frecuentes causadas por los efectos combinados de factores intrínsecos (genes de susceptibilidad y estado inmunológico) y el ambiente externo. Los análisis de los ascendientes familiares con enfermedad atópica indican que la RA y la dermatitis atópica (DA) podrían compartir antecedentes genéticos similares.
Objetivo: Llevar a cabo un estudio de casos y controles en una población china de la etnia Han para evaluar la posible influencia de los polimorfismos de un solo nucleótido (SNP) en *FLG*, 5q22.1, 11q13.5, 14q11.2 y 20q13.33 en la RA.
Métodos: Se genotiparon diez SNP (rs11204971 y rs3126085 en *FLG*, rs10067777, rs7701890, rs13360927 y rs13361382 en 5q22.1, rs6010620 en 20q13.33, rs7936562 y rs7124842 en 11q13.5, y rs4982958 en 14q11.2) en 363 casos y 668 controles mediante el sistema MassArray de Sequenom. Los datos se analizaron con el software PLINK 1.07.
Resultados: Se observó que el alelo T de rs4982958 en 14q11.2 se asoció de forma significativa a la RA ($p = 0{,}002$, OR = 0,73, $p_{Bonferroni} = 0{,}02$). Las pruebas de asociación basadas en el genotipo revelaron que el modelo recesivo podría ser el que mejor se ajusta a rs4982958 ($p_{Bonferroni} = 0{,}01$). En los análisis de subfenotipo, el alelo T de rs4982958 también se asoció de forma significativa a la RA persistente ($p = 0{,}01$) y más de 2 pruebas de punción cutánea positivas ($p = 0{,}038$).
Conclusión: Se identificó un nuevo locus de susceptibilidad de 14q11.2 para la RA que podría contener genes candidatos que confieren susceptibilidad a la RA y afectan a los fenotipos de la enfermedad.

Palabras clave: Rinitis alérgica. Genético. Susceptibilidad. 14q11.2. Polimorfismo.

Introduction

Allergic rhinitis (AR) is one of the most common diseases caused by the combined interaction between susceptibility genes, the host's environment, and immunological factors [1]. It is characterized by mucosal inflammation following exposure to an allergen. AR has become a global health problem, with prevalences ranging from 9% to 42% in the general population worldwide [2] and from 8.7% to 24.1% in China [3].

Atopic diseases, such as AR, asthma, and atopic dermatitis (AD), are closely related to the clinical phenotypes that are often observed with allergic processes. A number of genetic factors had been observed in patients with atopic diseases [4], which often show stronger familial and intraindividual clustering, suggesting that common predisposing genetic factors might be involved in different diseases [5]. We recently completed a genome-wide association study (GWAS) of AD in a Chinese Han population and identified 7 disease-associated single nucleotide polymorphisms (SNPs): rs11204971 and rs3126085 at *FLG*, rs10067777, rs7701890, rs13360927, and rs13361382 at 5q22.1, and rs6010620 at 20q13.33 [6]. A similar study conducted in a German population identified a new susceptibility locus, 11q13.5 [7], while a genome-wide study of 3 racial groups reported a potential link between a region of 14q11.2 and an asthma-associated phenotype [8]. The aim of the current study was to investigate associations between 10 SNPs (the 7 identified in our GWAS of AD in a Chinese Han population and 3 new SNPs—rs7936562 and rs7124842 at 11q13.5 and rs4982958 at 14q11.2—selected as promising candidate loci for atopic diseases) and AR in 363 cases and 668 controls from the Chinese Han population.

Materials and Methods

Study Participants

The study included 363 patients with AR (cases) and 668 sex- and age-matched controls. The characteristics of the study population are shown in Table 1. Cases were recruited at the department of otolaryngology head and neck at the First Affiliated Hospital of Anhui Medical University in China. AR was diagnosed on the basis of a positive skin test and the presence of nasal itching, sneezing, watery rhinorrhea, and nasal obstruction, with at least 3 of these symptoms occurring for more than 30 minutes on most days and persistent symptoms for at least 2 years [9]. The controls were recruited from the medical examination center at the same hospital, with the following inclusion criteria: 1) no symptoms or history of AR, 2) no symptoms or history of allergy, 3) no first-degree relatives with a history of AR or atopy, and 4) negative allergy test results. All participants were of Han Chinese origin and from the central region of China. Written informed consent was

Table 1. Demographic Characteristic of the Study Population

	Cases[a] (n=363)	Controls (n=668)
Age, mean (SD) (range), y	31.68 (12.97) (4-74)	31.50 (12.52) (4-83)
Age at onset, mean (SD), y	24.18 (12.43)	–
Sex		
Male, no. (%)	184 (50.68)	341 (51.05)
Female, no. (%)	179 (49.32)	327 (48.95)
Type of allergic rhinitis		
Intermittent, no. (%)	190 (52.34	–
Persistent, no. (%)	173 (47.66)	
Allergens, no. (%)		
House dust mites	269 (74.10)	–
Pollens	30 (8.26)	–
Mixed allergens	26 (7.16)	–
Mixed vaccines	16 (4.40)	–
Mycetes	13 (3.28)	–
Other allergens	9 (2.80)	–

[a]Patients with allergic rhinitis.

obtained from all participants (or from their parents in the case of children). The study protocol was approved by the university's ethics committee and conducted according to the Declaration of Helsinki principles.

The cases were divided into 2 groups: early-onset AR (onset before 7 years of age) and late-onset AR (onset after 7 years of age) [10]. According to the 2008 updated Allergic Rhinitis and its Impact on Asthma guidelines [9], AR was classified as intermittent or persistent. Severity was classified as mild or moderate/severe depending on symptoms and quality of life. A family history of atopy was defined as the presence of atopy in at least 1 family member (including first-degree, second-degree, and third-degree relatives). Atopy was defined as the presence of at least 1 of the following conditions: asthma, AD, or food allergy.

Skin Prick Tests

Skin prick tests (SPTs) to 21 common inhalant allergens (house dust, *Dermatophagoides farinae*, cotton, summer-autumn pollens I-II, *Piemarker*, fowl feather, polyvalent fur, mulberry silk, cigarette smoke, mixed antigen, spring pollens I-, *Artemisia sieversiana*, *Ambrosia artemisiifolia*, polyvalent molds I-, polyvalent insect, and mixed vaccines) were performed using a commercially available testing kit (Allergy Therapeutics, Peking Union Medical College Hospital, Beijing, China). Saline buffer and histamine chloride (10 mg/mL) were used as negative and positive controls, respectively. A positive skin prick test was recorded when an individual had at least 1 positive allergen test response with a mean wheal diameter 3 mm larger than the negative control, which roughly corresponds to a +++ or ++++ reaction when compared with histamine [11]. Antihistamine therapy was discontinued on day 7 before skin testing.

Genotyping

Genomic DNA was extracted using Flexi Gene DNA kits (QIAGEN, Hilden, Germany). All 10 SNPs were genotyped using the Sequenom MassArray system at the State Key Laboratory Incubation Base of Dermatology (Ministry of National Science and Technology, Hefei, Anhui, China). According to the manufacturer's introductions, 15 ng of genomic DNA was used to genotype each sample. Locus-specific polymerase chain reaction (PCR) and detection primers were designed using the MassARRAY Assay Design 3.0 software (Sequenom, San Diego, USA). The DNA of each sample was amplified by multiplex polymerase chain reaction (PCR) and the resulting PCR products used for locus-specific single-base extension reaction. Genotyping primers and PCR conditions are shown in Table 2. The resulting products were desalted and transferred to a 384-element SpectroCHIP array (Sequenom).

Table 2. Details of Primers Used in the Screening of SNPs by MassArray and Direct PCR Sequencing[a]

SNP_ID	Chr Pos	Allele	Direction	PCR Primer Sequence	Extension Primer
rs11204971	1q21.3:150525702	A/G	fwd	ACGTTGGATGAAACCTCACAGTCTCTGTGC	GCTCAAACTTTATTGAAGTTGT
			rev	ACGTTGGATGGTACACTGATTTTGTATGCTC	
rs3126085	1q21.3:150567441	G/A	fwd	ACGTTGGATGATGTTTGGACAATTCTATTA	GCCATGTTTTGGCTTTATGTAAGT
			rev	ACGTTGGATGTAAGAAACCATGTTTTGGC	
rs10067777	5q22.1:109854195	G/A	fwd	ACGTTGGATGCAAGAATAGCCAAAACAGTC	CCACAGTTTGAAATTAAAGAAG
			rev	ACGTTGGATGGTCAGTCCCACAGTTTGAAA	
rs7701890	5q22.1:109886720	G/A	fwd	ACGTTGGATGCTGATTCAATCTCCATAGTAG	CCATAAAACCTACCAAGTCTAAAT
			rev	ACGTTGGATGGAAACATAAAACCTACCAAG	
rs13360927	5q22.1:110063655	G/A	fwd	ACGTTGGATGAAGCTGAATAATGGCTATC	ATAAAATTGCTTAGTGGATTTTTC
			rev	ACGTTGGATGCTGTCTTCAGCTGTCTGCTT	
rs13361382	5q22.1:110076853	A/G	fwd	ACGTTGGATGCTCACTTCTGTCCCACCAC	GGTAGTACAGGCTGGGAAAG
			rev	ACGTTGGATGGAACTCATGGAGATAGTACA	
rs7936562	11q13.5:75955906	T/C	fwd	ACGTTGGATGCACACTCTTCTGTATATATT	CGGGTGGTAGGAATGGATG
			rev	ACGTTGGATGACAGCCTTGGGTGGTAGGAA	
rs7124842	11q13.5:75989268	A/G	fwd	ACGTTGGATGCTGTGATGAATGTCATTGTG	TTGGCTCAGCCCCACTCCC
			rev	ACGTTGGATGAGATTATCCACAGAGTTGGC	
rs4982958	14q11.2:24057705	T/C	fwd	ACGTTGGATGTCCTCACTATCATTAAGCCC	GTGACTTTGGGTGCATTTCTTTATCT
			rev	ACGTTGGATGTGTGACTTTGGGTGCATTTC	
rs6010620	20q13.33:61780283	G/A	fwd	ACGTTGGATGGCCTGTTTTCCCTTTTTGAG	TAGATCATGCAAAGCAGG
			rev	ACGTTGGATGCCTCTCAACATCTCAGCAAC	

Abbreviations: Chr Pos, chromosome position; fwd, forward; PCR, polymerase chain reaction; rev, reverse; SNP, single nucleotide polymorphism.
[a]PCR conditions: 94°C 15 min→(94°C 20s→56°C 30s→72°C 1 min) ×44 cycles→72°C 3min→4°C incubation.

Allele detection was performed using MALDI-TOF MS (matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry). The mass spectrograms were analyzed by the MassARRAY TYPER software (Sequenom).

Statistical Analysis

Possible associations between the 10 SNPs analyzed and AR were explored by comparing the minor allele frequency between cases and controls using PLINK 1.07 software [12] and testing for significant deviation from Hardy–Weinberg equilibrium in controls. Significance was established as $P > .05$. In addition to the allelic test of association, the genetic models (dominant and recessive) were also calculated for the SNPs analyzed. Association with subphenotype was analyzed by comparing cases with a given subphenotype with controls. Case-only analyses were performed to examine the susceptibility to AR conferred by these SNPs. *P* values, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each subphenotype (age of onset, clinical classification, severity, number of positive SPTs, and family history of atopy or AR). The Fisher exact test was used to compare the frequencies of variables when the expected count was less than 5. *P* values of less than .05 were considered to be statistically significant (with Bonferroni corrections for multiple testing where necessary). The genetic statistical power for all genotyped SNPs was estimated using the CaTS-Power Calculator software [13].

Results

Association Between AR and SNPs

The genotype distributions of the 10 SNPs did not deviate from the Hardy–Weinberg equilibrium ($P > .05$). Table 3 shows the association analysis for the 10 SNPs for cases and controls. The T allele of rs4982958 at 14q11.2 was significantly associated with AR ($P = .002$; OR=0.73; 95% CI, 0.60-0.89), even after correcting for multiple testing ($P_{Bonferroni} = .02$). The genotype model for rs4982958 in cases and controls is shown in Table 4. Association at the genotype level was strong, with

Table 3. Associations for 10 SNPs Between Cases[a] and Controls

SNP_ID	Minor Allele	Gene Symbol[b]	MAF (%) Cases	MAF (%) Controls	OR (95% CI)	*P*	$P_{Bonferroni}$	P_{HWE}	Callrate
Crs11204971	A	FLG	44.08	42.87	1.05 (0.87-1.26)	.60	1.00	.09	0.98
rs3126085	G	FLG	43.66	42.39	1.05 (0.88-1.27)	.58	1.00	.30	0.98
rs10067777	G	TMEM232/SLC25A46	10.89	11.53	0.94 (0.70-1.26)	.67	1.00	.84	0.94
rs7701890	G	TMEM232/SLC25A46	12.12	13.42	0.89 (0.68-1.17)	.40	1.00	.87	1.00
rs13360927	G	TMEM232/SLC25A46	11.59	13.73	0.82 (0.62-1.09)	.17	1.00	.32	0.99
rs13361382	A	TMEM232/SLC25A46	14.31	13.68	1.05 (0.78-1.42)	.73	1.00	.32	0.88
rs7936562	T	C11orf30	40.64	43.58	0.89 (0.74-1..07)	.20	1.00	.48	0.99
rs7124842	A	C11orf30	23.46	28.47	0.77 (0.62-0.95)	.016	0.17	1.00	0.92
rs4982958	T	CMA1	30.57	37.58	0.73 (0.60-0.89)	.002	0.02	.22	0.97
rs6010620	G	TNFRSF6B/ZGPA	28.69	25.23	1.19 (0.97-1.46)	.09	0.91	.26	0.98

Abbreviations: CI, confidence interval; HWE, Hardy-Weinberg equilibrium; MAF, minor allele frequency; OR, odds ratio.
[a]Patients with allergic rhinitis.
[b]The annotated nominal gene was taken from the Illumina SNP database.

Table 4. Genotype-Based Association Test for Allergic Rhinitis

SNP_ID	Minor Allele	Major Allele	Model[a]	Genotype	Cases (%) (n=332)[b]	Controls (%) (n=664)[b]	OR (95% CI)	*P* ($P_{Bonferroni}$)
rs4982958	T	C	Full genotype	TT	20 (6.04)	86 (12.95)	0.39 (0.23-0.66)	.0017 (.02)
				TC	163 (49.24)	327 (49.25)	0.84 (0.64-1.11)	
				CC	149 (44.72)	251 (37.80)	Reference[c]	
			Dominant	TT+TC	183 (55.28)	413 (62.20)	0.75	.03 (.44)
				CC	149 (44.72)	251 (37.80)	(0.57-0.98)	
			Recessive	TT	20 (6.04)	86 (12.95)	0.43	.0008 (.01)
				TC+CC	312 (93.96)	578 (87.05)	(0.26-0.71)	

Abbreviation: CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism.
[a]Full genotype: DD vs Dd vs dd; dominant model: (DD,Dd) vs dd; recessive model: DD vs (Dd,dd), where D is the minor allele and d the major allele.
[b]Genotyping of 31 cases and 4 controls failed.
[c]Taking genotype CC as the reference genotype.

Table 5. Associations Between rs4982958 and Allergic Rhinitis in Subphenotype Control- and Case-Only Analyses

Subphenotypes	Genotype/Allele Frequency (%)					Subphenotype vs Controls		Cases Only	
	TT	TC	CC	T	C	OR (95% CI)	P^c	OR (95% CI)	P^{ci}
Age at onset									
Early onset (n=33)	0 (0.00)	21 (63.64)	12 (36.36)	21 (31.82)	45 (68.18)	0.78 (0.46-1.32)	.35	1.07 (0.62-1.84)	.82
Late onset (n=299)	20 (6.69)	142 (47.49)	137 (45.82)	182 (30.43)	416 (69.57)	0.73 (0.60-0.89)	.002		
Classification									
Persistent (n=153)	7 (4.58)	65 (42.48)	81 (52.94)[a]	79 (25.82)	227 (74.18)	0.58 (0.44-0.76)	.00009[e]	0.66 (0.47-0.92)	.01
Intermittent (n=179)	13 (7.26)	98 (54.75)	68 (37.99)	124 (34.64)	234 (65.36)	0.88 (0.70-1.12)	.31		
Severity									
Mild (n=80)	5 (6.25)	39 (48.75)	36 (45.00)	49 (30.63)	111 (69.37)	0.74 (0.52-1.05)	.09	1.00 (0.68-1.48)	.99
Moderate/severe (n=252)	15 (5.95)	124 (49.21)	113 (44.84)	154 (30.56)	350 (69.44)	0.73 (0.59-0.91)	.005		
No. of positive SPTs									
>2 (n=242)	14 (5.79)	109 (45.04)	119 (49.17)[b]	137 (28.31)	347 (71.69)	0.66 (0.52-0.82)	.0003[f]	0.68 (0.47-0.98)	.038
≤2 (n=90)	6 (6.67)	54 (60.00)	30 (33.33)	66 (36.67)	114 (63.33)	0.96 (0.70-1.33)	.81		
Family history									
Atopy (n=149)	8 (5.37)	76 (51.00)	65 (43.63)	92 (30.87)	206 (69.13)	0.74 (0.57-0.97)	.03	1.03 (0.74-1.43)	.88
No atopy (n=183)	12 (6.56)	87 (47.54)	84 (45.90)	111 (30.33)	255 (69.67)	0.72 (0.56-0.93)	.01		
Allergic rhinitis (n=126)	7 (5.56)	63 (50.00)	56 (44.44)	77 (30.56)	175 (69.44)	0.73 (0.55-0.98)	.03	1.00 (0.71-1.40)	.99
No allergic rhinitis (n=206)	13(6.31)	100(48.54)	93(45.15)	126(30.58)	286(69.42)	0.73 (0.58-0.93)	.01		

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]P=.006; OR=1.83; 95% CI, 1.19-2.85 (vs intermittent allergic rhinitis).
[b]P=.01; OR=1.94; 95% CI; 1.17-3.21 (vs ≤ 2 positive SPTs in patients with allergic rhinitis).
P^c and P^{ci} for allele using a 2 × 2 contingency table.
[e]P=.00009 (intermittent allergic rhinitis vs controls).
[f]P=.0003 (>2 positive SPTs in patients with allergic rhinitis vs controls).

Pgenotype=.0017 ($P_{Bonferroni}$=.02). Similarly, genotype-based association testing revealed that the recessive model might provide the best fit for rs4982958 ($P_{Bonferroni}$=.01). There was no significant association for any other SNPs in FLG, or at the loci 5q22.1, 11q13.5, or 20q13.33 in the control group ($P_{Bonferroni}$ >.05) (Table 3).

Subphenotype Stratification Analyses

We also performed a stratified analysis according to AR subphenotypes. Table 5 shows the stratification association results for rs4982958 and AR. The T allele of rs4982958 was associated with significant differences between patients with persistent AR and controls (P=9.32×10-5; OR=0.58; 95% CI, 0.44-0.76), but not between those with intermittent AR and controls (P=.31; OR=0.88; 95% CI, 0.70-1.12). Moreover, in the case-only analysis, there was also a significant difference between patients with persistent AR and intermittent AR for the T allele of rs4982958 (P=.01; OR=0.66; 95% CI, 0.47-0.92). For the same T allele, we also observed a significant difference between cases with more than 2 positive SPTs and those with 2 or fewer positive SPTs (P=.038; OR=0.68; 95% CI, 0.47-0.98).

Discussion

We have evaluated the associations between susceptibility to AR in a Chinese Han population and10 SNPs selected from several GWAS of AD. Our findings provide novel evidence for an association between rs4982958 [T] at 14q11.2 and susceptibility to AR. The protective T allele was the minor allele in the population analyzed. Furthermore, we performed a genotype–phenotype analysis of rs4982958 to explore whether

this SNP might be associated with specific subphenotypes of AR. As shown in Table 5, the T allele was more likely to be associated with a protective role in patients with persistent AR and the presence of more than 2 positive SPTs, possibly giving new insights into the etiology and pathogenesis of AR.

At 14q11.2, several genes were annotated within a single 220-kb linkage disequilibrium (LD) block surrounding the associated SNP rs4982958 (Figure). Biologically, the chymase 1 (*CMA1*) and cathepsin G (*CTSG*) genes might be involved in the overall pathogenesis of allergic diseases, including AR. *CMA1* is a protease involved in inflammatory mechanisms that acts in concert with histamine, which is released from activated mast cells (MCs) in asthmatic airways and has profound effects on inflammation, airway smooth muscle cell functioning, and airway remodeling, as has been observed in the lungs of asthmatics, thus marking *CMA1* as a candidate to be studied in asthma and atopy [14,15]. There have been several reports describing significant associations between *CMA1* (and the promoter polymorphism rs1800875 in particular) and atopy or asthma [16-18]. Rs4982958 is located at 8.5 kb upstream of the *CMA1* promoter region. We observed an LD between rs4982958 and rs1800875 in the 1000 human genomes project JPT+CHB panel (D'=1.00, r^2=0.50), which showed that the 2 SNPs were moderately correlated with each other in this population. CTSG is a major secreted serine peptidase of neutrophils and mast cells, and could trigger changes in

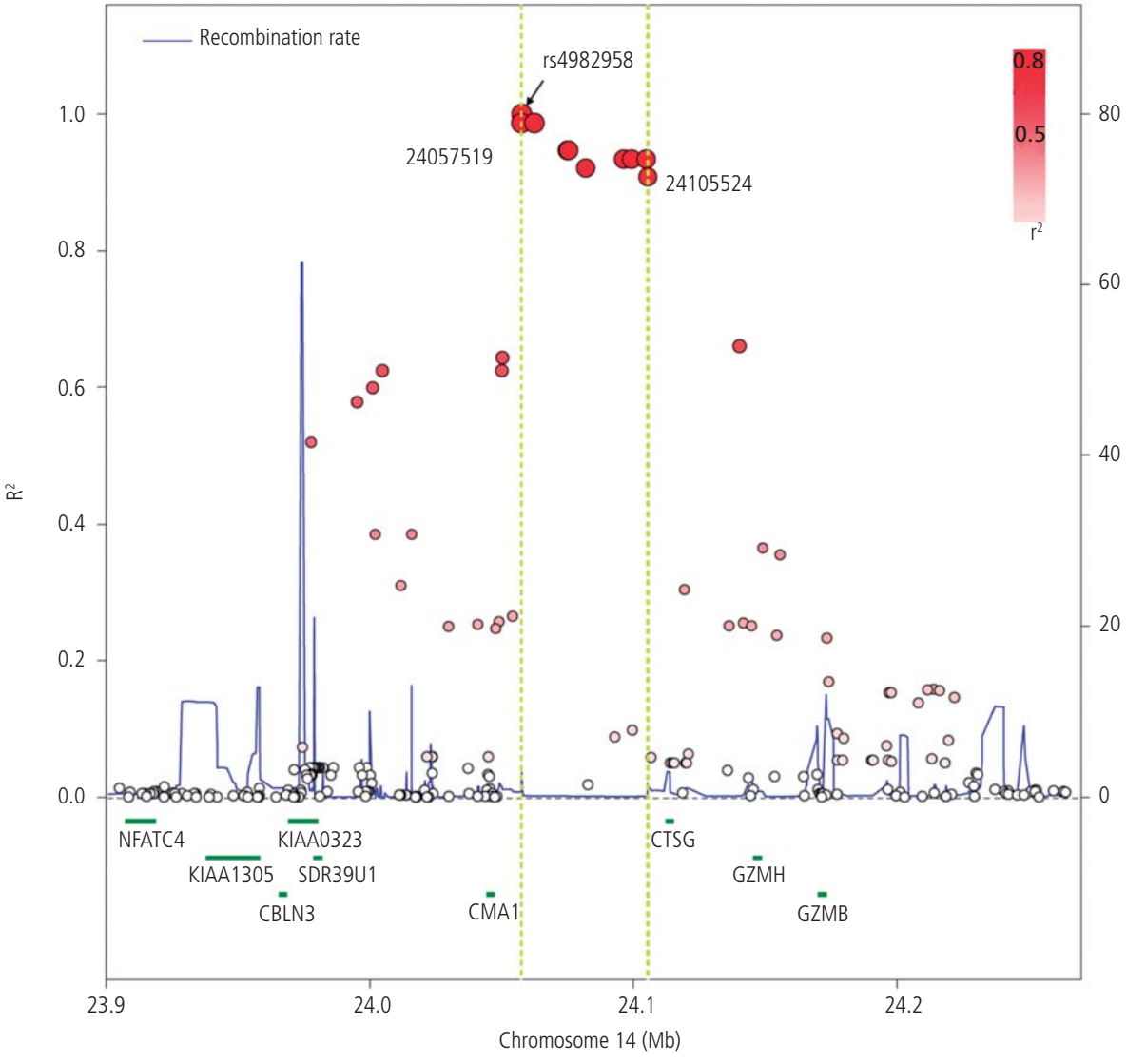

Figure. Regional linkage disequilibrium plots for associated rs4982958 single nucleotide polymorphism (SNP) ($P_{Bonferroni}$=.02) at 14q11.2. The r^2 values of SNPs were plotted against their map positions (x axis). The color of each SNP (ranging from red to white) reflects its r^2 with the top SNP (large red diamond) within each locus. Estimated recombination rates (based on the combined CHB and JPT samples from the HapMap project [30]) are plotted in light blue. Gene annotations were adapted from the University of California, Santa Cruz Genome Browser (http://genome.ucsc.edu/).

cellular behavior through the activation of 1 or more members of a unique family of G protein–coupled receptors termed proteinase-activated receptors [19]. These receptors are widely expressed by cells involved in immune responses and inflammation, including AR [20] and asthma [21].

CMA1 and *CTSG* have been shown to be cotranscribed in human MCs [22]. MC accumulation in the airway mucosa is an important pathophysiologic event in AR as inhaled allergens impact the mucosal surfaces of the nose. MCs are key effector cells of immunoglobulin (Ig) E–dependent immediate reactions, and also contribute significantly to certain features of IgE-associated late-phase reactions and chronic allergic inflammation [23]. It is widely accepted that MC inflammatory mediators play a key role in the initiation and progression of allergic immune responses in AR [24, 25]. On the other hand, *CMA1* and *CTSG* may also indirectly serve to limit some of the pathological features of chronic inflammatory diseases. Taking all of this together, we postulated that the genetic variant rs4982958 might affect *CMA1*/*CTSG* biological function, and in turn, play a key role in the development of AR (especially in patients with persistent AR and more than 2 positive SPTs) via the progression of allergic immune responses.

To date, GWAS of AD has identified 4 susceptibility loci (*FLG*, 5q22.1, 11q13.5, and 20q13.33) in Chinese and German populations [6,7]. We detected 9 of the 10 SNPs analyzed in this study in the 4 susceptibility loci but found no evidence of an association with AR. This lack of association does not mean that the loci cannot be considered candidates as loci for allergic diseases because additional genetic variants within the loci might be involved in conferring susceptibility to AR. For example, 11q13.5 was recently identified as a new susceptibility factor for asthma and hay fever in the population-based ALSPAC cohort [26]. We suppose that, like other complex disorders, AR involves complicated mechanisms linked to numerous genetic factors, many of which exert additive or synergistic effects, but have only a small role when considered in isolation [27,28]. Our limited sample size would also have resulted in lower statistical power, which might be another reason why we failed to detect common variants with small effects on susceptibility to complex disorders [29]. Larger samples are therefore warranted to investigate the genetic factors that confer a smaller susceptibility to AR.

In conclusion, we performed a case-control association analysis of AR in a Chinese Han population. Our study indicates that locus 14q11.2 is associated with AR and confers susceptibility to AR, especially in patients with persistent AR and an increased number of positive SPTs. Fine mapping and functional studies are warranted to confirm the true susceptibility gene for AR within this locus and to gain a better understanding of the pathogenesis of AR.

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