



Association of polymorphisms in the promoter region of FCER1A gene with atopic dermatitis, chronic urticaria, asthma, and serum immunoglobulin E levels in a Han Chinese population

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ABSTRACT

The high-affinity receptor for immunoglobulin E (IgE) plays a central role in allergy diseases. Previous studies have reported the association of variants in the proximal promoter of FCER1A with IgE levels as well as allergy disorders. Another promoter gene polymorphism that is located upstream of exon 1 has not been investigated. We investigated the association of variants in the promoter located upstream of FCER1A exon 1 with serum IgE levels and allergy diseases in a Han Chinese population. A total of 97 patients with atopic dermatitis (AD), 123 patients with chronic urticaria (CU), 286 children with asthma, and control groups were screened for polymorphisms in the promoter region located upstream of FCER1A exon 1 by the polymerase chain reaction–ligation detection reaction method. Total serum IgE levels were tested in groups. The rare allele A of the rs2427837 A/G polymorphism was significantly different in the AD group compared with the controls. No association with the polymorphism was observed in the CU group. In asthmatic patients, IgE levels were higher in the mutation genotypes GA of rs2427837 and TC of rs2251746 compared with normal genotype individuals. The minor allele of rs2427837 and rs2251746 in FCER1A is a genetic risk factor of high IgE levels.

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1. Introduction

Cross-linking of immunoglobulin E (IgE) to its high-affinity receptor by multivalent antigens induces allergy activation, resulting in secretion of inflammatory mediators and induction of cytokine gene transcription. Therefore, ligation of IgE to FcεR1 plays a critical role in the induction of allergy diseases [1,2]. FcεR1 is composed of three different subunits: the α subunit to which IgE binds at a proximal membrane extracellular region; the β subunit; and the γ chain dimer that commonly acts as a signaling component [3,4]. Consequently, the α subunit is a unique component of FcεR1 whose role in the development of allergy diseases is indispensable, for knockout of the FCER1A in mice caused the disappearance of allergy [6]. In addition, an expression increase in the α-chain of FcεR1 on the cell surface accelerates the IgE-mediated allergic reaction [5,6]. Therefore, the amount of FcεRIα expression on the surface of effector cells, such as mast cells and basophils, determines the activation and maintenance of allergy diseases.

The FCER1A gene, encoding the α chain of FcεRI, is located on human chromosome 1q23 [7]. The gene consists of six exons (NT_004487.19 GI: 224514980) and has two transcripts (ENST00000368115); consequently there are two promoter re-

gions. One of these regions, known as the proximal promoter, which is located upstream of exon2, has been reported to be associated with IgE expression levels as well as the susceptibility to atopic diseases in many previous studies [8–11]. It is common to use sequencing to identify genetic variants that may be contributing to understand the pathogenesis of common diseases. Studying mutated versions of the FCER1A promoter may also be useful for further study of the induction of allergic reaction. It is possible that the polymorphisms in this region may be associated with allergy diseases [4]. Given the roles of FcεRI and IgE in the pathogenesis of allergies [1], in the present study, we analyzed the FCER1A to identify common genetic variants and to determine whether there are linkages to allergic diseases. We then screened the polymorphisms in the region upstream of exon1 within FCER1A for associations with allergy disorders in a Han Chinese population.

2. Subjects and methods

2.1. Selection and description of participants

This study included 220 patients with allergic skin diseases who were enrolled from the Outpatient Department of Dermatology at the First People's Hospital of Shanghai, and 286 children with asthma who were recruited from hospital-based clinics associated with Xinhua Hospital and Shanghai Children's Hospital. The patients with allergic skin diseases were divided into two groups (97

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patients with atopic dermatitis and 123 patients with chronic urticaria). According to the criteria of Williams et al. (ie, an individual must have an itchy skin condition plus three or more of the following: history of flexural involvement, a history of asthma/hay fever, a history of a generalized dry skin, onset of rash under the age of 2 years, or visible flexural dermatitis) [12], 97 patients (40 male and 57 female) were diagnosed with atopic dermatitis (AD). Patients ranged in age range from 4 to 80 years (average age, 46.1 ± 21.3 years), with an average course of disease of 11.1 ± 15.1 months. A total of 123 subjects were diagnosed with chronic urticaria (CU), including 47 male and 76 female subjects aged 11 to 95 years (average age 46.8 ± 17.4 years), with an average course of disease of 10.1 ± 13.4 months. Patients with chronic urticaria had recurring itchy wheals that lasted for no more than 24 hours at least twice per week and persisting for more than 6 weeks with unknown cause of urticarial vasculitis, physical urticaria, infectious agents, or parasites. This study also included 286 children aged 1 to 12 years (average age 4.1 ± 2.2 , 170 male and 116 female children), with a diagnosis of asthma according to the Global Initiative for Asthma Committee's revised diagnostic criteria.

A total of 283 adults aged 18 to 85 years (average age 35.0 ± 10.6 , 131 males and 152 females) and 208 children aged 1 to 12 years (average age 8.1 ± 2.6 , 118 males and 90 females) without any history of allergy disease were used as controls. The study was approved by the ethics committee of Shanghai First People's Hospital.

2.2. DNA extraction/isolation and genotyping

For single nucleotide polymorphism (SNP) preliminary screening, genomic DNA was extracted using a Genomic DNA Kit (Axygen, Hangzhou, China) from peripheral blood samples of 28 healthy individuals. Gene fragments of approximately 1000 bp in the promoter located upstream of FCER1A exon1 were amplified by PCR, and the products were sequenced with DNA Analyzer (ABI3730, Invitrogen Company). After sequence alignment, two polymorphic sites, rs2427837 A/G and rs61828219 A/C, were identified and then screened on a larger scale.

Subsequently, genomic DNA was extracted from the blood of patients and controls using a Genomic DNA Kit (Axygen, Hangzhou, China); then, PCR and ligase detection reaction (LDR) were used for mutation screening in the targeted gene. The primers and probes were synthesized by the Invitrogen Company. PCR amplifications were carried out in 20 μ L buffer that consisted of 1 $\times$ PCR Buffer, 1x Q-Solution, 3 mmol/L MgCl₂, 2 mmol/L dNTP, 50 pmol/ μ L primer, 1 U of Qiagen Hotstar Taq DNA Polymerase (Qiagen, Chatsworth, CA), and 50 ng of template. The amplification was performed on a PE 9600 at 95°C for 15 minutes of predenaturation, 94°C for 30 seconds of denaturation, 56°C for 1.5 minutes of annealing, and 72°C for 1 minute of extension, repeated for 35 cycles, followed by a final extension of 7 minutes at 72°C. PCR products were observed by agarose gel electrophoresis (3.0%), visualized with ImageMaster VDS (Pharmacia Biotech, Piscataway, NJ), and then used as templates in LDR. The LDR reactions were carried out in 10 μ L of buffer consisting of 1 $\times$ Buffer, 12.5 pmol/ μ L Probe mix, 2 U NEB Taq DNA ligase, and 100 ng/ μ L PCR product. The LDR was performed on a PE 9600 thermal cycler by incubating at 95°C for 2 minutes and cycling for 30 cycles at 95°C for 30 seconds and 50°C for 2 minutes. The products were submitted for sequencing with the ABI377 (ABI) sequencer, and the results were analyzed with GeneMapper software.

2.3. Detection of total IgE in sera

Sera were frozen at -80°C , when blood samples were centrifuged, until assayed. Total IgE in sera from the patients and controls was detected by immune nephelometry with a SIEMANS immunoglobulin E kit (N Latex IgE mono, Siemens Healthcare Diagnostics

Products, Marburg, Germany) on an automatic protein analyzer (Siemens BNII, Siemens Healthcare Diagnostics Products, Marburg, Germany).

2.4. Data analyses

All of the data in this study were analyzed using SPSS 17.0 software (SPSS Inc., Chicago, IL). We tested for Hardy-Weinberg equilibrium (HWE) in cases and controls separately using the χ^2 test. A comparison of the distribution in genotype frequency between patients and controls was also performed using the χ^2 test, and the odds ratio was calculated with a 95% confidence interval (CI). Total serum IgE levels in subjects were analyzed by using the nonparametric test and logistic regression. *p* Values less than 0.05 were considered statistically significant.

3. Results

3.1. Association of polymorphisms within FCER1A in atopic dermatitis and chronic urticaria

The SNPs of rs2427837 A/G and rs61828219 T/G which were identified through direct sequencing were located upstream of exon 1 of FCER1A, then they were detected by multi-polymerase chain reaction-ligation detection reaction (PCR-LDR) on a larger scale. Both SNPs were observed to have genetic variants. The genotype distribution of rs2427837 A/G and rs61828219 T/G was in Hardy-Weinberg equilibrium. Considering that only one rs2427837 AA homozygote and no rs61828219 TT homozygotes were observed in atopic dermatitis patients, we analyzed only the genotype and allele frequencies in dominant mode for the polymorphic sites rs2427837 A/G and rs61828219 T/G in patients and control groups (Table 1). The genotype frequencies of rs2427837A/G were significantly different between AD patients and control patients; the frequency of the A allele was higher in AD patients than in the control group ($p < 0.05$). Furthermore, the polymorphism increased the risk of development of AD (odds ratio [OR] = 2.124, 95% CI = 1.137–3.967). When we controlled for the influence of age, there was no effect on the OR. The rare allele A of rs2427837 contributed to disease susceptibility. However, the distribution of rs2427837A/G genotypes was not different between CU patients and controls. According to these data, we have not observed a difference in the distribution of rs61828219 T/G genotype in the CU or AD compared with the control groups.

3.2. Association of polymorphisms within FCER1A in asthma

Given the role of IgE and Fc ϵ R1 in the pathogenesis of asthma, we tested the two SNPs, rs2427837 and rs61828219, for association with asthma in a child patient group and controls with no allergy diseases. We detected genetic variants in the rs2427837 loci located in the promoter upstream of FCER1A exon1, and the

Table 1
Association of susceptibility variants with allergy disorders in a Han Chinese population

Loci	Genotype	Genotype distribution			<i>p</i> Value
		Atopic dermatitis n (%)	Chronic urticaria n (%)	Controls n (%)	
rs2427837	GG	80 (82.5)	107 (87.0)	259 (91.5)	0.01 ^a
	GA	16 (16.5)	16 (13.0)	22 (7.5)	0.16 ^b
	AA	1 (1.0)	0 (0.0)	2 (1.0)	
rs61828219	GG	96 (99.0)	121 (98.4)	277 (97.9)	0.8 ^a
	GT	1 (1.0)	2 (1.6)	6 (2.1)	1.0 ^b
	TT	0 (0.0)	0 (0.0)	0 (0.0)	

^aGG vs GA + AA or GG vs GT + TT in atopic dermatitis (AD) patients compared with healthy subjects.

^bGG vs GA + AA or GG vs GT + TT in chronic urticaria (CU) patients compared with healthy subjects.

rs61828219 was homozygous, which differed from the preliminary results with allergic skin diseases. The genotype distribution of rs2427837 A/G was in Hardy–Weinberg equilibrium testing by Haploview. Because no homozygous rs2427837 AA patients were observed, we analyzed only the genotype frequencies in dominant mode in patients and control groups. The genotype frequencies of rs2427837 A/G were not significantly different between the asthma patients and the control group (Table 2).

To date, some studies have reported that the polymorphisms in the proximal promoter of FCER1A which located upstream of exon2 were related to atopic diseases, especially the polymorphisms rs2427827 and rs2251746, although there is no consistency in these reports [13,14]. We were also interested in whether the proximal promoter genetic variations, such as the rs2427827 and rs2251746 in FCER1A, have any influence on the development of asthma in the Chinese population. Therefore, we genotyped the rs2427827 and rs2251746 polymorphisms in the proximal promoter of FCER1A on a larger scale in this group. The genotypic frequencies of both the rs2427827 and rs2251746 loci showed no significant differences between asthmatic individuals and controls (Table 2), suggesting that they may not be candidate genes for asthma.

3.3. Association of polymorphisms within FCER1A to total serum IgE levels

Total serum IgE level was examined for associations with three polymorphisms of the FcεRI gene, including the rs2427837, rs2427827 and rs2251746 in patients with allergic skin diseases and asthma. However, no such associations with IgE were found in the case of patients with allergic skin disease for the three polymorphisms in the FCER1A promoter that were screened in our study. Significant associations with IgE levels were noted for the two SNPs (rs2427837 and rs2251746) in asthmatic patients. Furthermore, the asthmatic patients carrying the GA genotype at FCER1A rs2427837 had a significantly higher total IgE levels than patients with the GG genotype ($p = 0.014$; Fig. 1). The C allele of the rs2251746 genetic polymorphism also positively correlated with serum IgE level in asthmatic individuals, whereby patients carrying the TC genotype exhibited a significantly higher IgE concentration than those with the homozygous TT genotype in asthmatic individuals ($p = 0.047$; Fig. 2). Finally, by evaluating the LD of three loci by Haploview, we found that two SNPs rs2427837 and rs2251746 were in linkage disequilibrium ($D' = 0.91$, $LOD = 38.66$, $r^2 = 0.74$). Haplotype association analysis was then conducted with these two SNPs (Table 3). The GT and AC were the most common haplotypes, mainly accounting for 95.5% and 3.5% of all individuals, respectively. However, no association with asthma was observed with the two haplotypes [24,25].

Table 2
Association of genetic variants with asthma in a Han Chinese population

Loci	Genotype	Genotype distribution		p Value
		Asthma patients n (%)	Controls n (%)	
rs2427837	GG	245 (92.1)	189 (91.3)	0.753
	GA	21 (7.9)	18 (8.7)	
	AA	0 (0)	0 (0)	
rs2251746	TT	265 (93.0)	193 (92.3)	0.788
	TC	20 (7.0)	16 (7.7)	
	CC	0 (0.0)	0 (0.0)	
rs2427827	CC	161 (56.5)	111 (53.1)	0.455 ^a
	CT	104 (36.5)	86 (41.1)	
	TT	20 (7.0)	12 (5.8)	

^aCC vs CT + TT or GG vs GT + TT in AD patients compared with healthy subjects.

^bTT vs CT + CC or GG vs GT + TT in CU patients compared with healthy subjects.

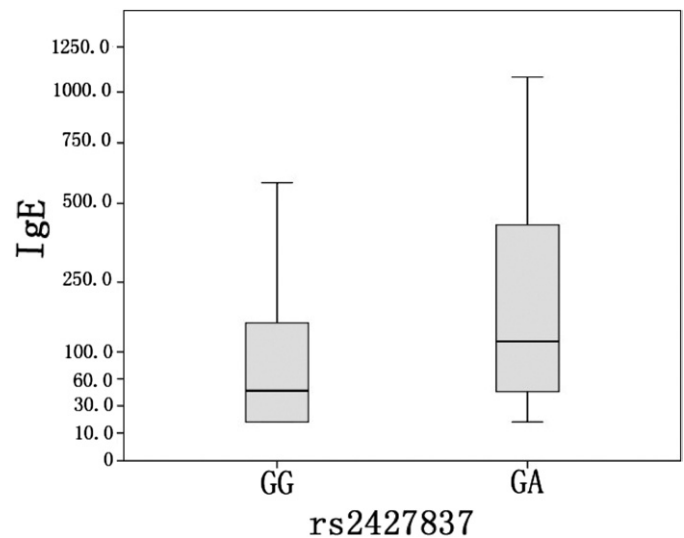


Fig. 1. IgE levels were higher in the GA group compared with the GG group for rs2427837 loci.

3.4. Association of total serum IgE levels with skin disease patients and asthma

Because total IgE values did not follow a normal distribution, as well as a logarithmic transformation (natural log) of total IgE, we used a nonparametric test to detect the distribution of total IgE in the different groups. Compared with the control group, we found that the total IgE differed in the atopic dermatitis ($p = 0.006$) and chronic urticaria ($p = 0.019$) patient groups. However, it did not differ between the asthma patients and controls ($p = 0.06$).

4. Discussion

In the present study, we report an association of single nucleotide polymorphisms in the promoter of FCER1A, which codes for the α -subunit of the high-affinity receptor of IgE, with skin allergy patients and asthmatic children in a Chinese population by a case-control approach. Upon examination of two genetic polymorphisms within skin allergy patients and three SNPs within asthmatic children in the promoter region of FCER1A, the results indicated that rs2427837 A/G was significantly associated with the development of atopic dermatitis ($p = 0.013$). In addition, linkage

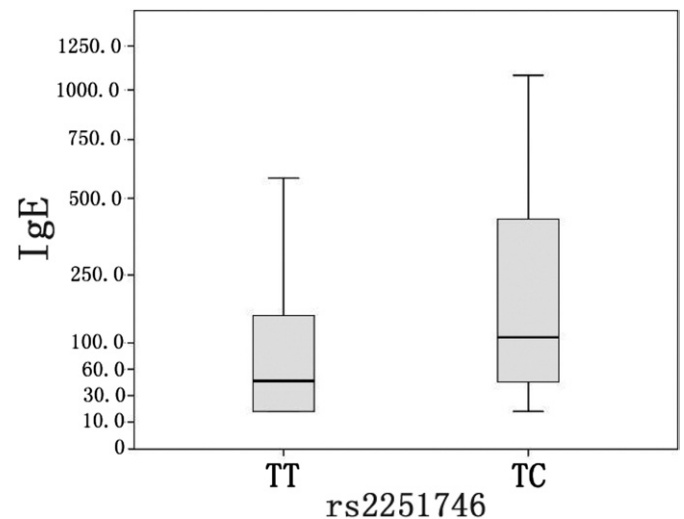


Fig. 2. IgE levels were higher in the TC group compared with the TT group for rs2251746 loci.

Table 3
Linkage disequilibrium (D' , r^2) for all single nucleotide polymorphism (SNPs)

	$D'(r^2)$	
	rs2427837	rs2427827
rs2251746	0.91 (0.74)	0.99 (0.01)
rs2427837	– (–)	0.8 (0.01)

was found between two SNPs (rs2427837 and rs2251746) in FCER1A and total serum IgE level in asthmatic patients.

The high-affinity receptor for IgE represents the central component of IgE-induced type I hypersensitivity reactions [4,15]. Thus, it is not surprising that many recent studies focused on its α subunit and so much attention has been paid to FCER1A variability [9,11,16,17]. Previous studies have suggested the linkage of two functional polymorphisms –66T > C (rs2251746) and –315C>T (rs2427827), which are located in the proximal promoter of FCER1A, to allergic disorder [9,11,16,17], especially the –315C>T variant, which creates a new transcription factor-binding motif affecting the transcription and activation of FCER1A [9]. Furthermore, previous reports show that they are significantly associated with the total IgE level in sera [17]. However, the association with allergic disorders or IgE level has not reached agreement among investigators [13,14]. The finding that the mutation is correlated with atopic diseases is inconsistent. In this study, we found that the new rs2427837 variant significantly increased the risk of atopic dermatitis, but there was no relationship between rs2427837 and total IgE levels in atopic dermatitis patients. We cannot rule out the possibility that the results may be caused by the small sample size of AD population in our experiment. The data in this study of the group of asthmatic children also suggests that the rs2251746 mutation, but not the rs2427827 locus, has a relationship with total serum IgE level. One research study using whole genome association analysis revealed that two polymorphisms, rs2251746 and rs2427837, located on FCER1A are of major importance for the regulation of IgE levels, demonstrating that FCER1A is a novel susceptibility gene for IgE levels [18]. In our case-control study, the rs2427837 G/A and rs2251746 C/T genetic variants in FCER1A were also demonstrated to be closely related to a high level of IgE in sera in children with asthma. However, the results suggest no relationship between the rs2427837 genotype and asthma. It is seemingly contradictory that the rs2427837 is associated with the high IgE concentration but not asthma; this may due to the total IgE level, which was not increased in every asthmatic child. Both the rs2427837 and rs2251746 in the FCER1A promoter located upstream of exon 1 in FCER1A may be susceptibility loci for high IgE levels. It is well known that IgE can cause mast cell degranulation, resulting in allergy. In addition, autoantibodies, such as anti-Fc ϵ RI α and anti-IgE, can also produce allergy. These results may explain why there is no association between mutations in FCER1A and IgE levels in some allergy-related diseases, such as chronic urticaria.

So far, the mechanisms regulating expression of Fc ϵ RI on the surfaces of effector cells is not well understood, but it is well known that serum IgE can regulate Fc ϵ RI expression [4,19–21]. Expression of Fc ϵ RI on the cell surface is substantially influenced by binding to IgE and vice versa, because binding to IgE apparently protects the receptor from degradation caused by endocytosis, thus enhancing surface expression. Whether new receptor synthesis has taken place is not agreed upon [21,22]. However, the genetic regulatory mechanism is likely crucial for Fc ϵ RI expression, which can also determine the levels of free serum IgE [23] clarifying the regulatory mechanism between Fc ϵ RI α subunit expression and serum IgE levels may provide important information about allergy pathogenesis. Therefore, it is necessary to study gene variants that may regulate the expression of FCER1A and its association with total IgE

concentrations (as reported in previous studies) [23]. The results should be repeated to confirm allergy disorders.

In summary, we discovered that several sequence variants in the promoter of FCER1A are associated with high IgE levels in serum. We also assessed the association of the variants with disease states and found rs2427837 to be strongly associated with AD. Although our findings show significant association between rs2427837 and atopic dermatitis, further studies that replicate our findings are needed. However, our results also demonstrate genetic susceptibility for a high IgE level in the mutated FCER1A promoter loci. In addition, studies should be performed to address the issue of whether rs2427837 A/G resulted in functional changes in transcription factor activation in the promoter region of FCER1A, as well as the regulation of total IgE levels in sera.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.humimm.2011.12.001.

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