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ORIGINAL PAPER

Association and functional relevance of E237G, a polymorphism of the high-affinity immunoglobulin E-receptor β chain gene, to airway hyper-responsiveness

Y.-K. Kim*, H.-W. Park†, J.-S. Yang*, S.-Y. Oh*, Y.-S. Chang†, E.-S. Shin‡, J.-E. Lee‡, S. Kim*, Y. S. Gho*, S.-H. Cho†, K.-U. Min† and Y.-Y. Kim†

**Department of Life Science, Postech Biotech Center, Pohang University of Science and Technology, Pohang, Korea, †Department of Internal Medicine, Institute of Allergy and Clinical Immunology, Seoul National University College of Medicine, Seoul, Korea and ‡DNA Link, Seoul, Korea*

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Summary

Background The hyper-sensitivity reaction of IgE, with its high-affinity receptors (FcεRI), is central to the phenomenon of atopic diseases.

Objective To evaluate the genetic effects of non-synonymous single-nucleotide polymorphisms (SNPs) of FcεRI on intermediate phenotypes of asthma, i.e. atopy and airway hyper-responsiveness (AHR), in the Korean general population.

Subjects and methods Atopy and AHR were evaluated in a cohort of 2055 subjects, aged 10–18 years, using skin prick tests (SPTs) for common aeroallergens and total serum IgE and methacholine bronchial provocation tests. All FcεRI-α, FcεRI-β, and FcεRI-γ gene exons of 24 healthy subjects were sequenced to locate informative non-synonymous SNPs (minor allele frequency $>2\%$). Informative SNPs were then scored, using the high-throughput single base extension method. Relative risk (RR) was determined by multiple logistic regression analysis, after adjusting for confounding factors. The functional relevance of non-synonymous SNPs was analysed using the sorting intolerant from tolerant (SIFT) program.

Results The SNP search found only one informative non-synonymous SNP in FcεRI-β: E237G (minor allele frequency = 0.21). The positive rate of AHR was lower among subjects with the 237*E allele than among those with 237*G [RR (95% confidence interval) = 0.41 (0.19–0.89); $P = 0.01$]. However, the E237G substitution was not associated with either a positive SPT response or total serum IgE levels. Sequence evolution analysis predicted that the E237G variation is an intolerant amino acid substitution, with functional importance.

Conclusion In the Korean general population, AHR is significantly associated with the E237G polymorphism of FcεRI-β, which results in an intolerant amino acid substitution.

Correspondence:
Sanguk Kim, Department of Life Science, Postech Biotech Center, Pohang University of Science and Technology, Pohang, Korea.
E-mail: sukim@postech.ac.kr

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Introduction

Asthma is a chronic inflammatory disease of the airways and is associated with intermittent respiratory symptoms, such as recurrent wheezing and nocturnal cough, airway hyper-responsiveness (AHR), and/or reversible airflow obstruction [1]. Population studies conducted with asthma families have suggested that the disease has a genetic component [2]. Atopy, a genetic predisposition to IgE-mediated allergic diseases, is characterized by enhanced IgE responses to common allergens [3]. In terms of phenotypes, asthma is complex, with its intermediate phenotypes including atopy and AHR.

The IgE-mediated hyper-sensitivity reaction is initiated when an allergen cross-links IgE antibodies that are bound to their high-affinity Fc receptor (FcεRI) on tissue mast cells or blood basophils [4]. FcεRI consists of one α chain, one β chain, and two γ chains [5, 6]. The α chains are type I membrane proteins and contain the Fc binding sites in their extracellular (N-terminal) region, whereas the β and γ chains exert mainly cytoplasmic functions and act in cell signalling [7]. Among genetic variations of the FcεRI gene,

the β chain shows considerable variation, although the α and γ chains are highly conserved among species [8]. Previous linkage studies have suggested that atopy, AHR, or both are linked to the β chain of the high-affinity IgE receptor (FcεR1-β) on chromosome 11q13 [9–11]. The coding regions of FcεR1-β contain some non-synonymous single-nucleotide polymorphisms (SNPs) [12, 13]. Two amino acid substitutions in exon 6, isoleucine to leucine at residue 181 (I181L) and valine to leucine at residue 183 (V183L), were initially identified in the coding sequence of the FcεRI-β gene [14]. A previous association study found that the I181L variant was strongly associated with high total serum IgE levels [13]. An additional substitution, E237G, has been identified in exon 7 of the FcεRI-β gene, and the 237*G allele was found to be more prevalent in an Australian population of asthma subjects [15].

Mediator releasability from mast cells or basophils may be influenced by genetic factors [16]. Our previous study revealed that IgE-receptor-mediated histamine release from basophils is linked to a microsatellite marker of chromosome 11q13 [17]. We also found that histamine release from basophils was higher in asthmatic patients with the 237*G allele than in those with the 237*E allele [18]. The process of tyrosine phosphorylation in FcεRI signalling leads to the assembly of a 'signalling complex' of receptor-associated proteins [7]. This, in turn, leads to the production of inositol phospholipids, which signal a rise in the intracellular calcium essential for the release of preformed, granule-associated and newly generated mediators [19].

SNPs are used as markers in association studies to detect which regions of the human genome may be involved in diseases. SNPs in coding and regulatory regions may be implicated in disease pathogenesis. Non-synonymous SNPs that result in an amino acid change in the protein product are of major interest [20]. However, determining the functional importance of non-synonymous SNPs *in vitro* is time consuming and difficult. The sorting intolerant from tolerant (SIFT) program uses sequence evolutionary information to predict whether an amino acid substitution will affect protein function, and hence, potentially alter the phenotype [21].

We investigated whether non-synonymous SNPs of FcεRI (-α, -β, and -γ chains) genes were associated with atopy and AHR in a Korean population. We also tested the disease-causing potential of the genetic variations using SIFT analysis [22], which uses multiple sequence information to predict whether an amino acid substitution affects protein function.

Methods

Study subjects

All the subjects enrolled in this study gave written informed consent, and the study protocol was approved by the Ethics Committee of Seoul National University Hospital. A cohort of 2055 ethnically identical subjects from 10 to 18 years of age, living in rural areas of Jeju Island, Korea, was randomly recruited. The demographic characteristics of the cohort have been previously described [23].

Clinical phenotyping

Total serum IgE levels were determined by ELISA, as previously described [23]. To evaluate IgE responses to common aeroallergens, we performed skin prick test (SPT) of 11 locally common aeroallergens (Allergopharma, Reinbek, Germany), as described previously [23]. We defined atopy as a positive SPT response (allergen/histamine ratio >1.0, plus a mean weal size >4 mm) to one or more aeroallergens. To evaluate AHR, methacholine bronchial challenges were performed, as described earlier [23]. Methacholine AHR was expressed as PC20 and regarded as positive if <16 mg/mL. As a quantitative trait of AHR, the slope of the dose–response curve (DRS) was calculated as the percentage fall of forced expiratory volume in 1 s (FEV_1) divided by the last concentration (mg/mL) of methacholine.

Genotyping

Based on genomic sequences from GenBank, we designed primers to amplify six exons of FcεRI-α, seven exons of FcεRI-β, and five exons of FcεRI-γ genes. To identify informative SNPs (minor allele frequency $>2\%$), all of the exons were amplified on genomic DNA from 24 healthy subjects. All PCR products were sequenced, using Big Dye Terminator sequencing chemistry (Applied Biosystems, Foster City, CA, USA) in both directions, according to standard protocols. The sequencing of the FcεRI genes revealed one informative non-synonymous SNP (E237G, rs569108) from the FcεRI-β gene.

This SNP was scored via the high-throughput single base pair extension method (SNP-IT™ assay) using an SNPstream25K system (Orchid Biosciences, Princeton, NJ, USA), which was customized to automatically genotype DNA samples in 384-well plates and provide a colorimetric readout, as previously described [24]. The PCR forward and reverse primers were AGAGGATCGTGTTTATGAAGAATTAAAC and GAATCAGAGTGTTCTGGACACGT, respectively, and genotyping primer CTTACAGTGAGTTGGAAGACXCAGGGG.

Assessing the disease-causing potential of the E237G polymorphism

To test the pathological ramifications of the E237G polymorphism, we evaluated the likely effect of an amino acid alteration using the SIFT program [22]. We obtained amino acid sequences encoded by 16 FcεRI-β genes from the NCBI (US National Center for Biotechnology Information) database and used each entire sequence in FASTA

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format to run the SIFT program under its default settings. The SIFT algorithm estimates the effects of amino acid substitutions based on the assumption that amino acid positions that are important for the biological function of a protein are conserved across the protein family. It calculates normalized probabilities for all possible substitutions at each examined position of the protein and outputs the estimated tolerability, ranging from 0 to 1. When the calculated score is less than 0.05, the impact of the amino acid change is considered deleterious.

Statistical analysis

Student's t and χ^2 tests were used for continuous and categorical variables, respectively. The genotype was examined as a three-component variable (i.e. AA, AB, and BB; where A is the major frequency allele and B is the minor frequency allele). To determine whether one of the homozygous genotypes had an effect that differed from the common effects of the heterozygous genotype and the other homozygote, we obtained the P-value using χ^2 tests employing both the recessive (AA vs. AB+BB) and dominant (BB vs. AB+AA) models of the major allele. To determine the relative risk (RR) and 95% confidence interval (CI), we performed multiple logistic regression modelling to adjust for confounding variables, such as age, sex, family history of allergic diseases, and history of passive smoking. The Hardy–Weinberg equilibrium of the study population was tested using the χ^2 test ($P = 0.803$). All statistical analyses were performed using SAS software (version 8.1; Cary, NC, USA). $P < 0.05$ was regarded as significant.

Results

Lack of an association between E237G and atopy and total serum immunoglobulin E levels

We found that the positive rate of atopy was similar in subjects with the 237*E and those with the 237*G allele [$P = 0.23$ in a recessive model of the major allele; RR (95% CI) = 1.11 (0.90–1.38)]. Moreover, the total serum IgE levels were similar in the two groups ($P = 0.27$). Table 1 shows the relationship between the E237G genotype and atopy prevalence and total serum IgE levels in the cohort.

Positive association between E237G and a positive rate of airway hyper-responsiveness

Table 2 shows the relationship between E237G and the positive rate of AHR in the cohort. Our data showed that the positive rate of AHR was significantly lower among subjects with the 237*E allele than those with the 237*G allele [$P = 0.01$ in a recessive model; RR (95% CI) = 0.41 (0.19–0.89)]. The positive rate of AHR was significantly lower in atopic subjects with the 237*E allele than in those with the 237*G allele [$P = 0.01$ in a recessive model; RR (95% CI) = 0.29 (0.10–0.84)]. However, the positive rate of AHR was similar in non-atopic subjects with the 237*E allele and those with the 237*G allele [$P = 0.26$; RR (95% CI) = 0.83 (0.62–1.13)]. As a quantitative trait of AHR, DRS was compared according to geneotypes. The present study also showed that DRS was significantly higher in subjects with 237*G allele than in those with 237*E allele ($P = 0.02$ in a recessive model) (Fig. 1).

Sorting intolerant from tolerant analysis of disease-causing potential of E237G

SIFT analysis was performed to assess the functional importance of the E237G non-synonymous SNP. The 237*G allele was assigned a 0.01 SIFT score, which indicates a possible disease-causing mutation (SIFT score < 0.05). The glycine substitution at 237 was intolerant. The sequence alignment comparing the substitution was made on seven different homologues of FcεRI-β. As shown in Fig. 1, position 237 is highly conserved, with positive charged amino acids, such as glutamate and aspartate. Thus, the sequence evolution analysis predicted

Table 1. Relationship between the E237G polymorphism of FcεRI-β and atopy and total serum IgE levels

Genotypes	E237G				
Phenotypes	EE	EG	GG	P*	RR (95% CI)†
Atopy‡					
+	568 (80.8%)	120 (17.1%)	15 (2.1%)	0.23	1.11 (0.90–1.38)
−	936 (77.4%)	259 (21.4%)	15 (1.2%)		
log (total IgE)§	1.86 ± 0.78	1.83 ± 0.80	1.87 ± 0.76	0.27	

*χ^2 test (recessive model of major allele: EE vs. EG+GG).

†Multiple logistic regression analysis, after adjusting for confounders, such as, age, sex, family history of allergic disease, and history of passive smoking.

‡A positive skin test response to one or more common aeroallergens, expressed as the number (%).

§Mean ± SD.

RR, relative risk; CI, confidence interval.

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Table 2. Relationship between the E237G polymorphism of FcεRI-β and airway hyper-responsiveness (AHR)

Genotypes / Phenotypes	E237G EE	EG	GG	*P**	RR (95% CI)†
AHR‡					
+	372 (76.2%)	103 (21.1%)	13 (2.7%)	0.01	0.41 (0.19–0.89)
−	1116 (79.4%)	274 (19.5%)	16 (1.1%)		
Atopic AHR§					
+	169 (77.5%)	40 (18.3%)	9 (4.1%)	0.01	0.29 (0.10–0.84)
−	383 (82.2%)	77 (16.5%)	6 (1.3%)		
Non-atopic AHR¶					
+	196 (74.8%)	62 (23.7%)	4 (1.5%)	0.26	0.83 (0.62–1.13)
−	717 (77.9%)	193 (21.0%)	10 (1.1%)		

*χ^2 test (recessive model of major allele: EE vs. EG+GG).

†Multiple logistic regression analysis after adjusting for confounders, such as, age, sex, family history of allergic disease, and history of passive smoking.

‡PC_{20}-methacholine <16 mg/mL, expressed as a number (%).

§PC_{20}-methacholine <16 mg/mL in atopic subjects, expressed as a number (%).

¶PC_{20}-methacholine <16 mg/mL in non-atopic subjects, expressed as a number (%).

RR, relative risk; CI, confidence interval.

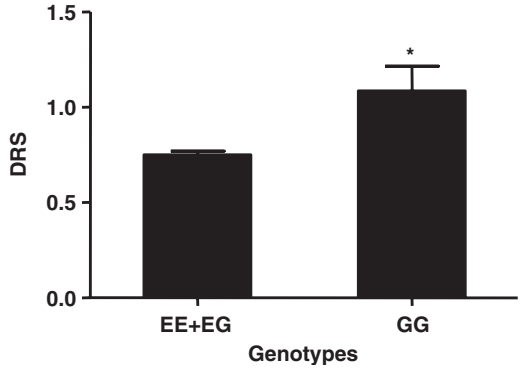

Fig. 1. Slope of dose–response curve (DRS) of methacholine challenge, a quantitative trait of airway hyper-responsiveness, according to genotypes of FcεRI-β. *$P < 0.05$ using recessive model of minor allele.

the E237G variation to be an intolerant amino acid substitution having functional relevance.

Discussion

Responses by T lymphocyte T-helper type 2 (Th2) to common environmental aeroallergens are a primary factor in the development of atopic asthma [25]. Th2 responses are classically associated with IgE, FcεRI, and mast cells in mucosal tissues. *In situ* assays have revealed that FcεRI is copiously expressed on mucosal mast cells in the nose and lungs, and further up-regulated in subjects with allergic rhinitis and asthma [26]. FcεRI is expressed as an αβγ2 heterotetramer in mast cells and basophils (possibly eosinophils), and as an αγ2 heterotrimer in monocytes and platelets [27]. The α chains (FcεRI-α) are type I integral membrane proteins and contain the Fc binding sites in their extracellular (N-terminal) region, whereas the β and γ chains exert mainly cytoplasmic functions and act in cell signalling (Fig. 2). Moreover, the β chain enhances the strength of signal transduction and assists in transporting the receptor to the cell surface [7, 28].

Cookson and colleagues found evidence linking a gene on the chromosome 11q12–13 region to atopy [9, 10]. The linkage between this region of chromosome 11 and atopy, AHR, or both has been replicated by some, but not all, studies working with independent sets of probands, suggesting heterogeneity in genetic susceptibility to atopy and AHR [17, 29]. The FcεRI-β gene consists of seven exons, spans about 11 kb, and contains an upstream TATA box. Exon 1 encodes the 5′-untranslated region and a portion of the N-terminal cytoplasmic tail. Transmembrane (TM) domain 1 is encoded by exons 2 and 3, TM2 by exons 3 and 4, TM3 by exon 5, and TM4 by exon 6. Exon 7 encodes the end of the C-terminal cytoplasmic tail, including the FcεRI-β immunoreceptor tyrosine-based activation motif (ITAM) and the 3′-untranslated region [30]. Several coding sequence polymorphisms in the FcεRI-β gene that are associated with allergic phenotypes were subsequently identified [31–33]. The first to be described is in the fourth TM domain and consists of a leucine substitution for isoleucine at position 181 [31]. Subsequent analyses showed that this polymorphism is generally found together with a second amino acid change (V183L) and that this double substitution is associated with atopy [33]. However, these polymorphisms are uncommon in the general population [33]. Indeed, in a Korean population, direct sequencing of the FcεRI-β gene failed to reveal any variation in these regions.

A third polymorphism of the FcεRI-β gene consists of a glutamate to glycine substitution at position 237 (E237G). This polymorphism was reported to be strongly associated

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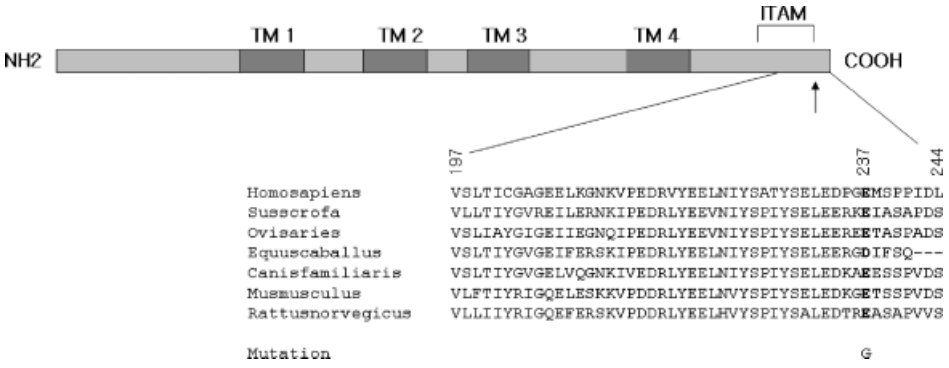

Amino acid change	Protein	Amino acid	Prediction	Score	Median sequence IC
E237G	Fc ε RI-β	G	Damaging	0.01	3.53
		E	Tolerated	1.00	

Fig. 2. Topology of FcεRI-β and the deleterious substitution predicted by sorting intolerant from tolerant program. E237G single-nucleotide polymorphism lies adjacent to an immunoreceptor tyrosine-based activation motif (ITAM, 216-DxxYxxLX_6YxxL-232) of FcεRI-β [30].

with atopy and AHR and was present in 5% of an Australian population [32]. Interestingly, the E237G substitution occurs at a higher frequency (21%) in the Korean general population, as well as Japanese (23%) and Chinese (18%) populations [12, 34] than in populations of English-speaking countries [32, 35]. However, our study showed that the E237G substitution was not associated with a positive rate of atopy or total serum IgE levels, which suggests that genetic variations other than FcεRI-β E237G play an important role in the predisposition of a Korean population to atopy.

AHR is closely associated with asthma, and is believed to be an important risk factor in its development [36]. Our data, however, indicate that the 237*G allele frequency is positively associated with a positive rate of AHR, especially among atopic subjects, but not among non-atopic subjects. Mast cell infiltration into the airways is Th2 cytokine dependent, and recent data have demonstrated that the essential difference between asthma and non-asthmatic eosinophilic bronchitis (a condition characterized by a recurrent cough without AHR) is the infiltration of mast cells into the airway smooth muscle cells [37, 38]. Moreover, mediators from mast cells, including IL-13, have been shown to enhance AHR [38, 39]. Taken together, these findings suggest that FcεRI-β-mediated signalling is important in the expression of AHR.

Until now, the functional importance of the E237G substitution in FcεRI-β-mediated signalling has been unclear [40]. Our previous data demonstrated that FcεRI-mediated histamine release from basophils was significantly higher in subjects with the 237*G allele than in those with the 237*E allele [18]. To further evaluate the functional relevance of E237G substitution, we performed a SIFT analysis, resulting in a score of 0.01 for the 237*G allele, which is lower than that for a possible disease-causing mutation (SIFT score < 0.05). Moreover, the sequence evolution analysis showed that E237G variation is an intolerant amino acid substitution, which has a functional importance. These findings suggest that the E237G substitution in the FcεRI-β gene may enhance FcεRI signalling and result in the release of proinflammatory mediators and cytokines in response to receptor cross-linking.

Many immunoglobulin and antigen receptors are thought to transduce signals through cytoplasmic ITAM tail structures [41]. The ITAM consensus sequence is (D/E)xxYxxLX_{7-11}YxxL(L/I), where the tyrosine residues are phosphoacceptor sites for the action of receptor-associated protein tyrosine kinases [41]. Two forms of ITAM appear in FcεRI, one in the β chain and the other in the γ chain [19]. It has been proposed that FcεRI-γ functions as an autonomous activation module, whereas FcεRI-β has the functional properties of an amplifier [7]. In contrast, the idea that FcεRI-β functions as a negative regulator of FcεRI-γ-mediated signalling was suggested by the finding that FcεRI-β ITAM, but not FcεRI-γ ITAM, binds *in vitro* to SH2-containing tyrosine (SHP-1 and SHP-2) and SH2-containing inositol-5′-phosphatase (SHIP), which are negative regulators in signalling pathways [42, 43]. E237G lies adjacent to the FcεRI-β ITAM, as shown in Fig. 1. A Glu → Gly substitution adjacent to the FcεRI-β ITAM may alter the hydrophilic nature of the C-terminus of the β chain adjacent to ITAM by substituting a polar uncharged glycine for the larger negatively charged polar glutamic acid residue. Based on our previous finding that the E237G substitution enhances histamine release from

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basophils [18], we postulate that the E237G substitution modulates FcεRI-mediated intracellular signalling ability and results in the enhanced production of proinflammatory mediators and cytokines, which enhances AHR, especially in atopic subjects. However, we cannot exclude the possibility that the significant association may be due to linkage disequilibrium with other potential markers on chromosome 11q13 [44].

In summary, to our knowledge, this is the first report demonstrating a significant association and functional relevance of a non-synonymous SNP (E237G) of FcεRI-β with AHR in the general population. These findings indicate the importance of the E237G allele as a genetic marker to predict asthma susceptibility in the Korean population.

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