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Association between atopic asthma and a coding variant of FcεRIβ in a Japanese population

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A genetic association study was performed with coding variants of FcεRIβ in relation to atopic and non-atopic asthma in a Japanese population (n = 400). A coding variant of Gly237Glu in exon 7 of FcεRIβ gene showed association with atopic asthma (OR = 3.00, χ^2 = 5.10, p <0.03), but not with non-atopic asthma; this was seen particularly in childhood asthma (OR = 3.92, χ^2 = 8.66, p <0.005). This variant is also associated with very high total serum IgE levels (>mean + 3 SD, OR = 8.56, χ^2 = 46.2, p <0.0001), but not any allergen specific IgE. However, Leu181Ile, another variant of FcεRIβ related to atopy in British and Australian populations, was not found in this Japanese population. These results suggest that variants of FcεRIβ may be an important genetic cause of the atopic asthma.

INTRODUCTION

Atopy is a common disorder characterized by increased general IgE responsiveness. At most, 60% of atopic asthmatic families in Caucasian populations are linked to chromosome 11q13 through the maternal line (1,2). Data from Japan using lod scores (3) and the Netherlands using affected sib-pair method (4) have confirmed linkage in families with marked atopic asthmatics. The β subunit of the high affinity IgE receptor (FcεRIβ) gene, mapped there is one of the candidate genes for atopy because of its important role in initiating type I allergic reaction in mast cells and basophils (1,2). Leu 181 variant of FcεRIβ was identified in 15% of English asthmatic families, was maternally inherited in each and showed significant association with atopy (5). However, there has been difficulty in replicating this finding (6,7). We therefore developed a simple PCR-based *Rsa*I RFLP within intron 2 of FcεRIβ and showed that atopy is strongly associated with FcεRIβ (8). Furthermore a new coding variant Gly237Glu in exon 7 of FcεRIβ has been found in 5% of the Australian population and associates with atopy and bronchial hyperresponsiveness (BHR) (9).

We therefore tested whether Gly237Glu and Leu181Ile variants of FcεRIβ are associated with atopy in a Japanese population.

RESULTS

We failed to detect Leu181 in the Japanese population by ARMS testing, and by sequencing samples from 10 atopic subjects.

In the control sample, Gly237 was found in 6%, of whom all were heterozygous. There was a significantly higher prevalence of Gly237 in atopic asthma (OR = 3.43, χ^2 = 10.6, p = 0.002). This is clearer in childhood asthma (OR = 3.92, χ^2 = 8.66, p = 0.005) than adult asthma (OR = 3.00, χ^2 = 5.10, p = 0.025). Non-atopic asthma showed no association (OR = 1.36, χ^2 = 0.31, p = 0.78) with Gly237 in FcεRIβ. Adult asthma including atopic and non-atopic asthma also did not associate (OR = 2.13, χ^2 = 3.55, p = 0.07) with this variant. The Gly237 was associated with atopy (OR = 2.86, χ^2 = 9.72, p = 0.001). This variant is especially associated with very high IgE (>1000 IU/ml, OR = 8.56, χ^2 = 46.2, p <0.0001), but not with any allergen specific IgE. No individual homozygous for Gly237 was found in our population (Table 1).

DISCUSSION

The genetics of atopy is complex and heterogeneous (1–5). Recent studies on linkage analysis have provoked lively debate on the importance of different loci, and in particular the putative atopy locus on chromosome 11q (6,7).

In order to rigorously test the possible importance of this locus we have conducted a large-scale genetic association study in a clinically well characterized Japanese population (8). We have previously utilized a robust PCR/restriction digest-based assay for an intronic polymorphism within FcεRIβ, the principal candidate gene at this location (1–3).

We now demonstrate association between a coding variant Gly237Glu of FcεRIβ, and atopic asthma (OR = 3.00), and with elevated IgE levels (OR = 8.56). We found a strong association with childhood asthma (OR = 3.92).

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Table 1. Association between Gly237Glu of FcεRI and asthma, specific and total IgE

	FcεRIβ					
	No. of cases	Glu237/ Glu237	Glu237/ Gly237	OR	χ^2	*p*
Control	100	94	6			
Atopic asthma						
adult+child	200	164	36	3.43	10.6	0.002
adult	100	84	16	3.00	5.10	0.025
child	100	80	20	3.92	8.66	0.005
Non-atopic asthma						
adult	100	92	8	1.36	0.31	NS
Non-atopic	178	166	12			
Atopic	222	184	38	2.86	9.72	0.001
very high (>1000) IgE[a]	46	26	20			
lower (<1000) IgE	364	334	30	8.56	46.2	0.0001
anti-HD IgE negative	204	179	25			
anti-HD IgE positive	196	161	35	1.55	2.86	NS

[a]Of 46 cases, 32 cases are adult asthma. 1000 IU/ml is based on mean + 3 SD in both adult and child populations in Japan.
HD: house dust, NS: not significant. No one with homozygous Gly237 was found.

Van Herwerden and co-workers report a sib-pair study which is concordant with our linkage between atopic asthma and FcεRIβ, but which emphasizes that this linkage may be with BHR rather than atopy (10). Data on a Western Australian population shows co-association of Gly237 with atopy and BHR (9). However, our Japanese data show no association between this variant and non-atopic asthma, characterized by BHR but not atopy, suggesting that the linkage with BHR in an Eastern Australian population (11) is secondary to the strong linkage with atopy. Further replication studies and, more particularly, biological studies of the functional consequences of this variant of FcεRIβ are required.

MATERIALS AND METHODS

One hundred subjects were selected as controls from clients in a commercial-based medical examination company. Sex and age were adjusted on the basis of those in this area. Patient samples (100 each with adult atopic asthma, adult non-atopic asthma, childhood atopic asthma, atopic rhinitis and eczema) were recruited from Kawai Clinic, Osaka Medical College Hospital, Wakayama Red Cross Hospital and Osaka University Hospital, respectively. There were no heavy smokers (>20 cigarettes per day) in those subjects.

Atopy, defined as IgE responsiveness, may be diagnosed as the presence of high concentration of total serum IgE, a positive specific IgE titre against one or more of 15 highly-purified aero-allergens, or a combination of these two features as we have previously shown (1,2). Non-atopy was defined as none of those three IgE responsiveness. Specific IgE was detected by MAST (Hitachi, Tokyo, Japan) and the criteria for a positive titre were as used previously (1,2). A high total IgE (CAP, Uppsala, Sweden) was taken to be greater than published normal values for children or greater than 400 kU/l (mean + 2SD) in adults.

DNA samples were extracted using a commercial kit (IsoQuick, Microprobe Corporation, Garden Grove, USA). A polymerase chain reaction (PCR) in a mixture including 1.5 mmol/l of magnesium chloride was performed in a Perkin Elmer Cetus thermal cycler using a preliminary cycle (94°C denaturation for 5 min, 60°C annealing for 1 min, and 72°C extension for 1 min) and then 39 cycles (94°C for 30 s, 60°C for 30 s, and 72°C for 30 s). In order to incorporate the polymorphic site (Gly237Glu) into an *Xmn*I recognition site, primers were 5′CAGGTTCCAGAGGACGT and 5′CTTATAAATCAATGGG AGGAAACA (11).

Allele specific DNA amplification (ARMS) for Leu181Ile variant of FcεRIβ was also performed with positive control DNA (homozygous Leu181Ile from a British family) (5).

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