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ORIGINAL INVESTIGATION

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Association between nasal allergy and a coding variant of the *FcεRIβ* gene Glu237Gly in a Japanese population

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Abstract The gene for the β-chain of the high-affinity receptor for IgE (*FcεRIβ*) has been proposed as a candidate gene for atopy. A coding variant Glu237Gly has been studied in various populations with asthma and atopy, and the results were controversial for association of the variant with atopy/asthma. Because nasal allergy is a more common atopic disease and shows less remission than asthma, we analyzed whether the Glu237Gly variant is correlated with nasal allergy. The study enrolled 233 patients with nasal allergy and 100 control subjects. Further, three subgroups were selected: patients with perennial nasal allergy (*n*=149), Japanese cedar pollinosis (*n*=189), and allergy to multiple allergens (*n*=45). The allele frequency of Gly237 in the controls and patients was 0.14 and 0.20, and the frequency of Gly237-positive subjects was 0.23 and 0.356, respectively. There was a significant association between Gly237-positivity and nasal allergy, perennial nasal allergy, Japanese cedar pollinosis, and allergy to multiple allergens. Among all 333 subjects we observed a significant relationship between Gly237 and elevated levels of serum total IgE (>250 IU/ml) and very high IgE (>1000 IU/ml). Among patients positive for a specific IgE, Gly237 was significantly associated with high IgE for house dust, mite, and Japanese cedar pollen. These results suggest that the Glu237Gly variant of the *FcεRIβ* gene is involved in the development of nasal allergy through the process for the production of both specific and nonspecific IgE antibodies.

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Introduction

Nasal allergy is a common atopic disease, the prevalence of which is around 20% or more in Western countries (Sly 1999; Strachan et al. 1997). Various factors such as duration of breast feeding, maternal age, social class, heating with wood or coal, and exposure to diesel exhaust fumes are believed to affect the prevalence of nasal allergy (Butland et al. 1997; Duhme et al. 1998). However, it is generally accepted that the best established risk factor for nasal allergy is a family history of allergy, especially nasal allergy (Bahna 1992; Sibbald and Rink 1991; Wright et al. 1994), indicating that genetic factors strongly influence nasal allergy.

Many studies have been performed on the genetics of atopy since Cookson et al. (1989) first described a linkage between serum IgE level and a DNA marker for chromosome 11q in British families. Regarding the chromosome 11q some studies have confirmed the linkage of atopy and bronchial hyperresponsiveness to markers on 11q13 (Adra et al. 1999; Collée et al. 1993; Daniels et al. 1996; van Herwerden et al. 1995; Mao et al. 1997; Shirakawa et al. 1994a; Young et al. 1992), while others have failed to find the linkage (Amelung et al. 1992; Collaborative Study on the Genetics of Asthma 1997; Hizawa et al. 1992; Lympany et al. 1992; Malerba et al. 1999; Ober et al. 1998; Rich et al. 1992; Wjst et al. 1999; Yokouchi et al. 2000). Meanwhile, the gene for the β-chain of the high-affinity receptor for IgE (*FcεRIβ*) has been identified as a candidate gene for this linkage between atopy and 11q13 (Sandford et al. 1993), and two coding variants in exon 6 of *FcεRIβ*, Ile181Leu/Ile183Val and Ile181Leu, are reported to be associated with atopy in British subjects (Shirakawa et al. 1994b). These variants subsequently proved to be rare in other races, and another coding variant Glu237Gly in exon 7 was identified as a more common coding variant (Hill and Cookson 1996). Some reports show an association of this variant with atopy and/or bronchial hyperresponsiveness while others do not. Thus, it appears to await clarification whether this coding variant of *FcεRIβ* influ-

ences the development of atopic diseases, by studying different populations with various phenotypes. Because nasal allergy is a more common atopic disease and shows less chance of remission than bronchial asthma (Sly 1999), it would be interesting to perform a genetic study in a population with nasal allergy. However, such studies are very few, and there has been no report to date studying the association between nasal allergy and the coding variant of *FcεRIβ* Glu237Gly. Therefore in the present study we analyzed whether this coding variant of *FcεRIβ* shows association with nasal allergy.

Materials and methods

Subjects

This study enrolled 233 subjects with nasal allergy (age 7–71 years) and 100 control subjects (age 15–79 years). All the subjects were unrelated Japanese and residents in the Tokyo area, mainly in Chiba prefecture, a suburb of Tokyo. They were outpatients of Chiba University Hospital and affiliated hospitals. All patients underwent measurement of total serum IgE levels (IU/ml) and specific IgE antibody levels (UA/ml) to at least six inhalant allergens including house dust (HD; Greer Labs, Lenoir, N.C., USA), mite (*Dermatophgoides pteronyssinus*), pollens of Japanese cedar (*Cryptomeria japonica*), common ragweed (*Ambrosia artemisiifolia*), cocksfoot (*Dactylis glomerata*), and mugwort (*Artemisia vulgaris*) by radioallergosorbent test (RAST). The level of a specific antibody (RAST score) was classified as follows; score 6, higher than 100 UA/ml; score 5, 50.0–99.9 UA/ml; score 4, 17.5–49.9 UA/ml; score 3, 3.50–17.4 UA/ml; score 2, 0.70–3.49 UA/ml; score 1, 0.35–0.69; score 0, less than 0.34 UA/ml. Generally a RAST score of 2 or more is regarded as positive, a score of 0 is negative, and a score of 1 is equivocal.

The diagnosis of nasal allergy was made on the basis of a positive RAST score (≥2) for an allergen and a history of reasonably recurrent sneezing, watery rhinorrhea, and nasal obstruction. Further, three patient subgroups were selected among the 233 patients with nasal allergy; (a) patients with perennial nasal allergy (n=149) who were positive for HD and mite; (b) patients with Japanese cedar pollinosis (n=189); and (c) patients with allergy to multiple inhalant allergens (n=45) who were included in the former two subgroups and positive for HD, mite, Japanese cedar pollen, and another or more allergens. The subgroups a and b shared 103 patients who had Japanese cedar pollinosis and perennial allergy. Twenty-seven of the 149 patients with perennial nasal allergy and two other patients with Japanese cedar pollinosis had a history of asthma. Controls were patients with chronic sinusitis, hypertrophic rhinitis, smell disturbance, or throat discomforts, unassociated with a history of nasal allergy or other atopic diseases, and negative for specific IgE antibodies. This study was approved by the ethics committee of Graduate School of Medicine, Chiba University.

The levels of total serum IgE were 56.1±59.2 IU/ml in controls (n=100), 641.5±1234 IU/ml in patients with nasal allergy (n=233), 906.5±1474 IU/ml in patients with perennial nasal allergy (n=149), 662.3±1309 IU/ml in patients with Japanese cedar pollinosis (n=189), and 1437±2190 IU/ml in patients with allergy for multiple allergens (n=45). The RAST scores were 4.05±1.41 UA/ml for HD and 4.12±1.42 UA/ml for mite in patients with perennial nasal allergy (n=149), and those for Japanese cedar pollen in patients with Japanese cedar pollinosis (n=189) were 3.47±1.17 UA/ml.

Analysis of the *FcεRIβ* polymorphism

A restriction endonuclease fragment length polymorphism (RFLP) of a polymerase chain reaction (PCR) product was used for analysis of the Glu237Gly polymorphism. Genomic DNA extracted from peripheral blood was amplified by the PCR with primers 5′CAGGTTCCAGAGGATCGTGTTTATG3′ (upstream) and 5′GATTCTTAT AAATCAATGGGAGGAAAC 3′ (downstream) to incorporate the Glu237Gly polymorphic site into an *Xmn*I recognition site (Shirakawa et al. 1996). PCR was performed with reagents composed of 200 nmol/l primers, 150 μmol/l dNTPs, 20 mmol/l Tris HCl, pH 8.4, 50 mmol/l KCl, 1.5 mmol/l $MgCl_2$, and 1.5 U *Taq* DNA polymerase in a 100 μl reaction solution. The program was 94°C for 1 min, 55°C for 1 min, and 72°C for 1 min for 35 cycles. The PCR product was precipitated with 20 μg Glycogen (Roche Diagnostic, Mannheim, Germany), dissolved in 35 μl distilled water, and 10 μl of this was digested with 5 U *Xmn*I (New England Biolabs, Beverly, Mass., USA) at 37°C overnight. Digested fragments were separated on a 6% polyacrylamide gel. The size of the PCR product was 107 bp, and digested fragments derived from the Glu237 allele were 80 bp and 27 bp. PCR products from the Gly237 allele were not cut with *Xmn*I (Fig. 1). The results of the analysis were confirmed by direct sequencing of PCR products amplified from three genotypes, Glu/Glu, Glu/Gly, and Gly/Gly. If a PCR-RFLP analysis showed uncut bands, i.e., the subject was positive for Gly237, the analysis was repeated to confirm the results.

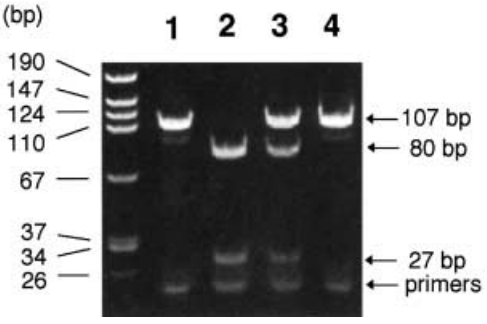

Fig. 1 PCR-RFLP analysis with *Xmn*I for the Glu237Gly polymorphism of the *FcεRIβ* gene. *Lanes 2–4* Digested PCR products from a Glu237 homozygote (*lane 2*), a Glu/Gly237 heterozygote (lane 3), and a Gly237 homozygote (*lane 4*); *lane 1* an undigested control. The size marker is Molecular Weight Marker VIII (Roche Diagnostic, Mannheim, Germany)

Statistical analysis

The association of the Glu237Gly variant with the patient groups, elevated serum total IgE, and the level of specific IgE for HD, mite, and Japanese cedar pollen was analyzed by χ^2 test (SPSS, USA). In addition, the level of serum total IgE was compared between genotypic groups by Student's unpaired t test. Statistical significance was defined as P<0.05; P<0.01 was regarded as highly significant.

Results

The frequency of the Glu237 and the Gly237 alleles and the genotypes is presented in Table 1. Because the frequency of homozygotes of Gly237 was low, and the Gly237 allele appeared to be associated with nasal allergy, the χ^2 test for a 2×2 table was performed for homozygotes of Glu237 versus heterozygotes and homozygotes of Gly237 between the controls and the patient groups (Table 1). The χ^2 test showed that the Gly237 allele was significantly associated with nasal allergy for any allergens (P<0.05),

Table 1 Association between Glu237Gly and nasal allergy, and total and specific IgE

	No. of subjects	Glu237 homozygotes	Gly237 (heterozygotes, homozygotes)	χ^2	P
Control	100	77	23 (18, 5)		
Nasal allergy					
Total	233	150	83 (76, 7)	5.137	0.023
Positive for HD and mite	149	96	53 (46, 7)	4.459	0.035
Positive for cedar pollen	187	117	70 (64, 6)	6.197	0.013
Positive for multiple allergen	45	21	24 (21, 3)	13.035	<0.001
Control + nasal allergy (*n*=333)					
High IgE (≥250)	112	67	45 (40, 5)	5.418	0.020
Lower IgE (<250)	221	160	61 (54, 7)		
Very High IgE (≥1000)	37	14	23 (19, 4)	17.647	<0.001
Lower IgE (<1000)	296	213	83 (75, 8)		
Perennial nasal allergy (*n*=149)					
High RAST score for HD (6)	29	14	15 (12, 3)	4.100	0.043
Lower RAST score for HD (2–5)	120	82	38 (34, 4)		
High RAST score for mite (6)	34	17	17 (15, 2)	4.002	0.045
Lower RAST score for mite (2–5)	115	79	36 (31, 5)		
Japanese cedar pollinosis (n=187)					
High RAST score for cedar pollen (5, 6)	36	17	19 (18, 1)	4.482	0.034
Lower RAST score for cedar pollen (2–4)	151	100	51 (46, 5)		

perennial nasal allergy (P<0.05), and Japanese cedar pollinosis (P<0.05). Further, nasal allergy to multiple allergens showed a strong association with Gly237 (P<0.001).

Among all 333 subjects, including controls and patients with nasal allergy, we found a statistically significant relationship between the Gly237 allele and the level of serum total IgE (Table 1). When a cutoff level was set at 250 IU/ml, Gly237-positive subjects were significantly associated with total IgE higher than 250 IU/ml (P<0.05). When a cutoff level was set at 1000 IU/ml, the P value fell below 0.001. In addition, the serum total IgE level was significantly higher in the heterozygotes and homozygotes of Gly237 than in the homozygotes of Glu237 (695.5±1161 vs. 358.4±1005 IU/ml, P=0.007).

In terms of specific IgE, we performed the χ^2 test between the Glu237Gly polymorphism and various levels of RAST scores for HD, mite or Japanese cedar pollen among subjects who were positive for respective allergens (Table 1). As a result we found a significant association between the Gly237 allele and high RAST scores for HD (score 6, P<0.05) and mite (score 6, P<0.05) as well as high RAST scores for Japanese cedar pollen (scores 5 and 6, P<0.05).

Discussion

The present findings show that the Glu237Gly variant of the *FcεRIβ* gene is associated with nasal allergy and atopy in a Japanese population. To our knowledge, this is the first report studying the association between a candidate gene for atopy and nasal allergy. The results showed that the Gly237 allele was associated with cedar pollinosis, which is the most common seasonal allergy in Japan, as well as perennial nasal allergy to HD and mite. In addition, the Gly237 allele was associated with an elevated level of serum total IgE, specific IgE to HD, mite and Japanese cedar pollen. Moreover, a strong association was found between the Gly237 allele and very high total IgE (>1000 IU/ml) as well as nasal allergy to multiple inhalant allergens. Furthermore, the serum total IgE level was highly elevated in subjects with the Gly237 allele compared with the homozygotes of Glu237.

These results suggest that the Glu237Gly variant of the *FcεRIβ* gene is involved in the development of nasal allergy through the process for the production of both specific and nonspecific IgE antibodies. One of the possible mechanisms for this is that the Gly237 allele elevates the signaling activity and expression of FcεRI on mast cells and let them release more proallergic cytokines including interleukin 4, which is essential for synthesis of IgE. Indeed, the β-chain of FcεRI is reported to act as an amplifier of FcεRI-mediated cell activation signals (Lin et al. 1996) and of receptor expression (Donnadieu et al. 2000b), and the Glu237Gly site is located in close proximity to the immunoreceptor tyrosine activation motif in the β-chain (Hill and Cookson 1996). However, Donnadieu et al. (2000a) recently showed that transfection of a variant β-chain with Gly237 to human monocytic and basophilic cell lines have no direct effect on the amplifier functions of the β-chain. Moreover, Furumoto et al. (2000) reported that introduction of Glu228Gly, which is a mouse homologue for the Glu237Gly variant in human, to murine mast cells does not elevate IgE-mediated mast cell activation.

Therefore the basic mechanisms for the elevation of IgE antibodies and the development of nasal allergy by the Glu237Gly polymorphism remain to be clarified. As suggested by Donnadieu et al. (2000a), the variant β-chain may be in linkage disequilibrium with other more relevant polymorphisms or affecting unknown β-chain functions.

It is known that the prevalence of the Glu237Gly variant varies greatly by ethnicity. The frequency of the Gly237 allele has been reported to be 0.026 in an Australian general population (Hill and Cookson 1996), none in another Australian population (Dickson et al. 1999), 0.026 in Swiss controls without atopy (Rohrbach et al. 1998), 0.185 in Japanese controls in the northern Kyushu area (Takabayashi et al. 2000), 0.103 and 0.13 in Japanese controls in Tsukuba and Fukuoka, respectively (Ishizawa et al. 1999), 0.03 in another Japanese control population (Shirakawa et al. 1996), 0.20 and 0.05 in black and white controls, respectively, in South Africa (Green et al. 1998), 0.01 in French-Canadian controls (Laprise et al. 2000), 0.04 in Italian controls (Trabetti et al. 1998), and 0.159 and 0.032 in Asian and White infants, respectively, in Canada (Zhu et al. 2000). In the present study the allele frequency of Gly237 in the nonatopic controls was 0.14. In the Japanese population the frequency in controls reported by Shirakawa et al. (1996) was much lower than those in the other studies; this may be due to the difference in recruitment of the controls since their controls were clients of a commercial medical examination company. In general, the frequency of the Gly237 allele appears to be higher in Japanese and other Asian populations than in white populations. Thus, it may be that the Glu237Gly variant is one of major genes involved in nasal allergy in Japanese.

The association of the Glu237Gly polymorphism with atopy and/or asthma has been controversial. Hill and Cookson (1996) observed that the Glu237Gly polymorphism is associated with atopy and bronchial hyperresponsiveness in an Australian population. Shirakawa et al. (1996) reported that the polymorphism was associated with atopic asthma but not with nonatopic asthma in a Japanese population. Laprise et al. (2000) used strict criteria for asthma and atopy and observed a strong association between atopy and the Glu237Gly variant in a French-Canadian population. On the other hand, neither of two Japanese groups found an association between the Glu237Gly polymorphism and atopy or asthma in Japanese children (Ishizawa et al. 1999; Takabayashi et al. 2000). Likewise, no association between the Glu237Gly polymorphism and atopy or asthma was detected in Swiss children (Rohrbach et al. 1998).

Discrepancies between the findings of these studies may be partly accounted for by genuine genetic heterogeneity, but they may also be due to differences in method among the groups. In particular, there is no consensus on the definition of a condition of atopic and nonatopic asthma. In addition, there is the problem that younger controls may develop atopy and asthma in the future and thus do not serve as good controls. Thus individuals may be classified both as normal and affected by atopic or nonatopic asthma. In contrast, a great majority of patients with allergic nasal symptoms and positive RAST scores for inhalant allergens are considered to have nasal allergy. In addition, the 10-year remission rates of allergic rhinitis are as low as 10–20%, and the prevalence of nasal allergy is higher than that of asthma (Sly 1999). Therefore nasal allergy appears to be more commonly associated with atopy than asthma, and consequently a genetic study on nasal allergy probably provides us with useful knowledge for genetic mechanism for atopy. Moreover, because the mechanisms for the development of atopic diseases such as asthma, nasal allergy, and atopic dermatitis should vary somewhat, more genetic studies on nasal allergy and atopic dermatitis would help us in understanding the significance of the Glu237Gly polymorphism in the development of atopic diseases.

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References

Adra CN, Mao XQ, Kawada H, Gao PS, Korzycka B, Donate JL, Shaldon SR, Coull P, Dubowitz M, Enomoto T, Ozawa A, Syed SA, Horiuchi T, Khaeraja R, Khan R, Lin SR, Flinter F, Beales P, Hagihara A, Inoko H, Shirakawa T, Hopkin JM (1999) Chromosome 11q13 and atopic asthma. Clin Genet 55:431–437

Amelung PJ, Panhuysen CI, Postma DS, Levitt RC, Koeter GH, Francomano CA, Bleecker ER, Meyers DA (1992) Atopy and bronchial hyperresponsiveness: exclusion of linkage to markers on chromosomes 11q and 6p. Clin Exp Allergy 22:1077–1084

Bahna SL (1992) Factors determining development of allergy in infants. Allergy Proc 13:21–25

Butland BK, Strachan DP, Lewis S, Bynner J, Butler N, Britton J (1997) Investigation into the increase in hay fever and eczema at age 16 observed between the 1958 and 1970 British birth cohorts. BMJ 315:717–721

Collée JM, ten Kate LP, de Vries HG, Kliphuis JW, Bouman K, Scheffer H, Gerritsen J (1993) Allele sharing on chromosome 11q13 in sibs with asthma and atopy. Lancet 342:936

Cookson WO, Sharp PA, Faux JA, Hopkin JM (1989) Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. Lancet I:1292–1295

Collaborative Study on the Genetics of Asthma (1997) A genome-wide search for asthma susceptibility loci in ethnically diverse populations. Nat Genet 15:389–392

Daniels SE, Bhattacharrya S, James A, Leaves NI, Young A, Hill MR, Faux JA, Ryan GF, le Souef PN, Lathrop GM, Musk AW, Cookson WO (1996) A genome-wide search for quantitative trait loci underlying asthma. Nature 383:247–250

Dickson PW, Wong ZY, Harrap SB, Abramson MJ, Walters EH (1999) Mutational analysis of the high affinity immunoglobulin E receptor β subunit gene in asthma. Thorax 54:409–4412

Donnadieu E, Cookson WO, Jouvin MH, Kinet JP (2000a) Allergy-associated polymorphisms of the FcεRIβ subunit do not impact its amplification functions. J Immunol 165:3917-22

Donnadieu E, Jouvin MH, Kinet JP (2000b) A second amplifier function for the allergy-associated Fc (epsilon) RI-beta subunit. Immunity 12:515–523

Duhme H, Weiland SK, Rudolph P, Wienke A, Kramer A, Keil U (1998) Asthma and allergies among children in West and East Germany: a comparison between Münster and Greifswald using the ISAAC phase I protocol. International Study of Asthma and Allergies in Childhood. Eur Respir J 11:840–847

Furumoto Y, Hiraoka S, Kawamoto K, Masaki S, Kitamura T, Okumura K, Ra C (2000) Polymorphisms in FcεRI β chain do not affect IgE-mediated mast cell activation. Biochem Bioph Res Co 273:765–771

Green SL, Gaillard MC, Song E, Dewar JB, Halkas A (1998) Polymorphisms of the beta chain of the high-affinity immunoglobulin E receptor (FcεRI-β) in South African black and white asthmatic and nonasthmatic individuals. Am J Respir Crit Care Med 158:1487–1492

Herwerden L van, Harrap SB, Wong ZY, Abramson MJ, Kutin JJ, Forbes AB, Raven J, Lanigan A, Walters EH (1995) Linkage of high-affinity IgE receptor gene with bronchial hyperreactivity, even in absence of atopy. Lancet 346:1262–1265

Hill MR, Cookson WO (1996) A new variant of the beta subunit of the high-affinity receptor for immunoglobulin E (FcεRI-β E237G): associations with measures of atopy and bronchial hyper-responsiveness. Hum Mol Genet 5:959–962

Hizawa N, Yamaguchi E, Ohe M, Itoh A, Furuya K, Ohnuma N, Kawakami Y (1992) Lack of linkage between atopy and locus 11q13. Clin Exp Allergy 22:1065–1069

Ishizawa M, Shibasaki M, Yokouchi Y, Noguchi E, Arinami T, Yamakawa-Kobayashi K, Matsui A, Hamaguchi H (1999) No association between atopic asthma and a coding variant of *FcεR1β* in a Japanese population. J Hum Genet 44:308–311

Laprise C, Boulet LP, Morissette J, Winstall E, Raymond V (2000) Evidence for association and linkage between atopy, airway hyper-responsiveness, and the beta subunit Glu237Gly variant of the high-affinity receptor for immunoglobulin E in the French-Canadian population. Immunogenetics 51:695–702

Lin S, Cicala C, Scharenberg AM, Kinet JP (1996) The FcεRIβ subunit functions as an amplifier of FcεRIγ-mediated cell activation signals. Cell 85:985–995

Lympany P, Welsh KI, Cochrane GM, Kemeny DM, Lee TH (1992) Genetic analysis of the linkage between chromosome 11q and atopy. Clin Exp Allergy 22:1085–1092

Malerba G, Trabetti E, Patuzzo C, Lauciello MC, Galavotti R, Pescollderungg L, Boner AL, Pignatti PF (1999) Candidate genes and a genome-wide search in Italian families with atopic asthmatic children. Clin Exp Allergy 29:27–30

Mao XO, Shirakawa T, Sasaki S, Enomoto T, Morimoto K, Hopkin JM (1997) Maternal inheritance of atopy at the FcεRIβ locus in Japanese sibs. Hum Hered 47:178–180

Ober C, Cox NJ, Abney M, Di Rienzo A, Lander ES, Changyaleket B, Gidley H, Kurtz B, Lee J, Nance M, Pettersson A, Prescott J, Richardson A, Schlenker E, Summerhill E, Willadsen S, Parry R, the Collaborative Study on the Genetics of Asthma (1998) Genome-wide search for asthma susceptibility loci in a founder population. Hum Mol Genet 7:1393–1398

Rich SS, Roitman-Johnson B, Greenberg B, Roberts S, Blumenthal MN (1992) Genetic analysis of atopy in three large kindreds: no evidence of linkage to D11S97. Clin Exp Allergy 22:1070–1076

Rohrbach M, Kraemer R, Liechti-Gallati S (1998) Screening of the FcεRI-β-gene in a Swiss population of asthmatic children: no association with E237G and identification of new sequence variations. Dis Markers 14:177–186

Sandford AJ, Shirakawa T, Moffatt MF, Daniels SE, Ra C, Faux JA, Young RP, Nakamura Y, Lathrop GM, Cookson WO, et al (1993) Localisation of atopy and the beta subunit of the high-affinity IgE receptor (FcεRI) on chromosome 11q. Lancet 341: 332–334

Shirakawa T, Hashimoto T, Furuyama J, Takeshita T, Morimoto K (1994a) Linkage between severe atopy and chromosome 11q13 in Japanese families. Clin Genet 46:228–232

Shirakawa T, Li A, Dubowitz M, Dekker JW, Shaw AE, Faux JA, Ra C, Cookson WO, Hopkin JM (1994b) Association between atopy and variants of the β subunit of the high-affinity immunoglobulin E receptor. Nat Genet 7:125–129

Shirakawa T, Mao XQ, Sasaki S, Enomoto T, Kawai M, Morimoto K, Hopkin J (1996) Association between atopic asthma and a coding variant of FcεRIβ in a Japanese population. Hum Mol Genet 5:1129–1130

Sibbald B, Rink E (1991) Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. Thorax 46: 895–901

Sly RM (1999) Changing prevalence of allergic rhinitis and asthma. Ann Allergy Asthma Immunol 82:233–248

Strachan D, Sibbald B, Weiland S, Ait-Khaled N, Anabwani G, Anderson HR, Asher MI, Beasley R, Bjorksten B, Burr M, Clayton T, Crane J, Ellwood P, Keil U, Lai C, Mallol J, Martinez F, Mitchell E, Montefort S, Pearce N, Robertson C, Shah J, Stewart A, von Mutius E, Williams H (1997) Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). Pediatr Allergy Immunol 8:161–176

Takabayashi A, Ihara K, Sasaki Y, Suzuki Y, Nishima S, Izuhara K, Hamasaki N, Hara T (2000) Childhood atopic asthma: positive association with a polymorphism of IL-4 receptor α gene but not with that of IL-4 promoter or Fc ε receptor I β gene. Exp Clin Immunogenet 17:63–70

Trabetti E, Cusin V, Malerba G, Martinati LC, Casartelli A, Boner AL, Pignatti PF (1998) Association of the FcεRIβ gene with bronchial hyper-responsiveness in an Italian population. J Med Genet 35:680–681

Wjst M, Fischer G, Immervoll T, Jung M, Saar K, Rueschendorf F, Reis A, Ulbrecht M, Gomolka M, Weiss EH, Jaeger L, Nickel R, Richter K, Kjellman NI, Griese M, von Berg A, Gappa M, Riedel F, Boehle M, van Koningsbruggen S, Schoberth P, Szczepanski R, Dorsch W, Silbermann M, Loesgen S, Scholz M, Bickeboller H, Wichmann HE, et al (1999) A genome-wide search for linkage to asthma. Genomics 58:1–8

Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM (1994) Epidemiology of physician-diagnosed allergic rhinitis in childhood. Pediatrics 94:895–901

Yokouchi Y, Nukaga Y, Shibasaki M, Noguchi E, Kimura K, Ito S, Nishihara M, Yamakawa-Kobayashi K, Takeda K, Imoto N, Ichikawa K, Matsui A, Hamaguchi H, Arinami T (2000) Significant evidence for linkage of mite-sensitive childhood asthma to chromosome 5q31–q33 near the interleukin 12 B locus by a genome-wide search in Japanese families. Genomics 66:152–160

Young RP, Sharp PA, Lynch JR, Faux JA, Lathrop GM, Cookson WO, Hopkin JM (1992) Confirmation of genetic linkage between atopic IgE responses and chromosome 11q13. J Med Genet 29:236–238

Zhu S, Chan-Yeung M, Becker AB, Dimich-Ward H, Ferguson AC, Manfreda J, Watson WT, Pare PD, Sandford AJ (2000) Polymorphisms of the IL-4, TNF-α, and FcεRIβ genes and the risk of allergic disorders in at-risk infants. Am J Respir Crit Care Med 161:1655–1659