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Evidence for association and linkage between atopy, airway hyper-responsiveness, and the β subunit Glu237Gly variant of the high-affinity receptor for immunoglobulin E in the French-Canadian population

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Abstract Following detection of linkage between atopy and chromosome 11q13 markers, association between this disorder and variants of the β subunit of the high-affinity receptor for immunoglobulin E (FcεRI-β, a candidate gene for asthma-related conditions co-localizing within the same region) was reported in Australian, British and Japanese populations. Investigations in several other ethnic groups failed to replicate these observations. Due to the complexity of defining intermediate phenotypes related to asthma, detection of such associations may have been hampered by clinical misclassifications. To assess whether the FcεRI-β gene was involved in atopy and/or airway hyperresponsiveness (AHR) in the French-Canadian population, we conducted a case-control study in 200 subjects using strict criteria for asthma and related conditions. The Ile181Leu and Glu237Gly FcεRI-β sequence variants were tested exploiting two amplification refractory mutation systems. No association was detected between atopy or AHR and the Ile181Leu FcεRI-β variant. However, a strong association was observed between atopy and the Glu237Gly FcεRI-β variant (odds ratio=12.25). Four large Eastern Québec families (n=106 subjects) were also recruited to perform a genetic linkage study. We observed suggestive evidence of linkage between atopy and the Glu237Gly FcεRI-β variant (Z_{max}=2.30). This study is the first to detect the presence of an association between atopy and the Glu237Gly FcεRI-β variant in French-Canadians. Our data suggest that a susceptibility locus for atopy is located on chromosome 11q13 in this population.

Key words Asthma · Atopy · High-affinity receptor for immunoglobulin E · Chromosome 11q13 · French-Canadians

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Introduction

Asthma is a heterogeneous disorder characterized by increased responsiveness of the tracheobronchial tree to a variety of stimuli. Respiratory symptoms such as intermittent dyspnea, wheezing, and cough may vary from mild and almost undetectable, to severe and unremitting (ATS 1987). Such increased responsiveness, which may occur in asymptomatic individuals, is termed airway hyperresponsiveness (AHR) and represents an important risk factor for the disorder (Cockcroft and Bercheid 1992; Laprise et Boulet 1997; Zhong et al. 1992). A second risk factor in the development of asthma is atopy (Burrows et al. 1989), defined by the presence of positive responses to skin-prick tests with common allergens in addition to an increase in total serum immunoglobulin E (IgE) level (Pepys 1973). Clinical investigations are aimed at determining whether atopy, AHR, and asthma are variable expressions of the same primary defect or

whether they represent common pathological pathways caused by distinct etiologies.

Twin, family and population studies clearly established that genetic components were implicated in susceptibility to either asthma and/or atopy (Duffy et al. 1990; Edfors-Lubs 1971; Sibbald et al. 1980). To understand the molecular basis of these conditions, a search for the disease-causing gene was initiated in several ethnic groups. During the past few years, genetic-linkage studies reported the mapping of several susceptibility loci for AHR and/or atopy (for a review see Sandford et al. 1996). Following the demonstration of linkage between atopy and polymorphic markers on Chromosome (Chr) 11q13 (Cookson et al. 1989), the β subunit of the high-affinity IgE receptor (FcεRI-β) gene co-localizing within the same region became a candidate for the disorder (Sandford et al. 1993; Shirakawa et al. 1994a). Indeed, the FcεRI-β is a tetrameric complex ($\alpha\beta\gamma_2$) found on the surface of mast cells (Stevenson et al. 1996) and basophils (Blank et al. 1989). Its β chain contains four transmembrane segments and long cytoplasmic domains that are thought to play an important role in intracellular signaling. The gene spans approximatively 10 kb and contains seven exons (Küster et al. 1992). Binding of allergen to receptor-bound IgE leads to cell activation and the release of mediators responsible for the manifestation of allergy (Küster et al. 1992). Stimulation of this receptor on mast cells induces the release of interleukin-4 and other cytokines that may increase the synthesis of IgE and inflammatory processes (Plaut et al. 1989).

Shirakawa and colleagues (1994b) identified a FcεRI-β variant, converting isoleucine 181 to leucine (Ile181Leu) within the fourth transmembrane domain of the receptor, which was found to be associated with atopy (Shirakawa et al. 1994a). In a study of the South Western Australian population, a Leu181/leu183 FcεRI-β variant was also detected in 15% of a random asthmatic patient sample, compared to a value of 4.5% in the general population of this region (Hill et al. 1995). The variant was maternally inherited in the asthmatic group and showed a significant association with atopy and AHR (Hill et al. 1995). However, Hizawa (1995) and colleagues reported association only between high serum total IgE levels and D11S97 at Chr 11q13 in Japanese subjects. Also, these authors confirmed evidence against linkage at the locus and absence of the leucine substitution at position 181 (Hizawa et al. 1995) while Duffy and co-workers (1995) and Martinati and co-workers (1996) were unable to find the Ile181Leu variant in an Australian twin study and an Italian population, respectively.

More recently, a second coding variant was identified in exon seven of the FcεRI-β gene (Hill and Cookson 1996). An adenine to guanine substitution resulted in a glutamic acid to glycine conversion at residue 237 (Glu237Gly) in the cytoplasmic tail of the protein. The Glu237Gly FcεRI-β variant was found in 5% of the Australian population suffering from atopy and AHR (Hill and Cookson 1996). In a subsequent study, using a Japanese population and a diagnostic of asthma made by local physicians, the Glu237Gly variant was found in 18% of asthmatic-atopic subjects, and in 45% of the subjects with very high IgE level, compared to a value of 6% in the general population of Japan (Shirakawa et al. 1996).

These results showed that associations between atopy, AHR, and distinct forms of the FcεRI-β gene varied amongst different ethnic groups and supported the notion that these pathological traits were manifesting genetic heterogeneity (Sandford et al. 1996). Alternatively, the differences in classifying the asthma and/or asthma-related phenotypes observed in these studies may have led to positive or negative bias in the estimation of odds ratios (OR) and other measures of association (Morton 1996).

The population of the province of Québec is particularly well suited for genetic investigations. Due to social and linguistic reasons, this population has maintained for the past three centuries a demographic growth with minimal immigration and, until recently, a high birth rate with large sibships averaging 10–15 sibs per generation (Bouchard and De Braekeleer 1991). We exploited these particularities to test French-Canadian subjects for an association and linkage between atopy and AHR, and two of the FcεRI-β variants previously described.

To counteract the discrepancies that may result from any lack of standardization in the approaches used to classify atopy and/or AHR phenotypes (Weiss et al. 1996), we used strict criteria for asthma and atopy determined by allergy skin-prick tests, total serum IgE level, total blood eosinophil count and methacholine challenge. We report, herein, the presence of a very strong association between atopy and the Glu237Gly FcεRI-β variant in the French-Canadian population. Our data also demonstrate the presence of linkage between AHR and the Glu237Gly FcεRI-β variant in four large families living in Eastern Québec.

Materials and methods

Definitions

Asthma was defined according to the criteria suggested by the American Thoracic Society (ATS 1994). In this study, asymptomatic AHR was defined as a PC_{20}=8 mg/ml in the absence of symptoms suggestive of asthma in subjects who had never required anti-asthma medication (Laprise and Boulet 1997). Atopy was defined as the presence of at least one positive response (wheal diameter=3 mm at 10 min) to skin-prick tests with a battery of 26 common airborne allergens (Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology 1989) in addition to a total serum IgE level >280 μg/l. To ensure proper phenotypic classification in our case-control study, we selected only patients who fulfilled criteria for a high atopic status. These criteria included a positive response to skin-prick tests to three of the six allergens cat-

egories (animal danders, housedust, housedust mite, tree pollen, mixed grasses, ragweed pollen, and molds) in addition to a total serum IgE level >280 μg/l. The atopic index was the number of aero-allergen categories (0–6) to which the subject showed at least one positive response. The atopic score was the sum of all positive responses in millimeters.

Initial clinical assessment and pulmonary function tests

First visit

The study was approved by our local ethics committee and all subjects confirmed their willingness to take part in this study and signed an informed-consent form. Each subject completed a general questionnaire on respiratory health and family history of asthma and/or atopy. Measurements of expiratory flows were made with a Vitalograph PFT II spirometer (Vitalograph Medical Instrumen-tation, Lenexa, Kan.) according to ATS recommendations (ATS 1994). The best of three FEV_1 curves was used to determine forced vital capacity and FEV_1. Bronchodilator response was measured as the increase in FEV_1 at 15 min after a 200 μg dose of inhaled salbutamol. Peak expiratory flow (PEF) were measured with a mini-Wright peak-flow meter (Armstrong Medical, Scarborough, Ont.) in the morning and evening over a period of 2 weeks. The best of three repeated measurements was noted on the diary card.

Skin-prick tests were done with a battery of 26 inhalant allergens, which were divided into the six main categories of animal danders, housedust, housedust mite, tree pollen, grass pollen (including ragweed) and molds. Serum IgE was measured with enzyme immunofluorometry. Blood eosinophils were counted on a Coulter STKS (Hialeah, Fla.).

Second visit

Methacholine inhalation tests were done according to the method described by Juniper and co-workers (1991). Briefly, aerosols were generated from a Wright nebulizer (Roxon Medi-Tech, Montreal, Que.) with an output of 0.13 ml/min. After the initial control saline inhalation, increasing double-concentrations of methacholine (0.03–128 mg/ml) were inhaled by tidal breathing for 2 min at intervals of 5 min. The response, recorded as the percent decrease in FEV_1, was measured at 30 s and 90 s, and then at 2-min intervals if necessary, to determine the lowest value after each inhalation. The test was stopped when the FEV_1 had fallen by 20%, or when the maximum concentration of methacholine had been inhaled. The results were expressed as the PC_{20} methacholine.

DNA testing

A blood ample (20 ml) was drawn by venipuncture in heparinized tubes from each subject enrolled in the study. DNA was extracted using the guanidine hydrochloride-proteinase K method (Jeanpierre 1987). Associations between atopy and the FcεRI-β 181 or 237 residue substitution were assessed using the amplification refractory mutation system (ARMS; Newton et al. 1989). To test the presence of the Ile181Leu variant of the Fcε RI-β gene, ARMS was carried out as described by Shirakawa and co-workers (1994b). As positive control for the Leu181Ile sequence, ARMS was performed with DNA obtained from a homozygote person kindly provided by W.O.C.M. Cookson (Shirakawa et al. 1994b). Four primers were used to detect either the Glu237Gly variant or its wild-type counterpart (Hill and Cookson 1996). The first two primers, B7FA1 and B7FA2, amplified the control fragment and gave a 446-bp band. The third primer, B7W2, was used to detect the wild-type sequence (280-bp band) in conjunction with primer B7FA1 whereas the fourth primer, B7M1, was used in conjunction with B7FA2 to detect the Glu237Gly variant, giving a 238-bp band. PCR was performed in a Perkin Elmer Cetus DNA thermal cycler using a preliminary cycle (94 °C denaturation for 5 min and a hot start at 80 °C while adding taq), 35 cycles (94 °C denaturation for 1 min, 60 °C annealing for 2 min and 72 °C extension for 2 min) and an end cycle (72 °C extension for 10 min). Amplification products were electrophoresed in 3% agarose gels before ethidium staining (run for 2 h at 60 V) and scoring by two independent observers. Genotyping and phenotyping were carried out in a randomized double blind fashion. The atopy phenotype was evaluated prior to the ARMS test. All DNA samples were coded. The ARMS analysis was performed in duplicate with positive and negative controls. The presence of the FcεRI-β Glu237Gly variant was tested and confirmed by DNA sequencing in five atopic subjects and in at least one subject in each family, except in the family of the homozygote where all first degree relatives were sequenced.

Data analysis

Phenotypes and genotypes were entered in a Statview database (version 4.51) for Macintosh. Results were expressed as mean ± SEM values for FEV_1, variability of PEF, atopic score and eosinophil counts. Total serum IgE level and PC_{20} were expressed as the geometric mean ± SEM. Significance was accepted at the 95% level. OR and ANOVA were calculated using Statview. For linkage analysis, data were transfered from the Macintosh to a Sun Sparc 4 workstation on an Ethernet network, using the UNIX Appleshare server CAP. Linkage computation was done with FASTLINK (version 3.0P; Cottingham et al. 1993; Schaffer et al. 1994), an optimized C version of the linkage package (Lathrop and Lalouel 1984; Lathrop et al. 1985). Z_{max} and θ_{max} were estimated by the lodscore program using an autosomal dominant model and one liability class. Penetrance of atopy and AHR for linkage analysis was adjusted to the prevalence of these diseases in the French-Canadian population: 12% for AHR (Malo et al. 1983) and 25% for atopy (Holdford et al. 1984). Allelic frequency for FcεRI-β Glu237Gly polymorphism was evaluated at 0.015 in 200 French Canadian subjects (116 women and 84 men, mean age: 34.12±3.7 years) randomly selected. An OR and its 95% confidence interval were calculated as a measure of the strength of association.

Results

Association between atopy, AHR and the Glu237Gly FcεRI-β variant

It is well recognized that penetrance of atopy varies with age, with a peak between 20–45 years (Barbee et al. 1987; Boulet et al. 1997). To ensure maximum expression of the disease in our population, we therefore recruited 100 unrelated French-Canadian subjects (41 women and 59 men), aged 18–35 years (mean=27± 2 years) who fulfilled inclusion criteria for a highly atopic status (positive response to skin-prick tests to three of the six allergens in addition to a total serum IgE level >280 μg/l). They were paired for age and gender with 100 non-atopic unrelated individuals. All subjects were non-smokers.

Twenty-five atopic subjects had a diagnosis of asthma in comparison to none in the non-atopic subjects (P<0.0001). Fourteen atopic subjects had asymptomatic AHR, compared to ten in the non-atopic group (P=0.5). A significantly higher degree of airway

responsiveness was found in the atopic group (geometric mean of PC_{20} = 12.7±1.2 mg/ml) as compared to the non-atopic control group (geometric mean of PC_{20} = 30.9±1.1, $P<0.0001$). In the atopic group, the mean value of serum IgE level was higher than that observed in the non-atopic control group (611±82.6 µg/l and 53±7.1 µg/l, respectively, $P<0.0001$), as was blood eosinophil count ($0.3\pm0.02\times10^9$/l and $0.1\pm0.01\times10^9$/l, respectively, $P<0.0001$). There were no significant differences in regard to FEV_1 and bronchodilator response. In atopic subjects, sensitization to allergens was, in decreasing order of prevalence: housedust (85%), animal danders (71%), housedust mite (57%), tree pollens (42%), grass pollens (36%), and molds (22%).

We first looked for an association between atopy and the Ile181Leu FcεRI-β variant. Out of the 200 participants who were tested, none harbored the 181Leu allele. To confirm these results, we sequenced genomic DNA obtained from five severely atopic subjects. None carried the polymorphism. However, the Glu237Gly FcεRI-β variant was found in 20 of our 100 atopic subjects (20%). Only two of 100 nonatopic subjects (2%) had this mutation, with an OR of 12.25. Interestingly, one of these carriers was homozygous for this variant (Fig. 1 A) and, as depicted in Table 1, this mutant homozygote displayed a clinical status of atopy and asthma that was clearly more severe than his/her heterozygotic counterparts. As expected, heterozygotic subjects had a higher airway responsiveness and a significantly greater degree of atopy than normal individuals carrying the Glu237 allele on both chromosomes, with respective values of 3.7±1.3 mg/ml

Table 1 Physiological and immunological parameters associated with the presence of the Glu237Gly variant of the FcεRI-β

Parameters	Glu/Glu	Glu/Gly	Gly/Gly
Number of subjects	178	21	1
Age (years)	29±1	24±2	35 (90)[e]
FEV_1 (% predicted)	107.6±3.1	91.2±4.3	73 (1)
PC_{20} methacholine (mg/ml)[a]	25.6±1.1	3.7±1.3[d]	Saline (1)[f]
Atopic index (/6)[b]	1.9±0.2	4.4±0.4[d]	6 (90)
Atopic score (mm)[c]	35.4±3.2	77.6±6.7[d]	140 (100)
Eosinophils (10^9/l)	0.2±0.001	0.3±0.03[d]	0.4 (75)
IgE (µg/l)[a]	271±42	826±225[d]	955 (75)

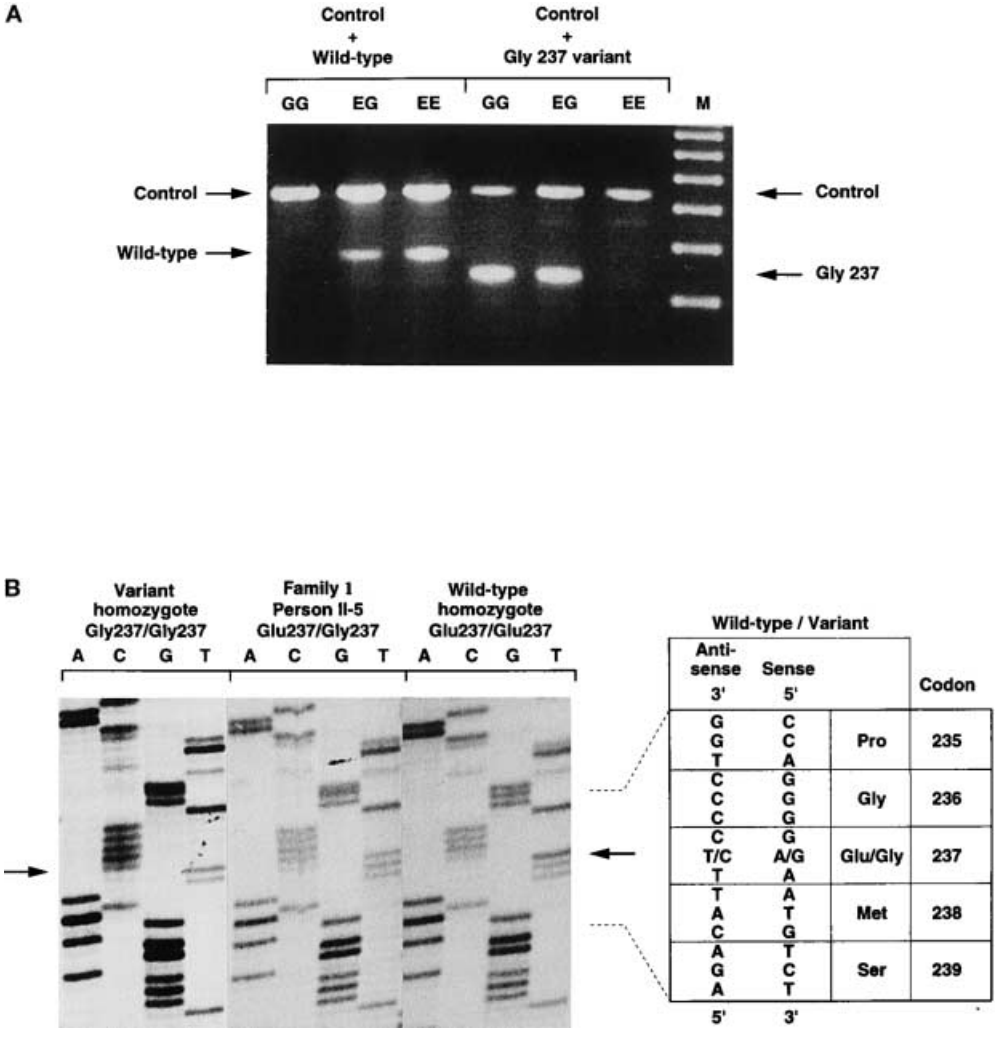

Fig. 1A,B Testing for the Glu237Gly FcεRI-β variant in atopic families. **A** ARMS tests were performed with genomic DNA obtained from three persons. The two sets of primers selected to perform ARMS in each test are shown *above* the gel picture. DNA molecular weight markers are depicted at the *far right*. An asthmatic-atopic individual (*GG*) was homozygous for the Gly variant at the position 237 in the FcεRI-β gene, a second person (*EG*) with atopic status is heterozygous for the Glu237Gly FcεRI-β variant and a non-atopic non-asthmatic control person (*EE*) is homozygous for the wild-type allele. The ARMS test depicts a 446-bp control band and the 280-bp band indicates the presence of the wild-type allele, whereas the 238-bp band denotes the presence of the Glu237Gly variant. **B** Sequence of genomic DNA. Asthmatic-atopic individual homozygote (GG) for the CCT encoding glycine residue at codon 237 of the FcεRI-β is represented by an *arrow* showing the single nucleotide substitution from adenine to guanine. An atopic person depicts a heterozygote sequence (EG) at the same position and non-atopic non-asthmatic individual is homozygous for the wild-type sequence (EE) allele

Table 2 Relative risk of atopy associated with with the Glu237Gly FcεRI-β variant and exposure to animal danders

Gly237/Exposure to animal danders	Number of subjects			Odds ratio (CI[a]=95%)
	Atopics	Non-atopics	Total	
–/–	56	72	128	–
–/+	24	26	50	1.19
+/–	8	1	9	10.29
+/+	12	1	13	15.43

[a]Confidence interval

and 25.6±1.1 mg/ml for PC_{20} methacholine, and 4.4± 0.4 and 1.9±0.2 for the atopic index.

Table 2 gives the relative risk of atopy associated with the Glu237Gly FcεRI-β variant and exposure to animal danders. In our case-control group of subjects, exposure to animal danders represented a low risk of developing atopy (OR=1.19). The presence of the Glu237Gly FcεRI-β variant increased the risk of developing atopy by an OR of 10.29. When subjects harboring the Glu237Gly variant were exposed to allergens, this OR increased even more, to a value of 15.43. These results clearly demonstrated that the association of the Glu237Gly variant with exposure to animal danders greatly increased the risk of developing atopy in our French-Canadian population.

Linkage studies

Four families, including a total of 106 persons, participated in our genetic linkage studies (Fig. 2). These subjects were aged 6–61 years (mean=30±4 years). In children below age 12 (n=5 children), the asthma phenotype was determined by a respiratory questionnaire, mean daily PEF fluctuation and medical history. In addition, the methacholine test was performed on subjects aged over 12 years. Twenty-seven (25.5%) had the asthma phenotype, 51 (48.1%) had a positive skin-prick test, 34 (34%) were atopic (positive skin-prick test in addition to serum IgE level >280 µg/l) and six (5.7%) had asymptomatic AHR (Fig. 2). In subjects with a positive skin-prick test, sensitization to allergens was, in decreasing order of prevalence: housedust (88%), animal danders (80%), house dust mite (78%), tree pollens (72%), grass pollens (52%), and molds (11%). As shown in Fig. 2, airway hyperresponsiveness and atopy appeared to segregate in these families as an autosomal dominant trait with 35% of subjects carrying the Glu237Gly variant of the FcεRI-β. This was confirmed by DNA sequencing of at least one subject in each family (Fig. 1B). No members in these kindreds harbored the Ile181Leu variant of the FcεRI-β. We observed a total of 14 (54%) affected sib pairs who shared their maternal allele. Fourteen persons (52%) shared their paternal allele (Fig. 2).

A two-point linkage analysis was made using the lod score computer program to estimate the maximum value of recombination frequency and its corresponding lod score. As atopic and AHR did not manifest a clear pattern of expressivity, we assumed only one liability class. Penetrance value of the Glu237Gly FcεRI-β variant in our atopic population was estimated at 76%, as 29 persons out of 38 carriers of the variant were affected by the disorder. In the AHR individuals, this value was estimated at 55%, as only 21 subjects out of 38 carriers had AHR. The phenocopy rate was evaluated at 22% and 9% for atopy and AHR, respectively, as we found 20 atopic subjects and 15 AHR subjects who did not harbor the Glu237Gly variant in their families. The results of the two-point linkage analysis for the Glu237Gly variant to the AHR phenotype showed a maximal lod score (Z_{max}) of 1.1 (θ_{max}=0). The lod scores for atopy and positive skin-prick test to animal danders were respectively measured at 2.30 and 1.47 (θ_{max}=0). These results suggest evidence for linkage between the AHR condition and the Glu237Gly FcεRI-β variant as well as between atopy and this same mutation.

Discussion

It is well recognized that atopy is among the strongest known risk factors for developing AHR and symptomatic asthma, and exposure to natural allergens has been shown to increase airway responsiveness (Boulet et al. 1983; Cockcroft and Berscheid 1983; Platt-Mill 1991). The respective contributions of genetic and environmental influences on sensitization to allergens and/or AHR, however, remains unclear. To evaluate the contributions of these two influences on the atopic phenotype, we conducted association and linkage studies using strict criteria to assess asthma-related conditions. In the present study, we observed that inheritance of the Glu237Gly FcεRI-β variant was clearly associated with an increased risk of developing atopy and AHR.

Two different studies reported that the FcεRI-β Ile181Leu or Leu181/leu183 variants were associated with atopy in a British cohort and in an Australian population (Hill et al. 1995; Shirakawa et al. 1994b). In the Québec population, however, the Ile181Leu variant seemed to be a rare allele, as none of the 200 subjects who participated in our case-control study carried this variant. However, Hill and Cookson (1996) detected the Glu237Gly variant in 5.3% of a large Australian population sample. According to their

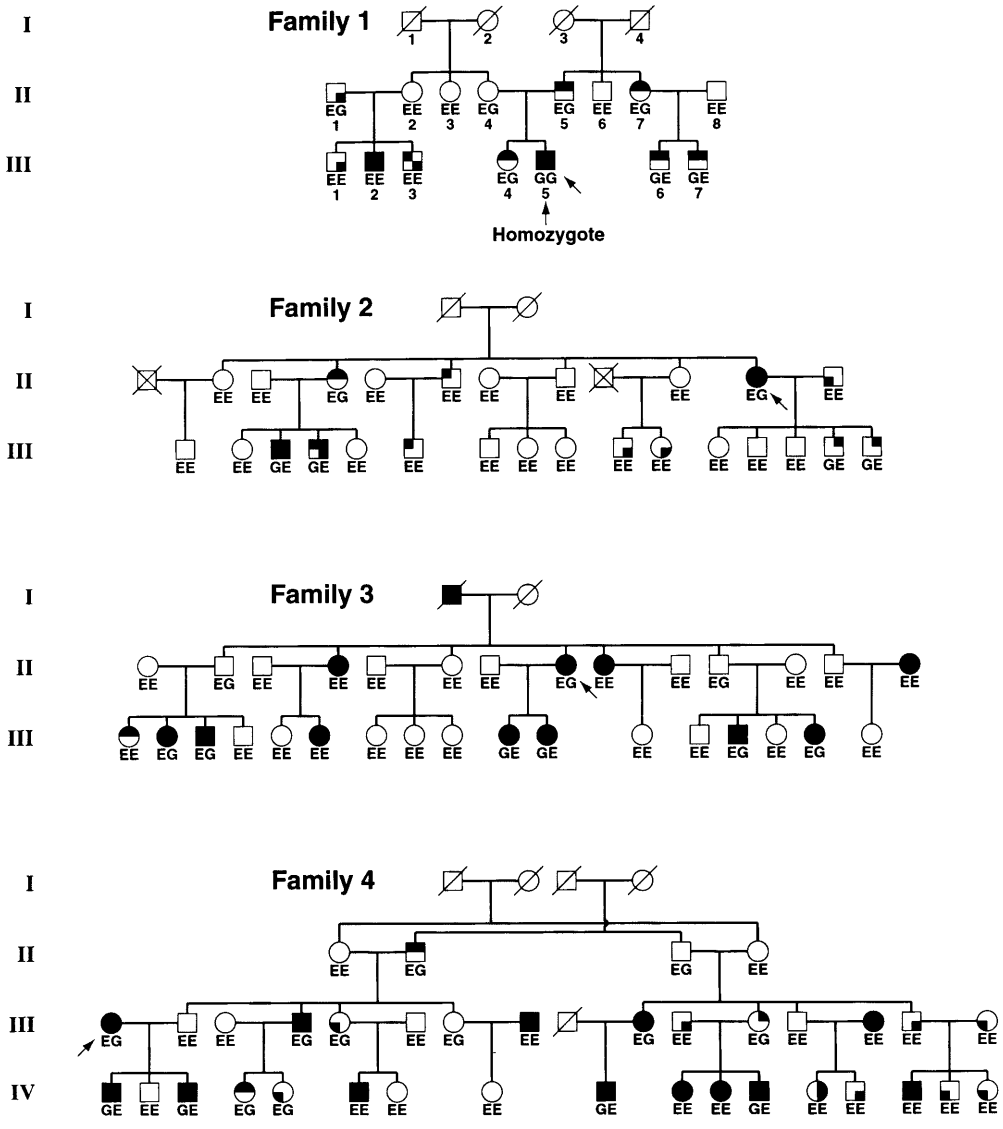

Fig. 2 Autosomal dominant atopy pedigrees. All living persons, except *II-1* and *II-9* in family 2, were examined and enrolled in the linkage study. Individuals with airway hyperresponsiveness and atopy are depicted by *solid black symbols*; unaffected persons by *open symbols*, those with airway hyperresponsiveness are depicted by a *black solid quadrant in the lower left part* of their respective symbols, persons with total serum IgE level >280 μg/l by a *black solid quadrant in the top left part* of their respective symbols, subjects showing positive skin-prick test to indoor allergens (animal danders, housedust and housedust mites) are represented by a *black solid quadrant in the top right part* of their respective symbols and subjects showing positive skin-prick test to outdoor allergens (tree pollens and grass pollens) by a *black solid quadrant in the lower right part* of their respective symbols. *Diagonal lines* denote deceased individuals. Persons unavailable for testing are indicated by *doubled-crossed symbols*. Carriers of the Glu237Gly FcεRI-*β* variant are indicated by *the letter G* (single letter code for glycine) and persons harboring a wild-type allele are depicted by *the letter E* (single letter code for glutamic acid) under their respective symbols. *The right side of each allele*, either *G* or *E*, indicates the allele inherited from the father and *the left side* indicates the allele inherited from the mother, except for person *III-4* in family 1, for whom both parents were heterozygotes

results, the OR of individuals carrying the Glu237Gly variant having atopy and asthma compared to the subjects without the variant was 2.3 (Hill and Cookson 1996). Interestingly, we found 20% of atopic subjects and 2% of non-atopic control subjects with the Fcε RI-*β* Glu237Gly variant, suggesting an even stronger association between the variant and atopy with an OR of 12.25 in our case-control population. Our results also showed that sensitization to animal danders was even more specifically associated with the Glu237Gly variant. In agreement with these findings, we have recently demonstrated that subjects with asymptomatic AHR, sensitized to animal dander allergens and recruited in asthmatic families, have a much higher risk of developing asthma symptoms (Laprise and Boulet 1997).

How inflammation induced by exposure of sensitized airways to allergens leads to AHR is not yet clear. It is well recognized that natural allergen exposure can increase airway responsiveness (Boulet et al.

1983; Cockcroft and Berscheid 1983; Platt-Mills 1991). However, the respective contribution of genetic and environmental influences on sensitization to allergens and/or AHR remains unclear. A major strength of this study is the evaluation of the influence of both genetic and environmental factors on atopic phenotype.

In order to assess the segregation and linkage of atopy and AHR in a family of subjects carrying the FcεRI-β Glu237Gly variant, four families were tested using ARMS. Many members in these families were diagnosed with severe atopy and/or AHR with or without respiratory symptoms. In each family, transmission of AHR and atopic status (positive skin-prick tests in addition to abnormal elevation of serum IgE level) occurred vertically, establishing that the disease phenotype was segregating as an autosomal dominant trait in these families (Fig. 2). A significant lod score was obtained between AHR and the FcεRI-β gene using a bi-allelic marker system, replicating the presence of linkage between another asthma-related condition, atopy, and markers located at 11q13. However, no difference was observed for gender between the alleles inherited from either the mother or the father in affected children (Fig. 2). These results therefore did not substantiate previous observations made by Cookson and coworkers (1992), who had suggested that transmission of atopy at this locus occurred through the maternal lineage.

In Eastern Québec, atopic individuals continuously exposed to allergens, and more specifically those exposed to animal danders, are at risk of developing airway inflammation and remodeling and, subsequently AHR (Laprise and Boulet 1997). However, overlap between the subsets of atopy and AHR in our population makes it, however, difficult to evaluate whether the Glu237Gly FcεRI-β variant is specifically associated with AHR, or whether these results reflect the fact that a large proportion of hyperresponsive subjects is also atopic (75%). Studies using larger cohorts of subjects are now being performed to elucidate this question.

The present data showed that a susceptibility locus for two asthma-related conditions, atopy and AHR is been located on Chr 11q13 in the French-Canadian population. As atopy and AHR both have highly pleiotrophic clinical expressions and their pattern of transmission is not completely understood, we believe that, in addition to the FcεRI-β locus, several other genetic loci may be implicated in asthma-related symptoms in our population. Further investigations on FcεRI-β functions, as well as on other distinct genetic components that may be involved in increasing susceptibility to atopy and/or asthma, are thus essential to improve our understanding of these highly prevalent illnesses. The large size of French-Canadian families will be a tremendous asset to overcome the difficulties raised by the genetic heterogeneity of these disorders.

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