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FcεRI-β polymorphism and risk of atopy in a general population sample

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Abstract

Objective—To establish the prevalence of *FcεRI-β* polymorphisms *Leu181* and *Leu181/Leu183* on chromosome 11q13 in the general population and to examine whether when maternally inherited they confer a risk of atopy.

Design—A population based survey for measures of atopy (skin prick test reactions, specific IgE titres, total serum IgE concentration), bronchial hyper-responsiveness, and carriage of *FcεRI-β Leu181* and *Leu181/Leu183*.

Setting—The rural coastal town of Busselton, Western Australia.

Subjects—1004 members of 230 two generation families identified through adults aged under 55.

Results—*FcεRI-β Leu181/Leu183* was identified in 45 subjects (4.5%). All 13 children who had inherited the variant maternally were atopic. Six had asthma and nine rhinitis. The odds ratio of a positive skin prick test reaction to house dust mite or grass pollen in these children compared with the other 523 children was 7.37 (95% confidence interval 1.62 to 33.60). The 95% confidence interval for the odds ratio of a positive specific IgE response (radio-allergosorbent test) was 3.00 to ∞, and the odds ratio for bronchial hyperresponsiveness was 3.70 (1.21 to 11.60). By contrast, the eight children who had derived the variant paternally had negative skin prick and radioallergosorbent test results and did not have increased bronchial responsiveness.

Conclusion—*FcεRI-β Leu181/Leu183* when inherited maternally identifies a genetic risk factor for atopy and bronchial hyperresponsiveness.

Introduction

Atopy is a familial syndrome of asthma, rhinitis, and eczema which is due to the interaction of genetic and environmental factors. Genetic linkage of atopic IgE responses to chromosome 11q13¹ was initially controversial² but has now been replicated by several groups³⁻⁵. Linkage was strongest in maternally derived alleles,^{5,6} which may contribute to the maternal inheritance of atopy evident from many studies.⁷⁻¹¹ The gene for the β chain of the high affinity receptor for IgE (*FcεRI-β*)

is a candidate for the chromosome 11q13 effect.¹² Sequencing of *Fc-βRI-β* has detected polymorphisms (variants)—*FcεRI-β Leu181/Leu183* (*Leu 181/Leu183*) and *FcεRI-β Leu181* (*Leu181*)—which were associated with atopy.¹³

We examined the prevalence of *Leu181* and *Leu181/Leu183* in an Australian general population sample and tested whether when inherited maternally the polymorphisms endowed a risk of atopy.

Subjects and methods

The subjects were from the rural coastal town of Busselton, South Western Australia. The aim was to recruit young nuclear families. Children under 5 were excluded because they could not complete respiratory testing. Families were identified through adults aged 55 or under from an electoral roll of around 9000. Families were serially recruited until a predetermined target of 1000 subjects was reached. The final sample comprised 1004 members of 230 nuclear families.

A total of 1867 subjects were approached. Of these, 177 refused to take part; 140 were not contactable; and 434, though contacted, had not been tested by the end of the study. Seven hundred and eight subjects were excluded because their spouses were aged over 55 or because they were not married with two or more natural children over the age of 5. The remaining 408 subjects and their spouses and children not on the electoral roll completed the study. Subjects knew the respiratory interest of the investigation before agreeing to participate. We emphasised that normal people were important to the study.

Clinical protocol—Testing took place in May, June, and July 1992. A respiratory questionnaire based on the American Thoracic Society questionnaire but including questions on rhinitis and allergies was administered. Skin prick testing to house dust mite (*Dermatophagoides pteronyssinus*), mixed grass pollen, cat and dog dander, *Aspergillus fumigatus*, *Alternaria alternata*, and a negative control (Dome-Hollister-Steir, Spokane, United States) was carried out as described.⁶ Weal diameters were calculated minus the negative control. Bronchial responsiveness to methacholine (maximum dose 12 μmol) was measured.^{14,15}

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TABLE I—Clinical details of children with maternally and paternally inherited *FcεRIβ* *Leu181/Leu183*

Pedigree No	Age (years)	Sex	Skin prick test		Radioallergosorbent test		Total IgE (kU/l)	PD ₂₀ (μmol)	Eosinophils (×10 ⁹ /l)	Wheeze	Asthma	Hay fever
			House dust mite (mm)	Grass (mm)	House dust mite	Grass						
Paternally inherited <i>FcεRI-β Leu181/Leu183</i>												
6	17	F	5	5	4	3	92	NR†	0.54	No	No	Yes
6	7	M	5	0	5	0	201	7.21	1.63	Yes	Yes	Yes
29	20	F	6	11	5	4	243	NR	0.58	No	No	Yes
29	18	F	7	0	3	0	63	8.87	0.01	No	No	Yes
29	14	F	7	5	4	2	166	0.19	0.44	No	Yes	No
61	8	F	17	0	5	0	215	1.94	1.10	Yes	Yes	Yes
61	14	M	8	8	5	3	550	3.18	0.70	Yes	Yes	Yes
95	11	M	6	4	4	1	178	6.67	0.59	No	No	Yes
95	10	M	3	2	4	2	137	0.14	0.66	Yes	Yes	No
162	14	F	9	4	2	2	15	NR	0.42	Yes	No	Yes
181	8	M	6	3	1	2	88	NR	0.19	Yes	Yes	No
181	7	M	4	3	2	2	235	2.5	0.23	No	No	Yes
209	17	F	3	0	0	1	70	NR	0.18	No	No	No
Maternally inherited <i>FcεRI-β Leu181/Leu183</i>												
103	5	F	0	0	0	0	162	2.66	0.32	No	No	No
141	13	F	0	0	0	0	44	NR	0.05	Yes	No	No
150	10	F	0	0	0	0	131	1.31	0.30	Yes	Yes	Yes
157	6	F	0	0	0	0	117	NR	0.25	No	No	No
171	14	M	0	0	0	0	6	NR	0.10	No	No	Yes
171	12	F	0	0	0	0	30	NR	0.04	—	No	—
203	21	M	0	0	0	0	8	NR	0.19	No	No	No
214	19	M	0	0	0	0	80	NR	0.02	No	No	No

†NR=Not reactive to maximum dose of methacholine.

TABLE II—Comparison of children with maternally or paternally derived *FcεRIβ* *Leu181/Leu183* and children without variant

Parameter	Maternal <i>Leu181/Leu183</i> (n=13)	Paternal <i>Leu181/Leu183</i> (n=8)	Others (n=523)
Skin prick test:			
House dust mite (mm)†	6.65 (3.61) [<0.0001]	0 [0.1]	2.55 (3.28)
Grass (mm)†	3.46 (3.33) [0.03]	0 [0.03]	2.07 (3.33)
Radioallergosorbent test:			
House dust mite‡	3.38 (1.66) [0.0001]	0 [0.03]	1.37 (1.94)
Grass	1.69 (1.25) [0.08]	0 [0.01]	1.18 (1.56)
Total IgE (kU/l)‡	129.0 (0.41) [0.08]	43.38 (3.55) [0.5]	66.82 (5.49)
Eosinophils (10 ⁹ /l)†	0.56 (0.42) [0.03]	0.16 (0.12) [0.02]	0.34 (0.30)
PD ₂₀ (μmol)‡	8.76 (10.3) [0.03]	36.97 (6.37) [0.7]	28.62 (7.03)

†Values are means (SD)
[P compared with others by Mann-Whitney U test]
‡Values are geometric means (SD)
[P compared with others by Mann-Whitney U test]

The dose required to provoke a 20% fall in forced expiratory volume in one second (PD₂₀) was estimated by linear interpolation. Subjects in whom a 20% fall was not achieved by the maximum dose of methacholine were assigned an arbitrary PD₂₀ of 100.¹⁵ Blood was taken by venepuncture for IgE assays, eosinophil and white cell counts, and DNA studies.

Serological tests for IgE, and white cell counts—Total serum IgE and specific IgE responses to whole *D pteronyssinus* and *Phleum pratense* (timothy grass) were determined (Pharmacia CAP system, fluorescent enzyme immunoassay, Sweden). A specific IgE radioallergosorbent test class 1 result (>0.35 kU/l) was considered positive. Eosinophils and white cells were counted automatically (Western Diagnostic Laboratories, Western Australia).

DNA testing—DNA was extracted from peripheral blood leucocytes by phenol-chloroform. *FcεRIβ* *Leu181* was detected by the amplification refractory mutation system polymerase chain reaction¹⁶ and by sequencing¹⁷ (see appendix). Genotyping and phenotyping were performed double blind.

Statistical analysis—Subjects with different *FcεRIβ* genotypes were compared non-parametrically by the Mann-Whitney U test (SPSS program, SPSS Inc, United States). Contingency table analysis, odds ratios, and 95% confidence intervals were estimated by exact methods (STATXACT program, Cytel, United States).

Results

A total of 502 subjects were male. The parents (n=460) were aged 30–55 years (mean 40.2 (SD 4.98) years) and the children (n=544) 5–27 years (mean 12.6 (4.73) years). Forty five per cent of the parents (n=207) and 43% of the children (n=234) had a positive skin prick test reaction ≥ 4 mm to house dust

mite or rye grass or both; 41% of parents (n=189) and 44% of children (n=239) had positive specific IgE titres (radioallergosorbent tests) to either house dust mite or grass pollen or both. Twenty three per cent of the parents (n=106) and 24% of the children (n=131) reported wheezing or whistling in their chest in the previous year, and 8% of the parents (n=37) and 14% of the children (n=76) reported an attack of asthma in the same interval. Half of the parents (n=230) and 42% of the children (n=228) reported episodic sneezing. Forty two per cent of the parents (n=193) and 8% of the children (n=44) had smoked cigarettes.

The assay for *Leu181* failed to amplify in five subjects (0.5%). Of the remaining 999 subjects, 45 (4.5%) were positive for *Leu181*. Twenty one of these were children; eight (seven sibships) had inherited the variant paternally, and 13 (seven sibships) had inherited it maternally. Sequencing of an individual from each family showed that in each case *Leu181* was accompanied by *Leu183*, so that only the *Leu181/Leu183* polymorphism was found in this population.

All 13 children who had inherited *Leu181/Leu183* maternally were atopic (table I). Eleven had wheeze or rhinitis or both, and a 12th, who denied symptoms, had had asthma previously, diagnosed and treated by a physician. Compared with the 523 children in the population without *Leu181/Leu183* the 13 had significantly increased skin prick test reactions and radioallergosorbent test results to house dust mite and grass pollen (table II). The odds ratio for a positive skin prick test reaction ≥ 4 mm to house dust mite or grass or both, compared with other children, was 7.37 (table III). The 95% confidence interval for the odds ratio of a positive radioallergosorbent test result to either or both allergens was 3.00 to ∞ . When compared only with children with skin prick test reactions ≥ 4 mm or positive radioallergosorbent test results, or both, children with maternal *Leu181/Leu183* still had greater skin prick test reactions and radioallergosorbent test results to house dust mite (P=0.005 and P=0.035 respectively). Hence children with the variant were discernibly more atopic than other children with atopy. The trend was for the total serum IgE concentration to be raised, though the differences were not significant (P=0.08).

The eosinophil counts in the 13 children were significantly raised, and the PD₂₀ was significantly lower (table II). Seven children had increased bronchial responsiveness (PD₂₀ ≤ 10 μmol methacholine¹⁴; odds ratio 3.70) (table III).

TABLE III—Odds ratios of measures of atopy and bronchial responsiveness and maternally inherited *FceRI-β* *Leu181/Leu183*

Parameter	<i>Leu181/Leu183</i>		Others		Odds ratio	95% Confidence interval	P
	Affected	Normal	Affected	Normal			
Positive skin prick test result to house dust mite and/or grass (≥ 4 mm > negative control)	11	2	284	212	7.37	1.62 to 33.60	0.002
Positive radioallergosorbent test result to house dust mite or grass (≥ 0.35 kU/l)	13	0	293	230	∞	3.0 to ∞	0.001
Raised total serum IgE ($> 70\%$ of age matched population)	6	7	170	364	1.80	0.61 to 5.54	0.28
Raised eosinophil count ($\geq 0.3 \times 10^9/l$)	9	4	222	284	2.90	0.87 to 9.45	0.07
Bronchial hyperresponsiveness ($PD_{20} \leq 10 \mu\text{mol}$ methacholine)	8	5	159	372	3.70	1.21 to 11.60	0.02

The eight children who had inherited *Leu181/Leu183* paternally were, by contrast, non-atopic with negative skin prick and radioallergosorbent test results (table I). Skin prick and radioallergosorbent test results and eosinophil counts were less than those of other children (table II). The odds ratio for a positive skin prick test reaction was 0 (95% confidence interval 0 to 0.62; $P=0.015$), as was the odds ratio for a positive radioallergosorbent test result (0 to 0.36; $P=0.002$).

Of the 24 parents with *Leu181/Leu183*, 11 had negative skin prick and radioallergosorbent test results to house dust mite and grass pollen, whereas 13 were positive in both skin prick and radioallergosorbent tests to one or more allergens.

Discussion

Within this sample maternal inheritance of *FceRI-β* *Leu181/Leu183* was associated with an increased risk of IgE responses to common allergens, raised eosinophil counts, and bronchial hyperresponsiveness. The variant therefore identified a genetic risk factor for atopy.

The study aimed at recruiting nuclear families in whom age had minimally affected measures of atopy and respiratory function. One hundred and seventy seven subjects declined to take part, and participants knew the survey was to study asthma. The sample may therefore not be completely representative, and the estimated 4.5% prevalence of *Leu181/Leu183* may be higher than the true value. The high frequency of positive skin prick test results and atopic symptoms is, however, consistent with previous surveys in Busselton¹⁸ and other Western populations.^{19,20}

The calculations of risk assume independence of observations, though the 13 maternal inheritors of *Leu181/Leu183* were from only seven sibships. The odds ratios for the various associations may therefore be somewhat higher than their true value. Nevertheless, the *Leu181/Leu183* polymorphism is clearly associated with a clinically significant risk of atopy.

Though *Leu181/Leu183* is comparatively rare, it should be considered to be a variant of normal rather than a mutation. The leucine substitutions are conser-

vative but it is not possible to predict whether they are functionally important.^{21,22} It is likely that other common polymorphisms in and around *FceRI-β* exist and that haplotypes of these may better define genetic risk due to *FceRI-β*.

Leu181/Leu183 was found exclusively in Busselton, though *Leu181* seems much more common in native British people.¹³ This may be due to variation in the prevalence of *FceRI-β* polymorphisms between populations. The possibility that the amplification refractory mutation assay failed to amplify *Leu181* when it was not accompanied by *Leu183* was monitored by the use of positive controls.

In order to interpret the presence of *Leu181/Leu183* its parental origin needs to be known. The negative skin test results and specific IgE titres of subjects who had inherited *Leu181/Leu183* paternally were unexpected given the high background level of atopy in Busselton. Thirteen of the 24 parents carrying *Leu181/Leu183* were atopic and 11 were not, consistent with active and inactive alleles in the 0.5:0.5 proportion expected from a maternal effect. Possible mechanisms for the maternal effect include genomic imprinting or influences through the placenta or breast milk.⁶

The timing and degree of exposure to allergen in early life determine the subsequent probability of atopic disease,²³ so that recognition of genetic susceptibility may result in prevention of illness.⁹ The results suggest that polymorphism in *FceRI-β* is one factor that can be used to assign genetic risk.

The prevalence of atopy in these subjects cannot be explained alone by the chromosome 11 effect or by variation in *FceRI-β*. The TCR- α region on chromosome 14²⁴ and the interleukin 4 cluster on chromosome 5²⁵ also show linkage to IgE responses. Prospective testing for *FceRI-β* polymorphisms and examination of the effects of other genes and the environment are required before genotyping at the *FceRI-β* locus can be used clinically for genetic risk estimation.

Dr Kevin Cullen pioneered studies of the Busselton population for epidemiological research and contributed to this study until his death on 9 February 1994. We thank the people of Busselton and the volunteers who carried out field testing. Gordon Rich (Western Diagnostic Laboratories) provided laboratory facilities. WOCMC is a Wellcome Trust senior clinical research fellow.

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Conflict of interest: The University of Oxford holds a patent protecting the commercial use of *FceRI-β*. Two of us (WOCMC and JMH) were coinventors.

Appendix

DNA METHODS

The amplification refractory mutation assay was carried out with the following oligonucleotide primers: (a) 5FU—TGT ATG TGT CAC TTT AAA AGG ACT GGT CAG; (b) 5WK—TTG TCA TTT GTT GCT GTT CAA TAG GAA GTT; (c) 3M—AAT GGT GAG AAA CAG CAT CAT CAT TAC CAA; (d) 3FU—TAA CAT ATC AGT CCT ATT ATC CCA ACC CTC. Genomic DNA samples (0.25–0.30 μg) were amplified in a total volume of 50 μl containing 0.5

Key messages

- Atopy and atopic asthma are familial and due to a genetic predisposition interacting with strong environmental factors: identifying which genes predispose to atopy may improve the prevention and treatment of asthma and allergy
- A potential genetic risk factor—the *FceRI-β* polymorphism *Leu181/Leu183*—has been found previously on chromosome 11
- Among 1000 members of 230 families from the rural coastal town of Busselton, Western Australia, over 4% were carriers of *Leu181/Leu183*
- When inherited maternally the polymorphism is associated with a significant risk of atopy and bronchial hyperresponsiveness
- *Leu181/Leu183* is the first genetic risk factor for atopy to be recognised but accounted for only a portion of atopy and asthma in the Busselton population

μM oligonucleotide primers *5FU*, *3FU*, and *5WK*; 0.1 μM *3M*; 200 μM dNTPs; 1 $\times$ reaction buffer (43 mM potassium chloride, 8.6 mM Tris-hydrochloric acid (pH 8.3), 2.5 mM magnesium chloride, 0.008% gelatin); and 2 units DNA Taq polymerase (Boehringer Mannheim) overlaid with mineral oil.

The reaction mixture (40 μl) without enzyme was heated to 95°C for five minutes in a thermal cycler (Hybaid) and held at 80°C for the addition of enzyme (2 units of enzyme in 10 μl reaction buffer). Reaction conditions then followed 35 cycles of 94°C for one minute, 60°C for two minutes, and 72°C for two minutes and one cycle of 72°C for 10 minutes. Amplified products were separated in a 3% (3:1 LMP agarose:Nusieve) gel containing ethidium bromide and visualised under ultraviolet light. Three bands potentially resulted from the primer combinations: *5FU-3FU* gave a 459 bp control band; *5WK-3FU* gave a 353 bp band in the presence of the "wild type" *Ile181*; *3M-5FU* gave a 163 bp band in the presence of *Leu181*.

A member of each family segregating *Leu181* was sequenced by the method of Sanger *et al*¹⁷ to ensure accuracy of the polymerase chain reaction and to determine whether *Leu183* was present. The 459 bp *5FU-3FU* band from the above reaction was taken to second round polymerase chain reaction with the following internal primers: *5D* (5'biotinylated)—AAG GACTGGTCAGATGGTAG; *3D*—GGCTTCCTAT CTA CCT TGT TTC. A single strand template was prepared with streptavidin labelled magnetic beads (Dynal, Oslo, Norway), and direct solid phase sequencing followed with the sequencing primer 3GS—TCC TTT GAG TTC TTC CCC A.

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Total cholesterol concentration and mortality at a relatively young age: Do men and women differ?

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Abstract

Objective—To investigate the relation between total cholesterol concentration and mortality from coronary heart disease, cardiovascular diseases, non-cardiovascular causes, and all causes.

Design—Population based cohort study.

Subjects—23 000 men and 26 000 women aged 30–54 years examined between 1974 and 1980.

Main outcome measures—Mortality for the above mentioned end points for fifths of cholesterol distribution, and relative risks estimated by using Cox's proportional hazard (survival) analysis. Adjustment was made for age, smoking, systolic blood pressure, and body mass index.

Results—Mortality from coronary heart disease in men was five times higher than that in women. A strong positive association between total cholesterol concentration and mortality from coronary heart disease and cardiovascular diseases was observed in both men and women. The relative risk for the highest compared with the lowest fifth of the cholesterol distribution was for mortality from coronary

heart disease 3.0 (95% confidence interval 1.8 to 5.1) in men and 3.8 (1.1 to 13.1) in women) and for mortality from cardiovascular disease 2.8 (1.8 to 4.2) in men and 2.9 (1.4 to 6.0) in women). No increase of non-cardiovascular mortality at low cholesterol concentration was observed. All cause mortality was significantly higher in the highest compared with the lowest fifth of the cholesterol distribution: relative risk 1.6 (1.3 to 2.0) in men and 1.5 (1.1 to 1.9) in women.

Conclusion—Total cholesterol concentration is a strong predictor of mortality from coronary heart disease, cardiovascular diseases, and all causes in women as well as in men. Low cholesterol concentrations are not associated with increased mortality from non-cardiovascular causes.

Introduction

There is growing awareness that cardiovascular diseases are not only an important public health problem in men but also in women.^{1,2} In the Netherlands

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