

Polymorphisms in the *IL4*, *IL4RA*, and *FCER1B* genes and asthma severity

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Background: Genetic polymorphisms have been associated with asthma and asthma severity.

Objective: We sought to determine whether 3 polymorphisms were associated with severe asthma indicated either by the occurrence of a fatal (or near-fatal) asthma attack or by severe airflow obstruction.

Methods: We obtained DNA and clinical data from asthmatic subjects who either died or nearly died during an asthma attack and from a group of subjects with mild-to-moderate asthma who had never experienced a fatal or near-fatal asthma episode. These groups were compared with a group of nonatopic nonasthmatic control subjects. The level of airflow obstruction (FEV₁ percent predicted) in the subjects with mild-to-moderate asthma was used as an additional measure of disease severity. The subjects were genotyped for the *IL4**C-589T promoter polymorphism and the *IL4RA**Q576R and the *FCER1B**E237G amino acid substitutions.

Results: The results showed that the *FCER1B**E237G and *IL4RA**Q576R polymorphisms were not associated with fatal or near-fatal asthma. However, the *IL4**-589T allele was significantly increased in the subjects with fatal or near-fatal asthma compared with nonasthmatic subjects (odds ratio [OR], 1.8; *P* = .02) and subjects with mild-to-moderate asthma (OR, 1.9; *P* = .02). There was no interaction between the *IL4**-589T and *IL4RA**576R alleles. Of the 3 polymorphisms, only the *IL4RA**576R allele was associated with severe airflow obstruction (OR, 8.2; *P* = .01).

Conclusion: These data suggest that the *IL4**-589T allele is a risk factor for life-threatening asthma and that the *IL4RA**576R allele is a risk factor for a low level of lung function in asthmatic subjects. (*J Allergy Clin Immunol* 2000;106:135-40.)

Key words: Asthma, severity, *IL-4*, *IL-4* receptor, IgE receptor

The cause of asthma involves both environmental and genetic risk factors. Several genes have been implicated

Abbreviation used
OR: Odds ratio

in the pathogenesis of asthma (Fig 1).¹ The results of a twin study suggested that there is also a genetic component to the severity of asthma.²

IL-4 is the major cytokine responsible for B-cell class switching from IgM to IgE. The region of chromosome 5q31 that contains the *IL4* gene has been linked to total serum IgE levels.^{3,4} A nucleotide substitution (C → T) at position -589 of the *IL4* gene promoter is present in approximately 27% of white subjects.⁵ The *IL4**-589T allele was associated with increased *IL4* gene expression in vitro and increased total serum IgE levels in vivo.⁵ The association with IgE levels was not replicated in a subsequent study,⁶ but these authors did find an association with asthma. In another study the *IL4**-589T allele was associated with wheeze and increased levels of specific IgE to house dust mite.⁷ Recently, the *IL4**-589T allele was associated with probable asthma, rhinitis, and atopy in a cohort of infants at risk for allergic disease.⁸ In addition, the *IL4**-589T allele was associated with lower FEV₁ values in a population of white subjects with asthma.⁹ These data suggest that the *C-589T polymorphism may influence asthma severity.

The *IL4RA* gene is another candidate gene for atopy and asthma. An amino acid substitution in *IL4RA* (glutamine → arginine) at position 576 of the protein is present in 36% of white subjects.¹⁰ The 576 arginine (*576R) allele was found to be associated with atopy. Functional studies have revealed that the *576R allele produces a receptor that shows enhanced signal transduction in vitro. Linkage of atopy with markers in and around the *IL4RA* gene on chromosome 16p12 was shown in a separate population.¹¹ Recently, homozygosity for the *576R allele was shown to be associated with severe asthma (defined as FEV₁ percent predicted <60%).¹²

The β-chain of the high-affinity receptor for IgE (FcεR1β) is found on mast cells and basophils. Cross-linking of this receptor leads to increased IL-4 production by these cells. Mutations in the *FCER1B* gene could alter IL-4 production and thus modify IgE levels. The *FCER1B* gene is located on chromosome 11q13, which is a region that has shown linkage to atopy and asthma.¹³⁻¹⁵ An amino acid substitution (glutamic acid → glycine) at posi-

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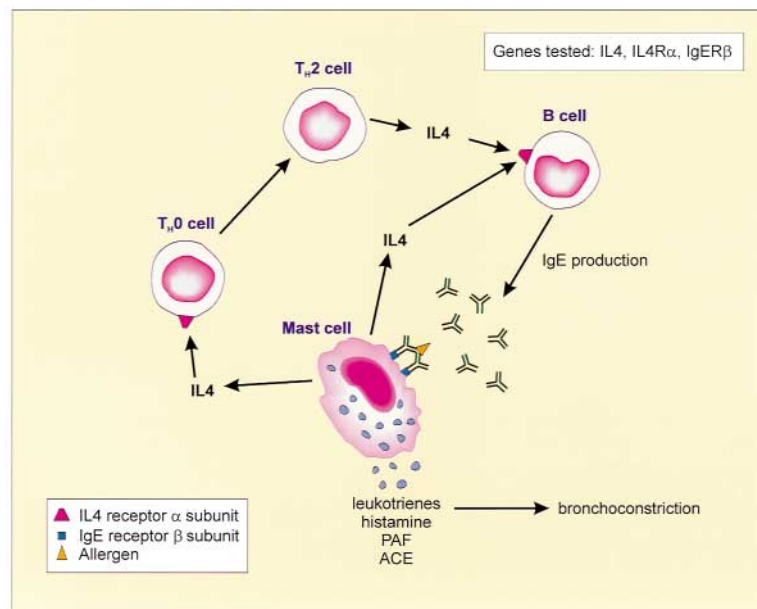


FIG 1. Relationship of 3 genes implicated in the pathogenesis of asthma. The *IL4**C-589T polymorphism, the *IL4RA**Q576R amino acid substitution, and the *FCERIB**E237 amino acid substitution were tested in the present study.

tion 237 in the *FCERIB* gene has been associated with total and specific IgE levels and with atopic asthma.^{16,17} The 237 glycine allele (*237G) is present in approximately 5% of Japanese and white populations.^{16,17}

The associations of the *IL4* and *IL4RA* polymorphisms with asthma severity have not been replicated. It is not yet known whether the *FCERIB* polymorphism affects asthma severity. To date, genetic studies of asthma have only used level of lung function as a marker of severity. Therefore we investigated the prevalence of the polymorphisms in two well-defined groups of asthmatic subjects: a group of subjects with mild-to-moderate asthma and a group of subjects with severe asthma who died or nearly died during an asthma attack. We genotyped the subjects in these groups for the polymorphisms by using PCR-based techniques. The prevalence of each polymorphism was compared with that found in a group of nonatopic nonasthmatic control subjects. We also used the level of airflow obstruction (FEV₁ percent predicted) in the subjects with mild-to-moderate asthma as a measure of disease severity.

METHODS

Subjects

The subjects were divided into 3 groups. The group of subjects with fatal or near-fatal asthma consisted of 130 subjects with fatal and 27 subjects with near-fatal asthma. To minimize possible confusion with other diseases, such as chronic obstructive pulmonary disease, all of the subjects with fatal asthma were less than 50 years of age. Subjects with fatal asthma had a history of asthma with recent worsening of symptoms leading to the fatal asthmatic episode. In addition, classical asthmatic histopathology was confirmed on microscopic study of the lung by two patholo-

gists. Of the subjects with fatal asthma, 101 were from New Zealand, 16 were from Vancouver, and 13 were from Perth, Australia. Subjects with near-fatal asthma had a history of asthma and were intubated in a hospital emergency department ($n = 26$) or had hypercapnic respiratory failure ($\text{Paco}_2 > 45$ mm Hg) during an acute asthmatic episode ($n = 1$). All of the subjects with near-fatal asthma had reversible airflow obstruction and were recruited for a retrospective study of near-fatal asthma in Vancouver. Lung function data were available for only 2% of the subjects with fatal or near-fatal asthma.

The mild-to-moderate asthma group consisted of subjects who had mild-to-moderate asthma and were not taking oral steroids ($n = 90$). These subjects included patients screened for inclusion in clinical trials, and all subjects fulfilled American Thoracic Society diagnostic criteria for asthma. All these subjects were atopic, which was defined by a positive skin test response (2 mm greater than a saline control) for at least one of 6 common aeroallergens. Eighty of these subjects were recruited from Vancouver, and 10 were recruited from Perth. For 62 of the asthmatic subjects in the mild-to-moderate group, measurements of FEV₁ were made while their disease was stable and well controlled. These measurements were made because the patients were recruited as part of a clinical study. The values for FEV₁ were expressed as percent predicted by using the prediction equations of Crapo et al.¹⁸ The subjects with mild-to-moderate asthma were further categorized into severity groups by using level of FEV₁ percent predicted, as previously described.¹² The patients were classified as having mild (FEV₁ >80%), moderate (FEV₁ 60%-80%), or severe (FEV₁ <60%) airflow obstruction.

In addition, we recruited a group of 143 nonasthmatic control subjects, all of whom were nonatopic. Nonasthmatic subjects had no personal history of asthma or atopy and had negative skin test responses (<1 mm wheal greater than saline) to common aeroallergens (from cats, dogs, house dust mites, grass, molds, and trees). These control subjects were all recruited from Vancouver.

All of the above subjects were white. Ethical approval for the study was obtained from the University of British Columbia and St Paul's Hospital Ethics Review Boards.

Genotyping

DNA from 127 of the subjects with fatal asthma and 13 of the subjects with mild-to-moderate asthma was extracted from paraffin-embedded, formalin-fixed, tissue samples, as previously described.¹⁹ All other DNA samples were extracted from samples of whole blood, as described previously.²⁰ The subjects were genotyped for the *FCERIB**E237G polymorphism by using an allele-specific amplification, as described previously.¹⁶

The subjects were genotyped for the *IL4RA**Q576R polymorphism by means of restriction enzyme digestion. The region surrounding the polymorphism was amplified with the following primers: 5'-GCC CCC ACC AGT GGC TAC C-3' and 5'-GCC TTG TAA CCA GCC TCT CCT-3'. PCR was performed by using 1 μ mol/L of each primer. Amplification conditions were 94°C for 5 minutes, 80°C for the addition of the Taq DNA polymerase, and then 40 cycles of 94°C for 30 seconds, 55°C for 30 seconds, and 72°C for 1 second. The PCR product was 123 bp in length and was digested with 10 U of *MspI* restriction enzyme. The digest produced 107- and 16-bp fragments from the *Q576 allele and 89-, 18-, and 16-bp fragments from the *576R allele.

A two-step protocol was used for detection of the *IL4**C-589T polymorphism. The following primers were designed: 5'-TAG ACC TAC CTT GCC AAG GGC-3' (P3F); 5'-TGC ATA GAA GGG AGA GGC CAC-3' (P3R); 5'-CTC AAA ACA CTA AAC TTG GGA GAA CAT TCT C-3' (PW2); and 5'-AGA CTC TCC TAC CCC AGC ACT GGC GA-3' (PM2). In the first PCR primers P3F and P3R produce a 350-bp control band, irrespective of the genotype at the -589 position. Primer PW2 is complementary to the wild-type sequence and produces a 260-bp fragment with P3R only when the wild-type sequence is present. PCR was performed by using 1 μ mol/L P3R and PW2 and 0.0625 μ mol/L P3F. Touchdown PCR²¹ was performed for 14 cycles of 94°C for 30 seconds, annealing for 30 seconds, and 72°C for 1 second, decreasing the annealing temperature by 1°C every 2 cycles from 63°C to 57°C. Then 27 cycles were performed with an annealing temperature of 56°C. In the second PCR primer PM2, which is complementary to the mutant sequence, produces a 148-bp band with P3F only when the mutant sequence is present. In this PCR 0.5 μ mol/L of each primer (P3F, P3R, and PM2) was used. Amplification conditions were 40 cycles of 94°C for 30 seconds, 61°C for 30 seconds, and 72°C for 1 second.

The allele-specific PCR assay described above was unsuccessful for most of the samples extracted from paraffin-embedded tissue. Therefore the *IL4**C-589T polymorphism was detected in these samples by using a modification of a previously described restriction enzyme assay.⁷ The upstream primer was AW41A, described previously,⁷ and the downstream primer was 5'-GCA TAG AGG CAG AAT AAC AGG C-3'. PCR was performed by using 2 μ mol/L of each primer. Amplification conditions were 94°C for 5 minutes, 80°C for the addition of the Taq DNA polymerase, and then 40 cycles of 94°C for 30 seconds, 57°C for 60 seconds, and 72°C for 30 seconds. The PCR product was digested with 6 U of *BsmFI* restriction enzyme overnight at 65°C. The wild-type allele generated a product that was cut into 62- and 48-bp fragments, whereas the mutant product remained uncut at 110 bp. The products of each PCR reaction were resolved by electrophoresis on a 3% agarose gel stained with ethidium bromide.

Data analysis

The genotype distributions in the different groups were compared by using χ^2 analysis for a 2×2 table or by using the Fisher exact test. Because there were few homozygotes for each mutation, they were analyzed together with the heterozygous subjects. Odds ratios (ORs) were calculated as previously described.²² Interactions between the *IL4* and *IL4RA* polymorphisms were assessed by examining the appropriate term in a logistic regression model.

RESULTS

The phenotypic characteristics of the 3 study groups are shown in Table I. The genotype distributions of all 3 polymorphisms were in the Hardy-Weinberg equilibrium, both within each phenotypic group and in the population as a whole. We found no significant difference in the prevalence of the *FCERIB**E237G polymorphism between any of the study groups (Table II). The samples extracted from paraffin-embedded tissue were sometimes difficult to genotype unequivocally. Therefore we were unable to genotype 18 of the subjects with fatal and one of the subjects with mild-to-moderate asthma for this polymorphism.

There was also no significant difference in the prevalence of the *IL4RA**Q576R polymorphism between any of the study groups (Table II). Genotyping for this polymorphism was unsuccessful in 22 of the subjects with fatal or near-fatal asthma and 4 of the subjects with mild-to-moderate asthma. However, in a subset of the asthmatic subjects (58 with mild-to-moderate and 2 with fatal asthma), lung function (FEV₁ percent predicted) and *IL4RA* genotypic data were available. There were no significant differences ($P > .31$) in age, sex, or the proportion of smokers between this subset and the remaining asthmatic subjects. In view of the previous report showing association of the *576R allele with lower FEV₁ percent predicted,¹² we determined whether there was a similar association in this subset. We found a significant increase in the prevalence of individuals who had the *576R allele in asthmatic subjects with severe airflow obstruction compared with those who had moderate or mild obstruction (OR, 8.0 and 8.2, respectively; Table III). The association of *576R with severe obstruction was still significant ($P = .02$) if the two subjects with fatal asthma were removed from the analysis. The mean FEV₁ percent predicted was not significantly different in the asthmatic subjects with *576R (77.7% predicted) compared with those without this allele (82.3% predicted).

The *IL4**-589T allele was present (either in the heterozygous or homozygous state) in a significantly higher proportion of subjects with fatal or near-fatal asthma than nonasthmatic control subjects (OR, 1.8; Table II). The *-589T allele was also present in a significantly higher proportion of subjects with fatal or near-fatal asthma than subjects with mild-to-moderate asthma (OR, 1.9). Genotyping for this polymorphism was unsuccessful in 13 of the subjects with fatal or near-fatal asthma and one of the subjects with mild-to-moderate asthma. In the subset of asthmatic subjects (56 with mild-to-moderate and 2 with fatal asthma) in which lung function and *IL4* genotypic data were available, we determined whether there was an association of the *-589T allele with lower FEV₁ percent predicted, as reported previously.⁹ We found no significant difference in the level of lung function in heterozygotes for the *-589T allele (mean $\pm$ SE FEV₁ percent predicted, 78.9 $\pm$ 4.1) compared with wild-type individuals (mean $\pm$ SE FEV₁ percent predicted, 81.9 $\pm$ 2.8). Lung function data were not available for the two *IL4**-589 TT homozygotes.

Because the IL-4 and IL-4R α proteins interact, we investigated whether there was an interaction between the

TABLE I. Characteristics of the study subjects

Phenotype	Study group			P value
	No asthma	Mild-to-moderate asthma	Fatal or near-fatal asthma	
Age, y (mean $\pm$ SE)	37.7 $\pm$ 1.1	34.4 $\pm$ 1.4	34.4 $\pm$ 1.4	.11
Male (%)	54.1	47.8	44.2	.22

There were no significant differences between any two groups.

TABLE II. Genotype frequencies in the study groups

Phenotype	FCER1B*E237G			IL4RA*Q576R			IL4*C-589T			P value*
	EE	EG	GG	QQ	QR	RR	CC	CT	TT	
No asthma (%)	134 (94)	7 (5)	2 (1)	95 (66)	43 (30)	5 (4)	100 (70)	41 (29)	2 (1)	.02
Mild-to-moderate asthma (%)	82 (92)	7 (8)	0	61 (71)	22 (26)	3 (3)	64 (72)	23 (26)	2 (2)	.02
Fatal or near-fatal asthma (%)	133 (96)	6 (4)	0	84 (62)	47 (35)	4 (3)	82 (57)	55 (38)	7 (5)	—

There were no significant differences between any groups for the FCER1B*E237G and IL4RA*Q576R polymorphisms.

*CC versus CT combined with TT.

TABLE III. Genotype frequencies for IL4RA*Q576R in the asthmatic subjects classified according to severity on the basis of the level of lung function

Severity of airflow obstruction	Genotype			P value*	P value vs severe asthma*
	QQ	QR	RR		
Mild obstruction (%)	22 (73)	7 (23)	1 (3)	.03	.01
Moderate obstruction (%)	16 (73)	5 (23)	1 (5)		.02
Severe obstruction (%)	2 (25)	5 (63)	1 (12)		—

*QQ versus QR combined with RR.

TABLE IV. Distribution of IL4*C-589T and IL4RA*Q576R genotypes

Phenotype	Value	Neither IL4*-589T nor IL4R α *576R	IL4*-589T only	IL4R α *576R only	Both IL4*-589T and IL4R α *576R	P value for interaction
No asthma	No. (%)	69 (48)	27 (19)	32 (22)	15 (11)	—
Mild-to-moderate asthma	No. (%)	46 (54)	15 (18)	15 (18)	9 (11)	—
Fatal or near-fatal asthma	No. (%)	50 (39)	30 (24)	20 (16)	27 (21)	—
	OR (95% CI)	—	1.5 (0.8-2.9)	0.9 (0.4-1.7)	2.5 (1.2-5.1)	.24
	vs no asthma					
	OR (95% CI) vs mild-to-moderate asthma	—	1.8 (0.9-3.8)	1.2 (0.6-2.7)	2.8 (1.2-6.5)	.75

Individuals with each allele include heterozygotes and homozygotes.

CI, Confidence interval.

IL4*C-589T and IL4RA*Q576R polymorphisms. We calculated ORs for fatal or near-fatal asthma versus absence of asthma and mild-to-moderate asthma for individuals who had neither, one, or both mutant alleles from these polymorphisms (Table IV). However, there was no statistically significant interaction between the polymorphisms, as determined by logistic regression (Table IV). There was also no interaction between the polymorphisms for severity of airflow obstruction as the outcome variable.

DISCUSSION

We have determined the prevalence of the FCER1B*E237G, IL4*C-589T, and IL4RA*Q576R poly-

morphisms in a group of subjects with mild-to-moderate asthma and in a group of subjects with fatal or near-fatal asthma. This is the first study to investigate the potential role of these polymorphisms in the pathogenesis of fatal or near-fatal asthma. The prevalence of the IL4*-589T allele was not significantly increased in the subjects with mild-to-moderate asthma compared with the control subjects. Two previous studies have found associations between the *-589T allele and measures of IgE.^{5,7} However, in both of these studies there was no association of *-589T with physician-diagnosed asthma. The lack of association with mild-to-moderate asthma in this study is consistent with these previously presented data.

Interestingly, the prevalence of the *-589T allele was

increased in subjects with fatal or near-fatal asthma compared with the nonasthmatic subjects and those with mild-to-moderate asthma. To our knowledge, this is the first study to find a genetic association with fatal or near-fatal asthma. A recent study of 682 white asthmatic subjects also showed that the **-589T* allele was associated with more severe asthma.⁹ In that study the level of lung function was used as a measure of severity. The FEV₁ percent predicted in the CC, CT, and TT individuals was 56%, 54%, and 52%, respectively. We were unable to show a significant difference in lung function associated with the **-589T* allele in our asthmatic group. However, the sample size was much smaller than that of the previous study, and the patients in our study had less severe airflow obstruction. Therefore the failure to replicate the result of Burchard et al⁹ may have been due to insufficient power.

The reason for the involvement of the *IL4* gene in the pathogenesis of fatal or near-fatal asthma remains to be determined. However, atopy is a risk factor for various markers of asthma severity, including frequency of wheezing,²³ medication use,²⁴ emergency department visits for acute asthma,^{25,26} intubation for acute asthma,²⁷ and rapidly progressing asthma attacks leading to death.²⁸ The prevalence of wheeze, airway hyperresponsiveness, and use of asthma medication in schoolchildren have been related to the size of skin wheal in response to common aeroallergens.^{23,24,29} In addition, exposure to aeroallergen has been suggested as an important factor in precipitating respiratory arrest and fatal asthma attacks.^{30,31} If the **-589T* allele is associated with more severe atopy and higher IgE responses to allergens, it could contribute to the risk for rapidly progressing fatal asthma.

We found no association of *FCER1B*E237G* with mild-to-moderate or fatal or near-fatal asthma. This result suggests that *FCER1B*E237G* does not contribute to susceptibility to asthma or to disease severity. This conclusion does not support the findings of two previous studies. A study of 1004 white Australian subjects found that subjects with the **237G* allele had a relative risk for asthma of 2.3 compared with wild-type subjects. The **237G* allele was also associated with increased skin test responses to aeroallergens and increased bronchial reactivity to methacholine.¹⁶ In a study of 200 Japanese patients who had atopic asthma, the prevalence of **237G* was significantly increased in the patients compared with nonasthmatic nonatopic control subjects (OR, 3.4).¹⁷ In our study there was no association between **E237G* and asthma. The lack of association may reflect genetic heterogeneity in the pathogenesis of asthma. The presence of several risk alleles for asthma, atopy, or both would make replicating linkage and association studies difficult. Different risk alleles may be important in different populations. Alternatively, the lack of association may be due to differences between populations in amount or type of exposure to environmental factors.

Similarly, we found no association of the *IL4RA*Q576R* polymorphism with mild-to-moderate or fatal or near-fatal asthma. Previously, the **576R* allele was shown to increase the signal transduction of the receptor and was associated with atopy.¹⁰ Other studies have

implicated the *IL4RA* gene in the genetic basis of asthma. The region containing the *IL4RA* gene was linked to atopy in a German population,¹¹ and a different amino acid substitution (I50V) was associated with total serum IgE and asthma in a Japanese population.³²

We were able to show a significant association of the *IL4RA*576R* allele with the level of lung function in the asthmatic subjects. We used the definition of asthma severity described in a previous study.¹² In that study 33% of subjects with severe asthma (FEV₁ <60% predicted) were heterozygous and 19% were homozygous for the **576R* allele. In the subjects with mild asthma, 20% were heterozygous and 10% were homozygous for **576R*. In our study we also found a marked increase in the prevalence of individuals with the **576R* allele in individuals with an FEV₁ of less than 60%. This is the first study to replicate the association of the **576R* allele with a low level of lung function in patients who have asthma. These data suggest that *IL4RA*576R* is a risk factor for airflow obstruction in asthmatic subjects but does not increase the risk of a fatal or near-fatal asthma attack.

It is currently unknown why the *IL4RA*576R* allele is associated with a lower level of lung function in asthmatic subjects. The polymorphism has been shown to affect receptor signaling.¹⁰ PBMCs from individuals who had the **576R* isoform of the IL-4 receptor were shown to have higher levels of IL-4-induced CD23 expression. The enhanced IL-4 receptor signaling associated with the **576R* isoform may have relevance to the severity of asthma. Previous studies have shown that steroid-resistant asthmatic subjects have increased IL-4 expression compared with steroid-sensitive asthmatic subjects.³³ Furthermore, T cells from steroid-resistant asthmatic subjects demonstrate reduced glucocorticoid receptor binding affinity.³⁴ Treatment of these cells in culture with IL-2 and IL-4 maintained this abnormally low binding affinity. These data suggest that IL-4 may cause decreased sensitivity to steroids and therefore more severe asthma. This decreased sensitivity to steroids may be more easily achieved in individuals with the **576R* form of the IL-4 receptor because it is associated with enhanced IL-4 responsiveness.

There are at least 5 common amino acid substitutions in the human *IL4RA* gene, including the **Q576R* polymorphism.³⁵ These polymorphisms may interact with each other to influence the functioning of the IL-4 receptor. However, to our knowledge, none of the other polymorphisms have been associated with any measure of asthma severity.

In this study we also investigated whether there was an interaction between polymorphisms in the *IL4* and *IL4RA* genes. Because *IL4* and *IL4RA* interact at the protein level, there could have been an association (either additive or synergistic) of the two polymorphisms. For example, *IL4RA*576R* may have had a significant effect on the fatal or near-fatal asthma phenotype in combination with *IL4*589T*, despite the lack of association of **576R* by itself. This is the first study to test whether there was an interaction between these two polymorphisms. However, there was no statistically significant interaction between the polymorphisms, as determined by logistic regression.

The definition of asthma severity is difficult because markers of severity not only reflect inherent pathophysiologic abnormality but are also affected by such factors as the appropriateness of medical care and patient compliance. In addition, asthma severity can vary over time in the same individual. We chose to use fatal or near-fatal asthma as one of our markers of severity. Although it may be affected by the factors mentioned above, it has the advantage that it represents a clearly defined clinical endpoint. It would be of great importance to define any predictors of potentially fatal disease.

The results of this study suggest that genetic markers of asthma severity can be identified. It is conceivable that these genetic markers could be used in the clinical setting to identify individuals at risk for more severe asthma. These individuals could then be targeted for more rigorous education and preventative measures, particularly in early childhood. However, more research is required to accurately quantify the risk associated with these genetic markers before they could be used in the clinical setting. Ideally, these studies would be longitudinal in design.

In conclusion, we have studied genetic polymorphisms known to be involved in the development of atopy to determine whether they are also risk factors for severe disease. We have shown that the *IL4**-589T allele may be involved in determining disease severity, as defined by the occurrence of a fatal or near-fatal asthma attack. We have also shown that the *IL4RA**Q576R polymorphism may influence the level of lung function in individuals who have asthma.

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