

The IL-1 β genotype carries asthma susceptibility only in men

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One proinflammatory cytokine possibly implicated in the pathogenesis of asthma is IL-1 β . We analyzed the polymorphism of the IL-1 β gene (single nucleotide exchange at position -511) in a cohort of 245 patients with asthma (mean age, 58 years; age range, 31-84 years) and 405 controls. There were no differences in the allele frequencies. However, in men the genotype distribution differed significantly between asthmatic and control subjects ($P = .03$). The number of 1.2 heterozygotes was decreased in the patient group ($P = .01$). In subgroup analysis, the genotype distributions between cases and controls proved significantly different only in men with lower serum IgE (<100 IU/mL; $P = .009$). The odds ratio of the 1.2 heterozygote men was 0.37 (95% CI, 0.19-0.71). Thus in the case of men the effect of the IL-1 β locus is clear, whereas in women there is no effect. In men this might make a significant contribution to the total asthma prevalence because of the high number of functional genotypes (ie, 50/50 IL-1 β homozygote/heterozygote ratio). (J Allergy Clin Immunol 2002;109:514-6.)

Key words: Asthma, inflammation, IL-1 β , sex difference

One of the major characteristics of asthma is airway inflammation. Many mediators of the inflammatory process have been shown to contribute to the disease. One proinflammatory cytokine possibly implicated in the pathogenesis of asthma is IL-1 β .¹ The IL-1 gene complex is located in chromosome 2, whose linkage to asthma has been reported in more than one study. The IL-1 family of molecules is among candidate genes.²

In vitro findings have implied that a genetic influence on the strength of inflammation is exerted by polymorphisms of the cytokine genes. Several of these polymorphisms have been shown to be associated with either severity of or susceptibility to many inflammatory diseases.³ Furthermore, recent studies have revealed signif-

icant sex-dependent differences in the strength of the immune and inflammatory responses.⁴ Sex also has a significant impact on asthma morbidity. Among adults, both the prevalence and the incidence of asthma are higher in women.⁵ We therefore analyzed the role of one of the major regulators of inflammation, IL-1 β , in susceptibility to asthma separately in male and female adults.

METHODS

The patients and controls here were participants in a Finnish population-based study aimed at identifying risk factors and predictors of the outcome of adult asthma. Inclusion criteria for asthmatic subjects were age greater than 30 years and entitlement to special reimbursement for asthma medication from the Social Insurance Institution of Finland. The phenotype studied was persistent asthma. The diagnoses were made by chest physicians on the basis of clinical and physiologic criteria recently described and evaluated.⁶ One or 2 controls who did not have asthma or chronic obstructive pulmonary disease were initially selected for each subject through use of a registry covering the entire population. Subjects and controls were matched for age, sex, and area of residence. In all, there were 245 asthma patients (mean age, 58 years; age range, 31-84 years; mean duration of asthma, 11 years) and 405 controls (mean age, 60 years; age range, 31-89 years) in the study group.

IL-1 β genotyping (C to T base exchange at position -511) was carried out through use of PCR and *AvaI* enzyme digestion, as previously described.⁷ Total serum IgE detections were made through use of an immunoluminometric method in an accredited laboratory according to the manufacturer's instructions (Ciba Corning Diagnostics, Halstead, United Kingdom).

When used, the statistical methods selected are indicated in the Results section. All calculations were made with SPSS 10.1 (SPSS Inc, Chicago, Ill). Approval for the study was obtained from the ethics committee at Tampere University Hospital. All subjects gave informed consent to participate.

RESULTS

IL-1 β genotyping results are presented in Table I. The allele frequencies were closely similar in the different groups. The genotype distribution did not differ significantly between asthmatic and control subjects ($P = .105$; χ^2 testing, $df = 2$) when the sexes were analyzed together. However, in men the genotype distribution differed significantly between asthmatic and control subjects ($P = .031$; χ^2 testing, $df = 2$), this being due mainly to the decreased number of the 1.2 heterozygotes in the patient group ($P = .011$; χ^2 testing, $df = 1$; Table I). Consequently, heterozygosity must be seen to exert a significant protective effect (odds ratio [OR], 0.50; 95% CI, 0.30-0.86).

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TABLE I. The IL-1 β (single nucleotide polymorphism –511) genotypes in male and female patients with asthma and controls

	Men				Women			
	Asthma (n = 92) (%)	Control (n = 150) (%)	OR	95% CI	Asthma (n = 151) (%)	Control (n = 250) (%)	OR	95% CI
Genotype								
1.1	43.5	34.7	1.45	0.85-2.47	40.4	34.0	1.32	0.87-2.00
1.2	35.9	52.7	0.50	0.30-0.86	46.4	49.6	0.88	0.59-1.32
2.2	20.7	12.7	1.79	0.89-3.60	13.2	16.4	0.78	0.44-1.39
Allele frequency								
Allele 1	61	61	—	—	64	59	—	—
Allele 2	39	39	—	—	36	41	—	—

IL-1 β genotyping was successful in 243 of 245 asthma patients and in 400 of 405 controls.

TABLE II. The effect of IL-1 β (SNP –511) genotypes on susceptibility to asthma in men in relation to serum IgE level

Serum IgE (IU/mL)	Genotype	Asthma		Control		χ^2 test (df = 2)	OR	95% CI
		N	%	N	%			
≥100	1.1	11	36.7	13	37.1	.964	0.98	0.36-2.69
	1.2	14	46.7	17	48.6		0.93	0.35-2.46
	2.2	5	16.7	5	14.3		1.20	0.31-4.62
<100	1.1	29	46.8	38	33.3	.009	1.76	0.93-3.31
	1.2	19	30.6	62	54.4		0.37	0.19-0.71
	2.2	14	22.6	14	12.3		2.08	0.92-4.72

In women, no significant differences were found between patients and controls in corresponding analyses.

To establish whether the effect of the IL-1 β genotypes is stronger in an asthma subgroup, the patients and controls were divided into groups with serum IgE level used as the criterion. The genotype distribution between cases and controls was significantly different only in men with lower IgE levels (serum IgE < 100 IU/mL; Table II). The OR of the 1.2 homozygotes was further decreased (0.37; 95% CI, 0.19-0.71), and that of the pooled homozygotes was increased (2.70; 95% CI, 1.40-5.19). In women, no significant differences were found in either high-IgE or low-IgE groups.

DISCUSSION

We here undertook to analyze the association of the polymorphism of the IL-1 β gene with susceptibility to asthma in men and women. The positive predictive value of our asthma definition is high.⁶ Inasmuch as our definition includes only persistent cases of asthma, our results apply to susceptibility to this disease form.

IL-1 β is a major proinflammatory cytokine, and the polymorphisms of this gene have been shown to be of importance in a number of diseases.⁸ Although it has not been the major cytokine of interest among asthma researchers, IL-1 has been suspected of involvement in asthma pathogenesis.¹ Total serum IgE, one of the major phenotypes of atopy, has strong heritability. There is evi-

dence for separate genes controlling asthma susceptibility and atopy.⁹ Because there is no evidence to show that the IL-1 gene complex is involved in the regulation of the atopic reaction, its possible contribution to asthma pathogenesis must be assumed to proceed via an effect on the intensity of the inflammatory process.

The effect of homozygosity/heterozygosity on biological mechanisms—eg, IL-1 β protein production—is unknown. It has recently been observed, however, that IL-1 β (single nucleotide polymorphism –511) heterozygosity has a protective effect against serious manifestations of meningococcal disease.¹⁰ Such a heterozygote advantage might thus be valid in several diseases of an inflammatory or infectious nature.

There are clear sex-dependent differences in the body's defense mechanisms in response to invading microbes and likewise in the prevalences of inflammatory and autoimmune diseases.⁴ Because it is highly unlikely that the frequencies of the alleles of the cytokine genes vary between men and women, one might argue that the functions of a given allele are sex-dependent. This could be manifested, for example, in different allelic associations in some diseases. We now know that after puberty females run a higher risk of developing new asthma.⁵

In summary, our data demonstrate that the genetic background of asthma differs between men and women. In the case of men, the effect of the IL-1 β locus is clear, whereas in women it has no effect. The observed ORs in men are of the same magnitude as those for other asthma susceptibility

genes. However, the findings described here can make a significant contribution to the total asthma prevalence because of the high frequency of the functional genotypes (ie, 50/50 IL-1 β homozygote/heterozygote ratio in the population). It also is noteworthy that susceptibility was associated with the genotype, not with the presence or absence of a certain allele.

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