

C-C/C-C genotypes ($n = 7$) revealed a 19.8-fold increase of PGE_2 ($P < .001$) and a 7.4-fold increase of PGD_2 ($P = .024$) in unstimulated monocytes with the variant genotype. In LPS-stimulated cells, these differences were respectively 19.6-fold and 11.5-fold ($P = .001$).

There was uniformly strong linear correlation between the number of C-C haplotype copies and capacity for biosynthesis of PGE_2 (log-transformed data, Pearson $r = 0.80$; $P < .001$) and PGD_2 ($r = 0.69$; $P = .002$). Stimulation of monocytes with LPS resulted in a very similar correlation for PGE_2 ($r = 0.80$; $P < .001$) and PGD_2 ($r = 0.78$; $P < .001$). The C-C haplotype had no effect on magnitude of PG induction by LPS.

We analyzed haplotypes of 2 functional SNP candidates within *COX-2* gene. One of the loci— $G_{-765}C$ —was previously studied by us in opposite homozygotes with asthma. We now expanded this group, adding 8 subjects heterozygous for this SNP. In these heterozygotes, PG biosynthetic capacity of monocytes was in between CC and GG homozygotes (data not shown). Haplotypes of the 2 SNPs were reconstructed, and PG levels in monocyte cultures were reanalyzed using arbitrary classes of compound genotype. The haplotype variant C-C was expected^{1,4} to associate with the highest activity of *COX-2*. Indeed, there was a very strong linear correlation between the number of C-C haplotype copies and PG levels in monocyte cultures. Because our subjects with asthma were selected for functional studies of *COX-2* polymorphisms by $G_{-765}C$ genotypes, estimated haplotype frequencies are not representative for a random sample of subjects. The haplotypes of *COX-2* were in linkage disequilibrium both in a group of controls without asthma and in subjects with asthma. The difference in PG production by peripheral blood monocytes of subjects with asthma with extreme compound genotypes G-T/G-T and C-C/C-C was striking. Our data suggest an additive effect of C-C *COX-2* haplotype on gain of function, because the difference between the extreme compound genotypes (C-C vs G-T) in PGE_2 levels was by 65% greater than the one between opposite homozygotes $-765CC$ and $-765GG$.¹ The presented haplotype approach was validated by several pharmacogenomic studies⁶ and identified the *COX-2* variant related to overproduction of prostaglandins. No complete study on the interaction between the 3' untranslated region $\text{COX2.8473T} \rightarrow \text{C}$ polymorphism and promoter $G_{-675}C$ variants was possible because of a low frequency of some haplotypes. However, altered promoter activity of *COX-2* gene related to $G_{-765}C$ SNP seemed to be predominant but additive with stabilization of the mRNA transcript as a result of $\text{COX2.8473 T} \rightarrow \text{C}$. Because *COX-2* activity plays a pivotal role in inflammation, this overproducing genetic C-C variant of the gene seems worthy of study in several human pathologies that, apart from asthma, are mediated by the inducible activity of the isoenzyme.

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The work benefited from the experience gained in the European Community Program Global Allergy and Asthma European Network. Supported by Jagiellonian University Grants PKL/8 and KL/611 and Polpharma Foundation Grant F/P/4.

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Available online April 25, 2005.
doi:10.1016/j.jaci.2005.03.010

Childhood cat exposure-related tolerance is associated with *IL1A* and *IL10* polymorphisms

To the Editor:

Atopic parents have been advised not to acquire pets to reduce their child's risk of allergic diseases. However, it has been shown that the presence of a cat in the home might decrease the risk of sensitization to cat allergen,¹ and exposure to domestic pets in the first year of life significantly reduces the risk of allergic sensitization in children.^{2,3}

IL-1 is a potent inducer of *IL-10* and also plays a role in early T-cell priming, which has been considered to be one key point of interest in the development of tolerance.⁴ We have previously studied *IL1A* (G/T base exchange at +4845) and *IL10* promoter region polymorphism in atopy and asthma.^{5,6}

Now we investigated whether the genes encoding the cytokines *IL-1 α* (*IL1A*) and *IL-10* (*IL10*) affect exposure-related tolerance. Therefore we analyzed the association of cat and dog exposure in childhood with the sensitization to cat and dog allergens in a population-based sample of adult asthmatic subjects ($n = 245$) and their nonasthmatic control subjects ($n = 405$). Detailed information on the study population has been presented previously in this journal.⁵

TABLE I. Prevalence of positive reactions to cat in skin prick tests in subjects with and without childhood exposure to cat

	N	%Exp	Childhood exposure to cat		P value	OR	95% CI
			Yes	No			
All asthmatic subjects	241	58.1	17.1	28.7	.032	0.51	0.28-0.95
Asthmatic or allergic parent							
Yes	78	56.4	15.9	44.1	.013	0.24	0.08-0.69
No	163	58.9	17.7	20.9	.610	0.82	0.37-1.79
All control subjects	401	62.8	8.7	11.4	.382	0.74	0.38-1.45
Asthmatic or allergic parent							
Yes	50	64.0	12.5	33.3	.077	0.29	0.68-1.20
No	351	62.7	8.2	8.4	.944	0.97	0.44-2.13

P values were calculated with the χ^2 test ($df = 1$).

%Exp, Proportion of subjects with childhood exposure to cat within the group.

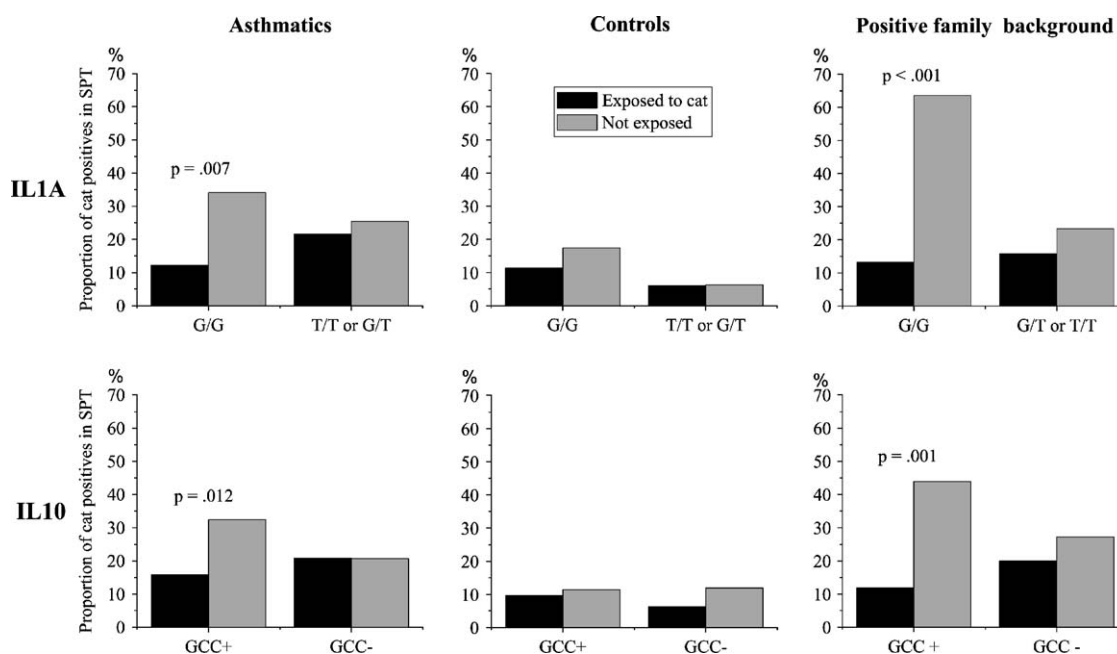


FIG 1. Proportion of cat-sensitized subjects with or without childhood exposure to cat in relation to *IL1A* (+4845G>T) genotype and *IL10* haplotype GCC in asthmatic subjects (n = 239), in control subjects (n = 396), and in all subjects (both asthmatic and control subjects) with a family history of allergy or asthma (n = 128). P values were calculated with the χ^2 test ($df = 1$).

Patients were considered to be exposed to cat, dog, or both if they answered yes to the following question: "Were you in the same room with a cat (dog) daily or almost daily in early childhood?" Sensitization to cat and dog was tested with the skin prick method, as described previously.⁵ The *IL1A* (+4845G>T) polymorphism and *IL10* promoter region haplotypes (formed by -1082G>A, -819C>T, and -592C>A) were analyzed as previously described.^{5,6} For frequency analyses, the *IL-10* genotypes were further categorized to *IL-10* high producer (GCC+; genotypes GCC/GCC, GCC/ATA, and GCC/ACC) and *IL-10* low producer (GCC-; genotypes ACC/ATA, ACC/ACC, and ATA/ATA) groups on a biologic basis.⁷

As expected, asthmatic subjects had more often a parent with asthma or allergy than control subjects (32.1% vs

12.6%; $P < .001$, χ^2 test; $df = 1$). Daily exposure to cat (as well as to dog) in childhood was equally common in families with or without parental asthma or allergy (Table I). Neither of the childhood animal exposures studied was significantly associated with asthma. The number of positive reactions to cat allergen was markedly lower in asthmatic subjects with daily cat exposure in childhood when compared with nonexposed asthmatic subjects (Table I). The effect of cat exposure increased in asthmatic subjects with a family background of asthma or allergy (Table I). There were no significant associations between dog exposure in childhood and sensitization to dog in any of the groups (data not shown).

In asthmatic subjects the protective effect was observed only in *IL1A* (+4845) allele G homozygotes (odds ratio [OR], 0.27; 95% CI, 0.10-0.72; $P = .007$; Fig 1) and in

subjects with high IL-10 producer haplotype GCC (OR, 0.39; 95% CI, 0.19-0.82; $P = .012$; Fig 1). The strongest cat exposure-related protective effect against cat sensitization was found in the combined group of asthmatic and control subjects with a history of parental asthma or allergy. In this group ($n = 128$) the prevalence of a positive reaction to cat allergen was 14.5% in exposed and 40.4% in nonexposed subjects (OR, 0.25; 95% CI, 0.11-0.58; $P = .001$). When the *IL1A* and *IL10* polymorphisms were taken into the analyses, yet stronger associations were found in *IL1A* (+4845) allele G homozygotes (OR, 0.09; 95% CI, 0.02-0.31; $P < .001$; Fig 1) and *IL10* haplotype GCC carriers (OR, 0.17; 95% CI, 0.060-0.49; $P = .001$; Fig 1).

In our study we show for the first time that the *IL1A* and *IL10* genes are substantially related to the development of cat exposure-induced tolerance. Because *IL1A* (+4845) G homozygosity and *IL10* GCC carrier states are very common, these observations have a substantial effect on the risk of sensitization at the population level. Exposure-related tolerance is strongest in subjects reporting a family history of atopy.^{1,8} *IL1A* (+4845) G homozygosity is more common in subjects with atopy,⁵ and it could be one of the factors that mediate the effect of family background.

It can be further concluded from our results that avoiding pets cannot be recommended as a preventive measure to avoid atopy. The associations of *IL1A* and *IL10* illustrated in the present study indicate that exposure-related tolerance is a biologic phenomenon with demonstrable genetic background. It further remains to be elucidated whether the *IL1A* and *IL10* genotypes mediate the responses in induced tolerance (ie, in immunotherapy).

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Supported by the Academy of Finland, the Rehabilitation Funds of the Finnish Social Insurance Institution, the Medical Research Fund of Tampere University Hospital, and the Tampere Tuberculosis Foundation.

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Available online May 16, 2005.
doi:10.1016/j.jaci.2005.03.026

Rapid intravenous cephalosporin desensitization

To the Editor:

On review of the literature, 2 protocols for intravenous cephalosporin desensitization were found requiring either a 2-day¹ or 14-day² period of time. Although cephalosporins are commonly prescribed in numerous nonemergency clinical settings, situations arise in which urgent cephalosporin therapy is the best or only treatment option available. One such setting is in the patient with cystic fibrosis who requires either an intravenous third- or fourth-generation cephalosporin for the treatment of *Pseudomonas aeruginosa*-induced pneumonia. It would thus be desirable to have a rapid protocol for cephalosporin desensitization, as is currently available for penicillin. Here we report rapid intravenous cephalosporin desensitization protocols that have been used successfully at the University of Iowa Hospitals and Clinics (UIHC) and Barnes-Jewish Hospital (BJH) over the past several years.

After institutional review board approval at both institutions, a retrospective chart review was performed. There were 49 patients who were seen between July 1997 and June 2002 at UIHC and 44 patients who were seen between January 1999 and January 2004 at BJH in whom penicillin and cephalosporin skin testing was performed. The 8 individuals, 2 from UIHC and 6 from BJH, included in this retrospective study were those who had positive skin test results and eventually underwent rapid intravenous desensitization to a cephalosporin (Table I). At both UIHC and BJH, it is our practice not to give cephalosporins to patients with penicillin allergy without prior penicillin and cephalosporin skin testing. Patients who had uniquely positive skin test results to penicillin determinants (negative skin test results to cephalosporins) were not desensitized to cephalosporin before receiving cephalosporin therapy. The remainder of the 93 subjects had negative skin test results and received a β -lactam antibiotic without adverse events. Given that this is a retrospective study, we