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Genetic Predisposition to Latex Allergy

Role of Interleukin 13 *and* Interleukin 18

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Background: **Occupational exposure of healthcare workers to natural rubber latex has led to sensitization and potentially life-threatening anaphylaxis. Although environmental exposure to natural rubber latex products is necessary for sensitization, it is not sufficient. A number of genetic factors also seem to contribute to the latex sensitization; however, the multigenic nature of the allergic phenotype has made the identification of susceptibility genes difficult. The current study tests the hypothesis that known functional polymorphisms in genes encoding interleukin 4, interleukin 13, and interleukin 18 occur in a higher frequency in healthcare workers with natural rubber latex allergy.**

Methods: **Four hundred thirty-two healthcare workers with occupational exposure to natural rubber latex were screened using a clinical history questionnaire and latex-specific immunoglobulin E serology. Genomic DNA was extracted from peripheral blood lymphocytes and analyzed for single-nucleotide polymorphisms in candidate genes of interest. Data from cases and controls were analyzed by nominal logistic regression, with $P < 0.05$ considered significant.**

Results: **The latex allergy phenotype was significantly associated with promoter polymorphisms in *IL13* −1055 ($P = 0.02$), *IL18* −607 ($P = 0.02$), and *IL18* −656 ($P = 0.02$) compared with nonatopic controls.**

Conclusions: **The significant association of *IL13* and *IL18* promoter polymorphisms with latex allergy suggests a potential location for genetic control in the induction of latex allergy in individuals and extends the understanding of the genetic basis for the induction of immediate-type hypersensitivity in healthcare workers occupationally exposed to natural rubber latex.**

THE National Institute for Occupational Safety and Health estimates that at least 7.7 million people are employed in the healthcare industry in the United States.** During the past decade, occupational exposure of healthcare workers to natural rubber latex (NRL), principally through use of latex medical gloves, has led to sensitization and potentially life-threatening type I (immunoglobulin E [IgE]–mediated) hypersensitivity to NRL allergens, which are subsequently referred to as *latex allergy*. Conservative prevalence estimates place between 2.9% and 12.1% of healthcare workers at risk for development of this potentially life-threatening disease.[1] Although exposure to NRL products is necessary for sensitization, it is not sufficient. A number of other environmental and genetic factors seem to contribute to the latex-sensitive phenotype. Known risk factors for latex allergy include an atopic history, concomitant food allergies, and delayed skin reactions to NRL-containing products.[2] Although there is overwhelming support for a genetic component for allergic disease, the multigenic nature of the phenotype has made the identification of susceptibility genes a difficult task. A large number of studies have explored general risk factors for allergic disease by the candidate gene approach or genome-wide analyses. Polymorphisms in more than 30 genes located on 15 different chromosomes have been associated with human allergy.[3]

Genes for interleukin 4 (*IL4*),[4] interleukin 13 (*IL13*),[5] and interleukin 18 (*IL18*)[6] have been implicated in the development of allergic disease. A promoter polymorphism at position −589 of *IL4* is associated with asthma and an increased serum IgE concentration.[7] A significant positive association was also reported between atopic disease and the *IL13* promoter −1055 TT genotype, a polymorphism that results in an increase in IL13 protein production through putative dysregulation of *IL13* transcription.[5] *IL18* has been implicated in atopic dermatitis, and *IL18* −137 and −607 promoter polymorphisms have been associated with altered cytokine expression[8] and autoimmune disease.[9] The goal of the current study was to test the hypothesis that known functional polymorphisms in *IL4*, *IL13*, and *IL18* occur in a higher frequency in healthcare workers with NRL allergy. Dysregulation of the production of one or a combination of these cytokines has the potential to influence the latex-sensitive phenotype.

Materials and Methods

Population

After institutional review board approval from the Johns Hopkins Medical Institutions, (Baltimore, Mary-

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Table 1. Study Population Demographics

	Total (n = 432)	Latex Allergy Cases (n = 24)	Atopic Controls (n = 130)	Nonatopic Controls (n = 101)
Sex, M/F, %	49%/51%	62%/38%	51%/49%	52%/48%
Age, mean ± SD, yr	41 ± 9	41 ± 8	41 ± 9	40 ± 10
White, %	69	71	67	65
African-American, %	9	0	8	11
Asian-American, %	12	16	9	12
Hispanic-American, %	2	4	1	3
Other race, %	5	8	5	6
Atopic status, %	64	100	100	0
Food allergy, %	16	67	0	0
Latex-specific IgE positive, %	5.6	100	0	0

IgE = immunoglobulin E.

land) and written informed consent, 432 healthcare workers (anesthesiologists, surgeons, and operating room nurses) with occupational exposure to NRL were screened using a clinical history questionnaire (see appendix). Occupational exposure consisted of physical contact and inhalation of airborne NRL proteins from latex-containing medical gloves and supplies. The questionnaire examined the participants' history of atopic disease (seasonal rhinitis, asthma, eczema, and food allergies), symptoms associated with the use of latex gloves and other NRL-containing devices, and the consistency and frequency of any suggestive delayed-type or immediate-type hypersensitivity reactions. The demographics of the participants are presented in table 1.

Latex allergy cases (24 of 432) were defined as subjects with a positive latex-specific IgE serology and symptoms consistent with a type I hypersensitivity to latex (table 2). Symptoms were required to be immediate in nature (over a few minutes) and not limited to only the area of contact with the latex-containing product. Two control groups were characterized. The first control group consisted of 130 individuals who were negative for latex allergen–specific IgE and asymptomatic for all latex exposures but atopic by history (*i.e.*, had a history of either seasonal rhinitis, asthma, eczema, or food allergies). The second control group consisted of 101 individuals who were identified as latex-allergen IgE negative, asymptomatic for latex exposures, and nonatopic by history (*i.e.*, no history of seasonal rhinitis, asthma, or eczema) and with an absence of food allergy. Of the remaining 177 individuals who were screened, all were latex-specific IgE antibody negative but reported either allergic symp-

Table 2. Demographics, Latex-specific IgE Serology, and Symptoms History for Latex-allergic Cases

Case	Age, yr	Sex	IgE Anti-latex, kUa/l*	Symptoms†
1	46	F	1.55	1
2	41	M	1.32	2
3	46	F	0.48	1,2,3,4,5
4	36	M	2.05	1,2
5	39	M	0.63	1,2,3
6	42	M	0.64	1
7	33	M	2.49	2,3
8	48	M	0.48	1,2,3,4,5
9	59	F	0.4	1
10	36	F	0.71	1,2,3,4
11	40	F	1.72	1
12	65	M	0.65	1,2,3,4
13	36	F	‡	1,2,3,4
14	33	F	‡	1
15	46	M	1.77	1,2,3
16	38	M	3.73	2
17	37	M	1.67	1,2,3
18	35	M	0.57	1
19	45	M	0.57	1,2,3
20	40	M	2.93	1,2,3,4,5
21	43	F	10.9	1,2,3
22	35	M	0.64	1,2,3
23	27	F	0.39	1
24	49	M	4.19	1,2,3

* Immunoglobulin E (IgE) values expressed as kilo units of allergen-specific IgE antibody per liter with positive results greater than 0.35 kUa/l. † Symptoms. 1 = skin symptoms, not limited to contact area; 2 = eye symptoms; 3 = upper airway symptoms; 4 = lungs (wheezing); 5 = cardiovascular—hypotension, anaphylaxis. ‡ Previously tested positive.

Table 3. Primer Sequences and Annealing Temperatures

Method	Polymorphism	Sense Primer	Antisense Primer	Annealing Temperature, °C
Sequencing	*IL13* −1055	tcggggaggaagtgggta	gatcaacccctgccgtct	58
	IL18 −137	aatcttaatggcctgtatc	gcactccttgggcccgcctt	58
	IL18 −656	taacatgttgaacataagc	gatacaggccattaagatt	52
	IL18 +113/+127	agcttgctgagccctttgct	actgctcatcgtagtgatgct	62
Sequencing/RFLP	*IL4* −589	actaggcctcacctgatacg	gttgtaatgcagtcctcctg	58
	IL18 −607	taacatgttgaacataagc	gatacaggccattaagatt	52
MS-PCR	*IL13* −1055	ggggtttctggaggacttctaggaacac aatgccgtggcctctgctgtgttgg tttctggaggacttctaggaaagt	gatcaacccctgccgtct	64
	IL18 −137	cagagccccaacttttacggaagaacag ggtacaggttttggaaggcatggagcccc aacttttacggaagaaatc	gcactccttgggcccgcctt	60
	IL18 −656	aatatttgccctcttacctgaattttggaag aacactggaaactgcaagtacgtatttgc cctcttacctgaattttggtct	gatacaggccattaagatt	60
Allelic discrimination	*IL18* +113/+127	tgtctcccagtgcatttttgc	ggtctgaggttcctttcctcttc	
	IL18 +113 probes	tgccaactctggctg (Vic labeled)	ctgccaacgctgg (6Fam labeled)	
	IL18 +127 probes	ctgctaaagcggctg (Vic labeled)	ctgctaaagtggctgc (6Fam labeled)	

IL = interleukin; MS-PCR = mutagenically separated polymerase chain reaction; RFLP = restriction fragment length polymorphism.

toms consistent with contact dermatitis upon latex glove use (delayed reactions usually occurring over days and limited to the area of contact with the gloves) or a food allergy. We intentionally excluded individuals with a history consistent with contact dermatitis symptoms because they can still be sensitized to latex.[2] These 177 individuals were excluded from further analyses.

Serology

Whole blood (10 ml) was collected by venipuncture from each subject using synthetic gloves and tourniquet. The specimen was clotted for 30 min and centrifuged, and the serum was separated. Samples were coded and stored at −20°C. Each serum specimen was analyzed for the presence and quantity of IgE antibody specific to NRL allergens using the Pharmacia CAP System (Pharmacia Diagnostics, Kalamazoo, MI), which uses a solid matrix covalently attached to native latex allergenic proteins derived from nonammoniated latex (K82). Results are reported in kilounits of allergen-specific IgE antibody per liter (kUa/l) with a positive result greater than 0.35 kUa/l. All latex-specific IgE measurements were repeated for confirmation of results. The diagnostic sensitivity and specificity of the latex allergen IgE CAP System assay have been reported at 74.8% and 93.8%, respectively.[10]

Genotyping

An additional 10 ml whole blood was drawn from each subject into a tube containing K_3 EDTA and stored frozen at −80°C. Genomic DNA was extracted from peripheral lymphocytes using the sodium perchlorate/chloroform extraction protocol as described by Johns *et al.*,[11] resuspended in sterile Tris-EDTA buffer, and stored at 4°C. DNA was measured using a DU640 Spectrophotometer (Beckman Coulter Inc., Fullerton, CA). To analyze the single-nucleotide polymorphisms in the candidate genes of interest, we used various polymerase chain reaction (PCR)–based techniques, including direct sequencing, PCR–restriction fragment length polymorphism, mutagenically separated PCR, and allelic discrimination using TaqMan probes.

To confirm the presence of each single-nucleotide polymorphism within the population under study and validate the accuracy of the publicly available genomic DNA sequence data, automated sequencing was performed on a subset of individuals using primers (Invitrogen, Carlsbad, CA) designed to flank each polymorphism (table 3). PCR amplifications were performed according to Nadif *et al.*[12] in a GeneAmp PCR System 9700 (Applied Biosystems, Foster City, CA), using annealing temperatures as indicated in table 3. Products were resolved on low-melt agarose (Invitrogen) gels containing ethidium bromide and 1× Tris-borate-EDTA buffer, visualized and cut over ultraviolet light, and purified using the QIAquick Gel Extraction Kit (Qiagen, Valencia, CA) according to manufacturer's recommended protocol. Purified PCR products were then mixed with sense primer and sequenced. Results were analyzed using the basic local alignment search tool software available from the National Center for Biotechnology Information Web site.[13] Assays were subsequently designed for each single-nucleotide polymorphism.

Subjects were genotyped for the *IL18* −607[8] and *IL4* −589[4] polymorphisms using PCR-restriction fragment length polymorphism. Sense and antisense primers were designed for *IL18* −607 (table 3) and synthesized by Invitrogen. Amplification reactions used the FailSafe PCR System (Epicenter Technologies, Madison, WI) containing 1× FailSafe PCR premix B, 0.4 μM of each primer, 0.375 units FailSafe PCR Enzyme mix, and 60 ng DNA. Digestion of the PCR products was carried out with 7.5 units *Mse*I (New England Biolabs, Beverly, MA), 1×

buffer 2, and 1× bovine serum albumin at 37°C for 3 h. Primers for *IL4* −589 were synthesized according to the design of Walley *et al.*[4] (table 3). Amplification reactions were performed according to Nadif *et al.*[12] in a final volume of 15 μl. Digestion was achieved by incubation of PCR products with *BsmF*I (New England Biolabs) and 1× buffer 4 at 65°C for 1.5 h. Cycling for both polymorphisms was performed in a GeneAmp PCR System 9700 (Applied Biosystems) with the following parameters: 94°C for 5 min; 30 cycles of 94°C for 30 s, annealing temperature (table 3) for 30 s and 72°C for 30 s; final extension at 72°C for 7 min. Products were resolved by electrophoresis on 2% agarose gels (Invitrogen) containing ethidium bromide and 1× Tris-borate-EDTA buffer; imaging and analysis were accomplished using a GelDoc 2000 (BioRad, Hercules, CA). Resultant product sizes for *IL18* −607 were 14, 37, 60, 199 base pairs (bp) for individuals homozygous for the C allele; 14, 37, 60, 98, 101, 199 bp for heterozygotes; and 14, 37, 60, 98, 101 bp for individuals homozygous for the A allele. The resultant product sizes for *IL4* −589 were 192 bp for C allele homozygotes, 252 and 192 bp for heterozygote alleles, and 252 bp for A allele homozygotes.

Promoter polymorphisms *IL13* −1055 (C->T),[5] *IL18* −137 (G->C),[8] and *IL18* −656 (T->G)[8] were analyzed by mutagenically separated PCR, a modification of allele-specific PCR in which reactions for all alleles of each single-nucleotide polymorphism are carried out in a single tube.[14] A pair of sense primers and a single antisense primer per polymorphism were designed (table 3), and assays were optimized according to the guidelines of Rust *et al.*[14] Final concentration reaction mixtures contained 1.5 mM $MgCl_2$, 200 μM GeneAmp dNTP mix (Applied Biosystems); 0.15 μM wild-type sense primer; 0.12 or 0.08 μM mutant sense primer for *IL13* or *IL18* polymorphisms, respectively; 0.2 μM antisense primer; 0.5 units *Taq*DNA Polymerase (Invitrogen); and 60 ng DNA. The cycling parameters were as follows: 94°C for 5 min; 40 cycles of 94°C for 30 s, annealing temperature (table 3) for 45 s and 72°C for 45 s; final extension at 72°C for 7 min. Amplification products were resolved on 3% agarose gels (Invitrogen) containing ethidium bromide and 1× Tris-borate-EDTA buffer, and both imaging and analysis were performed on a GelDoc 2000 (BioRad). Resultant product sizes for the two alleles differed by 20 bp.

Allelic discrimination with TaqMan Probes was used to genotype *IL18* +113 (T->G) and *IL18* +127 (C->T) polymorphisms. A set of common primers and unique pairs of TaqMan MGB probes were designed for each assay utilizing Primer Express software version 2.0 (Applied Biosystems). Primers (table 3) were synthesized by Invitrogen, and TaqMan MGB probes were synthesized by Applied Biosystems. Reactions contained 900 nM of each primer, 200 nM of each TaqMan probe, 1× TaqMan Universal PCR MasterMix with No AmpErase UNG, and 20 ng DNA. Cycling was performed according to the manufacturer's recommended protocol, consisting of 95°C for 10 min followed by 40 cycles of 92°C for 15 s and 60°C for 1 min. After amplification, plate reads were performed in the Prism 7000 Sequence Detection System (Applied Biosystems). Genotypes were determined by manual clustering using Prism 7000 SDS software version 1 (Applied Biosystems).

Table 4. Allelic Frequencies of Polymorphisms in *IL13*, *IL18*, and *IL4* among Atopic Controls, Nonatopic Controls, and Latex-allergic Cases

	Allelic Frequencies, %		
Polymorphism	Atopic Controls (n = 130)	Nonatopic Controls (n = 101)	Latex-allergic Cases (n = 24)
IL13 −1055T	23.3	16.8	54.2
IL18 −137C	27.9	26.7	39.6
IL18 −607C	46.2	38.6	54.2
IL18 −656G	46.2	38.6	54.2
IL18 +113G	28.2	26.7	39.6
IL18 +127T	27.9	26.7	39.6
IL4 −589T	26.0	23.3	27.1

IL = interleukin.

Statistical Analyses

The results of the latex-sensitive case group were compared separately to each control group (A and B) using nominal logistic regression analysis. $P < 0.05$ was considered statistically significant.

Results

Population Characteristics

Twenty-four of the 432 individuals studied (5.6%) were identified as sensitized to NRL allergens based on a positive latex-specific IgE and a positive clinical history for latex allergy (table 2). All 24 of these subjects were atopic by history. Eight of the 24 had a history of allergy to avocados, bananas, and/or kiwi. Fifteen of the 24 had documented systemic symptoms, *i.e.*, more than one organ system involvement, associated with occupational latex glove exposure.

Allele Frequencies

Genotypes were determined in all individuals for all polymorphisms assayed, except for one individual in control group A for *IL18* −656. The allele frequencies for all polymorphisms studied are shown in table 4. Allele frequencies for polymorphisms in *IL4* and *IL13* were similar to those reported previously.[4,5] Polymorphisms *IL18* −607 and −656 were in linkage disequilibrium in this population. Allele frequencies for polymorphisms in *IL18* varied slightly from those of Kruse *et al.*,[6] who reported frequencies of 28.3, 40.3, 35.7, 27.4, and 25.9% for *IL18* −137, −607, −656, +113, and + 127, respectively. The different frequencies may be due to

Table 5. Statistical Comparisons of Nonatopic Controls and Latex-allergic Cases Heterozygous or Homozygous for Mutant Alleles Compared with Those Who Were Homozygous Wild Type for IL13, IL18, and IL4 Polymorphisms

Polymorphism	Chi-square	Odds Ratio (95% CI)	*P* Value
***IL13* −1055**	**5.83**	**3.08 (1.24–7.82)**	**0.02**
IL18 −137	3.98	2.59 (1.04–6.91)	0.05
***IL18* −607**	**5.50**	**4.59 (1.46–20.33)**	**0.02**
***IL18* −656**	**5.50**	**4.59 (1.46–20.33)**	**0.02**
IL18 +113	3.98	2.59 (1.04–6.91)	0.05
IL18 +127	3.98	2.59 (1.04–6.91)	0.05
IL4 −589	0.21	1.24 (0.49–3.04)	0.65

Boldface entries refer to significant results. CI = confidence interval; IL = interleukin.

populations sampled (subjects in the Kruse *et al.* study were from Southwestern Germany), sample sizes, or both. Genotype distributions for all of the polymorphisms studied fit predictions for Hardy-Weinberg equilibrium.

Genetic Associations

The latex allergy phenotype was significantly associated with three of the promoter polymorphism when latex allergic cases were compared with the nonatopic control group. We found a significant association with the *IL13* −1055 promoter polymorphism (chi-square = 5.83, $P = 0.02$; table 5), the *IL18* −607 promoter polymorphism (chi-square = 5.50, $P = 0.02$; table 5), and the *IL18* −656 promoter polymorphism (chi-square = 5.50, $P = 0.02$; table 5) in the latex allergic cases compared to the nonatopic controls. The *IL18* +113 and the *IL18* +127 polymorphisms were only weakly associated, and no association was found with the *IL4* −589 promoter polymorphism in the latex allergic cases compared with the nonatopic controls (table 5). Furthermore, when we examined these same promoter polymorphisms in a group of atopic controls, we found no significant associations among any of the polymorphisms in the latex allergic cases compared with the atopic controls (table 6).

We also compared the frequencies of these promoter polymorphisms between the atopic and nonatopic control groups. We found no significant associations among any of the promoter polymorphisms in the atopic controls compared with the nonatopic controls (*IL13* − 1055, $P = 0.05$; *IL18* −137, $P = 0.53$; *IL18* −607, $P = 0.07$; *IL18* −656, $P = 0.07$; *IL18* +113, $P = 0.46$; *IL18* +127, $P = 0.53$; *IL4* −589, $P = 0.52$).

Table 6. Statistical Comparisons of Atopic Controls and Latex-allergic Cases Heterozygous or Homozygous for Mutant Alleles Compared with Those Who Were Homozygous Wild Type for IL13, IL18, and IL4 Polymorphisms

Polymorphism	Chi-square	Odds Ratio (95% CI)	*P* Values
IL13 −1055	1.64	1.77 (0.73–4.33)	0.20
IL18 −137	2.83	2.19 (0.90–5.74)	0.09
IL18 −607	2.50	2.78 (0.89–12.28)	0.11
IL18 −656	2.50	2.78 (0.89–12.28)	0.11
IL18 +113	2.61	2.13 (0.87–5.57)	0.11
IL18 +127	2.83	2.19 (0.90–5.74)	0.09
IL4 −589	0.01	1.03 (0.42–2.50)	0.93

CI = confidence interval; IL = interleukin.

Discussion

The current findings are the first to associate specific genetic polymorphisms with occupational latex allergy and thus extend our understanding of the induction of latex allergy in healthcare workers exposed to NRL. These results support the hypothesis that functional polymorphisms in *IL13* and *IL18* are risk factors for the development of latex allergy in occupationally exposed individuals.

The role of genetic background in susceptibility to other allergic diseases has been well documented. Genome scans have identified quantitative trait loci for asthma and asthma subphenotypes, including airways hyperreactivity, serum IgE, eosinophilia, and atopy on 13 chromosomes.[15] Multiple candidate genes have been investigated in asthma and allergy, including *IL4*, *IL13*, and *IL18*.[4–6] A strong immunologic rationale for investigation of these genes is provided by studies in mice and humans. Specific IgE production is initiated by T_H2 cells that release IL-4 and IL-13 in response to allergen exposure. Together with signals from the CD40 B-cell surface molecule, the binding of IL-4 and IL-13 to the α chain of the IL-4-receptor activates germline transcription of the epsilon heavy chain gene locus and isotype switching of B-cells to IgE production.[16] Evidence also exists that IL-18, depending on the specific circumstances, can stimulate T_H1-mediated immune responses (*e.g.*, interferon-γ production)[17] or enhance T_H2 cytokine production (IL-4 and IL-13) and IgE production in mice.[18] However, the potential contributions of these genes in allergy associated with occupational exposures to NRL allergens have not been previously investigated.

The current study tested the hypothesis that functional polymorphisms in *IL4*, *IL13*, and *IL18* are associated with latex-specific IgE antibody production and a clinical history of allergic symptoms following NRL exposure. Significant associations were identified with the latex allergy status of cases and promoter polymorphisms in *IL13* (−1055) and *IL18* (−607 and −656) when compared with the nonatopic control group.

For our cases, we attempted to use the most conservative definition of a latex allergic individual. Optimally, we would have preferred to skin test all the subjects in the study. However, there is no currently available Food and Drug Administration–approved skin testing material in the United States. Therefore, we used a commercially available serologic test that measured IgE against all 13 known native *Hevea brasiliensis* allergens to verify the

clinical history. The test is 98% specific.[10] However, it is only 75% sensitive.[10] Although we would correctly determine true positives, we would potentially have a significant number of false negatives. Therefore, to improve our ability to differentiate cases and controls, we included symptoms. The addition of symptoms along with a positive serology probably did not significantly increase our true positives. More important, with the removal of all individuals with any symptoms associated with latex glove use from the control groups, we believe that we improved our ability to identify true negatives.

We previously documented that atopy was a major risk factor for development of an allergy to NRL.[2] In those studies, we identified a number of individuals who were atopic and sensitized to NRL but had no symptoms and a negative serology but a positive skin test.[2] This potential number of false negatives among the atopic controls may be a factor in our finding of a lack of significant differences between the latex-allergic cases and atopic controls.

Our study found no association of the *IL4* −589 polymorphism with general atopy or specific latex allergy. The role of *IL4* in atopy has been implied in some linkage and association studies[7] but has been only weakly associated[19] or not associated at all[4,20] in others. For example, Rosenwasser *et al.*[7] found an association of *IL4* −589 with increased transcriptional levels of IL-4 and total serum IgE. Conversely, Beghe *et al.*[20] were unable to find association of *IL4* (−34, −589) or *IL4* receptor polymorphisms with any measure of atopy, including total or specific IgE in a white population in Southampton, England. An explanation for the apparent discrepancies between studies is not clear. However, a more complete understanding of the role of *IL4* in atopy will be gained by investigating all of the functional *IL4* single-nucleotide polymorphisms individually and by haplotype.[19]

It was also interesting that we found no significant statistical differences among any of the promotor polymorphisms between the atopic compared with the nonatopic control groups, although *IL13* −1055, *IL18* −607, and *IL18* −656 all approached statistical significance. It is important to note that this study was not designed to measure associations between atopic and nonatopic controls.

Identification of significant differences between the latex allergic cases and the nonatopic controls and not between the latex allergic cases and atopic controls was not surprising. Atopy is a major risk factor for the development of a latex allergy.[2] The molecular events that lead to the development of latex allergy are similar to those that lead to the development of food and other life-threatening allergies. Subtle changes in the immune system dictate the difference between an annoying and a catastrophic response. For example, many people are atopic, but only a few have life-threatening latex allergic reactions. To determine the genetic polymorphisms that can differentiate latex allergic from atopic individuals, a much larger study population would likely be needed.

The current findings extend our understanding of the genetic basis for the induction of latex allergy in healthcare workers occupationally exposed to NRL. These results support the hypothesis that genetic background is a risk factor for the development of latex allergy in occupationally exposed individuals, depending on the immunogenic stimulation of the subjects: environmental (food allergy) or occupational (latex).

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Appendix

Date: ___/___/___

Patients Initials: _ _ _

Patient Code: _ _ _ _ _ _

Age: ___

Gender [ ] M
[ ] F

Race: [ ] Native American
[ ] Asian/ Pacific Islander
[ ] African American (black)
[ ] Hispanic American
[ ] Caucasian, not Hispanic American
[ ] Other (specify) _____

Years since start of residency___

Medications taken in last week_____
_____

Previous evaluation for latex allergy: Y N
What tests, where, when?
_____
_____

ATOPIC HISTORY:
Seasonal rhinitis Y N
If Y, note season, severity, medication:_____
_____
Early onset asthma Y N
Eczema Y N
Food allergy Y N
List food allergens and type of reaction:
_____
_____
_____
Avocado/kiwi/banana? Y N
Results of acroallergen or food skin tests:
_____
_____

REACTIONS TO LATEX:

Skin:	[ ]	hives	[ ]	itch
	[ ]	rash	[ ]	rednes
	[ ]	swelling	[ ]	irritation
Eyes:	[ ]	itchy		
	[ ]	tearing/watering		
	[ ]	watering		
Upper Airway:	[ ]	runny nose		
	[ ]	itchy/ tight throat		
	[ ]	swelling		
	[ ]	sneezing		
Lungs:	[ ]	asthma, bronchospasm		
	[ ]	wheezing, cough		
	[ ]	shortness of breath		
	[ ]	chest discomfort		
Gastrointestinal:	[ ]	nausea		
	[ ]	vomiting		
Cardiovascular:	[ ]	chest pain		
	[ ]	palpitations		
	[ ]	hypotension (low blood pressure)		
	[ ]	light-headedness		
	[ ]	tachycardia (fast pulse)		
Number of reactions to latex:	[ ]	None		
	[ ]	Single event		
	[ ]	Many times (>1)		

Any latex exposures not resulting in a reaction:
_____
_

Number of previous surgeries:

Do you wear latex gloves Y N
If Y Powdered Nonpowdered
Do your coworker wear latex gloves Y N
If Y Powdered Nonpowdered

Chronological description of last 2 reactions: (exposure, onset, duration, severity estimates):
_____
_____
_____
_____
_____