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IMPACT OF INTERLEUKIN-13 AND -18 PROMOTER POLYMORPHISMS IN HEALTH CARE WORKERS WITH NATURAL RUBBER LATEX ALLERGY

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It is a matter of debate whether single nucleotide polymorphisms (SNP) in the promoter region of interleukin (IL)-13, an IgE regulator, and IL-18, an inducer of immune responses, modulating the respective protein expression, are accompanied by an increased risk of atopy, allergic asthma, and total IgE levels. The suspected associations were noted in health care workers (HCW) with and without latex allergy. IL-13 (–1055C>T) and three IL-18 (–656T>G, –607C>A, –137G>C) SNP were studied in 523 HCW with natural rubber latex (NRL) exposure and diagnosis in the late 1990s. Three hundred and thirty-four HCW displayed NRL sensitization and allergic symptoms, 93 with latex-allergic asthma, and 189 HCW with neither symptoms nor NRL sensitization. SNP analyses were performed by real-time polymerase chain reaction (PCR) using newly developed LightCycler assays. Analysis of IL-13 –1055C>T by analysis of variance (ANOVA) revealed significantly elevated total IgE levels in HCW carrying the CT or TT variant compared with the CC variant. None of the studied SNP showed an association with NRL-specific IgE. The IL-18 variants –656GG and –607CC displayed 99.5% linkage disequilibrium. Frequencies of alleles –656GG and –607CC were elevated in HCW with NRL asthma (48.4%) compared with HCW without symptoms (37.6%). In contrast, IL-18 –137G>C variants displayed an overall homogenous distribution. The association between the IL-13 –1055T allele and elevated total IgE levels confirms the role of a genetic background for total IgE regulation. The studied IL-18 SNP demonstrated no significant association with the clinical outcome, total IgE, or specific IgE in HCW with natural rubber latex allergy.

Both genetic effects and environmental stimuli are responsible for the development of allergic asthma, where the overall genetic contribution may contribute up to 60% (Hopp et al. 1984). The gene of interleukin-13 (IL-13), a cytokine produced by Th2 cells, is located on chromosome 5q31, a region that has been described to be linked to asthma-related phenotypes (Hizawa et al. 1998; Ober and Cox 1998; Postma et al. 2005). Laundry et al. (2000) reported that the

T-variant of the rs1800925 promoter polymorphism (–1055C>T) also known as –1024C>T and –1112C>T with a frequency of 0.167 (1) affects the expression level, (2) is associated with allergic asthma (Howard et al. 2001; van der Pouw Kraan et al. 1999), and (3) is related to chronic obstructive pulmonary disease (van der Pouw Kraan et al. 2002). In addition, the IL-13 –1055 T allele was found to be associated with higher IgE levels (Kim et al. 2006; Liu et al. 2003), atopy (Beghé et al. 2009;

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Hummelshoj et al. 2003), and rhinitis (Bottema et al. 2010).

The *IL-18* gene comprises 6 exons with a length of 20.8 kb, located on chromosome 11q22 (Smith and Humphries 2009; Thompson and Humphries 2007), and harbors a candidate region for asthma genes (Koppelman et al. 2002; Xu et al. 2001). Several studies showed that patients with asthma or atopic dermatitis display higher IL-18 concentrations compared to controls (El Mezzein et al. 2001; Tanaka et al. 2001). In vitro studies (Giedraitis et al. 2001) reported a decreased promoter activity for the $-607A$ and $-137C$ allele.

A few association studies using single-nucleotide polymorphism (SNP) markers in the *IL-18* gene and promoter were performed to elucidate the impact of these SNP in the pathogenesis of bronchial asthma (Harada et al. 2009; Heinzmann et al. 2004; Higa et al. 2003; Imboden et al. 2006; Lachheb et al. 2007; Pawlik et al. 2007; Shin et al. 2005) and atopic eczema (Novak et al. 2005). Heinzmann et al. (2004) did not find a significant association between *IL-18* $-607C$ and $-137C$ alleles and three other SNP and bronchial asthma. In contrast, Imboden et al. (2006) reported that the *IL-18* $-137G$ allele was associated with an increased prevalence of atopic asthma, where none of the 74 incident asthma cases with atopy at baseline exhibited the CC genotype. One year later, Pawlik et al. (2007) observed in patients with severe asthma that the $-607CC$ and the $-137GG$ genotype was significantly more frequent, whereas in patients with mild or moderate asthma, the $-137CC$ genotype was more prevalent. A Japanese association study (Higa et al. 2003) analyzed three SNP $-607C>A$, $-137G>C$, and $105A>C$ (Ser35Ser; *rs549908*) in 221 children and 276 adults who suffered from asthma, and a further 85 adult controls were studied. None of the SNP showed an asthma susceptibility association, but an association with asthma severity was found for the $-607A$ variant. A Korean study by Shin et al. (2005) was performed with 435 adult asthmatics and 140 controls. This study also failed to find an association between five *IL-18* polymorphisms and risk

of developing asthma. However, Shin et al. (2005) reported an association between the $-137C$ allele and for *rs549908* and elevated specific IgE values to house dust mite allergens *Dermatophagoides farinae* and *D. pteronyssinus*. Lachheb et al. (2007) did not observe an association between the $-607A$ variant and total IgE levels in 105 Tunisian asthmatic children and 112 controls. Although asthma severity was not associated with the SNP, data suggested an association with an increasing risk of developing atopic asthma. In contrast, a more recent Japanese study (Harada et al. 2009) performed with adults reported an association between asthma severity and the *IL-18* G variant of *rs5744247C>G*. This SNP also displayed an association with elevated IL-18 levels in patients' sera.

In the field of occupational diseases, especially occupational asthma and allergy, less information is available. Concerning natural rubber latex (NRL) allergy, the study by Brown and coworkers (2005) showed evidence that NRL allergy phenotype was associated with certain promoter polymorphisms of *IL-13* ($-1055T$) and *IL-18* ($-656G$ and $-607C$) compared to nonatopic controls. Several investigations described linkages and associations between certain gene variants and total and specific IgE levels against environmental allergens and different clinical outcomes, like asthma or atopic dermatitis (Kruse et al. 2003; Lachheb et al. 2007; Liu et al. 2003; Maier et al. 2006; Rihs et al. 2002; Tanaka et al. 2001). In general the confirmation of these findings in the field of occupational allergy is difficult to prove due to mostly small available number of patients. The aim of this study was to analyze the role of 4 promoter polymorphisms, namely, *IL-13* $-1055C>T$ (*rs1800925*), *IL-18* $-656T>G$ (*rs1945619*), *IL-18* $-607C>A$ (*rs1945618*), and *IL-18* $-137G>C$ (*rs187238*), in a cohort of 523 health care workers (HCW) with occupational exposure to NRL before the implementation of the "latex powdered glove avoidance strategy" in Germany. In contrast to other studies in the field of occupational allergy, this HCW cohort is sufficiently large enough to compile significant conclusions.

METHODS

Study Participants

The participants included in this study were part of a large HLA study in the 1990s and described in detail previously (Rihs et al. 2002). Briefly, between July 1996 and September 1999, experienced physicians examined 523 German HCW from different German hospitals. Informed consent was obtained from all participants. A detailed clinical history referring to, for contact with natural rubber latex (NRL) articles, allergic symptoms after NRL exposure was taken. In the case of NRL, our skin prick test (SPT) solution (0.01 mg of protein/ml) was used (Chen et al. 1997) or undiluted Regent latex milk. In addition, up to further 19 ubiquitous commercial allergens were tested by SPT as described by Rihs et al. (2002). NRL-specific IgE levels were determined in all 523 HCW sera using the Phadia ImmunoCAP system (k82), and total IgE values were measured in 299 sera according to the manufacturer's instructions (Phadia AB, Uppsala, Sweden). Specific IgE values >0.35 kU/L were regarded as positive. Atopy was diagnosed if there was a history of any atopic disease (rhinitis, conjunctivitis, asthma, or atopic eczema), at least one positive SPT reaction to one of the allergens tested, or both. Some important characteristics of the study population are summarized in Table 1. The excess of females in the latex-allergic phenotypes is the consequence of the unequal distribution of gender in HCW.

Genotyping

Genomic DNA was extracted from white blood cells by standard protocols of the manufacturer (Qiagen; Hilden, Germany). Primers and fluorescence resonance energy transfer (FRET) probes were designed and synthesized based on published nucleotide sequences (IL-13: AY008331, IL-18: AP002884). Primer sequences for the IL-13-specific polymerase chain reaction (PCR) were IL-13-F: 5'-TGGGGG TTTCTGGAGGACT-3' and IL-13-R: 5'-AAA TTTCCCTTCTGCAGAATGA-3'. Amplifications

TABLE 1. Some Important Characteristics of the Study Population

Characteristics	Health care workers (HCW)			
	Total	With symptoms and sensitization	With NRL asthma	Without symptoms and sensitization
Number of participants	523	334	93	189
Mean age (yr)	33.5	32.0	32.0	36.2
Number of male/female	91/432	48/286	14/79	43/146
Median latex-specific IgE (kU/L)	8.2	12.8	10.2	<0.35
Median total IgE (kU/L), range	112 2–2000	147 7–2000	174 19–2000	55 2–1627
[number tested]	[299]	[230]	[63]	[69]

of certain IL-18 SNP regions were performed with the following primer pairs: IL-18-FW: 5'-GTCAGTCTTTGCTATCATTCCAGG-3'; IL-18-RE: 5'-CCCTTCCTCCCAAGCTCAAT-3' (for IL-18 -656), IL-18-se: 5'-GTCTTT GCTATCATTCCAGGAATAG-3'; IL-18-as: 5'-CTCCCAAGCTCAATATGGTGTC-3' (for IL-18 -607), and IL-18-S: 5'-AGTGGCAGAGGATA CGAG-3'; IL-18-R: 5'-GCTTCTAATGGACTAA GGAG (for IL-18 -137).

The following probes were used in all experiments: IL-13 -1055C>T (rs1800925): Anchor: 5'-CCCCTGCAGCCATGTCGCCTT-FL Sensor C: 5'-LC640-CCTGCTCTTCCCTCGTT TTCCTA-PH. IL-18 -656T>G (rs1945619): Anchor: 5'-LC640-CCCAAGCTTACTTTCTG TTGCAGAA-PH, Sensor T: 5'-CTTACCTGAA TTTTGGTATCCCTC-FL. IL-18 -607C>A (rs1945618): Anchor: 5'-LC705-TGGTATCC GTGTGGCTTGCATCTGATAC-PH Sensor C: 5'-GTG TAA AAATTATTACATAAAATTCTAATG-FL. IL-18 -137G>C (rs187238): Anchor: 5'-LC640-GGGGCTCTGTGCCTTCCAAAA-PH, Sensor C: 5'-TCATGAAATCTTTTCTTCCGT AAAAGT-FL.

LightCycler amplification for genotyping was carried out in a final volume of 20 µl, together with 50 ng genomic DNA, 20 pmol of each primer, 1.6 µl MgCl₂ (25 mM), 3 pmol of each probe, and 2 µl of LightCycler DNA Master Hybridisation Probes

mix (Roche Diagnostics; Mannheim, Germany) on a LightCycler 1.0 instrument. Only in the case of *IL-18* -137 typing, 4.8 μ l MgCl₂ (25 mM) was used. After an initial denaturation at 95°C for 5 min, reactions conditions had been 45 cycles (30 cycles in the case of *IL-18* -607C>A) denaturation at 95°C for 5 s (*IL-13* -1055, *IL-18* -137) or 10 s (*IL-18* -607 and -656), annealing at 55°C for 20 s (*IL-18* -607), at 56°C for 20 s (*IL-18* -137, *IL-18* -656), at 59°C for 15 s (*IL-13* -1055), and extension at 72°C for 25 s. In the latter case and for the *IL-18* -137 SNP the ramping time was 5 s at 95°C, annealing at 59°C for 15 s, and elongation at 72°C for 25 s.

After the amplification, the melting curves were generated by denaturation at 95°C for 5 s, cooling to 40°C for 90 s, followed by slowly heating to 80°C with a ramp rate of 0.2°C/s. Melting curves were converted to melting peaks by calculating the negative derivative of the fluorescence with respect to the temperature ($-dF/dT$) versus temperature. The plots showed the following melting peak temperatures and allowed the distinction between the different genotypes: *IL-13* -1055: 65°C (CC), 65°C and 59°C (CT), 59°C (TT); *IL-18* -656: 61°C (TT), 61°C and 55°C (TG), 55°C (GG); *IL-18* -607: 54°C (CC), 54°C and 47°C (CA), 47°C (AA); *IL-18* -137: 63°C (GG), 63°C and 54°C (GC), 54°C (CC).

Statistical Analyses

Median and range were presented to describe the distribution of total IgE and NRL-specific IgE. Deviations from Hardy-Weinberg equilibrium were examined for each single-nucleotide polymorphism (SNP) with exact tests. To analyze the group effect (HCW with symptoms and sensitization versus HCW without symptoms and sensitization) and the SNP effects, an analysis of variance (ANOVA) with total IgE (log-transformed) as dependent variable was performed. Total IgE was log-transformed due to the skewness of its distribution. Main effects in the model were group, *IL-13* -1055 C>T, *IL-18* -656 T>G, *IL-18* -607 C>A, and *IL-18* -137 G>C (data shown),

age, and gender (data not shown). In the subgroup of HCW with NRL asthma the same analysis was performed without group as main effect. Differences in NRL-specific IgE levels by genotypes were tested with Wilcoxon rank-sum tests. Bonferroni correction was applied to solve the problem of multiple comparisons. Five tests were conducted in the first ANOVA of total IgE, 4 tests in the second ANOVA of total IgE in HCW subgroups, and 4 Wilcoxon rank-sum tests to analyze NRL-specific IgE, resulting in a Bonferroni correction factor of 13. All statistical analyses were performed using SAS/STAT software, version 9.2. The criterion for significance was set at $p < .05$.

RESULTS

The study group comprised 334 NRL-exposed German HCW with NRL sensitization and NRL symptoms including 93 HCW with latex-allergic asthma. A further 189 exposed HCW showed neither symptoms nor sensitization. The mean age in all HCW was 33.5 yr (range: 32–36 yr). The female gender frequency in the different HCW subgroups displayed a range between 78 and 86%. NRL-specific IgE was determined in all 523 HCW, whereby total IgE measurements were only available for approximately 57% of HCW (Table 1). Genotypes were determined successfully in all HCW, with the exception of one missing for *rs187238* (*IL-18* -137G>C) and three missing results in the case of *rs1945618* (*IL-18* -607C>A).

The genotype frequencies for the SNP *IL-13* -1055C>T (*rs 1800925*) in the different HCW subgroups are shown in Figure 1. The Hardy-Weinberg equilibrium was fulfilled (pHWE = 0.73). The distribution in the different HCW subgroups was almost equal, where the HCW subgroup without symptoms and sensitization displayed the highest frequency for the CC variant (64.5%) and lowest frequency for the TT variant (3.2%).

Using an ANOVA model (Table 2), significant differences between total IgE values in HCW with symptoms compared to HCW without symptoms were detected. Analysis of total

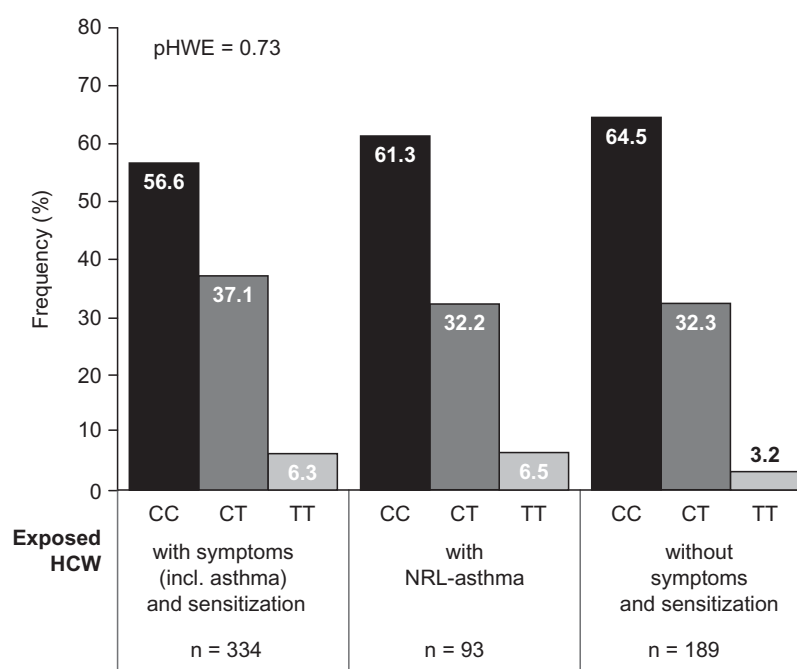


FIGURE 1. Distribution of promoter polymorphism *IL-13* -1055C>T in exposed health care workers (HCW) with and without symptoms.

TABLE 2. Analysis of Variance (ANOVA) of Total IgE of HCW and HCW With NRL asthma (Log-Transformed) With Dependence of Study Groups and SNP Adjusted for Age and Gender

Variable		DF	Typ III SS	Mean squared	F Value	p	p _c
Total IgE values of all HCW (N = 296)	HCW with symptoms and sensitization vs HCW without symptoms and sensitization	1	9.56	9.56	31.81	<.0001	<.0001
	<i>IL-13</i> -1055 C>T (CC vs. CT and TT)	1	2.61	2.61	8.70	.0034	.045
	<i>IL-18</i> -656 T>G (TT vs. TG and GG)	1	0.27	0.27	0.91	.342	1.000
	<i>IL-18</i> -607 C>A (CC vs. CA and AA)	1	0.69	0.69	2.29	.132	1.000
	<i>IL-18</i> -137 G>C (GG vs. GC and CC)	1	0.55	0.55	1.82	.179	1.000
	R ²						.163
Total IgE values of HCW with NRL asthma (N = 63)	<i>IL-13</i> -1055 C>T (CC vs. CT and TT)	1	1.33	1.33	6.61	.013	.166
	<i>IL-18</i> -656 T>G (TT vs. TG and GG)	1	0.03	0.03	0.17	0.682	1.000
	<i>IL-18</i> -607 C>A (CC vs. CA and AA)	1	0.07	0.07	0.36	0.551	1.000
	<i>IL-18</i> -137 G>C (GG vs. GC and CC)	1	0.57	0.57	2.81	0.099	1.000
	R ²						.212

Note. p_c: corrected p value for multiple testing; DF = degree of freedom, Typ III SS = sum of squares; mean squared = mean squared error; F Value = test statistic.

IgE values in dependence on the C and T allele distribution by ANOVA, in HCW with symptoms and sensitization, showed significant higher total IgE values in CT and TT allele carriers than in CC allele carriers. As noted in Table 2, a marked association between total IgE values and *IL-13* variant -1055T in the subgroup of HCW with NRL asthma was observed.

However, this association was no longer significant when adjusted for multiple testing. Regarding the NRL-specific IgE values (Table 3), a numerical difference was observed when comparing C alleles with T alleles.

Table 4 summarizes the distribution of the three *IL-18* promoter polymorphisms -656T>G (*rs1945619*), -607C>A (*rs1945618*),

TABLE 3. Results of Wilcoxon Rank-Sum Tests to Analyze Differences in NRL-Specific IgE by Genotypes

Variables	<i>p</i>	<i>p_c</i>
<i>IL-13</i> –1055 C>T (CC vs. CT and TT)	0.088	1.000
<i>IL-18</i> –656 T>G (TT vs. TG and GG)	0.790	1.000
<i>IL-18</i> –607 C>A (CC vs. CA and AA)	0.306	1.000
<i>IL-18</i> –137 G>C (GG vs. GC and CC)	0.511	1.000

Note. *p_c*: corrected *p* value for multiple testing.

and –137G>C (*rs187238*) correlated to different clinical outcomes in HCW. The Hardy–Weinberg equilibrium was fulfilled for all three *IL-18* SNP (*IL-18* –656T>G: pHWE = 0.14, *IL-18* –607C>A: pHWE = 0.17, *IL-18* –137G>C: pHWE = 0.76). With the exception of one sample, a complete linkage disequilibrium (99.5%) between *IL-18 rs1945618* (–607C>A) and *IL-18 rs1945619* (–656T>G) was observed, where the –607CC variant of *rs1945618* matched perfectly with the double-mutated –656GG variant frequency. Regarding the different clinical outcomes, the highest –607CC frequency (48.8%) was found in HCW with NRL asthma and the lowest in HCW without symptoms and sensitization (37.6%). Although HCW with latex-allergic asthma displayed the highest –137GG frequency (61.3%), the distributions of the different variants of *IL-18* –137G>C (*rs187238*) were rather homogeneous for all clinical outcomes. None of the *IL-18* polymorphisms showed an association with the measured total IgE levels in the ANOVA model (Table 2), and the latex-specific IgE measured in the serum of all exposed participants also demonstrated no association with one of the *IL-18* SNP analyzed in this study (Table 3).

DISCUSSION

The aim to this study was to analyze the role of four promoter polymorphisms of the genes *IL-13* and *IL-18* in 523 HCW with occupational exposure to NRL who had a high frequency of participants (*n* = 334) suffering from latex allergy in terms of displaying NRL-related symptoms and a positive NRL-specific IgE serology. Analysis by the ANOVA model in this study showed for the first time a significant association between the T-allele of *IL-13* –1055C>T (*rs1800925*) and total IgE level in a large occupational cohort of 299 NRL-exposed HCW (Table 2). In addition, regarding our subgroup of HCW with NRL asthma and available total IgE measurements a significant association between the T-allele of *IL-13 rs1800925* and the measured total IgE levels (*N* = 63, Table 2) was observed, which was no longer significant when corrected for multiple testing probably due to the relative small size of this subgroup.

Brown et al. (2005) screened a larger panel of NRL-exposed HCW (*n* = 423), but this cohort included only 24 HCW suffering from latex allergy and displayed positive NRL-specific IgE antibodies. In contrast to our study, Brown et al. (2005) found an association between T-allele of *IL-13 rs1800925* and latex allergy phenotype, when data were compared to their NRL allergy cases with a nonatopic control group. No information concerning an influence of SNP on total IgE levels was given.

The first study reporting an association between the T-allele of *IL-13* –1055C>T

TABLE 4. Distribution of Three *IL-18* Promoter Polymorphisms (–656T>G, –607C>A, –137G>C) in NRL-Exposed Health Care Workers (HCW) due to Its Clinical Outcome

Outcome	Number	<i>IL-18 rs1946519</i> –656T>G frequency (%)			<i>IL-18 rs1946518</i> –607C>A frequency (%)			<i>IL-18 rs187238</i> –137G>C frequency (%)		
		TT	TG	GG	CC	CA	AA	GG	GC	CC
HCW with symptoms and sensitization	334	17.1	41.3	41.6	41.6	41.3	17.1	54.5	37.4	8.1
HCW with NRL asthma	93	15.0	36.6	48.4	48.4	36.6	15.0	61.3	32.2	6.5
HCW without symptoms and sensitization	189	15.9	46.6	37.6	37.6	46.6	15.9	51.9	41.8	6.3

(*rs 1800925*) and higher total serum IgE levels was published by Graves et al. (2000), who studied 1399 white, skin-test-positive children from the United States and Germany. This observation in children was confirmed by Liu et al. (2003), who studied 832 German children and 382 complete parent trios, and by Kim et al. (2006), who studied 615 Korean children where 358 suffered from atopic asthma. This association also exists in adults, as shown in a large study by Maier et al. (2006), who screened the British 1958 birth cohort, ranging between the ages of 44 and 45 years at the date of analysis. Black et al. (2009) investigated 2918 adults from the MRC National Survey of Health and Development (NSHD) study and reported an interaction between smoking and the *IL-13* T allele of *rs1800925* with allergy as outcome. Hong et al. (2010) found that this SNP was also associated with elevated cord blood IgE concentrations across different ethnicities or populations.

In the case of the NRL-specific IgE, which was determined for all 523 participants in this study (Table 1), a numerical difference was observed when comparing C alleles with T alleles of *IL-13* SNP *rs1800925* (Table 3). Concerning the studied *IL-18* promoter polymorphisms, our results are in agreement with that of Heinzmann et al. (2004), who did not find a general association between the $-607C>A$ and the $-137G>C$ polymorphisms and bronchial asthma. Furthermore, it was not possible to confirm an association between the $-137G>C$ polymorphism and high total IgE levels or specific sensitization, as reported by Kruse et al. (2003). In addition, the *IL-18* polymorphisms in positions -656 and -607 that displayed a 99.5% complete linkage disequilibrium, an observation also reported by Harada et al. (2009), demonstrated no marked association with NRL-specific IgE levels (Table 3). In our subgroup of 93 HCW suffering from NRL asthma (Table 4) a high $-137 GG$ frequency of 61.3% was observed and $-607CC$ frequency (48.3%) was elevated. This observation is in agreement with the results of Pawlik et al. (2007), who studied both polymorphisms in a group of 80 adults with severe asthma

and found similar enhanced frequencies for $-137GG$ (63.8%) and $-607CC$ (48.8%). Further, Imboden et al. (2006) reported that the $-137G$ allele was associated with an increasing risk for the prevalence of asthma with concomitant skin reactivity to common allergens. The frequency of the $-137GG$ variant in 268 patients with atopic asthma was 58.2%. Since it is known that the $-137G$ allele and the $-607C$ allele are associated with a high *IL-18* expression (Giedraitis et al. 2001), the elevated frequencies of both alleles in all three studies indicate the possibility for a modulating involvement of *IL-18* in severe atopic asthma. In contrast, our HCW without symptoms and sensitization showed also a high $-137GG$ allele frequency of 51.9% (Table 4), and a high frequency of 55% was noted when 80 healthy nonatopic controls were analyzed (data not shown). These findings indicate a more or less equal distribution of the three *IL-18* SNP in the different subgroups of our study (Table 4).

In summary, the results of this study confirmed the association between the *IL-13*-1055 T-allele and elevated total IgE levels in a large historic cohort of HCW occupationally exposed to NRL. None of the SNP studied showed any significant association with NRL-specific IgE. A significant association between the *IL-13* and the *IL-18* polymorphisms on the one side and the clinical outcome NRL asthma on the other side was also not found. In the case of the *IL-13* polymorphism (*IL-13* $-1055C>T$), one reason might be that the number of HCW suffering from NRL asthma was too small; a further explanation may be that this SNP plays no major role in NRL asthma since it is associated with the total IgE levels. When the general possibility of a modulating role of *IL-18* polymorphisms in HCW with NRL is considered, no significant association was detectable.

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