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Research Article

Systematic Evaluation of Genetic Variants in the Inflammation Pathway and Risk of Lung Cancer

Eric A. Engels,[1] Xifeng Wu,[2] Jian Gu,[2] Qiong Dong,[2] Jun Liu,[2] and Margaret R. Spitz[2]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland and [2]Department of Epidemiology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Abstract

Inflammatory responses to environmental exposures, such as tobacco smoke, may play a role in lung carcinogenesis. To test this hypothesis, we studied genetic polymorphisms in the inflammation pathway in relation to lung cancer risk. We evaluated a panel of 59 single nucleotide polymorphisms (SNP) in 37 inflammation-related genes among non-Hispanic Caucasian lung cancer cases (*N* = 1,553) and controls (*N* = 1,730) from Houston, Texas. Logistic regression was used to assess associations with lung cancer under a dominant genetic model adjusted for sex, age, and smoking. Haplotypes were estimated with the expectation-maximization algorithm. False-positive report probabilities (FPRP) were calculated for significant associations. Interleukin 1β (*IL1B*) C3954T was associated with lung cancer [odds ratio (OR), 1.27; 95% confidence interval (95% CI), 1.10–1.47; FPRP 0.148]. Two *IL1A* SNPs (C-889T and Ala^{114}Ser) were also related to lung cancer (OR, 1.18–1.22), although FPRPs were higher. One *IL1A-IL1B* haplotype, containing only the *IL1B* 3954T allele, was associated with elevated lung cancer risk (OR, 1.80; 95% CI, 1.24–2.61). These associations were stronger in heavy smokers, particularly for *IL1B* C3954T (OR, 1.59; 95% CI, 1.28–1.97; FPRP 0.004). Lung cancer risk was unrelated to polymorphisms in IL1 receptor or antagonist genes. Associations with lung cancer were also seen for SNPs in granulocyte macrophage colony stimulating factor and peroxisome proliferator-activated factor-δ, but FPRPs were high. *IL1A* and *IL1B* polymorphisms are associated with increased lung cancer risk, especially among heavy smokers. IL1A and IL1B are critical signals in initiating inflammation. Our results suggest that a dysregulated inflammatory response to tobacco-induced lung damage promotes carcinogenesis. [Cancer Res 2007;67(13):6520–7]

Introduction

Lung cancer is responsible for ~162,000 deaths annually (1). Although tobacco use is the major environmental determinant of lung cancer risk, most smokers never develop lung cancer, and because lung cancer occasionally arises in nonsmokers, other factors are likely important as well.

Inflammation may play a role in the etiology of lung cancer (2–4). Individuals with tuberculosis, HIV infection, or chronic lung infection with *Chlamydia pneumoniae* seem to have an excess risk of lung cancer independent of tobacco use (5–7). Environmental agents associated with elevated lung cancer risk, such as silica or asbestos, may damage the lung by inducing chronic inflammation. Lung cancer risk is elevated in individuals with emphysema (8), interstitial lung disease (9), and asthma (10), which could similarly reflect effects of the underlying inflammatory disorders. Conversely, use of nonsteroidal anti-inflammatory drugs has been associated with decreased lung cancer risk (11).

In response to microbial agents and various environmental stimuli, macrophages and other cells trigger and sustain inflammation through a complex network of signaling molecules. In the lung, release of toxic oxygen radicals by macrophages and neutrophils participating in the inflammatory response can damage lung epithelial cells and induce DNA mutations. Although an appropriately limited inflammatory response may protect the host, an abnormally prolonged or intense inflammatory response could create a microenvironment that might promote carcinogenesis (2–4).

A few prior studies have examined lung cancer risk in relation to polymorphisms in the genes coding for inflammation pathway signaling molecules, such as interleukin 1β (IL1B; refs. 12–14), IL1 receptor antagonist (IL1RN; refs. 15, 16), IL6 (13, 17), IL10 (18), cyclooxygenase 2 (17), and tumor necrosis factor α (19). These studies have yielded mixed results, and some were limited by small sample size. No large study has systematically assessed lung cancer risk with respect to a range of polymorphisms in inflammation-related genes. In the present case-control analysis, we evaluated lung cancer risk in relation to a large number of candidate polymorphisms in inflammation-related genes.

Materials and Methods

Study subjects. The study design has been described previously (20). Briefly, newly diagnosed patients with histologically confirmed lung cancer were recruited at The University of Texas M. D. Anderson Cancer Center (Houston, TX). Controls without a prior history of cancer (except nonmelanoma skin cancer) were recruited from patients attending appointments for routine medical care at the Kelsey-Seybold Clinics, a large multispecialty physician practice in Houston. Controls were frequency matched to cases by age, sex, ethnicity, and smoking status (never, former, current). Questionnaire data included demographic characteristics, prior medical history, and family history of cancer in first-degree relatives. The present study includes only non-Hispanic Caucasians, the major racial/ethnic subgroup of subjects, to control for genetic differences across racial/ethnic populations (21).

The study was approved by institutional review boards at M.D. Anderson and Kelsey-Seybold Clinics. All subjects provided written informed consent for participation.

Genetic polymorphisms and laboratory methods. We selected for genotyping single nucleotide polymorphisms (SNP) in inflammation-related genes that met at least two of three criteria: (*a*) minor allele frequency of at least 5%; (*b*) location in the promoter, untranslated region (UTR), or coding region of the gene; and (*c*) previous report of an association with an

Requests for reprints: Eric A. Engels, Viral Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, EPS 7076, Rockville, MD 20892. E-mail: engelse@exchange.nih.gov.

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inflammatory disorder, lung cancer, or another cancer. Coding SNPs are described according to the amino acid change, whereas other SNPs are described according to the nucleotide change or location in the UTR. All SNPs were genotyped using SNPlex, a technology developed by Applied Biosystems that enables simultaneous genotyping of up to 48 SNPs in a single tube using an oligonucleotide ligation assay. The assay principle and procedures are detailed in the manufacturer's user guide (PN4360858). Briefly, a list of candidate SNPs was submitted to Applied Biosystems, which evaluated the SNPs for suitability for the assay and designed a pool of SNP-specific ligation probes. Genomic DNA was fragmented at 99°C for 10 min, and 37 ng of fragmented DNA was dried down on each well of a 384-well plate. The SNP-specific ligation probes and a universal linker were phosphorylated and ligated together, and the mixture was then treated with exonuclease. Following purification, the probe mixture was added to the genomic DNA, which was amplified by PCR in the presence of biotinylated universal primers. The biotinylated amplicons were denatured and captured on streptavidin-coated plates. To decode the genotype information, single-stranded PCR products were hybridized with a universal set of fluorescent dye-labeled, mobility-modified fragments (Zipchutes, Applied Biosystems), which were then eluted and separated with the Applied Biosystems 3730 Capillary DNA Analyzer. Genotypes were called by Applied Biosystems GeneMapper software, using an analysis template file provided with each custom SNPlex assay.

The variable nucleotide tandem repeat (VNTR) polymorphism in intron 2 of the IL1 receptor antagonist gene (*IL1RN*) was determined as previously described (22). Briefly, primers (5′-CTCAGCAACACTCCTAT-3′ and 5′-TCCTGGTCTGCAGGTAA-3′) flanking the 86-bp tandem repeat region were used to amplify a DNA fragment containing the polymorphic region. The PCR conditions were as follows: 94°C for 1 min; 30 cycles of 94°C for 1 min, 60°C for 1 min, and 70°C for 1 min; followed by final extension at 72°C for 5 min. Products were separated by 2% agarose gel electrophoresis. Five different alleles have been reported. The wild-type allele (containing four 86-bp repeats) generated a 410-bp PCR product. The other alleles gave rise to PCR products of ~240 bp (two repeats), 325 bp (three repeats), 500 bp (five repeats), and 595 bp (six repeats).

Statistical methods. We compared descriptive characteristics of cases and controls using the χ^2 test and Wilcoxon rank sum test. For each SNP, Hardy-Weinberg equilibrium was assessed among controls using a χ^2 test.

We used logistic regression to assess associations of lung cancer case-control status with each SNP, adjusting for sex, age, and cumulative tobacco exposure. Cumulative tobacco exposure was measured by "logcig-years," where logcig-years = log(cigarettes per day + 1) × duration of smoking in years (23). We focus on SNPs for which there was a statistically significant ($P < 0.05$) effect in an additive model (i.e., trend in lung cancer risk with increasing copies of the less common, "mutant" allele), and for which there was also a significant association with lung cancer risk for the mutant allele under a dominant model; given the rarity of homozygotes for the mutant allele, these two models could not be distinguished (24). We also examined recessive models, but none of these showed significant associations with lung cancer risk (not shown). In addition, we used logistic regression to compare genotype frequencies in cases and controls with respect to the *IL1RN* VNTR polymorphism, adjusting for sex, age, and logcig-years.

We observed significant associations with lung cancer case-control status for several SNPs in interleukin 1α (*IL1A*) and *IL1B*, both located in a 60-kb region on chromosome 2q13 (see Results). We therefore calculated D' as a measure of pairwise linkage disequilibrium (LD) for SNPs in this region. *IL1A-IL1B* haplotypes were estimated using the expectation-maximization algorithm (Helixtree, version 5.0.7, Golden Helix). Haplotypes estimated with at least 95% certainty were considered known and were included in the analysis, and haplotypes occurring at <1% frequency were grouped together. Because each subject had two haplotypes (one on each chromosome), we doubled the data (i.e., considering the haplotype as the unit of analysis) to conduct an unadjusted logistic regression analysis of the association between haplotypes and case-control status (24). For *IL1A-IL1B* haplotypes that showed a significant association with lung cancer, we then returned to an analysis in which the subject was the unit of analysis, using logistic regression to evaluate associations with paired haplotypes (i.e., diplotypes), adjusting for sex, age, and logcig-years. A dominant model (comparing individuals with one or two copies of the haplotype of interest versus those with zero copies) seemed to fit best.

In stratified analyses, we used logistic regression to examine associations of selected SNPs or diplotypes with lung cancer case-control status for subgroups of subjects defined by sex, age, smoking status, history of emphysema or hay fever, or family history of lung cancer. We also tested for interactions (polymorphism × stratification variable) using appropriate logistic regression models. Similarly, we examined associations between these polymorphisms and specific histologic subtypes and stages of non–small cell lung cancer, comparing each subgroup of cases against the entire group of controls.

Because we evaluated associations with multiple SNPs and haplotypes, some associations would arise by chance. To correct for multiple comparisons, we calculated the false-positive report probability (FPRP) for those associations observed to be statistically significant in the overall analysis or which seemed to differ within subgroups in the stratified analyses (25). The FPRP is the probability that the observed association is a false positive (i.e., the result of chance). FPRP depends on the observed result, the prior probability of an association, and the study's power to detect an association. For these calculations, we assumed prior probabilities for associations with lung cancer status under a dominant model of 0.01 for each SNP and 0.001 for each haplotype. The calculations further assume that the power is to detect, under the dominant model, an odds ratio (OR) of 1.3 for SNPs in the overall study population, 1.6 for haplotypes in the overall population or SNPs in subsets of the population, and 2.0 for haplotypes in subsets of the population. In accordance with Wacholder et al. (25), we considered FPRP <0.200 to indicate a noteworthy association (i.e., unlikely to be due to chance).

Results

Study subjects. Characteristics of the non-Hispanic Caucasians lung cancer cases (N = 1,553) and controls (N = 1,730) are presented in Table 1. By design, the proportions of current and former smokers were similar in cases and controls, although as expected, cases reported greater cumulative tobacco exposure than controls (median 46 versus 40 pack-years, $P < 0.0001$). As reported previously for a subset of these subjects (26), cases were significantly more likely than controls to report a physician-diagnosed history of emphysema and less likely to report a physician-diagnosed history of hay fever. Family history of lung cancer in a first-degree relative was more common in cases than controls. The most common histologic type of lung cancer was adenocarcinoma, followed by squamous cell carcinoma, and most cancers presented at advanced stage (Table 1).

Associations of lung cancer with genetic polymorphisms and haplotypes. We successfully genotyped 59 SNPs in 37 genes. Data were available on at least 90% of cases and controls for all SNPs except two (*TNFR1* G-610T and *IL4R* Glu^{400}Ala; Table 2). For three SNPs (*TNFA* T-857C, *IFNAR1* Val^{168}Leu, *IL13* Arg^{130}Gln), the P values for the Hardy-Weinberg χ^2 statistic were below 0.05, consistent with lack of equilibrium among controls. However, it is expected that 3 of 59 SNPs would have significant χ^2 tests by chance alone, and the overall distribution of P values for the Hardy-Weinberg χ^2 statistics in the controls resembled the expected uniform distribution.

Associations of each SNP with lung cancer are shown in Table 2. Five SNPs showed significant trends in risk with increasing copy number of the minor allele: *IL1A* C-889T, *IL1A* Ala^{114}Ser, and *IL1B* C3954T, all of which are on chromosome 2q13; granulocyte macrophage colony stimulating factor (*GM-CSF*) Ile^{117}Thr on chromosome 5q31, for which the P value for trend was borderline (P = 0.0498); and peroxisome proliferator-activated factor-δ

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(*PPARD*) 5′-UTR(T/C) on chromosome 6p21. As shown in Table 2, for each of these five SNPs, ORs for lung cancer under the dominant model for the mutant allele were in the range 1.18 to 1.27, with 95% confidence intervals (95% CI) excluding 1.00 (although for *GM-CSF* Ile^{117}Thr, this association was again borderline, $P = 0.056$).

Results for the multiallelic VNTR polymorphism in *IL1RN,* also on 2q13, are presented in Table 3. Alleles 4 and 2 were most common (73.4% and 23.7% of alleles, respectively). The overall distribution of *IL1RN* genotypes was similar in cases and controls ($P = 0.91$; Table 3).

The two SNPs within *IL1A* (Ala^{114}Ser and C-889T) were in almost complete LD with each other ($D' = 1.00$). Likewise, the three SNPs within *IL1B* (C3954T, T-31C, C-511T) were in strong LD (D' ranging from 0.62 to 1.00). The two SNPs in *IL1A* were each in LD with *IL1B* C3954T, the closest SNP in *IL1B* ($D' = 0.76$–0.77), but the *IL1A* SNPs showed less LD with the other two *IL1B* SNPs.

Using the five SNPs in *IL1A* and *IL1B,* we identified 15 haplotypes, seven of which were estimated to be present in at least 1% of cases and controls (Table 4). The overall distribution of haplotypes differed between cases and controls ($P = 0.004$). As shown in Table 4, two haplotypes were associated with increased lung cancer risk compared with the w-w-w-w-w haplotype: the w-w-m-w-w haplotype, in which the only mutant allele was *IL1B* 3954T (OR, 1.80; 95% CI, 1.25–2.59), and the m-m-m-w-w haplotype, in which mutant alleles in *IL1A* Ala^{114}Ser and *IL1A* C-889T were present with *IL1B* 3954T (OR, 1.18; 95% CI, 1.00–1.39). In an analysis of *IL1A-IL1B* diplotypes in relation to lung cancer risk, we found that possessing one or two copies of w-w-m-w-w, or one or two copies of m-m-m-w-w, was associated with increased lung cancer risk compared with other diplotypes (OR, 1.80; 95% CI, 1.24–2.61 and OR, 1.26; 95% CI, 1.05–1.51, respectively, adjusted for age, sex, and logcig-years).

Associations with polymorphisms within subgroups of subjects. Associations with the five SNPs of interest in *IL1A, IL1B, GM-CSF,* and *PPARD* were mostly similar in magnitude and did not differ significantly across subgroups of subjects defined by sex, age, presence of hay fever, or family history of lung cancer (Table 5). Of note, however, associations with lung cancer seemed stronger for *IL1A* and *IL1B* SNPs within the stratum of heavy smokers (OR, 1.42; 95% CI, 1.15–1.74 for *IL1A* C-889T; OR, 1.38; 95% CI, 1.12–1.70 for *IL1A* Ala^{114}Ser; and OR, 1.59; 95% CI, 1.28–1.97 for IL1B C3954T) than for light smokers or never smokers ($P \leq 0.12$ for interaction for each SNP). Similarly, the associations for the *IL1A* SNPs were stronger among subjects with emphysema than among those without emphysema ($P = 0.02$ for each interaction; Table 5).

Table 1. Characteristics of lung cancer cases and controls

Characteristic	Cases (N = 1,553)	Controls (N = 1,730)	P*
Male, *n* (%)	818 (52.7)	894 (51.7)	0.57
Age (y), *n* (%)			0.04
<50	266 (17.1)	212 (12.3)	
50–59	362 (23.3)	441 (25.5)	
60–64	235 (15.1)	417 (24.1)	
65–69	258 (16.6)	353 (20.4)	
70+	432 (27.8)	307 (17.8)	
Age (y), median	63	62	
Smoking status, *n* (%)			0.07
Current	626 (40.3)	659 (38.1)	
Former	653 (42.1)	795 (46.0)	
Never	274 (17.6)	276 (16.0)	
Pack-years, median (IQR), among ever smokers	46 (30-68)	40 (26-60)	<0.0001
History of emphysema, *n* (%)	288 (18.5)	145 (8.4)	<0.0001
History of hay fever, *n* (%)	265 (17.1)	383 (22.1)	0.0003
Family history of lung cancer, *n* (%)	312 (20.1)	260 (15.0)	0.0002
Lung cancer histology, *n* (%)			
Adenocarcinoma	849 (54.7)	—	
Squamous cell carcinoma	326 (21.0)	—	
Other/unspecified non–small cell carcinoma	263 (16.9)		
Small cell carcinoma	95 (6.1)	—	
Other/unspecified	20 (1.3)	—	
Lung cancer stage, *n* (%) †			
I	318 (22.1)	—	
II	108 (7.5)	—	
III	472 (32.8)	—	
IV	440 (30.6)	—	
Unknown/missing	102 (7.1)	—	

Abbreviation: IQR, interquartile range.
*P values are derived by χ test, except for age and pack-years, where the Wilcoxon rank sum test was used.
† Stage is limited to non–small cell carcinomas.

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Table 2. Associations of SNPs in inflammation pathway genes with lung cancer

SNP name*	Identifier	Subjects with data, *N*		Mutant allele frequency, %		Heterozygote	Homozygote for mutant allele	P_{trend}	Combined heterozygote and homozygote mutant	
		Cases	Controls	Cases	Controls	OR (95% CI) †	OR (95% CI) †		OR (95% CI) †	*P*
Proinflammatory cytokines, receptors, and related molecules										
IL1A C-889T	rs1800587	1,533	1,700	31.1	28.2	1.21 (1.05–1.41)	1.23 (0.96–1.58)	0.01	1.22 (1.06–1.40)	0.006
IL1A Ala^{114}Ser	rs17561	1,537	1,707	30.3	27.8	1.17 (1.01–1.36)	1.21 (0.94–1.57)	0.03	1.18 (1.03–1.36)	0.02
IL1B C-511T	rs16944	1,526	1,696	32.9	34.4	0.92 (0.79–1.07)	0.88 (0.70–1.11)	0.20	0.91 (0.79–1.05)	0.21
IL1B T-31C	rs1143627	1,534	1,707	32.8	34.4	0.92 (0.79–1.06)	0.86 (0.68–1.09)	0.14	0.91 (0.79–1.04)	0.17
IL1B C3954T	rs1143634	1,538	1,705	23.9	20.9	1.26 (1.09–1.47)	1.32 (0.96–1.83)	0.002	1.27 (1.10–1.47)	0.001
IL1R1 Ala^{124}Gly	rs2228139	1,532	1,708	6.4	6.5	1.00 (0.80–1.24)	0.90 (0.30–2.72)	0.93	0.99 (0.80–1.23)	0.95
IL2 T-330G	rs2069762	1,525	1,693	29.3	30.1	1.00 (0.86–1.16)	0.93 (0.71–1.20)	0.68	0.99 (0.86–1.13)	0.84
IL2RB Asp^{391}Glu	rs228942	1,523	1,695	17.5	18.8	0.91 (0.78–1.06)	0.86 (0.57–1.28)	0.17	0.90 (0.78–1.05)	0.17
IL6 G-174C	rs1800795	1,532	1,698	41.3	42.3	0.94 (0.81–1.10)	0.96 (0.79–1.18)	0.62	0.95 (0.82–1.10)	0.48
IL6R Asp^{358}Ala	rs8192284	1,539	1,704	39.3	39.3	0.97 (0.83–1.13)	1.01 (0.82–1.25)	0.96	0.98 (0.85–1.13)	0.75
IL8 T-251A	rs4073	1,522	1,703	53.8	54.7	1.00 (0.84–1.20)	0.93 (0.77–1.14)	0.45	0.97 (0.82–1.16)	0.77
IL8RA Ser^{276}Thr	rs2234671	1,536	1,706	5.4	4.8	1.15 (0.91–1.46)	1.48 (0.39–5.65)	0.20	1.16 (0.92–1.46)	0.22
IL12B A1188C	rs3212227	1,530	1,690	19.6	20.6	0.89 (0.77–1.04)	1.03 (0.72–1.48)	0.33	0.91 (0.78–1.05)	0.20
IL12RB Met^{365}Thr	rs375947	1,532	1,705	33.0	31.5	1.04 (0.89–1.20)	1.15 (0.91–1.45)	0.27	1.06 (0.92–1.22)	0.42
IL16 T-295C	rs4778889	1,537	1,710	19.2	20.7	0.84 (0.72–0.98)	1.09 (0.76–1.55)	0.18	0.87 (0.75–1.00)	0.06
IL16 Asn^{446}Lys	rs17875535	1,530	1,707	26.9	26.4	1.01 (0.88–1.18)	1.11 (0.84–1.48)	0.54	1.03 (0.89–1.18)	0.69
TNFA T-1031C	rs1799964	1,535	1,705	21.9	21.9	0.97 (0.84–1.13)	1.04 (0.74–1.47)	0.92	0.98 (0.85–1.13)	0.80
TNFA T-857C	rs1799724	1,500	1,675	12.1	11.2	1.05 (0.86–1.29)	1.15 (0.82–1.62)	0.36	1.08 (0.90–1.29)	0.42
TNFA G-308A	rs1800629	1,533	1,701	16.9	16.3	1.05 (0.90–1.23)	1.05 (0.68–1.61)	0.55	1.05 (0.90–1.22)	0.54
TNFA A-238C	rs361525	1,539	1,710	5.9	5.3	1.21 (0.97–1.52)	0.38 (0.08–1.92)	0.22	1.18 (0.95–1.48)	0.14
TNFB Arg^{13}Cys	rs2857713	1,507	1,675	28.2	28.6	0.90 (0.78–1.04)	1.07 (0.82–1.41)	0.63	0.93 (0.80–1.07)	0.29
TNFB His^{51}Pro	rs3093543	1,527	1,689	6.5	6.8	0.92 (0.74–1.14)	1.57 (0.58–4.28)	0.70	0.94 (0.76–1.16)	0.55
TNFR1 G-610T	rs4149570	1,274	1,437	29.0	28.5	1.04 (0.89–1.22)	—	0.61	1.04 (0.89–1.22)	0.61
TNFR1 Arg^{121}Gln	rs4149584	1,526	1,696	2.1	2.2	0.92 (0.65–1.30)	—	0.64	0.92 (0.65–1.30)	0.64
TNFR2 Met^{196}Arg	rs1061622	1,490	1,640	23.0	23.3	0.99 (0.85–1.15)	1.02 (0.73–1.40)	0.98	0.99 (0.86–1.15)	0.93
TNFR2 Glu^{232}Lys	rs5746026	1,466	1,622	3.3	3.8	0.88 (0.66–1.16)	—	0.36	0.88 (0.66–1.16)	0.36
IFNAR1 Val^{168}Leu	rs2257167	1,539	1,705	13.9	14.1	1.01 (0.85–1.19)	0.87 (0.56–1.34)	0.77	0.99 (0.85–1.17)	0.93
IFNAR2 Phe^{10}Val	rs7279064	1,534	1,712	30.7	32.5	0.89 (0.77–1.03)	0.85 (0.66–1.08)	0.08	0.88 (0.77–1.01)	0.08
IFNG T-1615C	rs2069705	1,536	1,705	34.4	34.5	0.99 (0.85–1.15)	1.03 (0.82–1.29)	0.92	1.00 (0.86–1.15)	0.95
IFNG A874T	rs2430561	1,521	1,692	44.1	44.5	0.98 (0.83–1.15)	0.94 (0.77–1.15)	0.57	0.97 (0.83–1.13)	0.67
GM-CSF T-1916C	rs2069614	1,527	1,696	43.1	43.8	1.01 (0.86–1.19)	0.93 (0.76–1.14)	0.57	0.99 (0.85–1.15)	0.90
GM-CSF Ile^{117}Thr	rs25882	1,484	1,613	21.1	19.2	1.14 (0.98–1.33)	1.26 (0.87–1.83)	0.05	1.16 (1.00–1.34)	0.06
MCP1 A-2518G	rs1024611	1,535	1,699	26.3	28.2	0.94 (0.81–1.09)	0.77 (0.59–1.01)	0.08	0.91 (0.79–1.05)	0.18
MIF G-173C	rs755622	1,530	1,690	17.4	16.8	1.01 (0.86–1.18)	1.24 (0.82–1.86)	0.51	1.03 (0.89–1.20)	0.70
Anti-inflammatory cytokines, receptors, and related molecules										
IL4 C-590T	rs2243250	1,485	1,631	14.8	14.0	1.10 (0.93–1.30)	1.06 (0.65–1.75)	0.31	1.09 (0.93–1.29)	0.27
IL4 5′-UTR(C/T)	rs2070874	1,539	1,709	14.8	14.2	1.03 (0.88–1.22)	1.22 (0.76–1.96)	0.46	1.05 (0.89–1.23)	0.57
IL4R Ile^{75}Val	rs1805010	1,541	1,706	45.8	46.3	0.93 (0.79–1.10)	0.96 (0.79–1.17)	0.65	0.94 (0.81–1.10)	0.43
IL4R Glu^{400}Ala	rs1805011	1,177	1,377	0.1	0.0	2.87 (0.25–32.7)	—	0.40	2.87 (0.25–32.7)	0.40
IL4R Ser^{503}Pro	rs1805015	1,531	1,694	17.7	17.2	1.08 (0.92–1.26)	0.90 (0.60–1.37)	0.65	1.06 (0.91–1.23)	0.46
IL4R Gln^{576}Arg	rs1801275	1,536	1,704	22.0	21.4	1.03 (0.89–1.19)	1.06 (0.76–1.47)	0.65	1.03 (0.89–1.19)	0.67
IL4R Ser^{752}Ala	rs1805016	1,512	1,674	6.1	5.9	1.03 (0.83–1.30)	0.93 (0.33–2.61)	0.83	1.03 (0.83–1.28)	0.79
IL5 C-745T	rs2069812	1,475	1,624	28.4	30.2	0.97 (0.84–1.13)	0.75 (0.57–0.97)	0.09	0.93 (0.81–1.07)	0.32
IL10 A-1082G	rs1800896	1,524	1,693	48.7	49.5	0.94 (0.79–1.12)	0.94 (0.77–1.15)	0.54	0.94 (0.80–1.10)	0.46
IL10 C-819T	rs1900871	1,507	1,696	0.8	0.6	1.43 (0.78–2.63)	—	0.24	1.43 (0.78–2.63)	0.24
IL10 C-592A	rs1800872	1,531	1,692	22.8	23.4	0.92 (0.79–1.07)	1.00 (0.73–1.37)	0.45	0.93 (0.80–1.07)	0.31
IL10RA Ser^{159}Gly	rs3135932	1,540	1,709	16.4	17.4	0.95 (0.81–1.11)	0.80 (0.54–1.20)	0.27	0.93 (0.80–1.09)	0.37
IL10RB Lys^{47}Glu	rs2834167	1,534	1,704	26.2	24.8	1.02 (0.88–1.18)	1.24 (0.93–1.67)	0.27	1.05 (0.91–1.21)	0.50
IL13 C-1112T	rs1800925	1,528	1,695	21.9	20.6	1.06 (0.91–1.23)	1.33 (0.94–1.88)	0.14	1.08 (0.94–1.25)	0.27
IL13 Arg^{130}Gln	rs20541	1,536	1,707	20.1	19.6	1.11 (0.95–1.29)	0.92 (0.65–1.29)	0.53	1.08 (0.93–1.25)	0.29
Prostaglandins and nitric oxide										
COX2 G-765C	rs20417	1,516	1,683	17.4	17.4	0.97 (0.83–1.14)	0.96 (0.63–1.44)	0.70	0.97 (0.83–1.13)	0.70
COX2 3′-UTR(T/C)	rs5275	1,504	1,684	34.8	35.8	0.93 (0.80–1.09)	0.88 (0.70–1.10)	0.22	0.92 (0.80–1.06)	0.27
COX2 3-′UTR(C/T)	rs689470	1,537	1,706	3.2	2.9	1.02 (0.75–1.38)	1.93 (0.45–8.27)	0.65	1.04 (0.78–1.41)	0.77
INOS Leu^{608}Ser	rs2297518	1,530	1,708	19.2	18.5	1.15 (0.98–1.34)	0.84 (0.57–1.24)	0.41	1.11 (0.96–1.29)	0.16

(*Continued on the following page*)

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Table 2. Associations of SNPs in inflammation pathway genes with lung cancer (Cont'd)

SNP name*	Identifier	Subjects with data, *N*		Mutant allele frequency, %		Heterozygote	Homozygote for mutant allele	P_{trend}	Combined heterozygote and homozygote mutant	
		Cases	Controls	Cases	Controls	OR (95% CI) †	OR (95% CI) †		OR (95% CI) †	*P*
ENOS Glu[298]Asp	rs1799983	1,479	1,630	33.2	32.8	1.04 (0.89–1.21)	1.04 (0.82–1.32)	0.64	1.04 (0.90–1.20)	0.61
Intracellular signaling molecules										
IKB C-420T	rs2233409	1,524	1,690	23.4	23.3	0.92 (0.80–1.07)	1.11 (0.81–1.53)	0.75	0.95 (0.82–1.09)	0.44
IKB 3′-UTR(C/T)	rs8904	1,531	1,705	36.2	37.6	1.02 (0.87–1.18)	0.85 (0.68–1.06)	0.29	0.98 (0.85–1.13)	0.74
PPARA Leu[162]Val	rs1800206	1,542	1,712	6.5	6.1	1.13 (0.91–1.39)	0.81 (0.21–3.06)	0.35	1.12 (0.90–1.38)	0.31
PPARD 5′-UTR(T/C)	rs2016520	1,531	1,698	20.1	18.0	1.21 (1.04–1.42)	1.15 (0.80–1.66)	0.02	1.21 (1.04–1.40)	0.01
PPARG Pro[12]Ala	rs1801282	1,529	1,703	11.2	12.0	0.97 (0.81–1.15)	0.62 (0.33–1.14)	0.29	0.94 (0.79–1.11)	0.47

NOTE: Abbreviations for SNP names are standard and can be referenced to the rs identifier.
*The SNP allele specified second is the less common allele, called the "mutant" allele.
†ORs are in reference to subjects homozygous for the wild-type allele and are adjusted for sex, age, and logcig-years as a measure of cumulative tobacco exposure (see Materials and Methods). ORs that differ significantly from 1.00 are underlined. $P < 0.05$ are underlined.

Results for *IL1A-IL1B* haplotypes are also shown for subgroups of subjects (Table 5). Again, associations were similar across most subgroups. The exception was that the effect of the w-w-m-w-w haplotype, which isolates the mutant allele in the *IL1B* C3954T SNP, was stronger in subjects older than 62 years (OR, 3.53; 95% CI, 2.05–6.10) than among younger subjects ($P = 0.0001$ for interaction), and for heavy smokers (OR, 3.18; 95% CI, 1.78–5.67) than for light smokers or never smokers ($P = 0.03$ for interaction).

Associations with these SNPs and haplotypes did not vary according to subtype or stage of non–small cell lung cancer (Table 5).

False-positive report probabilities. Table 6 shows FPRP estimates for selected results. In the analyses including all lung cancer cases and controls, only the association for *IL1B* C3954T yielded a FPRP below 0.200 (FPRP 0.148), suggesting that this association is unlikely to represent a false-positive result. Associations for other SNPs showed substantially higher FPRPs, in the range 0.429 to 0.854. For associations with *IL1A-IL1B* haplotypes, the associations also yielded high FPRPs (0.878–0.925; Table 6).

FPRP estimates are also shown for analyses restricted to subgroups of subjects (Table 6). Notably, FPRP was below 0.200 for the three SNPs in *IL1A* and *IL1B* within the subgroup of heavy smokers, and the FRPP was especially low for *IL1B* C3954T (FPRP 0.004). In contrast, FPRP was substantially higher for the w-w-m-w-w haplotype in *IL1A-IL1B* among heavy smokers, although the association was strong, because we specified a low prior probability. FPRP was 0.223 for the association of the w-w-m-w-w haplotype with lung cancer among older subjects (Table 6).

Table 3. Associations with lung cancer for interleukin 1 receptor antagonist gene VNTR polymorphisms

IL1RN VNTR genotype*	Cases, *n* (%)	Controls, *n* (%)	OR † (95% CI)
44	828 (56.3)	908 (55.8)	1.00
22	118 (8.0)	118 (7.3)	1.09 (0.83–1.43)
24	449 (30.5)	509 (31.3)	0.99 (0.84–1.16)
25	19 (1.3)	18 (1.1)	1.28 (0.66–2.48)
45	45 (3.1)	58 (3.6)	0.86 (0.57–1.29)
Other	13 (0.9)	15 (0.9)	0.99 (0.46–2.11)

NOTE: Results were available for 1,472 cases and 1,626 controls.
*IL1RN genotype refers to the number of 86-bp repeats present in the intron of each copy of the gene (e.g., 24 refers to two repeats on one chromosome and four repeats on the other chromosome). "Other" VNTR genotypes include 23 (1 case, 1 control), 33 (3 cases, 1 control), 34 (4 cases, 6 controls), 46 (2 cases, 2 controls), and 55 (3 cases, 5 controls).
† ORs are adjusted for age, sex, and logcig-years as a measure of cumulative tobacco exposure (see Materials and Methods).

Table 4. Associations with lung cancer for haplotypes of *IL1A* and *IL1B* on chromosome 2q13

Haplotype*	Case haplotypes, *n* (%)	Control haplotypes, *n* (%)	OR (95% CI)
w-w-w-w-w	1,113 (47.3)	1,316 (48.9)	1.00
w-w-w-m-m	561 (23.8)	715 (26.5)	0.93 (0.81–1.06)
m-m-m-w-w	368 (15.6)	370 (13.7)	1.18 (1.00–1.39)
m-m-w-w-w	139 (5.9)	134 (5.0)	1.23 (0.96–1.58)
m-m-w-m-m	48 (2.0)	65 (2.4)	0.87 (0.60–1.28)
w-w-m-w-w	76 (3.2)	50 (1.9)	1.80 (1.25–2.59)
m-m-m-m-m	32 (1.4)	31 (1.2)	1.22 (0.74–2.01)
Other	17 (0.7)	13 (0.5)	1.55 (0.75–3.20)

NOTE: The table shows haplotypes for 1,177 cases and 1,347 controls (2,354 haplotypes for cases, 2,694 haplotypes for controls). Overall, haplotypes differ significantly between cases and controls ($P = 0.004$). Abbreviations: w, wild-type allele; m, mutant allele.
*Haplotypes refer to the wild-type and mutant alleles for polymorphisms in the following order: *IL1A* Ala[114]Ser, *IL1A* C-889T, *IL1B* C3954T, *IL1B* T-31C, and *IL1B* C-511T.

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Discussion

Our study systematically evaluated associations with a wide range of polymorphisms in inflammation-related genes. The strongest finding was the observed associations of polymorphisms in *IL1A* and *IL1B* with lung cancer, especially among older individuals and those with a history of heavy smoking. IL1A and IL1B are secreted by macrophages and other cells in response to microbial infection or tissue damage. Together with tumor necrosis factor α, they act as critical signals in the initiation of acute inflammation (27). IL1A and IL1B also induce stromal cells to secrete proteases and angiogenic molecules, which could facilitate tumor invasion (27). We did not find associations with lung cancer risk for polymorphisms in *IL1R1* (coding for the IL1 receptor) or *IL1RN* (IL1 receptor antagonist), two other components of the IL1 signaling pathway.

Individuals heterozygous or homozygous for the mutant allele at *IL1B* C3954T had an increased risk of lung cancer (OR, 1.27; 95% CI, 1.10–1.47). This association manifested a low FPRP, indicating that the finding was unlikely due to chance. Although the C3954T SNP in exon 5 of *IL1B* is synonymous (i.e., it does not result in an amino acid change in the IL1B protein), it may affect levels of gene transcription or translation. The relevance of this SNP was supported by Pociot et al. (28), who described a dose-response increase in IL1B secretion by monocytes with increasing copy number of the mutant allele; one explanation may be that *IL1B* C3954T is in LD with another polymorphism that affects IL1B expression. In addition, some research groups (29, 30), although not all (31), have reported that individuals possessing the *IL1B* C3954T polymorphism manifest elevated levels of C-reactive protein, an acute phase protein secreted by the liver during acute inflammation. One recent case-control study in China examined the association between lung cancer and *IL1B* C3954T (14); although results were negative, the study was limited by low statistical power (n = 119 cases). The *IL1B* C3954T polymorphism has been associated with risk of cervical dysplasia (32) and mortality after pancreatic cancer diagnosis (33). Some studies also found this polymorphism associated with risk of gastric cancer (34).

Our finding of an association of lung cancer risk with the *IL1B* C3954T polymorphism supports the hypothesis that heightened production of IL1B in response to inflammatory stimuli or lung damage may promote carcinogenesis. We did not find associations

Table 5. Associations with lung cancer for selected genetic polymorphisms, for subgroups of cases and controls

Subgroup	OR (95% CI)*						
	IL1A C-889T	*IL1A* Ala^{114}Ser	*IL1B* C3954T	*GM-CSF* Ile^{117}Thr	*PPARD* 5′-UTR(T/C)	*IL1A-IL1B* w-w-m-w-w	*IL1A-IL1B* m-m-m-w-w
Male	1.21 (0.99–1.47)	1.16 (0.95–1.41)	1.18 (0.97–1.45)	1.19 (0.97–1.47)	1.30 (1.05–1.59)	2.01 (1.22–3.31)	1.15 (0.89–1.48)
Female	1.24 (1.01–1.51)	1.22 (0.99–1.49)	1.37 (1.12–1.69)	1.12 (0.91–1.39)	1.12 (0.91–1.39)	1.62 (0.93–2.83)	1.40 (1.07–1.82)
Age <62 y	1.18 (0.96–1.44)	1.16 (0.95–1.42)	1.16 (0.94–1.42)	1.09 (0.88–1.35)	1.09 (0.88–1.34)	0.76 (0.43–1.34) †	1.32 (1.02–1.71)
Age 62+ y	1.24 (1.02–1.50)	1.19 (0.98–1.44)	1.32 (1.09–1.61)	1.19 (0.97–1.45)	1.30 (1.07–1.60)	3.53 (2.05–6.10) †	1.21 (0.94–1.56)
Heavy smoker ‡	1.42 (1.15–1.74) ‡	1.38 (1.12–1.70) ‡	1.59 (1.28–1.97) ‡	1.24 (0.99–1.54)	1.15 (0.93–1.44)	3.18 (1.78–5.67) ‡	1.41 (1.07–1.86)
Light smoker	1.09 (0.86–1.38)	1.05 (0.83–1.33)	1.03 (0.81–1.31)	1.11 (0.86–1.43)	1.19 (0.93–1.53)	1.19 (0.63–2.23)	1.14 (0.84–1.55)
Never smoker	1.04 (0.74–1.46)	0.98 (0.70–1.37)	1.12 (0.80–1.58)	1.04 (0.73–1.49)	1.37 (0.96–1.96)	0.92 (0.36–2.33)	1.24 (0.81–1.89)
Emphysema	1.93 (1.27–2.96) §	1.85 (1.22–2.82) §	1.43 (0.93–2.20)	1.11 (0.71–1.74)	1.37 (0.88–2.12)	1.55 (0.49–4.95)	1.49 (0.85–2.61)
No emphysema	1.15 (0.98–1.33) §	1.11 (0.95–1.29) §	1.25 (1.07–1.46)	1.15 (0.97–1.35)	1.18 (1.00–1.38)	1.76 (1.18–2.64)	1.25 (1.03–1.53)
Hay fever	1.01 (0.73–1.39)	0.95 (0.69–1.31)	1.15 (0.83–1.59)	1.39 (0.99–1.96)	1.24 (0.89–1.72)	1.59 (0.71–3.56)	1.04 (0.70–1.56)
No hay fever	1.28 (1.09–1.50)	1.25 (1.07–1.46)	1.32 (1.12–1.55)	1.10 (0.93–1.30)	1.22 (1.03–1.44)	1.86 (1.22–2.86)	1.34 (1.09–1.64)
Family history of lung cancer	1.40 (1.00–1.98)	1.38 (0.98–1.94)	1.36 (0.95–1.95)	1.02 (0.71–1.46)	1.16 (0.81–1.66)	1.75 (0.70–4.40)	1.54 (0.95–2.50)
No family history of lung cancer	1.20 (1.03–1.40)	1.15 (0.99–1.35)	1.28 (1.09–1.49)	1.18 (1.00–1.39)	1.22 (1.04–1.44)	1.81 (1.20–2.73)	1.25 (1.02–1.52)
Adenocarcinoma	1.18 (1.00–1.40)	1.14 (0.96–1.34)	1.25 (1.05–1.48)	1.22 (1.02–1.45)	1.27 (1.06–1.51)	1.78 (1.16–2.75)	1.23 (0.99–1.53)
Squamous cell carcinoma	1.22 (0.96–1.57)	1.23 (0.96–1.57)	1.28 (1.00–1.65)	1.11 (0.86–1.44)	1.15 (0.89–1.49)	1.81 (0.98–3.38)	1.31 (0.95–1.81)
Stage I/II cancer ‖	1.06 (0.85–1.32)	1.06 (0.85–1.31)	1.27 (1.01–1.58)	1.27 (1.01–1.60)	1.13 (0.90–1.42)	2.06 (1.21–3.50)	1.31 (0.99–1.73)
Stage III cancer ‖	1.42 (1.15–1.75)	1.38 (1.12–1.69)	1.37 (1.11–1.69)	1.11 (0.89–1.38)	1.19 (0.96–1.48)	1.57 (0.91–2.69)	1.47 (1.13–1.91)
Stage IV cancer ‖	1.21 (0.98–1.51)	1.13 (0.91–1.40)	1.22 (0.98–1.53)	1.11 (0.88–1.40)	1.33 (1.06–1.67)	1.79 (1.05–3.04)	1.11 (0.83–1.47)

*All ORs are under a dominant model for the specified polymorphism, and are adjusted for age, sex, and logcig-years, with the following exceptions due to stratification: ORs stratified by sex are not adjusted for sex, ORs stratified by age are not adjusted for age, and ORs by smoking status are not adjusted for logcig-years.

† The OR for the IL1A-IL1B w-w-m-w-w haplotype was significantly stronger in older subjects than in younger subjects ($P_{interaction}$ = 0.0001).

‡ Heavy smoking and light smoking were defined based on the median logcig-years of cigarette use among controls. Interactions with genetic polymorphisms were significant or borderline significant; that is, ORs were higher in heavy smokers than in never smokers, for *IL1A* C-889T (P = 0.12), *IL1A* Ala^{114}Ser (P = 0.08), *IL1B* C3954T (P = 0.10), and *IL1A-IL1B* diplotypes containing the w-w-m-w-w haplotype (P = 0.03).

§ The ORs for *IL1A* C-889T and *IL1A* Ala^{114}Ser were each significantly stronger in subjects with emphysema than in subjects without emphysema ($P_{interaction}$ ($P_{interaction}$ = 0.02 for each SNP).

‖ Analyses by stage are limited to subjects with non–small cell lung carcinoma.

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Table 6. FPRPs for selected associations between genetic polymorphisms and lung cancer risk

SNP or haplotype*	Subset of subjects	OR (95% CI) †	*P*	Prior probability	FPRP ‡
IL1A C-889T	All	1.22 (1.06–1.40)	0.006	0.01	0.429
IL1A Ala^{114}Ser	All	1.18 (1.03–1.36)	0.020	0.01	0.687
IL1B C3954T	All	1.27 (1.10–1.47)	0.001	0.01	0.148
GM-CSF Ile^{117}Thr	All	1.16 (1.00–1.34)	0.056	0.01	0.854
PPARD 5′-UTR(T/C)	All	1.21 (1.04–1.40)	0.013	0.01	0.604
IL1A and *IL1B* m-m-m-w-w	All	1.26 (1.05–1.51)	0.012	0.001	0.925
IL1A and *IL1B* w-w-m-w-w	All	1.80 (1.24–2.61)	0.002	0.001	0.877
IL1A C-889T	Emphysema	1.93 (1.27–2.96)	0.002	0.01	0.544
IL1A Ala^{114}Ser	Emphysema	1.85 (1.22–2.82)	0.004	0.01	0.620
IL1A C-889T	Heavy smoker	1.42 (1.15–1.74)	0.001	0.01	0.098
IL1A Ala^{114}Ser	Heavy smoker	1.38 (1.12–1.70)	0.002	0.01	0.187
IL1B C3954T	Heavy smoker	1.59 (1.28–1.97)	2×10^{-5}	0.01	0.004
IL1A and *IL1B* w-w-m-w-w	Age 62+ y	3.53 (2.05–6.10)	6×10^{-6}	0.001	0.223
IL1A and *IL1B* w-w-m-w-w	Heavy smoker	3.18 (1.78–5.67)	9×10^{-5}	0.001	0.601

*All comparisons are for combined heterozygotes and homozygotes for mutant allele of SNP or specified haplotype, versus all others.
† ORs for lung cancer are adjusted for age, sex, and logcig-years as a measure of cumulative tobacco exposure; see also Tables 2 and 5.
‡ FPRP calculations are based on Wacholder et al. (25) and the spreadsheet program provided with that article at http://jncicancerspectrum.oupjournals.org/jnci/content/vol96/issue6. The calculations assume that power is to detect an OR of 1.3 for SNPs in the overall study population, 1.6 for haplotypes in the overall population or SNPs in subsets of the population, and 2.0 for haplotypes in subsets of the population.

with lung cancer status for two SNPs in the *IL1B* promoter (Table 2). Two small case-control studies have shown an association between *IL1B* C-511T and lung cancer risk (12, 14), but previous results for *IL1B* T-31C have been inconsistent (12–14).

We also found increased lung cancer risk among individuals homozygous or heterozygous for the mutant alleles of two *IL1A* SNPs, C-889T and Ala^{114}Ser. These SNPs were in complete LD (D' = 1.000), so it was not possible to determine which was more relevant for lung cancer. We are unaware of data relating the IL1A SNPs to differences in the level of expression or function of IL1A. The change in amino acids coded for by the Ala^{114}Ser polymorphism is not predicted to have a strong effect on IL1A function (SIFT score 0.38, PolyPhen score 1.3).

Given the close physical proximity of *IL1A* and *IL1B* and the observed LD between SNPs in these genes, we evaluated associations of *IL1A-IL1B* haplotypes with lung cancer risk (Table 4). Lung cancer risk was substantially elevated among individuals who had at least one copy of the w-w-m-w-w haplotype (OR, 1.80; 95% CI, 1.24–2.61). Because this haplotype contains only the mutant allele of *IL1B* C3954T, which is synonymous, its association with elevated lung cancer risk might be due to LD with an unmeasured risk polymorphism nearby on chromosome 2q13. Interestingly, the m-m-m-w-w haplotype, which included mutant alleles at the two linked SNPs in *IL1A,* was actually associated with a lower level of risk (OR, 1.26; 95% CI, 1.05–1.51), and haplotypes that included only the mutant alleles in *IL1A* (but not the mutant allele of *IL1B* C3954T) were not associated with increased lung cancer risk (Table 4). These observations suggest that the *IL1A* SNPs do not affect lung cancer risk themselves, but rather are associated with lung cancer through their LD with *IL1B* C3954T.

Notably, we found especially strong associations with lung cancer risk for the *IL1A* and *IL1B* polymorphisms among heavy smokers (ORs 1.38–1.59). Likewise, the *IL1A-IL1B* haplotype w-w-m-w-w was associated with markedly elevated risk among both heavy smokers and older subjects. The interpretation of these finding is uncertain, but they are consistent with the possibility that the effects of *IL1A* and *IL1B* polymorphisms are subtle and manifest in pulmonary damage only after prolonged or heavy exposure to tobacco smoke. Our analyses also suggested that polymorphisms in *IL1A* may be important in influencing lung cancer risk among individuals with emphysema. However, the high FPRPs for associations with *IL1A* SNPs in this subgroup suggest chance could also be an explanation.

In addition, we found associations with lung cancer risk for polymorphisms in *GM-CSF* and *PPARD*. GM-CSF regulates macrophage and neutrophil function during inflammatory reactions (35). Blockade of GM-CSF signaling reduces airway inflammation and hyperresponsiveness in mouse models of environmentally induced lung damage and asthma (36, 37). The mutant allele at *GM-CSF* Ile^{117}Thr, which we found associated with increased lung cancer risk, has previously been linked to an elevated risk for atopic asthma (38). PPARD is a member of the family of peroxisome proliferator-activator receptors, which act as nuclear transcription factors to regulate lipid metabolism and inflammation (39). Although the associations of lung cancer risk with SNPs in *GM-CSF* and *PPARD* may have a plausible basis, the FPRP values for the associations were high.

A strength of our study was the large number of lung cancer cases and controls, and the availability of supporting data on lung cancer subtype and important covariates, such as smoking behavior and medical history. Another major strength was our systematic evaluation of a large number of known polymorphisms in inflammation-related genes, which facilitated comprehensive assessment of this pathway. The inclusion of a large number of polymorphisms was also a potential weakness because it raises the possibility that some statistically significant associations were due to chance alone. To mitigate this problem, we have presented FPRP

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statistics for all significant results and emphasize results where the FPRP is below 0.200 (25). Another potential limitation is the use of controls from a physician practice instead of the general population, but it is unlikely that control selection biased our analyses of genetic polymorphisms (20). By including only non-Hispanic Caucasian subjects, we reduced the likelihood that population stratification materially affected the results (21). In addition, we had no data on use of nonsteroidal anti-inflammatory drugs, which might modify the effects of these polymorphisms.

In conclusion, our results concerning *IL1B* C3954T, and to a lesser extent the *IL1A* polymorphisms, support a role for inflammation in the etiology of lung cancer. These associations were modest in magnitude, but they suggest that, in the setting of heavy or prolonged exposure to tobacco or other agents, an aberrant inflammatory response may promote lung damage, eventually leading to lung cancer. Future studies may focus on identifying additional polymorphisms within the *IL1* locus, characterizing their function, and assessing their relationship with lung cancer risk.

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