Published in final edited form as:
Arthritis Rheum. 2007 August ; 56(8): 2679–2686. doi:10.1002/art.22804.

Clinical and Genetic Risk Factors for Pneumonia in Systemic Lupus Erythematosus

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Abstract

Objective—To define the contribution of polymorphisms in genes encoding tumor necrosis factor (*TNF*), mannose-binding lectin (*MBL*), and Fcγ receptor IIa (*FCGR2A*) as well as clinical factors, to the development of pneumonia in patients with systemic lupus erythematosus (SLE).

Methods—We studied 282 SLE patients from a multiethnic cohort. Pneumonia events and clinical risk factors for pneumonia were identified through medical record review. Genotyping was performed for *MBL* (+223, +230, and +239), *TNF* (−308, −238, and +488), and *FCGR2A* (−131H/R) polymorphisms. Univariate analyses were performed to identify clinical and genetic risk factors for pneumonia. Covariates for multivariate analysis included sex, ethnicity, treatment with immunomodulators, and leukopenia.

Results—Forty-two patients (15%) had at least 1 episode of pneumonia. Polymorphism of the *TNF* gene, particularly the −238A allele and a related haplotype, revealed the most striking and consistent association with pneumonia in univariate analyses. Results of multivariate analyses indicated an odds ratio (OR) for the *TNF* −238A allele of 3.5 ($P = 0.007$) and an OR for the related haplotype of 5.4 ($P = 0.001$). Male sex, treatment with immunomodulators, and leukopenia also influenced the risk of pneumonia.

Conclusion—These findings suggest that specific *TNF* variants may identify SLE patients who are at particularly high risk of developing pneumonia. Given the prevalence and excessive morbidity associated with pneumonia in SLE, these findings have clinical relevance and provide insight into the pathogenesis.

Pneumonia causes substantial morbidity and mortality in systemic lupus erythematosus (SLE) and represents the most common lung disease in this population. The contribution of genetic risk factors to susceptibility to pneumonia in patients with SLE has not been thoroughly investigated. Recently, investigators have identified genetic polymorphisms associated with an increased risk of infection in healthy hosts and patients with autoimmune disease (1–4).

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AUTHOR CONTRIBUTIONS

Dr. Criswell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Kinder, Freemer, King, Edberg, Criswell.

Acquisition of data. Kinder, Freemer, Edberg, Bridges, Criswell.

Analysis and interpretation of data. Kinder, Freemer, Nititham, Taylor, Edberg, Bridges, Criswell.

Manuscript preparation. Kinder, Freemer, King, Edberg, Bridges, Criswell.

Statistical analysis. Kinder, Lum, Nititham, Taylor, Criswell.

Some of these same polymorphisms have also been associated with SLE itself (5,6) and with specific disease manifestations, such as nephritis (7).

Infection contributes substantially to morbidity and mortality in SLE (8–10), and the rate of infection in SLE appears to exceed that in other autoimmune diseases and immunocompromised states by as much as 8-fold (11). Given the clinical importance of infection in SLE, previous investigations have assessed demographic and clinical risk factors for infection, including age, race, education level, insurance status, SLE severity or duration, immunosuppressive therapy, and leukopenia (8,9,12,13). However, the results of these studies have been inconsistent, perhaps because of methodologic differences.

The role of specific genetic polymorphisms in susceptibility to infection has been investigated in multiple populations, and the results suggest the importance of polymorphisms in the genes that encode tumor necrosis factor (TNF), Fcγ receptor (FcγR), and mannose-binding lectin (MBL).

The proinflammatory cytokine TNF plays an important role in the immune response to infection. TNF blockade ex vivo inhibits the expression of Toll-like receptor 4 (TLR-4) on dendritic cells from rheumatoid arthritis (RA) patients and controls, potentially leading to susceptibility to multiple infectious organisms, such as *Pseudomonas* (14). A promoter polymorphism of *TNF* (−308) has been shown to influence the risk of severe sepsis in children (15), although no significant association has been demonstrated in adults (16). Similarly, in a cohort of patients with early RA, the *TNF* −238 promoter polymorphism conferred a 2.5-fold increased risk of urinary tract infection (1).

Functional genetic polymorphisms of *FCGR*, such as *FCGR2A*, which play an important role in host defense against encapsulated bacteria, have been investigated (17,18). For example, invasive pneumococcal infections were observed in 5 SLE patients carrying the *FCGR2A-131R* allele, in the absence of significant levels of immunosuppressive drugs, severely abnormal complement levels, decreased IgG2 levels, or neutropenia (4).

Polymorphisms of *MBL*, one of the serum lectins produced by the liver as an acute-phase protein, have also been investigated as contributors to infection risk. These variant *MBL* genotypes result in lower serum levels of functional MBL protein and have been associated with an increased incidence of infection (19–21). Among an ethnically homogenous (Caucasian) cohort of 91 Danish SLE patients, those who were homozygous for *MBL* variant alleles had an 8.6-fold increased risk of infection requiring hospitalization as compared with those who were homozygous or heterozygous for the normal *MBL* allele (22). Patients homozygous for the variant *MBL* alleles (O/O genotype) had a 133-fold increased risk of developing pneumonia as compared with SLE patients with functional MBL protein (A/A genotype). A followup study of a similar Danish population confirmed both findings (23); however, these findings have not been evaluated in other ethnic populations.

The goal of this study was to define the contribution of polymorphisms in the *TNF*, *MBL*, and *FCGR* genes, as well as clinical factors, to the development of pneumonia among SLE patients from a multiethnic cohort.

PATIENTS AND METHODS

Study subjects

Study subjects were derived from the University of California, San Francisco (UCSF) Lupus Genetics Project collection, which is an ethnically diverse cohort of SLE patients recruited from several sources, including UCSF rheumatology clinics, private rheumatology practices

in Northern California, and nationwide outreach. The study was approved by the Institutional Review Board at UCSF, and the study subjects provided their informed consent. Enrollment in this cohort includes completion of a written survey, provision of DNA samples for genotyping, and permission to review all medical records. The diagnosis of SLE, according to the American College of Rheumatology criteria (24,25), was confirmed by medical records review.

Since the UCSF Lupus Genetics Project was not designed originally for the evaluation of pneumonia, our study focused on patients who received the majority of their care at UCSF to ensure that all relevant data (including inpatient and outpatient records) were available for re-review and classification by key outcomes and predictors of pneumonia. Ethnicity of the patients was based on the countries of origin of their grandparents. Patients were classified as being of mixed ethnicity if fewer than 3 grandparents were from a single ethnic group.

Data collection

Data were collected in a blinded manner with regard to the genotypes of the patients. All UCSF medical records, as well as available records from any non-UCSF health care providers who participated in an SLE patient's care, were reviewed. Socioeconomic status was evaluated using a scoring system based on education and income, and was available for those patients (42%) who were also participating in a longitudinal followup study.

Pneumonia classification

The diagnosis of pneumonia was established through review of medical records spanning the period from the onset of SLE symptoms to entry into the study, which was, on average, 12 years of disease for these patients. All pneumonia events were recorded using the criteria shown in Table 1. These criteria are based on the published literature for the classification of ventilator-associated pneumonia (excluding factors specific to the ventilator) (26–29) as well as the Canadian guidelines for the management of community-acquired pneumonia (30).

For the primary outcome analysis, patients with episodes of either definite or probable pneumonia (as defined in Table 1), but not reported events alone (as defined in Table 1), were considered to have had pneumonia. Sensitivity analyses were performed to examine the impact of variations in the pneumonia definition (i.e., the inclusion of reported pneumonia events) on the results. The type of pathogen (bacterial, fungal, viral, polymicrobial, negative sputum and blood cultures, or no microbial specimen obtained), date of the event, and source of the infection (nosocomial versus community acquired) for each episode of pneumonia were also documented. The Pneumonia Patient Outcomes Research Team (Pneumonia PORT) score (31), a validated pneumonia severity index, was defined for each pneumonia event.

Genotyping

FCGR2A polymorphisms—*FCGR2A-H131/R131* alleles were determined by Pyrosequencing using a nested polymerase chain reaction (PCR) approach to ensure gene-specific amplification (32). An initial *FCGR2A*-specific amplification was prepared, and then a second nested PCR reaction was performed around the single-nucleotide polymorphism (SNP) site, using a biotinylated primer, followed by Pyrosequencing of a short segment of DNA including the *FCGR2A* SNP. Primer sequences and assay conditions are available upon request from the authors.

TNF polymorphisms—The *TNF* −238, −308, and +488 polymorphisms were genotyped by PCR amplification of genomic DNA and Pyrosequencing on a PSQ 96 instrument (Pyrosequencing, Uppsala, Sweden). For all Pyrosequencing applications, the PCR reactions were performed in a 9600 PCR system (PerkinElmer Life and Analytical Sciences, Waltham,

MA) with 10 ng of genomic DNA, 200 n*M* of each primer, 200 μM of dNTPs, 2.0 m*M* $MgCl_2$, and 2.5 units of *Taq* DNA polymerase in a 50-μl reaction volume.

MBL polymorphisms—The 3 known exon 1 variants of *MBL* (the B, C, and D alleles) were determined by Pyrosequencing (primer and assay conditions available upon request from the authors). Donors who were heterozygous for the functional *MBL* allele (the A allele), and any of the 3 structural variant alleles were coded A/O for analysis. Donors who lacked the functional A allele were coded O/O for analysis, as described by Garred et al (23).

Statistical analysis

Clinical characteristics potentially influencing susceptibility to pneumonia, and the SNP alleles, were analyzed for association. Each potential predictor variable was analyzed using Fisher's exact test, and odds ratios (ORs), 95% confidence intervals (95% CIs), and *P* values were determined. Univariate analyses were performed for the entire cohort and for ethnic strata to identify polymorphisms and/or haplotypes associated with the risk of pneumonia. Results of the univariate analyses were used to develop a multivariable model of potential predictors of pneumonia. The following covariates were examined in multivariate logistic regression analyses: sex, ethnicity, age at SLE diagnosis (by tertiles), duration of followup, history of nephritis, exposure to tobacco smoke, treatment with corticosteroids, treatment with immunomodulators, and leukopenia. Additional covariates and alternative definitions of pneumonia were evaluated in sensitivity analyses. *TNF* haplotypes (−308/−238/+488) were defined using the Phase program (33).

The specific polymorphisms examined in the current study were chosen a priori based on evidence of association with infection; however, given the number of comparisons, there is an increased likelihood of false-positive results. It is difficult to determine the appropriate level of statistical adjustment for these analyses, since polymorphisms within the same gene or region, such as the *TNF* polymorphisms, may not be independent because of linkage disequilibrium. Therefore, all *P* values shown are nominal (i.e., uncorrected). All analyses were performed using Stata statistical software (StataCorp, College Station, TX).

RESULTS

Demographic and clinical characteristics of the 282 SLE patients studied are shown in Table 2. Eighty-nine percent of the patients were women. The median duration of disease was 12 years. At some point during their disease course, 91.5% of patients had received corticosteroids and 57.4% had received ≥1 immunomodulator medications.

A total of 84 pneumonia events were observed in 65 patients (23.0%). Fifty-eight of these events, in 42 patients (14.9%), met our stringent definition of pneumonia (see Table 2). Among these 58 pneumonia events, 50% occurred during treatment with immunomodulator medications. Seventy-nine percent of the pneumonia events were community-acquired. Thirty percent of patients presented with a pneumonia severity index (PORT score) of 4 or 5, corresponding to a predicted mortality rate of 9–27% (31). Of those pneumonia events with positive findings of microbiologic specimen analysis (n = 43), 75% were bacterial, 12% were mycobacterial, 7% were fungal, and 5% were viral.

Allele frequencies were examined in the entire cohort as well as by ethnic subgroups (Table 3). Genotype frequencies were also examined, and the results were similar. Observed differences in allele and genotype frequencies between ethnic groups were generally similar to those reported by other investigators (1,23). Genotype frequencies did not deviate substantially from the frequencies expected based on allele frequencies in the study population.

In particular, none of our significant findings were dependent on genotypes that were out of Hardy-Weinberg equilibrium.

Results of the univariate analyses are summarized in Table 4. Male sex, history of nephritis or leukopenia, treatment with immunomodulator medications, and *TNF* −238 A carrier status and the related haplotype were associated with an increased risk of pneumonia, as defined according to our stringent criteria. We found no evidence of a significant association of age, duration of followup, treatment with corticosteroids or hydroxychloroquine, or smoking with the risk of developing pneumonia. Among the subset of patients with available socioeconomic status data (~42%), socioeconomic status was not associated with the risk of pneumonia (Table 4). Among the individual genetic polymorphisms studied, only the *TNF* −238 allele (A) showed a consistent association with pneumonia across the ethnic strata. We found no association between the *FCGR2A* or *MBL* alleles and pneumonia, including the analyses stratified by ethnicity. In addition, we found no significant associations between genotype and pneumonia severity as defined by the PORT score, although our power for these analyses was more limited.

Of interest, analysis of haplotypes defined by the 3 *TNF* polymorphisms revealed a stronger and more significant association with the risk of pneumonia. Specifically, a haplotype containing the *TNF* −238A allele (−308G/−238A/+488 A or G) was associated with risk of pneumonia, with an OR of 4.0 (95% CI 1.5–9.8). In sensitivity analysis, when the definition of pneumonia was broadened to include the less specific “reported” category (see Table 1), the association of the TNF −238A carrier state with pneumonia was less significant (OR 2.3 [95% CI 0.9–5.6], $P = 0.06$).

The association between the *TNF* −238A carrier state (i.e., presence of 1 or 2 copies of the A allele) and the related haplotype (*TNF* −308G/−238A/+488 A or G) and the risk of pneumonia was assessed using multivariate logistic regression (Table 5), adjusting for ethnicity, use of immunomodulators (but not steroids), sex, and leukopenia; for the final multivariate model, we retained TNF haplotypes, ethnicity, and covariates with *P* values less than 0.1 following stepwise backward elimination. The results indicated that the *TNF* −238A carrier state was independently associated with a 3.5-fold increased odds of pneumonia as compared with that in *TNF* −238G homozygotes (OR 3.5 [95% CI 1.4–8.8], $P = 0.007$). Further, the related haplotype (TNF −308G/−238A/+488 A or G) was even more strongly associated with the risk of pneumonia (OR 5.4 [95% CI 2.03–14.5], $P = 0.001$).

Last, the *TNF* −238A allele and related haplotype were strongly associated with the risk of having multiple pneumonia events ($P = 0.003$ for the −238A allele and $P = 0.001$ for the haplotype in 3-way analyses comparing patients with multiple, single, and no pneumonia events). Male sex ($P = 0.04$), leukopenia ($P = 0.06$), and immunomodulator use ($P = 0.03$) were also associated with a history of multiple pneumonia events (data not shown).

DISCUSSION

We found that SLE patients who have inherited specific genetic variants of the *TNF* gene are at a significantly increased risk of developing pneumonia. Furthermore, the strength of this association is considerably stronger than that of conventionally accepted clinical risk factors for pneumonia or other infections, such as leukopenia, nephritis, and immunomodulator use (indicators of severe disease).

TNF is a molecule of central importance to cellular immunologic defense against a variety of pathogens. Several lines of evidence, both ex vivo and in vivo, support an important biologic role of TNF in host defense (14). The Th1 cytokine interferon-γ (IFNγ) is critical for proper activation of phagocytosis and destruction of intracellular bacteria, and its production is stimulated by TNF. TNF-blocking treatment ex vivo has been shown to significantly inhibit

TLR-4 expression on dendritic cells and to decrease the production of IFNγ in RA patients and healthy controls (14). TLR-4 is important for the recognition of bacterial and fungal pathogens by host cells, such as dendritic cells and macrophages. Treatment with infliximab, a humanized monoclonal antibody against TNF, has been associated with an increased risk of tuberculosis (34) and other infections (35). While TNF promoter variants have been associated with changes in the production of lymphotoxin α (36), one in vitro study suggests that the *TNF* −238A allele itself may not have a direct effect on transcriptional activation of the *TNF* gene (37). Thus, it is possible that this polymorphism may be a marker for another polymorphism(s) within the gene or the gene region that influences the risk of infection. Our results are consistent with this possibility, since a specific *TNF* haplotype was more strongly associated with pneumonia risk as compared with individual *TNF* alleles.

In contrast to the results for the *TNF* gene, we found no evidence in our large multiethnic cohort that the specific *FCGR2A* or *MBL* polymorphisms we studied influenced the risk of pneumonia. Although the power of our study to detect modest associations with these other genetic variants was limited, it was well powered to detect genetic associations comparable in magnitude to our findings for the *TNF* −238A allele and its related haplotype. Specifically, we had >80% power to detect ORs of 3.0 for the *MBL* and *FCGR2A* variants, and >70% power to detect ORs of 2.5 for these variants. Inspection of the upper limit of the confidence intervals for these variants suggests that we might have failed to detect associations with ORs in the range of 1.8 (upper limit of the 95% CI for the *FCGR2A* polymorphism) and 2.5 (upper limit of the 95% CI for *MBL* carriers).

Previous studies of *FCGR2A* have examined the *FCGR2A-R/R131* genotype as a risk factor for *invasive* pneumococcal or meningococcal disease (bacteremia or meningitis) in case–control designs (2,4). There are several potential explanations for the discrepant findings between these studies and ours. Our study was powered to evaluate pneumonia and not rarer outcomes, such as bacteremia or invasive infections. Only 29% of the pneumonia episodes we identified (n = 12 patients) were associated with documented bacteremia. It is possible that the *FCGR2A-R/R131* genotype predisposes individuals to invasive disease should they develop infection, but not necessarily to pneumonia per se. However, we did not observe a significant association between the *FCGR2A-R/R131* genotype and severe pneumonia, as defined by PORT scores (data not shown). We also did not confirm the association between the *MBL* O/O genotype and pneumonia as reported in Danish SLE patients (22). One potential explanation for this difference is that although we had a larger sample size, we had fewer patients with the *MBL* O/O genotype, which limited our power to detect smaller increases in pneumonia risk. The sole Caucasian patient in our study who had the *MBL* O/O genotype did not have pneumonia. Other studies have shown an increased risk of infection in young children with *MBL* variants (19,20); however, we had no patients with an SLE diagnosis prior to the age of 5 years. It is possible that *MBL* polymorphisms play a larger role earlier in life, before the immune system has sufficiently developed.

Several characteristics of our study, including the large size, ethnic diversity, systematic application of prespecified criteria for the diagnosis of pneumonia, determination of pneumonia severity, collection of important clinical covariate data, and the use of multivariate methods, enhance the validity of the results and underscore the important contribution of our findings. This study is also the first to examine the association of *TNF* and *FCGR2A* polymorphisms with susceptibility to pneumonia in a large, well-characterized cohort of SLE patients, and the first to assess *MBL* variant alleles with the risk of pneumonia in non-Caucasian SLE populations.

There are also several limitations of this study. First, although the total number of patients is substantial, the relatively smaller size of non-Caucasian ethnic groups limited the power of our

study to examine these groups individually. The retrospective design limited the covariates we could examine. For example, we were unable to assess the impact of diabetes, dosage of corticosteroid or immunomodulator, immunization status, or prophylactic use of antibiotics on the risk of pneumonia. It is also possible that we did not identify all pneumonia events because of incomplete medical records and tertiary referral patterns. However, we attempted to compensate for this weakness by limiting our study to patients who received the majority of their care from 1 institution, and we attempted to obtain all medical records from the referring physicians. Although these patients might not be representative of the entire population of SLE, this selection criterion should not have biased our findings since both the cases (SLE patients with pneumonia) and the controls (SLE patients without pneumonia) were drawn from the same population.

Although patients had a wide range of followup duration, potentially leading to misclassification of patients who will develop pneumonia at a later date, the median disease duration was 12 years, allowing a substantial period of time for the development of pneumonia. Furthermore, to examine this potential bias, we analyzed followup duration as a covariate, and we did not identify a significant association with the risk of pneumonia. Last, although the specific polymorphisms examined in the current study were chosen a priori based on evidence of association with infection, given the number of comparisons performed, there is an increased likelihood of false-positive results. However, our main findings related to the *TNF* −238 polymorphism and its related haplotype are still significant, even after a very conservative Bonferroni correction.

Identification of genetic risk factors for pneumonia in patients with SLE may have a considerable impact on our ability to prevent such infections through prophylaxis and/or immunizations. Currently, although pneumococcal vaccines have been shown to be safe and quite effective in SLE patients (38), adult immunization recommendations by the Centers for Disease Control and Prevention do not include specific guidelines for immunizing SLE patients (except for the general recommendations for patients who are receiving long-term immunosuppressive treatment) (39). In addition, because infectious disease consultants vary in their opinions with respect to the need for antibiotic prophylaxis in SLE patients undergoing invasive procedures (40), a better understanding of the inherent risk of infection in SLE patients would provide valuable data to inform such clinical decisions.

In summary, we have demonstrated that the *TNF* −238A allele and a related haplotype have a strong influence on the risk of developing pneumonia among SLE patients in a large multiethnic cohort. These results provide insight to the pathogenesis of pneumonia in SLE and could have a future impact on the management of individual cases. These findings identify a number of important areas for future investigation. First, it will be important to confirm the association with *TNF* genetic variation and to define more precisely the disease-associated variant in other SLE cohorts. The translation of these findings in terms of interventions to prevent pneumonia in SLE patients identified as being at high risk will also be required in order to clarify the relevance of our results to clinical practice.

Acknowledgments

Supported by the Arthritis Foundation, the NIH (National Institute of Arthritis and Musculoskeletal and Skin Diseases grants K24-AR-02175, R01-AR-44804, and P01-AR-49084), the University of California Tobacco-Related Disease Research Program, and the National Center for Research Resources (General Clinical Research Center grant M01-RR-00032 to the University of Alabama at Birmingham). These studies were performed in part at the General Clinical Research Center, Moffitt Hospital, University of California, San Francisco, with funds provided by the National Center for Research Resources (grant 5-M01-RR-00079). Dr. Criswell is recipient of a Kirkland Scholar Award.

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Table 1

Diagnostic criteria for pneumonia in patients with systemic lupus erythematosus*

Diagnosis	Criteria
Definite pneumonia	Presence of the following: **1** At least 1 of the following symptoms: fever, cough, or shortness of breath **2** Alveolar opacities on chest radiograph **3** Microbiologic specimen (from respiratory secretion, pleural fluid, or blood) with pathogenic organism or rapid cavitation of the radiographic opacity, and **4** Resolution of symptoms with antimicrobial therapy
Probable pneumonia	Presence of the following: **1** At least 1 of the following symptoms: fever, cough, or shortness of breath **2** Alveolar opacities on chest radiograph, and **3** Resolution of symptoms with antimicrobial therapy
Reported pneumonia	Medical record or patient report of a history of pneumonia in the absence of available documenting data
Not pneumonia	Respiratory symptoms and radiographic lung disease not meeting any of the above criteria, or alveolar opacities on chest radiograph that resolve in less than 48 hours, or resolution of symptoms without antimicrobial therapy

* Pneumonia classification criteria are based on the published literature for the classification of ventilator-associated pneumonia (excluding factors specific to the ventilator) (26–29) as well as the Canadian guidelines for the management of community-acquired pneumonia (30).

Table 2

Characteristics of the 282 systemic lupus erythematosus (SLE) patients

Females, no. (%)	251 (89.0)
Ethnicity, no. (%)	
Caucasian	127 (45.0)
Hispanic	52 (18.4)
African American	33 (11.7)
Asian/Pacific Islander	55 (19.5)
Other/mixed ethnicity	15 (5.3)
Age at SLE diagnosis, median (range) years	27 (5–83)
Duration of SLE, median (range) years	12 (2–40)
History of renal disease, no. (%)*	104 (36.9)
History of leukopenia, no. (%)	114 (40.4)
History of immunomodulator therapy, no. (%)†	162 (57.4)
Prednisone therapy, no. (%)	258 (91.5)
Any pneumonia event, no. (%)‡	65 (23.0)
Pneumonia event meeting stringent criteria, no. (%)§	42 (14.9)

*Includes the presence of lupus nephritis on renal biopsy or the development of end-stage renal disease.

†Includes cyclophosphamide, azathioprine, methotrexate, and cyclosporine.

‡Includes definite, probable, or reported episodes of pneumonia (see Table 1 for definitions).

§Includes only definite and probable episodes of pneumonia (see Table 1 for definitions).

Table 3

SNP allele frequencies among the entire cohort and by ethnic group*

SNP	Allele	All subjects, no. of minor alleles/total no. of genotyped alleles (%)	Ethnic group, no. (%) of chromosomes					*P*
			Caucasian	Hispanic	African American	Asian/Pacific Islander	Other/mixed ethnicity	
MBL	O vs. A†	124/552 (23)	55 (23)	25 (25)	20 (31)	15 (14)	9 (30)	0.08
TNF −308	A vs. G	84/554 (15)	52 (21)	11 (11)	9 (14)	9 (8)	3 (10)	0.02
TNF −238	A vs. G	30/554 (5)	11 (5)	8 (8)	3 (5)	4 (4)	4 (13)	0.3
TNF +488	A vs. G	71/554 (13)	35 (14)	19 (19)	4 (6)	11 (10)	2 (7)	0.07
FCGR2A	H vs. R	247/478 (52)	92 (45)	53 (59)	22 (42)	68 (67)	12 (43)	0.002

*P values were determined by Fisher's exact test. SNP = single-nucleotide polymorphism.

†O represents the B, C, and D variant alleles (see Patients and Methods for details).

Table 4

Factors associated with ≥1 pneumonia event on univariate analyses*

	No pneumonia events (n = 217)	≥1 pneumonia event (n = 42)	Odds ratio (95% CI)	*P*
Covariate				
Male sex	20 (9)	9 (21)	2.7 (0.98–6.8)	0.03
Ethnicity†				
Hispanic	35 (16)	12 (29)	2.2 (0.9–5.7)	0.07
African American	26 (12)	7 (17)	1.8 (0.5–5.2)	0.3
Asian	45 (21)	6 (14)	0.9 (0.3–2.6)	1
Age‡				
<21 years	70 (33)	15 (36)	1.2 (0.5–2.6)	0.7
>40 years	37 (17)	7 (17)	1.0 (0.3–2.8)	1
Followup >12 years	100 (47)	22 (52)	1.2 (0.6–2.6)	0.6
Nephritis§	75 (35)	23 (55)	2.3 (1.1–4.7)	0.02
Medication history				
Immunomodulators¶	125 (58)	33 (79)	2.7 (1.2–6.7)	0.01
Corticosteroids	197 (91)	40 (95)	2.0 (0.5–18.6)	0.5
Hydroxychloroquine	175 (81)	33 (79)	0.9 (0.4–2.3)	0.8
Leukopenia	84 (39)	24 (57)	2.1 (1.0–4.4)	0.04
Ever smoker	67 (35)	11 (30)	0.8 (0.3–1.8)	0.6
Low socioeconomic status#	41 (42)	8 (62)	2.2 (0.6–9.1)	0.2
Genetic risk factors				
TNF −238 A carrier**	19 (9)	11 (28)	4.0 (1.5–9.8)	0.002
TNF −308 A carrier**	63 (29)	9 (23)	0.7 (0.3–1.64)	0.5
TNF +488 A carrier**	47 (22)	9 (23)	1 (0.4–2.5)	1.0
Haplotypes††				
AGx haplotype	69 (16)	9 (11)	0.8 (0.3–1.7)	0.6
GGA haplotype	45 (11)	10 (13)	1.5 (0.6–2.9)	0.5
GAx haplotype	16 (4)	11 (14)	4.1 (1.6–9.9)	0.002
MBL exon 2 O carrier**	90 (41)	18 (46)	1.2 (0.6–2.5)	0.6
MBL exon 2 OO genotype‡‡	5 (2)	2 (5)	2.4 (0.2–15.9)	0.3
FCGR2A (H) carrier‡‡	142 (75)	21 (68)	0.7 (0.3–1.8)	0.4
FCGR2A HH genotype‡‡	46 (24)	14 (45)	1.4 (0.5–4)	0.5

*Values are the number (%) of patients. *P* values less than 0.05 were considered significant, as determined by Fisher's exact test.

†Caucasian patients were the reference group.

‡Patients ages 21–40 years were the reference group.

§Defined as the presence of lupus nephritis on renal biopsy or the development of end-stage renal disease.

¶Included cyclophosphamide, azathioprine, methotrexate, and cyclosporine.

[#] Socioeconomic status data were available for 97 patients with no pneumonia events and 13 patients with ≥1 pneumonia event.

[**] Carrier status included those who were heterozygous and those who were homozygous for the risk allele (e.g., AG and AA, respectively).

[††] Patients with haplotype GGG were the reference group. AGx combines AGA (overall 0.5%) with AGG (overall 16.4%). GAx combines GAA (overall 0.5%) with GAG (overall 4.6%).

[##] Patients homozygous for major alleles (e.g., *MBL* AA, *FCG2A* RR) were the reference group.

Table 5

Factors associated with ≥1 pneumonia event based on multivariate logistic regression analysis*

Predictor variable	Odds ratio (95% CI)	*P*
Male sex	2.62 (0.97–7.04)	0.056
Immunomodulator use	2.04 (0.88–4.76)	0.097
Leukopenia	2.28 (1.07–4.88)	0.034
TNF haplotypes		
AGx	0.81 (0.33–1.98)	0.638
GGA	1.23 (0.49–3.10)	0.657
GAx	5.43 (2.03–14.5)	0.001
Ethnicity		
Hispanic	2.10 (0.80–5.53)	0.134
African American	2.44 (0.82–7.24)	0.109
Asian/Pacific Islander	1.07 (0.35–3.22)	0.910
Other ethnicity	0.51 (0.08–3.14)	0.467

* Immunomodulators included cyclophosphamide, azathioprine, methotrexate, and cyclosporine. Tumor necrosis factor (TNF) haplotypes were defined by the alleles at positions −308/−238/+488; patients with haplotype GGG were the reference group. Caucasian patients were the reference group for ethnicity. 95% CI = 95% confidence interval.