Published in final edited form as:
Respirology. 2010 January ; 15(1): 160–164. doi:10.1111/j.1440-1843.2009.01661.x.

C-reactive Protein Gene Variation and Risk of Community-Acquired Pneumonia

Kenneth J. Mukamal[1], **Jennifer K. Pai**[2,3], **Ellen S. O'Meara**[4], **Russell P. Tracy**[5], **Bruce M. Psaty**[6,7], **Lewis H. Kuller**[8], **Anne B. Newman**[8], **Sachin Yende**[9], **Gary C. Curhan**[2,3,10], **David S. Siscovick**[6,7], and **Eric B. Rimm**[2,3,11]

[1]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA

[2]Department of Epidemiology, Harvard School of Public Health, Boston, MA

[3]Channing Laboratory, Department of Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, MA

[4]Department of Biostatistics, University of Washington, Seattle, WA

[5]Department of Pathology, College of Medicine, University of Vermont, Burlington, VT

[6]Department of Epidemiology, University of Washington, Seattle, WA

[7]Department of Medicine, University of Washington, Seattle, WA

[8]Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA, USA

[9]Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA

[10]Renal Division, Department of Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, MA

[11]Department of Nutrition, Harvard School of Public Health, Boston, MA

Abstract

Background and Objective—C-reactive protein (CRP) has several potentially antibacterial effects, and variation in the *CRP* gene is known to influence CRP levels. Whether this variation influences risk of infection, and hence whether CRP has anti-infective activity in humans, is uncertain.

Methods—We evaluated a series of haplotype-tagging single nucleotide polymorphisms among 5374 individuals in the Cardiovascular Health Study (CHS), a cohort of older adults from four communities, who were followed for community-acquired pneumonia for 12-13 years. Secondarily, we evaluated whether these polymorphisms varied among men in the Health Professionals Follow-up Study (HPFS) who self-reported pneumonia on biennial questionnaires.

Results—There were 581 (507 white and 74 black) CHS participants with incident hospitalizations for pneumonia. No SNPs or haplotypes were associated with risk among white CHS participants. Among black participants, the haplotype tagged by A790T was associated with lower risk of incident pneumonia (hazard ratio 0.5; 95% confidence interval, 0.3-0.9) and with higher CRP levels. In HPFS,

Address for Correspondence: Kenneth J. Mukamal, MD, MPH, MA, Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, RO-114, Boston, MA 02215, Telephone: (617) 667-4476, Facsimile: (617) 667-2854, kmukamal@bidmc.harvard.edu.

Conflict of Interest Statement: No conflicts of interest related to this work are present. A draft of this manuscript was reviewed for consistency with previous CHS publications by the NHLBI, but the study sponsors had no other role in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

a separate haplotype was associated with less frequent self-reported pneumonia but not with circulating CRP levels.

Conclusions—Some genetic variants in *CRP* may be associated with risk of pneumonia, but haplotypes associated with risk are variably associated with baseline CRP levels. If CRP is a relevant component of innate immunity in humans, the inducibility or tissue-specificity of expression may be at least as important as chronic circulating levels.

Keywords

C-reactive protein; single nucleotide polymorphism; pneumonia; cohort studies; epidemiology

Introduction

C-reactive protein (CRP) is encoded by 1.9kb single-intron gene on chromosome 1q.(1) CRP has anti-infective properties, including foreign molecule recognition, complement activation, and phosphocholine binding, but its role in human immunity is uncertain. Human CRP protects mice from *S. pneumoniae*,(2,3) but mice do not produce CRP with infection as do humans. CRP is also an acute phase reactant, and higher levels have been associated with clinical infection(4-7) even if CRP itself may be protective.

One alternate approach is to evaluate genetic variants in the *CRP* gene that alter CRP levels, as these are randomly distributed within founder populations.(8) One case-control study of invasive pneumococcal infection found increased risk associated with a dinucleotide repeat polymorphism in the *CRP* intron.(9) Genetic variation in other pattern recognition molecules has also been reported to influence infection risk.(10-17)

To evaluate *CRP* more fully, we determined the association of *CRP* variants with risk of pneumonia in a prospective cohort study, using haplotype-tagging single nucleotide polymorphisms (SNPs) linked to CRP levels.(18,19) We also examined *CRP* variants in relation to self-reports of pneumonia in a second cohort.

Methods

Study Population and Design

We primarily examined the Cardiovascular Health Study (CHS), a prospective study of 5888 adults aged 65 years or older from four U.S. communities.(20) Participants were not institutionalized or wheelchair-dependent and were not under treatment for cancer at enrollment. In 1989-90, 5201 participants were recruited; in 1992-93, 687 additional black participants were enrolled. The institutional review board at each center approved the study, and each participant gave informed consent. The baseline examination included standardized questionnaires, physical examination, and laboratory examination. We include here all 5374 black or white participants who permitted genetic testing for studies of non-cardiovascular diseases.

Determination of Genotypes

Four tagging SNPs in the *CRP* gene were genotyped with Taqman and Applied Biosystems primers: 1919 (rs1417938); 2667 (rs1800947); 3872 (rs1205); and 5237 (rs2808630).(18,19) A fifth, 790 (rs3093058), was genotyped in black participants; it is rare in whites.(19) P-values for Hardy-Weinberg equilibrium are published (18).

We derived haplotypes using expectation-maximization–based algorithms with the HAPPY macro, assuming additive inheritance.(21) Only haplotypes with estimated frequencies >5% were included.

Assessment of CRP Levels and Pneumonia

CRP concentrations were measured on stored EDTA plasma from baseline with a high-sensitivity enzyme-linked immunosorbent assay (coefficient of variation, 6.2%).(22) Cases of pneumonia required hospitalization for pneumonia (fatal or not) from study entry through June 2003 (based upon primary discharge ICD-9 codes 480-486).(23) To evaluate validity, medical records from all 138 cases through June 2001 at the Pittsburgh site were reviewed. A clinical diagnosis of pneumonia was recorded in 96% of cases, pneumonia was confirmed radiographically in 92%, and the organism was identified in 41%.

Other Covariates

Smoking was defined in CHS as current, former, and never. Baseline CVD included adjudicated coronary heart disease, stroke, and congestive heart failure (24). Study technicians measured height and weight, and diabetes was ascertained using American Diabetes Association criteria.

Statistical Methods

We present adjusted hazard ratios and 95% confidence intervals (CI), setting wild-type homozygotes as the referent and evaluating time to incident pneumonia in Cox models; time-dependent covariates confirmed proportional hazards.(25) We tested haplotypes in comparable models. Although no confounding is expected in genetic studies, we adjusted risk estimates for age, sex, and smoking, known risk factors for pneumonia in CHS.(23,26) We adjusted for baseline CVD in sensitivity analyses. We also explored adjustment for baseline CRP levels to determine whether the association of *CRP* variants with risk is mediated by baseline levels.

Health Professionals Follow-up Study

Secondarily, we examined these variants and self-reported pneumonia in the Health Professionals Follow-up Study (HPFS), a cohort of 51,529 predominately white male health professionals from throughout the US (online supporting information). For a case-control study of coronary heart disease, we identified 830 men with incident coronary heart disease between 1994 and 2000 from 18,225 men with archived blood samples. We identified 1660 controls randomly matched on age, smoking, and date of blood draw. In the 2412 white men who were successfully genotyped, we genotyped the four SNPs used in the white CHS population.(27) All participants self-reported both recent and earlier cases of radiologically-confirmed pneumonia biennially from 1992 through 2004, but no medical record review was performed. Analyses of HPFS estimated odds ratios for any self-report of pneumonia with unconditional logistic regression.

Results

Table 1 shows selected characteristics of the two populations. Among 5374 CHS participants, 581 cases of incident pneumonia occurred (507 white and 74 black).

Individual Tagging SNPs

Allele frequencies for black CHS participants differed from whites but resembled black populations elsewhere (Table 2).(19) Individual SNPs were not related to pneumonia in white CHS participants. Among black participants, 790 AT heterozygotes had a lower risk of incident pneumonia and significantly higher CRP levels.

CRP Haplotypes

Haplotypes were not associated with risk of pneumonia among white CHS participants, despite strong associations with CRP levels (Table 3). Among black CHS participants, the haplotype tagged with the 790 T allele was associated with lower risk of incident pneumonia. The haplotype tagged by 5237 SNP also tended toward lower risk among blacks (p=0.13).

Baseline CVD was associated with higher risk for pneumonia, but additional adjustment for CVD did not materially influence the associations of *CRP* haplotypes with risk. Baseline CRP levels were associated with incident pneumonia among white CHS participants (age-, sex-, smoking-, and CVD-adjusted hazard ratio per 1-standard deviation increment in log(CRP) 1.12; 95% CI, 1.02-1.22), but not among black participants (hazard ratio 1.07; 95% CI, 0.85-1.35). However, additional adjustment for baseline CRP levels in did not materially alter associations of haplotype with risk.

Discussion

Although variation in the *CRP* gene is related to resting levels of CRP, those haplotypes most closely tied to lower risk in this study were not necessarily those with the strongest effect on circulating CRP levels, and not always in the same direction. Likewise, the $(GT)^{16}$ intronic repeat allele is associated with lower CRP levels than the $(GT)^{20}$ but not the $(GT)^{21}$ allele, (28) although the latter two alleles confer similar, lower risks of invasive infection than the more common $(GT)^{16}$ allele.(9) In our secondary analyses of 353 cases of self-reported pneumonia in HPFS, an outcome of uncertain validity, *CRP* variants were associated with CRP levels almost identically to white CHS participants. Only the haplotype tagged by A5237G was associated with less frequently reported pneumonia (odds ratio 0.8; 95% confidence interval, 0.6-0.9), but it did not relate to circulating CRP levels.

These complexities illustrate the difficulties in tying resting CRP levels to infection. In humans, CRP levels can rise 1000-fold in response to inflammatory stimuli, a greater rise than other acute phase reactants.(29) Assuming this inducibility is important, *CRP* variants may shape risk of clinical infection chiefly by influencing CRP production in response to infectious challenge. These variants may also influence tissue-specificity, as *CRP* is expressed in both alveolar macrophages and lung epithelium.(30-32)

Our findings must be placed in clinical context. The 790T-tagged haplotype was associated with markedly lower risk, with a hazard ratio of 0.5, stronger than many risk factors for pneumonia in CHS.(23) For example, the hazard ratios for never smoking and absence of coronary disease were 0.57 and 0.66, respectively. However, no haplotypes were protective in older white adults, and even 790T was infrequent in blacks, so any benefit attributable to *CRP* variants will be limited to a minority of individuals and unlikely to assist clinical prediction or management of pneumonia and its complications.(33)

We acknowledge important limitations. Participants were past middle age, and we missed cases of pneumonia that occurred earlier in life. Cases in HPFS (but not CHS) were self-reported and hence of uncertain validity, although a parallel cohort of nurses with identical follow-up procedures confirmed a radiographic diagnosis in 82% of cases with available radiographs. (26)

Microbiological diagnosis was not required, and even in hospitalized patients from CHS, an etiology was defined in less than half of cases. Even in prospective studies with systematic invasive diagnostic strategies, a microbiological diagnosis is made in only ~60% of cases, (34) but *CRP* variants may have the most effect on specific pathogens, such as *S. pneumoniae*.

We did not have information on clinical complications or severity. It is possible that *CRP* variation influences not only risk of pneumonia, but also its prognosis, severity, or recurrence. Future studies with additional clinical detail may clarify the full spectrum of clinical manifestations that *CRP* variants confer.

Summary at a Glance

We tested whether variation in the *CRP* (C-reactive protein) gene was associated with risk of pneumonia. We found that some genetic variants in *CRP* may be associated with risk of pneumonia, but not consistently in the manner expected from circulating CRP levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The research reported in this article was supported by contracts N01-HC-35129, N01-HC-45133, N01-HC-75150, N01-HC-85079 through N01-HC-85086, N01 HC-15103, N01 HC-55222, and U01 HL080295 from the National Heart, Lung, and Blood Institute (NHLBI) to CHS, with additional contribution from the National Institute of Neurological Disorders and Stroke. It was further supported by grants HL71862, HL35464, and HL34594 from NHLBI, CA55075 from the National Cancer Institute, and an established investigator award from the American Heart Association to Dr. Rimm. A full list of participating CHS investigators and institutions can be found at http://www.chs-nhlbi.org.

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Table 1

Characteristics of white and black CHS participants

	White (n=4540)	Black (n=834)
Age (years)	73 ±6	73 ±6
Male	1964 (43)	313 (38)
Current Smoker	497 (11)	130 (16)
Former Smoker	1947 (43)	294 (35)
Diabetes	656 (15)	202 (25)
Body Mass Index (kg/m^2)	25.9 (23.4-28.7)	27.8 (24.6-31.6)

Counts and percentages are shown for binary variables. Means with standard deviations are shown for normally distributed continuous variables, medians with interquartile ranges for skewed variables.

Table 2

CRP single nucleotide polymorphism frequencies, median levels of CRP, and adjusted hazards ratios with 95% confidence intervals for pneumonia among white and black CHS participants

	White			Black		
SNP	**Genotype Frequency**	**Median CRP**	**HR for Pneumonia**	**Genotype Frequency**	**Median CRP**	**HR for Pneumonia**
790						
AA				575 (69)	3.0	1.0
AT				237 (28)	4.2	0.6 (0.3-1.0)
TT				22 (3)	7.0	*
1919						
AA	2188 (48)	2.3	1.0	621 (74)	3.4	1.0
AT	1934 (43)	2.5	1.0 (0.9-1.2)	194 (23)	3.1	1.0 (0.6-1.7)
TT	413 (9)	2.6	1.1 (0.8-1.5)	18 (2)	6.2	*
2667						
GG	3935 (87)	2.5	1.0	810 (97)	3.4	*
GC	582 (13)	1.8	1.1 (0.9-1.4)	24 (3)	2.4	*
CC	19 (<1)	1.8	*	0		
3872						
GG	1995 (44)	2.7	1.0	545 (65)	3.6	1.0
GA	2010 (44)	2.2	1.0 (0.8-1.2)	257 (31)	3.0	0.8 (0.5-1.4)
AA	532 (12)	1.8	0.9 (0.6-1.1)	32 (4)	1.9	*
5237						
AA	2367 (52)	2.3	1.0	550 (66)	3.6	1.0
AG	1830 (40)	2.5	1.0 (0.8-1.2)	255 (31)	3.1	0.6 (0.4-1.1)
GG	343 (8)	2.5	1.0 (0.8-1.4)	29 (8)	2.2	*

Numbers of participants and proportions are shown for genotype frequencies. Median CRP values in mg/L are shown. Hazard ratios and 95% confidence intervals for pneumonia adjusted for age, sex (in CHS), and smoking are shown relative to wild-type homozygotes; odds ratios for variant homozygotes are not shown if 5 or fewer cases of pneumonia occurred.

Table 3

Estimated *CRP* haplotypes, adjusted differences in log(CRP) levels, and hazard ratios with 95% confidence intervals for pneumonia among white and black CHS participants

CRP SNP		1919	2667	3872	5237	Frequency (%)	Hazard Ratio (95% CI)	Log(CRP) (±SE)
White								
H1		A	C	A	A	6.8	1.0 (0.9-1.2)	−0.31 ±0.05
H2		A	G	A	A	27.1	0.9 (0.8-1.0)	−0.20 ±0.03
H3		A	G	G	G	27.6	1.0 (0.9-1.1)	−0.07 ±0.03
H4		T	G	G	A	30.3	1.0	Ref
H5		A	G	G	A	8.1	1.0 (0.9-1.2)	+0.13 ±0.04
p-value							0.58	<0.001
Black	790	1919	2667	3872	5237			
H2	A	A	G	A	A	17.8	0.7 (0.5-1.2)	−0.27 ±0.08
H3	A	A	G	G	G	18.8	0.7 (0.4-1.1)	−0.19 ±0.08
H4	A	T	G	G	A	13.8	0.8 (0.5-1.3)	−0.08 ±0.08
H5	A	A	G	G	A	31.3	1.0	Ref
H6	T	A	G	G	A	16.8	0.5 (0.3-0.9)	+0.29 ±0.08
p-value							0.14	<0.001

Differences in log(CRP) values are shown for CHS participants. Differences in log(CRP) values and hazard ratios for pneumonia are adjusted for age, sex, and smoking with the most common haplotype as the referent; further adjustment for case-control status in baseline cardiovascular disease had little effect. Only haplotypes with frequencies>5% are shown. P-values derive from global tests of haplotype association with risk of pneumonia.