Meta-Analysis of Genome-Wide Association Studies in >80 000 Subjects Identifies Multiple Loci for C-Reactive Protein Levels

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Background—C-reactive protein (CRP) is a heritable marker of chronic inflammation that is strongly associated with cardiovascular disease. We sought to identify genetic variants that are associated with CRP levels.

Methods and Results—We performed a genome-wide association analysis of CRP in 66 185 participants from 15 population-based studies. We sought replication for the genome-wide significant and suggestive loci in a replication

Received February 24, 2010; accepted November 23, 2010.

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†Dr Peltonen passed away in March 2010.

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Guest Editor for this article was Kari E. North, PhD.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.110.948570/DC1.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.110.948570**

panel comprising 16 540 individuals from 10 independent studies. We found 18 genome-wide significant loci, and we provided evidence of replication for 8 of them. Our results confirm 7 previously known loci and introduce 11 novel loci that are implicated in pathways related to the metabolic syndrome (*APOC1*, *HNF1A*, *LEPR*, *GCKR*, *HNF4A*, and *PTPN2*) or the immune system (*CRP*, *IL6R*, *NLRP3*, *IL1F10*, and *IRF1*) or that reside in regions previously not known to play a role in chronic inflammation (*PPP1R3B*, *SALL1*, *PABPC4*, *ASCL1*, *RORA*, and *BCL7B*). We found a significant interaction of body mass index with *LEPR* ($P<2.9\times10^{-6}$). A weighted genetic risk score that was developed to summarize the effect of risk alleles was strongly associated with CRP levels and explained ≈5% of the trait variance; however, there was no evidence for these genetic variants explaining the association of CRP with coronary heart disease.

Conclusions—We identified 18 loci that were associated with CRP levels. Our study highlights immune response and metabolic regulatory pathways involved in the regulation of chronic inflammation. **(*Circulation*. 2011;123:731-738.)**

Key Words: genetics ■ inflammation ■ meta-analysis ■ myocardial infarction ■ genome-wide association study

C-reactive protein (CRP) is a general marker of systemic inflammation. High CRP levels are associated with increased risks of mortality[1] and major diseases including diabetes mellitus,[2] hypertension,[3] coronary heart disease (CHD),[4] and stroke.[5] The heritability of CRP levels is estimated to be 25% to 40%,[6–8] suggesting that genetic variation is a major determinant of CRP levels. A genome-wide association (GWA) study in 6345 women found 7 loci associated with CRP levels.[9] These loci were in or close to genes encoding CRP (*CRP*), leptin receptor (*LEPR*), interleukin-6 receptor (*IL6R*), glucokinase regulator (*GCKR*), hepatic nuclear factor 1-α (*HNF1A*), apolipoprotein E (*APOE*), and achaete-scute complex homolog 1 (*ASCL1*). Findings from other GWA studies did not extend the number of loci related to CRP.[10,11]

Clinical Perspective on p 738

In this study, we sought to discover additional genes related to CRP levels using GWA scans in 66 185 participants from 15 population-based cohort studies and replicate our findings in 16 540 participants from 10 independent studies. To investigate whether the genetic variants identified interact with nongenetic determinants of CRP such as age, sex, smoking, and body mass index (BMI), we examined gene-environment interactions. Finally, the extent to which the genes associated with circulating CRP levels, individually or jointly, affect the risk of cardiovascular diseases is still unknown. To address this question, we examined the association of genetic variants with myocardial infarction (MI) and CHD.

Methods

Subjects and Measurements

Participants were of European ancestry. All studies had protocols approved by local institutional review boards. Participants provided written informed consent and gave permission to use their DNA for research purposes. Baseline characteristics for all participating studies are presented in Table I in the online-only Data Supplement. Baseline measures of clinical and demographic characteristics were obtained at the time of cohort entry except for British 1958 Birth Cohort (B58C), the Framingham Heart Study (FHS), Northern Finland Birth Cohort 66 (NFBC66), and the Atherosclerosis Risk in Communities (ARIC) study, in which measures were obtained at the time of phenotype measurement.

GWA Analysis

Genome-wide scans were performed independently in each cohort with the use of various genotyping technologies (Table VII in the online-only Data Supplement). Investigators in each study performed association analysis using the genotype-phenotype data within their cohort. Each study imputed single-nucleotide polymorphisms (SNPs) with reference to HapMap release 22 CEU and provided results for a common set of SNPs for meta-analysis. Except for the FHS, all studies conducted a linear regression analysis adjusted for age (except for NFBC66 and B58C), sex (except for the Women's Genome Health Study [WGHS]), and site of recruitment (if necessary) for all SNPs based on an additive genetic model. In the Erasmus Rucphen Family (ERF) study, adjustments for the family structure in the GWA analysis were based on the model residuals in the score test, which accounted for pedigree structure as implemented in GenABEL software[12] function "mmscore."[13] In the FHS, a linear mixed effects model was employed with the use of the lmekin function of the kinship package in R with a fixed additive effect for the SNP genotype, fixed covariate effects, and random family-specific additive residual polygenic effects.[14] In each study, we estimated the genomic inflation rate, stated as lambda (λgc), by comparing each study's median χ^2 value to 0.4549, the median χ^2 for the null distribution[15] (Table I in the online-only Data Supplement). *P* values for each cohort were adjusted for underlying population structure with the genomic inflation coefficient.

Discovery Panel and Replication Panel

The 15-study discovery panel included 5 studies from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium,[16] 4 studies from the European Special Population Network (EUROSPAN), and 6 additional independent studies comprising 66 185 participants. The replication studies included 10 independent studies and 16 540 participants.

Meta-Analysis

To calculate the combined *P* values and β coefficients, we used an inverse-variance weighted fixed-effects meta-analysis. We used METAL, a software package designed to perform meta-analysis on GWA data sets.[17] We applied an a priori threshold 5.0×10^{-8} for genome-wide significance.[18] When >1 genome-wide significant SNP clustered at a locus, we took the SNP with the smallest *P* value as the lead SNP. To investigate the validity of our findings, we sought replication of the lead SNP in genome-wide significant ($P<5\times10^{-8}$) loci and sought additional evidence for suggestive loci ($5\times10^{-8}<P<10^{-5}$) in our replication panel. We ran a fixed-effect meta-analysis to combine the results of the discovery and replication panels. The first GWA study on serum CRP published by Ridker et al[9] was based on part of the WGHS population. To confirm that our findings were not entirely influenced by these previously published results, we performed a meta-analysis excluding the WGHS population.

Examination of Heterogeneity

We examined between-study heterogeneity with Cochran's Q test. On the basis of Bonferroni adjustment for 18 tests, heterogeneity was

Table 1. Association of 17 Genome-Wide Significant Loci With CRP Levels in the Discovery Panel

SNP	Band	Significant SNPs	Coded Allele	Allele Frequency	β* (SE)	P	Gene
rs2794520	1q23.2	121	C	0.66	0.193 (0.007)	9.5×10^{-189}	*CRP*
rs4420638	19q13.32	16	A	0.80	0.240 (0.010)	2.1×10^{-129}	*APOC1*
rs1183910	12q24.31	186	G	0.67	0.152 (0.007)	3.3×10^{-113}	*HNF1A*
rs4420065	1p31.3	291	C	0.61	0.111 (0.007)	3.2×10^{-64}	*LEPR*
rs4129267	1q21.3	90	C	0.60	0.094 (0.007)	1.1×10^{-47}	*IL6R*
rs1260326	2q13	54	T	0.41	0.089 (0.007)	5.4×10^{-43}	*GCKR*
rs12239046	1q44	13	C	0.61	0.048 (0.007)	1.6×10^{-13}	*NLRP3*
rs6734238	2p23.3	92	G	0.42	0.047 (0.007)	3.4×10^{-13}	*IL1F10*
rs9987289	8p23.1	15	G	0.90	0.079 (0.011)	2.3×10^{-12}	*PPP1R3B*
rs10745954	12q23.2	22	A	0.50	0.043 (0.006)	1.6×10^{-11}	*ASCL1*
rs1800961	20q13.12	1	C	0.95	0.120 (0.018)	2.3×10^{-11}	*HNF4A*
rs340029	15q22.2	25	T	0.62	0.044 (0.007)	2.6×10^{-11}	*RORA*
rs10521222	16q12.1	6	C	0.94	0.110 (0.017)	1.3×10^{-10}	*SALL1*
rs12037222	1p32.4	11	A	0.24	0.047 (0.008)	4.5×10^{-10}	*PABPC4*
rs13233571	7q11.23	7	C	0.86	0.054 (0.010)	2.8×10^{-8}	*BCL7B*
rs2836878	21q22.2	2	G	0.72	0.040 (0.007)	4.0×10^{-8}	*PSMG1*
rs4903031	14q24.2	1	G	0.21	0.046 (0.008)	4.6×10^{-8}	*RGS6*

*β coefficient represents 1-unit change in the natural log–transformed CRP (mg/L) per copy increment in the coded allele.

considered significant at a P value $<2.8\times10^{-3}$. We explored the source of heterogeneity for significant SNPs by fitting a covariate (age, gender, BMI, or smoking) in a meta-regression model.

Gene-Environment Interaction

For all genome-wide significant SNPs, we examined gene-by-age, gene-by-sex, gene-by-BMI, and gene-by-smoking interactions in each study by introducing an interaction term into a linear model with age, sex, and the covariate of interest as the independent variables and natural log–transformed CRP as the outcome. A meta-analysis was performed to combine the reported interaction β and P values across studies for each of the top SNPs. On the basis of Bonferroni adjustment for 72 tests (18 SNPs for 4 environmental factors), we used a significance threshold at $6.9\times10.^{-4}$

Table 2. Association of 17 Genome-Wide Significant Loci With CRP Levels in the Replication Panel and Combined With the Discovery Results

		Replication		Discovery+Replication				
SNP	Coded Allele	β* (SE)	P	Beta*(SE)	P	R^2†	P for Heterogeneity	Closest Gene
rs2794520	C	0.086 (0.010)	9.9×10^{-19}	0.160 (0.006)	2.0×10^{-186}	1.38	7.4×10^{-26}	*CRP*
rs4420638	A	0.200 (0.032)	3.0×10^{-10}	0.236 (0.009)	8.8×10^{-139}	0.93	0.03	*APOC1*
rs1183910	G	0.122 (0.021)	8.3×10^{-14}	0.149 (0.006)	2.1×10^{-124}	0.76	0.08	*HNF1A*
rs4420065	C	0.045 (0.009)	1.5×10^{-6}	0.090 (0.005)	3.5×10^{-62}	0.39	1.1×10^{-9}	*LEPR*
rs4129267	C	0.045 (0.010)	7.3×10^{-6}	0.079 (0.005)	2.1×10^{-48}	0.31	2.4×10^{-4}	*IL6R*
rs1260326	T	0.031 (0.010)	1.9×10^{-3}	0.072 (0.005)	4.6×10^{-40}	0.24	2.6×10^{-6}	*GCKR*
rs12239046	C	0.042 (0.018)	1.8×10^{-3}	0.047 (0.006)	1.2×10^{-15}	0.09	0.77	*NLRP3*
rs6734238	G	0.072 (0.017)	4.9×10^{-6}	0.050 (0.006)	1.8×10^{-17}	0.14	0.95	*IL1F10*
rs9987289	A	0.003 (0.031)	3.5×10^{-2}	0.069 (0.011)	3.4×10^{-13}	0.08	0.04	*PPP1R3B*
rs10745954	A	0.018 (0.015)	1.3×10^{-1}	0.039 (0.006)	1.6×10^{-11}	0.06	1.1×10^{-3}	*ASCL1*
rs1800961	C	0.023 (0.026)	3.7×10^{-1}	0.088 (0.015)	2.2×10^{-9}	0.06	0.07	*HNF4A*
rs340029	T	0.004 (0.010)	5.2×10^{-1}	0.032 (0.006)	4.1×10^{-9}	0.08	0.05	*RORA*
rs10521222	C	0.089 (0.028)	1.4×10^{-3}	0.104 (0.015)	8.5×10^{-13}	0.09	0.34	*SALL1*
rs12037222	A	0.035 (0.017)	3.9×10^{-2}	0.045 (0.007)	6.4×10^{-11}	0.06	0.40	*PABPC4*
rs13233571	C	0.049 (0.025)	4.5×10^{-2}	0.054 (0.009)	3.6×10^{-9}	0.08	0.13	*BCL7B*
rs2836878	G	0.013 (0.011)	2.3×10^{-1}	0.032 (0.006)	1.7×10^{-7}	0.05	0.18	*PSMG1*
rs4903031	G	0.001 (0.012)	9.1×10^{-1}	0.032 (0.007)	5.1×10^{-6}	0.04	0.21	*RGS6*

*β coefficient represents 1-unit change in the natural log–transformed CRP (mg/L) per copy increment in the coded allele.
†Median percentage of CRP variance explained by the SNP reported in all participating studies.

Table 3. Association of 3 Suggestive Loci With CRP Levels That Reached Genome-Wide Significance After Combining Discovery and Replication Panel

SNP	Coded Allele	Discovery		Replication		Discovery+Replication		R^2†	*P* for Heterogeneity	Closest Gene
		β* (SE)	*P*	β* (SE)	*P*	β* (SE)	*P*			
rs2847281	A	0.034 (0.007)	1.7×10^{-7}	0.018 (0.016)	4.2×10^{-2}	0.031 (0.006)	2.2×10^{-8}	0.04	0.97	*PTPN2*
rs6901250	A	0.034 (0.007)	1.2×10^{-6}	0.038 (0.015)	1.2×10^{-2}	0.035 (0.006)	4.8×10^{-8}	0.02	0.89	*GPRC6A*
rs4705952	G	0.038 (0.008)	4.1×10^{-6}	0.065 (0.018)	3.0×10^{-4}	0.042 (0.007)	1.3×10^{-8}	0.05	0.47	*IRF1*

*β coefficient represents 1-unit change in the natural log–transformed CRP (mg/L) per copy increment in the coded allele.
†Median percentage of CRP variance explained by the SNP reported in all participating studies.

Genetic Risk Score

To model the cumulative effect of the identified loci, we created a genetic risk score comprising information from the genome-wide significant SNPs. The risk score was computed for each subject by multiplying the number of alleles associated with higher CRP by the β coefficient from the combined meta-analysis and taking the sum over the SNPs. To make the genetic risk score easier to interpret, we rescaled to range from zero (low CRP level) to 100 (high CRP level).

Association With MI and CHD

The association of the genome-wide significant SNPs and the genetic risk score with clinical events was tested in the ARIC study, the Age, Gene/Environment Susceptibility-Reykjavik (AGES) study, the Cardiovascular Health Study (CHS), the FHS, the Rotterdam Study (RS), and the WGHS with the use of incident cases of MI and CHD (ie, occurring after CRP concentrations were measured). Incident MI included fatal and nonfatal MI. Incident CHD included incident fatal and nonfatal MI, fatal CHD, and sudden death. Each study examined the associations with the use of a Cox proportional hazards model adjusted for age and sex. We subsequently combined these results by performing a meta-analysis.

Results

The basic characteristics of the participating studies are shown in Table I in the online-only Data Supplement. Figure I in the online-only Data Supplement shows the QQ plot ($\lambda=1.09$), and Figure II in the online-only Data Supplement presents the *P* values for >2.5 million SNPs across 22 autosomal chromosomes. A total of 953 SNPs in 17 loci exceeded the genome-wide significance threshold ($P<5\times10^{-8}$) (Table 1). Moreover, we found suggestive signals ($P<10^{-5}$) in 47 loci. Sixty-four lead SNPs including 17 SNPs from the genome-wide significant loci and 47 SNPs from the suggestive loci were chosen for the replication stage (Table II in the online-only Data Supplement). Six SNPs close to *CRP*, *APOC1*, *HNF1A*, *LEPR*, *IL6R*, and *IL1F10* exceeded the Bonferroni significance level ($0.05/64=7.8\times10^{-4}$) in the replication stage. In a fixed-effects meta-analysis of the discovery and replication panels, 18 loci showed a genome-wide significant association: 15 loci of the 17 genome-wide significant loci (Table 2) and 3 loci of the 47 suggestive loci (Table 3). In addition to confirming 7 previously reported associations, the genome-wide significant signals marked 11 novel associations within or close to the NLR family, pyrin domain containing 3 (*NLRP3*), interleukin-1 family, member 10 (*IL1F10*), protein phosphatase 1, regulatory (inhibitor) subunit 3B (*PPP1R3B*), hepatocyte nuclear factor 4-α (*HNF4A*), RAR-related orphan receptor A (*RORA*), Sal-like 1 (*SALL1*), poly(A) binding protein, cytoplasmic 4 (inducible form) (*PABPC4*), B-cell chronic lymphocytic leukemia/lymphoma 7B (*BCL7B*), proteasome assembly chaperone 1 (*PSMG1*), protein tyrosine phosphatase, nonreceptor type 2 (*PTPN2*), G protein–coupled receptor, family C, group 6, member A (*GPRC6A*), and interferon regulatory factor 1 (*IRF1*). Furthermore, our meta-analysis excluding the WGHS population (Table III in the online-only Data Supplement) confirmed the association of 7 previously known genes,[9] *CRP*, *APOE* (*APOC1*), *HNF1A*, *LEPR*, *IL6R*, *GCKR*, and *ASCL1*, with CRP levels (Bonferroni significance level: $0.05/7=7.1\times10^{-3}$).

Figure 1 presents the average CRP levels across the genetic risk score in the whole population. Individuals in the highest gene score group had a mean CRP level (4.12 mg/L; 95% confidence interval, 4.96 to 5.25) that was more than double the level observed for individuals in the lowest gene score group (1.40 mg/L; 95% confidence interval, 1.31 to 1.49). The percentage of overall variance in CRP that was explained by the genetic risk score ranged from 1.2% to 10.3% across studies in the discovery and replication panels and was more than 5% in half of the studies.

After adjustment for number of tests, significant heterogeneity was found for rs2794520, rs4420065, rs4129267, rs1260326, and rs10745954 (Tables 2 and 3). Meta-regression was used to explore the source of heterogeneity. Sex was associated with heterogeneity for rs10745954 ($P<2.8\times10^{-5}$) (Table VI in the online-only Data Supplement).

All 18 SNPs that showed genome-wide significant results in the combined meta-analyses were studied for interactions

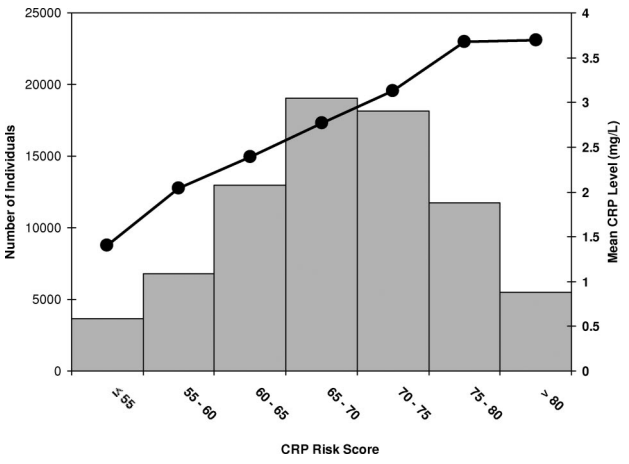

Figure 1. Mean CRP level (right vertical axis) shown as solid black dots connected by solid lines for categories of the genetic risk score. The shaded bars show the distribution of the genetic risk score in the whole population (left vertical axis). The CARdiovascular disease, Living and Aging in Halle (CARLA) Study was not included because of missing values for some of the selected SNPs.

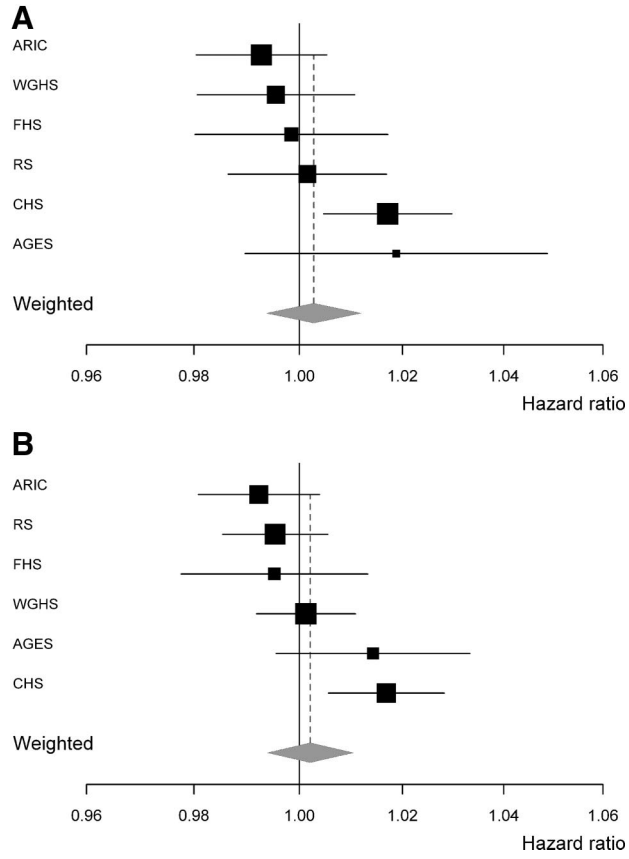

Figure 2. The forest plots show the meta-analysis of the association of the CRP genetic risk score with MI (A) and CHD (B). The horizontal axis indicates the hazard ratio for MI or CHD per unit increase in the rescaled genetic risk score. ARIC indicates Atherosclerosis Risk in Communities; RS, Rotterdam Study; FHS, Framingham Heart Study; WGHS, Women's Genome Health Study; AGES, Age, Gene/Environment Susceptibility-Reykjavik; and CHS, Cardiovascular Health Study.

with age, sex, BMI, and smoking (Table IV in the online-only Data Supplement). After adjustment for the number of tests, we found a significant interaction between BMI and the *LEPR* SNP rs4420065 ($P<2.9\times10^{-6}$).

We examined the association of the SNPs related to CRP with risk of MI and CHD. These studies comprised 1845 cases of MI and 2947 cases of CHD. Neither the individual SNPs nor the combined genetic risk score showed consistent or genome-wide significant associations with risk of clinical events (Figure 2).

Discussion

Through a meta-analysis of GWA scans from 15 cohort studies comprising 66 185 subjects and a replication sample of 16 540 subjects, we identified 18 loci associated with circulating CRP levels and provided evidence of replication for 8 of them. Our results confirm 7 gene-annotated loci reported by Ridker et al.[9] Furthermore, we introduce 11 novel loci associated with CRP levels, annotating *NLRP3*, *IL1F10*, *PPP1R3B*, *HNF4A*, *RORA*, *SALL1*, *PAPBC4*, *BCL7B*, *PTPN2*, *GPRC6A*, and *IRF1*.

A number of these genes including *APOC1*, *HNF1A*, *LEPR*, *GCKR*, *HNF4A*, and *PTPN2* are directly or indirectly related to metabolic regulatory pathways involved in diabetes mellitus. Mutations in *HNF1A* are associated with impaired insulin secretion and maturity-onset diabetes mellitus of the young (MODY) type 3.[19] *HNF4A* is part of a complex regulatory network in the liver and pancreas for glucose homeostasis.[20] Mutations in the *HNF4A* gene cause MODY type 1.[21] *HNF4A* is a transcription factor involved in the expression of several liver-specific genes including *HNF1A*.[21] Defects in the expression of *GCKR* result in deficient insulin secretion.[22] *PTPN2*, which modulates interferon gamma signal transduction at the β cell level,[23] was recently identified as a novel susceptibility gene for type 1 diabetes mellitus.[24] *PTPN2* also is linked to the inflammatory pathway. The nuclear isoform of PTPN2 is a regulator of transcription factor STAT3 in the downstream of interleukin-6 signaling and may affect CRP expression in Hep3B cells.[25]

CRP, *IL6R*, *NLRP3*, *ILF10*, and *IRF1* are associated with CRP levels at least partly through pathways related to innate and adapted immune response. *NLRP3* encodes a member of the NALP3 inflammasome complex.[26] The NALP3 inflammasome triggers an innate immune response and can be activated by endogenous "danger signals," as well as compounds associated with pathogens.[27,28] Activated NALP3 inflammasome functions as an activator of nuclear factor-κB signaling. Nuclear factor-κB is a transcription factor that affects CRP expression in Hep3B cells.[29]

Our genetic risk score explained $\approx$5% of the variation in CRP levels, showing that genetic factors are of importance in determining CRP levels. In comparison, BMI as the main nongenetic determinant of CRP was reported to explain 5% to 7% of the variation in CRP levels in AGES[30] and up to 15% in FHS.[31] Ridker et al reported that 7 SNPs discovered in their study explained 10.1% of the variation in CRP levels after adjustment for age, smoking, BMI, hormone therapy, and menopausal status.[9] However, without adjustment for these covariates, $<$5% of the variation in CRP levels was explained (D. Chasman, PhD, personal written communication, May 2009).

Adipose tissue can induce chronic low-grade inflammation by producing proinflammatory cytokines such as interleukin-6.[32] Therefore, we examined whether adiposity modifies the effect of any of the 18 genes on CRP. We found that BMI modifies the strength of the association between *LEPR* and *CRP*. This interaction was initially found in WGHS.[33]

There is ample evidence that chronic inflammation is involved in atherosclerosis and cardiovascular disease. In this study, we found no association between genetically elevated CRP and risk of CHD. In agreement with our results, Elliott et al[10] reported in a recent study that variations in the *CRP* gene are not associated with risk of MI and CHD, but they found associations of *LEPR*, *IL6R*, and *APOCE-CI-CII* with CHD. However, the lack of association with clinical events in our study could also be due to lack of power.

Our study has the benefit of a large and homogeneous sample size of 82 725 subjects of European ancestry. This enabled us to find novel genes with small effect on CRP level. Furthermore, this large sample size enabled us to study gene-environment interaction, which hitherto has been less

feasible. In contrast to most other studies, we used only incident cases of cardiovascular events from well-defined population-based studies to examine the relation between the identified SNPs and clinical disease. The study has several limitations. Although we identified 18 loci associated with CRP levels, other genetic loci associated with CRP concentrations may still be missed by our study. Six of the genome-wide significant loci from the discovery panel were significant after Bonferroni correction in the replication panel. The other identified loci need replication for confirmation in larger samples. We acknowledge that our genetic risk score is based on our own findings and may be less efficient when used in another population. Finally, we did not fine map the identified loci; we therefore acknowledge that the identified SNPs may be in linkage disequilibrium with non-HapMap variants causally related to CRP levels.

In conclusion, we identified 11 novel loci and confirmed 7 known loci to affect CRP levels. The results highlight immune response and metabolic regulatory pathways involved in the regulation of chronic inflammation, as well as several loci previously unknown to be related to inflammation. Furthermore, *LEPR* was found to affect CRP differently in the presence of low or high BMI, which may lead to new insights in the mechanisms underlying inflammation.

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See the online-only Data Supplement.

Sources of Funding

See the online-only Data Supplement.

Disclosures

Dr Ridker has received research grant support from Roche, AstraZeneca, and Amgen and is listed as a coinventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes mellitus.

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CLINICAL PERSPECTIVE

C-reactive protein (CRP) is a heritable marker of chronic inflammation that is strongly associated with cardiovascular disease. Although environmental factors such as obesity, smoking, and hormone therapy influence levels of serum CRP, genes play an important role in determining serum CRP levels. The advent of genome-wide association studies has provided an opportunity to identify previously unsuspected genetic loci that influence complex traits. In this study, we collected data on >80 000 subjects from 25 studies and identified 18 genetic loci that are associated with serum CRP levels. These genetic loci provide valuable insights into the pathways that affect serum levels of CRP. Although further investigations are needed to understand the exact mechanisms, our findings highlight immune response and metabolic regulatory pathways involved in the regulation of chronic inflammation, as well as several loci previously unknown to be related to inflammation. However, these single-nucleotide polymorphisms were not associated with incident myocardial infarction or coronary heart disease, either individually or in combination. A better knowledge of the molecular mechanisms that control serum CRP levels may lead to a deeper understanding of the complex interactions underlying the inflammatory response in cardiovascular disease.