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

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Meta-analysis of genome-wide association studies in >80,000 subjects identifies multiple loci for C-reactive protein levels

Abbas Dehghan, MD PhD^{1,2,*}, Josée Dupuis, PhD^{3,4,*}, Maja Barbalic, PhD^{5,*}, Joshua C Bis, PhD^{6,*}, Gudny Eiriksdottir, MSc^{7,*}, Chen Lu, M.A.³, Niina Pellikka, BEng⁸, Henri Wallaschofski, MD⁹, Johannes Kettunen, MSc¹⁰, Peter Henneman, MSc¹¹, Jens Baumert, PhD¹², David P Strachan, MD¹³, Christian Fuchsberger, PhD¹⁴, Veronique Vitart, PhD¹⁵, James F Wilson, BSc DPhil¹⁶, Guillaume Paré, MD MSc¹⁷, Silvia Naitza, PhD¹⁸, Megan E Rudock, PhD¹⁹, Ida Surakka, BSc²⁰, Eco JC de Geus, PhD²¹, Behrooz Z Alizadeh, PhD²², Jack Guralnik, MD, PhD²³, Alan Shuldiner, MD²⁴, Toshiko Tanaka, PhD^{25,26}, Robert YL Zee, PhD²⁷, Renate B Schnabel, MD MSc²⁸, Vijay Nambi, MD²⁹, Maryam Kavousi, MD MSc^{1,2}, Samuli Ripatti, PhD²⁰, Matthias Nauck, MD⁹, Nicholas L Smith, PhD^{30,31}, Albert V Smith, PhD⁷, Jouko Sundvall, PhD³², Paul Scheet, PhD³³, Yongmei Liu, MD PhD¹⁹, Aimo Ruukonen, MD PhD³⁴, Lynda M Rose, MSc²⁷, Martin G Larson, ScD⁴, Ron C Hoogeveen, PhD²⁹, Nelson B Freimer, MD¹⁷, Alexander Teumer, Dipl-Math³⁵, Russell P Tracy, PhD³⁶, Lenore J Launer, PhD²³, Julie E Buring, DSc²⁷, Jennifer F Yamamoto, MA⁴, Aaron R Folsom, MD MPH³⁷, Eric JG Sijbrands, MD PhD³⁸, James Pankow, PhD³⁷, Paul Elliott, MBBS PhD FMedSci³⁹, John F Keaney, MD⁴, Wei Sun, MD PhD⁴⁰, Antti-Pekka Sarin, BSc²⁰, João D Fontes, MD⁴, Sunita Badola, MSc⁴¹, Brad C Astor, PhD MPH²⁹, Albert Hofman, MD PhD^{1,2}, Anneli Pouta, MD PhD⁴², Karl Werdan, MD⁴³, Karin H Greiser, MD^{44,45}, Oliver Kuss, PhD⁴⁴, Henriette E Meyer zu Schwabedissen, MD⁴⁶, Joachim Thiery, MD⁴⁷, Yalda Jamshidi, PhD^{48,49}, Ilja M Nolte, PhD²², Nicole Soranzo, PhD⁵⁰, Timothy D Spector, MD MSc FRCP⁵¹, Henry Völzke, MD⁵², Alexander N Parker, PhD⁴¹, Thor Aspelund, PhD^{7,53}, David Bates, MD MSc²⁷, Lauren Young⁴¹, Kim Tsui⁴¹, David S Siscovick, MD MPH⁵⁴, Xiuqing Guo, PhD⁵⁵, Jerome I Rotter, MD⁵⁵, Manuela Uda, PhD¹⁸, David Schlessinger, PhD⁵⁶, Igor Rudan, MD^{16,57}, Andrew A Hicks, PhD¹⁴, Brenda W Penninx, PhD⁵⁸, Barbara Thorand, PhD MPH¹², Christian Gieger, PhD MS¹², Joe Coresh, MD PhD²⁹, Gonneke Willemsen, PhD²¹, Tamara B Harris, MD MSc²³, Andre G Uitterlinden, PhD^{2,38}, Marjo-Riitta Järvelin, MD PhD^{39,42,59}, Kenneth Rice, PhD⁶⁰, Dörte Radke⁵², Veikko Salomaa, MD PhD⁶¹, Ko Willems van Dijk, PhD⁶², Eric Boerwinkle, PhD⁵, Ramachandran S Vasan, MD^{4,63}, Luigi Ferrucci, MD PhD²⁵, Quince D Gibson, MBA²⁴, Stefania Bandinelli, MD⁶⁴, Harold Snieder, PhD²², Dorret I Boomsma, PhD²¹, Xiangjun Xiao³³, Harry Campbell, MBChB MD¹⁶, Caroline Hayward, PhD¹⁵, Peter P Pramstaller, MD^{14,65,66}, Cornelia M van Duijn, PhD^{1,2}, Leena Peltonen, MD PhD¹⁰, Bruce M Psaty, MD PhD^{54,67}, Vilmundur Gudnason, MD PhD^{7,53}, Paul M Ridker, MD MPH²⁷, Georg Homuth, PhD^{35,*}, Wolfgang Koenig, MD, PhD^{68,*}, Christie M Ballantyne, MD^{29,*}, Jacqueline CM Witteman, PhD^{1,2,*}, Emelia J Benjamin, MD, ScM^{4,63,*}, Markus Perola, MD, PhD^{8,*}, and Daniel I Chasman, PhD^{27,*}

¹Correspondence: Jacqueline CM Witteman, Erasmus Medical Center, Dr Molewaterplein 50, 3015 GE Rotterdam, The Netherlands, Phone: 0031107087488, Fax: 0031107044657, j.witteman@erasmusmc.nl. ²Daniel I. Chasman, Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston MA 02215, Phone: 0016172780821, Fax: 0016177313843, dchasman@rics.bwh.harvard.edu.

*Individuals contributed equally to the project

†Prof Peltonen passed away in March, 2010.

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¹Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands ²Member of Netherlands Consortium for Healthy Aging (NCHA) sponsored by Netherlands Genomics Initiative (NGI), Leiden, The Netherlands ³Department of Biostatistics, School of Public Health, Boston University, Boston, MA, USA ⁴The NHLBI and Boston University's Framingham Heart Study, Framingham, MA, USA ⁵Human Genetics Center and Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, TX, USA ⁶Department of Medicine, University of Washington, Seattle, WA USA ⁷Icelandic Heart Association, Kopavogur, Iceland ⁸Unit of Public Health Genomics, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland ⁹Institute of Clinical Chemistry and Laboratory Medicine, University of Greifswald, Germany ¹⁰Department of Human Genetics, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK ¹¹Department of Human Genetics, Leiden University Medical Centre, Leiden, The Netherlands ¹²Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany ¹³Division of Community Health Sciences, St George's University of London, London, UK ¹⁴Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Bolzano, Italy. Affiliated Institute of University of Lübeck, Lübeck, Germany ¹⁵MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, UK ¹⁶Centre for Population Health Sciences, University of Edinburgh, Edinburgh EH89AG, UK ¹⁷Center for Cardiovascular Disease Prevention, Harvard Medical School, Boston, MA, USA ¹⁸Istituto di Neurogenetica e Neurofarmacologia, Consiglio Nazionale delle Ricerche, Cagliari, Italy ¹⁹Department of Epidemiology and Prevention, Wake Forest University School of Medicine, Wake Forest, USA ²⁰Institute for Molecular Medicine Finland FIMM, University of Helsinki, Helsinki, Finland ²¹Department of Biological Psychology, VU University, Amsterdam, The Netherlands ²²Unit of Genetic Epidemiology and Bioinformatics, Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands ²³Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging, NIH, Bethesda, MD, USA ²⁴Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, Maryland, USA ²⁵Clinical Research Branch, National Institute on Aging, Baltimore, Maryland, USA ²⁶Medstar Research Institute, Baltimore MD, USA ²⁷Division of Preventive Medicine, Brigham and Women's Hospital, Boston, USA ²⁸Department of Medicine, Johannes Gutenberg-University, Mainz, Germany ²⁹Department of Medicine, Baylor College of Medicine and Center for Cardiovascular Prevention, Methodist DeBakey Heart and Vascular Center, Houston, USA ³⁰Department of Epidemiology, University of Washington, Seattle, WA, USA ³¹Seattle Epidemiologic Research and Information Center of the Department of Veterans Affairs Office of Research and Development, Seattle, WA, USA ³²Unit of Disease Risk, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland ³³Department of Epidemiology, MD Anderson Cancer Center, University of Texas, Houston, Texas, USA ³⁴Department of Clinical Chemistry, University of Oulu, Oulu, Finland ³⁵Interfaculty Institute for Genetics and Functional Genomics, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany ³⁶Departments of Pathology and Biochemistry, Colchester Research Facility, Colchester, VT, USA ³⁷Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, USA ³⁸Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands ³⁹MRC-HPA Centre for Environment and Health, Department of Epidemiology and Biostatistics, School of Public Health, St Mary's Campus, Imperial College London, London, UK ⁴⁰Department of Biostatistics, Department of Genetics, University of North Carolina, Chapel Hill, NC, USA ⁴¹Amgen, Inc, Cambridge, MA, USA ⁴²Department of Life course and Services, National Institute for Health and Welfare, Helsinki, Finland ⁴³Department of Medicine III, Martin-Luther-University Halle-Wittenberg, Germany ⁴⁴Institute for Medical Epidemiology, Biostatistics, and Informatics, Martin-Luther-University Halle-Wittenberg, Germany ⁴⁵Division of Cancer Epidemiology, German Cancer Research Centre, Heidelberg, Germany ⁴⁶Department of Pharmacology, Ernst-Moritz-Arndt-University of Greifswald, Germany ⁴⁷Institute of Laboratory

Medicine, Clinical Chemistry and Molecular Diagnostics (ILM), University of Leipzig, Germany
⁴⁸Division of Clinical Developmental Sciences, St George's University of London, London, UK
⁴⁹Department of Twin Research and Genetic Epidemiology Unit, St Thomas' Campus, King's College London, St Thomas' Hospital, London, UK
⁵⁰Wellcome Trust Sanger Institute, United Kingdom
⁵¹Department of Twin Research and Genetic Epidemiology Unit, King's College London, United Kingdom
⁵²Institute for Community Medicine, Ernst-Moritz-Arndt-Universität Greifswald, Greifswald, Germany
⁵³University of Iceland, Reykjavik, Iceland
⁵⁴Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, WA, USA
⁵⁵Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA
⁵⁶Laboratory of Genetics, National Institute on Aging, Baltimore, MD 21224, USA
⁵⁷Croatian Centre for Global Health, University of Split Medical School, Split, Croatia
⁵⁸Department of Psychiatry/EMGO Institute/Neuroscience Campus, VU University Medical Centre, Amsterdam, The Netherlands
⁵⁹Institute of Health Sciences and Biocenter Oulu, Faculty of Medicine, University of Oulu, Oulu, Finland
⁶⁰Department of Biostatistics, University of Washington, Seattle, WA, USA
⁶¹Unit of Chronic Disease Epidemiology and Prevention, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland
⁶²Departments of Internal Medicine and Human Genetics, Leiden University Medical Centre, Leiden, The Netherlands
⁶³Preventive Medicine and Cardiology Sections, Department of Medicine, Boston University School of Medicine, Boston, MA, USA
⁶⁴Geriatric Unit, Azienda Sanitaria Firenze, Florence, Italy
⁶⁵Department of Neurology, General Central Hospital, Bolzano, Italy
⁶⁶Department of Neurology, University of Lübeck, Lübeck, Germany
⁶⁷Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA
⁶⁸Department of Internal Medicine II - Cardiology, University of Ulm Medical Center, Ulm, Germany

Abstract

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

Methods and Results—We performed a genome wide association (GWA) 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 panel comprising 16,540 individuals from ten independent studies. We found 18 genome-wide significant loci and we provided evidence of replication for eight of them. Our results confirm seven 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*), 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 significant interaction of body mass index (BMI) with *LEPR* ($p < 2.9 \times 10^{-6}$). A weighted genetic risk score that was developed to summarize the effect of risk alleles was strongly associated with CRP levels and explained approximately 5% of the trait variance; however, there was no evidence for these genetic variants explaining the association of CRP with coronary heart disease.

Conclusion—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.

Keywords

genome-wide association; C-reactive protein; inflammation; epidemiology; coronary heart disease

C-reactive protein (CRP) is a general marker of systemic inflammation. High CRP levels are associated with increased risks of mortality¹ and major diseases including diabetes mellitus², hypertension³, coronary heart disease⁴, and stroke⁵. The heritability of CRP levels is estimated to be 25–40%^{6–8}, suggesting that genetic variation is a major determinant of CRP levels. A genome-wide association (GWA) study in 6,345 women found seven loci associated with CRP levels⁹. 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 alpha (*HNF1A*), apolipoprotein E (*APOE*), and achaete-scute complex homolog 1 (*ASCL1*). Findings from other genome-wide association studies did not extend the number of loci related to CRP^{10,11}.

In this study, we set out 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 ten independent studies. To investigate whether the genetic variants identified interact with non-genetic determinants of CRP such as age, sex, smoking and body mass index (BMI) we examined gene-environment interactions. Finally, it is still unknown to what extent the genes associated with circulating CRP levels, individually or jointly, affect the risk of cardiovascular diseases. To address this question we examined the association of genetic variants with myocardial infarction (MI) and coronary heart disease (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 Supplementary Tables 1. Baseline measures of clinical and demographic characteristics were obtained at the time of cohort entry except for B58C, FHS, NFBC66, and ARIC in which measures were obtained at the time of phenotype measurement.

GWA analysis

Genome-wide scans were performed independently in each cohort using various genotyping technologies (Supplementary Table 7). Each study carried out association analysis using the genotype-phenotype data within their cohort. Each study imputed SNPs with reference to HapMap release 22 CEU and provided results for a common set of SNPs for meta-analysis. Except for FHS, all studies conducted a linear regression analysis adjusted for age (except for NFBC66 and B58C), sex (except for WGHS), and site of recruitment (if necessary) for all SNPs based on an additive genetic model. In the ERF study, adjustments for the family structure in the GWA analysis was based on the model residuals in the score test, which accounted for pedigree structure as implemented in GenABEL software¹² function “mmscore”¹³. In FHS, a linear mixed effects model was employed using 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 effects¹⁴. In each study, we estimated the genomic inflation rate, stated as lambda (λ_{gc}), by comparing each study's median chi-square value to 0.4549, the median chi-square for the null distribution¹⁵ (Supplementary Table 1). P-values for each cohort were adjusted for underlying population structure using the genomic inflation coefficient.

Discovery panel and the replication panel

The 15 study discovery panel included five studies from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium¹⁶, four studies from the European Special Population Network (EUROSPAN), and six additional independent studies comprising 66,185 participants. The replication studies included ten independent studies and 16,540 participants.

Meta-analysis

To calculate the combined p-values and beta coefficients we used an inverse-variance weighted fixed-effects meta-analysis. We used METAL, a software package designed to perform meta-analysis on GWA datasets¹⁷. We applied an *a priori* threshold 5.0×10^{-8} for genome-wide significance¹⁸. When more than one 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 ($p < 5 \times 10^{-8}$) loci and sought additional evidence for suggestive loci $5 \times 10^{-8} < p < 10^{-5}$) 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 al⁹ was based on part of the WGHS population. In order 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 using Cochran's Q test. Based on Bonferroni adjustment for 18 tests, heterogeneity was considered significant at a p-value less than 2.8×10^{-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 beta and p-values across studies for each of the top SNPs. Based on Bonferroni adjustment for 72 tests (18 SNPs for four environmental factors), we used a significance threshold at 6.9×10^{-4} .

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 beta 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 ARIC, AGES, CHS, FHS, RS, and WGHS using incident cases of MI and CHD (i.e. occurring after CRP concentrations were measured). Incident MI included fatal and non-fatal MI. Incident CHD included incident fatal and non-fatal MI, fatal CHD and sudden death. Each study examined the associations using 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 Supplementary Table 1. Supplementary Figure 1 shows the QQ-plot ($\lambda = 1.09$) and Supplementary Figure 2 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 ($p < 5 \times 10^{-8}$) (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 (Supplemental Table 2). Six SNPs close to *CRP*, *APOC1*, *HNF1A*, *LEPR*, *IL6R*, and *IL1F10* exceeded the Bonferroni significance level ($0.05/64 = 7.8 \times 10^{-4}$) in the replication stage. In a fixed-effects meta-analysis of the discovery and replication panel, 18 loci showed a genome-wide significant association; 15 loci out of the 17 genome-wide significant loci (Table 2) and three loci out of the 47 suggestive loci (Table 3). In addition to confirming seven 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, alpha (*HNF4A*), RAR-related orphan receptor A (*RORA*), Sal-like 1 (*SALL1*), poly(A) binding protein, cytoplasmic 4 (inducible form) (*PABPC4*), B-cell CLL/lymphoma 7B (*BCL7B*), proteasome assembly chaperone 1 (*PSMG1*), protein tyrosine phosphatase, non-receptor 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 (Supplementary Table 3) confirmed the association of seven previously known genes⁹, *CRP*, *APOE* (*APOC1*), *HNF1A*, *LEPR*, *IL6R*, *GCKR*, and *ASCL1* with CRP levels (Bonferroni significance level: $0.05/7 = 7.1 \times 10^{-3}$).

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% CI: 4.96–5.25) that was more than double the level observed for individuals in the lowest gene score group (1.40 mg/L; 95% CI: 1.31–1.49). The percentage of overall variance in CRP which was explained by the genetic risk score ranged from 1.2% to 10.3% across studies in the discovery and replication panel 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 & 3). Meta-regression was used to explore the source of heterogeneity. Sex was associated with heterogeneity for rs10745954 ($p < 2.8 \times 10^{-5}$) (Supplementary Table 6).

All 18 SNPs that showed genome-wide significant results in the combined meta-analyses were studied for interactions with age, sex, BMI and smoking (Supplementary Table 4). After adjustment for the number of tests we found a significant interaction between BMI and the *LEPR* SNP, rs4420065 ($p < 2.9 \times 10^{-6}$).

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 eight of them. Our results confirm seven gene annotated loci reported by Ridker et al⁹. 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. Mutations in *HNF1A* are associated with impaired insulin secretion and maturity onset diabetes of the young (MODY) type 3¹⁹. *HNF4A* is part of a complex regulatory network in the liver and pancreas for glucose homeostasis²⁰. Mutations in the *HNF4A* gene cause MODY type 1²¹. *HNF4A* is a transcription factor involved in the expression of several liver-specific genes including *HNF1A*²¹. Defects in the expression of *GCKR* results in deficient insulin secretion²². *PTPN2*, which modulates interferon gamma signal transduction at the beta cell level²³, was recently identified as a novel susceptibility gene for type 1 diabetes²⁴. *PTPN2* also is linked to the inflammatory pathway. The nuclear isoform of *PTPN2* is a regulator of transcription factor STAT3 in the downstream of IL-6 signaling and may affect CRP expression in Hep3B cells²⁵.

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 complex²⁶. 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 NF-kappaB signaling. NF-kappaB is a transcription factor which affects CRP expression in Hep3B cells²⁹.

Our genetic risk score explained approximately 5% of the variation in CRP levels, showing that genetic factors are of importance in determining CRP levels. In comparison, BMI as the main non-genetic determinant of CRP was reported to explain 5–7% of the variation in CRP levels in AGES³⁰ and up to 15% in FHS³¹. Ridker et al reported that seven 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. However, without adjustment for these covariates, less than 5% of the variation in CRP levels was explained (D. Chasman, personal communication).

Adipose tissue can induce chronic low-grade inflammation by producing proinflammatory cytokines such as interleukin-6³². 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 WGHS³³.

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, Elliot et al 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 CHD¹⁰. 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 homogenous 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 render less efficient when used in another population. Finally, we did not fine map the identified loci; so we 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 seven 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supplementary text

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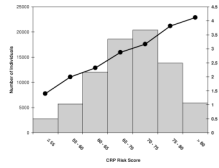


Figure 1.

This figure shows the mean CRP level (right vertical axis) 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 CARLA Study was not included due to missing values for some of the selected SNPs.

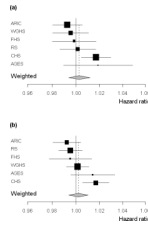


Figure 2. The forest plots show the meta-analysis of the association of the CRP genetic risk score with MI(a) and CHD(b). The horizontal axis indicates the hazard ratio for MI or CHD per unit increase in the rescaled genetic risk score.

Table 1

Association of 17 genome-wide significant loci with CRP levels in the discovery panel

SNP	Band	Significant SNPs	Coded allele	Allele frequency	Beta* (SE)	P-value	Gene
rs2794520	1q23.2	121	C	0.66	0.193 (0.007)	9.5×10^{-189}	<i>CRP</i>
rs4420638	19q13.32	16	A	0.80	0.240 (0.010)	2.1×10^{-129}	<i>APOC1</i>
rs1183910	12q24.31	186	G	0.67	0.152 (0.007)	3.3×10^{-113}	<i>HNF1A</i>
rs4420065	1p31.3	291	C	0.61	0.111 (0.007)	3.2×10^{-64}	<i>LEPR</i>
rs4129267	1q21.3	90	C	0.60	0.094 (0.007)	1.1×10^{-47}	<i>IL6R</i>
rs1260326	2q13	54	T	0.41	0.089 (0.007)	5.4×10^{-43}	<i>GCKR</i>
rs12239046	1q44	13	C	0.61	0.048 (0.007)	1.6×10^{-13}	<i>NLRP3</i>
rs6734238	2p23.3	92	G	0.42	0.047 (0.007)	3.4×10^{-13}	<i>IL1F10</i>
rs9987289	8p23.1	15	G	0.90	0.079 (0.011)	2.3×10^{-12}	<i>PPP1R3B</i>
rs10745954	12q23.2	22	A	0.50	0.043 (0.006)	1.6×10^{-11}	<i>ASCL1</i>
rs1800961	20q13.12	1	C	0.95	0.120 (0.018)	2.3×10^{-11}	<i>HNF4A</i>
rs340029	15q22.2	25	T	0.62	0.044 (0.007)	2.6×10^{-11}	<i>RORA</i>
rs10521222	16q12.1	6	C	0.94	0.110 (0.017)	1.3×10^{-10}	<i>SALL1</i>
rs12037222	1p32.4	11	A	0.24	0.047 (0.008)	4.5×10^{-10}	<i>PABPC4</i>
rs13233571	7q11.23	7	C	0.86	0.054 (0.010)	2.8×10^{-8}	<i>BCL7B</i>
rs2836878	21q22.2	2	G	0.72	0.040 (0.007)	4.0×10^{-8}	<i>PSMG1</i>
rs4903031	14q24.2	1	G	0.21	0.046 (0.008)	4.6×10^{-8}	<i>RG36</i>

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

Table 2

Association of 17 genome-wide significant loci with CRP levels in the replication panel and combined with the discovery results

SNP	Coded allele	Replication		Discovery + replication		R-square ^{**}	P-value for heterogeneity	Closest Gene
		Beta [*] (SE)	P-value	Beta [*] (SE)	P-value			
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

* Beta coefficient represents one 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 three suggestive loci with CRP levels that reached genome-wide significance after combining discovery and replication panel

SNP	Coded allele	Discovery		Replication		Discovery + replication		R-square**	P-value for heterogeneity	Closest Gene
		Beta* (SE)	P-value	Beta* (SE)	P-value	Beta* (SE)	P-value			
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	<i>PTPN2</i>
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	<i>GPRC6A</i>
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	<i>IRF1</i>

* Beta coefficient represents one 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