IBBJ

Spring 2018, Vol 4, No 2

Short Communication

The Single Nucleotide Polymorphisms in the C-reactive Protein Gene: are they Biomarkers of Cardiovascular Risk?

Alexander Berezin*

Internal Medicine Department of Internal Medicine, State Medical University for Zaporozhye, Zaporozhye, Ukraine.

Submitted 14 Jan 2018; Accepted 4 Feb 2018; Published 4 Mar 2018

Recent pre-clinical and clinical studies have revealed the C-reactive protein gene (CRP) is related to the degree of acute rise in plasma C-reactive protein (CRP) levels. Moreover, single nucleotide polymorphisms (SNPs) in the CRP gene could associate with increased risk of cancer, atherosclerosis, diabetes mellitus, bowel disease, rheumatoid arthritis, psoriasis, obstructive pulmonary disease, periodontitis, nonalcoholic fatty liver disease and cardiovascular (CV) diseases. Less is known about the role of variabilities of circulating levels of CRP due to SNPs as an individual biological marker of CV risk and poor clinical outcomes due to CV reasons. The results of clinical trials and some meat-analysis are controversial in this issue. The short commentary is depicted the possible role of SNPs in CRP gene as a personified biological marker of CV risk. It has concluded that the inconsistent results in determination of the predictive role of SNPs in CRP gene as a biological marker of CV disease and CV events require more investigations.

Keywords: Cardiovascular risk, biological markers, C-reactive protein, single nucleotide polymorphisms, prognosis, prediction

There is a large body of evidence that there are possible associations between selected single nucleotide polymorphisms (SNPs) in genes involved in systemic inflammation reaction, and disease development (1, 2). In this context, plasma levels of systemic inflammation biomarkers might be extremely variable depending on immune phenotypes of cells (CD8dim, GZB+, CD13+ and CD56+) that are involved into immunocom-promised state and regulate the production of pro-inflammatory cytokines, such as C-reactive protein (CRP) (3). CRP is predominantly secreted by the liver and adipose tissues in response to inflammatory stress, and is predominantly regulated by interleukin (IL)-6 and some chemokines produced by a wide spectrum of immune cells. Despite the fact that *CRP* rs1205 polymorphism is associated with circulating plasma CRP levels and cardiovascular disease susceptibility in some populations, there is evidence that several mutant alleles of *IL-1* and *IL-6* genes may promote an elevated level of CRP regardless of SNPs presentation in *CRP* gene (4). Numerous clinical studies have revealed that SNPs in the *CRP* gene are associated with increased risk of cancer, atherosclerosis, diabetes mellitus, bowel disease, rheumatoid arthritis, psoriasis, obstructive pulmonary disease, periodontitis, nonalcoholic fatty

*Correspondence: Internal Medicine Department, State Medical University for Zaporozhye, Zaporozhye, Ukraine.
E-mail: aeberezin@gmail.com

[Downloaded from ibbj.org on 2026-11-25]

liver disease, and cardiovascular diseases (5-9). However, *CRP* genotype mediated rather CRP levels at acute phase of inflammation than at constitutional levels beyond antigen stimulation that is one of intriguing facts explaining controversial results of numerous pre-clinical and clinical studies depicting this issue (10). On the other hand, the polymorphisms of *CRP* were found to be in mild-to-moderate association with the basal CRP levels in healthy men and women. Current evidence confirmed that cardiovascular risk factors including lipids' metabolism may correspond to CRP levels, and thereby directly affect local inflammation especially in the plaques, sub-intima of vascular walls, kidney, and adipose tissues (11). Interestingly, low 25-hydroxyvitamin D level was found to be associated with SNPs in *CRP* gene and thereby may mediate lowered concentration of CRP in plasma (12). The average CRP level in plasma was significantly higher in the smokers, with the highest level found among those with the *CRP* rs1800947 CC genotype (13). These facts illustrate the interrelation between SNPs in *CRP* gene and numerous traditional cardiovascular risk factors. Whether SNPs in *CRP* gene are powerful individual predictor of cardiovascular disease and poor clinical outcomes in patients with established cardiovascular disease is not fully clear (14). In Framingham heart study twelve clinical covariates (body mass index, diabetes mellitus, obesity, hypertension, heart failure, etc.) explained 26% of the individual variability in CRP level in the participants (15). Moreover, a triallelic SNP in *CRP* gene (C-->T-->A), located in the promoter sequence, explained 1.4% of total serum CRP variation, and haplotypes harboring the minor T and A alleles of the SNP were closely associated with higher CRP level (15). In a meta-analysis performed by Zhu et al (2013) (16) *CRP* rs3093059 (T>C) polymorphism was found as a marker of lowered risk of myocardial infarction, especially among Asian populations. However, similar associations were not observed in *CRP* rs1800947 (G>C) and rs2794521 (G>A) polymorphisms (all P> 0.05) among both Asian and Caucasian populations (16). González-Giraldo et al. (2016) (17) in a meta-analysis of clinical trials did not find significant associations between SNPs in *CRP* gene reported as rs1800947 (5 studies) and rs1205 (3 studies), and a risk of ischemic stroke. Another meta-analysis has revealed that the *CRP* +1059G/C polymorphism did not demonstrate a significant association with susceptibility to coronary artery disease in Caucasian, Asian and African populations (18). Elliott et al. (2009) (19) have shown that rs7553007 in *CRP* gene was strongly associated with coronary artery disease, but a concordance between the effect on coronary artery disease risk of *CRP* genotypes and CRP levels argued against a causal association of *CRP* with coronary artery disease. In contrast, Kolz et al. (2008) (20) reported two polymorphisms (rs1800947 and rs1205) within the *CRP* gene, of which the minor alleles were strongly associated with lower levels of CRP protein and increased survival after myocardial infarction. It has suggested that increased plasma levels of CRP were associated with higher rates of acute and / or recurrent coronary atherothrombotic events, while this was not found in stable coronary artery disease (21). However, CRP has been reported in number of studies to be a risk factor for cardiovascular disease and to have prognostic impact in patients with coronary artery disease, although a genetic variation in *CRP* and risk of cardiovascular disease were related modestly. Probably, there is need to reassess the role of CRP variability as a biological marker in general population and discover novel indicators of the individual cardiovascular risk (22-24). Indeed, Schulz et al. (2016) (25) added rs1800947 in the *CRP* gene to the elevated concentration of the CRP (⩾5mg/L) into predictive model of cumulative cardiovascular events (cardiovascular death, death from stroke, myocardial infarction, and stroke/TIA). They found that this novel model was superior to standard model (CRP ⩾5mg/L) within three years follow-up. Future large clinical studies are required

[Downloaded from ibbj.org on 2026-11-25]

to identify additional genetic risk factors for cardiovascular disease in different populations. In conclusion, inconsistent results in determination of the predictive role of SNPs in *CRP* gene as a biological marker of cardiovascular disease and cardiovascular events require more investigations. Probably, ethnic and race particularities are the main factors contributing to higher individual variability in CRP concentrations in different population. Finally, it is concerned that SNPs in *CRP* gene are promising biomarkers for cardiovascular risk stratifications.

Conflict of interest

The authors declare that they have no competing interest.

References

1. Markt S C, Rider J R, Penney K L, et al. Genetic variation across C-reactive protein and risk of prostate cancer. Prostate. 2014;74:1034-42.

2. Hage F G and Szalai A J. The role of C-reactive protein polymorphisms in inflammation and cardiovascular risk. Curr Atheroscler Rep. 2009;11:124-30.

3. Berezin A. Prognostication in Different Heart Failure Phenotypes: The Role of Circulating Biomarkers. J Circ Biomark. 2016;5:6.

4. Dehghan A, Dupuis J, Barbalic M, et al. Meta-analysis of genome-wide association studies in >80 000 subjects identifies multiple loci for C-reactive protein levels. Circulation. 2011;123:731-8.

5. Nimptsch K, Aleksandrova K, Boeing H, et al. Association of CRP genetic variants with blood concentrations of C-reactive protein and colorectal cancer risk. Int J Cancer. 2015;136:1181-92.

6. Danik J S and Ridker P M. Genetic determinants of C-reactive protein. Curr Atheroscler Rep. 2007;9:195-203.

7. Henderson P, Kennedy N A, Van Limbergen J E, et al. Serum C-reactive protein and CRP genotype in pediatric inflammatory bowel disease: influence on phenotype, natural history, and response to therapy. Inflamm Bowel Dis. 2015;21:596-605.

8. Papaoikonomou S, Tousoulis D, Tentolouris N, et al. Genetic Variant of the C-reactive Protein Gene and Prevalence of Peripheral Arterial Disease in Patients with Type 2 Diabetes Mellitus. J Diabetes Metab. 2015;6.

9. Nasibullin T R, Yagafarova L F, Yagafarov I R, et al. Combinations of Polymorphic Markers of Chemokine Genes, Their Receptors and Acute Phase Protein Genes As Potential Predictors of Coronary Heart Diseases. Acta Naturae. 2016;8:111-6.

10. Nath A P, Ritchie S C, Byars S G, et al. An interaction map of circulating metabolites, immune gene networks, and their genetic regulation. Genome Biol. 2017;18:146.

11. Wang JR, Zhang YL. Association between ATP-binding cassette transporter A1 R219K gene polymorphisms and acute mocardial infarction. Academic Journal of Chinese PLA Medical School. 2013:777–78.

12. Myburgh P H, Towers G W, Kruger I M, et al. CRP Genotypes Predict Increased Risk to Co-Present with Low Vitamin D and Elevated CRP in a Group of Healthy Black South African Women. Int J Environ Res Public Health. 2018;15:111.

13. Luetragoon T, Rutqvist L E, Tangvarasittichai O, et al. Interaction among smoking status, single nucleotide polymorphisms and markers of systemic inflammation in healthy individuals. Immunology. 2018;154:98-103.

14. Omland T and White H D. State of the Art: Blood Biomarkers for Risk Stratification in Patients with Stable Ischemic Heart Disease. Clin Chem. 2017;63:165-76.

15. Kathiresan S, Larson M G, Vasan R S, et al. Contribution of clinical correlates and 13 C-reactive protein gene polymorphisms to interindividual variability in serum C-reactive protein level. Circulation. 2006;113:1415-23.

16. Zhu Y, Liu T, He H, et al. C-reactive protein gene polymorphisms and myocardial infarction risk: a meta-analysis and meta-regression. Genet Test Mol Biomarkers. 2013;17:873-80.

17. Gonzalez-Giraldo Y, Barreto G E, Fava C, et al. Ischemic Stroke and Six Genetic Variants in CRP, EPHX2, FGA, and NOTCH3 Genes: A Meta-Analysis. J Stroke Cerebrovasc Dis. 2016;25:2284-9.

18. Li J F, Peng D Y, Ling M, et al. Evaluation of Adenosine Triphosphate-Binding Cassette Transporter A1 (ABCA1) R219K and C-Reactive Protein Gene (CRP) +1059G/C Gene Polymorphisms in Susceptibility to Coronary Heart Disease. Med Sci Monit. 2016;22:2999-3008.

[Downloaded from ibbj.org on 2026-11-25]

19. Elliott P, Chambers J C, Zhang W, et al. Genetic Loci associated with C-reactive protein levels and risk of coronary heart disease. JAMA. 2009;302:37-48.

20. Kolz M, Koenig W, Muller M, et al. DNA variants, plasma levels and variability of C-reactive protein in myocardial infarction survivors: results from the AIRGENE study. Eur Heart J. 2008;29:1250-8.

21. Suk Danik J, Chasman D I, Cannon C P, et al. Influence of genetic variation in the C-reactive protein gene on the inflammatory response during and after acute coronary ischemia. Ann Hum Genet. 2006;70:705-16.

22. Berezin AE, Kremzer A A, Martovitskaya Y V, et al. The utility of biomarker risk prediction score in patients with chronic heart failure. Clin Hypertens. 2015;22:3.

23. Berezin A E. Diabetes mellitus related biomarker: The predictive role of growth-differentiation factor-15. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2016;10:S154-S7.

24. Berezin A E. Up-to-date clinical approaches of biomarkers' use in heart failure. Biomedical Research and Therapy. 2017;4:1344-73.

25. Schulz S, Lüdike H, Lierath M, et al. C-reactive protein levels and genetic variants of CRP as prognostic markers for combined cardiovascular endpoint (cardiovascular death, death from stroke, myocardial infarction, and stroke/TIA). Cytokine. 2016;88:71-6.

[Downloaded from ibbj.org on 2026-11-25]