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

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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 risk 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 immunocompromised state and regulate the production of proinflammatory 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

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-tomoderate 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 kidney, and adipose tissues (11). walls. 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  $(\geq 5 \text{mg/L})$  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  $\geq$  5mg/L) within three years follow-up. Future large clinical studies are required

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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.

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