

## Can C-reactive Protein Genetic Variants Identify Patients with Higher and Lower Cardiovascular Risk?

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### Abstract

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 meta-analysis are controversial in this issue. The short commentary is depicted the possible role of SNPs in CRP gene as a personalized biological marker of CV risk.

**Keywords:** Cardiovascular risk; Biological markers; C-reactive protein; Single nucleotide polymorphisms; Prognosis; Prediction

### Short Communication

There is a large body of evidence that there are the possible interactions among selected single nucleotide polymorphisms (SNPs) in genes associated with systemic inflammation reaction [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 immune-compromised state and regulate producing of pro-inflammatory cytokines, such as C-reactive protein (CRP) [3]. CRP blood level closely relates to CRP genetic variants (SNPs) and it could be a good candidate for personal biological marker of cardiovascular disease (CVD) because recent studies have yielded strong association of several CRP genetic variants with increased mortality risk in general population as well as in patients with established CVD (Table 1). Moreover, CRP SNPs suggest a possible role of the inflammatory system as link between CVD risk factors and poor prognosis [3,4].

CRP SNP	Population	Relation to circulating plasma CRP level	Relation to the CVD	Reference
rs1205	Caucasian populations of healthy men and women	Positive relation	Increase of CVD susceptibility	4
rs1205	Caucasian populations of healthy men and women with risk factors of CVD	Lack of relation	Lack of association with CVD	15

rs1205	Caucasian populations of healthy men and women	Lack of relation	Lack of association with CVD	10
rs1205	Caucasian population of patients with established CVD	Positive relation	Predictor of CVD	11,16
rs1800947 CC genotype	patients with risk factors of CVD	Positive relation in smokers	Predictor of atherosclerosis, myocardial infarction and	12,16
triallelic SNP (C-->T-->A)	Caucasian patients with risk factors of CVD	Positive relation that explains 26% of the individual variability in CRP level	Predictor of CVD	13
rs3093059 (T>C)	Asian populations	Negative relation	A marker of lowered risk of myocardial infarction	14
rs1800947 (G>C) and rs2794521 (G>A)	Asian and Caucasian populations	Positive relation	Lack of association	14,15

**Table 1:** The controversial results of CRP SNPs in prediction of CVD; CRP: C-Reactive Protein; CVD: Cardiovascular Disease; SNPs: Single Nucleotide Polymorphism.

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 chemokine produced by wide spectrum of immune cells. Despite SNP CRP rs1205 polymorphism associated with circulating plasma CRP levels and CVD susceptibility in some populations, there is evidence that several mutant alleles of *IL-1* gene

and *IL-6* gene 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 have associated with increased risk of cancer, atherosclerosis, diabetes mellitus, bowel disease, rheumatoid arthritis, psoriasis, obstructive pulmonary disease, periodontitis, nonalcoholic fatty liver disease and CVD [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 fact explaining controversial results of numerous pre-clinical and clinical studies depicted this issue [10]. On the other hand, in healthy men and women the polymorphisms of CRP were found in mild-to-moderate association with the basal CRP levels. Whether SNPs in *CRP* genes are powerful individual predictor of CV disease and poor clinical outcomes in patients with established CV is not fully clear [11].

Current evidence confirmed that CV risk factors may correspond to CRP levels and thereby directly affect local inflammation especially in the plaques, sub-intima of vascular walls, kidney and adipose tissues. 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 [12]. 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 [13]. Moreover, 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 close associated with higher CRP level [13]. In meta-analysis performed by Zhu et al. [14] 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 [14]. González-Giraldo et al. [15] in meta-analysis of clinical trials did not find significant associations between SNPs in *CRP* gene reported as CRP-rs1800947 (5 studies) and CRP-rs1205 (3 studies) and a risk of ischemic stroke. In contrast, Kolz et al. [16] reported found two polymorphisms within the C-reactive protein (*CRP*) gene rs1800947 and rs1205, of which the minor alleles were strongly associated with lower levels of C-reactive 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 [17]. However, CRP has been reported in number of studies to be a risk factor for CV disease and to have prognostic impact in patients with coronary artery disease, although a genetic variation in CRP and risk of CV 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 CV risk [18-20]. Future large clinical studies are required to identify additional genetic risk factors for CV disease in different populations.

In conclusion, 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. Probably, ethnic and race particularities are 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 CV risk stratifications.

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