GENETICS

CRP gene variants complicate diagnosis and treatment of inflammatory conditions

Serum levels of C-reactive protein (CRP)—used to inform diagnostic and treatment decisions in inflammatory disease—are strongly affected by genetic variation at the *CRP* locus. Not only is this relationship true for the acute rise in CRP after surgery or myocardial infarction, as suggested by previous data, but also for CRP responses in chronic inflammation, which could lead to inappropriate clinical recommendations. "We are not aware that the *CRP* genetic effect is widely appreciated in clinical rheumatology practice," says Ben Rhodes, author of the report that sounds this cautionary note. He adds that the contribution of genetic variation to patients' CRP levels is "surprisingly large".

To find out whether *CRP* variants have a clinically relevant effect in chronic inflammatory disease, the investigators needed an independent measure of global inflammation. Conveniently, erythrocyte sedimentation rates (ESR) are routinely measured alongside CRP in patients with rheumatoid arthritis (RA). The team used single nuclotide polymorphism (SNP) tagging to capture the full extent of *CRP* genetic variation in two independent cohorts, comprising 695 patients with RA.

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Three *CRP* SNPs were significantly associated with serum CRP levels, but not with ESR. However, as Rhodes notes, "it was only when haplotypes were analyzed that the full magnitude of [the] genetic effect ... could be seen." Five haplotypes were identified and their frequencies calculated. The expected median CRP level for individuals homozygous for the most frequent haplotype was 2.32 times higher than that for homozygotes with the least frequent haplotype. Large differences in acute-phase CRP levels were also seen in heterozygotes, over and above the variation attributable to their underlying inflammatory status. The difference is great enough, potentially, for a patient's CRP status to offer false reassurance or cause for concern, or to cause expensive biologic therapies to be inappropriately withheld or dispensed.

The authors now aim to show that the *CRP* genetic effect is, as they suspect, general across inflammatory conditions. "In addition," adds Rhodes, "we would like to demonstrate in a formal, prospective manner that the use of a genetically adjusted CRP measurement improves the diagnostic or predictive utility of algorithms that incorporate CRP levels."

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Original article Rhodes, B. *et al*. A genetic association study of serum acute-phase C-reactive protein levels in rheumatoid arthritis: implications for clinical interpretation. *PLoS Med*. **7**, e1000341 (2010)