Metabolic genes tied to inflammatory predictor of heart disease and stroke risk

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Two new studies provide evidence that differences in people's blood levels of C reactive protein (CRP) stem in part from natural variation in known metabolic genes. The researchers report their findings in the May *American Journal of Human Genetics*, a publication of Cell Press.

" Many years ago, we showed that CRP levels in healthy, middle aged men can predict—better than cholesterol—who would die from a cardiac event," said Paul Ridker of Harvard Medical School, who led one of the two studies. "We've now confirmed that the CRP gene itself plays a role in setting CRP levels. And the most extraordinary finding is that some of the other genes involved relate to metabolic syndrome pathways."

The findings come just weeks after the "JUPITER Trial," designed to test whether cholesterol-lowering statins can prevent heart disease in people with normal cholesterol but increased CRP levels, was ended early. The drug company AstraZeneca announced that they were halting the trial of rosuvastatin calcium (trade name Crestor) because early results showed that the drug reduced death and risk of heart problems in patients compared to placebo.

CRP has long been considered a hallmark of low-grade, systemic inflammation. Although researchers have known for more than a decade that CRP levels can predict the risk of heart disease, stroke, metabolic syndrome and diabetes, it hasn't been entirely clear why. Environmental factors, including obesity, smoking and stress, contribute to CRP, but

studies have also shown that its levels have a strong genetic component.

In search of the genes responsible, Ridker's team conducted a genome-wide association study among 6,345 apparently healthy women participating in the Women's Genome Health Study. Specifically, the women were evaluated for hundreds of thousands of single nucleotide polymorphisms (sites in the genome that harbor lots of variation among individuals) that they thought might possibly determine plasma CRP level.

The study turned up seven sites that were significantly associated with CRP. Two of those, responsible for proteins known as glucokinase regulatory protein (GCKR) and hepatic nuclear factor-1A (HNF1A), are suspected or known to be associated with maturity-onset diabetes of the young, they noted. GCKR had earlier been linked to triglyceride and glucose levels, but not to CRP, Ridker said.

A second report of two additional genetic association studies (from the Pharmacogenomics and Risk of Cardiovascular Disease study and the Cardiovascular Health Study), each including thousands of participants, provided independent and confirmatory evidence for an association between common variants of HNF1A and CRP concentrations.

HNF1A is produced in the liver and pancreas, where it regulates the activity of other genes, he explained. An earlier study also showed that the promoter region of the human CRP gene contains an HNF1A-binding site.

" The protein products of six of the seven loci [we've uncovered] are directly involved in metabolic syndrome, insulin resistance, [insulin-producing] beta-cell function, weight homeostasis, and/or premature atherothrombosis," Ridker's team concluded. "Thus, common variation in several genes involved in metabolic and inflammatory regulation have

significant effects on CRP levels, consistent with CRP's identification as a useful biomarker of risk for incident vascular disease and diabetes."

" Together, these observations suggest the possibility that CRP and metabolic phenotypes may, at least in part, be under coordinate genetic control," Reiner and his colleagues said. "Given the association between plasma CRP concentration and various metabolic and cardiovascular diseases, larger studies assessing the potential association of HNF1A genotype with more complex, clinical disease-related endpoints may shed additional light on the role of genetic regulation of CRP in the occurrence of disorders such as myocardial infarction, stroke, diabetes, and metabolic syndrome."

Source: Cell Press