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Stress reaction gene linked to death, heart attacks

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A genetic trait known to make some people especially sensitive to stress also appears to be responsible for a 38 percent increased risk of heart attack or death in patients with heart disease, scientists at Duke Medicine report.

The finding outlines a new biological explanation for why many people are predisposed to cardiovascular disease and death, and suggests that behavior modification and drug therapies could reduce deaths and disability from heart attacks.

The study appears in the Dec. 18, 2013, issue of the journal *PLOS ONE*.

"We've heard a lot about personalized medicine in cancer, but in cardiovascular disease we are not nearly as far along in finding the genetic variants that identify people at higher risk," said senior author Redford B. Williams Jr., M.D. director of the Behavioral Medicine Research Center at Duke University School of Medicine. "Here we have a paradigm for the move toward personalized medicine in cardiovascular disease."

Williams and colleagues built on previous work at Duke and elsewhere that identified a variation in a DNA sequence, known as a single nucleotide polymorphism (SNP), where one letter in the genetic code is swapped for another to change the gene's function. The SNP the Duke team focused on occurs on the gene that makes a serotonin receptor, and causes a hyperactive reaction to stress.

In a study published last year, the researchers reported that men with this genetic variant had twice as much cortisol in their blood when exposed to stress, compared to men without the genetic variant. Known as a "stress hormone," cortisol is produced in the adrenal gland to support the body's biological response when reacting to a situation that causes negative emotions.

"It is known that cortisol has effects on the body's metabolism, on inflammation and various other biological functions, that could play a role in increasing the risk of cardiovascular disease," said lead author Beverly H. Brummett, Ph.D., associate professor of Psychiatry and Behavioral Sciences at Duke. "It has been shown that high cortisol levels are predictive of increased heart disease risk. So we wanted to examine this more closely."

Using a large database of heart catheterization patients at Duke who were studied over several years, the researchers ran genetic analyses of more than 6,100 white participants, two-thirds of whom were men, and one-third women. About 13 percent of this group had the genetic variation for the overactive stress response.

Patients who carried the genetic variation had the highest rates of heart attacks and deaths over the median follow-up time of six years. Even adjusting for age, obesity, smoking history, other illnesses and the severity of their heart disease, the genetic trait was associated with a 38 percent increased risk of heart attack and death.

"This finding requires independent replication and evaluation in a more diverse population," said Peter Kaufmann, Ph.D., deputy branch chief of the Clinical Applications and Prevention Branch at the NIH's National, Heart, Lung, and Blood Institute (NHLBI). "This research may one day help to identify patients who should be candidates for more intensive disease prevention and treatment strategies."

Williams and Brummett said the researchers have a working hypothesis about why this genetic trait leads to problems. Their efforts are now focusing on a compound in the blood that becomes elevated when cortisol levels rise. This substance, an enzyme known as MMP9, works to soften hard plaques that build up on blood vessel walls, making them more likely to rupture and produce clots that cause a heart attack or death.

"We plan to study this further," Williams said. "But what this work suggests already is that we have a found genetic variant that can be easily identified, so we can begin to develop and test early interventions for those heart patients who are at high risk of dying or having a heart attack."

"The exciting part to me this is that this genetic trait occurs in a significant proportion of people with heart disease," Brummett said. "If we can replicate this and build on it, we may be able to find ways to reduce the cortisol reaction to stress – either through behavior modification or drug therapies – and reduce deaths from heart attack."

More information: dx.plos.org/10.1371/journal.pone.0082781

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