Genetic septet in control of blood platelet clotting

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In what is believed to be the largest review of the human genetic code to determine why some people's blood platelets are more likely to clump faster than others, scientists at Johns Hopkins and in Boston have found a septet of overactive genes, which they say likely control that bodily function.

"Our results give us a clear set of new molecular targets, the proteins produced from these genes, to develop tests that could help us identify people more at risk for blood clots and for whom certain blood-thinning drugs may work best or not," says co-senior study investigator and cardiologist Lewis Becker, M.D.

"We can even look toward testing new treatments that may speed up how the body fights infection or recovers from wounds," says Becker, a professor at the Johns Hopkins University School of Medicine.

Platelets are key to fighting infection and sealing wounds and, adversely, can speed up cardiovascular diseases that can lead to potentially fatal heart attacks or strokes.

Reporting in the issue of Nature Genetics online June 7, researchers tested the platelet "stickiness" in blood samples from some 5,000 American men and women and compared the results to some 2.5 million single possible changes in the human genetic code to see which genes stood out across the entire group as speeding up or slowing down platelet clumping. Study participants included both whites and blacks with no

previously known chronic health problems, representing what researchers say is "a solid cross-section of American society."

Seven genes were found on their own to be hugely significant in affecting how fast or how long it took for platelets to stick together or how many platelets would clump. (The seven were more than 500 million times more likely than other genes to impact clumping, whereas the next most influential genes, a set of 15, were found to be 10,000 times more likely to affect clumping function.)

According to Becker, three of the seven genes had been previously reported as having some role in platelet aggregation, but "it was not until now that we put together all the major pieces of the genetic puzzle that will help us understand why some people's blood is more or less prone to clot than others and how this translates into promoting healing and stalling disease progression."

He points out that the latest study was made possible by combining data from two longstanding studies of why seemingly healthy people get heart disease. Results came from some 2,800 white men and women participating in the Massachusetts-based Framingham Heart Study, all since 2003, when researchers in the decades-long study began collecting platelet samples. Platelet samples came from another 2,000 similar participants, including 800 blacks, enrolled in the Genetic Study of Aspirin Responsiveness (GeneSTAR) under way at Johns Hopkins since 2002 and led by Becker's wife and study co-investigator Diane Becker, M.P.H., Sc.D., a professor at the both Hopkins' School of Medicine and the University's Bloomberg School of Public Health.

According to Diane Becker, a health epidemiologist, generalizing the data to the broader American population was only made possible by combining these large study populations, as neither on their own was sufficient for such a genome-wide scan.

In the study, platelet samples were tested for their "stickiness" in response to adding various concentrations of three chemicals commonly found in the blood, including adenosine diphosphate, or ADP, which is an energy molecule released by platelets into the blood to attract and clump with other platelets; epinephrine, a stress hormone tied to inflammation and vascular disease; and collagen, the most common protein in the human body.

Clumping results were then cross-matched with results from gene chip surveys of the human genome, which allow researchers to sort through millions of different genetic modifications to see which specific genes are more active than others. Diane Becker says the genetic analysis alone was a massive undertaking and took some two years to complete.

Lewis Becker says the teams' next steps are to test various platelet antagonists, or blood-thinning agents, like aspirin, the most common drug treatment in heart and vascular diseases, to find out precisely which hereditary factors may distinguish people who are so-called aspirin-resistant or not, and why the medication works for most but not all.

"Our combined study results really do set the path for personalizing a lot of treatments for cardiovascular disease to people based on their genetic make up and who is likely to benefit most or not at all from these treatments," says Lewis Becker.

More information: www.nature.com/ng/journal/vaop … rent/abs/ng.604.html

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