Getting at the 'heart' of Kawasaki disease

Researchers link an immune system-regulating gene to heart disease.

Kawasaki disease (KD) has long been suspected not only of having a strong genetic component but also of being mediated by the immune system. These two ideas have now dovetailed in a new study reported in the Dec. 16 online edition of *Nature Genetics*. The findings, resulting from an international collaborative effort among Japanese and U.S. researchers, are the first to strongly associate a genetic variation with increased KD susceptibility and with increased risk for a specific type of heart disease arising from disease.

This team was led by Yoshihiro Onouchi and Akira Hata of the RIKEN SNP Research Center, and included Jane Burns of the University of California San Diego and Jane Newburger of Boston Children's Hospital. The study elegantly combines genetics and immunity in the causes of KD by demonstrating how a change in a gene that regulates the immune response intersects with the peculiar pathology of the disease.

KD typically affects very young children, its symptoms including a long-lasting fever, skin rashes, swollen glands, and a type of arterial inflammation that can weaken and widen blood vessels to form aneurysms, including within the heart. Most of the disease symptoms can be successfully treated with intravenous immunoglobulins, a type of purified antibodies. Because 15-25% of untreated KD patients develop potentially fatal coronary artery aneurysms, KD is the main cause of acquired heart disease among children in developed countries.

The blood vessel inflammation and other symptoms suggest an immune-mediated basis for KD. A strong genetic component to the disease is also suspected, given the higher prevalence of KD in Japanese children than in European children and the fact that KD often runs in families. Indeed, the RIKEN scientists had already previously pinpointed the genetic influence in KD within chromosome 19, paving the way for the more sophisticated and refined genetic methodology used here: examining the linkage between tiny but critical changes in DNA sequences - called single nucleotide polymorphisms (SNPs) - and hundreds of Japanese and American KD patients.
The researchers quickly narrowed the field of possible SNP contenders from 1,222 to 131 and finally, zoomed in on just four candidate SNPs resting within separate genes in chromosome 19. The scientists then used their knowledge of the biological functions of the four genes to focus on the gene coding for inositol 1,4,5-triphosphate 3-kinase C (ITPKC) because this enzyme plays an important role in a calcium-signaling pathway that regulates the immune system.

Through biochemical analyses, and by changing the expression levels of ITPKC in cells, the group determined that ITPKC regulates the levels of NFAT, a major DNA-binding protein that controls the expression of cytokines, central players of immune responses. Since IL-2, a cytokine that is decreased by ITPKC, also activates T-cells - one of the many cell types the body marshals in immune responses - ITPKC must be a key negative regulator of T-cells. Critically, the KD-linked ITPKC SNP lowers the expression of the ITPKC protein, which in turn increases IL-2 levels, leading to T-cell over-activation. T-cell activation is extremely complicated and when the process goes awry, immune dysfunction often results. Indeed, special subtypes of T-cells have been found within the coronary arteries of deceased KD children.

This study will dramatically impact future research in this and related fields. Because patients harboring this SNP are less likely to respond to standard therapies and are at higher risk for developing heart problems, these findings should drive the development of diagnostic genetic tests and alternative clinical remedies. Moreover, this SNP may also affect other similar inflammatory disorders - treatments for other maladies might only be an SNP and a heartbeat away.

Original work:
ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms
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