Editorial

Genetics Insights Into the Pathogenesis of Kawasaki Disease

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First described by a Japanese pediatrician in 1967, Kawasaki disease (KD) is an acute vasculitis of infancy and childhood that has become the leading cause of acquired heart disease in children in the developed world. No single etiologic agent of KD has been found despite 4 decades of investigation. In the absence of a causative agent or definitive laboratory test, its diagnosis is made by a constellation of clinical criteria, including fever, rash, nonexudative conjunctivitis, inflammation of the oral mucosa, findings in the extremities (erythema of the palms and sole, edema of the digits, and later subungual peeling), and unilateral cervical adenopathy. Without treatment, 1 in 5 children develops coronary artery aneurysms; administration of high-dose intravenous immunoglobulin (IVIG) during the acute phase of illness reduces the likelihood of such coronary abnormalities 5-fold.

Although an etiologic agent(s) has not been found, the role of genetic susceptibility to KD has long been evident through its striking predilection for children of Japanese ethnicity regardless of their country of residence; compared with Caucasian children, Japanese children have a relative risk of KD that is 10 to 15 times higher. Siblings of KD children have a relative risk that is 6 to 10 times greater than that of children without a family history, and the parents of Japanese children with KD are twice as likely to have had KD themselves as children than other adults in the general Japanese population. Recognition that genetic factors play a role in susceptibility to KD has led to an increasing body of literature exploring the association of genetic variations to disease susceptibility, and outcome.

The goal of genetic studies in KD is not so much to predict disease susceptibility, but rather to understand disease pathogenesis. To date, 3 important signaling pathways in KD have been discovered, and the single nucleotide polymorphisms (SNPs) reported by Shrestha et al belong to 1 of these. The first pathway to be identified was the calcineurin-nuclear factor of activated T-cells pathway, in which a functional SNP in the gene encoding 1,4,5-trisphosphate 3-kinase C on chromosome 19q13.2 contributes to host susceptibility and coronary artery aneurysm formation. An intronic SNP located 9 nucleotides from the splice site and was shown through an elegant series of in vitro experiments to influence T-cell activation through increased calcium signaling associated with the risk allele. The association of this functional SNP with KD susceptibility has been confirmed in 2 different genome-wide association studies performed on both European descent and Asian cohorts. Based on this information, coupled with observations of activated T-cells in the tissues, calcineurin inhibitors that block this activation pathway have been used for refractory KD patients, thus demonstrating a rapid translation of genetic discovery into clinical practice.

The second pathway discovered through genetic association studies was the transforming growth factor-β (TGFβ) signaling pathway, in which SNPs in TGFβ2, TGFβR2, and SMAD3 contribute to risk of coronary artery aneurysm formation, the most important complication of this self-limited vasculitis. Supporting the contribution of SMAD3 to a severe phenotype in KD, a recent report has identified coding mutations within SMAD3 in 3 Dutch families affected by a new aortic aneurysm syndrome. Further strengthening the importance of this pathway, an additional association was discovered through a Japanese sibling pair linkage study and later confirmed by a genome-wide association study in Japanese children that implicated genetic variation in the gene encoding Caspase 3, a multifunctional protein that, in concert with TGFβ, modulates T-cell differentiation and activation.

Understanding the importance of the TGFβ signaling pathway led to a new hypothesis regarding aneurysm formation and the role of myofibroblasts in vessel wall damage, and has inspired a clinical trial of atorvastatin to inhibit this process during the acute phase of the disease (www.clinicaltrials.gov; unique identifier: NCT 01431105). This again illustrates how quickly new understanding can be translated into new treatment.

Finally, a genome-wide association study in KD subjects of European descent identified a nonsynonymous SNP in the FCGR2A (encoding FcγRIIa) as influencing disease susceptibility, and was validated in Korean and Han Chinese populations. In the study by Shrestha et al, an association to this same SNP in FCGR2A was replicated, and variation in a second gene encoding FcγRIIB was implicated as influencing response to treatment with high-dose IVIG. Several studies have tested the association of KD with genetic variation within the complex locus that contains the FcγR-encoding genes. One complicating factor in the study of this region is copy number variation (CNV) in FCGR2C, FCGR3A, and FCGR3B, which was not examined in the...
study by Shrestha et al.\textsuperscript{14} It is possible that taking CNV into account might have yielded different results. An FCGR-specific multiplex ligation-dependent probe amplification assay is an approach that might yield a more comprehensive snapshot of the FcγRs by incorporating both SNP genotyping and assessment of CNV in a single assay.\textsuperscript{27} The biological significance of CNV in these genes is suggested by the association of low FCGR3B copy number with the development of systemic autoimmunity.\textsuperscript{28}

Because both FCGR2A and FCGR3B encode for low-affinity immunoglobulin G receptors, one must proceed with caution before assigning major biological significance to genetic variation in these receptors. Future studies should address the contribution of this locus to KD outcome with a much larger scale analysis with functional evaluation and consideration of CNV. Understanding the role of the FCγ receptors in KD pathogenesis may lead us to an understanding of how IVIG down-regulates the destructive immune response in these patients. That understanding, in turn, may help us to devise more readily available and affordable treatments for this disease, as large numbers of affected children live in countries where IVIG is simply not available.

From the larger perspective, KD offers us the opportunity to study a population of otherwise healthy children with a unique susceptibility to an environmental trigger, possibly an infectious agent, which sets in motion a host immune response that targets the coronary arterial wall. Why and how this happens remain a mystery. Identifying minor genetic variation in these receptors may lead us to an understanding of how IVIG down-regulates the destructive immune response in these patients. That understanding, in turn, may help us to devise more readily available and affordable treatments for this disease, as large numbers of affected children live in countries where IVIG is simply not available.

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