Unraveling the Genetic Predisposition for Aortic Aneurysms: Is it Time for Tailored Medicine?

Debabrata Mukherjee

Aneurysms and dissections are the major pathologies affecting the thoracic aorta. Based on available data, up to 20% of individuals with thoracic aortic aneurysms (TAAs) may have a first-degree relative with aortic aneurysms or dissection, indicating a strong genetic predisposition. Within families, TAAs are inherited primarily in an autosomal dominant manner, with decreased penetrance and variable expression. Moreover, they are often asymptomatic until a catastrophic event occurs, which may be prevented if family members can be identified prior to such events. Based on this premise, recent studies have begun to elucidate the genetic factors that predispose an individual to TAA.

The first genetic predisposition for TAA was detected by use of families with multiple members with the disorder. The locus was mapped to the long arm of chromosome 5 (5q13-14), termed the TAA1 locus. Genetic heterogeneity was indicated by the fact that only one-half of the identified families mapped to this locus and was confirmed by mapping another gene causing TAA to the long arm of chromosome 11, 11q23-24 (termed the FAA1 locus). Hasham et al. also mapped another locus for TAA to 3p24-25, termed the TAA2 locus, by using a family with multiple affected members. Having mapped a TAA locus to 3p24-25, they sequenced the gene for transforming growth factor-β receptor type 2 (TGFB2) and demonstrated that germline TGFB2 mutations are responsible for the predisposition to familial TAA in 5% of these cases.

In this issue of the Journal, Kato et al. performed an association study for 142 polymorphisms of 119 candidate genes and TAA in 1,351 hypertensive Japanese individuals to identify genetic variants that confer susceptibility to TAA. They report that the variant G allele of THBS2 was a risk factor for TAA, whereas the variant C allele of HSPA8, T allele of GPX1, A allele of AGT, and T allele of TNF were protective against this condition. The authors suggest that the determination of genotypes for these polymorphisms may prove informative for assessment of the genetic risk for TAA and may contribute to the personalized prevention of this condition.

Although a particular combination of polymorphisms may predispose to TAA, any individual gene is likely to have only a limited effect. The role of hypertension, smoking, gender, and age must be taken into consideration when considering the likelihood of TAA in a given patient. The true mechanism underlying TAA probably involves the interplay between genetic predisposition and acquired risk factors listed above. The study by Kato et al. is important because understanding the genetic predisposition to TAA development will provide a better understanding of the pathophysiology and may help identify potential new targets for therapeutic intervention. However, at this point in time, genetic predisposition studies should be considered for research, and clinicians should focus on appropriate history, physical examination, and imaging tests to diagnose TAA. In individuals with a family history of TAA, it is extremely important to control blood pressure optimally and convince individuals who smoke to quit. Additional studies with larger cohorts will be required to verify and better characterize the actual magnitude of the risk/benefit of the individual alleles reported, and we hope that in the future genetic makeup of an individual may help quantify their risk of developing TAA and other disease conditions.

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