The genome-wide association studies (GWAS) of recent years have provided the first unbiased views of genes contributing to cardiovascular disorders in European and some Asian and African populations. In addition to extending these studies using techniques such as deep sequencing, the major challenge at present is to understand how the novel genes contribute to disease. The goal of this series of essays is to provide some perspective on how this might be accomplished.

The essay by Seraya Maouche and Heribert Schunkert summarizes the recent findings from GWAS for atherosclerosis and discusses their functional, biological, and clinical implications.

Recent progress in the genetics and genomics fields has been driven in large part by the development of high-throughput technologies. Yvonne Döring, Heidi Noels, and Christian Weber discuss the various technologies and how they are being used to investigate vascular inflammation and atherosclerosis.

In many GWAS studies of atherosclerosis, the most significant locus by far is a region on chromosome 9p21 that contains a gene for a long noncoding RNA. Lesca Holdt and Daniel Teupser review efforts to understand the underlying mechanisms.

The effect sizes of the individual loci identified in GWAS studies tend to be very modest and, coupled with the ethical and practical constraints associated with human sampling, it is likely to be difficult in most cases to address biological functions of the loci directly in human populations. In her essay, Carrie Welch discusses the importance of mouse genetics in understanding the complex etiology of atherosclerosis.

One of the promising approaches to address the functional consequences of genetic variation is “systems genetics,” which integrates intermediate molecular traits such as gene expression with classic genetic analysis. Xia Yang reviews how such a functional genomics approach is being applied to understand the pathways involved in common forms of atherosclerosis.

Statistical modeling is likely to play a central role in understanding the overall architecture of complex diseases such as atherosclerosis. In his essay, Stephen Schwartz addresses the fundamentals of causal inference and their application to genetic and genomic studies of vascular biology.
Life After GWAS: Functional Genomics in Vascular Biology

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