REVIEW ARTICLE

Paul G. Barash, MD
Giovanni Landoni, MD
Section Editors

The Genetic Basis of Coronary Artery Disease and Atrial Fibrillation: A Search for Disease Mechanisms and Therapeutic Targets

Jacques Neelankavil, MD,* Christoph D. Rau, PhD,* and Yibin Wang, PhD*†

CORONARY ARTERY disease (CAD) and arrhythmias such as atrial fibrillation (AF) significantly contribute to perioperative mortality and morbidity. The 30-day postoperative mortality rate is increased significantly in patients with AF (6.4%) and (CAD) (2.9%).[1] The VISION trial found that 11.6% of patients undergoing noncardiac surgery had increased troponin levels postoperatively, and these patients had an increased 30-day mortality compared with the reference group.[2] Postoperative AF patients have longer hospital stays and increased mortality.[3–6] Postoperative AF is common not only after cardiac surgery, but is seen after major noncardiac surgery as well.

As anesthesiologists continue to focus on perioperative care for surgical patients, they must examine all options for decreasing mortality and morbidity for patients with coronary artery disease and arrhythmias undergoing noncardiac surgery. The genetic predisposition for CAD and AF has garnered more attention in the past decade due to innovative technology and ready access to human genomic information that has improved the ability to identify single nucleotide polymorphisms in the genome. Although advances continue to be made in the management of CAD and AF, prevention likely will be the most effective way to decrease ischemic heart disease and atrial fibrillation in the patient population. Medical management has an important role for perioperative prevention of major adverse cardiac events; however, the 2014 ACC/AHA guidelines reflect important contributions from recent studies regarding the safety and efficacy of perioperative beta-blockade. The only class I recommendation for perioperative beta-blockade is the continuation of beta-blockers for patients who have been taking them chronically.[1] The initiation of beta-blockers for patients with high-risk myocardial ischemia or for patients with multiple risk factors is a class IIb recommendation. There is continued concern about the risk of perioperative stroke related to beta-blockers and the safest time to initiate beta-blockers before surgery. Perioperative myocardial revascularization has been examined as a method to decrease major perioperative adverse cardiac events. The CARP trial showed that at medial long-term follow-up, there was no difference in mortality between revascularized and nonrevascularized patients undergoing vascular surgery even in high-risk groups such as those with multivessel coronary artery disease[7] Therefore, medical and surgical interventions have limited ability to decrease perioperative risk when there is a clear unmet need for better risk assessment and management strategy. This review will focus on the recent progress made in establishing the genetic basis for coronary artery disease and atrial fibrillation. The clinical relevance of CAD and perioperative myocardial infarction are closely linked; however, they do not share many genetic variants. These genetic differences will be highlighted using specific genes as examples, including 9p21. A thorough understanding of the genes and their contribution to these disease processes may lead to improved risk stratification and prevention of these common perioperative complications.

GENETIC VARIATION

The human genome is 99.5% identical for all humans, and the variation across the rest of the 0.5% accounts for uniqueness in terms of susceptibility to various diseases.[8] These variants result from many forms of alterations in the human genome, including deletions, amplifications, and inversions. However, the most common form is single nucleotide changes, called single nucleotide polymorphisms (SNPs).[9] On average, one SNP can be detected in approximately every 300-100 base pairs in a single individual.[10] Depending on the potential impact of the SNPs on the genome, they can lead to deleterious mutations in the coded RNA transcripts and protein products, or have benign consequence if the changes are synonymous for the potential codon. In addition, SNPs can be located in the nontranscribed regions of the genome but with potential to affect the transcriptional level, splicing, or other gene expression processes. Among the total 3 million potential SNPs sites, however, most are nonfunctional, occurring in $>5\%$ of the populations, and only small minorities are direct disease causal mutations detected usually in $<0.1\%$ of the populations.[10] Nevertheless, these common SNPs account for a large portion of the heritability of many human traits, including disease susceptibilities, suggesting multi-loci contributions in inheritable characteristics of individuals.

*From the *Department of Anesthesiology, and the †Department of Medicine and Physiology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA.*

This work was supported in part by NIH grants HL114437 and HL123295 to Dr. Wang.

Address reprint requests to Yibin Wang, PhD, Mail Code: 711520, Department of Anesthesiology, UCLA, Los Angeles, CA 90095. E-mail: yibinwang@mednet.ucla.edu

1053-0770/2601-0001$36.00/0
http://dx.doi.org/10.1053/j.jvca.2015.01.031
Key words: genetics, GWAS, heart disease, coronary artery disease, atrial fibrillation, arrhythmia

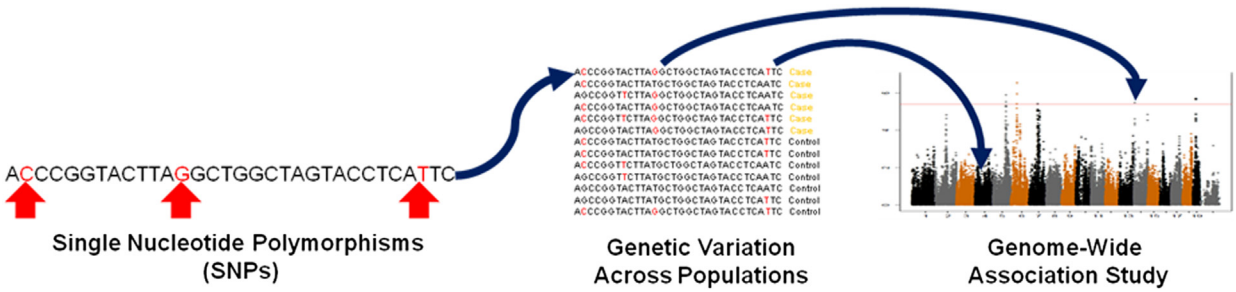

Fig 1. Genome-wide association study (GWAS) for clinical traits. From single nucleotide polymorphisms (SNPs, left) to statistical correlation between the case and control populations (middle), to a composite "Manhattan" plot, where the y axis is the p value and the x axis is the genomic position for each SNP analyzed across the entire genome. GWAS from human patient populations or disease models as depicted will allow the discovery of potential contributing genes for specific clinical traits, including the onset, progression, and severity of cardiovascular diseases such as coronary heart disease, arrhythmia, and heart failure.

In genome-wide association studies (GWAS), SNPs commonly are used as the basis of genotyping. Distribution of SNP genotypes across the entire genome in the cases versus controls is statistically analyzed for significant deviations. A significant deviation in frequency of a particular SNP in a particular disease population, such as coronary artery disease from the observed frequency in the general population or the disease-free controls, would indicate that the genotype associated with this SNP has a significant contribution to that trait or the disease (Fig 1). A commonly accepted threshold for significant association is set as Bonferroni corrected p value at $5 \times 10e\text{-}8$ based on the estimate of $1 \times 10e6$ linkage disequilibrium blocks in the human population. In order to support the validity of such association, several criteria usually are required. First, the sample size should be sufficiently large and the composition is representative of the general patient population; second, the same association should be replicated using independent patient cohorts. A GWAS finding (or hit) provides suggested genes with potential contribution to a particular trait or disease when they are located in the same linkage disequilibrium block as the associated SNPs. Ultimately, the causal gene(s) will need to be identified among the candidate genes based on functional validation in cellular or animal models. This approach has been used extensively to map the genes associated with coronary artery disease.[9]

GENETICS OF CORONARY ARTERY DISEASE

Human coronary artery disease (CAD) is by and large an inherited disease. It is estimated that genetic variants account for approximately 40% to 60% of the pathogenesis of coronary artery disease,[11] and it is established that more than 70% of blood low-density lipoprotein and high-density lipoprotein blood levels are due to genetic factors.[12] A family history of coronary artery disease has been known to confer increased risk of acquiring coronary artery disease since the Framingham study, but specific genetic risk factors only have been elucidated since 2005 with the initiation of the GWAS.

The first genetic locus identified using this technology, 9p21, has received a great deal of attention, and inspired a multicenter GWAS called the Coronary Artery Disease Genome-wide Replication and Meta-Analysis, which used 87,000 patients as its initial population and 56,000 patients in its confirmation population.[13] 9p21 is associated significantly with early-onset CAD and homozygotes have 2 times the risk of developing early-onset CAD, which is equivalent to the risk associated with tobacco use in CAD.[14] This is significant for risk stratification because it is estimated that more than 1 billion people are homozygous for 9p21.[8] The 9p21 chromosome consists of 2 important protein kinase inhibitors, CDKN2A and CDKN2B, which influence the function of retinoblastoma (Rb) protein.[15] Rb is a key component of transcriptional regulatory complex, important for cell proliferation, differentiation, and cellular identities. Knock-out models of CDKN2A or CDKN2B show increased risk for cancer. 9p21 is thought to increase the risk for CAD through accelerated atherosclerosis in the vessel wall without associated plaque rupture or thrombosis.[15] There may be an association between 9p21 and atherosclerosis due to the regulation of cell proliferation or other unknown targets related to these 2 proteins.[15] The association with atherosclerosis and lack of association with plaque rupture may explain why 9p21 has been shown to have an effect on atherosclerosis but not myocardial infarction.

To date, more than 30 genetic loci for CAD have been identified (Table 1); however, it is unknown by which mechanisms many of these genes increase the risk for CAD. These variants are common in the population,[11] and many increase risk for CAD independent of known risk factors such as blood lipid levels, hypertension, diabetes, and tobacco use. Of the many loci associated with CAD, only 1 has been shown to be associated with myocardial infarction (9q34), which is thought to increase the risk of thrombosis.

Many of these genetic variants may be related to the regulation of protein expression, but the mechanisms are unclear. In the interim, there has been discussion about incorporating genetic risk factors (such as the presence of 9p21) into risk stratification for the patients. One potential possibility is to incorporate genetic information in the revised cardiac risk index for perioperative noninvasive stress testing in the ACC/AHA algorithm. Another way to incorporate genetic variants into risk stratification was demonstrated by using 9p21 genotype to improve the ability to predict mortality after coronary artery bypass grafting.[16] Currently, however, creating a genetic risk score has not added valuable information to risk