EDITORIAL COMMENT

Irrelevance of the Chromosome 9p21.3 Locus for Acute Cardiovascular Events and Restenosis*

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The study of the genetic basis of common complex disease (e.g., coronary heart disease [CHD]) is of scientific interest for multiple reasons (1,2), including understanding disease pathogenesis, predicting disease risk, and developing new therapies (e.g., statins were developed after the discovery that primary familial hypercholesterolemia arose from mutations in \textit{LDLR}). Not associated with established risk factors (3), the chromosome 9p21.3 locus represents a new genetic risk factor for CHD. This locus was identified by multiple genome-wide association studies (GWAS) in 2007 (4,5) and has been replicated in dozens of subsequent studies (3,6,7). It is located in a chromosomal region devoid of traditional genes but resides at the site of \textit{CDKN2BAS}, an anti-sense noncoding ribonucleic acid (RNA) (also commonly known as \textit{ANRIL}) (3).

Clinical Risk Prediction

Although 9p21.3 might eventually provide new insights into the pathogenesis of atherosclerosis or provide a new drug target, the present clinical question is whether it is useful in clinical CHD risk prediction and, if so, for which subphenotypes (e.g., statins were developed after the discovery that primary familial hypercholesterolemia arose from mutations in \textit{LDLR}). Not associated with established risk factors (3), the chromosome 9p21.3 locus represents a new genetic risk factor for CHD. This locus was identified by multiple genome-wide association studies (GWAS) in 2007 (4,5) and has been replicated in dozens of subsequent studies (3,6,7). It is located in a chromosomal region devoid of traditional genes but resides at the site of \textit{CDKN2BAS}, an anti-sense noncoding ribonucleic acid (RNA) (also commonly known as \textit{ANRIL}) (3).

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Unfortunately, initial GWAS and most subsequent replications of 9p21.3 single nucleotide polymorphisms (SNPs) evaluated cases where the majority had experienced MI and compared them with control subjects who were population normal subjects with no evidence of CHD (3–5). Although not an incorrect or valueless design, this comparison evaluates a complex of multiple subphenotypes within both cases (including MI and CAD) and control subjects (i.e., those with and without subclinical CAD).

Especially in the clinical arena, the phenotype that a genetic factor associates with must be precise and accurate to enable meaningful risk assessment and medical decision-making. For example, the occurrence of acute MI requires the presence of some degree of coronary atherosclerosis (except in rare cases involving atypical mechanisms such as coronary dissection, embolism, or spasm). Beyond CAD, however, MI specifically requires acute precipitating mechanisms, including endothelial erosion or plaque rupture and superimposed intracoronary thrombosis, regardless of the degree of coronary stenosis (8,9). Coronary artery disease apart from MI, in contrast, involves initiation and expansion of atherosclerotic plaques, a decades-long chronic and often subclinical process. Restenosis, an iatrogenic lesion that shares some common features with CAD, also has a distinct proliferative pathophysiology (10).

The question, then, is: What specific clinical and pathological phenotypes do SNPs at chromosome 9p21.3 actually predict?

CHD Phenotypes

In bringing crucial information to bear to address this important question, Hoppmann et al. (11), in this issue of \textit{JACC: Cardiovascular Interventions}, are to be congratulated. Their study reports the results of 9p21.3 SNP associations with the incidence of the composite end point of death, MI, or target lesion revascularization (i.e., clinical restenosis) among a CAD population during longitudinal observation following coronary revascularization with drug-eluting stents. The pathophysiologically-precise end point of angiographic in-segment restenosis could be addressed given routine angiography at 6 to 8 months.

The study found that the composite primary end point, each event individually, and stent thrombosis were not predicted by 9p21.3 SNPs. Hence, by exclusion in the present study and by previous demonstration, 9p21.3 seems to specifically mark the risk of intrinsic atherosclerotic plaque development (and not the extent of CAD or acute CHD events) (11,12). Furthermore and uniquely, it dem-

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onstrates that restenosis after stenting is pathophysiologically distinct from CAD, because it is not driven by genetic factors at 9p21.3.

The negative genetic association results by Hoppmann et al. (11) might be puzzling to some who have become accustomed to the excessively low p values and uncharacteristically consistent 9p21.3 findings in CHD. Confounding by some undescribed pharmacogenetic effect of drug-eluting stents cannot be ruled out. More likely, however, the apparent discrepancy simply highlights the critical importance of phenotype definition. Hoppmann et al. (11), in contrast to most prior investigators: 1) evaluated control subjects who all suffered from clinically significant CAD; and 2) assessed the impact of 9p21.3 on coronary events. Their study included no angiographically normal control subjects but rather evaluated CAD patients who, after stenting, did or did not suffer various clinical and angiographic end points over 6 months to 3 years. These points cannot be overstated, if genetic research results are to be used clinically.

Without a clear clinical definition of specific phenotype, predictive genetics is of little clinical value. Clinical genetic testing will require, in addition to significant epidemiologic associations, appropriate levels of sensitivity, specificity, positive predictive value, and negative predictive value—all of which operate explicitly on the phenotype definition for both affected and unaffected status. Additionally, only a few studies have modeled patient risk reclassification by 9p21.3 to evaluate potential clinical utility (6,7). Cost-benefit data and the investigation of improvement in outcomes (e.g., lower CHD incidence) in actual practice are also necessary for diagnostic or prognostic application.

The biological pathway influenced by 9p21.3 is unknown. The investigation of its biological effects might substantively augment the understanding of the pathophysiology of atherosclerosis. According to Hirschorn (13), this aim is the primary purpose of GWAS. Such contribution to biological understanding, however, is also contingent on a clear identification of which phenotype 9p21.3 actually predicts. If the risk pathway is through plaque erosion, rupture, or thrombosis, for example, then biological investigation of 9p21.3 as a predictor of MI pathogenesis is appropriate. Because Hoppmann et al. (11) and Horne et al. (12) have found evidence indicating otherwise, efforts to investigate the biology of MI or restenosis with 9p21.3 might be mis-directed, as might be the search for pharmaceutical agents that target its (RNA?) product. Rather, a renewed search for genetic factors predisposing to these distinct processes is indicated.

Conclusions

Clinical testing of the 9p21.3 SNPs at the present time remains “recreational genomics” (as Dr. David Goldstein [14] described direct-to-consumer testing), because of the issues relating to the definition of CHD (14). Before clinical application of genetic risk prediction in cardiology, further refinement and testing of the locus versus specific clinical phenotypes will be required. GWAS of greater sample sizes and studies of rare variants also are important (13,15), but phenotype clarity should also be a foremost consideration. Established primary and secondary prevention measures continue to represent best care and should include efforts to maximize adherence to a healthy lifestyle and appropriate medical interventions.

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