Opposing Effects of ABCG5/8 Function on Myocardial Infarction and Gallstone Disease*

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The research paradigm of using human genetic variation to unequivocally, causally, and directionally link a specific gene with a specific phenotype, trait, or disease has yielded extraordinary discoveries at an accelerating pace (1–3). Increasingly, this approach has been of interest as a way of “validating” targets for novel therapeutic intervention (4). For example, the promising low-density lipoprotein cholesterol (LDL-C)–lowering drug target PCSK9 was initially linked to LDL metabolism by the discovery of gain-of-function mutations causing elevated LDL-C (5). Subsequently, it was validated as a drug target by the discovery that loss-of-function mutations cause low LDL-C (6) and markedly protect against the development of coronary heart disease (7,8). PCSK9 inhibitors are now in late-stage clinical development and have superior LDL-lowering capacity with an apparent high margin of safety and tolerability (9). The story of PCSK9 has been repeatedly held up as a prime example of the power of human genetics to identify and validate new therapeutic targets, and many efforts are underway to duplicate this scenario for other unmet medical needs by searching for both common and rare genetic variants that are compellingly associated with the disease of interest.

However, a key aspect of the PCSK9 story—and indeed the overall approach of using human genetics to validate new therapeutic targets—is related to the ability of human genetics to not only inform potential efficacy but also safety of targeting a particular molecule. Studies of individuals carrying loss-of-function variants in PCSK9 revealed no evidence of adverse effects of reduced PCSK9 protein or activity (7). The approach of starting with 1 or more variants in a specific gene and asking broadly what phenotypes are associated with those variants—a so-called “phenome scan”—has been less—commonly reported in the literature, perhaps due to the fact that the bioinformatic methodology involved has only recently been validated (10). Phenome-wide association studies (PheWAS) have the potential to provide critical information on pleiotropic and perhaps unexpected effects associated with variation in genes of interest (11,12). In fact, a number of groups have recently elucidated unexpected phenotypic associations with certain genetic variants found in genome-wide association studies for other traits (13–16). For example, a recent PheWAS analysis of 81 single-nucleotide polymorphisms (SNPs) associated with platelet count and volume revealed previously unknown associations with myocardial infarction (MI), autoimmune, and hematologic disorders (15).

In this issue of the Journal, Stender et al. (17) highlight the pleiotropic effects of functional variants in 2 related genes, ATP-binding cassette, sub-family G, member 5 (ABCG5) and ABCG8, on MI and gallstone disease, 2 seemingly unrelated diseases. These 2 genes each encode ABCG5/8 genes are shown to affect the risk of MI and gallstone disease in opposite directions, presumably based on the transporter’s role influencing both LDL metabolism and biliary cholesterol metabolism.

The authors chose to address this question because variants in ABCG5/8 had, in different studies and cohorts, been previously associated with MI (21) and gallstones (22), and also because the physiology of ABCG5/8 is consistent with its influencing both LDL-C levels (a risk factor for MI) (23) and biliary cholesterol (a risk factor for gallstones) (24,25). To this end, the authors made use of 3 Danish cohorts totaling >60,000 subjects including >5,500 with MI and >3,000 with symptomatic gallstone disease. They genotyped 5 common nonsynonymous and 1 known functional intronic variant in ABCG5/8 and calculated a weighted genotype score based on their percentage reductions in LDL-C compared to the reference genotypes. As expected, the genotype score was significantly associated with lower LDL-C levels. The major finding of the study was that genotype score was related to MI and gallstone disease in opposite directions: the higher the score was, the lower the risk of MI was, but the higher the risk of symptomatic gallstone disease was.

The best studied of the 6 variants was the D19H variant in ABCG8, a known gain-of-function variant that had previously been shown to be a monogenic determinant of gallstone disease risk (25,26). Importantly, the relationship of genotype score to MI and gallstone disease persisted when a genotype score was calculated independently of the D19H
variant. Overall, these findings are consistent with genetically manipulated animal studies (27–29), and support a model that gain of function of ABCG5/8 in humans increases cholesterol flux from hepatocytes to bile, thus directly increasing the lithogenicity of bile while indirectly reducing plasma LDL-C and risk of MI.

These results reinforce an important paradigm, namely that single gene variants may have multiple effects on seemingly unrelated phenotypes or diseases. This principle has important implications for using human genetics for validation of new therapeutic targets. For example, based on these data, one may anticipate that a therapeutic intervention to up-regulate expression or function of ABCG5/8 would reduce LDL-C and risk of MI, but increase risk of gallstone disease. Importantly, the ability to detect the association of ABCG5/8 variants with gallstone disease required a very large sample size of subjects for whom data on gallstone disease were available. Depending on the trait or disease, an appropriately phenotyped sample of the necessary size will not always be available to address such questions.

Nevertheless, as the interest in human genetics for target validation continues to grow, the importance of broad phenome scans to address potential safety issues will increase as well. The goal is to generate confidence that perturbation of a target’s function will not lead to “on-target” adverse effects that would compromise its value as a therapeutic target. Large-scale genotyping and sequencing of potential targets in very large cohorts that have been phenotyped in great detail will be needed in order to perform the necessary phenome scans to provide confidence that a target is adequately safe to merit a full-scale developmental program. Stender et al. (17) have provided a compelling and easily understood example of the clinical “catch-22” that will likely be associated with many human genetic variants and, if discovered, will impact on drug discovery decisions.

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