ABCA1 Single Nucleotide Polymorphisms

Snipping at the Pathogenesis of Atherosclerosis

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Identification of genetic variants that predispose to complex traits is a major goal of the biomedical investigators of the post–Human Genome Project era, for whom the entire reference genome sequence and some of its frequent variants are a given. The most common form of genomic variation is the single nucleotide polymorphism (SNP). Indeed, SNP search has become a busy industry, as evidenced by the panoply of industrial methodologies. Although common diseases do not follow Mendelian inheritance patterns and the contribution of heredity to their pathogenesis may be hard to pinpoint, the genetic determinants of these complex traits are tractable. Knowledge of genetic predisposition will have broad consequences for preclinical diagnostics, preventive maneuvers, and therapeutic strategies.

Coronary heart disease (CHD) constitutes the major public health burden of industrialized nations. It causes nearly half a million deaths in the United States yearly (making it the single leading cause of death in the United States) and accounts for 13.7% of total mortality worldwide (7,375,000 deaths, according to World Health Organization estimates for 1998).1 CHD is multifactorial, and its progression is known to be influenced by risk factors such as cigarette smoking, elevated blood pressure, diabetes mellitus, obesity, aging, elevated serum LDL-cholesterol (LDL-C), and low-serum HDL cholesterol (HDL-C). Thus, plasma lipoprotein disturbances are among the most common biochemical abnormalities observed in patients with CHD. Moreover, many patients with CHD do not have markedly elevated LDL-C but rather have low HDL-C levels, either alone or accompanied by hypertriglyceridemia.

An important goal is to determine why certain people are singled out to suffer low HDL-C and CHD. We have learned that both diseases can be affected by certain behaviors, such as exercise, mild alcohol consumption, and hormone (estrogen) replacement therapy, yet there seem to be strong genetic influences on the HDL-C level. According to theories of inheritance of quantitative traits, disorders like HDL-C short-age involve many genetic determinants, the individual contributions of which can account for only a relatively small fraction of the variance.2 Thus, both low HDL-C and CHD present a much greater challenge for mapping and identification than do inherited Mendelian traits. The study by Lutucuta et al3 in this issue of Circulation Research describes 3 novel polymorphisms in the ATP-binding cassette transporter (ABCA1; formerly ABC1) gene: −477CT, −419A/C, and −320G/C. Their study provides evidence showing an association between the −477CT polymorphism and low HDL-C and CHD. Furthermore, these findings link CHD, a complex trait that involves multiple loci with a plethora of risk alleles, to Tangier disease, a trait that exhibits a major gene defect with Mendelian inheritance in affected families.

Tangier disease is a rare autosomal recessive genetic disorder with <100 cases reported in the literature so far. It is characterized by a severe deficiency or absence of HDL in plasma and an excess accumulation of cholesteryl esters in macrophages and other reticuloendothelial cells in a variety of tissues, resulting in neuropathies, splenomegaly, hepato-megaly, ocular abnormalities, and premature CHD. Tangier homozygotes also exhibit reduced LDL-C (~40% of normal).4 Using a graphical linkage exclusion strategy, Rust et al5 assigned the Tangier disease locus to a 7-cM region of chromosome 9q31. Subsequently, 3 separate study groups independently identified the Tangier disease gene to be ABCA1 and reported the gene locus and several mutations simultaneously in the August 1999 issue of Nature Genetics.6–8

The ABCA1 protein belongs to a superfamily of membrane transporters that bind and hydrolyze ATP to drive diverse substrates across membranes. ABCA1 stimulates cholesterol and phospholipid efflux to apolipoprotein (apo) A1 and may act as a cholesterol/phospholipid flipase at the plasma membrane level. This step is the first stage in reverse-cholesterol transport (RCT), which mediates the movement of cholesterol from peripheral cells, including macrophage-derived foam cells in the arterial wall, back to the liver, where it is catabolized. This pathway is crucial to counteract deposition of cholesterol by oxidized or otherwise modified LDL in macrophages that have infiltrated the arterial wall; ineffective cholesterol efflux promotes the formation of foam cells, the precursors of arterial lesions. Acquisition of cholesterol and phospholipid also protects the nascent lipid-poor apoA1 particles from rapid catabolism, thus enabling their transition to mature HDL.4

Patients heterozygous for ABCA1 mutations (Tangier dis-
ease heterozygotes or familial HDL deficiency) have about half-normal HDL concentrations, which correlates with the relative activity of the cholesterol efflux pathway in their cultured fibroblasts. This suggests that the ABCA1-mediated lipid secretory pathway contributes to a rate-limiting step in the production of HDL. Transfection of cells with the ABCA1 gene increases their capacity for cholesterol efflux. Thus, ABCA1 is the gatekeeper for cholesterol flux from tissues into the lipoprotein pathway-RCT.4

Genetic survey of the ABCA1 gene has revealed 23 variants in patients with Tangier disease or familial HDL deficiency.9 The study by Lutucuta et al3 characterizes 3 novel mutations in the ABCA1 gene, extending the number of mutations to 26. These authors demonstrate that −477CT heterozygotes display a modest reduction in HDL-C and apoA1 levels and a lesser response to treatment with fluvastatin. Furthermore, more patients with −477TT or CT genotypes had ≥1 coronary lesion than those with the CC genotype, and the mean number of coronary lesions causing 30% to 75% diameter stenosis was greater in patients with the TT or CT genotypes than those with the CC genotype.3

These data provide valuable insights for risk assessment of CHD and low HDL at the genetic level. However, because the data to some extent challenge previous observations with the ABCA1 gene, they will need to be confirmed with future studies. First, the lack of significant reduction in HDL-C and apoA1 (marker genotypes) in subjects with −477CT genotype makes the association of −477TT with CHD less clear. Previous studies have indicated that ABCA1 gene mutations result in a low HDL-C level, which, in turn, induces CHD. Thus, low HDL-C serves as a link between ABCA1 mutations and CHD.5 It must be noted, however, that in addition to its fundamental role in RCT, ABCA1 has diverse functions, all of which could contribute to atherogenesis. These include engulfment of apoptotic cells by macrophages, macrophage interleukin-1β secretion, and caveolae processing. Additional examination of these effects in vivo and acquisition of additional data in a larger cohort will likely reestablish the missing link. Second, the study was carried out in the Lipoprotein and Coronary Atherosclerosis Study patient population, which included men and women 35 to 75 years of age who had a mean LDL-C concentration of 115 to 190 mg/dL on a prescribed diet and showed angiographic evidence of ≥1 coronary atherosclerotic lesion causing 30% to 75% diameter stenosis. Studies on groups from different ethnic origins will help establish the association between −477CT, HDL levels, and CHD in a more generalized population. Furthermore, low HDL and CHD, because they are complex traits, involve a rather large number of common variants. The isolated effects of these variants on the disorder should be modest, but the attributable risk could be substantial. Indeed, several SNPs in multiple genes have been shown to influence lipoprotein levels or CHD. Such a list is expected to grow rapidly, because SNPs are receiving more and more attention in their use as genetic determinants for the study of complex human traits. The variants reported in this study probably represent a few of the many mutations, the effects of which are not negligible.

The ultimate goal is to search for a means of upregulating ABCA1 and correcting low HDL-C, thereby hindering the development of CHD. Recent progress has revealed that activation of peroxisome proliferator–activated receptors (PPARs), including PPAR-α and PPAR-γ, induces the expression of the ABCA1 gene via liver X receptor-α, and such induction of ABCA1 results in increased apoA1-induced cholesterol efflux from macrophages.10 Interestingly, gemfibrozil, a classic peroxisome proliferator, can reduce coronary events in patients with mild-to-moderate deficiency in HDL-C,11 although it is unclear whether such a strategy could be successful with individuals suffering from marked reduction in HDL-C. Furthermore, the responsiveness of patients with mutations in the ABCA1 gene, such as the −477CT polymorphism reported by Lutucuta et al,3 to such hypolipidemic fibric acid drugs remains to be determined. Nonetheless, identification of polymorphisms in the ABCA1 gene, as well as in other disease-related genes, may help to design new drugs that are most effective in a particular population with specific gene variants and to avoid exposing individuals to drugs that could be less effective or even harmful.

References


**Key Words:** polymorphisms ■ Tangier disease ■ HDL cholesterol ■ atherosclerosis ■ genetics
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