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Genetic underpinnings of LDL size and density: a role for hepatic lipase?[1,2]

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Plasma lipoprotein abnormalities underlie and may even be essential for the common occurrence of atherosclerotic vascular diseases in Western societies. The abnormalities include elevated concentrations of LDLs and VLDLs and reduced concentrations of HDLs, as generally estimated from measurements of plasma cholesterol, triacylglycerol, and HDL cholesterol. Drug therapies, particularly with compounds of the statin class, have revolutionized the treatment of these diseases and have prevented or postponed them in high-risk individuals. These interventions favorably affect all the major lipoprotein classes, but their effects have been attributed mainly to reduced concentrations of LDL cholesterol. This interpretation is consistent with the reduced incidence of arteriosclerotic manifestations produced by lipid-lowering therapies in patients with heterozygous familial hypercholesterolemia, whose predominant lipoprotein abnormality is an elevated concentration of LDL (1).

Other studies, however, indicate that the most pronounced lipoprotein abnormalities in patients with early-onset coronary heart disease are high plasma triacylglycerol and low HDL cholesterol, with lesser elevations of LDL cholesterol. But the LDL particles in these individuals are somewhat smaller and more dense than in those with a more favorable lipoprotein profile. As shown by Austin et al (2) at the Donner Laboratory, the occurrence of small, dense LDL particles has some genetic influence, but is more common in men than in premenopausal women and is strongly affected by plasma triacylglycerol concentrations. Persons with plasma triacylglycerol concentrations > 1.69 mmol/L (150 mg/dL) usually have small, dense LDL particles together with low concentrations of HDL cholesterol, whereas persons with triacylglycerol concentrations < 1.24 mmol/L (110 mg/dL) seldom have a predominance of small, dense LDL particles and usually have higher concentrations of HDL cholesterol as well. The constellation of small, dense LDL particles; high plasma triacylglycerol; and low HDL cholesterol has been termed the "atherogenic lipoprotein phenotype" (ALP). The relative contribution of the individual lipoprotein abnormalities that constitute the ALP to the increased risk of atherosclerotic vascular disease is unclear; however, plausible arguments for the atherogenicity of small, dense LDL particles, particularly an increased susceptibility to oxidative modification as compared with larger, more buoyant LDL particles, have heightened interest in this component of the ALP.

Predominance of small, dense LDL particles, which is commonly determined by gradient gel electrophoresis of apolipoprotein B–containing lipoproteins, is called LDL-subclass pattern B, whereas predominance of larger LDL particles is called pattern A. Small, dense LDL particles can be produced by the action of hepatic lipase on larger LDL species that are triacylglycerol enriched (3, 4). Triacylglycerol enrichment of LDL occurs through the action of plasma cholesteryl ester transfer protein (CETP) by exchanging cholesteryl esters of LDL with triacylglycerol contained in triacylglyceryl-rich lipoproteins (chylomicrons and VLDL) (5). Increased activity of CETP, but not its mass, in persons with hypertriglyceridemia promotes the heteroexchange of these nonpolar lipids. A similar situation occurs during postprandial hypertriglyceridemia, in which the concentration of cholesteryl esters in LDL falls as that in VLDL and chylomicrons rises.

The remodeling of LDL by hepatic lipase, however, is not wholly dependent on the action of CETP. In mice, which lack CETP activity, gene knockout of hepatic lipase drastically impairs the conversion of small VLDL remnants [chiefly, intermediate-density lipoproteins (IDLs)] to LDL, and the LDL particles of these animals are more buoyant than are those of wild-type mice (6). A human subject with genetically determined hepatic lipase deficiency was likewise found to have impaired conversion of IDL to LDL and to have unusually buoyant LDL (7).

Studies of twins indicate a strong genetic influence on hepatic lipase activity (8). By using sibling-pair analyses, Cohen et al (9) showed that a considerable fraction of the variation in human hepatic lipase activity can be accounted for by a single haplotype that defines 4 linked polymorphisms in the 5′-flanking region of the hepatic lipase gene. Homozygosity for the haplotype associated with low hepatic lipase activity occurs in ≈15% of whites of European origin but is 3 times more common in African Americans and contributes to the latter's significantly higher HDL-cholesterol concentrations. A similar situation was observed in Japanese (9, 10). The extent to which this common variation in the hepatic lipase gene—or in genes for other proteins that affect LDL remodeling directly or indirectly—contributes to LDL-subclass patterns remains to be determined. Zambon et al (10), however, recently reported that 1 of the 4 linked alleles in the 5′-flanking region

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(250G→A) was associated with high LDL buoyancy. Expression of another allele (514C→T) has been shown to lead to reduced transcription of the hepatic lipase gene (11).

Diets severely restricted in fat often lead to elevated plasma triacylglycerol concentrations and, not surprisingly, cause some individuals with LDL-subclass pattern A to convert to pattern B (12). As reported in this issue (13), the Donner Laboratory group assessed the heritability of this tendency to convert to pattern B in children of parents who had known LDL-subclass patterns when consuming ordinary diets. Because children seldom express pattern B, it was anticipated that most of them would express pattern A while consuming their usual diets, irrespective of the LDL pattern of their parents. This was indeed the case, but after 10 d of an isoenergetic diet with only 10% fat, none of the 19 offspring with 2 pattern A parents expressed pattern B whereas 9 of 21 offspring with 2 pattern B parents did. Of 10 offspring of A×B pattern parents, 1 expressed pattern B while consuming the 10%-fat diet.

The LDL peak particle diameter, assessed by gradient gel electrophoresis, fell on average in offspring of B×B and A×B parents but not in offspring of A×A parents; however, the change in LDL particle size correlated neither with basal plasma triacylglycerol concentrations nor with changes in triacylglycerol produced by the diet. Plasma triacylglycerol increased by 57%, 45%, and 17%, respectively, in offspring of B×B, A×B, and A×A parents, but differences among groups were not significant. An apparent anomaly in the 3 groups of children was a significantly higher basal concentration of LDL cholesterol in those with B×B parents; their LDL-cholesterol concentrations fell about twice as much as did those of the other 2 groups. Previous studies from the Donner Laboratory showed that individuals who express pattern B while consuming ordinary diets experience a larger decrease in LDL cholesterol when consuming low-fat diets than do individuals who express pattern A (12). Hepatic lipase activity in postheparin plasma usually decreases slightly (≈10%) when healthy persons consume low-fat diets (14, 15). Thus, changes in hepatic lipase activity are not likely to contribute to the expression of pattern B when these diets are consumed.

In an earlier study of lipoprotein responses to low- and high-fat diets by the Donner Laboratory group, men who expressed LDL-subclass pattern B while consuming both diets had higher hepatic lipase and lower lipoprotein lipase activities than did those who expressed pattern A with both diets, whereas those whose pattern changed from A to B had intermediate lipase activities (14). Postheparin lipase activities were not assessed in the children (all offspring of white parents) in the current study (RM Krauss, personal communication, 2000).

The potential clinical significance of heritability of LDL-subclass pattern is heightened by a recently reported subgroup analysis of outcomes in the Familial Atherosclerosis Treatment Study, in which men with documented coronary heart disease and high concentrations of apolipoprotein B were treated intensively with hypolipidemic drug combinations (16). In addition to lowering LDL concentrations, treatment was associated with increased LDL buoyancy and reduced hepatic lipase activity. Furthermore, in multivariate analysis, change in LDL buoyancy was most strongly associated with regression of atherosclerotic lesions of the coronary arteries as assessed by angiography; reduction in apolipoprotein B concentration had little independent effect. The changes in LDL buoyancy were highly correlated with (and likely caused by) changes in hepatic lipase activity.

Overall, the results of the study by Dreon et al (13) clearly support a strong genetic influence on the expression of LDL-subclass pattern in children exposed to the stress of a diet very low in fat and high in carbohydrate. Given the emerging evidence for an influence of genetic variation in hepatic lipase on LDL as well as on HDL particle size and density, it is reasonable to postulate that genetically determined variation in hepatic lipase activity contributes to familial aggregation of LDL-subclass patterns. Such genetic variation may also influence the response of LDL subclasses to diet and lipid-lowering drugs.

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