Editorial Comment

Familial Hypercholesterolaemia in Greece

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Heterozygous familial hypercholesterolaemia (FH), an autosomal dominant disorder due to a defect in the low-density lipoprotein receptor (LDLR) gene, is characterised by a pronounced increase in plasma total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) concentrations and clinically by premature cardiovascular disease (CVD). About 50% of individuals with FH die before the age of 60 due to myocardial infarction.[1] The frequency of heterozygous FH is estimated to be 1:500.[1]

The wide variability in the biochemical expression of FH has been explained by mutational heterogeneity, variations in the type of LDLR gene mutation, allelic variations at other gene loci, as well as environmental factors.[2,3] Data from Canada [French Canadians from Quebec show a higher frequency of FH (1/270)] suggest that the phenotype of a "simple" monogenic disorder, such as FH, is in fact a complex trait.[2] It is therefore important to examine the range of phenotypic variability associated with a single LDLR gene mutation. Few have had this opportunity because of the lack of sufficiently large groups of patients carrying the same mutation.[4-6]

Apolipoprotein (apo) E plays a central role in the metabolism of cholesterol and triglycerides (TG). The apoE gene locus on chromosome 19 is polymorphic with 3 common alleles: 2, 3, and 4, encoding the 3 different protein isoforms E2, E3, and E4, respectively. The E2 and E4 variants differ from the more common E3 variant by a single amino acid substitution. These substitutions affect ligand binding of TG-rich lipoproteins to their receptors.[7] In healthy adults, between 4% and 8% of the total variance in plasma LDL-C concentrations can be attributed to the common apoE polymorphism.[7]

The paper by Miltiadous et al in this issue[8] describes the genetic database of FH in north-western Greece and elucidates the geographic distribution of the most frequent mutations. Also, the study suggests that heterozygous FH is associated with lower high-density lipoprotein cholesterol (HDL-C) levels, compared to the general population and that this decrease is related to apoE gene polymorphism. The results of the study also indicate that the type of the LDLR gene mutation may affect not only the conventional lipid parameters, but also lipoprotein (a) [Lp(a)] levels in patients with homozygous FH.

The identification of individuals with FH to date in Greece has been based on lipid levels and segregation of these levels within the family. However, phenotypes overlap and family history is not always informative. Therefore, a DNA-based genetic test for FH appears to offer the best alternative. The FH test is a definitive tool for the identification of affected family members. The approach of targeted family genetic screening to find new pa-

tients is faster and more reliable compared with a biochemical form of screening. Early identification and efficient treatment of such patients is important and highly cost effective.[1] There is evidence to suggest that the nature of the LDLR mutation influences the degree of cholesterol lowering achieved by statins. Thus, the construction of a database of FH in Greece is per se highly important.

It has been suggested that the apoE genotype does not contribute significantly to the risk for CVD.[9] A study from Spain reported that heterozygous men with FH have a very high risk of CVD for a Mediterranean country, and the apoE genotype in this group of adults with FH is not associated either with CVD or lipid values, in contrast with the established effect in the general population.[9]

This finding is not in agreement with those of other studies from Holland, Spain and Greece.[10-12] The study from Holland reported that in FH children the E4 allele was associated with lower HDL-C levels in an affected sib-pair analysis, thus suggesting an additional disadvantage for FH children.[10] The study from Spain investigated 108 heterozygous FH subjects aged >35 years (41 males). It was a cross-sectional study comparing individuals with FH and myocardial infarction (MI) with individuals with FH without MI. The results suggested that in FH subjects aged >35 years, MI is associated with age, plasma TC and LDL-C values, TC/HDL-C ratio and the E4 genotype.[11] Finally, the study from Greece concluded that HDL-C levels in heterozygous FH patients may be affected by the apoE gene polymorphism.[12]

The class of the LDLR gene mutation can affect not only HDL-C but also the LDL-C response to statins.[13] Subjects with FH with null mutations (class I) showed lower plasma HDL-C values and an inferior LDL-C response to simvastatin treatment.[13] This finding was confirmed by another study,[14] which reported that among heterozygotes for a receptor-negative LDLR mutation, 51% of the variability in LDL-C response was explained by variations in the dosage of simvastatin expressed in mg/kg/day ($p=0.0028$).[14] The results of this study showed that the contribution of apoE polymorphism and the dosage of simvastatin to the LDL-C responsiveness are influenced by the nature of the LDLR gene mutation.[14]

Lp(a) is a quantitative genetic trait that in the general population is largely controlled by 1 major locus: the locus for the apolipoprotein(a) [apo(a)] gene. Sib pair studies in families including FH heterozygotes have demonstrated that mutations in the LDLR gene may affect Lp(a) plasma concentrations.[15] Raised plasma Lp(a) is associated with increased risk of CVD. Given the interactive effect of elevated LDL-C and high Lp(a) on CVD risk the data suggest that elevated Lp(a) may add to the CHD risk in FH subjects.[16,17] This is an important consideration in Afrikaner FH families, where plasma levels of Lp(a) have been shown to be elevated significantly in FH patients compared with non-FH individuals.[18]

Lp(a) levels are genetically predetermined. The therapeutic option for high-risk FH heterozygotes with raised plasma Lp(a) is LDL apheresis,[18] which is very expensive. Nevertheless, primary angiographic endpoints showed that decreasing Lp(a) seems unnecessary if LDL-C is reduced below 130 mg/dl.[19]

The results of an interventional study with statins, including a large cohort (n=325) of FH heterozygotes,[20] showed that long term statin treatment (2 years) significantly lowers Lp(a) in FH patients, although this reduction was unrelated to changes in carotid intima-media thickness.

The relationships shown between LDLR mutation types and lipid levels, and the response of lipid levels to statin treatment, will have to be investigated within the framework of pharmacogenetic studies.[1] The variables that are important in determining the overall atherosclerosis risk are the result of combined activity in a dynamic network of numerous genes and environment. Candidate genes for atherosclerosis need to be further tested and validated. Future research should be directed at determining the significance of such targets, as well as the identification of high-risk FH patients.

Genetics-based diagnostics will favour the rapid identification of FH, as well as early diagnosis and treatment leading to the prevention of CVD.

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