NEW GENETIC MARKERS IN THE ASSESSMENT OF THE PROGNOSIS OF CORONARY ARTERY DISEASE

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Abstract. From work done in the lipoprotein area to this point a clear case that can be made for: 1) the genetic influence over the phenotypic response to an environmental stimulus; 2) the environmental modulation of the phenotypic expression of severe genetic defects. In the realm of gene-environment interactions that affect lipoprotein phenotype, diet is the best-studied environmental factor.

Introduction. There are numerous risk factors (proven and theoretical) for atherosclerosis. Epidemiologic studies have shown that one factor which is strongly associated with atherosclerosis risk is the plasma concentration of lipids. The strongest association between dyslipidemia and heart disease occurs in patients with a family history of dyslipidemia and heart disease. However, serum levels of lipoproteins are neither exclusively nor infallibly predictive of atherosclerosis risk. Examination of the component of atherosclerosis risk that is attributable to dyslipidemia indicates that both environmental and genetic factors influence the metabolism of lipoproteins within the whole person. Genes and environmental factors interact in complex ways to modulate lipoprotein levels. Identification of individual genetic and environmental components is complicated, but is essential for a clear understanding of the evolution of the disease and for development of interventional strategies.

The four categories of gene products that determine the genetic component of inter-individual variation in lipoproteins are: 1) the apolipoproteins (apo-A1, AII, AIV, H, CI, CII, CIII, E and apo[a]); 2) receptors (low density lipoprotein receptor [LDLR], LDLR-related protein [LRP or 2-macroglobulin receptor], and the "scavenger" receptor); and 3) modifying enzymes (lipoprotein lipase [LPL], hepatic lipase [HL], lecithin:cholesterol acyltransferase [LCAT] and cholesterol ester transfer protein [CETP]), and 4) undefined or uncharacterized proteins involved in lipoprotein synthesis or secretion. The genes for most protein products involved in lipoprotein metabolism have been cloned, and genetic variants have been identified. Genetic markers for these proteins, whose function is at least partly understood, permits the analysis of the contribution of variation at candidate genes to lipid phenotype.

Once the genetic factor has been identified, the interactive effect of other genetic and/or environmental factors upon the lipoprotein phenotype can be assessed using a variety of approaches. Dietary cholesterol and fat induce increases in plasma cholesterol and lipoproteins. Although of potentially great clinical and biological importance, the role of genotype-diet interaction in human lipoprotein metabolism is still poorly understood. Recently, analytic strategies have been described that can address this issue.

Because of the problems related to identifying the effects of genes within unrelated subjects, the best strategies will identify GxE interactions in kindreds, and the results might then be applicable to subgroups within the general population. There is evidence for significant gene-environment (GxE) interactions in humans. Kagan, et al showed that mean cholesterol levels in ethnic Japanese men whose predecessors had migrated to Hawaii were higher than those of similarly aged men in Japan. Furthermore, levels among ethnic Japanese immigrants in California were higher still. With some simple tests to ensure that the groups were genetically comparable, the authors concluded that environmental factors had an impact on the expression of phenotype.

Cox, et al showed that among homozygotes for a mutant form of apoCII, those who remained on their home island in the Caribbean never had hypertriglyceridemia severe enough to produce pancreatitis. However, among those who had moved to the mainland, the incidence of pancreatitis was alarmingly high. This would suggest that some feature of island life (likely diet) was helping to restrain the expression of the most debilitating symptom related to this dyslipidemia. A change in environment, however, resulted in decompensation and excess morbidity. A recent case report described an 88-year-old man who, despite consuming two dozen hard boiled eggs per day for two decades had normal plasma cholesterol and no evidence of atherosclerotic disease. The author hypothesized that this patient had extremely effective compensatory mechanisms that developed in response to the high cholesterol diet. The implication was that the only unusual feature of this man was his dietary habit and that most people, given sufficient time, could de-
velop a similar tolerance to a high cholesterol diet. But the mechanism for this man's remarkable resistance to dietary cholesterol could not have been merely reactive to diet and independent of unique endogenous genetic biochemical and metabolic characteristics. If there was no role for the endogenous component, then the reasoning carried to its extreme would suggest that a sustained high cholesterol diet could be used therapeutically in everyone in order to lower cholesterol over the long term. Even the most strident critic of the cholesterol-atherosclerosis hypothesis might balk at this suggestion. A likely explanation for the strong resistance to diet in this unique subject is that he is endowed with a genetic armamentarium that allowed him to combat an environmental ballistic assault of dietary cholesterol.

Finally, in a unique study of an eight-generation Utah Mormon family that had a large number of individuals with FH due to a proven genetic LDL-receptor lesion showed that mutant gene carriers who lived in the 1800s survived on average 10-15 years longer than contemporary carriers of the same gene defect. The explanation for this observation is likely the difference in lifestyle factors, especially diet, in the 1800s compared with the current century. The Utah pioneers were physically active, agrarian and largely vegetarian in the early years after migrating to the Salt Lake Valley. Livestock were few and valuable and thus not often consumed as meat. Data from this study, and others, seem to indicate that cultural factors at different times in history, such as diet, can alter the severity of a normally prematurely fatal phenotype. Non-molecular studies in other Mormon FH families confirmed the paradigm of gene-diet interactions manifested as differences in longevity. In practical terms, we were able to advise these families that if they adopted the more prudent diet and more active lifestyle of their ancestors, they could be expected to overcome the severe prematurity of the CAD conferred by the genetic problem.

It is clear that genetic and dietary factors can interact to varying degrees in a given individual to determine lipid phenotype. A number of the components involved in these interactions can be discerned in those individuals who have specific lipid phenotypes that have a proven biochemical and molecular basis. However, some vegetarians with "acceptable" cholesterol levels suffer myocardial infarctions in their 30's. Other individuals, like Winston Churchill, seem to live forever despite personal stress, smoking, obesity and poor adherence to a Heart Association-approved diet. These examples may be equally convincing of the existence of GxE interactions. In some cases, genetically-determined resistance to CAD (conferred by genetic hyperalpha- or hypobeta-lipoproteinemia), or genetically-determined susceptibility to CAD (conferred by high Lp(a) levels — a genetic trait) may not be significantly modulated by a prudent diet.

Estimates of the prevalence in the general population of these genetic extremes average around 5%. In the remaining 95% of cases, nature and nurture interact. For example, a genetic flaw that is usually expressed phenotypically as premature death due to CAD (e.g., some cases of FH) can be ameliorated by a prudent diet. Alternatively, genetic factors (such as apoE phenotype) can strongly affect an individual's response to diet.

There is little doubt that an individual's responsiveness to various environmental factors can be determined by many different genes. The precise candidate gene mutations and the nature of most of the genetic changes affecting response to environment still need to be determined. Once identified, they may one day form the basis for early diagnosis of metabolic problems and prescribing individually-tailored diet and drug treatment.

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REFERENCES


