Annotation

Genetics of the responsiveness of serum cholesterol to diet

In developed nations most people eat diets high in saturated fat and cholesterol, but not all of them are hypercholesterolaemic. Such hypercholesterolaemia is occasionally secondary to diseases such as hypothyroidism and, in a minority of patients, results from a major inherited disorder of lipoprotein metabolism. A sizable proportion of the mild hypercholesterolaemia that is so widely found in developed nations must, however, result from some interaction between genes and environment: some people appear to be genetically more sensitive than others to environmental causes of hypercholesterolaemia.

Xu et al [1] searched for a basis for genetic susceptibility to diet-induced hypercholesterolaemia by analyzing the DNA of 107 Finnish men and women who had participated in trials of a cholesterol-lowering diet in the early 1980s. Blood lipid levels were first measured when participants were eating their self-selected diets high in saturated fat and cholesterol, and again after six weeks of a diet low in total and saturated fat and cholesterol, and high in polyunsaturated fat. Both serum low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels fell markedly on this diet. Recently the Finnish investigators went back to this study group and obtained blood for analysis of DNA. By combining resources from Helsinki, London, Houston, and Dallas, Xu et al were able to measure the extent of heterogeneity at various sites in the gene for the LDL receptor and in the genes for most apolipoproteins. The responses of lipoprotein concentration to the diet were related to genetic makeup. Only one strongly significant relationship was found: a single base pair mutation (guanine -> adenine) in the cutting site for the MspI restriction enzyme in the gene for apoB was associated with a difference in the response of serum apoA-I concentration to the diet used.

A major problem in such studies is deciding how strong an association must be before it may be considered significant. Because Xu et al were entering a new field, they used a broad approach, relating differences in 16 genetic loci to changes in all seven plasma lipids and apolipoproteins that had been measured. In such a situation, the use of a conventional significance level of 5 percent is likely to lead to the result that one of the 7 x 16 = 112 associations would prove to be statistically 'significant' by chance. The authors therefore set P at 1 percent. This reduces the occurrence of spurious correlations, but increases the risk that experimental 'noise' will obscure a real association.

The problem is illustrated by two other papers, in which Tikkanen et al [2,3], analyzing the same data in a different manner, concluded that significant associations did exist between differences in the response of plasma lipids to diet and differences in the genes for both apoB and apoE. Individuals whose apoB gene possessed a sequence recognizable by the XbaI restriction enzyme showed a greater fall in plasma cholesterol, LDL and HDL cholesterol, and plasma apoB levels than did those whose apoB gene lacked this site [2]. Also, the eight participants whose apoE was exclusively of the E4 type, i.e., who were E4/E4 homozygotes, showed a significantly larger fall in plasma and LDL cholesterol than did the other 102 subjects, who had E3/E4, E3/E3, or E3/E2 phenotypes [3]. This finding is in partial agreement with the observation by Miettinen et al [4] that the response of LDL and total cholesterol to egg yolk was higher in nine men with the apoE3/E4 and one with the E4/E4 phenotype than in six E3/E2 and E2/E2 men. Other groups, however, have failed to find an association between apoE phenotype and response of plasma lipids to diet [5,6]. Clarification of these relationships will require total control of diets in large studies that will obtain large numbers of measurements for each participant to reduce experimental 'noise'. In the meantime, evidence that the response of plasma lipids to diet is determined genetically remains circumstantial.

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Meetings

May 13–16, 1992; Florence, Italy
XIth International Symposium on Drugs Affecting Lipid Metabolism (DALM) (Palazzo dei Congressi-Palazzo Affari, Piazza Adua I, Florence, Italy; Phone 029 7838 68)

May 17–21, 1992; Nice, France
59th European Atherosclerosis Society (EAS) (Acropolis Congress Center, Nice, France; Phone: 33 9 316 0803)

May 21–23, 1992; Orlando, FL USA
International Symposium on Coronary Risk Factors in Youth (Conference Manager, 875 Kings Highway, West Deptford, NJ 08096, USA; Phone: 609 845 7220, Fax: 609 853 0411)

August 30–September 3, 1992; Barcelona, Spain
XIVth Congress of the European Society of Cardiology (ECCO, Clarastrasse 57, PO Box 6, CH-4005, Basel, Switzerland; Phone: 61 691 5111, Fax: 61 691 8189)

October 5–8, 1992; Osaka, Japan
2nd International Symposium on Multiple Risk Factors in Cardiovascular Disease (5-7-1 Fujishirodai, Suita City, Osaka 565, Japan; Phone: 81 06 833 5012, Fax: 81 06 872 7485)

November 16–19, 1992; New Orleans, LA, USA
65th Scientific Sessions of the American Heart Association (American Heart Association, Scientific and Corporate Meetings, 7320 Greenville Ave, Dallas, TX 75231, USA; Phone: 214 706 1253, Fax: 214 373 3406)

Published by Current Medical Literature Ltd, 40–42 Osnaburgh Street, London NW1 3ND

ISSN 0950–5857

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4-94 MVC-92-R-17035-NL-CCS