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Short Quick Report

Smoking and reverse cholesterol transport: evidence for gene-environment interaction

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Lipid metabolism, like all other life processes, is determined by genetic factors, environmental influences and their joint action. In quantitative genetics we usually model this process as the linear effects of genes, environment and their interactions. Recently Kondo et al. (1989) reported that DNA polymorphisms at the locus for human cholesteryl ester transfer protein (CETP) were associated with interindividual differences in plasma levels of apolipoprotein A-I. The genetic effect was found in non-smokers only. We report here another example of the role of gene-environment interaction in determining the components of lipid metabolism.

We have examined the impact of a polymorphic structural variation of a candidate gene, Apolipoprotein (apo) H, on nine lipid and apolipoprotein phenotypes (Kaprio et al. 1989). Apo H has recently been assigned to the class of apolipoproteins, but its physiological role is still poorly understood. Structural heterogeneity of apo H has recently been determined (Kamboh et al. 1988) and three common alleles of the structural gene coding for the protein have been observed in Caucasians.

We identified 567 unrelated adults aged 26–62 from the Rochester Family Heart Study (Moll et al. 1989, Turner et al. 1989). After excluding persons (n = 72) using medications that may influence plasma lipid levels and those who had not been genotyped for apo H (n = 15), 480 persons (240 men, 140 women) formed the sample for analysis. Ninety-two were current smokers and 388 had never smoked or were former smokers.

We found (Kaprio et al. in preparation) that smoking has a significant effect on HDL-cholesterol, apo A-I and apo A-II levels (adjusted for date of assay, age, age^2, weight and height) in men and women. As the apo H polymorphism showed significant effects after each phenotype was also adjusted for smoking status, we decided to test for an interaction between apo H genotypes and smoking. The rarer genotypes of apo H were combined in this analysis to create two groups: genotype apo H 2-2 (n = 390) and all others (n = 90). HDL-cholesterol, apo A-I and apo A-II values were adjusted by linear regression for date of assay, age, age^2, weight and height for each gender separately. A general linear model (SAS Institute

Inc. 1985) was used with three independent variables: smoking status (current vs non-current), genotype (apo H 2-2 vs. others) and gender to test for main effects and interactions. Results for the analysis of apo A-II are shown in Table 1. The three-way interaction of gender, smoking and genotype was non-significant. Thus the three two-way interactions could be examined. Only the interaction of genotype and smoking was found to be statistically significant at the 0.05 level of probability. The main effects were significant for genotype and smoking. The effect of smoking was to decrease apo-AII levels in subjects with the apo H 2-2 genotype, but not in subjects with other genotypes. For HDL and apo-AI, the interactions of genotype and smoking were not statistically significant.

Apo A-I and apo A-II are the major protein components of HDL, which participates in the 'reverse cholesterol transport' of excess cholesterol from the extrahepatic tissues to the liver for catabolism. CEPT is also involved in this process. Smoking is known to depress levels of HDL-cholesterol and apo A-I (Berg et al. 1979), as was found in the present study. Our study and the report of Kondo et al. (1989) suggest that the effects of smoking are dependent on the genotype of certain genes coding for proteins participating in reverse cholesterol transport. We can only speculate on the mechanism for this process, because smoking affects many metabolic parameters (Laustiola et al. 1988). There may be chemical components of tobacco smoke that directly modify the composition or structure of HDL-particles. Alternatively smoking may alter the physicochemical milieu, which indirectly affects the metabolic pathways that are involved. It is known that smoking has a significant impact on quantitative levels of a number of plasma proteins involved in determining cardiovascular disease risk (Berg et al. 1979, Wilhelmsen et al.

Table 1

Interaction of smoking with apo H genotypes on levels of apo A-II. Mean levels of apo A-II (mg/dl) by smoking status and apo-H genotype (2-2 vs non:2-2) in unrelated individuals from Rochester, Minnesota. (N of subjects in parentheses)

Smoking status	Men Genotype 22	Men Genotype Non-22	Women Genotype 22	Women Genotype Non-22	Total Genotype 22	Total Genotype Non-22
Smoker	32.25 (39)	36.21 (8)	31.55 (31)	33.13 (10)	31.94 (70)	34.50 (18)
Non-smoker	34.91 (159)	34.12 (34)	34.34 (161)	35.25 (38)	34.64 (320)	34.71 (72)

Analysis of variance

Source	Partial Sum of Squares	F-value	P-value
Main effects:			
Smoking	84.9	4.42	0.036
Genotype	91.1	4.74	0.030
Gender	29.6	1.54	0.22
Two-way interactions:			
Genotype by smoking	84.0	4.37	0.037
Smoking by gender	53.9	2.81	0.09
Genotype by gender	1.32	0.07	0.79
Three-way interaction:			
Genotype by gender by smoking	47.3	2.46	0.12

1984). It will be of interest to determine whether these effects are genotype specific.

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