PRELIMINARY REPORT

The Relationship Between Smoking and Triglyceride-Rich Lipoproteins Is Modulated by Genetic Variation in the Glycoprotein IIIa Gene

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In the last year, several studies have reported conflicting results concerning an association between the PI^{A2} allele of the $PI^{A1/A2}$ polymorphism of platelet glycoprotein IIIa and the risk of myocardial infarction. In the present study, we analyzed the hypothesis of whether glycoprotein IIIa genotypes have any association with lipids and lipoproteins as classical cardiovascular risk factors. Smoking, associated with changes in triglyceride-rich lipoprotein (TRL) concentrations and with both hypercoagulability and reduced fibrinolysis, was also analyzed as an environmental factor. Blood samples were obtained from 170 subjects (83 men and 87 women; mean age, 57 years; SD 15) recruited by random sampling from the census of Girona, Spain. Subjects were classified as current smokers (n = 41) and nonsmokers or exsmokers (n = 129). Whereas no differences were found in lipid and lipoprotein concentrations between smokers and nonsmokers in subjects with the $PI^{A1/A1}$ genotype, smokers with the $PI^{A1/A2}$ or $PI^{A2/A2}$ genotypes showed significantly higher triglyceride and very-low-density lipoprotein (VLDL) triglyceride concentrations than nonsmokers or exsmokers with the same genotypes. Similarly, the VLDL triglyceride/HDL cholesterol ratio was significantly different in subjects with the $PI^{A1/A2}$ or $PI^{A2/A2}$ genotypes stratified according to smoking status. Further analysis revealed a significant interaction between smoking and genotype when those homozygous for the allele PI^{A1} were compared with one or two PI^{A2} alleles for the three lipidic parameters. The observed effects appear to show links between smoking, triglyceride metabolism, and a glycoprotein involved in platelet aggregation. It is likely that the PI^{A} polymorphism is in linkage disequilibrium with other functional mutations that might influence triglyceride metabolism under some environmental factors such as smoking. This finding may provide a new perspective in the complex relationship between glycoprotein IIIa gene, environment, and their interactions.

IN THE LAST YEAR, several studies have reported conflicting results concerning an association between the PI^{A2} allele of the $PI^{A1/A2}$ polymorphism of platelet glycoprotein IIIa and the risk of myocardial infarction.[1-4] On the other hand, the existence of an interracial heterogeneity of PI^{A} alleles appears to be demonstrated. Coronary artery disease has a multifactorial origin in which gene-gene and/or gene-environment interactions may be required among specific ethnic groups for the disease to develop. In the present study, we analyzed the hypothesis of whether glycoprotein IIIa genotypes have any association with lipids and lipoproteins as classical cardiovascular risk factors. Smoking, associated with changes in triglyceride-rich lipoprotein (TRL) concentrations and with both hypercoagulability and reduced fibrinolysis, was also analyzed as an environmental factor.

SUBJECTS AND METHODS

Blood samples were obtained from 170 subjects (83 men and 87 women; mean age, 57 years; SD 15) recruited by random sampling from the census of Girona, Spain. The $PI^{A1/A2}$ polymorphism of platelet glycoprotein IIIa was identified by polymerase chain reaction. Serum cholesterol and triglyceride levels were analyzed by enzymatic procedures together with very-low-density lipoprotein (VLDL)-, low-density lipoprotein (LDL)-, and high-density lipoprotein (HDL)-lipid concentrations after their isolation by ultracentrifugation. Information on smoking was recorded with a standardised questionnaire. Accordingly, subjects were classified as current smokers (n = 41) and nonsmokers or exsmokers (n = 129).

RESULTS

One hundred twenty-nine individuals (75.9%) had the $PI^{A1/A1}$ genotype, 38 (22.4%) the $PI^{A1/A2}$ genotype, and three (1.8%) the $PI^{A2/A2}$ genotype. Subjects were classified into two groups: those who were homozygous for the PI^{A1} allele and those who had one or two PI^{A2} alleles.

The two-genotype groups were comparable for age, physical activity (kcal/d) and alcohol consumption (g/wk). Also, no significant differences were observed between PI^{A} genotypes in lipid and lipoprotein concentrations.

In a following step, subjects were classified according to smoking status. No significant differences were found on age, physical activity, and alcohol consumption between smokers and nonsmokers. However, whereas no differences were found in lipid and lipoprotein concentrations between smokers (n = 28) and nonsmokers (n = 101) in subjects with the $PI^{A1/A1}$ genotype, smokers with the $PI^{A1/A2}$ or $PI^{A2/A2}$ genotypes (n = 13) showed significantly higher triglyceride and VLDL triglyceride concentrations than nonsmokers or exsmokers (n = 28) with the same genotypes (138 mg/dL [87 to 244 mg/dL] *v* 86 mg/dL [65 to 122 mg/dL], $P = .02$; and 98 mg/dL [39 to 175 mg/dL] *v* 36 mg/dL [12 to 53 mg/dL], $P = .02$, respectively; median [interquartile range]). Similarly, the VLDL triglyceride/HDL cholesterol ratio, which reflects triglyceride catabolism,[5,6] was significantly different in subjects with the $PI^{A1/A2}$ or $PI^{A2/A2}$ genotypes stratified according to smoking status (2.72 [0.76 to 4.29] in smokers *v* 0.61 [0.20 to 1.10] in nonsmokers or exsmokers; $P = .01$). Two-way interaction between PI^{A} geno-

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Table 1. Interaction of PI^A Genotype With Smoking on Levels of Serum Triglycerides, VLDL Triglycerides, and VLDL Triglyceride/HDL Cholesterol Ratio

	Triglycerides		VLDL Triglycerides		VLDL Triglyceride/HDL Cholesterol Ratio	
Variable	F Value	*P* Value	F Value	*P* Value	F Value	*P* Value
Covariables						
Sex	3.76	.054	5.72	.018	5.49	.021
Body-mass index	13.06	.000	11.00	.001	11.32	.001
Main effects						
Smoking	7.76	.006	9.15	.003	4.86	.029
Genotype	3.20	.075	5.58	.020	2.50	.116
Interaction						
Genotype by smoking	8.17	.005	8.59	.004	4.49	.036

type and smoking in the determination of $\log_{10}$-transformed serum triglyceride levels, VLDL triglycerides, and the VLDL triglyceride/HDL cholesterol ratio was estimated by ANOVA adjusting by body-mass index and sex (Table 1). This analysis showed a significant interaction between smoking and genotype when those homozygous for the allele PI^{A1} were compared with those with one or two PI^{A2} alleles for the three lipidic parameters.

DISCUSSION

The observed effects appear to show links between smoking, triglyceride metabolism, and a glycoprotein involved in platelet aggregation, with the latter being an important step in blood coagulation. TRL are thought to activate the intrinsic coagulation pathway and positive correlations are observed between their levels and fibrinogen, the most important ligand of platelet glycoprotein IIb/IIIa. Since, theoretically, the PI^A polymorphism should not regulate lipoproteins, it is likely that the PI^A polymorphism is in linkage disequilibrium with other functional mutations that might influence triglyceride metabolism under some environmental factors such as smoking. Thus, the PI^{A2} allele might be disadvantageous if it is associated with increased TRL levels. Although it will be necessary to examine interactions in other studies, preferably of a prospective nature, the relationship between smoking and TRL may be modulated by genetic variation at the glycoprotein IIIa gene. This finding may provide a new perspective in the complex relationship between glycoprotein IIIa gene, environment, and their interactions.

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