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Mini Review

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Apoprotein E and lipoprotein (a) genetics as markers for coronary heart disease

Abstract

This review focuses on two apolipoproteins markers for coronary heart disease; Apoprotein E and lipoprotein (a) with their respective genetic characteristics. The E2E2 genotype determines lower levels of LDL-c than those observed for the other two phenotypes. The mechanism by which the E2 allele would be related to low LDL-c levels seems to be the weak binding that E2 establishes with the receptor protein, which decreases and/or delays the removal of chylomicrons and VLDL-c. Decreased rates of coronary heart disease were not observed in individuals carrying the E2 allele, and it has been suggested that the lack of protection is due to the hypertriglyceridemia associated with it. Plasma lipid levels of diabetics with this gene were not different from those observed in diabetics without E4. The E4 allele also seems to be associated with a type of hypercholesterolemia, determined by a polygenic genetic mechanism, in which those affected have LDL-c levels above 190 mg/dl and do not have xanthomas. Those affected are more often of homo or heterozygous genotype for this allele. Lipoprotein (a) is a genetic marker with an inheritance pattern involving the action of an autosomal gene with the main effect on determining its levels, which also suffer the action of polygens. The interest in this lipoprotein stems from several clinical studies, which have established a significant correlation between its high levels and the development of coronary and cerebrovascular disease. Individuals with levels above 30 mg/dl have a two-fold higher risk of developing coronary atherosclerosis. It has been suggested that Lipoprotein (a) competes with plasminogen in its binding with its endothelial receptor, which is a dependent domain. Such competition would interfere with the mechanism of fibrinolysis, facilitating atherosclerosis.

Keywords: Apoprotein E, lipoprotein (a), genetic markers, risk factors, coronary heart disease

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Abbreviations: Apo, apolipoprotein; LDL-c, low density lipoprotein cholesterol; Lp(a), lipoprotein (a); VLDL-c, very low density lipoprotein cholesterol

High-risk genetic markers

It has been suggested that apolipoprotein (Apo) E (E2 and E4) alleles may represent genetic markers for identifying individuals at high risk for developing coronary heart disease. Individuals with genotype E4E4 and E4E3 have higher levels of low-density lipoprotein cholesterol (LDL-c) and total cholesterol than E3E3 individuals, and are particularly susceptible to the early development of coronary heart disease. Van Bockxmeer, Mamotte[1] described a 16-fold higher prevalence of the E4E4 genotype among men under 40 years of age who were referred for angioplasty, and Lenzen et al.[2] reported that the E3E4 genotype seems to be associated with the earlier age of individuals with myocardial infarction. The E2E2 genotype determines lower levels of LDL-c than those observed for the other two phenotypes. The mechanism by which the E2 allele would be related to low LDL-c levels seems to be the weak binding that E2 establishes with the receptor protein, which decreases and/or delays the removal of chylomicrons and very low density lipoprotein cholesterol (VLDL-c).[3,4] Decreased rates of coronary heart disease were not observed in individuals carrying the E2 allele, and it has been suggested that the lack of protection is due to the hypertriglyceridemia associated with it.[5,6] In the study by Wilson et al.[7] triglyceride levels were moderately high in women and quite high in men, both with the E3 allele and with the E4 allele, but the risks in both sexes for the development of coronary heart disease were significant only for E4. In this study, 15% of the prevalence of coronary heart disease (11% in men and 19% in women) was attributed to this allele. Confirming results from several other studies, total cholesterol and LDL-c levels were lower for the E2 allele and higher for the E4[8-12] allele.

In a study that evaluated the occurrence of the E4 phenotype in 113 individuals with hypertension, Kesäniemi et al.[13] did not observe differences in the frequency of this gene between hypertensive and control individuals, but hypertensive individuals with E4 presented higher levels of VLDL-c and triglycerides than controls of the same genotype. The lipid levels observed were particularly high in E4 individuals using diuretics and beta-blockers, which, according to the authors, is suggestive that hypertensive individuals with E4 may develop severe dyslipidemias, particularly when submitted to those medications. In another study[14], the same group evaluated whether the risk of developing coronary heart disease in non-insulin-dependent individuals with diabetes mellitus would be related to the phenotypic pattern of Apo E. The results obtained showed that the presence of E4 increased the risk, but the plasma lipid levels of diabetics with this gene were not different from those observed in diabetics without E4. The E4 allele also seems to be associated with a type of hypercholesterolemia, determined by a polygenic genetic mechanism, in which those affected have LDL-c levels above 190 mg/dl and do not have xanthomas. Those affected are more often of homo or heterozygous genotype for this allele.[15-17]

Another genetic variant that has received attention is lipoprotein (a) - Lp(a). The interest in this lipoprotein stems from several clinical studies, which have established a significant correlation between its high levels and the development of coronary and cerebrovascular disease. Individuals with levels above 30 mg/dl have a two-fold higher risk of developing coronary atherosclerosis, and if there is concomitance with high LDL-c levels, the risk is five times higher.[18,19] It has also been shown that high levels of Lp(a) are predictors of stenosis in saphenous veins transplanted in myocardial revascularization.[20]

The described association between elevated Lp(a) levels and coronary heart disease is not observed in all racial groups. Guyton et al.[21] recorded levels almost twice as high in black individuals than those observed in whites. However, the mortality rate from coronary heart disease in blacks is lower than that recorded in whites.

Lp(a) is a genetic marker with an inheritance pattern involving the action of an autosomal gene with the main effect on determining its levels, which also suffer the action of polygens.[19] Two proteins enter its composition: Apo B-100 and Apo(a), which is a protein rich in carbohydrates and bound to Apo B by bisulfide bonds. It presents remarkable heterogeneity in molecular weight, with phenotypes ranging from 280,000 to 700,000 daltons and great homology with plasminogen.[19] In fact, Lp(a) without Apo(a) resembles LDL, which is evidenced by the binding with the latter's receptor, when the bisulfide bridges are broken and Apo(a) is separated from the rest of the particle.[22-26]

Several phenotypes of Apo(a) have been described based on polyacrylamide gel mobility when compared to Apo B-100. Phenotypes F and B correspond to greater motility identical to that of Apo B-100, respectively. S1, S2, S3 and S4 are slower forms, to varying degrees. In the same individual, there is more often only one phenotype, that is, only one band is visualized in the electrophoresis gel.[27] This fact led Utermann et al.[27] to suggest that the polymorphism of Apo(a) is conditioned by codominant alleles and a null allele, which has been confirmed in family studies.[28] Phenotypes B, S1 and S2 are associated with high levels of Lp(a). Low levels of this lipoprotein are observed in association with the S3 and S4[29] phenotypes. Another interesting aspect related to Lp(a) concerns the fact that nutritional factors, physical activity and hormonal factors, which have a significant influence on cholesterol and triglyceride levels, have practically no impact on the levels of this lipoprotein.

The gene encoding Apo(a) presents a sequence of 37 copies of plasminogen domain (kringle) 4, a domain 5 followed by the protease domain, both highly conserved in relation to plasminoquine.[19] The heterogeneity observed in the molecular weight of this protein seems to be related to the variability of the number of repetitions of domain 4. The origin of Apo(a) probably occurred by duplication of the plasminogen gene, with subsequent deletions of the coding exons of the terminal region and domains 1, 2 and 3. Support for this hypothesis comes from the fact that these genes are both located in close proximity on chromosome 6 (6q26-27).[30,31]

It has been suggested that Lp(a) competes with plasminogen in its binding with its endothelial receptor, which is a dependent domain.[32-34] Such competition would interfere with the mechanism of fibrinolysis, facilitating atherosclerosis. Lp(a) thus seems to exert its effect by promoting this type of alteration by two mechanisms: its own deposition in the arterial walls and inhibition of fibrinolysis.

Although the screening of individuals at risk of coronary heart disease by lipid measurements and traditional measures of risk factors is economically advantageous, the relationships pointed out between the higher risk of coronary heart disease due to the presence of E4, Lp(a) and other genetic markers portend the adoption, in the near future, of techniques that enable the detection of these alleles.

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Conflict of interest

None.

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