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SHORT COMMUNICATION

Rare Variant of Apolipoprotein E (Arg136→Cys) in a Subject with Normal Lipid Values

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Summary

During the screening of apolipoprotein (apo) E gene polymorphism with PCR and subsequent restriction analysis, we have identified a female carrier with a mutant allele Arg136 → Cys. This proband had normal lipid parameters and no history of coronary artery disease (CAD). We did not confirm the previously described connection between apo E Arg136 → Cys mutation and elevated lipid levels. In the case of this mutation, other factors (environmental and/or genetic) are important for the development of lipid metabolism disorders.

Key words

Apolipoprotein E • Rare mutation • Lipid metabolism

Apolipoprotein E (apo E) gene determines three common variants – apo E2 (Arg 158 → Cys), apo E3 and apo E4 (Cys 112 → Arg). The frequency of apo E alleles varies among different populations; however, the E3 allele and the E 3/3 genotype are invariably dominant (Davignon *et al.* 1988, Gerdes *et al.* 1992, Hubáček and Poledne, 1998). A large number of rare variants has been described (for review see Hubáček *et al.* 2000).

Apo E, found at first in very low density lipoproteins (VLDL) plays an important role in the metabolism of triacylglycerol-rich lipoproteins and is described as an important determinant of serum cholesterol levels. In common population, higher levels of plasma low-density lipoproteins (LDL) cholesterol is connected with the allele E4 and lower levels with the allele E2 (Davignon *et al.* 1988). In some cases, homozygosity for apo E2 allele is an important genetic determinant of type III hyperlipoproteinemia.

In apo E polymorphism population screening in the region Benesov (1 % population sample, Hubáček *et al.* 1999) with the polymerase chain reaction (PCR) and restriction analysis with restriction enzyme Cfo I (Hixson and Vernier 1990), heterozygosity for an uncommon restriction fragment of the size about 110 bp, originated from the loss of Cfo I restriction site in the apo E gene, was found in one proband. This fragment is characteristic for a rare mutation in position 3817 of apo E cDNA (Walden *et al*. 1994, Feussner *et al.* 1996).

Through the additional mismatched PCR amplification (primers apo E 3817-A 5´ CGG CTG GGC GCG GAC ATG GAG GAC G, and apo E 3817-B 5´ CAG CTT GCG CAG GTG GGA GGC GAG GT created

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a new Rsa I restriction site in carriers of the known rare mutation) and the restriction analysis of the PCR product with Rsa I, carrier of the apo E 2* allele with substitution C3817 → T (Arg 136 → Cys) was confirmed. The second allele was the common apo E3 variant.

The proband was a postmenopausal, non-smoker caucasian woman, aged 73, without history of coronary artery disease and with apparently normal lipid values (total cholesterol: 5.17 mmol/l, LDL cholesterol: 2.81 mmol/l, HDL cholesterol: 0.98 mmol/l, apo B: 1.39 g/l) and blood pressure (SBP 139 mm Hg, DBP 87 mm Hg). The proband and her family did not agree with more detailed examination.

In our laboratory, about 3 500 individuals in projects with different designs (Hubáček 2001) have till now been genotyped for common apo E polymorphism. We have already found one family with this mutation in the same geographic region (Hubáček *et al*. 2000), and although the recent connection between the examined individual and previously described family has not been confirmed, the geographical localization supports the idea that both probands could have had a common ancestor. Thus, we can estimate that the population frequency of this mutation is far lower than 1:1000.

Rare mutations in the apo E gene have very often been described in patients with different types of severe hyperlipoproteinemia.

The apo E 2* allele (Arg136 → Cys) was formerly detected in subjects with a normal and late-onset of type III hyperlipoproteinemia as well as in subjects with normal lipid parameters (Walden *et al*. 1994, Feussner *et al.* 1996, Hubáček *et al.* 2000). Together with our presented results, the apo E allele (Arg136 → Cys) itself in heterozygous form is not sufficient for expression of obvious dyslipidemia.

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Reprint requests

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