Hyperlipidemia in Patients with Apolipoprotein E 2/2 Phenotype: Apolipoprotein A5 S19W Mutation as a Cofactor

To the Editor:

Apolipoprotein (apo) E, an arginine-rich glycoprotein with a molecular mass of 34 kDa, is localized on chylomicrons, VLDL, intermediate-density lipoprotein, and HDL particles. Apo E is important for the regulation of triglyceride-rich lipoproteins in humans and binds to the VLDL receptor, LDL receptor, and LDL-receptor-related protein. This process allows apo E to compensate partially for the function of defective apo B-100 in humans (1). There are three different apo E alleles, e2 (frequency, 10%), e3 (frequency, 75%), and e4 (frequency, 15%), that code different apo E isoforms. Apo E 3/3 is the most commonly found phenotype. Apo E 2/2 and/or apo A5 S19W, as described recently (4). Apo E bands were immunoprecipitated within the gel, and silver staining was performed after extensive washing and eluting of all nonprecipitated proteins. We used denaturing gradient gel electrophoresis (DGGE) (5) to screen for the apo A5 S19W mutation in the gene. In all patients with an abnormal DGGE profile, apo A5 was sequenced, and single-nucleotide polymorphisms were confirmed by PCR with restriction fragment length polymorphism analysis. In addition, apo C-II was analyzed by isoelectric focusing (6) and the LDL receptor by DGGE (5) in all patients with apo E 2/2 and/or apo A5 S19W, as described recently.

A total of 7 of our 170 screened hypertriglyceremic patients had an apo E 2/2 phenotype; 6 of these 7 apo E 2/2 patients were also heterozygous carriers for the apo A-5 S19W mutation. The mean (SD) triglyceride concentration in these patients was 4958 (1462) mg/L, their mean total cholesterol was 2683 (886) mg/L, and their mean HDL-cholesterol was 382 (117) mg/L. This finding is interesting for several reasons. Our study confirms earlier observations that apo E 2/2 is a rare cause for hypertriglyceridemia. It was present in our study population at a rate of 4.1%. Interestingly, almost all of these (six of seven) hypertriglyceridemic apo E 2/2 individuals had also the apo A5 S19W defect. The frequency of the apo A5 S19W polymorphism has been reported to be 10.9% in the general population (7). Furthermore, we failed to identify a normolipidemic apo E 2/2 individual who had the apo A5 S19W polymorphism. From this observation we conclude that apo A5 S19W is a crucial cofactor for developing hypertriglyceridemia in patients with apo E2/2. This hypothesis clearly needs to be confirmed in larger study populations, but it is consistent with our current knowledge of hypertriglyceridemia in apo E2/2. Apo E 2/2 is found in 0.6% of our population (8), and ~10% of them will develop hyperlipidemia. The rate of 10% is identical to the frequency of the apo A5 S19W polymorphism in humans; we therefore conclude that apo A5 S19W is an important cofactor for hyperlipidemia in individuals with the apo E2/2 phenotype.

References


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DOI: 10.1373/clinchem.2004.037689