Apolipoprotein A5 S19W May Play a Role in Dysbetalipoproteinemia in Patients with the Apo E2/E2 Genotype

To the Editor:
Apolipoprotein (apo) E is one of the constituents of triglyceride-rich lipoproteins (chylomicrons and VLDL). Its interaction with the LDL receptor (LDLR), LDL-receptor related protein (LRP), and VLDL receptor permits clearance of triglyceride-rich lipoprotein remnants. The 3 common isoforms of the apo E protein, apo E2, apo E3, and apo E4, differ in their ability to bind lipoprotein receptors. Apo E3 is the most common isoform (frequency 75%). Apo E2 and apo E4 result from nucleotide substitutions affecting amino acid residues 158 and 112, respectively.

Homozygosity for apo E2 is the cause of familial dysbetalipoproteinemia (Fdisβ), an autosomal, recessively transmitted disease in which reduced catabolism leads to dyslipemic phenotype type III, a characteristic accumulation of chylomicrons and VLDL remnants. Because only a small proportion (10%–20%) of persons with apo E2/E2 develop the dysbetalipoproteinemic phenotype, the clinical expression of this disorder is thought to depend on the presence of other genetic or environmental factors, such as diabetes, hypothyroidism, obesity, or insulin resistance. On the other hand, apo A5 variants have been associated with hypertriglyceridemia. A recent study (1) showed that 6 of 7 hypertriglyceridemic patients with an apo E2/E2 phenotype were also heterozygous carriers for the apo A5 S19W variant. The authors suggested that apo A5 S19W could play a crucial role in the hypertriglyceridemia often observed in patients with apo E2/E2, but this hypothesis remains to be confirmed.

We analyzed the apo A5 S19W variant in a group of 30 patients with Fdisβ, 9 women and 21 men (age 20 to 75 years, body mass index 22.3 to 39.0 kg), 29 with apo E2/E2 and 1 with apo E2/Chirstchurch genotype. Apo E-Christchurch (R136S) is a relatively frequent mutation associated with Fdisβ in Spain (2). After the patients had fasted overnight, we used blood specimens collected into EDTA-containing tubes and obtained from patients who had fasted overnight. We determined apo E genotype by PCR amplification and digestion with Cfo I (2) and apo A5 by PCR amplification and fluorescence detection with a specific TaqMan® single-base variation genotyping assay and a 7000 sequence detection system (Applied Biosystems). The blood samples were leftover samples and were obtained and used with the approval of the hospital Clinical Research Committee.

We found that 10 of the patients (33.3%) were carriers of the S19W variant, 9 heterozygous and 1 homozygous. Because some patients were on hypolipidemic therapy, we could not study the association between the S19W variant and the concentrations of plasma triglyceride, although several apo A5 gene variants have been associated with increased plasma concentrations of triglycerides, as reported previously (3, 4). Thus the frequency of S19W carriers in our E2/E2 patient group (0.33) was considerably lower than that (0.86) obtained by Schaeffer et al. (1).

We also studied a group of 56 non-apo E2/2 healthy controls and identified 5 heterozygous S19W carriers (8.9%)—a frequency of 0.045 for the rare allele, similar to that of previous studies in European populations (5). After results were adjusted for sex and age, we observed substantial differences in S19W genotype distribution between patients with Fdisβ and controls (odds ratio = 6.66; 95% CI, 1.68–26.40; \( P = 0.0047 \)). Therefore, the S19W variant could, in the 33% of cases in which it was present, have been involved in the development of Fdisβ in individuals with the E2/E2 genotype.

A previous study on the prevalence of type III hyperlipoproteinemia (HLP) in apo E2 homozygotes (6) showed that 3% of the variability in expression of type III HLP in apo E2/2 genotypes could be explained by sex, age, body mass index, and alcohol consumption, whereas 25%
could be explained by hyperinsulinemia. Thus, it would be of special interest in the future to study whether an interaction exists between the S19W variant and hyperinsulinemia. Also, it will be important to compare the frequency of the S19W variant in apo E2/E2 individuals with and without Fdisβ to delineate the potential impact of this sequence variant on Fdisβ development.

We conclude that the S19W variant of apoA5 is a potentially important, although not crucial, factor in determining Fdisβ development in our patients with an apo E2/E2 genotype.

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References

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Correction

In the article entitled “Curriculum Content and Evaluation of Resident Competency in Clinical Pathology (Laboratory Medicine): A Proposal” by B.R. Smith, A. Wells, C.B. Alexander, E. Bovill, S. Campbell, A.A. Dasgupta, M. Fung, B. Haller, J.G. Howe, C. Farvin, E. Peerschke, H. Rinder, S. Spitalnik, R. Weiss, and M. Wener, for the Academy of Clinical Laboratory Physicians and Scientists (Clin Chem 2006;52:917–49), there is an error in the Hematology Reference Materials section on page 932. The reference for Glassy EF erroneously lists the American Society of Clinical Pathology as the publisher. The correct reference citation should read as follows:


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