Donor Splice-Site Mutation (210+1G_C) in the ApoB Gene Causes a Very Low Level of ApoB-100 and LDL Cholesterol

To the Editor:

Apolipoprotein (apo) B, the main protein in LDL, exists in 2 isoforms in plasma: apoB-100, which is produced in the liver, and apoB-48, which is a naturally occurring truncation of apoB-100 and is secreted in the intestine in response to dietary fat. Heterozygous subjects for hypobetalipoproteinemia (HBLP), an autosomal codominant disorder, have LDL cholesterol (C) levels between 0.52 and 1.29 mmol/L (20 to 50 mg/dL) and have variable clinical symptoms including retinitis pigmentosa, fat malabsorption, acanthocytosis, ataxia, and debilitating neurological diseases. The reasons for the variability in clinical symptoms have been unclear. Welty et al previously reported an asymptomatic, 54-year-old subject heterozygous for an apoB-44.4 truncation who had an undetectable plasma level of LDL-C and a very low level of apoB-100, findings suggesting that he was a compound heterozygote with a second apoB gene mutation. To locate this mutation, we amplified the entire apoB gene by using polymerase chain reaction (PCR) primers and reaction conditions as previously described. The PCR products were purified and sequenced by using PCR priming oligonucleotides. Sequencing revealed a G-to-C transition at the first nucleotide of the donor splice site in intron 1 (210+1G_C) in the proband and a son (Figure).

The lack of symptoms in the proband, a compound heterozygote, and the location of his 2 mutations, coupled with a review of the literature of compound heterozygous and homozygous subjects, suggested that the variability in symptoms was related to the length of the truncated apoB and its ability to form chylomicrons and absorb fat-soluble vitamins (E and A) and essential fatty acids rather than the level of LDL-C. For example, subjects with truncations close to the length of apoB-48 or longer appear to have normal intestinal absorption and, thus, be asymptomatic. This concept is supported by the following cases. A 45-year-old woman homozygous for apoB-45.2 has no detectable LDL-C, is asymptomatic, and has normal plasma vitamin E levels. Two asymptomatic subjects homozygous for apoB-87 are 48 and 41 years old and have LDL-C levels of 0.18 and 0.10 mmol/L (7 and 4 mg/dL). They have normal intestinal absorption in response to a fat load and no classic neurological manifestations of HBLP; however, both have slow nerve-conduction velocity by electromyography. Three subjects who are compound heterozygotes for apoB-37/B-866 and three who are compound heterozygotes for apoB-40/B-87 are completely asymptomatic. The apoB-44.4 proband described in the current study is a compound heterozygote and is asymptomatic.

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We hypothesized that subjects with very short apoB truncations would have the full spectrum of symptoms. This hypothesis is supported by 2 siblings who are compound heterozygotes for apoB-2 and apoB-9, have no detectable LDL-C in plasma, and presented with retinitis pigmentosa, neurological deficits, and steatorrhea at 4 months and 10 years of age. We further hypothesized that subjects with intermediate-length truncations (apoB-25 to 39) would have less severe symptoms; this is supported by 4 subjects. A subject homozygous for apoB-25 had no detectable LDL-C and presented with fatty diarrhea during the first year of life. A 21-year-old subject homozygous for apoB-27.6 had no detectable LDL-C in plasma and presented with chronic fatty diarrhea and acanthocytosis but no retinitis pigmentosa or neurological disease. A 21-year-old woman who is a compound heterozygote for apoB-39 (LDL-C not measured) and a second mutation causing a low level of apoB-100 had fat malabsorption but no retinitis pigmentosa or neurological disease. Finally, a 57-year-old subject who had a 20-year history of diabetes and was homozygous for apoB-38.7 had no detectable LDL-C and no symptoms of diarrhea or malabsorption but did have retinitis pigmentosa, acanthocytosis, and loss of deep tendon reflexes despite normal vitamin E levels. An exception to our hypothesis was an 8-year-old girl who was homozygous for a truncated apoB-49.6, had no detectable LDL-C, and manifested severe neurological abnormalities resulting from a nearly-complete absence of vitamin E in the plasma despite adequate intestinal fat absorption. Because the homozygous apoB-38.7 and apoB-45 subjects had normal vitamin E levels, the lack of vitamin E in the apoB-49.6 subject probably did not result from the apoB mutation. In summary, the amino terminal 45% of apoB appears adequate for normal function and development. Future studies correlating the clinical sequelae of HBLP with the length of apoB mutations should provide further insight into structural/functional domains of apoB.

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