Homozygous LPL p.Gly188Glu Mutation in a Mexican Girl With Lipoprotein Lipase Deficiency

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Dear Editor,

Lipoprotein lipase (LPL) deficiency is a rare disease characterized by severe hypertriglyceridemia due to mutations in the LPL gene. It shows an autosomal recessive inheritance pattern and has a general prevalence of 1:1,000,000 [1]. Patients typically present abdominal pain, hemorrhage, failure to thrive, jaundice, eruptive xanthomas, lipemia retinalis, neurological complications, hepatosplenomegaly, and life-threatening pancreatitis [2]. The LPL gene is located on chromosomal band 8p22, contains 10 exons, and codes for a 475-amino acid protein that is active only in its dimeric form. The LPL protein has two functions in lipid metabolism: it hydrolyzes triglycerides and functions as a ligand [3]. The aim of this work is to describe the biochemical, clinical, and molecular features of a Mexican girl with LPL deficiency.

We report the case of a girl living in a small community in the state of Guanajuato, Mexico. At five years of age, she experienced recurrent episodes of abdominal pain and nosebleeds. Physical examination revealed an age-appropriate size and weight, although eruptive xanthomas on the dorsal side of the hands were observed. Severe hypertriglyceridemia (triglycerides >11.29 mmol/L) was detected; since that time, the index case (IC) has been under pharmacological treatment (200 mg of bezafibrate per day) together with a fat-restricted diet. However, her triglyceride levels ranged from 10.16 to 67.60 mmol/L, and when she was six years old, she developed pancreatitis with the latter value. After pancreatitis, the IC, her parents, and 19 family members were tested. Informed consent was obtained from all family members for genetic analysis and for publication of this study. This work was reviewed and approved by the ethics committee of the Western Biomedical Research Center.

The results are summarized in Table 1. The IC’s parents are consanguineous, sharing a common ancestor three generations back (Fig. 1A). Clinical and biochemical characteristics of the IC were consistent with a diagnosis of primary hypertriglyceridemia; therefore, LPL was analyzed. Molecular screening of LPL by polymerase chain reaction and bi-directional Sanger sequencing revealed the presence of the p.Gly188Glu mutation (rs118204057 or c.644G>A) in the homozygous state in the IC and in 11 relatives who were heterozygotes (Fig. 1A-D) (primer sequences and conditions are available on request). The mutation was corroborated by digestion analysis with the restriction enzyme AvaII. All heterozygote individuals, except one (V-10), had low levels of HDL cholesterol (HDL-C), whereas, only the IC’s parents and a

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We describe the case of a Mexican girl with LPL deficiency. The IC was homozygous for p.Gly188Glu mutation, which has a worldwide frequency of 23.5% in individuals with LPL deficiency [4], while its frequency in the general population is less than 0.03%. In subjects with Mexican ancestry, this variant has not been observed [5]. The p.Gly188Glu mutation affects the lipid-binding region, leading to a complete loss of LPL function [3, 6].

The main clinical manifestations of LPL deficiency were present in the IC from an early age, except neurological complications, cardiovascular symptoms, and lipemia retinalis. Although the IC is under pharmacological treatment and consuming a low-fat diet, her triglyceride levels remained very high (>9.03 mmol/L), and thus she is at risk of experiencing additional episodes of pancreatitis.

Eleven of the IC’s relatives were carriers of the p.Gly188Glu mutation, and previous studies showed that heterozygote individuals with this variant have decreased LPL activity (~50%), reduced plasma HDL-C levels, increased triglyceride levels, and higher risk of ischemic heart disease compared with individuals without this mutation [3, 7]. Three of the 11 heterozygote individuals showed elevated triglycerides and all except one showed low HDL-C (Table 1). Such heterogeneity may be related to environmental conditions, age, diet, lifestyle, and genetic background. This family should be under medical surveillance because high triglyceride and low HDL-C levels are characteristic traits of atherogenic dyslipidemia [3, 8].

Patients with LPL deficiency rarely show triglyceride levels below 11.29 mmol/L, even after conventional therapy. Recently, the drug Glybera was approved by European Commission, which is based on expression of the gain-of-function S447X variant of.
human LPL. Clinical studies have shown that Glybera decreases both plasma triglyceride (40–60%) and incidence of pancreatitis episodes [9]. This therapy may be ideal for treatment of the two LPL-deficient cases reported in Mexico: the girl in this study and a 6-month-old boy from the state of Chiapas who was homozygous for a novel LPL mutation (c.94_98del5) [10].

In summary, we report a case of LPL deficiency in Mexico related to the p.Gly188Glu LPL mutation in the homozygous state. In Mexico, neither the frequency of LPL deficiency nor distribution of LPL variants is known; however, the Mexican population contains individuals with LPL variants that cause hypertriglyceridemia.

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REFERENCES

3. Ooi EM, Russell BS, Olson E, Sun SZ, Diffenderfer MR, Lichtenstein AH, et al. Apolipoprotein B-100-containing lipoprotein metabolism in sub-

Authors’ Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.