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Case Report

A novel mutation in *GPIHBP1* causes familial chylomicronemia syndrome

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Abstract: Familial chylomicronemia syndrome is characterized by severe elevation in serum triglycerides and an increased risk of acute pancreatitis. Although familial chylomicronemia syndrome is mainly caused by mutations in the lipoprotein lipase (*LPL*) gene, few causal mutations in other genes (ie, *APOC2*, *APOA5*, *LMF1*, and *GPIHBP1*) have also been reported. In this case report, we present the discovery of a novel mutation in the glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (*GPIHBP1*) gene and discuss its pathogenicity through a familial segregation study.

Introduction

Familial chylomicronemia syndrome (FCS) or type I hyperlipoproteinemia (T1HLP) (OMIM number 238600) is an autosomal recessive lipid disorder affecting ∼1:100,000 to ∼1:1,000,000 individuals worldwide.[1] This rare monogenic disease is caused by loss of function mutations in lipoprotein lipase (*LPL*) gene in >90% of cases. LPL, an enzyme produced by parenchymal cells (adipocytes and myocytes), is involved in the lipolysis of triglyceride (TG)-rich lipoproteins in the capillary lumen. Mutations in apolipoprotein C2 (*APOC2*), apolipoprotein A5 (*APOA5*), lipase maturation factor 1 (*LMF1*), and glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (*GPIHBP1*) genes have also been reported to cause FCS.[1] These mutations lead to the pathological persistence of chylomicrons in blood even in the fasting state. Therefore, patients affected by FCS have severe elevation in serum TGs (fasting TG levels >10 mmol/L [>880 mg/dL]), which can be easily noticed by the lipemic appearance of the serum sampling.[1] The clinical features associated with FCS include the presence of eruptive xanthomas, lipemia retinalis, failure to thrive, hepatosplenomegaly, abdominal pain, nausea, vomiting, and TG-associated pancreatitis, which is the most serious complication associated with FCS.[1] Treating FCS remains a clinical challenge. Indeed patients with FCS show little

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or no response to TG-lowering pharmacotherapies, although novel therapies such as antisense oligonucleotides targeting APOC3 and ANGPTL3 mRNAs show promise as a future therapy.[2] The backbone of the FCS therapy remains the adherence to an extremely restrictive low-fat diet.[3]

GPIHBP1 is the most recently discovered FCS-related gene. More than 20 different mutations in the *GPIHBP1* gene have been identified so far.[4] GPIHBP1 is a 184 amino acid protein expressed on capillary endothelial cells that belong to the lymphocyte antigen 6 (Ly6) superfamily.[5] The major functions of GPIHBP1 are to bind LPL in the subendothelial space (where LPL is secreted) and to transport it across endothelial cells to the capillary lumen where the lipolysis occurs. GPIHBP1 deficiency leads to LPL accumulation in the subendothelial space. Therefore, LPL cannot reach its site of action, resulting in severe chylomicron accumulation in blood (Fig. 1).[6,7] GPIHBP1 comprised 4 principal domains: the signal peptide, the acidic domain, the Ly6 domain, and the GPI anchor. Two of these domains, the Ly6 domain and the acidic domain, are involved in the trafficking of GPIHBP1 to the cell surface and in the binding of LPL and chylomicrons.[8–10] Although FCS-causing mutations have been reported in all of these domains, the majority of identified missense mutations are located in the Ly6 domain.[4] Furthermore, autoantibodies against GPIHBP1 have been shown to cause hyperchylomicronemia.[11]

Case presentation

Clinical presentation

The proband is a 33-year-old woman of Vietnamese origin who presented at the lipid clinic with a history of TG concentration of 20 mmol/L (1771 mg/dL) despite compliance with fenofibrate of 145 mg daily. She was first diagnosed with hypertriglyceridemia at the age of 25 years. There was no known consanguinity among the parents. The patient reported familial history of dyslipidemia from her maternal grandmother and her father, without further details. At the time of the first evaluation in January 2017, the fasting TGs, high-density lipoprotein cholesterol, and total cholesterol levels were 20.32 mmol/L (1800 mg/dL), 0.34 mmol/L, (13 mg/dL) and 3.97 mmol/L (154 mg/dL), respectively. The patient denied alcohol use, had a normal glucose level, a BMI and waist circumference in the normal ranges (19.7 kg/m^2 and 74 cm, respectively), and a negative history of coronary artery disease. No other biochemical abnormalities were observed. The patient had been hospitalized for acute pancreatitis 5 times between 2009 and 2013. The first and the second episodes occurred in the context of oral contraceptive medication use. During this period, the patient was sedentary or mildly active and reported to consume a highly refined carbohydrate and high-fat diet (precise quantification of total fat intake was not available). The 2 latest episodes occurred during her pregnancy in August 2013 and October 2013 (28 and 35 weeks of pregnancy, respectively). TG values were very elevated but variable and reached maximal values (67.43 mmol/L or 5973 mg/dL) during the third trimester of pregnancy (Fig. 2). Lipoprotein ultracentrifugation and electrophoresis demonstrated the presence of chylomicrons, confirming hyperchylomicronemia. After her first episode of pancreatitis, therapy with insulin was initiated in the hope of reducing her TGs; unfortunately little effect was noted. Insulin therapy was stopped at delivery. She consulted a registered dietitian in December 2016 following her last episode of acute pancreatitis. The patient reported a good compliance (~80%) to dietary recommendations that emphasized on low-fat diet (50 g of lipid per day), although this recommendation was suboptimal for a patient with FCS. She tried medium chain triglycerides (MCT) oil for the first time during her pregnancy but no longer uses it. No eruptive xanthomas, lipemia retinalis, or hepatosplenomegaly was documented at the physical examination. At her first visit to the Institut de recherches cliniques de Montreal lipid clinic, the patient met a registered dietitian who taught her the adequate

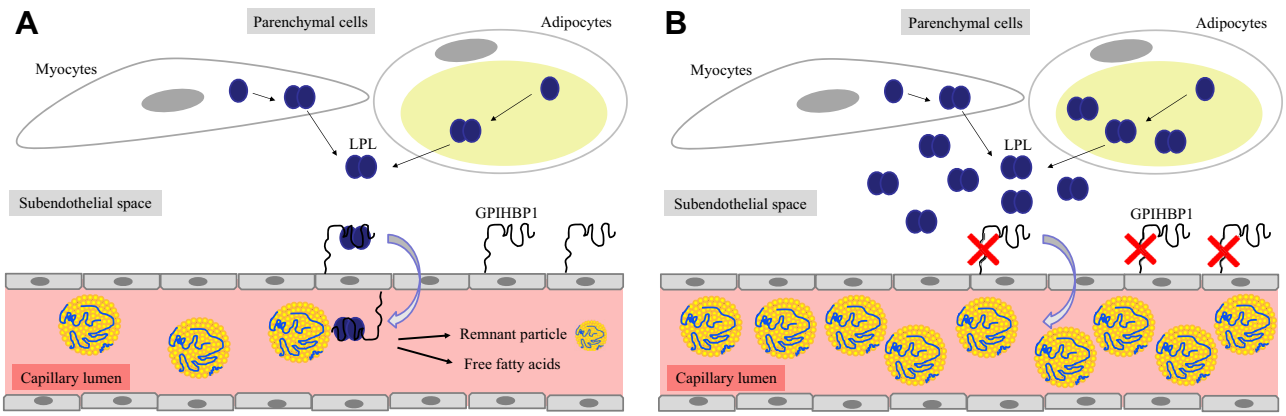

Figure 1 (A) Overview of GPIHBP1 and function in normal condition. (B) The physiopathology of familial chylomicronemia syndrome caused by GPIHBP1 deficiency. GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; LPL, lipoprotein lipase.