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Whole-Exome Sequencing Reveals *GPIHBP1* Mutations in Infantile Colitis With Severe Hypertriglyceridemia

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Abstract

Severe congenital hypertriglyceridemia (HTG) is a rare disorder caused by mutations in genes affecting lipoprotein lipase (LPL) activity. Here we report a 5-week-old Hispanic girl with severe HTG (12,031 mg/dL, normal limit 150 mg/dL) who presented with the unusual combination of lower gastrointestinal bleeding and milky plasma. Initial colonoscopy was consistent with colitis, which resolved with reduction of triglycerides. After negative sequencing of the *LPL* gene, whole-exome sequencing revealed novel compound heterozygous mutations in *GPIHBP1*. Our study broadens the phenotype of *GPIHBP1*-associated HTG, reinforces the effectiveness of whole-exome sequencing in Mendelian diagnoses, and implicates triglycerides in gastrointestinal mucosal injury.

Keywords

chylomicronemia; colitis; hyperlipoproteinemia; lipoprotein lipase; next-generation sequencing

Severe congenital hypertriglyceridemia (HTG), also known as familial chylomicronemia or type 1 hyperlipoproteinemia (Online Mendelian Inheritance in Man #238600), is a rare disorder of lipid metabolism that has an estimated incidence of between 1 in 500,000 and 1 in 1 million, globally. The most severe patients present in infancy or early childhood with serum triglycerides >1000 mg/dL, abdominal pain often related to acute pancreatitis, lipemia

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retinalis, eruptive xanthomata, or, more commonly, incidentally detected lipemic serum. In rare cases, bleeding from the lower gastrointestinal (GI) tract has been described as the primary presenting symptom (1); however, the mechanisms underlying this latter observation remain obscure, because the relative rarity of this presentation has precluded systematic investigation.

Most cases of severe, isolated HTG are caused by autosomal recessive mutations in the lipoprotein lipase gene *LPL* (Online Mendelian Inheritance in Man #609708). *LPL* encodes a hydrolase of the same name (LPL) that cleaves circulating triglycerides to liberate fatty acids for uptake in surrounding tissues. Recently, rare mutations in a number of genes encoding co-factors required for LPL activity have also been described, including apolipoprotein lipase C-II (*APOC2*) (2), apolipoprotein lipase A-V (*APOA5*) (3), lipase maturation factor 1 (*LMF1*) (4), and, most recently, glycosylphosphatidylinositol (GPI)-anchored high-density lipoprotein (HDL)-binding protein 1 (*GPIHBP1*) (5). This expanding list of disease loci makes genetic diagnoses in HTG challenging, especially in *LPL* gene-negative cases. Genomic next-generation sequencing approaches, such as whole-exome sequencing (WES), are uniquely placed to meet this challenge; WES has enabled the novel identification and molecular characterization of genetic defects in a wide spectrum of rare and genetically heterogeneous Mendelian traits (6-9), and has gradually come to the fore in the diagnosis of genetic disorders (10-16).

We report on a 5-week-old girl with severe HTG who presented with lipemic serum and colitis. Initial biochemical evaluation demonstrated reduced LPL activity; however, sequencing of the *LPL* gene was negative. With her unusual presentation, WES was undertaken to evaluate the possibility that her HTG was the result of mutations either in one of the lesser-recognized HTG genes or in a novel gene affecting LPL activity.

METHODS

Participants

Adult members of the study family, which consisted of the proband, mother, and father, provided written informed consent for themselves and their child for sequencing of the *LPL* gene and subsequent enrollment in the Centers for Mendelian Genomics research program (7), to identify the molecular cause of the patient's phenotype. The study protocols were approved by the institutional review board of Baylor College of Medicine (BCM).

Whole-Exome Next-Generation Sequencing

Whole-exome next-generation sequencing methods have been described previously (17). In brief, genomic DNA was extracted from peripheral blood of the proband and parents. For WES of the proband, DNA was fragmented by sonication. We used the BCM Human Genome Sequencing Center (HGSC) Core exome design for targeted whole-exome capture followed by sequencing on the Illumina HiSeq 2000 platform (Illumina, San Diego, CA). Mapping and alignment were performed using the BCM HGSC Mercury pipeline to map to the human genome reference assembly GRCh37 (hg19). A total of 8.5 Gb of sequence data were produced with an average depth of coverage of 102 times and 90% of the total bases

covered at 20 times. Variant calling from the aligned BAM file was performed using the ATLAS (18) and SAMtools (19) suites. Annotation and variant filtering were performed using the in-house developed Sacbe annotation pipeline (20) that uses ANNOVAR (21) and additional databases for informing variant annotation. Annotated high-quality variants were subsequently filtered to exclude common variants (>1% minor allele frequency) observed in population databases such as the NHLBI Exome Sequencing Project (ESP6500), 1000 Genomes Project, dbSNP135, and internal databases of in-house sequenced exomes. Variants of interest were subsequently confirmed in the proband and parents by dideoxy Sanger sequencing after polymerase chain reaction amplification.

RESULTS

Unusual Clinical Presentation of Severe HTG

The proband was a 5-week-old girl with a 2-week history of intermittent lower GI bleeding. This was initially attributed to a rectal tear, but had progressed in frequency and severity such that the primary physician referred her for a hospital evaluation. Subsequently, she had an episode of blood-tinged sputum, which prompted additional evaluation for a bleeding diathesis. On phlebotomy, the resulting serum was described as having a “milky, Creamsicle” appearance (Fig. 1), and initial serological studies could not be processed under standard laboratory conditions. She had mild abnormalities in her coagulation profile, including a mildly elevated international normalized ratio of 1.4 (upper limit of normal 1.2), and a low factor VIII activity (30 IU/dL, lower limit of normal 60 IU/dL); the remainder of the hematological evaluation was unremarkable. Eventually, a lipid profile obtained revealed a severely elevated triglyceride level of 12,031 mg/dL (upper limit of normal 150 mg/dL) with a low HDL of 11 mg/dL (lower limit of normal 20 mg/dL). Head and renal ultrasounds were normal as were initial liver function tests.

The remainder of the medical history was largely unremarkable. She had initially been breast-fed exclusively, with the parents introducing Enfamil (Mead Johnson, Glenview, IL) and Similac Advance (Abbott Nutrition, Abbott Park, IL) formulas after the initial lower GI bleeding. The family history was revealing only for 2 maternal half-siblings who died during the first week of life of uncertain causes. Both parents were of Hispanic heritage, and there was no reported consanguinity. On physical examination, the proband was in no distress, and was nondysmorphic with no organomegaly, petechiae, or abnormal skin findings.

Histopathological Resolution of Colitis With Treatment of HTG

The proband was made nil per os shortly after admission and remained so for <48 hours before being placed on Enfaport, a nonhydrolyzed formula containing caseinates with high medium-chain triglyceride (84% of fat) and low long-chain triglyceride (from soy oils) content. During the next 10 days Enfaport delivery was intermittently disrupted by total parenteral nutrition without lipids for procedures and high triglyceride (9286 and 4672 mg/dL) levels. Colonoscopy performed on day 2 after admission, before the resolution of HTG, revealed a mild acute colitis with neutrophil and eosinophil infiltration of the lamina propria (Fig. 2A). After the imposition of dietary restrictions, no further episodes of hematochezia were observed and her coagulation profile gradually returned to normal.

Unprepared sigmoidoscopy performed 6 days after admission, at which time her triglyceride level had fallen to 626 mg/dL, revealed her colitis to be histologically resolved (Fig. 2B). She was discharged home on Enfaport ad libitum and never required partially or fully hydrolyzed formulas. Her total triglyceride level was 842 mg/dL at the time of discharge. On her most recent follow-up evaluation at 30 months, she was clinically well with normal development and growth on a fat-restricted diet. She has had occasional facial xanthomatous eruptions and 1 episode of acute pancreatitis at 24 months that required a 3-day hospital admission. Her triglyceride levels fluctuate between 900 and 1500 mg/dL, and she has not had any additional bleeding episodes.

Negative Sequencing of the *LPL* Gene Despite Reduced LPL Activity

Biochemical testing shortly after initial hospital admission revealed a reduced plasma LPL activity of $9 \text{ nmol} \cdot \text{mL}^{-1} \cdot \text{min}^{-1}$ —<5% of control, and hepatic lipase activity was low-normal at $97 \text{ nmol} \cdot \text{mL}^{-1} \cdot \text{min}^{-1}$. These values were consistent with levels seen in individuals with congenital LPL deficiency. We thus undertook Sanger dideoxy sequencing of the 5' UTR, all coding exons, intronic splice sites, and 3' UTR of *LPL*. This was unremarkable, revealing only 2 common (minor allele frequency >1%), nonpathogenic exonic variants (see supplementary data, <http://links.lww.com/MPG/A313>).

Whole-Exome Next-Generation Sequencing Reveals Mutations in *GPIHBP1*

After the unrevealing genetic evaluation of *LPL*, we considered that the proband's HTG may be the consequence of mutations in genes less commonly observed in HTG, or, given the atypical clinical presentation, mutations in a novel gene affecting LPL activity. Therefore, rather than attempting ad hoc sequential sequencing of candidate genes, we undertook WES on the patient, which also allowed us to interrogate novel disease gene candidates. WES identified 24,338 variants in coding regions, of which 11,686 were nonsynonymous, splicing, or frame-shifting variants with protein-altering effects. First, we used a recessive disease model to analyze the observed variation in the known HTG genes *LPL*, *LMF1*, *APOC2*, *APOA5*, and *GPIHBP1*. This candidate gene analysis revealed 2 novel compound heterozygous mutations in exon 4 of *GPIHBP1* (NM_178172), both predicted to be deleterious to the resulting protein. The first was a missense mutation, p.T111P (g.chr8:144297169 A>C; c.A331C), predicted to be damaging by PolyPhen-2, a Bayesian algorithm that evaluates the probability of deleteriousness of an amino acid substitution to the stability and function of the protein using structural and evolutionary comparisons (22,23). The other was a 17-bp frame-shifting deletion, p.V138fs (g.chr8:144297251 – 144297267 del17 bp; c.413_429del), predicted to be deleterious not only by the large structural frame-shifting effect on the protein amino acid sequence but also by the Protein Variation Effect Analyzer algorithm (PRO-VEAN score=−25.482), which analyzes Indel and single-nucleotide variants based on a comparative alignment score of the variant's neighborhood sequence (24). Polymerase chain reaction amplification of exon 4 followed by Sanger dideoxy sequencing in the proband and both parents confirmed the variants and their inheritance in *trans* (Fig. 3). No rare variants were identified in any of the other candidate genes.

DISCUSSION

Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) transports and anchors LPL to its site of action in the lumen of endothelial cells, where it hydrolyzes circulating triglycerides packaged in large triglyceride-rich lipoproteins (chylomicrons) to facilitate triglyceride uptake by other tissues. The specific binding of GPIHBP1 to LPL and chylomicrons has been shown in vitro using cultured cells and the expression pattern of GPIHBP1 across tissue types is the same as that of LPL (25), highlighting the co-dependence of the 2 proteins in the lipolytic processing of triglycerides. Moreover, the knockout mouse model of *Gpihbp1* presents with high levels of plasma triglycerides and accumulation of chylomicrons as observed in human patients (26) and shows abnormal LPL release into the plasma (27).

To date, fewer than 20 patients have been reported worldwide with severe HTG and mutations in *GPIHBP1*, and although all have strikingly high triglyceride levels (>700 to >35,000 mg/dL) (5,28-33), there is some variability in the spectrum of additional associated clinical features (summarized by Rios et al (31)). Our proband is one of the youngest reported to date, bolstering previous assertions that *GPIHBP1* mutations can result in an early and severe disease phenotype; this is in contrast to *Gpihbp1* null mice, in which the onset of HTG occurs later in life (25,26). In addition, our proband presented with GI bleeding; this is a rarely recognized complication of HTG that has not been previously described in patients with *GPIHBP1* mutations. The etiology of the bleeding in HTG remains uncertain; however, our histopathological findings suggest a role for either direct local inflammation or indirect sensitization of the colon in response to elevated triglycerides. This is consistent with reports of serum triglycerides modulating immune responses (34,35) and with animal models of triglyceride-induced pancreatitis (36). There is an intriguing link between HTG and infantile colitis that is underscored by our observation of virtually complete resolution of colitis with acute control of triglyceride levels. Dietary protein delivery was only modified significantly while the patient was nil per os or on total parenteral nutrition (she never received partially or fully hydrolyzed formulas), and never for >96 hours. Therefore, it is less likely that the cessation of the patient's hematochezia was the consequence of the temporary changes in dietary protein, although this possibility of dietary change cannot be ruled out. Further investigation of the mechanism of mucosal injury in HTG is an area for future study.

The mutations observed in our case are consistent with present molecular paradigms of pathogenic *GPIHBP1* mutations. *GPIHBP1* includes a cysteine-rich Ly6 domain between amino acids 51 and 151 that binds LPL and facilitates its hydrolytic activity on the endothelial surface (37,38). Virtually all previous reports of *GPIHBP1*-related HTG have included at least 1 mutation affecting this region, with most reporting substitution of 1 of the critical cysteine residues (28-30,32). The 2 exceptions are a homozygous deletion of *GPIHBP1* reported in an infant with a triglyceride level twice that observed in our patient (31), and a missense mutation occurring in the distal GPI-binding domain in a 26-year-old adult who was otherwise asymptomatic (5). The p.T111P variant in our patient is within the Ly6 critical region, adjacent to an important cysteine that comprises the central 3-finger binding portion of the domain, and contained within the most highly conserved domain of

the protein (between AA positions 101 and 121) (39). This mutation would thus be expected to impair LPL binding. The 17-bp frame-shift deletion is also in the Ly6 domain, and is anticipated to result in a read-through of the transcript, thereby producing a longer protein that could be subject to nonstop mediated decay or one that could give rise to an aberrant, nonfunctional protein with altered LPL binding. The predicted loss of LPL binding on both alleles would be expected to result in significantly reduced LPL activity (5), which is consistent with our biochemical observations. The 2 mutations observed in our proband are thus highly likely to be causing her HTG phenotype.

Our study also illustrates the diagnostic capabilities of WES—providing a molecular diagnosis in a patient with an atypical presentation and obviating the need for sequential diagnostic tests. Given recent advances in gene therapy for *LPL* deficiency (40,41), determining the genetic etiology of HTG helps to clarify therapeutic options and enables appropriate genetic counseling for the family. Mutations in *GPIHBP1* remain a particularly rare cause of HTG and assessments of candidate genes in patients with HTG (32) emphasize that there are likely to be a number of as yet unrecognized genes that are important for LPL activity and HTG. Presently, molecular clinical testing is only available for LPL in a few laboratories in Europe and Australia (www.genetests.org). Thus, for LPL-negative HTG cases, WES is likely to be the only available diagnostic approach (38,39,42,43). The cost of clinical exome sequencing varies with the capture design size and depth of coverage; however, present costs will continue to fall in the years to come, making it an even more affordable, first-tier diagnostic test. This will almost certainly be true when compared with time-consuming stepwise clinical sequencing of disease genes, but perhaps even compared with targeted next-generation sequencing panels, as WES allows for the simultaneous querying of known genes and pathogenic variants as well as the identification of mutations within novel candidate genes.

Our report provides new insight into the role of triglycerides in the etiology of GI bleeding. Furthermore, by identifying compound heterozygous mutations in *GPIHBP1* as the cause of HTG in this atypical case, it expands the clinical and molecular phenotypes of *GPIHBP1*-associated HTG to include GI bleeding and 2 novel, likely disease-causing, mutations. Finally, our report reinforces the utility of WES in the diagnosis of Mendelian disorders, particularly those with significant locus heterogeneity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1. Lipemic serum. Postcentrifugation sample from the Proband shows the “milky, Creamsicle” appearance of the serum fraction (white arrow; inset).

FIGURE 2.

Pre- and posttreatment histopathology. A, Mild acute colitis with eosinophil infiltration of the lamina propria (arrows point to eosinophil invasion of crypts). B, After the resolution of the chylomicronemia secondary to medium-chain triglyceride diet, eosinophils were significantly decreased, but were not absent (arrow points to an eosinophil infiltrating a crypt). Original magnification $\times 250$.

FIGURE 3.

Compound heterozygous mutations in *GPIHBP1*. A, Whole-exome sequencing (WES) reads (horizontal gray bars) in the affected proband reveal an A to C missense substitution and a 17-bp deletion (purple-shaded boxes) in approximately one-half of reads encompassing the 2 genomic positions in exon 4 of *GPIHBP1*. WES reads that span both mutations (red boxes) show the mutations to be in a *trans* configuration. B, Confirmation of *trans* configuration and validation of variants using Sanger dideoxy sequencing in the proband and both parents. The missense variant can be seen to be paternally inherited and the frame-shifting deletion maternally inherited.