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A novel p.Gly417Valfs*12 mutation in the *MTTP* gene causing abetalipoproteinemia: Presentation of the first patient in Mexico and analysis of the previously reported cases

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Abstract

Background: Our aims were to describe the first Mexican patient with abetalipoproteinemia and to perform a comparative analysis of biochemical, clinical, and genetic characteristics of 100 cases reported in the literature.

Methods: We performed biochemical and molecular screenings in a Mexican girl with extremely low lipid levels and in her family. Further, we integrated and evaluated the characteristics of the cases with abetalipoproteinemia described in the literature.

Results: Our patient is a six-year-old girl who presented vomiting, chronic diarrhea, failure to thrive, malabsorption, acanthocytosis, anemia, transaminases elevation, and extremely low lipid levels. *MTTP* gene sequencing revealed homozygosity for a novel mutation p.Gly417Valfs*12 (G deletion c.1250). With the analysis of the reported cases, 60 clinical features (14 classical and 46 non-classical) were observed, being the most common acanthocytosis (57.5%), malabsorption (43.7%), and diarrhea (42.5%); 48.8% of the patients presented only classic clinical features, while the remaining 51.2% developed secondary effects due to a fat-soluble vitamin deficiency. An odds ratio analysis disclosed that patients diagnosed after 10 years of age have an increased risk for presenting clinical complications (OR = 18.0; 95% CI 6.0-54.1, $p < 0.0001$). A great diversity of mutations in *MTTP* has been observed (n = 76, being the most common p.G865X and p.N139_E140) and some of them with possible residual activity.

Conclusion: The first Mexican patient with abetalipoproteinemia presents a novel *MTTP* mutation p.Gly417Valfs*12. Three factors that could modulate the phenotype in abetalipoproteinemia were identified: age at diagnosis, treatment, and the causal mutation.

KEYWORDS

abetalipoproteinemia in Mexico, analysis of 100 cases with abetalipoproteinemia, diarrhea, low lipid levels, *MTTP* gene, novel mutation p.Gly417Valfs*12

1 | INTRODUCTION

Abetalipoproteinemia (ABL) is an autosomal recessive disease characterized by an inability to assemble and secrete apolipoprotein B–containing lipoproteins[1]; its worldwide incidence is less than 1 in 1,000,000. The absence of VLDL and chylomicrons is associated with a variety of biochemical and clinical abnormalities, as extremely low values of lipids in plasma [triglycerides (TG) <17.7mg/dL, total cholesterol (TC) <30 mg/dL, LDL-C < 3.9mg/dL, and apoB < 10mg/dL], elevation of transaminases, low concentration of vitamins, intolerance to fat intake, fat malabsorption, liver steatosis, diarrhea with steatorrhea, malnutrition, and growth retardation. Liposoluble vitamin deficiency has severe consequences, particularly the lacking of vitamin E, A, K, or D, each of which is respectively associated with neurological, ophthalmological, hematological, and bone symptoms.[2,3] The treatment of patients with ABL consists of a low-fat diet (less than 30%) enriched with medium-chain fatty acids and complemented with vitamins. The recommended doses of vitamins A, D, E, and K are 100 to 400 IU/kg/day, 800-1200 IU/day, 100 to 300mg/kg/day, and 10-20 mg/week, respectively.[2]

ABL is caused by mutations in the *MTTP* gene, which is located in the chromosomal band 4q23 and encodes the large M subunit of the MTP-PDI heterodimer (microsomal triglyceride transfer protein—protein disulfide isomerase).[3] PDI (P subunit) is a multifunctional protein that confers lipid transfer activity to this dimer.[4] The M subunit is composed of 894 aa and has three major domains: an N-terminal β-barrel domain (residues 22 to 297) that interacts with the N-terminus of apoB protein; a central α-helix domain (residues 298 to 603) that binds both to the apoB protein and PDI subunit; and a C-terminal lipid–binding domain (residues 604 to 894) responsible for triglyceride transfer.[5] The MTP-PDI complex is required for the assembly of VLDL (in liver) and chylomicrons (in intestine).[4] To date, more than 75 ABL causative mutations affecting the *MTTP* gene have been described (Table 1).

The aim of this report was to describe the first case of abetalipoproteinemia in Mexican population, whose clinical and biochemical characteristics resulted from a novel mutation in the *MTTP* gene. In addition, we present the analysis of 100 patients with this dyslipidemia who had been previously reported.

2 | MATERIAL AND METHODS

We performed biochemical and molecular screenings both in a Mexican girl with extremely low lipid levels and in her family. The diagnosis of familial hypobetalipoproteinemia-1 (OMIM 615558, *APOB* gene), an autosomal codominant disease, was ruled out, after finding the lipid levels (TC, TG, ApoB, and LDL-C) of the patient's relatives within normal ranges (Table 2). Anderson's disease (246 700, SAR1B gene) was also ruled out because our patient had extremely low TG levels; hence, ABL (OMIM 200 100, *MTTP* gene) or familial hypobetalipoproteinemia-2 (OMIM 605 019, *ANGPTL3* gene) was suspected. We started a molecular screening by analyzing the 18 exons and the promoter region of the *MTTP* gene. Before sampling, the patient's parents signed an informed consent following the recommendations of our institutional ethics and research committees; moreover, the children also signed a letter of assent. DNA was obtained from 4 ml of peripheral blood collected in a tube with EDTA and processed by the DTAB/CTAB method.[6] Polymerase chain reaction (PCR) and Sanger sequencing were performed using primers designed with the Oligo 6 program (primer sequences and conditions are available on request). Integrity and size of the amplicons were verified in 6% polyacrylamide gels before proceeding with the purification of the PCR products using the ExoSAP-IT kit (Applied Biosystems).

For the sequencing reaction, the BigDye v.3.1 kit was used following the conditions proposed by the supplier. The products of the sequencing reaction were purified with Sephadex G-50 columns, and capillary electrophoresis was performed on the ABI Prism 310 equipment. Electropherograms were analyzed with the Chromas program. Any change in the sequence was confirmed by bidirectional sequencing.

On the other hand, we integrated and evaluated the clinical, biochemical, and genetic characteristics of 100 cases with abetalipoproteinemia, described in the literature (Supplementary table S1). Abetalipoproteinemia cases were searched in multiple electronic databases (NCBI, PubMed, National Library of Medicine, Google Scholar, Research Gate, B-ON, ScienceDirect, SciELO, The Cochrane Library, and OMIM) using the following keywords: abetalipoproteinemia, ABL, MTTP, MTTP gene mutation, and ABL variant; furthermore, to avoid duplicating information, the list of references of some reports was revised. Two reviewers independently conducted the literature research and selected the 45 articles (published between 1993 and 2020) that were included. All the cases considered for this analysis had pathogenic mutations in the *MTTP* gene.

In order to unify the nomenclature of the causal variants of ABL—according to the standards of the Human Genome Variation Society—each one of them was reviewed using the sequence of both the *MTTP* gene and its protein, reported in the Genome Browser and Ensembl databases, respectively.

Descriptive and comparative analyses were carried out for quantitative (Student's t test) and qualitative (chi-square test) variables. Odds ratio was calculated to measure the association between age at diagnosis and clinical complications. The software used to analyze the data was Statgraphics Centurion XVI.I

3 | RESULTS

3.1 | Clinical, biochemical, and molecular description of the Mexican family with ABL

A six-year-old female patient was born by cesarean section at 37 weeks of gestation; her weight and height at birth were 2.2 kg and 50 cm. She was the third child of consanguineous parents (sharing the same grandparent) from Guadalajara, Jalisco, Mexico; the

TABLE 1 Mutations detected in the *MTTP* gene causing abetalipoproteinemia

MN[Reference]	Exon/ Intron	Nucleotide substitution	Variant name	Alleles§	Unrelated alleles¶	MN (Reference)	Exon-intron	Nucleotide substitution	Variant name	Alleles§	Unrelated alleles¶
1[21]	E1	c.1A > G	p.0?	1	1	39[22]	E11	c.1448_1461del	p.Pro483GInfs*25	2	1
2[9,14]	E1	c.59_75del	p.K20Tfs*5	4	2	40[23]	E11	c.1508_1515del	p.Leu503Hisfs*7	2	1
3[24]	I1	c.61 + 1G>C	p.G21Dfs*7	1	1	41[25]	E12	c.1582T > C	p.Y528H‡‡‡‡	1	1
4[26]	I1	c.61 + 2T>C	p.G21Dfs*7	1	1	42[27]	E12	c.1586A > G	p.H529R	2	1
5[19]	I1	c.148-2A > G‡		2	1	43[13,25]	E12	c.1618C > T	p.R540C§§§§	2	2
6[25]	E2	c.103_127del	p.K35Ffs*37	1	1	44[12,28,29]	E12	c.1619G > A	p.R540H¶¶¶¶¶	4	4
7[7,8]	E2	c.136C > G	p.R46G††	4	4	45[21,30]	E12	c.1655C > T	p.P552L	4	4
8[21]	E2	c.154C > T	p.Q52X	1	1	46[24,31]	E12	c.1691C > T	p.I564T	3	3
9[32]	E2	c.215del	p.P72Lfs*8	2	1	47[12,33]	E12	c.1769G > T	p.S590I	4	4
10[19]	E3	c.307A > T	p.K103X	2	2	48[12]	I12	c.1770-1G > A†	p.S590Rfs*2	1	1
11[34]	I3	c.393 + 3A>T†	p.V132_E167del	1	1	49[11,14]	E13	c.1783C > T	p.R595X	3	3
12[35]	I3	c.394-2A > C	p.V132_E167del	2	1	50[12]	E13	c.1820del	p.R607Lfs*15	2	1
13[9,10,36]	E4	c.398_399del	p.V132Nfs*140	6	4	51[37]	E13	c.1834G > C	p.G612R	2	2
14[11,15,26,38]	E4	c.419insA	p.N139_E140insX	9	9	52[13,15]	I13	c.1867 + 1G>A	p.S624Gfs*3	3	3
15[39,40]	E5	c.506A > T	p.D169V‡‡	4	3	53[15,41]	I13	c.1867 + 5G>A	p.S624Ifs*31††††††	3	3
16[14]	E5	c.582C > A	p.C194X	2	1	54[22]	I13	c.1867 + 6T>A	p.S624Gfs*3	2	1
17[42]	I5	c.619-5_619-2del	p.V207Afs*28§§	1	1	55[8]	E14	c.1868G > T	p.R623L‡‡‡‡‡	1	1
18[43]	I5	c.619-3T > G	p.V207Afs*28§§	2	1	56[25]	E14	c.1946A > G	p.N649S§§§§§	1	1
19[16]	E6	c.619G > T	p.V207Afs*28§§	1	1	57[44]	E14	c.1982G > C	p.G661A‡‡‡	1	1
20[28]	E6	c.708_709del	p.H236Qfs*11	1	1	58[15]	E14	c.1989G > A	p.S624Gfs*3	1	1
21[25]	E7	c.790G > C	p.G264R	1	1	59[19]	E15	c.2211del	p.H737fs*9	2	2
22[21]	I7	c.910-1G > T	p.L304Tfs*28	2	2	60[15]	E15	c.2212del	p.S738Lfs*10	2	2
23[43,45]	E8	c.923G > A	p.W308X	4	2	61[46]	E15-E16	c.2076-39_2303 + 52del‡		2	1
24[21,47]	I9-E9	c.1067 + 1217_1141del	p.P357Ffs*4	3	3	62[11,21]	I15	c.2218-2A > G	p.E740Gfs*8	2	2
25[8]	E9	c.1081G > T	p.D361Y¶¶	2	2	63[12]	E16	c.2237G > A	p.G746E	1	1
26[15]	E9	c.1147del	p.S383Vfs*26	2	1	64[17,48]	E16	c.2313T > A	p.Y771X	4	2
27[44]	E9	c.1151A > C	p.D384A††† ‡‡‡	1	1	65[11]	E16	c.2338A > T	p.N780Y¶¶¶¶¶¶	2	1
28[44]	E9	c.1229_1231delinsT	p.A410_L411delinsV	2	1	66[49]	I16	c.2342 + 1G>A	p.V782Xfs*1††††††	2	1
29[17,49]	I9	c.1236 + 2T>G	p.P357Vfs*17§§§	4	2	67[30]	I16	c.2342 + 2dup	p.V782_R838del	2	2
30[44,50]	I9	c.1237-1G > A	p.S413_K448del	3	3	68[51]	E17	c.2346_2347insACTG	p.V784Dfs*7	2	1

(Continues)

TABLE 1 (Continued)

MN[Reference]	Exon/ Intron	Nucleotide substitution	Variant name	Alleles§	Unrelated alleles¶	MN (Reference)	Exon-intron	Nucleotide substitution	Variant name	Alleles§	Unrelated alleles¶
31[16]	I9	c.1237-28A > G	p.S413_ K448del¶¶¶	1	1	69[21]	E17	c.2445del	p.T816Qfs*10	1	1
32[29]	E10	c.1237_1344del	p.S413_K448del	1	1	70[12]	E18	c.2524A > T	p.K842X	1	1
33[42]	E10	c.1304T > A	p.L435H††††	1	1	71[12,19,20]	E18	c.2593G > T	p.G865X‡‡‡‡‡‡	10	9
34[12]	E10	c.1342A > T	p.K448X	1	1	72[45]	E18	c.2611del	p.H871I fs*29	2	1
35[15]	I10	c.1344 + 5_1344+11del	p.S413_K448del	2	2	73[34]		*MTTP* gene deletion		1	1
36[11]	E11	c.1389del	p.A462Qfs14	2	1	74[52]		MTTP gene deletion and other six genes		2	2
37[21]	E11	c.1392del	p.E465Rfs*13	2	2	75[19]		MTTP gene deletion and other eight genes		2	1
38[15]	E11	c.1401insA	p.E467_D468insR	1	1						
							Total number of alleles		167	136	

Abbreviations: MN, mutation number; †: variants whose nomenclature was modified according to the standards of the Human Genome Variation Society. ‡: variants whose nomenclature is wrong but could not be corrected. §: alleles observed in unrelated patients. ¶: number of alleles with ABL variants eliminating the chromosomes of the parents with consanguinity. Functional effects of some variants: ††: no triglyceride transfer activity[7]; promotes apoB48 secretion.[8] ‡‡: low transfer capacity to triglycerides (13%) and phospholipids (9%).[39] §§: deletion of exon 6 and a 233 aa protein is generated; despicable residual activity.[16,42,43] ¶¶: 22% of apoB48 secretion.[8] †††: promotes apoB48 secretion.[44] ‡‡‡: p.H297, p.D384A, and p.G661A variants promote apoB48 secretion, both individually and jointly.[8] §§§: deletion of exon 9 producing a 372 aa protein.[49] ¶¶¶: deletion of exon 10 producing an 858 aa protein with despicable residual activity.[16] ††††: low triglyceride transfer activity (1.9% /30 μg protein/h).[42] ‡‡‡‡: low residual activity (10%).[25] §§§§: residual activity 12%.[25] ¶¶¶¶: low-level apoB was detected.[29] †††††: two isoforms: integration of intron 13, resulting a 653 aa protein; deletion exon 13, producing a 590 aa protein.[41] ‡‡‡‡‡: residual activity 60%-65%; two isoforms: include the intron 13 and produce a 653 aa protein; and 28pb deletion of exon 14, generating a 623 aa protein.[8] §§§§§: residual activity 57%.[25] ¶¶¶¶¶: negligible residual activity.[11] ††††††: introduction of intron 16 producing a 781 aa protein.[49] ‡‡‡‡‡‡: loss of the last 30 aa and no MTTP activity was detected.[20]

TABLE 2 Biochemical findings of the Mexican patient and her relatives

	Proband	Mother	Father	Sister I	Sister II	Reference values
Age (y)	6	30	28	8	10	
Glucose mg/dL	81	87	65	78	80	72-108[53]
Urea mg/dL	7	16	26	21	11	12.0-54.0[54]
Creatinine mg/dL	0.3	0.6	0.9	0.4	0.4	0.6-1.20[55]
TC mg/dl	<50	169	141	116	124	104-220[23]
HDL-C mg/dL	25	38	55	30	36	35-85[13]
LDL-C mg/dL	20	119.2	79.5	74.1	75.9	70-120[17]
TG mg/dL	<10	144	111	73	53	60-150[23]
apoB mg/dL	<35	91.1	65.7	61.5	64.0	55-125[44]

Abbreviations: apoB, apolipoprotein B; HDL-C, High-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

mother developed preeclampsia during pregnancy. The proband was referred to the pediatric gastroenterology service of the National Medical Center of the West, affected with vomiting since her first month of life and by chronic diarrhea (with steatorrhea, but neither mucus nor blood) from her third one. During the two years that preceded her diagnosis, she monthly presented three diarrheal events lasting three days each and with at least 10 daily evacuations. Consequently, she failed to thrive.

Under physical exploration, the proband presented a distended abdomen (without organomegaly); however, neurodegeneration, dehydration, abnormal skin coloration, cardiopulmonary defects, retinitis pigmentosa, and areflexia were not detected. Laboratory data revealed malabsorption, anemia, and acanthocytosis; concentrations of aspartate transaminase (AST) (126U/L) and alanine transaminase (ALT) (93 U/L) were high. Values of TC (<50 mg/dL), TG (<10 mg/dL), VLDL (<2 mg/dL), HDL-c (25 mg/dL), and apolipoprotein B (<35 mg/dL) were extremely low (Table 2). Values of albumin protein (3.0 mg/dL) and CPK (191 U/L) were within normal range, and a coprological study ruled out pathogens.

A patient's intestinal tissue biopsy revealed that the mucosa of the duodenal portion had preserved villus with a focal loss of the brush border, severe steatosis, increased leukocyte intraepithelial films, presence of plasma cells, and scarce eosinophils. In addition, a liver ultrasound showed steatosis.

The proband started treatment at the age of two years with the administration of 50,000 IU of vitamin A every 8 hours, 800 IU/day of vitamin E, 100 mg/day of thiamine, 5 mg/day of pyridoxine, 50 μg/day of cyanocobalamin, and 15 mg of vitamin K per week. In addition, therapy was accompanied by a hydrolyzed formula containing medium-chain TG and foods rich in essential oils. She responded successfully to the treatment, reaching the appropriate weight and height values at 6 years of age.

In the molecular analysis, we found a homozygous G deletion of the nucleotide c.1250, within exon 10 of the *MTTP* gene (Figure 1). This deletion causes both a glycine to valine substitution at residue 417 (p.Gly417Valfs*12) and a premature stop codon at position 429, rendering the loss of 465 aa of the protein. The parents and the two sisters were heterozygous for the deletion. To our knowledge, this mutation has not been previously reported.

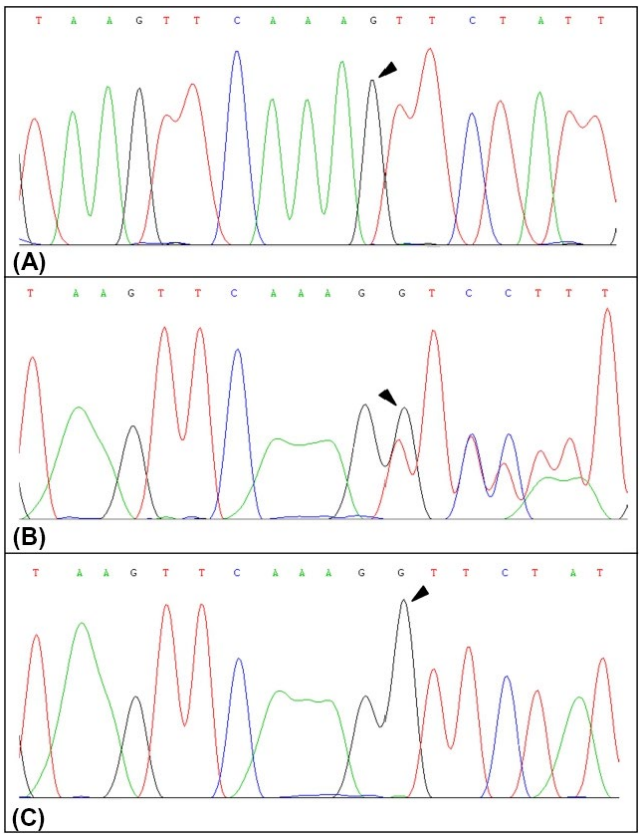

FIGURE 1 Partial electropherograms showing the deletion of a G nucleotide at position c.1250, within exon 10 of the *MTTP* gene. A, Homozygous deletion observed in the patient, B) heterozygous deletion, and C) homozygous wild. Arrowheads pinpoint the key positions

The analysis of the *MTTP* gene in this family revealed the presence of six polymorphisms (5'-rs1800803A > T (promoter), rs2306986 G > C (exon 3), rs3792683 A > G (exon 4), rs99589702 T > C (exon 4), rs982424 T > C (exon 5), and rs2306985 C > G (exon

TABLE 3 Clinical characteristics observed in patients with abetalipoproteinemia

Clinical feature	Affected patients %	Clinical feature	Affected patients %
Acanthocytosis	57.5	Dysarthria	2.3
Malabsorption	43.7	Psychomotor retardation	2.3
Diarrhea	42.5	Inguinal hernia	2.3
Failure to thrive	35.6	Umbilical hernia	2.3
Retinal degeneration	32.2	Oral moniliasis	2.3
Areflexia	27.6	Dysmorphic face	2.3
Steatorrhea	27.6	Hypothyroidism	2.3
Enterocyte steatosis	24.1	Hammertoes	2.3
Hepatic steatosis	20.7	Kyphoscoliosis	2.3
Vomiting	18.4	Pes cavus	2.3
Retinitis pigmentosa	17.2	Nystagmus	2.3
Anemia	17.2	Short-term memory loss	1.2
Pale-yellow discoloration of the small bowel mucosa	16.1	Liver dysfunction	1.2
Abdominal distension	11.5	Hepatic cirrhosis	1.2
Malnutrition	10.3	Scoliosis	1.2
Ataxia	10.3	Obesity	1.2
Hepatomegaly	10.3	Xerophthalmia	1.2
Loss vibration sense	6.9	Keratinization of the bulbar conjunctiva	1.2
Spinocerebellar degeneration	6.9	Ptosis	1.2
Dehydration	5.8	Paresthesia	1.2
Loss of proprioception sense	4.6	Corneal ulcer	1.2
Muscle weakness	4.6	Progressively worsening coordination	1.2
Neuropathy	4.6	Delayed puberty	1.2
Reduced subcutaneous fat tissue	4.6	Neurogenic atrophy	1.2
Positive Romberg's sign	4.6	Difficulty with fine motor skills	1.2
Hair brittle and sparse	3.5	Weight loss	1.2
Hypotonia	3.5	Ileal adenocarcinoma	1.2
Hypotrophy	3.5	Dilatation of small bowel	1.2
Difficulty walking	3.5	Edema of the intestinal lining	1.2
Mental retardation	3.5	Abdominal pain	1.2

7)-3'), which were used to establish a haplotype linked to the causal mutation of ABL, which was TCGCCG.

3.2 | Description of the patients with ABL reported in the literature

Supplementary table shows the biochemical, clinical, and molecular characteristics of 100 cases (belonging to 83 families) with ABL, identified through the bibliographic search. The average age of diagnosis was 12.2 ± 14.2 years (n = 89; range 0-60 years), and 44.1% were female (37/84). The lipid levels stood within the following ranges: TC, undetectable to 85.1 mg/dL; TG, undetectable to 105 mg/dL; LDL-C, undetectable to 36 mg/dL; apoB, undetectable to 27 mg/dL; and HDL-C, 14.3 to 62.3 mg/dL. Additionally, a significant percentage of patients showed low levels of vitamins E (94.3%, 50/53 patients) and A (84.0%, 21/25 patients).

At least 60 signs and symptoms have been described for ABL, of which five are the most frequent: acanthocytosis (57.5%), malabsorption (43.7%), diarrhea (42.5%), failure to thrive (35.6%), and retinal degeneration (32.2%); however, 50% of the symptoms were observed in no more than two patients (Table 3).

We analyze the clinical phenotype of the patients with ABL classifying them into two groups: a) moderate phenotype (MP): patients who presented only classic clinical symptoms such as vomiting, chronic diarrhea, failure to thrive, anemia, and acanthocytosis, among others; and b) severe phenotype (SP): patients who, in addition to the classical characteristics, presented, among others, complications of neurological, ophthalmological, or hematological origin, considered as non-classical features (Supplementary table S1).

Of the 100 patients with ABL reported to date, only 86 had data for both age and clinical features. Forty-two (48.8%) were classified as MP (age range: 0 months to 39 years) and 44 (51.2%) as SP (age range: 4 months to 60 years). The distribution of cases between the two phenotypes, classified by ranges of 10 years, was different (chi-square with the Yates correction; $P < .00001$, 3 *df*) due to the larger number of MP patients in cases younger than 10 years (36 vs 11), and the larger number of SP patients in the 10-20 year range (3 vs 18) (Supplementary table S1). Odds ratio analysis showed that patients diagnosed after 10 years of age have an increased risk for presenting clinical complications (SP 33 vs MP 6; OR = 18.0; 95% CI 6.0-54.1, $P < .0001$).

Patients with SP showed from 1 to 9 different clinical complications. The percentage of subjects with less than 3 and with 3 or more non-classical characteristics were 59.1% and 40.9%, respectively. Moreover, the number of complications was not directly related to the age of diagnosis (< 3 complications: 4 months to 60 years; ≥ 3 complications: 1.1 to 32 years) (Supplementary table S1).

To date, 75 causal mutations of ABL have been reported throughout the *MTTP* gene: splicing (n = 22), deletion (n = 20), nonsense (n = 9), insertion (n = 3), indel (n = 1), and missense (n = 20) (Table 1). 83 of the 100 cases with ABL were unrelated, and 167 mutated alleles were observed (patient number 64 in supplementary table had three pathogenic mutations). The most common variants were p.G865X (6.0%, 10/167 chromosomes) and p.N139_E140insX (5.4%, 9/167 chromosomes) (Table 1).

On the other hand, 79.0% (79/100) of the patients had homozygous genotypes, with alleles mostly coming together from consanguineous parents, and the remaining 21.0% (21/100) had a compound heterozygous genotype (Supplementary table S1).

In order to relate the clinical phenotype and the causal variant of the disease, we classified the patients into two groups: a) patients who had a null variant in both alleles (truncated protein or alteration in the splicing sites) hypothetically resulting in less than 2% residual protein activity and b) patients who presented a missense variant in at least one allele, where the mutated protein could have a significant residual activity. In the first and second groups, 64 (28 with MP and 36 with SP) and 22 (14 MP and 8 SP) patients were included, respectively. No significant differences were observed between these groups when comparing the distribution of patients according to the clinical phenotype (28 MP and 36 SP vs. 14 MP and 8 SP, $P = .11$) or age of diagnosis (in ranges of 10 years, $P = .63$).

On the other hand, in order to establish the phenotype-genotype relationship, it is necessary to know the residual activity of the variants. Unfortunately, only in 14 of 75 variants have information on the residual activity of the protein been reported (p.R46H, p.D169V, p.C194X, p.G264R, p.D361Y, p.D384A, p.L435H, p.R540H, p.R540C, p.R623L, p.N649S, p.G661A, p.N780Y, and p.G865X); therefore, in more than 80% of the variants is their functional effect unknown. Furthermore, in vitro studies have reported different results for the p.R46G mutation. Liu et al found null activity in induced pluripotent stem cells,[7] and Walsh et al observed both TG transfer activity and secretion of APOB48.[8]

4 | DISCUSSION

In this work, we report a six-year-old girl who presented the typical symptoms of ABL. The molecular analysis of the *MTTP* gene revealed a novel variant within the exon 10, p. Gly417Valfs*12 (deletion of a G nucleotide at position 1250). The proband was homozygous for the mutation, whereas her parents and her sisters were heterozygous. This variant generates both a premature stop codon and a truncated protein of 429 aa with a loss of 465 aa. The resulting protein lacks both the central α-helix and the C-terminal domains. The first is involved in both the binding to PDI and the integration of the active MTTP-PDI complex, whereas the second participates in the transference of triglycerides to nascent APOB molecules. Therefore, the main consequence of this mutation is a significant reduction of lipoproteins rich in TG. Considering the importance of these two domains for the proper functioning of MTTP, we conclude that the p.Gly417Valfs*12 variant is the cause of the clinical-biochemical phenotype of our index case.

4.1 | Comparative analysis of patients with abetalipoproteinemia

Although the average age of diagnosis of the reported cases was 12.6 ± 14.7 years, a significant percentage of these patients (39.3%, 35/89) was diagnosed in the first two years of life, which might be due to the early presentation of symptoms threatening their survival, as was the case of our patient, who required hospitalization due to severe and prolonged episodes of diarrhea and vomiting.

It is well known that the main biochemical finding shown by ABL patients consists of extremely low levels of lipoproteins rich in TG. The mean values of those patients below 3 years of age (n = 35) were TC 39.1 ± 14.3 mg/dL, TG 9.9 ± 6.7 mg/dL, LDL-C 8.3 ± 7.5 mg/dL, and APOB 2.3 ± 5.5 mg/dL; values were similar to those presented by our proband (Table 2). However, the ranges of lipid levels in

these 35 patients were highly heterogeneous (TC, undetectable to 85.1 mg/dL; TG, undetectable to 19.5 mg/dL; LDL-C, undetectable to 24.4 mg/dL; and ApoB, undetectable to 18 mg/dL), even overlapping, in some instances, the normal values (Supplementary table S1).

Additionally, a significant percentage of patients showed low levels of vitamins E (93.8%) and A (76.2%). Although vitamins were not quantified in our proband, she might have been deficient for both (E and A), since her health improved significantly once they were included in the treatment. The current standard treatment for ABL is based on a low-fat diet, eventually supplemented with medium-chain triglyceride and administration of fat-soluble vitamins. All the patients who had an appropriate management immediately after diagnosis have had an adequate response to vitamin treatment, except for five cases.[9-13]

At least 60 signs and symptoms for ABL have been described, of which 50% have been observed in no more than two patients. This may be due to the absence of an intentional search for the clinical features in each patient or to omission of such information in the reports. Our Mexican patient showed features relatively common in patients below 3 years of age and MP: failure to thrive (66.7%), acanthocytosis (45.5%), diarrhea (42.4%), steatorrhea (30.3%), vomiting (30.3%), and anemia (15.2%).

The making of an early diagnosis could be influenced by the severity of the clinical manifestations and by the degree of impairment in the quality of life of each patient. Classic symptoms of the disease are likely to be more severe in the MP group than in the SP group, requiring health services at an early age and thus increasing the chance for being diagnosed. In concordance with this, some classic features were more frequent in patients with MP than with SP: failure to thrive (53.5% vs. 18.2%, $P = .0006$), vomiting (27.9% vs. 9.1%, $P = .002$), and abdominal distension (20.9% vs. 2.3%, $P = .006$). However, other factors as the expertise of the medical workers and the quality of the available health systems could also influence the diagnosis of ABL.

At the time of the report, our, then, six-year-old patient presented no observable complications in the neurological, ophthalmological, or hematological areas. Of the forty-four cases ≤6 years of age previously described, 78.6% had MP, as our proband did. The remaining 21.4% had SP, and although it has been suggested that non-classical clinical features occur after childhood (due to deficiency of fat-soluble vitamins), these children presented symptoms such as areflexia,[11,14-17] hypotonia,[9,15,17] psychomotor retardation,[9] decreased vibration sense,[15] muscle weakness,[17] and retinitis pigmentosa.[11] An analysis showed that patients diagnosed after 10 years of age had an increased risk of presenting clinical complications (OR = 18.0; 95% CI 6.0/54.1, $p < 0.0001$), possibly derived from vitamin deficiency.

A clinical heterogeneity was more evident in patients with SP, in whom, from 1 to 9 clinical complications have been described. Interestingly, the number of complications was not directly related to the age of diagnosis (Supplementary table S1). Hence, other factors, as the causal mutation of ABL or the presence of modifier genes may influence the clinical expression.

A great diversity of mutations (n = 76, including our patient) in ABL patients has been observed (Table 1), where the two most common do not exceed 10% (p.G865X (7.0%) and p.N139_E140 (6.3%)) and around 50 of them were only present in no more than two chromosomes. These data show that most of the mutations are population-specific, so, it is not surprising that the variant detected in the first Mexican patient with ABL has not been previously reported. ABL is a recessive disease, and the percentage of inbreeding was 76.1% (54/71, including our patient), which is comparable to that reported by Shawky et al[18] (78.8%) (Supplementary table S1).

In an attempt to correlate phenotype-genotype, we classified the patients into two groups: individuals who had a null variant in both alleles and patients with at least one missense variant. However, we did not find significant differences between the two groups, in either clinical severity or age of diagnosis. Therefore, we consider essential to evaluate the residual or functional activity of each pathogenic variant to perform a proper classification of the patients and thus obtain reliable conclusions.

Although the phenotype-genotype relationship with the classification that we carried out was not conclusive, a phenotypic scope can be estimated by comparing non-related individuals sharing the same mutation. As an example, we may consider seven patients from five families sharing the p.G865X mutation in homozygous state. They all had a very wide range of age at diagnosis (from 12 to 57 years; patients 10-14, 42, and 85, supplementary table S1). Also, all seven presented the classic clinical characteristics and retinal degeneration. The two oldest (52 and 57 years old, patients 85 and 10, supplementary table S1) also had retinitis pigmentosa.[12,19,20] However, the patient reported by Wang & Hegele[12]—diagnosed at 12 years of age—(patient 42, supplementary table S1) iin addition to the aforementioned characteristics, also presented ataxia and areflexia, and passed away 6 years later from a severe neuropathy that resulted in pneumonia and respiratory failure. It is important to emphasize that all the patients carrying the p.G865X mutation developed retinal degeneration despite the fact that this condition has only been observed in 32.2% of cases with ABL (Table 3).

Conversely, patients with the p.V132Nfs*140 mutation showed clinical heterogeneity. Five homozygote patients from three families were diagnosed in the first year of life. Out of three affected sibs, two were included in the MP group, without any clinical complication (patients 46 and 47, supplementary table S1). However, the third sib was described with SP (patient 45) and at two years of age presented both delayed psychomotor development and hypotonia.[9] The fourth case died at 13 months of age (patient 9, supplementary table S1), apparently without clinical complications, but did not respond to vitamin treatment. The clinical characteristics of the fifth patient (patient 37) were, unfortunately, not described (supplementary table S1).

To date, two patients homozygous for the variant p.R46G have been reported: The first was diagnosed at age 5 and only had diarrhea and steatorrhea[8] (patient 87, supplementary table S1), and the second (patient 38, supplementary table S1), diagnosed at 60 years of age, presented steatorrhea, hepatic steatosis, spinocerebellar degeneration, and retinal deterioration.[7] The phenotype of these patients is congruent with what is expected: The earlier the diagnosis, the lower the risk of presenting clinical complications.

In general, it is difficult to define a clear clinical pattern in ABL patients, since it can be influenced by several factors such as the specific kind of mutation, different degrees of activity of mutated proteins, synergy of modifier genes, the limited number of patients with the same variant, the scarce reports of patient's follow-up, or even other concomitant diseases, among others.

In conclusion, we report the first ABL case in Mexico: a six-year-old girl with a moderate phenotype and a novel mutation, p. Gly417Valfs*12. In addition, with the analysis of the 100 ABL patients, we concluded the following: a) A diagnosis at an early age is a crucial factor to avoid or delay clinical complications in these patients; b) both an adequate treatment and an appropriate follow-up immediately after the diagnosis are relevant and favorable for patients constituting invaluable cost-benefit; c) at least 60 signs and symptoms have been described for ABL, being the most common acanthocytosis (57.5%), malabsorption (43.7%), diarrhea (42.5%), failure to thrive (35.6%), and retinal degeneration (32.2%); and d) at least 76 variants of the *MTTP* gene causing of ABL have been detected, being the two most frequent p.G865X (7.0%) and p.N139_E140 (6.3%), which evidences a wide mutational spectrum. The establishment of an adequate genotype-phenotype correlation is limited by a series of circumstances, including a broad mutational spectrum causing the disease, few cases sharing the same mutation, reports lacking all the clinical-biochemical findings of the patients, and the paucity of studies on the residual activity of mutant proteins.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

P. G. R. G was involved in laboratory activities, conducted the literature review, and wrote the article. J. R. G. G. collaborated in the bibliographic search, elaboration of the figure, and discussion of results. Y. A. C. L. and J. R. Z. G. remitted the patient and made the clinical and biochemical diagnosis of ABL. M. T. M. T. designed the study, and worked on PCR and sequencing reaction, as well as in the electropherogram analysis. She performed the analysis of the results.

All authors read, approved, and agreed with the material contained in this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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