Original article

Niemann-Pick disease A or B in four pediatric patients and SMPD1 mutation carrier frequency in the Mexican population

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ABSTRACT

Introduction and Objectives: Niemann-Pick disease type A (NPD-A) and B (NPD-B) are lysosomal storage diseases with a birth prevalence of 0.4–0.6/100,000. They are caused by a deficiency in acid sphingomyelinasen, an enzyme encoded by SMPD1. We analyzed the phenotype and genotype of four unrelated Mexican patients, one with NPD-A and three with NPD-B.

Patients and methods: Four female patients between 1 and 7 years of age were diagnosed with NPD-A or NPD-B by hepatosplenomegaly, among other clinical characteristics, and by determining the level of acid sphingomyelinsen enzymatic activity and sequencing of the SMPD1 gene. Additionally, a 775 bp amplicon of SMPD1 (from 11:6393835,6394609, including exons 5 and 6) was analyzed by capillary sequencing in a control group of 50 unrelated healthy Mexican Mestizos.

Results: An infrequent variant (c.1343A>G p.Tyr448Cys) was observed in two patients. One is the first NPD-A homozygous patient reported with this variant and the other a compound heterozygous NPD-B patient with the c.1829_1831delGCC p.Arg610del variant. Another compound heterozygous patient had the c.1547A>G p.His516Arg variant (not previously described in affected individuals) along with the c.1805G>A p.Arg602His variant. A new c.1263+8C>T pathogenic variant was encountered in a homozygous state in a NPD-B patient. Among the healthy control individuals there was a heterozygous carrier for the c.1550A>T (rs142787001) pathogenic variant, but none with the known pathogenic variants in the 11:6393835,6394609 region of SMPD1.

Conclusions: The present study provides further NPD-A or B phenotype-genotype correlations. We detected a heterozygous carrier with a pathogenic variant in 1/50 healthy Mexican mestizos.

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1. Introduction

Niemann-Pick disease (NPD) type A (NPD-A, OMIM 257200) or type B (NPD-B, OMIM 607616) are caused by mutations in the sphingomyelin phosphodiesterase-1 gene (SMPD1, OMIM 607608; NG_011780.1 reference sequence) on 11p15.4 that encodes for the acid sphingomyelinase enzyme (ASM, EC 3.1.4.12, SMPD1) [1–3]. ASM catalyzes the hydrolytic cleavage of sphingomyelin in lysosomes, producing phosphocholine and ceramide [4,5]. Low levels of enzyme activity cause the progressive accumulation of sphingomyelin and other lipids in target tissues, and is clinically manifested as ASM deficiency disease (ASMD) responsible for the clinical spectrum of NPD-A or NPD-B metabolic phenotypes [4,5]. The pattern of inheritance of ASMD is autosomal recessive, with a birth prevalence of 0.4–0.6/100,000 worldwide [4]. More than 180 variants of SMPD1 have been described, some of them restricted to certain families. Carrier frequency varies among populations [4.6–8]. Another class of Niemann-Pick disease is the type C (NPD-C, OMIM 257220), which is due to pathologic variants in NPC1 (95% of the cases, OMIM 607623) or NPC2 (5% of the cases, OMIM 601015) genes that encode cholesterol-binding proteins; it is also an autosomal recessive disease with a variable phenotype different from NPD-A or NPD-B [4,5].

In NPD-A (the infantile neurovisceral form), patients are diagnosed mainly in early childhood with hepatosplenomegaly, failure to thrive and hypotonia, and most die by three years of age [3,9]. They have high serum triglycerides and cholesterol levels, a cherry spot in the macula, and central nervous system abnormalities [3.5,10]. NPD-B (the chronic visceral form) represents a less severe phenotype and some patients survive well into adulthood. As there is no neurological affection, the association of hepatosplenomegaly and hypersplenism to NPD-B may be underestimated. The intermediate form (chronic neurovisceral), NPD-A/B (OMIM 607616), leads to a better average survival and less progression of neurological symptoms than NPD-A [4]. NPD-A and NPD-B patients also present thrombocytopenia, hyperlipidemia, osteopenia, impaired lung function and liver dysfunction [4,11,12]. Bone marrow and hepatic biopsies show sea-blue histiocytes or foam cells (lipid-laden macrophages) [13]. There is no treatment for ASMD. Its management has included a low-fat diet and bone marrow transplant [10].

We herein report four cases of unrelated female Mexican mestizo patients suffering from NPD-A or NPD-B. A control group of 50 unrelated healthy individuals was screened for four of the five variants of SMPD1 found in these patients, demonstrating an unexpectedly high carrier frequency of one pathogenic variant (1/50). The general implications, case management and genetic assessment are discussed.

2. Subjects and methods

Four patients were clinically studied in our Institution; at the time of their first consultation blood samples were taken, and enzymatic and molecular analyses for NPD-A or B were performed at external laboratories. As a control group, fifty healthy unrelated Mexican Mestizos were analyzed in our laboratory for the four previously known variants. To assess an ethnic homogeneity, only subjects with both parents and four grandparents, from Mexican Mestizo origin were included. In total, 10 ml of peripheral blood was collected from each subject in Vacutainer tubes with acid citrate dextrose. Genomic DNA was isolated by standard techniques, and was subsequently quantified and checked for purity. DNA samples analyzed in our laboratory were stored at 4 °C until used. Direct Sanger sequencing was performed from genomic DNA isolated from peripheral blood leukocytes. The pathogenic variants identified in patients 1 and 2 were confirmed in their parents by Direct Sanger sequencing in our laboratory. A 775 bp amplicon of SMPD1 from 11:6393835-6394609, including exon 5 (nt: 6,393,896) to exon 6 (nt: 6,394,609), was amplified using Taq DNA polymerase with forward primer (5′–3′): TCTCCCCAGATCTTCCTA located in 11:6393835-6393854 and reverse primer CCCTACAAAAACGTCGCCT in 11:6394590-6394609 according to Genome Reference Consortium Human Build 38 (GRCh38) [15]. The current investigation was conducted in accordance with the Helsinki Declaration and was approved by the Ethics in Research committee of the Hospital Infantil de México Federico Gómez.

3. Clinical reports

3.1. Patient 1

A female of 1 year and 3 months of age was referred with hepatosplenomegaly. Her young, unrelated parents were healthy, as was her 3-years-old sister. The 37-week pregnancy was complicated in the first trimester by a threat of miscarriage. The patient was born by cesarean section, with a weight of 2,700 kg (percentile (P) 25), a stature of 48 cm (P25), and an Apgar score of 8/9. She exhibited jaundice in her first two weeks of life and suffered from psychomotor developmental delay as well as recurrent infections of the upper airway and pneumonia. At 4 months old, she showed a gradual increase in abdominal volume and growth arrest. Scoliosis, abnormal eye movements and progressive feeding difficulty were diagnosed at 7 months of age, and gastroenteritis required hospitalization at 11 months of age. When she was 1 year and 3 months old, her weight was 6.190 kg (below P3), and stature of 69 cm (below P3). She was hypotrophic and had thin hair, intermittent nystagmus, a broad nasal bridge, a protruding tongue, hepatosplenomegaly, and fine maculopapular dermatitis. The patient died from pneumonia in another medical institution at 1 year and 5 months of age.

3.2. Patient 2

A female of 5 years of age was referred with enlarged abdominal circumference. Her parents were non-consanguineous. Her 44-years-old father had undergone unilateral nephrectomy due to kidney cancer and her 40-years-old mother was diagnosed with hypothyroidism. Her 12-year-old brother was healthy. The 33-weeks pregnancy ended in delivered by cesarean section due to oligohydramnios. She once had melaena and epistaxis. At 3 years of age she presented fever, hyaline rhinorrhea and hepatosplenomegaly, which was attributed to cytomegalovirus. The symptoms went into remission but returned again one year later. She had elevated indirect bilirubin, which was persistent. A hepatic virus etiology was discarded and the discomfort went into remission. She had a weight of 15.1 kg (<P3) and stature of 98 cm (<P3), and a body mass index of 15.6. She was pale and suffered from jaundice associated to increased indirect bilirubine, hepatosplenomegaly, limb hypotrophy and failure to thrive. The patient is managed with multivitamins, a low-fat diet and ferrous sulfate, and her general condition has improved.

3.3. Patient 3

A female of seven years of age, was born to young and non-consanguineous parents that were healthy, as is her 10-year-old brother. After a 39-week pregnancy, delivery was by cesarean section (iterative for the mother). At birth, her weight was 2.900 kg (P50), and stature of 49 cm (P50). Her psychomotor development
was normal. At 2 years of age she presented pneumonia and vis-
ceromegaly and was diagnosed with Epstein Barr virus infection. At 3 years of age a hepatic biopsy showed foam cells. Her weight is now 18.2 kg (P3) and stature of 114 cm (P3). She has a long face, a slight palpebral inferior edema, and a discrete protrusion on her thorax. The abdomen is distended, the liver and the spleen were enlarged with a volume of 249.1 cm³, and 219 cm³, respectively. She is managed with a low-fat diet.

3.4. Patient 4

A female of 6 years of age, was born to young, non-
consanguineous parents who were healthy, as were her two eldest 
brothers. She was born at term and delivered by cesarean sec-
tion (iterative for the mother), with a weight of 2.500 kg (P25), 
a stature of 49 cm (P50), and jaundice in her first two weeks of life. 
Her psychomotor development was normal. An enlarged abdomi-
nal circumference was noted at 2 years of age, and several diarrhea 
episodes were reported at 4 years of age. Epstein Barr virus was 
discovered. Her weight is now 18 kg (P25) and stature of 108 cm 
(P10). She has a long face, a slight palpebral inferior edema, and a 
discrete protrusion on her thorax. The abdomen is distended; 
the liver and the spleen are enlarged with a volume of 230 cm³, and 
216 cm³, respectively. Epistaxis episodes occur once a month on 
the average. She is managed with low-fat diet.

Hepatitis A, B and C Laboratory analyses were negative in Patient 
2, 3 and 4, it was not possible to carry out this analysis in Patient 1. 
The clinical characteristics, biochemical results and SMPD1 variants 
identified in the four patients are described in Table 1 and Figs. 1–3.

4. SMPD1 variants

The five SMPD1 variants detected in the four patients are the following: (1) the previously unreported intron 3 variant c.1263+8C>T; (2) the variant c.1547A>G p.His516Arg (rs754979734) described in the general population, but never before in NPD patients [15]; and (3) the variants already recognized as pathogenic, c.1343A>G p.Tyr448Cys (rs747143343, Fig. 3a), c.1829_1831delGCC p.Arg610del (rs794727780, Fig. 3b), and c.1805G>A p.Arg602His, (rs370129081). The variants were 
analyzed according to the GenBank Accession Number NM_000543.4 reference sequence.

5. Sequencing analysis in controls

To establish the frequency of the four previously recognized 
variants in the Mexican population, analysis was made of 50 healthy 
unrelated control individuals from Mexico City and surrounding 
areas (76% female, 24 ± 6 years old, ranging from 19–50 years). 
Although none of the four variants investigated were observed in 
this sample, sequencing analysis identified other variants. In 
one homozygous and 10 heterozygous people in the control 
group, c.1487_36C>T (rs11601088) (of unknown clinical signifi-
cance) was found, representing an allelic frequency of T = 0.120. The 
benign variant c.1522G>A p.Gly508Arg (rs1050239) was observed 
in 18 heterozygous and two homozygous controls, evidencing an 
allelic frequency of A = 0.220. Finally, the pathogenic vari-
c.1550A>T p.Glu517Val (rs142778001) (www.ensemble.org) 
[3,16] was encountered in a heterozygous state in one control indivi-
dual, presenting an allelic frequency of T = 0.010.

6. Discussion

We herein describe four cases of NPD-A or B in unrelated female 
Mexican mestizo patients. One had a new pathogenic variant of the 
SMPD1 gene, while three showed recurrent variants. All the patients 
were diagnosed at pediatric age. Their clinical data included fail-
ure to thrive, hepatosplenomegaly, epistaxis, high triglycerides and 
cholesterol levels, and lung infiltration. Therefore, NPD was consid-
ered in the four patients after other more frequent etiologies were 
discounted. The diagnosis was confirmed by finding a low level of 
ASM activity.

The c.1343A>G p.Tyr448Cys mutation, a very infrequent SMPD1 
pathogenic variant, was identified in Patients 1 and 2. This variant, 
associated by bioinformatics predictive analyses with diminished 
protein stability, was first documented in a 6-month-old NPD-A 
heterozygous Japanese boy in whom a second variant was not 
detected [3,17–19]. It has been recently described in a 19-year-old 
compound heterozygous NPD-B female Mexican patient [20], but 
Patient 1 is the first NPD-A homozygous patient reported to have it.

To compare the tridimensional structure of the wild-type and 
mutated (p.Tyr448Cys) acid sphingomyelinase protein, we built 
tridimensional models [21,22] that showed an altered structure in 
the mutated enzyme (Fig. 3c and d), which could be associated with 
a decrease in its activity. In fact, the finding of such an alteration 
related with the reduced acid sphingomyelinase activity detected 
in Patient 1 (homozygous for the variant), as well as with the low 
enzyme activity in the previously reported heterozygous patients 
[17,20] and heterozygous Patient 2. By using the Human Splic-
ing Finder software [23], it was predicted that this mutation could 
generate an aberrant new splicing donor site, perhaps altering the 
reading frame of the protein, a possibility that should be confirmed 
experimentally. Patient 2 has NPD-B and is a compound heterozy-
gous for the p.Tyr448Cys and p.Arg610del variants. The latter allele 
is the most frequent pathogenic variant and accounts for 100% of 
the patients in the Canary Islands and 61.5% in Spain [3,9]. This 
variant impairs the proteolytic maturation of ASM while retaining 
a high residual enzyme activity (21.5%), and has only been 
identified in NPD-B patients [3]. It is considered neuro-protective [4], 
which may explain the less severe phenotype observed in Patient 2. 
A similar situation was suggested for the p.Arg476Trp variant in a 
compound heterozygous patient in Mexico with p.Tyr448Cys [20]. 
The parents of Patient 1 and the father of Patient 2 are asymp-
tomatic heterozygous carriers of the p.Tyr448Cys mutation. To our 
knowledge, none of the families in the current study are related 
and do not share a common region of origin or have links to the 
Japanese ethnic group where this variant was first described [3,17]. 
The carrier status of the afore mentioned three parents might be 
due to a founder effect for the p.Tyr448Cys variant. Nevertheless, 
the screening conducted in 50 unrelated healthy Mexican Mestizos 
fail to find this mutation.

The SMPD1 locus is close to the 11p15.5 imprinted region and is 
likely inactive in the paternally imprinted allele. Therefore, any 
given mutation in the preferentially expressed maternal allele 
might influence the clinical presentation of the disease in some 
cases [6,24]. Since Patient 2 inherited the p.Tyr448Cys mutation 
from her father, it would be the preferentially silenced allele. The 
active p.Arg610del allele inherited from her mother could explain 
the less severe phenotype.

Though never before described in NPD-A or B patients, the 
c.1547A>G p.His516Arg variant has a documented heterozygous 
frequency of 3:60,691 in the general population [15]; a similar 
variant, p.His516Gln, has been previously identified in NPD-A or B 
patients [3]. The p.His516Arg variant was detected in Patient 3, who 
also carries the c.1805G>A p.Arg602His pathogenic variant, which 
retains a high residual activity (13%), corresponding to a NPD-B 
phenotype.

The previously unreported intron 3 c.1263+8C>T variant 
was identified in a homozygous state in Patient 4 (with NPD-B). The 
in-silico analysis of this mutation (www.umd.be/HSF3/index.html)
showed a new splicing site that inserts six new nucleotides in the mRNA open reading frame, and therefore could be pathogenic. The family of Patient 3 comes from a small community in the West of Mexico. Though an endogamy effect cannot be ruled out, the parents are not related as far as they know and apparently there are not similar cases in their village.

The sequencing analyses also demonstrated that Patients 1 and 2 were homozygous for the p.Val86Ala variant (rs1050228), which has a frequency from 0.26 to 0.85, depending on the population studied. It is not highly conserved among mammals [3,25]. Patient 2 also exhibited the c.-229G>C variant (rs2682090) in a heterozygous state. Both variants, considered benign, are not associated with the phenotype of the patients [3,26].

A carrier frequency of 1:50 for the p.Glu517Val variant was estimated in spite of no finding of any of the four previously reported pathogenic variants in the control group. This variant was previously reported in a cohort study of NPD-B patients [16]. Interestingly, the frequency of heterozygous individuals for two other SMPDJ variants (c.1166G>A p.Arg389His and c.1563C>T p.Thr488Ile) was 1:10,009 in a screening of a closed Mexican health system for newborn lysosomal diseases [27]. Furthermore, both NPD-A [28] and NPD-B phenotypes have already been described in the Mexican population [16,29]. Those studies suggest that the frequency of ASMD is underestimated in the Mexican population, as found in another Latin-American country [7]. This may be relevant to the differential diagnosis of patients with hepatosplenomegaly and other clinical characteristics such as epistaxis, low platelet count, and altered hepatic function. If ASMD is indeed underestimated, considering it would be very important after discarding other more frequent etiologies.

Since a specific treatment is not yet available, the only therapeutic intervention that can be offered is a carbohydrate and low-fat diet. Simvastatin has been indicated in older patients but there is some debate about the benefits of this therapy [11]. Also, a presymptomatic cord blood or liver transplantation approaches have been proposed [30,31]. There is an ongoing phase II study regarding an enzyme replacement therapy with recombinant human acid sphingomyelinase for NPD-B [32]. In contrast to NPD-A or B, there is one approved pharmacological treatment for NPD-C that inhibits the synthesis of glycosphingolipids [33,34]. The three surviving NPD-B patients herein reported are under follow up and their general condition is presently stable. Genetic assessment was offered to their parents, determining a recurrent risk of 25%.

In conclusion, the finding of the present study include: (1) The novel c.1263+8C>T variant in a homozygous NPD-B patient; (2)

### Table 1

Molecular data and clinical characteristics of the four female Mexican patients with ASMD.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NPD form</strong></td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td><strong>Age</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1y 5m&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5y</td>
<td>7y</td>
<td>6y</td>
</tr>
<tr>
<td><strong>ASM</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.61 µmol/L/h</td>
<td>1.3 µmol/L/h</td>
<td>0.42 µmol/L/h</td>
<td>0.53 µmol/L/h</td>
</tr>
<tr>
<td><strong>SMPDJ</strong></td>
<td>Homozygous</td>
<td>Compound heterozygous</td>
<td>Compound heterozygous</td>
<td>Homozygous&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Pathogenic variants</strong></td>
<td>p.Tyr448Cys&lt;sup&gt;e&lt;/sup&gt; rs747134343</td>
<td>p.Tyr448Cys&lt;sup&gt;e&lt;/sup&gt; rs747134343</td>
<td>p.Asp1831delGCC&lt;sup&gt;e&lt;/sup&gt; rs794727780</td>
<td>p.Asp1831delGCC&lt;sup&gt;e&lt;/sup&gt; rs794727780</td>
</tr>
<tr>
<td><strong>Other variants</strong></td>
<td>Homozygous&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Homozygous&lt;sup&gt;f&lt;/sup&gt;</td>
<td>c.107T&gt;C&lt;sup&gt;e&lt;/sup&gt; p.Val36Ala&lt;sup&gt;e&lt;/sup&gt;</td>
<td>c.107T&gt;C&lt;sup&gt;e&lt;/sup&gt; p.Val36Ala&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Hematomagaly</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Splenomegaly</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Short stature</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Epistaxis</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Abnormal bone, X-ray analysis</strong></td>
<td>+</td>
<td>FEF, growth arrest bands</td>
<td>+&lt;sup&gt;g&lt;/sup&gt;</td>
<td>FEF</td>
</tr>
<tr>
<td><strong>Hb</strong></td>
<td>11.5 g/dL</td>
<td>11.5 g/dL</td>
<td>12.7 g/dL</td>
<td>12.9 g/dL</td>
</tr>
<tr>
<td><strong>Platelet count</strong>&lt;sup&gt;h&lt;/sup&gt;</td>
<td>154,000&lt;sup&gt;i&lt;/sup&gt;</td>
<td>130,000&lt;sup&gt;h&lt;/sup&gt;</td>
<td>173,000</td>
<td>216,000</td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td>NCO</td>
<td>260 mg/dL</td>
<td>228 mg/dL</td>
<td>235 mg/dL</td>
</tr>
<tr>
<td><strong>Tryglicerides</strong>&lt;sup&gt;i&lt;/sup&gt;</td>
<td>NCO</td>
<td>501 mg/dL</td>
<td>187 mg/dL</td>
<td>462 mg/dL</td>
</tr>
<tr>
<td><strong>AST</strong></td>
<td>336 U/L</td>
<td>69 U/L</td>
<td>61 U/L</td>
<td>227 U/L</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td>331 U/L</td>
<td>78 U/L</td>
<td>72 U/L</td>
<td>231 U/L</td>
</tr>
<tr>
<td><strong>GCT</strong></td>
<td>88 U/L</td>
<td>301 U/L</td>
<td>27 U/L</td>
<td>293 U/L</td>
</tr>
<tr>
<td><strong>PT/PTT</strong></td>
<td>NCO</td>
<td>11.6/32 s</td>
<td>12.45/34.3 s</td>
<td>12.5/33 s</td>
</tr>
<tr>
<td><strong>Hepatitis A/B</strong></td>
<td>NCO</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Abdominal US</strong>&lt;sup&gt;j&lt;/sup&gt;</td>
<td>NCO</td>
<td>HM-SM</td>
<td>HM-HS</td>
<td>HM-HS</td>
</tr>
<tr>
<td><strong>Lung CT scan</strong></td>
<td>NCO</td>
<td>Lung infiltration</td>
<td>Intestinal deposits</td>
<td>NCO</td>
</tr>
<tr>
<td><strong>Hepatic biopsy</strong>&lt;sup&gt;k&lt;/sup&gt;</td>
<td>NCO</td>
<td>Foam cells lipid-laden macrophages; NP cells</td>
<td>Vacularated macrophages, microvesicular steatosis</td>
<td>NCO</td>
</tr>
<tr>
<td><strong>Bone marrow</strong>&lt;sup&gt;l&lt;/sup&gt;</td>
<td>NCO</td>
<td>Foam cells</td>
<td>Foam cells</td>
<td>NCO</td>
</tr>
</tbody>
</table>

<sup>a</sup> Age of death.
<sup>b</sup> Variant not previously reported.
<sup>c</sup> Scoliosis.
<sup>d</sup> Discrete pectum corinatum.
<sup>e</sup> Platelet with increased size, atypical lymphocytes, dacrocytes, hypochromia, microcytosis and schistocytosis.
<sup>f</sup> Alternating acid sphingomyelinase enzymatic activity (normal value > 2.17 µmol/L/h).
<sup>g</sup> AST: Aspartate aminotransferase hepatic enzyme; FEF: Femur Erlenmeyer flask-like image; GGT: gamma-glutamyl transferase hepatic enzyme; HM: hepatheromegaly; HS: hepatic steatosis;
<sup>h</sup> m: months; NCO: none carried out; NR: not reported; PPT: partial thromboplastine time; PT: prothrombine time; SM: splenomegaly; US: ultrasound scan.
<sup>i</sup> years, +/-: positive, –: negative.
<sup>j</sup> SMPDJ variants are described according with the GeneBank Accession Number NM_000543.4 reference sequence.
a homozygous p.Tyr448Cys pathogenic variant in a NPD-A case associated with severe clinical manifestations, and the modification of its phenotypic expression in a compound heterozygous NPD-B patient; (3) the presence of a NPD-B phenotype in a compound heterozygous patient with the p.His516Arg variant, not previously described in affected individuals; and (4) a pathogenic SMPD1 variant found in the control population. These results could be indicative of an underestimation of the frequency of ASMD in the Mexican mestizo population. The further phenotype-genotype correlation herein provided for this disease in NPD-A and B emphasizes the need in Mexico to take it into account during a differential diagnosis. We consider that the identification of the different pathogenic variants described in our population and the genotype-phenotype correlations analyzed, will help to achieve a better understanding of the process underlying the presentation of NPD-A and NPD-B. The current data also underline the importance of molecular diagnosis in order to offer accurate genetic assessment and management.
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