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Characterization of Niemann-Pick diseases genes mutation spectrum in Iran and identification of a novel mutation in *SMPD1* gene

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Abstract

Background: Niemann-Pick diseases are rare inherited lipid storage disorders caused by mutations in the *SMPD1, NPC1,* and *NPC2* genes. The aim of this study was to assess the mutation spectrum of a cohort of Iranian Niemann-Pick patients.

Methods: A consanguineous couple with a child suspected of having Niemann-Pick disease type A (died at age 2) was screened for gene mutations in the *SMPD1* gene. Sanger sequencing was performed for all exons and exon-intron boundary regions. A literature review on *SMPD1, NPC1,* and *NPC2* genes mutations in Iran was conducted using published original papers on this subject.

Results: A novel frameshift c.762delG (p.Leu256fs*) at a heterozygous state was identified in the parents. According to the review study, identified mutations in 39 Iranian patients were concentrated in exon 2 of the *SMPD1* gene and exons 8 and 9 of the *NPC1* gene.

Conclusion: Niemann-Pick diseases genes mutation analysis (*SMPD1, NPC1,* and *NPC2*) in Iran shows the genetic heterogeneity of these diseases in this country. More studies with larger sample sizes should be conducted to further examine genetic changes associated with Niemann-Pick diseases in Iran.

Keywords: Niemann-Pick disease type A, Type B, Type C NPD, *SMPD1, NPC1, NPC2*

Conflicts of Interest: *None declared*
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Introduction

Niemann-Pick diseases (NPD) are a heterogeneous group of autosomal recessive disorders with common features of hepatosplenomegaly and neurologic deficits. These disorders are classified into 4 main types: type A, type B, type C1, and type C2 (1-4). The prevalence of types A and B is approximately1/250 000 in general population and the incidence of type C is about 1/120 000 per live birth (5, 6).

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Niemann-Pick type A and B

Type A and B (also called acid sphingomyelinase deficiency or ASMD) are caused by different *SMPD1* (sphingomyelin phosphodiesterase 1) mutations (7-9). The *SMPD1* gene, on 11p15, consists of 6 exons and produces several types of transcripts, which (NM_000543) encodes the lysosomal enzyme acid sphingomyelinase with 631 amino acids. This enzyme hydrolyzes sphingomyelin to

↑What is "already known" in this topic:
Niemann-Pick disease (NPD) is a heterogeneous group of neurodevelopmental disorders which are characterized by severe damage in various fields of growth. A high rate of consanguineous marriages in countries such as Iran can be associated with a higher incidence of autosomal recessive diseases, including NPD.

→What this article adds:
Here, we present a novel mutation in *SMPD1* gene and review reports on molecular studies on *SMPD1*, *NPC1*, and 2 genes in Iran.

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phosphocholine and ceramide. The defect in acid sphingomyelinase results in lysosomal accumulation of sphingomyelin. The progressive deposition of this phospholipid in the central nervous system leads to the classical infantile form (type A) of NPD (NPA; MIM# 257200), which is a very severe subtype of Niemann-Pick disease. NPA usually occurs in infancy or early childhood and is characterized by hepatosplenomegaly, failure to thrive, and progressive neurodegeneration (3, 4, 10, 11). NPD type B patients (NPB, MIM# 607616) display no central nervous system involvement (1, 12). Variety of symptoms, including hepatosplenomegaly, respiratory problems, hyperlipidemia, and thrombocytopenia, may be presented in childhood or adulthood (12).

Niemann-Pick type C1 and C2

NPD types C1 and C2 have very similar clinical manifestations. They are caused by mutations in *NPC1* (in 95% of cases) and *NPC2* genes, respectively. *NPC1* gene has 25 exons and located in 18q11.2. This gene produces several transcripts, one of which (NM_000271) encodes NPC1 protein with 1278 amino acids. NPC intracellular cholesterol transporter 2 or *NPC2* gene (14q24.3) has 5 exons and produces different types of transcripts, one of which (NM_006432) encodes NPC2 protein with 151 amino acids (13-19).

Mutations in either gene result in impaired intracellular lipids trafficking, leading to overaccumulation of lipids in cells (20, 21). NPD types C1 and C2 show a highly variable clinical presentation, including progressive neurodegeneration, liver and lung disease, which can develop at any age (22, 23).

The Islamic Republic of Iran is a country in the Middle East with a high rate (~ 38%) of consanguineous marriages (24). Previous studies have shown that consanguineous marriages are associated with an increased risk of autosomal recessive disorders. Therefore, a higher incidence of rare diseases such as NPD is expected in Iran, showing the importance of molecular studies on NPD and other autosomal recessive disorders in developing cost- and time-saving diagnostic approaches for these diseases (25, 26).

Here, we report a novel mutation in the *SMPD1* gene in an Iranian family with a child affected with NPA. We also review molecular studies on NPD in Iran and describe the spectrum of NPD mutations in Iranian population.

Methods

Mutational analysis

Screening of the *SMPD1* gene was performed for a consanguineous couple with a child suspected of NPA who had died at the age of 2. The affected child was noted to have hepatosplenomegaly, hypotonia, developmental delay, cherry-red maculae, and frequent respiratory infections. The parents completed and signed an informed consent form. Peripheral blood samples were collected from the couple. Genomic DNA was extracted using the salting out method according to the standard protocol. Primers were designed for amplification of exons and exon-intron boundaries of *SMPD1* gene by Primer3 online software. The amplification reaction was performed in a MyCycler™ thermal cycler (Bio-Rad, USA). Then, 5µL of the PCR products were loaded on a 1.5% agarose gel. All exons and exon-intron boundary regions of the *SMPD1* gene were sequenced on both strands (ABI3130 Genetic Analyzer). The sequences were compared against reference sequence of *SMPD1* gene using nucleotide BLAST.

Search strategy

PubMed/MEDLINE, Scopus, Google Scholar, SID, Medlib, and Magiran databases were searched up to August 2018 using the keywords: Niemann-Pick diseases in all types A, B and C, mutation, Iran, *SMPD1*, *NPC1, and NPC2*. After removal of duplicates, reviews and unrelated articles, 9 articles and abstracts were included in the current study.

Results

Molecular analysis

A novel heterozygous frameshift deletion (c.762delG)

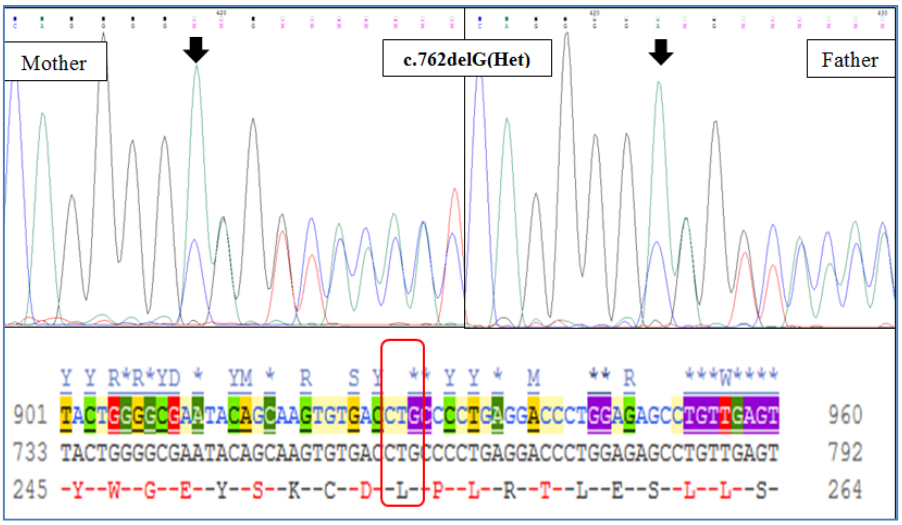

Fig. 1. Sanger sequencing of *SMPD1* are indicated for mother and father of the affected child. The black arrows show the novel heterozygous deletion at the position c.760delG of the *SMPD1* gene in the carrier cases (NM_000543.4:c.762delG (Het)).

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(p.Leu256fs*) and a previously reported benign variant (c.107T>C) were identified in the *SMPD1* gene in the couple. Examining the potential consequences of a single nucleotide deletion (G) at position 762 showed that this change results in a premature stop codon at position 256 (Fig. 1).

Overview of the studies in Iran

PubMed/MEDLINE, Scopus, Google scholar, SID, Medlib, and Magiran databases were searched and 20 related articles and abstracts retrieved, among which 9 studies that presented the results of mutation analysis of NPD genes in 39 patients were selected for a more detailed analysis. The spectrum and frequency of the NPD genes mutations among Iranian reported patients are presented in Table 1. A total of 17 pathogenic variants were found in the investigated studies. Four of 7 pathogenic mutations detected in the *SMPD1* gene were in exon 2 (27-29). Also, more than half of the identified mutations in the *NPC1* gene were in exons 8 and 9 (30-33). There was only 1 report of *NPC2* mutation in Iran, which was reported in 2 Iranian siblings (34). Figure 2 shows the position of reported mutations in the NPD genes.

Discussion

Previous studies have shown that NPD diseases are rare disorders and more prevalent in populations with a high rate of consanguinity such as Ashkenazi Jewish, French Canadians, and Arabs in Saudi Arabia (35, 36). Unfortunately, there is no information about the prevalence of these diseases in Iran, but due to the high frequency of consanguineous marriages in this country, an increased frequency of NPD diseases is expected. Therefore, the development of a stepwise strategy based on common mutations for rapid and cost-effective NPD molecular genetic testing is necessary in Iran to confirm the diagnosis of the NPD diseases, carrier detection, prenatal diagnosis (PND), and preimplantation genetic diagnosis (PGD) of these diseases in families (26). The aim of this study was to take a step in this direction by reporting a new case of NPA and reviewing all reported NPD genes mutations in Iran.

In the molecular analysis, we found a novel frameshift deletion at position 762 of the *SMPD1* gene, which results in a premature stop codon TGA. The variant may lead to an unstable mRNA, which can be degraded by nonsense-mediated decay, or produce a truncated nonfunctional protein of 256 amino acid residues. Pathogenicity of this variant can be supported by the pathogenic effect of downstream nonsense mutations such as p.Glu260Ter (CM961340) and p.Leu263Ter (CM920623) reported in NPA patients (7-9). To date, more than 100 mutations responsible for NPA and NPB have been reported in the *SMPD1* gene (Human Gene Mutation Database: http://www.hgmd.org/). Mutations such as small deletions or nonsense mutations in *SMPD1* (NM_000543) gene, which result in truncated proteins, can produce type A (7-9).

So far, several common NPD mutations have been

Table 1. Mutation spectrum of the genes associated with NPD in Iranian patients

Nucleotide changes	Protein changes	rs number	Genes	Exon/Intron	Number of alleles in Iran	MAF[1]	References
c.762delG	p.Leu256fs*		SMPD1	E2	2	-	Our cases
c.740delG	p.Gly247Alafs*9	-	SMPD1	E2	2	-	(Galehdari. et al. 2013)
c.1033-1034insT	p.Glu345Valfs*46	-	SMPD1	E2	2	-	(Manshadi. et al. 2015)
c.573delT	p.Ser192Alafs*65	rs727504167	SMPD1	E2	2	-	(Manshadi .et al. 2015)
c.946-961del16	p.Pro316Metfs*64	-	SMPD1	E2	2	-	(Mikaeeli. et al. 2016)
c.1155T>A	p.Asn385Lys	-	SMPD1	E3	1	-	(Manshadi. et al. 2015)
c.1417-1418delCT	p.Leu473Glufs*20	rs398123476	SMPD1	E5	2		(Manshadi. et al. 2015)
c.1166G>T	p.Arg389Leu	-	NPC1	E8	2	-	(Karimzadeh. et al. 2013)
c.1192C>T	p.His398Tyr	-	NPC1	E8	2	-	(Tonekaboni. et al. 2015)
c.1415T>C	p.Leu472Pro	-	NPC1	E9	4	-	(Noroozi Asl. et al. 2017)
c.1433A>C	p.Asn478Thr	-	NPC1	E9	2(2sister)	-	(Tonekaboni. et al. 2015)
c.1547 G>A/ c.2728 G>A	p.Cys516Tyr/ p.Gly910Ser	rs751951695/ rs768999208	NPC1	E9/E18	1+1[2]		(Rohanizadegan. et al. 2017)
c.2657dupG	p.Pro887Serfs*31	-	NPC1	E18	2	-	(Karimzadeh. et al. 2013)
c.2925-2928delCTGC	p.Cys976Phefs*6	-	NPC1	E20	2	-	(Karimzadeh.et al. 2013)
c.3478-6T>A	-	-	NPC1	I22	2	-	(Karimzadeh. et al. 2013)
c.358C>T	p.Pro120Ser	rs104894458	NPC2	E3	2	-	(Alavi.et al. 2013)

1: MAF: Minor allele frequency (Highest population MAF: < 0.01) .2: Patient was compound heterozygote for two variants. E: Exon, I: Introne. The Ser357Leu/Tyr394His (NPC1) and Leu137Pro (SMPD1) were excluded from our table because of ambiguous nomenclatures and sequence position respectively (Tonekaboniet al. 2015 and Abedini et al. 2016).

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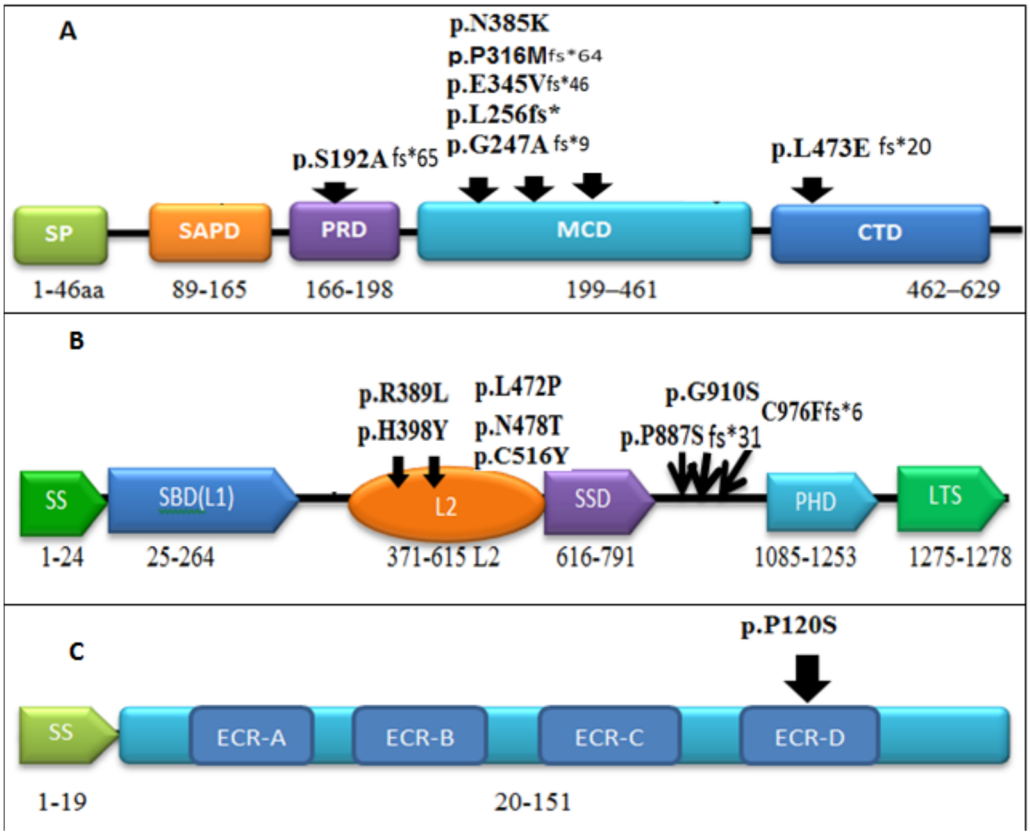

Fig. 2. Schematic illustration and overall distribution of pathogenic variants in coding regions of *SMPD1/NPC1/NPC2* genes in Iranian patients with NPD disease (19, 20, 23). aa: amino acid. A: SMPD1 protein, SP: Signal peptide (aa1–46), SAPD: a saposin-like (SAP) domain (aa89–165), PRD: Pro-rich domain (aa166–198), MCD: metallophoesterase/catalytic domain (aa199–461), CTD: C-terminal domain (aa462–629). Exon 2 had the highest percentage of mutations. B: NPC1 protein, SS: signal sequence (aa1-46), SBD: sterol-binding domain or luminal loop-1(aa25-264), L2: luminal loop-2 (aa371–615), SSD: sterol-sensing domain (aa 616-791), PHD: patched homology domain (aa 1085-1253), LTS: a lysosomal targeting signal at the C terminus (aa 1275–1278). NPC2 binds to the L2 of NPC1. L2 region had the highest percentage of mutations in Iranian studies. C: NPC2 protein, SS: signal sequence (aa 1-19), ECR: evolutionary constrained regions (A-D). ECR-D is the cholesterol binding region.

found in different populations. Two pathogenic variants in *SMPD1*, c.911T>C (p.Leu304Pro), and c.1493G>T (p.Arg498Leu) have been identified as the most common cause of NPA in Ashkenazi Jewish population (7, 37). On the other hand, c.1829_1831delGCC (p.Arg610del) variant is known as a common mutation in NPB patients in different populations (38). A mutation c.1267C>T (p.His423Tyr) in *SMPD1* is also reported as the most common cause of NPB in Saudi Arabia (37). Two variants, c.3019C>G (p.Pro1007Ala) and c.3182T>C (p.Ile1061Thr), are also known as the most common genetic causes of NPC in different populations (39). A review of all reported NPD mutations in Iran showed that the majority of them are private. These mutations are mainly located in exon 2 of the *SMPD1* gene and exons 8 and 9 of the *NPC1* gene. These findings can be useful in developing a stepwise strategy to molecular diagnosis of the NPD in Iran. The most frequent benign variants reported in NPD genes in Iran are c.1522G>A, c.106_107insCGCTGG, and c.107T>C in *SMPD1* (28, 40). Several benign variants have been incorrectly classified as pathogenic or likely pathogenic in some reports (28). These variants are not shown in Table 1.

Conclusion

A novel mutation in *SMPD1* gene has been reported in this study. A review on all NPD genes mutations reported from Iran has also been presented here. However, more studies should be conducted on larger groups of NPD patients to characterize mutations in NPD genes in Iran.

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Conflict of Interests

The authors declare that they have no competing interests.

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