Advances in Clinical and Translational Research
Volume 3
Article ID: 100024

Case Report

Novel Frameshift Variant in the NPC1 Gene Underlies Niemann Pick Disease Type 1 in a Consanguineous Indian Pedigree

Pratiksha Chheda[1*], Shailesh Pande[2], and Sushant Vinarkar[1]

[1]Department of Molecular Pathology, Metropolis Healthcare Ltd., India

[2]Department of Medical Genetics, Metropolis Healthcare Ltd., India

***Corresponding authors**: Pratiksha Chheda, Department of Molecular Pathology, Metropolis Healthcare Ltd., Mumbai-400 070, India, Tel: +91-022 50560787; E-mail: pratiksha.chheda@metropolisindia.com

Received: June 24, 2019; **Accepted**: August 05, 2019; **Published**: August 12, 2019

Abstract

Genetic analysis was performed on a consanguineously married couple of Indian origin with a deceased child suspected to be affected with Niemann-Pick disease. A panel of 3 genes (NPC1, NPC2 and SMPD1) was analyzed by next generation sequencing (NGS). A novel heterozygous single base pair deletion (c.147delT, p.Lys49AsnfsTer10) was identified in NPC1 in both the parents. This frameshift variant was classified as a 'Pathogenic Variant' using variant classification guidelines based on all the available evidences. Though the deceased child was not directly tested for the presence of genetic variants, there is an increased likelihood that he must have carried two copies of this pathogenic variant, thereby causing the disease phenotype. However, since there is no direct evidence the presence of another disease-causing variant cannot be ruled out. The study lays emphasis on genetic analysis of suspected cases of Niemann-Pick disease as well as testing of first-degree relatives for identification of carriers, which may assist in prenatal diagnosis in subsequent pregnancy.

Keywords: *Niemann-Pick disease, NPC1, NPC2, SMPD1*

Introduction

Niemann Pick disease (NPD) is a heterogeneous disease with variations in pathological and clinical features and incidence of approximately 1:150 000 live births [1]. NPD is classified into three most commonly recognized forms: Niemann-Pick Types A and B characterized by Acid sphingomyelinase (ASM) deficiency that leads to excessive sphingomyelin accumulation in all phagocytic cells and in neurons and Niemann-Pick Disease Type C (NP-C) with defective intracellular processing and transporting of LDL cholesterol [1]. NP-C is a rare autosomal recessive disease and mutations in one of two lysosome-related genes - NPC1 (about 95% of patients have NPC1 disease) or NPC2 (5% NPC2 disease) have been identified to be associated with the occurrence of this disease [2,3]. About two-thirds of patients have infantile or juvenile onset and is characterized by hepatosplenomegaly, delayed developmental milestones, interstitial lung disease, and failure to gain weight, followed by cognitive decline. The diagnosis can be confirmed by identifying mutations in the NPC1 or NPC2 genes in the majority of cases.

Case Description

A consanguineously married couple of Indian origin with a deceased child suspected to be affected with Niemann-Pick disease had come to us for genetic confirmation of carrier status. Their son, first of the dichorionic diamniotic (DCDA) twin, with birth weight of 1.9 kg, had cried immediately, was exclusively breastfed till 4 months of age and had no postnatal complications. There was no significant family history. After 4 months of age, he had developed abdominal distension, recurrent cough and nasal discharge. By the age of one year nine months the child presented with hepatosplenomegaly and global developmental delay mainly involving motor and speech domain. He was able to sit with support and was able to speak 1-2 words. Glycogen storage disease was suspected, and his bone marrow aspiration and biopsy were planned. Bone-marrow examination revealed presence of storage cells suggestive of Niemann-Pick disease. There were several episodes of pulmonary infections with repeated hospital admissions. The child survived till 3 years 10 months of age. The twin sibling of the index case did not display any characteristic symptoms related to NP-C till four years of age.

Genetic studies were performed on parents after obtaining informed consent. A panel of 3 genes (*NPC1, NPC2 and SMPD1*) with 100% coverage of coding region was analyzed by Next Generation Sequencing (NGS) on Illumina Sequencing Platform. The libraries were sequenced to mean >80-100X coverage and the sequences obtained were aligned to the human reference genome (GRCh37/hg19).

A heterozygous single base pair deletion (c.147delT) in exon 2 of the NPC1 gene (chr18:21153449delT; Depth: >97x) that results in a frameshift and premature truncation of the protein 10 amino acids downstream of codon 49 (p.Lys49AsnfsTer10; ENST00000269228) was detected in both the parents. This novel NPC1 variant has not been reported in the 1000 genomes and ExAC databases and the *in silico* prediction of the variant was damaging by Mutation Taster [2]. The variant was classified as 'Likely Pathogenic' based on recommended guidelines laid by the ACMG, the Association for Molecular Pathology (AMP) and the College of American Pathologists (CAP) for classifying the genetic variants [4].

Discussion

NP-C is a rare autosomal recessive neurovisceral lysosomal storage disorder, characterized biochemically by a lipid trafficking defect resulting in the intracellular accumulation of unesterified cholesterol and other compounds [5,6]. The disorder presents with an extensive phenotypic variability, ranging from fatal neonatal disease to chronic neurological deterioration in late adulthood. NPC is caused by homozygous or compound heterozygous mutations of either NPC1 (95% of cases) or NPC2 [7]. The diagnosis of NP-C is established by a combination of genetic and biochemical testing. Genetic confirmation of NP-C has been increasingly carried out over the last decade, specifically amongst patients with non-specific clinical symptoms [8].

In the present study, we report the case of an Indian newborn with early-infantile onset Niemann–Pick disease type C who displayed prolonged hepatosplenomegaly, global developmental delay and repeated pulmonary infections. NP-C was confirmed on the basis of bone marrow examination and further genetic evaluation was not performed. The Patient was put on a high ventilator support due to pneumonia and there was an early mortality at the age of 3 years 10 months. The parents of the deceased child, a consanguineous couple was tested for the genetic mutations for a set of 3 genes (NPC1, NPC2 and SMPD1) by NGS. The genetic testing was not performed on the twin sibling since parents didn't give consent for the same.

A heterozygous variant, c.147delT; p.Lys49AsnfsTer10 was identified in each of the parents. This is a novel unreported variant leading to a premature truncation of the protein. Based on ACMG guidelines and other supporting evidences the variant was classified as 'Pathogenic'. There is a very strong possibility that the deceased child must have

carried two copies of this pathogenic variant, thereby causing the disease phenotype. However, the presence of heterozygous c.147delT variant along with another unidentified mutation cannot be ruled out. Alternate tissue material such as FFPE tissue of deceased child was also not available to confirm the genetic findings. Although the deceased child was not directly genetically tested for the presence of the homozygous variant for NP-C, but it does seem that this is the most likely genetic pedigree based off the clinical symptoms.

More than 300 disease-causing mutations have been identified in NPC1; the majority of them (~70%) being missense pathogenic variants that affect the cysteine-rich luminal domain and lead to variable clinical presentations [9]. The case discussed in the present study is postulated to carry a chain terminating frameshift variant on both the chromosomes, which may have led to early symptoms and eventual death.

In view of this case, we consider it important to examine all new-borns and children who display symptoms of hepatosplenomegaly, recurrent pulmonary infections and developmental delay during the first months of life as signs of possible NP-C. Genetic testing and counseling of each newly diagnosed patient is important to establish genotype-phenotype correlation for NP-C. Targeted mutation analysis on his/her first-degree relatives is highly advisable for the identification of carriers, which can further open up the possibility to offer prenatal diagnosis in high risk families.

Conflict of Interest

The authors declare that they have no conflict of interest related to this article.

References

1. Galehdari H, Tangestani R, Ghasemian S (2013) New Single Nucleotide Deletion In the SMPD1 Gene Causes Niemann Pick Disease Type A in a Child from Southwest Iran: A Case Report. Iran J Pediatr 23: 233-236.
2. Harzer K, Beck-Wödl S, Bauer P (2014) Niemann-Pick Disease Type C: New Aspects in a Long Published Family-Partial Manifestations in Heterozygotes. JIMD Rep 12: 25-29.
3. Zhang H, Wang Y, Lin N, Yang R, Qiu W, et al. (2014) Diagnosis of Niemann-Pick disease type C with 7-ketocholesterol screening followed by NPC1/NPC2 gene mutation confirmation in Chinese patients. Orphanet J Rare Dis 9: 82.
4. Richards S, Aziz N, Bale S, Bick D, Das S, et al. (2015) Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17: 405-424.
5. Dougherty M, Lazar J, Klein JC, Diaz K, Gobillot T, et al. (2016) Genome sequencing in a case of Niemann–Pick type C. Cold Spring Harb Mol Case Stud 2: a001222.
6. Bountouvi E, Papadopoulou A, Vanier MT, Nyktari G, Kanellakis S, et al. (2017) Novel NPC1 mutations with different segregation in two related Greek patients with Niemann-Pick type C disease: molecular study in the extended pedigree and clinical correlations. BMC Med Genet 18: 51.
7. Zech M, Nübling G, Castrop F, Jochim A, Schulte EC, et al. (2013) Niemann-Pick C Disease Gene Mutations and Age-Related Neurodegenerative Disorders. PLoS One 8: e82879.
8. Degtyareva AV, Mikhailova SV, Zakharova EY, Tumanova EL, Puchkova AA (2016) Visceral symptoms as a key diagnostic sign for the early infantile form of Niemann–Pick disease type C in a Russian patient: a case report. J Med Case Rep 10: 143.
9. Cervera-Gaviria M, Alcántara-Ortigoza MA, González-Del Angel A, Moyers-Pérez P, Legorreta-Ramírez BG, et al. (2016) An uncommon inheritance pattern in Niemann-Pick disease type C: identification of probable paternal germline mosaicism in a Mexican family. BMC Neurol 16: 147.