Hajira Karim et al. JBC Genetics. 2024;7(1):056-060
DOI: 10.24911/JBCGenetics.183-1718405078

CASE REPORT

Genetic and clinical characterization of Niemann-Pick disease type C with homozygous *NPC1* gene mutation: insights from whole exome sequencing and advanced neuroimaging of two familial cases

Hajira Karim[1*], Lima Oria[1], Muhsin Elmas[1]

ABSTRACT

Background: Niemann-Pick disease Type C (NPC) is a rare genetic lipid storage disorder characterized by heterogeneous clinical presentations primarily affecting the neurological and visceral systems. This study aims to elucidate the clinical manifestations, radiological findings, and genetic characteristics of NPC, emphasizing the implications of familial aggregation and consanguinity.

Case Presentation: We present two cases from a single family, detailing the clinical progression, radiological findings, and genetic mutations. Case 1 involves a 39-year-old male exhibiting symptoms such as dysarthria, cerebellar ataxia, and progressive neurological decline over eight years. Case 2, a relative aged five, displays similar early-onset neurological symptoms. Both cases demonstrate significant cerebellar atrophy on MRI and share a familial *NPC1* gene mutation, suggesting a hereditary pattern influenced by consanguineous relationships. Whole Exome Sequencing identified a pathogenic homozygous mutation in the *NPC1* gene, confirming the diagnosis of NPC. This finding underscores the genetic basis of the disease and highlights the role of familial genetics in its pathogenesis.

Conclusion: These cases underscore the critical role of genetic testing, particularly whole exome sequencing, in diagnosing NPC, which can often present with diverse clinical symptoms. The familial clustering observed also draws attention to the genetic counseling needs in populations with high rates of consanguinity, emphasizing the importance of community genetic studies to understand and manage such rare disorders.

Keywords: Niemann-Pick disease, *NPC1* mutation, cerebellar atrophy, case report, familial disease, whole exome sequencing.

Introduction

Niemann-Pick disease (NPD) represents a group of rare inherited lysosomal storage disorders characterized by the accumulation of sphingomyelin in the lysosomes due to enzyme deficiencies. This disease is genetically and clinically heterogeneous, divided into several subtypes: A, B, and C, each associated with distinct genetic mutations and clinical manifestations. Types A and B are linked to mutations in the *SMPD1* gene, leading to sphingomyelinase deficiency, while Type C typically

Correspondence to: Hajira Karim
*Medical Genetics Department, Istanbul Medipol University, International School of Medicine, Istanbul, Turkey.
Email: Hajira.karim @ std.medipol.edu.tr
Full list of author information is available at the end of the article.
Received: 14 June 2024 | **Accepted:** 09 September 2024

results from mutations in the *NPC1* or *NPC2* genes, which affect lipid transport within cells. Type A, known as the acute neuronopathic form, is marked by early onset, rapid progression of neurodegeneration, and severe hepatosplenomegaly, leading to death usually by three years of age. Type B, the chronic visceral form, involves prominent hepatosplenomegaly but spares the central nervous system, allowing for a longer lifespan. Type C, the most prevalent form, presents with variable onset, typically in childhood or adolescence, and is characterized by neurological decline and systemic involvement [1-2]. The clinical complexity of NPD poses significant challenges in diagnosis and management, necessitating a multidisciplinary approach. Advances in genetic testing, particularly whole exome sequencing (WES), have played a pivotal role in the early identification and subtype classification of this disease, facilitating targeted therapeutic interventions [3]. In Turkey, the incidence of NPD, especially Type C, remains underreported, but it is estimated to follow the global prevalence of approximately 1 in 150,000 live births. Consanguinity is relatively common in Turkey, with rates as high as 20%-25% in certain regions, contributing to a higher incidence of autosomal recessive disorders such as NPD. The high rate of consanguineous marriages increases the likelihood of homozygous mutations within families, underscoring the need for genetic counseling and screening in at-risk populations [4-5]. The characteristic facial grimacing due to cerebellar ataxia is shown in Figure 1. In this context, we present two case studies that illustrate the diverse clinical spectrum and genetic variability of NPD. These cases emphasize the importance of considering a broad differential diagnosis when confronted with symptoms suggestive of lysosomal storage disorders, as well as the utility of comprehensive genetic analysis in confirming the diagnosis and guiding treatment strategies. Figure 2 illustrates the significant muscle wasting and contractures, a consequence of progressive neurological impairment.

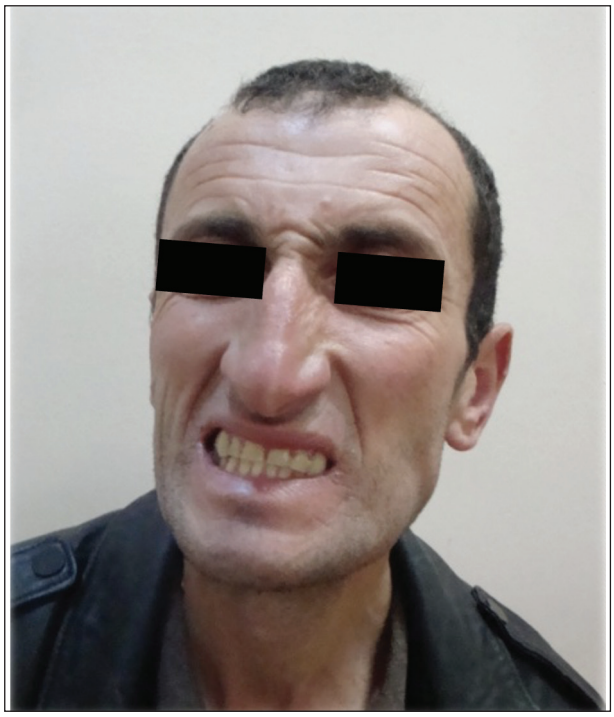

Figure 1. *Facial expression showcasing characteristic grimacing due to cerebellar ataxia and neurological decline.*

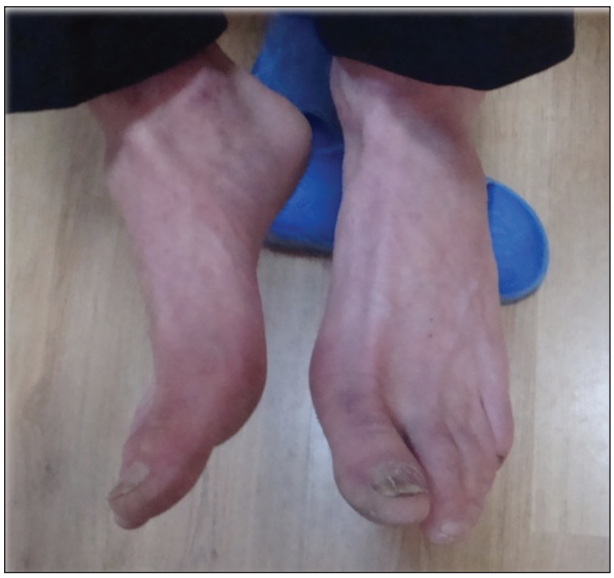

Figure 2. *Deformities in the feet demonstrate significant muscle wasting and contractures, a consequence of progressive neurological impairment.*

Case Presentation

Patient 1 (39-year-old male)

Patient 1 is a 39-year-old male who presented with progressive walking and speech difficulties over the past 8 years. He reported additional symptoms of chest wheezing and difficulty expelling phlegm. Patient 1 has no history of surgeries but experienced seizures a few times 7–8 years ago. His parents are first cousins from Turkiye, and there are similar cases in the family. Detailed examination and investigations led to the diagnosis of NPD.

The patient has no history of surgeries but experienced seizures a few times 7–8 years ago, and currently has difficulty expelling phlegm and chest wheezing. The patient's parents are first cousins from Turkiye, and there are similar cases in the family. Physical examination revealed slight facial asymmetry to the right, restricted vertical gaze (especially downward), normal muscle strength, hyperactive deep tendon reflexes, a Babinski flexor response, an ataxic gait, dysarthric speech, possible cataplexy, and clumsy cerebellar tests. Brain MRI findings indicated volume loss in the cerebellar hemispheres and vermis, a minimal diffuse volume loss in both cerebellar hemispheres and the vermis, a slight signal increase in the white matter near the ventricles on T2A-FLAIR images, mild dilation of the ventricular system, and no periventricular demyelination-compatible signal change. The other myelin pathways appear normal, bilateral basal ganglia and thalami are normal, the corpus callosum is normal with no significant signal changes, major vascular structures are unremarkable, orbital

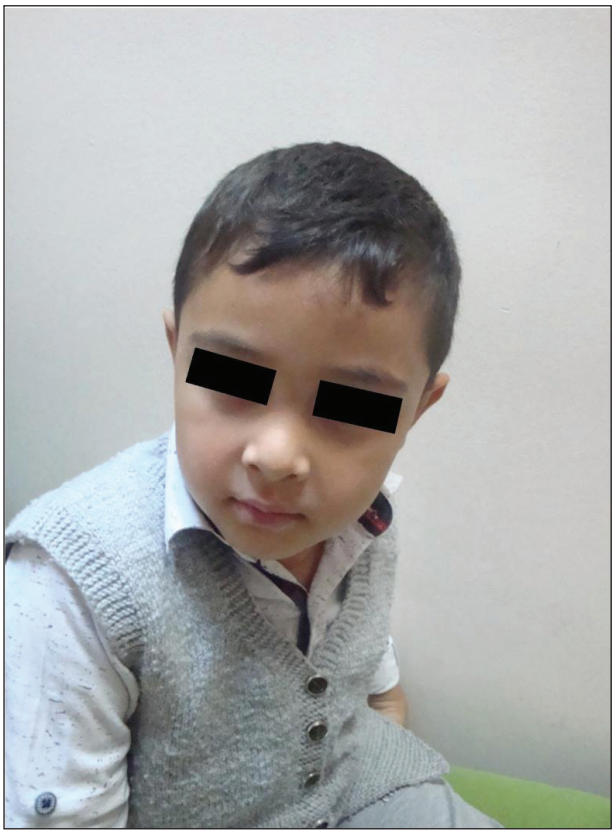

Figure 3. *Anterior profile displaying subtle facial asymmetry.*

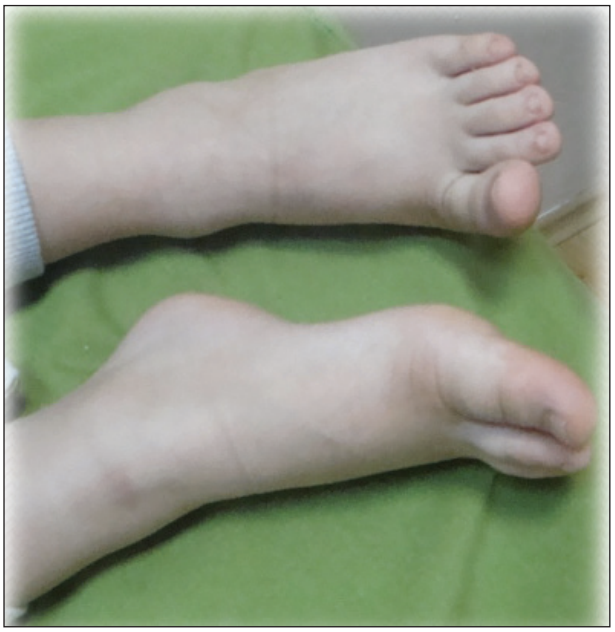

Figure 4. *Deformities in the feet illustrate the impact on early childhood development, including muscle weakness and contractures.*

structures and masticatory nuclei are present, bilateral paranasal sinuses are clear, and cranial bone structures are normal. WES revealed a primary finding of a phenotype-related variant, *NPC1*:c.1421C>T / p.Pro474Leu Class 1, and a secondary finding of a variant related to another phenotype not investigated, *BTD*: c.1330 G>C / p.D444H Class 1, with no incidental findings detected. The WES results confirmed a diagnosis of Niemann-Pick disease type C (NPC) caused by a homozygous mutation in the *NPC1* gene.

Patient 2 (5-year-3 months-old male)

Patient 2 is a 5-year-3 months-old male who presented with balance issues and difficulty speaking. Anterior profile displaying subtle facial asymmetry is captured in Figure 3. His physical examination revealed hypermobility in joints, lateral and vertical nystagmus in both eyes, and cerebellar vermis hypoplasia. The family history indicated a consanguineous marriage between his parents who are third cousins from Turkiye.

The patient has no history of surgeries or seizures but has a diagnosis of chronic bronchitis. Developmental milestones include walking at the age of 3 years, speaking single words at 1 year, and achieving fluent speech at 5 years. The patient's parents are third cousins from Turkey. Physical examination reveals lateral and vertical nystagmus in both eyes, normal muscle strength, lively deep tendon reflexes in the lower extremities, a negative Babinski sign, clumsy cerebellar tests, and hypermobile joints. Brain MRI findings show cerebellar vermis hypoplasia, minimal diffuse volume loss in both cerebellar hemispheres, a slight signal increase in the white matter near the ventricles on T2A-FLAIR images, mild dilation of the ventricular system, and no periventricular demyelination-compatible signal change. Other myelin pathways appear normal, bilateral basal ganglia and thalami are normal, the corpus callosum is normal with no significant signal changes, major vascular structures are unremarkable, orbital structures and masticatory nuclei are present, bilateral paranasal sinuses are clear, and cranial bone structures are normal. WES revealed primary findings related to a phenotype variant and secondary findings related to another phenotype not investigated, with no incidental findings detected.

Discussion

NPD is a rare autosomal recessive lysosomal storage disorder characterized by the accumulation of sphingomyelin in various tissues, leading to multi-organ dysfunction. Deformities in the feet that highlight the impact on early childhood development, including muscle weakness and contractures, are demonstrated in Figure 4. The disease is classified into several types based on clinical presentation and genetic mutations, with Types A, B, and C being the most recognized. Type A is the classic infantile form marked by severe hepatosplenomegaly and central nervous system (CNS) involvement, typically leading to death before age three. Type B presents predominantly with visceral involvement and relatively preserved CNS function. Type C is the most common, characterized by a later onset and slower progression, with CNS symptoms often preceding hepatosplenomegaly. In the cases presented, both patients exhibited symptoms consistent with NPC, confirmed by WES. The first patient, Patient 1, presented with progressive neurological symptoms, including

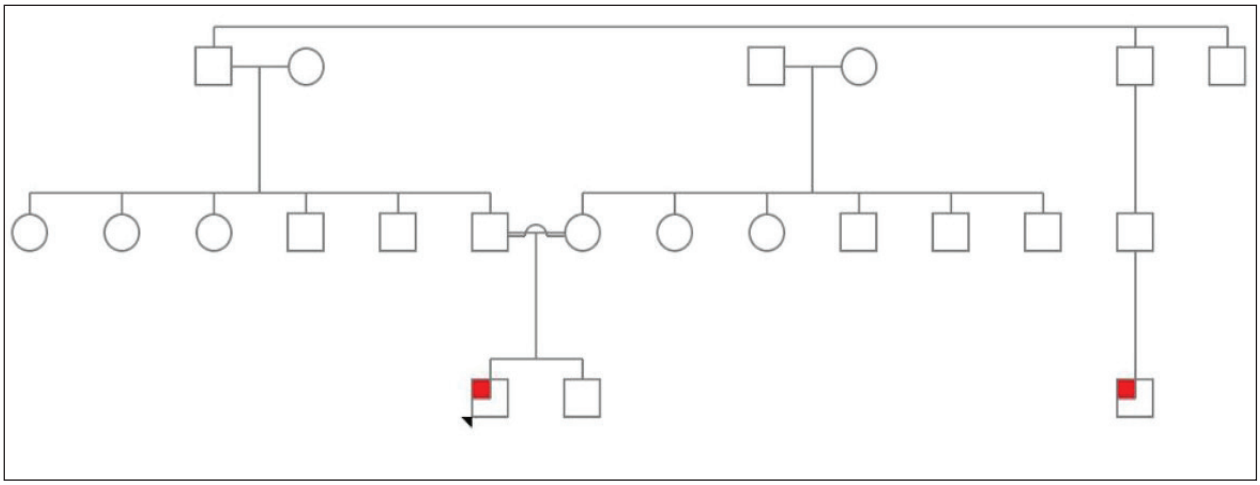

Figure 5. *Family pedigree of patients 1 & 2.*

ataxic gait, dysarthric speech, and chest wheezing, which are indicative of cerebellar ataxia and pulmonary involvement. His brain MRI findings of cerebellar volume loss and signal changes in the white matter further supported the diagnosis. The WES analysis identified a homozygous mutation in the *NPC1* gene, confirming the diagnosis of NPC. The second patient, Patient 2, exhibited balance issues and difficulty speaking, with physical examination findings of hypermobility in joints and nystagmus. His brain MRI revealed cerebellar vermis hypoplasia, and the WES analysis identified a relevant genetic variant. The family pedigree of patients 1 and 2 is shown in Figure 5, illustrating the genetic relationships and implications. The consanguineous marriage in the family history of both patients underscores the importance of considering genetic factors and the increased risk of autosomal recessive disorders in such populations.

Diagnostic approach

The diagnostic approach for NPC includes a combination of clinical assessment, radiological imaging, and genetic testing. Initial suspicion arises from characteristic symptoms such as vertical supranuclear gaze palsy, ataxia, and hepatosplenomegaly. Brain MRI often reveals cerebellar atrophy and white matter changes. The definitive diagnosis is made through genetic testing, with WES being particularly useful in identifying pathogenic mutations in the *NPC1* or *NPC2* genes.

Treatment options

Currently, there is no cure for NPC, and treatment primarily focuses on managing symptoms and improving quality of life. Miglustat, an inhibitor of glycosphingolipid synthesis, has shown some efficacy in stabilizing neurological symptoms. Supportive therapies, including physical therapy, occupational therapy, and speech therapy, are essential for maintaining functional abilities. Regular monitoring and multidisciplinary care involving neurologists, hepatologists, and geneticists are crucial for managing the disease's progression.

Prognosis

The prognosis of NPC varies widely depending on the age of onset and severity of symptoms. Early-onset cases tend to have a more rapid progression and poorer prognosis, while later-onset cases may progress more slowly. Lifespan can range from childhood to adulthood, with many patients succumbing to complications such as respiratory infections. Genetic counseling is vital for families with a history of consanguinity to understand the risks and implications of the disease. Choosing WES as the first-tier testing over single gene or gene panel testing offers significant advantages in terms of cost-effectiveness and turnaround timing. Although the initial cost of WES might seem higher than single gene tests or targeted gene panels, WES provides a comprehensive analysis of the entire exome, thereby increasing the likelihood of identifying the causative mutation in one test. This comprehensive approach can be more cost-effective in the long run by eliminating the need for multiple, sequential single gene tests or panels, which can quickly add up in cost and time. Furthermore, the turnaround time for WES has significantly improved with advances in sequencing technology, often providing results within 4-8 weeks. This is comparable to or even

Category	Patient one and patient two
Inheritance	Autosomal recessive
Head & neck	Vertical supranuclear gaze palsy
Abdomen	
Liver	Hepatomegaly, neonatal jaundice
Spleen	Splenomegaly
Gastrointestinal	Dysphagia
Neurologic	
Central nervous system	
- Hypotonia	Present

Category	Patient one and patient two
- Developmental delay	Present
- Dysarthria	Present
- Loss of speech	Present
- Mental deterioration	Present
- Dementia	Present
- Spasticity	Present
- Dystonia	Present
- Seizures	Present
- Cerebellar ataxia	Present
- Cataplexy	Present
Behavioral psychiatric manifestations	Poor school performance, behavioral problems, psychosis
Hematology	Foam cells in bone marrow biopsy
Prenatal manifestations	
	Fetal ascites
Laboratory abnormalities	
	Mild or markedly reduced sphingomyelinase activity
	Low cholesterol esterification rates
	Abnormal cholesterol homeostasis
	Foam cells in visceral organs and CNS
	Foam cells containing polymorphic cytoplasmic inclusions consisting of lamellar osmiophilic membranes on electron microscopy
Miscellaneous	Genetic heterogeneity (see NPC2, 607625)
	Disease usually becomes apparent in early childhood
	Death usually in teenage years
	Variable phenotype
	Four major groups: early infantile, late infantile, juvenile, adult
	Earlier onset associated with faster progression and shorter life span
	Incidence of 1 in 150,000 live births in the general population
Molecular basis	Caused by mutation in the NPC intracellular cholesterol transporter 1 gene (NPC1, 607623.0001

faster than the cumulative time required for sequential single gene or panel testing, making WES a practical and timely choice for diagnosing genetically heterogeneous disorders like NPC. The table below summarizes the findings in both the designated patients 1 and 2 with NPC.

Conclusion

WES is an invaluable tool for diagnosing rare genetic disorders like NPD. The detailed genetic analysis provided by WES allows for accurate diagnosis and a better understanding of the disease's clinical variability. A multidisciplinary approach, including thorough clinical evaluation and advanced genetic testing, is essential for managing complex cases of NPD.

Acknowledgment
The authors thank the patients and their families for their cooperation. The authors also thank the Intergern Genetic Center for molecular analysis.

Conflict of interest
The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Consent for publication
Informed consent was obtained from the patients.

Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

Funding
None.

Author details
Hajira Karim[1], Lima Oria[1], Muhsin Elmas[1]
1. Medical Genetics Department, Istanbul Medipol University, International School of Medicine, Istanbul, Turkey

References

1. Schuchman EH, Desnick RJ. Types A and B niemann-pick disease. Mol Genet Metab. 2017;120(1-2):27–33. https://doi.org/10.1016/j.ymgme.2016.12.008
2. Vanier MT. Niemann-pick disease type C. Orphanet J Rare Dis. 2010;5:16. https://doi.org/10.1186/1750-1172-5-16
3. Patterson MC, Hendriksz CJ, Walterfang M, Sedel F, Vanier MT, Wijburg F. Recommendations for the diagnosis and management of Niemann-Pick disease type C: an update. Mol Genet Metab. 2012;106(3):330–44. https://doi.org/10.1016/j.ymgme.2012.03.012
4. Tadmouri GO, Nair P, Obeid T, Al Ali MT, Al Khaja N, Hamamy HA. Consanguinity and reproductive health among Arabs. Reprod Health. 2009 Dec;6:1–9. https://doi.org/10.1186/1742-4755-6-17
5. El Mouzan MI, Al Salloum AA, Al Herbish AS, Qurachi MM, Al Omar AA. Consanguinity and major genetic disorders in Saudi children: a community-based cross-sectional study. Ann Saudi Med. 2008 May;28(3):169–73. https://doi.org/10.5144/0256-4947.2008.169