

Niemann-Pick Disease, Type C

FACT SHEET



Clinical Features

Niemann-Pick disease type C (NP-C) is a genetic lipid storage disease that leads to a heterogeneous spectrum of symptoms and variable age of onset. Live expectancy is reduced^{1,3} and the incidence is estimated at around 1 in 120,000 births^{1,2}.

In newborns, NP-C can present with ascites and severe liver disease and/or respiratory failure from infiltration of 'foamy cells' in the lung (lipid-laden macrophages). Other infants may present hypotonia and developmental delay as well as hepatosplenomegaly, which often goes undetected. Classic presentation occurs in mid-to-late childhood with insidious onset of ataxia, vertical supranuclear gaze palsy, and dementia. Dystonia and seizures are common features. Adults are likely to present with dementia or psychiatric symptoms³.

The clinical diagnosis of NP-C should be considered in individuals (depending on the onset age) presenting with the following^{1,3}:

- Fetal ascites or neonatal liver disease, particularly when the latter is accompanied by prolonged jaundice and pulmonary infiltrates
- Infantile hypotonia without evidence of progression for months to years
- Vertical supranuclear gaze palsy, progressive ataxia, dysarthria, dystonia, and in some cases, seizures and gelastic cataplexy, beginning in middle childhood and progressing slowly over many years
- Psychiatric presentations mimicking depression or schizophrenia with few or subtle neurologic signs, which begin in adolescence or adulthood
- Enlargement of the liver or spleen, particularly in early childhood (an absence never eliminates the diagnosis of NP-C)

Biochemical testing has traditionally demonstrated impaired cholesterol esterification and positive filipin staining in patient fibroblasts. However, this testing requires a skin biopsy³. CENTOGENE has developed the biomarker lyso-SM509 that is highly specific and sensitive for Niemann-Pick disease⁹.

NP-C is due to variants either in NPC1 (in 95% of cases) or NPC2 (in 5% of the cases) genes^{1,3,10}. Molecular genetic testing of NPC1 and NPC2 detects pathogenic variants in approximately 94% of individuals with NP-C. Most NPC1 cases involve compound heterozygotes for single-nucleotide variants^{4,5}. So far, over 511 variants have been described in NPC1 to cause Niemann Pick disease type C^{4,5,6,10,11}, and over 27 different variants in NPC2^{7,4,5}.

Gene(s) name (OMIM, HGNC)	NPC1, NPC2
Gene OMIM	*607623, *601015
Disease OMIM	#257220, #607625
Gene location	18q11.2, 14q24.3

INHERITANCE PATTERN

Autosomal recessive

DISEASE SYNONYMS

Niemann-Pick disease, type C, NP-C, Niemann-Pick disease type C1, NPC1, Niemann-Pick disease, type C2, Niemann-Pick disease with cholesterol esterification block, Niemann-Pick disease, subacute juvenile form, Niemann-Pick disease, chronic neuronopathic form, Niemann-Pick disease without sphingomyelinase deficiency, Neurovisceral storage disease with vertical supranuclear ophthalmoplegia, Niemann-Pick disease type D, Niemann-Pick disease Nova Scotian type

OPTIONS

TESTING REQUIREMENTS	MINIMUM DNA (µg)	MINIMUM EDTA BLOOD (ml)	MINIMUM FILTERCARDS (pcs)	TAT (days)
Sequencing (NPC1, NPC2)	2	1	1	15
Deletion/duplication test (NPC1, NPC2)	1	1	1	15
Biomarker (lyso-SM509)	Not applicable	2	1	7

Clinical Features

The differential diagnosis of NPC1 and/or NPC2-related disorders – depending on the major symptoms in the initial case – includes the following diseases:

- **Neonatal and infantile presentations:** Biliary atresia, congenital infections, alpha-1-antitrypsin deficiency, tyrosinemia, malignancies (leukemia, lymphoma, histiocytosis), other storage diseases (e.g., Gaucher disease, Niemann-Pick disease type A/B)
- **Childhood presentations:** Pineal region or midbrain tumors, hydrocephalus, GM2 gangliosidosis, mitochondrial diseases, maple syrup urine disease, absence seizures, idiopathic torsion dystonia, dopa-responsive dystonia, Wilson disease, neuronal ceroid-lipofuscinosis
- **Adolescent and adult presentations:** Alzheimer disease, Pick's disease, frontotemporal dementias, progressive supranuclear palsy, primary psychiatric illnesses

Diagnostic Strategy

CENTOGENE offers the following testing strategy for NPC1/NPC2 gene testing:

- **Step 1:** Sequence analysis of NPC1 and NPC2 genes. Measurement using biomarker lyso-SM509 in parallel with sequence analysis is recommended. NPC1/NPC2 gene sequencing covers the entire coding regions, exon/intron boundaries, and 524 bp of the gene's promoter. Additionally, lyso-SM509 is a highly specific and sensitive biomarker for Niemann-Pick Type C disease. Performing both in parallel offers significant advantages, such as accelerating the diagnostic process reducing ambiguity in variant interpretation, and detecting the basal line for further evaluation of disease progression and treatment monitoring
- **Step 2:** Deletion/duplication analysis of NPC1/NPC2

Referral Reasons

The following individuals are candidates for NPC1/NPC2 gene testing:

- Individuals with a family history of NP-C disease and presentation of the most common symptoms
- Individuals without a positive family history, but with symptoms resembling NP-C disease
- Individuals with a negative but suspected family history, in order to perform proper genetic counseling (prenatal analysis in families with affected individuals is recommended)

Test Utility

Sequencing, deletion/duplication of the NPC1/NPC2 genes, and related genes should be performed in all individuals suspected of having this particular phenotype. In parallel, other genes reported to be related with this clinical phenotype should also be analyzed for the presence of pathogenic variants due to the overlap in many clinical features of Niemann Pick disease type C.

For the families, establishing a diagnosis allows for genetic counselling and may direct medical management. Genetic counseling can provide a patient and/or family with the natural history of Niemann Pick disease, identify at-risk family members, provide information about reproductive risks as well as preconception/prenatal options, and allow for appropriate referral for patient support and/or resources.

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