CENTOGENE
THE RARE DISEASE COMPANY

Complementary Genetic and Biochemical Approaches
CASE STUDY

CASE HISTORY

The patient was a 10-month-old-male born to non-consanguineous parents. He presented with hypotonia, hepatosplenomegaly, motor delay, and minor facial dysmorphism. Biochemistry testing revealed elevated liver transaminases, cholesterol, and triglycerides. Foamy macrophages were detected from bone marrow aspiration.

REASONS FOR TESTING

Clinical suspicion of Niemann-Pick disease.

TEST ORDERED

Sequencing and CNV analysis of all three genes known to be associated with Niemann-Pick disease: *SMPD1*, *NPC1* and *NPC2*.

RESULTS

Two heterozygous variants were detected in the *SMPD1* gene (NM_000543.4)

GENE	VARIANT	ZYGOSITY	FINAL CLASSIFICATION	INHERITANCE
SMPD1	c.725 G>A (p.Gly242Asp)	Het.	Likely pathogenic	Unknown
	c.1371 T>G (p.Phe457Leu)	Het.	Likely pathogenic	Unknown

- **c.725 G>A (p.Gly242Asp)** had neither been reported in individuals with disease nor in the general population before. It is located at a weakly conserved nucleotide position and moderately conserved amino acid position, with moderate physicochemical difference between the amino acids glycine and aspartic acid. Initial classification of this variant per ACMG guidelines was VUS (Variant of Unknown Significance)

- **c.1371T>G (p.Phe457Leu)** had neither been reported in individuals with disease nor in the general population before. It is located at a weakly conserved nucleotide position and moderately conserved amino acid position, with small physicochemical difference between the amino acids phenylalanine and leucine. Initial classification of this variant per ACMG guidelines was VUS (Variant of Unknown Significance)

- Parental samples were unavailable for segregation analysis

- Subsequent enzymatic testing showed pathologically decreased levels of ASM, the enzyme encoded by the *SMPD1* gene, to 0.4 µmol/l/h (normal ≥ 1.7 µmol/l/h). Furthermore, the concentration of the Niemann-Pick disease-specific biomarker Lyso-SM-509 was pathologically increased to 5.5 ng/µl, (normal ≤ 0.9 ng/µl)[1]

› The American College of Medical Genetics and Genomics (ACMG) guidelines for variant classification recommend to complement genetic testing with well-established in vitro studies, if available. CENTOGENE follows this recommendation by applying enzymatic tests and also biomarker quantification for many disorders including Niemann-Pick disease. **The present case exemplifies how the use of complementary genetic and biochemical testing enables the final classification of two novel *SMPD1* variants as likely pathogenic**

POST-TESTING

› Genetic and biochemical confirmation of Niemann-Pick disease type A allowed for an early diagnosis and appropriate management of symptoms
› Risk counseling for pregnancy planning was then possible for the family

DISEASE INFORMATION

Bi-allelic variants in the *SMPD1* gene are associated with Niemann-Pick disease type A/B, an autosomal recessive disorder. Niemann-Pick disease is a condition that affects many organs. It has a wide range of symptoms that vary in severity. Niemann-Pick disease type A is a very severe subtype of Niemann-Pick disease and is characterized clinically by onset in infancy or early childhood with failure to thrive, hepatosplenomegaly, and rapidly progressive neurodegenerative disorders. Infants with Niemann-Pick disease type A usually develop an enlarged liver and spleen (hepatosplenomegaly) by age 3 months and fail to gain weight and grow at the expected rate (failure to thrive). Type B children develop normally until around age 1 year when they experience a progressive loss of mental abilities and movement (psychomotor regression). Children with Niemann-Pick disease type A also develop widespread lung damage (interstitial lung disease) that can cause recurrent lung infections and eventually lead to respiratory failure. All affected children have an eye abnormality called a cherry-red spot, which can be identified with an eye examination.

CONCLUSION

The use of complementary genetic and biochemical approaches facilitated the conclusive diagnosis of Niemann-Pick disease type A for this patient, who otherwise would have had an uncertain diagnosis based on genetic testing alone. The results ended the diagnostic odyssey and allowed appropriate treatment and management of the patient's symptoms. The confirmed diagnosis also provided risk information to help the family with pre-conceptional counseling for future pregnancies.

REFERENCE

[1] Miyanawala, Vindhya Lakmali, et al. "Metabolic biomarker testing facilitates genetic diagnosis of Niemann–Pick disease by enabling classification of novel *SMPD1* variants." Journal of Biochemical and Clinical Genetics 2.2 (2019): 147-150.

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