



Acid Sphingomyelinase Deficiency

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Summary

Clinical characteristics

The phenotype of acid sphingomyelinase deficiency (ASMD) occurs along a continuum. Individuals with the severe early-onset form, infantile neurovisceral ASMD, were historically diagnosed with Niemann-Pick disease type A (NPD-A). The later-onset, chronic visceral form of ASMD is also referred to as Niemann-Pick disease type B (NPD-B). A phenotype with intermediate severity is also known as chronic neurovisceral ASMD (NPD-A/B). Enzyme replacement therapy (ERT) is currently FDA approved for the non-central nervous system manifestations of ASMD, regardless of type. As more affected individuals are treated with ERT for longer periods of time, the natural history of ASMD is likely to change. The most common presenting symptom in untreated NPD-A is hepatosplenomegaly, usually detectable by age three months; over time the liver and spleen become massive in size. Growth failure typically becomes evident by the second year of life. Psychomotor development progresses no further than the 12-month level, after which neurologic deterioration is relentless. This feature may not be amenable to ERT. A classic cherry-red spot of the macula of the retina, which may not be present in the first few months, is eventually present in all affected children, although it is unclear if ERT will have an impact on this. Interstitial lung disease caused by storage of sphingomyelin in pulmonary macrophages results in frequent respiratory infections and often respiratory failure. Most untreated children succumb before the third year of life. NPD-B generally presents later than NPD-A, and the manifestations are less severe. NPD-B is characterized in untreated individuals by progressive hepatosplenomegaly, gradual deterioration in liver and pulmonary function, osteopenia, and atherogenic lipid profile. No central nervous system manifestations occur. Individuals with NPD-A/B have symptoms that are intermediate between NPD-A and NPD-B. The presentation in individuals with NPD-A/B varies greatly, although all are characterized by the presence of some central nervous system manifestations. Survival to adulthood can occur in individuals with NPD-B and NPD-A/B, even when untreated.

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Diagnosis/testing

The diagnosis of ASMD is established by detection of biallelic pathogenic variants in *SMPD1* by molecular genetic testing and residual acid sphingomyelinase enzyme activity that is less than 10% of controls (in peripheral blood lymphocytes or cultured skin fibroblasts).

Management

Targeted therapies: Olipudase alfa (Xenpozyme®) enzyme replacement therapy (ERT) helps to reduce the accumulation of sphingomyelin in the lung, liver, spleen, and other non-central nervous system organs. It does not impact the central nervous system and therefore does not impact the neurocognitive issues seen in individuals with NPD-A or NPD-A/B. Hematopoietic stem cell transplantation (HSCT) can correct the metabolic defect, improve blood counts, and reduce increased liver and spleen volumes but does not stabilize neurologic disease. The morbidity and mortality associated with HSCT limit its use, and it is likely to become obsolete now that enzyme replacement therapy is available.

Supportive care: Feeding therapy and/or feeding tube as needed for nutritional support; supportive management of coagulopathy and end-stage liver disease manifestations; transfusion of blood products for life-threatening bleeding; partial splenectomy may be considered for individuals with severe hypersplenism; supplemental oxygen for symptomatic pulmonary disease; physical and occupational therapy to maximize function and to prevent contractures; early intervention and developmental support for those with developmental issues; treatment of hyperlipidemia in adults; calcium and vitamin D for osteopenia/osteoporosis; sedatives for irritability and sleep disturbance as indicated.

Prevention of secondary complications: Monitor liver function in individuals receiving hepatotoxic medications (e.g., statins for hypercholesterolemia).

Surveillance: Periodic assessments of nutritional status; annual EKG; echocardiogram every two to four years; liver transaminases (ALT, AST), albumin, clotting factors, and platelet count at least annually; assess for fatigue, abdominal pain, and/or increased bleeding at least annually; radiologic measurements of liver and spleen size as needed; assess for shortness of breath at each visit; annual pulmonary function testing; chest radiograph every two to four years; assess neurologic function and frequency of headaches at least annually; monitor developmental progress, educational needs, and occupational and physical therapy needs at each visit; fasting lipid profile at least annually; assess for extremity pain at each visit; bone density assessment every two to four years; assess need for family support and resources at each visit.

Agents/circumstances to avoid: Contact sports in those who have splenomegaly.

Pregnancy management: For pregnant women with ASMD, prenatal care by a high-risk obstetrician is indicated to ensure appropriate monitoring of pulmonary function and hematologic status. Olipudase alfa ERT has not been studied in pregnant women, but animal studies have identified a potential impact on fetal development. Therefore, ERT is not recommended during pregnancy.

Genetic counseling

All forms of ASMD (NPD-A, NPD-A/B, and NPD-B) are inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *SMPD1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier. Once the *SMPD1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible. Biochemical prenatal diagnosis for a pregnancy at 25% risk is also possible by testing of acid sphingomyelinase enzyme activity.

GeneReview Scope

Acid Sphingomyelinase Deficiency: Included Phenotypes

- Infantile neurovisceral ASMD (Niemann-Pick disease type A; NPD-A)
- Chronic neurovisceral ASMD (intermediate form; NPD-A/B)
- Chronic visceral ASMD (Niemann-Pick disease type B; NPD-B)

ASMD = acid sphingomyelinase deficiency, which includes NPD-A, NPD-A/B, and NPD-B

Diagnosis

Acid sphingomyelinase deficiency (ASMD) cannot be diagnosed solely on clinical grounds.

Suggestive Findings

Scenario 1 – Abnormal Newborn Screening (NBS) Result

NBS for ASMD is primarily based on quantification of acid sphingomyelinase activity on dried blood spots. At the time of writing, ASMD is not included on the United States Recommended Uniform Screening Panel and is performed in a limited number of states within the US. Several pilot studies have also been performed in Europe.

Acid sphingomyelinase activity values below the cutoff reported by the screening laboratory are considered positive and require follow-up biochemical and/or molecular genetic testing for confirmation.

- Follow-up biochemical testing can include quantification of lipid biomarkers such as lyso-sphingomyelin and/or lyso-sphingomyelin-509, although the validity of these biomarkers in asymptomatic newborns with ASMD remains to be determined.
- Molecular genetic testing involves sequence analysis of *SMPD1*.

Referral to a metabolic or genetic disease specialist should be made immediately on receipt of an abnormal NBS result while additional testing is performed to determine whether this a true positive NBS result and to establish the diagnosis of ASMD.

Scenario 2 – Symptomatic Individual

A symptomatic individual who has findings associated with ASMD (infantile neurovisceral ASMD [NPD-A], chronic neurovisceral ASMD [NPD-A/B], or chronic visceral ASMD [NPD-B]) may present because of any of the following: NBS was not performed, the NBS result was false negative, and/or caregivers were not adherent to or aware of recommended treatment.

In these situations, supportive – but nonspecific – clinical, radiographic, and laboratory findings to assist in diagnosis can include the following (by phenotype).

Infantile neurovisceral ASMD (NPD-A)

- Hepatosplenomegaly
- Developmental delay
- Evidence of interstitial lung disease on chest radiograph
- Cherry-red maculae
- Failure to thrive
- Presentation before age three years

Chronic neurovisceral ASMD (intermediate form; NPD-A/B)

- Hepatosplenomegaly

- Interstitial lung disease
- Dyslipidemia
- Central nervous system manifestations such as learning difficulties, ataxia, or developmental delay
- Thrombocytopenia
- Coarse facial features (present in a subset of individuals with NPD-A/B)

Chronic visceral ASMD (NPD-B)

- Hepatosplenomegaly
- Interstitial lung disease
- Dyslipidemia
- Thrombocytopenia
- Growth restriction in children

Establishing the Diagnosis

The diagnosis of ASMD is established in a proband with biallelic pathogenic (or likely pathogenic) variants in *SMPD1* identified by molecular genetic testing (see Table 1) and residual acid sphingomyelinase enzyme activity that is less than 10% of controls (in peripheral blood lymphocytes or cultured skin fibroblasts). *SMPD1* molecular genetic testing is increasingly the preferred test for ASMD, but demonstration of low acid sphingomyelinase enzyme activity is required to confirm the diagnosis.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of biallelic *SMPD1* variants of uncertain significance (or of one known *SMPD1* pathogenic variant and one *SMPD1* variant of uncertain significance) does not establish or rule out a diagnosis.

Molecular Genetic Testing

Approaches include **single-gene testing**, use of **multigene panels**, and **genomic testing** (exome sequencing, genome sequencing).

Scenario 1 – abnormal NBS result. When NBS results and/or clinical, radiographic, and laboratory findings suggest the diagnosis of ASMD, **single-gene testing** can be considered.

- **Sequence analysis** of *SMPD1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected.
- Typically, if only one or no variant is detected by the sequencing method used, the next step is to perform **gene-targeted deletion/duplication analysis** to detect exon and whole-gene deletions or duplications; however, to date such variants have not been identified as a cause of this disorder.

Note: Targeted analysis for specific pathogenic variants can be performed first in individuals of Ashkenazi Jewish, North African, Chilean, Saudi Arabian, and Turkish ancestry (see Table 7).

Scenario 2 – symptomatic individual. When a symptomatic individual presents with typical or atypical findings associated with later-onset ASMD or untreated infantile-onset ASMD (resulting from NBS not performed or false negative NBS result), a **multigene panel** or **genomic testing** can be considered:

- **A multigene panel** that includes *SMPD1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain

significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

- When the phenotype is indistinguishable from many other inherited biochemical disorders, **comprehensive genomic testing** (which does not require the clinician to determine which gene is likely involved) is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

Table 1. Molecular Genetic Testing Used in Acid Sphingomyelinase Deficiency

Gene ¹	Method	Proportion of Pathogenic Variants ² Detectable by Method
<i>SMPD1</i>	Targeted analysis for pathogenic variants ³	90% ^{4, 5}
	Sequence analysis ⁶	>95% ⁷
	Gene-targeted deletion/duplication analysis ⁸	Unknown ⁹

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Pathogenic variants included in a panel may vary by laboratory.

4. In NPD-A, three variants (p.Arg498Leu, p.Leu304Pro, p.Phe333SerfsTer52) account for approximately 90% of pathogenic alleles in the Ashkenazi Jewish population. Note: Two numbering systems are currently in use to describe *SMPD1* variants that differ by two amino acids due to a polymorphism in the length of *SMPD1*. For example, p.Arg498Leu is also described as p.Arg496Leu; p.Leu304Pro is also described as p.Leu302Pro; and p.Arg610del is also described as p.Arg608del (see Molecular Genetics).

5. In NPD-B, the variant p.Arg610del may account for almost 90% of pathogenic alleles in individuals from the Maghreb region of North Africa (i.e., Tunisia, Algeria, and Morocco); 100% of pathogenic alleles in Gran Canaria Island [Fernández-Burriel et al 2003]; and about 20%-30% of pathogenic variants in the US.

6. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

7. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

8. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

9. No deletions or duplications involving *SMPD1* have been reported to cause acid sphingomyelinase deficiency. While new deletion/duplication testing methods may identify such pathogenic variants in individuals who did not have a pathogenic variant identified by sequence analysis, the detection rate is unknown and may be very low.

Other Testing

Measurement of acid sphingomyelinase enzyme activity in peripheral blood lymphocytes, cultured skin fibroblasts, or dried blood spots. Compared to controls, affected individuals typically have less than 10% residual ASM activity, although these activities vary based on the testing laboratory [van Diggelen et al 2005].

Note: (1) Low acid sphingomyelinase activity is required to confirm the diagnosis of ASMD. (2) The level of residual enzyme activity is not a reliable predictor of phenotype.

Bone marrow examination. Because of the bone marrow involvement in ASMD, in some instances specialists have performed bone marrow examination to identify lipid-laden macrophages as part of the diagnosis. Note that bone marrow examination is **not** necessary for diagnosis and should not be performed unless specific clinical indications are present.

Clinical Characteristics

Clinical Description

Although the phenotype of acid sphingomyelinase deficiency (ASMD) occurs along a continuum, individuals with the severe early-onset infantile neurovisceral phenotype (Niemann-Pick disease type A, or NPD-A) can often be distinguished from those with the intermediate chronic neurovisceral phenotype (NPD-A/B) and chronic visceral ASMD (Niemann-Pick disease type B, or NPD-B) based on clinical presentation. Enzyme replacement therapy (ERT) is currently FDA approved for the non-central nervous system manifestations of ASMD, regardless of type (see Management, Targeted Therapies). As more affected individuals are treated with ERT for longer periods of time, the natural history of ASMD is likely to change. ERT has been shown to improve many of the visceral and growth issues in affected individuals with NPD-A/B and NPD-B, but this therapy is not expected to have an impact on the central nervous system disease and neurocognitive issues.

Infantile Neurovisceral ASMD (NPD-A)

Feeding problems/growth. Feeding problems are severe, resulting in growth failure. Initially, feeding issues appear to result from early satiety because of gastric compression due to hepatosplenomegaly, but as the neurologic decline progresses, infants lose the ability to coordinate sucking and swallowing. As ERT currently does not treat the central nervous system findings, feeding issues due to neurologic decline is still predicted to be an issue, even for those who may be given ERT. Frequent vomiting can also contribute to insufficient caloric intake. Linear growth is within the normal range during the first year, whereas in untreated individuals weight attainment declines in the first year of life. ERT has been shown to improve growth in individuals with NPD-A/B and NPD-B, but has not been specifically studied in those with NPD-A.

Gastrointestinal manifestations (in addition to vomiting) include constipation and diarrhea. Some infants have abdominal discomfort and gassiness, which may result in irritability and sleep disturbance.

Liver manifestations. The first symptom in most children with NPD-A is hepatomegaly, which typically is noted by age three months [McGovern et al 2006]. Transaminases are persistently elevated. In untreated individuals, the hepatomegaly worsens with time; eventually, the liver becomes massive. Over time, infants with NPD-A who are untreated can exhibit evidence of liver failure, such as coagulopathy and ascites. ERT has been shown to improve hepatomegaly and reduce transaminase levels in affected individuals with NPD-A/B and NPD-B and has the potential to address these issues in those with NPD-A.

Splenic manifestations. Enlargement of the spleen is often noted by age three months. Blood counts can be abnormal, reflective of hypersplenism. ERT has been shown to improve splenomegaly in affected individuals with NPD-A/B and NPD-B and has the potential to address these issues in those with NPD-A.

Pulmonary disease. On chest radiograph, affected infants have evidence of interstitial lung disease caused by storage of sphingomyelin in the pulmonary macrophages. In untreated individuals, low pO₂ on arterial blood gas determination is usually found later in the disease course. Frequent respiratory infections are common, and respiratory failure can be a cause of death. With ERT, pulmonary function may be improved, although this has not been specifically studied in individuals with NPD-A.

Ophthalmologic findings. Fundus examination reveals retinal changes at the time of diagnosis in most children. The accumulation of lipids in the retinal ganglion cells results in a white ring of lipid-laden neurons

encircling the red, ganglion cell-free fovea and manifests as either a macular halo or a cherry-red macula, depending on the degree of opacity and diameter of the white annulus surrounding the fovea. Although a classic cherry-red spot may not be present early in the disease course, all untreated children with NPD-A develop one with time. There is not enough data on the use of ERT to know if this will change the development of cherry-red macula in individuals with NPD-A.

Neurologic findings. The neurologic examination at the time of presentation can be normal except for slight hypotonia. Hypotonia is progressive and deep tendon reflexes are lost with time. Cranial nerve function remains intact.

Psychomotor development does not progress beyond the 12-month level for any domain and skills are lost with disease progression [McGovern et al 2006]. Developmental age usually does not progress beyond age ten months for adaptive behavior, 12 months for expressive language, nine months for gross motor skills, and ten months for fine motor skills.

Neurologic deterioration is relentless and not significantly impacted by ERT. Most untreated children succumb before the third year. It is unclear what impact ERT may have on life expectancy due to improvements in the non-neurologic manifestations. The most common immediate cause of death is respiratory infection [Author, personal observation].

Chronic Neurovisceral ASMD (NPD-A/B)

Individuals with ASMD who survive early childhood but have progressive and/or clinically significant neurologic manifestations have chronic neurovisceral ASMD (NPD-A/B). Most individuals with NPD-A/B survive into adulthood, even when untreated. The extent of visceral organ involvement is variable, similar to NPD-B.

Liver dysfunction. In untreated individuals, the degree of hepatosplenomegaly ranges from mild to massive. Transaminases are often elevated, and some individuals have histologic abnormalities ranging from hepatic fibrosis to frank cirrhosis [Thurberg et al 2012]. Prior to ERT, liver failure was sometimes treated with liver transplantation [McGovern et al 2013]. However, ERT has been shown to improve hepatomegaly and reduce transaminase levels in affected individuals [Diaz et al 2022]. ERT is not expected to impact pre-existing liver fibrosis or cirrhosis.

Splenic involvement. In untreated individuals, hypersplenism leads to secondary thrombocytopenia and can cause acute abdominal pain. However, ERT has been shown to improve the splenomegaly and thrombocytopenia in affected individuals [Diaz et al 2022].

Pulmonary involvement. In untreated individuals, interstitial lung disease may result in oxygen dependence and severe limitations of activity. With ERT, pulmonary function may significantly improve. Out of nine affected children who were given ERT for 24 months, eight children experienced improvements in lung function to the point where they had no or mild impairment [Diaz et al 2022].

Neurologic signs. In individuals with NPD-A/B, the neurologic findings can include cerebellar signs and nystagmus [Obenberger et al 1999], extrapyramidal involvement, intellectual disability, and psychiatric disorders. In a review of 64 persons initially classified as having NPD-B, Wasserstein et al [2006] determined that 19 (30%) had neurologic abnormalities. Of the 19, 14 (22%) had minor and non-progressive findings and five (8%) had global and progressive findings (peripheral neuropathy, retinal abnormalities) with onset between ages two and seven years. The five with progressive findings had the p.Gln294Lys pathogenic variant. ERT does not improve or prevent neurologic issues in affected individuals.

Growth. Abnormal linear growth and delayed skeletal maturation are common in untreated children and adolescents with ASMD and can result in significant short stature in adulthood. In one study, the mean z scores

for height and weight were -1.24 (29th centile) and -0.75 (34th centile), respectively, and skeletal age in children under age 18 years was delayed by an average of 2.5 years [Wasserstein et al 2003]. Short stature and low weight are correlated with large organ volumes, delayed bone age, and low serum insulin-like growth factor 1 (IGF-1) concentrations. However, improvements in both growth and skeletal age have been documented in children who received ERT [Diaz et al 2022].

Hyperlipidemia. In untreated individuals, low serum concentration of high-density lipoprotein cholesterol (HDL-C) is accompanied by hyperlipidemia characterized by hypertriglyceridemia and elevated serum concentration of low-density lipoprotein cholesterol (LDL-C). Lipid abnormalities are evident from the earliest age studied and contribute to cardiac disease. However, in those receiving ERT, lipid profiles improved [Diaz et al 2022].

Coarse facial features are present in a subset of individuals with NPD-A/B.

Osteopenia or osteoporosis may lead to an increase in fractures. ERT has been shown to improve bone mineral density, but the impact on fracture frequency in treated individuals is not yet known.

Chronic Visceral ASMD (NPD-B)

NPD-B, later in onset and milder in manifestations, is characterized in untreated individuals by hepatosplenomegaly, liver dysfunction, progressive hypersplenism, worsening atherogenic lipid profile, and gradual deterioration in pulmonary function [Wasserstein et al 2004, McGovern et al 2008], all of which have been shown to improve with the use of ERT [Diaz et al 2022]. Most untreated individuals with NPD-B survive into adulthood.

Liver dysfunction. Liver enlargement is common in untreated individuals. The degree of hepatosplenomegaly ranges from mild to massive, but can be improved through ERT. Many untreated individuals with NPD-B have elevated transaminases and some have histologic abnormalities ranging from hepatic fibrosis to frank cirrhosis [Thurberg et al 2012]. In rare instances, liver failure has required liver transplantation [McGovern et al 2013]. However, ERT has been shown to improve hepatomegaly and reduce transaminase levels in affected individuals [Diaz et al 2022], which are likely to reduce the risk of liver failure and the need for liver transplantation in the future.

Splenic involvement. Those with significant organomegaly have hypersplenism with secondary thrombocytopenia. Infarction of the spleen can cause acute abdominal pain. However, ERT has been shown to improve the splenomegaly and thrombocytopenia in affected individuals [Diaz et al 2022].

Pulmonary involvement is common in affected individuals of all ages [Minai et al 2000, Mendelson et al 2006]. In untreated individuals, clinical impairment ranges from none to oxygen dependence and severe limitations of activity. Most untreated affected individuals have evidence of interstitial lung disease on chest radiographs and thin-section CT. While most individuals have progressive gas exchange abnormalities, the extent of the radiographic findings may not correlate with impairment of pulmonary function. With ERT, pulmonary function, as measured by percent predicted diffusing capacity of the lung for carbon monoxide, significantly improved [Diaz et al 2022].

Calcified pulmonary nodules can also be seen in untreated individuals and were not specifically studied in those receiving ERT.

Ophthalmologic manifestations. Up to one third of individuals with NPD-B have a macular halo or a cherry-red macula. Most have no evidence of progressive neurologic disease; the presence of a macular halo or a cherry-red macula is not an absolute predictor of neurodegeneration [McGovern et al 2004b], and there do not appear to be any clinical consequences with respect to visual function. This aspect of ASMD was not studied in children who received ERT.

Growth. Abnormal linear growth and delayed skeletal maturation are common in untreated children and adolescents and can result in significant short stature in adulthood. In one study, the mean z scores for height and weight were -1.24 (29th centile) and -0.75 (34th centile), respectively, and skeletal age in children under age 18 years was delayed by an average of 2.5 years [Wasserstein et al 2003]. Short stature and low weight are correlated with large organ volumes, delayed bone age, and low serum IGF-1 concentrations. However, improvements in both growth and skeletal age have been documented in children who received ERT [Diaz et al 2022].

Hyperlipidemia. Low serum concentration of HDL-C is common in NPD-B [McGovern et al 2004a]. In most individuals the low serum concentration of HDL-C is accompanied by hyperlipidemia characterized by hypertriglyceridemia and elevated serum concentration of LDL-C. Lipid abnormalities are evident from the earliest age studied. However, in those receiving ERT, lipid profiles improved [Diaz et al 2022].

Cardiac disease. Early coronary artery disease, identified in some adults with NPD-B, is presumably related to the dyslipidemia. Some individuals have valvular heart disease due to sphingomyelin deposition. This specific end point has not been studied in individuals who have received ERT.

Osteopenia. Skeletal involvement is common in untreated individuals with NPD-B. In one study, lumbar spine z scores for children ranged from 0.061 to -4.879. Most untreated adults with NPD-B had osteopenia or osteoporosis at one or more sites according to the WHO classification of bone marrow density [Wasserstein et al 2013]. Pathologic fractures have been reported, and the impact of ERT is unknown. However, in children ERT did increase growth z scores and improved bone mineral density [Diaz et al 2022].

Other. Calcifications in organs other than the lungs, such as the adrenal glands, have been described. There are no known clinical consequences of these findings, and it is unknown if these findings will be impacted by ERT.

Pregnancy and childbirth. Pregnancy in a mildly affected untreated woman has been reported, and 17 pregnancies monitored in untreated women with a wide spectrum of clinical manifestations have been successful [MM McGovern, personal communication]. Most affected women, even those with significant pulmonary disease, can have normal pregnancies and childbirth. Hepatosplenomegaly does not usually pose a threat to fetal growth.

Genotype-Phenotype Correlations

In the United States about two thirds of newly diagnosed affected individuals have a unique genotype. Although no firm genotype-phenotype correlations exist for this disease, there are some pathogenic variants for which enough data has been generated to make some conclusions. For example, the p.Arg610del pathogenic variant appears to be neuroprotective; individuals with at least one copy of p.Arg610del will not develop neurologic manifestations and will have NPD-B disease. Individuals homozygous for p.Arg610del will have less severe disease than those with one copy in combination with a more severe variant [Wasserstein et al 2004]. In contrast to individuals with other pathogenic variants, individuals homozygous for the p.Arg610del pathogenic variant usually have normal height and weight, markedly less hepatosplenomegaly and bone age delay, and normal serum concentration of IGF-1. Lipid abnormalities occur with all genotypes, including homozygosity for the p.Arg610del pathogenic variant.

Some evidence suggests that the p.Leu139Pro, p.Ala198Pro, and p.Arg476Trp pathogenic variants also result in a less severe form of NPD-B.

The p.His423Tyr and p.Lys578Asn pathogenic variants, found most commonly in individuals from Saudi Arabia, lead to an early-onset severe form of the disease that is most consistent with the intermediate chronic neurovisceral phenotype (NPD-A/B) [Simonaro et al 2002].

The p.Gln294Lys pathogenic variant, associated with intermediate phenotypes with later-onset neuronopathic disease (NPD-A/B), appears to be relatively common in individuals of Czech and Slovak heritage [Pavlů-Pereira et al 2005].

Homozygosity or compound heterozygosity for some combination of the common *SMPD1* pathogenic variants observed in individuals with NPD-A predicts the severe infantile neurovisceral phenotype. For example, any combination of the p.Arg498Leu, p.Leu304Pro, or p.Phe333SerfsTer52 variants results in NPD-A.

Prevalence

The estimated prevalence of ASMD is 1:250,000 [Meikle et al 1999]. However, population-wide screening has not been performed, and this and other estimates are based on the number of clinically diagnosed individuals referred for biochemical and/or molecular confirmation. In Chile, screening of 1,691 healthy individuals for a common *SMPD1* pathogenic variant, p.Ala359Asp, found a heterozygote frequency of 1:105.7, predicting a disease incidence of 1:44,960 [Acuña et al 2016].

Pathogenic variants causing the severe neurodegenerative form of ASMD (NPD-A) are more prevalent in the Ashkenazi Jewish population, in which the combined carrier frequency for the three common *SMPD1* pathogenic variants (p.Arg498Leu, p.Leu304Pro, and p.Phe333SerfsTer52) is between 1:80 and 1:100. Carrier screening programs and the availability of prenatal testing have resulted in a low birth incidence in this population.

All forms of ASMD are pan ethnic. Genotype information on individuals with NPD-B from 29 different countries has been reported [Simonaro et al 2002].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SMPD1*.

Differential Diagnosis

Lysosomal storage diseases (LSD). The clinical features of acid sphingomyelinase deficiency (ASMD) may overlap with other lysosomal storage diseases such as [Gaucher disease](#); however, biochemical and/or molecular genetic testing permits clear distinction between these disorders. Recent studies of individuals with hepatosplenomegaly whose testing for Gaucher disease was normal were subsequently found to have ASMD [Author, personal communication]. Pulmonary infiltration and the low serum concentration of high-density lipoprotein cholesterol are distinctive features that are present very early in individuals with ASMD but not in those with Gaucher disease.

Hepatosplenomegaly. Other hereditary disorders associated with hepatosplenomegaly are summarized in Table 2.

Table 2. Disorders with Hepatosplenomegaly in the Differential Diagnosis of Acid Sphingomyelinase Deficiency

Gene(s)	Differential Diagnosis Disorder	MOI	Distinguishing Features
<i>ASAHI</i>	Farber disease (See ASAHI-Related Disorders .)	AR	Joint nodules & hoarseness in Farber disease
<i>G6PC</i> <i>SLC37A4</i>	Glycogen storage diseases (e.g., GSD1)	AR	Hypoglycemia in glycogen storage diseases

Table 2. continued from previous page.

Gene(s)	Differential Diagnosis Disorder	MOI	Distinguishing Features
<i>GALNS</i> <i>GNS</i> <i>HGSNAT</i> <i>IDS</i> <i>IDUA</i> <i>NAGLU</i> <i>SGSH</i>	Mucopolysaccharidoses (e.g., MPS I , MPS II , MPS III , MPS IVA)	AR XL	Coarse facial features & dysostosis multiplex in mucopolysaccharidoses
<i>GBA1</i> (<i>GBA</i>)	Gaucher disease	AR	Interstitial lung disease in ASMD; more prominent skeletal disease in Gaucher disease
<i>GNPTAB</i> <i>GNPTG</i> <i>MCOLN1</i>	Oligosaccharidoses (e.g., GNPTAB-related disorders , mucopolipidosis III gamma , mucopolipidosis IV)	AR	Coarse features & dermatologic & ophthalmologic abnormalities may be present in oligosaccharidoses.
<i>HEXA</i>	Tay-Sachs disease (See HEXA Disorders .)	AR	Hepatosplenomegaly & lung disease are not common in Tay-Sachs disease.
<i>HEXB</i>	Sandhoff disease	AR	Hepatosplenomegaly & lung disease are not common in Sandhoff disease.
<i>LIPA</i>	Wolman disease (See Lysosomal Acid Lipase [LAL] Deficiency .)	AR	Interstitial lung disease is not common in LAL deficiency; splenomegaly is less pronounced than in ASMD.
<i>NPC1</i> <i>NPC2</i>	Niemann-Pick disease type C (NPD-C)	AR	Specific neurologic findings in NPD-C
<i>PRF1</i> <i>STX11</i> <i>STXBP2</i> <i>UNC13D</i>	Familial hemophagocytic lymphohistiocytosis (HLH)	AR	Familial HLH may present w/fever & inflammation & may have involvement of organs not typically affected in ASMD.

ASMD = acid sphingomyelinase deficiency

Hepatosplenomegaly can also accompany some infectious diseases (e.g., Epstein-Barr virus, cytomegalovirus). The diagnosis in infants with NPD-A is sometimes delayed during evaluation for an infectious etiology.

Hematologic malignancies such as leukemia may present with hepatosplenomegaly and pancytopenia. The presence of interstitial lung disease and dyslipidemia may help distinguish ASMD from acute presentation of a hematologic malignancy.

Interstitial lung disease can result from many causes, including environmental exposures, connective tissue diseases, and infections. However, the presence of hepatosplenomegaly in ASMD helps distinguish it from these other causes of interstitial lung disease.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with acid sphingomyelinase deficiency (ASMD), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Acid Sphingomyelinase Deficiency

System/Concern	Evaluation	Comment
Growth/Nutrition	<ul style="list-style-type: none"> Growth assessment Gastroenterology / nutrition / feeding team eval 	<p>In persons w/NPD-A:</p> <ul style="list-style-type: none"> Incl eval of aspiration risk & nutritional status. Consider eval for gastrostomy tube placement in those w/dysphagia &/or aspiration risk. <p>In persons w/NPD-B:</p> <ul style="list-style-type: none"> Assess nutritional status incl appropriate caloric, calcium, & vitamin D intake.
	Bone age in children age <18 yrs	<ul style="list-style-type: none"> Skeletal age, often delayed, is useful for interpreting DXA scans. Knowledge about additional potential growth yrs can be reassuring to families concerned about child's stature.
Liver function	Serum chemistries incl liver transaminases (ALT, AST), albumin, & clotting factors	To evaluate for progression of hepatic dysfunction
	Liver elastography or FibroScan®	To evaluate for hepatic fibrosis & cirrhosis
	Liver biopsy in persons w/evidence of deteriorating liver function may be indicated if noninvasive means to ascertain fibrosis are not available.	
Hepatosplenomegaly	Radiologic exam w/measurement of liver & spleen size	
Hematologic	Complete blood count	To evaluate for thrombocytopenia, leukopenia, & anemia
Pulmonary	Chest radiograph	<ul style="list-style-type: none"> To assess extent of interstitial lung disease Should be done at time of diagnosis regardless of age
	Pulmonary function testing, incl assessment of diffusing capacity	In persons old enough to cooperate
Ophthalmologic	Ophthalmologic exam	<ul style="list-style-type: none"> Optional No visual consequences of cherry-red spots are known; their presence does not imply neuronopathic disease, as they are found in many adults w/NPD-B.
Neurologic	Comprehensive neurologic eval	Esp important in infants when NPD-A diagnosis is under consideration
Hyperlipidemia	Fasting lipid profile	In those w/NPD-B & NPD-A/B
Cardiac	CT exam of coronary artery status	
Musculoskeletal	Assess for frequent fractures &/or extremity pain.	
Developmental	Developmental assessment	<ul style="list-style-type: none"> To incl motor, adaptive, cognitive, & speech-language eval Eval for early intervention / special education

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals ¹	To inform affected persons & their families re nature, MOI, & implications of ASMD to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: <ul style="list-style-type: none"> • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ALT = alanine aminotransaminase; ASMD = acid sphingomyelinase deficiency; AST = aspartate aminotransferase; DXA = dual-energy x-ray absorptiometry; MOI = mode of inheritance; NPD-A = infantile neurovisceral ASMD (Niemann-Pick disease type A); NPD-A/B = chronic neurovisceral ASMD (intermediate form); NPD-B = chronic visceral ASMD (Niemann-Pick disease type B)

1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

There is no cure for ASMD.

Targeted Therapies

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Olipudase alfa (Xenpozyme[®]) enzyme replacement therapy (ERT) for ASMD has been approved by the FDA in the United States, the EMA in Europe, and other global regulatory authorities. This therapy helps to reduce the accumulation of sphingomyelin in the lung, liver, spleen, and other non-central nervous system organs. It does not impact the central nervous system and therefore does not impact the neurocognitive issues seen in individuals with NPD-A or NPD-A/B. It represents the first disease-specific treatment for the non-central nervous system manifestations of this disorder. See Table 4 for dosage information.

Hematopoietic stem cell transplantation (HSCT) has yielded variable results. Shah et al [2005] reported successful HSCT for infantile neurovisceral ASMD (NPD-A). Successful engraftment can correct the metabolic defect, improve blood counts, and reduce increased liver and spleen volumes. Similar to ERT, stabilization of the neurologic component following HSCT has not been reported; therefore, any attempts to perform HSCT in individuals with clinically evident neurologic disease should be considered experimental. The morbidity and mortality associated with HSCT limit its use, and it is likely to become obsolete now that ERT is available.

Table 4. Targeted Treatment of Acid Sphingomyelinase Deficiency

Targeted Treatment	Dosage	Consideration
Olipudase alfa (Xenpozyme®) ERT ¹	Dose escalation: <ul style="list-style-type: none"> • Children: starting dose of 0.03 mg/kg w/ dose escalation over at least 16 weeks to maintenance goal of 3 mg/kg • Adults: starting dose of 0.1 mg/kg w/dose escalation over at least 14 weeks to maintenance goal of 3 mg/kg Target maintenance dose for children & adults: <ul style="list-style-type: none"> • 3 mg/kg IV infusion every 2 weeks² 	<ul style="list-style-type: none"> • The reported most common side effects incl cough, fever, headache, joint pain, diarrhea, & low blood pressure. • Severe hypersensitivity & anaphylaxis has been observed in a minority of persons.

ERT = enzyme replacement therapy; IV = intravenous

1. Olipudase alfa ERT has been studied in those with ASMD types NPD-A/B and NPD-B and has the potential to address these issues in those with NPD-A [Diaz et al 2022].

2. During the maintenance phase, infusions may take up to 3.5 to 4 hours.

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Supportive Treatment of Manifestations in Individuals with Acid Sphingomyelinase Deficiency

Manifestation/Concern ¹	Treatment ²	Considerations/Other
Growth/Nutrition	<ul style="list-style-type: none"> • Regular consultation w/dietician to assure that calorie intake is adequate for growth • Feeding therapy • Nasogastric tube feeding or surgical placement of feeding tube should be discussed. 	Feeding difficulties can make provision of adequate calories a major challenge.
Liver dysfunction	<ul style="list-style-type: none"> • Supportive mgmt may be indicated (e.g., diuretics for ascites, vitamin K for coagulopathy). • Liver transplantation has been used successfully in liver failure due to ASMD. 	
Bleeding disorder	Transfusion of blood products when bleeding is life threatening	
Splenomegaly	Partial splenectomy may be considered for persons w/ severe hypersplenism, although surgical risks are significant due to multisystemic disease & bleeding risks.	Total splenectomy should be avoided because removal of spleen exacerbates pulmonary disease.
Pulmonary disease	Supplemental oxygen for those w/symptomatic pulmonary disease	Other treatments for interstitial lung disease (e.g., steroids) have not been well studied. Several persons have undergone bronchopulmonary lavage w/variable results. ³
Progressive neurologic disease / Neurodevelopmental issues	<ul style="list-style-type: none"> • PT & OT to maximize function & prevent contractures • Early intervention & developmental support for those w/developmental issues 	Aggressive therapy for infants w/NPD-A is not warranted & plan for such treatment should be made in consultation w/neurologist, therapist(s), & family to establish realistic goals.
Hyperlipidemia	Adults w/hyperlipidemia may be treated to bring serum concentration of total cholesterol into normal range.	Although not studied specifically in ASMD, statins have been used in adults w/ASMD. ⁴
Osteopenia	Calcium & vitamin D for osteopenia/osteoporosis	

Table 5. continued from previous page.

Manifestation/Concern ¹	Treatment ²	Considerations/Other
Sleep disorder	Consider sedatives as needed.	Irritability & sleep disturbance are quality-of-life issues for entire family.

ASMD = acid sphingomyelinase deficiency; NPD-A = infantile neurovisceral ASMD (Niemann-Pick disease type A); OT = occupational therapy; PT = physical therapy

1. Some of these manifestations may be ameliorated by ERT (see Table 4).

2. Many of these treatments apply to those who are not receiving ERT or for whom ERT has not resulted in significant improvement to the manifestation or concern in question.

3. Nicholson et al [2002], Uyan et al [2005]

4. Author, personal observation

Prevention of Secondary Complications

Liver function needs to be monitored in individuals receiving medications with known hepatotoxicity (e.g., statins for treatment of hypercholesterolemia).

Surveillance

Recommendations for clinical monitoring of individuals with ASMD have been published [Wasserstein et al 2019]. These were published prior to the availability of ERT. However, such evaluations should still be considered, even for those on ERT, to assess for the individual's response to targeted and supportive care and the emergence of new manifestations.

Table 6. Recommended Surveillance for Individuals with Acid Sphingomyelinase Deficiency

System/Concern	Evaluation	Frequency
Growth/Nutrition	<ul style="list-style-type: none"> Measurement of growth parameters Eval of nutritional status & safety of oral intake 	At each visit
Cardiac	EKG	Annually
	Echocardiogram	Every 2-4 yrs
Liver function	Serum chemistries incl liver transaminases (ALT, AST), albumin, & clotting factors	At least annually
Hematologic	<ul style="list-style-type: none"> Assess for fatigue, abdominal pain, &/or ↑ bleeding. Platelet count 	
Hepatosplenomegaly	Radiologic measurements of liver & spleen size	At baseline & as needed
Pulmonary	Assess for shortness of breath.	At each visit
	Pulmonary function testing	Annually
	Chest radiograph	Every 2-4 yrs
Neurologic	Assess neurologic function & frequency of headaches.	At least annually
Developmental	<ul style="list-style-type: none"> Monitor developmental progress & educational needs. Evaluate OT & PT needs. 	At each visit
Hyperlipidemia	Fasting lipid profile	At least annually
Musculoskeletal	Assess for extremity pain.	At each visit
	Bone density assessment (DXA scan)	Every 2-4 yrs
Family support & resources	Assess for any change in social, domestic, or school- or work-related activities.	At each visit

ALT = alanine aminotransaminase; AST = aspartate aminotransferase; DXA = dual-energy x-ray absorptiometry; OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Individuals who have splenomegaly should avoid contact sports.

Evaluation of Relatives at Risk

Testing of all at-risk sibs of any age is warranted to allow for early diagnosis and targeted treatment of ASMD. For at-risk newborn sibs when prenatal testing was not performed: in parallel with newborn screening, testing for the familial *SMPD1* pathogenic variants or measurement of residual acid sphingomyelinase enzyme activity should be performed.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

For pregnant women with ASMD, prenatal care by a high-risk obstetrician is indicated to ensure appropriate monitoring of pulmonary function and hematologic status. Olipudase alfa ERT has not been studied in pregnant women, but animal studies have identified a potential impact on fetal development. Therefore, ERT is not recommended during pregnancy.

See [MotherToBaby](#) for further information on medication use during pregnancy.

Therapies Under Investigation

Search [ClinicalTrials.gov](#) in the US and [EU Clinical Trials Register](#) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

All forms of acid sphingomyelinase deficiency (ASMD), including infantile neurovisceral ASMD (Niemann-Pick disease type A, or NPD-A), chronic neurovisceral ASMD (NPD-A/B), and chronic visceral ASMD (Niemann-Pick disease type B, or NPD-B), are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *SMPD1* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *SMPD1* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
 - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband [Jónsson et al 2017].

- Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Some heterozygotes have been found to have low high-density lipoprotein (HDL) associated with ASMD.

Sibs of a proband

- If both parents are known to be heterozygous for an *SMPD1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of being a carrier (heterozygous), and a 25% chance of inheriting neither of the familial pathogenic variants and being unaffected and not a carrier.
- Phenotypic severity is similar overall among sibs with the same biallelic pathogenic variants, although some intrafamilial clinical variability may be observed.
- Some heterozygotes have been found to have low HDL associated with ASMD.

Offspring of a proband

- Individuals with NPD-A do not reproduce.
- The offspring of an individual with NPD-B or NPD-A/B are obligate heterozygotes (carriers) for a pathogenic variant in *SMPD1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SMPD1* pathogenic variant.

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *SMPD1* pathogenic variants in the family.

Note: Carrier identification by determination of acid sphingomyelinase enzyme activity is not reliable.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *SMPD1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Biochemical genetic testing. Prenatal testing for a pregnancy at 25% risk is also possible using biochemical testing of acid sphingomyelinase enzyme activity in cultured amniocytes obtained by amniocentesis or chorionic villus sampling.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **MedlinePlus**
Niemann-Pick disease
- **National Niemann-Pick Disease Foundation (NNPDF)**
Phone: 877-287-3672
Email: nnpdf@nnpdf.org
nnpdf.org
- **Metabolic Support UK**
United Kingdom
Phone: 0845 241 2173
metabolicsupportuk.org
- **National Tay-Sachs and Allied Diseases Association, Inc. (NTSAD)**
Phone: 617-277-4463
Email: info@ntsad.org
www.ntsad.org
- **Norton & Elaine Sarnoff Center for Jewish Genetics**
Phone: 312-357-4718
Email: jewishgenetics@juf.org
www.juf.org/cjg
- **International Niemann-Pick Disease Alliance (INPDA)**
Phone: 44 (0)191 4150693
Email: info@inpda.org
inpda.org
- **International Niemann-Pick Disease Registry**
INPDR

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Acid Sphingomyelinase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>SMPD1</i>	11p15.4	Sphingomyelin phosphodiesterase	SMPD1 database	SMPD1	SMPD1

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B. OMIM Entries for Acid Sphingomyelinase Deficiency ([View All in OMIM](#))

257200	NIEMANN-PICK DISEASE, TYPE A
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Table B. continued from previous page.

607608	SPHINGOMYELIN PHOSPHODIESTERASE 1, ACID LYSOSOMAL; SMPD1
607616	NIEMANN-PICK DISEASE, TYPE B

Molecular Pathogenesis

SMPD1 encodes acid sphingomyelinase (sphingomyelin phosphodiesterase; EC:3.1.4.12), a lysosomal enzyme responsible for hydrolyzing sphingomyelin to ceramide and phosphorylcholine. Acid sphingomyelinase deficiency (ASMD) is an inborn error of metabolism that results in the accumulation of sphingomyelin in cells and tissues. More than 150 pathogenic variants causing ASMD have been published [Simonaro et al 2002, Schuchman 2007, Zampieri et al 2016] including missense, nonsense, and frameshift variants and one in-frame three-nucleotide deletion that results in the removal of a single amino acid from the ASM polypeptide [Zampieri et al 2016]. Splice site alterations have also been described. In contrast to the Ashkenazi Jewish population (see Table 7), most individuals affected with infantile neurovisceral ASMD (NPD-A) studied in other populations have a unique *SMPD1* pathogenic variant. There are also a small number of *SMPD1* pathogenic variants that can predict chronic visceral ASMD (NPD-B) or chronic neurovisceral ASMD (NPD-A/B) in specific populations, but – as with NPD-A – most individuals will have unique variants.

Mechanism of disease causation. *SMPD1* pathogenic variants result in an enzyme with altered activity that leads to decreased hydrolysis of the substrate and its subsequent accumulation in cells, particularly in the monocyte macrophage system. Secondary to the primary substrate (sphingomyelin) accumulation, other lipids also accumulate, including cholesterol, lyso-sphingomyelin, and lyso-sphingomyelin-509. These accumulating lipids can also contribute to the pathogenesis of ASMD.

SMPD1-specific laboratory technical considerations

- Paternal imprinting of *SMPD1* has been described [Simonaro et al 2006]. The influence of imprinting on the ASMD phenotype has not been studied in detail.
- Two numbering systems to describe *SMPD1* variants that differ by two amino acids (due to a polymorphism in the length of *SMPD1*) are currently in use (see Table 7).

Table 7. Notable *SMPD1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias ¹)	Predicted Protein Change (Alias ¹)	Comment
NM_000543.3 NP_000534.3	c.416T>C	p.Leu139Pro (p.Leu137Pro)	Some evidence suggests that these pathogenic variants are assoc w/less severe form of NPD-B [Simonaro et al 2002].
	c.592G>C	p.Ala198Pro (p.Ala196Pro)	
	c.874C>A	p.Gln294Lys (p.Gln292Lys)	<ul style="list-style-type: none"> • Assoc w/intermediate phenotypes w/late-onset neuronopathic disease • Appears to be relatively common in persons of Czech & Slovak descent [Pavlů-Pereira et al 2005]
	c.911T>C	p.Leu304Pro (p.Leu302Pro)	1 of 3 common variants that accounts for >90% of pathogenic variants in persons of Ashkenazi Jewish ancestry w/NPD-A [Levran et al 1992]
	c.996delC (c.990delC)	p.Phe333SerfsTer52 (p.Pro330SerfsTer382 or fsP330)	1 of 3 common variants that accounts for >90% of pathogenic variants in persons of Ashkenazi Jewish ancestry w/NPD-A [Levran et al 1993]

Table 7. continued from previous page.

Reference Sequences	DNA Nucleotide Change (Alias ¹)	Predicted Protein Change (Alias ¹)	Comment
	c.1076C>A	p.Ala359Asp	In Chile, screening of 1,691 healthy persons for this common <i>SMPD1</i> pathogenic variant found heterozygote frequency of 1:105.7, predicting disease incidence of 1:44,960 [Acuña et al 2016].
	c.1267C>T	p.His423Tyr (p.His421Tyr)	<ul style="list-style-type: none"> Found most commonly in persons from Saudi Arabia Leads to early-onset severe form of NPD-A [Simonaro et al 2002]
	c.1426C>T	p.Arg476Trp (p.Arg474Trp)	Some evidence suggests that this pathogenic variant is assoc w/less severe form of NPD-B [Simonaro et al 2002].
	c.1493G>T	p.Arg498Leu (p.Arg496Leu)	1 of 3 common variants that accounts for >90% of pathogenic variants in persons of Ashkenazi Jewish ancestry w/NPD-A [Scott et al 2010]
	c.1734G>C	p.Lys578Asn (p.Lys576Asn)	<ul style="list-style-type: none"> Found most commonly in persons from Saudi Arabia Leads to early-onset severe form of NPD-A [Simonaro et al 2002]
	c.1828_1830del	p.Arg610del (p.Arg608del or DeltaR608)	<ul style="list-style-type: none"> Homozygotes have milder clinical course [Wasserstein et al 2004]. One of the most common pathogenic variants in persons w/NPD-B In persons w/NPD-B originating from Maghreb region of North Africa (i.e., Tunisia, Algeria, Morocco), accounts for almost 90% of mutated alleles On Gran Canaria Island, accounts for 100% of pathogenic alleles [Fernández-Burriel et al 2003] Accounts for ~20%-30% of pathogenic variants in those w/NPD-B in US

NPD-A = infantile neurovisceral ASMD (Niemann-Pick disease type A); NPD-B = chronic visceral ASMD (Niemann-Pick disease type B)

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

Chapter Notes

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