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Alpha-Mannosidosis

Synonym: α-Mannosidosis

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Summary

Clinical characteristics

The clinical phenotype of alpha-mannosidosis varies considerably, with a wide spectrum of clinical findings and broad variability in individual presentation. At least three clinical types have been suggested in untreated individuals: mild (clinically recognized after age ten years, with myopathy, slow progression, and absence of skeletal abnormalities); moderate (clinically recognized before age ten years, with myopathy, slow progression, and presence of skeletal abnormalities); and severe (obvious progression leading to early death from primary central nervous system involvement or infection). Core features of untreated individuals generally include early childhood-onset non-progressive hearing loss, frequent infections due to immunodeficiency, rheumatologic symptoms (especially systemic lupus erythematosus), developmental delay / intellectual disability, low tone, ataxia, spastic paraplegia, psychiatric findings, bone disease (ranging from asymptomatic osteopenia to focal lytic or sclerotic lesions and osteonecrosis), gastrointestinal dysfunction (including diarrhea, swallowing issues / aspiration, and enlarged liver and spleen), poor growth, eye issues (including tapetoretinal degeneration and optic nerve atrophy), cardiac complications in adults, and pulmonary issues (including parenchymal lung disease). However, with the advent of enzyme replacement therapy, the natural history of this condition may change. Long-term velmanase alfa (VA) treatment outcomes are still being elucidated, but may include improvement in hearing, immunologic profile, and quality of life (improved clinical outcomes for muscle strength). Similarly, affected individuals who underwent hematopoietic stem cell transplantation (HSCT) experienced improvement in development (with preservation of previously learned skills), ability to participate in activities of daily living, stabilization or improvement in skeletal abnormalities, and improvement in hearing ability, although expressive speech and hearing deficiencies remained the most significant clinical problems after HSCT.

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Diagnosis/testing

The diagnosis of alpha-mannosidosis is established in a proband by identification of deficiency of lysosomal enzyme acid alpha-mannosidase (typically 5%-10% of normal activity) in leukocytes or other nucleated cells AND/OR by the identification of biallelic pathogenic variants in *MAN2B1* by molecular genetic testing.

Management

Targeted therapies: Velmanase alfa (Lamzede®) enzyme replacement therapy (ERT) has been very well tolerated and is now regarded as a standard treatment for alpha-mannosidosis; improvement in both biochemical and functional parameters have been reported in treated individuals. Hematopoietic stem cell transplantation (HSCT) has been offered as a treatment for severe alpha-mannosidosis. While HSCT carries risks, the data suggests it is a feasible therapeutic option for alpha-mannosidosis, with better outcomes achieved by performing it early before complications arise, balancing the risks and benefits.

Supportive care: Hearing aids may be helpful for those with sensorineural hearing loss, whereas pressure-equalizing tubes may be helpful for those with conductive hearing loss. Consider palmidronate (Aredia®) monthly or zoledronic acid (Aclasta®) once a year for osteoporosis or osteopenia. Standard treatment for immunodeficiency / recurrent infections, systemic lupus erythematosus, communicating hydrocephalus, ataxia / gait abnormalities, poor weight gain / growth issues, eye/vision issues, cardiac valve dysfunction / dilated cardiomyopathy, recurrent chest infections / respiratory dysfunction, developmental delay / intellectual disability, and psychiatric manifestations.

Surveillance: At each visit, measure weight, length/height, head circumference, and BMI; monitor growth pattern, developmental progress, and educational needs; assess for depression, including sleep disturbances, anxiety, &/or findings suggestive of psychosis; assess for new manifestations such as ataxia and gait abnormalities; evaluate for asthenia and signs/symptoms of communicating hydrocephalus; assess for muscle pain, joint aches, reduced range of motion, and bone pain; monitor for diarrhea and for size of the liver and spleen; and assess for the number and type of infections. Every six to 12 months in childhood and annually in adults, assess fine motor function, gross motor function, endurance, and muscle strength and tone by physical therapy; and assess for features of ataxia. Every one to two years, or as clinically indicated in those with hearing aids, perform an audiology evaluation. Every two to five years in children, adolescents, and adults, consider DXA bone densitometry scan to assess for osteopenia or osteoporosis; radiographs of the hips/spine may be indicated. Annually (or as clinically indicated), routine biochemical lab assessment to include liver and kidney health, blood glucose levels, fluid and electrolyte balance, and complete blood count (with platelets); consider immunlobulin levels, ESR and C-reactive protein; pulmonary function tests; and ophthalmology evaluation. At regular intervals based on clinical features, consider endocrinology evaluations, including hormonal and lipid profiles; consider assessment of liver and spleen size through ultrasound or MRI imaging; consider electrocardiogram, 24-hour electrocardiogram, and echocardiogram; consider sleep study. For those on ERT, plasma oligosaccharides to assess treatment response as clinically indicated. Post-HSCT evaluation of standard surveillance per hematologist/oncologist, which may include ongoing assessment for chimerism and enzyme activity if indicated.

Evaluation of relatives at risk: Testing of all at-risk sibs of any age (including prenatal diagnosis) is warranted to allow for early diagnosis and targeted treatment of alpha-mannosidosis. Evaluations can include molecular genetic testing if the pathogenic variants in the family are known or assay of acid alpha-mannosidase enzyme activity in leukocytes or other nucleated cells if the pathogenic variants in the family are not known.

Genetic counseling

Alpha-mannosidosis is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives is possible if the pathogenic variants in the family are known. Prenatal testing for a pregnancy at increased risk is possible by assay of acid alpha-mannosidase enzymatic activity or molecular genetic testing once the pathogenic variants have been identified in the family.

GeneReview Scope

Alpha-Mannosidosis: Included Phenotypes [1]
• Mild form (type 1): typically recognized after age ten years, with myopathy, slow progression, and no skeletal abnormalities • Moderate form (type 2): typically recognized before age ten years, with myopathy, slow progression, and presence of skeletal abnormalities • Severe form (type 3): Obvious progression leading to early death from primary central nervous system involvement or infection

For synonyms and outdated names, see Nomenclature.
1. For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

A proposed diagnostic algorithm for alpha-mannosidosis has been published, but clinical findings alone are not enough to establish the diagnosis because they overlap with clinical findings in other storage disorders [Guffon et al 2019].

Suggestive Findings

Alpha-mannosidosis **should be suspected** in individuals with the following clinical, radiographic, supportive laboratory, pathology, and family history findings.

Clinical features

- Macrocephaly with coarsening facial features. The facial features may progress to include:
  - Prominent forehead
  - Highly arched eyebrows
  - Depressed nasal bridge
  - Widely spaced teeth
  - Macroglossia
  - Prognathism
- Hearing loss (sensorineural or mixed)
- Frequent infections
- Developmental delay / intellectual disability
- Ataxia

Radiographic features. Skeletal radiographs demonstrating one or more of the following:

- Dysostosis multiplex
- Focal lytic or sclerotic lesions
- Osteonecrosis
- Osteopenia

Supportive laboratory features. Elevated urinary excretion of mannose-rich oligosaccharides demonstrated by thin-layer chromatography or capillary high-performance anion exchange chromatography

Histopathology. Light microscopy demonstrates vacuoles in lymphocytes from peripheral blood [Govender & Mubaiwa 2014].

Note: Histopathologic evaluation of peripheral blood lymphocytes is not required to make the diagnosis and absence of this finding does not preclude the diagnosis.

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of alpha-mannosidosis **is established** in a proband by identification of deficiency of lysosomal enzyme acid alpha-mannosidase (MAN2B1) in leukocytes or other nucleated cells AND/OR by identification of biallelic pathogenic (or likely pathogenic) variants in *MAN2B1* by molecular genetic testing (Table 1).

- In affected individuals, alpha-mannosidase enzyme activity in peripheral blood leukocytes is 5%-10% of normal activity.
- This "residual" enzyme activity appears to represent mannosidase from other organelles or compartments (e.g., Golgi apparatus or cytosol), since they also show some activity at low pH.

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 likely pathogenic variants. (2) Identification of biallelic *MAN2B1* variants of uncertain significance (or of one known *MAN2B1* pathogenic variant and one *MAN2B1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of alpha-mannosidosis, molecular genetic testing approaches can include **single-gene testing*** or use of a **multigene panel**.

* **Before single-gene testing,** the activity of lysosomal alpha-mannosidase should be determined.

- **Single-gene testing.** Sequence analysis of *MAN2B1* 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. 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.
- **A lysosomal storage disease multigene panel** that includes *MAN2B1* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel 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. (3) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (4) In individuals with only *MAN2B1* variants of uncertain significance identified, DNA sequencing should be followed by testing alpha-mannosidase activity in peripheral blood leukocytes.

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

Option 2

When the diagnosis of alpha-mannosidosis is not considered because an individual has atypical phenotypic features, comprehensive genomic testing may be considered.

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **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 Alpha-Mannosidosis

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
MAN2B1	Sequence analysis [3]	98.5% [4]
	Gene-targeted deletion/duplication analysis [5]	<2% [6]

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. 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.
4. More than 130 *MAN2B1* pathogenic variants have been reported [Berg et al 1999, Kuokkanen et al 2011, Riise Stensland et al 2012]; reviewed in Riise Stensland et al [2015].
5. 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.
6. A few affected individuals were found to have a deletion of one or more exons [Riise Stensland et al 2012].

Clinical Characteristics

Clinical Description

The clinical phenotype of alpha-mannosidosis varies considerably, with a wide spectrum of clinical findings and broad variability in individual presentation. Designating clinical types can be useful in prognosis and management. At least three clinical types (mild, moderate, and severe) have been suggested [Malm & Nilssen 2008] based on individuals who have not been treated with enzyme replacement therapy (ERT; see Management). Most individuals described fit into the moderate type.

- **Mild form.** Clinically recognized after age ten years, with myopathy, slow progression, and absence of skeletal abnormalities (type 1)
- **Moderate form.** Clinically recognized before age ten years, with myopathy, slow progression, and presence of skeletal abnormalities (type 2)

- **Severe form.** Obvious progression leading to early death from primary central nervous system involvement or infection (type 3)

However, with the advent of ERT, the natural history of this condition may change.

Long-term velmanase alfa (VA) treatment outcomes are still being elucidated (see also Management, Targeted Therapies).

- Treatment with VA reduced serum oligosaccharide levels and elevated serum immunoglobulin G levels in affected individuals [Borgwardt et al 2022].
  - With up to 48 months of VA treatment, only 12% (4/33) of individuals with alpha-mannosidosis developed treatment-related anti-drug antibodies (ADAs).
  - Clinical outcomes assessed by the three-minute stair climb test (3MSCT) and the six-minute walk test (6MWT) were similar regardless of genotype or ADA status.
- In a study of six individuals younger than age six years who received 1 mg/kg of VA intravenously (IV) once a week for at least 24 months [Guffon et al 2023]:
  - All children improved in one or more efficacy assessments of serum oligosaccharide concentrations (decreased), hearing, immunologic profile, and quality of life, suggesting a beneficial effect of early treatment;
  - It was suggested that long-term VA treatment has an acceptable safety profile, is well tolerated, and may provide potential benefits to individuals with alpha-mannosidosis younger than age six years.
- The prognosis for individuals receiving VA treatment is not yet known.

Hematopoietic stem cell transplantation (HSCT). The primary indication to offer HSCT in people with alpha-mannosidosis is the preservation of neurocognitive function and the prevention of early death. As such, HSCT should be pursued as early as possible, preferably in the first decade of life, to minimize accumulation of storage material and irreversible pathologic changes. Even late transplantation can help resolve some systemic features and may stabilize cerebral function [Broomfield et al 2010, Yesilipek et al 2012] (see Management). However, expressive speech and hearing deficiencies remained the most significant clinical problems after HSCT.

Post-transplant mannosidase activity was within normal limits in all eight affected individuals tested [Mynarek et al 2012]. In terms of clinical outcomes, HSCT has led to:

- Developmental improvement in all affected individuals, though none have reached typical development levels for age;
- Preservation of previously learned skills in all affected individuals;
- Ability to participate in activities of daily living, with one affected plerson reported to be able to live independently;
- Stabilization or improvement in skeletal abnormalities, despite difficulties in quantifying changes in a growing skeleton [Mynarek et al 2012];
- Improvement in hearing ability in some affected individuals, though hearing disability was not completely resolved.

HSCT has shown beneficial effects on the central nervous system pathology in individuals with alpha-mannosidosis, as follows [Avenarius et al 2011]:

- Diminished white matter abnormalities, reduced demyelination, and decreased gliosis compared to untreated affected individuals
- Normalization of abnormal signals on cerebral magnetic resonance spectroscopy (MRS) that are present in untreated affected individuals

The morbidity and mortality rate associated with HSCT must be balanced against the benefits and is comparable to other non-malignant disases (88% survival rate). The benefits are greater in younger affected individuals before disease-related complications have developed.

Clinical Features in Treatment-Naïve Individuals

The first decade of life is characterized by a high incidence of recurrent infections, including the common cold, pneumonia, gastroenteritis, and, more rarely, infections of the urinary tract. Serous otitis media is common and is usually not bacterial [Hennermann et al 2022].

The infections diminish in the second and third decade, when ataxia and muscular weakness are more prominent. However, many individuals are able to ski, ride a bike, or play soccer up to the third decade. At any time, individuals risk setbacks in the form of acute necrotizing arthritis or acute hydrocephalus, both requiring surgery. Worsening of the myopathy has also been described and can be seen in affected individuals post-HSCT as an immune-mediated mechanism [Kawai et al 1985, Mulrooney et al 2003]. In one person strength improved after a single plasma exchange [Mulrooney et al 2003].

Facial features. Independent of family and ancestry, untreated individuals have typical Hurler-like facies (see Mucopolysaccharidosis Type 1) or coarse facial features, macrocephaly with a prominent forehead, highly arched eyebrows, depressed nasal bridge, widely spaced teeth, macroglossia, and prognathism [Wiesinger et al 2020]. In milder forms, the features can be so subtle that they may be overlooked by an inexperienced observer [C Ficicioglu & K Stepien, personal observations].

Hearing loss. Most untreated individuals have early childhood-onset non-progressive hearing loss. In many if not most individuals, the hearing loss is partly conductive and partly sensorineural [Iwanicka-Pronicka et al 2023]. Individuals typically experience early ear infections with fluid in the middle ear, probably as the result of immunodeficiency and bony abnormalities of the skull leading to closure of the eustachian tubes. If ear infections and/or effusions are untreated in early childhood, reduced hearing contributes to disturbances in speech and cognitive function.

Immunodeficiency. Individuals with untreated alpha-mannosidosis have frequent infections.

- Individuals with alpha-mannosidosis appear to have decreased ability to produce specific antibodies in response to antigen presentation compared to typical individuals [Malm et al 2000].
- Although infections generate compensatory mechanisms in leukocytes to improve phagocytosis, these mechanisms are inadequate because of disease-induced phagocyte-blocking agents in the serum or because of the lack of specific antibodies.
- Leukocytes in affected individuals have a decreased capacity for intracellular killing, which may contribute to the often serious outcome of bacterial infections.

Rheumatologic. Systemic lupus erythematosus (SLE) has been frequently observed in untreated individuals with alpha-mannosidosis.

Developmental delay (DD) and intellectual disability (ID). Most affected individuals described have been children who have not been treated with VA ERT or HSCT (see Management); therefore, information on the natural course of alpha-mannosidosis is based on a limited number of observations in untreated individuals. Of note, ERT is not thought to impact the neurocognitive findings in affected individuals. Early psychomotor development may appear normal, but intellectual disability has been reported to occur in all individuals.

- Individuals with adult onset typically have mild-to-moderate intellectual disability with an IQ of 60-80.
- The measurement of total cognitive performance is very complex, and individuals tend to score better in nonverbal tests.

- Some investigators suggest that intellectual disability progresses slowly, whereas others suggest that disease progression ceases after puberty.
- In a few individuals undergoing neurodevelopmental assessment, general intelligence, language skills, visual-spatial skills, and overall adaptive abilities appeared stable over a period of two years [Noll et al 1989].

Speech/language. Individuals are late in initiating speech (sometimes as late as the second decade) and have restricted vocabulary and difficult-to-understand pronunciation – possibly the results of congenital and/or later-onset hearing loss.

In a longitudinal study of a brother and sister over a period of 25 years, decreased speech capacity was seen in one sib but not the other [Ara et al 1999].

Motor function. Affected children learn to walk somewhat later than typical.

Follow-up observations have also suggested progressive impairment of motor function with age (see also **Other neurodevelopmental features**).

A longitudinal study of a brother and sister indicated no progression over a period of 25 years [Ara et al 1999]. However, as their basic neuropsychological impairment was described as severe, progression would be difficult to detect.

Neurologic features

- Ataxia is the most characteristic and specific motor disturbance and affected children are often noted to be "clumsy."
- Muscular hypotonia is common.
- Communicating hydrocephalus can occur at any age.
- Spastic paraplegia has also been described [Kawai et al 1985], but in general, spasticity, rigidity, and dyskinesia are not observed.

Neurobehavioral/psychiatric manifestations may affect 25% or more of persons with untreated alpha-mannosidosis. Onset is typically from late puberty to early adolescence. Episodes may be recurrent and of limited duration; medication may be necessary to alleviate symptoms. Psychosis seems to be a more common feature in adults with alpha-mannosidosis [Gutschalk et al 2004; C Ficicioglu & K Stepien, personal observations]. Secondary mitochondrial dysfunction has been proposed as a potential mechanism contributing to neuropsychiatric symptoms in people with alpha-mannosidosis [Dewsbury et al 2024].

In nine individuals with alpha-mannosidosis and psychiatric symptoms, a physical or psychological stressor preceded the rapid development of confusion, delusions, hallucinations, anxiety, and often depression, leading to severe loss of function usually lasting three to 12 weeks, and followed by a period of somnolence, asthenia, and prolonged sleep [Malm et al 2005]. In four of the nine individuals, evaluation of the psychiatric syndrome did not reveal an underlying organic cause.

Bone disease in untreated individuals ranges from asymptomatic osteopenia to focal lytic or sclerotic lesions and osteonecrosis. Clinical or radiographic evidence of mild-to-moderate dysostosis multiplex occurs in 90% of individuals diagnosed with alpha-mannosidosis; however, intrafamilial variation is considerable. Additionally, skeletal abnormalities may decrease with age.

- Genu valgum is common and contributes to the gait disturbance.
- Hip pathology includes osteoarthritis, dysplasia of the hip, subarticular cystic changes in the femoral head and acetabulum with loss of joint space, and mild flattening of the femoral head. These findings point toward degenerative disease with possible ischemic changes [C Ficicioglu & K Stepien, personal observations] and may lead to hip joint destruction if not surgically corrected [Gerards et al 2004].

- Conventional radiographs may reveal:
  - Thickened calvaria;
  - Ovoid configuration, flattening, and hook-shaped deformity of the vertebral bodies;
  - Hypoplasia of the inferior portions of the ilia;
  - Mild expansion of the short tubular bones of the hands.
- Cranial MRI, including sagittal T_1 and axial T_2 sections, may demonstrate brachycephaly, thick calvarium, and poor pneumatization of the sphenoid body [Dietemann et al 1990].

Gastrointestinal dysfunction is a common feature in individuals with alpha-mannosidosis.

- Untreated affected individuals often report increased frequency of bowel movements or diarrhea [C Ficicioglu & K Stepien, personal observations].
  - D-mannose has a laxative effect, and clinical evidence demonstrates that this significantly increases the gastrointestinal transit ratio in people with alpha-mannosidosis.
  - In one case of a 13-year-old boy, HSCT led to resolution of diarrhea and recurrent infections [Grewal et al 2004].
- Affected individuals may develop swallowing issues and experience aspiration; in some, a more permanent gastrostomy tube may be necessary.
- The liver and spleen are often enlarged, especially in more severely affected individuals who have not been treated with ERT or HSCT; however, this has no clinical significance. Liver function is typically normal, and liver biopsy reveals the same vacuoles in hepatocytes as is described in several hematologic cell lines.

Growth. Some affected individuals have growth restriction and short stature due to skeletal abnormalities. Following birth, children with alpha-mannosidosis grow slowly with no growth accceleration observed during adolescence; this may lead to a final adult height at the 3rd centile (or values below the 3rd centile) for the general population [Lipiński et al 2021]. Natural history studies by Beck et al [2013] and by Lipiński et al [2021] found the following:

- Only four out of 45 individuals with alpha-mannosidosis had a height that was two standard deviations (SD) below the mean.
- Mean height of adults with alpha-mannosidosis was 162 cm, with a SD of ±9 cm, encompassing a broad range from 145 cm to 179 cm.
- In some affected individuals, shorter length of the lower extremities was noted with normal trunk length, which could contribute to the short stature observed in adolescent individuals.
- Narrow shoulders and convex chest were characteristic of the individuals in the study populations.
- Craniometric analysis showed that head circumference did not differ from typical unaffected peers but had a tendency to be slightly shorter and broader than in the general population.

Eye findings. A review of the ophthalmic findings in 32 affected individuals reported that tapetoretinal degeneration and optic nerve atrophy may be a common feature of alpha-mannosidosis [Matlach et al 2018]. Retinal dystrophy can lead to vision loss over time [Courtney & Pennesi 2011, Sandal et al 2021].

A number of other ocular findings have also been reported in affected individuals, including hyperopia, myopia, strabismus, lenticular changes, superficial corneal opacities, and blurred discs.

Fortunately, many ophthalmologic findings can be remedied (see Management).

Neuroimaging. Alpha-mannosidosis particularly affects areas of the brain responsible for fine motor function and muscular coordination, consistent with observed neurologic findings in affected individuals. The most common neuroimaging features, especially in untreated individuals, are white matter abnormalities consistent with dysmyelination and progressive cortical and cerebellar atrophy (especially of the cerebellar vermis) [Majovska et al 2021]. Other neuroimaging findings may include thin corpus callosum, prominent Virchow-

Robin and perioptic cerebrospinal fluid spaces, a partially empty sella turcica, and abnormal T_2 intensities in the basal ganglia, thalami, dentate nuclei, or cerebellum [Malaquias et al 2022].

Cardiac complications are observed more in adults than in children. Aortic regurgitation/stenosis and mitral stenosis/regurgitation may be more common in affected individuals compared to those in the general population and can require cardiothoracic surgery [C Ficicioglu & K Stepien, personal observations]. Some affected individuals have developed dilated cardiomyopathy.

Respiratory. Regular cardiopulmonary evaluations and a careful airway evaluation prior to any surgical intervention under general anesthesia is recommended (see Management) [Hallas et al 2011; C Ficicioglu & K Stepien, personal observations].

Parenchymal lung disease was evident in three of five individuals with alpha-mannosidosis on CT [Nir et al 2020]. Pulmonary function tests were abnormal in all five affected individuals and showed obstructive/restrictive impairment with air trapping.

Prognosis. Hennermann et al [2022] reviewed cause of death and age of death in fifteen untreated individuals with alpha-mannosidosis, as reported by clinicians and patient organizations. The mean age of death was 45 years (mean: 40.3±13.2, range: 18-56, n=15), with most affected individuals being female (53%). Seven of 15 deaths (46.7%) were reported as being due to pneumonia and three (20.0%) due to cancer. Other causes of death reported included acute renal failure due to sepsis after intestinal perforation, decrease of red blood cells of unknown origin, kidney failure with systemic lupus erythematosus, aortic valve insufficiency leading to heart failure, and dehydration due to catatonia.

In a literature review, Hennermann et al [2022] identified seven additional deceased individuals. Three of seven causes of death (42.9%) reported in the literature were associated with septicaemia, two (28.6%) with respiratory failure, and one with pneumonia following aspiration.

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known.

Nomenclature

Alpha-mannosidosis may also be referred to as lysosomal alpha-d-mannosidase deficiency.

Prevalence

General estimates for the prevalence of alpha-mannosidosis vary. The most recent study estimated the prevalence to be 1:1,000,000 [Zielonka et al 2019].

- A study from Australia reported a prevalence of 1:500,000 [Meikle et al 1999].
- Studies from Norway reported six individuals in a population of 4.5 million [Malm et al 1995, Malm & Nilssen 2008].
- A prevalence of 1:300,000 was reported in the Czech Republic [Poupetová et al 2010].

The disease is not specific to individuals of any specific ancestry; individuals from all parts of the world have been described [Riise Stensland et al 2012].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *MAN2B1*.

Differential Diagnosis

Lysosomal storage disorders. The main clinical features in alpha-mannosidosis – intellectual disability, ataxia, coarse face, and dysostosis multiplex – may overlap with other lysosomal storage disorders (e.g., mucopolysaccharidosis type I and II). However, the distinctive clinical features associated with other lysosomal storage disorders, the availability of biochemical testing in clinical laboratories, and an understanding of their natural history should help in distinguishing between them.

Table 2. Genes of Interest in the Differential Diagnosis of Alpha-Mannosidosis

Gene(s)	Disorder	MOI	Key Clinical Features of Disorder	
			Overlapping w/alpha-mannosidosis	Distinguishing from alpha-mannosidosis
ABCC9 *KCNJ8*	Cantú syndrome	AD	• Coarse facial features • Thickened ribs	• Heart defects • Hypertrichosis
ARSB *ARSK* *GALNS* *GLB1* *GNS* *GUSB* *HGSNAT* *HYAL1* *IDS* *IDUA* *NAGLU* *SGSH*	Mucopolysaccharidoses (OMIM PS607014)	AR XL [1]	• Coarse facial features • Dysostosis multiplex • ID	• Short stature • Contractures
GNE	Sialuria (OMIM 269921)	AD	• Hypotonia • Coarse facial features • DD • Frequent upper respiratory infections	• Joint stiffness • Seizures • Microcytic anemia
GNPTAB	Mucolipidosis II (See *GNPTAB*-Related Disorders.)	AR	• Coarse facial features • Dysostosis multiplex	• Short stature • Failure to thrive
	Mucolipidosis IIIα/β (See *GNPTAB*-Related Disorders.)			• Short stature • Normal-to-mildly impaired cognitive development
NEU1	Sialidosis (OMIM 256550)	AR	• Coarse facial features • Dysostosis multiplex • ID	Cherry-red spot of the macula
SUMF1	Multiple sulfatase deficiency	AR	• Similar to MPS II • DD	• Poor feeding • Retinopathy

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. The mucopolysaccharidoses are inherited in an autosomal recessive manner with the exception of mucopolysaccharidosis type II, which is associated with pathogenic variants in *IDS* and inherited in an X-linked manner.

Management

No clinical practice guidelines for alpha-mannosidosis have been published.

Evaluations Following Initial Diagnosis

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

Table 3. Alpha-Mannosidosis: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measurement of weight, length/height, & head circumference	To assess for poor growth &/or macrocephaly
Hearing	Audiologic eval & assessment for middle ear effusions	Assess for both sensorineural & conductive hearing loss.
Immunologic/ Rheumatologic	Assess for signs/symptoms of frequent infections.	Consider referral to immunologist.
	Clinical & laboratory assessment for features of SLE	• To incl immunologic testing such as anti-nuclear antibodies & anti-double-stranded-DNA antibodies • Consider referral to rheumatologist.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl depression, sleep disturbances, anxiety, &/or findings suggestive of psychosis (delusions, hallucinations)
Neurologic	Neurologic eval	• Assess for asthenia [1] & signs/symptoms of communicating hydrocephalus. [2] • Consider head CT to assess size of ventricles & shape/size of cerebellum, particularly if signs/symptoms of hydrocephalus are present. • Assess for signs/symptoms of ataxia & gait abnormalities.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Muscle pain, joint aches, reduced range of motion, & bone pain • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
	Plain radiographs of head, knees (AP view), spine (lateral view), & any symptomatic sites	To assess for lytic bone lesions
	Consider DXA bone densitometry scan to assess for osteopenia or osteoporosis.	In older children, adolescents, & adults
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in persons w/ dysphagia &/or aspiration risk.
	Assess for evidence of diarrhea & for enlarged liver &/or spleen via physical exam & imaging	• Ultrasound is often done, although abdominal MRI may be more informative to calculate organ volumes. • Although organomegaly typically does not cause clinical symptoms, this finding can be used as a clinical marker to assess treatment response.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic eval	To assess for reduced vision, best corrected visual acuity, refractive errors, strabismus, & more complex findings (e.g., corneal opacities, retinal dystrophy) that may require referral for subspecialty care &/or low vision services
Cardiovascular	Auscultation w/consideration of echocardiogram	• To assess for aortic or mitral stenosis/regurgitation &/or cardiomyopathy • Consider referral to cardiologist.
Respiratory	Baseline pulmonary function tests in those older than age 6 yrs	Consider referral to pulmonologist.
Genetic counseling	By genetics professionals [3]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of alpha-mannosidosis 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: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

Based on Ficicioglu et al [2024]
ADL = activities of daily living; DXA = dual-energy x-ray absorptiometry; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; SLE = systemic lupus erythematosus
1. Such as change in social, domestic, or school- or work-related activities or in ability to walk distances
2. Including headache, increasing gait ataxia, nausea, and/or papilledema
3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for alpha-mannosidosis.

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

Velmanase alfa (Lamzede®) enzyme replacement therapy (ERT) has been approved by the FDA for the treatment of the non-central nervous system features of alpha-mannosidosis.

Table 4. Alpha-Mannosidosis: Targeted Treatment

Targeted Treatment	Dosage	Consideration
Velmanase alfa (Lamzede®) ERT	1 mg/kg IV infusion once a week [1]	• Improvement in both biochemical & functional parameters have been reported. [2] • Velmanase alfa has been very well tolerated & is now regarded as standard treatment for alpha-mannosidosis.

ERT = enzyme replacement therapy
1. For individuals who weigh less than 49 kg, IV infusion is typically given over a minimum of 60 minutes; for those who weigh 50 kg or more, infusion rate is typically 25 mL/hour.
2. Borgwardt et al [2018], Lund et al [2018]

Hematopoietic stem cell transplantation (HSCT) has been offered as a treatment for severe alpha-mannosidosis. While HSCT carries risks, the data suggests it is a feasible therapeutic option for alpha-mannosidosis, with better outcomes achieved by performing it early before complications arise, balancing the risks and benefits.

The key points are:

- In a study by Mynarek et al [2012] involving 17 affected individuals who underwent HSCT for alpha-mannosidosis, the overall survival rate was 88% with a median follow up of 5.5 years. This survival rate is comparable to HSCT for other non-malignant diseases.
- Two affected individuals died within five months post-HSCT, likely due to transplant-related complications [Mynarek et al 2012]. However, the remaining 15 affected individuals achieved stable engraftment.
- While normal development was not achieved, affected individuals showed developmental progress after HSCT, with some improvements in hearing ability [Mynarek et al 2012].
- The benefits of HSCT are greater in younger individuals before the disease has significantly progressed, as transplant-related risks increase with age [Malm & Nilssen 2008]. Early identification of affected individuals is therefore crucial.
- HSCT can halt the progressive cognitive decline in individuals with alpha-mannosidosis when performed early, though the outcomes have been variable.

Note: Most affected individuals are clinically normal at birth. Since alpha-mannosidosis can be treated with ERT or HSCT, there is a pressing need for newborn screening to identify affected individuals early, before the onset of severe irreversible pathology [Meikle et al 2006].

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. Alpha-Mannosidosis: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Sensorineural hearing loss	Hearing aids may be helpfulas per otolaryngologist/audiologist.	Community hearing services through early intervention or school district
Conductive hearing loss	Consider insertion of pressure-equalizing tubes. [1]	
Immunodeficiency / Recurrent infections	Standard treatment per immunologist	• Early antibiotics for bacterial infections • Bacterial & viral infections must be treated w/ vigilance.
Systemic lupus erythematosus	Standard treatment per rheumatologist	
Communicating hydrocephalus	Standard treatment per neurosurgeon	• This typically includes consideration of a ventriculocaval shunt. [1] • Ventriculoperitoneal shunts may cause ascites because of reduced absorptive capacity of peritoneal cavity. [2] Therefore, ventriculocaval shunts are preferred.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Ataxia / Gait abnormalities	Orthopedics / physical medicine & rehab / PT & OT	• Hydrotherapy helps to avoid strain on joints. • Special shoes may help w/ankle & foot support. • Consider need for mobility devices (incl wheelchair, if needed) & disability parking placard.
Osteoporosis/ Osteopenia	Consider palmidronate (Aredia®) monthly or zoledronic acid (Aclasta®) once a year.	
Arthropathy	Standard treatment per orthopedist.	May include need for surgical intervention [1]
Poor weight gain / Growth issues	• Standard treatment per gastroenterologist &/or endocrinologist • Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Hepatosplenomegaly	May improve or resolve w/targeted therapy (See Table 4.)	
Eye/vision issues	Standard treatment per ophthalmologist	For refractive errors, strabismus
	Ophthalmic subspecialist	• Although lens replacement for cataract is a standard procedure, corneal transplantation can be difficult in persons w/alpha-mannosidosis. [1] • Postoperative complications incl astigmatism (which may be correctable w/repeat surgery, laser treatment, or optical devices). • More complex findings (e.g., retinal dystrophy) may require further input from subspecialists.
	Low vision services	• Children: through early intervention programs &/or school district • Adults: low vision clinic &/or community vision services / OT / mobility services
Cardiac valve dysfunction / Cardiomyopathy	Standard treatment per cardiology/ cardiothoracic team [1]	
Respiratory dysfunction / Recurrent chest infections	Standard treatment per pulmonologist [1]	
Family/Community	• Ensure appropriate social work involvement to connect families w/ local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

OT = occupational therapy; PT = physical therapy

1. Regular cardiopulmonary evaluations and a careful airway evaluation prior to any surgical intervention under general anesthesia is recommended.

2. Authors, personal observations

Developmental Delay / Intellectual Disability / Neurobehavioral Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).

- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For affected individuals on ERT, a Bruininks-Oseretsky test can be used to assess motor proficiency in children and young adults [Phillips et al 2020].

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric Concerns

Consultation with a developmental pediatrician may be helpful in guiding parents/caregivers through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about confusion, delusions, hallucinations, anxiety, and depression can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. Alpha-Mannosidosis: Recommended Surveillance [1]

System/Concern	Evaluation	Frequency
Constitutional / Poor growth	Measurement of weight, length/height, head circumference, & BMI; [2] monitoring of growth pattern	At each visit
	Consider endocrinology evals, incl hormonal & lipid profiles	Regular intervals based on clinical features

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Neurodevelopment	Monitor developmental progress & educational needs. [3]	At each visit
Neurobehavioral/ Psychiatric	Assessment for depression, sleep disturbances, anxiety, &/or findings suggestive of psychosis (delusions, hallucinations)	
Neurologic	• Assess for new manifestations such ataxia & gait abnormalities. • Evaluate for asthenia [4] & signs/symptoms of communicating hydrocephalus. [5]	
Musculoskeletal	Assessment for muscle pain, joint aches, reduced range of motion, & bone pain [6]	
	PT assessment of fine motor function, gross motor function, endurance (e.g., via the 6MWT, the 3MSCT, or the 9-hole peg test), ataxia (e.g., via the SARA), & muscle strength & tone	• Every 6-12 mos in childhood • Annually in adults
	• Consider DXA bone densitometry scan [7] to assess for osteopenia/osteoporosis. • Radiographs of hips/spine may be indicated.	Every 2-5 yrs in children, adolescents, & adults
Gastrointestinal	• Monitoring for diarrhea • Assessment of liver & spleen size through physical exam	At each visit
	Consider assessment of liver & spleen size through ultrasound or MRI imaging.	As clinically indicated or as a clinical marker to assess treatment response
	Routine biochemical lab assessment incl liver & kidney health, blood glucose levels, fluid & electrolyte balance, & complete blood count (w/platelets)	Annually
Eyes	Ophthalmology eval	Annually, or more frequently as clinically indicated
Hearing	Audiology eval	Every 1-2 yrs, or as clinically indicated in those w/hearing aids
Immunologic/ Rheumatologic	Assessment for number & type of infections	At each visit
	Consider assessment of immunlobulin levels, ESR, & C-reactive protein.	Annually
Cardiovascular	Consider electrocardiogram, 24-hour electrocardiogram, & echocardiogram.	At regular intervals
Respiratory	Pulmonory function tests	Annually
	Consider sleep study.	As clinically indicated
For those on ERT	Plasma oligosaccharides	As clinically indicated to assess treatment response to ERT
Post-HSCT eval	Standard surveillance, which may incl ongoing assessment for chimerism & enzyme activity if indicated	Per hematologist/oncologist

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

3MSCT = three-minute stair climb test; 6MWT = six-minute walk test; BMI = body mass index; DXA = dual-energy x-ray absorptiometry; ERT = enzyme replacement therapy; ESR = erythrocyte sedimentation rate; HSCT = hematopoietic stem cell transplant; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia

1. It is unclear how many of the medical complications will improve or resolve with targeted ERT/HSCT.

2. In those over age two years; in those younger than age two years, assessment of weight for length may be more appropriate.

3. For affected individuals on ERT, a Bruininks-Oseretsky test can be used to assess motor proficiency in children and young adults [Phillips et al 2020].

4. Such as change in social, domestic, or school- or work-related activities or in ability to walk distances

5. Including headache, increasing gait ataxia, nausea, and/or papilledema

6. Consider plain radiographs of the head, knees (AP view), spine (lateral view), and any symptomatic sites.

7. Typically done after age four years

Evaluation of Relatives at Risk

Testing of all at-risk sibs of any age (including prenatal diagnosis) is warranted to allow for early diagnosis and targeted treatment of alpha-mannosidosis (see Table 4). Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Assay of acid alpha-mannosidase enzyme activity in leukocytes or other nucleated cells if the pathogenic variants in the family are not known.

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

Therapies Under Investigation

Gene therapy is also being studied as a possible therapy for some lysosomal storage disorders. Given the permanent transfer of the normal gene, which can produce active enzyme, this form of therapy is theoretically most likely to lead to a cure. However, at this time, there are many technical difficulties to resolve before gene therapy can succeed.

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. Note: There may not be clinical trials for this disorder.

Other

Because of the limited number of affected individuals with psychiatric symptoms, no conclusion about the benefit of various psychotropic drugs can be made at this time. However, to date, 5-15 mg of olanzapine at bedtime has been used in several affected individuals with some success [D Malm, personal observations].

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

Alpha-mannosidosis is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *MAN2B1* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *MAN2B1* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *MAN2B1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Affected sibs (with identical pathogenic variants) may present with different phenotypes [Riise Stensland et al 2012, Govender & Mubaiwa 2014].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has alpha-mannosidosis or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *MAN2B1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *MAN2B1* pathogenic variant.

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *MAN2B1* pathogenic variants in the family.

Biochemical testing. Measurement of acid alpha-mannosidase enzyme activity is not a reliable method of carrier determination because acid alpha-mannosidase enzyme activity values in carriers and non-carriers sometimes overlap.

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.
- It is appropriate to offer molecular genetic testing of *MAN2B1* to the reproductive partner of a person with alpha-mannosidosis.

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 both *MAN2B1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Biochemical testing, by analysis of acid alpha-mannosidase enzymatic activity in fetal cells, is an option if the familial *MAN2B1* pathogenic variants are not known.

Note: Given the wide variability in phenotype and lack of genotype-phenotype correlation, severity of disease cannot be predicted based on the results of molecular genetic or biochemical testing.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most centers would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

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.

- **International Advocate for Glycoprotein Storage Diseases (ISMRD)**
  Email: info@ismrd.org
  www.ismrd.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **National MPS Society**
  Phone: 877-MPS-1001
  mpssociety.org

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. Alpha-Mannosidosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

MAN2B1	19p13.13	Lysosomal alpha-mannosidase	MAN2B1 database	MAN2B1	MAN2B1

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 Alpha-Mannosidosis (View All in OMIM)

248500	MANNOSIDOSIS, ALPHA B, LYSOSOMAL; MANSA
609458	MANNOSIDASE, ALPHA, CLASS 2B, MEMBER 1; MAN2B1

Molecular Pathogenesis

Alpha-mannosidosis belongs to a group of disorders called glycoproteinoses, which are caused by lack of one of the many enzymes required for the sequential degradation of asparagine-linked oligosaccharides from glycoproteins in the lysosomes. During normal turnover and catabolism, glycoproteins are digested by proteinases and glycosidases within the lysosomes. These enzymes degrade glycoproteins into fragments small enough to be excreted or transported to the cytosol for reuse. Lack of any one of these enzymes, including alpha-mannosidase, will compromise the degradation pathway as a whole, resulting in accumulation of oligosaccharides or glycopeptides in the lysosomes. Accumulation of storage material is thought to impair lysosomal function and thereby harm cellular functions such as vesicle maturation, endocytosis, exocytosis, and calcium homeostasis [Schultz et al 2011]. However, the pathophysiology of lysosomal storage disorders is complex, and accumulation of storage material alone cannot fully explain disease mechanisms.

Mechanism of disease causation. Loss of function. The Alpha-Mannosidosis Mutation Database compiles genotypes, clinical phenotypes, demography, and biochemical and structural data of mutated *MAN2B1* in alpha-mannosidosis [Riise Stensland et al 2015].

Table 7. *MAN2B1* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_000528.3 NP_000519.2	c.2248C>T	p.Arg750Trp	Founder variant accounting for 27% of pathogenic alleles in European population [1]

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. Riise Stensland et al [2012], Riise Stensland et al [2015]

Chapter Notes

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