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NLM Citation: Malm D, Nilssen Ø. Alpha-Mannosidosis. 2001 Oct 11 [Updated 2019 Jul 18]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Alpha-Mannosidosis

Synonym: α-Mannosidosis

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Created: October 11, 2001; Revised: July 18, 2019.

Summary

Clinical characteristics

Alpha-mannosidosis encompasses a continuum of clinical findings from mild to severe. Three major clinical subtypes have been suggested:

- A mild form recognized after age ten years with absence of skeletal abnormalities, myopathy, and slow progression (type 1)
- A moderate form recognized before age ten years with presence of skeletal abnormalities, myopathy, and slow progression (type 2)
- A severe form manifested as prenatal loss or early death from progressive central nervous system involvement or infection (type 3)

Individuals with a milder phenotype have mild-to-moderate intellectual disability, impaired hearing, characteristic coarse features, clinical or radiographic skeletal abnormalities, immunodeficiency, and primary central nervous system disease – mainly cerebellar involvement causing ataxia. Periods of psychiatric symptoms are common. Associated medical problems can include corneal opacities, hepatosplenomegaly, aseptic destructive arthritis, and metabolic myopathy. Alpha-mannosidosis is insidiously progressive; some individuals may live into the sixth decade.

Diagnosis/testing

The diagnosis of alpha-mannosidosis is established in a proband by identification of deficient acid alpha-mannosidase enzyme activity in peripheral blood leukocytes or other nucleated cells such as fibroblasts. Identification of biallelic pathogenic variants in *MAN2B1* by molecular genetic testing can confirm the diagnosis and allow for family studies.

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Management

Treatment of manifestations: The enzyme replacement therapy velmanase alfa has been approved in some European countries for treatment of alpha-mannosidosis. Treatments aimed at preventing complications and optimizing quality of life also include early use of antibiotics for bacterial infections, hearing aids for hearing loss, insertion of pressure-equalizing tubes if fluid accumulates in the middle ear, glasses to correct refractive error, physiotherapy, use of a wheelchair, orthopedic intervention, and shunting as needed for hydrocephalus. Educational considerations include use of sign language for individuals with hearing loss, early educational intervention for development of social skills, speech therapy, and special education to maximize learning.

Prevention of secondary complications: Prophylactic vaccinations because of immunodeficiency.

Surveillance: Annual or semiannual medical history and physical examination and specific otolaryngology, audiometry, ophthalmologic, neuropsychological, and skeletal examinations, along with blood tests and CT scans of the brain.

Evaluation of relatives at risk: Test at-risk newborn sibs to permit early intervention for affected children.

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.

Diagnosis

Suggestive Findings

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

Clinical features

- Facial features (e.g., coarse facial features, macrocephaly, prominent forehead, highly arched brows, depressed nasal bridge, widely spaced teeth, macroglossia, prognathism)
- Skeletal abnormalities (e.g., dysostosis multiplex, focal lytic or sclerotic lesions, osteonecrosis, osteopenia)
- Hearing loss, mixed
- Frequent infections
- Developmental delay
- Intellectual disability
- Ataxia

Laboratory features. Elevated urinary excretion of mannose-rich oligosaccharides can be demonstrated by thin-layer chromatography [Humble & Collart 1975] or capillary high-performance anion exchange chromatography [Bruggink et al 2012].

Histopathology. Light microscopy demonstrates vacuoles in lymphocytes from peripheral blood in 90% of affected individuals.

Establishing the Diagnosis

The diagnosis of alpha-mannosidosis **can be established** in a proband by identification of deficiency of lysosomal enzyme acid alpha-mannosidase (MAN2B1) in leukocytes or other nucleated cells. In affected individuals, alpha-mannosidase enzyme activity in peripheral blood leukocytes is 5%-10% of normal activity. Note: This "residual" enzyme activity appears to represent mannosidase from other organelles or compartments (e.g., Golgi apparatus or cytosol) since they show some activity also at low pH.

Molecular genetic testing. Identification of biallelic pathogenic variants in *MAN2B1* by molecular genetic testing can establish the diagnosis (see Table 1). Approaches can include **single-gene testing***, use of a **multigene panel,** and **comprehensive genomic testing**.

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

- **Single-gene testing.** Sequence analysis of *MAN2B1* is then performed, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- **A 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.
- **Comprehensive genomic testing.** When the diagnosis of alpha-mannosidosis is not considered because an individual has atypical phenotypic features, comprehensive genomic testing (which does not require the clinician to determine which gene[s] are likely involved) is the best option. Exome sequencing is the most commonly used genomic testing method; 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] Detectable 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 allelic 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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; 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]. 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.** With obvious progression leading to early death from primary central nervous system involvement or infection (type 3)

Motor function. Affected children learn to walk somewhat later than normal. They are generally clumsy; ataxia is the most characteristic and specific motor disturbance. In addition to joint abnormalities and a metabolic myopathy [Alroy et al 1984], the disease particularly affects those areas of the brain responsible for fine motor function and muscular coordination. Muscular hypotonia is common. Spastic paraplegia has also been described [Kawai et al 1985], but in general, spasticity, rigidity, and dyskinesia are not observed. Follow-up observations have also suggested progressive impairment of motor function with age [Autio et al 1982]. A longitudinal clinical study on 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.

Intellectual disability. Early psychomotor development may appear normal, but intellectual disability occurs in all individuals. Individuals with adult-onset disease are usually mildly or moderately intellectually disabled with an IQ of 60-80 [Aylsworth et al 1976, Bach et al 1978]. The measurement of total mental performance is very complex, and individuals tend to score better in nonverbal tests. 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.

Most affected individuals described have been children; therefore, information on the natural course of alpha-mannosidosis is based on a limited number of observations. Some investigators suggest that intellectual disability progresses slowly [Autio et al 1982]; others suggest that disease progression ceases after puberty [Yunis et al 1976]. 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]. 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].

Psychiatric symptoms distinct from the intellectual disability may affect 25% or more of persons with 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.

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.

Neuroimaging. Brain MRI including sagittal T_1 and axial T_2 sections reveals a partially empty sella turcica, cerebellar atrophy, and white matter signal modifications. Progressive cortico-subcortical atrophy, especially in the cerebellar vermis, has been described [Ara et al 1999]. High signal abnormalities involving the parieto-occipital white matter are identified on axial T_2-weighted scans in some individuals and are probably related to demyelination and associated gliosis as described by Dietemann et al [1990].

Hearing loss. Most individuals appear to have early-childhood-onset non-progressive hearing loss. In many if not most individuals, the hearing loss is partly conductive and partly sensorineural [Autio et al 1982]. Individuals typically experience early ear infections with fluid in the middle ear, probably the result of immunodeficiency and bony abnormalities of the skull leading to closure of the eustachian tubes. If untreated in early childhood, reduced hearing contributes to disturbances in speech and mental function.

Facial features. Independent of family and ethnicity, 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. The features can also be so subtle that they may be overlooked by an inexperienced observer.

Bone disease 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 [Chester et al 1982]; intrafamilial variation is considerable. Conventional radiographs (x-rays) may reveal thickened calvaria; ovoid configuration, flattening, and hook-shaped deformity of the vertebral bodies; hypoplasia of the inferior portions of the ilia; and mild expansion of the short tubular bones of the hands.

Knock-knee is common and contributes to the gait disturbance.

The skeletal abnormalities may decrease with age [Spranger et al 1976].

Cranial MRI, including sagittal T_1 and axial T_2 sections, demonstrates several skeletal abnormalities including brachycephaly, thick calvarium, and poor pneumatization of the sphenoid body [Dietemann et al 1990].

Immunodeficiency. Individuals with alpha-mannosidosis have frequent infections. Malm et al [2000] compared humoral and cellular immunocompetence in six affected individuals to that of six healthy controls. They determined that individuals with alpha-mannosidosis appear to have decreased ability to produce specific antibodies in response to antigen presentation. 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. In addition, leukocytes have a decreased capacity for intracellular killing, which may contribute to the often serious outcome of bacterial infections.

Hepatosplenomegaly. The liver and spleen are often enlarged, especially in more severely affected individuals; however, this has no clinical significance. Liver function is normal. Liver biopsy reveals the same vacuoles in hepatocytes as described in several hematologic cell lines.

Ocular features. Hyperopia, myopia, or slight strabismus is common. Lenticular changes, superficial corneal opacities [Bach et al 1978], and blurred discs [Kjellman et al 1969] have been reported. Most of these ophthalmologic findings can be remedied (see Management).

Other

- Communicating hydrocephalus can occur at any age [Halperin et al 1984].
- Cardiac and renal complications are rarely observed; however, aortic regurgitation may be more common in individuals with alpha-mannosidosis.
- Systemic lupus erythematosus has been frequently observed in individuals with alpha-mannosidosis.

Natural course of the disease. 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.

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 [Kawai et al 1985, unpublished personal data].

Pathophysiology. 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 or deficiency of a hydrolase, such as lysosomal alpha-mannosidase, results in the multisystemic accumulation of undigested oligosaccharides in the lysosomes. However, the pathophysiology of lysosomal storage disorders is complex, and accumulation of storage material alone cannot fully explain disease mechanisms.

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known.

Nomenclature

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

Prevalence

Little is known about the prevalence of alpha-mannosidosis. A study from Australia reported a prevalence of one in 500,000 [Meikle et al 1999]. A study from Norway reported six individuals in a population of 4.5 million [Malm et al 1995], and a prevalence of one in 300,000 was reported in the Czech Republic [Poupetová et al 2010].

The disease is not specific to any ethnic group; 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 pathogenic variants in *MAN2B1*.

Differential Diagnosis

Lysosomal storage disease. The main clinical features in alpha-mannosidosis – intellectual disability, ataxia, coarse face, and dysostosis multiplex – may show overlap with other lysosomal storage diseases (e.g., mucopolysaccharidosis type 1). However, the distinctive clinical features associated with these other lysosomal storage diseases, the availability of biochemical testing in clinical laboratories, and an understanding of their natural history should help in distinguishing between them.

Table 2. Disorders to Consider in the Differential Diagnosis of Alpha-Mannosidosis

Disorder	Gene(s)	MOI	Clinical & Laboratory Features of Disorder	
			Overlapping w/α-mannosidosis	Distinguishing from α-mannosidosis
Mucopolysaccharidoses (See MPS I.)	Many	AR XL	Coarse facial features, dysostosis multiplex, ID	Short stature, contractures
Sialidosis (OMIM 256550)	*NEU1*	AR	Coarse facial features, dysostosis multiplex, ID	Cherry red spot of the macula
Mucolipidosis II (See *GNPTAB*-Related Disorders.)	*GNPTAB*	AR	Coarse facial features, dysostosis multiplex	Short stature, failure to thrive
Mucolipidosis III alpha/beta (See *GNPTAB*-Related Disorders.)	*GNPTAB*	AR	Coarse facial features, dysostosis multiplex	Short stature, normal-to-mildly impaired cognitive development
Cantú syndrome	*ABCC9* *KCNJ8*	AD	Coarse facial features, thickened ribs	Heart defects, hypertrichosis
Sialuria (OMIM 269921)	*GNE*	AD	Hypotonia, coarse facial features, DD, frequent upper-respiratory infections	Joint stiffness, seizures, microcytic anemia

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

Management

Evaluations Following Initial Diagnosis

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

- **Medical history** including evidence of hearing loss, irritability, depression; change in social, domestic, school- or work-related activities or in ability to walk distances; diarrhea or incontinence, muscle pain, joint aches, reduced range of movement, and bone pain
- **Physical examination** including otoscopy, ophthalmoscopy, assessment of liver and spleen size, auscultation of heart and lungs, neurologic status including gait, and orthopedic evaluation including joint range of motion. In children, attention to growth (plot height, weight, and especially head circumference using standardized growth charts)
- **Examination by an otolaryngologist** to detect impaired hearing and middle-ear infections

- **Audiometry.** If intellectual disability or young age makes cooperation difficult, brain stem evoked response testing
- **Ophthalmologic examination** to evaluate for corneal opacities, myopia, hyperopia, and strabismus
- **Neuropsychological testing** to establish functional level and learning capacity
- **Blood tests.** Clinical examination and immunologic tests (e.g., antinuclear antibodies, anti-ds-DNA antibodies) to exclude systemic lupus erythematosus (SLE)
- **Skeletal assessment.** Plain radiographs of the head, knees (anterior-posterior view), spine (lateral view), and any symptomatic sites
- **Bone densitometry** to detect osteopenia or osteoporosis in older individuals
- **CT scan of the brain** to evaluate the size of the ventricles and shape and size of the cerebellum, particularly if signs and symptoms of hydrocephalus are present (e.g., headache, increasing gait ataxia, nausea, papilledema)
- **Consultation** with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Enzyme replacement therapy (ERT). Velmanase alfa has been developed as a treatment for alpha-mannosidosis. Improvement in both biochemical and functional parameters have been reported [Borgwardt et al 2018, Lund et al 2018]. ERT with velmanase alfa was approved by the European Medical Agency in July 2018. Velmanase alfa has been very well tolerated and is now regarded as a standard treatment for alpha-mannosidosis.

Note: ERT has been studied extensively as a treatment for alpha-mannosidosis. The effects of ERT in knockout mice could be seen in both thin layer chromatography and histology. At lower doses, the clearing of oligosaccharides in spleen and kidney tissue was obvious, but not in brain. However, with increased enzyme doses there was also an effect both in the peripheral and central nervous system. In addition to reduced brain pathology, the mice showed reduced ataxia on treadmill testing. Although only a stabilization of findings was expected, a significant improvement both on pathologic and clinical parameters was observed in the animals [Damme et al 2015, Stroobants et al 2017].

Some affected individuals, including those who have had bone marrow transplantation (BMT), may require symptomatic treatment. The overall aim is to prevent complications and to optimize quality of life.

Medical measures

- **Early use of antibiotics** for bacterial infections. A clinical consequence of the immunodeficiency is that bacterial and viral infections must be treated with vigilance.
- **Hearing aids** as early as possible for individuals with sensorineural hearing loss to improve hearing and enhance speech development and social functioning
- **Insertion of PE (pressure-equalizing) tubes** to reduce the conductive/mechanical component of hearing loss from fluid in the middle ear
- **Glasses (spectacles)** to correct refractive error to improve vision. Although lens replacement for cataract is a standard procedure in alpha-mannosidosis, corneal transplantation can be difficult; postoperative complications include astigmatism (which may be correctable with repeat surgery, laser treatment, or optical devices).
- **Physiotherapy** including hydrotherapy to avoid strain on the joints
- Use of a wheelchair if necessary

- **Treatment of osteoporosis or osteopenia** identified on bone densitometry with palmidronate (Aredia®) monthly or zoledronic acid (Aclasta®) once a year
- **Orthopedic intervention** if necessary. Special shoes may help with ankle and foot support.
- **Ventriculocaval shunt** for communicating hydrocephalus

  Note: Ventriculoperitoneal shunts may cause ascites because of the reduced absorptive capacity of the peritoneal cavity [Malm, personal communication]. Therefore, ventriculocaval shunts are preferred.

Educational opportunities / social considerations

- **Use of sign language** in individuals with significant hearing loss
- **Early educational intervention** for development of social skills
- **Speech therapy** to improve speech
- **Special education** to maximize learning
- **Planning housing** for possible future wheelchair use

Prevention of Primary Manifestations

Most affected individuals are clinically normal at birth. Since alpha-mannosidosis can be treated with BMT, and possibly also by ERT in the future, there is a pressing need for newborn screening to identify affected individuals early, before the onset of severe irreversible pathology [Meikle et al 2006].

Prevention of Secondary Complications

Because of immunodeficiency, affected individuals should be included in prophylactic vaccination programs.

The tendency to develop caries as a result of poor tooth quality can be reversed or delayed by good tooth hygiene or dental support [Malm, personal observation].

Regular physiotherapy to increase muscle strength may help compensate for the slowly progressive ataxia [Malm, personal observation].

Surveillance

Suggested serial monitoring to evaluate severity and rate of disease progression:

- **Medical history** (annually) including number and type of infections, hearing, weight, development, irritability, depression, change in social, domestic, school- or work-related activities, ability to walk distances, diarrhea, muscle pain, joint aches or reduced range of movement, and bone pain
- **Physical examination** (annually) including otoscopy, ophthalmoscopy, heart and lungs, joint range of motion, gait, neurologic status, and orthopedic evaluation. In children, attention to growth (height, weight, and especially head circumference using standardized growth charts)
- **Examination by an otolaryngologist** to detect impaired hearing and middle-ear infections
- **Audiometry.** If intellectual disability makes cooperation difficult, brain stem evoked response testing
- **Ophthalmologic examination** to detect corneal opacities, myopia, hyperopia, and strabismus
- **Neuropsychological testing** to establish functional level and learning capacities
- **Blood tests.** PLOT and C-reactive protein in case of inflammation, serum concentrations of alanine aminotransferase for evaluation of concomitant liver disease, and creatinine for assessment of renal function. Immunologic status, focusing on SLE, is recommended.
- **Skeletal assessment.** Plain radiographs of the head, knees (anterior-posterior view), spine (lateral view), and any symptomatic sites
- **Bone densitometry** every two to five years to assess osteopenia

Evaluation of Relatives at Risk

At-risk sibs should be tested either prenatally or in the newborn period as they will benefit from early intervention (see Treatment of Manifestations).

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

Bone marrow transplantation (BMT) has been tried as a treatment for alpha-mannosidosis. Early diagnosis and prompt treatment with BMT increases the chances of preventing cognitive decline and improving symptoms. However, more research is necessary to determine the long-term safety and efficacy of this potential therapy. BMT is not without drawbacks. The procedure carries the risk of serious complications including graft-versus-host disease (GVHD) and other long-term and late effects as described by Mynarek et al [2012]. Two of 17 individuals died of procedure-related causes, two developed severe GVHD, and six developed chronic GVHD. After BMT, affected individuals made developmental progress, although normal development was not achieved. The perfect donor is familial HLA-identical, but often this type of donor cannot be identified, in which case enzyme replacement therapy (ERT) will be the best option.

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, olanzapine 5-15 mg at bedtime, has been used in several affected individuals with some success [Malm, unpublished 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 a proband are obligate heterozygotes (i.e., carriers of one *MAN2B1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- 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.
- 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 individual with alpha-mannosidosis has children with an affected individual or a carrier, his/her 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 testing

- Carrier testing is most informative if the pathogenic variants have been identified in the family.
- It is appropriate to offer molecular genetic testing of *MAN2B1* to the reproductive partner of a person with alpha-mannosidosis.

Biochemical testing. When molecular genetic testing is unavailable or has been uninformative, some laboratories may offer carrier testing by enzyme analysis. Note, however, that acid alpha-mannosidase activity is usually 40%-60% of normal in carriers, and thus 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, clarification of carrier status, 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).

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once both *MAN2B1* pathogenic variants have been identified in an affected family member, molecular genetic prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Biochemical testing, by analysis of acid alpha-mannosidase enzymatic activity in fetal cells, is an option if genetic data are not available.

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.

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
  www.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
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

Introduction

- Alpha-mannosidosis belongs to a group of disorders called glycoproteinoses.
- They are caused by lack of one of the many enzymes required for the sequential degradation of asparagine-linked oligosaccharides from glycoproteins in the lysosomes.
- 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].

Mechanism of disease causation. All known *MAN2B1* pathogenic variants are predicted to result in loss of alpha-mannosidase 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 3. Notable *MAN2B1* Pathogenic Variants

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 the 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

Author Notes

Dr Malm was the initiator of the "Tromsø Mannosidosis Group" in 1991. He is a member of the professional advisory board of ISMRD and the father of two children with alpha-mannosidosis.

Acknowledgments

The authors would like to thank former ISMRD president John Forman (Hutt City, New Zealand) for valuable comments on the original manuscript.

Revision History

- 18 July 2019 (aa) Revision: velmanase alfa included in Summary
- 21 February 2019 (sw) Comprehensive update posted live
- 3 May 2012 (me) Comprehensive update posted live
- 26 August 2008 (cg) Comprehensive update posted live
- 25 January 2006 (me) Comprehensive update posted live
- 3 December 2003 (me) Comprehensive update posted live
- 11 October 2001 (me) Review posted live
- April 2001 (dm) Original submission

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