Understanding alpha-mannosidosis

A guide for parents and caregivers

Saffron
living with alpha-mannosidosis

Emma
living with alpha-mannosidosis

Marc
living with alpha-mannosidosis

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MPS Society

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Who is this booklet for?

This booklet has been developed to support you if you have alpha-mannosidosis yourself, or if you care for a child or adult with alpha-mannosidosis. It aims to answer some of the questions you might have and to provide information about the disease.

We have also included some useful websites if you would like to find out more or need extra support.

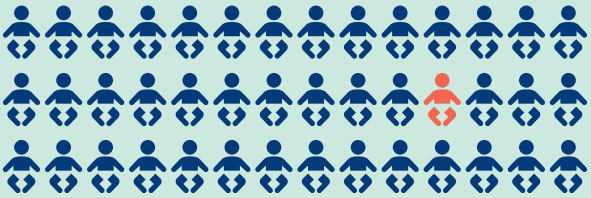
What is alpha-mannosidosis?[1-3]

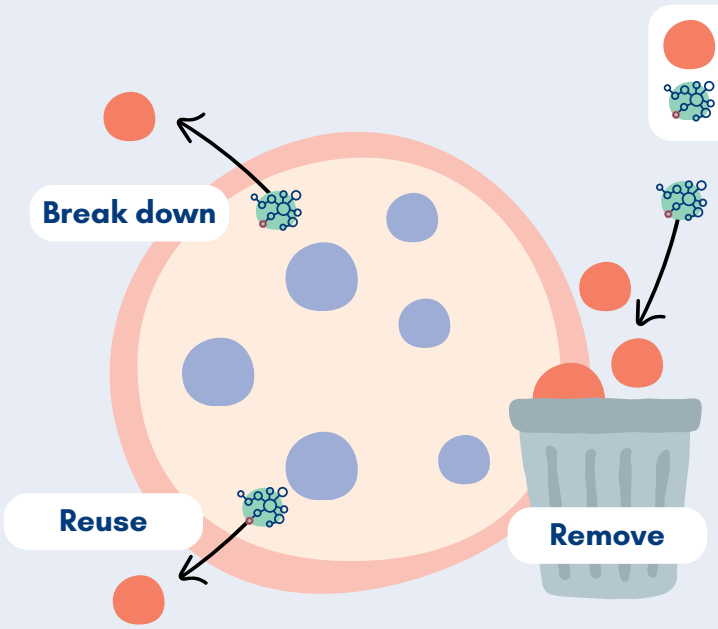
Alpha-mannosidosis is a very rare condition that people are born with and inherit from their parents. It affects many parts of the body and gets worse over time. Most children appear healthy when they are born, but as they grow, symptoms become more noticeable.

Alpha-mannosidosis is one of a group of conditions called **lysosomal storage disorders**. These affect how the body cleans up waste products inside cells.

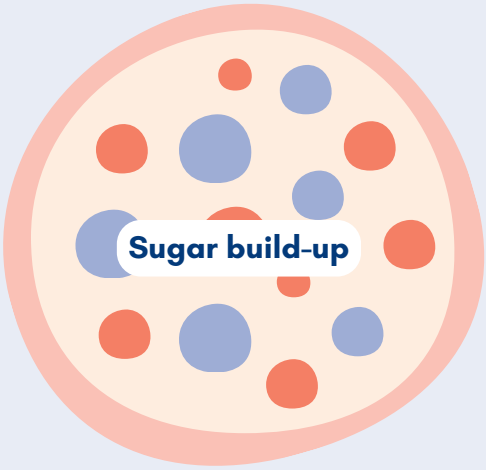
How rare is alpha-mannosidosis?[1]

Only one baby in every million is born with alpha-mannosidosis.





Healthy cell



Lysosomal storage disorder cell

Inside each of our cells are very small structures called **lysosomes**, which act like the recycling centre for waste that is no longer needed in the cell. Lysosomes contain special waste-cleaning proteins called **enzymes**, which break down this waste into smaller pieces that the body can reuse or remove.

In people with alpha-mannosidosis, an important waste-cleaning enzyme called **alpha-mannosidase** is either missing or does not work properly. This means that the body cannot fully break down certain waste sugars (called oligosaccharides). Over time, these sugars build up in cells and cause damage to tissues and organs across the body, leading to the range of symptoms seen in alpha-mannosidosis.

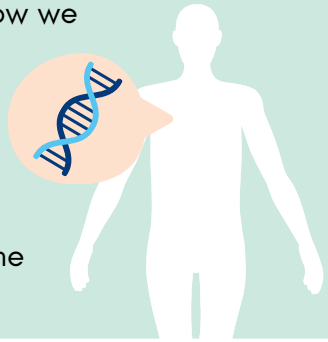
What causes alpha-mannosidosis?[1]

Alpha-mannosidosis is a genetic condition, which means that it is caused by a change in a gene. This gene change is called a **pathogenic variant**.

What are genes?

Genes are a set of instructions inside every cell in our body that help guide how we look, grow, develop and function. These instructions tell our body how to build important things like enzymes, which help our cells work properly. Sometimes, a change (**pathogenic variant**) can happen in a gene. This can affect how the body works and may cause certain conditions or diseases.

We have two copies of each gene, one that we inherit from our mother and one from our father.



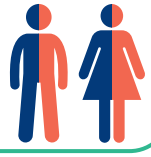
What gene causes alpha-mannosidosis?[1-3]

Alpha-mannosidosis is caused by a **pathogenic variant** in a specific gene called ***MAN2B1***. This gene gives the body instructions on how to make the waste-cleaning enzyme alpha-mannosidase.

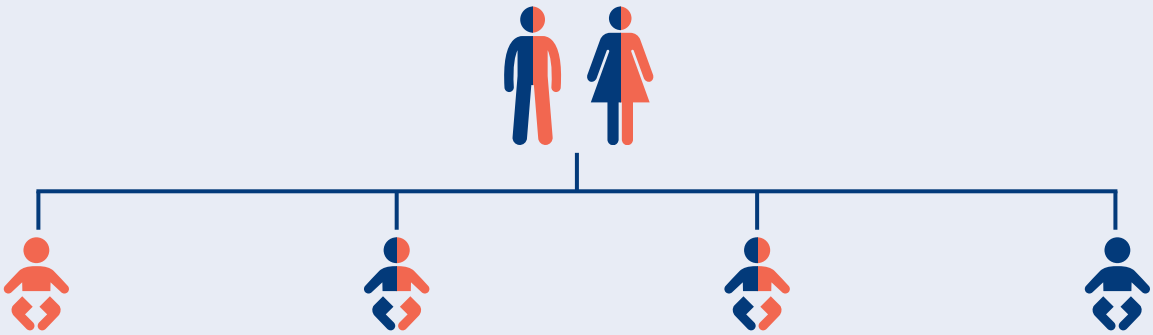
How is alpha-mannosidosis passed down through families?[1,2]

Those with alpha-mannosidosis will have inherited two copies of the pathogenic variant gene: one from their mother and one from their father. The mother and father are known as **carriers** of the disease. Carriers may pass on a normal ***MAN2B1*** gene or the pathogenic variant gene to their children.

A **carrier** has one normal ***MAN2B1*** gene and one pathogenic variant gene. They do not have any symptoms of alpha-mannosidosis and therefore do not know that they carry the pathogenic variant.



For each pregnancy, when both parents are carriers, there is a **1 in 4 chance** of the **baby having alpha-mannosidosis**:



The risk of each parent passing on the **pathogenic variant** gene resulting in an affected child is **25%** with each pregnancy.

The risk of having a child who is a **carrier** like the parents is **50%** with each pregnancy.

The chance of a child receiving normal genes from both parents is **25%** with each pregnancy.

Planning for future children: what you need to know as a parent[1]

If you already have a child with alpha-mannosidosis, any future children could also be affected. Each pregnancy has the same 1 in 4 chance of the baby having alpha-mannosidosis and this does not change if you already have a child with alpha-mannosidosis or if the child is a boy or girl.

If you are expecting another child, tests can be performed during pregnancy to find out if the baby is affected. A geneticist or genetic counsellor can help you better understand the options and help you decide what is best for you and your family. Please speak to your child's genetic specialist to learn more.

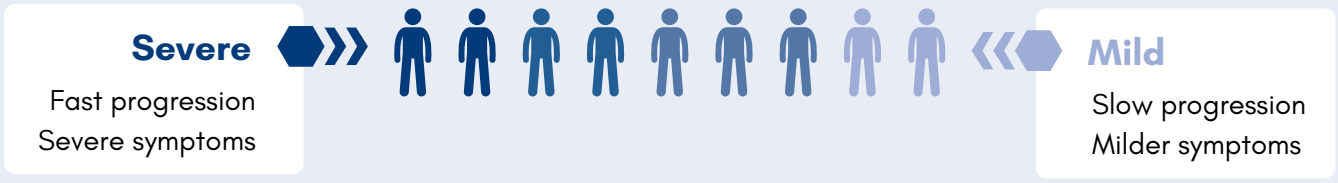
Do other family members need to be tested?[1]

Being diagnosed early can make sure the right care is available, which may help to slow the progression of alpha-mannosidosis. Testing recommendations can vary depending on your individual circumstances and geographic location, but it is generally recommended that your child's brothers and sisters should be tested, even if they do not have symptoms, to establish if they have alpha-mannosidosis or are carriers. Testing of other relatives may also be recommended. You may hear the medical team call this process 'genetic counselling'.

What will the future hold?[1–7]

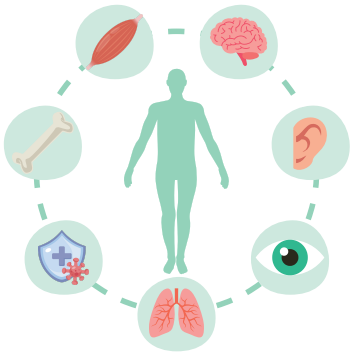
It is difficult to predict how alpha-mannosidosis will affect an individual and how severe their symptoms will be. While the most severe forms can shorten life expectancy, most individuals have a slowly progressing form of the disease and live into their 50s and beyond. How long someone lives for can vary depending on other health conditions that may occur alongside alpha-mannosidosis. Over time, challenges with mobility will likely increase - most people will eventually use a wheelchair and may need additional support to live as independently as possible, with some requiring residential care. A dedicated care team can help anticipate these changes and provide resources to adapt and maximize independence at every stage.

The outcome may be predicted to some extent based on the age that symptoms appear and how serious they are. In the past, alpha-mannosidosis was divided into three types (mild, moderate and severe).[1,2] Today, doctors usually describe it as a broad spectrum of symptoms and severities that can vary from person to person:[6,7]



It is important to remember that **everyone with alpha-mannosidosis is unique**. Doctors will consider your or your child's specific symptoms and needs when planning care.

What are the symptoms of alpha-mannosidosis?[1-3,7-10]



The symptoms and severity of alpha-mannosidosis can vary greatly from person to person, even within the same family. All areas of the body may be affected, but those more commonly affected are shown here.

While some symptoms are likely to start at an early age, others may not appear until adolescence or adulthood, and some may not appear at all.

Symptoms can appear at any age but some are more common to have at certain life stages:

Early childhood

Hearing and speech

Most people have hearing loss from an early age, caused by changes in the structure of the ear and damage to the hearing nerves. Ear infections and fluid behind the eardrum (glue ear) can also lead to hearing problems. Speech may be hard to understand, partly because of hearing loss and muscle weakness in the mouth and face.

Frequent infections

The immune system may be weaker than in young children without alpha-mannosidosis, making infections such as colds, chest infections, stomach bugs and ear infections very common in early childhood.

Development and learning

Children with alpha-mannosidosis may take longer to learn how to walk and talk than other children.

Childhood and adolescence

Movement and coordination

Difficulties with coordinating movement (ataxia), muscle weakness and low muscle tone can lead to clumsiness and difficulties with mobility and daily life, which may get worse over time. Joint and muscle pain can contribute to reduced mobility. Even with these challenges, many children and adults enjoy sports and activities like cycling or football.

Brain and behavioural issues

Behavioural issues may arise and become more common with age. Childrens' learning might seem typical at first, but over time, most will have some level of learning difficulty.

Bones and joints

Growth may be slower than normal, but many people with alpha-mannosidosis reach normal height by adulthood. Bone and joint problems can include:

- Arthritis and a curved spine (scoliosis or kyphosis)
- Knock knees (genu valgum)
- Thickened bones (multiple dysostosis)
- Weaker bones (osteopenia)
- Hip joint changes that require surgery

Some of these symptoms may be present at birth but become more noticeable in childhood and adolescence.

Adulthood

Heart

In adults, heart valve problems can develop.

Immune system

Infections tend to become less frequent in adulthood, but the immune system remains weaker than usual.

Brain and behavioural issues

Most adults will have some level of learning difficulty, and some may also have lifelong challenges with attention. In more extreme cases, adults may experience confusion or even hallucinations (psychosis). These episodes can last a few weeks and may need medical treatment.

Some other symptoms of alpha-mannosidosis include:[1–3,7–13]

Eyes

Vision loss may occur over time. Other possible issues include near sightedness, inward turning eyes, cloudy corneas or lens changes.

Face

Many people have distinctive facial features, which can include a large head with a broad forehead, a flattened nose bridge, wide-spaced teeth, a large tongue and a prominent jaw. In milder cases, these features may not be obvious. In some cases, people may have a distinctively shaped head (craniosynostosis).

Eating and digestion

Many people experience frequent bowel movements or diarrhoea.
Some may find swallowing difficult, and a in a few cases, extra support might be required to make sure they get the nutrition they need.

Internal organs and glands

Some people have lung and/or breathing problems like lung scarring or air trapped in the airways. People can also experience sleep apnoea, where breathing stops and starts while sleeping.

The liver and spleen may be enlarged but usually work normally. People may experience hernias, and the endocrine glands that produce hormones (e.g. the thyroid) can also be affected.

Brain and mental health

People may experience anxiety or depression, especially during times of stress or illness. Some people may develop hydrocephalus (build-up of fluid on the brain). Some also experience seizures.

Everyone with alpha-mannosidosis is unique: you or your loved one may experience some of these symptoms, but not necessarily all at once, and some may never appear.

Alpha-mannosidosis is a progressive disease; this means that it slowly gets worse over time. You or your loved one might not notice big changes right now, but symptoms can build up gradually. Development of a new symptom may be a sign that the disease is progressing. Getting support and medical care early can help manage the condition and improve quality of life.

Can alpha-mannosidosis be treated?[1,14]

While there are currently no treatments to cure alpha-mannosidosis, symptoms can be managed through supportive care to improve quality of life. For further information and guidance on management options, including specialised care, please refer to a specialist centre or your geneticist.

Care and support[1,14]

Early support for learning, medical care, supportive therapies and surgery can all help to manage the symptoms of alpha-mannosidosis. Because alpha-mannosidosis affects many parts of the body, care is often provided by a team of specialists. They provide supportive care to improve comfort, independence, day-to-day quality of life and prevent infections. Care will often involve hospital, community and educational providers. To evaluate specialised care, you must refer to a specialist centre or genetic specialist.

Some of the specialists that may support you with best supportive care include:

Concern	Specialists	Support
Overall care	• Paediatrician, metabolic specialist, specialist metabolic nurse	• Coordinating overall care, follow-up and referrals • Alpha-mannosidosis specific treatment
Hearing and speech	• Ear, nose and throat (ENT) doctor, audiologist	• Hearing aids, managing ear infections/glue ear
	• Speech and language therapist	• Communication and language development • Alternative communication methods and devices
Developmental delay and learning disability	• Developmental paediatrician, neuropsychologist	• Child development
	• Early intervention and educational support providers in the community/school • May include special educational needs teacher, physical therapist (physiotherapist), occupational therapist, speech and language therapist	• Tailored education plans (known as Individualised Education Plans/Programs in the US and UK) for accommodations helping children to access education
Mobility, movement and balance	• Physical therapist (physiotherapist), orthopaedic specialist/surgeon	• Maximise mobility and reduce risk of joint issues (e.g. hip dislocation), surgery (if needed) • Assistive devices (walking aids, wheelchairs)
	• Occupational therapist	• Daily living skills like eating, writing or self-care
Infections and immunity	• Immunologist, allergologist	• Immune system and management of infections
Vision and eyes	• Ophthalmologist, optician	• Glasses, treatment of eye issues/low vision
Eating, weight gain, growth and swallowing	• Occupational or speech therapist	• Feeding therapy to help with coordination and sensory issues
	• Gastroenterologist, endocrinologist, nutritionist	• Growth support, feeding support (if needed)
Heart and lungs	• Cardiologist and pulmonologist	• Treatment of any issues
Brain, mental health and behavioural issues	• Developmental paediatrician, psychologist, psychiatrist, neuropsychiatrist, neurologist	• Brain and mental health issues, behavioural management strategies
Family	• Social worker, patient organisations	• Connect families to local resources, respite and support

Regular check-ups and tests[14]

An important part of your care will be regular checks for any disease progression, to assess how well treatments are working and to make sure you or your loved one receive appropriate care and support.

When alpha-mannosidosis is first diagnosed, your healthcare team will perform baseline tests to understand how the condition is affecting you or your loved one. Details of these can be found below.

After diagnosis, regular visits are needed to keep track of symptoms and catch any new problems early. Tests are repeated at different times depending on age, symptoms and treatments received, but a check-up every year is usual. Doctors will use a range of tests to see how alpha-mannosidosis is affecting different areas of the body, how it affects daily life and what effect the management of symptoms is having on you or your loved one.

Muscles

- Difficulties with walking and balance
- Ability to eat, dress and bathe

T**ests/referrals:** muscle function, strength and coordination, questionnaires. Physical therapist/physiotherapist/occupational therapist follow-up if needed.

Bones and joints

- Difficulty walking
- Pain

Tests/referrals: X-rays or other imaging to look for any changes in the bones or joints (e.g. curvature of the spine), measures of bone density. Referral for physical therapy/physiotherapy or surgery as needed.

Brain and nervous system

- Difficulty with coordinating movement, falls
- Developmental delay
- Fluid build-up in the brain (hydrocephalus)
- Seizures
- Learning disability
- Attention and memory
- Speech and communication
- Socialisation
- School/work performance
- Behavioural issues
- Mental health

Tests/referrals: neurological exam, brain imaging if necessary. Questionnaires, intelligence tests, school assessments with a neuropsychologist, referrals to neurologist or psychologist as needed. Review of symptoms and questionnaires. Referral to a psychiatrist or psychologist as needed.

Hearing and eyesight

- Reduced hearing or eyesight

Tests/referrals: hearing and eye tests.

Immune system

- Frequent infections

Tests/referrals: blood tests and vaccinations. Referral to an immunologist when necessary.

Lungs

- Shortness of breath
- Poor sleep
- Exercise intolerance
- Respiratory infections

Tests/referrals: lung function tests and sleep studies to see how breathing is at night.

Heart

- Exercise intolerance
- Irregular heartbeat

Tests/referrals: blood pressure, ECG (echocardiogram), heart magnetic resonance imaging (MRI). Referral to a cardiologist if needed.

Other

Dental check-ups, assessments of growth and hormone function, review of new symptoms, quality of life questionnaires.

Glossary

Airway obstruction	A blockage or narrowing of the air passages that make it hard to breathe.
Alpha-mannosidase	An enzyme that helps break down certain complex sugars in the body.
Arthritis	Inflammation of the joints that causes pain, stiffness and swelling. It can make moving or walking difficult.
Ataxia	A problem with balance and coordination. People with ataxia may walk unsteadily or have trouble with fine movements.
Carrier	A person who has one copy of a changed (pathogenic variant) gene that can cause a disease, but who usually does not have symptoms themselves.
Cloudy cornea	When the clear front part of the eye (the cornea) becomes less transparent, which can make vision blurry or hazy.
Developmental delay	When a child takes longer than expected to reach milestones such as walking, talking or learning new skills.
Enzyme	A type of protein in the body that speeds up chemical reactions. Enzymes help break down food, build tissues and remove waste products.
Gene	A small section of DNA that carries instructions for making a specific protein or enzyme.
Genu valgum	A condition also known as 'knock knees,' where the knees angle in and touch each other when the legs are straightened.
Glue ear	A common condition in children where thick fluid builds up behind the eardrum, often causing hearing problems.
Hydrocephalus	A build-up of fluid in the brain.
Immunity	The body's ability to protect itself from infections, such as bacteria and viruses.
Lysosomal storage disorders	A group of rare genetic conditions, including alpha-mannosidosis, where substances build up inside parts of the cells called lysosomes because an enzyme is missing or not working properly.
Lysosomes	Small structures inside cells that act like recycling centres. They break down waste materials and unwanted substances.
Mobility	The ability to move around easily, such as walking or climbing stairs.
Near sightedness	A vision problem where close objects are clear but things far away look blurry.
Osteopenia	Lower-than-normal bone density, which makes bones weaker and more likely to break.
Pathogenic variant	A change in a gene that can increase your risk for a specific health condition.
Physical examination	A check-up performed by a doctor to assess general health, looking at things like weight, height and blood pressure.
Side effects	Unwanted or unexpected reactions to a medicine or treatment.
Socialisation	The process of learning to interact with other people, make friends and take part in everyday activities.
Supportive therapy	Treatments and care that help manage symptoms and improve comfort and quality of life, such as physiotherapy, speech therapy or hearing aids.

Support from the alpha-mannosidosis community

Living with alpha-mannosidosis can be challenging — but you don't have to face it alone. Around the world, there are communities of people, families and professionals who understand what you're going through and are ready to support you. Patient organisations and support groups often provide information and support from others who have been through similar diagnoses as a family:

- ISMRD - International Society for Mannosidosis & Related Disorders: **www.ismrd.org**
- MPS Society (UK): **www.mpssociety.org.uk**
- NORD - National Organization for Rare Disorders (US): **www.rarediseases.org**

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Notes

QR code link

MPS Society

www.mpssociety.org.uk/conditions/research/alpha-mannosidosis-patient-and-caregiver-resources

The MPS Society (www.mpssociety.org.uk), the Society for Mucopolysaccharide Diseases, is the only registered charity providing professional support to individuals and families affected by MPS, Fabry and related lysosomal conditions in the UK. We are committed to transforming lives through specialist knowledge, support and research, making sure anyone affected by these conditions gets to live the life they want.

ISMRD (www.ismrd.org), the International Society for Mannosidosis and Related Diseases, is an internationally focused not-for-profit organization whose mission is to advocate for families and patients. We are The International Advocate for Glycoprotein Storage Diseases. Our mission, through partnerships built with medicine, science and industry, is to seek, detect and cure these diseases while providing a global network of support and information.

Rare Disease Research Partners (www.rd-rp.com) is a wholly owned, not for profit subsidiary of the MPS Society. Its social objectives are to reinvest any surplus to support the mission of the MPS Society to transform the lives of patients through specialist knowledge, support, advocacy and research.

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