Minicore (multicore) myopathy

Minicore myopathy is a rare inherited muscle condition that causes muscle weakness and wasting. It gets its name from small ‘core’ structures that can be seen when the muscle cells are viewed under a microscope and ‘myopathy’ which means muscle disease.

It is one of several muscle conditions classed as congenital myopathies. ‘Congenital’ means from birth. Minicore myopathy is a highly variable condition with different people experiencing different levels of severity and rates of progression. The symptoms of minicore myopathy are usually present from birth but diagnosis may not occur until several years later. Occasionally the onset of symptoms is in adulthood.

It is not known how common minicore myopathy is, but it is estimated that congenital myopathies as a whole affect around 1 in every 20 000 babies born, and a small proportion of these have minicore myopathy.

Minicore myopathy is often referred to by other names including:

- Multicore myopathy
- multi-minicore disease (MmD)
- multi-minicore myopathy

What causes minicore myopathy?

Minicore myopathy is a genetic condition caused by the presence of a mistake in the DNA (which is often referred to as a 'mutation'). Mutations in two genes called SEPN1 and RYR1 have been found to cause minicore myopathy.

The RYR1 gene contains the instructions for the production of the ‘ryanodine receptor 1’ protein. Mutations in the RYR1 gene are known to also cause other types of congenital myopathy – central core disease and congenital fiber-type disproportion. RYR1 mutations cause a wider range of severity of minicore myopathy and generally the muscles are weaker than those of people with SEPN1 mutations.

The SEPN1 gene contains the instructions for the construction of a protein called ‘selenoprotein N’. Mutations in this gene are also known to cause a related condition called ‘congenital muscular dystrophy with rigidity of the spine (RSMD)’. This condition has many similar symptoms to minicore myopathy and it is now thought that they are the same condition and are collectively termed SEPN1-related myopathies.

The ryanodine receptor 1 protein is thought to play an important role in the movement of calcium into and out of muscle cells – a process that is necessary for muscles to contract and relax normally. The function of selenoprotein N protein is not as well understood, but it is thought that it may also be involved in the same process as well as in the antioxidant defense systems of the body.
About a third of people with minicore myopathy are found not to have SEPN1 or RYR1 mutations and the cause remains unknown but researchers are working to find additional causative genes so that more people can gain a genetic diagnosis.

Recently, changes to the MYH7 gene which contains the instruction for the ‘beta myosin heavy chain’ protein have been implicated in causing some cases of minicore myopathy but research into this is still ongoing. People with MYH7 mutations have been found to have a high risk of heart problems (cardiomyopathy).

**How is minicore myopathy inherited?**

This condition is usually inherited in an autosomal recessive pattern, which means that two mutated genes are inherited – one from the mother and one from the father. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. If both parents are carriers the likelihood of a child inheriting the condition is 25 percent, or 1 in 4.

There have been a few cases of dominant inheritance of minicore myopathy (including those with mutations in the MYH7 gene). This is when only one copy of the genetic mutation (from either parent) is required for the disease to develop. There is a 50 percent chance of a child of an affected parent to inherit the condition.

**What are the symptoms and how can they be managed?**

The symptoms of minicore myopathy are highly variable from person to person and to some extent depend on what the genetic cause is, as described above. There is currently no curative treatment for minicore myopathy but a team of multidisciplinary health professionals can help to manage the symptoms. It is important to note that intelligence is not affected by minicore myopathy so children should be encouraged and helped to reach their full potential at school and beyond.

**Muscle weakness**

Symptoms that are usually first noticed are floppiness (hypotonia) and muscle weakness, especially of the muscles closest to the body. Delayed motor milestones such as sitting unaided and crawling are what often raise the alarm that something is wrong. Weakness of the facial and neck muscles may also be noticed along with a characteristically long face and a high pitched voice. Poor head control is a common sign. Although children with minicore myopathy are late with their motor milestones most do learn to walk with the help of physiotherapy and retain this well into adulthood. However, as mentioned above, it is a highly variable condition and some more severely affected children are not able to walk.

Regular physiotherapy can help to preserve muscle function and prevent contractures, particularly those of the Achilles tendon. This tightening of the muscle tendons restricts the movement of limbs and joints. Physiotherapy can help prevent this and a program of exercises should be worked out with a physiotherapist very soon after diagnosis. Exercises that strengthen the core muscles such as swimming may be particularly recommended. Some people experience muscle pain on exercise so help may be needed to choose suitable exercises to keep fit. Braces or calipers may be provided to help some children to walk.
Failure to thrive may also be what brings the child to the attention of doctors. This inability to put on weight may be attributed to feeding difficulties, but a lack of muscle bulk and the extra energy burned by individuals with muscle weakness just doing day-to-day activities also may contribute. Some people eventually opt for a feeding tube (gastrostomy) to be inserted directly into the stomach so that extra nutrition can be provided.

Fatigue and falling are common problems and walking aids or a wheelchair may be needed for longer distances. Tasks such as getting up from chairs and climbing stairs tend to become increasingly problematic and ways to manage need to be found with advice from a physiotherapist and/or occupational therapist. Children may need assistance at school for when they get tired, both in the classroom and with outdoor activities.

Orthopedics
A rigid or stiff spine and curvature of the spine (scoliosis) are also classic symptoms of minicore myopathy. Most will eventually need surgery in early adolescence to manage the scoliosis. As with all neuromuscular conditions, getting moving soon after surgery is important to avoid further muscle weakness and wasting.

Babies may be born with clubfoot or other foot deformities and/or a high arched or cleft palate. Surgery is sometimes required to correct these.

Lungs and heart
Trouble with breathing is a common symptom of minicore myopathy, especially for those with mutations in the SEPN1 gene. Even those who are able to walk independently can develop breathing difficulties at night so the signs should be looked out for – early morning headaches, loss of appetite and daytime drowsiness. Regular breathing tests including overnight monitoring should be done. Treatment involves non-invasive ventilation using a special facial or nasal mask, usually just at night. Ventilation may be required in childhood or not until adulthood. Rarely, babies are born with severe minicore myopathy and require the insertion of a tracheostomy tube for ventilation.

Respiratory infections can be problematic in people with breathing difficulties. Immunisations, including the flu vaccine should be kept up to date and respiratory infections promptly treated. If the cough is measured to be weak, assistance with coughing on a daily basis helps to clear secretions and prevent chest infections. This is usually done with a cough assist machine.

The heart is not always directly affected by minicore myopathy, but nonetheless, regular heart monitoring is strongly recommended. This is because in a proportion of people, heart problems (cardiomyopathy) are a potentially serious and life threatening complication, but if diagnosed, medication is available to manage it. It has been reported in a few patients that the cardiomyopathy has developed as a result of problems with the valves of the heart - mitral valve prolapse. In addition, breathing difficulties can put stress on the heart which over time can cause cardiomyopathy. Regular cardiac assessments, usually annually, should include cardiac ultrasounds (echocardiogram).

Malignant hyperthermia
People with minicore myopathy are known to be susceptible to malignant hyperthermia (MH) – a life threatening reaction to general anaesthetics. This is especially a risk for those known to have a
mutation in the RYR1 gene. The symptoms of a malignant hyperthermia reaction include muscle contraction, rapid temperature rise, fast heartbeat and breathing, dark brown urine and muscle aches. The muscles start to break down and organs can fail. Treatment includes the administration of a drug called dandrolene, giving fluids and cooling the patient down, but all precautions should be taken to avoid such a reaction by taking extra care when going for any medical procedure. The anaesthetist must be well aware of the condition and avoid certain anaesthetics and muscle relaxants.

A reaction called ‘awake malignant hyperthermia’ has been known to occur in stressful situations without exposure to anaesthesia. Hot weather, viral illness, strenuous exercise and emotional stress have been known to bring on the life threatening fever. Care should be taken to avoid these triggers and be prepared to take action if a suspected episode does develop. This will involve lowering the temperature with cooling blankets or spray bottles and having plenty of water to drink.

Other possible symptoms
A small proportion of people have additional symptoms that result in a diagnosis of a subtype of minicore myopathy. ‘Minicore myopathy with external ophthalmoplegia’ affects the muscles that control the eyes, and another type affects the hands (‘moderate minicore myopathy with hand involvement’). Another form of minicore myopathy is referred to as ‘antenatal onset minicore myopathy with arthrogryposis’. In this more severe type, muscle weakness in the womb leads to reduced movement and babies are born with contractures or tightness of the joints, especially the elbows, hips, shoulders and knees.

Prognosis
The symptoms of minicore myopathy can stay the same, show slight improvement in adulthood or the muscle weakness can very slowly get worse. It can be a life threatening condition due to respiratory complications and, if people are unaware, malignant hyperthermia. In general, the more severe the condition is as a child the more likely it is that life expectancy is shortened. However, people with minicore myopathy can live well into adulthood and even old age, despite the need for ventilation support. With the right help and support many work, remain independent and live very fulfilling lives.

How is minicore myopathy diagnosed?
As minicore myopathy is a rare condition, gaining a diagnosis can take many months to years, which is very frustrating for families. Doctors will first rule out more common reasons for the muscle weakness. When a neuromuscular disorder is suspected referral to a specialist will be made and after thorough physical examination a muscle biopsy will be requested. A muscle biopsy is a surgical procedure in which a small sample of muscle is removed and examined. It is considered to be “minor” surgery, and is usually conducted as day surgery, under local or general anaesthetic. Diagnosis of minicore myopathy is made based on the appearance of the muscle cells under a microscope.

MRI scans are increasingly being used to aid with diagnosis as different muscle diseases, and even different genetic mutations causing the same condition, cause different patterns of muscles involvement.
Genetic testing for SEPN1 and RYR1 mutations may then follow which is done on a blood sample. However, this testing is only available at a limited number of laboratories around the world so results may take some time to come back.

**What research is being done?**

About a third of people diagnosed with minicore myopathy do not have a mutation in either of the genes known to cause it – RYR1 and SEPN1. Therefore, some of the ongoing research is focussing on discovering more of the causative genes. Finding more genes will improve diagnosis and is a vital step for the development of treatments in the future. A research group at Boston Children’s Hospital led by Dr Alan Beggs is particularly active in this area. They are also involved in developing animal models of the condition – that is, animals that carry the genetic mutations causing minicore myopathy and displaying similar symptoms. So far, zebrafish and mouse models have been developed with RYR1 mutations and a mouse model is available with the SEPN1 mutation. A zebrafish model for SEPN1 is under development.

Experiments on muscle cells in the laboratory have shown that treatment with antioxidants such as N-acetylcysteine may be beneficial for people with SEPN1 or RYR1 mutations. This has also been tested in zebrafish with the RYR1 mutation and there are plans to test such drugs in animal models with the SEPN1 mutation.

One small clinical trial involving five children with minicore myopathy (plus eight with central core disease) has already been completed which tested the asthma drug salbutamol for its ability to improve muscle strength. The results of the trial, which were published in 2004, appeared to be positive but a larger clinical trial is required to confirm its safety and effectiveness.

You may be interested in registering with the [Congenital Muscle Disease International Registry](https://cmdir.org) (CMDIR). This is a patient registry: a database that contains information about patients with a particular condition. Clinical trial organisers and other researchers use this (anonymous) information to learn more about the conditions and plan clinical trials. If a clinical trial were to start, the registry would be used to contact suitable potential participants and invite them to take part. Patient registries are also a useful source of information for patients and their families as regular newsletters are sent out. You can find out more about patient registries on our website.

**NOTE:** Research is moving forward at a fast pace, so this research summary may not be up-to-date at the time of reading. Feel free to contact MDA’s Scientific Communications Officer for an update on the latest developments - kristina.elvidge@mda.org.au. Further information

Many thanks to Fiona Anderson of The Minicore Project for her help with this document.

**Further information**

- [The Minicore Project](https://www.minicore.org.uk) is a UK-based, patient run, support and information resource, advocating and being there for families affected by the rare muscle condition around the world.
Clinical trials – your questions answered

Read about the research MDA funds which aims to reduce inflammation in the muscles and improve muscle regeneration

For definitions of any terms that you are not familiar with please take a look at our glossary

Research news is available on the MDA website

You can get regular updates by becoming a friend of the MDA Facebook page or follow our Scientific Communications Officer on Twitter (@kelvidge)

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References


The Minicore Project website