What is MDC1A?
MDC1A is a hereditary muscle disorder often noticed at birth or within the first few months of life. There are at least 30 different types of congenital muscular dystrophy (CMD) and each has a different genetic cause and a different range of symptoms, but they are all present at birth or soon after and primarily affect the muscles used for movement. MDC1A is one of the most common types of congenital muscular dystrophy (CMD).

MDC1A is caused by a change to the LAMA2 gene which is responsible for the production of laminin α2 protein (previously called merosin). MDC1A is sometimes referred to as LAMA2-related muscular dystrophy.

In some rare cases, changes to the LAMA2 gene allow a small amount of functional laminin α2 protein to be produced which results in a milder limb girdle muscular dystrophy which is first noticed later in childhood.

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What are the symptoms of MDC1A and how is the condition managed?
Babies with merosin-deficient congenital muscular dystrophy often appear floppy (decreased muscle tone) and may not move as much as other babies. Sometimes the first signs are only noted after a few months when the children have difficulties holding their head up or have a delay in learning new skills such as sitting unaided.

Children with MDC1A reach motor milestones later than other children and only a very small proportion of children with MDC1A are able to walk independently. Unlike some other types of muscular dystrophy, muscle weakness does not tend to rapidly progress and motor function remains relatively stable throughout childhood. When children reach puberty however, and grow taller and heavier, children might experience additional difficulties.

Children may develop, or be born with, ‘contractures’. This tightening of the muscle tendons restricts the movement of limbs and joints. Physiotherapy can help prevent this and a programme of exercises should be worked out with a physiotherapist very soon after diagnosis. Even a very young baby can be helped to maintain flexibility. Children may be encouraged to use a standing frame and
hydrotherapy can also be helpful. Splints, orthoses, and night positioning by casts are used to prevent progression of joint deformities but surgery is often eventually required to release contractures.

A very common problem in children with MDC1A is weakness of the respiratory muscles, which results in frequent chest infections and poor breathing at night. It is therefore very important to monitor respiratory function during the night by checking oxygen levels on a regular basis, usually once a year and when signs such as sleepiness during the day, morning headaches and weight loss are noticed. If the level of oxygen recorded at night is not satisfactory, children will start to use a ventilator at night with a special facial or nasal mask. For some patients this is insufficient and a tracheostomy is needed. Respiratory issues usually stabilise or improve in the first few years. In adolescence however, respiratory function may begin to decline requiring more ventilator support. 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.

Most children with MDC1A also develop a curvature of the spine (scoliosis), this can be helped by promoting appropriate sitting support and, if required, a brace. Sometimes surgery is eventually required.

Another frequent problem is feeding difficulties and the accompanied weight loss so it is important to monitor weight and height to make sure children with MDC1A are well nourished. Often the swallowing muscles are weak and feeding supplements are needed. Sometimes a surgical procedure called a gastrostomy is performed so that feeding can occur via a tube directly into the stomach. Weakness of the muscles of the face can also affect speech - a speech therapist can help to manage this.

Brain scans are often done to confirm a diagnosis of MDC1A as there is a particular pattern that can been seen, but these changes in the brain usually don’t cause any problems and intellect is normal. Only a small proportion of children with MDC1A (less than seven percent) have a mild intellectual disability or communication difficulties. Some children do develop seizures in late childhood which are usually well controlled with drugs.

More detailed information on the medical management of congenital muscular dystrophy can be found in the family guide to the Care Standards for CMD.

What causes MDC1A?
MDC1A is a genetic condition caused by the presence of a mistake in the DNA (which is often referred to as a 'mutation'). The mutation is in the LAMA2 gene which contains the instructions for the production of laminin α2 protein. This protein is one of three subunits making up laminin 2 (previously called merosin) which is an important structural component of the muscles. Without laminin α2 the muscles are fragile and degenerate.

Is MDC1A inherited?
MDC1A is inherited in an autosomal recessive manner. This means that an individual with MDC1A inherits two altered LAMA2 genes – one from their mother and one from their father. The parents
of an individual with MDC1A each have one copy of the altered LAMA2 gene and are known as carriers, but they typically do not show signs and symptoms of the condition. Their other ‘good’ copy of the gene is enough to prevent the condition developing. If both parents are carriers the likelihood of a child inheriting the condition is 25 percent, or 1 in 4.

Soon after the diagnosis of MDC1A genetic counselling should be arranged, together with appropriate tests for those members of the family who are at risk of being carriers. Genetic counselling provides information on the inheritance pattern, risks to other family members, and the ‘prognosis’ (likely outcome of the disorder). Family members who are found to be carriers of the condition can discuss with a genetic counsellor family planning options to reduce the risk of passing the condition on to future children.

**How is MDC1A diagnosed?**

The diagnosis of MDC1A is usually suspected from the history and examination. A blood test may also be done which measures the level of a muscle enzyme (creatine kinase or CK). This is usually very much raised (more than 10 times the normal values) but could also be indicative of several other muscle disorders.

The specific diagnosis is generally made by looking at a piece of muscle (muscle biopsy) under a microscope. Uneven sized muscle fibres and the presence of fat and fibrous tissue indicate muscular dystrophy. It is also possible to stain the muscle sample for laminin 2 (merosin) and if the levels are reduced this strongly indicates MDC1A. Sometimes a skin biopsy rather than a muscle biopsy is used for diagnosis because it is less invasive to obtain, but more information can be gained from a muscle sample so this is usually preferred.

MRI scans of the brain may be able to pick up changes to the white matter that can help with diagnosis.

The ultimate diagnosis is obtained by analysing the DNA for changes to the LAMA2 gene. This genetic testing is available at specialised laboratories.

**What research is being done?**

A lot has been learned about MDC1A by scientists in recent years and importantly models to study the condition in the laboratory have been developed. This has led to several possible therapies being developed, three of which are described below.

A company called Santhera is planning to conduct a clinical trial of a drug called omigapil in the USA. Omigapil is an oral drug which was originally developed for the treatment of neurological disorders including Parkinson's disease and amyotrophic lateral sclerosis (ALS). It is thought to work by preventing cells dying. Omigapil does not target the primary genetic cause of CMD and so it cannot be considered a 'cure', but testing in a mouse model of MDC1A has shown that it may be able to reduce the severity of symptoms. The trial will involve children with CMD, including MDC1A. Patient enrolment is expected to start in late 2014. More information about the [Omigapil trial](#).
Researchers in Boston have taken a multi-pronged approach – inhibiting cell death and increasing muscle regeneration in mice with MDC1A. Although the techniques used in this study would not be applicable to humans, the approach showed promise with the treated mice proving to be much stronger and healthier than their untreated counterparts. Now scientists are looking for drugs that have the same effect for testing in humans.

Researchers in the USA have recently published results of their work which shows that another laminin protein complex called laminin-111 could substitute for the missing laminin-2 in mice with MDC1A. This protein complex is naturally present in developing embryos but is not normally present in adult muscles. The substitute protein was injected into the mice improving muscle health, strength and life expectancy. Laminin-111 also shows promise for other types of muscular dystrophy and the company Prothelia is currently developing this approach.

You may be interested in registering with the Congenital Muscle Disease International Registry (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

- 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
- US based organisation CureCMD is a useful source of information relating to all types of CMD
- Download the Care Standards for CMD
- 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)

For further information on any of the areas discussed above, please contact MDA:

Phone: (03) 9320 9555
Email: info@mda.org.au

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References


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