

This fact sheet describes a group of conditions known as **muscular dystrophies** and includes the symptoms, causes, and any treatment or testing that is available.

In summary

- The term muscular dystrophy refers to a group of conditions characterised by the progressive loss of muscle function
- Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are two childhood-onset muscular dystrophies caused by mutations in the same gene, *DMD*
- The *DMD* gene produces a protein called dystrophin, and mutations in the gene results in an abnormal form of dystrophin or even no dystrophin at all
- DMD and BMD usually affect males and are inherited in an X-linked recessive pattern
- Clinical and genetic testing is available and should be discussed with a health professional
- Women with a family history of DMD or BMD can have testing to determine whether they are carriers of a *DMD* mutation which would mean they could have a son affected by the condition.

WHAT ARE MUSCULAR DYSTROPHIES?

The term muscular dystrophy refers to a group of conditions that involve progressive degeneration of muscle. There are over 30 types of muscular dystrophies which differ by:

- Rate of progression of muscle weakness
- Which muscle groups are most severely affected
- Age at which symptoms first appear ranging from childhood through adult life
- Underlying genetic causes.

This fact sheet will focus on the two most common childhood-onset muscular dystrophies, Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD).

Historically, DMD and BMD were thought to be separate diseases due to differences in severity. However, genetic testing has allowed us to identify the same underlying cause and to appreciate that they exist on a spectrum, with DMD on the more severe end and BMD on the milder end. Both DMD and BMD mainly affect boys, with DMD presenting around 3-5 years of age while BMD is much more variable in onset from childhood through to adulthood. Features of DMD and BMD may include:

- Delayed motor milestones caused by muscle weakness which affects posture, walking and running. These are usually noticeable by 2-3 years of age in DMD but may occur much later in BMD.
- Progression of muscle weakness over time which usually leads to reliance on a wheel chair by early teens. The distinction between DMD and BMD in the past has been determined by age at which mobility is lost, with individuals with DMD requiring a wheelchair by age 16 while individuals with BMD usually maintaining the ability to walk for longer. Newer therapies are prolonging mobility so this is no longer a reliable distinction.
- Shortening of muscles which may lead to restrictions of joint movement (contractures) that add to disability. Stretching exercises are employed to try to minimise these.
- Development in adolescence of a sideways curvature of the spine (scoliosis) which impairs breathing and adds to discomfort. It is often corrected surgically and is much more common in DMD than BMD.
- Problems with the heart muscle that may require monitoring and treatment. Typically these will be less severe in BMD, however occasionally they may be more severe due to better mobility placing more strain on weakened heart muscle.
- Difficulty with breathing as weakness progresses, with DMD being more severe and some young men may need mechanical assistance with breathing especially during sleep.

- Most individuals with DMD and BMD have no intellectual impairment, but particularly for DMD the frequency of intellectual disability is greater than in the general population. Unlike the physical disabilities, the intellectual disability is not progressive.

The current average survival of individuals with DMD is typically into their early 20s but ranges from mid-teens to mid-30s and occasionally outside that range. Breathing complications are the usual cause of death. For BMD, survival is often to middle age and survival beyond 80 years of age has been seen.

WHAT CAUSES DMD and BMD?

Our body is made up of millions of cells, and in each cell there are instructions, called genes, that make all the necessary structural components and chemicals for the body to function. These genes are packaged onto little long strands known as chromosomes.

We all have 46 chromosomes arranged into 23 pairs. One copy of each pair is inherited from our mother and the other from our father. The first 22 chromosome pairs are numbered and are known as autosomal chromosomes. The 23rd pair is made up of the sex chromosomes called X and Y. Males have an X and a Y chromosome and females have two copies of the X chromosome.

Since all our chromosomes come in pairs, all our genes also come in pairs. Sometimes, a gene may have a variation in the instruction that causes the gene to no longer function properly. This variation is called a **mutation** or **pathogenic variant**, and means that the product produced by the gene, called a protein, is impaired or even absent.

Gene mutations may be inherited from a parent, or occur for the first time in an individual. Once you have a gene mutation however, it may be passed on to future generations. This is referred to as genetic inheritance.

DMD and BMD are both caused by mutations in the **DMD** gene, which produces a protein called **dystrophin**. Since the underlying cause of these two conditions has been identified to be the same, they are sometimes referred to as **dystrophinopathies** as they both result from changes in the functionality of dystrophin. Dystrophin is mainly found in the muscles and the heart where it acts as part of a complex of proteins that strengthen muscle fibres and provide support during the cycle of contraction and relaxation that allows our bodies to move and our heart to pump. The differences in severity between DMD and BMD are related to how the mutation affects the production of dystrophin.

Mutations that cause DMD result in no dystrophin or an abnormal form of dystrophin being produced, meaning that muscle cells lack an integral component of the complex that helps to strengthen and support them.

For BMD, a mutation causes a reduced amount of dystrophin to be produced therefore muscle cells maintain a low level of usable dystrophin and this accounts for the milder symptoms. Over time muscle cells in both DMD and BMD become damaged and die off, resulting in the range of problems seen in these conditions.

HOW ARE DMD and BMD INHERITED?

DMD and BMD are inherited in an X-linked recessive pattern due to the **DMD** gene being located on the X chromosome. You may recall that females have two X chromosomes and this means that if one copy of their **DMD** gene has a mutation the other copy still works correctly and they are called **genetic carriers**. Males have one X chromosome and one Y chromosome, which means that they only have one copy of the **DMD** gene and if it has a mutation they do not have a back-up copy to maintain function. This is the reason that we mainly see males affected with DMD and BMD.

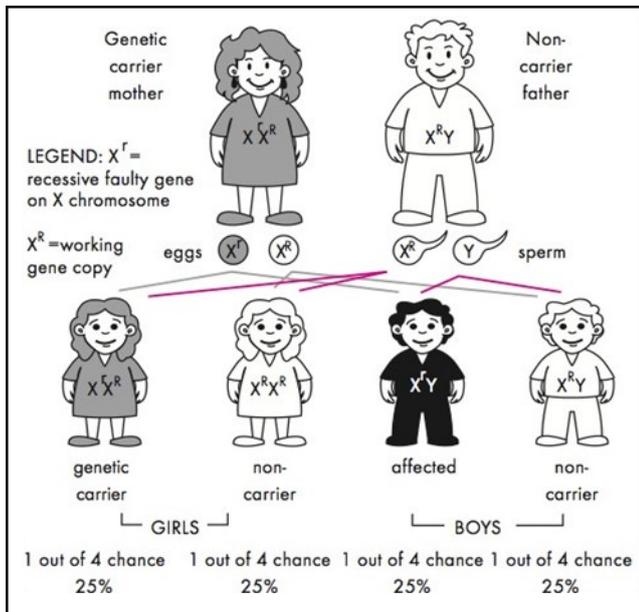


Figure 53.1: X-linked recessive inheritance where the mother is a carrier of the faulty copy of the X-linked gene. The X-linked recessive faulty gene copy is represented by 'r'; the working copy by 'R'.

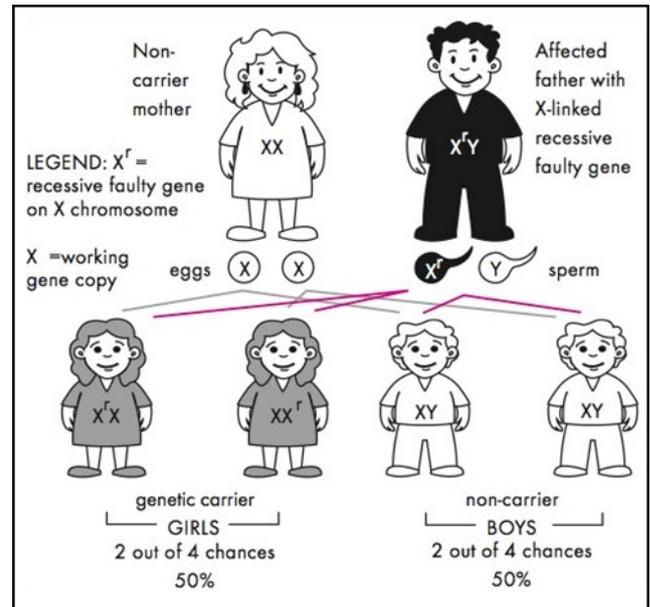


Figure 53.2: X-linked recessive inheritance where the father has the faulty copy of the X-linked gene. The X-linked recessive faulty gene copy is represented by 'r'

A woman may be a DMD mutation carrier without having any symptoms themselves and often without any known family history. Because the DMD mutation is linked to the X chromosome, the chances of having an affected child are different for the woman's sons and daughters (Figure 53.1). In every pregnancy the chances are:

- 1 chance in 4, (25% chance) that a **son** will inherit the Y chromosome from his father and the **DMD gene mutation** from his mother. In this case, he has no working copy of the DMD gene and will be affected with either DMD or BMD.
- 1 chance in 4, (25% chance) that a **son** will inherit the Y chromosome from his father and the **working copy of the DMD gene** from his mother. He will not be affected by the condition.
- 1 chance in 4, (25% chance) that a **daughter** will inherit **both working copies of the DMD genes**: one copy from her father and one from her mother. In this case she will not only be unaffected by the condition but she will also NOT be a carrier of the X-linked DMD gene mutation.

- 1 chance in 4, (25% chance) that a **daughter** will inherit from her father the **working copy of the DMD gene** and the **DMD gene mutation** from her mother. She will be a genetic carrier of the condition like her mother and will usually be unaffected.

If a male is affected with DMD or BMD (Figure 53.2), the chance of passing on the DMD gene mutation is also different for his sons and daughters. This is because he passes his Y chromosome to his sons and his X chromosome to his daughters. This means that in every pregnancy

- All **sons** will inherit the **working DMD gene copy** from their mother and the **Y chromosome from their father** and will therefore not have the condition
- All **daughters** will inherit a **working copy of the DMD gene** from their mother and **DMD gene mutation** from their father. They will be carriers of the X-linked recessive gene mutation and can pass the gene mutation on to their children. They will usually be unaffected by the condition.

In some cases the *DMD* gene mutation is not inherited from a parent but occurs by chance for the first time in the egg or sperm, during or shortly after conception. This is called a **spontaneous mutation** and means that the individual will be the first in the family to have the mutation. If they are male they will have DMD or BMD and may pass their *DMD* gene mutation on to their daughters, and if they are female they will generally be unaffected but may pass the *DMD* gene mutation onto their sons (affected) and daughters (carriers).

What does it mean to be a genetic carrier?

To ensure that men and women have the same amount of genetic information sent to their cells, one of the X chromosomes in the cells of a woman is 'switched off' or inactivated. This means that only one copy of the X chromosome genes in a woman is working, just like in men. This is a random process and results in approximately half of her cells having the X chromosome copy with the *DMD* mutation 'switched off' and the other half of her cells having the X chromosome with the working copy 'switched off' – known as **X-inactivation**. This means that a woman who is carrier of a *DMD* gene mutation will produce half of the amount of dystrophin compared to a woman who has only working copies of the gene. This is, however, usually enough for normal muscle function.

In a very small number of women who are carriers of a *DMD* gene mutation, there may be a problem in this 'switching off' system or X-inactivation that means that more than half of her cells have the working copy of the gene 'switched off'. This means that not enough functioning dystrophin is produced in their muscles. These women are **manifesting genetic carriers** and may have significant muscle weakness and some minor heart problem; a very small minority may have severe disability.

IS THERE ANY TESTING AND TREATMENT FOR DMD and BMD?

A number of different tests are available to help diagnose an individual suspected of having DMD or BMD. First line testing involves a blood test to look at levels of an enzyme in the blood called **creatin kinase (CK)**.

This enzyme has an important function in muscle cells, however when muscle is being damaged CK leaks out of the muscle cells and into the blood stream causing elevated levels of CK. CK levels can be elevated in a number of different conditions that affect the muscles and are therefore not diagnostic of DMD or BMD on their own.

Historically, muscle biopsy was used to look at how much protein, such as dystrophin, muscle cells were producing and this may still be a useful test in some individuals and can help to distinguish between DMD and BMD as diagnoses. The gold standard test currently is genetic testing of the *DMD* gene to look for a causative mutation. In many cases information from the genetic test can differentiate between DMD and BMD with a high certainty and may avoid the need for an invasive test like muscle biopsy. It's best to talk to a genetic counsellor or other specialist about what genetic testing is available.

Testing for genetic carrier status

Female relatives of males with DMD or BMD can undergo DNA testing to see if they are genetic carriers of the disease, this is called **predictive testing**.

Prenatal testing and PGD

For couples where the familial mutation is identified testing may be available during a pregnancy to determine whether or not the baby has inherited the mutation. It may also be possible to undergo **pre-implantation genetic diagnosis** (PGD) on an embryo created using in vitro fertilisation (IVF). These options are best discussed and considered before pregnancy, when possible, in order to ensure all possible risks, benefits and outcomes are explored.

Treatment Options

New therapies are always being developed to help prolong the mobility of individuals with DMD and BMD. Corticosteroid therapy has been shown to be helpful and should be discussed with the treating physician.