

Important points

- The muscular dystrophies are a group of genetic conditions that are characterised by progressive muscle weakness. Two of these types affect only males, with rare exceptions
- Duchenne muscular dystrophy (DMD) affects about 1 in 3,500 males
- Becker muscular dystrophy (BMD) affects about 1 in 30,000 males although this may be an underestimate due to its variable severity
- DMD and BMD are due to different changes in the *dystrophin* gene, which contains information for a protein that is important for muscle cells to work properly. This gene is located on the X chromosome
- Females have two copies of the X chromosome (XX); those with a faulty *dystrophin* gene on one X chromosome and a correct copy on the other partner X chromosome are genetic carriers for DMD or BMD and would not usually be affected
- Males have only one X chromosome and a Y (XY); those with a faulty *dystrophin* gene on their X chromosome will have DMD or BMD as they have no working gene copy on the Y chromosome
- For men and women to have the same amount of genetic information produced in their cells, one X chromosome copy is usually randomly 'switched off' or inactivated in a woman's cells. In a small number of women, who are genetic carriers for DMD or BMD, this 'switching off' system results in more cells containing the active X chromosome with the faulty *dystrophin* gene copy than the working copy. These women are 'manifesting genetic carriers' and may have significant weakness; a very small minority have severe disability
- Genetic carriers for DMD or BMD may have some changes in their heart muscle and it is recommended that they consult a heart specialist and be advised as to how often their heart function should be assessed
- The pattern of inheritance of the faulty *dystrophin* gene causing DMD or BMD in families is described as X-linked recessive inheritance
- Where the mother is a carrier of a faulty copy of the *dystrophin* gene and the father has a working copy of the gene, in every pregnancy, the risks for their children is as follows:
 - Their sons have 1 chance in 2, or a 50% chance, of inheriting the faulty *dystrophin* gene for DMD or BMD and of therefore having the condition
 - Their daughters have 1 chance in 2, or a 50% chance, of inheriting the faulty *dystrophin* gene copy and being a genetic carrier for DMD or BMD. Carriers would usually be unaffected
- If in a couple, the woman is a known genetic carrier or suspected genetic carrier for DMD or BMD, they may seek genetic counselling for information about the condition. They can discuss all the implications of having a family member affected with DMD or BMD and their personal risks for having related health problems themselves, or having children affected with the condition (see Genetics Fact Sheet 3). Genetic testing may be an option
- This information may also be used in planning pregnancies and using prenatal testing if they choose to do so (see Genetics Fact Sheets 17C & 18)

The muscular dystrophies are a group of genetic conditions that are characterised by progressive muscle weakness.

There are differences in the various types of muscular dystrophy in the rate at which the muscle weakness progresses and the muscle groups which are most severely affected. The age at which symptoms first appear ranges from childhood through adult life.

While there are a number of different types of muscular dystrophy, this Fact Sheet focuses on two types which affect only males, with rare exceptions:

Duchenne muscular dystrophy (DMD)

- Named after Dr Duchenne who wrote an excellent description of DMD (but not actually the first description) in 1861
- Affects about 1 in 3,500 males

Becker muscular dystrophy (BMD)

- Named after Professor Becker who drew attention to a less severe form of muscular dystrophy in 1955
- Affects about 1 in 30,000 males although this may be an underestimate due to its variable severity

All males with DMD or BMD have a markedly increased level of an enzyme called *creatin kinase* (CK) in their blood from birth. Other features of the condition however, are not apparent at birth.

There is a continuous spectrum of severity from 'classical' DMD at one end to unusually mild BMD at the other.

Where the line is drawn between BMD and DMD is arbitrary. Usually, a male is said to have BMD rather than DMD if he can still walk at age 16 years.

Duchenne muscular dystrophy (DMD)

Features of DMD **may** include:

- Muscle weakness that affects posture, walking and running, usually noticeable by 2-3 years of age
- Progressive muscle weakness which usually leads to reliance on a wheelchair for mobility by the early teens
- 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
- Problems with the heart muscle but usually not to the extent of causing symptoms or requiring treatment, although this occasionally occurs

Individuals with DMD usually have no intellectual impairment but 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 to approximately their early 20s but ranges from mid-teens to mid 30s and occasionally outside that range. Breathing complications are the usual cause of death.

Some young men choose to have mechanically assisted breathing with a ventilator for example during sleep when impairment of breathing reaches the point of causing symptoms

Becker muscular dystrophy (BMD)

BMD is a relatively mild form of DMD and is highly variable in severity. The pattern of progressive muscle weakness and the muscles that are affected, however, are the same in both conditions.

- The severity of weakness is less in BMD than in DMD
- Usually symptoms appear at a later age and the condition may not be diagnosed until adolescence or adulthood
- The effects on the joints are generally much less severe than with DMD and scoliosis is seldom a problem
- Significant impairment of breathing, if it occurs at all, occurs at a later age than with DMD
- The heart is less often affected than in DMD but is occasionally severely affected
- Some people with BMD are able to walk only until late teens, others to an advanced age
- Survival in some men with BMD is to middle age but others have survived beyond 80 years of age

What causes the muscle weakness seen in DMD and BMD?

In 1987 it was found that both DMD and BMD are due to an impaired ability of the muscle fibres to make a protein called dystrophin. The level of dystrophin in the muscle can help determine the precise diagnosis of the type of muscular dystrophy.

- Males with DMD nearly always have no detectable dystrophin or extremely small amounts in their muscle fibres
- Males with BMD have some dystrophin but in diminished amounts and often of a chemical structure which is different from normal (the dystrophin protein is faulty)

What causes reduced or faulty dystrophin protein in the muscles of family members with DMD or BMD?

The cells contain our genes, and these are located on our chromosomes. They provide the information for the growth, development and function of our bodies (see Genetics Fact Sheet 1).

A gene that contains a variation in the information that stops it working properly is described as faulty. The variation that makes the gene faulty is called a *mutation*. The information contained in the faulty gene, and its product, is impaired (see Genetics Fact Sheets 4 & 5).

The *dystrophin* gene is located on the X chromosome. Women usually have two copies of the *dystrophin* gene and men one copy.

All males with DMD or BMD have a faulty *dystrophin* gene copy so they do not make enough of the protein in their muscles (see Genetics Fact Sheets 1 and 4). There are hundreds, and probably thousands, of ways in which the function of the *dystrophin* gene can be changed. The types of changes that can make the gene faulty include:

- Most frequently, a deletion where part of the information in the gene is missing
- Less often, duplication (doubling) of part of the information in the gene
- Sometimes a change in a single letter in the information (see Genetics Fact Sheet 5)

What does it mean to have a faulty X-linked dystrophin gene copy?

In each family the faulty gene is passed down through the family unchanged so that all affected family members are usually affected

in a very similar way. This is particularly so in DMD but there may be variation between family members in BMD.

Having a faulty *dystrophin* gene copy affects men and women in different ways.

Men have only one X chromosome and a Y chromosome. If their X chromosome carries a faulty *dystrophin* gene copy, they will have DMD or BMD

Women have two copies of the X chromosome. Women with a faulty *dystrophin* gene on one copy of their X chromosomes, and a working *dystrophin* gene copy on the other partner X chromosome, can still produce enough of the working *dystrophin* protein. They are carriers of the faulty gene involved ie. genetic carriers for DMD or BMD, and are usually unaffected, although rarely can be affected (see Genetics Fact Sheet 14 and later).

- Genetic carriers can pass the faulty gene onto their children

In some cases, the faulty *dystrophin* gene is inherited from a parent. In other cases the change in the *dystrophin* gene that makes it faulty will have occurred by chance in the formation of an egg or a sperm, during or shortly after conception, with no known cause (described as a 'spontaneous' mutation).

- That individual will be the first in the family to have the faulty *dystrophin* gene
- If it is a male, they will have DMD or BMD
- If it is a female, they will generally be unaffected but may then pass the faulty gene onto their children

Are there any personal health implications for a woman who is a genetic carrier for DMD or BMD?

Women who are carriers of the X-linked faulty genes for *dystrophin*, ie. they are genetic carriers for DMD or BMD, nearly always have normal muscle function.

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 (see Genetics Fact Sheet 14).

- This means that only one copy of the X chromosome genes in a woman is working, just like in men
- This is usually a random process
- Half of her cells will have the X chromosome copy with the faulty gene 'switched off' and the other half of her cells will have the X chromosome with the working copy 'switched off'
- This means that a woman who is carrier of a faulty *dystrophin* gene will produce half of the amount of dystrophin compared to a woman who has only working copies of the gene. This is, however, enough for normal muscle function

In a very small number of women who are carriers of a faulty *dystrophin* gene, there may be a problem in this 'switching off' system or inactivation. This means that not enough functioning dystrophin is produced in their muscles. These women are 'manifesting genetic carriers' and may have significant weakness; a very small minority may have severe disability.

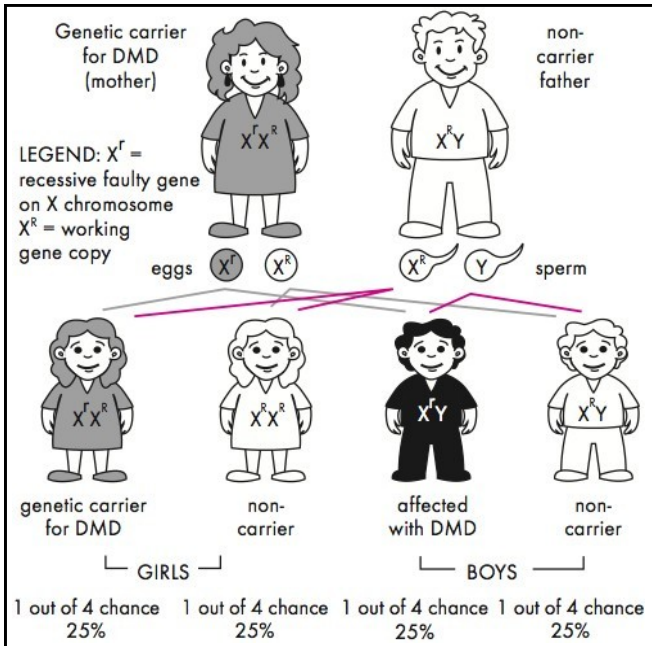


Figure 41.1: X-linked recessive inheritance where the mother is a carrier of the faulty *dystrophin* gene copy. The faulty *dystrophin* gene copy is represented by 'r'; the working copy by 'R'.

What is the pattern of inheritance of DMD and BMD in families?

The pattern of inheritance of both DMD and BMD is the same. Two factors influence the pattern of inheritance of the faulty *dystrophin* gene causing DMD and BMD in families.

- The *dystrophin* gene is located on the X chromosome
- The effect of the change in the *dystrophin* gene is 'recessive' or hidden by the presence of the working copy of the gene (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance in families of the faulty *dystrophin* gene causing DMD and BMD is therefore described as **X-linked recessive inheritance** (see Genetics Fact Sheet 10).

In *Figure 41.1*, the faulty *dystrophin* gene is represented by 'r' on the X chromosome; the working copy by 'R'. The mother is a carrier of the faulty *dystrophin* gene and the father has a working copy of the gene. The chances for having an affected child are different for their sons and daughters:

- Their sons have 1 chance in 2, or a 50% chance, of inheriting the faulty gene for DMD or BMD and having the condition
- Their daughters have 1 chance in 2, or a 50% chance, of inheriting the faulty *dystrophin* gene copy and being a genetic carrier for DMD or BMD. Carriers would usually be unaffected

This is because there are four possibilities, **in every pregnancy**, for the combination of the *dystrophin* gene copies passed from the parents. There is

- 1 chance in 4, or 25% chance, that a son will inherit the X chromosome carrying the faulty *dystrophin* gene copy from his mother. In this case, his cells will either not produce the right amount of dystrophin or not produce dystrophin at all and he will have DMD or BMD

- 1 chance in 4, or 25% chance, that a son will inherit the working copy of the X-linked gene from his mother and will not have DMD or BMD
- 1 chance in 4, or 25% chance, that a **daughter** will inherit the working copy of the X-linked gene from her mother and a working copy from her father. In this case she will not only be unaffected by DMD or BMD but she will also NOT be a carrier of the faulty X-linked *dystrophin* gene
- 1 chance in 4, or 25% chance, that a **daughter** will inherit the faulty X-linked *dystrophin* gene copy from her mother and a working copy from her father. She will be a genetic carrier like her mother and will generally be unaffected

What genetic counselling and advice can be given to DMD and BMD families?

Genetic testing and counselling in DMD and BMD families usually focus on one or both of two issues.

- The first is the probability that a particular female member of the family is a carrier of the faulty *dystrophin* gene
- The second is whether testing for the condition in pregnancy can be offered and with what degree of reliability

The probability of being a carrier of a faulty *dystrophin* gene is first assessed by examining the family tree.

- If a woman has an affected son and an affected brother, uncle or cousin, it is certain that the faulty gene has passed through her to her son and she is called an *obligate* genetic carrier
- If she has an affected son and no other affected relatives she is *possibly* a genetic carrier, because the faulty gene may have occurred for the first time when her son was conceived
- A woman who has passed a faulty gene to two offspring, and who has no other relevant family history, is called a *probable* genetic carrier

A blood test to look at the levels of the enzyme *creatine kinase* (CK) in the blood is of some use in assessing the probability of genetic carrier status but gives an abnormal result in only about two thirds of genetic carriers. It is very helpful if it is consistently abnormal in a possible genetic carrier but is of limited value if the results are consistently normal.

Genetic counselling can provide the most current information regarding these conditions and any tests, including DNA tests, which may be appropriate (see Genetics Fact Sheet 3).

It is an opportunity to discuss all the implications of having a family member affected with DMD or BMD and the personal risks for family members of being affected themselves or having children affected with the condition. This information may then provide options for use in testing a baby in pregnancy or testing an embryo before pregnancy if they choose to do so (see Genetics Fact Sheets 17C & 18).

If a gene mutation causing DMD or BMD is identified in an affected male, with either of these conditions testing will be possible for other members (see Genetics Fact Sheet 21 for more information on the types of test that may be used). Genetic testing may also be possible in some family members where a gene mutation has not been previously identified.

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 3, 4, 5, 10, 14, 17C, 18, 21