Duchenne and Becker Muscular Dystrophy

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Introduction

Neuromuscular disorders and what people commonly call muscular dystrophies are very complex and often devastating conditions. Some strike children, others do not display symptoms until well into adult life. Most are progressively disabling, getting worse over time and some are fatal, often in childhood. Some affect primarily muscles, others can affect a wide spectrum of health, including; personality and intellectual functioning, the eyes, the bones, digestion and diabetes to list just a few. There are over 100 different types of disorders and variations listed under this umbrella. Many disorders have genetic causes but in many cases, just how these genetic mutations cause the symptoms we see is not yet understood. Every day, medicine is making progress in understanding these disorders, but at the present time, there are more theories than facts. Sadly there are no direct treatments yet.

Usually thousands of pages of information can be found on each disorder on the internet. This synopsis is yet another contribution to the public knowledge base. The reader is cautioned that no overview can be comprehensive and cover every question or situation. While a given type of disorder shares the same basic mechanisms and patterns, one of the features of these illnesses is that they are quite variable in how they affect people and no two people will have quite the same symptoms or experiences of the condition. For a given disorder, there is often wide variation between patients concerning how “big” the mutations are and this causes wide differences in how the disorder affects different people. The main aspects that differ are at what age the disorder strikes, how severe the symptoms are in an individual and exactly what is affected.

This is general information and should not be seen as medical advice. The best advice for you and your family is obtained from the doctor and the team of health care specialists who are diagnosing and following your case or that of your child.

The biggest impact of a muscular disorder is on lifestyle. Be it a child who is affected or an adult, the lifestyle of the whole family will be impacted. Yet, ironically, lifestyle is barely covered here. Why? Because the psychological and lifestyle impacts of these disorders are quite unique and evolve over time as the condition emerges, is diagnosed and progresses. It is not practical to offer advice on these complex and individual experiences on a general page like this. There are excellent peer support groups and discussion groups for all disorders on the internet. For even the rarest conditions, there are many others like you and it is usually helpful to discuss your feelings and questions with others who "are in your shoes."

Please feel free to contact Muscular Dystrophy Canada if you have suggestions or questions about this page. Our website is: http://www.muscle.ca/ or e-mail us at info@muscle.ca Thank you.

1). GENERAL OVERVIEW

1-A). What is Duchenne and Becker muscular dystrophy?

Duchenne [DO-shin]

Duchenne muscular dystrophy (DMD) is a genetic disorder affecting a protein that is vital to the structural integrity of the muscles. It is marked by a childhood onset with progressive muscular weakness eventually leading to respiratory distress and death, commonly in the late teens or early twenties.

There is a continuum of severity; more severe cases are classified as DMD and milder cases, often with a later onset are classified as Becker muscular dystrophy (BMD). Both disorders involve the same genetic mutation, however, the severity of the mutation and its impact on muscle function varies.

Dr. Guillaume-Benjamin Duchenne de Boulogne was a famous French neurologist who helped develop the field of neurology. He discovered that external electrical stimulation could cause muscle movements and in 1861, he described a boy with the form of muscular dystrophy we now call Duchenne. Becker muscular dystrophy is named after the German doctor Peter Emil Becker, who first described this milder variant of Duchenne muscular dystrophy in the 1950s.

Due to their X-linked genetic inheritance, both disorders usually only affect males. In general, Duchenne starts with weakness in the pelvis and upper limbs, resulting in clumsiness, frequent falling, an unusual walk and general weakness. Some 30% of patients display mild but non-progressive mental retardation. As DMD progresses, weakness spreads and skeletal deformities may contribute to breathing disorders. Most

patients die in their early twenties because of muscle-based breathing and heart problems. Becker symptoms are similar to those seen in Duchenne but are milder and tend to be more variable.

1-B). Quick Facts about Duchenne and Becker muscular dystrophy.

What: Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD).
Who: Usually only males but in some rare cases females can display symptoms as well. DMD and BMD occur in all races and ethnic/cultural groups (without predilection for a specific one).
When: Duchenne symptoms usually appear between 18 months and 4 years, Becker from three to later in life
Where: All muscles are potentially affected
Why: Muscle weakness and degeneration is caused by a well understood genetic mutation affecting an important muscle protein (dystrophin)

1-C). How common are Duchenne and Becker muscular dystrophy?

Duchenne muscular dystrophy (DMD) is the most common type of muscular dystrophy (MD), affecting 1 in 3,000 to 1 in 3,500 male births with an estimated overall prevalence of 63 per million people in the population. Becker is less common, affecting about 1 in 5,000 male births with an estimated overall prevalence of 24 per million population.

1-D). Are there different types of Duchenne and Becker muscular dystrophy?

No, these two terms describe variations of the same basic disorder and both involve the same basic mutation.

1-E). What other names do people use for Duchenne and Becker muscular dystrophy?

- Duchenne Muscular Dystrophy, DMD
- Becker Muscular Dystrophy, BMD
- Dystrophin-associated muscular dystrophy
- Dystrophinopathy (a pathology of the dystrophin protein)
- Pseudohypertrophic muscular dystrophy

1-F). Are there other disorders related to Duchenne and Becker muscular dystrophy?

Disorders of a similar type: There are no directly related disorders. Other X-linked disorders include; X-linked myotubular myopathy, fragile-X Syndrome, red and green color blindness and Hemophilia A.

2). SYMPTOMS

2-A). What are the symptoms of Duchenne and Becker muscular dystrophy?

- Muscle weakness, usually first seen in the legs
- Symmetrical muscle involvement
- There is early selective involvement of hip muscles, followed rapidly by weakness of the shoulder girdle muscles
- Frequent falls are a common early sign
- The mean age of walking is about 18 months (range 12-24 months).
- Calf enlargement (hypertrophy) is evident until the child can no longer walk (becomes non-ambulatory) and represents changes in the diseased muscle fibres
- Proximal weakness causes a waddling gait and difficulty climbing
- Difficulty with motor skills (running, hopping, jumping)
- Progressive and relentless weakness moving into the neck, shoulders, and arms
- Predilection to rapid weight gain and obesity
- By around the age of 8, most patients have difficulty ascending stairs and respiratory muscle strength begins a slow but steady decline
- By age 10 or 12, most children with the disease are confined to a wheelchair
- Once wheelchair bound, patients become much more susceptible to scoliosis, contractures, and impaired pulmonary function.
- Excessive fatigue is common
- Intellectual impairment occurs in about 30% of Duchenne patients
- Common complications can include: skeletal deformities, chest and back abnormalities (scoliosis), muscle deformities and severe progressive contractures, especially of the heels and legs
- Heart problems are common and serious and can include cardiac fibrosis and cardiac conduction abnormalities that may induce fatal arrhythmias. Cardiomyopathy is also common. In the majority of boys with Duchenne muscular dystrophy, the heart muscle enlarges and weakens, causing problems with the heartbeat, which show up on an electrocardiogram
- Respiratory disorders are common during the later stages due to impaired pulmonary function. Pneumonia and aspiration of food or fluid into the lungs are common complications
- Death from respiratory complications usually occurs between 18 to 25 years of age; survival beyond the late twenties is rare

Muscle wasting (atrophy) begins in the legs and pelvis, then progresses to the muscles of the shoulders and neck, followed by loss of arm muscles and respiratory muscles. Calf muscle enlargement (hypertrophy or pseudohypertrophy – means the muscle gets bigger but not stronger) is quite obvious.

The progressive muscle weakness of the legs and pelvis is associated with a loss of muscle mass (wasting). Muscle weakness also occurs in the arms, neck, and other areas, but not as severely or as early as in the lower half of the body. Muscle contractures occur in the legs, rendering the muscles unusable because the muscle fibers shorten and fibrosis occurs in connective tissue.

Becker symptoms are generally the same as those seen in DMD, including weakness and wasting, first affecting the muscles of the hips, pelvic area, thighs and shoulders. BMD is often much less severe than DMD and patients with BMD will experience less disability compared to DMD (a wheelchair may not be required until well into adulthood). Lifespan may be reduced (average age of death in BMD cases is in the forties) but some patients live a relatively normal lifespan.

From: http://www.hndp.chb-genomics.org/pat_fam-dmd_bmd.php

ANESTHESIA WARNING: A higher rate of complications is associated with general anesthesia in patients with neuromuscular disorders. Even mildly affected patients may have complications. Patients with DMD or BMD or a family history of DMD or BMD need to discuss this with their surgeons.

2-B). What is the age of onset of Duchenne and Becker muscular dystrophy?

Duchenne symptoms usually appear anywhere between 18 months and 4 years of age, BMD follows a much more variable course, manifesting any time from age 3 years to adulthood.

2-C). Are different age-groups affected differently?

The symptoms of DMD/BMD vary according to the severity of the mutation and its subsequent impact on the muscles. Children are affected more severely because they have the more severe type of mutation that also causes the early onset. Later onset cases are

usually less affected and progression is slower because they have the milder form of the mutation.

2-D). Who can be affected by Duchenne and Becker muscular dystrophy?

Duchenne affects males, usually before the age of six and Becker muscular dystrophy affects males over a wide age range, into midlife. Females who carry the mutation usually do not manifest symptoms but some do in rare cases (explained below).

2-E). How does Duchenne and Becker muscular dystrophy progress and what is the prognosis?

DMD/BMD is a progressive disorder, which means the symptoms worsen over time. How rapidly the disability progresses and the extent of muscle loss may differ considerably, based upon the severity of the mutation.

In DMD, the onset tends to be early and the progression slow but steady, ultimately affecting all voluntary muscles. With progression, muscle weakness and atrophy affect trunk and forearms, gradually progressing and involving most major muscles of the body. Loss of ambulation typically occurs at age 10-12 years old. Death usually results from respiratory complications (18-25 years old). Survival is rare beyond the late twenties.

Becker may progress at a much slower rate, for example, the ability to walk may continue to age 40 or older and many cases live an almost normal lifespan.

Prognosis is a prediction of the course of a disorder – how is it going to unfold and develop in the future – what is the outcome going to be? We need to caution that DMD/BMD are extremely variable in individuals depending upon the exact impact of the mutation involved in each case. Because the condition presents with widely varying degrees of severity, it is not advisable to generalize about prognosis.

2-F). Are there non-neuromuscular problems associated with Duchenne and Becker muscular dystrophy?

A number of secondary issues can arise, including problems with the joints, the spine, the heart and the function of the lungs.

Joints tend to become restricted in their range of movements. This is called contracture. The ankles are usually affected early, then the hips and knees and lastly the joints of the upper limbs. Physiotherapy and occupational therapy are directed against contractures.

Surgery is sometimes used to correct contractures. Medical opinions vary as to when surgery is advisable.

Curvature of the spine (scoliosis) is a common and serious complication. This is a curvature to the side, convex to one side and concave to the other and is accompanied by rotation of the spine distorting the shape of the chest wall. Scoliosis, if severe, can be uncomfortable, disfiguring or painful and limits the function of the lungs and the upper limbs. Scoliosis worsens most rapidly when growth is most rapid, in the latter stages of puberty. If scoliosis is not severe by the time the peak rate of growth in height has been passed, it is unlikely to become severe. Increasingly, scoliosis in DMD is treated surgically. This involves a major operation and the insertion of a long metal rod to hold the spine straight.

From: http://www.orthone.com/spine/scoliosis.asp

Pneumonia or other respiratory infections are common due to poor air movement.

2-G). How “serious” or disabling are Duchenne and Becker muscular dystrophy?

A wide variation in symptoms is seen. Duchenne is a very serious disorder causing major weakness, disability and premature death. Becker is more variable and at its mildest, Becker patients may still be able to walk at age forty and many live a relatively normal lifespan.

2-H). Does Duchenne or Becker muscular dystrophy affect thinking or behaviour?

Mental impairment is observed in about 30% of DMD cases but does not worsen as the disorder progresses.

3). DIAGNOSIS

3-A). How do I know if I have Duchenne or Becker muscular dystrophy?

Generally, parents will notice symptoms in their child, including generalised muscular weakness. Many children display what is called the Gower sign: to get up from sitting on the floor, they have to assist their back muscles by putting their hands on their knees and

thighs. The child will not appear to walk normally (waddling gait, toe walking) and will have difficulty climbing stairs.

Older patients with Becker will notice a slowly developing weakness, affecting the muscles of the hips, pelvic area, thighs and shoulders. Calves are often enlarged.

3-B). How is Duchenne and Becker muscular dystrophy diagnosed and what tests are performed?

There are three main diagnostic approaches:

- Clinical diagnosis: the doctor looks at you and notes your pattern of symptoms.
- Diagnostic tests: These can include blood tests, x-rays and other types of scans, tests of muscle and nerve function and different types of biopsies.
- Molecular and genetic testing: This method looks at genetic material taken from blood samples to see if there is a genetic problem.

Diagnostic approaches for DMD/BMD involve clinical diagnosis, diagnostic testing and molecular (genetic) diagnosis.

Clinical diagnosis involves a doctor or neurologist looking for key symptoms to identify the distinctive pattern of muscle involvement. Symptoms of DMD are easy to see in most cases but clinical diagnosis is complicated because other types of muscular dystrophy can have very similar symptoms (for example, types of Limb Girdle Muscular Dystrophy). Protein and genetic tests to confirm the diagnosis are important.

Diagnostic testing includes doing studies of the electrical pattern of the muscles using electromyography (EMG). Tiny needles are placed in a muscle and hooked up to a computer to measure the electrical activity of the muscle as it contracts and relaxes. In addition, the physician will do a blood test called a creatine kinase (CK) level (also known as a phosphocreatine kinase (CPK) level) to test the health of the muscles. If muscles are abnormally breaking down, they release elevated levels of the enzyme creatine kinase into the blood. Other tests may include a Nerve Conduction Velocity (NCV) test to measure how fast electrical signals are moving along the nerves.

A muscle biopsy may be suggested at this stage. A small piece of muscle is surgically removed and examined in the laboratory.

Once a clinical diagnosis has been suggested, the patient and doctor can discuss genetic testing. Molecular (genetic) diagnosis is often used to confirm the clinical diagnosis.

Molecular (genetic) diagnosis involves a much more accurate test than clinical diagnosis and is often used to confirm clinical suspicions. Molecular diagnosis involves a genetic understanding of the disorder and the ability to test the DNA (or RNA) in the blood for specific mutations as compared to a healthy sample.

In the past, Duchenne muscular dystrophy was diagnosed when blood tests showed the gene for the protein dystrophin to be absent or abnormal or a muscle biopsy showed extremely low levels of dystrophin protein in the muscle. Today, it is suggested that a definitive diagnosis of DMD requires muscle biopsy evidence of complete absence of dystrophin. A reduction in dystrophin does not always indicate that the patient has a dystrophinopathy (Griggs and Bushby, 2005).

Griggs and Bushby (2005) further note that "without a definitive diagnosis of DMD, it is not possible to counsel families concerning the implications of an x-linked vs an autosomal disorder, and in the future, specific therapies for DMD may depend on the precise delineation of the mutation." Whenever possible, patients need to be diagnosed based on fully characterized biochemical (protein) and molecular (genetic) analysis.

3-C). Is there a genetic test for it?

Yes, very accurate diagnostic tests of the DNA taken from the blood can show the presence and size of the mutation and permit DNA diagnosis in many cases. The cloning of the dystrophin gene in 1987 led to the first genetic diagnosis of a muscular dystrophy: the Duchenne (DMD) and Becker (BMD) muscular dystrophies. Screening for mutations in the dystrophin gene is now a routine diagnostic test for patients suspected of having DMD or BMD. Testing for Duchenne and Becker muscular dystrophy usually can detect up to 98% of the large-scale dystrophin gene deletions and duplications that occur in about 70% of male patients (and in females who carry the mutation). The detection of point mutations that underlie the disorder in up to 30% of patients is much more problematic and there are patients in whom a precise molecular diagnosis has not been possible. Recent improvements in molecular diagnosis mean that it is now possible to identify mutations in up to 90% of patients with DMD symptoms but these techniques are not universally available (Mendell, 2001).

Prenatal testing is generally available.

Gene Tests DMD/BMD testing:
http://www.genetests.org/servlet/access?prg=j&db=genetests&site=gt&id=8888892&fcn=c&qry=53738&res=&key=QCugt9yNtR8qG&show_flag=c

3-D). Should other members of my family be tested for Duchenne and Becker muscular dystrophy?

As DMD/BMD are genetic disorders, it is possible that parents, siblings, or children may also carry the mutation responsible for the disorder.

Testing for any genetic disorder is a personal choice and, when done on a seemingly healthy individual, that choice should not be made lightly. This question should be discussed with your family and with your doctor.

An excellent site for information on genetic testing is the GeneTests Web site, funded by the National Institutes of Health (USA); see the section on educational materials. http://www.genetests.org/

3-E). Can I be confident in the diagnosis?

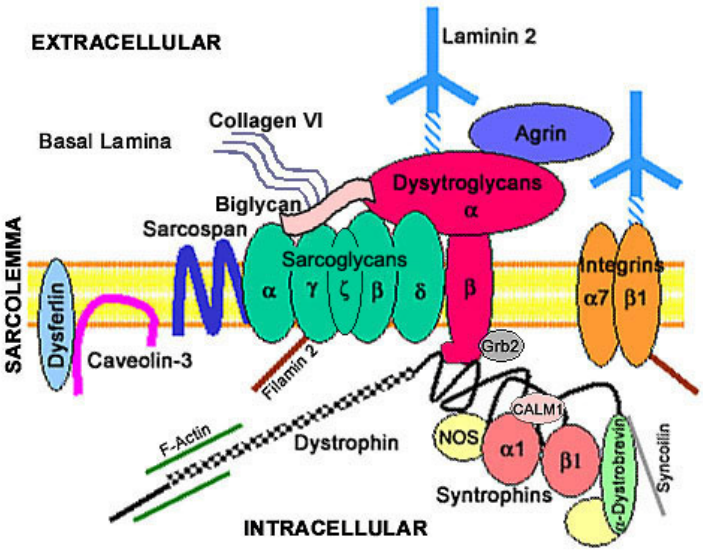
Over the years, neuromuscular disorders have developed a reputation as sometimes being difficult to diagnose. Modern diagnostic procedures are a combination of good clinical judgment and very accurate tests. If you feel unsure about your diagnosis, it is important that you discuss your concerns and options for further testing or a second opinion with your neurologist or doctor.

As more is discovered about the genetic mutations involved in different forms of muscular dystrophy, better and better diagnosis is possible. This is important as many different forms have similar symptoms. A recent study looking at a group of DMD patients discovered that about 10% (13 of 102 cases) were misdiagnosed and actually had a form of Limb Girdle muscular dystrophy (LGMD type 2I) (Schwartz, 2005). Patients need to be diagnosed based on fully characterized biochemical and molecular analysis.

4). CAUSES and PATHOLOGY

4-A). What causes Duchenne and Becker muscular dystrophy?

DMD and BMD are caused by several different types of mutations occurring in different locations in a gene on the X chromosome. The gene makes a protein called dystrophin. Normally, the gene makes several slightly different forms of dystrophin protein and some of these play different roles in different tissues in the body, for example, dystrophin is needed in the muscles, in the brain and in the retina of the eye. Dystrophin is especially important for long term muscle function. If there is not enough dystrophin, the muscle cells breakdown and eventually die. In many patients with Duchenne muscular dystrophy no dystrophin protein can be found. Patients with Becker muscular dystrophy usually have more mild mutations (point mutations) and may produce some partially functioning dystrophin, with a relatively slower degeneration of muscles.



From: http://www.neuro.wustl.edu/neuromuscular/musdist/dag2.htm

4-B). How does a person get Duchenne and Becker muscular dystrophy?

As genetic disorders, DMD and BMD are passed from generation to generation through inheritance. Mothers who carry the mutation (and who may or may not know that they have the disorder) can pass it on to their children.

Many cases of DMD/BMD arise as a new or spontaneous mutation. In these cases the parent's DNA that is passed on is healthy. In the development of new cells after conception, the DNA is copied over and over. In this copying process, a mistake can occur and the child's DNA suffers a new mutation. Research studies indicate that at least 30% of DMD/BMD cases appear to be caused by spontaneous (new) mutations.

4-C). Is Duchenne and Becker muscular dystrophy anyone's fault? Is it contagious?

No. The mutations that cause DMD/BMD occur by chance and are passed from generation to generation or arise as a new genetic mutation, again by chance. Because of the relatively late onset of the disorder, many people are not aware that they have a problem until after they have had children and have passed on the mutation. Today, if DMD/BMD is suspected or if there is a family history of the disorder, a prenatal test is available.

Is it contagious? DMD/BMD is not contagious; it is a genetic disorder and therefore cannot be passed from person to person by any sort of physical contact. Genetic disorders can only be passed on through reproduction.

5). GENETICS

5-A). Does genetics play a role in Duchenne and Becker muscular dystrophy?

Yes. Duchenne and Becker muscular dystrophy are genetic disorders caused by mutations occurring in the dystrophin gene on the X chromosome.

The dystrophin gene is the largest yet found in humans, containing some 2,220,223 “letters” of genetic code making up 79 protein forming segments (exons), coding for 3685 amino acids in the final protein (by comparison, the gene for insulin protein contains just 3 exons coding for only 51 amino acids). [But dystrophin protein is not the largest protein found, another muscle protein called titan is the largest in the body.]

All of the 79 exons have to be present, lined up and spaced correctly for dystrophin protein to be made perfectly. Mutations cause deficiencies in one or more of these exons leading to abnormal, decreased or absent dystrophin in cells – this causes the symptoms of Duchenne and Becker.
Because dystrophin is affected, these disorders are now often cited as examples of a dystrophinopathy – [DIS-trow-fin-OP-path-ee] – a pathology of dystrophin.

Several different kinds of mutations are seen, in three major categories: deletions of DNA code, duplications of DNA code or point mutations in the DNA code. In Duchenne, 65% of patients have gene deletions and about 10% have duplications. Point mutations are found in about 70% of patients who do not display deletions or duplications. Generally, point mutations have a less severe impact.

Patients with DMD often have very severe out of frame deletions (60%) of the dystrophin gene that are readily detectable on routine molecular testing. These out of frame mutations result in the virtually complete absence of dystrophin in muscle, while in frame point mutations in the dystrophin gene causing partial loss of dystrophin often account for the milder symptoms of Becker.

5-B). What genes are related to Duchenne and Becker muscular dystrophy?

Mutations of the dystrophin gene found on the X chromosome cause DMD and BMD.

5-C). Is Duchenne and Becker muscular dystrophy inherited and if so, how?

Yes, DMD/BMD are inherited in a special way because the gene is found on the X chromosome. They are X-linked (X chromosome) recessive disorders.

Certain genes are usually found on certain chromosomes, in our case, we are interested in the dystrophin gene found on the X chromosome. The other 22 pairs of chromosomes carry two copies of their genetic code, one copy inherited from mom and one version

inherited from dad. The X and Y chromosomes are different in that the Y chromosome does not carry second copies of the majority of the genes found on the X. This means that boys who carry an XY pair (the Y inherited from dad and the X from mom) will usually be affected by any disorders found on their single X chromosome. Because females carry an XX pair (one X inherited from mom, one from dad) they will usually be protected from an X recessive disorder like DMD/BMD as their second X copy is usually normal and is able to contribute enough healthy dystrophin to avoid symptoms.

A mother passes on one of her X chromosomes to her child, if she has a mutated X chromosome there is a 50% chance of transmitting on this mutated X in each pregnancy. If a boy recieves it, he will display the disorder. If a female child recieves it, she will be a carrier but will likely not display symptoms. Likewise, the mother has a 50% chance of passing on her healthy X chromosome, a child receiving it will be normal and a non carrier.

An affected male will pass on the mutation to daughters who become carriers (dad has only one X and it is passed onto each of his daughters, dad's sons are unaffected as they receive his Y chromosome).

X-linked recessive disorders show some special features:

- X-linked genes are never passed from father to son. The Y chromosome is the only sex chromosome that passes from father to son.
- Males are never simply carriers of X-linked disorders – if they have a mutated gene on the X chromosome, it will be expressed, usually as a disorder.
- Affected males inherit the disease from the X they receive from their mother or it arises as a new mutation
- All daughters of affected males will be carriers (the male's one X is passed on to daughters along with the second X from the mother)
- Sons of females with one copy of a mutated X gene have a 50% chance of receiving the mutation and developing the disorder
- Because it is a recessive disorder, females are usually protected by their second X chromosome. Females with the mutation are carriers who can pass the mutation on to children, but are usually not directly affected by the disorder and do not show symptoms
- In some rare cases of what is called skewed X chromosome inactivation, (explained below) females can develop DMD/BMD symptoms and are referred to as "manifesting carriers"

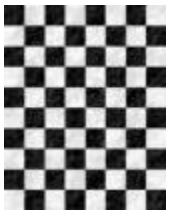
Skewed X chromosome inactivation: Human females inherit two X chromosomes while males only inherit one copy. If both X copies were active in females, they would receive a double dose of the X chromosome genes. To prevent this, early in embryonic development, in each cell of the female, one of the two X chromosomes is randomly selected and inactivated. Thus, although they receive two copies of the X at conception, females only have a single active X chromosome in each cell. The female's cells are found in a mosaic pattern; in about half of the cells, the X chromosome received from

dad remains active while in the other half, the X chromosome received from mom is active. If a female receives a mutated X from one parent, the other X is usually healthy and at 50% activation, is enough to prevent major symptoms from developing. The female is a carrier but with no manifestation of the disorder. In some rare cases, X inactivation is not 50/50, it is skewed and more of the healthy X chromosomes are inactivated leaving more of the mutated ones active. In some cases more than 90% of the healthy X chromosomes are inactivated. When this happens, the mutation causes disease symptoms, in some cases, very similar in severity to those seen in males. The female is called a manifesting carrier.

Somatic and Germline (gonadal) mosaicism:

This next section is complicated but we need to be aware of it, as it impacts many people with DMD/BMD.

The above description of inheritance assumes that if there is a mutation that all of the cells will have it. This does not always happen, sometimes some cells will have the mutation and other cells will be healthy. This complicated scenario is called mosaicism and the individual is referred to as a mosaic. Think of the crisscross pattern of tiles on a black and white mosaic floor – the white tiles are healthy and the black ones are mutated – this is the type of pattern seen in the cells, some are healthy and some carry the mutation.



How does this happen? As described above, genetic mutations are not always inherited from a parent (through an egg or sperm cell), some may occur spontaneously as a new mutation after conception and during the early days of embryonic development – in the case of DMD/BMD, up to 30 percent of cases involve spontaneous mutations.

Very early in the development of an embryo, ancestor cells that are the child's future sperm or egg cells separate from the rest of the developing cells. This batch of cells, called the germline, is set aside – eggs in a female and sperm in a male. Germline cells divide and multiply in the embryo and this division continues after the child’s birth. For males, sperm cells don't complete their development until the child becomes an adolescent. A female’s egg cells complete part of their development during fetal life and part at puberty. New mutations can occur in the genes of these cells at any stage during this process. If mutations occur early in development, they often affect many of the subsequent sperm or egg daughter cells. If they occur later, mutations may affect very few cells, or maybe even just one cell. In DMD, 10% to 20% of new mutations are gonadal mosaic.

[We should mention here that new mutations are not uncommon and geneticists estimate that about 30 negative mutations occur during an average lifetime. These mutations accumulate as we age and increase in frequency as we age, this is one of the reasons why birth defects become much more common when the parents are 35 and older.]

The person with a new mutation may display the disorder and will be the first in the family to show it. Other relatives in the family will not be at risk as this was a new mutation and it has not had a chance to be passed on yet.

Whether or not a condition will affect the individual depends in part on the inheritance pattern of the disorder. If the new mutation involves a gene on the X chromosome, a male will be affected, while a female will usually not show symptoms, however, she may pass this mutation on to any children – the scenario in Duchenne and Becker muscular dystrophy.

[If a new mutation involves an autosome and a dominant disorder, for example, as is the case with FSHD, the affected person will be the first in the family to display the condition and may subsequently pass on the mutation if they have children. If the disorder is autosomal and is recessive, the person will not be affected by the new mutation because he or she still has another correct copy of the gene to provide the information for the cell to work normally. In these cases, the mutation may be passed on.]

When mutations occur after the germline has separated, there's a good chance they'll affect many sperm or egg cells but not the other cells in the body, such as blood or skin cells – these are the cells commonly used in genetic testing. A genetic test of these cells will not suggest any problems. Even if a sample of sperm or egg cells is tested and shows no mutations, other egg or sperm cells could still carry the mutation. Just one mutated cell is all it takes. Once a mutation has been inherited by a child, it becomes part of his or her DNA and can be passed on to future generations if he or she subsequently has children – the children would have the mutation in every cell.

[During a person’s lifetime, new mutations are also occurring in the somatic (body) cells. These mutations cannot be passed on to future children (because they are not in sperm or egg cells), but they can cause illness in the person’s lifetime. Common examples are mutations in skin cells causing skin cancer or in breast cells causing breast cancer.]

In summary, these mutations may affect only some cells, leaving others healthy and leading to mosaicism in the individual. In about 10 to 20% of DMD/BMD cases, we find that only some of the person’s egg or sperm cells (the germline cells) actually have the mutation.

Mosaicism greatly complicates making predictions about inheritance or the severity of a disorder in children of mosaic parents.

In patients who display mild DMD/BMD symptoms but whose genetic testing suggests a more severe type of mutation, mosaicism should be suspected. In these cases, special genetic testing can be done to reveal the mosaicism.

6). TREATMENT and MEDICAL MANAGEMENT

6-A). How can we cope with this diagnosis?

A diagnosis of DMD/BMD comes as a shock, and brings challenges and difficult adjustments for an individual, their family, and their friends. At first you may experience many mixed emotions, especially grief, anger, and fear. Giving yourself time to adjust, talking to family, friends and professionals, and reading about DMD/BMD, may help as you deal with this diagnosis. Talking to other people living with DMD/BMD, parents of children with DMD/BMD, or health professionals may also be helpful.

Children with DMD/BMD will experience physical limitations as they grow and their body changes. Even so, like other children, they need to have as normal a life as possible. Developing self-esteem, having fun, participating in recreational activities, living a normal life with family and friends at home, at school and in the community are all very important aspects in coping with a chronic disorder.

6-B). How can I best manage my life with my symptoms?

You need to manage your symptoms in close liaison with your medical team. You need to keep on top of things as they change or as new symptoms develop and discuss options with your medical team, family and others who have DMD/BMD. The overall condition needs to be kept in mind as each symptom emerges and is managed as the need arises.

6-C). How can doctors and specialists (like neurologists) help?

Neurologists are doctors who specialize in disorders affecting the nervous system and the muscles. They are often consulted for patients who may have Duchenne and Becker muscular dystrophy. Where your family doctor may not be able to offer specialized advice about DMD/BMD, they should be able to recommend you to a neurologist in a neuromuscular clinic who is better equipped to diagnose your disorder and answer questions about possible management options. There are neuromuscular clinics and hospitals across Canada that are equipped to do the necessary diagnostic testing and to offer advice and support regarding the ongoing management of DMD/BMD.

6-D). Are there treatments or medications for Duchenne or Becker muscular dystrophy?

There are currently no direct treatments for DMD/BMD that can halt or reverse the symptoms and muscle weakness. Each symptom displayed reflects an underlying issue

and each needs to have a treatment plan developed to best address the concern on an individual basis.

The best advice is to discuss medications with you doctor or neurologist.

6-E). Can surgery help?

People living with DMD/BMD might be recommended for certain surgical procedures to stabilize the spine.

6-F). Can physiotherapy help?

Once a diagnosis is confirmed, a person living with DMD/BMD may be assessed in physiotherapy in order to evaluate their joint mobility, test their facility to move from one position to another, test their ability to walk, and to evaluate their capacities in activities involving gross motor skills (jumping, running, or climbing stairs). A regular or control monitoring may be suggested and depending on each person's needs, completed with a program of activities to practice at home. These programs are aimed at strengthening or maintaining range of motion, coordination, and balance.

A physiotherapist may also prescribe a program of moderate exercise, especially swimming, under their supervision.

6-G). How can occupational therapy help?

The role of the occupational therapist is to foster fine motor skills development and lessen the impact of the disorder on lifestyle. Accessible transportation is often a requirement. Physical education (for children) or ongoing physical activities need to be adjusted to each person's capacities as soon as possible.

An occupational therapist can also recommend braces, girdles, or special belts to help compensate for weakened muscles. Muscular Dystrophy Canada's equipment loan program relies on the expertise of occupational therapists to recommend equipment required by people living with disorders such as DMD/BMD.

In the work environment, it is the responsibility adults living with DMD/BMD to negotiate employment conditions with their superiors and co-workers.

6-H). How can a nurse help?

The nurse may provide additional information about DMD/BMD and available services and resources. A nurse may offer support to help the individual and family members cope with the disorder, provide guidance with the administrative processes when required, and liaise with the various health care professionals from the clinic and other external services.

6-I). How can a genetic counselor help?

Geneticists, doctors who specialize in medical genetics, molecular geneticists, and genetic counselors are employed in major hospitals across Canada and are available to people and their families for the purpose of diagnosis and counselling. Genetic specialists can inform the person living with DMD/BMD and their family members about the specific inheritance processes involved, the genetic testing available, as well as family planning alternatives they may wish to consider. The information provided by a genetic counselor can be specifically tailored to an individual's family history and this knowledge might be very useful in further understanding how the disorder has affected him or her and his or her family.

6-J). How can a dietician help?

A balanced, nutritional diet is essential to achieve the maximum function of muscles. It is often a challenge for the average person to keep fit and keep their weight from rising as the years go by. This is especially true in patients who have muscle disorders because their ability to exercise and burn off calories is usually greatly impaired. Excessive weight gain by people living with DMD/BMD is not recommended. The extra work that weakened muscles must do to lift excess weight adds to the challenge.

A high prevalence of obesity at an early stage of Duchenne muscular dystrophy (DMD) is a commonly seen complication. Relative inactivity may lower the child's caloric requirements to the point where even a normal diet leads to obesity. In teenagers and adults, obesity may further compromise both lung expansion and function.

A dietician can offer advice in building a balanced diet for anyone living with a neuromuscular disorder. Some specific advantages to working with a dietician may include weight control and finding a proper balance of food that will keep the body healthy. Parents may need to provide their child with support and information about healthy nutrition based on work with a dietician. The ongoing support and understanding of family where nutrition is concerned is very important.

6-K). What is ventilation and will I need it?

In some types of neuromuscular disorders the muscles that control breathing are weakened. In these cases machines may be needed to help air move in and out of the lungs.

People living with DMD usually die due to respiratory complications and BMD patients also often experience respiratory complications. Mechanical ventilation is a complex and specialized topic. If this is required, the best advice is to discuss this with your doctors and peer support people who have also faced similar issues.

7). LIFESTYLE IMPACTS

7-A). How will Duchenne or Becker muscular dystrophy affect my lifestyle?

It is very difficult to answer this question due to the wide range of symptoms seen in DMD/BMD. Perhaps the most honest answer is “it depends.” Lifestyle impacts will depend upon the type and severity of symptoms you experience. When you experience them (at what stage in your life) may also be a big factor.

Neuromuscular disorders may have wide impacts on many different aspects of our lifestyle. These may include physical aspects like impacts on breathing, swallowing, bathroom habits, one’s sex-life and other day-to-day activities. In addition, there are major psychological impacts on the patient and on the rest of the family as the disorder progresses and adaptations have to be made. Progressive disorders involve progressive changes and progressive impacts. As you adjust to things, things often change again. Lifestyle impacts and psychological adaptations are therefore an unfolding process that mirrors the progression of the disorder.

8). RESEARCH

8-A). What research is being done on Duchenne and Becker muscular dystrophy?

One of the keys to treating DMD/BMD will be to develop ways to block or repair the genetic mutations involved. Alternate approaches may look at other ways to help muscle cells cope with absent or defective dystrophin. Currently, research on DMD/BMD is very active.

Muscular Dystrophy Canada funds an active and broad research agenda. You can find out more information about recent DMD/BMD research funded by Muscular Dystrophy Canada at: http://www.muscle.ca/content/index.php?id=90

8-B). Are there clinical trials for this disorder?

As of November 2005, several trials are active in North America:

1. ☐ **Not yet recruiting** Safety and Efficacy Study of Antisense Oligonucleotides in Duchenne Muscular Dystrophy
   Condition: Duchenne Muscular Dystrophy
2. ☐ **Recruiting** High-Dose Prednisone in Duchenne Muscular Dystrophy
   Condition: Duchenne Muscular Dystrophy
3. ☐ **Recruiting** Test-Retest Reliability of Pulmonary Function Tests in Patients with Duchenne's Muscular Dystrophy
   Conditions: Duchenne's Muscular Dystrophy; Scoliosis

4. ☐ **Recruiting** Pentoxifylline in Duchenne Muscular Dystrophy
Condition: Muscular Dystrophy, Duchenne

5. ☐ **Recruiting** A Double-Blinded Randomized Placebo Controlled Study of Daily Pentoxifylline as a Rescue Treatment in Duchenne Muscular Dystrophy
Conditions: Duchenne; Muscular Dystrophy

6. ☐ **Recruiting** Study Evaluating MYO-029 in Adult Muscular Dystrophy
Conditions: Becker Muscular Dystrophy; Facioscapulohumeral Muscular Dystrophy; Limb-Girdle Muscular Dystrophy

You can search for the latest clinical trials by entering the term Duchenne at: http://clinicaltrials.gov/

9). MUSCULAR DYSTROPHY CANADA SUPPORTS

9-A). How can organizations like MDC help?

Muscular Dystrophy Canada provides a number of services to registered clients, including: Information and Education, Equipment, Peer Support, Chapter Support, Referral, Social Action.

9-B). What kind of information is available?

Muscular Dystrophy Canada provides information to people registered with us, their families, community professionals, and the general public about neuromuscular disorders and related issues. Information is available in the form of disorder specific information sheets, research updates, brochures, videos, and books. An extensive and dynamic website (www.muscle.ca) provides access to electronic copies of all our publications, plus links to news and in depth coverage of our research funding. Muscular Dystrophy Canada publishes a national newsmagazine, Connections, available in both French and English. The magazine features information on a variety of neuromuscular disorders as well as related topics such as research, genetics, parenting, and quality of life. Regional offices may also keep people registered in their area up to date through regional newsletters. Services staff in our regional offices will respond to any request for information that you may have, or they will help you find the information that you need.

9-C). What kind of assistance is available for medical equipment?

The Muscular Dystrophy Canada equipment loan program provides basic medical equipment, on loan, from a stock of recycled devices such as scooters, manual and electric wheelchairs, and hospital beds. Some funding assistance may be available for the purchase of new equipment. If a request is made for a device that the Association does not cover, or only partially covers, Muscular Dystrophy Canada staff may be able to

suggest other sources of funding. For more information about equipment funding, call the regional office nearest you.

9-D). What is peer support and how can it help?

Peer support means getting help or advice from, or just plain talking to other people who have experience with DMD/BMD. Often others who have the same disorder are good people to ask questions and to get advice from, especially in terms of how to manage the small day-to-day frustrations that come up.

Support comes in many forms and is dependent on individual needs. Some people already have strong support systems in place through family, community, and church and their needs are minimal. Other people are facing stresses such as financial difficulties or family problems, in addition to the day-to-day reality of life with a neuromuscular disorder. Life can become difficult at particular times, such as when the diagnosis is made or when symptoms seem to get suddenly worse.

The Muscular Dystrophy Canada Peer Support Program offers those facing challenges the chance to talk to someone who has gone through a similar experience. People registered with the Association, family members, and close friends – trained by Muscular Dystrophy Canada staff – offer information about resources, tips on coping, and an "understanding ear" to people who are looking for support.

For people registered with Muscular Dystrophy Canada who might prefer support in a group setting, Association staff can refer you to a local network or support, or even help you to create a new one.

Also see: http://muscle.ca/content/index.php?id=145

9-E). How can Chapters help?

Muscular Dystrophy Canada Chapters form a nationwide network of people registered with the Association, their families, and volunteers. They actively help Muscular Dystrophy Canada to achieve our common objectives especially at a local level. Chapter activities can include support, social events, and fund raising.

Chapter members are often people registered with the Association and their families. However, anyone who is interested in furthering the aims and objectives of Muscular Dystrophy Canada is welcome to join. In communities across Canada, dedicated Chapter members provide valuable time, energy, and experience that ultimately benefit people with neuromuscular disorders and the communities they live in. For the location of the Chapter nearest you, call your regional or community office.

9-F). What kinds of referrals are made?

Staff can provide referrals and contact information to neuromuscular clinics, agencies, and other community resources, to help people registered with Muscular Dystrophy Canada find solutions to problems they face in their daily lives.

9-G). What is Muscular Dystrophy Canada's Social Action Plan?

Muscular Dystrophy Canada engages in social action to ensure that people with neuromuscular disorders can participate fully in all aspects of daily living. It aims to do this by working with other organizations to bring about policy changes in provincial and federal governments and providing volunteers in local Chapters and communities with tools they need to participate in local and community advocacy efforts.

9-H). How can I receive Muscular Dystrophy Canada services?

If you wish to receive more information about one or more of the neuromuscular disorders under the Muscular Dystrophy Canada service umbrella, or about the Association itself, please contact the regional office nearest you. Services staff can provide you with general information in response to your needs, or help you in registering with Muscular Dystrophy Canada to receive direct services.

9-I). What is the mission of Muscular Dystrophy Canada?

Muscular Dystrophy Canada supports the independence and full participation of Canadians with neuromuscular disorders. We assist individuals to participate in the decisions that affect them and collaborate with others for social change. We fund research to improve the quality of life of people with neuromuscular disorders and to find a cure.

9-J). How can I help?

Muscular Dystrophy Canada conducts year-round fund raising campaigns to support our diverse programs. Your gift will help the Association provide the dollars necessary to assist individuals living with neuromuscular disorders, and fund much-needed medical research and educational information. Please make a gift through our National office or any Regional or Community Muscular Dystrophy Canada office.

9-K). How can family and friends help?

Family support is a critical part of any illness, especially a chronic and progressive one like DMD/BMD. Sometimes family will also need to go through a period of adjustment and "getting used to" a new diagnosis. Over time, family members can learn about DMD/BMD and how they can best help you meet your particular challenges. Family can also play an important role in looking out for symptoms and in helping deal with the health care system.

Friendships are important to everyone. Regular interaction with friends and social groups can encourage positive attitudes and a positive sense of worth for both children and

adults. Regular interaction and playtime with siblings and children in the neighborhood and at school help a child learn necessary social and problem-solving skills. Adults also benefit from a social network that is satisfying to them and that understands their needs. Friends play an integral role in the emotional well-being of those living with any neuromuscular disorder.

Family and friends also play a critical role in helping the person liaise with Muscular Dystrophy Canada and with other persons with disorders. Muscular Dystrophy Canada also thanks family and friends for their tremendous efforts in fund raising and the many other activities they become involved with, including raising awareness and in advocacy of persons with muscular dystrophy.

10). OTHER RESOURCES

10-A). What other resources are available to people living with Duchenne or Becker muscular dystrophy?

There are literally thousands of web pages on myotonic dystrophy. Readers will discover a wide range of information both in complexity and credibility. Generally, the web pages of National organizations, the Government and of educational facilities are usually credible sources. The best approach is to compare several sources of information with each other to gather a consensus of facts.

A DMD/BMD Peer Support or Contact group enables individuals and families to access a wealth of information and assistance before a need arises in order to better 'manage' their disability.

Internet sources:

eMedicine Article: http://www.emedicine.com/neuro/topic670.htm

Gene Tests (National Library of Medicine, University of Washington): http://www.genetests.org/

Gene Tests DMD/BMD testing: http://www.genetests.org/servlet/access?prg=j&db=genetests&site=gt&id=8888891&fcn=c&qry=53738&res=&key=YGgw11uTD9AYT&show_flag=c

Gene Tests DMD/BMD Review: http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=YGgw11uTD9AYT&gry=&fcn=y&fw=8aG1&filename=/profiles/dbmd/index.html

Muscular Dystrophy Association (USA): http://www.mdausa.org/disease/dmd.cfm and http://www.mdausa.org/publications/fa-dmdbmd.html

Neuromuscular Disease Center, Washington University, St. Louis, MO. (USA):
http://www.neuro.wustl.edu/neuromuscular/musdist/dmd.html#ref1

Online Mendelian Inheritance in Man (OMIM). This database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by NCBI, the National Center for Biotechnology Information, National Institutes of Health (NIH):
Page on DMD: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=310200
Page on BMD: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=300376

10-B). References used in this paper.

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Mendell JR, Buzin CH, Feng J, et al. Diagnosis of Duchenne dystrophy by enhanced detection of small mutations. Neurology 2001;57:645–650.

Schwartz Marianne, PhD; Hertz, Jens Michael MD, PhD; Sveen, Marie Louise MD; and Vissing, John MD, PhD LGMD2I presenting with a characteristic Duchenne or Becker muscular dystrophy phenotype NEUROLOGY 2005;64:1635–1637

Please feel free to search for specific terms on the internet. A number of excellent medical and genetic dictionaries are now online.

For example:
http://www.nlm.nih.gov/medlineplus/mplusdictionary.html

http://cancerweb.ncl.ac.uk/omd/

http://www.stedmans.com/

http://www.dorlands.com/wsearch.jsp

http://www.onelook.com/

END.