Muscular Dystrophy Tasmania

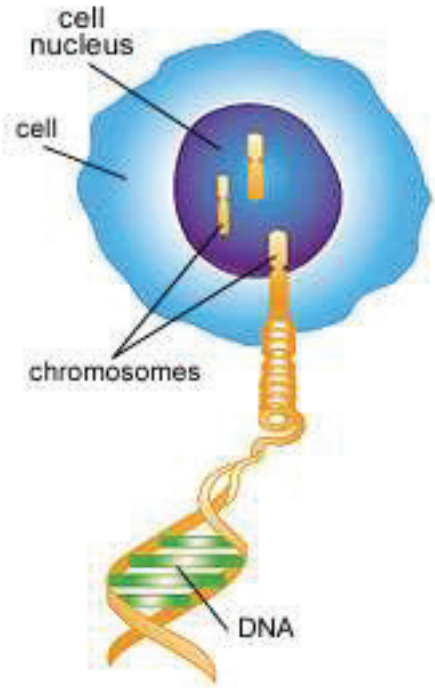
Facts About Genetics and Neuromuscular Diseases

Introduction

Since the mid-1980s, science has made tremendous progress in understanding genetics, including the roles that genes play in certain diseases.

"Genetics and Neuromuscular Diseases" gives an up-to-date review of genetics information relating to neuromuscular diseases.

This fact sheet describes just what a genetic disorder is, and explains how genetic testing and counselling can help people understand how disorders that may affect themselves or their children are inherited. It also gives examples of the major patterns of inheritance, with specific neuromuscular diseases as examples. Finally, it looks at a little-known aspect of genetics called mitochondrial inheritance.



If you have a neuromuscular disease, or would like to know more about a particular neuromuscular disease, you can find the specific fact sheet on the MDT website (www.musculardystrophytasmania.com.au),diseases involve more than one gene or have several inheritance patterns. If you want to learn about the genetics of your particular neuromuscular disorder, you'll need to consult a specialist. Your doctor can refer you to a geneticist or genetic counsellor for testing and information or you can contact the Centre for Genetics Education (www.genetics.com.au).

What is a genetic disorder?

A genetic disorder is a condition that's caused by a change or mistake, called a mutation, in a gene. A disease-causing mutation generally interferes with the body's production of a particular protein.

What is a gene?

Genes, made of the chemical known as DNA (deoxyribonucleic acid), are strings of chemicals that form a "rough draft" of the recipes (often called codes) for the thousands of proteins our bodies use to build cellular structures and carry out the functions of our cells. DNA is stored on strands called chromosomes, located mostly in the nucleus of each cell in the body.

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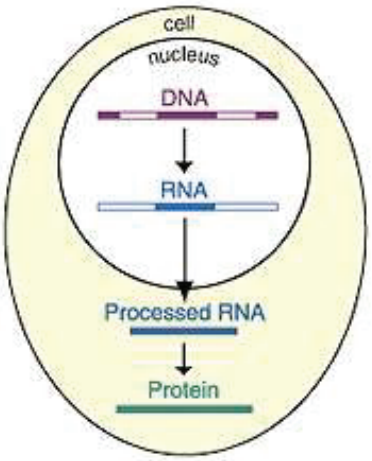
How do genes lead to proteins?

The final copies of the protein recipes are actually carried in RNA (ribonucleic acid), a very close chemical cousin of DNA. The cell converts DNA to RNA in its nucleus. Each RNA recipe then leaves the cell's nucleus and becomes the instruction manual for the manufacturing of a protein outside the nucleus.



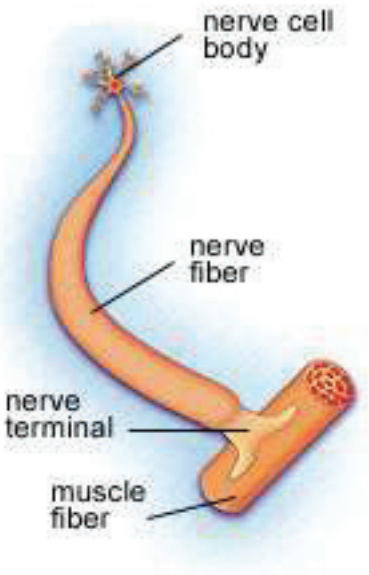
How do mutations in genes lead to problems in proteins?

A mutation in the DNA for any protein can become a mutation in the RNA recipe and then an error in the protein made from those RNA instructions. Some mutations are worse than others for the cell. Some mutations lead to production of a slightly abnormal protein, while others lead to a very abnormal protein or to the complete absence of a particular protein.

How do protein problems affect people?

The effects of a mutation in DNA in a person depend on many factors, among them exactly how the mutation affects the final protein (whether the protein is made at all and, if so, how close to normal it is), and how crucial that protein is in the body.

For example, some mutations in the gene for the protein dystrophin lead to relatively mild muscle weakness, while others lead to very severe weakness, depending on how much dystrophin is produced and how close it is to normal dystrophin. The mutations leading to severe weakness ultimately threaten life because dystrophin is needed for cardiac and respiratory muscle functions. All this may seem like a lot of explanation, but it's the basis for how you and the professionals you consult can make decisions about any genetic disorder that may be in your family.



What do proteins do?

The functions of proteins include such things as sending or receiving signals to or from other cells, breaking down large molecules into smaller ones, combining smaller molecules to make larger ones, and producing energy for all cellular activities. These activities ultimately result in functions like muscle contraction, digestion and metabolism of food, and regulation of blood pressure and temperature, as well as seeing, hearing, thinking and feeling.

What about the proteins in neuromuscular disorders?

The proteins involved in the genetic neuromuscular disorders are normally present in nerve cells or muscle cells. Proteins in nerve cells affect the way a nerve cell receives signals from other cells or transmits signals to other cells, including muscle cells.

Proteins in muscle cells affect the functions of the muscle cell, such as contraction (the action that moves muscles), the way in which the muscle cell receives signals from a nerve cell or the various mechanisms by which a muscle cell protects itself from the stresses of its own workload. When genes for these nerve and muscle proteins are mutated, loss of, or abnormalities in these proteins cause genetic neuromuscular disorders.

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What is genetic testing?

Genetic testing usually means the direct examination of the DNA (it can sometimes mean RNA or the protein product of the DNA and RNA) in a gene associated with a particular disorder. The examination is usually made in order to enhance the understanding of symptoms (for example, to confirm a diagnosis of a muscular dystrophy), or to predict the occurrence of a genetic disorder in which symptoms haven't yet appeared.

Usually, only a blood sample is needed, but occasionally other tissues are used for the testing.

Genetic counsellors can helppeople make decisions about genetic testing and childbearing

Are there risks associated with genetic testing?

Yes. You hear a lot about genetic testing these days, not just in the clinic or other medical settings, but in the newspaper and on TV, as gene after gene is discovered to be associated with everything from cancer or heart disease to rare disorders of metabolism or muscle function.

Privacy concerns are real. Some people are very concerned that genetic testing can interfere with privacy, insurance eligibility or even employment. Unfortunately, these fears aren't easily dismissed.

However, you can minimize the risks by going to a qualified clinical geneticist (genetics doctor) and genetic counsellor and discussing your concerns about privacy. In some situations, you may decide not to have a genetic test.

Mistakes can occur, and results can be unclear. Genetic tests, like any other tests, are subject to error. Accuracy in a qualified laboratory is high but never perfect. Also, the results of a test can sometimes be hard to interpret.

For example, testing may reveal a mutation the significance of which is unclear. Professionals may not know the effects of a previously undetected change in a gene. Not all changes are harmful.

Prenatal testing can prompt difficult examination of beliefs and values. Predictive, or pre-symptomatic, genetic tests are often done on fetuses in the womb or embryos created by in vitro (out of the body) fertilization. This is known as prenatal genetic testing.

A test result that suggests it's likely the baby will develop a serious genetic disorder makes parents face some very tough decisions. Genetic counselling, perhaps aided by psychological and spiritual counselling for both parents, can be of help.

Pre-symptomatic or carrier testing of children is controversial. Many professional organizations strongly discourage and some medical centres may refuse to perform genetic testing of minors unless there is a compelling medical reason (such as treatment that can be started prior to symptoms) to do so.

Thoughtful professionals have reasoned that testing children or adolescents for a mutation that may cause an adult-onset disorder or confer carrier status may actually do more harm than good, and that people should be allowed to make the decision about testing for themselves when they reach adulthood.

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Genetic testing is so new that the legal, ethical and medical implications are far from clear. In the meantime, parents may elect to wait until their child is old enough to make an informed choice about genetic testing. Again, this is something to discuss with your physician or genetic counsellor.

Testing of symptomatic, at-risk or carrier adults can have unintended consequences. Testing of adults who may have symptoms of a genetic disorder or a family history of a genetic disorder is perhaps the least controversial type of genetic testing. However, it, too, can have unintended consequences. For example, test results on one person may suggest the genetic status of other family members, causing a dilemma about whether to inform the family or not.

Results may also cause anxiety or depression in the person being tested, particularly if there's no effective treatment for the condition or if it affects plans for having a family.

Test results demonstrating that a disorder came from one parent or the other can cause a strain in the parents' relationship or excessive guilt on the part of the parent whose gene was involved. Again, help from a genetic counselor and other counsellors is strongly recommended.

How much does genetic testing cost?

Costs of genetic tests vary widely, depending on the availability of the test, and how complicated and time consuming the test is to perform. They can range from about hundreds of dollars to several thousands of dollars.

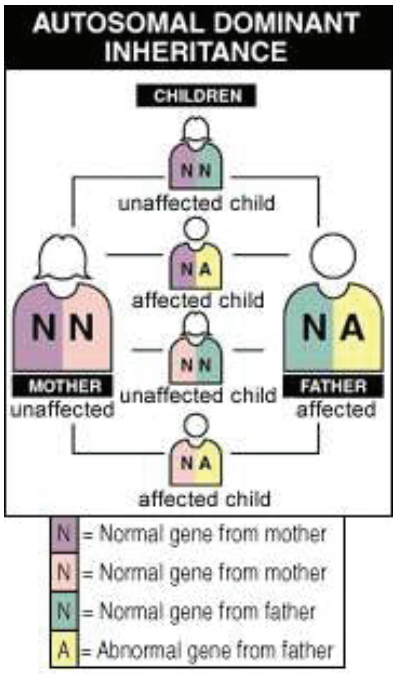
How are genetic disorders inherited?

Long before the advent of genetic testing or even complete understanding of DNA and RNA, astute observers noticed that genetic traits, including many disorders, were passed from one generation to another in somewhat predictable patterns. These came to be known as autosomal dominant, autosomal recessive, X-linked recessive and Xlinked dominant patterns of inheritance. To understand heredity, you have to know a little about human chromosomes and how they work.

Chromosomes come in pairs in the cell's nucleus. Humans have 46 chromosomes in each cell nucleus, which are actually 23 pairs of chromosomes. For 22 of these pairs, numbered chromosome 1 through chromosome 22, the chromosomes are the same; that is, they carry genes for the same traits. One chromosome comes from a person's mother, the other from his father. The 23rd pair is an exception and determines gender. The 23rd chromosomal pair differs according to whether you're a male or a female.

Males have an X and a Y chromosome, while females have two Xs for this 23rd pair of chromosomes. Every female gets one X chromosome from her mother and one X from her father. Every male gets an X chromosome from his mother and a Y from his father. Y chromosomes are unique to males and, in fact, determine maleness. If a man passes to his child an X chromosome from this 23rd pair, it will be a girl; if he passes on a Y, it will be a boy.

Autosomal dominant conditions require only one mutation to show themselves as a disease.



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When specialists use the term autosomal dominant, they mean that the genetic mutation is on an autosome, one of the chromosomes that's not an X or a Y. They also mean that the condition caused by the mutation can occur even if only one of the two paired autosomes carries the mutation. It's a way of saying that the mutated gene is dominant over the normal gene.

In autosomal dominant disorders, the chance of having an affected child is 50 percent with each conception.

Autosomal recessive conditions require two mutations to show themselves. When they use the term autosomal recessive, they mean that the disorder is again located on chromosomes that aren't Xs or Ys. However, when a disorder is recessive, it takes two mutated genes to cause a visible disorder in a person.

The word "recessive" comes from the idea that, when only one gene mutation exists, it may remain undetected ("recede" into the background) for several generations in a family - until someone has a child with another person who also has a mutation in that same autosomal gene. Then, the two recessive genes can come together in a child and produce the signs and symptoms of a genetic disorder.

You can think of recessive genes as "weaker" than "dominant" genes, in that it takes two of them to cause a problem.

People with one gene mutation for disorders that require two to produce the disorder are said to be carriers of the disorder. Carriers are usually protected from showing symptoms of a genetic disease by the presence of a normal corresponding gene on the other chromosome of each chromosome pair.

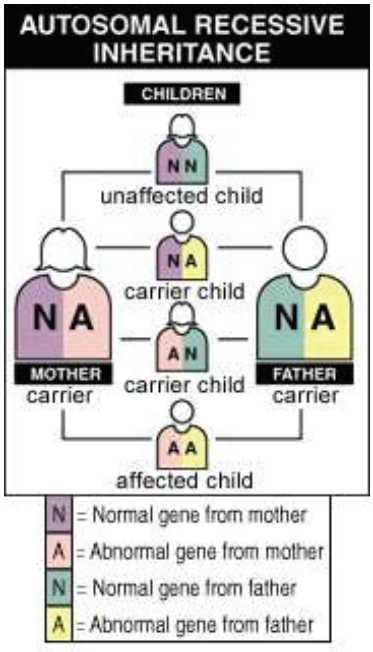
Sometimes, biochemical or other electrical testing, or certain conditions (for example, vigorous exercise or fasting) will reveal subtle cellular abnormalities in carriers of various genetic conditions.

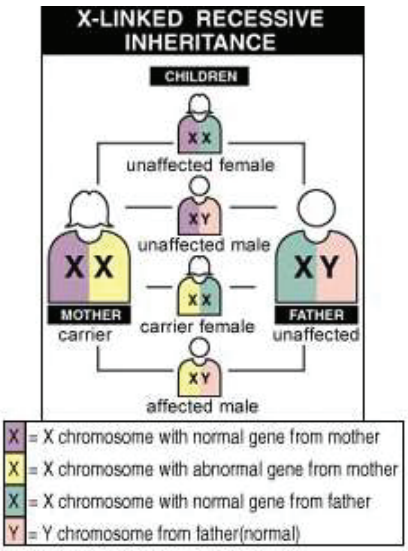
In autosomal recessive disorders, the chance of having an affected child is 25 percent with each conception.

X-linked disorders affect males and females differently. Another important inheritance pattern is the X-linked pattern. X-linked disorders come from mutations in genes on the X chromosome.

X-linked disorders affect males more severely than they do females. The reason is that females have two X chromosomes, while males have only one. If there's a mutation in an X-chromosome gene, the female has a second, "backup" X chromosome that almost always carries a normal version of the gene and can usually compensate for the mutated gene. The male, on the other hand, has no such backup; he has a Y chromosome paired with his sole X. In reality, females sometimes have disease symptoms in X-linked conditions despite the presence of a backup X chromosome. In some X-linked disorders, females routinely show symptoms of the disease, although they're rarely as serious (or lethal) as those in the males.

Some experts prefer the term X-linked recessive for the type of X-linked disorder in which females rarely show symptoms and X-linked dominant for the type in which females routinely show at least some disease symptoms.





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Females with mild or no disease symptoms who have one mutated gene on an X chromosome and a normal version of the gene on the other X chromosome are called carriers of an X-linked disorder.

In X-linked recessive disorders, when the mother is a carrier, the chance of having an affected child is 50 percent for each male child. If the father has the mutation and is able to have children, boys won't be affected, because they receive only a Y chromosome from him. Girls receive his X chromosome and will be carriers.

Can inheritance diagrams predict what my family will look like?

No. Many of us have seen diagrams like those of autosomal dominant, autosomal recessive and X-linked recessive inheritance during our school years or perhaps in medical offices (such as those above). Unfortunately, these diagrams very often lead to misunderstandings.

The diagrams are mathematical calculations of the odds that one gene or the other in a pair of genes will be passed on to a child during any particular conception.

These are the same kinds of calculations one would make if asked to predict the chances of a coin landing as heads or tails. With each coin toss (assuming the coin isn't weighted and the conditions are otherwise impartial), the chances that the coin will land in one position or the other are 50 percent.

In reality, if you were to toss a coin six times, you might come up with any number of combinations: All your tosses might be heads, or five could be heads with one tails, or four might be tails with two heads.

In fact, every coin toss was a new set of odds: 50 percent heads, 50 percent tails. The second coin toss wasn't the least bit influenced by the first, nor the third by the first two, nor the sixth by the previous five.

So it is with the conception of children. If the odds of passing on a certain gene (say a gene on the X chromosome that carries a mutation versus a gene on the other X chromosome that doesn't) are 50 percent for each conception, they remain 50 percent no matter how many children you have.

Don't be misled by an orderly diagram that shows one out of two children getting each gene so that a family of four children has two children with and two children without the gene in question. Like the coin toss where six tosses turned up six heads, you could have six children who all inherit the gene.

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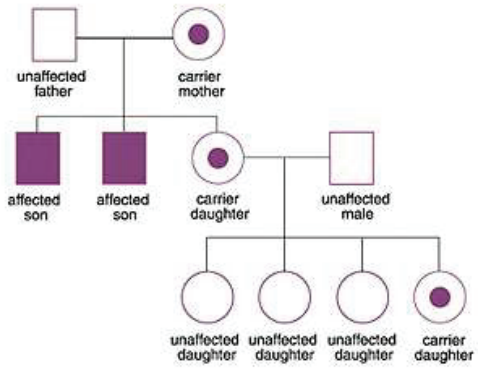
What happens in actual families?

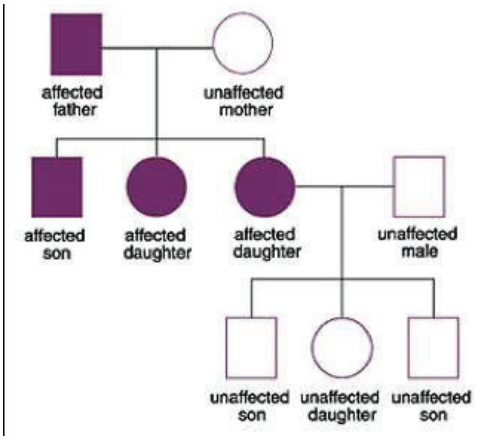
In real life, it's impossible to predict which genes will be passed on to which children at each conception. This kind of prediction would be the same as trying to predict the outcome of any particular coin toss. Even though the overall odds are 50 percent heads and 50 percent tails, you can get six heads in a row.

This fact sheet offers some examples of what could happen in actual situations.

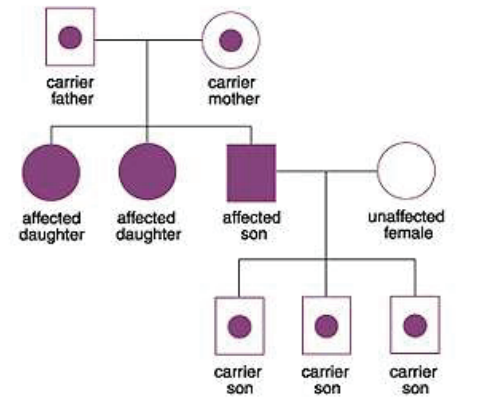
These types of diagrams (see below) are called a family tree or pedigree. Clinical geneticists and genetic counsellors may construct a pedigree or tree as you give your family history, or you may see these in books or on Web sites.



Example of a family tree (pedigree) in Duchenne muscular dystrophy (x-linked)



Example of a family tree (pedigree) in myotonic dystrophy (autosomal dominant)



Example of a family tree (pedigree) inspinal muscular atrophy (autosomal recessive)

How can a disease be genetic if no one else in the family has it?

This is a question often asked by people who have received a diagnosis of a genetic disorder or who have had a child with such a diagnosis. "But, doctor," they often say, "There's no history of anything like this in our family, so how can it be genetic?" This is a very understandable source of confusion.

Very often, a genetic (or hereditary) disorder occurs in a family where no one else has been known to have it.

One way for this to happen is the mechanism of recessive inheritance. In recessive disorders, it takes two mutated genes to cause disease symptoms. A single genetic mutation may have been present and passed down in a family for generations but only now has a child inherited a second mutation from the other side of the family and so developed the disease.

A similar mechanism occurs with X-linked disorders. The family may have carried a mutation on the X chromosome in females for generations, but until someone gives birth to a male child with this mutation, the genetic disorder remains only a potential, not an actual, disease. Females rarely have significant symptoms in X-linked disorders.

Another way for a child to develop a dominant or X-linked disease that's never been seen in the family follows this scenario: One or more of the father's sperm cells or one or more of the mother's egg cells develops a mutation (which is not present in other cells such as blood cells). Such a mutation would never be detected by standard medical tests or even by DNA tests, which generally sample the blood cells. However, if this particular sperm or egg is used to conceive a child, he or she will be born with the mutation. This scenario isn't rare and is called germline mosaicism.

Until recently, when parents who didn't have a genetic disorder and tested as "noncarriers" gave birth to a child with a genetic disorder, they were reassured that the mutation was a one-time event in a single sperm or egg cell and that it would be almost impossible for it to happen again.

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Unfortunately, especially in the case of Duchenne dystrophy, this proved to be false reassurance. We now know that sometimes more than one egg cell can be affected by a mutation that isn't in the mother's blood cells and doesn't show up on standard carrier tests. Such mothers can give birth to more children with Duchenne dystrophy because subsequent egg cells with the Duchenne mutation can be used to conceive a child.

In a sense, these mothers actually are carriers - but carriers only in some of their cells. They can be thought of as "partial" carriers. Another term is mosaic carrier. It's very hard to estimate the precise risk of passing on the disorder in these cases.

It's very likely that this kind of situation occurs in other neuromuscular genetic disorders, although most haven't been as well studied as Duchenne dystrophy. For example, more than one sperm or egg cell could pass on a dominant mutation to more than one of a parent's children. Or, in a recessive disorder like spinal muscular atrophy, a child could inherit one mutation from a parent who's a full carrier, and then acquire a second genetic mutation from the other parent, a mosaic carrier. Standard carrier testing wouldn't pick up any problem in the latter parent.

In practical terms, the most important message of recent research is that a genetic test that looks only at blood cells and shows that a parent is not a carrier can't be completely relied upon with regard to the risk of having another affected child. The mutation may be present in cells that weren't tested, and if those include some of the sperm or egg cells, there's a risk that more than one affected child could be born.

A clinical geneticist or genetic counsellor can help you make informed decisions regarding childbearing if you've already had a child with a genetic disorder. The recurrence risk is different in different disorders.

Are there genes outside the cell's nucleus?

Yes. There's actually another small set of genes that we all possess, inside our cells but outside the cell nucleus. The cell nucleus is where most of our genes reside on the 23 pairs of chromosomes already discussed. The additional genes, which make up less than 1 percent of a cell's DNA, are the mitochondrial genes, and they exist on circular chromosomes inside mitochondria, the "energy factories" of cells. (The singular for mitochondria is mitochondrion.)

What are genes doing inside the mitochondria?

There are about 37 genes, mostly involved in energy production, inside the mitochondria. Scientists believe that mitochondria were once independent organisms resembling today's bacteria, and that when they became part of human and animal cells, they kept their own genes. These genes, arranged on circular chromosomes, carry the recipes for 13 proteins needed for mitochondrial functions. They also code for 24 specialized RNA molecules that are needed to assist in the production of other mitochondrial proteins. For reasons that will become clear, it's important to know that mitochondria also use proteins made by genes in the cell's nucleus. These proteins are "imported" into the mitochondria.

Can disease-causing mutations occur in mitochondrial genes?

Yes. Disease-causing mutations can occur in the mitochondrial genes. The disorders are often, as one would predict, associated with energy deficits in cells with high energy requirements, such as nerve and muscle cells. The disorders as a whole are called mitochondrial disorders. Mitochondrial disorders affecting muscle are known as mitochondrial myopathies.

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How are mitochondrial mutations inherited?

Mitochondrial DNA inheritance comes only through the mother and is therefore completely different from nuclear (from the nucleus) DNA inheritance. The rules for recessive, dominant and X-linked inheritance don't apply at all. An embryo receives its mitochondria from the mother's egg cell, not the father's sperm cell, at conception. (Research suggests that sperm mitochondria are eliminated by the egg cell.)

Mutations can exist in some of the mitochondria in a person's cells and never cause much, if any, trouble. (In fact, one theory of aging says that it's caused by an accumulation of mutations in mitochondrial DNA.) The normal mitochondria are usually enough to produce the needed energy for the body. But once a person has a certain percentage of mutated mitochondria (perhaps 30 percent or so), the energy deficits become crucial and a mitochondrial disorder can result.

Mothers can pass on mitochondrial mutations to their children, but fathers can't, so mitochondrial DNA inheritance follows a pattern called maternal inheritance. The severity of the child's disorder depends on how many normal versus abnormal mitochondria the child receives from the mother.

Mitochondrial DNA mutations can also occur during development of an embryo. Not all mitochondrial mutations are inherited. Some occur as an embryo is developing in the womb. Researchers have found that embryonic mitochondrial mutations generally occur after sperm or egg cells have formed in the affected embryo, so, as far as has been observed, these mutations are not passed on to the next generation.

Does DNA from the cell's nucleus affect the mitochondria?

Yes. DNA from the nucleus also affects mitochondrial function, so some mitochondrial disorders are inherited according to the same rules as are other genetic disorders. Most mitochondrial proteins aren't made in the mitochondria but come from genes in the cell's nucleus. These nuclear proteins are later imported into the mitochondria, where they too help with energy production.

As you may have guessed, mutations can also occur in these nuclear genes that affect mitochondria. So, that's another way to get a "mitochondrial disorder" - but one that's not caused by mutated mitochondrial DNA. Nuclear DNA that affects mitochondrial function is inherited according to the autosomal and X-linked patterns.

For family planning, it's important to know exactly what kind of DNA mutation exists in a family with a mitochondrial disorder - whether it's a mitochondrial DNA mutation or a nuclear DNA mutation. As you can see, these have very different patterns of inheritance and implications for the family.

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