



Genetics Home Reference

Your Guide to Understanding Genetic Conditions

Handbook

Help Me Understand Genetics

Inheriting Genetic Conditions

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Chapter 4

Inheriting Genetic Conditions

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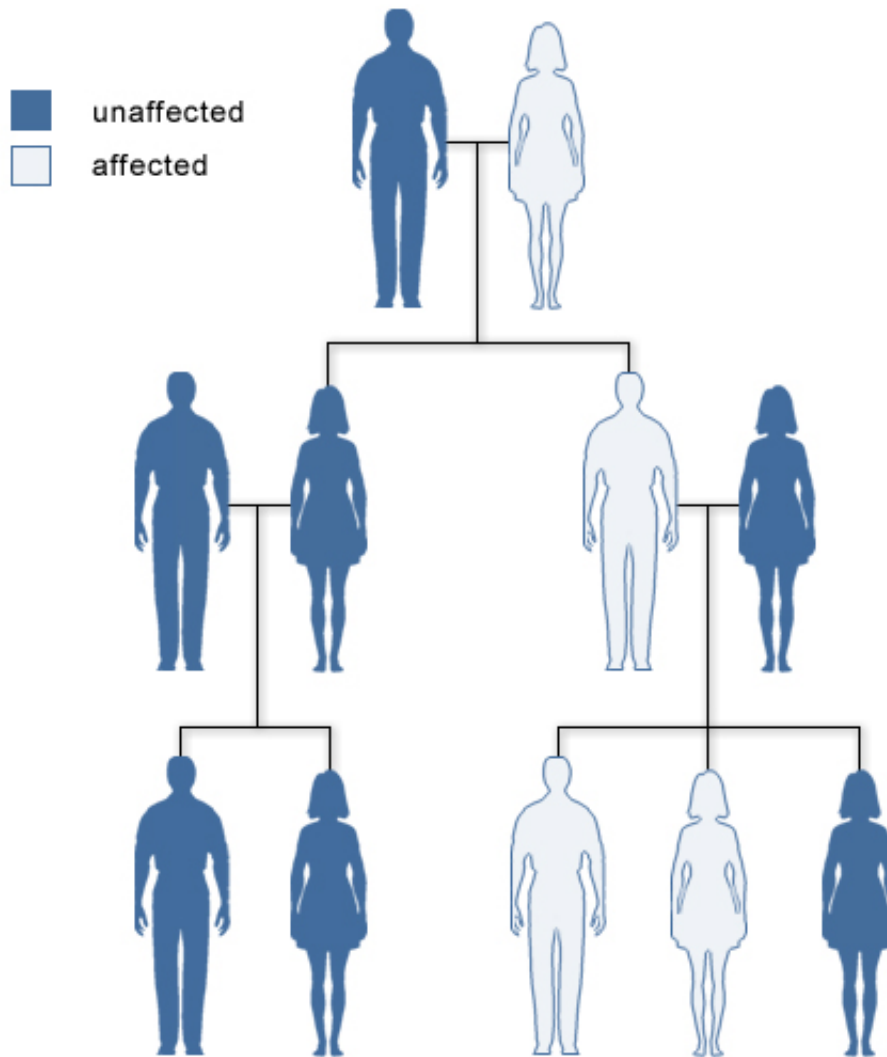
What does it mean if a disorder seems to run in my family?

A particular disorder might be described as “running in a family” if more than one person in the family has the condition. Some disorders that affect multiple family members are caused by gene mutations, which can be inherited (passed down from parent to child). Other conditions that appear to run in families are not caused by mutations in single genes. Instead, environmental factors such as dietary habits or a combination of genetic and environmental factors are responsible for these disorders.

It is not always easy to determine whether a condition in a family is inherited. A genetics professional can use a person’s family history (a record of health information about a person’s immediate and extended family) to help determine whether a disorder has a genetic component. He or she will ask about the health of people from several generations of the family, usually first-, second-, and third-degree relatives.

Degrees of relationship	<i>Degrees of relationship</i> Examples
First-degree relatives	Parents, children, brothers, and sisters
Second-degree relatives	Grandparents, aunts and uncles, nieces and nephews, and grandchildren
Third-degree relatives	First cousins

Condition affecting members of a family



U.S. National Library of Medicine

Some disorders are seen in more than one generation of a family.

For general information about disorders that run in families:

Genetics Home Reference provides consumer-friendly summaries of genetic conditions (<http://ghr.nlm.nih.gov/BrowseConditions>). Each summary includes a brief description of the condition, an explanation of its genetic cause, and information about the condition's frequency and pattern of inheritance.

The Genetic Science Learning Center at the University of Utah offers an interactive discussion of what it means to be at risk (<http://learn.genetics.utah.edu/content/health/history/>) for disorders that run in families.

The National Human Genome Research Institute offers a brief fact sheet called Frequently Asked Questions About Genetic Disorders (<http://www.genome.gov/19016930>).

The Centre for Genetics Education provides an overview of genetic conditions (<http://www.genetics.com.au/factsheet/fs2.html>).

The Department of Energy offers a fact sheet called Genetic Disease Information—Pronto! (http://www.ornl.gov/TechResources/Human_Genome/medicine/assist.html)

Why is it important to know my family medical history?

A family medical history is a record of health information about a person and his or her close relatives. A complete record includes information from three generations of relatives, including children, brothers and sisters, parents, aunts and uncles, nieces and nephews, grandparents, and cousins.

Families have many factors in common, including their genes, environment, and lifestyle. Together, these factors can give clues to medical conditions that may run in a family. By noticing patterns of disorders among relatives, healthcare professionals can determine whether an individual, other family members, or future generations may be at an increased risk of developing a particular condition.

A family medical history can identify people with a higher-than-usual chance of having common disorders, such as heart disease, high blood pressure, stroke, certain cancers, and diabetes. These complex disorders are influenced by a combination of genetic factors, environmental conditions, and lifestyle choices. A family history also can provide information about the risk of rarer conditions caused by mutations in a single gene, such as cystic fibrosis and sickle cell anemia.

While a family medical history provides information about the risk of specific health concerns, having relatives with a medical condition does not mean that an individual will definitely develop that condition. On the other hand, a person with no family history of a disorder may still be at risk of developing that disorder.

Knowing one's family medical history allows a person to take steps to reduce his or her risk. For people at an increased risk of certain cancers, healthcare professionals may recommend more frequent screening (such as mammography or colonoscopy) starting at an earlier age. Healthcare providers may also encourage regular checkups or testing for people with a medical condition that runs in their family. Additionally, lifestyle changes such as adopting a healthier diet, getting regular exercise, and quitting smoking help many people lower their chances of developing heart disease and other common illnesses.

The easiest way to get information about family medical history is to talk to relatives about their health. Have they had any medical problems, and when did they occur? A family gathering could be a good time to discuss these issues. Additionally, obtaining medical records and other documents (such as obituaries and death certificates) can help complete a family medical history. It is important to keep this information up-to-date and to share it with a healthcare professional regularly.

For more information about family medical history:

The Centers for Disease Control and Prevention (CDC) provides consumer-friendly information about the importance of family medical history (<http://www.cdc.gov/>)

[genomics/public/famhistMain.htm](http://ghr.nlm.nih.gov/genomics/public/famhistMain.htm)). This resource also includes links to tools for recording family health information.

Information about collecting and recording a family medical history (<http://www.nsgc.org/consumer/familytree/>) is also available from the National Society of Genetic Counselors.

The American Medical Association provides family history tools (<http://www.ama-assn.org/ama/pub/category/2380.html>), including questionnaires and forms for collecting medical information.

Links to additional resources (<http://www.kumc.edu/gec/pedigree.html>) are available from the University of Kansas Medical Center. The Genetic Alliance also offers a list of links to family history resources (http://www.geneticalliance.org/ws_display.asp?filter=resources_family_history_URLs).

What are the different ways in which a genetic condition can be inherited?

Some genetic conditions are caused by mutations in a single gene. These conditions are usually inherited in one of several straightforward patterns, depending on the gene involved:

Patterns of inheritance

Inheritance pattern	Description	Examples
Autosomal dominant	One mutated copy of the gene in each cell is sufficient for a person to be affected by an autosomal dominant disorder. Each affected person usually has one affected parent (illustration on page 13). Autosomal dominant disorders tend to occur in every generation of an affected family.	Huntington disease, neurofibromatosis type 1
Autosomal recessive	Two mutated copies of the gene are present in each cell when a person has an autosomal recessive disorder. An affected person usually has unaffected parents who each carry a single copy of the mutated gene (and are referred to as carriers) (illustration on page 14). Autosomal recessive disorders are typically not seen in every generation of an affected family.	cystic fibrosis, sickle cell anemia
X-linked dominant	X-linked dominant disorders are caused by mutations in genes on the X chromosome. Females are more frequently affected than males, and the chance of passing on an X-linked dominant disorder differs between men (illustration on page 15) and women (illustration on page 16). Families with an X-linked dominant disorder often have both affected males and affected females in each generation. A striking characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).	fragile X syndrome
X-linked recessive		hemophilia, Fabry disease

Inheritance pattern	Description	Examples
	<p>X-linked recessive disorders are also caused by mutations in genes on the X chromosome. Males are more frequently affected than females, and the chance of passing on the disorder differs between men (illustration on page 17) and women (illustration on page 18). Families with an X-linked recessive disorder often have affected males, but rarely affected females, in each generation. A striking characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).</p>	
Codominant	<p>In codominant inheritance, two different versions (alleles) of a gene can be expressed, and each version makes a slightly different protein (illustration on page 19). Both alleles influence the genetic trait or determine the characteristics of the genetic condition.</p>	<p>ABO blood group, alpha-1 antitrypsin deficiency</p>
Mitochondrial	<p>This type of inheritance, also known as maternal inheritance, applies to genes in mitochondrial DNA. Mitochondria, which are structures in each cell that convert molecules into energy, each contain a small amount of DNA. Because only egg cells contribute mitochondria to the developing embryo, only females can pass on mitochondrial conditions to their children (illustration on page 20). Mitochondrial disorders can appear in every generation of a family and can affect both males and females, but fathers do not pass mitochondrial traits to their children.</p>	<p>Leber hereditary optic neuropathy (LHON)</p>

Many other disorders are caused by a combination of the effects of multiple genes or by interactions between genes and the environment. Such disorders are more difficult to analyze because their genetic causes are often unclear, and they do not follow the patterns of inheritance described above. Examples of conditions caused by multiple genes or gene/environment interactions include heart disease, diabetes, schizophrenia, and certain types of cancer. For more information, please see What

are complex or multifactorial disorders? (<http://ghr.nlm.nih.gov/handbook/mutationsanddisorders/complexdisorders>).

Disorders caused by changes in the number or structure of chromosomes do not follow the straightforward patterns of inheritance listed above. To read about how chromosomal conditions occur, please see [Are chromosomal disorders inherited?](http://ghr.nlm.nih.gov/handbook/inheritance/chromosomalinheritance) (<http://ghr.nlm.nih.gov/handbook/inheritance/chromosomalinheritance>).

Other genetic factors can also influence how a disorder is inherited: What are genomic imprinting and uniparental disomy? (<http://ghr.nlm.nih.gov/handbook/inheritance/updimprinting>)

For more information about inheritance patterns:

The Genetics and Public Policy Center provides an introduction to hereditary mutations (<http://www.dnapolicy.org/genetics/geneticsAndDisease.jhtml.html#hered>), including their patterns of inheritance.

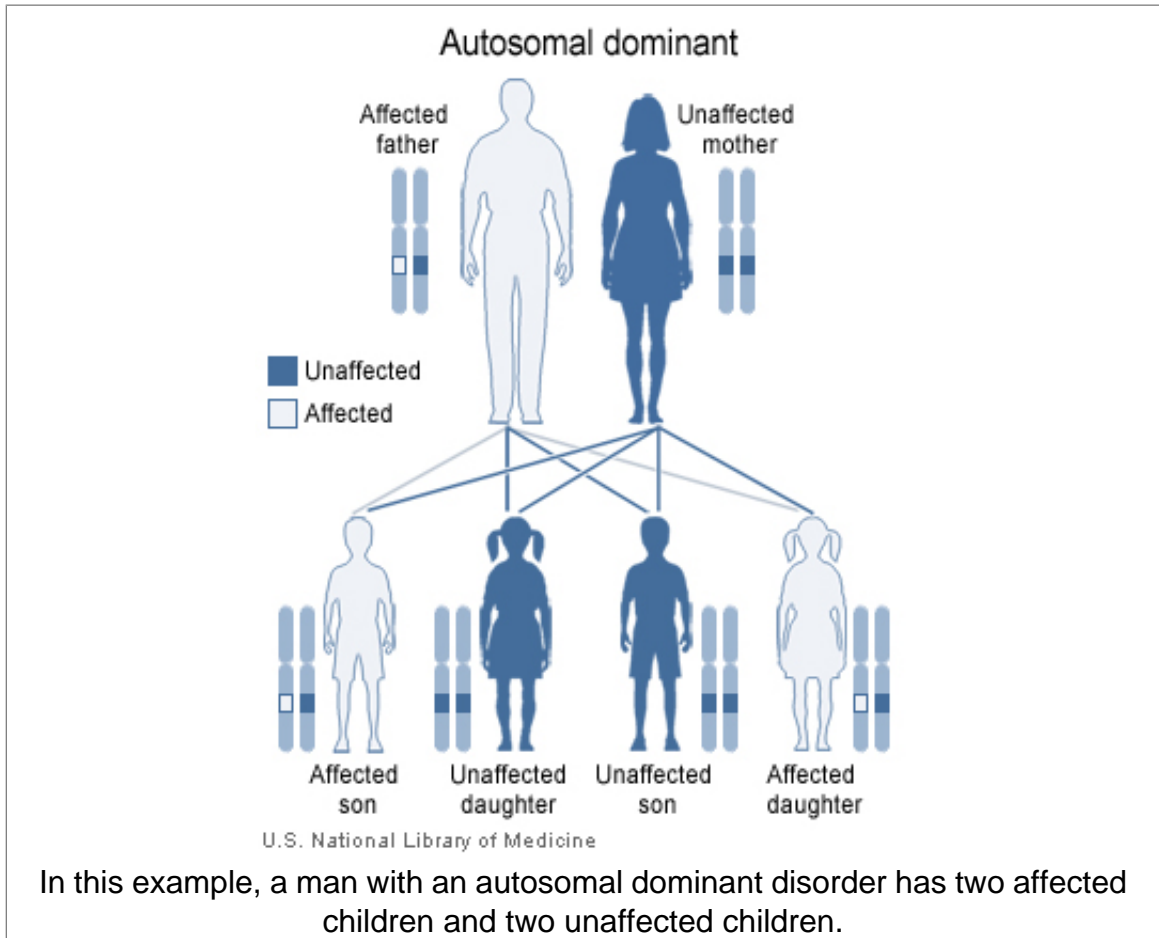
The Wellcome Trust offers a brief overview of single gene disorders and their patterns of inheritance (http://genome.wellcome.ac.uk/doc_WTD020848.html). This fact sheet has links to more specific information about dominant, recessive, and X-linked inheritance patterns.

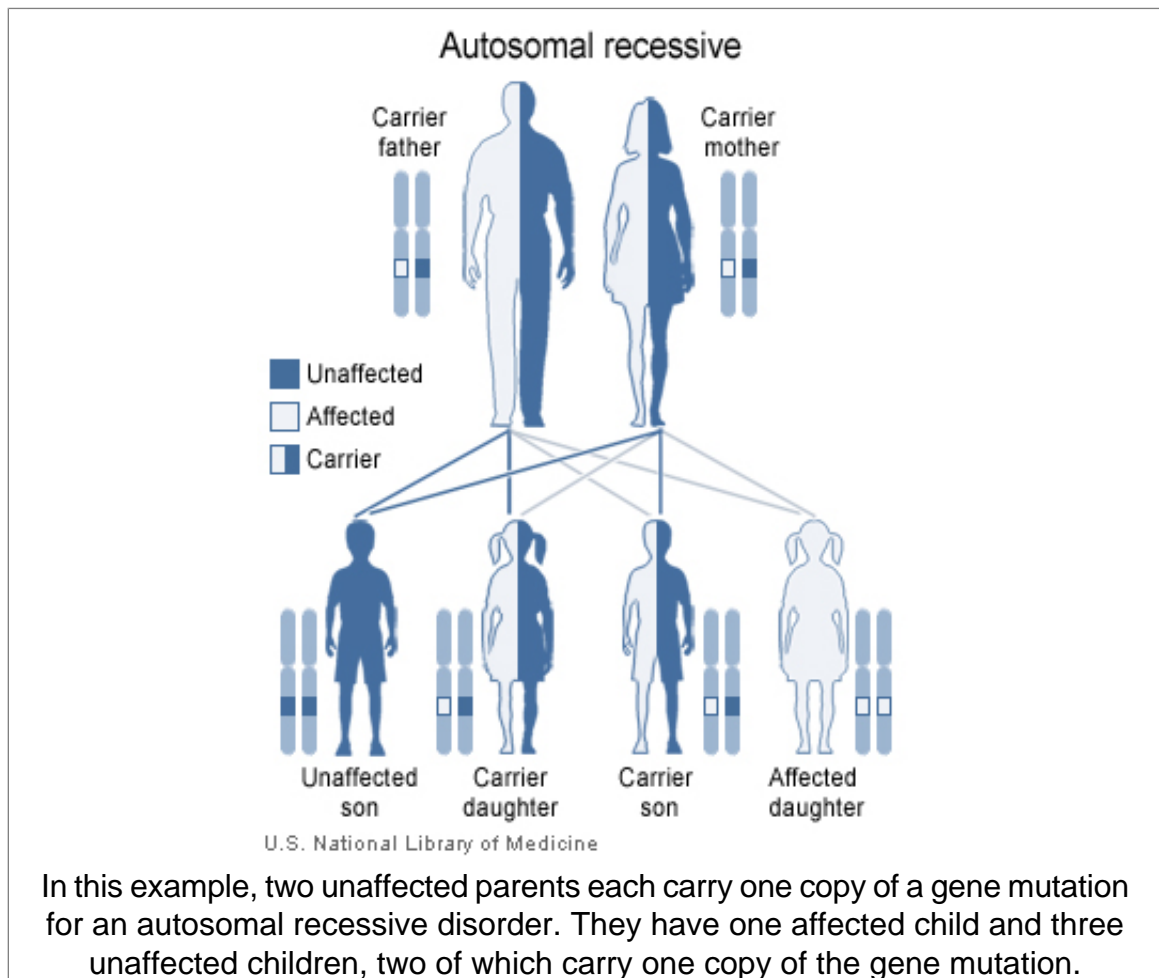
The Centre for Genetics Education provides information about each of the inheritance patterns outlined above:

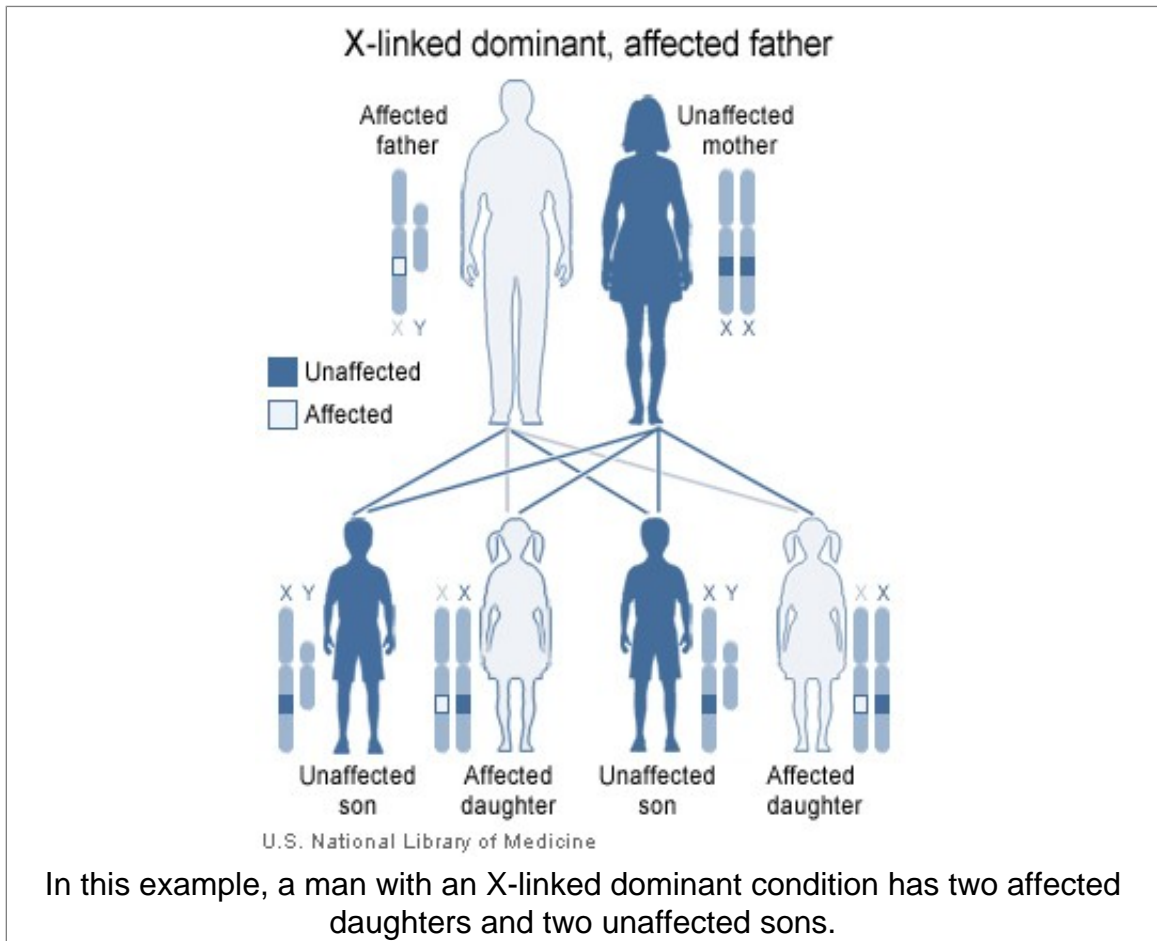
- Autosomal dominant inheritance (<http://www.genetics.com.au/pdf/factsheets/fs09.pdf>)
- Autosomal recessive inheritance (<http://www.genetics.com.au/pdf/factsheets/fs08.pdf>)
- X-linked inheritance (<http://www.genetics.com.au/pdf/factsheets/fs10.pdf>)
- Mitochondrial inheritance (<http://www.genetics.com.au/pdf/factsheets/fs12.pdf>)

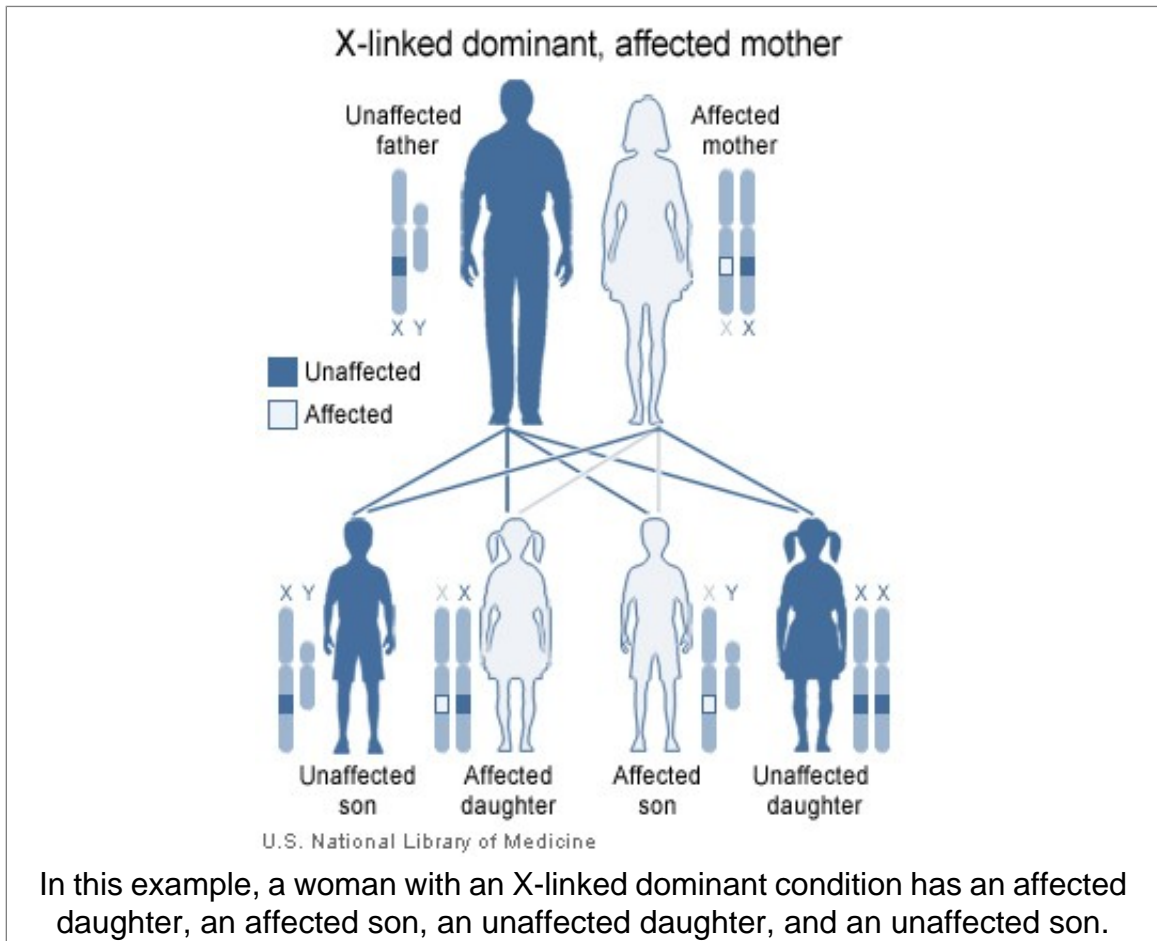
Additional information about inheritance patterns, including codominant inheritance, is available from The Merck Manual of Diagnosis and Therapy (<http://www.merck.com/mrkshared/mmanual/section21/chapter286/286b.jsp>).

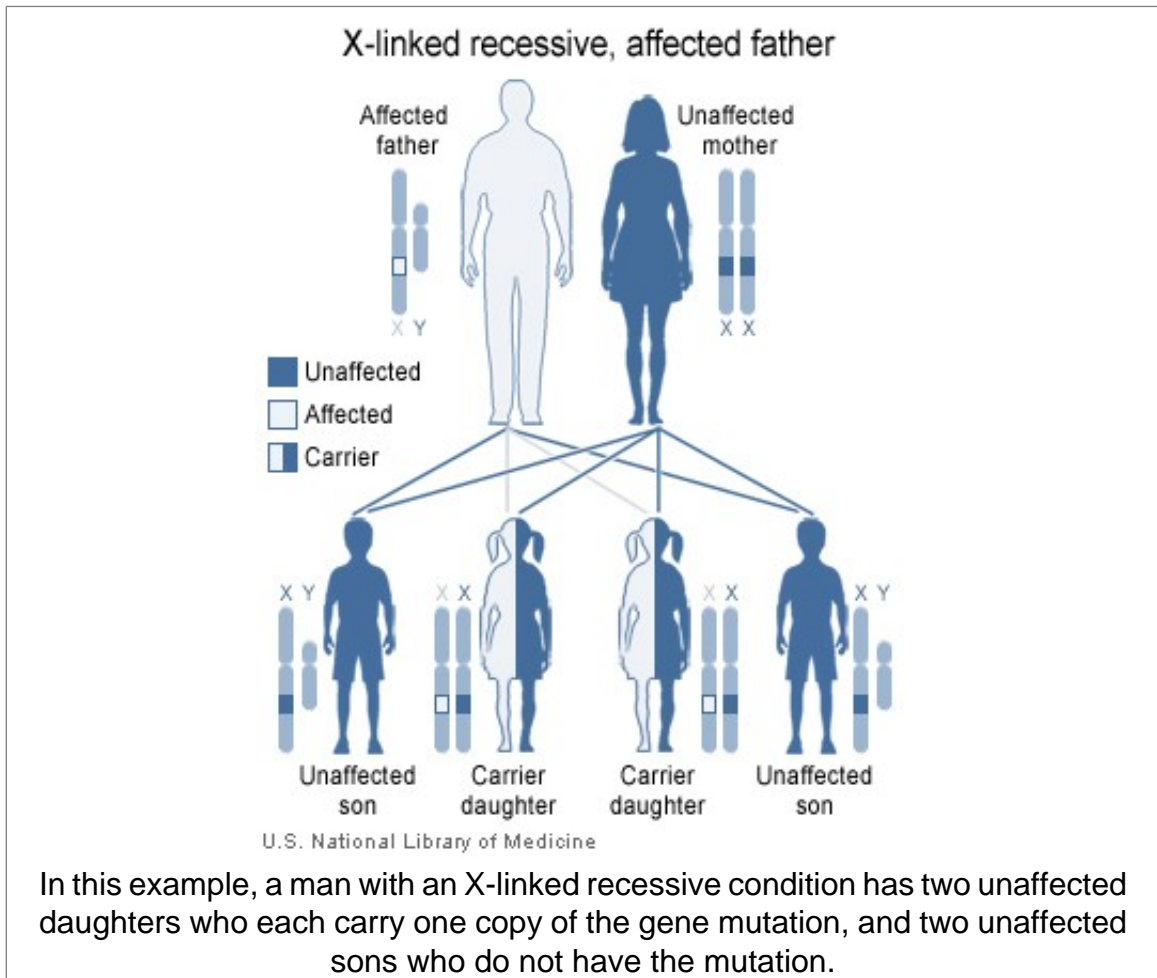
Illustrations

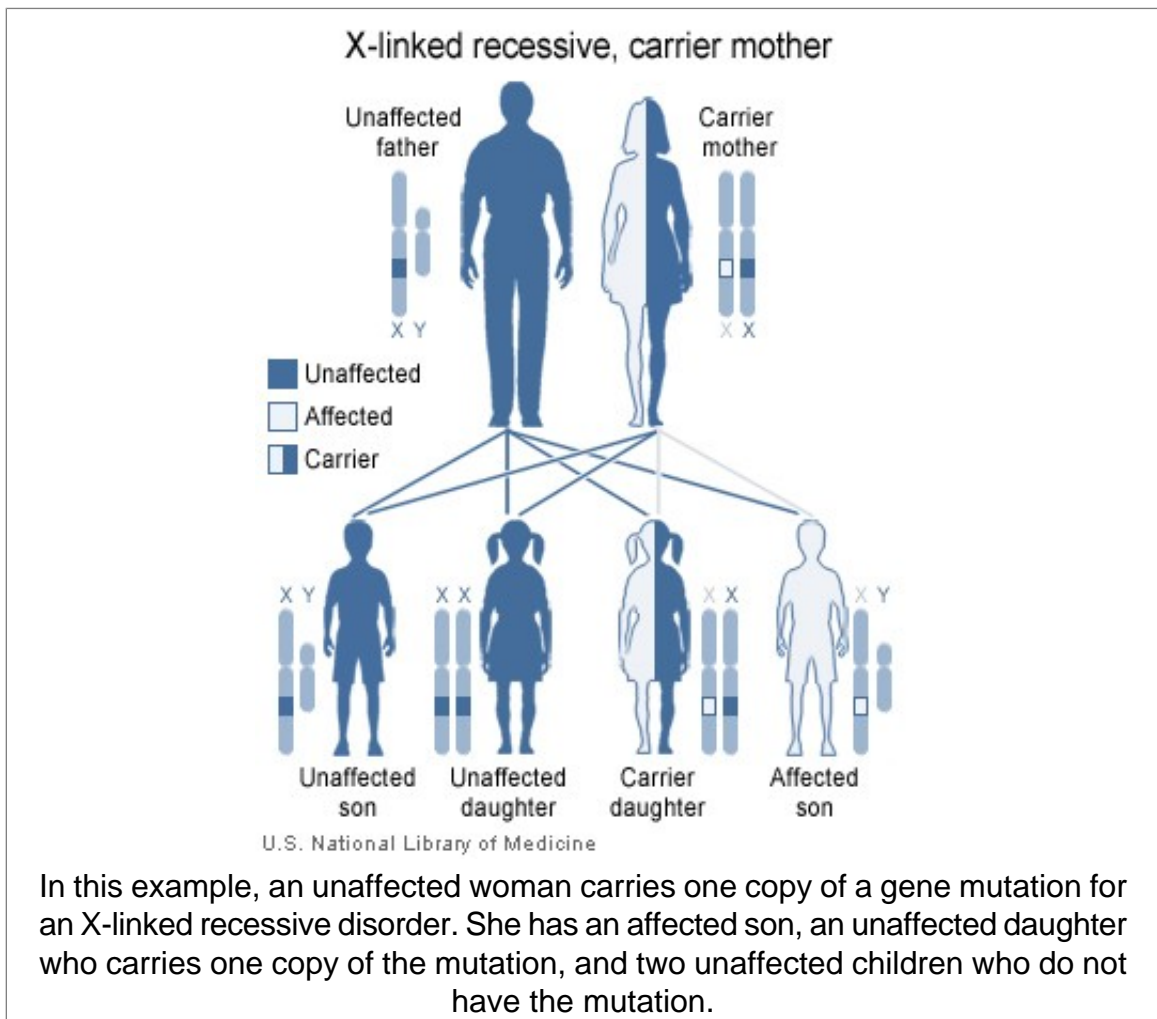


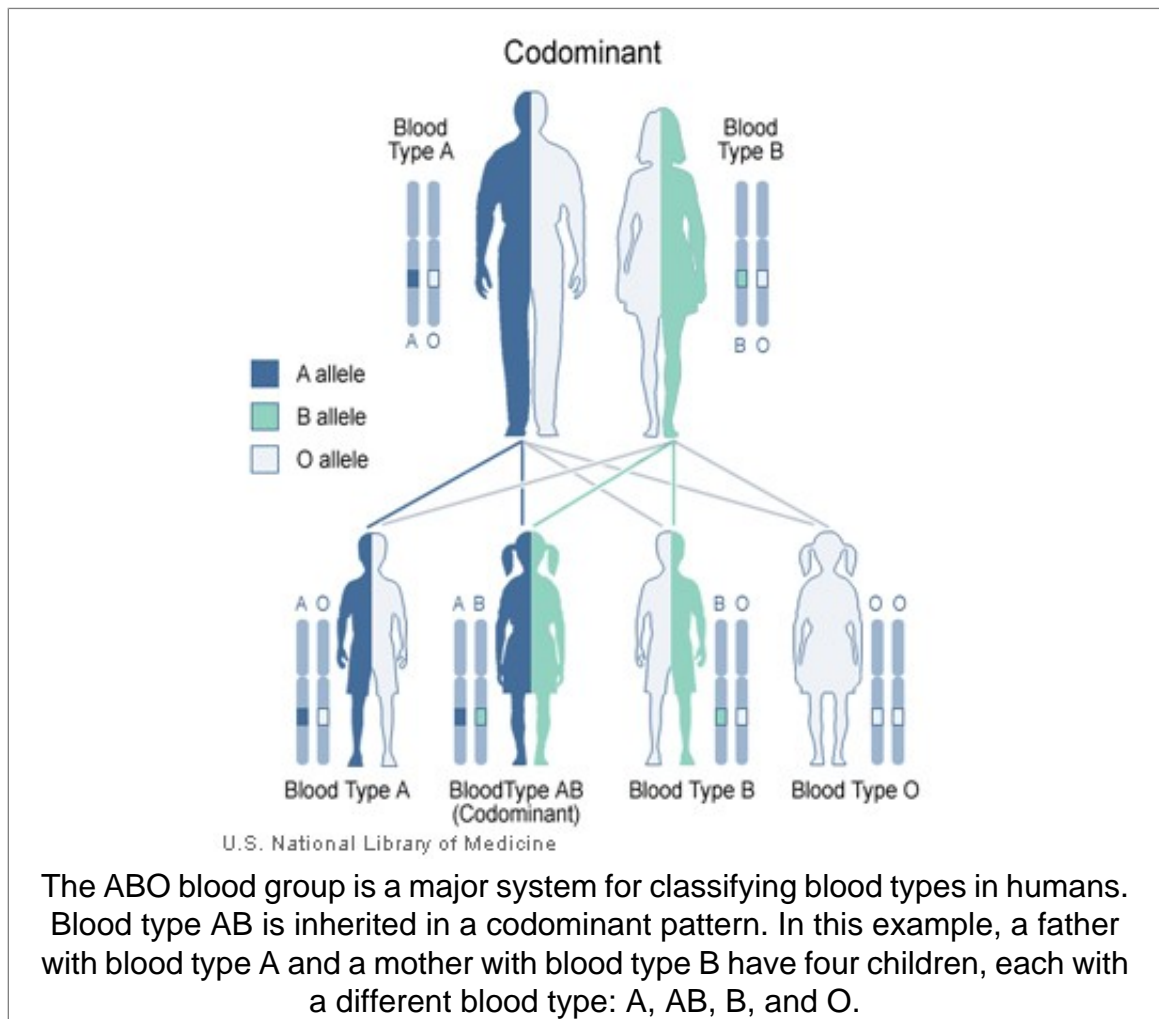


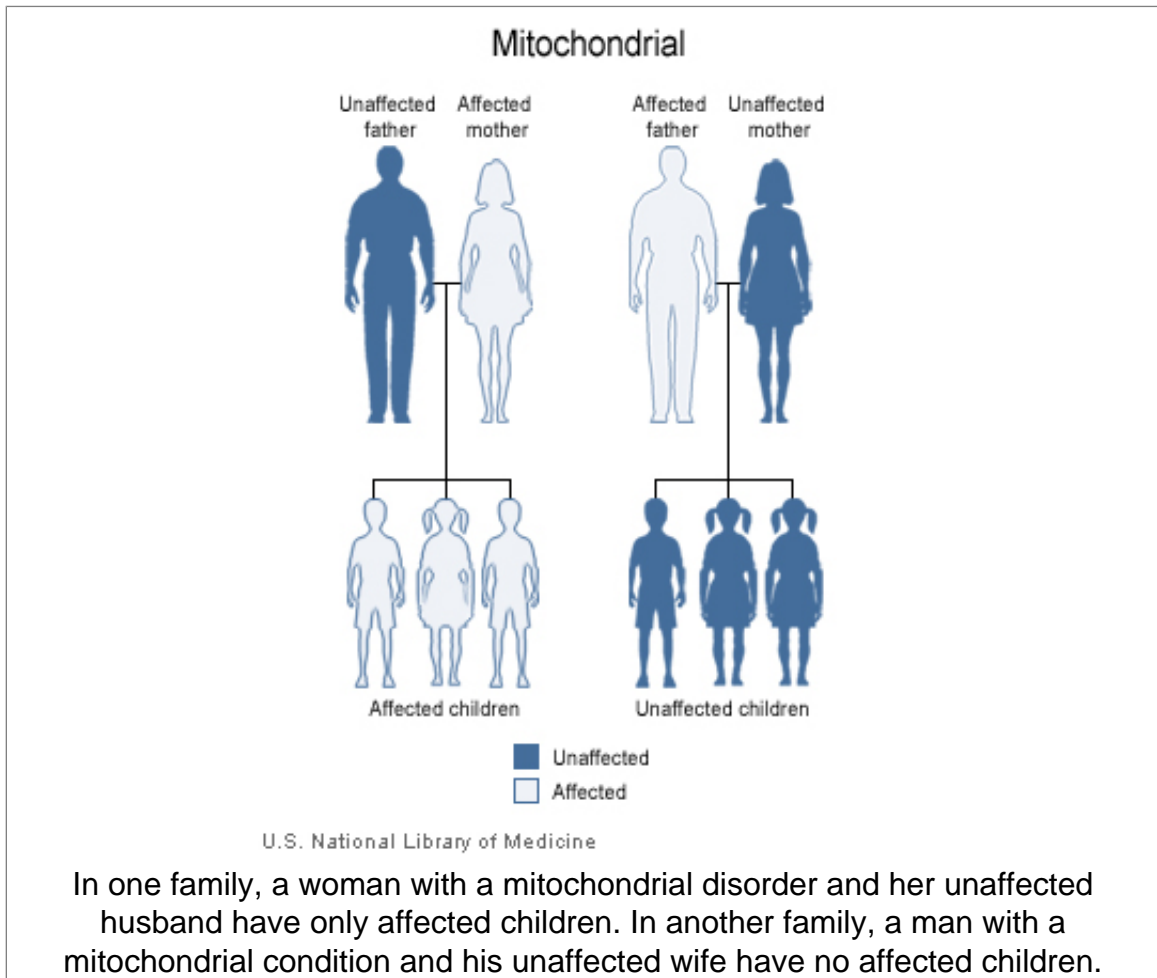












If a genetic disorder runs in my family, what are the chances that my children will have the condition?

When a genetic disorder is diagnosed in a family, family members often want to know the likelihood that they or their children will develop the condition. This can be difficult to predict in some cases because many factors influence a person's chances of developing a genetic condition. One important factor is how the condition is inherited. For example:

- **Autosomal dominant inheritance:** A person affected by an autosomal dominant disorder has a 50 percent chance of passing the mutated gene to each child. The chance that a child will not inherit the mutated gene is also 50 percent (illustration on page 13).
- **Autosomal recessive inheritance:** Two unaffected people who each carry one copy of the mutated gene for an autosomal recessive disorder (carriers) have a 25 percent chance with each pregnancy of having a child affected by the disorder. The chance with each pregnancy of having an unaffected child who is a carrier of the disorder is 50 percent, and the chance that a child will not have the disorder and will not be a carrier is 25 percent (illustration on page 14).
- **X-linked dominant inheritance:** The chance of passing on an X-linked dominant condition differs between men and women because men have one X chromosome and one Y chromosome, while women have two X chromosomes. A man passes on his Y chromosome to all of his sons and his X chromosome to all of his daughters. Therefore, the sons of a man with an X-linked dominant disorder will not be affected, but all of his daughters will inherit the condition (illustration on page 15). A woman passes on one or the other of her X chromosomes to each child. Therefore, a woman with an X-linked dominant disorder has a 50 percent chance of having an affected daughter or son with each pregnancy (illustration on page 16).
- **X-linked recessive inheritance:** Because of the difference in sex chromosomes, the probability of passing on an X-linked recessive disorder also differs between men and women. The sons of a man with an X-linked recessive disorder will not be affected, and his daughters will carry one copy of the mutated gene (illustration on page 17). With each pregnancy, a woman who carries an X-linked recessive disorder has a 50 percent chance of having sons who are affected and a 50 percent chance of having daughters who carry one copy of the mutated gene (illustration on page 18).

- **Codominant inheritance:** In codominant inheritance, each parent contributes a different version of a particular gene, and both versions influence the resulting genetic trait. The chance of developing a genetic condition with codominant inheritance, and the characteristic features of that condition, depend on which versions of the gene are passed from parents to their child (illustration on page 19).
- **Mitochondrial inheritance:** Mitochondria, which are the energy-producing centers inside cells, each contain a small amount of DNA. Disorders with mitochondrial inheritance result from mutations in mitochondrial DNA. Although mitochondrial disorders can affect both males and females, only females can pass mutations in mitochondrial DNA to their children. A woman with a disorder caused by changes in mitochondrial DNA will pass the mutation to all of her daughters and sons, but the children of a man with such a disorder will not inherit the mutation (illustration on page 20).

It is important to note that the chance of passing on a genetic condition applies equally to each pregnancy. For example, if a couple has a child with an autosomal recessive disorder, the chance of having another child with the disorder is still 25 percent (or 1 in 4). Having one child with a disorder does not “protect” future children from inheriting the condition. Conversely, having a child without the condition does not mean that future children will definitely be affected.

Although the chances of inheriting a genetic condition appear straightforward, factors such as a person’s family history and the results of genetic testing can sometimes modify those chances. In addition, some people with a disease-causing mutation never develop any health problems or may experience only mild symptoms of the disorder. If a disease that runs in a family does not have a clear-cut inheritance pattern, predicting the likelihood that a person will develop the condition can be particularly difficult.

Estimating the chance of developing or passing on a genetic disorder can be complex. Genetics professionals can help people understand these chances and help them make informed decisions about their health.

For more information about passing on a genetic disorder in a family:

The National Library of Medicine MedlinePlus web site offers information about the chance of developing a genetic disorder on the basis of its inheritance pattern. Scroll down to the section “Statistical Chances of Inheriting a Trait” for each of the following inheritance patterns:

- Autosomal dominant (<http://www.nlm.nih.gov/medlineplus/ency/article/002049.htm>)

- Autosomal recessive (<http://www.nlm.nih.gov/medlineplus/ency/article/002052.htm>)
- X-linked dominant (<http://www.nlm.nih.gov/medlineplus/ency/article/002050.htm>)
- X-linked recessive (<http://www.nlm.nih.gov/medlineplus/ency/article/002051.htm>)

The University of Virginia Health System provides a basic explanation of mitochondrial inheritance (http://www.healthsystem.virginia.edu/uvahealth/peds_genetics/mitochon.cfm).

What are reduced penetrance and variable expressivity?

Reduced penetrance and variable expressivity are factors that influence the effects of particular genetic changes. These factors usually affect disorders that have an autosomal dominant pattern of inheritance, although they are occasionally seen in disorders with an autosomal recessive inheritance pattern.

Reduced penetrance

Penetrance refers to the proportion of people with a particular genetic change (such as a mutation in a specific gene) who exhibit signs and symptoms of a genetic disorder. If some people with the mutation do not develop features of the disorder, the condition is said to have reduced (or incomplete) penetrance. Reduced penetrance often occurs with familial cancer syndromes. For example, many people with a mutation in the BRCA1 or BRCA2 gene will develop cancer during their lifetime, but some people will not. Doctors cannot predict which people with these mutations will develop cancer or when the tumors will develop.

Reduced penetrance probably results from a combination of genetic, environmental, and lifestyle factors, many of which are unknown. This phenomenon can make it challenging for genetics professionals to interpret a person's family medical history and predict the risk of passing a genetic condition to future generations.

Variable expressivity

Although some genetic disorders exhibit little variation, most have signs and symptoms that differ among affected individuals. Variable expressivity refers to the range of signs and symptoms that can occur in different people with the same genetic condition. For example, the features of Marfan syndrome vary widely—some people have only mild symptoms (such as being tall and thin with long, slender fingers), while others also experience life-threatening complications involving the heart and blood vessels. Although the features are highly variable, most people with this disorder have a mutation in the same gene (FBN1).

As with reduced penetrance, variable expressivity is probably caused by a combination of genetic, environmental, and lifestyle factors, most of which have not been identified. If a genetic condition has highly variable signs and symptoms, it may be challenging to diagnose.

For more information about reduced penetrance and variable expressivity:

The Cancer Institute of New Jersey provides a brief explanation of reduced penetrance and variable expressivity (http://www.cinj-genetics.org/health_pro/health_pro.htm#patterns_inherit) as part of their discussion of autosomal dominant inheritance.

A more in-depth explanation of these factors is available from the textbook Human Molecular Genetics 2 in chapter 3.2, Complications to the Basic Pedigree Patterns (<http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hmg.section.286#288>).

What do geneticists mean by anticipation?

The signs and symptoms of some genetic conditions tend to become more severe and appear at an earlier age as the disorder is passed from one generation to the next. This phenomenon is called anticipation. Anticipation is most often seen with certain genetic disorders of the nervous system, such as Huntington disease, myotonic dystrophy, and fragile X syndrome.

Anticipation typically occurs with disorders that are caused by an unusual type of mutation called a trinucleotide repeat expansion. A trinucleotide repeat is a sequence of three DNA building blocks (nucleotides) that is repeated a number of times in a row. DNA segments with an abnormal number of these repeats are unstable and prone to errors during cell division. The number of repeats can change as the gene is passed from parent to child. If the number of repeats increases, it is known as a trinucleotide repeat expansion. In some cases, the trinucleotide repeat may expand until the gene stops functioning normally. This expansion causes the features of some disorders to become more severe with each successive generation.

Most genetic disorders have signs and symptoms that differ among affected individuals, including affected people in the same family. Not all of these differences can be explained by anticipation. A combination of genetic, environmental, and lifestyle factors is probably responsible for the variability, although many of these factors have not been identified. Researchers study multiple generations of affected family members and consider the genetic cause of a disorder before determining that it shows anticipation.

For more information about anticipation:

The Merck Manual of Diagnosis and Therapy provides a brief explanation of anticipation as part of its chapter on nontraditional inheritance (<http://www.merck.com/mrkshared/mmanual/section21/chapter286/286d.jsp>). Scroll down to the sections “Triplet Repeat, Unstable Mutations” and “Anticipation.”

Additional information about anticipation is available from the textbook Human Molecular Genetics 2 in chapter 3.2, Complications to the Basic Pedigree Patterns (<http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hmg.section.286#293>).

What are genomic imprinting and uniparental disomy?

Genomic imprinting and uniparental disomy are factors that influence how some genetic conditions are inherited.

Genomic imprinting

People inherit two copies of their genes—one from their mother and one from their father. Usually both copies of each gene are active, or “turned on,” in cells. In some cases, however, only one of the two copies is normally turned on. Which copy is active depends on the parent of origin: some genes are normally active only when they are inherited from a person’s father; others are active only when inherited from a person’s mother. This phenomenon is known as genomic imprinting.

In genes that undergo genomic imprinting, the parent of origin is often marked, or “stamped,” on the gene during the formation of egg and sperm cells. This stamping process, called methylation, is a chemical reaction that attaches small molecules called methyl groups to certain segments of DNA. These molecules identify which copy of a gene was inherited from the mother and which was inherited from the father. The addition and removal of methyl groups can be used to control the activity of genes.

Only a small percentage of all human genes undergo genomic imprinting. Researchers are not yet certain why some genes are imprinted and others are not. They do know that imprinted genes tend to cluster together in the same regions of chromosomes. Two major clusters of imprinted genes have been identified in humans, one on the short (p) arm of chromosome 11 (at position 11p15) and another on the long (q) arm of chromosome 15 (in the region 15q11 to 15q13).

Uniparental disomy

Uniparental disomy (UPD) occurs when a person receives two copies of a chromosome, or part of a chromosome, from one parent and no copies from the other parent. UPD can occur as a random event during the formation of egg or sperm cells or may happen in early fetal development.

In many cases, UPD likely has no effect on health or development. Because most genes are not imprinted, it doesn’t matter if a person inherits both copies from one parent instead of one copy from each parent. In some cases, however, it does make a difference whether a gene is inherited from a person’s mother or father. A person with UPD may lack any active copies of essential genes that undergo genomic imprinting. This loss of gene function can lead to delayed development, mental retardation, or other medical problems.

Several genetic disorders can result from UPD or a disruption of normal genomic imprinting. The most well-known conditions include Prader-Willi syndrome, which

is characterized by uncontrolled eating and obesity, and Angelman syndrome, which causes mental retardation and impaired speech. Both of these disorders can be caused by UPD or other errors in imprinting involving genes on the long arm of chromosome 15. Other conditions, such as Beckwith-Wiedemann syndrome (a disorder characterized by accelerated growth and an increased risk of cancerous tumors), are associated with abnormalities of imprinted genes on the short arm of chromosome 11.

For more information about genomic imprinting and UPD:

The University of British Columbia's web site about chromosomal mosaicism provides an explanation of UPD and genomic imprinting (<http://www.medgen.ubc.ca/wrobinson/mosaic/clinical/prenatal/upd.htm>), including diagrams illustrating how UPD can occur.

The Wellcome Trust provides a brief overview of imprinting (http://genome.wellcome.ac.uk/doc_WTD020853.html).

Additional information about genomic imprinting (<http://www.genetics.com.au/pdf/factsheets/fs15.pdf>) is available from the Centre for Genetics Education.

Are chromosomal disorders inherited?

Although it is possible to inherit some types of chromosomal abnormalities, most chromosomal disorders (such as Down syndrome and Turner syndrome) are not passed from one generation to the next.

Some chromosomal conditions are caused by changes in the number of chromosomes. These changes are not inherited, but occur as random events during the formation of reproductive cells (eggs and sperm). An error in cell division called nondisjunction results in reproductive cells with an abnormal number of chromosomes. For example, a reproductive cell may accidentally gain or lose one copy of a chromosome. If one of these atypical reproductive cells contributes to the genetic makeup of a child, the child will have an extra or missing chromosome in each of the body's cells.

Changes in chromosome structure can also cause chromosomal disorders. Some changes in chromosome structure can be inherited, while others occur as random accidents during the formation of reproductive cells or in early fetal development. Because the inheritance of these changes can be complex, people concerned about this type of chromosomal abnormality may want to talk with a genetics professional.

Some cancer cells also have changes in the number or structure of their chromosomes. Because these changes occur in somatic cells (cells other than eggs and sperm), they cannot be passed from one generation to the next.

For more information about how chromosomal changes occur:

As part of its fact sheet on chromosome abnormalities, the National Human Genome Research Institute provides a discussion of how chromosome abnormalities happen (<http://www.genome.gov/11508982#6>).

The University of British Columbia's web site about chromosomal mosaicism explains chromosomal changes, including a detailed description of how trisomy (the presence of an extra chromosome in each cell) happens:

- [Changes to the Chromosomes \(http://www.medgen.ubc.ca/wrobinson/mosaic/intro/changes.htm\)](http://www.medgen.ubc.ca/wrobinson/mosaic/intro/changes.htm)
- [How Does Trisomy Arise? \(http://www.medgen.ubc.ca/wrobinson/mosaic/intro/tri_how.htm\)](http://www.medgen.ubc.ca/wrobinson/mosaic/intro/tri_how.htm)

The Chromosome Deletion Outreach fact sheet Introduction to Chromosomes (<http://www.chromodisorder.org/CDO/General/IntroToChromosomes.aspx>) explains how structural changes occur.

Why are some genetic conditions more common in particular ethnic groups?

Some genetic disorders are more likely to occur among people who trace their ancestry to a particular geographic area. People in an ethnic group often share certain versions of their genes, which have been passed down from common ancestors. If one of these shared genes contains a disease-causing mutation, a particular genetic disorder may be more frequently seen in the group.

Examples of genetic conditions that are more common in particular ethnic groups are sickle cell anemia, which is more common in people of African, African-American, or Mediterranean heritage; and Tay-Sachs disease, which is more likely to occur among people of Ashkenazi (eastern and central European) Jewish or French Canadian ancestry. It is important to note, however, that these disorders can occur in any ethnic group.

For more information about genetic disorders that are more common in certain groups:

The National Coalition for Health Professional Education in Genetics offers Some Frequently Asked Questions and Answers About Race, Genetics, and Healthcare (<http://www.nchpeg.org/raceandgenetics/index.asp>).



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Inheriting Genetic Conditions	January 2003

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