



Alport syndrome

Alport syndrome is a genetic condition characterized by kidney disease, hearing loss, and eye abnormalities.

People with Alport syndrome experience progressive loss of kidney function. Almost all affected individuals have blood in their urine (hematuria), which indicates abnormal functioning of the kidneys. Many people with Alport syndrome also develop high levels of protein in their urine (proteinuria). The kidneys become less able to function as this condition progresses, resulting in end-stage renal disease (ESRD).

People with Alport syndrome frequently develop sensorineural hearing loss, which is caused by abnormalities of the inner ear, during late childhood or early adolescence. Affected individuals may also have misshapen lenses in the eyes (anterior lenticonus) and abnormal coloration of the light-sensitive tissue at the back of the eye (retina). These eye abnormalities seldom lead to vision loss.

Significant hearing loss, eye abnormalities, and progressive kidney disease are more common in males with Alport syndrome than in affected females.

Frequency

Alport syndrome occurs in approximately 1 in 50,000 newborns.

Genetic Changes

Mutations in the *COL4A3*, *COL4A4*, and *COL4A5* genes cause Alport syndrome. These genes each provide instructions for making one component of a protein called type IV collagen. This protein plays an important role in the kidneys, specifically in structures called glomeruli. Glomeruli are clusters of specialized blood vessels that remove water and waste products from blood and create urine. Mutations in these genes result in abnormalities of the type IV collagen in glomeruli, which prevents the kidneys from properly filtering the blood and allows blood and protein to pass into the urine. Gradual scarring of the kidneys occurs, eventually leading to kidney failure in many people with Alport syndrome.

Type IV collagen is also an important component of inner ear structures, particularly the organ of Corti, that transform sound waves into nerve impulses for the brain. Alterations in type IV collagen often result in abnormal inner ear function, which can lead to hearing loss. In the eye, this protein is important for maintaining the shape of the lens and the normal color of the retina. Mutations that disrupt type IV collagen can result in misshapen lenses and an abnormally colored retina.

Inheritance Pattern

Alport syndrome can have different inheritance patterns. About 80 percent of cases are caused by mutations in the *COL4A5* gene and are inherited in an X-linked pattern. This gene is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the *COL4A5* gene in each cell is sufficient to cause kidney failure and other severe symptoms of the disorder. In females (who have two X chromosomes), a mutation in one copy of the *COL4A5* gene usually only results in hematuria, but some women experience more severe symptoms. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

In approximately 15 percent of cases, Alport syndrome results from mutations in both copies of the *COL4A3* or *COL4A4* gene and is inherited in an autosomal recessive pattern. The parents of an individual with the autosomal recessive form of this condition each have one copy of the mutated gene and are called carriers. Some carriers are unaffected and others develop a less severe condition called thin basement membrane nephropathy, which is characterized by hematuria.

Alport syndrome has autosomal dominant inheritance in about 5 percent of cases. People with this form of Alport syndrome have one mutation in either the *COL4A3* or *COL4A4* gene in each cell. It remains unclear why some individuals with one mutation in the *COL4A3* or *COL4A4* gene have autosomal dominant Alport syndrome and others have thin basement membrane nephropathy.

Other Names for This Condition

- congenital hereditary hematuria
- hematuria-nephropathy-deafness syndrome
- hematuric hereditary nephritis
- hemorrhagic familial nephritis
- hemorrhagic hereditary nephritis
- hereditary familial congenital hemorrhagic nephritis
- hereditary hematuria syndrome
- hereditary interstitial pyelonephritis
- hereditary nephritis

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Alport syndrome
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1567741/>
- Genetic Testing Registry: Alport syndrome, autosomal dominant
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1567743/>
- Genetic Testing Registry: Alport syndrome, autosomal recessive
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1567744/>
- Genetic Testing Registry: Alport syndrome, X-linked recessive
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1567742/>

Other Diagnosis and Management Resources

- GeneReview: Alport Syndrome and Thin Basement Membrane Nephropathy
<https://www.ncbi.nlm.nih.gov/books/NBK1207>
- MedlinePlus Encyclopedia: Alport Syndrome
<https://medlineplus.gov/ency/article/000504.htm>
- MedlinePlus Encyclopedia: End-Stage Kidney Disease
<https://medlineplus.gov/ency/article/000500.htm>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Alport Syndrome
<https://medlineplus.gov/ency/article/000504.htm>
- Encyclopedia: End-Stage Kidney Disease
<https://medlineplus.gov/ency/article/000500.htm>

- Health Topic: Kidney Diseases
<https://medlineplus.gov/kidneydiseases.html>
- Health Topic: Kidney Failure
<https://medlineplus.gov/kidneyfailure.html>

Genetic and Rare Diseases Information Center

- Alport syndrome
<https://rarediseases.info.nih.gov/diseases/5785/alport-syndrome>
- Autosomal dominant Alport syndrome
<https://rarediseases.info.nih.gov/diseases/624/autosomal-dominant-alport-syndrome>
- Autosomal recessive Alport syndrome
<https://rarediseases.info.nih.gov/diseases/625/autosomal-recessive-alport-syndrome>

Additional NIH Resources

- National Institute of Diabetes and Digestive and Kidney Diseases
<https://www.niddk.nih.gov/health-information/kidney-disease/glomerular-diseases>

Educational Resources

- Disease InfoSearch: Alport Syndrome
<http://www.diseaseinfosearch.org/Alport+Syndrome/335>
- Disease InfoSearch: Alport Syndrome Dominant Type
<http://www.diseaseinfosearch.org/Alport+Syndrome+Dominant+Type/336>
- Disease InfoSearch: Alport Syndrome Recessive Type
<http://www.diseaseinfosearch.org/Alport+Syndrome+Recessive+Type/337>
- MalaCards: alport syndrome
http://www.malacards.org/card/alport_syndrome
- Merck Manual Consumer Version
<http://www.merckmanuals.com/home/kidney-and-urinary-tract-disorders/kidney-filtering-disorders/hereditary-nephritis>
- My46 Trait Profile
<https://www.my46.org/trait-document?trait=Alport%20syndrome&type=profile>
- Orphanet: Alport syndrome
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=63

Patient Support and Advocacy Resources

- Alport Syndrome Foundation
<http://alportsyndrome.org/>
- National Organization for Rare Disorders (NORD)
<https://rarediseases.org/rare-diseases/alport-syndrome/>
- The Kidney Foundation of Canada
<https://www.kidney.ca/sslpage.aspx?pid=324>

GeneReviews

- Alport Syndrome and Thin Basement Membrane Nephropathy
<https://www.ncbi.nlm.nih.gov/books/NBK1207>

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22alport+syndrome%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Nephritis,+Hereditary%5BMAJR%5D%29+AND+%28Alport+syndrome%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D>

OMIM

- ALPORT SYNDROME, AUTOSOMAL DOMINANT
<http://omim.org/entry/104200>
- ALPORT SYNDROME, AUTOSOMAL RECESSIVE
<http://omim.org/entry/203780>
- ALPORT SYNDROME, X-LINKED
<http://omim.org/entry/301050>

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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/23165304>
- Pescucci C, Longo I, Bruttini M, Mari F, Renieri A. Type-IV collagen related diseases. *J Nephrol*. 2003 Mar-Apr;16(2):314-6. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/12768082>
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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/17396119>
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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/17570934>

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<https://ghr.nlm.nih.gov/condition/alport-syndrome>

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Genetics
Home
Reference

Help Me Understand Genetics
Inheriting Genetic Conditions

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Inheriting Genetic Conditions

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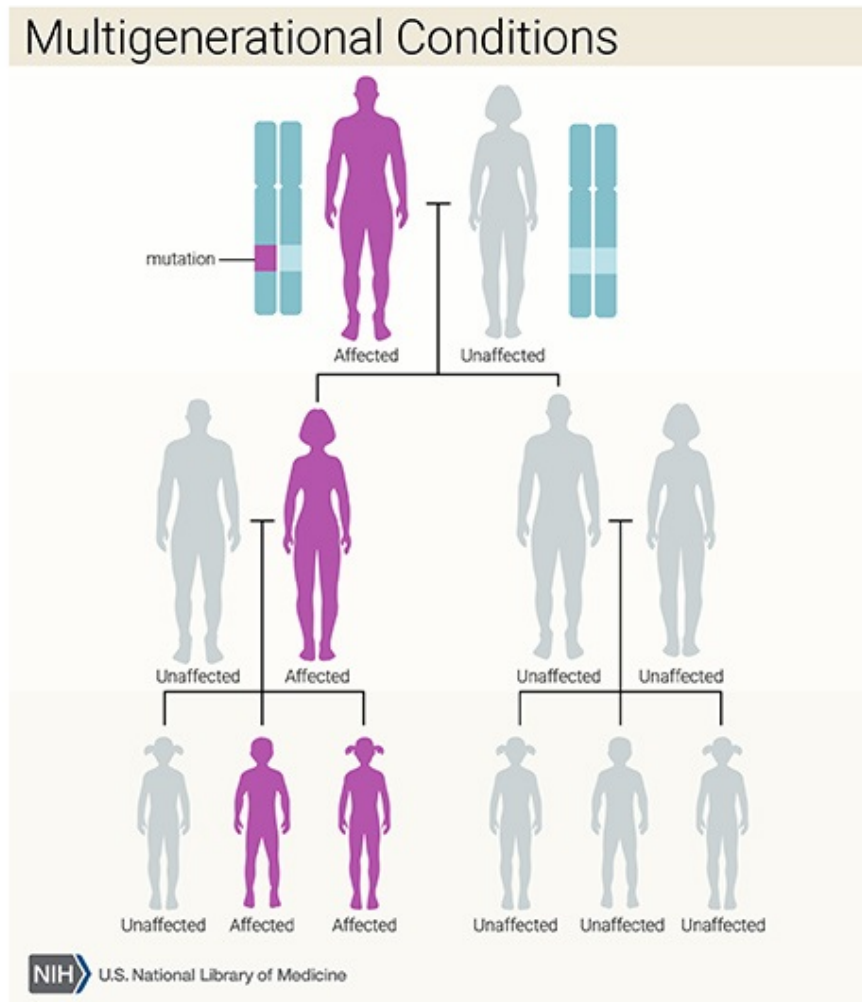
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What does it mean if a disorder seems to run in my family?

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.

	<i>Degrees of relationship</i>
Degrees of relationship	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



This condition affects members in each generation of a family.

For general information about disorders that run in families:

Genetics Home Reference provides consumer-friendly summaries of genetic conditions (<https://ghr.nlm.nih.gov/condition>). 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 Coriell Personalized Medicine Collaborative provides a brief introduction to heritable diseases in the article *Heredity: It Runs in the Family* (<https://cpmc.coriell.org/genetic-education/it-runs-in-the-family>).

The Genetic Science Learning Center at the University of Utah offers interactive tools about disorders that run in families (<http://learn.genetics.utah.edu/content/history>).

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

The Centre for Genetics Education provides an overview of genetic conditions (<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-5-genetic-conditions>).

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 disease.

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:

Educational resources related to family health history (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=5&sid=13) are available from GeneEd. Additional information about family history (<https://medlineplus.gov/familyhistory.html>) is available from MedlinePlus.

The Centers for Disease Control and Prevention's (CDC) Office of Public Health Genomics provides information about the importance of family medical history (<https://www.cdc.gov/genomics/famhistory/>). This resource also includes links to publications, reports, and tools for recording family health information.

The Office of the Surgeon General offers a tool called My Family Health Portrait (<https://familyhistory.hhs.gov/>) that allows you to enter, print, and update your family health history.

The American Medical Association provides family history tools (<https://www.ama-assn.org/delivering-care/collecting-family-history>), including questionnaires and forms for collecting medical information. The National Institute on Aging provides suggestions on how to obtain a health history form older individuals (<https://www.nia.nih.gov/health/obtaining-older-patients-medical-history>).

The Genetic Alliance also offers a list of links to family history resources (<http://www.geneticalliance.org/programs/genesinlife/fhh>).

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 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. In some cases, an affected person inherits the condition from an affected parent (image on page 12). In others, the condition may result from a new mutation (image on page 13) in the gene and occur in people with no history of the disorder in their family.	Huntington disease, Marfan syndrome
Autosomal recessive	In autosomal recessive inheritance (image on page 14), both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Autosomal recessive disorders are typically not seen in every generation of an affected family.	cystic fibrosis, sickle cell disease

Inheritance pattern	Description	Examples
X-linked dominant	X-linked dominant (image on page 15) disorders are caused by mutations in genes on the X chromosome, one of the two sex chromosomes in each cell. In females (who have two X chromosomes), a mutation in one of the two copies of the gene in each cell is sufficient to cause the disorder. In males (who have only one X chromosome), a mutation in the only copy of the gene in each cell causes the disorder. In most cases, males experience more severe symptoms of the disorder than females. A 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	X-linked recessive (image on page 16) disorders are also caused by mutations in genes on the X chromosome. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).	hemophilia, Fabry disease
Y-linked	A condition is considered Y-linked (image on page 17) if the mutated gene that causes the disorder is located on the Y chromosome, one of the two sex chromosomes in each of a male's cells. Because only males have a Y chromosome, in Y-linked inheritance, a mutation can only be passed from father to son.	Y chromosome infertility, some cases of Swyer syndrome

Inheritance pattern	Description	Examples
Codominant	In codominant inheritance (image on page 18), two different versions (alleles) of a gene are expressed, and each version makes a slightly different protein. Both alleles influence the genetic trait or determine the characteristics of the genetic condition.	ABO blood group, alpha-1 antitrypsin deficiency
Mitochondrial	Mitochondrial inheritance (image on page 19), 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 mutations to their children. Conditions resulting from mutations in mitochondrial DNA can appear in every generation of a family and can affect both males and females, but fathers do not pass these disorders to their daughters or sons.	Leber hereditary optic neuropathy (LHON)

Many health conditions are caused by the combined effects of multiple genes or by interactions between genes and the environment. Such disorders usually 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?](https://ghr.nlm.nih.gov/primer/mutationsanddisorders/complexdisorders) (<https://ghr.nlm.nih.gov/primer/mutationsanddisorders/complexdisorders>)

Disorders caused by changes in the number or structure of chromosomes also do not follow the straightforward patterns of inheritance listed above. To read about how chromosomal conditions occur, please see [Are chromosomal disorders inherited?](#) on page 28

Other genetic factors sometimes influence how a disorder is inherited. For an example, please see [What are genomic imprinting and uniparental disomy?](#) on page 26

For more information about inheritance patterns:

Resources related to heredity/inheritance patterns (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=5) and Mendelian inheritance (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=5&sid=6) are available from GeneEd.

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

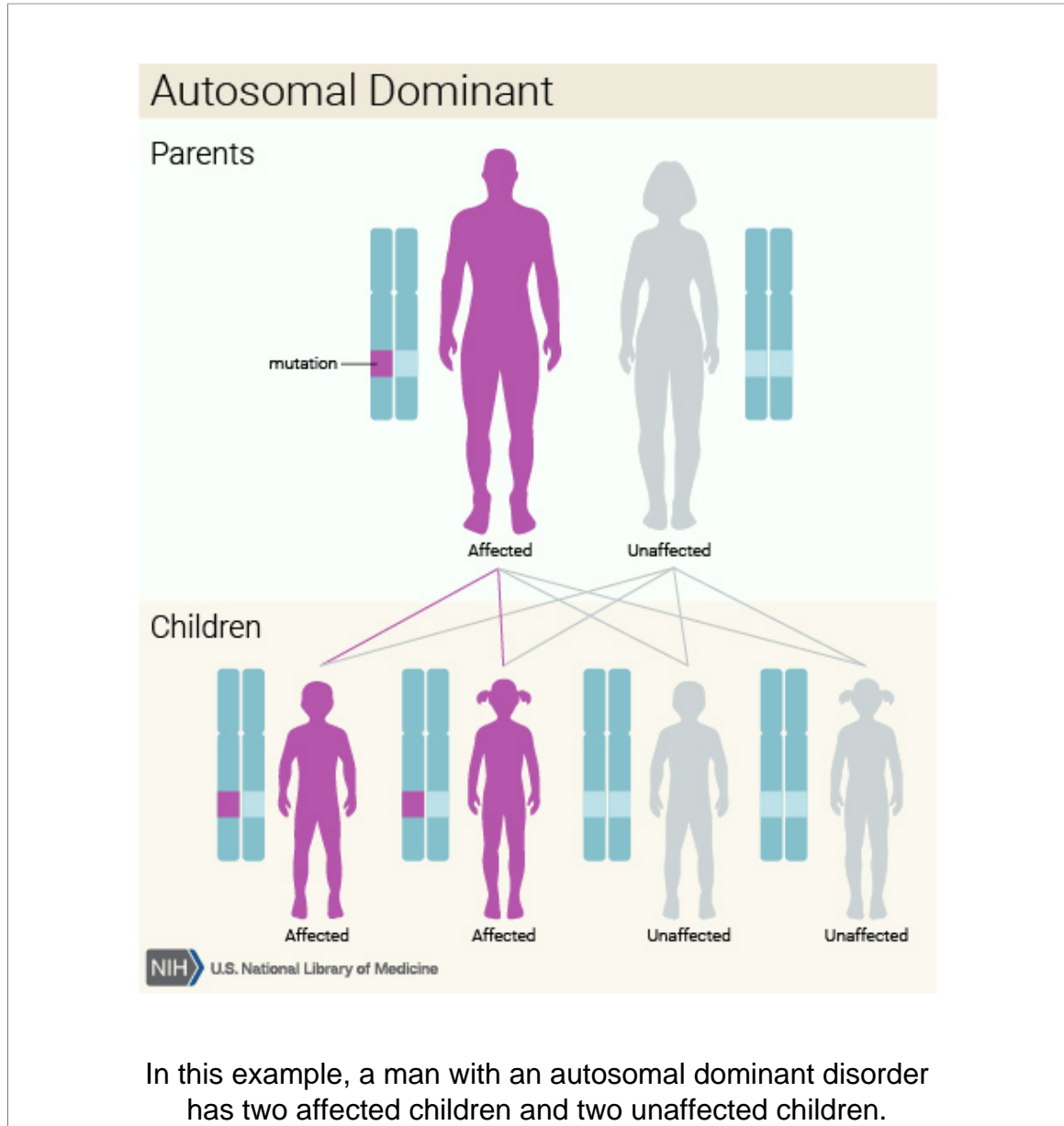
- Autosomal dominant inheritance (<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-8-autosomal-dominant-inheritance>)
- Autosomal recessive inheritance (<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-7-autosomal-recessive-inheritance>)
- X-linked dominant inheritance (<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-10-x-linked-dominant-inheritance>)
- X-linked recessive inheritance (<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-9-x-linked-recessive-inheritance>)
- Mitochondrial inheritance (<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-12-mitochondrial-inheritance>)

EuroGentest also offers explanations of Mendelian inheritance patterns:

- Autosomal dominant inheritance (<http://www.eurogentest.org/index.php?id=614>)
- Autosomal recessive inheritance (<http://www.eurogentest.org/index.php?id=619>)
- X-linked inheritance (<http://www.eurogentest.org/index.php?id=623>)

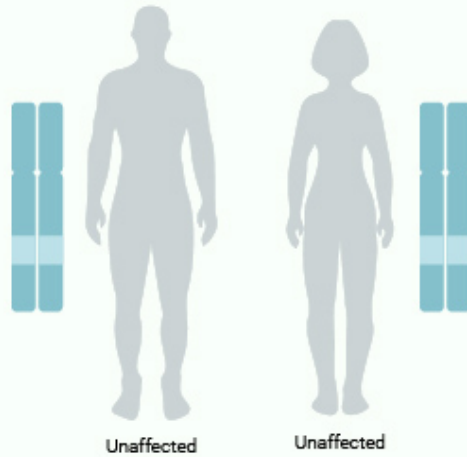
Additional information about inheritance patterns is available from The Merck Manual (<http://www.merckmanuals.com/professional/special-subjects/general-principles-of-medical-genetics/single-gene-defects>).

Images

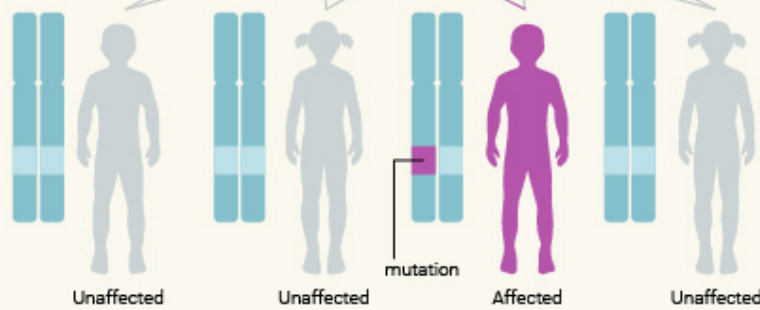


Autosomal Dominant - New Mutation

Parents



Children

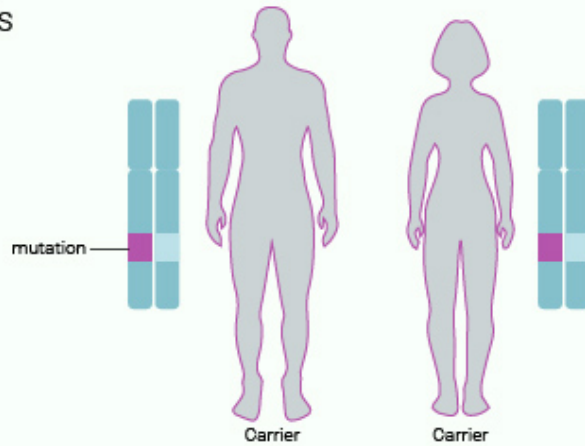


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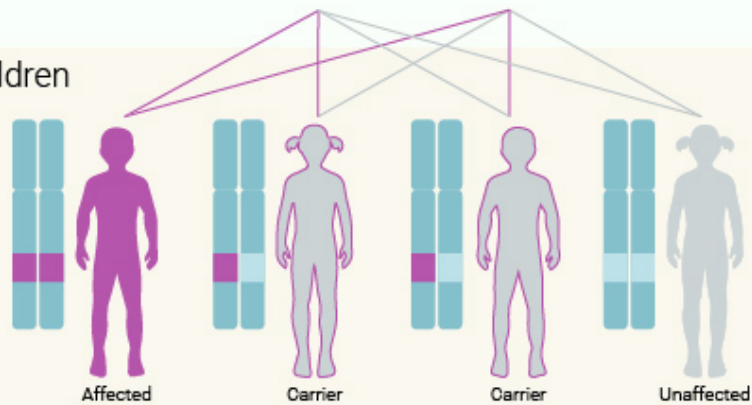
In this example, a child with an autosomal dominant condition has the disorder as a result of a new (de novo) mutation that occurred during the formation of an egg or sperm cell or early in embryonic development.

Autosomal Recessive

Parents

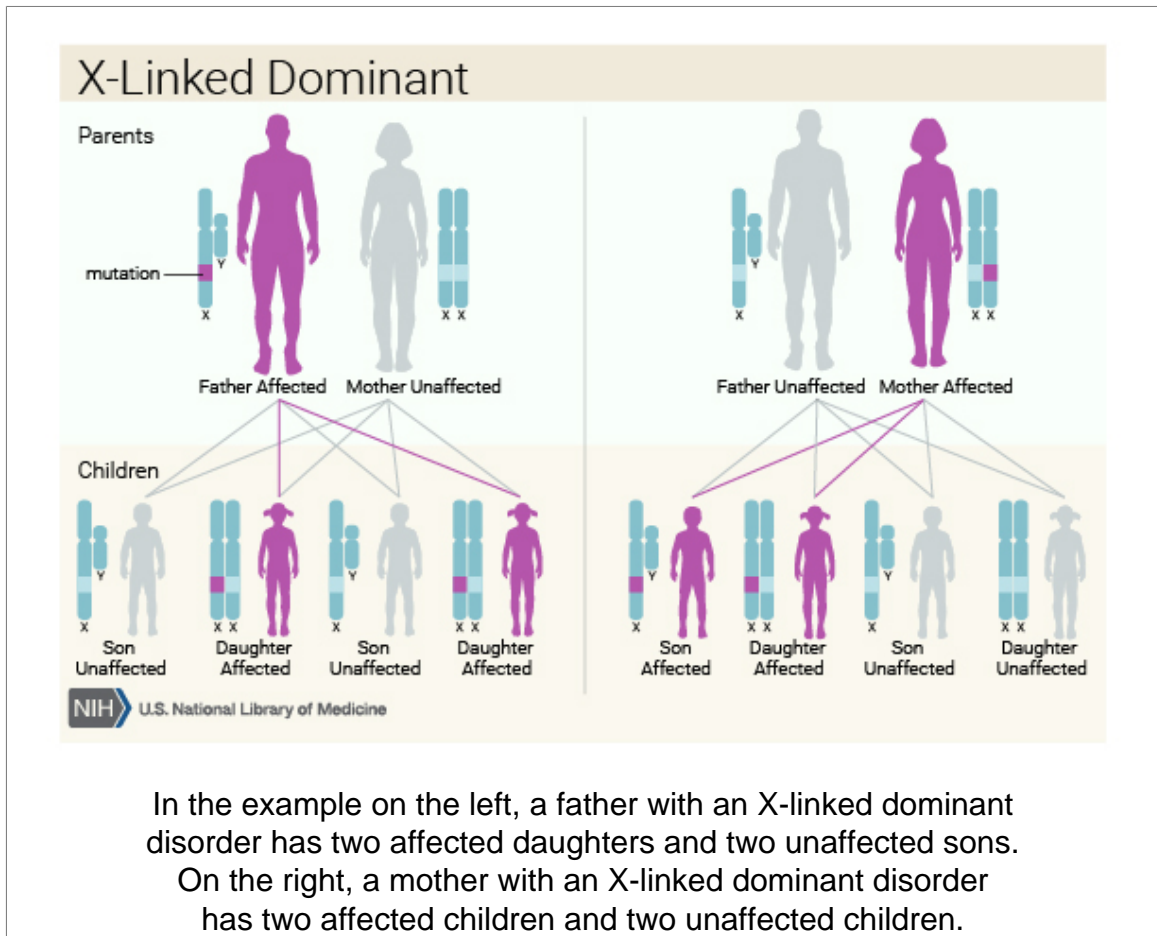


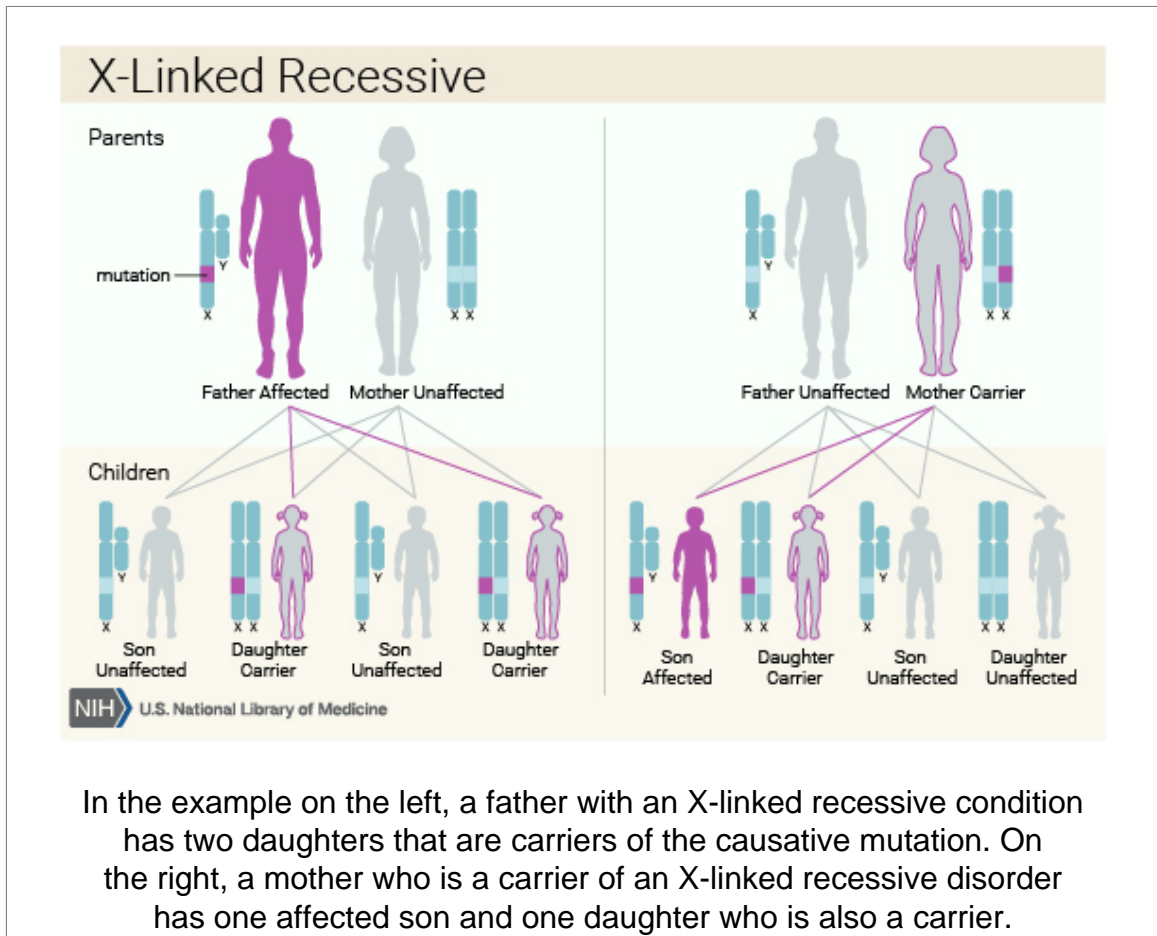
Children



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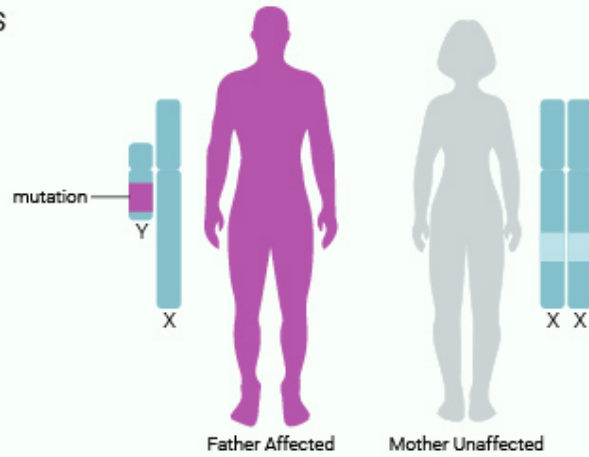
In this example, two unaffected parents each carry one copy of a gene mutation for an autosomal recessive disorder. They have one affected child and three unaffected children, two of which carry one copy of the gene mutation.



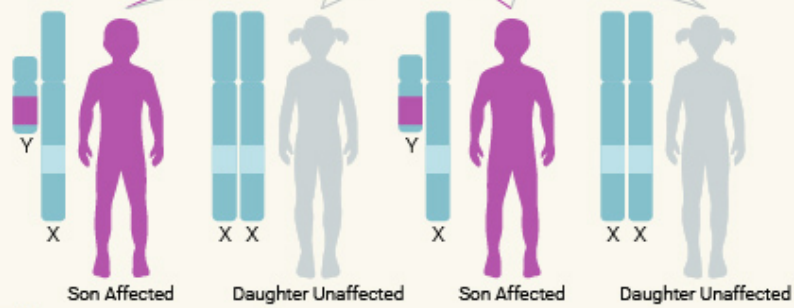


Y-Linked

Parents

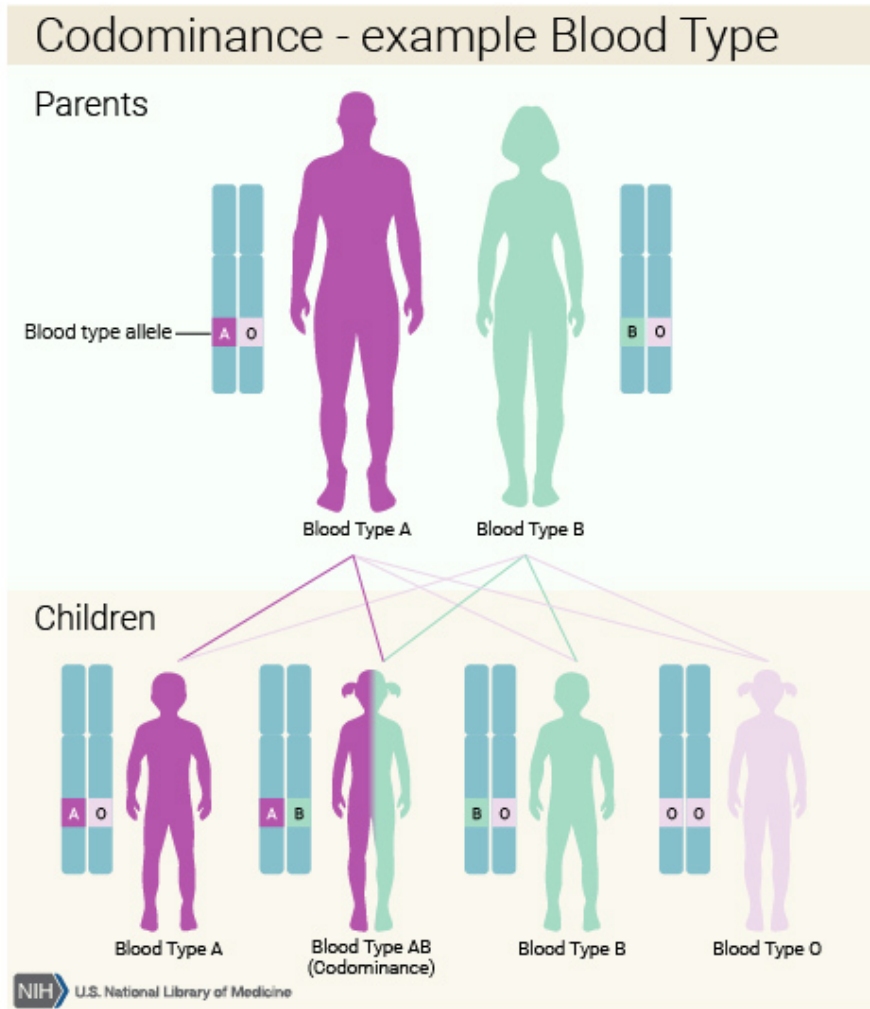


Children

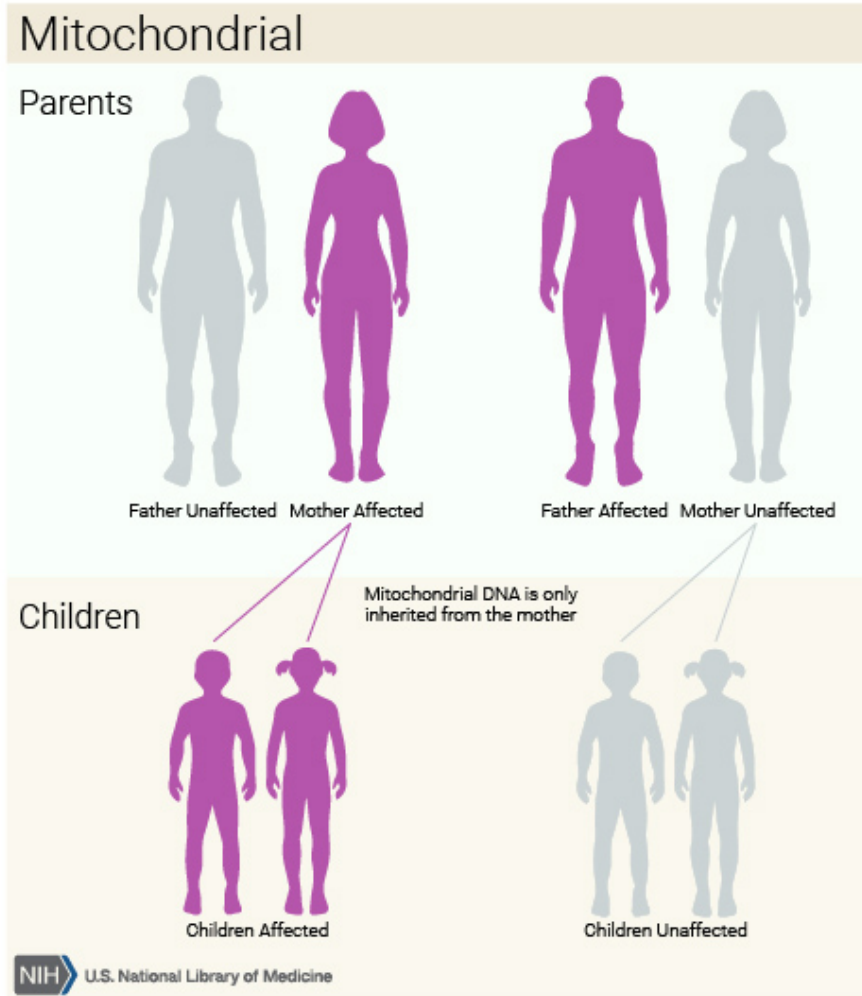


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In this example, a father with a Y-linked condition has two affected sons. His daughters are unaffected.



The ABO blood group is a major system for classifying blood types in humans. Blood type AB is inherited in a codominant pattern. In this example, a father with blood type A and a mother with blood type B have four children, each with a different blood type: A, AB, B, and O.



In the family on the left, a woman with a disorder caused by a mutation in mitochondrial DNA and her unaffected husband have children who are all affected by the condition. In the family on the right, a man with a condition resulting from a mutation in mitochondrial DNA and his unaffected wife have no affected children.

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 (image on page 12) 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. However, in some cases an autosomal dominant disorder results from a new (de novo) mutation (image on page 13) that occurs during the formation of egg or sperm cells or early in embryonic development. In these cases, the child's parents are unaffected, but the child may pass on the condition to his or her own children.
- **Autosomal recessive inheritance:** Two unaffected people who each carry one copy of the mutated gene for an autosomal recessive disorder (image on page 14) (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.
- **X-linked dominant inheritance:** The chance of passing on an X-linked dominant condition (image on page 15) 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. 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.

- **X-linked recessive inheritance:** Because of the difference in sex chromosomes, the probability of passing on an X-linked recessive disorder (image on page 16) 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. 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.
- **Y-linked inheritance:** Because only males have a Y chromosome, only males can be affected by and pass on Y-linked disorders (image on page 17). All sons of a man with a Y-linked disorder will inherit the condition from their father.
- **Codominant inheritance:** In codominant inheritance (image on page 18), 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.
- **Mitochondrial inheritance:** Mitochondria, which are the energy-producing centers inside cells, each contain a small amount of DNA. Disorders with mitochondrial inheritance (image on page 19) result from mutations in mitochondrial DNA. Although these 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.

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 website offers information about the chance of developing a genetic disorder on the basis of its inheritance pattern:

- Autosomal dominant (<https://medlineplus.gov/ency/article/002049.htm>)
- Autosomal recessive (<https://medlineplus.gov/ency/article/002052.htm>)
- X-linked dominant (<https://medlineplus.gov/ency/article/002050.htm>)
- X-linked recessive (<https://medlineplus.gov/ency/article/002051.htm>)

The Centre for Genetics Education provides an explanation of mitochondrial inheritance (<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-12-mitochondrial-inheritance>).

The Muscular Dystrophy Association explains patterns and probabilities (https://www.mda.org/sites/default/files/publications/Facts_Genetics_P-210_1.pdf) of inheritance.

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 PHG Foundation offers an interactive tutorial on penetrance (<http://www.phgfoundation.org/tutorials/penetrance/>) that explains the differences between reduced penetrance and variable expressivity.

Additional information about penetrance and expressivity (<http://www.merckmanuals.com/home/fundamentals/genetics/inheritance-of-single-gene-disorders>) is available from the Merck Manual Home Health Handbook for Patients & Caregivers.

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 for Healthcare Professionals provides a brief explanation of anticipation as part of its chapter on nontraditional inheritance (<http://www.merckmanuals.com/professional/special-subjects/general-principles-of-medical-genetics/unusual-aspects-of-inheritance>).

The Myotonic Dystrophy Foundation describes anticipation in the context of myotonic dystrophy (<http://www.myotonic.org/what-dm/disease-mechanism>). (Click on the tab that says "Anticipation.")

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, intellectual disability, or other health 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 intellectual disability 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 National Human Genome Research Institute provides a definition of genetic imprinting (<https://www.genome.gov/glossary/index.cfm?id=92>) in its Talking Glossary of Genetic Terms.

The University of Utah offers a basic overview of genomic imprinting (<http://learn.genetics.utah.edu/content/epigenetics/imprinting/>).

Additional information about epigenetics, including genomic imprinting (<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-14-epigenetics>) is available from the Centre for Genetics Education.

Geneimprint, a website about genomic imprinting, provides an introduction to imprinting (<http://www.geneimprint.com/site/what-is-imprinting>) as well as related articles and a list of imprinted genes (<http://www.geneimprint.com/site/genes-by-species>).

An animated tutorial from the University of Miami illustrates how uniparental disomy occurs (<http://hihg.med.miami.edu/code/http/modules/education/Design/animate/uniDisomy.htm>).

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. (<https://www.genome.gov/11508982#6>)

The Chromosome Disorder Outreach fact sheet Introduction to Chromosomes (<https://chromodisorder.org/introduction-to-chromosomes/>) explains how structural changes occur.

The March of Dimes discusses the causes of chromosomal abnormalities in their fact sheet Chromosomal Conditions (<http://www.marchofdimes.org/baby/chromosomal-conditions.aspx>).

Additional information about how chromosomal changes happen (<https://www.urmc.rochester.edu/encyclopedia/content.aspx?ContentTypeID=90&ContentID=P02126>) is available from the University of Rochester Medical Center.

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

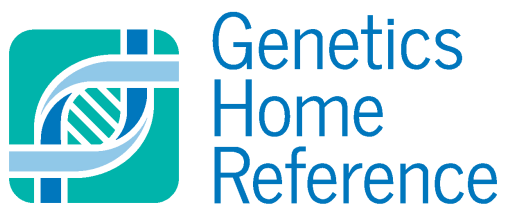
Some genetic disorders are more likely to occur among people who trace their ancestry to a particular geographic area. People in an ethnic group often share certain versions of their genes, which have been passed down from common ancestors. If one of these shared genes contains a disease-causing mutation,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

Know Your Genes from the Genetic Disease Foundation offers a list and descriptions of genetic disorders (http://www.knowyourgenes.org/genetic_diseases.shtml) that occur more frequently in people of various ethnic groups.

The Norton & Elaine Sarnoff Center for Jewish Genetics provides information on disorders that occur more frequently in people with Jewish ancestry, including genetic traits that tend to be more common in Ashkenazi Jews (<http://www.jewishgenetics.org/cjg/Ashkenazi-Jewish-Disorders.aspx>) and Sephardic Jews (<http://www.jewishgenetics.org/cjg/Sephardic-Jewish-Disorders.aspx>).



<https://ghr.nlm.nih.gov/>

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Down syndrome

Down syndrome is a chromosomal condition that is associated with intellectual disability, a characteristic facial appearance, and weak muscle tone (hypotonia) in infancy. All affected individuals experience cognitive delays, but the intellectual disability is usually mild to moderate.

People with Down syndrome may have a variety of birth defects. About half of all affected children are born with a heart defect. Digestive abnormalities, such as a blockage of the intestine, are less common.

Individuals with Down syndrome have an increased risk of developing several medical conditions. These include gastroesophageal reflux, which is a backflow of acidic stomach contents into the esophagus, and celiac disease, which is an intolerance of a wheat protein called gluten. About 15 percent of people with Down syndrome have an underactive thyroid gland (hypothyroidism). The thyroid gland is a butterfly-shaped organ in the lower neck that produces hormones. Individuals with Down syndrome also have an increased risk of hearing and vision problems. Additionally, a small percentage of children with Down syndrome develop cancer of blood-forming cells (leukemia).

Delayed development and behavioral problems are often reported in children with Down syndrome. Affected individuals' speech and language develop later and more slowly than in children without Down syndrome, and affected individuals' speech may be more difficult to understand. Behavioral issues can include attention problems, obsessive/compulsive behavior, and stubbornness or tantrums. A small percentage of people with Down syndrome are also diagnosed with developmental conditions called autism spectrum disorders, which affect communication and social interaction.

People with Down syndrome often experience a gradual decline in thinking ability (cognition) as they age, usually starting around age 50. Down syndrome is also associated with an increased risk of developing Alzheimer disease, a brain disorder that results in a gradual loss of memory, judgment, and ability to function. Approximately half of adults with Down syndrome develop Alzheimer disease. Although Alzheimer disease is usually a disorder that occurs in older adults, people with Down syndrome usually develop this condition in their fifties or sixties.

Frequency

Down syndrome occurs in about 1 in 800 newborns. About 5,300 babies with Down syndrome are born in the United States each year, and approximately 200,000 people in this country have the condition. Although women of any age can have a child with

Down syndrome, the chance of having a child with this condition increases as a woman gets older.

Genetic Changes

Most cases of Down syndrome result from trisomy 21, which means each cell in the body has three copies of chromosome 21 instead of the usual two copies.

Less commonly, Down syndrome occurs when part of chromosome 21 becomes attached (translocated) to another chromosome during the formation of reproductive cells (eggs and sperm) in a parent or very early in fetal development. Affected people have two normal copies of chromosome 21 plus extra material from chromosome 21 attached to another chromosome, resulting in three copies of genetic material from chromosome 21. Affected individuals with this genetic change are said to have translocation Down syndrome.

A very small percentage of people with Down syndrome have an extra copy of chromosome 21 in only some of the body's cells. In these people, the condition is called mosaic Down syndrome.

Researchers believe that having extra copies of genes on chromosome 21 disrupts the course of normal development, causing the characteristic features of Down syndrome and the increased risk of health problems associated with this condition.

Inheritance Pattern

Most cases of Down syndrome are not inherited. When the condition is caused by trisomy 21, the chromosomal abnormality occurs as a random event during the formation of reproductive cells in a parent. The abnormality usually occurs in egg cells, but it occasionally occurs in sperm cells. An error in cell division called nondisjunction results in a reproductive cell with an abnormal number of chromosomes. For example, an egg or sperm cell may gain an extra copy of chromosome 21. If one of these atypical reproductive cells contributes to the genetic makeup of a child, the child will have an extra chromosome 21 in each of the body's cells.

People with translocation Down syndrome can inherit the condition from an unaffected parent. The parent carries a rearrangement of genetic material between chromosome 21 and another chromosome. This rearrangement is called a balanced translocation. No genetic material is gained or lost in a balanced translocation, so these chromosomal changes usually do not cause any health problems. However, as this translocation is passed to the next generation, it can become unbalanced. People who inherit an unbalanced translocation involving chromosome 21 may have extra genetic material from chromosome 21, which causes Down syndrome.

Like trisomy 21, mosaic Down syndrome is not inherited. It occurs as a random event during cell division early in fetal development. As a result, some of the body's cells

have the usual two copies of chromosome 21, and other cells have three copies of this chromosome.

Other Names for This Condition

- 47,XX,+21
- 47,XY,+21
- Down's syndrome
- trisomy 21
- trisomy G

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Complete trisomy 21 syndrome
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0013080/>

Other Diagnosis and Management Resources

- National Down Syndrome Congress: Health Care
<http://www.ndsccenter.org/health-care/>
- National Down Syndrome Congress: Speech and Language
<http://www.ndsccenter.org/speech-and-language/>
- National Down Syndrome Society: Health Care
https://www.ndss.org/rescat_lifespan/tax/health-care-research/
- National Down Syndrome Society: Therapies and Development
<https://www.ndss.org/resources/therapies-development/>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Down Syndrome
<https://medlineplus.gov/ency/article/000997.htm>
- Health Topic: Congenital Heart Defects
<https://medlineplus.gov/congenitalheartdefects.html>
- Health Topic: Down Syndrome
<https://medlineplus.gov/downsyndrome.html>

Genetic and Rare Diseases Information Center

- Down syndrome
<https://rarediseases.info.nih.gov/diseases/10247/down-syndrome>

Additional NIH Resources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development
<https://www.nichd.nih.gov/health/topics/downsyndrome>
- GeneEd
https://geneed.nlm.nih.gov/topic_subtopic.php?tid=142&sid=147
- National Human Genome Research Institute
<https://www.genome.gov/19517824/>
- National Institute of Diabetes and Digestive and Kidney Diseases: Hypothyroidism
<https://www.niddk.nih.gov/health-information/endocrine-diseases/hypothyroidism>

Educational Resources

- Boston Children's Hospital
<http://www.childrenshospital.org/conditions-and-treatments/conditions/d/down-syndrome>
- Centre for Genetics Education (Australia)
<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-36-trisomy-21-down-syndrome>
- Cleveland Clinic: Alzheimer's Disease and Down Syndrome
<https://my.clevelandclinic.org/health/diseases/9173-alzheimers-disease-and-down-syndrome>
- Disease InfoSearch: Down Syndrome
<http://www.diseaseinfosearch.org/Down+Syndrome/2327>
- Down Syndrome: Health Issues (Len Leshin, M.D., F.A.A.P.)
<http://www.ds-health.com/>

- Genetic Science Learning Center, University of Utah
<http://learn.genetics.utah.edu/content/disorders/chromosomal/>
- Genetics Education Materials for School Success (GEMSS)
<https://www.gemssforschools.org/conditions/down/default>
- Kennedy Krieger Institute
<https://www.kennedykrieger.org/patient-care/diagnoses-disorders/down-syndrome>
- KidsHealth from the Nemours Foundation
<http://kidshealth.org/en/kids/down-syndrome.html>
- MalaCards: down syndrome
http://www.malacards.org/card/down_syndrome
- Merck Manual Consumer Version
<http://www.merckmanuals.com/home/children-s-health-issues/chromosome-and-gene-abnormalities/down-syndrome-trisomy-21>
- My46 Trait Profile
<https://www.my46.org/trait-document?trait=Down%20syndrome&type=profile>
- Orphanet: Down syndrome
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=870
- Your Genes Your Health from Cold Spring Harbor Laboratory
<http://www.ygyh.org/ds/whatisit.htm>

Patient Support and Advocacy Resources

- Chromosome Disorder Outreach
<https://chromodisorder.org/>
- LuMind Research Down Syndrome Foundation
<https://www.lumindrds.org/>
- LuMind Research Down Syndrome Foundation
<https://www.lumindrds.org/>
- National Down Syndrome Congress
<http://www.ndsccenter.org/>
- National Down Syndrome Society
<http://www.ndss.org>
- Resource list from the University of Kansas Medical Center
http://www.kumc.edu/gec/support/down_syn.html

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22down+syndrome%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Down+Syndrome%5BMAJR%5D%29+AND+%28Down+syndrome%5BTI%5D%29+AND+review%5Bpt%5D+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D>

OMIM

- DOWN SYNDROME
<http://omim.org/entry/190685>

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<https://ghr.nlm.nih.gov/condition/down-syndrome>

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Fragile X syndrome

Fragile X syndrome is a genetic condition that causes a range of developmental problems including learning disabilities and cognitive impairment. Usually, males are more severely affected by this disorder than females.

Affected individuals usually have delayed development of speech and language by age 2. Most males with fragile X syndrome have mild to moderate intellectual disability, while about one-third of affected females are intellectually disabled. Children with fragile X syndrome may also have anxiety and hyperactive behavior such as fidgeting or impulsive actions. They may have attention deficit disorder (ADD), which includes an impaired ability to maintain attention and difficulty focusing on specific tasks. About one-third of individuals with fragile X syndrome have features of autism spectrum disorders that affect communication and social interaction. Seizures occur in about 15 percent of males and about 5 percent of females with fragile X syndrome.

Most males and about half of females with fragile X syndrome have characteristic physical features that become more apparent with age. These features include a long and narrow face, large ears, a prominent jaw and forehead, unusually flexible fingers, flat feet, and in males, enlarged testicles (macroorchidism) after puberty.

Frequency

Fragile X syndrome occurs in approximately 1 in 4,000 males and 1 in 8,000 females.

Genetic Changes

Mutations in the *FMR1* gene cause fragile X syndrome. The *FMR1* gene provides instructions for making a protein called FMRP. This protein helps regulate the production of other proteins and plays a role in the development of synapses, which are specialized connections between nerve cells. Synapses are critical for relaying nerve impulses.

Nearly all cases of fragile X syndrome are caused by a mutation in which a DNA segment, known as the CGG triplet repeat, is expanded within the *FMR1* gene. Normally, this DNA segment is repeated from 5 to about 40 times. In people with fragile X syndrome, however, the CGG segment is repeated more than 200 times. The abnormally expanded CGG segment turns off (silences) the *FMR1* gene, which prevents the gene from producing FMRP. Loss or a shortage (deficiency) of this protein disrupts nervous system functions and leads to the signs and symptoms of fragile X syndrome.

Males and females with 55 to 200 repeats of the CGG segment are said to have an *FMR1* gene premutation. Most people with a premutation are intellectually normal. In some cases, however, individuals with a premutation have lower than normal amounts of FMRP. As a result, they may have mild versions of the physical features seen in fragile X syndrome (such as prominent ears) and may experience emotional problems such as anxiety or depression. Some children with a premutation may have learning disabilities or autistic-like behavior. The premutation is also associated with an increased risk of disorders called fragile X-associated primary ovarian insufficiency (FXPOI) and fragile X-associated tremor/ataxia syndrome (FXTAS).

Inheritance Pattern

Fragile X syndrome is inherited in an X-linked dominant pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes. (The Y chromosome is the other sex chromosome.) The inheritance is dominant if one copy of the altered gene in each cell is sufficient to cause the condition. X-linked dominant means that in females (who have two X chromosomes), a mutation in one of the two copies of a gene in each cell is sufficient to cause the disorder. In males (who have only one X chromosome), a mutation in the only copy of a gene in each cell causes the disorder. In most cases, males experience more severe symptoms of the disorder than females.

In women, the *FMR1* gene premutation on the X chromosome can expand to more than 200 CGG repeats in cells that develop into eggs. This means that women with the premutation have an increased risk of having a child with fragile X syndrome. By contrast, the premutation in men does not expand to more than 200 repeats as it is passed to the next generation. Men pass the premutation only to their daughters. Their sons receive a Y chromosome, which does not include the *FMR1* gene.

Other Names for This Condition

- fra(X) syndrome
- FRAXA syndrome
- FXS
- marker X syndrome
- Martin-Bell syndrome
- X-linked mental retardation and macroorchidism

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Fragile X syndrome
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0016667/>

Other Diagnosis and Management Resources

- GeneReview: FMR1-Related Disorders
<https://www.ncbi.nlm.nih.gov/books/NBK1384>
- MedlinePlus Encyclopedia: Fragile X syndrome
<https://medlineplus.gov/ency/article/001668.htm>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Fragile X syndrome
<https://medlineplus.gov/ency/article/001668.htm>
- Health Topic: Fragile X Syndrome
<https://medlineplus.gov/fragilexsyndrome.html>

Genetic and Rare Diseases Information Center

- Fragile X syndrome
<https://rarediseases.info.nih.gov/diseases/6464/fragile-x-syndrome>

Additional NIH Resources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development
<https://www.nichd.nih.gov/health/topics/fragilex>
- Eunice Kennedy Shriver National Institute of Child Health and Human Development: Primary Ovarian Insufficiency
<https://www.nichd.nih.gov/health/topics/poi>

Educational Resources

- American College of Medical Genetics and Genomics Practice Guideline
<https://www.acmg.net/StaticContent/StaticPages/FragileX.pdf>
- Boston Children's Hospital
<http://www.childrenshospital.org/conditions-and-treatments/conditions/fragile-x-syndrome>
- Centre for Genetics Education (Australia)
<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-54-fragile-x-syndrome>
- Disease InfoSearch: Fragile X Syndrome
<http://www.diseaseinfosearch.org/Fragile+X+Syndrome/2906>
- Emory University School of Medicine: Fragile X Premutation--a Cause of Premature Ovarian Failure
<http://genetics.emory.edu/documents/resources/factsheet46.pdf>
- Emory University School of Medicine: Fragile X Syndrome
<http://genetics.emory.edu/documents/resources/factsheet47.pdf>
- Genetics Education Materials for School Success (GEMSS)
<https://www.gemssforschools.org/conditions/fragile-x/default>
- Kennedy Krieger Institute
<https://www.kennedykrieger.org/patient-care/diagnoses-disorders/fragile-x-syndrome>
- MalaCards: fragile x syndrome
http://www.malacards.org/card/fragile_x_syndrome
- My46 Trait Profile
<https://www.my46.org/trait-document?trait=Fragile%20X%20syndrome&type=profile>
- Orphanet: Fragile X syndrome
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=908
- Your Genes Your Health from Cold Spring Harbor Laboratory
<http://www.ygyh.org/fragx/whatisit.htm>

Patient Support and Advocacy Resources

- FRAXA Research Foundation
<https://www.fraxa.org/>
- March of Dimes
<https://www.marchofdimes.org/baby/fragile-x-syndrome.aspx>

- National Fragile X Foundation
<https://fragilex.org/>
- National Organization for Rare Disorders (NORD)
<https://rarediseases.org/rare-diseases/fragile-x-syndrome/>

GeneReviews

- FMR1-Related Disorders
<https://www.ncbi.nlm.nih.gov/books/NBK1384>

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22fragile+x+syndrome%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Fragile+X+Syndrome%5BMAJR%5D%29+AND+%28fragile+X+syndrome%5BTI%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D>

OMIM

- FMR1 GENE
<http://omim.org/entry/309550>

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Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3110946/>
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<https://ghr.nlm.nih.gov/condition/fragile-x-syndrome>

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National Institutes of Health

Department of Health & Human Services



Hemophilia

Hemophilia is a bleeding disorder that slows the blood clotting process. People with this condition experience prolonged bleeding or oozing following an injury, surgery, or having a tooth pulled. In severe cases of hemophilia, continuous bleeding occurs after minor trauma or even in the absence of injury (spontaneous bleeding). Serious complications can result from bleeding into the joints, muscles, brain, or other internal organs. Milder forms of hemophilia do not necessarily involve spontaneous bleeding, and the condition may not become apparent until abnormal bleeding occurs following surgery or a serious injury.

The major types of this condition are hemophilia A (also known as classic hemophilia or factor VIII deficiency) and hemophilia B (also known as Christmas disease or factor IX deficiency). Although the two types have very similar signs and symptoms, they are caused by mutations in different genes. People with an unusual form of hemophilia B, known as hemophilia B Leyden, experience episodes of excessive bleeding in childhood but have few bleeding problems after puberty.

Frequency

The two major forms of hemophilia occur much more commonly in males than in females. Hemophilia A is the most common type of the condition; 1 in 4,000 to 1 in 5,000 males worldwide are born with this disorder. Hemophilia B occurs in approximately 1 in 20,000 newborn males worldwide.

Genetic Changes

Changes in the *F8* gene are responsible for hemophilia A, while mutations in the *F9* gene cause hemophilia B. The *F8* gene provides instructions for making a protein called coagulation factor VIII. A related protein, coagulation factor IX, is produced from the *F9* gene. Coagulation factors are proteins that work together in the blood clotting process. After an injury, blood clots protect the body by sealing off damaged blood vessels and preventing excessive blood loss.

Mutations in the *F8* or *F9* gene lead to the production of an abnormal version of coagulation factor VIII or coagulation factor IX, or reduce the amount of one of these proteins. The altered or missing protein cannot participate effectively in the blood clotting process. As a result, blood clots cannot form properly in response to injury. These problems with blood clotting lead to continuous bleeding that can be difficult to control. The mutations that cause severe hemophilia almost completely eliminate the activity of coagulation factor VIII or coagulation factor IX. The mutations responsible for

mild and moderate hemophilia reduce but do not eliminate the activity of one of these proteins.

Another form of the disorder, known as acquired hemophilia, is not caused by inherited gene mutations. This rare condition is characterized by abnormal bleeding into the skin, muscles, or other soft tissues, usually beginning in adulthood. Acquired hemophilia results when the body makes specialized proteins called autoantibodies that attack and disable coagulation factor VIII. The production of autoantibodies is sometimes associated with pregnancy, immune system disorders, cancer, or allergic reactions to certain drugs. In about half of cases, the cause of acquired hemophilia is unknown.

Inheritance Pattern

Hemophilia A and hemophilia B are inherited in an X-linked recessive pattern. The genes associated with these conditions are located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, it is very rare for females to have hemophilia. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

In X-linked recessive inheritance, a female with one altered copy of the gene in each cell is called a carrier. Carrier females have about half the usual amount of coagulation factor VIII or coagulation factor IX, which is generally enough for normal blood clotting. However, about 10 percent of carrier females have less than half the normal amount of one of these coagulation factors; these individuals are at risk for abnormal bleeding, particularly after an injury, surgery, or tooth extraction.

Other Names for This Condition

- Hemophilia, familial
- Hemophilia, hereditary

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Hemophilia
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0684275/>
- Genetic Testing Registry: Hemophilia b(m)
<https://www.ncbi.nlm.nih.gov/gtr/conditions/CN043453/>

- Genetic Testing Registry: Hereditary factor IX deficiency disease
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0008533/>
- Genetic Testing Registry: Hereditary factor VIII deficiency disease
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0019069/>

Other Diagnosis and Management Resources

- GeneReview: Hemophilia A
<https://www.ncbi.nlm.nih.gov/books/NBK1404>
- GeneReview: Hemophilia B
<https://www.ncbi.nlm.nih.gov/books/NBK1495>
- Genomics Education Programme (UK): Haemophilia A
<https://www.genomicseducation.hee.nhs.uk/resources/genetic-conditions-factsheets/item/79-haemophilia-a/>
- MedlinePlus Encyclopedia: Factor IX Assay
<https://medlineplus.gov/ency/article/003679.htm>
- MedlinePlus Encyclopedia: Factor VIII Assay
<https://medlineplus.gov/ency/article/003678.htm>
- MedlinePlus Encyclopedia: Hemophilia A
<https://medlineplus.gov/ency/article/000538.htm>
- MedlinePlus Encyclopedia: Hemophilia B
<https://medlineplus.gov/ency/article/000539.htm>
- National Heart, Lung, and Blood Institute: How is Hemophilia Diagnosed?
<https://www.nhlbi.nih.gov/health-topics/hemophilia#Diagnosis>
- National Heart, Lung, and Blood Institute: How is Hemophilia Treated?
<https://www.nhlbi.nih.gov/health-topics/hemophilia#Treatment>
- National Hemophilia Foundation: Hemophilia Treatment Centers
<https://www.hemophilia.org/Researchers-Healthcare-Providers/Comprehensive-Medical-Care-Hemophilia-Treatment-Centers>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>

- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Factor IX Assay
<https://medlineplus.gov/ency/article/003679.htm>
- Encyclopedia: Factor VIII Assay
<https://medlineplus.gov/ency/article/003678.htm>
- Encyclopedia: Hemophilia A
<https://medlineplus.gov/ency/article/000538.htm>
- Encyclopedia: Hemophilia B
<https://medlineplus.gov/ency/article/000539.htm>
- Health Topic: Hemophilia
<https://medlineplus.gov/hemophilia.html>

Genetic and Rare Diseases Information Center

- Acquired hemophilia
<https://rarediseases.info.nih.gov/diseases/10350/acquired-hemophilia>
- Hemophilia
<https://rarediseases.info.nih.gov/diseases/10418/hemophilia>
- Hemophilia A
<https://rarediseases.info.nih.gov/diseases/6591/hemophilia-a>
- Hemophilia B
<https://rarediseases.info.nih.gov/diseases/8732/hemophilia-b>

Additional NIH Resources

- GeneEd
https://geneed.nlm.nih.gov/topic_subtopic.php?tid=142&sid=148
- National Heart, Lung, and Blood Institute
<https://www.nhlbi.nih.gov/health-topics/hemophilia>
- National Human Genome Research Institute
<https://www.genome.gov/20019697/>

Educational Resources

- Boston Children's Hospital
<http://www.childrenshospital.org/conditions-and-treatments/conditions/p/pediatric-hemophilia>
- Centers for Disease Control and Prevention
<https://www.cdc.gov/ncbddd/hemophilia/>
- Centre for Genetics Education (Australia)
<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-52-haemophilia>
- Cincinnati Children's Hospital Medical Center
<https://www.cincinnatichildrens.org/health/h/hemophilia>
- Cleveland Clinic
<https://my.clevelandclinic.org/health/diseases/14083-hemophilia>
- Disease InfoSearch: Hemophilia
<http://www.diseaseinfosearch.org/Hemophilia/3311>
- KidsHealth from the Nemours Foundation
<http://kidshealth.org/en/parents/hemophilia.html>
- MalaCards: hemophilia
<http://www.malacards.org/card/hemophilia>
- Merck Manual Home Health Handbook
<http://www.merckmanuals.com/home/blood-disorders/bleeding-due-to-clotting-disorders/hemophilia>
- My46 Trait Profile: Hemophilia A
<https://www.my46.org/trait-document?trait=Hemophilia%20A&type=profile>
- My46 Trait Profile: Hemophilia B
<https://www.my46.org/trait-document?trait=Hemophilia%20B&type=profile>
- Orphanet: Hemophilia
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=448
- Your Genes Your Health from Cold Spring Harbor Laboratory
<http://www.ygyh.org/hemo/whatisit.htm>

Patient Support and Advocacy Resources

- Canadian Hemophilia Society
<http://www.hemophilia.ca/>
- Hemophilia Federation of America
<http://www.hemophiliafed.org/>

- National Hemophilia Foundation
<https://www.hemophilia.org/>
- National Organization for Rare Disorders (NORD): Hemophilia A
<https://rarediseases.org/rare-diseases/hemophilia-a/>
- National Organization for Rare Disorders (NORD): Hemophilia B
<https://rarediseases.org/rare-diseases/hemophilia-b/>
- Resource list from the University of Kansas Medical Center
<http://www.kumc.edu/gec/support/hemophil.html>
- World Federation of Hemophilia
<https://www.wfh.org/>

GeneReviews

- Hemophilia A
<https://www.ncbi.nlm.nih.gov/books/NBK1404>
- Hemophilia B
<https://www.ncbi.nlm.nih.gov/books/NBK1495>

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22hemophilia%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28Hemophilia+A%5BMAJR%5D%29+OR+%28Hemophilia+B%5BMAJR%5D%29%29+AND+%28hemophilia%5BTI%5D%29+AND+review%5Bpt%5D+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D>

OMIM

- HEMOPHILIA A
<http://omim.org/entry/306700>
- HEMOPHILIA B
<http://omim.org/entry/306900>

MedGen

- Acquired hemophilia
<https://www.ncbi.nlm.nih.gov/medgen/204253>
- Hemophilia
<https://www.ncbi.nlm.nih.gov/medgen/146334>

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Huntington disease

Huntington disease is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition).

Adult-onset Huntington disease, the most common form of this disorder, usually appears in a person's thirties or forties. Early signs and symptoms can include irritability, depression, small involuntary movements, poor coordination, and trouble learning new information or making decisions. Many people with Huntington disease develop involuntary jerking or twitching movements known as chorea. As the disease progresses, these movements become more pronounced. Affected individuals may have trouble walking, speaking, and swallowing. People with this disorder also experience changes in personality and a decline in thinking and reasoning abilities. Individuals with the adult-onset form of Huntington disease usually live about 15 to 20 years after signs and symptoms begin.

A less common form of Huntington disease known as the juvenile form begins in childhood or adolescence. It also involves movement problems and mental and emotional changes. Additional signs of the juvenile form include slow movements, clumsiness, frequent falling, rigidity, slurred speech, and drooling. School performance declines as thinking and reasoning abilities become impaired. Seizures occur in 30 percent to 50 percent of children with this condition. Juvenile Huntington disease tends to progress more quickly than the adult-onset form; affected individuals usually live 10 to 15 years after signs and symptoms appear.

Frequency

Huntington disease affects an estimated 3 to 7 per 100,000 people of European ancestry. The disorder appears to be less common in some other populations, including people of Japanese, Chinese, and African descent.

Genetic Changes

Mutations in the *HTT* gene cause Huntington disease. The *HTT* gene provides instructions for making a protein called huntingtin. Although the function of this protein is unknown, it appears to play an important role in nerve cells (neurons) in the brain.

The *HTT* mutation that causes Huntington disease involves a DNA segment known as a CAG trinucleotide repeat. This segment is made up of a series of three DNA building blocks (cytosine, adenine, and guanine) that appear multiple times in a row. Normally, the CAG segment is repeated 10 to 35 times within the gene. In people with Huntington disease, the CAG segment is repeated 36 to more than 120 times. People with 36 to 39

CAG repeats may or may not develop the signs and symptoms of Huntington disease, while people with 40 or more repeats almost always develop the disorder.

An increase in the size of the CAG segment leads to the production of an abnormally long version of the huntingtin protein. The elongated protein is cut into smaller, toxic fragments that bind together and accumulate in neurons, disrupting the normal functions of these cells. The dysfunction and eventual death of neurons in certain areas of the brain underlie the signs and symptoms of Huntington disease.

Inheritance Pattern

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. An affected person usually inherits the altered gene from one affected parent. In rare cases, an individual with Huntington disease does not have a parent with the disorder.

As the altered *HTT* gene is passed from one generation to the next, the size of the CAG trinucleotide repeat often increases in size. A larger number of repeats is usually associated with an earlier onset of signs and symptoms. This phenomenon is called anticipation. People with the adult-onset form of Huntington disease typically have 40 to 50 CAG repeats in the *HTT* gene, while people with the juvenile form of the disorder tend to have more than 60 CAG repeats.

Individuals who have 27 to 35 CAG repeats in the *HTT* gene do not develop Huntington disease, but they are at risk of having children who will develop the disorder. As the gene is passed from parent to child, the size of the CAG trinucleotide repeat may lengthen into the range associated with Huntington disease (36 repeats or more).

Other Names for This Condition

- Huntington chorea
- Huntington chronic progressive hereditary chorea
- Huntington's chorea
- Huntington's disease

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Huntington's chorea
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0020179/>
- Genetic Testing Registry: Juvenile onset Huntington's disease
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0751208/>

Other Diagnosis and Management Resources

- GeneReview: Huntington Disease
<https://www.ncbi.nlm.nih.gov/books/NBK1305>
- Huntington's Disease Society of America: HD Care
<http://hdsa.org/living-with-hd/>
- MedlinePlus Encyclopedia: Huntington Disease
<https://medlineplus.gov/ency/article/000770.htm>
- University of Washington Medical Center: Testing for Huntington Disease: Making an Informed Choice
<http://depts.washington.edu/neurolog/images/neurogenetics/hungtinton.pdf>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Huntington Disease
<https://medlineplus.gov/ency/article/000770.htm>
- Health Topic: Huntington's Disease
<https://medlineplus.gov/huntingtonsdisease.html>

Genetic and Rare Diseases Information Center

- Huntington disease
<https://rarediseases.info.nih.gov/diseases/6677/huntington-disease>
- Juvenile Huntington disease
<https://rarediseases.info.nih.gov/diseases/10510/juvenile-huntington-disease>

Additional NIH Resources

- GeneEd
https://geneed.nlm.nih.gov/topic_subtopic.php?tid=142&sid=169
- National Human Genome Research Institute: Learning About Huntington's Disease
<https://www.genome.gov/10001215/>
- National Institute of Neurological Disorders and Stroke: Huntington's Disease Information Page
<https://www.ninds.nih.gov/Disorders/All-Disorders/Huntingtons-Disease-Information-Page>
- National Institute of Neurological Disorders and Stroke: Huntington's Disease: Hope Through Research
<https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Huntingtons-Disease-Hope-Through>

Educational Resources

- Centre for Genetics Education
<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-55-huntington-disease>
- Disease InfoSearch: Huntington disease
<http://www.diseaseinfosearch.org/Huntington+disease/3497>
- Genetic Science Learning Center, University of Utah
<http://learn.genetics.utah.edu/content/disorders/singlegene/>
- HOPES: Huntington's Outreach Project for Education, at Stanford
https://web.stanford.edu/group/hopes/cgi-bin/hopes_test/
- Johns Hopkins Medicine
https://www.hopkinsmedicine.org/psychiatry/specialty_areas/huntingtons_disease/patient_family_resources/education_what.html
- MalaCards: huntington disease
http://www.malacards.org/card/huntington_disease
- Merck Manual Consumer Version
<http://www.merckmanuals.com/home/brain-spinal-cord-and-nerve-disorders/movement-disorders/huntington-disease>
- My46 Trait Profile
<https://www.my46.org/trait-document?trait=Huntington%20Disease&type=profile>

- Orphanet: Huntington disease
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=399
- Your Genes Your Health from Cold Spring Harbor Laboratory
<http://www.ygyh.org/hd/whatisit.htm>

Patient Support and Advocacy Resources

- Family Caregiver Alliance
<https://www.caregiver.org/health-issues/huntingtons>
- HDBuzz
<https://en.hdbuzz.net/>
- Hereditary Disease Foundation
<http://www.hdfoundation.org/>
- Huntington Society of Canada
<https://www.huntingtonsociety.ca/>
- Huntington's Disease Society of America
<http://hdsa.org/>
- National Organization for Rare Disorders (NORD)
<https://rarediseases.org/rare-diseases/huntingtons-disease/>
- Resource list from the University of Kansas Medical Center
<http://www.kumc.edu/gec/support/huntingt.html>

GeneReviews

- Huntington Disease
<https://www.ncbi.nlm.nih.gov/books/NBK1305>

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22huntington+disease%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Huntington+Disease%5BMAJR%5D%29+AND+%28Huntington+disease%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D>

OMIM

- HUNTINGTON DISEASE
<http://omim.org/entry/143100>

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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/15132037>
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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/20923757>
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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/14702246>
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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/17240289>
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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/20301482>
- Young AB. Huntingtin in health and disease. *J Clin Invest.* 2003 Feb;111(3):299-302. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/12569151>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC151871/>

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<https://ghr.nlm.nih.gov/condition/huntington-disease>

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National Institutes of Health
Department of Health & Human Services



Maple syrup urine disease

Maple syrup urine disease is an inherited disorder in which the body is unable to process certain protein building blocks (amino acids) properly. The condition gets its name from the distinctive sweet odor of affected infants' urine. It is also characterized by poor feeding, vomiting, lack of energy (lethargy), abnormal movements, and delayed development. If untreated, maple syrup urine disease can lead to seizures, coma, and death.

Maple syrup urine disease is often classified by its pattern of signs and symptoms. The most common and severe form of the disease is the classic type, which becomes apparent soon after birth. Variant forms of the disorder become apparent later in infancy or childhood and are typically milder, but they still lead to delayed development and other health problems if not treated.

Frequency

Maple syrup urine disease affects an estimated 1 in 185,000 infants worldwide. The disorder occurs much more frequently in the Old Order Mennonite population, with an estimated incidence of about 1 in 380 newborns.

Genetic Changes

Mutations in the *BCKDHA*, *BCKDHB*, and *DBT* genes can cause maple syrup urine disease. These three genes provide instructions for making proteins that work together as part of a complex. The protein complex is essential for breaking down the amino acids leucine, isoleucine, and valine, which are present in many kinds of food, particularly protein-rich foods such as milk, meat, and eggs.

Mutations in any of these three genes reduce or eliminate the function of the protein complex, preventing the normal breakdown of leucine, isoleucine, and valine. As a result, these amino acids and their byproducts build up in the body. Because high levels of these substances are toxic to the brain and other organs, their accumulation leads to the serious health problems associated with maple syrup urine disease.

Researchers are studying other genes related to the same protein complex that may also be associated with maple syrup urine disease.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal

recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- BCKD deficiency
- branched-chain alpha-keto acid dehydrogenase deficiency
- branched-chain ketoaciduria
- ketoacidemia
- MSUD

Diagnosis & Management

Formal Diagnostic Criteria

- ACT Sheet: Increased leucine
<https://www.ncbi.nlm.nih.gov/books/NBK55827/bin/Leucine.pdf>

Formal Treatment/Management Guidelines

- British Inherited Metabolic Disease Group: MSUD Clinical Management Guidelines
http://www.bimdg.org.uk/store/enbs//Final_MSUD_clinical_management_guidelines_v11_Jan_2017_647074_25042017.pdf
- British Inherited Metabolic Disease Group: MSUD Dietetic Management Pathway
http://www.bimdg.org.uk/store/enbs//MSUD_Dietetic_management_pathway_April_2015_660203_12052015.pdf
- New England Consortium of Metabolic Programs: Acute Illness Protocol
<http://newenglandconsortium.org/for-professionals/acute-illness-protocols/organic-acid-disorders/maple-syrup-urine-disease-msud/>

Genetic Testing

- Genetic Testing Registry: Classical maple syrup urine disease
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268568/>
- Genetic Testing Registry: Intermediate maple syrup urine disease
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1621920/>
- Genetic Testing Registry: Maple syrup urine disease
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0024776/>

Other Diagnosis and Management Resources

- Baby's First Test
<http://www.babysfirsttest.org/newborn-screening/conditions/maple-syrup-urine-disease-msud>
- GeneReview: Maple Syrup Urine Disease
<https://www.ncbi.nlm.nih.gov/books/NBK1319>
- MedlinePlus Encyclopedia: Maple Syrup Urine Disease
<https://medlineplus.gov/ency/article/000373.htm>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Maple Syrup Urine Disease
<https://medlineplus.gov/ency/article/000373.htm>
- Health Topic: Amino Acid Metabolism Disorders
<https://medlineplus.gov/aminoacidmetabolismdisorders.html>
- Health Topic: Genetic Brain Disorders
<https://medlineplus.gov/geneticbraindisorders.html>
- Health Topic: Newborn Screening
<https://medlineplus.gov/newbornscreening.html>

Genetic and Rare Diseases Information Center

- Maple syrup urine disease
<https://rarediseases.info.nih.gov/diseases/3228/maple-syrup-urine-disease>

Educational Resources

- Disease InfoSearch: Maple syrup urine disease
<http://www.diseaseinfosearch.org/Maple+syrup+urine+disease/4453>
- Genetic Science Learning Center, University of Utah
<http://learn.genetics.utah.edu/content/disorders/singlegene/>
- Illinois Department of Public Health Genetics and Newborn Screening Program
<http://www.idph.state.il.us/HealthWellness/fs/msud.htm>
- MalaCards: intermediate maple syrup urine disease
http://www.malacards.org/card/intermediate_maple_syrup_urine_disease
- MalaCards: maple syrup urine disease, mild variant
http://www.malacards.org/card/maple_syrup_urine_disease_mild_variant
- Merck Manual Consumer Version: Disorders of Amino Acid Metabolism
<http://www.merckmanuals.com/home/children-s-health-issues/hereditary-metabolic-disorders/disorders-of-amino-acid-metabolism>
- Michigan Department of Community Health
http://www.michigan.gov/documents/msud_79207_7.pdf
- My46 Trait Profile
<https://www.my46.org/trait-document?trait=Maple%20syrup%20urine%20disease&type=profile>
- New England Consortium of Metabolic Programs
<http://newenglandconsortium.org/for-families/other-metabolic-disorders/organic-acid-disorders/msud/>
- Orphanet: Classic maple syrup urine disease
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=268145
- Orphanet: Intermediate maple syrup urine disease
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=268162
- Orphanet: Maple syrup urine disease
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=511
- Screening, Technology, and Research in Genetics
<http://www.newbornscreening.info/Parents/aminoaciddisorders/MSUD.html>
- Virginia Department of Health
http://www.vdh.virginia.gov/content/uploads/sites/33/2016/11/Parent-Fact-Sheet_MSUD_English.pdf
- Washington State Department of Health
<https://www.doh.wa.gov/Portals/1/Documents/5220/5220-MSUD-GO.pdf>

Patient Support and Advocacy Resources

- CLIMB: Children Living with Inherited Metabolic Diseases (UK)
<http://www.climb.org.uk/>
- MSUD Family Support Group
<http://www.msud-support.org/>
- National Organization for Rare Disorders
<https://rarediseases.org/rare-diseases/maple-syrup-urine-disease/>
- Organic Acidemia Association
<http://www.oaanews.org/>
- Resource List from the University of Kansas Medical Center
<http://www.kumc.edu/gec/support/maple.html>

GeneReviews

- Maple Syrup Urine Disease
<https://www.ncbi.nlm.nih.gov/books/NBK1319>

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22Maple+Syrup+Urine+Disease%22+OR+%22maple+syrup+urine+disease%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Maple+Syrup+Urine+Disease%5BMAJR%5D%29+AND+%28maple+syrup+urine+disease%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D>

OMIM

- MAPLE SYRUP URINE DISEASE
<http://omim.org/entry/248600>
- MAPLE SYRUP URINE DISEASE, MILD VARIANT
<http://omim.org/entry/615135>

MedGen

- Classical maple syrup urine disease
<https://www.ncbi.nlm.nih.gov/medgen/78689>
- Intermittent maple syrup urine disease
<https://www.ncbi.nlm.nih.gov/medgen/78690>

- Maple syrup urine disease
<https://www.ncbi.nlm.nih.gov/medgen/6217>
- Mild maple syrup urine disease
<https://www.ncbi.nlm.nih.gov/medgen/541364>

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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/28599741>
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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/23086801>
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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/17063375>
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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/20301495>

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Phenylketonuria

Phenylketonuria (commonly known as PKU) is an inherited disorder that increases the levels of a substance called phenylalanine in the blood. Phenylalanine is a building block of proteins (an amino acid) that is obtained through the diet. It is found in all proteins and in some artificial sweeteners. If PKU is not treated, phenylalanine can build up to harmful levels in the body, causing intellectual disability and other serious health problems.

The signs and symptoms of PKU vary from mild to severe. The most severe form of this disorder is known as classic PKU. Infants with classic PKU appear normal until they are a few months old. Without treatment, these children develop permanent intellectual disability. Seizures, delayed development, behavioral problems, and psychiatric disorders are also common. Untreated individuals may have a musty or mouse-like odor as a side effect of excess phenylalanine in the body. Children with classic PKU tend to have lighter skin and hair than unaffected family members and are also likely to have skin disorders such as eczema.

Less severe forms of this condition, sometimes called variant PKU and non-PKU hyperphenylalaninemia, have a smaller risk of brain damage. People with very mild cases may not require treatment with a low-phenylalanine diet.

Babies born to mothers who have PKU and uncontrolled phenylalanine levels (women who no longer follow a low-phenylalanine diet) have a significant risk of intellectual disability because they are exposed to very high levels of phenylalanine before birth. These infants may also have a low birth weight and grow more slowly than other children. Other characteristic medical problems include heart defects or other heart problems, an abnormally small head size (microcephaly), and behavioral problems. Women with PKU and uncontrolled phenylalanine levels also have an increased risk of pregnancy loss.

Frequency

The occurrence of PKU varies among ethnic groups and geographic regions worldwide. In the United States, PKU occurs in 1 in 10,000 to 15,000 newborns. Most cases of PKU are detected shortly after birth by newborn screening, and treatment is started promptly. As a result, the severe signs and symptoms of classic PKU are rarely seen.

Genetic Changes

Mutations in the *PAH* gene cause phenylketonuria. The *PAH* gene provides instructions for making an enzyme called phenylalanine hydroxylase. This enzyme converts the amino acid phenylalanine to other important compounds in the body. If gene mutations

reduce the activity of phenylalanine hydroxylase, phenylalanine from the diet is not processed effectively. As a result, this amino acid can build up to toxic levels in the blood and other tissues. Because nerve cells in the brain are particularly sensitive to phenylalanine levels, excessive amounts of this substance can cause brain damage.

Classic PKU, the most severe form of the disorder, occurs when phenylalanine hydroxylase activity is severely reduced or absent. People with untreated classic PKU have levels of phenylalanine high enough to cause severe brain damage and other serious health problems. Mutations in the *PAH* gene that allow the enzyme to retain some activity result in milder versions of this condition, such as variant PKU or non-PKU hyperphenylalaninemia.

Changes in other genes may influence the severity of PKU, but little is known about these additional genetic factors.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- deficiency disease, phenylalanine hydroxylase
- Folling disease
- Folling's disease
- PAH deficiency
- Phenylalanine Hydroxylase Deficiency
- phenylalanine hydroxylase deficiency
- phenylalanine hydroxylase deficiency disease
- PKU

Diagnosis & Management

Formal Diagnostic Criteria

- ACT Sheet: Increased phenylalanine
<https://www.ncbi.nlm.nih.gov/books/NBK55827/bin/Phenylalanine.pdf>

Formal Treatment/Management Guidelines

- National PKU Alliance: Medical and Dietary Guidelines for PKU
<https://www.npkua.org/Education/PKU-Medical-Guidelines>

Genetic Testing

- Genetic Testing Registry: Phenylketonuria
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0031485/>

Other Diagnosis and Management Resources

- Baby's First Test
<http://www.babysfirsttest.org/newborn-screening/conditions/classic-phenylketonuria-pku>
- GeneReview: Phenylalanine Hydroxylase Deficiency
<https://www.ncbi.nlm.nih.gov/books/NBK1504>
- MedlinePlus Encyclopedia: Phenylketonuria
<https://medlineplus.gov/ency/article/001166.htm>
- MedlinePlus Encyclopedia: Serum Phenylalanine Screening
<https://medlineplus.gov/ency/article/003362.htm>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Phenylketonuria
<https://medlineplus.gov/ency/article/001166.htm>
- Encyclopedia: Serum Phenylalanine Screening
<https://medlineplus.gov/ency/article/003362.htm>
- Health Topic: Newborn Screening
<https://medlineplus.gov/newbornscreening.html>
- Health Topic: Phenylketonuria
<https://medlineplus.gov/phenylketonuria.html>

Genetic and Rare Diseases Information Center

- Phenylketonuria
<https://rarediseases.info.nih.gov/diseases/7383/phenylketonuria>

Additional NIH Resources

- National Human Genome Research Institute
<https://www.genome.gov/25020037/>
- National Institute of Child Health and Human Development
<https://www.nichd.nih.gov/health/topics/pku>

Educational Resources

- Disease InfoSearch: Phenylketonuria
<http://www.diseaseinfosearch.org/Phenylketonuria/5714>
- Genetic Science Learning Center, University of Utah
<http://learn.genetics.utah.edu/content/disorders/singlegene/>
- Genetics Education Materials for School Success (GEMSS)
<https://www.gemssforschools.org/conditions/pku/default>
- MalaCards: phenylketonuria
<http://www.malacards.org/card/phenylketonuria>
- March of Dimes
<https://www.marchofdimes.org/baby/phenylketonuria-in-your-baby.aspx>
- Montreal Children's Hospital
<http://www.pahdb.mcgill.ca/?Topic=Information&Section=Clinical&Page=1>
- My46 Trait Profile
<https://www.my46.org/trait-document?trait=Phenylketonuria&type=profile>
- New England Consortium of Metabolic Programs
<http://newenglandconsortium.org/for-families/phenylketonuria-pku/pku-a-guide-for-parents-of-babies-recently-screened/>
- Orphanet: Phenylketonuria
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=716
- Screening, Technology, and Research in Genetics
<http://www.newbornscreening.info/Parents/aminoaciddisorders/PKU.html>
- Swedish Information Center for Rare Diseases
<http://www.socialstyrelsen.se/rarediseases/phenylketonuria>

- Virginia Department of Health
http://www.vdh.virginia.gov/content/uploads/sites/33/2016/11/Parent-Fact-Sheet_PKU_English.pdf
- Your Genes Your Health from Cold Spring Harbor Laboratory
<http://www.ygyh.org/pku/whatisit.htm>

Patient Support and Advocacy Resources

- Children Living with Metabolic Disorders (CLIMB) (UK)
<http://www.climb.org.uk>
- National Organization for Rare Disorders (NORD)
<https://rarediseases.org/rare-diseases/phenylketonuria/>
- National PKU Alliance
<https://npkua.org/>
- National PKU News
<https://pkunews.org/>
- NBS Connect
<https://nbs.patientcrossroads.org/>
- Resource List from the University of Kansas Medical Center
<http://www.kumc.edu/gec/support/pku.html>
- University of Washington PKU Clinic
<http://depts.washington.edu/pku/>

GeneReviews

- Phenylalanine Hydroxylase Deficiency
<https://www.ncbi.nlm.nih.gov/books/NBK1504>

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22phenylketonuria%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Phenylketonurias%5BMAJR%5D%29+AND+%28%28phenylketonuria%5BTI%5D%29+OR+%28folling+disease%5BTI%5D%29+OR+%28pku%5BTI%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D>

OMIM

- PHENYLKETONURIA
<http://omim.org/entry/261600>

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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/17443661>
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Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/12961938>
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Sickle cell disease

Sickle cell disease is a group of disorders that affects hemoglobin, the molecule in red blood cells that delivers oxygen to cells throughout the body. People with this disorder have atypical hemoglobin molecules called hemoglobin S, which can distort red blood cells into a sickle, or crescent, shape.

Signs and symptoms of sickle cell disease usually begin in early childhood. Characteristic features of this disorder include a low number of red blood cells (anemia), repeated infections, and periodic episodes of pain. The severity of symptoms varies from person to person. Some people have mild symptoms, while others are frequently hospitalized for more serious complications.

The signs and symptoms of sickle cell disease are caused by the sickling of red blood cells. When red blood cells sickle, they break down prematurely, which can lead to anemia. Anemia can cause shortness of breath, fatigue, and delayed growth and development in children. The rapid breakdown of red blood cells may also cause yellowing of the eyes and skin, which are signs of jaundice. Painful episodes can occur when sickled red blood cells, which are stiff and inflexible, get stuck in small blood vessels. These episodes deprive tissues and organs of oxygen-rich blood and can lead to organ damage, especially in the lungs, kidneys, spleen, and brain. A particularly serious complication of sickle cell disease is high blood pressure in the blood vessels that supply the lungs (pulmonary hypertension). Pulmonary hypertension occurs in about one-third of adults with sickle cell disease and can lead to heart failure.

Frequency

Sickle cell disease affects millions of people worldwide. It is most common among people whose ancestors come from Africa; Mediterranean countries such as Greece, Turkey, and Italy; the Arabian Peninsula; India; and Spanish-speaking regions in South America, Central America, and parts of the Caribbean.

Sickle cell disease is the most common inherited blood disorder in the United States, affecting 70,000 to 80,000 Americans. The disease is estimated to occur in 1 in 500 African Americans and 1 in 1,000 to 1,400 Hispanic Americans.

Genetic Changes

Mutations in the *HBB* gene cause sickle cell disease.

Hemoglobin consists of four protein subunits, typically, two subunits called alpha-globin and two subunits called beta-globin. The *HBB* gene provides instructions for making beta-globin. Various versions of beta-globin result from different mutations in the *HBB*

gene. One particular *HBB* gene mutation produces an abnormal version of beta-globin known as hemoglobin S (HbS). Other mutations in the *HBB* gene lead to additional abnormal versions of beta-globin such as hemoglobin C (HbC) and hemoglobin E (HbE). *HBB* gene mutations can also result in an unusually low level of beta-globin; this abnormality is called beta thalassemia.

In people with sickle cell disease, at least one of the beta-globin subunits in hemoglobin is replaced with hemoglobin S. In sickle cell anemia, which is a common form of sickle cell disease, hemoglobin S replaces both beta-globin subunits in hemoglobin. In other types of sickle cell disease, just one beta-globin subunit in hemoglobin is replaced with hemoglobin S. The other beta-globin subunit is replaced with a different abnormal variant, such as hemoglobin C. For example, people with sickle-hemoglobin C (HbSC) disease have hemoglobin molecules with hemoglobin S and hemoglobin C instead of beta-globin. If mutations that produce hemoglobin S and beta thalassemia occur together, individuals have hemoglobin S-beta thalassemia (HbSBetaThal) disease.

Abnormal versions of beta-globin can distort red blood cells into a sickle shape. The sickle-shaped red blood cells die prematurely, which can lead to anemia. Sometimes the inflexible, sickle-shaped cells get stuck in small blood vessels and can cause serious medical complications.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- HbS disease
- Hemoglobin S Disease
- SCD
- Sickle cell disorders
- Sickling disorder due to hemoglobin S

Diagnosis & Management

Formal Diagnostic Criteria

- ACT Sheet: FS
https://www.ncbi.nlm.nih.gov/books/NBK55827/bin/HbSS_FS.pdf
- ACT Sheet: FSA
https://www.ncbi.nlm.nih.gov/books/NBK55827/bin/Hb_Sbeta_plus_thal_FSA.pdf
- ACT Sheet: FSC
https://www.ncbi.nlm.nih.gov/books/NBK55827/bin/Hb_SC_FSC.pdf

Genetic Testing

- Genetic Testing Registry: Hb SS disease
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0002895/>

Other Diagnosis and Management Resources

- Baby's First Test: S, Beta-Thalassemia
<http://www.babysfirsttest.org/newborn-screening/conditions/s-beta-thalassemia>
- Baby's First Test: S, C Disease
<http://www.babysfirsttest.org/newborn-screening/conditions/s-c-disease>
- Baby's First Test: Sickle Cell Anemia
<http://www.babysfirsttest.org/newborn-screening/conditions/sickle-cell-anemia>
- GeneReview: Sickle Cell Disease
<https://www.ncbi.nlm.nih.gov/books/NBK1377>
- Genomics Education Programme (UK)
<https://www.genomicseducation.hee.nhs.uk/resources/genetic-conditions-factsheets/item/86-sickle-cell-anaemia/>
- Howard University Hospital Center for Sickle Cell Disease
<http://huhealthcare.com/healthcare/hospital/specialty-services/sickle-cell-disease-center/disease-information>
- MedlinePlus Encyclopedia: Sickle Cell Anemia
<https://medlineplus.gov/ency/article/000527.htm>
- MedlinePlus Encyclopedia: Sickle Cell Test
<https://medlineplus.gov/ency/article/003666.htm>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Sickle Cell Anemia
<https://medlineplus.gov/ency/article/000527.htm>
- Encyclopedia: Sickle Cell Test
<https://medlineplus.gov/ency/article/003666.htm>
- Health Topic: Newborn Screening
<https://medlineplus.gov/newbornscreening.html>
- Health Topic: Sickle Cell Anemia
<https://medlineplus.gov/sicklecellanemia.html>

Genetic and Rare Diseases Information Center

- Sickle cell anemia
<https://rarediseases.info.nih.gov/diseases/8614/sickle-cell-anemia>

Additional NIH Resources

- GeneEd
https://geneed.nlm.nih.gov/topic_subtopic.php?tid=142&sid=149
- National Heart, Lung, and Blood Institute
<https://www.nhlbi.nih.gov/health-topics/sickle-cell-disease>
- National Human Genome Research Institute
<https://www.genome.gov/10001219/learning-about-sickle-cell-disease/>
- National Library of Medicine: Changing the Face of Medicine
https://cfmedicine.nlm.nih.gov/activities/sickle_cell.html

Educational Resources

- About Sickle Cell Disease
<http://www.sicklecellinfo.net/>
- Action Medical Research for Children (UK)
<https://www.action.org.uk/category/sickle-cell-anaemia-children>
- Disease InfoSearch: Sickle cell anemia
<http://www.diseaseinfosearch.org/Sickle+cell+anemia/6589>
- Genetic Science Learning Center, University of Utah
<http://learn.genetics.utah.edu/content/disorders/singlegene/>
- Genetics Education Materials for School Success (GEMSS)
<https://www.gemssforschools.org/conditions/sickle-cell-disease/default>
- Illinois Department of Public Health
<http://www.idph.state.il.us/HealthWellness/fs/sickle.htm>
- Information Center for Sickle Cell and Thalassemic Disorders
http://sickle.bwh.harvard.edu/menu_sickle.html
- MalaCards: sickle cell disease
http://www.malacards.org/card/sickle_cell_disease
- Merck Manual of Medical Information, Second Home Edition
<http://www.merckmanuals.com/home/blood-disorders/anemia/sickle-cell-disease>
- Michigan Department of Community Health
http://www.michigan.gov/documents/sicklecell_79213_7.pdf
- My46 Trait Profile
<https://www.my46.org/trait-document?trait=Sickle%20cell%20disease&type=profile>
- Nemours Foundation
<http://kidshealth.org/en/parents/sickle-cell-anemia.html>
- Orphanet: Sickle cell anemia
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=232
- Swedish National Board of Health and Welfare
<http://www.socialstyrelsen.se/rarediseases/sicklecellanaemia>
- University of Rochester Medical Center
<https://www.urmc.rochester.edu/encyclopedia/content.aspx?ContentTypeID=85&ContentID=P00101>
- Virginia Department of Health
http://www.vdh.virginia.gov/content/uploads/sites/33/2016/11/Parent-Fact-Sheet_SICKLE-CELL-ANEMIA_English.pdf

- Washington State Department of Health: Hemoglobin S Fact Sheet
<https://www.doh.wa.gov/Portals/1/Documents/5220/HbSFactSheet.pdf>
- Your Genes Your Health from Cold Spring Harbor Laboratory
<http://www.ygyh.org/sickle/whatisit.htm>

Patient Support and Advocacy Resources

- American Sickle Cell Anemia Association
<http://www.ascaa.org/index.php>
- March of Dimes
<https://www.marchofdimes.org/baby/sickle-cell-disease-and-your-baby.aspx>
- National Organization for Rare Disorders (NORD)
<https://rarediseases.org/rare-diseases/sickle-cell-disease/>
- Sickle Cell Disease Association of America
<http://www.sicklecelldisease.org>
- The Sickle Cell Information Center
<http://scinfo.org/>

GeneReviews

- Sickle Cell Disease
<https://www.ncbi.nlm.nih.gov/books/NBK1377>

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22sickle+cell+anemia%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Anemia,+Sickle+Cell%5BMAJR%5D%29+AND+%28sickle+cell+anemia%5BTI%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D>

OMIM

- SICKLE CELL ANEMIA
<http://omim.org/entry/603903>

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Turner syndrome

Turner syndrome is a chromosomal condition that affects development in females. The most common feature of Turner syndrome is short stature, which becomes evident by about age 5. An early loss of ovarian function (ovarian hypofunction or premature ovarian failure) is also very common. The ovaries develop normally at first, but egg cells (oocytes) usually die prematurely and most ovarian tissue degenerates before birth. Many affected girls do not undergo puberty unless they receive hormone therapy, and most are unable to conceive (infertile). A small percentage of females with Turner syndrome retain normal ovarian function through young adulthood.

About 30 percent of females with Turner syndrome have extra folds of skin on the neck (webbed neck), a low hairline at the back of the neck, puffiness or swelling (lymphedema) of the hands and feet, skeletal abnormalities, or kidney problems. One third to one half of individuals with Turner syndrome are born with a heart defect, such as a narrowing of the large artery leaving the heart (coarctation of the aorta) or abnormalities of the valve that connects the aorta with the heart (the aortic valve). Complications associated with these heart defects can be life-threatening.

Most girls and women with Turner syndrome have normal intelligence. Developmental delays, nonverbal learning disabilities, and behavioral problems are possible, although these characteristics vary among affected individuals.

Frequency

This condition occurs in about 1 in 2,500 newborn girls worldwide, but it is much more common among pregnancies that do not survive to term (miscarriages and stillbirths).

Genetic Changes

Turner syndrome is related to the X chromosome, which is one of the two sex chromosomes. People typically have two sex chromosomes in each cell: females have two X chromosomes, while males have one X chromosome and one Y chromosome. Turner syndrome results when one normal X chromosome is present in a female's cells and the other sex chromosome is missing or structurally altered. The missing genetic material affects development before and after birth.

About half of individuals with Turner syndrome have monosomy X, which means each cell in the individual's body has only one copy of the X chromosome instead of the usual two sex chromosomes. Turner syndrome can also occur if one of the sex chromosomes is partially missing or rearranged rather than completely absent. Some women with Turner syndrome have a chromosomal change in only some of their cells,

which is known as mosaicism. Women with Turner syndrome caused by X chromosome mosaicism are said to have mosaic Turner syndrome.

Researchers have not determined which genes on the X chromosome are associated with most of the features of Turner syndrome. They have, however, identified one gene called *SHOX* that is important for bone development and growth. The loss of one copy of this gene likely causes short stature and skeletal abnormalities in women with Turner syndrome.

Inheritance Pattern

Most cases of Turner syndrome are not inherited. When this condition results from monosomy X, the chromosomal abnormality occurs as a random event during the formation of reproductive cells (eggs and sperm) in the affected person's parent. An error in cell division called nondisjunction can result in reproductive cells with an abnormal number of chromosomes. For example, an egg or sperm cell may lose a sex chromosome as a result of nondisjunction. If one of these atypical reproductive cells contributes to the genetic makeup of a child, the child will have a single X chromosome in each cell and will be missing the other sex chromosome.

Mosaic Turner syndrome is also not inherited. In an affected individual, it occurs as a random event during cell division in early fetal development. As a result, some of an affected person's cells have the usual two sex chromosomes, and other cells have only one copy of the X chromosome. Other sex chromosome abnormalities are also possible in females with X chromosome mosaicism.

Rarely, Turner syndrome caused by a partial deletion of the X chromosome can be passed from one generation to the next.

Other Names for This Condition

- 45,X
- monosomy X
- TS
- Turner's syndrome
- Ullrich-Turner syndrome

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Turner syndrome
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0041408/>

Other Diagnosis and Management Resources

- MedlinePlus Encyclopedia: Ovarian Hypofunction
<https://medlineplus.gov/ency/article/001163.htm>
- MedlinePlus Encyclopedia: Turner Syndrome
<https://medlineplus.gov/ency/article/000379.htm>
- Turner Syndrome Foundation: Diagnosing
https://turnersyndrome.org/turner_syndrome/diagnosing/
- Turner Syndrome Foundation: Specialized Centers of Care
<https://turnersyndrome.org/turner-syndrome-across-the-lifespan/specialized-centers/>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Ovarian Hypofunction
<https://medlineplus.gov/ency/article/001163.htm>
- Encyclopedia: Turner Syndrome
<https://medlineplus.gov/ency/article/000379.htm>
- Health Topic: Turner Syndrome
<https://medlineplus.gov/turnersyndrome.html>

Genetic and Rare Diseases Information Center

- Turner syndrome
<https://rarediseases.info.nih.gov/diseases/7831/turner-syndrome>

Additional NIH Resources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development
<https://www.nichd.nih.gov/health/topics/turner>
- National Human Genome Research Institute
<https://www.genome.gov/19519119/>

Educational Resources

- Boston Children's Hospital
<http://www.childrenshospital.org/conditions-and-treatments/conditions/turner-syndrome>
- Centre for Genetics Education (Australia)
<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-40-turner-syndrome>
- Disease InfoSearch: Turner syndrome
<http://www.diseaseinfosearch.org/Turner+syndrome/7268>
- Genetic Science Learning Center, University of Utah
<http://learn.genetics.utah.edu/content/disorders/chromosomal/>
- MalaCards: turner syndrome
http://www.malacards.org/card/turner_syndrome
- March of Dimes: Chromosomal Conditions
<https://www.marchofdimes.org/baby/chromosomal-conditions.aspx>
- Merck Manual Consumer Version
<http://www.merckmanuals.com/home/children-s-health-issues/chromosome-and-gene-abnormalities/turner-syndrome>
- My46 Trait Profile
<https://www.my46.org/trait-document?trait=Turner%20syndrome&type=profile>
- Orphanet: Turner syndrome
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=881
- TeensHealth from the Nemours Foundation
<http://kidshealth.org/en/teens/turner.html>
- The MAGIC Foundation
<https://www.magicfoundation.org/Growth-Disorders/Turner-Syndrome/>

Patient Support and Advocacy Resources

- National Organization for Rare Disorders
<https://rarediseases.org/rare-diseases/turner-syndrome/>
- Resource list from the University of Kansas Medical Center
<http://www.kumc.edu/gec/support/chromoso.html#xo>
- Turner Syndrome Foundation
<https://turnersyndromefoundation.org/>
- Turner Syndrome Society of the United States
<http://www.turnersyndrome.org/>

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22turner+syndrome%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Turner+Syndrome%5BMAJR%5D%29+AND+%28Turner+syndrome%5BTI%5D%29+AND+english%5BIa%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D>

MedGen

- Mosaic Turner syndrome
<https://www.ncbi.nlm.nih.gov/medgen/873772>
- Turner syndrome
<https://www.ncbi.nlm.nih.gov/medgen/21734>

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Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3114458/>
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Type 2 diabetes

Type 2 diabetes is a disorder characterized by abnormally high blood sugar levels. In this form of diabetes, the body stops using and making insulin properly. Insulin is a hormone produced in the pancreas that helps regulate blood sugar levels. Specifically, insulin controls how much glucose (a type of sugar) is passed from the blood into cells, where it is used as an energy source. When blood sugar levels are high (such as after a meal), the pancreas releases insulin to move the excess glucose into cells, which reduces the amount of glucose in the blood.

Most people who develop type 2 diabetes first have insulin resistance, a condition in which the body's cells use insulin less efficiently than normal. As insulin resistance develops, more and more insulin is needed to keep blood sugar levels in the normal range. To keep up with the increasing need, insulin-producing cells in the pancreas (called beta cells) make larger amounts of insulin. Over time, the beta cells become less able to respond to blood sugar changes, leading to an insulin shortage that prevents the body from reducing blood sugar levels effectively. Most people have some insulin resistance as they age, but inadequate exercise and excessive weight gain make it worse, greatly increasing the likelihood of developing type 2 diabetes.

Type 2 diabetes can occur at any age, but it most commonly begins in middle age or later. Signs and symptoms develop slowly over years. They include frequent urination (polyuria), excessive thirst (polydipsia), fatigue, blurred vision, tingling or loss of feeling in the hands and feet (diabetic neuropathy), sores that do not heal well, and weight loss. If blood sugar levels are not controlled through medication or diet, type 2 diabetes can cause long-lasting (chronic) health problems including heart disease and stroke; nerve damage; and damage to the kidneys, eyes, and other parts of the body.

Frequency

Type 2 diabetes is the most common type of diabetes, accounting for 90 to 95 percent of all cases. In 2015, more than 23 million people in the United States had diagnosed diabetes and an additional 7 million people likely had undiagnosed diabetes. The prevalence of diabetes increases with age, and the disease currently affects more than 20 percent of Americans over age 65. It is the seventh leading cause of death in the United States.

The risk of diabetes varies by ethnic and geographic background. In the United States, the disease is most common in Native Americans and Alaska Natives. It also has a higher prevalence among people of African American or Hispanic ancestry than those of non-Hispanic white or Asian ancestry. Geographically, diabetes is most prevalent in the southern and Appalachian regions of the United States.

The prevalence of diabetes is rapidly increasing worldwide. Due to an increase in inactive (sedentary) lifestyles, obesity, and other risk factors, the frequency of this disease has more than quadrupled in the past 35 years.

Genetic Changes

The causes of type 2 diabetes are complex. This condition results from a combination of genetic and lifestyle factors, some of which have not been identified.

Studies have identified at least 150 DNA variations that are associated with the risk of developing type 2 diabetes. Most of these changes are common and are present both in people with diabetes and in those without. Each person has some variations that increase risk and others that reduce risk. It is the combination of these changes that helps determine a person's likelihood of developing the disease.

The majority of genetic variations associated with type 2 diabetes are thought to act by subtly changing the amount, timing, and location of gene activity (expression). These changes in expression affect genes involved in many aspects of type 2 diabetes, including the development and function of beta cells in the pancreas, the release and processing of insulin, and cells' sensitivity to the effects of insulin. However, for many of the variations that have been associated with type 2 diabetes, the mechanism by which they contribute to disease risk is unknown.

Genetic variations likely act together with health and lifestyle factors to influence an individual's overall risk of type 2 diabetes. All of these factors are related, directly or indirectly, to the body's ability to produce and respond to insulin. Health conditions that predispose to the disease include overweight or obesity, insulin resistance, prediabetes (higher-than-normal blood sugar levels that do not reach the cutoff for diabetes), and a form of diabetes called gestational diabetes that occurs during pregnancy. Lifestyle factors including smoking, a poor diet, and physical inactivity also increase the risk of type 2 diabetes.

Inheritance Pattern

Type 2 diabetes does not have a clear pattern of inheritance, although many affected individuals have at least one close family member, such as a parent or sibling, with the disease. The risk of developing type 2 diabetes increases with the number of affected family members. The increased risk is likely due in part to shared genetic factors, but it is also related to lifestyle influences (such as eating and exercise habits) that are shared by members of a family.

Other Names for This Condition

- adult-onset diabetes
- adult-onset diabetes mellitus
- AODM

- diabetes mellitus, adult-onset
- diabetes mellitus, non-insulin-dependent
- diabetes mellitus, type 2
- diabetes mellitus, type II
- maturity-onset diabetes
- maturity-onset diabetes mellitus
- NIDDM
- noninsulin-dependent diabetes mellitus
- T2D
- type 2 diabetes mellitus

Diagnosis & Management

Formal Diagnostic Criteria

- National Guideline Clearinghouse: Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (Institute for Clinical Systems Improvement)
<https://www.guideline.gov/summaries/summary/48544/diagnosis-and-management-of-type-2-diabetes-mellitus-in-adults>
- U.S. Preventive Services Task Force: Abnormal Blood Glucose and Type 2 Diabetes Mellitus: Screening
<https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/screening-for-abnormal-blood-glucose-and-type-2-diabetes>

Formal Treatment/Management Guidelines

- Joslin Diabetes Center: Clinical Guidelines
<http://www.joslin.org/info/joslin-clinical-guidelines.html>
- National Guideline Clearinghouse: Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (Institute for Clinical Systems Improvement)
<https://www.guideline.gov/summaries/summary/48544/diagnosis-and-management-of-type-2-diabetes-mellitus-in-adults>
- National Guideline Clearinghouse: Type 2 Diabetes in Adults: Management (National Institute for Health and Care Excellence)
<https://www.guideline.gov/summaries/summary/49931/type-2-diabetes-in-adults-management>

Genetic Testing

- Genetic Testing Registry: Diabetes mellitus type 2
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0011860/>

Other Diagnosis and Management Resources

- American Diabetes Association: Diagnosis
<http://www.diabetes.org/diabetes-basics/diagnosis/>
- American Diabetes Association: Treatment & Care
<http://www.diabetes.org/living-with-diabetes/treatment-and-care/>
- MedlinePlus Encyclopedia: Diabetes and Exercise
<https://medlineplus.gov/ency/patientinstructions/000083.htm>
- MedlinePlus Encyclopedia: Diabetes Type 2: Meal-Planning
<https://medlineplus.gov/ency/article/007429.htm>
- MedlinePlus Encyclopedia: Type 2 Diabetes: Self-Care
<https://medlineplus.gov/ency/patientinstructions/000328.htm>
- MedlinePlus Encyclopedia: Type 2 Diabetes: What To Ask Your Doctor
<https://medlineplus.gov/ency/patientinstructions/000217.htm>
- National Institute of Diabetes and Digestive and Kidney Diseases: Diabetes Tests & Diagnosis
<https://www.niddk.nih.gov/health-information/diabetes/overview/tests-diagnosis>
- National Institute of Diabetes and Digestive and Kidney Diseases: Managing Diabetes
<https://www.niddk.nih.gov/health-information/diabetes/overview/managing-diabetes>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Diabetes and Exercise
<https://medlineplus.gov/ency/patientinstructions/000083.htm>
- Encyclopedia: Diabetes Type 2: Meal-Planning
<https://medlineplus.gov/ency/article/007429.htm>
- Encyclopedia: Type 2 Diabetes
<https://medlineplus.gov/ency/article/000313.htm>
- Encyclopedia: Type 2 Diabetes: Self-Care
<https://medlineplus.gov/ency/patientinstructions/000328.htm>
- Encyclopedia: Type 2 Diabetes: What To Ask Your Doctor
<https://medlineplus.gov/ency/patientinstructions/000217.htm>
- Health Topic: Diabetes Type 2
<https://medlineplus.gov/diabetestype2.html>

Additional NIH Resources

- National Institute of Diabetes and Digestive and Kidney Diseases: Prediabetes & Insulin Resistance
<https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/prediabetes-insulin-resistance>
- National Institute of Diabetes and Digestive and Kidney Diseases: Risk Factors for Type 2 Diabetes: Family Health History Quiz
<https://www.niddk.nih.gov/health-information/diabetes/overview/risk-factors-type-2-diabetes/family-health-history-quiz>
- National Institute of Diabetes and Digestive and Kidney Diseases: Type 2 Diabetes
<https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/type-2-diabetes>

Educational Resources

- American Diabetes Association: Genetics of Diabetes
<http://www.diabetes.org/diabetes-basics/genetics-of-diabetes.html>
- Disease InfoSearch: Diabetes mellitus type 2
<http://www.diseaseinfosearch.org/Diabetes+mellitus+type+2/8215>
- Hormone Health Network
<https://www.hormone.org/diseases-and-conditions/diabetes/types-of-diabetes/type-2-diabetes>
- Joslin Diabetes Center: Genetics & Diabetes: What's Your Risk?
http://www.joslin.org/info/genetics_and_diabetes.html

- KidsHealth from Nemours
<http://kidshealth.org/en/kids/type2.html>
- The Genetic Landscape of Diabetes (2004)
<https://www.ncbi.nlm.nih.gov/books/NBK1667/>
- Type 2 Diabetes Knowledge Portal
<http://www.type2diabetesgenetics.org/>

Patient Support and Advocacy Resources

- American Diabetes Association
<http://www.diabetes.org/diabetes-basics/type-2/>
- Diabetes Research Institute
<https://www.diabetesresearch.org/what-is-type-two-diabetes>
- The diaTribe Foundation
<https://diatribe.org/foundation/>

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22type+2+diabetes%22>

Scientific Articles on PubMed

- PubMed
https://www.ncbi.nlm.nih.gov/pubmed?term=%28Diabetes+Mellitus,+Type+2%5BMAJR%5D%29+AND+%28genetic*%5BTI%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D

OMIM

- DIABETES MELLITUS, NONINSULIN-DEPENDENT
<http://omim.org/entry/125853>

MedGen

- Diabetes mellitus type 2
<https://www.ncbi.nlm.nih.gov/medgen/41523>

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Williams syndrome

Williams syndrome is a developmental disorder that affects many parts of the body. This condition is characterized by mild to moderate intellectual disability or learning problems, unique personality characteristics, distinctive facial features, and heart and blood vessel (cardiovascular) problems.

People with Williams syndrome typically have difficulty with visual-spatial tasks such as drawing and assembling puzzles, but they tend to do well on tasks that involve spoken language, music, and learning by repetition (rote memorization). Affected individuals have outgoing, engaging personalities and tend to take an extreme interest in other people. Attention deficit disorder (ADD), problems with anxiety, and phobias are common among people with this disorder.

Young children with Williams syndrome have distinctive facial features including a broad forehead, a short nose with a broad tip, full cheeks, and a wide mouth with full lips. Many affected people have dental problems such as teeth that are small, widely spaced, crooked, or missing. In older children and adults, the face appears longer and more gaunt.

A form of cardiovascular disease called supravalvular aortic stenosis (SVAS) occurs frequently in people with Williams syndrome. Supravalvular aortic stenosis is a narrowing of the large blood vessel that carries blood from the heart to the rest of the body (the aorta). If this condition is not treated, the aortic narrowing can lead to shortness of breath, chest pain, and heart failure. Other problems with the heart and blood vessels, including high blood pressure (hypertension), have also been reported in people with Williams syndrome.

Additional signs and symptoms of Williams syndrome include abnormalities of connective tissue (tissue that supports the body's joints and organs) such as joint problems and soft, loose skin. Affected people may also have increased calcium levels in the blood (hypercalcemia) in infancy, developmental delays, problems with coordination, and short stature. Medical problems involving the eyes and vision, the digestive tract, and the urinary system are also possible.

Frequency

Williams syndrome affects an estimated 1 in 7,500 to 10,000 people.

Genetic Changes

Williams syndrome is caused by the deletion of genetic material from a specific region of chromosome 7. The deleted region includes 26 to 28 genes, and researchers believe

that a loss of several of these genes probably contributes to the characteristic features of this disorder.

CLIP2, *ELN*, *GTF2I*, *GTF2IRD1*, and *LIMK1* are among the genes that are typically deleted in people with Williams syndrome. Researchers have found that loss of the *ELN* gene is associated with the connective tissue abnormalities and cardiovascular disease (specifically supravalvular aortic stenosis) found in many people with this disease. Studies suggest that deletion of *CLIP2*, *GTF2I*, *GTF2IRD1*, *LIMK1*, and perhaps other genes may help explain the characteristic difficulties with visual-spatial tasks, unique behavioral characteristics, and other cognitive difficulties seen in people with Williams syndrome. Loss of the *GTF2IRD1* gene may also contribute to the distinctive facial features often associated with this condition.

Researchers believe that the presence or absence of the *NCF1* gene on chromosome 7 is related to the risk of developing hypertension in people with Williams syndrome. When the *NCF1* gene is included in the part of the chromosome that is deleted, affected individuals are less likely to develop hypertension. Therefore, the loss of this gene appears to be a protective factor. People with Williams syndrome whose *NCF1* gene is not deleted have a higher risk of developing hypertension.

The relationship between other genes in the deleted region of chromosome 7 and the signs and symptoms of Williams syndrome is under investigation or unknown.

Inheritance Pattern

Most cases of Williams syndrome are not inherited but occur as random events during the formation of reproductive cells (eggs or sperm) in a parent of an affected individual. These cases occur in people with no history of the disorder in their family.

Williams syndrome is considered an autosomal dominant condition because one copy of the altered chromosome 7 in each cell is sufficient to cause the disorder. In a small percentage of cases, people with Williams syndrome inherit the chromosomal deletion from a parent with the condition.

Other Names for This Condition

- Beuren syndrome
- elfin facies syndrome
- elfin facies with hypercalcemia
- hypercalcemia-supravalvar aortic stenosis
- infantile hypercalcemia
- supravalvar aortic stenosis syndrome
- WBS
- Williams-Beuren syndrome

- WMS
- WS

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Williams syndrome
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0175702/>

Other Diagnosis and Management Resources

- GeneReview: Williams Syndrome
<https://www.ncbi.nlm.nih.gov/books/NBK1249>
- MedlinePlus Encyclopedia: Williams Syndrome
<https://medlineplus.gov/ency/article/001116.htm>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Williams Syndrome
<https://medlineplus.gov/ency/article/001116.htm>
- Health Topic: Developmental Disabilities
<https://medlineplus.gov/developmentaldisabilities.html>
- Health Topic: Heart Diseases
<https://medlineplus.gov/heartdiseases.html>
- Health Topic: Neurologic Diseases
<https://medlineplus.gov/neurologicdiseases.html>

Genetic and Rare Diseases Information Center

- Supravalvular aortic stenosis
<https://rarediseases.info.nih.gov/diseases/743/supravalvular-aortic-stenosis>
- Williams syndrome
<https://rarediseases.info.nih.gov/diseases/7891/williams-syndrome>

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke
<https://www.ninds.nih.gov/Disorders/All-Disorders/Williams-Syndrome-Information-Page>

Educational Resources

- Disease InfoSearch: Williams syndrome
<http://www.diseaseinfosearch.org/Williams+syndrome/7501>
- Genetic Science Learning Center, University of Utah
<http://learn.genetics.utah.edu/content/disorders/chromosomal/>
- Genetics Education Materials for School Success (GEMSS)
<https://www.gemssforschools.org/conditions/williams/default>
- MalaCards: williams-beuren syndrome
http://www.malacards.org/card/williams_beuren_syndrome
- My46 Trait Profile
<https://www.my46.org/trait-document?trait=Williams%20syndrome&type=profile>
- Orphanet: Williams syndrome
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=904
- University of Michigan Health System
<http://www.med.umich.edu/yourchild/topics/williams.htm>

Patient Support and Advocacy Resources

- Chromosome Disorder Outreach
<https://chromodisorder.org/>
- National Organization for Rare Disorders (NORD)
<https://rarediseases.org/rare-diseases/williams-syndrome/>
- Resource list from the University of Kansas Medical Center
<http://www.kumc.edu/gec/support/williams.html>
- Williams Syndrome Association
<https://williams-syndrome.org/>

GeneReviews

- Williams Syndrome
<https://www.ncbi.nlm.nih.gov/books/NBK1249>

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22williams+syndrome%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Williams+Syndrome%5BMAJR%5D%29+AND+%28Williams+syndrome%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D>

OMIM

- WILLIAMS-BEUREN SYNDROME
<http://omim.org/entry/194050>

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