



## Klinefelter syndrome

Klinefelter syndrome is a chromosomal condition in boys and men that can affect physical and intellectual development. Its signs and symptoms vary among affected individuals. In some cases, the features of the condition are so mild that the condition is not diagnosed until puberty or adulthood, and researchers believe that some affected men and boys are never diagnosed.

Boys and men with Klinefelter syndrome typically have small testes that produce a reduced amount of testosterone. Testosterone is the hormone that directs male sexual development before birth and during puberty. Without treatment, the shortage of testosterone can lead to delayed or incomplete puberty, breast enlargement (gynecomastia), and a reduced amount of facial and body hair. As a result of the small testes and decreased hormone production, affected males are unable to father biological children (infertile) without assisted reproductive technologies. Some affected individuals also have differences in their genitalia, including undescended testes, the opening of the urethra on the underside of the penis (hypospadias), or an unusually small penis (micropenis).

Other physical changes associated with Klinefelter syndrome are usually subtle. Older children and adults with the condition tend to be somewhat taller than their peers. Other differences can include abnormal fusion of certain bones in the forearm (radioulnar synostosis), curved pinky fingers (fifth finger clinodactyly), and flat feet (pes planus).

Children with Klinefelter syndrome may have weak muscle tone (hypotonia) and problems with coordination that delay the development of motor skills, such as sitting, standing, and walking. Affected boys often have learning disabilities, problems with reading, and mild delays in speech and language development. Boys and men with Klinefelter syndrome tend to have better receptive language skills (the ability to understand speech) than expressive language skills (vocabulary and the production of speech) and may have difficulty communicating and expressing themselves. They tend to have anxiety, impaired social skills, a short attention span, and limited problem-solving skills (executive functioning).

Compared with unaffected men, adults with Klinefelter syndrome have an increased risk of developing type 2 diabetes, blood clots, involuntary trembling (tremors), breast cancer (if gynecomastia develops), thinning and weakening of the bones (osteoporosis), and autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis. (Autoimmune disorders are a large group of conditions that occur when the immune system attacks the body's own tissues and organs.)

## Frequency

Klinefelter syndrome affects 1 in 500 to 1,000 newborn boys. It is among the most common sex chromosome disorders, which are conditions caused by changes in the number of sex chromosomes (the X chromosome and the Y chromosome).

## Causes

Klinefelter syndrome is a sex chromosome disorder in boys and men that results from the presence of an extra X chromosome in cells. People typically have 46 chromosomes in each cell, two of which are the sex chromosomes. Females have two X chromosomes (46,XX), and males have one X and one Y chromosome (46,XY). Most often, boys and men with Klinefelter syndrome have the usual X and Y chromosomes, plus one extra X chromosome, for a total of 47 chromosomes (47,XXY).

Boys and men with Klinefelter syndrome have an extra copy of multiple genes on the X chromosome. The activity of these extra genes affects many aspects of development, including sexual development before birth and at puberty. Researchers are working to determine which genes contribute to the specific developmental and physical differences that can occur with Klinefelter syndrome.

Some people with features of Klinefelter syndrome have an extra X chromosome in only some of their cells; other cells have one X and one Y chromosome. In these individuals, the condition is described as mosaic Klinefelter syndrome (46,XY/47,XXY). Boys and men with mosaic Klinefelter syndrome may have milder signs and symptoms than those with the extra X chromosome in all of their cells, depending on what proportion of cells have the additional chromosome.

Several conditions resulting from the presence of more than one extra sex chromosome in each cell are sometimes described as variants of Klinefelter syndrome. These conditions include 48,XXXYY syndrome, 48,XXYY syndrome, and 49,XXXXYY syndrome. Like Klinefelter syndrome, these conditions affect male sexual development and can be associated with learning disabilities and problems with speech and language development. However, the features of these disorders tend to be more severe than those of Klinefelter syndrome and affect more parts of the body. As doctors and researchers have learned more about the differences between these sex chromosome disorders, they have started to consider them as separate conditions.

## Inheritance Pattern

Klinefelter syndrome is not inherited; the addition of an extra X chromosome occurs during the formation of reproductive cells (eggs or sperm) in one of an affected person's parents. During cell division, an error called nondisjunction prevents X chromosomes from being distributed normally among reproductive cells as they form. Typically, as cells divide, each egg cell gets a single X chromosome, and each sperm cell gets either an X chromosome or a Y chromosome. However, because of nondisjunction, an egg cell or a sperm cell can also end up with an extra copy of the X chromosome.

If an egg cell with an extra X chromosome (XX) is fertilized by a sperm cell with one Y chromosome, the resulting child will have Klinefelter syndrome. Similarly, if a sperm cell with both an X chromosome and a Y chromosome (XY) fertilizes an egg cell with a single X chromosome, the resulting child will have Klinefelter syndrome.

Mosaic Klinefelter syndrome (46,XY/47,XXY) is also not inherited. It occurs as a random error during cell division early in fetal development. As a result, some of the body's cells have the usual one X chromosome and one Y chromosome (46,XY), and other cells have an extra copy of the X chromosome (47,XXY).

### **Other Names for This Condition**

- 47,XXY syndrome
- Klinefelter syndrome (KS)
- Klinefelter's syndrome
- XXY syndrome
- XXY trisomy

### **Diagnosis & Management**

#### Formal Diagnostic Criteria

- Radicioni AF, Ferlin A, Balercia G, Pasquali D, Vignozzi L, Maggi M, Foresta C, Lenzi A. Consensus statement on diagnosis and clinical management of Klinefelter syndrome. *J Endocrinol Invest.* 2010 Dec;33(11):839-50. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/21293172>

#### Formal Treatment/Management Guidelines

- Radicioni AF, Ferlin A, Balercia G, Pasquali D, Vignozzi L, Maggi M, Foresta C, Lenzi A. Consensus statement on diagnosis and clinical management of Klinefelter syndrome. *J Endocrinol Invest.* 2010 Dec;33(11):839-50. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/21293172>

#### Genetic Testing Information

- What is genetic testing?  
[/primer/testing/geneticTesting](#)
- Genetic Testing Registry: Klinefelter's syndrome, XXY  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0022735/>

#### Research Studies from ClinicalTrials.gov

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

### Other Diagnosis and Management Resources

- Children's Hospital of Philadelphia  
<https://www.chop.edu/conditions-diseases/klinefelter-syndrome>
- Eunice Kennedy Shriver National Institute of Child Health and Human Development: How Do Health Care Providers Diagnose Klinefelter Syndrome (KS)?  
<https://www.nichd.nih.gov/health/topics/klinefelter/conditioninfo/diagnosed>
- Eunice Kennedy Shriver National Institute of Child Health and Human Development: What Are the Treatments for Symptoms in Klinefelter Syndrome (KS)?  
<https://www.nichd.nih.gov/health/topics/klinefelter/conditioninfo/treatments>
- eXtraordinary Kids Clinic, Children's Hospital Colorado  
<https://www.childrenscolorado.org/research-innovation/research-area/neurology-neurosurgery/sex-chromosome-aneuploidy/>
- Johns Hopkins Medicine: Klinefelter Syndrome Center  
<http://klinefelter.jhu.edu/>

### **Additional Information & Resources**

#### Health Information from MedlinePlus

- Encyclopedia: Klinefelter Syndrome  
<https://medlineplus.gov/ency/article/000382.htm>
- Encyclopedia: Testicular Failure  
<https://medlineplus.gov/ency/article/000395.htm>
- Health Topic: Klinefelter's Syndrome  
<https://medlineplus.gov/klinefelterssyndrome.html>

#### Genetic and Rare Diseases Information Center

- 47, XXY  
<https://rarediseases.info.nih.gov/diseases/11920/47-xyy>
- Klinefelter syndrome  
<https://rarediseases.info.nih.gov/diseases/8705/klinefelter-syndrome>

#### Additional NIH Resources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development  
<https://www.nichd.nih.gov/health/topics/klinefelter>
- National Human Genome Research Institute  
<https://www.genome.gov/19519068/>

## Educational Resources

- Centre for Genetics Education  
<http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-39-klinefelter-syndrome>
- Genetic Science Learning Center, University of Utah: Extra or Missing Chromosomes  
<https://learn.genetics.utah.edu/content/disorders/extraormissing/>
- March of Dimes: Chromosomal Conditions  
<https://www.marchofdimes.org/baby/chromosomal-conditions.aspx>
- Merck Manual Consumer Version  
<https://www.merckmanuals.com/home/children-s-health-issues/chromosome-and-gene-abnormalities/klinefelter-syndrome>
- NHS Choices (UK)  
<https://www.nhs.uk/conditions/klinefelters-syndrome/>
- Orphanet: NON RARE IN EUROPE: Klinefelter syndrome  
[https://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=484](https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=484)
- TeensHealth from Nemours  
<https://kidshealth.org/en/teens/klinefelter.html>

## Patient Support and Advocacy Resources

- Accord Alliance  
<http://www.accordalliance.org/>
- Association for X and Y Chromosome Variations (AXYS)  
<https://genetic.org/variations/about-47xxy/>
- Focus Foundation  
<https://thefocusfoundation.org/x-y-chromosomal-variations/xxy/>
- National Center for Learning Disabilities  
<https://www.nclld.org/>
- National Organization for Rare Disorders (NORD)  
<https://rarediseases.org/rare-diseases/klinefelter-syndrome/>
- Resolve: The National Infertility Association  
<https://resolve.org/>
- Resource list from the University of Kansas Medical Center  
<http://www.kumc.edu/gec/support/chromoso.html#xxy>

## Scientific Articles on PubMed

- PubMed  
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Klinefelter+Syndrome%5BMAJR%5D%29+AND+%28Klinefelter+syndrome%5BTI%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D>

## Medical Genetics Database from MedGen

- Klinefelter Syndrome, Variants  
<https://www.ncbi.nlm.nih.gov/medgen/107774>
- Klinefelter syndrome, XXY  
<https://www.ncbi.nlm.nih.gov/medgen/44033>

## **Sources for This Summary**

- Boada R, Janusz J, Hutaff-Lee C, Tartaglia N. The cognitive phenotype in Klinefelter syndrome: a review of the literature including genetic and hormonal factors. *Dev Disabil Res Rev.* 2009;15(4): 284-94. doi: 10.1002/ddrr.83. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/20014369>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3056507/>
- Davis S, Howell S, Wilson R, Tanda T, Ross J, Zeitler P, Tartaglia N. Advances in the Interdisciplinary Care of Children with Klinefelter Syndrome. *Adv Pediatr.* 2016 Aug;63(1):15-46. doi: 10.1016/j.yapd.2016.04.020. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/27426894>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5340500/>
- Frühmesser A, Kotzot D. Chromosomal variants in klinefelter syndrome. *Sex Dev.* 2011;5(3): 109-23. doi: 10.1159/000327324. Epub 2011 Apr 29. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/21540567>
- Giltay JC, Maiburg MC. Klinefelter syndrome: clinical and molecular aspects. *Expert Rev Mol Diagn.* 2010 Sep;10(6):765-76. doi: 10.1586/erm.10.63. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/20843200>
- Groth KA, Skakkebaek A, Høst C, Gravholt CH, Bojesen A. Clinical review: Klinefelter syndrome-- a clinical update. *J Clin Endocrinol Metab.* 2013 Jan;98(1):20-30. doi: 10.1210/jc.2012-2382. Epub 2012 Nov 1. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/23118429>
- Herlihy AS, Gillam L. Thinking outside the square: considering gender in Klinefelter syndrome and 47, XXY. *Int J Androl.* 2011 Oct;34(5 Pt 2):e348-9. doi: 10.1111/j.1365-2605.2010.01132.x. Epub 2011 Mar 31.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/21453406>
- Nieschlag E, Ferlin A, Gravholt CH, Gromoll J, Köhler B, Lejeune H, Rogol AD, Wistuba J. The Klinefelter syndrome: current management and research challenges. *Andrology.* 2016 May;4(3): 545-9. doi: 10.1111/andr.12208.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/27147398>

- Nieschlag E. Klinefelter syndrome: the commonest form of hypogonadism, but often overlooked or untreated. *Dtsch Arztebl Int.* 2013 May;110(20):347-53. doi: 10.3238/arztebl.2013.0347. Epub 2013 May 17. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/23825486>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3674537/>
  - Sokol RZ. It's not all about the testes: medical issues in Klinefelter patients. *Fertil Steril.* 2012 Aug; 98(2):261-5. doi: 10.1016/j.fertnstert.2012.05.026. Epub 2012 Jun 15. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/22704628>
  - Swerdlow AJ, Schoemaker MJ, Higgins CD, Wright AF, Jacobs PA; UK Clinical Cytogenetics Group. Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study. *J Natl Cancer Inst.* 2005 Aug 17;97(16):1204-10.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/16106025>
  - Tartaglia N, Ayari N, Howell S, D'Epagnier C, Zeitler P. 48,XXYY, 48,XXXY and 49,XXXXY syndromes: not just variants of Klinefelter syndrome. *Acta Paediatr.* 2011 Jun;100(6):851-60. doi: 10.1111/j.1651-2227.2011.02235.x. Epub 2011 Apr 8. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/21342258>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3314712/>
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<https://ghr.nlm.nih.gov/condition/klinefelter-syndrome>

Reviewed: September 2018

Published: December 11, 2018

Lister Hill National Center for Biomedical Communications  
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National Institutes of Health  
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