



Klinefelter syndrome

Klinefelter syndrome is a chromosomal condition that affects male physical and cognitive development. Its signs and symptoms vary among affected individuals.

Affected individuals typically have small testes that do not produce as much testosterone as usual. Testosterone is the hormone that directs male sexual development before birth and during puberty. A shortage of testosterone can lead to delayed or incomplete puberty, breast enlargement (gynecomastia), reduced facial and body hair, and an inability to have biological children (infertility). Some affected individuals also have genital differences including undescended testes (cryptorchidism), the opening of the urethra on the underside of the penis (hypospadias), or an unusually small penis (micropenis).

Older children and adults with Klinefelter syndrome tend to be taller than their peers. Compared with unaffected men, adults with Klinefelter syndrome have an increased risk of developing breast cancer and a chronic inflammatory disease called systemic lupus erythematosus. Their chance of developing these disorders is similar to that of women in the general population.

Children with Klinefelter syndrome may have learning disabilities and delayed speech and language development. They tend to be quiet, sensitive, and unassertive, but personality characteristics vary among affected individuals.

Frequency

Klinefelter syndrome affects 1 in 500 to 1,000 newborn males. Most variants of Klinefelter syndrome are much rarer, occurring in 1 in 50,000 or fewer newborns.

Researchers suspect that Klinefelter syndrome is underdiagnosed because the condition may not be identified in people with mild signs and symptoms. Additionally, the features of the condition vary and overlap significantly with those of other conditions.

Genetic Changes

Klinefelter syndrome is a condition related to the X and Y chromosomes (the sex chromosomes). People typically have two sex chromosomes in each cell: females have two X chromosomes (46,XX), and males have one X and one Y chromosome (46,XY). Most often, Klinefelter syndrome results from the presence of one extra copy of the X chromosome in each cell (47,XXY). Extra copies of genes on the X chromosome interfere with male sexual development, often preventing the testes from functioning normally and reducing the levels of testosterone. Most people with an extra

X chromosome have the features described above, although some have few or no associated signs and symptoms.

Some people with features of Klinefelter syndrome have more than one extra sex chromosome in each cell (for example, 48,XXXXY or 49,XXXXXY). These conditions, which are often called variants of Klinefelter syndrome, tend to cause more severe signs and symptoms than classic Klinefelter syndrome. In addition to affecting male sexual development, variants of Klinefelter syndrome are associated with intellectual disability, distinctive facial features, skeletal abnormalities, poor coordination, and severe problems with speech. As the number of extra sex chromosomes increases, so does the risk of these health problems.

Some people with features of Klinefelter syndrome have the extra X chromosome in only some of their cells; in these individuals, the condition is described as mosaic Klinefelter syndrome (46,XY/47,XXY). Individuals with mosaic Klinefelter syndrome may have milder signs and symptoms, depending on how many cells have an additional X chromosome.

Inheritance Pattern

Klinefelter syndrome and its variants are not inherited; these chromosomal changes usually occur as random events during the formation of reproductive cells (eggs and sperm) in a parent. 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 one or more extra copies of the X 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 one or more extra X chromosomes in each of the body's cells.

Mosaic 46,XY/47,XXY is also 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 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

- Klinefelter's syndrome
- XXY syndrome
- XXY trisomy

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Klinefelter's syndrome, XXY
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0022735/>

Other Diagnosis and Management Resources

- MedlinePlus Encyclopedia: Klinefelter Syndrome
<https://medlineplus.gov/ency/article/000382.htm>
- MedlinePlus Encyclopedia: Testicular Failure
<https://medlineplus.gov/ency/article/000395.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: 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>
- 48,XXYY syndrome
<https://rarediseases.info.nih.gov/diseases/5677/48xyy-syndrome>
- 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>
- Disease InfoSearch: Klinefelter syndrome
<http://www.diseaseinfosearch.org/Klinefelter+syndrome/4010>
- Genetic Science Learning Center, University of Utah
<http://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>
- Orphanet: NON RARE IN EUROPE: Klinefelter syndrome
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=484

Patient Support and Advocacy Resources

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

ClinicalTrials.gov

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

Scientific Articles on PubMed

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

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/>
- 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>
- Graham JM Jr, Bashir AS, Stark RE, Silbert A, Walzer S. Oral and written language abilities of XXY boys: implications for anticipatory guidance. *Pediatrics.* 1988 Jun;81(6):795-806.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/3368277>
- 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>
- Simpson JL, de la Cruz F, Swerdloff RS, Samango-Sprouse C, Skakkebaek NE, Graham JM Jr, Hassold T, Aylstock M, Meyer-Bahlburg HF, Willard HF, Hall JG, Salameh W, Boone K, Staessen C, Geschwind D, Giedd J, Dobs AS, Rogol A, Brinton B, Paulsen CA. Klinefelter syndrome: expanding the phenotype and identifying new research directions. *Genet Med.* 2003 Nov-Dec;5(6): 460-8.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/14614399>
- 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/>
 - Visootsak J, Aylstock M, Graham JM Jr. Klinefelter syndrome and its variants: an update and review for the primary pediatrician. *Clin Pediatr (Phila).* 2001 Dec;40(12):639-51. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/11771918>
 - Visootsak J, Rosner B, Dykens E, Tartaglia N, Graham JM Jr. Behavioral phenotype of sex chromosome aneuploidies: 48,XXYY, 48,XXXY, and 49,XXXXY. *Am J Med Genet A.* 2007 Jun 1; 143A(11):1198-203.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/17497714>
 - Wattendorf DJ, Muenke M. Klinefelter syndrome. *Am Fam Physician.* 2005 Dec 1;72(11):2259-62. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/16342850>
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