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.

Causes

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,XXXY or 49,XXXXY). 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

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
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21293172
Formal Treatment/Management Guidelines

  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

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-xy
- 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  
- 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  
- 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

• TeensHealth from Nemours

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
  http://thefocusfoundation.org/x-y-chromosomal-variations/xyy/

• National Center for Learning Disabilities
  https://www.ncld.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%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

Medical Genetics Database from MedGen

• Klinefelter Syndrome, Variants

• Klinefelter syndrome, XXY
**Sources for This Summary**

  *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/*

  *Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21540567*

  *Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20843200*

  *Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23118429*

  *Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21453406*

  *Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27147398*

  *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/*

  *Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22704628*

  *Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16106025*

  *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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