49,XXXXY syndrome

Description

49,XXXXY syndrome is a chromosomal condition that causes intellectual disabilities, developmental delays, changes in sex characteristics and other physical features, and an inability to have biological children (infertility). Some of these signs and symptoms vary among affected individuals.

People with 49,XXXXY syndrome have mild or moderate intellectual disabilities with learning difficulties. Speech and language development are particularly affected. Most affected individuals are better at understanding what other people say (receptive language) than producing speech (expressive language). Because many individuals with 49,XXXXY have difficulty making the mouth movements needed to speak, they are often diagnosed with a condition called childhood apraxia of speech.People with 49, XXXXY syndrome tend to be shy and friendly, but problems with speech and communication can contribute to behavioral issues, including irritability, difficulty tolerating frustration, defiant behavior, and outbursts or temper tantrums.

49,XXXXY syndrome is also associated with weak muscle tone (hypotonia) and problems with coordination that delay the development of motor skills, such as sitting, standing, and walking. Some people with 49,XXXXY have involuntary tensing of the neck, which causes the head to tilt or turn (torticollis).Affected infants and children are often shorter than their peers, but some catch up in height later in childhood or adolescence.

The physical differences that are associated with 49,XXXXY syndrome include the fusion of bones in the forearm (radioulnar synostosis), an unusually large range of joint movement (hyperextensibility), elbow abnormalities, curved pinky fingers (fifth finger clinodactyly), and flat feet (pes planus). Affected individuals have distinctive facial features that can include widely spaced eyes (ocular hypertelorism), an upward tilt to the outside corners of the eyes (upslanting palpebral fissures), skin folds that cover the inner corner of the eyes (epicanthal folds), and a flat bridge of the nose. Dental abnormalities are also common in people with 49,XXXXY syndrome.

49,XXXXY syndrome disrupts the development of typically male sex characteristics. The penis is often short and underdeveloped, and the testes may be undescended, which means they are located inside the pelvis or abdomen instead of outside of the body. The testes are small and do not produce sperm, so all individuals with 49,XXXXY syndrome are infertile. 49,XXXXY syndrome reduces the production of testosterone,

which is the hormone that directs male sexual development. Without treatment, the shortage of testosterone often leads to incomplete puberty. Starting in adolescence, affected individuals may have sparse body hair, and some experience breast enlargement (gynecomastia).

Frequency

49,XXXXY syndrome affects an estimated 1 in 85,000 to 100,000 babies born with a Y chromosome. It is among the rarest of the sex chromosome disorders, which are conditions caused by changes in the number of sex chromosomes (the X chromosome and the Y chromosome).

Causes

49,XXXXY syndrome is a sex chromosome disorder is caused by having three extra X chromosomes in each cell. People typically have 46 chromosomes in each cell, two of which are the sex chromosomes. Females typically have two X chromosomes (46,XX), and males typically have one X chromosome and one Y chromosome (46,XY). People with 49,XXXXY syndrome have a single Y chromosome and four copies of the X chromosome, for a total of 49 chromosomes in each cell.

Individuals with 49,XXXXY syndrome have extra copies of multiple genes on the X chromosome. The activity of these extra genes affects many aspects of development, including the development of sex characteristics before birth and at puberty. Researchers are working to determine which genes contribute to the specific developmental and physical differences that occur in people with 49,XXXXY syndrome.

49,XXXXY syndrome is sometimes described as a variation of another sex chromosome disorder called Klinefelter syndrome. People with Klinefelter syndrome have one extra copy of the X chromosome, for a total of 47 chromosomes in each cell (47,XXY). Like 49,XXXXY syndrome, Klinefelter syndrome affects the development of sexual characteristics that are typical for males and can be associated with learning disabilities and problems with speech and language development. However, the features of 49,XXXXY syndrome tend to be more severe than those of Klinefelter syndrome, and they 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 separate conditions.

Learn more about the chromosome associated with 49,XXXXY syndrome

- x chromosome

Inheritance

49,XXXXY syndrome is not inherited; it occurs as a random event during the formation of reproductive cells (eggs) in an affected person's parent. During cell division, an error called nondisjunction prevents X chromosomes from being distributed among egg cells

as they form. Typically, as cells divide, each egg cell gets a single X chromosome. However, because of nondisjunction, a single egg cell can end up with four X chromosomes that would normally have been distributed among four separate egg cells. If a sperm cell containing a single Y chromosome fertilizes this egg cell, the resulting child will have four X chromosomes and one Y chromosome (49,XXXXY) in each of the body's cells.

Other Names for This Condition

- 49,XXXXY chromosomal anomaly
- Chromosome XXXXY syndrome
- XXXXY aneuploidy
- XXXXY syndrome

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: 49,XXXXY syndrome (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0265499/)

Genetic and Rare Diseases Information Center

- 49,XXXXY syndrome (https://rarediseases.info.nih.gov/diseases/5679/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%2249,XXXXY syndrome%22)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28XXXXY%5BTIAB%5D%29+OR+%2849,XXXXY%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D)

References

- Counts DR, Yu C, Lasutschinkow PC, Sadeghin T, Gropman A, Samango-Sprouse CA.Evidence of intrauterine growth restriction and growth hormone deficiency in49, XXXXY syndrome. Am J Med Genet A. 2021 Dec;185(12):3547-3553. doi:10.1002/ajmg.a.61738. Epub 2020 Jul 2. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/32618131)
- Gropman AL, Porter GF, Lasutschinkow PC, Sadeghin T, Tipton ES, Powell S, Samango-Sprouse CA. Neurocognitive development and capabilities in boys with49, XXXXY syndrome. Am J Med Genet A. 2021 Dec;185(12):3541-3546. doi:10.1002/ajmg.a.61736. Epub 2020 Jul 14. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/32662248)
- Samango-Sprouse C, Lasutschinkow PC, Mitchell F, Porter GF, Hendrie P, PowellS, Sadeghin T, Gropman A. 49,XXXXY syndrome: A study of neurological function inthis uncommon X and Y chromosomal disorder. Am J Med Genet A. 2021Dec;185(12):3557-3566. doi: 10.1002/ajmg.a.61742. Epub 2020 Jul 13. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/32656941)
- Samango-Sprouse CA, Gropman AL. Introduction: Comprehensive investigation intoan international cohort of boys with 49,XXXXY. Am J Med Genet A. 2021Dec;185(12):3554-3556. doi: 10.1002/ajmg.a.61739. Epub 2020 Jul 13. No abstractavailable. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/32656873)
- Samango-Sprouse CA, Lasutschinkow PC, McLeod M, Porter GF, Powell S, StLaurent J, Sadeghin T, Gropman AL. Speech and language development in childrenwith 49,XXXXY syndrome. Am J Med Genet A. 2021 Dec;185(12):3567-3575. doi:10.1002/ajmg.a.61767. Epub 2020 Jul 28. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/32725750)

Last updated April 3, 2024