SSBP Syndrome Sheets

Triply X Syndrome (47,XXX; TriX)

First description and alternative names
In 1959, Jacobs (Jacobs, Baikie, Brown, et al., 1959) first described triple X syndrome (TriX) in an infertile patient. The term “super female” is considered controversial (Jacobs, Baikie, Court Brown, et al., 1959). The terms triple X syndrome, trisomy X syndrome and 47,XXX syndrome are generally preferred. Until now, triple X syndrome has been abbreviated to TXS, but TriX is easier to pronounce.

After the first description, there was a period of research in biased populations, e.g., in institutes for the mentally disabled, asylums and forensic psychiatric hospitals (Olanders, 1975b). In 1974, it was decided to screen 200,000 newborns for chromosomal disorders in several hospitals. TriX cases in this study have been evaluated several times for at least 20 years. These newborn-screening studies yielded unbiased data (Robinson et al., 1990). After 1990, two of these hospitals (Denver and Edinburgh) published follow-up data in young adults (Otter et al., 2010). Other studies reported results from mixed-sex groups of participants and mixed groups of sex chromosome trisomies: 47,XXX, 47,XXY, and 47,XYY (Bouw, Swaab, Tartaglia, et al., 2022).

Genetics and molecular biology
In TriX, there is an extra X chromosome in all cells or, in mosaic cases, in almost all cells. In other cases, there are three cell types, with XO, XX, and XXX chromosome counts (Nielsen & Thomsen, 1968; Olanders, 1975a). Today, most cases are diagnosed through prenatal diagnostic examinations (Otter et al., 2021). Other girls and women may be diagnosed postnatally because of infertility/recurrent abortions, atypical development or when a family member appears to have a genetic condition (Otter et al., 2021).

In typical 46,XX females, the extra X chromosome is silenced through a process known as Lyonization, also referred to as X chromosome inactivation (XCI) (Lyon, 1961, 1962). The additional X chromosome in TriX is also silenced. In typical females, one-third of the genes on the X chromosome escape silencing (Carrel & Willard, 2005; Migeon, 2007). XCI is a dynamic process. Diverse patterns of X chromosome regulation have been observed during development, in various tissues and diseases (Deng et al., 2014; Loda et al., 2022). The so-called ‘late-replicating’ X chromosome is the second X chromosome in typical women. In TriX, there is another late-replicating chromosome, resulting in an increase in replication time, which affects each cell division (Barlow, 1973). The extra X chromosome also influences nuclear architecture and epigenetic processes (Jowhar et al., 2018; Kelkar & Deobagkar, 2010). Whether incomplete silencing of the extra X chromosome, prolonged cell cycle during division, or epigenetic phenomena are relevant during development in 47,XXX requires further research (Wainer-Katsir & Linial, 2019). It has been demonstrated that the extra X chromosome affects gene expression. However, there is still a need for studies that might explain the behavioural phenotype. Modern biotechnology may help elucidate the biological relationship between the extra X chromosome and behavioural patterns in TriX (Astro et al., 2025; Otter, 2025a; Schulte et al., 2023; Tallaksen et al., 2023; Zhao et al., 2025).

Incidence/prevalence
One in 1,000 females has an extra X chromosome (Jacobs, 1979).

Physical features and natural history
Tartaglia et al. (2010) reviewed the physical findings in TriX. Since most of these findings (such as clinodactyly, epicanthal folds or hypertelorism) are minor physical features, most cases remain undiagnosed. Tall stature is common, and especially the underarms and legs are longer. The girls may have their growth spurt earlier than controls. Clinically speaking, decreased head circumference and smaller brains might be the most common physical features (Ratcliffe et al., 1994; Serrarens et al., 2022). Motor and coordination abilities seem to be somewhat retarded, and the girls are sometimes described as being clumsy (Otter et al., 2010).

Since 1959, many physical disorders associated with TriX have been reported, most of which do not exceed the population prevalence numbers. However, some disorders seem to be more common in TriX: urogenital anomalies, (partial) epilepsy and Primary Ovarian Insufficiency (POI), Premature Ovarian Failure (POF) and infertility (Berglund et al., 2022; Davis et al., 2020; Tartaglia et al., 2010). A recent Danish database study using clinical diagnoses and medication use in women with TriX, mosaics and controls revealed additional physical comorbidities, like gastrointestinal symptoms, including gastroesophageal reflux, constipation, and abdominal pain; dental problems; and increased risk of thrombophilia, venous thrombosis, and pulmonary embolism (Berglund et al., 2022).

Behavioural and psychiatric characteristics
The behavioural phenotype is far more important than the physical phenotype. Low self-esteem appears to be the most common psychological feature in TriX (Freilinger et al., 2018; Otter et al., 2022; Otter et al., 2010). Social anxiety, shyness and executive dysfunction are common in TriX girls (Lenroot et al., 2014; van Rijn, Stockmann, Borghgraef, et al., 2014; van Rijn, Stockmann, van Buggenhout, et al., 2014; van Rijn & Swaab, 2015). Social cognitive problems are common in TriX girls, probably due to language disorders (Bishop et al., 2011; Wilson et al., 2019). Developmental issues in language development have been described in TriX and other sex chromosome trisomies as well (Zampini et al., 2022; Zanchi et al., 2024); however, the problems seem to be slightly more severe in TriX girls. Larger groups of participants are required to investigate differences between the three different sex chromosome trisomies, and linguistic studies in adults are urgently needed (Capelli et al., 2022; Zampini et al., 2025). Another study in TriX girls showed a developmental pattern that resembled the development of girls with autism and mild or late presenting autism symptoms (van Rijn, Stockmann, van Buggenhout, et al., 2014). Numerous studies have been conducted in toddlers and very young children to investigate issues in social communication and social interaction, as well as the regulation of emotion, cognition, and behaviour (Bouw, 2023; Kuiper, 2023; Urbanus, 2022; van Rijn et al., 2023). Externalising behaviours, such as challenging behaviour, may be the result of any of these developmental difficulties and are more common in TriX than in controls (Otter et al., 2022; Otter et al., 2012). However, early recognition of limitations in social functioning, social cognition and linguistic limitations may enable early intervention (Bouw, 2023; Bouw, Swaab, & van Rijn, 2022). As in linguistic studies, larger groups of participants are required in this field to investigate differences between the three different sex chromosome trisomies. The TriX girls seem to be less able to cope in a stressful environment. TriX girls living in a stable family function better than

those in an unstable family (Netley, 1986). After leaving school, most TriX girls will find a job that reflects their non-verbal abilities (Robinson et al., 1990). Adults might face occupational problems (Attfield, 2020, 2021; Otter et al., 2012; Stochholm et al., 2013). However, a more benign perspective was shown in a study among American veterans (Davis et al., 2024).

There appears to be a higher prevalence of psychiatric illness in general in TriX. A study from Germany demonstrated that the extra X chromosome may influence mental health and well-being from childhood into adulthood. This study made clear that about half of the women with TriX do not experience major mental health problems (Freilinger et al., 2018). A recent study in a larger group of adults with TriX confirmed this (Otter et al., 2022). This study showed a higher prevalence of major depressive episodes (43.3%), psychotic disorders (29.4%), suicidality (23.5%) and frequent increased levels of anxiety. Impaired social functioning was found to be an important risk factor for psychotic disorders, affective disorders, trait anxiety, and low self-esteem (Otter et al., 2022). This Dutch study revealed no differences between women with TriX and controls in psychiatric medication use (Otter et al., 2022), which contrasts with the results of a Danish study, which showed slightly higher levels of psychiatric medication use, especially antipsychotics and medication used for ADHD (Berglund et al., 2022).

Neuropsychological characteristics

Data on intelligence in girls and adolescents are consistent, indicating that the full-scale IQ is approximately 20 points lower in these girls than expected within their families (Otter, 2025b; Robinson et al., 1990). Whether the girls exhibit problems in reading or arithmetic is not uniformly reported in the case reports and has not been confirmed in adults (Otter, 2025b). Clinical experience suggests that some difficulties during arithmetic lessons result from language disorders. Mild or severe academic problems/special educational needs are common (Attfield, 2020; Bishop et al., 2011; Robinson et al., 1990). Further research is needed to confirm the findings on the increased prevalence of attention problems and explain these attention problems: are they due to receptive language disorder, auditory processing disorders, anxiety disorders, attention deficit disorder (ADD) or even epilepsy (Lenroot et al., 2014; Otter, 2025b; Tartaglia et al., 2012)? Clinical experience treating ADD with medication suggests that the treatment is less effective than in 46,XX cases; however, controlled treatment studies are lacking. A recent study in adults revealed that women with TriX score lower in general intellectual functioning and exhibit impairments in motor processing speed and attention compared to controls, but do not differ in executive functioning, except for the women with TriX and impaired social functioning (Otter, 2025b). Women with TriX performed worse on an Emotion Recognition Task, particularly concerning recognising sadness, fear and disgust, so-called negative emotions (Otter, 2025b; Otter et al., 2021).

Findings from neuroimaging studies

Neuroimaging findings in girls with an extra X chromosome demonstrated affected brain regions and related phenotypic characteristics such as language delay (thinner cortex was found in the lateral temporal lobes related to language functions), poor executive function and heightened anxiety (increased thickness in the medial temporal lobe in the vicinity of the amygdala, a region important for social cognition and linked to anxiety) through differences in cortical thickness (Lenroot et al., 2014). Poor executive function and frontal lobe abnormalities have been suggested to be related (van Rijn & Swaab, 2015).

Two groups have recently published on neuroimaging in sex chromosomal disorders. The first group, from the National Institute of Mental Health, examined the impact of extra X or Y chromosomes in a group of adolescents and young adults. The second study, a Dutch case-control study in 22 adults with TriX, focused on adults (Serrarens, 2024). The impact of the extra X chromosome on brain size has been confirmed in adolescents, young adults (Raznahan et al., 2016), and adults (Serrarens et al., 2022). These studies, for instance, have revealed changes in cortical thickness and surface areas of the brain, as well as their relationship to cognitive changes (Warling et al., 2020). As social functioning is key to the behavioural phenotype of TriX, studies are warranted that further investigate the relationship between the brain and social functioning in TriX (Serrarens et al., 2024). Another key feature in the behavioural phenotype is anxiety (Otter et al., 2022). A very recent study revealed changes in the limbic areas and their relationship to anxiety (Domes et al., 2025). These studies are of scientific importance, but to date, no clinical progress is expected from neuroimaging in individual cases (Raznahan & Disteche, 2021), and the variability in the behavioural phenotype has not yet been explained (Otter, 2025a).

Available guidelines for behavioural assessment/treatment/management

There is no evidence-based management guideline; however, Otter et al. have proposed a guideline for medical and behavioural/psychiatric assessment (Otter et al., 2010). It is our advice to use a broad set of tools when psychological complaints are present in children and to consider language impairments when composing the test battery (Capelli et al., 2022; Zampini et al., 2022). Furthermore, impairments in social functioning (Otter et al., 2021; van Rijn et al., 2023), as well as neurocognitive problems in children (Urbanus et al., 2020) and adults (Otter, 2025b), should be assessed. A psychiatric interview should be included in a thorough examination of children (van Rijn, 2019) and adults (Otter et al., 2022).

Useful websites/associations for more information

Unique, a parents' support group from the United Kingdom, provides a syndrome sheet with information on physical and behavioural developmental issues:
https://rarechromo.org/media/information/Chromosome_X/Disclosing_about_XXX_for_girls%20FTNW.pdf
https://rarechromo.org/media/information/Chromosome_X/Disclosing_about_XXX_for_parents%20FTNW.pdf
https://rarechromo.org/media/information/Chromosome_X/X%20inactivation%20QFN.pdf

The AXYS website:
https://genetic.org/variations/about-trisomy-x/ Especially parents and TriX girls/women in the United States will find opportunities to meet experts, other parents and TriX girls/women. AXYS is actively involved in fundraising to support scientific research.

Updated in 2025 by Maarten Otter

References

1. Astro, V., Cardona-Londono, K. Y., Cortes-Medina, L. V., Alghamdi, R., Ramirez-Calderon, G., Kefalas, F., Dilme-Capo, J., Radio, S., & Adamo, A. (2025). An iPSC-based model of 47,XYY Jacobs syndrome reveals a DNA methylation-independent transcriptional dysregulation shared with male X aneuploid cells. Genome Res, 35(7), 1503-1517. https://doi.org/10.1101/gr.279716.124
2. Attfield, K. (2020). Triple X supergirls: Their special educational needs and social experience. Int J Educ Res, 102, 101588. https://doi.org/10.1016/j.ijer.2020.101588
3. Attfield, K. (2021). Triple X superwomen: their post-compulsory education and employability. J Educ Work, 34(1), 81-94. https://doi.org/10.1080/13639080.2021.1875126
4. Barlow, P. W. (1973). X-chromosomes and human development. Dev Med Child Neurol, 15(2), 205-208. https://doi.org/10.1111/j.1469-8749.1973.tb15163.x
5. Berglund, A., Stochholm, K., & Gravholt, C. H. (2022). The comorbidity landscape of 47,XXX syndrome: A nationwide epidemiologic study. Genet Med, 24(2), 475-487. https://doi.org/10.1016/j.gim.2021.10.012
6. Bishop, D. V., Jacobs, P. A., Lachlan, K., Wellesley, D., Barnicoat, A., Boyd, P. A., Fryer, A., Middlemiss, P., Smithson, S., Metcalfe, K., Shears, D., Leggett, V., Nation, K., & Scerif, G. (2011). Autism, language and communication in children with sex chromosome trisomies [Research Support, Non-U.S. Gov't]. Arch Dis Child, 96(10), 954-959. https://doi.org/10.1136/adc.2009.179747
7. Bouw, J. C. (2023). What's in a face? The early developmental impact of Sex Chromosome Trisomies (XXX, XXY, XYY) on social cognition. Chapter 1: General introduction. Leiden University. Leiden. https://hdl.handle.net/1887/3589855
8. Bouw, N., Swaab, H., Tartaglia, N., Jansen, A. C., & van Rijn, S. (2022). Early impact of X- and Y-chromosome variations (XXX, XXY, XYY) on social communication and social emotional development in 1-2-year-old children. Am J Med Genet A, 188(7), 1943-1953. https://doi.org/10.1002/ajmg.a.62720
9. Bouw, N., Swaab, H., & van Rijn, S. (2022). Early Preventive Intervention for Young Children With Sex Chromosome Trisomies (XXX, XXY, XYY): Supporting Social Cognitive Development Using a Neurocognitive Training Program Targeting Facial Emotion Understanding. Front Psychiatry, 13, 807793. https://doi.org/10.3389/fpsyt.2022.807793
10. Capelli, E., Silibello, G., Ajmone, P. F., Altamore, E., Lalatta, F., Vizziello, P. G., Costantino, M. A., & Zampini, L. (2022). Language Development in Sex Chromosome Trisomies: Developmental Profiles at 2 and 4 Years of Age, and Predictive Measures. Developmental neurorehabilitation, 25(5), 337-348. https://doi.org/10.1080/17518423.2021.2020925
11. Carrel, L., & Willard, H. F. (2005). X-inactivation profile reveals extensive variability in X-linked gene expression in females. Nature, 434(7031), 400-404. https://doi.org/https://doi.org/10.1038/nature03479
12. Davis, S. M., Soares, K., Howell, S., Cree-Green, M., Buyers, E., Johnson, J., & Tartaglia, N. R. (2020). Diminished Ovarian Reserve in Girls and Adolescents with Trisomy X Syndrome. Reprod Sci, 27(11), 1985-1991. https://doi.org/10.1007/s43032-020-00216-4
13. Davis, S. M., Teerlink, C. C., Lynch, J. A., Klamut, N., Gorman, B. R., Pagadala, M. S., Panizzon, M. S., Merritt, V. C., Genovese, G., Ross, J. L., & Hauger, R. L. (2024). An extra X chromosome among adult women in the Million Veteran Program: A more benign perspective of trisomy X. American journal of medical genetics. Part C, Seminars in medical genetics, e32083. https://doi.org/10.1002/ajmg.c.32083
14. Deng, X., Berletch, J. B., Nguyen, D. K., & Disteche, C. M. (2014). X chromosome regulation: diverse patterns in development, tissues and disease. Nat Rev Genet, 15(6), 367-378. https://doi.org/10.1038/nrg3687
15. Domes, G., Croye, M. A., Freilinger, P., Bohlscheid, A., Willinek, W. A., & Meyer, J. (2025). Brain structure in triple X syndrome: regional gray matter volume and cortical thickness in adult women with 47,XXX karyotype. J Neurodev Disord, 17(1), 18. https://doi.org/10.1186/s11689-025-09608-6
16. Freilinger, P., Kliegel, D., Hanig, S., Oehl-Jaschkowitz, B., Henn, W., & Meyer, J. (2018). Behavioral and psychological features in girls and women with triple-X syndrome. Am J Med Genet A, 176(11), 2284-2291. https://doi.org/10.1002/ajmg.a.40477
17. Jacobs, P. A. (1979). The incidence and etiology of sex chromosome abnormalities in man. Birth Defects Orig Artic Ser, 15(1), 3-14. https://www.ncbi.nlm.nih.gov/pubmed/444646
18. Jacobs, P. A., Baikie, A. G., Brown, W. M., Macgregor, T. N., Maclean, N., & Harnden, D. G. (1959). Evidence for the existence of the human "super female". Lancet, 2(7100), 423-425. https://doi.org/10.1016/s0140-6736(59)90415-5
19. Jacobs, P. A., Baikie, A. G., Court Brown, W. M., Harnden, D. G., Macgregor, T. N., & Maclean, N. (1959). Use of the term "Superfemale" [Letter]. Lancet, 274(7112), 1145. https://www.sciencedirect.com/science/article/pii/S0140673659901321

20. Jowhar, Z., Shachar, S., Gudla, P. R., Wangsa, D., Torres, E., Russ, J. L., Pegoraro, G., Ried, T., Raznahan, A., & Misteli, T. (2018). Effects of human sex chromosome dosage on spatial chromosome organization. Mol Biol Cell, 29(20), 2458-2469. https://doi.org/10.1091/mbc.E18-06-0359
21. Kelkar, A., & Deobagkar, D. (2010). Methylation profile of genes on the human X chromosome. Epigenetics, 5(7). https://doi.org/10.4161/epi.5.7.12797
22. Kuiper, K. C. (2023). Neurodevelopmental impact of sex chromosome trisomy in young children: the regulation of emotion, cognition, and behavior [Doctoral thesis; Leiden University]. Leiden. https://hdl.handle.net/1887/3638781
23. Lenroot, R. K., Blumenthal, J. D., Wallace, G. L., Clasen, L. S., Lee, N. R., & Giedd, J. N. (2014). A case-control study of brain structure and behavioral characteristics in 47,XXX syndrome. Genes Brain Behav, 13(8), 841-849. https://doi.org/10.1111/gbb.12180
24. Loda, A., Collombet, S., & Heard, E. (2022). Gene regulation in time and space during X-chromosome inactivation. Nat Rev Mol Cell Biol, 23(4), 231-249. https://doi.org/10.1038/s41580-021-00438-7
25. Lyon, M. F. (1961). Gene action in the X-chromosome of the mouse (Mus musculus L.). Nature, 190, 372-373. https://doi.org/10.1038/190372a0
26. Lyon, M. F. (1962). Sex chromatin and gene action in the mammalian X-chromosome. Am J Hum Genet, 14, 135-148. https://pmc.ncbi.nlm.nih.gov/articles/PMC1932279/
27. Migeon, B. R. (2007). Females are MOSAICS: X inactivation and sex differences in disease. Oxford University Press.
28. Netley, C. T. (1986). Summary overview of behavioural development in individuals with neonatally identified X and Y aneuploidy. Birth Defects Orig Artic Ser, 22(3), 293-306. https://www.ncbi.nlm.nih.gov/pubmed/3814782
29. Nielsen, J., & Thomsen, N. (1968). A psychiatric-cytogenetic study of a female patient with 45-46-47 chromosomes and sex chromosomes XO-XX-XXX. Acta Psychiatr Scand, 44(2), 141-155. https://doi.org/10.1111/j.1600-0447.1968.tb07501.x
30. Olanders, S. (1975a). Cytogenetic investigation (G. R. Otter, Trans.). In Females with supernumerary X chromosomes: a study of 39 psychiatric cases. (Vol. 11, pp. 21-36). University of Göteborg.
31. Olanders, S. (1975b). Females with supernumerary X chromosomes: a study of 39 psychiatric cases. [Doctoral thesis; University of Göteborg]. Göteborg.
32. Otter, M. (2025a). General discussion and future perspectives. In Triple X syndrome in adults: cognitive, psychiatric and neuroanatomical profile (pp. 175-205). Maastricht University. https://doi.org/10.26481/dis.20250404mo
33. Otter, M. (2025b). Neurocognitive findings in adults with triple X syndrome: towards personalized support. In Triple X syndrome in adults: cognitive, psychiatric and neuroanatomical profile (pp. 111-145). Maastricht University. https://doi.org/10.26481/dis.20250404mo
34. Otter, M., Campforts, B. C. M., Stumpel, C. T. R. M., van Amelsvoort, T. A. M. J., & Drukker, M. (2022). Triple X syndrome: Psychiatric disorders and impaired social functioning as a risk factor. European psychiatry: the journal of the Association of European Psychiatrists, 66(1), e7. https://doi.org/10.1192/j.eurpsy.2022.2355
35. Otter, M., Crins, P. M. L., Campforts, B. C. M., Stumpel, C. T. R. M., van Amelsvoort, T. A. M. J., & Vingerhoets, C. (2021). Social functioning and emotion recognition in adults with triple X syndrome. BJPsych Open, 7(2), e51. https://doi.org/10.1192/bjo.2021.8
36. Otter, M., Schrander-Stumpel, C. T. R. M., & Curfs, L. M. (2010). Triple X syndrome: a review of the literature. Eur J Hum Genet, 18(3), 265-271. https://doi.org/10.1038/ejhg.2009.109
37. Otter, M., Schrander-Stumpel, C. T. R. M., Didden, R., & Curfs, L. M. (2012). The psychiatric phenotype in triple X syndrome: new hypotheses illustrated in two cases [Case Reports]. Developmental neurorehabilitation, 15(3), 233-238. https://doi.org/10.3109/17518423.2012.655799
38. Ratcliffe, S. G., Masera, N., Pan, H., & McKie, M. (1994). Head circumference and IQ of children with sex chromosome abnormalities. Dev Med Child Neurol, 36(6), 533-544. https://doi.org/10.1111/j.1469-8749.1994.tb11884.x
39. Raznahan, A., & Disteche, C. M. (2021). X-chromosome regulation and sex differences in brain anatomy. Neurosci Biobehav Rev, 120, 28-47. https://doi.org/10.1016/j.neubiorev.2020.10.024
40. Raznahan, A., Lee, N. R., Greenstein, D., Wallace, G. L., Blumenthal, J. D., Clasen, L. S., & Giedd, J. N. (2016). Globally Divergent but Locally Convergent X- and Y-Chromosome Influences on Cortical Development. Cereb Cortex, 26(1), 70-79. https://doi.org/10.1093/cercor/bhu174
41. Robinson, A., Bender, B. G., & Linden, M. G. (1990). Summary of clinical findings in children and young adults with sex chromosome anomalies. Birth Defects Orig Artic Ser, 26(4), 225-228. https://www.ncbi.nlm.nih.gov/pubmed/2090320
42. Schulte, E. C., Kohshour, M. O., Tkachev, A., Khaitovich, P., & Schulze, T. G. (2023). Multiomics

Approaches in Psychiatric Disorders. In A. Tasman, M. B. Riba, R. D. Alarcón, C. A. Alfonso, S. Kanba, D. M. Ndetei, C. H. Ng, T. G. Schulze, & D. Lecic-Tosevski (Eds.), Tasman's Psychiatry (pp. 1-16). Springer International Publishing. https://doi.org/10.1007/978-3-030-42825-9_30-1
43. Serrarens, C. (2024). eXtraordinary brains? The impact of the eXtra X on the brain: 7 Tesla MRI studies in adult individuals with 47,XXX Maastricht. https://cris.maastrichtuniversity.nl/en/publications/extraordinary-brains-the-impact-of-the-extra-x-on-the-brain-7-tes
44. Serrarens, C., Otter, M., Campforts, B. C. M., Stumpel, C. T. R. M., Jansma, H., van Amelsvoort, T. A. M. J., & Vingerhoets, C. (2022). Altered subcortical and cortical brain morphology in adult women with 47,XXX: a 7-Tesla magnetic resonance imaging study. J Neurodev Disord, 14(1), 14. https://doi.org/10.1186/s11689-022-09425-1
45. Serrarens, C., Ruiz-Fernandez, J., Otter, M., Campforts, B. C. M., Stumpel, C., Linden, D. E. J., van Amelsvoort, T., Kashyap, S., & Vingerhoets, C. (2024). Intracortical myelin across laminae in adult individuals with 47,XXX: a 7 Tesla MRI study. Cerebral cortex, 34(8). https://doi.org/10.1093/cercor/bhae343
46. Stochholm, K., Juul, S., & Gravholt, C. H. (2013). Poor socio-economic status in 47,XXX --an unexpected effect of an extra X chromosome. Eur J Med Genet, 56(6), 286-291. https://doi.org/10.1016/j.ejmg.2013.03.008
47. Tallaksen, H. B. L., Johannsen, E. B., Just, J., Viuff, M. H., Gravholt, C. H., & Skakkebaek, A. (2023). The multi-omic landscape of sex chromosome abnormalities: current status and future directions. Endocr Connect, 12(9). https://doi.org/10.1530/EC-23-0011
48. Tartaglia, N. R., Ayari, N., Hutaff-Lee, C., & Boada, R. (2012). Attention-deficit hyperactivity disorder symptoms in children and adolescents with sex chromosome aneuploidy: XXY, XXX, XYY, and XXYY. J Dev Behav Pediatr, 33(4), 309-318. https://doi.org/10.1097/DBP.0b013e31824501c8
49. Tartaglia, N. R., Howell, S., Sutherland, A., Wilson, R., & Wilson, L. (2010). A review of trisomy X (47,XXX). Orphanet J Rare Dis, 5(1), 8. https://doi.org/10.1186/1750-1172-5-8
50. Urbanus, E., van Rijn, S., & Swaab, H. (2020). A review of neurocognitive functioning of children with sex chromosome trisomies: Identifying targets for early intervention. Clin Genet, 97(1), 156-167. https://doi.org/10.1111/cge.13586
51. Urbanus, E. L. (2022). Social communication in young children with sex chromosome trisomy: neurocognitive building blocks of behavioral outcomes. Chapter 1: General Introduction Leiden University. Leiden. https://hdl.handle.net/1887/3455060
52. van Rijn, S. (2019). A review of neurocognitive functioning and risk for psychopathology in sex chromosome trisomy (47,XXY, 47,XXX, 47, XYY). Current opinion in psychiatry, 32(2), 79-84. https://doi.org/10.1097/YCO.0000000000000471
53. van Rijn, S., Kuiper, K., Bouw, N., Urbanus, E., & Swaab, H. (2023). Neurocognitive and behavioral development in young children (1-7 years) with sex chromosome trisomy. Endocr Connect, 12(5). https://doi.org/10.1530/EC-22-0494
54. van Rijn, S., Stockmann, L., Borghgraef, M., Bruining, H., van Ravenswaaij-Arts, C., Govaerts, L., Hansson, K., & Swaab, H. (2014). The social behavioral phenotype in boys and girls with an extra X chromosome (Klinefelter syndrome and Trisomy X): a comparison with autism spectrum disorder. J Autism Dev Disord, 44(2), 310-320. https://doi.org/10.1007/s10803-013-1860-5
55. van Rijn, S., Stockmann, L., van Buggenhout, G., van Ravenswaaij-Arts, C., & Swaab, H. (2014). Social cognition and underlying cognitive mechanisms in children with an extra X chromosome: a comparison with autism spectrum disorder. Genes Brain Behav, 13(5), 459-467. https://doi.org/10.1111/gbb.12134
56. van Rijn, S., & Swaab, H. (2015). Executive dysfunction and the relation with behavioral problems in children with 47,XXY and 47,XXX. Genes Brain Behav, 14(2), 200-208. https://doi.org/10.1111/gbb.12203
57. Wainer-Katsir, K., & Linial, M. (2019). Chromosome X factors and phenotype variability. Obstetrics and Gynecology Reports, 3(1), 1-3. https://doi.org/10.15761/ogr.1000132
58. Warling, A., Liu, S., Wilson, K., Whitman, E., Lalonde, F. M., Clasen, L. S., Blumenthal, J. D., & Raznahan, A. (2020). Sex chromosome aneuploidy alters the relationship between neuroanatomy and cognition. Am J Med Genet C Semin Med Genet, 184(2), 493-505. https://doi.org/10.1002/ajmg.c.31795
59. Wilson, A. C., King, J., & Bishop, D. V. M. (2019). Autism and social anxiety in children with sex chromosome trisomies: an observational study. Wellcome Open Res, 4(32), 32. https://doi.org/10.12688/wellcomeopenres.15095.2
60. Zampini, L., Lorini, A., Zanchi, P., Scionti, N., Silibello, G., Dall'Ara, F., Ajmone, P. F., Monti, F.,

Costantino, M. A., & Vizziello, P. G. (2025). Neurodevelopment in Young Children With Sex Chromosome Trisomies Diagnosed Before Birth: A Cluster Analysis Study. Am J Med Genet A, 197(2), e63895. https://doi.org/10.1002/ajmg.a.63895
61. Zampini, L., Silibello, G., Mastromattei, D., Pagliaccia, E., Monti, F., Zanchi, P., Ajmone, P. F., Costantino, M. A., & Vizziello, P. G. (2022). Short report. Narrative competence in Italian preschool children with sex chromosome trisomies. Res Dev Disabil, 130, 104341. https://doi.org/10.1016/j.ridd.2022.104341
62. Zanchi, P., Provera, A., Silibello, G., Ajmone, P. F., Altamore, E., Lalatta, F., Costantino, M. A., Vizziello, P. G., & Zampini, L. (2024). Prosody in narratives: An exploratory study with children with sex chromosomes trisomies. Speech Communication, 163, 103107. https://doi.org/https://doi.org/10.1016/j.specom.2024.103107
63. Zhao, H., Zhou, D., Feng, Y., & Haddad, G. G. (2025). Klinefelter syndrome: A neurodevelopmental disease of the synapse. Neurobiol Dis, 107010. https://doi.org/10.1016/j.nbd.2025.107010

Updated in 2025 by Maarten Otter