# SSBP Syndrome Sheets

## Triple-X Syndrome (47,XXX; TXS)

### First description and alternative names

In 1959 Jacobs (Jacobs et al., 1959) first described triple-X syndrome (TXS) in an infertile patient. The term “super female” is considered controversial and the term triplo-X syndrome is old fashioned. The terms triple-X syndrome, trisomy-X syndrome and 47,XXX syndrome are generally preferred.

After the first description there was a period of research in biased populations, e.g., in institutes for mentally retarded, asylums and forensic psychiatric hospitals (Olanders, 1975). In 1974 it was decided to screen 200,000 newborns for chromosomal disorders in several hospitals. TXS 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). Recent studies from other research groups published data from biased groups of cases (Wilson et al., 2019). Other studies reported results of mixed sex groups of participants and mixed groups of sex chromosome trisomies (47,XXX, 47,XXY, and 47,XYY). Some of the 47,XXY cases have received testosterone treatment, and others did not (Bouw, Swaab, Tartaglia, et al., 2022). These issues should be considered in the appraisal of study results.

### Genetics and molecular biology

In TXS, there is an extra X chromosome in all cells or, in mosaic cases, in almost all cells. Most of the cases are diagnosed through prenatal diagnostic examinations. 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 46,XX females the extra X chromosome is silenced through lionization. The extra X chromosome in TXS is also silenced. In 46,XX females one-third of the genes on the X chromosome escape silencing (Migeon, 2007), and diverse patterns of X chromosome regulation have been shown during development, and 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 46,XX women. In TXS, there is another late-replicating chromosome, so replication time increases during each cell division (Barlow, 1973). The extra X chromosome also influences the nuclear architecture and epigenetic processes (Jowhar et al., 2018; Kelkar & Deobagkar, 2010). Whether incomplete silencing of the extra X chromosome, the prolonged cell cycle during division or epigenetic phenomena are relevant during development in 47,XXX, requires further research (Wainer-Katsir & Linial, 2019). Knowledge about sex differences in the brain (Raznahan & Disteche, 2021) and modern technology (Tallaksen et al., 2023) may help elucidate the biological relationship between the extra X chromosome and behavioural patterns in TXS.

### Incidence/prevalence

1/1000 females have an extra X chromosome (Otter et al., 2010).

### Physical features and natural history

Tartaglia et al. (Tartaglia et al., 2010) reviewed the physical findings in TXS. Since most of these findings (such as clinodactyly, epicanthal folds or hypertelorism) are minor physical features, the majority of 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 is probably the most important common feature (Patwardhan et al., 2002; Ratcliffe et al., 1994). 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 TXS have been reported, most of which do not exceeding the population prevalence numbers. But there are some disorders that seem to be more common in TXS: urogenital anomalies, (partial) epilepsy and Premature Ovarian Failure (POF) and infertility (Tartaglia et al., 2010). A recent Danish database study using clinical diagnoses and medication use in women with TXS, 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

Low self-esteem seems to be the most common psychological feature in TXS (Freilinger et al., 2018; Otter et al., 2010). Social anxiety/shyness and executive dysfunction are common in TXS girls (Lenroot et al., 2014; van Rijn, Stockmann, Borghgraef, et al., 2014; van Rijn & Swaab, 2015). Social cognitive problems are common in TXS girls, probably due to language disorders (Bishop et al., 2011; Wilson et al., 2019). Developmental problems in language development have been described in TXS and in other sex chromosome trisomies as well, but the problems seem to be more severe in TXS girls (Capelli et al., 2022). Another study in TXS girls showed a developmental pattern that resembled the development of girls with autism with mild or late presenting autism symptoms (van Rijn, Stockmann, van Buggenhout, et al., 2014). Even in toddlers and very young children, problems in social communication and social interaction have been revealed (Bouw et al., 2023; Bouw, Swaab, Tartaglia, et al., 2022). Challenging behaviour may be the result of any of these developmental difficulties. However, early recognition of limitations in social functioning, in social cognitions and linguistic limitations may enable early intervention (Bouw, Swaab, & van Rijn, 2022). TXS girls living in a stable family function better than TXS girls in an unstable family (Netley, 1986). The TXS girls seem to be less able to cope in a stressful environment. After leaving school, most of the girls will find a job that reflects their non-verbal abilities (Robinson et al., 1990). Adults might face occupational problems (Attfield, 2021; Otter et al., 2012; Stochholm et al., 2013).

There seems to be a higher prevalence of psychiatric illness in general in TXS (van Rijn, 2019). 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 TXS do not experience major mental health problems (Freilinger *et al.* 2018). This was confirmed by a recent study in a larger group of adults with TXS (Otter, Campforts, Stumpel, van Amelsvoort, & Drukker, 2022). This study showed a higher prevalence of major depressive episodes (43.3%, psychotic disorders (29.4%), suicidality (23.5%) and higher 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, Campforts, Stumpel, van Amelsvoort, & Drukker, 2022). This Dutch study revealed no differences between women with TXS and controls in psychiatric medication use, which contrasts with the results of a Danish study, which revealed slightly higher levels psychiatric medication use, especially antipsychotics and medication used for ADHD (Berglund et al., 2022).

## Scientific progress through neuroimaging findings

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).

A group from National Institute of Mental Health (A. Raznahan) published several papers on neuroimaging in sex chromosomal disorders. These studies revealed changes in cortical thickness and surface areas of the brain (Warling et al., 2020). These studies are of scientific importance, but until now, there is no clinical progress to be expected from neuroimaging in individual cases (Raznahan & Disteche, 2021) and the variability in the behavioural phenotype has not been explained (Otter, Campforts, Stumpel, van Amelsvoort, & Drukker, 2022).

## Neuropsychological characteristics

Data on intelligence in girls and adolescents are consistent, indicating that the full-scale IQ is almost 20 points lower in these girls than expected in the family (Robinson et al., 1990). Whether the girls show problems in reading or arithmetic is not uniformly reported in the case reports. Clinical experience suggests that some difficulties during arithmetic lessons result from language disorders. Mild or serious academic problems/special educational needs are common (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 or attention deficit disorder (ADD) (Lenroot et al., 2014)? Clinical experience treating ADD with medication suggests that the treatment is less effective than in 46,XX cases; however, controlled treatment studies are lacking (Leggett et al., 2010). A recent study in adults revealed that women with TXS score lower in general intellectual functioning and have impairments in motor processing speed and attention compared to controls, but do not differ with respect to executive functioning (Otter, Campforts, Stumpel, van Amelsvoort, Vingerhoets, et al., 2022). Women with TXS performed worse on an Emotion Recognition Task, particularly concerning recognising sadness, fear and disgust, so-called negative emotions (Otter et al., 2021).

## Available guidelines for behavioural assessment/treatment/management

There is no evidence-based management guideline, although Otter et al. have proposed a guideline of 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 since recent studies indicate language impairments in children (Bishop et al., 2018; Capelli et al., 2022), social-behavioural problems in children (Wilson et al., 2019) and adults (Otter et al., 2021), and neurocognitive problems in children (Urbanus et al., 2020) and adults (Otter, Campforts, Stumpel, van Amelsvoort, Vingerhoets, et al., 2022). A psychiatric interview should be included in a careful examination of children (van Rijn, 2019) and adults (Otter, Campforts, Stumpel, van Amelsvoort, & Drukker, 2022).

## Useful websites/associations for more information

- The Dutch parents' support website: http://triple-x-syndroom.nl/. This website shows many links to scientific papers and useful links, e.g., links to international chat pages for parents and TXS girls/women. Scientific papers and syndrome sheets are available in several languages: English, French, Spanish, German and Dutch.
- Unique, a parents support group from the United Kingdom provides a syndrome sheet with information on physical and behavioural developmental issues: https://www.rarechromo.org/media/information/Chromosome_X/Triple_X_syndrome%20Trisomy_X%20FTNW.pdf_; 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 and https://rarechromo.org/media/information/Chromosome_X/X%20inactivation%20QFN.pdf .

- The AXYS website provides a lot of information: https://genetic.org/variations/about-trisomy-x/. Especially parents and TXS girls/women in the United States will find opportunities to meet experts, other parents and TXS girls/women. AXYS is active in fundraising for the support of scientific research.

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