



SOCIETY FOR THE STUDY OF BEHAVIOURAL PHENOTYPES

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Triple-X syndrome (47,XXX)

First description and alternative names:

In 1959 Jacobs (Jacobs *et al.* 1959) first described triple-X syndrome in an infertile patient. The term “super female” is considered to be 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 institutions, asylums and forensic psychiatric hospitals (Olanders 1975). In 1974 200,000 newborns were screened for chromosomal disorders in several hospitals. The triple-X 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).

Genetics and molecular biology:

In triple-X syndrome 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. In 46,XX females one X chromosome is silenced. The extra X chromosome in triple-X women is also silenced through Lyonization. In 46,XX females one-third of the genes on the X chromosome escape silencing (Migeon 2007). The so-called ‘late-replicating’ X chromosome is found on the second X chromosome. In cases of an extra X chromosome there is another late-replicating chromosome, so replication time increases during each cell division (Barlow 1973). The extra X chromosome might also have some influence on the nuclear architecture and on epigenetic processes (Kelkar and Deobagkar 2010). The question of 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.

Incidence/prevalence:

1/1000 females have an extra X chromosome (Jacobs 1979).

Physical features and natural history:

Tartaglia *et al.* (2010) reviewed the physical findings in triple-X syndrome. Since most of these findings (such as clinodactyly, epicanthal folds or hypertelorism) were minor, the majority of cases remain undiagnosed. Tall stature is common, and especially the arms and legs are longer. Girls have their growth spurt earlier than do controls. Clinically speaking, decreased head circumference is probably the most important common feature; a relationship has been reported between head circumference and level of cognitive functioning (Ratcliffe *et al.* 1994). Motor and coordination abilities seem to be somewhat impaired, and the girls are sometimes described as being clumsy. Neuroimaging studies revealed a smaller head circumference and a lower brain volume (Patwardhan *et al.* 2002).

Since 1959 many physical disorders associated with a triple-X finding have been reported, most of which do not exceed the population prevalence numbers. But some disorders seem to be more common in triple-X cases: urogenital anomalies, (partial) epilepsy and Premature Ovarian Failure (POF) (Tartaglia *et al.* 2010).

Behavioural and psychiatric characteristics:

Low self-esteem seems to be the most common feature, and shyness is also common in triple -X females. Receptive and expressive language disorders are common. These language disorders may be responsible for social problems, as is challenging behaviour, although this behaviour is less common. Both individuals living in a stable family and controls in unstable families function better than triple-

X girls do (Netley 1986). The triple-X 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).

There seems to be a higher prevalence of psychiatric illness in general, especially in cases of less severe global intellectual disability. More specifically, there is a higher prevalence of psychotic disorders and adjustment disorders (Olanders 1975). Newborn-screening studies have not continued to the age at which psychotic disorders could have become noticeable. Further psychiatric research with standardised psychiatric diagnostic tools is warranted in these females.

Neuropsychological characteristics:

Neuropsychological, physical and developmental data on triple-X syndrome have recently been reviewed by Leggett *et al.* (2010), Tartaglia *et al.* (2010) and Otter *et al.* (2010).

Data on intelligence are consistent, indicating that Full Scale IQs are almost 20 points lower than would be expected in the family. Whether the girls show problems in reading or arithmetic is not uniformly reported in the case reports. Mild or serious academic problems are quite common. In individual cases support may be necessary and beneficial. Further research is needed to determine whether there are attention problems due to receptive language disorder, auditory processing disorders or attention deficit disorder (ADD). Clinical experience in 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).

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 assessment (Otter *et al.* 2010).

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 triple-X girls/women. Scientific papers and syndrome sheets are available in English, French, Spanish, German and Dutch.
- <http://www.rarechromo.org/information/Chromosome%20X/Triple%20X%20FTNW.pdf> provides a syndrome sheet with information on physical and behavioural developmental issues.
- The KS&A (Klinefelter Syndrome and Associates) website <http://www.genetic.org>. Parents and triple-X girls/women in the United States have the opportunity to meet experts, other parents and triple-X girls/women.

References:

1. Barlow P.W. (1973) X-chromosomes and human development. *Dev Med Child Neurol* **15**, 205-8.
2. Jacobs P. A. (1979) The incidence and etiology of sex chromosome abnormalities in man. *Birth Defects Orig Artic Ser* **15**, 3-14.
3. Jacobs P.A., Baikie A.G., Court Brown W.M., MacGregor T.N., Maclean N. & Harnden D.G. (1959) Evidence for the existence of the human "super female". *Lancet* **274**, 423-5.
4. Kelkar A. & Deobagkar D. (2010) Methylation profile of genes on the human X chromosome. *Epigenetics* **5**.
5. Leggett V., Jacobs P., Nation K., Scerif G. & Bishop D.V. (2010) Neurocognitive outcomes of individuals with a sex chromosome trisomy: XXX, XYY, or XXY: a systematic review. *Dev Med Child Neurol* **52**, 119-29.
6. Migeon B.R. (2007) *Females are MOSAICS; X inactivation and sex differences in disease*, (Trans. OUP, New York).
7. Netley C.T. (1986) Summary overview of behavioural development in individuals with neonatally identified X and Y aneuploidy. *Birth Defects Orig Artic Ser* **22**, 293-306.
8. Olanders S. (1975) Females with supernumerary X chromosomes; a study of 39 psychiatric cases. In: *St. Jörgen's hospital* (ed H. Forssman). pp. 223. University of Göteborg, Göteborg, Sweden.
9. Otter M., Schrander-Stumpel C.T. & Curfs L.M. (2010) Triple X syndrome: a review of the literature. *Eur J Hum Genet* **18**, 265-71.
10. Patwardhan A.J., Brown W.E., Bender B.G., Linden M.G., Eliez S. & Reiss A.L. (2002) Reduced size of the amygdala in individuals with 47,XXY and 47,XXX karyotypes. *Am J Med Genet* **114**, 93-8.
11. 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**, 533-44.
12. 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**, 225-8.
13. Tartaglia N.R., Howell S., Sutherland A., Wilson R. & Wilson L. (2010) A review of trisomy X (47,XXX). *Orphanet J Rare Dis* **5**, 8.

Maarten Otter, summer 2010