



Klinefelter Syndrome (47,XXY)

First description and alternative names

“Klinefelter Syndrome” or “Klinefelter’s Syndrome,” sometimes abbreviated as KS, was first described by Dr. Harry Klinefelter in 1942 as an endocrine disorder characterized by small firm testes, hypogonadism, gynecomastia, and increased levels of follicle-stimulating hormone. Patricia Jacobs determined in 1959 that the clinical phenotype was due to a 47,XXY genotype.

Genetics and molecular biology

47,XXY (KS) is a chromosomal variation in males in which one extra X chromosome is present, resulting in an XXY karyotype. 47,XXY (KS) is not inherited. The additional X chromosome arises from non-disjunction either during germ-cell development or in early embryonic cell divisions. Approximately 50% of non-disjunctions appear to be of maternal origin (Iitsuka et al., 2000). The cause of the non-disjunction is not known.

Some cases may have 46,XY/47,XXY mosaicism. Mosaic 47,XXY occurs because of an error in the division of the sex chromosomes in the zygote after fertilization.

Incidence/prevalence

The prevalence of 47,XXY is the most common sex chromosome disorder, currently estimated to affect approximately 1:650 males. 47,XXY (KS) is an underdiagnosed condition, as only 25% of all cases are diagnosed. Of those diagnosed, less than 10% of cases were diagnosed before puberty (Bojesen & Gravholt, 2007). However, 47,XXY may be prenatally diagnosed through cytogenetic analysis after amniocentesis or chorionic villus sampling. It may also be prenatally detected through noninvasive prenatal testing (NIPT) and then confirmed prenatally or postnatally. After pregnancy, 47,XXY may be diagnosed through a chromosome karyotype also performed by a blood sample or by a chromosomal microarray (CMA) test. A CMA test consists of a blood sample or oral cheek (buccal) swab. Cheek swab is an easy and painless way to detect abnormalities of chromosome numbers to provide a definitive diagnosis.

Physical features and natural history

Although 47,XXY is associated with a characteristic pattern of physical differences, the degree to which an individual is affected varies widely. Males with 47,XXY have been traditionally described as tall, with narrow shoulders, broad hips, sparse body hair, gynecomastia, small testes, and androgen deficiency. Post-pubertal males may manifest infertility, gynecomastia, lack of complete pubertal virilization, testicular failure, azoospermia and elevated gonadotropin levels, with decreased 17-ketosteroid levels. Studies investigating the efficacy of targeted administration of male hormones (androgens), such as testosterone enanthate, in boys with 47,XXY have shown to alleviate feminization effects that may have occurred due to insufficient testosterone levels, while also promoting the development of secondary male sexual characteristics. Other areas of increased risk developing over adulthood include low energy and libido, osteoporosis, thromboembolic disease, obesity, and diabetes mellitus. Recently, studies have demonstrated the positive effect of testosterone treatment on the well-being and neurocognitive profiles of boys with 47,XXY (Samango-Sprouse et al., 2013; 2018). Testosterone treatment in boys with 47,XXY

have also been shown to decrease anxiety and increase motor proficiency (Samango-Sprouse et al. 2013; 2015). Individuals with a mosaic form are often less affected and may have normal fertility.

Behavioral and psychiatric characteristics

Individuals with 47,XXY are at increased risk for behavioral problems and psychiatric disorders. Behavioral problems are variable in incidence—although the child with a prenatal diagnosis presents with fewer problems (Ross et al., 2012; Samango-Sprouse et al., 2013; 2015). Additionally, boys receiving early hormonal treatment in infancy or early childhood have fewer problems than the untreated child or the child postnatally diagnosed (Samango-Sprouse et al., 2015). School aged children frequently show problems with anxiety and mood dysregulation, self-esteem, and socialization. Socialization problems frequently relate to inhibition and anxiety, and they may become more pronounced during adolescence especially without hormonal treatment. Some of these problems may originate from frustration stemming from a relatively low expressive ability as compared to receptive skills (Simpson et al., 2003; van Rijn et al., 2006). Testosterone replacement therapy may minimize these neurodevelopmental dysfunction (Ross et al., 2014; Samango-Sprouse et al., 2011, 2013, 2015, 2018).

Neuropsychological characteristics

Emerging neuroimaging technology has increased and improved our understanding of the relationship among brain development, neurocognition, and behavioral outcome—especially in boys with 47,XXY (Giedd et al., 2007). Studies on boys with 47,XXY utilizing these neuroimaging techniques have revealed reduced total brain volumes that are specifically seen in the frontal, caudate, and temporal (especially left) regions of the brain (Giedd et al., 2007). Abnormalities in frontal and caudate brain MRIs are similar to those seen in MRIs of boys with ADHD, and indicative of the executive dysfunction seen in boys with 47,XXY (Giedd et al., 2007; van Rijn and Swaab, 2015). The temporal lobes are associated with language capacities involving reading, social language, and processing of spoken information—all of which are notably impaired in untreated males with 47,XXY (Shen et al., 2004; Savic, 2012). Abnormalities in the caudate nucleus are believed to adversely affect speech and language, as well as to manifest as the dyspraxia and oral motor dysfunction that is often found in 47,XXY boys (Giedd et al., 2007). The gray matter density in the insula region of the brain in these boys is also decreased, which is linked to social and emotional processing issues (Nagai et al., 2007). The parietal lobe, however, is relatively unaffected when measured by cortical thickness and volume (Giedd et al., 2007). The preservation of this region is evident in the enhanced spatial cognitive skills in males with 47,XXY (Samango-Sprouse and Law, 2001; Savic, 2012). Many 47,XXY males have normal or above average cognitive capacity with mean IQ values that fall within the normal to low normal range.

These neuroanatomical findings in 47,XXY boys have revealed several salient characteristics that are morphologically different from neurotypically developing peers. Several studies, however, have suggested that more normalized brain development is possible through the utilization of hormonal treatment (Patwardhan et al., 2000; Samango-Sprouse et al., 2015). Patwardhan et al. (2000) compared two groups of 47,XXY individuals (one receiving hormonal treatment therapy versus no treatment) and found that temporal gray matter was preserved in the treated group, but diminished in the untreated group. Further studies are warranted to confirm these findings and investigate whether other abnormal brain areas, as described above, show similar normalization after hormonal treatment therapy.

Available guidelines for behavioral assessments/treatment/management

Once the individual or fetus is diagnosed with 47,XXY, it is important to seek consultation with medical professionals and health care professionals who are familiar with 47,XXY for recommendations regarding

resources, appropriate biological and neurodevelopmental therapies, as well as medications for ADHD or anxiety. Early interventional therapies (e.g., physical, occupational, and speech therapies) are recommended throughout early childhood when discrepancies or deficits are identified to enhance early neurodevelopmental outcomes. Physical therapy is indicated when there is hypotonia, motor delay, and/or poor coordination and is most effective between 4 and 18 months in order to develop independent ambulation skills. Occupational therapy should be considered for the boys with decreased muscle tone in the trunk or upper body, because these deficits will affect handwriting, posture, attention, and eventual school success. This type of evaluation may be most beneficial between 4 and 6 years of age and typically is needed for 12 months. Specific speech and language therapies should address speech delays with motor planning deficits, language formulation abnormalities and syntactical delays. Because of decreased muscle tonus and androgen deficiency, an active health style is encouraged from infancy through adulthood. Androgen replacement therapy can improve bone density, increase muscle mass and strength, produce more masculine body contour, and decrease body fat. It can produce adequate pubertal maturation with increased body hair, penile enlargement, and male distribution facial and body hair.

Useful websites/associations for more information

- **The Association for X and Y Chromosome Variations (AXYS)**
<https://genetic.org/variations/about-47xxy/>
- **The Focus Foundation**
<http://thefocusfoundation.org/x-y-chromosomal-variations/xxx/>
- **Genetics Home Reference**
<https://ghr.nlm.nih.gov/condition/klinefelter-syndrome>
- **Genetic and Rare Diseases (GARD) Information Center**
<https://rarediseases.info.nih.gov/diseases/11920/47-xy>
- **Klinefelter's Syndrome Association UK**
<http://www.ksa-uk.co.uk/>
- **National Organization for Rare Disorders**
<https://rarediseases.org/rare-diseases/klinefelter-syndrome/>

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