



XYY Syndrome

First description and molecular biology

47,XYY; XYY syndrome; YY Syndrome; Jacob's syndrome. The first case of XYY syndrome was reported as an incidental finding by Adam Sandberg and colleagues in 1961. Four years later, Patricia Jacobs, a British geneticist, further researched this chromosome aneuploidy and described it in great detail; thus, the presence of an extra Y chromosome is also called Jacob's syndrome.

Genetics and molecular biology

The majority of cases of XYY syndrome are due to a paternal non-disjunction during meiosis II, following a normal meiosis I; a few cases resulting in an additional Y chromosome. In some cases, it arises during early embryogenesis in a post-zygotic mitotic error, in which case it can result in a 46,XY/47,XYY mosaic form (Robinson & Jacobs, 1999).

Incidence/prevalence

The prevalence of 47,XYY is currently estimated at approximately 1:1000 males. Since 47,XYY is typically not associated with marked phenotypic characteristics, it remains frequently under-detected with 90% of cases never diagnosed in their lifetime (Abramsky & Chapple, 1997). Of those diagnosed, most cases are diagnosed postnatally and late in life. 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) which then must be confirmed. Postnatally, 47,XYY may be diagnosed through a chromosome karyotype analysis performed by a blood sample or by a chromosomal microarray (CMA) test. A CMA test can consist of an oral cheek (buccal) swab or blood test. A cheek swab is an easy and painless way to detect abnormalities of chromosome numbers to provide a definitive diagnosis.

Physical features and natural history

Physical phenotypic differences associated with XYY syndrome are usually mild. Hypertelorism, macrodontia, pes planus, central adiposity, clinodactyly, larger head circumference than typically developing boys have been described (Bardsley et al., 2013; Lalatta et al., 2012). Speech delay is common. Delayed development of motor skills (such as sitting and walking), weak muscle tone (hypotonia), and behavioral and emotional difficulties are also frequent. Boys have increased growth velocity during childhood, and adult height is usually increased approximately 7cm (3") above what is expected. 47,XYY men are usually taller than 1.85m or 6 ft 5 inches, and the tall stature can be explained by the presence of additional copies of the SHOX gene (and possibly also other genes related to stature). Cystic acne may develop during adolescence. Asthma prevalence is greater in XYY than in the general population (Bardsley et al., 2013).

Puberty, testicular function, and fertility are usually normal (only a trend to macroorchidism has been signaled in early puberty), whereas boys with Klinefelter syndrome (KS) experience testicular failure.

Behavioral and psychiatric characteristics

Individuals with XYY syndrome may be at increased risk for behavioral problems and psychiatric disorders. There is a high rate of diagnosis of Attention Deficit Disorder (more marked than in 47,XXY (KS)), and increased risk of problems with distractibility, impulsivity, difficulties with temper management. Problems with social relatedness are also common. Individuals with XYY have been reported as having increased scores on measures of autistic spectrum disorders (ASD) symptoms however studies have been confounded by many factors. Further investigation is needed before a definitive answer can be given on the association of ASD and XYY.

Prenatal diagnosis was associated with higher cognitive function and less likelihood of an ASD diagnosis (Ross et al., 2015). Further, expression of NLGN4Y, a gene that may be involved in synaptic function, is increased in boys with XYY vs. XY controls (Ross et al., 2015).

Psychiatric diagnoses are more common in boys diagnosed postnatally and are often the reason these boys had karyotype evaluation (Bardsley et al., 2013). Risk for psychosis may be increased in men with 47,XXY (Verri et al., 2008).

Since the discovery of the 47,XYY karyotype, many studies have focused the relationship between a 47,XYY karyotype, aggressiveness, and deviance—attempting to associate this syndrome with criminal and deviant behavior. These studies, however, never reached statistical significance, and may be quite representative of the population due to selection bias.

Neuropsychological and neurological characteristics

47, XYY syndrome is usually associated with normal to slightly diminished cognitive function as measured with IQ; verbal IQ may be more affected than performance IQ. Many boys require speech therapy in their early years. Reading may be particularly affected. Difficulties with attention and impulse control are frequently reported.

47,XYY syndrome is associated to higher risk for seizures, focal epilepsy, and an electroclinical pattern characterized by focal spike and waves (similar to benign focal epilepsy) has been described in 47,XYY boys (Torniero, 2010).

Neuroimaging

Males with 47,XYY show increased total gray matter (GM) and white matter (WM) volume when compared to 46,XY and 47,XXY males (Bryant, 2012). Increased grey matter may be the result of reduced synaptic pruning, leading to altered synaptic function and perhaps increased seizure risk (Bardsley, 2013).

Voxel-based morphology (VBM) revealed that boys with 47,XYY have altered GM volume in the insular and parietal regions relative to neurotypically developing boys (Lepage et al., 2014). Alterations in gray matter volume may account for the reduced motor coordination typically seen in 47,XYY boys. VBM also found extensive WM modifications bilaterally in the frontal and superior parietal lobes in 47,XYY boys (Lepage et al., 2014). These white matter differences in the frontal and superior parietal lobes parallel a high prevalence of language-based learning difficulties, spatial orientation deficits, and graphomotor dysfunction characterized in the 47,XYY profile.

White matter volumes are typically larger in the frontotemporal region of the brain, which allows for efficient brain signaling and coordination between visual memories, language comprehension, and emotional association systems. Insular and frontotemporal gray and white matter is reduced in males with XYY, specifically in known language areas (Bryant et al., 2012). These patterns are distinctive and distinguishable from neuroanatomical patterns in typically developing boys and those with XXY. The patterns of regional gray matter and white matter variation in XYY boys are associated with deficits in motor and language abilities (Bryant et al., 2012). These studies further link brain development, behavior, and developmental outcome in another XY chromosomal disorder and provide a possible mechanistic support that X and Y chromosomes may differentially impact brain morphology.

Available guidelines of behavioral assessment/treatment/management

Once 47,XYY has been diagnosed, a comprehensive neurodevelopmental evaluation is important for the management of this syndrome. Occupational and physical therapy may be recommended for infants and young boys who have low muscle tone (hypotonia), and speech therapy may be needed for boys who have speech delay. Behavioral therapy or medication for boys may be prescribed for 47,XYY boys with ADHD and/or behavioral problems. Hormonal therapy may be also recommended to supplement development and growth.

Useful websites/associations for more information

- **The Association for X and Y Chromosome Variations (AXYS)**
<https://genetic.org/variations/about-xyy/>
- **The Focus Foundation**
<http://thefocusfoundation.org/x-y-chromosomal-variations/xyy/>
- **Genetics Home Reference**
<https://ghr.nlm.nih.gov/condition/47xyy-syndrome>
- **Genetic and Rare Diseases (GARD) Information Center**
https://rarediseases.info.nih.gov/diseases/5674/47-xyy-syndrome#ref_9860
- **National Organization for Rare Disorders (NORD)**
<https://rarediseases.org/rare-diseases/xyy-syndrome/>

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