SSBP Syndrome Sheets

47,XYY Syndrome

First description

47,XYY syndrome; Jacob's syndrome. The first case of 47,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 47,XYY syndrome are due to a paternal nondisjunction during meiosis II, following a normal meiosis I. In some cases, it arises during early embryogenesis in a postzygotic 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, the incidence of prenatal detection of 47,XYY may be increasing due to non-invasive prenatal screening (NIPS). Results of this screening should be confirmed prenatally (via amniocentesis or chorionic villus sampling) or postnatally (via chromosome karyotype analysis performed by a blood sample or by a chromosomal microarray). A chromosomal microarray (CMA) test can consist of an oral cheek (buccal) swab or blood test. A cheek swab is an easy and painless way to detect chromosomal abnormalities and provide a definitive diagnosis.

Physical features and natural history

Physical phenotypic differences associated with 47,XYY syndrome are usually mild. Hypertelorism (wide spaced eyes), macrodontia, pes planus (flat feet), central adiposity, clinodactyly, and larger head circumferences than typically developing boys have been described in boys with this disorder (Bardsley et al., 2013; Lalatta et al., 2012). Speech delays are common. Motor developmental delays in sitting and walking, decreased muscle tone (hypotonia), and behavioral and emotional difficulties may occur. Boys have increased growth velocity during childhood, and adult height is usually increased by approximately 7 cm (3 in) above what is expected (Aksglaede et al, 2008). 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 other genes related to stature). Cystic acne may develop during adolescence. Asthma

prevalence is greater in 47,XYY than in the general population (Bardsley et al., 2013).

For adolescents with 47,XYY puberty proceeds normally and there are typically no issues related to testicular function nor fertility, as opposed to boys with 47,XXY (KS) who experience testicular failure. A trend of macroorchidism has been noted during early puberty for boys with 47,XYY (Bardsley et al., 2013).

Behavioral and mental health characteristics

Individuals with 47,XYY syndrome may be at increased risk for behavioral problems and mental health issues. There is an increased rate of attention deficit hyperactivity disorder (ADHD) (more marked than in 47,XXY (KS)), and increased risk of challenges within classroom behavior. Problems with social interactions with peers and in confrontational situations are also common. Individuals with 47,XYY have been reported as having increased scores on measures of autistic spectrum disorders (ASD) symptoms, however, previous studies have been confounded by many factors. Further investigation is necessary before a definitive answer can be given on the association of ASD and 47,XYY. ASD is a highly inheritable genetic disorder; therefore, multigenerational family histories should be completed in order to determine familial risk for ASD.

Prenatal diagnosis is associated with higher cognitive function and less likelihood of an ASD diagnosis (Ross et al., 2015). Further, the expression of NLGN4Y, a gene that may be involved in synaptic function, is increased in boys with 47,XYY when compared to the neurotypical 46,XY controls (Ross et al., 2015). The importance of this finding has not been determined in the neurodevelopment of the boy with 47,XYY.

Developmental delays, behavioral dysfunction, and mental health disturbances may be more common in boys diagnosed postnatally and are often the reason these boys had a chromosomal evaluation (Bardsley et al., 2013). Since the discovery of the 47,XYY karyotype, many early studies have focused on the relationship between a 47,XYY karyotype, aggressiveness, and behavioral disturbances —attempting to associate this syndrome with a characteristic profile. However, these studies are not scientifically sound due to selection bias and small samples. Additionally, 90% of the boys with 47,XYY are unidentified, therefore, the developmental and behavioral profile of these boys is largely unknown and requires further investigation.

Neuropsychological and neurological characteristics

47,XYY syndrome is usually associated with a normal IQ. However, verbal IQ may be more affected than performance IQ. There is an increased incidence of reading disorders in boys in 47,XYY which is highly associated with early speech delay.

Many boys require speech therapy in their early years, as they exhibit a speech delay. The incidence of learning disabilities in boys with 47,XYY are increased, with reading and written language skills particularly affected. Difficulties with attention and impulse control are frequently reported and are characteristic of ADHD.

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 white mattermodifications 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 (specifically dyslexia), spatial orientation deficits, and graphomotor dysfunction/dysgraphia 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 47,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 47,XXY (KS). The patterns of regional gray matter and white matter variation in 47,XYY boys are associated with deficits in motor and language abilities (Bryant et al., 2012). These studies further link brain development, behavior, and developmental outcomes in another XY chromosomal disorders and provide a possible mechanistic support that X and Y chromosomes may differentially impact brain morphology.

47,XYY syndrome is associated with higher risk for seizures, focal epilepsy, and an electroclinical pattern characterized by focal spike and waves (similar to benign focal epilepsy (Torniero, 2010). Males with 47,XYY show increased total gray matter and white matter volume when compared to 46,XY and 47,XXY (KS) males (Bryant, 2012). Increased gray matter may be the result of reduced synaptic pruning, leading to altered synaptic function and possible increased seizure risk (Bardsley, 2013).

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 (Samango-Sprouse & Gropman, 2016). 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 a speech delay. Speech therapy should focus on eliminating the underlying oral motor weakness and dysfunction through a targeted approach . In the school setting, assistance from special educators or individualized education programs (IEPs) will be helpful to address challenges with executive dysfunction, reading disorders, ADHD, or other disabilities.

Behavioral therapy or medication for boys may be prescribed for 47,XYY boys with ADHD and/or behavioral problems. In some cases, acne treatment may be beneficial in boosting self-confidence. 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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