XXYY Syndrome Summary

Epidemiology
There is an estimated incidence of 48,XXYY in 1/18,000 to 1/50,000 male births.

Clinical description
48,XXYY syndrome is often described as a variant of Klinefelter syndrome (see term) as it shares a similar physical phenotype (tall stature and small, dysfunctional testes), however the medical and neurodevelopmental features are more complex than typically seen in 47,XXY/Klinefelter syndrome. There is an increased risk for congenital heart defects, renal abnormalities, and non-specific dysmorphic features (epicanthal folds, hypertelorism, clinodactyly). In infancy and early childhood, hypotonia is frequently observed and can be associated with motor delays, flat feet, and plagiocephaly (occipital flattening). Skeletal abnormalities including club foot, radioulnar synostosis, prominent elbows with cubitus varus, scoliosis, and kyphosis can be present. Many medical conditions are more frequent in 48,XXYY syndrome including epilepsy (~15%), tremor (~60% of adults), asthma/allergies (~60%), strabismus (~15%), scoliosis (~25%), significant dental problems (~90%), gastrointestinal problems (feeding intolerance, reflux, constipation), thrombosis (~18%), and type 2 diabetes (~20% in adulthood). Testicular hypogonadism is nearly universal starting in adolescence and persisting in adulthood. Hypogonadism is associated with low testosterone production and infertility. Cryptorchidism, micropenis, and gynecomastia have been reported but are not present in the majority.

48,XXYY syndrome also presents with more significant cognitive impairments and behavior challenges compared to 47,XY. Developmental delays are often present in the first 3 years of life in the areas of speech and motor development. Overall cognitive abilities tend to be in the borderline range (70 – 80) with approximately 1/3 of males with 48,XXYY with full scale IQ in the intellectual disability range. A pattern of significantly lower verbal reasoning skills learning disabilities are often present (e.g., specific learning disability in reading). Relative to IQ, adaptive functioning is significantly impaired, with common deficits in communication, social skills, self-care, and self-direction.

Behavioral characteristics can include executive function impairments (e.g., organizational skills), difficulties with attention, impulsivity, and hyperactivity. Attention-deficit/hyperactivity disorder (ADHD) is often diagnosed. Mood instability, anxiety, obsessive-compulsive behaviors, and emotional immaturity are also characteristic of 48, XXYY. Additional challenges include nail biting, sugar cravings, and strong interests. There is increased risk for social difficulties, including difficulties in social skills, reciprocal social interactions, and insight into social relationships. As a result, there is an increased risk for autism spectrum disorder (ASD), and approximately half of males with 48,XXYY met DSM-5 criteria for ASD in a research study.

Etiology
48,XXYY syndrome results from nondisjunction events of sex chromosomes primarily during spermatogenesis (meiosis I and/or meiosis II) or less often from post-zygotic mitotic
nondisjunction during cell division. There are no commonly known factors predisposing to the specific occurrence of these nondisjunction events resulting in 48,XXYY.

**Diagnostic methods**

48, XXYY is most commonly identified by a standard karyotype or chromosomal microarray (CMA) performed on peripheral blood, amniotic fluid or buccal swab. Fluorescence In Situ Hybridization (FISH) is another approach to investigate the presence of extra copies of chromosomes X and Y, yielded on a larger sample of cells. Although prenatal diagnosis occurs, 48,XXYY is currently most commonly diagnosed during childhood during evaluation of physical and/or developmental concerns that warrant genetic testing. A 2008 study looking at 95 males with 48, XXYY syndrome reported the mean age of diagnosis to be 7.7 years of age.

**Differential diagnosis**

Hypergonadotropic hypogonadism can be seen in other male sex chromosome aneuploidies including Klinefelter (47,XXY) syndrome, 48,XXXY syndrome and 49,XXXXY syndrome (see these terms) as well as 45,X/46,XY mosaicism and 46,XX sex reversal. Other genetic conditions that may have overlap with some of the features seen in 48,XXYY syndrome include Fragile X Syndrome, Jacob syndrome, Prader Willi Syndrome, Soto syndrome, Börjeson-Forssman-Lehman Syndrome, Weaver syndrome, Cohen syndrome.

**Antenatal diagnosis**

Antenatal diagnosis of 48, XXYY is possible by screening and/or diagnostic testing of chromosomes in fetal tissue. Noninvasive Prenatal Screening (NIPS) analyzes maternal peripheral blood for small fragments of cell-free fetal DNA, which is then processed through an algorithm to determine if there is an increased risk for chromosome aneuploidy in the fetus during pregnancy. The positive predictive value for identifying 48,XXYY by NIPS is highly variable and ranges from 30-80%, with the recommendation for diagnostic testing to confirm a screen positive result. Diagnostic testing is directly performed on fetal DNA obtained by amniocentesis or chorionic villus sample (CVS), which is then analyzed by a standard karyotype, chromosomal microarray (CMA), and/or Fluorescence In Situ Hybridization (FISH) to determine the number and structure of chromosomes in the fetus during pregnancy.

**Genetic Counseling**

48,XXYY is a rare condition typically due to a sporadic aneuploidy event with an estimated recurrence risk of <1% (may be higher for cases of advanced maternal age). Genetic counseling for this condition should include a review of the possible and highly variable physical, medical, developmental and psychological features of 48,XXYY. Prenatal counseling should address the accuracy of prenatal screening (if applicable) and the importance of confirmatory diagnostic testing, either before and/or after birth. Postnatal confirmatory testing is recommended to ensure the diagnosis accurate and properly documented in the patient’s medical record. Pediatric patients should be counseled for presenting features likely attributed to 48,XXYY and provided recommendations for further evaluation and potential treatment for possible medical, developmental and psychological features as the child develops. Counseling discussions should also address possible unexpected distressing problems associated with the diagnosis (ie.
Management and treatment
Comprehensive interdisciplinary care is important to evaluate for and manage developmental, medical, and psychological conditions that may be associated with 48,XXYY syndrome. At diagnosis, a thorough physical exam, renal ultrasound and echocardiography should be performed to evaluate for congenital defects. Vision and hearing screening and routine dental care are important throughout the lifespan. Starting around age 10, pubertal examinations and serum hormone profiles should be monitored by endocrinology, and testosterone supplementation should be considered when evidence of hypogonadism is present. Routine screening for hyperlipidemia, diabetes, and autoimmune thyroid disease is recommended starting in adolescence. Symptoms suggestive of any associated medical comorbidities should be promptly evaluated and treated as appropriate.

The neurodevelopmental and behavioral phenotype in 48,XXYY warrants a comprehensive interdisciplinary evaluation to include psychological functioning (cognitive, learning, executive, social, emotional, and behavioral functioning), speech/language skills, motor skills, and self-care skills. For infants and young children, close developmental screening is important identify delays and the need for early intervention therapies. Further, speech-language therapy to target developmentally-appropriate goals around oral-motor planning deficits, apraxia of speech, expressive and receptive language skills, and pragmatic language may be necessary through early adulthood. Occupational and/or physical therapies to target decreased motor skills, dyspraxia, coordination, sensory sensitivities, and overall self-care are also often warranted.

Documentation of comorbid psychological diagnoses (such as learning or intellectual disability, ADHD, anxiety, and/or autism spectrum disorder) is important for qualification and access to community-based services. Interventions are recommended when psychological diagnoses are present, and treatments for emotional and behavioral disorders should be evidence-based, individualized, and chosen with consideration of language deficits, learning disabilities, and comorbid diagnoses. Social skills therapy can also address difficulties with social understanding, relationships, and pragmatics. Services that are tailored to developmental disability or ASD population and delivered by providers who specialize DD and/or ASD are often a good fit for 48,XXYY. School-based supports including services outlined by an Individualized Education Plan (IEP) are most often a part of the treatment plan, and evidence-based interventions for learning disabilities do not differ from those used with the general population. Through adolescence and early adulthood, adaptive skills, transition services, and community-based supports are important areas of focus.

Consultation with other medical specialists including developmental pediatrics, psychiatry, and/or neurology may also help to develop treatment plans and provide medication management. Psychopharmacologic medications, in conjunction with behavioral therapy, may
be warranted for behavioral and emotional symptoms. Positive response to standard medication treatments for internalizing and externalizing symptoms is seen in 48,XXYY.

**Prognosis**
While there is no cure for 48,XXYY syndrome, most individuals will have a normal life expectancy with appropriate treatment for associated medical and psychiatric conditions. Health-related quality of life varies depending on the severity of symptoms. Cognitive functioning, impairments in adaptive behavior, and psychiatric concerns contribute largely to adult outcomes, including degree of independence and quality of life. Long-term outcomes are improved with consistent access to appropriate health care and additional services, including school and community supports, therapies, and medication management.

**Authors:**
Susan Howell, MS, CGC, Shanlee Davis, MD, Adrienne Villagomez, PhD, , Catherine Buchanan, BS, Nicole Tartaglia, MD. University of Colorado School of Medicine, Children’s Hospital Colorado.