R.C.P.U. NEWSLETTER

R.C. Philips Research and Education Unit

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A statewide commitment to the problems of mental retardation June 2020

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Sex Chromosome Abnormalities

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Introduction

A person's sex complement determines human sexual differentiation. Females typically have two X chromosomes and males have a single X chromosome and a single Y chromosome; any numerical divergences from these complements can cause sex chromosome abnormalities. These typically result from nondisjunction events in the formation of egg or sperm cells in the parents, although they can also occur due to nondisjunction in one of the early post-conception cell divisions. Abnormalities in sex chromosomes can cause several conditions, including Turner Syndrome, Trisomy X, Klinefelter Syndrome, 47, XYY, and 48, XXXY. This article provides a brief history of these conditions, general information about their clinical features, methods of diagnosis, and the latest advances in research and treatment.

Turner Syndrome (Monosomy X)

In 1938, Dr. Henry Turner was the first to describe a group of female patients who shared the clinical features of a condition that was later named Turner Syndrome. The condition, which affects females with a missing or altered X chromosome in their cells, may occur as a result of:

- Monosomy - the absence of an X chromosome due to an error in the sperm or the egg
- Mosaicism - an error in cell division in early pregnancy, where some cells have the normal number of cells and some have only one X chromosome.
- X chromosome abnormalities - abnormal or missing parts of the X chromosome
- The presence of part of an X chromosome along with Y chromosome material in some cells

About 1 in 2,500 newborn girls are born with Turner syndrome, although Turner syndrome is also a common cause of pregnancy loss. Genetic testing during pregnancy, either by Noninvasive Prenatal Screening (NIPS), amniocentesis or Chorionic Villus Sampling (CVS), may reveal the presence of the condition, and a prenatal ultrasound may identify heart or kidney malformations or extra fluid at the back of the neck. At birth, newborns with Turner syndrome may have a broad neck, with low hairline and low-set ears (Figure 1), edema of the backs of the hands and tops of the feet (Figure 2), and a broad chest with widely-spaced nipples. Heart defects and renal malformations are common and cause serious complications.

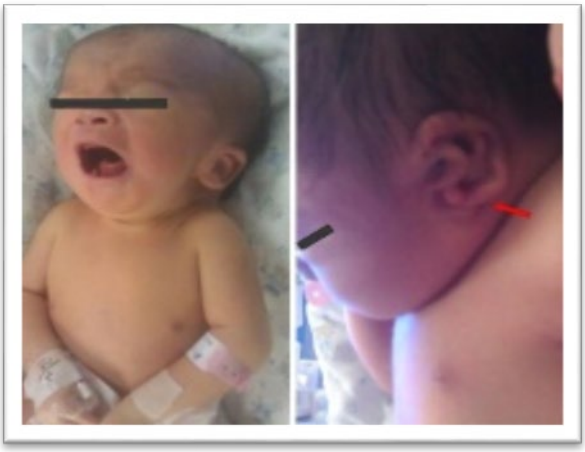

Figure 1. Low-set placement or abnormal formation of the ears are seen in some girls with Turner Syndrome

Figure 2. Swelling of the feet, a clinical feature of some girls with Turner Syndrome

The hallmark signs of Turner Syndrome are delayed linear growth, which leads to lesser than average height, and abnormal functioning of the ovaries, which leads to infertility and delayed or absent pubertal signs if treatment is not initiated. Treatments

include growth hormone therapy to increase height and maximize bone growth, as well as hormone therapy to assist with secondary sexual development. Visual and spatial learning problems are common in girls with Turner syndrome and can lead to difficulties with math, riding a bike, or driving.
Currently, researchers are examining heart defects in adult women with Turner syndrome that might put them at risk for complications. In addition, researcher are working to develop a newborn screening test to increase the number of girls with Turner syndrome who are diagnosed at an early age. For more information, see https://www.nichd.nih.gov/health/topics/turner/researchinfo/activities.

Trisomy X (XXX)
In 1959, Dr. Patricia Jacobs examined a female patient who was experiencing early menopause. On examination of her karyotype, Jacobs found that the patient had three X chromosomes in her cells instead of the usual two (Figure 3). It is estimated that approximately 1 in 1,000 newborn girls have Trisomy X, but only around 10 percent are diagnosed because symptoms are usually mild. Females with the condition are typically taller than average and may experience delays in speech-language and motor development; they may also have difficulty learning in school. Some studies (Wigby et al., 2016) show that girls who are diagnosed before they are born have improved outcomes because they receive early intervention. Girls with Trisomy X benefit from physical therapy to increase muscle tone and strength and speech and language therapy to reduce deficits in oral and written language skills. Current research focuses on assessing development over time in girls with Trisomy X, and identifying early markers of behavioral problems to increase the likelihood of early intervention and treatment. For more information, see https://medschool.cuanschutz.edu/pediatrics/sections/developmental-pediatrics/extraordinary-kids-program/our-research.

Klinefelter Syndrome (XXY)
In 1942, Dr. Harry Klinefelter was the first to describe a group of patients who shared the clinical features of a condition that was later named Klinefelter Syndrome. Klinefelter Syndrome affects males with an extra X chromosome in their cells. Approximately 1 in every 500 newborn boys have Klinefelter syndrome. About 10% of individuals with Klinefelter syndrome are diagnosed by prenatal testing. Often the diagnosis is not made until adolescence or adulthood, when abnormalities in sexual development or infertility are noted. Until then, boys with Klinefelter syndrome often appear normal, except for possible delays in speech-language and motor development. However, during puberty, the primary symptom of Klinefelter syndrome—a decrease in testosterone production—becomes evident as it leads to enlarged breast tissue (Figure 4), smaller than normal testicles, and a decrease in muscle mass and facial/body hair. Men with Klinefelter syndrome are very frequently infertile and taller than average, and nearly half have a metabolic syndrome, which is characterized by type 2 diabetes, hypertension, and high levels of fat in the belly and blood. Males with Klinefelter syndrome are also at increased risk for a variety of learning and mental health problems, such as ADHD, anxiety, and depression. A variety of symptom-specific treatments are available, including: surgical removal of breast tissue, speech and physical therapy, hormone therapy, and counseling. Researchers are currently working to better understand the different ways genes are expressed in males with the disorder. This understanding may lead to new approaches to treatment, such as the optimal timing for testosterone replacement therapy, or advanced fertility treatments that allow men with Klinefelter Syndrome to have children. For more information, see https://www.nichd.nih.gov/health/topics/klinefelter/researchinfo/activities.

47,XYY
In 1961, Dr. Avery Sandberg described a 44-year old male patient with an extra Y chromosome in his cells. The condition, which became known as 47,XYY affects approximately 1 in 1,000 newborn boys each year. However, because many affected males have no symptoms other than tall stature, 47,XYY is diagnosed in less than 10 percent of cases, often during routine prenatal testing. Male infants and toddlers with the condition have a higher risk of learning disabilities and may experience delays in speech, language, and motor development. As they grow older, males with the condition may show physical signs, such as flat feet, large teeth, low muscle tone, widely-spaced eyes, abnormal curvature of the spine, and fifth fingers that curve inward.

They may also experience symptoms of anxiety, depression, autism spectrum disorder, and attention-deficit/hyperactivity disorder. Boys affected by 47,XYY may benefit from early intervention that includes speech, behavioral, and physical therapy as well as help for any learning disabilities that may arise in school. Currently, researchers are working to better understand learning and brain development among children with 47,XYY syndrome and the effects of diagnosis of XYY on quality of life. For more information, see https://genetic.org/about/research/opportunities-for-families/.

48, XXXY
In 1959, Dr. Murray Barr described three male patients who had two extra X chromosomes (3 total) in their cells. The condition, which was named 48,XXXY, affects between 1 in 17,000 and 1 in 50,000 newborn boys. Many males with the condition have lower than average IQs, severe deficits related to speech and language, and delayed development of motor skills. Abnormal sexual development also leads to infertility and a small penis and testes. Males with 48,XXXY are typically taller than average, and they may have unique facial features.
Boys affected by the condition can benefit from early interventions by a team of specialists that may include cardiologists, orthopedists, speech therapists, psychologists, neurologists, and endocrinologists, depending on their complications.

Family Support
Family support groups are vital to providing mental, emotional, and financial support to parents who have a child with chromosomal abnormalities. The following is a list of the largest and most active family support groups available:

- The Association for X and Y Chromosome Variations (AXYS) – AXYS has both national and international support groups that serve people with X and Y chromosome variations as well as support groups that serve people with specific chromosome

conditions.
https://genetic.org/im-medical-professional/support-groups/

- Triple X Support Group – This support group provides support, resources, and information to caregivers of children with Triple X Syndrome.
https://rarediseases.org/organizations/triple-x-support-group/
- Turner Syndrome Society of the United States – This organization provides an active network program for individuals affected by Turner Syndrome and refers them to support and treatment.
https://www.turnersyndrome.org/
- The American Association for Klinefelter Syndrome Information and Support – This association has regional support groups available to help individuals affected with Klinefelter Syndrome and their caregivers.
http://www.aaksis.org/
- The Focus Foundation – This foundation helps children and families who are affected by X & Y chromosome variations by facilitating early identification, intervention, and treatment.
https://thefocusfoundation.org/

Selected Resources

- Centers for Disease Control and Prevention – Data and Statistics on Birth Defects:
https://www.cdc.gov/ncbddd/birthdefects/data.html
- Mayo Clinic – Amniocentesis:
https://www.mayoclinic.org/tests-procedures/amniocentesis/about/pac-20392914
- National Institutes of Health – Turner Syndrome (Monosomy X)
https://ghr.nlm.nih.gov/condition/turner-syndrome
- National Institutes of Health –Trisomy X
https://ghr.nlm.nih.gov/condition/triple-x-syndrome
- National Institutes of Health – Klinefelter Syndrome
https://ghr.nlm.nih.gov/condition/klinefelter-syndrome
- National Institutes of Health – 47,XYY
https://ghr.nlm.nih.gov/condition/47xyy-syndrome
- National Institutes of Health – 48, XXXY
https://ghr.nlm.nih.gov/condition/48xxxy-syndrome
- National Institutes of Health – Non-Invasive Prenatal Testing: https://ghr.nlm.nih.gov/primer/testing/nipt
- National Institutes of Health – Newborn Screening Procedures
https://ghr.nlm.nih.gov/primer/newbornscreening/nbsprocedure

References

Bearelly P, Oates R. Recent advances in managing and understanding Klinefelter syndrome. F1000Research. 2019;8.
Berglund A, Stochholm K, Gravholt CH. The epidemiology of sex chromosome abnormalities. Am J Med Genet C Semin Med Genet. 2020 Jun 7 – online ahead of print.
Shankar RK, Backeljauw PF. Current best practice in the management of Turner syndrome. Therapeutic Advances in Endocrinology and Metabolism. 2018 Jan;9(1):33-40.
Tartaglia N, Ayari N, Howell S, D'Epagnier C, Zeitler P. 48, XXYY, 48, XXXY and 49, XXXXY syndromes: not just variants of Klinefelter syndrome. Acta Paediatrica. 2011 Jun;100(6):851-60.
Tartaglia NR, Howell S, Sutherland A, Wilson R, Wilson L. A review of trisomy X (47, XXX). Orphanet Journal of Rare Diseases. 2010 Dec 1;5(1):8.
van Rijn S, Swaab H. Executive dysfunction and the relation with behavioral problems in children with 47, XXY and 47, XXX. Genes, Brain and Behavior. 2015 Feb;14(2):200-8.
Wigby K, D'Epagnier C, Howell S, Reicks A, Wilson R, Cordeiro L, Tartaglia N. Expanding the phenotype of Triple X Syndrome: A comparison of prenatal versus postnatal diagnosis. Am J Med Genet A 170(11):2870-2881, 2016.

About the RCPU

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects.
Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health.

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