



# SEX CHROMOSOME VARIATIONS

BY VIRGINIA  
ISAACS COVER,  
MSW, MBA

**M**ark had always had challenges. As a toddler, he had speech and physical therapy through Early Intervention to address delays in meeting milestones. Although he managed to earn B's and C's in elementary school with the assistance of 504 accommodations, by Fifth grade he was falling behind, academically and socially. A developmental pediatrician diagnosed ADHD.



**EXTRAORDINARY:** In contrast to most human trisomies, such as Down syndrome (Trisomy 21) or Edwards syndrome (Trisomy 18), that cause significant intellectual disability and medical complications, X and Y variations cause milder developmental delays.

Six months later, the school psychologist suggested an evaluation for autism spectrum disorder. Testing found Mark to score high on a number of domains, just barely missing the autism range. By Eighth grade, he admitted to feeling depressed and “different.” At a pediatrician visit, the doctor asked his mother to leave the room, and began examining Mark. Mark opened up to the doctor about his fears that his body wasn’t changing. The doctor noticed that his testicles were abnormally small and firm, and that Mark had not developed increased body hair distribution consistent with progress through puberty. He called Mark’s mother into the room and suggested that a specialized genetic test might explain Mark’s difficulties. Three weeks later, the pediatrician called Mark and his parents to tell them that the testing revealed that he had Klinefelter syndrome, or an extra X chromosome in a male.

In her first pregnancy, Jeanne was offered “non-invasive prenatal testing,” also called “cell free DNA testing”. This testing can determine the probability that a human fetus has additional chromosomes beyond the expected 46. Although Jeanne thought that her baby-to-be was being tested for Down syndrome or other significant disabilities, her obstetrician phoned her to let her know that the fetus had a high probability of having Trisomy X, or an extra X chromosome in a female.

Klinefelter Syndrome and Trisomy X are known as sex chromosome aneuploidy, or variations in the typical number of chromosomes. Instead of having two sex chromosomes, an X and Y in a male, or two X’s in a female, Jeanne’s baby-to-be and Mark had three, known as a “trisomy”. Klinefelter syndrome is also known by the genetic signature of 47,XXY. Trisomy X is written as 47,XXX.

X and Y variations are surprisingly common. One male in 600 is born with Klinefelter syndrome. One female in each 1000 live births has Trisomy X. A male can also have an extra Y chromosome, known as XYY syndrome. Less common variations involve two or more extra sex chromosomes, including 48, XXYY. X and Y chromosome variations occur more often than Down syndrome.

In contrast to most human trisomies, such as Down syndrome (Trisomy 21) or Edwards syndrome (Trisomy 18), that cause significant intellectual disability and med-

ical complications, X and Y variations cause milder developmental delays. There is little dysmorphia, unusual facial and physical features that mark the conditions. Even when the child displays a whole constellation of speech, learning and other developmental delays, such as autism spectrum disorder, pediatricians do not often think of genetic disorder and test for an extra chromosome.

X and Y variations remain relatively unknown, both to the general public as well as within the health professions. Individuals with X and Y variations display a wide range of functioning, from having no symptoms at all to those who are severely impacted and require life-long support services. Less than one-third are ever properly diagnosed in their lifetimes.

Mark and his parents learned that Klinefelter syndrome (47,XXY) is the most common of the sex chromosome aneuploidy conditions. Although some boys with XXY experience few challenges, at least two thirds will have early speech delay, fine and gross motor skill deficits, learning disabilities, ADHD, and some degree of social skill impairment. Mood disorders, such as depression, are more common in X and Y variations. XXY boys tend to be taller than normal, and to have long limbs, although this is not always the case. Approximately 20 percent will meet the criteria for autism spectrum disorder, although it will be mild. Many have expressive language skill impairment, and subtle difficulty with reading social cues. This may be why teachers will often describe these boys as immature. It also appears that men with XXY take longer to achieve independence in adulthood, to complete their educations, and to become established in careers.

Although many boys will start puberty normally, the extra X chromosome interferes with the body’s ability to produce testosterone. Puberty may stall, and need to be helped along with supplemental testosterone. Although boys with XXY will usually produce some sperm in their teen years, this falls off dramatically by early adulthood. Men with Klinefelter syndrome are almost all infertile. Within the last decade, however, assisted reproduction techniques have allowed a number of XXY men to become biological parents. XXY teens are also being offered the option of providing sperm samples that can remain frozen until needed to produce a pregnancy.

Mark was referred to a pediatric endocrinologist. He and his parents, along with his doctor, decided that treatment with testosterone was appropriate. He started with testosterone injections every 10 days. Disliking shots, however, Mark soon began using testosterone gel daily. He began developing a beard and a deeper voice even as he entered a growth spurt and grew to be 6' 4" tall.

Jeanne and her husband were referred to a genetic counselor who explained that the prenatal blood test results only predicted with a fair amount of certainty that their daughter would have Trisomy X. If they wanted to know definitively before birth, Jeanne would have to undergo amniocentesis, an invasive test using a nee-



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dle through the uterine wall to draw out a sample of amniotic fluid. The fetal cells are then tested to determine if they contain an extra X chromosome. The genetic counselor explained that girls with Trisomy X often have speech delays in early childhood, may be slower to walk and develop motor skills, and frequently have learning disabilities. Approximately two-thirds of girls will need special education services. While their fertility may be reduced somewhat, and they may experience premature ovarian failure, women with Trisomy X have few health care complications. Most women with 47,XXX, live fairly normal lives, although the risk of mood disorder is somewhat higher.

The genetic counselor also mentioned to Jeanne that termination of the pregnancy was an option. The couple did not think that the relatively mild disabilities the counselor was discussing with them would merit a second trimester abortion. They also decided to wait until their baby was born to confirm the diagnosis with a simple blood test.

The challenge for parents of children with one of these common genetic disorders is that few health care providers or educators are familiar with the diagnoses. Parents often have to describe the condition as "like Asperger syndrome" or "ADHD, learning disabilities, low muscle tone and poor coordination, all wrapped up together."

As more children are diagnosed prenatally, due to the ease of newly available non-invasive testing, it is expected that schools and pediatricians will understand the disorders and the symptoms associated with them.

Mark's mother discovered AXYS, the national organization for advocacy and education for those with X and Y variations. She obtained educational materials from the AXYS website, [www.genetic.org](http://www.genetic.org). She and Mark traveled to an AXYS Family Conference, where they met others with similar concerns. The conference featured national experts in X and Y variations, in disciplines like endocrinology, psychiatry and special education. They learned that AXYS was in the process of developing a Clinic and Research Consortium comprised of eight academic medical centers offering multidisciplinary evaluation and treatment recommendations.

Mark and his parents visited Denver for an evaluation at the EXtraordinaryY Kids Clinic at Colorado Children's Hospital, one of the member clinics. With the written report provided after several days of exams and neuropsychological testing at the clinic, Mark was able to obtain an IEP (Individualized Education Plan) that addressed his need for additional special education services in high school. Mark graduated on schedule and is progressing through community college part-time. His college provides special accommodations for his learning disabilities that include a note-taker, additional time for tests and regular tutoring. He is also an accomplished golfer, playing on the community college team. Mark credits the pediatrician who suspected and tested him for Klinefelter syndrome with turning his life around so that he could obtain the medical treatment and specialized learning services that he required.

**A**fter Jeanne's baby, Arianna, was born, a blood test confirmed the diagnosis of Trisomy X. Arianna's development was normal until she reached 18 months, when the pediatrician recommended an early intervention evaluation for speech and motor delays. Arianna made substantial progress with speech and physical therapy, making up for most of her delay. She then entered kindergarten in a mainstream class, with speech and occupational therapy services. She is very shy and attends a social skills group to help her develop conversational abilities and friendships. Her mother has her followed every six months at one of the multi-specialty X and Y variation clinics. She is a quiet but happy little girl, and her parents are very glad that they had an awareness of the extra chromosome so that they could access special services immediately— rather than waiting for additional delay to develop. • *(Editor's note: Mark's and Arianna's names have been changed to protect their privacy.)*

#### ABOUT THE AUTHOR:

Virginia Isaacs Cover, MSW, MBA, has worked with children and adults with developmental disabilities and chronic medical conditions throughout her career in healthcare agencies and universities. Now retired, Ms. Cover maintains a private practice assisting young adults and their families in developing and managing self-determination supports to permit them to live and work in the community rather than in segregated settings. She is the parent of a young adult who has Klinefelter syndrome. She serves as a Board Member for AXYS as well as a member of the AXYS Professional Advisory Board. She is the author of the book, "Living with Klinefelter Syndrome, Trisomy X and 47, XYY: [www.genetic.org/wp-content/uploads/2016/08/LivingWithKlinefelter\\_SyndromeTrisomyX47XYY.pdf](http://www.genetic.org/wp-content/uploads/2016/08/LivingWithKlinefelter_SyndromeTrisomyX47XYY.pdf)

#### X AND Y VARIATION RESOURCES



Please visit AXYS, the national organization for X and Y Variation advocacy and education at [www.genetic.org](http://www.genetic.org). The website includes information on genetic conditions involving extra X and Y chromosomes, support groups, the AXYS Clinic Consortium, and current research. There is a toll free Help Line, 888-999-9428.