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## Sex Chromosome Aneuploidies

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### 1. Introduction

Sex chromosome aneuploidy is defined as a numeric abnormality of an X or Y chromosome, with addition or loss of an entire X or Y chromosome. Sex chromosome mosaicism, in which one or more populations of cells have lost or gained a sex chromosome, also is common. The most commonly occurring sex chromosome mosaic karyotypes include 45,X/46XX, 46XX/47,XXX, and 46,XY/47,XXY. Less frequent are those sex chromosome abnormalities where addition of more than one sex chromosome or a structural variant of an X or Y chromosome occur.

The X chromosome is one of the two sex-determining chromosomes in many animal species, including mammals and is common in both males and females. It is a part of the XY and XO sex-determination system. The X chromosome in humans represents about 2000 out of 20,000 - 25,000 genes. Normal human females have 2 X-chromosomes (XX), for a total of nearly 4000 "sex-tied" genes (many of which have nothing to do with sex, other than being attached to the chromosome that is believed to cause sexual bimorphism (or polymorphism if you count more rare variations). Men have, depending on the study, 1400-1900 fewer genes, as the Y chromosome is thought to have only the remaining genes down from an estimated 1438 -~2000 (Graves 2004).

The Y chromosome is the other sex-determining chromosome in most mammals, including humans. The Y chromosome likely contains between 70 and 200 genes. Because only males have the Y chromosome, the genes on this chromosome tend to be involved in male sex determination and development. Sex is determined by the SRY gene, which triggers embryonic development as a male if present. Other genes on the Y chromosome are important for male fertility. Many genes are unique to the Y chromosome, but genes in areas known as pseudoautosomal regions are present on both sex chromosomes. As a result, men and women each have two functional copies of these genes. Many genes in the pseudoautosomal regions are essential for normal development.

Given that the X chromosome carries more than one thousand genes it is surprising that individuals with X chromosome aneuploidies survive and may reproduce. The reason

appears to be that, according to the Lyon hypothesis, one of the two X chromosomes in each female somatic cell is inactivated genetically early in embryonic life (on or about day 16), that means that genes are expressed from only one of the two X chromosomes. This can be understood as “dosage compensation” between males and females that ensures that genes on the X are expressed to approximately the same extent in either sex.

Whether the maternal or paternal X is inactivated, usually is a random event within each cell at the time of inactivation; that same X then remains inactive in all descendant cells. The result of X inactivation is that all normal females are mosaics with regard to this chromosome, meaning that they are composed of some cells that express genes only from the maternal X chromosome and others that express genes only from the paternal X chromosome.

It is hypothesized that there is an autosomally-encoded 'blocking factor' which binds to the X chromosome and prevents its inactivation. The model postulates that there is a limiting blocking factor, so once the available blocking factor molecule binds to one X chromosome the remaining X chromosome(s) are not protected from inactivation. This model is supported by the existence of a single Xa in cells with many X chromosomes and by the existence of two active X chromosomes in cell lines with twice the normal number of autosomes.

The rule is that one X remains active, and extra X's are inactivated. Why then does the absence or presence of an extra X have any effect? The explanation appears to be that the small class of genes that is present on both X and Y chromosomes in the pseudoautosomal regions is protected from inactivation on the inactive X in females. Again this can be seen as a compensatory mechanism ensuring equivalence of gene dosage in males (XY) and females (XX). But when the number of sex chromosomes is increased above two or decreased to one, it is the genes that are present on both the X and the Y that are abnormally expressed.

Thus the phenomena of sex chromosome aneuploidy point to the selective involvement of X-Y homologous genes: the features of Klinefelter's and Turner's syndrome etc are attributable to this small class. For example the changes in stature are almost certainly due to the expression of three doses of a growth factor gene located within the pseudoautosomal (exchange) region in Klinefelter's syndrome and one dose in Turner's syndrome.

## **2. Klinefelter syndrome and Klinefelter variants**

### **2.1 Definition**

The term Klinefelter syndrome describes a group of chromosomal disorder in which there is at least one extra X chromosome to a normal male karyotype, 46,XY (Visootsak et al 2006 bis). The classic form is the most common chromosomal disorder, in which there is one extra X chromosome resulting in the karyotype of 47,XXY. XXY aneuploidy is the most common disorder of sex chromosomes in humans, with prevalence of one in 500 males (Nielsen et al 1991).

### **2.2 Background**

In 1942, Klinefelter et al published a report on 9 men who had enlarged breasts, sparse facial and body hair, small testes, and an inability to produce sperm. At that time it was believed (Klinefelter et al 1942) to be an endocrine disorder of unknown etiology. In 1959, these men with Klinefelter syndrome were discovered to have an extra sex chromosome (genotype

XXY) instead of the usual male sex complement (genotype XY) (Jacobs et al 1959). The extra X chromosome in 47,XXY results sporadically from either meiotic nondisjunction where a chromosome fails to separate during the first or second division of gametogenesis *or* from mitotic nondisjunction in the developing zygote. The likelihood of X chromosome nondisjunction increases with advancing maternal age. The addition of more than one extra X chromosome to a male karyotype results in variable physical and cognitive abnormalities. In general, the extent of phenotypic abnormalities, including mental retardation, is directly related to the number of supernumerary X chromosomes. As the number of X chromosomes increases, somatic and cognitive development are more likely to be affected. Each extra X is associated with an IQ decrease of approximately 15–16 points, with language most affected, particularly expressive skills (Linden et al 1995).

Postfertilization nondisjunction is responsible for mosaicism, which is seen in approximately 10% of Klinefelter syndrome patients. Men with mosaicism are less affected and are often not diagnosed (Paduch et al 2008). The androgen receptor (AR) gene encodes the androgen receptor, which is located on the X chromosome. The AR gene contains a highly polymorphic trinucleotide (CAG) repeat sequence in exon 1, and the length of this CAG repeat is inversely correlated with the functional response of the androgen receptor to androgens. Thus, a short AR CAG repeat sequence correlates with a marked effect of androgens. In individuals with Klinefelter syndrome, the X chromosome with the shortest AR CAG repeat has been demonstrated to be preferentially inactivated; this process is called skewed or nonrandom X-chromosome inactivation. Individuals with short AR CAG repeats have been found to respond better to androgen therapy, to form more stable partnerships, and to achieve a higher level of education compared with individuals with long CAG repeats (Zitzmann et al 2004, Bojesen et al 2007). Conversely, long AR CAG repeat lengths are associated with increased body height and arm span, decreased bone density, decreased testicular volume, and gynecomastia. Nonrandom X-chromosome inactivation, which preferentially leaves the allele with the longest AR CAG repeat active, may actually contribute to the hypogonadal phenotype found in Klinefelter syndrome and may also explain some of the diverse physical appearances observed in affected individuals.

In boys with Klinefelter syndrome, the paternal origin of the supernumerary X chromosome is associated with later onset of puberty and longer CAG repeats of the androgen receptor, with later pubertal reactivation of the pituitary-testicular axis.

### 2.3 Physical characteristics

If the diagnosis is not made prenatally, 47,XXY males may present with a variety of subtle clinical signs that are age-related.

Infants and children achieve normal height, weight, and head circumference. Height velocity increases by age 5 years, and adults with Klinefelter syndrome are usually taller than adults who do not have the syndrome. Affected individuals also have disproportionately long arms and legs (Ratcliffe et al 1999, Schibler et al 1974). About 25% have clinodactyly.

Boys with 47,XXY have variable phenotypic characteristics and do not have obvious facial dysmorphism; thus, they are indistinguishable from other boys with normal karyotypes (Caldwell et al 1972). Many 47,XXY boys appear to enter puberty normally with a tendency

for testosterone concentrations to decline at late adolescence and early adulthood. With a decrease in androgen production, secondary sexual characteristics do not completely develop, and features of eunuchoidism and gynecomastia can develop. This also results in sparse facial, body, and sexual hair (Robinson et al).

About 40% of patients have taurodontism, which is characterized by enlargement of the molar teeth by an extension of the pulp. The incidence rate is about 1% in healthy XY individuals.

## 2.4 Fertility

Androgen deficiency causes eunuchoid body proportions; sparse or absent facial, axillary, pubic, or body hair; decreased muscle mass and strength; feminine distribution of adipose tissue; gynecomastia; small testes and penis; diminished libido; decreased physical endurance; and osteoporosis. The loss of functional seminiferous tubules and Sertoli cells results in a marked decrease in inhibin B levels, which is presumably the hormone regulator of the follicle-stimulating hormone (FSH) level. The hypothalamic-pituitary-gonadal axis is altered in pubertal patients with Klinefelter syndrome.

Although most patients with Klinefelter syndrome are infertile, there have been a few patients with reports of pregnancy without assisted medical technology, typically in mosaic cases. With the introduction of intracytoplasmic sperm injection, which involves the use of sperm extraction from deep within the testicles of patients with nonmosaic Klinefelter syndrome, some XXY men will have an increased chance of fathering a child (Kaplan et al 1963, Okada et al 1999, Ron-El et al 2000, Schiff et al 2005, Paduch et al 2009).

Guidelines for the assessment and treatment of people with fertility problems have been established (Guideline 2004).

## 2.5 Intelligence

Contrary to other genetic syndromes that arise from chromosomal trisomy (eg, Down syndrome, trisomy 18), the general cognitive ability of patients with Klinefelter syndrome is not typically in the intellectual disability range (Boada et al 2009). A wide range of intelligence quotient (IQ) has been noted and extends from well below average to well above average. Several longitudinal studies of males with 47,XXY have revealed a tendency in about 70% of patients for language deficits that often causes academic difficulties during the school years, delayed speech and language acquisition, diminished short-term memory, decreased data-retrieval skills, reading difficulties, dyslexia, and attention deficit disorder.

## 2.6 Psychological aspects

Patients may exhibit behavioral problems and psychological distress. This may be due to poor self-esteem and psychosocial development or a decreased ability to deal with stress. Most 47,XXY boys have a lag in language skills with mildly delayed expression of single words. These individuals also demonstrate that the production of expressive language is affected more than that of comprehension or receptive skills (Graham et al 1988).

The personalities of 47,XXY males are variable. One study characterized 47,XXY males as timid, immature, and reserved, with difficulty relating to their peer group, whereas other



studies described 47,XXY subjects as friendly, kind, helpful, and relates well with other people. Most are described to be quiet, sensitive, and unassertive. The majority of 47,XXY males rate themselves as more sensitive, apprehensive, and insecure than their peers. An increased incidence of anxiety, depression, neurosis, psychosis and substance abuse is reported in adolescents with 47,XXY (Bender et al 1995). The language difficulty experienced by these males possibly contributes to the challenges in behavioral and social domains (Bancroft et al 1982, Jimenez 1991).

## 2.7 Complications

Associated endocrine complications include diabetes mellitus, hypothyroidism, and hypoparathyroidism (Hsueh et al 1978). Autoimmune diseases, such as systemic lupus erythematosus, Sjogren syndrome, and rheumatoid arthritis, are more common in Klinefelter syndrome, with frequencies similar to those found in 46,XX females. Development of varicose veins and leg ulcers may result from venous stasis (Campbell et al 1981). Decreased bone density occurs in 25% of patients with Klinefelter syndrome, possibly reflecting the impact of decreased bone formation, increased bone resorption and/or hypogonadism (Horowitz et al 1992).

Risk of acquiring breast carcinoma in 47,XXY is relatively increased, with relative risk exceeding 200 times (Swerdlow et al 2005). The cause may result from the estradiol to testosterone ratio being severalfold higher than that of karyotypically normal men or possibly due to an increased peripheral conversion of testosterone to estradiol in men with Klinefelter syndrome (Swerdlow et al 2005). Patients may have an increased frequency of extragonadal germ cell tumors such as embryonal carcinoma, teratoma, and primary mediastinal germ cell tumor.

The mortality rate is not significantly higher than in healthy individuals.

## 2.8 Diagnosis

Klinefelter syndrome goes undiagnosed in most affected males; among males with known Klinefelter syndrome, many do not receive the diagnosis until they are adults. Infertility and gynecomastia are the 2 most common symptoms that lead to diagnosis in patients with Klinefelter syndrome.

A karyotype analysis of peripheral blood is the gold standard. Follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol are elevated, and testosterone level are low to low-normal without testosterone therapy. Urinary gonadotropins are increased due to abnormal Leydig cell function. The decline in testosterone production is progressive over the life span, and not all men suffer from hypogonadism (Vorona et al 2007).

## 2.9 Differential diagnosis

The physical manifestations of Klinefelter syndrome are often variable. When the following features: small testes, infertility, gynecomastia, long legs and arms, developmental delay, speech and language deficits, learning disabilities or academic issues, psychosocial difficulties, behavioral issues are present in an undiagnosed male, a karyotype analysis may be indicated. Other causes of hypogonadism need to be considered, such as Kallmann syndrome. Fragile X Syndrome and Marfan Syndrome should also be differentiated.

### 2.10 Genetic counseling

The recurrence risk is not increased above that of the general population. There is no evidence to suggest that a chromosomal nondisjunction process is likely to repeat itself in a particular family.

### 2.11 Antenatal diagnosis

Klinefelter syndrome can be detected prenatally by chorionic villous sampling and amniocentesis. Prenatal test consists in chorionic villous sampling (CVS) or amniocentesis. Currently available methods for rapid aneuploidy detection (RAD) include fluorescence in situ hybridization (FISH) and quantitative fluorescence polymerase chain reaction (QF-PCR). Multiplex ligation-dependent probe amplification (MLPA) is a newer technology under investigation that is proving to, have similar sensitivity and specificity to full cytogenetic karyotyping (the current “gold standard”) for the detection of fetal aneuploidy (for chromosomes 13, 18, and 21 and the sex chromosomes) (Sparkes et al 2008).

Parents should be counseled based on recent prospective and unbiased information. About 40% of concepti with Klinefelter syndrome survive the fetal period.

### 2.12 Management

Androgen replacement therapy should begin at puberty, around age 12 years, in increasing dosage sufficient to maintain age appropriate serum concentrations of testosterone, estradiol, FSH, and LH. Androgen replacement promotes normalization of body proportions or development of normal secondary sex characteristics, but does not treat infertility, gynecomastia, and small testes. Testosterone replacement also results in general improvement in behavior and work performance (Nielsen et al 1988). Testosterone also has beneficial long-term effects that might reduce the risk of osteoporosis, autoimmune disease, and breast cancer (Kocar et al 2000).

Early identification and anticipatory guidance are important in boys with 47,XXY. Early speech/language therapy is particularly essential in helping the child to develop skills in the understanding and production of more complex language. Physical therapy should be considered for boys who have hypotonia or delayed in gross motor skills which may impact the muscle tone, balance, and coordination.

## 3. Klinefelter variants

### 3.1 48,XXYY

Much less frequent are 48,XXYY and 48,XXXY being present in 1 per 17,000 to 1 per 50,000 male births (Linden et al 1995). Extra copies of genes from the pseudoautosomal region of the extra X and Y chromosome contribute to the signs and symptoms of 48,XXYY syndrome; however, the specific genes have not been identified. Males with 48,XXYY are often tall, with an adult height above 6 feet. They may have an eunuchoid habitus with long legs, sparse body hair, small testicles and penis, hypergonadotropic hypogonadism, and gynecomastia. Peripheral vascular disease may result in leg ulcers and varicosities. Their IQ level is in the range of 60–80, with delayed speech and they are at risk for academic,

behavioral, and social deficits. They are usually shy but can be aggressive and impulsive (Linden et al 1995, Visootsak et al 2001, Visootsak et al 2006). In a study of 16 males with 48,XXYY compared to 9 males with 47,XXY between the ages of 5 and 20, findings indicate that 48,XXYY males have verbal and full scale IQ's significantly lower than males with 47,XXY (Tartaglia et al 2005).

48,XXYY males are also prone to have problems with hyperactivity, aggression, conduct, and depression compared to males with 47,XXY. Their mean scores in these areas are in the clinically significant range and males with 47,XXY have scores in the average range. Furthermore, 48,XXYY males have significantly lower adaptive functioning than males with 47,XXY (Tartaglia et al 2005).

### **3.2 48,XXXY**

Males with 48,XXXY chromosome karyotype can be of average or tall stature, have abnormal face (epicanthal folds, hypertelorism, protruding lips with ocular hypertelorism, flat nasal bridge), radioulnar synostosis, fifth-finger clinodactyly, gynecomastia (33-50%) and hypoplastic penis and testicles with hypergonadotropic hypogonadism, infertility and benefit from testosterone therapy. They typically have mild-to-moderate mental retardation and their IQs are usually between 40 and 60, with severely delayed speech. They present slow motor development, poor coordination. Their behavior is often immature and consistent with their IQ level, and they are typically described as passive, cooperative, and not particularly aggressive (Linden et al, Visootsak et al 2001, Visootsak et al 2006).

### **3.3 49,XXXXY**

The incidence of 49,XXXXY is 1 per 85,000 to 100,000 male births (Linden et al 1995). Males with 49,XXXXY are severely affected. The classic triad is mild-to-moderate mental retardation, radioulnar synostosis, and hypergonadotropic hypogonadism. Other clinical features include severely impaired language, behavioral problems, low birthweight, short stature in some individuals, abnormal face (round face in infancy, coarse features in older age, hypertelorism, flat nasal bridge, upslanting palpebral fissures, epicanthal folds, prognathism), short or broad neck, gynecomastia (rare), congenital heart defects (patent ductus arteriosus is most common), skeletal anomalies (genu valgus, pes cavus, fifth finger clinodactyly), muscular hypotonia, hyperextensible joints, hypoplastic genitalia, and cryptorchidism. Pea-sized testes, hypoplastic penis, and infantile secondary sex characteristics are characteristic in patients with 49,XXXXY. Their IQ ranges between 20 to 60. They tend to be shy and friendly, with occasional irritability and temper tantrums, low frustration tolerance, and difficulty changing routines (Linden et al 1995, Visootsak et al 2001, Visootsak et al 2006).

### **3.4 49,XXYY**

This is a rare aneuploidy and only a few cases of liveborn males have been described. Patients typically have moderate-to-severe mental retardation with passive but occasionally aggressive behavior and temper tantrums, tall stature, dysmorphic facial features, gynecomastia, and hypogonadism (Linden et al 1995).



### 3.5 46,XX male

XX male syndrome occurs when the affected individual appears as a normal male, but has a female genotype. XX male syndrome occurs in approximately 1/20000 -1/25000 individuals. XX male syndrome can occur in any ethnic background and usually occurs as a sporadic event, not inherited from the person's mother or father. However, some exceptions of more than one affected family member have been reported.

46,XX male chromosomal karyotype is caused by translocation of Y material including sex determining region (SRY) to the X chromosome during paternal meiosis. Two types of XX male syndrome can occur: those with detectable SRY gene and those without detectable SRY.

In XX male syndrome where the SRY gene is *detectable*, a translocation between the X chromosome and Y chromosome causes the condition. In XX male syndrome, the tip of the Y chromosome that includes SRY is translocated to the X chromosome. As a result, an embryo with XX chromosomes with a translocated SRY gene will develop the physical characteristics of a male. Typically, a piece of the Y chromosome in the pseudoautosomal region exchanges with the tip of the X chromosome. In XX male syndrome, this crossover includes the SRY portion of the Y.

Males with SRY positive XX male syndrome look like and identify as males. They have normal male physical features including normal male body, genitals, and testicles, but hypospadias or cryptorchidism may be seen (Yencilek et al 2005). Males with 46,XX have decreased testosterone level with high levels of LH and FSH and infertility may be present (Yencilek et al 2005).

In individuals with XX male syndrome that *do not have an SRY gene detectable* in their cells, the cause of the condition is not known. Scientists assert that one or more genes that are involved in the development of the sex of an embryo are mutated or altered and cause physical male characteristics in a chromosomally female person. These genes could be located on the X chromosome or on one of the 22 pairs of autosomes that males and females have in common. As of 2001, no genes have been found to explain the female to male sex reversal in people affected with XX male syndrome that are SRY negative. Approximately 20% of XX males do not have a known cause and are SRY negative. It is thought that SRY is a switch point, and the protein that is made by SRY regulates the activity of one or more genes (likely on an autosomal chromosome) that contribute to sex development.

## 4. Other sex chromosomal aneuploidies

### 4.1 47,XYY

There are three plausible mechanisms by which an extra Y chromosome can be generated: 1) non-disjunction at male meiosis II following a normal chiasmate meiosis I (MI) in which recombination occurs between the X and Y chromosomes within the Xp/Yp pseudoautosomal region (MII-C); 2) non-disjunction at male meiosis II (MII) following a meiosis I in which recombination between the X and Y chromosomes does not occur (MII-NC) or 3) postzygotic mitotic (PZM) non-disjunction. One in 800 to 100 males has an extra Y chromosome (Nielsen et al 1991).

Males with 47,XYY syndrome have one X chromosome and two Y chromosomes in each cell, for a total of 47 chromosomes. This arises through nondisjunction at paternal meiosis II. It is

unclear why an extra copy of the Y chromosome is associated with tall stature, learning problems, and other features in some boys and men.

Physical phenotype is normal (Robinson et al 1979), with tall stature (75th percentile) by adolescence. There are no problems associated with puberty or fertility. Among the 39 boys followed prospectively, full-scale IQ averaged 105 (range 65-129). Speech delay was noted in approximately half of the boys, and half of the sample needed part-time or fulltime educational intervention. There was no consistent behavioral phenotype. Several investigators reported an increase in temper tantrums and distractibility among boys. Aggression was not frequently observed in children and adolescents (Linden et al 2002).

The condition is clearly variable. Most blend into the population as normal individuals. Better outcomes seem to be associated with a supportive, stable environment.

#### **4.2 47,XXX**

Normal females possess two X chromosomes, and in any given cell one chromosome will be active (designated as X<sub>a</sub>) and one will be inactive (X<sub>i</sub>). However, studies of individuals with extra copies of the X chromosome show that in cells with more than two X chromosomes there is still only one X<sub>a</sub>, and all the remaining X chromosomes are inactivated. This indicates that the default state of the X chromosome in females is inactivation, but one X chromosome is always selected to remain active.

Trisomy X is a sex chromosome anomaly with a variable phenotype caused by the presence of an extra X chromosome in females (47,XXX instead of 46,XX). The 47,XXX karyotype originally described as the "superfemale" in 1959 (Jacobs et al 1959 bis) in a 35-year-old woman with normal intellectual abilities who presented with secondary amenorrhea at 19 years of age, is known as triple X or triplo-X. Its incidence is approximately 1/1000 (Tartaglia et al 2010). It is estimated that only approximately 10% of cases are diagnosed (Nielsen 1990).

Although rare, 48,XXXX and 49,XXXXX females exist. There is no consistent phenotype. The risk of intellectual disability and congenital anomalies increases markedly when there are more than three X chromosomes. The genetic imbalance in early embryonic life may cause anomalous development

#### **4.3 Etiology**

Trisomy X occurs from a nondisjunction event, in which the X chromosomes fail to properly separate during cell division either during gametogenesis (resulting in a trisomic conceptus), or after conception (known as post-zygotic nondisjunction). Similar to other trisomies, trisomy X has been shown to have a statistically significant correlation with advancing maternal age, as the likelihood of nondisjunction events during meiosis increases with increasing maternal age.

#### **4.4 Physical characteristics**

Significant facial dysmorphology or striking physical features are not commonly associated with 47,XXX, however, minor physical findings can be present in some individuals

including epicanthal folds, hypertelorism, upslanting palpebral fissures, clinodactyly, overlapping digits, pes planus, and pectus excavatum. Hypotonia and joint hyperextensibility may also be present (Linden et al 1988).

Length and weight at birth is usually normal for gestational age, however, stature typically increases in early childhood, and by adolescence most girls with 47,XXX are at or above the 75th percentile for height (Linden et al 1988). A few cases have been ascertained due to tall stature, and current evaluation of tall stature in females should include karyotype analysis to evaluate for 47,XXX. Cases of short stature have also been described (unrelated to a known 45,X mosaicism). Body segment proportions typically show long legs, with a short sitting height. Studies of bone age have shown no significant differences from 46,XX females (Webber et al 1982). The average head circumference is below the 50th percentile, however, there is a lot of individual variation.

#### 4.5 Clinical characteristics

Although major medical problems are not present in most cases, other medical problems may be associated with trisomy X. The most common are genitourinary abnormalities, congenital heart defects, seizure disorders and EEG abnormalities in approximately 15% of cases with good responses to standard anticonvulsant treatments (Roubertie et al 2006). Gastrointestinal problems, including constipation and abdominal pain, are also common.

Pubertal onset and sexual development are usually normal in trisomy X, however, there have been cases of ovarian or uterine dysgenesis described in children and young adults with trisomy X. Premature ovarian failure (POF) is a condition in which the ovarian functions of hormone production and oocyte development become impaired before the typical age for menopause.

There have been no direct studies of fertility in trisomy X, however, many reports of successful pregnancies have been described, and fertility is likely normal in most cases unless complicated by a genitourinary malformation or POF as described above (Linden et al 1988).

#### 4.6 Psychological characteristics

There is significant variability in the developmental and psychological features of children and adults with trisomy X, ranging from those with minimal involvement to those with clinically significant problems requiring comprehensive intervention services.

Infants and toddlers are at increased risk for early developmental delays, especially in speech-language development and motor development related to hypotonia. Average age at walking independently is 16.2 months (range 11-22 months), and for first words is 18.5 months (range 12 - 40 months) (Linden et al 1988). Expressive language may be more impaired than receptive language, with a pattern described as developmental dyspraxia in some patients. Speech and language deficits may continue throughout childhood into adulthood.

Studies on cognitive abilities in trisomy X also show a wide range of cognitive skills, with full scale IQ's ranging from 55-115. While there are clearly many girls with trisomy X with cognitive skills in the average to above average range, cognitive deficits and learning

disabilities are more common than in the general population and when compared to sibling controls.

Motor skill deficits may also be present. Walking may be delayed, and decreased muscle tone and lack of coordination are often clinically significant. (Linden et al 1988). Attentional problems, poor executive function, and decreased adaptive functioning skills may also impact educational and home functioning. There is a paucity of research on mental health problems in trisomy X, however, increased rates of anxiety, depression/dysthymia and adjustment disorders have been described in previous studies (Linden et al 1988, Bender et al 1995). Anxiety concerns are mostly related to social avoidance, generalized anxiety and separation anxiety, and can present in the early school age years or in adolescence. Language deficits may also impact social adjustment in some children when they have difficulty communicating with playmates and when self-expression is limited in older children and adolescents. Again, the variability in the phenotype needs to be emphasized, since many females with trisomy X have minimal cognitive, social, or emotional difficulties.

#### **4.7 Diagnosis**

Karyotype analysis of peripheral blood is the most standard test used to make the diagnosis. Prenatal amniocentesis or CVS also identify a percentage of patients with trisomy X, however, confirmation studies are recommended after birth via FISH to study 50+ cells in order to evaluate for mosaicism. It is also important to identify mosaicism with a Turner syndrome (45,X) cell line in order to determine appropriate medical evaluations and treatments needed for Turner syndrome.

#### **4.8 Prognosis and genetic counseling**

The prognosis of trisomy X is variable. As noted, there is significant variability in developmental delays, learning disabilities and psychological characteristics in trisomy X. Couples should be informed of the high frequency of trisomy X and that most girls go undiagnosed, in order to support them in understanding and accepting that their diagnosis is not an isolated case with a predetermined outcome (Warwick et al 1999).

### **5. 45,X**

Turner syndrome is most commonly the result of an absence of an entire X chromosome resulting in a 45,X karyotype. The Turner phenotype can also be produced by various partial X deletions or other structural abnormalities. No cause has been identified for Turner syndrome.

Turner syndrome (TS) affects 1:2500 live females (Tan et al 2009) and thus it occurs considerably less frequently than the other sex chromosome aneuploidies. At least 99% of all 45,X pregnancies are aborted spontaneously in early pregnancy. Usually, the phenotype is obvious in infancy and childhood, and thus most cases are identified at an early age (Vakrilova et al 2010).

#### **5.1 Physical characteristics**

Short stature is a hallmark of Turner syndrome. These females are usually small at birth, do not experience an adolescent growth spurt, and reach an adult height of approximately 4'6"

(144cm, below the fifth percentile). Using current therapy, most of these girls can now be treated with recombinant human growth hormone injections, usually beginning in childhood, and can expect to reach an average height of at least 4'11" (150 cm, fifth percentile).

Patients with deletions of the distal segment of the short arm of X chromosome (Xp-) including haplo insufficiency of the SHOX (short stature homeobox) have, more often, short stature, skeletal abnormalities and hearing impairments (Oliveria et al 2011).

## 5.2 Fertility

The other significant feature of Turner syndrome is gonadal dysgenesis. Therefore, 45,X women are usually infertile, and in very rare cases have spontaneous menses followed by early menopause. Only 2% of the women have natural pregnancies, with high rates of miscarriages, stillbirths and malformed babies. Their pregnancy rate in oocyte donation programs is 24-47%, but even these pregnancies have a high rate of miscarriage, probably due to uterine factors. A possible future prospect is cryopreservation of ovarian tissue containing immature follicles before the onset of early menopause, but methods of replantation and in-vitro maturation still need to be developed. Should these autologous oocytes indeed be used in the future, affected women would need to undergo genetic counseling before conception, followed by prenatal assessment (Abir et al 2001).

## 5.3 Other somatic features

These can include cardiac and kidney abnormalities, webbed neck and lymphedema. Congenital heart disease was found in 26%. When compared with the general population a higher incidence was present for all types of congenital heart diseases observed. Among cardiac anomalies in Turner's patients, aortic malformations (aortic coarctation and bicuspid aorta) were the most frequent, followed by patent ductus arteriosus and pulmonary valve stenosis. We have observed that the most severe malformations were preferably found with the 45,X karyotype. Pulmonary valve stenosis was found in a mosaicism 45,X/46,XX case (Couceiro et al 1996).

Aortic dilation and dissection is reported in patients with Turner's syndrome, both with and without cardiovascular risk factors. The bicuspid aortic valve is closely associated with dilated aortic root, although expression of aortic dilation is variable. The determinants for variable expression of aortic dilation in individuals with Turner's syndrome, however, are unknown. A primary mesenchymal defect is prevalent in individuals with Turner's syndrome, suggested by having abnormalities in bone matrix, and lymphatic and peripheral blood vessels. The studies are hypothesized that an abnormal intrinsic elastic property of aorta is a forerunner of aortic dilation in Turner's syndrome (Sharma et al 2009).

Renal/collecting system anomalies are found in 29.3% of patients with Turner's syndrome who underwent ultrasonography. Among them, duplication of the collecting system and hydronephrosis (25% each) and horseshoe kidney (21.2%) were the most frequent (Carvalho et al 2010).

These females are at an increased risk of otitis media, cardiovascular disease, hypertension, diabetes mellitus, thyroid disorders, and obesity. Careful medical management can assist in identifying and treating most of these problems.



#### 5.4 Intelligence and psychological issues

Genetic, hormonal, and medical problems associated with TS are likely to affect psychosexual development of female adolescent patients, and thus influence their psychological functioning, behavior patterns, social interactions and learning ability.

Mental retardation is not prevalent in Turner syndrome, and most girls have normal IQ's. Usually, verbal IQ is significantly greater than performance IQ, resulting in a visual-spatial deficit. Many investigators have noted deficits in left-right orientation, copying shapes, handwriting, and solving math problems.

Girls with Turner syndrome did not differ on untimed arithmetic calculations or problem verification accuracy, but they had limited mastery of counting skills and longer response times to complete the problem verification task (Murphy et al 2008).

In general, speech is normal, but expression can be compromised if recurrent otitis media has not been treated successfully. These women have a high occurrence of ear and hearing problems, and neurocognitive dysfunctions, including reduced visual-spatial abilities; it is assumed that estrogen deficiency is at least partially responsible for these problems.

The results of TEOAE, ABR and speech recognition scores in noise were all indicative of cochlear dysfunction as the cause of the sensorineural impairment. Phase audiometry, a test for sound localization, showed mild disturbances in the Turner women compared to the reference group, suggesting that auditory-spatial dysfunction is another facet of the recognized neurocognitive phenotype in Turner women (Hederstierna et al 2009).

Motor skills can be delayed slightly, and poor gross and fine motor coordination has been observed frequently.

Turner syndrome occurs approximately threefold more frequently in female schizophrenics compared to the general female population. A polymorphism of the HOPA gene within Xq13 termed HOPA(12bp) is associated with schizophrenia, mental retardation, and hypothyroidism. Interestingly, Xq13 is the X-chromosome region that contains the X-inactivation center and a gene escaping X-inactivation whose gene product may be involved in the X-inactivation process as well as in the pathogenesis of sex chromosome anomalies such as Turner syndrome. These genes that escape X-inactivation may produce their gene products in excess, influencing normal brain growth and differentiation (Roser et al 2010).

#### 5.5 Treatment

Women with Turner's syndrome should be carefully followed throughout life. Growth hormone therapy should be started at age 2-5 years. Early treatment with r-hGH helps to prevent natural evolution towards short stature in most girls with TS. IGF1 levels and glucose metabolism should be monitored routinely during r-hGH therapy (Linglart et al 2011). Hormone replacement therapy for the development of normal female sexual characteristics should be started at age 12-15 years and continued for the long term to prevent coronary artery disease and osteoporosis.

Although TS constitutes a chronic medical condition, with possible physical, social and psychological complications in a woman's life, hormonal and estrogen replacement therapy

and assisted reproduction, are treatments that can be helpful for TS patients and improve their quality of life (Christopoulos et al 2008).

## 6. Mosaicism

Sex chromosome mosaic karyotypes are most often 45,X/46,XX, 46,XX/47,XXX or 46,XY/47,XXY, but many other combinations are possible. In general, the presence of a normal 46,XX or 46,XY cell line tends to modify the effects of the aneuploid cells. Twenty-two mosaics have been followed prospectively, including 11 45,X mosaics, six 47,XXY mosaics, and five 47,XXX mosaics (Linden et al 1996). On evaluations of intelligence, educational intervention, motor skills, and behavioral problems, those with mosaicism scored similarly to controls, and no significant differences were determined. Fertility may vary, depending on the chromosomal constitution. Although 46,XX/47,XXX females usually can be assumed to be fertile, the prognosis for 45,X/46,XX mosaics and 46,XY/47,XXY mosaics is less definitive. Although many may have normal reproductive competency, appropriate tests must be performed at puberty or later to establish fertility status. The international investigators have long recognized that an element of the self-fulfilling prophecy could affect the study results. In question is whether early identification and disclosure of a sex chromosome aneuploidy to parents, physicians and affected individuals would influence development and behavior over the course of infancy and into adulthood.

## 7. Discussion

Aneuploidies of the sex chromosomes are present in the general population with a frequency of approximately 1 in a 1000 for each syndrome. The effects of X/Y chromosome anomalies are not as severe as those from analogous autosomal anomalies. Females with 3 X chromosomes often appear normal physically and mentally and are fertile. In contrast, all known autosomal trisomies have devastating effects. Similarly, whereas the absence of one X chromosome leads to a specific syndrome (Turner's syndrome), the absence of an autosome is invariably lethal.

While sex chromosome aneuploidies can include a variety of abnormalities of the sex chromosomes, by far the most commonly occurring SCA involve the deletion (45,X or partial X monosomy) or addition (47,XXY, 47,XYY, 47,XXX) of an X or Y chromosome. Often these individuals are unaware of their disorder. Of these conditions, only Turner syndrome, caused by the loss of all or part of an X chromosome, results in an easily identifiable physical phenotype. Subtle language, neuromotor, and learning difficulties have been identified in most forms of SCA, however.

Sex chromosome anomalies are common and cause syndromes that include a range of congenital and developmental anomalies. They are rarely suspected prenatally but may be incidentally discovered if karyotyping is done for other reasons. They are often hard to recognize at birth and may not be diagnosed until puberty.

The prognosis of sexual aneuploidies is variable, with some individuals doing extremely well with minimal manifestations of the disorder, and others with more significant physical, endocrine, cognitive and psychological involvement as described above and it is not yet possible to predetermine which child will exhibit any or all of these concerns.

It is evident that prevention or reduction of deviation from the normal range in mental development in children with sex chromosome abnormalities is possible if educational and social resources are available, early intervention is offered and the parents are well informed and counseled regularly. Parents having a child with a sex chromosome abnormality need information, counseling, and assistance. The type and magnitude of this assistance depend on the individual child, the specific sex chromosome abnormality, and the parents' own resources, psychologically, socially, and otherwise.

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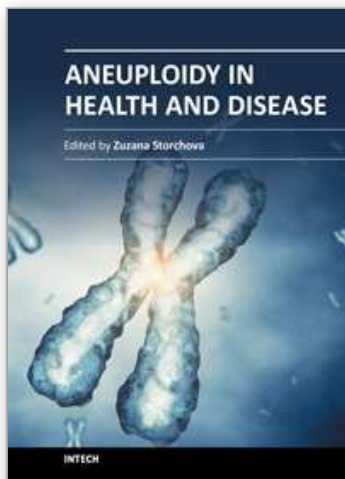


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## **Aneuploidy in Health and Disease**

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Aneuploidy means any karyotype that is not euploid, anything that stands outside the norm. Two particular characteristics make the research of aneuploidy challenging. First, it is often hard to distinguish what is a cause and what is a consequence. Secondly, aneuploidy is often associated with a persistent defect in maintenance of genome stability. Thus, working with aneuploid, unstable cells means analyzing an ever changing creature and capturing the features that persist. In the book *Aneuploidy in Health and Disease* we summarize the recent advances in understanding the causes and consequences of aneuploidy and its link to human pathologies.

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