World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/

Vol. 8, Issue 1, 2019 ISSN: 2319-5622 USA CODEN: JPROK3

Review Article

GENETIC ASPECTS OF KLINEFELTER'S SYNDROME

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Received on: 25-12-2018; Revised and Accepted on: 27-01-2019

ABSTRACT

K*linefelter's syndrome (KS) is the most common chromosome aneuploidy in males, characterized by at least one supernumerary X chromosome. Although extensively studied, the pathophysiology, i.e. the link between the extra X and the phenotype, largely remains unexplained. The scope of this review is to summarize the progress made in recent years on the role of the supernumerary X chromosome with respect to its putative influence on the phenotype. In principal, the parental origin of the X chromosome, gene-dosage effects in conjunction with (possibly skewed) X chromosome inactivation, and especially concerning spermatogenesis meiotic failure may play pivotal roles. One of the X chromosomes is inactivated to achieve dosage-compensation in females and probably likewise in KS. Genes from the pseudoautosomal regions and an additional 15% of other genes, however, escape X inactivation and are candidates for putatively constituting the KS phenotype. Examples are the SHOX genes, identified as likely causing the tall stature regularly seen in KS. Lessons learned from comparisons with normal males and especially females as well as other sex chromosomal aneuploidies are presented. In addition, genetic topics concerning fertility and counseling are discussed. Klinefelter syndrome, affecting males, is a collection of characteristics that occurs as a result of two or more X chromosomes. The syndrome was named after Harry Klinefelter, an American endocrinologist, and is common - occurring in all races. It is thought that one male in every 500 live births is affected and the incidence is rising. However, this may be due to increasing awareness, reflective of the sophistication of the methods to diagnose. Most men with Klinefelter syndrome produce little or no sperm, but assisted reproductive procedures may make it possible for some men with Klinefelter syndrome to father children.*

KEY WORDS: *Klinefelter syndrome, SHOX genes, X chromosome, Testicular growth, Testosterone.*

INTRODUCTION

What is Klinefelter Syndrome? :

Everything from your height to your hair color goes back to your genes. They hold the code for how your body looks and works. Genes are bundled into chromosomes. One pair, called the sex chromosomes, determine whether you're male or female.

Usually, females have two X chromosomes (XX). Males have an X and a Y (XY).

But in rare cases, a male is born with an extra X chromosome (XXY). This is Klinefelter syndrome. It's also called Klinefelter's or XXY.

Often, men don't even know they have Klinefelter until they run into problems trying to have a child. There's no cure, but it can be treated. With the right care, most men with Klinefelter lead normal, healthy lives.

Klinefelter's syndrome (KS) was first described in 1942 (Klinefelter), and the cause for the syndrome was later found in 1959 as a supernumerary X chromosome resulting in the karyotype 47,XXY (Jacobs and Strong, 1959). About 80–90% of KS cases bear this 'original' karyotype, whereas the remaining exhibit (in decreasing frequency) varying mosaicism (e.g. 47, XXY/46, XY), carry additional sex chromosomes (48, XXXY; 48, XXYY; 49, XXXXY) or structurally abnormal X chromosomes. In the late 1960s and early 1970s, six large surveys of consecutive newborns (summarized by Hook and Hamerton, 1977) among other chromosomal aneuploidies established the prevalence of KS as 1 per 1000 same sex births. Later studies found a higher prevalence of up to 1 in 500 boys (Nielsen and Wohlert, 1990), and recently an increase in the prevalence of KS in opposition to the other sex chromosome trisomies (47, XYY males and 47, XXX females) has been described. In any case, KS is the most common chromosomal aberration in men with 0.1–0.2% of the male population affected. When considering infertile men, the prevalence of KS is even much higher and increases from ~3% in unselected to ~13% in azoospermic patients which we recently confirmed in our patient cohort, making KS the most frequent genetic cause of azoospermia.

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DOI: https://doi.org/10.5281/zenodo.2571900

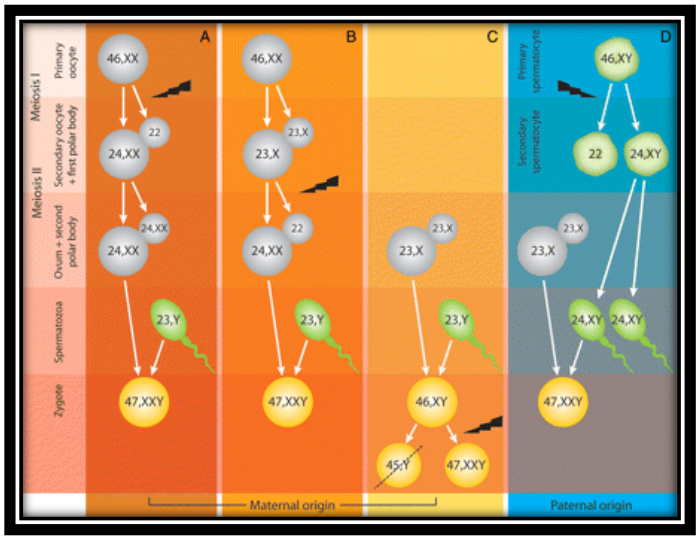
KS is regularly associated with hypergonadotropic hypogonadism and infertility due to azoospermia, but with marked variations in the phenotype. The 'prototypic' man with KS has traditionally been described as tall, with sparse body hair, gynecomastia, small testes and decreased verbal intelligence (Bojesen and Gravholt, 2007). Yet, the clinical picture of XXY males may range from severe signs of androgen deficiency, or even a lack of spontaneous puberty, to normally virilised males who only consult a doctor because of their infertility. This variability is most likely explaining why only 10% of KS men are diagnosed until puberty and only ~25% during their lifetime according to a large Danish registry study in accordance with an earlier report (Abramsky and Chapple, 1997).

The increased morbidity and mortality in KS underline the need for an early diagnosis of a larger proportion of KS and necessitate a more widespread screening. Unchanged, the gold standard for diagnosing KS remains karyotyping of metaphase spreads from cultured peripheral blood lymphocytes. The major benefit of karyotype analysis is the simultaneous evaluation of the chromosome structure with respect to translocations, inversions and deletions. Nevertheless, a suspected diagnosis of KS may be quickly corroborated by analysis of a buccal smear to detect Barr bodies i.e. the inactivated supernumerary X chromosomes, but does not reach an adequate sensitivity to serve for screening (Pena and Sturzeneker, 2003). In the last years, new screening methods have been published: fluorescence *in situ* hybridization (FISH) may be used to estimate mosaicism in more detail by analyzing a larger number of interphase nuclei. The extra X can also be detected by quantitative real-time PCR (qPCR) of, for example, the androgen receptor (*AR*) gene or array comparative genomic hybridization .In comparison to karyotyping, the benefit of both methods is the lack of time-consuming and costly cell culture, and whereas qPCR can be considered a quick and inexpensive method, the main advantage of array CGH is the higher resolution of up to or even below 1 kb of altered DNA.

Although KS has been studied extensively in the last decades, the pathophysiology, i.e. the link between the supernumerary X and the phenotype, largely remains unclear and the variability unexplained. Apart from normal interindividual genetic variation, several genetic mechanisms may explain the variability of the phenotype, clinical features, life circumstances, life expectancy and fertility in principal, the parental origin of the X chromosome, gene-dosage effects in conjunction with (possibly skewed) X chromosome inactivation (XCI) (Samango-Sprouse, 2001), and—especially concerning spermatogenesis—meiotic failure may play pivotal roles. Much knowledge was and will be gained from the available mouse models of KS, which is dealt with in detail in a separate paper in this issue (Wistuba, 2010). The scope of this review is to summarize, from a genetical viewpoint, the progress made in recent years on the role of the supernumerary X chromosome with respect to its putative influence on the phenotype.

Origin of Klinefelter's Syndrome:

In opposition to autosomal trisomies, which only in a minority of ~10% are paternally derived, the supernumerary X in half of KS cases originates from paternal non-disjunction (Thomas and Hassold, 2003). Although maternal XXY can be caused by non-disjunction during the first and second meiotic divisions or during early postzygotic mitotic divisions in the developing zygote, XXY of paternal origin can arise only by meiosis I errors as paternal non-disjunction during meiosis II leads to XXX or XYY zygotes. An association of the frequency of KS with increasing maternal age at conception has been reported in accordance with other (primarily 13, 18, 21) chromosome trisomies (Hook, 1981) and could attribute this increase of KS to maternal meiosis I errors. In contrast, an association of paternally derived XXY with the father's age remains debatable among some confirming studies. Evidence for such an association would come from the finding that sperm aneuploidies increase with age. The reported increase in KS prevalence over the last decades was attributable only to paternal origin and hypothesized to be caused by environmental factors interfering with paternal meiosis I. As Herlihy and Halliday (2008) pointed out, a more obvious reason might well be an overall increasing paternal age, but this needs to be tested by detailed analyses of larger cohorts.



What causes it? :

Klinefelter syndrome occurs as a result of a random error that causes a male to be born with an extra sex chromosome. It isn't an inherited condition.

Humans have 46 chromosomes, including two sex chromosomes that determine a person's sex. Females have two X sex chromosomes (XX). Males have an X and a Y sex chromosome (XY).

Klinefelter syndrome can be caused by:

- One extra copy of the X chromosome in each cell (XXY), the most common cause
- An extra X chromosome in some of the cells (mosaic Klinefelter syndrome), with fewer symptoms
- More than one extra copy of the X chromosome, which is rare and results in a severe form

Extra copies of genes on the X chromosome can interfere with male sexual development and fertility.

Signs and Symptoms may include:

- ❖ Taller than average stature.
- ❖ Longer legs, shorter torso and broader hips compared with other boys.
- ❖ Absent, delayed or incomplete puberty.
- ❖ After puberty, less muscle and less facial and body hair compared with other teens.
- ❖ Small, firm testicles.
- ❖ Small penis.
- ❖ Enlarged breast tissue (gynecomastia)

Symptoms: vary with age, and you don't always get all of them. Some males show symptoms early on, but others don't realize they have Klinefelter until puberty or into adulthood. And many men never even realize they have it.

Babies: They may have problems at birth, such as a hernia or testicles that haven't dropped into the scrotum. You may see the following other signs in babies with Klinefelter:

- More quiet than usual
- Slower to learn to sit up, crawl, and talk
- Weaker muscles

Children: Boys may have low energy levels or any of the following:

- A hard time making friends and talking about feelings
- Problems learning to read, write, and do math
- Shyness and low confidence

Teenagers: During the teenage years, puberty may come on later, not quite finish, or not happen at all. Other possible symptoms include:

- Larger breasts than normal
- Less facial and body hair, and it comes in later
- Less muscle tone, and muscles grow slower than usual
- Longer arms and legs, wider hips, and a shorter torso than other boys their age
- Small penis and small, firm testicles
- Taller than usual for the family

Adults: In addition to the symptoms teenagers show, men may have:

- Infertility (can't have children because they can't make enough sperm)
- Low sex drive
- Low testosterone levels
- Problems getting or keeping an erection

How does Klinefelter Syndrome affect a Person? :

Klinefelter syndrome is a chromosomal condition that affects male physical and cognitive development. Its signs and symptoms vary among affected individuals. Affected individuals typically have small testes that do not produce as much testosterone as usual.

Can a Female have Klinefelter's Syndrome? :

Usually, females have two X chromosomes (XX). Males have an X and a Y (XY). But in rare cases, a male is born with an extra X chromosome (XXY). This isKlinefelter syndrome.

Are Klinefelter Males Sterile? :

Klinefelter syndrome (KS) also known as 47, XXY or XXY, is the set of symptoms that result from two or more X chromosomes in males. The primary features are infertility and small testicles. Often, symptoms may be subtle and many people do not realize they are affected.

Risk Factors:

Klinefelter syndrome stems from a random genetic event. The risk of Klinefelter syndrome isn't increased by anything a parent does or doesn't do. For older mothers, the risk is higher but only slightly.

You get the extra X chromosome by chance. Either the egg or sperm that came together to make you just happened to have an extra X chromosome. Older moms have a slightly higher chance of having a boy with Klinefelter, but the increase in probability is very small.

Can it Lead to other Conditions? :

Many problems caused by Klinefelter are because of lower testosterone levels. You may have a slightly higher chance of:

- ➢ Autoimmune problems, such as lupus and rheumatoid arthritis, where your immune system attacks healthy parts of your body
- ➢ Breast cancer and cancers that affect blood, bone marrow, and lymph nodes
- ➢ Conditions with your hormone glands, such as diabetes
- ➢ Heart disease and problems with blood vessels
- ➢ Lung disease
- ➢ Mental health problems, such as anxiety and depression
- ➢ Weak bones, called osteoporosis.

Health Issues in Klinefelter Syndrome:

- ❖ Most boys and men with Klinefelter syndrome will not be significantly affected and can live normal, healthy lives.
- ❖ Infertility tends to be the main problem, although there are treatments that can help.
- ❖ But men with Klinefelter syndrome are at a slightly increased risk of developing other health problems, including:
- ❖ Type 2 diabetes
- ❖ Weak and fragile bones (osteoporosis)
- ❖ Cardiovascular disease and blood clots
- ❖ Autoimmune disorders (where the immune system mistakenly attacks the body), such as lupus
- ❖ An underactive thyroid gland (hypothyroidism)
- ❖ Anxiety, learning difficulties and depression – although intelligence is usually unaffected
- ❖ Male breast cancer – although this is very rare
- ❖ These problems can usually be treated if they do occur and testosterone replacement therapy may help reduce the risk of some of them.

Testing for Klinefelter Syndrome:

- ✓ See your GP if you have concerns about your son's development or you notice any troubling symptoms of Klinefelter syndrome in yourself or your son.
- ✓ Klinefelter syndrome isn't necessarily anything serious, but treatment can help reduce some of the symptoms if necessary.
- ✓ In many cases, it's only detected if a man with the condition undergoes fertility tests.
- ✓ Your GP may suspect Klinefelter syndrome after a physical examination and may suggest sending off a sample of blood to check reproductive hormone levels.
- ✓ The diagnosis can be confirmed by checking a sample of blood for the presence of the extra X chromosome.

Diagnosis:

Your doctor will likely do a thorough physical exam and ask detailed questions about symptoms and health. This may include examining the genital area and chest, performing tests to check reflexes, and assessing development and functioning.

The main tests used to diagnose Klinefelter syndrome are:

- **Hormone testing:** Blood or urine samples can reveal abnormal hormone levels that are a sign of Klinefelter syndrome.
- **Chromosome analysis:** Also called karyotype analysis, this test is used to confirm a diagnosis of Klinefelter syndrome. A blood sample is sent to the lab to check the shape and number of chromosomes.

A small percentage of males with Klinefelter syndrome are diagnosed before birth. This might be identified after a pregnant woman has a procedure to examine fetal cells drawn from the amniotic fluid (amniocentesis) or placenta for another reason, such as being older than age 35 or having a family history of genetic conditions.

Treatment:

If you or your son is diagnosed with Klinefelter syndrome, your health care team may include a doctor who specializes in diagnosing and treating disorders involving the body's glands and hormones (endocrinologist), a speech therapist, a pediatrician, a physical therapist, a genetic counselor, a reproductive medicine or infertility specialist, and a counselor or psychologist.

Although there's no way to repair the sex chromosome changes due to Klinefelter syndrome, treatments can help minimize its effects. The earlier a diagnosis is made and treatment is started, the greater the benefits. But it's never too late to get help.

Treatment for Klinefelter syndrome may include:

- **Testosterone replacement therapy:** Starting at the time of the usual onset of puberty, testosterone replacement can be given to help stimulate changes that normally occur at puberty, such as developing a deeper voice, growing facial and body hair, and increasing muscle mass and penis size. Testosterone therapy can also improve bone density and reduce the risk of fractures. It will not result in testicle enlargement or improve infertility.
- **Breast tissue removal:** In males who develop enlarged breasts, excess breast tissue can be removed by a plastic surgeon, leaving a more normal-looking chest.
- **Speech and physical therapy:** These treatments can help boys with Klinefelter syndrome overcome problems with speech, language and muscle weakness.
- **Educational evaluation and support:** Some boys with Klinefelter syndrome have trouble learning and socializing and can benefit from extra assistance. Talk to your child's teacher, school counselor or school nurse about what kind of support might help.
- **Fertility treatment:** Most men with Klinefelter syndrome are unable to father children because few or no sperm are produced in the testicles. For some men with minimal sperm production, a procedure called intracytoplasmic sperm injection (ICSI) may help. During ICSI, sperm is removed from the testicle with a biopsy needle and injected directly into the egg.
- **Psychological counseling:** Having Klinefelter syndrome can be a challenge, especially during puberty and young adulthood. For men with the condition, coping with infertility can be difficult. A family therapist, counselor or psychologist can help work through the emotional issues.

Coping and Support:

Treatment, health education and social support can greatly benefit individuals with Klinefelter syndrome.

Boys with Klinefelter syndrome:

If you have a son with Klinefelter syndrome, you can help promote healthy mental, physical, emotional and social development.

- **Learn about Klinefelter syndrome:** Then you can provide accurate information, support and encouragement.
- **Monitor your son's development carefully:** Seek help for problems you notice, such as trouble with speech or language.
- **Keep regular follow-up appointments with medical professionals:** This may help prevent future problems.
- **Encourage participation in sports and physical activities:** These activities will help build muscle strength and motor skills.
- **Encourage social opportunities and participation in group activities:** These activities can help develop social skills.
- **Work closely with your son's school:** Teachers, school counselors and administrators who understand your son's needs can make a big difference.
- **Learn what support is available:** For example, ask about special education services, if needed.
- **Connect with other parents:** Klinefelter syndrome is a common condition, and you — and your son — aren't alone. Ask your doctor about internet resources and support groups that may help answer questions and ease concerns.

Men with Klinefelter syndrome:

If you have Klinefelter syndrome, you may benefit from these self-care measures:

- **Work closely with your doctor:** Appropriate treatment can help you maintain your physical and mental health and prevent problems later in life, such as osteoporosis.
- **Investigate your options for planning a family:** You and your partner may want to talk to a doctor or other health professional about your options.
- **Talk with others who have the condition:** There are a number of resources that provide information about Klinefelter syndrome and can offer the perspectives of other men and their partners who cope with the condition. Many men also find it helpful to join a support group.

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How to cite this article:

K. Kavitha, et al. GENETIC ASPECTS OF KLINEFELTER'S SYNDROME. J Pharm Res 2019;8(1):41-45.
DOI: https://doi.org/10.5281/zenodo.2571900

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil