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Klinefelter Syndrome: Review of the Literature

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Klinefelter's syndrome (KS) is a syndrome with extra X chromosome(s), in XY individuals, characterized by gynecomastia, small testes, and infertility. Additional X chromosomes can be present as variable karyotypic forms, including mosaicism (47,XXY/46,XY). The reported prevalence of KS ranges from one in 500 to one in 1,000 live males, but is probably underestimated. The classic phenotype is small, firm testes and infertility resulting from seminiferous tubule dysgenesis and androgen deficiency. The spectrum of KS includes tall stature with relatively long legs and arm span, decreased body hair, learning disabilities, behavioral problems, poor motor skills, and other important medical issues, such as metabolic syndrome, diabetes, autoimmune diseases, cardiovascular disease, certain neoplasia. The increased risk of certain medical problems in KS can be attributed to a direct effect of the extra X chromosome, the combined action of multiple genomic and epigenetic factors, or the hormonal imbalances. Typically, chromosome analysis is not ordered for adult patients with general medical conditions, except for suspected cases of hematologic and lymphoid disorders. Even though it was found during work-up for certain disorders in adult patient, most physicians do not suspect KS or consider its impact. Therefore, understanding the pathophysiology and variable manifestation in KS is necessary, and discussions with multidisciplinary teams will help to diagnose and treat males with KS.

Key words: Klinefelter syndrome, Pathophysiology, XXY

REVIEW ARTICLE

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INTRODUCTION

Klinefelter's syndrome (KS) was first described 80 years ago [1]; 5 years after this initial publication, researchers found that men with KS have an excess number of X chromosomes [2]. KS is the most frequent chromosomal disorder in males, with an estimated prevalence of 1:500 to 1:1,000 live male births [3,4]. However, the actual prevalence is probably greater due to failure to identify, and a marked delay in diagnosing the syndrome may occur due to its variable phenotype.

Sometimes, the clone with extra-X chromosome has been found in bone marrow aspiration during work-up for hematologic or lymphoid disease in adult males. In these cases, additional tests should be performed to distinguish between malignant clones with extra X chromosome(s) and constitutional clones with KS. Most physicians do not suspect KS and do not consider its impact.

Here, I will review the prevalence of KS according to epidemiological studies, the pattern of karyotypes, KS genomics and epigenetics, and the risk for certain diseases in KS patients.

Prevalence of KS

KS is the most common chromosomal disorder in males. The prevalence is estimated to be 85 to 223 per 100,000 liveborn males [95% confidence interval 121 to 188 per 100,000] [3-5], but this is probably an underestimate, as many cases go undiagnosed due to variable phenotype and severity.

According to the data from the Korean Statistical Information Service (KOSIS)

of the Ministry of Health and Welfare, the prevalence of KS in South Korea was extremely low in 2006: 3 per 100,000 live-birth males. (https://kosis.kr/statHtml/statHtml.do?orgId=117&tblId=DT_11776_N001) However, this KOSIS data is unreliable because the survey included only newborns. Danish data showed that 65% of prenatally diagnosed KS males are legally aborted, only small fraction are diagnosed in childhood, and a minority are diagnosed late in life. [3,4,6,7] This may have been a similar situation in Korea. Moreover, the prevalence differs among different racial groups within general population. In a study from the United States, the prevalence of KS in males with white ethnicity was 166 per 100,000 but 355 per 100,000 in males with Asian ethnicity [8].

Karyotype variability in KS

The genotypes of KS are highly variable. Among them, the variation in phenotypes most likely depends on the number of extra X chromosomes, the number of abnormal cells, and their location in body tissues. The classic karyotypes seen at diagnosis of KS encompass 47,XXY or the various grades of mosaic karyotype 46,XY/47,XXY. Most KS males have the karyotype of 47,XXY. Approximately 15% of KS males are mosaic XY/XXY.

In comparison to XY/XXY, mosaicism with XX (46,XX/47,XXY) is rarely encountered. Mosaic XX/XXY is associated with a broad spectrum of phenotypes, from true hermaphroditism or genital ambiguity to (extremely rarely) normal female phenotype [9-13]. It is well known that both the phenotypic sex and the gonadal phenotype are influenced by the percentage and distribution of Y chromosome-bearing cells in the gonads, but not necessarily in the blood [14,15]. If the cell line in the gonads bearing a Y chromosome is predominant, the phenotype develops as male. This effect is based on the expression above a critical threshold level of the *SRY* gene (MIM*480000) in the developing urogenital ridge [16].

The reason for the rarity of XX/XXY cases is thought to be underestimated due to failure to detect the 46,XX cell line in the peripheral blood. Peripheral blood specimens are usually used for constitutional cytogenetic investigation. In prenatal study, mixed cells with 46,XX and 47,XXY in a culture dish might be considered contamination with the mother's cells. The presence of a 46,XX cell line has also been reported in cases of KS patients who have been mosaic for more than two different cell lines, XXY/XX/XY/X, XX/XY/XXY/XXXY, XX/XY/XXY/XXXY, XXY/XX/XY, XX/XY/XXY/XXYY, etc. [17,18]

In addition, there are rare cases including higher-grade X or Y chromosome aneuploidies (48,XXXY, 48,XXYY, 49,XXXYY) [19]. Previously, 48,XXYY has been reported as a variant of 47,XXY KS due to a shared physical and endocrinologic phenotype. However, it is now understood that 48,XXYY differs in its medical, neurodevelopmental, and behavioral characteristics [20]. Therefore, the karyotype of 48,XXYY was excluded in the classification of KS. Moreover, Tartaglia et al. [21] have emphasized that 48,XXYY, 48,XXXY and 49,XXXXY characterize a different syndrome from the classic 47,XXY KS, causing the development of more severe phenotypes. The most important reasons for exclusion are related to recognition of the associated medical problems that are more common in XXXY or XXXXY than in XXY, which often require additional evaluations, interventions, and treatments. Additionally, cognitive and behavioral problems in 48,XXYY, 48,XXXY, and 49,XXXXY tend to be more severe than in 47,XXY and require additional interventions and community supports [21].

Genomics and epigenetics in KS

For decades now, phenotypic variability between individual and associated co-morbidities has been demonstrated. However, the effect of an additional X chromosome on the genome is still poorly understood. Several hypotheses concerning genetic mechanisms have been proposed and investigated.

Mosaicism between different tissue types

Mosaicism is considered one of the most important factors affecting clinical manifestation [22,23]. Usually, males with mosaic XY/XXY karyotype in blood samples present with a milder phenotype with reduced severity compared to non-mosaic KS males [24,25]. Moreover, evidence suggests that mosaicism may vary between tissue types and be more frequent than previously thought, based on conventional chromosome analysis using blood samples. Moreover, it is more frequent in cell types other than lymphocytes [26]. Garcia-Quevedo et al. [26] reported the highest degree of mosaicism in Sertoli cells (42.3±11.1%) and the lowest degree of mosaicism in lymphocytes (4.8±2.5%), whereas the degree of mosaicism was 21.9±10.9% in buccal mucosa.

Parental origin and inactivation of X chromosome

In 1989, it was proposed that imprinted genes on the X chromosome might be involved in the phenotypic variability of KS [27]. In addition, the hypothesis of skewed X chromosome inactivation has been suggested to explain the clinical heterogeneity of KS [28]. However, no imprinted genes on the

X chromosome have been identified, and other studies have not been able to find evidence of a parent-of-origin effect on phenotypes [23,29,30]. Moreover, evidence has not been found that there are different phenotypes between cases of skewed X chromosome and random inactivation in KS patients [31-33]. In order to establish this hypothesis, much larger unbiased studies are needed.

Genetic variants of *AR* genes or autosomal genes

Usually, genetic variants can affect disease susceptibility or phenotype. The variants of *AR* gene (MIM*313700) on the X chromosome (Xq12) could be considered to influence phenotypic variabilities in KS patients [34]. The combined action of extra X chromosome(s) and autosomal or X-linked genetic risk variants might explain the increased risk of some disorders in KS patients [35]. To date, information to support these hypotheses is sparse. Additional, larger studies are needed to determine whether variants affect the phenotype of KS patients.

Copy number variants on X chromosomes

According to a study, a proportion of KS males carrying X chromosome-linked copy number variants is significantly higher compared to controls [36]. Furthermore, some of the duplicated regions include genes in the pseudoautosomal region or genes escaping X-inactivation [36].

The X and Y chromosomes are comprised of two identical pseudoautosomal regions, PAR1 (24 genes) and PAR2 (4 genes). KS patients have an additional copy of the pseudoautosomal regions due to the extra X chromosome. A total of 15% of genes on the X chromosome, including all genes within PAR1, escape X-inactivation. Genes escaping X-inactivation are possible candidates affecting the phenotype due to a dosage effect. So far, only one pseudoautosomal gene, *SHOX* gene (MIM*312865), has been convincingly linked to the increased height of KS patients. Other genes in the pseudoautosomal region have been found to have different expression in KS, but the associations to phenotype have not been demonstrated [37,38].

Other genetic studies

In one cell study, gain or loss of an X chromosome results in epigenetic instability by modifying the regulation process of transcriptional and translational pathways in the cells [39]. Epigenetic mechanisms, including DNA methylation, may be altered in KS, causing pervasive and global impact, and could therefore play a crucial role in KS phenotype [37,40]. To date, studies for transcriptome and epigenetics in KS patients indicate that the genetics behind KS may be more complex than previously assumed.

Phenotype in KS

Many boys and men with KS do not realize that they have KS because the phenotype and severity of KS is highly variable. During the prenatal period, physicians may have the opportunity to diagnose and manage KS with prenatal genetic testing. Prepubertal features of KS are variable, and there are no symptoms that are present in all diagnosed cases. KS infants may have subtle dysmorphic signs and some degree of hypotonia [30,41]. Genital anomalies, such as micropenis, undescended testis, bifid scrotum, and hypospadias, are found more frequently in KS infants as compared to infants with a normal karyotype [42]. Congenital anomalies such as renal malformation and cardiac defect are rarely reported, and pathognomonic symptoms are not noted. According to some studies of testicular histology in KS males, the number of germ cells is already reduced at early age, whereas the number of Leydig cells appears to be normal [43-46].

Developmental delay is common in KS. Neurodevelopmental symptoms such as speech disturbance, adaptation problems, attention deficits, and social skill impairments can be found during the early pediatric period. As a result, KS males may be prone to learning difficulties [10,47,48].

The pubertal onset in KS boys occurs at the same time as in normal boys. Gynecomastia can develop due to the negative feedback of Luteinizing hormone elevation increasing estradiol levels. The signs of hypogonadism, such as poor muscular development and reduced facial and body hair, are noticeable during the adolescent period. Host et al. reported that most KS patients present signs of overt hypogonadism after the age of 25 [49].

In adulthood, KS males may have infertility, as diagnosed by azoospermia and oligospermia [31,50,51]. Previously, KS was considered to be a condition of absolute infertility. However, reports from many different centers revealed high sperm retrieval rates, excellent pregnancy rates, and healthy offspring with normal karyotype resulting from KS fathers after microdissection and testicular sperm extraction [51,52].

Important medical conditions in KS

Apart from the apparent phenotypical features, KS is accompanied by a series of comorbidities and increased mortality risk [31]. Conditions leading to hospitalization include dyslip-

Table 1. Adult cases confirmed as Klinefelter syndrome in the work-up for hematologic disorder in Korea

Case	Age[1]	Karyotype	FISH,X/Y[2]	Hematologic disease	Etc.
1	59	47,XXYc,add (11) (q13) [20]	2G1R	Bleeding tendency	Infertility, Follow-up *No physical signs of KS
2	63	47,XXYc	2G1R	Aplastic anemia, T-cell lymphoma	allo-SCT after 1 yr 9 mo of Dx; Death after 2 yr 7 mo of Dx

[1]Age at confirmation of KS; [2]FISH on Buccal epithelial cells.

idemia, obesity, metabolic syndrome, prothrombotic tendency, autoimmune disease, osteoporosis, and cancers [51,53].

Serum testosterone levels are independently associated with insulin resistance, which suggests that low testosterone might be responsible for type 2 diabetes and the five-fold increase in metabolic syndrome has been observed in KS males [54,55]. We therefore could expect high efficacy for testosterone replacement therapy (TRT) on glucose metabolism in KS; however, TRT has not been shown to improve metabolic syndrome or diabetes in KS patients, compared to other types of hypogonadism [55,56]. This indicates that there are more complex mechanisms associated with KS and glucose metabolism.

In vascular and cardiac disease, KS males exhibit increased risk of venous thromboembolism: hazard ratio (HR) 5.29 for thrombophlebitis and venous thrombosis, HR 3.60 for pulmonary embolism, and HR 1.71 for ischemic heart disease [42,57,58].

A retrospective study from England has demonstrated a significant increased risk in KS relative to controls regarding Sjogren's syndrome (risk ratio (RR) 19.3), systemic lupus erythematosus (RR 18.1), Addison's disease (RR 11.7), diabetes mellitus type 1 (RR 6.1), multiple sclerosis (RR 4.3), rheumatoid arthritis (RR 3.3), and acquired hypothyroidism (RR 2.7) [59]. It was reported that the human X chromosome contains the largest number of immune-related genes, and around 10% of all microRNAs, from the whole human genome. Some microRNAs on the X chromosome have important immune-related functions.

KS is also an important risk factor for osteoporosis and osteopenia [31,60]. Bone disease in KS was eight-fold higher than the incidence in non-KS [61]. The etiology is multifactorial, with testosterone deficiency as the primary cause. Testosterone deficiency can lead to lower bone formation and higher bone resorption. TRT has been shown to improve bone mineral density (BMD) on some levels, but vitamin D repletion has been demonstrated to be superior to TRT for improving BMD [61-63].

In terms of the incidence of cancers, the difference of overall cancer risk is no significant between KS and the general male population. However, certain cancers, such as breast cancer and germ cell tumors, especially extragonadal tumors, occur more frequently in KS males than in the general population [64]. Compared with non-KS, the incidence of breast cancer is increased 4 to 30-fold, and the mean onset age of breast cancer is earlier (58 years vs. 67 years) in KS. This supports the idea that KS is the strongest independent risk factor for breast cancer in males [65-67]. In extragonadal germ cell tumors, higher prevalence is observed in KS with presentation at a younger age than in normal males [68]. On the other hand, the prevalence of prostate cancer and its associated mortality have been reported to be lower in KS than in normal-karyotype men [69,70].

Published studies regarding the risk of hematological and lymphoid malignancies in KS present conflicting evidence. Some publications suggest an increased risk of leukemia development in KS, whereas others have determined that there is only a chance association [69,71,72]. A Swedish registry study reported a notable increase in hematologic malignancies (standardized incidence ratio (SIR) 2.72) such as non-Hodgkin lymphoma (SIR 3.02) and acute leukemias (SIR 3.62) [69]. The underlying mechanisms for the increased incidence of these malignancies in KS are not clear and need to be investigated.

In my experience as a cytogeneticist, I have analyzed approximately 3,200 karyotypes of bone marrow specimens (1,800 cases of male patients) during a 10-year-period, 2011-2020. I met four adult men suspected to have KS; they were involved in the work-up for hematologic disorder. Patients suspected of having KS should undergo karyotyping on peripheral blood lymphocytes in remission state or fluorescence in situ hybridization (FISH) on buccal epithelial cells. Using this method, I was able to confirm KS in two patients aged 60-70s (Table 1). The others were not performed further evaluation.

CONCLUSION

KS is the most common sex chromosome disorder in males. Despite increasing knowledge of the natural history of KS, di-

agnosis often does not occur throughout the lifespan. Earlier diagnosis of KS may provide greater opportunities for earlier intervention and effective treatment. Once the diagnosis of KS has been established, careful management and appropriate treatment are possible with multidisciplinary teams, including physicians. To help these patients early and achieve proper diagnosis, the deeper understanding of the pathophysiology of KS will be helpful.

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CONFLICTS OF INTEREST

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