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## KLINFELTER SYNDROME: ETIOLOGY AND PREVENTION

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**Abstract** Klinefelter syndrome (KS) is one of the most common sex chromosome aneuploidies affecting males and is most frequently characterized by the 47,XXY karyotype. The condition is associated with hypogonadism, infertility, metabolic disorders, and neurocognitive impairments. Despite its relatively high prevalence, Klinefelter syndrome often remains underdiagnosed. This article provides an evidence-based overview of the etiology, genetic mechanisms, clinical significance, diagnostic approaches, and preventive strategies related to Klinefelter syndrome, in accordance with contemporary medical literature.

**Keywords** Klinefelter syndrome; 47,XXY; sex chromosome aneuploidy; male hypogonadism; genetic counseling; prevention

### Introduction

Klinefelter syndrome is a chromosomal disorder affecting approximately 1 in 500–600 male births worldwide. First described by Harry Klinefelter and colleagues in 1942, the syndrome results from the presence of one or more additional X chromosomes in males. Due to its variable clinical presentation, many individuals are not diagnosed until adolescence or adulthood, often during evaluation for infertility or delayed puberty. Understanding the etiology and preventive aspects of KS is essential for improving early diagnosis and long-term outcomes.

#### Etiology and Genetic Basis

The primary cause of Klinefelter syndrome is meiotic nondisjunction during gametogenesis, leading to the presence of an extra X chromosome. Approximately 80–90% of cases are caused by the classic 47,XXY karyotype. Other genetic variants include mosaic forms (46,XY/47,XXY) and higher-order aneuploidies such as 48,XXXYY or 48,XXYY.[1,2,34]

Both maternal and paternal nondisjunction events may contribute to the development of KS. Advanced maternal age has been identified as a modest risk factor; however, the condition can occur in offspring of mothers of any age.[5]

#### Pathophysiology

The additional X chromosome leads to impaired testicular development and progressive degeneration of seminiferous tubules. This results in reduced testosterone production, elevated gonadotropin levels, and hypergonadotropic hypogonadism. These hormonal disturbances underlie many of the physical, reproductive, and metabolic manifestations of the syndrome.[6]

#### Clinical Manifestations



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Clinical features of Klinefelter syndrome vary widely. Common characteristics include tall stature, small firm testes, gynecomastia, decreased muscle mass, reduced facial and body hair, and infertility. Neurodevelopmental and psychosocial issues, such as learning difficulties, language impairment, and reduced social adaptation, are also frequently observed.

#### Diagnostic Approaches

Definitive diagnosis of Klinefelter syndrome is achieved through cytogenetic analysis, primarily standard karyotyping of peripheral blood lymphocytes. Additional diagnostic techniques include fluorescence in situ hybridization (FISH) and chromosomal microarray analysis. Endocrine evaluation typically reveals low serum testosterone levels accompanied by elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

#### Prevention and Prophylaxis

There is no absolute method to prevent Klinefelter syndrome, as it results from spontaneous chromosomal nondisjunction. Preventive strategies therefore focus on secondary prevention, including early diagnosis, genetic counseling, and timely medical intervention. Prenatal screening and diagnostic testing can identify sex chromosome aneuploidies, allowing families to receive appropriate counseling and make informed reproductive decisions.

#### Management and Prognosis

Early diagnosis and testosterone replacement therapy can significantly improve physical development, bone density, metabolic health, and quality of life. Advances in assisted reproductive technologies, such as testicular sperm extraction combined with intracytoplasmic sperm injection, have enabled some individuals with KS to achieve biological fatherhood. With appropriate medical care, life expectancy is near normal.[7]

**Conclusion** Klinefelter syndrome is a common yet frequently underdiagnosed chromosomal disorder with significant medical, reproductive, and psychosocial consequences. Although primary prevention is not possible, early detection, genetic counseling, and comprehensive medical management serve as effective preventive measures against long-term complications. Increased awareness among healthcare professionals is essential to improve diagnostic rates and patient outcomes.

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