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REVIEW ARTICLE

The Role of Genetic Mutations in XX Male Syndrome

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Abstract

The XX male syndrome results from crossover between the X and Y chromosomes outside of the pseudoautosomal region during Meiosis I, which transfers the *SRY* (sex-determining region) of the Y chromosome to the X chromosome, such that testicular rather than ovarian development occurs.

Keywords: XX Male Syndrome, SRY gene, Y chromosome, X chromosome, Testicular developmental disorder.

1 | INTRODUCTION

Generalities of XX Male Syndrome

XX Male syndrome, also known as testicular developmental disorder 46, XX, is a chromosomal disorder in which individuals with two sex X chromosomes per cell, commonly found in women, are identified and these individuals appear They have men. People with this disorder have a male external penis[1].

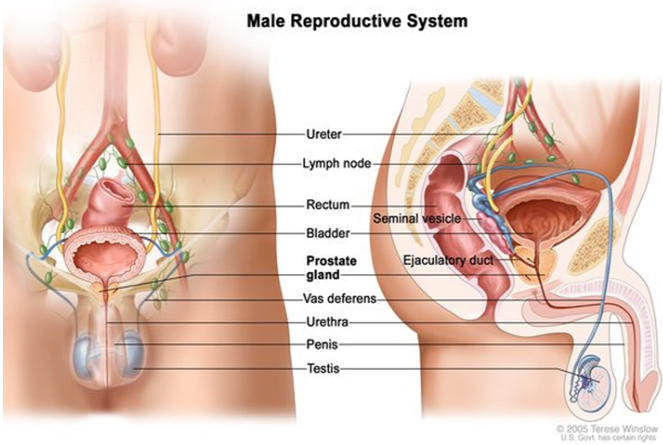

FIGURE 1: Schematic of the structure of the male reproductivesystem[1].

Signs and Symptoms of XX Male Syndrome

Patients with XX male syndrome generally have small testicles and may have the testicles descend into the scrotum or the urethra is located below the penis (hypospadias). A small number of patients with this syndrome have ambiguities in the external penis that are not identifiable as male or female. Children affected by this syndrome are commonly identified as male and have a male sexual identity (1), (2).

During puberty, most people with this syndrome are treated with the male sex hormone testosterone, a process that leads to the development of secondary male sexual characteristics such as facial hair and

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hoarseness. In addition, hormone therapy can help prevent breast enlargement (gynecomastia) in patients. Adults with this disorder are usually shorter than men their own age and are unable to have children (infertile)[1, (3)].

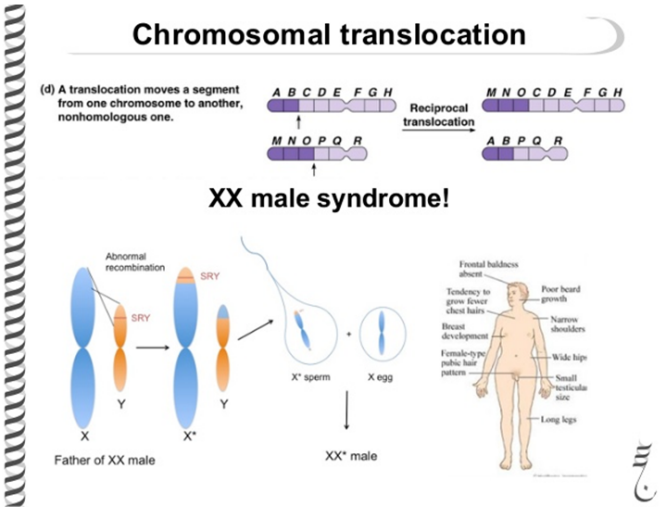


FIGURE 2: Schematic of chromosomal translocation in XX malesyndrome[1].

Etiology of XX Male Syndrome

Humans usually have 46 chromosomes in each of their cells, two of which are sexual and are known as X and Y, because these chromosomes determine the sexual identity of males or females in humans. Women usually have two sex chromosomes XX and men usually have two sex chromosomes X and Y[1, (4)] .

The SRY gene, located on the short arm of the Y sex chromosome at Yp11.2, provides the instructions for Y-region protein synthesis. Zone Y protein determines male gender in humans[1, (4)] .

In about 80% of people with XX man syndrome, this condition results from an unusual exchange of genetic material between chromosomes (translocation). This exchange appears to occur as a random event during the formation of sperm cells in the infected father. This exchange causes the SRY gene to almost always be mistakenly replaced on the X sex chromosome. If a fetus is born with the X sex chromosome, which contains the SRY gene, it will have a male sexual identity even though it does not have the Y sex chromosome. This condition is known as XX man syndrome or SRY + -46, XX disorder[1, (5)].

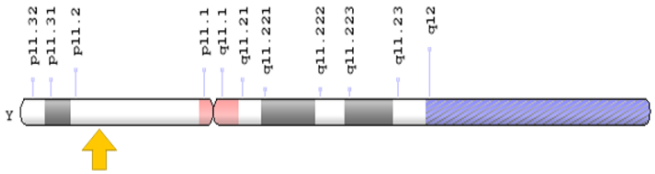
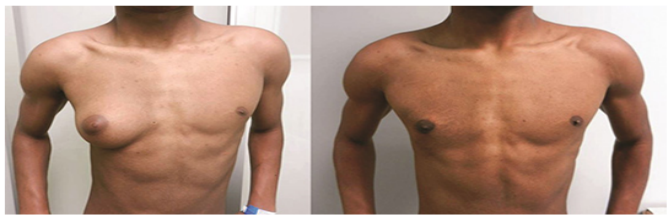


FIGURE 3: Schematic view of the Y sex chromosome where the SRY geneis located in the short arm of this chromosome as Yp11.2.[1]

It is worth noting that about 20% of people with XX male syndrome do not have the SRY gene, which is known as SRY-46, XX disorder. The cause of the disorder in these people is often unknown, although changes that affect other genes have been identified. People with SRY-46, XX are more likely to have a fuzzy external penis than people with SRY-46, XX . [1, (6)]

SRY + -46, XX disorder is almost never inherited and does not follow any inherited pattern. This condition is caused by the transfer of a portion of the Y sex chromosome containing the SRY gene during sperm formation (spermatogenesis). Affected people typically have no family history of the disorder and cannot get over it because they are infertile[1, (7)] .

In rare cases, the SRY gene may be replaced on a chromosome other than the X sex chromosome. This transmission may be carried out by an unaffected father and is passed on to two children with two X chromosomes, leading to Male Syndrome XX. In a very rare situation, a man may carry the SRY gene on both the X and Y chromosomes, and a boy who inherits his X chromosome in this case does not have the characteristics of a male despite having a Y chromosome.[1, (7)]



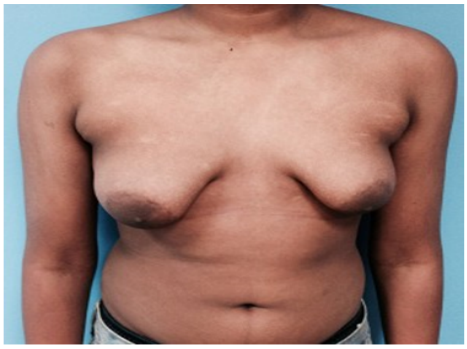


FIGURE 4: Images of gynecomastia disorder in men with XX malesyndrome.[1]

The hereditary pattern of SRY - 46, XX is unknown. In some cases, the disorder follows an autosomal recessive inherited pattern. Therefore, two copies of the mutated SRY gene (one from the father and the other from the mother) are required to cause the syndrome, and the chance of having a child with the autosomal recessive syndrome is 25% for each possible pregnancy . [1, (8)]

Frequency of XX Male Syndrome

XX male syndrome is a genetic disorder that has a prevalence of about 1 in 20,000 worldwide.[1, (8)]

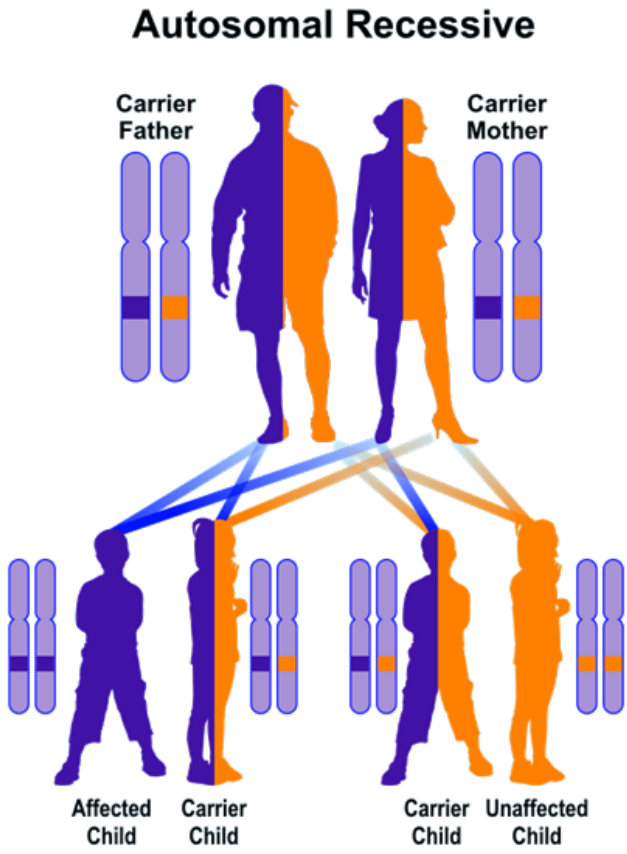


FIGURE 5: Schematic of the autosomal reces inherited patternthat XX male syndrome can follow.[1]

Diagnosis of XX Male Syndrome

XX male syndrome is diagnosed based on clinical and physical findings of patients and some pathologi-cal tests. The most accurate way to diagnose this syn-drome is to test molecular genetics and molecular cytogenetics with the in situ fluorescence hybridization (FISH) technique to check for possible mutations in the SRY gene[1, (9)] .

Treatments for XX Male Syndrome

The treatment strategy and management of XX male syndrome is symptomatic and supportive. Treatment may be done with the help and coordination of a team of specialists, including hormone therapists, urolo-gists, surgeons, and other health care professionals. There is no definitive cure for this syndrome. Genetic counseling is also essential for all parents who want a healthy baby[1, (9)].

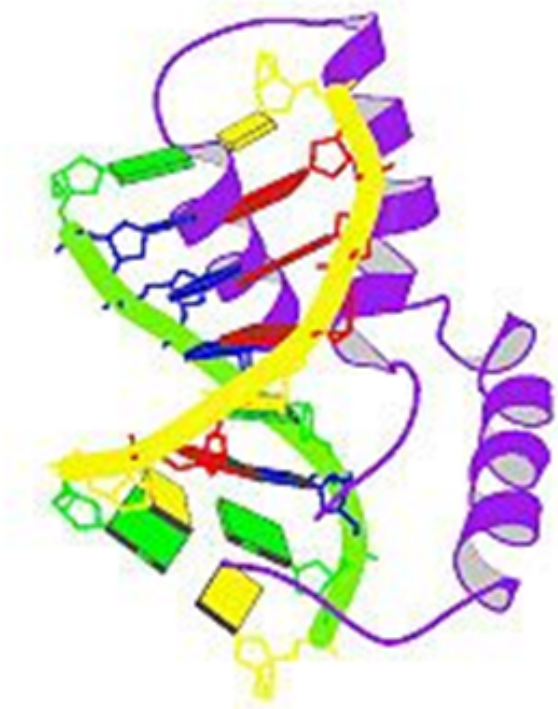


FIGURE 6: Schematic of the structure of the SRY protein.[1]

Discussion

Frequently, XX males have a genetic translocation involving the testis-determining gene, SRY. SRY, which encodes a DNA-binding protein, is normally located near the pseudo-autosomal region of the short arm of the Y chromosome. In most XX males, SRY has been incorporated into the X chromosome or another autosome.This is thought to result from aberrant recombination between the X and Y chro-mosomes.

Two-thirds of XX males have detectable Y chromosomal sequences in the distal region of the X chromosome. Some XX males have a mosaic pattern of expression, with a few cell lines expressing 46,XY and the rest expressing 46,XX. Interestingly, all known XX males with hypospadias and genital ambiguity have been found to lack the SRY gene. Hence, the disorder is heterogeneous, and some cases remain unexplained. Although most cases are spo-radic, there are familial cases of 46,XX males, with all familial cases having genital ambiguity[1, (9)].

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