

## 46XX Testicular Deficiency (Man Syndrome)

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### ABSTRACT

46, XX male is a rare (1:20 000 in newborn males) syndrome. The main issue influencing sex determination of associate embryo is that the Sex-Determining Region Y (SRY), a master cistron settled on the Y chromosome. The presence of SRY causes the bipotential gonad to differentiate into a testis and SRY positivity is responsible for this condition in approximately 90% of these subjects. External genitals of 46,XX SRY-positive males seem as traditional male external genitals, and such cases square measure diagnosed once they gift with tiny testes and/or sterility once pubescence. Here, we report a 29 year old male was admitted to the outpatient clinic with the complaint of infertility. He showed normal external male genitalia except for small testes. Through reportage this rare case and reviewing previous literatures, the aim of this report is to focus on the worth of genetically screening all males with azoospermia agency gift for analysis of sterility, since the composition doesn't invariably correlate with the genotype.

**Abbreviations:** DSD: Disorder of Sex Development; SRY: Sex-Determining Region Y Gene; TDF: Testis Determining Factor; FISH: Fluorescence In Situ Hybridization; PCR: Polymerase Chain Reaction; HMG: High Mobility Group; SOX9: SRY (Sex Determining Region Y)-Box 9 Gene; WT1: Wilms Tumor 1 Gene; WNT4: Wingless-Type MMTV Integration Site Family, Member 4 Gene; FGF9: Fibroblast Growth Factor 9 Gene; RSP01: R-Spondin 1 Gene

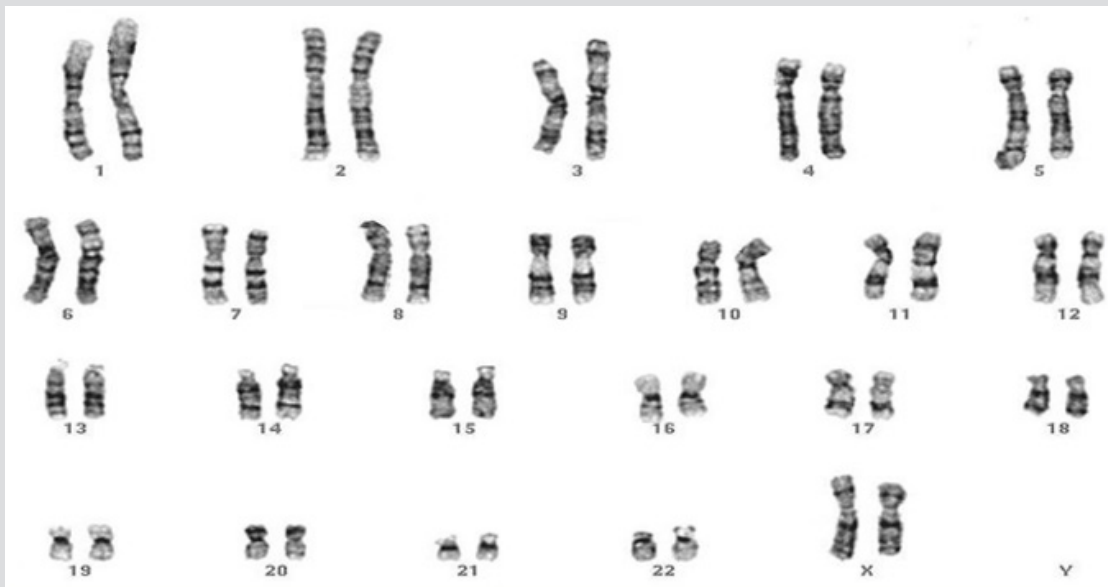
### Introduction

46XX testicular deficiency (male syndrome) is a sexual developmental disorder which has the incidence of 1/20000 male births [1]. These cases are diagnosed after puberty with hypogonadism, gynecomastia and infertility. Karyotype analysis is important for the differential diagnosis of sex chromosome anomalies. The aim of this case report is to analyse hormonal, molecular and cytogenetic conditions of an adult male who got diagnosed with 46,XX testicular deficiency in our clinic.

### Case Report

29 year old male was admitted to the outpatient clinic with the complaint of infertility. His past medical history and family history had no characteristics. His height was 175 cm, weight 77 kilogram, BMI 25.6 kg/m<sup>2</sup> and waist circumference 90 centimetres. His facial, axillary and pubic hairs were normal. Bilateral grade 2 gynecomastia was present. Testicles were bilaterally atrophic on physical

examination. Penis size measurement was normal. On laboratory examination, fasting blood glucose was 123 mg/dl, fasting insulin level 54.3µu/l, HOMA-IR 29.7, FSH 42.23 µu/ml, LH 23.08, total testosterone 1.32 ng/ml (1.42-10.000), 17 oh progesterone 1 ng/ml. On scrotal ultrasound examination, right testis was 16x8 mm and left testis was 15x8 mm in size (infantile appearance). Mammalian ultrasonography was reported as bilateral retroareolar fibro glandular tissue. On pelvic MRI, both testicle and prostate were highly atrophic, ovarian and uterine tissue were not present. No sperm was observed on spermogram. On bone mineral density measurement, Z score of L1-4 was -2.10 and femur neck-trochanter-wards Z score was -3.34, indicating osteoporosis. Genetical examination was carried out with the suspected diagnosis of hypergonadotropic hypogonadism. 46XX male karyotype was established on cytogenetic examination ( Figure 1). Testosterone replacement and metformin treatment were started.



**Figure 1:**Chromosome analysis of 46 XX testicular deficiency (man syndrome).

## Discussion

46, XX male syndrome could be a rare sex reversal syndrome characterised by a feminine makeup in discordance with a male composition. By 1996, one hundred fifty patients with classical XX male syndrome had been reportable, and quite a hundred cases of this disorder are described between 1996 and 2006 worldwide [2,3].

It can be classified into two subgroups, SRY-positive or SRY-negative, according to the presence or absence of the Sex-Determining Region Y (SRY) gene. Approximately 80% of patients with 46,XX testicular Disorder of Sexual Development (DSD) have SRY on one of two X chromosomes, which results from abnormal chromosomal translocation during gametogenesis. That might be that each one males were SRY-positive, that translocated on the short arm of X chromosome, and absent of the spermatogenic factors coding sequence on Yq, like AZFa, AZFb and AZFc region in Y chromosome. And a number of other genes such as SOX9, DAX-1, WT1 WNT4, FGF9 and RSP01 have been involved in the process of gonadal differentiation. At least three mechanisms have been suggested for the etiology of 46,XX male disorder of sexual development:

- a) Translocation of Y chromosome including the SRY gene on the X chromosome or on autosomal chromosomes,
- b) X-linked mutation/overexpression in the genes that cause testis differentiation or mutation/overexpression in autosomal genes [e.g. SRY Box-Related Gene 9 (SOX9)] in SRY negative XX males, and
- c) Secret Y mosaicism found only in the gonads. SOX9 on chromosome 17q24.3 is one of the genes that plays an important role in the development of the skeleton and genital organs.

During embryogenesis, SOX9 is expressed immediately downstream of SRY and functions as a critical Sertoli cell differentiation factor. In addition, differentiated Sertoli cells express anti-Müllerian hormone, which is required for Müllerian duct regression and differentiation of male genitalia.

Clinical phenotypes about 46, XX DSD have been identified to three groups, including males with normal phenotype, males with genital ambiguities and males with true hermaphrodites [4]. Otovestibular DSD, that is characterised by the presence of each gonad and female internal reproductive organ tissue within the gonads of constant individual, and gonad DSD characterised by a full development of each gonads as testes with none proof of female internal reproductive organ tissue [5]. Most patients have traditional male phenotypes at birth, and area unit typically diagnosed in late adolescence owing to delayed time of life, abnormal condition, or physiological state. Approximately 15% of XX males have hypospadias, cryptorchidism, or more severe genital ambiguity [6].

Classical 46 XX male have normal testosterone level and free testosterone level during adolescence, but may decrease in adulthood, leading to hypergonadotropic hypogonadism [7]. Our cases had normal genitalia and were diagnosed for infertility after puberty. Treatment of manifestations; just like that for different causes of androgenic hormone deficiency. when age fourteen years, low-dose androgenic hormone medical aid is initiated and step by step increased to achieve adult levels. In affected individuals with short stature who are eligible for growth hormone therapy, testosterone therapy is either delayed or given at lower doses initially in order to maximize the growth potential. Reduction mammoplasty might have to be thought-about if abnormal condition remains a difficulty following androgenic hormone replacement medical aid. Treatment for osteopenia is by standard protocols.

## Conclusion

A multidisciplinary approach, in which endocrinology, psychiatry, urology and medical genetic departments are taking part, is needed and genetical consulting is essential for these cases.

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