

# Adolescent females with 46, XY Disorders of Sexual Differentiation

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## Abstract

Disorders of sex development are congenital conditions where chromosomal, gonadal and anatomical sex of an individual is atypical. The sex of an individual is governed by chromosomal complement, which in turn decides the development of bi-potential gonad and differentiation of external as well as internal genitalia into a definitive human sex either male or female. Though this is the general plan of sex development, most of the times in spite of being normal chromosomal complement, the gonadal and/ or genital sex is discordant leading to conditions known as disorders of sex development. Depending upon the chromosomal complement, these conditions are classified as (a) sex chromosome DSD (b) 46, XY DSD and (c) 46, XX DSD. Though most of the DSDs present at infancy with genital ambiguity and other clinical features, some of these conditions may not present or get recognized until adolescence and presenting as lack of pubertal development or primary amenorrhea. This leads to a social stigma to the patient as well as the family members and proper counselling and management of these cases can be improved by understanding the molecular pathology of these conditions. This review helps to understand the molecular genetics of 46, XY DSD in adolescent females who present as lack of puberty and primary amenorrhea.

**Keywords:** Disorders of sex differentiation (DSD); Primary amenorrhea; 46, XY gonadal dysgenesis; Complete androgen insensitivity syndrome; Molecular genetics.

## INTRODUCTION

Disorders of sex development are congenital conditions where chromosomal, gonadal and anatomical sex of an individual is atypical.<sup>1</sup> The

sex of an individual is determined by the genetic constitution, which in turn gives rise to formation of appropriate gonads and these gonads along with the hormones secreted by them with appropriate receptors leads to the formation of external as well as internal genitalia. Differences of sex development also known as disorders of sex development (DSD) consists of large group of congenital conditions which affects the development of urogenital tract and reproductive systems affecting human sex determination and/or differentiation.<sup>2</sup> Though there are several evidences on the anatomical and hormonal defects of sex determination and/or differentiation in the past, the extensive advances in this era of molecular genetics has improved our knowledge of various genes critical to normal sex development as well as genetic mechanisms

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underlying DSDs. The expression of various genes like *SRY*, *SOX9*, *DAX1* and *WNT4* controls the direction of gonadal differentiation as an ovary or testis.<sup>3</sup> The other genes which are required for early gonadal development are *SF1*, *WT1* and *DMRT1*. Depending upon the expression levels of these genes there occurs differentiation of gonads as testis or ovary. Though the process is much more complicated, mutations in these genes leads to defects in gonadal and genital development leading to the disorders of sex differentiation. These conditions are formerly referred as ambiguous genitalia or intersex disorders or pseudo-hermaphroditism which are now replaced with disorders of sexual differentiation or differences in sexual differentiation. Though there are various types of DSDs, the focus of this review is mainly females with 46, XY karyotype and presenting as lack of puberty and primary amenorrhea.

## EMBRYOLOGY AND GENETICS OF DSD

The gonads develop from the cells which migrates from urogenital ridge at around 4-6 weeks and they remain undifferentiated till 6 weeks. The *NR5A1/SF1* and *WT1* are the genes controlling the formation of gonads at earlier stage and are responsible for migration of the cells from urogenital ridge. These genes are also responsible for development of adrenal gland and kidney respectively. Once there occurs migration of the cells from urogenital ridge then the presence or absence of *SRY* gene will decide the formation of testis or ovary.<sup>3</sup> If the *SRY* gene is present then it sends downstream signaling for the expression of *NR5A1* and *SOX9* gene resulting in formation of testis from the undifferentiated gonads. Once the testis is formed, the Sertoli cells secrete antimullerian hormone which will lead to regression of mullerian structures. Leydig cells of the testis secrete testosterone. This testosterone is converted into its active form dihydrotestosterone (DHT) by the enzyme 5 alpha reductase type 2 and will give rise to formation of external genitalia and testosterone itself along with the androgen receptor leads to formation of internal genitalia.<sup>4</sup> If the DHT is not formed due to deficient 5 alpha reductase type 2 enzyme, then the external genitalia are under virilized and may not be like that of normal male. During puberty the testosterone secretion rises, which acts on the androgen receptors present on external genitalia leading to virilization of the external genitalia. So the female child whose external genitalia are under virilized at the time of birth and not looking like that of male get virilized at the time of puberty, the deficiency of 5 alpha

reductase type 2 enzyme can be suspected. On the other hand when there is androgen receptor defect, in spite of having normal amount of testosterone and DHT, the external genitalia are under virilized and when there is testosterone surge at the time of puberty, this androgen gets aromatized in the peripheral tissues leading to development of secondary sexual characters like that of female. Thus the under virilized female child at the time of birth feminizing at the time of puberty, one should suspect complete androgen insensitivity syndrome.<sup>5</sup>

In the absence of *SRY* gene, there is downstream regulation of *FOX2*, *WNT4*, *DAX1* and *RSPO1* genes and the ovary develops, theca cells of which secrete androstenedione and granulosa cells secreting estrogen.<sup>3</sup> Also one should note the fact that for the in utero development of ovary, there is no necessity of both the X chromosomes to be present.

## 46, XY DSD CONDITIONS PRESENTING AT THE TIME OF PUBERTY

### *XY gonadal dysgenesis/Swyer syndrome*

These conditions, also known as pure gonadal dysgenesis or 46, XY sex reversal (OMIM#233420). These cases are characterized by female phenotype with dysgenetic testicular tissue due to mutation in *SRY* gene leading to abnormal function of fetal testis. Though there is *SRY* gene leading to formation of testis, there is a mutation in this gene leading to abnormal testicular development giving rise to streak gonads. As these gonads lack Sertoli cells, in the absence of AMH, there occurs development of mullerian structures in these females. Also due to absence of Leydig cells, testosterone is deficient which fails to virilize the external genitalia and therefore external genitalia looks like that of female.<sup>6</sup> *SRY* gene mutations appear to be responsible for about 20% of 46, XY gonadal dysgenesis and most of these mutations are lying within the specific HMG-box region.<sup>7</sup> Though the incidence of *SRY* gene mutation is reported to be 20%, an Indian survey by Nagaraja et al mentioned only 7 cases of *SRY* gene mutation till date.<sup>8</sup>

### *Complete androgen insensitivity syndrome*

The most common clinical condition found in phenotypic female with primary amenorrhea and 46, XY DSD is Complete androgen insensitivity syndrome (CAIS) (#300068), the X-linked recessive condition. At the time of puberty, these females present as primary amenorrhea, but with breast

development and with minimal or no pubic hair development, and previously un-noted palpable labial testes. In spite of having normal male karyotype and *SRY* gene being normal there occurs normal testicular development but due to absence of androgen receptors testis remain undescended. Normal breast development occurs because of peripheral aromatization of androgen. External genitalia are female, including a vaginal orifice but with shortened vagina. The mullerian duct derivatives are absent as a consequence of normal Sertoli secretion of AMH, but as there is defective androgen action during fetal life, there is lack of development of wolffian duct derived structures, including the epididymis and vas deferens. The etiology of this syndrome is end organ unresponsiveness to androgen. Androgen action is mediated by the androgen receptor, which is a ligand dependent transcription factor. Our extensive literature search revealed that *AR* gene mutations ranging from a single nucleotide variations to complete gene deletion including intronic mutations<sup>9,10</sup> are responsible for variable phenotypes in 46, XY DSD subjects leading to either complete or partial androgen insensitivity syndrome.<sup>8</sup> Complete loss-of-function mutations of the androgen receptor are usually associated with complete androgen insensitivity. Numerous *AR* mutations have been described in affected individuals. So far, 32 different mutations in *AR* gene were reported in Indian ethnics.<sup>8</sup>

### **5 Alpha reductase type-2 deficiency**

The second gene associated with 46, XY DSD and responsible for primary amenorrhea in adolescent females is steroid 5 alpha-reductase 2 gene (*SRD5A2*) (cytogenetic location: 2p23.1). 5 $\alpha$ -reductase deficiency (#264600) involves a defect in the conversion of testosterone to dihydrotestosterone (DHT) as a consequence of deletions and mutations of the 5 $\alpha$ -reductase type 2 gene (*SRD5A2*). Due to absent DHT, which is required for normal male external genitalia, development, these cases show varying degrees of genital ambiguity including a blind vaginal pouch with variable phallic development. Since AMH is secreted, mullerian-derived structures do not develop. The presence of a bifid scrotum and a urogenital sinus resembling female genitalia, may lead to a female sex of rearing. At puberty, among those with significant testosterone production, striking virilization occurs, with phallic growth and male-type muscle and skeletal development. In a survey by Nagaraja et al, a total of 19 mutations were reviewed in *SRD5A2* gene from various

studies among Indian ethnics, and were found to be the second most frequently reported among the genes causing 46, XY DSD.

### **17 Beta hydroxysteroid dehydrogenase deficiency**

17 $\beta$ -hydroxysteroid dehydrogenase (17-HSD) deficiency (MIM#309150) results from loss of function mutations of the 17 $\beta$ -hydroxysteroid dehydrogenase (*HSD17B3*) gene. This gene, located at chromosome 9q22, is expressed primarily in the testes; mutations in this gene results in undervirilization and as this gene is not expressed in ovary so these cases have a typical female phenotype. Progressive, marked virilization may occur at puberty, with some individuals changing to a male gender role. Clinical findings may be similar to those found with 5 $\alpha$ -reductase deficiency and androgen insensitivity.<sup>11</sup> B.B Mendonca et al in 2016 study, quoted almost 37 mutations reported in the literature in the *HSD17B3* gene and which were found to be missense, nonsense, exonic deletion, duplication, intronic splice site and amplification mutations.<sup>12</sup>

### **46, XY Sex reversal due to SF1 gene mutation**

The other gene which is responsible for 46, XY DSD is *SF1* (Steroidogenic Factor 1) (MIM#184757), located at 9q33, also known as *NR5A1* gene. It encodes a nuclear transcription factor regulating the expression of a number of genes that participate in sexual development. In humans, heterozygous *SF1* mutations in XY individuals lead to adrenal and gonadal failure<sup>13</sup>, cryptorchidism<sup>14</sup>, micropenis, and infertility.<sup>15</sup> H. Fabbri-Scaliet et al in 2019 reviewed 188 *SF1* gene mutations from 238 published cases of both 46, XX and XY DSD and observed the frequency of 12% (25/205) variations in 46, XY DSD cases with predominance of mutation in DBD (35%) and LBD (42.3%) domains.<sup>16</sup> Nagaraja et al reviewed 4 cases of *SF1* gene mutations in gonadal dysgenesis among Indian ethnics, out of which 3 were reported by *Chauhan* et al. in 2017 in male patients and 1 was reported by *Paliwal* et al. in 2011 in a female patient.<sup>17</sup>

## **CONCLUSION**

In this review we have discussed the disorders of sex differentiation presenting during adolescence, the clinical features and the molecular genetic basis for these clinical conditions. This will help the clinicians to plan the management of these conditions and to take care of the adolescent females with DSD with multidisciplinary approach.

The multi-faceted approach should consist of early diagnosis by advising cytogenetic and molecular evaluation by using modern techniques like next generation sequencing (NGS), medical and surgical treatment of these conditions, psychological and genetic counselling for the gender reassignment and infertility. As 46,XY DSDs are rare conditions, large multi-center studies are required for the better outcomes as well as to develop educational programs for the professionals dealing with DSDs. Though this review has discussed the development and genetics of sex from adult studies, more research is needed in the childhood stages of sex development to understand and differentiate the pattern of DSD in adolescent and children.

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