Review

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Unraveling the genetic and pathophysiological mechanisms underlying disorders of sex development

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SUMMARY: Disorders of sex development (DSDs) encompass a spectrum of congenital conditions characterized by discordance among chromosomal, gonadal, and anatomical sex. Advances in genetic and molecular technologies have elucidated a complex landscape of underlying etiologies, including mutations in genes regulating sex determination and differentiation, copy number variations, and epigenetic alterations. These discoveries have not only enhanced diagnostic accuracy but also deepened our understanding of the molecular mechanisms driving DSDs. This review provides a comprehensive overview of the genetic architecture in DSDs, with a focus on key regulatory genes and their network interactions. We also highlight emerging concepts in the field, such as oligogenic inheritance and regulatory genomic elements, and discuss implications for personalized diagnosis, classification, and therapeutic strategies. By integrating recent advances from both clinical and basic research, this review aims to offer a framework for future investigations and translational applications in the management of DSDs.

Keywords: disorders of sex development (DSD), diagnostics, genetics, pathogenesis

1. Introduction

Disorders of sex development (DSD) is a type of congenital disease with atypical chromosomes, gonads, or anatomical sex or abnormal development, with high heterogeneity in clinical manifestations and heredity, and a prevalence of about 1: 5500 - 1 :4500 (*1*). Its incidence and rate of diagnosis are low, and multidisciplinary comprehensive evaluation is often required. Molecular genetic technology mediates in the diagnosis and has guiding significance for the early diagnosis of DSD. According to the consensus of the Chicago Conference in 2006, DSD are divided into 46, XX DSD, 46, XY DSD, and sex chromosome DSD (*2*). 46, XY DSD has a variety of causes and clinical manifestations, is difficult to diagnose clinically, and most patients require surgery.

However, the diagnosis of DSD is primarily determined by a comprehensive evaluation encompassing a medical history, physical examination, laboratory analysis, genetic evaluation, and imaging studies, among other factors. The predominant advance during the preceding decade pertains to the evolution of genetic testing. In the event that patients undergo genetic testing, approximately one-third are found to possess mutant genes (Figure 1). For children with vague external genitalia or without secondary sexual development in adolescence, the evaluation and diagnosis should be completed with the cooperation of a multidisciplinary team (MDT), which should consist of pediatric endocrinology, pediatric (urological) surgery, obstetrics and gynecology, imaging, psychology, molecular genetics, or other related departments (*3*). At the same time, if the pathogenesis can be clarified, then it can be followed by precise treatment.

2. 46, XX DSD of adrenal origin

46, XX DSD is mainly related to SRY gene translocation, excessive factors related to promoting development and differentiation in the fetus and androgen excess, including 46, XX testicular DSD and congenital adrenal hyperplasia (CAH). In 46, XX cases, adrenal steroid production disorder is the cause of genital abnormalities, and patients may display an aldosterone deficiency, which may lead to life-threatening salt consumption crisis (*4*). Adrenal steroidogenic defects leading to 46, XX DSD are a 21-hydroxylase deficiency, which is by far the most prevalent, and an 11β-hydroxylase deficiency.

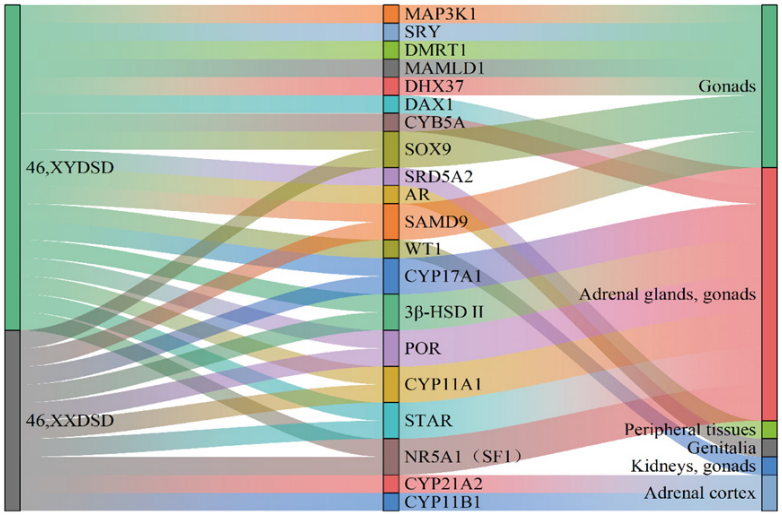

Figure 1. Karyotype and tissue flow of representative DSD pathogenic genes to Sankey diagram.

2.1. Pathogenesis of 46, XX DSD

2.1.1. 21- hydroxylase deficiency

The enzyme 21OH (P450c21) catalyzes the conversion of 17- hydroxyprogesterone to 11-deoxycortisol in the fascicular zone and progesterone to 11-deoxycorticosterone (DOC) in the adrenal cortical zone. 21OHD (MIM 201910) caused by a CYP21A2 (MIM 613815) mutation is the most common form, accounting for about 95% (*5*) of CAH. According to neonatal screening, the incidence of a 21- hydroxylase deficiency is estimated to be between 1/14 000 and 18 000 live births (*6*). Life-threatening forms of salt consumption, accounting for about 75% of classical CAH, are usually due to gene deletion or transformation or a stop codon or frameshift mutation, which seriously affects the activity of 21OH, thus hampering the synthesis of glucocorticoid and mineralocorticoid. Although the genetic test for a CYP21A2 mutation is not a first-line diagnostic test at present, genotyping is the key to determining affected carriers in the family (*7*). At the same time, variants in more genes involved in glucocorticoid biosynthesis, such as STAR, CYP11A1, 3β-HSD II, CYPB11B1, CYP17A1, and POR, have been identified as the cause of CAH (*8*).The p.A218V mutation in the acute regulatory gene (StAR) of steroid synthesis, which regulates ovarian steroid production and aldosterone and cortisol synthesis and secretion pathways, limits its binding activity to cholesterol and is a pathogenic variant (*9*). An increasing number of pathogenic variants are being found to be associated with 46, XX DSD.

2.1.2. 11β-hydroxylase deficiency

Microsomal cytochrome P450c11β with 11β-hydroxylase activity is coded as CYP11B1 (MIM 610613), which catalyzes the last step of cortisol biosynthesis. Mutation of the CYP11B1 gene leads to 11βOHD (MIM 202010), which is the second most common form of CAH, accounting for 0.2-8% of all cases. The prevalence of this disease is estimated to be 1 in 100,000, and the prevalence is higher among Muslims and Moroccan Jews in the Middle East (*10*). Compared to women with 21OHD, women with 11βOHD are more masculine; interestingly, however, the degree of masculinity is not related to the degree of hyperandrogenism (*11*). The patient's fertility rate is low. Simm *et al*. reported the first successful pregnancy of a 26-year-old woman who was seriously deficient in 11βOHD (*12*). The diagnosis of 11βOHD is based on an increase in the basal concentration of DOC and the high reactivity of 11-deoxycortisol (> 3 times the upper limit of the normal value) in an ACTH test. There is also low cortisol and normal or inhibited plasma renin activity (*6*). Diagnosis is difficult because neonates are usually free of hypertension and renin suppression, but molecular genetic testing can confirm the diagnosis of 11β OHD when CYP11B1 gene mutations are identified.

The advent of gene sequencing technologies, such as whole-exome sequencing (WES) and whole-genome sequencing (WGS), has precipitated a paradigm shift in the field of genetic analysis. These technologies are anticipated to facilitate the expeditious and precise identification of genetic mutations associated with 46, XX DSD, thereby enabling earlier diagnosis, particularly during the neonatal and even prenatal period. This will assist in the timely interventions required to mitigate the occurrence of severe complications, including salt depletion crises. The integration of multi-omics techniques (*e.g.* proteomics and metabolomics) may reveal a greater number of biomarkers associated with adrenal steroid synthesis disorders and provide a more comprehensive basis for diagnosis.

2.2. DSD and female reproductive capacity

In patients with DSD, fertility problems are caused by endocrine, gonad, or anatomical abnormalities inherent in the disease (*5*). In addition, medical and surgical treatment will affect the fertility of these patients. Age at diagnosis of DSD is another factor related to fertility (*13*). Because the fertility problem affects quality of life to a great extent, the fertility potential of patients with DSD needs to be considered in other medical management (*14*).

2.2.1. Excessive androgen

CAH leads to a higher adrenal androgen or progesterone level, interferes with gonadotropin secretion, and produces a series of pathophysiological consequences, leading to different degrees of chronic anovulation (*15*). Gender role reversal is relatively common among affected adult women. In addition, pre-adolescent girls with CAH may exhibit masculine and slightly feminine interests and preferences (*16*).

A wide range of pathophysiological symptoms and varying fertility rates were reported in 46,XX patients with DSD, with the most severe classic type of CAH, 21-OHD, exhibiting the lowest pregnancy and success rates (*15*). In contrast, the pregnancy rate of patients with mild CAH is closer to the normal rate (*17*). One of the less common causes of CAH is a 17- hydroxylase deficiency (17-OHD), which occurs in less than 1% (*18*). This condition could be resulted from biallelic mutations in the *CYP17A1* gene (*19*). Women with complete defects develop amenorrhea, sexual infantile syndrome, impaired secondary sexual development, and primary infertility, while some defects may manifest as female infertility in adulthood (*20*). Successful pregnancy has been reported with the help of *in vitro* fertilization cycle and frozen embryo transfer (*21*). However, there is no information about pregnancy in women with a 3β-hydroxysteroid dehydrogenase type II deficiency (3β-HSD II). Preimplantation genetic diagnosis (PGD) technology has been utilized to detect affected embryos prior to their transfer with assisted reproductive technology. Moreover, PGD necessitates the timely identification of pertinent CAH mutations in order to detect this autosomal recessive disorder. Women with CAH are vulnerable to age-related decline in oocyte quality and fertility, but few studies have reported that patients with CAH retain fertility (*22*).

2.2.2. Disorders of ovarian development

Normal ovarian tissue determines the final phenotype of external genitalia and internal genitalia. Ovotesticular DSD, also known as true hermaphroditism, is related to different karyotypes, including 46, XX (60% of cases), chimera 46, XX/XY (33% of cases) and 46, XY (7% of cases) (*23*). This DSD is characterized by bilateral ovular testes or a healthy ovary/testis and contra-lateral ovular testis; the ovular testis may contain many primordial follicles. Excision of all inconsistent male testicles and Wolffian tissues can maximize the fertility potential of patients with ovular testicular DSD as women with complete Mullerian duct structure. At the same time, it helps to reduce the level of androgen and increase the chance of ovulation. Because of the high rate of premature delivery, neonatal death, or delivery problems reported (*24*), it should be closely monitored after pregnancy. In 46, XX gonadal dysgenesis (GD) cases, most successful pregnancies were the result of assisted reproductive technology (*24,25*). A 24-year-old woman successfully became pregnant and delivered after receiving controlled ovarian stimulation and *in vitro* fertilization (*26*). However, these pregnancies are accompanied by obvious complications, including oligohydramnios, pregnancy-induced hypertension, preeclampsia, premature delivery, premature rupture of membranes, and spontaneous abortion (*14*).

2.2.3. Mullerian agenesis

The secondary sexual characteristics of patients with MRKH syndrome seem normal, but the lack of a vagina and uterus is the second most common cause of primary amenorrhea (*27*). Uterine transplantation is an innovative method in reproductive medicine that is used to treat infertility caused by an abnormal uterus. However, there are few reported cases of human uterine transplantation worldwide, and Brännström *et al*. reported the first live birth as a result of IVF after uterine transplantation (*28*). Correct and comprehensive diagnosis and psychological consultation are necessary to determine the best treatment for patients with Mullerian duct hypoplasia. (The effects of 46,XX DSD on fertility are shown in Table 1)

3. 46, XY DSD of adrenal origin

In 46, XY patients, DSD is caused by related testicular dysfunction, and the most common is primary adrenal insufficiency characterized by decreased cortisol secretion and excessive adrenocorticotropic hormone secretion. The nutritional function of ACTH causes CAH. The etiology and pathogenesis of 46, XY DSD are complex and diverse, and any factor that affects testicular differentiation or testosterone synthesis or action can lead to 46, XY DSD (*29*). There are many genes involved, and different pathogenic genes will cause different accompanying symptoms. The level of miRNA210 expression in 46, XY DSD patients is higher than in normal patients, which may be related to the development of cryptorchidism, confirming that RNA is one of the causative causes of 46, XY DSD (*30*). Abnormal gonadal differentiation and development have been found to be related to SRY, WT1, SF1,

Table 1. Summary of the different types of 46, XX DSD and their effects on fertility

Category	Specific type	Karyotype	Pathogenesis	Clinical manifestations	Impact on fertility	Ref.
46, XX DSD	46, XX DSD	46, XX	SRY gene translocation; excess fetal development factors; androgen excess	Ambiguous external genitalia; possible salt-wasting crisis	Fertility affected by endocrine, gonadal, or anatomical abnormalities; some patients may become pregnant with assisted reproductive technology	*4*
	21-hydroxylase deficiency	46, XX	CYP21A2 gene mutation	Salt-wasting crisis; masculinized external genitalia	Low fertility in classic 21-hydroxylase deficiency; near-normal fertility in mild cases	*5-7*
	11β-hydroxylase deficiency	46, XX	CYP11B1 gene mutation	Masculinized external genitalia; hypertension (in adults)	Low fertility in females; successful pregnancies reported	*11-12*
	17- hydroxylase deficiency	46, XX	CYP17A1 gene mutation	Amenorrhea, sexual infantile syndrome, impaired secondary sexual development, and primary infertility	Successful pregnancies reported	*15-21*
	MRKH syndrome	46, XX	Mullerian duct hypoplasia	Lack of vagina and uterus	Live birth as a result of IVF after uterine transplantation	*27-28*

SOX9, DAX-1, DMRT1, and other genes(*31*). DAX1-/Y mice displayed a female phenotype, and mating with DAX1/Y male mice produced singleton offspring, while DAX1-/Y mating with DAX1/female mice did not produce viable offspring (*32*). As shown in mice, a comprehensive evaluation of fertility following sexual reversal is imperative. A mutation in the DHX37 gene upregulates the β-catenin protein and activates the Wnt/β-catenin pathway, which may be the cause of DSD (*33*). Mutations in CYP17A1, SRD5A2, and other genes can cause abnormal development of enzymes involved in androgen synthesis, thus leading to androgen synthesis disorder. Androgen dysfunction is mainly related to the androgen receptor (AR) gene. Compared to these single-gene inheritance patterns, patients with Mastermind-like domain-containing 1(MAMLD1) associated 46,XY DSD may carry variants in other DSD-related genes, and the phenotypic outcome of affected individuals might be determined by multiple genes. A study has indicated that male mice with deletion of the causative gene MAMLD of DSD have normal reproductive organs and reproductive capacity (*34*). Recent studies have further demonstrated that DSDs caused by MAMLD1 follow a pattern of oligogenic inheritance (*35,36*).

3.1. Pathogenesis

An astrocyte deficiency or a cytochrome P450scc and P450c17 deficiency can lead to CAH in 46, XY newborns. The mutation of SF1 may also lead to the combined failure of adrenal glands and testes, and the detection of DSD and NR5A1 mutations in 46, XY individuals can confirm the diagnosis (*37*). A 17,20-lyase deficiency (MIM 202110) is a rare cause of CAH, which is caused by any mutation of three different genes: CYP17A1, POR, or CYB5A (*13*). 46, XY patients with a 17,20-lyase deficiency had ambiguous genitalia at birth. 3β HSD 2 (*38*) or impaired POR activity (*39*) may lead to DSD in 46, XX and 46, XY individuals, which can be confirmed by detection of a gene mutation. The biological activity in the gonads is dependent on glycosylation of gonadotropins and their receptors. Glycosylation processes are essential for the correct gonad migration and genitalia morphogenesis. Conserved oligomeric Golgi complex 6-congenital disorder of glycosylation (COG6-CDG) is a type of metabolic disorder with abnormal protein glycosylation. A patient with COG exome deletion presents with a normal male karyotype, though the patient has an underdeveloped scrotum with no palpable testes and a micropenis (*40*). A study has found that COG6-CDG can manifest as sex differentiation disorder with chromosome karyotype 46, XY and external female genitalia (*41*). Other studies have indicated a relationship between COG6 impairment and DSD, glycoprotein metabolism, and sex development; however the mechanism of action is unclear. Some deleterious variants of the COG gene are associated with

46, XY DSD because of gonadal dysgenesis.

3.2. DSD and female reproductive capacity

3.2.1. Disorders of androgen-dependent target tissues

Androgen sensitivity syndrome (AIS) phenotypes range from the appearance of infertile men to women with typical external genitalia (*42*). The degree of insufficient masculinization of external genitalia at birth and adolescence depends on the level of androgen insensitivity in the target tissue. Because the risk of premature germ cell tumors is extremely low, it is reasonable to recommend that gonadectomy be postponed until adulthood (*43*). At present, patients with complete AIS (CAIS) are considered infertile because they have no ovaries or uterus. However, a study has detected germ cells in the abdominal gonads (*42*). The existence of germ cells improves the possibility of future fertility through preservation, but this option is only experimental at this stage.

3.2.2. Disorders of androgen synthesis or action

Patients with a 5α-reductase -2 (5α-RD-2) deficiency exhibit normal female genitalia with male internal ducts. After birth, under the influence of testosterone, somatic cells are masculinized. During sexual maturity, testosterone can also induce muscle enlargement, penis growth, and testicular decline (*14*). Li *et al*. demonstrated that an SRD5A2 mutation decreased the catalytic efficiency of the 5α-reductase type 2 enzyme and dihydrotestosterone (DHT) production (*44*). Similar to CAIS cases, the impaired function of 17β-HSD III can lead to clinical manifestations of female external genitalia before puberty(*42*). With the testes in place, masculinization occurs in adolescence, similar to what happens with a 5α-RD-2 deficiency(*42*).

3.2.3. Disorders of testicular development

46, XY gonadal dysplasia (GD) is caused by any gene mutation involved in gonadal formation. NR5A1, MAP3K1, and SRY are the genes often reported to be related to 46, XY GD . Complete 46, XY GD, also known as Swyer syndrome, is characterized by bilateral GD and physiologically effective uterine and normal endometrial reactions (*45*). These individuals have streak gonads, fallopian tubes, a small uterus, and female external genitalia. Striped gonads cannot produce normal amounts of sex hormones, so secondary sexual characteristics do not all develop. Although the gonads are poorly developed, a successful pregnancy can result from oocyte donation (*45*). However, there are very few live births among such patients (*45*). Taneja *et al*. reported that a patient with Swyer syndrome had a normal pregnancy and delivery as a result of donor oocytes (*45*). Winkler *et al*. reported a successful twin pregnancy in a patient with Swyer syndrome after oocyte donation and an *in vitro* fertilization cycle (*46*).

Partial 46, XY GD is an uncommon disease that is characterized by ambiguous genitalia and different degrees of testicular dysplasia, with or without a Mullerian duct structure. Hormone therapy includes administering estrogen and progesterone to individuals with a uterus to induce menstruation and administering estrogen to individuals without a uterus at the age of 10 to avoid excessive bone maturation (*47*).A recent report described how MIRAGE syndrome caused by the sterile alpha motif domain-containing protein-9 (SAMD9) gene was responsible for an 46, XY sexual developmental disorder and adrenal insufficiency (*48*). MIRAGE syndrome is a multisystem and multiphenotypic genetic disorder. SAMD9 is expressed in a variety of tissues, and its role in the adrenal glands is often overlooked. SAMD9 mutations can directly limit testicular development while affecting placental development and HCG levels (*49*). However, reports of female patients with karyotype 46, XX are even rarer. (The effects of 46,XY DSD on fertility are shown in Table 2)

4. Sex chromosome in DSD

4.1. Turner syndrome

Partial or complete deletion of the X chromosome or a structural change in the sex chromosome will lead to a female phenotype, which is called Turner syndrome (TS). The complete deletion of the sex chromosome can be defined as 45, X/46, XX chimera or 45, XO. The infertility of women with X haploid TS is mainly due to premature ovarian failure (POF) with few or no oocytes (*50*). However, individuals with 45, X haploid or 45, X/46, XX chimera have normal puberty and regular menstruation, and have a natural pregnancy, giving birth to a healthy baby (*51*). TS cases experiencing natural pregnancy usually have mosaic genotype (*50*). Assisted reproductive technology has increased the probability of successful pregnancy of TS women using their own fresh or donor oocytes (*52,53*). In these cases, however, the risk of various complications increases, including pregnancy-induced hypertension, pre-eclampsia, gestational diabetes, premature delivery, multiple pregnancies, low birth weight, spontaneous abortion, inherent sex chromosome or endometrial abnormalities, and even death due to complications of aortic dissection or rupture (*54*). The uterus of TS women is smaller than a normal uterus, so single embryo transfer is performed (*51*).

4.2. Mixed gonadal dysgenesis

The main characteristic of mixed gonadal hypoplasia (MGD) is a 45, X/46, XY karyotype. The affected

Table 2. Summary of the different types of 46, XYDSD and their effects on fertility

Category	Specific type	Karyotype	Pathogenesis	Clinical manifestations	Impact on fertility	Ref.
46, XY DSD	46, XY DSD	46, XY	Adrenal dysfunction; gonadal dysgenesis	Ambiguous external genitalia; possible other endocrine abnormalities	Fertility affected by gonadal development and androgen action; some patients may become pregnant with assisted reproductive technology	*29-36*
	17,20-lyase deficiency	46, XY	SF1,NR5A1,3β-HSD II,CYP17A1, POR, or CYB5A gene mutation	Ambiguous external genitalia	Low or absent fertility	*13;37-39*
	Complete androgen insensitivity syndrome (CAIS)	46, XY	AR gene mutation	Female external genitalia; no uterus or ovaries	Typically infertile; experimental germ cell preservation studies	*31;42-43*
	5α-reductase-2 deficiency	46, XY	SRD5A2 gene mutation	Female external genitalia; masculinization at puberty	Low or absent fertility	*14;44*
	Partial 46, XY gonadal dysgenesis	46, XY	NR5A1, MAP3K1, SRY, SAMD9 gene mutations	Ambiguous external genitalia; gonadal dysgenesis	Low or absent fertility	*45-46*

individuals have streak ovaries and testes with ipsilateral dysplasia, which leads to structural abnormalities, such as a primitive Mullerian duct structure, incomplete Wolff duct development, and insufficient masculinization of external genitalia (*55,56*). Despite the lower natural fertility seen in MGD patients, some may be able to conceive through the use of assisted reproductive technologies, such as egg donation and *in vitro* fertilization (*55*).

4.3. Klinefelter syndrome (KS)

The karyotypes of KS are 47, XXY, 47, XXY/46, XY, 47, XXY/46, XX and 47, XXY/48, XXXY/49, XXXXY. The karyotype of patients is mainly 47, XXY, and the phenotype of patients with KS gradually deviates from normal due to the escape and inactivation of multiple genes on the redundant X chromosome. Some patients with KS have no obvious clinical manifestations themselves, and about 64% patients have never been diagnosed throughout their lives (*57*). KS accounts for 3-4% of patients with infertility and 10-12% with azoospermia (*58*). In some patients, the clinical manifestations are being tall or having small testicles, a sparse beard, or an inconspicuous Adam's apple. There are also KS patients with psychological, behavioral, learning, and mental disorders, including impaired language ability. The specific mechanism is not clear, though it may be directly related to chromosomal abnormalities or may be caused by hypogonadism. Aksglaede *et al*. (*59*) reported that only 10% of patients were diagnosed before puberty. A study has shown that patients with KS have an increased risk of male breast cancer and extragonadal germ cell tumors (*60*). Therefore, early accurate diagnosis and close clinical monitoring of KS patients are crucial to preventing the development of tumors. (The effects of Sex chromosome DSD on fertility are shown in Table 3)

5. Conclusion

The diagnosis and treatment of DSD is very complicated, and individualized treatment is particularly important. At present, surgery is still the main treatment, and gender psychological determination and gender distribution are the most critical links in the treatment of patients with 46, XY DSD. The opinions of multidisciplinary teams, family members, and/or children themselves should be integrated, along with factors such as the patient's sexual psychology, sexual role, and sexual orientation, the risk of gonadal cancer, fertility potential, follow-up treatment, and the social and cultural environment so as to avoid a change in gender in adulthood.

In addition, other treatments mainly include correct identification of gender and upbringing, hormone replacement therapy, and preservation of fertility. The improper identification of DSD and gender can lead

Table 3. Summary of the different types of sex chromosome DSD and their effects on fertility

Category	Specific type	Karyotype	Pathogenesis	Clinical manifestations	Impact on fertility	*Ref.*
Sex chromosome DSD	Turner syndrome	45, X/46, XX	Partial or complete X chromosome deletion	Female phenotype: short stature, underdeveloped secondary sexual characteristics	Most patients are infertile due to premature ovarian failure; some patients may become pregnant with assisted reproductive technology	*50-53*
	Mixed gonadal dysgenesis	45, X/46, XY	Sex chromosome mosaicism	Ambiguous external genitalia: Gonadal dysgenesis	Low or absent fertility	*55-56*
	Klinefelter syndrome	47, XXY	Inactivation of multiple genes on the extra X chromosome	Tall stature, small testes, underdeveloped male secondary sexual characteristics	Azoospermia or oligospermia; some patients may become pregnant with assisted reproductive technology	*57-60*

to an inconsistency between the patient's physical and psychological gender, resulting in profound mental stress and psychological obstacles, so attention should be paid to social and psychological support for and long-term follow-up of patients.

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