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The Genetics of Sexual Development Disorders

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Review

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ABSTRACT

Sexual development is one of the significant stages of the embryogenesis. In this process, the gonadal differentiation taking place on a genetic basis (sex chromosomes) determines the sexual identity of the individual. Initially, the gonads are considered bipotential because the gonadal primordium can turn into a testicle or ovary through the activation of certain genetic elements in the subsequent period. When there is a disruption at any phase of this period, various clinical conditions called disorders of sexual development (DSD) arise. These conditions, often accompanied by various mutations or sex chromosome abnormalities, may include gonadal dysgenesis and result in a male (46, XY) or female (46, XX) sex reversal. DSD with 46,XY usually contains ambiguous condition, or the presence of female external and/or internal genitalia depending on whether Müllerian tissues are present. On the other hand, different enzyme defects, again, on a genetic basis can lead to disorders of sex development in both males (e.g. 5α-reductase) and females (e.g. aromatase). Congenital adrenal hyperplasia is a relatively common, autosomal recessive enzyme defect, especially in 46,XX DSD cases. A number of syndromes lead to a certain degree of inadequate sexual development in males or masculinization in females. Patients also have some characteristic physical symptoms accompanied by mental problems. Gonadal dysgenesis can be caused by various mutations, mainly in the SRY gene (e.g. Swyer syndrome) or sex chromosome disorder (Turner syndrome). In cases of 46,XY DSD, mixed gonadal dysgenesis, and some other conditions, prophylactic gonadectomy may be considered because of the malignancy risk.

Keywords: Sexual development, mutation, chromosomal abnormality, gonadal dysgenesis, sex reversal.

Cinsel Gelişim Bozukluklarının Genetiği

Derleme

Süreç

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ÖZET

Cinsel gelişim embriyogenezin önemli aşamalarından biridir. Bu süreçte, genetik temelde (seks kromozomları) gerçekleşen gonadal farklılaşma bireyin cinsel kimliğini belirler. Başlangıçta gonadlar bipotansiyel olarak kabul edilir çünkü gonadal primordium sonraki dönemde belirli genetik unsurların aktivasyonu ile testis veya overe dönüşebilir. Bu dönemin herhangi bir aşamasında bir aksama olduğunda, cinsel gelişim bozuklukları (DSD) adı verilen çeşitli klinik durumlar ortaya çıkar. Genellikle çeşitli mutasyonlar veya cinsiyet kromozomu anormalliklerinin eşlik ettiği bu koşullara, gonadal disgenezi dahil olabilir ve erkek (46, XY) veya dişi (46, XX) cinsiyet dönüşümü ile sonuçlanabilir. 46,XY DSD genellikle belirsiz bir durumu veya dişi dış ve/veya Müllerian dokuların mevcut olup olmamasına bağlı olarak iç genital organların varlığını içerir. Öte yanda, yine genetik bazda farklı enzim defektleri, hem erkeklerde (örn. 5α-redüktaz) hem de dişilerde (örn. aromataz) cinsiyet gelişimi bozukluklarına yol açabilmektedir. Konjenital adrenal hiperplazi, özellikle 46,XX DSD olgularında, nispeten sık görülen, otozomal resesif bir enzim defektidir. Bir dizi sendrom, erkeklerde belirli ölçüde yetersiz cinsel gelişime veya dişilerde erkekleşmeye yol açar. Hastalar da, ayrıca mental problemlerin eşliğinde bazı karakteristik fiziksel semptomlar bulunur. Gonadal disgeneziye, başta SRY geni olmak üzere, çeşitli mutasyonlar (örneğin Swyer sendromu) veya cinsiyet kromozom bozukluğu (Turner sendromu) neden olabilir. Netice itibarıyla, 46,XY DSD, karma gonadal disgenezi ve diğer bazı durumlarda, malignite riski nedeniyle profilaktik gonadektomi düşünülebilir.

Anahtar Kelimeler: Cinsel gelişim, mutasyon, kromozomal anormallik, gonadal disgenezi, cinsiyet dönüşümü.

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Introduction

Sexual development is an important process that determines the identity, mental health and social position of the individual, independent of physical development. The formation of male and female characteristics in the organism is one of the most important stages of the embryonic period. Gonadal development begins from the 3rd to 4th weeks of embryogenesis, with the emergence of an undifferentiated structure in embryos with XX and XY karyotypes.[1] Initially, gonads are defined as bipotential since the gonadal primordium can differentiate into the testicle or ovary through the activation of some genetic elements during this process.[2] A disruption at any stage of sexual differentiation causes a clinical condition called disorder of sexual development (DSD), and this problem can occur as ovarian, testicular, ovotesticular or complete gonadal dysgenesis. Gonadal dysgenesis can be defined as the termination of gonadal development prior to testicular or ovarian differentiation and may present with chromosomal and phenotypic changes such as Turner syndrome or in the form of pure gonadal dysgenesis without chromosomal abnormalities such as Swyer syndrome.[3] A well-known concept in terms of sexual development disorders is hermaphroditism. True hermaphroditism can be described as the presence of both ovarian and testicular tissue in the same organism with ambiguous genitalia regardless of karyotype,[4] while pseudohermaphroditism is the presence of external genitalia that does not match the karyotype (feminization in males or virilization in females). Hermaphroditism has a multidimensional genetic basis related to different genes. However, to avoid terminological confusion in this article, we use "Disorders of Sexual Development" as a concept, hence DSD as an acronym. Disorders of sexual development can be roughly classified as 46,XY DSD, 46,XX DSD and sex chromosome disorders. DSD with 46,XY involves disorders of testicular development (ovotesticular DSD, complete or partial gonadal dysgenesis, etc.), androgen synthesis-activity disorders (5-α-reductase deficiency, complete or partial androgen insensitivity syndrome, Leydig cell hypoplasia or aplasia), LH and AMH defects, while 46,XX DSD may be a disorder of ovarian development (Ovotesticular DSD, gonadal dysgenesis), congenital adrenal hyperplasia, SRY translocation, placental aromatase deficiency and similar syndromes.[5] Sex chromosome disorders include Turner syndrome, Klinefelter syndrome, and mixed gonadal dysgenesis (45,X/46,XY mosaicism), etc.[6] DSD with 46,XY often involves ambiguous gender, or the presence of female external and/or internal genitalia, depending on whether Müllerian tissues are present.[7] These DSD cases may have phenotypes ranging from fully female external and in some cases internal genitalia to male genitalia with hypospadias, bifid scrotum and undescended testicle.[8] Gonadectomy is recommended for female patients with 46 XY karyotype because of the risk of malignancy and MRI is a more robust and sensitive method than ultrasound to determine the location of the gonads in the preoperative evaluation.[9]

Numerous gene mutations, and enzyme defects on a genetic basis are effective in disorders of sexual development. The relevant gene mutations can cause phenotypic changes at different levels and can also be involved in the etiology of gonadal dysgenesis. The main genes associated with complete or partial gonadal dysgenesis in the human genome include *SRY, SOX9, DHH, AMH, CBX2, DMRT1, GATA4, WNT4, WT1, MAP3K1, DAX1, FGFR2, FOXL2, FGF9, NR5A1* and *RSPO1* gene.[10] Furthermore, in terms of 46,XX ovarian dysgenesis, *FSHR*, *BMP15*, *PSMC3IP, MCM9, SOHLH1, NUP107, MRPS22* and *ESR2* gene mutations can also lead to such a clinic.[11]

The key element for the development of masculinity is the *SRY* (Sex-determining region Y) gene (Yp11.2). This gene on the short arm of the Y chromosome encodes a transcription factor that triggers male sex development at the 6th week and it is necessary for the activation of SOX9, which leads to the differentiation of the Sertoli cells from the somatic precursor cells of the primitive gonad. In this context, the SRY protein initiates a genetic cascade that directs testicular differentiation by activating the expression of SOX9 along with SF-1, encoded by the *NR5A1* gene (9q33.3).[12] Activation of SOX9 expression induces a male-specific process and inhibits ovarian development.[13] *SOX9* (17q24.3) loss-of-function mutations can lead to autosomal sex reversal, gonadal dysgenesis and campomelic dysplasia.[14] Besides SOX9, SRY also triggers the expression of several other elements that promote masculinity, such as FGF9 and PGD2.[15] Fibroblast growth factor 9 (FGF9) is essential for proliferation in a cell population including Sertoli cell precursors in early testicular development and is effective in the nuclear localization of FGFR2 in precursor Sertoli cells.[16] FGFR2 is an important marker of testicular differentiation. Nuclear receptor subfamily 5 group A member 1 (NR5A1) , involved in SRY function, is known to be highly expressed in Sertoli and Leydig cells of the gonads, and mutations of the *NR5A1* gene have been identified as the main cause of gonadal dysgenesis in a proportion of 46,XY DSD patients.[17] SRY and SRY-activated SOX9 transcription factor and RSPO1-WNT4-β-Catenin signaling serve as antagonistic pathways to direct testicular and ovarian differentiation respectively, from the existing primitive gonad.[18] Inhibition of WNT/beta-catenin signaling is crucial for fetal testicular development and increased or stimulated WNT/β-catenin signaling in testicles causes disruption of seminiferous cord structures, decreased SOX9/AMH expression, loss of germ cell population, and significant deterioration of Leydig cell function.[19]

Swyer syndrome, a pure gonadal dysgenesis, is a type of DSD characterized by a 46,XY male karyotype and a complete female phenotype and thus sex reversal.[20] This form of complete gonadal dysgenesis should be considered together with the complete absence of masculinization in the external genitalia and the presence of Müllerian tissues, due to testosterone and AMH deprivation.[21] The *SRY* gene mutations or deletions come to mind first for this syndrome, and mutations in genes such as *SOX9, SF1* and *WT1* can also disrupt SRY function. Mutations of *SRY* is found in approximately 15% of females with Swyer syndrome, while mutations of other testicular determinants (MAP3K1, DHH, NR5A1 etc.) are responsible for the remainder of cases, independent of the *SRY* gene.[22]

Table 1. *Mutations and enzyme defects in Disorders of Sexual Development.*

46,XY DSD		46,XX DSD	
Mutation	**Enzyme defect**	**Mutation**	**Enzyme defect**
SRY/SOX9	5α-reductase 2	WNT4	17-α-hydroxylase/ 17,20-lyase
NR5A1/FGF9	(SRD5A2)	FOXL2	(CYP17A1)
WT1/DHH	17-α-hydroxylase/17,20-lyase	RSPO1	P450-oxidoreductase
MAP3K1	(CYP17A1)	FSHR/NR3C1	(POR)
GATA4	3-beta-hydroxysteroid dehydrogenase	DAX1	21-hydroxylase
CBX2/DAX1	(HSD3B2)	BMP15	(CYP21A2)
FGFR2/DMRT1	P450-oxidoreductase	MCM9/ESR2	11-β-hydroxylase
LHCGR /AR	(POR)	SOHLH1	(CYP11B1)
AMH/AMHR		MRPS22	Aromatase (CYP19A1)

WNT4, RSPO1 and FOXL2 are among the elements that function in the early ovarian development. These repress male development by restricting SOX9 expression and support female structures by maintaining Müllerian differentiation.[23] The *WNT4* gene (1p.36.1), a member of the WNT family, is involved in female development and the inhibition of testicular formation. Mutations of this gene have been associated with disorders such as Mullerian aplasia, sex reversal, premature ovarian failure and endometriosis.[24] Furthermore, high FGF9 may inhibit WNT4 expression in the embryonic structure, and SRY-negative 46,XX male cases may be associated with a gain in copy numbers of FGF9.[25] In mammals, RSPO1 (R-spondin 1) synergizes with specific Wnt ligands in favor of intracellular β-catenin and in this context, it plays a role in ovarian differentiation.[26] Consequently, in the absence of the *SRY* gene, *WNT4/RSPO1* and beta-catenin pathways present activity for ovarian development, and pathogenic variants of these genes may lead to 46,XX DSD.[27] In addition, *FOXL2* (3q22.3), encoding a forkhead transcription factor, can also arrange early ovarian growth via repressing the expression of testicular genes.[28]

Wilms-tumor 1 (WT1), Chromobox 2 (CBX2) and NR5A1 are expressed at early stages for undifferentiated gonad and the association of relevant genes with gonadal development has been well documented along with their mutations leading to gonadal dysgenesis.[29] The *WT1* gene (11p13) makes a fundamental contribution to the embryonic development of various systems, such as the urogenital and central nervous system.[30] *WT1* encodes a protein including four zinc fingers involved in urogenital development and pathogenic variants of this gene are linked to abnormalities in testicular development and DSD with 46,XY.[31] *WT1* mutations have been implicated in various syndromes including Denys-Drash syndrome, Frasier syndrome (glomerular nephropathy and complete gonadal dysgenesis with 46,XY karyotype), and WAGR syndrome (Wilms tumor, aniridia, genitourinary malformations, and mental retardation).[32] Denys-Drash syndrome is a rare disorder with pseudohermaphroditism, nephroblastoma (Wilms tumor) and diffuse mesangial sclerosis and is mostly linked with *WT1* mutations.[33] Frasier syndrome is an inherited disease caused by an intron 9 mutation of the *WT1* gene, presenting with gonadal dysgenesis and progressive nephropathy.[34] On the other hand, CBX2 is also known to be effective in gonadal differentiation in mammals, and mutations of *CBX2* (17q25.3) can lead to sex reversal.[35] Loss of function in this gene, which is needed for early gonadal development, can be found in 46,XY DSD cases with gonadal dysgenesis and completely female phenotype.[36]

DMRT1 (*9p24.3)* is found in a gene family containing a zinc finger-like DNA-binding motif. Deletions of chromosome 9p involving *DMRT1* can cause 46,XY sex reversal in humans and are associated with the formation of gonadoblastoma.[37] Point mutations and deletions of *DMRT1* have also been linked to the 46,XY complete gonadal dysgenesis.[38]

The protein encoded by *DHH* gene (12q13.1), a member of the Hedgehog gene family, is clearly expressed in Sertoli cells and it can regulate testicular development and spermatogenesis, in addition, this gene may be necessary for the differentiation of Leydig cells.[39] DHH is involved in the interaction between Sertoli cells and germ cells, and *DHH* gene mutations may be responsible for male infertility and gonadal dysgenesis.[40]

Although the *GATA4* gene (8p23.1) is known to cause congenital heart disease, its mutations are now also thought to be linked to disorders of sexual development (46,XY DSD).[41] A transcription factor encoded by this gene interacts with certain proteins, such as NR5A1, WT1 to regulate the expression of SRY, SOX9 and AMH etc., and its function appears to be essential for testicular development.[42]

MAP3K1 (5q11.2), which is a signal transduction gene, is a member of the gene network involved in gonadal development.[43] *MAP3K1* gain-of-function mutations disrupt the balance by increasing *WNT*/beta-catenin/*FOXL2* expression and decreasing *SOX9/FGF9/FGFR2/SRY* expression in 46,XY karyotype and are therefore responsible for a proportion of 46,XY DSD cases.[44]

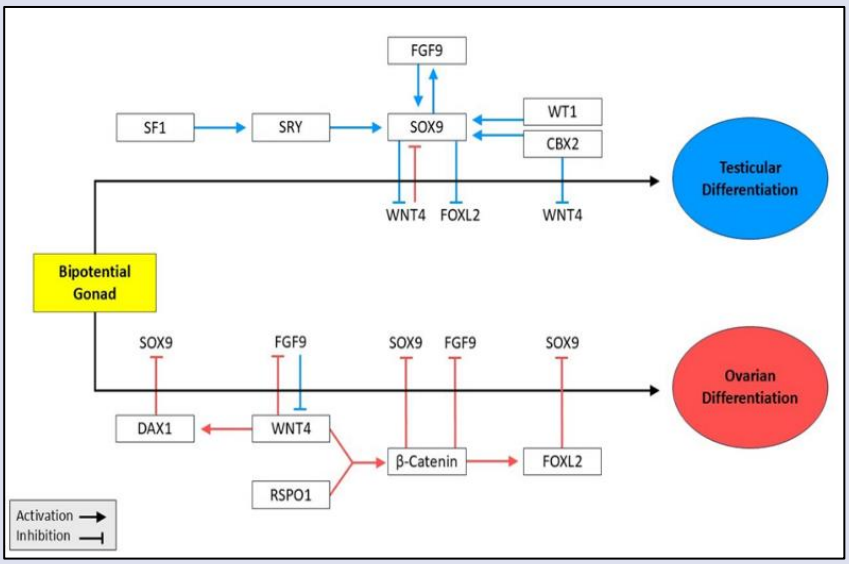

Figure 1. Genes of the gonadal differentiation pathway.

Table 2. DSD-related receptor defects

Receptor (46,XX DSD)	Clinical status	Inheritance
FSHR	Ovarian dysgenesis / Ovarian hyperstimulation syndrome	AR / AD
NR3C1	Glucocorticoid resistance / Hypertension / Hyperandrogenism	AD
ESR2	Ovarian dysgenesis	AD
DAX1	Hypogonadotropic hypogonadism	XL
Receptor (46,XY DSD)	**Clinical status**	**Inheritance**
AR	Androgen insensitivity, Spinal and bulbar muscular atrophy	XLR
LHCGR	Leydig cell hypoplasia with hypergonadotropic hypogonadism, pseudohermaphroditism	AR
AMHR	Persistent Mullerian duct syndrome	AR
FGFR2	Craniosynostosis / 46,XY DSD	AD
DAX1	46,XY Sex-reversal / Con. adrenal hypoplasia	XL

DAX1 is a nuclear receptor protein encoded by the *DAX1* gene (Xp21.2) and has a role in the development of hypothalamo-pituitary axis, gonadal and adrenal tissues.[45] Congenital adrenal hypoplasia with X-linked inheritance is a rare disorder resulting from mutations in the *DAX1* gene (NR0B1) and manifests as adrenal insufficiency in infancy and later pubertal failure based on hypogonadotropic hypogonadism.[46] On the other hand, duplications of *DAX1* gene in cases with XY karyotype can lead to male-to-female sex reversal, gonadal dysgenesis, or more precisely, DSD known as dosage-sensitive sex reversal (DSS).[47]

The main function of Leydig cells, as interstitial cells located near the seminiferous tubules, is to produce testosterone under the influence of luteinizing hormone (LH).[48] Testosterone produced by Leydig cells is crucial in the development of the male phenotype, as it causes the Wolffian ducts to differentiate into male genitalia.[49] Leydig cell hypoplasia can be defined as a disorder of sexual development (46,XY DSD) caused by a mutation in the luteinizing hormone/chorionic gonadotropin hormone receptor (LHCGR).[50] It is a type of disease in which the female phenotype predominates, but is characterized by primary amenorrhea and the presence of testicular tissue.[51] Another receptor dysfunction is primary glucocorticoid resistance caused by mutations in the glucocorticoid receptor gene, *NR3C1* (5q31.3), and may result in phenotypic changes from androgen excess in cases with 46,XX normal ovarian development due to ACTH overproduction.[27]

Anti-Müllerian Hormone (AMH) is a structure secreted by Sertoli cells and is involved in the regression of Müllerian ducts as an element of the sexual differentiation period in males.[52] *AMH* (19p13.3) or *AMHR*, AMH receptor gene (12q13.1) mutations are associated with the development of a persistent Müllerian duct syndrome, and such patients with male genotype and phenotype have female internal organs (upper vagina, cervix, uterus and oviducts) from a lack of anti-Müllerian hormone or insensitivity of tissues to anti-Müllerian hormone.[53]

Androgen insensitivity syndrome (AIS), known as one of the most common disorders of sexual development (DSD) in cases with 46XY karyotype, is an X-linked recessive disease caused by mutations in the androgen receptor (*AR*) gene (Xq12).[54] It can be described as a disorder that occurs due to complete or partial resistance to the effects of androgens in XY males despite a normal testicular structure and proper androgen production.[55] As

a nuclear receptor, AR enables cells in different tissues to respond to testosterone derivatives and AIS occurs through phenotypic expression of *AR* gene defects.[56] The phenotype of the disease varies from all female external genitalia in the complete form (CAIS), to underdeveloped male external genitalia in the partial form (PAIS), and even normal male external genitalia in the mild form (MAIS) manifested by infertility and/or gynecomastia.[57]

Another important issue regarding the problems of sexual development is sex chromosome disorders. Turner syndrome, also called monosomy X (45,X) in females, is a disease characterized by hypergonadotropic hypogonadism, short stature, low hairline, webbed neck, low-set ears, micrognathia, lymphedema of the hands and feet, and cardiac defects, and in most cases a streak gonad is likely to be encountered. The phenotype of Turner syndrome can also result from structural X chromosome abnormalities such as Xp or Xq deletion, isochromosome, 46,X,i(X), or ring chromosome, 46,X,r(X).[58] The short stature in Turner syndrome is very likely to be related to loss of the *SHOX* gene (Xp22.3), i.e. haploinsufficiency. Klinefelter syndrome, with a karyotype of 47,XXY is characterized by small testicles, delayed puberty, tall stature, gynecomastia and poor body hair growth, and infertility is often present.

A rare condition among 46,XX DSD cases is 46 XX male syndrome, also known as De la Chapelle syndrome, in which an individual has a male phenotype despite the 46,XX karyotype.[59] It is accepted that an abnormal change known as a translocation between the X-Y chromosomes may occur during sperm meiosis and leads to offspring with 46,XX male phenotype carrying the *SRY* gene as a result of fertilization, but upregulation of SOX9 expression because of chromosomal abnormalities or various mutations can also cause a similar phenotype without the *SRY* gene.[60]

On the other hand, there are a number of multisystemic syndromes that can be accompanied by disorders of sexual development. These include Kallmann syndrome, characterized by hypogonadotropic hypogonadism and olfactory dysfunction; McCune-Albright syndrome, described as fibrous dysplasia of bone with café-au-lait spots, and precocious puberty[61]; and Prader Willi syndrome, which results from paternal chromosome 15 deletion and presents with hypotonia, obesity, cognitive impairments, and hypogonadism. While McCune-Albright syndrome is caused by *GNAS* (20q13) gene mutations, multiple genes are responsible for Kallman syndrome. Prader Willi syndrome most often occurs with a deletion of paternal 15. chromosome, although less commonly patients may inherit both chromosomes 15 from the mother (maternal uniparental disomy).

Although certain gene mutations are reflected directly in the phenotype, some enzyme defects in the genetic background also lead to disorders of sexual development. In this regard, one of the relatively common enzyme disorders is congenital adrenal hyperplasia (CAH). The concept of congenital adrenal hyperplasia refers a group of autosomal recessive diseases arised from defects in the adrenal steroidogenic pathway due to diverse enzyme deficiencies.[62] The most prevalent type is 21-hydroxylase deficiency, resulting from mutations in the *CYP21A2* gene (6p21), while less common cases comprise 3β-hydroxysteroid dehydrogenase and 11β-hydroxylase deficiencies due to mutations in the *HSD3B2* (1p12) and *CYP11B1* (8q24) genes, respectively.[63] 21-Hydroxylase deficiency may lead to hyponatremia, hyperkalemia, dehydration in patients and ambiguous genitalia in females. Children with 3β-HSD deficiency often suffer from adrenal insufficiency and salt loss, and in male infants, masculinization of the external genitalia is impaired to varying degrees (Pseudohermaphroditism).[64] Congenital adrenal hyperplasia resulting from 11Beta-Hydroxylase deficiency may present with hypertension, hypokalemia, short stature, as well as virilization in females (DSD) on the basis of increased adrenal androgens.[65] CAH accompanied by genital virilization is the most common cause of 46,XX DSD cases. CAH mostly occurs because of the 21-hydroxylase defect, resulting in impaired cortisol production and this causes overproduction of hormonal precursors and then conversion into androgens.[66] In addition, congenital adrenal hyperplasia (CAH) can rarely be caused by 17 α-hydroxylase deficiency and/or 17,20 lyase deficiency on the basis of *CYP17A1* gene mutations.[67] In this disease, the synthesis of cortisol and sex steroids decreases, and mineralocorticoid precursors increase, and therefore 46,XX or 46,XY DSD, hypertension and hypokalemia occur.[68] On the other hand, cytochrome P450 oxidoreductase deficiency (*POR* gene, 7q11.23) -a congenital adrenal hyperplasia subsequently identified- has a steroid nature suggesting impairment in both 17α-hydroxylase/17,20-lyase and 21-hydroxylase activity.[69] It is a steroidogenesis disorder with a wide phenotypic manifestation encompassing cortisol deficiency (usually partial), changes in the synthesis of sex steroids, disorders of sexual development (DSD), and some skeletal malformations.[70]

One of the enzyme defects involved in sexual development disorders is aromatase deficiency. This disease rarely occurs as a result of loss-of-function mutations in the *CYP19A1* gene (15q21.2).[71] Since cytochrome P450 aromatase is involved in estrogen synthesis from androgens and prevents the virilizing effect of androgens in the female fetus, aromatase deficiency should be kept in mind in terms of 46,XX DSD.[72] The main problem here is the masculinization of the female, and such infants usually have ambiguous genitalia. Patients have decreased estrogen and increased testosterone and are likely to experience ovarian cysts and hirsutism.

Another enzyme defect, called 5α-reductase type 2 (5α-RD2) deficiency, leads to a 46,XY disorder of sex development and occurs as a result of *SRD5A2* (2p23.1) mutations.[73] This disease is inherited in an autosomal recessive pattern. The steroid 5α-reductase type 2 enables the conversion of testosterone to dihydrotestosterone,[74] and respectively one is involved in

the transformation of Wolffian ducts into male internal genitalia, while the other, a more active form, is particularly vital for the development of male external genitalia.[75] The main problem of these patients is dihydrotestosterone deficiency. These cases have dysmorphological features ranging from nearly female external genitalia to underdeveloped male genitalia. Most patients present as male pseudohermaphroditism and can be bred as female. A certain amount of virilization may occur over time.

In conclusion, the genetics of DSD with various mutations, including enzyme defects, are complex and require careful approach in terms of diagnosis, treatment, follow-up, and genetic counseling for subsequent generations. The relevant genetic defect may originate from the parent's germ cells or arise during embryogenesis. It is possible that gene therapy will come into play in the near future, alongside classical medical interventions and surgery. DSDs affect people's psychological and social life, mental development and even personality in some way. If untreated and/or psychological support is not provided, it is likely that depression, anxiety, bipolar disorder, etc. may be seen in these people based on the sexual development disorder. Therefore, in addition to surgical and medical treatment, these patients should receive psychiatric and/or psychological support as needed.

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