TABLE 410-3 SELECTED GENETIC CAUSES OF 46,XY DISORDERS OF SEX DEVELOPMENT (DSDs)

Gene	Inheritance	Gonad	Uterus	External Genitalia	Associated Features
Disorders of Testis Development					
WT1	AD	Dysgenetic testis	+/–	Female or ambiguous	Wilms' tumor, renal abnormalities, gonadal tumors (WAGR, Denys-Drash and Frasier's syndromes)
CBX2	AD	Ovary	+	Female	
SF1	AR/AD (SL)	Dysgenetic testis/Leydig dysfunction	+/–	Female or ambiguous	Primary adrenal failure; primary ovarian insufficiency in female (46,XX) relatives
SRY	Y	Dysgenetic testis or ovotestis	+/–	Female or ambiguous	
SOX9	AD	Dysgenetic testis or ovotestis	+/–	Female or ambiguous	Campomelic dysplasia
MAP3K1	AD (SL)	Dysgenetic testis	+/–	Female or ambiguous	
DHH	AR	Dysgenetic testis	+	Female	Minifascicular neuropathy
GATA4	AD	Dysgenetic testis	–	Ambiguous or male	Congenital heart disease
ATRX	X	Dysgenetic testis	–	Female or ambiguous	α Thalassemia, developmental delay
ARX	X	Dysgenetic testis	–	Male or ambiguous	Developmental delay; X-linked lissencephaly
MAMLD1	X	Dysgenetic testis/Leydig dysfunction	–	Hypospadias	
DAX1	dupXp21	Dysgenetic testis	+/–	Female or ambiguous	
WNT4/RSPO1	dup1p35	Dysgenetic testis	+	Ambiguous	
Disorders of Androgen Synthesis					
LHR	AR	Testis	–	Female, ambiguous or micropenis	Leydig cell hypoplasia
DHCR7	AR	Testis	–	Variable	Smith-Lemli-Opitz syndrome: coarse facies, second-third toe syndactyly, failure to thrive, developmental delay, cardiac and visceral abnormalities
StAR	AR	Testis	–	Female or ambiguous	Congenital lipoid adrenal hyperplasia (primary adrenal failure)
CYP11A1	AR	Testis	–	Ambiguous	Primary adrenal failure
HSD3B2	AR	Testis	–	Ambiguous	CAH, primary adrenal failure ± salt loss, partial androgenization due to ↑ DHEA
CYP17	AR	Testis	–	Female or ambiguous	CAH, hypertension due to ↑ corticosterone and 11-deoxycorticosterone, except in isolated 17,20-lyase deficiency
CYB5A	AR	Testis	–	Ambiguous	Apparent isolated 17,20-lyase deficiency; methemoglobinemia
POR	AR	Testis	–	Ambiguous or male	Mixed features of 21-hydroxylase deficiency and 17α-hydroxylase/17,20-lyase deficiency, sometimes associated with Antley-Bixler craniosynostosis
HSD17B3	AR	Testis	–	Female or ambiguous	Partial androgenization at puberty, ↑ androstenedione-to-testosterone ratio
SRD5A2	AR	Testis	–	Ambiguous or micropenis	Partial androgenization at puberty, ↑ testosterone-to-dihydrotestosterone ratio
AKR1C2 (*AKR1C4*)	AR	Testis	–	Female or ambiguous	Decreased fetal DHT production
Disorders of Androgen Action					
Androgen receptor	X	Testis	–	Female, ambiguous, micropenis or normal male	Phenotypic spectrum from complete androgen insensitivity syndrome (female external genitalia) and partial androgen insensitivity (ambiguous) to normal male genitalia and infertility

Abbreviations: AD, autosomal dominant; *AKR1C2*, aldo-keto reductase family 1 member 2; AR, autosomal recessive; *ARX*, aristaless related homeobox, X-linked; *ATRX*, α-thalassemia, mental retardation on the X; CAH, congenital adrenal hyperplasia; *CBX2*, chromobox homologue 2; *CYB5A*, cytochrome b5 POR, P450 oxidoreductase; *CYP11A1*, P450 cholesterol side-chain cleavage; *CYP17*, 17α-hydroxylase and 17,20-lyase; *DAX1*, dosage sensitive sex-reversal, adrenal hypoplasia congenita on the X chromosome, gene 1; DHEA, dehydroepiandrosterone; *DHCR7*, sterol 7 δ reductase; *DHH*, desert hedgehog; *GATA4*, GATA binding protein 4; *HSD17B3*, 17β-hydroxysteroid dehydrogenase type 3; *HSD3B2*, 3β-hydroxysteroid dehydrogenase type 2; *LHR*, LH receptor; *MAP3K1*, mitogen-activated protein kinase kinase kinase 1; *SF1*, steroidogenic factor 1; SL, sex-limited; *SOX9, SRY*-related HMG-box gene 9; *SRD5A2*, 5α-reductase type 2; *SRY*, sex-related gene on the Y chromosome; *StAR*, steroidogenic acute regulatory protein; WAGR, Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation; *WNT4*, wingless-type mouse mammary tumor virus integration site, 4; *WT1*, Wilms' tumor–related gene 1.

(due to aromatization of testosterone), a short vagina but no uterus (because MIS production is normal), scanty pubic and axillary hair, and a female gender identity and sex role behavior. Gonadotropins and testosterone levels can be low, normal, or elevated, depending on the degree of androgen resistance and the contribution of estradiol to feedback inhibition of the hypothalamic-pituitary-gonadal axis. AMH/MIS levels in childhood are normal or high. Most patients present with inguinal hernias (containing testes) in childhood or with primary amenorrhea in late adolescence. Gonadectomy sometimes is offered for girls diagnosed in childhood, because there is a low risk of malignancy, and estrogen replacement is prescribed. Alternatively, the gonads can be left in situ until breast development is complete and removed because of tumor risk. Some adults with complete AIS decline gonadectomy, but should be counseled about the risk of malignancy, especially because early detection of premalignant changes by imaging or biomarkers is currently not possible. The use of graded dilators in adolescence is usually sufficient to dilate the vagina for sexual intercourse.