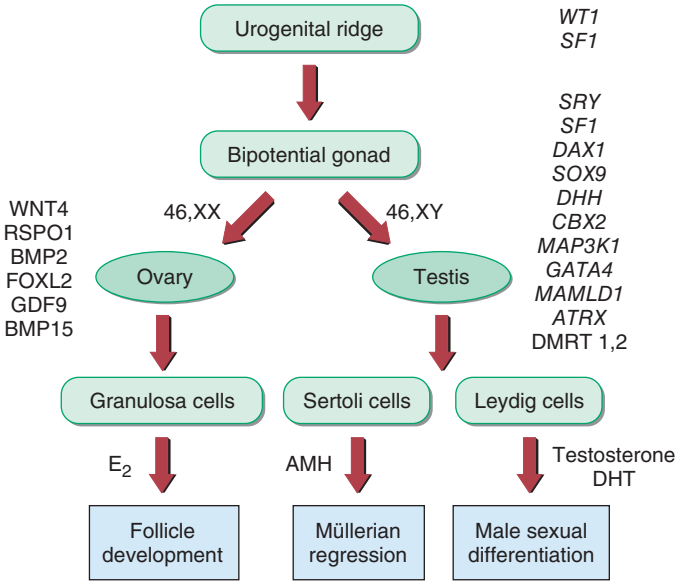

FIGURE 410-2 The genetic regulation of gonadal development. AMH, anti-müllerian hormone (müllerian-inhibiting substance); *ATRX*, α-thalassemia, mental retardation on the X; BMP2 and 15, bone morphogenic factors 2 and 15; *CBX2*, chromobox homologue 2; *DAX1*, dosage sensitive sex-reversal, adrenal hypoplasia congenita on the X chromosome, gene 1; *DHH*, desert hedgehog; DHT, dihydrotestosterone; *DMRT 1,2*, doublesex MAB3-related transcription factor 1,2; *FOXL2*, forkhead transcription factor L2; *GATA4*, GATA binding protein 4; GDF9, growth differentiation factor 9; *MAMLD1*, mastermind-like domain containing 1; *MAP3K1*, mitogen-activated protein kinase kinase kinase 1; RSPO1, R-spondin 1; *SF1*, steroidogenic factor 1 (also known as NR5A1); *SOX9*, *SRY*-related HMG-box gene 9; *SRY*, sex-determining region on the Y chromosome; *WNT4*, wingless-type MMTV integration site 4; *WT1*, Wilms' tumor–related gene 1.

KS. Results may be better in younger men. After ICSI and embryo transfer, successful pregnancies can be achieved in ~50% of these cases. The risk of transmission of this chromosomal abnormality needs to be considered, and preimplantation screening may be desired, although this outcome is much less common than originally predicted. Long-term monitoring of men with KS is important given the increased risk of breast cancer, cardiovascular disease, metabolic syndrome, and autoimmune disorders. Because most men with KS are never diagnosed, it is important that all internists consider this diagnosis in men with these features who might be seeking medical advice for other conditions.

TURNER'S SYNDROME (GONADAL DYSGENESIS; 45,X)

Pathophysiology Approximately one-half of women with TS have a 45,X karyotype, about 20% have 45,X/46,XX mosaicism, and the remainder have structural abnormalities of the X chromosome such as X fragments, isochromosomes, or rings. The clinical features of TS result from haploinsufficiency of multiple X chromosomal genes (e.g., short stature homeobox, *SHOX*). However, imprinted genes also may be affected when the inherited X has different parental origins.

Clinical Features TS is characterized by bilateral streak gonads, primary amenorrhea, short stature, and multiple congenital anomalies in phenotypic females. It affects ~1 in 2500 women and is diagnosed at different ages depending on the dominant clinical features (Table 410-2). Prenatally, a diagnosis of TS usually is made incidentally after chorionic villus sampling or amniocentesis for unrelated reasons such as advanced maternal age. Prenatal ultrasound findings include increased nuchal translucency. The postnatal diagnosis of TS should be considered in female neonates or infants with lymphedema, nuchal folds, low hairline, or left-sided cardiac defects and in girls with unexplained growth failure or pubertal delay. Although limited spontaneous pubertal development occurs in up to 30% of girls with TS (10%, 45,X; 30–40%, 45,X/46,XX) and ~2% reach menarche, the vast majority of women with TS develop complete ovarian insufficiency. Therefore, this diagnosis should be considered in all women who present with primary or secondary amenorrhea and elevated gonadotropin levels.

TREATMENT TURNER'S SYNDROME

The management of girls and women with TS requires a multidisciplinary approach because of the number of potentially involved organ systems. Detailed cardiac and renal evaluation should be performed at the time of diagnosis. Individuals with congenital heart

TABLE 410-2 CLINICAL FEATURES OF CHROMOSOMAL DISORDERS OF SEX DEVELOPMENT (DSD)

Disorder	Common Chromosomal Complement	Gonad	Genitalia		Breast Development
			External	Internal	
Klinefelter's syndrome	47,XXY or 46,XY/47,XXY	Hyalinized testes	Male	Male	Gynecomastia
	Clinical Features				
	Small testes, azoospermia, decreased facial and axillary hair, decreased libido, tall stature and increased leg length, decreased penile length, increased risk of breast tumors, thromboembolic disease, learning difficulties, speech delay and decreased verbal IQ, obesity, diabetes mellitus, metabolic syndrome, varicose veins, hypothyroidism, systemic lupus erythematosus, epilepsy				
Turner's syndrome	45,X or 45,X/46,XX	Streak gonad or immature ovary	Female	Hypoplastic female	Immature female
	Clinical Features				
	Infancy: lymphedema, web neck, shield chest, low-set hairline, cardiac defects and coarctation of the aorta, urinary tract malformations, and horseshoe kidney				
	Childhood: short stature, cubitus valgus, short neck, short fourth metacarpals, hypoplastic nails, micrognathia, scoliosis, otitis media and sensorineural hearing loss, ptosis and amblyopia, multiple nevi and keloid formation, autoimmune thyroid disease, visuospatial learning difficulties				
	Adulthood: pubertal failure and primary amenorrhea, hypertension, obesity, dyslipidemia, impaired glucose tolerance and insulin resistance, autoimmune thyroid disease, cardiovascular disease, aortic root dilation, osteoporosis, inflammatory bowel disease, chronic hepatic dysfunction, increased risk of colon cancer, hearing loss				
45,X/46,XY mosaicism	45,X/46,XY	Testis or streak gonad	Variable	Variable	Usually male
	Clinical Features				
	Short stature, increased risk of gonadal tumors, some Turner's syndrome features				
Ovotesticular DSD (true hermaphroditism)	46,XX/46,XY	Testis and ovary or ovotestis	Variable	Variable	Gynecomastia
	Clinical Features				
	Possible increased risk of gonadal tumors				