TABLE 410-4 SELECTED GENETIC CAUSES OF 46,XX DISORDERS OF SEX DEVELOPMENT (DSDs)

Gene	Inheritance	Gonad	Uterus	External Genitalia	Associated Features
Testicular/Ovotesticular DSD					
SRY	Translocation	Testis or ovotestis	–	Male or ambiguous	
SOX9	dup17q24	Unknown	–	Male or ambiguous	
RSPO1	AR	Testis or ovotestis	±	Male or ambiguous	Palmar plantar hyperkeratosis, squamous cell skin carcinoma
WNT4	AR	Testis or ovotestis	–	Male or ambiguous	SERKAL syndrome (renal dysgenesis, adrenal and lung hypoplasia)
Increased Androgen Synthesis					
HSD3B2	AR	Ovary	+	Clitoromegaly	CAH, primary adrenal failure, mild androgenization due to ↑ DHEA
CYP21A2	AR	Ovary	+	Ambiguous	CAH, phenotypic spectrum from severe salt-losing forms associated with adrenal failure to simple virilizing forms with compensated adrenal function, ↑ 17-hydroxyprogesterone
POR	AR	Ovary	+	Ambiguous or female	Mixed features of 21-hydroxylase deficiency and 17α-hydroxylase/17,20-lyase deficiency, sometimes associated with Antley-Bixler craniosynostosis
CYP11B1	AR	Ovary	+	Ambiguous	CAH, hypertension due to ↑ 11-deoxycortisol and 11-deoxycorticosterone
CYP19	AR	Ovary	+	Ambiguous	Maternal virilization during pregnancy, absent breast development at puberty
Glucocorticoid receptor	AR	Ovary	+	Ambiguous	↑ ACTH, 17-hydroxyprogesterone and cortisol; failure of dexamethasone suppression

Abbreviations: ACTH, adrenocorticotropin; AR, autosomal recessive; CAH, congenital adrenal hyperplasia; *CYP11B1*, 11β-hydroxylase; *CYP19*, aromatase; *CYP21A2*, 21-hydroxylase; DHEA, dehydroepiandrosterone; *HSD3B2*, 3β-hydroxysteroid dehydrogenase type 2; *POR*, P450 oxidoreductase; *RSPO1*, R-spondin 1; *SOX9*, *SRY*-related HMG-box gene 9; *SRY*, sex-related gene on the Y chromosome.

Biochemical features of acute salt-wasting 21-OHD are hyponatremia, hyperkalemia, hypoglycemia, inappropriately low cortisol and aldosterone, and elevated 17-hydroxyprogesterone, ACTH, and plasma renin activity. Presymptomatic diagnosis of classic 21-OHD is now made by neonatal screening tests for increased 17-hydroxyprogesterone in many centers. In most cases, 17-hydroxyprogesterone is markedly increased. In adults, ACTH stimulation (0.25 mg of cosyntropin IV) with assays for 17-hydroxyprogesterone at 0 and 30 min can be useful for detecting nonclassic 21-OHD and heterozygotes (Chap. 406).

TREATMENT CONGENITAL ADRENAL HYPERPLASIA

Acute salt-wasting crises require fluid resuscitation, IV hydrocortisone, and correction of hypoglycemia. Once the patient is stabilized, glucocorticoids must be given to correct the cortisol insufficiency and suppress ACTH stimulation, thereby preventing further virilization, rapid skeletal maturation, and the development of polycystic ovaries. Typically, hydrocortisone (10–15 mg/m^2 per day in three divided doses) is used in childhood with a goal of partially suppressing 17-hydroxyprogesterone (100 to <1000 ng/dL). The aim of treatment is to use the lowest glucocorticoid dose that adequately suppresses adrenal androgen production without causing signs of glucocorticoid excess such as impaired growth and obesity. Salt-wasting conditions are treated with mineralocorticoid replacement. Infants usually need salt supplements up to the first year of life. Plasma renin activity and electrolytes are used to monitor mineralocorticoid replacement. Some patients with simple virilizing 21-OHD also benefit from mineralocorticoid supplements. Parents and patients should be educated about the need for increased doses of steroids during sickness, and patients should carry medic alert systems.

Steroid treatment for older adolescents and adults varies depending on lifestyle, age, and factors such as a desire to optimize fertility. Hydrocortisone remains a useful approach, but treatment with prednisolone at night may provide more complete ACTH suppression. Steroid doses should be adjusted to individual requirements because overtreatment can result in iatrogenic Cushing's-like features, including weight gain, insulin resistance, hypertension, and osteopenia. Because it is long acting, dexamethasone given at night is useful for ACTH suppression but is often associated with more side effects, making hydrocortisone or prednisolone preferable for most patients. Androstenedione and testosterone may be useful measurements of long-term control, with less fluctuation than 17-hydroxyprogesterone. Mineralocorticoid requirements often decrease in adulthood, and doses should be reassessed and reduced to avoid hypertension in adults. In very severe cases, adrenalectomy has been advocated but incurs the risks of surgery and total adrenal insufficiency.

Girls with significant genital androgenization due to classic 21-OHD usually undergo vaginal reconstruction and sometimes clitoral reduction (maintaining the glans and nerve supply), but the optimal timing of these procedures is debated, as is the need for the individual to be able to consent. There is a higher threshold for undertaking clitoral surgery in some centers because long-term sensation and ability to achieve orgasm can be affected, but the long-term results of newer techniques are not yet known. Full information about all options should be provided. If surgery is performed in infancy, surgical revision or regular vaginal dilatation may be needed in adolescence or adulthood, and long-term psychological support and psychosexual counseling may be appropriate. Women with 21-OHD frequently develop polycystic ovaries and have reduced fertility, especially when control is poor. Fecundity is achieved in 60–90% of women with good metabolic control, but ovulation induction (or even adrenalectomy) may be required. Dexamethasone should be avoided in pregnancy. Men with poorly controlled 21-OHD may develop testicular adrenal rests and are at risk for reduced fertility. Prenatal treatment of 21-OHD by the administration of dexamethasone to mothers is still under evaluation. However, pending methods to diagnose the disorder early in pregnancy, both affected and nonaffected fetuses will be exposed because treatment is started ideally before 6 to 7 weeks. The long-term effects of prenatal dexamethasone exposure on fetal development are still under evaluation, and current guidelines recommend full informed consent before treatment, ideally in a protocol that allows long-term follow-up of all children treated. Newer techniques such as cell-free fetal DNA testing may potentially reduce treatment of nonaffected fetuses.