**TABLE 411-2 CAUSES OF CONGENITAL HYPOGONADOTROPIC HYPOGONADISM**

| Gene | Locus | Inheritance | Associated Features |
|---|---|---|---|
| **A. Hypogonadotropic Hypogonadism due to GnRH Deficiency** | | | |
| **A1. GnRH Deficiency Associated with Hyposmia or Anosmia** | | | |
| *KAL1* | Xp22 | X-linked | Anosmia, renal agenesis, synkinesia, cleft lip/palate, oculomotor/visuospatial defects, gut malformations |
| *NELF* | 9q34.3 | AR | Anosmia, hypogonadotropic hypogonadism |
| *FGFR1* | 8p11-p12 | AD | Anosmia, cleft lip/palate, synkinesia, syndactyly |
| *PROK2* | 3p21 | AR | Anosmia/sleep dysregulation |
| *PROK2R* | 20p12.3 | AR | Variable |
| *CHD7* | 8q12.1 | | Anosmia, other features of CHARGE syndrome |
| **A2. GnRH Deficiency with Normal Sense of Smell** | | | |
| *GNRHR* | 4q21 | AR | None |
| *GnRH1* | 8p21 | AR | None |
| *KISS1R* | 19p13 | AR | None |
| *TAC3* | 12q13 | AR | Microphallus, cryptorchidism, reversal of GnRH deficiency |
| *TAC3R* | 4q25 | AR | Microphallus, cryptorchidism, reversal of GnRH deficiency |
| *LEPR* | 1p31 | AR | Obesity |
| *LEP* | 7q31 | AR | Obesity |
| *FGF8* | 10q24 | AR | Skeletal abnormalities |
| **B. Hypogonadotropic Hypogonadism not due to GnRH Deficiency** | | | |
| *PC1* | 5q15-21 | AR | Obesity, diabetes mellitus, ACTH deficiency |
| *HESX1* | 3p21 | AR | Septo-optic dysplasia, CPHD |
| | | AD | Isolated GH insufficiency |
| *LHX3* | 9q34 | AR | CPHD (ACTH spared), cervical spine rigidity |
| *PROP1* | 5q35 | AR | CPHD (ACTH usually spared) |
| *FSHβ* | 11p13 | AR | ↑ LH |
| *LHβ* | 19q13 | AR | ↑ FSH |
| *SF1 (NR5A1)* | 9p33 | AD/AR | Primary adrenal failure, XY sex reversal |

***Abbreviations:*** ACTH, adrenocorticotropic hormone; AD, autosomal dominant; AR, autosomal recessive; CHARGE, eye coloboma, choanal atresia, growth and developmental retardation, genitourinary anomalies, ear anomalies; CPHD, combined pituitary hormone deficiency; *DAX1*, dosage-sensitive sex-reversal, adrenal hypoplasia congenita, X-chromosome; *FGFR1*, fibroblast growth factor receptor 1; FSH, follicle-stimulating hormone; *FSHβ*, follicle-stimulating hormone β-subunit; GH, growth hormone; GnRH, gonadotropin-releasing hormone; *GNRHR*, gonadotropin-releasing hormone receptor; *GPR54*, G protein–coupled receptor 54; *HESX1*, homeo box gene expressed in embryonic stem cells 1; *KAL1*, interval-1 gene; *LEP*, leptin; *LEPR*, leptin receptor; LH, luteinizing hormone; *LHβ*, luteinizing hormone β-subunit; *LHX3*, LIM homeobox gene 3; *NELF*, nasal embryonic LHRH factor; *PC1*, prohormone convertase 1; *PROK2*, prokineticin 2; *PROP1*, Prophet of Pit 1; *SF1*, steroidogenic factor 1; *TAC3*, tachykinin 3; *TAC3R*, tachykinin 3 receptor.

in some families with normosmic IHH. Mutations in more than one gene (digenicity or oligogenicity) may contribute to clinical heterogeneity in IHH patients. X-linked hypogonadotropic hypogonadism also occurs in *adrenal hypoplasia congenita*, a disorder caused by mutations in the *DAX1* gene, which encodes a nuclear receptor in the adrenal gland and reproductive axis. Adrenal hypoplasia congenita is characterized by absent development of the adult zone of the adrenal cortex, leading to neonatal adrenal insufficiency. Puberty usually does not occur or is arrested, reflecting variable degrees of gonadotropin deficiency. Although sexual differentiation is normal, **most** patients have testicular dysgenesis and impaired spermatogenesis despite gonadotropin replacement. Less commonly, adrenal hypoplasia congenita, sex reversal, and hypogonadotropic hypogonadism can be caused by mutations of steroidogenic factor 1 (SF1). Rarely, recessive mutations in the *LHβ* or *FSHβ* gene have been described in patients with selective deficiencies of these gonadotropins. In approximately 10% of men with IHH, reversal of gonadotropin deficiency may occur in adult life. Also, a small fraction of men with IHH may present with androgen deficiency and infertility in adult life after having gone through apparently normal pubertal development.

A number of homeodomain transcription factors are involved in the development and differentiation of the specialized hormone-producing cells within the pituitary gland (Table 411-2). Patients with mutations of *PROP1* have combined pituitary hormone deficiency that includes GH, prolactin (PRL), thyroid-stimulating hormone (TSH), LH, and FSH, but not ACTH. *LHX3* mutations cause combined pituitary hormone deficiency in association with cervical spine rigidity. *HESX1* mutations cause septo-optic dysplasia and combined pituitary hormone deficiency.

*Prader-Willi syndrome* is characterized by obesity, hypotonic musculature, mental retardation, hypogonadism, short stature, and small hands and feet. Prader-Willi syndrome is a genomic imprinting disorder caused by deletions of the proximal portion of the paternally derived chromosome 15q11-15q13 region, which contains a bipartite imprinting center, uniparental disomy of the maternal alleles, or mutations of the genes/loci involved in imprinting (Chap. 83e). *Laurence-Moon syndrome* is an autosomal recessive disorder characterized by obesity, hypogonadism, mental retardation, polydactyly, and retinitis pigmentosa. Recessive mutations of leptin, or its receptor, cause severe obesity and pubertal arrest, apparently because of hypothalamic GnRH deficiency (Chap. 415e).

**Acquired Hypogonadotropic Disorders** • ***SEVERE ILLNESS, STRESS, MALNUTRITION, AND EXERCISE*** These factors may cause reversible gonadotropin deficiency. Although gonadotropin deficiency and reproductive dysfunction are well documented in these conditions in women, men exhibit similar but less pronounced responses. Unlike women, most male runners and other endurance athletes have normal gonadotropin and sex steroid levels, despite low body fat and frequent intensive exercise. Testosterone levels fall at the onset of illness and recover during recuperation. The magnitude of gonadotropin suppression generally correlates with the severity of illness. Although hypogonadotropic hypogonadism is the most common cause of androgen deficiency in patients with acute illness, some have elevated levels of LH and FSH, which suggest primary gonadal dysfunction. The pathophysiology of reproductive dysfunction during acute illness is unknown but likely involves a combination of cytokine and/or glucocorticoid effects. There is a high frequency of low testosterone levels in patients with chronic illnesses such as HIV infection, end-stage renal disease, chronic obstructive lung disease, and many types of cancer and in patients receiving glucocorticoids. About 20% of HIV-infected men with low testosterone levels have elevated LH and FSH levels; these patients presumably have primary testicular dysfunction. The remaining 80% have either normal or low LH and FSH levels; these men have a central hypothalamic-pituitary defect or a dual defect involving both the testis and the hypothalamic-pituitary centers. Muscle wasting is common in chronic diseases associated with hypogonadism, which also leads to debility, poor quality of life, and adverse outcome of disease. There is great interest in exploring strategies that can reverse androgen deficiency or attenuate the sarcopenia associated with chronic illness.

Men using opioids for relief of cancer or noncancerous pain or because of addiction often have suppressed testosterone and LH levels and high prevalence of sexual dysfunction and osteoporosis; the degree of suppression is dose-related and particularly severe with long-acting opioids such as methadone. Opioids suppress GnRH secretion and alter the sensitivity to feedback inhibition by gonadal steroids. Men who are heavy users of marijuana have decreased testosterone secretion and sperm production. The mechanism of marijuana-induced hypogonadism is decreased GnRH secretion. Gynecomastia observed in marijuana users can also be caused by plant estrogens in crude preparations. Androgen deprivation therapy in men with prostate cancer has been associated with increased risk of bone fractures, diabetes mellitus, cardiovascular events, fatigue, sexual dysfunction, and poor quality of life.

***OBESITY*** In men with mild to moderate obesity, SHBG levels decrease in proportion to the degree of obesity, resulting in lower