

Rites of passage through puberty: A complex genetic ensemble

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Worldwide, puberty is recognized by various cultures and celebrated as a rite of passage into adulthood.

The methodical drumbeat of these religious and social ceremonies foreshadows the rhythm of reproduction that, in many ways, marks the final stage of development. Despite its social and physiological significance, including perpetuation of the species, the pathways that regulate the onset of puberty have evaded traditional physiological inquiries. No clear hormonal or metabolic trigger has been identified as a switch that activates the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator (1). Instead, genetic abnormalities that preclude puberty have provided the major insights into the pathways that are critical for the development and maturation of the reproductive axis (2, 3). Perhaps the best candidate for regulating the onset of puberty is kisspeptin, the ligand for the receptor encoded by *GPR54*, a gene identified as a cause of recessive hypogonadotropic hypogonadism (4, 5). The report by Pitteloud *et al.* (6) in this issue of PNAS identifies loss-of-function mutations in the prokineticin 2 (*PROK2*) gene, which encodes a secreted peptide that regulates the development and migration of the olfactory tract and GnRH neuron progenitors. The *PROK2* mutations caused hypogonadotropic hypogonadism in both males and females. Using *Prok2*^{-/-} knockout mice, the GnRH neuron progenitors were shown to cross the cribriform plate but fail to migrate into and populate the hypothalamus. Interestingly, olfactory tract development in humans with *PROK2* mutations was variable, resulting in both nonanosmic and anosmic forms of hypogonadotropic hypogonadism. This report highlights the role of genetics as a means to unravel complex developmental processes and helps explain why anosmia is a frequent, but variable, feature of inherited forms of hypogonadotropic hypogonadism.

Delayed puberty is a common clinical presentation and is often accompanied by delayed growth (7). The challenge for the practitioner is to distinguish those individuals with constitutional delay of growth and puberty (CDGP) from those with more serious conditions such as

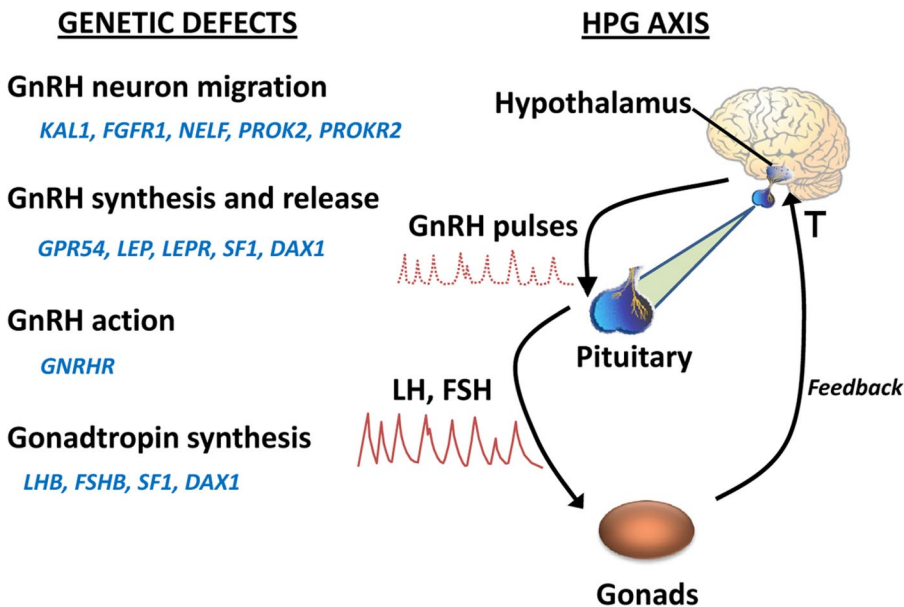


Fig. 1. Genetic causes of hypogonadotropic hypogonadism. The hypothalamic-pituitary-gonadal (HPG) axis is depicted in *Right*. Hypothalamic gonadotropin-releasing hormone (GnRH) pulses stimulate pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH) pulses that act on the gonads to stimulate gametogenesis and sex steroid, which feed back to regulate the hypothalamus and pituitary. Genes associated with hypogonadotropic hypogonadism are listed in *Left* below the steps they regulate. *KAL1*, Kallmann syndrome gene 1 (encodes anosmin 1); *FGFR1*, fibroblast growth factor receptor 1; *NELF*, nasal embryonic luteinizing hormone releasing hormone factor; *PROK2*, prokineticin 2; *PROKR2*, prokineticin receptor 2; *GPR54*, G protein receptor 54; *LEP*, leptin; *LEPR*, leptin receptor; *SF1*, steroidogenic factor 1 (also *FTZF1* or *NR5A1*); *DAX1*, dosage-sensitive sex reversal adrenal hypoplasia congenita critical region on X chromosome 1 (also, *NROB1*); *GNRHR*, GnRH receptor; *LHB*, LH- β ; *FSHB*, FSH- β .

panhypopituitarism, growth hormone deficiency, or hypogonadotropic hypogonadism. When pubertal delay extends beyond 2–2.5 standard deviations of the mean age of puberty (approximately age 13 years in girls and 14 years in boys), it is termed idiopathic hypogonadotropic hypogonadism (IHH). Pubertal delay is more common in boys than in girls, and IHH is approximately five times more frequent in males. These observations suggest an important role for genes on the X chromosome or perhaps fundamental differences in the sensitivity of the neuronal circuitry to disruption by genetic, hormonal, or environmental effects in males. The genetic basis of X-linked Kallmann syndrome was identified in 1991 based on a contiguous gene syndrome that included the locus encoding anosmin (*KAL1*) (8, 9). Initially, it was thought that mutations in the X-linked *KAL1* gene might explain why the disorder is more common in boys.

Moreover, the gene product affects migration of the precursor cells for the GnRH-producing neurons and the olfactory tracts, providing an explanation for the association of IHH and anosmia (10). Subsequent studies, however, identified *KAL1* mutations in a minority of patients with familial or sporadic forms of IHH (2, 3). Moreover, pedigrees with clear-cut autosomal dominant and recessive patterns of transmission suggested the involvement of other genes (11). The ensuing years have yielded a surprising array of genetic causes of gonadotropin deficiency, affecting multiple steps in the pathways that culminate in GnRH and gonadotropin synthesis and

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