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Releasing the Brake on Puberty

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What is so magical about the age at onset of puberty in humans — currently set at approximately 11 years of age?[1] Why not 6 or 16? Indeed, addressing this question from the perspective of evolutionary biology[2] suggests that puberty, as defined by age at menarche in girls, was earlier in Neolithic times and became delayed during the Industrial Revolution before reverting over the past two centuries to the present set point.[3] The shortened life span and the need to reach reproductive capacity would seem to have been predominant influences on the age of menarche thousands of years ago, whereas the more recent fluctuations in the age at onset of puberty have been attributed to poor nutrition followed by social improvement. How can one explain the underlying cause of the early onset of puberty in a child brought to the clinic at 5 years of age? It clearly cannot be explained on environmental grounds, even allowing for the secular trends in puberty ascribed to increasing obesity in the childhood population.[4,5] Influences on the timing of puberty, for the most part, remain unknown; the endocrinologist still cannot explain simply to parents why puberty generally starts at the age of 11 years, let alone why their child has entered puberty at 6 years of age.

The role of genetic factors in the control of the onset of puberty is vividly illustrated by a report in this issue of the *Journal* of a familial form of precocious puberty caused by loss-of-function mutations in an imprinted gene.[6] The authors had access to 40 members of 15 families in whom affected probands had central precocious puberty — that is, premature reactivation of the pulse GnRH generator that underscores the onset of normal puberty.[7] Applying whole-exome sequencing in multiply affected families adequately phenotyped for central precocious puberty, the authors identified deleterious mutations in a paternally expressed imprinted gene, *MKRN3.* (Imprinted genes have a "sex bias" in that they are expressed only from the maternal or the paternal chromosome; some genes are paternally imprinted, whereas others are maternally imprinted. *MKRN3* is maternally imprinted; expression from the maternally inherited copy of the gene is suppressed. MKRN3 protein is thus derived from RNA transcribed exclusively from the paternally inherited copy of the gene.)

MKRN3 encodes makorin RING-finger protein 3, which is involved with ubiquitination and cell signaling. The makorin family of proteins is abundantly expressed in the developing brain,

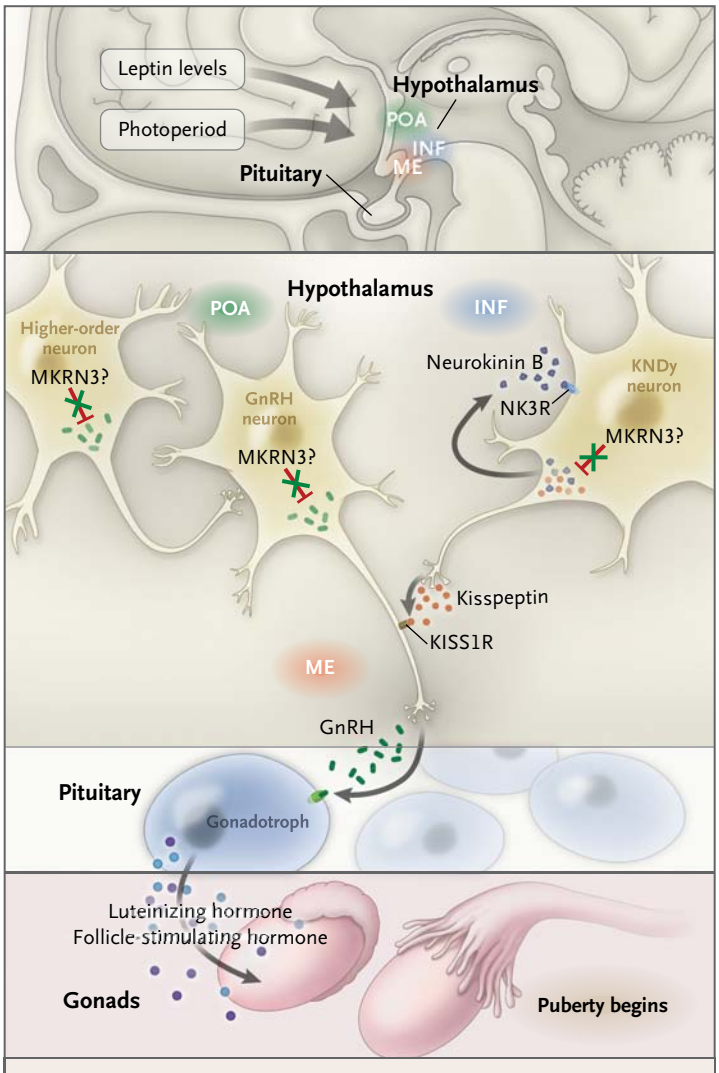

Figure 1. Timing of Puberty.

A pivotal event in the onset of puberty in mammals is the resumption of pulsatile release of gonadotropin-releasing hormone (GnRH) from neurons of the hypothalamus. Known influences on the timing of the onset of puberty in mammals include the photoperiod, leptin levels, and the increased expression of neurokinin B, kisspeptin, and their receptors (NK3R and KISS1R, respectively). Abreu et al.[6] implicate MKRN3, a protein that is believed to mediate ubiquitination, in puberty onset. In contrast with kisspeptin and neurokinin B, which stimulate the commencement of puberty, MKRN3 seems to inhibit puberty: Abreu et al. show that mutations in *MKRN3* predicted to cause loss of function of the protein cause central precocious puberty. KNDy denotes kisspeptin–neurokinin B–dynorphin, INF infundibular nucleus, ME median eminence, and POA preoptic area.

including the arcuate nucleus, where there is a repository of genes whose expression is relevant to puberty.[8,9] The authors showed that the expression of *Mkrn3* in mice of both sexes was highest at postnatal day 10 and declined thereafter to reach a nadir precisely consonant with the onset of puberty. It is also at this point that the expression of genes considered central to the activation of puberty (e.g., the kisspeptins and neurokinin B) begins to increase.[10]

So what is the effect of this study of familial central precocious puberty on our knowledge about the way in which the onset of puberty is controlled in humans? More is known about why puberty may be delayed than why it commences precociously. Any chronic disease process, such as severe malnutrition or a systemic disease such as cystic fibrosis, will delay or halt the progression of puberty. More specifically, the hypothalamic–pituitary–gonadal endocrine pathway can harbor specific defects in hormone production that are the result of known mutations. Hypogonadotropic hypogonadism caused by loss-of-function mutations affecting the G-protein–coupled receptor KISS1R (also known as GPR54) and those involving neurokinin B result in failure of the normal pattern of pulsatile GnRH secretion required to stimulate gonadotropin production and subsequently gonadal steroid secretion.[11,12] The discovery of the effect of mutations in *MKRN3* in humans and of a suggested role for its mouse orthologue in the arcuate nucleus appears to cement the idea that puberty starts only with the release of a restraint mechanism on the GnRH pulse generator, which in turn releases the brake on puberty (Fig. 1). A release of this restraint mechanism probably also explains why intracranial damage from conditions as diverse as head trauma and hydrocephalus and the effects of cranial irradiation can lead to precocious puberty.

Although the finding of a genetic cause for central precocious puberty is a significant contribution to further understanding human puberty, an explanation is lacking about why puberty starts at about the time of the junction of the first and second decades of human life. How MKRN3, an exemplar of a neurobiologic brake, interacts with other major players of puberty, such as kisspeptin, GnRH, leptin, and a host of neurotransmitters (excitatory and inhibitory), will certainly continue to exercise the minds of the puberty pundits.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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G Proteins — The Disease Spectrum Expands

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G proteins (guanine nucleotide-binding proteins) are heterotrimers composed of guanosine triphosphate–binding alpha subunits and tightly linked beta and gamma subunits. They couple a vast array of receptors (G-protein–coupled receptors, the subject of the Nobel Prize in Chemistry this past year[1]) to effectors that regulate diverse cellular processes. Of 15 human alpha-subunit genes, some, such as *GNAS*, are expressed ubiquitously; others are expressed only in specialized cells. G_s (the G protein encoded by *GNAS*) couples many hormone and neurotransmitter receptors to cyclic AMP stimulation, and it was the first G protein to be associated with human disease. Germline mutations that inactivate $G\alpha_s$ (the G-protein subunit α_s) were shown to cause the prototypical hormone-resistance disorder, pseudohypoparathyroidism.[2] Somatic activating mutations cause sporadic endocrine tumors and the McCune–Albright syndrome.[2] Mutations subsequently were identified in genes that encode dysfunctional $G\alpha$ proteins in rod photoreceptors in forms of night blindness and in cone photoreceptors in forms of color blindness, and mutations in *GNAL* have been linked to primary torsion dystonia.[3]

Somatic mutations that activate $G\alpha_q$ (the G-protein subunit α_q) and $G\alpha_{11}$ (the G-protein subunit α_{11}), closely related G proteins that activate intracellular ionized calcium–mediated signaling, have been associated with uveal melanoma.[4] In this issue of the *Journal*, Nesbit[5] and Mannstadt[6] and their colleagues report that germline mutations that inactivate $G\alpha_{11}$ cause hypercalcemic disorders and germline mutations that activate $G\alpha_{11}$ cause hypocalcemic disorders.

Calcium homeostasis is tightly regulated by parathyroid hormone. Parathyroid hormone secretion from the parathyroid glands is inhibited directly by increased serum levels of calcium. Primary hyperparathyroidism, the major cause of hypercalcemia in patients seen in an ambulatory setting, is caused by a neoplastic process in one or more parathyroid glands. This process leads to excess parathyroid hormone secretion, despite increased serum levels of calcium.

Familial hypocalciuric hypercalcemia is an autosomal dominant disease that, like primary hyperparathyroidism, is characterized by hypercalcemia and normal or elevated levels of serum parathyroid hormone.[7] However, renal and skeletal manifestations of primary hyperparathyroidism are generally absent in patients with familial hypocalciuric hypercalcemia. Partial parathyroidectomy does not correct the hypercalcemia; thus, surgery is not indicated. The patient's family history and measurement of urinary calcium:creatinine ratios are key to distinguishing familial hypocalciuric hypercalcemia from primary hyperparathyroidism.

Previous studies have shown that many cases of familial hypocalciuric hypercalcemia are caused by heterozygous germline inactivating mutations in the gene encoding the calcium-sensing receptor (*CASR*). The calcium-sensing receptor is a G-protein–coupled receptor that is highly ex-