

**Editor's Comment:** *It is striking that such financial analyses are now needed to justify growth screening, a fundamental tenet of pediatric care. However, as highlighted by this paper, many of the considerations remain elusive. What is the optimal height cut-off to identify likely pathology? What is the optimal screening paradigm? Serial height measurements will capture cases of growth deceleration before they become severe enough to cross the single height cut-off for pathology, but how frequent and how many are needed to balance improved sensitivity with increased cost? What is the actual cost of missed or delayed diagnoses and how are QALYs estimated, especially since the impact of short stature on quality of life remains so controversial? And what about the cost of height monitoring itself? Height*

*measurements in the United States are performed as part of routine pediatric well child care,<sup>2</sup> and the cost of a stadiometer spread across the patient population is so negligible that it seems virtually free. The only real cost is the time to accurately measure the child and plot the measurements on the appropriate growth chart. With the increasing pressures to expedite patient flow faster and faster, time may be the most expensive aspect of growth screening.*

Adda Grimberg, MD

#### References

1. National Screening Committee. Child health sub-group report: growth disorders. Leeds: National Screening Committee; 2004.
2. American Academy of Pediatrics Policy Statement - Committee on Practice and Ambulatory Medicine. Pediatrics. 2000;105:645.

## Histrelin Subdermal Implant in Central Precocious Puberty

This important article describes efficacy and safety data related to the use of a single annual subcutaneous implantation of a gonadotropin-releasing hormone analogue (GnRHa) to induce pituitary gonadotropin suppression in children with central precocious puberty. Histrelin provides a continuous slow release at an average rate of 65 µg/d of GnRHa. Its use as a single yearly implant has previously been shown to effectively suppress LH, FSH and testosterone secretion in adult males with prostate cancer.<sup>1,2</sup> This report is the first in children with precocious puberty.

The procedure of implantation will require more detailed examination with wider clinical use. A pediatric surgeon is required to perform this procedure and in this study, local or general anesthetic or sedation was used. There is no comment about any practical difficulties with the implantation in terms of interference with daily activities such as sports and recreation, or whether the implant became dislodged in some patients.

Eugster EA, Clarke W, Kletter GB, et al. Efficacy and safety of histrelin subdermal implant in children with central precocious puberty: A multicenter trial. J Clin Endocrinol Metab. 2007;92:1697-704.

**Editor's Comment:** *The data on sex steroid, LH and FSH evaluation are impressive and clearly show that effective suppression of gonadotrope function occurs for 12 months after a single subcutaneous implantation. The choice of patients may need to be individualized and an implantation technique which avoids general anesthetic would clearly be preferable. Longer term studies to assess recovery of the pituitary-gonadal axis following discontinuation of treatment are important. This first report in children is encouraging and may eliminate the discomfort of monthly or three-monthly injections as currently practiced.*

Martin O. Savage, MD

#### References

1. Schlegel PN, Kuzma P, Frick J, et al. Urology. 2001;58:578-82.
2. Chertin B, Spitz IM, Lindenberg T, et al. J Urol. 2000;163:838-44.

## Hypogonadotropic Hypogonadism—Mutations and Phenotypes

Isolated hypogonadotropic hypogonadism (IHH) has been associated with mutations in 7 genes to date (Table). The products of the genes encoded by *KAL1*, *FGFR1*, *PROK2*, *PROKR2*, and *NELF* assist in the regulation of neural movement within the CNS—particularly the migration of olfactory and gonadotropin releasing hormone (GnRH)-containing neurons from the olfactory placode during early embryogenesis. Mutations in these genes result in abnormalities of GnRH secretion and the reproductive endocrine system (delayed adolescence, hypogonadotropism) and the sense of smell (hyposmia, anosmia), and those afflicted often display other neurologic (bimanual synkinesia) and somatic (renal agenesis) anomalies. These traits

are transmitted in an autosomal dominant manner often with incomplete penetrance and substantial inter- and intrafamilial variability in clinical manifestations. Mutations of *GPR54* limit release of GnRH while those of the *gonadotropin-releasing hormone receptor (GNRHR)* impair its function at the gonadotroph membrane. These disorders are transmitted in an autosomal recessive manner and are not associated with other specific clinical or anatomic abnormalities.

Intrigued by the variable clinical manifestations of IHH, Pitteloud and colleagues examined the genotype of 2 families in which single gene defects thought to have resulted in IHH had been previously identified. In pedigree #1, a 21-year-old male with IHH and

**Table: Genetic causes of isolated hypogonadotropic hypogonadism.**

Gene	Locus	Gene product	OMIM
<i>KAL1</i>	Xp22.2	Anosmin (KAL1)	308700
<i>FGFR1</i>	8p11.2-p11.1	Fibroblast growth factor receptor 1 (KAL2)	136350
<i>PROK2</i>	3p21.1	Prokineticin 2 (KAL4)	607002
<i>PROKR2</i>	20p13	Prokineticin receptor 2 (KAL3)	607123
<i>NELF</i>	9q34.3	Nasal embryonic luteinizing hormone-releasing factor	608137
<i>GPR54</i>	19p13.3	G-protein coupled receptor 54	604161
<i>GNRHR</i>	4q21.1	Gonadotropin-releasing hormone receptor	138850

hyposmia was initially found to have a heterozygous mutation in *FGFR1* (Ser342Leu—chromosome 8p11.2-p11.1); the proband's father and sister had the same *FGFR1* mutation; the father had delayed onset and the sister normal timing of puberty. In vitro studies demonstrated that the Ser342Leu mutant of *FGFR1* acted in a dominant-negative manner. A heterozygous 8 bp deletion in the negative elongation factor (*NELF*) resulting in a truncated product was later identified in the proband, his mother and his brother; the latter 2 subjects underwent normal puberty. The authors suggested that loss of a single copy of *FGFR1* resulted in a less severe phenotype than did loss of a single copy (allele) of both *FGFR1* and *NELF*. In pedigree #2, two sisters with IHH (no evident spontaneous ovarian function) were found to have inactivating mutations in both *GNRHR* alleles (Gln106Arg, Arg262Gln—chromosome 4q21.2) ie, the sisters had compound heterozygosity. Their father had a history of delayed puberty and carried the Arg262Ser mutation, while

both *GNRHR* and *FGFR1* manifested only delayed puberty is uncertain. The investigators concluded that disorders thought to be monogenic in origin and that manifest variable degrees of clinical involvement may actually be oligogenic due to the involvement of 2 (possibly even more) different genes whose mutations sum to produce the clinical phenotype.

Pitteloud N, Quinton R, Pearce S, et al. Digenic mutations account for variable phenotypes in idiopathic hypogonadotropic hypogonadism. *J Clin Invest.* 2007;117:457-63.

**Editor's Comment:** A gene mutation has been found in only 30% of patients with IHH. Other genes that regulate migration of GnRH neurons and synthesis and release of or response to GnRH await identification. Clearly the concept of digenic inheritance of disease is one that may well be applicable to many disorders of the endocrine and other systems.

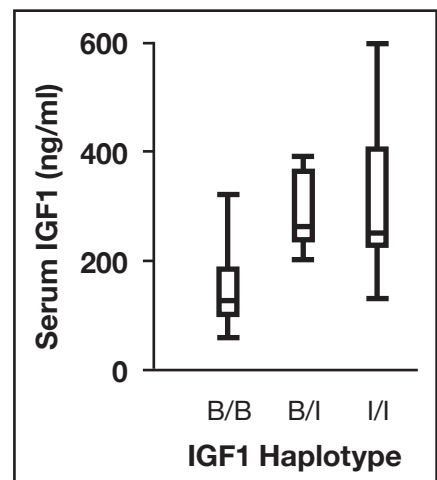
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## IGF-I Allele in Small Size Dogs

Intrigued by the great diversity in size among the dog family (Canidae), these investigators first identified by genome-wide scan a skeletal size-related quantitative trait locus (QTL) on chromosome 15 within a single breed—the Portuguese water dog (PWD), a breed with great inter-individual variation in size. They next examined the relationship of single-nucleotide polymorphisms (SNPs) within this QTL to skeletal size in large and small Portuguese water dogs. They found one such SNP in this QTL to be associated with size that was near the gene encoding insulin-like growth factor-I (*IGF1*). Designating the haplotypes I and B, the investigators found that Portuguese water dogs homozygous for haplotype I were larger in size and had higher serum IGF-I concentrations than did dogs that were homozygous for haplotype B; they calculated that 15% of the variability of skeletal size within this breed could be accounted for by this *IGF1* haplotype (Figure 1). Performing the same SNP analyses in more size-homogeneous small ( $n=23$ , <9 kg) and giant ( $n=20$ , >30 kg) canid breeds, the authors found skeletal size to be related to an *IGF1* haplotype characterized

by 20 SNPs that was shared by all small breed dogs (and one in particular designated SNP 5 A) (Figure 2). Sequencing of *IGF1* revealed a SNP in exon 3 and several

**Figure 1.** Serum levels of IGF1 protein (ng/ml) as a function of haplotype. Serum levels of IGF1 protein were assayed in 31 PWDs carrying haplotypes B and I. Box plots show the median (center line in box), first and third quartile (box ends), and maximum and minimum values (whiskers) obtained for each category: homozygous B/B ( $n=15$ ), heterozygous B/I ( $n=7$ ), and homozygous I/I ( $n=9$ ).



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