

A Gene Regulator of Puberty

While evaluating a Saudi family with several first cousin marriages in which many offspring had “idiopathic hypogonadotropic hypogonadism” transmitted as an autosomal recessive trait, the authors identified a locus on chromosome 19p13.3.^{1,2} This locus had a homozygous mutation of *GPR54* (chromosome 19p13.3, OMIM 604161, encoding an orphan G-protein receptor termed GPR54) at codon 148 in which serine was substituted for leucine (Leu148Ser). An unrelated patient was demonstrated to be a compound heterozygote with mutations in both alleles of *GPR54* - Arg331Stop leading to a truncated product and Stop399Arg - the latter resulting in an elongated protein product. *In vitro*, all mutations were found to decrease signal transduction through phospholipase C in response to the natural ligand of this receptor - kisspeptin-1 - sequence 112-121 (encoded by *KISS1*, chromosome 1q32, OMIM 603286). Kisspeptin-1 [sequence 68-121] suppresses metastases of melanoma and breast carcinoma experimentally. This 54 amino acid peptide, termed metastatin, is secreted by the placenta. In the compound heterozygotic subject, there were low basal concentrations of LH and testosterone that increased during pulsatile administration of exogenous GnRH; interestingly, this patient was more sensitive to the gonadotropin stimulating effects of GnRH than were comparable patients with hypogonadotropic hypogonadism without this specific genetic mutation.

The investigators extended these studies by developing a “knock-out” mouse model of *GPR54*^{-/-} that reproduced the clinical picture. The *GPR54*^{+/-} heterozygous mice had normal growth and fertility. The *GPR54*^{-/-} deficient animals of both genders were hypogonadotropic with small gonads, hypotrophic internal genitalia, and absence of secondary sexual characteristics. Interestingly, the adrenal glands of the *GPR54*^{-/-} animals were immature as well. Serum gonadotropin and sex hormone levels were low in *GPR54*^{-/-} animals, but LH and FSH values increased following administration of exogenous GnRH, but the hypothalamic concentrations of GnRH were normal. The authors conclude that the kisspeptin-GPR54 system is

important in the regulation of GnRH processing or secretion in the hypothalamus rather than in the movement of GnRH secreting neurons from their embryologic site of origin in the olfactory placode (the error in Kallmann syndrome) or in the synthesis of GnRH itself.

Seminara SB, et al. The *GPR54* gene as a regulator of puberty *N Engl J Med* 2003;349:1614-1627.

Editor’s Comment: *This exciting report exemplifies the best of clinical investigation employing the most up-to-date technology in a multi-institutional collaborative that should serve as a model for future studies. The identification of a G-protein receptor (and its aptly named endogenous ligand - kisspeptin) that are involved in the regulation of GnRH release opens an entirely new control system of the reproductive endocrine axis,³ a finding analogous in importance to the discovery of the role of ghrelin in the regulation of growth hormone secretion⁴ and energy metabolism. Elucidation of the mechanism(s) by which this unit regulates GnRH secretion is eagerly anticipated. One can envision many future studies of the kisspeptin-GPR54 axis. Perhaps it is involved in the development of normal puberty. Might polymorphisms of its component genes or signal transduction system account for variations in the early or delayed onset of adolescence? Are gain-of-function mutations in *GPR54* present in some children with idiopathic central precocious puberty? Does the development of gonadotropin secreting tumors involve this pathway? Since metastatin is secreted by the placenta, this suggests that it has a physiologic role during gestation - possibly in regulation of fetal gonadotropin secretion. Future studies are eagerly and impatiently awaited.*

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References

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Growth Hormone Effects on Quality of Life of Young Adults

The investigators’ goals were to document changes in quality of life (QoL) over the course of the first year post-growth hormone (GH) withdrawal, and to subsequently assess the psychological effects of reinstating GH. Participants in the GH discontinuation study were recruited from a Dutch outpatient clinic and comprised of 14 males, 8 females (ages 15 to 22 years, mean = 19 years), 11 with isolated GH deficiency (IGHD), and 11 with multiple pituitary hormone deficits (MPHD). All had

achieved adult height and were receiving adequate replacement of other hormones. Although all tested GH deficient (GHD) as children, 8 of 11 IGHD retested GH-sufficient as young adults. In contrast, all MPHD patients retested as GHD in early adulthood.

During the first six months of discontinuation of GH, a statistically significant increase in psychiatric symptoms (assessed by Hopkins Symptom Checklist) was observed, with no further increases between 6 and

12 months. There were no differences in symptoms between IGHD and MPHD, or between GHD and non-GHD. These findings corresponded temporally with a decline in IGF-I. IGF-I concentrations did not differentiate the MPHD and IGHD groups. Depressive symptoms, assessed by the Profile of Mood States (POMS), increased in both IGHD and MPHD groups by 6 months of GH discontinuation and thereafter increased further for the IGHD, but decreased within the MPHD group. The opposite pattern was observed for the POMS Tension scale, which increased across the 12 months for the MPHD group, but declined for those with IGHD. Lower IGF-I concentrations were associated with more negative mood states and somatic complaints for the combined group, whereas higher IGF-I was associated with greater 'vigor'.

Nine of 14 patients (64%; 4 males, 5 females; 2 with IGHD and 7 with MPHD) from the GH discontinuation study who remained GHD when retested as adults subsequently participated in the GH treatment study. This sample was augmented with an additional 11 patients (6 males and 5 females; 3 IGHD and 8 MPHD) who were GHD both as children and adults, had not been treated with GH in the past year, and had not participated in the GH discontinuation study. Upon reintroduction of GH to only those patients meeting adult criteria for GHD, IGF-I levels increased between 0 and 6 months in both IGHD and MPHD, but without further change by 12 months. Accompanying this increase, scores on the insecure and depression scales (of the SCL-90) decreased across the entire 12 months for both IGHD and MPHD groups, whereas anxiety (assessed by the State-Trait Anxiety Scale) decreased significantly only from baseline to 6 months. QoL scores showed a significant improvement from 0 to 6 months of GH treatment. IGF-I levels were negatively correlated with negative mood states, but positively correlated with vigor, QoL, and short-term memory. The investigators concluded that GH-modulation of IGF-I concentrations is responsible both for deteriorating mood states during GH discontinuation and improved psychological status during the return to treatment.

Stouthart PJ, et al. Quality of Life of Growth Hormone (GH) Deficient Young Adults During Discontinuation and Restart of GH Therapy. *Psychoneuroendocrinology* 2003;28:612-626.

Editor's Comment: As recognition has grown that the actions of GH extend beyond linear growth, the practice of treating GHD in adulthood has become more widely accepted. Unlike most studies assessing the benefits of adult GH replacement, these outcome variables were psychological rather than metabolic. In this study, both the IGHD (73% of whom retested GH-sufficient by adult criteria) and MPHD subgroups exhibited similar deterioration in emotional state upon discontinuation of GH with improvement after reinstating GH therapy. The investigators related these psychological changes to lower and subsequently improved IGF-I concentrations.

Several methodological features of this study should be taken into account before factoring them into clinical management algorithms. For instance, the investigators provide no indication of how representative study participants were of those in this clinic in meeting diagnostic and age criteria. Were those who agreed to participate more emotionally symptomatic? Research suggests considerable variability among patients in responsiveness to the QoL benefits of adult GH replacement.^{1,2} The potential contribution of a placebo effect to mental health indices also needs to be considered. A meta-analysis suggests that placebo effects are stronger in small trials with continuous subjective outcomes.³ The investigators may be attributing some psychological benefits to GH that are potentially due to response bias or placebo effect. Nonetheless this study is of great interest and provides important information.

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References

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Non-Hormonal Genetic Influence on Brain Development

Current dogma holds that differences in brain development and behavior between males and females depend primarily on gonadal steroid hormones, especially testosterone and its metabolites that induce the masculine pattern and inhibit the female pattern of brain development. However, there is also evidence that genetic factors may act directly on the developing brain contributing to these differences. Until recently, this alternative view has been difficult to document, but Dewing et al provide new and convincing evidence for non-hormonal genetic effects.

Their work was done in a mouse embryo 10.5 days

after conception. This is just before the first sign of sexual differentiation of the genital ridges occurs, thus the influence of gonadal hormones could be excluded. Their strategy was to harvest whole heads from the embryos, isolate RNA into separate pools for males and females and then analyze for differential gene expression in the male and female brains. For screening analysis, they used gene (microarray) chip (Affymetrix) technology which allowed the relative expression of nearly 10,000 characterized mouse genes and over 3,000 less well defined expressed sequences (Expressed Sequence Tags – ESTs) to be determined. The normalized gene