

(17.3%) were found to have persistent GHD and 43 (82.7%) to be transiently GH deficient. On the other hand, among patients with MPHD only 2 patients (11.1%) were transiently GH deficient.

None of the parameters differed significantly with respect to gender. There were significant positive correlations between peak GH and IGF-I, and IGFBP-3 levels in all patients (IGF-1  $r=0.297$ ,  $p=0.036$ ; IGFBP-3  $r=0.45$ ,  $p=0.03$ ). The IGF-I and IGFBP-3 SDS values were lower in the group that had peak GH values  $<3$  ng/mL. When the cut-off was taken as  $-2$  SD, specificity and sensitivity of IGF-I in confirming persistency of GHD were 65.7% and 73.3%, respectively. Its positive predictive value and negative predictive value were 33.3% and 85.2%, respectively. For IGFBP-3, specificity and sensitivity were 84%, and 60%, respectively. The positive and negative predictive values were 60%, and 84%, in the same order. Finally, while the negative predictive values were high for both of these parameters, an IGFBP-3 value below  $-2$  SD was found to be more specific than an IGF-I value below  $-2$  SD.

The data in this study confirmed that there were no auxological and clinical signs to predict the transiency or the persistence of GHD except for a history of organic disease and presence of MPHD. The authors concluded that most patients with childhood onset GHD were idiopathic and GHD was frequently transient in this group of patients. In contrast, GHD was persistent in patients with MPHD. They emphasized the high negative predictive values for IGF-I and IGFBP-3 (85.1% and 84%, respectively) suggesting that normal IGF-I and IGFBP-3 levels highly exclude the diagnosis of GHD.

Berberoglu M, Siklar Z, Darendeliler F, et al. Evaluation of permanent growth hormone deficiency (GHD) in young adults with childhood onset GHD: a multicenter study. *J Clin Res Ped Endo*. 2008;1:30–37.

**Editor's Comment:** *The question of how to confirm the diagnosis of adult GHD in an adolescent patient who has completed linear growth is still being debated. The Growth Hormone Research Society guidelines suggest a peak GH response on ITT of  $<3$  ng/mL as being diagnostic*

*of GHD in adulthood.<sup>1</sup> Although patients with MPHD have peak GH levels  $<3$  ng/mL, it is not clear whether this value can confirm adult GHD exactly. In addition, despite the high negative predictive values of IGF-I and IGFBP-3, the use of serum IGF-I and IGFBP-3 alone to predict GHD cannot be recommended. The majority of children with GHD, when retested as adults, do not have the classical severe GHD.<sup>2</sup> This high incidence (70%) of normal GH responses on retesting has been shown in patients with idiopathic and isolated GHD.<sup>3</sup> This finding indicates that the organic etiologies are often severe and can be assumed to be permanent at the beginning of the therapy. Therefore, those patients with organic MPHD could be excluded from retesting.*

*The patients who have peak GH cut-off values between 3-5 ng/mL might be GH deficient as well. In fact, in the transition period in late adolescence a cut-off value of 5 ng/mL is advocated for the diagnosis of persistent GHD and continuation of GH therapy because adolescents have higher GH levels than adults. In this study, there were 3 additional patients with peak GH level between 3-5 ng/mL in the isolated GHD group and none in the MPHD group. Therefore, no suggestion is available for patients in this gray zone. Furthermore, the prognosis of patients with a GH response of 5-10 ng/mL is not known. Therefore, it is important to keep in mind that clinical signs of GHD may occur later in life and the clinician must look for these manifestations in patients with a history of childhood GHD.<sup>3</sup>*

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## References

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## IGFBP-3 Promoter Polymorphism Affects Response to GH Treatment for GH Deficiency

Growth responses to growth hormone (GH) therapy vary considerably among children with GH deficiency despite receiving standardized per kg body weight doses. Several clinical factors have been identified in influencing responsiveness to treatment,<sup>1</sup> but about half of the variation remains unexplained. These clinical factors only indirectly consider genetic traits, by including parental target heights.

Thus, Costalonga et al sought to examine the effects of an *insulin-like binding protein (IGFBP)-3* promoter polymorphism on growth velocity during the first year

of GH treatment in prepubertal children with severe GH deficiency. In twin studies, about 60% of the interindividual variability in circulating IGFBP-3 levels was found to be genetically determined.<sup>2</sup> A single nucleotide change 202 bp upstream of the transcription start site was found to affect IGFBP-3 promoter activity in vitro and in vivo; mean circulating IGFBP-3 levels in healthy adults were highest in those with AA genotype at the  $-202$  position, less in AC and lowest in those with CC.

Costalonga et al studied 48 boys and 23 girls with severe GH deficiency (mean height z-score of  $-4.3 \pm 1.4$  SD,

mean bone age delay of  $4.3 \pm 2.7$  years, and peak GH response in 2 stimulation tests ranging from  $<0.1$  to  $3.3$  mcg/L). All children were prepubertal with a mean age of  $8.6 \pm 4.1$  years, and treated exclusively with GH at a mean dose of  $32$  mcg/kg/day adjusted to weight every 3 to 4 months. Seventeen percent of subjects had a defined genetic etiology for GH deficiency, 63% had ectopic posterior pituitary and 25% had interrupted stalk on MRI imaging; only 8% had idiopathic GH deficiency, and patients with central nervous system tumors, meningoencephalocele or previous radiation therapy were excluded from the study.

Among the 71 subjects, 21% had  $-202$  IGFBP3 genotype of AA, 54% had AC, and 25% had CC. The genotype subgroups did not differ clinically at the start of treatment, nor in mean GH treatment doses. Mean circulating IGFBP-3 levels also were not significantly different at baseline, they gained significance with GH treatment; AA subjects had higher IGFBP-3 levels than C allele carriers in codominant ( $P<0.005$ ) and recessive models ( $P<0.001$ ), and developed greater increases in IGFBP-3 z-scores with treatment. The IGFBP3 polymorphism accounted for 19% of variability in circulating IGFBP-3 levels ( $P<0.001$ ) and 54% of variability when combined with age and gender.

The IGFBP3 polymorphism did not associate with IGF-I levels either at baseline or during GH treatment, but it did affect growth response to treatment. Mean first year growth velocity was  $13.0 \pm 2.1$  cm/year in AA subjects,  $11.4 \pm 2.5$  cm/year in AC subjects, and  $10.8 \pm 1.9$  cm/year in CC subjects ( $P<0.05$ ). Single and multiple linear regression analyses found the effect of IGFBP3 polymorphism independent of other variables in associating with growth velocity. It accounted for 10% of variability in growth velocity ( $P<0.005$ ) and 29% of variability when combined with height z-score and age at start of treatment.

This is the first study of the  $-202$  A/C IGFBP3 polymorphism in children. Because the genotype was significantly associated with circulating IGFBP-3 levels in healthy adults and in children with severe GH deficiency only after GH treatment but not at baseline, the authors concluded the effect is at least in part dependent on GH action.

Costalonga EF, Antonini SR, Guerra-Junior G, Mendonca BB, Arnhold IJ, Jorge AA. The  $-202$  A allele of insulin-like growth factor binding protein-3 (IGFBP3) promoter polymorphism is associated with higher IGFBP-3 serum levels and better growth response to growth hormone treatment in patients with severe growth hormone deficiency. *J Clin Endocrinol Metab.* 2009;94:588-595.

**Editor's Comment:** This study conveys 2 important lessons. First, the results may seem counter-intuitive: the genotype associated with the highest IGFBP-3 levels had the greatest growth response to GH treatment. The IGFBP3s were defined by their high-affinity IGF binding that renders them competitive inhibitors for IGF binding to the type 1 IGF receptor (IGF1R), and hence inhibitors of IGF action.<sup>3</sup> This is an isolated effect. The situation in vivo and some in vitro cell models is more complex, because the balance of ligand binding protein receptor and post-receptor signaling pathways is modulated by multiple factors. Such factors include, but are not limited to, changes in ligand half-life, local IGFBP proteases that convert the high-affinity IGF binders to lower affinity IGFBP fragments, IGF1R trafficking and down-regulation, and interactions with other cell signaling systems. Plus, we now appreciate that the IGFBP3s exert IGF-independent actions of their own.

Secondly, this study highlights yet another factor that influences patient responsiveness to GH treatment. I applaud the authors' focus on clearly defined subjects with severe GH deficiency, rather than opening up their sample size to less severe and thus, heterogeneous, patients who may harbor other alterations in their GH/IGF axis function. The authors concluded their paper with the suggestion that future pharmacogenetic studies may support adjusting GH treatment to genotype in order to individualize and thereby optimize therapy. Before moving to genotyping—which is expensive and not readily available—clinicians already have tools to individualize therapy. For example, titrating GH dose to achieve desired IGF-I z-scores, as the principle mediator and biomarker of GH effects, is akin to titrating l-thyroxine dose to thyroid function tests when treating patients with hypothyroidism.<sup>4</sup> This paper provides additional data supporting the notion that the traditional, cookie cutter, one-size-fits-all, weight-based dosing of GH therapy can be improved by individualized approaches to optimize treatment efficacy and safety.

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## GH Treatment for Growth Failure in Pediatric Patients with Crohn's Disease

Heyman and colleagues studied the effects of growth hormone (GH) treatment ( $0.043$  mg/kg/day;  $0.3$  mg/kg/week) on height velocity, body composition,

and disease activity in a group of children and adolescents (mean age  $12.6 \pm 4.5$  years; 6 males) with Crohn's Disease (CD) and growth failure. All