

growth failure. Sequencing revealed substitution of the phylogenetically highly conserved arginine at position 481 to glutamate (R481Q) in the IGF-1R of both the patient and the maternal aunt. This arginine is in the N-terminal fibronectin type III domain, and situated near the first disulfide bond (Cys 514) between the 2 α -subunits. Either wild-type or R481Q IGF-1R was over-expressed in NIH-3T3 fibroblasts to conduct functional assays. R481Q IGF-1R altered neither surface expression nor ligand binding capacity. However, as demonstrated by Western blotting under reducing and non-reducing conditions, the mutant receptor had incomplete dimerization likely related to impairment of that first disulfide bond; the mutant, but not wild-type, IGF-1R showed monomeric forms of the β -subunit under non-reducing conditions. Further, compared to wild-type, R481Q IGF-1R had blunted IGF-I induction of IGF-1R autophosphorylation, p42/44MAPK phosphorylation, Akt phosphorylation, and cellular proliferation.

Thus, the authors concluded that R481Q disturbs the first disulfide bond of IGF-1R, thereby impairing its dimerization and ligand-stimulated conformational change that is required for signal transduction. This translated clinically into IGF-I resistance and growth failure.

Inagaki K, Tiulpakov A, Rubtsov P, et al. A familial insulin-like growth factor-I receptor mutant leads to short stature: clinical and biochemical characterization. *J Clin Endocrinol Metab.* 2007;92:1542-8.

Editor's Comment: *The authors astutely recognized the severe pre- and post-natal growth failure of their patient as indicative of reduced IGF-I activity; measurement of basal IGF-I concentration quickly ruled out IGF-I deficiency in favor of IGF-I resistance. The authors are to be commended on their detective work, which led to the discovery of a novel mechanism of IGF-I resistance that joins the short list of previously reported IGF-1R mutations.*

This illustrative case also highlights the importance of obtaining a good family history in the evaluation of a poorly growing child. Most often, we ascribe similar multigenerational height z-scores to familial short stature, which is considered a normal variant. However, when the growth failure is severe and affects a subset of relatives, as exemplified by this patient's family, an inherited growth defect should be considered. Another example would be autosomal dominant (type 2) isolated GH deficiency.^{1,2} Although the child may be short "like the parent," it is possible that they are sharing an underlying pathologic process.

Adda Grimberg, MD

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2. Salemi S, Yousefi S, Lochmatter D, et al. *Endocrinology.* 2007;148:45-53.

Ultimate Height of Growth Hormone Deficient Patients who Normalized Growth Hormone Secretion in Puberty

The objectives of the study by Zucchini et al were to establish the percentage and the characteristics of subjects diagnosed with isolated growth hormone

deficiency (GHD) in childhood who normalized their GH secretion in puberty and discontinued treatment at that time. The final height attained by this group

was compared with that of subjects with persistent GHD who continued on GH therapy after retesting. Sixty-nine subjects (40 males, 29 females) with a diagnosis of isolated GHD before puberty were evaluated by means of arginine and l-dopa testing and were reevaluated after at least 2 years of GH therapy and after the onset of puberty. If peak GH levels were $>10 \mu\text{g/L}$ therapy was withdrawn.

At retesting, 44 subjects (63.7%; 24 males, 20 females) had a peak GH $<10 \mu\text{g/L}$. Patients with confirmed GHD were not different from subjects with normalized GH secretion regarding: height

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deficit at diagnosis, first year growth response to GH, age and height at onset of puberty, or height and insulin-like growth factor (IGF)-I at retesting. Males who continued treatment achieved an adult height of 165.1 ± 4.5 cm, while those who suspended therapy after retesting had an adult height of 164.0 ± 3.4 cm. Final height of females who continued treatment was 153.2 ± 4.1 cm, whereas those who suspended therapy after retesting were 152.9 ± 5.2 cm. Duration of therapy and GH levels at diagnosis and at retesting were found to be unrelated to achieved adult height or to height increments obtained during the period of observation.

Zucchini S, Pirazzoli P, Baronio F, et al. Effect on adult height of pubertal growth hormone retesting and withdrawal of therapy in patients with previously diagnosed growth hormone deficiency. *J Clin Endocrinol Metab.* 2006;91:4271-6.

First Editor's Comment: *A significant number of children diagnosed with GHD before entering puberty, particularly those with non-severe GHD not associated with multiple pituitary hormone deficiencies or with alterations of the pituitary anatomy, display normal GH secretion when retested after the completion of puberty. This discrepancy in GH testing before and after puberty could be the result of a transient deficiency which tends to normalize with the secretion of gonadal steroids or could be due to the unreliability of pharmacological tests when repeated over time.*

Zucchini et al suggested that GH retesting should take place at midpuberty when GH secretion rises and not after the attainment of final height and completion of puberty, thus avoiding unnecessary treatment of subjects who have normal GH secretion when retested at puberty. The final height attained by subjects with normal GH secretion at retesting, who discontinued therapy, was similar to that of individuals with confirmed GHD who continued treatment. Therefore, the withdrawal of GH therapy after retesting did not lead to a reduction in ultimate height. There were no clinical or laboratory parameters that allowed for the differentiation of patients with or without persistent GHD after puberty. In subjects with non-severe GHD it seems advisable to retest GH secretion during puberty and to discontinue treatment in those individuals that are no longer deficient, thus avoiding unnecessary treatment during and beyond puberty in these subjects.

Roberto Lanes, MD

Second Editor's Comment: *Several years ago we described the recovery of patients with isolated suboptimal GH secretion after a short trial of GH releasing hormone (GHRH).¹ Why wait until puberty?*

Fima Lifshitz, MD

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