

Jorge AA, Marchisotti FG, Montenegro LR, Carvalho LR, Mendonca BB, Arnhold IJ. Growth hormone (GH) pharmacogenetics: influence of GH receptor exon 3 retention or deletion on first-year growth response and final height in patients with severe GH deficiency. *J Clin Endocrinol Metab.* 2006;9:1076–1080.

Editor's Comment: Different variables can influence the growth velocity and the final height of children treated with rhGH, but so far there is no way of accurately predicting response to therapy. Duration of treatment, height SDS at the start of treatment, bone age delay, midparental height, and growth velocity during the first year of treatment, are some of the variables which could influence final height after therapy. However, as suggested by Jorge et al, these variables only partially explain the inter-individual variability response to rhGH treatment in children with GHD. The GHR gene is an obvious candidate to influence the response to rhGH. The GHR gene is located in the short arm of chromosome 5; two of the most common isoforms of GHR in humans are generated by retention of GHRf1 or exclusion of GHRd3. The frequency of each allele in humans ranges from 68% to 75% for GHRf1 and from 25% to 32% for GHRd3.

Patients reported in this paper with GHD who were homozygous for GHR exon 3f1 were less responsive to short- and long-term rhGH therapy. However, Pilotta et al recently evaluated 54 GHD children treated for at least one year with rhGH; they found no significant differences in growth velocities between groups of subjects defined by polymorphic genotypes, and concluded that the

most common polymorphisms, alone or in association, did not appear to affect the growth response to rhGH in GHD children. On the other hand, studies by Dos Santos et al² and Binder et al³ support the theory that there is increased responsiveness to high dose rhGH in association with GHRd3 genotype in patients with Turner syndrome, small for gestational age (SGA), and idiopathic short stature; the magnitude of this effect may depend on the primary cause of the short stature. The Binder group demonstrated that girls with Turner syndrome who were homozygote for the GHRd3 variant showed the highest increment in height velocity and exceeded their growth prediction, whereas short children born SGA demonstrated only a mildly increased response to high-dose rhGH in the presence of the GHRd3 variant. Genotyping of the GHRd3 protein polymorphism may prove to be a tool for a more precise understanding of rhGH effects on growth and for the individualization of rhGH dosing in both GHD and non-GHD children; however, its effectiveness is still in doubt.

Roberto Lanes, MD

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IGF-I and IQ in Middle Childhood

Gunnell et al examined the association between circulating levels of insulin-like growth factor (IGF)-I, its main binding protein, IGFBP-3, and subsequent measures of IQ. Data were obtained from the Avon Longitudinal Study of Parents and Children (ALSPC, n=13 617). The study consisted of 547 white singleton children (301 boys, 246 girls), with IGF-I and IGFBP-3 measurements obtained at a mean age of 8 years and IQ measured with the Wechsler Intelligence Scale for Children (WISC-III) at a mean age of 8.7 years. Speech and language were also measured by the Wechsler Objective Reading Dimensions (WORD; assessed at 8.7 years) and Wechsler Objective Language Dimensions (WOLD; assessed at 7.5 years) tests. Some children (n=407) had IGF-I levels measured at approximately 5 years of age in a previous study.

The mean IGF-I (ng/mL) level at age 8 years was 142.6 (\pm 53.9) and 154.4 (\pm 51.6) for boys and girls, respectively. For every 100 ng/mL increase in IGF-I, IQ increased by 3.18 points ($p=.019$) for boys and girls combined. This relationship achieved statistical significance only for girls. A statistically significant association was not detected between IGFBP-3 or IGF-I/IGFBP-3 ratios and IQ. WISC-III subtests are classified as Verbal or Performance: associations between IGF-I and IQ were restricted to the

Verbal component. The IGF-I levels were not significantly associated with either WOLD or WORD test scores for the combined sample of boys and girls. A positive statistically significant association between IGF-I levels and WORD scores was detected for girls, but not for boys. Associations between IGF-I levels at age 5 and WISC-III scores were similar to those for IGF-I levels measured at age 7 to 8, applied to both the boys and girls, but were restricted to the Verbal IQ.

Follow-up analyses were performed statistically, controlling for potential confounding variables. Introducing birth weight (adjusted for gestation), breastfeeding, and BMI to the regression model strengthened the association between IGF-I and IQ; whereas controlling for maternal education and IGFBP-3 attenuated the association, as did adjustment for housing status and family socioeconomic status. The authors suggest that rather than confounding the associations of IGF-I levels with IQ, parental education and socioeconomic status may serve as markers of their offspring's intelligence. The authors concluded "Offspring IGF-I levels are likely to be associated with parental IGF-I levels, through shared genetic influences. This study provides some preliminary evidence that IGF-I is associated with brain development in childhood. Additional

longitudinal research is required to clarify the role of IGF-I in neurodevelopment. Because IGF-I levels are modifiable through diet and other environmental exposures, this may be one pathway through which the childhood environment may influence neurodevelopment.”

Gunnell D, Miller LL, Rogers I, Holly JMP, the ALSPAC Study Team. Association of insulin-like growth factor I and insulin-like growth factor-binding protein-3 with intelligence quotient among 8- to 9-year-old children in the Avon Longitudinal Study of parents and children. *Pediatrics*. 2005;116:e681–e686.

Editor’s Comment: *The prospect of an association between IGF-I, brain development, and intelligence is not new,¹ but remains intriguing. The importance of the Gunnell study lies in the cohort design of the ALSPAC, the quality of the psychological/cognitive assessments, and detailed characterization of important contextual variables in child development (eg, diet and socioeconomic status of the family). Evidence that growth factors (rather than psychosocial stress associated with short stature) may be responsible for educational and vocational outcomes suggests that stature and growth can be viewed as proxies for other biologic events rather than as a focus for its own sake.*

Findings from a controlled study by Kranzler and colleagues² on the intellectual ability of children with growth hormone receptor deficiency (GHRD) (and accompanying severe IGF-I deficiency) are difficult to reconcile with the Gunnell report. Kranzler compared the intellectual ability of 18 school-age Ecuadorian GHRD probands with that of 42 relatives and 28 controls. The intellectual ability of those with GHRD was not significantly different from their relatives, and was

comparable to controls. Furthermore, homozygosity or heterozygosity for the mutation in the GHR gene common to Ecuadorian patients was unrelated to intelligence. The authors concluded that GH-induced IGF-I production is not required for normal brain growth in utero or for postnatal intellectual development.

It may be overly simplistic to question, but if circulating values of IGF-I are positively related to intellectual function, then would GH-mediated increases in IGF-I result in higher performance? Indirect supportive evidence comes from a study of the effects on IQ scores of GH administered to children born small for gestational age.³ Growth hormone treatment was associated with significant increases in relative height along with improved IQ. Because it can be assumed that GH treatment raised IGF-I levels, then perhaps IGF-I effects on the central nervous system mediated the effects of GH on intellectual ability. Interestingly, it was only the Performance IQ that showed improvement with GH treatment; the opposite pattern was observed in the Gunnell study. Clearly, all these findings require replication, and hopefully future investigations will be guided by a priori predictions regarding the effects of growth factors on brain development and function in order to reduce the probability of Type I errors.

David E. Sandberg, PhD

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