

Editor's Comment: Loss of *SOX3* (OMIM 313430, chromosome Xq26.3) activity in man is associated with X-linked GH deficiency and mental retardation.² Reynaud and co-workers³ reported the distribution of mutations in *PROP1*, *POU1F1*, *LHX3*, *LHX4*, and *HESX1* in a population of 165 unrelated families (195 patients) with deficiencies of multiple anterior pituitary hormones (combined pituitary hormone deficiency [CPHD]) with or without SOD or pituitary stalk interruption syndrome (PSIS). Overall mutations in one of the 5 transcription factor genes examined were found in 22 of 165 index patients (13.3%). CPHD was familial in 21 families, with mutations identified in 10 of these 21 families (52.4%). Homozygous or double heterozygous mutations in *PROP1* were identified in 20 patients, in 8 of whom CPHD was familial. A mutation in *POU1F1* or *LHX4* was identified in only one patient each, and no mutations in *LHX4* or *HESX1* were found in this CPHD population. Although mutations of *HESX1* have been found in patients with SOD, none were identified in the report of Reynaud and co-workers. It would be of interest to analyze *SOX2* in these subjects. Reynaud et al also correlated phenotype with genotype and outlined a schematic algorithm through which gene analysis of patients with CPHD and associated anomalies might be pursued (Figure).

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References

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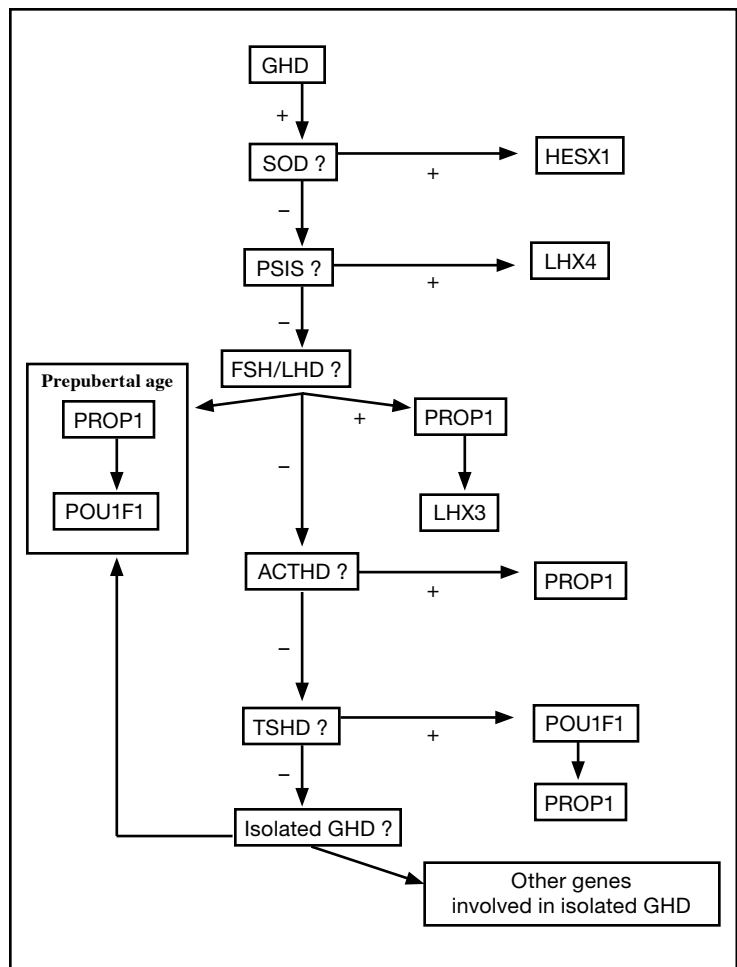


Figure. Algorithm of CPHD genetic screening. FSH/LHD, FSH and LH deficiencies; ACTHD, ACTH deficiency.

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Clinical Significance of a 6 Hr Exon 3-deletion Polymorphism

Audi and colleagues from the Spanish SGA Study Group reported the relative frequencies of the deleted and full-length exon 3 growth hormone receptor (GHR) polymorphisms in 247 short stature children and adolescents with birth weight small for gestational age (SGA) and 289 normal stature adult control subjects. The homozygous or heterozygous inheritance of the exon 3 deleted isoform has been reported to enhance GH action, although the significance of this genotype on GHR function is unknown. There was a 2-fold increase of the biologically less active homozygous full-length exon 3 isoform genotype in the SGA subjects. In the control population, there was no relationship between the height phenotypes and genotypes of the subjects. Therefore, it is suggested that in short stature SGA subjects, the presence of the full-length isoform may have impeded post-natal catch-up growth.

Carrascosa et al, also from the Spanish SGA Hormone Study Group, reported the results of GH

therapy in patients from the same cohort of SGA subjects as described by Audi and colleagues. Previous reports have demonstrated an increased growth response to GH therapy in SGA subjects who have the deleted exon 3 isoform, compared to those with the full-length receptor.¹ In contrast, this paper reported no differences in first- or second-year growth velocity and height gain between the different genotypes of 86 GH-treated SGA subjects. These patients were treated with a GH dose of 66 µg/kg/day, an amount that is at the upper end of the recommended dose and higher than in other reported series. It was suggested that these high GH doses might over-ride a more subtle effect reported with lower GH regimens.

Jorge and colleagues from São Paulo, Brazil performed a retrospective genetic analysis for the retained or deleted exon 3 GHR genotypes in 75 patients with severe isolated or combined GH deficiency. Clinical and laboratory data were similar at baseline in patients with different

genotypes. However, patients on GH therapy who were carrying at least one GHRd3 allele demonstrated a higher first-year height velocity ($P < 0.05$), compared to those with the full-length isoform. Final height was also greater in the GHRd3 subjects. No parental height data were given. Jorge et al hypothesized that manipulation of GH dose following genotype characterization might become a reality in the future.

Blum and colleagues from Eli Lilly in Germany studied 107 patients with severe idiopathic GH deficiency. In contrast to the Jorge group, they found no difference in growth responses to GH therapy between the subjects with the d3-GHR allele and those with the full-length receptor.

Audi L, Esteban C, Carrascosa A, et al. Exon 3-deleted/full-length growth hormone receptor polymorphism (d3/fl-GHR) genotype frequencies in Spanish short small-for-gestational-age (SGA) children and adolescents ($n=247$) and in an adult control population ($n=289$) show increased fl/fl in short SGA. *J Clin Endocrinol Metab.* 2006;91:5038-43.

Carrascosa A, Esteban C, Espadero R, et al. The d3/fl-growth hormone (GH) receptor polymorphism does not influence the effect of GH treatment (66 microg/kg per day) or the spontaneous growth in short non-GH-deficient small-for-gestational-age children: results from a two-year controlled prospective study in 170 Spanish patients. *J Clin Endocrinol Metab.* 2006;91:3281-6.

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;91:1076-80.

Blum WF, Machinis K, Shavrikova EP, et al. The growth response to growth hormone (GH) treatment in children with isolated GH deficiency is independent of the presence of the exon 3-minus isoform of the GH receptor. *J Clin Endocrinol Metab.* 2006;91:4171-4.

Editor's Comment: *Several large studies that look at the possible influence on responses to GH therapy of homozygous or heterozygous inheritance of the deleted exon 3 GHR isoform have now been performed. The results are conflicting in SGA subjects as no difference in growth response was found in the Spanish study, contrasting with the original description of an apparent growth-enhancing effect shown in the French study. However, Binder et al² reported significantly increased responses in both SGA and Turner syndrome patients carrying the exon 3-deleted isoform. Now, Jorge and Blum have reported different outcomes and conclusions in patients with GH deficiency.*

With such differing conclusions, it is hard to imagine that an effect of real clinical relevance exists from the inheritance of the deleted isoform. No doubt further studies will be published with probably differing conclusions. At this stage, the prospective genotyping of short patients in order to optimize their responses to GH therapy seems premature.

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