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A novel variant in an intron consensus sequence associated with familial growth hormone deficiency

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Splicing variants in the exon-intron boundaries of the GH1 gene have been reported to cause autosomal dominant growth hormone deficiency (GHD type 2). However, whether variants in the intron consensus sequence (XGGG repeats) have an important role in GH1 gene splicing has not been established. Two siblings (proband 1 and 2) were diagnosed with growth hormone deficiency due to poor linear growth at age 4 years (height SDS -2.2 and – 1.6, respectively). Peak serum GH levels with provocative testing were 4.39 ng/ml and 2.77 ng/ml, respectively. They had no other pituitary hormone deficiencies and their pituitary MRIs were normal. Both children are being treated with recombinant human GH (rhGH) with excellent responses in linear growth. Their mother also had a history of GHD in childhood and received rhGH from ages 4 to 13 years. After GH treatment, she reached a normal adult height. The remainder of her pituitary function was normal. Exome sequencing was performed on the probands, their affected mother, and unaffected maternal grandparents to identify the underlying genetic cause. Exome sequencing revealed that the affected mother carried a de novo variant in intron 3 of the GH1 gene (c.291+34G>A, NM_000515.5), and the intronic variant was passed on to the two probands. The variant is not found in the general population according to gnomAD. No other variants in GH1 or other genes were detected to cosegregate with GHD in this family. The intronic variant was located in one of the two intron consensus regions in intron 3 and was predicted by ESEfinder to create a new splicing enhancer (SF2/ASF) binding site. Because intron consensus sequence repeats are important for spliceosome assembly, the variant is predicted to cause aberrant pre-mRNA splicing but not affecting the donor or acceptor site. Previously, a variant in the intron consensus sequence, c.291+28G>A, was found to cause exon 3 skipping, presumably generating a small amount of 22 kDa GH but a large amount of 17 kDa GH. Small deletions in intron 3 (c.291 +28_45del and c.291+56_77del) have also been reported to cause exon 3 skipping, categorized as GHD type 2. In vitro studies with the new variant will be required to confirm exon 3 skipping as the mechanism of GHD in this family. This novel intronic variant which creates a new splicing enhancer-binding site supports the previous finding that the intron consensus sequence plays a significant role in the splicing of GH1 pre-mRNA and results in autosomal dominant GHD. As other variants in intron consensus sequence sites may cause GHD type 2, we recommend genetic testing in patients with GHD include the intron consensus sequence regions.

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