Contribution of functionally assessed GHRHR mutations to idiopathic isolated growth hormone deficiency in patients without GH1 mutations

Titre	Contribution of functionally assessed GHRHR mutations to idiopathic isolated growth hormone deficiency in patients without GH1 mutations
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Résumé en anglais	Isolated growth hormone deficiency (IGHD) is a rare condition mainly caused by mutations in GH1. The aim of this study was to assess the contribution of GHRHR mutations to IGHD in an unusually large group of patients. All GHRHR coding exons and flanking intronic regions were sequenced in 312 unrelated patients with nonsyndromic IGHD. Functional consequences of all newly identified missense variants were assessed in vitro (i.e., study of the expression of recombinant GHRHRs and their ability to activate the cyclic adenosine monophosphate (cAMP) signaling pathway). Genotype-phenotype correlation analyses were performed according to the nature of the identified mutation. We identified 20 different disease-causing GHRHR mutations (truncating and missense loss-of-function mutations), among which 15 are novel, in 24 unrelated patients. Of note, about half (13/24) of those patients represent sporadic cases. The clinical phenotype of patients with at least one missense GHRHR mutation was found to be indistinguishable from that of patients with bi-allelic truncating mutations. This study, which unveils disease-causing GHRHR mutations in 8% (24/312) of IGHD cases, identifies GHRHR as the second IGHD gene most frequently involved after GH1. The finding that 8% of IGHD cases without GH1 mutations are explained by GHRHR molecular defects (including missense mutations), together with the high proportion of sporadic cases among those patients, has important implications for genetic counseling.
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Liens

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