**Introduction**

Growth is a complex phenomenon that depends on several factors including growth hormone (GH) secretion, the GH releasing hormone (GHRH) and its receptor (GHRHr), and ghrelin (GHSR) and its receptor (GHSR). Although GH, GHRHR and GHSR have been recognized as key etiologic factors in non-syndromic forms of isolated growth hormone deficiency (IGHD), a small number of mutations have been identified in this rare condition. Depending on the studies, GH and GHRHR defects would account for 6-12.5% and 0-6.7% of IGHD cases. So far, as for GHRHR and GHSR, very few functional studies have been performed in order to assess the consequences of the identified variants.

**Objective**

With the aim to assess the contribution of the GH, GHRHR and GHSR genes in the pathogenesis of IGHD, we screened for mutations all coding exons and flanking intronic sequences of these three genes by Sanger sequencing or Next Generation Sequencing in a large cohort of patients with a non-syndromic form of IGHD characterized by a small or normal anterior pituitary and an eutopic posterior pituitary.

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**GH variations**

The GH gene was first analyzed in a total of 360 independent patients. Variations were identified in 40 patients (11%), 17 of them (17/40, 43%) representing familial forms of IGHD. These include 9 novel mutations, among which 2 frameshifts, 2 splicing defects and 5 missense mutations. Whole gene deletions and truncating mutations were associated with a recessive GH defect; missense mutations and mutations affecting exon 3 splicing were associated with a dominant deficit.

**GHSR variations**

Finally, the GHSR gene was analyzed in the last 295 independent patients in whom no GH nor GHRHR defect was found. This allowed us to identify variations in 12 patients (4%), 5 of them (5/12, 42%) representing familial cases. In our cohort, the 10 novel variations of GHSR consist in 1 whole gene deletion, 2 truncating mutations and 7 missense mutations.

**Conclusion**

Overall, this study performed in a large cohort of patients, which identified deleterious or potentially deleterious molecular defects in the GH, GHRHR or GHSR gene in 72 out of 360 independent patients (20%), reveals the importance of those three genes in the pathogenesis of non-syndromic IGHD with a normal location of the posterior pituitary. Noteworthy, up to 61% (43/72) of the patients with a GH, GHRHR or GHSR germline mutation represent sporadic cases.

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