HIGH FREQUENCY OF HYPMORPHIC ALLELIC HAPLOTYPES OF THE GH1 PROXIMAL PROMOTER IN PATIENTS WITH PROPORTIONAL UNDERGROWTH AND ISOLATED GH DEFICIENCY


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BACKGROUND AND AIM

- Isolated GH deficiency (IGHD) is one of the most frequent causes of postnatal proportional undergrowth (1/3000-4000).
- 85-90% of IGHD cases are still classified as idiopathic.
- A very high rate of interlocus gene conversion (Sedman et al., 2008) between the 5 highly homologous genes present in the chr. 17 GH cluster (Fig. 1), generates up to 40-60 different GH1 proximal promoter haplotypes through the combination of 16 SNPs (Table 1) (Horan et al., 2003; Wolf et al., 2008).
- GH gene (GH1) expression is highly influenced by the GH1 proximal promoter haplotypes (Horan et al., 2003).
- At least 12 of the generated proximal promoter haplotypes show hypomorphic effects, significantly affecting GH1 expression levels in luciferase assays (Fig. 2) (Horan et al., 2003).

AIM

To investigate the frequency of GH1 proximal promoter hypomorphic allelic haplotypes in a cohort of patients with IGHD.

METHODS

Subjects: 53 children (23 females, 30 males) with proportional undergrowth (height < -2.5 SDS) and IGHD (peak GH <10ng/ml).

Molecular studies: Mutation screening/genotyping of the coding sequences, intron-exon boundaries and regulatory regions of GH1. GH1 proximal promoter haplotype classification was performed according to Horan et al. (2003) (Table 1) and Wolf et al. (2009).

RESULTS

1. 19 out of 53 (35.8%) patients presented with hypomorphic allelic haplotypes of the GH1 proximal promoter. Their main clinical characteristics are summarized in the enclosed table.
2. Only three out of 53 (5.7%) patients presented with three previously described heterozygous GH1 mutations: c.291+1G>A, p.Arg42Cys, and p.Arg209His.

CONCLUSIONS

- Up to 35.8% of the examined IGHD patients presented with hypomorphic allelic haplotypes of the GH1 proximal promoter.
- The associated clinical phenotype is very similar to that presented by patients with type II IGHD (height < -2.5 SDS; GH peak < 10 ng/ml; low IGF-I; SGA; pituitary hypoplasia; delayed bone age; good response to rhGH treatment).
- Hypomorphic allelic haplotypes of the GH1 promoter may represent an important causative or contributing factor to IGHD, which has been underestimated so far.

References


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