

Genotyping *IGFBP3* Gene Polymorphism Improves the Diagnostic Efficiency of IGFBP-3 Measurements in the Differential Diagnosis between Growth Hormone Deficiency and Idiopathic Short Stature

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Background

Markers of growth hormone (GH) action, including insulin-like growth factor I (IGF-I), IGFBP-3 and the acid labile subunit (ALS), have been proposed for use in the diagnosis of growth hormone deficiency (GHD). However, low IGF-I, IGFBP-3, and ALS levels are found in some children with idiopathic short stature (ISS).

Objective

The aim of this study was to determine the diagnostic efficiency (DE) for GHD of IGF-I, IGFBP-3 and ALS, and genetic polymorphisms in the genes encoding these proteins.

Subjects and Methods

187 normal (age range 4.9–16.6 years), 86 ISS (3.1–17.6 years), and 24 GHD (3.1–17.6 years) children were studied. Serum IGF-I and ALS were determined by radioimmunoassays and IGFBP-3 by immunoradiometric assay

(IRMA), and levels were expressed as standard deviation score (SDS). The following polymorphisms were determined: IGF1.PCR1 and rs6220 (C/T) in the *IGF1* gene; rs2854744 (–202 A/C) and rs13241830 (–185 C/T) in the *IGFBP3* gene, and rs3751893 (C/T, D70D) and five single nucleotide polymorphisms in the promoter region of the *IGFALS* gene. Cutoff levels for maximal DE were calculated by receiver operating characteristic (ROC) analysis.

Results

The only statistically significant association between serum levels and gene polymorphism was found for IGFBP-3 and the –202 A/C polymorphism. Values (mean \pm SEM) in normal subjects were: AA: 0.34 ± 0.16 , AC: 0.13 ± 0.11 , CC: -0.30 ± 0.11 ; ANOVA: $p = 0.0032$; AA > CC and AC > CC, $p < 0.05$; linear trend (LT): $p = 0.0036$. In ISS children, values were: AA: -0.14 ± 0.28 , AC: -0.81 ± 0.17 , CC: -1.25 ± 0.22 ; ANOVA: $p = 0.0147$; AA > CC, $p < 0.05$; LT: $p = 0.0039$. In GHD children there was a non-significant trend with: AA: -1.87 ± 0.36 , AC: -2.47 ± 0.52 , CC: -2.87 ± 0.55 .

Table 1. DE of markers of GH action

Test	Cutoff SDS	Sensitivity %	Specificity %	DE %
IGF-I	-2.12	66.7	79.1	77.3
ALS	-2.74	66.7	91.9	86.4
IGFBP-3	-1.69	70.8	83.7	80.9
Genotypes				
AA	-1.26	70.8	89.5	85.4
AC	-1.73			
CC	-2.56			

Conclusions

ALS levels showed higher specificity and higher overall DE, but also poor sensitivity. Genotype-specific IGFBP-3 cutoff levels improved specificity and DE of IGFBP-3 measurements, reaching a similar DE as ALS

measurements, but with a slightly higher sensitivity. Moreover, this study extends the association of IGFBP-3 levels with the -202 *IGFBP3* gene polymorphism to ISS children.

Disclosure Statement

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