Genetic Polymorphisms as Predictive Markers of Response to Growth Hormone Therapy in Paediatric Growth Hormone Deficiency

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Introduction

Linear growth is regulated by the interaction of different hormones. One of the most important regulators is growth hormone (GH), which is produced by the pituitary gland. GH deficiency (GHD) is the most common endocrine cause of impaired growth and is commonly treated with recombinant human GH (rGH). Response to treatment is highly variable and a considerable proportion of patients do not reach an adult height within the target range for their family even after long-term rGH therapy (1). The influence of clinical factors such as age and height at treatment initiation, treatment duration and genetic target size on the success of rGH therapy are estimated at 40–61% (2). By contrast, the influence of genetic factors on growth remains poorly understood. There is, nonetheless, a growing body of evidence that variation in growth-related genes, e.g. deletion of exon 3 in the growth hormone receptor (GHR) gene, may impact response to GH treatment (3).

The aim of our study was to identify genetic factors that might serve as predictive markers of response to rGH treatment. To this end, we analysed thirteen known single nucleotide polymorphisms (SNPs) and investigated whether the complete deletion of exon 3 in the growth hormone receptor (GHR) and the growth response were associated.

Materials & Methods

In total, 101 children with GHD receiving rGH therapy at our paediatric endocrinology outpatient clinic underwent genetic analysis for 13 known SNPs in genes of the GH axis (SOIS1, IGFIR, GAB1, LHX4, IGFBP3, GRB10, GHRHR, GHSR), growth plate (VDR, ESR1) and cell cycle (CDK4) by high resolution melting analysis (HRM) and sequencing (see figure 1).

The stage of pubertal development was not to exceed Tanner 2, i.e. before the beginning of the puberty growth spurt. GHR analysis was performed in all patients and prepubertal participants (<9Y children) were additionally examined for complete deletion of exon 3 in the GHR gene by PCR (4). Patients with GHD after treatment for malignant disease were excluded from participation (see table 1).

An objective measure of response to rGH therapy is provided by the index of responsiveness (IOr), which is calculated from the observed height velocity and the predicted height velocity based on factors such as age at treatment initiation, dosage, maximum GH concentration after stimulation, height and weight at treatment initiation, birth weight and mid-parental height (5). Individual index of responsiveness (IOr) values were calculated and analysed by genotype by one-way analysis of variance (ANOVA). P < 0.05 was considered statistically significant.

Results

Two of the SNPs we analysed, rs2885586 in the SOIS1 gene and rs209592 in the CDK4 gene, were associated with statistically significant differences in IOr (see table 2).

With rs2885586 in SOIS1, the TT genotype was associated with higher IOr values than the CT or the CC genotype (P = 0.014).

With rs209592 in CDK4, the GG allele was associated with increased IOr values than the CC or the AA genotype (P = 0.011).

Furthermore, we analysed the association between the exon 3 deletion of GHR and the IOr. Our results show that patients with the exon 3 deletion had higher IOr values than those with the full-length variant of the receptor whether homozygous or heterozygous deletion variant (P = 0.002). Comparison by unpaired t-test of the mean IOr values for the specific genotypes revealed a higher median IOr for the homozygous deletion than for the homozygous full length GHR variant (P = 0.016). Interestingly, patients who were heterozygous for the deletion had lower IOr values than those who carried two copies of the full length variant (P = 0.006).

Conclusions

In conclusion, we found two of the 13 SNPs investigated and the exon 3 deletion in the GHR gene to be associated with the IOr in paediatric GHD patients. As regards the rs2885586 SNP in the SOIS1 gene, patients with the TT genotype showed better response to rGH therapy than those with the CT or CC genotype. Furthermore, the GG and AG genotypes of the rs209592 SNP in the CDK4 gene were associated with better response to rGH treatment than was the AA genotype. Complete deletion of exon 3 in the GHR gene was also associated with better response to rGH therapy. Thus, the genetic variations we studied may serve as predictive markers of response to rGH therapy in paediatric patients with GHD. The results of the present study indicate that genetic analyses are a valid starting point for the individualized treatment of GHD. Further prospective studies are needed to overcome the limitations of our study.

Table 1: Study population characteristics by type of analysis

<table>
<thead>
<tr>
<th>SNP Gene</th>
<th>Alleles</th>
<th>Mean IOr</th>
<th>SD (SD)</th>
<th>GH and IGF Treatment</th>
<th>Anna-Maria Jung</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2885586</td>
<td>SOIS1</td>
<td>TT</td>
<td>0.748</td>
<td>0.099</td>
<td>0.016</td>
</tr>
<tr>
<td>rs209592</td>
<td>CDK4</td>
<td>TT</td>
<td>1.067</td>
<td>0.174</td>
<td>0.271</td>
</tr>
</tbody>
</table>

Table 2: Mean IOr values in relation to genotypes for the SNPs/Exon 3 Deletion analysed in the present study and respective P-values of the analysis of variance (ANOVA)