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Original Article

Correlation between exon 3 polymorphism of growth hormone receptor gene and the responses to rhGH therapy

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Abstract: Objective: To investigate the correlation between the exon 3 polymorphism of growth hormone receptor (GHR) gene and the responses to the recombinant human growth hormone (rhGH) therapy in children with short stature. Methods: Forty-five growth hormone deficiency (GHD) children (male: 30, female: 15, aged 10.39±2.73 yrs) and twenty-five idiopathic short stature (ISS) children (male: 15, female: 10, aged 10.58±2.56 yrs) admitted to our hospital were included. The polymorphism of exon 3 of GHR gene was determined using multiple PCR amplification. Treatment duration for each subject was at least 12 months. On this basis, we evaluated the correlation between treatment efficiency of rhGH therapy and GHR exon 3 polymorphism, GHD, and treatment duration. Results: Significant difference was noted in the growth velocity (GV) of GHD children with a genotype of GHRfl compared with those with a genotype of GHRd3 (9.44±2.35 vs. 11.36±2.49, $P < 0.05$). Meanwhile, the GV of ISS patients with a genotype of GHRfl were remarkably decreased compared with those with a genotype of GHRd3 (8.74±2.36 vs. 11.18±2.44, $P < 0.05$). For the children with peak GH response of less than 5 ng/ml, statistical difference was noted in the GV of children with a genotype of GHRfl compared with those with a genotype of GHRd3 (9.55±2.76 vs. 10.84±1.53, $P < 0.05$). For the patients with peak GH response to clonidine or pyridostigmine bromide of > 5 ng/ml, a satisfactory response to rhGH therapy was noted in children with a genotype of GHRd3 compared with those of GHRfl ($P < 0.05$). Conclusions: GHRd3 was correlated with the response to rhGH therapy in children with short stature. For the patients with the same genotype, GHD caused no obvious effects on the final height. However, for the patients with peak GH response of > 5 ng/ml, a satisfactory response to rhGH therapy was noted in children with a genotype of GHRd3 compared with those of GHRfl ($P < 0.05$). A higher treatment efficiency was obtained in those received rhGH at an early age.

Keywords: Recombinant human growth hormone, short stature, growth hormone receptor, growth hormone deficiency

Introduction

Recombinant human growth hormone (rhGH) has been licensed for treating short stature closely related with growth hormone deficiency (GHD). Currently, increasing evidence indicates rhGH contributes to the growth velocity (GV) of non-GHD short stature [1]. Nevertheless, its clinical application is still limited due to complications, such as hyperglycemia, increased free fatty acids, and triglycerides [2].

To date, a large variance is still available for the treatment efficiency of rhGH on short stature [3, 4]. For example, for the GHD children with satisfactory response to rhGH, an increased height of 10-12 cm was noted, while those with poor response merely increased about 6-7 cm in height. To explain the difference of the variance, the potential factors that may affect the treatment efficiency of rhGH in clinical practices have been investigated, including bone age, dosage of rhGH administration and initial age before rhGH therapy. All these lead us to investigate the effects of genetic background on the treatment efficiency of rhGH for treating short stature.

Growth hormone receptor (GHR) gene, located in the short arm of chromosome 5 (p13.1-p12) containing nine coding exons [5, 6], has been considered as the major candidate gene that

may involved in modulating the response to rhGH therapy in GHD children. The most common isoforms of GHR in human were retention (full-length GHR, GHRfl) or exclusion of exon 3 (exon 3-deleted GHR, GHRd3), and their roles in the modulating of responses to rhGH is still controversial [7, 8]. According to the literature review, rare studies have been carried out to investigate the polymorphism of GHR on the responses to rhGH in GHD children. In this study, we aim to investigate the correlation between the polymorphism of GHR on the treatment efficiency of rhGH therapy. The results indicated that the responses to rhGH in GHD children with a genotype of GHRd3 were superior to those with a genotype of GHRfl. In addition, a remarkable response to rhGH was noted in the GHD children at an early stage.

Materials and methods

Patients

Forty-five GHD children (male: 30, female: 15, aged 10.39±2.73 yrs) and twenty-five ISS children (male: 15, female: 10, aged 10.58±2.56 yrs) admitted to our hospital were included in this retrospective analysis. The inclusion criteria for GHD were: (i) height deficiency of at least 2 standard deviation scores; (ii) a GV of less than 4 cm per year; (iii) those with delayed bone age; (iv) those with peak GH response to two pharmacological tests (clonidine or pyridostigmine bromide) of less than 10 ng/ml. The exclusion criteria were: (i) GHD children with height deficiency due to chronic disorders such as hypothyroidism, maldevelopment of bone, as well as chromosome abnormality disorders; (ii) those with abnormal development of pituitary gland. The inclusion criteria for ISS were: (i) height deficiency of at least 2 standard deviation scores; (ii) a GV of less than 5 cm per year; (iii) those with peak GH response to two pharmacological tests (clonidine or Pyridostigmine Bromide) of ≥ 10 ng/ml; and (iv) those diagnosed with delayed or normal bone age at a stage of Tanner I. ISS children with chronic organic disease, mental or affective disorder, as well as those received administration of growth hormone previously, were excluded from this study.

Written informed consents were obtained from each subject. The protocols were approved by the Ethic Committee of Tianjin Medical University (Tianjin, China).

Molecular assay

Genomic DNA was isolated from peripheral blood using standard methods. The frequency of GHR transcript variants including the retention or exclusion of exon 3 was analyzed in all patients using a simple multiplex PCR amplification as previously described [6]. The PCR results were analyzed by electrophoresis on a 1.0% gel. The fl allele (GHRfl) and the d3 allele (GHRd3) were represented by a 935-bp fragment and a 532-bp fragment, respectively.

Treatment

All the patients received administration of rhGH (GeneScience Pharmaceuticals Co., Ltd., Changchun, China) for at least 12 months. The dosage was 0.1 IU/Kg per day for GHD children, while for the ISS children the dosage was 0.15 IU/Kg per day. The rhGH was administrated in the evening before sleeping via subcutaneous injection. No other hormone therapy was given to these patients.

The body weight and height of the patients were determined by a physician blinded to the study. All the determination was carried out in triplicate. The X-ray images of the left hand and wrist were collected from each subject, and then the evaluation of bone age was performed by an experienced physician according to the previous report [9]. The level of serum free triiodothyronine (FT3), free thyroxin (FT4), thyroid stimulating hormone (TSH), glutamic acid, the retardation of bone age to actual age (AA-BA), insulin-like growth factor-I (IGF-1), IGF-binding protein-3 (IGFBP-3) was determined according to the previous report by Iwaku et al [10]. The growth velocity was calculated according to the following formula:

$$\text{Growth velocity (cm/year)} = (Hf-Hi)/T \times 12$$

Where Hf and Hi stands for the final height after rhGH therapy and the initial height before rhGH therapy, respectively; T stands for the time interval of the rhGH therapy.

Follow-up

The mean duration for the follow up was 12 months. The body weight, height, adverse reac-

Table 1. Demographic data of the ISS children before treatment

Genotype	Gender (M:F)	Birth weight (kg)	Birth height (cm)	Current height	Current weight	Parental height	Maternal height	Actual age	Bone age
GHRfl	7:5	3.21±0.43	49.89±2.15	134.91±16.68	33.78±9.59	170.72±2.82	154.44±5.88	10.12±3.02	9.66±3.28
GHRd3	8:5	3.40±0.62	50.19±1.60	132.82±13.18	31.64±11.87	169.62±2.99	158.50±5.40	11.14±2.06	10.03±2.24

Table 2. Demographic data of the GHD children before treatment

Genotype	Gender (M:F)	Birth weight (kg)	Birth height (cm)	Current height	Current weight	Parental height	Maternal height	Actual age	Bone age	Peak GH response (ng/ml)
GHRfl	15:8	3.31±0.50	49.86±1.46	129.57±20.16	30.20±14.33	168.73±5.07	158.41±4.59	10.37±3.06	8.35±3.36	4.47±2.27
GHRd3	15:7	3.27±0.49	49.65±1.85	124.07±19.32	27.61±12.92	169.39±4.02	157.35±5.51	10.98±2.61	8.67±2.79	4.69±2.20

tions, bone age, concentration of FT3, FT4 and TSH, as well as the blood sugar, and IGF-1/IGFBP3 were determined at an interval of 3 months.

Statistical analysis

All the data were presented as mean ± standard deviation (SD). Student's t test was performed for the inter-group comparison. Pearson correlation analysis was carried out using SPSS 16.0 software. $P < 0.05$ demonstrated statistical difference.

Results

Demographic data of the patients

The demographic data of the ISS children and GHD children with different genotypes before treatment were summarized in **Tables 1** and **2**, respectively. No statistical difference was noted in the age, birth weight, birth height, peak GH response and bone age ($P > 0.05$). In addition, no statistical difference was noted in the height of the patients' parents ($P > 0.05$, **Table 1**). For the GHD children, no statistical difference was noted in the age, birth weight and height, current body weight and height, the height of the parents, bone age and peak GH response, respectively ($P > 0.05$, **Table 2**).

Effects of exon 3 polymorphism on the response to rhGH

In this study, the GV of ISS children and GHD children was evaluated, which indicated a remarkable increase was noted in the GV of the ISS children and GHD children after administration of rhGH compared with their baseline levels, respectively ($P < 0.05$, **Table 3**).

Correlation between GHD and patient response to rhGH

For the GHD patients with the same genotype, no statistical effects were caused on the height by GHD ($P > 0.05$, **Table 4**). With regards to the GHD patients with peak GH response of 5-10 ng/m1, no significant effects were caused on the height by the genotype ($P > 0.05$, **Table 5**). However, for the patients with a peak GH response of less than 5 ng/ml, significant increase was noted in the GV of GHD patients with a genotype of GHRd3 compared with the patients with a genotype of GHRfl ($P < 0.05$).

Correlation between the gender and patient response to rhGH

For the GHD patients with a genotype of GHRfl, remarkable increase was noted in the growth rate in the male patients compared with the female ones ($P < 0.05$, **Table 6**). On the contrary, no statistical difference was noted in the GV of the male patients with a genotype of GHRd3 compared with the female ones with the same genotype ($P > 0.05$). After administration of rhGH, the growth rate of the male patients with a genotype of GHRfl showed no statistical difference with that of the counterparts with a genotype of GHRd3 ($P > 0.05$). Nevertheless, for the female patients with a genotype of GHRfl, statistical difference was identified in the growth rate compared with the counterparts with a genotype of GHRd3 ($P < 0.05$).

Factors associated with the patient response to rhGH

To identify the factors associated with the growth velocity of the patients, we analyzed the

Table 3. Growth velocity of the children after administration of rhGH

Genotype	GV of ISS children	GV of GHD children
GHRfl	8.74±2.36	9.44±2.35
GHRd3	11.18±2.44*	11.36±2.49*

*P < 0.05, compared with control group; GV: Growth velocity.

Table 4. Association between GH deficiency and treatment outcome of rhGH

Genotype	Peak GH response (ng/ml)	N	Growth velocity (cm/y)
GHRfl	< 5	14	9.55±2.76
	5-10	9	9.11±1.47
	t value	-	0.436
GHRd3	< 5	12	10.84±1.53
	5-10	10	12.31±3.11
	t value	-	-1.445

Table 5. Outcome of GHD children with the same genotype

Genotype	Gender	N	Growth velocity (cm/y)
GHRfl	Male	15	10.19±2.07
	Female	8	7.86±2.05
GHRd3	Male	15	11.22±1.69
	Female	7	12.13±3.67*

*P < 0.05 vs. the female subjects with GHRfl genotype.

Table 6. Outcome of GHD children of the same gender with various genotype

Gender	Genotype	N	Growth velocity (cm/y)
Male	GHRfl	15	10.19±2.07
	GHRd3	15	11.22±1.69
Female	GHRfl	8	7.86±2.05*
	GHRd3	7	12.13±3.67

*P < 0.05 vs. the male subjects with a genotype of GHRfl.

correlation between GV and the birth height and weight, peak GH response, as well as the age, height, weight, and bone age of the GHD patients before rhGH administration. The results indicated that GV was closely associated with the peak GH response (**Table 7**).

In this study, we also detected the level of serum FT3, FT4, TSH, glutamic acid, AA-BA, IGF-1, IGFBP-3. On this basis, we aim to identify the potential factors that could be used as a predictor of the treatment outcome. Compared with the baseline levels, no statistical difference was noted in the concentrations of the above-mentioned parameters 6 months or 12 months after administration of rhGH (**Table 8**).

Discussion

To date, rhGH has been considered as the golden standard for the treatment of GHD children. According to the previous studies, rhGH has been reported to contribute to the growth and final body height for the children with Turner syndrome, chronic renal failure, infants born small for gestational age (SGA), Prader-Willi syndrome, or ISS [11, 12]. Several potential factors have been reported to be positively correlated with the treatment efficiency of rhGH for the GHD children such as the administration duration of rhGH [13], height standard deviation score [14], delayed bone age and parents' height [15], and the first-year GV after administration of rhGH [16]. On the contrary, age and peak GH response were negatively correlated with the treatment efficiency [17]. Although these factors have been considered to explain the variance of treatment efficiency in GHD children after administration of rhGH, no study has been carried out to explain the potential mechanism from genetic background.

The regulation of growth hormone in the height of children is largely depended on the growth hormone receptor (GHR). GH could bind to the membrane receptor, which resulted in dimerization of GHR that triggering the activation of Janus Kinase 2 (JAK 2) [18]. Subsequently, JAK2 contributed to the self-phosphorylation and the phosphorylation of GHR, and triggered the transmission of GH signals to the downstream of the pathway, which enhanced the expression of genes largely correlated with the IGF-1 and the other growth hormones. On this basis, we speculated that mutation of GHR gene may affect the signal transmission of GH, and finally affect the growth and development of an individual. The most frequent mutation sites of GHR gene have been localized into exons 3, 7, 9 and 10, which may lead to functional deficiency of GHR and transmission disorder of the signaling pathway [19]. In this study, we aim to investigate the mutation of exon 3 on the treatment efficiency of rhGH on ISS children and GHD children.

Table 7. Correlation between GHD and various parameters

		Birth height	Birth weight	Initial height	Pre-treatment height	Pre-treatment age	Pre-treatment bone age	Peak GH response
GV	CV	-0.210	-0.122	-0.222	-0.194	-0.133	-0.149	0.311
	P value	0.426	0.426	0.143	0.202	0.385	0.328	0.008*

*P < 0.05; CV, coefficient of variation.

Table 8. Laboratory tests for patients underwent rhGH therapy

Month	0 month	6 month	12 month	t1#	t2##
FT3	6.14±0.12	6.47±0.12	6.36±0.37	-1.845	0.770
FT4	155.38±1.16	158.82±1.64	159.86±2.10	-0.890	-0.126
TSH	2.98±1.99	2.56±1.21	2.98±1.41	0.735	-1.791
GLU	5.06±1.18	5.29±0.41	5.22±0.44	-1.333	1.111
IGF-1/IGFBP3	0.05±0.003	0.07±0.002	0.06±0.002	0.797	0.964
AA-BA	1.47±0.79	1.46±0.33	1.46±0.41	-0.788	1.342
GV	< 4	12.45±2.03	10.19±2.07	-	-2.512*

#compared with 0 month; ##Compared with 6 month2; *P < 0.05.

GHR is an obvious candidate gene affecting the response to rhGH therapy. To date, two of the most common isoforms of GHR in humans are generated by retention or exclusion of exon 3. In GHRfl, retroelements with a similarity of 99% were noticed in the flanking exon 3, while for GHRd3, a sequence deletion of 2.7 kb was noticed in exon 3 [8]. To our knowledge, no statistical difference among the binding capacity to GH between GHRfl and GHRd3, and both of them were enough to maintain the normal growth and development.

To date, there are still controversies on the effects of GHR-exon-3 polymorphism on the response to rhGH therapy in GHD children. In a retrospective analysis enrolled 75 GHD children, patients with GHD who were homozygous for GHR exon 3 were less responsive to short- and long-term rhGH therapy, while patients carrying GHRd3 allele showed a significant improvement in the growth velocity in the first year of rhGH replacement [8]. In the same year, Pilotta et al reported that there was no correlation between the GHR polymorphisms and the response to the rhGH in GHD children [20]. Subsequently, a retrospective analysis carried out in Germany indicated that the growth response to rhGH is independent of the exon 3-minus isoform in GHD children [21]. Recently, Raz et al reported that GHR-3d and GHRfl caused no effects on the final height of the GHD children [22]. We speculate the variances of response to rhGH therapy may be associated with the treatment duration and dosage, especially the baseline information of the children such as age, height standard deviation score and growth velocity.

In this study, we analyzed the correlation between the gene distribution of GHR3d and GHRfl and the response to rhGH therapy in 45 GHD children and 25 ISS children. For the children in a pre-adolescent stage, a significant improvement was noted in the GV in the children with treatment duration of more than 12 months. No statistical difference was noted in the GV in the male patients compared with the female ones with the same genotype. For the children with the same genotype, no obvious effects on the final height were noted by the GHD extent. The genotype caused no obvious influence on the final height of the GHD children in those with a peak GH response of 5-10 ng/ml. However, for the children with a peak GH response of less than 5 ng/ml, a satisfactory response to rhGH was noted in those with a genotype of GHRd3 compared with those with a genotype of GHRfl. The responses to rhGH varied in the male GHD children compared with the female ones with a genotype of GHRfl. To further evaluate the treatment efficiency, we also detected the level of serum FT3, FT4, TSH, glutamic acid, AA-BA, IGF-1, IGFBP-3. No statistical difference was noted in these parameters abovementioned. Further, we confirmed GHD extent was negatively correlated with the responses to rhGH in GHD children.

In summary, the growth response to rhGH varied in the GHD children with different GHR genotypes. No obvious effects were caused on the height by GHD in the children with the same genotype. For the children with severe GHD, the

responses to rhGH in children with a genotype of GHRd3 were superior to those with a genotype of GHRfl. A remarkable response to rhGH was noted in the GHD children at an early stage.

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Disclosure of conflict of interest

None.

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