Influences of Growth Hormone Receptor Exon 3 and -202 A/C IGFBP3 Polymorphism on 1-year Follow-up Outcome of Growth Hormone Treatment in Korean Children with Growth Hormone Deficiency

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Disclosure of conflict of interest None to declare

OBJECTIVES

The growth hormone receptor (GHR) exon3 and the -202 A/C IGFBP3 polymorphisms have been suggested to affect responses to recombinant human growth hormone (rhGH) therapy in some individuals with short stature.

This study aims

1)To investigate the influences of the GHR-exon 3 and the -202 A/C IGFBP3 polymorphisms on baseline height and the 1 year follow-up outcomes of GH treatment in Korean children with growth hormone deficiency (GHD)

2)To assess the combined effect of the two polymorphisms on first year outcome of GH therapy

METHODS

1.Subjects
- 1) genotyping: 72 patients with GHD (32 girls and 40 boys)
- 2) 1-yr treatment outcome
  :49 patients who remained prepubertal state after 1-yr GH therapy

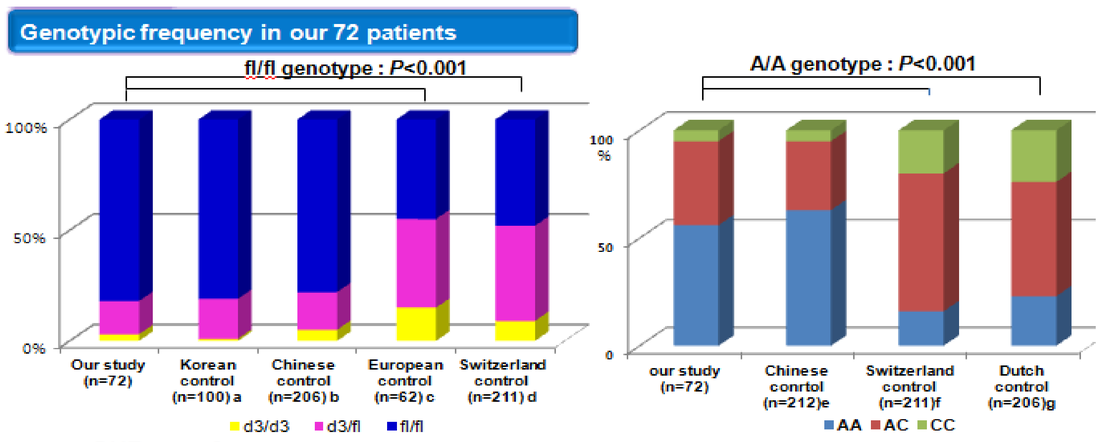
2. anthropometry
- height, weight, body mass index
- standard deviation score (SDS)
  : 2007 growth reference for Korean children and adolescents

3. Molecular analysis
  genotyping : multiplex PCR assay
  1) GHR-exon 3 genotypes: d3/d3, d3/fl, fl/fl
  2)-202 A/C IGFBP3 genotypes: A/A, A/C, C/C

4. Hormonal assays
  IGF-I (SDS), IGFBP-3 (SDS)
  :linear interpolation based on the percentile data by Korean reference (2012)

RESULTS

Genotypic frequency in our 72 patients



GHR exon 3

d3/d3 : d3/fl : fl/fl = 2 : 11 : 59
(3%) : (15%) : (82%)

-202 A/C IGFBP3

A/A : A/C : C/C = 40 : 28 : 4
(56%) : (39%) : (5%)

a. Clinical Endocrinology 2009;70:82–87
b. Pediatric Diabetes 2011: 12: 429–434
c. J ClinEndocrinol Metab 2006;91:1076-1080
d. J Clin Endocrinol Metab 2008;93: 974–980
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g. Growth Horm IGF Res. 2011;21:318-24

Table 1. Baseline characteristics of according to GHR exon3 and -202 IGFBP3 genotypes in 49 prepubertal children with GHD

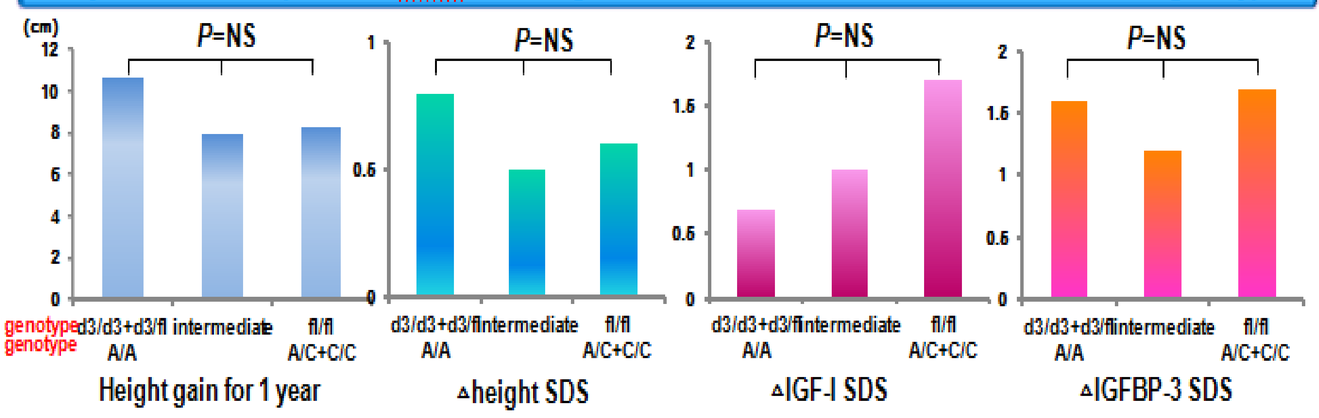
	GHR exon 3 genotype			-202 A/C IGFBP3 genotype		
	d3/d3+d3/fl	fl/fl	*P*	A/A	A/C+C/C	*P*
Number	7	42		22	27	
Sex (M:F)	3 : 4	25 : 17		11 : 11	17 : 10	
CA (year)	9.0±3.5	8.9±2.4	0.933	9.1±2.4	8.8±2.7	0.732
BA (year)	6.2±3.6	6.7±2.5	0.635	6.8±2.5	6.5±2.8	0.641
BW (kg)	2.7±0.7	3.1±0.6	0.198	3.0±0.6	3.1±0.8	0.621
MPH SDS	-0.1±0.5	-1.1±0.7	0.005	-0.9±0.8	-0.9±0.7	0.929
Height SDS	**-2.2±0.8**	**-2.3±0.6**	**0.962**	**-2.2±0.5**	**-2.3±0.7**	**0.685**
BMI SDS	-0.2±0.8	-0.4±1.0	0.742	-0.4±1.0	-0.3±1.0	0.631
IGF-I SDS	-1.3±0.7	-0.8±0.6	0.086	-0.9±0.7	-0.9±0.6	0.936
IGFBP-3 SDS	0.7±1.8	1.7±1.3	0.064	1.5±1.3	1.8±1.6	0.491

CA,chronological age; BA, bone age; BW, birth weight; MPH, midparental height; BMI, body mass index; SDS, standard deviation score

Table 2. First year Follow-up outcome of Growth Hormone Treatment according to genotypes in 49 children

	GHR exon 3 genotype			-202 A/CIGFBP3 genotype		
	d3/d3+d3/fl	fl/fl	*P*	A/A	A/C+C/C	*P*
Number	7	42		22	27	
CA (year)	10.0±3.5	9.9±2.4	0.936	10.1±2.4	9.8±2.7	0.737
BA (year)	7.8±3.9	8.0±2.7	0.858	8.2±2.8	7.8±2.8	0.660
GH dose (μg/kg/d)	32.3±1.7	33.6±1.8	0.082	32.9±1.1	33.8±2.2	0.074
Height gain (cm)	**9.4±2.2**	**8.1±1.7**	**0.086**	**8.3±2.0**	**8.3±1.7**	**0.976**
△height SDS	0.7±0.5	0.5±0.3	0.191	0.6±0.4	0.6±0.3	0.987
△BMI SDS	0.3±1.1	0.0±0.5	0.597	0.0±0.4	0.1±0.8	0.328
△IGF-I SDS	0.8±0.8	1.4±0.9	0.099	1.0±0.7	1.6±1.0	0.022
△IGFBP-3 SDS	1.3±1.1	1.5±1.3	0.754	1.4±0.9	1.6±1.5	0.514

First year Growth response to rhGH according to combined GHR exon 3 and -202 A/C IGFBP3 genotypes



NS = not significant, Intermediate: (d3/d3+d3/fl and A/C+C/C) or (fl/fl and A/A)

SUMMARY

1.Our results demonstrated that the frequency of fl/fl and AA genotype in our subjects was higher than the frequency in European population.
2. Baseline height SDS was not differ among children with each GHR exon 3 genotypes and each -202 A/C IGFBP-3 genotypes.
3. Height gain during the first year of GH replacement therapy was slightly higher in subjects who have GHRd3 allele. However, we did not demonstrated a significant difference between the presence and absence of GHRd3 allele.
4. There was no significant difference in height gain between two -202 IGFBP-3 genotype groups.
5. Combined analysis showed that GHR exon3 and -202 A/C IGFBP3 genotypes had no interactive effect on the first year growth velocity

CONCLUSION

In our study, 1-year treatment outcomes were similar among GHD patients with each genotypic variation, suggesting that the two polymorphisms may not be major factors in the modulation of individual responses to GH therapy in Korean children with GHD.

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Growth

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