

Prediction of response to growth hormone treatment in Korean girls with Turner syndrome

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Introduction

Growth hormone (GH) treatment has become common practice in Turner syndrome (TS) to improve final adult height. However, there are only a few studies on the analysis of good responders to GH treatment in TS. The aim of this study is to predict the responsiveness to growth hormone therapy in Turner syndrome.

Methods

Among 197 TS patients registered in LG Growth study, 92 patients were excluded because of systemic illness or hypothyroidism. The clinical and biochemical parameters of 105 girls with TS patients were retrospectively reviewed. Patients were divided into subgroups (minimal, intermediate, good responders) according to the increment of height standard deviation score (SDS) during the first year of GH treatment, and the prognostic factors for good responders were identified.

Results

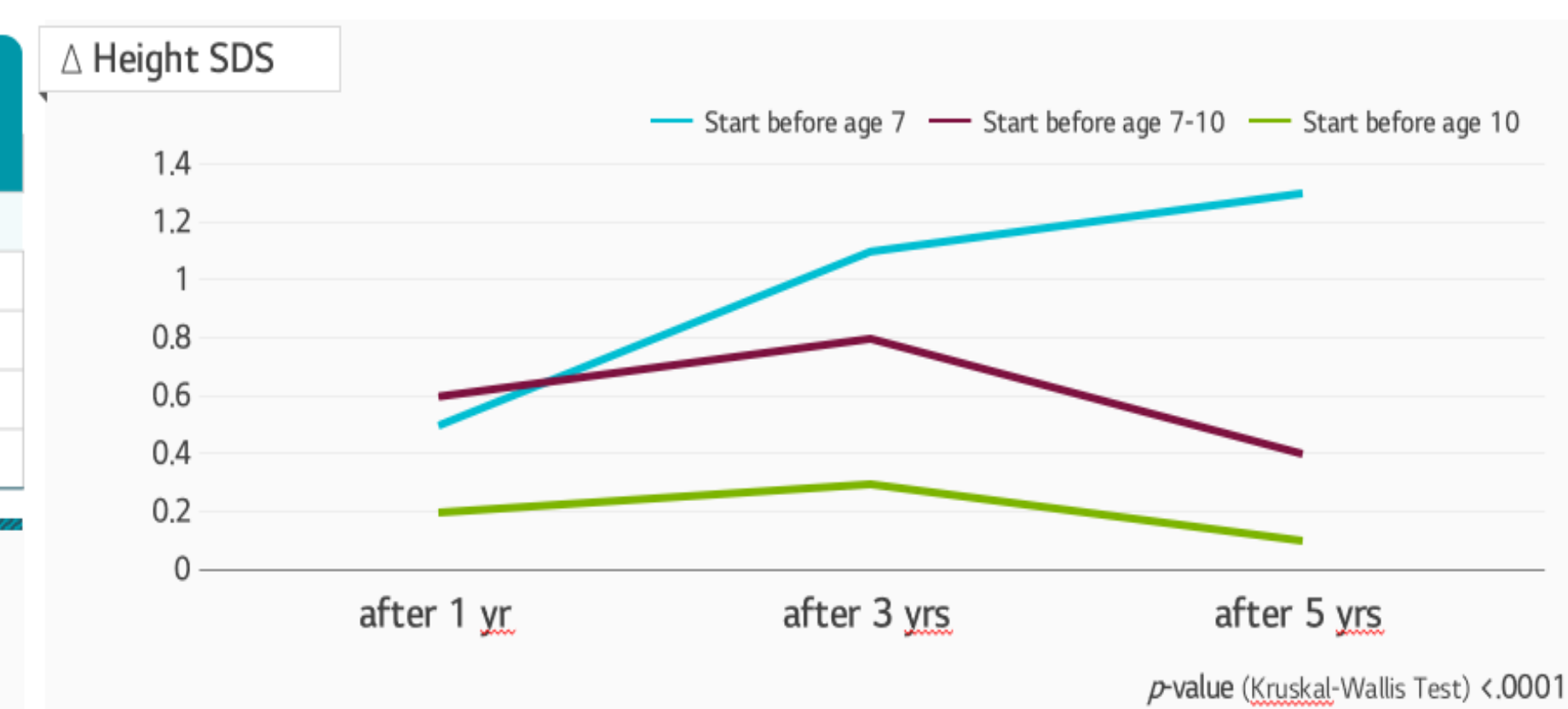
Table 1. Baseline characteristics of TS patients and clinical profiles according to responsiveness to growth hormone therapy. (N=105)

	Minimal responder (N=35)	Intermediate responder (N=35)	Good responder (N=35)	P-value
CA (yr)	10.5 ± 2.8	7.8 ± 3.3	7.3 ± 3.4	<.0001**
BA (yr)	10.2 ± 2.8	7.5 ± 3.2	5.7 ± 2.8	<.0001**
CA - BA (yr)	0.7 ± 1.3	0.9 ± 1.3	1.4 ± 0.9	0.088*
Height (cm)	126.0 ± 12.7	112.5 ± 16.2	108.5 ± 14.8	<.0001**
Height SDS	-2.5 ± 0.8	-2.5 ± 0.7	-2.9 ± 0.8	0.045*
BMI SDS	0.1 ± 1.1	0.4 ± 1.0	0.4 ± 0.9	0.544*
GH dose (mg/kg/week)	0.3 ± 0.1	0.3 ± 0.0	0.3 ± 0.1	0.4935*
IGF-1 SDS	-0.6 ± 1.3	-0.2 ± 1.2	-0.8 ± 0.7	0.1033**
MPH (cm)	158.1 ± 4.3	160.0 ± 4.3	159.1 ± 4.3	0.153**
PAH (cm)	143.3 ± 3.7	145.9 ± 7.6	146.1 ± 5.4	0.3978**
Δ height SDS (screening to 1 yr)	0.1 ± 0.2	0.4 ± 0.1	0.8 ± 0.2	
Δ IGF-1 SDS (screening to 1 yr)	1.4 ± 1.1	2.0 ± 2.4	1.8 ± 1.4	0.8960**
Δ PAH (screening to 1 yr) (cm)	2.65 ± 3.1	0.84 ± 5.8	4.18 ± 1.7	0.4203**

Table 2. The height response of TS patients according to start age of GH treatment.

	Start before Age 7 (N=34)	Start Age 7-10 (N=26)	Start after Age 10 (N=45)	P-value (intercomparison)
Height gain (cm)	M ± SD	M ± SD	M ± SD	
after 1yr	8.0 ± 1.5	7.9 ± 1.4	6.5 ± 1.6	<.0001**
after 3yr	20.9 ± 1.8	20.7 ± 2.7	14.8 ± 2.8	0.0000*
after 5yr	32.1 ± 3.2	28.0 ± 1.2	18.8 ± 4.1	0.0000*
GH Tx Cessation	-	31.7 ± 2.0	18.1 ± 3.0	0.0011*

Figure 1. Height gain of TS patients according to start age of GH treatment.



	Start before Age 7 (N=34)	Start Age 7-10 (N=26)	Start after Age 10 (N=45)	P-value (intercomparison)
Δ Height SDS	M ± SD	M ± SD	M ± SD	
after 1yr	0.5 ± 0.3	0.6 ± 0.2	0.2 ± 0.3	<.0001**
after 3yr	1.1 ± 0.5	0.8 ± 0.4	0.3 ± 0.6	0.0000*
after 5yr	1.3 ± 0.7	0.4 ± 0.1	0.1 ± 0.6	0.0005**

In good responders, chronologic age (CA) and bone age (BA) at the start of GH treatment were significantly earlier than the other groups ($P < 0.001$). They were not significantly associated with initial height SDS, GH treatment dose, midparental height (MPH), predicted adult height (PAH). Accordingly, height response was significantly related with earlier CA and BA at start of GH treatment ($P < 0.001$).

	Start before Age 13 (N= 10)	Start at Age 13-14 (N= 8)	Start after Age 14 (N= 17)	P-value (intercomparison)			
GH Treatment Duration	N	M ± SD	N	M ± SD	N	M ± SD	
Height gain (cm)	10	5.6 ± 1.8	8	5.8 ± 2.6	17	5.3 ± 3.3	0.9290*
after 1yr	10	7.5 ± 1.0	8	6.7 ± 1.6	17	6.3 ± 1.5	0.1064*
after 3yr	8	18.8 ± 2.6	7	15.9 ± 4.1	15	16.0 ± 3.3	0.1471*
after 5yr	1	22.2 ± 0.0	4	21.9 ± 7.2	6	27.2 ± 7.9	0.3372**
GH Tx Cessation	0	-	3	28.9 ± 6.5	2	16.5 ± 3.0	0.0918*
Δ PAH							
after 1yr	5	2.1 ± 3.5	5	2.2 ± 4.1	7	1.1 ± 5.7	0.9143**
after 3yr	3	6.6 ± 2.3	5	3.0 ± 1.9	8	4.4 ± 6.7	0.6402*
after 5yr	0	-	3	6.4 ± 3.9	3	5.9 ± 9.6	0.9361*
Δ Height SDS							
after 1yr	10	0.4 ± 0.2	8	0.2 ± 0.2	17	0.3 ± 0.3	0.3811*
after 3yr	8	0.4 ± 0.5	7	0.2 ± 0.7	15	0.7 ± 0.6	0.1806*
after 5yr	1	0.1 ± 0.0	4	0.0 ± 0.4	6	0.6 ± 0.8	0.3372**
GH Tx Cessation	0	-	3	0.4 ± 0.7	2	1.4 ± 0.7	0.2083*

Table 3. The height response of TS patients according to start age of estrogen treatment.

	N	M ± SD	P-value
after 1yr	10	7.5 ± 1.0	0.1064*
after 3yr	8	18.8 ± 2.6	0.1471*
after 5yr	1	22.2 ± 0.0	0.3372**
GH Tx Cessation	0	-	0.0918*
Δ PAH			
after 1yr	5	2.1 ± 3.5	0.9143**
after 3yr	3	6.6 ± 2.3	0.6402*
after 5yr	0	-	0.9361*
Δ Height SDS			
after 1yr	10	0.4 ± 0.2	0.3811*
after 3yr	8	0.4 ± 0.5	0.1806*
after 5yr	1	0.1 ± 0.0	0.3372**
GH Tx Cessation	0	-	0.2083*

Additionally, the start age of estrogen therapy was not significantly correlated with height SDS increment in estrogen treatment group.

Among 105 patients, 34 patients were started GH treatment before 7 years, 26 patients were started between 7-10 years, and 45 patients were started after 10 years. Especially, patients who started GH treatment before 7 years showed significantly higher height SDS increment than patients treated after 7 years ($P < 0.001$). Also the increment of height SDS in subgroup started GH treatment before 7 years was significantly higher than other groups. The increment of height SDS was 0.5 ± 0.3 after 1 year, 1.1 ± 0.5 after 3 years, and 1.3 ± 0.7 after 5 years of GH treatment.

Table 5. The prediction model of the increment of height SDS in TS patients

Δ Height SDS = -9.6 -0.56* CA - 0.07* BA + 1.67* GH dose + 0.09*IGF-1 SDS + 0.12 * Height - 0.65 * Height SDS + 0.07 *BMI SDS

(At Screening)	ΔHeight SDS (1 year - Screening) (N= 48)	
	Coefficient	P-value
Intercept	-9.6000	0.0014
CA	-0.5634	0.0015
BA	-0.0670	0.0403
GH dose	1.6724	0.0389
IGF-1 SDS	0.0860	0.0486
Height	0.1158	0.0007
Height SDS	-0.6523	0.0017
BMI SDS	0.0735	0.0407
R-Square		0.5678
Adjusted R-square		0.4922

(At Screening)	Δ Height SDS (1 year - Screening)
MPH	0.1500
CA	1.0091
BA	0.4621
CA-BA	0.1915
GH dose	0.1931
IGF-1 SDS	0.1479
Height	0.4678
Weight	0.2600
BMI	0.1457
Height SDS	0.0960
Weight SDS	0.1145
BMI SDS	0.1058
(CA-BA)/CA	0.3746
Father Height	0.2714
Mother Height	0.1076

machine-learning approach

Variable importance measure

- %IncMSE: Percent increase of the mean squared error
- IncNodePurity: Cumulative increase in node purity

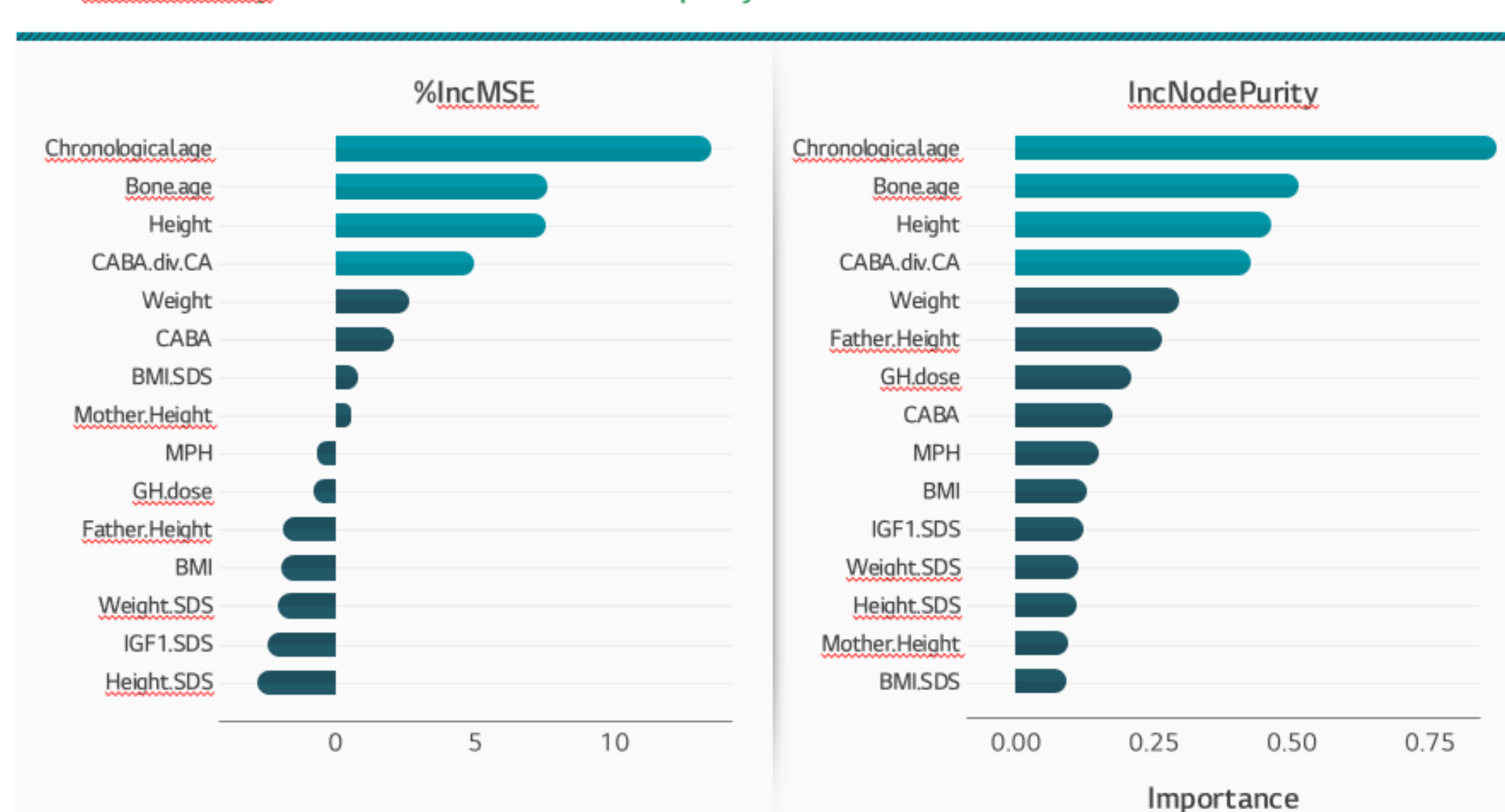


Table 4 & Figure 2. Variable Importance Score (Random Forest Method) of ΔHeight SDS (1 year - Screening)

For further investigation, variable importance measures were introduced by random forest method. As a result, the highest importance score was revealed as CA at start of GH treatment. Subsequently, BA and height at start of GH treatment had relatively high scores.

Conclusion

This study suggests that CA and BA at the start of GH treatment are significant factors in good responders in TS patients. Early intervention with growth hormone treatment is needed in TS patients.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.