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Validating genetic markers of response to recombinant human growth hormone (r-hGH) in children with growth hormone deficiency (GHD) or Turner Syndrome (TS): Results from the PREDICT Validation study

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Background

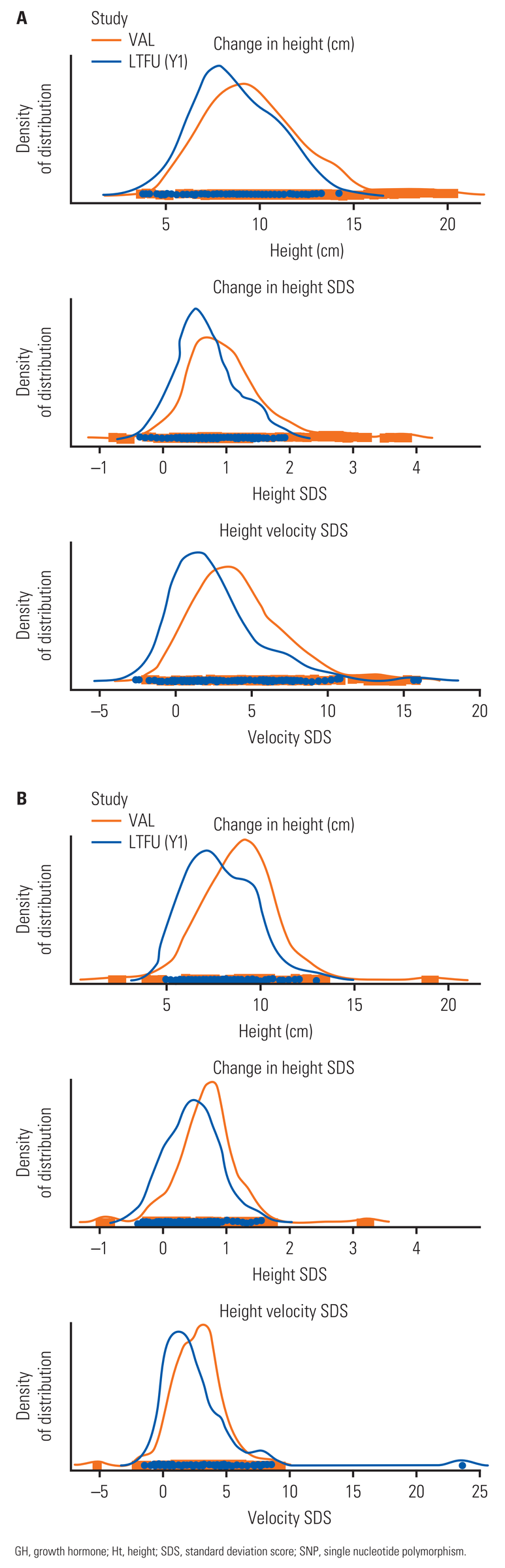
- Genetic markers associated with the response to recombinant human growth hormone (r-hGH) treatment have been identified in growth hormone (GH)-naïve, pre-pubertal children with growth hormone deficiency (GHD) in the PREDICT Long-Term Follow-Up (LTFU) prospective study (NCT00699855).[1]
- A validation (VAL) study (NCT01419249) was conducted to confirm association of these markers in an independent study group.

Patients and methods

- Inclusion criteria common to both the LTFU and VAL studies included:
  - Documented pre-established diagnosis of GHD with a GH peak response of <10 µg/L with 2 GH stimulation tests, without priming with oestradiol; eligible for r-hGH therapy.
  - Pre-pubertal status according to Tanner (stage 1).
  - Pre-established history of normal thyroid function or adequate substitution for at least 3 months.
- Exclusion criteria common to both studies included:
  - Acquired GHD due to central nervous system tumour, trauma, infection, infiltration (documented by imaging), and history of irradiation or cranial surgery.
  - Previous treatment with GH, GH-releasing hormone, anabolic steroids or any treatment affecting growth.
- Children in the VAL study had already completed one r-hGH treatment year (i.e. the analysis was retrospective).
- Twenty-two single nucleotide polymorphisms (SNPs) in GHD and 26 SNPs in Turner Syndrome (TS) found to be associated with growth response to GH therapy at year one in patients with TS were tested, and the VAL study was powered to validate at least one marker in each case.
- For the VAL study, a total of 318 patients with GHD and 140 with TS were recruited from 29 sites in 9 countries; 293 with GHD and 132 with TS were included in the full analysis set. There were 113 and 63 patients, respectively in the analysis sets from the LTFU study. SNPs identified as associated with growth response in the LTFU study were genotyped in the VAL cohort.
- In both the LTFU and VAL studies, growth response variables (see below) were used as dependent variables in a regression analysis:
  - centimetres grown (cm)
  - change in height (Ht) standard deviation score (SDS)
  - Ht velocity SDS over 1 year of treatment with r-hGH.

Results

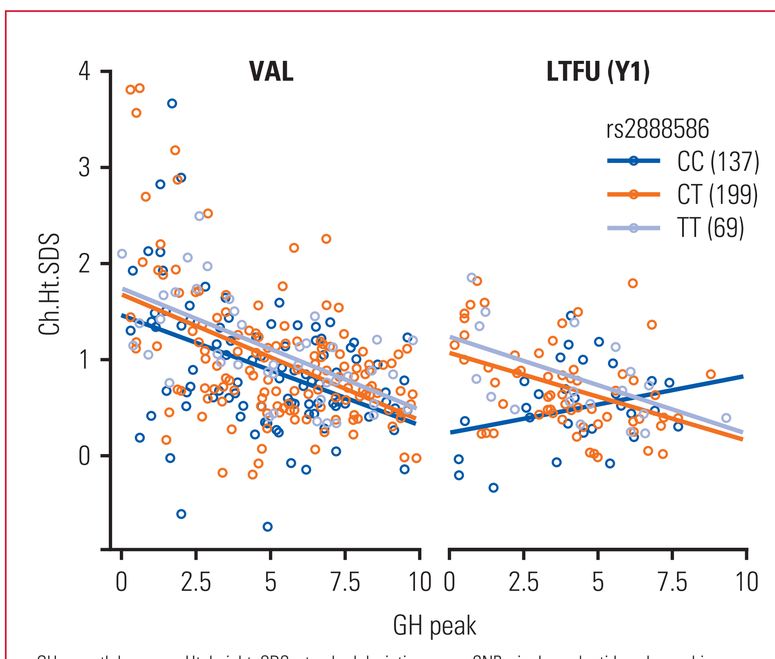
- In GHD patients, there were no differences in gender distribution (data not shown) and SNP allele frequencies between the LTFU and VAL studies, but age, [Ht – Mid-parental Ht SDS] (this is a measure of distance to target height) and GH dose were lower ($p<1.7x10^{-8}$; **Table 1**) and GH peak, mid-parental Ht SDS (both $p<6x10^{-5}$; **Table 1**) and first year growth responses were higher in the VAL study (**Figure 1A**) than in the LTFU study.
- In TS patients, there were no differences in SNP allele frequencies between the LTFU and VAL studies, but age, [Ht – Mid-parental Ht SDS] and GH dose were lower ($p<1.2x10^{-5}$; **Table 1**), and mid-parental Ht SDS ($p<2.1x10^{-8}$; **Table 1**) and first year growth response were higher in the VAL study (**Figure 1B**) than in the LTFU study.



GH, growth hormone; Ht, height; SDS, standard deviation score; SNP, single nucleotide polymorphism.

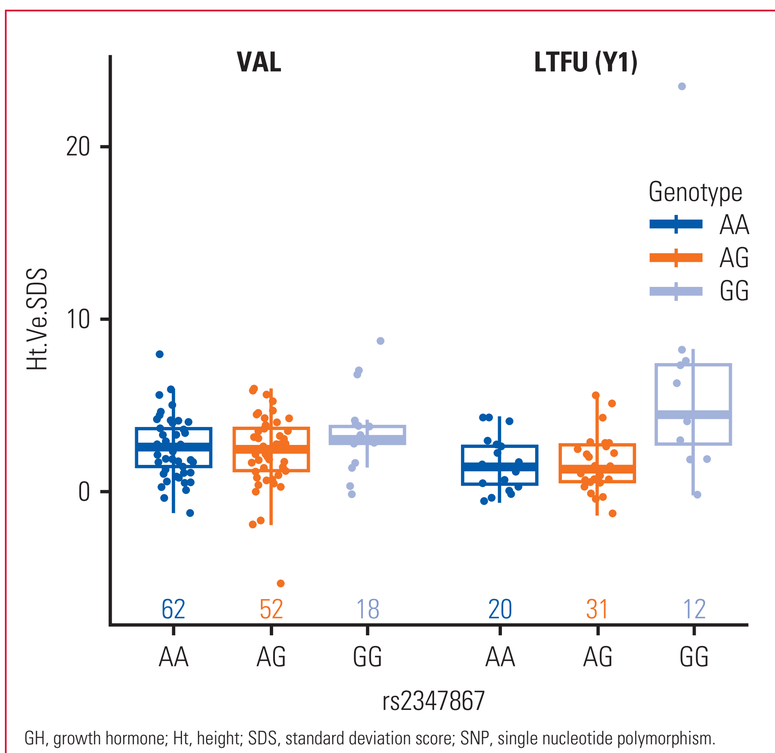
Figure 1. Comparisons of growth parameters between the LTFU and VAL studies. A) in GHD patients, B) in TS patients.

- *INPPL1* (rs2276048) was associated with growth in cm in an interaction with distance from target Ht (p=0.0057 VAL, p=0.0144 LTFU).
- *PTPN1* (rs2038526) was associated with change in Ht SDS in an interaction with mid-parental Ht SDS (p=0.0113 VAL, p=0.0055 LTFU).
- Regression modelling to control for differences between the studies and investigate interactions with covariates indicated that:
  - In GHD, the *SOS1* SNP rs2888586 was associated with change in Ht SDS in an interaction with GH peak as covariate (p=0.0036 VAL, p=0.0009 LTFU; **Figure 2**).
  - In TS, *ESR1* SNP rs2347867 was associated with Ht velocity SDS in both VAL (p=0.0304) and LTFU ($p=4.3x10^{-5}$; **Figure 3**).



GH, growth hormone; Ht, height; SDS, standard deviation score; SNP, single nucleotide polymorphism.

Figure 2 – GHD. The SOS1 SNP rs2888586 is associated with change in Ht SDS in an interaction with GH peak as covariate (p=0.0036 VAL; p=0.0009 LTFU). Change in Ht SDS is negatively correlated to peak GH level in a stimulation test. However, this relationship is dependent on the SOS1 genotype and, overall, there is a better Ht SDS associated with the carriage of the T allele at a low GH peak (severe GHD).



GH, growth hormone; Ht, height; SDS, standard deviation score; SNP, single nucleotide polymorphism.

Figure 3 – TS. The ESR1 SNP rs2347867 associated with Ht velocity SDS in both the VAL and LTFU studies (p=0.0304 and $p=4.3x10^{-5}$, respectively) and, in particular, the ESR1 GG genotype was associated with a greater Ht velocity SDS than the other genotypes.

Table 1. Comparison of variables between the LTFU (Y1) and VAL studies.

		GHD		TS	
Characteristics	**Statistics**	**VAL**	**Y1**	**VAL**	**Y1**
Age (years)	Mean ± SD	6.65 ± 3.18	8.88 ± 3.27	6.35 ± 3.01	8.88 ± 3.34
	Min; Max	0.4; 16.3	1.5; 14.8	1.1; 14.4	3.1; 16.3
	Median	6.2	9.6	5.75	8.8
	Q1; Q2	4.5; 9.1	6.8; 11.3	3.9; 8.5	6.0; 11.7
GH peak (ng/mL)	Mean ± SD	5.06 ± 2.57	4.03 ± 2.15	–	–
	Min; Max	0; 9.9	0.2; 9.3	–	–
	Median	5.2	4.1	–	–
	Q1; Q2	2.9; 7	2.5; 5.6	–	–
[Ht – Mid-parental Ht SDS]	Mean ± SD	–2.35 ± 1.27	–1.37 ± 1.43	–2.45 ± 1.10	–2.16 ± 1.35
	Min; Max	–7.335; 1.075	–5.66; 3.25	–6.532; 0.344	–5.34; 1.11
	Median	–2.317	–1.32	–2.4285	2.08
	Q1; Q2	–2.999; –1.542	–2.18; –0.57	–3.1215; –1.8035	–3.09; –1.375
Mid-parental height SDS	Mean ± SD	–0.26 ± 1.10	–0.96 ± 1.18	0.28 ± 1.01	–0.24 ± 1.12
	Min; Max	–3.333; 3.083	–3.554; 2.118	–2.518; 3.554	–3.656; 2.105
	Median	–0.25	–0.85;	0.339	–0.166
	Q1; Q2	–1; 0.5	–1.72; -0.15	–0.219; 0.786	–0.869; 0.552
Average daily GH dose (mg/kg)	Mean ± SD	0.027 ± 0.004	0.034 ± 0.006	0.046 ± 0.008	0.05 ± 0.01
	Min; Max	0.016; 0.050	0.022; 0.062	0.017; 0.08	0.005; 0.086
	Median	0.026	0.0347	0.046	0.050
	Q1; Q2	0.024; 0.029	0.031; 0.037	0.042; 0.050	0.049; 0.053

GH, growth hormone; GHD, growth hormone deficiency; Ht, height; LTFU, long-term follow-up; Q1; Q2, interquartile range; SDS, standard deviation score; TS, Turner Syndrome; VAL, validation study

Conclusions

- The PREDICT VAL study has confirmed, in an independent cohort, the association of genetic markers with growth response to r-hGH treatment in pre-pubertal children with GHD or TS, but only after controlling for covariates.

References

1. Clayton P et al. Eur J Endocrinol 2013;169:277–289.

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