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

P Chetail, A Stevens, C De Leonibus, P Clayton, J Wojcik* on behalf of the PREDICT Investigators

Department de Pédiatrie, Université Claude Bernard, Lyon, France

Manchester Academic Health Sciences Centre, Royal Manchester Children’s Hospital, Manchester, United Kingdom

Quartier, Geneva, Switzerland

33rd Annual ESPGHAN Meeting; 18–20 September, Dublin

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 (NCT00698858).

○ A validation (VAL) study (NCT01491249) 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 oestriol, eligible for r-hGH therapy.
- Pre-pubertal status according to Tanner (stage 1).
- Pre-established history of normal thyroid function or normal thyroid gland size and function.
- 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; 299 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.

○ 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) and GH dose were lower (p<2.1x10−8; Table 1), and mid-parental HSD (p=2.1x10−8) and height SDS associated with the carriage of the T allele at a low frequency (4.7% 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<2.1x10−8; Table 1) and first year growth response were higher in the VAL study (Figure 1B; than in the LTFU study.

○ In TS, SNP rs2888586 was associated with growth in cm in an interaction with distance from target Ht (p=0.0057 VAL; p=0.0144 LTFU).

○ SNP rs2038526 was associated with change in Ht SDS in an interaction with GH peak as covariate (p=0.0064 VAL; p=0.0009 LTFU).

○ Regression modeling 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=0.0064 VAL; p=0.0009 LTFU). Change in Ht SDS is negatively correlated to peak GH level in a simulation 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 (sevem GHD).

○ In TS, the ESR1 SNP rs2347067 was associated with Ht velocity SDS in both the VAL and LTFU studies (p=0.00345 and VAL; p=0.00544 LTFU).

○ In particular, the ESR1 GG genotype was associated with a greater Ht velocity SDS than the other genotypes.

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.

Disclosures

P Clayton has received research support from Merck Serono, Diapath, and has provided consultative work in support of the development. The authors also thank Simon Lancaster, in Science Communications, UK supported by Merck Serono. – Switzerland, for assistance with the preparation of this paper.

*An affiliate of Merck KGaA, Darmstadt, Germany.

References


The study was supported by Merck Serono S.A. – Switzerland*, which also provided funding for further development. The authors also thank Simon Lancaster, in Science Communications, UK supported by Merck Serono S.A. – Switzerland, for assistance with the preparation of this paper.

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

<table>
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<th>SNP</th>
<th>Ht velocity SDS</th>
<th>Height SDS</th>
<th>Change in height SDS</th>
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<th>Min; Max</th>
<th>Median</th>
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</table>

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=0.0064 VAL; p=0.0009 LTFU). Change in Ht SDS is negatively correlated to peak GH level in a simulation 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 (several GHD).

Figure 3 – TS. The ESR1 SNP rs2347067 is associated with Ht velocity SDS in both the VAL and LTFU studies (p=0.00345 and VAL; p=0.00544 LTFU). In particular, the ESR1 GG genotype was associated with a greater Ht velocity SDS than the other genotypes.