Genetic aetiology predicts growth hormone treatment outcomes in children born small-for-gestational-age with persistent short stature (SGA-SS). Lessons from a single-centre cohort.

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Introduction and objectives

Introduction: SGA-SS, defined as birth weight and/or birth length below -2SD for gestational age and postnatal statural height below -2.5SD according to age- and sex-specific standards, is a heterogeneous condition reflexing exogenous (maternal, placental) or endogenous (foetal) inadequacies. Within the past two decades, a handful of genetic causes of SGA-SS have been elucidated. However, how each genetic aetiology impacts individual GH treatment outcomes awaits clarification.

Objectives: To analyse treatment outcomes in genetically defined subgroups of SGA-SS children originating from a single-centre cohort.

Methods

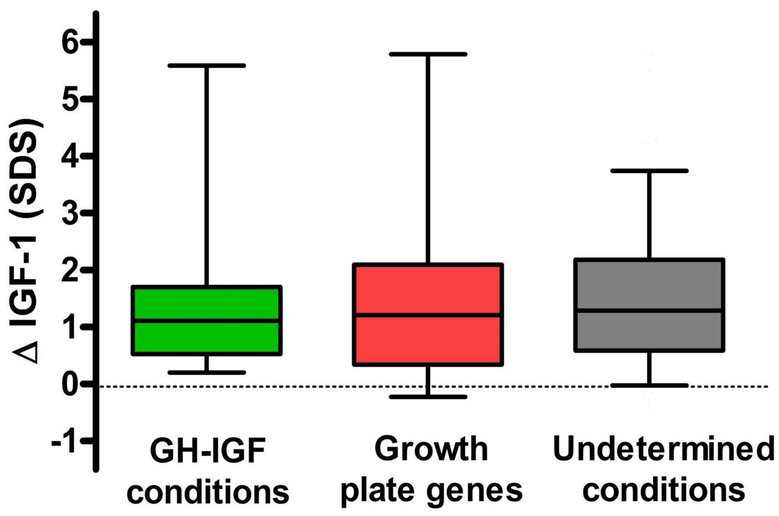
A single-centre cohort consists of 445 SGA-SS children (221 females; Turner syndrome was excluded) aged 1.3-27.0 years at this evaluation (median 11.8). Of these, genetic aetiology was thus far elucidated in 60 children (33 females) – 24 carried a pathogenic variant of genes affecting the cartilage (*ACAN* in two, collagen genes in nine, and *SHOX* gene in 13), 19 had pathogenic genetic variants perturbing GH-IGF axis and signalling (*GHSR* [1], *HGMA2* [3], *OTX2* [1], *STAT3* [1], *IGFALS* [1], *IGF1R* [2], Silver-Russell syndrome [SRS; 10]), and 17 had miscellaneous single-gene or chromosomal conditions.

We analysed (1) systemic response to GH administration expressed as delta-IGF-1_SDS prior to and while on treatment and (2) target tissue (growth plate) response expressed as delta-height_SDS on treatment.

Results

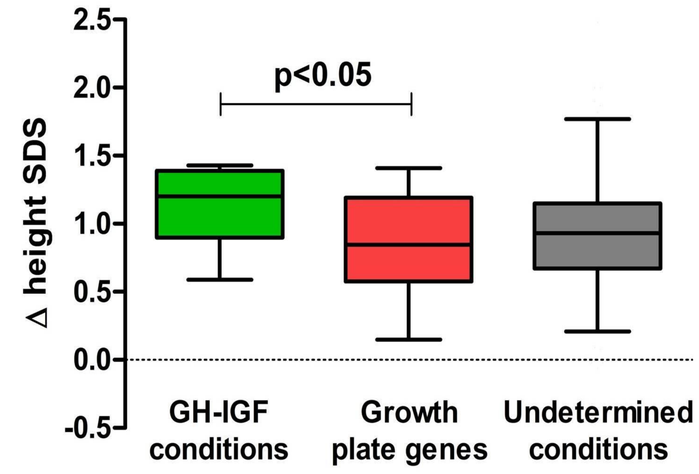
"Systemic response" to GH was equivalent in children with undetermined aetiology of SGA-SS (delta-IGF-1_SDS following the first 3-6 months of GH: +1.50±0.10; mean±SEM) and the subcohorts with growth plate gene defects (+1.47±0.36) and GH-IGF axis condition (+1.42±0.46).

Systemic response to GH:
Δ IGF-1 (SDS) after initiation of therapy

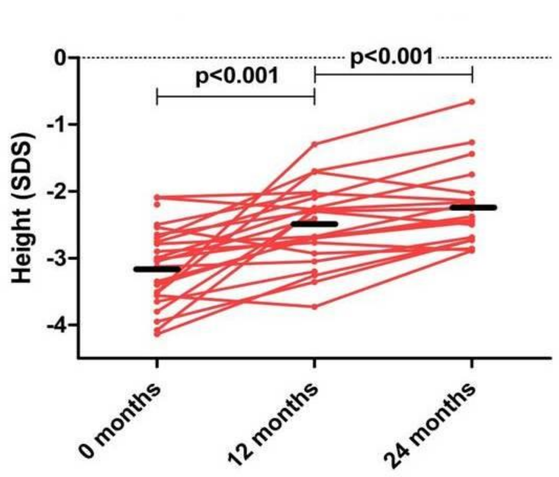


"Growth plate response" to GH clearly differed. The height gain following first two years of prepubertal GH therapy was higher in the sub-cohort with GH-IGF axis conditions (delta-height SDS: +1.12±0.09) than in children with growth plate gene defects (delta-height SDS: +0.84±0.09; p=0.046), whereas children with undetermined aetiology had an intermediate two-year growth response (delta-height SDS: +0.96±0.04).

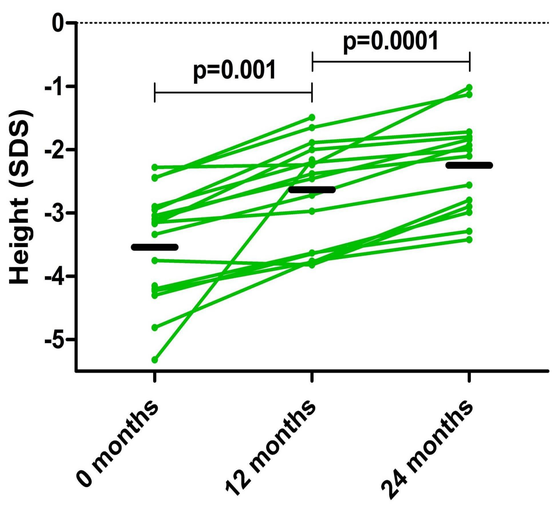
Growth plate response to GH:
Δ height SDS following 24 months of therapy



Growth plate genes
Response to GH therapy



GH-IGF axis conditions
Response to GH therapy



Conclusions

- The best GH responders among SGA-SS children are those with perturbed GH-IGF axis and signalling, incl. SRS.
- The treatment response in growth plate disorders (*SHOX* or matrix gene defects) was rather modest.
- The change of IGF-1 following therapy is a poor predictor of growth response.
- Our results open the first insight into treatment outcome among genetically defined sub-cohorts of SGA-SS children.

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