Deciphering genetic aetiology among children born small-for-gestational-age with persistent short stature (SGA-SS): Phenotypic characteristics at diagnosis in a large single-centre cohort

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Introduction and objectives

Introduction: SGA-SS is a heterogeneous condition 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 normative values. Despite being an indication for growth hormone (GH) therapy in Europe for 15 years, the aetiology and prediction of treatment outcomes in most of individual SGA-SS children awaits elucidation.

Objectives: To decipher genetic aetiologies among a large single-centre cohort of children born SGA and to define phenotypic characteristics at diagnosis in genetically defined subcohorts.

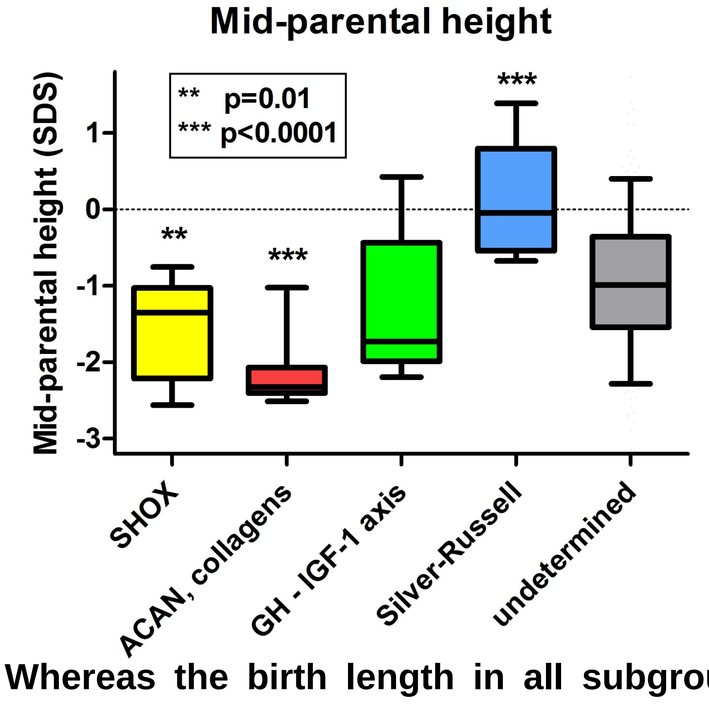
Methods/Subjects

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). We searched for the genetic aetiology in majority of the cohort using individualised phenotype-based genetic techniques that included standard karyotyping, array comparative genomic hybridization (CGH), targeted or whole exome sequencing in selected individuals, and methylation studies in phenotype of Silver-Russell syndrome (SRS).

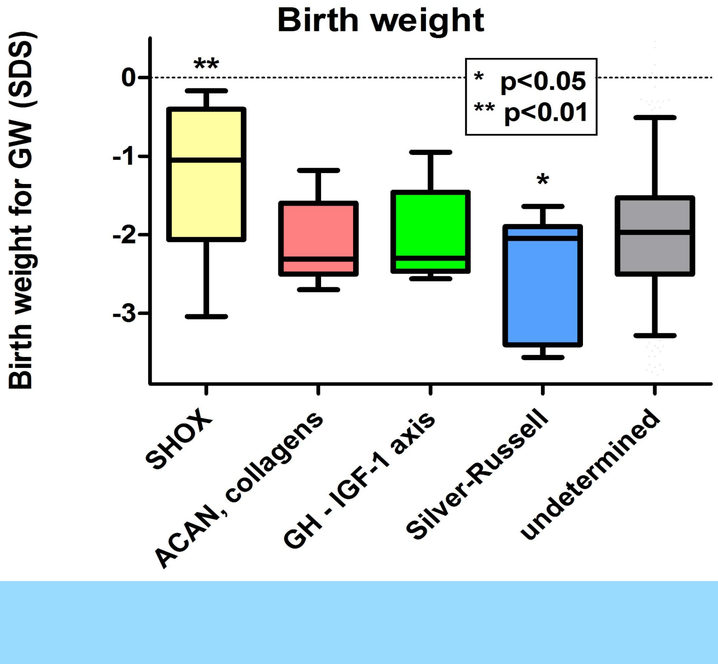
Results

Thus far, genetic aetiology was elucidated in 60 children (33 females). Of these, 11 had a pathogenic variant of genes encoding cartilaginous matrix components (*ACAN* or one of genes encoding collagen structures [assigned here as *COL_X*]), 13 had *SHOX* defects, 9 had pathogenic genetic variants perturbing the GH-IGF-1 axis (*GHSR, HGMA2, OTX2, STAT3, IGFALS, IGF1R*), 10 had SRS, and 17 had miscellaneous single-gene or chromosomal conditions.

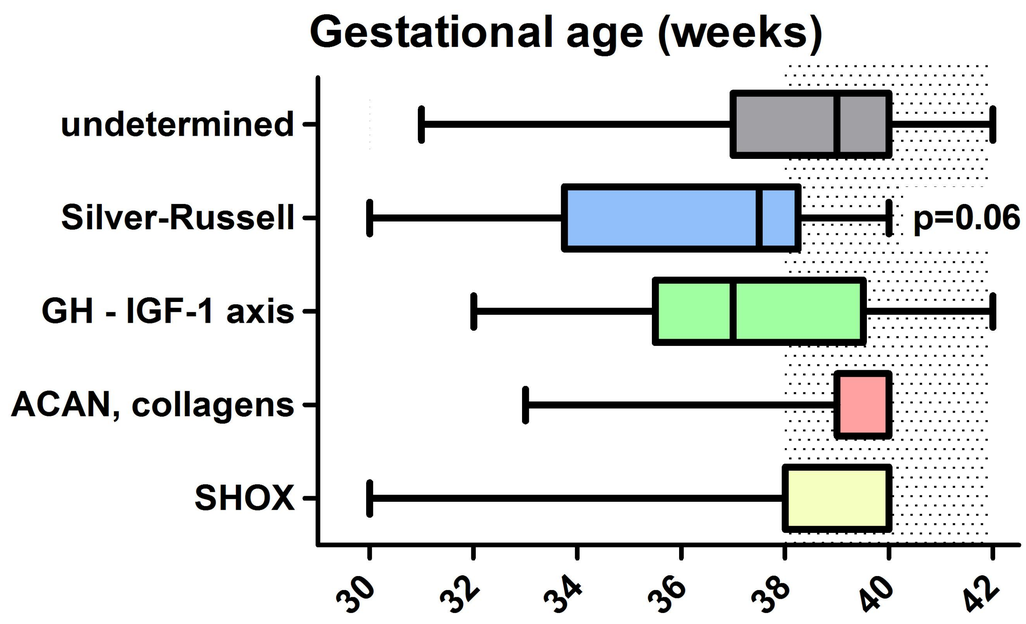
Whereas the mid-parental height-SDS in children with undertemined genetic aetiology (n=385) was -0.94±0.04 (mean±SEM), parents were shorter in *ACAN/COL_X* (-2.10±0.15; p<0.0001) and in *SHOX* (-1.51±0.17; p=0.01) and taller in SRS (+0.17±0.27; p<0.0001).



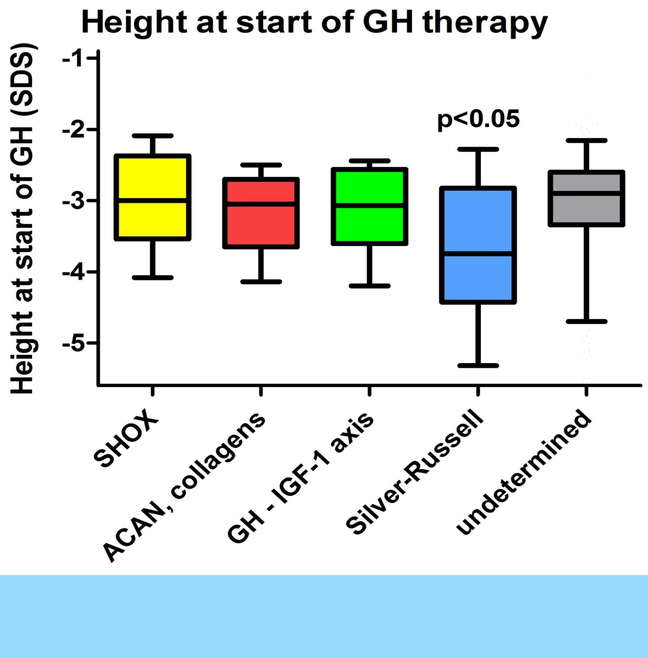
Whereas the birth length in all subgroups was similar, birth weight-SDS was -1.96±0.04 (mean±SEM) in SGA-SS children with undetermined aetiology but lower in SRS (-2.53±0.25; p<0.05) and higher in SHOX (-1.31±0.25; p<0.01).



SRS children tended to be born earlier (gestational week 36.2±1.1 vs. 38.1±0.2; p=0.06).



The postnatal growth failure was more pronounced in SRS (height-SDS at start of GH therapy -3.84±0.41; p<0.05) than in SGA-SS children with undetermined aetiology (-3.06±0.06), in ACAN/COL_X (-2.97±0.14; n.s.), in SHOX (-3.02±0.25; n.s.), and in the perturbed GH-IGF-1 axis (-3.13±0.21; n.s.)



Conclusions

Subcohorts of SGA-SS children defined by genetic aetiology display specific phenotypic characteristics and differ in parental heights, gestational age, size at birth and the severity of postnatal growth failure. These variables may facilitate predicting the genetic background in some SGA-SS children. Nevertheless, in SGA-SS children genetic diagnosis remains a challenging task at the current level of knowledge.

The study was supported by grant AZV No. NV18-07-00283.