

HIGH RATE OF POSITIVE GENETIC FINDINGS IN CHILDREN BORN SMALL FOR GESTATIONAL AGE WITH PERSISTENT SHORT STATURE (SGA-SS): GROWTH PLATE GENES AS KEY REGULATORS OF INTRAUTERINE GROWTH

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INTRODUCTION

Ten percent of children born small for gestational age fail to catch-up and remain short during childhood (SGA-SS). Several genes causing SGA-SS have been described, however, in most cases, the mechanisms of prenatal and postnatal growth impairment remain unknown.

AIM

To decipher genetic etiologies within a large single-center cohort of SGA-SS children in order to better understand the pathophysiological mechanisms leading to prenatal and postnatal growth failure.

PATIENTS AND METHODS

822 patients treated with growth hormone (GH) (2008-2018)

306 children born SGA-SS

166/306 families agreed to take part in the study

Out of all growth-hormone treated patients in our centre 306 children met the criteria of being SGA-SS (birth length and/or birth weight <-2 SD for their gestational age and sex, height <-2.5 SD after 4 years of life). Of these in 166 the DNA of the child and both of his/her parents was available for genetic testing - these were included to the study. In case of a clinical suspicion on a specific genetic disorder, targeted genetic examination (karyotype/FISH/MLPA/Sanger sequencing) was performed. Children with unknown genetic SGA-SS etiology were subsequently examined using next-generation sequencing methods (whole exome sequencing or targeted panel of 399 growth-related genes). All the genetic variants were classified using American College of Genetics and Genomics (ACMG) guidelines. The parents' DNA was examined by Sanger sequencing to evaluate the segregation of the genetic variants in the families.

RESULTS

Genes affecting components of cartillagenous matrix	Genes involved in paracrine regulation of chondrocytes	SHOX gene defects	Silver-Russell syndrome	Genes affecting intracelular regulation and signaling	Genes affecting pituitary development and/or the GH-IGF-1 axis	Miscellaneous single-gene or chromosomal aberrations
ACAN [3], COL11A1 [5], COL1A1, COL1A2, COL2A1 [5], COL9A2, FLNB [5], MATN3	FGFR3 [2], NPR2 [3], SOX9	SHOX [11]	11p15 [8], UPD7 [4],	CDC42, KMT2A, KMT2D, LMNA, NSD1, SON, SOS1 [2], SON, SRCAP, PTPN11 [2],	GHR, GHSR, HGMA2 [2], IGFALS, IGF1R [3], IGF1, LHX4, OTX2, STAT3, PTCH1	TRPS1, TRHR, RAI1, chromosomal microdeletions and/or translocations
22/84 (26%)	6/84 (7%)	11/84 (13%)	12/84 (14%)	11/84 (13%)	13/84 (16%)	9/84 (11%)

The genetic aetiology was elucidated in 84/166 (51%) children so far

CONCLUSIONS

The mechanisms leading to SGA-SS can frequently be identified by current genetic techniques. The etiological spectrum reflects the complexity of growth regulation. Genes affecting the structure and function of the growth plate play a key role.

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