GROWTH PLATE DISORDERS ARE THE MAIN CAUSE OF SEVERE FAMILIAL SHORT STATURE IN CHILDREN CLASSIFIED AND TREATED AS SGA OR GHD

Lukáš Plachý, Veronika Straková, Lenka Elbliová, Dana Zemková, Marta Šnajderová, Barbora Obermannová, Stanislava Koloušková, Zdeněk Šumník, Jan Lebl, Štěpánka Průhová

Department of Pediatrics, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic

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Introduction:
Familial short stature (FSS) is a very heterogeneous condition. Especially milder forms may result from the combined effect of multiple genes (polygenic inheritance), more severe short stature is often a monogenic disorder. Multiple genes causing monogenic FSS have been discovered. The aim of the study was to identify genetic etiology of short stature in children from families with severe FSS treated with GH and classified as SGA and/or GHD.

Materials and methods:
Out of 555 children treated with GH for GHD and/or SGA, 33 (5.8 %) had severe FSS defined as live-minimum height ≤ 2.5 SD in both patient and his/her shorter parent. Those were included into further study. Twenty-one were born SGA, 24 had GHD (median of GH level after stimulation 6.7 ug/l). In five, genetic etiology had already been known (ACAN variants in 2 families, NF1, PTPN11 and SOS1 variants each in single family). In the remaining 28 patients (20 boys, median age 10.2 years, median age at start of GH therapy 7 years) no genetic cause of short stature was elucidated prior the study. Whole exome sequencing was performed and the obtained results were evaluated using ACMG standards and guidelines.

Results:
In 90 % (30/33) children we found at least one genetic variant with potential clinical significance in the genes with known impact to the growth. A genetic cause was confirmed in 18/33 (55 %) children. Gene variants affected growth plate were found in 9/18 (COL2A1, COL11A1 and ACAN [all in two]) and FLNB, FGFR3 and IGF1R, in 3/18 gene variants affected IGF-associated proteins (IGFALS [in two] and HMGA2). In the remaining 6/18, the discovered genetic mechanisms were miscellaneous (TRHR, MBTPS2, GHSR, NF1, PTPN11, SOS1).

Conclusion:
In children from families with severe familial short stature who are classified as SGA and/or GHD, genetic etiology of short stature is heterogeneous. Interestingly, genes affecting the structure and function of the growth plate play an important role.

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