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

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Introduction:

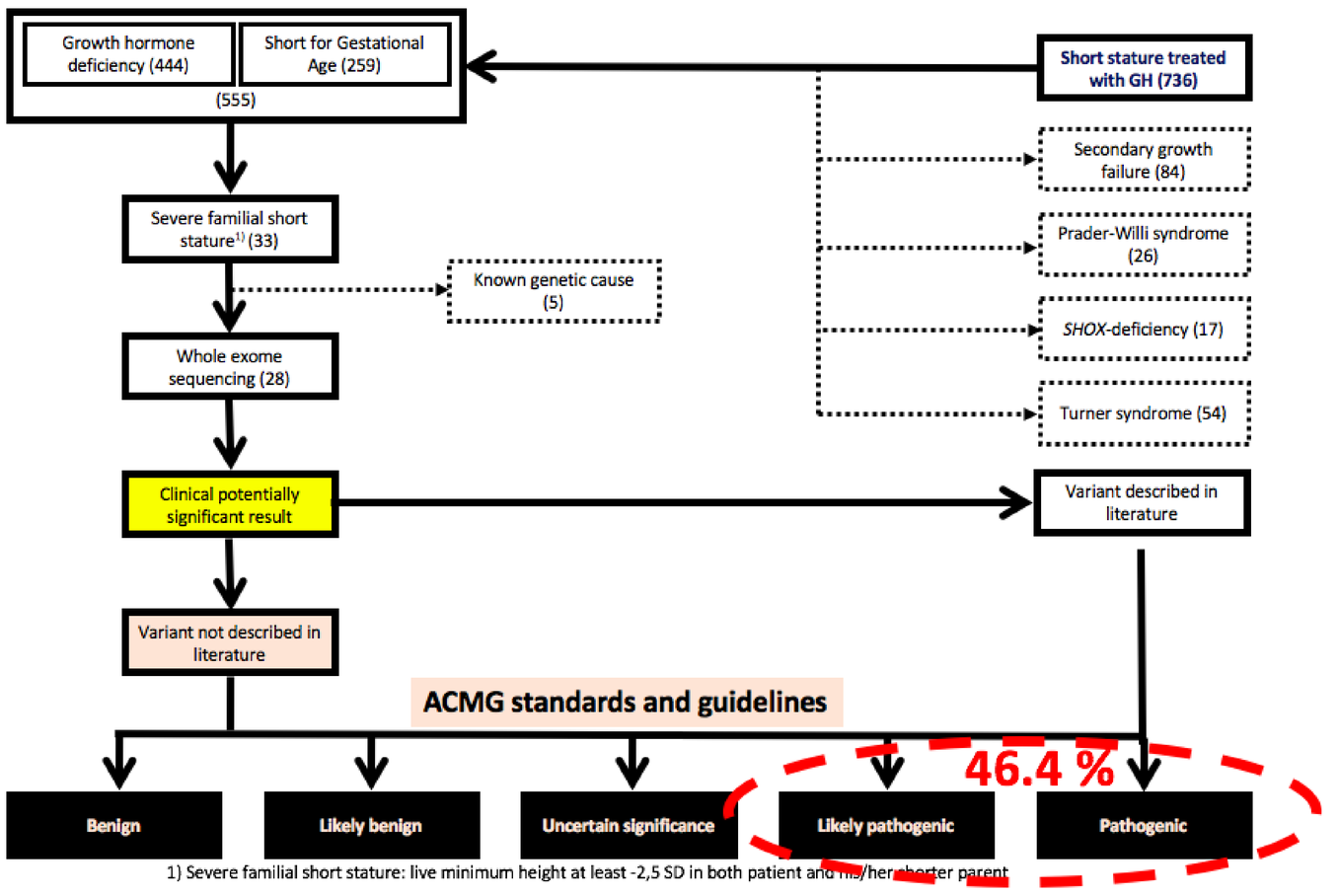
Familiar short stature (FSS) is a very heterogeneous condition. Especially milder forms may result from the combined effect of multiple genes (polygenic inheritance), more severe short stature is often a monogenic disorder. Multiple genes causing monogenic FSS have been discovered. The aim of the study 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, GSHR, NF1, PTPN11, SOS1*).



Growth plate disorders		IGF-related proteins		Miscellaneous etiology	
SGA	**non-SGA**	**SGA**	**non-SGA**	**SGA**	**non-SGA**
COL11A1 (2) COL2A1 (2) ACAN (2) IGF1R FLNB	FGFR3	-	IGFALS (2) HGMA2	TRHR GHSR SOS1 PTPN11 NF1	MBTPS2

n=28	Median	Range
Age (years)	10	5 to 16
rGH initiation age (years)	7	3 to 13
Height (SD)	-3.26	-2.53 to -4.95
Shorter parent`s height (SD)	-2.89	-2.59 to -4.03
GH deficiency (n=20)		
Stimulated GH (ug/l)	6.70	1.24 to 9.40
SGA (n=19)		
Birth weight (SD)	-1.94	-0.60 to -3.01
Birth length (SD)	-3.00	-1.23 to -4.14

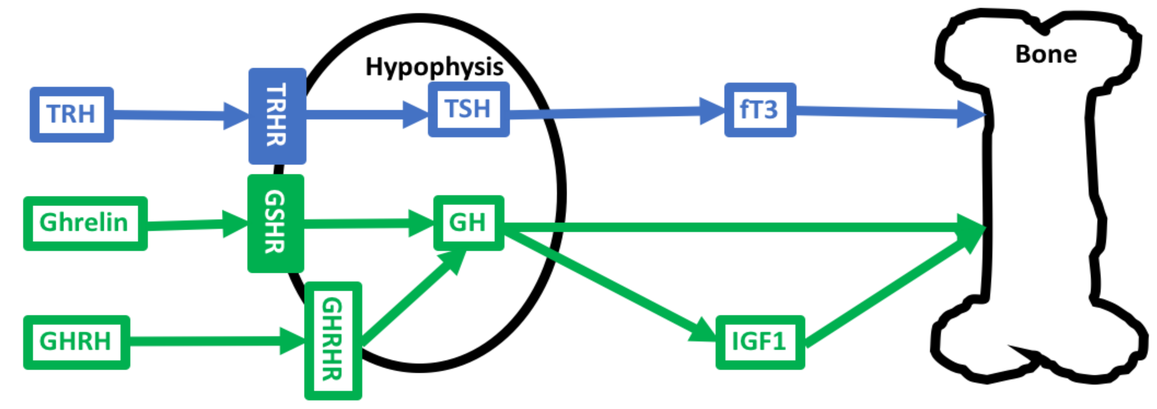


Figure 1 (up) – *TRHR* gene encodes receptor for thyrotropin releasing hormone (TRH). After TRH binds to TRHR, thyroid-stimulating hormone (TSH) is secreted from the pituitary. TSH stimulates secretion of thyroid hormones (e.g. fT3) those are essential for bone growth. *GHSR* is a gene for ghrelin receptor that has an important role in regulating GH secretion [additional to growth hormone releasing hormone (GHRH) stimulation].

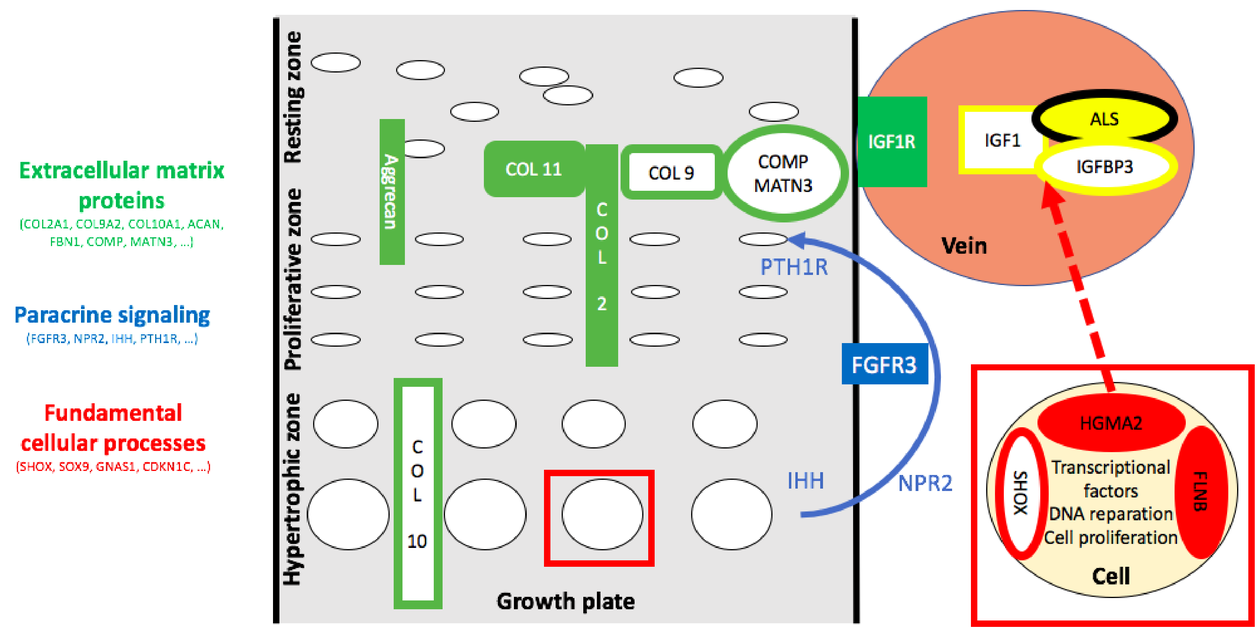


Figure 2 (right) – Growth plate disorders are caused by extracellular matrix proteins defects (green), paracrine signaling impairment (blue) and disorders in fundamental cellular processes (red). *COL11A1* is a gene encoding pro-alfa 1 chain of collagen IX (COL 11), *COL2A1* gene encodes pro-alfa 1 chain of collagen II (COL 2), *ACAN* gene proteoglycan aggrecan and *IGF1R* gene receptor for insulin-like growth factor 1 (IGF1). *FGFR3* product is an important for paracrine signaling and *FLNB* product for microtubule formation. *IGFALS* gene encodes acid-labile subunit (ALS) that together with IGF1 and IGFBP3 forms ternary complex (responsible for transport of IGF1 in the circulation). *HMGA2* encodes a transcriptional factor that affects IGF2 protein.

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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