A HOMOZYGOUS PATHOGENIC VARIANT IN THE *TRHR* GENE IN A BOY WHO PRESENTED WITH SEVERE FAMILIAL SHORT STATURE AND CENTRAL HYPOTHYROIDISM

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Introduction and objectives:

Congenital central hypothyroidism (CCH) is a rare disease with inappropriate thyroid hormone secretion due to impaired TSH stimulation. TSH levels are not elevated; the patients are not diagnosed in TSH-based newborn screening. Biallelic variants in *TRHR* gene (encoding TRH receptor) are one of four genetic defects known to cause isolated CCH (*THRH*, *THSB*, *IGSF1*, *TBL1X*). The phenotype is variable but generally mild (neonatal jaundice, short stature, delayed bone maturation); the mental development is not significantly impaired. Only four patients have been described so far, thus the information about the phenotype is limited.

Case presentation:

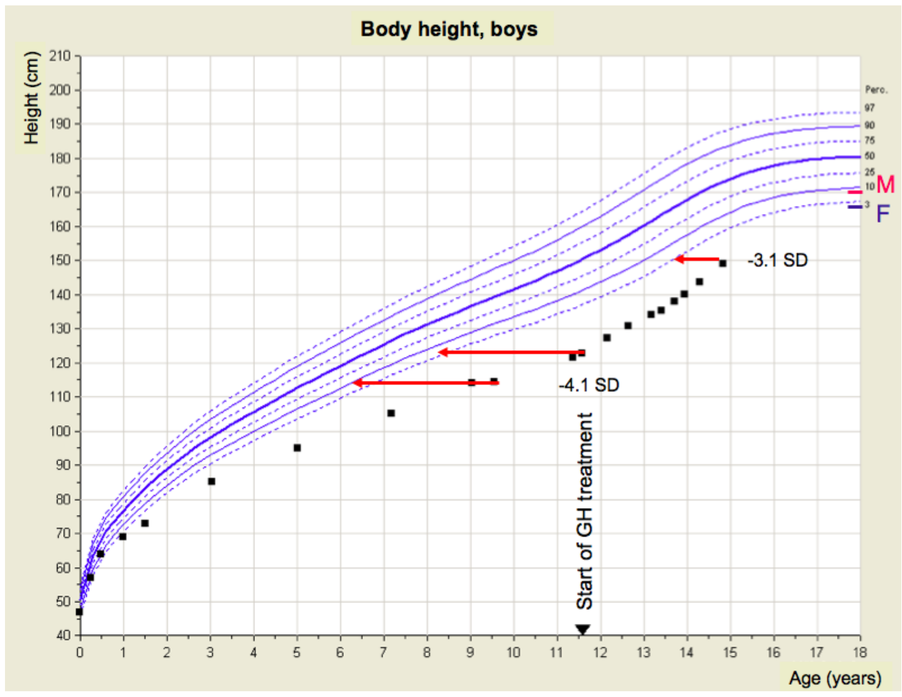
A boy with familial short stature (father 160 cm [-2.89 SD], mother 156.6 cm [-1.7 SD]) was born to nonconsanguineous parents in the 40th week of gestation small for gestational age – birth height 2900 g (-1.64 SD), birth length 47 cm (-2.39 SD). He was endocrinologically examined in 9.6 years for severe short stature (114.3 cm, -4.27 SD) and significantly delayed bone age (6.2 years). His mental status was normal; he had no other signs of hypothyroidism. Tests showed central hypothyroidism (fT4 8.65 pmol/l, TSH 1.642 mIU/l), low IGF-1 level (80 ug/l -3.68 SD), maximum stimulated growth hormone level was 10 ug/l. TRH stimulated TSH concentration was lower-normal (10.9 mIU/l). L-thyroxin substitution and recombinant growth hormone treatment was initiated (due to SGA indication) with relatively mild effect to proband's height (14.8 years, 3.5 years after the treatment initiation: height 149 cm [-3.1 SD]).

Table 1 – data at the first endocrinological examination

Age	9.6 years
Height	114.3 cm (-4.27 SD)
Bone age (TW3 RUS)	6.2 years
fT4	8.65 pmol/l
TSH	1.642 mIU/l
IGF-1	80 ug/l (-3.68 SD)
GH_{max} (clonidine test)	10 ug/l

TRH test:

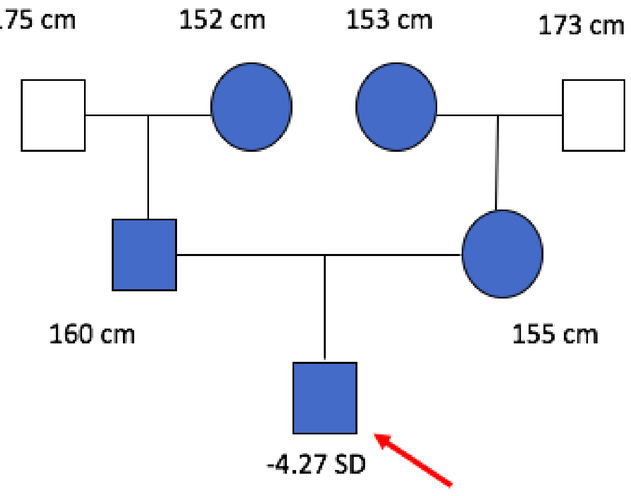
	0 min	15 min	30 min	60 min	120 min
TSH (mIU/l)	3.887	10.900	10.000	6.586	3.726
fT4 (pmol/l)	9.71	8.93	8.94	9.05	9.99



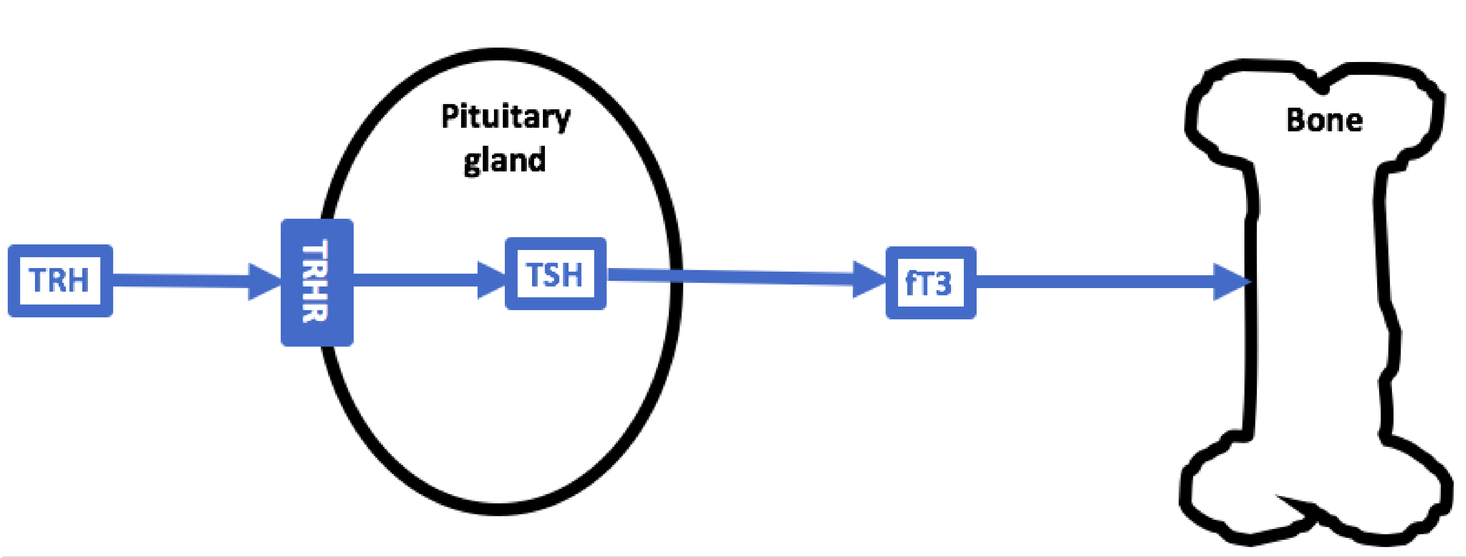
F – father`s age, M – mother`s age, red arrows – bone age

Genetic examination:

Whole exome sequencing was performed and a homozygous variant p.Ile131Thr in the *TRHR* gene discovered. The variant has already been described as pathogenic. The replacement adds a polar hydroxyl group to the highly conservated hydrophobic position. It reduces the receptor affinity for TRH and impairs signal transduction as proven in functional studies. The result fully explained proband's short stature and central hypothyroidism, but as the disease is inherited in the autosomal recessive way it did not give any information about the causes of short stature in the family.



M/M – homozygote, M/N – heterozygote, arrow - proband



Conclusion:

Homozygous variants in the *TRHR* gene may cause central congenital hypothyroidism. As the associated symptoms are generally mild and the mental development normal, the diagnosis may be difficult. Short stature may be the only symptom leading to the correct diagnosis.

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