GOOD CLINICAL RESPONSE TO GROWTH HORMONE THERAPY IN A BOY WITH A COMBINATION OF FAMILIAR SHORT STATURE CAUSED BY NOVEL p.Val478Serfs*14 MUTATION IN *ACAN* GENE AND ISOLATED GROWTH HORMONE DEFICIENCY

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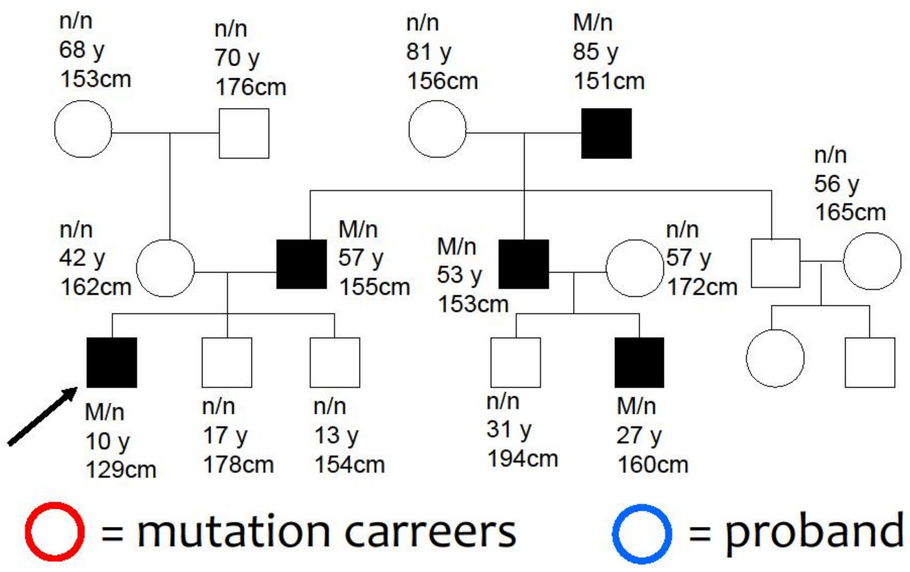
The authors have no relevant conflicts of interest.

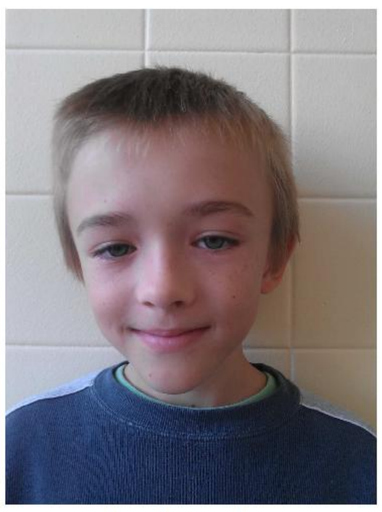
Background and aims

Recently, heterozygous mutations in *ACAN* gene encoding protein aggrecan have been described as a cause of familiar short stature (FSS) combined with accelerated bone age. Aggrecan is an extracellular proteoglycan in growth plate cartilage that plays an important role in biological and biomechanical properties of cartilage.

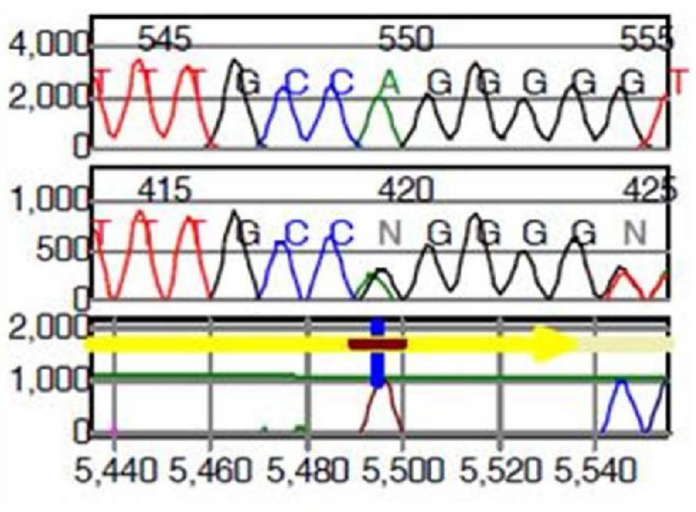
Objective and hypotheses

We provided genetic screening for *ACAN* variants within families with FSS and subsequently analyzed efficacy of growth hormone therapy in an affected individual.

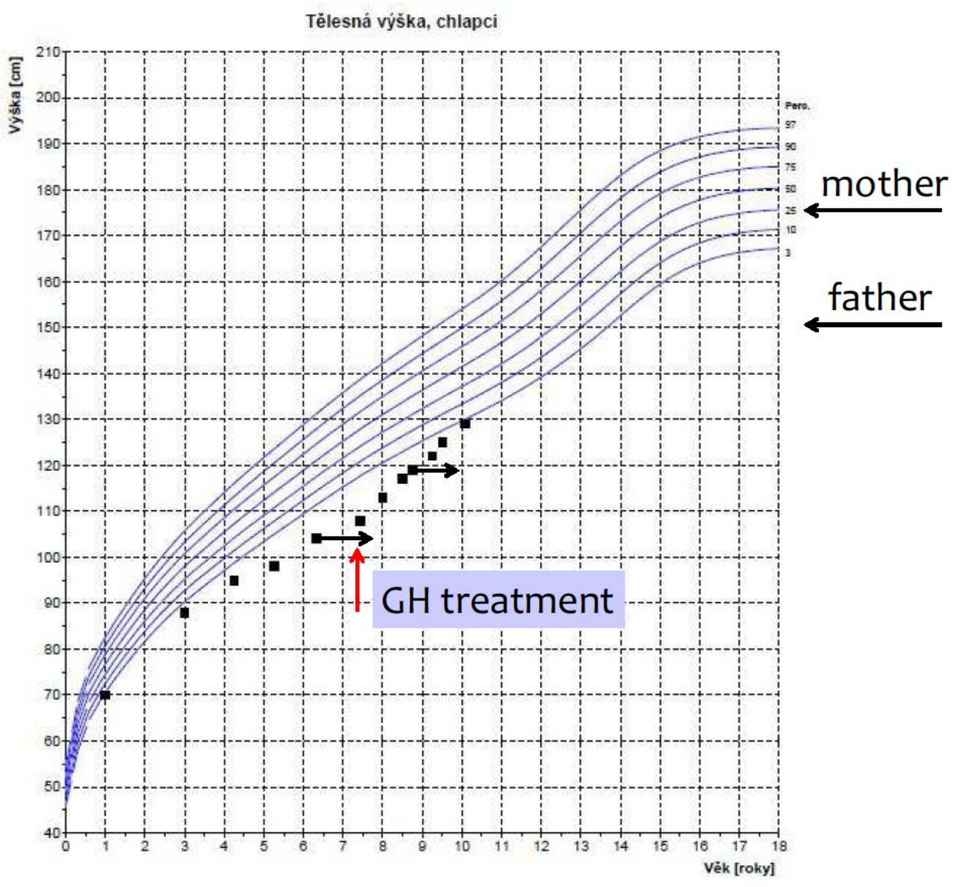




Proband



p.Val478Serfs*14



Methods

The direct sequencing of the exons and exon – intron boundaries of the *ACAN* gene.

Results

A novel heterozygote frameshift mutation p.Val478Serfs*14 has been found in a 10-year-old male proband and in his father from a family with FSS that was especially apparent among males (proband's father: 155cm (-3.6 SD), paternal grandfather: 151 cm (-4.3 SD), paternal uncle: -3.7 SD, his son: -3.2 SD). The height of proband's mother is 162 cm (-0.84 SD). The proband was born short for gestational age (2920 g / 45 cm at 40th GW), with no perinatal problems. Low-normal IGF-1 (-1.59 SD) and insufficient growth hormone response after stimulation (maximum peak in clonidine test: 3.54 ug/l; after insulin hypoglycemia: 3.05 ug/l) led to diagnosis of isolated growth hormone deficiency at age 7 years. MRI scan revealed normal pituitary. Growth hormone treatment was started at age 7 years 4 months with height -3.7 SD (108 cm) using dose 0.028 mg/kg/day. After 3.5 years of treatment, his height increased to -2.5 SD following growth velocity 10 cm/year (year 1 of treatment) and 8 cm/year (years 2 and 3). His bone age was accelerated by 1.5 years both at onset of therapy and 3 years later. No adverse events have been observed within 3.5 years of treatment.

Conclusions

This is the first description of a novel mutation in the *ACAN* gene as a cause of familiar short stature in Czech population. The patient clinically displayed a combination of isolated growth hormone deficiency and FSS. The response to growth hormone was excellent and the bone age remained steadily accelerated.

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