A new mutation in IHH gene causing severe short stature

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Background

IHH gene , located on long arm of chromosome 2, is a member of Hedgedog family and plays a role in endochondral ossification, according to its expression in prehypertrophic condrocytes.
Heterozygous mutation in IHH are known to cause Brachydactyly A-1, in which the typical clinical features are bilaterally shortening or absence of the middle phalanges of most digits of hands and feet, shortness of 1st proximal bone and short stature ; althougt short stature is considered part of BDA1, in most reported cases is not always present or unrelevant compared to the stature of unaffected relatives.

Case presentation

A girl of 11years and 7 months was referred to our clinic for short stature. She was born from unrelated parents at 40 weeks of a pregnancy complicated by threats of abortion, birth parameters were weight 2.7 kg (-1.85DS) , length 48 cm (-1.32DS), head circumference 35 cm (0.53DS).

The mother's height was 150.2 cm (-2.1 DS), the father's height was 166.1 cm (-1.6 DS) , target height 151.6 cm (-1.8DS).After one year of life she had a poor growth, psycomothor development was normal, menarche occurred at 11 years.

At the first visit she showed height 129.1 cm (-2.9 SDS), sitting height 65.6 cm, sitting height/ height ratio 0.51 (-0.65DS), armspan 127.5 cm , armspan/height ratio 0.98, head circumference 49 cm (-2.7SDS), weight 30.8 kg (-1.64DS), BMI 18.5 (-0.34DS), pubertal stage PH4 B3, cubitus valgus and scoliosis. The karyotype ,thyroid function and IGF1 were normal, SHOX gene defects were excluded, hand radiograph showed adult bone age.

Considering the poor height prognosis given the very advanced bone age, we performed a whole exome sequencing analysis (NGS) by a panel including 254 genes causing short stature.

The NGS analysis revealed a new mutation in IHH gene, exon3:c.G1045A:p.A349T, that was confirmed by Sanger sequencing, the same mutation was found in the mother. Our mutation is located in the C-terminal domain of IHH protein.
The prediction software SIFT, Polyphen and Mutation Tester confirmed the pathogenicity of the identified variant.

Discussion

Recently Vasques et al. found heterozygous mutations in IHH in children and adults with short stature without specific skeletal signs of BDA1, adding IHH defects among genetic causes of short stature. In this report the mean height SDS was in Brazilian children (twelve subjects) -2.6 +/-0.9DS and in Spanish children (five subjects) -3.2 +/-0.6DS, in adults the mean height SDS (ten Brazilian and four Spanish) was -3 +/-1.1 DS.

Our case is in line with this findings but with a more remarkable short stature (height 129.4 cm, -5.6 SDS considering adult bone age); hand radiograph of patient showed no classical features of BDA1, but an overtubulation of distal phalanges.

Conclusion

Our case confirms the role of IHH gene in short stature and add new phenotypic features: very short stature, SGA, very mild radiographic features and great phenotypic variability in the same family.

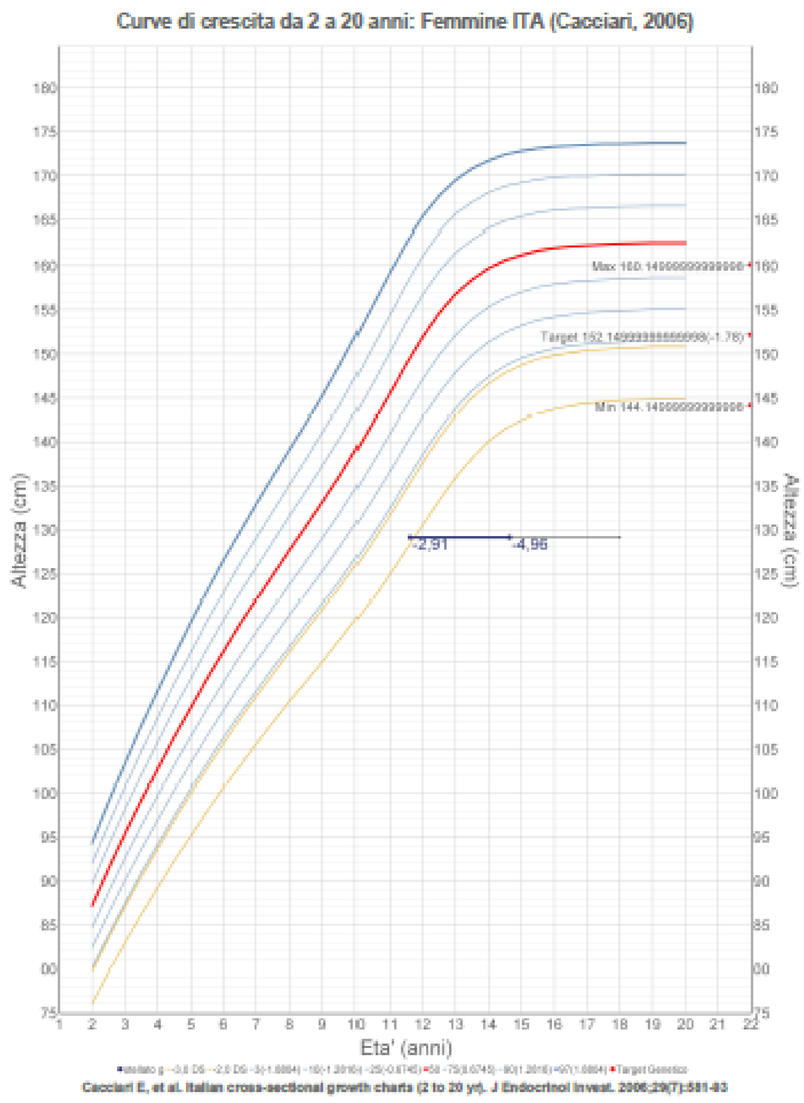

Figure 1. Patient's growth chart .

References

Vasques G.A. et al. *IHH* gene mutations causing short stature with non-specific skeletal abnormalities and response to growth hormone therapy J Clin Endocrinol Metab. 2018 Feb 1;103(2): 604-614.
Gao et al. Mutations in IHH, encodng Indian hedgehog, cause brachydactyly type A-1.Nature Genetics 2001, 28:386-388.

No conflict of interest to declare

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