Two different variants of Short Stature Homeobox-Containing gene (SHOX) mutation in the same family

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Introduction

- Deficiency of the short stature homeobox-containing (SHOX) gene is a potential etiology of short stature in children.
- It is caused by haploinsufficiency of the SHOX-gene and inherited in a pseudo-autosomal dominant manner.
- The phenotypic spectrum of SHOX deficiency is highly variable, even within the same family.
- SHOX deficiency can be caused either by single nucleotide variants or deletions encompassing the SHOX coding region and/or the enhancer region regulating SHOX expression.

Objectives

- We describe two otherwise healthy brothers with short stature and disproportion (Fig.1).
- The parents presented both with short stature, but the father was proportioned, while the mother showed stigmas indicating Leri Weill dyschondrosteosis (Fig. 2).
- In both children laboratory was noncontributory for common causes of short stature and growth hormone stimulation test showed normal response.
- Due to family history, we performed SHOX gene analysis with a surprising result.

Methods

- Multiplex Ligation-dependent Probe Amplification (MLPA) of the PAR region (4-6) on Xp22.32 and Yp11.32 containing the coding region and 5’ and 3’ flanking sequences of the SHOX gene was performed
- MRC-Holland kit P018-G1 according to the manufacturer’s instructions was used

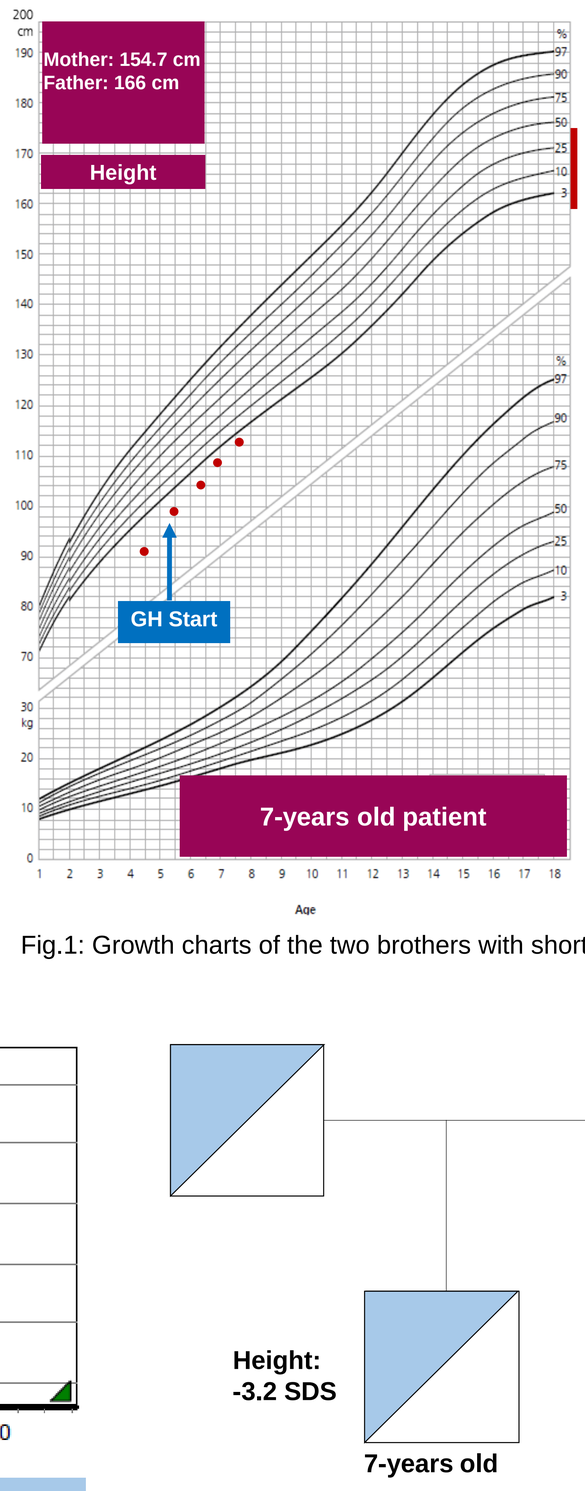

Fig.1: Growth charts of the two brothers with short stature

Results

- SHOX gene analysis revealed a known heterozygous ~47,5 kb deletion in the 3’-flanking region (probes L25091-L24249) in the mother and the older child (Fig. 3)
- A novel duplication in the SHOX 5'-flanking sequence (probes L24430-L20651) was found in the father and the younger child (Fig. 4)
- This duplication has not been described previously, but likely influences the regulation of SHOX protein expression.

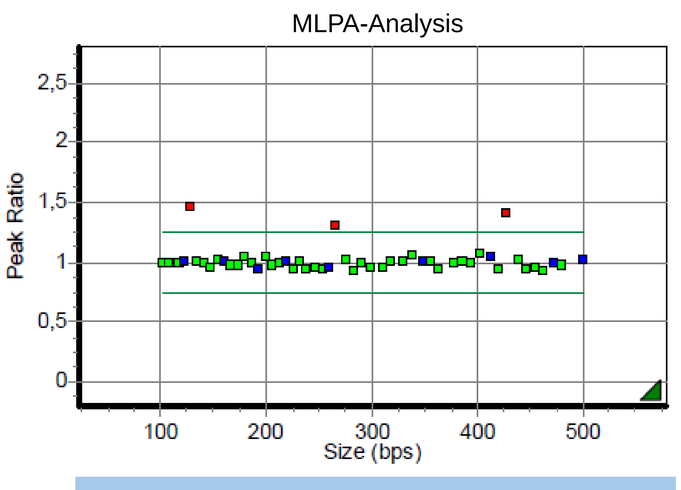

Fig. 4: Novel duplication in the SHOX 5‘-flanking sequence found in the father and the younger child

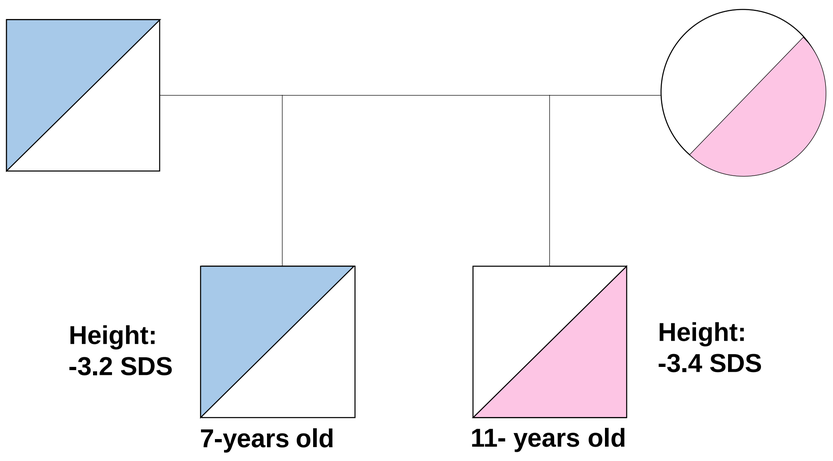

Fig. 2 Pedigree of the family

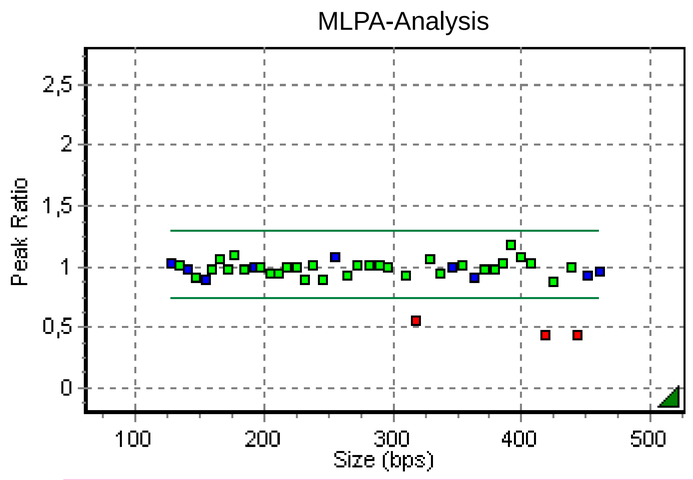

Fig. 3: known heterozygos ~47,5 kb deletion in the 3‘-flanking region of the SHOX gene found in the mother and the older child

Conclusion

- Short stature can be caused by different SHOX gene mutations and there is no established correlation between the severity of phenotype and the underlying pathogenic variant.
- The penetrance of SHOX deficiency is high, and it’s clinical expression highly variable, even in the same family.
- Phenotypic characteristics become more pronounced with age and are more severe in females.
- All the more it was a surprise to find two different *SHOX* gene variants in two short siblings.

References:
Benito-Sanz S. et al; J Med Genet 2012;49:442-450, Binder G: Short stature due to SHOX deficiency: genotype, phenotype, and therapy. Horm Res Paediatr 2011;75:81-89.