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Two duplications within PAR1 in a family with idiopathic short stature

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The authors have nothing to disclose

BACKGROUND

SHOX deficiency is a frequent cause of short stature. The short stature homeobox-containing gene (*SHOX*) resides in the telomeric PAR1 region on the short arm of both sex chromosomes and escapes X inactivation (Fig. 1). SHOX is a nuclear protein that binds to DNA and acts as a transcriptional activator. In the growth plate, hypertrophic chondrocytes express *SHOX* where it seems to have antiproliferative potency. The penetrance of SHOX deficiency is high, but its clinical expression is very variable becoming more pronounced with age and being more severe in female. Growth failure starts early during the first years of life and the height deficit present at preschool age seems not to deteriorate further. The mean adult height is –2.2 SDS.

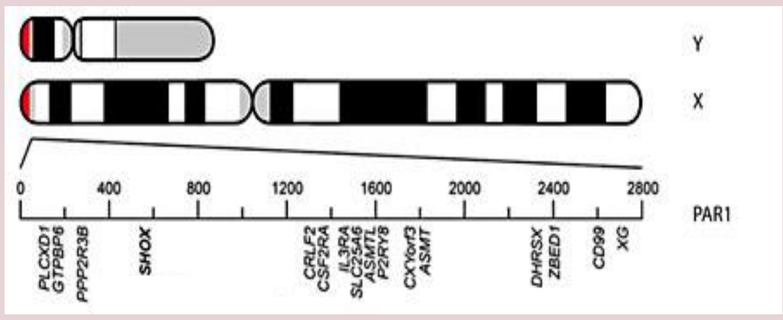


Figure 1.: *SHOX* gene resides in the telomeric PAR1 region on the short arm of both sex chromosomes (Binder G. 2011. Horm Res Paediatr; 75:81–89).

Auxological analysis of the body proportions (mesomelia), the presence of minor abnormalities, and the search for subtle radiographic signs are important keys to the diagnosis which has to be confirmed by genetic analysis. The growth-promoting effect of GH therapy approved for individuals with *SHOX* mutations seems to be equal to the effect seen in Turner syndrome (Binder G. 2011. Horm Res Paediatr; 75:81–89).

SHOX **mutations** and PAR1 **deletions** encompassing *SHOX* or its upstream/downstream enhancers have been identified in ~60% of Léri-Weill dyschondrosteosis (LWD) and ~5–15% of idiopathic short stature (ISS) patients (Rappold. *et al* 2007. J Med Genet; 44:306–313).

Recently SHOX **duplications** have been described in LWD (7.3%)/ISS (1.0%) individuals (Benito-Sanz S. *et al.* 2011. J Clin Endocrinol Metab; 96:404–412).

CASE OBSERVATION

The boy was born full-term, BW 3200 g, BL 47 cm (-2.0 SD).
His father and paternal mother have short stature (final height −3.2 SD; −4.6 SD respectively); Fig. 2.
At the first endocrine investigation of proband for short stature at 11 years, his height was 128.5 cm (−2.9 SD), Tanner was P2, testes 5/5 ml, bone age slightly advanced up to 12.6 years (TW3-RUS).
Neither proband nor family members have Madelung deformity, other skeletal deformities or mesomelic disproportion of the extremities.
The basic laboratory work up in proband was normal: chronic inflammation, thyroid disease, celiac disease was excluded, IGF1 was normal (241 µg/L; −0.57 SD).

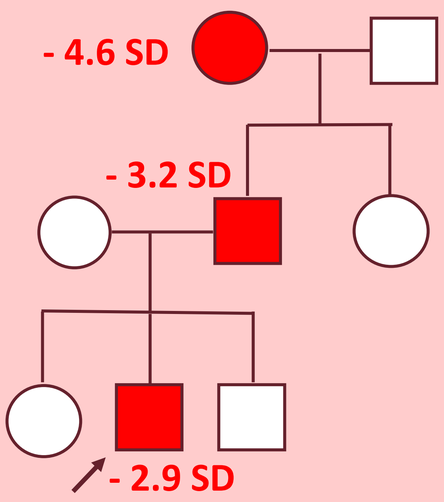


Figure 2.: Pedigree of affected family.

GENETIC TESTING

Method: We performed FISH; MLPA and array-CGH in proband and his father.

Results: Both of them carry **two novel duplications within the PAR1 region** (Fig. 3.).
First large duplication of 267 kbp reaches the Y subtelomere.
The second duplication, potentially pathogenic, is consisting of 58 kbp is located upstream from *SHOX* gene in the region of gene transcription regulatory elements.

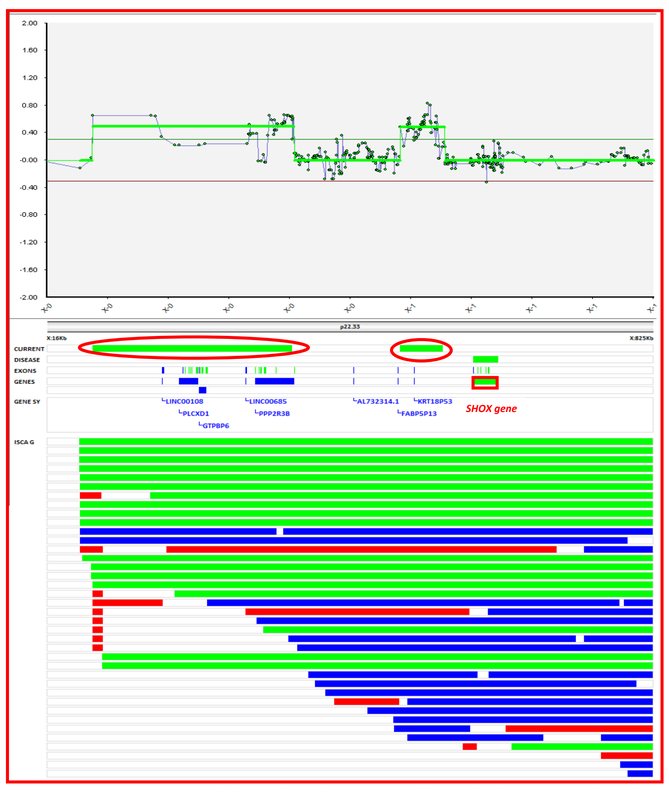
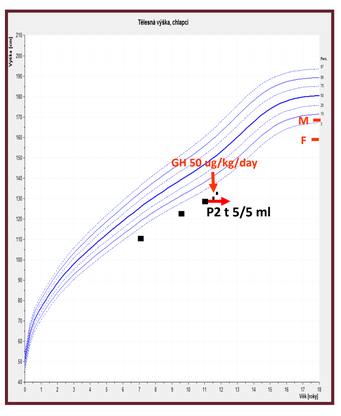


Figure 3.: array-CGH of the proband: position of two duplications within the PAR region located upstream from *SHOX* gene are displayed as ellipsoids.



THERAPY AND FOLLOW UP

Following these findings in proband we started GH administration in dose 50 µg/kg per day at age 11.5 years.

The growth velocity accelerated up to 10 cm/year (Fig 4.).

Figure 4.: Growth chart of the proband: axis x displays age in years; axis y height in centimetres. Percentiles are performed for Czech standards.

CONCLUSION

In conclusion, we have identified the first PAR1 duplication encompassing the upstream *SHOX* transcription regulatory elements in a family with ISS.
The loss of these elements may result in *SHOX* haploinsufficiency because of decreased *SHOX* transcription.

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