Two duplications within PAR1 in a family with idiopathic short stature

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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, hypothyropic 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 SD.

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).

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.

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.).

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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