SHOX mutation spectrum in an unbiased cohort of 585 patients referred for Leri-Weill dyschondrosteosis or idiopathic short stature

Alberta Belinchón (1,2), Sara Benito-Sanz (1,2), Carolina de la Torre (1), Ana Coral Barreda-Bonis (2,3), Isabel González-Casado (2,3), Karen E. Heath (1,2)

(1) Institute of Medical and Molecular Genetics (INGEMM), Hospital Universitario La Paz, Universidad Autónoma de Madrid (UAM), IdiPAZ and CIBERER, ISCIII, Madrid, Spain, (2) Skeletal Dysplasia Multidisciplinary Unit (UMDE), Hospital Universitario La Paz, UAM, IdiPAZ, (3) Dept. of Pediatric Endocrinology, Hospital Universitario La Paz, UAM, Madrid, Spain.

Disclosure statement: This work was partially sponsored by a research grant from Eli Lilly, Spain.

Background

- SHOX encodes a transcription factor implicated in skeletal development.
- Approximately 70% of Leri-Weill dyschondrosteosis (LWD) and 2.5% of idiopathic short stature (ISS) patients have a defect in SHOX or its regulatory regions.

Aims

1) To perform SHOX mutation screening in a cohort of 585 patients (562 probands, 23 family members), referred during the last 16 months, with a clinical suspicion of LWD or ISS.
2) To determine the SHOX mutation spectrum in this unbiased cohort.

Methods

- Mutation screening of SHOX and its regulatory regions was performed by MLPA, HRM and Sanger sequencing.

Results

- Molecular defects in SHOX or its enhancers were identified in 75 probands (13%), 65 referred for LWD & 10 for ISS (Fig 1A & B).
- The most frequent mutation type was deletions of the enhancer regions (36%), and in particular the common ~47.5 kb deletion (24%) (Fig 1C).
- Four novel mutations were identified: three missense (p.G155E, p.W164L, p.V161E) and a single exon deletion (exon 6a).

![Fig 1: Summary of the mutations identified in 585 LWD and ISS patients; (A) Total number of stested amles with/without SHOX/PAR1 alteration; (B) Distribution of probands with an identified alteration, diagnosed as LWD or ISS; (C) Classification of the 75 SHOX/PAR1 alterations.](image)

Interesting cases:

1) We have identified a rare single SHOX exon deletion in a patient with LWD.
2) The identification of a LWD patient homozygote for the ~47.5 kb SHOX downstream enhancer deletion, shows the variable expressivity of some SHOX alterations.
3) Two possible pathogenic SHOX variants were identified in one family but cosegregation analysis permitted the identification of the pathogenic mutation (Fig 2).

![Fig 2: Cosegregation analysis of the two possibly pathogenic variants in a family with LWD. SHOX genotypes are indicated below each family member. The pathogenic alteration is shown in red and the non-pathogenic alteration in grey.](image)

Conclusions

- SHOX or PAR1 mutations were identified in 13% of the cohort (87% of which were referred for LWD and 13% ISS).
- Enhancer deletions are the most common SHOX/PAR1 alteration in our cohort.
- We recommend offering NPR2 genetic testing for disproportionate short stature cases where a defect in SHOX has not been identified, as recent studies have shown that 3.5% of these patients have mutations in this gene (Hisado-Oliva A. et al., 2015; J Clin Endocrinol Metab 100(8):E1133-42).