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

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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).**

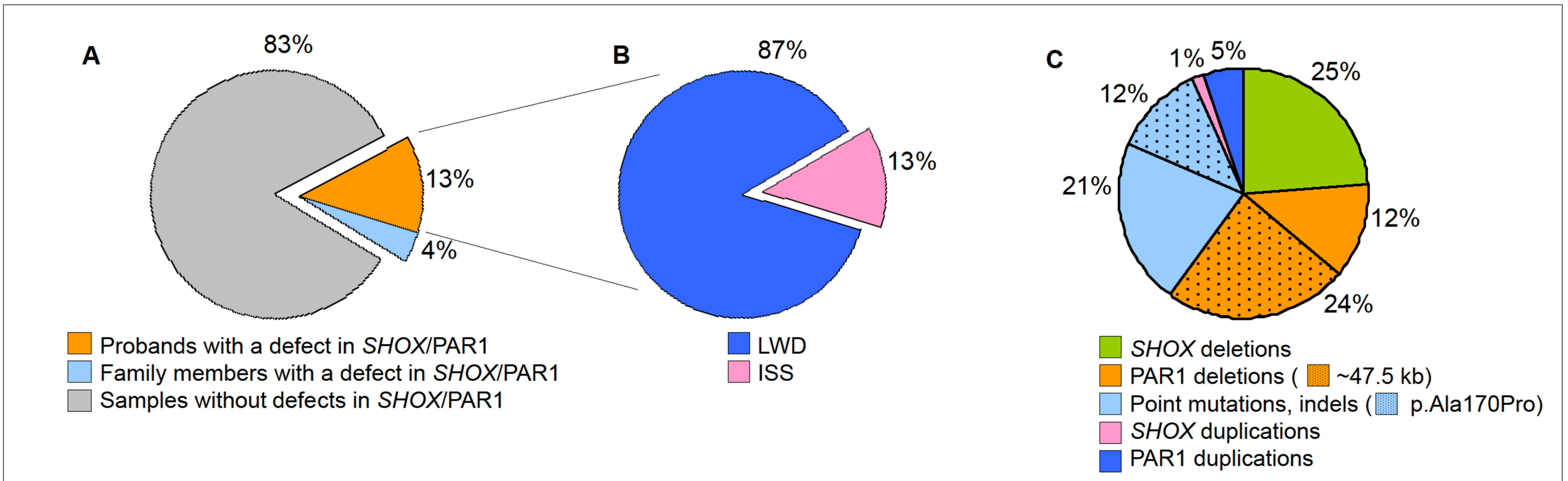

Fig 1: Summary of the mutations identified in 585 LWD and ISS patients; (A) Total number of stested amples with/without *SHOX*/PAR1 alteration; (B) Distribution of probands with an identified alteration, diagnosed as LWD or ISS; (C) Classification of the 75 *SHOX*/PAR1 alterations.

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).**

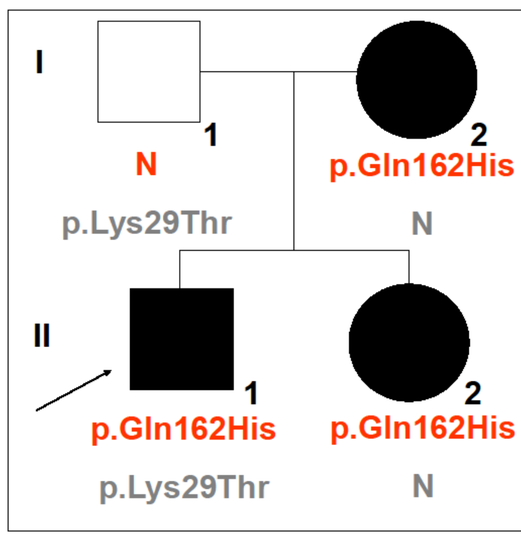

Fig 2: Cosegregation analysis of the two possibly pathogenic variants in a family with LWD. *SHOX* genotypes are indicated below each family member. The pathogenic alteration is shown in red and the non-pathogenic alteration in grey.

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 recommed 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).**

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