Sitting height/Height ratio: An indicator for genetic study of the SHOX gene in children with disharmonic short stature.

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INTRODUCTION

•Gene *SHOX* defect are the most prevalent cause of genetic short stature.

•Gene *SHOX* haploinsufficiency due to deletions or mutations in heterozygosis causes a wide spectrum of phenotypes ranging from very severe disharmonic short stature (S. Léri-Weil, S. Turner) to very mild forms with the appearance of idiopathic short stature (IST) of difficult clinical recognition.

•Auxological study directed at evaluating body disproportions such as the sitting height/height (SH/H) ratio in patients with IST has been postulated as useful for orienting the study of the *SHOX* gene.

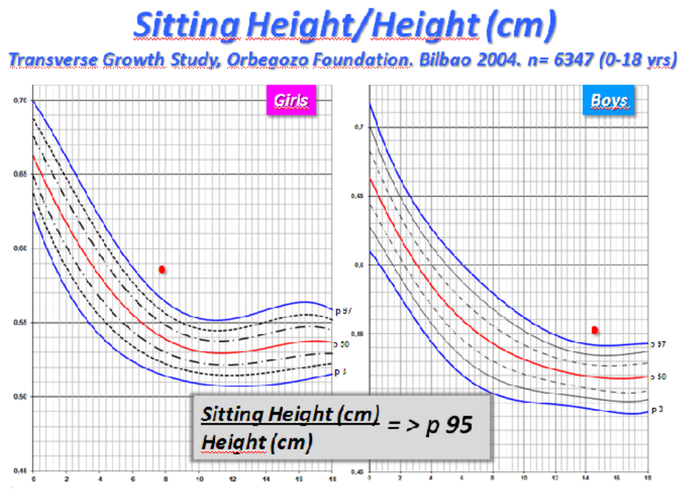
AIMS

• To establish the prevalence of *SHOX* gene defects in children with disharmonic short stature evaluated by the (SH/H) ratio regardless of the presence of dysmorphic features and radiological anomalies.

PATIENTS & METHODS

• Prospective study of 37 consecutive patients with height < -2 SD and (SH/H) ratio > +2SD.
• All patients initially underwent Genetic Study using:
-MPLA (P018, MRC Holland) or CGH array (Desing ISCA 8x60, Agilent).
-Sequencing of all exons of the SHOX gene and flanking intronic regions was carried out in patients without SHOX gene deletion or its regulating regions.

•Normal Growth Reference Patterns:
- Height (Spanish Growth Study 2010).
- Sitting Height/Height (Orbegozo F. Cross-sectional Study. Bilbao 2001) An Esp Ped 2002,56: suppl. 4, 141.



RESULTS

SHOX GENE DEFECTS IN CHILDREN WITH DISHARMONIC SHORT STATURE

	n = 11	Age (x ± SD)	Height (x ± SD)	X-ray	Disharmonic Familial Height
SHOX Gene defects	8 (6 M, 2 V) 2 Complete deletion 2 Complex reorganisation of regulating region. 1 Regulating region deletion 1 Partial deletion 1 Duplication 0.56 Mb 1 Mutation in exon 5 (p.Ala267dup)	9.9 ± 3.3	-2.7 ± 0.9	n= 6 -Madelung deformity	6/8
Turner syndrome	3 46 XX(65%), 45 XO 46 X, +mar1 45 XO	9.3 ± 3.3	-3.0 ± 0.9	n=2 -5º MT short -4º MT short -Madelung deformity	0/3

PATIENTS WITHOUT SHOX GENE DEFECTS IN CHILDREN WITH DISHARMONIC SHORT STATURE

	n = 26	Age (x ± SD)	Height (x ± SD)	X-ray	Disharmonic Familial Height
Disharmonic	24 (14 M, 10 V) 1 PseudoHPT Phenotype	10.2 ± 1.1	-2.5 ± 1.1	•5 Not done •7 Normal •7 Radial incurvation and/or short metacarpus •4 Madelung def	•Yes - 8 •No - 8 •Not done - 9
Harmonic	2 (1 M, 1 V)	9.3 ± 3.3	-2.7 ± 0.1	1 Radial incurvation and disalignment	2/2

FREQUENCY GEN SHOX DEFECTS (n= 11): 29.7%

CONCLUSIONS

1. The frequency of SHOX gene defects in our cohort with disharmonic IST evaluated by the (SH/H) ratio was 29.7%.
2. The (SH/H) ratio is a highly useful parameter for identifying patients with disharmonic IST and orienting SHOX gene study.
3. A significant proportion of patients with disharmonic IST remain undiagnosed, which renders this an open field for clinical research.

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