

HAPLOINSUFFICIENCY OF THE SHOX GENE ASSOCIATED WITH MOSAICISM 45,X/46,XY WITH CHROMOSOME Y RING AS CAUSES OF DELAYED GROWTH AND PUBERTY



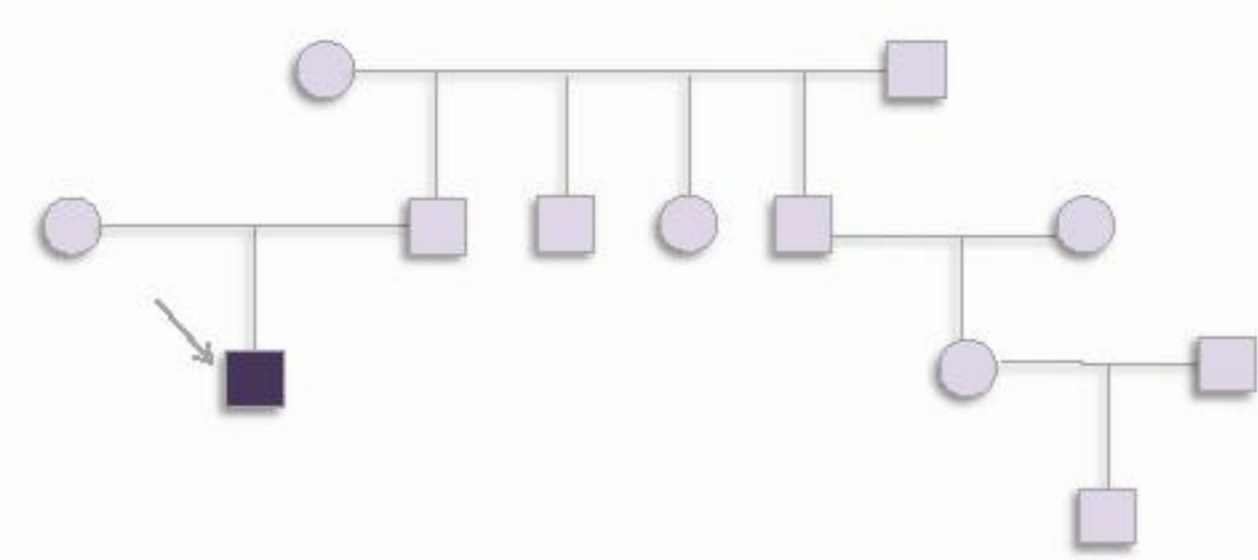
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INTRODUCTION: The height growth is regulated by multiple factors, including specific genetic mutations that ensure correct differentiation and proliferation of chondrocytes, as the example of the hGH-IGF1 axis and the SHOX gene, located on pseudoautosomal region 1 of the sex chromosomes (Xp22.3, Yp11.3). The presence of karyotype in mosaic 45X / 46XY may also require delay height growth, in addition to intrinsic gonadal failure. We present a case of double association of haploinsufficiency of the SHOX gene with a mosaic 45,X/46,X,r(Y) karyotype responsible for growth and pubertal delay.

CLINICAL REPORT:

- Male, 19 years old
- **Personal history:** constitutional delay of growth (below the 5th percentile) and pubertal delay.



Paternal height= 159 cm
 Maternal height =160 cm
 Target height:166 ± 8 cm

12 years old SDS -2,925

ENDOCRINOLOGY, DIABETES AND METABOLISM DEPARTMENT

Objective examination (OE): Height = 1,28m, Weight = 28Kg; Testis volume: 8mL (bilateral)

Analyte	Result	Reference
FSH (mUI/mL)	1,5	-
LH (mUI/mL)	0,5	-
Prolactin (ng/mL)	6,7	<18,0
TSH (mUI/mL)	1,8	0,4-4,0
T4L (ng/mL)	1,3	0,8-1,9
Cortisol (µg/dL)	5,1	5-25
GH (ng/mL)	0,08	<4
IGF-1 (ng/mL)	207	183-996
Total Testosterone (ng/mL)	0,2	2,7-11
DHEA-SO4 (µg/dL)	0,6	0,8-5,6
Androstenedione	0,3	0,6-3,7
Antibodies anti-gliadin IgA and IgG	Negative	

Priming: Testoviron depot® 62,5mg/month (1 cycle)

GH stimulation test (Clonidine)

Analyte	Result
HGH -15' (ng/mL)	2,8
HGH (ng/mL)	20
HGH 15' (ng/mL)	23
HGH 30' (ng/mL)	24
HGH 45' (ng/mL)	27
HGH 60' (ng/mL)	25
HGH 90' (ng/mL)	18
HGH 120' (ng/mL)	11

LH/RH Stimulation Test

Parâmetros	Resultado
LH (mUI/mL)	0,5
LH 20MIN (mUI/mL)	6,2
LH 60MIN (mUI/mL)	8,6
FSH (mUI/mL)	1,5
FSH 20MIN (mUI/mL)	2,3
FSH 60MIN (mUI/mL)	3,6

Bone age X-ray
 "The bone age corresponds to chronological age between 10 and 11 years"

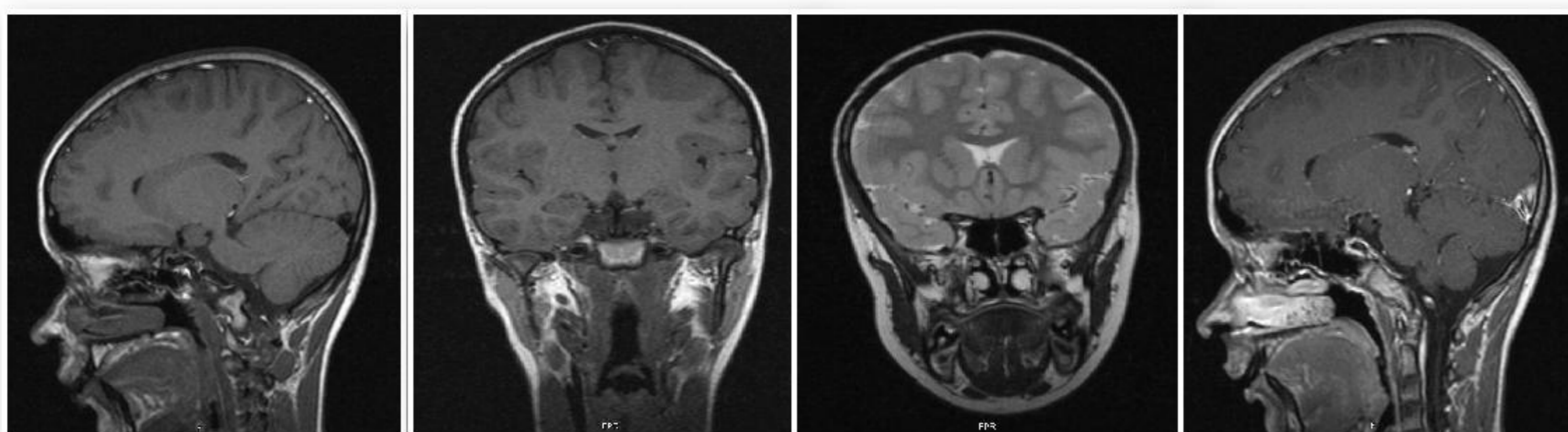
Greulich-Pyle Method

Abdominal and scrotal ultrasound

"Abdominal exam without changes. Well positioned testis of normal morphology, measuring the right testicle 2,9x11x0,9cm and left 2.2x1.4x0.9cm."

Magnetic resonance imaging (MRI) scan - pituitary gland

"No changes in morphology, size and signal intensity of the pituitary gland."



13 years and 4 months SDS -2,686

OE: Height = 1,37 m, Weight = 33Kg; Testis volume: 9mL (bilateral)

Analyte	Result	Reference
HGH (ng/mL)	0,1	<4
IGF-1 (ng/mL)	339	183-996
Total Testosterone (ng/mL)	2,6	2,7-11

Bone age X-ray
 "The bone age corresponds to 13 years"

Testoviron depot® 62,5mg/mês (2 ciclos of 4months)

15 years and 8 months SDS -2,397

OE: Height = 1,50 m, Weight = 39,2 Kg; Testis volume: 12mL

Analyte	Result	Reference
HGH (ng/mL)	0,5	<4
IGF-1 (ng/mL)	348	183-996
Testosterona total (ng/mL)	4,2	2,7-11

Bone age X-ray
 "A idade óssea corresponde a 14 anos e 7 meses, traduzindo maturação esquelética de 85,1%"

16 years and 5 months SDS -2,591

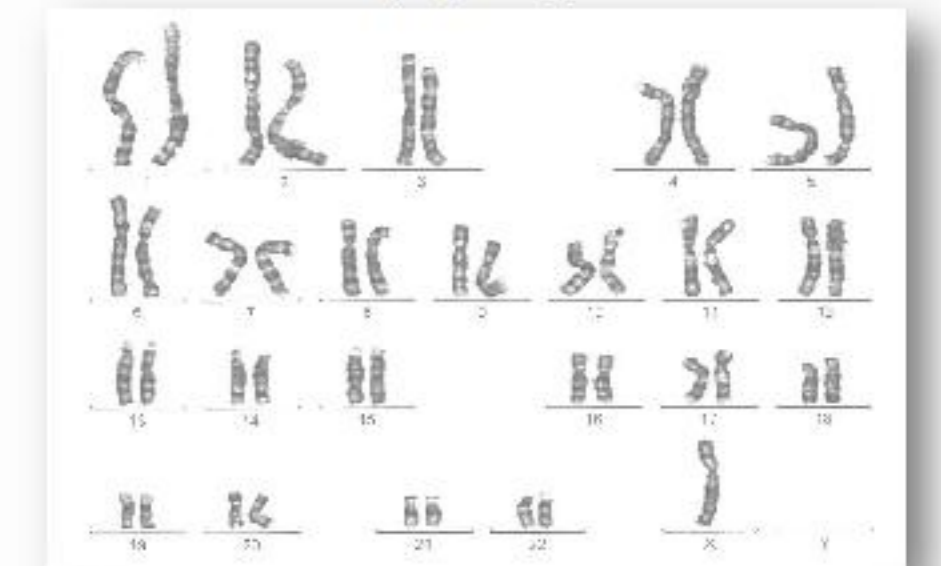
OE: Height = 1,54 m, Weight = 41 Kg; Testis volume: 15mL

17 years and 6 months SDS -2,591

OE: Height = 1,55 m, Weight = 49,6 Kg

Analyte	Result	Reference
FSH (mUI/mL)	2,8	-
LH (mUI/mL)	7,1	-
Prolactin (ng/mL)	4,5	<18,0
TSH (mUI/mL)	1,1	0,4-4,0
T4L (ng/mL)	1,4	0,8-1,9
Cortisol (µg/dL)	11	5-25
GH (ng/mL)	0,08	<4
IGF-1 (ng/mL)	464	183-996
Total Testosterone (ng/mL)	5,1	2,7-11
DHEA-SO4 (µg/dL)	2,0	0,8-5,6
Androstenedione (ng/mL)	1,6	0,6-3,7
17-OHP (ng/mL)	2,5	0,6-3,4

Karyotype study
 45,X/46,XY



FISH analysis
 Aneuploid line for the Y chromosome (45,X) without SRY gene

Transthoracic echocardiogram

"Cardiac cavities and big vessels with normal dimensions. LVEF = 60%. Valve structures without organ involvement"

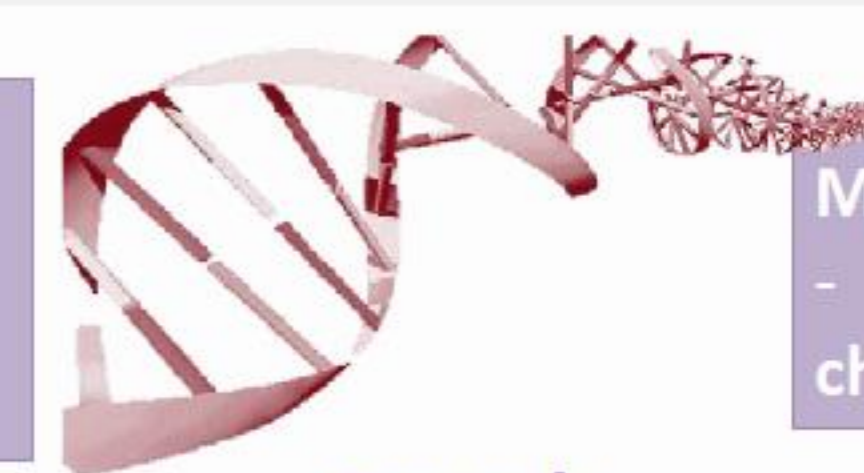
18 years and 7 months SDS -2,838

OE: Height = 1,558 m, Weight = 49,1 Kg

Karyotype study with extended banding

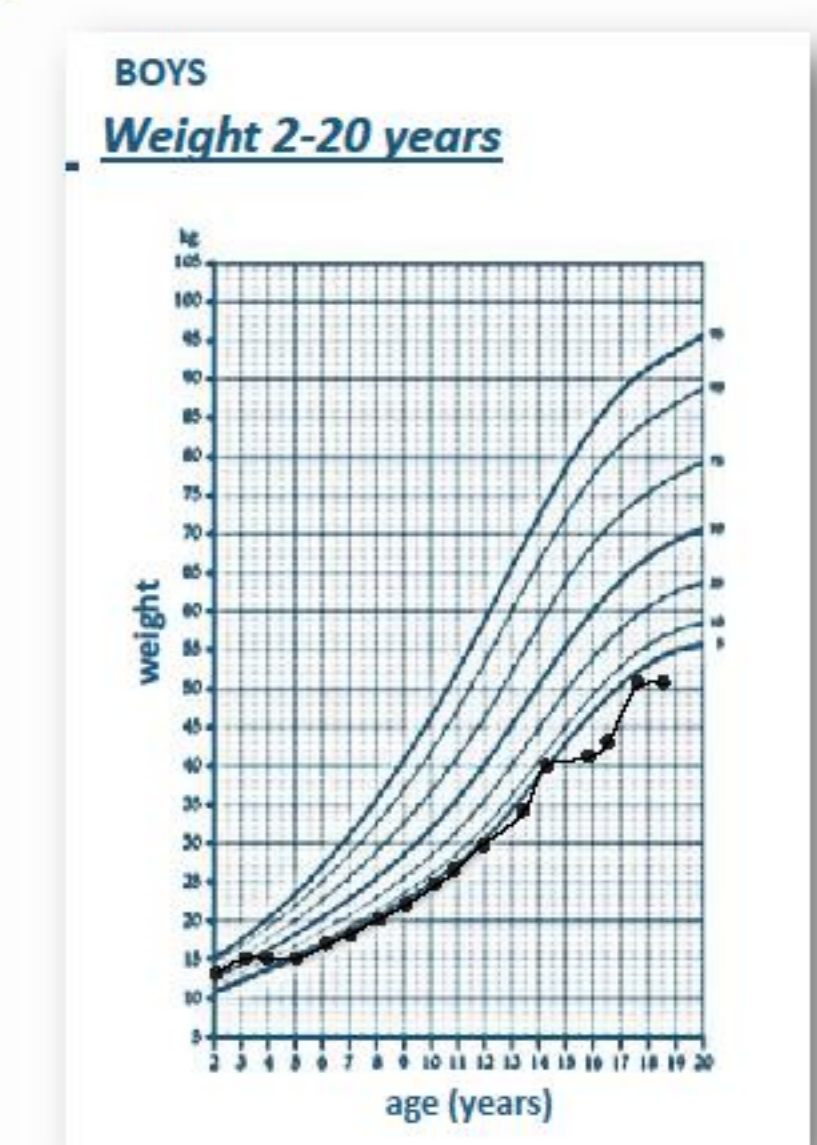
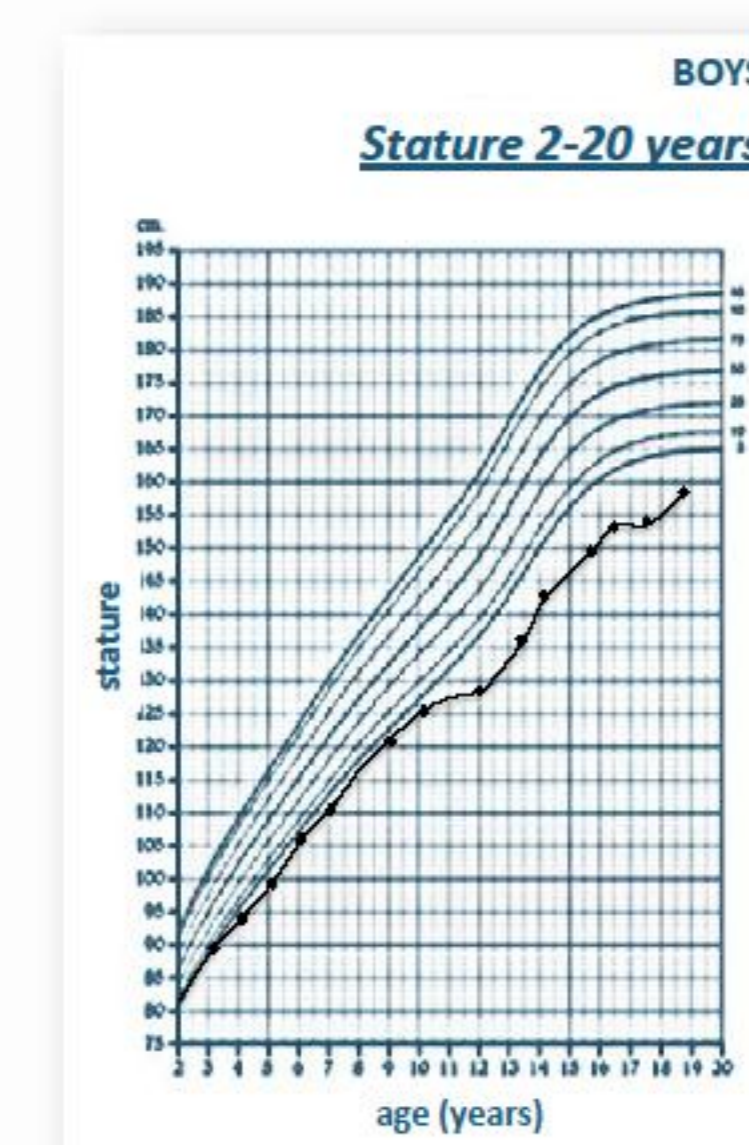
- TWO CELL LINES:
 - aneuploid line for the Y chromosome (45,X) without SRY gene (60%)
 - line with a ring Y chromosome (46,X,r(Y)) without the SHOX gene and the presence of SRY (40%)

FISH analysis
 - 45,X: without SRY gene
 - 46,X,r(Y): without SHOX gene, with SRY



MLPA analysis
 - 45,X/46,X,r(Y) chromosome mosaicism

Growth charts



CONCLUSIONS: This case highlights the importance of accurate diagnosis of sex chromosome abnormalities and mutations of the SHOX gene to establish a diagnostic strategy and appropriate therapy in patients with constitutional delay of growth and puberty. We also advise for the need of regular monitoring, because of the potentially associated complications.

BIBLIOGRAPHY: Binder G. et al. Short stature due to SHOX Deficiency: Genotype, Phenotype, and Therapy, Horm Res Paediatr 2011; 75:81-89; Rey G. et al. El gen Shox y el crecimiento corporal: descripción, estructura y nuevas técnicas de diagnóstico, Journal of Basic & Applied Genetics 2010, Volume 21, Issue 2, Article 4; Teng Yen-Ni et al. A simplified gene-specific screen for Y chromosome deletions in infertile men, Fertility and Sterility, 1291:1300, Vol.87, No.6, June 2007; Lawrence L., Phenotypic spectrum of 45,X/46,XY males with a ring Y chromosome and bilaterally descended testes, Fertility and Sterility 791:797, Vol. 91, No. 3, March 2009; Alexander J. et al., Baixa estatura por Haploinsuficiência do gene SHOX: do diagnóstico ao tratamento, Arq Bras Endocrinol Metab, 765:773, 2008, 52/5

