

SHOX Deficiency in Argentinean Cohort: Long-Term Auxological Follow-Up and a Family's New Mutation

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Abstract

A cohort study on the growth of 19 Argentinean children, aged 0 to 18 years, and 11 of their first-degree relatives with alterations in the *SHOX* gene or its regulatory regions is reported. Children are born shorter and experience a growth delay during childhood with a stunted pubertal growth spurt. Body disproportion, with a sitting height/height ratio above +2 standard deviation score (SDS), was already present as early as 2 years old. Hand length was normal. Shortening of the radius, with a length below –1.9 SDS, was the earliest and most frequent radiological sign detected as early as 45 days old. We found a previously unreported mutation in a family with a highly variable phenotype, the boy had a severe phenotype with a milder presentation in other affected members of the family. We conclude that body disproportion and a shorter radius length on X-ray are useful tools for selecting children to undergo *SHOX* molecular studies.

Keywords

- ▶ *SHOX* gene
- ▶ Leri–Weill dyschondrosteosis
- ▶ body disproportion

Introduction

SHOX (short stature homeobox-containing gene) haploinsufficiency may result in the skeletal dysplasia, Leri–Weill dyschondrosteosis (LWD),^{1,2} characterized by disproportionate short stature due to mesomelic limb shortening and Madelung deformity (the bowing and shortening of the radius, distal dislocation of the ulna, and a pyramidal configuration of the carpal bones). Other physical features may include a high-arched palate, cubitus valgus, short fourth metacarpal, micrognathia, and muscular hypertrophy.^{3,4}

The penetrance of *SHOX* haploinsufficiency is high, but its clinical expression is variable. The clinical and radiological features become more pronounced with increasing age and are often more severe in females.^{5–8} Short stature and features of LWD in Turner syndrome are secondary to *SHOX* haploinsufficiency and there are some studies describing longitudinal growth in Turner syndrome.^{9,10} However, there is limited information regarding longitudinal growth of children with isolated LWD.^{4–10}

LWD patients have been reported to have a mildly reduced birth length, which, paired with growth retardation during infancy and childhood, results in short stature.¹¹ The pubertal growth spurt also seems to be stunted, resulting in an additional height deficit during adolescence.¹¹

Here, we report the results of an observational and retrospective cohort study on the longitudinal growth of 19

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Argentinean children with molecularly confirmed alterations in *SHOX* or its regulatory regions. Data include anthropometric and X-ray follow-up. We also report this data in 11 first-degree relatives.

Patients and Methods

Patients

All children, aged 0 to 18 years, included in this study, were patients between 1992 and 2017 at the multidisciplinary growth clinic in the Department of Growth and Development in the Hospital Garrahan, Buenos Aires, Argentina, the main tertiary public pediatric hospital in Argentina, where children with skeletal dysplasias are referred to.

Testing for alterations in *SHOX* or its regulatory regions was performed in children if they fulfilled two or more of the following criteria:

- (1) Short stature, defined as height < 2 standard deviation score (SDS) below the mean for age and sex for Argentinean references¹² or < 2 SDS for target height without any other identified etiology to explain it and/or a family history of short stature.
- (2) Arm span < 2 SDS below the mean for age and sex using Turkish references.¹³
- (3) Body disproportion, defined as: (i) Sitting height/height ratio (SH/H) > 2 SDS for age and sex compared with the Argentinean references,¹⁴ and/or (ii) extremities-trunk ratio (calculated by the sum of the arm span and subischial leg length divided by the sitting height) for height ratio < 1 SDS below the mean.⁷
- (4) Clinical signs of mesomelic shortening of the forearms, lower limbs, or Madelung deformity.

Exclusion criteria for this study included: (1) presence of any other chronic disease or comorbidities that could affect growth, and (2) patients who had received growth hormone treatment. Group 1 consisted of 19 children who complied with these clinical criteria and were found to have an alteration of *SHOX* or its regulatory regions. Group 2 consisted of the cross-sectional data from 11 adults, who were first-degree relatives of the selected children and who had the familial *SHOX* alteration.

Methods

All patients, parents, or guardians gave their written informed consent to participate in the study. The following information was collected for each patient:

Anthropometric measurements: Birth weight, birth length, and head circumference were obtained from information registered on perinatal forms provided by the parents.

Height, weight, head circumference, arm span, total hand length, and sitting height were measured during each clinical follow-up. All patient measurements were initially taken and followed up by the same trained observer during the entire study period (1992–2017), with standardized anthropometric techniques.¹⁵

Height, sitting height, and hand length were measured with Harpenden instruments; head circumference was mea-

sured with a nonstretchable, plastic tape measure; arm span with a rule with 1 mm divisions; and weight with bean balance scales. Mean intraobserver technical error of measurement for height, weight, head circumference, and arm span were 0.10 cm, 0.10 kg, 0.10 cm, and 0.66 cm, respectively. Weight/height² (body mass index), SH/H, extremities-trunk, and head circumference/height (HC/H) ratios were calculated as previously described.^{7,14,16}

Individual growth curves of height, SH/H, and HC/H for age were plotted on national references graphs.^{12,14,16}

Height, SH/H, and HC/H for age and sex SDS scores were estimated from local data references.^{12,14,16}

Arm span and hand length for age was transformed into SDS based on Turkish and U.S. references, respectively.^{13,17}

Pubertal development: Genital development in boys (G) was scored visually on the Tanner scale and by palpation of testicular volume by Prader orchidometer. Testicular volume > 3 mL was considered pubertal onset.^{18,19} Breast development in girls (B) was scored both visually and by palpation to detect the budding in stage 2 and to discriminate mammary gland tissue from fat tissue.^{18,20}

X-rays: Bilateral anterior-posterior hand and forearm X-rays were analyzed according to X-ray signs of wrist dysplasia described by Binder et al.⁷

Measurements of the maximum length of the radius were made to the nearest 0.1 cm, along its longitudinal axis. The majority of the measurements were digitally performed but a few were manually measured using a millimeter ruler, again to the nearest 0.1 cm. Radius length SDS scores, for age and sex, were estimated based on Gindhart's references.²¹

Molecular analysis: Genetic analysis included the analysis of deletions or duplications of *SHOX* and its regulatory regions using the MLPA P018G1 kit according to the manufacturer's instructions (MRC Holland, The Netherlands). Subsequently, negative cases were analyzed for mutations within exons 2 to 6 of *SHOXa* (NM_000451.3) using a combination of high-resolution melting and DNA sequencing. Analysis of the coding exons and intron:exon boundaries of the *SHOX* modifier, *CYP26C1* (NM_183374.2), was also performed in all individuals from both groups by Sanger sequencing. Primers and PCR conditions are shown in ► **Table 1**.

Statistical analysis: Results were expressed as mean + standard deviation (SD). SDS was determined using the LMS method^{22,23} with the LMSgrowth Program.²⁴

Results

A total of 19 children from 15 families with *SHOX* deficiency were studied in addition to first-degree relatives in an observation and retrospective study of their longitudinal growth.

Molecular results: Fourteen of 15 families had pseudoautosomal region 1 (PAR1) deletions, 13 including *SHOX* and 1 including only the four downstream regulatory regions (both father and his children, 2 boys) (► **Table 2**). One family had a previously undescribed missense variant in

Table 1 List of the primer sequences, amplicon size, and PCR conditions for the amplification of *CYP261* (NM_183374.2)

Ex	Oligonucleotide (F 5'-3')	Oligonucleotide (R 5'-3')	Size (bp)	Temp (°C)
1	TTTTGCGGACGGAACAGG	CATGGGCATTGAGACTGAGGAG	392	56 ^a
2	GCTGGAAGGTCTGGGTCA	CGGGTTCACAGTGTATCCAAC	400	57 ^a
3	GGAAGTGGCCTCTGGCTAC	GTGCGCCGAGGGCGT	446	62 ^a
4	CACAAGGATGTTGGCAGAGC	AAAGTGGGGCCACACAAGAT	365	60
5	GGCGACTCCACCGCCGAGACT	GGCCATGGGCTGGCAGGCGCACTT	500	65 ^a
6	TCCTCTGGTTTTCGGAAGC	CTACAATGGGGAGCGGCAGA	569	TD ^a

Abbreviations: bp, base pair; DMSO, dimethyl sulfoxide; PCR, polymerase chain reaction; TD, touchdown.

^a5% DMSO added to PCR; PCR starting at an annealing temperature of 65°C for 16 cycles, decreasing 0.5°C each cycle and then 20 cycles at 57°C.

Table 2 List of *SHOX* alterations identified in 15 families

Family (GARR)	MLPA P018 version	Molecular results ^a	<i>SHOX</i> transcription regions included in deletion	<i>SHOX</i> alteration classification
1	F1	Del L10292 - L19677	CNE-5, -3, -2, <i>SHOX</i> , CNE4, 5, ECR1, CNE9	<i>SHOX</i> deletion
2	F1	Del L20651 - L15507	<i>SHOX</i> , CNE4, 5	<i>SHOX</i> deletion
3	F1	Del L20651 - L00712	CNE-5, -3, -2, <i>SHOX</i> , CNE4, 5, ECR1, CNE9 (Extends to ASMT)	<i>SHOX</i> deletion
4	F1	Del L20651 - L20177	<i>SHOX</i> , CNE4, 5	<i>SHOX</i> deletion
5	F1	Del L10292 - L19679	CNE-5, -3, -2, <i>SHOX</i> , CNE4, 5, ECR1, CNE9.	<i>SHOX</i> deletion
6	G1	Del L24430 - L24247	CNE-3, CNE-2, <i>SHOX</i>	<i>SHOX</i> deletion
7	G1	Del L25088 - L24250	CNE-2, <i>SHOX</i> , CNE4, 5, ECR1, CNE9	<i>SHOX</i> deletion
8	G1	Exon 2 variant: c.243A > T (p.Lys81Asn)	-	<i>SHOX</i> mutation
9	G1	Del L10292 - L24245	CNE-5, -3, -2, <i>SHOX</i> , CNE4, 5, ECR1, CNE9	<i>SHOX</i> deletion
10	G1	Del L10292 - L24245	CNE-5, -3, -2, <i>SHOX</i> , CNE4, 5, ECR1, CNE9	<i>SHOX</i> deletion
11	G1	Del L05096 - L15055	CNE4, 5, 9 (Extends to IL3RA)	<i>SHOX</i> enhancer deletion
12	G1	Del L10292 - L24245	CNE-5, -3, -2, <i>SHOX</i> , CNE4, 5, ECR1, CNE9	<i>SHOX</i> deletion
13	G1	Del L20651 - L24247	<i>SHOX</i>	<i>SHOX</i> deletion
14	G1	Del L10292 - L24245	CNE-5, -3, -2, <i>SHOX</i> , CNE4, 5, ECR1, CNE9	<i>SHOX</i> deletion
15	G1	Del L25087 - L24249	CNE-5, -3, -2, <i>SHOX</i> , CNE4, 5, ECR1	<i>SHOX</i> deletion

^aAll variants are in heterozygosity.

exon 2, c.243A > T (p.Lys81Asn). This variant is absent from the gnomAD population database (<http://gnomad.broadinstitute.org/>). It affects a moderately conserved amino acid in the N-terminal of *SHOX*, but the pathogenicity predictors are inconclusive. The variant is present in a mother and her children, a boy and a girl with LWD. According to the American College of Medical Genetics and Genomics variant classification, this variant has been classified as a variant of unknown significance.

We also performed genetic testing of the recently described *SHOX* modifier, *CYP26C1*,²⁵ in all children and adults, but no variant of interest was detected.

Anthropometric Characteristics

Mean birth weights and lengths were 2.950 ± 360 and 3.040 ± 570 g, and 47.7 ± 1.75 and 46.3 ± 1.92 cm for boys and girls, respectively, lower than Argentinean reference data ($p < 0.001$).¹²

The summary of the anthropometric data taken at the patient's first appointment for both children and adults is shown in ► **Table 3**. The median age of children at the first appointment was 4.46 years (range: 0.14–12.07 years) with a median follow-up of 6.67 years (range: 3.13–19.07). All children and adults had arm spans shorter than –2 SDS for age and sex and extremities: trunk ratio < –1 SDS (► **Table 3**).

The height and SH/H growth curves for boys and girls are shown in ► **Figs. 1 and 2**. ► **Fig. 1A and B** show that 5 boys and 2 girls had growth within normal range while all other children were below percentile 3. Mean SDS heights + SD at their last prepubertal appointment were -2.03 ± 1.14 and -2.08 ± 0.81 for boys and girls, respectively. Growth delay was observed during childhood with a mean delta SDS height prepubertal – SDS birth length of -0.98 ± 1.19 . Only 5 of the 19 children had reached adult height, with a mean delta SDS adult height – SDS prepubertal of -0.45 ± 0.93 . Mean adult height was -2.61 ± 1.52 SDS.

Table 3 Clinical and anthropometrics characteristics at first appointment in the pediatric ($n = 19$) and adult ($n = 11$) cohorts with *SHOX* deficiency

Children	Total ($n = 19$), mean \pm SD	Boys ($n = 10$), mean \pm SD	Girls ($n = 9$), mean \pm SD
Age, y	4.46 \pm 3.41	4.46 \pm 2.97	4.48 \pm 3.99
Birth length SDS	-1.45 \pm 0.97	-1.29 \pm 0.96	-1.65 \pm 1.06
Height SDS	-2.16 \pm 1.34	-2.35 \pm 1.34	-1.97 \pm 1.42
Arm span SDS	-3.67 \pm 0.86	-3.48 \pm 0.92	-3.83 \pm 0.83
SH/H SDS	4.32 \pm 3.25	4.63 \pm 4.30	4.02 \pm 1.98
Extremities-trunk ratio ^a below -1 SDS	19/19 (100%)	10/10 (100%)	9/9 (100%)
HC/H ratio SDS	1.53 \pm 0.89	1.05 \pm 1.31 ($n = 9$)	1.76 \pm 0.82
Total hand length SDS	-1.33 \pm 0.77	-1.17 \pm 0.94	-1.50 \pm 0.57
BMI SDS (range)	0.94	+1.12 (-0.57/ +2.95)	+0.75 (-0.63/ +1.87)
X-ray: Radius length SDS	-3.65 \pm 1.77	-3.91 \pm 2.38 ($n = 10$)	-3.36 \pm 0.71 ($n = 8$)
Adults	Total ($n = 11$)	Male ($n = 2$)	Female ($n = 9$)
Height SDS	-2.70 \pm 1.29	-1.68 \pm 0.98	-2.93 \pm 1.28
Arm span SDS	-4.15 \pm 1.07	-3.65 \pm 0.30	-4.27 \pm 1.16
SH/H SDS	3.98 \pm 0.98	4.57 \pm 1.50	3.83 \pm 0.90
Extremities-trunk ratio ^a below -1 SD	13/13 (100%)	2/2 (100%)	9/9 (100%)
HC/H SDS	2.24 \pm 1.1	1.57	2.34 \pm 1.15
Total hand length SDS	-2.21 SD = 1.09	-0.96 ($n = 1$)	-2.39 SD = 1.04
X-ray: Radius length SDS	-4.83 SD = 1.24 ($n = 8$)	-3.67 ($n = 1$)	-5.00 SD = 1.24 ($n = 7$)

Abbreviations: BMI, body mass index; HC/H, head circumference/height; SD, standard deviation; SDS, standard deviation score; SH/H, sitting height/height. ^aBinder G, Ranke MB, Martin DD. Auxology is a valuable instrument for the clinical diagnosis of *SHOX* haploinsufficiency in school-age children with unexplained short stature. *J Clin Endocrinol Metab* 2003;88(10):4891-4896.

Eight of nine women and one of the two adult male first-degree relatives had short stature (plotted at 18 years of age).

► **Fig. 2A** and **B** show that disproportionate growth, an SH/H ratio of above 2 SDS, was detected by the age of 8 years in 18/19 children compared with Argentinean references according to age and sex. Some children presented with body disproportion as early as 2 years old. Median (range) SH/H SDS ratios were 4.53 (0.74/14.18) and 5.24 (1.7/18.63) for the first and last appointments ($p = 0.30$).

Mean prepubertal SH/H SDS ratios were 5.92 \pm 4.14 and 4.89 \pm 1.34 for boys and girls, respectively.

The SH/H of first-degree relatives (adults) were plotted at age 17 and all were disproportionate.

The HC/H curves are shown in ► **Fig. 3**. Although a total of three males and five females had relative macrocephaly, that is, a HC/H ratio greater than +2 SDS, no real macrocephaly (head circumference for age greater than +2 SDS) was observed in children or adults.

X-rays: All children had a radius length below -1.9 SDS for age and sex at first appointment as early as 45 days old (► **Table 3** and ► **Fig. 4**). At mean age of 4.46 years, 4/18 children had lucency of the distal ulnar border of the radius and 5/18 triangularization of the distal radial epiphysis and pyramidalization of the distal carpal row. At the last appointment, at mean age of 10.67 years, 8/18 children had lucency of the distal ulnar border of the radius, 10/18 triangulariza-

tion of the distal radial epiphysis, and 9/18 pyramidalization of the distal carpal row.

In first-degree relative adults ($n = 10$), 100% had a bowing of the distal end of the radius and 70% had triangularization of the distal radial epiphysis. All adults had a radius length below -2.0 SDS. X-ray assessment was not possible in one adult because he had previously undergone wrist surgery.

► **Fig. 4** shows X-rays of the forearms, a highly variable radiological sign we observed within and between families.

Discussion

We performed a detailed longitudinal evaluation of the anthropometric data in 19 Argentinean children with molecularly confirmed *SHOX* alterations and cross-sectional study of 11 of their first-degree relatives with comparisons to Argentine growth references. There are many reports with anthropometric data of patients with *SHOX* haploinsufficiency, but very few do so longitudinally, and they do not compare measurements with local references. Variations in height, arm span, and changes in body proportions evaluated by SH/H ratio were observed.

Children with *SHOX* haploinsufficiency were born shorter (-1.45 SDS) than the Argentinean references, suffering growth retardation during childhood with a mean prepubertal height of -2.05 SDS, similar to that described by others.^{5,7,11}

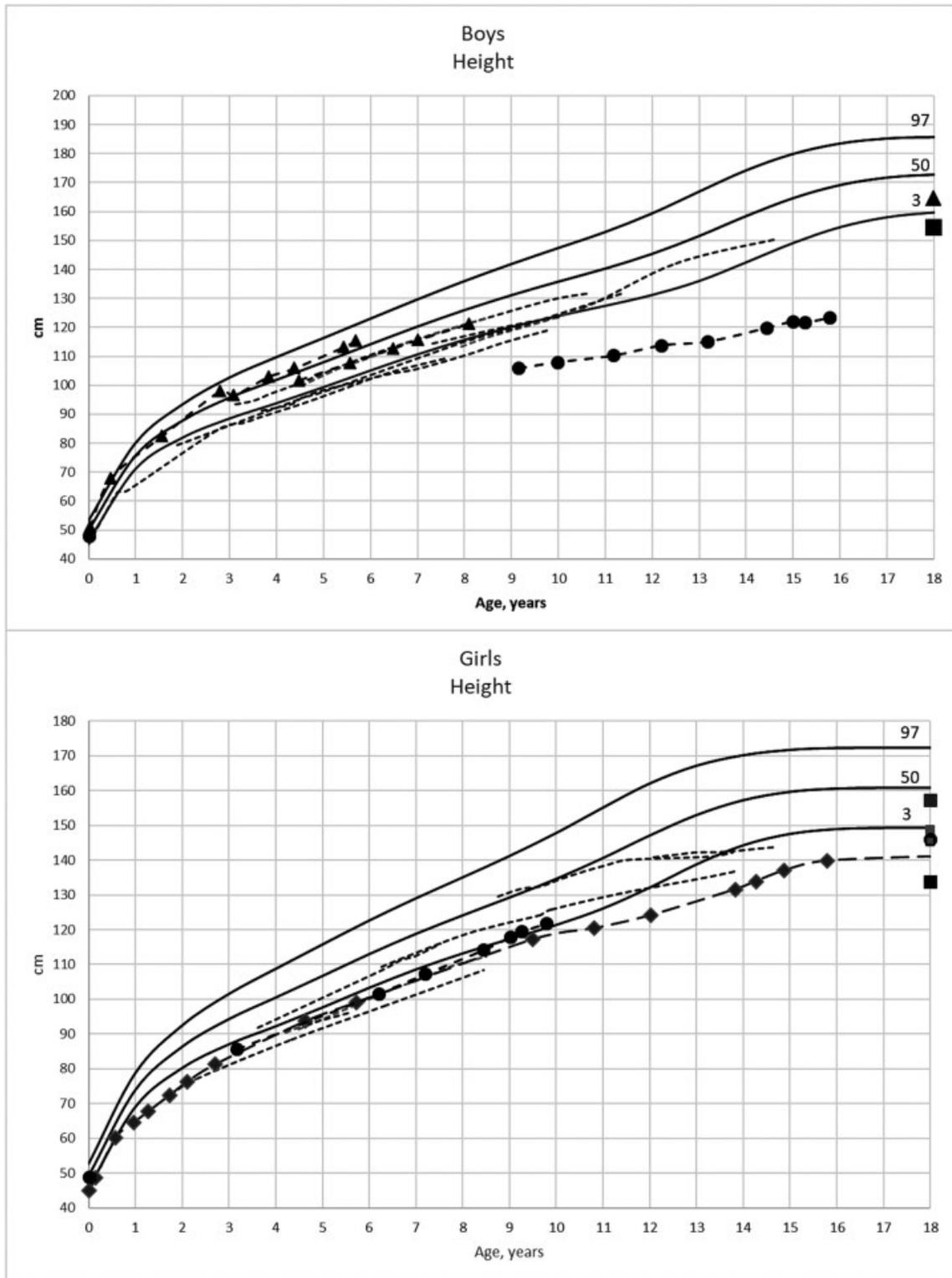


Fig. 1 Height growth curves for all boys and male adults (A) and girls and female adults (B). Members of the family with a previously undescribed missense variant in exon 2, c.243A > T (p. Lys81Asn). The height of the mother was at -2.41 standard deviation score (SDS) and for the girl was at -1.70 SDS, at 9.79 years. The boy had severe growth retardation with a height deficit of -4.43 SDS at 9.15 years and -5.76 SDS at 15.77 years for Argentine references. Members of the family with deletion only in the four downstream regulatory regions of the pseudoautosomal region 1. The father and children (two boys) had normal growth in height. Girl from family 5 with *SHOX* deletion. Birth length 45 cm (-2.36 SDS). Adult height 141.4 cm at -3.17 SDS for Argentine references. Circles: Members of the family with a previously undescribed missense variant in exon 2, c.243A > T (p. Lys81Asn). The height of the mother was at -2.41 SDS and for the girl was at -1.70 SDS, at 9.79 years old. The boy had severe growth retardation with a height deficit of -4.43 SDS at 9.15 years old and -5.76 SDS at 15.77 years old for Argentine references. Triangle: Members of the family with deletion only in the four downstream regulatory regions of the pseudoautosomal region 1. The father and children (two boys) had normal growth in height. Squares: Girl from family 5 with *SHOX* deletion. Birth length 45 cm (-2.36 SDS). Adult height 141.4 cm at -3.17 SDS for Argentine references.

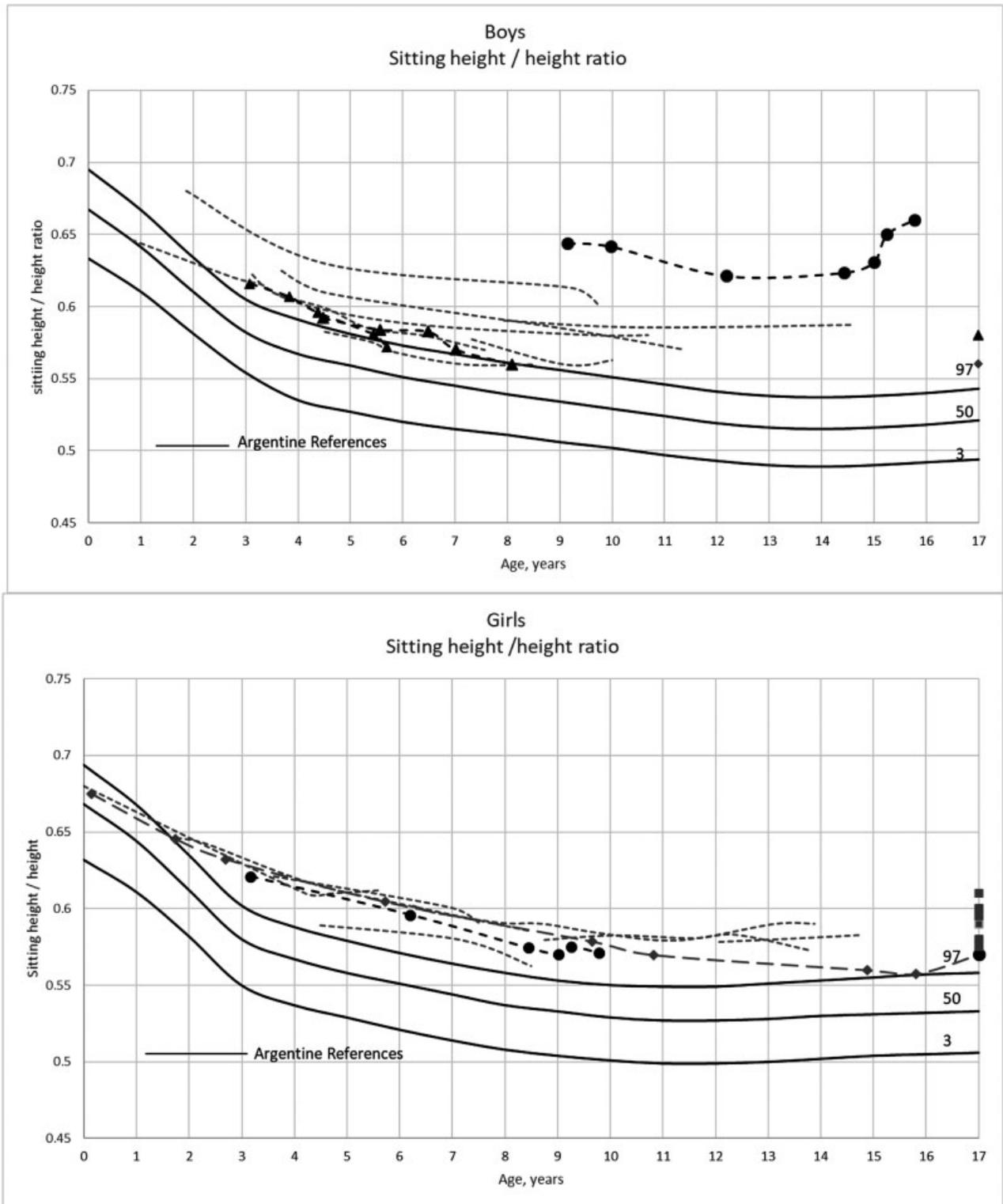


Fig. 2 Sitting height/height growth curves for boys and male adults (A) and girls and female adults (B). Members of the family with a previously undescribed missense variant in exon 2, c.243A > T (p. Lys81Asn). The adult sitting height/height ratio of the mother was +2.96 standard deviation score (SDS) and the sitting height/height ratio of the girl at 9.79 years was +4.22 SDS. The boy had severe body disproportion with a sitting height/height ratio of +14.19 SDS at 9.15 years and +18.63 SDS at 15.77 years for Argentine references. Circles: Members of the family with deletion only in the four downstream regulatory regions of the pseudoautosomal region 1. The father and children (two boys) had body disproportion. The sitting height/height ratio of the father was +3.51 SDS. The sitting/height ratio were +2.23 SDS and +2.21 SDS at 7.01 and 5.43 years for the two boys, respectively. Squares: Girl from family 5 with *SHOX* deletion. At first appointment, 45 days old, her sitting height/height ratio was 0.67, +0.41 SDS. Adult sitting height/height ratio 0.57, +2.79 SDS for Argentine references.

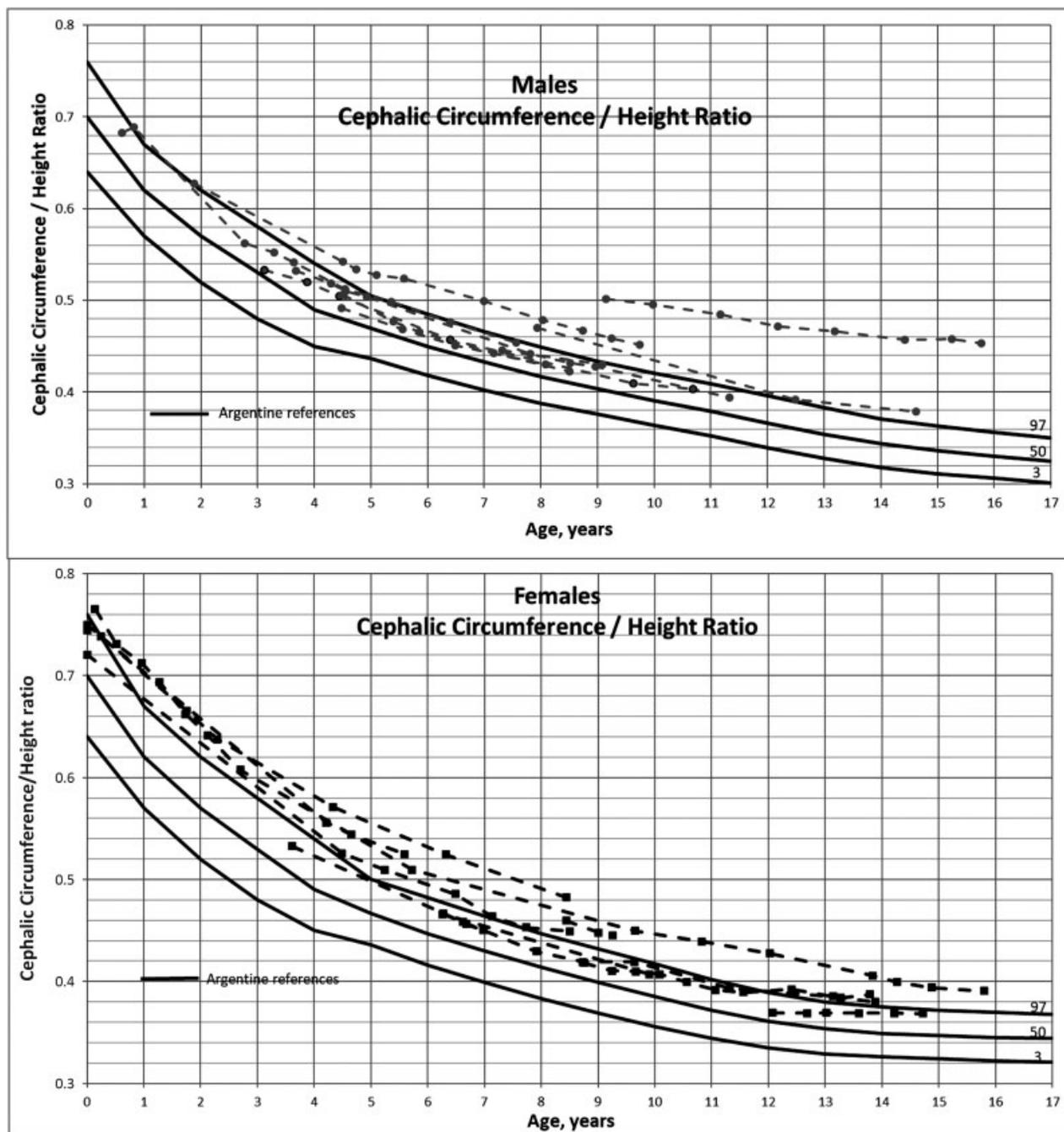


Fig. 3 Growth curves of the head circumference/height ratio in the pediatric cohort: boys (A) and girls (B). Although a total of three males and five females had relative macrocephaly, that is, a head circumference/height ratio greater than +2 standard deviation score (SDS), no real macrocephaly (head circumference for age greater than 2 SDS) was observed in children or adults. Circle: Girls with SHOX deficiency; squares: Boys with SHOX deficiency.

Insufficient data were available to analyze the effect of puberty on the growth of group 1, but height was even shorter after puberty in the five children who reached adult height, with a mean of -2.6 SDS, indicating a stunted pubertal spurt. These results agree with those observed by Binder et al and Fukami et al.^{11,26}

In first-degree relatives of the children, short stature was present in 9/11 adults and females were more affected than males with a similar deficit to that previously reported.

The longitudinal follow-up of body proportions of children compared with local references revealed an SH/H ratio

of above +2 SDS, an indicator of disproportionately short legs, which was already present as early as 2 years old and persisted during follow-up. Body disproportion, assessed as SH/H ratio, in adults was similar, at approximately +4 SDS. Previous reports described an SH/H ratio above +2 SDS in children older than age of 6 years.^{5,7} Body proportion changes with age and is different in different populations,^{27,28} so disproportion may be detected before school age if compared with local references for age and sex.¹⁴

Arm span was reduced for age in all children and adults. We compared our data with Turkish references.¹³ The Turkish

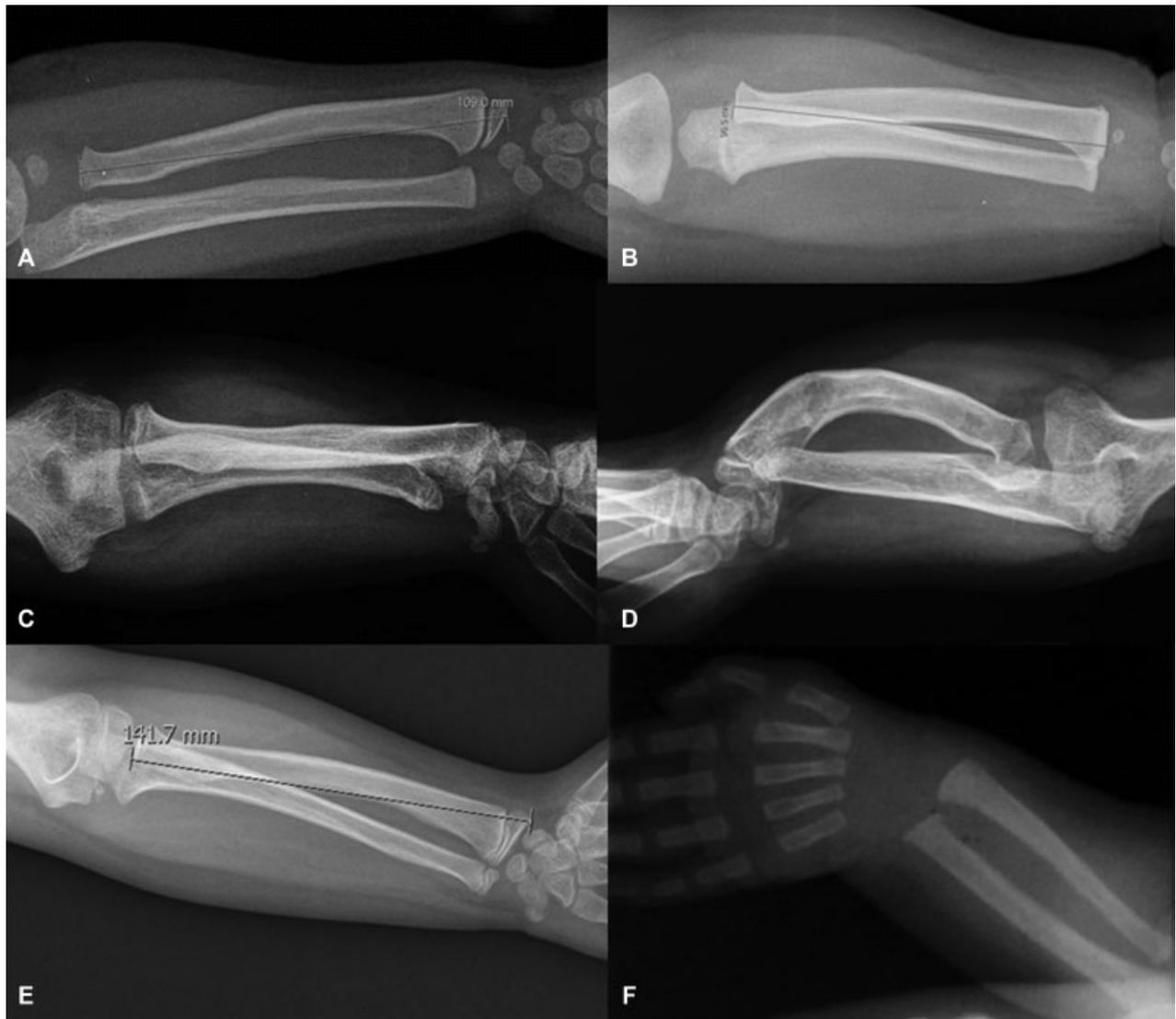


Fig. 4 X-ray of the forearm: Boys (A) and (B) from family with deletion only in the four downstream regulatory regions of the pseudoautosomal region 1. Boy (A) at 4.47 of years, the X-ray radius length was 109.0 mm (-3.43 standard deviation score [SDS]). Boy (B), at 1.83 years, the X-ray radius length was 90.4 mm (-1.93 SDS). Boy (C) and girl (D) from family with undescribed missense variant in exon 2, c.243A > T (p. Lys81Asn). Boy (C), at 12.19 of years had severely compromised radius and ulna more pronounced at the right side. Girl (D), at 8.56 years X-ray radius length was 48 mm (-2.65 SDS). Girl (E), from family 5, with *SHOX* deletion. At 45 days old, X-ray radius length was 48 mm (-2.6 SDS). Boy (C) at 12.19 years old, severe compromised of radius and ulna, more pronounced at the right side.

populations have a mean limb length shorter than that of the Argentinean population, thus it is likely that the SDS of the arm span in our patients would be more compromised if the data were analyzed with local references.^{13,14}

Hand length was slightly reduced in a few patients, but the majority was normal, as expected. Thus, normal hand length is an important clinical sign to help in the differentiation of *SHOX* deficiency disorders from other mild skeletal dysplasias due to mutations in *NPR2*, *ACAN*, *NPPC*, or *IHH*.^{29–33}

We also examined the X-rays of the children to assess the presence of Madelung deformity and other suggestive signs of *SHOX* haploinsufficiency.

Shortening of the radius, with a length below -1.9 SDS for age and sex, was found to be the earliest and most frequent radiological sign. All children demonstrated this feature at the first appointment, being as young as 45 days old.

Binder et al described that during infancy and early childhood, children with LWD may have subtle radiologic signs of Madelung deformity (i.e., lucency of the distal radius), but they are usually asymptomatic, and the physical examination is normal.⁷ In our study, we detected a short radius for age and sex even without the lucency of the distal radius. Normalized measurements of the radius, to calculate SDS for age and sex, have not previously been reported in children with *SHOX* deficiency. We think this would be a useful tool for selecting children to undergo *SHOX* molecular studies, especially if they have short stature without a clinically evident mesomelia.

In our study, all members of the family with a deletion only in the four downstream regulatory regions of the PAR1 had a milder phenotype with normal height, milder body disproportion, and short radius for age and sex. On the

contrary, in the family with a previously undescribed missense variant in exon 2, c.243A > T (p.Lys81Asn), the boy has a severe phenotype with a milder presentation in other affected members of the family.

Highly variable phenotypes were seen even within the same family. No correlation has been established between the severity of phenotype and the underlying *SHOX* pathogenic variant.^{8,34–37} However, based on reports in the French population, deletions of the downstream enhancer region of *SHOX* appear to be associated with a milder phenotype.⁶

Variations in the clinical phenotype observed between individuals may be due to different genetic background. To date, only one *SHOX* modifier has been discovered, *CYP26C1*.²⁵ Individuals with *SHOX* mutations were reported to have a more severe phenotype, when in association with a *CYP26C1* mutation, compared with individuals with a sole *SHOX* mutation.²⁵ However, the incidence was very low. Thus, it was not that unexpected when we did not detect any mutation in this study and therefore this gene cannot explain any of the variations observed in our cohort.

In conclusion, Argentinean children with *SHOX* deficiency are born shorter and experience a growth delay during childhood as well as a stunted pubertal growth spurt.

Body disproportion, evaluated by SH/H ratio, an indicator of short legs, was already present in some children as early as 2 years.

Shortening of the radius, with a length below -1.9 SDS, for age and sex, was found to be the earliest and most frequent radiological sign detected, even as early as 45 days old.

We found a previously unreported mutation and add the description of this family.

The combination of body disproportion, evaluated with local references, and a shorter radius for age and sex in children without a clinically evident mesomelia with or without short stature may be useful in early detection of children with *SHOX* deficiency.

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Conflict of Interest

None declared.

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