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Growth Topics in FGFR3-Related Skeletal Dysplasias

R Ramos Mejia[*]
M del Pino
V Fano

Address
[*]Growth and Development, Hospital Garrahan, Combate de los Pozos 1881, 1245, Buenos Aires, Argentina
Email: crecimientoydesarrollogarrahan@gmail.com

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Abstract

Purpose of Review Describe growth at different periods of life to understand the effects of genetic impairment in *FGFR3*-related conditions. We hope this data will be used to compare different populations and the effects of future treatments towards growth improvement.
Recent Findings The *FGFR3* plays a critical role in early mammalian skeletal development, especially in postembryonic linear bone growth; however, little is known about its role during all of the growth process stages. In the achondroplasia growth curve, infancy, childhood, and puberty periods can be well recognized, coexisting with fast changes in body proportions.
Summary FGFR3 gain-of-function mutations are responsible for autosomal dominant chondrodysplasias characterized by a severe disproportionate short stature, as thanatophoric dysplasia, severe achondroplasia with developmental delay and acanthosis nigricans, achondroplasia, and hypochondroplasia. While achondroplasia is homogeneous with low variability, hypochondroplasia findings are less constant due to genotypic heterogeneity. In both conditions, birth size is slightly reduced, followed by a period of fast growth deceleration during infancy and a low magnitude pubertal growth spurt, most evident in sitting height. Some phenomena as shifting centile lines during infancy and parent-child height correlation are well described. A slight variability is shown between achondroplasia and hypochondroplasia populations within different ethnic backgrounds.

Introduction

In the general population, the pattern of human linear growth is well documented [1, 2]. During the first years of life, the postnatal growth velocity is very fast, then continuously decreases becoming relatively steady during the late preschool years [1]. During those times, shifts in linear growth may be seen, with almost 50% of infants crossing centile lines, either up or down [3, 4]. When puberty begins, children experience a period of fast growth, called "adolescent growth spurt" [1, 2]. This milestone occurs, at different ages, with variable intensity and duration between children; consequently, a shift in growth channels may appear. Besides, secondary sexual signs, as the occurrence of breast button or increase in testis size, are linked to this period of fast growth [1].

Thus, in the human growth curve, we can recognize three periods, infancy, childhood, and puberty, with different major factors involved in their regulation [1, 2].

Additionally, body proportions and the ratio between limbs and trunk length undergo important changes from birth to adulthood. Crown-rump length is 67% of total length at birth and only 55% at 6 years of age, due to fast postnatal leg growth, changing body proportions. During prepuberty, the sitting height/height (SH/H) ratio remains quite uniform increasing during puberty due to the spine growth spurt [5, 6].

The fibroblast growth factor receptor 3 (FGFR3) plays a critical role in the early mammalian skeletal development, especially in postembryonic linear bone growth [7–9]; however, further studies are needed to investigate the role of FGFR3 during all stages of the growth process.

In consequence, most FGFR3 gain-of-function mutations are responsible for a family of autosomal dominant chondrodysplasias characterized by a severe and disproportionate short stature with short limbs, narrow trunk, and macrocephaly. This group is comprised by a spectrum of conditions with variable severity in its clinical and radiological presentation, ranging from mild hypochondroplasia (HCH) (MIM 146000) to achondroplasia (ACH) (MIM 100800), severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) (MIM 616482), and the neonatal lethal thanatophoric dysplasia type 1 (TD1) (MIM 187600) and type 2 (TD2) (MIM 187601) [10, 11•].

Achondroplasia is the most common form of inherited disproportionate short stature with a prevalence between 1 in 10,000 to 1 in 30,000 live births [12]. Approximately 99% of patients have one of the two heterozygous gain-of-function mutations leading to the same change in the FGFR3 protein: the amino acid arginine replaces glycine at the position 380 (Gly380Arg or G380R) [13, 14]. Suspected homozygous achondroplasia is a very severe, perinatal lethal condition [15, 16].

Hypochondroplasia is phenotypically milder than ACH, also characterized by disproportionate short stature and macrocephaly. Because it is radiologically milder, diagnosis may be difficult, especially in young infants [17–19•]. Most HCH cases are caused by the recurrent heterozygous C1620A or C1620G transversion in the proximal tyrosine kinase domain, causing the change p.Asn540Lys (N540K) [20, 21]. However, different mutations have been described, with genetic and clinical heterogeneity [22, 23].

Thanatophoric dysplasia is usually lethal perinatally and is due to a de novo change in the FGFR3 gene. This condition is divided into TD type 1 (micromelia with bowed femur) and type 2 (micromelia, straight femur, and cloverleaf skull deformity). The prevalence of TD is 0.47 per 10,000 live births in Latin America [24].The most common TD1 mutations affect intra- or extracellular domain while the TD2 mutation affects the tyrosine kinase domain of the FGFR3 protein [25–27]. This condition may be detected in utero by ultrasound studies on the basis of short limbs and the narrow thorax. After birth, respiratory insufficiency develops and, with intensive medical intervention, a few patients have survived for a long period [10, 28].

Finally, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) is rare, characterized by severe short stature, tibial bowing, profound developmental delay, and acanthosis nigricans. The acanthosis nigricans is not evident in early childhood because it develops late in childhood [29]. Although initially reported as a unique entity, there is significant radiographic and clinical overlap between SADDAN and TD. An FGFR3 gain-of-function p.Lys650Met mutation (K650M) has been identified in affected individuals [29, 30]. This mutation occurs within the FGFR3 tyrosine kinase domain activation loop and affects the same codon altered in TD2 (Lys650Glu) but results in a phenotype somewhat different from TD2. Although they share the severe skeletal dysplasia and CNS malformation, extended survival has not been reported in TD2, and it is not known whether acanthosis nigricans would develop in these individuals [29].

This review describes the growth patterns in the spectrum of skeletal dysplasias related to FGFR3 gene mutations, in the different periods of the human growth curve, to better understand its impact on skeletal development. Different studies have described the growth of individuals with ACH from birth to adulthood [31–39••]. However, few studies describe growth in HCH [40••, 41], even less in those infrequent conditions as TD and SADDAN, with fewer than 10 patients having a molecular confirmation of the latter [29, 30, 42–49].

Size at birth

Size at birth in ACH and HCH is only slightly reduced (Table 1).

In ACH, the mean birth weight and length are between 3.15 to 3.5 kg and 46 to 50 cm, respectively, depending on different populations (Table 1) [31, 32••, 36••, 37••, 38••, 50••, 51••].

Despite size at birth in HCH was found to be between normal ranges [17], in an Argentinian cohort of 66 children and adults carrying N540K HCH, size was somewhat lower than in the general population, with a mean weight and length between 3.3 to 3.1 kg and 48 to 45.7 cm respectively [40••].

In children with HCH caused by different mutations than N540K, the size at birth ranges from normal to slightly shortened, with an evident prenatal femoral shortening (supplementary table 1) [52–63••, 64].

One child affected by a homozygous N540K mutation was reported with normal weight at birth, body length in the third centile, and greater cephalic circumference than the normal population (+2.3 SDS) [65].

The common features described in TD1 at birth are macrocephaly, extremely short limbs, and narrow chest. Most of those born alive die afterwards due to respiratory failure [66]. Baker et al. described the auxological data of a newborn boy, with a normal weight, 3.25 kg; length, 41 cm; and cephalic circumference, 39.5 cm (−3.3 SDS and +2.35 SDS for CDC references) [45].

In reports of six SADDAN term newborns, weight and length at birth were normal, ranging 2.8 to 3.7 kg and 43.0 to 48.3 cm respectively. The head circumference was large, between 37.5 and 41.5 cm. Long bones were short in the prenatal ultrasound examination [30, 46•, 49].

Growth in infancy and childhood

In the ACH population, studies of growth in height show that children experience a period of fast growth decreasing during infancy [31, 32••, 35, 38••, 39••, 50••, 66], with a curve which is similar in shape but lower in magnitude in comparison to the general population [35].

After a period of fast decreasing growth velocity since birth, with a mean growth velocity of approximately 15.5 cm/year and 9.5 cm/year at 6 month and 1 year old, respectively, the growth velocity is stable in late preschool years, with a mean of 4.3 cm/year in both sexes [35, 39••, 66]. Therefore, the length at 12 and 24 months old is approximately −4.3 and −4.8 SDS respectively when compared to the general population [32••, 35–36••, 37••, 38••, 67]. At 5 years old, the growth velocity is between 2.6 and 5.9 cm/year and the growth deficit remains constant during childhood until puberty begins [35].

Table 1. **Height, at different ages in cm and SDS relative to local and WHO references, in achondroplasia and hypochondroplasia cohorts**

ACHONDROPLASIA							
body length / height cm (min/max)	Argentine del Pino, 2010 Local:Lejarraga 2009	USA Hoover-Fong 2017 Local:CDC 2000	Australia Tofts, 2017	Northern Europe Merker,l 2018 Local: Wiklan, 2002	Japan Tachibana,, 1997	China W. Q Dai, 2020	Egypt S Ismail, 2019
Birth							
Males	45.9 (41-49.4)	50.2 (45 -55.4)	49 (46-52)	47.7 (43.9-51.5)	47.5	49.2	
SDS local	-2.26	0.08		-1.48	-1.3	-1.22	
SDS WHO	-2.1	0.17	-0.47	-1.15	-1.26	-0.36	
Females	46.7(42.7-50.7)	49.6 (44-55.2)	48 (44-50)	47.3 (43.2-51.5)	47.0	48.4	
SDS local	-1.43	0.13		-1.33	-1.2	-2.0	
SDS WHO	-1.31	0.24	-0.62	-0.99	-1.15	-0.4	
1 year							
Males	65.1	64.9 +/- 2.3	65.1	65.9 (SD 2.2)	66.3		66.6
SDS local	-4.49	-4.19		-3.98			
SDS WHO	-4.48	-4.58	-4.48	-4.14	-3.98		-3.85
Females	63.1	63.9+/-2.6	63.5	64.6 (SD 2.4)	64.2		66.14
SDS local	-4.24	-3.29		-3.89			
SDS WHO	-4.24	-3.93	-4.08	-3.66	-3.81		-3.06
5 years							
Males	87.3	86.1 +/-3.4	87	87.2 (SD 3.1)	86.1		85.2
SDS local	-4.58	-4.78		-5.09			
SDS WHO	-4.89	-5.15	-4.96	-4.91	5.15		-5.34
Females	85.1	85.2+/-3.7	86.7	85.7 (SD 3.9)	86		88.5
SDS local	-4.51	-5.32		-5.37			
SDS WHO	-5.11	-5.09	-4.78	-4.99	-4.92		-4.4
8 years							
Males	99.7	97.9 +/- 4.6	100.1	99.6 (SD 4.1)	98.3		101.9
SDS local	-4.87	-5.57		-5.48	-5.13		
SDS WHO	-4.88	-5.2	-4.81	-4.9			-4.49
Females	96.5	97.2 +/-4.8	99.5	98.3 (SD 4.7)	98.1		100.1
SDS local	-4.78	-5.99		-5.53			
SDS WHO	-5.18	-5.07	-4.67	-4.87	-4.91		-4.56
12 years							
Males	114.8	112.5 +/-6.6	115	113.6 (SD 4.7)	114.4	113.7	
SDS local	-4.08	-5.31		-5.14		-5.23	
SDS WHO	-4.84	-5.16	-4.81	-5.01	-4.98	-4.99	
Females	109.6	108.5 +/-6.8	113	113.3 (SD 5.3)	115.1	112.4	

Table 1. (Continued)

ACHONDROPLASIA						
SDS local	-4.73	-5.53		-5.40		-6.15
SDS WHO	-6.09	-6.24	-5.59	-5.55	-5.28	-5.68
Adolescence						
Age	18	18	18	18	17.9	
Males	128.3 (114-145)	Horton 132 (118-145)	134 (125-141)	131.7 (121.4-141.9)	130.4	
SDS local	-6.42	-5.83	-5.64	-7.4	-7.3	
SDS WHO	-6.4	-5.91		-6.06	-6.38	
Females	119.9 (108-132)	125 (112-136)	125 (116-132)	124.4 (114.9-133.9)	124.0	
SDS local	-6.72	-5.85		-7.1	-6.6	
SDS WHO	-6.53	-5.76	-5.76	-5.95	-5.99	
HIPOCHONDROPLASIA N540K						
Birth						
	Argentine Arenas 2018 Local:Lejarraga 2009	Russia Fofanova et al, 1998				
Males	48.0 (SD 2.9)					
SDS local	-1.11					
SDS WHO	-1.0					
Females	45.7 (SD 2.8)					
SDS local	-1.98					
SDS WHO	-1.85					
Adult height						
Males	143.6 (131.0–154.5)	-5.14 -(-)3.91				
SDS local	-4.21					
SDS WHO	-4.36					
Females	130.8 (124.0–138.0)	-3.62				
SDS local	-4.93					
SDS WHO	-4.88					

Interestingly, del Pino et al. described that during the first 5 years of life, 50% (41/84) of ACH children shift centile lines changing 1 SDS or more, with a similar number of children shifting upwards and downwards. Nevertheless, no shifting growth is seen in familial cases. A boy (heterozygous case) with both parents affected was reported growing up in the lower ACH centiles [35].

Regarding differences in height between sexes, during infancy and childhood, boys are approximately 1 to 3 cm taller than girls [32••, 36••, 38••, 67].

HCH children may have a broad spectrum of severity, including children with severe height deficit and body disproportion since birth, to children with growth close to normal until their adolescence, when disproportionate short stature becomes evident. In the UK and France historical cohorts of HCH children without molecular confirmation, a mean height between −2 and −3 SDS until 14 years of age has been reported, then falling below −3 SDS [68, 69].

As described in the ACH population, a growth study performed in children with N540K-related HCH in Argentina shows a period of decreasing growth during infancy. Most of the 66 children's height was below the 3rd centile of the general population reference. However, there is an overlap between the 97th centile of HCH children and the lower centiles of the general population, until they are 13 and 10 years old in males and females respectively [40••]. In other populations, the height of children with HCH caused by N540K mutation ranges from nearly below the 50th centile to severly short stature [70–76] (supplementary table 1).

In children with HCH caused by different mutations than N540K, the phenotypic variability is wide, ranging from a severe height impairment and body disproportion noticed since the prenatal period to children with a less height deficit and body disproportion secondary to greater growth of the lower limbs [52–61, 63••, 64, 77–83] (supplementary table 2).

In a child carrying a homozygous N540K mutation, severe postnatal growth retardation in body length was described at 16 months with −4.0 SDS and 6.2 SDS at 26 months compared to the general population. The cephalic circumference on both occasions was on 97th centile [65].

Regarding TD1, there are few long-term survivor descriptions including growth data [42, 43]. McDonald et al. reported two children alive at 4.0 and 4.75 years [44]. In addition, Baker et al. described the auxological data of a 9-year-old boy, with normal weight, severe length deficit, and macrocephaly at birth. During his follow-up, he showed severe growth retardation and the estimated adult height was near 85 cm (height at 8 years of age and at adulthood −11 SDS for CDC references) [45, 84, 85]. Body disproportion had persisted with marked short rhizomelic compromise; his head circumference shifted from near the 50th percentile to +1 SSD during childhood, compared to the general population [45].

The last reported height in two SADDAN children was 63.5 cm at 5 years old and 103.6 cm at 16 years old (−9.2 SDS and −7.25 SDS for CDC references, respectively) with a head circumference of 51.0 and 50.0 cm respectively [30, 84, 85].

Growth during adolescence and puberty

When ACH children start puberty, their height is 5.00 SDS below the 50th centile for the general population, losing almost one additional SDS during adolescence. [34••, 36••, 37••, 38••, 39••].

In 1978, Horton et al. published the first growth charts from birth until adulthood. Unfortunately, beyond 10 years old, measurements were limited and Horton could not assure if this was a pubertal growth spurt [31]. Subsequently, no pubertal growth spurt was reported by Merker and Hoover Fong when they performed the analysis of the average curves in cross-sectional design studies [36••, 38••]. Nevertheless, some individual growth patterns published by Merker showed a clear acceleration in growth velocity during early pubertal ages [38••].

However, del Pino et al. clarified this point in a longitudinal design study, showing that during adolescence, there is a period of rapid increase of growth velocity with a later slowdown, confirming the "adolescent growth spurt." It is similar in shape and lesser in magnitude than in the general population, with a peak height velocity between 3.2 and 6 cm/year. The range for age at height velocity peak includes a period of about 3 years for boys and girls. After the height velocity peak, growth velocity decreases until they final growing stop. Moreover, del Pino described in ACH girls the presence of a pubertal growth spurt in the trunk, with a mean velocity peak of 3 cm/year [34••].

Merker found no differences in height between sexes from 10 to 14 years of age; however, in other studies, boys are taller in infancy, becoming more evident during adolescence [32••, 34••, 36••, 38••, 39••, 51••] (Table 1).

Regarding puberty, del Pino described starting during growth velocity increase in boys (genital stage 2 and testis volume of 4 mL), reaching adult stage (genital stage 5 and testis volume of 20 mL) after the height velocity peak, in the "adolescent growth spurt" deceleration phase. In girls, breast 2 befalls during the increase of growth velocity, breast 3 close to the mean age of the height velocity peak, and menarche in the deceleration phase of the growth spurt [34••].

Unfortunately, there are no growth longitudinal studies describing puberty in HCH; but in the Argentinian cohort, the analysis of the average curves shows that there is an evident pubertal growth spurt in the trunk length, which occurs between 11 and 14 years in males and between 10 and 13 years in females, being more prominent in first of them, but this was not evident in the lower limbs [40••].

In HCH children with N540K mutation as in a group without molecular confirmation, puberty onset befalls at similar ages than in general population adolescents [68, 86]. In twelve boys and six girls, the median age was at 12.2 and 11.1 years respectively [68]. These authors also reported that there was no peak of pubertal growth, causing an impact on adult height [68].

Adult height

For ACH patients, the mean height at 18 years of age or older is between 128 to 134 cm and 120 to 125 cm for males and females, respectively, with a sex difference between 6 to 9 cm according to different reports [32••, 36••, 37••, 38••, 50••] (Table 1). The adult height deficit corresponds to 5.8 SDS to 7.4 SDS below the median for national references.

Although the height in adults with ACH is quite homogeneous, argentine males and females are 2–5 and 4–5 cm shorter than people in Australia, the USA, Northern Europe, and Japan at 18 years of age [32••, 36••, 37••, 38••, 50••] (Table 1 and Fig. 1). It is difficult to know if this is a true difference in height between populations, explained by a population-wide phenomenon [31, 32••, 36••, 37••, 38••] or if it is due to other causes, such as methodological differences in data collection, sample size at older ages, or methods to process the data [31, 32••, 84, 85].

One of the first reports of HCH adult height was done by Maroteaux and Falzon, being 146.1 cm (138–153) in men and 137.6 cm (128–147) in women with clinical-radiological diagnosis [87]. Later, Appan and Pinto reported an adult height in the UK and France groups of HCH, between 145 to 165 cm and 133 to 151 cm for males and females respectively [68, 69].

The height in 33 Argentinian N540K HCH adults was between 131.0 and 154.5 and 124.0 to 138.0 cm in men and women, respectively, corresponding to −4.21 SDS and −4.93 SDS according to Argentina references [40••, 88]. Height in five Russian N540K HCH adults ranged from −3.62 to −5.14 SDS [71].

Stature in HCH adults carrying other mutations than N540K varies between severely short to normal in lower centiles [52, 53, 55–57, 59, 62–64, 77–79, 83] (supplementary table 2).

Nikkel et al. reported one of the older TD patients; she was 23 years old and her long bones were extremely short: the length of her femur and tibia was 8 and 5.7 cm [46•].

The oldest SADDAN patient reported was 30 years old; his height was 104 cm (−9.1 SDS for CDC references) [30].

Association between mid-parental height and offspring

Parental height of de novo ACH cases in the different reports is normal [38••, 89••, 90–91].

In 1970, Murdoch et al. found that mean parental height did not significantly influence the adult height in the novo ACH cases: in males, the correlation was +0.02 and in females +0.18 [90]. However, del Pino et al. estimated

parent-child correlations at different ages, finding that at birth, it is only 0.17, then it rises, and at 3 years of age, it reaches about 0.4, remaining stable thereafter until adulthood [89••]. Later, Merker reinforces this fact describing a positive association between parental and adult height in de novo ACH cases (r = 0.54) [38••].

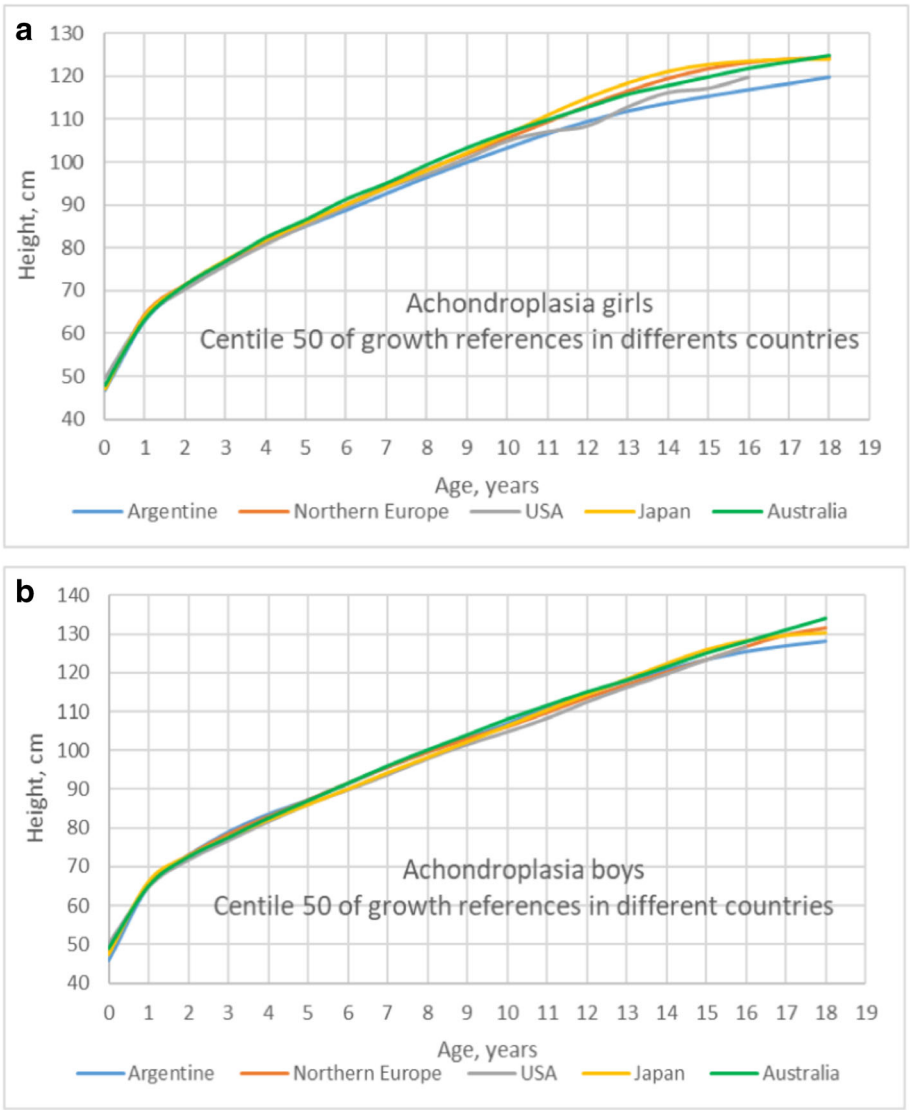

Fig. 1. Median growth curves of height in different cohorts of achondroplasia populations: females (**a**) and males (**b**).

Body proportions in FGFR3

FGFR3 plays an important role in prenatal skeletal development, with a greater negative influence in the epiphyseal growth plates of the limbs, inhibiting endochondral ossification and disturbing their growth [7–9]. Otherwise, despite modifying the anatomy of the vertebral bodies, the *FGFR3* mutation only slightly disturbs the growth of the trunk.

Consequently, at birth, ACH infants are severely disproportioned with short limbs. The sitting height/height ratio, which quantifies body disproportion, has a mean of + 5 SDS at birth compared to the general population, although the body length is slightly reduced [5, 33]. This body disproportion becomes more evident throughout their lifetime with a SH/H ratio of +10 SDS at 2 years of age, +20 SDS before puberty, and +17 SDS at adulthood compared to the general population [5, 33, 92].

Regarding leg length in ACH newborn, this is 3 cm shorter than in the general population, and this difference increases to 7 cm at 1 year, 10/14 cm at 2 years, 23 cm at 6 years, and 36/40 cm at 18 years of age [6, 31, 33, 92, 93].

Although del Pino, Horton, and Merker leg length growth charts show a similar slope, there are subtle differences between them, being in Argentinian females at 20 years of age 1 cm shorter than the USA and Northern Europe females. However, no differences are seen in males [31, 33, 92].

No pubertal growth spurt in leg length is observed in ACH adolescents; this maybe secondary to the severe growth retardation or to the legs bowing which shadows its detection [33, 34••, 38••, 92].

The spine, measured as sitting height, grows in the lower normal range during infancy and childhood. During adolescence, its growth decreases moderately and reaches 87 and 80 cm at 18 years of age in males and females, respectively, only 5 cm below the mean compared to the general population [6, 31, 33, 34••, 91, 92, 94]. Trunk length pubertal spurt in girls as published by del Pino is 3 cm/year, being 72% of the peak growth velocity [34••, 92].

As described for leg length, despite sitting height growth charts show a similar slope between different populations, there are subtle differences, being in Argentinian females at 20 years old 2.5 cm shorter than in USA and Northern Europe females. No differences were seen in males [31, 33, 92].

When the differences in segmental growth between Argentinian, USA, and North Europe females were analyzed, the sum of these differences is equal to the observed difference in total height, approximately 4 cm [31–33, 92].

As early as 2 years of age, arm span is 14 cm shorter than in non-ACH children and this deficit almost doubles at 5 years of age [92]. At adulthood, arm span is approximately 65 cm shorter than in the general population, with a mean of 124 ± 6 cm and 115 ± 9 cm in males and females respectively [92].

ACH population has real macrocephaly (head circumference more than + 2 SDS for age and sex) and relative macrocephaly (head circumference/height—HC/H—ratio more than 2 SDS for age and sex, i.e., big cephalic circumference for the subject's height). In ACH children, the HC/H ratio decreases from 0.79 at birth to 0.47 in the adolescence, compared to the general population [5, 33, 95].

Body disproportion due to limb shortening is a hallmark in HCH with variable severity [17]. It was described in N540K and in other mutations in different populations [52–64, 68–73, 77–83] (supplementary tables 1 and 2)

In the Argentinian N540K HCH cohort, body disproportion assessed as SH/H ratio was observed in early childhood, being evident in every child at 24 months of age, even in the absence of short stature. This disproportion increased with age due to a greater compromise in the growth of limbs compared to the trunk [40••].

Regarding pubertal growth spurt, the Argentinian N540K HCH cohort showed a "growth spurt" in the trunk length, which occurred between 11 to 14 years in males and 10 to 13 years of age in females, being more prominent in first of them. However, this spurt was not evident in the lower limb growth curves [40••]. At these ages, trunk and leg length are 7 and 25 cm shorter in HCH children compared to the general population, contributing to the loss in height and increasing body disproportion [40••].

A median head circumference of + 2.1 SSD compared to British standards has been described in the HCH Argentinian group, this being a predictor of N540K mutation in children with clinical and radiological findings suggestive of HCH. A head circumference >1.86 SSD has a sensitivity of 73.3%, a specificity of 100%, a positive and negative predictive value of 100%, and 73.3% for detecting the N540K mutation [41]. However, although not all of the children in the Argentinian N540K HCH cohort had real macrocephaly for age, all of them had relative macrocephaly, even evident in the first years of life [40••].

TD and SADDAN children are reported to have extreme micromelia and macrocephaly, evident at birth and when performing a prenatal ultrasound [30, 45, 47].

The severe growth retardation and increasing disproportion during infancy and teenagers in FGFR3-related disorders could be related to the fact that these periods are characterized by high velocity growth, especially in leg length, mostly affected in FGFR3 mutations [33, 35, 38••, 92].

Conclusion

The *FGFR3* plays an important role in prenatal skeletal development, inhibiting endochondral ossification and retarding growth, leading to a severe height deficit. Despite this, size at birth in ACH and HCH is only slightly reduced. During the whole growth process in ACH children, three periods are well recognized: infancy, childhood, and puberty, with similar shape but less magnitude in comparison with the general population [34••, 35, 39••].

On the other hand, there is a parental and offspring height positive correlation in ACH and an evident crossing of centiles, either up or down, during the first years of life; both phenomena are also described in the general population. These facts, together with the presence of the three periods in the growth curve, suggest that multigenic influences on growth are not fully abolished by the presence of the ACH mutation [35, 38••, 39••, 89••].

Unfortunately, no longitudinal growth studies allow us to confirm that HCH children have the three phases of the human growth curve similar to the general population. Nevertheless, the height curve of cross-sectional studies shows a period of fast growth during the first years of age and the slope seen

in the sitting height curve during teen ages could be the pubertal spurt [40••].

Even though height deficit and body disproportion at different ages in ACH and N540K HCH populations, with different ethnic backgrounds, seem to be similar, there are subtle differences [31, 32••, 36••, 37••, 38••]. It is difficult to interpret if this is a true difference in height or due to other causes, such as methodological issues [31, 32••, 84–86].

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s40746-021-00222-x.

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- • Of importance
- •• Of major importance

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