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Complete List of Authors:	Ferreira, Carlos; NIH, NHGRI Niiler, Timothy ; Alfred I. duPont Hospital for Children, Gait Laboratory Duker, Angela; Alfred I DuPont Hospital for Children, Division of Medical Genetics Jackson, Andrew; Institute of Genetics and Molecular Medicine Bober, Michael; Alfred I. duPont Hospital Hospital for Children, Genetics
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Growth in individuals with Saul-Wilson syndrome.

Carlos R. Ferreira,[1] Tim Niiler,[2] Angela L. Duker,[3] Andrew P. Jackson,[4] Michael B. Bober[3]

[1] Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

[2] Gait Laboratory, Nemours/A.I. duPont Hospital for Children, Wilmington, DE, USA

[3] Division of Orthogenetics, Nemours/A.I. duPont Hospital for Children, Wilmington, DE, USA

[4] MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

Corresponding author

Carlos R. Ferreira

10 Center Drive

Building 10, Room 9N248B

Bethesda, MD 20892-1851

ABSTRACT

Saul-Wilson syndrome (SWS) is a rare autosomal recessive disorder characterized by microcephalic primordial dwarfism, spondyloepimetaphyseal dysplasia, characteristic facial findings, clubfoot, brachydactyly, bilateral cataracts, and hearing loss. Recently, recurrent mutations in *COG4*, encoding a component of the Conserved Oligomeric Golgi (COG) complex, were identified. We created detailed growth curves for stature, weight, and head circumference, as well as weight-for-length and weight velocity charts for younger children, derived from hundreds of data points obtained by retrospective chart review from 14 individuals with molecularly-confirmed SWS. In addition, we performed statistical comparisons of height-for-age model fits before and after initiation of growth hormone supplementation, and found that this therapy does not appear to influence height in individuals with SWS. We hope that these charts will represent valuable tools for clinicians, both in assessing whether SWS seems an appropriate diagnosis, as well as to monitor growth of affected individuals. In particular, we hope that our detailed growth characterization will reduce morbidity resulting from unnecessarily aggressive nutritional interventions by well-intentioned physicians trying to promote weight gain, an unrealistic goal in this genetically-determined cause of primordial dwarfism.

Key Words

Saul-Wilson syndrome; primordial dwarfism; COG4; G516R.

INTRODUCTION

Saul-Wilson syndrome (SWS) belongs to a group of disorders called microcephalic primordial dwarfism, characterized by pre- and postnatal growth deficiency, and microcephaly. Other than the aforementioned features of microcephalic primordial dwarfism, affected individuals also exhibit blue sclerae, large anterior fontanelle, a prominent forehead, clubfoot, brachydactyly, bilateral cataracts, rod-cone dystrophy, hearing loss, and characteristic radiographic findings (Hersh et al., 1994; R. A. Saul & Wilson, 1990; Robert A. Saul, 1982). Recently, a recurrent heterozygous amino acid substitution (p.Gly516Arg) in COG4 was identified in 14 patients (Ferreira et al., 2018). COG4 is a component of the Conserved Oligomeric Golgi (COG) complex, a multi-subunit protein complex that participates in vesicular trafficking to and from the Golgi apparatus, and is essential for the latter's structure and function (Ungar, Oka, Krieger, & Hughson, 2006). Fibroblasts from patients with Saul-Wilson syndrome demonstrate disruption of vesicular trafficking, Golgi morphology, and decorin glycosylation (Ferreira et al., 2018).

As is the case with other types of microcephalic primordial dwarfism (Bober et al., 2012), it is our experience that individuals with SWS undergo aggressive feeding regimens in early childhood, in an attempt to improve growth. This overfeeding does not, however, lead to improved growth parameters, since the cause of growth failure does not lie in undernutrition, but in the genetic nature of the condition. This phenomenon of overfeeding is partly caused by a lack of established reference curves for stature, weight, and head circumference for individuals affected with the syndrome. As growth failure represents such a prominent feature of SWS, the establishment of normative growth curves would aid in the management of individuals with this condition, as well as in the diagnosis of patients with primordial dwarfism in general. Here, we provide an overview of growth in a unique cohort of 14 SWS patients, the largest cohort worldwide.

METHODS

Population

Data was obtained from 6 females and 8 males with molecularly-confirmed SWS, ranging in age from infancy to 39 years old. Written informed consent was obtained from all affected individuals or their parents/legal guardians. All were enrolled in at least one of the following research protocols, which were approved by their respective institutional review boards: 14-HG-0071, "Clinical and Basic Investigations into Known and Suspected Congenital Disorders of Glycosylation"; 76-HG-0238, "Diagnosis and Treatment of Patients with Inborn Errors of Metabolism or other Genetic Disorders"; "Enquiry of Participation in a Research Project about Clinical and Molecular Studies on Rare Congenital Skeletal Disorders"; or 83142, "Primordial Registry at Nemours/Alfred I. duPont Hospital for Children."

Growth calculated as standard deviations

Standard deviations (SDs) for length/height, weight, and OFC normalized for age and gender were calculated using the 2000 Centers for Disease Control and Prevention (CDC) growth charts (Kuczmarski et al., 2002). In addition, growth parameters for birth were calculated using the revised Fenton growth charts (Fenton & Kim, 2013). Data from Roche et al. was used for calculation of head circumference Z-scores in individuals older than 36 months (Roche, Mukherjee, Guo, & Moore, 1987). A Shapiro-Wilk normality test was performed for all growth parameters at birth and at last examination (not performed at skeletal maturity given the small number of patients, n=3). Given a normal distribution, an unpaired t test was subsequently performed comparing the mean Z-scores for each growth parameter against a mean Z-score of 0 for the control population. Statistical significance was assigned to a two-tailed p-value <0.05. Analysis was performed with Prism version 6.0c (Graphpad Software Inc, La Jolla, CA).

Growth charts

The growth pattern for stature, weight, and head circumference data sets (corrected for gestational age in case of preterm birth) were modeled using locally weighted scatterplot smoothing as implemented by the loess() function in R version 3.4.0 (R Core Team, 2017). The smoothness of fit when using loess() depends on a smoothing parameter; a higher smoothing parameter considers more points in the curve and results in smoother fits to the data, while a lower smoothing parameter will more precisely fit the data locally and the best fit curve will be rougher. In this case, the best smoothing parameter was estimated using leave-one-out k-fold cross-validation in order to minimize the root mean square error of the fit and fine-tuned to each dataset via visual inspection of the final generated growth curve (Lee & Cox, 2010). Then, using 20 equally sized bins for ages between zero and three years, and 40 equally sized bins for ages between zero and 9-12.5 years (dependent on the data being modeled), loess()

was used to model the mean and loess.sd() from the *msir* package (Scrucca, 2011) to model the standard deviations for the variables of interest. Prediction intervals (90%, 75%, and 50%) were obtained by multiplying the standard deviations by the usual multipliers (1.64, 1.15, and 0.67, respectively). Endpoint of data modeling occurred when there were either too few data so that loess() failed, or when trends fit by loess() turned non-physical (e.g., a downturn in mean head circumference in the teenage years as a result of single individuals representing the entire group when others dropped out of the cohort). Normative reference curves were taken from CDC references (Kuczmarski et al., 2002).

Growth hormone effect

In order to ascertain the effect of human growth hormone (HGH) treatment on height, single subject linear regression models using a square root fit of subjects' height-for-age data were implemented, where pre-HGH versus post-HGH conditions were considered for each of the four subjects who received HGH therapy. These two models were then compared using analysis of variance (ANOVA). Where models were found to be significantly different, it was presumed that HGH treatment had an effect. For one subject (P6.1) who interrupted HGH therapy for approximately one year, model fits were divided so that each pre- and post-HGH condition could be compared via curve fits. Besides modeling individual subjects, models were also fit using height-for-age data from all subjects who never received HGH, and height-for-age data before initiation of HGH from subjects who eventually received this therapy. All statistics were performed using R version 3.5.2.

RESULTS

The data that supports the findings of this study (absolute growth parameters for all individuals) are available in Table S1. In total, there were 297 available data points for length/height, 416 data points for weight, and 129 data points for head circumference.

Mean standard deviation scores of individuals with SWS at birth, at last examination and at skeletal maturity are presented in table 1. Comparison of birth length and birth weight Z-scores of individuals with SWS using CDC growth charts vs. prematurity-adjusted Fenton charts did not reveal a statistical significant difference (p-values 0.11 and 0.23, respectively); this is consistent with the fact that the mean gestational age for the whole cohort was 37 weeks 2 days, thus at term. When considering weight and length/height Z-scores of SWS patients, there was strong statistical difference compared to the control population across all ages, as expected (p-values for length/height 0.002 at birth, 0.0001 at last exam, 0.0026 at skeletal maturity; p-values for weight 0.0001 at birth and at last examination, 0.0069 at skeletal maturity). For birth head circumference in the SWS cohort, there was a statistically significant difference when using CDC growth charts versus preterm-adjusted Fenton charts (p-value 0.02). Thus, we chose to compare birth head circumference of the control population against the SWS cohort using Fenton charts, which interestingly did not reveal any statistical significance (p-value 0.13). However, comparison at a later age (at last examination of head circumference, mean age 9 years 6 months) did reveal a strong statistical difference between both groups (p-value 0.0001), indicating progression to microcephaly as individuals grow older.

Correction for gestational age was not necessary for this comparison, since age at least measurement of head circumference was >2 years for all individuals born prematurely. Interestingly, while there is an absolute microcephaly present in many affected individuals during growth and at skeletal maturity, the head circumference in all individuals with SWS exceeds the height by more than 2 SD, with consequent relative macrocephaly.

Table 2 presents growth parameters expressed as absolute values. The average birth length of affected individuals measured more than two weeks behind gestational age, while the average birth weight measured more than 3 weeks behind (mean gestational age at birth for males 37 weeks 1 day, mean gestational age at birth for females 37 weeks 4 days). The average birth head circumference for females also measured more than two weeks behind gestational age, while for males it measured 1 week 6 days behind gestational age.

Figure 1 presents growth curves for stature, weight and head circumference compared to the average population. Notably, although absolute microcephaly has been traditionally considered as a cardinal feature of Saul-Wilson syndrome, patients' head circumferences vary and can overlap the lower end of the general population distribution.

Growth charts without superimposition to average population standards, which can be used for monitoring growth of individuals with SWS, are included as supplementary figures S1-S6.

Weight velocity and weight-for-length charts are useful in assessing growth and estimating nutritional status in young children, and are thus presented in Figure 2.

Four subjects received HGH supplementation, and its effect on growth was evaluated by comparing height-for-age model fits before and after initiation of therapy for each subject (Figure 3). In all cases, statistical comparisons of the model fits were not significant, with the following p-values: 0.489 for P1.1; 0.068 (first few years of HGH supplementation) and 0.071 (resumption of HGH after interruption of about one year) for P6.1; 0.411 for P9.1; and 0.052 for P10.1. Consequently, it appears that HGH does not improve height in individuals with SWS.

DISCUSSION

We provide a careful characterization of growth in individuals with SWS confirmed molecularly. We believe that this work will be important in estimating nutritional needs of individuals with SWS, by providing appropriate standards by which to base growth expectations. Additionally, and when used in conjunction with other clinical features, it will also serve as a tool in the differential diagnosis of microcephalic primordial dwarfism. Based on growth parameters alone, SWS is distinguishable from microcephalic osteodysplastic primordial dwarfism type II (MOPDII), one of the most common causes of microcephalic primordial dwarfism. The average birth length, weight, and head circumference (corrected for gestational age) in patients with MOPDII was -7.0, -3.9, and -4.6 standard deviation scores from the population mean, much smaller at birth than patients with SWS (Bober et al., 2012).

An unexpected finding in our cohort is that head circumferences of individuals with Saul-Wilson syndrome can overlap the lower end of the general population distribution. This may in part be explained by head circumference percentiles being overestimated with CDC growth charts (Daymont, Hwang, Feudtner, & Rubin, 2010), with a lesser degree of overlap seen with other head circumference growth curves. Nevertheless, Saul-Wilson syndrome remains a microcephalic disorder for most affected individuals in absolute measurement terms, despite the appearance of relative macrocephaly. In fact, although head circumference was not statistically significantly different from the general population at birth, there was significant microcephaly that developed at a later age.

A potential limitation of our study is that a small number of individuals (with different number of measurements for each) were included for estimation of growth curves. Given this limitation, the growth data was not presented as percentiles but rather as prediction intervals, which estimate the likelihood that a future data point will fall within this interval. To generate the provided curves, one must make the assumption that these individuals are likely to be representative of the population of affected individuals. Therefore, our growth charts are provided with the expectation of assisting physicians in judging if future patients exhibit significant deviation from expected growth. In addition, we also provide actual data points in the supplementary table, as these absolute values might also prove useful in judging appropriate growth. While the curves provided were based on 14 individuals, hundreds of data points were used in each model to estimate prediction intervals. Ultimately, these curves are likely to be of diagnostic help when evaluating a child with primordial dwarfism at the bedside, and in monitoring growth of molecularly-confirmed individuals in the clinic.

In summary, we have carefully delineated the growth phenotype of SWS, creating growth charts that will be of assistance in the diagnosis of patients with primordial dwarfism in general, and in the management of individuals with SWS in particular. These charts will be useful in estimating nutritional needs of an individual with SWS by providing appropriate standards for comparison of growth parameters, and will thus likely decrease the risk of unnecessarily aggressive nutritional interventions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's website.

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TABLES

Table 1: Growth parameters as measured by standard deviation scores compared to the general population.

* For individuals > 36 months old, head circumference Z-scores were calculated using data from Roche, Mukherjee, Guo, & Moore, 1987 (Roche, A. F., Mukherjee, D., Guo, S. M., & Moore, W. M. (1987). Head circumference reference data: Birth to 18 years.

Pediatrics, 79(5), 706–712) rounding to the nearest age for which data is available, and using a cutoff of 18 years for patients above this age.

Table 2. Growth parameters expressed as absolute values.

For adult individuals, head circumference was plotted using charts from Rollins et al. (Rollins, J. D., Collins, J. S., & Holden, K. R. (2010). United States head circumference growth reference charts: Birth to 21 years. The Journal of Pediatrics, 156(6), 907-913.e2.)

FIGURE TITLES AND LEGENDS:

Figure 1. Growth in Saul-Wilson syndrome.

(A) Length-for-age 0-3 years. (B) Height-for-age 3-12.5 years. (C) Weight-for-age 0-3 years. (D) Weight-for-age 3-12.5 years. (E) Head circumference-for-age 0-3 years. PI: Prediction interval (used for the affected population), calculated using standard deviations, gives a sense of the probability that a new data point will lie within the indicated region. CI: Confidence interval (used for the normative population), calculated using standard errors, gives a sense of the probability that the mean from a new subject will lie within the indicated region.

Figure 2. Weight-for-length and weight velocity in Saul-Wilson syndrome.

(A) Weight-for-length 0-2.5 years. (B) Weight velocity 0-3 years. PI: Prediction interval; CI: Confidence interval.

Figure 3. Effect of human growth hormone (HGH) in Saul-Wilson syndrome.

Subject Pre: height-for-age model fit for that particular subject before initiation of HGH. Subject Post: height-for-age model fit for the same subject after initiation of HGH. No HGH Treatment: height-for-age model fit for subjects who never received HGH supplementation. Pre HGH Treatment: Height-for-age model fit before initiation of HGH supplementation for subjects who eventually received this therapy. No real difference is observed between the last two fits, or between pre-HGH and post-HGH model fits for each individual subject.

SUPPORTING INFORMATION:

Figure S1. Length-for-age 0-3 years.

Figure S2. Height-for-age 3-12.5 years.

Figure S3. Weight-for-age 0-3 years.

Figure S4. Weight-for-age 3-12.5 years.

Figure S5. Head circumference-for-age 0-3 years.

Figure S6. Head circumference-for-age 3-9 years.

	At birth (CDC)			At birth (Fenton)			At last examination (CDC*)			At skeletal maturity (CDC)		
	Mean ± SD	Range	n	Mean ± SD	Range	n	Mean ± SD	Range	n	Mean ± SD	Range	n
Length/height (SD)	-2.4 ± 1.5	-0.4 to -5.1	12	-1.4 ± 1.5	+2.0 to -3.3	11	-6.5 ± 1.6	-4.2 to -9.8	14	-8.9 ± 0.8	-8.3 to -9.8	3
Weight (SD)	-2.4 ± 0.7	-1.2 to -3.8	14	-2.1 ±1.0	-0.3 to -3.2	13	-4.0 ± 1.1	-1.5 to -5.6	14	-4.2 ± 0.6	-3.6 to -4.8	3
OFC (SD)	-2.0 ± 0.9	-0.8 to -3.9	11	-0.8 ± 1.4	+1.8 to -2.4	10	-1.9 ± 1.4	0.1 to -4.2	14	-3.4 ± 1.4	-2.2 to -5.0	2

	At birth				At skeletal maturity			
	Mean ± SD	Range	n	Average for (Fenton)	Mean ± SD	Range	n	Average for (CDC)
Length/height (cm)	44.1 ± 3.6	38.0 to 49.0	12	34 3/7-week neonate (males); 32 6/7-week neonate (females)	107.6 ± 1.9	106 to 109.7	3	4y 6m (male); 5y 1m (females)
Weight (kg)	2.09 ± 0.42	1.45 to 2.80	14	33 5/7-week neonate (males); 33 3/7-week neonate (females)	30.5 ± 7.4	25.3 to 39.0	3	11y 9m (male); 8y 3m (females)
OFC (cm)	31.7 ± 1.6	29.0 to 34.0	11	35 2/7-week neonate (males); 34 2/7-week neonate (females)	50.2 ± 1.7	49.0 to 51.4	2	4.5y (females*)

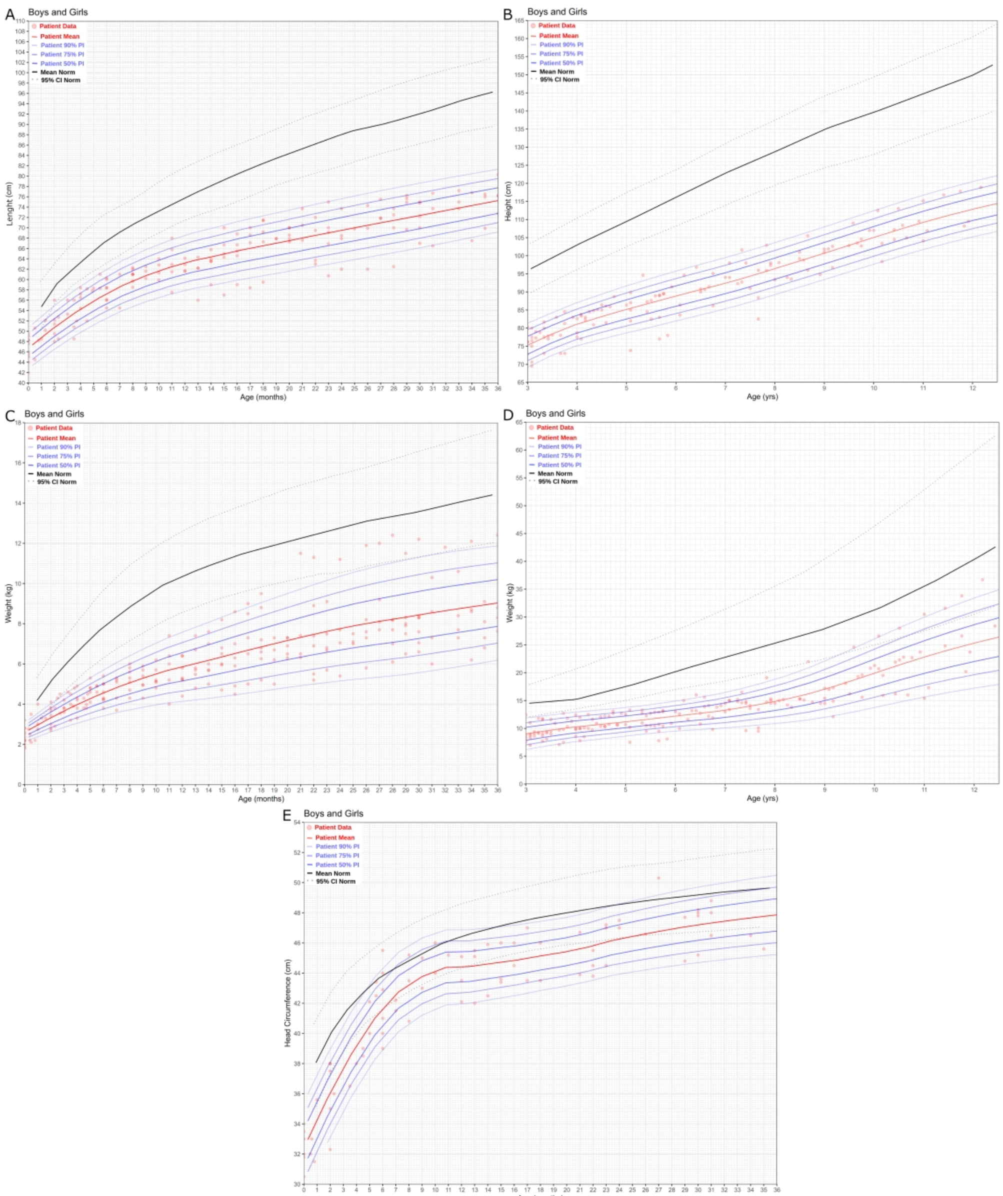


Figure 1. Growth in Saul-Wilson syndrome.(A) Length-for-age 0-3 years. (B) Height-for-age 3-12.5 years. (C) Weight-for-age 0-3 years. (D) Weight-for-age 3-12.5 years. (E) Head circumference-for-age 0-3 years. PI: Prediction interval (used for the affected population), calculated using standard deviations, gives a sense of the probability that a new data point will lie within the indicated region. CI: Confidence interval (used for the normative population), calculated using standard errors, gives a sense of the probability that the mean from a new subject will lie within the indicated region.

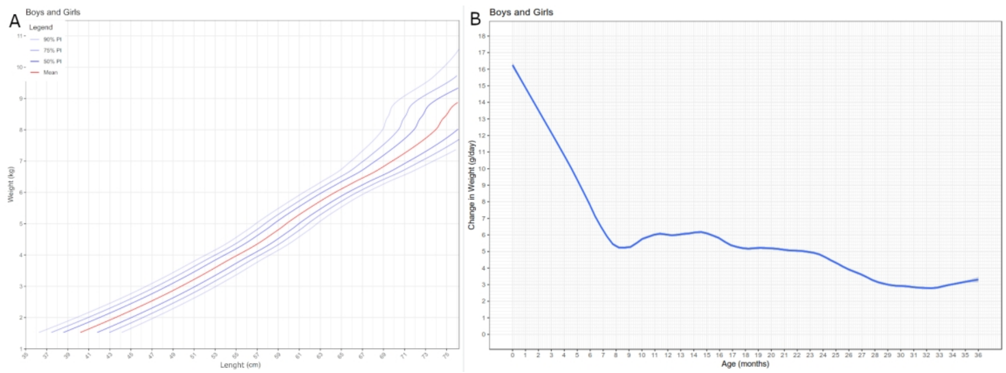


Figure 2. Weight-for-length and weight velocity in Saul-Wilson syndrome. (A) Weight-for-length 0-2.5 years. (B) Weight velocity 0-3 years. PI: Prediction interval; CI: Confidence interval.

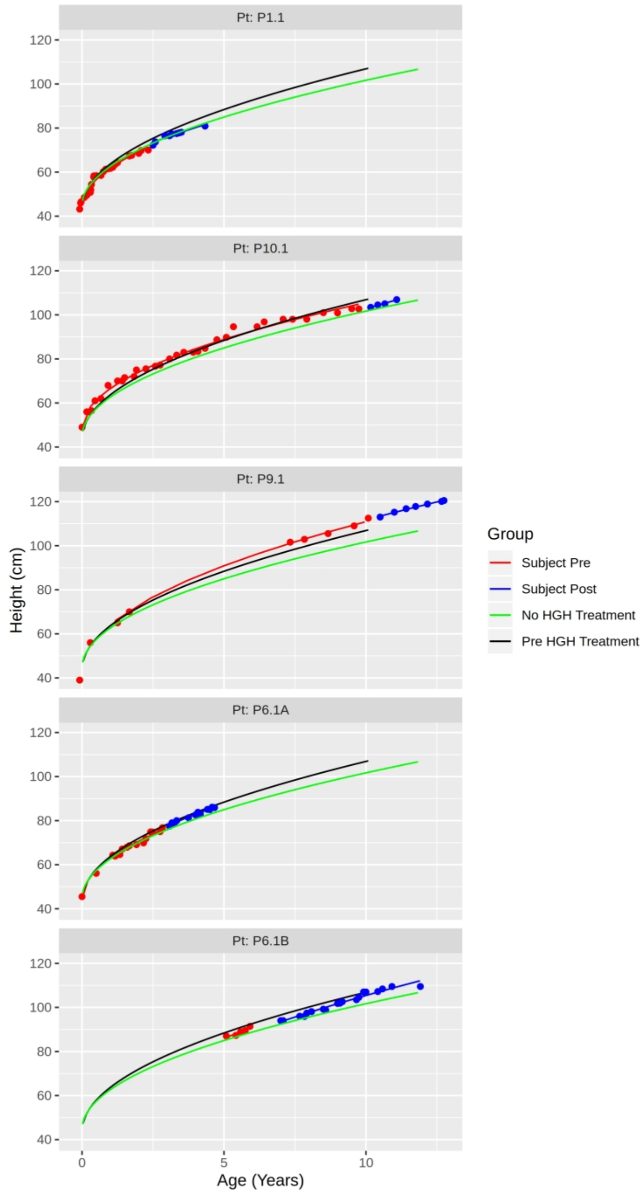


Figure 3. Effect of human growth hormone (HGH) in Saul-Wilson syndrome. Subject Pre: height-for-age model fit for that particular subject before initiation of HGH. Subject Post: height-for-age model fit for the same subject after initiation of HGH. No HGH Treatment: height-for-age model fit for subjects who never received HGH supplementation. Pre HGH Treatment: Height-for-age model fit before initiation of HGH supplementation for subjects who eventually received this therapy. No real difference is observed between the last two fits, or between pre-HGH and post-HGH model fits for each individual subject.

Patient / Age (mo)	P1.1 (male)	P2.1 (female)	P3.1 (male)	P4.1 (female)
0	43.2	48.3	44.0	38.0
0.4	46.0			
0.5				
0.6	46.5			
0.8				
1				
1.3				
1.4				
1.6				
2	48.5	51.4		
2.3				
2.5				
3	49.5			48.0
3.3				48.5
3.5			48.5	
4				
4.5	50.8			
4.7	52.0			
5	54.4			
5.5				52.0
5.9	57.8			
6	58.3	58.4	54.5	
7	58.4			
8		59.7		54.5
9	58.5			
10	60.2			
11	61.3			
12	61.5			57.5
13	61.7			
14	62.2		59.0	
15	63.5	66.7		
16	64.3			
17				59.0
18				
19				
20				
21	67.3			
22	67.6	69.5	63.7	
23				63.0
24				
25	68.5			

26	69.8			
27				
28				
29	70.0	75.6		
30			67.0	
31	72.2			
32	73.7			66.5
33				
34				
35		76.0	69.9	67.5
36	76.5			
37			69.5	
38	76.5			
39	77.3			
40				
41	77.5			
42	77.8			
43	78.1			
45			73.0	73.0
46				
47				
48				
49				
50		82.3		77.0
51				
52				
53	80.9			
54				
55				
56				
57				
60				
61			73.8	
62				
64				
65		84.5		
66				
67				
68			83.0	
69				77.0
71				78.0
72				
73			83.6	
74				

77			
78	90.0		
79			
80			
81		86.2	
84			
85			
87			
88			
89			
91			
92		88.4	
93			82.5
94			
95			
96			
97			
99			
100			
102			
103			
105			
107			
108			
109			
110	96.7		
114			
116			
117			
119			
120			
122			
123			
125			
127			
128			
131			
132	104.1		
133			
138			
142	108.2		
143			
147			
153			

154	
159	108.0
290	
331	
352	109.7
472	

P5.1 (male)	P5.2 (male)	P6.1 (male)	P7.1 (female)	P8.1 (male)
48.3	41.0	45.5		46.0
			48.2	
50.2				
	46.4			
	48.3			
	49.5		52.2	
52.7				
	50.6			
	52.1			
57.2				
			58.2	
				58.3
60.3	58.4	56.1		60.0
61.0				61.0
	61.0			62.5
	61.0			62.8
62.9	61.6			
64.1	64.0		62.9	
	65.8	64.3		
		63.9		
66.7	65.8	64.6		
68.6		67.1		
71.4	68.8		69.2	
		67.9		
		68.6		
73.7	67.9			
	67.9			
	70.5	69.1		
73.7				
	70.0			

		69.9	74.3
		71.8	
	71.9	74.9	76.2
	72.5	74.8	75.0
		75.0	
		76.8	
80.3			
		77.5	
	76.2	79.0	
	75.0	78.8	
		80.0	
	77.0		
84.5		81.3	
	78.0		
		82.6	
		83.8	
	77.5	83.0	
84.5			
		85.1	
86.4		85.0	
		86.1	
		85.9	
	81.5		
86.4			
		87.0	85.0
		87.3	
87.6			
		88.9	
89.1		89.0	
89.5		89.5	
		91.4	

90.8		
90.7		
91.4		
		95.1
	94.0	
	94.0	
92.3		
92.7		
	96.0	
	95.9	
	97.4	
93.4		
	98.1	
94.0		
93.5		
	99.2	
	98.8	
94.8		
	101.8	
	101.9	
	102.6	
	103.5	
	104.6	
	107.0	
	107.0	
	107.2	
	108.4	
	109.5	
	109.5	

108.0
107.3

P9.1 (female)	P10.1 (male)	P11.1 (female)	P12.1 (male)	P13.1 (female)
39.0	49.0	42.0		45.0
		44.5		
			47.6	
	56.0			
	56.0			53.3
	56.5			
56.0				
	61.0			
				56.0
	62.0			
			62.3	
				59.9
	68.0			
				61.6
		56.0		62.2
				63.5
	70.0	57.0		
65.0				65.5
	70.0	58.4		
	71.5	59.5		67.3
70.0			70.0	
	72.0			
	75.0	60.7		66.9
		62.0		67.9

	62.0		
75.5			
	62.5		
		73.7	69.7
			70.0
76.7			
77.2			
		73.7	
			72.8
80.0		76.2	70.6
81.7			73.0
83.0			
83.0			
83.4		78.7	
84.8			
88.7			
89.8			
		82.0	
94.6			
		82.5	
94.6		86.4	

	96.8	
	98.0	
101.6	98.0	
		91.0
102.9	98.0	
	101.0	
105.5		96.0
	100.9	
	102.8	
109.0		
	102.7	
112.5	103.4	
		98.4
	104.5	
113.0		
	105.0	
115.2	106.9	
116.8		
117.8		
118.9		
120.1		

120.5

106.0

Comment

12 do
15 do
20 do
23 do

40 do
42 do
49 do

68 do
77 do

100 do
106 do

136-141 do
143 do

164-169 do
178 do

Age (mo) \ Patient	P1.1 (male)	P2.1 (female)	P3.1 (male)	P4.1 (female)
0	2.2	2.5	1.9	1.5
0.4	2.1			
0.5				
0.6	2.3			
0.8				
1	2.6			
1.3	2.8			
1.4				
1.6				
2	2.8	2.8		
2.3				
2.5				
2.6	3.3			
3	3.4			2.7
3.3				2.9
3.5			3.2	
3.7	3.6			
4	3.8			
4.5	4.0			
4.7	3.9			
5	4.3			3.3
5.3				
5.5				
5.8	4.5			
6	4.8	3.8	4.2	
7	4.6			
8		4.3		3.7
9	5.1			
10	5.0			
11	5.2			
12	5.2			4.0
13	5.3			
14	5.7		5.0	
15	5.7	6.0		
16	6.0			
17				4.5
18				
19				
20	6.2			
21	6.3			
22	6.5	6.9	5.5	

23				5.2
24	6.8			
25	7.1			
26	7.0			
27				
28				
29	7.7	6.5		
30	7.5		6.6	
31	7.6			
32	7.3			6.0
33				
34	7.3			
35		7.3	6.8	6.2
36	8.1			
37			7.0	
38	8.3			
39	8.6			
40				
41	8.7			
42	9.4			
43	9.0			
44				
45			7.5	7.1
46				
47				
48				
49				
50		8.5		7.8
51				
52				
53	9.7			
54				
55				
56				
57				
58				
59				
60				
61			7.5	
64				
65		9.5		
66				
67				
68			9.5	

69			7.8
71			8.1
72			
73		10.0	
74			
75			
76			
77			
78	10.8		
79			
80			
81		9.8	
82			
83			
84			
85			
87			
88			
89			
90			9.6
92		10.1	
93			9.5
94			
95			
96			
97			
98			
99			
100			
102			
103			
105			
107			
108			
109			
110	12.1		
113			
114			
116			
117			
119			
120			
121			
122			

123	
125	
126	
127	
128	
129	
131	
132	15.4
133	
137	
138	
141	
142	20.2
143	
147	
149	
153	
154	
159	20.0
165	
172	20.4
205	22.7
233	22.7
262	24.9
290	
298	24.5
331	
352	25.3
472	

P5.1 (male)	P5.2 (male)	P6.1 (male)	P7.1 (female)	P8.1 (male)
2.2	1.8	2.2	2.0	2.8
2.5				
			2.2	
3.3				
	2.8			
	3.0			
	3.2		3.0	
3.8				
	3.5			
3.8	4.0			
4.2	4.1			
4.3	4.3		3.8	
	4.5			
4.6				4.8
	4.6			
4.9				4.9
	4.8			
5.0	4.9	4.3		5.0
5.1	5.3			5.3
5.3	5.4			5.6
5.4	5.2			5.7
5.1	5.8			5.7
6.0	5.9			
6.4	6.2	5.8	5.2	
7.4	6.4	5.8		
7.6	6.4	6.0		
	6.7			
8.6	7.0	6.3		
9.0	6.8	6.5		
9.5	7.0	6.6	6.8	
	7.3	6.7		
	7.2	6.9		
11.5	7.3			
11.3	7.3			

	7.4	7.5	
11.2	7.4		
11.9	7.7	7.6	7.3
12.0	7.5	7.7	
12.4	8.2	8.2	
11.5	8.1	7.9	8.0
12.2	8.2	8.3	8.3
	8.3		
11.8	8.4		
	8.6	8.4	
12.1		8.7	
		9.1	
12.4	8.6		
		8.7	
	8.8	9.4	
11.8	9.0	9.1	
11.7	9.1	9.1	
	9.3		
11.6			
	9.2		
	9.5		
12.7		9.8	
11.8	9.7		
12.4		10.0	
		10.0	
	9.8	10.1	
12.5	10.0		
	10.0	10.9	
12.1		10.4	
12.2		10.4	
12.2		10.7	
12.7	10.3		
		10.6	
12.7			
12.5	10.7		10.7
		10.2	
12.7		11.0	
12.3		10.5	
12.7			
12.9		10.4	
12.9		10.7	

13.2	10.4	
	10.9	
13.0		
	11.6	
13.2		
13.2		
12.7		
13.9		
14.1	12.2	
		11.9
13.8		
14.1		
14.5	13.0	
15.0	13.4	
15.2	14.8	
14.6		
14.5		
14.1	13.6	
	13.4	
	14.7	
14.5	15.0	
14.5		
	15.0	
	15.2	
14.2		
13.8		
	15.3	
	15.1	
14.7		
14.5		
14.5	17.2	
	17.0	
14.9	17.3	
	18.1	
	19.3	
	19.6	
	20.8	
	21.3	
	20.7	

21.9
22.3
22.8

22.7
23.7

24.8

26.6

23.7

28.4

23.8

30.2

P9.1 (female)	P10.1 (male)	P11.1 (female)	P12.1 (male)	P13.1 (female)	Comment
2.1	2.8	1.8	1.5	2.2	
				2.2	12 do
		2.1			15 do
					20 do
					23 do
			2.4	3.0	
					40 do
					42 do
					49 do
	3.8			3.7	
					68 do
					77 do
					81 do
	4.2			3.6	
					100 do
					106 do
					112 do
	3.8				
4.5					136-141 do
		3.8		4.0	143-147 do
				4.1	
					161 do
	4.6				164-169 do
					171-178 do
				4.3	
				4.3	
	6.0				
		4.3	4.7	5.0	
		4.8		5.1	
	7.4				
		4.4		5.2	
		4.8		5.5	
				5.7	
	8.2	4.7			
6.5		4.9		5.9	
	8.5	5.0			
	8.8	5.2		6.3	
		5.0			
7.3			6.5	6.3	
	8.9				

9.1	5.7		6.7
	5.4		
			7.1
	5.8		
9.2			
	6.1		
		7.0	
			7.1
10.3			
10.6			
		7.7	
			7.6
11.0		8.3	
11.6			7.7
			8.1
10.9			
10.3			
11.3			
12.0		8.6	
11.6			
13.1			
13.3			
13.3			
		10.5	

	13.0	
	15.0	12.6
	16.0	
	15.6	
	15.0	
16.5	14.8	
19.1	15.3	
	15.3	
22.0		
	15.4	
	16.2	
24.6		
	15.6	
26.6	15.9	

		19.5
	16.2	
28.0		
	16.0	
30.5	17.3	
31.6		
33.8		
36.7		
36.8		
37.1		
37.6		
		39.0

Age (mo) \ Patient	P1.1 (male)	P2.1 (female)	P3.1 (male)	P4.1 (female)
0		31.8	30.0	29.0
0.5				
0.6	32.7			
0.8				
1				
2		32.3		
3	38.0			
3.3				36.0
3.5			36.5	
4				
4.5				
5				
5.5				39.0
6	42.1	39.0	40.0	
7	42.9			
8		40.8		41.5
10	45.0			43.0
11				
12				
13	45.1			
14	45.5		42.5	
15		43.6		
16	46.0			
17				44.5
18				
21				
22		44.5	43.8	
23				45.5
24	47.0			
25	47.5			
26				
29		44.8		
30			45.2	
31	48.2			
32	48.8			46.5
33				
35		45.6		46.5
37			45.8	
39				
45			46.0	47.5
46				

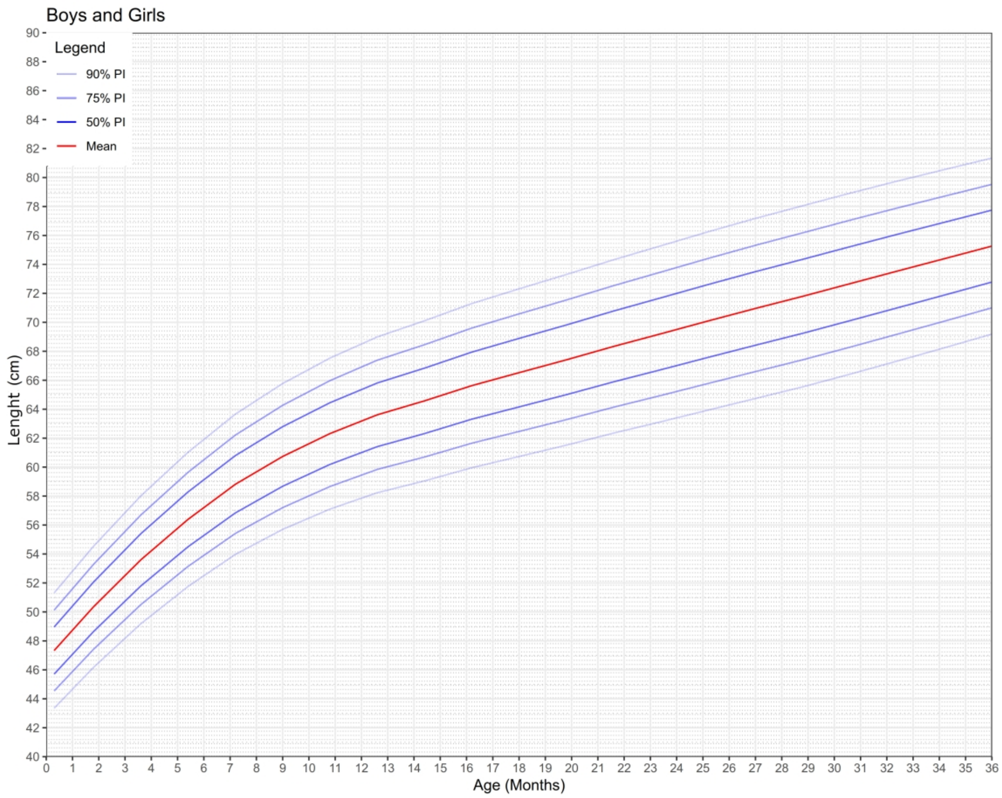
49			
50			48.0
54			
57			
61			
62			
64			
65	45.6		
69			48.0
71			48.0
78	46.0		
79			
81		46.5	
88			
92		47.1	
93			48.5
95			
96			
97			
102			
105			
107			
108			
110	46.6		
114			
116			
120			
123			
132	47.0		
172	47.8		
205	47.5		
233	48.5		
262	49.5		
290			
327			
352	49.0		

P5.1 (male)	P5.2 (male)	P6.1 (male)	P7.1 (female)	P8.1 (male)
33.0	31.5	30.5		33.5
			31.5	
			35.0	
			38.5	
				43.4
45.5				44.0
				45.2
				46.0
			43.5	
		45.9		
			46.0	
			46.6	
	50.3			
			48.0	
	50.7			
	51.2			

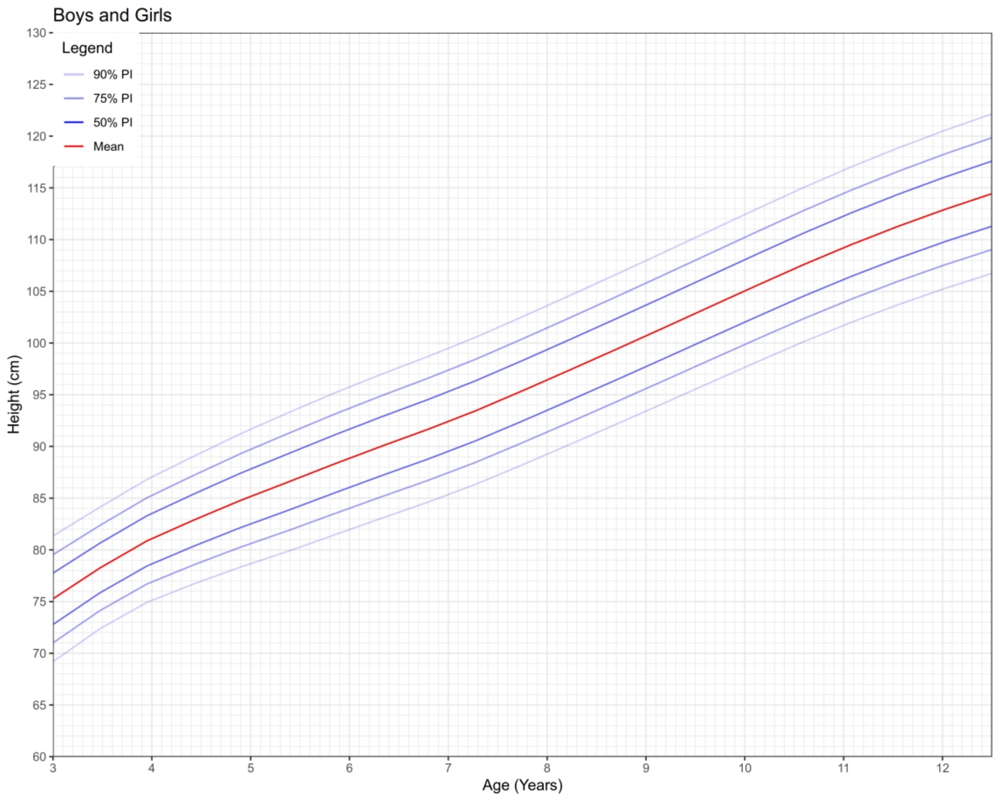
51.6
49.0
50.5
50.6
49.2
50.7
50.6
50.0
50.7
50.0
51.0
51.4

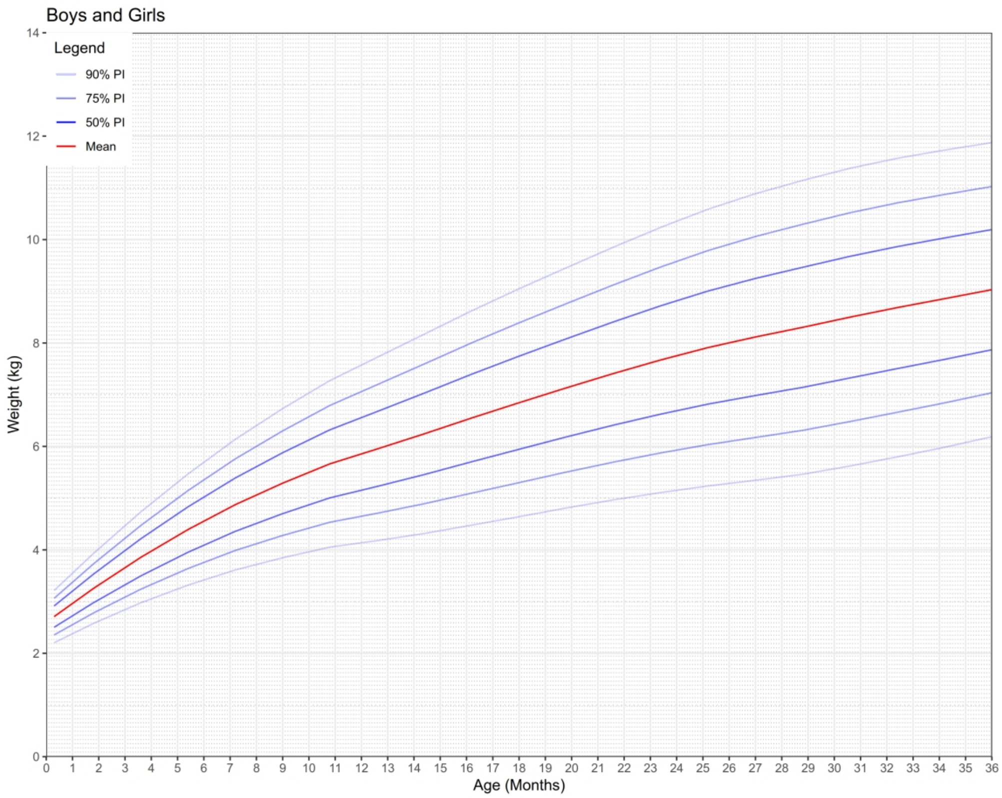
P9.1 (female)	P10.1 (male)	P11.1 (female)	P12.1 (male)	P13.1 (female)	Comment
	34.0			32.0	
		32.0			15 do
				33.0	20 do
					23 do
				35.6	
	38.0			37.5	
					100 do
					106 do
	38.0				
					139 do
				40.0	
	42.5				164-169 do
				41.0	
				42.2	
	43.5				
				44.0	
	45.2				
		42.1			
		42.0		45.1	
		43.4			
				46.0	
	47.0	43.5			
		43.5			
		43.9		46.7	
	47.2	44.5			
				47.0	
				47.7	
				47.8	
	48.0				
				48.5	

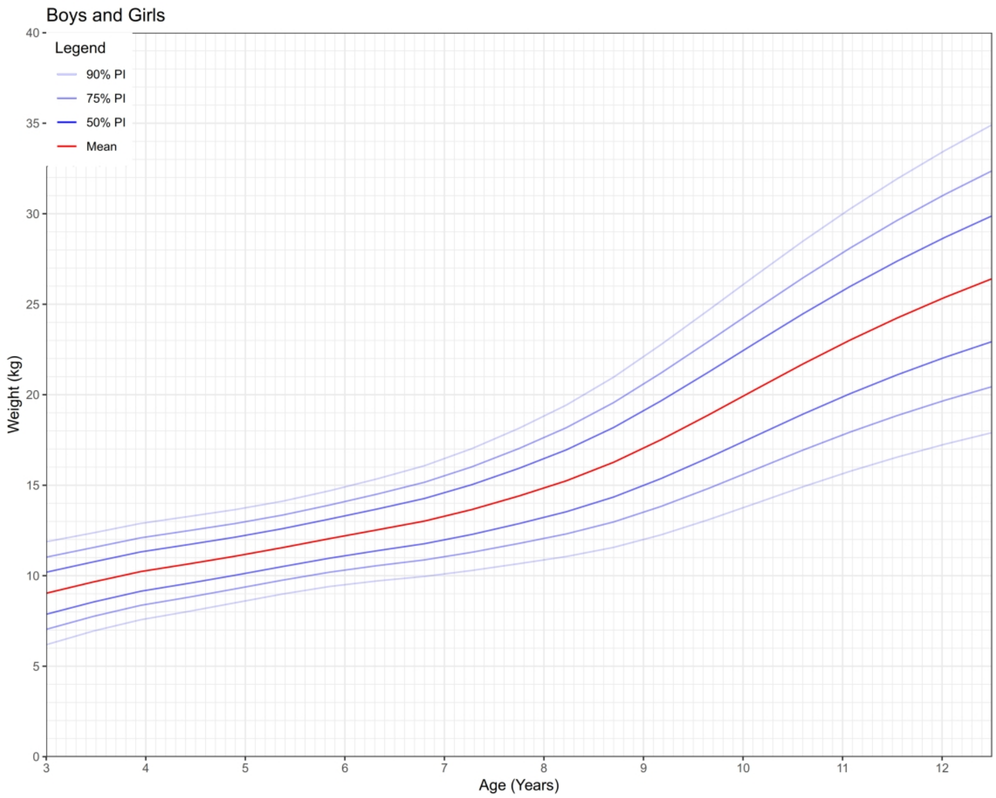
		48.0
	49.5	
		48.7
	49.2	
	50.0	
	50.4	
	50.4	
		49.8
	50.3	
	49.7	
51.0		
		50.0

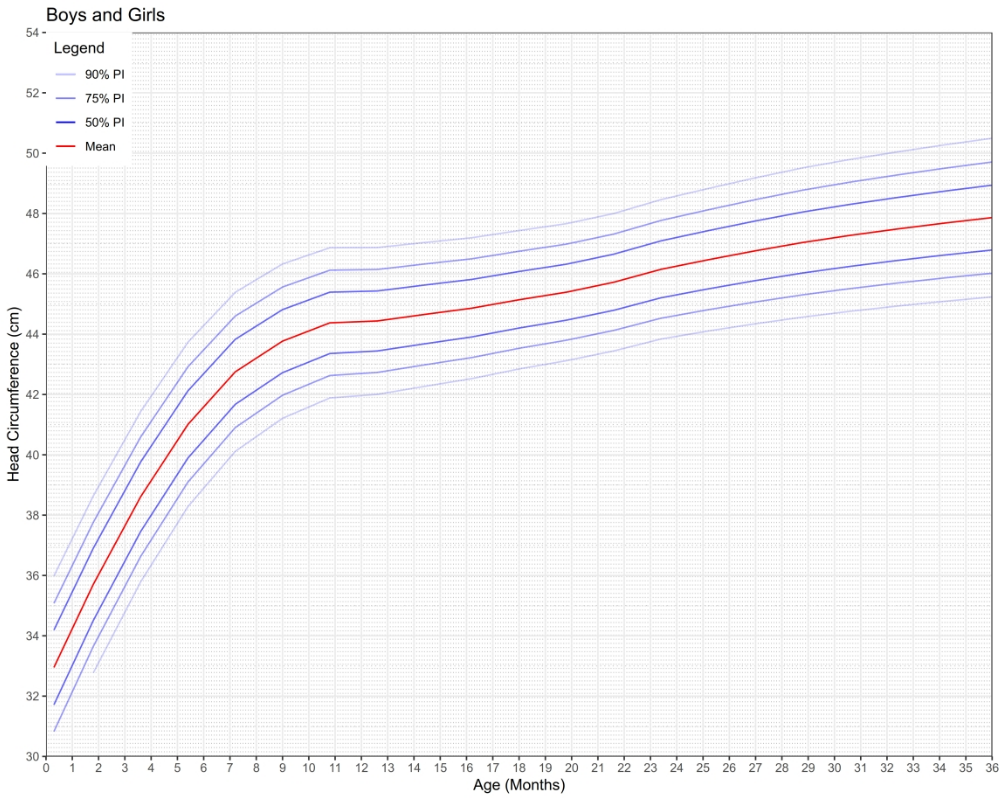


Boys and Girls
Legend
90% PI
75% PI
50% PI
Mean
Lenght (cm)
Age (Months)

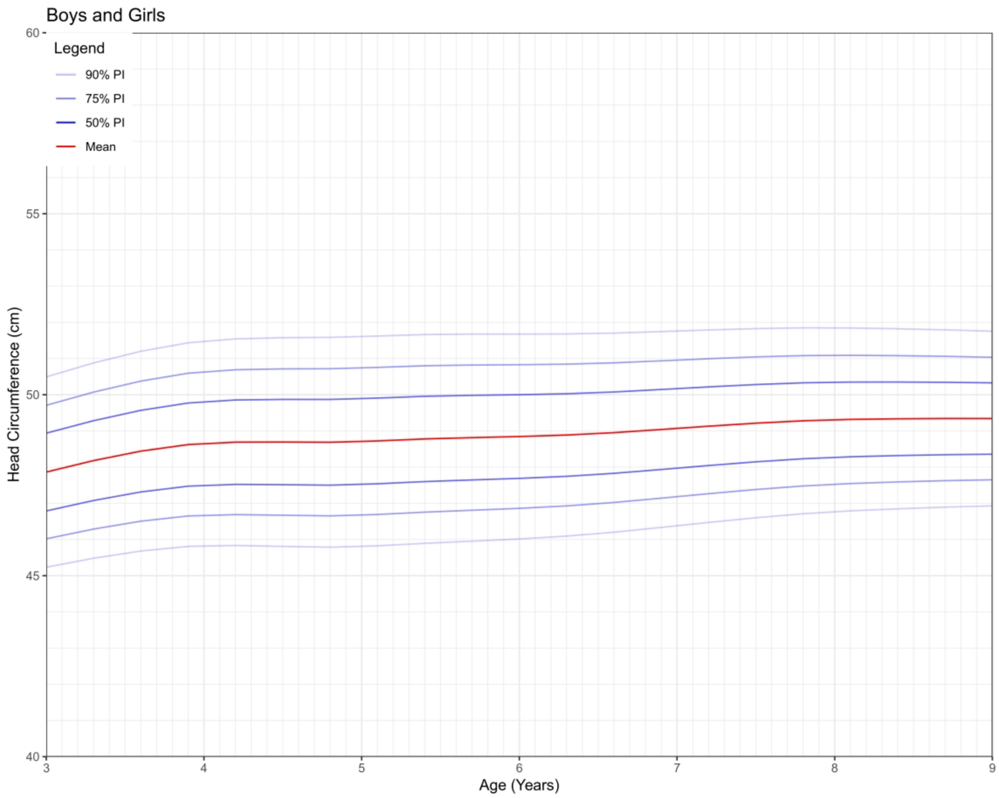

Boys and Girls
Legend
90% PI
75% PI
50% PI
Mean
Height (cm)
Age (Years)
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
3
4
5
6
7
8
9
10
11
12


Boys and Girls
Legend
90% PI
75% PI
50% PI
Mean
Weight (kg)
Age (Months)


Boys and Girls
Legend
90% PI
75% PI
50% PI
Mean
Weight (kg)
Age (Years)
0
5
10
15
20
25
30
35
40
3
4
5
6
7
8
9
10
11
12



Boys and Girls
Legend
90% PI
75% PI
50% PI
Mean
Head Circumference (cm)
Age (Months)


Boys and Girls
Legend
90% PI
75% PI
50% PI
Mean
Head Circumference (cm)
Age (Years)
60
55
50
45
40
3
4
5
6
7
8
9