

Growth Charts for 22q11 Deletion Syndrome

Daniel C. Tarquinio,¹ Marilyn C. Jones,^{2,3} Kenneth Lyons Jones,³ and Lynne M. Bird^{2,3*}

¹Department of Pediatric Neurology, Miami Children's Hospital, Miami, Florida

²Division of Dysmorphology/Genetics, Rady Children's Hospital, San Diego, California

³Department of Pediatrics, University of California, San Diego, San Diego, California

Manuscript Received: 10 January 2012; Manuscript Accepted: 25 April 2012

The purpose of this work was to create growth curves specific to the 22q11.2 deletion syndrome. Growth parameters on 188 patients (86 females, 102 males) followed by a group of three dysmorphologists were collected by retrospective chart review. Growth charts for body mass, length/height, and head circumference were generated using a semi-parametric model with goodness-of-fit tests. The resulting charts show that between 25 and 50% of children with 22q11.2 deletion syndrome fall below the 2nd centile for the normal population for all growth parameters. Establishing norms of growth for 22q11.2 deletion syndrome allows the clinician to identify and investigate those children who deviate substantially from the growth profile of this condition. © 2012 Wiley Periodicals, Inc.

Key words: DiGeorge syndrome; velo-cardio-facial syndrome; 22q11.2 deletion syndrome; growth; stature

INTRODUCTION

The chromosome 22q11.2 deletion syndrome (DiGeorge syndrome, velo-cardio-facial syndrome) is the most common microdeletion syndrome, with an estimated incidence of 1/3,000–1/4,000 live births [Devriendt et al., 1998; Goodship et al., 1998; McDonald-McGinn & Sullivan, 2011]. Features include conotruncal cardiac and aortic arch malformations [Momma et al., 1999], hypoplasia of the thymus gland (leading to low T-cell numbers but usually adequate functional immunity) [Markert et al., 1998; Jawad et al., 2001], hypoplasia of the parathyroid glands (causing hypocalcemia which is usually transient) [McDonald-McGinn et al., 1999], facial dysmorphism, palatal cleft and/or velopharyngeal dysfunction [McDonald-McGinn et al., 1999], cognitive impairment [Woodin et al., 2001; Swillen et al., 2000], expressive language disorder [Gerdes et al., 1999; Moss et al., 1999; Solot et al., 2000; Scherer et al., 2001; Solot et al., 2001], and neuropsychiatric disorders [Swillen et al., 2000; Niklasson et al., 2001; Fine et al., 2005; Jolin et al., 2009].

Growth deficiency is common in the 22q11.2 deletion syndrome, particularly in infancy and early childhood, but final adult height is usually normal [McDonald-McGinn et al., 1997; Ryan et al., 1997; Digilio et al., 2001; Bassett et al., 2011]. Growth hormone deficiency is responsible for short stature in a minority of patients [Weinzimer et al., 1998] and growth velocity can be

How to Cite this Article:

Tarquinio DC, Jones MC, Jones KL, Bird LM. 2012. Growth charts for 22q11 deletion syndrome.

Am J Med Genet Part A 158A:2672–2681.

improved with the administration of recombinant growth hormone [Weinzimer, 2001]. Growth curves specific to the 22q11.2 deletion will assist the pediatric clinician in deciding which children with this syndrome need further investigation of their growth deficiency.

METHODS

Patient Population and Data Collection

This study was approved by the Human Research Protection Program of the University of California, San Diego. One hundred eighty eight patients followed by three clinical geneticists/dysmorphologists in San Diego were identified using the diagnoses of DiGeorge syndrome and velo-cardio-facial syndrome. Only patients with a 22q11.2 deletion confirmed by molecular cytogenetics or DNA analysis were included. One patient with a second genetic diagnosis (Duchenne muscular dystrophy) was excluded. One set of monozygotic twins were included. Retrospective review was undertaken to gather growth data from visits to the dysmorphology clinic as well as growth parameters recorded in the hospital medical record from other outpatient or inpatient visits. Ages were adjusted for prematurity through 2 years if gestational age (GA) was less than 37 weeks. All individuals were included without regard to presence or absence of a cardiac anomaly, as no relationship between stature and cardiac disease status has been demonstrated in 22q11 deletion syndrome [Ryan et al., 1997].

*Correspondence to:

Lynne M. Bird, MD, Division of Genetics/Dysmorphology, Rady Children's Hospital San Diego, 3020 Children's Way #5031, San Diego, CA 92123. E-mail: Lbird@rchsd.org

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 6 August 2012

DOI 10.1002/ajmg.a.35485

Growth Chart Generation

The data were screened using multiple exploratory data analysis techniques, including individual scatterplots for each participant, summary boxplots, histograms and quantile-quantile plots to identify outliers and compare distributions at target measurement ages. Outliers were investigated through source documentation, and if no resolution could be achieved the data were discarded. Less than 1% of the data were discarded after this process.

Growth references for the 2nd, 10th, 25th, 50th, 75th, 90th, and 98th centiles were modeled using the LMS method [Cole and Green, 1992], a semiparametric technique which normalizes the data using a power transformation (L), and summarizes the distribution based on the median (M) and coefficient of variation (S). Notably, after transformation the mean and median are equivalent. The values of L , M , and S are constrained to change smoothly with age using a penalized maximum likelihood approach. The estimated degrees of freedom (EDF) of curves for L , M , and S can be manipulated based on examination of goodness of fit testing [Pan and Cole, 2004], and choice of EDF values allows the user to strike a balance between charts that are empirically valid and aesthetically pleasing as well as biologically plausible. These centiles were chosen based on standard deviation (SD) scores separated by 0.667 SD. The 2nd and 98th centiles are equivalent to -2 SD and $+2$ SD, extremes used in recent references such as the WHO growth standards. Normative growth references [Cole et al., 1998] were compared to the 22q11.2 deletion syndrome references through visual inspection and using t -test at certain ages with $P < 0.05$ considered significant.

RESULTS

Demographics

The ethnic background of the patients included in this study was 45% Caucasian, 37% Hispanic, 6% Asian/Pacific Islander, 2% African-American, and 10% other/unknown. GA at birth ranged from 29.7 weeks to 41.4 weeks.

Measurements

A total of 1,148 height measurements, 1,235 weight measurements, and 458 occipito-frontal circumference (OFC) measurements were available on 86 females. A total of 1,327 height measurements, 1,423 weight measurements, and 551 OFC measurements were available on 102 males. An average of 13 height measurements, 14 weight measurements, and five OFC measurements per patient were available.

Summary Statistics

Mean birth height, weight, and OFC measurements of infants with the 22q11.2 deletion syndrome are between 0.5 and 1.0 SD below the mean compared to the normative population. Kolmogorov–Smirnov test on birth data indicated that they were normally distributed.

Figures 1–3 illustrate growth of female infants with the 22q11.2 deletion syndrome from 0 to 36 months. Figures 4–6 illustrate the growth of male infants with the 22q11.2 deletion syndrome from 0 to 36 months. Figures 7–10 illustrate the growth of females with the 22q11.2 deletion syndrome from 2 to 20 years. Figures 11–14

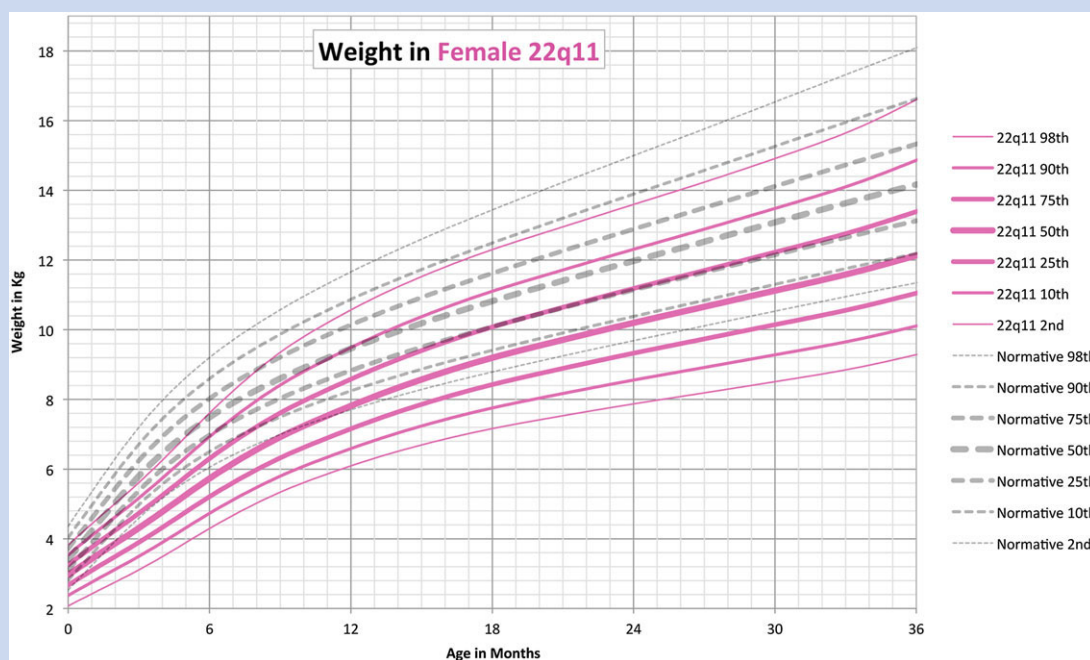


FIG. 1. Weight in girls with 22q11 deletion syndrome, ages 0–36 months.

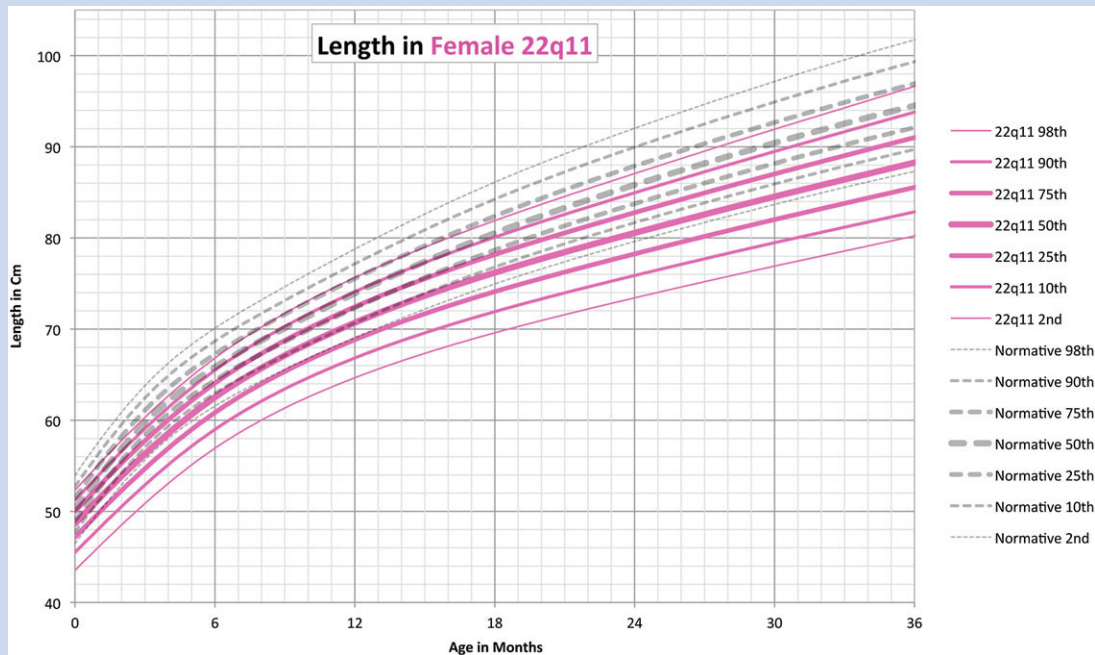


FIG. 2. Length in girls with 22q11 deletion syndrome, ages 0–36 months.

illustrate the growth of males with the 22q11.2 deletion syndrome from 2 to 20 years.

Growth rate through infancy and childhood is slower than the normal population, with 25–50% of children with 22q11.2 deletion

syndrome growing below the 2nd centile for the normal population for height, weight, and head circumference through the majority of childhood. Notably, although the BMI distribution is much wider in 22q11.2 deletion syndrome, mean BMI is similar to the normal

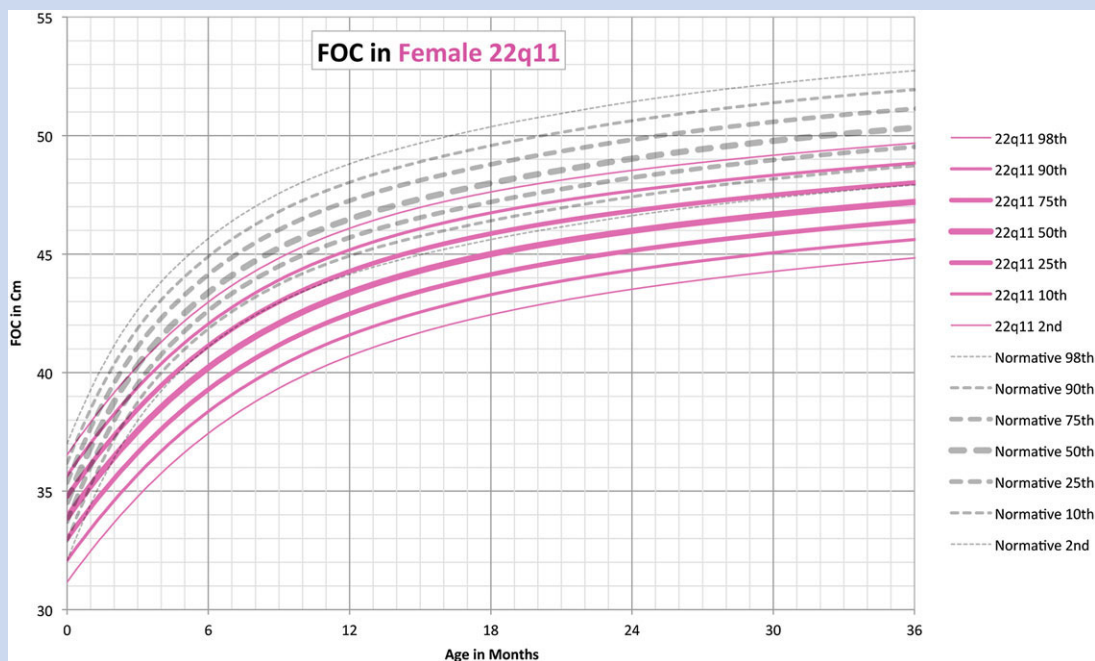


FIG. 3. Occipito-frontal head circumference in girls with 22q11 deletion syndrome, ages 0–36 months.

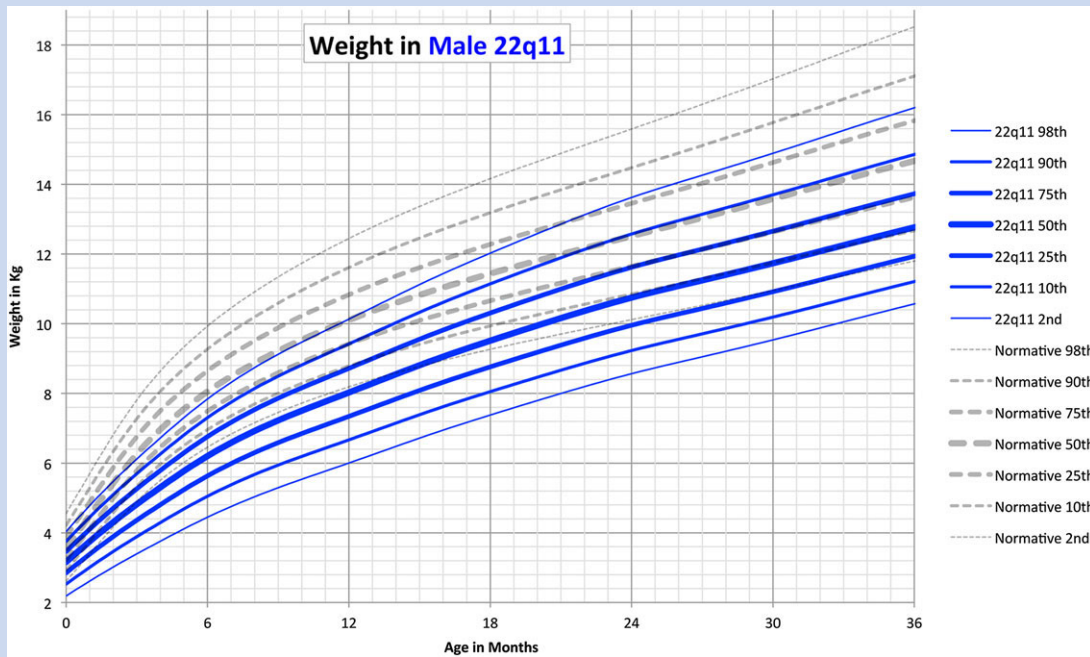


FIG. 4. Weight in boys with 22q11 deletion syndrome, ages 0–36 months.

population. Although adult values for weight, BMI, and OFC were similar to the normal population, adult height was lower in 22q11.2 deletion syndrome compared to the normal population ($P < 0.05$, Table I).

DISCUSSION

The primary goal of this study was to provide clinicians with a practical way to assess the growth of children with 22q11.2 deletion syndrome.

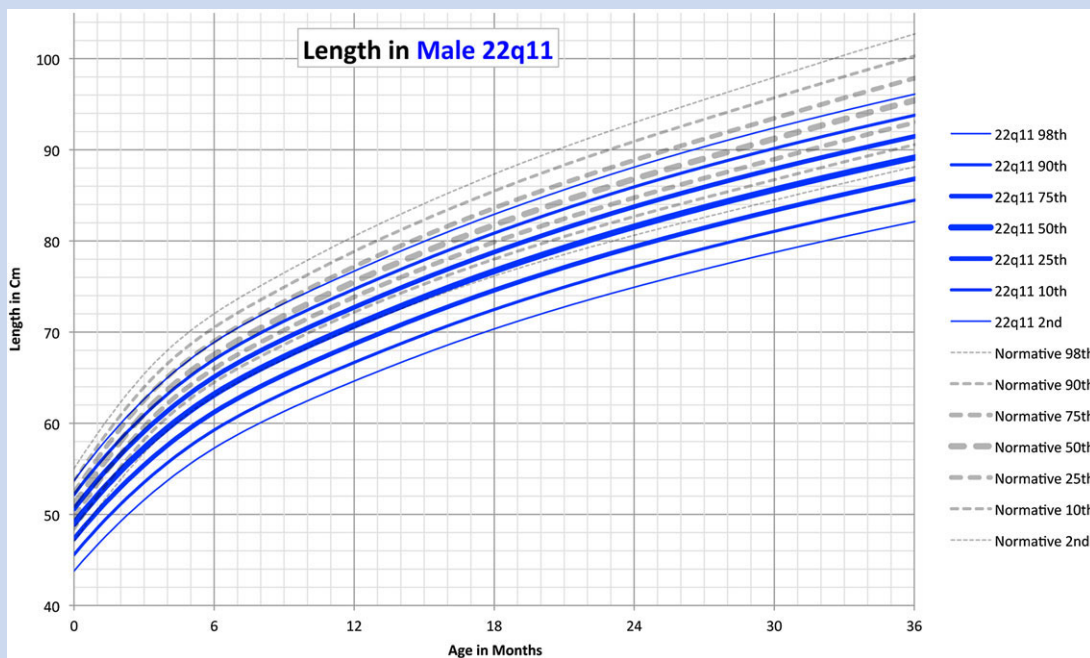


FIG. 5. Length in boys with 22q11 deletion syndrome, ages 0–36 months.

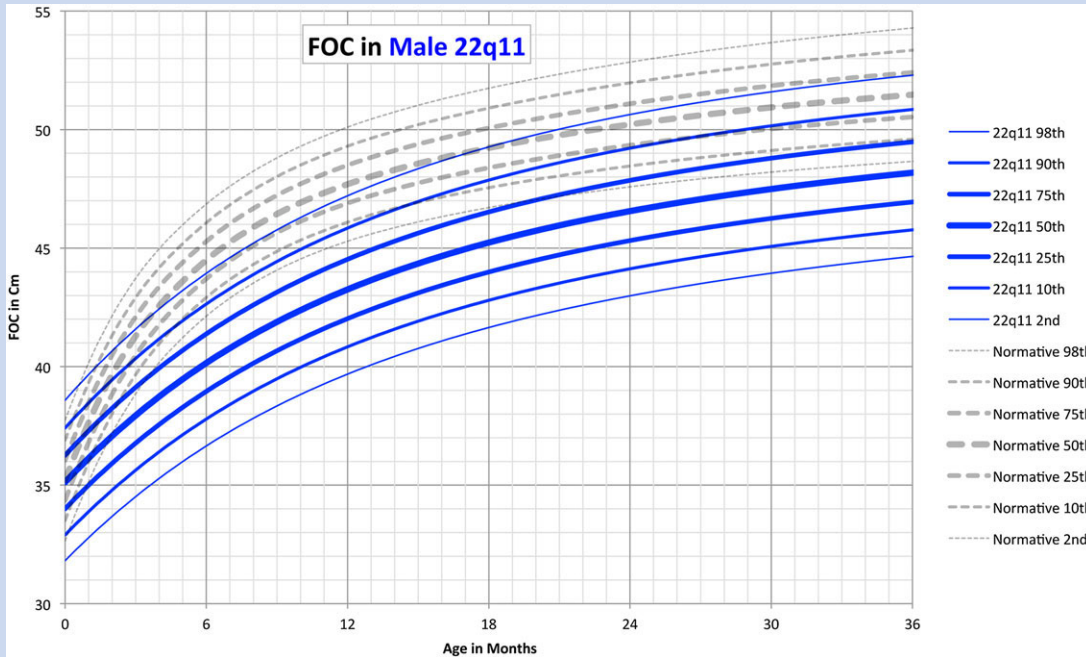


FIG. 6. Occipito-frontal head circumference in boys with 22q11 deletion syndrome, ages 0–36 months.

Newborns with the 22q11.2 deletion syndrome are smaller than the normal population by 0.5–1.0 SDs. These data are in agreement with the findings of Brauner et al. [2003] and Choi et al. [2005]. Growth in the 22q11.2 deletion syndrome is slower in infancy and

childhood, and Goldberg et al. [1993] have asserted that growth impairment is due in part to constitutional delay of growth. According to several authors, adolescent [Digilio et al., 2001] and final adult heights [Ryan et al., 1997] in the 22q11.2 deletion

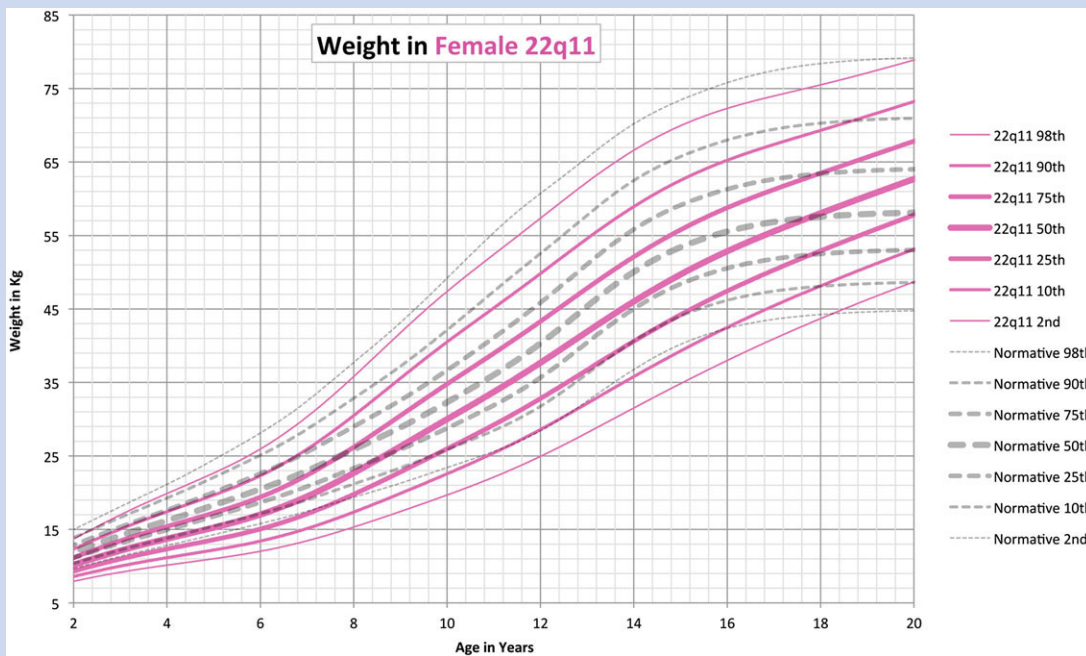


FIG. 7. Weight in females with 22q11 deletion syndrome, ages 2–20 years.

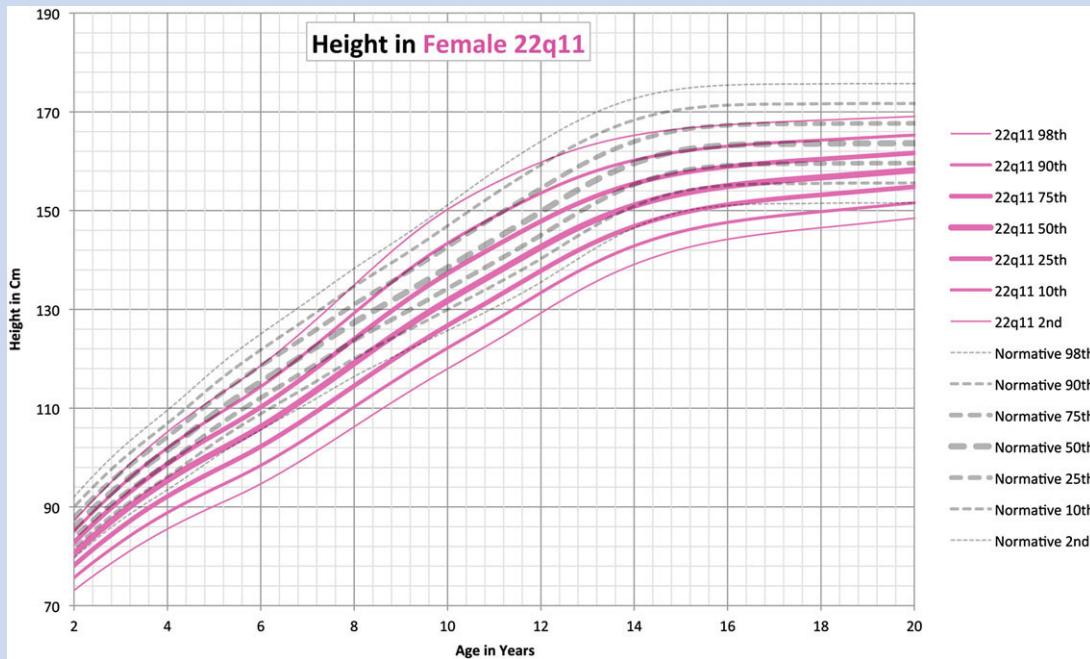


FIG. 8. Height in females with 22q11 deletion syndrome, ages 2–20 years.

syndrome are usually in the normal range. Notably, some large reviews [Shprintzen, 2008; McDonald-McGinn and Sullivan, 2011] do not discuss growth in the 22q11.2 deletion syndrome, implying that growth in this condition does not differ significantly enough

from that of the general population to warrant discussion. However, we found that a substantial percentage of adult individuals remain below the 2nd centile for the general population, which other authors have noted [Bassett et al., 2011].

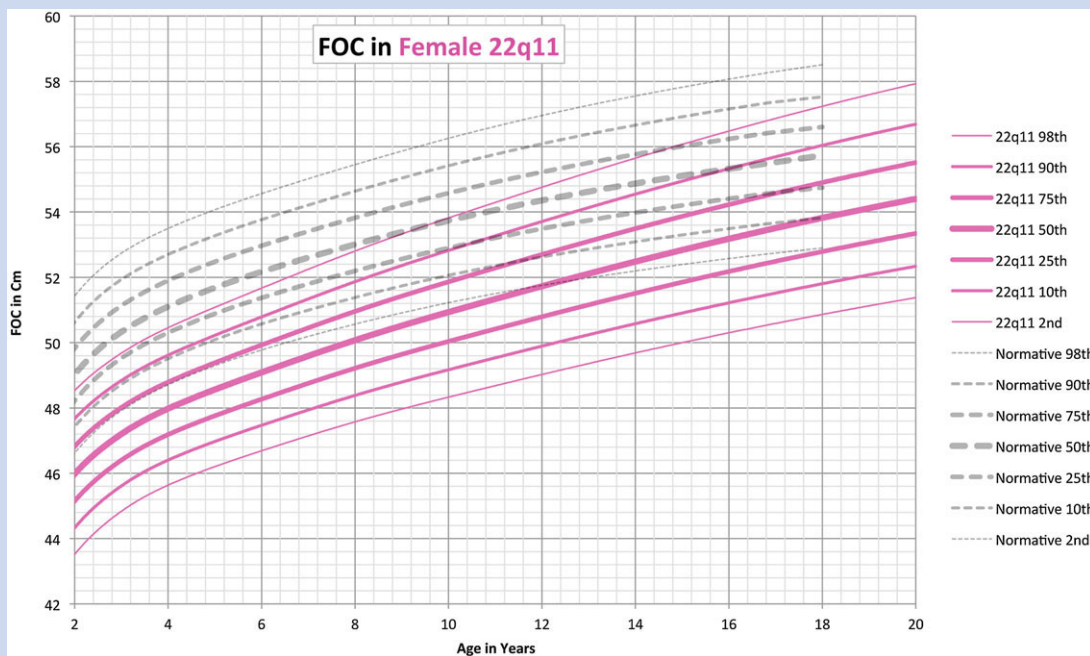


FIG. 9. Occipito-frontal head circumference in females with 22q11 deletion syndrome, ages 2–20 years.

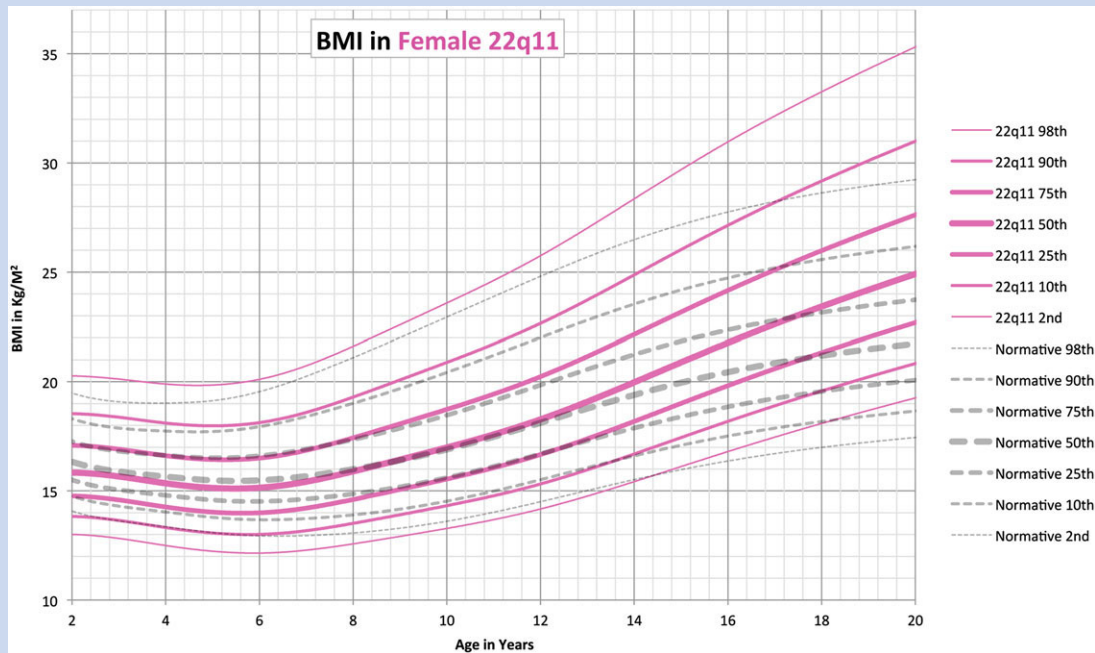


FIG. 10. BMI in females with 22q11 deletion syndrome, ages 2–20 years.

Growth hormone deficiency has been documented in a minority of children with 22q11.2 deletion syndrome [Weinzimer, 2001]. Weinzimer et al. [1998] found 4 of 95 patients (all with height below -2.5 SDs units) had subnormal GH secretory responses

to stimulation with clonidine and arginine. Two patients who were treated showed a response to GH administration, but it is unknown if this response was sustained and resulted in improved adult stature.

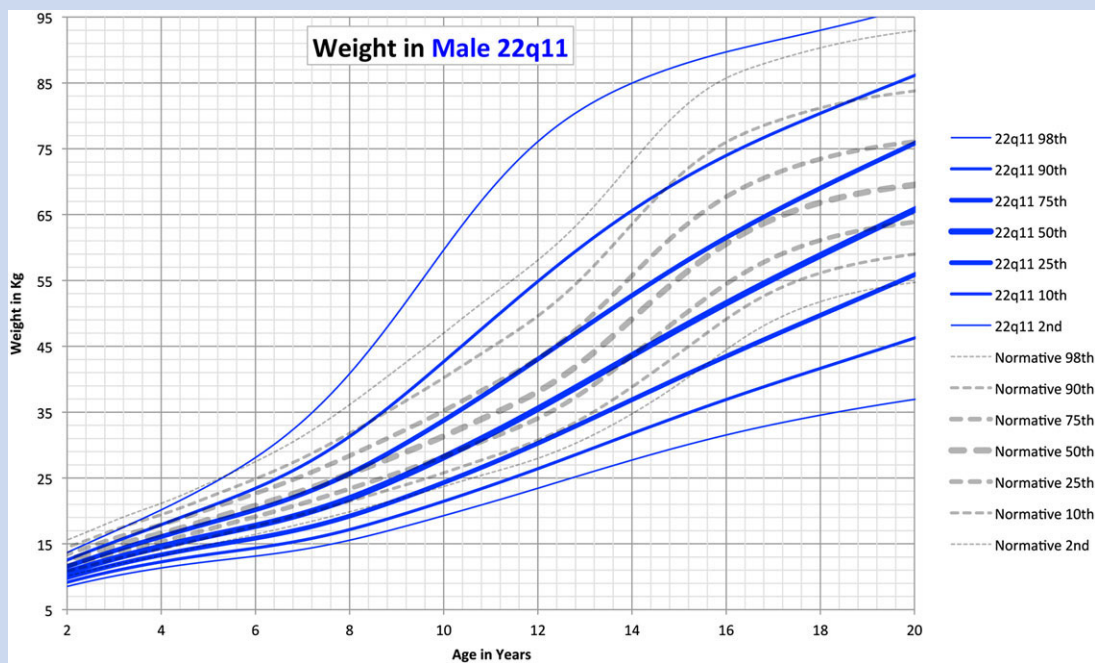


FIG. 11. Weight in males with 22q11 deletion syndrome, ages 2–20 years.

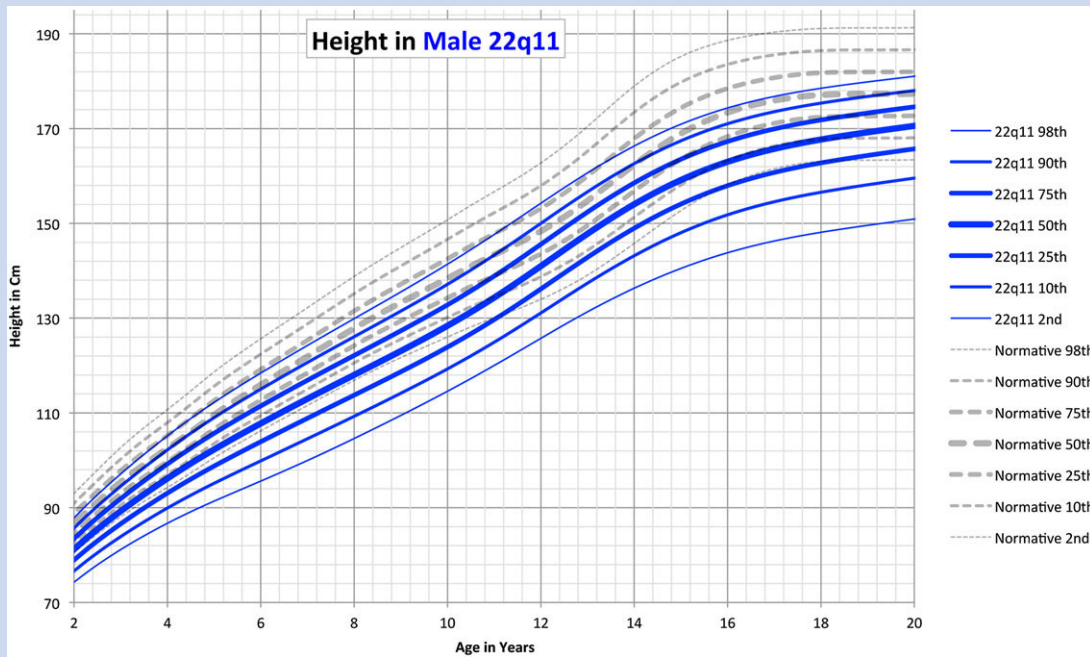


FIG. 12. Height in males with 22q11 deletion syndrome, ages 2–20 years.

Limitations of this study include (1) pooling of data from varied racial backgrounds and (2) lack of standardized measurement methods. A stadiometer was not consistently used, and for some visits it is unknown if the patient was disrobed for weighing.

However, these data reflect the imperfect way growth data are collected in a typical practice. Since this was not a prospective study, other data of interest, such as bone age, parental heights, and pubertal maturation status, were not routinely collected.

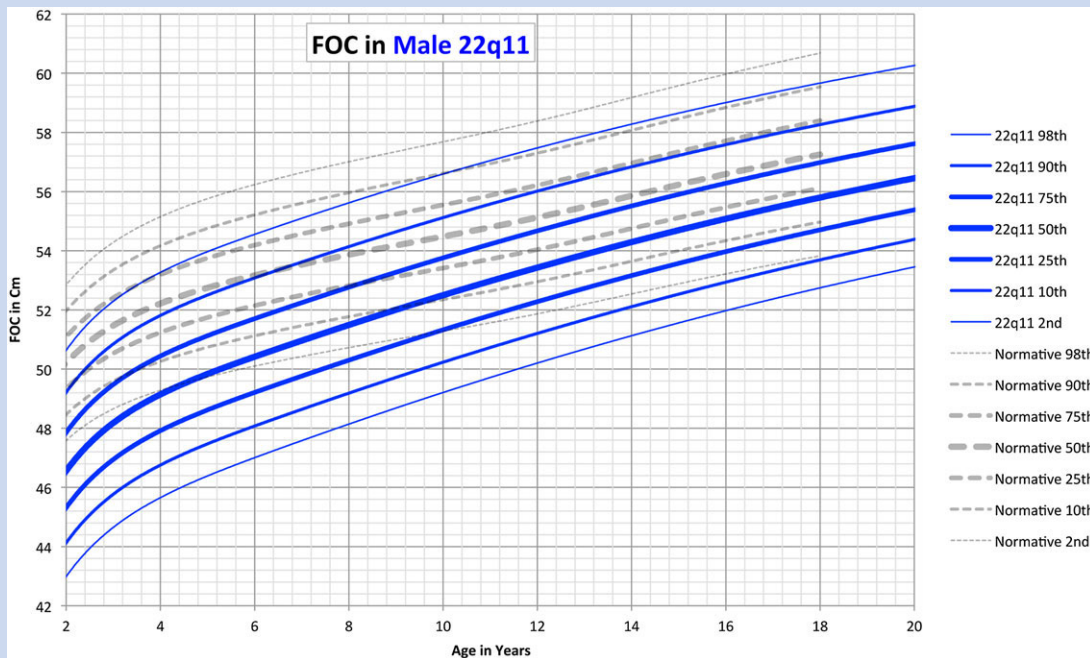


FIG. 13. Occipito-frontal head circumference in males with 22q11 deletion syndrome, ages 2–20 years.

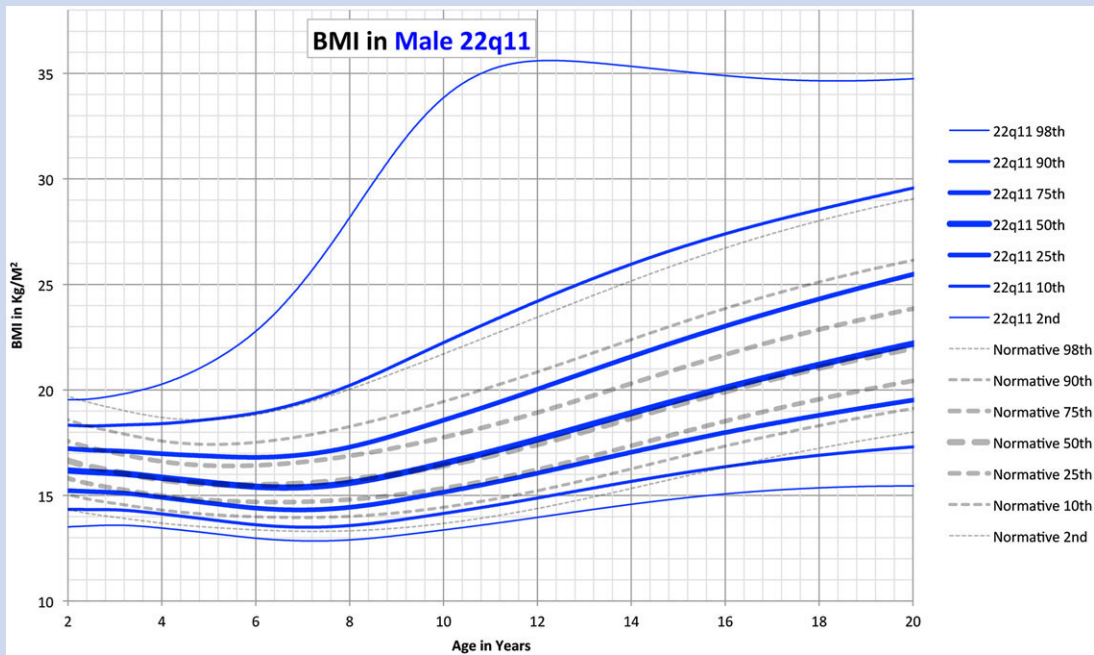


FIG. 14. BMI in males with 22q11 deletion syndrome, ages 2–20 years.

TABLE I. Average and Extreme Values for Male and Female Adults With 22q11 Deletion Syndrome

Measurement	Mean (N: Z-score)	Minimum (Z-score)	Maximum (Z-score)
Male			
Weight (kg)	60.5 (13: -0.7)	27.0 (-8.7)	87.7 (1.8)
Height (cm)	167.4 (12: -1.4)	151.0 (-3.7)	181.0 (0.6)
FOC (cm)	56.1 (4: -0.7)	55.0 (-1.3)	57.5 (0.1)
BMI (kg/m ²)	22.5 (12: 0.5)	16.8 (-2.3)	30.4 (2.4)
Female			
Weight (kg)	59.0 (12: 0.2)	45.6 (-1.8)	77.0 (1.9)
Height (cm)	158.2 (12: -0.9)	147.0 (-2.7)	168.3 (0.8)
FOC (cm)	54.8 (2: -0.5)	54.0 (-1.1)	55.5 (0.0)
BMI (kg/m ²)	23.7 (11: 0.8)	17.4 (-1.8)	31.2 (2.5)

Establishing growth references for 22q11.2 deletion syndrome allows the clinician to (1) identify children who deviate substantially from the growth profile of this condition, so they can be evaluated promptly for another contributor to their growth aberration and (2) avoid needless investigation of growth deficiency in those who are exhibiting a growth profile which is typical for this condition.

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