

Growth and Maturation in Marfan Syndrome

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Understanding the growth pattern in Marfan syndrome is important for prediction of expected growth, prevention of excessive growth by hormone therapy, timing of surgical epiphysiodesis for cessation of growth, and instituting brace treatment for scoliosis. In this study, we analyze growth patterns and generate growth charts for persons with Marfan syndrome. From the charts of 180 clinically diagnosed Marfan patients, longitudinal height and weight measurements were obtained. From this data, growth charts and growth velocity charts were generated for males and females. Skeletal maturation was studied by determining the Risser signs from the x-rays of 71 males and 56 females. From 22 female patients, age of menarche was available and retrieved either by reviewing the charts or contacting the patients. Mean length at birth was 53 ± 4.4 cm for males and 52.5 ± 3.5 cm for females. Mean final height was 191.3 ± 9 cm for males and 175.4 ± 8.2 cm for females. Mean birth weight was 3.51 ± 0.74 kg for males and 3.48 ± 0.68 kg for females. The puberty-associated peak in growth velocity was 2.4 years earlier than the gender-matched general population for males with Marfan syndrome and 2.2 years earlier for females. Age of menarche was 11.7 ± 2 years of age, which is also early compared to the general population. This study suggests that the growth spurt and pubertal skeletal maturation occur early in Marfan syndrome. The growth curves generated should help more accurately predict adult stature, as well as monitor progression toward it. © 2002 Wiley-Liss, Inc.

KEY WORDS: Marfan syndrome; growth; maturation; growth chart

INTRODUCTION

The Marfan syndrome (MFS) is a heritable connective tissue disorder affecting multiple organ systems, with an approximately 0.01% prevalence in the population [Pyeritz and McKusick, 1979; Pyeritz and Francke, 1993]. Mutations in the gene coding for fibrillin-1, the principal component of microfibrils in the extracellular matrix, produce the phenotype [Dietz et al., 1991a,b]. While the autosomal dominant inheritance pattern of MFS demonstrates high penetrance, the phenotype is widely variable in its involvement of different organ systems, which in part may be due to quantitative differences in biosynthesis and deposition of fibrillin-1 [Hollister et al., 1990; Aoyama et al., 1994; Aoyama et al., 1995].

The skeletal manifestations of MFS, such as tall, disproportionate stature, scoliosis, and anterior chest deformities, evolve with age [McKusick, 1972; Robins et al., 1975; Pyeritz et al., 1985; Birch and Herring, 1987; Pyeritz et al., 1988; Stern, 1988; Joseph et al., 1992; Sponseller et al., 1995; DePaepe et al., 1996]. Because skeletal features are an important component of the diagnostic criteria [DePaepe et al., 1996], establishing the diagnosis of MFS can be especially difficult in children. Additionally, in patients with clear MFS, important management decisions, such as bracing or instrumentation for spinal deformities, epiphysiodesis for leg-length discrepancies, or institution of hormones for growth modulation, often must be considered at an early age. Diagnostic and therapeutic decisions would be facilitated by a better understanding of linear and body mass growth in MFS. Predicting growth patterns in MFS can be very difficult, given that even the mean Marfan height falls above the 95th centile of normal height at many points in development [Pyeritz et al., 1985]. The few studies of growth in MFS have involved relatively few patients and were largely cross-sectional in design [McKusick, 1972; Pyeritz et al., 1985]. Accordingly, we have reviewed the growth parameters of a group of children and adolescents with MFS for whom serial data were available.

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METHODS

Definition of Study Group and Data Collection

From the approximately 600 individuals who have carried a diagnosis of MFS in the Medical Genetics Clinics at the Johns Hopkins and Allegheny General Hospitals, we excluded any patient who did not meet the Ghent diagnostic criteria [DePaepe et al., 1996]. Patients who had scoliosis of greater than 25 degrees, kyphosis greater than 60 degrees, leg length discrepancy of over 3 cm, or any history of spinal surgery were also removed from the study group. Finally, any patient who had received hormone treatment, epiphyseodesis, or any other height-altering treatment or injury to the growth plates before their 20th year were excluded.

For the remaining group of patients, longitudinal height and weight measurements were obtained by a retrospective review of clinic records and of measure-

ments made by health care providers. Because diagnosis of MFS is frequently delayed, many of the eligible patients did not have records from their childhood and adolescent years available. Therefore, the vast majority of the exclusions from the initial 600 were due to initial patient presentation after the age of 20 years. The final group included 81 females and 99 males, with seven females and nine males having measurements from birth through the 20th year. The rest of the patients had longitudinal data; no patient with only a single recorded measurement was included in the study.

Growth Chart Generation

The data were stratified by chronological age using intervals of up to six months (shorter intervals were used in the charts for the first three years of life). For each group, defined by a time-window, an abscissa value was produced by the mean of the varied ages in

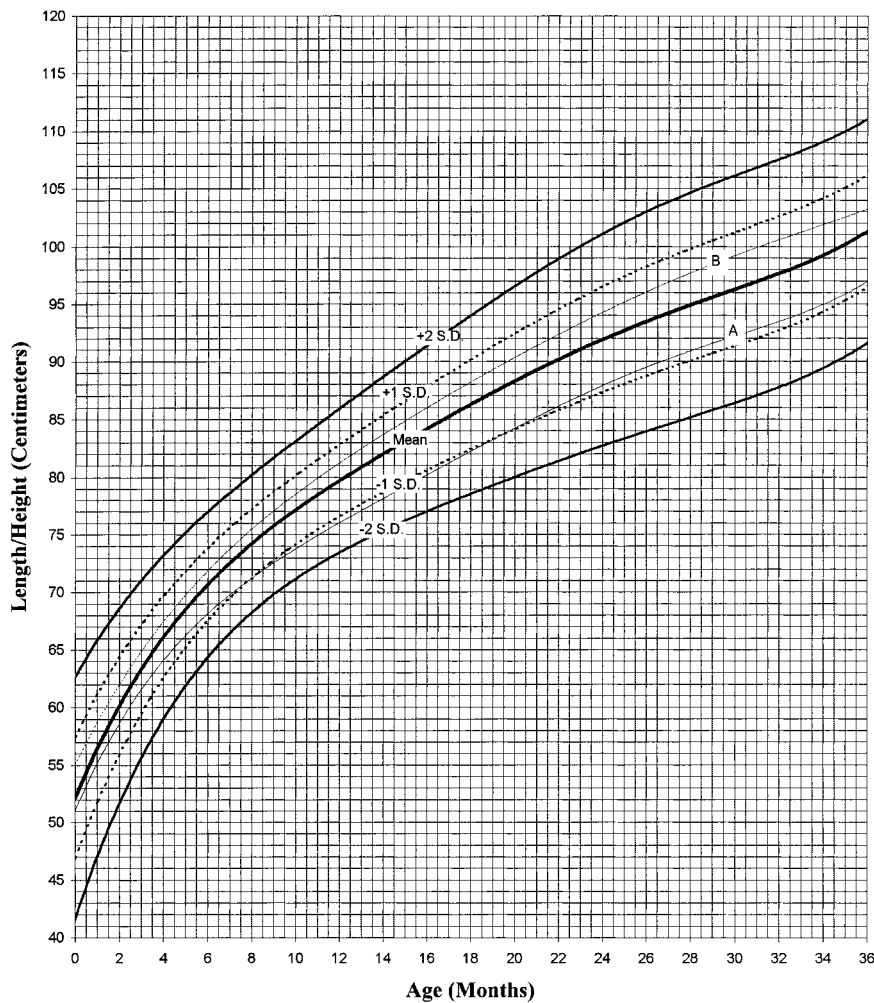


Fig. 1. Total body length in cm vs. age in months for male infants and toddlers with MFS. The curves are fifth-degree polynomial least squares regressions from the mean \pm one and two SD. The thin curves are for comparison to the general population's 50th (A) and 95th centile (B), as determined by Hamill et al. [1979].

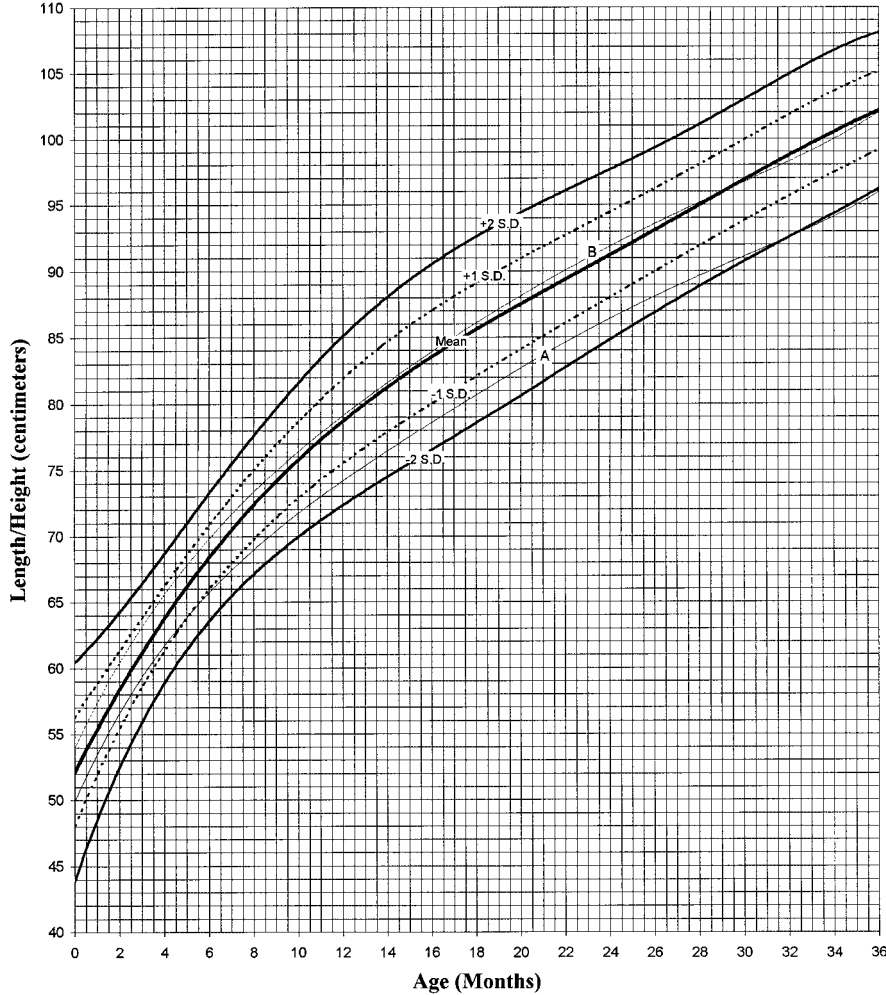


Fig. 2. Total body length in cm vs. age in months for female infants and toddlers with MFS. The curves are fifth-degree polynomial least squares regressions from the mean \pm one and two SD. The thin curves are for comparison to the general population's 50th (A) and 95th centile (B), as determined by Hamill et al. [1979].

months of the individuals included. An ordinate value was produced for each group for each of the following five-point series in both statural and body mass measurements: the mean of all measurements falling within the time-window; the group's calculated standard deviation (SD) added to that mean; the SD subtracted from that mean; twice the SD added to the mean; and twice the SD subtracted from the group mean. The five series were plotted on a total of eight graphs that included stature or body mass for each gender, and were divided chronologically into two graphs for each measurement: zero to 36 months and two to 20 years. Least-squares regression to a fifth-degree polynomial function was performed for each individual series, insuring that R-squared values were above 0.990.

Comparison to Normal

Plots of the general population 50th centile and 95th centile, adapted from Hamill et al. [1979], were also placed on each graph. Least-squares regressions to fifth-degree

polynomials of these plots were also obtained to permit derivations of slope for comparison and contrast.

Body Mass by Stature Graph Generation

Body mass by stature graphs were generated by grouping data for each gender into 5-cm height measurement increments, starting at 45 cm length or stature. Each abscissa value was the mean height of the group. Five series of ordinate values were calculated as the following: the mean body mass of the group; the SD of the group added to the mean; the SD subtracted from the mean; twice the SD added to the mean; and twice the SD subtracted from the mean. For comparison, general population curves of the 5th, 50th, and 95th centiles were also generated from data from Hamill et al. [1979] and superimposed on the charts.

Growth Velocity

To facilitate analysis of mean Marfan growth, a function of the slope, or the growth velocity of the Marfan

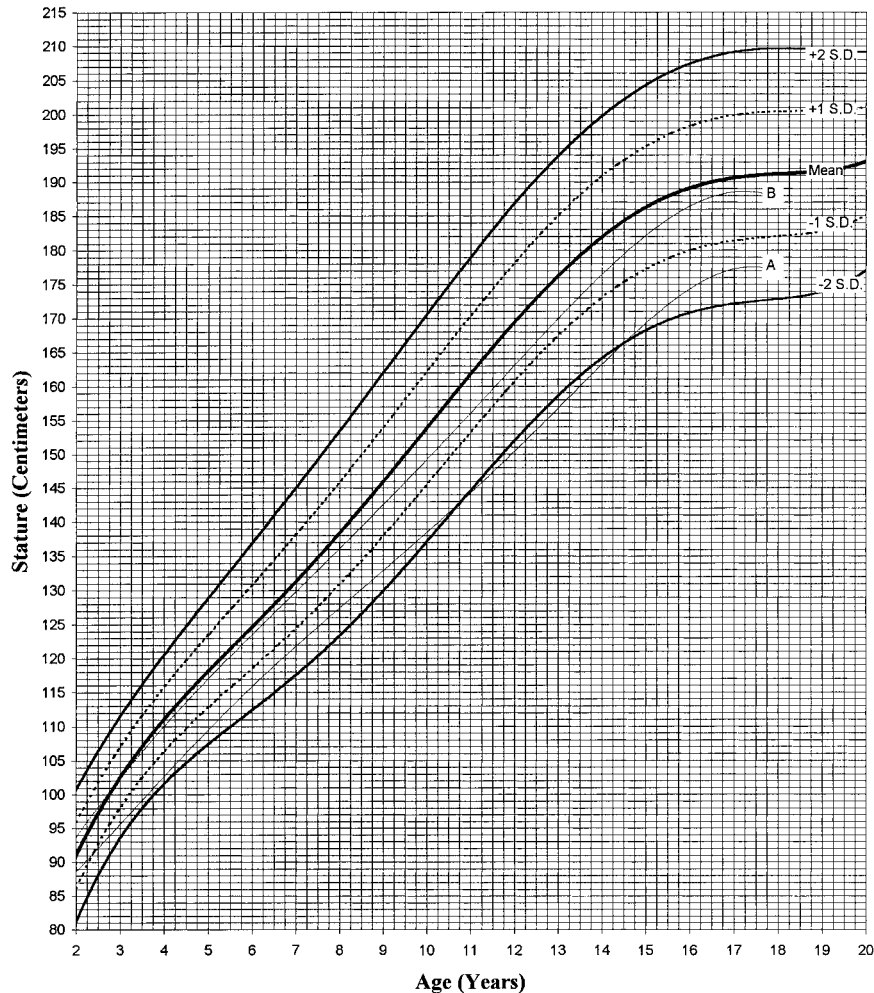


Fig. 3. Statural height in cm vs. age in years for male children and adolescents with MFS. The curves are fifth-degree polynomial least squares regressions from the mean \pm one and two SD. The thin curves are for comparison to the general population's 50th (A) and 95th centile (B), as determined by Hamill et al. [1979].

mean, was generated for each parameter by taking the first derivative of each mean growth curve as a function of time. These were plotted on graphs for qualitative analysis of contour and comparison to the first derivative of the general population 50th centile growth curves by Hamill et al. [1979].

Point growth velocities for individuals were calculated as the linear rate of growth between two measurements and assigned to an abscissa of the mean age between those measurements. For each individual, the greatest velocity thus generated, with a reduced velocity both before and after it chronologically, was recorded as the puberty-associated peak growth velocity. While the vast majority of subjects had multiple measurements in the adolescent period, only 25 male and 23 female subjects had sufficient adolescent measurements to confidently determine the peak velocity by definite troughs before and after. These were compared to mean peak growth velocities and mean ages at

peak growth velocity for the general population, as generated by Tanner et al. [1966].

Skeletal Maturity

Maturation of the iliac crest apophysis (the Risser sign) was graded in a standard fashion as follows: 0 = no ossification; 1 = lateral one-quarter ossified; 2 = lateral one-half ossified; 3 = lateral three-fourths ossified; 4 = entire apophysis ossified; 5 = entire apophysis fused to the ilium [Risser, 1958]. These were read from pelvic radiographs of Marfan patients, when available, to assess the timing of the attainment of skeletal maturity. Seventy-one Risser signs were collected from males, and 56 were collected from females.

Because of its significance to growth in women, age at menarche was also retrieved from records of females when available. When it was not, patients were contacted and asked if they remembered at what age

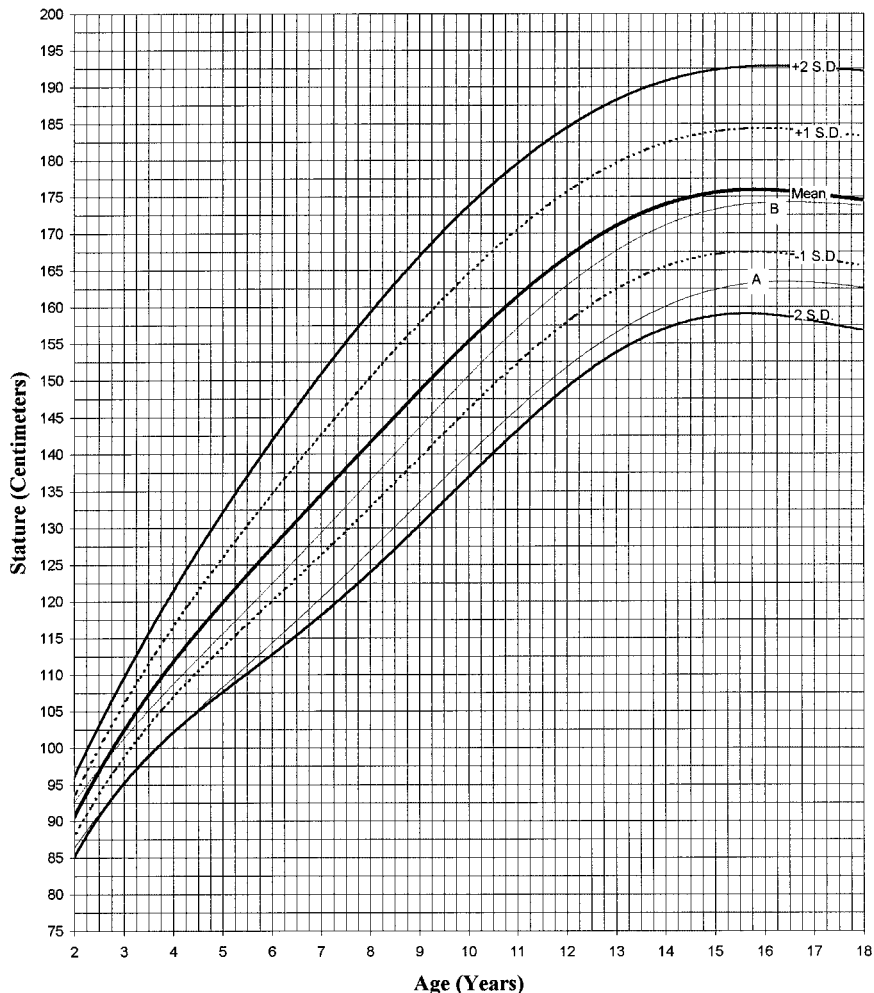


Fig. 4. Statural height in cm vs. age in years for female children and adolescents with MFS. The curves are fifth-degree polynomial least squares regressions from the mean \pm one and two SD. The thin curves are for comparison to the general population's 50th (A) and 95th centile (B), as determined by Hamill et al. [1979].

menarche occurred. This information was available from only 22 of the females in the study. A mean and SD were calculated.

RESULTS

Statural Growth

Mean length at birth was 53.0 ± 4.4 cm for males and 52.5 ± 3.5 cm for females with MFS. Mean linear growth of males in the first three years of life fell consistently between the 50th and 95th centiles for normal growth [as per Hamill et al., 1979], but the general population 50th centile was one SD below the MFS mean by eight months of age (Fig. 1). Mean female linear growth in this period met the 95th centile of general population growth by about 12 months of age (Fig. 2). By 32 months of age, the 50th centile of general population female height was two SD below the MFS mean for girls. Statural development resulted in attainment of a height of 191.3 ± 9.0 cm in males and 175.4 ± 8.2 cm in females with MFS. On average for

MFS, 75% of adult height was reached by the age of nine years in boys and 6.5 years in girls. For both boys and girls with MFS, a stature equal to the 95th centile of general population was passed at three years of age (Figs. 3 and 4).

Body Mass Growth

Mean birthweight for males with MFS was 3.51 ± 0.74 kg, and 3.48 ± 0.68 kg for females with MFS. Mean male and female body mass growth in MFS matched the 50th centile of general population for the first year of life (Figs. 5 and 6). Thereafter, boys and girls with MFS began to exceed the 50th centile of the general population.

The adult body mass was 80.8 ± 13.8 kg in males and 65.0 ± 7.9 kg in females. The female body mass curve for the 50th centile of general population remained steadily one SD below the mean for females with MFS, but by attainment of adult body mass, the general population 95th centile nearly coincided with

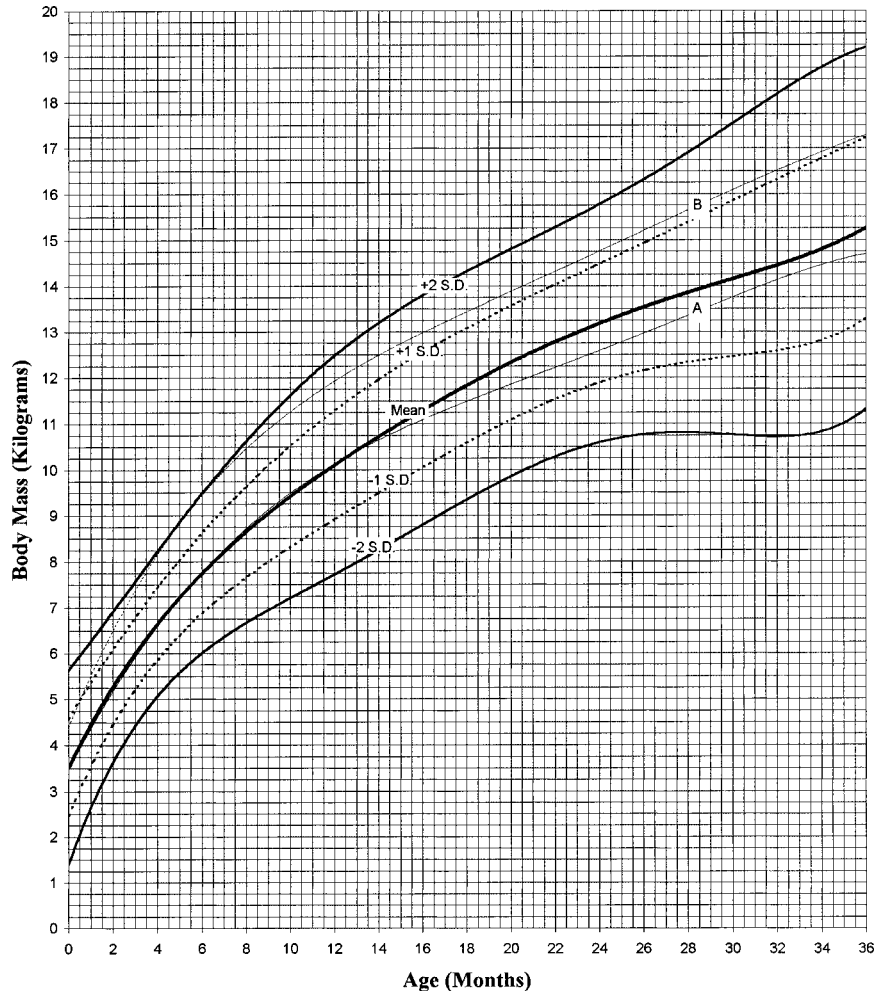


Fig. 5. Total body mass in kg vs. age in months for male infants and toddlers with MFS. The curves are fifth-degree polynomial least squares regressions from the mean \pm one and two SD. The thin curves are for comparison to the general population's 50th (A) and 95th centile (B), as determined by Hamill et al. [1979].

measurements two SD above the MFS female mean (Figs. 7 and 8). Mean body mass growth in males with MFS remained consistently between the 50th and 95th centiles of general population. During the pre-adolescent years, the MFS mean was at its greatest disparity, one SD above the male general population 50th centile for body mass.

Body Mass by Stature Growth

Other than for the range of toddler-age heights for girls with MFS, in which the mean matched the 50th centile for the general population of females, the mean body mass curves for males and females with MFS were below the 50th centile of the general population, but never separated by a SD (Figs. 9 and 10).

Growth Velocities

The MFS male mean statural growth curve reached a puberty-associated peak velocity of 8.0 cm/year at 10.4

years of age (Fig. 11). The MFS female mean statural growth demonstrated no true peak associated with puberty, but continued to decline in growth rate, with a small plateau at 7.4 years of age and 7.0 cm/year. These were contrasted with curves from the female 50th centile of the general population, which peaked at 9.4 years of age and 6.6 cm/year, and male 50th centile curves, which peaked at 12.8 years and 6.6 cm/year. MFS male and female growth curves demonstrated a consistently faster rate in the first decade of life, but two years after reaching their respective peaks, linear growth velocities fell below those of the 50th centiles for both genders in the general population.

For body mass growth velocity mean curves, the growth acceleration associated with puberty peaked at a rate of 6.5 kg/year at 11.8 years of age for the male MFS curve, and at a rate of 5.3 kg/year at 10.4 years of age for the Marfan female mean curve (Fig. 12). The analogous peak for the curve of the 50th centile of general population males produced a rate of 5.8 kg/year at 14.2 years of age; the general population female

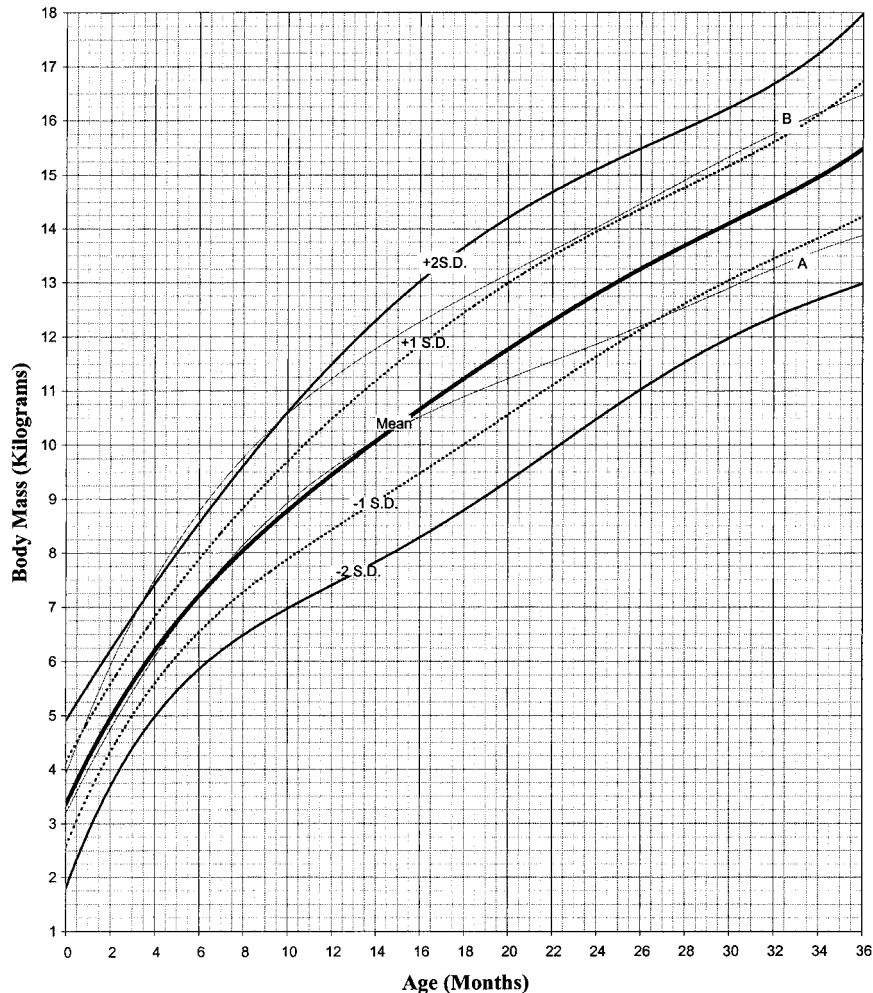


Fig. 6. Total body mass in kg vs. age in months for female infants and toddlers with MFS. The curves are fifth-degree polynomial least squares regressions from the mean \pm one and two SD. The thin curves are for comparison to the general population's 50th (A) and 95th centile (B), as determined by Hamill et al. [1979].

curve peaked at 11.6 years of age and 4.7 kg/year. While mean body mass growth velocities in MFS curves started and peaked higher than the 50th centile of general populations, by two years after the peak, the rate in MFS growth curves declined to below the 50th centile of general population for both males and females.

For individual peak height velocities, MFS males reached a mean peak of 10.2 ± 2.0 cm/year at a mean age of 11.7 ± 1.9 years old (Fig. 13); females peaked at 10.5 ± 2.8 cm/year at the mean age of 9.9 ± 1.9 years old (Fig. 14). While the individual peak height velocities for both genders were not consistently above the mean, most occurred at a younger than average age. In addition, the majority of the individual growth velocity curves demonstrated multiple peaks, usually two during pre-adolescence and adolescence. General population males, consistently having one major growth spurt in this period, peaked at 10.3 ± 1.5 cm/year at 14.1 ± 0.9 years of age; their female counterparts peaked at 9.0 ± 1.0 cm/year at 12.1 ± 0.8 years of age

[Tanner et al., 1966]. Thus, males and females with MFS peaked on average 2.4 and 2.2 years, respectively, earlier than their general population counterparts.

Individual peak body mass growth velocities averaged 11.9 ± 4.7 kg/year at a mean of 13.1 ± 2.1 years of age ($N = 23$) for MFS males (Fig. 15) and 11.4 ± 3.2 kg/year at a mean of 11.0 ± 2.0 years of age ($N = 19$) for MFS females (Fig. 16). The mean general population male body mass growth velocity peak of 9.8 ± 2.0 kg/year occurred at a mean age of 14.3 ± 0.9 years old. General population females averaged a peak of 8.8 ± 1.5 kg/year at a mean age of 12.9 ± 1.0 years old.

Attainment of Skeletal Maturity

The mean age of patients with MFS whose pelvic radiographs demonstrated a Risser sign of 1 was 12.8 ± 2.6 years old for females and 11.4 ± 2.5 years old for males (Figs. 17 and 18). For Risser sign of 4, signifying near completion of bony maturation, the mean ages were 15.8 ± 1.2 and 14.8 ± 1.1 years of age

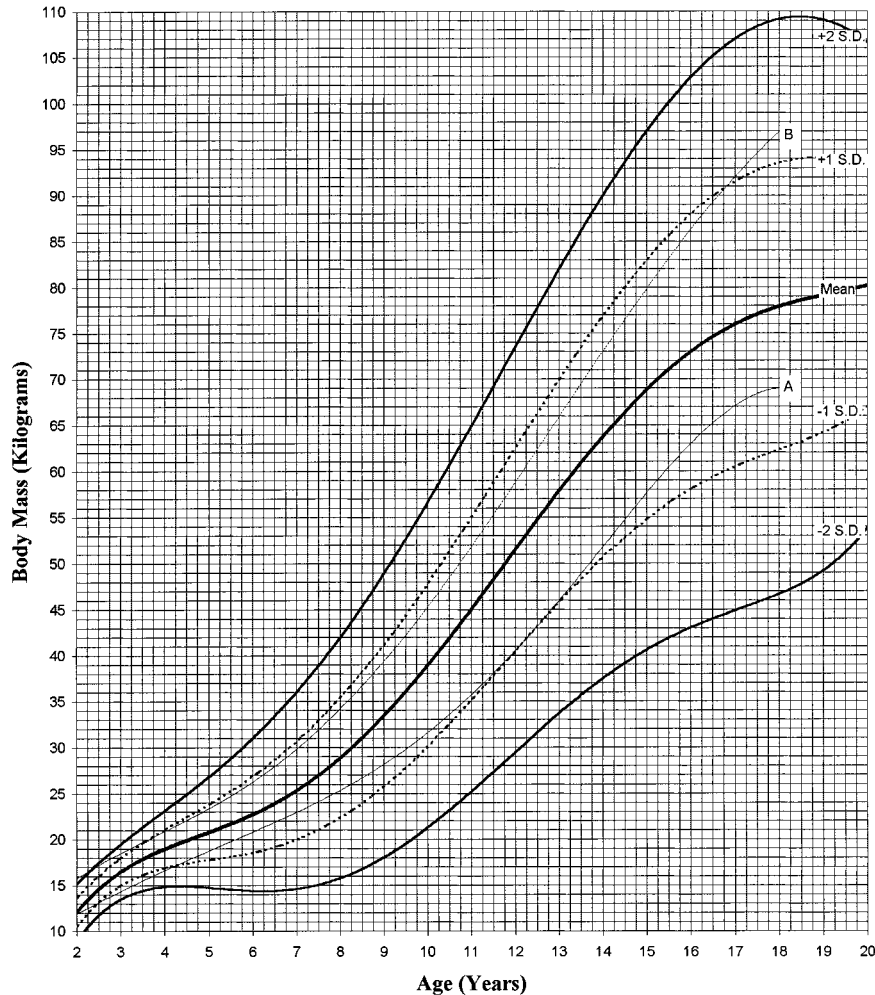


Fig. 7. Total body mass in kg vs. age in years for male children and adolescents with MFS. The curves are fifth-degree polynomial least squares regressions from the mean \pm one and two SD. The thin curves are for comparison to the general population's 50th (A) and 95th centile (B), as determined by Hamill et al. [1979].

for males and females, respectively. The mean age at menarche in MFS was 11.7 years old with a SD of 2.0 years of age.

DISCUSSION

This study was intended both to document observations of the patterns of growth and to equip physicians with a practical set of tools for improved monitoring of patients with MFS. Its limitations are three-fold. Because the diagnosis of MFS is difficult to confirm, in part because the features are age dependent, patients often fail to receive the attention of a tertiary care genetics facility until later in life. Presentation at an early age stems from either concern due to family history or an especially severe phenotype. Our study group consisted primarily of patients with known family histories of MFS who were screened and followed from an early age. Individuals with MFS due to spontaneous mutation are probably under-represented by the study group. However, until broad-based

genetic screening becomes available and widely used, the study group's bias matches the bias of the population to which the charts would be most likely applied. The second limitation is the potential lack of precision in height and weight measurements. Ideal would be a prospective study in which all measurements could be made by a single observer using the same equipment each time, but it seemed reasonable to utilize the height and weight measures recorded during past clinic visits, as methods for obtaining such measurements are relatively standard throughout medical practice. The third limitation of the study is the low availability and precision of the maturation data. Risser signs were much more available than any other radiographic record of bone age because most individuals with MFS have anteroposterior spine films, which include the iliac crests, taken to follow or rule out scoliosis.

Excessive linear growth in MFS begins prenatally. Mean length at birth in MFS falls near the 90th centile of general population for both males and females. Mean linear growth continues at an abnormally high rate

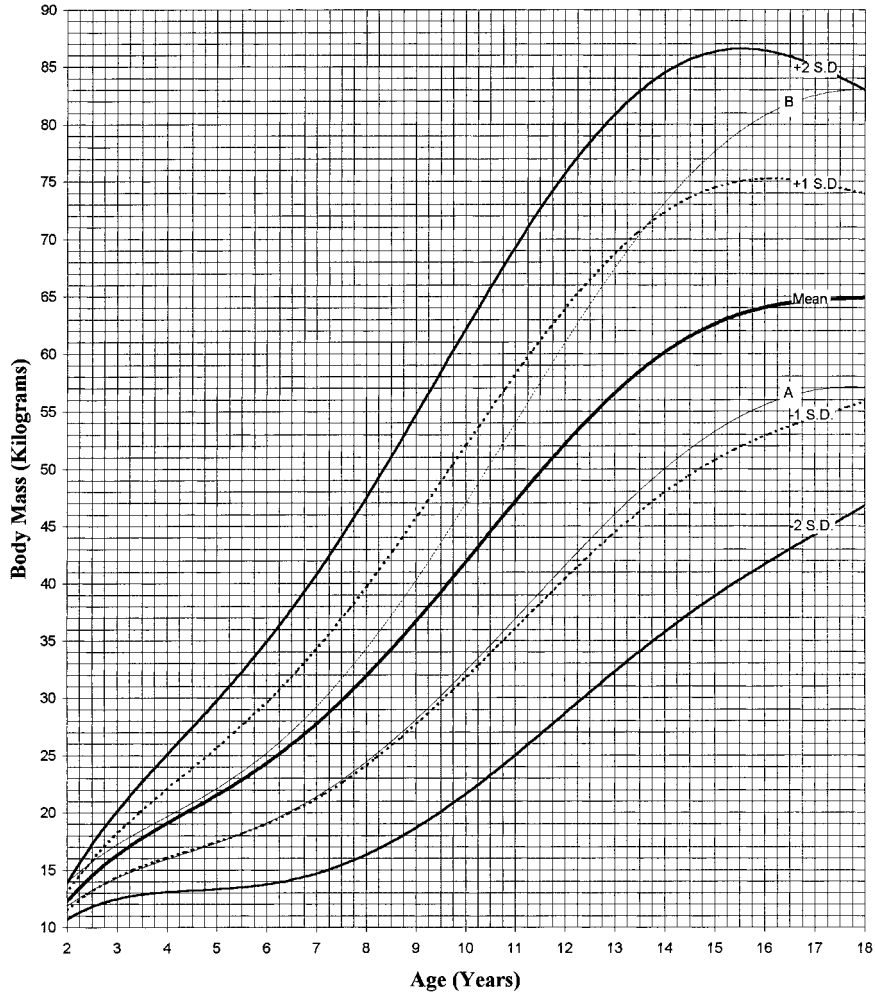


Fig. 8. Total body mass in kg vs. age in years for female children and adolescents with MFS. The curves are fifth-degree polynomial least squares regressions from the mean \pm one and two SD. The thin curves are for comparison to the general population's 50th (A) and 95th centile (B), as determined by Hamill et al. [1979].

during infancy and the toddler years to produce mean heights above the 95th centile of the general population by age three.

Growth velocity in persons with MFS is consistently higher than the general population for the duration of childhood development. The mean growth curves from the MFS population also reach their puberty-associated peak rates at earlier ages and higher velocities than the curve of the general population median. That the timing of the peak velocity from the MFS population mean curve comes earlier than for the general population median curve is corroborated by the timing of individual peak height velocities, which are earlier than the general population average for the vast majority of MFS individuals, averaging 2.4 years early for males and 2.2 year early for females. The early growth is well associated with a young average age for Risser 1 signs and a mean menarchal age that falls earlier than the 12.5 to 14.5 years reported in several studies as the general population mean age for

menarche [Vicdan et al., 1996; Chompootawee et al., 1997; Montero et al., 1999; Papadimitriou et al., 1999; Marrodan et al., 2000]. Individuals with MFS appear to have their puberty-associated growth spurt earlier than their general population counterparts. As for the multiple growth velocity peaks, simple measurement error cannot be totally excluded as a possible cause, but at the very least these represent prolonged duration of high velocity growth.

The height of the peak from the MFS male mean statural growth curve can be theoretically explained in two ways. Either MFS individuals have, as a group, excessively high individual growth velocities, or the mean curve demonstrates the compounding effect of more or less normal peak growth velocities less variably spaced in time, an effect that Tanner et al. [1966] explored in their assessments of growth velocities. The individual growth velocities of MFS individuals shed some light on these theories. While some MFS males did experience excessive rates of statural growth, their

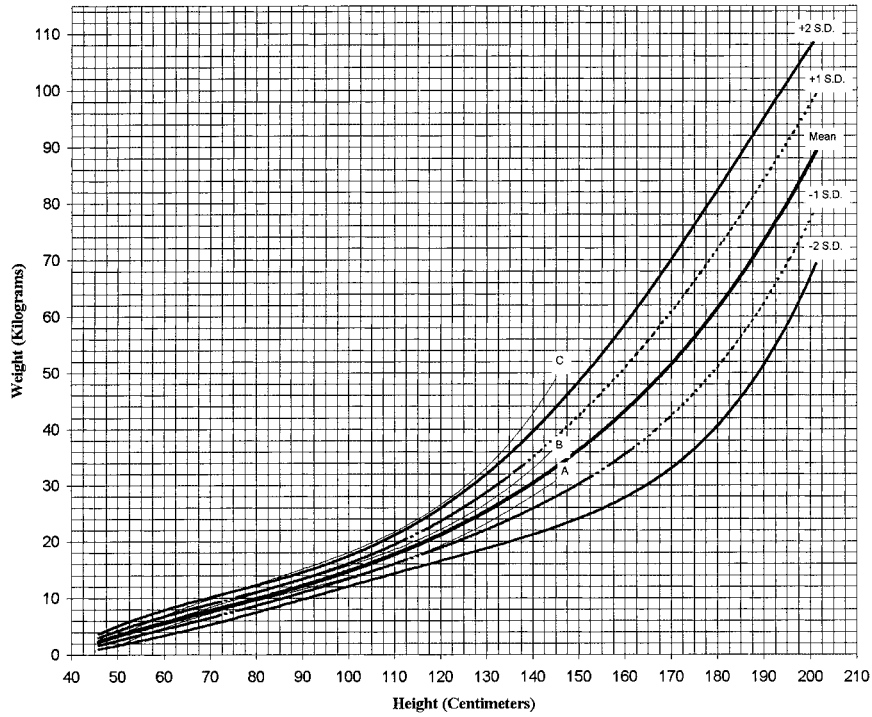


Fig. 9. Total body mass in kg vs. statural height in cm for male infants, children, and adolescents with MFS. The curves are fifth-degree polynomial least squares regressions from the mean \pm one and two SD. The thin curves are for comparison to the general population's 5th (A), 50th (B), and 95th centile (C), as determined by Hamill et al. [1979].

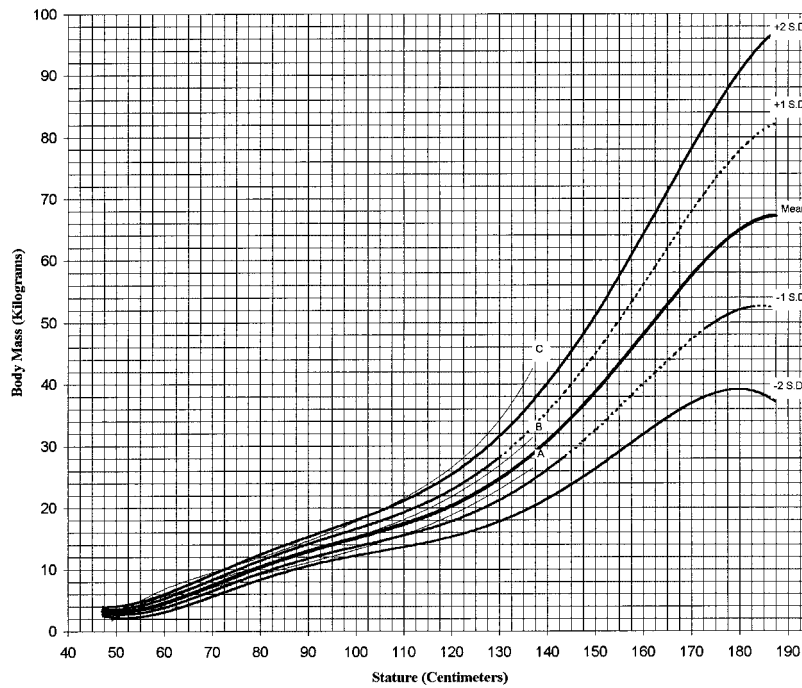


Fig. 10. Total body mass in kg vs. statural height in cm for female infants, children, and adolescents with MFS. The curves are fifth-degree polynomial least squares regressions from the mean \pm one and two SD. The thin curves are for comparison to the general population's 5th (A), 50th (B), and 95th centile (C), as determined by Hamill et al. [1979].

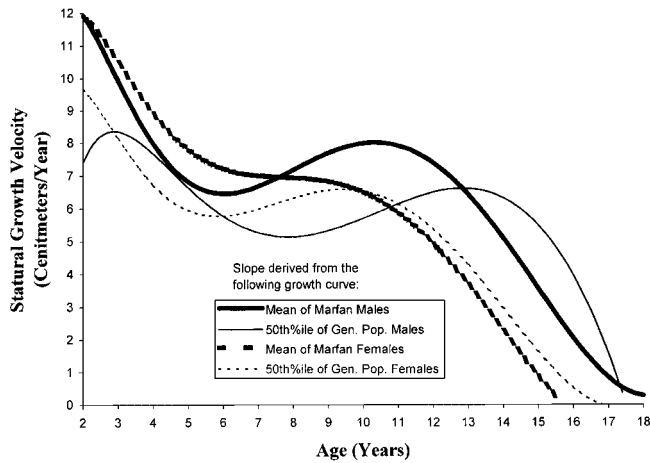


Fig. 11. Population-based velocity of statural growth velocity in cm/year vs. age in years for the 50th centile of males in the general population (thin line), males with MFS (heavy line), the 50th centile of females in the general population (dashed line), and females with MFS (dotted line). These lines were obtained by plotting the first derivatives of the growth curves for MFS means and general population medians [Hamill et al., 1979].

individual peak velocities did not average to be much faster than the mean growth velocity of males from the general population. However, the wide SD in age at peak growth velocity suggests that the MFS population is not especially aligned in the timing of individual growth velocity peaks. Alternatively, the multiple peaks (usually two), noted in the growth velocities of many individuals, and the generally long duration of peak velocities, permit a compounding peaks effect even in the absence of closely timed maximum-peaks. This multiple growth spurt phenomenon added to the generally early timing of the peak growth velocities

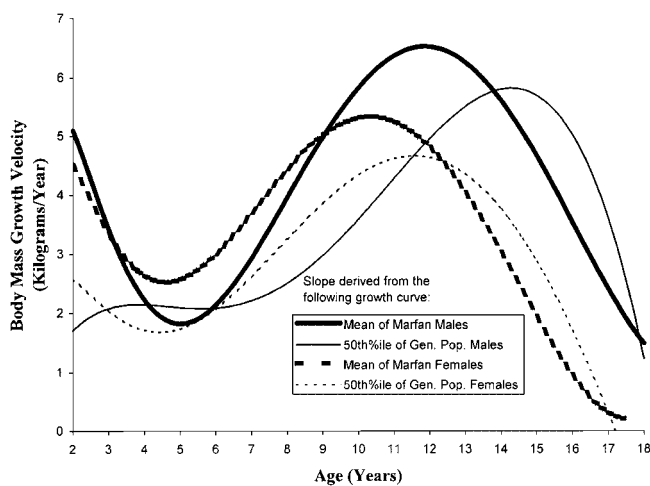


Fig. 12. Population-based velocity of body mass growth in kg/year vs. age in years for the 50th centile of males in the general population (thin line), males with MFS (heavy line), the 50th centile of females in the general population (dashed line), and females with MFS (dotted line). These lines were obtained by plotting the first derivatives of the growth curves for MFS means and general population medians [Hamill et al., 1979].

probably creates the plateau and lack of true peak noted in the rate of the MFS female mean curve.

While the MFS mean growth curves fall below the general population median curves in terms of rate, it cannot be concluded that the early MFS growth spurts lead to early bony maturation and closure of the physes. Although the rate falls below the general population median curve's velocity, the actual cessation of meaningful growth matches or extends beyond that of the general population growth curves. The MFS curves demonstrate broader, higher velocity growth of longer duration, in opposition to the abrupt climb and decline of the general population growth curves. This is corroborated by both the individual growth velocities, with multiple, long peaks, and the bony maturation timing, with MFS individuals demonstrating Risser signs of 4 having a mean age of almost 16 for males and almost 15 for females. The excessive height attained in MFS is achieved through rapid early growth of a long duration, punctuated by multiple growth spurts during the pre-adolescent and adolescent years.

In partial explanation of the frequently described tall, slender habitus of MFS, body mass does not exceed the general population body mass growth proportional to height. This is clearly illustrated by the plot of body mass against stature, which finds mean curves for MFS falling below the 50th centile of the general population. The asthenic habitus of MFS could be due to a general deficiency of skeletal muscle, subcutaneous adipose tissue, or both. How defects in extracellular microfibrils could account for these developmental deficiencies is unknown.

In contrast to the mean trends noted, certain individuals with MFS were clinically obese. This can be of special concern in patients with compromised cardiac function. Individuals with MFS are not constitutionally freed from susceptibilities to excessive weight gain. To explain the atypical habitus of these normal body mass or obese individuals with MFS, it is possible that some mutations in *FBN1* have a specifically reduced effect on muscle and fat. The observation that some asthenic young persons with MFS may develop excessive central depositions of adipose tissue in adulthood may alternately lead to the reasoning that rather than constitutional asthenism, MFS delays bulk growth of muscle and adipose tissue by a linear growth that outstrips the overall anabolic, tissue-building capabilities of the growing youth. Notably, the body mass growth velocities of both genders in the general population peak before the respective statural growth velocities. In contrast, the body mass growth velocity peaks after the associated statural growth velocity peak for both males and females with MFS.

As with many hereditary disorders, discovering the cause of MFS at the genetic level has shed little light on the pathogenesis of some individual features of the phenotype. How mutations in the gene encoding fibrillin-1 result in overgrowth of tubular bones remains unclear. However, a number of features of fibrillin-1 and microfibrils offer some clues upon which to base hypotheses. Microfibrils have been documented in both the cartilage matrix and the perichondrium

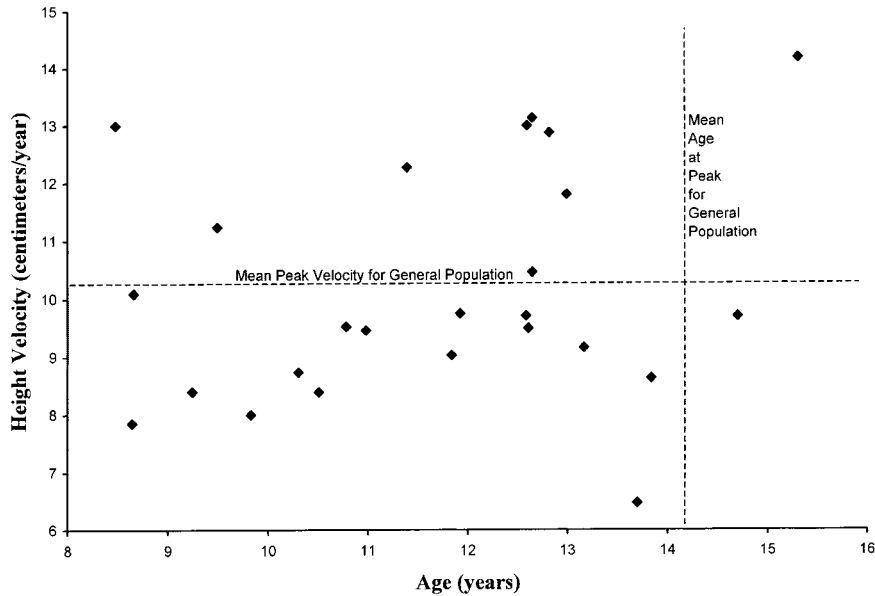


Fig. 13. Individual peak velocities of statural growth for males with MFS are plotted against the age at which they occurred. Reference lines indicate the mean peak height velocity and mean age at peak height velocity for males in the general population, as reported by Tanner et al. [1966].

[Keene et al., 1997]. Because growth of the long bones is controlled, in part, by tension of the periosteum [Houghton and Dekel, 1979], it is possible that this tension is abnormal in MFS [Nogami et al., 1979]. In both perichondrial and periosteal membranes, the number of elastic fibers is reduced in MFS [Gigante et al., 1999].

Furthermore, both fibrillin-1 and fibrillin-2 contain multiple motifs that are homologous to transforming-growth-factor- β (TGF- β) binding protein, and both

molecules are capable of binding to TGF- β , a protein known to be involved in bone growth [Smallridge et al., 1999]. It is possible that specific mutations in *FBN1*, or resultant defects in microfibril assembly, result in abnormal concentrations of TGF- β in the microenvironment of the growth plate of tubular bones. The data reported here suggest that the overgrowth of the long-bones in MFS follows a pattern of disorganized or poorly controlled growth, rather than an excessive stimulation of growth. Further molecular investigation

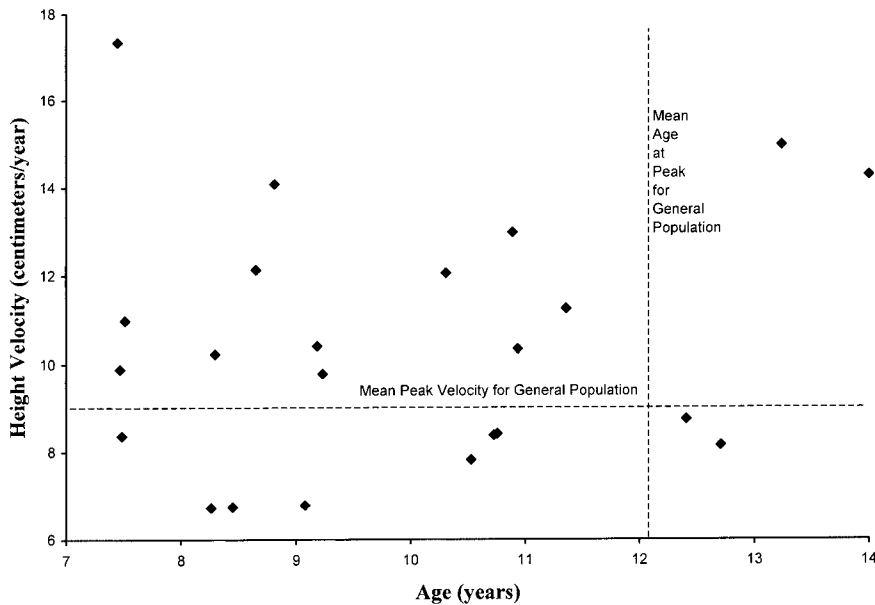


Fig. 14. Individual peak velocities of statural growth for females with MFS are plotted against the age at which they occurred. Reference lines indicate the mean peak height velocity and mean age at peak height velocity for females in the general population, as reported by Tanner et al. [1966].

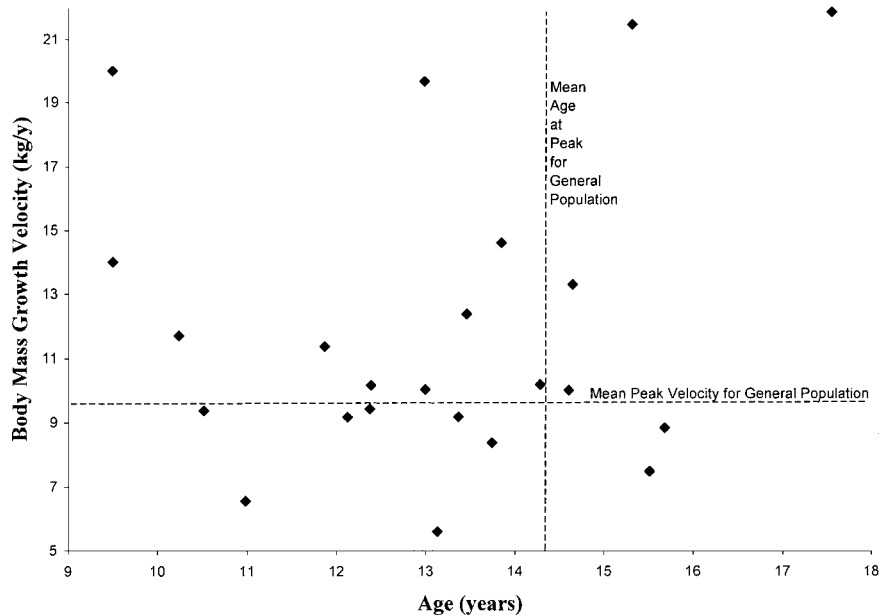


Fig. 15. Individual peak velocities of body mass growth for males with MFS are plotted against the age at which they occurred. Reference lines indicate the mean peak weight velocity and mean age at peak weight velocity for males in the general population, as reported by Tanner et al. [1966].

of the relative overgrowth in MFS may well provide information about the normal processes that control linear growth, and suggest novel approaches to modulating growth before irreversible deformity occurs.

The implications of the disordered, rapid growth itself on the etiology of other manifestations of MFS are manifold. Vetter et al. [1990] found a positive and

significant correlation between body growth during infancy and adolescence and aortic dilatation. In addition, the tall stature and rapid, early growth, all of which have been implicated in the etiology of idiopathic scoliosis [Gross et al., 1983; Lonstein and Carlson, 1984; Shohat et al., 1988; Loncar-Dusek et al., 1991; Goldberg et al., 1993; Nissinen et al., 1993], may

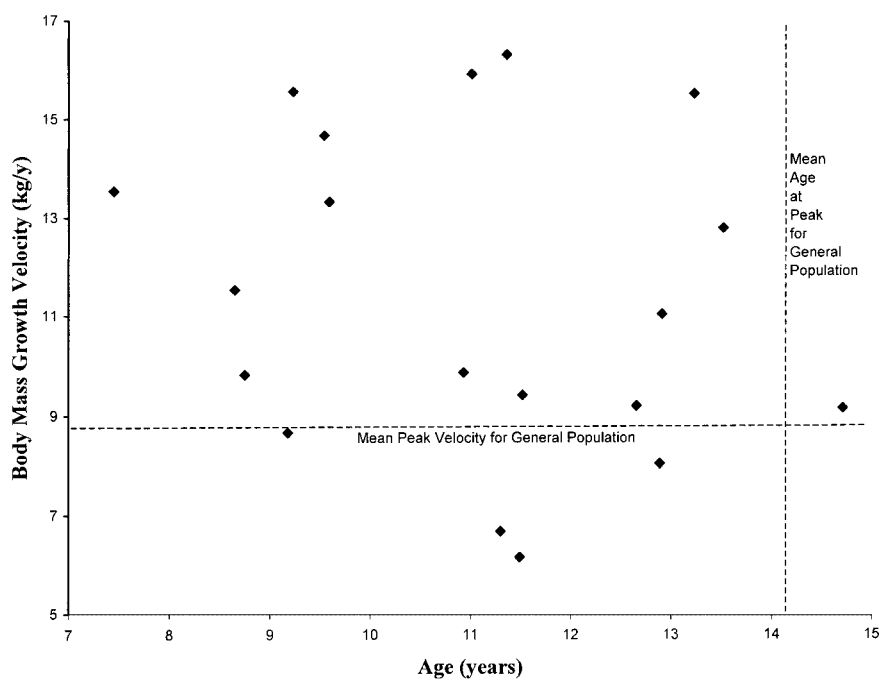


Fig. 16. Individual peak velocities of body mass growth for females with MFS are plotted against the age at which they occurred. Reference lines indicate the mean peak weight velocity and mean age at peak weight velocity for females in the general population, as reported by Tanner et al. [1966].

Interestingly, neither of the two studies published have found any locus on chromosome 15, suggesting that genetic variation in *FBN1* does not likely play an important role in controlling human height in general. However, the knowledge gained from understanding the protein products of these loci and their potential interrelations with fibrillin-1 may, in the future, further elucidate the pathogenesis of the unique growth patterns and extreme height that are characteristic of MFS.

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