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Presentation, Heritability, and Genome-Wide Linkage Analysis of the Midchildhood Growth Spurt in Healthy Children from the Fels Longitudinal Study

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Abstract

Growth is a complex process composed of distinct phases over the course of childhood. Although the pubertal growth spurt has received the most attention from auxologists and pediatricians, the midchildhood growth spurt has been less well studied. The midchildhood growth spurt refers to a relatively small increase in growth velocity observed in some, but not necessarily all, children in early to middle childhood. If present, the midchildhood growth spurt typically occurs sometime between the ages of 4 and 8 years, well before the onset of the far more pronounced pubertal growth spurt. In this study we used a triple logistic curve-fitting method to fit individual growth curves to serial stature data from 579 healthy participants in the Fels Longitudinal Study, 479 of whom have been genotyped for about 400 short tandem repeat (STR) markers spanning the genome. We categorized individuals according to the presence or absence of a midchildhood growth spurt and then conducted heritability and genome-wide linkage analyses on the dichotomous trait. In the total sample of 579 individuals, 336 (58%) were found to have evidence of having had a midchildhood growth spurt. There was a marked sex difference in presence of the midchildhood growth spurt, however, with 232 of the 293 males (79%) having had a midchildhood growth spurt but just 104 of the 286 females (36%) having had one. Presence of a midchildhood growth spurt was found to have a significant heritability of 0.37 ± 0.14 ($p = 0.003$). Two quantitative trait loci with suggestive LOD scores were found: one at 12 cM on chromosome 17p13.2 (LOD = 2.13) between markers *D17S831* and *D17S938* and one at 85 cM on chromosome 12q14 (LOD = 2.06) between markers *D12S83* and *D12S326*.

Keywords

Midchildhood Growth Spurt; Heritability; Linkage; Fels Longitudinal Study

Growth is a complex process composed of distinct phases and events that take place over the course of childhood. For example, the pubertal growth spurt has received considerable attention from auxologists and pediatricians. In contrast, the midchildhood growth spurt has been much less well studied. The midchildhood growth spurt refers to a relatively small and transient increase in growth velocity observed in some, but not necessarily all, children in early to middle childhood. This growth spurt, first called the “midgrowth spurt” by Tanner (1947) but described earlier by Robertson (1915), occurs sometime between the ages of 4 and 8 years (Robertson 1915; Tanner 1962), well before the onset of the far more pronounced pubertal growth spurt that all normal and healthy children evidence to one degree or another. The midchildhood growth spurt in height has been identified in a number of analyses and studies (Berkey et al. 1983; Bock and Thissen 1980; Gasser et al. 1985a, 1985b, 1993; Molinari et al. 1980; Sheehy et al. 1999; Stutzle et al. 1980). Some have observed this growth spurt in boys but not girls (Sheehy et al. 1999) or have observed an earlier onset or increased intensity in one sex or the other (Molinari et al. 1980), whereas others have observed no differences in occurrence or intensity between the sexes (Gasser et al. 1985a). When the midchildhood growth spurt occurs, it typically lasts for approximately 2 years (Gasser et al. 1985a, 1991; Sheehy et al. 1999).

The goals of the present study are to characterize the presentation of the midchildhood growth spurt in individuals participating in the Fels Longitudinal Study and to conduct heritability and genome-wide linkage analyses of the presence of a midchildhood growth spurt among those individuals. To our knowledge, the study presented here is the first statistical genetic analysis of the midchildhood growth spurt.

Materials and Methods

Study Population

Data for this study were collected from participants in the Fels Longitudinal Study (see Roche 1992). The Fels Longitudinal Study began in 1929 in Yellow Springs, Ohio (located near Dayton), as a community-based study of normal childhood growth and development; it continues to this day with broader research interests focused largely on examining body composition and associated risks for various complex diseases from birth through old age. Since the inception of the Fels Longitudinal Study, participants have not been selected for the presence or absence of any particular medical condition or other features. Unlike other growth studies initiated in the United States during the 1920s and 1930s, the Fels Longitudinal Study began collecting familial data almost from its beginning. The Fels Longitudinal Study has thus emerged over the last three-quarters of a century as a rare resource for examining genetic contributions to complex traits measured over the entire life span.

To date, more than 1,200 participants have been enrolled in the serial aspect of the Fels Longitudinal Study (i.e., individuals enrolled as children and subsequently examined at regular intervals). Participants in the Fels Longitudinal Study are from about 150 families, ranging in size from small nuclear families to large four-generation extended families. For the most part, participants in the serial aspect of the Fels Longitudinal Study are examined within the first month of postnatal life, and at 3, 6, 9, and 12 months during their first year. After 1 year of age children are examined at 6-month intervals until the age of 18 years, after which they are examined every 2 years until age 24, and then they are examined every 2–5 years in adulthood.

Study Sample

Data used in the study presented here are from 579 individuals (293 males and 286 females) from 132 nuclear and extended families in the Fels Longitudinal Study, each family having from 1 to 56 individuals with growth data. Forty-six families had just one individual with longitudinal growth data, but these individuals were included in the analyses to provide a full description of the presentation of the midchildhood growth spurt in the Fels Longitudinal Study and thus also for better parameter estimation in the genetic analyses. These 579 individuals were born between 1930 and 1989. Minimally, each individual in this study sample had at least one measure of stature taken in each of four age ranges during childhood (2 to < 6 years, 6 to < 10 years, 10 to < 14 years, and 14 to < 18 years) and one measure of adult stature (defined as taken at age 18 years, or at an older age closest to age 18 if no measurement at age 18 was available). The number of measures of stature taken of individuals in the study sample from ages 2 to 18 years (or at an older age in some cases) ranged from 5 to 42, with an average of 27 observations per subject.

Growth Curves

We used the triple logistic BTT (Bock-Thissen-du Toit; Bock et al. 2003) model [version 3.1 (2003)] implemented in the AUXAL software package (Scientific Software International, Lincolnwood, Illinois) to fit growth curves to serial stature data from the study individuals [see also Bock and du Toit (2004) as well as Gasser et al. (2004) and Hauspie and Molinari (2004) for discussion of other growth curve modeling procedures]. The BTT method is a maximum-likelihood-based method using Bayes modal estimation to specify the most probable growth curve of an individual based on that individual's data. The BTT model is able to detect and locate growth velocity minima and maxima during both midchildhood (i.e., the midchildhood growth spurt) and adolescence (i.e., the pubertal growth spurt), and thus the age, stature, and growth velocity of the individual at those minima and maxima are obtained. The BTT structural model was developed using data from the Fels Longitudinal Study. For the purposes of the present study, individuals with estimated age, stature, and growth velocity parameter values at the early childhood minima and midchildhood maxima were categorized as having had a midchildhood growth spurt, whereas those individuals with no such estimated parameter values were categorized as not having had a midchildhood growth spurt.

Genetic Markers

Of the 579 individuals with growth curve data, 479 (233 males and 246 females) have been genotyped for about 400 highly polymorphic markers spanning the genome at a resolution of about 10 cM using ABI Prism Linkage Mapping Set-MD10 (PE Biosystems, Foster City, California). In the linkage analysis method used in this study, all information regarding linkage is a function of identity-by-descent (IBD) matrices. For each pedigree, we calculated an estimate of all the elements of a location-specific IBD probability matrix jointly using a Markov chain Monte Carlo method implemented in the computer program LOKI (Heath 1997). Multipoint-based IBD matrices were calculated for each centimorgan across each chromosome.

Statistical Genetic Analyses

Heritability and linkage analyses were conducted using SOLAR (Almasy and Blangero 1998), a maximum-likelihood variance-components-based method for analysis of familial data from pedigrees of arbitrary size and complexity. Heritability analysis of presence of a midchildhood growth spurt was conducted on the full data set of 579 individuals, whereas linkage analysis of presence of a midchildhood growth spurt was conducted on the subset of 479 genotyped individuals. The midchildhood growth spurt was defined as a dichotomous

trait that is assumed to follow a standard normal threshold model of liability. The likelihood of a given pedigree involves the computation of high-dimensional multivariate normal integrals, which are approximated using an accurate numerical method (Duggirala et al. 1997; Williams et al. 1999). Because of marked sex differences in childhood growth patterns, including sex differences in the presentation of the midchildhood growth spurt, as reported by earlier investigators, sex was included as a covariate in the analyses. In addition, because the birthdates of individuals providing data for the analyses spanned six decades from 1930 to 1989, provision was made to consider the possibility of a secular trend in presentation of a midchildhood growth spurt by including birth year as a covariate. Finally, sex $\times$ secular trend (i.e., birth year) interaction also was included as a covariate.

Results

Presentation of the Midchildhood Growth Spurt

In the total study sample of 579 individuals, 336 (58%) were found to have evidence of a midchildhood growth spurt. There was, however, a marked sex difference in the presentation of a midchildhood growth spurt, with 232 of the 293 males (79%) but just 104 of the 286 females (36%) having had one. [Essentially the same findings were reflected in the subsample of 479 individuals with whole genome marker data, with 187 (80%) of the 233 males having had a midchildhood growth spurt and 90 (37%) of the 246 females having had one.]

Table 1 shows the descriptive statistics for the six midchildhood growth spurt parameters in those 232 males and 104 females in the full study sample of 579 individuals for whom those parameters were estimated using the curve-fitting procedure. On average, males who had a midchildhood growth spurt were 4.84 years old at its onset and 6.25 years old at its peak. The midchildhood growth spurt in those females experiencing one generally occurred earlier than in males; on average, females who had a midchildhood growth spurt were 3.93 years old at its onset and 4.83 years old at its peak. In both males and females who had a midchildhood growth spurt, the increase in growth velocity from its onset to its peak was small: on average, an increase of 6.51 cm/yr to 6.62 cm/yr in males and an increase of 6.87 cm/yr to 6.92 cm/yr in females.

To provide a visual illustration, Figure 1 and Figure 2 show the growth and growth velocity curves of a male and female, respectively, in the Fels Longitudinal Study who each had a relatively pronounced midchildhood growth spurt.

Heritability of the Midchildhood Growth Spurt

Because the individuals in the study sample are from families, including several large extended families, a variety of types of relationships among them span multiple households and generations. Table 2 shows the number and type of biological pairwise relationships that the 579 individuals with longitudinal growth data in 132 families have among themselves (more specifically, among the 533 individuals from 86 families containing at least 2 individuals with longitudinal growth data). In all, there are 2,743 relative pairings represented in the full study sample. All these familial data, consisting of those from first-degree relatives to tenth-degree relatives (and including data from 46 individuals from families with only one individual with longitudinal growth data) were used in the heritability of the midchildhood growth spurt analysis.

The heritability of presence of a midchildhood growth spurt in the full study sample of 579 individuals is highly significant at 0.37 ± 0.14 ($p = 0.003$), indicating that approximately one-third of the observed variation among these individuals with respect to having had a midchildhood growth spurt is due to the effects of genes. In this analysis, given the

pronounced sex difference in presentation of the midchildhood growth spurt, sex was a significant covariate ($\beta = 1.1624652 \pm 0.1114957$; $p < 0.0001$). Secular trend and sex $\times$ secular trend were not significant covariates. [Essentially the same results were obtained from heritability analysis of the midchildhood growth spurt in the subsample of 479 individuals with whole genome marker information. In that subsample the heritability of the midchildhood growth spurt was estimated at 0.32 ± 0.17 ($p = 0.015$) and, again, sex was the only significant covariate.]

Linkage Analysis of the Midchildhood Growth Spurt

Figure 3 shows the results of the whole-genome linkage scan for presence of a midchildhood growth spurt in the subset of 479 individuals with genomic marker data. For this pedigree structure and configuration of typed markers, we used the method of Feingold et al. (1993) to calculate that a LOD score of 1.67 would be expected to occur only once per genome scan by chance. We define this cutoff as representing a suggestive linkage [similar to that defined by Lander and Kruglyak (1995) for the complete information case]. Suggestive linkage was found for presence of the midchildhood growth spurt to markers on chromosome 17p13.2 between markers *D17S831* and *D17S938* (12 cM; peak LOD = 2.17) and chromosome 12q14 between markers *D12S83* and *D12S326* (85 cM; peak LOD = 2.06). Figure 4 shows that the suggestive linkage signal (i.e., quantitative trait locus; QTL) on chromosome 17 spans a region of about 20 cM, and Figure 5 shows that the suggestive QTL on chromosome 12 spans a region of about 40 cM.

Discussion

The midchildhood growth spurt is a relatively small acceleration in growth observed in many children, but not all. Few studies of the midchildhood growth spurt have been conducted, and it is rarely possible to make direct comparisons of findings between those few that exist. The potentially transient nature of its presentation and insufficient observations over the entire course of childhood, especially during the critical ages of 4 to 8 years, has made identification of the midchildhood growth spurt problematic. Bogin (1999) notes that there are several possible reasons for discrepancies among studies with regard to the prevalence, sex difference, timing, and magnitude of the midchildhood growth spurt. Most important, these include the use of different statistical methods (including some that do not model the midchildhood growth spurt or are insufficiently sensitive to the expression of a midchildhood growth spurt if present) and the number and frequency of serial observations. In general, studies that report finding a midchildhood growth spurt in at least some of their study sample tend to be those that avoided these pitfalls.

Tanner and Cameron (1980) found no midchildhood growth spurt in a sample of London girls but did observe a midchildhood growth spurt in boys, which they described as a checking of the deceleration of growth taking place at that age in boys, but not an increase in growth velocity as observed in other populations. Berkey et al. (1983) observed the same thing in a sample of Boston boys and girls. A midchildhood growth spurt has been observed in several analyses using data from the Zurich Longitudinal Study (Gasser et al. 1985a, 1985b, 1993; Molinari et al. 1980; Sheehy et al. 1999; Stutzle et al. 1980). For example, Gasser et al. (1985b), using a kernel estimation procedure, report a midchildhood growth spurt in 42 of 45 boys (93%) and 37 of 45 girls (82%). In the study presented here, we found a somewhat lower prevalence in males (79%) and a markedly lower prevalence in females (36%). More relevant to the study presented here are the findings of Gasser et al. (1985b) with regard to the timing of the midchildhood growth spurt. In addition to using a kernel estimation procedure, Gasser and colleagues also used the triple logistic method (which was used in the present study) to fit individual growth acceleration curves to their sample of 45 boys and 45 girls with extensive serial data throughout childhood. Using that method, they

found that the mean age at midchildhood maximum growth velocity was 6.4 years in males and 5.9 years in females. Making a direct comparison to our study results, we found a slightly earlier mean age at midchildhood maximum growth velocity in males of 6.25 years but a significantly earlier mean age at midchildhood maximum growth velocity of 4.83 years in females.

The midchildhood growth spurt has also been observed in other anthropometrics, and in some of these other measures its presentation is more dramatic than that observed for stature (Gasser et al. 1991, 1993). For example, Tanner and Cameron (1980) observed midchildhood growth spurts between ages 5.5 years and 10 years in a variety of anthropometrics, including weight, upper arm circumference, calf circumference, and subscapular and triceps skinfold thicknesses. Of these, the midchildhood growth spurt of calf circumference was the most pronounced. Meredith (1981) found generally similar results in a sample of Iowa City boys and girls; more direct skeletal measures (e.g., height, hip width, and arm length) did not evidence a midchildhood growth spurt, but measures incorporating a significant amount of soft tissues (e.g., weight, calf circumference, and upper arm circumference) did evidence a midchildhood growth spurt. And Sheehy et al. (1999) found that the timing of the midchildhood growth spurt appears to be variable depending on the location and type of tissue examined (e.g., skeletal versus soft tissue).

The cause of the midchildhood growth spurt, an increase in growth velocity some years ahead of the pubertal growth spurt, is not known. It has been suggested that it is related to adrenarche and the increase in androgen hormones before puberty (Molinari et al. 1980), but more recent work has found no evidence to support this hypothesis (Remer 2000; Remer and Manz 2001).

To our knowledge, the study presented here is the first statistical genetic analysis of the midchildhood growth spurt—one conducted in a large sample of healthy children examined regularly from infancy to adulthood. We found that the midchildhood growth spurt had a significant heritability of 37% and suggestive linkages to markers on chromosomes 17 and 12.

The suggestive QTL on chromosome 17 does not contain an immediately obvious positional candidate gene(s), but the Miller-Dieker lissencephaly syndrome (MDLS, OMIM 247200), which often includes growth delays and short stature as part of its etiology, has been mapped to chromosome 17p13.3, a region within the suggestive QTL for the midchildhood growth spurt reported here. *LIS1* has been identified as the specific gene responsible for the classical brain and facial abnormalities of MDLS, but other genes in the region are thought to contribute to associated features often observed in the syndrome, including somatic growth retardation. Also of interest is the study by Vissers et al. (2007), who recently reported a number of complex chromosomal rearrangements in proximal 17p (including the suggestive QTL at 17p13.2 reported here for the midchildhood growth spurt) in patients with several developmental abnormalities, including significantly reduced growth. Thus it is possible that the proximal region of chromosome 17p contains as yet unidentified genes that might influence features of normal growth such as the midchildhood growth spurt.

The suggestive QTL on chromosome 12 is broad and is composed of four conjoined linkage peaks with relatively little diminution of linkage signal between them. Moving from the centromere to the q terminus, the first peak (LOD = 1.79) is at 71 cM between markers *D12S368* and *D12S83* (12q13.13–14.1); the second peak (LOD=2.06) is at 85 cM between markers *D12S83* and *D12S326* (12q14.1–21.2); the third peak (LOD = 1.99) is at 98 cM between markers *D12S326* and *D12S351* (12q21.2–21.33); and the fourth peak (LOD = 1.90) is at 105 cM between markers *D12S351* and *D12S346* (12q21.33–23.1). Hirschhorn et

al. (2001) reported significant linkage ($LOD = 3.35$) of adult stature in a study population from Finland to markers at 12p11.2–q14, a genomic region overlapping the suggestive linkage signal for the midchildhood growth spurt reported here. Geller et al. (2003) reported a modestly suggestive linkage ($LOD = 1.70$) of adult stature in a sample from the Framingham Heart Study to a region of chromosome 12q between 70 cM and 77 cM, an area contained within our suggestive linkage signal for the midchildhood growth spurt. And in recent genome-wide association studies, Weedon et al. (2007) and Lettre et al. (2008) reported significant associations between height and SNP rs1042725 located in the 3' UTR of the high mobility group AT-hook 2 (*HMGA2*) gene, which has been suggested as a strong candidate gene for height. *HMGA2* is located on chromosome 12q14.3 between markers *D12S83* and *D12S326*, directly under our peak suggestive linkage signal for the midchildhood growth spurt.

It is worth at least noting two additional possible positional candidate genes in the immediate vicinity of the QTL reported here on chromosome 12 for the midchildhood growth spurt. First, the vitamin D receptor gene (*VDR*) is located at 12q13.11, approximately where our broad linkage signal begins at approximately 64 cM (i.e., $LOD \approx 1.0$). Allelic variants of *VDR* have been associated with height in several studies of children and adults (e.g., Dempfle et al. 2006; Fang et al. 2007; Ferrara et al. 2002; Lorentzon et al. 2000; Minamitani et al. 1998; van der Sluis et al. 2003; Xiong et al. 2005). And, the insulinlike growth factor 1 (*IGF1*) gene is at chromosome 12q23.2 between markers *D12S346* and *D12S78*, approximately where our broad linkage signal ends at approximately 112 cM (i.e., $LOD \approx 1.0$). *IGF1* is well established as one of several hormones working in concert to ensure normal growth and development.

The findings presented here of a significant heritability of the midchildhood growth spurt treated as a qualitative trait and suggestive linkage of the midchildhood growth spurt to chromosomal regions harboring plausible candidate genes for growth-related traits (e.g., height and *HMGA2*) provide additional substantiation that the midchildhood growth spurt is a genuine biological phenomenon occurring in most boys and many girls. Our future work on elucidating the genetic architecture of growth and maturation throughout childhood will include examination of associations between qualitative and quantitative measures of growth and maturation during middle childhood with those observed at other stages (e.g., infancy and puberty), as well as sex differences in particular aspects of growth and maturation at different times during childhood. Detailed studies such as these are needed to obtain a comprehensive understanding of genetic influences on the varied processes that make up growth and development.

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Figure 1.
Midchildhood growth spurt in a male from the Fels Longitudinal Study.

Figure 2.
Midchildhood growth spurt in a female from the Fels Longitudinal Study.

Figure 3. Genome-wide LOD score plot of the midchildhood growth spurt in 479 children in the Fels Longitudinal Study. Note: LOD score scale provided only on those chromosomes with peak LOD scores greater than 1.5.

Figure 4.
LOD score plot on chromosome 17 of the midchildhood growth spurt in 479 children in the Fels Longitudinal Study.

Figure 5.
LOD score plot on chromosome 12 of the midchildhood growth spurt in 479 children in the Fels Longitudinal Study.

Table 1

Descriptive Statistics of Midchildhood Growth Spurt Parameters in Fels Longitudinal Study Subjects Evidencing a Midchildhood Growth Spurt

Variable	Range	Mean	SD
Males (<i>n</i> = 232)			
Age at early childhood minimum growth velocity (years)	3.65–6.37	4.84	0.49
Age at midchildhood maximum growth velocity (years)	4.88–7.45	6.25	0.43
Stature at early childhood minimum growth velocity (cm)	90.9–122.9	107.9	5.2
Stature at midchildhood maximum growth velocity (cm)	102.2–133.1	117.2	4.6
Velocity at early childhood minimum growth velocity (cm/yr)	5.30–8.06	6.51	0.46
Velocity at midchildhood maximum growth velocity (cm/yr)	5.32–8.16	6.62	0.50
Females (<i>n</i> = 104)			
Age at early childhood minimum growth velocity (years)	2.79–4.96	3.93	0.39
Age at midchildhood maximum growth velocity (years)	4.01–5.55	4.83	0.32
Stature at early childhood minimum growth velocity (cm)	86.1–110.9	99.7	4.4
Stature at midchildhood maximum growth velocity (cm)	98.2–115.4	105.8	3.2
Velocity at early childhood minimum growth velocity (cm/yr)	5.87–8.72	6.87	0.58
Velocity at midchildhood maximum growth velocity (cm/yr)	5.90–8.80	6.92	0.59

Table 2

Biological Relative Pairings Represented Among the Full Study Sample of 579 Individuals

Type of Relative Pairing	Number of Pairings	Degree of Relationship
Parent-offspring	221	First
Siblings	446	First
Grandparent-grandchild	32	Second
Avuncular	436	Second
Half-siblings	33	Second
Great avuncular	43	Third
Half-avuncular	19	Third
First cousins	486	Third
Half-grand avuncular	4	Fourth
First cousins once removed	442	Fourth
Half-first cousins	14	Fourth
First cousins twice removed	39	Fifth
Second cousins	284	Fifth
Second cousins once removed	166	Sixth
Third cousins	48	Seventh
Third cousins once removed	17	Eighth
Third cousins twice removed	8	Ninth
Fourth cousins	3	Ninth
Fourth cousins once removed	2	Tenth
Total number of pairings	2,743	