The Biology of Stature

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Most pediatricians are attuned to their patients' linear growth (height gain). At each visit, the child's height should be carefully measured and plotted. The clinician can then scrutinize the temporal pattern, and, if the linear growth appears abnormal, initiate an investigation to uncover the underlying problem. Despite this close interest in our patients' statural gains, linear growth itself often is considered as a "black box," a mysterious process regulated by nutrition, hormones, genetics, and overall health. Recently, there have been exciting advances in understanding the biological basis of linear growth. We have gained new insights as to why linear growth is rapid in infancy, then slows in childhood, accelerates in adolescence, then slows again and ceases by adulthood. We now understand much better the mechanisms by which hormones, nutrition, and systemic illness regulate linear growth. Perhaps most exciting, genome-wide association (GWA) studies and exome sequencing have begun to identify numerous novel genes that regulate linear growth, and, when mutated, cause childhood growth disorders.

To understand these important new findings and their implications for our patients, we must look inside the black box of linear growth. Just as we can only understand children's respiratory physiology in terms of lung biology, so too we can only understand linear growth and growth disorders in terms of the underlying biological process, growth plate chondrogenesis.

Clinical Vignette

A 6-year-old boy presents for evaluation of short stature. He was born at term with a length and weight appropriate for gestational age. By 2 years of age, his length percentile had dropped below the third percentile. Weight was less affected. He has been otherwise healthy. His mother and father are both 160 cm (63 in) tall. On physical examination, the boy's height is below the first percentile at −2.2 SDS. His sitting to standing height ratio is at the 95th percentile for age. His father's sitting to standing height ratio is greater than the 95th percentile for age.

In this review, we will discuss a variety of novel concepts that will aid in the assessment of such children. We will see that this child's altered body proportions indicate that the condition affects the growth plates in the lower extremities more than the growth plates of the vertebrae. This disproportion suggests a primary linear growth condition, that is, an underlying mechanism that is intrinsic to the growth plate. The similar phenotype of the father suggests a dominant inheritance. Targeted sequencing by a commercial laboratory showed a mutation in SHOX, which encodes a transcription factor required for normal growth plate chondrocyte function. Heterozygous SHOX mutations account for approximately 2%-5% of children with formerly idiopathic short stature. SHOX lies on the X chromosomes, but, unlike most X-chromosome genes, a second copy is present on the Y chromosome in boys, and consequently SHOX mutations are inherited in a pseudoautosomal pattern.

GWA	Genome-wide association
IGF-I	Insulin-like growth factor-I

Linear Growth in Children Is Driven by Growth Plate Chondrogenesis

Children grow taller because their bones grow longer. This bone elongation occurs at the growth plate, a cartilaginous structure that is located near the ends of many bones in children, including long bones, the short tubular bones of the hands and feet, and the vertebrae. The growth plate comprises 3 distinct layers: the resting, proliferative, and hypertrophic zones (Figure 1). Each zone has unique roles. The resting zone serves as a reservoir of progenitor chondrocytes.[1] The proliferative zone, which contains chondrocytes arrayed in columns, is the site of rapid cell proliferation (Figure 1).[2] At the edge of the proliferative zone closest to the metaphysis, the cells stop dividing and become enlarged to form hypertrophic chondrocytes (Figure 1).[2] This cell proliferation and cell hypertrophy, combined with extracellular matrix secretion, result in chondrogenesis, that is, the production of more and more cartilage.[2] In isolation, this chondrogenesis would cause the cartilaginous growth plate to become progressively wider with age. Simultaneously, blood vessels, osteoclasts, and osteoblasts, however, invade the hypertrophic zone and remodel the newly formed cartilage into bone.[2] The net result is that new bone is formed at the boundary between the growth plate and the metaphysis, causing the bones to grow longer and the child to grow taller.

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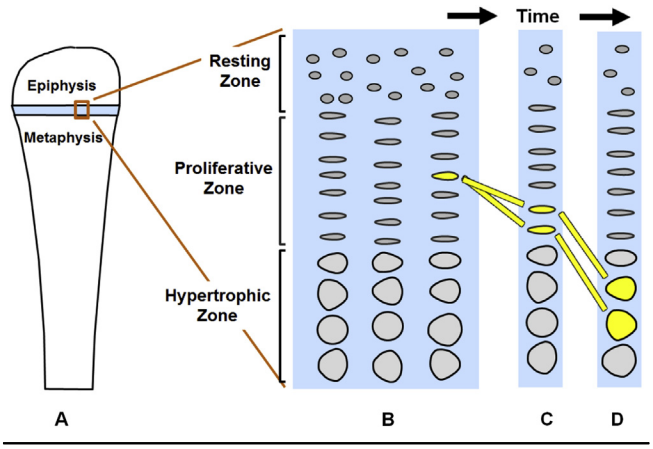

Figure 1. Growth plate chondrogenesis diagram. **A,** Growth plate (*light blue*) lies near the end of a long bone. **B,** Enlarged view of the growth plate illustrating its 3 zones. **C,** The proliferative zone chondrocytes, which are arranged in columns, undergo cell divisions (*yellow bars* trace a single cell over time). **D,** When chondrocytes reach the border of the proliferative zone closest to the metaphysis, they cease proliferating and instead hypertrophy. Proliferation, hypertrophy, and extracellular matrix secretion contribute to chondrogenesis (cartilage formation). At the boundary of the growth plate and the metaphysis, the newly formed cartilage is remodeled into bone (not shown).

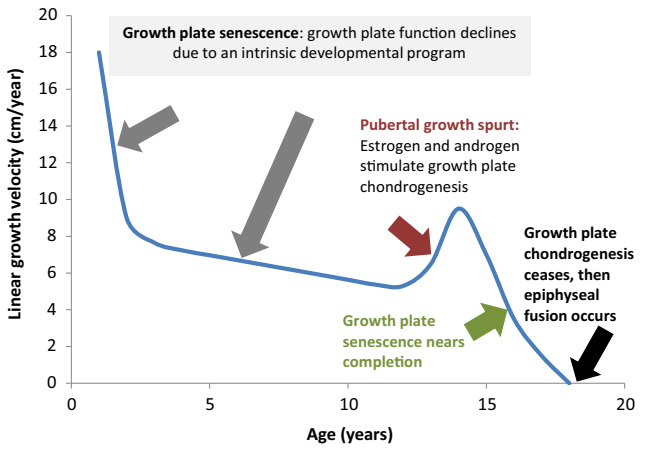

Figure 2. Changes in linear growth velocity with age. The linear growth velocity (change in body length per year) is rapid in infancy, declines in childhood, accelerates in adolescence, and then declines and ceases by adulthood. The principal underlying mechanisms are shown. The **Figure** represents typical growth for a boy. Girls usually show an earlier growth spurt and earlier cessation of growth. The timing of the growth spurt and cessation of growth often are shifted to the right in malnutrition, chronic systemic disease, and in healthy children with a slow developmental tempo. A shift to the left occurs in children with rapid developmental tempo.

Linear Growth Is Rapid in Infancy but Subsequently Slows as the Result of Programmed Senescence of the Growth Plate

The human fetus grows rapidly. From 12 weeks of gestation until term, the length of the fetus increases from approximately 6 to 50 cm, an average growth velocity of 82 cm/year.[3] If newborns were to maintain this growth rate after birth, the child would reach adult size before 2 years of age. The growth rate, however, declines rapidly after birth. The decline is temporarily interrupted by the pubertal growth spurt but then resumes until the growth rate reaches zero (**Figure 2**).[4]

The decline in the linear growth rate during childhood appears to be driven primarily by local mechanisms within the growth plate, rather than by systemic mechanisms. There are no growth-regulating hormones whose concentration changes in a pattern that would explain the decline in growth rate. For example, the concentration of insulin-like growth factor-I (IGF-I) actually increases with age during childhood.[5] Furthermore, growth plates have been transplanted between rabbits of different ages, and the growth rate of the transplanted growth plates depends on the age of the donor, not the recipient, suggesting that the decline in growth rate is caused by a local, growth plate mechanism, rather than a systemic mechanism.[6]

Recent studies have identified a developmental program intrinsic to the growth plate cartilage, termed "growth plate senescence," which is responsible for the decline in growth rate with age. With increasing age, the growth plate gradually involutes, so that the number of cells in each zone diminishes.[7-9] Concurrently, the rate of proliferation and the extent of cell hypertrophy diminish,[7,8] causing the child's linear growth to slow. Eventually, proliferation ceases altogether, and the nonfunctional growth plate is resorbed and replaced by bone, an event termed epiphyseal fusion or growth plate closure (**Figure 2**).[10] Thus, epiphyseal fusion does not cause growth cessation, as often is assumed, but instead fusion is the result of growth cessation.[11] Growth plate senescence appears to be driven by an extensive genetic program that involves the down-regulation with age of many growth-promoting genes.[12] A related growth-limiting genetic program occurs in other tissues, causing somatic growth also to slow and eventually cease in other major organ systems.[13-15]

In children, the progression of growth plate senescence can be assessed indirectly from a radiograph of the left hand and wrist. On these radiographs, the child's bone age is evaluated by observing the extent to which the cartilage skeletal elements have been converted into bone. The bone age appears to serve as a radiologic marker for growth plate senescence in that it predicts the amount of linear growth remaining and therefore helps predict the adult height.

Variations in Tempo of Growth, Including Catch-Up Growth

Importantly, growth plate senescence is not driven by time but rather by the process of growth itself.[7,16] Consequently, childhood malnutrition or systemic illness slows not just the rate of linear growth but also the rate of growth plate senescence.[7,17] If the illness resolves, the growth plates do not just resume a normal growth rate. Instead, the growth plates, which are less senescent than normal for age, function at the more rapid rate that would be appropriate for a younger child, resulting in catch-up growth.[7,16-18] Previously, catch-up growth had been thought to result from a central nervous system mechanism,[19] but recent studies favor this local mechanism[7,16-18] involving delayed growth plate senescence, although it remains unclear whether other mechanisms also contribute.[20]

The pace of growth plate senescence also appears to vary among healthy children and to be associated with the child's overall tempo of maturation. For example, some otherwise-healthy children show a slow overall tempo of maturation, with slower childhood growth, delayed puberty, and continued growth into late adolescence. In this condition, termed constitutional delay of growth and puberty, the presence of prolonged growth and a delayed bone age, even before puberty, suggests that the pace of growth plate senescence also is slowed. This condition appears to be familial, suggesting a genetic basis. In some children, the delay in maturation appears to be driven by subtle undernutrition due to diminished appetite.[21,22]

The Pubertal Growth Spurt

As reviewed previously, a local developmental program termed growth plate senescence causes the linear growth velocity in children to decline through infancy and childhood, reaching 5 cm/per year just before the onset of puberty (**Figure 2**)[4]; however, with puberty, the gonads increase production of sex steroids, which exert strong positive effects on linear growth (**Figure 2**). Estrogen contributes to the linear growth acceleration, in part by stimulating secretion of growth hormone by the pituitary gland.[23] Androgen, either from the adrenal glands or gonads, appears to contribute to the pubertal growth spurt in part through conversion to estrogens by the enzyme aromatase, but androgen also appears to have a stimulatory effect on the growth plate which is not mediated by conversion to estrogen or by increased growth hormone.[24] This effect may explain the growth-stimulating effect of androgens that cannot be converted to estrogens, for example, oxandrolone treatment in Turner syndrome.[25]

Estrogen exerts another important effect on the growth plate; it accelerates growth plate senescence apparently by depleting the pool of chondrocyte progenitor cells.[8] This phenomenon has important clinical implications. Early exposure to estrogen, in children with precocious puberty, causes not only accelerated growth but also accelerated growth plate senescence (reflected by an advanced bone age) and consequently early cessation of growth, early epiphyseal fusion, and a diminished adult stature.[26] Conversely, delayed puberty slows growth plate senescence (reflected by a delayed bone age), causing delayed growth cessation, delayed epiphyseal fusion, and an augmented adult stature.[27] Similar effects are seen in men with either estrogen resistance attributable to mutations in estrogen receptor-α or with estrogen deficiency attributable to mutations in the enzyme aromatase, which is required for estrogen synthesis by converting androgen to estrogen, both of which continue to grow gradually well into adulthood, resulting in marked tall stature.[28,29] The recognition of this effect of estrogen on the growth plate has given rise to a new experimental treatment for short stature in boys, using aromatase inhibitors,[30] although the long-term efficacy and safety are not yet established.

Short and Tall Stature Are Caused by Altered Rates of Growth Plate Chondrogenesis

Because linear growth in children is driven primarily by growth plate chondrogenesis, short stature is essentially always caused by decreased chondrogenesis in the growth plate and tall stature by increased chondrogenesis. The primary causes of short or tall stature can lie either in the growth plate itself (primary linear growth condition) or can lie outside the growth plate but affect chondrocytes through abnormal concentrations of hormones, cytokines, nutrients, and other molecules necessary for normal chondrocyte function (secondary linear growth condition).

Regulation of Linear Growth

The rate of growth plate chondrogenesis, and therefore the rate of linear growth in children, is subject to extensive regulation by nutritional intake, hormones, inflammatory cytokines, paracrine growth factors, extracellular matrix factors, and intracellular proteins.

Nutritional Intake

Both inadequate and excessive nutritional intake alter longitudinal bone growth. In nutritional deficiency, much of the effect appears to be mediated by endocrine factors: decreased IGF-I, sex steroids, and thyroid hormone and increased glucocorticoids, as may be observed in children with anorexia nervosa.[31] In nutritional excess causing obesity, linear growth may be accelerated, resulting in tall stature and advanced bone age, but the adult height is not substantially affected.[32] The underlying mechanisms remain poorly understood.

Hormones

Thyroid hormone, growth hormone, IGF-I, androgen, and estrogen all positively regulate linear growth. Consequently, deficiency of these hormones can present clinically with decreased linear growth.[33-35] In contrast, glucocorticoid in excess negatively regulates linear growth, accounting for the

poor linear growth of children with endogenous or exogenous Cushing syndrome.[36] Each of these hormones acts in part through a direct, local effect on growth plate chondrogenesis,[37-40] although there are also complex interactions among these systems; for example, thyroid hormone and estrogen positively regulate growth hormone secretion.[23,40,41]

Inflammatory Cytokines

Tumor necrosis factor-α, interleukin-1β, and interleukin-6 all negatively regulate growth plate chondrogenesis. There is evidence for both direct, local actions on growth plate chondrocytes as well as indirect actions, involving IGF-I suppression.[42] These adverse effects of circulating proinflammatory cytokines likely contribute to the linear growth impairment in children with inflammatory bowel disease or juvenile idiopathic arthritis.[42,43]

Paracrine Growth Factors

Multiple paracrine growth factors are produced locally in the growth plate, and these paracrine growth factors, including IGFs, C-natriuretic peptide, bone morphogenetic proteins, and fibroblast growth factors, affect adjacent chondrocytes by acting on specific cell-surface receptors.[44-47] Consequently, patients with mutations in genes involved in these signaling systems can present with linear growth failure or overgrowth (Table). For example, homozygous inactivating mutations in NPR2, the receptor for C-natriuretic peptide, cause a skeletal dysplasia with severe short stature,[48] whereas heterozygous inactivating mutations present as idiopathic short stature[49,50] and activating mutations produce tall stature.[51,52]

Extracellular Matrix

The extracellular matrix of growth plate cartilage is composed of collagens (including collagen II and X), proteoglycans (including aggrecan and perlecan), and noncollagenous proteins (including cartilaginous oligomeric matrix protein).[53] Mutations affecting these proteins can present clinically either as short stature with minimal bone deformity, as seen in heterozygous aggrecan mutations, or as a skeletal dysplasia as seen in collagen type 10 or cartilaginous oligomeric matrix protein (Table).[54,55]

Intracellular Proteins

Transcription factors such as RUNX2, SOX9, and SHOX play major roles in growth plate chondrogenesis. For example, mutations in RUNX2 cause cleidocranial dysplasia and mutations in SOX-9 cause campomelic dysplasia.[56,57] Homozygous mutations in SHOX cause severe short stature in Langer

Table. Examples of monogenic short stature

Genes	Proteins	Disorders	Specific clinical findings
Paracrine signaling			
FGFR3	Fibroblast growth factor receptor-3	Achondroplasia Hypochondroplasia Thanatophoric dysplasia ISS	Varies from severe disproportionate skeletal growth failure to proportionate short stature
GNAS	G-protein α subunit	Albright hereditary osteodystrophy	Brachydactyly, short fourth and fifth metacarpal bones, subcutaneous ossifications
PTH1R	Parathyroid hormone-1 receptor	Blomstrand chondrodysplasia	Severe skeletal growth failure, advanced skeletal maturation
NPR2	Natriuretic peptide receptor-2	ISS (heterozygous) Acromesomelic dysplasia, Maroteaux type (homozygous)	Short stature, ↑S/S ratio in some patients
PTPN11, SOS1, RAF1, others	Various proteins involved in RAS/MAPK signaling	Noonan syndrome	Cardiac anomalies, characteristic facies, other developmental anomalies
Cartilage extracellular matrix			
ACAN	Aggrecan	ISS (heterozygous) Spondyloepiphyseal dysplasia Kimberly type (heterozygous), Spondyloepimetaphyseal dysplasia, aggrecan type (homozygous)	Osteochondritis dissecans, early-onset osteoarthritis
COL2A1	Collagen type 2 alpha 1	Spectrum of chondrodysplasias	Disproportionate short stature, arthropathy, eye abnormalities, cleft palate, hearing loss
Col10A1	Collagen type 10 alpha 1	Metaphyseal chondrodysplasia, Schmid type	Disproportionate short stature, bowing of long bones
COMP	Cartilage oligomeric matrix protein	Pseudoachondroplasia	Disproportionate short stature, early-onset osteoarthritis
Intracellular regulation			
SHOX	Short stature homeobox	ISS (heterozygous) Leri–Weill dyschondrosteosis (heterozygous) Langer mesomelic dysplasia (homozygous)	↑S/S ratio, Madelung deformity
CUL7	Cullin 7	3M syndrome	IUGR
OBSL1	Obscurin-like 1		
SOX9	SRY box 9	Campomelic dysplasia	Shortening and bowing of limbs, characteristic facies, 46 XY sex reversal

ISS, idiopathic short stature; *IUGR*, intrauterine growth retardation; *MAPK*, mitogen-activated protein kinase; *RA*, rat sarcoma; *S/S ratio*, increased sitting to standing height ratio.

mesomelic dysplasia, whereas heterozygous mutations can present as a milder skeletal dysplasia, Leri-Weill dyschondrosteosis, or more commonly as "idiopathic" short stature with or without disproportion.[58] Heterozygous SHOX deficiency is also the principal cause of short stature in Turner syndrome because the SHOX gene is located in the pseudoautosomal region of the X-chromosome. Genes that affect epigenetic modifications have emerged as a cause of overgrowth syndromes.[59] For example, mutations in histone methyltransferases EZH2 and NSD1 cause Weaver syndrome and Sotos syndrome, respectively.[60,61]

Short Stature Can Result from Numerous Genetic Defects Affecting Growth Plate Chondrogenesis

As discussed previously, growth plate chondrogenesis is under complex regulation at multiple levels, including nutritional, endocrine, cytokine, paracrine, extracellular matrix, and intracellular protein factors. Consequently, mutations in genes that participate in any of these levels of regulation can result in short stature. Even a mutation that diminishes growth plate chonodrogenesis by only 10% will produce clinically-significant short stature. The Table provides examples of the genetic causes of short stature that affect growth plate chondrogenesis locally. Depending on the nature of the gene involved, the number of alleles affected, and the severity of the mutation, the short stature can be proportionate or disproportionate, syndromic or nonsyndromic, prenatal or postnatal in onset, and associated with skeletal malformation (a chondrodysplasia) or not. Often, specific manifestations of the genetic defect can aid in clinical diagnosis, for example, dysmorphic facies in Noonan syndrome, increased sitting/standing height ratio in SHOX deficiency[62] or hypochondroplasia,[63] short fourth and fifth metacarpal bones in Albright hereditary osteodystrophy,[64] or early-onset osteoarthritis due to aggrecan mutations.[54] Specific genetic testing has become increasingly available at commercial diagnostic laboratories. Recently, exome sequencing has emerged as a powerful new approach to identify novel genetic causes of growth disorders. Exome sequencing uses high-throughput sequencing techniques to detect mutations in exons.[65] During the 5-year period since its first application, exome sequencing has identified novel mutations in known genes to cause growth disorders and also discovered mutations in genes not previously implicated in childhood growth, either in subjects with syndromic short stature such as CEP152 mutations in Seckel syndrome[66] and CCDC8 mutations in 3M syndrome[67] or patients presenting with nonsyndromic short stature, such as ACAN mutations.[54]

Normal Variation in Height and Polygenic Short Stature

Recent GWA studies have provided important new insights into the genetic determinants of stature. Large meta-analyses of GWA studies have identified more than 400 loci scattered throughout the genome that are associated with adult height in the general population.[68] Although the precise gene that affects height at each locus cannot always be pinpointed, bioinformatics analyses indicate that a large subset of these genes affect height because of a role in growth plate cartilage.[68,69] Although these genes were identified because they modulate height within the normal range, it seems likely that polymorphisms in these genes may also result in polygenic short stature.[70]

Conclusion

Growth plate chondrogenesis is the fundamental biological process that drives linear growth in children and therefore determines stature. Recently, a complex cartilage developmental program, termed growth plate senescence, has been elucidated that is responsible for the normal deceleration and eventual cessation of linear growth. Recent laboratory and clinical studies have revealed that estrogen accelerates growth plate senescence, thus explaining the clinical growth patterns seen in patients with precocious and delayed puberty and patients treated with aromatase inhibitors to prolong linear growth. Powerful new genetic approaches, including exome sequencing and GWA studies, have helped identify new genes that regulate growth plate chondrogenesis. Polymorphisms in these genes modulate height within the normal range and likely contribute to polygenic short stature, whereas more severe mutations in these genes may present as monogenic isolated short stature, syndromic short stature, or skeletal dysplasia.

Understanding the biology of stature provides the clinician with a broad framework to conceptual the myriad of conditions that present with short and tall stature. In the near future, it seems likely that the diagnostic approach to children with severe short or tall stature will include exome or whole-genome sequencing. By conceptualizing linear growth in terms of the underlying growth plate biology, the clinician will be better equipped to interpret the resultant genetic findings. ■

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