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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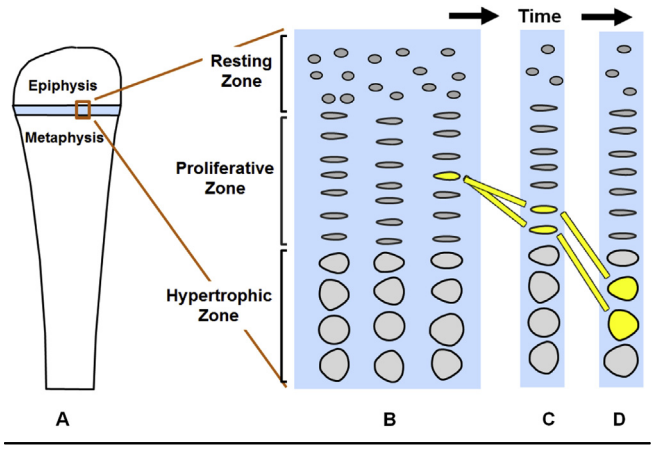

Figure 1. Growth plate chondrogenesis diagram. **A,** Growth plate (*light blue*) lies near the end of a long bone. **B,** Enlarged view of the growth plate illustrating its 3 zones. **C,** The proliferative zone chondrocytes, which are arranged in columns, undergo cell divisions (*yellow bars* trace 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).

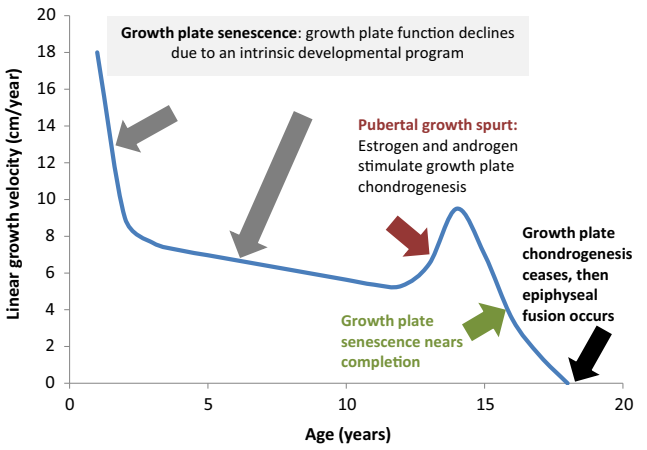

Figure 2. Changes in linear growth velocity with age. The linear growth velocity (change in body length per year) is rapid in infancy, declines in childhood, accelerates in adolescence, and then declines and ceases by adulthood. The principal underlying mechanisms are shown. The **Figure** represents 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.