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## Short and tall stature: a new paradigm emerges

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### Abstract

In the past, the growth hormone (GH) – insulin-like growth factor-I (IGF-I) axis was thought to be the central system regulating childhood growth and therefore responsible for short stature and tall stature. However, recent findings have revealed that the GH-IGF-I axis is just one of many regulatory systems that control chondrogenesis in the growth plate, the biological process that drives height gain. Consequently, normal growth in children depends not only on GH and IGF-I but on multiple hormones, paracrine factors, extracellular matrix molecules, and intracellular proteins that regulate growth plate chondrocytes. Mutations in genes encoding many of these local proteins cause short stature or tall stature. Similarly genome-wide association studies have revealed that the normal variation in height appears to be due largely to genes outside the GH-IGF-I axis that affect growth at the growth plate through a wide variety of mechanisms. These findings point to a new conceptual framework for understanding short and tall stature, which is centered not on two particular hormones but rather on the growth plate, the structure responsible for height gain.

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## Introduction

For decades, the conceptual framework for understanding short stature and tall stature has been centered on the growth hormone (GH) – insulin-like growth factor-I (IGF-I) axis. Children grew taller, it was thought, primarily because the pituitary gland produces GH, which stimulates the liver to produce IGF-I, which makes children grow in height. This mindset was quite understandable historically because the role of the GH-IGF-I axis in longitudinal bone growth was discovered by the 1950s,<sup>1</sup> and the measurement of these two circulating factors, GH and IGF-I, was readily accomplished by radioimmunoassay by the 1960s and 1970s respectively,<sup>2,3</sup> and also because treatment with GH has been the main therapeutic approach available to treat short stature. Based on this paradigm, short stature has sometimes been divided into defects within the GH-IGF-I system versus those outside the axis.<sup>4</sup> This thinking also tended to dominate our speculations about the causes of idiopathic short stature; ISS might be due to either (1) secondary IGF deficiency (due to subtle disorders of GH secretion), (2) primary IGF deficiency (low serum IGF-I with a normal GH secretion), (3) IGF resistance and (4) “other causes”.<sup>5,6</sup> Similarly, it has been suggested that the normal variation in height in the general population is due to subtle modulation of the GH – IGF-I axis.<sup>7,8</sup>

However, unambiguous defects in the GH-IGF-I axis can only be identified in a small minority of children with short stature.<sup>9</sup> In some of these children, the underlying molecular defects have been identified, including mutations causing GH deficiency (including *GHI*, *GHRHR*), GH insensitivity/primary IGF-I deficiency (including *GHR*, *IGFI*, *IGFALS*, *STAT5B*) and IGF insensitivity (*IGF1R*).<sup>10</sup> However, these genetic abnormalities are rare. Far more children fail GH stimulation tests, but this failure appears primarily to result from poor test specificity.<sup>11,12</sup> Similarly, many short children have IGF-I levels in the lower part of the normal range or even below the normal range. This condition has been labeled primary IGF-I deficiency, but it is unclear how many of these children have low IGF-I levels secondary to poor nutritional intake,<sup>13</sup> for example due to diminished appetite,<sup>14</sup> subtle chronic disease,<sup>15</sup> other primary disorders<sup>16</sup> or simply due to a delay in the physiological increase in IGF-I that occurs with age and puberty, since many short children have delayed maturation of other physiological processes.<sup>13</sup> Thus, the vast majority of short children do not have a well-substantiated defect in the GH-IGF-I axis.<sup>9</sup>

GH and IGF-I stimulate linear growth (gain in stature) in children by acting on the growth plate (Figure 1). The growth plate is a thin layer of cartilage that is found in most bones outside the skull and face, including the long bones and vertebrae. In the growth plate, chondrocytes proliferate, hypertrophy, and secrete cartilage extracellular matrix (Figure 1). These processes generate new cartilage tissue, which is subsequently remodeled into bone tissue.<sup>17,18</sup> The net result is that new bone is progressively created at the growth plate, causing bones to grow longer and children to grow taller. GH acts on the growth plate to stimulate new bone formation both through circulating IGF-I and also locally, in part through local IGF-I production.<sup>1,18</sup>

However, recent findings, in both basic and clinical studies, have revealed that the GH – IGF-I axis is just one of many regulatory systems that control chondrogenesis in the growth

plate and therefore regulate linear growth in children (Figure 2). Consequently, normal growth in children requires not just normal concentrations of GH and IGF-I but also normal production and action of multiple other hormones, paracrine factors, and extracellular matrix molecules, as well as normal function of multiple intracellular processes required for chondrocyte proliferation, hypertrophy, and extracellular matrix production. Recent studies have identified many new genes that, when mutated, cause short stature or tall stature, the large majority of which do not participate in the GH-IGF-I system. Similarly normal variation in height appears to be due largely to genes outside the GH-IGF-I axis that affect growth at the growth plate through a wide variety of mechanisms.<sup>19</sup> These new findings point to a new conceptual framework for understanding short and tall stature, a framework which is centered not on two particular hormones but rather on the growth plate itself, the structure responsible for height gain.

### **Normal growth requires normal signaling through many pathways at the growth plate**

In the past, the study of childhood growth was severely limited by available experimental methods. Endocrine factors could be measured by immunoassay in the circulation, but there were few available methods to study, for example, paracrine factors that act locally in the growth plate without entering the circulation, or to study intracellular molecular pathways that regulate chondrocyte proliferation and differentiation. However, in the past few decades a wide variety of new experimental approaches have yielded an explosion of information about the function of the growth plate. For example, knockout of many genes not previously known to be important in the growth plate have produced phenotypes involving skeletal growth at the growth plate, thus opening up unexpected new areas of growth plate physiology. In parallel, new molecular genetic techniques used in clinical research have identified genetic abnormalities causing short stature, many of which occur in genes involved, not in the GH-IGF-I axis, but in other, often local, pathways necessary for normal growth plate function. Together, the basic biology and clinical genetic studies have synergistically expanded our view of childhood growth physiology and pathophysiology.

### **Multiple hormones and cytokines directly regulate growth plate function**

In addition to GH and IGF-I, multiple other hormones regulate linear growth, including thyroid hormone, glucocorticoids, estrogens, and androgens. There is evidence that each of these endocrine factors regulate growth in part by a direct action on the growth plate. For example, infusion of dexamethasone, a synthetic glucocorticoid, directly into the growth plate causes local slowing of growth in that growth plate and addition of dexamethasone to culture medium slows growth of cultured fetal metatarsal bones.<sup>20,21</sup> Clinically, treatment with GH can partially compensate for a low dose of glucocorticoid, improving linear growth, but has little effect at high concentrations of glucocorticoids.<sup>22</sup> Similarly, there is evidence for direct effects of thyroid hormone,<sup>23,24</sup> androgen,<sup>25,26</sup> and estrogen.<sup>27,28</sup> In addition, there is interaction among these hormonal systems. For example, glucocorticoids have complex effects on GH production<sup>29</sup> and inhibit thyroid hormone production.<sup>30</sup>

Estrogen has complex effects on the growth plate, not only altering growth rate, but also accelerating loss of progenitor cells in the resting zone and thereby accelerating the developmental program of growth plate senescence, causing earlier cessation of growth.<sup>31,32</sup>

Consequently, inactivating mutations in the estrogen receptor ER $\alpha$ <sup>33,34</sup> or in aromatase,<sup>35</sup> the enzyme that converts androgens to estrogens, cause the program of growth plate senescence to progress more slowly and thereby allow prolonged linear growth beyond adolescence and therefore adult tall stature. Aromatase inhibitors produce similar effects and thus are under investigation as a treatment for short stature in boys.<sup>36,37</sup> Some of the estrogen that modulates growth physiologically may be locally produced by growth plate chondrocytes which express aromatase and other steroid-metabolizing enzymes.<sup>28,38</sup>

Proinflammatory cytokines are endogenously produced by growth plate chondrocytes and may act intrinsically to modulate longitudinal bone growth.<sup>39</sup> Furthermore, the growth plate is targeted by extrinsic factors including cortisol and proinflammatory cytokines, both induced by stress and chronic inflammation.<sup>40</sup> Some of these proinflammatory cytokines negatively regulate growth plate function.<sup>41</sup> There is evidence that tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , and interleukin-6 act directly on growth plate cartilage to suppress bone growth.<sup>39,42,43</sup> These cytokines may act in synergy further potentiating their negative effects on growth plate cartilage function.<sup>43</sup>

Longitudinal bone growth is also regulated by nutritional intake, mediated in part through a complex endocrine network that includes leptin, IGF-I, sex steroids, thyroid hormone, and glucocorticoids.<sup>18</sup> As a result, undernourished children have impaired linear growth (despite elevated GH levels) whereas obese children have normal or mildly accelerated growth (despite low GH levels).<sup>44</sup>

Growth plate function can also be affected by physical mechanisms. Even relatively low doses of ionizing radiation, such as 10 Gy, can impair longitudinal growth.<sup>45</sup> Mechanical compression across the growth plate also impairs bone elongation<sup>46</sup> in part due to decreased enlargement of hypertrophic chondrocytes.<sup>47</sup> It has been suggested that the inhibitory effects of compression on the growth plate contributes to progression of scoliosis and tibia vara (Blount's disease).<sup>46</sup> Similarly, physical compression is used clinically to correct limb length inequalities and angular deformities.<sup>48</sup> The effects of dynamic load variation due to exercise in children has not been well established.<sup>49</sup>

### **Multiple paracrine factors in the growth plate regulate linear growth**

One area in which our understanding has advanced enormously involves the role of paracrine signals in the growth plate. Paracrine factors are secreted by growth plate chondrocytes, or sometimes cells in the surrounding perichondrium, and act locally on chondrocytes to regulate proliferation and differentiation. In vitro and in vivo approaches have uncovered a host of paracrine factors necessary for normal growth plate function, including multiple fibroblast growth factors (FGFs),<sup>50–53</sup> bone morphogenetic proteins (BMPs),<sup>54–56</sup> WNTs,<sup>57,58</sup> the parathyroid hormone-related protein (PTHrP) and Indian hedgehog (IHH) pathway,<sup>17</sup> and the C-type natriuretic peptide (CNP)-NPR2 pathway.<sup>59</sup> Mutations in genes involved in these paracrine signaling systems can severely impair bone growth in both mice and humans.

For example, fibroblast growth factor receptor-3 (FGFR3) acts as a negative regulator of growth plate chondrogenesis. Consequently, activating mutations in FGF receptor-3 impair

bone elongation in patients with achondroplasia, hypochondroplasia and thanatophoric dysplasia. A recent report has identified an activating FGFR3 mutation in a family with autosomal dominant proportionate short stature<sup>60</sup>. Conversely, heterozygous<sup>61</sup> and homozygous<sup>62</sup> inactivating mutations in FGFR3 have been reported in individuals with tall stature. At the growth plate, FGF signaling through FGFR3 leads to activation of several pathways including the MAPK and JAK/STAT pathways and negatively regulates growth by decreasing proliferation in the proliferative zone, decreasing matrix production, accelerating the onset of hypertrophic differentiation, and decreasing the size of the hypertrophic chondrocytes<sup>53,63–65</sup>. These effects are at least in part due to interaction with other paracrine factors including downregulation of IHH expression, as well as interactions with CNP and BMP signaling.<sup>65–67</sup>

The PTHrP and IHH paracrine system also plays a critical role in the regulation of growth plate function. These two paracrine factors form a negative feedback loop within the growth plate that regulates chondrocyte hypertrophy and proliferation.<sup>17</sup> Consequently, mutations in the genes for IHH, PTHrP, and PTH1R cause specific skeletal dysplasias. For example, heterozygous mutations in *PTH1R*, the gene that encodes PTHrP, cause short stature and short fingers in individuals with brachydactyly, type E2.<sup>68</sup>

Another paracrine factor of importance in the growth plate is CNP. This peptide was named based on its structural similarity to atrial natriuretic peptide (ANP), but has a very different physiological role, serving instead as a local, positive regulator of growth plate function.<sup>69–71</sup> Consequently, homozygous inactivating mutations in *NPR2*, the receptor for CNP, cause a severe skeletal dysplasia, termed acromesomelic dysplasia, Moroteaux type.<sup>72</sup> Interestingly, heterozygous mutations cause a milder phenotype, presenting as short stature without clear signs of a skeletal dysplasia.<sup>16</sup> Recent studies suggest that approximately 2% of children presenting with idiopathic short stature have mutations in this gene.<sup>73–75</sup> Conversely, overexpression of CNP<sup>76,77</sup> or activating mutations in *NPR2*<sup>78,79</sup> cause tall stature. Binding of CNP to NPR2 stimulates the receptor guanylyl cyclase activity thereby increasing synthesis of cGMP, activating the type II cGMP-dependent protein kinase.<sup>80</sup> Therefore, mice deficient in that protein kinase also show severely impaired growth plate function.<sup>81</sup> This signaling system leads to inhibition of the MAPK pathway, thus antagonizing FGFR signaling<sup>82</sup>, providing an explanation for the beneficial effects of CNP in a mouse model of achondroplasia.<sup>83</sup>

Bone morphogenetic proteins (BMPs), also known as growth and differentiation factors (GDFs), belong to the transforming growth factor-beta (TGF $\beta$ ) superfamily of paracrine factors. The BMPs were originally discovered as the component of demineralized bone matrix that is able to induce ectopic bone formation and later found to regulate a multitude of processes in skeletal development, including spatial regulation of proliferation and differentiation in the growth plate.<sup>59</sup> Consistently, inactivating mutations in the genes for several BMPs, their receptors, and antagonists cause skeletal dysplasias, including brachydactyly A2 (BMP2 or BMPR1B), brachydactyly A1 and C (GDF5), chondrodysplasia, Grebe type (GDF5), Klippel-Feil syndrome 1 (GDF6), proximal symphalangism 1A (NOGGIN). Local modulation by antagonists and sequestration by extracellular matrix molecules are crucial for local regulation of BMP and TGF $\beta$  signaling

during development and growth. Consequently, excessive TGF $\beta$  signaling has been identified as an important pathogenic mechanism for Marfan's syndrome,<sup>84</sup> which includes disproportionate overgrowth and aortic dilation,<sup>85</sup> caused by mutations in the fibrillin 1 (FBN1) gene. Angiotensin II receptor blockers act as TGF $\beta$  antagonists and are therefore being evaluated in clinical studies for prevention of aortic dilatation in Marfan's syndrome.<sup>86</sup>

### **Cartilage extracellular matrix is crucial for linear growth**

Chondrocytes secrete a unique extracellular matrix containing specific collagens, non-collagenous proteins, and proteoglycans, which also are vital to normal growth plate function. This extracellular matrix provides the compressible, resilient structural properties of cartilage and also interacts with signaling molecules to regulate growth plate chondrogenesis.<sup>87</sup> As a result, mutations in genes that encode matrix proteins and proteoglycans often interfere with growth plate function.<sup>88</sup> For example, mutations in *COL10A1*, the gene encoding collagen type X, causes a skeletal dysplasia termed metaphyseal chondrodysplasia, Schmid type.

Mutations in the gene *ACAN*, encoding aggrecan, a major proteoglycan component of the cartilage extracellular matrix, also affect linear growth. Homozygous mutations cause a severe skeletal dysplasia, spondyloepimetaphyseal dysplasia aggrecan type.<sup>89</sup> Heterozygous mutations can present as a milder skeletal dysplasia, spondyloepiphyseal dysplasia type Kimberley<sup>90</sup> or as short stature without an evident radiographic skeletal dysplasia, which can either be disproportionate<sup>91</sup> or proportionate.<sup>92</sup> The short stature is typically associated with an advanced bone age and early cessation of growth.<sup>92</sup> In some patients, this disorder affects not only the growth plate cartilage but also the articular cartilage, causing osteochondritis dissecans and early-onset osteoarthritis.<sup>91,92</sup> In animal models, *ACAN* deficiency causes growth plate dysfunction, including decreased chondrocyte proliferation and accelerated hypertrophic chondrocyte differentiation associated with disrupted IHH, FGF, and BMP signaling.<sup>93,94</sup>

There is evidence that other non-collagenous matrix proteins also interact with paracrine signals. For example biglycan and decorin modulate growth and bone formation by interactions with TGF $\beta$  as evidenced by postnatal growth retardation and osteoporosis of biglycan deficient mice.<sup>95</sup> Similarly, excessive TGF $\beta$  signaling has been identified as an important pathogenic mechanism in Marfan's syndrome, which includes disproportionate overgrowth, aortic dilation, and is caused by heterozygous mutations in the fibrillin 1 (FBN1) gene.<sup>84,85</sup> Interestingly, FBN1 mutations also cause short stature in Weill-Marchesani syndrome, geleophysic dysplasia, and acromicric dysplasia.<sup>96</sup>

### **Intracellular pathways regulate growth plate function and linear growth**

A variety of intracellular pathways that play important roles in growth plate chondrogenesis have also been discovered. For example, transcription factors Sox5, 6, and 9 are critical regulators of chondrocyte differentiation.<sup>97</sup> As one would expect, mutations affecting key intracellular pathways cause growth disorders in humans. For example, inactivating mutations in *SOX9* cause a severe skeletal dysplasia, campomelic dysplasia.<sup>97</sup>

As another example, homozygous inactivating mutations in *SHOX*, another transcription factor expressed in the growth plate,<sup>98</sup> cause Langer mesomelic dysplasia, which includes severe defects in bone growth. Heterozygous inactivating mutations, or deletions of *SHOX* or its enhancer regions, cause a milder skeletal dysplasia, Leri-Weill dyschondrosteosis or can present clinically as idiopathic short stature, with body proportions that are mildly affected or sometimes within the normal range.<sup>99</sup> *SHOX* mutations account for 2–15% of individuals presenting with idiopathic short stature, depending on the study.<sup>100</sup> Conversely, increased copies of *SHOX* are associated with tall stature in individuals with Klinefelter syndrome and other type of sex chromosome aneuploidy.<sup>101</sup>

Another pathway important for skeletal growth due to its effect on cellular proliferation and differentiation of growth plate chondrocytes is the Ras/Mitogen activated protein kinase (MAPK) signaling pathway. This pathway integrates signals from several growth factors including FGFs, CNP, and EGF.<sup>102</sup> Ras, a small GTPase, signals through MAPK cascades to phosphorylate numerous cytoplasmic and nuclear proteins, regulating cell proliferation and differentiation.<sup>103</sup> Activation of this pathway results in a number of overlapping syndromes including Noonan, LEOPARD, Costello, cardio-facio-cutaneous, and neurofibromatosis-Noonan syndrome, all characterized by neurocutaneous manifestations but also postnatal growth failure of varying degree.<sup>104,105</sup> In contrast, Sotos syndrome (characterized by tall stature) is associated with decreased activity of the Ras/MAPK pathway.<sup>106</sup>

Skeletal growth is also regulated by Nuclear Factor kappa B (NF- $\kappa$ B), a group of seven transcription factors, including p65 (RelA), c-Rel, RelB, p50/p105 (NF- $\kappa$ B1), and p52/p100 (NF- $\kappa$ B2). In growth plate chondrocytes, NF- $\kappa$ B p65 helps mediate the stimulatory effects of GH and IGF-1 on chondrogenesis.<sup>107</sup> In humans, heterozygous loss of function mutations in I $\kappa$ B $\alpha$ , an essential component of the NF- $\kappa$ B pathway, result in GH insensitivity and growth failure as well as ectodermal dysplasia and immunodeficiency.<sup>108</sup>

Mutations in genes encoding proteins involved in fundamental cellular processes can produce severe global growth deficiencies, termed primordial dwarfisms, which affect not just the growth plate but multiple other tissues and typically impair both pre- and postnatal growth.<sup>109</sup> For example, 3M syndrome, which includes severe intrauterine growth retardation and postnatal short stature, is caused by defects in one of three genes: *CUL7*,<sup>110</sup> *OBSL1*,<sup>111</sup> and *CCDC8*.<sup>112</sup> The products of these three genes form a complex that plays a critical role in maintaining microtubule integrity with defects leading to aberrant cell division.<sup>113</sup> Similarly, mutations in the centrosomal protein, pericentrin, cause microcephalic osteodysplastic primordial dwarfism (MOPD) type II<sup>114</sup> while other centrosomal proteins are implicated in Seckel syndrome. Mutations in the DNA origin recognition complex underlie Meier-Gorlin Syndrome,<sup>115,116</sup> and defects in DNA damage repair underlie growth disorders such as Cockayne Syndrome and Bloom Syndrome.

Interestingly, tall stature can be caused by mutations in genes that control epigenetic modifications, including DNA and histone methylation, and thereby chromatin formation and gene expression. Heterozygous mutations in DNA methyltransferase 3A (*DNMT3A*) cause tall stature, a distinctive facial appearance, and intellectual disability.<sup>117</sup> Similarly, heterozygous mutations in *EZH2*, an enzyme that specifically methylates lysine residue 27

of histone 3 (H3K27) which is associated with transcriptional repression, causes Weaver syndrome, characterized by pre- and postnatal overgrowth, and a markedly advanced bone age.<sup>118</sup> In addition, most cases of Sotos syndrome are caused by mutations in *NSD1*, which acts as a methyltransferase to methylate histone H3 lysine 36 (H3K36) and other substrates and also interacts with nuclear hormone receptors, thereby regulating transcription of target genes.<sup>106</sup>

### Copy number variation and short stature

Recent evidence suggests that approximately 10% of patients with idiopathic short stature carry a disease-causing copy number variation (CNV).<sup>119–121</sup> The phenotype of subjects with CNVs includes both growth failure of prenatal onset and postnatal onset, both proportionate and disproportionated short stature, and both syndromic and nonsyndromic short stature.<sup>120,121</sup> However, in individual subjects, it is often difficult to know whether the growth failure was due to the CNV, and therefore additional studies are needed to define better the prevalence and phenotypes of CNV-associated short stature.

### Normal variation in adult height

It has long been known that the normal variation in human stature has a large genetic component and shows a polygenic inheritance pattern. Only recently have the specific genes involved begun to be elucidated. A large meta-analysis of genome-wide association studies identified 423 loci that contribute to normal adult stature variation.<sup>122</sup> Presumably each locus contains at least one gene in which common polymorphisms affect human linear growth. Although the precise gene within each locus that is responsible for the effect typically cannot be pinpointed with certainty, there is evidence that a large number of the causative genes are expressed in and function in the growth plate.<sup>122,123</sup> These implicated genes include multiple genes involved in paracrine signaling by the PTHrP-IHH feedback loop, BMPs, FGFs, WNTs/ $\beta$ -catenin, and CNP. These loci also contain a much smaller number of genes known to participate in the GH-IGF-I axis, including *GHI*, which encodes GH, *GHSR*, which encodes the GH secretagogue receptor, and *IGF1R*, which encodes the principal receptor for IGF-I. It is likely that many children with short stature, particularly those with mild short stature with a pedigree suggesting a polygenic inheritance, have inherited multiple polymorphisms which negatively modulate linear growth associated with short stature. Interestingly, a recent study in tall Europeans reported that common sequence variants are also associated with tall stature.<sup>124</sup>

### Current findings require a broader conceptual framework for short stature

The findings discussed above necessitate a new framework with which to conceptualize short stature. The categorization of idiopathic short stature into subtypes of GH deficiency, GH insensitivity, IGF-I deficiency and IGF-I insensitivity, which seemed reasonable when we could only measure hormones and knew little about the causes of short stature, now is not nearly broad enough. Using this system would require us to jam all the myriad abnormalities involving intracellular, extracellular matrix, and paracrine signaling defects into the category “IGF-I insensitivity.” Instead, the large picture emerging from recent findings places GH and IGF-I as important factors for growth but as only two of many factors that influence growth plate function and therefore human growth.



A broader conceptual framework can now be formulated that is centered, not on the GH-IGF-I axis, but on the growth plate (Figure 2), the biological structure that is responsible for linear growth. Short stature is caused by growth plate dysfunction that can result either from a primary defect, that is, a disorder intrinsic to the growth plate, or a secondary defect, in which the growth plate is adversely affected by a disorder elsewhere in the body (Table 1, Figure 2). Primary defects may involve: 1) Paracrine signaling systems in the growth plate, 2) Cartilage extracellular matrix molecules, and 3) Intracellular pathways in growth plate chondrocytes. In secondary disorders, growth plate chondrocytes can be adversely affected through a variety of mechanisms, including abnormal: 1) Nutritional effects (mediated in part by endocrine signals), 2) Endocrine signaling, 3) Inflammatory cytokines, 4) Extracellular fluid (such as acidosis), and 5) Physical factors (such as radiation). This scheme provides a conceptual framework based on the underlying biological mechanisms. For some disorders, including many dysmorphic syndromes, constitutional delay of growth, and idiopathic short stature, the mechanism responsible for growth plate dysfunction remains unknown. A classification scheme proposed by the European Society for Paediatric Endocrinology, which also divides the causes of short stature into primary and secondary defects, is less mechanism-based but useful for practical clinical purposes<sup>125</sup>. Although growth disorders can be environmental or polygenic in etiology, many growth disorders arise from single gene defects (Table 2).

### **Skeletal dysplasias, isolated short stature, stature within the normal range, and tall stature represent a spectrum at the molecular level**

Previously, skeletal dysplasias and idiopathic short stature were considered to be largely distinct entities. However, recent findings indicate that defects in the same genes, such as *SHOX*, *NPR2*, *ACAN*, and *FGFR3* can present clinically either as a skeletal dysplasia or as idiopathic short stature. The more severe phenotype tends to occur when the gene involved is critical for growth plate function, the mutation severely alters protein function, and/or the mutation occurs in the homozygous state, whereas the milder phenotype, short stature with normal bone morphology, tends to occur when the gene involved is less critical for growth plate function, the mutation only partially disrupts protein function, and/or when the mutation occurs in the heterozygous state. (Figure 3). Furthermore genome-wide association studies suggest that stature in the lower part of the normal range can also be considered part of this spectrum since it appears to be due in part to polymorphisms in the same genes in which mutations cause skeletal dysplasia, such as *COL10A1* (responsible for metaphyseal chondrodysplasia, Schmid type), *ACAN* (spondyloepimetaphyseal dysplasia, aggrecan type), and *HOXD13* (Brachydactyly, type E).<sup>123</sup> Thus polymorphisms, which have a mild effect on protein function or expression, tend to cause stature in the lower part of the normal range, mildly deleterious and/or heterozygous mutations tend to present as idiopathic short stature or a mild skeletal dysplasia, and strongly deleterious and/or homozygous mutations tend to cause a more severe skeletal dysplasia (Figure 3).

In some cases, tall stature can involve the same genes as those for short stature, but in tall stature, the mutation causing tall stature has the opposite functional effect on the gene product (Figure 3). For example, as discussed above, homozygous inactivating mutation in *NPR2* cause a skeletal dysplasia with severe short stature, heterozygous inactivating

mutations present as a milder skeletal dysplasia or idiopathic short stature, and activating mutations in *NPR2* cause tall stature.<sup>78,79</sup> Another example mentioned previously is *FGFR3*, in which activating mutations cause proportionate short stature, hypochondroplasia, achondroplasia, and thanatophoric dysplasia, whereas inactivating mutations have been reported to cause tall stature.<sup>61,62</sup> Similarly, loss of function mutations or decreased copy number of *SHOX* cause short stature whereas increased copy number, including that of Klinefelter syndrome, is associated with tall stature.

### **The temporal and spatial distribution of gene expression and function affect the phenotype**

Some genetic defects, such as activating mutations in *FGFR3* causing achondroplasia, present with short stature at birth, whereas other genetic defects, such as heterozygous inactivating mutations in *SHOX* that cause Leri-Weill dyschondrosteosis, often result in a normal birth length with short stature developing at a later age. In some cases, this difference may be due to the severity of the growth plate abnormality. For example, severe activating mutations in *FGFR3* associated with thanatophoric dysplasia and achondroplasia cause growth failure of prenatal onset,<sup>126,127</sup> whereas a milder mutation causing hypochondroplasia often produces a birth length within the normal range with short stature developing later. However, in other cases, the temporal onset, pre- vs. postnatal, may depend on whether the gene is important in the fetal growth plate, which is morphologically and functionally somewhat different from the growth plate in childhood.

As described above, some defects in genes required for growth plate function produce proportionate short stature whereas others produce disproportionate short stature. Presumably, disproportionate short stature indicates that the gene product involved has a more critical role in some growth plates than in others. Many genetic defects tend to affect growth plates in the long bones more than growth plates in the vertebrae, causing a disproportionate short stature with a greater reduction in leg and arm lengths than in trunk length. We speculate that this common pattern may reflect the fact that the growth plates in the long bones function at a much greater pace than each of the individual growth plates in vertebrae and thus may be more susceptible to dysregulation. On the other hand, some disorders, such as brachyolmia, tend to affect the spine more than the long bones, causing disproportionate short stature with a short trunk. Brachyolmia is genetically heterogeneous, including mutations in *PAPSS2* which encodes a sulfotransferase, required for sulfation of a variety of molecules, including cartilage glycosaminoglycans and DHEA.<sup>128</sup>

Mutations in some genes impair development and/or function not only of the growth plate but also non-skeletal structures, causing associated congenital anomalies, that is, syndromic short stature. For example, Noonan syndrome, which is caused by mutations in genes involved in the Ras/MAPK pathway such as *PTPN11*, often cause short stature associated with distinctive facies, cardiac and renal anomalies, developmental delay, and/or coagulation defects.<sup>129</sup> However, mutations in *PTPN11* have also been reported in patients who presented with short stature and were not recognized to have Noonan syndrome prior to sequencing.<sup>130</sup>

## Growth hormone therapy for short stature

Although most short stature is caused by defects outside the GH-IGF-I system, treatment with recombinant GH is still somewhat effective in accelerating linear growth in many children with short stature. For example, GH treatment increases the linear growth rate of children with SHOX deficiency,<sup>131</sup> Noonan syndrome,<sup>132</sup> and idiopathic short stature.<sup>133,134</sup> Indeed, endogenous growth hormone excess due to a pituitary adenoma can cause remarkable tall stature in otherwise normal children. These findings indicate that the stimulatory effect of GH on growth plate chondrocyte proliferation and hypertrophy, which is partly mediated by increased IGF-I,<sup>135–137</sup> can, in many cases, non-specifically accelerate linear growth and thereby partially compensate for unrelated molecular defects affecting the growth plate.

## Conclusions

For decades, the dominant conceptual framework for understanding short and tall stature was centered on the GH-IGF-I axis. However, recent findings in basic molecular and cellular biology and in clinical genetics have uncovered a vast array of other regulatory systems that control skeletal growth and an accompanying vast array of genetic defects outside the GH-IGF-I axis that can cause disorders of linear growth. As a result, the traditional view of short or tall stature that is centered on the GH-IGF-I axis is now far too narrow to encompass the ever-growing catalogue of defects that cause abnormal linear growth. A much broader conceptual framework can be based on the simple concept that linear growth disorders necessarily are due to dysfunction of the skeletal growth plate, the structure responsible for bone elongation and therefore overall body size. Consequently, short stature can more generally be conceptualized as a primary or secondary disorder of the growth plate chondrocytes. A related concept that has emerged is that sequence variants in genes that affect growth plate function can produce a phenotypic spectrum that ranges from a severe skeletal dysplasia to disproportionate or proportionate short stature, to normal variation in height, to tall stature. It is likely that high-throughput sequencing approaches will continue to expand the list of genetic defects that can cause growth plate dysfunction and disorders of linear growth. The clinical application of these broad sequencing approaches will allow the physician to identify the etiology of growth failure from among the myriad possibilities. We can therefore anticipate that the number of children who receive the unhelpful diagnosis of idiopathic short stature will continue to diminish. With these advances, we can look forward to treatment approaches that are tailored to the specific genetic cause of the disorder.

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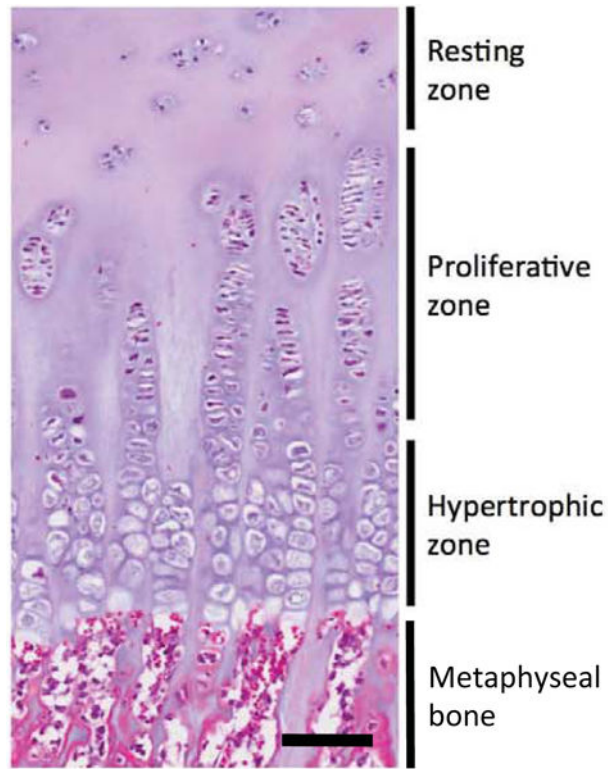
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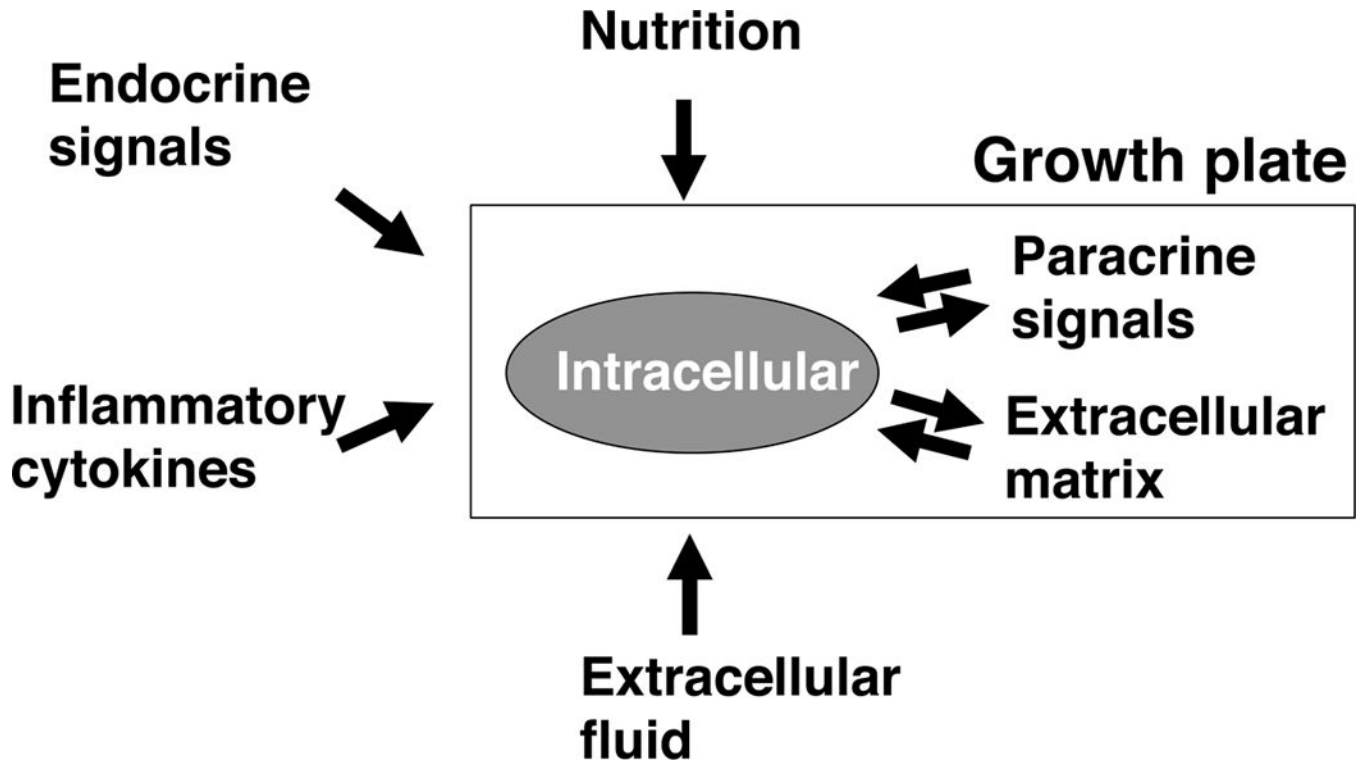


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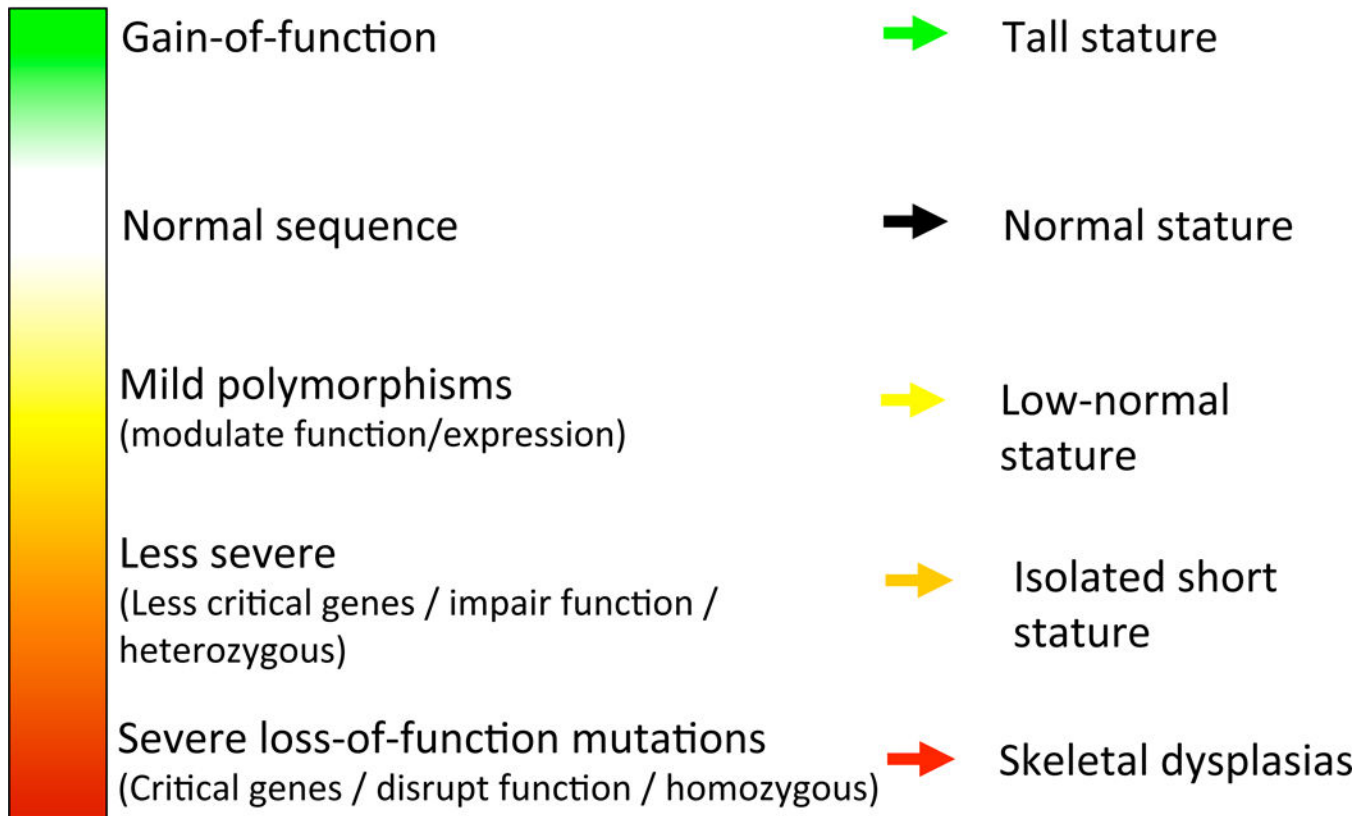


**Figure 1.** Human growth plate histology from an 11-year old boy. The growth plate comprises three histologically and functionally distinct zones; the resting, proliferative, and hypertrophic zones. Bar represents 100  $\mu\text{m}$ .



**Figure 2.** Schematic diagram depicting the regulation of growth plate function. Growth plate chondrocyte (grey oval) proliferation and differentiation are regulated by many factors, including nutritional, endocrine, inflammatory cytokines, extracellular fluid (e.g. oxygen, pH), paracrine, extracellular matrix, and intracellular mechanisms. Not depicted are the interactions among many of these systems; for example, nutritional intake strongly affects endocrine regulators of the growth plate.

## Sequence variants in growth plate genes and height



**Figure 3.**

Diagram depicting the phenotypic spectrum that can be caused by sequence variants in genes that regulate growth plate chondrogenesis. The spectrum shown here applies to genes that promote longitudinal bone growth, such as NPR2. For genes that inhibit longitudinal bone growth, such as FGFR3, the spectrum is reversed in that gain-of-function mutations cause short stature while loss-of-function causes tall stature.

**Table 1**

Etiology of short stature, organised by mechanism of growth plate dysfunction

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**Intrinsic to growth plate**

**Paracrine**

- C-type natriuretic peptide signaling (deficiency)
- Fibroblast growth factor signaling (excess)
- Parathyroid hormone-related protein signaling (deficiency, excess)

**Cartilage extracellular matrix**

- Abnormal structural properties
- Effects on growth factor signaling

**Intracellular**

- Chondrocyte transcription factors (deficiency)
- Ras–MAPK signaling (deficiency)

**Extrinsic to growth plate**

**Nutritional intake**

- Calories (deficiency)
- Protein (deficiency)
- Zinc (deficiency)
- Vitamin A (excess)

**Endocrine**

- Growth hormone (deficiency or insensitivity)
- Insulin-like growth factor 1 (deficiency or insensitivity)
- Thyroid hormone (deficiency or insensitivity)
- Glucocorticoid (excess)
- Estrogen (excess results in early growth termination)
- Androgen (deficiency)

**Inflammatory cytokines**

- IL-1 $\beta$  (excess)
- IL-6 (excess)
- Tumour necrosis factor (excess)

**Extracellular fluid**

- Oxygen (deficiency)
- Acidosis

**Physical factors**

- Mechanical trauma
- Ionizing radiation

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This list provides examples of disorders affecting linear growth but is not exhaustive.

**Table 2**

Examples of single gene defects that cause disorders of childhood growth.

Intrinsic to growth plate				
Mechanism	Gene	Effect on protein	Disorder	Inheritance
<b>Paracrine</b>				
CNP signaling	NPR2	Loss of function	ISS	Short stature AD*
		Loss of function	Moroteaux acromesomelic dysplasia	Short stature AR*
FGF signaling	FGFR3	Gain of function	Overgrowth with or without skeletal deformities	Tall stature AD*
		Gain of function	Hypochoondroplasia Achoondroplasia Thanatophoric dysplasia ISS	Short stature AD
		Loss of function	CATSHL syndrome	Tall stature AD
PTHrP signaling	GNAS	Loss of function	Albright hereditary osteodystrophy	Short stature AD
	PTH1R	Loss of function	Blomstrand chondrodysplasia	Short stature AD
		Gain of function	Jansen metaphyseal dysplasia	Short stature AD
<b>Cartilage extracellular matrix</b>				
Extracellular matrix structure/function	ACAN	Abnormal structure	ISS	Short stature AD*
			Spondyloepiphyseal dysplasia type Kimberley	Short stature AD*
	COL2A1	Abnormal structure	Spondyloepimetaphyseal dysplasia aggrecan type	Extreme short stature AR*
			Multiple skeletal dysplasias	Short stature AD
	COL10A1	Abnormal structure	Metaphyseal chondrodysplasia, Schmid type	Short stature AD
	COMP	Abnormal structure	Pseudoachondroplasia	Short stature AD
	FBN1	Abnormal structure	Marfan syndrome	Tall stature AD
<b>Intracellular</b>				
Transcription factors	SOX9	Loss of function	Campomelic dysplasia	Short stature AD
		Loss of function	ISS	Short stature AD*
	SHOX	Loss of function	Leri-Weill dyschondrosteosis	Short stature AD*
		Loss of function	Langer mesomelic dysplasia (homozygous)	Extreme short stature AR*

Intrinsic to growth plate					
Mechanism	Gene	Effect on protein	Disorder	Effect on linear growth	Inheritance
Microtubule function	CUL7	Loss of function	3M syndrome 1	Short stature	AR
	OBSL1	Loss of function	3M syndrome 2	Short stature	AR
RAS-MAPK signaling	PTPN11 KRAS Others	Gain of function	Noonan syndrome	Short stature	AD
	NSD1	Loss of function	Sotos syndrome	Tall stature	AD
Epigenetic defects	EZH2	Uncertain	Weaver syndrome	Tall stature	AD
	DNMT3A	Loss of function	DNMT3A overgrowth syndrome	Tall stature	AD
Extrinsic to growth plate					
<b>Endocrine</b>					
	GHI	Loss of function	Isolated GH deficiency	Short stature	AR, AD
GH signaling	GHRHR	Loss of function	Isolated GH deficiency	Short stature	AR
	POU1F1 PROPI LHX3 others	Loss of function	Combined pituitary hormone deficiency	Short stature	AR
	GHR	Loss of function	GH insensitivity syndrome	Short stature	AR
	STAT5B	Loss of function	Growth hormone insensitivity with immune dysfunction	Short stature	AR
	IGF1	Loss of function	IGF-1 deficiency	Short stature	AD, AR
	IGFIR	Loss of function	IGF resistance	Short stature	AD, AR
IGF-1 signaling	ALS	Loss of function	ALS deficiency	Short stature	AR
	TSHR PAX8 NKX2-1 FOXE1 NKX2-5	Loss of function	Thyroid dysgenesis	Short stature	AD, AR
Thyroid hormone signaling	SLC5A5 TP DUOX2, SLC26A4 TG IYD/DEHAL1	Loss of function	Thyroid dysmorphogenesis	Short stature	AR
	THRB	Loss of function	Thyroid hormone resistance	Short stature	AD, AR
	THRA	Loss of function	Thyroid hormone resistance	Short stature	AD
	PRKARIA	Loss of function	Camey complex (including glucocorticoid excess)	Short stature	AD



Intrinsic to growth plate					
Mechanism	Gene	Effect on protein	Disorder	Effect on linear growth	Inheritance
Estrogen signaling	MC2R	Loss of function	Familial glucocorticoid deficiency	Tall stature	AR
	ESR1 (estrogen receptor)	Loss of function	Estrogen resistance	Tall stature	AR
	CYP19A1 (aromatase)	Loss of function	Estrogen deficiency	Tall stature	AR

Notes: This list provides examples of single gene defects affecting linear growth but is not exhaustive. Abbreviations: ISS, idiopathic short stature; AD, autosomal dominant; AR, autosomal recessive.

\* Mutations in these genes can be considered semidominant in that heterozygous mutations produce a mild phenotype while homozygous mutations produce a more severe phenotype.