Genetic regulation of linear growth

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Linear growth occurs at the growth plate. Therefore, genetic defects that interfere with the normal function of the growth plate can cause linear growth disorders. Many genetic causes of growth disorders have already been identified in humans. However, recent genome-wide approaches have broadened our knowledge of the mechanisms of linear growth, not only providing novel monogenic causes of growth disorders but also revealing single nucleotide polymorphisms in genes that affect height in the general population. The genes identified as causative of linear growth disorders are heterogeneous, playing a role in various growth-regulating mechanisms including those involving the extracellular matrix, intracellular signaling, paracrine signaling, endocrine signaling, and epigenetic regulation. Understanding the underlying genetic defects in linear growth is important for clinicians and researchers in order to provide proper diagnoses, management, and genetic counseling, as well as to develop better treatment approaches for children with growth disorders.

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Introduction

Height, as a measure of linear growth, is highly heritable, and genetics plays a major role in the regulation of linear growth.[1] To understand the genetic mechanisms of linear growth, various efforts have been made for decades, and recently genome-wide approaches such as genome-wide association (GWA) studies or exome/whole genome sequencing have been performed successfully, identifying many genomic loci associated with height variation in the general population as well as identifying monogenic changes that cause either syndromic or isolated short stature or overgrowth/tall stature.[2-4] Combining these newly discovered findings obtained from genome-wide approaches into important growth-regulating genes, we now possess a better understanding of human growth disorders.[4] It is now understood that: (1) linear growth occurs at the growth plate and many genes that affect height variation or cause growth disorders play major roles in growth plate biology[5]; (2) the type of mutation can determine the growth outcome; both loss or gain of function mutations can cause either short or tall stature. For example, loss-of-function mutations in *NPR2* cause short stature while gain-of-function mutations in the same gene cause tall stature. On the other hand, loss-of-function mutations in *FGFR3* cause tall stature while gain-of-function mutations cause short stature.[4]; (3) the severity of the genetic abnormality can determine the severity of disease. For example, for some genes, a biallelic mutation can cause severe skeletal dysplasia while a monoallelic mutation in the same gene can cause isolated short stature, as seen in *SHOX* deficiency or *ACAN* mutations.[6,7]; (4) lastly any genetic defect that alters the biology of chondrocytes in the growth plate can potentially cause growth disorders and these genetic defects can be very heterogeneous.[4]

With recent remarkable advances in discoveries of genes responsible for regulating childhood growth disorders, it has become more important for pediatricians, pediatric endocrinologists and geneticists to understand the underlying genetic defects in children

who present with growth concerns in order to provide genetic diagnoses, proper management, and genetic counseling. Therefore, this review aims to provide an update on genes known to cause human growth disorders specifically by focusing on those also found through GWA studies to be associated with normal height variation. The genes noted in this review are particularly important because single nucleotide polymorphisms (SNPs) in these genes (presumably causing mild changes) cause height variation in the normal range, but mutations (causing more deleterious changes) in the same gene cause distinctive linear growth disorders. Moreover, combined polymorphisms in these genes could potentially be genetic causes of isolated short stature in an oligo/polygenic manner. The listed genes reviewed here are categorized by their function in the growth plate with the mutations and their corresponding phenotype are described.

Growth regulating mechanisms

Linear growth occurs at the growth plate, a cartilaginous structure between the epiphysis and metaphysis (Fig. 1A). It is composed of 3 distinct layers; resting, proliferative and hypertrophic zones, which are temporally and spatially regulated (Fig. 1B).[8,9] This regulation results in a unique differentiation process from resting chondrocytes to proliferating chondrocytes and finally hypertrophic chondrocytes. Ultimately, at the terminal zone of hypertrophic chondrocytes, hypertrophic chondrocytes undergo apoptosis and blood vessels invade, resulting in remodeling of the cartilage into newly formed bone.[8] Constant repetition of this process produces new bone and leads to the elongation of bones. Many genes play a role in this process and so far, hundreds of genes have been implicated in either human growth disorders or height variation by affecting chondrogenesis at the growth plate.[5]

The growth mechanisms regulated by these genes can be divided into five different categories: (1) extracellular matrix, (2) intracellular signaling, (3) paracrine signaling, (4) endocrine signaling, and (5) epigenetic regulation (Fig. 1C).
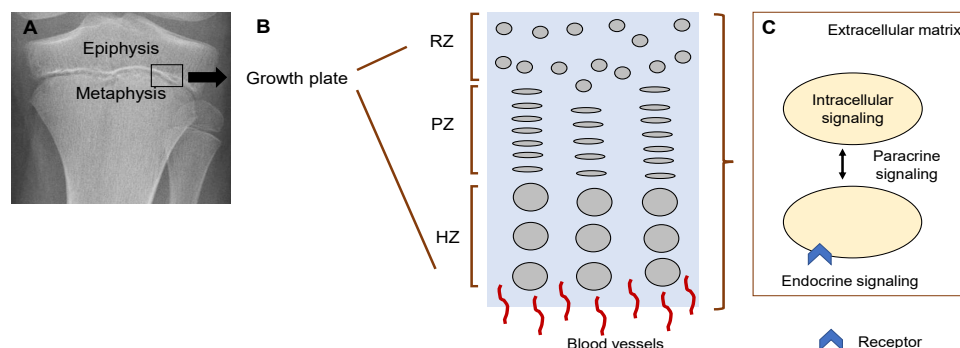
1. Cartilage extracellular matrix

Growth plate chondrocytes secrete an extracellular matrix that is essential for proper functioning of the growth plate. The extracellular matrix consists of collagens, proteoglycans, and glycosaminoglycans and along with secreted growth factors and the modifying enzymes, extracellular matrix serves as a dynamic scaffold that supports and orients growth plate chondrocyte differentiation.[10] Mutations in extracellular matrix-regulating genes can cause isolated short stature or severe skeletal dysplasia, supporting the idea that extracellular matrix plays a critical role in growth plate regulation in humans.[11]

1) Aggrecan (*ACAN*)

Aggrecan, encoded by *ACAN*, is a chondroitin sulfate proteoglycan, one of the main components of the extracellular matrix in growth plate cartilage that has been shown to modulate hedgehog signaling in a mouse model.[12] In aggrecan-null mice, growth plates were devoid of matrix, showed abnormal chondrocyte organization and differentiation, and the expression of important growth plate regulatory genes such as *Col10a1*, *Sox9*, and *Ihh* was also affected.[13] Therefore, alterations in the structure or function of aggrecan can significantly affect the growth plate cartilage resulting in a change in linear growth. Biallelic mutations in *ACAN* cause spondyloepimetaphyseal dysplasia and monoallelic mutations cause isolated short stature with or without advanced bone age causing early cessation of linear growth in most cases.[6,14] Patients with mutations in *ACAN* may also present with premature and severe osteoarthritis and osteochondritis dissecans.[15,16] Heterozygous *ACAN* mutations are one of common causes of idiopathic short stature; in a cohort of 428 patients with idiopathic short stature, 6 potential disease-causing heterozygous *ACAN* mutations were found (1.4% of patients).[17] Thus, in children who have a family history of short stature and early-onset arthritis, *ACAN* mutations should be considered.

Fig. 1. Mechanisms regulating chondrocytes in the growth plate. (A) Growth plate on X-ray. Black box indicates where growth plate is located. (B) Diagram of the 3 layers in the growth plate. (C) Diagram of chondrocyte-regulating mechanisms. RZ, resting zone; PZ, proliferative zone; HZ, hypertrophic zone. Modified from Jee YH, et al. Endocrinol Metab Clin North Am 2017;46:259-81.[15]

2) Fibrillins (*FBN1*)

Fibrillins are the major components of microfibrils in the extracellular matrix, and 2 genes in particular, fibrillin 1 (*FBN1*) and fibrillin 2 (*FBN2*), have been implicated in growth-regulating mechanisms, which regulate transforming growth factor beta (TGF-β) and bone morphogenetic factor (BMP) signaling in the extracellular matrix.[3,18] Monoallelic mutations in *FBN1* give rise to acromelic dysplasia, a group of disorders that include Weill-Marchesani syndrome (WMS), acromicric dysplasia and gelophysic dysplasia.[18]

Latent transforming growth factor-beta-binding protein 2 (LTBP2) is an extracellular matrix protein, which is a member of superfamily composed of three fibrillins and four other LTBP proteins and also participates in the regulation of TGF-β release in the extracellular matrix. Therefore biallelic mutations in *LTBP2* can also cause WMS.[19] Patients with WMS present with short stature with brachydactyly, stiff joints, muscular build, thick skin, ectopia lentis and cardiac valvular problems.[18,20] Interestingly, mutations in *FBN1* can also result in Marfan syndrome, an autosomal dominant inherited connective tissue disorder.[21] Individuals with Marfan syndrome have tall stature, skeletal and ocular abnormalities, and over 80% of Marfan syndrome patients have cardiovascular complications.[22] Although it has been proposed that mis-assembled microfibrils leads to decreased extracellular matrix integrity and the mis-regulation of TGFβ ligands leads to a Marfan syndrome phenotype, the precise mechanisms of how mutations in the same gene could cause 2 opposing phenotypes, short stature versus tall stature, is still unclear.[23,24] Monoallelic mutations in fibrillin 2 (*FBN2*) have been reported to cause a Marfan-like disorder with tall stature and congenital contractural arachnodactyly, which further confirms the importance of microfibrils in the regulation of linear growth.[25] However, it is not known yet if other mutations in *FBN2* can also cause acromelic dysplasia.

3) Metalloproteinases (*ADAMTS17*)

Metalloproteinases are enzymes that degrade extracellular proteins. There are various kinds of metalloproteinases, such as matrix metalloproteinases (MMPs), a disintegrin and metalloproteinase (ADAMs), a disintegrin and metalloproteinase with thrombospondin motifs (ADALTSs) and ADAMTS-like proteins (ADAMTSLs). MMPs have been shown to play an integral role in regulating chondrocyte proliferation, extracellular matrix degradation, and release of extracellular matrix proteins.[26] However, there have not yet been reports of mutations in MMP-encoding genes causing skeletal defects in humans, although there has been a case report of Winchester syndrome due to a hypomorphic mutation in *MMP14*.[27] The precise functions of these enzymes have not been well-established but many family members were identified by GWA studies to be associated with height variation (*ADAM28*, *ADAMTS19*, *ADAMTS2*, *ADAMTS3*, *ADAMTS6*, *ADAMTSL1*, *ADAMTSL3*) suggesting a possible role in linear growth. However, it is also possible that these genes may have been just innocent neighbors to other important genes associated with height variation. Among these, *ADAMTS17* has been recognized as a modulator of fibrillin microfibrils, and therefore it is not surprising that biallelic mutations in *ADAMTS17* cause Weill-Marchesani-like syndrome, where individuals present with short stature and spherophakia, but do not have brachydactyly and joint stiffness.[28-30]

4) Collagens (*COL9A2*, *COL11A1*, *COL27A1*) and matrilin 3 (*MATN3*)

Cartilage fibrils are complex structures containing collagens II and XI with or without collagen IX and collagen XVI.[31] These, together with other fibrils containing small leucine-rich proteins or proteoglycans, such as decorin, biglycan and fibromodulin, make up the fibrillar matrix.[11] The interaction of the fibrillar and extrafibrillar matrix then form a fibrillar periphery.[31] *COL11A1* and *COL27A1* are important for the organization of the proliferative zone, play a structural role in the pericellular extracellular matrix of the growth plate, and are thought to be important for the transition of cartilage to bone.[32-34] Mutations in these proteins underlie a broad spectrum of skeletal dysplasias (Table 1). Monoallelic mutations in *COL2A1*, *COL11A1*, *COL11A2*, *COL9A1*, *COL9A2*, and *COL9A3* genes cause Stickler syndrome.[35] Heterozygous mutations in *COL11A1* have also been implicated in Marshall syndrome, a chondrodysplasia that is phenotypically very similar to Stickler syndrome. There is some debate as to whether these disorders are separate entities or different expressions of the same disorder. They present with chondrodysplasias characterized by midfacial hypoplasia, myopia, sensorineural-hearing deficits, and short stature in the patient relative to their unaffected family

Table 1. Genetic causes of linear growth disorders

Gene	Protein	Disorders	Clinical presentation	Height-associated SNP ID[2,3]
Extracellular matrix				
ACAN	Aggrecan	Isolated short stature (monoallelic)	Short stature with or without advanced bone age, short legs, long arms, midface hypoplasia, osteochondritis dissecans[14-16]	rs2280470, rs3817428, rs11633371, rs16942341
		Spondyloepimetaphyseal dysplasia (biallelic)	Extreme short stature, increased upper/lower segment ratio, rhizomelia, mesomelia, brachydactyly, midface hypoplasia, short neck, lumbar lordosis, early onset arthritis[6,15]	

Table 1. Genetic causes of linear growth disorders (continued)

Gene	Protein	Disorders	Clinical presentation	Height-associated SNP ID[2,3]
ADAMTS17	ADAM metallopeptidase with thrombospondin type 1 Motif 17	Weill-Marchesani syndrome (biallelic)	Short stature without brachydactyly and joint stiffness, short hands and feet, spherophakia, myopia, cataract, thick skin[27-29]	rs2573625, rs4246302, rs4548838
COL9A2	Collagen type IX alpha 2 chain	Multiple epiphyseal dysplasia (monoallelic) Stickler syndrome (biallelic)	Short stature, early onset osteoarthritis, brachydactyly[41,42]	rs209918
COL11A1	Collagen type XI alpha 1 chain	Stickler syndrome, Marshall syndrome (monoallelic) Fibrochondrogenesis 1 (biallelic)	Short stature, midface hypoplasia, short nose, myopia, sensorineural-hearing deficits[34-36] Short-limbed skeletal dysplasia, flat midface, small nose with anteverted nares, relatively normal hands and feet, small thorax[37]	rs7517682
COL27A1	Collagen type XXVII alpha 1 chain	Steel syndrome (biallelic)	Short stature, bilateral hip and radial head dislocations, scoliosis, carpal coalitions, *pes cavus*, facial dysmorphism (long oval face, prominent forehead, hypertelorism, broad nasal bridge)[38-40]	rs999599
FBN1	Fibrillin 1	Acromelic dysplasia;Weill-Marchesani syndrome, acromicric dysplasia, gelophysic dysplasia (monoallelic) Marfan syndrome (monoallelic)	Short stature, spherophakia, brachydactyly, joint stiffness, thick skin, cardiac valvular abnormalities[17] Tall stature, arachnodactyly, dolichostenomelia, joint hypermobility, ectopia lentis, aortic root enlargement, aortic dissection[20-23]	rs1036477
FBN2	Fibrillin 2	Marfan like-disorder (monoallelic)	Tall stature, congenital contractural arachnodactyly, dolichostenomelia, joint hypermobility, without occular or cardiac manifestations[24]	rs26024
LTBP2	Latent transforming growth factor beta binding protein 2	Weill-Marchesani syndrome (biallelic)	Short stature, brachydactyly, joint stiffness, short hands and feet, spherophakia, myopia, cataract, thick skin[18]	rs862034, rs10140101
MATN3	Matrilin-3	Multiple epiphyseal dysplasia (monoallelic) Spondyloepimetaphyseal dysplasia (biallelic)	Short stature, early onset osteoarthritis, brachydactyly[43] disproportionate early-onset dwarfism, bowing of lower limbs, lumbar lordosis, and normal hands, abnormal skeletal X-rays (short, wide, and stocky long bones with severe epiphyseal and metaphyseal changes, hypoplastic iliac bones, and flat-ovoid vertebral bodies)[45]	rs52826764
Intracellular signaling				
CREBBP	CREB (cAMP response element-binding protein) binding protein	Rubinstein-Taybi syndrome (monoallelic)	Short stature, intellectual disability, broad and deviated thumbs and halluces, distinct craniofacial characteristics[52,53]	rs129963
GNAS	Guanine nucleotide binding protein, alpha stimulating subunit	Albright's hereditary osteodystrophy with hormone resistance-pseudohypoparathyroidism (monoallelic, maternally inherited) Albright's hereditary osteodystrophy without hormone resistance-pseudohypoparathyroidism (monoallelic, paternally inherited)	Short stature, brachydactyly, rounded face, short neck, centripetal obesity, developmental delay, subcutaneous ossifications, multihormonal resistance to PTH, TSH and gonadotropins[50,51] Short stature, brachydactyly, rounded face, short neck, subcutaneous ossification[50,51]	rs2057291
PDE3A	Phosphodiesterase 3A	Mendelian hypertension with brachydactyly type E (monoallelic)	Short stature, brachydactyly, salt-independent and age-dependent hypertension, an increased fibroblast growth rate, and other cardiovascular complications[54,55]	rs4326884

Table 1. Genetic causes of linear growth disorders (continued)

Gene	Protein	Disorders	Clinical presentation	Height-associated SNP ID[2,3]
SOX9	SRY-box 9	Campomelic dysplasia (monoallelic)	Congenital bowing of long bones, with or without sex reversal[46,47]	rs10083886
Paracrine signaling				
GDF5	Growth differentiation factor 5 (cartilage-derived morphogenic protein 1)	Brachydactyly, type A1, A2, C (monoallelic)	Short stature and brachydactyly[75-77]	rs143384
		Chondrodysplasia - Grebe type (biallelic)	Severe dwarfism with micromelia, deformation of limbs, disproportionate short stature, brachydactyly[77,78]	
		Chondrodysplasia - Hunter-Thompson type (biallelic)	Short long bones (most severe in hands and feet), joint dislocations, normal craniofacial skeleton[79]	
IGF2	Insulin-like growth factor II	Growth restriction (monoallelic)	Paternally inherited, pre- and postnatal growth restriction with the features of Silver-Russell syndrome[87]	rs4320932
IHH	Indian hedgehog	Brachydactyly type A1 (monoallelic)	Shortening of the metacarpals or metatarsals, and short stature[57,58]	rs142036701
		Acrocapitofemoral dysplasia (biallelic)	Short stature with short limbs, shortening of the metacarpals or metatarsals, thorax deformities, cone-shaped epiphyses in hands and femur head[59]	
NPPC	C-type natriuretic peptide	Isolated short stature (monoallelic, loss-of-function mutation)	Short stature[64]	rs749052
		Overgrowth (*NPPC* overexpression)	Tall stature, long halluses, spine and joint deformities, Marfanoid habitus[66]	
NPR2	Natriuretic peptide receptor B	Isolated short stature (monoallelic)	Isolated short stature[65]	rs3763631
		Acromesomelic dysplasia, Maroteaux type (biallelic)	Severe short stature, short bowing limbs, phalangeal-metacarpal abnormalities, brachydactyly of hands and feet[70]	
		Overgrowth (gain-of-function mutation, monoallelic)	Tall stature, macrodactyly of big toes[67]	
PTH1R	PTH/PTH-related peptide receptor, type 1	Blomstrand chondrodysplasia (loss-of-function mutation, biallelic)	Extremely advanced endochondral bone maturation, increased bone density,[61]	rsl21434601
		Jansen's metaphyseal chondrodysplasia (gain-of-function mutation, monoallelic)	Short-limbed dwarfism, hypercalcemia and hypophosphatemia, normal or undetectable PTH and PTHrP[62]	
PTHLH	Parathyroid hormone-related peptide	Brachydactyly type E (monoallelic)	Short stature, shortening of the metacarpals or metatarsals[60]	rs10492364
WNT5A	Wnt family member 5A	Robinow syndrome (monoallelic)	Short stature, limb shortening, genital hypoplasia, mandibular hypoplasia, hypertelorism[84,85]	rs2034172
Endocrine signaling				
CYP19A1	Aromatase (cytochrome p450 family 19 subfamily A member 1)	Aromatase excess syndrome (monoallelic)	Short stature, gynecomastia in males, macromastia in females[98]	rs16964211
		Aromatase deficiency (biallelic)	Tall stature compared to midparental height, delayed bone age, delayed puberty, ambiguous genitalia at birth, elevated androgens, low estrogen[96,97]	

Table 1. Genetic causes of linear growth disorders (continued)

Gene	Protein	Disorders	Clinical presentation	Height-associated SNP ID[2,3]
ESR1	Estrogen receptor	Estrogen resistance (biallelic)	Tall stature (variable), estrogen insensitivity, delayed skeletal maturation, no breast development in women[99,100]	rs3020418, rs6902771
IGF1R	Insulin-like growth factor I receptor	Isolated short stature (monoallelic)	Small for gestational age, short stature[90]	rs2871865
		Prenatal and postnatal growth failure (biallelic)	Intrauterine growth retardation, severe postnatal growth failure, microcephaly, developmental delay[91]	
PIK3R1	Phosphoinositide-3-kinase regulatory subunit 1	SHORT syndrome (monoallelic)	Short stature, hyperextensibility of joints, ocular defect (Rieger anomaly), lipodystrophy, insulin resistance, low birth weight, delayed bone age, triangular facies, hypoplastic nasal alae, low set ears[93-95]	rs9291926
Epigenetic regulation				
DNMT3A	DNA methyltransferase 3 alpha	DNMT3A syndrome (monoallelic)	Tall stature, intellectual disability, round face, heavy and horizontal eyebrows, narrow palpebral fissures[103,104]	rs2289195, rs10460566
EZH2	Enhancer of Zeste homolog 2	Weaver syndrome (monoallelic)	Tall stature, advanced bone age, macrocephaly, hypertelorism, retrognathia, variable learning disability[106,107]	rs822531
HIST1H1E	H1 histone family, member 4	Rahman syndrome (monoallelic)	Variable stature, intellectual disability and head circumference, facial dysmorphism (full cheeks, high hairlines, telecanthus)[105]	rs4141885
NSD1	Nuclear receptor binding SET domain protein 1	Sotos syndrome (monoallelic)	Overgrowth, advanced bone age, macrocephaly, pointed chin, receding hairline, downslanting palpebral fissures, intellectual disability, brain anomalies, seizures[109]	rs11950938, rs12055154
		Beckwith-Weidemann syndrome (monoallelic)	Overgrowth, ear and renal anomalies, macroglossia, abdominal wall defects, visceromegaly, embryonic tumors, hemihyperplasia, neonatal hypoglycemia[111]	
SETD2	SET domain containing 2	Sotos syndrome (monoallelic)	Overgrowth, macrocephaly, finical dysmorphism, long and large hands and feet, advanced bone age, mild intellectual disability[110]	rs76208147

SNP, single nucleotide polymorphism; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

members.[36-38] On the other hand, biallelic mutations cause fibrochondrogenesis 1, a skeletal dysplasia presenting with short limbs, flat midface and protrudent abdomen.[39] Furthermore, biallelic mutations in *COL27A1* cause Steel syndrome.[40-42] The main clinical features of this disorder are bilateral hip and radial head dislocations, scoliosis, short stature, carpal coalitions, and *pes cavus*, with some patients also having facial dysmorphism.[42] Patients with monoallelic mutations in *COL9A2* and *MATN3* can present with multiple epiphyseal dysplasia, a clinically variable disease characterized by short stature and early onset osteoarthritis.[43-45] Conversely, biallelic mutations in *COL9A2* and *MATN3* cause a more severe form of skeletal dysplasia.[44,47]

2. Intracellular signaling

Various intracellular signaling pathways have been recognized as causative factors of linear growth impairment, and mutations in intracellular signaling have been identified to significantly impair linear growth. However, surprisingly, not many SNPs in these genes were identified to be associated with height variation. It may be because not all the functions of identified genes are well-established or the functions of these genes may be too critical and essential, such as transcriptional regulation, cyclic AMP (cAMP) production, and DNA repair, therefore preventing frequent changes (SNPs) that can affect linear growth.

1) Transcriptional regulation (*SOX9*)

SOX9 is a critical transcriptional factor for sex development during embryogenesis and for skeletal development and also plays an important role in chondrogenesis at the growth plate by regulating chondrocyte differentiation.[48,49] In humans, dominant mutations in *SOX9* cause campomelic dysplasia (which means "bent limb" in Greek) with or without sex reversal.[48,49]

2) G protein alpha-subunit (*GNAS*), cAMP pathway
   (*CREBBP*, *PDE3A*)

The parathyroid hormone-related protein-Indian hedgehog (PTHrP-IHH) negative feedback loop is a major regulator of chondrogenesis in the growth plate, and PTHrP acts through the PTH1 receptor which activates both Gs and Gq family heterotrimeric G proteins.[50] The activation of Gs leads to cAMP production and protein kinase A (PKA) activation, and subsequent phosphorylation of the cAMP response element-binding (CREB) family of transcription factors.[51]

GNAS encodes the G protein alpha-subunit (Gs alpha), which, when activated, increases cAMP production to mediate downstream signaling.[52] Impairment of the cAMP signaling pathway through heterozygous loss-of-function mutations in Gs alpha leads to Albright's hereditary osteodystrophy (AHO) with or without hormone resistance. Maternal inheritance of Gs alpha mutations leads to AHO and pseudohypoparathyroidsim type 1a (PHP1a), which can include multihormone resistance, while patients with paternally inherited mutations of Gs alpha have only the AHO phenotype, termed pseudopseudohypo arathyroidism.[52] Phenotypically, patients with AHO present with short stature, brachydactyly, rounded face, and short neck.[53] Patients who have both AHO and PHP1a also have multihormone resistance to PTH, TSH, and gonadotropins, all of which act through G-protein-coupled receptors.[52] *CREBBP* encodes a nuclear transcriptional coactivator protein, CREB (cAMP-response element binding protein)-binding protein, that binds specifically to the PKA-phosphorylated form of the CREB protein. Rubinstein-Taybi syndrome (RSTS) is a rare condition characterized by short stature, intellectual disability, broad and deviated thumbs and halluces, and distinct craniofacial characteristics.[54] Over 65% of cases of RSTS are caused by dominant mutations in *CREBBP*.[55]

PDE3A encodes a cyclic GMP (cGMP) and AMP (cAMP) phosphodiesterase 3A. Missense mutations in *PDE3A* have been shown to cause Mendelian hypertension and brachydactyly type E in seven unrelated families.[56,57] This syndrome has symptoms of short stature, brachydactyly, salt-independent and age-dependent hypertension, an increased fibroblast growth rate, and other cardiovascular complications. The identified mutations increase PKA-mediated PDE3A phosphorylation and increase cAMP-hydrolytic activity, thereby decreasing cAMP production.[56]

3. Paracrine signaling pathways

Paracrine factors, such as fibroblast growth factors (FGFs), C-type natriuretic peptide (CNP), IHH, PTHrP encoded by *PTHLH*, and BMPs, play many critical roles in the growth plate, including chondrocyte proliferation, differentiation, hypertrophy, and matrix assembly.[8] Mutations in these genes have been identified to cause certain growth disorders with unique phenotype.

1) IHH-PTHrP pathway (*IHH*, *PTHLH*, *PTH1R*)

In the growth plate, IHH-PTHrP participates in a negative feedback loop that modulates chondrocyte differentiation.[58] Therefore, mutations in *IHH*, *PTHLH*, and the PTHrP receptor, *PTH1R*, result in disorders that affect skeletal growth. Mutations in *IHH* lead to brachydactyly type A1 and acrocapitofemoral dysplasia, and also can present with isolated short stature.[59-61] Mutations in *PTHLH* cause brachydactyly type E with short stature and the most prominent symptoms of these disorders are shortening of the metacarpals or metatarsals and short stature.[62] Loss-of-function mutations in *PTH1R* cause Blomstrand chondrodysplasia and gain-of-function mutations cause Jansen's metaphyseal chondrodysplasia, both of which are characterized primarily by short-limbed dwarfism.[63,64]

2) CNP-NPR2 Pathway (*NPPC*, *NPR2*)

The CNP is encoded by the *NPPC* gene and exerts its effects through the natriuretic peptide receptor B (NPR-B) encoded by *NPR2*.[65] Loss of function mutations in *NPPC* and *NPR2* cause short stature, while overexpression in *NPPC* or gain-of-function mutations in *NPR2* cause overgrowth.[66-69] Binding of CNP to NPR-B stimulates guanylyl cyclase activity, increasing the synthesis of cGMP and activating the type 2 cGMP-dependent protein kinase, which then inhibits the MAPK pathway and antagonizes FGFR signaling.[70,71] Because FGFR signaling induces growth arrest of chondrocytes, CNP promotes chondrocyte proliferation. Biallelic *NPR2* mutations cause acromesomelic dysplasia, Maroteaux type (AMDM), an autosomal recessive skeletal dysplasia characterized by severe short stature and short limbs.[72] Multiple mutations causing loss of function in NPR-B have been associated with AMDM. Nonsense mutations in the intracellular kinase homology domain (KHD) of NPR-B lead to impaired cGMP production, providing evidence that this domain is essential for skeletal growth.[73,74] Gain-of-function mutations in the *NPR2* gene have also been described, and these patients have tall stature and macrodactyly of the big toes.[69,74,75] It has been shown that a gain-of-function mutation in the KHD domain of NPR-B results in an increase in cGMP activity compared to the wild-type protein.[76]

3) TGF-β signaling (*GDF5*)

The *GDF5* gene encodes growth differentiation factor 5 (also known as cartilage-derived morphogenic protein) which acts through BMP receptors. Mutations in this gene can cause brachydactyly (type A1, A2, and C) with short stature, chondrodysplasia - Grebe type, characterized by severe dwarfism, disproportionate short stature, and brachydactyly, and Hunter-Thompson type, characterized by skeletal abnormalities that are restricted to the limbs and limb joints.[77-81] Early studies showed that *GDF5* is primarily expressed in long bones during human embryonic development[82] and recent studies revealed that *GDF5* enhances cartilage formation and *GDF5* and TGFβ synergistically induce mesenchymal stem cell differentiation into chondrocytes, providing evidence for its important role in

cartilage development.[83,84]

4) WNT signaling (*WNT5A*)

The canonical WNT signaling pathway is important for cell proliferation and cell fate change during development. Studies in Wnt5a-null mice showed a defect in cell polarization in the growth plate.[85] Dominant mutations in *WNT5A* are associated with Robinow syndrome, a disorder characterized by short stature, limb shortening, genital hypoplasia, and craniofacial abnormalities.[86,87]

5) *IGF2*

IGF2 encodes insulin-like growth factor 2, an important fetal growth factor that binds to the type 1 IGF receptor to regulate cell proliferation. Recently, studies showed that growth plates in *Igf2*- null mice show a disproportionally larger hypertrophic zone and delayed secondary ossification center, and, in humans, paternally inherited mutations in IGF2 in human cause postnatal growth failure in addition to prenatal growth.[88,89] The dysmorphic features of affected family members were similar to those of individuals with IGF-2 deficiency seen in Silver-Russell syndrome.[89] *IGFBP2BP2* and *IGF2BP3*, encoding the IGF2 binding proteins, are identified to be associated with height variation but mutations have not yet been found in human disorders.

4. Endocrine signaling

Endocrine signaling pathways are the clinical causes most extensively evaluated in children who present with short stature since endocrine causes and hormonal abnormalities are relatively easily tested in clinical practice. Growth hormone, thyroid hormone, glucocorticoids, and sex steroids affect chondrocyte proliferation and hypertrophy in the growth plate, altering linear growth if there is a defect in the corresponding axis.

1) GH-IGF1 axis (*IGF1R*)

The GH-IGF1 axis is one of the main regulatory systems that controls chondrogenesis in the growth plate, whereby GH acts directly on the growth plate to stimulate chondrogenesis or indirectly through circulating and local insulin-like growth factor-1 (IGF-1).[90,91] There have been multiple genes identified that cause growth hormone deficiency or impair downstream signaling of the GH-IGF1 axis. For the scope of this review, only genes identified by GWA studies are mentioned. Mutations in the IGF-1 receptor gene, *IGF1R*, can cause both prenatal and postnatal growth failure. Monoallelic mutations may cause short stature in children born small for gestational age.[92] Biallelic mutations cause severe short stature.[93] Fibroblast cultures from these patients showed decreased IGF1R function and a reduced number of IGF1 receptors, which could lead to IGF1 insensitivity.[93] SNPs in *IGFBP3*, *IGFBP4*, *STC2*, *PAPPA*, *PAPPA2*, which regulate the free form of IGF-1 by functioning as a binding protein (*IGFBP3*, *IGFBP4*), binding-protein-cleaving enzymes (*PAPPA*, *PAPPA2*), or as a regulator of PAPPA (*STC2*), have been identified by GWA studies to be associated with height variation, likely by affecting IGF-1 bioavailability and therefore the GH-IGF1 axis. However, only mutations in *PAPPA2*, encoding Pappalysin-2, a protein that cleaves IGFBP-3 and -5, have been identified in humans where the patients have decreased free IGF-1 levels.[94]

2) Insulin signaling (*PIK3R1*)

PIK3R1 is a gene involved in insulin signaling. Patients with mutations in *PIK3R1* have SHORT syndrome, hallmarks of which include short stature, hyperextensibility of joints, ocular depression, Rieger anomaly, teething decay, and insulin resistance.[95-97] However, the role of *PIK3R1* in the growth plate is not yet known.

3) Aromatase (*CYP19A1*)

Estrogen plays an important role in skeletal maturation and mineralization, and defects in estrogen signaling can lead to a variety of disorders that manifest with short or tall stature by altering the timing of growth plate senescence.[98] Since estrogen normally accelerates growth plate senescence and skeletal maturation, children with aromatase deficiency, a rare autosomal recessive disorder caused by mutations in the *CYP19A1* gene, present with delayed bone age and delayed puberty which lead to tall stature. This presentation is due to a lack of estrogen converted from androgen.[99,100] On the other hand, overexpression of *CYP19A1* can result in aromatase excess syndrome. Affected adults present with short stature, gynecomastia in males, and macromastia in females.[101] Patients with mutations in the estrogen receptor gene *ESR1* have estrogen resistance. To date, there have been 5 patients described who have mutations in *ESR1*, with varying phenotypes and varying degrees of estrogen insensitivity, likely due to different mutation sites and differences in penetrance of the particular mutation.[102,103] However, all patients had delayed skeletal maturation, with some having tall stature in adulthood also due to a lack of estrogen effects on the growth plate.[104]

5. Epigenetic control of height (*DNMT3A*, *HIST1H1E*, *EZH2*, *NSD1*, *SETD2*)

DNA and histone methylation are one of the main gene regulatory mechanisms and play crucial roles in growth and development. The best example of epigenetic regulation of growth is the epimutations in the telomeric imprinting control region 1 (ICR1), which alters *H19* and *IGF2* expression. Hypermethylation of the ICR1 causes biallelic expression of *IGF2* presenting as Beckwith-Wiedemann syndrome (BWS) (overgrowth) while hypomethylation of the ICR1 causes suppression of *IGF2* expression presenting as Silver-Russell syndrome (short stature).[105] Moreover, many genes involved in DNA methylation have been identified to cause growth

disorders, especially overgrowth syndromes. Studies have found *de novo* mutations in *DNMT3A*, a gene that encodes a DNA methyltransferase, which establishes methylation during embryogenesis.[106] These mutations cause an overgrowth syndrome called DNMT3A syndrome. Patients present with tall stature, intellectual disability, and distinctive facial appearance with a round face, heavy, horizontal eyebrows, and narrow palpebral fissures.[106,107] In addition to DNA methylation, histone methylation has been implicated in growth disorders. *HIST1H1E* encodes histone H1.4, and in humans, H1.4 mediates the formation of higher-order chromatin structures, thus regulating the accessibility of histone modification factors, regulatory proteins, and chromatin modifiers to target sites on this chromatin structure.[108] Mutations in this gene cause Rahman syndrome. Individuals with this disease have overgrowth with varying degrees of intellectual disability and a distinctive facial appearance in childhood - full cheeks, high hairlines, and telecanthus.[108] Additionally, monoallelic mutations in genes that encode other histone methyltransferases cause Weaver syndrome and Sotos syndrome. Weaver syndrome is caused by mutations in *EZH2* (Enhancer of Zeste homolog 2).[109,110] This gene encodes a histone methyltransferase that is part of the polycomb repressive complex 2, which catalyzes the methylation of lysine residue 27 of histone 3 (H3K27), thus causing transcriptional repression.[111] Patients with Weaver syndrome have tall stature, advanced bone age, dysmorphic facial features, and variable learning disability.[109,110] Sotos syndrome is another overgrowth syndrome characterized by overgrowth, advanced bone age, dysmorphic facial features, and intellectual disability, and patients with Sotos syndrome also often have brain anomalies and seizures.[112] However, in contrast to Weaver syndrome, Sotos syndrome and Sotos-like syndrome are caused by mutations in genes that cause transcriptional activation: *NSD1* and *SETD2*.[112,113] These 2 genes encode histone methyltransferases which catalyze the methylation of histone 3 lysine 36 to allow for transcriptional activation.[112,113] Interestingly, mutations in *NSD1* have been detected in 2 patients with BWS, another overgrowth condition characterized by macroglossia, abdominal wall defects, visceromegaly, embryonic tumors, hemihyperplasia, and neonatal hypoglycemia.[114]

Conclusion

In this review, we reviewed the genes that cause linear growth disorders in humans, focusing on their functions at the growth plate and their clinical phenotype. These genes are also identified by GWA studies which suggest that a mild change of function or expression in these genes may modulate linear growth within the normal ranges. The genetic evidence supports the idea that genes causing linear growth are highly heterogeneous, so that any regulatory mechanisms that alter chondrogenesis in the growth plate could be the genetic cause of growth disorders, either syndromic or isolated. With the aid of genome-wide approaches, it is expected that additional regulating mechanisms in growth disorders will be discovered and broaden our knowledge of the underlying causes of these disorders.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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