New Genetic Diagnoses of Short Stature Provide Insights into Local Regulation of Childhood Growth

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Abstract

Idiopathic short stature is a common condition with a heterogeneous etiology. Advances in genetic methods, including genome sequencing techniques and bioinformatics approaches, have emerged as important tools to identify the genetic defects in families with monogenic short stature. These findings have contributed to the understanding of growth regulation and indicate that growth plate chondrogenesis, and therefore linear growth, is governed by a large number of genes important for different signaling pathways and cellular functions, including genetic defects in hormonal regulation, paracrine signaling, cartilage matrix, and fundamental cellular processes. In addition, mutations in the same gene can cause a wide phenotypic spectrum depending on the severity and mode of inheritance of the mutation.

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Introduction

Longitudinal growth occurs by chondrogenesis at the growth plate and is regulated by a complex network of local and systemic factors [1]. Decreased growth plate chondrogenesis results in short stature, which is a common concern during childhood and a frequent cause for referral to pediatric endocrinologists. During evaluation for short stature, causative and modifiable factors including environmental factors, malnutrition, hormonal disorders, as well as inflammatory and other systemic diseases are identified or excluded. In addition, signs or symptoms indicative of syndromic short stature and skeletal dysplasias are noted. Still, in most cases, the specific etiologic factors or causative gene mutations remain unknown. Recent advances in large-scale genomic analysis have resulted in an improved understanding of the genetic complexity of short stature [1, 2]. For example, the most recent meta-analysis of genome-wide association studies of adult height identified 697 variants at 423 genomic loci [3, 4], with each loci only explaining a small fraction of the variability and all loci together explaining about 20% of height heritability, thus confirming that height is a truly polygenic trait [3]. Furthermore, next-

generation sequencing techniques have emerged as useful tools to elucidate the genetic defects underlying monogenic growth disorders [2] and have provided new insights into gene function and genetic regulation of longitudinal bone growth [1]. Taken together, the population-based genome-wide association studies and genetic studies of individuals and families with monogenic growth failure indicate that growth is regulated by hundreds, perhaps thousands of genes, which participate in signaling pathways and cellular functions that are important for the function of the growth plate [1].

Improved knowledge and diagnosis will provide an increasing number of short stature patients with an etiological/genetic diagnosis. In this review, we will provide an overview of genetic syndromes associated with impaired growth plate chondrogenesis and therefore growth failure. The syndromes have been categorized based on the process affected, including genetic defects in hormonal regulation, paracrine signaling, cartilage matrix, and fundamental cellular processes (Table 1; Fig. 1).

Molecular Mechanism Involved in Longitudinal Growth

Defects in Hormonal Signaling

Defects in genes within the growth hormone (GH)/insulin-like growth factor (IGF)1 system can cause growth failure and short stature (Table 1). It is essential that GH and IGF1 deficiencies are ruled out because they are treatable causes of short stature. Isolated GH deficiency (GHD) is usually caused by mutations in the gene encoding GH (*GH1*) and the receptor for GHRH (*GHRHR*). Isolated GHD may also be the only or first presentation of mutations in genes encoding early (*Hesx1*, *Sox2*, *Sox3*, *Lhx3*, *Lhx4*, *Ptx1*, *Ptx2*, and *Otx2*) or late (*PRO1* and *POU1F1*) transcription factors important for the development of the pituitary [5]. Mutations in early transcription factors are commonly associated with other developmental abnormalities, including variants of septo-optic dysplasia and/or ocular defects (*HESX1*, *OTX2*, *SOX2*, and *SOX3*), skeletal defects (*LHX3* and *PITX2*), and intellectual impairment (*SOX3* and *SOX2*) with or without other pituitary hormone deficiencies [6]. Severe isolated GHD and pituitary hypoplasia can also be caused by biallelic mutations in *RNPC3*, which encodes a minor spliceosome protein required for U11/U12 small nuclear ribonucleoprotein (snRNP) formation and splicing of U12-type introns [7]. The *BTK* (Bruton tyrosine kinase) gene, a key regulator of B-cell development, has been as-

sociated with X-linked GHD associated with agammaglobulinemia [8].

GH resistance is caused by mutations in the growth hormone receptor gene (*GHR*) or *STAT5B* [9, 10]. In contrast to GH, *IGF1* and *IGF1R* are critical for fetal growth and brain development. Consequently, mutations in *IGF1* or *IGF1R* cause intrauterine growth restriction, microcephaly, and various degrees of developmental delay [11–14]. Mutations in *IGFALS*, a gene that encodes a protein that stabilizes IGF1 by forming the IGF1-IGFBP3-ALS complex, cause mild short stature associated with insulin resistance and osteoporosis [15, 16]. A novel syndrome of progressive postnatal growth failure in 2 families with markedly elevated serum concentrations of IGF1, IGFBP3, IGFBP5, acid labile subunit, and IGF2 concentrations, resulting from homozygous loss of function of *PAPPA2*, was recently reported [17]. Both mutations caused a complete absence of *PAPPA2*, a pregnancy-associated plasma protein-A2 that plays a critical role in releasing IGF1 from IGFBP3 and IGFBP5. Decreased proteolytic activity of *PAPPA2* was associated to a significant increase in IGF1 bound in its ternary complex and low concentrations of free IGF1. Other findings include moderate microcephaly, thin long bones, and mildly decreased bone density [17].

Abnormal Paracrine Signaling

Fibroblast Growth Factor and Fibroblast Growth Factor Receptor Signaling

Fibroblast growth factor (FGF)-FGF receptor (FGFR) signaling is important in various cellular processes, including proliferation, differentiation, and cell survival. Binding of the FGF ligand, in concert with heparan sulfate, induces FGFR dimerization and transphosphorylation, followed by activation of downstream signal transduction pathways [18, 19]. In growth plate chondrocytes, FGFR3 signaling results in inhibition of proliferation and hypertrophy and may ultimately result in apoptosis [20]. Consequently, activating mutations in fibroblast growth factor receptor 3 (*FGFR3*) result in inhibition of growth, which can result in skeletal dysplasias ranging from moderate disproportionate short stature (*hypochondroplasia*) to severe short stature and bone malformation (*achondroplasia*), and to the most severe form (*thanatophoric dysplasia*), a lethal skeletal dysplasia with very short limbs and underdeveloped ribs [21–23]. Recently, a report of several families with autosomal dominant proportionate short stature and mild activating mutations of *FGFR3* has expanded the phenotype of *FGFR3* mutations [24]. Conversely, inactivating mutations in *FGFR3* can cause an

Table 1. Growth disorders

Disorder	Genes	Function	OMIM	Clinical features
Hormonal signaling				
Isolated GH deficiency	<i>GH, GHRHR, BTK</i>	GH, GH receptor	262400, 612781, 307200	No IUGR, postnatal growth failure, short stature, low GH, and low IGF1
GH deficiency (isolated or combined with multiple hormonal deficiencies and anomalies)	<i>HESX1, OTX2, SOX2, SOX3, LHX3, PITX2</i>	Transcription factors	182230, 613986, 206900, 312000, 221750	Short stature combined with multiple hormonal deficiencies and anomalies
GH resistance (Laron syndrome)	<i>GHR</i>	GH receptor	262500	Severe short stature, IUGR, elevated or normal GH, and low IGF1
GH resistance with immune deficiency	<i>STAT5B</i>	GH signaling	245590	No IUGR, short stature and immunodeficiency, elevated GH, and low IGF1 or IGFBP3
IGF1 deficiency ¹	<i>IGF1</i>	IGF1	608747	Severe prenatal and postnatal growth failure, microcephaly, sensorineural deafness, mental retardation, elevated random GH, and low IGF1
IGF1 resistance ¹	<i>IGF1R</i>	IGF receptor	270450	Short stature, IUGR, normal GH stimulation tests, normal to high IGF1 level
ALS deficiency	<i>IGFALS</i>	ALS	615961	Mild growth retardation, IUGR variable, pubertal delay in boys, insulin insensitivity, normal GH response to provocative tests but very low IGF1 and IGFBP3
Donohue syndrome (leprechaunism)	<i>INSR</i>	Insulin signaling	246200	Early growth failure, IUGR, severe insulin resistance, peculiar facies (gnome-like), severe insulin resistance, emaciation, enlargement of breasts and clitoris, skin abnormalities, muscular hypotrophy, and enlarged external genitalia in both males and females
Paracrine signaling				
IGF2 deficiency	<i>IGF2</i>	Secreted signaling molecule (IGF2)	616489	Severe growth restriction, IUGR, and Silver-Russell-like facies
Achondroplasia, hypochondroplasia, thanatophoric dysplasia, proportionate short stature ¹	<i>FGFR3</i> (activating)	Fibroblast growth factor receptor	100800, 146000, 187600	Short stature, average-size trunk, short arms and legs, limited range of motion at the elbows, enlarged head (macrocephaly) with a prominent forehead, fingers are typically short and hand with a trident appearance, normal intelligence, hypochondroplasia features tend to be milder
Brachydactyly, type E2	<i>PTH1LH</i>	Secreted signaling molecules (PTHrp)	613382	Short stature, no IUGR, delayed tooth eruption, oligodontia, short metacarpals and metatarsals, sometimes intellectual deficiency and learning disabilities
Blomstrand chondrodysplasia, Jansen metaphyseal chondrodysplasia	<i>PTH1R</i>	PTH and PTHrP receptor	215045, 156400	Short-limbed dwarfism, no IUGR, enlarged joints, broad skull, prominent forehead, micrognathia, generalized demineralization, and advanced skeletal maturation
Acrocapitofemoral dysplasia, brachydactyly type A1	<i>IHH</i>	Secreted signaling molecule (Indian hedgehog)	607778, 112500	Short-limbed dwarfism, no IUGR, brachydactyly, relative large head circumference, variable short stature that becomes more pronounced with age, and normal psychomotor development
Brachydactyly type A2	<i>BMPR1B</i>	BMP receptor	603248,	Short limbs, brachydactyly, foot abnormalities
Brachydactyly type A1, A2, C	<i>GDF5</i>	TGFβ superfamily	601146	
Robinow syndrome (brachydactyly type B)	<i>ROR2, WNT5A, DVL1</i>	WNT signaling pathway	268310, 180700, 616331, 616894	Short-limbed dwarfism, mesomelic brachymelia, fetal face appearance and hypogenitalism, vertebral defects, brachydactyly with small hands for age, mesomelic shortening, cleft of distal phalanx of thumb, rib anomalies, and chest deformities
Acromesomelic dysplasia, Maroteaux type, short stature with nonspecific skeletal abnormalities ¹	<i>NPR2</i> (inactivating)	CNP-NPR2 signaling	602875, 616255	Disproportionate shortening of skeletal elements, predominantly affecting the middle segments (forearms and forelegs) and distal segments (hands and feet) of the appendicular skeleton, relatively large head, midface hypoplasia with depressed nasal bridge and small nose
Cartilage extracellular matrix				
Achondrogenesis type II, hypochondrogenesis, spondyloepiphyseal dysplasia congenita, spondyloepiphyseal dysplasia Strudwick type, Stickler syndrome type 1, Czech dysplasia	<i>COL2A1</i>	Extracellular matrix, collagen 2	200610, 183900, 184250, 108300, 609162	Severe micromelic dwarfism, IUGR, incomplete ossification of the vertebral bodies, and disorganization of the costochondral junction
Stickler syndrome type 2, fibrochondrogenesis, otospondylomegalophyseal dysplasia	<i>COL11A1, COL11A2</i>	Extracellular matrix, collagen 11	604841, 228520, 215150	Short-limbed skeletal dysplasia, enlarged epiphyses, relatively normal hands and feet, small bell-shaped thorax with a protuberant abdomen, and flat midface with a small nose and anteverted nares
Schmid type metaphyseal chondrodysplasia	<i>COL10A1</i>	Extracellular matrix, collagen 10	156500	Short stature, no IUGR, relatively short limbs, coxa vara, bowed legs, and waddling gait
Multiple epiphyseal dysplasia	<i>COL9A1, COL9A2, COL9A3, MATN3, COMP</i>	Extracellular matrix, cartilage oligomeric matrix protein, collagen, matrilin-3	132400, 600204, 600969, 607078, 132400	Moderate short stature with normal body proportions, no IUGR, painful joints with restricted mobility, waddling gait, frequently accentuated thoracic kyphosis
Spondyloepimetaphyseal dysplasia, spondyloepiphyseal dysplasia Kimberly type, isolated short stature with advanced bone age ¹	<i>ACAN</i>	Extracellular matrix, aggrecan	612813, 608361, 165800	IUGR, severe short stature, relative macrocephaly, midface hypoplasia, short neck, barrel chest, brachydactyly, and advanced bone age

Table 1 (continued)

Disorder	Genes	Function	OMIM	Clinical features
Pseudoachondroplasia, dominant multiple epiphyseal dysplasia	<i>COMP</i>	Extracellular matrix, cartilage oligomeric matrix protein	177170	Growth retardation after first year of life, no IUGR, short arms and legs, disproportionately long trunk with accentuated lumbar lordosis, knock-knee, bowed legs, waddling walk, early-onset joint pain (osteoarthritis), hypermobility of all joints, except the elbows and hips
Acromicric dysplasia, geleophysic dysplasia 2	<i>FBN1</i>	Extracellular matrix, fibrillin 1	102370, 614185	Severe short stature, no IUGR, short hands and feet, joint limitations, and skin thickening
Defects in fundamental (intracellular) processes				
<i>Transcriptional factors</i>				
Campomelic dysplasia	<i>SOX9</i>	Chondrocyte differentiation factor	114290	Congenital shortness and bowing of long bones, short legs, dislocated hips, ambiguous genitalia, distinctive facial features; often lethal in the first year of life due to respiratory insufficiency
Léri-Weill dyschondrosteosis, Langer mesomelic dysplasia, proportionate short stature ¹	<i>SHOX</i>	Transcription factor	127300, 249700	No IUGR, short stature, mesomelia, and Madelung wrist deformity; Langer mesomelic dysplasia has a more severe phenotype
Alazami syndrome	<i>LARP7</i>	Transcriptional regulator of RNA polymerase II	615071	Primordial dwarfism, facial dysmorphism (triangular face), severe intellectual disability, no frank dysplasia, and a bone age consistent with chronological age
Cerebellofaciodental syndrome	<i>BRF1</i>	Transcriptional regulator of RNA polymerase III	616202	Facial dysmorphism and dental findings, cerebellar hypoplasia, delayed development, markedly delayed bone age
Rubinstein-Taybi syndrome	<i>CREBBP, EP300</i>	Transcriptional coactivator	180849	Postnatal growth deficiency, microcephaly, intellectual disability, broad thumbs and first toes, facial dysmorphism, and increased risk of tumor formation
Kabuki syndrome	<i>KMT2D (MLL2), KDM6A</i>	Transcriptional coactivator	147920, 300867	Postnatal dwarfism, congenital mental retardation, peculiar facies (long palpebral fissures with eversion of the lateral 3rd of the lower eyelids), problems involving the heart, skeleton, teeth, and immune system
KBG syndrome	<i>ANKRD11</i>	Transcription regulator	148050	Short stature, facial dysmorphism, hearing loss, congenital heart defect, skeletal anomalies, developmental delay, intellectual disability
<i>Intracellular pathways</i>				
Albright hereditary osteodystrophy, PHPIA, PPHP	<i>GNAS1</i> (loss of function)	G protein alpha subunit	103580, 602463	Short stature, IUGR, obesity, round-shaped face, subcutaneous ossifications and brachymetacarp (mainly of the 4th and 5th ray)
Acrodysostosis (Maroteaux-Malamut syndrome)	<i>PRKARIA, PDE4D</i>	cyclic AMP-protein kinase A pathway	101800, 614613	Short stature, IUGR, severe brachydactyly, facial dysostosis, nasal hypoplasia; it is common to find advanced bone age, obesity, and resistance to multiple hormones
Noonan syndrome or Noonan-like syndrome	<i>PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF, RIT1, SHOC2, CBL</i>	RAS-MAP kinase	163950, 605275, 609942, 610733, 611553, 607721	Short stature, distinctive facial dysmorphism, a broad or webbed neck, a wide spectrum of congenital heart defects, bleeding problems, skeletal malformations, and developmental delay
Multiple lentigines syndrome (LEOPARD syndrome)	<i>PTPN11, RAF1, BRAF</i>	RAS-MAP kinase	151100, 611554, 613707	No IUGR, lentigines, hypertrophic myopathy, electro-cardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormalities of genitalia, sensorineural deafness [75–79]
Costello syndrome (faciocutaneouskeletal or FCS syndrome)	<i>HRAS</i>	RAS-MAP kinase	218040	No IUGR, delayed development and intellectual disability, distinctive facial features, loose folds of extra skin (especially on the hands and feet), flexible joints [69]
Cardiofaciocutaneous syndrome	<i>BRAF, KRAS, MAP2K1/2</i>	RAS-MAP kinase	115150, 615278, 615279, 615280	Short stature, distinctive facial appearance, heart defects, mental retardation, and phenotypic overlap with Noonan syndrome and Costello syndrome
Neurofibromatosis type 1, Legius syndrome (NF1-like)	<i>NF1, SPRED1</i>	RAS-MAP kinase	162200, 611431	Short stature, no IUGR, café-au-lait spot, Lisch nodules in the eyes, osteoporosis, and increased susceptibility to malignancy (pheochromocytoma and gastrointestinal stromal tumor); Legius syndrome is less severe
Coffin-Lowry syndrome	<i>RPS6KA3</i>	ERK-MAPK pathway	303600	Growth retardation, no IUGR, microcephaly, facial dysmorphism, skeletal malformations, hypotonia, and cognitive impairment in affected males (X-linked)
Aarskog-Scott syndrome (faciogenital dysplasia)	<i>FGD1</i>	Guanine nucleotide exchange factor (GEF)/EGFR1 signalling pathway	305400	Short stature, IUGR, hypertelorism, shawl scrotum, everted lower lip, hyperextensibility, ptosis, finger abnormalities, brachydactyly
SHORT syndrome	<i>PIK3R1</i>	PI3K-AKT-mTOR pathway	269880	Short stature, hyperextensibility of joints and/or hernia (inguinal), ocular depression, Rieger anomaly, teething delay
<i>DNA repair</i>				
Seckel syndrome	<i>ATR, ATRIP, RBBP8 (CTIP), CEP152, DNA2, TRAP</i>	Defective ATR-dependent damage	210600, 606744, 613823, 615807, 616777	Primordial dwarfism, IUGR, microcephaly with mental retardation, and a characteristic “bird-headed” facial appearance
Nijmegen breakage syndrome	<i>NBS1 (NBN)</i>	DNA double-strand break repair	251260	Growth retardation, no IUGR, microcephaly, distinctive facial features, immunodeficiency, and cancer predisposition
Schimke immuno-osseous dysplasia	<i>SMARCA1</i>	DNA double-strand break repair	242900	Short stature, IUGR, immune deficiency, progressive steroid-resistant nephropathy, strokes, bone marrow failure, and kidney failure

Table 1 (continued)

Disorder	Genes	Function	OMIM	Clinical features
LIG4 syndrome	<i>LIG4</i>	DNA double-strand break repair	606593	No IUGR, distinctive facial features, microcephaly, pancytopenia, various skin abnormalities, immunodeficiency; phenotypic overlap with Nijmegen breakage syndrome
Short stature, microcephaly and endocrine dysfunction syndrome	<i>XRCC4, MCM9</i>	DNA double-strand break repair	616541	Short stature and microcephaly apparent at birth, progressive postnatal growth failure, distinctive facial features, microcephaly, pancytopenia, various skin abnormalities; endocrine dysfunction, including hypergonadotropic hypogonadism, multinodular goiter, and diabetes mellitus, is present in affected adults
Bloom syndrome	<i>BLM (RECQL3)</i>	DNA helicase disorders	210900	IUGR, proportionate short stature, a high-pitched voice, distinctive facial features, including a long, narrow face, small lower jaw, large nose, and prominent ears, predisposition to malignancy and sun-sensitive skin, telangiectatic, hypo-, and hyperpigmented skin
Rothmund-Thomson syndrome, Baller-Gerold syndrome, RAPADILINO syndrome	<i>RECQL4</i>	DNA helicase disorders	268400, 218600, 266280	Short stature, premature aging, and increased risk of malignant disease, skin atrophy, telangiectasia, and congenital skeletal abnormalities; the cardinal features of Baller-Gerold syndrome are craniosynostosis and radial aplasia; radial and patellar aplasia or hypoplasia are the main features in RAPADILINO syndrome
Cockayne syndrome, cerebro-oculo-facio-skeletal syndrome	<i>ERCC6, ERCC8</i>	Defect in nucleotide excision repair	216400, 133540	Cachectic dwarfism (progeroid appearance), microcephaly with delayed development, photosensitivity, progressive pigmentary retinopathy, and sensorineural deafness
<i>Cell proliferation and other fundamental processes</i>				
IMaGE syndrome	<i>CDKN1C</i>	Control of cell growth and cell division	614732	Growth restriction (IUGR), short stature, metaphyseal dysplasia, congenital adrenal hypoplasia, and genitourinary abnormalities in males (cryptorchidism, micropenis, and hypospadias); adrenal insufficiency typically presenting in the first month of life as an adrenal crisis or rarely later in childhood with failure to thrive and recurrent vomiting
Seckel syndrome	<i>CENPJ, CEP152, CEP63, NIN</i>	Centrosome integrity and cell division	613676, 613823, 614851	Primordial dwarfism, IUGR, microcephaly with mental retardation, and a characteristic “bird-headed” facial appearance
Primordial dwarfism (short stature, microcephaly and distinctive facies)	<i>CRIP1</i>	Protein interaction with cytoskeleton	615789	Prenatal and postnatal growth failure, facial dysmorphism, microcephaly, intellectual disabilities, ocular and skeletal abnormalities, such as hypoplastic terminal phalanges with brachydactyly
MOPD1	<i>RNU4ATAC</i>	snRNA function and splicing	210710	Short stature, IUGR, dysmorphic face, microcephaly, mental retardation, brain malformations, and ocular/auditory sensory deficits
MOPD2	<i>PCNT</i>	Centrosome/ microtubules and cytoskeleton structure	210720	IUGR, severe proportionate short stature, microcephaly, facial dysmorphism, near-normal intelligence, and cancer susceptibility
SOFT syndrome	<i>POC1A</i>	Centriole assembly and ciliogenesis	614813	IUGR, disproportionate and severe short stature, nail anomalies, paucity of hair, and facial dysmorphism
3-M syndrome	<i>CUL7, OBSL1, CCDC8</i>	Microtubule stabilization and genome stability	273750, 612921, 614205	Severe prenatal and postnatal growth retardation, delayed bone age, distinctive facial features, normal mental development
Meier-Gorlin syndrome	<i>ORC1, ORC4, ORC6, CDT1, CDC6</i>	Pre-replication complex	224690, 613800, 613803, 613804, 613805	Severe intrauterine and postnatal growth retardation, facial dysmorphism, microcephaly, and aplasia or hypoplasia of the patellae
Cornelia de Lange syndrome	<i>NIPBL</i> (50%), <i>SMC1A, HDAC8, RAD21, SMC3</i>	Cohesin complex and chromosome stability	122470, 300590, 300882, 614701, 610759	Prenatal and postnatal growth retardation, characteristic facial features (low anterior hairline, arched eyebrows, synophrys, hirsutism), microcephaly, mental retardation, upper limb anomalies, and cardiac defect
Hutchinson-Gilford Progeria	<i>LMNA</i>	Nuclear shape and stability	176670	Postnatal short stature, low body weight, early alopecia, lipodystrophy, scleroderma, decreased joint mobility, osteolysis, and aged facial features; cognitive development is normal
Mulibrey nanism	<i>TRIM37</i>	Peroxisomal protein, ubiquitination of positive regulators of centriole reduplication	253250	IUGR, dysmorphic craniofacial features, heart disease (constrictive pericardium), hepatomegaly, failure of sexual maturation, insulin resistance with type 2 diabetes, and an increased risk for Wilms tumor
CHARGE syndrome	<i>CHD7</i>	Chromatin remodeling	214800	Retardation of mental and somatic development, facial dysmorphism, CHARGE association (coloboma of the eye, heart anomaly, atresia, choanal, microphallus, ear abnormalities, and/or deafness)
Floating-Harbor syndrome	<i>SRCAP</i>	Chromatin remodeling	136140	Proportionate short stature, delayed bone age, delayed speech development, and typical facial features
Smith-Lemli-Opitz syndrome	<i>DHCR7</i>	Steroid biosynthesis	270400	Prenatal and postnatal growth, distinctive facial features, microcephaly, intellectual disability and behavioral problems, multiple malformations of the heart, lungs, kidneys, gastrointestinal tract, and genitalia

GH, growth hormone; IUGR, intrauterine growth restriction; IGF, insulin-like growth factor; ALS, acid labile subunit; PTH, parathyroid hormone; PTHrp, parathyroid hormone-related protein; PHPIA, pseudohypoparathyroidism type 1a; PPP, pseudopseudohypoparathyroidism; MOPD, microcephalic osteodysplastic primordial dwarfism.

¹ Isolated short stature.

Fig. 1. Molecular mechanisms of growth failure. Growth failure is caused by multiple molecular defects involving hormones, paracrine factors, extracellular matrix molecules, and intracellular processes. Examples of affected genes are listed for each subgroup. Ovoid shapes represent growth plate chondrocytes. Thin arrows indicate mechanisms regulating chondrocytes. Thick, curved arrows indicate the 2-step differentiation program from resting to proliferative chondrocytes and from proliferative to hypertrophic chondrocytes, respectively. RZ, resting zone; PZ, proliferative zone; HZ, hypertrophic zone.

overgrowth syndrome including tall stature, scoliosis, camptodactyly, and hearing loss [25–27].

Parathyroid Hormone-Related Protein and Indian Hedgehog Signaling

In the growth plate, Indian hedgehog (IHH) and parathyroid hormone-related protein (PTHrP) form a feedback loop that controls the size of the proliferative pool of chondrocytes [1]. The *PTH1R* gene encodes PTHrP, a member of the parathyroid hormone (PTH) family, which regulates the balance between chondrocyte proliferation and the onset of hypertrophic differentiation during endochondral bone development. In humans, mutations in *PTH1R* are associated with brachydactyly type E2 (BDE2) [28, 29], and inactivating mutations in its receptor (*PTH1R*) result in *Blomstrand dysplasia*, a recessive lethal chondrodysplasia characterized by very short limbs and dwarfism due to advanced skeletal maturation [30]. Interestingly, activating mutations in the same receptor cause short-limbed dwarfism, *Jansen metaphyseal dysplasia*, an autosomal dominant disorder accompanied by hypercalcemia and normal or low serum concentrations of PTH and PTHrP [31, 32]. Mutations in IHH, a

signaling molecule, leads to brachydactyly type A1 (BDA1) [33]. Recently, mutations in the IHH gene have been reported as the cause of acrocapitofemoral dysplasia, a new autosomal recessive skeletal dysplasia characterized clinically by short stature with short limbs, cone-shaped epiphyses, and premature fusion of growth plates [34, 35].

Bone Morphogenetic Protein Signaling

Genetic defects in the TGF β superfamily, including several bone morphogenetic proteins (BMPs) and growth differentiation factors are associated with skeletal dysplasias characterized by brachydactyly [135, 136]. Brachydactyly type A2 (BDA2) is caused by mutations in *BMPR1B* [36], and mutations affecting growth differentiation factor 5 (*GDF5*) have been identified in several individuals with brachydactyly [37].

WNT Signaling Pathway

The Wnt signaling pathway is an evolutionarily conserved pathway that regulates crucial aspects of cell fate determination, cell migration, cell polarity, neural patterning, and organogenesis during embryonic development [38].

Disruption of Wnt signaling through mutations in *ROR2*, *WNT5A* (the ligand of *ROR2*), or *DVL1* genes causes *Robinson syndrome*, a skeletal dysplasia characterized by dysmorphic facial features, short-limbed dwarfism, vertebral segmentation, and genital hypoplasia [39]. In particular, the *ROR2* protein appears to be critical for the normal formation of the skeleton, heart, and genitals [40, 41].

C-Type Natriuretic Peptide Signaling

C-natriuretic peptide (CNP) acts as an important paracrine factor in the growth plate and a positive regulator of endochondral ossification [1]. In humans, overexpression of *CNP* results in overgrowth [42, 43]. Conversely, homozygous inactivating mutations in natriuretic peptide receptor 2 (*NPR2*), the primary receptor for CNP, cause *acromesomelic dysplasia, Maroteaux type* [44], whereas heterozygous mutations can present as *idiopathic short stature* with no or only subtle signs of a skeletal dysplasia [45, 46]. In 2 recent studies of idiopathic short stature, cohorts identified heterozygous *NPR2* mutations in 0–6% of the patients [47, 48]. Interestingly, activating mutation in *NPR2* can cause tall stature [47, 49].

Insulin-Like Growth Factor 2

IGF2 is an important growth factor during intrauterine growth. In mice, disruption of the paternal *Igf2* allele causes severe prenatal growth retardation, and an influence on postnatal growth has also been observed [50]. In humans, there is only 1 report of a single family with a known pathogenic mutation in this gene, causing severe growth restriction and postnatal growth failure resulting in short stature [51]. Consistent with the maternal imprinting status of *IGF2*, the phenotype affects only family members who have inherited the variant through paternal transmission. Furthermore, the dysmorphic features of affected family members are consistent with the hypothesis that the pathogenic mechanism of *Russell-Silver syndrome* (RSS), at least in part, is due to *IGF2* deficiency [51]. In RSS, loss of methylation at the imprinting control region (ICR1) on chromosome 11p15.5 region results in dysregulation of the *H19* gene (encoding a long noncoding RNA) and *IGF2* expression, which most likely explains the growth failure and other characteristic features of RSS [52].

Defects in Cartilage Extracellular Matrix

Mutations in genes that encode matrix collagens, proteoglycans, and noncollagenous proteins affect growth plate chondrogenesis by several mechanisms, cause

growth failure with a wide phenotypic spectrum, and may also affect connective tissue beyond the growth plate, causing various skeletal and joint problems, and sometimes medical problems related to other organ systems.

Collagen Synthesis

Genetic defects of collagen formation (collagenopathies) affect almost every organ and tissue in the body. In the growth plate, the most important *collagenopathies* are due to mutations in genes that encode Col2, Col9, Col10, and Col11 [53]. Mutations in type II collagen (*COL2A1*) gene cause a spectrum of rare autosomal dominant conditions characterized by skeletal dysplasia, short stature, and ocular defects [54–56]. Premature osteoarthritis (OA) is a common feature of type II collagenopathies [57]. Mutations in glycine residues disrupt the collagen triple helix and cause disease in the heterozygous state, often with a severe phenotype, including *achondrogenesis type II* or *hypochondrogenesis*, *spondyloepiphyseal dysplasia congenita*, or *spondyloepimetaphyseal dysplasia Strudwick type* [57]. Nonsense and frameshift mutations result in haploinsufficiency and usually a less severe phenotype such as Stickler syndrome I, the most frequent type II collagenopathy. Especially the p.Arg275Cys substitution is found in all patients with *COL2A1*-associated *Czech dysplasia* [57].

The flexible nature of type IX collagen allows it to act as a bridge that connects type II collagen with other cartilage components and interacts with matrilin-3 (*MATN3*) and cartilage oligomeric matrix protein (*COMP*) genes, important components of the extracellular matrix. Mutations in alpha 1–3 chains of type IX collagen (*COL9A1*, *COL9A2*, *COL9A3*), in addition to mutations in *COMP* and *MATN3* genes, can cause *multiple epiphyseal dysplasia*, a relatively common skeletal dysplasia mainly involving the epiphyses of long bones and characterized by mild short stature, intermittent joint pain, and early-onset OA [58].

Heterozygous mutations in type X collagen (*Col10a1*) are associated with *Schmid type metaphyseal chondrodysplasia* and *Japanese type spondylometaphyseal dysplasia*, which, apart from exhibiting a mild spinal phenotype, share striking clinical and radiographic similarities [59–62]. Type XI collagen is a minor component of cartilage collagen [63]. Alterations of type XI collagen caused by mutations of the $\alpha 1$ chain of type XI collagen (*COL11A1*) gene lead to *Stickler dysplasia type 2* with ocular alterations [64, 65]. Mutations in the gene coding for the $\alpha 2$ chain of type XI collagen (*COL11A2*) cause heterozy-

gous and homozygous *otospondylomegaepiphyseal dysplasia* [66]. It is notable that heterozygous mutations in *COL11A2* can cause autosomal dominant otospondylomegaepiphyseal dysplasia and nonocular Stickler syndrome type 2 as well as other nonchondrodysplasia disorders [67].

Synthesis of Non-Collagen Matrix Proteins

Aggrecan is the most abundant proteoglycan of articular and growth plate cartilage and is crucial for their structure and function. Mutations in the aggrecan gene (*ACAN*) cause accelerated hypertrophic differentiation of growth plate chondrocytes [68]. Homozygous *ACAN* mutations have been reported in 1 family and cause a severe skeletal dysplasia characterized by extreme short stature, brachydactyly, and severe midface hypoplasia, termed *spondyloepimetaphyseal dysplasia* [69]. In contrast, heterozygous *ACAN* mutations cause mild to moderate growth failure with adult height SDS commonly in the -2 to -4 range [69] and are sometimes associated with accelerated skeletal maturation [69] or early-onset OA as in familial osteochondritis dissecans [69, 70] and *spondyloepiphyseal dysplasia Kimberley type* [71].

The COMP protein is an important component of the extracellular matrix and also binds strongly to calcium, being essential for the normal development of cartilage and for its conversion to bone. COMP mutations lead to the improper folding of the COMP protein in the endoplasmic reticulum, which cannot be transported out of the cell, builds up inside the chondrocyte, and ultimately leads to early cell death and prevents normal bone growth, which causes short stature and bone abnormalities seen in *pseudoachondroplasia* and *dominant multiple epiphyseal dysplasia* [58, 69]. The abnormal cartilage probably breaks down easily, which results in early-onset OA [72]. Mutations in matrilin (*MATN3*) [73] are also responsible for *dominant multiple epiphyseal dysplasia* [58]. Mutations in the fibrillin 1 (*FBN1*) gene, which encode TGF β -binding protein-like domain 5 (TB5) of *FBN1*, are found as a cause for *geleophysic* and *acromicric dysplasia*, both characterized by severe short stature, short extremities, and stiff joints [74, 75]. Interestingly, mutations in this gene have been described in Marfan syndrome, which is characterized by tall stature and arachnodactyly. There is some evidence that *FBN1* mutations in geleophysic dysplasia, acromicric dysplasia, and Marfan syndrome enhance TGF β signaling, and it is unclear how these defects can produce either tall stature or severe short stature [75].

Defects in Fundamental Cellular Processes

Short stature can also result from mutations in genes involved in fundamental cellular processes that are important in all cells, not just those of the growth plate. These mutations typically impair growth and development in the fetus, leading to severe intrauterine growth retardation and postnatal growth abnormalities. These disorders often present as microcephalic primordial dwarfism, characterized by a proportionate reduction in growth, not related to GHD or other hormonal deficiencies [76], and can be associated with microcephaly, skeletal dysplasia, distinctive facial features, and other abnormalities in diverse organ systems [77].

In this section, due to the diversity of mechanisms involved, we have grouped the conditions in 4 subgroups: transcriptional factors, intracellular pathways, DNA repair, and cell proliferation and other fundamental processes.

Transcription Factors

SRY-related HMG-Box Gene 9 (*SOX9*) is a transcription factor and master regulator of chondrocyte differentiation essential for the normal development of the skeleton and nonskeletal tissues. Disruption of *SOX9* causes *campomelic dysplasia*, a severe disorder that affects the development of the skeleton and other organ systems, and complete sex reversal in about two-thirds of patients with an XY karyotype [78]. *Sox5* and *Sox6* are coexpressed with *Sox9* in mesenchymal cells and proliferating chondrocytes, forming a complex [79]. Inactivation of *Sox5* and *Sox6* in mice results in a defect in the differentiation of proliferating chondrocytes and, therefore, a major disruption in endochondral bone formation [80, 81].

Short stature homeobox-containing gene (*SHOX*) encodes another transcription factor important for growth plate chondrocyte function [77]. *SHOX* mutations can cause a broad phenotypic spectrum. Homozygous mutations cause a severe skeletal dysplasia, *Langer mesomelic dysplasia*, which is characterized by severe short stature, extreme shortening of the long bones in the arms and legs (mesomelia), and Madelung deformity [82]. Heterozygous mutations in *SHOX* cause a milder skeletal dysplasia, *Léri-Weill dyschondrosteosis* [83, 84], or can present as idiopathic short stature [85, 86]. Additionally, deficiency of *SHOX* protein contributes to the short stature and skeletal abnormalities seen in females with Turner syndrome, where one of the sex chromosomes, including the pseudoautosomal region 1

(PAR1), which contains *SHOX*, is missing or structurally altered [87].

Other Regulators of Transcription

LARP7 is a component of the small nuclear ribonucleoprotein (7SKsnRNP) complex required for the stability and function of the RNA, by regulating RNA polymerase II at a promoter to begin transcription elongation [88, 89]. Mutations in *LARP7* cause severe primordial dwarfism named *Alazami syndrome* [90–92]. Additionally, mutations in the *BRF1* gene, which encodes 1 of the 3 subunits of the RNA polymerase III transcription factor complex, cause the cerebellofaciodental syndrome, characterized by severe short stature, delayed bone age, cerebellar hypoplasia, delayed development and intellectual disability, as well as facial dysmorphic features, microcephaly, and dental anomalies [93, 94].

CREBBP (CREB binding) and *EP300* encode histone acetyltransferases, which are transcriptional coactivators involved in many signaling pathways [95]. Mutations in both genes cause most of the cases of *Rubinstein-Taybi syndrome*, a rare condition characterized by distinctive facial features, short stature, broad and often angulated thumbs, and moderate to severe intellectual disability [95–97]. *Kabuki syndrome*, a multisystem disorder that presents with short stature and characteristic facies, is caused by mutations in *KMT2D* (*MLL2*) and *KDM6A* genes, which disrupt normal histone methylation [98, 99]. Mutations in *ANKRD11* have been associated with KBG syndrome, characterized by macrodontia, distinctive craniofacial features, short stature, skeletal anomalies, global developmental delay, seizures, and intellectual disability [100–102]. *ANKRD11* provides instructions for making a protein that interacts with other proteins called histone deacetylases and inhibits ligand-dependent activation of transcription.

Intracellular Signaling

RASopathies are a group of genetic syndromes that are caused by germ-line mutations in genes that encode components or regulators of the Ras/mitogen-activated protein kinase (MAPK) pathway [103, 104]. The vast majority of these mutations result in increased signal transduction down the Ras/MAPK pathway, but usually to a lesser extent than somatic mutations associated with oncogenesis. Each syndrome exhibits unique phenotypic features, but they also share numerous overlapping phenotypic features, including characteristic facial features, short stature, cardiac defects, cutaneous abnormalities, neurocognitive delay, and a predisposition to malignancies

[105]. The most common *RASopathies* are as follows: (1) *Noonan syndrome*, caused by mutations in *PTPN11* (~50%), *SOS1* (11%), *RAF1* (5%), *KRAS*, *NRAS*, *SHOC2*, *BRAF*, *CBL*, and *RIT1* [105–107]; (2) *Noonan syndrome with multiple lentigines* (also called *LEOPARD syndrome*), caused by mutations in *PTPN11* (~85%) and *RAF1* (~10%), and, in rare cases, in *BRAF* and *MAP2K1* genes [108, 109]; (3) *Noonan-like syndrome*, caused by mutations in *SHOC2* or *CBL* [110–112]; (4) *Costello syndrome*, caused by activating mutations in *HRAS* [113]; (5) *cardiofaciocutaneous syndrome*, caused by mutations in *BRAF*, *MAP2K1/2*, and *KRAS* [114, 115]; (6) *neurofibromatosis type 1*, caused by haploinsufficiency of neurofibromin, which acts as a tumor suppressor [116]; and (7) *Legius syndrome* (*neurofibromatosis type 1-like syndrome*), caused by haploinsufficiency of *SPRED1* [106, 117]. Molecular analysis is beneficial to both confirm clinical diagnoses and perform follow-up according to the unique characteristics of each disorder within the *RASopathies*.

The *RPS6KA3* gene encodes RSK2, a growth-factor-regulated protein kinase that acts at the distal end of the Ras/MAPK signaling pathway [118]. Mutations in the *RPS6KA3* gene cause *Coffin-Lowry syndrome*, a syndromic form of X-linked mental retardation, which is characterized in male patients by psychomotor and growth retardation, various skeletal anomalies, and typical facial changes [119, 120]. *RPS6KA3* mutations are extremely heterogeneous and lead to loss of phosphotransferase activity in the RSK2 kinase that is directly phosphorylated and activated by ERK1/2 in response to growth factors, many polypeptide hormones, and neurotransmitters. In addition, it has recently been shown that *FGFR3*, by interacting with, and phosphorylating 2 tyrosine residues within the C-terminal region of RSK2, influences RSK2 activation [121].

Mutations in *FGD1* cause *Aarskog-Scott syndrome*, also known as faciodigitogenital dysplasia, an X-linked human disorder characterized by short stature, hypertelorism, shawl scrotum, and brachydactyly [122]. *FGD1* encodes a member of the Dbl family of guanine nucleotide exchange factors that activates CDC42 (Cell Division Control protein 42 homolog) which has a core function in remodeling the extracellular matrix and in the transcriptional activation of many modulators of development [123].

In growth plate cartilage, PTHrP delay hypertrophic differentiation and disruption of PTHrP receptor signaling result in accelerated hypertrophic differentiation, decreased proliferation, and early growth cessation [124].

Heterozygous loss-of-function mutations in *GNAS1* lead to *Albright hereditary osteodystrophy* (AHO) – a disease characterized by short stature, obesity, and skeletal defects – and are sometimes associated with progressive osseous heteroplasia. The manifestations of $G_{s\alpha}$ mutations are further modified by parental inheritance because $G_{s\alpha}$ is imprinted in a tissue-specific manner. Inactivating $G_{s\alpha}$ mutations leads to *pseudohypoparathyroidism type 1a* (PHPIA) or *pseudopseudohypoparathyroidism* (PPHP). Maternal inheritance of inactivating $G_{s\alpha}$ mutations (PHPIA) or an imprinting defect that leads to a paternal-specific imprinting pattern on both parental alleles lead to renal PTH resistance due to loss of expression of $G_{s\alpha}$ from the active maternal allele in renal proximal tubules. $G_{s\alpha}$ is not imprinted in growth plate chondrocytes, and therefore mutations on either the maternal (PHPIA) or paternal (PPHP) allele result in haploinsufficiency and the AHO phenotype that is present in both PHPIA and PPHP patients. Disturbance of cyclic AMP (cAMP) signaling can also be caused by mutations in *PRKARIA* (the cAMP-dependent regulatory subunit of protein kinase A) and *PDE4D* (phosphodiesterase 4D, cAMP-specific), which leads to *acrodysostosis* (*Maroteaux-Malamut syndrome*), a skeletal dysplasia characterized by peripheral dysostosis, short stature, midface hypoplasia, developmental delay, accompanied with or without hormone resistance, respectively [125, 126]. The skeletal dysplasia characteristic of acrodysostosis resembles the AHO seen in patients with PHPIA. In the absence of cAMP, the protein kinase A (PKA) exists as an inactive tetrameric holoenzyme. It is likely that the mechanism of reduced PKA signaling causes the hormonal and skeletal phenotype of acrodysostosis and AHO [127].

The phosphatidylinositol 3 kinase (*PI3K*) signaling pathway is central to the action of many hormones and growth factors, including insulin, and is essential for the differentiation of pre-adipocytes to adipocytes [128, 129]. Mutations in the *PI3K* gene cause *SHORT syndrome*, a rare and multisystem disease characterized by short stature, anterior-chamber eye anomalies, characteristic facial features, lipodystrophy, hyperextensibility, and delayed dentition [130–132].

DNA Repair

Four subtypes of the microcephalic primordial dwarfism Seckel syndrome (SCKL) are caused by mutations in genes related to defects in DNA repair and stability (Table 1): *ATR* and *ATR-ATRIP complex* (*SCKL1*), *RBBP8* (*SCKL2*), *DNA2* (*SCK8*), and *TRAIP* (*SCKL9*). Mutations in the *ATR* gene, known as the ataxia-telangiectasia and

Rad3-related protein gene, was the first gene associated with mutations in *SCKL1* [133, 134]. Defects in the *ATR*-signaling pathway result in failed checkpoint arrests and genomic instability, which in part may be due to impaired telomere maintenance [77]. The *ATRIP* gene encodes ATR-Interacting Protein (ATRIP), a partner protein of ATR required for ATR stability and recruitment to the site of DNA damage, and is a novel causal genetic defect for *SCKL1* [135]. Interestingly, impaired function of *CEP152*, besides acting in centrosome integrity, also leads to accumulation of genomic defects resulting from replicative stress through enhanced activation of ATM signaling [136]. Three other genes affected in SCKL are also involved in DNA repair, but not in the ATR mechanism. *SCKL2* is caused by mutations in *RBBP8* (*CTIP*), which encodes a nuclear protein that regulates cell proliferation and may itself be a tumor suppressor acting in the same pathway as *BRCA1* in transcriptional regulation, DNA repair, and/or cell cycle checkpoint control [137]. Mutations in *DNA2*, a member of the DNA2/NAM7 helicase family, are involved in the maintenance of mitochondrial and nuclear DNA stability and have been found as the cause of *SCKL8* [138]. Recently, identification of mutations in the *TRAIP* gene, encoding an E3 RING ubiquitin ligase, cause *SCKL9*. TRAIP relocates to sites of DNA damage, where it is required for optimal phosphorylation of H2AX and RPA2 during S-phase in response to ultraviolet irradiation, as well as fork progression through ultraviolet-induced DNA lesions [139].

Nijmegen breakage syndrome is a recessive genetic disorder characterized by progressive microcephaly, intrauterine growth retardation and short stature, and an increased sensitivity to ionizing radiation and premature ovarian failure in females (Table 1). NBS1, a product of the mutated gene in Nijmegen breakage syndrome, is one of the first factors to accumulate at sites of double-strand DNA breaks (DSB) and acts as a sensor or mediator of DSB damage responses [140, 141]. *Schimke immuno-osseous dysplasia* is caused by mutations in the *SMARCA1* gene and characterized by severe growth restriction, immune deficiency, as well as renal and bone marrow failure [142, 143]. SMARCA1 is an ATPase in the SNF2 family that functions at damaged replication forks to promote their stability and restart [144–146]. Mutations in *LIG4* and *XRCC4* genes, also implicated in the process of DSB, have been discovered in short individuals. *LIG4 syndrome* is characterized by growth retardation, microcephaly, unusual facial features, developmental delay, skin anomalies, and a variable immunodeficiency [147–150]. LIG4 syndrome

results from mutations in the DNA ligase IV gene, which encodes an enzyme that plays a pivotal role in repairing DSB [151, 152]. The degree of protein truncation appears to correlate with phenotype severity of LIG4 syndrome, varying from the most severe phenotype with severe combined immunodeficiency to a global growth reduction without clinically apparent immunodeficiency before investigation [150].

Mutations in *XRCC4* cause a new syndrome named SSMED, which stands for short stature, microcephaly, and endocrine dysfunction [138, 153, 154]. The *XRCC4* gene encodes a protein that functions together with DNA ligase IV and the DNA-dependent protein kinase in the repair of DSB. In addition, recessive missense mutations in the homologous DNA repair enzyme *MCM9* lead to a genomic instability syndrome associated with hypergonadotropic hypogonadism and short stature, much like the *XRCC4* phenotype [155]. Gonadal failure appears to be a consistent finding in a number of these DNA damage repair syndromes. Insulin resistance is also a common feature, but the precise mechanism linking it to DNA damage repair is yet to be determined. Additional forms of syndromic short stature can be caused by mutations in other DNA repair genes encoding DNA helicases and other enzymes important for DNA nucleotide excision repair and DNA cross-link repair (Table 1).

Defect in Cell Proliferation and Other Fundamental Processes

IMAGe syndrome, originally defined as an association of intrauterine growth restriction, metaphyseal dysplasia, congenital adrenal hypoplasia, and genital anomalies, has recently been shown to be caused by “gain-of-function” mutations in the proliferating cell nuclear antigen-binding domain of the paternally imprinted cyclin-dependent kinase inhibitor 1C gene (*CDKN1C*) resulting in decreased proliferation [156, 157]. Interestingly, silencing mutations in the same gene can cause *Beckwith-Wiedemann syndrome*, an overgrowth syndrome [158].

Majewski/microcephalic “osteodysplastic” primordial dwarfism presents with generalized bony anomalies (“osteodysplastic”), and patients reach the average length of a newborn by the age of 3 or 5 years [77]. Microcephalic “osteodysplastic” primordial dwarfism type 1 is caused by mutations in the *RNU-4ATAC* gene, which impairs its role in splicing a small subset of introns present in approximately 700 human genes that encode proteins with a diverse range of functions, including those involved in DNA replication and repair, transcription, RNA processing, and translation [159].

Similarly, defects of the prereplication complex cause *Meier-Gorlin syndrome*, which is due to mutations in 1 of several genes (*ORC1*, *ORC4*, *ORC6*, *CDT1*, and *CDC6*) that governs production of the proteins in the prereplication complex [160, 161]. Interestingly, in this syndrome, tissues are disproportionately reduced in size, most readily apparent in the ears and patellae [161]. *3-M syndrome*, characterized by severe pre- and postnatal growth retardation, characteristic facies, normal intelligence, and skeletal abnormalities, is caused by mutations in 1 of 3 genes, *CUL7*, *OBSL1*, and *CCDC8*, all core components of the 3M complex and required to regulate microtubule dynamics and genome integrity [162, 163].

In addition, impairment of other fundamental cellular processes, including centrosome/microtubule and cytoskeleton structure, chromatin remodeling, genome stability, and steroid biosynthesis, results in a large range of syndromic short stature, some of which are listed in Table 1.

Conclusions and Future Implications

Advances in genetic technologies allow for unbiased approaches to polygenic traits, as well as rare monogenic conditions, and have advanced the understanding of the genetic regulation of the growth plate and longitudinal bone growth [1]. These studies also point towards a new level of complexity in growth plate regulation, suggesting that genes from a multitude of different signaling pathways and cellular functions are involved.

Recent reports have highlighted that mutations in the same gene, e.g., *SHOX*, *NPR2*, *ACAN*, *IGF1*, *IGF1R*, and *FGFR3*, can cause a wide phenotypic spectrum, from skeletal dysplasias to isolated short stature, without any other characteristic features. With increasing use of genetic testing in children with growth failure, the number of children who receive the unhelpful diagnosis of idiopathic short stature will hopefully decrease. This testing includes conventional chromosome analysis and microarray analysis, to sequencing of single genes, sequencing of a panel of genes, or to exome sequencing [164]. For some disorders, identifying the causative genetic defect will enable lifestyle modifications, close follow-up to anticipate detect complications early. Moreover, identifying the genetic causes of growth failure is the first step toward the development of specific treatments tailored to the underlying pathogenic mechanisms.

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