

# Genetics of Short Stature

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## KEYWORDS

- Short stature • Genetic causes • Growth plate • Genome-wide association study • Exome sequencing

## KEY POINTS

- Over the past decades, advances in clinical genetics, including exome sequencing, have accelerated the identification of new genetic growth disorders and thereby greatly contributed to the understanding of the underlying molecular mechanisms of longitudinal bone growth and growth failure.
- This new knowledge will help the individual patient seeking medical attention due to severe short stature, as it will improve the chances of an exact **mechanistic diagnosis**, which in turn enables individualized diagnosis/management, prognostic accuracy, and better genetic counseling and may also help avoid unnecessary testing for endocrine and other disorders.
- As more genetic causes become identified, better classifications of growth disorders will become possible.

## INTRODUCTION

Short stature is a common medical concern that pediatricians and pediatric endocrinologists often evaluate in their daily practice because poor growth may be a symptom of an underlying, treatable medical condition.<sup>1</sup> Linear growth is the result of

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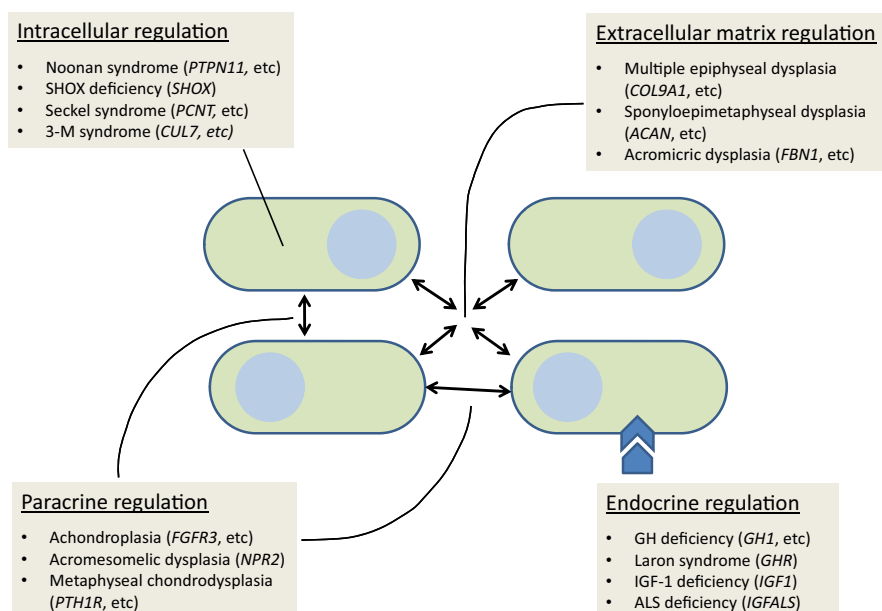
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chondrogenesis at the growth plate and all forms of short stature are therefore due to decreased **chondrogenesis at the growth plates**.<sup>2</sup> Growth plate chondrogenesis and therefore linear growth are regulated by multiple systemic factors, including nutritional intake, hormones, and inflammatory cytokines.<sup>3</sup> Consequently, systemic diseases, such as **hypothyroidism**, **celiac disease**, and other **chronic disorders impair** childhood growth. In addition, growth plate chondrogenesis is regulated by multiple local factors, including **intracellular regulatory mechanisms** in the growth plate chondrocytes, cartilage **extracellular matrix components**, and **paracrine factors** in the growth plate. As a result, **genetic defects** in these local growth plate systems can also **result in short stature** (Fig. 1).

Height variation within the normal range involves similar mechanisms. In 2010, a genome-wide association (GWA) study revealed 180 loci that explain approximately 10% of height variation<sup>4</sup> and a more recent GWA study identified approximately 400 loci that are associated with adult height in the general population.<sup>5</sup> It is likely that many children have mild short stature because they have inherited multiple polymorphisms, each of which tends to slightly inhibit growth plate chondrogenesis and in fact, the loci implicated by GWA studies are shown enriched in genes that are expressed and important for growth plate function.<sup>4-6</sup> Taken together, these findings suggest that **normal growth is modulated by several hundred or maybe even thousands of genes that affect growth plate function**. Therefore, **polymorphism and mild mutations in** these identified genes may modulate height within the **normal range** and perhaps cause **mild polygenic short stature**, whereas mutations with a stronger effect on protein function and/or biallelic mutations may cause significant monogenic short stature or skeletal dysplasias.



**Fig. 1.** Molecular mechanisms of short stature. Short stature is caused by multiple molecular defects, including intracellular signaling, extracellular matrix, and paracrine and endocrine regulation. Ovoid shapes represent growth plate chondrocytes. Arrows indicate mechanisms regulating chondrocytes. Examples of clinical syndrome and the genetic cause under different molecular mechanisms are shown in each box.

The high-throughput sequencing and bioinformatics approaches have enabled identification of genetic causes for many human disorders.<sup>7,8</sup> In particular, exome sequencing has been successfully applied to reveal genetic variants responsible for unknown causes of rare diseases.<sup>7,8</sup> Consequently, **exome sequencing** has become a powerful research tool to identify the etiology of disorders with a monogenic pattern of inheritance. Using this approach, an increasing number of **monogenic causes of growth disorders are being identified, thereby gradually diminishing the number** of children who **receive the unhelpful diagnosis** of “idiopathic” short stature. The GWA studies on height variation as well as the expanding genetic diagnoses of growth disorders indicate that childhood growth disorders are **highly genetically heterogeneous**<sup>1,2</sup> and that **a large fraction of the genes important for growth are involved in cellular processes** previously not implicated in regulation of growth. **These findings will likely affect the way we diagnose childhood growth disorders.** Previously, the approach to short stature was primarily focused on clinical manifestations; for example, primordial dwarfism, syndromic short stature, or skeletal dysplasia to categorize them by similar clinical features. Currently, the combination of the clinical approach and improved genetic diagnosis is advancing our understanding of genetic growth disorders and has helped to further widen the understanding of the clinical variability and genetic heterogeneity of short stature syndromes.

Identifying and understanding the genetic basis of short stature will have significant impact on the care of children seeking medical attention for severe short stature. An **accurate genetic diagnosis** will guide management and help limit unnecessary testing, recognize associated health risks, enable proper genetic counseling, and improve basic understanding of skeletal development and growth and may eventually lead to the development of new treatment approaches.<sup>1,2</sup> Therefore, we here review genetic causes of growth disorders by the molecular mechanisms (see **Fig. 1; Table 1**), emphasizing recently discovered causes of childhood growth disorders.

## GENETICS OF SHORT STATURE

### **Defects in Intracellular Pathways**

Mutations causing loss-of-function or gain-of-function of proteins important for fundamental cellular processes often result in severe short stature with or without an obvious skeletal dysplasia. The mutations also may be associated with **microcephaly, intellectual disability, distinctive facial features,** or other clinical abnormalities (see **Table 1**).

### **Intracellular signaling pathways**

Depending on the pathway affected, defects in intracellular signaling cause a wide spectrum in the degree of growth failure, as well as in the conditions associated with each defect. The intracellular defects are highly heterogeneous, such as the RAS (rat sarcoma)-MAPK (mitogen-activated protein kinase) pathway,<sup>9–20</sup> guanine nucleotide exchange factor,<sup>21–23</sup> cyclic AMP (cAMP)-dependent regulatory subunit of protein kinase A,<sup>24</sup> and other signaling proteins.<sup>25–32</sup> Especially, altered RAS-MAPK signaling has been identified as a key pathway in regulation of growth plate chondrogenesis and is affected in several disorders, referred to as RASopathies.<sup>33</sup> These conditions include Coffin-Lowry syndrome,<sup>9,10</sup> Costello (faciocardioskeletal syndrome),<sup>11</sup> multiple lentigines syndrome (LEOPARD syndrome),<sup>12–16</sup> neurofibromatosis type 1,<sup>17,18</sup> and **Noonan syndrome** or **Noonan-like syndrome.**<sup>1,19,20</sup> Patients with these disorders have overlapping phenotypes of short stature, skin manifestation, cardiovascular abnormalities, and variable degree of learning disability/cognitive dysfunction and/or predisposition to cancers. RAS cycles between a guanosine

**Table 1**  
**Genetics of short stature**

Genes	Function	Disorder	Key Clinical Features	<sup>a</sup> GWA List
1. Defects in intracellular pathways				
Intracellular signaling pathways				
<i>FGD1</i>	Guanine nucleotide exchange factor	Aarskog-Scott (faciogenital dysplasia)	IUGR, hypertelorism, ptosis, everted lower lip vermilion, joint hyperextension, finger abnormalities, shawl scrotum <sup>21–23</sup>	No
<i>PRKAR1A</i>	cAMP-dependent regulatory subunit of protein kinase A	Acrodysostosis, type 1	IUGR, skeletal dysplasia, severe brachydactyly, facial dysostosis, nasal hypoplasia, advanced bone age, obesity, hormone resistance <sup>24</sup>	No
<i>PDE4D</i>	cAMP-specific 3', 5'-cyclic phosphodiesterase 4D	Acrodysostosis, type 2	IUGR (variable), skeletal dysplasia, accelerated bone age progression, variable hormone resistance <sup>25</sup>	No
<i>GNAS</i>	G protein alpha subunit	Albright hereditary osteodystrophy	IUGR, obesity, round-shaped face, subcutaneous ossifications and brachymetacarpal bone (4th and 5th) <sup>26–28</sup>	Yes
<i>RPS6KA3</i>	Serine/threonine kinase in RAS-MAPK pathway	Coffin-Lowry syndrome	No IUGR, microcephaly, facial dysmorphism, skeletal abnormalities, intellectual disability, hypotonia, X-linked disorder <sup>9,10</sup>	No
<i>HRAS</i>	Signal transduction with GTPase activity in RAS-MAPK pathway	Costello (faciocutaneouskeletal syndrome)	No IUGR, delayed development, intellectual disability, distinctive facial features, loose folds of extra skin (especially, hands and feet), flexible joints <sup>11</sup>	No
<i>PTPN11, RAF1, BRAF</i>	Protein-tyrosine phosphatase/RAS-MAPK regulation	Multiple lentiginos syndrome (LEOPARD syndrome)	No IUGR, lentiginos, hypertrophic myopathy, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormalities of genitalia, sensorineural deafness <sup>12–16</sup>	Yes ( <i>RAF1</i> )

<i>NF1</i>	RAS signal transduction	Neurofibromatosis type 1	No IUGR, cafe-au-lait spot, malignancy (pheochromocytoma and gastrointestinal stromal tumor), Lisch nodules, osteoporosis <sup>17,18</sup>	No
<i>PTPN11, BRAF, SOS1, KRAS, RAF1, NRAS, RASA2, SHOC2, CBL, RIT1 (activating)</i>	Protein-tyrosine phosphatase/RAS-MAPK regulation	Noonan syndrome or Noonan-like syndrome	No IUGR, distinctive facial appearance, a broad or webbed neck, congenital heart defects, coagulopathy, skeletal malformations, developmental delay <sup>11,19,20</sup>	Yes ( <i>RAF1</i> )
<i>ROR2, WNT5A, DVL1</i>	Cell surface receptor, secreted signaling protein	Robinow syndrome (acral dysostosis with facial and genital abnormalities)	IUGR (variable), short-limb dwarfism, costovertebral segmentation defects, abnormalities of head, face and external genitalia, chest deformities, rib fusions, scoliosis, brachydactyly, aplasia/hypoplasia of the phalanges and metacarpal/metatarsal bones <sup>29–32</sup>	Yes ( <i>WNT5A</i> )
Transcriptional regulation				
<i>LARP7</i>	Transcriptional regulator of polymerase II genes	Alazami syndrome	IUGR (variable), facial dysmorphism (triangular face), intellectual disability, tendon or skeletal abnormalities <sup>48,49</sup>	No
<i>SOX9</i>	Chondrocyte differentiation factor	Campomelic dysplasia	IUGR, born with bowing of the long bones, short legs, dislocated hips, ambiguous genitalia, distinctive facial features <sup>39–41</sup>	Yes
<i>BRF1</i>	RNA polymerase III transcription initiation factor	Cerebello-facio-dental syndrome	IUGR, facial dysmorphism, hypoplastic cerebellum, markedly delayed bone age <sup>50,150</sup>	No
<i>SOX11</i>	Transcriptional regulation of GDF5	Coffin-Siris syndrome	IUGR (variable), mental retardation, facial dysmorphism, hearing or vision impairment, severe scoliosis <sup>51</sup>	No

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**Table 1**  
(continued)

Genes	Function	Disorder	Key Clinical Features	<sup>a</sup> GWA List
<i>MLL2 (KMT2D), KDM6A</i>	Histone methyltransferase/ Histone demethylase	Kabuki syndrome	IUGR (variable), facial features that resemble the make-up worn by actors of Kabuki (long eye openings slanting upwards, arched eyebrows, prominent ears, and corners of the mouth turning downward), mild to moderate intellectual disability, problems involving heart, skeleton, teeth, and immune system <sup>45-47</sup>	No
<i>ANKRD11</i>	Transcription regulator	KBG syndrome	IUGR (variable), facial dysmorphism, hearing loss, congenital heart defect, skeletal anomalies, global developmental delay, seizures, intellectual disability <sup>52,53</sup>	No
<i>SHOX</i>	Transcription factor	Leri-Weill dyschondrosteosis, mesomelic dysplasia (Langer type)	No IUGR, skeletal dysplasia, Madelung deformity <sup>42-44</sup>	No
<i>CREBBP, EP300</i>	Transcriptional coactivator	Rubinstein-Taybi syndrome	IUGR (variable), facial dysmorphism, moderate to severe intellectual disability, broad thumbs and first toes <sup>54,55</sup>	Yes ( <i>CREBBP</i> )
DNA repair				
<i>BLM</i>	DNA repair enzyme	Bloom syndrome	IUGR (as case report), increased risk of cancer, sun-sensitive skin changes on face, hands and/or arms, a high-pitched voice, distinctive facial features, including a long, narrow face, small lower jaw, large nose, and prominent ears <sup>72,73</sup>	No
<i>ERCC6, ERCC8</i>	DNA repair	Cockayne syndrome	IUGR (variable), microcephaly, photosensitivity progeroid appearance, progressive pigmentary retinopathy, sensorineural deafness <sup>74,75</sup>	No
<i>FANCA, FANCC, FANCG</i>	DNA repair	Fanconi anemia	IUGR, absence of thumb, hyperpigmentation, early-onset bone marrow failure, predisposition to cancers <sup>56</sup>	Yes ( <i>FANCA</i> )
<i>LIG4</i>	DNA repair	LIG 4 syndrome	No IUGR, distinctive facial features, microcephaly, pancytopenia, various skin abnormalities, immune deficiency <sup>69</sup>	No

<i>NSMCE2</i>	DNA repair	Microcephalic primordial dwarfism-insulin resistance syndrome	No IUGR reported, microcephaly, insulin resistance <sup>76</sup>	No
<i>NBN (NBS1)</i>	DNA repair	Nijmegen breakage syndrome	No IUGR, microcephaly, distinctive facial features, immunodeficiency, and cancer predisposition <sup>70,71</sup>	No
<i>SMARCA1</i>	DNA repair	Schimke immunoosseous dysplasia	IUGR, kidney disease, immune deficiency, stroke, bone marrow failure, kidney failure <sup>77</sup>	No
<i>ATR, ATRIP, CENPJ, CEP152, CEP63, DNA2, PCNT, PLK4, RBBP8, XRCC4</i>	DNA repair, centrosome maintenance, DNA stability	Seckel syndrome	IUGR, microcephaly, beaklike protrusion of nose, facial dysmorphism <sup>56-66</sup>	Yes ( <i>DNA2</i> )
Other fundamental cellular processes				
<i>CUL7, OBSL1, CCDC8</i>	Microtubule stabilization and genome stability	3-M syndrome	IUGR, facial dysmorphism (triangular face), relatively large head circumference, prominent fleshy heels <sup>78-80</sup>	No
<i>ALMS1</i>	Microtubule organization	Alström syndrome	No IUGR, vision and hearing abnormalities, childhood obesity, diabetes mellitus, heart disease, and slowly progressive kidney dysfunction <sup>96</sup>	No
<i>SMARCB1, SMARCE1, SMARCA4, ARID1A, ARID1B</i>	Chromatin remodeling	Coffin-Siris syndrome	IUGR (variable), mental retardation, facial dysmorphism, hearing or vision impairment, severe scoliosis <sup>89</sup>	Yes ( <i>ARD1B</i> )
<i>NIPBL (50%), SMC1A, HDAC8, RAD21, SMC3</i>	Cohesin pathway (sister chromatid cohesion)	Cornelia de Lange syndrome	IUGR, dysmorphic facial features (facial hirsutism), microcephaly, limb reduction defects, cardiac defect, and intellectual disability <sup>81</sup>	Yes ( <i>NIPBL</i> )

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**Table 1**  
*(continued)*

Genes	Function	Disorder	Key Clinical Features	<sup>a</sup> GWA List
<i>SRCAP</i>	Chromatin remodeling	Floating-Harbor syndrome	IUGR (variable), facial dysmorphism, abnormal thumb, delayed bone age, early puberty, delay in expressive language <sup>86-88</sup>	No
<i>LMNA</i>	Nuclear stability	Hutchinson-Gilford Progeria	No IUGR, failure to thrive, distinctive facial features (aged-looking skin), alopecia, loss of subcutaneous fat, joint abnormalities <sup>82,83</sup>	No
<i>RNU4ATAC</i>	Minor intron splicing	MOPD I	IUGR, microcephaly, dysmorphic face, skin and skeletal abnormalities, developmental delay <sup>90,91</sup>	No
<i>PCNT</i>	Mitotic spindle/chromosome segregation	MOPD II	IUGR, facial dysmorphism, microcephaly, near normal intelligence, cancer susceptibility <sup>67,68</sup>	No
<i>TRIM37</i>	Peroxisomal protein, possibly ubiquitin-dependent degradation	Mulibrey nanism	IUGR, dysmorphic craniofacial features, heart disease (constrictive pericardium), hepatomegaly, Wilms tumor <sup>92-94</sup>	No
<i>CRIP1</i>	Interaction with cytoskeleton	Primordial dwarfism	IUGR (not established), facial dysmorphism, microcephaly, ophthalmologic abnormalities, intellectual disabilities, skeletal abnormalities, pigmentation abnormalities <sup>95</sup>	No
<i>POC1A</i>	Centriole assembly/ciliogenesis	SOFT syndrome	IUGR, disproportionate short stature, onychodysplasia, facial dysmorphism, and hypotrichosis <sup>84,85</sup>	No
<i>DHCR7</i>	Steroid biosynthesis	Smith-Lemli-Opitz syndrome	IUGR, distinctive facial features, microcephaly, intellectual disability or learning problems, behavioral problems, and malformations of heart, lungs, kidneys, gastrointestinal tract, and genitalia <sup>97</sup>	No



## 2. Defects in cartilage extracellular matrix

<i>COL2A1</i>	Extracellular matrix, collagen	Achondrogenesis (Type II), hypochondrogenesis, Kniest dysplasia, Spondylo-epiphyseal dysplasia congenita, Stickler syndrome type 1	IUGR, skeletal abnormalities and problems with vision and hearing <sup>101,102</sup>	No
<i>FBN1</i>	Extracellular matrix, fibrillin 1	Acromicric dysplasia, Geleophysic dysplasia 2	No IUGR, short hands and feet, thickened skin and joint contractures, limited range of motion in fingers, toes, wrists, and elbows, cardiac issue <sup>109</sup>	Yes
<i>COL11A1</i>	Extracellular matrix, collagen 11	Fibrochondrogenesis	IUGR (variable), skeletal dysplasia, broad long bone metaphyses, pear-shaped vertebral bodies, flat midface with a small nose and anteverted nares, significant shortening of all limb segments <sup>103</sup>	Yes
<i>COL10A1</i>	Extracellular matrix, collagen 10	Metaphyseal dysplasia, Schmid type	No IUGR, coxa vara, relatively short limbs, bow legs, waddling gait <sup>104</sup>	No
<i>MATN3, COL9A1, COL9A2, COL9A3</i>	Extracellular matrix, cartilage oligomeric matrix protein, collagen, matrillin-3	Multiple epiphyseal dysplasia	No IUGR, skeletal dysplasia, joint pain, joint deformity, waddling gait <sup>105–108,112</sup>	Yes ( <i>COL9A2</i> )
<i>COMP</i>	Extracellular matrix, cartilage oligomeric matrix protein	Multiple epiphyseal dysplasia, pseudoachondroplasia	No IUGR, short arms and legs, a waddling walk, early-onset joint pain (osteoarthritis), limited range of motion at elbows and hips <sup>110,111</sup>	No
<i>HSPG2</i>	Extracellular matrix, perlecan	Schwartz-Jampel syndrome	IUGR (not established), permanent myotonia (prolonged failure of muscle relaxation), skeletal dysplasia, kyphoscoliosis, bowing of diaphyses and irregular epiphyses <sup>115</sup>	No

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**Table 1**  
*(continued)*

Genes	Function	Disorder	Key Clinical Features	<sup>a</sup> GWA List
<i>ACAN</i>	Extracellular matrix, aggrecan	Spondyloepimetaphyseal dysplasia, aggrecan/Kimberly type	IUGR, macrocephaly, severe midface hypoplasia, short neck, barrel chest, brachydactyly, advanced bone age <sup>113,114</sup>	Yes
<b>3. Defects in paracrine signaling</b>				
<i>FGFR3 (activating)</i>	Fibroblast growth factor receptor	Achondroplasia, hypochondroplasia	IUGR, short upper arms and thighs, limited range of motion at elbows, relative macrocephaly with a prominent forehead, trident hand <sup>119–121</sup>	No
<i>IHH</i>	Secreted signaling molecule, Indian hedgehog	Acrocapitofemoral dysplasia, brachydactyly, type A1	No IUGR, brachydactyly <sup>129</sup>	No
<i>NPR2 (inactivating)</i>	CNP receptor	Acromesomelic dysplasia, Maroteaux type	IUGR (variable), short limbs and hand/foot malformations <sup>126</sup>	Yes
<i>BMPR1B, GDF5</i>	BMP receptor/interacting protein (ligand)	Brachydactyly, type A1 and A2	No IUGR, brachydactyly <sup>135,136</sup>	Yes ( <i>GDF5</i> )
<i>PTHLH</i>	Secreted signaling molecules (PTH-related protein)	Brachydactyly, type E2	No IUGR, shortening of fingers mainly in metacarpals and metatarsals <sup>130,131</sup>	No
<i>IGF2</i>	Secreted signaling molecule (insulinlike growth factor-II)	IGF2 deficiency	IUGR, Silver-Russel like facies <sup>137</sup>	No

<i>PTH1R</i>	PTH and PTHrP receptor	Metaphyseal chondrodysplasia (Jansen type), Eikan dysplasia, chondrodysplasia (Blomstrand type)	No IUGR, skeletal dysplasia, micrognathia, failure of tooth eruption, low-set/posteriorly rotated ears, proptosis <sup>132,133</sup>	No
<b>4. Defects in endocrine ligands, receptors, and signaling pathways</b>				
<i>IGFALS</i>	Acid labile subunit	ALS deficiency	IUGR (variable), low IGF-1 and IGF-BP3 <sup>148,149</sup>	No
<i>GH1, GHRHR, SOX3, BTK</i>	GH production	GH deficiency	No IUGR, GH deficiency <sup>138</sup>	No
<i>IGF1</i>	IGF-1	IGF-1 deficiency	IUGR, microcephaly, mental retardation, low IGF-1 level <sup>143,144</sup>	No
<i>IGF1R</i>	Insulin-like growth factor receptor	IGF-1 insensitivity	IUGR, normal to high IGF-1 level <sup>145-147</sup>	Yes
<i>STAT5B</i>	Growth hormone signaling	Immune deficiency and GH resistance	No IUGR, elevated random GH but low IGF-1 or IGFBP-3, immunodeficiency <sup>142</sup>	No
<i>GHR</i>	Growth hormone receptor	Laron syndrome	IUGR, elevated GH and low IGF-1 <sup>139-141</sup>	No

**Abbreviations:** ALS, acid labile subunit; BMP, bone morphogenetic protein; cAMP, cyclic AMP; CNP, C-type natriuretic peptide; GH, growth hormone; GTP, guanosine triphosphate; GWA, genome-wide association; IGF-1, insulin-like growth factor 1; IUGR, intrauterine growth restriction; MAPK, mitogen-activated protein kinase; MOPD, microcephalic osteodysplastic primordial dwarfism; PTH, parathyroid hormone; PTHrP, PTH-related protein; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma.

<sup>a</sup> 670 height-associated single-nucleotide polymorphisms according to GWA study by Wood et al.<sup>5</sup>

diphosphate-bound form (inactive) and GTP-bound form (active),<sup>34</sup> and RAS-GTP activates a large number of effector pathways facilitating downstream signaling taking an important role in cell proliferation and differentiation.<sup>35,36</sup> Moreover, RAS-MAPK is downstream of fibroblast growth factor (FGF) signaling, which is another major pathway involved in skeletal disease.<sup>37</sup> Some of the conditions caused by defects in the RAS-MAPK pathway carry higher risks of malignancies, including mutations in neurofibromin (*NF1*), RAS, or RAFs.<sup>38</sup> Mutations in *FGD1*, which encodes a protein similar to small GTP-binding proteins, cause Aarskog-Scott syndrome presenting with disproportionate short stature, skeletal and urogenital anomalies.<sup>21–23</sup>

Interestingly, impairment of signaling through the cAMP-protein kinase A also causes skeletal dysplasias with growth failure associated with accelerated bone age progression and/or poor pubertal growth spurts that include Acrodysostosis, type 1 (caused by mutations in *PRKAR1A* that encodes cAMP-dependent protein kinase type I-alpha regulatory subunit<sup>24</sup>), Acrodysostosis, type 2 (caused by mutations in *PDE4D* that encodes cAMP-specific 3', 5'-cyclic phosphodiesterase 4D<sup>25</sup>), and Albright hereditary osteodystrophy (caused by mutations in *GNAS* that encodes guanine nucleotide-binding protein stimulatory G subunit alpha protein<sup>26–28</sup>). Mutations in these genes may not only result in skeletal dysplasias but also variable hormone resistance, thus demonstrating the important role of this pathway both in the regulation of growth plate chondrogenesis and in signaling of the G-protein-coupled hormone receptors.<sup>25</sup> In addition, defects in the *WNT5A/JNK* signaling pathway, including mutations in *ROR2*, *DVL1*, as well as *Wnt5a*, the ligand of *ROR2*, cause skeletal dysplasia and Robinow syndrome, characterized by dysmorphic facial features, frontal bossing, hypertelorism, broad nose, short-limbed dwarfism, vertebral segmentation, and genital hypoplasia.<sup>29–32</sup>

### **Transcriptional regulation**

Mutations in transcriptional factors or genes that are involved in transcription repression can cause short stature. Mutations in *SOX9*, an important transcription factor for sex development and chondrocyte differentiation, cause Campomelic dysplasia, which can cause sex reversal, ambiguous genitalia, chondrodysplasia, and bent bones.<sup>39–41</sup> *SHOX* is another transcription factor that is important in growth plate chondrocytes.<sup>42</sup> Homozygous mutations cause severe short stature in Langer mesomelic dysplasia, whereas heterozygous mutations can present either as a milder skeletal dysplasia, Leri-Weill dyschondrosteosis, or as isolated short stature.<sup>43,44</sup> Mutations in *MLL2* (*KMT2D*) and *KDM6A* cause abnormal histone methylation and demethylation, respectively, resulting in short stature and unique facial features of Kabuki syndrome.<sup>45–47</sup> Mutations in transcriptional regulator of polymerase II genes (*LARP7*) cause Alazami syndrome,<sup>48,49</sup> whereas mutations in the transcription initiator factor for RNA polymerase III (*BRF1*) cause the newly identified cerebello-facio-dental syndrome.<sup>50,150</sup> Mutations in *SOX11* can cause an autosomal dominant mental retardation 27, a form of Coffin-Siris syndrome presenting with relatively mild mental retardation, microcephaly, short stature, and hypoplastic fifth toenails.<sup>51</sup> Similarly, the ankyrin repeat domain-containing protein 11 (*ANKRD11*) interacts with nuclear receptor complexes to modify transcriptional activation, and mutations in this gene cause short stature, developmental delay, and seizures, as well as other features of the KBG syndrome, including macrodontia of the upper central incisors, and skeletal anomalies.<sup>52,53</sup> In addition, heterozygous mutations in transcription coactivators (*CREBBP* and *EP300*) cause Rubinstein-Taybi syndrome, characterized by severe short stature, intellectual disability, microcephaly, hearing loss, broad thumbs/halluces, and distinct facial features.<sup>54,55</sup>

### **DNA repair**

Impairment of DNA repair can result in severe short stature (often primordial dwarfism), microcephaly, photosensitivity, and/or predisposition to leukemia/other cancers. Skeletal abnormalities may not be prominent (see [Table 1](#)). Especially, Seckel syndrome has many subtypes that are caused by mutations in several genes but mostly involved in DNA repair processes.<sup>56–66</sup> Pericentrin (*PCNT*) encodes a centrosomal protein in the microtubule network and the mutations cause microcephalic osteodysplastic primordial dwarfism type 2 (MOPD II), but also Seckel syndrome.<sup>66</sup> Moreover, clinical overlaps may occur among Seckel syndrome,<sup>56,66</sup> MOPD II,<sup>56,66–68</sup> Fanconi anemia (*FANC*),<sup>56</sup> LIG4 syndrome (*LIG4*),<sup>56,69</sup> and Nijmegen breakage syndrome (*NBS1*).<sup>56,70,71</sup> Mutations in *BLM* cause Bloom syndrome, which manifests as sun-sensitive skin and increased risk of malignancies, including leukemia, lymphoma, adenocarcinoma, and squamous cell carcinoma.<sup>72,73</sup> Due to the increased risk of malignancy, growth hormone treatment in children with Bloom syndrome is not recommended.<sup>73</sup> Impaired DNA repair mechanisms may also cause short stature and microcephaly without an increased risk of malignancies. For example, no cancer predisposition has been demonstrated for Cockayne syndrome.<sup>74,75</sup> In addition, recent reports show that heterozygous mutation in *NSMCE2* causes microcephalic primordial dwarfism with severe insulin resistance<sup>76</sup> and homozygous mutation in *SMARCAL1* causes Schimke immuno-osseous dysplasia, characterized by severe growth restriction, immune deficiency, and renal and bone marrow failure,<sup>77</sup> but no known increased risk of malignancies.

### **Other fundamental cellular processes**

This group of syndromes can be caused by mutations in genes important for genome or nuclear stability (3M syndrome,<sup>78–80</sup> Cornelia de Lange syndrome,<sup>81</sup> Hutchinson-Gilford Progeria,<sup>82,83</sup> MOPD II,<sup>67,68</sup> SOFT syndrome<sup>84,85</sup>), chromatin remodeling (Floating-Harbor syndrome,<sup>86–88</sup> Coffin-Siris syndrome<sup>89</sup>), RNA processing (microcephalic osteodysplastic primordial dwarfism type 1, MOPD I<sup>90,91</sup>), ubiquitination (Mulibrey nanism<sup>92–94</sup>), cytoskeletal interaction (primordial dwarfism due to *CRIP1* mutation<sup>95</sup>), microtubule organization (Alström syndrome<sup>96</sup>), or cholesterol biosynthesis (Smith-Lemli-Opitz syndrome<sup>97</sup>) (see [Table 1](#)). The patients are often born small for gestational age indicating that growth is affected during intrauterine life. Interestingly, although the molecular mechanisms are different, the clinical phenotype may have significant overlap. For example, Cornelia de Lange syndrome caused by mutation in the *NIPBL* has similar features with Rubinstein-Taybi syndrome caused by *EP300*,<sup>98</sup> although their molecular mechanisms are different.

### **Defects in Cartilage Extracellular Matrix Defect**

Growth plate chondrocytes also secrete a characteristic extracellular matrix rich in collagens and proteoglycans that are critical to maintain structure and function of the growth plate.<sup>99</sup> The extracellular matrix does not only provide support, but also interacts with paracrine signaling molecules regulating chondrocyte proliferation and differentiation.<sup>99,100</sup> Therefore, mutations in genes that encode matrix collagens, proteoglycans, noncollagenous proteins, and their processing enzymes affect growth plate chondrogenesis by several mechanisms and cause growth failure with a wide phenotypic spectrum (see [Table 1](#)). For example, mutations in collagens,<sup>101–108</sup> fibrillin 1,<sup>109</sup> cartilage oligomeric matrix protein,<sup>110,111</sup> matrilin-3,<sup>112</sup> aggrecan,<sup>113,114</sup> and perlecan<sup>115</sup> have been reported to cause short stature of variable severity. Mutations in genes encoding extracellular matrix proteins also may affect connective tissue beyond the growth plate, causing various degrees of skeletal and joint problems, as well as some conditions with low bone mineral density (see [Table 1](#)).

### **Abnormal Paracrine Signaling**

In the growth plate, paracrine factors coordinate sequential changes in chondrocyte morphology, proliferation, differentiation, and matrix assembly.<sup>116</sup> The understanding of the paracrine mechanisms acting in the growth plate has advanced substantially during the past decade. Some of the identified factors include FGFs, C-type natriuretic peptide (CNP), Indian hedgehog (IHH), parathyroid hormone–related protein (PTHrP) encoded by *PTH1R*, and bone morphogenetic factors (BMPs). FGF receptor-3 (*FGFR3*) signals through several pathways, including the MAPK and JAK/STAT pathways, and acts as a negative regulator of growth plate chondrogenesis.<sup>117,118</sup> Consequently, activating mutations in *FGFR3* result in inhibition of growth,<sup>119</sup> 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 perinatal lethal skeletal dysplasia with very short limbs and underdeveloped ribs.<sup>120</sup> In addition, several families with autosomal dominant proportionate short stature were recently reported to have mild activating mutations of *FGFR3*, further expanding the phenotype.<sup>121</sup> Interestingly, both heterozygous and homozygous inactivating mutations in *FGFR3* have been reported in patients with a tall stature syndrome, including scoliosis, camptodactyly, and hearing loss.<sup>122,123</sup>

Despite its name, CNP acts as an important paracrine factor in the growth plate. Homozygous knockout of CNP causes dwarfism in mice.<sup>124</sup> In humans, overexpression of CNP results in overgrowth,<sup>125</sup> whereas homozygous inactivating mutations of its receptor, *NPR2*, cause a skeletal dysplasia with short stature and heterozygous inactivating mutations present as isolated short stature.<sup>126</sup> Conversely, activating mutation in *NPR2* can cause tall stature.<sup>127</sup> CNP inhibits MAPK signaling and thus antagonizes *FGFR3* signaling, and has therefore been proposed as a potential treatment for achondroplasia.<sup>128</sup>

PTHrP and IHH form a negative feedback loop critical to the spatial coordination of proliferation and differentiation of growth plate chondrocytes.<sup>116</sup> Consequently, mutations in the genes for IHH,<sup>129</sup> PTHrP,<sup>130,131</sup> and PTH1R (the receptor for both PTH and PTHrP),<sup>132,133</sup> as well as mutations in their signaling pathway cause specific skeletal dysplasias. Disorders of linear growth also can result from genetic defects in other paracrine signaling systems. For example, BMP signaling is important for endochondral ossification and growth plate regulation,<sup>134</sup> and defects in BMP family members or the receptors cause skeletal dysplasia,<sup>135,136</sup> characterized by brachydactyly. Mutation in *IGF2*, which encodes insulinlike growth factor-II, a paracrine factor that is important for intrauterine growth, was recently reported to cause prenatal and postnatal growth failure.<sup>137</sup>

### **Abnormal Hormone, Receptor, or Signaling Pathway**

Growth hormone (GH) plays a major role in childhood growth and has, especially since the development of recombinant GH, been the main therapeutic approach available to treat patients with short stature. It is therefore common that children presenting with sub-optimal growth are subjected to clinical testing for GH deficiency or resistance even though true GH deficiency or resistance is a rare cause of short stature.<sup>2</sup> Patients with mutations in *GH1*, *GHRHR*, *SOX3*, and *BTK* present with isolated GH deficiency.<sup>138</sup> On the other hand, mutations in *GHR*<sup>139–141</sup> and *STAT5B*<sup>142</sup> cause GH resistance. *GHR* encodes the growth hormone receptor. Because an extracellular cleavage fragment of the GH receptor circulates as a growth hormone binding protein (GHBP), mutations in the extracellular domain of *GHR* tend to cause low GHBP, whereas mutations in

intracellular (signaling) domain cause normal or high GHBP.<sup>139–141</sup> STAT5 proteins contribute to the common pathway of GH and interleukin-2 cytokine family signaling; therefore, mutations in *STAT5B* cause growth failure and immune deficiency.<sup>142</sup> Mutations in *IGF1* or *IGF1R* cause intrauterine growth restriction (because IGF-1 signaling is important for intrauterine growth, whereas GH is not required), postnatal growth failure, microcephaly, and other various anomalies, including developmental delay.<sup>143–147</sup> Mutations in a gene that stabilizes IGF-1, *IGFALS*, forming an IGF-1-IGFBP3-ALS complex, cause growth deficiency, insulin resistance, and osteoporosis.<sup>148,149</sup>

### MUTATIONS IN THE SAME GENE MAY CAUSE A WIDE PHENOTYPIC SPECTRUM

For many genes that support growth plate chondrogenesis, homozygous and/or severe mutations cause bones to be markedly short and malformed, presenting clinically as a chondrodysplasia, whereas heterozygous and/or milder mutations may cause “isolated” short stature, with no or only subtle signs of a skeletal dysplasia. For example, *SHOX*,<sup>43</sup> *NPR2*,<sup>125</sup> *ACAN*,<sup>114</sup> *IGF1*,<sup>143</sup> *IGF1R*,<sup>146</sup> or *FGFR3*<sup>120</sup> have been associated with “isolated” short stature without other prominent phenotypic features. There are likely numerous genetic causes still remaining to be discovered to fully explain the molecular mechanism of “isolated” growth disorders. It is likely that there soon will be a large number of genetically characterized monogenic short stature syndromes with no or only minor associated abnormalities. A suitable term for this group of patients would be “isolated” short stature.

### SUMMARY AND FUTURE CONSIDERATIONS

Over the past decades, advances in clinical genetics, including exome sequencing, have accelerated the identification of new genetic growth disorders and thereby greatly contributed to the understanding of the underlying molecular mechanisms of longitudinal bone growth and growth failure. This new knowledge will help the individual patient seeking medical attention due to **severe short stature**, as it will improve the chances of **an exact mechanistic diagnosis**, which in turn enables **individualized management**, improved prognosis, and better genetic counseling, and may also help avoid unnecessary testing for endocrine and other disorders. As more genetic causes become identified, **better classifications** of growth disorders become possible. Fewer children will receive the unhelpful diagnosis of “idiopathic” short stature, and instead will be categorized clinically as having a skeletal dysplasia, syndromic short stature, or isolated short stature, will be **categorized genetically** as having polygenic or monogenic short stature, and will be categorized mechanistically depending on how their specific genetic defects diminish growth plate chondrogenesis and therefore linear growth.

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