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Advances in Skeletal Dysplasia Genetics

Krista A. Geister[2] and **Sally A. Camper**[1,2]

[1]Department of Human Genetics, University of Michigan, Ann Arbor, Michigan 48109

[2]Graduate Program in Cell and Molecular Biology, University of Michigan, Ann Arbor, Michigan 48109

Abstract

Skeletal dysplasias result from disruptions in normal skeletal growth and development and are a major contributor to severe short stature. They occur in approximately 1/5,000 births, and some are lethal. Since the most recent publication of the Nosology and Classification of Genetic Skeletal Disorders, genetic causes of 56 skeletal disorders have been uncovered. This remarkable rate of discovery is largely due to the expanded use of high-throughput genomic technologies. In this review, we discuss these recent discoveries and our understanding of the molecular mechanisms behind these skeletal dysplasia phenotypes. We also cover potential therapies, unusual genetic mechanisms, and novel skeletal syndromes both with and without known genetic causes. The acceleration of skeletal dysplasia genetics is truly spectacular, and these advances hold great promise for diagnostics, risk prediction, and therapeutic design.

Keywords

Growth insufficiency; mosaicism; imprinting; primordial dwarfism; ciliopathy; epigenetics

INTRODUCTION

This review provides background information on skeletal development and a historical perspective on skeletal dysplasia genetics. Skeletal dysplasias are a vast area of investigation, and owing to space constraints, we focus mainly on selected recent genetic discoveries that illustrate the genetic heterogeneity and diversity of processes that affect skeletal development. We present disorders with unique forms of inheritance, such as mutations in imprinted genes and somatic mosaicism for deleterious mutations. We discuss mutations that affect epigenetic programming and the potential role of microRNAs (miRNAs) in severe short stature. Primordial dwarfisms and skeletal ciliopathies receive considerable attention because of the rapid rate at which their causative mutations and molecular mechanisms are being uncovered. Each of these cases highlights how these discoveries are adding to our understanding of the pathology of skeletal dysplasias and the fundamentals of normal skeletal growth and development.

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OVERVIEW OF EARLY SKELETAL DEVELOPMENT AND ENDOCHONDRAL OSSIFICATION

The bones of the skeleton are formed through two processes: intramembranous ossification and endochondral ossification. Both of these developmental programs begin with the condensation of mesenchymal cells in areas of the body where a skeletal element will eventually form (67, 71, 73). The condensations that will form the cranium and parts of the clavicle and pubic bone undergo intramembranous ossification, in which mesenchymal cells differentiate directly into osteoblasts that transform the condensation into true bone tissue.

The bones of the body that form through endochondral ossification are the main determinants of final stature (71). Early on, the mesenchymal cells of the condensation differentiate into chondrocytes instead of osteoblasts. These intermediary chondrocytes proliferate and undergo terminal hypertrophic differentiation, which directs the addition of mature bone tissue (67, 71, 73). The progressive mineralization and maturation of the cartilage template occur along its length and at either end. As this new element takes on more characteristics of a true bone, undifferentiated chondrocytes become sealed within either end of the forming element. These pools of chondrocytes are known as the epiphyseal growth plates.

The growth plate is a highly organized tissue. It is composed of three distinct zones—the resting zone, the proliferative zone, and the hypertrophic zone—followed by the ossification front (67, 71, 73, 119) (Figure 1). Lesser-differentiated cells in the resting zone enter the proliferative zone, where they divide perpendicular to the plane of the growth plate, intercalate over each other, and form pillars of discoid chondrocytes (73, 84, 119, 132). Eventually, the cells receive signals that promote their differentiation into hypertrophic chondrocytes, leading to a tremendous increase in cell volume. Until recently, it was thought that the primary method for deposition of bone matrix involved chondrocyte cell cycle exit followed by cell death, concomitant with recruitment of osteoblasts to remodel the hypertrophic scaffold. New studies have shown that chondrocytes differentiate into osteoblasts during their terminal differentiation and contribute to the addition of mature bone matrix (155a, 155b, 158a). Regulation of chondrocyte proliferation, differentiation, transdifferentiation into osteoblasts, and mineralization controls the growth of each skeletal element and of the individual.

CELLULAR PROCESSES THAT CONTRIUTE TO NORMAL SKELETAL GROWTH AND SKELTAL DYSPLASIA

Several signaling pathways are known to regulate chondrocyte transition through the growth plate (Figure 1). Indian Hedgehog (IHH), parathyroid hormone–related peptide (PTHrP), fibroblast growth factor (FGF), C-type natriuretic peptide (CNP), TGF-β, bone morphogenetic protein (BMP), Notch, and WNT (canonical and noncanonical) signaling pathways all aid and guide chondrocytes through the growth plate and regulate functions in the perichondrium/periosteum (9, 67, 73) (Figure 1). The functions of these signaling pathways in growth, patterning, and mineralization are illustrated in Figure 1 and have been

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reviewed extensively (9, 67, 73). Here, we discuss selected recent genetic discoveries in signal transduction.

Figure 1 also highlights the direction of cell division as chondrocytes progress from the resting zone to the proliferative zone (arrows in Figure 1). In the resting zone, chondrocytes divide in roughly any orientation (84), with division occurring along the long axis of the cell (118a). Once the chondrocytes are in the proliferative zone, division occurs perpendicular to the direction of longitudinal growth, followed by chondrocyte rotation to form an ordered columnar array of cells (84). Recent work has demonstrated a requirement for noncanonical WNT signaling (84), likely through the planar-cell polarity (PCP) pathway (43a, 118a, 147a), and the appearance of a cadherin- and β-catenin-based cell adhesion surface between daughter cells (118a) for column formation. Following cell division, daughter cells remain closely associated and use the adhesion-laden surface to spread over one another (118a). The primary cilium also plays a role in regulating growth plate architecture, as defective intraflagellar transport through conditional loss of the gene encoding motor protein *Kif3a* leads to disordered columns in the mouse (132). The connection between the primary cilium and canonical and noncanonical WNT signaling pathways are currently mired in controversy (12a, 45a; reviewed extensively in 147). However, it is intriguing that both the primary cilium and the PCP pathway appear to be required for proper column formation. Future work on the growth plate will clarify the nature of the connection between these two regulators of growth plate architecture, if it exists.

Cell adhesion, a critical regulator of column formation (118a)], and the composition of the extracellular matrix can be directly affected by a defect in intracellular trafficking (139b). This process involves the endoplasmic reticulum, Golgi apparatus, and secretory vesicles. Without proper trafficking of extracellular matrix and cell adhesion components, as well as ligands for critical signaling pathways, the function of the growth plate can be profoundly compromised. Often, the result is profound endoplasmic reticulum stress, which is a common pathogenic mechanism in disorders of the skeleton, including osteogenesis imperfecta (87a, 105a, 116a, 136a).

THE SKELETAL DYSPLASIAS

The term skeletal dysplasia is typically used to describe bone and cartilage disorders that cause dwarfism, but this set of disorders is highly diverse and also includes overgrowth syndromes. Numerous genetic mutations have the ability to disrupt the organization and function of the growth plate (9, 59, 67, 71, 149). Studies in humans and mice have identified many genes, including those that disrupt the processes discussed in the section above (Figure 1) that can profoundly affect the growth of the individual, preventing achievement of adult height that is normal for age, ethnicity, and sex.

There are more than 400 skeletal dysplasias documented in the medical literature (149). They are predicted to occur in approximately 1/5,000 children (71) and can range from relatively mild anomalies to lethality. Most lethal forms of skeletal dysplasia result from thoracic hypoplasia, where the rib cage is not large enough to permit proper lung development (34). In such cases, the infant dies of respiratory distress soon after birth.

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Many forms of skeletal dysplasia result in severe short stature but are compatible with life. In some cases, other organ systems are affected because the causative gene also has functional roles in tissues other than the skeleton. For example, many skeletal dysplasia patients have hearing loss (8, 71, 78, 138). In patients with achondroplasia, the most common nonlethal form of skeletal dysplasia (71), hearing loss could be due to chronic otitis media (138). Individuals may also have neurological involvement and vision problems (71). Patients should be carefully monitored for all of these potential complications, as they may require immediate intervention (71, 122).

There currently are no pharmacological therapies for individuals affected with skeletal dysplasia, although there are some promising candidates worthy of discussion below. Enzyme therapies available for some mucopolysaccharidoses improve lung function, but they are not effective for skeletal and joint abnormalities associated with these disorders (99). Growth hormone therapy can accelerate growth rate, but in cases of achondroplasia or idiopathic short stature, final adult height is not substantially improved (3a, 56). Controversial surgical procedures can successfully lengthen the limbs of a child, but the surgeries are numerous, expensive, and require dedicating much of the childhood years to medical care (71, 122). Molecular diagnosis of skeletal dysplasias is highly desired, and many patients and their families seek treatment options.

THE GENETICS OF SKELETAL DYSPLASIA

Historically, skeletal dysplasias have been characterized by inheritance pattern, associated symptoms, and radiological features. Mutations in the same gene can cause many different forms of skeletal dysplasia (149). One example of this is the features associated with mutations in *FGFR3*, the gene that encodes fibroblast growth factor receptor 3. Mutations in this gene represent an allelic series in clinical severity ranging from nonlethal achondroplasia and hypochondroplasia to thanatophoric dysplasia types I and II, which are lethal. Mutations in different genes can cause the same form of skeletal dysplasia. Osteogenesis imperfecta is a premier example of this phenomenon. Genes that encode collagens (*COL1A1* and *COL1A2*) are a major cause of this disorder, but other cases are caused by mutations in genes that encode molecular chaperones (e.g., *SERPINH1* and *FKBP10*) (87a).

Throughout the 1980s, a great deal of excitement arose from the discoveries that mutations in collagen genes cause conditions such as osteogenesis imperfecta (33, 115), Stickler syndrome (1a, 41), and spondyloepiphyseal dysplasia (82). The involvement of collagen genes in skeletal dysplasia was first suggested by protein analysis of cartilage (reviewed in 77). These studies made use of genetic material collected from nuclear families with multiple affected individuals and utilized such techniques as linkage analysis, positional cloning (41, 82, 137), and traditional Sanger sequencing to uncover the causative mutations. The discovery of collagen mutations in skeletal disorders heralded a new era, one where molecular genetic causes could be used for diagnostics and risk prediction in conjunction with family history, clinical examination, and radiographs (71).

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These successes were quickly followed by the discovery of the genetic etiology of achondroplasia. In 1994, three groups mapped achondroplasia to a region on human chromosome 4 (42, 80, 142). All three studies included multiple unrelated nuclear families ($N = 6–18$) with multiple affected individuals for linkage analysis. A locus on chromosome 4p16.3 cosegregated with achondroplasia in all of the families, providing evidence for genetic homogeneity. Munnich and colleagues (80) included patients with hypochondroplasia, which was thought to be allelic to achondroplasia. Their results supported this hypothesis, because both conditions mapped to the same region on chromosome 4. This region included several candidate genes, one of which was *FGFR3*.

Only a few months after achondroplasia and hypochondroplasia were mapped, the achondroplasia mutation in *FGFR3* was discovered (120, 129). Astonishingly, all of the patients screened had the same mutated nucleotide—the guanosine at position 1138 of the *FGFR3* transcript was substituted with an adenosine or cytosine, resulting in a missense mutation that substituted an arginine for a glycine at codon 380 (p.G380R). We now know that the frequency of this mutation is higher with advanced paternal age, and the high incidence may be due to the presence of a highly mutable CpG at the site and/or to a selective advantage for sperm with this mutation (46). When the p.G380R mutation was discovered to cause achondroplasia, its detrimental effects were speculated to be due to dominant negative action. Subsequently, normal FGF signaling was shown to have an inhibitory effect on the regulation of skeletal growth (32), and the molecular mechanism underlying achondroplasia was recognized as constitutive activation of FGFR3 by the p.G380R substitution (150, 151). As predicted, mutations that activate FGFR3 by altering other functional domains cause hypochondroplasia and thanatophoric dysplasia types I and II (40, 41, 43).

The time elapsed from the initial mapping of the achondroplasia mutant locus to the discovery of mutations in *FGFR3* was only approximately one year. This timeline is impressive given the technology of the time and that all of these studies took place before the release of the human genome sequence. Soon thereafter, mutations in two related genes, *FGFR2* and *FGFR1*, were discovered to cause other types of skeletal dysplasia (9, 149). The rate of mutation discovery has accelerated with the availability of the reference genome sequence and high-throughput genomic mapping and sequencing technologies, which have revolutionized the way these studies are conducted.

HIGH-THROUGHPUT TECHNOLOGIES AND MUTATION DISCOVERY

Many genetic causes of defects in skeletal growth and/or development have been discovered since the most recent version of the Nosology and Classification of Genetic Skeletal Disorders was published in 2011 (149) (Table 1). Recent studies have made use of high-throughput technologies, including whole-genome single-nucleotide polymorphism (SNP) mapping, comparative genomic hybridization arrays, whole-exome or whole-genome next-generation sequencing, and targeted enrichment of a locus followed by next-generation sequencing. Most of the mutations listed in Table 1 were discovered by next-generation sequencing of patient genomic DNA samples. As more efficient and cost-effective sequencing technologies are developed, whole-genome sequencing will likely become the

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preferred strategy (10, 92). The discovery of causal variants will substantially aid in the diagnosis, understanding, and treatment of many genetic disorders, including those that affect the skeleton (10). We discuss a selection of the genetic causes listed in Table 1 in more detail below.

IMAGE SYNDROME: THE EFFECTS OF IMPRINTING

IMAGe syndrome is characterized by intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital abnormalities (145). The IMAGe phenotype encompasses many organ systems and leads to hypoplasia of affected tissues. The variable skeletal abnormalities in these patients include defects at the level of the growth plate (metaphyseal dysplasia, epiphyseal dysplasia, and short arms and legs) and the bone tissue itself (osteopenia and delayed bone age) (5, 145). This disorder is caused by mutations in *CDKN1C*, which encodes cyclin-dependent kinase inhibitor 1C, also known as $p57^{Kip2}$. *CDKN1C* is imprinted, resulting in silencing of the paternal allele, which explains the apparent autosomal dominant inheritance. This phenomenon was observed in all tested patients in a large five-generation Argentinian family.

Mutations that cause IMAGe syndrome (Table 1) occur specifically in the domain of CDKN1C responsible for binding proliferating cell nuclear antigen (PCNA), which marks CDKN1C for ubiquitin-targeted protein degradation (5). The mutant form of CDKN1C does not bind PCNA, resulting in abnormal stabilization of the cell cycle inhibitor. Normally, transcriptional activation of *CDKN1C* by C/EPBβ is thought to regulate the transition from proliferation to hypertrophic differentiation in the growth plate (54). Thus, the mutant CDKN1C likely prematurely inhibits chondrocyte division, leading to premature differentiation and ultimately dwarfism. This mechanism underlies the pathophysiology of skeletal dysplasias associated with IHH and parathyroid hormone (PTH) mutations (146). PTHrP promotes chondrocyte proliferation and is thought to downregulate $p57^{Kip2}$, making it an attractive therapeutic candidate for counteracting the effects of the stabilizing mutations (74).

PROTEUS SYNDROME: A DISORDER OF SOMATIC MOSAICISM

Proteus syndrome is a very rare, highly sporadic, and debilitating condition characterized by patches of tissue overgrowth, or asymmetrical hyperplasia, in a variety of tissues, including bone and connective tissue (18, 85). Hyperplasia of affected tissues begins approximately a year after birth (18). The bones of the limbs are particularly affected, with the hyperplasia altering normal bone patterning and sometimes leading to joint immobility and/or bowing and rotation of the long bones. There is a 20% rate of premature death, typically caused by venous thrombosis and pulmonary embolism. Vascular abnormalities and tumors also occur (18, 85).

The asymmetric nature of the hyperplasia in Proteus syndrome patients led to the hypothesis that it results from somatic mosaicism, in which a *de novo* mutation occurs after the fertilized egg has begun to develop, causing a subset of cells to undergo excessive cell division (51). Genetic analysis of cells from hyperplastic regions and normal regions of

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Proteus syndrome patients led to the discovery of the causative mutation, and additional work revealed a shared etiology between Proteus and SOLAMEN syndromes (the latter of which is characterized by segmental overgrowth, lipomatosis, arteriovenous malformation, and epidermal nevus) (25, 85). Tissues affected by Proteus syndrome harbor a missense mutation (c.49G→A, p.Glu17Lys) in *AKT1* and increased phosphorylated AKT1, indicating overactivation of the phosphoinositide 3-kinase (PI3K)–AKT pathway (85). SOLAMEN syndrome patients are somatic mosaics with loss of function in the tumor suppressor PTEN, leading to AKT activation (25). The affected areas of SOLAMEN patients are nullizygous for *PTEN*, the result of an inherited germline mutation in *PTEN* and a de novo somatic mutation in the affected area. Because *PTEN* inhibits activation of AKT kinase, *PTEN* deficiency leads to overactivation of the PI3K-AKT signaling pathway in the affected areas, resulting in increased cell proliferation and reduced apoptosis (25, 85).

How does overactive AKT1 cause the skeletal phenotypes in Proteus and SOLAMEN syndromes? The role of PI3K-AKT signaling in bone is controversial (14). Most data are consistent with promotion of hypertrophic differentiation of growth plate chondrocytes (14, 40, 58, 118, 155). Overactivation of this pathway in mice through the conditional loss of *PTEN* activity leads to an overgrowth of skeletal elements, disorganized growth plates, and chondrocytes with altered cellular morphologies indicative of accelerated hypertrophic differentiation (14, 40, 58, 155). Known downstream effectors of the PI3K-AKT pathway in the growth plate include mTOR, SOX9 [also involved upstream (61a)], IHH, RUNX2, COL2A1, and proteoglycans (reviewed in 14), with additional targets discovered through microarray analyses (139a). Although more work is necessary to define the PI3K-AKT pathway function(s) in bone, it is clear that the primary role of AKT is to promote endochondral ossification in both humans and mice (14, 85). In Proteus syndrome patients, the mutant AKT1 protein causes accelerated disorganized bone growth in asymmetric patches, leading to the debilitating phenotype (18). Inhibitors of AKT1 or its downstream effectors may provide therapeutic targets.

Somatic mosaicism underlies some cases of McCune-Albright syndrome, a genetically heterogeneous disorder that affects the skeleton, skin, and endocrine system (152). Similarly, somatic mosaicism for mutations in isocitrate dehydrogenase (IDH1) or mitochondrial IDH2 underlies some cases of Ollier disease and Maffucci syndrome, which are characterized by periosteal cartilaginous tumors, gliomas, and acute myelogenous leukemia (110). The IDH1 tumors are associated with hypermethylation and gene silencing in cartilage tumors, suggesting an epigenetic aspect of tumorigenesis. Thus, somatic mosaicism may contribute more to genetic disorders than was previously appreciated.

EPIGENETIC CONTROL: MUTATIONS IN HISTONE ACETYLTRANSFERASE GENES CAUSE A VARIETY OF DISORDERS

The modification of histones by chromatin-modifying enzymes maintains cellular identity and regulates cell fate transitions during differentiation (15a, 148a). These processes are important to ensure proper organogenesis and growth. Chromatin-modifying enzymes include histone methyltransferases, histone demethylases, histone acetyltransferases, histone

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deacetylases (HDACs), and enzymes that phosphorylate and ubiquitinate histones (10a, 15a, 148a). Recently, skeletal growth disorders have been shown to result from loss of function in *HDAC4* (152b) and mutations in the genes encoding other chromatin-modifying enzymes. For example, mutations in the gene encoding histone H3.3 are drivers of both chondroblastoma and giant cell tumors of bone (13), and mutations in the histone acetyltransferase gene *KAT6B* cause two distinct skeletal development disorders (23, 27).

KAT6B is a member of the MYST family of histone acetyltransferase genes. Mutations at the 3′ end of *KAT6B* have been reported in patients with Say-Barber-Biesecker-Young-Simpson (SBBYS) syndrome, a variant of Ohdo syndrome. This disorder causes intellectual disability, facial abnormalities, and distinct skeletal characteristics, including hypoplastic or absent patellae, joint laxity, and abnormally long first digits. These patients are heterozygous for de novo mutations that disrupt the RUNX2-binding domain (27). RUNX2 is a homeodomain transcription factor that regulates chondrocyte hypertrophy and osteoblast differentiation (36, 67). Thus, the skeletal phenotype in these patients could be due to defects in chondrocytes, osteoblasts, or both cell types. Specific loss-of-function mutations in *KAT6B* cause genitopatellar syndrome, a disorder characterized by intellectual disability, absence or hypoplasticity of the patellae, craniofacial abnormalities, and genital malformations (23). The pathogenic mutations are de novo insertions or deletions that cause frameshifts or nonsense mutations at the start of the last exon of *KAT6B* (23). The mutant forms of KAT6B lack the transcription-activation domain and the RUNX2-binding domain and may have dominant negative effects (23, 27). If mutant KAT6B is unable to acetylate histones, HDAC inhibitors might counteract the loss of function, provided that appropriate specificity can be achieved. Future studies will clarify the molecular mechanisms underlying the role of histone acetyltransferases and other chromatin-modifying enzymes in skeletal development and growth.

MUTATIONS IN MIRNAs AND SEVERE SHORT STATURE

Mutations in *MYCN*, or N-*myc*, and a miRNA cluster cause Feingold syndrome, a disorder that can involve multiple organ systems but consistently affects the skeleton (39). The hallmark skeletal anomalies are short stature, microcephaly, brachydactyly of the second and fifth digits of the hands, and brachysyndactyly of the toes. A nonrecombinant interval for Feingold syndrome was mapped to human chromosome 2p23–p24 (26), and subsequent analysis identified heterozygous mutations in *MYCN* (141). Genomic DNA from Feingold patients negative for mutations in *MYCN* was analyzed by comparative genomic hybridization arrays to screen for disease-causing copy-number variations. These patients are heterozygous for microdeletions on human chromosome 13q31.3 that encompass the miR-17~92 miRNA cluster, known as *MIR17HG* (26, 28, 31, 39). This was confirmed by the observation that mice homozygous for deletion of the *MIR17HG* locus develop a Feingold syndrome–like phenotype (144).

MYCN appears to directly activate transcription of this miRNA cluster (31), explaining why the hemizygous loss of function of either *MYCN* or the miR cluster leads to very similar skeletal phenotypes in mice and humans (31, 97, 103, 108). Defining the targets of these miRNAs will give a deeper understanding of the pathophysiology of Feingold syndrome.

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THE PRIMORDIAL DWARFISMS

Many of the skeletal dysplasias are characterized by disproportionate bone growth, with long bones being most affected (69, 71). Primordial dwarfism, on the other hand, causes a proportionate reduction in growth, similar to that caused by deficiencies in insulin-like growth factor 1 (IGF-1) or growth hormone (GH) (69). Patients with IGF-1 deficiency and primordial dwarfism are smaller at birth and are sometimes ascertained in utero, whereas patients with GH deficiency are normally sized at birth and are usually identified later in childhood. Primordial dwarfisms include Seckel syndrome, Meier-Gorlin syndrome (MGS), and microcephalic osteodysplastic primordial dwarfism types I–III (MOPD I–III) and have been recently reviewed (69).

GH/IGF-1-deficient patients do not have skeletal dysplasia or microcephaly (9). They typically exhibit delayed bone age, and many patients respond to hormone supplementation (47b), unlike traditional skeletal dysplasia patients (71). Primordial dwarfisms cause reductions in the overall cell number but do not affect endocrine processes (69). It is not clear whether the reduction in cell number is due to augmentation of cell death, delay or reduction in cell proliferation, or both. Mouse models and cell culture studies should clarify the roles of mechanisms that underlie primordial dwarfisms.

The forms of primordial dwarfism vary significantly in severity (69). Seckel syndrome patients tend to have moderate to mild intellectual disability, microcephaly, and distinctive facies. MOPD I and III cause curvature of the long bones, drastic growth insufficiency, and death by three years of age, as well as skin abnormalities and sparseness of hair. MOPD II is compatible with life, and patients have normal intellect. They are predisposed to vascular abnormalities and insulin resistance, which can lead to type II diabetes. MGS causes hypoplasia or complete absence of the patellae, microtia, and microcephaly and presents with highly variable growth outcomes (20, 30). Not all forms of primordial dwarfism are included in the most recent version of the Nosology and Classification of Genetic Skeletal Disorders (149), but we have included recent genetic discoveries for all the forms in the same classification in Table 1 (group 19, which includes forms of MOPD).

Primordial dwarfism patients have genetic aberrations in genes with diverse functions that are likely to affect all of the cells in the body and are connected to the cell cycle (69) (Figure 2). Seckel syndrome is associated with mutations in the DNA-damage response genes *ATR* (106), *RBBP8* (116), and possibly *ATRIP* (107), and the centriole-associated genes *CPAP* (*CENPJ*) (3) and *CEP152* (65). MOPD II is caused by mutations in *PCNT*, which encodes a pericentriolar protein involved in the generation of the mitotic spindle and centrosome maturation. Microcephalic primordial dwarfism has been associated with mutations in *NIN*, which encodes the centrosomal protein ninein (29). Little is known about the function of ninein, although it is thought to regulate asymmetric cell division (70, 114, 148). Mutations in *XRCC4* (encoding a component of the nonhomologous end joining DNA repair pathway), and *CENPE* (encoding a centromere-associated protein) are also associated with microcephalic primordial dwarfism (96, 102a). Mutations in genes that encode components of the origin recognition complex (ORC), which regulates the licensing of DNA replication origins, cause MGS (16, 17, 30, 49) (Table 1). MOPD I is caused by mutations in *U4ATAC*,

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which is involved in splicing U12 introns, present in a subset of human genes (37, 52). MOPD II is likely caused by alterations in the splicing of specific transcripts required for modulation of cellular growth and cell number (69). Thus, genes that contain U12 introns could be involved in other forms of primordial dwarfism.

Primordial dwarfisms correspond phenotypically and genetically with one of two major affected processes: DNA repair and replication or centrosome-associated proteins. MOPD I is an exception, as mutations in *U4ATAC* likely disrupt multiple cellular functions, causing pleiotropic effects and early lethality. Mutations of *ATR* and *CEP152* in Seckel syndrome cause similar phenotypes: moderate learning disability and a more marked reduction in the size of the skull. Patients with mutations in *CENPJ* (*CPAP*) have clinical features similar to those of MOPD II patients with mutations in *PCNT*, in that both groups have a proportionate reduction in head size and body size. Intellectual disability in the Seckel *CENPJ* patients is mild, whereas MOPD II/*PCNT* patients have a normal intellect. ORC-associated proteins such as ORC1 associate with the centrosome (53, 57), and mutations in *ORC1* cause more severe reductions in height and head circumference than any other cause of MGS (30, 57). All but one of these *ORC1* patients had normal intellect, and the one exception had mild intellectual disability.

The effect of the centrosome-associated genes on stature may be due to the requirement of the centrosome to form the primary cilium, a structure necessary to maintain the organization of the growth plate (59, 119, 132). There are exceptions to these general correlations between clinical features and the type of gene mutated. For example, mutations in the centrosomal protein encoded by *NIN* cause both severe short stature and profound intellectual disability (29). Morpholino-induced knockdown of NIN in zebrafish or loss of ninein in mice reduces the number of cells in a distinct part of the developing nervous system (148). Although NIN deficiency does not appear to affect overall cell division, it could affect asymmetric divisions required for specific populations of cells, and it could have important undiscovered functions distinct from its role in centrosome biology.

Mechanistic details of MGS have emerged from studies of *ORC1*. ORC1 binds dimethylated lysine 20 of histone H4 (H4K20me2), a chromatin modification commonly present at replication origins, and mutation of the H4K20me2 binding domain causes MGS (75). In vitro studies suggest that slow progression through S phase is not a determinant of the MGS phenotype (133). Additional work has shown that *ORC1* regulates centrosome duplication (57, 105). MGS-associated mutations of *ORC1* reduce the rate of primary cilium formation and alter the collection of signaling components present within the primary cilium, but the cilia that form have a normal appearance (133). These studies demonstrate that MGS and related forms of primordial dwarfism potentially have mechanistic connections to the centrosome and the primary cilium, and these connections should be explored to determine whether these disorders represent a subset of skeletal ciliopathies.

THE SKELETAL CILIOPATHIES

Mutation of centrosome-associated genes in primordial dwarfisms could influence the formation and maintenance of the primary cilium, formation of the mitotic spindles and cell

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division, and/or secretory pathways (133). The primary cilium maintains the architecture of the growth plate (132), and disruptions in ciliogenesis can lead to many severe forms of skeletal dysplasia (59). These forms of skeletal dysplasia are known as the skeletal ciliopathies and may include some forms of primordial dwarfism (133). Some of these disorders spare the tissues typically damaged in ciliopathies (such as kidney, retina, brain, and liver) and are embryonic or perinatal lethal, and many of them result in short ribs and polydactyly, presumably resulting from altered IHH signaling. The short ribs may impair lung development and function, causing lethality at birth (34, 59).

The primary cilium is a microtubule-based structure present on the majority of noncycling cell types, including chondrocytes. The axoneme of this nonmotile cilium extends outward from the basal body, the foundation of the cilium generated by the mother centriole of the centrosome (62) (Figure 3). Sheathed in plasma membrane and decorated with numerous receptors and ion channels, the primary cilium serves as a major signaling center, particularly for the Hedgehog and WNT signaling pathways (147). IHH signaling is a major regulator of skeletal growth, so perturbation of the primary cilium has the potential to disrupt IHH signaling and growth of long bones.

The primary cilium maintains growth plate architecture and organization (132). Chondrocytes are normally organized in columns within the proliferative zone. As the chondrocytes divide, the daughter cells divide perpendicular to the column and spread over one another to align within the column (84, 118a). This process, called chondrocyte rotation (132), is regulated by WNT signaling through the planar-cell polarity pathway (84, 119). Mouse models of skeletal ciliopathies have disorganized growth plates that underlie the growth insufficiency. The disorganized growth plate may arise from perturbation of cell polarity (WNT) and/or the rate of growth plate chondrocyte proliferation and hypertrophic differentiation (IHH), or through some other means. Mouse models of skeletal ciliopathies should help clarify the role of the primary cilium in the development of growth insufficiency.

Many genes implicated in skeletal ciliopathies regulate intraflagellar transport (IFT), the mechanism responsible for trafficking components into (IFT complex B) or out of (IFT complex A) the cilium (Figure 3). Kinesin motors carry IFT-B components, whereas dynein motors carry IFT-A components. This trafficking system ensures that the cilium is maintained and lengthened and that receptors and downstream effectors of signaling pathways are targeted properly to the cilium. Mutation of basal body–associated genes (Figure 3) could cause disruptions in primary cilium formation and maintenance or affect mitotic spindle formation and orientation.

Mutations in *NEK1*, a basal body–associated component of the cilium, cause short-rib polydactyly syndrome type Majewski (135). The never-in-mitosis gene A–related kinases (NEKs) constitute a large gene family composed of 11 members (*NEK1–NEK11*) (43). NEKs regulate microtubule dynamics, cell cycle progression, and ciliogenesis. Mutations in other *NEK* genes may cause skeletal dysplasia (including but not limited to primordial dwarfisms), classical ciliopathies, or cancer. Several other gene families, including *WDR* and *CEP*, are associated largely with the primary cilium and are excellent candidates for human disease genes and worthy of functional analysis in model organisms.

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The newest potential member of the skeletal ciliopathies is a novel form of primordial dwarfism caused by mutation of *POC1A*, encoding protein of centriole 1A. Patients are smaller than average size in utero and remain so throughout their lives (121, 124). Two homozygous mutations were found in highly consanguineous families: a premature stop codon (R81X) (124) and a missense mutation (L171P) (121). Surprisingly, the premature stop codon undergoes efficient read-through in patient fibroblast cultures, and POC1A protein levels are reduced by only 15–50% (124). The fibroblasts have abnormal mitotic spindle orientation, form multipolar spindles, and have multiple centrosomes in noncycling cells. The frequency of primary cilium detection is only approximately half of the control, and the cilia that do form are approximately two-thirds normal size. The missense mutation is a nonconservative change in a region conserved from mammals to algae. Skin fibroblasts from these patients exhibit centrosome amplification (124) and alterations in cholera toxin trafficking (121). There are shared and distinct clinical features between the two families.

The effects both mutations have on cilia and centrosomes may be sufficient to produce the growth insufficiency. Two lines of evidence support this idea. First, knockdown of both *POC1A* and the related *POC1B* gene in HeLa cells alters the orientation of the mitotic spindle, causing unequal bipolar, monopolar, or even multipolar spindles (143). These knockdowns cause failure of daughter centrioles to mature into new mother centrioles. The lack of mother centrioles could affect the cells' abilities to form primary cilia, as the mother centriole is responsible for the formation of the basal body and the extension of the ciliary axoneme (62). This could affect growth plate organization and signaling (132, 147), leading to severe short stature. The defects noted in mitotic spindles could affect orientation of chondrocyte cell division, leading to improper chondrocyte placement and faulty rotation. Additionally, mutations in *POC1A*, *ORC1*, *CENPJ*, and *PCNT* cause very similar growth deficiencies and microcephaly, and all of these genes encode proteins associated with the centrosome (3, 47, 57, 117, 133, 143).

It will be interesting to determine whether defects in the other primordial dwarfism genes cause the cilium defects similar to those observed in cells from *POC1A* patients, or whether, like *ORC1* mutations, the cells form relatively normal cilia but at a slower rate (133). Histology of the growth plates in skeletal ciliopathy mouse models could determine which genes cause disorganization of the growth plate, and primary fibroblasts could be used to study the primary cilium. Both approaches will clarify the roles of these genes in the development of postnatal growth retardation in skeletal ciliopathy patients, a class that may include some forms of primordial dwarfism. These analyses could also shed light on the potential connection between the primary cilium, planar-cell polarity, and components of the cell cycle such as ORC1 that are linked to the centrosome/primary cilium (53, 57, 133). Although there is clearly a role for both the planar-cell polarity pathway (43a, 84, 119, 147a) and the primary cilium (132) in skeletal development and growth, their functional relationship is intensely debated (12a, 147). Clearly, there is much work to be done to clarify these associations, but the data collected will certainly be of clinical and basic significance.

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NOVEL SKELETAL DISORDERS OF UNKNOWN ETIOLOGY

Although genetic causes of the >450 forms of skeletal disorders (149) are being uncovered quite rapidly, distinct skeletal disorders are still being discovered with no known genetic etiology. We do not have the ability to cover all of these disorders here, but the best strategy for identifying the genetic etiology of these new disorders may be exome sequencing or genome sequencing. In sporadic cases, analysis of trios may reveal de novo mutations. In familial cases, a combination of exome sequencing and either genome sequencing or SNP typing could yield linkage information for prioritization of rare variants. Current trends indicate that the causative mutations for these novel disorders will be uncovered very soon, with mechanistic details and therapeutic avenues likely to follow closely behind.

SKELETAL DYSPLASIA GENETICS AND HUMAN HEIGHT VARIATION

Do mutations in skeletal dysplasia patients provide information relevant to height variation in the human population? The answer is probably yes, because some skeletal dysplasia–associated genes have already been implicated in human height. Two genome-wide association studies (GWAS) conducted on human height variation (77a, 152c) have revealed height-associated loci that partially overlap with genes known to cause skeletal disorders. A GWAS from 2010 reported that 21 of 241 genes (8.7%) are known to cause a human growth disorder in their height-associated genomic loci, including genes influencing the endocrine system and skeleton (77a). The more recent GWAS, published in 2014, found 697 variants that explain one-fifth of the height heritability in individuals of European ancestry (152c). Of the genes that are specifically mentioned in the article, 20% of them are associated with a human skeletal disorder, and the majority of them are in some way connected to the signaling pathways and/or cellular processes discussed elsewhere in this review (152c). Approximately 8% of these genes had no previous association with skeletal growth, meaning that GWAS could provide new loci for consideration in the genetic analysis of skeletal disorders (152c). An important next step is to identify functional variants in the GWAS-associated candidate genes and determine how genetic interactions between these loci contribute to human height variation.

FUTURE DIRECTIONS: HUMAN STUDIES, MOUSE MODELS, AND IN VITRO TECHNOLOGIES IMPACT SKELETAL DYSPLASIA RESEARCH

The contributions of genetics to understanding skeletal dysplasia begin by assigning a gene to a disorder and extend to understanding the pathophysiology of the disease and development of treatments. Receiving a molecular diagnosis often gives patients and their families relief because they can understand the cause, the progression of disease over a lifetime, and the risk for future pregnancies. Human disease gene discovery is a starting point for understanding the normal regulation of skeletal growth and for studying development in model systems. Mouse models of human skeletal dysplasias and development of chondrocyte cell lines have been invaluable for mechanistic insight that explains the clinical features at the molecular level. These data provide a foundation for developing and testing therapeutic interventions, completing the circle from bedside to bench and back to bedside.

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Studies in mice have contributed to understanding the genetic basis of skeletal dysplasias, disease pathophysiology, and therapeutic testing (6, 7, 19, 35, 66, 81, 100, 104, 109, 131, 134, 144). The data collected from skeletal dysplasia patients are usually limited by the necessity for minimal invasiveness, and include radiographs; photographs; measurements of height, weight, and hormone levels; and isolation of skin fibroblasts, blood leukocytes, and genomic DNA. By contrast, mouse models provide researchers with accessible tissue throughout development, the potential to assess genetic interactions underlying digenic or oligogenic disease using complementation studies, and piloting treatments (44, 63, 64, 68, 87, 101, 130, 153, 158).

In many of these studies, the description of the mouse model was followed by reports of mutations in the orthologous human gene that cause similar skeletal abnormalities. For example, Smits et al. (131) recently found that an ethylnitrosourea (ENU)–induced mutation in mice is a model of achondrogenesis type 1A in humans. This autosomal recessive mutation caused perinatal lethality, severely disrupted endochondral ossification, greatly reduced the mineralization of skeletal elements, and disturbed the trafficking of extracellular matrix proteins, resulting in acute intracellular stress in affected chondrocytes. The mutant locus was mapped to mouse chromosome 12 using a SNP array and subsequently narrowed to a 3.7-Mb interval. Candidate gene screening led to the discovery of a nonsense mutation (c.5003T→A, p.L1668X) in *Trip11*, which encodes Golgi microtubule-associated protein 210 (GMAP-210). *TRIP11* was evaluated as a candidate gene for achondrogenesis type 1A because of similarities in the mouse and human phenotypes. Indeed, 10 out of 10 achondrogenesis type 1A patients screened had mutations in *TRIP11*. Thus, the discovery of mouse mutations contributes significantly to understanding the genetic basis for skeletal dysplasias in humans.

In addition to mouse models, induced pluripotent stem cells (iPS cells) generated from skeletal dysplasia patients have the potential to serve the research community as a tool for drug discovery and design (107a, 154a). Successful generation of chondrocytes from dermal fibroblasts from mice and humans has been reported (53a, 109a, 109b), but more importantly, the analysis of these cells provides valuable insight into possible treatment regimes. In the case of type 2 collagen disorders, patient-derived dermal fibroblasts that either were stimulated to form chondrocytes directly or differentiated following an induction of pluripotency revealed that matrix-promoting treatments such as ascorbate worsen the cellular pathology (107a). However, treatment with the chemical chaperone trimethylamine *N*-oxide (TMAO) resulted in an amelioration of the cellular phenotype, making it an attractive therapeutic candidate (107a). Another study, in which iPS cells derived from a patient with achondroplasia and thanatophoric dysplasia type I were differentiated into chondrocytes, revealed a safe, effective therapy for these two forms of skeletal dysplasia: the statins (154a). Statin therapy in vitro rescued the cellular phenotypes, which included a reduced level of collagen 2 and other known chondrocyte markers. Remarkably, statin treatment also increased the longitudinal growth of *Fgfr3*^{ach} mice. Although there are major caveats, such as the lack of true growth plate architecture in iPS-chondrocyte cultures, iPS cell–based strategies could provide a wealth of new information, including new therapeutic avenues, through large-scale drug screens.

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Developing a therapy for achondroplasia is a top priority, given that it is the most common form (71), and it is one of the best examples of the progression from gene discovery to potential therapies in less than ~20 years. Mutations in *FGFR3* cause a number of additional disorders (9), meaning that a treatment for achondroplasia could be an appropriate therapy for these other FGFR3-related disorders or vice versa. Interestingly, the discovery of mutations in *NPR2* in acromesomelic dysplasia type Maroteaux (AMDM) patients (12) has helped shape the trajectory of this area of research, as work in cell culture and mouse models has revealed that the genetic and molecular etiologies of the two disorders are intertwined. Activation of NPR2 inhibits FGFR3-mediated activation of the MEK/ERK mitogen-activated protein kinase (MAPK) pathway (72), which allows the growth plate to promote chondrocyte differentiation. Loss of CNP-NPR2-mediated inhibition of FGF signaling in the mouse model of AMDM leads to overactivation of the MEK/ERK MAPK pathway (44), and treatment of chondrocytes with CNP leads to reduced ERK activation (72). Treating achondroplasia patients with CNP, the ligand for NPR2, was a rational therapy based on knowledge of the effect of the FGF mutation on MEK/ERK and the oppositional effects of CNP signaling. This therapy is somewhat successful in mouse models with various methods of continuous administration (156–158). Statins (154a), soluble “decoy” human FGFR3 (43c), PTH (153), FGFR3 inhibitors (63, 64), CNP (152a, 156–158), CNP analogs (87), and meclozine (87d) are all being explored as potential treatments for achondroplasia. The administration of MEK/ERK inhibitors has been postulated as an intervention in mouse models of Apert syndrome (gain-of-function mutation in *FGFR2*) (130) and AMDM (44). Although these therapies are still under development, it is promising that targeting these pathways has improved growth in vitro and even in vivo in some cases. Future research may involve identifying additional compounds that modulate this interconnected signaling network with greater specificity, and improving delivery of therapeutics to the growth plate. The progression from mutation discovery to therapies in achondroplasia should serve as a model for research on other forms of skeletal dysplasia.

CONCLUDING REMARKS

There has been remarkable progress recently in understanding the genetic and molecular etiologies of skeletal dysplasias. Genetic causes of fifty-six disorders have been uncovered (Table 1). The speed and volume of these discoveries lead us to propose the construction of a Database of Nosology and Classification of Genetic Skeletal Disorders, where new information can be submitted as it is published. Such a database could be expanded to other types of growth disorders, providing a valuable resource for clinical, basic, and translational research. Finally, the progress made in therapeutics through in vitro and in vivo work represents a spectacularly promising start toward developing therapies for all skeletal disorders.

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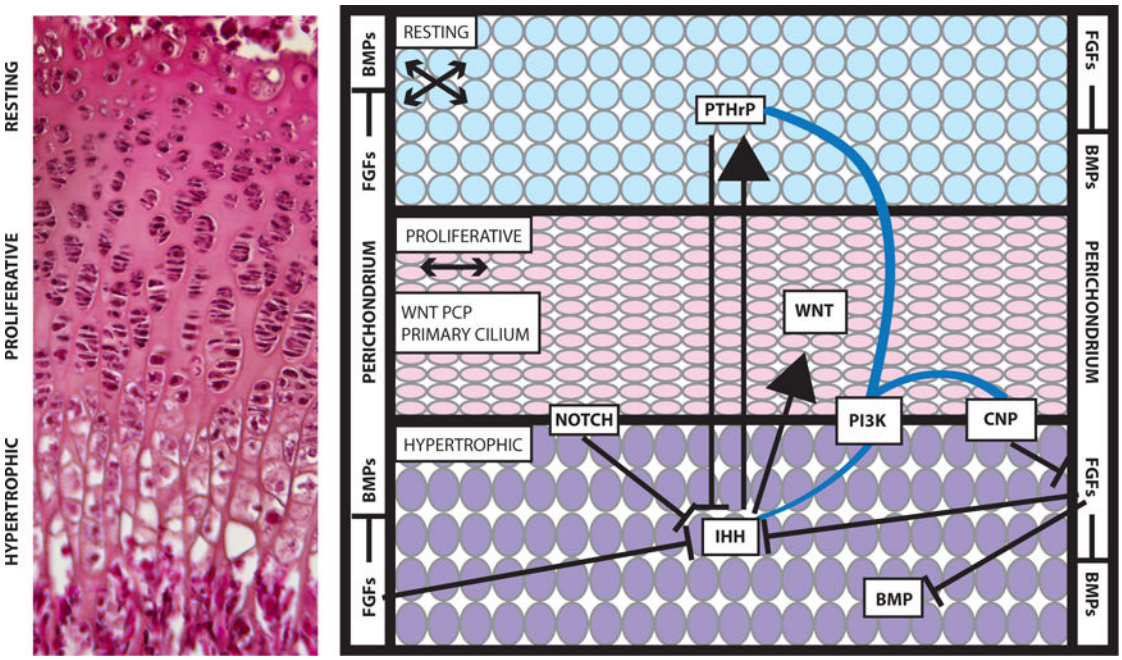

Figure 1. Overview of the growth plate

Cells within the resting, proliferative, and hypertrophic zones of the growth plate have a distinctive morphology and organization, which is visible in a section through a three-week-old mouse growth plate stained with eosin and hematoxylin (*left*). The Notch, WNT, FGF, Hedgehog, and BMP signaling pathways act on the cells of the growth plate (*right*). Arrows indicate activation of one pathway by another, and lines with a bar at the end indicate inhibition of the pathway. Blue lines indicate crosstalk between pathways. For example, PI3K is thought to affect the CNP, IHH, and PTHrP signaling pathways. Many of these pathways have been implicated in multiple skeletal dysplasias. The arrows underneath the names of the resting and proliferative zones indicate the orientation of cell division within these zones. Abbreviations: BMP, bone morphogenetic protein; CNP, C-type natriuretic peptide; FGF, fibroblast growth factor; IHH, Indian Hedgehog; PCP, planar-cell polarity; PI3K, phosphoinositide 3-kinase; PTHrP, parathyroid hormone–related peptide.

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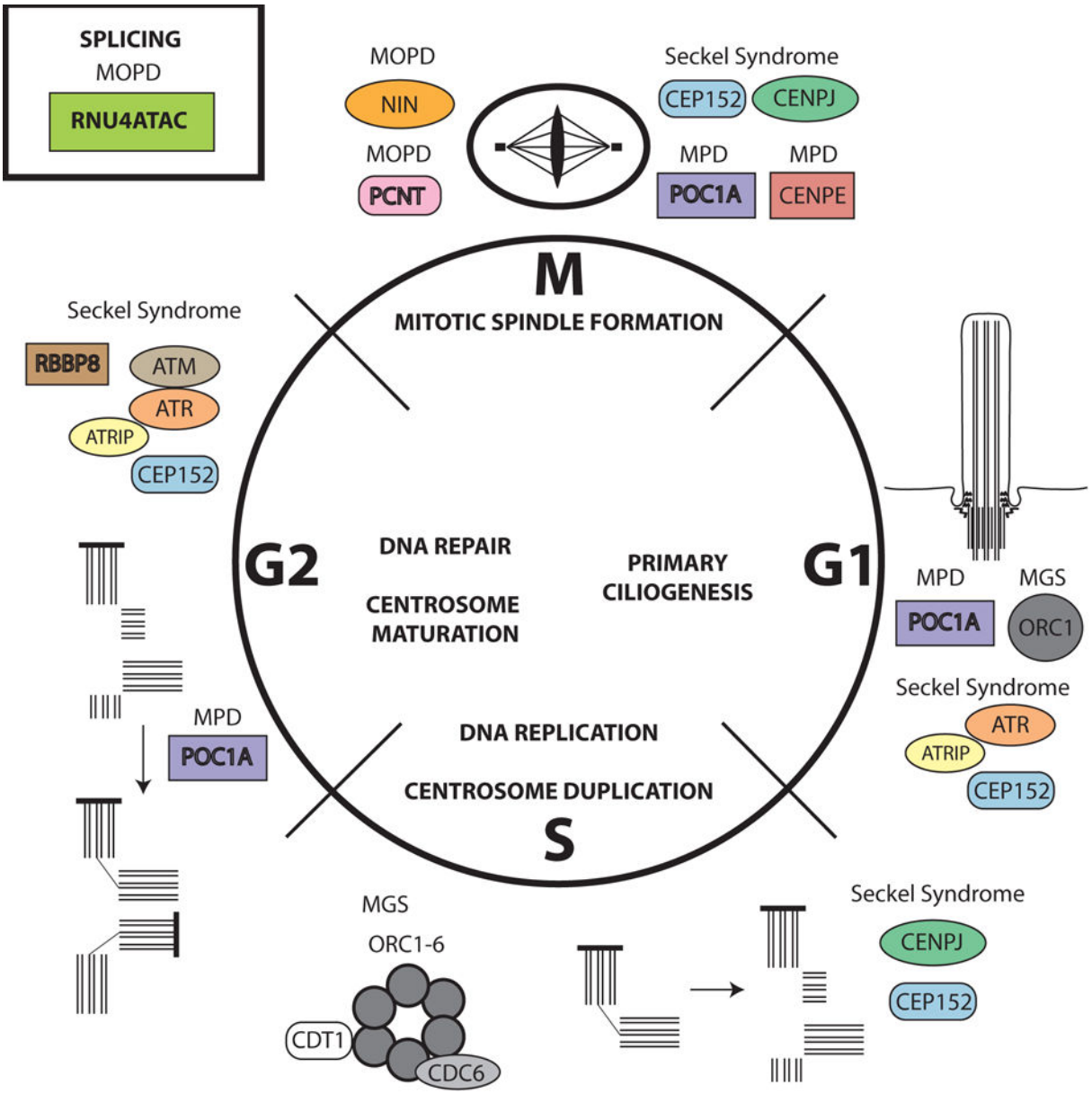

Figure 2. Cellular pathways disrupted in primordial dwarfism

Most genes implicated in primordial dwarfism (MGS, MOPD I and II, Seckel syndrome, and SOFT syndrome) are involved in cell cycle regulation and cell division. These processes include primary ciliogenesis (G_1 phase), DNA replication and centrosome duplication (S phase), DNA repair and centrosome maturation (G_2 phase), and mitotic spindle formation and mitosis (M phase). Many of the genes function in more than one phase of the cell cycle. Some genes affect the rate of progression through the cell cycle, and some lead to aneuploidy, probably due to defects in DNA repair or mitotic spindle formation. In some cases, the cell cycle becomes disrupted after several rounds of cell division owing to disturbances in centriole duplication and/or maturation. All the processes shown involve replication and repair or maturation of the genome and the centrosome except *RNU4ATAC*. *RNU4ATAC* has a critical role in splicing, which could affect genes involved in cell cycle

regulation or division. Abbreviations: MGS, Meier-Gorlin syndrome; MOPD, microcephalic osteodysplastic primordial dwarfism; MPD, microcephalic primordial dwarfism; SOFT, short stature, onychodysplasia, facial dysmorphism, and hypotrichosis.

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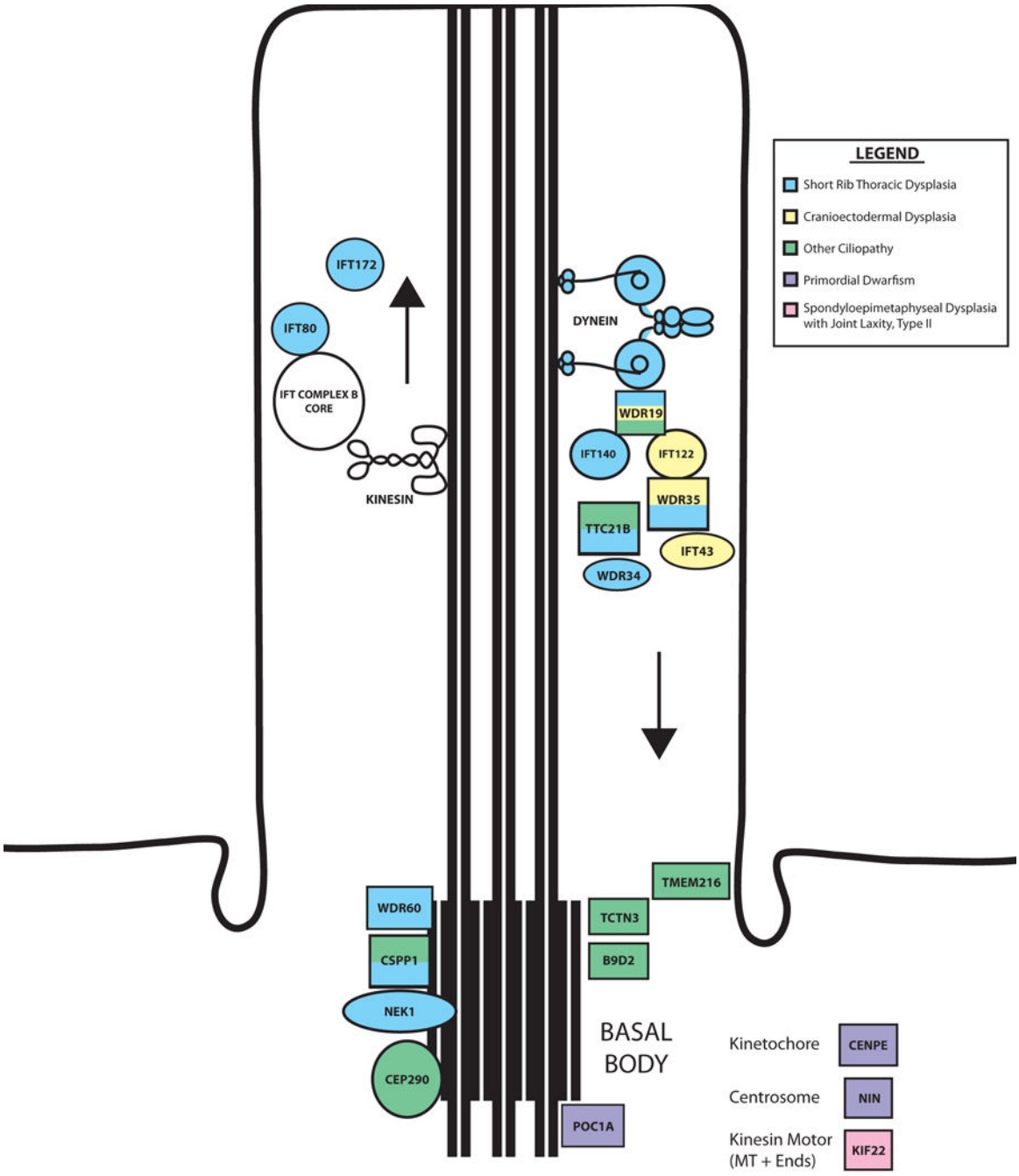

Figure 3. Primary cilium proteins implicated in skeletal dysplasias

Components of the primary cilium are disrupted in many forms of skeletal dysplasia. These components include genes that encode parts of motor proteins (e.g., dynein) and parts of both the IFT-A and IFT-B complexes, which regulate retrograde and anterograde ciliary trafficking, respectively. The colors of the cilium components signify the types of disorders with which they are associated.

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Table 1

Causative mutations of skeletal disorders discovered since the most recent publication of the Nosology and Classification of Genetic Skeletal Disorders (149)

Group	Disorder	Inheritance	MIM number	Locus	Gene	Notes/function
9	Short rib thoracic dysplasia (new form)	AR	NA	5q23.2	*CEP120* (centrosomal protein, 120 kDa (124a)	Four separate families with same missense variant
9	Short-rib thoracic dysplasia 4 with or without polydactyly	AR	613819	2q24.3	*TTC21B* (Tetratricopeptide repeat domain-containing protein 21B) (29a)	Retrograde ciliary transport (IFT-A)
9 15	Short-rib thoracic dysplasia 5 with or without polydactyly Cranioectodermal dysplasia 4	AR	614376 614378	4p14	*WDR19* (WD-repeat containing protein 19) (22)	IFT-A complex, retrograde ciliary trafficking, ciliogenesis
9 15	Short-rib thoracic dysplasia 7 with or without polydactyly Cranioectodermal dysplasia 2	AR	614091 613610	2p24	*WDR35* (WD repeat-containing protein 35) (94)	Ciliogenesis and cilium maintenance
9	Short-rib thoracic dysplasia 8 with or without polydacyly	AR	615503	7q36.3	*WDR60* (WD repeat-containing protein 60) (89)	Ciliogenesis, Hedgehog signaling
9	Short-rib thoracic dysplasia 9 with or without polydactyly	AR	266920	16p13.3	*IFT140* (intraflagellar transport 140, *Chlamydomonas*, homolog of) (111)	Ciliogenesis, part of IFT-A complex (retrograde ciliary transport)
9	Short-rib thoracic dysplasia 10 with or without polydactyly	AR	615630	2p23.3	*IFT172* (intraflagellar transport 172, *Chlamydomonas*, homolog of) (50)	Anterograde ciliary transport (IFT-B)
9	Short-rib thoracic dysplasia 11 with or without polydactyly	AR	615633	9q32.11	*WDR34* (WD repeat-containing protein 34) (61, 123)	Retrograde ciliary transport (IFT-A), NF-κB signaling
9	Joubert syndrome 18 Orofaciodigital syndrome IV	AR	614815 258860	10q24.1	*TCTN3* (Tectonic family, member 3) (136)	Cilogenesis, Hedgehog signaling
9	Orofaciodigital syndrome V	AR	174300	1q32.1	*DDX59* (DEAD box polypeptide 59) (127)	RNA helicase, RNA metabolism
12	Spondylometaphyseal dysplasia with cone-rod dystrophy	AR	608940	3q29	*PCYT1A* (phosphate cytidylyltransferase 1, choline, alpha isoform) (55, 154)	Phosphotidylcholine metabolism
13	Spondyloepimetaphyseal dysplasia with joint laxity, type 2	AD	603546	16p11.2	*KIF22* (Kinesin family member 22) (21, 95)	Unknown (speculated role in intracellular trafficking or ciliary transport)
13 19	Spondyloepimetaphyseal dysplasia with joint laxity, type 2 Seckel Syndrome 7	AR	603546 614851	14q22.1	*NIN* (Ninein) (29, 47a)	Centrosome-mediated asymmetric cell division

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Group	Disorder	Inheritance	MIM number	Locus	Gene	Notes/function
14	Novel spondylodysplastic dysplasia	AR	NA	16p13.3	*PAM16* (presequence translocase-associated motor 16) (90)	Mitochondrial transport
14	Opsismodysplasia	AD	258480	11q13.4	*INPPL1* (15, 60) Inositol polyphosphate phosphatase-like 1	PI3K-AKT signaling modulation
15	Acrodysostosis 1, with or without hormone resistance	AD	101800	17q24.2	*PRKAR1A* (protein kinase, cAMP dependent, regulatory, type 1, alpha) (86)	PKA/cAMP mediated signaling
15	Acrodysostosis 2, with or without hormone resistance	AD	614613	5q12.1	*PDE4D* (phosphodiesterase 4D) (83, 93)	Degradation of cAMP/inhibiting signaling pathway
15	Acromicric dysplasia Geleophysic dysplasia 2	AD AR	102370 614185	15q21.1	*FBN1* (fibrillin 1) (79)	Integrin and TGF-β signaling
18	Bent bone dysplasia syndrome	AD	614592	10q26.13	*FGFR2* (fibroblast growth factor receptor 2) (91)	Proper regulation of chondrocyte proliferation and differentiation
19	Microcephalic Primordial Dwarfism	AR	NA	5q14.2	*XRCC4* (X-ray repair, complementing defective, in Chinese hamster, 4) (102a)	Nonhomologous end joining DNA repair
19	Microcephaly and chorioretinopathy, autosomal recessive, 2	AR	616171	4q28.2	*PLK4* (Polo-like kinase 4) (87b, 123c)	Centrosome duplication and maturation
19	New form of primordial dwarfism	AR	NA	8q24.13	*NSMCE2* (non-SMC element 2 homolog) (110a)	E3 SUMO-ligase
19	Microcephaly 13, primary, autosomal recessive	AR	616051	4q24	*CENPE* (centromeric protein E) (96)	Kinetochore-associated chromosome alignment
19	Short stature, onychodysplasia, facial dysmorphism and hypotrichosis	AR	614813	3p21.1–21.31	*POC1A* (POC1 centriolar protein, *Chlamydomonas*, homolog of, A) (121, 124)	Centrosome maintenance, Golgi retrograde trafficking, proper mitotic spindle polarity, cilogenesis
19	IMAGe syndrome	AD, maternally imprinted	614732	11p15	*CDKN1C* ($p57^{Kip2}$) (5)	Inhibition of cell cycle progression
19	Seckel syndrome 2	AR	606744	18q11.2	*RBBP8* (retinoblastoma-binding protein 8) (116)	DNA repair
19	Microcephalic osteodysplastic primordial dwarfism, type I	AR	210710	2q14.2	*RNU4ATAC* (RNA, U4ATAC small nuclear) (52, 37)	RNA splicing
20	Disorder of glycosylation resembling Desbuquois dysplasia	AR	NA	6q14.1–14.2	*PGM3* (phosphoglucomutase 3) (134a)	Generates substrates for protein glycosylation
20	Desbuquois dysplasia 2	AR	615777	16p12.3	*XYLT1* (xylosyltransferase 1) (22a, 123a)	Glycosaminoglycan synthesis

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Group	Disorder	Inheritance	MIM number	Locus	Gene	Notes/function
25	Bone fragility with craniosynostosis, ocular proptosis, hydrocephalus, and distinctive facial features	AR	112240	4q26	*SEC24D* (SEC24-related gene family, member D) (43b)	Component of COPII-coated vesicles
25	Osteogenesis imperfecta, type V	AD	610967	11p15.5	*IFITM5* (interferon-induced transmembrane protein 5) (26a, 123b)	Stimulates mineralization when overexpressed
25	Osteogenesis imperfecta, type XIII	AR	614856	8p21.3	*BMP1* (bone morphogenetic protein 1) (7a, 87c)	BMP ligand
25	Osteogenesis imperfecta, type XIV	AR	615066	9q31.2	*TMEM38B* (transmembrane protein 38B) (123d)	Intracellular cation channel
25	Osteogenesis imperfecta type XV	AR	615220	12q13.12	*WNT1* (wingless-type MMTV integration site family member 1) (68a)	WNT ligand
25	Osteogenesis imperfecta, type XVI	AR	616229	11p11.2	*CREB3L1* (cAMP response element-binding protein 3–like 1) (134b)	Unfolded protein response
30	Proteus syndrome, somatic	AD, somatic mosaicism	176920	14q32.33	*AKT1* (V-AKT murine thymoma ciral ocongene homolog 1) (85)	PI3K-AKT signaling, cell proliferation, cell growth
32	Yunis-Varon syndrome	AR	216340	6q21	*FIG4* (FIG4, *S. cerevisiae*, homolog of) (24)	PI(3,5)P_2 signaling
35	Klippel-Feil syndrome 2	AR	214300	17q21.31	*MEOX1* (mesenchyme homeobox 1) (98)	Transcription factor involved in somitogenesis
36	Genitopatellar syndrome SBBYSS syndrome	AD	606170 603736	10q22.2	*KAT6B* (lysine acetyltransferase 6B) (23, 27)	Histone acetyltransferase
36	Meier-Gorlin syndrome 1	AR	224690	1p32.3	*ORC1* (origin recognition complex, subunit 1, *S. cerevisiae*, homolog of) (17, 16)	ORC subunit, DNA replication
36	Meier-Gorlin syndrome 2	AR	613800	2q22.3–23.1	*ORC4* (origin recognition complex, subunit 4, *S. cerevisiae*, homolog of) (49) (16)	ORC subunit, DNA replication
36	Meier-Gorlin syndrome 3	AR	613803	16q11.2	*ORC6* (origin recognition complex, subunit 6, *S. cerevisiae*, homolog of) (16)	ORC subunit, DNA replication
36	Meier-Gorlin syndrome 4	AR	613804	16q24.3	*CDT1* (16) Chromatin licensing and DNA replication factor 1	Recruited to fully assembled prereplication complex

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Group	Disorder	Inheritance	MIM number	Locus	Gene	Notes/function
36	Meier-Gorlin syndrome 5	AR	613805	17q21.2	*CDC6* (cell division cycle 6, *S. cerevisiae*, homolog of) (16)	Recruited to fully assembled prereplication complex
37	Myhre syndrome	AD	139210	18q21.2	*SMAD4* (mothers against decapentalplegic, *Drosophila*, homolog of, 4) (78)	TGF-β and BMP signaling modulation
37	Feingold syndrome 2	AD	614326	13q31.3	*MIR17HG* (micro RNA 17 host gene) (31)	miRNA cluster transcriptionally regulated by N-MYC
39	Meckel syndrome 2	AR	603194	11p12–q13.3	*TMEM216* (transmembrane protein 216) (140)	Ciliogenesis, cilium maintenance, planar-cell polarity signaling
39	Meckel syndrome 10	AR	614175	19q13.2	*B9D2* (B9 domain–containing protein 2) (35)	Ciliogenesis, ciliary protein localization, Hedgehog signaling
39	Joubert syndrome 21	AR	615636	8q13.1–13.2	*CSPP1* (centrosome spindle pole associate protein 1) (2, 125, 139)	Some patient phenotypes resembled Meckel syndrome
?	New syndrome with short stature and several additional clinical features, including neurodegeneration and photosensitivity	AR	NA	20p13–p12	*PCNA* (proliferating cell nuclear antigen) (10b)	Required for DNA repair

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; BMP, bone morphogenetic protein; IMAGe, intraunterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital abnormalities; MIM, Mendelian Inheritance in Man; miRNA, microRNA; NA, not applicable; ORC, origin recognition complex; PI3K, phosphoinositide 3-kinase; SBBYS, Say-Barber-Biesecker-Young-Simpson.

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