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Review article

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The genetic basis of human height

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Abstract

Human height is a model polygenic trait — additive effects of many individual variants create continuous, genetically determined variation in this phenotype. Height can also be severely affected by single-gene variants in monogenic disorders, often causing severe alterations in stature relative to population averages. Deciphering the genetic basis of height provides understanding into the biology of growth and is also of relevance to disease, as increased or decreased height relative to population averages has been epidemiologically and genetically associated with an altered risk of cancer or cardiometabolic diseases. With recent large-scale genome-wide association studies of human height reaching saturation, its genetic architecture has become clearer. Genes implicated by both monogenic and polygenic studies converge on common developmental or cellular pathways that affect stature, including at the growth plate, a key site of skeletal growth. In this Review, we summarize the genetic contributors to height, from ultra-rare monogenic disorders that severely affect growth to common alleles that act across multiple pathways.

Sections

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Introduction

The origins of human height — the distance from the sole of the foot to the crown of the head while standing on a flat surface and fully extended — have long held strong interest[1]. From the nineteenth century, comprehensive surveys were undertaken to map human height, initially in adults but eventually also in children. These surveys provided early evidence that environmental factors such as nutrition, health during childhood and overall lifestyle have important roles in determining final adult height and confirmed links between poverty and height, a pursuit known as auxological epidemiology. As these population surveys became more comprehensive, growth velocity was calculated, the rate at which a person grows in height over a specific period (measured in centimetres per year), which helped establish growth charts for use in medical practice to identify normal and abnormal growth patterns. Early observations of a hereditary component involved in height were based on studying families, as Galton[2] observed that offspring height resembled the average of both parents. In the twentieth century, there was expanding scientific and social interest in familial disorders of extreme disruption of typical growth, with the genetic underpinnings of many single-gene disorders being described through multi-generational family or animal model studies[3]. In parallel, polygenic explanations for height were starting to be explored, building on theories from Fisher that stature is heritable because of small effects of variants in many different genes acting in combination in each person[4]. Today, estimates from twin studies attribute up to 90% of an individual's height to their genetic makeup[5,6].

Although average height differs between countries, population variation seems to be very similar, reinforcing ideas that many common variants exert individually weak effects[6]. Despite height being highly heritable within a given population at a given time, average height has increased considerably over the past several centuries. Although initial theories might have been based around genetics and migration, recent data point to improved nutritional levels as the predominant cause of increased growth[7].

Understanding the genetic architecture of human height not only provides an understanding of the biology of growth but is also of clinical relevance. Differences in height are associated with altered risks of some diseases; for example, compared with population averages, taller people have an increased risk of cancer, whereas shorter people have an increased risk of coronary heart disease and diabetes mellitus[8–13]. The rapid adoption of sequencing technology — from SNP arrays and gene panels to whole-exome and whole-genome sequencing — has enabled the systematic investigation of the genetic contributors to height. Gene discovery efforts have led to the characterization of many single-gene disorders, with more than 500 genes listed in the Online Mendelian Inheritance in Man (OMIM) database harbouring pathogenic variants that cause monogenic syndromes including short stature or overgrowth. Moreover, large-scale, genome-wide association studies (GWAS) have revealed the common alleles that contribute to the high heritability of height, recently reaching the point of saturation, at least in European-ancestry populations[14].

Here, we review the genetic contributors to human height implicated by both monogenic and polygenic studies and discuss common pathways that have an impact on height, including those that affect the function of the growth plate (physis), a key site of skeletal growth (Box 1).

Monogenic conditions linked to height

Hundreds of monogenic disorders exhibit alterations in growth as a clinical feature. Studying these phenotypes at both ends of the stature spectrum has generated insights into the molecular mechanisms regulating human height (Fig. 1). Frequently caused by pathogenic variants in genes with important roles in the regulation of longitudinal growth, monogenic conditions that lead to short stature are more common than

Box 1 | Skeletal development and longitudinal growth

Formation of the skeletal bones (osteogenesis) in humans begins between the sixth and eighth week of embryonic development[175] and continues until about 25 years of age. The length of the fetus increases on average from ~5.5 cm at 12 weeks of gestation to ~50.0 cm at term. This rapid growth rate naturally decreases after birth (although it is still relatively high in the first 1–2 years of postnatal life) and then remains constant in early childhood until puberty, where there is acceleration of growth velocity that then gradually declines until the growth rate reaches zero in young adults, indicating growth plate fusion[176].

Two types of osteogenesis exist. Intramembranous ossification forms the flat bones of the skull, part of the clavicle and most of the cranial bones, by converting mesenchymal tissue directly to bone, whereas during endochondral ossification (the major mechanism of skeletogenesis), mesenchymal tissue is first transformed into a cartilage template (anlagen) that is subsequently replaced by bone. The long bones of the appendicular skeleton, including the femur, tibia and fibula of the legs, the humerus, radius and ulna of the arms, the clavicle and the small bones in the hands and feet, account for the majority of postnatal linear growth.

The fundamental biological process that drives longitudinal growth throughout childhood and adolescence is chondrogenesis, the generation of a cartilage model that is converted by osteoblasts to bone (Fig. 2). In brief, the growth plates at the ends of long bones are separated into various zones based on physiological characteristics: chondrocytes in the resting zone are characterized by slow cell cycle progression and serve as a progenitor pool for the proliferative zone, which is made up of differentiating and proliferating chondrocytes; in the hypertrophic zone, chondrocytes enlarge, mature and secrete extracellular matrix components; in the mineralization zone, which connects the epiphyseal plate to the diaphysis, calcified matrix restricts the diffusion of nutrients, leading to apoptosis of chondrocytes, which leaves cavities that are invaded by blood vessels depositing osteoblasts that build bone.

Growth plate chondrogenesis is regulated by complex interactions of molecular signals acting systemically as well as locally within the growth plate. Genetic factors, nutritional intake, hormones, inflammatory cytokines, paracrine growth factors, extracellular matrix factors and intracellular proteins all contribute to the extensive regulation of longitudinal growth, which continues until the epiphyses fuse with the metaphysis, marking the end of bone lengthening. The short stature observed in many genetic skeletal conditions is caused by downregulation in the proliferation or hypertrophy of growth plate chondrocytes, whereas genetic forms of tall stature result from increased chondrogenesis[177].

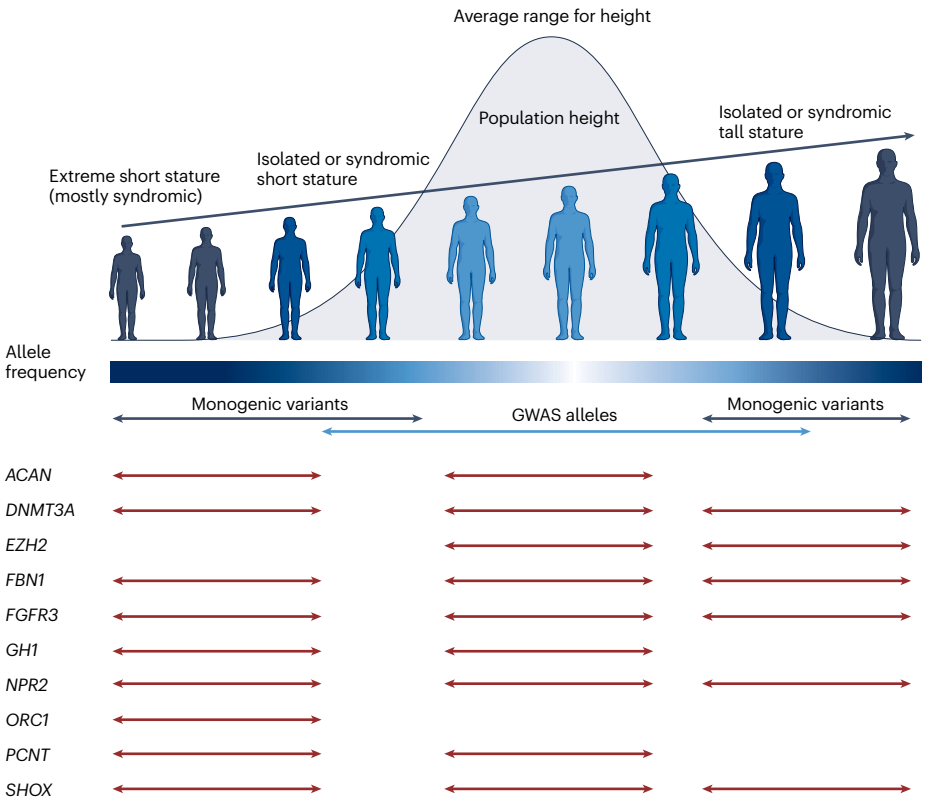

Fig. 1 | Genetic contributions to the spectrum of height. Genetic variants that contribute to height have been identified either through familial studies in which height alterations are extreme (either short or tall stature), or through genome-wide association study (GWAS) approaches, in which individual variants each exert a weak effect on overall height. Although weak-effect variants likely account for the variation seen for the majority of humans, stronger rare variants can also cause reduced height or overgrowth. Common variants in genes that regulate growth plate chondrogenesis modulate height within the average range and contribute to the polygenic basis of short stature, whereas more severe variants in these genes may present as isolated short stature, syndromic short stature or skeletal dysplasia.

those causing tall stature (based on OMIM entries). Here, we focus on several illustrative groups of disorders (Table 1) and provide manually curated lists of genes associated with disorders that have short or tall stature as a feature (Supplementary information). Monogenic disorders that affect stature can generally be categorized into syndromic (involving additional clinical features beyond differences in height) and non-syndromic conditions (changes in height are an isolated anthropometric feature). Changes in stature can be proportionate, where the body is affected evenly, or disproportionate, for example, with short limbs relative to trunk or vice versa.

Syndromic short stature

Syndromic conditions that cause short stature include skeletal dysplasias (abnormalities of formation, growth or maintenance of the human skeleton), a collectively common group of conditions often associated with severe (and often disproportionate) short stature or 'dwarfism' (medically defined as a final adult height of less than 4 feet 10 inches or ~147 cm, regardless of sex)[15]. Most of the variants in genes underlying skeletal dysplasias exert their primary effects at the level of the growth plate of the human skeleton[15] (Box 1). Similarly, microcephalic primordial dwarfism (MPD) syndromes are rarer syndromes of severe short stature, where growth failure is linked to altered rates of cell proliferation. Many other syndromic conditions exhibit reduced stature as a variable clinical feature, which can be a secondary consequence of impaired nutrition, failure to thrive, pleiotropic (multiple phenotypic) effects of underlying genes, including on the growth plate, or epigenetic abnormalities (such as in Silver–Russell syndrome).

Disorders of the growth hormone and IGF axis. Altered height owing to growth hormone (GH; also known as somatotropin) deficiencies has been recognized since the 1920s[16], and this lengthy research history helped support the first discovery of a genetic variant causing monogenic short stature in humans, with variants in *GHR*, the gene that encodes GH receptor, in individuals with Laron syndrome reported in 1989 (refs. 17,18). Since the initial molecular characterization of Laron syndrome, variants in almost all genes encoding common components of GH signalling (*GH1*, *IGF1*, *IGF2*, *IGF1R*, *GHR*, *STAT3*, *STAT5* and *IGFALS*) have been identified in individuals with short stature[19–22] (Table 1). GH activates the GH receptor, which in turn supports the synthesis of insulin-like growth factors insulin-like growth factor (IGF) 1 and IGF2, and accessory proteins such as IGF-binding proteins and ALS (acid-labile subunit). Accessory proteins support IGF in the circulation through complex formation. At the growth plate, IGF1 and IGF2 serve as endocrine factors to activate pro-proliferation pathways. GH has also been shown to have a direct role, stimulating local production of IGF1 (ref. 16). These conditions are clinically variable but, if untreated, are characterized by severe postnatal growth retardation and moderate-to-severe short stature and final adult height (−2 to −4 standard deviations below the population mean) that is proportionate. Disorders of pituitary development can also result in a lack of GH production, resulting in similar effects on stature in addition to variable other features (chubby build, craniofacial skeletal underdevelopment)[23]. Typically, the clinical phenotype of children with GH deficiency and resistance is indistinguishable from each other.

Interestingly, epidemiological studies indicate that individuals with Laron syndrome have a much lower risk of cancer and

Table 1 | Examples of genes with both monogenic and polygenic links to height

Gene	Protein	Monogenic disorders			Height GWAS		Biology
		Name	OMIM	Inheritance	*n* associations	Min. *P*-value	
ACAN	Aggrecan core protein	Spondyloepiphyseal dysplasia, Kimberley type	608361	AD	88	1×10^{-300}	ECM
		Short stature and advanced bone age, with or without early-onset osteoarthritis and/or osteochondritis dissecans	165800	AD			
		Spondyloepimetaphyseal dysplasia, aggrecan type	612813	AR			
ATR	Serine/threonine kinase ATR	Seckel syndrome 1	210600	AR	1	1×10^{-11}	DDR
ATRIP	ATR-interacting protein	Seckel syndrome	606605	AR	1	1×10^{-9}	DDR
CEP63	Centrosomal protein of 63 kDa	Seckel syndrome 6	614728	AR	4	6×10^{-34}	Centrioles and centrosome
CEP152	Centrosomal protein of 152 kDa	Seckel syndrome 5	613823	AR	10	9×10^{-35}	Centrioles and centrosome
CHD8	Chromodomain-helicase-DNA-binding protein 8	Intellectual developmental disorder with autism and macrocephaly	615032	AD	9	8×10^{-40}	Chromatin remodelling
DNMT3A	DNA (cytosine-5)-methyltransferase 3A	Tatton-Brown–Rahman syndrome	615879	AD	20	1×10^{-300}	DNA methylation
		Heyn–Sproul–Jackson syndrome	618724	AD			
DONSON	Protein downstream neighbour of Son	Microcephaly–micromelia syndrome	251230	AR	1	1×10^{-29}	DNA replication
		Microcephaly, short stature and limb abnormalities	617604	AR			
EED	Polycomb protein EED	Cohen–Gibson syndrome	617561	AD	4	1×10^{-82}	Histone methylation
EZH2	Histone-lysine *N*-methyltransferase EZH2	Weaver syndrome	277590	AD	1	1×10^{-52}	Histone methylation
FBN1	Fibrillin 1	Acromicric dysplasia	102370	AD	37	4×10^{-237}	ECM
		Geleophysic dysplasia 2	614185	AD			
		Marfan lipodystrophy syndrome	616914	AD			
		Marfan syndrome	154700	AD			
		MASS syndrome	604308	AD			
		Stiff skin syndrome	184900	AD			
		Weill–Marchesani syndrome 2	608328	AD			
FBN2	Fibrillin 2	Contractural arachnodactyly, congenital	121050	AD	18	4×10^{-161}	ECM
FGFR3	FGF receptor 3	Achondroplasia	100800	AD	9	4×10^{-63}	FGF signalling
		CATSHL syndrome	610474	AD, AR			
		Hypochondroplasia	146000	AD			
		LADD syndrome 2	620192	AD			
		Muenke syndrome	602849	AD			
		SADDAN	616482	AD			
		Thanatophoric dysplasia, type I	187600	AD			
		Thanatophoric dysplasia, type II	187601	AD			
GH1	GH1	GH deficiency, isolated, type IA	262400	AR	9	1×10^{-300}	GH pathway
		GH deficiency, isolated, type IB	612781	AR			
		GH deficiency, isolated, type II	173100	AD			
		Kowarski syndrome	262650	AR			
GHR	GH receptor	Partial GH insensitivity	604271	AD	26	1×10^{-300}	GH pathway
		Increased responsiveness to GH	604271	AD			
		Laron dwarfism	262500	AR			

Table 1 (continued) | Examples of genes with both monogenic and polygenic links to height

Gene	Protein	Monogenic disorders			Height GWAS		Biology
		Name	OMIM	Inheritance	*n* associations	Min. *P*-value	
GPC3	Glypican 3	Simpson–Golabi–Behmel syndrome, type 1	312870	XLR	1	2×10^{-8}	Proteoglycan
GPC4	Glypican 4	Keipert syndrome	301026	XLR	0	NA	Proteoglycan
HIST1H1E	Histone H1.4	Rahman syndrome	617537	AD	6	1×10^{-300}	Chromatin
IGF1R	IGF1 receptor	IGF1 resistance	270450	AD, AR	49	1×10^{-300}	GH pathway
IGF1	IGF1	IGF1 deficiency	608747	AR	56	1×10^{-300}	GH pathway
IGF2	IGF2	Silver–Russell syndrome 3	616489	AD	19	3×10^{-308}	GH pathway
IGFALS	IGF-binding protein complex acid labile subunit	Acid-labile subunit deficiency	615961	AR	2	2×10^{-17}	GH pathway
IHH	Indian hedgehog protein	Acrocapitofemoral dysplasia	607778	AR	16	1×10^{-300}	Hedgehog signalling
		Brachydactyly, type A1	112500	AD			
MCM5	DNA replication licensing factor MCM5	Meier–Gorlin syndrome 8	617564	AR	1	3×10^{-9}	DNA replication
MCPH1	Microcephalin	Primary microcephaly 1	251200	AR	3	1×10^{-37}	DDR
NFIX	Nuclear factor I X-type	Malan syndrome	614753	AD	0	NA	Transcription
		Marshall–Smith syndrome	602535	AD			
NPPC	C-type natriuretic peptide	Idiopathic short stature	600296	AD	22	1×10^{-300}	FGF signalling
NPR2	Atrial natriuretic peptide receptor 2	Acromesomelic dysplasia 1, Maroteaux type	602875	AR	9	6×10^{-181}	FGF signalling
		Epiphyseal chondrodysplasia, Miura type	615923	AD			
		Short stature with nonspecific skeletal abnormalities	616255	AD			
NSD1	Histone-lysine *N*-methyltransferase, H3 lysine 36 specific	Sotos syndrome	117550	AD	14	7×10^{-310}	Histone methylation
PCNA	Proliferating cell nuclear antigen	Ataxia-telangiectasia-like disorder 2	615919	AR	2	3×10^{-97}	DNA replication
PCNT	Pericentrin	Microcephalic osteodysplastic primordial dwarfism, type II	210720	AR	2	4×10^{-39}	Centrioles and centrosome
POC1A	POC1 centriolar protein homologue A	Short stature, onychodysplasia, facial dysmorphism and hypotrichosis	614813	AR	2	6×10^{-12}	Centrioles and centrosome
PTH1R	PTH/PTHr receptor	Chondrodysplasia, Blomstrand type	215045	AR	4	9×10^{-128}	PTH signalling
		Eiken syndrome	600002	AR			
		Metaphyseal chondrodysplasia, Murk Jansen type	156400	AD			
SETD2	Histone lysine *N*-methyltransferase SETD2	Luscan–Lumish syndrome	616831	AD	2	1×10^{-7}	Histone methylation
		Rabin–Pappas syndrome	620155	AD			
STAT3	STAT3	Hyper-IgE syndrome 1 with recurrent infections	147060	AD	1	3×10^{-56}	GH pathway
STAT5B	STAT5B	GH insensitivity with immune dysregulation 1	245590	AR	1	1×10^{-26}	GH pathway
		GH insensitivity with immune dysregulation 2	618985	AD			
SUZ12	Polycomb protein SUZ12	Imagawa–Matsumoto syndrome	618786	AD	4	1×10^{-169}	Histone methylation

AD, autosomal dominant; AR, autosomal recessive; DDR, DNA damage repair; ECM, extracellular matrix; FGF, fibroblast growth factor; GH, growth hormone; GWAS, genome-wide association study; IGF, insulin-like growth factor; NA, not applicable; PTH, parathyroid hormone; PTHr, PTH-related peptide; STAT, signal transducer and activator of transcription; XLR, X-linked recessive.

type 2 diabetes mellitus compared with variant carriers and the general population[24,25], reinforcing biological links between height and genetically complex diseases.

Achondroplasia and FGFR3-related forms of short stature. Achondroplasia is a skeletal dysplasia that results in disproportionate (predominantly short-limbed) short stature. The onset of delayed skeletal growth is from the last trimester of pregnancy[26], with decreased annual growth velocities from birth resulting in a final height of −5.0 to −7.0 standard deviations (for both sexes) compared with corresponding charts for average-statured individuals[27]. Achondroplasia is caused by a recurrent, dominant gain-of-function pathogenic variant in the *FGFR3* gene, which encodes fibroblast growth factor receptor (FGFR) 3 (refs. 28,29). The p.Gly380Arg variant results in activation of an inhibitory pathway in growth plate chondrocytes, which leads to their decreased proliferation and differentiation, as well as reduced extracellular matrix production and impaired endochondral ossification of the skeleton[28] (Box 1). The spine is less affected than the appendicular skeleton in individuals with achondroplasia, which results in an increased upper-to-lower segment ratio compared with average-statured children and adults[26]. Impaired ossification of the base of the skull and spine causes compression of the brainstem and spinal cord, consequent to decreased growth and subsequent stenosis of the foramen magnum and spinal canal, respectively, which underlies the neurological complications seen in many infants and adults with achondroplasia[30].

Some variants in *FGFR3* cause hypochondroplasia, a milder syndrome in which growth and final height are typically −2.5 to −4.0 standard deviations below average[31]. Medical complications are less prevalent and severe than those seen in individuals with achondroplasia. Other pathogenic variants in *FGFR3* lead to thanatophoric dysplasia, a lethal skeletal dysplasia in which children have extreme short-limbed short stature and respiratory insufficiency owing to severely impaired growth of the thoracic cage[32]. There have been reports of families in which proportionate short stature (without clinical or radiographic evidence of skeletal dysplasia) segregates as an autosomal dominant trait, with likely pathogenic variants in *FGFR3* reported[33,34]. These reports suggest that abnormalities in the FGFR3 pathway are potentially a more common cause underlying 'familial' and 'idiopathic' short stature than previously suspected.

Other pathway-specific skeletal dysplasias. In addition to FGFR3 signalling, pathogenic variants in several pathways relevant to skeletal growth plate homeostasis cause skeletal disorders that have marked (and often disproportionate) short stature as a phenotypic hallmark[15]. For example, abnormalities in components of the transforming growth factor-β (TGFβ)/bone morphometric protein (BMP) signalling pathway are common for various skeletal dysplasias with both short and tall stature[35]. Impaired TGFβ function has been demonstrated in conditions such as acromelic dysplasia, where short stature is a clinical hallmark, whereas increased TGFβ signalling is associated with elongated skeletal elements and tall stature observed in Marfan syndrome[35]. BMP and TGFβ are cytokines that activate various pathways — both SMAD-dependent and SMAD-independent — to affect osteoblast and osteoclast differentiation[36].

Both dominant and recessive forms of short stature are caused by variants in the gene *NPR2* (refs. 37–39). C-type natriuretic peptide (CNP), a key regulator of bone growth, acts as a ligand for NPR2 (atrial natriuretic peptide receptor 2), which dimerizes upon ligand binding and activates type II cGMP-dependent protein kinase. Increased cGMP levels inhibit the mitogen-activated protein kinase cascade, antagonizing FGFR3. This signalling supports increased proliferation and differentiation of chondrocytes (Box 1). Gain-of-function variants in *NPR2*, loss-of-function variants in *NPR3*, which encodes the clearance receptor of CNP, and a translocation causing overexpression of CNP have also been associated with tall stature[40–43].

Another signalling pathway crucial for bone growth is the parathyroid hormone (PTH) pathway, in which PTH (or the PTH-related protein, PTHrP) acts through their receptor, PTH1R, to control differentiation and mineralization in the growth plate during bone production (Box 1). Although variants affecting the PTH ligand cause familial isolated hypoparathyroidism[44], biallelic loss-of-function variants in *PTH1R* underlie the skeletal dysplasias Blomstrand chondrodysplasia or Eiken syndrome[45,46], and monoallelic variants in *PTH1R* leading to its constitutive activation cause Jansen metaphyseal chondrodysplasia[47]. *IHH* encodes Indian hedgehog, a paracrine regulator of endochondral ossification (Box 1), that is expressed in pre-hypertrophic chondrocytes and acts to regulate proliferation and differentiation of chondrocytes[48], acting in a feedback loop in the growth plate with PTHrP[49]. Biallelic variants in *IHH* have long been established to cause severe short stature in acrocapitofemoral dysplasia[50]; more recently, monoallelic variants have been linked to familial short stature[51].

Disrupted interactions between the extracellular environment and signalling pathways have also been implicated in disorders of altered stature. Genetic variants in *ACAN* are a common cause of familial short stature, which can be either isolated or syndromic[52,53]. *ACAN* encodes aggrecan core protein, a proteoglycan crucial for both extracellular matrix stability and supporting proliferation and differentiation of the growth plate. In addition to its architectural role, absence of aggrecan in animal models has shown disruption of IHH and FGFR3 signalling pathways, with alterations in gene expression in growth plates[54–56].

Primordial dwarfism

MPD is a specific form of reduced height where body ratios are severely reduced, often in proportion, including a reduction in brain size, with the reduction in growth starting in utero. MPD is used as an umbrella term for several conditions that are almost always inherited in an autosomal recessive manner.

Biallelic loss-of-function variants in *PCNT* cause microcephalic osteodysplastic primordial dwarfism type II, the most established form of MPD. These variants cause a loss of pericentrin, a key scaffolding protein for the centrosome, which forms the base of the mitotic spindle[57–59]. The centrosome is formed by a pair of centrioles, surrounded by pericentriolar matrix. Errors in centriole duplication are a common disease mechanism underlying primary microcephaly[60], and variants in some of the same genes or pathway (such as *CEP63*, *PLK4*, *CEP152*, *CENPJ* and *MCPH1*) can also cause a concomitant reduction in height, then categorized as MPD[61–65]. Several familial examples of trial-lelism (in which there are three variants in two related genes) or genetic modifiers from the same pathways exist, whereby additional variants seem to increase severity of the phenotype beyond microcephaly to MPD[66], suggesting that digenic or oligogenic mechanisms could cause expansion of the reduced growth phenotype beyond the brain.

Delays in progression through the cell cycle are also a common cause of MPD. Biallelic hypomorphic loss-of-function variants in a number of genes (*ORC1*, *ORC4*, *ORC6*, *CDT1*, *CDC6*, *MCM5*, *MCM7*, *CDC45*, *GINS2*, *GINS3* and *DONSON*) or de novo dominant-negative variants in

GMNN, which together encode the earliest proteins required for DNA replication, cause Meier–Gorlin syndrome[67–77], a type of MPD with a proportionate reduction in brain and body growth, alongside small or simply formed ears (microtia) and absent or small kneecaps[77,78]. Many genes encoding components of the replisome — the DNA replication machinery that coordinates activity and progression of the polymerases along DNA — including *POLE2*, *POLD1* and *PCNA* are similarly linked to reduced growth, although often with additional clinical features that affect other body systems, such as the immune or skeletal systems[79–83].

Components of the DNA damage response and DNA repair pathways also affect height in a syndromic form; hypomorphic variants in *ATR*, which encodes a key kinase responding to replication stress, are the main cause of Seckel syndrome[84]. More recently, genetic variants in *ATRIP*, which encodes the ATR interacting protein, have also been implicated in Seckel syndrome[85]. Proteins involved in the DNA damage response, such as CHK1, can localize at the centrosome[86], suggesting further links between MPD-related pathways that could be controlling overall growth[57].

A considerable number of cellular pathways have now been associated with MPD, all of which are fundamental systems for cell functioning[83,87]. The mechanisms leading to reduced growth are not yet resolved for many forms of MPD but likely involve the global reduced proliferation of stem cells resulting in reduced total cell numbers[87], with potential specific effects on the growth plate not yet explored. Reduced proliferation could be caused through increased replication stress and apoptosis, delays to the cell cycle or perturbations to mitosis through altered spindle formation or plane of division.

Isolated short stature

Isolated short stature refers to a group of conditions with heterogeneous aetiology that present with proportionate short stature with no obvious underlying endocrine cause on relevant hormonal (that is, GH–IGF1 axis) testing or skeletal dysplasia on radiographic survey of the skeleton. Many of these isolated forms of short stature represent the mildest end of a monogenic spectrum; for example, *SHOX* pathogenic variants can cause syndromic (Léri–Weill dyschondrosteosis) or isolated short stature[88]. Additionally, alleles in other growth-related genes could act as genetic modifiers to influence effects of variants, with potential genetic modifiers in genes encoding retinoic acid signalling identified in individuals with *SHOX* variants[89]. In many cases, isolated short stature likely reflects the cumulative, polygenic effects of height-associated variants of modest effect. The large number of common variants (>10,000) that contribute to height (discussed subsequently) enables their combined additive contribution to have substantial effects on stature, although individual effect sizes are small[14]. Indeed, individuals at the shorter (or taller) tails of the height distribution typically have lower (or higher) predicted height from common variants, consistent with these variants collectively explaining nearly half of the population variation in height. The small number of individuals whose heights substantially deviate from their predicted heights are more likely to have rare variants in monogenic genes[90], making them exceptions that prove the rule.

Genomic conditions altering height

Short stature is a common feature of chromosomal disorders, most notably Down syndrome and Turner syndrome. However, although altered height is commonly a dominant feature of these and other syndromes involving chromosomal abnormalities or genomic deletions, the underlying genetic defects often encompass multiple genes, making it more difficult to decipher the precise mechanisms related to height. Patient case series can help refine critical boundaries for specific genomic structural variants and, together with smaller variants identified within individual genes, have helped tease out associations between specific genes and a range of phenotypes, including short stature[91–93]. Hundreds of different copy number variants have been identified in patients presenting with a likely genetic disorder[94], with at least 50 recurrent enough to be defined as a genomic condition in DECIPHER or ClinGen resources. Of these, ~20% include short or tall stature as a defining characteristic. Changes in height, particularly short stature, are present as a variable feature in many more genomic conditions. For most conditions, a clear gene-to-phenotype relationship has not been established, either because the developmental influences of each gene in the locus remain incompletely understood, or possibly because clinical features such as short stature are caused by synergistic effects across multiple developmentally relevant pathways affected by genes in the critical genomic region associated with the condition.

A classic example of a single gene influencing one phenotypic feature in a genomic condition is *SHOX*, which lies in the pseudoautosomal region on the X and Y chromosomes. One copy is absent in Turner syndrome, where females exhibit short stature, whereas syndromes with additional copies of the X chromosome, such as Klinefelter syndrome (also known as XXY syndrome), exhibit tall stature[95], highlighting the bidirectional control of growth (discussed subsequently). As with single-nucleotide variants, combined effects of multiple structural variants can cause short stature[96].

Genetic causes of tall stature and overgrowth

On the other side of the stature spectrum, conditions in which individuals exhibit height above the 97th percentile for corresponding age and sex, such as Marfan syndrome, give insights into the roles of extracellular matrix proteins and related signalling molecules in growth homeostasis. Atypically tall stature can be associated with intellectual disability and macrocephaly.

Marfan syndrome is one of the most common genetic disorders of tall stature. Long bones and joint laxity are a common characteristic in this connective-tissue syndrome, although the primary focus is on cardiac issues, as serious morbidity can occur from artery enlargement, dilatation or aorta and valve prolapse[97]. Marfan syndrome arises from variants in *FBN1*, which encodes fibrillin 1, a macromolecule that polymerizes into microfibrils. A mouse model showed that altered function of the perichondrium, a layer of dense irregular connective tissue that surrounds the cartilage of developing bone, underlies the bone lengthening and therefore likely tall stature in patients with Marfan syndrome[98].

Simpson–Golabi–Behmel syndrome is an X-linked overgrowth disorder that causes tall stature and intellectual disability, with the condition mostly affecting men, although female carriers can have a mild version. Loss-of-function variants occur in either *GPC3* or *GPC4*, which encode the proteoglycan proteins glypican 3 and glypican 4, respectively. These proteins bind to the plasma membrane and regulate signalling pathways strongly linked to bone growth, including Wnt, BMP and FGF signalling[99,100] (Fig. 2).

Several monogenic overgrowth syndromes are linked to variants in epigenetic regulators. For example, loss-of-function variants in three of the four subunits of the key chromatin modifier polycomb repressive complex 2 (PRC2), a H3K27 methyltransferase, cause tall stature: *EED* (Cohen–Gibson syndrome), *SUZ12* (Imagawa–Matsumoto syndrome) and *EZH2* (Weaver syndrome)[101,102]. The H3/H4 histone

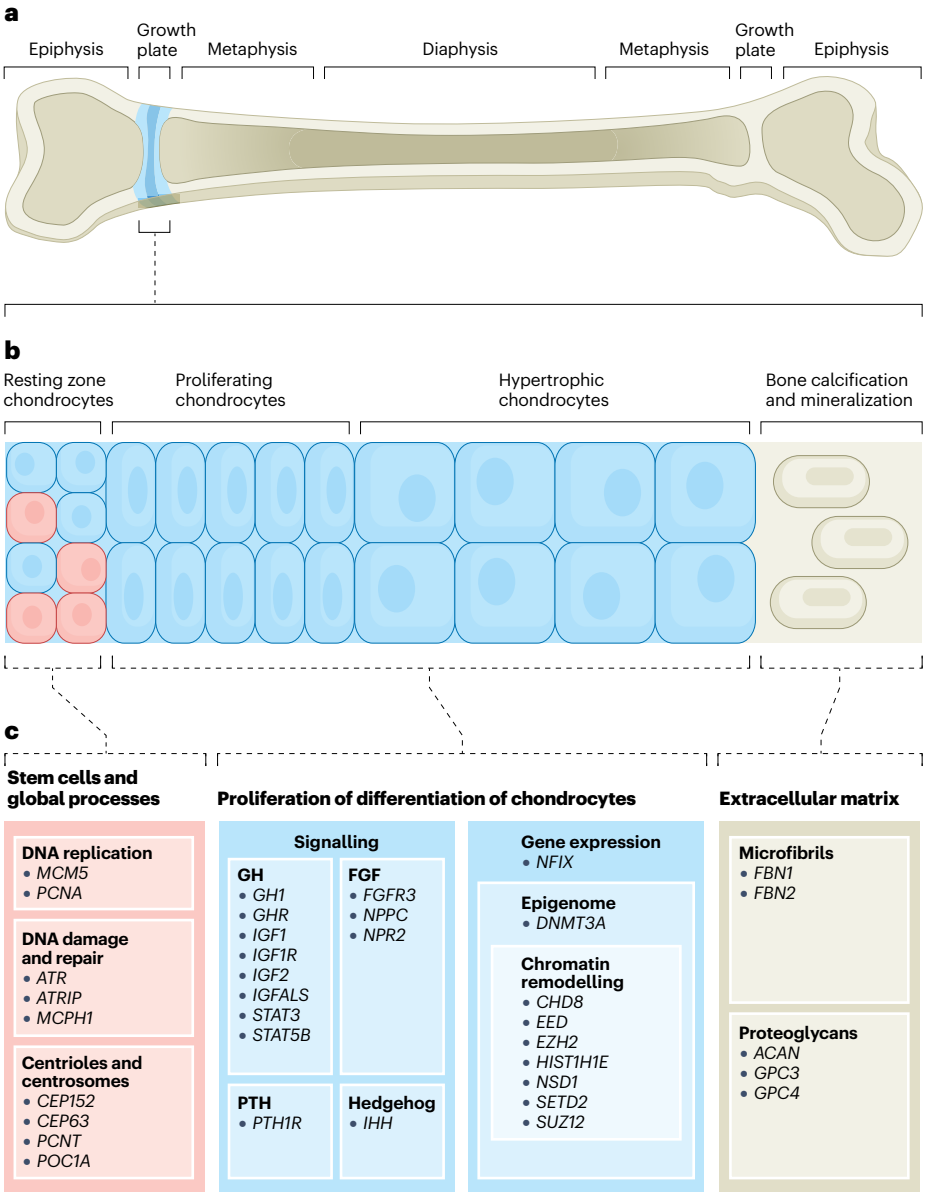

Fig. 2 | Height-associated genes cluster into common processes and pathways that affect activity in the growth plate. a, The growth plate (physis) within growing bones. **b**, In the growth plate, chondrocytes proliferate, differentiate and secrete cartilage, which is calcified and mineralized, subsequently turning into bone (Box 1). **c**, Examples of genes that affect stature (Table 1) cluster into common cellular processes, categorized here into their primary effects on the proliferation and differentiation of chondrocytes, the extracellular matrix, stem cells or global processes that could occur across the growth plate. Given the complexity and feedback mechanisms that exist, many of these pathways likely act in multiple layers and cell types within the growth plate. Note that the listed genes are illustrative examples described in this Review and not intended to be comprehensive. Moreover, the biology is more complex than depicted, with specific processes not necessarily attributable to specific parts of the growth plate; for example, for the stem cell categories, functional evidence to support a direct connection is minimal. FGF, fibroblast growth factor; GH, growth hormone; PTH, parathyroid hormone.

methyltransferase NSD1 mediates the interplay between the PRC2 subunit EZH2 and another chromatin remodelling complex, SWI/SNF[103]. Loss-of-function variants in *NSD1* cause Sotos syndrome[104], one of the most common overgrowth conditions, which affects 1 in 14,000 individuals. SETD2 is a histone methyltransferase with a similar domain structure to NSD1. Haploinsufficiency for *SETD2* can also cause tall stature (Luscan–Lumish syndrome)[105], but this feature is much more variable, with some patients showing reduced height[106]. Pathogenic variants in multiple subunits of the SWI/SNF complex are linked with Mendelian forms of neurological impairment, but many affected individuals also present with altered height, albeit with mild short stature rather than overgrowth[107]. Other chromatin remodellers such as CHD8, the linker histone H1 (encoded by *HIST1H1E*) or transcription factors such as NFIX have also been implicated in overgrowth conditions, with tall stature being a common albeit not consistent feature[108–110]. Loss-of-function variants in *DNMT3A*, which encodes one of the core methyltransferases responsible for de novo methylation, cause the overgrowth condition Tatton-Brown–Rahman syndrome[111]. Reduced DNMT3A activity causes hypomethylation across the genome, particularly at genes linked to development and differentiation[112]. Mouse models studying the orthologous mutation for the most common human missense variant, p.Arg882His, show longer bones and thicker growth plates in the proximal tibia. However, this increased thickness is not attributable to alterations to any specific cell type or layer within the growth plate[113,114]. Arg882His is a hotspot residue for somatic driver mutations in acute myelogenous leukaemia. In vitro studies of mutating this residue confirm a dominant-negative effect, in which the mutant DNMT3A protein sequesters wild-type DNMT3a, thereby reducing

overall function[115]. Other genes involved in chromatin may also regulate growth; for example, a single patient with an overgrowth syndrome harbouring a variant in *SPIN4* has been described[116].

Polygenic contributors to human height

Most children with short stature do not have a clear monogenic cause. Estimates of diagnostic rates even in the select group of patients with short stature who are referred to specialists are typically 30% or less[117,118]; the majority of (but not all) children who have a monogenic cause of short stature have either severe short stature or accompanying syndromic features. This observation is consistent with at least half of the ~80% heritability of height seen in many studies being explained by common genetic variation.

Common genetic variants and GWAS of height

Human height has high heritability; inherited variation is estimated to explain 80% or more of the phenotypic variance within populations of relatively homogeneous ancestries and birth eras, as is true for populations included in most genetic studies[119]. Height has been used to develop numerous methods and ideas in statistics and genetics, including the concept of regression analysis (regression of child height towards the mean)[2], demonstrations of confounding of genetic association studies by cryptic population structure[120], methods for assessing heritability[119,121] and methods to gain biological insights from genetic association data[122].

Common genetic variants with allele frequencies above ~1% have been estimated (and subsequently confirmed) to explain about half of the heritability and nearly half of overall phenotypic variation in height[14,121]. In 2007, GWAS emerged as an effective means to discover common genetic variants that influence polygenic traits such as height[123,124]. In part because of the high heritability of height and its ease of measurement, more common variants have been discovered to be associated with height than with any other human phenotype. Indeed, the most recent GWAS, from the GIANT (Genetic Investigation of ANthropometric Traits) consortium, identified 12,111 approximately independent signals of association with height at common genetic variants that reached genome-wide significance ($P < 5 \times 10^{-8}$)[14].

Several key findings emerged from the GIANT study, which included data from more than 5 million people, including more than 1 million with substantial non-European-like genetic ancestries. First, additive effects of the 12,111 variants account for the majority (>80%) of the heritability predicted to be attributable to common genetic variation, at least in individuals of European ancestry. Specifically, this heritability of height is captured by a polygenic score, in which the number of height-increasing alleles carried at each variant is summed and weighted by each variant's effect on height. More comprehensive polygenic scores that include variants not reaching genome-wide significance can account for essentially all the common variant heritability in European-ancestry populations. Partitioning of heritability showed that genomic regions within 35 kb of the 12,111 variants, together comprising ~23% of the genome, could explain nearly all the heritability attributable to common variants, even in populations with substantial non-European-like genetic ancestries. In addition, many signals were clustered non-randomly in this subset of the genome, often near biologically relevant genes such as those that cause monogenic disorders of skeletal growth. These results indicate that, at this sample size, the GWAS produced a saturated map of height-associated regions in the genome. Finally, downsampling of the GWAS data showed that much smaller sample sizes were sufficient to outline broad brushstrokes of relevant biological pathways (at least using current tools of implicating genes and gene sets from GWAS results)[14].

One of the challenges of GWAS for height, as for other complex traits, has been that most of the associated common variants are non-coding. Together with correlated nearby variants (in linkage disequilibrium) and the relative inability to determine the consequence of non-coding variation, this presents a major challenge to definitively identify the genes that mediate any associations. A recent whole-genome sequencing study identified rare non-coding variants in multiple loci that influence height, likely through gene regulation[125]. As whole-genome sequencing data sets of larger cohorts become available, it is likely that more signals will be identified. Of note, many GWAS associations are near genes underlying monogenic syndromes of abnormal skeletal growth (much more often than expected by chance[126]), but many loci do not overlap with known height genes, indicating that GWAS signals are also implicating previously unknown genes or biology. Understanding the relevant genes and pathways is essential to translate the results of GWAS into new insights into the biology of human skeletal growth. Thus, in addition to large genetic discovery efforts using GWAS, additional computational analysis, functional experiments and other types of genetic studies are needed to identify the genes through which associated variants from GWAS exert their effects on human skeletal growth.

Rare coding variants and association with height

One genetic approach to identify relevant genes for height is to focus on rare coding variants. Studies using a microarray designed to genotype known rare or low frequency (minor allele frequency as low as ~0.1%) missense and loss-of-function variants across the exome identified 83 such variants associated with height, including several in genes underlying monogenic disorders (for example, *ACAN*, *IHH* and *PTH1R*)[127]. Because variants below a certain allele frequency are too infrequently observed to be assessed on their own, analyses typically aggregate variants (for example, missense variants in the same gene) using burden tests or similar approaches[128–130]. These approaches can test for associations of a collection of rare variants with the presence of polygenic disorders or changes in polygenic traits such changes in height and are now being applied to biobanks with sequencing data from hundreds of thousands of individuals[131,132]. These studies have begun to identify multiple genes in which rare missense or loss-of-function variants have strong aggregate evidence of an association with height[132,133].

Examination of the Genebass browser, which makes publicly available rare variant association tests for 394,841 individuals from the UK Biobank[132], reveals 78 genes in the UK Biobank in which loss-of-function variants are in aggregate associated with height using SKAT-O[128] after correction for multiple testing. Of note, of these 78 genes, 18 are known to cause monogenic disorders of skeletal growth. Consistent with the strong bias of monogenic disorders causing short rather than tall stature, rare loss-of-function variants decrease rather than increase height for 15 of these 18 genes (one of the three genes in which loss-of-function variants increase height is *FBN1*). Many of these 18 genes are near GWAS signals of association (for example, *ACAN*, *IHH* and *NPR2*). Furthermore, genes with nominally significant ($P < 0.05$) associations with height include about twice as many monogenic height genes as expected by chance (~6.2% versus ~3.1%). Thus, a substantial increase in sample size of these sequencing studies will definitively identify many more genes as having rare coding variants that affect height, further implicating known and new genes in skeletal growth.

From genes to biology: common pathways in monogenic and complex regulators of height

The overlap in genes implicated in alterations of height, identified using different genetic approaches, indicates that some genes have an 'allelic spectrum' of variants that influence height (Fig. 3). These variants range from extremely rare with large effects, causing monogenic syndromes, to rare coding variants that increase or decrease height by 1–2 standard deviations or less[127], to common, typically non-coding variants that have much smaller effects[14]. Although the mechanisms of action for common non-coding variants remain largely unknown, they presumably act by modulating the expression of important genes in relevant tissues (such as the growth plate), perhaps during key specific periods of fetal or childhood growth and development (Box 1).

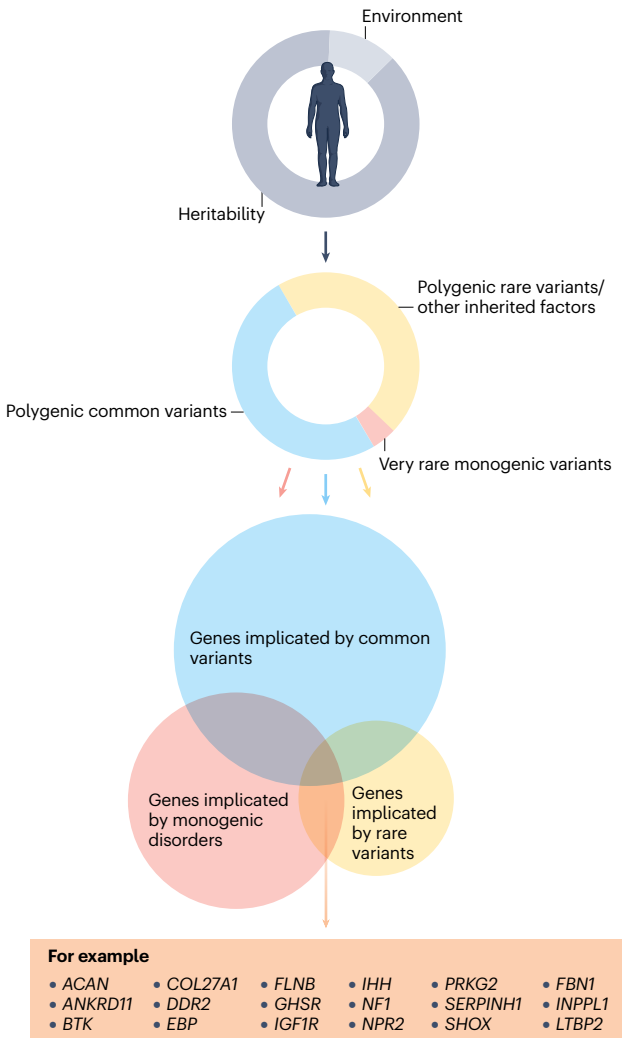

Fig. 3 | The determinants of height. Although environmental factors can influence stature, the heritability of height is high, indicating a strong genetic influence. Almost half of the heritability is associated with polygenic common variation. The majority of the remaining heritability is accounted for by polygenic rare variants or other inherited factors, with only a small amount of heritability accounted for by very rare monogenic variants. Of this genetic variation, the genes implicated by common or rare variants (blue and yellow, respectively), and genes implicated by monogenic disorders of altered height (red). There are genes that overlap among all three groups: genes that are associated with both common and rare variants (green), genes associated with both common variants and monogenic disorders (purple), genes that are associated with both rarer variation and monogenic disorder (orange) and genes common to all three sources of variation (brown). Examples of genes associated with rare variation and monogenic disorders are listed, in which for 13 of the 17 autosomal genes (all but *ANKRD11*, *BTK*, *INPPL1* and *NF1*), height is the phenotype most strongly associated with the gene in the genome-wide association study catalogue.

Skeletal development and signalling

As GWAS reaches the saturation point for identification of genomic regions associated with height (not including variants that are common only in certain ancestries and will be found only by studying larger samples from more diverse populations), the identified genes and genomic loci now cover all known aspects in the signalling pathways influencing bone growth (Fig. 2). These include subtle influences on activity of morphogen signalling, signal transduction, control of gene expression, cell proliferation and differentiation, all affecting chondrocyte biology and development and composition of the extracellular matrix, and production of hormones such as GH and downstream factors that act on the growth plate.

Although well-established coding variants in *FGFR3* cause a severe reduction in height causing achondroplasia, non-coding SNPs within this gene locus also show a strong association with height, albeit with weaker effect[14,134–136]. Multiple GWAS signals have also been detected at loci related to the CNP–NPR2 pathway[126,137–139], building on the foundation of the Mendelian forms of short stature linked to these genes[37–39]. In line with the well-established monogenic forms of short stature, genes encoding multiple components of the GH–IGF1 growth axis have also been associated with height, with many independent signals observed in tens of different GWAS. *ACAN* is a long-established gene implicated in monogenic and polygenic contributions to height[52,53,140–142]. A GWAS meta-analysis was able to identify missense variants, as well as variants within multiple enhancers and a variable-number tandem repeat, that contributed to the high density of GWAS signals at the *ACAN* locus[14], further adding to the range of genetic alterations identified in *ACAN* which can modulate height. Although Mendelian forms of altered growth provide a powerful fast-track to link GWAS loci to phenotype, large-scale functional studies can also prove an efficient method for linking genotype to phenotype. A large-scale in vitro CRISPR knockout screen identified 145 genes with effects on chondrocyte proliferation and maturation in mice[143]. Included in these results were several chromatin-related proteins, reaffirming links between Mendelian stature conditions, GWAS signals and functional roles in the growth plate.

Cell cycle regulation and mitosis

Perturbation of the cell cycle or mitosis can either slow overall proliferation during organism development or can act more specifically at the growth plate. Many cell cycle regulators associated with height are involved in S phase progression, with underlying genes associated with different types of MPD. These examples tend to affect all body systems, and so there is a proportionate reduction in size of the whole body. Although many genes linked to MPD have not featured strongly in GWAS of height, studying gene set enrichments identified several MPD genes (for example, *PCNT*, *ATR*, *TRAIP* and *CENPJ*), which suggests that there could also be polygenic signals that have an impact on height for MPD genes, which has yet to be explored[14]. Although effects on bone growth have not been broadly explored in MPD, growth plates examined in an autopsy of a child with microcephalic osteodysplastic primordial

dwarfism II (caused by loss-of-function variants in *PCNT*) showed a lack of chondrocyte columnar formation and fewer but larger cells in this region[144]. *POC1A* encodes protein of centriole 1A, a protein involved in centriole duplication, and biallelic variants in *POC1A* cause the short stature SOFT syndrome[145]. A *Poc1a* mouse model showed a disorganized growth plate with altered polarity of chondrocytes and increased apoptosis[146]. Together, these studies suggest links between centrosomes and primary cilia in cell polarity and the required polarity for correct chondrocyte column formation in growth plates.

Conversely, the growth plate can be specifically affected by effects on the cell cycle. The activating homeobox transcription factor encoded by *SHOX* shows highest expression in the terminally differentiated chondrocytes in the growth plate, and SHOX directs a programme of cell cycle arrest and apoptosis to balance proliferation and apoptosis in the growth plate[147].

Chromatin remodelling and gene regulation

Our understanding of the regulation and dynamics of chromatin modifications and signalling has markedly increased in the past decade, with common areas emerging as central development hubs relevant to height[148]. The PRC2 complex, which methylates H3K27 to induce transcriptional silencing, is a key example. Reduced activity of any of the three PRC2 subunits EED, SUZ12 and EZH2 has a similar developmental impact on humans with similar clinical phenotypes, which aligns with the recent observation that variants in all three genes cause the same epi-signature in patient blood cells[149] — patterns of methylation in blood-derived DNA specific to a gene or disorder that are becoming useful for differential diagnosis or resolution of variants of uncertain significance[150]. An opposite epi-signature was observed in an individual with reduced growth, caused by a gain-of-function variant in *EZH2* that increased enzymatic activity in an in vitro assay[149]. Epi-signatures are analogous to a methylation 'scar' left by altered epigenetic processes — similar scars or patterns suggest the same pathophysiological mechanism occurred in early developing cells to cause the resultant phenotype.

The effects of reducing either EZH2 (ref. 144) or EED[145] on the growth plate have been explored using lineage-specific mouse knockout models. *Eed* deficiency caused a reduction in chondrocyte proliferation and an increase in the differentiation of hypertrophic chondrocytes and cell death, all of which contribute to reduced elongation of the growth plate[151] (Box 1). Overactivation of both TGFβ signalling and Wnt signalling was identified as key proponents of these mechanistic consequences. In a mouse model with complete knockout of *Ezh1* and cartilage-specific knockout of *Ezh2*, loss of PRC2 methyltransferase activity in the growth plate led to severe impairment in longitudinal bone growth, as a result of decreased chondrocyte proliferation and reduced hypertrophic chondrocyte cell size[152]. Focusing on candidate loci, altered methylation patterns were observed for cell cycle regulators and members of the IGF pathway. Transcriptomic analysis further pointed to Wnt–β-catenin signalling as another pathway altered in the genetic model[152].

Pathways or gene sets linked to gene regulation and expression are strongly represented in GWAS[142], and many non-coding variants are thought to influence chromatin state by altering binding motifs for transcription regulation. One intriguing example is a causal height variant that lies within an EZH2 binding site within the imprinted *KCQN1* locus[153], in which maternal inheritance has been shown to reduce height[154]. Altered imprinting and gene expression at this locus cause either the overgrowth condition Beckwith–Wiedemann syndrome or the short stature condition Russell–Silver syndrome.

The bidirectional regulation of height

Many genetic loci linked to tall stature have a reciprocal short stature condition resulting from an opposing mechanism, which illustrates the bidirectional control of growth (Fig. 4a). Notably, genes that can be linked to both short and tall stature can serve to illuminate specific critical components within the complex biological pathways associated with growth during organism development.

As mentioned earlier, pathogenic variants in *FBN1* throughout the gene can cause the tall stature condition Marfan syndrome. However, variants that affect the fourth or fifth 8-cysteine protein domains tend to cause Weill–Marchesani syndrome or congenital scleroderma, respectively, both of which are associated with short stature[155]. Pathogenic variants in the paralogue *FBN2*, which encodes fibrillin 2, also affect height in both directions. Although short-stature-related variants, causing FBN2-related acromelic dysplasia, are located in similar protein domains as FBN1-related short stature variants, variants linked to tall stature are spread more broadly throughout the middle of the gene. How variants that lie in different regions of the encoded protein cause FBN-related opposing growth conditions is not immediately clear, and more than one molecular mechanism, such as alterations in protein binding or cell signalling, might be involved[156].

Another example of the bidirectional effects on growth in humans can be seen in the CNP–NPR2 ligand–receptor interaction, in which loss-of-function variants in *NPR2* and *NPPC* (the gene encoding CNP) cause a varying severity of short stature[37,38] and overexpression of CNP causes skeletal overgrowth[157]. Similarly, increased and decreased expression of *FGFR3* has been shown to cause short and tall stature, respectively[28,158]. These bidirectional effects on growth consequent to increased or decreased expression of CNP and FGFR3 (refs. 159,160) were key clues that this pathway might be a common regulator of human growth (Fig. 4b). Further studies in murine models of achondroplasia showed that treatment with a modified form of CNP, engineered to extend its half-life, resulted in significant recovery of bone growth by inhibiting FGF-mediated mitogen-activated protein kinase activation[161] (Box 2).

DNMT3A variants are well established to cause overgrowth. More recently, gain-of-function variants specifically in the PWWP domain were reported to cause Heyn–Sproul–Jackson syndrome, a type of MPD[162]. The molecular mechanism that underlies the opposing disorders is becoming clearer. The hypomethylation observed owing to DNMT3a deficiency (as observed in Tatton-Brown–Rahman syndrome patient cells[114]) causes increased H3K27me3 marks and increased PRC2 at DNMT3a target genes, facilitating a stem-cell-like state, whereas hypermethylation in Heyn–Sproul–Jackson syndrome patient fibroblasts reduces specific H3K27me3 marks while increasing methylation at PRC2-target genes, pushing the cells towards a differentiation pathway[162,163] (Fig. 4c). Other overgrowth conditions first linked to copy number alterations also show a bidirectional influence. One example is *NSD1*, genomic deletions of which cause Sotos syndrome (Fig. 4c), whereas, more rarely, duplications of *NSD1* can lead to reduced growth[164,165]. *Drosophila* studies suggest that apoptosis related to the mTOR pathway could have a role during development to reduce growth[165].

The identification of genes and pathways with bidirectional effects on height can be an important method of maximizing the potential of these pathways to be therapeutically manipulated. Bidirectionally selected drug target genes have shown to be 3.8 times more likely to gain approval than those without such effects[166]. These bidirectional phenotypic data led to the first therapeutic trials of a modified CNP analogue (vosoritide) in humans with achondroplasia (Box 2).

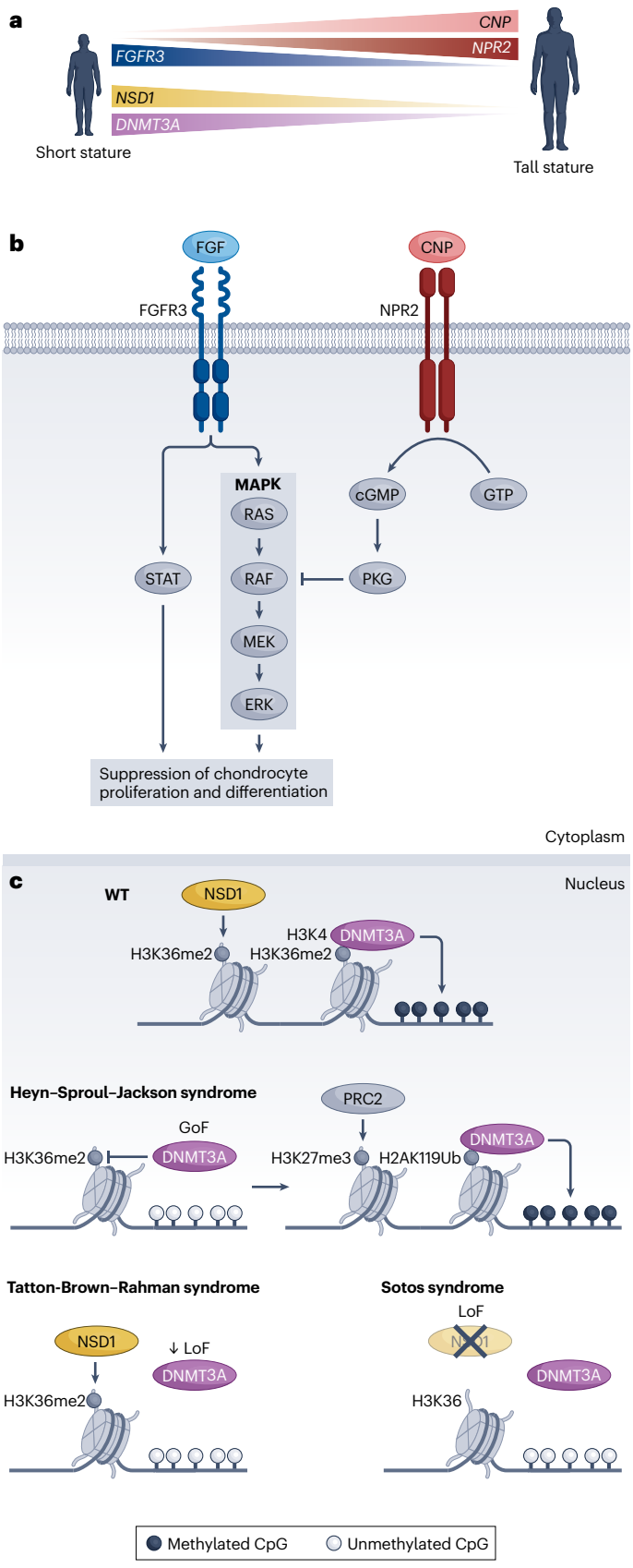

Fig. 4 | Bidirectional regulators of height. a, Several pathways have been linked to both increased and decreased height, depending on the altered function of the affected protein and its consequences on the pathway. **b**, Activation of the receptor tyrosine kinase fibroblast growth factor receptor 3 (FGFR3) by FGF stimulates the mitogen-activated protein kinase (MAPK)/signal transducer and activator of transcription (STAT) downstream cascade, which inhibits chondrocyte proliferation and extracellular matrix synthesis in the growth plate, decreasing the rate of endochondral bone growth. For C-type natriuretic peptide (CNP), upon binding to its transmembrane receptor NPR2, cGMP levels in the cell are elevated (from GTP), activating protein kinase G (PKG), which inhibits the MAPK cascade via RAF1 (ref. 171). The FGFR3–CNP–NPR2 pathways are interlinked and have multiple factors that can increase or decrease activity of the MAPK cascade and thereby influence chondrocyte proliferation or differentiation. Whereas constitutively active variants in FGFR3 reduce height, increased activity of CNP or NPR2 has been linked to increased height[41]. **c**, The Pro-Trp-Trp-Pro (PWWP) domain of DNMT3A preferentially interacts with dimethylated histone H3 lysine 36 (H3K36me2) deposited by NSD1, promoting widespread de novo DNA methylation (DNAme). Gain-of-function (GoF) variants in the PWWP domain of DNMT3A, as observed in Heyn–Sproul–Jackson syndrome, prevent the interaction between H3K36me2 and DNMT3A (left). This leads to aberrant deposition of DNAme by mutant DNMT3A at regions typically marked by polycomb repressive complex 2 (PRC2)-deposited H3K27me3 through an interaction with monoubiquitylated histone H2A lysine 119, deposited by PRC1 (not shown)[172]. Amino acid substitutions within the PWWP domain of DNMT3A associated with the overgrowth disorder Tatton-Brown–Rahman syndrome impair chromatin occupancy and reduce cellular levels of the protein, thus causing hypomethylation of intergenic DNA. In Sotos syndrome, another overgrowth syndrome, haploinsufficiency of NSD1 and the resulting depletion of intergenic H3K36me2 levels abrogate PWWP-mediated intergenic recruitment of DNMT3A, which leads to hypomethylation of intergenic DNA, whereas a hypermethylation signature has been observed in individuals with microduplications of *NSD1*, who present with reduced stature (not shown)[173,174]. LoF, loss-of-function; WT, wild type.

Conclusions and future perspectives

The most recent GWAS of height produced a saturated map of associated loci that together account for a substantial fraction of the heritability of height and incorporated multiple ancestries in their meta-analyses[14]. However, many risk alleles in populations that have been underserved by current large GWAS remain to be discovered. Increasing the diversity of populations studied will identify new variants and likely new loci that influence height. We must ensure that genomic studies benefit all involved[167,168] and incorporate FAIR and CARE principles for genetic studies[169,170], in particular for Indigenous populations.

Genetic studies in rare disorders and GWAS of height can be mutually beneficial. The genetic power of monogenic disorders has been very useful to identify the 'right' gene at some GWAS loci. The balance may now swing in the other direction. Given the revolution in monogenic disease gene identification over the past 20 years, it is now less common to have large phenotypically homogeneous patient cohorts to aid in the identification of a novel disease gene. Perhaps, loci underpinning GWAS signals will in fact act as supportive evidence for candidate genes for novel height-related conditions. Large-scale sequencing studies are underway and will implicate many more genes as being important for normal skeletal growth.

As with other polygenic traits and disease GWAS, there remains considerable need to narrow associated loci to the precise causal variants and then to connect these variants to the effector genes and biological mechanisms that lead to alterations in height. Although

Box 2 | From genes to therapeutic potential

Historically, few treatment options have been available for individuals with genetic conditions affecting stature. Growth hormone (GH) was established as a treatment option for short stature, with first trials in the late 1950s using human-derived GH[178,179]. However, this treatment was stopped when treated adults were reported with Creuzfeldt–Jacob disease[180], although recombinant GH production enabled resumption of GH as a first-tier treatment to address growth concerns in childhood[181]. Human GH is approved by the FDA for the treatment of some genetic conditions with short stature, including Turner syndrome, Noonan syndrome and Prader–Willi syndrome, as well as children classified as having idiopathic short stature, some of which might have a monogenic underlying cause (reviewed elsewhere[182]). GH is not as effective (in terms of increasing final adult height) in most genetic skeletal conditions with short stature, as these individuals are not typically GH-deficient. The exception to this is individuals with SHOX-related growth impairment (isolated short stature and Leri–Weill dyschondrosteosis).

The possibility that C-type natriuretic peptide (CNP) might be a possible treatment option for achondroplasia in humans came from observations that loss-of-function variants in its receptor, NPR2, cause a severe form of dwarfism and that overexpression on CNP causes overgrowth[37,43]. The therapeutic potential of a modified CNP (vosoritide) has since been harnessed in pioneering clinical trials in children with achondroplasia that collectively demonstrated that this medication is safe and results in sustained increases in annualized growth velocity[183–187]. Vosoritide works by binding to the NPR2, which reduces the activity of the overactive FGFR3 to promote bone growth, by blocking its downstream inhibitory signalling at the level of RAF1 (ref. 171). These trials led to approval of vosoritide to increase linear growth in children with achondroplasia from birth until growth plate closure in the USA, Australia and Japan and from age 4 months in the European Union. It also catalysed a number of emerging clinical drug development programmes for children with achondroplasia aimed at targeting the FGFR3–CNP signalling pathways. These currently include a long-acting form of CNP (navepegritide), a FGFR3 antagonist (infigratinib)[188] and an antibody to FGFR3 (SAR-442501) (reviewed elsewhere[189]). Clinical trials are also underway to assess the effect of vosoritide on other FGFR3-related skeletal dysplasias, such as hypochondroplasia, and in children with isolated short stature. Plans are underway to assess its effects in other monogenic conditions that affect growth such as Turner syndrome, Noonan syndrome and SHOX deficiency.

The new therapies that are emerging for conditions such as achondroplasia are considered controversial by some, who consider that they primarily address height and consequent perceived social benefits. However, precision therapies for altered height syndromes can also have a positive impact on comorbidities of growth disorders. For example, in achondroplasia, therapy with CNP has shown increases in the size of the foramen magnum and facial skeleton that could translate to decreased spinal cord compression symptoms and improve sleep-disordered breathing in these children[187]. These preliminary data are now being followed up by long-term extension studies and real-world evidence to evaluate the long-term health benefits of this therapy.

some inroads for GWAS signals are being made by considering effects on gene expression and the clustering of signals into genomic regions sharing similar annotations, for monogenic disorders there has been less traction. As the cost of genome sequencing, including long-read sequencing, decreases, it is likely that non-coding variants will become more routinely identified in monogenic disorders of altered growth. In addition to increasing our fundamental understanding of the biology of skeletal growth, understanding cellular mechanisms could be relevant to address other diseases where altered height is a risk factor, such as heart disease and cancer, or diseases that share the biological pathways that are defined by studies of height.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

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Supplementary Table 1. Genes associated with monogenic forms of short stature . (Note
AARS1
ACAN
ACP5
ACTB
ACTG1
ADAMTS10
ADAMTS17
ADAMTS2
ADAMTSL2
AFF4
AGA
AGL
AGPS
AIFM1
ALDH18A1
ALG12
ALMS1
ALPL
ALX3
AMER1
AMMECR1
ANAPC1
ANKRD11
ANTXR1
ARCN1
ARHGAP31
ARID1A
ARID1B
ARID2
ARSB
ARSE
ARSL
ASPM
ASXL1
ATP6V0A2
ATP7A
ATP8B1
ATR
ATRX
B3GALT6
B3GAT3
B3GLCT
B4GALT7
BANF1
BCOR
BCS1L
BGN
BMP1
BMP2
BMPER
BMPR1B
BPNT2

BRAF
BRCA1
BRCA2
BRF1
BRIP1
BRPF1
BTK
BUB1
BUB1B
C15orf41
C21ORF2
CA2
CANT1
CASR
CBL
CCDC8
CCN6
CCNQ
CDC42
CDC45
CDC45L
CDC6
CDK10
CDK5RAP2
CDKN1C
CDT1
CENPE
CENPJ
CEP120
CEP152
CEP57
CEP63
CFAP410
CHD7
CHMP1A
CHRNG
CHST3
CHSY1
CKAP2L
CLCN5
CLCN7
COG1
COG4
COG7
COL10A1
COL11A1
COL11A2
COL1A1
COL1A2
COL27A1
COL2A1
COL5A1
COL9A1

COL9A2
COL9A3
COLEC10
COMP
CREB3L1
CREBBP
CRIPT
CRTAP
CSF1R
CSGALNACT1
CSNK2A1
CTC1
CTDP1
CTNS
CTSA
CTSK
CUL4B
CUL7
CWC27
CYP11B1
CYP21A2
CYP27B1
CYP2R1
DDR2
DDRGK1
DDX48
DDX58
DHCR7
DLL3
DLX5
DMP1
DNA2
DNAJC21
DNMT3A
DONSON
DPF2
DPH1
DVL1
DVL3
DYM
DYNC1I2
DYNC2H1
DYNC2LI1
DYNLT2B
DYRK1A
EBF3
EBP
EFL1
EFNB1
EFTUD2
EIF2AK3
EIF2S3
EIF4A3

EIF5A
ENPP1
ERCC2
ERCC3
ERCC4
ERCC6
ERCC8
ESCO2
EVC
EVC2
EXOC6B
EXOSC2
EXT1
EXT2
EXTL3
FAM111A
FAM20C
FAM50A
FANCA
FANCB
FANCC
FANCD2
FANCF
FANCG
FANCI
FANCL
FAT4
FBN1
FBXL3
FBXO11
FGD1
FGF23
FGFR1
FGFR3
FKBP10
FLNA
FLNB
FN1
FOSL2
FOXG1
FTO
FUCA1
FUT8
FZD2
G6PC
G6PC1
GALNS
GDF5
GH1
GHR
GHRHR
GHSR

GINS1
GINS3
GJA1
GLB1
GLI1
GLI2
GLI3
GMNN
GNAS
GNPAT
GNPTAB
GNPTG
GNPTG
GPC6
GPX4
GRHL2
GSC
GTF2E2
GUSB
GZF1
HAAO
HCCS
HDAC8
HES7
HESX1
HGSNAT
HHAT
HMGA2
HOXD13
HPRT1
HRAS
HSPA9
HSPG2
HUWE1
HYAL1
IARS2
IDUA
IFIH1
IFITM5
IFT122
IFT140
IFT172
IFT43
IFT52
IFT57
IFT80
IGF1
IGF1R

IGF2
IGFALS
IHH
IMPAD1
INPP5K
INPPL1
INSR
INTS1
INTU
JAG1
JAK1
KCNJ2
KDELR2
KDM3B
KDM5C
KDM6A
KIAA0753
KIF22
KIFBP
KMT2A
KMT2C
KMT2D
KNL1
KRAS
KYNU
LAMTOR2
LARP7
LBR
LFNG
LHX3
LHX4
LIFR
LIG4
LMNA
LMNB1
LMX1B
LONP1
LPIN2
LRP5
LRRK1
LTBP2
LTBP3
LZTR1
MAB21L2
MAF
MAGEL2
MAP2K1
MAP2K2

MAP3K7
MASP1
MATN3
MBTPS1
MBTPS2
MCM4
MCM7
MCPH1
MECOM
MECP2
MESDC2
MESP2
MGAT2
MMP13
MMP2
MPLKIP
MRAS
MTHFS
MYCN
MYH3
MYO18B
MYSM1
NAA10
NANS
NBAS
NBN
NDE1
NDUFAF6
NEK1
NEPRO
NEU1
NF1
NFIX
NIN
NIPBL
NKX3-2
NOTCH2
NPR2
NRAS
NSMCE2
NSUN2
NTRK1
NXN
OBSL1
OCRL
OFD1
ORC1
ORC4

ORC6
OSGEP
OSTM1
OTX2
P3H1
P4HB
PALB2
PAM16
PAPSS2
PCDH12
PCGF2
PCNT
PCYT1A
PDE3A
PDE4D
PEX19
PEX5
PEX7
PGM1
PGM3
PHEX
PHF6
PHGDH
PIEZO2
PIK3C2A
PIK3R1
PISD
PITX1
PKDCC
PLK4
PLOD2
PNPLA6
POC1A
POGZ
POLA1
POLE
POLR1A
POLR1C
POLR3A
POLR3B
POP1
POU1F1
PPFIBP1
PPIB
PPM1D
PPP1CB
PPP1R15B
PPP2R3C

PPP3CA
PQBP1
PRIM1
PRKAR1A
PRKG2
PRMT7
PROP1
PTDSS1
PTH1R
PTHLH
PTPN11
PUF60
PUS7
PYCR1
RAB23
RAB33B
RAB3GAP1
RAB3GAP2
RAD21
RAD50
RAD51C
RAF1
RALA
RBBP8
RBM8A
RECQL2
RECQL3
RECQL4
RFT1
RINT1
RIT1
RMRP
RNF113A
RNF168
RNPC3
RNU4ATAC
ROR2
RPGRIP1L
RPL11
RPL13
RPL35A
RPL5
RPS17
RPS19
RPS26
RPS28
RPS6KA3
RPS7

RRAS2
RSPRY1
RTTN
RUNX2
SBDS
SDHAF1
SEC23A
SEC24D
SERPINF1
SERPINH1
SETBP1
SETD2
SF3B4
SGMS2
SH3PXD2B
SHH
SHOC2
SHOX
SIK3
SIL1
SLC10A7
SLC17A5
SLC25A24
SLC26A2
SLC29A3
SLC2A2
SLC34A1
SLC34A3
SLC35C1
SLC35D1
SLC37A4
SLC39A13
SLC39A8
SLC4A4
SLC6A8
SLX4
SMAD2
SMAD4
SMARCA2
SMARCA4
SMARCAL1
SMARCB1
SMARCE1
SMC1A
SMC3
SMPD1
SMS
SNRPB

SON
SOS1
SOS2
SOST
SOX11
SOX2
SOX3
SOX9
SP7
SPARC
SPART
SPG20
SPRED2
SRCAP
SRP54
STAG2
STAMBP
STAT5B
SUMF1
SVBP
TAB2
TALDO1
TBCE
TBL1XR1
TBX1
TBX15
TBX2
TBX3
TBX4
TBX6
TCF4
TCTEX1D2
TCTN3
TECPR2
TGDS
TGFB3
THOC2
THOC6
THRA
TKT
TMEM165
TMEM38B
TMEM67
TNFRSF11A
TNFRSF11B
TONSL
TOP3A
TP53

TP63
TRAIP
TRAPPC2
TRAPPC6B
TRIM37
TRIP11
TRMT1
TRMT10A
TRPS1
TRPV4
TTC21B
TTI2
TUBGCP6
TWIST1
UBE3B
UBR1
UFSP2
USB1
USP9X
VDR
VPS13B
VPS4A
WDR19
WDR35
WDR37
WDR4
WDR60
WDR81
WIPI2
WISP3
WNT1
WNT5A
WNT7A
XRCC4
XYLT1
XYLT2
YARS1
ZC4H2
ZMPSTE24
ZNF148

e that this is an interim freeze [November 2024] of an ongoing manual curation effort).

Supplementary Table 2. Genes associated with monogenic forms of tall stature and ove

CHD8
CYP19A1
CYP19A1
DNMT3A
EED
EZH2
FBN1
FIBP
GPC3
H1-4
LOX
NFIX
NPR2
NPR3
NSD1
PDGFRB
RNF125
SETD2
SMAD2
SUZ12

rgrowth. (Note that this is an interim freeze [November 2024] of an ongoing manual cur

ation effort).