Current Osteoporosis Reports (2019) 17:301–323
https://doi.org/10.1007/s11914-019-00527-9

SKELETAL DEVELOPMENT (R MARCUCIO AND JQ FENG, SECTION EDITORS)

Complex Phenotypes: Mechanisms Underlying Variation in Human Stature

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Published online: 22 August 2019

Abstract

Purpose of Review The goal of the review is to provide a comprehensive overview of the current understanding of the mechanisms underlying variation in human stature.

Recent Findings Human height is an anthropometric trait that varies considerably within human populations as well as across the globe. Historically, much research focus was placed on understanding the biology of growth plate chondrocytes and how modifications to core chondrocyte proliferation and differentiation pathways potentially shaped height attainment in normal as well as pathological contexts. Recently, much progress has been made to improve our understanding regarding the mechanisms underlying the normal and pathological range of height variation within as well as between human populations, and today, it is understood to reflect complex interactions among a myriad of genetic, environmental, and evolutionary factors. Indeed, recent improvements in genetics (e.g., GWAS) and breakthroughs in functional genomics (e.g., whole exome sequencing, DNA methylation analysis, ATAC-sequencing, and CRISPR) have shed light on previously unknown pathways/mechanisms governing pathological and common height variation. Additionally, the use of an evolutionary perspective has also revealed important mechanisms that have shaped height variation across the planet.

Summary This review provides an overview of the current knowledge of the biological mechanisms underlying height variation by highlighting new research findings on skeletal growth control with an emphasis on previously unknown pathways/mechanisms influencing pathological and common height variation. In this context, this review also discusses how evolutionary forces likely shaped the genomic architecture of height across the globe.

Keywords Height · Complex traits · Genetics · Heritability · GWAS · Environment · Evolution · Natural selection · GDF5 · Chondrocyte · Gene regulation

Introduction

Among anthropometric traits, human height has been the most extensively studied across the sciences, due in part to the desire among researchers to understand the mechanisms underlying its marked variation across the globe. Typically, height within any population follows a normal distribution, with a small fraction (3–5%) of individuals exhibiting extreme short and tall height phenotypes and most others hovering around the mean. While the height distributions of any two human populations usually overlap, differences in mean and variance reflect genetic, environmental, and evolutionary factors shaping growth phenotypes. For example, regardless of sampled population, height is approximately 60–70% heritable, indicating a strong role for genetics underlying variation [1]. Yet, environmental factors also significantly influence differences in height attainment around the world; for example, despite its high heritability, there has been a secular increase in height in Western populations arising in part from improvements in nutrition and infectious disease prevention [2]. Importantly, evolutionary forces, such as natural selection, gene flow, genetic drift, and mutation, in concert with environmental and genetic factors, shape height phenotypes and its underlying genomic architecture within and between populations. For example, recent work has revealed that natural selection and other evolutionary forces likely shaped the genomic architecture of heights in different peoples around the globe [3•].

This article is part of the Topical Collection on *Skeletal Development*

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What has become evident after hundreds of years of study is that genetic, environmental, and evolutionary factors often impinge directly or indirectly on skeletal growth, and specifically on how chondrocytes, the key cell type responding to growth signals, are regulated during development. During endochondral ossification, mesenchymal cells in the embryonic limb bud or vertebrae respond to signaling cues to condense and differentiate into chondrocytes to form transient models of future calcified bones. At the ends of each model, cartilaginous growth plates form, consisting of distinct zones of gradually differentiating chondrocytes (Fig. 1). Initially, resting zone chondrocytes replicate at a slow rate and give rise to proliferative chondrocytes, which in turn divide relatively quickly into clonally related daughter cells. These daughter cells typically align into columns along the model's longitudinal axis and through their expansion and proliferation bones elongate [4, 5]. Proliferative chondrocytes eventually stop dividing and terminally differentiate into hypertrophic chondrocytes, which then increase in size up to twenty-fold, significantly contributing to longitudinal bone growth [6••]. Hypertrophic chondrocytes calcify the surrounding extracellular matrix, undergo apoptosis, all the while secreting signaling factors that attract invading osteoblasts and osteoclasts into the model in order to form bone and remove cartilage, respectively [7••]. A small proportion of hypertrophic chondrocytes also directly differentiate into osteoblasts [7••, 8••].

While endochondral ossification begins in embryogenesis, in humans, long bone growth plates remain cartilaginous and active centers of proliferation and differentiation through the first two decades of life, and it is at these sites that height variation is chiefly mediated. Indeed, it is the balance of growth plate chondrocyte proliferation, hypertrophy, and senescence as well as the timing of growth plate (epiphyseal) closure that determines bone length over the lifetime, in both normal and pathological phenotypes [9]. Recent improvements in genetics and functional genomics have shed light on the complex genetic architecture underlying this balance but have also revealed additional biological, environmental, and evolutionary factors that drive height variation within and between populations (Fig. 2). Here, we discuss novel findings on skeletal growth control and highlight previously unknown pathways influencing growth control in the context of extreme and common height variation. We conclude with a discussion on how evolutionary factors have likely shaped heights' genetic architecture across the globe.

Genetics and Height Variation

Extreme Height Phenotypes

Among the most commonly studied human traits are extreme tall or short height phenotypes, defined as heights greater than two standard deviations above and below the mean, respectively [10, 11]. Typically, these growth phenotypes are heterogeneous in etiology, resulting from a myriad of different inputs, most notably genetic factors influencing chondrogenesis and growth. In cases where genetic mutations have been identified, they often consist of nucleotide changes localized to coding regions, are extremely rare in populations (i.e., have minor allele frequencies, MAF < 0.01), are of strong effect in their influence on growth, and are often evident as dominant negative or recessive genotypes [12] (individual loci involved in extreme height phenotypes are reviewed in Table 1).

Recently, whole exome sequencing (WES) on affected and unaffected siblings has permitted the rapid identification of relatively large effect, rare variant loci underlying Mendelian inherited height phenotypes. For example, WES of three families with autosomal-dominant short stature, advanced bone age, and premature growth cessation identified heterozygous mutations in *ACAN* (*Aggrecan*) [76•], as did a larger study on

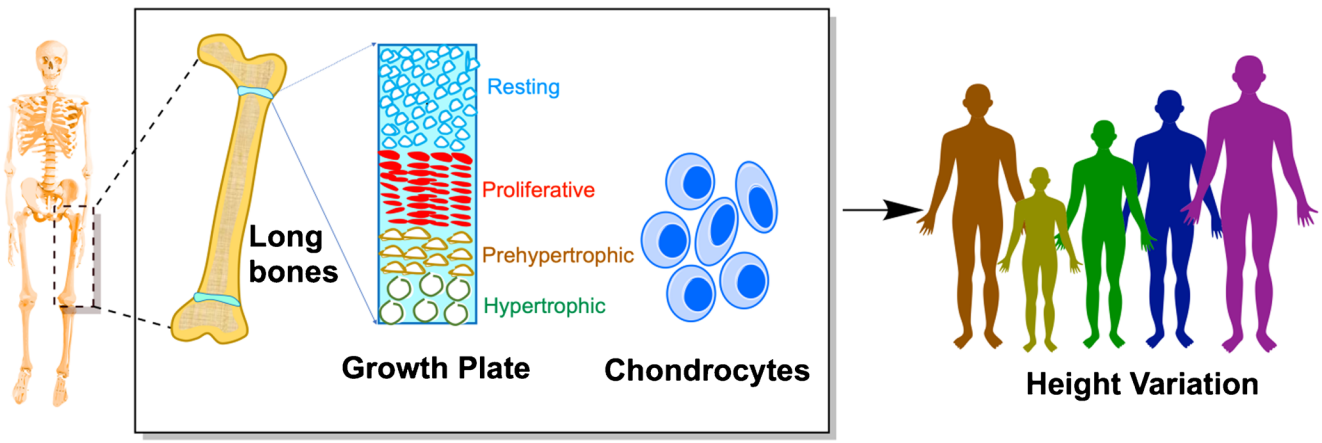

Fig. 1 Growth plates in bones and height variation. The growth plate is a cartilaginous structure situated in the ends of long bones. It consists of special cells called chondrocytes that are arranged into distinct zones: resting, proliferative, pre-hypertrophic, and hypertrophic zones. The complex regulation at the growth plate determines length of long bones and human height (see text for details)

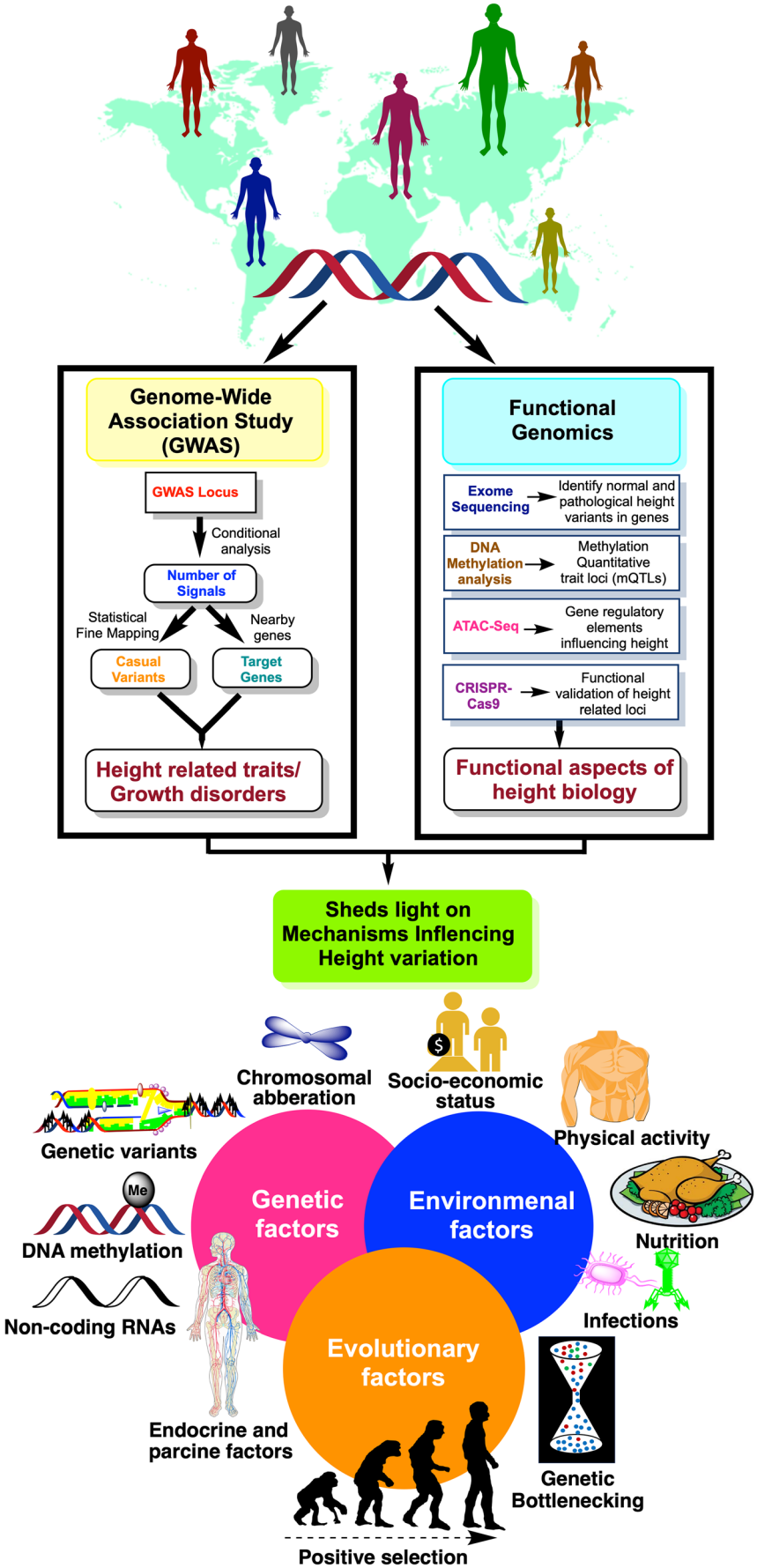

Fig. 2 Genomic approaches provide insight into biological mechanisms underlying height variation. GWAS and functional genomic approaches (e.g., exome sequencing, DNA methylation analysis, ATAC-seq and CRISPR-Cas9) have contributed to discovery of novel height related traits and shed light into the complex biological mechanisms that drive variation in human height (see text for details)

200 short stature patients, which identified variants in about 16.5% of affected individuals, with *ACAN* mutations being most prevalent (2.5%) [77]. ACAN is an integral part of the extracellular matrix (ECM) in cartilaginous tissue, and disruptions to it influence growth plate organization and chondrocyte differentiation ultimately impacting longitudinal growth [78]. WES on other severe short stature patients also identified mutations in *B4GALT7*, *CUL7*, *FAM111A*, *OBSL1*, and *SRCAP* [79••], while exome sequencing on a family with hypochondroplasia identified a novel missense mutation in *FGFR3* [80], a negative regulator of bone growth [81]. Most recently, WES on 20 short stature patients lead to the potential cause of short stature in half with pathological alleles at *ACAN*, *BRAF*, *COL2A1*, *HRAS*, *LMNA*, *PRKAR1A*, *PTPN11*, and *SLC7A7* [82].

WES and Sanger sequencing methods are efficient for identifying mutations in coding regions, yet patients can also have large effect non-coding alterations, especially those influencing chromosome structure and organization. Scanning patient chromosomes for large structural modifications using karyotyping and fluorescence in situ hybridization [83] has been somewhat effective in identifying these larger regions, which at times can be quite broad (i.e., megabase intervals) and contain many affected coding and non-coding features making the specific causative mutation difficult to pinpoint. By altering large swaths of sequence, chromosomal modifications also can have detectable impacts on the regulatory control of gene expression further obscuring causal variant discovery. Such modifications can impact topologically associating domains (TAD) that are believed to stabilize regulatory element-gene promoter interactions that initialize and maintain transcription [84]. For example, alterations to a TAD boundary spanning the *WNT6/IHH/EPHA4/PAX3* locus are implicated in human limb and digit developmental defects [85•], whereas chromosomal rearrangements in the regulatory landscape of *PITX1*, a major hind limb transcription factor, cause Liebenberg syndrome, an autosomal-dominant upper-limb malformation in which arms acquire morphological characteristics of legs [86, 87]. Interestingly, in these cases, rare coding mutations specific to *IHH* and *PITX1* also underlie extreme short stature [88], likely due to their disruption of chondrocyte differentiation, whereas higher frequency genetic variants located in non-coding regions have been implicated in normal height variation, likely due to more subtle *cis*-regulatory effects on growth plate dynamics (see below).

There are more classic examples of chromosomal alterations influencing specific coding regions underlying extreme stature phenotypes including Turner syndrome (missing or incomplete X chromosome), manifesting as short height, and Klinefelter syndrome (47, XXY), manifesting as tall height [89, 90]. For example, one major locus, *SHOX* (short stature homeobox), present at Xp22.3, encodes a transcription factor expressed in the developing limbs that regulates chondrocyte differentiation and proliferation [91]. Increased copy number variation (CNV) of *SHOX* may be in part responsible for the taller height phenotypes of Klinefelter patients, whereas chromosomal deletions encompassing *SHOX* have been linked to Leri-Weill dyschondrosteosis (LWD), a rare genetic disorder characterized by forearm and leg shortening, and associated short stature [92] (for more detailed reviews on extreme height genetics, please see [71, 93], and Table 1).

Common Height Variation

In general, it is believed that rare (MAF < 0.01) variants of large effect (i.e., mutations) that typically underlie pathological height do not individually reach high enough allele frequencies within populations to account for the observed patterns of non-pathological, heritable variation in height. As a result, geneticists have sought to identify higher frequency—i.e., common (MAF > 0.01) variants— using genome-wide association studies (GWAS). GWAS involve revealing statistical correlations between common single nucleotide polymorphisms (SNPs), densely genotyped across the genome using a SNP array or chip, and height, measured using standardized protocols. SNPs are considered significantly associated if they fall below a standardized GWAS association *p* value of 5×10^{-8}. Often significantly detected loci contain numerous SNPs that are each roughly correlated with height because they are inherited in sequence blocks (i.e., haplotypes), are in modest to strong linkage disequilibrium (LD), and are generally at similar frequencies in sampled populations. This issue of having numerous linked associated SNPs makes identifying the causal variant extremely difficult. Recent improvements in genomic sequencing, haplotype imputation methods, statistical approaches, functional genomics assays, and the formation of large consortia (e.g., Genetic Investigation of Anthropometric Traits (GIANT) focusing on hundreds of thousands of people) as well as more focused investigations (e.g., population-specific GWAS) has led to increases in variant discovery and the whittling down of haplotypes to smaller lists of putatively causal variants. While the geographic region of focus of GWAS has been predominantly Europe, those conducted on Asians [94–99] and African/African-Americans [100–102] have revealed shared as well as novel height signals. More recently, population-specific GWAS on Greenland Inuits [103•], Sardinians [104•], and Peruvians [105•] have also contributed novel loci driving height variation (see below).

Of the many height GWAS (e.g., [99, 101, 102, 103•, 104•, 105•, 106–112, 113••]), currently, the largest study by Yengo and colleagues [113••] is on ~ 700,000 people predominantly of European descent. At the GWAS association *p* value, they revealed 3290 associated common variants found across 712 genomic loci, revealing loci with multiple independent signals. For example, nineteen significant signals were found

Table 1 Pathogenic coding variants underlying growth disorders

Growth disorders	Clinical features	Affected gene(s)	Gene functions
Short stature phenotypes			
Microcephalic osteodysplastic primordial dwarfism type 1 (MOPD1)	Small head size (microcephaly); abnormal bone growth (skeletal dysplasia); distinctive facial features; brain anomalies; sparse hair and eyebrows; dry skin; short limbs; dislocation of the hips and elbows; seizures; and intellectual disability	***RNU4ATAC*** [13, 14]	Small nuclear RNA (snRNA) that is part of the U12-dependent minor spliceosome complex and necessary for proper splicing of U12-dependent introns.
Microcephalic osteodysplastic primordial dwarfism type II (MOPDII)	Short stature (dwarfism) with other skeletal abnormalities (osteodysplasia); unusual small head size (microcephaly); high-pitched nasal voice; some have a narrowing of the voicebox (subglottic stenosis); facial features include a prominent nose, full cheeks, a long midface, and a small jaw; small teeth (microdontia)	***PCNT*** [15]	Pericentrin (PCNT) is important for normal functioning of the centrosomes, cytoskeleton, and cell cycle progression.
Multiple epiphyseal dysplasia	Mild short stature, malformations of the hands, feet, and knees and abnormal curvature of the spine (scoliosis); inward- and upward-turning foot (club foot), an opening in the roof of the mouth (cleft palate), an unusual curving of the fingers or toes (clinodactyly), ear swelling, abnormality of the kneecap (double-layered patella)	***COL9A1***, ***COL9A2***, ***COL9A3*** [16], ***MATN3***, ***COMP*** [17], ***SLC26A2*** [18]	COL9A1, COL9A2, and COL9A3 proteins strengthen and support connective tissues such as skin, bone, cartilage, tendons, and ligaments. MANT3 protein play a role in the organization of collagen and other cartilage proteins. COMP is an extracellular matrix protein that play role in cell growth, cell division and apoptosis. SLC26A2 protein transports charged molecules (ions), particularly sulfate ions, across cell membranes and is essential for normal cartilage formation.
IMAGe syndrome	Short stature, distinctive facial features, such as a prominent forehead, low-set ears, and a short nose with a flat nasal bridge, premature fusion of certain bones of the skull (craniosynostosis), a split in the soft flap of tissue that hangs from the back of the mouth (cleft or bifid uvula). Other possible features include high levels of calcium in the blood (hypercalcemia) or urine (hypercalcuria) and a shortage of growth hormone in childhood	***CDKN1C*** [19]	CDKN1C protein encoded by this gene is involved in controlling growth before birth and preventing the developing fetus from becoming too large.
Infantile nephropathic cystinosis	Severe short stature, blond hair, fair skin, moderate dehydration, generalized impaired proximal tubular reabsorptive capacity with severe fluid-electrolyte balance alterations, hypophosphatemic rickets that causes bone deformities	***CTNS*** [20]	The causative gene, *CTNS* encodes cystinosin, a lysosomal membrane protein that specifically moves the amino acid cystine out of the lysosome.
Dyggve-Melchior-Clausen (DMC) dysplasia and Smith-McCort (SMC) dysplasia	Progressive short stature with short trunk dwarfism, microcephaly, protruding sternum, and psychomotor retardation, generalized abnormalities of the epiphyses and metaphyses, and a distinctive lacy appearance of the iliac crest	***DYM*** [21]	This gene encodes dymeclin which regulates Golgi-associated secretory pathways that are essential to endochondral bone formation during early development.
Seckel syndrome	Short stature (dwarfism); abnormally small head (microcephaly); moderate to severe mental retardation; unusual characteristic of facial features including	***PCNT*** [22]; ***CENPJ*** [23]; ***ATR*** [24], ***ATRIP*** [25], ***CEP152*** [26], ***CtIP*** [27]	*PCNT* is important for centrosomal function. *CENPJ*, *ATR*, ATRIP, *CEP152*, and *CtIP*

Table 1 (continued)

Growth disorders	Clinical features	Affected gene(s)	Gene functions
	"beak-like" protrusion of the nose; abnormally large eyes, a narrow face, malformed ears, and/or an unusually small jaw (micrognathia); malformation of the foot in a twisted position (clubfoot), and/or absence of one pair of ribs		genes encoding proteins that control cellular responses to DNA damage.
Wolcott-Rallison syndrome	Short stature, walking difficulties, short trunk, excessive lordosis, a short and broad chest, and genu valgum, early infancy with symptoms of diabetes mellitus	***EIF2AK3*** [28]	The protein encoded by this gene phosphorylates the alpha subunit of eukaryotic translation-initiation factor 2 and reduce translational initiation and repression of global protein synthesis.
Fanconi anemia	Short stature, bone marrow failure, skin pigmentation abnormalities, and characteristic malformations of upper extremities, head, eyes, ears, kidneys, developmental defects, predisposition to cancer, GH deficiency (GHD), hypothyroidism, and hypogonadism	***FANCA*** [29, 30]	The gene encodes FANCA proteins which involved in Fanconi anemia (FA) pathway that operates as a post-replication repair or a cell cycle checkpoint.
Achondroplasia, hypochondroplasia, thanatophoric dysplasia, proportionate short stature	Short stature, short arms and legs, enlarged head (macrocephaly) with a prominent forehead, fingers are typically short and hand with a trident appearance, normal intelligence, hypochondroplasia features tend to be milder	***FGFR3*** (gain of function mutation) [31]	FGFR3 protein regulates bone growth by limiting the formation of bone from cartilage (a process called ossification), particularly in the long bones. It serves as negative regulator of bone growth.
Small for gestational age, familial short stature, idiopathic short stature	Advanced bone age, short stature, early growth cessation, midface hypoplasia, flat nasal bridge, prognathism, posteriorly rotated ears, broad forehead, broad great toes, short thumbs, brachydactyly, joint problems, exaggerated lumbar lordosis, and genu valgum	***ACAN*** [32–34]	Extracellular matrix, aggrecan.
Brachydactyly type A1, A2, C	Short limbs, brachydactyly, foot abnormalities	***GDF5*** [35, 36]	This gene encodes a secreted ligand of the TGF-beta (transforming growth factor-beta) superfamily of proteins that bind various TGF-beta receptors leading to recruitment and activation of SMAD family transcription factors that regulate gene expression.
Meier-Gorlin syndrome	Short stature, narrow long bones in the arms and legs, a deformity of the knee joint, and delayed bone age, small mouth (microstomia), underdeveloped lower jaw (micrognathia), full lips, and a narrow nose with a high nasal bridge, testes are small or undescended (cryptorchidism) in males, small external genital folds (hypoplasia of the labia majora) and small breasts in affected females	***ORC1***, ***ORC4***, ***ORC6***, ***CDT1***, ***CDC6*** [37, 38]	Components of the DNA pre-replication complex which ensure that DNA replication occurs only once per cell division and is required for cells to divide.
Silver-Russell syndrome	Low birth weight, postnatal short stature, characteristic facial features, and body asymmetry	***IGF2*** [39, 40]	Secreted signaling molecule (IGF2) that promotes growth and division of cells in many tissues, including cartilage development during postnatal long bone growth.
Laron syndrome	Dwarfism, facial phenotype, obesity and hypogenitalism, hypoglycemia, hypercholesterolemia, and sleep disorders	***GHR*** [41]	GHR gene encodes for growth hormone receptor that play critical role in growth hormone signaling.

Table 1 (continued)

Growth disorders	Clinical features	Affected gene(s)	Gene functions
Brachydactyly type A1	Short limbs, brachydactyly, foot abnormalities	***BMPR1B*** [42]	This gene encodes a member of the bone morphogenetic protein (BMP) receptor involved in endochondral bone formation and embryogenesis.
Acrocapitofemoral dysplasia, brachydactyly type A1	Short-limbed dwarfism, relatively large head circumference, short stature becomes more pronounced with age, cone-shaped epiphyses observed in ACFD patient	***IHH*** [43]	This gene encodes a member of the hedgehog family of protein that regulates a variety of developmental processes including growth, patterning and morphogenesis.
Rainbow syndrome	Shortening of long bones in arms and legs, particularly the forearms, brachydactyly, wedge-shaped spinal bones, fused or missing ribs and short stature, distinctive facial features, such as a broad forehead, widely spaced eyes, short nose, triangle shaped mouth, increased bone mineral density (osteosclerosis) affecting the bones of the skull	***ROR2*** [44], ***FZD2*** [45], ***WNT5A*** [46], ***DVL1*** [47], ***DVL3*** [45]	These genes encodes proteins that involved in chemical signaling pathways called Wnt signaling, which affect many aspects of development.
Leri-Weill dyschondrosteosis	Shortening of the long bones in the arms and legs (mesomelia), short stature, abnormality of the wrist and forearm bones (Madelung deformity), increased muscle mass (muscle hypertrophy), bowing of a bone in the lower leg called the tibia, a greater-than-normal angling of the elbow away from the body, and a high arched palate	***SHOX*** [48]	*SHOX* gene is essential for the development of the skeleton. It plays a particularly important role in the growth and maturation of bones in the arms and legs.
Noonan syndrome	Mildly unusual facial features, short stature, heart defects, bleeding problems, skeletal malformations, delayed puberty, short neck, excess neck skin, abnormal side-to-side curvature of the skin	***PTPN11*** [49], ***SOS1*** [50], ***RAF1*** [51], and ***RIT1*** [52]	These genes encode proteins important in the RAS/MAPK cell signaling pathway, which is needed for cell division and growth.
Costello syndrome	Characteristic coarse facies, short stature, distinctive hand posture and appearance, severe feeding difficulty, and failure to thrive	***HRAS*** [53]	H-Ras protein is part of a RAS-MAP kinase pathway that helps control cell growth and division.
Coffin-Lowry syndrome	Short stature, facial dysmorphism, development retardation, and hearing defect	***RPS6KA3*** [54]	This gene encodes RSK proteins that play a role in several important cellular processes including cell growth and division, cell differentiation, and apoptosis.
Bardet-Biedl syndrome	Short stature and brachydactyly, stemming, intellectual disability, and retinitis pigmentosa	***SCAPER*** [55]	This gene encodes SCAPER protein, which is associated with mitotic progression.
Peters plus syndrome	Short stature, an opening in the lip (cleft lip) with or without an opening in the roof of the mouth (cleft palate), eye abnormality, distinctive facial features, and intellectual disability	***B3GALTL*** [56]	This gene encodes an enzyme called beta 3-glucosyltransferase (B3Glc-T), which is involved in the glycosylation.
Acromesomelic dysplasia, Maroteaux type (AMDM)	Short stature and disproportionate shortening of limbs	***NPR2*** [57]	This gene encodes an NPR protein, which is the primary receptor for C-type natriuretic peptide (CNP) and it plays a role in regulation of skeletal growth.
3-M syndrome	Severe growth retardation, delayed bone age, distinctive facial features, normal mental development	***CUL7*** [58], ***OBSL1*** [59], ***CCDC8*** [60]	These genes play a role in microtubule stabilization and genome stability.
Campomelic dysplasia		***SOX9*** [61]	

Table 1 (continued)

Growth disorders	Clinical features	Affected gene(s)	Gene functions
	Short stature, distinctive facial features, including a small chin, prominent eyes, and a flat face, weakened cartilage, and difficulty in breathing		This gene encodes a protein SOX9, which is critical for the formation of many different tissues and organs during embryonic development. The SOX9 protein also regulates the activity of other genes, particularly genes involved in the development of the skeleton and reproductive organs.
Tall stature phenotypes			
Peutz-Jeghers syndrome (PJS)	Delayed development, hypermobility, tall stature, and advanced bone age	***STK11*** [62]	This gene encodes an enzyme, serine/threonine kinase 11, which is tumor suppressor and it helps to keep cells from growing and dividing too fast or in an uncontrolled way.
Extreme tall stature	Extreme tall stature and increased expression of androgen receptor	***IGF1R*** ^{R1353H} (activating mutation) [63]	This gene encodes for IGF1 receptor, which is activated by hormone called insulin-like growth factor 1 and it plays essential role in insulin signaling.
Weaver syndrome	Tall stature, intellectual disability, and distinct facial features	***EZH2*** [64]	This gene encodes an enzyme called histone methyltransferase that plays a role in histone methylation.
Marfan syndrome	Tall stature, abnormalities in the heart, blood vessels, eyes, bones, and joints	***FBN1*** [65]	This gene encodes a protein called fibrillin-1 that provide strength and flexibility to connective tissues.
Tatton-Brown-Rahman syndrome (TBRS)	Tall stature, intellectual disability, and a distinctive facial appearance	***DNMT3A*** [66]	This gene encodes an enzyme called DNA methyltransferase 3 alpha that involved in DNA methylation.
Malan syndrome	Tall stature, wide spectrum of malformations, intellectual disability, and/or macrocephaly	***NFIX*** [67]	NFIX are transcription factors play a pivotal role during the development of brain and skeleton.
Sotos syndrome	Tall stature, prominent forehead, coarse facial features, macrocephaly, large ears, and learning disability	***NSD1*** [68]	This gene encodes an enzyme called histone methyltransferase that plays an important role in histone methylation.
CATSHL syndrome	Camptodactyly, tall stature, abnormality of lower limb joint, scoliosis, and hearing loss	***FGFR3*** (partial loss of function mutation) [69]	FGFR3 protein regulates bone growth by limiting the formation of bone from cartilage (a process called ossification), particularly in the long bones. It serves as negative regulator of bone growth.
Estrogen deficiency	Tall stature, lack of pubertal development, and osteopenia (decrease in the mineral density of bone)	***CYP19A1*** [70]	The *CYP19A1* gene provides instructions for making an enzyme called aromatase, which is responsible for the aromatization of androgen into estrogens.
Estrogen resistance	Tall stature, elevated serum estrogen, abnormal serum gonadotropin, failure of epiphyseal fusion, and possibly insulin resistance	***ESR1*** (loss of function) [71]	This gene encodes for estrogen receptor that play an important role in regulation of eukaryotic gene expression, cellular proliferation, and differentiation in target tissues.
Beckwith-Wiedemann syndrome (BWS)	Affected infants are considerably larger than normal (macrosomia) and tend to be taller than their peers	***H19***, ***CDKN1C***, ***IGF2***, and ***KCNQ1OT1*** [72]	H19 is a long non-coding RNA that has a role in the negative regulation (or limiting) of body

Table 1 (continued)

Growth disorders	Clinical features	Affected gene(s)	Gene functions
	during childhood, abnormally large abdominal organs (visceromegaly), creases in the skin near the ears, low blood sugar (hypoglycemia) in infancy, and kidney abnormalities		weight and cell proliferation. CDKN1C protein is involved in controlling growth before birth. IGF2 promotes growth and division of cells in many tissues, including cartilage development during postnatal long bone growth. KCNQ1OT1 is a non-coding RNA, which regulate genes that are essential for normal growth and development before birth.
Childhood-onset obesity	Tall stature/increased growth velocity, development of severe obesity, persistent food-seeking behavior	***MC4R*** [73]	The protein encoded by this gene is a member of the melanocortin receptor family. The encoded protein interacts with adrenocorticotropic and MSH hormones and is mediated by G proteins.
Multiple synostosis syndrome 1	Progressive symphalangism, multiple joint fusions, conductive deafness, mild facial dysmorphism, delayed puberty bone age, and closure of the epiphyseal lines of long bones with tall stature	***NOG*** [74]	The protein encoded by this gene is called noggin, which involved in the development of many body tissues, including nerve tissue, muscles, and bones.
Isolated ACTH deficiency (IAD)	Tall stature, secondary adrenocortical insufficiency with low or absent cortisol production, normal secretion of pituitary hormones other than adrenocorticotropic hormone (ACTH), and the absence of structural pituitary defects	***TBX19*** [75]	This gene encodes for a transcriptional regulator involved in developmental processes.

within a 1.05Mb locus containing the *IGF1* gene involved in chondrogenesis. Independent signals within this locus may reflect distinct functional haplotypes harboring separate causative variants (i.e., those in very weak LD) each within some functionally relevant sequence, supporting the notion that genes have complex regulatory systems that both qualitatively (i.e., spatially) and quantitatively (i.e., level) mediate gene expression and phenotypic diversity.

Interestingly, these 3290 variants explain only ~ 24.6% of the predicted genetic variance in height, reflecting the well-known issue of "missing heritability" [114]. Several studies have offered insight into this issue by trying to find variants that account for the remaining unexplained heritability. Recent studies [115–120] used improved statistical modeling of a larger set of common variants to demonstrate that by factoring in those variants just failing significance, the missing heritability may be explained. However, a most recent study [121••] approached this issue from a different angle in which they used whole genome sequencing on 21,620 unrelated Europeans to partition variants into those that are rare versus more common and at varying levels of LD. When they applied these data in concert with height data, they identified that rare variants in low LD also significantly contribute to and largely explain this missing heritability. Indeed, while no individual rare variant explains any population-level associations with height, many rare variants in low to modest LD with common variants (i.e., even with those falling well above statistical thresholds) *en masse* tentatively appear to influence heritable variation in height [121••]. These findings also indicate that narrowing down association intervals to true causal variants may be much harder than previously thought.

A sheer number of independent associations, as well as the preliminary finding that rare variants significantly explain a portion of inherited variation, experimentally demonstrate that height is extremely polygenic. Analyses of variant effect size distributions reveal that only ~ 1% of variants have moderate effect sizes (i.e., ~ 0.5 cm/allele). For example, in three studies [111, 112, 113••], the *ZBTB38* locus (rs2871960) was the most significant locus identified with each allele increasing height by ~ 0.4 cm; similar to the effects of previously identified variants at *GDF5-UQCC* (rs6060369) [109] and *HMGA2* (rs1042725) [108]. Recently, GWAS on more localized populations reveal that common variants can have a much larger effect previously thought. In Sardinians, an intronic variant (rs150199504) in *KCNQ1*, a voltage-gated potassium channel encoding gene reduces height by ~ 1.8 cm [104•]; in Greenland Inuits, an intronic variant (rs7115739) in *FADS3*, a gene involved in fatty acid metabolism, reduces height by ~ 1.9 cm [103•] and in Peruvians, a missense variant (rs200342067) in *FBN1*, a gene encoding ECM glycoprotein that may interact with Transforming growth factor (TGF-β) in tissue homeostasis, reduces height by ~ 2.2 cm [105•]. Despite these findings, it is important to point out that greater than 99% of common GWAS and rare variants have extremely minor effects on height variation (i.e., < 5 mm/allele) [113]. These findings strongly support insights made in the early 1900s by R.A Fisher [122], who modeled height polygenicity and the infinitesimal effects of an extremely large number of Mendelian loci on height variation.

Given this extreme polygenicity and findings that height loci overlap with associated loci for other complex traits and diseases (reviewed in [123–125, 126••]), Boyle and Pritchard [126••] have suggested that height is an omnigenic trait, where the actions of large portions of the genome influence normal phenotypic variation and heritability. In this model, a sizable portion of overall allelic variation (~ 4%), overlapping a series of core regions (e.g., possibly growth/cartilage relevant pathways) and many peripherally acting ones (e.g., biological processes that indirectly impinge of height), drive height variation; with the largest effect variants only modestly enriched in sequences that act directly on height and the vast majority of variants instead distributed ubiquitously across the genome (e.g., every 100 kb on average) each contributing minimal amounts to height variation. These common variants, with effects well below 5 mm, are enriched in active chromatin regions, with little signal of variants influencing heritability in inactive sequences. Furthermore, while there are specific enrichment signals in regulatory elements for chondrocytes/cartilage (see below), there are nonetheless quite strong signals of enrichment in regulatory elements active across a number of cell types, and therefore, these more pleiotropic variants likely also mediate other observed trait and disease associations. Overall, it suggests that the effects of evolution in shaping other aspects of human biology may often indirectly impinge on growth altering pathways influencing height (see below).

As alluded to above, studies using GWAS data reveal that height-associated loci are enriched near genes involved in a number of different biological processes. Lango Allen and colleagues [111] discovered 180 height loci in a GWAS on 183,727 individuals and found that variants were enriched near genes involved in Hedgehog, TGF-β and growth hormone (GH) pathways, while Wood and colleagues [112] discovered 697 variants in a GWAS on 253,288 individuals and found additional enrichments in signaling by fibroblast growth factors (FGFs), WNT/beta-catenin, chondroitin sulfate–related genes, mechanistic target of rapamycin (mTOR), osteoglycin, and glycosaminoglycans. Yengo and colleagues [113••] identified the strongest enrichments near genes contributing to skeletal growth, chondrocyte biology, and cartilage/bone ECM (*ACAN*, *ADAMTS17*, *EFEMP1*, *FBLN5*), but also in bone morphogenetic protein (BMP) pathways (*BMP2*, *BMP6*, *GDF5*, and *NOG*) and Hedgehog pathways (*HHIP*, *IHH*, *PTCH1*). However, they also revealed signals near genes involved in chromatin remodeling (*DOT1L*, *HMGA1*, *HMGA2*, *SCHM1*), cell cycle regulation

(*ANAPC13*, *CABLES1*, *CDK6*, *NCAPG*), Glycosylphosphatidylinositol (GPI) anchor protein synthesis (*PIGP*), fatty acid elongation (*HSD17B12*), among many others processes [113••, 127]. Given the role of the Hippo-Yap pathway in size control in animals, GWAS has also identified signals near *LATS2*, *TEAD1*, *VGLL2-4*, and *YAP1*, with variants in *VGLL3* associated with height only in women and in *YAP1* and *VGLL3* associated with shorter stature during pubertal growth [128].

The finding that some loci have effects on height via their roles in pubertal growth and chondrocyte development is not surprising considering that comparisons of Mendelian genetics studies on extreme height phenotypes and GWAS meta-analyses have revealed that many loci harboring common height variants can also have rarer coding mutations involved in monogenic, often congenital growth and height disorders. Indeed, these studies reveal the importance of pre- and early postnatal mechanisms in height control [127] (see Table 1). For example, Eurasian individuals carrying a common high-frequency 130-kb haplotype spanning *GDF5-UQCC1* are ~ 0.4 cm shorter [109], the likely causal variant (rs4911178) in a *GDF5* growth plate enhancer [129•]. Conversely, Hunter-Thompson type chondrodysplasia [130], DuPan syndrome [131], and acromesomelic dysplasia type—Grebe [132] patients possess missense *GDF5* coding mutations, resulting in severe short stature and joint phenotypes, syndromes which phenocopy *brachypodism* mice harboring *Gdf5* coding mutations [133]. Likewise, a common variant at *HMGA2* (rs1042725) increases adult height by ~ 0.4 cm, whereas rare, severe coding mutations in *HMGA2* markedly alter body size in humans and "pygmy" mice [108]. A number of other height GWAS loci (*ACAN*, *C6orf173*, *HHIP*, *HLA*, *PTCH1*, *SF3B4*, *SPAG17*, and *ZNFX1*) are associated with infant length [134], whereas others (*CABLES1*, *CDK10*, *LCORL*, *TSEN15*, *ZBTB38*, and *ZNF638*) are associated with familial short stature [135], indicating the effects of variants during early development.

Given the relationships between common and rare variants and their respective effect sizes at a number of developmental loci, it has been suggested that the strongest phenotypic effects on height are most likely caused by rare variants, which unfortunately, may also be deleterious due to their generally pleiotropic nature. Marouli and colleagues [136••] tested the association between 241,453 variants (83% coding with MAF ≤ 0.05) and adult height variation in 711,428 individuals, and observed that the largest effect sizes were for four rare missense variants located in *AR* (rs137852591), *CRISPLD2* (rs148934412), *IHH* (rs142036701), and *STC2* (rs148833559). Carriers with the most significant rare variant at *STC2*, a regulator of postnatal growth [137], were ~ 2 cm taller than non-carriers, while carriers with rare variants at *AR*, *CRISPLD2*, and *IHH* were ~ 2 cm shorter than non-carriers. Importantly in all four cases, the genes within these loci also result in growth disorders when mutated. Given the recent initial findings [121••] on rare variants and their roles in height heritability, it is also likely that individual rare variants of modest effect will be found after more improved statistical modeling and by examining their roles in functional non-coding annotations.

With regard to the non-coding genome, GWAS has revealed an important functional impact that the non-coding genome has on height variation, evident by the finding that greater than 95% of GWAS height variants reside in non-coding regions. While many of these variants likely impact transcriptional regulation (see below), some signals likely impact RNA biology. Variants located within miRNA target sites at genes within associated loci likely contribute to variation in human stature. For example, *Let-7* miRNA-binding site polymorphisms in the 3′UTR of *CDK6*, *DOT1L*, *HMGA2*, *LIN28B*, and *PAPPA* alter miRNA binding and therefore influence miRNA-mediated gene regulation. Because miRNAs are critical post-translational regulators of gene expression, it would be interesting to test whether the other *Let-7* targets or *Let-7* itself are regulators of adult height [110, 127, 138]. Likewise, *hsa-miR-140-5p* plays an important role in skeletal development in vivo [139] and it has a target site polymorphism in *FGFRL1* 3′UTR that could modulate *FGFRL1* expression levels affecting bone formation and height variation [140]. Other miRNAs enriched in GWAS genes that may regulate adult height are described in [141]. Variants in long non-coding RNA (lncRNA) may also shape height variation. *H19* is a lncRNA with roles in the negative regulation of body weight and cell proliferation. Similarly, *KCNQ1OT1* is another that regulates genes that are essential for normal prenatal development and growth. The aberrant expression of *H19* and *KCNQ1OT1* appears involved in Beckwith-Wiedemann syndrome (BWS), where affected individuals are considerably larger than normal at birth and childhood [72]. Three GWAS variants, two (rs147239461 and rs7482510) at *IGF2-H19* and one (rs143840904) at *KCNQ1*, a gene encoded in the locus, are located within an imprinted 1.8Mb region on chromosome 11p15 and these may affect growth by paternal imprinting [142]. In a separate study on Sardinians, a different variant (rs150199504), one in moderate LD with rs143840904, may act via maternal imprinting and appears associated with shorter height [104•], further obscuring variant causality at the locus.

While GWAS have predominantly focused on overall (aka standing) height, the identified loci cannot easily be partitioned into those influencing hind limb length, vertebral height (trunk height), or head height. Understanding the different mechanisms controlling regional growth is important especially as these anatomical regions have different embryonic origins, respond differently to growth hormones pre- and postnatally, and markedly differ in proportion across human groups. GWAS on sitting height ratio (SHR), the ratio of

sitting height (measured from top of skull to surface upon which a person is sitting) to standing height, was performed on 3545 African-Americans and 21,590 Europeans [143•]. Chan and colleagues not only validated SHR differences between these groups, with African-Americans having lower SHR, but also found that SHR was quite heritable with common variants explaining 26% and 39% of the total variance in European and African-Americans, respectively. Their GWAS on African-Americans identified one locus (rs10736877) near *C10orf90*, whose function unfortunately remains unknown. Conversely, GWAS on Europeans identified several loci: (1) two novel loci at *PTPRM* (rs140449984), potentially involved in growth control and osteocyte biology [144], and *NFATC2* (rs228836), involved in growth plate chondrocyte differentiation [145]; (2) two loci previously reported as standing height loci, *Tbx2* (rs882367), whose loss of function results in skeletal malformations [146, 147] and *BCKDHB* (rs6931421), expressed in embryonic limb buds [148]; and (3) one locus containing *IGFBP3* (rs1722141), involved in IGF signaling and skeletal growth [149], where other SNPs not in LD independently correlate with standing height, suggesting different mechanisms controlling height at this locus. They also observed enrichments of standing height–associated variants [112] with SHR variants. For example, 71 (of 130) loci had height-increasing alleles predicted to decrease SHR, indicating that these act disproportionately on long bone growth, whereas 59 (of 130) loci had the height-increasing allele predicted to increase the SHR, indicating they act to affect head or spine length. Like overall height, most SHR variants reside in the non-coding genome and remain understudied.

To date, GWAS studies have predominantly focused on identifying SNP associations with height, although other variant types may also underlie normal height variation. While novel chromosomal-level alterations are often incompatible with life [150] and/or cause syndromic phenotypes (see above), most humans possess several large structural modifications that do not lead to overt, deleterious insults but instead may underlie normal variation in physical traits [151]. These features may increase or decrease gene CNV, but they could also have regulatory effects on gene expression in target tissues [152]. A genome-wide CNV association study for height in 618 Chinese subjects found four CNV at chromosomes 6p21.3, 8p23.3-23.2, 9p23, and 16p12.1, with a CNV gain at 8p23.3-23.2 associated with lower height, and a CNV loss at 6p21.3 associated with lower height. Likewise, another CNV analysis on a clinical cohort of children found that subjects with short stature had an increased CNV burden suggesting they might contribute to variation in stature in the general population [153]. In another study [154], CNV regions nearby genes from height GWAS were examined and a 17.7-kb deletion was identified at chromosomal position 12q24.33 downstream of *GPR133*, a locus linked with human height.

Transcriptomics, Epigenomics, and Height Variation

A recent focus has been on understanding how GWAS variants *en masse* influence functional aspects of height biology. In these studies, often the top GWAS variants and those in moderate to strong LD are examined for how often they overlap functionally annotated sequences in the genome. The functional annotations (e.g., marking gene bodies, promoters, enhancers, and CpG sites) derive from transcriptomic and functional epigenomics datasets from the ENCODE Project [155], the Roadmap Epigenomics Project [156], and the FANTOM5 Project [157] or individual research labs focusing on chondrocyte biology (e.g., [158, 159•]). In most cases, proximity-based approaches (i.e., the assignment of a variant in a genomic feature to its closest gene) are used to assess whether height variants are enriched near a particular functional class of genes relative to background. Consequently, these analyses also help whittle down non-coding signals to potential causal regulatory variants for functional follow-up, albeit there are only a couple of instances where follow-up functional validation experiments have been performed (see below). One of the earliest proximity-based enrichment studies, by Lui et al. [158], focused on the proximity of 207 GWAS height variants ([111] and others) to genes differentially expressed in the murine growth plate. After identifying 427 differentially growth plate expressed genes, they saw specific enrichments for height loci near these genes, indicating that variants often target chondrocyte gene expression.

A number of studies on common and pathological height variation have focused on whether genetic variants influence gene expression and/or function via gene promoter CpG methylation [160]. CpG methylation analysis revealed that 72 of 87 (82.8%) genes previously shown to be most associated with height contained CpG islands upstream of their transcription start sites and correlated with gene regulation. Yengo and colleagues [113] used methylation quantitative trait loci (mQTLs) derived from blood [161] to identify 775 methylation sites showing pleiotropic associations with height, and in the process revealing potential mechanisms. For example, at one CpG site (cg19825988) within *ZBTB38*, a zinc finger transcriptional activator that binds methylated DNA, they found that increased methylation had the largest mediation effect on height compared with other sites. Methylation has also been examined in the context of pathological phenotypes, but at candidate genes. For example, hypomethylation at CpG sites in the *HOXA4* promoter has been associated with Russell-Silver syndrome and growth restrictions in children [162], whereas abnormal methylation at the maternal *GNAS* promoter has been associated with severe obesity and short stature [163]. Moreover, Ouni and colleagues [164] found that CG methylation of the *P2* promoter of *IGF1* gene plays a role in idiopathic short stature. Interestingly, height GWAS also

identified significant associations at *IGF1* (rs17032362, rs1520223, rs5742692, rs35767, and rs1457595) [164].

Some studies have focused on height variation in the context of genome-wide regulatory functionality and chromatin accessibility. Trynka and colleagues [165] examined whether 697 associated variants (and those in LD) from Wood et al. [112] were enriched in DNase I open chromatin regions from 217 ENCODE cell types, and found the strongest enrichments for height variants overlapping sites in embryonic stem cells (H1-hESCs), indicating that the regulatory control of embryonic development may in part underlie height variation. Chan and colleagues [143•] examined whether SHR variants were enriched in FANTOM enhancer annotations, and of seven significant loci, six showed overlaps with enhancer elements, albeit FANTOM did not examine tissues directly relevant to cartilage growth. Furthermore, of the 130 height variants overlapping SHR variants, this group also had stronger enrichments for enhancer overlap than non-overlapping height variants, and when the 130 variants were divided into those likely influencing long bones (71 loci) versus head/spine (59 loci), stronger enrichment for long bone influencing variants was observed. In support of their omnigenic model, Boyle and Pritchard [126] also performed enrichment studies on height variants as well as general common variants and found that common variants are enriched in active chromatin regions across many cell types, indicative of pleiotropy, with little signal of variants influencing heritability in inactive sequences.

Capellini, Guo, and colleagues [159•] profiled open chromatin regions in chondrocytes of the developing femur in mice using ATAC-seq [166, 167]. After identifying thousands of orthologous human sites and intersecting them with GWAS height variants, they found substantial enrichment above genomic background levels. The specificity of their findings was supported by the lack of enrichments in these femur datasets for GWAS variants from other complex, polygenic traits and diseases, indicating that not all complex traits share the same underlying architectures. They also used transcriptomic data on the growth plate [158] and found height variants in open chromatin regions were enriched near genes that were also differentially expressed in the growth plate. To move closer towards causal variant discovery, they also performed follow-up functional tests in human chondrocytes on variants in the *Chondroitin Sulfate Synthase 1* (*CHSY1*) locus. *CHSY1* coding mutations in humans and mice cause severe skeletal phenotypes including Temtamy preaxial brachydactyly syndrome, characterized by short stature and preaxial brachydactyly [152, 168–170]. They identified that a C/T base-pair change at rs9920291 modified a repressor sequence which impacted gene expression in vitro, with the height-increasing allele (T) making the regulatory element a weaker repressor. In unpublished data, this variant position also mediates HOXD13 binding while overexpression of HOXD13 led to *CHSY1* upregulation in human chondrocytes. None of the remaining three ATAC-seq variants in *CHSY1* influenced reporter expression, pointing strongly towards rs9920291 as putatively causal. These in-depth studies reveal that not all variants in open chromatin regions need to effect expression. While all of these studies are compelling, much more focus should be spent on causal variant discovery especially at GWAS loci of large effect, those involved in extreme height phenotypes, as well as those shaped by natural selection and other evolutionary forces (see below).

Evolutionary Mechanisms and Conclusions

While reinforcing key roles that chondrocyte and skeletal pathways have in mediating height variation, GWAS have also revealed the sheer number of independent inputs controlling height as well as the importance of the non-coding genome. These two features should be thought of in the context of how evolution has shaped height phenotypes worldwide, given that it shapes the effect sizes, allelic frequencies, and types of loci mediating height attainment. The non-coding genome is an especially important place to investigate further because regulatory variants influencing phenotypes can increase in frequency within populations without the extreme pleiotropic consequences typically associated with coding variants. With this in mind, we delve into a brief discussion on how evolution shaped height loci, and we highlight areas of future inquiry.

There is a common (mis-) belief that in dispersing out-of-Africa (OoA), human height became extremely diverse as migratory populations adapted to new ecological settings in the Old World. However, prior to this OoA dispersal, which occurred between 130,000 and 50,000 years ago (reviewed in [171]), heights within Africa were already likely quite varied given the marked ecological diversity across the continent, and that modern Africans are markedly genetically diverse and varied in height [124, 172, 173]. In ancient Africa, the diversity of functional genetic haplotypes would have served as the standing genetic variation for which adaptive and non-adaptive regulatory evolution occurred within Africa as well as during OoA colonization. Future efforts must characterize the genetic architecture of height in Africa through GWAS on more localized populations, and how it relates to ancient genetic and phenotypic diversity across the continent.

Early OoA populations experienced a substantial genetic bottleneck reducing genetic variation [174, 175], but upon which a number of evolutionary forces acted. When groups entered Eurasia, they became quite dispersed, smaller in population size, and exposed to new interactions with ancient populations that exited Africa hundreds of thousands of years earlier (reviewed in [171]). For example, in living Eurasians, there are introgressed genomic sequences from Neanderthals

and Denisovans, each of which resided and ecologically adapted to different environments well before modern human contact [176–181]. Neanderthal alleles in human loci associated with sitting and standing height appear to influence modern human height attainment, an effect possibly on developmental growth [182]. Some of this introgressed variation consisted of novel sequences arising in these archaic hominins but some were older variants that became reintroduced into OoA groups that lost them in the bottleneck [183]. Regardless, these archaic haplotypes, and the novel epistatic interactions that arose via their introgression in modern human genomes, served as part of the genetic fodder upon which natural selection could shape modern height variation. Future efforts should be made to understand regulatory diversity in sitting and standing height, and the effects of archaic introgressed sequences on height biology.

Some of the possible natural selection pressures often invoked in early OoA populations and their descendants include thermoregulation, energy conservation, and positive assortative mating [184] [124], although, their effects have been examined mainly at individual loci. For example, at the *GDF5-UQCC1* locus, selection on a chondrocyte growth plate enhancer variant "A" (rs4911178) for its height- or growth-reducing effects increased a 130-kb haplotype, and likely contributed to shorter height in southern Europeans and in East Asians [129•, 185–187]. Here, the selection pressures may have related to thermoregulation and/or energy conservation in part because the specific genetic alterations appear to shorten limb lengths, and this may have been a mechanism to conserve body heat [188] and/or reduce overall body size for energy conservation during resource scarcity [185]. Analyses of the frequencies of the shorter height allele across parts of Asia suggest evidence of a geographic cline, such that populations living in colder climates (e.g., Siberians) appear to have increased frequencies of the "A" variant especially compared with southern Asians (unpublished data; [129•]), matching cold adaptation expectations. In Europe, the "A" variant is high in frequency in southern Europeans, a possible influence of gene flow and migration from earlier first farmer populations sharing genetic signals with these populations [189, 190] and potentially serving to maintain smaller body size during energetic scarcities. Interestingly, the short height "A" variant is also present in Neanderthals and Denisovans, who lived in Eurasia at times when it was markedly colder, albeit it been called into serious question. At least threeoccurs on a related haplotype that may have been independently selected for its effects on growth [129•]. When considering body size more broadly across mammals, the *GDF5-UQCC1* locus has repeatedly been shown to act as a key quantitative trait locus and under selection in species where body size has been artificially selected [109, 191–193], indicating that the locus presents with functional genetic diversity and may be evolvable, subject to repeated selection.

Other loci have been found associated with shorter height and likely under positive selection, although their signals were detected in geographically localized populations, and likely arose more recently. In Sardinians, a small stature population in Europe, selection on the short height intronic variant in *KCNQ1* potentially reflected an island biogeography response in which smaller body size aided in lowering energy requirements to accommodate limited caloric availability [104•]. In Greenland Inuits, selection on the short height intronic variant in *FADS3* may have been in response to their fat-rich diet, which indirectly decreased height, although it could be due to cold stress and the need for shortened extremities, as Inuit body and appendage sizes are often cited examples of cold adaptation [103•]. Most recently, in Peruvians, selection on a missense variant in *FBN1* may have reflected coastal lifestyles, which we are assuming to mean potentially lower energetic resource availabilities, although this remains unclear [105•]. Future GWAS efforts focused on more localized populations (as well as comparisons between closely related populations that differ in phenotype) will help to determine which other height loci appear under selection, as this should aid in understanding the diversity of selective pressures driving height variation across similar and different ecologies. To this end, genetic studies on different short stature "pygmy" populations in West and Central Africa [194–199] and Asia [200, 201•] have revealed a number of genes involved in height variation (*IGF-1*, *GH*, and other growth factors) and which show the effects of recent selection and convergence on growth control mechanisms.

There has been a recent desire to go beyond individual loci and ask whether GWAS height loci *en masse* show evidence of natural selection. In this regard, height has often been considered the quintessential example of a polygenic adaptation—i.e., reflecting directional (positive selective) changes via small allele frequency shifts at many phenotypically relevant sites [202]. A number of studies [104•, 123, 201•, 203, 204] have used genome-wide selection tests and polygenic risk scores (PRS) that take into consideration variation at multiple genetic loci and their associated weights and found subtle effects of positive selection in shaping height variation globally as well as within Europeans and other populations. Guo and colleagues [123] found evidence that selection altered the allele frequencies and LD patterns of height variants, and noted that PRS in Europeans were higher than in Africans, which were in turn higher than East Asians, matching expectations based on observed phenotypic differences in mean height across these geographic regions. Zoledziewska and colleagues [104•], Turchin and colleagues [203], and Robinson and colleagues [204] found that within Europeans, approximately half of GWAS loci show some evidence of positive selection along a north-south cline, with taller populations in the north

having an abundance of height-increasing alleles and shorter populations in the south having an abundance of height decreasing alleles. Field and colleagues [205] using their singleton-density score (SDS) on the UK10K Project data found that during the past 2000–3000 years, selection for increased height may have drove allele frequency shifts across most of the genome, favoring taller alleles in Britons. Finally, studies comparing ancient and modern genomes and using GWAS height data indicate that the patterns of height variant distribution in Europe could reflect contributions from at least three different founder human populations; each of these populations may have varied significantly in a number of anthropometric traits [189, 190].

Recently, the extent of polygenic selection for height has been called into serious question. At least three new studies [206••, 207••, 208] have re-examined the north-south cline in height variation in Europe and positive selection signals for taller heights in Britons, each originally determined using summary statistics from GIANT, but now reassessed using genotype and phenotype data from the larger, more homogeneous UK Biobank dataset. These new studies found that the signals for polygenic adaptation to be markedly attenuated especially when based on a large number of variants falling below genome-wide significance which are extremely sensitive to biases due to uncorrected population structure in GWAS [206••, 207••, 208]. They emphasize that while the height associations in the original studies are reproducible, the PRS calculated using this new dataset are not nearly as strong, putting into question the extent to which height loci in Europeans was shaped by positive selection rather than the effects of genetic drift or other population demographic processes.

GWAS height variants have also been studied for signals of stabilizing selection and negative selection. In both instances, height is modeled to reflect that it not only has many inputs (i.e., is highly polygenic) but is also deeply tied to other phenotypes (i.e., is highly pleiotropic). In the case of stabilizing selection, selection likely has not acted in a directional manner to shape only height or its architecture but rather on intermediate phenotypes that permit adaptive (and non-detrimental) changes in co-evolving traits. To this end, Sanjak and colleagues [3•] in their analysis of height associations from the UK biobank found signals of weak stabilizing selection of GWAS loci influencing height, while Simons and colleagues [209•] developed a model demonstrating the effects of stabilizing selection and pleiotropy on height. In the case of negative selection, selection against pleiotropically acting variants has likely had an impact on height variation. Zeng and colleagues [210] found in examining GWAS loci, that for height, lower MAF variants in general tended to have larger effect sizes than common variants suggesting that the former are tolerated in affecting height only because they occur at low frequencies. This was supported by findings on LD structure and allele frequency distributions by other studies [211, 212] that each found evidence of the effects of negative selection on height loci and other anthropometric traits. Finally, a recent whole genome sequencing study by Wainschtein and colleagues [121••] found that variants (MAF < 0.1) in low LD bins were enriched for non-synonymous and protein truncating variants, which also on average contributed much more to heritability estimates than synonymous or non-coding variants, and in turn may be indicative of negative selection.

Overall, future efforts need to improve methods to control for population demography, and better tease out the effects that each of these three different types of selection has had at GWAS height loci. Disentangling the influence of selection as compared with population demography is important especially because it helps focus causal variant discovery efforts and our understanding of why such variants rose to high levels in populations. To this end, it will still be important to study individual loci and their effects on height variation in individual populations in the past. Detailed understanding of the evolutionary history of the haplotypes harboring true causal height variants at individual loci will shed light on the extent to which height is pleiotropic versus modular, as well as whether signals of the polygenic basis of height are evenly distributed across the genome or focused in specific functional regions of importance (i.e., both insights impinge on our understanding of an omnigenic model [126]). Such an understanding may even help make connections between height and other disease risks or traits. For example, selection on the short height "A" regulatory variant (rs4911178) in the *GDF5-UQCC1* locus led to a substantial increase in frequency of its linked 130kb haplotype, which consequently is also associated with an increased risk of knee and hip osteoarthritis [129•]. On this haplotype, there are likely separate genetic regulatory variants, which have not themselves been under selection (i.e., since osteoarthritis typically occurs well after reproductive age), but which confer osteoarthritis risk at joint specific sites [129•]. Indeed, detailed studies at individual loci can reveal functional interconnections between variants that may be missed by broader, genome-wide scale investigations.

Finally, as humans have experienced recent environmental and cultural changes, such as the industrial revolution, and modern improvements in nutrition and infection disease prevention and treatment, cultural factors also have significantly shaped human height variation (reviewed in [124, 213]). There is a wealth of data on how infectious disease state, access to adequate nutrition, socioeconomic status, among other factors, influence human stature but they currently fall short of being directly connected to genetic and epigenetic mechanisms influencing underlying height biology. A greater understanding of how these factors epigenetically influence height loci and how genetic variants at these loci mediate such effects is needed. Ultimately, for these environmental and cultural factors to have an evolutionary effect on height variation,

it will be important to link them to specific functional loci and ultimately reveal how they impact fitness.

Acknowledgments The authors would like to thank Drs. Graham Coop (University of California, Davis) and Peter Visscher (University of Queensland) for helpful discussions on the genetics and evolution of height, as well as members of the Capellini Laboratory and the Department of Human Evolutionary Biology at Harvard University for many insightful discussions. We would also like to acknowledge the terrific community of scholars studying height for whom we were unable to cite their work; studies on the biology of height are vast and it was challenging to choose relevant articles from so much excellent work.

Funding This research has been funded in part by NIH NIAMS R01 (1R01AR070139-01A1) to TDC.

Compliance with Ethical Standards

Conflict of Interest Pushpanathan Muthuirulan and Terence D. Capellini declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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