Revisiting the Population Genetics of Human Height

Peter Rotwein

Department of Molecular and Translational Medicine, Paul L. Foster School of Medicine, Texas Tech Health University Health Sciences Center, El Paso, Texas 79905

ORCiD number: 0000-0002-9505-1817 (P. Rotwein).

Context: Recent advances in genetics and genomics present unique opportunities for enhancing knowledge of human physiology and disease susceptibility. An outstanding example of these new insights may be seen in the study of human height, of which it has been estimated that approximately 80% is genetically determined. Over the past decade, large-scale population analyses have led to the identification of novel variation in genes and loci individually associated with changes in adult height of as much as 2 cm.

Objective: To assess these same variants in the genomes of 213,158 individuals compiled by the Genome Aggregation Database (GnomAD) consortium, representing different population groups from around the world.

Results: The majority of these height-changing alleles are substantially less prevalent in GnomAD than found previously in other cohorts, with 4 of 5 amino acid substitution variants with the largest impact on adult height being more frequent in the European population than in other groups.

Conclusions: A larger-scale analysis of individuals from diverse backgrounds will be necessary to ensure a full and accurate understanding of the genetic underpinnings of human height throughout the world, and additional studies will be needed to discern the biochemical and molecular mechanisms governing the physiological processes that explain how these variant proteins might selectively impact the biology of the growth plate. Broader understanding of the genetics of height also should set the stage for more comprehensive investigation into the causes of prevalent polygenic human diseases.

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Key Words: population genetics, genome analysis, genetics of height

Over the past decade, the GIANT consortium and other research groups have applied genome-wide association studies (GWAS) and related approaches to identifying loci and individual genes that are linked with variation in adult human height [1–5]. The impetus for these studies has been severalfold. First, it is well known that human height is highly heritable and that it involves the contribution of many different genes [6]. Second, height is readily measurable, and thus can serve as an outstanding example for a variety of other traits and human diseases that also are thought to undergo polygenic inheritance but are more difficult to dissect [6]. Third, genetic variants that affect height can provide insight into the biology of human growth and growth disorders (eg, achondroplasia, hypochondroplasia,

Abbreviations: BP, binding protein; GnomAD, Genome Aggregation Database; GWAS, genome-wide association studies; IGF, insulin-like growth factor; MAF, minor allele frequency; PAPP-A, pregnancy-associated plasma protein-A; SNP, single nucleotide polymorphism.
fibroblast growth factor receptor 3 mutations [7, 8], Laron-type dwarfism, and growth hormone receptor mutations [9, 10]).

GWAS analyses have identified nearly 700 relatively common genome variants associated with adult height that collectively appear to account for more than 20% of the heritability of height, at least in a predominantly European population [1, 2]. More recent studies involving 711 428 individuals from a similar cohort have defined 83 coding and intron variants with minor allele frequencies (MAFs) of from 0.1% to 4.8% in this population, and with effect sizes of up to ± 2.1 cm on final adult height [3].

Genome Aggregation Database (GnomAD) [11], an extension of the Exome Aggregation Consortium [12–15], contains deoxyribonucleic acid sequence information from the exons or whole genomes from 213 158 unrelated individuals representing different population groups from around the world (GnomAD v2.1.1, 141 456 people, and GnomAD v3, 71 702). These data have revealed substantial variation within the coding regions of genes but also have shown that most alterations were uncommon, as more than half were detected in a single allele, and more than 99% were seen in less than 1% of the study group [15]. In addition, the vast majority of this variation has consisted of synonymous nucleotide changes that do not alter predicted amino acids [15].

In this manuscript, I have interrogated GnomAD with 66 of the genetic variants identified previously by Marouli et al. in a predominantly European cohort [3] that appeared to have the greatest effects on final adult height. The results show that the majority of these alleles are substantially less prevalent in the GnomAD data resource, and that 4 of the 5 amino acid substitution variants with the largest impact on height are far more frequent in a European population than in any other GnomAD group. More evidence for this statement comes from further evaluation of a recently identified predicted amino acid alteration in the FBN1 gene that is associated with reduced adult height in Peruvians [16]. The same variant is found nearly exclusively in GnomAD in a Latin American cohort, being essentially absent from other population groups. Collectively, these observations demonstrate that a larger-scale analysis of individuals from different backgrounds will be necessary to ensure a fuller understanding of the genetic underpinnings of human growth and adult height.

1. Materials and Methods

Data from Marouli et al [3] were retrieved from their Figure 1, their extended data Table 1, and their supplementary Tables, 7, 9, and 11, and are presented in Tables 1 and 2. Their initial study population consisted of 458 927 individuals, of whom 381 625 were reported to be of European origin, 27 494 were African, and 29 591 South Asian (the origins of the other individuals were not described) [3]. This was expanded to include an additional validation group of 252 501 European participants, for a total of 711 428 people [3]. I obtained additional information on the same human genes from the GnomAD genome browser, which contains results of sequencing of the exons or whole genomes from 141 456 unrelated individuals (GnomAD v2.1.1) and from 71 702 additional unrelated individuals (GnomAD v3) with the following approximate population-of-origin distributions: African, 16%; European, 45%; Finnish, 8%; Latino, 12%; East Asian, 5%; South Asian, 8%; and other groups, 6% (see: https://gnomad.broadinstitute.org/). Neither the health status nor heights of these individuals are available. These results are presented in Tables 3–5.

2. Results and Discussion

A. Established Genetic Links With Human Height

Marouli et al identified 83 genetic variants with MAFs in their study population; between 0.1% and 4.8% were associated with increased or decreased adult human height of up to 2.1 cm [3]. As nearly all of these deoxyribonucleic acid variants occurred in the coding regions of genes, and each were predicted to change an amino acid, the authors concluded that
they had identified both new genes and biological pathways that were implicated in human longitudinal growth [3]. My analysis of their data, as extracted from their Figure 1, their extended data Table 1, and supplementary Table 11, revealed that 66 of these variants had an effect on final adult height of between 0.3 and 2.1 cm (Tables 1 and 2) and that the other 17 had a smaller impact (not shown).

The proteins encoded by the 2 genes with the largest effects on height, **STC2** on chromosome 5 (stanniocalcin 2; amino acid substitution variant R44L; MAF 0.11%), +2.1 cm, and **AR** on the X chromosome (androgen receptor; amino acid substitution variant Q799E; combined discovery and validation MAF 0.52%), –2.0 cm, are both potential regulators of longitudinal growth at the growth plate of long bones, but by different mechanisms [17–22].

**STC2**, a 302-amino acid secreted protein, interacts physically with pregnancy-associated plasma protein-A (PAPP-A), a metalloproteinase that cleaves insulin-like growth factor (IGF) binding protein-4 (IGFBP-4), an inhibitory IGFBP that interferes with the actions of IGF1 and IGF2 [22–24]. By apparently binding PAPP-A more weakly than the normal version of the protein, the variant STC2 facilitates additional cleavage of IGFBP-4 by PAPP-A, thus releasing more IGF1 and IGF2 for signaling at different bodily compartments, including at the growth plate [22], with the long-term effect being increased adult height. In contrast, the variant AR protein presumably causes reduced adult height through its altered

| Gene      | Chromosome | SNP        | AA Change | MAF (%) | Effect on Height |
|-----------|------------|------------|-----------|---------|-----------------|
| **STC2**  | 5          | rs148833559| R44L      | 0.11    | + 2.1 cm        |
| **ZEAT**  | 8          | rs75596750 | R166W     | 0.16    | + 1.9 cm        |
| **PDE5A** | 4          | rs149385790| D803A     | 0.30    | + 1.5 cm        |
| **ZFAT**  | 8          | rs112892337| S470C     | 0.40    | + 1.2 cm        |
| **FBN2**  | 5          | rs78727187 | H1381N    | 0.60    | + 1.2 cm        |
| **SCMH1** | 1          | rs143365597| P313S     | 0.47    | + 1.2 cm        |
| **PTHR1** | 3          | rs121434601| R150C     | 0.28    | + 1.1 cm        |
| **‘NPR3** | 5          | rs146301345| G478S     | 0.28    | + 0.9 cm        |
| **SERPINA1** | 14     | rs28929474 | E366Q     | 1.85    | + 0.9 cm        |
|           |            |            | E366K     |         |                 |
| **PHKB**  | 16         | rs34667348 | Q657K     | 0.51    | + 0.6 cm        |
| **ARMC5** | 16         | rs141923065| splice acceptor | 0.91   | + 0.5 cm        |
| **MTMR11**| 1          | rs145659444| R521H     | 0.68    | + 0.5 cm        |
|           |            |            | R521L     |         |                 |
| **DLEU1** | 13         | rs2066674  | none: intron | 4.28  | + 0.5 cm        |
| **GRAMD2**| 15         | rs34815962 | A23T      | 2.07    | + 0.5 cm        |
| **MCL1**  | 1          | rs11580946 | A227V     | 1.45    | + 0.5 cm        |
| **NSD1**  | 5          | rs28932177 | A691T     | 2.77    | + 0.4 cm        |
| **NHEJ1** | 2          | rs16859517 | none: intron | 3.59  | + 0.4 cm        |
| **ZBTB7B**| 1          | rs141845046| P224S     | 2.68    | + 0.4 cm        |
| **‘KIAA0922** | 4       | rs34343821 | P1574L    | 1.26    | + 0.4 cm        |
| **PABPC4L**| 4          | rs116807401| R210G     | 1.67    | + 0.4 cm        |
| **CNOT4** | 7          | rs17480616 | A7V       | 2.87    | + 0.4 cm        |
|           |            |            | A7E       |         |                 |
| **GLT8D2**| 12         | rs117801489| Y24C      | 2.17    | + 0.4 cm        |
| **‘WDR76**| 15         | rs150494621| L535F     | 1.05    | + 0.4 cm        |
| **EPS15** | 1          | rs41292521 | S438L     | 2.11    | + 0.3 cm        |
| **SETD2** | 3          | rs76208147 | M1080I    | 1.79    | + 0.3 cm        |
| **ZNF300**| 16         | rs61733564 | F156S     | 3.18    | + 0.3 cm        |
| **ABCA6** | 17         | rs77542162 | C1359R    | 2.00    | + 0.3 cm        |
| **LAMB2** | 3          | rs35713889 | G914R     | 4.14    | + 0.3 cm        |

Abbreviations: AA, amino acid; SNP, single nucleotide polymorphism.

**a**As reported in Extended Data Table 1 and Supplementary Table 11 [3]. **b**MAF = minor allele frequency. **c**NPR3 = AC026703.1. **d**KIAA0922 = TMEM131L. **e**WDR76 = Y_RNA.
half-life or decreased transcriptional actions on genes of cells at the growth plate [17–22]. Additionally, if the mechanism of dysfunction involves diminished androgen binding by the variant AR, more aromatization could occur [18], leading to excessive estrogen effects at the growth plate [18] and, thus, reduced adult height. However, at this juncture, the specific molecular mechanisms of action of this altered AR protein have not been elucidated.

It is not clear how the other 3 gene variants with large effects on final adult height potentially alter growth, although IHH (Indian hedgehog, amino acid substitution variant R771S; MAF 0.20%), –1.8 cm, is known to act at the growth plate [25], and other mutations in this

| Gene      | Chromosome | SNP         | AA Change | MAF (%) | Effect on Height |
|-----------|------------|-------------|-----------|---------|------------------|
| AR        | X          | rs137852591 | Q799E     | 0.52    | –2.0 cm          |
| CRISPLD2  | 16         | rs148934412 | C290Y     | 0.10    | –2.0 cm          |
| IHH       | 2          | rs142036701 | R771S     | 0.20    | –1.8 cm          |
| HAPLN3    | 15         | rs141308595 | R71C      | 0.16    | –1.6 cm          |
| PIEZO1    | 16         | rs201226914 | L939M     | 0.19    | –1.3 cm          |
| ADAMTS6   | 5          | rs61736454  | S90L      | 0.21    | –1.0 cm          |
| 'HSD11B2' | 16         | rs140385822 | V273M     | 0.21    | –0.9 cm          |
| dIQCC     | 1          | rs150341307 | R491T     | 0.30    | –0.8 cm          |
| TSPAN31   | 12         | rs147996581 | A12T      | 0.29    | –0.8 cm          |
| ACAN      | 15         | rs16942341  | none      | 2.66    | –0.8 cm          |
| SNRPC     | 6          | rs34427075  | none      | 1.47    | –0.8 cm          |
| CCND3     | 6          | rs33966734  | E127 stop | 1.19    | –0.8 cm          |
| IL11      | 19         | rs4252548   | R112H     | 2.46    | –0.7 cm          |
| TIM2      | 6          | rs148543891 | Y141S     | 0.29    | –0.7 cm          |
| SCMH1     | 1          | rs114233776 | P17L      | 0.60    | –0.7 cm          |
| ADAMTS3   | 4          | rs141374503 | R565Q     | 0.35    | –0.7 cm          |
| FIBIN     | 11         | rs138273386 | R96H      | 0.42    | –0.7 cm          |
| CRISPLD2  | 16         | rs149615348 | M284I     | 0.76    | –0.6 cm          |
| AMOTL1    | 11         | rs138059525 | R363Q     | 0.84    | –0.6 cm          |
| ANAPC5    | 12         | rs13141     | A630V     | 0.96    | –0.6 cm          |
| 'ZNF628'  | 19         | rs147110934 | E292D     | 2.16    | –0.6 cm          |
| PTPN13    | 4          | rs61730641  | T2386K    | 1.55    | –0.6 cm          |
| NSD1      | 5          | rs78247455  | A2546T    | 2.36    | –0.5 cm          |
| DDR1      | 6          | rs7757648   | none: intron | 1.21  | –0.5 cm          |
| MATN3     | 2          | rs52826764  | E252K     | 2.68    | –0.5 cm          |
| SMG7      | 1          | rs144712473 | L132E     | 0.67    | –0.5 cm          |
| DISP1     | 11         | rs144673025 | M1096T    | 0.77    | –0.5 cm          |
| ABCB6     | 2          | rs147443238 | A492T     | 0.97    | –0.5 cm          |
| ELN       | 7          | rs41511151  | G711D     | 0.55    | –0.5 cm          |
| TTC28     | 22         | rs77885044  | E1054K    | 1.41    | –0.4 cm          |
| DIS3L2    | 2          | rs7571816   | none: intron | 2.43  | –0.4 cm          |
| DLG5      | 10         | rs41274586  | P1089L    | 1.71    | –0.4 cm          |
| TSGA10IP  | 11         | rs71455793  | R303Q     | 4.18    | –0.4 cm          |
| TBX15     | 1          | rs61730011  | M460R     | 4.36    | –0.4 cm          |
| LRRC36    | 16         | rs8052655   | G509S     | 4.31    | –0.3 cm          |
| CYTL1     | 4          | rs11722554  | R136 C    | 3.82    | –0.3 cm          |
| SLC8A3    | 14         | rs41286548  | G577S     | 2.31    | –0.3 cm          |
| IL11RA    | 9          | rs11575580  | R395W     | 1.78    | –0.3 cm          |

Abbreviations: AA, amino acid; SNP, single nucleotide polymorphism.

As reported in their Extended Data Table 1 and Supplementary Table 11 [3]. MAF = minor allele frequency. HSD11B2 = ATP6V0D1. dIQCC = RP4-622L5.7. ZNF628 = NAT14.
gene are associated with short limbs and fingers [25]. ZFAT (zinc-finger gene with AT-hook, amino acid substitution variant R166W; MAF 0.16%), +1.9 cm, is predominantly expressed in the spleen, thymus, and lymph node [26] and has been found via gene disruption studies in mice to be essential for red blood cell development in the fetal liver [27]. GWAS also have linked Zfat to final height in horses [28, 29]. Variants in CRISPLD2 (cysteine-rich secretory protein LCCL domain containing 2, amino acid substitution variant C290Y; MAF 0.10%), –2.0 cm, have been linked with both asthma susceptibility (single nucleotide polymorphism [SNP] rs12051168 [30]), and cleft lip/palate (SNP rs4783099 [31]). Neither ZFAT nor CRISPLD2 proteins have been associated previously with any growth-related physiological pathways, and their mechanisms of action in this regard are unknown.

B. Analyzing Height-Associated Gene Variants in Other Human Populations

The genome resource, GnomAD [11], versions 2.1.1 and 3, collectively consists of 213 158 individuals (population-of-origin distributions: African, 16%; European, 45%; Finnish, 8%; Latino, 12%; East Asian, 5%; South Asian, 8%; and other groups, 6%). My analysis of the frequency in this database of the 66 genetic variants identified by Marouli et al [3], associated with the largest alterations in adult height (see Tables 1 and 2), showed that of the 28 genes linked to increased height, 23 were reduced in population prevalence, 3 were unchanged (MAF ± 20% of Marouli et al [3]), 1 was not evaluable, and 1 gene variant was increased in frequency by 270% (SETD2; SET domain containing 2 [histone lysine methyltransferase], amino acid substitution variant M1080I; MAF 4.72%; see Table 3). Similarly, of the 38 genes associated with diminished adult height, 24 were reduced in population prevalence in GnomAD, 9 were unchanged, 2 were unevaluable, and 2 showed an increased prevalence of 180% (ACAN; aggrecan, synonymous amino acid change; MAF 4.75%, Table 3) and 280% (LRRC36; leucine-rich repeat containing 36, amino acid substitution variant G509S; MAF 12.04%, Table 4), respectively. Aggrecan is a proteoglycan and is a major component of extracellular matrix [32]. Remarkably, there are more than 20 predicted heterozygous amino acid substitution and truncation mutants identified to date in ACAN in cohorts with familial short stature, including individuals with or without skeletal dysplasias [33–35]. In contrast, LRRC36 has not been connected with any growth-related physiological pathways, and its mechanism of action is unknown.

For the 5 genes with the greatest effects on adult height according to Marouli et al ([3], see Tables 1 and 2), the frequency of the minor height-associated allele varied substantially among different population groups in the GnomAD data resource (Table 5). Of note was the 10-fold lower prevalence of the AR height-reducing variant in individuals of African, Latin American, East Asian, and South Asian origin and more than 5-fold diminished prevalence of both the STC2 and ZFAT height-enhancing alleles in individuals from Finland, East Asia, and South Asia (Table 5).

C. A Height-Associated Gene Variant in FBN1 With a Restricted Population Distribution

A recent publication from Asgari et al described the identification of a predicted missense variant in Peruvians in FBN1 (fibrillin 1; amino acid substitution variant E1297G; SNP rs200342067; MAF 4.7%) that was linked to a 2.2 cm reduction in stature (4.4 cm in homozygotes) [16]. According to the authors, this allele also showed widespread population variance in different regions of Peru (MAFs ranging from 0% to 9.7%) and had an MAF of 0.7% in individuals of Latin American background analyzed in the BioMe Biobank of the Icahn School of Medicine [16]. I found nearly identical results in the GnomAD database. The prevalence of this minor FBN1 variant was 0.72% in Latin American individuals (355 of 49 076 alleles). In contrast, this allele was essentially absent from all other populations (2 of ~183 000 Europeans, 2 of ~65 000 Africans, and 0 of ~90 000 alleles for other defined groups). FBN1 is a large and complicated gene found on chromosome 15q15-q21.1 and consists of 65 exons that span 230 kb [36]. The protein, which is found in the extracellular
matrix and assembles to form microfibrils, contains multiple different domains that can form extensive interactions with other extracellular matrix molecules [37]. Its growth-regulating properties may reflect the ability of FBN1 to bind and modulate the bioavailability of members of the transforming growth factor-β family, including bone morphogenic proteins [36]. At least 1800 different mutations in FBN1 have been found to cause Marfan syndrome, an autosomal dominant multiorgan disorder of connective tissue with a worldwide incidence of 1 in 3000 to 1 in 5000 births [36, 37]. Mutations in FBN1 also have been described in several other less common diseases that affect connective tissue, including individuals with acromelic dysplasias, which can manifest phenotypically with short stature, small hands and feet, and stiff joints [36]. Of note, the individuals identified by Asgari et al in Peru did not appear to have any of these features [16].

D. FBN2 and Height

The FBN1 protein is structurally related to FBN2, which is also localized to the extracellular matrix, and can be found physically associated with FBN1 in the same microfibrils [37] and also may interact with transforming growth factor-β family members [36]. Several mutations have been identified within human FBN2 and cause congenital contractual arachnodactyly, a rare autosomal dominant disorder that consists of joint contractures, scoliosis, arachnodactyly, and other manifestations, including tall stature in approximately 55% of patients [38]. Remarkably, the predicted amino acid substitution in FBN2 defined

| Gene     | MAF GnomAD v2.11a (%) | MAF GnomAD v3b (%) | Combined MAF GnomAD v2 + v3 | MAF vs Marouli et al |
|----------|-----------------------|--------------------|-----------------------------|----------------------|
| STC2     | 0.05                  | 0.05               | 0.05                        | 0.5X                 |
| ZFAT     | 0.05                  | 0.06               | 0.05                        | 0.3X                 |
| PDE5A    | 0.07                  | 0.05               | 0.06                        | 0.2X                 |
| ZFAT     | 0.20                  | 0.21               | 0.20                        | 0.5X                 |
| FBN2     | 0.37                  | 0.32               | 0.35                        | 0.6X                 |
| SCMH1    | 0.24                  | 0.25               | 0.24                        | 0.5X                 |
| PTH1R    | 0.17                  | 0.17               | 0.17                        | 0.6X                 |
| NPR3     | 0.20                  | 0.16               | 0.19                        | 0.7X                 |
| SERPINA1 | 1.13                  | 1.25               | 1.17                        | 0.6X                 |
| PKH2     | 0.27                  | 0.29               | 0.28                        | 0.5X                 |
| ARM5     | 0.31                  | N/A                | 0.21                        | 0.2X                 |
| MTMR11   | 0.42                  | 0.51               | 0.45                        | 0.7X                 |
| DLEU1    | N/A                   | 2.90               | 0.97                        | 0.2X                 |
| GRAMD2   | 1.38                  | 1.31               | 1.36                        | 0.7X                 |
| MCL1     | 0.82                  | 0.86               | 0.83                        | 0.6X                 |
| NSD1     | 2.06                  | 1.82               | 1.98                        | 0.7X                 |
| NHEJ1    | N/A                   | N/A                | N/A                         | N/A                  |
| ZBTB7B   | 2.10                  | 1.94               | 2.05                        | 0.8X                 |
| KIAA0922  | 0.78                  | 0.83               | 0.80                        | 0.6X                 |
| PABPC4L  | 0.59                  | 0.95               | 0.71                        | 0.4X                 |
| CNOT4    | 1.69                  | 1.77               | 1.72                        | 0.6X                 |
| GLT8D2   | 1.19                  | 1.14               | 1.17                        | 0.5X                 |
| WDR76    | 0.42                  | 0.41               | 0.42                        | 0.4X                 |
| EPS15    | 1.30                  | 1.35               | 1.32                        | 0.6X                 |
| SETD2    | 5.71                  | 2.83               | 4.75                        | 2.7X                 |
| ZNF500   | 3.11                  | 5.51               | 3.91                        | 1.2X                 |
| ABCA6    | 0.91                  | 1.03               | 0.95                        | 0.5X                 |
| LAMB2    | 3.21                  | 3.57               | 3.33                        | 0.8X                 |

Abbreviations: GnomAD, Genome Aggregation Database; MAF, minor allele frequency; N/A, not available.

*282 912 alleles. *143 404 alleles. *TMEM131L.
by Marouli et al [3] in individuals with a + 1.2 cm change in adult height (SNP rs78727187; H1381N; MAF 0.6%, Table 1) is located only 3 residues from a causal mutation for congenital contractural arachnodactyly, C1384F or C1384Y [38], so the potential impact of both variants on growth and stature may be similar. The data from GnomAD demonstrate that this SNP in FBN2 is only 60% as common as found by Marouli et al [3] (MAF 0.35%, Table 3), with a higher prevalence in European and Finnish populations (MAF 0.56% and 0.30%, respectively) than in others (MAFs of 0% to 0.16% in African, Latin American, East Asian, and South Asian groups).

### E. Final Comments

Recent large-scale population-based genomic analyses, such as presented by Marouli et al [3] and others [1, 2, 4, 5], have identified new alleles that potentially make major contributions to adult height, a complex polygenic trait [6]. For most of these genes, the variant is present

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Table 4. Revisiting Uncommon Coding And Noncoding Gene Variants That Decrease Adult Height

| Gene   | MAF GnomAD v2 (%) | MAF GnomAD v3 (%) | Combined MAF GnomAD v2 + v3 (%) | MAF vs Marouli et al |
|--------|-------------------|-------------------|-------------------------------|---------------------|
| AR     | 0.11              | 0.10              | 0.11                          | 0.2X                |
| CRISPLD2 | 0.50             | 0.50              | 0.50                          | 5.0X                |
| IHH    | 0.08              | 0.05              | 0.07                          | 0.3X                |
| HAPLN3 | 0.08              | 0.00              | 0.06                          | 0.4X                |
| PIEZO1 | 0.07              | 0.11              | 0.08                          | 0.4X                |
| ADAMTS6 | 0.14             | 0.16              | 0.15                          | 0.7X                |
| HSDB11B2 | 0.14            | 0.13              | 0.14                          | 0.7X                |
| IQCC   | 0.13              | 0.12              | 0.13                          | 0.5X                |
| TSPAN31 | 0.27             | 0.26              | 0.27                          | 0.9X                |
| ACAN   | 3.89              | 6.37              | 4.72                          | 1.8X                |
| SNRPC  | 0.89              | 1.16              | 0.98                          | 0.7X                |
| CCN3   | 1.12              | 0.99              | 1.08                          | 0.9X                |
| IL11   | 1.71              | 1.82              | 1.75                          | 0.7X                |
| TIAM2  | 0.33              | 0.27              | 0.31                          | 1.0X                |
| SCMHI  | 0.45              | 0.47              | 0.46                          | 0.8X                |
| ADAMTS3 | 0.22             | 0.23              | 0.22                          | 0.7X                |
| FIBIN  | 0.33              | 0.32              | 0.33                          | 0.8X                |
| CRISPLD2 | 0.51            | 0.50              | 0.51                          | 0.7X                |
| AMOTL1 | 0.68              | 0.72              | 0.69                          | 0.8X                |
| ANAPC5 | 0.44              | 0.60              | 0.49                          | 0.5X                |
| ZNF628 | 0.70              | 1.44              | 0.95                          | 0.4X                |
| PTPN13 | 0.89              | 0.93              | 0.90                          | 0.6X                |
| NSD1   | 2.34              | 2.24              | 2.31                          | 1.0X                |
| DDR1   | N/A               | N/A               | N/A                           | N/A                 |
| MATN3  | 2.14              | 1.92              | 2.07                          | 0.8X                |
| SMG7   | 0.47              | 0.40              | 0.45                          | 0.7X                |
| DISP1  | 0.59              | 0.52              | 0.57                          | 0.7X                |
| ABCB6  | 0.70              | 0.66              | 0.69                          | 0.7X                |
| ELN    | 0.29              | 0.009             | 0.20                          | 0.4X                |
| TTC28  | 0.48              | 0.81              | 0.59                          | 0.4X                |
| DIS3L2 | N/A               | N/A               | N/A                           | N/A                 |
| DLG5   | 1.18              | 1.19              | 1.18                          | 0.7X                |
| TSSA10IP | 2.06            | 2.64              | 2.25                          | 0.5X                |
| TXB15  | 4.26              | N/A               | 2.84                          | 0.7X                |
| LRRC56 | 8.89              | 18.33             | 12.04                         | 2.8X                |
| CYTL1  | 3.85              | 3.15              | 3.48                          | 0.9X                |
| SLCSA3 | 1.40              | 1.40              | 1.40                          | 0.6X                |
| IL11RA | 1.12              | 1.29              | 1.18                          | 0.7X                |

Abbreviations: GnomAD, Genome Aggregation Database; MAF, minor allele frequency; N/A, not available.

282 912 alleles. 143 404 alleles.
uncommonly in the population (MAFs of 0.1% to < 5%) and, as shown here, at different frequencies among diverse population groups (Tables 3–5), which, although potentially not surprising and previously suggested (eg, see reference 13), nevertheless shows that the accurate representation of allelic variants in different population groups is a work in progress. In addition, the biochemical and molecular mechanisms of action of many of these variants on somatic growth are as of yet undefined, thus providing opportunities to test new hypotheses and potentially describe the physiological processes that explain how these proteins might selectively alter longitudinal growth and impact the biology of the growth plate. The study of human height is also a leading indicator for other fields in which multiple gene inputs collectively shape disease risk and severity. Thus, improvement in insights focusing on the genetics of adult height should set the stage for a broader and more comprehensive understanding of the causes of polygenic diseases prevalent in the human population. This will require more clarity in future genetic analyses, including more thorough elucidation of the reported origins of individuals in study populations, identification of genetic admixture among these participants and, most importantly, an increase in the numbers of individuals from diverse population groups.

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Additional Information:

Correspondence: Peter Rotwein, Department of Molecular and Translational Medicine, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, 5001 El Paso Drive, El Paso, TX 79905. E-mail: peter.rotwein@ttuhsc.edu.

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