Rare and low-frequency coding variants alter human adult height

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SUMMARY

Height is a highly heritable, classic polygenic trait with ~700 common associated variants identified so far through genome-wide association studies. Here, we report 83 new height-associated coding variants with lower minor allele frequencies (range of 0.1-4.8%) and effects of up to 2 cm/allele (*e.g.* in *IHH*, *STC2*, *AR* and *CRISPLD2*), >10 times the average effect of common variants. In functional follow-up studies, rare height-increasing variants of *STC2* (+1-2 cm/allele) compromised proteolytic inhibition of PAPP-A and increased cleavage of IGFBP-4 *in vitro*, resulting in higher bioavailability of insulin-like growth factors. These 83 height-associated variants overlap genes mutated in monogenic growth disorders and highlight new biological candidates (*e.g. ADAMTS3, IL11RA, NOX4*) and pathways (*e.g.* proteoglycan/glycosaminoglycan synthesis) involved in growth. Our results demonstrate that sufficiently large sample sizes can uncover rare and low-frequency variants of moderate to large effect associated with polygenic human phenotypes, and that these variants implicate relevant genes and pathways.

INTRODUCTION

Human height is a highly heritable, polygenic trait[1,2]. The contribution of common DNA sequence variation to inter-individual differences in adult height has been systematically evaluated through genome-wide association studies (GWAS). This approach has thus far identified 697 independent variants located within 423 loci that together explain ~20% of the heritability of height[3]. As is typical of complex traits and diseases, most of the height alleles discovered so far are common (minor allele frequency (MAF) >5%) and are mainly located outside coding regions, complicating the identification of the relevant genes or functional variants. Identifying coding variants associated with a complex trait in new or known loci has the potential to pinpoint causal genes. Furthermore, the extent to which rare (MAF <1%) and low-frequency (1%< MAF ≤ 5%) coding variants also influence complex traits and diseases remains an open question. Many recent DNA sequencing studies have identified only few such variants[4-8], but this limited success could be due to their modest sample size[9]. Some studies have suggested that common sequence variants may explain the majority of the heritable variation in adult height[10], making it timely to assess whether and to what extent rare and low-frequency coding variation contributes to the genetic landscape of this model polygenic trait.

In this study, we used an ExomeChip[11] to test the association between 241,453 variants (83% coding with MAF ≤5%) and adult height variation in 711,418 individuals (discovery and validation sample sizes are 458,927 and 252,491, respectively). The main goals of our project were to determine whether rare and low-frequency coding variants influence the architecture of a model complex human trait, such as adult height, and to discover and characterize new genes and biological pathways implicated in human growth.

RESULTS

32 rare and 51 low-frequency coding variants associated with adult height

We conducted single-variant meta-analyses in a discovery sample of 458,927 individuals, of whom 381,625 were of European ancestry. We validated our association results in an independent set of 252,491 participants. We first performed standard single-variant association analyses; technical details of the discovery and validation steps are in the **Online Methods** (**Supplementary Figs 1-6**, **Supplementary Tables 1-11**). In total, we found 606 independent ExomeChip variants at array-wide significance ($P<2x10^{-7}$), including 252 non-synonymous or splice site variants **(Online Methods** and **Supplementary Table 11**). Focusing on non-synonymous or splice site variants with MAF <5%, our single-variant analyses identified 32 rare and 51 low-frequency height-associated variants (**Tables 1-2**). To date, these 83 height variants (MAF range 0.1-4.8%) represent the largest set of validated rare and low-frequency coding variants associated with any complex human trait or disease. Among these 83 variants, there are 81 missense, one nonsense (in *CCND3*), and one essential acceptor splice site (in *ARMC5*) variants.

We observed a strong inverse relationship between MAF and effect size that is consistent with our statistical power to discover genetic associations (**Fig. 1**). The largest effect sizes were observed for four rare missense variants, located in the androgen receptor gene *AR* (rs137852591, MAF=0.21%, $P_{combined}=2.7x10^{-14}$ under recessive model), in *CRISPLD2* (rs148934412, MAF=0.08%, $P_{combined}=2.4x10^{-20}$), in *IHH* (rs142036701, MAF=0.08%, $P_{combined}=1.9x10^{-23}$), and in *STC2* (rs148833559, MAF=0.1%, $P_{combined}=1.2x10^{-30}$). Carriers of the rare *STC2* missense variant are ~2.1 cm taller than non-carriers, whereas carriers of the remaining three variants (or hemizygous men that carry the X-linked *AR*-rs137852591 rare

allele) are ~2 cm shorter than non-carriers. In comparison, the mean effect size of common height alleles is ten times smaller in the same dataset. Across all 83 rare and low-frequency coding variants, the minor alleles were evenly distributed between height-increasing and -decreasing effects (48% vs. 52%, respectively) (**Fig 1.** and **Tables 1-2**).

Coding variants in new and known height loci, and heritability explained

As expected, many of the height-associated variants in this ExomeChip effort are located near common variants previously associated with height. Of the 83 rare and low-frequency coding variants, 49 fell within 1 Mb of a known height signal, but all were found to be independent after conditional analysis using the July 2015 release of the imputed UK Biobank dataset (which contains individual-level genotype data for both ExomeChip and previously associated common height variants); the remaining 34 define new loci. In addition, we found a further 85 common variants and one low-frequency synonymous variant (in *ACHE*) that define novel loci. Thus, our study identified a total of 120 new height loci, plus 49 additional independent signals from rare and low-frequency coding variants at known loci (**Supplementary Table 11**). Because the sample size of the UK Biobank is smaller than our discovery sample size (120,084 vs. 458,927, respectively), we sought to validate the UK Biobank conditional results using an orthogonal imputation-based methodology implemented in the full discovery set (**Online Methods**). As shown in **Supplementary Fig. 7**, both analytical frameworks produced largely compatible results.

We used the UK Biobank dataset to estimate the contribution of the new height variants to heritability, which is h^2~80% for adult height[2]. In combination, the 83 rare and low-frequency

variants explained 1.7% of the heritability of height. The newly identified novel common variants accounted for another 2.4%, and all independent variants, known and unknown, together explained 27.4% of heritability. By comparison, the 697 known height SNPs explain 23.3% of height heritability in the same dataset. We observed a modest yet significant positive trend between MAF and heritability explained per variant (P=0.012, **Supplementary Fig. 8**), with each common variant explaining slightly more heritability than rare or low-frequency variants (0.029% vs. 0.021%, **Supplementary Fig. 8**).

Gene-based association results

To increase power to find rare or low-frequency coding variants associated with height, we performed gene-based analyses (**Online Methods** and **Supplementary Tables 12-14**). In European-ancestry individuals, the SKAT[12] test (variants with MAF <5% annotated as nonsense, stop-loss, splice site, or damaging missense) identified 99 genes with >1 variant and P_{SKAT} $<2x10^{-6}$ (**Supplementary Table 13**). These 99 genes are enriched for those involved in syndromes of abnormal skeletal growth (previously identified from the Online Mendelian Inheritance in Man (OMIM) database), located near height SNPs identified by GWAS, or predicted to be causal with bioinformatic tools (**Supplementary Fig. 9**)[3,13].

After accounting for gene-based signals explained by a single variant driving the association statistics (**Supplementary Fig. 10**), we identified ten genes that harbor more than one coding variant associated with height variation, and for which the gene-based results remained significant after conditioning on genotypes at nearby common height-associated variants (**Table 3** and **Supplementary Table 15**). Using the same gene-based tests in an independent dataset of 59,804 individuals genotyped on the same exome array, we replicated three genes at P<0.05

(**Table 3**). Further evidence for replication in these genes was seen at the level of single variants (**Supplementary Table 16**). For one of the genes, *OSGIN1,* we found that conditioning on rare variants from this gene affected the results from the single variant analysis. Specifically, two independent variants in *CRISPLD2* (rs149615348, MAF=0.7%, P=9.1x10^{-12}; rs2326458, MAF=26%, P=2.7x10^{-15}) became less significant after conditioning on *OSGIN1* variants (**Supplementary Fig. 11**). Despite this result, *CRISPLD2* is a promising height candidate gene as a third variant in *CRISPLD2*, the rare missense rs148934412 (MAF=0.08%, P=7.6x10^{-14}), remains highly significant after conditioning on *OSGIN1* variants (**Supplementary Fig. 11**). From the gene-based results, three genes – *CSAD*, *NOX4*, and *UGGT2* – fell outside of the loci found by single-variant analyses and are implicated in human height for the first time.

Coding variants implicate biological pathways in human skeletal growth

Prior pathway analyses of height loci identified by GWAS have highlighted gene sets related to both general biological processes (such as chromatin modification and regulation of embryonic size) and more skeletal growth-specific pathways (chondrocyte biology, extracellular matrix (ECM), and skeletal development)[3]. We used two different methods, DEPICT[13] and PASCAL[14] (**Online Methods**), to perform pathway analyses using the ExomeChip results to test whether non-synonymous variants could either independently confirm the relevance of these previously highlighted pathways (and further implicate specific genes in these pathways), or identify new pathways. To compare the pathways emerging from coding and non-coding variation, we applied DEPICT separately on (1) exome array-wide significant coding variants independent of known GWAS signals and (2) non-coding GWAS loci, excluding all novel height-associated genes implicated by coding variants. We identified a total of 496 and 1,623 enriched gene sets,

146 respectively, at a false discovery rate (FDR) <1% (**Supplementary Tables 17-18**); similar
147 analyses with PASCAL yielded 362 and 278 enriched gene sets (**Supplementary Tables 19-20**).
148 Comparison of the results revealed largely shared biology for coding and non-coding variants,
149 especially in the DEPICT analyses, but some pathways showed stronger enrichment with either
150 coding or non-coding variation. In general, coding variants more strongly implicated pathways
151 specific to skeletal growth (such as ECM and bone growth), while GWAS signals highlighted
152 more global biological processes (such as transcription factor binding and embryonic
153 size/lethality)(**Supplementary Fig. 12)**. The two gene sets significant in both DEPICT and
154 PASCAL analyses and that were uniquely implicated by coding variants were "BCAN protein
155 protein interaction subnetwork" and "proteoglycan binding." Both of these pathways relate to the
156 biology of proteoglycans, which are proteins (such as aggrecan) that contain glycosaminoglycans
157 (such as chrondroitin sulfate) and that have well-established connections to skeletal growth[15].
158
159 We also examined which height-associated genes identified by ExomeChip analyses were
160 driving enrichment of pathways such as proteoglycan binding. Using unsupervised clustering
161 analysis to aid in visualization, we observed that a cluster of height-associated genes is strongly
162 implicated in a group of correlated pathways that include biology related to
163 proteoglycans/glycosaminoglycans (**Fig. 2** and **Supplementary Fig. 13**). Strikingly, many of
164 these genes are already annotated in OMIM as underlying disorders of skeletal growth; as such,
165 the remaining genes may be strong candidates for harboring variants that cause Mendelian
166 growth disorders. Within this group are genes that are largely uncharacterized (*SUSD5*), have
167 relevant biochemical functions (*GLT8D2*, a glycosyltransferase studied mostly in the context of
168 the liver[16]; *LOXL4*, a lysyl oxidase expressed in cartilage[17]), modulate pathways known to affect

skeletal growth (*FIBIN*, *SFRP4*)[18,19] or lead to increased body length when knocked out in mice (*SFRP4*)[20].

Functional characterization of rare STC2 variants

To begin exploring whether the identified rare coding variants affect protein function, we performed *in vitro* functional analyses of two rare coding variants in a particularly compelling and novel candidate gene, *STC2*. Over-expression of *STC2* diminishes growth in mice by covalent binding and inhibition of the proteinase PAPP-A, which specifically cleaves IGF binding protein-4 (IGFBP-4), leading to reduced levels of bioactive insulin-like growth factors (**Fig. 3A**)[21]. Although there was no prior genetic evidence implicating *STC2* variation in human growth, the *PAPPA* and *IGFBP4* genes were both implicated in height GWAS[3], and rare mutations in *PAPPA2* cause severe short stature[22], emphasizing the likely relevance of this pathway in humans. The two *STC2* height-associated variants are rs148833559 (p.Arg44Leu, MAF=0.096%, $P_{discovery}=5.7x10^{-15}$) and rs146441603 (p.Met86Ile, MAF=0.14%, $P_{discovery}=2.1x10^{-5}$). These rare alleles increase height by 1.9 and 0.9 cm, respectively, suggesting that they both partially impair STC2 function. In functional studies, STC2 with these amino acid substitutions were expressed at similar levels to wild-type, but showed clear, partial defects in binding to PAPP-A and in inhibition of PAPP-A-mediated cleavage of IGFBP-4 (**Fig. 3B-D**). Thus, the genetic analysis successfully identified rare coding alleles that have demonstrable and predicted functional consequences, strongly confirming the role of these variants and the *STC2* gene in human growth.

Pleiotropic effects and clinical significance

Previous GWAS studies have reported pleiotropic or secondary effects on other phenotypes for many common variants associated with adult height[3,23]. Therefore, we explored to which extent the identified coding variants are associated with 17 human complex phenotypes for which well-powered meta-analysis results were available. Of the 606 height variants identified by single-variant analyses in this study, we found that 96 were associated with at least one of the other investigated traits at array-wide significance ($P<2x10^{-7}$), including one rare and five low-frequency missense variants (see below, **Supplementary Fig. 14**, and **Supplementary Table 21**). Overall, the 606 height signals were enriched for variants nominally associated with body mass index (BMI; $P_{binomial}=1.2x10^{-10}$), LDL-cholesterol (LDL-C; $P_{binomial}=3.5x10^{-6}$), total cholesterol (TC; $P_{binomial}=4.4\ x10^{-8}$), triglycerides (TG; $P_{binomial}=8.9x10^{-7}$) and coronary artery disease (CAD; $P_{binomial}=6.0x10^{-10}$) (**Supplementary Table 22**).

Of the rare and low-frequency missense variants associated with other traits at array-wide significance, the minor alleles at rs77542162 (*ABCA6*, MAF=1.7%) and rs28929474 (*SERPINA1*, MAF=1.8%) were associated with increased height and increased levels of LDL-C and TC, whereas the minor allele at rs3208856 in *CBLC* (MAF=3.4%) was associated with increased height, HDL-cholesterol (HDL-C) and TG, but lower LDL-C and TC levels. The minor allele at rs141845046 (*ZBTB7B,* MAF=2.8%) was associated with both increased height and BMI. The minor alleles at the other two missense variants associated with shorter stature, rs201226914 in *PIEZO1* (MAF=0.2%) and rs35658696 in *PAM* (MAF=4.8%), were associated with decreased glycated haemoglobin (HbA1c) and increased type 2 diabetes risk, respectively. Consistent with a recent report[24], the most pleiotropic variant that we found was the missense rs13107325 (MAF=6.2%) in *SLC39A8*: the minor allele is associated with decreased height,

increased BMI, decreased HDL-C, LDL-C, and TC, but increased TG, and decreased systolic and diastolic blood pressure (**Supplementary Fig. 14** and **Supplementary Table 21**). Rare mutations in *SLC39A8* cause variable short stature phenotypes[25,26], whereas common variants in this gene were previously associated with metabolic syndrome, inflammation, and hypertension[27-30].

Our set of variants associated with height includes several missense variants in genes underlying monogenic syndromes affecting skeletal growth such as *ACAN* (MIM 165800, 608361), *PTH1R* (MIM 60002, 215045), *IHH* (MIM 607778, 112500), *FBN2* (MIM 121050), *ADAMTS10* (MIM 277600) and *ADAMTS17* (MIM 613195) (**Supplementary Table 11**). To further explore the clinical significance of height variants, we queried the ClinVar database and retrieved information on 8,736 variants, including 1,446 markers that are, or predicted to be, pathogenic (**Supplementary Fig. 15** and **Supplementary Table 23**). Of this group, The NIH Genetic Testing Registry recommends testing for four height-associated variants. Two coding variants (rs80356487, MAF=0.03%, β=-1.7 cm; rs1801175, MAF=0.04%, β=-1.2 cm) are located in *G6PC*. Mutations in *G6PC* cause glycogen storage disorder type Ia (von Gierke Disease), which is characterized by growth retardation, delayed puberty, and metabolic abnormalities (MIM 232200). The other two variants are rs1800562 (MAF=6.0%, β=+0.2 cm) in *HFE*, which causes type-1 hemochromatosis (MIM 235200), and rs28929474 (MAF=1.8%, β=+0.8 cm) in the α-1-antitrypsin gene *SERPINA1* (**Supplementary Table 23**). When homozygous, the *SERPINA1*-rs28929474 variant is a cause of emphysema and liver disease in European-descent individuals, and an important risk factor for severe liver disease in cystic fibrosis patients[31]. This is intriguing given that the low-frequency *SERPINA1* allele at rs28929474 is associated with increased height and milder complication in patients with cystic fibrosis due to improve lung functions[32].

DISCUSSION

We undertook an association study of nearly 200,000 non-synonymous variants in 711,418 individuals, and identified 32 rare and 51 low-frequency coding variants associated with adult height. Furthermore, gene-based testing discovered 10 genes that harbor several additional rare/low-frequency variants associated with height, including three genes (*CSAD*, *NOX4*, *UGGT2*) in loci not previously implicated in height. In total, our results highlight 89 genes (10 from gene-based testing and 79 from single-variant analyses (four genes have 2 independent coding variants)) that are likely to modulate human growth, and 24 alleles segregating in the general population that affect height by more than 1 cm (**Tables 1-3**). The rare and low-frequency coding variants explain 1.7% of the heritable variation in adult height. When considering all rare, low-frequency, and common height-associated variants validated in this study, we can now explain 27.4% of the heritability. On a per variant basis, we found that common height SNPs explain more heritability than rare or low-frequency variants (0.029% vs. 0.021%). This suggests that the effect size of rare/low-frequency variants, despite being larger than for common SNPs (**Fig. 1**), is not as large as initially anticipated. Overall, our findings provide strong evidence that rare and low-frequency coding variants contribute to the genetic architecture of height, a model complex human trait.

Our analyses revealed many coding variants in genes mutated in monogenic skeletal growth disorders (**Supplementary Fig. 9**), confirming the presence of allelic series (from familial penetrant mutations to mild effect common variants) in the same genes for related growth phenotypes in humans. We used gene set enrichment-type analyses to demonstrate the functional connectivity between the genes that harbor coding height variants, highlighting known as well as novel biological pathways that regulate height in humans (**Fig. 2**, **Supplementary Fig. 13** and

Supplementary Tables 17-20), and newly implicating genes such as *SUSD5, GLT8D2*, *LOXL4*, *FIBIN,* and *SFRP4* that have not been previously connected with skeletal growth. Additional interesting height candidate genes include *NOX4*, *ADAMTS3* and *ADAMTS6, PTH1R,* and *IL11RA* (**Tables 1-2**, **Supplementary Tables 15** and **24**). *NOX4*, identified through gene-based testing, encodes NADPH oxidase 4, an enzyme that produces reactive oxygen species, a biological pathway not previously implicated in human growth. *Nox4*$^{-/-}$ mice display higher bone density and reduced numbers of osteoclasts, a cell type essential for bone repair, maintenance, and remodelling[12]. We also found rare coding variants in *ADAMTS3* and *ADAMTS6*, genes that encode metalloproteinases that belong to the same family than several other human growth syndromic genes (e.g. *ADAMTS2*, *ADAMTS10*, *ADAMTSL2*). Moreover, we discovered a rare missense variant in *PTH1R* that encodes a receptor of the parathyroid hormone (PTH): PTH-PTH1R signaling is important for bone resorption and mutations in *PTH1R* cause chondrodysplasia in humans[33]. Finally, we replicated the association between a low-frequency missense variant in the cytokine gene *IL11*, but also found a new low-frequency missense variant in its receptor gene *IL11RA*. The IL11-IL11RA axis has been shown to play an important role in bone formation in the mouse[34,35]. Thus, our data confirm the relevance of this signaling cascade in human growth as well. Taken together, the identification of specific genes implicated in human height variation has the potential: (1) to elucidate biological mechanisms that control growth, (2) to provide candidate genes for orphan syndromes characterized by abnormal height phenotypes, and (3) to guide the development of new therapeutic strategies for growth defects. In that regard, the identification of rare missense height-increasing variants of large effect size in *STC2*, and the functional characterization of their effect on IGF signaling, is particularly promising.

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AUTHOR CONTRIBUTIONS

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Height meta-analyses (discovery and replication, single-variant and gene-based)

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UK Biobank-based integration of height association signals group and heritability analyses

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Functional characterization of STC2

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ONLINE METHODS

Study design & participants

The discovery cohort consisted of 147 studies comprising 458,927 adult individuals of the following ancestries: 1) European descent (N=381,625), 2) African (N=27,494), 3) South Asian (N=29,591), 4) East Asian (N=8,767); 5) Hispanic (N=10,776) and 6) Saudi (N=695). Discovery meta-analysis was carried out in each ancestry group (except the Saudi) separately as well as in the All group. Replication was undertaken in individuals of European ancestry only (**Supplementary Tables 1-3**). Conditional analyses were undertaken only in the European descent group (106 studies, N=381,625).

Phenotype

Height (in centimeters) was corrected for age and the genomic principal components (derived from GWAS data, the variants with MAF >1% on ExomeChip, or ancestry informative markers available on the ExomeChip), as well as any additional study-specific covariates (e.g. recruiting center), in a linear regression model. For studies with non-related individuals, residuals were calculated separately by sex, whereas for family-based studies sex was included as a covariate in the model. Additionally, residuals for case/control studies were calculated separately. Finally, residuals were subject to inverse normal transformation.

Genotype calling

The majority of studies followed a standardized protocol and performed genotype calling using the designated manufacturer software, which was then followed by zCall[36]. For 10 studies participating in the Cohorts for Heart and Aging Research in Genomic Epidemiology

(CHARGE) Consortium, the raw intensity data for the samples from seven genotyping centers were assembled into a single project for joint calling[11]. Study-specific quality control (QC) measures of the genotyped variants was implemented before association analysis (**Supplementary Tables 1-2**).

Study-level statistical analyses

Individual cohorts were analyzed separately for each ancestry population, with either RAREMETALWORKER (http://genome.sph.umich.edu/wiki/RAREMETALWORKER) or RVTEST (http://zhanxw.github.io/rvtests/), to associate inverse normal transformed height data with genotype data taking potential cryptic relatedness (kinship matrix) into account in a linear mixed model. These software are designed to perform score-statistics based rare-variant association analysis, can accommodate both unrelated and related individuals, and provide single-variant results and variance-covariance matrix. The covariance matrix captures linkage disequilibrium (LD) relationships between markers within 1 Mb, which is used for gene-level meta-analyses and conditional analyses[37]. Single-variant analyses were performed for both additive and recessive models.

Centralized quality-control

The individual study data were investigated for potential existence of ancestry population outliers based on 1000 Genome Project phase 1 ancestry reference populations. A centralized QC procedure implemented in EasyQC[38] was applied to individual study association summary statistics to identify outlying studies: (1) assessment of possible problems in height transformation, (2) comparison of allele frequency alignment against 1000 Genomes Project

phase 1 reference data to pinpoint any potential strand issues, and (3) examination of quantile-quantile (QQ) plots per study to identify any problems arising from population stratification, cryptic relatedness and genotype biases.

Meta-analyses

Meta-analyses were carried out in parallel by two different analysts at two sites. We excluded variants if they had call rate <95%, Hardy-Weinberg equilibrium $P<1x10^{-7}$, or large allele frequency deviations from reference populations (>0.6 for all ancestry analyses and >0.3 for ancestry-specific population analyses). We also excluded from downstream analyses markers not present on the Illumina ExomeChip array 1.0, variants on the Y-chromosome or the mitochondrial genome, indels, multiallelic variants, and problematic variants based on the Blat-based sequence alignment analyses. Significance for single-variant analyses was defined at array-wide level ($P<2x10^{-7}$, Bonferroni correction for 250,000 variants). For the gene-based analyses, we applied two different sets of criteria to select variants, based on coding variant annotation from five prediction algorithms (PolyPhen2 HumDiv and HumVar, LRT, MutationTaster and SIFT)[39]. The mask labeled *"broad"* included variants with a MAF <0.05 that are nonsense, stop-loss, splice site, as well as missense variants that are annotated as damaging by at least one program mentioned above. The mask labeled *"strict"* included only variants with MAF <0.05 that are nonsense, stop-loss, splice site, as well as missense variants annotated as damaging by all five algorithms. We used two tests for gene-based testing, namely the SKAT[12] and VT[40] tests. Statistical significance for gene-based tests was set at a Bonferroni-corrected threshold of $P<2x10^{-6}$ (threshold for 25,000 genes; we did not correct for the four tests given that they are correlated and that we sought validation in independent studies).

394

395 ***Genomic inflation***

396 We observed a marked genomic inflation of the test statistics even after adequate control for
397 population stratification (linear mixed model) arising mainly from common markers; λ_{GC} in
398 European-ancestry was 1.2 and 2.7 for all and common markers, respectively (**Supplementary**
399 **Fig. 2** and **Supplementary Table 8**). Such inflation is expected for a highly polygenic trait like
400 height, and is consistent with our very large sample size[3,41]. To confirm this, we applied the
401 recently developed linkage disequilibrium (LD) score regression method to our height
402 ExomeChip results[42], with the caveats that the method was developed (and tested) with >200,000
403 common markers available. We restricted our analyses to 15,848 common variants (MAF ≥5%)
404 from the European-ancestry meta-analysis, and matched them to pre-computed LD scores for the
405 European reference dataset[42]. The intercept of the regression of the χ^2 statistics from the height
406 meta-analysis on the LD score estimate the inflation in the mean χ^2 due to confounding bias,
407 such as cryptic relatedness or population stratification. The intercept is 1.4 (standard error =
408 0.07), which is small when compared to the λ_{GC} of 2.7. The ratio statistic of (intercept -1) /
409 (mean χ^2 -1) is 0.067 (standard error = 0.012), well within the normal range[42], suggesting that
410 most of the inflation (~93%) observed in the height association statistics is due to polygenic
411 effects (**Supplementary Fig. 3**).

412

413 Furthermore, to exclude the possibility that some of the observed associations between height
414 and rare/low-frequency variants could be due to allele calling problems in the smaller studies, we
415 performed a sensitivity meta-analysis with primarily Europe-ancestry studies totaling >5,000

participants. We found very concordant effect sizes, suggesting that smaller studies do not bias our results (**Supplementary Fig. 4**).

Conditional analyses

The RAREMETAL R-package[43] and the GCTA v1.24[44] software were used to identify independent height association signals across the European descent meta-analysis results. RAREMETAL performs conditional analyses by using covariance matrices in order to distinguish true signals from those driven by LD with adjacent known variants. First, we identified the lead variants ($P<2x10^{-7}$) based on a 1 Mb window centered on the most significantly associated variant and performed LD pruning ($r^2<0.3$) to avoid downstream problems in the conditional analyses due to co-linearity. We then conditioned on the LD-pruned set of lead variants in RAREMETAL and kept new lead signals at $P<2x10^{-7}$. The process was repeated until no additional signal emerged below the pre-specified P-value threshold. The use of a 1Mb window in RAREMETAL can obscure dependence between conditional signals in adjacent intervals in regions of extended LD. To detect such instances, we performed joint analyses using GCTA in the ARIC and UK ExomeChip reference panels, both of which comprise >10,000 individuals of European descent. Gene-based conditional analyses were also performed in RAREMETAL.

The newly discovered 120 height variants were conditioned on the previously published GWAS height variants[3] in the first release of the UK Biobank imputed dataset using regression methodology implemented in BOLT-LMM[45]. We also explored an alternative approach based on approximate conditional analysis[44]. This latter method relies on summary statistics available

from the same cohort, thus we first imputed summary statistics[46] for exome variants, using summary statistics from the Wood et *al*. 2014 study[3]. Conversely, we imputed the top variants from the Wood et *al*. 2014 study using the summary statistics from the ExomeChip. Subsequently, we calculated effect sizes for each exome variant conditioned on the Wood et *al*. 2014 top variants in two ways. First, we conditioned the imputed summary statistics of the exome variant on the summary statistics of the Wood et *al*. 2014 top variants that fell within 5 Mb of the target ExomeChip variant. Second, we conditioned the summary statistics of the ExomeChip variant on the imputed summary statistics of the Wood et *al*. 2014 hits. We then selected the option that yielded a higher imputation quality. For poorly tagged variants ($\hat{r}^2 < 0.8$), we simply used up-sampled HapMap summary statistics for the approximate conditional analysis. Pairwise SNP-by-SNP correlations were estimated from the UK10K data (TwinsUK[47] and ALSPAC[48] studies , N=3,781).

Description of the single-variant analyses

We conducted single-variant meta-analyses in a discovery sample of 458,927 individuals of different ancestries using both additive and recessive genetic models (**Supplementary Fig. 1** and **Supplementary Tables 1-4**). The combined additive analyses identified 1,455 unique variants that reached array-wide significance ($P<2x10^{-7}$), including 578 non-synonymous and splice site variants (**Supplementary Tables 5-7**). Under the additive model, we observed a high genomic inflation of the test statistics (*e.g.* λ_{GC} of 2.7 in European-ancestry studies for common markers, **Supplementary Fig. 2** and **Supplementary Table 8**), although replication results (see below) and additional sensitivity analyses (see above) suggest that it is consistent with polygenic inheritance as opposed to population stratification, cryptic relatedness, or technical artifacts

462 (**Supplementary Figs 3-4**). The majority of these 1,455 association signals (1,241; 85.3%) were
463 found in the European-ancestry meta-analysis (85.5% of the discovery sample size)
464 **(Supplementary Fig. 5)**. Nevertheless, we discovered eight associations within five loci in our
465 all-ancestry analyses that are driven by African studies (including one missense variant in the
466 growth hormone gene *GH1* (rs151263636), **Supplementary Fig. 6**), three height variants found
467 only in African studies, and one rare missense marker associated with height in South Asians
468 only (**Supplementary Table 7**).
469
470 Several studies, totaling 252,491 independent individuals of European ancestry, became
471 available after the completion of the discovery analyses, and were thus used for validation of our
472 experiment. First, we considered the 81 variants with suggestive association in the discovery
473 analyses ($2x10^{-7}<P_{discovery}\leq 2x10^{-6}$). Of those 81 variants, 55 reached significance after combining
474 discovery and replication results based on $P_{combined}<2x10^{-7}$ (**Supplementary Table 9**).
475 Furthermore, recessive modeling confirmed seven new independent markers with $P_{combined}<2x10^{-7}$
476 , including one rare missense variant (rs137852591, MAF 0.21%) in the *AR* gene
477 (**Supplementary Table 10**). To test the independence and integrate all height markers from the
478 discovery and replication phase, we used conditional analyses and GCTA "joint" modeling[44] in
479 the combined discovery and replication set. This resulted in the identification of 606 independent
480 height variants, including 252 non-synonymous or splice site variants (**Supplementary Table**
481 **11**). Of the 606 variants, 605 had concordant direction of effect between the discovery and
482 validation studies, and 595 variants had a $P_{validation}<0.05$ (482 variants with $P_{validation}<8x10^{-5}$,
483 Bonferroni correction for 606 tests), suggesting a very low false discovery rate (**Supplementary**
484 **Table 11**).

485

486 ***Pathway analyses***

487 DEPICT is a computational framework that uses probabilistically-defined reconstituted gene sets
488 to perform gene set enrichment and gene prioritization[13]. For a description about gene set
489 reconstitution please refer to references [13] and [49]. In brief, reconstitution was performed by
490 extending pre-defined gene sets (such as Gene Ontology terms, canonical pathways, protein-
491 protein interaction subnetworks and rodent phenotypes) with genes co-regulated with genes in
492 these pre-defined gene set using large-scale microarray-based transcriptomics data. In order to
493 adapt the gene set enrichment part of DEPICT for ExomeChip data, we made two principal
494 changes. First and foremost, because DEPICT for GWAS incorporates all genes within a given
495 LD block around each index SNP, we modified DEPICT to take as input only the gene directly
496 impacted by the coding SNP. Second, we adapted the way DEPICT adjust for confounders (such
497 as gene length) by generating null ExomeChip association results using Swedish ExomeChip
498 data (Malmö Diet and Cancer (MDC), All New Diabetics in Scania (ANDIS), and Scania
499 Diabetes Registry (SDR) cohorts, N=11,899) and randomly assigning phenotypes from a normal
500 distribution before conducting association analysis (see **Supplementary Note**). For the gene set
501 enrichment analysis of the ExomeChip data, we used significant non-synonymous variants
502 statistically independent of known GWAS hits (and that were present in the null ExomeChip
503 data; See Supplementary Note for details). For gene set enrichment analysis of the GWAS data,
504 we used all loci (1) with a non-coding index SNP and (2) that did not contain any of the novel
505 ExomeChip genes. In visualizing the analysis, we used affinity propagation clustering[50] to group
506 the most similar reconstituted gene sets based on their gene memberships (See Supplementary
507 Note). Within a "meta-gene set", the best P-value of any member gene set was used as

representative for comparison. DEPICT for ExomeChip was written using the Python programming language and the code can be found at https://github.com/perslab/ec-depict.

We also applied the PASCAL pathway analysis tool[14] to genome-wide association summary statistics for all coding variants. In brief, the method derives gene-based scores (both SUM and MAX statistics) and subsequently tests for the over-representation of high gene scores in predefined biological pathways. We used standard pathway libraries from KEGG, REACTOME and BIOCARTA, and also added dichotomized (Z-score>3) reconstituted gene sets from DEPICT[13]. To accurately estimate SNP-by-SNP correlations even for rare variants, we used the UK10K data (TwinsUK[47] and ALSPAC[48] studies , N=3781). In order to separate the contribution of regulatory variants from the coding variants, we also applied PASCAL to association summary statistics of only regulatory variants (20 kb upstream, gene body excluded) from the Wood et *al*. study[3]. In this way, we could classify pathways driven principally by coding, regulatory or mixed signals.

Validation

We performed single-variant and gene-based association analyses for eight validation studies, totaling 59,804 participants, genotyped on the Exomechip using RAREMETAL[37]. We sought additional evidence for association for the top signals in two independent studies in the UK (UK Biobank) and Iceland (deCODE), comprising 120,084 and 72,613 individuals, respectively. We used the same QC and analytical methodology as described above. Genotyping and study descriptives are provided in **Supplementary Tables 1-3**. For the combined analysis, we used the inverse-variance weighted fixed effects meta-analysis method using METAL[51]. Significant

associations were defined as those with a combined meta-analysis (discovery and validation) $P_{combined}<2x10^{-7}$.

STC2 functional experiments

Mutagenesis, cell culture and transfection. For the generation of STC2 mutants (R44L and M86I), wild-type STC2 cDNA contained in pcDNA3.1/Myc-His(-) (Invitrogen)[21] was used as a template. Mutagenesis was carried out using Quickchange (Stratagene), and all constructs were verified by sequence analysis. Recombinant wild-type STC2 and variants were expressed in human embryonic kidney (HEK) 293T cells (293tsA1609neo) maintained in high-glucose DMEM supplemented 10% fetal bovine serum, 2 mM glutamine, nonessential amino acids, and gentamicin. Cells ($6x10^6$) were plated onto 10 cm-dishes and transfected 18 h later by calcium phosphate coprecipitation using 10 μg plasmid DNA. Media were harvested 48 h post transfection, cleared by centrifugation, and stored at -20°C until use. Protein concentrations (58-66 nM) were determined by TRIFMA using antibodies described previously[21]. PAPP-A was expressed stably in HEK293T cells as previously reported[52]. Expressed levels of PAPP-A (27.5 nM) were determined by a commercial ELISA (AL-101, Ansh Labs, TX).

STC2 and PAPP-A complex formation. Culture supernatants containing wild-type STC2 or variants were adjusted to 58 nM, added an equal volume of culture supernatant containing PAPP-A corresponding to a 2.1-fold molar excess, and incubated at 37°C. Samples were taken at 1, 2, 4, 6, 8, 16, and 24 h and stored at -20^{o}C.

553 *Analysis of proteolytic activity.* Specific proteolytic cleavage of ^{125}I-labeled IGFBP-4 is
554 described in detail elsewhere[53]. Briefly, the PAPP-A:STC2 complex mixtures were diluted
555 (1:190) to a concentration of 145 pM PAPP-A and mixed with preincubated ^{125}I-IGFBP4 (10
556 nM) and IGF-1 (100 nM) in 50 mM Tris-HCl, 100 mM NaCl, 1 mM $CaCl_2$. Following 1 h
557 incubation at 37^{o}C, reactions were terminated by the addition of SDS-PAGE sample buffer
558 supplemented with 25 mM EDTA. Substrate and co-migrating cleavage products were separated
559 by 12% nonreducing SDS-PAGE and visualized by autoradiography using a storage phosphor
560 screen (GE Healthcare) and a Typhoon imaging system (GE Healthcare). Band intensities were
561 quantified using ImageQuant TL 8.1 software (GE Healthcare).
562
563 *Western blotting.* STC2 and covalent complexes between STC2 and PAPP-A were blotted onto
564 PVDF membranes (Millipore) following separation by 3-8% SDS-PAGE. The membranes were
565 blocked with 2% Tween-20, and equilibrated in 50 mM Tris-HCl, 500 mM NaCl, 0.1% Tween-
566 20, pH 9 (TST). For STC2, the membranes were incubated with goat polyclonal anti-STC2
567 (R&D systems, AF2830) at 0.5 μg/ml in TST supplemented with 2% skim milk for 1 h at 20°C.
568 For PAPP-A:STC2 complexes, the membranes were incubated with rabbit polyclonal anti-
569 PAPP-A[54] at 0.63 μg/ml in TST supplemented with 2% skim milk for 16 h at 20°C. Membranes
570 were washed with TST and subsequently incubated with polyclonal swine anti-rabbit IgG-HRP
571 (DAKO, P0217) or polyclonal rabbit anti-goat IgG-HRP (DAKO, P0449), respectively, diluted
572 1:2000 in TST supplemented with 2% skim milk for 1 h at 20°C. Following washing with TST,
573 membranes were developed using enhanced chemiluminescence (ECL Prime, GE Healthcare).
574 Images were captured using an ImageQuant LAS 4000 instrument (GE Healthcare).
575

576 ***Pleiotropy analyses***

577 We accessed ExomeChip data from GIANT (BMI, waist-hip ratio), GLGC (total cholesterol
578 (TC), triglycerides (TG), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C)), IBPC (systolic
579 and diastolic blood pressure), MAGIC (glycaemic traits), REPROGEN (age at menarche and
580 menopause), and DIAGRAM (type 2 diabetes). For coronary artery disease, we accessed 1000
581 Genomes Project-imputed GWAS data released by CARDIoGRAMplusC4D[55].
582

583 **URLs**

584 ClinVar, http://www.ncbi.nlm.nih.gov/clinvar/

585 DEPICT, http://www.broadinstitute.org/mpg/depict/

586 ExomeChip, http://genome.sph.umich.edu/wiki/Exome_Chip_Design

587 ExomeDEPICT, https://github.com/perslab/ec-depict

588 OMIM, http://omim.org/

589 PASCAL, http://www2.unil.ch/cbg/index.php?title=Pascal

590 RAREMETALWORKER, http://genome.sph.umich.edu/wiki/RAREMETALWORKER

591 RVTEST, http://zhanxw.github.io/rvtests/

Table 1. Rare variants associated with adult height. 32 coding or splice site variants with minor allele frequency <1% in European-ancestry participants that have $P_{combined}$ <2x10^{-7}. All markers are significant under an additive genetic model, except *AR*-rs137852591, which was discovered using the recessive model in the all-ancestry analysis. The direction of the effect (Beta) and effect allele frequency (AF) is given for the alternate (Alt) allele. Genomic coordinates are on build 37 of the human genome. For each variant, we provide the most severe annotation using the ENSEMBL Variant Effect Predictor (VEP) tool. N, sample size; Ref, reference allele; SE, standard error.

					Discovery (N up to 381,625)				Validation (N up to 252,491)				Combined (N up to 634,116)			
Variant	**Chr:Pos**	**Ref/Alt**	**Gene**	**Annotation**	**AF**	**Beta**	**SE**	**P-value**	**AF**	**Beta**	**SE**	**P-value**	**AF**	**Beta**	**SE**	**P-value**
rs150341307	1:32673514	G/C	*IQCC*	missense	0.002	-0.141	0.026	7.92E-08	0.004	-0.116	0.025	3.83E-06	0.003	-0.128	0.018	1.34E-12
rs143365597	1:41540902	G/A	*SCMH1*	missense	0.004	0.188	0.018	1.58E-25	0.006	0.169	0.024	9.42E-13	0.005	0.181	0.014	1.35E-36
rs114233776	1:41618297	G/A	*SCMH1*	missense	0.006	-0.119	0.015	1.92E-15	0.006	-0.11	0.019	1.32E-08	0.006	-0.116	0.012	1.80E-22
rs145659444	1:149902342	C/T	*MTMR11*	missense	0.007	0.067	0.015	4.16E-06	0.006	0.083	0.019	7.11E-06	0.007	0.073	0.012	3.03E-10
rs144712473	1:183495812	A/G	*SMG7*	missense	0.006	-0.094	0.014	4.97E-11	0.008	-0.067	0.017	8.94E-05	0.007	-0.083	0.011	1.61E-14
rs144673025	1:223178026	T/C	*DISP1*	missense	0.008	-0.078	0.013	1.11E-09	0.007	-0.086	0.018	1.22E-06	0.008	-0.081	0.011	1.27E-14
rs142036701	2:219924961	G/T	*IHH*	missense	0.001	-0.32	0.04	1.09E-15	0.003	-0.263	0.043	1.48E-09	0.002	-0.294	0.029	1.85E-23
rs147445258	2:220078652	C/T	*ABCB6*	missense	0.01	-0.086	0.012	3.43E-13	0.009	-0.064	0.018	4.40E-04	0.01	-0.079	0.01	2.47E-15
rs121434601	3:46939587	C/T	*PTH1R*	missense	0.003	0.154	0.023	1.30E-11	0.003	0.192	0.031	5.48E-10	0.003	0.168	0.019	1.14E-19
rs141374503	4:73179445	C/T	*ADAMTS3*	missense	0.003	-0.119	0.021	1.82E-08	0.004	-0.089	0.023	1.32E-04	0.004	-0.106	0.016	1.30E-11
rs149385790	4:120422407	T/G	*PDE5A*	missense	0.001	0.257	0.031	7.50E-17	0.005	0.19	0.033	1.28E-08	0.003	0.226	0.023	2.65E-23
rs146301345	5:32784907	G/A	*NPR3*	missense	0.003	0.128	0.022	1.05E-08	0.002	0.166	0.035	1.78E-06	0.003	0.139	0.019	7.91E-14
rs61736454	5:64766798	G/A	*ADAMTS6*	missense	0.002	-0.152	0.026	7.82E-09	0.002	-0.182	0.032	1.37E-08	0.002	-0.164	0.02	4.80E-16
rs78727187	5:127668685	G/T	*FBN2*	missense	0.006	0.183	0.015	2.47E-33	0.006	0.181	0.02	5.06E-20	0.006	0.182	0.012	1.47E-52
rs148833559	5:172755066	C/A	*STC2*	missense	0.001	0.29	0.037	5.69E-15	0.001	0.368	0.043	1.32E-17	0.001	0.323	0.028	1.15E-30
rs148543891	6:155450779	A/G	*TIAM2*	missense	0.003	-0.124	0.022	1.45E-08	0.001	-0.016	0.082	8.50E-01	0.003	-0.117	0.021	3.96E-08
rs41511151	7:73482987	G/A	*ELN*	missense	0.004	-0.086	0.018	2.63E-06	0.007	-0.061	0.019	1.51E-03	0.006	-0.074	0.013	2.31E-08
rs112892337	8:135614553	G/C	*ZFAT*	missense	0.004	0.196	0.019	4.42E-26	0.004	0.184	0.024	1.20E-14	0.004	0.191	0.015	6.12E-38
rs75596750	8:135622851	G/A	*ZFAT*	missense	0.001	0.255	0.036	1.54E-12	0.002	0.339	0.039	5.94E-18	0.002	0.293	0.027	2.05E-28
rs138273386	11:27016360	G/A	*FIBIN*	missense	0.004	-0.12	0.017	5.79E-12	0.005	-0.076	0.024	1.56E-03	0.004	-0.105	0.014	3.26E-14
rs138059525	11:94533444	G/A	*AMOTL1*	missense	0.009	-0.096	0.012	9.01E-16	0.007	-0.089	0.017	3.84E-07	0.008	-0.094	0.01	2.84E-21
rs147996581	12:58138971	G/A	*TSPAN31*	missense	0.003	-0.116	0.022	8.26E-08	0.001	-0.268	0.09	2.85E-03	0.003	-0.125	0.021	5.50E-09
rs13141	12:121756084	G/A	*ANAPC5*	missense	0.009	-0.082	0.012	1.09E-11	0.011	-0.105	0.016	1.44E-11	0.01	-0.091	0.01	1.45E-21
rs150494621	15:44153571	C/T	*WDR76*	missense	0.008	0.063	0.013	1.56E-06	0.014	0.054	0.015	3.42E-04	0.011	0.059	0.01	2.32E-09
rs141308595	15:89424870	G/T	*HAPLN3*	missense	0.001	-0.267	0.037	2.84E-13	0.002	-0.234	0.035	2.43E-11	0.002	-0.25	0.025	1.02E-22
rs141923065	16:31474091	A/G	*ARMC5*	splice_acceptor	0.006	0.104	0.015	5.88E-12	0.013	0.057	0.018	1.16E-03	0.009	0.084	0.011	1.62E-13
rs34667348	16:47684830	C/A	*PHKB*	missense	0.005	0.121	0.016	3.96E-14	0.005	0.033	0.020	1.04E-01	0.005	0.088	0.013	3.43E-12
rs140385822	16:67470505	G/A	*HSD11B2*	missense	0.002	-0.148	0.028	1.27E-07	0.002	-0.124	0.035	3.38E-04	0.002	-0.139	0.022	1.97E-10
rs149615348	16:84900645	G/A	*CRISPLD2*	missense	0.007	-0.095	0.014	9.13E-12	0.008	-0.098	0.017	4.34E-09	0.008	-0.096	0.011	2.92E-19
rs148934412	16:84902472	G/A	*CRISPLD2*	missense	0.001	-0.297	0.04	7.75E-14	0.001	-0.317	0.058	3.49E-08	0.001	-0.304	0.033	2.36E-20
rs201226914	16:88798919	G/T	*PIEZO1*	missense	0.002	-0.187	0.027	5.27E-12	0.002	-0.241	0.043	1.99E-08	0.002	-0.202	0.023	8.68E-19
rs137852591	23:66941751	C/G	*AR*	missense	0.002	-0.304	0.061	7.05E-07	0.008	-0.333	0.058	7.12E-09	0.005	-0.319	0.042	2.67E-14

598 **Table 2. Low-frequency variants associated with adult height.** 59 variants (51 coding) with minor allele frequency between 1 and 5% in
599 European-ancestry participants that have $P_{combined}$ <2x10^{-7} under an additive genetic model. For *TTN*-rs16866412 and *NOL8*-rs921122, the
600 association is significant (P<2x10^{-7}) upon conditional analysis. The direction of the effect (Beta) and effect allele frequency (AF) is given for the
601 alternate (Alt) allele. For each variant, we provide the most severe annotation using the ENSEMBL Variant Effect Predictor (VEP) tool. N, sample
602 size; Ref, reference allele; SE, standard error

					Discovery (N up to 381,625)				Validation (N up to 252,491)				Combined (N up to 634,116)			
Variant	**Chr:Pos**	**Ref/Alt**	**Gene**	**Annotation**	**AF**	**Beta**	**SE**	**P-value**	**AF**	**Beta**	**SE**	**P-value**	**AF**	**Beta**	**SE**	**P-value**
rs41292521	1:51873967	G/A	*EPS15*	missense	0.020	0.045	0.008	5.07E-08	0.023	0.065	0.010	7.60E-11	0.021	0.053	0.006	2.56E-17
rs61730011	1:119427467	A/C	*TBX15*	missense	0.042	-0.059	0.006	1.61E-24	0.046	-0.056	0.007	4.19E-15	0.044	-0.058	0.005	2.79E-36
rs11580946	1:150551327	G/A	*MCL1*	missense	0.014	0.061	0.010	2.16E-09	0.015	0.085	0.012	7.86E-12	0.015	0.070	0.008	1.55E-19
rs141845046	1:154987704	C/T	*ZBTB7B*	missense	0.028	0.058	0.007	7.30E-17	0.025	0.061	0.010	4.46E-10	0.027	0.059	0.006	3.46E-25
rs79485039	1:180886140	C/T	*KIAA1614*	missense	0.026	0.034	0.007	1.41E-06	0.031	0.030	0.009	4.51E-04	0.028	0.033	0.006	2.63E-09
rs52826764	2:20205541	C/T	*MATN3*	missense	0.026	-0.071	0.007	2.67E-23	0.028	-0.084	0.010	6.60E-19	0.027	-0.076	0.006	3.74E-41
rs16859517	2:219949184	C/T	*NHEJ1*	intron	0.036	0.059	0.006	5.96E-21	0.036	0.064	0.008	1.12E-15	0.036	0.061	0.005	8.20E-37
rs16866412	2:179474668	G/A	*TTN*	missense	0.013	-0.053	0.010	1.35E-07	0.010	-0.019	0.015	2.15E-01	0.012	-0.042	0.008	3.44E-07
rs7571816	2:233077064	A/G	*DIS3L2*	intron	0.025	-0.060	0.007	2.35E-16	0.023	-0.079	0.010	2.58E-15	0.024	-0.066	0.006	6.46E-31
rs2229089	3:14214524	G/A	*XPC*	missense	0.031	-0.038	0.007	1.22E-08	0.035	-0.020	0.008	1.68E-02	0.033	-0.030	0.005	1.29E-08
rs76208147	3:47162886	C/T	*SETD2*	missense	0.019	0.048	0.009	2.24E-08	0.016	0.062	0.012	2.22E-07	0.018	0.053	0.007	1.65E-13
rs35713889	3:49162583	C/T	*LAMB2*	missense	0.039	0.043	0.006	3.28E-12	0.045	0.060	0.007	1.33E-16	0.041	0.050	0.005	3.49E-27
rs9838238	3:98600385	T/C	*DCBLD2*	missense	0.047	0.029	0.005	1.23E-07	0.051	0.027	0.007	5.62E-05	0.048	0.028	0.004	1.68E-12
rs11722554	4:5016883	G/A	*CYTL1*	missense	0.040	-0.049	0.006	2.01E-17	0.034	-0.057	0.009	6.68E-11	0.038	-0.052	0.005	1.86E-25
rs61730641	4:87730980	C/T	*PTPN13*	missense	0.015	-0.086	0.010	1.94E-19	0.016	-0.094	0.012	1.38E-15	0.016	-0.089	0.008	9.43E-32
rs116807401	4:135121721	T/C	*PABPC4L*	missense	0.017	0.065	0.009	1.39E-13	0.016	0.045	0.012	1.33E-04	0.017	0.058	0.007	7.54E-16
rs28925904	4:144359490	C/T	*GAB1*	missense	0.019	-0.048	0.008	1.04E-08	0.023	-0.036	0.010	3.24E-04	0.021	-0.043	0.006	4.29E-12
rs34343821	4:154557616	C/T	*KIAA0922*	missense	0.011	0.059	0.011	7.75E-08	0.015	0.056	0.012	5.75E-06	0.013	0.058	0.008	2.18E-12
rs35658696	5:102338811	A/G	*PAM*	missense	0.048	-0.025	0.005	3.76E-06	0.053	-0.031	0.007	8.47E-06	0.050	-0.027	0.004	1.63E-10
rs34821177	5:126250812	C/T	*MARCH3*	missense	0.036	0.034	0.006	4.25E-08	0.029	0.027	0.009	2.45E-03	0.034	0.032	0.005	1.67E-10
rs62623707	5:135288632	A/G	*LECT2*	missense	0.044	-0.030	0.006	1.02E-07	0.049	-0.024	0.007	4.77E-04	0.046	-0.027	0.005	1.36E-09
rs34471628	5:172196752	A/G	*DUSP1*	missense	0.036	0.048	0.006	4.00E-14	0.042	0.036	0.007	1.26E-06	0.039	0.043	0.005	1.93E-20
rs28932177	5:176637471	G/A	*NSD1*	missense	0.028	0.063	0.007	2.38E-17	0.027	0.065	0.009	2.62E-12	0.028	0.064	0.006	4.27E-30
rs78247455	5:176722005	G/A	*NSD1*	missense	0.023	-0.083	0.008	1.86E-26	0.025	-0.085	0.010	8.42E-18	0.024	-0.084	0.006	2.32E-41
rs7757648	6:30851933	G/A	*DDR1*	intron	0.013	-0.075	0.013	1.11E-08	0.011	-0.079	0.018	1.24E-05	0.012	-0.076	0.011	4.64E-13
rs34427075	6:34730395	C/T	*SNRPC*	synonymous	0.014	-0.117	0.010	9.21E-33	0.016	-0.139	0.012	9.59E-31	0.015	-0.126	0.008	3.45E-60
rs33966734	6:41903798	C/A	*CCND3*	stop_gained	0.013	-0.140	0.017	5.51E-17	0.011	-0.101	0.018	3.41E-08	0.012	-0.122	0.012	1.28E-22
rs17277546	7:99489571	G/A	*TRIM4*	3'UTR	0.049	0.034	0.005	3.28E-10	0.052	0.038	0.007	2.26E-07	0.050	0.035	0.004	1.40E-17
rs7636	7:100490077	G/A	*ACHE*	synonymous	0.043	-0.037	0.006	8.59E-10	0.035	-0.019	0.009	2.92E-02	0.040	-0.031	0.005	2.98E-10
rs17480616	7:135123060	G/C	*CNOT4*	missense	0.028	0.060	0.007	2.31E-17	0.030	0.054	0.009	5.04E-10	0.029	0.058	0.005	3.90E-26
rs3136797	8:42226805	C/G	*POLB*	missense	0.018	0.044	0.009	1.95E-06	0.021	0.026	0.010	1.30E-02	0.019	0.036	0.007	1.88E-07
rs11575580	9:34660864	C/T	*IL11RA*	missense	0.016	-0.064	0.009	5.20E-13	0.020	-0.030	0.011	4.42E-03	0.018	-0.050	0.007	4.01E-13
rs921122	9:95063947	C/T	*NOL8*	missense	0.039	0.041	0.009	2.56E-06	0.040	0.018	0.008	3.45E-02	0.040	0.029	0.006	3.33E-06

rs41274586	10:79580976	G/A	*DLG5*	missense	0.017	-0.058	0.009	2.72E-11	0.017	-0.076	0.012	5.15E-11	0.017	-0.065	0.007	7.66E-20
rs41291604	10:97919011	A/G	*ZNF518A*	missense	0.040	0.031	0.006	9.94E-08	0.040	0.022	0.008	3.05E-03	0.040	0.028	0.005	3.91E-09
rs71455793	11:65715204	G/A	*TSGA10IP*	missense	0.039	-0.058	0.006	1.82E-21	0.046	-0.072	0.007	1.41E-23	0.042	-0.064	0.005	1.52E-43
rs4072796	12:7548996	C/G	*CD163L1*	missense	0.035	0.034	0.006	4.11E-08	0.037	0.015	0.008	6.68E-02	0.036	0.027	0.005	1.87E-08
rs61743810	12:69140339	G/C	*SLC35E3*	missense	0.022	-0.047	0.008	1.13E-09	0.023	-0.036	0.010	5.11E-04	0.022	-0.043	0.006	1.29E-11
rs117801489	12:104408832	T/C	*GLT8D2*	missense	0.017	0.053	0.009	8.72E-10	0.028	0.062	0.010	5.82E-10	0.022	0.057	0.007	1.60E-17
rs2066674	13:50842259	G/A	*DLEU1*	intron	0.044	0.073	0.006	2.33E-37	0.041	0.084	0.008	7.02E-25	0.043	0.077	0.005	5.66E-57
rs17880989	14:23313633	G/A	*MMP14*	missense	0.027	0.041	0.007	1.72E-08	0.029	0.052	0.009	7.81E-09	0.028	0.045	0.006	3.27E-16
rs34354104	14:24707479	G/A	*GMPR2*	missense	0.048	0.045	0.005	3.67E-16	0.050	0.047	0.007	1.34E-11	0.049	0.046	0.004	2.13E-29
rs117295933	14:45403699	C/A	*KLHL28*	missense	0.016	-0.045	0.009	1.55E-06	0.025	-0.036	0.010	4.13E-04	0.020	-0.041	0.007	3.05E-09
rs41286548	14:70633411	C/T	*SLC8A3*	missense	0.021	-0.054	0.008	2.49E-11	0.026	-0.045	0.009	2.02E-06	0.023	-0.050	0.006	2.03E-16
rs28929474	14:94844947	C/T	*SERPINA1*	missense	0.018	0.124	0.009	1.39E-45	0.019	0.139	0.011	2.50E-34	0.019	0.130	0.007	1.72E-75
rs41286560	14:101349454	G/T	*RTL1*	missense	0.024	-0.050	0.007	1.17E-11	0.028	-0.033	0.009	2.12E-04	0.026	-0.044	0.006	2.50E-15
rs116858574	15:34520687	T/C	*EMC4*	missense	0.014	0.047	0.010	1.16E-06	0.014	0.028	0.012	2.19E-02	0.014	0.040	0.008	1.60E-07
rs34815962	15:72462255	C/T	*GRAMD2*	missense	0.019	0.073	0.009	8.72E-17	0.023	0.074	0.010	3.66E-13	0.021	0.073	0.007	1.28E-27
rs16942341	15:89388905	C/T	*ACAN*	synonymous	0.026	-0.129	0.007	4.30E-72	0.028	-0.146	0.009	1.08E-56	0.027	-0.135	0.006	3.79E-130
rs61733564	16:4812705	A/G	*ZNF500*	missense	0.032	0.056	0.007	8.61E-17	0.032	0.044	0.009	2.34E-07	0.032	0.051	0.005	2.89E-21
rs113388806	16:24804954	A/T	*TNRC6A*	missense	0.040	0.036	0.006	1.08E-09	0.047	0.041	0.008	1.65E-07	0.043	0.038	0.005	1.90E-15
rs8052655	16:67409180	G/A	*LRRC36*	missense	0.043	-0.054	0.006	1.08E-18	0.043	-0.055	0.008	3.91E-13	0.043	-0.054	0.005	6.40E-31
rs77542162	17:67081278	A/G	*ABCA6*	missense	0.017	0.049	0.010	2.17E-06	0.023	0.051	0.010	5.58E-07	0.020	0.050	0.007	5.57E-12
rs77169818	18:74980601	A/T	*GALR1*	missense	0.047	-0.048	0.006	3.60E-18	0.038	-0.035	0.008	3.64E-05	0.044	-0.044	0.005	5.11E-19
rs3208856	19:45296806	C/T	*CBLC*	missense	0.034	0.036	0.007	1.48E-07	0.034	0.021	0.008	1.19E-02	0.034	0.030	0.005	2.96E-08
rs4252548	19:55879672	C/T	*IL11*	missense	0.026	-0.114	0.007	1.02E-57	0.022	-0.101	0.010	2.28E-23	0.025	-0.110	0.006	5.32E-81
rs147110934	19:55993436	G/T	*ZNF628*	missense	0.021	-0.084	0.010	2.28E-18	0.022	-0.098	0.011	1.17E-18	0.022	-0.090	0.007	6.33E-34
rs77885044	22:28501414	C/T	*TTC28*	missense	0.012	-0.067	0.010	9.47E-11	0.017	-0.069	0.012	3.24E-09	0.014	-0.068	0.008	3.93E-19
rs147348682	22:42095658	T/G	*MEI1*	missense	0.025	0.041	0.007	2.25E-08	0.034	0.024	0.009	6.59E-03	0.029	0.034	0.006	3.70E-10

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Table 3. Ten height genes implicated by gene-based testing. These genes meet our three criteria for statistical significance: (1) gene-based $P<2x10^{-6}$, (2) the gene does not include variants with $P<2x10^{-7}$, and (3) the gene-based P-value is at least two orders of magnitude smaller than the P-value for the most significant variant within the gene. For each gene, we provide P-values for the four different gene-based tests applied. P-values in bold are the most significant results for a given gene. [1]Replication results using the same test and (when possible) variants in 59,804 European-ancestry individuals. [2]When the gene is located in a locus identified by our single-variant analysis (1 Mb window), we conditioned the gene-based association result by genotypes at the single variant. [3]If the gene falls within a known GWAS height locus, we mention if it was predicted to be causal using bioinformatic tools (ref. [3]). NA, not applicable.

Gene	Discovery gene-based P-value				Replication P-value[1]	Conditional P-value[2]	Note[3]
	SKAT-broad	VT-broad	SKAT-strict	VT-strict			
OSGIN1	**$4.3x10^{-11}$**	$4.5x10^{-5}$	0.19	0.18	**0.048**	$7.7x10^{-11}$	Known locus. No predicted causal genes.
CRISPLD1	$2.2x10^{-7}$	**$1.5x10^{-10}$**	$8.5x10^{-6}$	$8.9x10^{-7}$	0.50	NA	Known locus, sentinel GWAS SNP not tested on ExomeChip. *CRISPLD1* was predicted to be causal.
CSAD	$2.3x10^{-8}$	**$6.0x10^{-10}$**	0.83	0.59	0.54	NA	New locus.
SNED1	$1.9x10^{-5}$	**$2.3x10^{-9}$**	NA	NA	0.083	$1.4x10^{-9}$	Known locus. *SNED1* was not predicted to be causal.
G6PC	$1.3x10^{-5}$	**$3.6x10^{-8}$**	$5.5x10^{-6}$	$1.3x10^{-6}$	0.24	$3.9x10^{-8}$	Known locus, *G6PC* was not predicted to be causal. *G6PC* is mutated in glycogen storage disease Ia.
NOX4	$5.1x10^{-6}$	**$1.8x10^{-7}$**	NA	NA	**0.013**	NA	New locus.
UGGT2	$3.0x10^{-5}$	**$2.0x10^{-7}$**	$2.3x10^{-5}$	$4.8x10^{-7}$	0.64	NA	New locus.
FLNB	$2.2x10^{-6}$	$5.1x10^{-4}$	**$2.4x10^{-9}$**	$3.2x10^{-6}$	**0.016**	$3.6x10^{-9}$	Known locus. *FLNB* was predicted to be causal. *FLNB* is mutated in atelosteogenesis type I.
B4GALNT3	$2.4x10^{-5}$	$1.9x10^{-5}$	$1.8x10^{-5}$	**$3.4x10^{-7}$**	0.79	$7.7x10^{-7}$	Known locus. *B4GALNT3* was predicted to be causal.
CCDC3	$6.3x10^{-4}$	$6.3x10^{-6}$	$3.0x10^{-7}$	**$5.5x10^{-9}$**	0.080	$1.6x10^{-9}$	Known locus. *CCDC3* was predicted to be causal.

Figure legends

Figure 1. Variants with a larger effect size on height variation tend to be rarer. We observe an inverse relationship between the effect size (from the combined "discovery+ validation" analysis, in cm on the *y*-axis) and the minor allele frequency (MAF) for the height variants (*x*-axis, from 0 to 50%). We included in this figure the 606 height variants with $P<2x10^{-7}$.

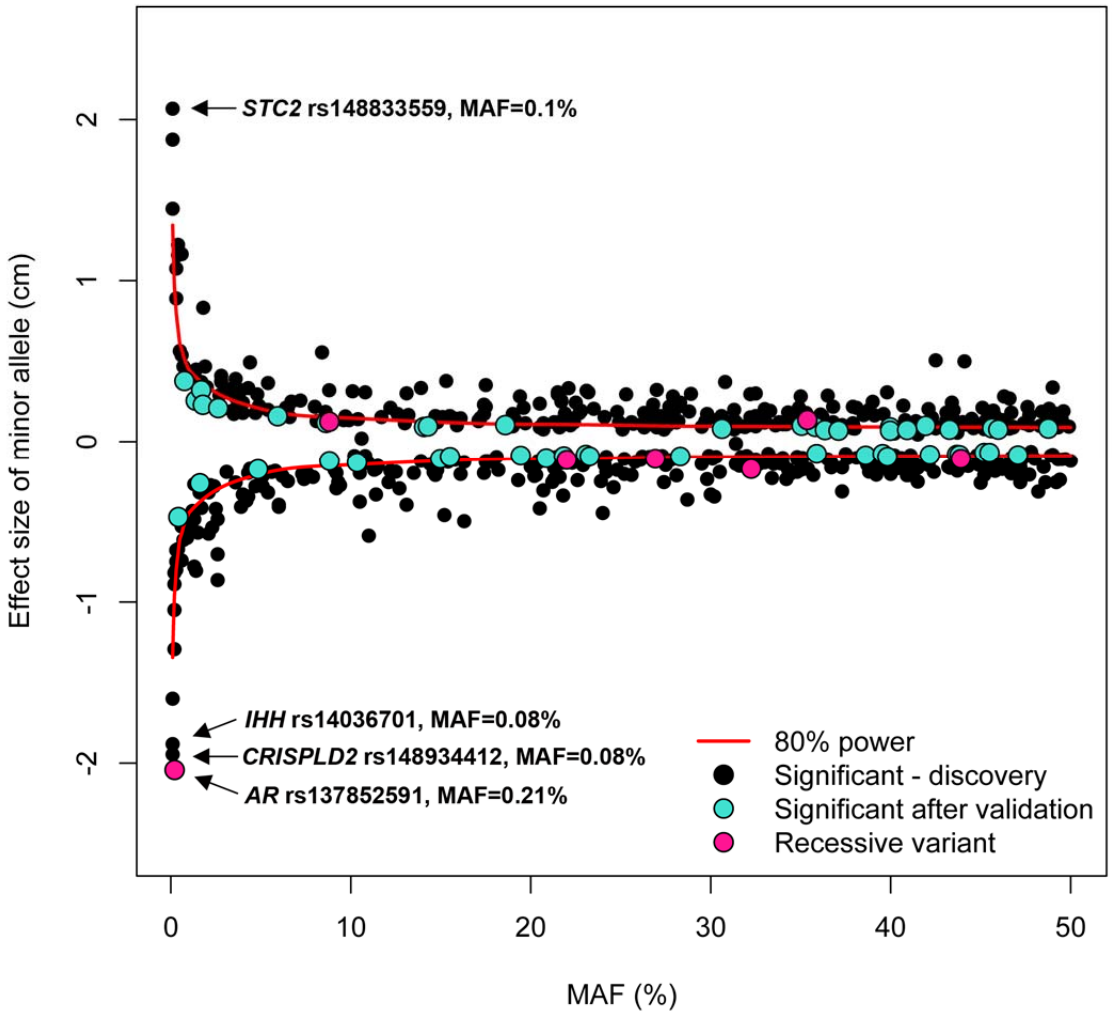


Figure 2. Heat map showing subset of DEPICT gene set enrichment results. The full heat map is available as **Supplementary Fig. 13**. For any given square, the color indicates how strongly the corresponding gene (shown on the x-axis) is predicted to belong to the reconstituted gene set (y-axis). This value is based on the gene's Z-score for gene set inclusion in DEPICT's reconstituted gene sets, where red indicates a higher Z-score and blue indicates a lower one. The proteoglycan binding pathway (bold) was uniquely implicated by coding variants (as opposed to common variants) by both DEPICT and the PASCAL method. To visually reduce redundancy and increase clarity, we chose one representative "meta-gene set" for each group of highly correlated gene sets based on affinity propagation clustering (**Supplementary Note**). Heat map intensity and DEPICT P-values correspond to the most significantly enriched gene set within the meta-gene set; meta-gene sets are listed with their database source. Annotations for the genes indicate whether the gene has OMIM annotation as underlying a disorder of skeletal growth (black and grey) and the minor allele frequency of the significant ExomeChip (EC) variant (shades of blue; if multiple variants, the lowest-frequency variant was kept). Annotations for the gene sets indicate if the gene set was also found significant for EC by the PASCAL method (yellow and grey) and if the gene set was found significant by DEPICT for EC only or for both EC and GWAS (purple and green). Abbreviations: GO: Gene Ontology; MP: mouse phenotype in the Mouse Genetics Initiative; PPI: protein-protein interaction in the InWeb database.

(Figure 2)

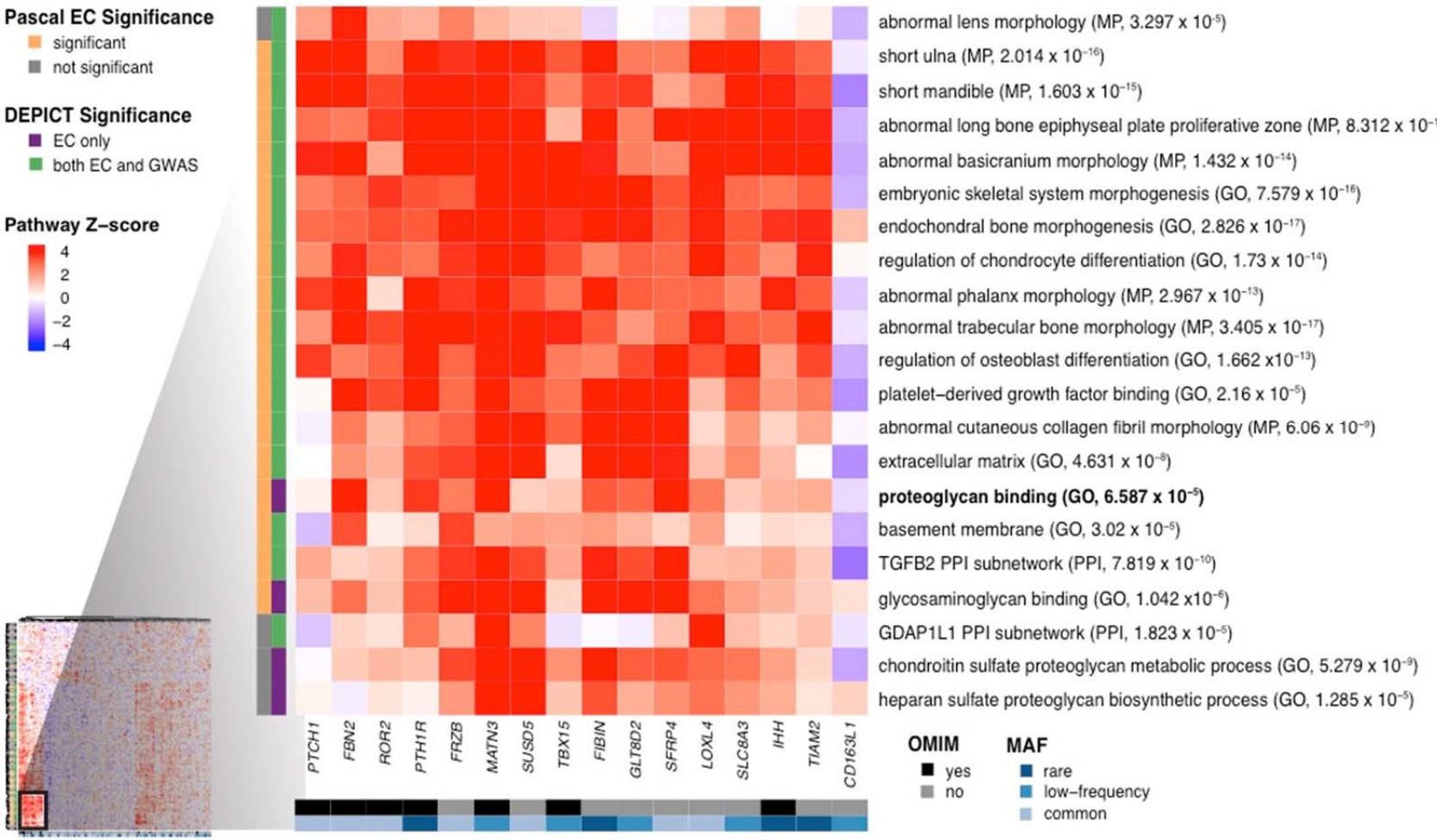
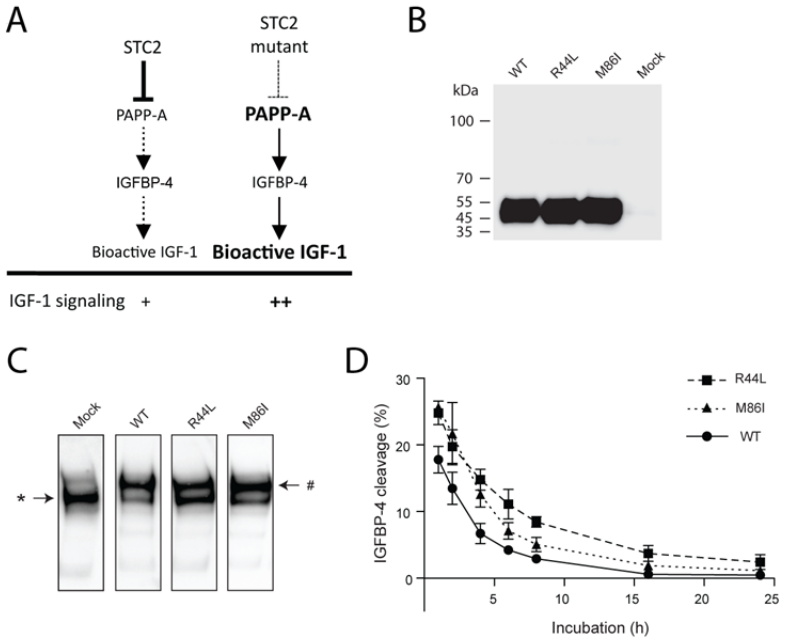

Pascal EC Significance
significant
not significant
DEPICT Significance
EC only
both EC and GWAS
Pathway Z–score
4
2
0
−2
−4
abnormal lens morphology (MP, 3.297 x 10-5)
short ulna (MP, 2.014 x 10-16)
short mandible (MP, 1.603 x 10-15)
abnormal long bone epiphyseal plate proliferative zone (MP, 8.312 x 10-18)
abnormal basicranium morphology (MP, 1.432 x 10-14)
embryonic skeletal system morphogenesis (GO, 7.579 x 10-16)
endochondral bone morphogenesis (GO, 2.826 x 10-17)
regulation of chondrocyte differentiation (GO, 1.73 x 10-14)
abnormal phalanx morphology (MP, 2.967 x 10-13)
abnormal trabecular bone morphology (MP, 3.405 x 10-17)
regulation of osteoblast differentiation (GO, 1.662 x10-13)
platelet–derived growth factor binding (GO, 2.16 x 10-5)
abnormal cutaneous collagen fibril morphology (MP, 6.06 x 10-9)
extracellular matrix (GO, 4.631 x 10-8)
proteoglycan binding (GO, 6.587 x 10-5)
basement membrane (GO, 3.02 x 10-5)
TGFB2 PPI subnetwork (PPI, 7.819 x 10-10)
glycosaminoglycan binding (GO, 1.042 x10-6)
GDAP1L1 PPI subnetwork (PPI, 1.823 x 10-5)
chondroitin sulfate proteoglycan metabolic process (GO, 5.279 x 10-9)
heparan sulfate proteoglycan biosynthetic process (GO, 1.285 x 10-5)
PTCH1
FBN2
ROR2
PTH1R
FRZB
MATN3
SUSD5
TBX15
FIBIN
GLT8D2
SFRP4
LOXL4
SLC8A3
IHH
TIAM2
CD163L1
OMIM
yes
no
MAF
rare
low–frequency
common

Figure 3. STC2 mutants p.Arg44Leu (R44L) and p.Met86Ile (M86I) show compromised proteolytic inhibition of PAPP-A. (**A**) Schematic representation of the role of STC2 in IGF-1 signaling. Partial inactivation of STC2 by height-associated DNA sequence variation could increase bioactive IGF-1 through reduced inhibition of PAPP-A. (**B**) Western blot analysis of recombinant STC2 wild-type and variants R44L and M86I. (**C**) Covalent complex formation between PAPP-A and STC2 wild-type or variants R44L and M86I. Separately synthesized proteins were analyzed by PAPP-A Western blotting following incubation for 8 h. In the absence of STC2 (Mock lane), PAPP-A appears as a single 400 kDa band (*). Following incubation with wild-type STC2, the majority of PAPP-A is present as the approximately 500 kDa covalent PAPP-A:STC2 complex (#), in which PAPP-A is devoid of proteolytic activity towards IGFBP-4. Under similar conditions, incubation with variants R44L or M86I appeared to cause less covalent complex formation with PAPP-A. The gels are representative of at least three independent experiments. (**D**) PAPP-A proteolytic cleavage of IGFBP-4 following incubation with wild-type STC2 or variants for 1-24 h. Wild-type STC2 causes reduction in PAPP-A activity, with complete inhibition of activity following 24 h incubation. Both STC2 variants show increased IGFBP-4 cleavage (*i.e.* less inhibition) for all time points analyzed. Mean and standard deviations of three independent experiments are shown. One-way repeated measures analysis of variance followed by Dunnett's post-test showed significant differences between STC2 wild-type and variants R44L ($P<0.001$) and M86I ($P<0.01$).

665 **(Figure 3)**



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