Introduction

Anthropometric traits, measuring body size and shape, are highly heritable and significant clinical risk factors for cardiometabolic disorders. Body mass index (BMI) is a standard measure of obesity, and waist/hip ratio (WHR) measures central adiposity, each of which are independent risk factors for both coronary heart disease and type 2 diabetes.\(^1,2\) Although height has been associated with lower odds of coronary artery disease and hypertension,
identified, but interpretation of these results in terms of genome-wide significant loci extensively studied in genome-wide association studies many small genetic effects. These traits have been extensively studied in genome-wide association studies (GWAS), with hundreds of genome-wide significant loci in numerous populations with a polygenic architecture of broad-sense heritability of height is estimated at 75% in numerous populations with a polygenic architecture of many small genetic effects. These traits have been extensively studied in genome-wide association studies (GWAS), with hundreds of genome-wide significant loci identified, but interpretation of these results in terms of functional genes remains a challenge. More recently, the Exome Chip genotyping array and target sequencing of functional genes remains a challenge. More recently, the Exome Chip genotyping array and target sequencing of functional genes remains a challenge. More recently, the Exome Chip genotyping array and target sequencing of functional genes remains a challenge. More recently, the Exome Chip genotyping array and target sequencing of functional genes remains a challenge.

This study presents the results of a whole-exome sequence association analysis of height, BMI, and WHR. In contrast with a GWAS design, where many common variants are genotyped or imputed, whole-exome sequencing focuses on the exons of protein-coding genes to identify variants that are not included in genotyping arrays or imputation reference panels. We meta-analyzed SNV and gene-based associations of whole-exome sequence variation with height, BMI, and WHR in up to 22,004 individuals. To take advantage of the high density of the exome sequence data, we investigated associations in candidate gene sets defined by known anthropometric GWAS loci, seeking to identify genes within those loci with evidence of a functional role in the trait outcome. We also examined genes harboring known monogenic or syndromic variants influencing related phenotypes (height, obesity for BMI, and lipids/insulin resistance for WHR) to identify additional low-frequency (minor allele frequency [MAF], 1%–5%) or rare (MAF, <1%) variants influencing our traits of interest.

Phenotypes

In each study, height was measured to the nearest centimeter using standard protocols. BMI was calculated from measured weight (kg) and height (m). WHR was calculated as waist circumference (cm) divided by hip circumference (cm). Study-specific phenotype descriptive statistics are provided in Table S1. All phenotypes were adjusted for covariates listed in the study-level statistical analyses section in linear regression models for the studies with unrelated samples and mixed models for the studies with related samples.

Exome sequencing and QC

As part of CHARGE-S (Cohorts for Heart and Aging Research in Genomic Epidemiology Sequencing), exome sequencing in ARIC, CHS, and FramHS was conducted at the Baylor College of Medicine Human Genome Sequencing Center (https://www.hgsc.bcm.edu/human/charge-consortium) as previously described. In brief, each single-nucleotide variant (SNV) called using the Atlas2 suite was filtered based on the following criteria to produce a high-quality variant list: low SNV posterior probability (<0.95), low variant read count (<3), variant read ratio <0.25 or >0.75, strand-bias of >99% variant reads in a single strand direction, or total coverage <10-fold. All variant calls filtered by these criteria and reference calls with <10-fold coverage were set to missing. The variant call filters were the same for indels, except a total coverage <30-fold was used for variant sites.

Variant-level quality control steps excluded variants outside the exon capture regions (VCRrome 2.1), with missing rate >20%, mappability score <0.8, and mean depth of coverage >500-fold. Variants not meeting Hardy-Weinberg equilibrium expectations (p < 5 × 10⁻⁶) in ancestry-specific groups were also excluded. Sample-level quality control metrics were calculated by cohort and ancestry group. A sample was excluded for missingness >20%, or if compared with the other samples it fell <6 standard deviations (SDs) for mean depth, more than 6 SDs for singleton count,
or outside of 6 SDs for heterozygote/homozygote ratio or transition/transversion (Ti/Tv) ratio.

The final sample for CHARGE contained 11,263 EA individuals (1,751 for CHS, 7,810 for ARIC, and 1,702 for FHS) and 3,180 AA from ARIC. In total, there were 2,556,859 SNVs and 76,133 indels after QC. The mean depth of coverage was 78-fold.

Exome sequencing for GO-ESP HeartGO was conducted at the University of Washington or the Broad Institute with quality control performed at the University of Michigan as part of the NHLBI GO-ESP HeartGO as previously described.17,18 In brief, samples were excluded from exome sequencing if DNA mass or concentration was low, genotyping of 96 common SNVs (MAF, 30%–50%) revealed genotype call rates <90%, or there were sex mismatches. Samples >99% concordant at the 96 genotyped SNVs and with targeted read coverage >8x for >90% of the exome target sequence (University of Washington) or targeted read coverage >20x for >70% of the exome target sequence (Broad Institute) were considered complete. SNVs were then jointly called for all ESP samples at the University of Washington using the UMAKE pipeline.19 Genotypes were excluded if the read depth was <10, the average per-SNV read depth was >500, or the genotype-calling quality score was <20. Variants identified as likely false-positives using a support vector machine classifier, with missing rate p any of the four capture arrays used in GO-ESP, with HWE p >10-5 in any of the four capture arrays used in GO-ESP, with HWE p <5 x 10-20 across all samples or HWE p <1 x 10-6 in control samples, found on only one array, and singletons, were excluded. Samples with homozygosity >0.3, sex mismatches, low concordance with GWAS array data, or of indeterminate genetic ancestry were excluded.

Exome sequencing was conducted separately in the ERF study, GOLDN, and RS, and exome sequencing, variant analysis, and quality control protocols are available elsewhere.20–22 In ERF, sequencing was performed at a median depth of 57x and after preprocessing, variant calling was completed using the Unified Genotyper tool from the Genome Analysis Toolkit (GATK) v.2.314.23 In GOLDN, variants were called with SAMtools version r963 and VarScan v.2.3.6.24–26 In the RS, variants were called using GATK’s Haplotyperccaller.7 All discovery studies were aligned to the human reference genome (hg19/GRCh37). Additional details on variant calling and QC for studies used in discovery are included in the supplemental information. Samples with low genotype array concordance (<95%), with ≥4 SDs from the mean number of variants detected per sample and high heterozygote/homozygote ratio or Ti/Tv ratio, or low call rate (<90%) were excluded from further analysis.20 We further excluded autosomal variants with call rates <0.8 and Hardy-Weinberg equilibrium p < 10^-4 from study-level analyses.

To identify study-specific quality control issues, including phenotype transformation errors using plots of the inverse of the median standard error (SE) of the effect estimates in all variants included in a study divided by the square root of the study sample size, strand flips by comparing allele frequencies across SNPs with an ancestry-specific reference (1000 Genomes European and 1000 Genomes African reference panels), and genomic inflation, we implemented a centralized procedure for cohort summary statistics in EasyQC.28 This procedure ensured that any study-specific data errors were identified and corrected prior to meta-analysis.

**Study-level statistical analyses**

For each ancestry and sex stratum, residuals were obtained by regressing each phenotype (height, BMI, and WHR) on age, phenotype-associated principal components to control for population stratification, and study site (for multisite studies). Additionally, BMI was regressed on age,2 and WHR was regressed on age2 and BMI to identify associations independent of overall adiposity. For population-based and case-control studies of unrelated individuals, residuals were calculated separately for each sex, whereas we included sex as a covariate in sexes combined models for family-based studies. Residuals for case-control studies were calculated separately. Study-specific residuals were inverse-normally transformed prior to genetic association analyses. For each trait, transformed residuals were regressed on each variant assuming an additive genetic model in either RAREMETALWORKER or RVTESTS.29,30 In GO-ESP, many individuals were selected because of extreme values of BMI, blood pressure, and low-density lipoprotein cholesterol. We used SCORE-SeqTDS31 to account for trait-dependent sampling when performing genetic association analyses in GO-ESP. We used PreMeta32 to convert the summary statistics in SCORE-SeqTDS format to RAREMETAL format to facilitate subsequent meta-analyses with the other studies.

**Meta-analyses**

Meta-analyses of single-variant results were performed using RAREMETAL.30 Only variants with a cumulative minor allele count (cMAC) ≥20 across studies were considered for single-variant meta-analysis. The exome-wide significance threshold was determined by Bonferroni correction as 0.05 divided by the number of variants examined in the full sample, which varied by trait because of sample size. For BMI (Figures S1 and S2), we considered 88,168 variants at a significance threshold of 5.67 x 10^-7. For height (Figures S3 and S4), we considered 455,318 variants at a significance level of 1.10 x 10^-7. For WHR (Figures S5 and S6), we considered 67,633 variants at a significance level of 7.39 x 10^-7.

**Gene-based analyses**

For the gene-based analyses of our meta-analysis results, we selected variants with a MAF <5% in either ancestry, with annotation as a non-synonymous, splice-site, stop or coding indel variant. These analyses were performed in RAREMETAL using the burden (GRANVIL) and sequence kernel association test (SKAT) methods.30 We excluded those genes with a cMAC <20 and a sample size less than one-third of the total sample for that stratum. Statistical significance was determined using a Bonferroni-corrected threshold of p < 3.83 x 10^-6 (0.05/13,055 genes tested).

**Validation**

We attempted to validate our single-variant and gene-based results that reached suggestive significance (p ≤ 1 x 10^-6) in the Transomics for Precision Medicine (TOPMed) Freeze5b data release, lifted over to hg19/GRCh37 to match the build used in the discovery analyses.33 Specifically, we followed up with four SNVs for BMI, eight SNVs for height, zero SNVs for WHR, as well as one gene for each of three traits. Replication analyses included 16,418 participants for BMI and height from 10 studies (Amish, BAGS, CFS, COPDGene, GENOA, GeneSTAR, HVH, HyperGEN, Mayo_VTE, and VU_AF) and 4,776 participants for WHR drawn from five cohorts (Amish, CFS, GENOA, GeneSTAR, and HyperGEN). Replication study descriptions are provided in the supplemental information. We implemented linear mixed-effects models with adjustment for an empirical kinship matrix to account for relatedness and population stratification. All analyses
were adjusted for the same covariates as the discovery models. Resid-
uals were created within each study by ancestry and sex and in-
verse-normal transformed, and SNV replication significance was
determined using a p value of 0.05/number of variants tested per
trait (BMI p = 0.0125, height p = 0.0063). For gene-based tests,
variants were included if they were annotated as either loss-of-
function, missense, or protein-altering indels with MAF <5%.
SKAT tests used the default weights of 1 and 25 for beta distribu-
tion. Analyses were restricted to those with African and Euro-
ancestry (n = 6,644, 6,644, and 3,547 African American and
n = 9,774, 9,774, and 1,229 European ancestry for BMI,
height, and WHR, respectively) and were conducted separately
by sex and ancestry, as well as in the combined sample.

Statistical power
We calculated statistical power to reject the null hypothesis for
single-variant tests at the exome-wide significance level of
1.09 × 10⁻⁷, in a sample of 22,000 participants, with MAFs
ranging from 0.01 to 0.45, and anthropometric trait allelic effect
sizes of 0.007–0.2 (Figure S7). Power calculations were per-
formed in R using the gwas-power functions described in Visscher
et al. Given our maximum sample size of ~22,000 participants
and a common MAF of 0.45, the allelic effect size must be
>0.060 to achieve 80% power and >0.055 to achieve 50% power.
For low-frequency variants with MAF = 0.03, the allelic effect size
must be ≥0.176 to achieve 80% power and ≥0.167 to achieve
50% power.

Expression quantitative trait locus (eQTL) analysis
To identify potential functional genes within known GWAS loci
for our three traits, we performed eQTL evaluations based on previ-
ously reported SNVs from the National Human Genome Research
Institute-European Bioinformatics Institute (NHGRI-EBI) GWAS
catalog. Associations between these SNVs and gene expression
levels in relevant tissues (skeletal muscle for height, five brain tis-
sues for BMI [cerebellar hemisphere, cerebellum, cortex, nucleus
accumbens, and putamen], and subcutaneous and visceral
omentum adipose for BMI and WHR) were downloaded from
Genotype-Tissue Expression (GTEx) v6p and filtered based on
p < 1 × 10⁻¹⁰. This provided a set of genes with evidence of
regulatory relationships to SNVs previously associated with
anthropometry traits. We hypothesized that if the expression
of these genes is involved in the causal mechanism of these
GWAS SNVs, rare variants within their exons may also affect
the same outcome. Thus, we considered the rare variant burden
and SKAT tests for genes overlapping the ±500-kb region of the
query SNV previously identified by GWAS.

Monogenic analysis
To identify low-frequency and rare variants that may contribute to
anthropometric traits at the population level in genes known to
influence these phenotypes, we curated lists of genes for each of
our traits associated with monogenic forms of each phenotype
(Table S6–S8). For height, we included genes associated with
monogenic short stature, pituitary disorders, and overgrowth syn-
dromes. For BMI, we included genes associated with monogenic
forms of obesity, while for WHR, our list included genes associated
with monogenic lipodystrophy or insulin resistance. We report
the association of low-frequency and rare variants within the
curated lists of genes that showed nominal significance in our
gene-based results. We further evaluated the significance of the
excess of nominally significant variants (with 5% expected) using
one-sided binomial tests.

Results
In this study, we used whole-exome sequencing to identify
SNVs and genes associated with three anthropometric
traits (BMI, height, and WHR) in seven discovery cohorts
(ARIC, CHS, GO-ESP, ERF, FramHS, GOLDN, and RS),
with validation in TOPMed Freeze5b cohorts. Phenotype
sample means (SD) and sample sizes for each cohort are
presented in Table S1.

Single-variant analyses
Two SNVs were identified at the exome-wide significance
level associated with BMI (Table 1). The first, rs1682
4283-C (Beta [SE] = 0.084 [0.017], p = 5.40 × 10⁻⁷ in
AA + EA women; Figure S8), is a nonsynonymous variant
in SPHKAP (SPHK1-interactor and AKAP domain-contain-
ing protein [MIM: 611646]) on chromosome 2, and the sec-
ond is a nonsynonymous variant, rs144506740-C (Beta
[SE] = −1.128 [0.221], p = 3.22 × 10⁻⁷ in European sexes
combined; Figure S9), in the 3’ UTR of PIEZO2 (piezo-type
mechanosensitive ion channel component 2 [MIM:
613629]) on chromosome 18. These findings were direc-
tionally consistent in the TOPMed sample (rs16824283-C
Beta [SE] = 0.0217 [0.023], p = 0.343; rs144506740-C
Beta [SE] = −0.396 [0.407], p = 0.330).

Two SNVs (rs11205303 and rs4911494) reached exome-
wide significance in our AA + EA sexes combined analysis of
height (Figures S10 and S11). The first, rs11205303-C
(rs11205303 and rs4911494) reached exome-
wide significance in our AA + EA sexes combined analysis of
height (Figures S10 and S11). The first, rs11205303-C
(Beta [SE] = 0.065 [0.011], p = 3.85 × 10⁻¹⁰), is a missense
variant previously associated with height in the gene
MTMR11 (a non-receptor myotubularin-related protein)
on chromosome 1. This finding was validated in the AA + EA
TOPMed sample (Beta [SE] = 0.044 [0.013],
p = 5.83 × 10⁻⁴). The second SNV reaching exome-wide
significance, rs4911494-T (Beta [SE] = −0.055 [0.010],
p = 6.09 × 10⁻⁸), is a missense variant in the height-asso-
ciated gene UQCC1 (ubiquinol-cytochrome c reductase
complex assembly factor 1 [MIM: 61797]). This finding
was also validated in the AA + EA TOPMed sample (Beta
[SE] = −0.055 [0.012], p = 2.21 × 10⁻⁶). Of 34 associa-
tions reported in/near UQCC1 in the GWAS catalog, 12
SNVs are associated with height. Although the specific
variant identified in this study was previously associated
with the WHR adjusted for BMI (WHRadBMI), it is in
high linkage disequilibrium (LD) with one of the variants
previously associated with height in this region (rs6088813:
R² = 0.998, D’ = 1.0) and moderate LD with five other height
SNVs (rs6060355: R² = 0.695, D’ = 0.853; rs878639: R² = 0.660, D’ = 0.909;
rs6060369: R² = 0.665, D’ = 0.913; rs6060373: R² =
0.668, D’ = 0.913; rs224329: R² = 0.677, D’ = 0.854) in the
1000 Genomes phase 3 African and European
(AF + EUR) reference populations.
No SNVs reached exome-wide significance for WHR in our analyses.

Gene-based analyses

Results of our gene-based analyses and their contributing SNVs for significant gene-based results are presented in Tables 2 and S2, respectively. The gene LECT2 (leukocyte cell-derived chemotaxin 2 [MIM: 602882]) was associated with height in European ancestry men (burden p = 2.56 × 10^{-6}, SKAT p = 1.69 × 10^{-5}). Both this gene and the top variant in our gene-based association (rs62623707: MAF = 0.044, Beta [SE] = -0.142 [0.040], p = 3.60 × 10^{-4}) have been previously associated with height in a sample of 381,625 European ancestry individuals (LECT2: SKAT p = 9.30 × 10^{-6}; rs62623707: MAF = 0.044, Beta [SE] = -0.30 [0.006], p = 1.02 × 10^{-7}). In our full sample, this gene attained nominal significance (burden p = 0.017, SKAT p = 0.047). This finding was significant in TopMed for the burden test in EA men (p = 0.020), but not for the SKAT test (0.084).

The gene AGBL1 (ATP/GTP-binding protein-like 1 [MIM: 615496]) was associated with BMI in the full sample (burden p = 9.59 × 10^{-7}, SKAT p = 5.02 × 10^{-5}). The most significant variant in this gene was rs73459659 (MAF = 0.036, Beta [SE] = -0.099 [0.030], p = 0.001), with an additional 14 of the 174 SNVs included in the test with p < 0.05. Dropping the top variant from the gene-based burden association reduced the significance to p = 1.15 × 10^{-4} (above our significance threshold of 3.83 × 10^{-6}), suggesting that much of this signal is driven by rs73459659. Our AGBL1 gene-based result for BMI was not replicated for either burden (p = 0.533) or SKAT (p = 0.569) tests in TOPMed EA + AA. RFT20 (keratin 20, type 1 [MIM: 608218]) was significantly associated with WHR in our AA women gene-based burden test results (p = 3.63 × 10^{-6}), but not the SKAT results (p = 3.20 × 10^{-4}). Of the 22 SNVs included in this gene-based test that were polymorphic in at least one cohort, only three were found in both AA women cohorts, and only one was significant (rs34006883, p = 4.58 × 10^{-4}). This result was not validated in TOPMed AA women (burden p = 0.263, SKAT p = 0.145).

eQTL analysis

For height, 697 genome-wide significant SNVs were available for analysis, and we had gene-based exome sequencing and GTEx eQTL results for 25 genes around those loci. The eQTL data in skeletal muscle suggest CEPE3 (centrosomal protein, 63 kDa [MIM: 614724]), as implicated in the GWAS signal at rs19774480/rs6762606 on chromosome 3 (eQTL p = 6.61 × 10^{-4}), burden test p = 0.007, SKAT p = 0.088) (Table 3). Additionally, RFT1 (RFT1 homolog [MIM: 611908]) in the rs22490919/rs2581830-tagged locus on chromosome 3 attained locus-specific significance (eQTL p = 3.09 × 10^{-7}, burden test p = 0.002, SKAT p = 0.021). Full height eQTL results for all genes with p < 0.05 in our gene-based results are presented in Table S3.

For BMI, 217 genome-wide significant SNVs were available, and we had gene-based exome sequencing
Table 2. Gene-based results passing significance threshold of 0.05 per number of genes with cumulative minor allele count (cMAC) > 20 = 3.83E-6

| Trait  | Gene | Discovery SNVs (N) | cMAC | Burden p | SKAT p | Replication SNVs (N) | Burden p | SKAT p | Previous findings |
|--------|------|--------------------|------|----------|--------|----------------------|----------|--------|------------------|
| BMI    | AGBL1| all ancestries     | 18,740 | 174 | 5,925 | 9.59E-7 | 5.02E-5 | 4,756 | 40 | 0.533 | 0.569 | Walford (2016)11 - BMI interaction |
| Height | LECT2| EA men             | 5,450 | 11 | 7,415 | 2.56E-6 | 1.69E-5 | 585  | 4   | 0.020 | 0.084 | Marouli12         |
| WHR    | KRT20| AA women           | 2,941 | 22 | 63    | 3.63E-6 | 3.20E-4 | 4,116 | 14 | 0.263 | 0.145 | –                 |

and GTEx eQTL results for 11 genes around those loci. For WHR, we identified 102 previously reported GWAS SNVs9,47,49–51 and had gene-based exome sequencing and GTEx eQTL results for seven genes around those loci. We had no gene-based exome sequencing results with cMAC > 20 for any of the eQTLs identified in the five brain tissues tested (data not shown) and no gene-based exome sequencing results for BMI or WHR in either subcutaneous or visceral fat tissue that met the threshold for locus-wide significance. BMI and WHR eQTL results with nominally significant gene-based results are presented in Tables S4 and S5, respectively.

Monogenic results

For height, we compiled a list of 187 autosomal genes with monogenic or syndromic effects on height (Table S6) and first examined our gene-based results, filtering out those genes with cMAC ≤ 20. A further 10 genes were not found in our results, leaving 132 genes, 7 of which were nominally significant for both gene-based tests (ACAN [MIM: 155760], ADAMTS10 [MIM: 608990], COL2A1 [MIM: 120140], CYTL1 [MIM: 607930], GLI3 [MIM: 165240], PEX7 [MIM: 601757], and RNF135 [MIM: 611358]), 6 of which were nominally significant for the burden test (COL11A2 [MIM: 120290], EXT1 [MIM: 608177], FGFR3 [MIM: 134934], NPR2 [MIM: 607072], ORC4 [MIM: 603056], SDHA [MIM: 600857]), and 2 for the SKAT test (GJA1 [MIM: 121014], TNFRSF11B [MIM: 602643]) (Table S9). Seventy-eight out of 1,201 SNVs in those 15 genes were nominally significant (Table S10), yielding a significant enrichment p value of 0.024 based on the binomial distribution, whereas none was significant after correction for the number of variants tested (Bonferroni-corrected p < 0.05/1,201 = 4.2 × 10⁻⁵).

For BMI, we identified 35 autosomal genes associated with monogenic or syndromic obesity (Table S9), 29 of which passed our filtering criteria (Table S11). Two genes were nominally significant for both burden and SKAT tests (LEPR [MIM: 601007] and KSR2 [MIM: 610737]), while CEP290 [MIM: 610142] was also nominally significant for the burden test. For those three nominally significant genes, we extracted results for 414 low-frequency or rare SNVs. Twenty-two SNVs were nominally significant, but none reached our Bonferroni-corrected significance threshold (p = 0.05/414 = 1.21 × 10⁻⁴) (Table S12).

For WHR, we identified 55 genes associated with monogenic or syndromic forms of lipodystrophy or maturity-onset diabetes of the young (MODY) (Table S13). Of those 55 genes, 39 were present in our results and passed our filtering criteria (Table S14). Two genes were nominally significant for the burden test (LMNA [MIM: 150330] and HNF4A [MIM: 600281]), and two genes were nominally significant in our SKAT results (WFS1 [MIM: 606201] and POLD1 [MIM: 174761]). We extracted 408 low-frequency or rare variants in these genes. Twenty-one SNVs were nominally significant in these four genes (Table S14), but none was significantly associated with WHR after Bonferroni correction for the number of variants tested (p ≤ 1.23 × 10⁻⁶).

Discussion

In this analysis of anthropometric traits using whole-exome sequencing data from the CHARGE consortium of up to 22,004 individuals of European or African ancestry, we identified two variants associated with BMI (rs16824283 in SPHKAP and rs144506740 in the 3′ UTR of PIEZO2) and two SNVs associated with height (rs1120 5303 in MTRMR11 and rs4911494 in UQCC1). The eQTL analysis implicated two potentially functional genes for GWAS loci of height (CEP63 and RFT1). Also, leveraging our aggregated association results for height, we found that the nominally significant genes with monogenic or syndromic effect showed enrichment for rare variants of nominal significance.

Two variants were associated with BMI (rs16824283 in SPHKAP in our women-only sample and rs144506740 in the 3′ UTR of PIEZO2 in the sexes combined European ancestry sample), which were directionally consistent in our TOPMed validation sample, although not statistically significant (rs16824283: p = 0.343, rs144506740: p = 0.330). rs16824283 is a nonsynonymous variant in the 11th of 12 exons in SPHKAP, which is highly expressed in the cerebellum and heart.57,58 This gene codes for an anchoring protein involved in transport of the type I regulatory subunit of cAMP-dependent protein kinases.53,54 Several intronic variants in this gene have been previously associated with BMI (rs4973618 and rs6436755) and predicted visceral adipose tissue (rs4500930) or type 2 diabetes (rs7561798), although these variants were not
in strong LD with our lead variant rs16824283 (1000 Genomes phase 3 AFR + EUR LD: $r^2 = 0.047-0.10$, $D' = 0.35-0.59$). SPHKAP knockout mice are obese, with increased subcutaneous, visceral, and total fat mass, and have increased plasma insulin levels and improved glucose tolerance compared with wild-type mice. rs144506740 is a nonsynonymous variant in the 3’ UTR of PIEZO2 on chromosome 18, which encodes a transmembrane protein that is involved in mechanically activated cation channels in somatosensory neurons and is expressed in the endothelial and enteroendocrine cells of the human gut.

For height, two SNVs (rs11205303 and rs4911494) reached exome-wide significance in our full sample analysis and were validated in TOPMed. The first, rs11205303, is a known missense height variant in MTMR11 on chromosome 1. The second, rs4911494, is a missense variant the second exon of UQCC1, a gene previously associated with human height that codes for a ZIC-binding transmembrane protein that is repressed by basic fibroblast growth factor. Of the dozen variants in or near this gene that have been previously reported for height, rs4911494 is in moderate LD ($r^2 \geq 0.6$) with half of them in 1000 Genomes AFR + EUR (rs224329, rs878639, rs6088813, rs6060355, rs6060369, and rs6060373), suggesting that these previously reported intronic or intergenic variants may be tagging our exonic variant.

The small number of sequence variants attaining exome-wide significance in the present study, relative to the findings of studies based on the Exome Chip, is consistent with the lower statistical power to detect associations due to differences in sample size. Our discovery sample sizes were between 17x and 25x smaller than those of the GIANT Exome Chip-based studies. However, the Exome Chip genotyping array was based on targeted exome sequencing of approximately 12,000 subjects and likely missed rare or private variants segregating in the population. In theory, the exome sequence data analyzed here did not suffer from this limitation, because all exonic variants in the study sample are observed. The majority of the additional sequence variants available in the present study have relatively low minor allele frequencies, and the rare variants may be monomorphic or not present in all studies, resulting in lower statistical power to detect associations at expected effect sizes. Extensive simulations to evaluate statistical power of rare variant tests in exome sequencing studies have found only modest power for most genetic models in samples of up to 10,000 individuals.

To combine the effects of rare variants and reduce the burden of multiple testing, we identified candidate gene sets based on previously published GWAS loci and eQTL associations. This approach implicated potentially functional genes in two loci for height on chromosome 3, CEP63 in the GWAS signal at rs4974480 and RFT1 in the rs2581830-tagged locus. rs4974480 is an intronic variant in ANAPC13 (MIM: 614484), the nearest gene tagged in Wood et al., which codes for a protein involved in mitosis. The candidate causal gene in this region identified in our eQTL analysis (CEP63) has been linked to Beckwith syndrome, a rare disorder characterized by microcephaly and short stature. rs2581830 is an intronic variant in RFT1, the nearest gene tagged in Wood et al., and identified as a candidate causal gene in our eQTL analysis. This gene codes for a protein involved in N-linked glycosylation, an essential post-translational modification of proteins, but it is unclear how this may affect human height. We also investigated potential causal low-frequency variants in genes associated with monogenic or syndromic forms of our traits or related phenotypes but found no additional significant SNVs in genes associated with monogenic or syndromic stature, obesity, MODY, or lipodystrophy after correction for multiple testing.

The identification or replication of variants associated with our traits and the findings with less frequency or rare variant enrichment in monogenic or syndromic genes highlight the opportunities and the importance of genomic sequencing to identify susceptibility variants and to better map causal associations at previously identified GWAS signals. However, the dearth of significant results in a sample size of ~20,000 individuals also illustrates the challenges in identifying effects of rare genetic variants. Future studies with much larger sample sizes are warranted.

### Data and code availability

Discovery meta-analysis results will be made available through the NHGRI-EBI GWAS catalog. Data from TOPMed replication cohorts are available in dbGaP (database of Genotypes and Phenotypes; accession numbers for each study are provided in the supplemental information and Table S15).

### Supplemental information

Supplemental information can be found online at [https://doi.org/10.1016/j.xhgg.2022.100163](https://doi.org/10.1016/j.xhgg.2022.100163).
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Declaration of interests

The authors declare no competing interests.

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Web resources

bam-readcount, https://github.com/genome/bam-readcount
CHARGE Exome Sequencing, https://www.hgsc.bcm.edu/human/charge-consortium
NHGRI-EBI GWAS catalog, https://www.ebi.ac.uk/gwas/
NCBI dbGaP, https://www.ncbi.nlm.nih.gov/gap/
OMIM, http://www.omim.org
Picard, http://picard.sourceforge.net
RevCov, http://gmt.genome.wustl.edu/packages/refcov/index.html
Seattle Seq, https://snp.gs.washington.edu/SeattleSeqAn notation138/
TOPMed Freeze 5b WGS QC, https://topmed.nhlbi.nih.gov/topmed-whole-genome-sequencing-project-freeze-5b-phases-1-and-2

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