



Universiteit
Leiden
The Netherlands

A saturated map of common genetic variants associated with human height

Yengo, L.; Vedantam, S.; Marouli, E.; Sidorenko, J.; Bartell, E.; Sakaue, S.; ... ; Arnett, D.K.

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Common single-nucleotide polymorphisms (SNPs) are predicted to collectively explain 40–50% of phenotypic variation in human height, but identifying the specific variants and associated regions requires huge sample sizes¹. Here, using data from a genome-wide association study of 5.4 million individuals of diverse ancestries, we show that 12,111 independent SNPs that are significantly associated with height account for nearly all of the common SNP-based heritability. These SNPs are clustered within 7,209 non-overlapping genomic segments with a mean size of around 90 kb, covering about 21% of the genome. The density of independent associations varies across the genome and the regions of increased density are enriched for biologically relevant genes. In out-of-sample estimation and prediction, the 12,111 SNPs (or all SNPs in the HapMap 3 panel²) account for 40% (45%) of phenotypic variance in populations of European ancestry but only around 10–20% (14–24%) in populations of other ancestries. Effect sizes, associated regions and gene prioritization are similar across ancestries, indicating that reduced prediction accuracy is likely to be explained by linkage disequilibrium and differences in allele frequency within associated regions. Finally, we show that the relevant biological pathways are detectable with smaller sample sizes than are needed to implicate causal genes and variants. Overall, this study provides a comprehensive map of specific genomic regions that contain the vast majority of common height-associated variants. Although this map is saturated for populations of European ancestry, further research is needed to achieve equivalent saturation in other ancestries.

Since 2007, genome-wide association studies (GWASs) have identified thousands of associations between common SNPs and height, mainly using studies with participants of European ancestry. The largest GWAS published so far for adult height focused on common variation and reported up to 3,290 independent associations in 712 loci using a sample size of up to 700,000 individuals³. Adult height, which is highly heritable and easily measured, has provided a larger number of common genetic associations than any other human phenotype. In addition, a large collection of genes has been implicated in disorders of skeletal growth, and these are enriched in loci mapped by GWASs of height in the normal range. These features make height an attractive model trait for assessing the role of common genetic variation in defining the genetic and biological architecture of polygenic human phenotypes.

As available sample sizes continue to increase for GWASs of common variants, it becomes important to consider whether these larger samples can ‘saturate’ or nearly completely catalogue the information that can be derived from GWASs. This question of completeness can take several forms, including prediction accuracy compared with heritability attributable to common variation, the mapping of associated genomic regions that account for this heritability, and whether increasing sample sizes continue to provide additional information about the identity of prioritized genes and gene sets. Furthermore, because most GWASs continue to be performed largely in populations

of European ancestry, it is necessary to address these questions of completeness in the context of multiple ancestries. Finally, some have proposed that, when sample sizes become sufficiently large, effectively every gene and genomic region will be implicated by GWASs, rather than certain subsets of genes and biological pathways being specified⁴.

Here, using data from 5.4 million individuals, we set out to map common genetic associations with adult height, using variants catalogued in the HapMap 3 project (HM3), and to assess the saturation of this map with respect to variants, genomic regions and likely causal genes and gene sets. We identify significant variants, examine signal density across the genome, perform out-of-sample estimation and prediction analyses within studies of individuals of European ancestry and other ancestries and prioritize genes and gene sets as likely mediators of the effects on height. We show that this set of common variants reaches predicted limits for prediction accuracy within populations of European ancestry and largely saturates both the genomic regions associated with height and broad categories of gene sets that are likely to be relevant; future work will be required to extend prediction accuracy to populations of other ancestries, to account for rarer genetic variation and to more definitively connect associated regions with individual probable causal genes and variants.

An overview of our study design and analysis strategy is provided in Extended Data Fig. 1.

A list of authors and their affiliations appears online. ✉e-mail: Lyengo@imb.uq.edu.au; yokada@sg.med.osaka-u.ac.jp; A.R.Wood@exeter.ac.uk; peter.visscher@uq.edu.au; Joel.Hirschhorn@childrens.harvard.edu

Table 1 Summary of results from within-ancestry and trans-ancestry GWAS meta-analyses

Cohort ancestry or ethnic group	Number of studies	Max <i>n</i> (mean <i>n</i>)	Number of GWS COJO SNPs ($P_{\text{GWS}} < 5 \times 10^{-8}$)	Number of GWS loci (35 kb)	Cumulative length of non-overlapping GWS loci in Mb (% of genome)
European (EUR)	173	4,080,687 (3,612,229)	9,863 (8,382)	6,386	552.5 (18.4%)
East Asian (EAS)	56	472,730 (320,570)	918 (807)	821	60.5 (2.0%)
Hispanic (HIS)	11	455,180 (431,645)	1,511 (1,195)	1,373	101.0 (3.3%)
African (AFR)	29	293,593 (222,981)	453 (404)	412	30.4 (1.0%)
South Asian (SAS)	12	77,890 (59,420)	69 (65)	66	4.7 (0.2%)
Trans-ancestry meta-analysis (META _{FE})	281	5,314,291* (4,611,160)	12,111 (9,920)	7,209	647.5 (21.6%)

n denotes the sample size for each SNP. GWS: genome-wide significant ($P < 5 \times 10^{-8}$). COJO SNPs: near-independent GWS SNPs identified using an approximate COJO analysis implemented in the GCTA software. P_{GWS} : *P* value from a marginal association test. GWS loci were defined as genomic regions centred around each GWS SNP and including all SNPs within 35 kb on each side of the lead GWS SNP. Overlapping GWS loci were merged so that the number and cumulative length of GWS loci are calculated on non-overlapping GWS loci. The percentage of the genome covered was calculated by dividing the cumulative of GWS loci by 3,039 Mb (the approximated length of the human genome).

*The number of individuals in the trans-ancestry meta-analysis ($n = 5,314,291$) is smaller than the sum of ancestry-group-specific meta-analyses ($n = 5,380,080$) because of variation in per-SNP sample sizes for SNPs included in the final analysis.

Meta-analysis identifies 12,111 height-associated SNPs

We performed genetic analysis of up to 5,380,080 individuals from 281 studies from the GIANT consortium and 23andMe. Supplementary Fig. 1 represents projections of these 281 studies onto principal components reflecting differences in allele frequencies across ancestry groups in the 1000 Genomes Project (1KGP)³. Altogether, our discovery sample includes 4,080,687 participants of predominantly European ancestries (75.8% of total sample); 472,730 participants with predominantly East Asian ancestries (8.8%); 455,180 participants of Hispanic ethnicity with typically admixed ancestries (8.5%); 293,593 participants of predominantly African ancestries—mostly African American individuals with admixed African and European ancestries (5.5%); and 77,890 participants of predominantly South Asian ancestries (1.4%). We refer to these five groups of participants or cohorts as EUR, EAS, HIS, AFR and SAS, respectively, while recognizing that these commonly used groupings oversimplify the actual genetic diversity among participants. Cohort-specific information is provided in Supplementary Tables 1–3. We tested the association between standing height and 1,385,132 autosomal bi-allelic SNPs from the HM3 tagging panel², which contains more than 1,095,888 SNPs with a minor allele frequency (MAF) greater than 1% in each of the five ancestral groups included in our meta-analysis. Supplementary Fig. 2 shows the frequency and imputation quality distribution of HM3 SNPs across all five groups of cohorts.

We first performed separate meta-analyses in each of the five groups of cohorts. We identified 9,863, 1,511, 918, 453 and 69 quasi-independent genome-wide significant (GWS; $P < 5 \times 10^{-8}$) SNPs in the EUR, HIS, EAS, AFR and SAS groups, respectively (Table 1 and Supplementary Tables 4–8). Quasi-independent associations were obtained after performing approximate conditional and joint (COJO) multiple-SNP analyses⁶, as implemented in GCTA⁷ (Methods). Supplementary Note 1 presents sensitivity analyses of these COJO results, highlights biases due to relatively long-range linkage disequilibrium (LD) in admixed AFR and HIS individuals⁸ (Supplementary Fig. 3), and shows how to correct those biases by varying the GCTA input parameters (Supplementary Fig. 4). Moreover, previous studies have shown that confounding due to population stratification may remain uncorrected in large GWAS meta-analyses^{9,10}. Therefore, we specifically investigated confounding effects in all ancestry-specific GWASs, and found that our results are minimally affected by population stratification (Supplementary Note 2 and Supplementary Figs. 5–7).

To compare results across the five groups of cohorts, we examined the genetic and physical colocalization between SNPs identified in the largest group (EUR) with those found in the other (non-EUR) groups. We found that more than 85% of GWS SNPs detected in the non-EUR groups are in strong LD ($r_{\text{LD}}^2 > 0.8$) with at least one variant reaching

marginal genome-wide significance ($P_{\text{GWS}} < 5 \times 10^{-8}$) in EUR (Supplementary Tables 5–8). Furthermore, more than 91% of associations detected in non-EUR meta-analyses fall within 100 kb of a GWS SNP identified in EUR (Extended Data Fig. 2). By contrast, a randomly sampled HM3 SNP (matched with GWS SNPs identified in non-EUR meta-analyses on 24 functional annotations; Methods) falls within 100 kb of a EUR GWS SNP 55% of the time on average (s.d. = 1% over 1,000 draws). Next, we quantified the cross-ancestry correlation of marginal allele substitution effects (ρ_b) at GWS SNPs for all pairs of ancestry groups. We estimated ρ_b using five subsets of GWS SNPs identified in each of the ancestry groups, which also reached marginal genome-wide significance in at least one group. After correction for winner's curse^{11,12}, we found that ρ_b ranged between 0.64 and 0.99 across all pairs of ancestry groups and all sets of GWS SNPs (Supplementary Figs. 8–12). We also extended the estimation of ρ_b for SNPs that did not reach genome-wide significance and found that $\rho_b > 0.5$ across all comparisons (Supplementary Fig. 13). Thus, the observed GWS height associations are substantially shared across major ancestral groups, consistent with previous studies based on smaller sample sizes^{13,14}.

To find signals that are specific to certain groups, we tested whether any individual SNPs detected in non-EUR GWASs are conditionally independent of signals detected in EUR GWASs. We fitted an approximate joint model that includes GWS SNPs identified in EUR and non-EUR, using LD reference panels specific to each ancestry group. After excluding SNPs in strong LD ($r_{\text{LD}}^2 > 0.8$ in either ancestry group), we found that 2, 17, 49 and 63 of the GWS SNPs detected in SAS, AFR, EAS and HIS GWASs, respectively, are conditionally independent of GWS SNPs identified in EUR GWASs (Supplementary Table 9). On average, these conditionally independent SNPs have a larger MAF and effect size in non-EUR than in EUR cohorts, which may have contributed to an increased statistical power of detection. The largest frequency difference relative to EUR was observed for rs2463169 (height-increasing G allele frequency: 23% in AFR versus 84% in EUR) within the intron of *PAWR*, which encodes the prostate apoptosis response-4 protein. Of note, rs2463169 is located within the 12q21.2 locus, where a strong signal of positive selection in West African Yoruba populations was previously reported¹⁵. The estimated effect at rs2463169 is $\beta \approx 0.034$ s.d. per G allele in AFR versus $\beta \approx -0.002$ s.d. per G allele in EUR, and the *P* value of marginal association in EUR is $P_{\text{EUR}} = 0.08$, suggesting either a true difference in effect size or nearby causal variant(s) with differing LD to rs2463169.

Given that our results show a strong genetic overlap of GWAS signals across ancestries, we performed a fixed-effect meta-analysis of all five ancestry groups to maximize statistical power for discovering associations due to shared causal variants. The mean Cochran's heterogeneity

Q-statistic is around 34% across SNPs, which indicates moderate heterogeneity of SNP effects between ancestries. The mean chi-square association statistic in our fixed-effect meta-analysis (hereafter referred to as $META_{FE}$) is around 36, and around 18% of all HM3 SNPs are marginally GWS. Moreover, we found that allele frequencies in our $META_{FE}$ were very similar to that of EUR (mean fixation index of genetic differentiation (F_{ST}) across SNPs between EUR and $META_{FE}$ is around 0.001), as expected because our $META_{FE}$ consists of more than 75% EUR participants and around 14% participants with admixed European and non-European ancestries that is, HIS and AFR). To further assess whether LD in our $META_{FE}$ could be reasonably approximated by the LD from EUR, we performed an LD score regression¹⁶ analysis of our $META_{FE}$ using LD scores estimated in EUR. In this analysis, we focused on the attenuation ratio statistic ($R_{LDSC-EUR}$), for which large values can also indicate strong LD inconsistencies between a given reference and GWAS summary statistics. A threshold of $R_{LDSC} > 20\%$ was recommended by the authors of the LDSC software as a rule-of-thumb to detect such inconsistencies. Using EUR LD scores in the GWAS of HIS, which is the non-EUR group that is genetically closest to EUR ($F_{ST} \approx 0.02$), yields an estimated $R_{LDSC-EUR}$ of around 25% (standard error (s.e.) 1.8%), consistent with strong LD differences between HIS and EUR. By contrast, in our $META_{FE}$, we found an estimated $R_{LDSC-EUR}$ of around 4.5% (s.e. 0.8%), which is significantly lower than 20% and not statistically different from 3.8% (s.e. 0.8%) in our EUR meta-analysis. Furthermore, we show in Supplementary Note 1 that using a composite LD reference containing samples from various ancestries (with proportions matching that in our $META_{FE}$) does not improve signal detection over using an EUR LD reference. Altogether, these analyses suggest that LD in our $META_{FE}$ can be reasonably approximated by LD from EUR.

We therefore proceeded to identify quasi-independent GWS SNPs from the multi-ancestry meta-analysis by performing a COJO analysis of our $META_{FE}$, using genotypes from around 350,000 unrelated EUR participants in the UK Biobank (UKB) as an LD reference. We identified 12,111 quasi-independent GWS SNPs, including 9,920 (82%) primary signals with a GWS marginal effect and 2,191 secondary signals that only reached GWS in a joint regression model (Supplementary Table 10). Figure 1 represents the relationship between frequency and joint effect sizes of minor alleles at these 12,111 associations. Of the GWS SNPs obtained from the non-EUR meta-analyses above that were conditionally independent of the EUR GWS SNPs, 0/2 in SAS, 5/17 in AFR, 27/49 in EAS and 27/63 in HIS were marginally significant in our $META_{FE}$ (Supplementary Table 9), and 24 of those (highlighted in Fig. 2) overlapped with our list of 12,111 quasi-independent GWS SNPs.

We next sought to replicate the 12,111 $META_{FE}$ signals using GWAS data from 49,160 participants in the Estonian Biobank (EBB). We first re-assessed the consistency of allele frequencies between our $META_{FE}$ and the EBB set. We found a correlation of allele frequencies of around 0.98 between the two datasets and a mean F_{ST} across SNPs of around 0.005, similar to estimates that were obtained between populations from the same continent. Of the 12,111 GWS SNPs identified through our COJO analysis, 11,847 were available in the EBB dataset, 97% of which (11,529) have a MAF greater than 1% (Supplementary Table 10). Given the large difference in sample size between our discovery and replication samples, direct statistical replication of individual associations at GWS is not achievable for most SNPs identified (Extended Data Fig. 3a). Instead, we assessed the correlation of SNP effects between our discovery and replication GWASs as an overall metric of replicability^{3,17}. Among the 11,529 out of 11,847 SNPs that had a MAF greater than 1% in the EBB, we found a correlation of marginal SNP effects of $\rho_b = 0.93$ (jackknife standard error; s.e. 0.01) and a correlation of conditional SNP effects using the same LD reference panel of $\rho_b = 0.80$ (s.e. 0.03; Supplementary Fig. 14). Although we had limited power to replicate associations with 238 GWS variants that are rare in the EBB (MAF < 1%), we found, consistent with expectations (Methods and Extended Data Fig. 3b), that 60% of them had a marginal SNP effect that was sign-consistent

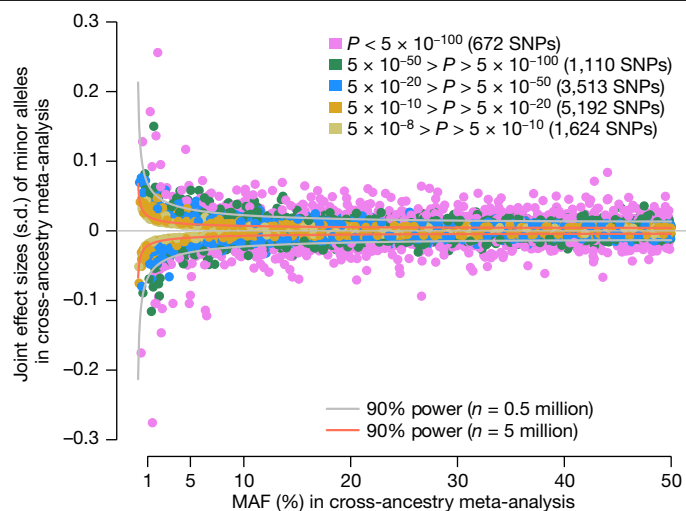


Fig. 1 | Relationship between frequency and estimated effect sizes of minor alleles. Each dot represents one of the 12,111 quasi-independent GWS SNPs that were identified in our cross-ancestry GWAS meta-analysis. Data underlying this figure are available in Supplementary Table 10. SNP effect estimates (y axis) are expressed in height standard deviation (s.d.) per minor allele as defined in our cross-ancestry GWAS meta-analysis. SNPs were stratified in five classes according to their P value of association. We show two curves representing the theoretical relationship between frequency and expected magnitude of SNP effect detectable at $P < 5 \times 10^{-8}$ with a statistical power of 90%. Statistical power was assessed under two experimental designs with sample sizes equal to $n = 0.5$ million and $n = 5$ million.

with that from our discovery GWAS (Fisher's exact test; $P = 0.001$). The proportion of sign-consistent SNP effects was greater than 75% (Fisher's exact test; $P < 10^{-50}$) for variants with a MAF greater than 1%—also consistent with expectations (Extended Data Fig. 3b). Altogether, our analyses demonstrate the robustness of our findings and show their replicability in an independent sample.

Genomic distribution of height-associated SNPs

To examine signal density among the 12,111 GWS SNPs detected in our $META_{FE}$, we defined a measure of local density of association signals for each GWS SNP on the basis of the number of additional independent associations within 100 kb (Supplementary Fig. 15). Supplementary Fig. 16 shows the distributions of signal density for GWS SNPs identified in each ancestry group and in our $META_{FE}$. We observed that 69% of GWS SNPs shared their location with another associated, conditionally independent, GWS SNP (Fig. 2). The mean signal density across the entire genome is 2.0 (s.e. 0.14), consistent with a non-random genomic distribution of GWS SNPs. Next, we evaluated signal density around 462 autosomal genes curated from the Online Mendelian Inheritance in Man (OMIM) database¹⁸ as containing pathogenic mutations that cause syndromes of abnormal skeletal growth ('OMIM genes'; Methods and Supplementary Table 11). We found that a high density of height-associated SNPs is significantly correlated with the presence of an OMIM gene nearby^{19,20} (enrichment fold of OMIM gene when density is greater than 1: 2.5×; $P < 0.001$; Methods and Extended Data Fig. 4a). Notably, the enrichment of OMIM genes almost linearly increases with the density of height-associated SNPs (Extended Data Fig. 4b). Thus, these 12,111 GWS SNPs nonrandomly cluster near each other and near known skeletal growth genes.

The largest density of conditionally independent associations was observed on chromosome 15 near *ACAN*, a gene mutated in short stature and skeletal dysplasia syndromes, where 25 GWS SNPs co-localize within 100 kb of one another (Fig. 2 and Supplementary Fig. 17). We show in

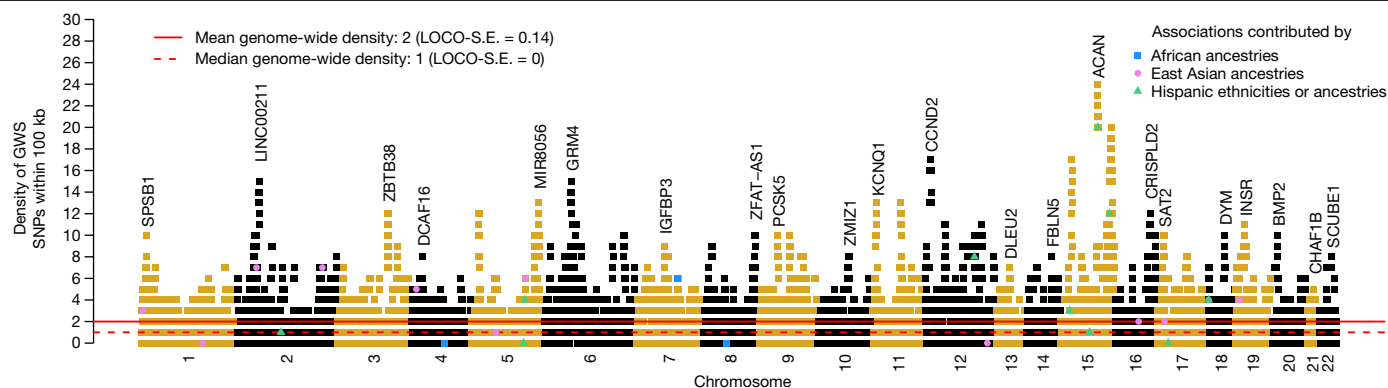


Fig. 2 | Brisbane plot showing the genomic density of independent genetic associations with height. Each dot represents one of the 12,111 quasi-independent GWS ($P < 5 \times 10^{-8}$) height-associated SNPs identified using approximate COJO analyses of our cross-ancestry GWAS meta-analysis. Data underlying this figure are available in Supplementary Table 10. GWS SNPs with the largest density on each chromosome were annotated with the closest gene. We highlight 24 of 12,111 associations that are mainly contributed by groups of non-European ancestry (3 from African ancestries, 10 from Hispanic ethnicities or ancestries and 11 from East Asian ancestries). The full list of height-associated SNPs detected in groups of non-European ancestry and

independent of associations detected in European ancestry GWASs is reported in Supplementary Table 9. Signal density was calculated for each associated SNP as the number of other independent associations within 100 kb. A density of 1 means that a GWS COJO SNP shares its location with another independent GWS COJO SNP within less than 100 kb. The mean signal density across the genome is 2 and the median signal density is 1 (s.e. 0.14 and 0.0, respectively). The s.e. values were calculated using a leave-one-chromosome-out jackknife approach (LOCO-S.E.). SNPs that did not reach genome-wide significance are not represented on the figure.

Supplementary Note 3 and Extended Data Fig. 5a–d, using haplotype- and simulation-based analyses, that a multiplicity of independent causal variants is the most likely explanation of this observation. We also found that signal density is partially explained by the presence of a recently identified^{21,22} height-associated variable-number tandem repeat (VNTR) polymorphism at this locus (Supplementary Note 3). In fact, the 25 independent GWS SNPs clustered within 100 kb of rs4932198 explain more than 40% of the VNTR length variation in multiple ancestries (Extended Data Fig. 5e), and an additional approximately 0.24% ($P = 8.7 \times 10^{-55}$) of phenotypic variance in EUR above what is explained by the VNTR alone (Extended Data Fig. 5f). Altogether, our conclusion is consistent with previous evidence of multiple types of common variation influencing height through *ACAN* gene function, involving multiple enhancers²³, missense variants²⁴ and tandem repeat polymorphisms^{21,22}.

Variance explained by SNPs within identified loci

To quantify the proportion of height variance that is explained by GWS SNPs identified in our $META_{FE}$, we stratified all HM3 SNPs into two groups: SNPs in the close vicinity of GWS SNPs, hereafter denoted GWS loci; and all remaining SNPs. We defined GWS loci as non-overlapping genomic segments that contain at least one GWS SNP, such that GWS SNPs in adjacent loci are more than 2×35 kb away from each other (that is, a 35-kb window on each side). We chose this size window because it was predicted that causal variants are located within 35 kb of GWS SNPs with a probability greater than 80% (ref. ²⁵). Accordingly, we grouped the 12,111 GWS SNPs identified in our $META_{FE}$ into 7,209 non-overlapping loci (Supplementary Table 12) with lengths ranging from 70 kb (for loci containing only one signal) to 711 kb (for loci containing up to 25 signals). The average length of GWS loci is around 90 kb (s.d. 46 kb). The cumulative length of GWS loci represents around 647 Mb, or about 21% of the genome (assuming a genome length of around 3,039 Mb)²⁶.

To estimate the fraction of heritability that is explained by common variants within the 21% of the genome overlapping GWS loci, we calculated two genomic relationship matrices (GRMs)—one for SNPs within these loci and one for SNPs outside these loci—and then used both matrices to estimate a stratified SNP-based heritability (h^2_{SNP}) of height in eight independent samples of all five population groups represented in our $META_{FE}$ (Fig. 3 and Methods). Altogether, our stratified

estimation of SNP-based heritability shows that SNPs within these 7,209 GWS loci explain around 100% of h^2_{SNP} in EUR and more than 90% of h^2_{SNP} across all non-EUR groups, despite being drawn from less than 21% of the genome (Fig. 3). We also varied the window size used to define GWS loci and found that 35 kb was the smallest window size for which this level of saturation of SNP-based heritability could be achieved (Supplementary Fig. 18).

To further assess the robustness of this key result, we tested whether the 7,209 height-associated GWS loci are systematically enriched for trait heritability. We chose body-mass index (BMI) as a control trait, given its small genetic correlation with height ($r_g = -0.1$, ref. ²⁷) and found no significant enrichment of SNP-based heritability for BMI within height-associated GWS loci (Supplementary Fig. 19). Furthermore, we repeated our analysis using a random set of SNPs matched with the 12,111 height-associated GWS SNPs on EUR MAF and LD scores. We found that this control set of SNPs explained only around 27% of h^2_{SNP} for height, consistent with the proportion of SNPs within the loci defined by this random set of SNPs (Supplementary Figs. 18 and 19). Finally, we extended our stratified estimation of SNP-based heritability to all well-imputed common SNPs (that is, beyond the HM3 panel) and found, consistently across population groups, that although more genetic variance can be explained by common SNPs that are not included in the HM3 panel, all information remains concentrated within these 7,209 GWS loci (Extended Data Fig. 6). Thus, with this large GWAS, nearly all of the variability in height that is attributable to common genetic variants can be mapped to regions comprising around 21% of the genome. Further work is required in cohorts of non-European ancestries to map the remaining 5–10% of the SNP-based heritability that is not captured within those regions.

Out-of-sample prediction accuracy

We quantified the accuracy of multiple polygenic scores (PGSs) for height on the basis of GWS SNPs (hereafter referred to as PGS_{GWS}) and on the basis of all HM3 SNPs (hereafter referred to as PGS_{HM3}). PGS_{GWS} were calculated using joint SNP effects from COJO, and PGS_{HM3} using joint effects calculated using the SBayesC method²⁸ (Methods). We denote R^2_{GWS} and R^2_{HM3} as the prediction accuracy of PGS_{GWS} and PGS_{HM3} , respectively. For conciseness, we also use the abbreviations PGS_{GWS-X} and PGS_{HM3-X} (and R^2_{GWS-X} and R^2_{HM3-X}) to specify which GWAS

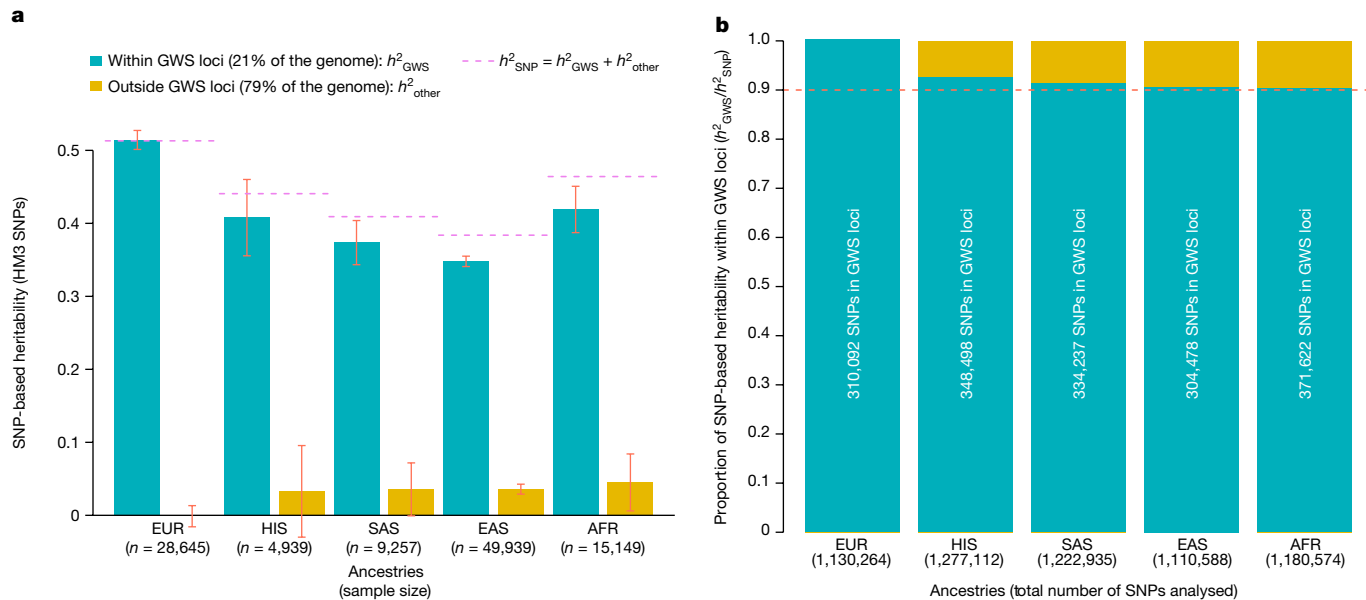


Fig. 3 | Variance of height explained by HM3 SNPs within GWS loci.

a, Stratified SNP-based heritability (h^2_{SNP}) estimates obtained after partitioning the genome into SNPs within 35 kb of a GWS SNP ('GWS loci' label) versus SNPs that are more than 35 kb away from any GWS SNP. Analyses were performed in samples of five different ancestries or ethnic groups: European (EUR: meta-analysis of UK Biobank (UKB) + Lifelines study), African (AFR: meta-analysis of UKB + PAGE study), East Asian (EAS: meta-analysis of UKB +

China Kadoorie Biobank), South Asian (SAS: UKB) and Hispanic (HIS: PAGE). Error bars represent standard errors. **b**, More than 90% of h^2_{SNP} in all ancestries is explained by SNPs within GWS loci identified in this study. The cumulative length of non-overlapping GWS loci is around 647 Mb; that is, around 21% of the genome, assuming a genome length of around 3,039 Mb (ref. ²⁶). The proportion of HM3 SNPs in GWS loci is around 27%.

meta-analysis each PGS (and corresponding prediction accuracy) was trained from. For example, $\text{PGS}_{\text{GWS-META}_{\text{FE}}}$ refers to PGSs based on 12,111 GWS SNPs identified from our META_{FE} .

We first present results from PGS_{GWS} across different ancestry groups. $\text{PGS}_{\text{GWS-META}_{\text{FE}}}$ yielded prediction accuracies greater than or equal to that of all other PGS_{GWS} (Fig. 4a), partly reflecting sample size differences between ancestry-specific GWASs and also consistent with previous studies²⁹. $\text{PGS}_{\text{GWS-EUR}}$ (based on 9,863 SNPs) was the second best of all PGS_{GWS} across ancestry groups except in AFR. Indeed, $\text{PGS}_{\text{GWS-AFR}}$ (based on 453 SNPs) yielded an accuracy of 8.5% (s.e. 0.6%) in AFR individuals from UKB and PAGE; that is, significantly larger than the 5.9% (s.e. 0.6%) and 7.0% (s.e. 0.6%) achieved by $\text{PGS}_{\text{GWS-EUR}}$ in these two samples, respectively (Fig. 4a). $\text{PGS}_{\text{GWS-META}_{\text{FE}}}$ was the best of all PGS_{GWS} in AFR participants with an accuracy $R^2_{\text{GWS-META}_{\text{FE}}} = (12.3\% + 9.9\%)/2 = 10.8\%$ (s.e. 0.5%) on average between UKB and PAGE (Fig. 4a). Across ancestry groups, the highest accuracy of $\text{PGS}_{\text{GWS-META}_{\text{FE}}}$ was observed in EUR participants ($R^2_{\text{GWS-META}_{\text{FE}}} \sim 40\%$; s.e. 0.6%) and the lowest in AFR participants from the UKB ($R^2_{\text{GWS-META}_{\text{FE}}} \sim 9.4\%$; s.e. 0.7%). Note that the difference in $R^2_{\text{GWS-META}_{\text{FE}}}$ between the EUR and AFR ancestry cohorts is expected because of the over-representation of EUR in our META_{FE} and consistent with a relative accuracy ($R^2_{\text{GWS-META}_{\text{FE}}}$ in AFR)/($R^2_{\text{GWS-META}_{\text{FE}}}$ in EUR) of around 25% that was previously reported³⁰. We extended analyses of PGS_{GWS} to PGS based on SNPs identified with COJO at lower significance thresholds (Extended Data Fig. 7). As in previous studies^{3,20}, the inclusion of sub-significant SNPs increased the accuracy of ancestry-specific PGSs. However, lowering the significance thresholds in our META_{FE} mostly improved accuracy in EUR (from 40% to 42%), whereas it slightly decreased the accuracy in AFR.

Overall, ancestry-specific PGS_{HM3} consistently outperform their corresponding PGS_{GWS} in most ancestry-groups. However, PGS_{HM3} was sometimes less transferable across ancestry groups than PGS_{GWS} , in particular in AFR and HIS individuals from PAGE. In EUR, PGS_{HM3} reaches an accuracy of 44.7% (s.e. 0.6%), which is higher than previously published SNP-based predictors of height derived from individual-level

data^{31–33} and from GWAS summary statistics^{28,34,35} across various experimental designs (different SNP sets, different sample sizes and so on). Finally, the largest improvement of PGS_{HM3} over PGS_{GWS} was observed in AFR individuals from the PAGE study ($R^2_{\text{GWS-AFR}} = 8.5\%$ versus $R^2_{\text{HM3}} = 15.4\%$; Fig. 4a) and the UKB ($R^2_{\text{GWS-AFR}} = 8.5\%$ versus $R^2_{\text{HM3}} = 14.4\%$; Fig. 4a).

Furthermore, we sought to evaluate the prediction accuracy of PGSs relative to that of familial information as well as the potential improvement in accuracy gained from combining both sources of information. We analysed 981 unrelated EUR trios (that is, two parents and one child) and 17,492 independent EUR sibling pairs from the UKB, who were excluded from our META_{FE} . We found that height of any first-degree relative yields a prediction accuracy between 25% and 30% (Fig. 4b). Moreover, the accuracy of the parental average is around 43.8% (s.e. 3.2%), which is lower than yet not significantly different from the accuracy of $\text{PGS}_{\text{HM3-EUR}}$ in EUR. In addition, we found that a linear combination of the average height of parents and of the child's PGS yields an accuracy of 54.2% (s.e. 3.2%) with $\text{PGS}_{\text{GWS-EUR}}$ and 55.2% (s.e. 3.2%) with $\text{PGS}_{\text{HM3-EUR}}$. This observation reflects the fact that PGSs can explain within-family differences between siblings, whereas average parental height cannot. To show this empirically, we estimate that our PGSs based on GWS SNPs explain around 33% (s.e. 0.7%) of height variance between siblings (Methods). Finally, we show that the optimal weighting between parental average and PGS can be predicted theoretically as a function of the prediction accuracy of the PGS, the full narrow sense heritability and the phenotypic correlation between spouses (Supplementary Note 4 and Supplementary Fig. 20).

In summary, the estimation of variance explained and prediction analyses in samples with European ancestry show that the set of 12,111 GWS SNPs accounts for nearly all of h^2_{SNP} , and that combining SNP-based PGS with family history significantly improves prediction accuracy. By contrast, both estimation and prediction results show clear attenuation in samples with non-European ancestry, consistent with previous studies^{30,36–38}.

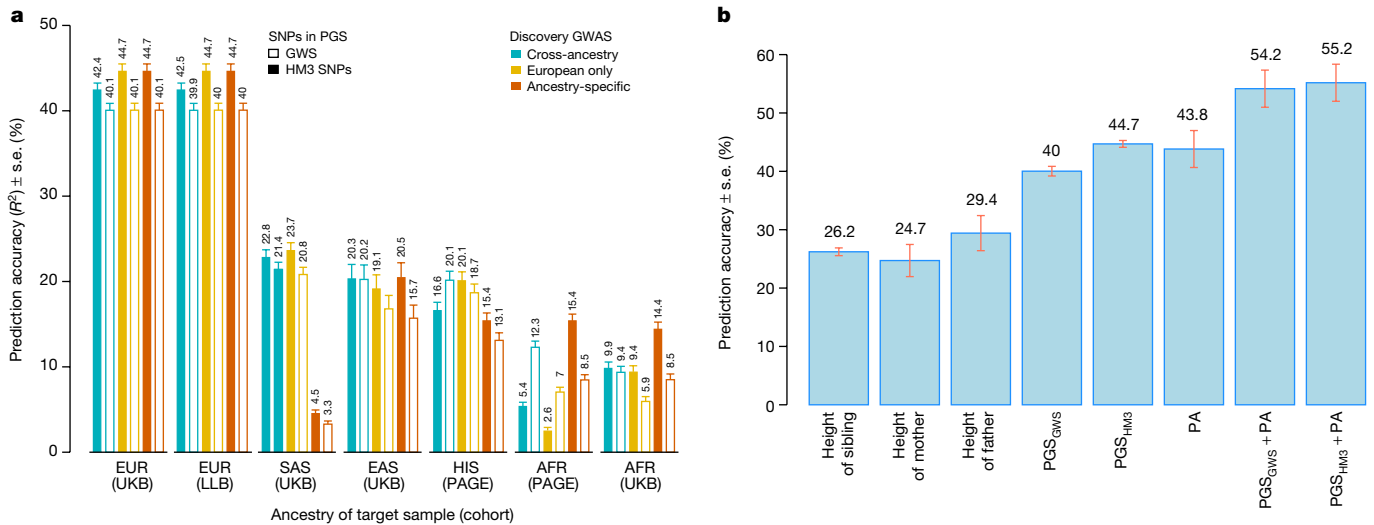


Fig. 4 | Accuracy of PGSs within families and across ancestries. Prediction accuracy (R^2) was measured as the squared correlation between PGS and actual height adjusted for age, sex and 10 genetic principal components. **a**, Accuracy of PGSs assessed in participants of five different ancestry groups: European (EUR) from the UKB ($n = 14,587$) and the Lifelines Biobank ($n = 14,058$); South Asian (SAS; $n = 9,257$) from UKB; East Asian (EAS; $n = 2,246$) from UKB; Hispanic (HIS; $n = 5,798$) from the PAGE study; and admixed African (AFR) from UKB ($n = 6,911$) and PAGE ($n = 8,238$). PGSs used for prediction, in **a**, are based on GWS SNPs or around 1.1 million HM3 SNPs. When using all HapMap 3 SNPs, SNP effects were calculated using the SBayesC method (Methods), whereas PGSs based on GWS SNPs used joint SNP effects estimated using the COJO method

(Methods). Both SBayesC and COJO were applied to (1) our cross-ancestry meta-analysis (turquoise bar); (2) our EUR meta-analysis (yellow bar); and (3) each ancestry-specific meta-analysis (red bar). **b**, Squared correlation of height between EUR participants in UKB and their first-degree relatives, and the accuracy of a predictor combining PGS (denoted PGS_{GWS}, as based on GWS SNPs) and familial information. The accuracies of PGS_{GWS} and PGS_{HM3} shown in **b** are the average of the respective accuracies of these PGSs in EUR participants from UKB and the Lifelines Biobank as shown in **a**. Sibling correlation was calculated in 17,492 independent EUR sibling pairs from the UKB and parent-offspring correlations in 981 EUR unrelated trios (that is, two parents and one child) from the UKB. PA, parental average.

GWAS discoveries, sample size and ancestry diversity

Our large study offers the opportunity to quantify empirically how much increasing GWAS sample sizes and ancestry diversity affects the discovery of variants, genes and biological pathways. To address this question, we re-analysed three previously published GWASs of height^{3,19,20} and also down-sampled our meta-analysis into four subsets (including our EUR and META_{FE} GWASs). Altogether, we analysed seven GWASs with a sample size increasing from around 0.13 million up to around 5.3 million individuals (Table 2).

For each GWAS, we quantified eight metrics grouped into four variant- and locus-based metrics (number of GWS SNPs; number of GWS loci; prediction accuracy (R^2_{GWS}) of PGS based on GWS SNPs; and proportion of the genome covered by GWS loci), a functional-annotation-based metric (enrichment statistics from stratified LDSC^{39,40}), two gene-based metrics (number of genes prioritized by summary-data-based Mendelian randomization⁴¹ (SMR; Methods) and proximity of variants with OMIM genes) and a gene-set-based metric (enrichment within clusters of gene sets or pathways). Overall, we found different patterns for the relationship between those metrics and GWAS sample size and ancestry composition, consistent with varying degrees of saturation achieved at different sample sizes.

We observed the strongest saturation for the gene-set and functional-annotation metrics, which capture how well general biological functions can be inferred from GWAS results using currently available computational methods. Using two popular gene-set prioritization methods (DEPICT⁴² and MAGMA⁴³), we found that the same broad clusters of related gene sets (including most of the clusters enriched for OMIM genes) are prioritized at all GWAS sample sizes (Supplementary Fig. 21, Extended Data Fig. 8, Supplementary Tables 13–15 and Supplementary Note 5). Similarly, stratified LDSC estimates of heritability enrichment within 97 functional annotations also remain stable across the range of sample sizes (Extended Data Fig. 9). Overall, we found no significant improvement for all these higher-level metrics from adding non-EUR

samples to our analyses. The latter observation is consistent with other analyses showing that GWASs expectedly implicate similar biology across major ancestral groups (Supplementary Note 5 and Supplementary Fig. 22).

For the gene-level metric, the excess in the number of OMIM genes that are proximate to a GWS SNP (compared with matched sets of random genes) plateaus at sample sizes of larger than 1.5 million, whereas the relative enrichment of GWS SNPs near OMIM genes first decreases with sample size, then plateaus when n is greater than 1.5 million (Supplementary Fig. 23a–c). Notably, the decrease observed for n values of less than 1.5 million reflects the preferential localization of larger effect variants (those identified with smaller sample sizes) closer to OMIM genes (Supplementary Fig. 23d) and, conversely, that more recently identified variants with smaller effects tend to localize further away from OMIM genes (Supplementary Fig. 23e). We also investigated the number of genes prioritized using SMR (hereafter referred to as SMR genes; Methods) using expression quantitative trait loci (eQTLs) as genetic instruments (Supplementary Table 16) as an alternative gene-level metric and found it to saturate for n values greater than 4 million (Supplementary Fig. 23f). Note that saturation of SMR genes is partly affected by the statistical power of current eQTL studies, which do not always survey biologically relevant tissues and cell types for height. Therefore, we can expect more genes to be prioritized when integrating GWAS summary statistics from this study with those from larger eQTL studies that may be available in the future and may involve more tissue types. Gene-level metrics were also not substantially affected by adding non-EUR samples, again consistent with broadly similar sets of genes affecting height across ancestries.

At the level of variants and genomic regions, we saw a steady and almost linear increase in the number of GWS SNPs as a function of sample size, as previously reported⁴⁴. However, given that newly identified variants tend to cluster near ones identified at smaller sample sizes, we also saw a saturation in the number of loci identified for n values greater than 2.5 million, where the upward trend starts to weaken (Supplementary

Table 2 Overview of five European-ancestry GWASs re-analysed in our study to quantify the relationship between sample size and discovery

Down-sampled GWAS	Max <i>n</i> (mean <i>n</i>)	Number of GWS COJO SNPs	Percentage of the genome covered by GWS loci (35 kb) (%)
Lango Allen et al. (2010) ^{19a}	130,010 (128,942)	240	0.5
Wood et al. (2014) ²⁰	241,724 (239,227)	633	1.4
Yengo et al. (2018) ³	695,648 (688,927)	2,794	5.8
GIANT-EUR (no 23andMe)	1,632,839 (1,502,499)	4,867	9.7
23andMe-EUR	2,502,262 (2,498,336)	7,020	13.6

Summary statistics from the three published GWASs were imputed using the ImpG-Summary software to maximize the coverage of HM3 SNPs (Methods). GWS loci are defined as in the legend of Table 1.

^aSummary statistics from the Lango Allen et al. study¹⁹, initially over-corrected for population stratification using a double genomic control correction, were re-inflated such that the LD score regression intercept estimated from re-inflated test statistics equals 1.

Fig. 24a). We found a similar pattern for the percentage of the genome covered by GWS loci, with the degree of saturation varying as a function of the window size used to define loci (Supplementary Fig. 24b). The observed saturation in PGS prediction accuracy (both within ancestry—that is, in EUR—and multi-ancestry) was more noticeable than that of the number and genomic coverage of GWS loci. In fact, increasing the sample size from 2.5 million to 4 million by adding another 1.5 million EUR samples increased the number of GWS SNPs from 7,020 to 9,863—that is, an increase of around 1.4-fold $((9,863 - 7,020)/7,020)$ —but the absolute increase in prediction accuracy is less than 2.7%. This improvement is mainly observed in EUR but remains lower than 1.3% in individuals of the EAS and AFR ancestry groups. However, adding another approximately 1 million participants of non-EUR improves the multi-ancestry prediction accuracy by more than 3.4% (Supplementary Fig. 24c), highlighting the value of including non-EUR populations.

Altogether, these analyses show that increasing the GWAS sample size not only increases the prediction accuracy, but also sheds more light on the genomic distribution of causal variants and, at all but the largest sample sizes, the genes proximal to these variants. By contrast, enrichment of higher-level, broadly defined biological categories such as gene sets and pathways and functional annotations can be identified using relatively small sample sizes ($n \approx 0.25$ million for height). Of note, we confirm that increased genetic diversity in GWAS discovery samples significantly improves the prediction accuracy of PGSs in under-represented ancestries.

Discussion

By conducting one of the largest GWASs so far in 5.4 million individuals, with a primary focus on common genetic variation, we have provided insights into the genetic architecture of height—including a saturated genomic map of 12,111 genetic associations for height. Consistent with previous studies^{19,20}, we have shown that signal density of associations (known and novel) is not randomly distributed across the genome; rather, associated variants are more likely to be detected around genes that have been previously associated with Mendelian disorders of growth. Furthermore, we observed a strong genetic overlap of association across cohorts with various ancestries. Effect estimates of associated SNPs are moderately to highly correlated (minimum = 0.64; maximum = 0.99), suggesting even larger correlations of effect sizes of underlying causal variants¹³. Moreover, although there are significant

differences in power to detect an association between cohorts with European and non-European ancestries, most genetic associations for height observed in populations with non-European ancestry lie in close proximity and in linkage disequilibrium to associations identified within populations of European ancestry.

By increasing our experimental sample size to more than seven times that of previous studies, we have explained up to 40% of the inter-individual variation in height in independent European-ancestry samples using GWS SNPs alone, and more than 90% of h^2_{SNP} across diverse populations when incorporating all common SNPs within 35 kb of GWS SNPs. This result highlights that future investigations of common (MAF > 1%) genetic variation associated with height in many ancestries will be most likely to detect signals within the 7,209 GWS loci that we have identified in the present study. A question for the future is whether rare genetic variants associated with height are also concentrated within the same loci. We provide suggestive evidence supporting this hypothesis from analysing imputed SNPs with $0.1\% < \text{MAF} < 1\%$ (Supplementary Note 6, Extended Data Fig. 10 and Supplementary Fig. 25). Our results are consistent with findings from a previous study⁴⁵, which showed across 492 traits a strong colocalization between common and rare coding variants associated with the same trait. Nevertheless, our conclusions remain limited by the relatively low performances of imputation in this MAF regime^{46,47}. Therefore, large samples with whole-genome sequences will be required to robustly address this question. Such datasets are increasingly becoming available^{48–50}. Separately, previous studies have reported a significant enrichment of height heritability near genes as compared to inter-genic regions (that is, >50 kb away from the start or stop genomic position of genes)⁵¹. Our findings are consistent with but not reducible to that observation, given that up to 31% of GWS SNPs identified in this study lie more than 50 kb away from any gene.

Our study provides a powerful genetic predictor of height based on 12,111 GWS SNPs, for which accuracy reaches around 40% (that is, 80% of h^2_{SNP}) in individuals of European ancestries and up to around 10% in individuals of predominantly African ancestries. Notably, we show using a previously developed method³⁸ that LD and MAF differences between European and African ancestries can explain up to around 84% (s.e. 1.5%) of the loss of prediction accuracy between these populations (Methods), with the remaining loss being presumably explained by differences in heritability between populations and/or differences in effect sizes across populations (for example, owing to gene-by-gene or gene-by-environment interactions). This observation is consistent with common causal variants for height being largely shared across ancestries. Therefore, we anticipate that fine-mapping of GWS loci identified in this study, ideally using methods that can accommodate dense sets of signals and large populations with African ancestries, would substantially improve the accuracy of a derived height PGS for populations of non-European ancestry. Our study has a large number of participants with African ancestries as compared with previous efforts. However, we emphasize that further increasing the size of GWASs in populations of non-European ancestry, including those with diverse African ancestries, is essential to bridge the gap in prediction accuracy—particularly as most studies only partially capture the wide range of ancestral diversity both within Africa and globally. Such increased sample sizes would help to identify potential ancestry-specific causal variants, to facilitate ancestry-specific fine-mapping and to inform gene–environment and gene–ancestry interactions. Another important finding of our study is to show how individual PGS can be optimally combined with familial information and thereby improve the overall accuracy of height prediction to above 54% in populations of European ancestry.

Although large sample sizes are needed to pinpoint the variants responsible for the heritability of height (and larger samples in multiple ancestries will probably be required to map these at finer scale), the prioritization of relevant genes and gene sets is feasible at smaller

sample sizes than that required to account for the common variant heritability. Thus, the sample sizes required for saturation of GWAS are smaller for identifying enriched gene sets, with the identification of genes implicated as potentially causal and mapping of genomic regions containing associated variants requiring successively larger sample sizes. Furthermore, unlike prediction accuracy, prioritization of genes that are likely to be causal and even mapping of associated regions is consistent across ancestries, reflecting the expected similarity in the biological architecture of human height across populations. Recent studies using UKB data predicted that GWAS sample sizes of just over 3 million individuals are required to identify 6,000–7,000 GWS SNPs explaining more than 90% of the SNP-based heritability of height⁵². We showed empirically that these predictions are downwardly biased given that around 10,000 independent associations are, in fact, required to explain 80–90% of the SNP-based heritability of height in EUR individuals. Discrepancies between observed and predicted levels of saturation could be explained by several factors, such as (i) heterogeneity of SNP effects between cohorts and background ancestries, which may have reduced the statistical power of our study as compared to a homogenous sample like UKB; (ii) inconsistent definitions of GWS SNPs (using COJO in this study versus standard clumping in ref.⁵²); and, most importantly, (iii) misspecification of the SNP-effects distribution assumed to make these predictions. Nevertheless, if these predictions reflect proportional levels of saturation between traits, then we could expect that two- to tenfold larger samples would be required for GWASs of inflammatory bowel disease ($\times 2$, that is, $n = 10$ million), schizophrenia ($\times 7$; $n = 35$ million) or BMI ($\times 10$; $n = 50$ million) to reach a similar saturation of 80–90% of SNP-based heritability.

Our study has a number of limitations. First, we focused on SNPs from the HM3 panel, which only partially capture common genetic variation. However, although a significant fraction of height variance can be explained by common SNPs outside the HM3 SNPs panel, we showed that the extra information (also referred to as ‘hidden heritability’) remains concentrated within GWS loci identified in our HM3-SNP-based analyses (Extended Data Fig. 6). This result underlines the widespread allelic heterogeneity at height-associated loci. Another limitation of our study is that we determined conditional associations using a EUR LD reference ($n \approx 350,000$), which is sub-optimal given that around 24% of our discovery sample is of non-European ancestry. We emphasize that no analytical tool with an adequately large multi-ancestry reference panel is at present available to properly address how to identify conditionally independent associations in a multi-ancestry study. Fine-mapping of variants remains a particular challenge when attempted across ancestries in loci containing multiple signals (as is often the case for height). A third limitation of our study is our inability to perform well-powered replication analyses of genetic associations specific to populations with non-European ancestries, owing to the current limited availability of such data. Finally, as with all GWASs, definitive identification of effector genes and the mechanisms by which genes and variants influence phenotype remains a key bottleneck. Therefore, progress towards identifying causal genes from GWAS of height may be achieved by a combination of increasingly large whole-exome sequencing studies, allowing straightforward SNP-to-gene mapping⁴⁵, the use of relevant complementary data (for example, context-specific eQTLs in relevant tissues and cell types) and the development of computational methods that can integrate these data.

In summary, our study has been able to show empirically that the combined additive effects of tens of thousands of individual variants, detectable with a large enough experimental sample size, can explain substantial variation in a human phenotype. For human height, we show that studies of the order of around 5 million participants of various ancestries provide enough power to map more than 90% (around 100% in populations of European ancestry) of genetic variance explained by common SNPs down to around 21% of the genome. Mapping the missing 5–10% of SNP-based heritability not accounted for in the four

non-European ancestries studied here will require additional and directed efforts in the future.

Height has been used as a model trait for the study of human polygenic traits, including common diseases, because of its high heritability and relative ease of measurement, which enable large sample sizes and increased power. Conclusions about the genetic architecture, sample size requirements for additional GWAS discovery and scope for polygenic prediction that were initially made for height have by-and-large agreed with those for common disease. If the results from this study can also be extrapolated to disease, this would suggest that substantially increased sample sizes could largely resolve the heritability attributed to common variation to a finite set of SNPs (and small genomic regions). These variants and regions would implicate a particular subset of genes, regulatory elements and pathways that would be most relevant to address questions of function, mechanism and therapeutic intervention.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41586-022-05275-y>.

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Loïc Yengo^{1,500,53}, Sailaja Vedantam^{2,3,500}, Eirini Marouli^{1,500}, Julia Sidorenko¹, Eric Bartell^{2,3,5}, Saori Sakaue^{3,6,7,8}, Marielisa Graff⁹, Anders U. Eliassen^{10,11}, Yunxuan Jiang¹², Sridharan Raghavan^{13,14}, Jenkai Miao^{2,3}, Joshua D. Arias¹⁵, Sarah E. Graham¹⁶, Ronen E. Mukamel^{13,17,18}, Cassandra N. Spracklen^{19,20}, Xianyong Yin²¹, Shyh-Huei Chen²², Teresa Ferreira²³, Heather H. Highland⁹, Yingjie Ji²⁴, Tugce Karaderi^{25,26}, Kuang Lin²⁷, Kreete Lüll²⁸, Deborah E. Malden²⁷, Carolina Medina-Gomez²⁹, Moara Machado³⁰, Amy Moore³⁰, Sina Rüeger^{31,32}, Xueling Sim³³, Scott Vrieze³⁴, Tarunveer S. Ahluwalia^{35,36}, Masato Akiyama^{6,37}, Matthew A. Allison³⁸, Marcus Alvarez³⁹, Mette K. Andersen⁴⁰, Alireza Ani^{41,42}, Vivek Appadurai⁴³, Liubov Arbeeva⁴⁴, Seema Bhaskar⁴⁵, Lawrence F. Bielak⁴⁶, Sailalitha Bollepalli⁴⁷, Lori L. Bonnycastle⁴⁸, Jette Bork-Jensen⁴⁰, Jonathan P. Bradfield^{49,50}, Yuki Bradford⁵¹, Peter S. Braund^{52,53}, Jennifer A. Brody⁵⁴, Kristoffer S. Burgdorf^{55,56}, Brian E. Cade^{5,57}, Hui Cai⁵⁸, Qiuyin Cai⁵⁸, Archie Campbell⁵⁹, Marisa Cañadas-Garre⁶⁰, Eulalia Catamo⁶¹, Jin-Fang Chai³³, Xiaoran Chai^{62,63}, Li-Ching Chang⁶⁴, Yi-Cheng Chang^{64,65,66}, Chien-Hsiun Chen⁶⁴, Alessandra Chesi^{67,68}, Seung Hoan Choi⁶⁹, Ren-Hua Chung⁷⁰, Massimiliano Cocca⁶¹, Maria Pina Concas⁶¹, Christian Couture⁷¹, Gabriel Cuellar-Partida^{12,72}, Rebecca Danning⁷³, E. Warwick Daw⁷⁴, Frauke Degenhard⁷⁵, Graciela E. Delgado⁷⁶, Alessandro Delitala⁷⁷, Ayse Demirkan^{78,79}, Xuan Deng⁸⁰, Poornima Devineni⁸¹, Alexander Dietl^{82,83}, Maria Dimitriou⁸⁴, Latchezar Dimitrov⁸⁵, Rajkumar Dorajoo^{86,87}, Arif B. Ekici⁸⁸, Jorgen E. Engmann⁸⁹, Zamy Fairhurst-Hunter²⁷, Aliko-Eleni Farmaki⁸⁴, Jessica D. Faul⁹⁰, Juan-Carlos Fernandez-Lopez⁹¹, Lukas Forer⁹², Margherita Francescato⁹³, Sandra Freitag-Wolf⁹⁴, Christian Fuchsberger⁹⁵, Tessel E. Galesloot⁹⁶, Yan Gao⁹⁷, Zishan Gao^{98,99,100}, Frank Geller¹⁰¹, Olga Giannakopoulou⁴, Franco Giuliani⁷³, Anette P. Gjesing⁴⁰, Anuj Goel^{26,102}, Scott D. Gordon¹⁰³, Mathias Gorski⁸², Jakob Grove^{104,105,106}, Xiuqing Guo¹⁰⁷, Stefan Gustafsson¹⁰⁸, Jeffrey Haessler¹⁰⁹, Thomas F. Hansen^{43,56,110}, Aki S. Havulinna^{47,111}, Simon J. Haworth^{112,113}, Jing He⁵⁸, Nancy Heard-Costa^{114,115}, Prashantha Hebbar¹¹⁶, George Hindy^{3,117}, Yuk-Lam A. Ho¹¹⁸, Edith Hofer^{119,120}, Elizabeth Holliday¹²¹, Katrin Horn^{122,123}, Whitney E. Hornsby¹⁶, Jouke-Jan Hottenga¹²⁴, Hongyan Huang¹²⁵, Jie Huang^{126,127}, Alicia Huerta-Chagoya^{128,129,130}, Jennifer E. Huffman¹¹⁸, Yi-Jen Hung¹³¹, Shaofeng Huo¹³², Mi Yeong Hwang¹³³, Hiroyuki Iha¹³⁴, Daisuke D. Ikeda¹³⁴, Masato Isono¹³⁵, Anne U. Jackson²¹, Susanne Jäger^{136,137}, Iris E. Jansen^{138,139}, Ingegerd Johansson^{140,141}, Jost B. Jonas^{142,143,144,145}, Anna Jonsson⁴⁰, Torben Jørgensen^{146,147}, Ioanna-Panagiota Kalafati⁸⁴, Masahiro Kanai^{3,6,7}, Stavroula Kanoni⁴, Line L. Kärhus¹⁴⁶, Anuradhani Kasturiratne¹⁴⁸, Tomohiro Katsuya¹⁴⁹, Takahisa Kawaguchi¹⁵⁰, Rachel L. Kember¹⁵¹, Katherine A. Kentistou^{152,153}, Han-Na Kim^{154,155}, Young Jin Kim¹³³, Marcus E. Kleber^{76,156}, Maria J. Knol⁷⁸, Azra Kurbasic¹⁵⁷, Marie Lauzon¹⁰⁷, Phuong Le^{158,159}, Rodney Lea¹⁶⁰, Jong-Young Lee¹⁶¹, Hampton L. Leonard^{162,163,164}, Shengchao A. Li^{15,165}, Xiaohui Li¹⁰⁷, Xiaoyin Li^{166,496}, Jingjing Liang¹⁶⁶, Honghuang Lin¹⁶⁷, Shih-Yi Lin¹⁶⁸, Jun Liu^{27,78}, Xueping Liu¹⁰¹, Ken Sin Lo¹⁶⁹, Jirong Long⁵⁸, Laura Lores-Motta¹⁷⁰, Jian'an Luan¹⁷¹, Valeriya Lyssenko^{172,173}, Leo-Pekka Lyytikäinen^{174,175,176}, Anubha Mahajan^{26,498}, Vasiliki Mamakou¹⁷⁷, Massimo Mangino^{178,179}, Ani Manichaikul¹⁸⁰, Jonathan Marten¹⁸¹, Manuel Mattheisen^{104,182,183}, Laven Mavarani¹⁸⁴, Aaron F. McDaid^{31,32}, Karina Meidtnie^{136,137}, Tori L. Melendez¹⁶, Josep M. Mercader^{185,188,186}, Yuri Milaneschi¹⁸⁷, Jason E. Miller^{188,189}, Iona Y. Millwood^{22,190}, Pashupati P. Mishra^{174,175}, Ruth E. Mitchell^{112,191}, Line T. Møllehave¹⁴⁶, Anna Morgan⁶¹, Soeren Mucha¹⁹², Matthias Munz¹⁹², Masahiro Nakatochi¹⁹³, Christopher P. Nelson^{52,53}, Maria Nethander^{194,195}, Chu Won Nho¹⁹⁶, Aneta A. Nielsen¹⁹⁷, Ilija M. Nolte⁴¹, Suraj S. Nongmalithem^{45,198}, Raymond Noordam¹⁹⁹, Ioanna Ntalla⁴, Teresa Nutile²⁰⁰, Anita Pandit²¹, Paraskevi Christofidou¹⁷⁸, Katri Pärna^{28,41}, Marc Paupere¹⁷⁰, Eva R. B. Petersen²⁰¹, Liselotte V. Petersen^{105,202}, Niina Pitkänen^{203,204}, Ozren Polasek^{205,206}, Alaitz Poveda¹⁵⁷, Michael H. Preuss^{207,208}, Saiju Pyarajan^{5,57,81}, Laura M. Raffield¹⁹, Hiromi Rakugi¹⁴⁹, Julia Ramirez^{4,209,210}, Asif Rasheed²¹¹, Dennis Raven²¹², Nigel W. Rayner^{26,198,213,214}, Carlos Riveros^{215,216}, Rebecca Rohde⁹, Daniela Ruggiero^{200,217}, Sanni E. Ruotsalainen⁴⁷, Kathleen A. Ryan^{218,219}, Maria Sabater-Lleal^{220,221}, Richa Saxena^{3,186}, Markus Scholz^{122,123}, Anoop Sendamarai⁸¹, Botong Shen²²², Jingchunzi Shi¹², Jae Hun Shin²²³, Carlo Sidore²²⁴, Colleen M. Sitlani¹⁵⁴, Roderick C. Sliker^{225,226,227}, Roelof A. J. Smit^{207,228}, Albert V. Smith^{46,229}, Jennifer A. Smith^{46,90}, Laura J. Smyth⁶⁰, Lorraine Southam^{213,230}, Valgerdur Steinthorsdottir²³¹, Liang Sun¹³², Fumihiko Takeuchi¹³⁵, Divya Sri Priyanka Tallapragada^{45,232}, Kent D. Taylor¹⁰⁷, Bamidele O. Tayo²³³, Catherine Tcheandjieu^{234,235}, Natalie Terzikhan⁷⁸, Paola Tesolin⁹³, Alexander Teumer^{236,237}, Elizabeth Theusch²³⁸, Deborah J. Thompson^{239,240}, Gudmar Thorleifsson²³¹, Paul R. H. J. Timmers^{152,181}, Stella Trompet^{199,241}, Constance Turman¹²⁵, Simona Vaccargiu²²⁴, Sander W. van der Laan²⁴², Peter J. van der Most⁴⁴, Jan B. van Klinken^{243,244,245}, Jessica van Setten²⁴⁶, Shefali S. Verma⁶⁷, Niek Verweij²⁴⁷, Yogasudha Veturi⁵¹, Carol A. Wang^{215,216}, Chaolong Wang^{86,248}, Lihua Wang⁷⁴, Zhe Wang²⁰⁷, Helen R. Warren^{4,249}, Wen Bin Wei²⁵⁰, Ananda R. Wickremasinghe¹⁴⁸, Matthias Wielscher^{251,252}, Kerri L. Wiggins⁵⁴, Bendik S. Winsvold^{253,254}, Andrew Wong²⁵⁵, Yang Wu¹, Matthias Wuttke^{256,257}, Rui Xia²⁵⁸, Tian Xie⁴¹, Ken Yamamoto²⁵⁹, Jingyun Yang^{260,261},

Jie Yao¹⁰⁷, Hannah Young³⁴, Noha A. Yousri^{262,263}, Lei Yu^{260,261}, Lingyao Zeng²⁶⁴, Weihua Zhang^{265,266}, Xinyuan Zhang⁵¹, Jing-Hua Zhao²⁶⁷, Wei Zhao⁴⁶, Wei Zhou^{3,268,269,270}, Martina E. Zimmermann⁸², Magdalena Zoledziowska²²⁴, Linda S. Adair^{271,272}, Hieab H. H. Adams^{273,274,275}, Carlos A. Aguilar-Salinas^{276,277}, Fahd Al-Mulla¹¹⁶, Donna K. Arnett²⁷⁸, Folkert W. Asselbergs^{246,279,280}, Bjørn Olav Åsvold^{281,282,283}, John Attia¹²¹, Bernhard Banas²⁸⁴, Stefania Bandinelli²⁸⁵, David A. Bennett^{260,261}, Tobias Bergler²⁸⁴, Dwaipayan Bharadwaj²⁸⁶, Ginevra Biino²⁸⁷, Hans Bisgaard¹⁰, Eric Boerwinkle²⁸⁸, Carsten A. Böger^{284,289,290}, Klaus Bønnelykke¹⁰, Dorret I. Boomsma¹²⁴, Anders D. Børglum^{104,105,291,292}, Judith B. Borja^{293,294}, Claude Bouchard²⁹⁵, Donald W. Bowden^{85,296}, Ivan Brandslund^{297,298}, Ben Brumpton^{281,299}, Julie E. Buring^{5,73}, Mark J. Caulfield^{4,249}, John C. Chambers^{265,266,300,301}, Giriraj R. Chandak^{45,302}, Stephen J. Chanock¹⁵, Nish Chaturvedi²⁵⁵, Yii-Der Ida Chen¹⁰⁷, Zhengming Chen^{27,190}, Ching-Yu Cheng^{62,303}, Ingrid E. Christophersen^{304,305}, Marina Ciullo^{200,217}, John W. Cole^{306,307}, Francis S. Collins⁴⁸, Richard S. Cooper²³³, Miguel Cruz³⁰⁸, Francesco Cucca^{224,309}, L. Adrienne Cupples^{80,115}, Michael J. Cutler³¹⁰, Scott M. Damrauer^{51,311,312}, Thomas M. Dantoft¹⁴⁶, Gert J. de Borst³¹³, Lisette C. P. G. M. de Groot³¹⁴, Philip L. De Jager^{3,315}, Dominique P. V. de Kleijn³¹³, H. Janaka de Silva¹⁴⁸, George V. Dedoussis⁸⁴, Anneke I. den Hollander¹⁷⁰, Shufa Du^{271,272}, Douglas F. Easton^{239,316}, Petra J. M. Elders³¹⁷, A. Heather Eliassen^{57,125,318}, Patrick T. Ellinor^{68,319,320}, Sölve Elmståhl³²¹, Jeanette Erdmann¹⁹², Michele K. Evans²²², Diane Fatkin^{322,323,324}, Bjarke Feenstra¹⁰¹, Mary F. Feitosa⁷⁴, Luigi Ferrucci³²⁵, Ian Ford³²⁶, Myriam Fornage^{258,327}, Andre Franke⁷⁵, Paul W. Franks^{157,318,328}, Barry I. Freedman³²⁹, Paolo Gasparini^{161,93}, Christian Gieger^{99,137}, Giorgia Grotto^{61,93}, Michael E. Goddard^{330,331}, Yvonne M. Golightly^{9,44,332,333}, Clicerio Gonzalez-Villalpando³³⁴, Penny Gordon-Larsen^{271,272}, Harald Grallert^{99,137}, Struan F. A. Grant^{49,335,336,337}, Niels Grarup⁴⁰, Lyn Griffiths¹⁶⁰, Vilmundur Gudnason^{229,338}, Christopher Haiman³³⁹, Hakon Hakonarson^{49,335,340,341}, Torben Hansen⁴⁰, Catharina A. Hartman²¹², Andrew T. Hattersley³⁴², Caroline Hayward¹⁸¹, Susan R. Heckbert³⁴³, Chew-Kiat Heng^{344,345}, Christian Hengstenberg³⁴⁶, Alex W. Hewitt^{347,348,349}, Haretsugu Hishigaki¹³⁴, Carel B. Hoyng¹⁷⁰, Paul L. Huang^{5,320,350}, Wei Huang³⁵¹, Steven C. Hunt^{262,352}, Kristian Hveem^{281,282}, Elina Hyppönen^{353,354}, William G. Iacono³⁴, Sahoko Ichihara³⁵⁵, M. Arfan Ikram⁷⁸, Carmen R. Isasi³⁵⁶, Rebecca D. Jackson³⁵⁷, Marjo-Riitta Jarvelin^{251,358,359,360}, Zi-Bing Jin^{145,361}, Karl-Heinz Jöckel¹⁸⁴, Peter K. Joshi¹⁵³, Pekka Jousilahti¹¹¹, J. Wouter Jukema^{241,362,363}, Mika Kähönen^{364,365}, Yoichiro Kamatani^{6,366}, Kui Dong Kang³⁶⁷, Jaakko Kaprio⁴⁷, Sharon L. R. Kardia⁴⁶, Fredrik Karpe^{214,368}, Norihiro Kato³³⁵, Frank Kee⁶⁰, Thorsten Kessler^{264,369}, Amit V. Khera^{3,186}, Chiea Chuen Khor⁸⁶, Lambertus A. L. M. Kiemeny^{36,370}, Bong-Jo Kim¹³³, Eung Kweon Kim^{371,372}, Hyung-Lae Kim³⁷³, Paulus Kirchhof^{374,375,376,377}, Mika Kivimäki³⁷⁸, Woon-Puay Koh³⁷⁹, Heikki A. Koistinen^{111,380,381}, Genovefa D. Kolovou³⁸², Jaspal S. Kooner^{265,301,383,384}, Charles Kooperberg¹⁰⁹, Anna Köttgen²⁵⁶, Peter Kovacs³⁸⁵, Adriaan Kraaijeveld²⁴⁶, Peter Kraft¹²⁵, Ronald M. Krauss²³⁸, Meena Kumari³⁸⁶, Zoltan Kutalik^{31,32}, Markku Laakso³⁸⁷, Leslie A. Lange³⁸⁸, Claudia Langenberg^{171,389}, Lenore J. Launer²²², Loic Le Marchand³⁹⁰, Hyejin Lee³⁹¹, Nanette R. Lee²⁹³, Terho Lehtimäki^{174,175}, Huaixing Li¹³², Liming Li^{1392,393}, Wolfgang Lieb³⁹⁴, Xu Lin^{132,395}, Lars Lind¹⁰⁸, Allan Linneberg^{146,396}, Ching-Ti Liu⁸⁰, Jianjun Liu⁸⁶, Markus Loeffler^{122,123}, Barry London²⁹⁷, Steven A. Lubitz^{69,319,320}, Stephen J. Lye³⁹⁸, David A. Mackey^{347,349}, Reedik Mägi¹²⁸, Patrik K. E. Magnusson³⁹⁹, Gregory M. Marcus⁴⁰⁰, Pedro Marques Vidal^{401,402}, Nicholas G. Martin¹⁰³, Winfried März^{76,403,404}, Fumihiko Matsuda¹⁵⁰, Robert W. McGarrah^{405,406}, Matt McGue³⁴, Amy Jayne McKnight⁶⁰, Sarah E. Medland⁴⁰⁷, Dan Mellström^{194,408}, Andres Metspalu²⁸, Braxton D. Mitchell^{218,219,409}, Paul Mitchell⁴¹⁰, Dennis O. Mook-Kanamori^{228,411}, Andrew D. Morris⁴¹², Lorelei A. Mucci¹²⁵, Patricia B. Munroe^{4,249}, Mike A. Nalls^{162,163,164}, Saman Nazarian⁴¹³, Amanda E. Nelson^{44,414}, Matt J. Neville^{214,368}, Christopher Newton-Cheh^{186,320}, Christopher S. Nielsen^{415,416}, Markus M. Nöthen⁴¹⁷, Claes Ohlsson^{194,418}, Albertine J. Oldehinkel²¹², Lorena Orozco⁴¹⁹, Katja Pahlkala^{203,204,420}, Päivi Pajukanta^{39,421}, Colin N. A. Palmer⁴²², Esteban J. Parra¹⁵⁹, Cristian Pattaro⁹⁰, Oluf Pedersen⁴⁰, Craig E. Pennell^{215,216}, Brenda W. J. H. Penninx⁸⁷, Louis Perusse^{71,423}, Annette Peters^{100,137,424}, Patricia A. Peyser⁴⁶, David J. Porteous⁵⁹, Danielle Posthuma¹³⁸, Chris Power⁴²⁵, Peter P. Pramstaller⁹⁵, Michael A. Province⁷⁴, Qibin Qi³⁵⁶, Jia Qu³⁶¹, Daniel J. Rader^{51,426}, Olli T. Raitakari^{203,204,427}, Sarju Ralhan⁴²⁸, Loukianos S. Rallidis⁴²⁹, Dabeeru C. Rao⁴³⁰, Susan Redline^{5,57}, Dermot F. Reilly⁴³¹, Alexander P. Reiner^{109,432}, Sang Youl Rhee⁴³³, Paul M. Ridker^{5,73}, Michiel Rienstra²⁴⁷, Samuli Ripatti^{3,47,434}, Marylyn D. Ritchie⁵¹, Dan M. Roden⁴³⁵, Frits R. Rosendaal²²⁸, Jerome I. Rotter¹⁰⁷, Igor Rudan¹⁵², Femke Rutters⁴³⁶, Charumathi Sabanayagam^{62,303}, Danish Saleheen^{211,437}, Veikko Salomaa¹¹¹, Nilesh J. Samani^{52,53}, Dharambir K. Sanghera^{438,439,440,441}, Naveed Sattar⁴⁴², Borge Schmidt¹⁸⁴, Helena Schmidt⁴⁴³, Reinhold Schmidt¹¹⁹, Matthias B. Schulze^{136,137,444}, Heribert Schunkert⁴⁴⁵, Laura J. Scott²¹, Rodney J. Scott⁴⁴⁶, Peter Sever³⁸⁴, Eric J. Shiroma²²², M. Benjamin Shoemaker⁴⁴⁷, Xiao-Ou Shu⁵⁸, Eleanor M. Simonsick³²⁵, Mario Sims⁹⁷, Jai Rup Singh⁴⁴⁸,

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Andrew B. Singleton¹⁶², Moritz F. Sinner^{369,449}, J. Gustav Smith^{450,451,452}, Harold Snieder⁴¹, Tim D. Specto¹⁷⁸, Meir J. Stampfer^{57125,318}, Klaus J. Stark⁸², David P. Strachan⁴⁵³, Leen M. 't Hart^{225,226,227,454}, Yasuharu Tabara¹⁵⁰, Hua Tang⁴⁵⁵, Jean-Claude Tardif^{168,456}, Thangavel A. Thanaraj¹¹⁶, Nicholas J. Timpson^{112,191}, Anke Tönjes³⁸⁵, Angelo Tremblay^{71,423}, Tiinamajja Tuomi^{147,173,457,458}, Jaakko Tuomilehto^{111,459,460}, Maria-Teresa Tusié-Luna^{461,462}, Andre G. Uitterlinden²⁹, Rob M. van Dam^{33,463,464}, Pim van der Harst^{246,247}, Nathalie Van der Velde^{29,465}, Cornelia M. van Duijn²⁷⁷⁸, Natasja M. van Schoor⁴⁶⁶, Veronique Vitart¹⁸¹, Uwe Völker^{237,467}, Peter Vollenweider^{401,402}, Henry Völzke^{236,237}, Niels H. Wachter-Rodarte⁴⁶⁸, Mark Walker⁴⁶⁹, Ya Xing Wang¹⁴⁵, Nicholas J. Wareham¹⁷¹, Richard M. Watanabe^{470,471,472}, Hugh Watkins^{26,102}, David R. Weir⁹⁰, Thomas M. Werge^{43,396,473}, Elisabeth Widen⁴⁷, Lynne R. Wilkens³⁹⁰, Gonneke Willemsen¹²⁴, Walter C. Willett^{125,318}, James F. Wilson^{152,181}, Tien-Yin Wong^{62,303}, Jeong-Taek Woo⁴³³, Alan F. Wright¹⁸¹, Jer-Yuarn Wu^{54,474}, Huichun Xu^{218,219}, Chittaranjan S. Yajnik⁴⁷⁵, Mitsuhiro Yokota⁴⁷⁶, Jian-Min Yuan^{477,478}, Eleftheria Zeggini^{213,230,479}, Babette S. Zemel^{51,68,337,340}, Wei Zheng⁵⁸, Xiaofeng Zhu¹⁶⁶, Joseph M. Zmuda⁴⁷⁸, Alan B. Zonderman²²², John-Anker Zwart^{253,480}, 23andMe Research Team*, VA Million Veteran Program*, DiscovEHR (DiscovEHR and MyCode Community Health Initiative)*, eMERGE (Electronic Medical Records and Genomics Network)*, Lifelines Cohort Study*, The PRACTICAL Consortium*, Understanding Society Scientific Group*, Daniel I. Chasman^{5,73}, Yoon Shin Cho²²³, Iris M. Heid⁸², Mark I. McCarthy^{26,214,497}, Maggie C. Y. Ng^{85,482}, Christopher J. O'Donnell^{15,57,483}, Fernando Rivadeneira²⁹, Unnur Thorsteinsdottir^{231,338}, Yan V. Sun^{484,485}, E. Shyong Tai^{33,463}, Michael Boehnke¹, Panos Deloukas^{4,486}, Anne E. Justice^{9,481}, Cecilia M. Lindgren^{3,23,26}, Ruth J. F. Loos^{40,207,208,487}, Karen L. Mohlke¹⁹, Kari E. North⁹, Kari Stefansson^{231,338}, Robin G. Walters^{27,190}, Thomas W. Winkler⁸², Kristin L. Young⁹, Po-Ru Loh^{3,1718}, Jian Yang^{1,488,489}, Tõnu Esko²⁸, Themistocles L. Assimes^{234,235}, Adam Auton¹², Goncalo R. Abecasis²¹, Cristen J. Willer^{16,268,490}, Adam E. Locke⁴⁹¹, Sonja I. Berndt¹⁵, Guillaume Lettre^{69,456}, Timothy M. Frayling²⁴, Yukinori Okada^{6,7,492,493,498,499,501} [✉], Andrew R. Wood^{24,501} [✉], Peter M. Visscher^{1,501} [✉] & Joel N. Hirschhorn^{2,494,495,501} [✉]

¹Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland, Australia. ²Division of Endocrinology, Boston Children's Hospital, Boston, MA, USA. ³Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, USA. ⁴William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK. ⁵Harvard Medical School, Boston, MA, USA. ⁶Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. ⁷Department of Statistical Genetics, Osaka University Graduate School of Medicine, Osaka, Japan. ⁸Divisions of Genetics and Rheumatology, Brigham and Women's Hospital and Department of Medicine, Harvard Medical School, Boston, MA, USA. ⁹Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ¹⁰COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark. ¹¹Section for Bioinformatics, Department of Health Technology, Technical University of Denmark, Copenhagen, Denmark. ¹²23andMe, Sunnyvale, CA, USA. ¹³Department of Veterans Affairs, Eastern Colorado Healthcare System, Aurora, CO, USA. ¹⁴Division of Biomedical Informatics and Personalized Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA. ¹⁵Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA. ¹⁶Department of Internal Medicine, Division of Cardiology, University of Michigan, Ann Arbor, MI, USA. ¹⁷Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA. ¹⁸Department of Medicine, Harvard Medical School, Boston, MA, USA. ¹⁹Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ²⁰Department of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA, USA. ²¹Department of Biostatistics and Center for Statistical Genetics, University of Michigan School of Public Health, Ann Arbor, MI, USA. ²²Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC, USA. ²³Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK. ²⁴Genetics of Complex Traits, College of Medicine and Health, University of Exeter, Exeter, UK. ²⁵Center for Health Data Science, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. ²⁶Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK. ²⁷Nuffield Department of Population Health, University of Oxford, Oxford, UK. ²⁸Institute of Genomics, Estonian Genome Centre, University of Tartu, Tartu, Estonia. ²⁹Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. ³⁰Division of Biostatistics and Epidemiology, RTI International, Durham, NC, USA. ³¹Center for Primary Care and Public Health, University of Lausanne, Lausanne, Switzerland. ³²Swiss Institute of Bioinformatics, Lausanne, Switzerland. ³³Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore, Singapore. ³⁴Department of Psychology, University of Minnesota, Minneapolis, MN, USA. ³⁵Steno Diabetes Center Copenhagen, Herlev, Denmark. ³⁶Department of Biology, The Bioinformatics Center, University of Copenhagen, Copenhagen, Denmark. ³⁷Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan. ³⁸Department of Family Medicine, University of California, San

Diego, La Jolla, CA, USA. ³⁹Department of Human Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA. ⁴⁰Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. ⁴¹Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. ⁴²Department of Bioinformatics, Isfahan University of Medical Sciences, Isfahan, Iran. ⁴³Institute of Biological Psychiatry, Mental Health Services, Copenhagen University Hospital, Copenhagen, Denmark. ⁴⁴Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ⁴⁵Genomic Research on Complex diseases (GRC-Group), CSIR-Centre for Cellular and Molecular Biology, Hyderabad, India. ⁴⁶Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI, USA. ⁴⁷Institute for Molecular Medicine Finland (FIMM), HILIFE, University of Helsinki, Helsinki, Finland. ⁴⁸Molecular Genetics Section, Center for Precision Health Research, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA. ⁴⁹Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA, USA. ⁵⁰Quantinuum Research, Wayne, PA, USA. ⁵¹Department of Genetics, University of Pennsylvania, Philadelphia, PA, USA. ⁵²Department of Cardiovascular Sciences, University of Leicester, Leicester, UK. ⁵³NHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, UK. ⁵⁴Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA. ⁵⁵Department of Clinical Immunology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark. ⁵⁶NovoNordic Center for Protein Research, Copenhagen University, Copenhagen, Denmark. ⁵⁷Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA. ⁵⁸Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. ⁵⁹Centre for Genomic and Experimental Medicine, Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK. ⁶⁰Centre for Public Health, Queen's University of Belfast, Belfast, UK. ⁶¹Institute for Maternal and Child Health – IRCCS, Burlo Garofolo, Trieste, Italy. ⁶²Ocular Epidemiology, Singapore Eye Research Institute, Singapore National Eye Centre, Singapore, Singapore. ⁶³Department of Ophthalmology, National University of Singapore and National University Health System, Singapore, Singapore. ⁶⁴Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan. ⁶⁵Graduate Institute of Medical Genomics and Proteomics, Medical College, National Taiwan University, Taipei, Taiwan. ⁶⁶Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan. ⁶⁷Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, USA. ⁶⁸Center for Spatial and Functional Genomics, Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA, USA. ⁶⁹Cardiovascular Disease Initiative, Broad Institute of MIT and Harvard, Cambridge, MA, USA. ⁷⁰Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan. ⁷¹Department of Kinesiology, Faculty of Medicine, Université Laval, Québec City, Quebec, Canada. ⁷²Diamantina Institute, The University of Queensland, Brisbane, Queensland, Australia. ⁷³Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA. ⁷⁴Division of Statistical Genomics, Department of Genetics, Washington University School of Medicine, St Louis, MO, USA. ⁷⁵Institute of Clinical Molecular Biology, Christian-Albrechts University of Kiel, Kiel, Germany. ⁷⁶Vth Department of Medicine, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany. ⁷⁷Dipartimento di Scienze Mediche Chirurgiche e Sperimentali, Università degli Studi di Sassari, Sassari, Italy. ⁷⁸Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. ⁷⁹Section of Statistical Multi-omics, Department of Clinical and Experimental Medicine, University of Surrey, Guildford, UK. ⁸⁰Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA. ⁸¹Center for Data and Computational Sciences, VA Boston Healthcare System, Boston, MA, USA. ⁸²Department of Genetic Epidemiology, University of Regensburg, Regensburg, Germany. ⁸³Department of Internal Medicine II, University Hospital Regensburg, Regensburg, Germany. ⁸⁴Department of Nutrition and Dietetics, School of Health and Education, Harokopio University of Athens, Athens, Greece. ⁸⁵Center for Precision Medicine, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC, USA. ⁸⁶Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore, Singapore. ⁸⁷Health Services and Systems Research, Duke-NUS Medical School, Singapore, Singapore. ⁸⁸Institute of Human Genetics, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany. ⁸⁹Institute of Cardiovascular Science, Faculty of Population Health, University College London, London, UK. ⁹⁰Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI, USA. ⁹¹Computational Genomics Department, National Institute of Genomic Medicine, Mexico City, Mexico. ⁹²Institute of Genetic Epidemiology, Medical University of Innsbruck, Innsbruck, Austria. ⁹³Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy. ⁹⁴Institute of Medical Informatics and Statistics, Kiel University, Kiel, Germany. ⁹⁵Eurac Research, Institute for Biomedicine, Affiliated Institute of the University of Lübeck, Bolzano, Italy. ⁹⁶Radboud University Medical Center, Radboud Institute for Health Sciences, Department for Health Evidence, Nijmegen, The Netherlands. ⁹⁷Jackson Heart Study, Department of Medicine, University of Mississippi, Jackson, MS, USA. ⁹⁸Nanjing University of Chinese Medicine, Nanjing, China. ⁹⁹Research Unit of Molecular Epidemiology, Institute of Epidemiology, Helmholtz Zentrum München Research Center for Environmental Health, Neuherberg, Germany. ¹⁰⁰Institute of Epidemiology, Helmholtz Zentrum München Research Center for Environmental Health, Neuherberg, Germany. ¹⁰¹Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark. ¹⁰²Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK. ¹⁰³Genetic Epidemiology, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia. ¹⁰⁴Department of Biomedicine (Human Genetics) and iSEQ Center, Aarhus University, Aarhus, Denmark. ¹⁰⁵The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus, Denmark.

- ¹⁰⁶BIRC—Bioinformatics Research Centre, Aarhus University, Aarhus, Denmark. ¹⁰⁷The Institute for Translational Genomics and Population Sciences, Department of Pediatrics, The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA, USA.
- ¹⁰⁸Department of Medical Sciences, Uppsala University, Uppsala, Sweden. ¹⁰⁹Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA. ¹¹⁰Danish Headache Center, Department of Neurology, Copenhagen University Hospital, Rigshospitalet, Rigshospitalet, Copenhagen, Denmark. ¹¹¹Department of Public Health and Welfare, Finnish Institute for Health and Welfare, Helsinki, Finland. ¹¹²MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK. ¹¹³Bristol Dental School, University of Bristol, Bristol, UK.
- ¹¹⁴Department of Neurology, Boston University School of Medicine, Boston, MA, USA.
- ¹¹⁵Framingham Heart Study, Framingham, MA, USA. ¹¹⁶Department of Genetics and Bioinformatics, Dasman Diabetes Institute, Kuwait City, Kuwait. ¹¹⁷Department of Clinical Sciences in Malmö, Lund University, Malmö, Sweden. ¹¹⁸Veterans Affairs Boston Healthcare System, Boston, MA, USA. ¹¹⁹Clinical Division of Neurogeriatrics, Department of Neurology, Medical University of Graz, Graz, Austria. ¹²⁰Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria. ¹²¹School of Medicine and Public Health, University of Newcastle, Callaghan, New South Wales, Australia. ¹²²Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Medical Faculty, Leipzig, Germany. ¹²³LIFE Research Center for Civilization Diseases, University of Leipzig, Medical Faculty, Leipzig, Germany. ¹²⁴Department of Biological Psychology, Behaviour and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.
- ¹²⁵Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA.
- ¹²⁶School of Public Health and Emergency Management, Southern University of Science and Technology, Shenzhen, China. ¹²⁷Institute for Global Health and Development, Peking University, Beijing, China. ¹²⁸Programs in Metabolism and Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA, USA. ¹²⁹Departamento de Medicina Genómica y Toxicología Ambiental, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México Ciudad Universitaria, Mexico City, Mexico. ¹³⁰Unidad de Biología Molecular y Medicina Genómica, Instituto Nacional de Ciencias Médicas y Nutrición, Mexico City, Mexico. ¹³¹Division of Endocrine and Metabolism, Tri-Service General Hospital Songshan Branch, Taipei, Taiwan. ¹³²Shanghai Institute of Nutrition and Health, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai, China. ¹³³Division of Genome Science, Department of Precision Medicine, National Institute of Health, Cheongju, Republic of Korea. ¹³⁴Biomedical Technology Research Center, Tokushima Research Institute, Otsuka Pharmaceutical Co., Tokushima, Japan. ¹³⁵Research Institute, National Center for Global Health and Medicine, Tokyo, Japan. ¹³⁶Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany. ¹³⁷German Center for Diabetes Research (DZD), Neuherberg, Germany. ¹³⁸Department of Complex Trait Genetics, Center for Neurogenetics and Cognitive Research, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands. ¹³⁹Department of Child and Adolescent Psychiatry and Pediatric Psychology, Section Complex Trait Genetics, Amsterdam Neuroscience, Vrije Universiteit Medical Center, Amsterdam, The Netherlands. ¹⁴⁰Department of Biobank Research, Umeå University, Umeå, Sweden. ¹⁴¹Department of Odontology, Umeå University, Umeå, Sweden. ¹⁴²Institute of Molecular and Clinical Ophthalmology Basel, Basel, Switzerland. ¹⁴³Privatpraxis Prof Jonas und Dr Panda-Jonas, Heidelberg, Germany.
- ¹⁴⁴Department of Ophthalmology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany. ¹⁴⁵Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Ophthalmology and Visual Sciences Key Laboratory, Beijing, China. ¹⁴⁶Center for Clinical Research and Prevention, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark.
- ¹⁴⁷Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. ¹⁴⁸Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka. ¹⁴⁹Department of Geriatric and General Medicine, Osaka University Graduate School of Medicine, Suita, Japan. ¹⁵⁰Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan. ¹⁵¹Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA. ¹⁵²Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, UK. ¹⁵³Centre for Cardiovascular Sciences, Queens Medical Research Institute, University of Edinburgh, Edinburgh, UK. ¹⁵⁴Medical Research Institute, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.
- ¹⁵⁵Department of Clinical Research Design and Evaluation (SAIHST), Sungkyunkwan University, Seoul, Republic of Korea. ¹⁵⁶SYNLAB MVZ Humangenetik Mannheim, Mannheim, Germany. ¹⁵⁷Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University, Malmö, Sweden. ¹⁵⁸Department of Computer Science, University of Toronto, Toronto, Ontario, Canada. ¹⁵⁹Department of Anthropology, University of Toronto at Mississauga, Mississauga, Ontario, Canada. ¹⁶⁰Genomics Research Centre, Centre for Genomics and Personalised Health, School of Biomedical Sciences, Queensland University of Technology, Kelvin Grove, Queensland, Australia. ¹⁶¹Oneomics, Soonchunhyang Mirai Medical Center, Bucheon-si, Republic of Korea. ¹⁶²Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA. ¹⁶³Center for Alzheimer's and Related Dementias, National Institutes of Health, Bethesda, MD, USA. ¹⁶⁴Data Tecnica International, Glen Echo, MD, USA. ¹⁶⁵Cancer Genomics Research Laboratory, Leidos Biomedical Research, Rockville, MD, USA. ¹⁶⁶Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH, USA. ¹⁶⁷Department of Medicine, University of Massachusetts Chan Medical School, Worcester, MA, USA. ¹⁶⁸Center for Geriatrics and Gerontology, Taichung Veterans General Hospital, Taichung, Taiwan. ¹⁶⁹Montreal Heart Institute, Montreal, Quebec, Canada. ¹⁷⁰Departments of Ophthalmology and Human Genetics, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.
- ¹⁷¹MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Cambridge, UK. ¹⁷²Department of Clinical Science, Center for Diabetes Research, University of Bergen, Bergen, Norway. ¹⁷³Department of Clinical Sciences, Lund University Diabetes Centre, Malmö, Sweden. ¹⁷⁴Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland. ¹⁷⁵Department of Clinical Chemistry, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland. ¹⁷⁶Department of Cardiology, Heart Center, Tampere University Hospital, Tampere, Finland. ¹⁷⁷National and Kapodistrian University of Athens, Dromokaiteio Psychiatric Hospital, Athens, Greece. ¹⁷⁸Department of Twin Research and Genetic Epidemiology, King's College London, London, UK. ¹⁷⁹NIHR Biomedical Research Centre at Guy's and St Thomas' Foundation Trust, London, UK. ¹⁸⁰Center for Public Health Genomics, University of Virginia School of Medicine, Charlottesville, VA, USA. ¹⁸¹MRC Human Genetics Unit, Institute of Genetics and Cancer, University of Edinburgh, Western General Hospital, Edinburgh, UK. ¹⁸²Department of Psychiatry and Department of Community Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada. ¹⁸³Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany. ¹⁸⁴Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, Essen, Germany. ¹⁸⁵Diabetes Unit, Massachusetts General Hospital, Boston, MA, USA. ¹⁸⁶Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA. ¹⁸⁷Department of Psychiatry, Amsterdam Public Health and Amsterdam Neuroscience, Amsterdam UMC and Vrije Universiteit, Amsterdam, The Netherlands. ¹⁸⁸Biomedical and Translational Informatics Institute, Geisinger, Danville, PA, USA. ¹⁸⁹Department of Genetics, Institute for Biomedical Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ¹⁹⁰MRC Population Health Research Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK. ¹⁹¹Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK.
- ¹⁹²Institute for Cardiogenetics, University of Lübeck, DZHK (German Research Centre for Cardiovascular Research) partner site Hamburg/Lübeck/Kiel and University Heart Center Lübeck, Lübeck, Germany. ¹⁹³Public Health Informatics Unit, Department of Integrated Health Sciences, Nagoya University Graduate School of Medicine, Nagoya, Japan. ¹⁹⁴Centre for Bone and Arthritis Research, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.
- ¹⁹⁵Bioinformatics Core Facility, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. ¹⁹⁶Korea Institute of Science and Technology, Gangneung Institute of Natural Products, Gangneung, Republic of Korea. ¹⁹⁷Department of Clinical Biochemistry, Lillebaelt Hospital, Kolding, Denmark. ¹⁹⁸Department of Human Genetics, Wellcome Sanger Institute, Hinxton, UK. ¹⁹⁹Department of Internal Medicine, Section of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands. ²⁰⁰Institute of Genetics and Biophysics A. Buzzati-Traverso, CNR, Naples, Italy. ²⁰¹Department of Clinical Biochemistry and Immunology, Hospital of Southern Jutland, Aabenraa, Denmark. ²⁰²The National Centre for Register-based Research, University of Aarhus, Aarhus, Denmark. ²⁰³Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland. ²⁰⁴Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland. ²⁰⁵Medical School, University of Split, Split, Croatia. ²⁰⁶Algebra University College, Zagreb, Croatia. ²⁰⁷The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ²⁰⁸Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ²⁰⁹Aragon Institute of Engineering Research, University of Zaragoza, Zaragoza, Spain. ²¹⁰Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Madrid, Spain. ²¹¹Center for Non-Communicable Diseases, Karachi, Pakistan. ²¹²Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion Regulation, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. ²¹³Institute of Translational Genomics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany. ²¹⁴Present address: Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, Churchill Hospital, Oxford, UK. ²¹⁵Hunter Medical Research Institute, New Lambton Heights, New South Wales, Australia. ²¹⁶School of Medicine and Public Health, College of Health, Medicine and Wellbeing, The University of Newcastle, New Lambton Heights, New South Wales, Australia. ²¹⁷IRCCS Neuromed, Pozzilli, Italy. ²¹⁸Department of Medicine, Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, Baltimore, MD, USA. ²¹⁹Program for Personalized and Genomic Medicine, University of Maryland School of Medicine, Baltimore, MD, USA. ²²⁰Unit of Genomics of Complex Diseases, Sant Pau Biomedical Research Institute (IIB Sant Pau), Barcelona, Spain. ²²¹Cardiovascular Medicine Unit, Department of Medicine, Karolinska Institutet, Center for Molecular Medicine, Stockholm, Sweden. ²²²Laboratory of Epidemiology and Population Sciences, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA. ²²³Department of Biomedical Science, Hallym University, Chuncheon, Republic of Korea. ²²⁴Istituto di Ricerca Genetica e Biomedica, Consiglio Nazionale delle Ricerche (CNR), Cagliari, Italy. ²²⁵Department of Cell and Chemical Biology, Leiden University Medical Center, Leiden, The Netherlands.
- ²²⁶Epidemiology and Data Science, Amsterdam UMC, location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands. ²²⁷Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands. ²²⁸Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands. ²²⁹Icelandic Heart Association, Kópavogur, Iceland. ²³⁰Wellcome Sanger Institute, Hinxton, UK. ²³¹deCODE Genetics/Amgen, Reykjavik, Iceland. ²³²Mohn Nutrition Research Laboratory, Department of Clinical Science, University of Bergen, Bergen, Norway. ²³³Department of Public Health Sciences, Parkinson School of Health Sciences and Public Health, Loyola University Chicago, Maywood, IL, USA. ²³⁴VA Palo Alto Health Care System, Palo Alto, CA, USA. ²³⁵Department of Medicine, Stanford University School of

Article

Medicine, Stanford, CA, USA. ²³⁶Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany. ²³⁷DZHK (German Centre for Cardiovascular Research), partner site Greifswald, Greifswald, Germany. ²³⁸Cardiology Division, Department of Pediatrics, University of California, San Francisco, Oakland, CA, USA. ²³⁹Centre for Cancer Genetic Epidemiology, University of Cambridge, Cambridge, UK. ²⁴⁰Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. ²⁴¹Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands. ²⁴²Central Diagnostics Laboratory, Division Laboratories, Pharmacy and Biomedical Genetics, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands. ²⁴³Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands. ²⁴⁴Laboratory Genetic Metabolic Diseases, Department of Clinical Chemistry, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands. ²⁴⁵Core Facility Metabolomics, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands. ²⁴⁶Department of Cardiology, Division Heart and Lungs, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands. ²⁴⁷Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. ²⁴⁸Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. ²⁴⁹NIHR Barts Cardiovascular Biomedical Research Centre, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK. ²⁵⁰Department of Ophthalmology, Beijing Tongren Hospital, Capital Medical University, Beijing, China. ²⁵¹Department of Epidemiology and Biostatistics, MRC-PHE Centre for Environment and Health, School of Public Health, Imperial College London, London, UK. ²⁵²Department of Dermatology, Medical University of Vienna, Vienna, Austria. ²⁵³Department of Research and Innovation, Division of Clinical Neuroscience, Oslo University Hospital, Oslo, Norway. ²⁵⁴Department of Neurology, Oslo University Hospital, Oslo, Norway. ²⁵⁵MRC Unit for Lifelong Health and Ageing at UCL, Institute of Cardiovascular Science, University College London, London, UK. ²⁵⁶Institute of Genetic Epidemiology, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany. ²⁵⁷Department of Medicine IV – Nephrology and Primary Care, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany. ²⁵⁸Institute of Molecular Medicine, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA. ²⁵⁹Department of Medical Biochemistry, Kurume University School of Medicine, Kurume, Japan. ²⁶⁰Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA. ²⁶¹Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA. ²⁶²Department of Genetic Medicine, Weill Cornell Medicine-Qatar, Doha, Qatar. ²⁶³Department of Computer and Systems Engineering, Alexandria University, Alexandria, Egypt. ²⁶⁴Department of Cardiology, German Heart Centre Munich, Technical University Munich, Munich, Germany. ²⁶⁵Department of Cardiology, Ealing Hospital, London North West University Healthcare NHS Trust, London, UK. ²⁶⁶Department of Epidemiology and Biostatistics, Imperial College London, London, UK. ²⁶⁷Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Cambridge, UK. ²⁶⁸Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI, USA. ²⁶⁹Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA. ²⁷⁰Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA. ²⁷¹Department of Nutrition, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ²⁷²Carolina Population Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ²⁷³Department of Clinical Genetics, Erasmus MC, Rotterdam, The Netherlands. ²⁷⁴Department of Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, The Netherlands. ²⁷⁵Latin American Brain Health (BrainLat), Universidad Adolfo Ibáñez, Santiago, Chile. ²⁷⁶Unidad de Investigación de Enfermedades Metabólicas and Direction of Nutrition, Instituto Nacional de Ciencias Médicas y Nutrición, Mexico City, Mexico. ²⁷⁷Escuela de Medicina y Ciencias de la Salud, Tecnológico de Monterrey, Monterrey, Mexico. ²⁷⁸Department of Epidemiology and Dean's Office, College of Public Health, University of Kentucky, Lexington, KY, USA. ²⁷⁹Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, UK. ²⁸⁰Health Data Research UK and Institute of Health Informatics, University College London, London, UK. ²⁸¹KG Jepsen Center for Genetic Epidemiology, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, NTNU, Trondheim, Norway. ²⁸²HUNT Research Centre, Department of Public Health and Nursing, Norwegian University of Science and Technology, Levanger, Norway. ²⁸³Department of Endocrinology, Clinic of Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. ²⁸⁴Department of Nephrology, University Hospital Regensburg, Regensburg, Germany. ²⁸⁵Geriatric Unit, Azienda Toscana Centro, Florence, Italy. ²⁸⁶Systems Genomics Laboratory, School of Biotechnology, Jawaharlal Nehru University (JNU), New Delhi, India. ²⁸⁷Institute of Molecular Genetics, National Research Council of Italy, Pavia, Italy. ²⁸⁸Human Genetics Center and Department of Epidemiology, University of Texas Health Science Center at Houston, Houston, TX, USA. ²⁸⁹Department of Nephrology and Rheumatology, Kliniken Südostbayern, Regensburg, Germany. ²⁹⁰KfH Kidney Center Traunstein, Traunstein, Germany. ²⁹¹Center for Genomics and Personalized Medicine (CGPM), Aarhus University, Aarhus, Denmark. ²⁹²Bioinformatics Research Centre, Aarhus University, Aarhus, Denmark. ²⁹³USC-Office of Population Studies Foundation, University of San Carlos, Cebu City, Philippines. ²⁹⁴Department of Nutrition and Dietetics, University of San Carlos, Cebu City, Philippines. ²⁹⁵Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA, USA. ²⁹⁶Department of Biochemistry, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC, USA. ²⁹⁷Department of Clinical Biochemistry, Lillebaelt Hospital, Vejle, Denmark. ²⁹⁸Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark. ²⁹⁹Clinic of Medicine, St. Olavs Hospital,

Trondheim University Hospital, Trondheim, Norway. ³⁰⁰Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore. ³⁰¹Imperial College Healthcare NHS Trust, Imperial College London, London, UK. ³⁰²Adjunct Faculty, JSS University Academy of Higher Education and Research (JSSAHER), JSS (Deemed to be) University, Mysuru, India. ³⁰³Ophthalmology and Visual Sciences Academic Clinical Program (Eye ACP), Duke-NUS Medical School, Singapore, Singapore. ³⁰⁴Department of Medical Genetics, Oslo University Hospital, Oslo, Norway. ³⁰⁵Department of Medical Research, Bærum Hospital, Vestre Viken Hospital Trust, Gjettem, Norway. ³⁰⁶Department of Neurology, Division of Vascular Neurology, University of Maryland School of Medicine, Baltimore, MD, USA. ³⁰⁷Baltimore Veterans Affairs Medical Center, Department of Neurology, Baltimore, MD, USA. ³⁰⁸Unidad de Investigación Médica en Bioquímica, Hospital de Especialidades, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico. ³⁰⁹Dipartimento di Scienze Biomediche, Università degli Studi di Sassari, Sassari, Italy. ³¹⁰Intermountain Heart Institute, Intermountain Medical Center, Murray, UT, USA. ³¹¹Department of Surgery, University of Pennsylvania, Philadelphia, PA, USA. ³¹²Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, USA. ³¹³Department of Vascular Surgery, University Medical Center Utrecht, University of Utrecht, Utrecht, The Netherlands. ³¹⁴Department of Human Nutrition, Wageningen University, Wageningen, The Netherlands. ³¹⁵Center for Translational and Computational Neuroimmunology, Department of Neurology, Columbia University Medical Center, New York, NY, USA. ³¹⁶Department of Oncology, University of Cambridge, Cambridge, UK. ³¹⁷Department of General Practice, Amsterdam Public Health Institute, Amsterdam UMC, location VUmc, Amsterdam, The Netherlands. ³¹⁸Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA. ³¹⁹Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston, MA, USA. ³²⁰Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA. ³²¹Department of Clinical Sciences in Malmö, Division of Geriatric Medicine, Lund University, Malmö, Sweden. ³²²Molecular Cardiology Division, Victor Chang Cardiac Research Institute, Darlinghurst, New South Wales, Australia. ³²³Cardiology Department, St Vincent's Hospital, Darlinghurst, New South Wales, Australia. ³²⁴Faculty of Medicine, UNSW Sydney, Kensington, New South Wales, Australia. ³²⁵Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA. ³²⁶Robertson Center for Biostatistics, University of Glasgow, Glasgow, UK. ³²⁷Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, USA. ³²⁸Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden. ³²⁹Department of Internal Medicine, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC, USA. ³³⁰Faculty of Veterinary and Agricultural Science, University of Melbourne, Parkville, Victoria, Australia. ³³¹Agriculture Victoria Research, Department of Jobs, Precincts and Regions, Bundoor, Victoria, Australia. ³³²Injury Prevention Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ³³³Division of Physical Therapy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. ³³⁴Centro de Investigación en Salud Poblacional Instituto Nacional de Salud Pública and Centro de Estudios en Diabetes, Cuernavaca, Mexico. ³³⁵Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA, USA. ³³⁶Departments of Pediatrics and Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ³³⁷Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, PA, USA. ³³⁸Faculty of Medicine, University of Iceland, Reykjavik, Iceland. ³³⁹Department of Preventive Medicine, Keck School of Medicine of USC, Los Angeles, CA, USA. ³⁴⁰Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ³⁴¹Division of Pulmonary Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA. ³⁴²Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK. ³⁴³Cardiovascular Health Research Unit, Department of Epidemiology, University of Washington, Seattle, WA, USA. ³⁴⁴Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore. ³⁴⁵Khoo Teck Puat - National University Children's Medical Institute, National University Health System, Singapore, Singapore. ³⁴⁶Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria. ³⁴⁷Menzies Research Institute Tasmania, University of Tasmania, Hobart, Tasmania, Australia. ³⁴⁸Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, University of Melbourne, Melbourne, Victoria, Australia. ³⁴⁹Lions Eye Institute, Centre for Ophthalmology and Vision Science, University of Western Australia, Perth, Western Australia, Australia. ³⁵⁰Cardiology Division, Massachusetts General Hospital, Boston, MA, USA. ³⁵¹Department of Genetics, Shanghai-MOST Key Laboratory of Health and Disease Genomics, Chinese National Human Genome Center and Shanghai Industrial Technology Institute, Shanghai, China. ³⁵²Department of Internal Medicine, University of Utah, Salt Lake City, UT, USA. ³⁵³Australian Centre for Precision Health, Clinical and Health Sciences, University of South Australia, Adelaide, South Australia, Australia. ³⁵⁴South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia. ³⁵⁵Department of Environmental and Preventive Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan. ³⁵⁶Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA. ³⁵⁷Division of Endocrinology, Diabetes and Metabolism, School of Medicine, Ohio State University, Columbus, OH, USA. ³⁵⁸Center for Life Course Health Research, Faculty of Medicine, University of Oulu, Oulu, Finland. ³⁵⁹Unit of Primary Health Care, Oulu University Hospital, OYS, Oulu, Finland. ³⁶⁰Department of Life Sciences, College of Health and Life Sciences, Brunel University London, Uxbridge, UK. ³⁶¹The Eye Hospital, School of Ophthalmology and Optometry, Wenzhou Medical University, Wenzhou, China. ³⁶²Eindhoven Laboratory for Experimental Vascular Medicine, LUMC, Leiden, The Netherlands. ³⁶³Netherlands Heart Institute, Utrecht, The Netherlands. ³⁶⁴Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland. ³⁶⁵Department of Clinical Physiology, Finnish Cardiovascular Research

Center - Tampere, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland.³⁶⁶Laboratory of Complex Trait Genomics, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan.³⁶⁷Department of Ophthalmology, The Catholic University of Korea Incheon St. Mary's Hospital, Incheon, Republic of Korea.³⁶⁸NHRI Oxford Biomedical Research Centre, Churchill Hospital, Oxford, UK.³⁶⁹German Centre for Cardiovascular Research (DZHK), partner site Munich Heart Alliance, Munich, Germany.³⁷⁰Radboud University Medical Center, Radboud Institute for Health Sciences, Department of Urology, Nijmegen, The Netherlands.³⁷¹Corneal Dystrophy Research Institute, Yonsei University College of Medicine, Seoul, Republic of Korea.³⁷²Saevit Eye Hospital, Goyang, Republic of Korea.³⁷³Department of Biochemistry, College of Medicine, Ewha Womans University, Seoul, Republic of Korea.³⁷⁴Department of Cardiology, University Heart and Vascular Center UKE Hamburg, Hamburg, Germany.³⁷⁵Institute of Cardiovascular Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK.³⁷⁶German Center for Cardiovascular Research, partner site Hamburg/Kiel/Lübeck, Hamburg, Germany.³⁷⁷Atrial Fibrillation Network, Münster, Germany.³⁷⁸Department of Epidemiology and Public Health, UCL Institute of Epidemiology and Health Care, University College London, London, UK.³⁷⁹Healthy Longevity Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore.³⁸⁰University of Helsinki and Department of Medicine, Helsinki University Hospital, Helsinki, Finland.³⁸¹Minerva Foundation Institute for Medical Research, Helsinki, Finland.³⁸²Department of Preventive Cardiology, Lipoprotein Apheresis Unit and Lipid Disorders Clinic, Metropolitan Hospital, Athens, Greece.³⁸³MRC-PHE Centre for Environment and Health, Imperial College London, London, UK.³⁸⁴National Heart and Lung Institute, Imperial College London, London, UK.³⁸⁵Medical Department III – Endocrinology, Nephrology, Rheumatology, University of Leipzig Medical Center, Leipzig, Germany.³⁸⁶Institute for Social and Economic Research, University of Essex, Colchester, UK.³⁸⁷Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland.³⁸⁸Department of Medicine, University of Colorado at Denver, Aurora, CO, USA.³⁸⁹Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Berlin, Germany.³⁹⁰Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA.³⁹¹Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, Republic of Korea.³⁹²Department of Epidemiology and Biostatistics, Peking University Health Science Center, Beijing, China.³⁹³Peking University Center for Public Health and Epidemic Preparedness and Response, Beijing, China.³⁹⁴Institute of Epidemiology and Biobank Popgen, Kiel University, Kiel, Germany.³⁹⁵Key Laboratory of Systems Health Science of Zhejiang Province, Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Hangzhou, China.³⁹⁶Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.³⁹⁷Division of Cardiovascular Medicine and Aboud Cardiovascular Research Center, University of Iowa Hospitals and Clinics, Iowa City, IA, USA.³⁹⁸Alliance for Human Development, Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, Ontario, Canada.³⁹⁹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.⁴⁰⁰Division of Cardiology, University of California, San Francisco, San Francisco, CA, USA.⁴⁰¹Department of Medicine, Internal Medicine, Lausanne University Hospital, Lausanne, Switzerland.⁴⁰²University of Lausanne, Lausanne, Switzerland.⁴⁰³SYNLAB Academy, SYNLAB Holding Deutschland, Mannheim, Germany.⁴⁰⁴Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria.⁴⁰⁵Department of Medicine, Division of Cardiology, Duke University School of Medicine, Durham, NC, USA.⁴⁰⁶Duke Molecular Physiology Institute, Duke University School of Medicine, Durham, NC, USA.⁴⁰⁷Psychiatric Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia.⁴⁰⁸Geriatric Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.⁴⁰⁹Geriatrics Research and Education Clinical Center, Baltimore Veterans Administration Medical Center, Baltimore, MD, USA.⁴¹⁰Centre for Vision Research and Department of Ophthalmology, Westmead Millennium Institute of Medical Research, University of Sydney, Sydney, New South Wales, Australia.⁴¹¹Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands.⁴¹²Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK.⁴¹³Electrophysiology Section, Division of Cardiovascular Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.⁴¹⁴Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.⁴¹⁵Department of Chronic Diseases, Norwegian Institute of Public Health, Oslo, Norway.⁴¹⁶Department of Pain Management and Research, Oslo University Hospital, Oslo, Norway.⁴¹⁷Institute of Human Genetics, School of Medicine and University Hospital Bonn, Bonn, Germany.⁴¹⁸Sahlgrenska University Hospital, Department of Drug Treatment, Gothenburg, Sweden.⁴¹⁹Laboratorio de Inmunogenómica y Enfermedades Metabólicas, Instituto Nacional de Medicina Genómica, CDMX, Mexico City, Mexico.⁴²⁰Paavo Nurmi Centre, Sports and Exercise Medicine Unit, Department of Physical Activity and Health, University of Turku, Turku, Finland.⁴²¹Institute for Precision Health, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA.⁴²²Pat MacPherson Centre for Pharmacogenetics and Pharmacogenomics, Division of Population Health and Genomics, School of Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK.⁴²³Centre Nutrition, Santé et Société (NUTRISS), Institute of Nutrition and Functional Foods, Université Laval, Québec City, Quebec, Canada.⁴²⁴BE-Chair of Epidemiology, LMU Munich, Neuherberg, Germany.⁴²⁵Population, Policy and Practice, UCL Great Ormond Street Hospital Institute of Child Health, London, UK.⁴²⁶Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA.⁴²⁷Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland.⁴²⁸Hero DMC Heart Institute, Dyanand

Medical College, Ludhiana, India.⁴²⁹Second Department of Cardiology, Medical School, National and Kapodistrian University of Athens, University General Hospital Attikon, Athens, Greece.⁴³⁰Division of Biostatistics, Washington University School of Medicine, St Louis, MO, USA.⁴³¹Genetics, Merck Sharp & Dohme, Kenilworth, NJ, USA.⁴³²Department of Epidemiology, University of Washington, Seattle, WA, USA.⁴³³Department of Endocrinology and Metabolism, Kyung Hee University School of Medicine, Seoul, Korea.⁴³⁴Department of Public Health, Clinicum, Faculty of Medicine, University of Helsinki, Helsinki, Finland.⁴³⁵Departments of Medicine, Pharmacology, and Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA.⁴³⁶Department of Epidemiology and Data Science, Amsterdam Public Health Institute, Amsterdam Cardiovascular Sciences Institute, Amsterdam UMC, location VUmc, Amsterdam, The Netherlands.⁴³⁷Department of Cardiology and Department of Medicine, Columbia University, New York, NY, USA.⁴³⁸Department of Pediatrics, Section of Genetics, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.⁴³⁹Department of Pharmaceutical Sciences, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.⁴⁴⁰Department of Physiology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.⁴⁴¹Oklahoma Center for Neuroscience, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.⁴⁴²Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK.⁴⁴³Gottfried Schatz Research Center (for Cell Signaling, Metabolism and Aging), Medical University of Graz, Graz, Austria.⁴⁴⁴Institute of Nutritional Science, University of Potsdam, Nuthetal, Germany.⁴⁴⁵Deutsches Herzzentrum München, Cardiology, Deutsches Zentrum für Herz- und Kreislaufrorschung (DZHK) – Munich Heart Alliance, and Technische Universität München, München, Germany.⁴⁴⁶School of Biomedical Science and Pharmacy, University of Newcastle, New Lambton Heights, New South Wales, Australia.⁴⁴⁷Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.⁴⁴⁸Central University of Punjab, Bathinda, India.⁴⁴⁹Department of Medicine I, University Hospital, LMU Munich, Munich, Germany.⁴⁵⁰Department of Cardiology, Clinical Sciences, Lund University and Skåne University Hospital, Lund, Sweden.⁴⁵¹The Wallenberg Laboratory, Department of Molecular and Clinical Medicine, Institute of Medicine, Gothenburg University and the Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden.⁴⁵²Wallenberg Center for Molecular Medicine and Lund University Diabetes Center, Lund University, Lund, Sweden.⁴⁵³Population Health Research Institute, St George's, University of London, London, UK.⁴⁵⁴Molecular Epidemiology Section, Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands.⁴⁵⁵Department of Genetics, Stanford University School of Medicine, Stanford, CA, USA.⁴⁵⁶Department of Medicine, Faculty of Medicine, Université de Montréal, Montreal, Quebec, Canada.⁴⁵⁷Helsinki University Central Hospital, Research Program for Clinical and Molecular Metabolism, University of Helsinki, Helsinki, Finland.⁴⁵⁸Folkhälsan Research Center, Helsinki, Finland.⁴⁵⁹Department of Public Health, University of Helsinki, Helsinki, Finland.⁴⁶⁰Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia.⁴⁶¹Unidad de Biología Molecular y Medicina Genómica, Instituto de Investigaciones Biomédicas, UNAM, Mexico City, Mexico.⁴⁶²Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.⁴⁶³Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore, Singapore.⁴⁶⁴Milken Institute School of Public Health, The George Washington University, Washington, DC, USA.⁴⁶⁵Department Geriatric Medicine, Amsterdam Public Health, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands.⁴⁶⁶Department of Epidemiology and Data Science, Amsterdam UMC, Amsterdam, The Netherlands.⁴⁶⁷Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, Germany.⁴⁶⁸Unidad de Investigación Médica en Epidemiología Clínica, Hospital de Especialidades, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico.⁴⁶⁹Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK.⁴⁷⁰Department of Population and Public Health Sciences, Keck School of Medicine of USC, Los Angeles, CA, USA.⁴⁷¹Department of Physiology and Neuroscience, Keck School of Medicine of USC, Los Angeles, CA, USA.⁴⁷²USC Diabetes and Obesity Research Institute, Keck School of Medicine of USC, Los Angeles, CA, USA.⁴⁷³Lundbeck Foundation Center for GeoGenetics, GLOBE Institute, University of Copenhagen, Copenhagen, Denmark.⁴⁷⁴School of Chinese Medicine, China Medical University, Taichung, Taiwan.⁴⁷⁵Diabetes Unit, KEM Hospital and Research Centre, Pune, India.⁴⁷⁶Kurume University School of Medicine, Kurume, Japan.⁴⁷⁷Division of Cancer Control and Population Sciences, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA.⁴⁷⁸Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA.⁴⁷⁹TUM School of Medicine, Technical University of Munich and Klinikum Rechts der Isar, Munich, Germany.⁴⁸⁰Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway.⁴⁸¹Department of Population Health Sciences, Geisinger, Danville, PA, USA.⁴⁸²Vanderbilt Genetics Institute, Division of Genetic Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.⁴⁸³Department of Medicine, Veterans Affairs Boston Healthcare System, Boston, MA, USA.⁴⁸⁴Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, USA.⁴⁸⁵Atlanta VA Health Care System, Decatur, GA, USA.⁴⁸⁶Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah, Saudi Arabia.⁴⁸⁷The Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA.⁴⁸⁸School of Life Sciences, Westlake University, Hangzhou, China.⁴⁸⁹Westlake Laboratory of Life Sciences and Biomedicine, Hangzhou, China.⁴⁹⁰Department of Human Genetics, University of Michigan, Ann Arbor, MI, USA.⁴⁹¹McDonnell Genome Institute and Department of Medicine, Washington University School of Medicine, St Louis, MO, USA.⁴⁹²Laboratory of Statistical Immunology, Immunology Frontier Research Center (WPI-IFReC), Osaka, Japan.⁴⁹³Integrated Frontier Research for Medical Science Division, Institute for Open and

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Transdisciplinary Research Initiatives, Osaka University, Osaka, Japan. ⁴⁹⁴Programs in Metabolism and Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, USA. ⁴⁹⁵Departments of Pediatrics and Genetics, Harvard Medical School, Boston, MA, USA. ⁴⁹⁶Present address: Department of Mathematics and Statistics, St Cloud State University, St Cloud, MN, USA. ⁴⁹⁷Genentech, South San Francisco, CA, USA. ⁴⁹⁸Present address: Laboratory for Systems Genetics, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan. ⁴⁹⁹Department of Genome Informatics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan. ⁵⁰⁰These authors contributed equally: Loïc Yengo, Sailaja Vedantam, Eirini Marouli. ⁵⁰¹These authors jointly supervised this work: Yukinori Okada, Andrew R. Wood, Peter M. Visscher, Joel N. Hirschhorn. *A list of authors and their affiliations appears online.

23andMe Research Team

Adam Auton¹², Gabriel Cuellar Partida¹², Yunxuan Jiang¹² & Jingchunzi Shi¹²

Full lists of members and their affiliations appear in the Supplementary Information.

VA Million Veteran Program

Saiju Pyarajan^{5,57,81} & Yan Sun^{484,485}

Full lists of members and their affiliations appear in the Supplementary Information.

DiscovEHR (DiscovEHR and MyCode Community Health Initiative)

Jason E. Miller^{188,189}, Shefali S. Verma⁶⁷ & Anne E. Justice^{9,481}

Full lists of members and their affiliations appear in the Supplementary Information.

eMERGE (Electronic Medical Records and Genomics Network)

Damien Croteau-Chonka⁵⁷

Full lists of members and their affiliations appear in the Supplementary Information.

Lifelines Cohort Study

Ilja M. Nolte⁴¹, Harold Snieder⁴¹, Peter M. Visscher^{1,501} & Judith M. Vonk⁴¹

Full lists of members and their affiliations appear in the Supplementary Information.

The PRACTICAL Consortium

Sonja I. Berndt¹⁵, Stephen Chanock¹⁵, Christopher Haiman³³⁹ & Loic Le Marchand³⁹⁰

Full lists of members and their affiliations appear in the Supplementary Information.

Understanding Society Scientific Group

Meena Kumari³⁸⁶

Full lists of members and their affiliations appear in the Supplementary Information.

Methods

A summary of the methods, together with a full description of genome-wide association analyses and follow-up analyses is described below. Written informed consent was obtained from every participant in each study, and the study was approved by relevant ethics committees (Supplementary Table 1).

Quality control checks of individual studies

All study files were checked for quality using the software EasyQC⁵³ that was adapted to the format from RVTESTS (versions listed in Supplementary Table 2)⁵⁴. The checks performed included allele frequency differences with ancestry-specific reference panels, total number of markers, total number of markers not present in the reference panels, imputation quality, genomic inflation factor and trait transformation. We excluded two studies that did not pass our quality checks in the data.

GWAS meta-analysis

We first performed ancestry-group-specific GWAS meta-analyses of 173 studies of EUR, 56 studies of EAS, 29 studies of AFR, 11 studies of HIS and 12 studies of SAS. Meta-analyses within ancestry groups were performed as described before^{19,20} using a modified version of RAREMETAL⁵⁵ (v.4.15.1), which accounts for multi-allelic variants in the data. Study-specific GWASs are described in Supplementary Tables 1–3. Details about imputation procedures implemented by each study are also given in Supplementary Table 2. We kept in our analyses SNPs with an imputation accuracy (r_{INFO}^2) > 0.3, Hardy–Weinberg Equilibrium (HWE) P value (P_{HWE}) > 10^{-8} and a minor allele count (MAC) > 5 in each study. Next, we performed a fixed-effect inverse variance weighted meta-analysis of summary statistics from all five ancestry groups GWAS meta-analysis using a custom R script using the R package meta (see ‘URLs’ section).

Hold-out sample from the UK Biobank

We excluded 56,477 UK Biobank (UKB) participants from our discovery GWAS for following analyses including quantification of population stratification. More precisely, our hold-out EUR sample consists of 17,942 sibling pairs and 981 trios (two parents and one child) plus all UKB participants with an estimated genetic relationship larger than 0.05 with our set of sibling pairs and trios. We identified 14,587 individuals among these 56,477 UKB participants who were unrelated (unrelatedness was determined as when the genetic relationship coefficient estimated from HM3 SNPs was lower than 0.05) to each other and used their data to quantify the variance explained by SNPs within GWS loci (described below) and the prediction accuracy of PGSSs.

COJO analyses

We performed COJO analyses of each of the five ancestry group-specific GWAS meta-analyses using the software GCTA (version v.1.93)^{6,7}. We used default parameters for all ancestry groups except in AFR and HIS, for which we found that default parameters could yield biased estimates of joint SNP effects because of long-range LD. This choice is discussed in Supplementary Note 1. The GCTA-COJO method implements a step-wise model selection that aims at retaining a set of SNPs the joint effects of which reach genome-wide significance, defined in this study as $P < 5 \times 10^{-8}$. In addition to GWAS summary statistics, COJO analyses also require genotypes from an ancestry-matched sample that is used as a LD reference. For all sets of genotypes used as LD reference panels, we selected HM3 SNPs with $r_{\text{INFO}}^2 > 0.3$ and $P_{\text{HWE}} > 10^{-6}$. For EUR, we used genotypes at 1,318,293 HM3 SNPs (MAC > 5) from 348,501 unrelated EUR participants in the UKB as our LD reference. For EAS, we used genotypes at 1,034,263 quality-controlled (MAF > 1%, SNP missingness < 5%) HM3 SNPs from a merged panel of $n = 5,875$ unrelated participants from the UKB ($n = 2,257$) and Genetic Epidemiology Research on Aging (GERA; $n = 3,618$). Data from the GERA study were obtained

from the database of Genotypes and Phenotypes (dbGaP; accession number: phs000788.v2.p3.c1) under project 15096. For SAS, we used genotypes at 1,222,935 HM3 SNPs (MAC > 5; SNP missingness < 5%) from 9,448 unrelated individuals. For AFR, we used genotypes at 1,007,949 quality-controlled (MAF > 1%, SNP missingness < 5%) HM3 SNPs from a merged panel of 15,847 participants from the Women’s Health Initiative (WHI; $n = 7,480$), and the National Heart, Lung, and Blood Institute’s Candidate Gene Association Resource (CARE⁵⁶, $n = 8,367$). Both WHI and CARE datasets were obtained from dbGaP (accession numbers: phs000386 for WHI; CARE including phs000557.v4.p1, phs000286.v5.p1, phs000613.v1.p2, phs000284.v2.p1, phs000283.v7.p3 for ARIC, JHS, CARDIA, CFS and MESA cohorts) and processed following the protocol provided by the dbGaP data submitters. After excluding samples with more than 10% missing values and retaining only unrelated individuals, our final LD reference included data from $n = 10,636$ unrelated AFR individuals. For HIS, we used genotypes at 1,246,763 sequenced HM3 SNPs (MAF > 1%) from $n = 4,883$ unrelated samples from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL; dbGaP accession number: phs001395.v2.p1) cohorts. Finally, we performed a COJO analysis of the combined meta-analysis of all ancestries (referred to as META_{FE} in the main text) using 348,501 unrelated EUR participants in the UKB as the reference panel.

To assess whether SNPs detected in non-EUR were independent of signals detected in EUR, we performed another COJO analysis of ancestry groups GWAS by fitting jointly SNPs detected in EUR with those detected in each of the non-EUR GWAS meta-analyses. For each non-EUR GWAS, we performed a single-step COJO analysis only including SNPs identified in that non-EUR GWAS and for which the LD squared correlation (r_{LD}^2) with any of the EUR signals (marginally or conditionally GWS) is lower than 0.8 in both EUR and corresponding non-EUR data. Single-step COJO analyses were performed using the --cojo-joint option of GCTA, which does not involve model selection and simply approximates a multivariate regression model in which all selected SNPs on a chromosome are fitted jointly. LD correlations used in these filters were estimated in ancestry-matched samples of the 1000 Genomes Project (1KGP; release 3). More specifically, LD was estimated in 661 AFR, 347 HIS (referred to with the AMR label in 1KGP), 504 EAS, 503 EUR and 489 SAS 1KGP participants. We used the same LD reference samples in these analyses as for our main discovery analysis described at the beginning of the section.

F_{ST} calculation and (stratified) LD score regression

We used two statistics to evaluate whether an EUR LD reference could approximate well enough the LD structure in our trans-ancestry GWAS meta-analysis. The first statistic that we used is the Wright fixation index⁵⁷, which measures allele frequency divergence between two populations. We used the Hudson’s estimator of F_{ST} ⁵⁸ as previously recommended⁵⁹ to compare allele frequencies from our META_{FE} with that from our EUR GWAS meta-analysis and an independent replication sample from the EBB. The other statistic that we used is the attenuation ratio statistic from the LD score regression methodology. These LD score regression analyses were performed using version 1.0 of the LDSC software and using LD scores calculated from EUR participants in the 1KGP (see ‘URLs’ section). Moreover, we performed a stratified LD score regression analysis to quantify the enrichment of height heritability in 97 genomic annotations curated and described previously⁴⁰, as the baseline-LD model. Annotation-weighted LD scores used for those analyses were also calculated using data from 1KGP (see ‘URLs’ section).

Density of GWS signal and enrichment near OMIM genes

We defined the density of independent signals around each GWS SNP as the number of other independent associations identified with COJO within a 100-kb window on both sides. Therefore, a SNP with no other associations within 100 kb has a density of 0, whereas a SNP colocalizing with 20 other GWS associations within 100 kb will have a density of 20.

We quantified the standard error of the mean signal density across the genome using a leave-one-chromosome-out jackknife procedure. We then quantified the enrichment of 462 curated OMIM¹⁸ genes near GWS SNPs with a large signal density, by counting the number of OMIM genes within 100 kb of a GWS SNP, then comparing that number for SNPs with a density of 0 and those with a density of at least 1. The strength of the enrichment was measured using an odds ratio calculated from a 2×2 contingency table: 'presence/absence of an OMIM gene' versus 'density of 0 or larger than 0'. To assess the significance of the enrichment, we simulated the distribution of enrichment statistics for a random set of 462 length-matched genes. We used 22 length classes (<10 kb; between $i \times 10$ kb and $(i+1) \times 10$ kb, with $i = 1, \dots, 9$; between $i \times 100$ kb and $(i+1) \times 100$ kb, with $i = 1, \dots, 10$; between 1 Mb and 1.5 Mb; between 1.5 Mb and 2 Mb; and >2 Mb) to match OMIM genes with random genes. OMIM genes within a given length class were matched with the same number of non-OMIM genes present in the class. We sampled 1,000 random sets of genes and calculated for each them an enrichment statistic. Enrichment P value was calculated as the number of times enrichment statistics of random genes exceeded that of OMIM genes. The list of OMIM genes is provided in Supplementary Table 11.

Genomic colocalization of GWS SNPs identified across ancestries

We assessed the genomic colocalization between 2,747 GWS SNPs identified in non-EUR (Supplementary Tables 5–8) and 9,863 GWS SNPs identified in EUR (Supplementary Table 4) by quantifying the proportion of EUR GWS SNPs identified within 100 kb of any non-EUR GWS SNP. We tested the statistical significance of this proportion by comparing it with the proportion of EUR GWS SNPs identified within 100 kb of random HM3 SNPs matched with non-EUR GWS SNPs on 24 binary functional annotations³⁹.

These 24 annotations (for example, coding or conserved) are thoroughly described in a previous study³⁹ and were downloaded from https://alkesgroup.broadinstitute.org/LDSCORE/baselineLD_v2.1_annot/.

Our matching strategy consists of three steps. First, we calibrated a statistical model to predict the probability for a given HM3 SNP to be GWS in any of our non-EUR GWAS meta-analyses as a function of their annotation. For that, we used a logistic regression of the non-EUR GWS status (1 = if the SNP is GWS in any of the non-EUR GWAS; 0 = otherwise) onto the 24 annotations as regressors. Second, we used that model to predict the probability to be GWS in non-EUR. Thirdly, we used the predicted probability to sample (with replacement) 1,000 random sets of 2,747 SNPs. Finally, we estimated the proportion of EUR GWS SNPs within 100 kb of SNPs in each sampled SNP set. We report in the main text the mean and s.d. over these 1,000 proportions.

To validate our matching strategy, we compared the mean value of each of these 24 annotations (for example, proportion of coding SNPs) between non-EUR GWS SNPs and each of the 1,000 random sets of SNPs, using a Fisher's exact test. For each of the 24 annotations, both the mean and median P value were greater than 0.6 and the proportion of P values < 5% was less than 1%, suggesting no significant differences in the distribution of these 24 annotations between non-EUR GWS SNPs and matched SNPs.

Replication analyses

To assess the replicability of our results, we tested whether the correlation ρ_b of estimated SNP effects between our discovery GWAS and our replication sample of 49,160 participants of the EBB was statistically different from 1. We used the estimator of ρ_b from a previous study⁶⁰, which accounts for sampling errors in both discovery and replication samples. Standard errors were calculated using a leave-one-SNP-out jackknife procedure. We quantified the correlation of marginal and also that of joint SNP effects. Joint SNP effects in our replication sample were obtained by performing a single-step COJO analysis of GWAS summary statistics from our EBB sample, using the same LD reference as in the discovery GWAS. Correlation of SNP effects were

calculated after correcting SNP effects for winner's curse using a previously described method¹². We provide the R scripts used to apply these corrections and estimate the correlation of SNP effects (see 'URLs' section). The expected proportion, $E[P]$, of sign-consistent SNP effects between discovery and replication was calculated using the quadrant probability of a standard bivariate Gaussian distribution with correlation $E[\rho_b]$, denoting the expected correlation between estimated SNP effects in the discovery and replication sample:

$$E[P] = \frac{1}{2} + \frac{\sin^{-1}(E[\rho_b])}{\pi}, \quad (1)$$

where $\sin^{-1}$ denotes the inverse of the sine function and $E[\rho_b]$ the expectation of the ρ_b statistic under the assumption that the true SNP effects are the same across discovery and replications cohorts. $E[\rho_b]$ was calculated as

$$E[\rho_b] = \frac{\sigma_b^2}{\sqrt{(\sigma_b^2 + [1 - \sigma_b^2 h_d]/(N_d h_d)) (\sigma_b^2 + [1 - \sigma_b^2 h_r]/(N_r h_r))}}, \quad (2)$$

where N_d and N_r denote the sizes of the discovery and replication samples, respectively; h_d and h_r the average heterozygosity under Hardy–Weinberg equilibrium (that is, $2 \times \text{MAF} \times (1 - \text{MAF})$) across GWS SNPs in the discovery and replication samples, respectively; and σ_b^2 the mean per-SNP variance explained by GWS SNPs, which we calculated (as per ref.⁶⁰) as the sample variance of estimated SNP effects in the discovery sample minus the median squared standard error.

Variance explained by GWS SNPs and loci

We estimated the variance explained by GWS SNPs using the genetic relationship-based restricted maximum likelihood (GREML) approach implemented in GCTA¹⁷. This approach involves two main steps: (i) calculation of genetic relationships matrices (GRM); and (ii) estimation of variance components corresponding to each of these matrices using a REML algorithm. We partitioned the genome in two sets containing GWS loci on the one hand and all other HM3 SNPs on the other hand. GWS loci were defined as non-overlapping genomic segments containing at least one GWS SNP and such that GWS SNPs in adjacent loci are more than 2×35 kb away from each other (that is, a 35-kb window on each side). We then calculated a GRM based on each set of SNPs and estimated jointly a variance explained by GWS alone and that explained by the rest of the genome. We performed these analyses in multiple samples independent of our discovery GWAS, which include participants of diverse ancestry. Details about the samples used for these analyses are provided below. We extended our analyses to also quantify the variance explained by GWS loci using alternative definitions based on a window size of 0 kb and 10 kb around GWS SNPs (Supplementary Figs. 18 and 19).

We also repeated our analyses using a random set of 12,111 SNPs matched with GWS SNPs on MAF and LD. Loci for these 12,111 random SNPs were defined similarly as for GWS loci. To match random SNPs with GWS SNPs on MAF and LD, we first created 28 MAF-LD classes of HM3 SNPs (7 MAF classes $\times$ 4 LD score classes). MAF classes were defined as <1%; between 1% and 5%; between 5% and 10%; between 10% and 20%; between 20% and 30%; between 30% and 40%; and between 40% and 50%. LD score classes were defined using quartiles of the HM3 LD score distribution. We next matched GWS SNPs in each of the 28 MAF-LD classes, with the same number of SNPs randomly sampled from that MAF-LD class.

Prediction analyses

Height was first mean-centred and scaled to variance 1 within each sex. We quantified the prediction accuracy of height predictors as the difference between the variance explained by a linear regression model of sex-standardized height regressed on the height predictor, age, 20

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genotypic principal components and study-specific covariates (full model) minus that explained by a reduced linear regression not including the height predictor. Genetic principal components were calculated from LD pruned HM3 SNPs ($r_{LD}^2 < 0.1$). We used height of siblings or parents as a predictor of height as well as various polygenic scores (PGSs) calculated as a weighted sum of height-increasing alleles. The direction and magnitude of these weights was determined by estimated SNP effects from our discovery GWAS meta-analyses. No calibration of tuning parameters in a validation was performed.

Between-family prediction. We analysed two classes of PGS. The first class is based on SNPs ascertained using GCTA-COJO. We applied GCTA-COJO to ancestry-specific and cross-ancestry GWAS meta-analyses using an ancestry-matched and an EUR LD reference, respectively. We compared PGSs based on SNPs ascertained at different significance thresholds: $P < 5 \times 10^{-8}$ (GWS: reported in the main text) and $P < 5 \times 10^{-7}$, $P < 5 \times 10^{-6}$ and $P < 5 \times 10^{-5}$. For all COJO-based PGS, we used estimated joint effects to calculate the PGS. The second class of PGS uses weights for all HM3 SNPs obtained from applying the SBayesC method²⁸ to ancestry-specific and cross-ancestry GWAS meta-analyses with ancestry-matched and EUR-specific LD matrices, respectively. The SBayesC method is a Bayesian PGS-method implemented in the GCTB software (v.2.0), which uses the same prior as the LDpred method^{61,62}. In brief, SBayesC models the distribution of joint effects of all SNPs using a two-component mixture distribution. The first component is a point-mass Dirac distribution on zero and the other component a Gaussian distribution (for each SNP) with mean 0 and a variance parameter to estimate. Full LD matrices (that is, not sparse) were calculated using GCTB across around 250 overlapping (50% overlap) blocks of around 8,000 SNPs (average size is around 20 Mb). These LD matrices were calculated using the same sets of genotypes used for COJO analyses (described above). We ran SBayesC in each block separately with 100,000 Monte Carlo Markov Chain iterations. In each run, we initialized the proportion of causal SNPs in a block at 0.0001 and the heritability explained by SNPs in the block at 0.001. Posterior SNP effects of SNPs present in two blocks were meta-analysed using inverse-variance meta-analysis.

Prediction accuracy was quantified in 61,095 unrelated individuals from three studies, including 33,001 participants of the UKB who were not included in our discovery GWAS (that is, 14,587 EUR; 9,257 SAS; 6,911 AFR and 2,246 EAS; Methods section ‘Samples used for prediction and estimation of variance explained’); 14,058 EUR participants from the Lifelines cohort study; and 8,238 HIS and 5,798 AFR participants from the PAGE study.

Within-family prediction. The prediction accuracy of sibling’s height was assessed in 17,942 unrelated sibling pairs from the UKB. Those pairs were determined by intersecting the list of UKB sibling pairs determined by Bycroft et al.⁶³ with a list of genetically determined European ancestry participants from the UKB also described previously³. We then filtered the resulting list for SNP-based genetic relationship between members of different families to be smaller than 0.05. The prediction accuracy of parental height (each parent and their average) was assessed in 981 unrelated trios obtained as described above by crossing information from Bycroft et al.⁶³ (calling of relatives) with that from Yengo et al.³ (calling of European ancestry participants). We quantified the within-family variance explained by PGS as the squared correlation of height difference between siblings with PGS difference between siblings. We describe in Supplementary Note 4 how familial information and PGS were combined to generate a single predictor.

Samples used for prediction and estimation of variance explained We quantified the accuracy of a PGS based on GWS SNPs as well as the variance explained by SNPs within GWS loci, in eight different datasets independent of our discovery GWAS meta-analyses. These datasets

include two samples of EUR from the UKB ($n = 14,587$) and the Lifelines study ($n = 14,058$), two samples of AFR from the UKB ($n = 6,911$) and the PAGE study ($n = 8,238$), two samples of EAS ($n = 2,246$) from the UKB and the China Kadoorie Biobank (CKB; $n = 47,693$), one sample of SAS from the UKB ($n = 9,257$) and one sample of HIS from the PAGE study ($n = 4,939$). Analyses were adjusted for age, sex, 20 genotypic principal components and study-specific covariates (for example, recruitment centres). Genotypes of EUR UKB participants were imputed to the Haplotype Reference Consortium (HRC) and to a combined reference panel including haplotypes from the 1KG Project and the UK10K Project. To improve variant coverage in non-EUR participants of UKB, we re-imputed their genotypes to the 1KG reference panel, as described previously³⁸. Lifelines samples were imputed to the HRC panel. PAGE and CKB were imputed to the 1KG reference panel. Standard quality control ($r_{INFO}^2 > 0.3$, $P_{HWE} > 10^{-6}$ and $MAC > 5$) were applied to imputed genotypes in each dataset.

Contribution of LD and MAF to the loss of prediction accuracy

We defined the EUR-to-AFR relative accuracy as the ratio of prediction accuracies from an AFR sample over that from a EUR sample. We used a previously published method³⁸ to quantify the expectation of that relative accuracy under the assumption that causal variants and their effects are shared between EUR and AFR, whereas MAF and LD structures can differ. In brief, this method contrasts LD and MAF patterns within 100-kb windows around each GWS SNPs and uses them to predict the expected loss of accuracy. As previously described³⁸, we used genotypes from 503 EUR and 661 AFR participants of the 1KGP as a reference sample to estimate ancestry-specific MAF and LD correlations between GWS SNPs and SNPs in their close vicinity, and defined candidate causal variants as any sequenced SNP with an $r_{LD}^2 > 0.45$ with a GWS SNP within that 100-kb window. Standard errors were calculated using a delta-method approximation as previously described³⁸.

Down-sampled GWAS analyses

In addition to our EUR GWAS meta-analysis and our trans-ancestry meta-analysis (META_{FE}), we re-analysed five down-sampled GWASs as shown in Table 2. These down-sampled GWASs include various iterations of previous efforts of the GIANT consortium and have a sample size varying between around 130,000 and 2.5 million (EUR participants from 23andMe). To ensure sufficient genomic coverage of HM3 SNPs we imputed GWAS summary statistics from Lango Allen et al.¹⁹, Wood et al.²⁰ and Yengo et al.³, with ImpG-Summary (v.1.0.1)⁶⁴ using haplotypes from 1KGP as a LD reference. GWAS summary statistics from Lango Allen et al. only contain P values (P), height-increasing alleles and per-SNP sample sizes (N). Therefore, we first calculated Z -scores (Z) from P values assuming that Z -scores are normally distributed, then derived SNP effects (β) and corresponding standard errors (s.e.) using linear regression theory as $\beta = Z / \sqrt{2MAF \times (1 - MAF) \times (N + Z^2)}$ and $SE = \beta / Z$. Imputed GWAS summary statistics from these three studies are made publicly available on the GIANT consortium website (see ‘URLs’ section). We next performed a COJO analysis of all down-sampled GWAS using genotypes of 348,501 unrelated EUR participants in the UKB as a LD reference panel, as for our META_{FE} and EUR GWAS meta-analysis.

Gene prioritization using SMR

We used SMR to identify genes whose expression could mediate the effects of SNPs on height. SMR analyses were performed using the SMR software v.1.03. We used publicly available gene eQTLs identified from two large eQTL studies; namely, the GTEx⁶⁵ v.8 and the eQTLgen studies (see ‘URLs’ section). To ensure that our SMR results robustly reflect causality or pleiotropic effects of height-associated SNPs on gene expression, we only report here significant SMR results (that is, $P < 5 \times 10^{-8}$), which do not pass the heterogeneity in dependent instrument (HEIDI) test (that is, $P > 0.01$; Methods). The significance threshold for the HEIDI test was chosen on the basis of recommendations from another study⁶⁶.

Selection of OMIM genes

To generate a list of genes that are known to underlie syndromes of abnormal skeletal growth, we queried the Online Mendelian Inheritance in Man database (OMIM; <https://www.omim.org/>). From July 2019 to August 2020, we performed queries using search terms of “short stature”, “tall stature”, “overgrowth”, “skeletal dysplasia” and “brachydactyly.” We then used the free text descriptions in OMIM to manually curate the resulting combined list of genes, as well as genes in our earlier list from Wood et al.²⁰ and all genes listed as causing skeletal disease in an online endocrine textbook (<https://www.endotext.org/>, accessed September 2020). For short stature, we only included genes that underlie syndromes in which short stature was either consistent (less than -2 s.d. in the vast majority of patients with data recorded), or present in multiple families or sibships and accompanied by (a) more severe short stature (-3 s.d.), (b) presence of skeletal dysplasia (beyond poor bone quality/fractures); or (c) presence of brachydactyly, shortened digits, disproportionate short stature or limb shortening (not simply absence of specific bones). We removed genes underlying syndromes in which short stature was likely to be attributable to failure to thrive, specific metabolic disturbances, intestinal failure or enteropathy and/or very severe disease (for example, early lethality or severe neurological disease). For tall stature or overgrowth, we only included genes underlying syndromes in which tall stature was consistent (more than $+2$ s.d. in the vast majority of patients with data recorded) or present in multiple families or sibships and accompanied by either (a) more severe tall stature ($>+3$ s.d.) or (b) arachnodactyly. For brachydactyly, we required more than only fifth finger involvement, and that brachydactyly be either consistent (present in the vast majority of patients) or accompanied by consistent short stature or other skeletal dysplasias. For skeletal dysplasias, we only considered genes that underlie syndromes in which the skeletal dysplasia involved long bones or the spine and was accompanied by short stature, brachydactyly or limb or digit shortening. We also included all genes in a list we generated in Lango Allen et al.¹⁹, which was curated using similar criteria. The resulting list contained 536 genes, of which 462 (Supplementary Table 11) are autosomal on the basis of annotation from PLINK (<https://www.cog-genomics.org/static/bin/plink/glist-hg19>).

URLs

GIANT consortium data files: https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files. Analysis script for within- and across-ancestry meta-analysis: https://github.com/loic-yengo/ScriptsForYengo2022_HeightGWAS/blob/main/run-meta-analyses-within-ancestries.R and https://github.com/loic-yengo/ScriptsForYengo2022_HeightGWAS/blob/main/run-meta-analyses-across-ancestries.R. Analysis script for correction of winner's curse: https://github.com/loic-yengo/ScriptsForYengo2022_HeightGWAS/blob/main/WC_correction.R. Genotypes from 1KG: <https://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/>. eQTL data for SMR: GTEx v.8: https://yanglab.westlake.edu.cn/data/SMR/GTEx_V8_cis_eqtl_summary.html; eQTLgen: <https://www.eqtlgen.org/cis-eqtl.html>. Annotation-weighted LD scores for stratified LD score regression analyses: <https://alkesgroup.broadinstitute.org/LDSCORE/>. LDSC software: <https://github.com/bulik/ldsc>.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Summary statistics for ancestry-specific and multi-ancestry GWASs (excluding data from 23andMe) as well as SNP weights for polygenic scores derived in this study are made publicly available on the GIANT

consortium website (see ‘URLs’ for GIANT consortium data files). GWAS summary statistics derived involving 23andMe participants will be made available to qualified researchers under an agreement with 23andMe that protects the privacy of participants. Application for data access can be submitted at <https://research.23andme.com/dataset-access/>. We used genotypes from various publicly available databases to estimate linkage disequilibrium correlations required for conditional analyses and genome-wide prediction analyses. These databases include the UK Biobank under project 12505 and the database of Genotypes and Phenotypes (dbGaP) under project 15096. Accession numbers for dbGaP datasets are phs000788.v2.p3.c1, phs000386, phs000557.v4.p1, phs000286.v5.p1, phs000613.v1.p2, phs000284.v2.p1, phs000283.v7.p3 and phs001395.v2.p1 cohorts. Details for each dbGaP dataset are given in the Methods. Source data are provided with this paper.

Code availability

We used publicly available software tools for all analyses. These software tools are listed in the main text and in the Methods. Source data are provided with this paper.

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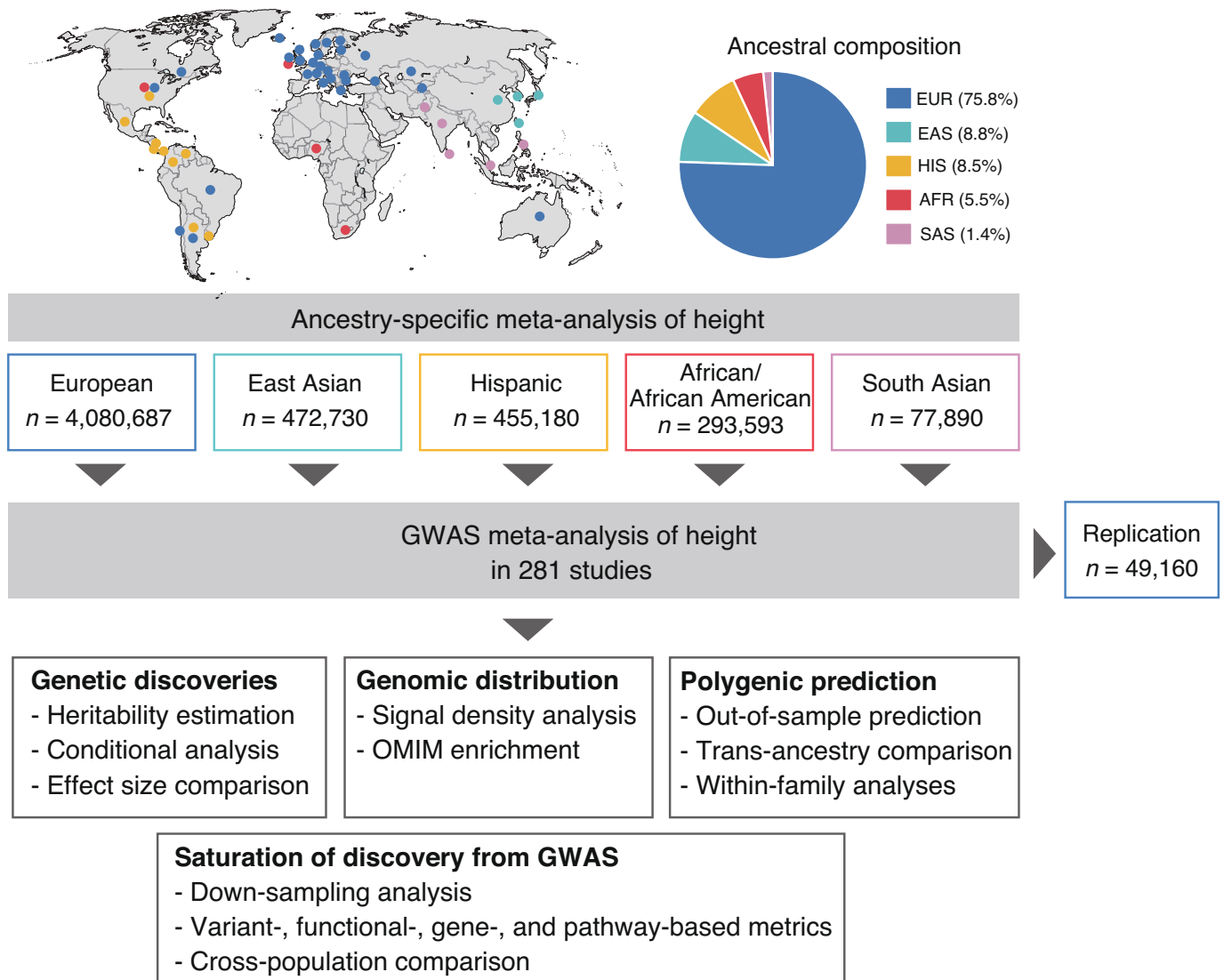
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Competing interests Y. Jiang is employed by and holds stock or stock options in 23andMe. T.S.A. is a shareholder in Zealand Pharma A/S and Novo Nordisk A/S. G.C.-P. is an employee of 23andMe. M.E.K. is employed by SYNLAB Holding Deutschland GmbH. H.L.L. receives support

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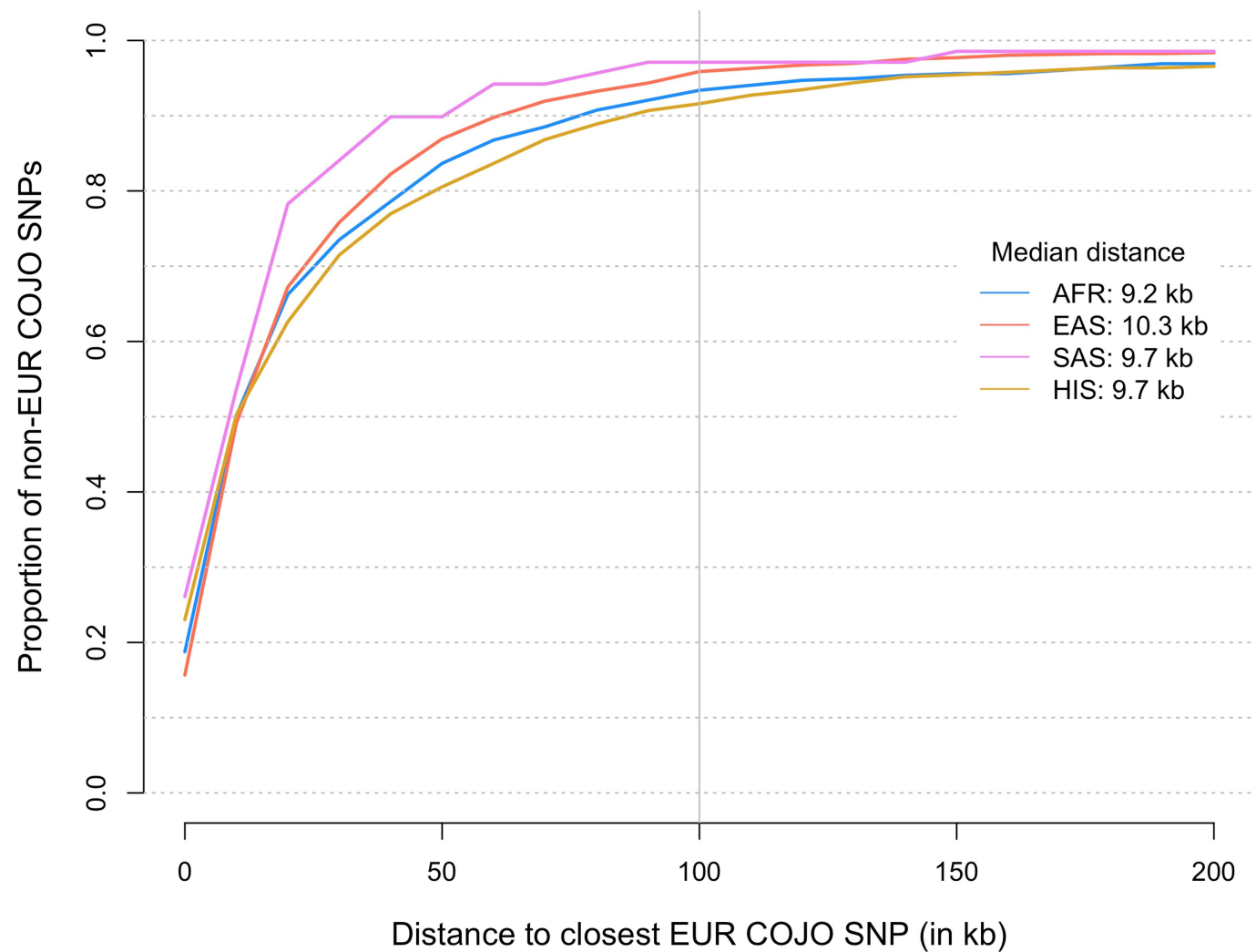
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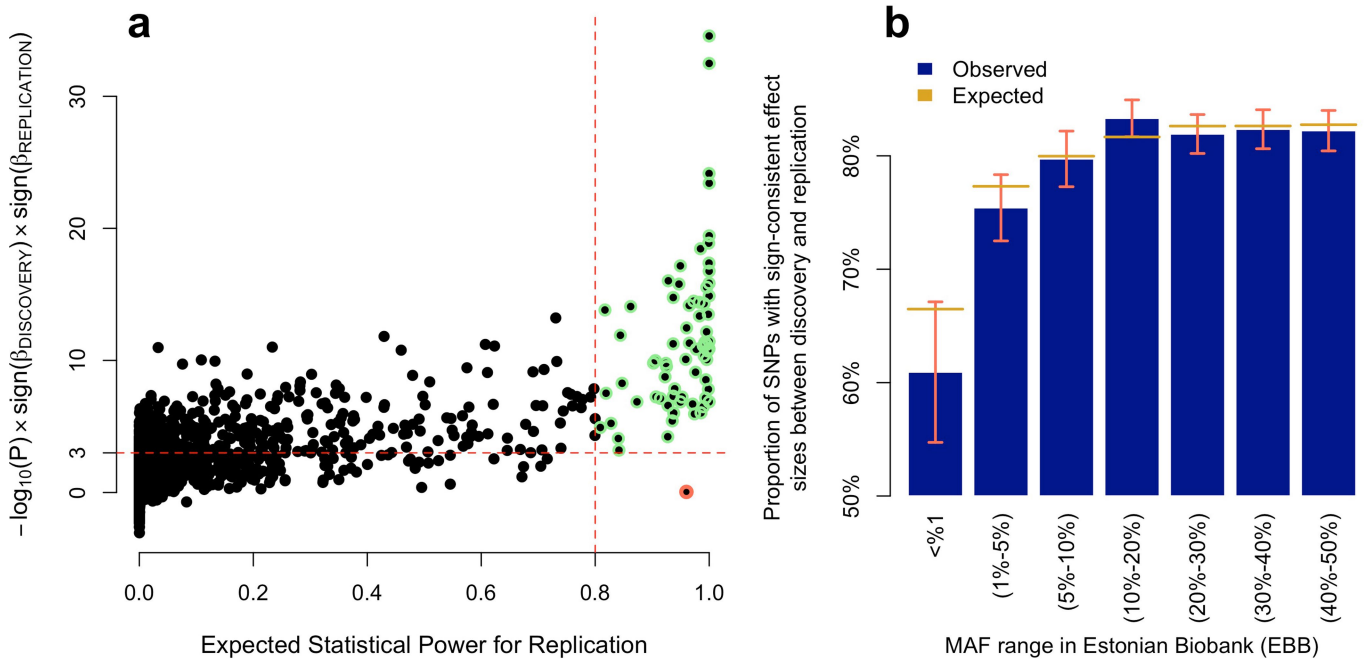


Extended Data Fig. 1 | Broad ancestries composition. Geographical mapping and ancestries composition of 281 studies meta-analysed in this study. Various analyses were performed including (1) detection of height-associated SNPs (Genetic discoveries box), (2) quantification of the genomic distribution of

height-associated loci (Genomic distribution box), (3) assessment of the performances of polygenic predictors of height (Polygenic prediction box), and (4) assessment of the relationship between GWAS sample size and discoveries (Saturation of discovery from GWAS box).



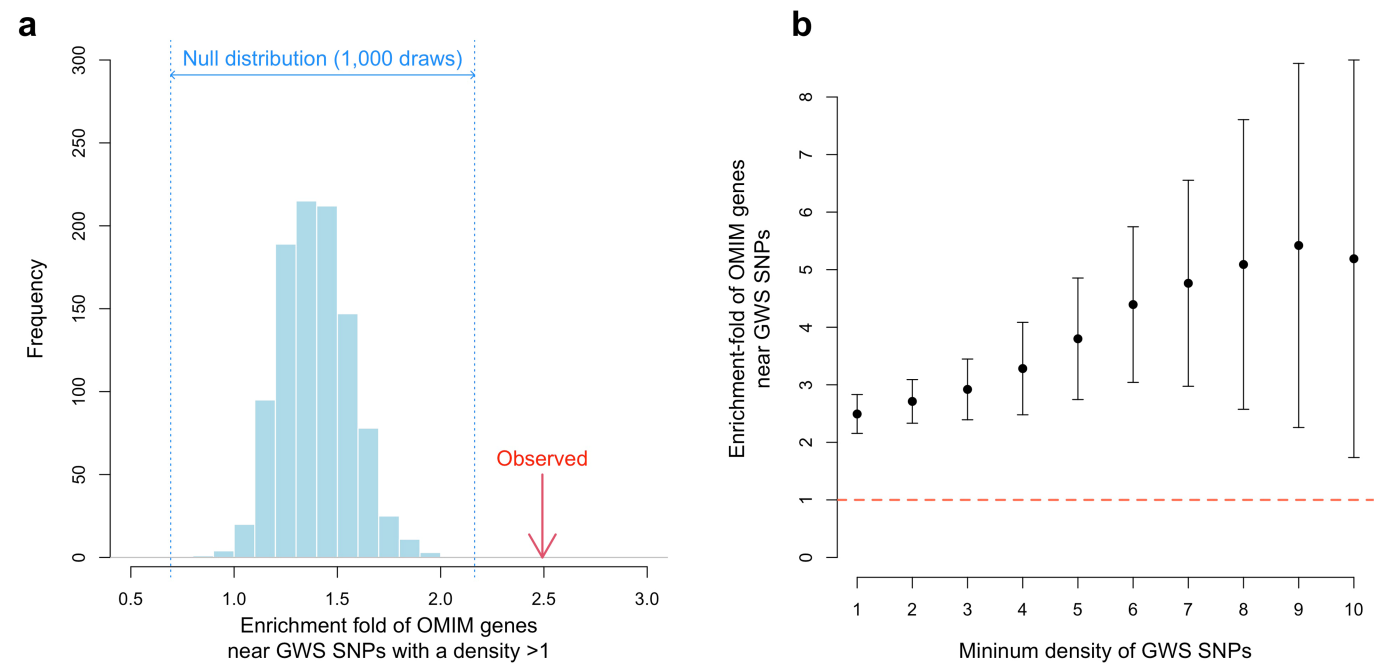
Extended Data Fig. 2 | Colocalization of height-associated signals across ancestries. Proportion (y-axis) of GWS SNPs identified in our GWAS meta-analyses of non-European (non-EUR: African – AFR; East Asian – EAS; South Asian – SAS; Hispanic – HIS) ancestry/ethnicity participants that are located within a certain distance (x-axis) of GWS SNPs identified in our GWAS meta-analysis of EUR participants only.



Extended Data Fig. 3 | Replication of marginal associations in the EBB.

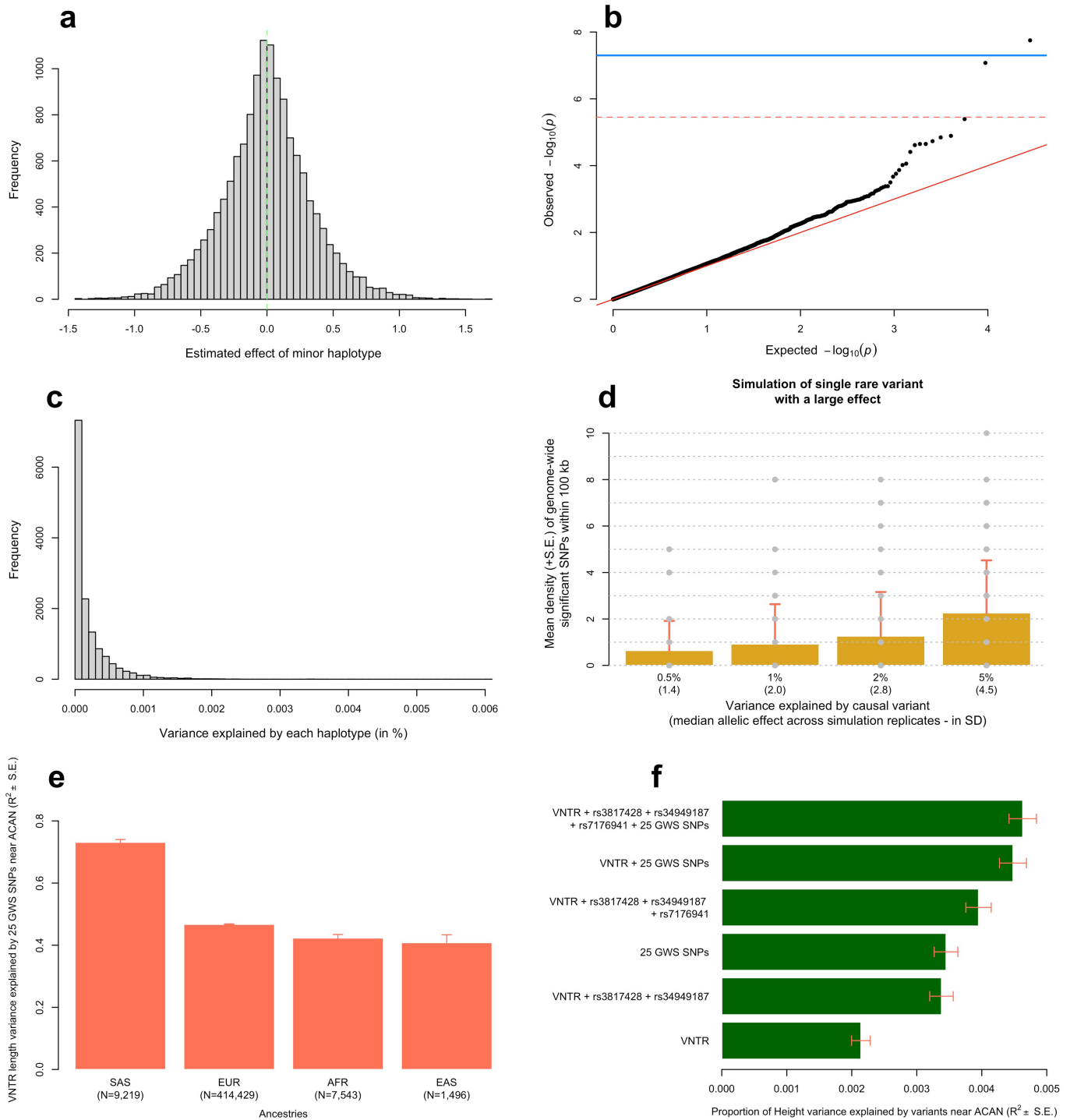
a, Each dot represents one of the 12,111 SNPs detected in our trans-ancestry meta-analysis. The x-axis represents the expected statistical power to replicate each association ($P < 0.05/9,473 = 5.3 \times 10^{-6}$; where 9,473 is the number of associations reaching marginal genome-wide significance in our discovery trans-ancestry GWAS and with a minor allele frequency $> 1\%$ in the EBB sample). The y-axis represents the $-\log_{10}$ of the association p-value in the EBB multiplied by the product of signs of estimated SNP effects in the discovery and in the EBB.

Horizontal dotted line represents replication at $P < 0.001$ and the vertical dotted line indicates 80% of statistical power. SNPs highlighted in green have an expected statistical power for replication $> 80\%$. One outlier (rs11100870), highlighted in red, does not replicate in the EBB sample. **b**, Proportion (P) of SNPs with a sign-consistent estimated effect between discovery GWAS (N=5.3M) and EBB. Expected proportions ($E[P]$) are calculated using equation (2) in the Methods. Error bars are defined as $1.96 \times \sqrt{P(1-P)/m}$, where m is the number of SNPs in the corresponding MAF interval.



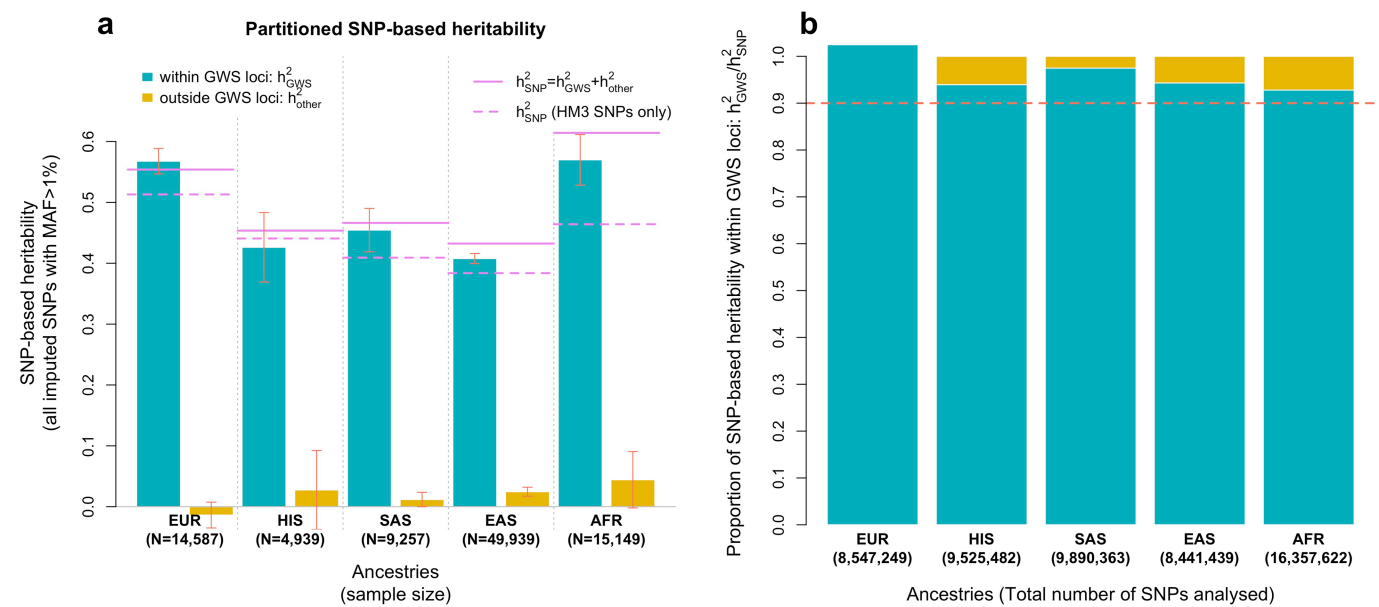
Extended Data Fig. 4 | Enrichment of genes containing pathogenic mutations that cause extreme height or abnormal skeletal growth syndromes near hotspots of GWS SNPs. Four hundred and sixty-two (462) autosomal genes were curated from the Online Mendelian Inheritance in Man (OMIM) database. **a**, Red arrow indicates the observed enrichment statistic (OR = 2.5-fold) measuring the odds ratio of the presence of an OMIM gene

within 100 kb of a GWS SNPs with a density >1. The blue histogram represents the distribution of enrichment statistics from 1,000 random genes matched, which length distribution matches that of the OMIM genes. **b**, Enrichment of OMIM genes near high density GWS SNPs. High density is defined by on the x-axis by the minimum number of other independent GWS SNPs detected within 100 kb.



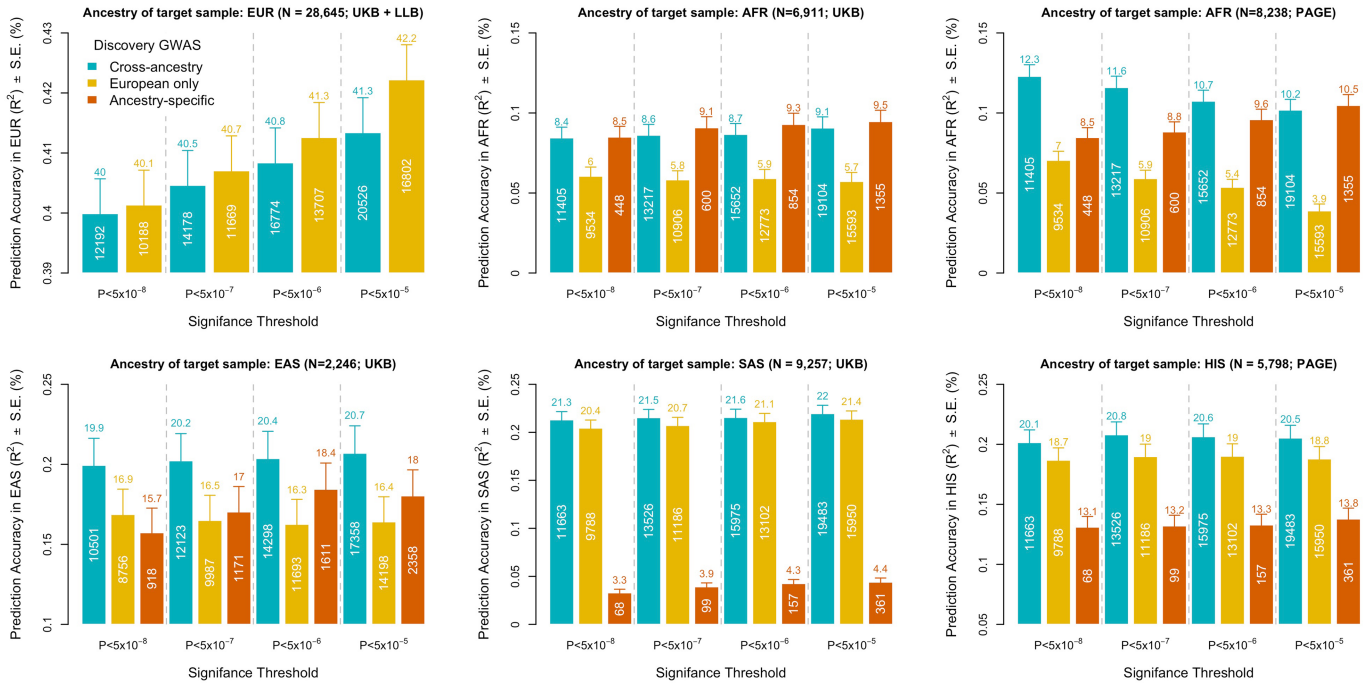
Extended Data Fig. 5 | Haplotypic analysis at the *ACAN* locus. **a**, Distribution of estimated haplotype effects from 14,117 haplotypes covering a 100 kb long genomic region near the *ACAN* gene (hg19 genomic coordinates: chr15:89,307,521-89,407,521). **b**, Quantile-quantile plot of associations between these 14,117 haplotypes and height. **c**, Distribution of the variance explained by each of the 14,117 haplotypes. **d**, Mean signals density (y-axis) across simulated data where 1 causal SNP within the locus explains between 0.5% and 5% (x-axis) of trait variance. Causal variants were sampled from a pool of 13 SNPs with a $1.4 \times 10^{-5} < \text{MAF} < 1\%$ genotyped in 291,683 unrelated EUR participants of the UKB, with no missing values at these 13 SNPs. Standard errors were calculated as the standard deviation (s.d.) of signal density across

100 simulation replicates. GCTA-COJO analyses to identify independent signals were performed using a subset of 10,000 unrelated EUR participants of the UKB to mimic the large discrepancy between the size of the discovery GWAS and that of the LD reference used in our real data analyses. **e**, Proportion of VNTR length explained by 25 GWS SNPs identified near *ACAN* in 4 ancestries (European: EUR; South Asian: SAS; East Asian: EAS; African: AFR). **f**, Proportion of height variance explained in a sample of EUR UK Biobank participants by various sets of polymorphisms at the *ACAN* locus. rs3817428 and rs34949187 are two missense variants and rs7176941 is an intronic variant with high posterior causal probability identified in ref.²⁸. In **e** and **f**, error bars represent standard error (s.e.).



Extended Data Fig. 6 | Variance of height explained by common SNPs within 35 kb of GWS SNPs. Stratified SNP-based heritability (h_{SNP}^2) estimates were obtained from a partition of the genome into two sets of 1000 Genomes imputed SNPs with a minor allele frequency (MAF) >1%: (1) SNPs within ± 35 kb of GWS (GWS loci) vs. all other SNPs. Analyses were performed in samples of

five different ancestry groups: European (EUR; UK Biobank only), African (AFR), East Asian (EAS) and South Asian (SAS) as described in the legend of Fig. 3. Estimates from stratified analyses were compared with SNP-based heritability estimates obtained from analysing HM3 SNPs only (dotted horizontal violet bar).



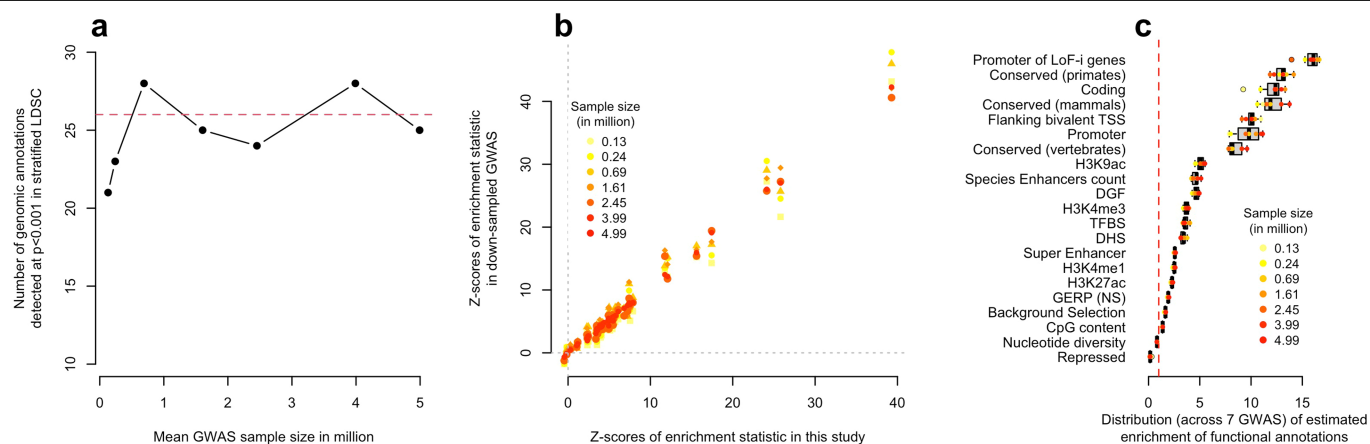
Extended Data Fig. 7 | Accuracy of PGSs derived from joint effects of SNPs ascertained at various significance thresholds. The six panels show on their y-axes the prediction accuracy (R^2) of multiple PGS across five target samples. The ancestry group and size of each target sample is indicated in the panel title. The top-left panel shows the averaged prediction accuracy in two European ancestry (EUR) target samples from the UK Biobank (UKB) and Lifelines Biobank (LLB). The other panels show prediction accuracies in individual target samples of African ancestry (AFR) from UKB and the PAGE study, East Asian ancestry (EAS) and South Asian ancestry (SAS) ancestry from the UKB and Hispanic ethnicity from the PAGE study. Each panel is divided in four columns

representing the four significance levels used to ascertain SNPs using the GCTA-COJO algorithm. GCTA-COJO was applied to each ancestry-group specific GWAS meta-analysis with an ancestry-match linkage disequilibrium (LD) reference. We used genotypes from 50,000 (vs 350,000 for results reported in the main text) unrelated EUR participants as LD reference to run GCTA-COJO on the EUR- and the cross-ancestry GWAS meta-analysis. For the other ancestry groups, we used genotypes from 10,636 AFR individuals, 5,875 EAS individuals, 4,883 HIS individuals and 9,448 SAS individuals as LD reference (as described in Methods). Error bars are standard error (s.e.). The number of SNPs used in each PGS is indicated (in white) within each bar.



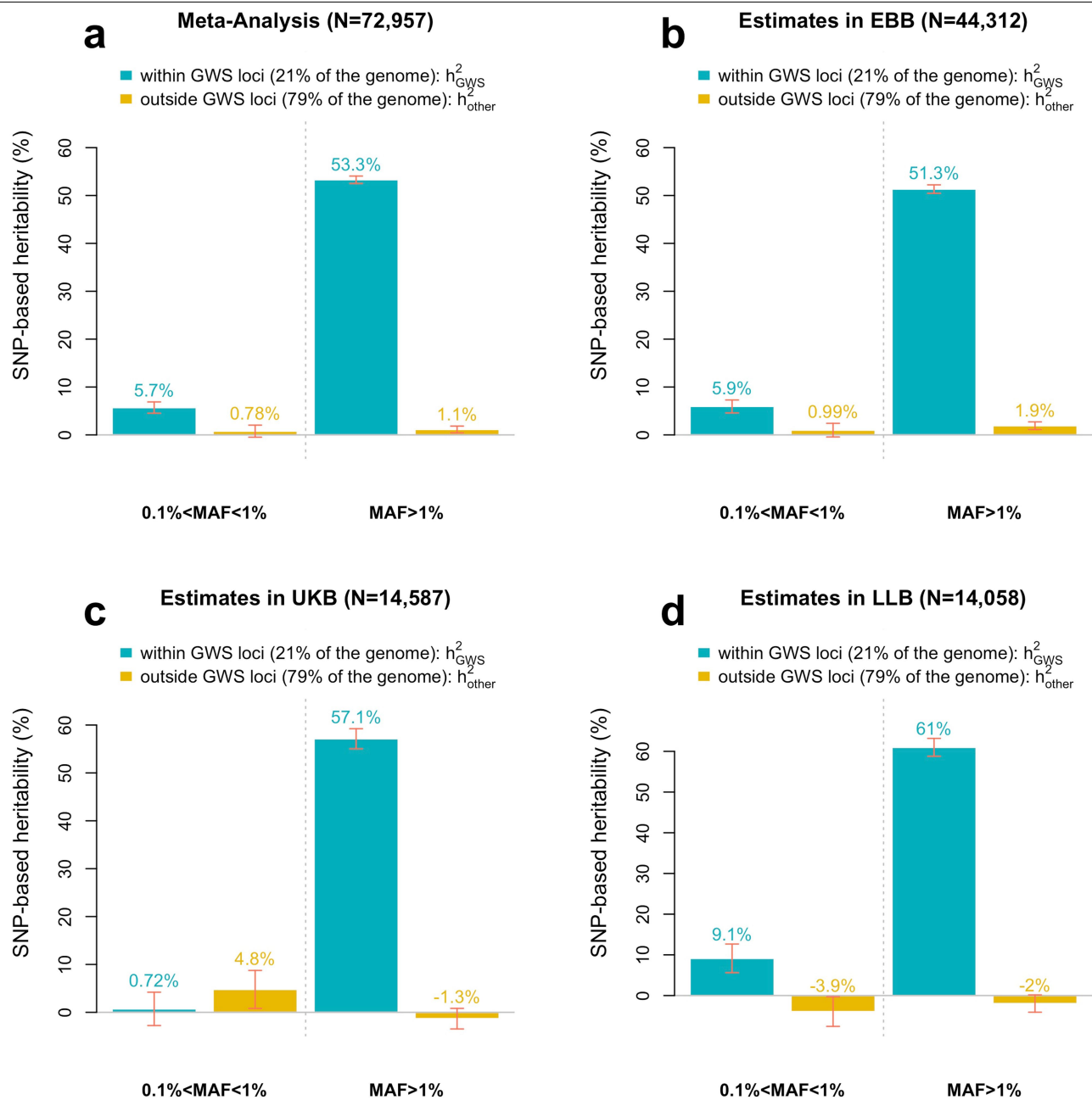
Extended Data Fig. 8 | Enrichment of height-associated genes identified at various GWAS sample sizes within 20 clusters of gene sets representing broad categories of biological pathways. Gene-set enrichment was performed with MAGMA and DEPICT across seven GWAS with increasing sample sizes. Samples used (Lango Allen et al. (2010), $n = 0.13\text{M}$; Wood et al. (2014), $n = 0.24\text{M}$; Yengo et al. (2018), $n = 0.7\text{M}$; GIANT-EUR (no 23andMe), $n = 1.63\text{M}$; 23andMe-EUR, $n = 2.5\text{M}$; European-ancestry meta-analysis, $n = 4.08\text{M}$; and cross-ancestry meta-analysis, $n = 5.31\text{M}$) are described in Tables 1–2. The degree of enrichment of gene sets (MAGMA, DEPICT) of known skeletal growth disorder genes catalogued in the Online Mendelian Inheritance in

Man (OMIM) database among 20 clusters of gene sets (see Methods section in Supplementary Note 5) is indicated by the blue-red colour scale. Enrichment for MAGMA and DEPICT was defined to be the number of prioritized gene sets (top 10% of gene sets) in each cluster divided by the 10% of the number of gene sets in the cluster. Enrichment for OMIM was defined to be the number of OMIM genes in a gene set ($Z > 1.96$) divided by the size of the gene set divided by the proportion of all genes in OMIM, then averaged across the cluster. Significant enrichment (compared to shuffled prioritization of gene sets or genes) is marked with *.



Extended Data Fig. 9 | Annotation-level saturation of GWAS discoveries as a function of sample size. Increase in sample size from ~4 million to ~5 million is achieved by including ~1 million participants of non-European ancestry. **a**, Number of annotations showing a significant heritability enrichment as function the function of the sample size of the GWAS used to estimate these enrichment. Heritability enrichment was detected using a stratified LD score regression (LDSC) analysis of 97 genomic annotations included in the “baseline + LD” model from Gazal et al. **b**, Correlation between Z-scores measuring

the statistical significance of heritability enrichments of 97 annotations (each dot is an annotation) in our largest GWAS (x-axis) as compared to down-sampled GWAS (y-axis). Sample size is denoted by the colour-code. **c**, Distribution of estimated enrichment statistics for 21 annotations found significantly enriched ($P < 0.05/97$) in at least 6 of the 7 GWAS analysed here. LoF-i genes: Loss of function intolerant genes; TSS: Transcription Start Sites; DGF: Digital genomic footprint; TFBS: Transcription Factor Binding Sites; DHS: DNase I hypersensitive sites; GERP (NS): GERP++ score (number of substitutions).



Extended Data Fig. 10 | Partitioning of low-frequency SNP-based heritability within GWS loci. Panels **b–d** represent partitioned SNP-based heritability estimates from three samples (EBB: Estonian Biobank; UKB: UK Biobank; LLB: Lifelines Biobank) of unrelated European ancestry individuals independent of our discovery GWAS. **a**, Partitioned SNP-based heritability estimates obtained from an inverse-variance weighted meta-analysis of

estimates shown in **b–d**. SNPs were partitioned into four classes according to their minor allele frequency (MAF: 0.1% < MAF < 1% vs. MAF > 1%) and their position within versus outside GWS loci. The SNP-based heritability contributed by SNPs within GWS loci is denoted h^2_{GWS} , and that contributed by SNPs outside these loci is denoted h^2_{other} . These results are further discussed in Supplementary Note 6.

Corresponding author(s): Dr Loic Yengo

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| ☒ | ☐ | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ | The statistical test(s) used AND whether they are one- or two-sided
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ | A description of all covariates tested |
| ☐ | ☒ | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| ☐ | ☒ | A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| ☐ | ☒ | For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
<i>Give P values as exact values whenever suitable.</i> |
| ☐ | ☒ | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☒ | ☐ | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☒ | ☐ | Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated |

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection Genotyping arrays and calling algorithms are listed for all cohorts in ST2.

Data analysis Statistical analyses were performed with R version v4.21 (for simulations, visualization, regression and prediction analyses), PLINK v1.9 for standard quality control and GWAS analyses, GCTA v1.93 for estimating SNP-based heritability and for conditional analyses (COJO algorithm), GCTB v2.0 for running the SBayesC model used in prediction analyses, BOLT-LMM v2 and rtest for mixed-model based GWAS analyses (versions listed in ST2), KING v2.2.5 for identifying relatives in certain cohorts, RAREMETAL v4.15.1 for running within-ancestry GWAS meta-analyses, LDSC v1.0.0 for LD score regression analyses, ImpG-Summary v1.0.1 for imputing GWAS summary statistics, SMR v1.03 for eQTL-based Mendelian Randomization analyses. Additional scripts used for analyses are listed in the Code Availability Statement.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

Summary statistics for ancestry-specific and multi-ancestry GWAS (excluding data from 23andMe) as well as SNP weights for polygenic scores derived in this study are made publicly available at https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files. GWAS summary statistics derived

involving 23andMe participants will be made available to qualified researchers under an agreement with 23andMe that protects the privacy of participants. Application for data access can be submitted at <https://research.23andme.com/dataset-access/>. We used genotypes from various publicly available databases to estimate linkage disequilibrium correlations required for conditional analyses and genome-wide prediction analyses. These databases include the UK Biobank under project 12505 and the database of Genotypes and Phenotypes (dbGaP) under project 15096. Accession numbers for dbGaP datasets are phs000788.v2.p3.c1, phs000386, phs000557.v4.p1, phs000286.v5.p1, phs000613.v1.p2, phs000284.v2.p1, phs000283.v7.p3 and phs001395.v2.p1 cohorts. Details for each dbGaP dataset are given in the Methods section.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We meta-analyzed GWAS data from 281 cohorts, with the aim to reach the largest possible sample size (here, N=5.4 million). Our sample size is larger than any previous GWAS of height, thereby expected to deliver additional associations.
Data exclusions	Samples were excluded based on heterozygosity, low call rate, relatedness relative to other participants of the same cohort. Details for each cohort are given in ST2. We analyzed SNPs with a minor allele frequency >1% in at least one of five ancestry groups. Other quality control exclusions are listed in ST2.
Replication	We replicated associations detected in our study in N=49,160 individuals in the Estonian Biobank. Quantification of variance explained by height-associated SNPs and prediction accuracy was performed in 61,095 individuals independent of our discovery dataset from four cohorts (hold-out sample from the UK Biobank, the Lifelines Study, the Chinese Kadoorie Biobank and the PAGE Study).
Randomization	N/A. Our study is observational and used data from all available participants. No intervention was implemented in any of the study participants, therefore randomization was not required.
Blinding	N/A. No intervention was implemented in any of the study participants, therefore blinding was not required.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	The mean/standard deviation/ minimum and maximum values for height and age is given separately for males and females of each cohort in ST3.
Recruitment	Study participants were recruited under various designs including population based, prospective studies, birth cohorts, family-based, hospital-based, (nested) case-controls, case-cohort, clinical trials. Designs for each cohort is listed in ST1.
Ethics oversight	Written informed consent was obtained from every participant in each study, and the study was approved by relevant ethics committees for each cohort. We provide a list of Institutional Review Boards in ST1.

Note that full information on the approval of the study protocol must also be provided in the manuscript.