Article

A saturated map of common genetic variants associated with human height

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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 sizes[1]. 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 panel[2]) 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 individuals[3]. 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 specified[4].

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.

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

Cohort ancestry or ethnic group	Number of studies	Max *n* (mean *n*)	Number of GWS COJO SNPs (P_{GWAS} <5×10^{-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<5×10^{-8}). COJO SNPs: near-independent GWS SNPs identified using an approximate COJO analysis implemented in the GCTA software. P_{GWAS}: 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)[5]. 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 panel[2], 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 analyses[6], as implemented in GCTA[7] (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 individuals[8] (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 ($r^2_{LD} > 0.8$) with at least one variant reaching marginal genome-wide significance ($P_{GWAS} < 5 \times 10^{-8}$) 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 ($r^2_{LD} > 0.8$ 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 reported[15]. 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 $P_{EUR} = 0.08$, 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 regression[16] analysis of our $META_{FE}$ using LD scores estimated in EUR. In this analysis, we focused on the attenuation ratio statistic ($R_{LDSC\text{-}EUR}$), 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 $R_{LDSC\text{-}EUR}$ 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 $R_{LDSC\text{-}EUR}$ 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 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.

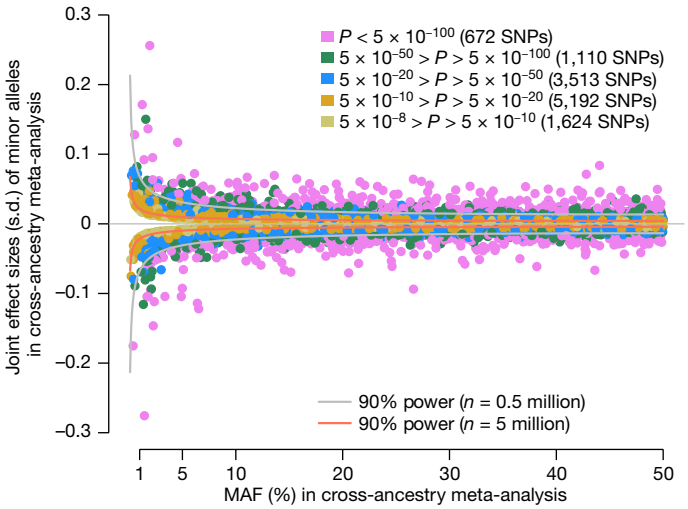

Fig. 1 | Relationship between frequency and estimated effect sizes of minor alleles. Each dot represents one of the 12,111 quasi-independent GWS SNPs that were identified in our cross-ancestry GWAS meta-analysis. Data underlying this figure are available in Supplementary Table 10. SNP effect estimates (*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 (*P*) 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.

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) database[18] 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

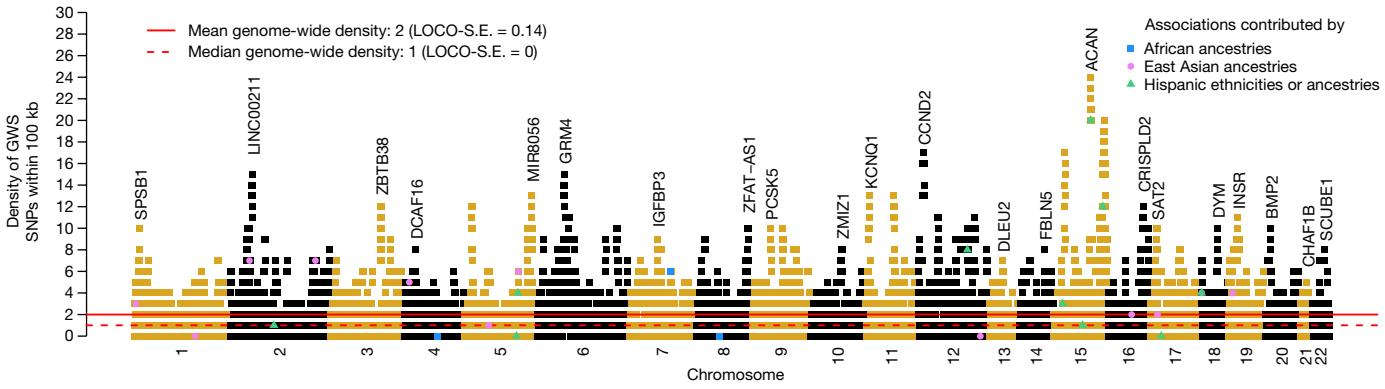

Fig. 2 | Brisbane plot showing the genomic density of independent genetic associations with height. Each dot represents one of the 12,111 quasi-independent GWS ($P < 5 \times 10^{-8}$) height-associated SNPs identified using approximate COJO analyses of our cross-ancestry GWAS meta-analysis. Data underlying 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 enhancers[23], missense variants[24] 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 method[28] (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 $PGS_{GWS\text{-}X}$ and $PGS_{HM3\text{-}X}$ (and R^2_{GWS-X} and R^2_{HM3-X}) to specify which GWAS

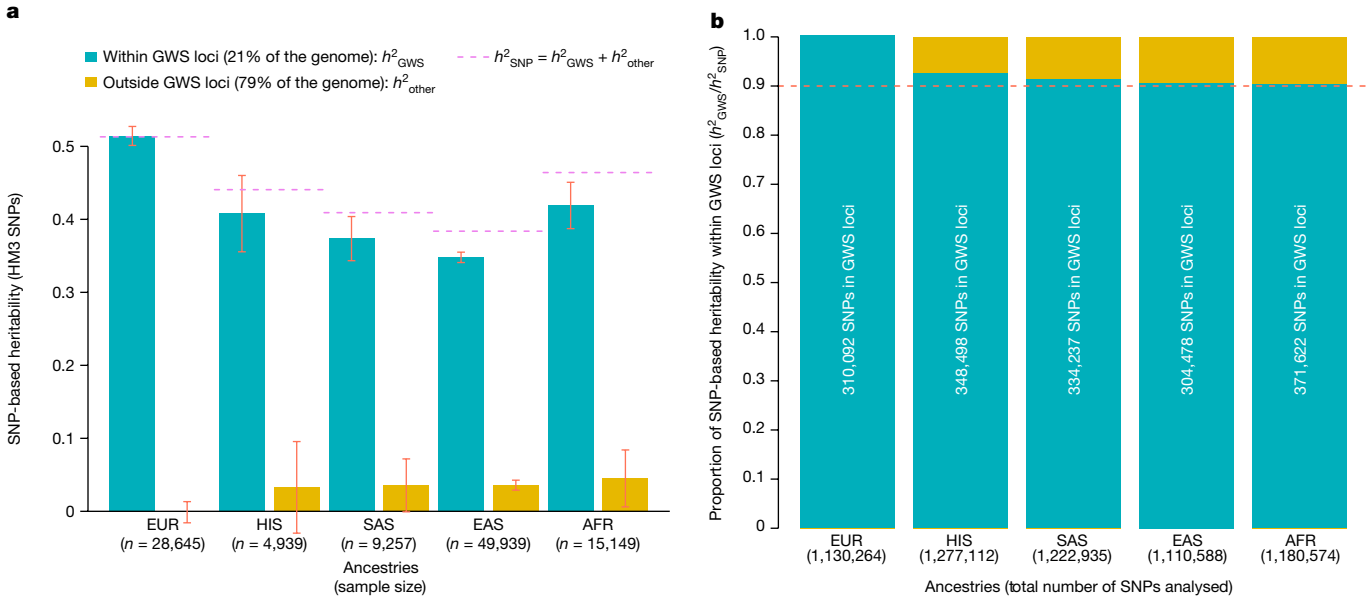

Fig. 3 | Variance of height explained by HM3 SNPs within GWS loci. **a**, Stratified SNP-based heritability (h^2_{SNP}) estimates obtained after partitioning the genome into SNPs within 35 kb of a GWS SNP ('GWS loci' label) versus SNPs that are more than 35 kb away from any GWS SNP. Analyses were performed 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, $PGS_{GWS\text{-}METAFE}$ 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. $PGS_{GWS\text{-}METAFE}$ 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 studies[29]. $PGS_{GWS\text{-}EUR}$ (based on 9,863 SNPs) was the second best of all PGS_{GWS} across ancestry groups except in AFR. Indeed, $PGS_{GWS\text{-}AFR}$ (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 $PGS_{GWS\text{-}EUR}$ in these two samples, respectively (Fig. 4a). $PGS_{GWS\text{-}METAFE}$ was the best of all PGS_{GWS} in AFR participants with an accuracy $R^2_{GWS-METAFE}$ = (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 $PGS_{GWS\text{-}METAFE}$ was observed in EUR participants ($R^2_{GWS-METAFE}$ ~40%; s.e. 0.6%) and the lowest in AFR participants from the UKB ($R^2_{GWS-METAFE}$ ≈ 9.4%; s.e. 0.7%). Note that the difference in $R^2_{GWS-METAFE}$ 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 ($R^2_{GWS-METAFE}$ in AFR)/($R^2_{GWS-METAFE}$ in EUR) of around 25% that was previously reported[30]. 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 ($R^2_{GWS-AFR}$ = 8.5% versus R^2_{HM3} = 15.4%; Fig. 4a) and the UKB ($R^2_{GWS-AFR}$ = 8.5% versus R^2_{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 $PGS_{HM3\text{-}EUR}$ 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 $PGS_{GWS\text{-}EUR}$ and 55.2% (s.e. 3.2%) with $PGS_{HM3\text{-}EUR}$. 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].

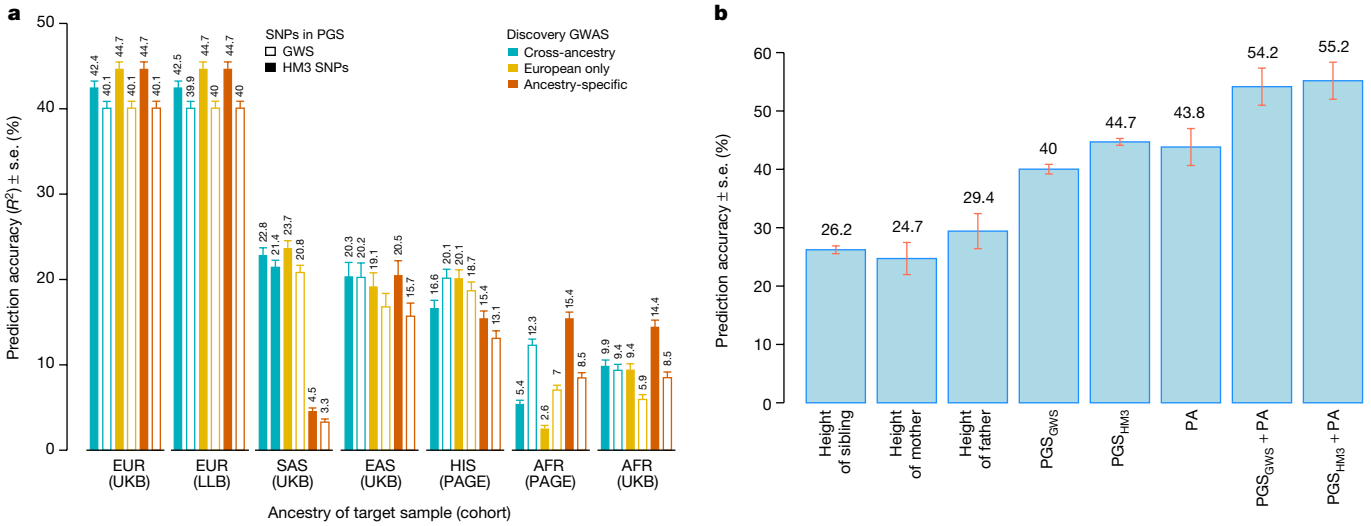

Fig. 4 | Accuracy of PGSs within families and across ancestries. Prediction accuracy (R^2) was measured as the squared correlation between PGS and actual height adjusted for age, sex and 10 genetic principal components. **a**, Accuracy of PGSs assessed in participants of five different ancestry groups: 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 randomization[41] (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 (DEPICT[42] and MAGMA[43]), 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 reported[44]. 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 *n* (mean *n*)	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.

[a]Summary statistics from the Lango Allen et al. study[19], 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 variants[13]. 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% < MAF < 1% (Supplementary Note 6, Extended Data Fig. 10 and Supplementary Fig. 25). Our results are consistent with findings from a previous study[45], 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 method[38] 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 height[52]. 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 (×2, that is, $n = 10$ million), schizophrenia (×7; $n = 35$ million) or BMI (×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 mapping[45], 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.

1. Yang, J. et al. Common SNPs explain a large proportion of the heritability for human height. *Nat. Genet.* **42**, 565–569 (2010).
2. The International HapMap 3 Consortium. Integrating common and rare genetic variation in diverse human populations. *Nature* **467**, 52–58 (2010).
3. Yengo, L. et al. Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. *Hum. Mol. Genet.* **27**, 3641–3649 (2018).
4. Flint, J. & Ideker, T. The great hairball gambit. *PLoS Genet.* **15**, e1008519 (2019).
5. The 1000 Genomes Project Consortium. A global reference for human genetic variation. *Nature* **526**, 68–74 (2015).
6. Yang, J. et al. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat. Genet.* **44**, 369–375 (2012).
7. Yang, J., Lee, S. H., Goddard, M. E. & Visscher, P. M. GCTA: a tool for genome-wide complex trait analysis. *Am. J. Hum. Genet.* **88**, 76–82 (2011).
8. Luo, Y. et al. Estimating heritability and its enrichment in tissue-specific gene sets in admixed populations. *Hum. Mol. Genet.* **30**, 1521–1534 (2021).
9. Berg, J. J. et al. Reduced signal for polygenic adaptation of height in UK Biobank. *eLife* **8**, e39725 (2019).
10. Sohail, M. et al. Polygenic adaptation on height is overestimated due to uncorrected stratification in genome-wide association studies. *eLife* **8**, e39702 (2019).
11. Palmer, C. & Pe'er, I. Statistical correction of the Winner's Curse explains replication variability in quantitative trait genome-wide association studies. *PLoS Genet.* **13**, e1006916 (2017).
12. Zhong, H. & Prentice, R. L. Bias-reduced estimators and confidence intervals for odds ratios in genome-wide association studies. *Biostatistics* **9**, 621–634 (2008).
13. Galinsky, K. J. et al. Estimating cross-population genetic correlations of causal effect sizes. *Genet. Epidemiol.* **43**, 180–188 (2019).
14. Guo, J. et al. Quantifying genetic heterogeneity between continental populations for human height and body mass index. *Sci. Rep.* **11**, 5240 (2021).
15. Voight, B. F., Kudaravalli, S., Wen, X. & Pritchard, J. K. A map of recent positive selection in the human genome. *PLoS Biol.* **4**, e72 (2006).
16. Bulik-Sullivan, B. K. et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47**, 291–295 (2015).
17. Turley, P. et al. Multi-trait analysis of genome-wide association summary statistics using MTAG. *Nat. Genet.* **50**, 229–237 (2018).
18. Lui, J. C. et al. Synthesizing genome-wide association studies and expression microarray reveals novel genes that act in the human growth plate to modulate height. *Hum. Mol. Genet.* **21**, 5193–5201 (2012).
19. Lango Allen, H. et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* **467**, 832–838 (2010).
20. Wood, A. R. et al. Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat. Genet.* **46**, 1173–1186 (2014).
21. Beyter, D. et al. Long-read sequencing of 3,622 Icelanders provides insight into the role of structural variants in human diseases and other traits. *Nat. Genet.* **53**, 779–786 (2021).
22. Mukamel, R. E. et al. Protein-coding repeat polymorphisms strongly shape diverse human phenotypes. *Science* **373**, 1499–1505 (2021).
23. Hu, G., Codina, M. & Fisher, S. Multiple enhancers associated with ACAN suggest highly redundant transcriptional regulation in cartilage. *Matrix Biol.* **31**, 328–337 (2012).
24. Marouli, E. et al. Rare and low-frequency coding variants alter human adult height. *Nature* **542**, 186–190 (2017).
25. Wu, Y., Zheng, Z., Visscher, P. M. & Yang, J. Quantifying the mapping precision of genome-wide association studies using whole-genome sequencing data. *Genome Biol.* **18**, 86 (2017).

26. Sun, H., Ding, J., Piednoël, M. & Schneeberger, K. findGSE: estimating genome size variation within human and *Arabidopsis* using *k*-mer frequencies. *Bioinformatics* **34**, 550–557 (2018).
27. Bulik-Sullivan, B. et al. An atlas of genetic correlations across human diseases and traits. *Nat. Genet.* **47**, 1236–1241 (2015).
28. Lloyd-Jones, L. R. et al. Improved polygenic prediction by Bayesian multiple regression on summary statistics. *Nat. Commun.* **10**, 5086 (2019).
29. Graham, S. E. et al. The power of genetic diversity in genome-wide association studies of lipids. *Nature* **600**, 675–679 (2021).
30. Martin, A. R. et al. Current clinical use of polygenic scores will risk exacerbating health disparities. *Nat. Genet.* **51**, 584–591 (2019).
31. Lello, L. et al. Accurate genomic prediction of human height. *Genetics* **210**, 477–497 (2018).
32. Privé, F. et al. Portability of 245 polygenic scores when derived from the UK Biobank and applied to 9 ancestry groups from the same cohort. *Am. J. Hum. Genet.* **109**, 12–23 (2022).
33. Patxot, M. et al. Probabilistic inference of the genetic architecture underlying functional enrichment of complex traits. *Nat. Commun.* **12**, 6972 (2021).
34. Ge, T., Chen, C.-Y., Ni, Y., Feng, Y.-C. A. & Smoller, J. W. Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nat. Commun.* **10**, 1776 (2019).
35. Márquez-Luna, C. et al. Incorporating functional priors improves polygenic prediction accuracy in UK Biobank and 23andMe data sets. *Nat. Commun.* **12**, 6052 (2021).
36. Duncan, L. et al. Analysis of polygenic risk score usage and performance in diverse human populations. *Nat. Commun.* **10**, 3328 (2019).
37. Marnetto, D. et al. Ancestry deconvolution and partial polygenic score can improve susceptibility predictions in recently admixed individuals. *Nat. Commun.* **11**, 1628 (2020).
38. Wang, Y. et al. Theoretical and empirical quantification of the accuracy of polygenic scores in ancestry divergent populations. *Nat. Commun.* **11**, 3865 (2020).
39. Finucane, H. K. et al. Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat. Genet.* **47**, 1228–1235 (2015).
40. Gazal, S. et al. Linkage disequilibrium-dependent architecture of human complex traits shows action of negative selection. *Nat. Genet.* **49**, 1421–1427 (2017).
41. Zhu, Z. et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat. Genet.* **48**, 481–487 (2016).
42. Pers, T. H. et al. Biological interpretation of genome-wide association studies using predicted gene functions. *Nat. Commun.* **6**, 5890 (2015).
43. de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput. Biol.* **11**, e1004219 (2015).
44. Visscher, P. M. et al. 10 years of GWAS discovery: biology, function, and translation. *Am. J. Hum. Genet.* **101**, 5–22 (2017).
45. Backman, J. D. et al. Exome sequencing and analysis of 454,787 UK Biobank participants. *Nature* **599**, 628–634 (2021).
46. Das, S. et al. Next-generation genotype imputation service and methods. *Nat. Genet.* **48**, 1284–1287 (2016).
47. Si, Y., Vanderwerff, B. & Zöllner, S. Why are rare variants hard to impute? Coalescent models reveal theoretical limits in existing algorithms. *Genetics* **217**, iyab011 (2021).
48. Halldorsson, B. V. et al. The sequences of 150,119 genomes in the UK Biobank. *Nature* **607**, 732–740 (2022).
49. Taliun, D. et al. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. *Nature* **590**, 290–299 (2021).
50. Wainschtein, P. et al. Assessing the contribution of rare variants to complex trait heritability from whole-genome sequence data. *Nat. Genet.* **54**, 263–273 (2022).
51. Yang, J. et al. Genome-partitioning of genetic variation for complex traits using common SNPs. *Nat. Genet.* **43**, 519–525 (2011).
52. O'Connor, L. J. The distribution of common-variant effect sizes. *Nat. Genet.* **53**, 1243–1249 (2021).

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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 EasyQC[53] 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 RAREMETAL[55] (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^2_{INFO}) > 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 PGSs.

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 stepwise 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 $r^2_{\mathrm{INFO}} > 0.3$ and $P_{\mathrm{HWE}} > 10^{-6}$. 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 (CARe[56], 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 $\mathrm{META}_{\mathrm{FE}}$ 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^2_{LD}) 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 index[57], which measures allele frequency divergence between two populations. We used the Hudson's estimator of F_{ST}[58] as previously recommended[59] to compare allele frequencies from our $\mathrm{META}_{\mathrm{FE}}$ 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 previously[40]. 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 OMIM[18] 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 $i = 1,\ldots,9$; between i × 100 kb and $(i+1) \times 100$ kb, with $i = 1,\ldots,10$; 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 annotations[39].

These 24 annotations (for example, coding or conserved) are thoroughly described in a previous study[39] and were downloaded from https://alkesgroup.broadinstitute.org/LDSCORE/baselineLD_v2.1_annots/.

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 study[60], 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 method[12]. 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:

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

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 × MAF × (1 − 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 GCTA[1,7]. 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 × 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

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 ($r^2_{LD} < 0.1$). 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 method[28] 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 previously[3]. 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 previously[38]. Lifelines samples were imputed to the HRC panel. PAGE and CKB were imputed to the 1KG reference panel. Standard quality control ($r^2_{INFO} > 0.3$, $P_{HWE} > 10^{-6}$ 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 method[38] 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 described[38], 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 $r^2_{LD} > 0.45$ with a GWS SNP within that 100-kb window. Standard errors were calculated using a delta-method approximation as previously described[38].

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 $\beta = Z/\sqrt{2\text{MAF} \times (1 - \text{MAF}) \times (N + Z^2)}$ and $\text{SE} = \beta/Z$. 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 GTEx[65] 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 study[66].

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-eqtls.html. Annotation-weighted LD scores for stratified LD score regression analyses: https://alkesgroup.broadinstitute.org/LDSCORE/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.

53. Winkler, T. W. et al. Quality control and conduct of genome-wide association meta-analyses. *Nat. Protoc.* **9**, 1192–1212 (2014).
54. Zhan, X., Hu, Y., Li, B., Abecasis, G. R. & Liu, D. J. RVTESTS: an efficient and comprehensive tool for rare variant association analysis using sequence data. *Bioinformatics* **32**, 1423–1426 (2016).
55. Feng, S., Liu, D., Zhan, X., Wing, M. K. & Abecasis, G. R. RAREMETAL: fast and powerful meta-analysis for rare variants. *Bioinformatics* **30**, 2828–2829 (2014).
56. Musunuru, K. et al. Candidate gene association resource (CARe): design, methods, and proof of concept. *Circ. Cardiovasc. Genet.* **3**, 267–275 (2010).
57. Wright, S. The genetical structure of populations. *Ann. Eugen.* **15**, 323–354 (1951).
58. Hudson, R. R., Slatkin, M. & Maddison, W. P. Estimation of levels of gene flow from DNA sequence data. *Genetics* **132**, 583–589 (1992).
59. Bhatia, G., Patterson, N., Sankararaman, S. & Price, A. L. Estimating and interpreting F_{ST}: the impact of rare variants. *Genome Res* **23**, 1514–1521 (2013).
60. Qi, T. et al. Identifying gene targets for brain-related traits using transcriptomic and methylomic data from blood. *Nat. Commun.* **9**, 2282 (2018).
61. Privé, F., Arbel, J. & Vilhjálmsson, B. J. LDpred2: better, faster, stronger. *Bioinformatics* **36**, 5424–5431 (2020).
62. Vilhjálmsson, B. J. et al. Modeling linkage disequilibrium increases accuracy of polygenic risk scores. *Am. J. Hum. Genet.* **97**, 576–592 (2015).
63. Bycroft, C. et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203 (2018).
64. Pasaniuc, B. et al. Fast and accurate imputation of summary statistics enhances evidence of functional enrichment. *Bioinformatics* **30**, 2906–2914 (2014).
65. The GTEx Consortium.The GTEx Consortium atlas of genetic regulatory effects across human tissues. *Science* **369**, 1318–1330 (2020).
66. Wu, Y. et al. Integrative analysis of omics summary data reveals putative mechanisms underlying complex traits. *Nat. Commun.* **9**, 918 (2018).

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HL54495, HL54496, HL54509, HL54515, U24 MH068457-06, R01D0042157-01A1, RO1 MH58799-03, MH081802, 1RC2MH089951-01, 1RC2 MH089995, R01 DK092127-04, R01DK110113 (R.J.F.L.), R01DK075787 (R.J.F.L.), R01DK107786 (R.J.F.L.), R01HL142302 (R.J.F.L.), R01HG010297 (R.J.F.L.), R01DK124097 (R.J.F.L.), R01HL151152 (R.J.F.L.), R01-HL046380, KL2-RR024990, R35-HL135818, R01-HL113338, R35HL135818 (S. Redline), HL 046389 (S. Redline), HL113338 (S. Redline), K01 HL135405 (B.E.C.), R03 HL154284 (B.E.C.), R01HL086718, HG011052 (X. Zhu), N01-HC-25195, HHSN268201500001I, N02-HL-6-4278, R01-DK122503, U01AG023746, U01AG023712, U01AG023749, U01AG023755, U01AG023744, U19AG063893, R01-DK-089256, R01HL117078, R01 HL09135701, R01 HL091357, R01 HL104135, R37-HL045508, R01-HL053353, R01-DK075787, U01-HL054512, R01-HL074166, R01-HL086718, R01-HG003054, U01HG004423, U01HG004446, U01HG004438, DK078150, TW005596, HL085144, RR020649, ES010126, DK056350, R01DK072193, R01 HD30880, R01 AG065357, R01DK104371, R01HL108427, Fogarty grant D43 TW009077, 263 MD 9164, 263 MD 821336, N.1-AG-1-1, N.1-AG-1-2111, HHSN268201800013I, HHSN268201800014I, HHSN268201800015I, HHSN268201800010I, HHSN268201800011I and HHSN268201800012I, KL2TR002490 (L.M.R.), T32HL129982 (L.M.R.), R01AG056477, R01AG034454, R01 HD056465, U01 HL054457, U01 HL054464, U01 HL054481, R01 HL119443, R01 HL087660, U01AG009740, RC2 AG036495, RC4 AG039029, U01AG009740 (W. Zhao.), RC2 AG036495 (W. Zhao.), RC4 AG039029 (W. Zhao.), 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-000040, UL1-TR-001079, UL1-TR-001420, N02-HL-64278, UL1TR001881, DK063491, R01-HL088457, R01-HL-60030, R01-HL067974, R01-HL-55005, R01-HL 067974, R01HL111249, R01HL111249-04S1, U01HL54527, U01HL54498, EY014684, EY014684-03S1, EY014684-04S1, DK063491, S10OD017985, S10RR025141, UL1TR002243, UL1TR000445, UL1RR024975, U01HG004798, R01NS032830, RC2GM092618, P50GM115305, U01HG006378, U19HL065962, R01HD074711, 5K08HL135275 (R.W.M.), R01 HL77398 (B.L.), NR013520 (Y.V.S.), DK125187 (Y.V.S.), HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700004I, HHSN268201700005I, R01HL087641, R01HL086694, U01HG004402, HHSN268200625226C, UL1RR025005, U01HG007416, R01DK101855, 15GRNT25880008, N01-HC65233, N01-HC65234, N01-HC65235, N01-HC65236, N01-HC65237, U01HG007376, HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, HHSN271201100004C, N01-AG-6-2101, N01-AG-6-2103, N01-AG-6-2106, R01-AG028050, R01-NR012459, P30AG10161, P30AG72975, R01AG17917, RF1AG15819, R01AG30146, U01AG46152, U01AG61256, AG000513, R01 HD58886, R01 HD100406, N01-HD-1-3228, N01-HD-1-3329, N01-HD-1-3330, N01-HD-1-3331, N01-HD-1-3332, N01-HD-1-3333, UL1 TR000077, R01 HD056465 (S.F.A.G.), R01 HG010067 (S.F.A.G.), R01CA64277, R01CA15847, UM1CA182910, R01CA148677, R01CA144034, UM1 CA182876, R01DK075787, R01DK075787 (J.N.H.), ZIA CP010152-20, U19 CA 148537-01, U01 CA188392, X01HG007492, HHSN268201200008I, Z01CP010119, R01-CA080122, R01-CA056678, R01-CA082664, R01-CA092579, K05-CA175147, P30-CA015704, CA063464, CA054281, CA098758, CA164973, R01CA128813, K25 HL150334 (R. 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Additional information

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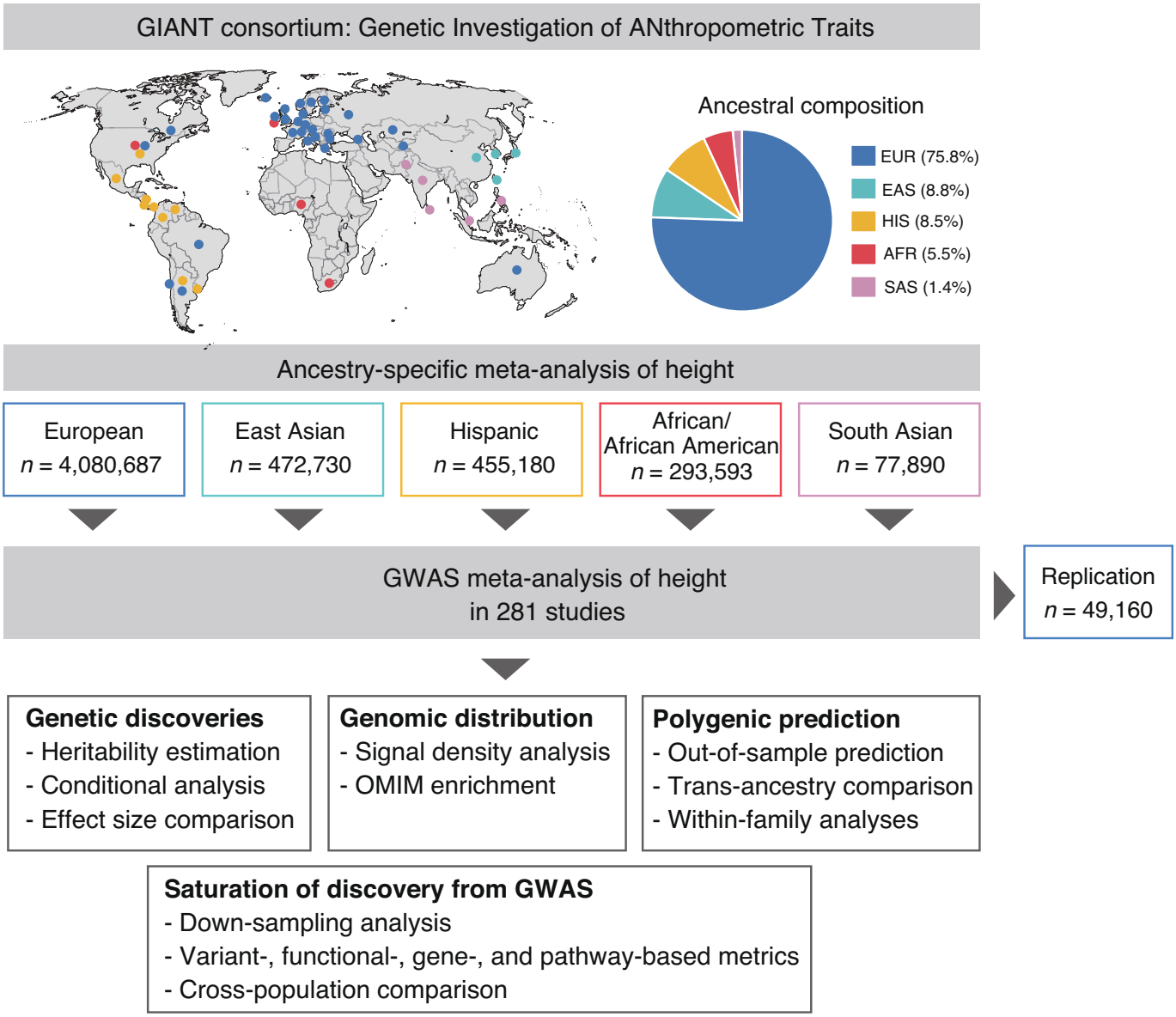
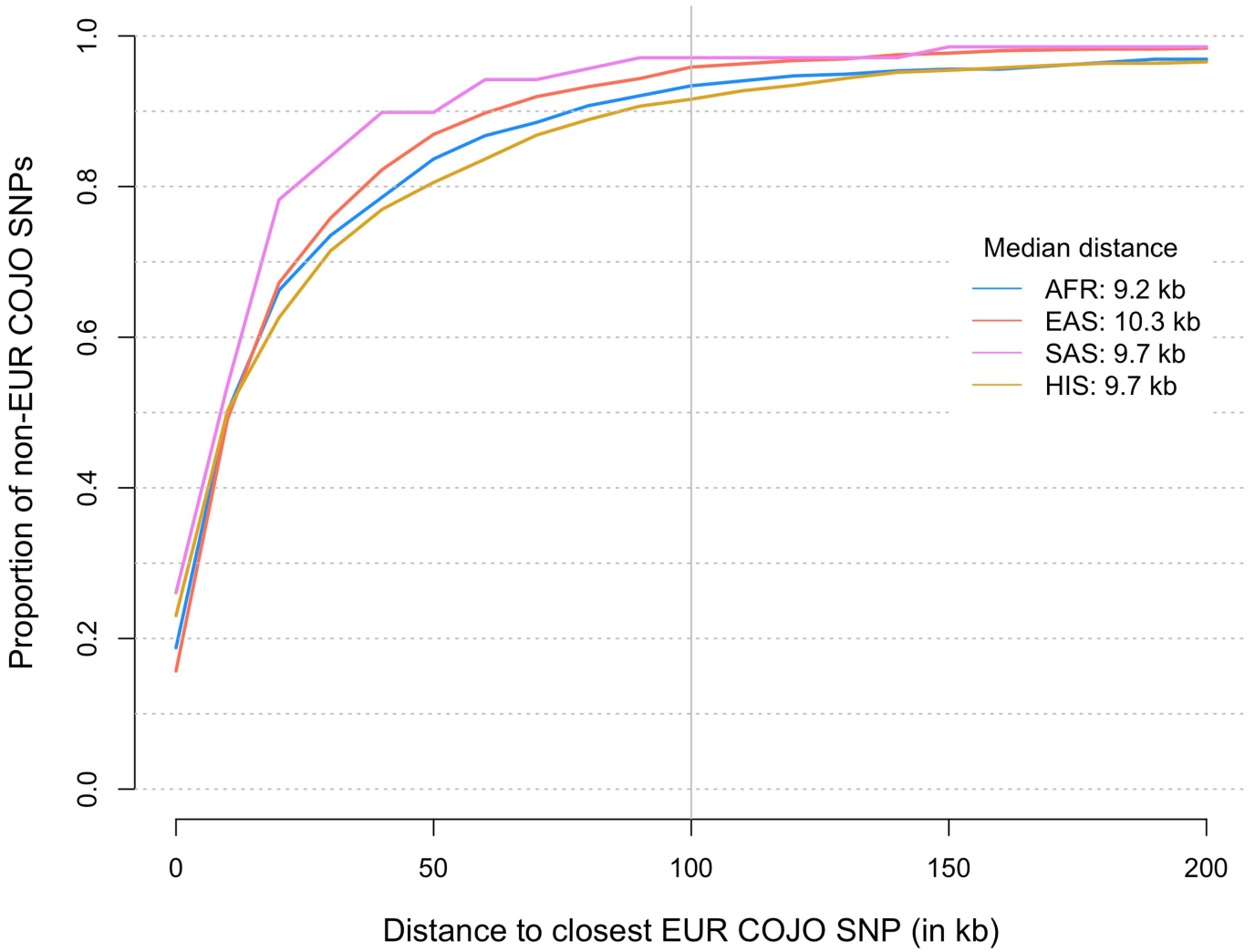
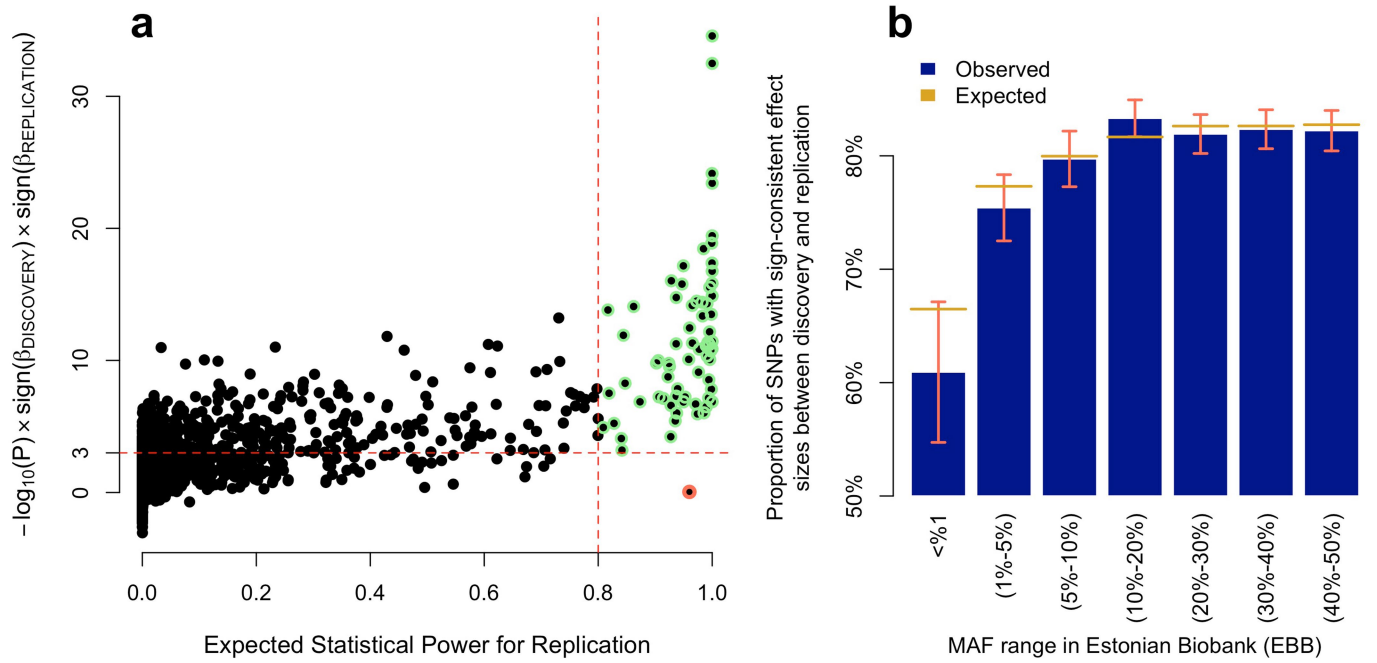


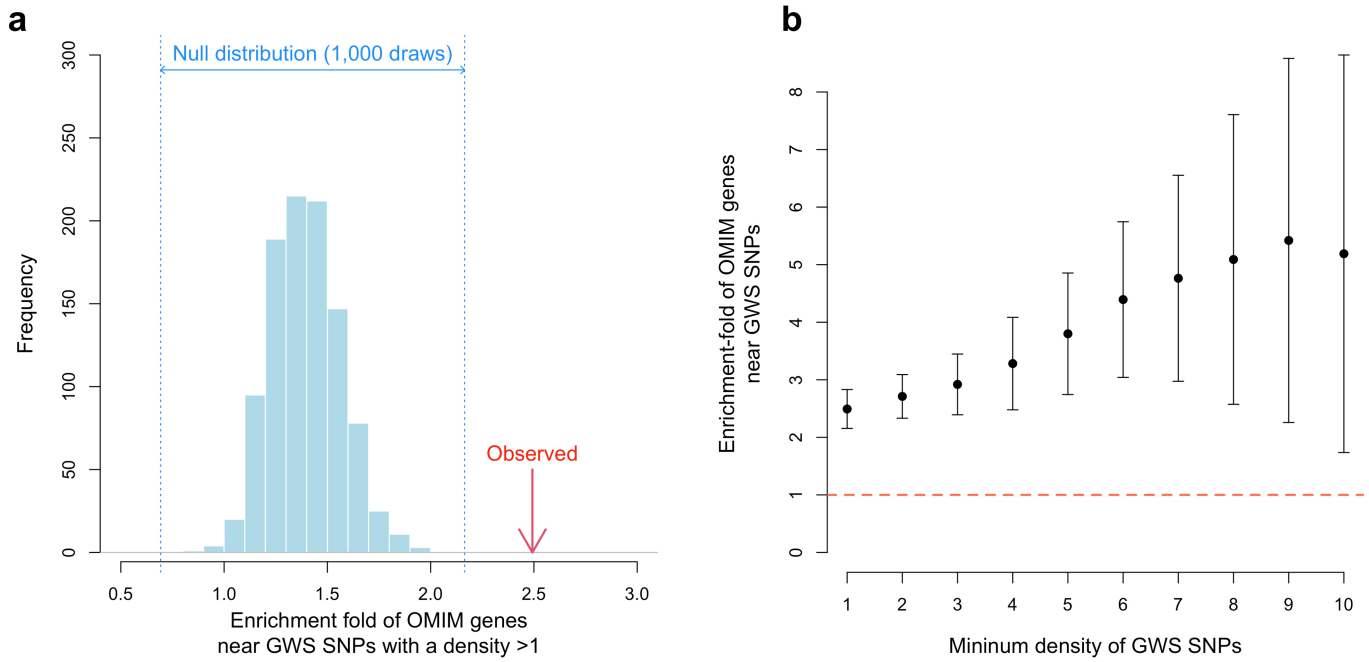
Extended Data Fig. 1 | Broad ancestries composition. Geographical mapping and ancestries composition of 281 studies meta-analysed in this study. Various analyses were performed including (1) dectection of height-associated SNPs (Genetic discoveries box), (2) quantification of the genomic distribution of height-associated loci (Genomic distribution box), (3) assessement 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).



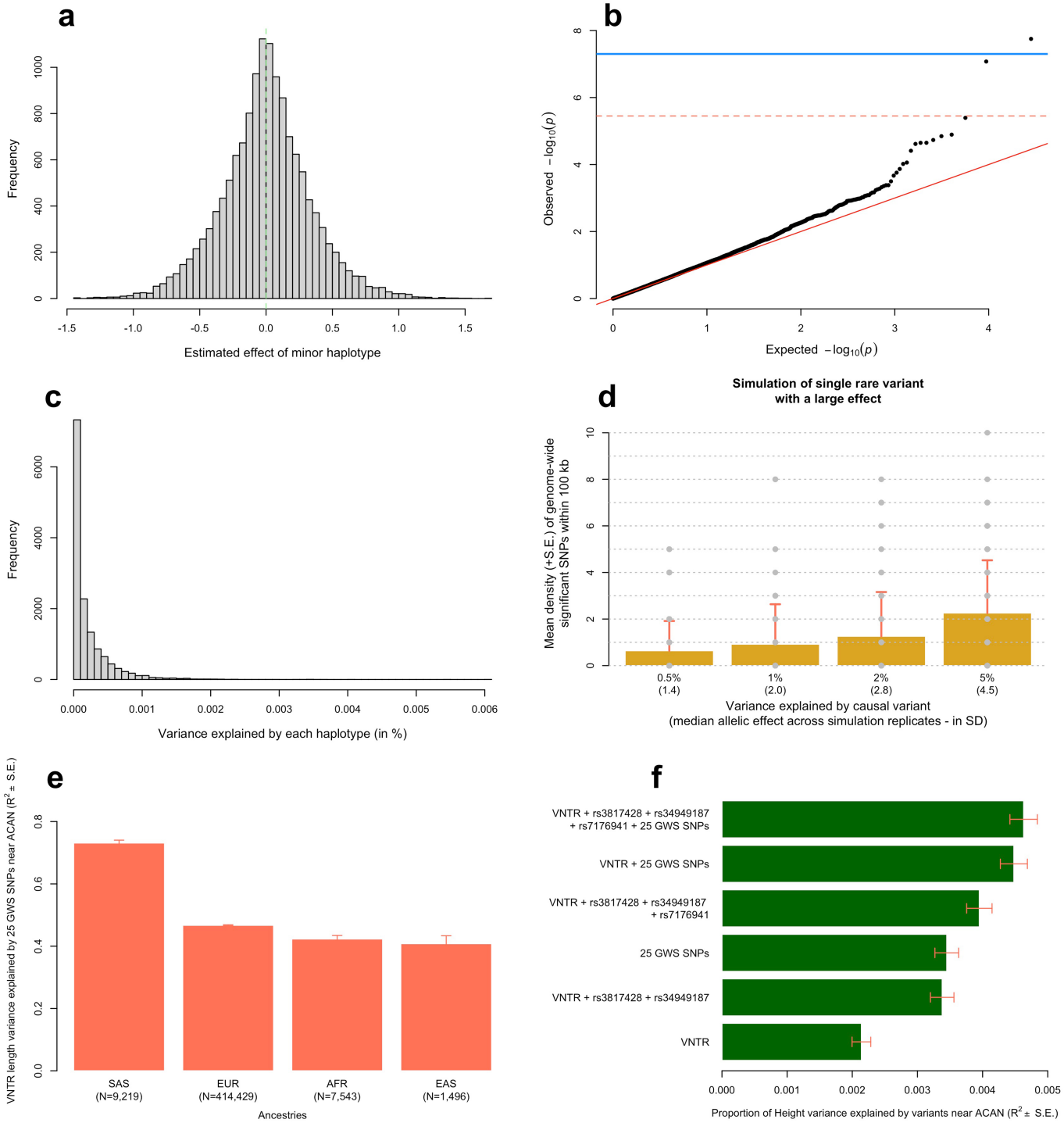
Extended Data Fig. 2 | Colocalization of height-associated signals across ancestries. Proportion (y-axis) of GWS SNPs identified in our GWAS meta-analyses of non-European (non-EUR: African – AFR; East Asian – EAS; South Asian – SAS; Hispanic – HIS) ancestry/ethnicity participants thar are located within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



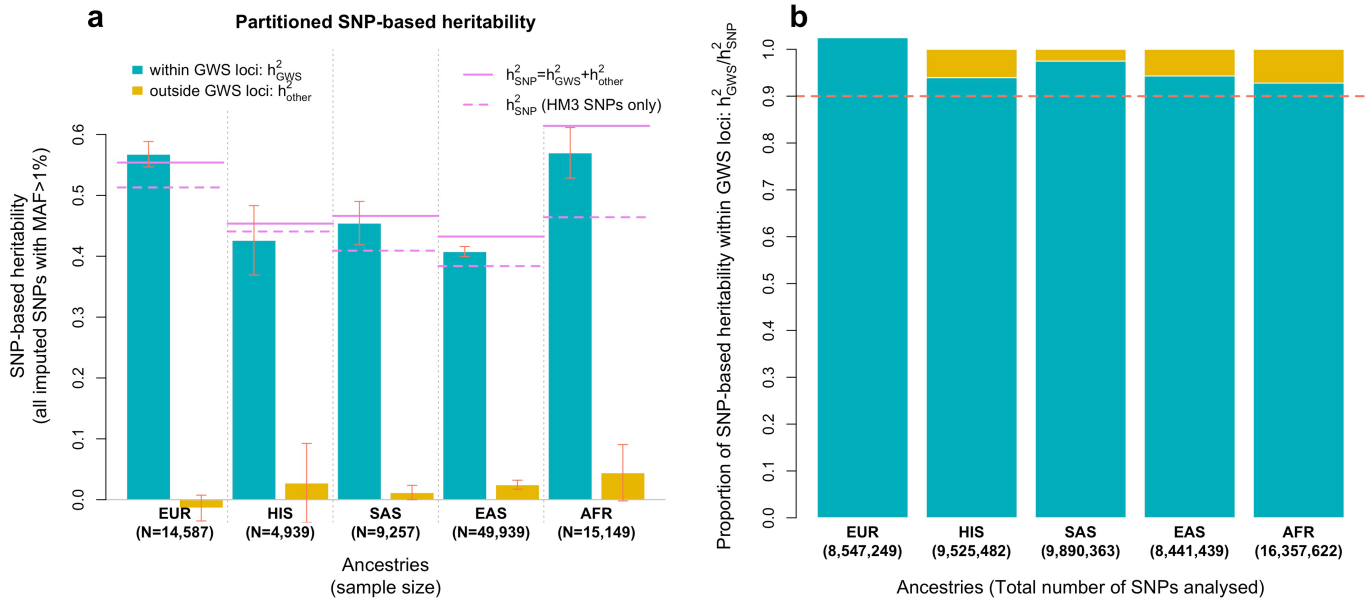
Extended Data Fig. 3 | Replication of marginal associations in the EBB. **a**, Each dot represents one the 12,111 SNPs detected in our trans-ancestry meta-analysis. The x-axis represents the expected statistical power to replicate each association ($P<0.05/9{,}473 = 5.3\times10^{-6}$; where 9,473 is 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.



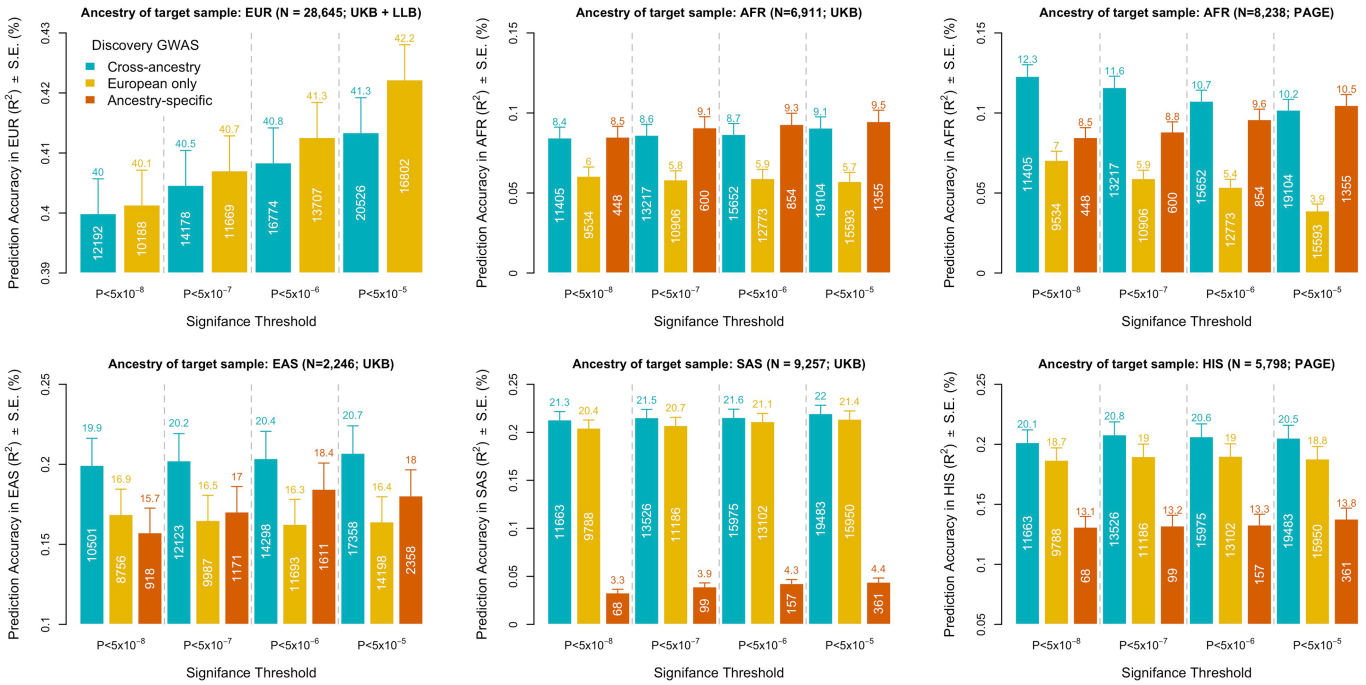
Extended Data Fig. 4 | Enrichment of genes containing pathogenic mutations that cause extreme height or abnormal skeletal growth syndromes near hotspots of GWS SNPs. Four hundred and sixty-two (462) autosomal genes were curated from the Online Mendelian Inheritance in Man (OMIM) database. **a**, Red 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 1.4×10^{-5} < 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.).

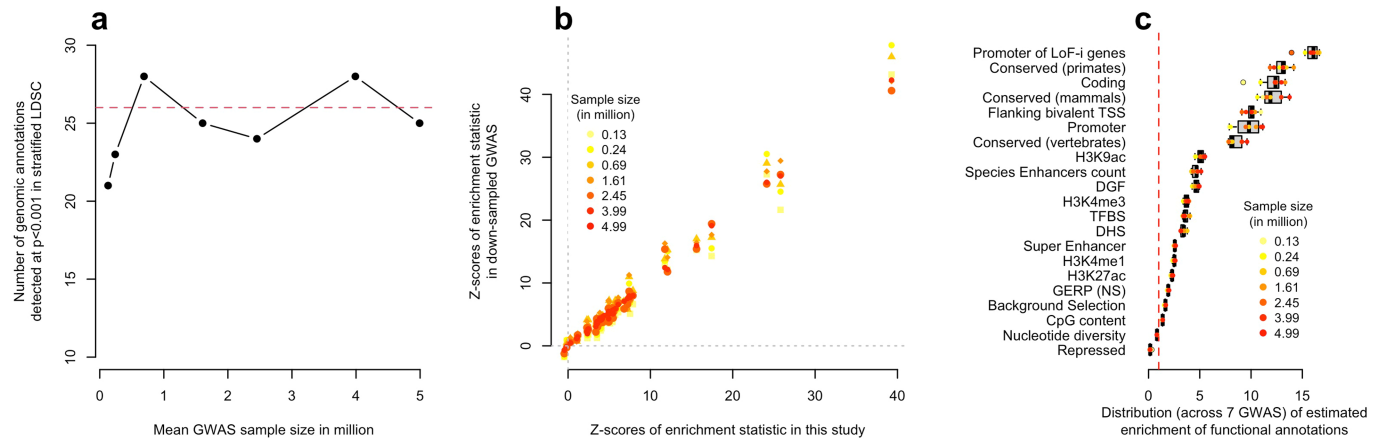


Extended Data Fig. 6 | Variance of height explained by common SNPs within 35 kb of GWS SNPs. Stratified SNP-based heritability (h^2_{SNP}) estimates were obtained from a partition of the genome into two sets of 1000 Genomes imputed SNPs with a minor allele frequency (MAF) >1%: (1) SNPs within +/− 35 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).

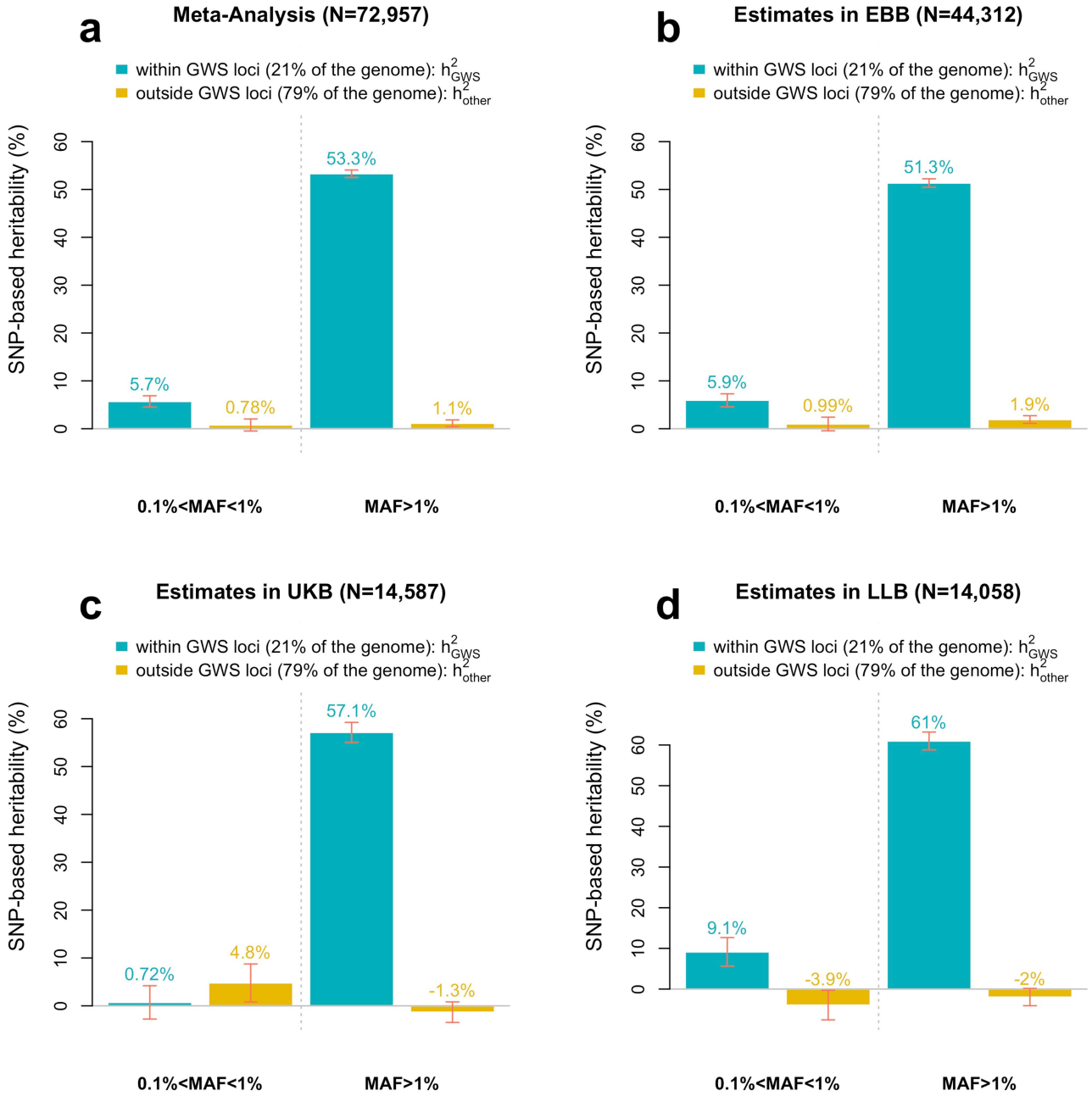


Extended Data Fig. 7 | Accuracy of PGSs derived from joint effects of SNPs ascertained at various significance thresholds. The six panels show on their y-axes the prediction accuracy (R^2) of multiple PGS across five target samples. The ancestry group and size of each target sample is indicated in the 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), $n = 0.13$M; Wood et al. (2014), $n = 0.24$M; Yengo et al. (2018), $n = 0.7$M; GIANT-EUR (no 23andMe), $n = 1.63$M; 23andMe-EUR, $n = 2.5$M; European-ancestry meta-analysis, $n = 4.08$M; and cross-ancestry meta-analysis, $n = 5.31$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.

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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 rvtest 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.

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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
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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.

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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.

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Supplementary information

A saturated map of common genetic variants associated with human height

In the format provided by the authors and unedited

A Saturated Map of Common Genetic Variants Associated with Human Height

Yengo L., Vedantam S., Marouli E., et al.

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Inter99
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The Multiethnic Cohort (MEC) is a population-based prospective cohort study including approximately 215,000 men and women from Hawaii and California. All participants were 45-75 years of age at baseline, and primarily of 5 ancestries: Japanese Americans, African Americans, European Americans, Hispanic/Latinos, and Native Hawaiians. (PMIDs: 10695593; 23449381) MEC was funded by the National Cancer Institute in 1993 to examine lifestyle risk factors and genetic susceptibility to cancer. All eligible cohort members completed baseline and follow-up questionnaires.

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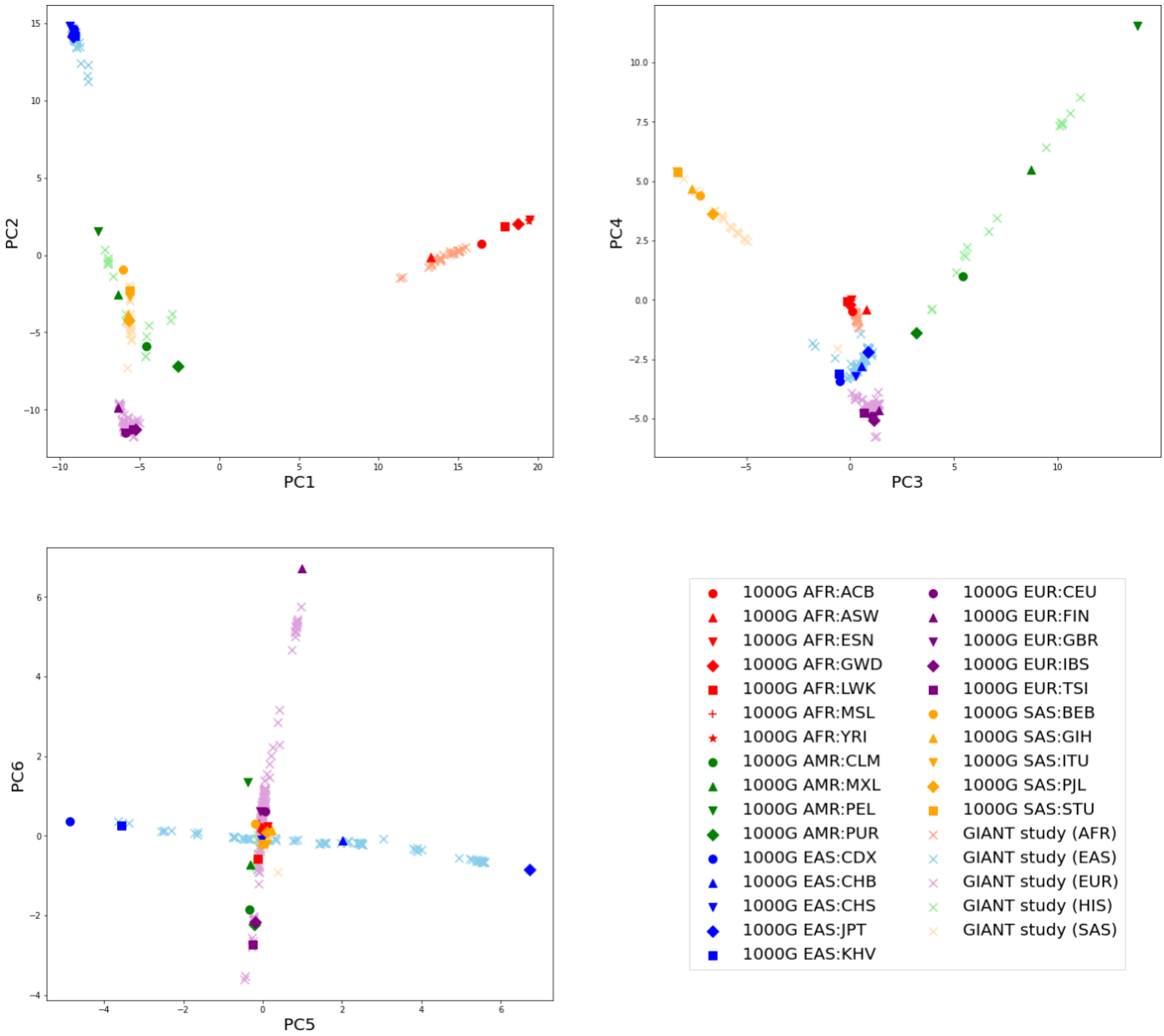
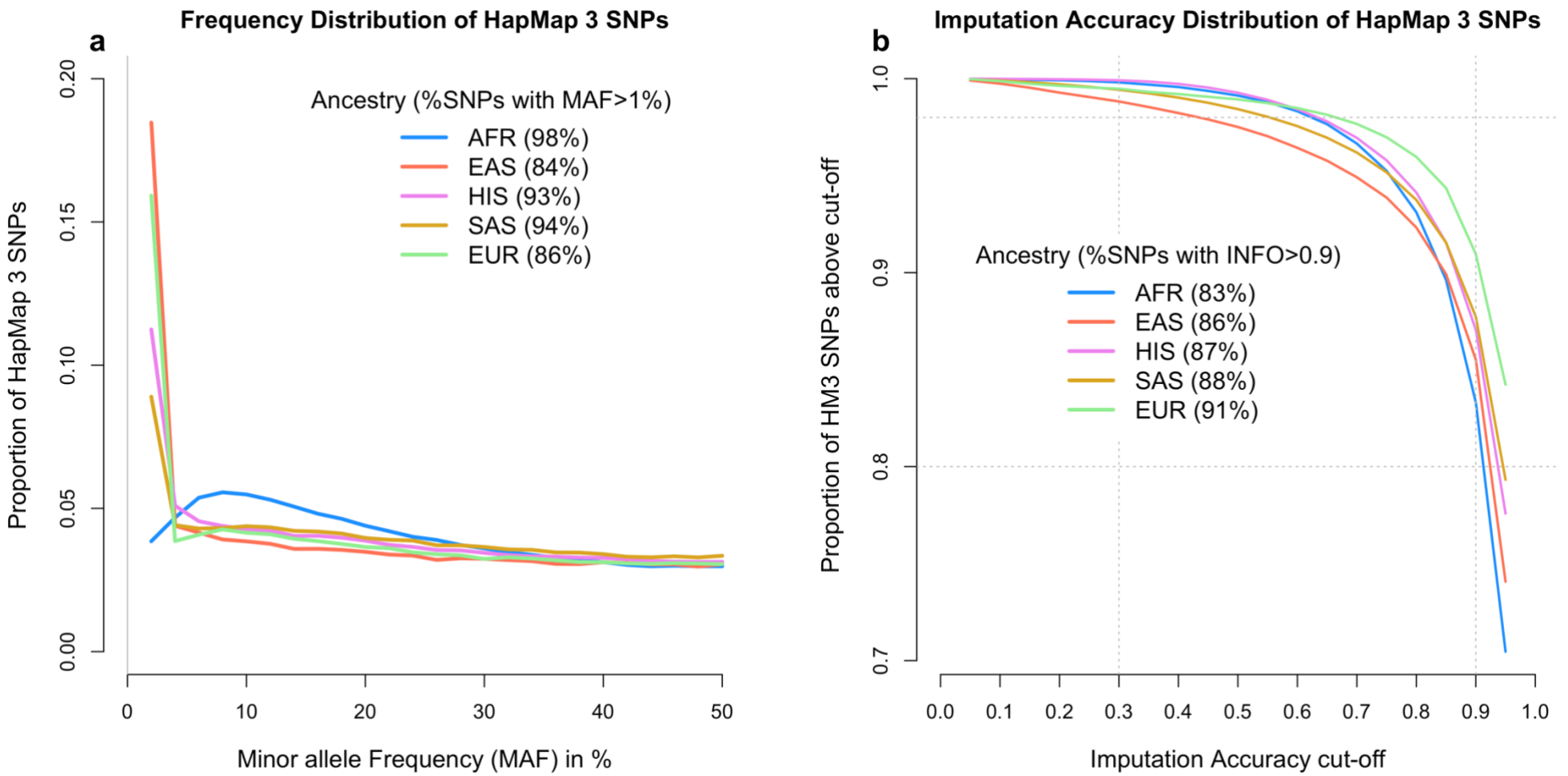
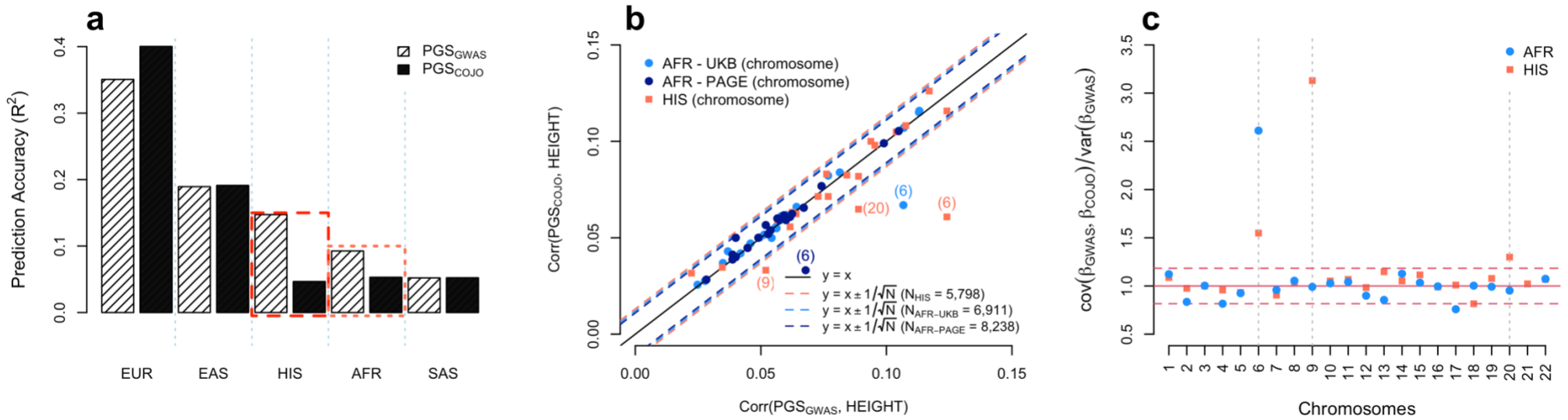
SUPPLEMENTARY FIGURES



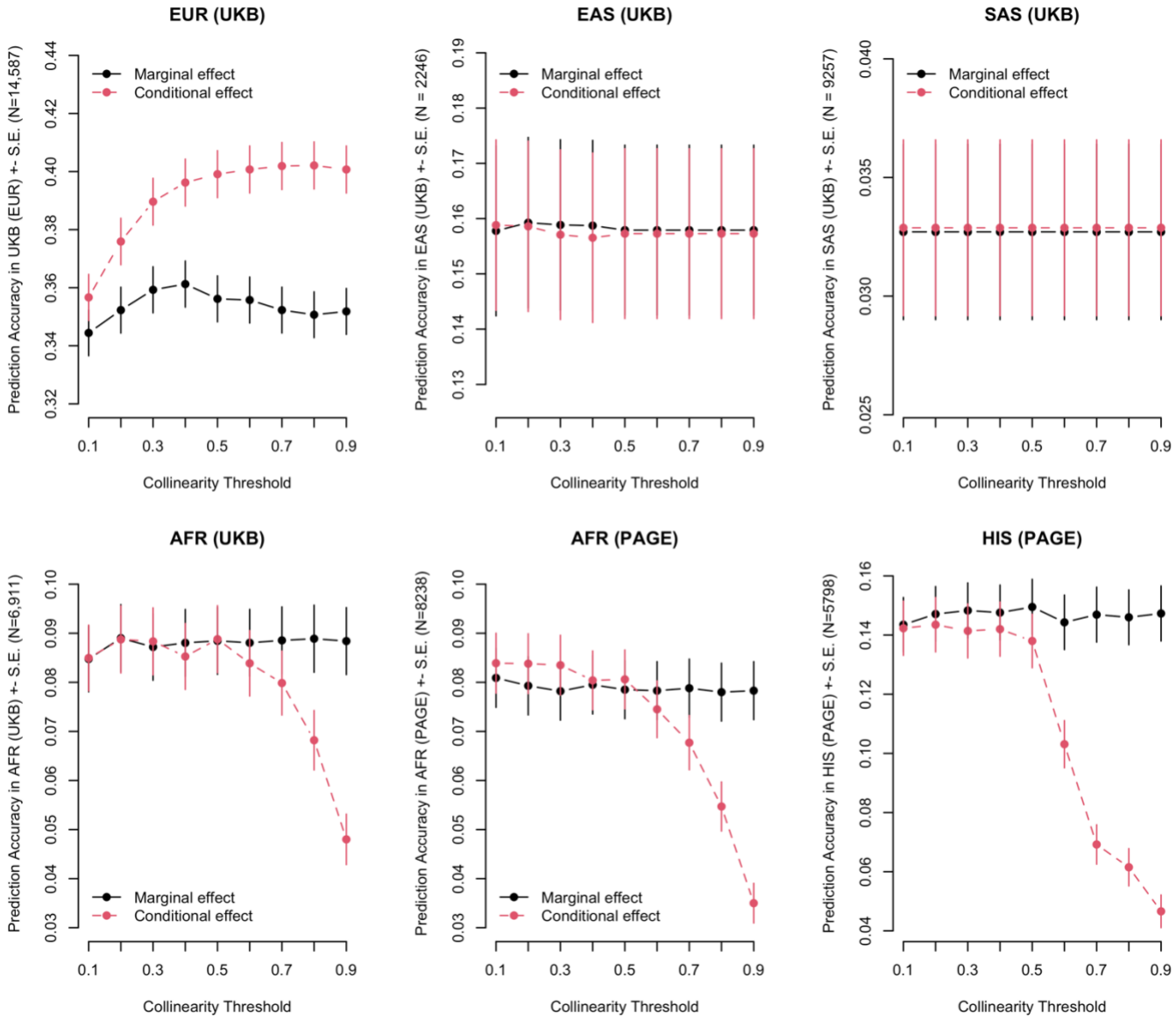
Suppl. Fig. 1. Principal components analysis of contributing studies to the height meta-analysis alongside 26 genetic ancestry groups from the 1000 Genomes Project. Using data from 2,504 samples from the 1000 Genomes Project (1KGP), genotypes for 354,568 HapMap3 SNPs with frequency data from all participating studies were extracted. LD-pruning was subsequently performed using PLINK with a window size of 1Mb, a shift size of 50 variants, and an LD r^2 cut-off of 0.1 (PLINK command: --indep-pairwise 1000 50 0.1). After LD-pruning, 18,125 SNPs remained for subsequent analysis. Allele frequencies for the pruned set of variants were subsequently calculated within each of the 26 1KGP ancestral groups and aligned to the same reference allele. Principal components analysis was subsequently performed by using the 1KGP frequency data to build the model prior to projection of participating studies, having ensured study allele frequencies were also aligned to the same 1KGP reference allele.



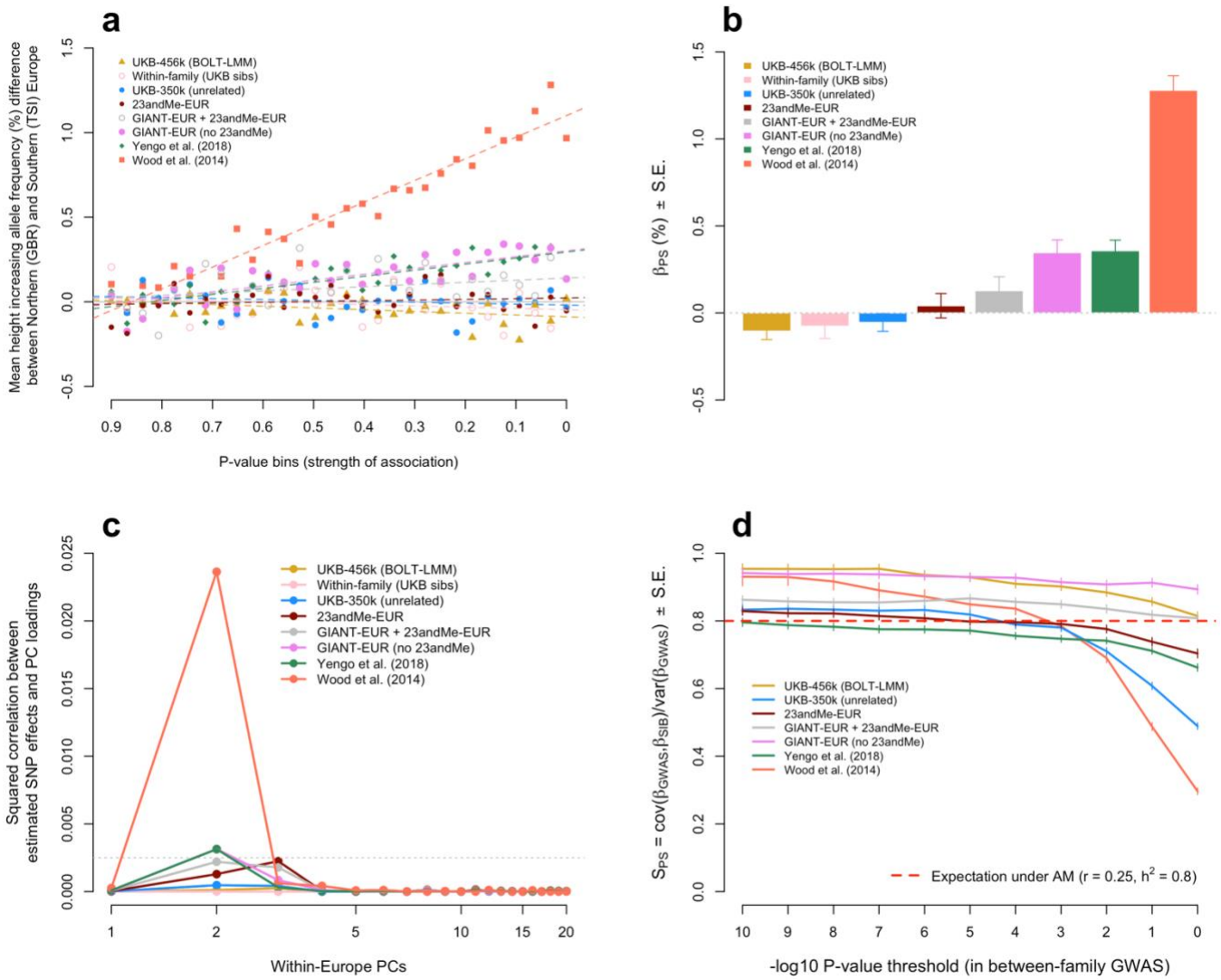
Suppl. Fig. 2. Frequency and imputation accuracy distribution of HapMap 3 SNPs across ancestry groups. **Panel a**. Minor allele frequency (MAF) distribution of HapMap 3 SNPs across 5 ancestries: European (EUR), Hispanic (HIS), African (AFR), East-Asian (EAS) and South-Asian (SAS). **Panel b**. Average (across cohorts) proportion (y-axis) of HapMap 3 SNPs with a imputation accuracy statistic (INFO) above a certain threshold (x-axis). Vertical lines highlight two thresholds (0.3 and 0.9) commonly used to ascertained SNPs on imputation accuracy. Overall, **Panel b** shows that HapMap 3 SNPs are well imputed across all ancestry groups with >98% of SNPs with INFO>0.3 and >80% of SNPs with INFO>0.9.



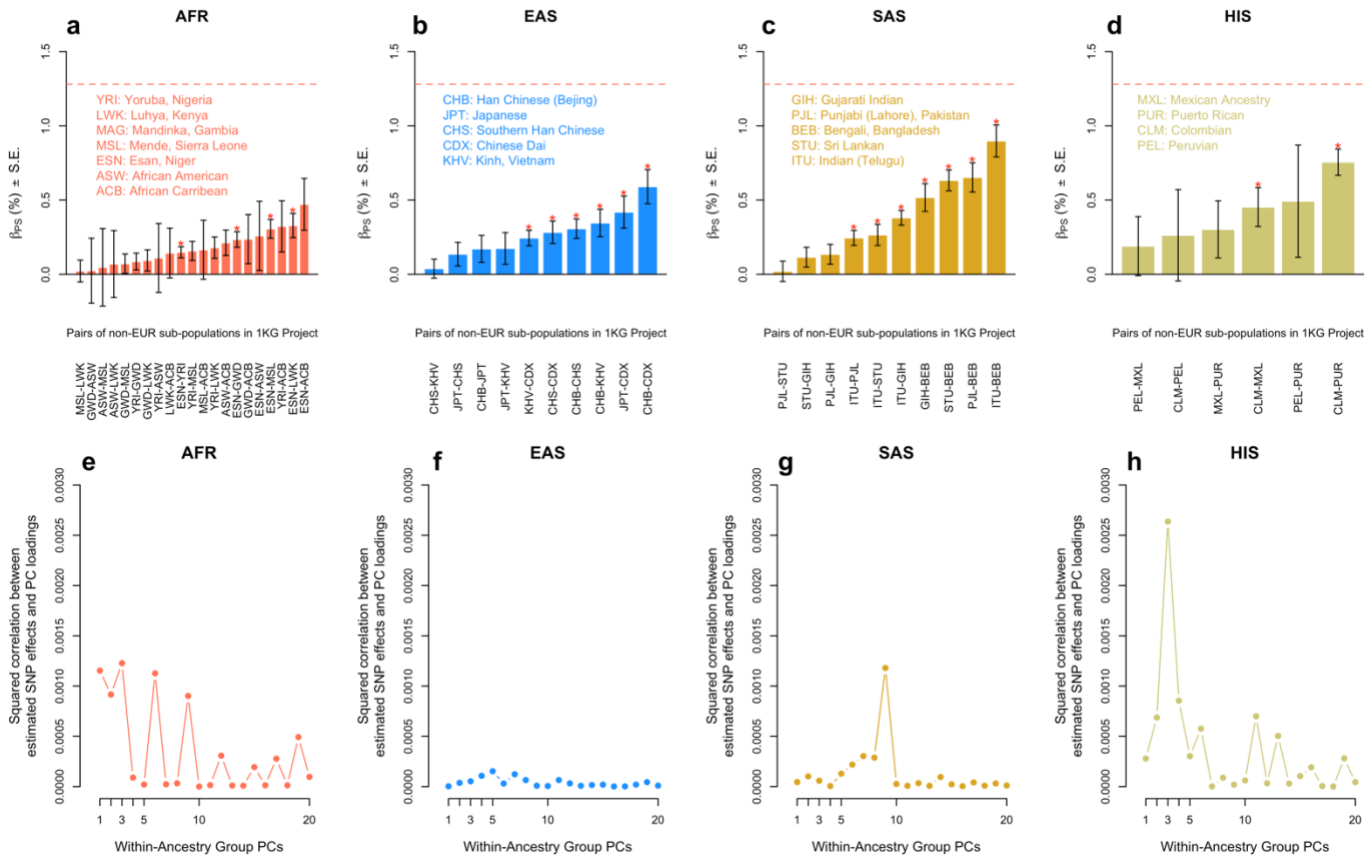
Suppl. Fig. 3. Biases in conditional and joint effect estimates. Panel a: Prediction accuracy (squared correlation R^2) of polygenic scores (PGS) based on genome-wide significant (GWS) SNPs identified in 5 ancestry groups (EUR: European, EAS: East-Asian, HIS: Admixed Hispanic ethnicity, AFR: African (mostly Admixed African American) and SAS: South-Asian). For each set of GWS SNPs, Panel a compares the prediction accuracy obtained when the PGS is calculated from marginal SNP effects (PGS_{GWAS}) versus when the PGS is calculated from joint SNP effects (PGS_{COJO}) estimated with the GCTA-COJO algorithm using default parameters. In ancestry groups, except HIS and AFR, the accuracy of PGS_{COJO} is larger than that of PGS_{GWAS}. **Panel b** contrasts the per-chromosome correlation between PGS_{GWAS} and height (x-axis) with the per-chromosome correlation between PGS_{COJO} and height (y-axis). These correlations were calculated in 2 samples of African ancestry participants from the UK Biobank (UKB, $N_{AFR-UKB}$=6,911) and the PAGE study ($N_{AFR-PAGE}$=8,238) and in 1 sample of Admixed Hispanic individuals also from the PAGE study ($N_{HIS-PAGE}$=5,798). **Panel c** represents for each chromosome (x-axis) the slope from regressing marginal SNP effects on joint SNP effects (y-axis). Regression slopes were estimated for GWS SNPs identified on each chromosome in GWAS meta-analyses in African and Hispanic ancestry groups. These results are further described and discussed in **Suppl. Note 1**.



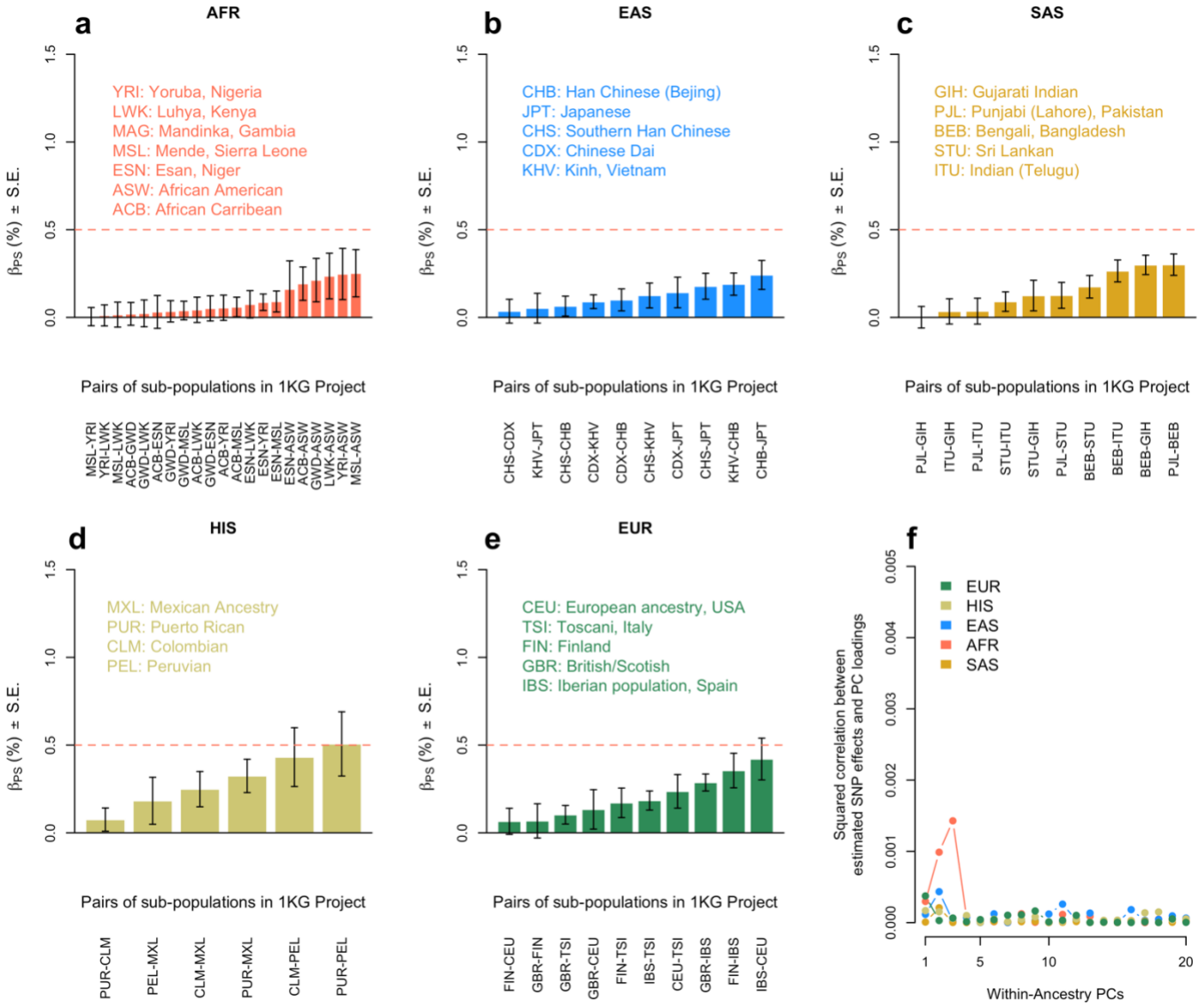
Suppl. Fig. 4. Impact of the collinearity threshold (CT) used in the GCTA-COJO algorithm on prediction accuracy of polygenic scores (PGS) based using estimates joint effects. By default, the GCTA-COJO algorithm implements a stepwise model selection to identify sets of jointly significant SNPs such that the variance of genotypes at any SNP retained in the final model is not explained at more than CT=90% by other SNPs included in the model. We varied the value of the CT between 0.9 (least stringent) and 0.1 (most stringent) and monitored the prediction accuracy of PGS in different samples. Each panel represents CT on the x-axis and the prediction accuracy on the y-axis in a given ancestry group match with the ancestry of GWAS participants. Red dots represent prediction accuracies of PGS calculated from joint effects (PGS_{COJO}) and black that from marginal effects (PGS_{GWAS}). Overall, using stringent CT values tend to degrade the performances of PGS_{COJO} in all ancestry groups (EUR: European, EAS: East-Asian and SAS: South-Asian) except in admixed individuals with African ancestries (AFR) and of Hispanic ethnicity (HIS). These results are further described and discussed in **Suppl. Note 1**.



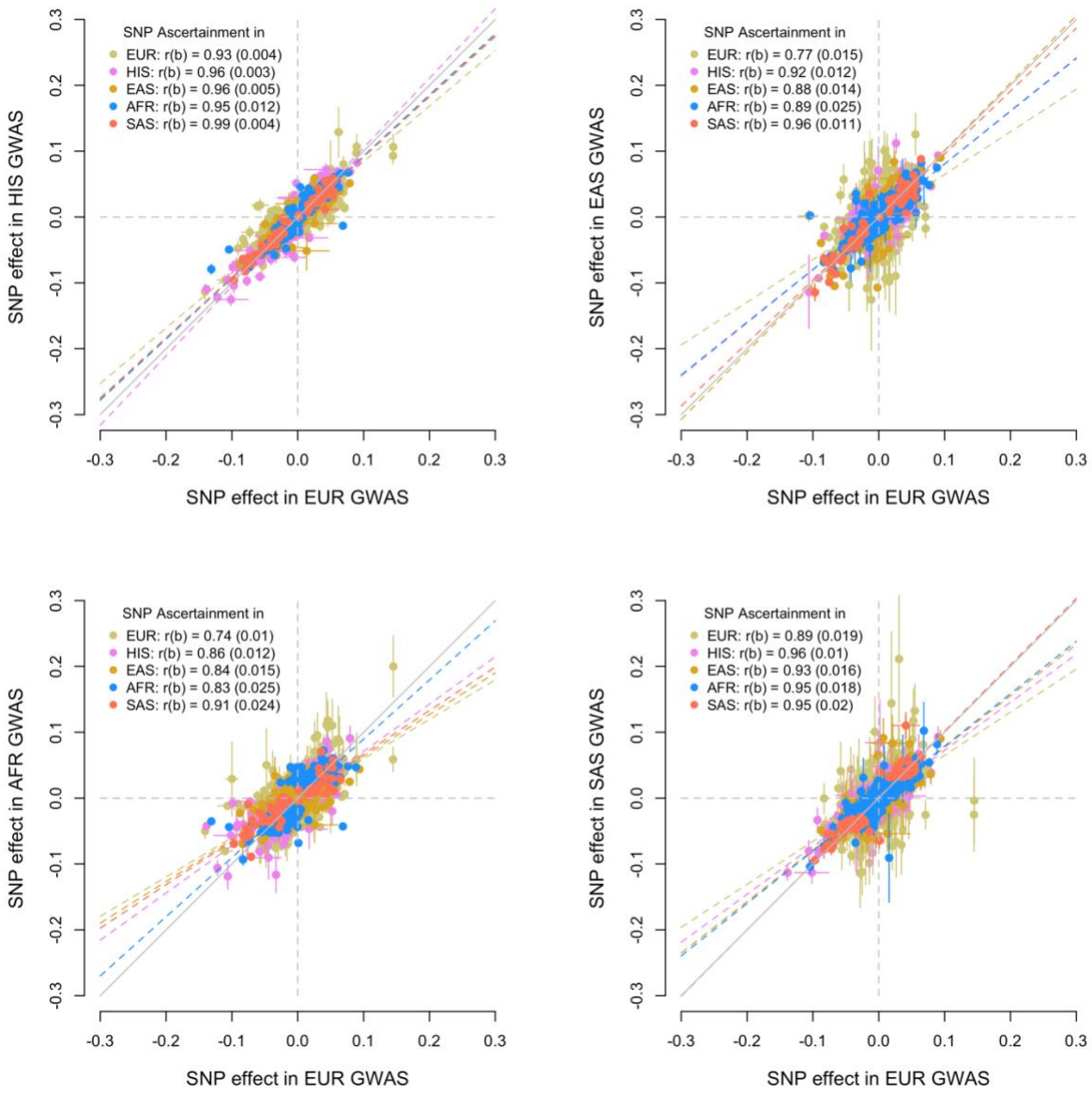
Suppl. Fig. 5. Quantification of confounding due to population stratification (PS) in various European ancestry (EUR) GWAS of height. UKB-456k (BOLT-LMM): GWAS in 456,414 EUR participants of the UKB. UKB-350k (unrelated): GWAS in 348,501 unrelated (i.e. estimated genetic relatedness <0.05) EUR participants of UKB. 23andMe-EUR: GWAS in EUR participants of 23andMe. GIANT-EUR: GWAS meta-analysis of 173 EUR cohorts from the GIANT consortium. Within-family (UKB): Family-based GWAS performed in 17,942 independent EUR sibling pairs from the UKB. **Panel a** represents the relationship between strength of association between 101,360 independent (LD r^2<0.1) HM3 SNPs and height (x-axis: 30 SNP bins) and height-increasing allele frequency differences between the British (GBR) and Tuscan (TSI) samples from the 1,000 Genomes Project (1KGP). A significant slope (β_{PS}) indicates uncorrected PS. **Panel b** shows estimates of β_{PS} for different GWAS and their associated leave-one-SNP-bin-out jackknife standard errors (S.E.). **Panel c** shows the variance in estimated SNP effects from various height GWAS that is explained by SNP loading on genotypic principal components (PC) calculated among 503 EUR samples from the 1KGP. The x-axis in **Panel c** indicates number of vectors of PC loadings including in the regression model (SNP effect regressed on PC loading). **Panel d** shows on the y-axis the slope ($S_{PS} = \mathrm{cov}(\beta_{GWAS}, \beta_{SIB})/\mathrm{var}(\beta_{GWAS})$) from regressing SNP effects estimated in a family-based GWAS (β_{SIB}) onto SNP effects estimated in a standard population-based GWAS (β_{GWAS}). The x-axis in **Panel d** is the -log10 of the p-value threshold used to ascertain SNPs for estimating the regression slope. For each p-value threshold, the effects of ascertained SNPs were corrected for winner's curse (**Methods**). The horizontal red dotted line represented the expected slope under assortative mating (AM) assuming an equilibrium heritability $h^2 = 0.8$ and a spousal correlation $r = 0.25$ (**Suppl. Note 2**).



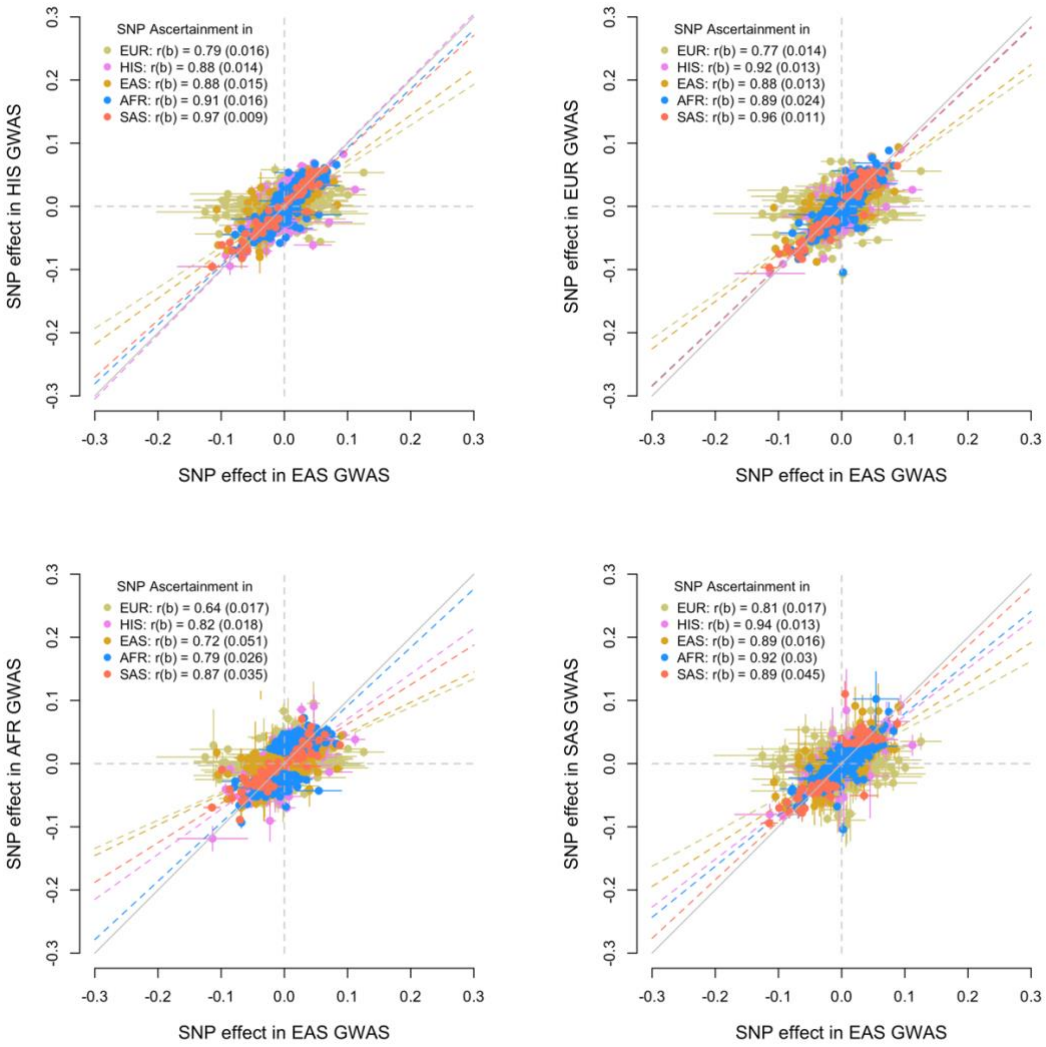
Suppl. Fig. 6. Quantification of confounding due to population stratification (PS) in various non-European ancestry (non-EUR) GWAS of height. Panels **a** and **e**, **b** and **f**, **c** and **g**, **d** and **h** represent quantifications of PS in GWAS conducted in individuals from the African (AFR), East-Asian (EAS), South-Asian (SAS) and Hispanic (HIS) ancestry groups, respectively. The x-axes in all the top panels (**a** – **d**) represent pairs of subpopulations in the 1000 Genomes Project (1KG) within the corresponding ancestry groups. The y-axes in Panels (**a** – **d**) show estimates of β_{PS} (+/- standard errors; S.E.) for SNP effects estimated in the corresponding ancestry group along axes of genetic differentiation between subpopulations indicated on the x-axis. Red dots on top of each bar indicate statistical significance as defined in **Suppl. Note 2** based on different thresholds according to the number of pairs of subpopulation within ancestry groups. The x-axes in all the bottom panels (**e** – **h**) correspond to 20 principal components (PC) calculated in 1KGP samples from the corresponding ancestry group. The y-axes in Panels **e** – **h** show the squared correlations between PC loadings and marginal SNP effects in the corresponding ancestry-specific GWAS meta-analysis. These results are further described and discussed in **Suppl. Note 2**.



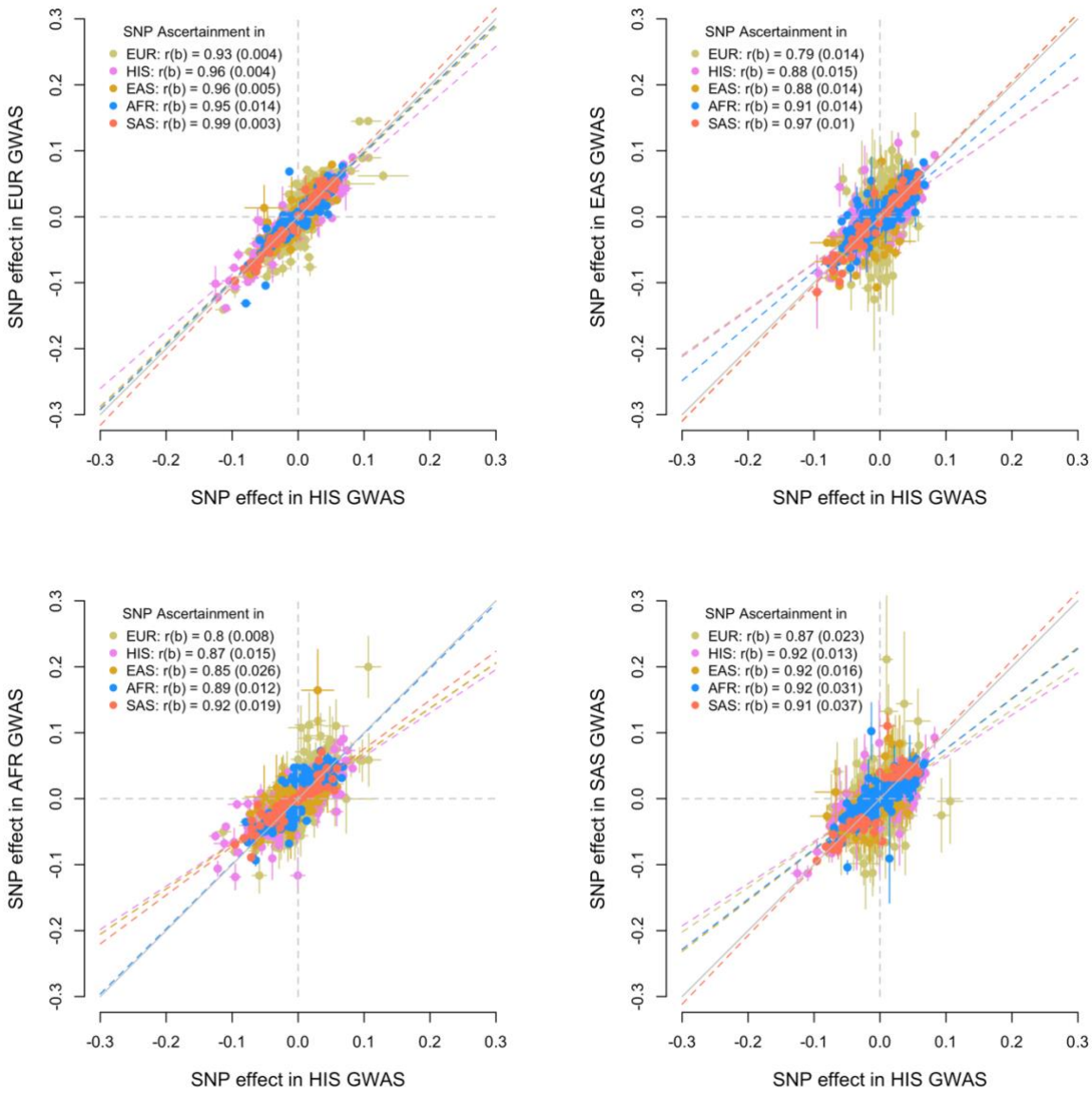
Suppl. Fig. 7. Quantification of confounding due to population stratification (PS) in our cross-ancestry GWAS meta-analysis of height. The x-axis in panels (a – e) shows pairs of subpopulations in the 1000 Genomes Project (1KG) within 5 ancestry groups indicated by the title of the panel (African: AFR, East-Asian: EAS, South-Asian: SAS, HIS: Hispanic, European: EUR). The y-axis in panels (a – e) shows estimates of β_{PS} (+/- standard errors; S.E.) for SNP effects in our cross-ancestry meta-analysis along axes of genetic differentiation between subpopulations indicated on the x-axis. Each dot in **Panel f** represents the squared correlation (y-axis) between SNP effects and loadings of principal components (PC: 1 to 20, indicated on the x-axis) calculated in 5 ancestry groups indicated in the panel legend. These results are further described and discussed in **Suppl. Note 2**.



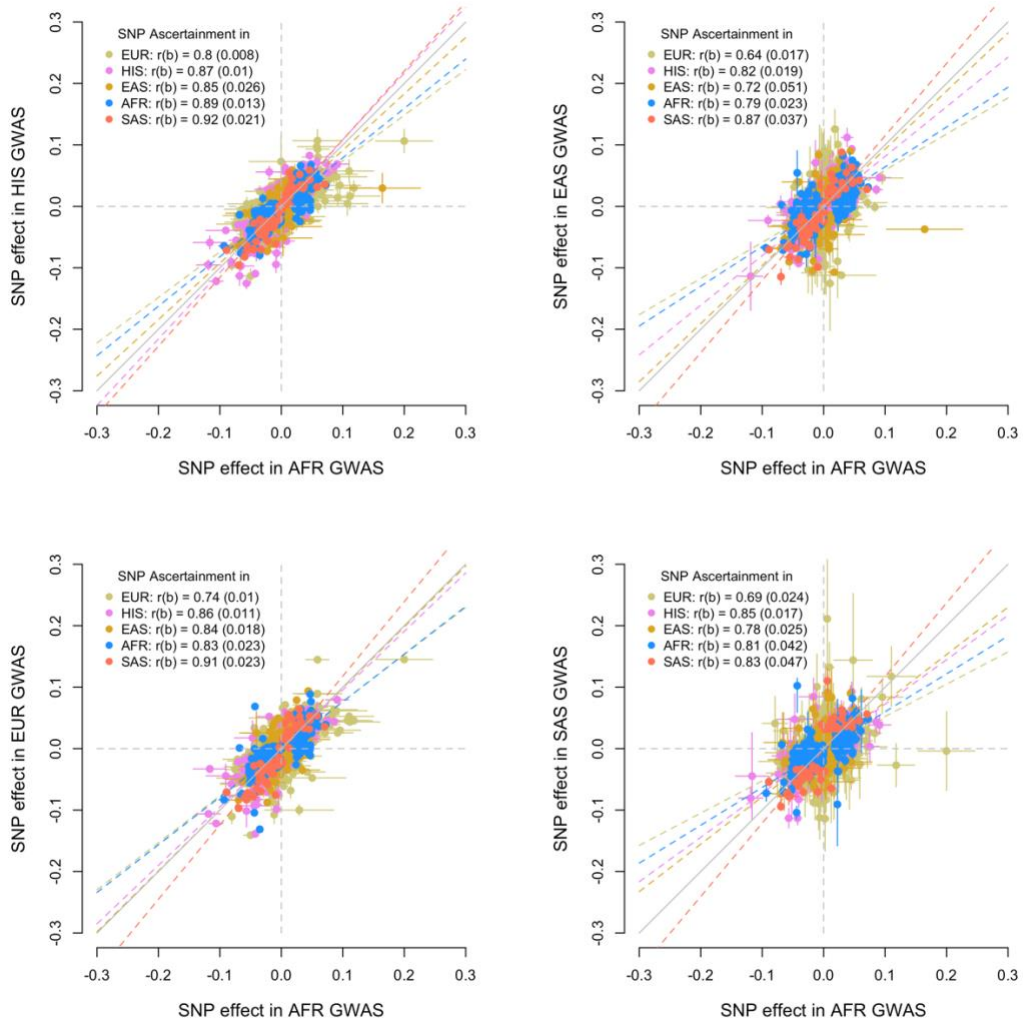
Suppl. Fig. 8. Correlation of marginal SNP effects between European ancestry (EUR, on the x-axis) and non-EUR GWAS (i.e. Hispanic (HIS), African (AFR), East-Asian (EAS) and South-Asian (SAS) on the y-axis). Correlations *r(b)* were corrected for estimation errors as described in the **Methods** section. Each estimate of the correlation of SNP effect is based on SNPs reaching marginal genome-wide significance in any of the 5 ancestries analysed. Standard errors for *r(b)* were obtained using jackknife. Error bars denote standard errors of SNP effects.



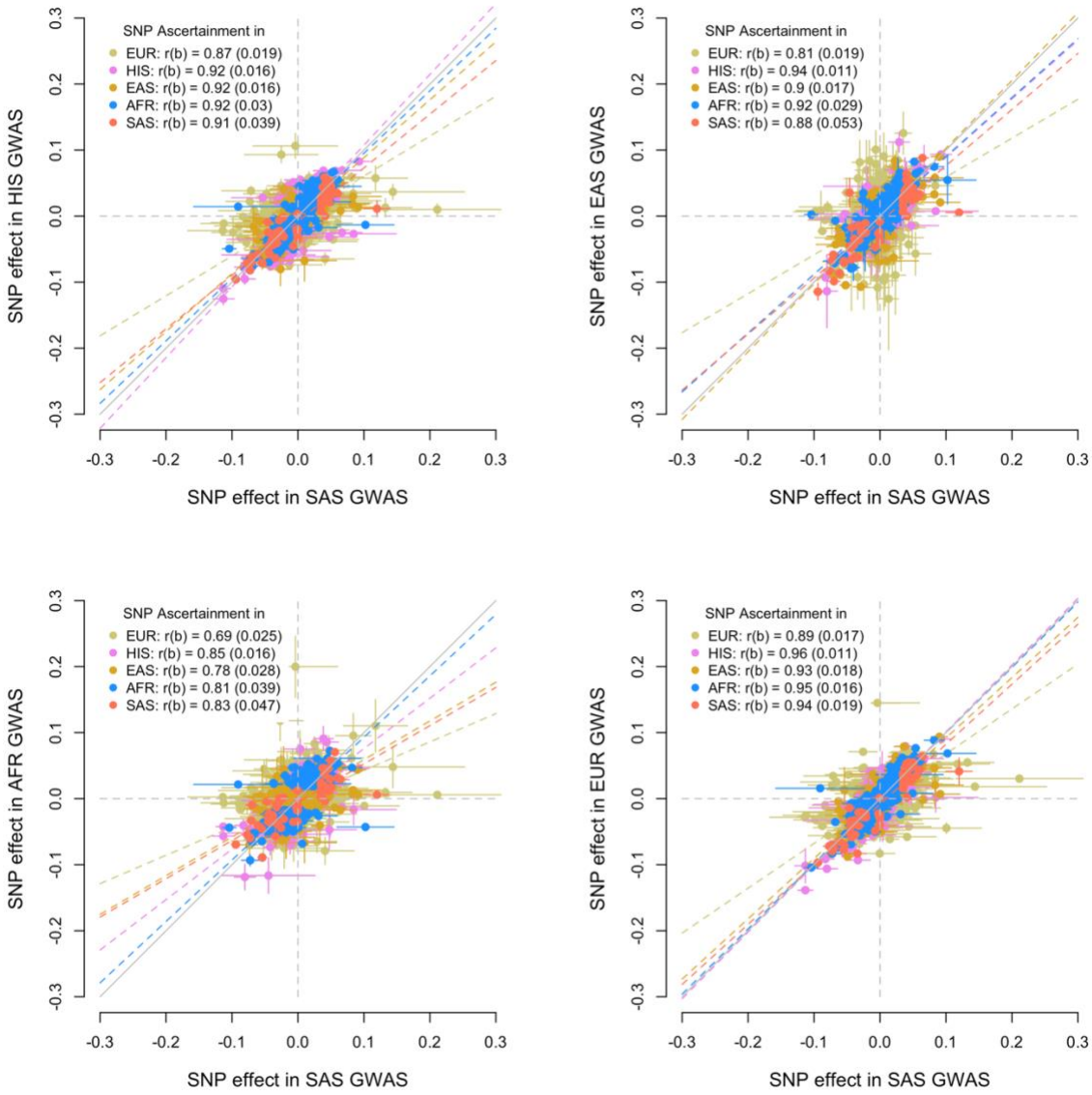
Suppl. Fig. 9. Correlation of marginal SNP effects between East-Asian ancestry (EAS, on the x-axis) and non-EAS GWAS (i.e. Hispanic (HIS), African (AFR), European (EUR) and South-Asian (SAS) on the y-axis). Correlations *r(b)* were corrected for estimation errors as described in the **Methods** section. Each estimate of the correlation of SNP effect is based on SNPs reaching marginal genome-wide significance in any of the 5 ancestries analysed. Standard errors for *r(b)* were obtained using jackknife. Error bars denote standard errors of SNP effects.



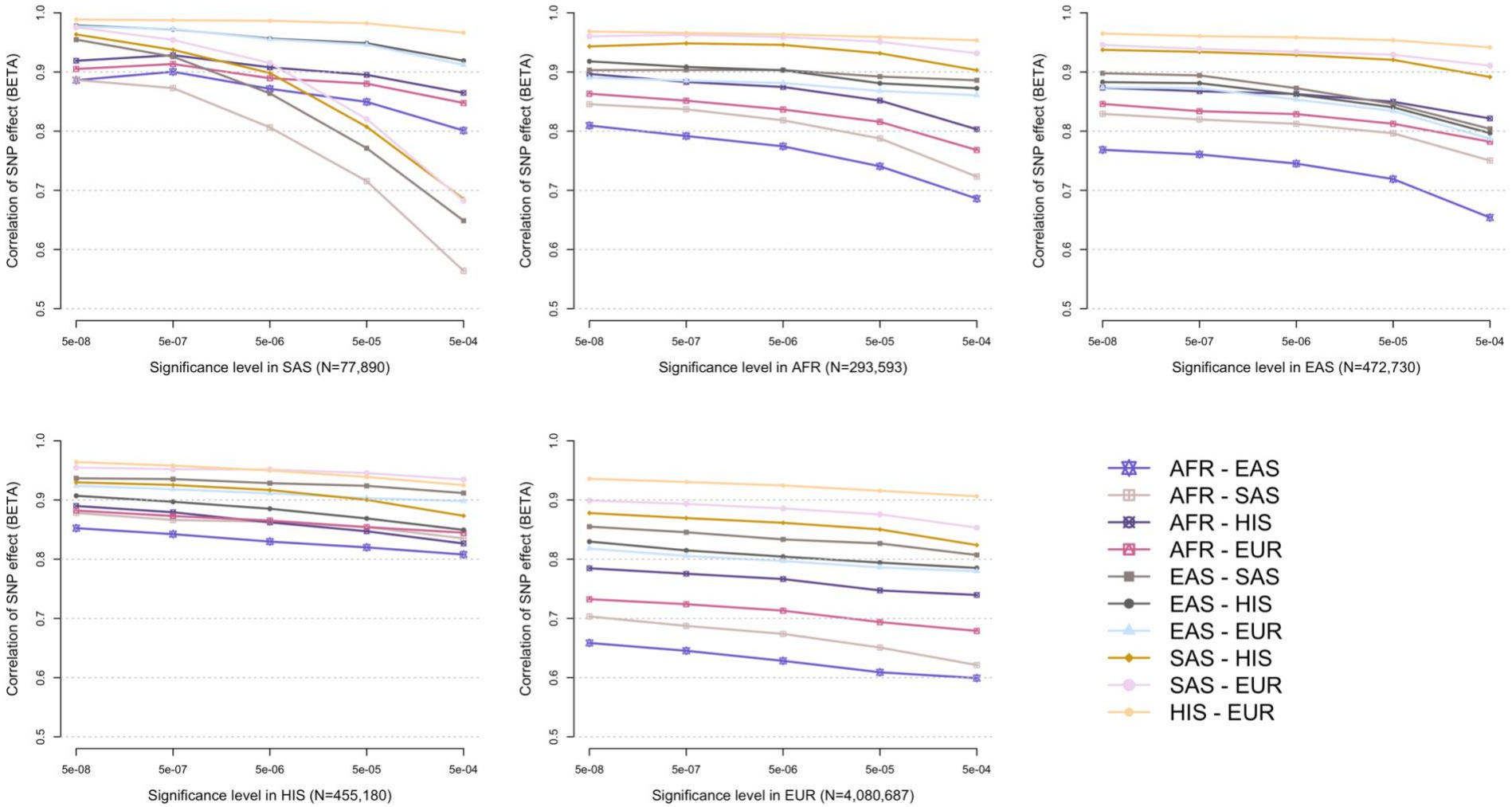
Suppl. Fig. 10. Correlation of marginal SNP effects between Hispanic ethnicity (HIS, on the x-axis) and non-HIS GWAS (i.e. European (EUR), African (AFR), East-Asian (EAS) and South-Asian (SAS) on the y-axis). Correlations *r(b)* were corrected for estimation errors as described in the **Methods** section. Each estimate of the correlation of SNP effect is based on SNPs reaching marginal genome-wide significance in any of the 5 ancestries analysed. Standard errors for *r(b)* were obtained using jackknife. Error bars denote standard errors of SNP effects.



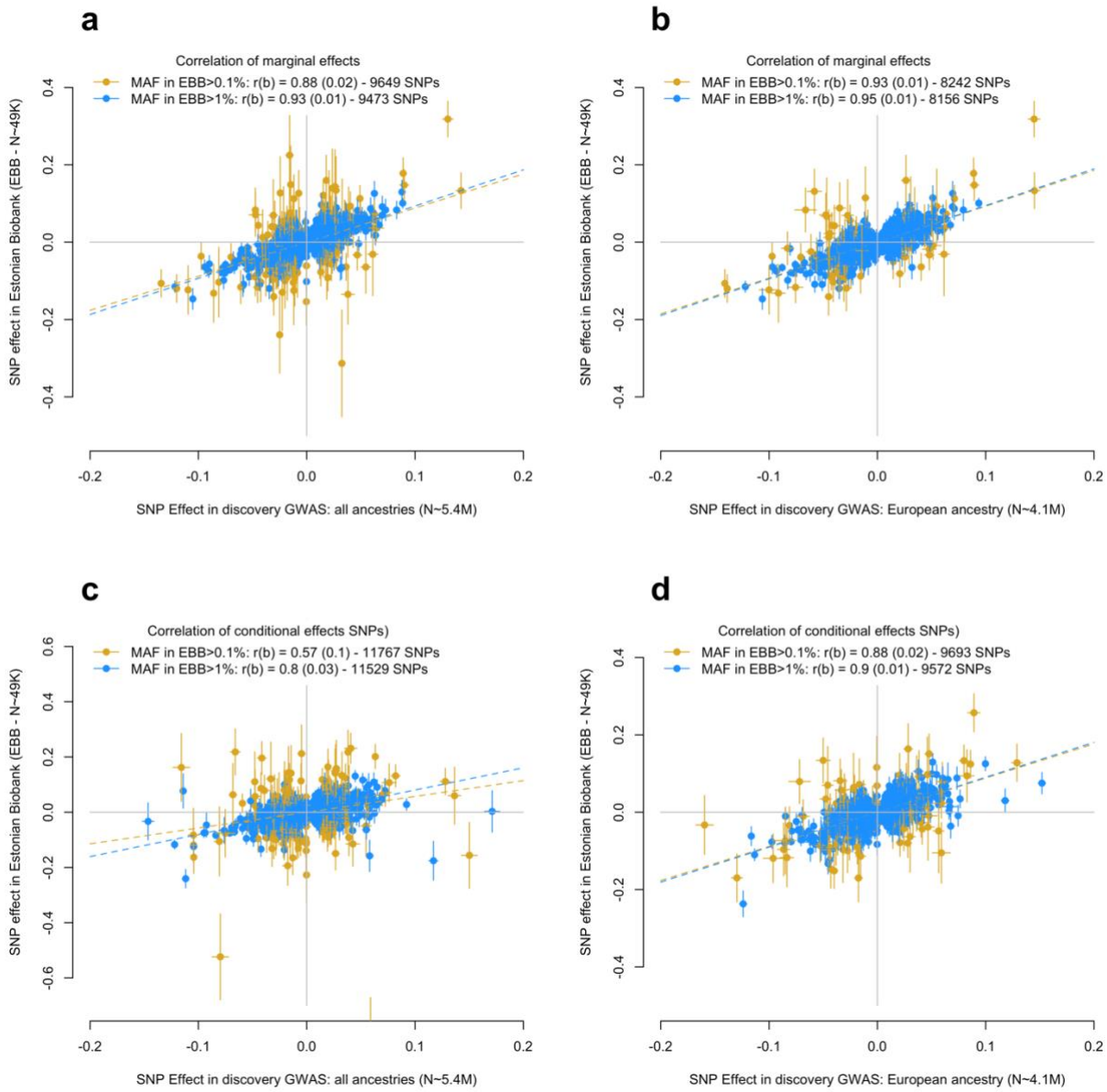
Suppl. Fig. 11. Correlation of marginal SNP effects between African ancestry (AFR, on the x-axis) and non-AFR GWAS (i.e. Hispanic (HIS), European (EUR), East-Asian (EAS) and South-Asian (SAS) on the y-axis). Correlations *r(b)* were corrected for estimation errors as described in the **Methods** section. Each estimate of the correlation of SNP effect is based on SNPs reaching marginal genome-wide significance in any of the 5 ancestries analysed. Standard errors for *r(b)* were obtained using jackknife. Error bars denote standard errors of SNP effects. Error bars denote standard errors of SNP effects.



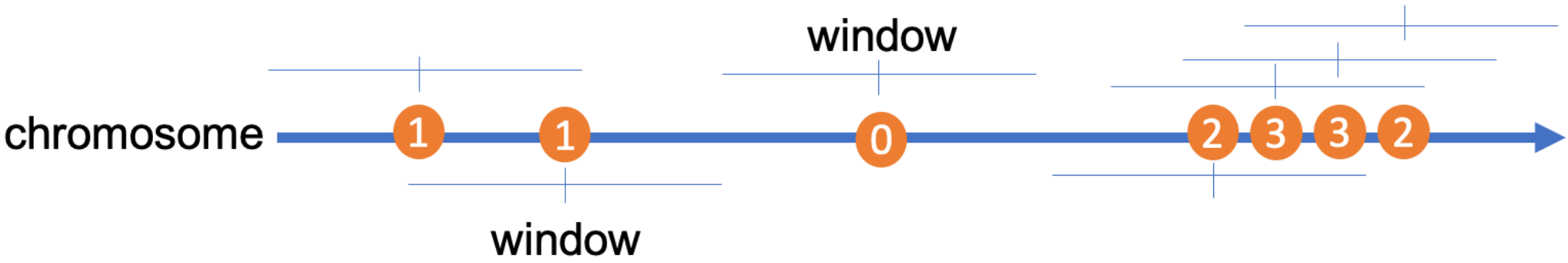
Suppl. Fig. 12. Correlation of marginal SNP effects between South-Asian ancestry (SAS, on the x-axis) and non-SAS GWAS (i.e. Hispanic (HIS), African (AFR), East-Asian (EAS) and European (EUR) on the y-axis). Correlations *r(b)* were corrected for estimation errors as described in the **Methods** section. Each estimate of the correlation of SNP effect is based on SNPs reaching marginal genome-wide significance in any of the 5 ancestries analysed. Standard errors for *r(b)* were obtained using jackknife. Error bars denote standard errors of SNP effects.



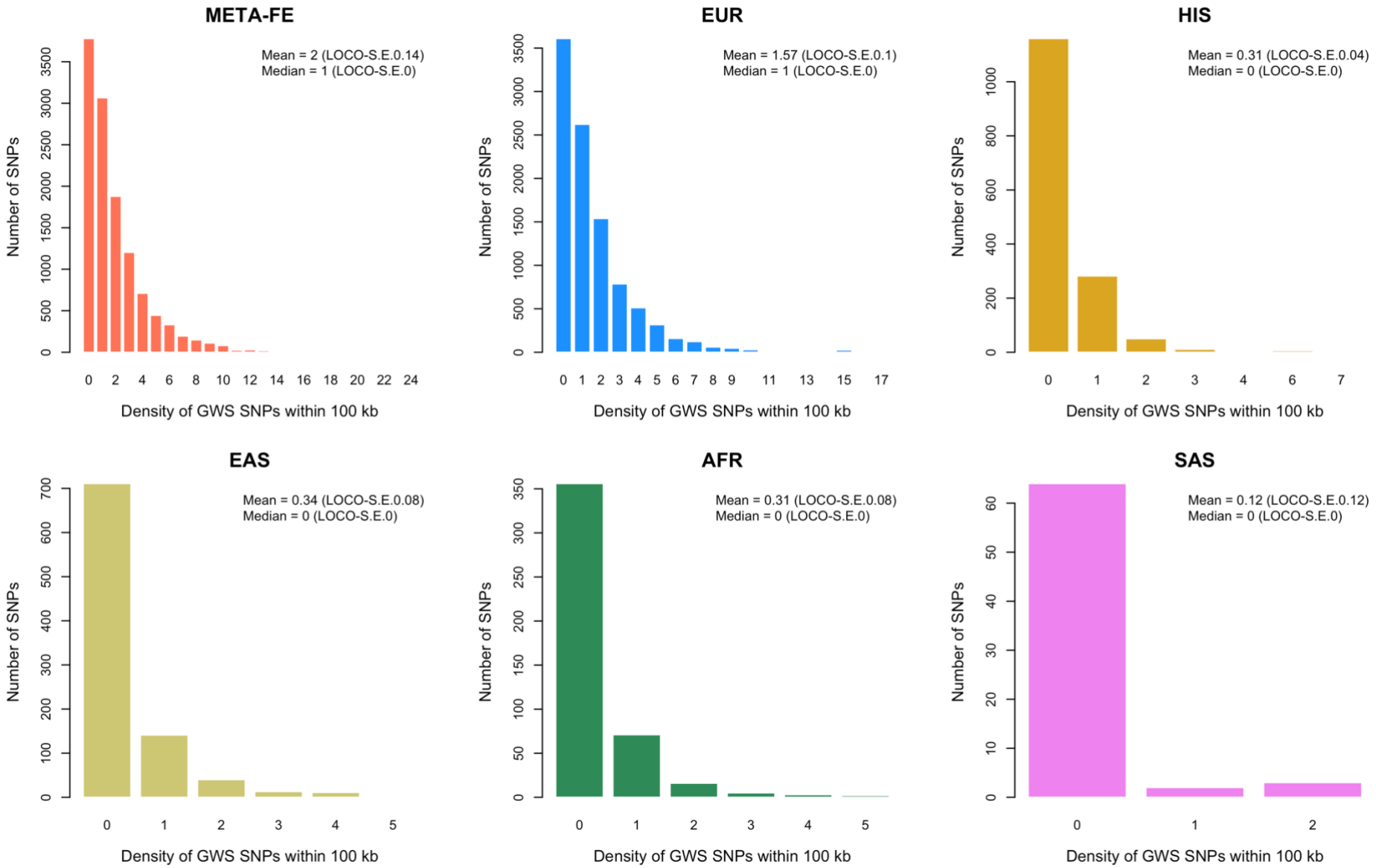
Suppl. Fig. 13. Cross-ancestry correlation of marginal SNP effects ascertained at various significant thresholds. The x-axis in each panel represents significance thresholds used to ascertained SNPs and the y-axis the correlation *r(b)* of estimated marginal effects (**Methods**) across 10 pairs of GWAS performed in 5 ancestry groups (African: AFR, East-Asian: EAS, South-Asian: SAS, HIS: Hispanic, European: EUR). Each panel represents which of the five ancestry-group specific GWAS was used to ascertain SNPs. SNPs were ascertained using GCTA-COJO with a linkage disequilibrium reference set from the corresponding ancestry group. Within each panel, correlations were calculated using the subset of COJO SNPs, which marginal significance also met the significance threshold indicated on the x-axis. Each colour represents a pair of ancestry group.



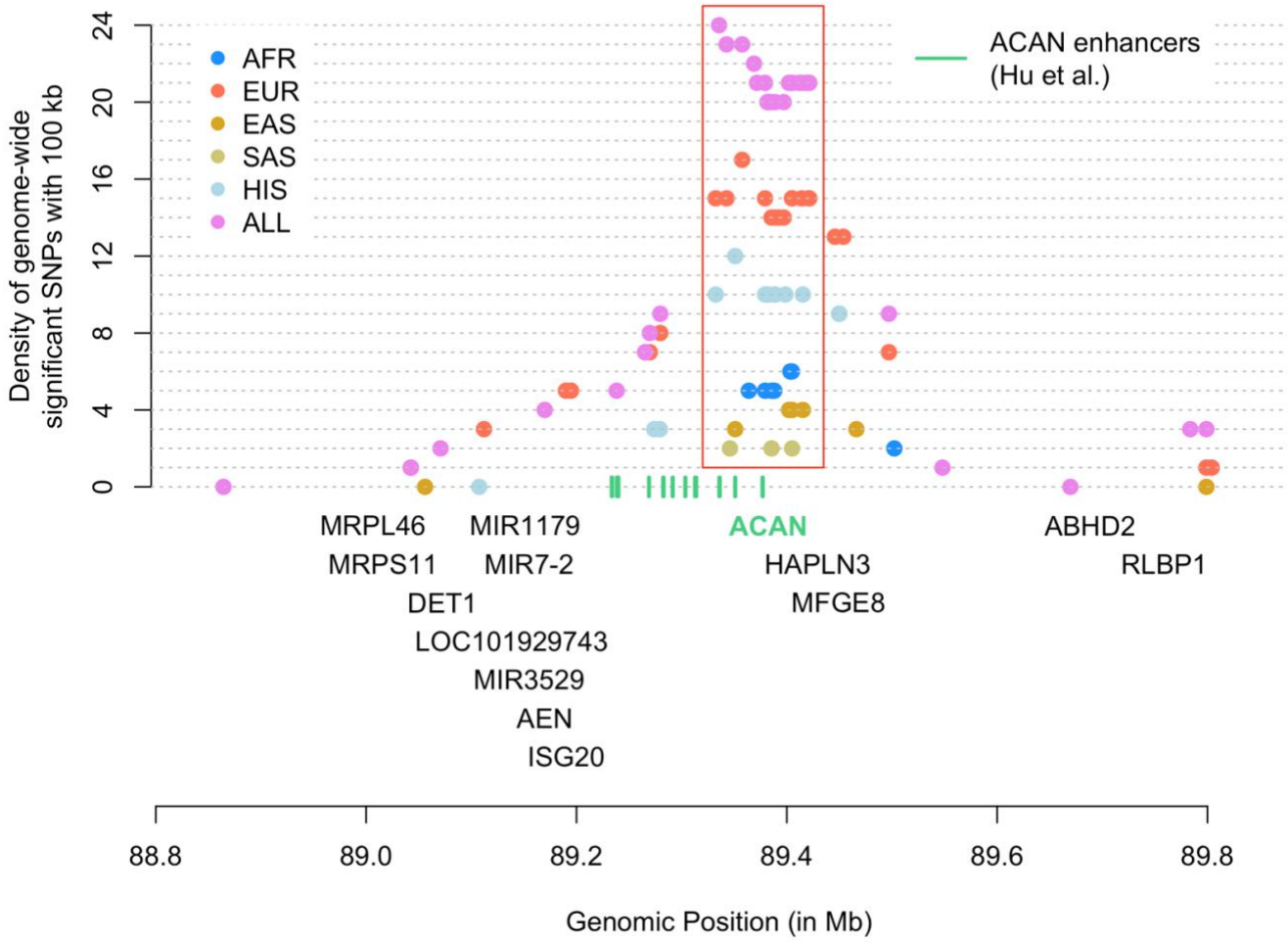
Suppl. Fig. 14. Correlation of marginal and conditional SNPs effects between discovery and replication (Estonian Biobank – EBB) GWAS. Panels a and **b** show correlations of marginal SNP effects for a subset of jointly associated SNPs (identified using the GCTA-COJO methods; **Methods**), which marginal effects also reach genome-wide significance. **Panels c** and **d** represent joint effect re-estimated using approximate conditional analyses (implemented in the GCTA software). Genotypes of ~350,000 unrelated participants of the UK Biobank were used as linkage disequilibrium (LD) reference.



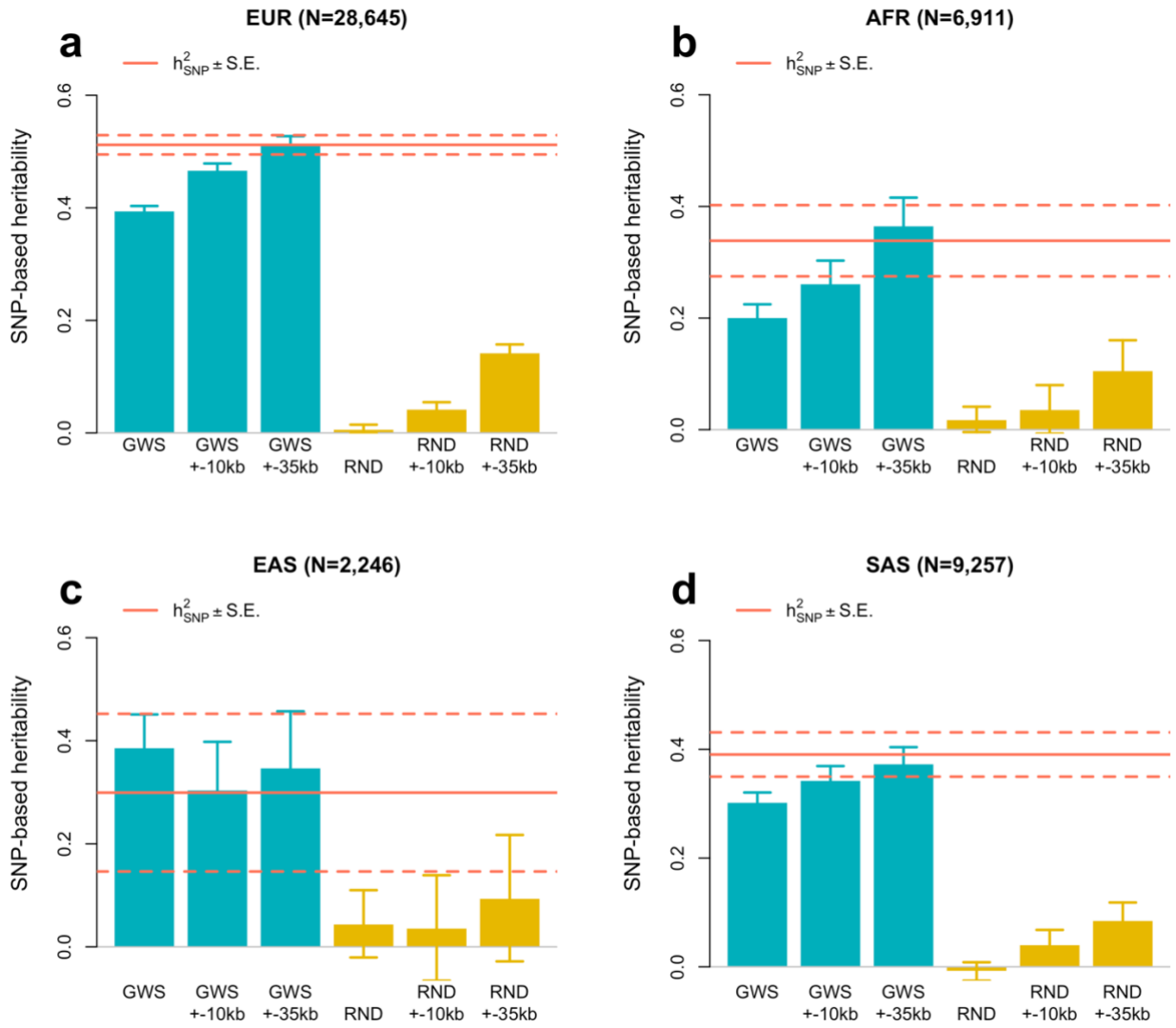
Suppl. Fig. 15. Schematic representation of the measure of signal density. The horizontal arrow represents a chromosome and each circle a specific association. For each association, the density is defined as the number of other independent associations within a certain window. In the example above, the window around the first SNP contains 1 SNP, so its density is 1. Similarly, the density at the third SNP (from the left) is 0 because the window around it does not contain any other association.



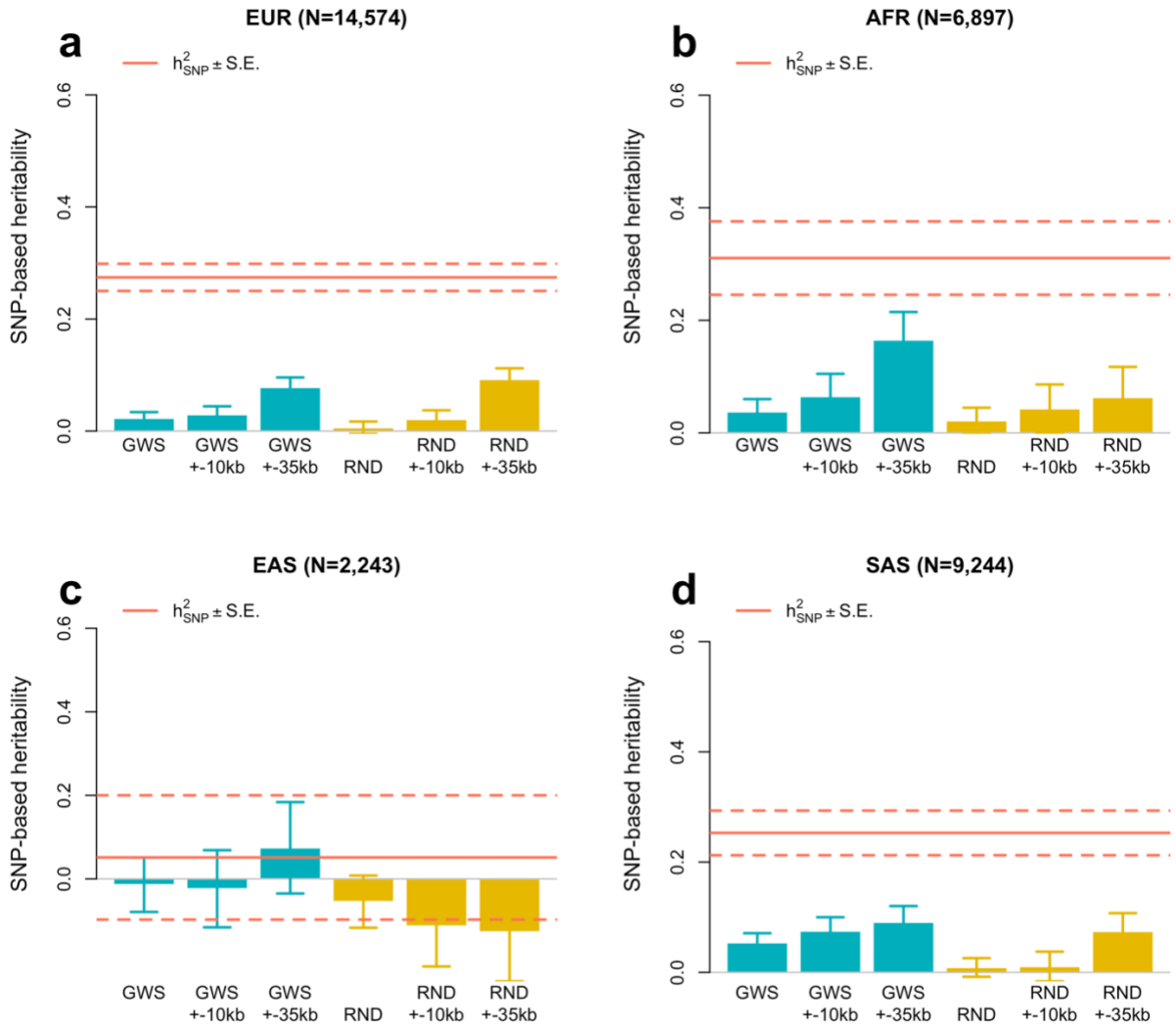
Suppl. Fig. 16. Distribution of signal density. Signal density (x-axes) is defined for each height-associated SNP as the number of other associations detected within 100 kb based on the META$_{FE}$ and ancestries group specific meta-analyses. Y-axes represent the number of height-associated SNPs with a signal density indicated on the x-axis.



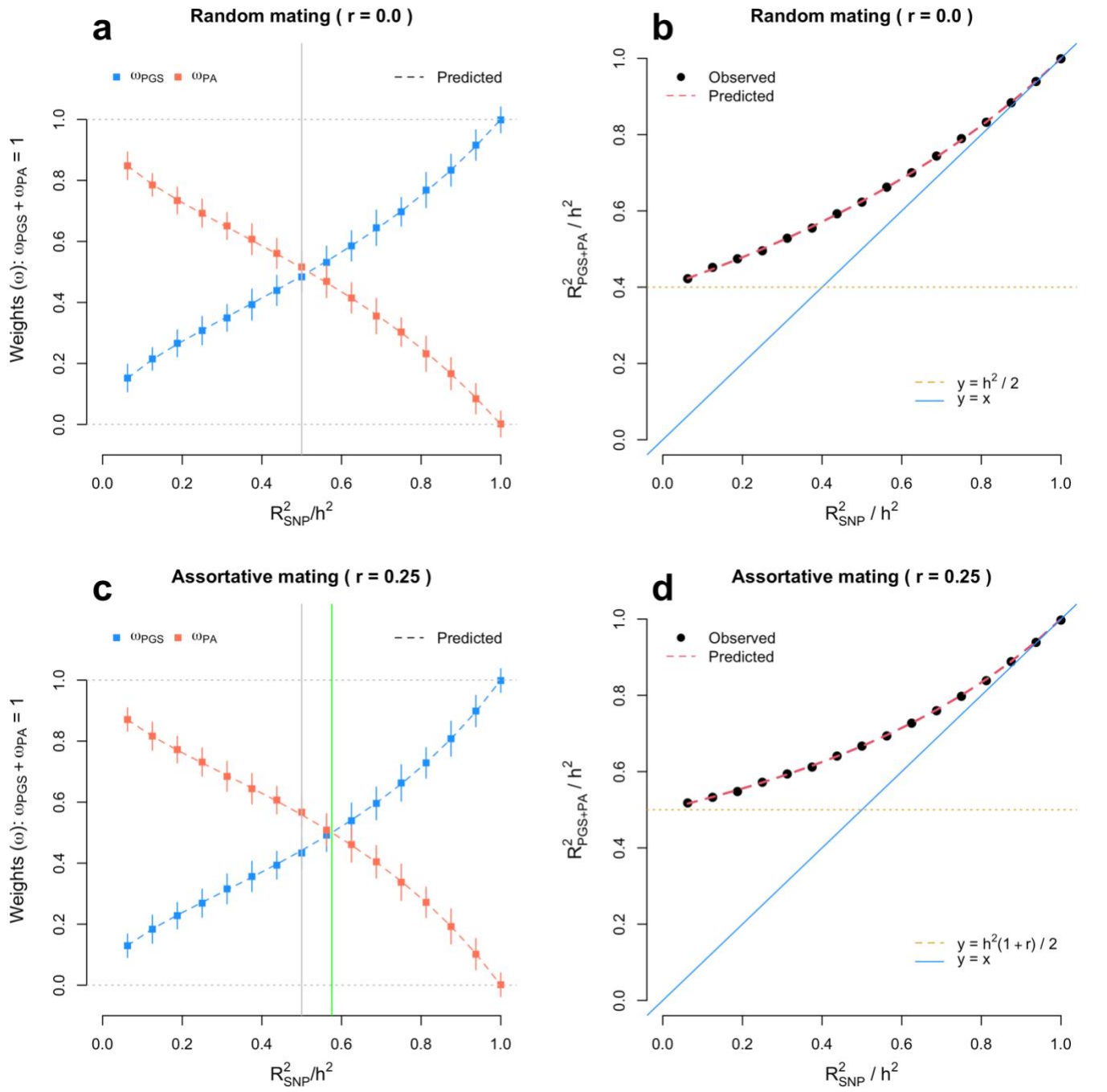
Suppl. Fig. 17. Independent signal density at the *ACAN* gene locus across ancestries. Independent associations were identified from GWAS performed in 5 ancestries (African: AFR; European: EUR; East-Asian: EAS; South-Asian: SAS and Hispanic: HIS) as well as from the meta-analysis of all ancestries (ALL). Genomic segments with a signal density >1 are found in each ancestry group.



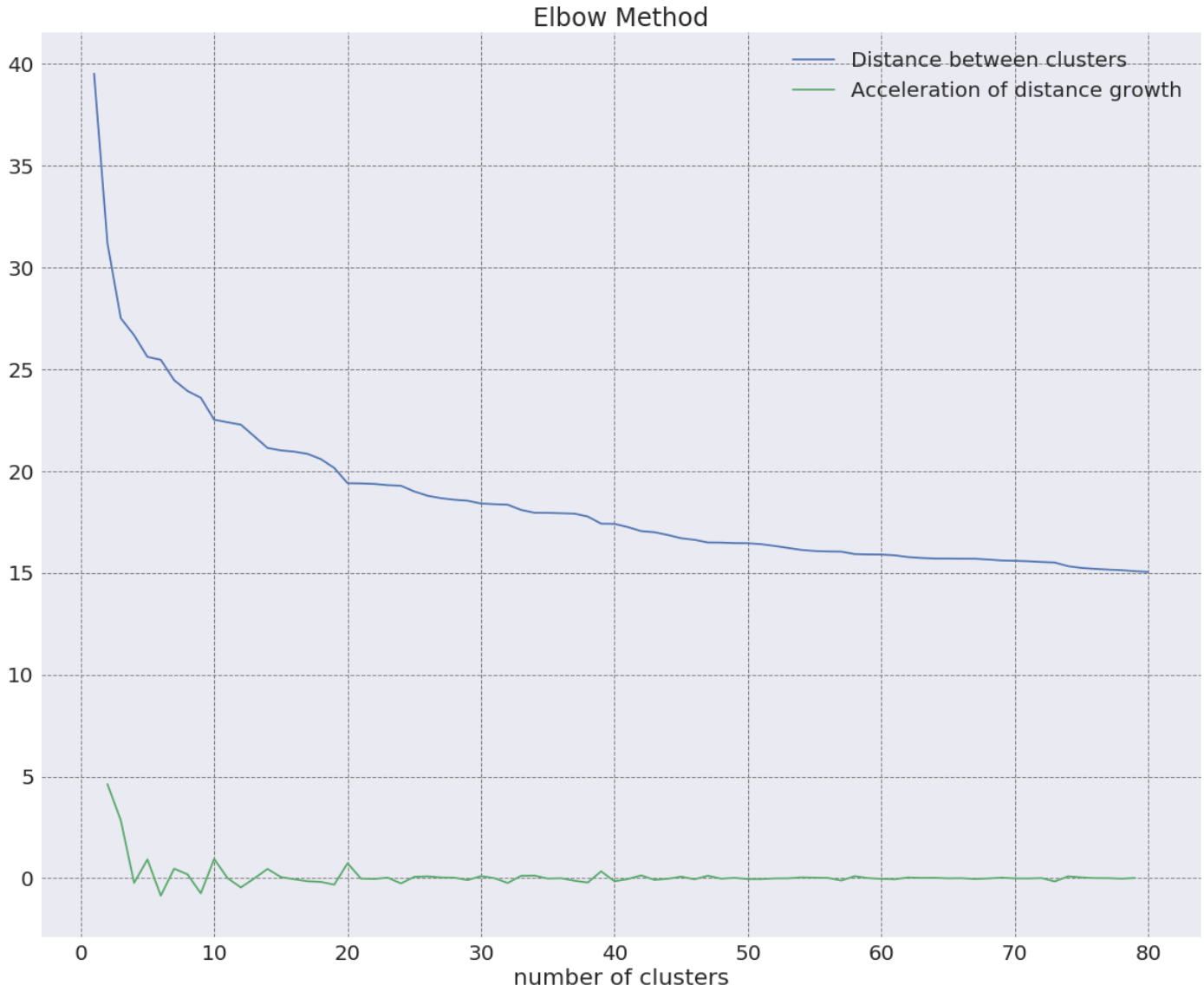
Suppl. Fig. 18. Variance of height explained by SNPs in genome-wide significant (GWS) loci defined with various window sizes. Stratified SNP-based heritability (h^2_{SNP}) estimates were obtained for three partitions of the genome: (1) GWS SNPs alone vs. all other HapMap 3 (HM3) SNPs; (2) GWS SNPs +/- all HM3 SNPs within 10 kb vs. all other HM3 SNPs and (3) GWS SNPs +/- all HM3 SNPs within 35 kb vs. all other HM3 SNPs. Analyses were performed in samples of four different ancestries: European (EUR: meta-analysis of UK Biobank (UKB); N=14,587 + Lifelines data; N=14,058), African (AFR: UKB), East-Asian (EAS: UKB) and South-Asian (SAS: UKB). Estimates from stratified analyses were compared with SNP-based heritability estimates obtained from analysing all SNPs jointly (horizontal red bar; dotted lines represented standard errors). Analyses were repeated using a random set of 12,111 SNPs (and redefining loci relative to those), which minor allele frequency and linkage disequilibrium distribution matched that of GWS SNPs (RND: gold bars).



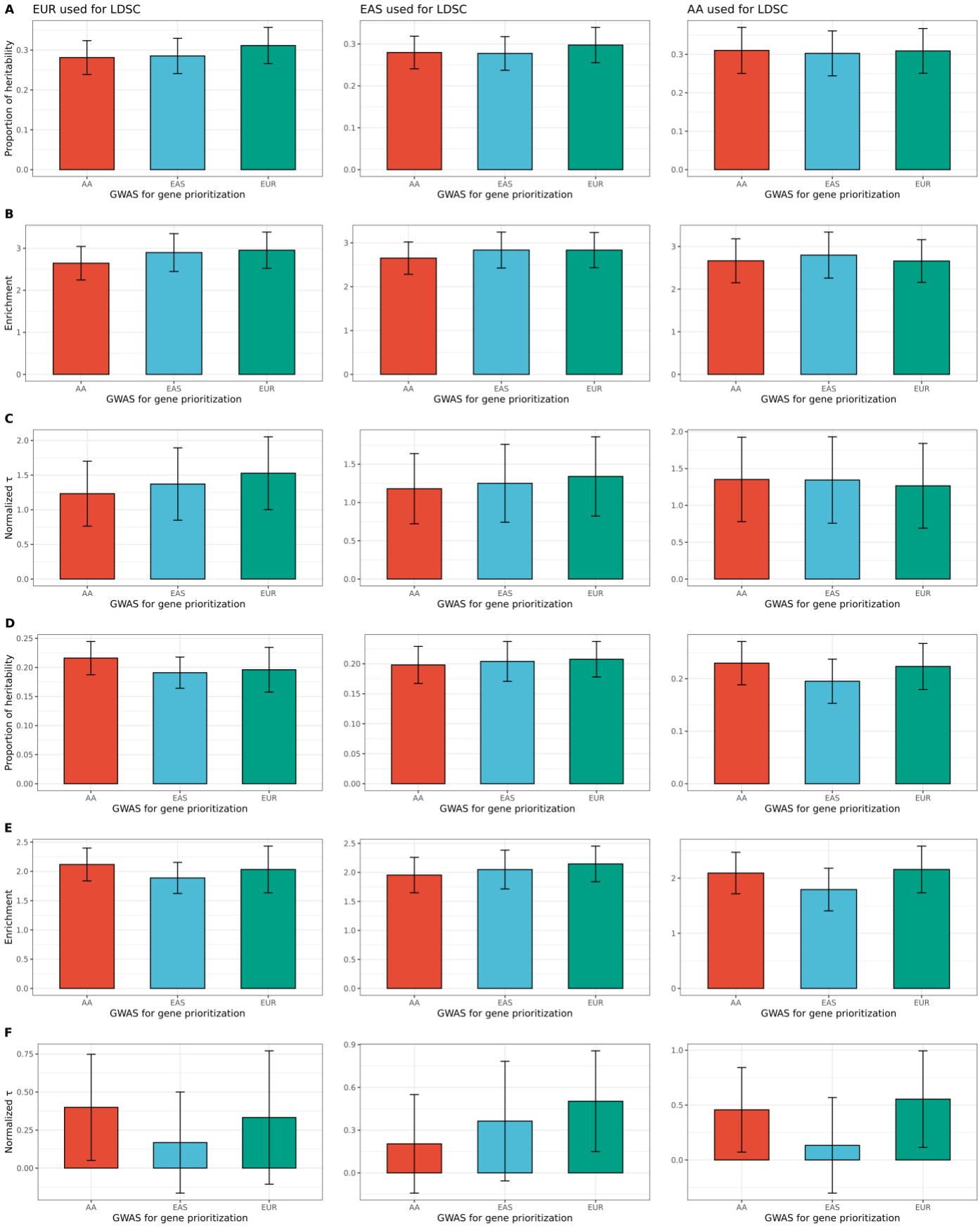
Suppl. Fig. 19. Variance of body mass index (BMI) explained by height-associated genome-wide significant (GWS) loci defined with various window sizes. Stratified SNP-based heritability (h^2_{SNP}) estimates were obtained for three partitions of the genome: (1) GWS SNPs alone vs. all other HapMap 3 (HM3) SNPs; (2) GWS SNPs +/- all HM3 SNPs within 10 kb vs. all other HM3 SNPs and (3) GWS SNPs +/- all HM3 SNPs within 35 kb vs. all other HM3 SNPs. Analyses were performed in UK Biobank samples of four different ancestries: European (EUR), African (AFR), East-Asian (EAS) and South-Asian (SAS). Estimates from stratified analyses were compared with SNP-based heritability estimates obtained from analysing all SNPs jointly (horizontal red bar; dotted lines represented standard errors). Analyses were repeated using a random set of 12,111 SNPs (and redefining loci relative to those), which minor allele frequency and linkage disequilibrium distribution matched that of GWS SNPs (RND: gold bars).



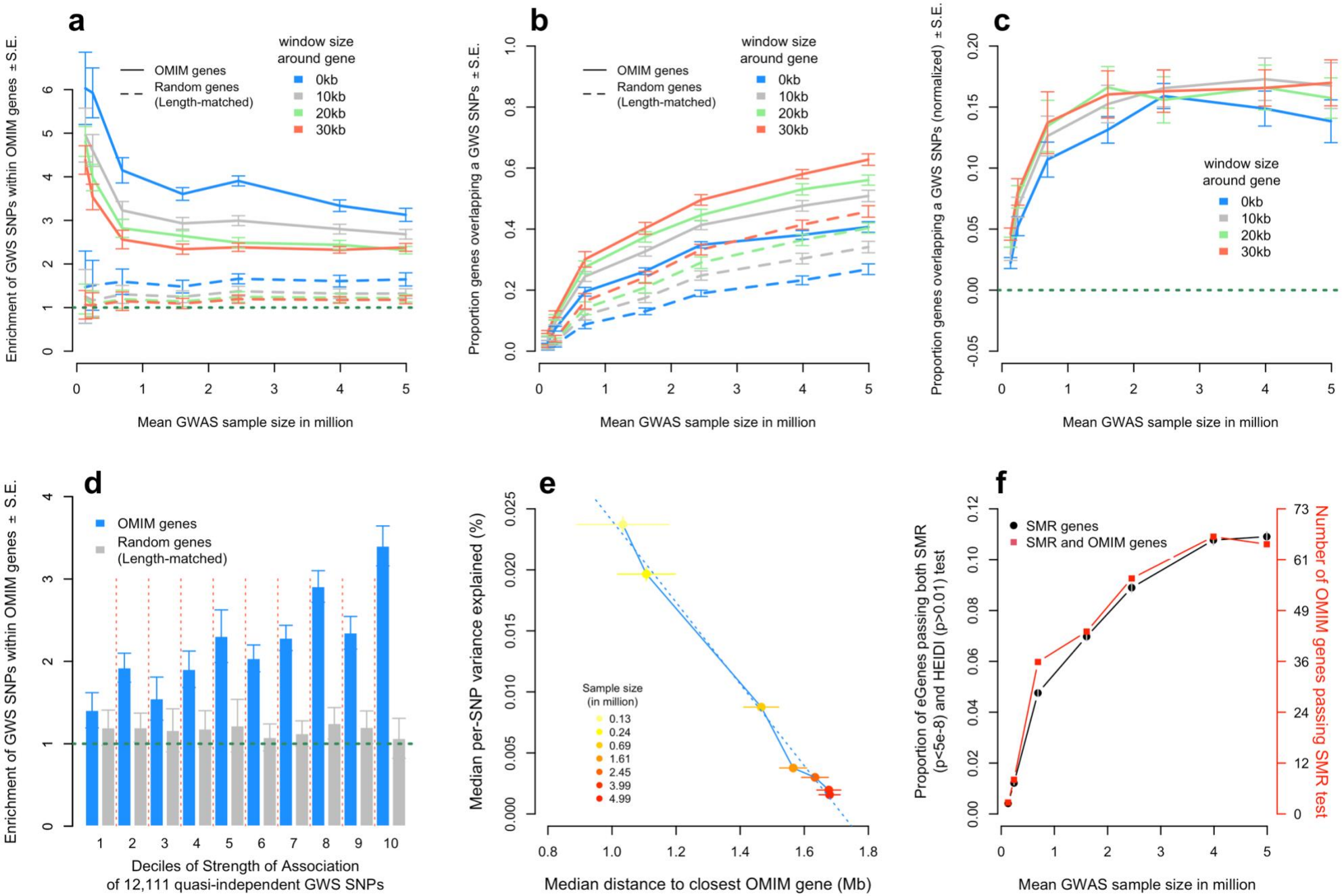
Suppl. Fig. 20. Optimal weighting of PGS and parental information in simulated data. We simulated a population of N=2,000 individuals and a trait controlled by M=1,000 causal variants. For simplicity, we assumed that a variable proportion of causal SNPs is used to calculate the PGS, and that SNP effects are estimated with negligible errors. We show below in Equation (3.11) how this proportion is chosen to achieve the desired prediction accuracy. We considered two scenarios: (i) random mating, i.e. r=0 (**Panels a** and **b**) and assortative mating (for 20 generations) based on a spousal phenotypic correlation r=0.25 (**Panels c** and **d**). In all simulations, we assumed a heritability $h^2 = 0.8$ and varied the expected prediction accuracy (R^2_{SNP}) between 0.05 and 0.8. The notation R^2_{SNP} is general and applies to any PGS based on independent SNPs, not just genome-wide significant as described in the main text. For each simulated population, we compared our predictions from Equation (S3.1) and (S3.2) with estimated regression coefficients obtained from regressing y on $\hat{y}$ and $\bar{y}_p$. The vertical green bar in panel **c**, denotes the threshold above which PGS information outweighs parental information. The vertical grey bar in panels **a** and **c** denotes the threshold when $R^2_{SNP} = h^2/2$. This threshold is predicted using Equation (S3.4). We also compared our variance explained by fitting both predictors with our predicted expectation from Equation (S3.3). Each dot is generated using 100 replicates. Overall, we found a perfect consistency between our theoretical and simulation results, which provides an empirical validation of these predictions.



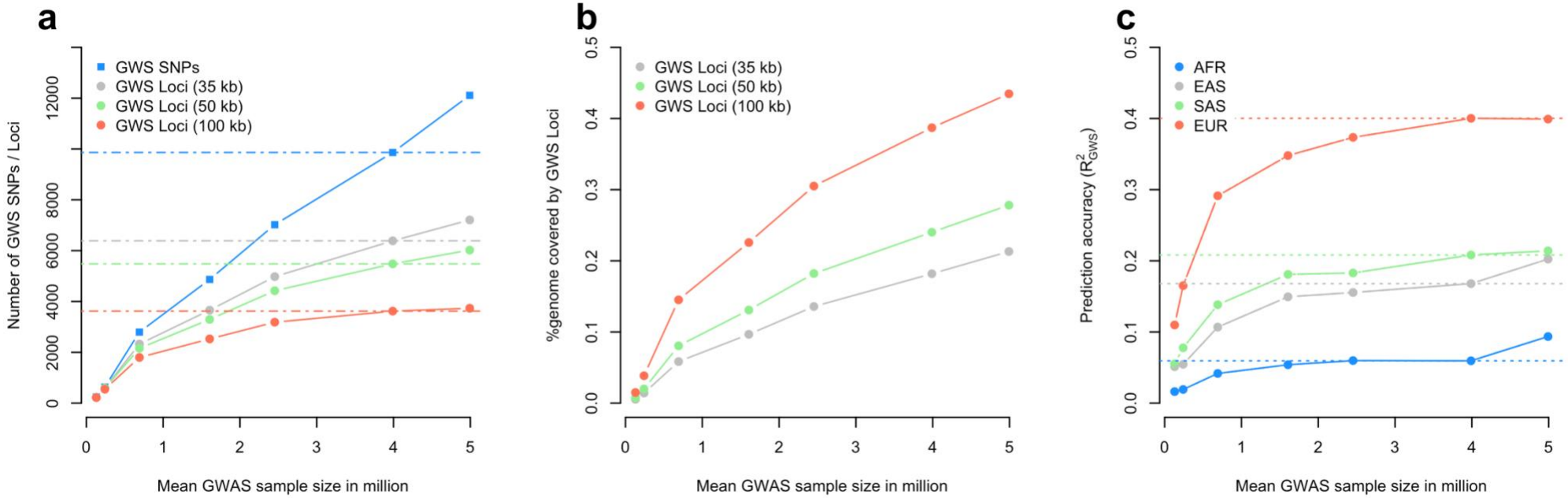
Suppl. Fig. 21. Selection of the number of gene set clusters using the "Elbow method". Gene sets were hierarchically clustered at different sizes and the distance between each cluster evaluated. 20 clusters was chosen as an appropriate number of gene set clusters to evaluate for enrichment.



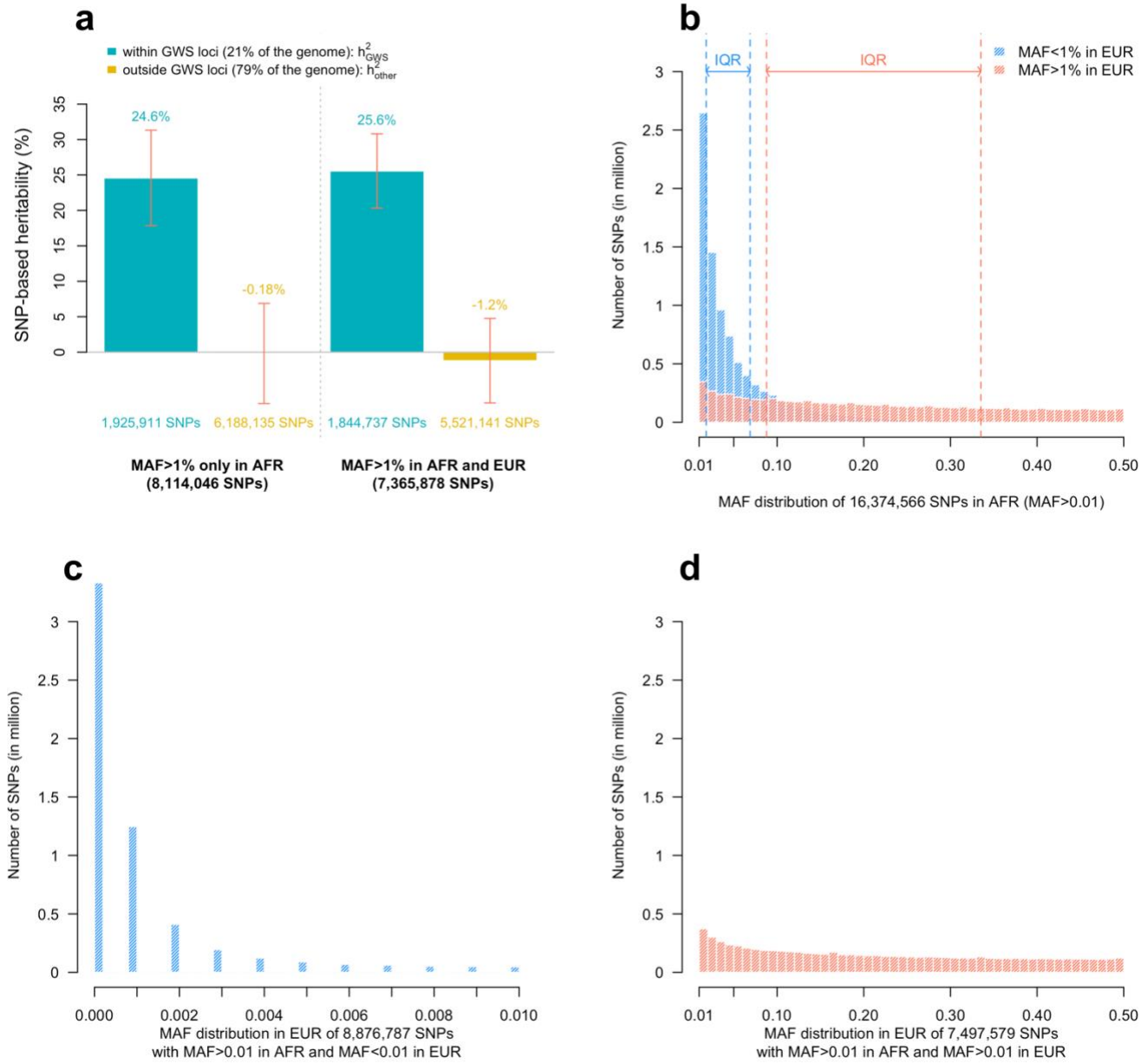
Suppl. Fig. 22. Proportional heritability (h^2) explained, enrichment, and normalized τ estimates for MAGMA (panels A-C) and DEPICT (panels D-F). The error bars represent the 95% confidence interval, calculated as estimate +/- 1.96*standard error. The labels for each subpanel indicate the ancestry represented in the GWAS used for LDSC, and the x-axis labels indicate the ancestry represented in the "discovery" GWAS used to prioritize the genes. EUR: European ancestry; AA: African-Americans of admixed European and African ancestries; EAS: East Asian ancestry. Analyses underlying this figure are further described in **Suppl. Note 5**.


a
Enrichment of GWS SNPs within OMIM genes ± S.E.
OMIM genes
Random genes
(Length-matched)
window size
around gene
0kb
10kb
20kb
30kb
Mean GWAS sample size in million
b
Proportion genes overlapping a GWS SNPs ± S.E.
OMIM genes
Random genes
(Length-matched)
window size
around gene
0kb
10kb
20kb
30kb
Mean GWAS sample size in million
c
Proportion genes overlapping a GWS SNPs (normalized) ± S.E.
window size
around gene
0kb
10kb
20kb
30kb
Mean GWAS sample size in million
d
Enrichment of GWS SNPs within OMIM genes ± S.E.
OMIM genes
Random genes
(Length-matched)
Deciles of Strength of Association
of 12,111 quasi-independent GWS SNPs
e
Median per-SNP variance explained (%)
Sample size
(in million)
0.13
0.24
0.69
1.61
2.45
3.99
4.99
Median distance to closest OMIM gene (Mb)
f
Proportion of eGenes passing both SMR
(p<5e-8) and HEIDI (p>0.01) test
SMR genes
SMR and OMIM genes
Number of OMIM genes passing SMR test
Mean GWAS sample size in million

Suppl. Fig. 23. Gene-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. **Panel a** shows the enrichment of genome-wide significant (GWS) SNPs identified from an approximate conditional and joint (COJO) analysis within 462 genes associated with skeletal growth disorders from the Online Mendelian Inheritance in Man (OMIM) database (y-axis) as a function of GWAS sample size (x-axis). Standard Error (S.E.) were calculated as the standard deviation of enrichment statistics (odds ratio in the 2x2 contingency table contrasting for each gene: "is the gene an OMIM gene" vs. "does the gene contain a GWS SNP") across 1,000 randomly sampled sets of 462 non-OMIM genes length-matched with OMIM genes. The average enrichment calculated across the 1,000 random gene sets is represented with dotted lines. Presence of a GWS SNP within a gene was assessed relative to gene start and stop position, considering flanking regions within 0 kb, 10 kb, 20 kb and 30 kb. **Panel b** shows the proportion of OMIM overlapping genes with at least one GWS SNPs (y-axis). As in **Panel a**, dotted lines represents the null distribution from 1,000 random sets of genes length-matched with OMIM genes. Standard errors (S.E.) were calculated as the standard deviation of the proportion observed across the 1,000 draws from the null distribution. **Panel c** represents the proportion of OMIM genes near GWS SNPs after subtracting the mean of the null distribution at each sample size. **Panel d** represents the enrichment of OMIM genes as a function of the strength of association of 12,111 independent GWS SNPs identified in our largest GWAS (N~5.4M). GWS SNPs were grouped into 10 decile groups of ~1,211 SNPs. Enrichment near OMIM genes is stronger of SNPs explaining a larger proportion of height variance (top decile). **Panel e** shows the median per-SNP variance explained (y-axis) as a function of the median distance to the closest OMIM gene. Large GWAS tend to identify variants with smaller effect sizes and further away from OMIM genes. **Panels f** shows the number of genes prioritised using Summary-data based Mendelian Randomization (SMR; $P<5\times10^{-8}$), which expression may act a mediator of the effects of SNP on height. SMR analyses were based on expression quantitative trait loci (eQTL) identified in the GTEx and eQTLgen studies (**Methods**). The z-axis (in red) shows the number of OMIM genes overlapping with SMR genes identified from analysing GWAS with various sample sizes (x-axis).



Suppl. Fig. 24. Variant-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. **Panel a** shows number of independent genome-wide significant (GWS) SNPs and loci identified at various GWAS sample sizes (Details about down-sampled GWAS are given in Table 2). GWS loci were defined using various window sizes including 35kb, 50kb and 100 kb. **Panel b** shows the percentage of the genome covered by GWS loci. Coverage was calculated as the cumulative length of GWS loci in Mb divided 3,039 Mb, the estimated length of the human genome. **Panel c** shows the prediction accuracy (R^2_{GWS}) of various polygenic scores on GWS SNPs identified at various sample sizes. In **Panels a** and **c**, dotted lines represent y-axis values for our largest European ancestry GWAS (N~4 million).



Suppl. Fig. 25. Partitioned SNP-based heritability of height in African ancestry individuals. Panels a represent partitioned SNP-based heritability estimates from a sample of 6,911 unrelated African ancestry (AFR) individuals from the UK Biobank, independent of our discovery GWAS. This analysis focuses on 16,374,566 SNPs with a minor allele frequency (MAF)>1% in AFR. These SNPs were further stratified according to their MAF in European ancestry (EUR) populations: 7,365,878 SNPs with MAF>1% in EUR (47%) vs. 8,114,046 SNPs with MAF<1% in EUR (53%) and their position within vs. outside genome-wide significant (GWS) loci. **Panel b** shows the MAF distribution of the 16M SNPs in AFR and panels (c – d) the distribution of these SNPs in EUR. The SNP-based heritability contributed by SNPs within GWS loci is denoted h^2_{GWS}, while that contributed by SNPs outside these loci is denoted h^2_{other}. These results are further discussed in **Suppl. Note 6**.

SUPPLEMENTARY NOTES

Supplementary Note 1: Sensitivity Analyses of COJO results

Long range LD in admixed populations can bias estimation of approximate conditional SNP effects

We compared the prediction accuracy of polygenic scores (PGS) based on genome-wide significant (GWS) SNPs identified in each ancestry groups. For each set of ancestry-specific GWS SNPs we calculated a PGS using either marginal SNP effects (hereafter denoted PGS_{GWAS}) or conditional effects (hereafter denoted PGS_{COJO}) approximated using GCTA-COJO (Methods). Given that COJO is designed to detect secondary signals, i.e. explaining additional trait variance, we expect the prediction accuracy of PGS_{COJO} to be similar, if not outperform, that of PGS_{GWAS}.

Consistently, we found that PGS_{COJO} yields a higher accuracy than PGS_{GWAS} in most cases except in HIS and AFR (**Suppl. Fig. 3a**). We further investigated that observation and found that the poor performances of PGS_{COJO} relative to PGS_{GWAS} in HIS and AFR were driven by specific chromosomes such chromosome 6, 9 and 20 (**Suppl. Fig. 3b**), where estimated conditional effects were abnormally large (**Suppl. Fig. 3c**).

We hypothesized that these unexpected observations could be explained by estimation errors during the stepwise model selection procedure, e.g., because of collinearity between SNPs included in the model. Note that GCTA sets a default threshold of 0.9 for collinearity between SNPs, which means that the variance of genotypes at a given SNP included in the model cannot be explained at >90% by all other SNPs included in the model. To explore the impact of this parameter on our observations we performed a sensitivity analysis by varying the collinearity threshold between 0.1 and 0.9.

We found that using a more stringent collinearity threshold reduces the prediction accuracy of PGS_{COJO} in EUR and EAS (accuracy in SAS remained unchanged) but produces an opposite effect in AFR and HIS (**Suppl. Fig. 4**). More specifically, setting the collinearity threshold below 0.5 restored the prediction accuracy of PGS_{COJO} up to a level comparable to that of PGS_{GWAS}. Therefore, our sensitivity analyses suggest that stringent collinearity thresholds are preferable when applying COJO to GWAS from admixed ancestry groups such as HIS and AFR.

Consequently, the COJO results presented in the main text are based upon a collinearity threshold of 0.1 for HIS and AFR and the default threshold of 0.9 for all other COJO analyses. We chose 0.1 because it produces the most parsimonious model (i.e. fewer number of associations) without impacting prediction accuracy.

Impact of ancestry composition of LD reference panel on COJO results

We re-analysed summary statistics from our cross-ancestry GWAS meta-analysis using two LD reference sets. First, we randomly selected 37,900 EUR, 4,400 EAS, 4,250 HIS, 2,750 AFR and 700 SAS individuals (i.e. 50000 individuals in total) to form a LD reference set with ancestries proportions matching that in our cross-ancestry meta-analysis. The second set contained 50,000 individuals with EUR ancestries. We restricted analyses with both LD reference sets to 882,755 HM3 SNPs, which passed quality control (Hardy-Weinberg Equilibrium test, missingness and imputation quality) in all five ancestry groups.

We found that COJO based on the multi-ancestry LD panel only detected 3,635 (3380 using a collinearity-threshold of 0.1) independent associations vs. 11,001 associations using the EUR LD reference. The latter number is smaller than the 12,111 reported in the main text but consistent with a ~10-15% smaller number of HM3 SNPs used as input. We also repeated analyses using the 37,900 EUR individuals as LD reference and found that COJO detects 11,065 SNPs, indicating that using this multi-ancestry LD panel leads to underestimation by COJO of the number of associations. This

conclusion is supported by the fact that a PGS based on 11,001 COJO SNPs detected using a EUR LD panel explains a significantly larger amount of height variance than that of a PGS based on only 3,380 COJO SNPs detected with a multi-ancestry panel (EUR: 38.2% vs 26.4%; SAS: 20.3% vs 13.4%; EAS: 19.5% vs 13.3% and AFR: 9.0% vs 5.0%). Moreover, we ran another COJO analysis of our cross-ancestry GWAS using LD information from 10,636 AFR individuals (i.e. same LD panel for our AFR GWAS meta-analysis). Note that 242,891 / 882,755 (i.e. 27.5%) SNPs were filtered out by GCTA prior to analysis because of expected large differences in allele frequencies between our cross-ancestry GWAS including >75% of EUR individuals and the AFR LD panel (by default GCTA exclude SNPs with an absolute frequency difference is >0.1). Nevertheless, we detected 5,701 quasi-independent joint associations (i.e. more associations than using a mix-ancestry panel), explaining 24.6%, 13.2%, 10.9% and 3.5% of height variance in EUR, SAS, EAS and AFR individuals respectively. The latter predictive performances are lower to that obtained with a PGS from 3,380 COJO SNPs.

Altogether, these results demonstrate that COJO with a composite LD reference panel does not improve and likely hinders the detection of associations in our cross-ancestry GWAS meta-analysis. We emphasize that extending the COJO methodology for analysing multi-ancestry GWAS is an independent research question, which goes beyond the scope of our study.

Supplementary Note 2: Investigation of population stratification in large GWAS of height

Assessment of population stratification in European ancestries GWAS

Recent studies[9,10] have shown evidence of significant confounding in estimated SNP effects induced by uncorrected population stratification (PS) in summary statistics from the Wood et al. (2014)[20] study. Importantly, Wood et al. (2014) also reported residual PS mostly affecting estimated effects of SNPs weakly associated with height (Figure 2a-c in ref.[20]). To ensure increased robustness and reliability of our findings, we perform here a series of analyses to quantify confounding effects of residual PS in all GWAS results reported in this study.

LD score regression analysis of European ancestries GWAS

First, we performed a LD score regression (LDSC) analysis[16] of our GWAS meta-analysis of EUR participants (N=4,080,687). We assessed the degree of PS using the attenuation ratio statistic (R_{LDSC}), which provides a quantification of PS that is independent of sample size. The estimated R_{LDSC} is ~3.8% (S.E. 0.8%), suggesting that most of the inflation of association test statistic is explained by polygenicity and not PS. In comparison, GWAS of height without any adjustment for population stratification produce values of R_{LDSC} ~10-13%.[67] Our estimated R_{LDSC} is slightly smaller than that from LDSC analyses of previously published GWAS of height (Wood et al. (2014): 4.3% (S.E. 1.3%); Yengo et al. (2018)[3] 4.0% (S.E. 1.2%)), which suggests a reduced effect of residual PS on our results. Note that the estimated R_{LDSC} shown here are obtained from analysing imputed GWAS summary statistics from Wood et al. (2014) and Yengo et al. (2018) (**Supplementary Methods**), which have a better coverage of HM3 SNPs; and thus explaining the difference with the ~6.0% (S.E. 1.0%) reported in Yengo et al. (2018). However, as a measure of PS, R_{LDSC} is not strictly comparable across studies. In fact, the expectation of R_{LDSC} (across repeated GWAS) not only depends on how much trait variance is explained by PS, but also on the degree of genetic differentiation between cohorts (F_{ST}) and the trait heritability within each cohort.[16] The last two factors can vary from one GWAS meta-analysis to another as a function of cohort composition. In summary, these LDSC analyses suggest that uncorrected PS only marginally affects SNP effects from our large GWAS of height in EUR participants.

Assessment of allele frequencies for height increasing alleles across the North-South axis of Europe reveals attenuated correlation relative to previous studies

As an alternative to R_{LDSC}, we next quantified PS in our GWAS using the correlation between strength of association (p-value) and height-increasing allele frequency differences between Great Britain (GBR sample in the 1000 Genomes Project – 1KGP) and the Italian Tuscan population (TSI sample in 1KGP). This statistic was previously introduced by Sohail and colleagues[10] to reveal biases in SNP effect estimates from the Wood et al. study, that were induced by uncorrected PS along the North-South gradient of Europe. More precisely, the strategy implemented by Sohail et al. consists in grouping SNPs based on strength of association, then regress the mean height-increasing allele frequency differences between GBR and TSI for each SNP bin onto the mean p-value of the corresponding bin. The slope of that linear regression (β_{PS}) measures the degree of PS. We estimated β_{PS} using 101,360 near independent HM3 SNPs with MAF>1% and calculated standard errors using a bootstrap strategy based on 1,000 independent draws.

As previously reported, we found a significant β_{PS} of ~1.28% (S.E. 0.08%; $P = 2.3 \times 10^{-61}$) using summary statistics of the Wood et al. (2014) study but no significant β_{PS} from within-family GWAS in 17,942 independent UKB siblings pairs (β_{PS}=-0.08%, S.E. = 0.07%; P=0.27). We show in **Suppl. Fig. 5a-b** estimates of β_{PS} from GWAS summary statistics of Yengo et al. (2018), EUR participants of 23andMe (23andME-EUR), all EUR participants of the UKB (UKB-456k; GWAS using BOLT-LMM), unrelated EUR participants of the UKB (UKB-350k; GWAS using PLINK), the meta-analysis EUR participants from multiple cohorts of the GIANT consortium (GIANT-EUR; N~1.6M); and the meta-analysis of GIANT-EUR and 23andMe-EUR. Overall, we find that β_{PS} decreases with sample size, consistent with an increased signal-to-noise ratio. In particular, β_{PS} is ~0.13% (P=0.1) in our largest GWAS meta-analysis of N~4.1M

EUR participants, which demonstrates a better correction of PS than previously published EUR GWAS of height.

Furthermore, we assessed the squared correlation between estimated effects at these 101,360 independent HM3 SNPs and SNP loadings from 20 principal components (PCs) calculated in 503 EUR samples from 1KGP. Across SNPs, we found that SNP loadings on PC2 explain most of the variance in estimated SNP effects (**Suppl. Fig. 5c**). This observation is not surprising given that PC2 is the PC that correlates the most with the North-South axis of Europe, and therefore explains the consistency with our results based on β_{PS}. However, <0.3% of the variance of SNP effects estimated in our largest GWAS is explained by SNP loadings, which is much lower than ~2.3% obtained when analysing SNP effects from Wood et al. (2014).

Comparison of estimated SNP effects between GWAS meta-analyses and family-based GWAS

Finally, we directly compared SNP effects from our GWAS (β_{GWAS}) with that of a within-family GWAS in 17,942 independent UKB siblings pairs (β_{SIB}). We used $S_{PS} = \mathrm{cov}(\beta_{GWAS}, \beta_{SIB})/\mathrm{var}(\beta_{GWAS})$ as our metric of interest in this comparison, where both $\mathrm{cov}(\beta_{GWAS}, \beta_{SIB})$ and $\mathrm{var}(\beta_{GWAS})$ are calculated across SNPs. When SNP effects are estimated using ordinary least-squares (OLS) regression, the expectation of S_{PS} in the absence of PS is $E[S_{PS}] = 1$. Therefore, a significant deviation of S_{PS} below 1, may indicate confounding due to residual PS. However, the statistical properties of S_{PS} based on SNP effects estimated using linear mixed models (LMM) (or meta-analyses of OLS and LMM estimates) are not well characterised, which may affect our interpretation below.

We found that estimates of S_{PS} based on SNPs strongly associated with height are much closer to 1 than when all SNPs are used, i.e. regardless of strength of association (P<1; **Suppl. Fig. 5d**). We observed the lowest value of S_{PS}~0.29 (S.E. 0.01) when using effects of all 101,360 SNPs estimated in the Wood et al. study. In comparison, estimated SNP effects from our largest EUR GWAS yields an S_{PS}>0.8 regardless of strength of association, yet still significantly lower than 1 ($P < 7 \times 10^{-30}$).

Lee et al.[68] previously showed that assortative mating (AM) on height can produce values of $S_{PS} < 1$. Under the assumption that the population has reached an equilibrium after many generations of AM with a constant spousal correlation (r), they showed that

$$E[S_{PS}] = 1 - rh^2, \quad (1.1)$$

where h^2 is the full narrow-sense heritability in the current generation (at equilibrium). We note here an error in the Supplementary Notes of Lee et al. (2018), who used in their derivations the heritability in the base population undergoing random mating (h_0^2) instead of the equilibrium heritability, h^2. In practice, differences between $h_0^2 = (h^2 - rh^4)/(1 - rh^4)$ and h^2 are small. Therefore, using one or the other heritability has a limited impact on the expected value of S_{PS}. Using Equation (1.1) and assuming an equilibrium heritability, $h^2 = 0.8$ and a spousal correlation, $r = 0.25$, we expect S_{PS} to be $\sim 1 - 0.8 \times 0.25 = 0.8$, which is consistent with our observations (**Suppl. Fig. 5d**).

Altogether, these analyses show that estimated SNP effects from our EUR GWAS are inflated by ~10-20% relative to that from a family-based GWAS and that this inflation is not larger than expected because of phenotypic AM on height.

Assessment of population stratification in non-European ancestries GWAS

We extended the previous analyses performed in EUR to quantify the impact of residual PS in GWAS of height performed in the four other ancestry groups, i.e. HIS, SAS, EAS and AFR.

LD score regression analysis of non-European ancestries GWAS

We performed LD score regression analyses using LD scores estimated from the same ancestry-matched samples as in our COJO analyses (i.e. 10,636 AFR samples, 5,875 EAS samples, 9,448 SAS

samples and 4,883 HIS samples). LD scores were calculated from imputed HapMap3 SNPs using the LDSC software (version 1.0.1) with a window size of 1 cM.

The R_{LDSC} statistic was 6.7% (S.E. 2.2%) in AFR, 9.5% (S.E. 1.4%) in HIS, 11.1% (S.E. 1.7%) in EAS, and 25.6% (S.E. 3.7%) in SAS. Previous studies have shown that longer range LD in admixed populations as compared to non-admixed populations can bias estimates from LD score regression.[8] Therefore, we repeated our analyses in AFR and HIS using 20 PCs adjusted LD scores based on a 20 cM window, as recommended by Luo et al. (2021).[8] The R_{LDSC} statistic decreased from 6.7% (S.E. 2.2%) to 0.9% (S.E. 1.9%) in AFR and from 9.5% (S.E. 1.4%) to 7.5% (S.E. 1.7%) in HIS. Importantly, using PC adjusted LD scores based on a 20cM window did not change estimates of R_{LDSC} in SAS (25.6%; S.E. 3.7% vs. 25.9%; S.E. 3.7%) nor in EAS (11.1%; S.E. 1.7% vs. 11.1%; S.E. 1.7%).

It is noteworthy that values of R_{LDSC} above 20%* as observed in our SAS GWAS may also reflect strong LD differences between GWAS participants and samples used to estimate LD scores. We applied the DENTIST method (Detecting Errors iN analyses of summary staTISTics) to distinguish these two potential explanations. In brief, DENTIST compares the observed distribution of Z-scores from GWAS to an expected distribution based on a reference LD matrix. Deviations from that expected distribution reflect errors in the GWAS summary statistics or inconsistencies in LD patterns. DENTIST detected 213 outlier SNPs in the SAS GWAS ($P<5 \times 10^{-8}$) relative to LD patterns from 9,448 unrelated SAS from the UKB. However, excluding these 213 outliers SNPs did not substantially affect the value of the R_{LDSC} statistic (26.2%; S.E. 3.6%).

Altogether, these LD score regression analyses suggest the presence of residual PS that might potentially confound estimates of SNP effects in our HIS, EAS and SAS GWAS.

Correlation between for height-increasing alleles frequencies and genetic differentiation within four ancestry groups

Next, we estimated β_{PS} for each non-EUR GWAS meta-analysis along various axes of within-continent genetic differentiation defined by pairs of 1KGP subpopulations. For example, we estimated β_{PS} in our AFR GWAS meta-analysis along an axis that differentiates Yoruba populations in Nigeria (West Africa) from Luhya populations in Kenya (East Africa), as well as in our EAS GWAS meta-analysis along an axis that differentiates Japanese populations from Han Chinese populations. We used ancestry-specific significance thresholds calculated as 0.05 divided by the number of pairs of subpopulations within the corresponding 1KGP ancestry group. More specifically, we considered 7 subpopulations in AFR (21 pairs), 5 subpopulations in EAS (10 pairs), 5 subpopulations in SAS (10 pairs) and 4 subpopulations in HIS (6 pairs).

We found significant β_{PS} in each non-EUR GWAS meta-analysis (**Suppl. Fig. 6a-d**). The largest magnitude of β_{PS} was observed in the SAS GWAS meta-analysis along the India-Bangladesh axis (β_{PS}=0.89%, S.E. 0.11%, P=6.2×10^{-17}, **Suppl. Fig. 6c**) and the second largest in the HIS GWAS meta-analysis along the Colombia-Puerto Rico axis (β_{PS}=0.75%, S.E. 0.08%, P=1.2×10^{-17}, **Suppl. Fig. 6d**). Importantly, estimated β_{PS} in non-EUR are significantly lower than 1.28% observed in the Wood et al. (2014) study.

Finally, we assessed the squared correlation between SNP effects estimated in each non-EUR GWAS meta-analysis and SNP loadings of 20 PCs calculated in corresponding superpopulations from 1KGP (**Suppl. Fig. 6e-h**). Overall, all squared correlations were smaller than 0.3% as observed with our largest EUR GWAS (N=4M), where PS was better controlled (**Suppl. Fig. 5c**).

*a rule-of-thumb recommended by the authors of the LDSC software.

In conclusion, we detected a small amount residual PS in all non-EUR GWAS meta-analyses, in particular in SAS (smallest sample size).

Effect of residual population stratification on cross-ancestry GWAS meta-analysis

In this final section, we focus on SNP effects from our cross-ancestry GWAS meta-analysis (referred to as $META_{FE}$ in the main text). Using these estimated SNP effects, we quantified β_{PS} along multiple axes of within-continent genetic differentiation and also the squared correlations between SNP effects and within-ancestry PC loadings and SNP effects (as in the previous section). Overall, β_{PS} remain below 0.5% across all pairs of 1KGP subpopulations (**Suppl. Fig. 7a-e**), and the squared correlation between SNP effects and PC loadings was also smaller than 0.15% (**Suppl. Fig. 7f**).

In summary, the various analyses shown here demonstrate that residual PS has a minimal confounding effect on estimated SNP effects from our cross-ancestry GWAS meta-analysis.

Supplementary Note 3: Distinguishing loss of tagging from multiplicity of causal variants at the *ACAN* locus

We observed the largest density of independent associations around rs4932198, where 24 other GWS SNPs were detected within less than 100 kb on each side (**Fig. 2**; **Suppl. Fig. 17**). We hereafter refer to the set of these 25 GWS SNPs as *ACAN* GWAS signals. A large density of signals may reflect the presence of multiple causal variants or the presence of poorly tagged causal variants with large effects at this locus. To disentangle these two possible explanations, we first used statistically phased haplotypes from 346,959 unrelated UKB participants of EUR and tested their association with height. We analysed 14,117 haplotypes covering a 100 kb long genomic region at this locus (hg19 genomic coordinates: chr15:89,307,521-89,407,521) and that were present in at least 5 UKB participants. We tested the association between each haplotype and height but could not identify a single haplotype with a large enough effect that can explain the majority of signals at this locus (**Extended Data Fig. 5**). In fact, *ACAN* GWAS signals cumulatively explain ~0.3% of height variance, while the two most associated haplotypes ($P<10^{-7}$) jointly only explain 0.01% of height variance.

Next, we used genotypes at this locus from 291,683 unrelated EUR participants of the UKB to simulate a trait controlled by a single rare biallelic variant (MAF<1%) explaining between η^2=0.5% and 5% of variance, then performed a GCTA-COJO analysis to estimate the density of independent signals. Previous studies have shown that large discrepancies in sample size between discovery GWAS and LD reference may contribute to inflate the number of independent associations detected with GCTA-COJO.[69] Therefore, to mimic that effect we used a random subset of 10,000 unrelated EUR participants of the UKB as LD reference, i.e. ~$1/30^{th}$ of the discovery sample. On average over 100 simulation replicates for each value of η^2, we observed a signal density lower than 2.3 associations per 100kb (**Extended Data Fig. 5**). The largest density of 10 associations per 100 kb was observed only when the simulated causal variant explains 5% of trait variance (i.e. β between ~2 and ~43 trait SD/allele), which is an extreme and unrealistic scenario. In contrast, even when the simulated causal variant explains 0.5% of trait variance, which in this case corresponds to a median allelic effect of ~1.4 SD/allele (~10cm, so very large) across simulations, we found that signal density never exceeded 7 associations per 100 kb. Altogether, the results of our haplotype- and simulation-based analyses suggest that a multiplicity of independent causal variants is the most likely explanation of our observations, although signal density is not a standard estimator of the number of causal variants.

Finally, we sought to quantify how much the presence of a recently identified[21,70] height-associated variable-number-of-tandem-repeat (VNTR) polymorphism in *ACAN* may contribute to the observed density of GWS SNPs. Therefore, we regressed VNTR length imputed in UKB participants[28] onto allele counts at *ACAN* GWAS signals and found that these 25 SNPs explain ~73%, ~47%, ~42% and ~40% of VNTR length variation in SAS (N=9,219), EUR (N=414,429), AFR (N=7,543) and EAS (N=1,496) respectively (**Extended Data Fig. 5e**). Consistent with partial tagging of VNTR length variation, *ACAN* GWAS signals explain ~0.24% ($R^2_{VNTR} = 0.21\%$ vs. $R^2_{VNTR+25\ SNPs} = 0.45\%$; $P=8.7 \times 10^{-55}$) additional height variance in EUR over what is explained by VNTR length variation alone (**Extended Data Fig. 5f**). In summary, these complementary analyses suggest that a large density of independent GWS SNPs near *ACAN* is partially explained by the presence of a VNTR at this locus and also by additional causal variants not yet identified.

Supplementary Note 4: Optimal weighting of PGS and parental information to maximize prediction accuracy in the presence of assortative mating

Overview of theory, simulations and application to real data from the UK Biobank

For a given individual, we denote y their phenotype, y_m and y_f the phenotypes of their mother and father respectively, $\bar{y}_p = (y_m + y_f)/2$ the average of their parents' phenotypes and $\hat{y}$ their own PGS. We consider combined predictor that is a linear combination of $\hat{y}$ and $\bar{y}_p$. Under the assumption that the resemblance between relatives is solely due to genetic factors, our main result is that the optimal weighting $\alpha_{PGS}\hat{y} + \alpha_{PA}\bar{y}_p$ is given by

$$(S3.1)\quad \alpha_{PGS} = \frac{R_{\hat{y},y}[1 - h^2(1 + r)/2]}{1 - R^2_{\hat{y},y}(1 + r)/2}$$

and

$$(S3.2)\quad \alpha_{PA} = \frac{h^2 - R^2_{\hat{y},y}}{1 - R^2_{\hat{y},y}(1 + r)/2}$$

where h^2 denotes the heritability of the trait in the current population, r the correlation between spouses phenotypes in the population, and $R^2_{\hat{y},y} = \mathrm{corr}(\hat{y}, y)^2$, the prediction accuracy of the PGS. The expected accuracy ($R^2_{\hat{y}+\bar{y}_p}$) of the combined predictor using these optimal weights, is given by

$$(S3.3)\quad R^2_{\hat{y}+\bar{y}_p} = \frac{R^2_{\hat{y},y} + \left(\frac{h^2}{2}\right)(1 + r)\left[h^2 - 2R^2_{\hat{y},y}\right]}{1 - R^2_{\hat{y},y}(1 + r)/2}$$

Suppl. Fig. 20 shows the results of simulations performed to verify the results from Equations (S3.1-S3.3). These simulations use an arbitrary number of SNPs included in the PGS and are not designed to match the number of SNPs used in various PGS analyses presented in the main text. Nevertheless, our conclusions are general and applicable to our empirical data under the assumption that each SNP in the PGS contributes about the same amount of genetic variance. We define the regression weights as $\omega_{PGS} = \alpha_{PGS}/(\alpha_{PGS} + \alpha_{PA})$ and $\omega_{PA} = \alpha_{PA}/(\alpha_{PGS} + \alpha_{PA})$. Therefore, values of ω_{PGS} such that $\omega_{PGS} > 0.5$ imply that the PGS has a stronger weight that the parental average.

Under assortative mating, **Suppl. Fig. 20** shows that ω_{PA} remains above 0.5 even when the PGS explains 50% of h^2. We show below that $\omega_{PGS} = \omega_{PA}$ if

$$(S3.4)\quad R_{\hat{y},y} = \frac{-[1 - h^2(1 + r)/2] + \sqrt{[1 - h^2(1 + r)/2]^2 + 4h^2}}{2}$$

For example, with $r = 0.25$ and $h^2 = 0.8$, Equation (S3.4) predicts an equal contribution of the PGS and parental information if $R^2_{\hat{y},y} \approx 0.46$.

Next, we estimated α_{PGS}, α_{PA} and $R^2_{\hat{y}+\bar{y}_p}$ in 981 trios from the UK Biobank (**Methods**). For this analysis, we used a PGS based on 12,111 GWS SNPs identified in our largest GWAS meta-analysis. We found $\hat{\alpha}_{PGS}$~0.375 (S.E. = 0.025) and $\hat{\alpha}_{PA}$~0.634 (S.E. = 0.034). The variance explained by fitting both predictors is $\hat{R}^2_{\hat{y}+\bar{y}_p}$ = 0.542 (S.E. = 0.032), which is larger than the accuracy of each single predictor ($R^2_{\hat{y}}$ = 0.38, S.E. 0.031; and $R^2_{\bar{y}_p}$ = 0.439, S.E. 0.032). Next, we estimated the spousal correlation $\hat{r}$ = 0.233 (S.E. = 0.031) and the heritability $\hat{h}^2$ = 0.894 (S.E. = 0.032) using mid-parent regression. Besides, the prediction accuracy of the PGS is $\hat{R}^2_{\hat{y},y}$~0.4. Therefore, from these estimates of r, h^2 and $R^2_{\hat{y},y}$

we predict using Equations (S3.1-S3.3) that $\alpha_{PGS} = 0.377$, $\alpha_{PA} = 0.656$ and $R^2_{\hat{y}+\bar{y}_p} = 0.599$. These three predictions are not statistically distinct from estimated values, which further validates our model.

Proof of theoretical results

The linear combination (y_{Opt}) of $\hat{y}$ and $\bar{y}_p$ that maximises prediction of y is derived from multivariate linear regression theory:

(3.1) $y_{Opt} = \alpha_{PGS}\hat{y} + \alpha_{PA}\bar{y}_p$

where

$$(3.2)\ \alpha_{PGS} = \frac{var(\bar{y}_p)cov(\hat{y},y) - cov(\hat{y},\bar{y}_p)cov(\bar{y}_p,y)}{var(\bar{y}_p)var(\hat{y}) - cov(\hat{y},\bar{y}_p)^2} = \frac{var(\bar{y}_p)var(\hat{y})}{var(\bar{y}_p)var(\hat{y})} \times \frac{cov(\hat{y},y)/var(\hat{y}) - \frac{cov(\hat{y},\bar{y}_p)cov(\bar{y}_p,y)}{var(\bar{y}_p)var(\hat{y})}}{1 - [cov(\hat{y},\bar{y}_p)^2]/[var(\bar{y}_p)var(\hat{y})]}$$

and

$$(3.3)\ \alpha_{PA} = \frac{var(\hat{y})cov(\bar{y}_p,y) - cov(\hat{y},\bar{y}_p)cov(\hat{y},y)}{var(\bar{y}_p)var(\hat{y}) - cov(\hat{y},\bar{y}_p)^2} = \frac{var(\bar{y}_p)var(\hat{y})}{var(\bar{y}_p)var(\hat{y})} \times \frac{cov(\bar{y}_p,y)/var(\bar{y}_p) - \frac{cov(\hat{y},\bar{y}_p)cov(\hat{y},y)}{var(\bar{y}_p)var(\hat{y})}}{1 - [cov(\hat{y},\bar{y}_p)^2]/[var(\bar{y}_p)var(\hat{y})]}$$

Without loss of generality, we assume that y and $\hat{y}$ are both centred (i.e. $E[y] = E[\hat{y}] = 0$) and scaled (i.e. $var[y] = var[\hat{y}] = 1$). Assuming that $var[y] = 1$ implies that $var[\bar{y}_p] = (1 + r)/2$, where r denotes the phenotypic correlation between mates in the population.

We also denote $R_{\hat{y},y} = corr(\hat{y},y) = cov(\hat{y},y)$, $R_{\bar{y}_p,y} = corr(\bar{y}_p,y)$ and $R_{\hat{y},\bar{y}_p} = corr(\bar{y}_p,y)$. Therefore, Equations (3.2) and (3.3) simplify as

$$(3.2')\ \alpha_{PGS} = \frac{cov(\hat{y},y)/var(\hat{y}) - \frac{cov(\hat{y},\bar{y}_p)}{\sqrt{var(\bar{y}_p)var(\hat{y})}} \times \frac{cov(\bar{y}_p,y)}{\sqrt{var(\bar{y}_p)var(y)}} \times \sqrt{\frac{var(y)}{var(\hat{y})}}}{1 - R^2_{\hat{y},\bar{y}_p}} = \frac{R_{\hat{y},y} - R_{\hat{y},\bar{y}_p}R_{\bar{y}_p,y}}{1 - R^2_{\hat{y},\bar{y}_p}}$$

and

$$(3.3')\ \alpha_{PA} = \frac{\frac{cov(\bar{y}_p,y)}{\sqrt{var(\bar{y}_p)var(y)}} \times \sqrt{\frac{var(y)}{var(\bar{y}_p)}} - \frac{cov(\hat{y},\bar{y}_p)}{\sqrt{var(\bar{y}_p)var(\hat{y})}} \times \frac{cov(\hat{y},y)}{\sqrt{var(\hat{y})var(y)}} \times \sqrt{\frac{var(y)}{var(\bar{y}_p)}}}{1 - R^2_{\hat{y},\bar{y}_p}}$$

$$= \sqrt{\frac{2}{1+r}}\left(\frac{R_{\bar{y}_p,y} - R_{\hat{y},\bar{y}_p}R_{\hat{y},y}}{1 - R^2_{\hat{y},\bar{y}_p}}\right)$$

and further as

$$(3.2'')\ \alpha_{PGS} = \frac{R_{\hat{y},y} - R_{\hat{y},\bar{y}_p}R_{\bar{y}_p,y}}{1 - R^2_{\hat{y},\bar{y}_p}}$$

and

$$(3.3'')\ \alpha_{PA} = \sqrt{\frac{2}{1+r}}\left(\frac{R_{\bar{y}_p,y} - R_{\hat{y},\bar{y}_p}R_{\hat{y},y}}{1 - R^2_{\hat{y},\bar{y}_p}}\right)$$

Equations (3.2'') and (3.3'') are expressed in function of $R_{\hat{y},y}$, $R_{\bar{y}_p,y}$, $R_{\hat{y},\bar{y}_p}$ and r.

We assume that $R_{\hat{y},y}$ is known, e.g., from quantifying the accuracy of the PGS in some validation sample. If we denote h^2 as heritability in the current population (which could be undergoing assortative mating, i.e. $r \neq 0$) and assume no shared environmental effects between parents and offspring then

$$(3.4) \quad h^2 = \text{cov}(\bar{y}_p, y)/\text{var}(\bar{y}_p) \Longrightarrow R_{\bar{y}_p,y} = h^2\sqrt{\frac{1+r}{2}}$$

Finally, denote $\hat{y}_p$ as the average PGS of parents. We can express $\bar{y}_p$ as a function of $\hat{y}_p$ as follows

$$(3.5) \quad \bar{y}_p = \frac{\text{cov}(\bar{y}_p, \hat{y}_p)}{\text{var}(\hat{y}_p)}\hat{y}_p + \varepsilon_p$$

where ε_p is a residual term with mean 0 and such that $\text{cov}(\varepsilon_p, \hat{y}_p) = 0$. Given that both phenotypes and PGS are centred, $\text{cov}(\bar{y}_p, \hat{y}_p)$ can be expressed as

$$\text{cov}(\bar{y}_p, \hat{y}_p) = \frac{1}{4}E\left[y_m\hat{y}_m + y_f\hat{y}_f + y_f\hat{y}_m + y_m\hat{y}_f\right] = \frac{1}{2}E\left[R_{\hat{y},y} + E[y_f\hat{y}_m|y_m]\right] = R_{\hat{y},y}(1+r)/2$$

Using a similar reasoning, we can show that $\text{var}(\hat{y}_p) = (1 + rR^2_{\hat{y},y})/2$. Therefore, Equation (3.5) can be rewritten as

$$(3.5') \quad \bar{y}_p = R_{\hat{y},y}\left(\frac{1+r}{1 + rR^2_{\hat{y},y}}\right)\hat{y}_p + \varepsilon_p$$

Besides, we can also write

$$(3.6) \quad \hat{y} = \hat{y}_p + \varepsilon_m,$$

where ε_m (Mendelian segregation) is independent of $\hat{y}_p$. Combining Equations (3.5') and (3.6) leads to

$$(3.7) \quad \text{cov}(\bar{y}_p, \hat{y}) = R_{\hat{y},y}\left(\frac{1+r}{1 + rR^2_{\hat{y},y}}\right)\text{cov}(\hat{y}_p, \hat{y}) + \text{cov}(\hat{y}, \varepsilon_p) = R_{\hat{y},y}\left(\frac{1+r}{1 + rR^2_{\hat{y},y}}\right)\text{var}(\hat{y}_p) + \text{cov}(\varepsilon_m, \varepsilon_p)$$

which, assuming $\text{cov}(\varepsilon_m, \varepsilon_p) = 0$, implies that $\text{cov}(\bar{y}_p, \hat{y}) = R_{\hat{y},y}\left(\frac{1+r}{1 + rR^2_{\hat{y},y}}\right)\text{var}(\hat{y}_p) = R_{\hat{y},y}(1+r)/2$.

Therefore,

$$(3.8) \quad R_{\hat{y},\bar{y}_p} = \text{corr}(\bar{y}_p, \hat{y}) = \frac{R_{\hat{y},y}(1 + r)}{\sqrt{2(1+r)}}.$$

It follows that

$$R^2_{\hat{y},\bar{y}_p} = \frac{R^2_{\hat{y},y}(1 + r)^2}{2(1+r)} = R^2_{\hat{y},y}(1+r)/2 \Leftrightarrow \frac{1}{1 - R^2_{\hat{y},\bar{y}_p}} = \frac{1}{1 - R^2_{\hat{y},y}(1+r)/2}$$

We now express below α_{PGS} and α_{PA} as a function of h^2, $R_{\hat{y},y}$, and r.

We first recall that $\alpha_{PGS} = \frac{R_{\hat{y},y} - R_{\hat{y},\bar{y}_p} R_{\bar{y}_p,y}}{1 - R^2_{\hat{y},\bar{y}_p}}$

$$R_{\hat{y},\bar{y}_p} R_{\bar{y}_p,y} = \frac{R_{\hat{y},y}(1 + r)}{\sqrt{2(1+r)}} \times h^2 \sqrt{\frac{1+r}{2}} = R_{\hat{y},y} h^2 (1 + r)/2.$$

$$R_{\hat{y},y} - R_{\hat{y},\bar{y}_p} R_{\bar{y}_p,y} = R_{\hat{y},y}[1 - h^2(1 + r)/2].$$

To calculate $\alpha_{PA} = \sqrt{\frac{2}{1+r}} \left(\frac{R_{\bar{y}_p,y} - R_{\hat{y},\bar{y}_p} R_{\hat{y},y}}{1 - R^2_{\hat{y},\bar{y}_p}} \right)$

$$\sqrt{\frac{2}{1+r}} \left(R_{\bar{y}_p,y} - R_{\hat{y},\bar{y}_p} R_{\hat{y},y} \right) = \sqrt{\frac{2}{1+r}} \left[h^2 \sqrt{\frac{1+r}{2}} - \frac{R^2_{\hat{y},y}(1 + r)}{\sqrt{2(1+r)}} \right] = h^2 - \frac{R^2_{\hat{y},y}(1 + r)}{1+r} = h^2 - R^2_{\hat{y},y}$$

Finally,

$$(3.2''') \quad \alpha_{PGS} = \frac{R_{\hat{y},y} - R_{\hat{y},\bar{y}_p} R_{\bar{y}_p,y}}{1 - R^2_{\hat{y},\bar{y}_p}} = \frac{R_{\hat{y},y}[1 - h^2(1 + r)/2]}{1 - R^2_{\hat{y},y}(1 + r)/2}$$

and

$$(3.3''') \quad \alpha_{PA} = \sqrt{\frac{2}{1+r}} \left(\frac{R_{\bar{y}_p,y} - R_{\hat{y},\bar{y}_p} R_{\hat{y},y}}{1 - R^2_{\hat{y},\bar{y}_p}} \right) = \frac{h^2 - R^2_{\hat{y},y}}{1 - R^2_{\hat{y},y}(1 + r)/2}$$

Special case: $r = 0$

$$\alpha_{PGS} = \frac{R_{\hat{y},y}[1 - h^2/2]}{1 - R^2_{\hat{y},y}/2} \quad \text{and } \alpha_{PA} = \frac{h^2 - R^2_{\hat{y},y}}{1 - R^2_{\hat{y},y}/2}$$

The relative contribution of $\hat{y}$ and $\bar{y}_p$, defined above as $\omega_{PGS} = \alpha_{PGS}/(\alpha_{PGS} + \alpha_{PA})$ and $\omega_{PA} = \alpha_{PA}/(\alpha_{PGS} + \alpha_{PA})$ can be expressed as

$$\omega_{PGS} = \frac{R_{\hat{y},y}[1 - h^2(1 + r)/2]}{R_{\hat{y},y}[1 - h^2(1 + r)/2] + h^2 - R^2_{\hat{y},y}} \quad \text{and } \omega_{PA} = \frac{h^2 - R^2_{\hat{y},y}}{R_{\hat{y},y}[1 - h^2(1 + r)/2] + h^2 - R^2_{\hat{y},y}}$$

These two relative contributions are equal when $\omega_{PA} = \omega_{PGS} = 1/2$, i.e. when

$$2h^2 - 2R^2_{\hat{y},y} = R_{\hat{y},y}[1 - h^2(1 + r)/2] + h^2 - R^2_{\hat{y},y} \Leftrightarrow R^2_{\hat{y},y} + R_{\hat{y},y}[1 - h^2(1 + r)/2] - h^2$$

or equivalently, when

$$R_{\hat{y},y} = \frac{-[1 - h^2(1 + r)/2] + \sqrt{[1 - h^2(1 + r)/2]^2 + 4h^2}}{2}$$

This therefore proves Equation (S3.4).

Prediction accuracy from a linear regression model fitting both PGS and parental average

The expected prediction accuracy ($R^2_{\hat{y}+\bar{y}_p}$) from combining PGS and parental information can be expressed as

$$R^2_{\hat{y}+\bar{y}_p} = \alpha_{PGS}\mathrm{cov}(\hat{y},y) + \alpha_{PA}\mathrm{cov}(\bar{y}_p,y) = \frac{R^2_{\hat{y},y}\left[1-h^2(1+r)/2\right]+h^2(h^2-R^2_{\hat{y},y})(1+r)/2}{1-R^2_{\hat{y},y}(1+r)/2}$$

which can be simplified as

$$(3.9)\quad R^2_{\hat{y}+\bar{y}_p} = \frac{R^2_{\hat{y},y}+\left(\frac{h^2}{2}\right)(1+r)\left[h^2-2R^2_{\hat{y},y}\right]}{1-R^2_{\hat{y},y}(1+r)/2}$$

Prediction accuracy and proportion of causal variants captured

We assume that the trait of interest in underlain by M independent causal SNPs and that m ($m \leq M$) of them are included in a PGS. Moreover, we assume that the population has been undergoing assortative mating for multiple generations, until an equilibrium is reached. We derive below how large m needs to be for the prediction accuracy of the derived PGS, in the equilibrium population, to equal $R^2_{\hat{y},y}$.

We denote $\rho = rh^2$, $f_0 = m/M$, $\gamma = \rho/(1-\rho)$, $\alpha = \gamma/(2M)$ the expected correlation between trait-increasing alleles induced by assortative mating, and $\sigma^2_{g,0}$ and $\sigma^2_{g,eq}$ the genetic variances in a randomly and assortatively mating populations, respectively.

In the equilibrium population, the variance of the PGS can be expressed as

(Int. 3.1) $\mathrm{var}(\hat{y}) \approx \sigma^2_{g,0} f_0(1+\gamma f_0)$, and the covariance between y and $\hat{y}$ as

(Int. 3.2) $\mathrm{cov}(\hat{y},y) \approx \sigma^2_{g,0} f_0(1+\gamma)$.

Equations (Int. 3.1) and (Int. 3.2) are proven below.

Therefore,

$$(3.10)\quad R^2_{\hat{y},y} = \frac{\mathrm{cov}(\hat{y},y)^2}{\mathrm{var}(\hat{y})\mathrm{var}(y)} \approx \sigma^2_{g,0} f_0 \frac{(1+\gamma)^2}{1+\gamma f_0}$$

We divide the previous equation by $\sigma^2_{g,eq}$ and define $\phi_{eq} = R^2_{\hat{y},y}/\sigma^2_{g,eq}$. Therefore, Equation (3.10) implies that

$$(3.11)\quad (1+\gamma f_0)\phi_{eq} \approx \left(\frac{\sigma^2_{g,0}}{\sigma^2_{g,eq}}\right) f_0(1+\gamma)^2 = f_0(1-\rho)(1+\gamma)^2 \Leftrightarrow f_0 \approx \frac{\phi_{eq}}{(1-\rho)(1+\gamma)^2 - \gamma\phi_{eq}}$$

where $\phi_{eq} = R^2_{\hat{y},y}/\sigma^2_{g,eq}$. Note that $\sigma^2_{g,eq}/\sigma^2_{g,0}$ is the inflation in genetic variance due to assortative mating, which is predicted in theory to equal $1/(1-\rho)$.

Using a similar reasoning, Yengo et al.[71] (Eq. 1.20 in their Supplementary Note) derived the relationship between f_0 and the proportion $f_{eq} = h^2_{SNP}/h^2$ of equilibrium heritability explained by the m SNPs included in the PGS as:

$$(3.12)\quad f_0 = \frac{1-\rho}{2\rho}\left[\sqrt{\left(1+\frac{4f_{eq}\rho}{(1-\rho)^2}\right)}-1\right] \underset{|\rho|\ll 1}{\approx} f_{eq}/(1-\rho).$$

Proof of Equation (Int. 3.1) and (Int. 3.2)

We assume an infinitesimal model, where each causal SNP explains the same amount of trait variance. For simplicity, we assume the squared effect size of each causal SNP to equal $b^2 = \sigma^2_{g,0}/M$; and that SNP

effects are estimated with negligible errors so that they could be assumed to be equal to their true value. Finally, we assume that the m first SNPs are included in the PGS.

Under these assumptions, the PGS (i.e. $\hat{y}$) can be written as

$$\hat{y} = \left(\frac{\sigma^2_{g,0}}{M}\right)\sum_{j=1}^{m} z_j$$

where $(z_j - 2p_j)/\sqrt{2p_j(1-p_j)}$ is the centred and scaled count of trait-increasing allele at SNP j and p_j the trait-increasing allele frequency at that same SNP. By definition, we have that $\mathrm{var}(z_j) = 1 + \alpha$, and that $\mathrm{cov}(z_j, z_k) = 2\alpha$. It follows that

$$\mathrm{var}(\hat{y}) = \frac{\sigma^2_{g,0}}{M}[m(1+\alpha) + m(m-1)2\alpha] = \sigma^2_{g,0}\left(\frac{m}{M}\right)[1 + (2m-1)\alpha] = \sigma^2_{g,0} f_0\left[1 + \left(f_0 - \frac{1}{2M}\right)(2M\alpha)\right]$$

For large values of M, this simplifies as $\mathrm{var}(\hat{y}) \approx \sigma^2_{g,0} f_0(1 + \gamma f_0)$.

Similarly, we can write $\mathrm{cov}(\hat{y}, y)$ as $\mathrm{cov}(\hat{y}, y) = \frac{\sigma^2_{g,0}}{M}[m(1+\alpha) + m(M-1)2\alpha] \approx \sigma^2_{g,0} f_0(1+\gamma)$.

Supplementary Note 5: Saturation of GWAS signals within pathways and gene sets

Overview and main results

We assessed the enrichment of broad categories of biological pathways for different GWAS sample sizes, using two different gene set enrichment methods, DEPICT[42] and MAGMA.[43] Specifically, we evaluated the prioritization of 14,462 gene sets, hierarchically clustered into 20 groups of related gene sets based on gene set membership (see Methods below, **Suppl. Fig. 21**, **Suppl. Table 13**). We observed an enrichment of OMIM genes in clusters 1, 2, 5, 6, 11, 16, and 17 (Bonferroni $P < 0.05$ vs. random genes (**Extended Data Fig. 8**, **Suppl. Table 14**). At all sample sizes tested (range N=130,010 to N=5,314,291), similar sets of the clusters consistently showed significant enrichments in DEPICT (clusters 2, 5, 11, 16, and 17) and MAGMA-prioritized gene sets (clusters 5, 11, 16, and 17; **Suppl. Fig. 21**). Thus, the broad patterns of gene set enrichment are apparent even at moderate sample sizes and remain quite stable as sample sizes increase.

In contrast with clusters of gene sets, individual genes may require larger sample sizes or multiple ancestries to be implicated by GWAS. To address these questions, we assessed the fraction of OMIM genes that contain an approximately independent genome-wide significant signal (identified with COJO) across the range of GWAS sample sizes. As sample size increases and the number of independent signals increases, the percent of the 462 OMIM genes overlapping a signal also increases (**Suppl. Fig. 23b**); however, after subtracting the null background from randomly sampled sets of 462 genes, the percentage above background of OMIM genes that overlap GWAS signal plateaus at a sample size of ~2.5 M (**Suppl. Fig. 23c**). In comparing the trans-ancestry meta-analysis with the largest European-ancestry-only GWAS with, we did not observe a noticeable increase in overlapping OMIM genes above background.

We also sought to examine more directly whether the height GWAS results implicate highly similar biology across different continental ancestries. We used MAGMA and DEPICT to prioritize genes based on GWAS results for EUR, EAS, and AA ancestries. We then compared the enrichment of heritability with stratified LD score regression (LDSC)[39,40] for each set of prioritized genes, evaluated either in the same ancestry or in the other two ancestries. Genes prioritized in one ancestry by both MAGMA and DEPICT showed comparable enrichment of heritability when evaluated either in that ancestry or in the other two ancestries (**Suppl. Fig. 22**, **Suppl. Table 15**), strongly confirming the shared biology implicated by GWAS results from different ancestries.

Methods

Evaluation of gene set enrichment analysis (GSEA) methods across sample sizes.

For GWAS summary statistics from multiple sample sizes (**Tables 1 - 2**) two GSEA approaches were applied (DEPICT and MAGMA). DEPICT release 173 was used; the top 1000 SNPs pruned by p-value from each set of summary statistics were used as input for each sample. MAGMA version v1.07b was used; SNPs were annotated with genes within 100kb, and genes were removed if the missingness of their pathway membership was over 0.2.

To evaluate the ability of GSEA methods to identify groups of gene sets at different sample sizes, 14,462 gene sets, each consisting of Z-scores for 19,987 genes (gene sets selected and gene membership Z-scores calculated in ref.[42]), were hierarchically clustered into 20 clusters as follows. Pairwise distances between gene sets were defined as the Euclidean distance between the gene sets' Z-scores and the elbow method was used to choose the number of clusters, evaluating average distances between cluster centroids as the number of clusters is varied (**Suppl. Fig. 21**). For DEPICT and MAGMA, enrichment of prioritization in each cluster was defined as the number of prioritized gene sets in each cluster divided by the size of each cluster; a gene set was considered prioritized if it was in the top 10% of gene sets as prioritized by the GSEA method. Enrichment of OMIM genes in each gene set was defined as the number of OMIM genes in each gene set divided by the size of each gene set divided by the proportion of all genes in OMIM, and then enrichment of OMIM genes in each cluster was defined as the average of the

enrichment of OMIM genes in each gene set in that cluster. Genes were defined to be "in a gene set" if the gene's gene-set Z-score is > 1.96, as described previously.[72] Null distributions for each cluster were generated by randomly selected prioritized gene sets (for DEPICT and MAGMA) or prioritized genes to evaluate enrichment significance.

To evaluate saturation of height-associated gene identification, the percentage of OMIM genes overlapping independent COJO signals was calculated. "Overlapping" was defined as having at least one COJO SNP within the gene body, as defined with the plink version 1.9 hg19 gene list (URL: https://www.cog-genomics.org/static/bin/plink/glist-hg19). A null distribution was calculated by drawing an equivalent number of random genes (binned by size into 20 bins, same number of genes per bin) to match OMIM genes, and calculating the percent of the random genes near a COJO SNP.

Benchmarking of gene prioritization across different ancestries

We applied DEPICT and MAGMA to prioritize genes on height GWAS of European, African-American and East Asian ancestry, resulting in three sets of prioritized genes for each method. To allow for a fair comparison, we used subsets of the available cohorts to create three equally sized GWAS (N~100,000). For MAGMA, we converted gene set prioritizations to gene prioritizations as described previously.[72] For both DEPICT and MAGMA, we then used Benchmarker[72] to evaluate the performance of these three sets of genes in each of the three different ancestries, resulting in three within-ancestry and six cross-ancestry scenarios.

The Benchmarker method is based on a leave-one-chromosome-out approach where one chromosome is withheld, and GWAS results for the remaining 21 chromosomes are used to prioritize genes on the withheld chromosome, iterating across each withheld chromosome. For each of the discovery GWAS ancestries, we selected the top 10% of the prioritized genes on each left out chromosome, resulting in 1,893 prioritized genes. We subsequently annotated SNPs within 50kb of the prioritized genes to generate a LD score annotation for these SNPs using LDSC.[16] Lastly, we applied stratified LDSC[39] (S-LDSC) to compare the three annotation sets to the full GWAS results for each of the three ancestries to determine whether the performance of genes prioritized and then evaluated across the same ancestry would be more enriched for heritability compared with those prioritized and evaluated in different ancestries. Reference panels were based on the 1000 Genomes Phase 3 reference panels[5] for LD score estimation, matching the reference panel ancestry with the GWAS results for that same ancestry. In addition, a category of SNPs that locate within 50kb of any gene in the prioritization method and a set of 53 annotations of known genomic importance were included in the S-LDSC as conditional covariates. The analysis was based on 1,217,311 HapMap3 SNPs. The results of the S-LDSC is summarized using proportional h^2_{SNP} (proportion of heritability explained by the annotation), the regression coefficient (average per-SNP contribution of the annotation to heritability), and enrichment in heritability (h^2 divided by the proportion of SNPs in the annotation). To assess the performance difference between two annotations, we calculated p-values based on standard errors from the different estimates.

Supplementary Note 6: Enrichment of SNP-based heritability from low-frequency variants within loci containing common SNPs associated with height

In this note, we quantify the enrichment of SNP-based heritability due to low-frequency SNPs (MAF<1%) in genomic loci containing common SNPs (MAF>1%) associated with height.

Heritability enrichment from low-frequency variants in European ancestry participants

We first analysed imputed SNPs (INFO>0.3) from 3 samples of unrelated European ancestry (EUR) individuals independent from our discovery GWAS. This analysis included 44,312 participants from the Estonian Biobank (EBB), 14,587 participants of the UK Biobank (UKB) and 14,058 participants from the Lifelines Biobank (LLB), so that the total sample size is N=72,957. We partitioned SNP-heritability estimates in each of the 3 samples, then meta-analysed the results using an inverse-variance weighting scheme. The number of SNPs with MAF>0.1% was 13,040,176 in UKB (incl. 8,547,170 SNPs with MAF>1%), 11,492,146 in LLB (incl. 7,659,695 SNPs with MAF>1%) and 13,695,032 in EBB (incl. 8,620,105 SNPs with MAF>1%). We stratified SNPs into 4 classes: (1) 0.1%<MAF<1% within genome-wide significant loci (GWS), (2) 0.1%<MAF<1% outside GWS loci, (3) MAF>1% within GWS loci and (4) MAF>1% outside GWS loci. Then, we calculated genetic relationship matrices (GRM) for each group of SNPs using GCTA and estimated SNP-based heritability from fitting these 4 GRMs jointly.

Extended Data Fig. 10 shows estimates of SNP-based heritability for each group of SNPs and each sample, as well as the meta-analysis of these estimates across the 3 EUR samples. We found consistent patterns across these samples and, therefore, hereafter focus on meta-analysed estimates. Approximately 88% (i.e. 5.7/(5.7 + 0.78)) of the SNP-based heritability of height explained by variants with 0.1%<MAF<1% is due to SNPs located within our 7,209 height-associated loci. Importantly, these analyses only implicate a fraction (approximately 4/5th, Wainschtein et al.[50]) of low-frequency variants with an imputation accuracy score >0.3, which limits generalisability to all low-frequency and rare variants. Nevertheless, these results suggest that rarer variants associated with height are likely be detected in (or near) the 7209 loci identified in this study.

Height-associated rare variants in European ancestries but common in African ancestries are enriched within GWS loci

Next, we analysed 16,374,566 SNPs with MAF>1% in African ancestries (AFR; N=661) individuals from the 1000 Genomes Project (1KG). We stratified these SNPs in two classes defined by their MAF in EUR individuals from 1KG (N=504). The first class contained 7,365,878 SNPs with a MAF>1% in EUR (47% of which had a MAF<0.1% in EUR; **Suppl. Fig. 25**), and the second one 8,114,046 SNPs with a MAF<1% in the same EUR individuals. We then quantified the enrichment of SNP-based heritability within GWS loci for both classes of variants in 6,911 AFR individuals from the UKB.

Overall, we found similar enrichments of SNP-based heritability within GWS loci for both classes of variants (**Suppl. Fig. 25a**). Therefore, assuming that causal variants for height are shared across ancestries, these results suggest that rare variants in EUR that are associated with height (at least those common enough in AFR) are also likely to be detected within these 7,209 genomic regions. Note that this class of rare variants in EUR could, in principle, be detected with large GWAS of height in AFR.

Conclusions

In summary, we performed two orthogonal analyses, with results suggest that rare variants associated with height in EUR are enriched within our GWS loci. Additional analyses using whole-genome sequence data in large samples are required to confirm these findings as well larger GWAS of height in non-EUR populations.

SUPPLEMENTARY REFERENCES

67. Loh, P.-R., Kichaev, G., Gazal, S., Schoech, A. P. & Price, A. L. Mixed-model association for biobank-scale datasets. *Nature Genetics* **50**, 906–908 (2018).
68. Lee, J. J. *et al.* Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat. Genet.* **50**, 1112–1121 (2018).
69. Chen, W. *et al.* Improved analyses of GWAS summary statistics by reducing data heterogeneity and errors. *bioRxiv* 2020.07.09.196535 (2020) doi:10.1101/2020.07.09.196535.
70. Mukamel, R. E. *et al.* Protein-coding repeat polymorphisms strongly shape diverse human phenotypes. *bioRxiv* 2021.01.19.427332 (2021) doi:10.1101/2021.01.19.427332.
71. Yengo, L. *et al.* Imprint of assortative mating on the human genome. *Nature Human Behaviour* **2**, 948 (2018).
72. Fine, R. S., Pers, T. H., Amariuta, T., Raychaudhuri, S. & Hirschhorn, J. N. Benchmarker: An Unbiased, Association-Data-Driven Strategy to Evaluate Gene Prioritization Algorithms. *Am J Hum Genet* **104**, 1025–1039 (2019).