A Saturated Map of Common Genetic Variants Associated with Human Height from 5.4 Million Individuals of Diverse Ancestries

ABSTRACT

Common 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. Here we show, using GWAS data from 5.4 million individuals of diverse ancestries, 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 median size of ~90 kb, covering ~21% of the genome. The density of independent associations varies across the genome and the regions of elevated density are enriched for biologically relevant genes. In out-of-sample estimation and prediction, the 12,111 SNPs account for 40% of phenotypic variance in European ancestry populations but only ~10%-20% in other ancestries. Effect sizes, associated regions, and gene prioritization are similar across ancestries, indicating that reduced prediction accuracy is likely explained by linkage disequilibrium and allele frequency differences within associated regions. Finally, we show that the relevant biological pathways are detectable with smaller sample sizes than needed to implicate causal genes and variants. Overall, this study, the largest GWAS to date, provides an unprecedented saturated map of specific genomic regions containing the vast majority of common height-associated variants.

INTRODUCTION

Since 2007, genome-wide association studies (GWAS) have identified thousands of associations between common single nucleotide polymorphisms (SNPs) and height, primarily using studies of European ancestry. The largest GWAS published to date for adult height focussed on common variation and reported up to 3,290 independent associations in 712 loci using a sample size of up to 700,000 individuals.[1] To date, 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 GWAS 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 GWAS 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 GWAS. 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 prioritised genes and gene sets. Furthermore, because most GWAS continue to be performed largely in populations of European ancestry, it is important 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 GWAS, rather than implicating specific subsets of genes and biological pathways.[2]

Using data from 5,380,080 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, explore signal density across the genome, perform out-of-sample estimation and prediction analyses within European and non-European ancestry studies, and prioritise 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 European-ancestry populations and largely saturates both the genomic regions associated with height and broad categories of likely relevant gene sets; future work remains to extend prediction accuracy to non-European ancestries and to more definitively connect associated regions with individual likely causal genes and variants.

RESULTS

An overview of our study design and analysis strategy is illustrated in Suppl. Fig. 1.

Multi-ancestry GWAS 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, Inc. including 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-Americans 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/cohorts by the shorthand EUR, EAS, HIS, AFR, and SAS, respectively, yet recognising that these commonly used groupings oversimplify the actual genetic diversity among participants. Cohort-specific information is provided in Suppl. Tables 1 – 3. We tested the association between standing height and 1,385,132 autosomal bi-allelic SNPs from the HM3 tagging panel[3], which contains >1,095,888 SNPs with a minor allele frequency (MAF) >1% in each of the five ancestral groups included in our meta-analysis. Suppl. Fig. 2 shows the frequency distribution of HM3 SNPs across all five groups of cohorts.

We first performed individual meta-analyses in each of the five groups of cohorts. We identified 9863, 1888, 918, 493 and 69 quasi-independent genome-wide significant (GWS; $P<5\times10^{-8}$) SNPs in the EUR, HIS, EAS, AFR and SAS groups, respectively (Table 1; Suppl. Tables 4 – 8). Quasi-independent associations were obtained after performing approximate conditional and joint multiple-SNP (COJO) analyses,[4] as implemented in GCTA[5] (**Suppl. Methods**). Previous studies have shown that confounding due to population stratification may remain uncorrected in large EUR GWAS meta-analyses.[6,7] Therefore, we specifically investigated confounding effects in our EUR GWAS and found no evidence that these GWAS results are driven by population stratification (**Suppl. Note 1**, Suppl. Fig. 3).

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 non-EUR groups. We found that over 83% of GWS SNPs detected in non-EUR are in strong linkage disequilibrium (LD; r^2_{LD}>0.8) with at least one variant reaching marginal genome-wide significance in EUR (Suppl. Tables 5 – 8) and over 87% of associations detected in non-EUR meta-analyses fall within 100 kb of at least one GWS SNP identified in EUR (Suppl. Fig. 4a). In contrast, a randomly sampled HM3 SNP falls within 100 kb of a EUR GWS SNP only about 68% of the time (standard error; S.E.=0.5% over 10,000 draws). Next, we quantified the cross-ancestry correlation of allele substitution effects (ρ_b) at GWS SNPs for all pairs of ancestry groups. We estimated ρ_b using five sets of GWS SNPs identified in each of ancestry group. After correction for winner's curse,[8,9] we found ρ_b to range between 0.64 and 0.99 across all pairs of ancestry groups and all sets of GWS SNPs (Suppl. Fig. 5 – 9). Thus, the observed GWS height associations are substantially shared across major ancestral groups, consistent with previous studies based on smaller sample sizes.[10,11]

To find signals that are specific to certain groups, we tested if any individual SNPs detected in non-EUR GWAS are conditionally independent of signals detected in EUR GWAS. 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, 19, 49 and 143 of the GWS SNPs detected in SAS, AFR, EAS and HIS GWAS respectively are conditionally independent of GWS SNPs identified in EUR GWAS (Suppl. 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 increased statistical power of detection. The largest frequency difference relative to EUR was observed for rs2463169 (height-increasing G allele frequency: 23% in AFR vs. 84% in EUR) within the intron of *PAWR*, which codes for the prostate apoptosis response-4 protein. Interestingly, rs2463169 is located within the 12q21.2 locus, where a strong signal of positive selection in West-African Yoruba populations was previously reported.[12] The estimated effect at rs2463169 is β ~0.034 standard deviation (SD) per G allele in AFR vs. β~-0.002 SD/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 demonstrate a strong genetic overlap of GWAS signals across ancestries, we performed a fixed-effect meta-analysis of all five ancestry groups to maximise statistical power for discovering associations due to shared causal variants. The mean Cochran's heterogeneity Q-statistic is ~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 ~36, and ~18% of all HM3 SNPs are marginally GWS. Moreover, we found allele frequencies in our $META_{FE}$ to be very similar to that of EUR (mean F_{ST} across SNPs between EUR and $META_{FE}$ is ~0.001), as expected because our $META_{FE}$ consists of >75% EUR participants and ~14% participants with admixed European and non-European ancestries (i.e. HIS and AFR). To further assess if LD in our $META_{FE}$ could be reasonably approximated by the LD from EUR, we performed LD score regression 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 values >20% classically indicate strong LD inconsistencies between a given reference and GWAS summary statistics. For example, using EUR LD scores in the GWAS of HIS, which is the non-EUR group genetically closest to EUR (F_{ST}~0.02), yields an estimated $R_{LDSC\text{-}EUR}$ of ~25% (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 ~4.5% (S.E. 0.8%), which is significantly lower than 20% and also not statistically different from 3.8% (S.E. 0.8%) in our EUR meta-analysis. Altogether, our LD score regression 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 ~350,000 unrelated EUR participants of 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 (Suppl. Table 10). 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, 5/19 in AFR, 27/49 in EAS, and 39/143 in HIS remained statistically significant in our $META_{FE}$ (Suppl. Table 9), meaning that a small number of additional signals were only identified in the ancestry-specific analyses.

We next sought replication of the 12,111 $META_{FE}$ signals using GWAS data from 49,160 participants of 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 ~0.98 between the two datasets and a mean F_{ST} across SNPs of ~0.005, similar to estimates 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 MAF>1% (Suppl. 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 (Suppl. Fig. 10a). Instead, we assessed the correlation of SNP effects between our discovery and replication GWAS as an overall metric of replicability.[1,13] Over the 11,529/11,847 SNPs with a MAF>1% in the EBB, we found a correlation of marginal SNP effects of ρ_b=0.93 (jackknife standard error; S.E. 0.01) and a correlation of conditional SNP effects using the same LD reference panel of ρ_b=0.80 (S.E. 0.03; Suppl. Fig. 11). 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 (**Suppl. Methods**; Suppl. Fig. 10b), that 60% of them have a marginal SNP effect that is sign-consistent with that from our discovery GWAS (Fisher exact test; P=0.001). The proportion of sign-consistent SNP effects was >75% (Fisher exact test; $P<10^{-50}$) for variants with a MAF>1%, also consistent with expectations (Suppl. Fig. 10b). Altogether, our analyses demonstrate the robustness of our findings and show their replicability in an independent sample.

Genomic distribution of height-associated SNPs

To examine signal density among the 12,111 GWS SNPs detected in our $META_{FE}$, we defined a measure of local density of association signals for each GWS SNP based on the number of additional independent associations within 100 kb (Suppl. Fig. 12). We observed that 69% of GWS SNPs shared their location with another associated, conditionally independent, GWS SNP (Fig. 1). The mean signal density across the entire genome is 2.0 (LOCO-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[14] as harbouring pathogenic mutations causing syndromes of abnormal skeletal growth ("OMIM genes"; **Suppl. Methods**; Suppl. Table 11). We found that a high density of height-associated SNPs is significantly correlated with the presence of an OMIM gene nearby (Enrichment fold of OMIM gene

when density >1: 2.5×; P<0.001; **Suppl. Methods,** Suppl. Fig. 13a).[15,16] Interestingly, the enrichment of OMIM genes almost linearly increases with the density of height-associated SNPs (Suppl. Fig. 13b). Thus, these 12,111 GWS SNPs nonrandomly cluster near each other and also 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-localise within 100 kb of one another (Fig. 1; Suppl. Fig. 14). We show in **Suppl. Note 2** and Suppl. Figs. 14-15, using haplotype- and simulation-based analyses, that a multiplicity of independent causal variants is the most likely explanation of this observation. Interestingly, we also found that signal density is partially explained by the presence of a recently identified[17,18] height-associated variable-number-of-tandem-repeat (VNTR) polymorphism at this locus (**Suppl. Note 2**). In fact, the 25 independent GWS SNPs clustered within 100 kb of rs4932198 explain >40% of the VNTR length variation in multiple ancestries (Suppl. Fig. 15e) and an additional ~0.24% ($P=8.7\times10^{-55}$) phenotypic variance in EUR above what is explained by the VNTR alone (Suppl. Fig. 15f). Altogether, our conclusion is consistent with prior evidence of multiple types of common variation influencing height through *ACAN* gene function, involving multiple enhancers,[19] missense variants[20] and tandem repeat polymorphisms.[17,18]

Variance explained by SNPs within identified loci

To quantify the proportion of height variance 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 containing at least 1 GWS SNP, such that GWS SNPs in adjacent loci are >2×35 kb away from each other (i.e. 35 kb window on each side). We chose a 35 kb threshold based on findings from Wu et al.[21] who previously showed that causal common variants are located within 35 kb of GWS SNPs with >80% probability. Accordingly, we grouped the 12,111 GWS SNPs identified in our $META_{FE}$ into 7,209 non-overlapping loci (Suppl. Table 12) with lengths ranging from 70 kb (for loci containing only 1 signal) to 711 kb (for loci containing up to 25 signals). The average length of GWS loci is ~90 kb (SD 46 kb). The cumulative length of GWS loci represent ~647 Mb, or ~21% of the genome (assuming a genome length of ~3039 Mb).[22]

To estimate what fraction of heritability 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 8 independent samples of all five population groups represented in our $META_{FE}$ (Fig. 2; **Suppl. Methods**). Altogether, our stratified estimation of SNP-based heritability shows that SNPs within these 7,209 GWS loci explain ~100% of h^2_{SNP} in EUR and >90% of h^2_{SNP} across all non-EUR groups, despite being drawn from less than a quarter of the genome (Fig. 2). 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 (Suppl. Fig. 16).

To further assess the robustness of this key result, we tested if 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.[23]) and found no significant

enrichment of SNP-based heritability for BMI within height-associated GWS loci (Suppl. Fig. 17). Furthermore, we repeated our analysis using a random set of SNPs with similar EUR MAF and LD scores as the 12,111 height-associated GWS SNPs. We found this control set of SNPs to explain only ~27% of h^2_{SNP} for height, consistent with the proportion of SNPs within the loci defined by this random set of SNPs (Suppl. Figs. 16 - 17). Finally, we extended our stratified estimation of SNP-based heritability to all well-imputed common SNPs (i.e. beyond the HM3 panel) and found, consistently across population groups, that although more genetic variance can be explained by common SNPs not included in the HM3 panel, all information remains concentrated within these 7,209 GWS loci (Suppl. Fig. 18). 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 ~21% of the genome.

Out-of-sample prediction accuracy

We quantified the accuracy of polygenic scores (PGS) for height based on GWS SNPs in 61,095 unrelated individuals from 3 studies, including 33,001 participants of the UKB who were not included in our discovery GWAS (i.e. 14,587 EUR; 9,257 SAS; 6,911 AFR and 2,246 EAS; **Suppl. Methods**), 14,058 EUR participants from the Lifelines cohort study; and 8,238 HIS and 5,798 AFR participants from the PAGE study. Prediction accuracy (R^2_{GWS}) was defined as the squared correlation between the PGS and actual height (corrected for mean and variance sex differences and 20 genotypic principal components). We found that PGS based on 12,111 GWS SNPs from our $META_{FE}$ systematically outperformed those based on GWS identified in ancestry-specific meta-analyses (Fig. 3a). The only exception was in EUR where both PGS performed equally. The largest prediction accuracy was observed in EUR participants (R^2_{GWS}~40%; S.E. 0.6%) and the smallest one in AFR participants from the UKB (R^2_{GWS}~9.4%; S.E. 0.7%). Note that the difference in R^2_{GWS} 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} in AFR)/(R^2_{GWS} in EUR) of ~25% previously reported.[24] Nevertheless, we found the accuracy of PGS based on GWS from our multi-ancestry $META_{FE}$ to be consistently larger than that of PGS based on GWS SNPs from a EUR GWAS (Fig. 3a). The largest improvement was observed in AFR, where the meta-analysed accuracy in AFR participants of UKB and PAGE was increased from R^2_{GWS}=6.6% (S.E. 0.4%) to R^2_{GWS}=10.8% (S.E. 0.5%), i.e. almost a ~1.6-fold improvement. This observation is partly explained by the increased statistical power but also by the refined estimation of SNP effects due to the inclusion of shorter and ancestry-specific LD blocks in AFR cohorts.

Furthermore, we sought to evaluate the prediction accuracy of PGS 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 (i.e. two parents and one offspring) 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. 3b). Moreover, the accuracy of the parental average is ~44% (S.E. 3.2%), which is larger but not significantly different from R^2_{GWS} in EUR. In addition, we found that a linear combination of the average height of parents and of the offspring's PGS yields an unprecedented accuracy of 54% (S.E. 3.2%). This observation reflects the fact that PGS can explain within-family differences between siblings, while average parental height cannot. To show this empirically, we estimate that our PGS based on GWS SNPs explain ~33% (S.E. 0.7%) of height variance between siblings (**Suppl. Methods**). Finally, we demonstrate that the optimal weighting between parental average and PGS

can be predicted theoretically as function of R^2_{GWS}, the full narrow sense heritability and the phenotypic correlation between spouses (**Suppl. Note 3**, Suppl. Fig. 19).

In summary, the estimation of variance explained and prediction analyses in European-ancestry samples show that the set of 12,111 GWS SNPs account for nearly all of h^2_{SNP} and that combining SNP-based PGS with family history significantly improves prediction accuracy. In contrast, both estimation and prediction results show clear attenuation in samples with non-European ancestry, consistent with previous studies.[24–27]

Relationship between GWAS discoveries, sample size and ancestry diversity

Our large study offers a unique opportunity to empirically quantify how increasing GWAS sample sizes and ancestry diversity affects discovery of variants, genes and biological pathways. To address this question, we re-analysed 3 previously published GWAS of height[1,15,16] and also down-sampled our meta-analysis into 4 subsets (including our EUR and $META_{FE}$ GWAS). Altogether we analysed 7 GWAS with a sample size increasing from ~0.13 M up to ~5.3 M individuals (Table 2).

For each GWAS, we quantified 8 metrics grouped into 4 *variant*- and *locus*-based metrics (number of GWS SNPs, number of GWS loci, prediction accuracy (R^2_{GWS}) of PGS based on GWS SNPs, the proportion of the genome covered by GWS loci), a *functional annotation*-based metric (enrichment statistics from stratified LDSC[28,29]), 2 *gene*-based metrics (number of genes prioritised by Summary data based Mendelian Randomization[30] (SMR; **Suppl. Methods**), proximity of variants with OMIM genes), and a *gene-set*-based metric (enrichment within clusters of gene sets/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 prioritisation methods (DEPICT[31] and MAGMA[32]), we found that the same broad clusters of related gene sets (including most of the clusters enriched for OMIM genes) are prioritised at all GWAS sample sizes (Suppl. Figs. 20-21; Suppl. Tables 13 – 15; **Suppl. Note 4**). Similarly, stratified LDSC estimates of heritability enrichment within 97 functional annotations also remain stable across the range of sample sizes (Suppl. Fig. 22). 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 demonstrating that GWAS expectedly implicate similar biology across major ancestral groups (**Suppl. Note 4**; Suppl. Fig. 23).

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 N>1.5M; while the relative enrichment of GWS SNPs near OMIM genes first decreases with sample size, then plateaus when N>1.5M (Suppl. Figs. 24a-c). Interestingly, the decrease observed for N<1.5M reflects the preferential localization of larger effect variants (those identified with smaller sample sizes) closer to OMIM genes (Suppl. Fig. 24d) and, conversely, that more recently identified variants with smaller effects tend to localize further away from OMIM genes (Suppl. Fig. 24e). We also investigated the number of genes prioritised using Summary-data based Mendelian

Randomization (hereafter referred to as SMR genes; **Suppl. Methods**) using expression quantitative trait loci (eQTL) as genetic instruments (Suppl. Table 16) as an alternative *gene*-level metric and found it to saturate for N>4M (Suppl. Fig. 24f). Note that saturation of SMR genes is partly affected by the biological relevance and statistical power of eQTL studies.[30] Therefore, we can expect more genes to be prioritised when integrating GWAS summary statistics from this study with that 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.[33] 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>2.5M, where the upward trend starts to weaken (Suppl. Fig. 25a). 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 (Suppl. Fig. 25b). The observed saturation in PGS prediction accuracy (both within ancestry, i.e. in EUR; and multi-ancestry) was more noticeable than that of the number and genomic coverage of GWS loci. In fact, increasing sample size from 2.5M to 4M by adding another 1.5M EUR samples increased the number of GWS SNPs from 7,020 to 9,863 (i.e. (9,863-7,020)/7,020 = ~1.4-fold increase) 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 EAS and AFR individuals. However, adding another ~1M participants of non-EUR improves the multi-ancestry prediction accuracy by over +3.4% (Suppl. Fig. 25c), highlighting the value of non-EUR populations for this purpose.

Altogether, these analyses show that increasing GWAS sample size not only increases 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/pathways and functional annotations can be identified using relatively small sample sizes (N~0.25M for height). Importantly, we confirm that increased genetic diversity in GWAS discovery samples significantly improves the prediction accuracy of PGS in under-represented ancestries.

DISCUSSION

By performing the largest GWAS to date in 5,380,080 individuals with a primary focus on common genetic variation, we have provided new insights into the genetic architecture of height – including a saturated genomic map of 12,111 genetic associations for height. Consistent with previous studies,[15,16] we have shown signal density of associations (known and novel) are not randomly distributed across the genome; rather, associated variants are more likely detected around genes previously associated with Mendelian disorders of growth. Furthermore, we observed strong genetic overlap of association across cohorts of various continental ancestries. Effect estimates are moderately to highly correlated (min=0.64, max=0.99), and while there are significant differences in power to detect an association between cohorts with European and non-European ancestries, the majority of 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 >7-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 >90% of h^2_{SNP} across diverse populations when incorporating all common SNPs within 35 kb of GWS SNPs. This result is important as it highlights that future investigation of common (MAF>1%) genetic variation associated with height in many ancestries will most likely detect signals within the 7,209 GWS loci identified in the present study. An interesting future question is whether rare genetic variants associated with height are also concentrated within the same loci. Of note, previous studies have reported significant enrichment of height heritability near genes as compared to inter-genic regions (e.g. up to >50 kb away from start/stop genomic position of genes).[34] Our findings are consistent but not reducible to that observation, given that up to ~31% of GWS SNPs identified in this study lie >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 ~40% (i.e. 80% of h^2_{SNP}) in individuals of European ancestries and up to ~10% in individuals of predominantly African ancestries. Importantly, we show using a new method developed by Wang and colleagues[27] that LD and MAF differences between European and African ancestries can explain up to ~84% (S.E. 1.5%) of the loss of prediction accuracy between these populations (**Suppl. Methods**), with the remaining loss being presumably explained by heritability differences between populations and/or differences in effect sizes across populations (e.g., due 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 non-European ancestry populations. Our study has a large number of participants with African ancestries as compared with previous efforts. However, we emphasise that further increasing the size of GWAS in non-European ancestry populations, 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 samples size would help to identify potential ancestry-specific causal variants, to facilitate ancestry-specific fine mapping, and to inform gene by environment/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 European ancestry populations.

Although large sample sizes are needed to pinpoint the common variants responsible for the heritability of height (and larger samples in multiple ancestries will likely 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 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 likely causal genes and even mapping of associated regions is consistent across ancestries, reflecting the expected similarity in the biological architecture of human height across populations.

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 from our HM3 SNPs based analyses (Suppl. Fig. 18). This result underlines the widespread allelic heterogeneity at height-associated loci. Another limitation of our study is that we determined conditional associations using an EUR LD reference (N~350,000), which is sub-optimal given that ~24% of our discovery sample is of non-EUR. We emphasise that no analytical tool with an adequately large multi-ancestry reference panel currently is 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, due to current limited availability of such data. Finally, as with all GWAS, 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 will be mostly driven by the availability of relevant complementary data (e.g., context-specific eQTL in relevant tissues and cell-types) and the power of computational methods that can integrate these data.

In summary, our study has been able to demonstrate 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 ~5 million participants of various ancestries provide enough power to map >90% of genetic variance explained by common SNPs down to ~21% of the genome. 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 enabling 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.

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Yu.J. is employed by and hold stock or stock options in 23andMe, Inc. T.S.A. is a shareholder in Zealand Pharma A/S and Novo Nordisk A/S. G.C-P is an employee of 23andMe Inc. M.E.K. is employed by SYNLAB Holding Deutschland GmbH. H.L.L. receives support from a consulting contract between Data Tecnica International and the National Institute on Aging (NIA), National Institutes of Health (NIH). As of January 2020, A.Mah. is an employee of Genentech, and a holder of Roche stock. I.N. is an employee and stock owner of Gilead Sciences; this work was conducted before employment by Gilead Sciences. Ji.S. is employed by and hold stock or stock options in 23andMe, Inc. Ca.S. is an employee of Regeneron, Inc. Va.S. is employed by deCODE Genetics/Amgen inc. Since completing the work contributed to this paper, D.J.T. has left the University of Cambridge and is now employed by Genomics plc. G.T. is employed by deCODE Genetics/Amgen inc. H.B. has consultant arrangements with Chiesi Pharmaceuticals and Boehringer Ingelheim. M.J.Ca. is Chief Scientist for Genomics England, a UK Government company. M.J.Cu. has served on Advisory Board or Consulted for Biosense Webster, Janssen Scientific Affairs and Johnson & Johnson. S.M.D. receives research support from RenalytixAI and personal consulting fees from Calico Labs, outside the scope of the current research. P.T.E. receives sponsored research support from Bayer AG and IBM Health, and he has served on advisory boards or consulted for Bayer AG, Quest Diagnostics, MyoKardia and Novartis. P.Ki. has received suppport from several drug and device companies active in atrial fibrillation, and has received honoraria from several such companies in the past, but not in the last three years. P.Ki. is listed as inventor on two patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). G.D.K. has given talks, attended conferences and participated in trials sponsored by Amgen, MSD, Lilly, Vianex, Sanofi, and have also accepted travel support to conferences from Amgen, Sanofi, MSD and Elpen. S.A.Lu. receives sponsored research support from Bristol Myers Squibb / Pfizer, Bayer AG, Boehringer Ingelheim, Fitbit, and IBM, and has consulted for Bristol Myers Squibb / Pfizer, Bayer AG, and Blackstone Life Sciences. W.M. reports grants and personal fees from AMGEN, BASF, Sanofi, Siemens Diagnostics, Aegerion Pharmaceuticals, Astrazeneca, Danone Research, Numares, Pfizer, Hoffmann LaRoche: personal fees from MSD, Alexion; grants from Abbott Diagnostics, all outside the submitted work. W.M. is employed with Synlab Holding Deutschland GmbH. M.A.N. receives support from a consulting contract between Data Tecnica International and the National Institute on Aging (NIA), National Institutes of Health (NIH). S.N. is a scientific advisor to Circle software, ADAS software, CardioSolv, and ImriCor and recieves grant support from Biosense Webster, ADAS software, and ImriCor. Her.S. has received honoraria for consulting from AstraZeneca, MSD/Merck, Daiichi, Servier, Amgen and Takeda Pharma. He has further received honoraria for lectures and/or chairs from AstraZeneca, BayerVital, BRAHMS, Daiichi, Medtronic, Novartis, Sanofi and Servier. P.S. has received research awards from Pfizer Inc. 23andMe Research team are employed by and hold stock or stock options in 23andMe, Inc. The views expressed in this article are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health. M.I.McC. has served on advisory panels for Pfizer, NovoNordisk and Zoe Global, has received honoraria from Merck, Pfizer, Novo Nordisk and Eli Lilly, and research funding from Abbvie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, NovoNordisk, Pfizer, Roche, Sanofi Aventis, Servier, and Takeda. As of June 2019, MMcC is an employee of Genentech, and a holder of Roche stock. C.J.O. is a current employee of Novartis Institute of Biomedical Research. U.T. is employed by deCODE Genetics/Amgen inc. K.S. is employed by deCODE Genetics/Amgen inc. Ad.A. is employed by and hold stock or stock options in 23andMe, Inc. C.J.W.'s spouse is employed by Regeneron. A.E.L. is currently employed by and holds stock in Regeneron Pharmaceuticals, Inc. J.N.H. holds equity in Camp4 Therapeutics.

Table 1. Summary of results from within-ancestry and trans-ancestry GWAS meta-analyses. 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 conditional and Joint analysis implemented in the GCTA software. P_{GWAS} : P-value from 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. Percentage of the genome covered was calculated by dividing the cumulative of GWS loci by 3,039 Mb, i.e. the approximated length of the human genome.

Cohort Ancestry/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 (% genome)**
European (EUR)	173	4,080,687 (3,612,229)	9,863 (8,382)	6,386	552.5 Mb (18.4%)
East-Asian (EAS)	56	472,730 (320,570)	918 (807)	821	60.5 Mb (2.0%)
Hispanic (HIS)	11	455,180 (431,645)	1,888 (1,332)	1,599	121.4 Mb (4.0%)
African (AFR)	29	293,593 (222,981)	493 (417)	436	32.5 Mb (1.1%)
South Asian (SAS)	12	77,890 (59,420)	69 (65)	66	4.7 Mb (0.2%)
Trans-ancestry meta-analysis ($META_{FE}$)	281	5,314,291* (4,611,160)	12,111 (9,920)	7,209	647.5 Mb (21.6%)

*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.

Table 2. Overview of 5 European ancestry GWAS re-analysed in our study to quantify the relationship between sample size and discovery. Summary statistics from the 3 published GWAS were imputed using the SSIMP software to maximise coverage of HapMap 3 SNPs (**Suppl. Methods**). GWS loci are defined as in the legend of Table 1.

Down-sampled GWAS	Max N (Mean N)	Number of GWS COJO SNPs	% of the genome covered by GWS loci (35 kb)
Lango-Allen et al.[15]*	130,010 (128,942)	240	0.5%
Wood et al.[16]	241,724 (239,227)	633	1.4%
Yengo et al.[1]	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 Lango-Allen et al. study, 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.

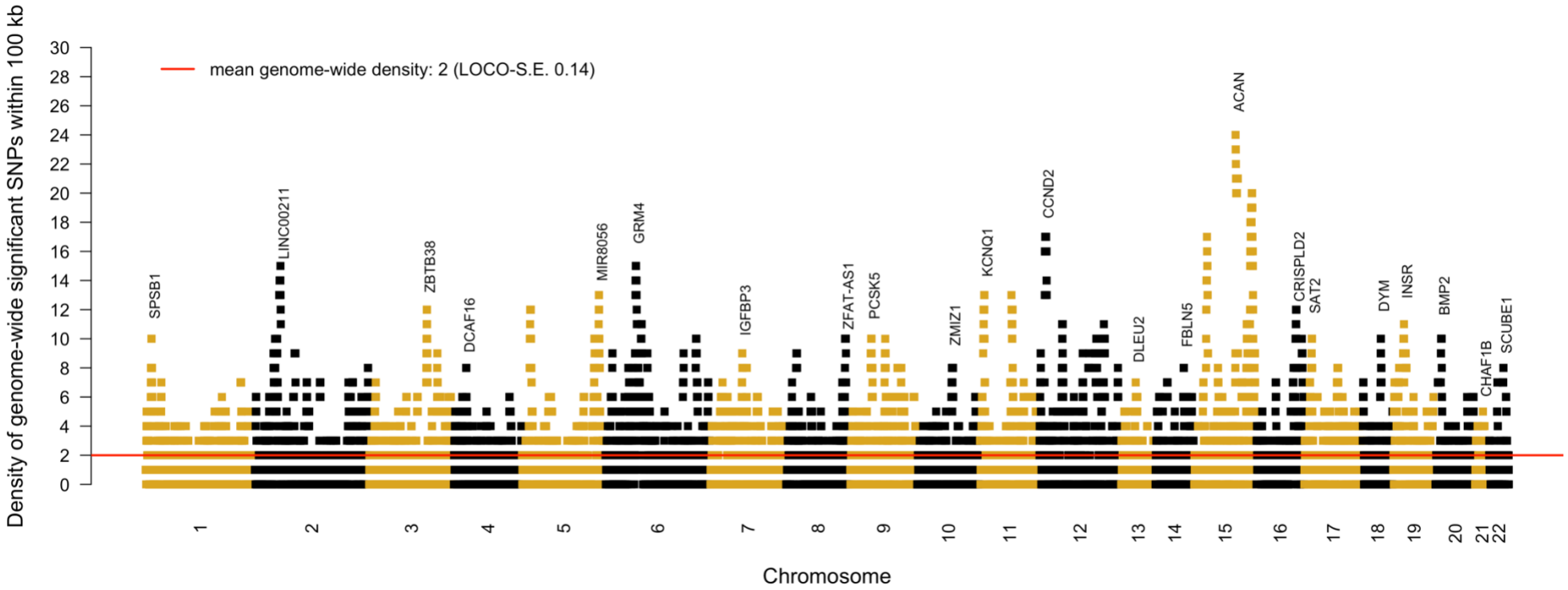

Fig. 1. Brisbane plot showing the genomic density of independent genetic associations with height. Each dot represents one of the 12,111 quasi-independent genome-wide significant (GWS; $P<5\times10^{-8}$) height-associated SNPs identified using approximate conditional and joint multiple-SNP (COJO) analyses of our trans-ancestry GWAS meta-analysis. 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 share its location with another independent GWS COJO SNP within <100 kb. The average signal density across the genome is 2 (standard error; S.E. 0.14). S.E. were calculated using a Leave-One-Chromosome-Out jackknife approach (LOCO-S.E.). Sub-significant SNPs are not represented on the figure.

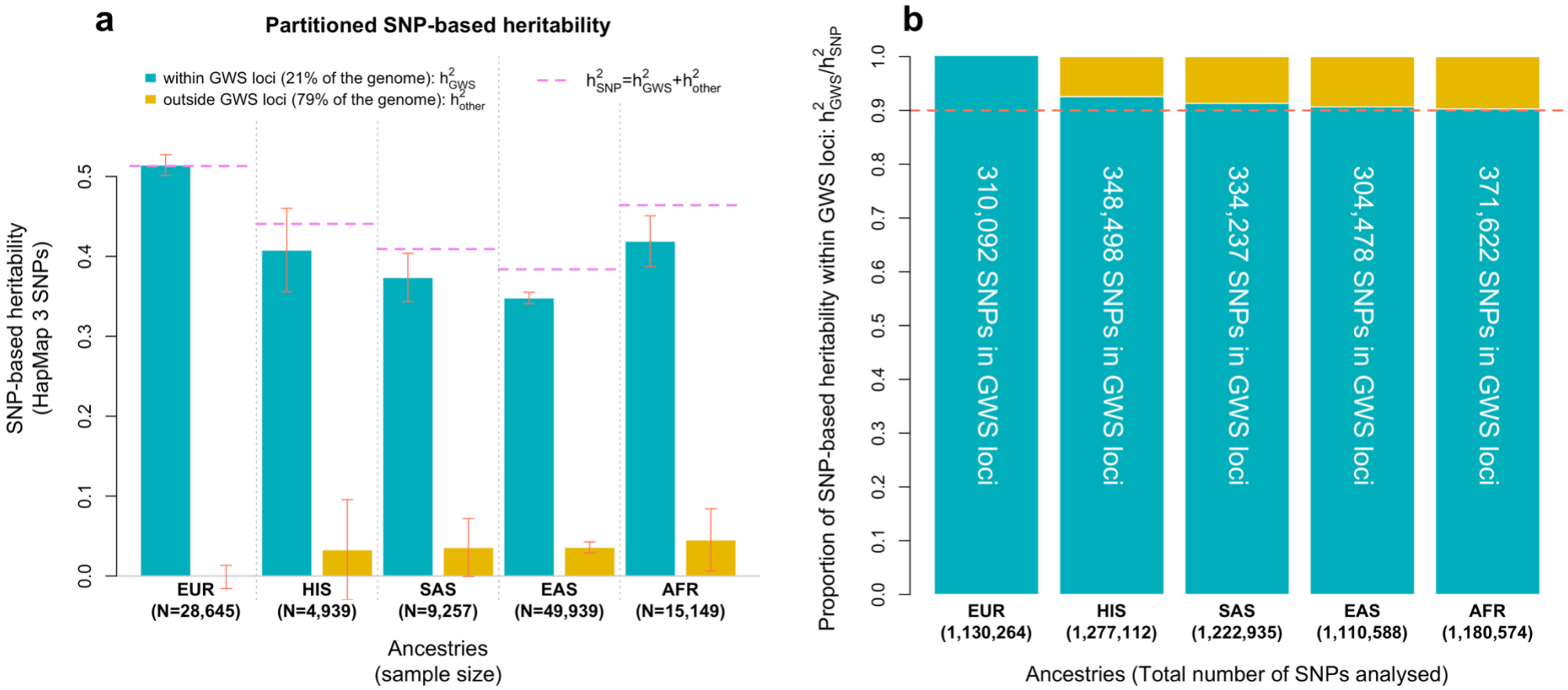

Fig. 2. Variance of height explained by HapMap 3 SNP within genome-wide significant (GWS) loci. **Panel a** shows stratified SNP-based heritability (h^2_{SNP}) estimates obtained after partitioning the genome into SNPs within 35 kb of a GWS SNP ("GWS loci" label) vs. SNPs >35 kb away from any GWS SNP. Analyses were performed in samples of five different ancestry/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 group (HIS: PAGE). **Panel b** shows that >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 ~647 Mb, i.e. ~21% of the genome assuming a genome length of ~3039 Mb.[22] The proportion of HapMap 3 SNPs in GWS loci is ~27%.

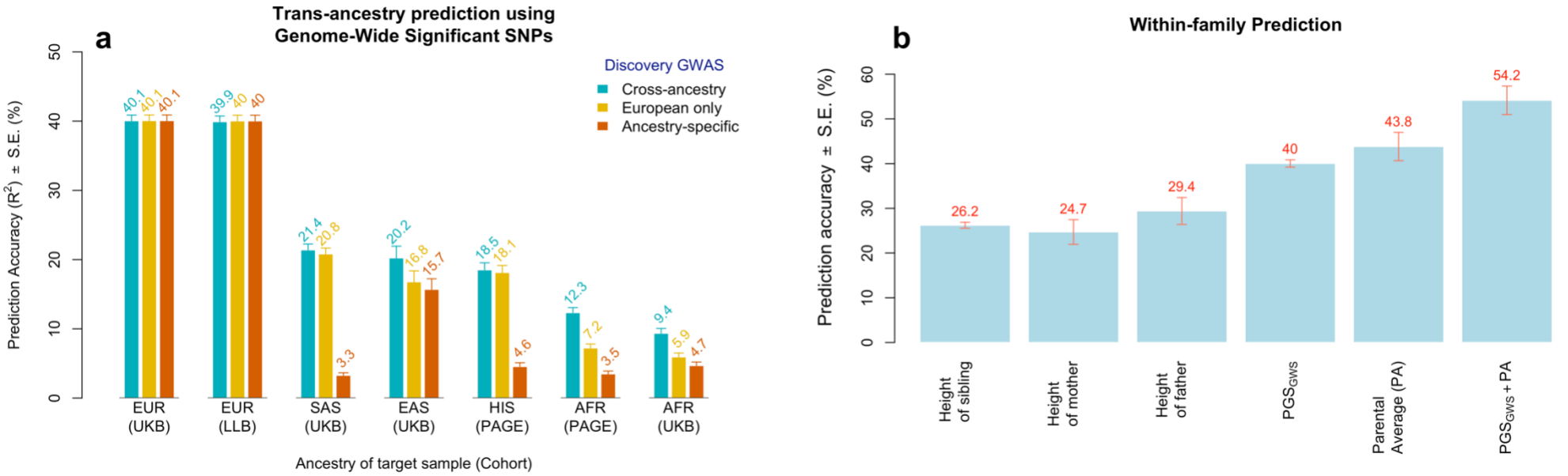

Fig. 3. Accuracy of a polygenic predictors of height (PGS) within-family and across ancestries. Prediction accuracy (R^2) was measured as the squared correlation between PGS and actual height adjusted for age, sex and 10 genetic principal components. **Panel a** shows the accuracy of PGSs assessed in participants of 5 different ancestry groups: European (EUR; N=14,587) from the UK Biobank (UKB) and the Lifelines Biobank (LLB; N=14,058) cohorts, South-Asian (SAS; N=9,257) from UKB, East-Asian (EAS; N=2,246) from UKB, Hispanic (HIS; N=8,238) from the PAGE study and admixed African (AFR) from UKB (N=6,911) and PAGE (N=5,798). PGSs used for prediction, in **Panel a**, are based on genome-wide significant (GWS) SNPs identified in (1) cross-ancestry meta-analysis (green bar), (2) EUR meta-analysis (yellow bar) and (3) ancestry-specific meta-analyses (red bars). **Panel b** shows the squared correlation of height between first-degree relatives of EUR participants in UKB and the accuracy of a predictor combining PGS (denoted , PGS_{GWS}, as based on GWS SNPs) and familial information. PGS_{GWS} accuracy shown in **Panel b** is the average accuracy in EUR participants from UKB and LLB from **Panel a**. Sibling correlation was calculated in 17,492 independent EUR sibling pairs from the UKB and parent-offspring correlations in 981 EUR unrelated trios (i.e. two parents and 1 child) from the UKB.