LETTER

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Genetic analyses of diverse populations improves discovery for complex traits

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Genome-wide association studies (GWAS) have laid the foundation for investigations into the biology of complex traits, drug development and clinical guidelines. However, the majority of discovery efforts are based on data from populations of European ancestry[1–3]. In light of the differential genetic architecture that is known to exist between populations, bias in representation can exacerbate existing disease and healthcare disparities. Critical variants may be missed if they have a low frequency or are completely absent in European populations, especially as the field shifts its attention towards rare variants, which are more likely to be population-specific[4–10]. Additionally, effect sizes and their derived risk prediction scores derived in one population may not accurately extrapolate to other populations[11,12]. Here we demonstrate the value of diverse, multi-ethnic participants in large-scale genomic studies. The Population Architecture using Genomics and Epidemiology (PAGE) study conducted a GWAS of 26 clinical and behavioural phenotypes in 49,839 non-European individuals. Using strategies tailored for analysis of multi-ethnic and admixed populations, we describe a framework for analysing diverse populations, identify 27 novel loci and 38 secondary signals at known loci, as well as replicate 1,444 GWAS catalogue associations across these traits. Our data show evidence of effect-size heterogeneity across ancestries for published GWAS associations, substantial benefits for fine-mapping using diverse cohorts and insights into clinical implications. In the United States—where minority populations have a disproportionately higher burden of chronic conditions[13]—the lack of representation of diverse populations in genetic research will result in inequitable access to precision medicine for those with the highest burden of disease. We strongly advocate for continued, large genome-wide efforts in diverse populations to maximize genetic discovery and reduce health disparities.

The PAGE study was developed by the National Human Genome Research Institute and the National Institute on Minority Health and Health Disparities to conduct genetic epidemiological research in ancestrally diverse populations within the United States. The study is drawn from three existing major population-based cohorts (Hispanic Community Health Study/Study of Latinos (HCHS/SOL), Women's Health Initiative (WHI) and Multiethnic Cohort (MEC)) and the Icahn School of Medicine at Mount Sinai BioMe biobank in New York City (BioMe). Genotyped individuals self-identified as Hispanic/Latino ($n = 22{,}216$), African American ($n = 17{,}299$), Asian ($n = 4{,}680$), Native Hawaiian ($n = 3{,}940$), Native American ($n = 652$) or Other ($n = 1{,}052$) (Supplementary Table 1 and Supplementary Information 1). These 49,839 individuals were genotyped on the Multi-Ethnic Genotyping Array (MEGA), which we developed to equitably capture global genetic variation[14] (Supplementary Fig. 1 and Supplementary Information 3). Given that PAGE participants reside on a continuum of genetic ancestry, rather than discrete population

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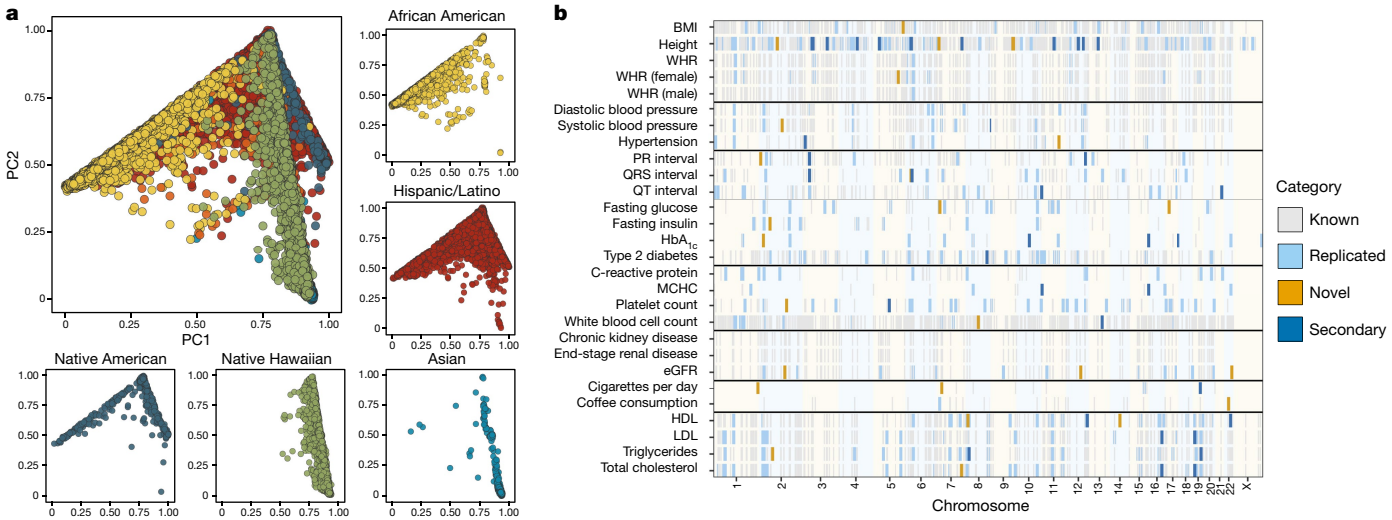

Fig. 1 | Inclusion of multi-ethnic samples enables discovery and replication in GWAS. a, The population substructure present in the multi-ethnic sample of PAGE ($n = 49{,}839$) revealed complex patterns preventing meaningful stratification. Here we show that PC1 and PC2 show major patterns of variation, stratified by self-identified race/ethnicity. Individuals denoted by orange self-identified as 'Other'. **b**, There are 8,979 previously reported trait–variant pairs, of which 1,444 replicated at a by-trait Bonferroni-adjusted significance level for *P* values estimated from a Wald test in SUGEN. In addition, we found 27 novel trait–variant pairs and 38 secondary signal pairs that remained after adjusting for known variants. BMI, body-mass index; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MCHC, mean corpuscular haemoglobin concentration; WHR, waist-to-hip ratio.

groups[15] (Fig. 1a and Supplementary Fig. 2), a joint analysis was optimally powered and the most parsimonious way to allow for heterogeneous variance across populations[16]. We then performed genome-wide association analyses on 26 traits harmonized across the four studies, adjusted for the top 10 principal components (PCs), indicators for study and self-identified race/ethnicity, as well as trait-specific covariates. We used extensions of previously developed analytical tools (SUGEN and GENESIS), which explicitly model population structure, relatedness between individuals and population-specific genetic heterogeneity[16–20]. For comparison against standard multi-ethnic approaches and to assess heterogeneity by ancestry, we also conducted analyses stratified by self-identified race/ethnicity and combined these analyses in a meta-analysis (Supplementary Table 3). We demonstrate that the joint analysis increased power for discovery compared to the meta-analysis approach, but that it did not increase the incidence of type-1 error (Supplementary Information 5; the pipeline for the analysis of diverse populations in genomic research is outlined in the Methods).

Given that genetic architecture and/or causal variants may differ between populations, we hypothesized that the examination of under-represented populations would reveal novel ancestry-specific associations. Using minor allele frequency (MAF)-specific *P*-value thresholds[21] ($P < 5 \times 10^{-8}$ for MAF > 5%; $P < 3 \times 10^{-9}$ for MAF < 5%), we identified 16 novel genome-wide significant trait–variant associations and

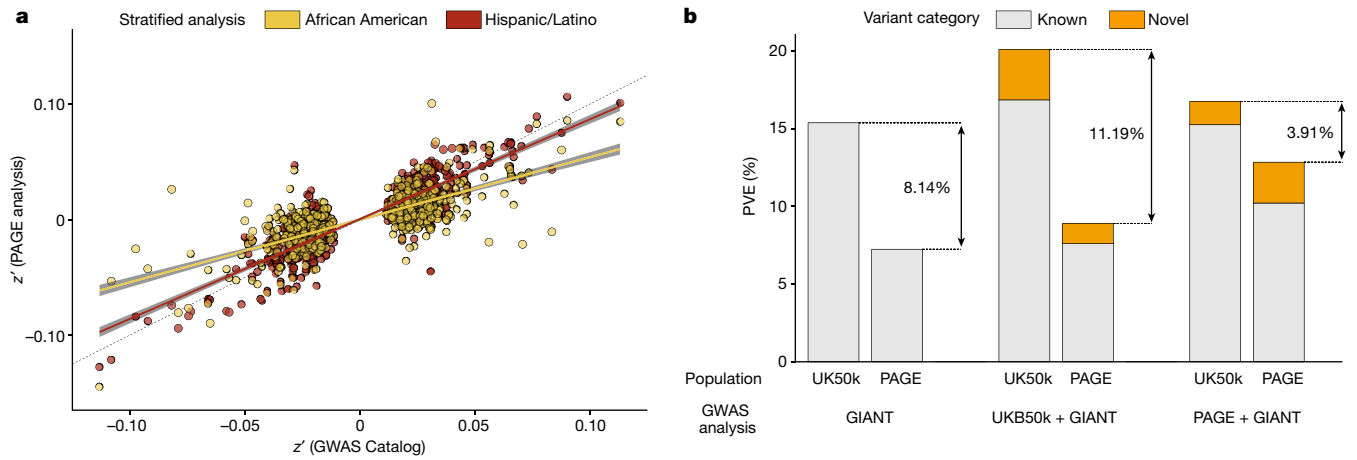

Fig. 2 | Weaker effect sizes of previously published trait–variant associations in non-European populations exacerbates disparity in PVE. a, Standardized effect sizes for the two largest self-reported subsets of the PAGE population show markedly weaker effect sizes in African Americans ($z'_{PAGE} = 0.54 \times z'_{prior}$ (yellow); z' is the z-score from the trait–variant association standardized by the sample size in PAGE or the 'prior' publication from the NHGRI-EBI GWAS Catalog) than in Hispanic/Latino participants ($z'_{PAGE} = 0.86 \times z'_{prior}$; red) compared to originally reported effect sizes from the NHGRI-EBI GWAS Catalog. Grey shading indicates the 95% confidence interval around the slope estimate. **b**, After identifying the SNP with the smallest *P* value in each locus, the PVE of height was calculated using the estimated effect size from this set of tag SNPs (left, GIANT-only GWAS; middle, UKB50k+GIANT meta-analysis; right, PAGE + GIANT meta-analysis). PVE was estimated independently in the UKB50k (White British) and PAGE (multi-ethnic) samples. The gap in PVE with previously reported loci from GIANT (8.14%) is exacerbated with the inclusion of 50,000 more individuals of European descent, to 11.19%. However, it narrows markedly with the inclusion of 50,000 multi-ethnic samples, to 3.91%.

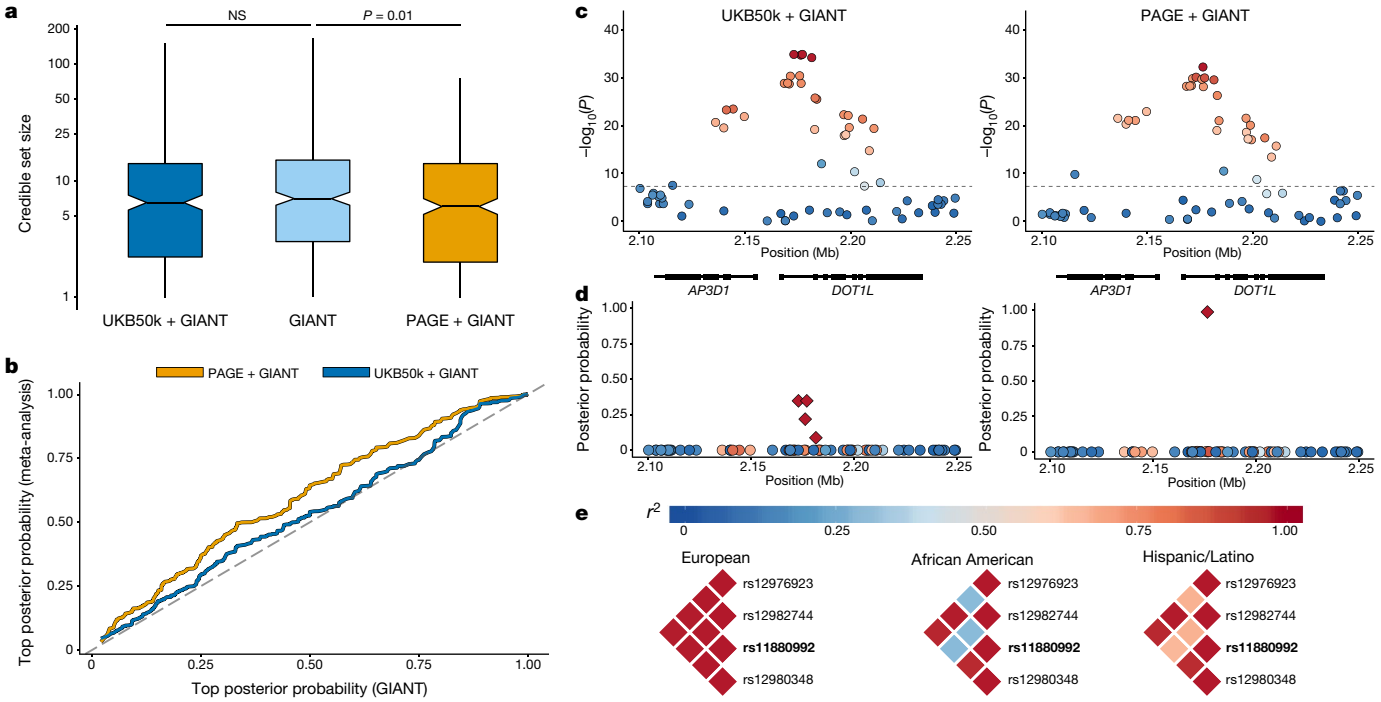

Fig. 3 | Fine-mapping with multi-ethnic PAGE versus homogeneous UK Biobank samples for height. a, Comparison of 95% credible sets for height, comparing GIANT alone ($n = 253{,}288$) to UKB50k + GIANT ($n = 303{,}288$; paired-sample t-test $P = 0.37$) and PAGE + GIANT ($n = 303{,}069$; paired-sample t-test $P = 0.01$). Box plots show the median as the line in the notch, with the top and bottom of the box indicating the interquartile range. Whiskers extend to either the minimum value or 1.5× the interquartile range. Notches indicate the 95% confidence interval of the medians. **b**, Top posterior probability from each 95% credible set for height, comparing GIANT ($n = 253{,}288$) to UKB50k + GIANT ($n = 303{,}288$) and PAGE + GIANT ($n = 303{,}069$). **c**, Example of results for a height locus from GWAS (rs11880992) in UKB50k + GIANT ($n = 303{,}288$) and PAGE + GIANT ($n = 303{,}069$), with linkage disequilibrium from weighted matrix from meta-analysis. **d**, Posterior probabilities for this signal with credible set in indicated by the diamond shapes. **e**, Linkage disequilibrium (r^2) for the original 95% credible set from GIANT results stratified by populations. The index association SNP (rs11880992) with the highest posterior probability is denoted in bold.

11 low-frequency loci with suggestive associations ($P < 5 \times 10^{-8}$; Fig. 1b, Extended Data Table 1, Supplementary Tables 2, 3 and Supplementary Information 8). In regions that have been previously identified in the NHGRI-EBI GWAS Catalog[22], we identified 32 significant trait–variant associations after conditioning on all trait-specific known variants in an 'adjusted' model, as well as 6 suggestive associations that had a low frequency or were rare variants (P_{cond} between 3×10^{-9} and 5×10^{-8}), further enriching our understanding of the genetic architecture of traits (Supplementary Table 3).

To tease apart the influence of specific ancestral components on the 27 novel and 38 secondary loci, we calculated the correlation between the risk allele genotype and each of the first 10 PCs (Extended Data Fig. 2). These correlations reveal a population structure that underlies many of our identified trait–variant associations, in which there are population differences in the frequencies of risk alleles. Notably, a novel single-nucleotide polymorphism (SNP) (rs182996728) was identified to be associated with the number of cigarettes smoked per day among smokers ($P = 3.1 \times 10^{-8}$) as well as with PC4, which represents the gradient of Native Hawaiian/Pacific Islander ancestry. Although the risk variant is absent or rare in most populations, it was found at a frequency of 17.2% in Native Hawaiian participants, in whom the signal was the strongest ($P_{stratified} = 2.28 \times 10^{-6}$). Our findings show that some trait-associated variants exhibit differential frequencies across populations, further illustrating a need for the inclusion of diverse groups.

In addition to identifying novel and secondary trait–variant associations, we also replicate a portion of the published GWAS literature (which is predominantly based on populations of European ancestry; Extended Data Fig. 1) for our 26 phenotypes from the GWAS Catalog[22]. Of 8,979 known variant–trait combinations, 1,444 replicated at the $P < 0.05$ significance threshold, after Bonferroni correction by trait. Of those meeting the genome-wide significance threshold ($P < 5 \times 10^{-8}$), we replicate 574 variant–trait associations in 261 distinct regions, of which 132 had significant evidence of effect heterogeneity by genetic ancestry (SNP × PC, $P < 8.71 \times 10^{-5}$), which is likely to be a conservative estimate given the limitations of statistical power. We further tested for effect heterogeneity by genetic ancestry by comparing the standardized effect sizes of PAGE analyses (joint and stratified) to available effect sizes from the GWAS Catalog. We observed effect sizes of the PAGE joint analyses to be significantly weaker than previous reports with a slope of 0.77 (95% confidence interval = 0.75–0.81). When stratified by self-identified race/ethnicity, the effect sizes for the Hispanic/Latino population remained significantly attenuated compared to the previously reported effect sizes ($\beta = 0.86$; 95% confidence interval = 0.83–0.90; Fig. 2a). Effect sizes for the African American population were even further diminished at nearly half the strength ($\beta = 0.54$; 95% confidence interval = 0.50–0.58; Fig. 2a). This is suggestive of truly differential effect sizes between ancestries at previously reported variants, rather than these effect sizes being upwardly biased in general (that is, exhibiting 'winner's curse'), which should affect all groups equally.

To quantify the added value of including multi-ethnic populations in GWAS, we used published data from GIANT (a study of more than 250,000 individuals of European descent for anthropometric traits[23,24]), for a meta-analysis with either PAGE (around 50,000 multi-ethnic individuals) or 50,000 randomly sampled White British participants from the UK Biobank (UKB50k). Stratified GWAS of height in PAGE and UKB50k were each combined in separate meta-analyses with GIANT using a fixed-effect model. When comparing these meta-analyses to the original GIANT analysis; both meta-analyses resulted in novel findings (PAGE + GIANT, 82 loci; UKB50k + GIANT, 107 loci; Extended Data Table 2). Although the number of novel loci is indicative of new insights into trait biology, understanding the proportion of phenotypic variance explained (PVE) by each locus has potentially important consequences

for personalized medicine[25]. The original loci that were identified by GIANT had more than twice the PVE using UKB50k summary statistics (15.4%) compared to multi-ethnic PAGE (7.2%; Fig. 2b). With the additional novel variants that were identified in UKB50k + GIANT, this gap between the PVE is exacerbated (UKB50k, 19.2%; PAGE, 8.3%), whereas the addition of variants identified in PAGE + GIANT diminished the gap in PVE (UKB50k, 16.1%; PAGE, 12.0%). Similar trends were also observed with analyses of body-mass index (Supplementary Fig. 14). These results suggest that, although an increased sample size within a homogenous population will identify more variants and explain a larger proportion of the variance within that same population, it will also further exacerbate existing disparities in genetic knowledge for non-European populations.

The meta-analysis results can also be used to fine-map associations at known loci, which is an important step in the identification of functional polymorphisms that underlie a statistically significant association. Comparing the 95% credible sets for 390 associated variants reported by GIANT for height, we observed that the addition of PAGE to GIANT significantly shrunk the credible sets from an average of 11.94 SNPs in GIANT to 9.68 in the meta-analysis ($P = 0.01$), whereas no significant differences were observed with the addition of UKB50k to GIANT ($P = 0.37$; Fig. 3a). Additionally, the posterior probabilities of the top-ranked SNP within these credible sets was significantly higher in the PAGE + GIANT meta-analysis compared to the GIANT analysis alone ($P = 1.9 \times 10^{-6}$) and the UKB50k + GIANT analysis ($P = 3.2 \times 10^{-3}$; Fig. 3b). The addition of the UKB50k data to the GIANT results did not significantly improve the top posterior probability ($P = 0.09$). Here we highlight as an example the previously identified intronic variant rs11880992, which is found in *DOT1L* ($P_{GIANT} = 7 \times 10^{-28}$)[24] (Fig. 3c, d). The 95% credible set was narrowed down from four to a single SNP with the addition of the PAGE data, owing to low linkage disequilibrium between these SNPs in the African American and Hispanic/Latino populations (Fig. 3e). Although trends were consistent, none of these analyses yielded significant results for body-mass index ($P > 0.05$), which is probably due to the smaller number of regions that were analysed ($n = 91$; Supplementary Fig. 15).

Finally, we examined the worldwide distribution of several medically actionable variants that were designed on MEGA[26] (Supplementary Information 11). One such variant was identified through an association between a missense variant in *HBB* (rs334) and HbA_{1c} levels ($P_{cond} = 6.87 \times 10^{-31}$; $n = 11{,}178$), with the majority of the signal originating from the Hispanic/Latino population ($P = 7.65 \times 10^{-27}$; $n = 10{,}408$; MAF = 0.01). Although this association has recently been reported in African Americans[27] (PAGE African Americans, $P = 5.62 \times 10^{-4}$; $n = 559$; MAF = 0.06), this is the first time—to our knowledge—that the association with HbA_{1c} levels has been reported in Hispanic/Latinos. The gene *HBB* encodes the adult haemoglobin β chain and is known for its role in sickle-cell anaemia. Genetic variants of haemoglobin are known to affect the performance of some HbA_{1c} assays[28–30], potentially leading medical professionals to incorrectly believe that a patient has achieved glucose control, increasing the risk of complications caused by type 2 diabetes. This result illustrates how ancestry-specific findings may be transferable to other groups that share components of genetic ancestry—in this case, the African ancestry present in both African Americans and some Hispanic/Latinos. The PAGE study can therefore aid in expanding the reach of precision medicine to encompass individuals of diverse ancestry, particularly when combined with other studies[31,32].

As large-scale biobanking, precision medicine and direct-to-consumer genetic testing become more common, it is critical that the genetics community takes a forward-thinking approach towards the opportunities presented by including diverse populations. Here we focused on quantifying the scientific value of including diverse populations in the discovery and replication phases of GWAS. As we move towards incorporating GWAS-based risk models in clinical care[33], our study as well as other recent studies[34] demonstrate that we risk exacerbating health disparities unless diverse, multi-ethnic studies are included. In the United States, the All of Us Research Program embraces the reality that the success of precision medicine requires precision genomics, and therefore emphasizes the recruitment and active participation of underrepresented populations[35]. It is in the best interest of our research community to follow suit and take steps to become more inclusive. As world populations become increasingly complex[36,37], geneticists and clinicians will be required to evaluate genetic predictors of complex traits in ever more diverse populations. Current genomic databases are under representative of populations with the greatest health burden and possibility of meaningful benefit. This realization, combined with the increased availability of resources for studying diverse populations, means that researchers and funders can no longer afford to ignore non-European populations. The PAGE study provides valuable resources in the design of MEGA and through the sharing of population-specific allele frequencies and analysis approaches, which will provide the motivation to make research in diverse populations a priority in the field of genetics.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at https://doi.org/10.1038/s41586-019-1310-4.

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METHODS

Studies. The PAGE study includes eligible participants with a minority ancestry from four studies. Written informed consent was obtained for all participants in this study at the relevant recruitment sites. The WHI is a long-term, prospective, multi-centre cohort study investigating the health of post-menopausal women in the United States that recruited women from 1993 to 1998 at 40 centres across the United States. WHI participants reporting European descent were excluded from this analysis. The HCHS/SOL is a multi-centre study including participants of Hispanic/Latino descent with the goal of determining the role of acculturation in the prevalence and development of diseases relevant to Hispanic/Latino health. Starting in 2006, household sampling was used to recruit self-identified Hispanic/Latinos from four sites in San Diego, Chicago, the Bronx and Miami. All SOL Hispanic/Latinos were eligible for this study. The MEC is a population-based prospective cohort study recruiting men and women from Hawaii and California, beginning in 1993, and examines lifestyle risk factors and genetic susceptibility to cancer. Only the African American, Japanese American and Native Hawaiian participants of MEC were included in this study. The BioMe BioBank is managed by the Charles Bronfman Institute for Personalized Medicine at Mount Sinai Medical Center. Recruitment began in 2007 and continues at 30 clinical care sites throughout New York City. BioMe participants were African American (25%), Hispanic/Latino, primarily of Caribbean origin (36%), Caucasian (30%) and Others who did not identify with any of the available options (9%). Biobank participants who self-identified as Caucasian were excluded from this analysis. The Global Reference Panel (GRP) was created from Stanford-contributed samples to serve as a population reference dataset for global populations. GRP individuals do not have phenotype data and were only used to aid in the evaluation of genetic ancestry in the PAGE samples. Study protocols were approved for all studies by the appropriate boards at their respective institutions: Fred Hutchinson Cancer Research Center Institutional Review Board (WHI), University of North Carolina Office of Human Research Ethics/IRB (OHRE/IRB; HCHS/SOL), University of Southern California IRB (MEC), University of Hawaii IRB (MEC), Icahn School of Medicine at Mount Sinai IRB (BioMe) and the Stanford University IRB (GRP). Additional information about each participating study can be found in the Supplementary Information.

Phenotypes. The 26 phenotypes included in this study were previously harmonized across the PAGE studies and white blood cell count, C-reactive protein, mean corpuscular haemoglobin concentration, platelet count, high-density lipoprotein, low-density lipoprotein, total cholesterol, triglycerides, glycated haemoglobin (HbA_{1c}), fasting insulin, fasting glucose, type 2 diabetes, cigarettes per day, coffee consumption, QT interval, QRS interval, PR interval, systolic blood pressure, diastolic blood pressure, hypertension, body mass index (BMI), waist-to-hip ratio (WHR), height, chronic kidney disease (CKD), end-stage renal disease, and estimated glomerular filtration rate assessed using the CKD-Epidemiology Collaboration (CKD-Epi) equation. Single-variant association testing was completed for all phenotypes using phenotype-specific models, adjusting by indicators for study, self-identified race/ethnicity as a proxy for cultural background, phenotype-specific standard covariates and the first 10 PCs. Additional information about phenotype-specific cleaning, exclusion criteria and the model covariates are included in the Supplementary Information.

Genotyping. A total of 53,338 PAGE and GRP samples were genotyped on the MEGA array at the CIDR, of which 52,878 samples successfully passed the quality control process of the CIDR. Genotyping data that passed initial quality control at CIDR were released to the quality assurance and quality control analysis team at the University of Washington Genetic Analysis Center, after which the data were further cleaned according to previously described methods[38] and genotypes for 51,520 subjects were returned. A total of 1,705,969 SNPs were genotyped on the MEGA. Quality control of genotyped variants was completed by filtering through various criteria, including the exclusion of (1) CIDR technical filters; (2) variants with missing call rate $\geq 2\%$; (3) variants with more than 6 discordant calls in 988 study duplicates; (4) variants with more than 1 Mendelian error in 282 trios and 1,439 duos; (5) variants with a Hardy–Weinberg $P < 1 \times 10^{-4}$; (6) SNPs with sex difference in allele frequency ≥ 0.2 for autosomes or XY; (7) SNPs with sex difference in heterozygosity > 0.3 for autosomes or XY; and (8) positional duplicates. Sites were further restricted to chromosomes 1–22, X or XY, and only variants with available strand information were included. After SNP quality control, a total of 1,402,653 MEGA variants remained for further analyses (for further details see Supplementary Information 3).

Imputation. To increase coverage, and thus improve power for fine-mapping loci, all PAGE individuals who were successfully genotyped on MEGA were subsequently imputed into the 1000 Genomes phase 3 data release[39]. Imputation was conducted at the University of Washington Genetic Analysis Center. Genotype data that passed the above quality control filters were phased with SHAPEIT2[40] and imputed into 1000 Genomes phase 3 reference data using IMPUTE version 2.3.2[41]. Segments of the genome that are known to contain gross chromosomal anomalies were filtered out of the final files of the genotype probabilities. Imputed sites were excluded if the IMPUTE information score was less than 0.4. A total of 39,723,562 imputed SNPs passed quality control measures (for further details see Supplementary Information 3).

Principal component analysis. The SNPRelate[42] package in R was used for principal components analysis (PCA) (see Supplementary Information for further details). The relevant PCs were selected using scatter plots. Scatter plots, with various PCs on the x and y axes, helped to assess the spread of genetic ancestry in the data for self-identified racial/ethnic clusters. A parallel coordinate plots for the first 10 PCs was generated, in which each PAGE individual is represented by a set of line segments connecting his or her PC values. The amount of variance explained diminished with each subsequent PC, and we estimated that the top 10 PCs provided sufficient information to explain the majority of genetic variation in the PAGE study population.

Genome-wide association testing. All imputed autosomal variants with IMPUTE information score > 0.4 ($M = 39{,}723{,}562$) were eligible for association testing in phenotype-specific models. An effective sample size (N_{eff}) was calculated for each SNP in a given phenotype-specific model, where $N_{\text{eff}} = 2 \times \text{MAF} \times (1 - \text{MAF}) \times N \times \text{info}$ where MAF is the minor allele frequency among the set of individuals included in a phenotype-specific model, N is the total sample size for a given phenotype and info is the IMPUTE information score of the SNP. Variants with $N_{\text{eff}} < 30$ (continuous phenotypes) or $N_{\text{eff}} < 50$ (binary phenotypes), were excluded from the final set of phenotype-specific results. The number of variants analysed per trait ranged from 21,894,105 to 34,656,550 for continuous phenotypes and 11,665,604 to 28,263,875 for binary phenotypes (Supplementary Table 1). Quantile–quantile plots and λ_{GC} (GC = genomic control) were used to assess genomic inflation in all phenotypes, for which λ_{GC} ranged from 0.98 to 1.15. Single-variant association testing for each phenotype used an additive model that was adjusted by indicators for study, self-identified race/ethnicity, the first 10 PCs and phenotype-specific covariates. Additional information about the phenotype-specific model covariates and transformations are included in the Supplementary Information. Association testing was completed in both SUGEN and GENESIS programs.

The GENESIS[17,18] program is a Bioconductor package made available in R that was developed for large-scale genetic analyses in samples with complex structure including relatedness, population structure and ancestry admixture. The current version of GENESIS implements both linear and logistic mixed model regression for genome-wide association testing. The software can accommodate continuous and binary phenotypes. The GENESIS package includes the program PC-Relate, which uses a PCA-based method to infer genetic relatedness in samples with unspecified and unknown population structure. By using individual-specific allele frequencies estimated from the sample with PC eigenvectors, it provides robust estimates of kinship coefficients and identity-by-descent sharing probabilities in samples with population structure, admixture and Hardy–Weinberg equilibrium departures. It does not require additional reference population panels or prior specification of the number of ancestral subpopulations.

The SUGEN program[19] is a command-line software program developed for genetic association analysis under complex survey sampling and relatedness patterns. It implements the generalized estimating equation method, which does not require modelling of the correlation structures of complex pedigrees. It adopts a modified version of the 'sandwich' variance estimator, which is accurate for low-frequency SNPs. Association testing in SUGEN requires the formation of 'extended' families by connecting the households who share first-degree relatives or either first- or second-degree relatives. Trait values are assumed to be correlated within families but independent between families. In our experience in analysing this dataset, it is sufficient to account for first-degree relatedness. The current version of SUGEN can accommodate continuous, binary and age-at-onset traits. A comparison of P values produced by SUGEN and GENESIS for all previously identified known loci are included in Supplementary Fig. 12 and Supplementary Table 4.

Conditional analyses. Phenotype-specific lists of previously identified loci were hand-curated for each phenotype and included SNPs indexed in the GWAS Catalog or identified through non-GWAS high-throughput methods (for example, metabochip, exomechip or immunochip). The full lists of known loci for each phenotype are available in Supplementary Table 5. Conditional analyses were conducted for all phenotypes by conditioning on all previously identified loci on a given chromosome. P values estimated in conditional analyses are denoted by 'P_{cond} in the main text; the SUGEN conditional results for all novel and secondary findings are shown in Supplementary Table 3.

SNP × PC effect heterogeneity by genetic ancestry and self-identified race/ethnicity. We used two approaches to assess effect heterogeneity within PAGE participants. First, we used interaction analyses with models that included variant by PC (SNP × PC) interaction terms for all 10 PCs. The fit of nested models was compared using the F-statistic, for which the associated interaction P value indicated whether the inclusion of the 10 SNP × PC interaction terms improved the model fit compared to a model that lacked the interaction terms. The overall

SNP × PC interaction *P* values evaluated whether the additional variance explained by variant × genetic ancestry interactions was statistically significant and represented effect modification driven by genetic ancestry. Interaction *P* values for all novel and secondary findings are included in Supplementary Table 3.

For comparison against more standard (stratified) analysis strategies, all analyses were also run stratified by self-identified race/ethnicity. A minor allele count of at least five was required for a stratified model to be run within an ethnic group. The stratified analyses were then meta-analysed using a fixed-effect model implemented in METAL[43]. I^2 and χ^2 heterogeneity *P* values were estimated for all meta-analysed results and represent effect size heterogeneity driven by self-identified race/ethnicity. The race/ethnicity-specific results, I^2 and χ^2 heterogeneity *P* values for all novel and secondary findings are included in Supplementary Table 3.

Standardized effect size analysis. The standardized effect size (z') analysis for Fig. 2a was performed as follows. To avoid double-counting of SNPs/loci, we constrained analysis for each trait to (1) the single previous report that (2) did not combine genome-wide genotypes with focused platforms such as the metabochip, (3) reported the direction of effect with the allele in the GWAS Catalog and (3) included the maximum total number of individuals after applying criteria (1) and (2). (1) We selected a single manuscript, because many traits already have serial meta-analyses published, where earlier publications represent a subset of individuals reported in later publications, so reported effect sizes in the GWAS Catalog are not necessarily independent. (2) We excluded meta-analyses using mixtures of agnostic GWAS data (consistent map density across the genome) with focused platforms (for example, metabochip, oncochip or exomechip), because the actual sample size varies markedly across the genome, with overlapping agnostic/focused regions having substantially greater numbers of individuals in the analysis. Most of these reports fail to specify the sample size on a per-SNP basis, making it impossible to confidently calculate z'. (3) Starting from the 22 quantitative traits, we found reference studies that explicitly reported the allele associated with direction of effect for 18. Furthermore, to be confident that the direction of effect was consistent between PAGE and previous reports, we restricted analysis to asymmetric SNPs (A/C, A/G, C/T and G/T). These criteria yielded 589 previously reported genome-wide significant variants, distributed across the 18 traits (Supplementary Table 7). Only 110 of these variants were traditionally genome-wide significant ($P < 5 \times 10^{-8}$) and therefore overlap with the SNP × PC heterogeneity analysis. We compared the PAGE z' (both pooled and stratified) to the GWAS Catalog z' in a linear regression.

Assessing single-variant results. SUGEN association results were used for the identification of novel and secondary findings for all phenotypes. The variant with the smallest *P* value in a 1-Mb region was considered the 'lead SNP'. A lead SNP was considered to be a novel locus if it met the following criteria: (1) the lead SNP was located greater than ±500 kb away from a previously known locus (per the phenotype-specific list of known loci); (2) had a SUGEN $P < 5 \times 10^{-8}$; (3) had a SUGEN conditional $P < 5 \times 10^{-8}$ after adjustment for all previously known loci on the same chromosome; and (4) had two or more neighbouring SNPs (within ±500 kb) with a $P < 1 \times 10^{-5}$. A lead SNP was considered to be a secondary signal in a previously known loci if it met the following criteria: (1) the lead SNP was located within ±500 kb of a previously known loci; (2) had a SUGEN $P < 5 \times 10^{-8}$; and (3) had a SUGEN conditional $P < 5 \times 10^{-8}$ after adjustment for all previously known loci on the same chromosome. Full results for all novel and secondary findings are included in Supplementary Tables 2, 3.

Effect size heterogeneity in the GWAS Catalog. The full GWAS Catalog[22] database was downloaded on 31 December 2016. The data were filtered to identify results relevant to any of the 26 PAGE phenotypes, producing a subset of 8,979 unique trait–SNP associations (3,322 unique variants) that were genome-wide significant ($P < 5 \times 10^{-8}$) in the GWAS Catalog. The PAGE results for each of the GWAS Catalog trait–SNP associations was examined to first identify the subset of pairs that replicated ($P < 5 \times 10^{-8}$) in PAGE unconditioned models. Pairs of replicated tag SNPs within 500,000 base pairs of each other were then merged into loci, to count 'unique' associated loci. Of the GWAS Catalog tag SNPs that were replicated in PAGE, SNPs that had a Bonferroni-corrected SNP × PC interaction heterogeneity *P* value ($P < 8.71 \times 10^{-5}$, 0.05/574) were considered to show evidence of significant effect size heterogeneity between ancestries. Effect heterogeneity was also assessed using the multi-ethnic study population of PAGE by first identifying the lead SNP in each locus with the smallest *P* value in PAGE, totalling 333 SNPs (302 known loci from the GWAS Catalog, plus 31 novel loci discovered in the present analysis). Among the 333 lead SNPs, 24 (7.2%) had a significant Bonferroni-corrected SNP × PC interaction heterogeneity *P* value ($P < 1.5 \times 10^{-4}$, 0.05/333).

Meta-analysis and fine-mapping with GIANT and UKB50k. *Meta-analysis.* We meta-analysed results for BMI and height in our PAGE multiethnic sample (around 50,000 individuals) with the published data from GIANT consortium[23,24], which included approximately 250,000 individuals of European descent for each trait. We also conducted a meta-analysis with 50,000 randomly sampled 'White British' individuals from the UK Biobank (UKB50k) for comparison. GWAS for both PAGE and UKB50k were estimated with analogous models for BMI and height traits. Within PAGE and UKB50k, we used the inverse normally transformed residuals for each trait by sex and race/ethnicity, and adjusted for population substructure, age, centre and racial/ethnic groups (if applicable). These methods were similar those used by GIANT, using inverse-normal-adjusted residuals for each trait outcome. We then separately meta-analysed results using a fixed-effects model for either PAGE or UKB50k combined with GIANT using the METAL software[43]. We retained only variants available across both the combined meta-analyses (for PAGE + GIANT or UKB50k + GIANT), which led to the inclusion of approximately 2.5 million variants. Significance was defined as $P < 5 \times 10^{-8}$. Novelty of a locus was defined as ±500 kb from any known loci for the respective trait based on the previously published GIANT data[23,24]. We also required the at least two SNPs within a 1-Mb results had $P < 1 \times 10^{-5}$ to be retained as a significant known or novel locus.

Fine-mapping. We used FINEMAP[44] for all fine-mapping analyses. For each previously reported locus for height[24] and BMI[23] in GIANT, a 1-Mb region was subset, using the summary statistics from GIANT, the PAGE + GIANT meta-analysis and the UKB50k + GIANT meta-analysis. The linkage disequilibrium for the fine-mapping analyses was calculated using each individual ancestry from the PAGE sample and using the 9,700 individuals of European descent from the ARIC study. For weighted linkage disequilibrium that included all ancestries, we weighted each ancestry in PAGE by the actual sample size and added in the ARIC sample but used the sample size from the GIANT consortium by trait. All analyses were run assuming one causal variant. The cumulative 95% credible set was calculated from the estimated posterior probabilities.

PVE analysis. Each PVE analysis considered a single combination of (1) trait, (2) the analysis from which *P* values were derived (GIANT, GIANT + PAGE or GIANT + UKB50k) and (3) the target population in which PVE was calculated (either PAGE or UKB50k). To avoid overweighting any single region owing to linkage disequilibrium between multiple associated SNPs, we first defined a 'locus' as a contiguous series of genome-wide significant tag SNPs with genome-wide significance, for which each tag SNP was less than 500 kb from the next. Then we selected the single SNP within each locus with the smallest *P* value in the given analysis (the best tag SNP) and calculated the PVE for that SNP in the target population. The meta-analysis was effectively limited to allele frequencies greater than 5%, so we used the standard $P < 5 \times 10^{-8}$ threshold for significance to define loci.

PVE was calculated for a given SNP using a previously published equation[25]:

$$\mathrm{PVE} \propto \frac{\hat{\beta}^{2} * 2p(1-p)}{\hat{\beta}^{2} * 2p(1-p) + (\mathrm{s.e.}(\hat{\beta}))^{2} * N * 2p(1-p)}$$

Input for this equation requires only the estimated effect size ($\hat{\beta}$), the standard error of the estimate ($\mathrm{s.e.}(\hat{\beta})$), the allele frequency (p) and the number of samples (N). PVE was then summed across all of the best tag SNPs in a given analysis.

Population allele frequencies of *HCP* rs2395029[G]. These 99 labels were compiled from self-identified ancestry information from the PAGE sample manifest, as well as self-reported country of origin from the Mount Sinai BioMe biobank. Per-population allele frequencies for rs2395029[G] were calculated in PLINK v.1.90 (http://www.cog-genomics.org/plink/1.9/)[38] and results were visualized in R.

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

Data availability

Individual-level phenotype and genotype data are available through dbGaP (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000356). Allele frequency data will be available for all genotyped sites on dbSNP (https://www.ncbi.nlm.nih.gov/projects/SNP/) and the University of Chicago Geography of Genetic Variants Browser (http://popgen.uchicago.edu/ggv/). Clinically relevant variant frequency data are available through ClinGen (https://curation.clinicalgenome.org/). Summary statistics for the genome-wide association study results are available through the NHGRI-EBI GWAS Catalog (https://www.ebi.ac.uk/gwas/downloads/summary-statistics).

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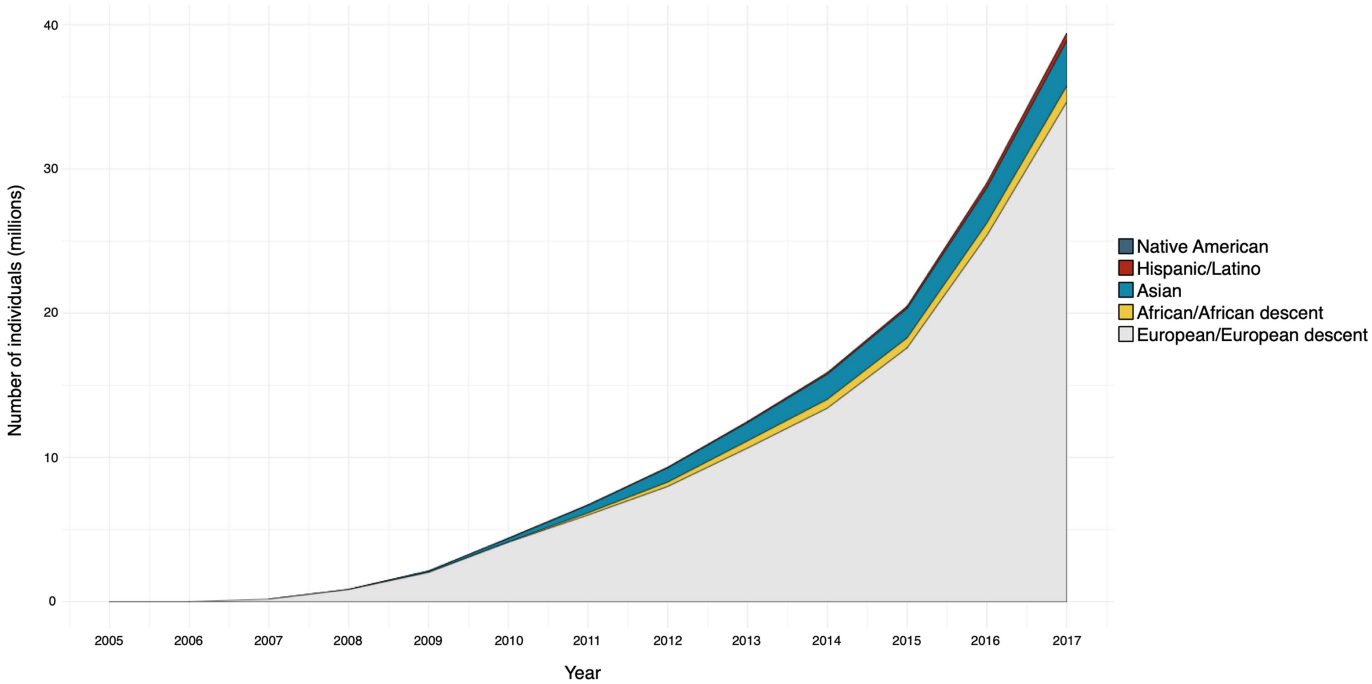
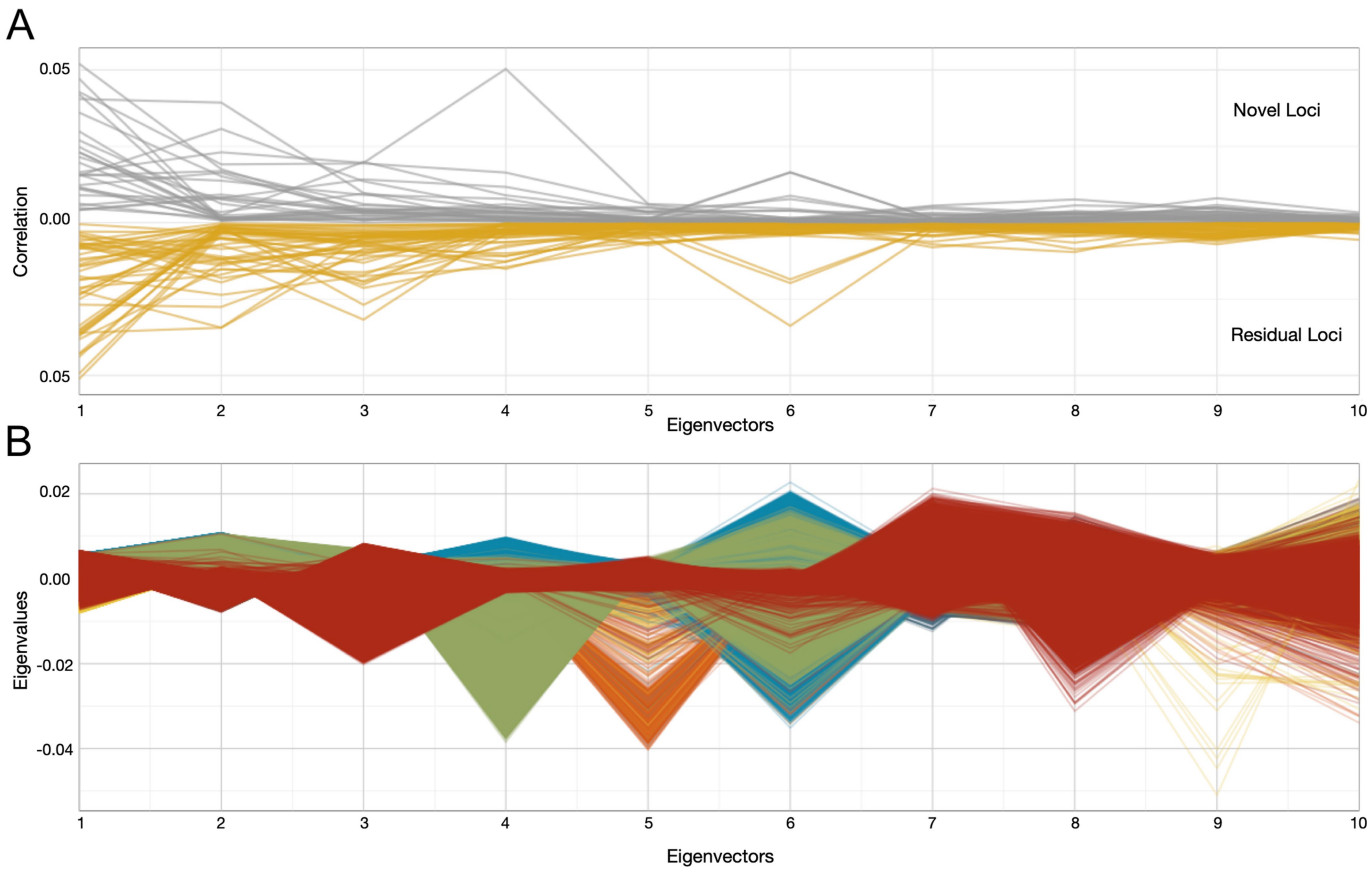


Extended Data Fig. 1 | Number of unique participants in the GWAS Catalog from 2006 to 2017 (inclusive). We observed that—although the number of unique participants (in millions) in the GWAS Catalog has grown substantially over the past decade—the relative proportion of participants of non-European descent has remained constant, with the majority of progress within Asian populations.



Extended Data Fig. 2 | Correlation between SNP genotype and PC1–PC10. a, The correlation (r^2) for novel and residual loci calculated by obtaining the individual level data for all PAGE participants and correlating the SNP genotype with each of the ten PCs. The correlation between each locus and each of the ten PCs was plotted on the *y* axis, novel loci are plotted in grey and residual loci are plotted in yellow. We observed an especially high correlation between a novel locus and PC4, which represents Native Hawaiian/Pacific Islander ancestry. **b**, The individual level data for all PAGE participants were obtained and plotted in a parallel coordinates plot, such that each PAGE individual is represented by a set of line segments connecting their eigenvalues. This allows us to see which race/ethnicity groups are differentiated at each PC. For example, we see predominantly green lines as outliers for PC4, which indicates that this vector represents a continuum of Native Hawaiian/Pacific Islander ancestry.

Extended Data Table 1 | GWAS Catalog heterogeneity by trait, including number of novel and secondary findings

	Largest GWAS catalog discovery population[1]					GWAS catalog tagSNPs			best PAGE tagSNPs			
Phenotype	European	East Asian	African	Hispanic/ Latino	PAGE	Unique	P<5x10^{-8}	Het[4]	P<5x10^{-8}	Het[5]	Novel Loci (count)[6]	Secondary Loci (count)[6]
Inflammatory Traits												
CRP	66,185	10,112	8,280	3,548	28,537	82	38	7	16	1	0	0
WBC	19,509	33,231	16,388	-	28,534	27	10	5	11	3	1	1
MCHC	62,553	-	16,485	-	19,803	21	9	1	5	0	0	2
Platelet Count	48,666	14,806	7,943	12,491	29,328	92	23	0	28	0	1	1
Lipid Traits												
HDL	99,900	12,545	7,917	4,383	33,063	244	71	8	21	1	2	2
LDL	94,595	12,545	7,861	4,383	32,221	192	46	12	18	0	0	2
TG	96,598	12,545	7,601	4,383	33,096	179	75	29	16	1	1	2
TC	100,184	8,344	6,480	4,383	33,185	166	31	4	20	0	1	2
Lifestyle Traits												
Cigarettes/Day Excluding Nonsmokers	74,035	11,696	32,389	-	15,862	12	0	0	3	0	2	1
Coffee Cups/Day	91,462	-	-	-	35,902	16	3	1	3	0	1	0
Glycemic Traits												
HbA1c	46,368	17,290	-	-	11,178	29	8	1	9	0	1	3
Fasting Insulin	51,750	7,696	1,040	229	21,596	34	0	0	3	0	1	0
Fasting Glucose	58,074	24,740	2,029	4,176	23,963	55	15	3	7	0	2	0
Type II Diabetes[2]	12,171/ 56,862	15,463/ 26,183	1,264/ 5,678	3,848/ 4,366	14,075/ 31,752	286	28	2	13	0	0	1
Electrocardiogram Traits												
QT Interval	71,061	6,805	13,105	-	17,348	183	39	1	11	0	0	2
QRS Interval	60,255	6,085	13,031	-	17,052	63	9	3	12	0	1	2
PR Interval	28,517	6,085	13,415	-	17,428	154	19	1	10	0	1	2
Blood Pressure Traits												
Systolic Blood Pressure	74,064	31,516	29,378	-	35,433	74	2	0	4	0	1	1
Diastolic Blood Pressure	74,064	31,516	29,378	-	35,433	81	2	0	4	0	0	0
Hypertension	74,064	31,516	29,378	-	49,158	111	0	0	2	0	1	1
Anthropometric Traits												
Waist-to-hip Ratio[3]	142,762	39,869	19,744	3,484	33,904	94	5	0	6	0	1	0
Height	253,288	36,227	20,427	-	49,781	698	99	42	93	18	5	13
Body Mass Index	236,781	82,438	39,144	3,484	49,335	572	41	12	13	0	1	0
Kidney Traits												
eGFR by CKD Epi Equation	133,413	23,536	16,840	16,325	27,900	135	1	0	5	0	3	0
Average	90,953	20,953	14,710	5,570	Total	3356	548	194	333	24	27	38

For more information, see Supplementary Table 6.
[1]Data only include studies indexed in the GWAS Catalog on 31 December 2016.
[2]Data are shown as cases/controls.
[3]Data include pooled and sex-stratified studies and/or results.
[4]$P < 8.71 \times 10^{-5}$ for genotype:PC interactions in PAGE, adjusting for multiple tests (0.05/574).
[5]$P < 1.50 \times 10^{-4}$ for genotype:PC interactions in PAGE, adjusting for multiple tests (0.05/333).
[6]Significant loci have $P < 5 \times 10^{-8}$ after conditioning on all known loci from the literature.

Extended Data Table 2 | Results of the meta-analysis

	Height[1]				BMI[2]			
Analysis	known loci[3]	novel loci[4]	novel, shared[5]	novel, unshared[6]	known[3]	novel[4]	novel, shared[5]	novel, unshared[6]
GIANT-only GWAS	425	0			74	0		
PAGE-only GWAS	46	8			9	0		
UKB50k-only GWAS	91	1			8	2		
GIANT+PAGE meta	405[7]	82	45	37	64[7]	38	7	31
GIANT+UKB50k meta	412[7]	107		62	67[7]	28		21

[1]Meta-analysis with previously reported height data[24].
[2]Meta-analysis with previously reported BMI data[23].
[3]Known loci include only the 425 height loci and 74 BMI loci from GIANT.
[4]Novel loci were identified as $P > 5 \times 10^{-8}$ in the GIANT-only dataset and $P > 5 \times 10^{-8}$ in the specified analyses.
[5]Novel, shared loci were identified as $P > 5 \times 10^{-9}$ in both GIANT+PAGE and GIANT+UKB50k datasets.
[6]Novel, unshared loci were identified as $P > 5 \times 10^{-9}$ in either GIANT+PAGE or GIANT+UKB50k, but not in both datasets.
[7]A modest number of known loci were significant in the GIANT-only GWAS, but not in the meta-analyses. These known loci were still included in PVE calculations.

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Reporting Summary

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

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☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
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☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☐	☒	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection.
Data analysis	Software used for data analysis in this manuscript includes: Plink (v1.90), R, Illumina's GenomeStudio, SNPRelate, PC-Relate, METAL, GENESIS, SUGEN, and FINEMAP (v1.3). All software used in this analysis is described in detail within the Methods section (Pg 14) and Supplemental Information.

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

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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 list of figures that have associated raw data
- A description of any restrictions on data availability

Data Availability: Individual-level phenotype and genotype data are available through dbGaP at https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000356. Allele frequency data will be available for all genotyped sites on dbSNP (https://www.ncbi.nlm.nih.gov/projects/SNP/) and the University of Chicago Geography of Genetic Variants Browser (http://popgen.uchicago.edu/ggv/). Clinically relevant variant frequency data is also available through ClinGen.

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Life sciences study design

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

Sample size	We conducted genome-wide association (GWAS) of 49,839 non-European individuals for 26 clinical and behavioral phenotypes. As far as we are aware, this is the largest study of multi-ethnic, non-European participants genotyped on a single array for GWAS. See Methods (Page 14) and Supplemental Information (Pages 2-3) for more information about the samples.
Data exclusions	Several rationale for data exclusions were deployed in this study. Participants were excluded from the analysis if they had missing or outlier phenotype values, confounding co-morbidities, medications, or otherwise non-standard measures of phenotype as described in the Supplementary Information. Genotyped or imputed variants were excluded if they failed quality control or technical filters described in the Methods section.
Replication	Over 95% of the findings of this study reproduced known, published genotype-phenotype associations in the GWAS catalog. In addition, 5% variants in this study (26 loci) reach the threshold of statistical significance, indicating novel findings. However, in the absence of independent large-scale studies for those in the same populations, these could not be independently reproduced.
Randomization	Models for variant association testing for each phenotype included covariates for gender and study center, to adjust for population group including self-identified race/ethnicity and the first 10 principal components of genetic ancestry, and phenotype-specific covariates (including, age of diagnosis/trait measurement, medications, smoking, and co-morbidities).
Blinding	All participating studies had population-base recruitment strategies, regardless of outcomes, therefore blinding was not necessary during data collection or analysis in this study.

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
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

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	A total of 49,839 individuals of non-European ancestry were included in this study, comprising of 15,381 men and 34,458 women. Genotyped individuals self-identified as Hispanic/Latino (N=22,216), African American (N=17,299), Asian (N=4,680), Native Hawaiian (N=3,940), 112Native American (N=652), or Other (N=1,052). Detailed population characteristics by study and phenotype harmonization information can be found in Supplemental Information Sections 1 and 2, as well as Supplementary Table 1.
Recruitment	All participating studies had population-based recruitment strategies, regardless of outcomes. Details can be found in Supplemental Materials (Section 1).
Ethics oversight	Study protocols were approved for all studies by the appropriate boards at their respective institutions: Fred Hutchinson Cancer Research Center Institutional Review Board (WHI), University of North Carolina Office of Human Research Ethics/IRB (OHRE/IRB; HCHS/SOL), University of Southern California IRB (MEC), University of Hawaii IRB (MEC), Icahn School of Medicine at Mount Sinai IRB (BioMe), and the Stanford University IRB (GRP).

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