Genetic Diversity Turns a New PAGE in Our Understanding of Complex Traits

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Summary/Abstract

Genome-wide association studies (GWAS) have laid the foundation for many downstream investigations, including the biology of complex traits, drug development, and clinical guidelines. However, the dominance of European-ancestry populations in GWAS creates a biased view of human variation and hinders the translation of genetic associations into clinical and public health applications. To demonstrate the benefit of studying underrepresented populations, the Population Architecture using Genomics and Epidemiology (PAGE) study conducted a GWAS of 26 clinical and behavioral phenotypes in 49,839 non-European individuals. Using novel strategies for multi-ethnic analysis of admixed populations, we confirm 574 GWAS catalog variants across these traits, and find 28 novel loci and 42 residual signals in known loci. Our data show strong evidence of effect-size heterogeneity across ancestries for published GWAS associations, which substantially restricts genetically-guided precision medicine. We advocate for new, large genome-wide efforts in diverse populations to reduce health disparities.

Introduction

A significant European-centric bias has been noted in the field of genome-wide association studies (GWAS), with the vast majority of discovery efforts conducted in populations of European ancestry [1–3] while individuals of African or Latin American ancestry account for only 4% of samples analyzed [3]. (**Extended Data Fig. 1**) Genetic data from ethnically diverse populations will be crucial to powering genome-phenome association studies. Recent publications have reported that some genetic predictors are restricted to certain ancestries, and thus may partially explain risk differences among racial/ethnic groups. [4–9] Additionally, as the field shifts its attention towards low frequency variants, which are more likely to be population specific, we can no longer rely on the transferability of findings from one population to another, a complication that has also been observed with some common variants. [10,11]

The lack of representation of diverse populations in genetic research will exacerbate health disparities that exist for many diseases. In the US, minority populations have a disproportionately higher burden of chronic conditions. [12] Globally, developing countries account for 89% of the world's population and 93% of the global disease burden. [13] By the encouragement of diversity in genomics research, new opportunities for discovery will emerge, and the precision of translational applications will improve. It is imperative that the research community rectifies the imbalance in representation, not only because it is vital for precision medicine and translational research, but also because it is the right thing to do.

Many factors contribute to this bias in genetic research, including the paucity of studies recruiting minorities, lack of information and access to available studies, and complex statistical analyses required for multi-ethnic and admixed study populations.[14] However, recent advancements in statistical analyses and genotyping technologies have lessened many methodological concerns, removing barriers that had previously made researchers reluctant to recruit and analyze heterogeneous samples. The Population Architecture using Genomics and Epidemiology (PAGE) study focuses on exploring the genetics of underrepresented populations.[15,16] In a study of 49,839 individuals of non-European ancestry, we describe strategies for addressing challenges unique to multi-ethnic studies, investigate population bias in the current GWAS literature, identify numerous new population-specific findings across 26 traits and diseases, consider the implications for clinical genetics, and illustrate the many advantages of genetic inclusion.

Unique Methodological Challenges Inherent to Multi-ethnic Studies

GWAS in diverse populations have many complexities that must be considered and addressed. PAGE was specifically developed by the National Human Genome Research Institute and the National Institute on Minority Health and Health Disparities to conduct genetic epidemiology research in ancestrally diverse populations, including three major population-based cohorts (HCHS/SOL, WHI, and MEC) and one metropolitan biobank (BioMe). Eligible participants self-identified as Hispanic/Latino (N=22,250), African American (N=17,328), Asian (N=4,696), Native Hawaiian (N=3,944), Native American (N=653), or Other (N=1,056), which includes participants who did not identify with any of the available options and primarily includes those from South Asia or with mixed heritage (**Supplementary Table 1**). Utilizing the detailed phenotype data collected and harmonized across studies, we present genetic association results from 26 phenotypes related to inflammation, diabetes, hypertension, kidney function, cardiac electrophysiology, dyslipidemias, anthropometry, and behavior/lifestyle (smoking and coffee consumption).

Another major challenge in multi-ethnic studies is the limited availability of genotyping arrays that comparably tag variation in multiple genetic ancestries, especially in those with African ancestry. To address this, a collaboration among PAGE, Illumina, the Consortium on Asthma among African-ancestry Populations in the Americas (CAAPA) [17], and other academic partners developed the Multi-Ethnic Genotyping Array (MEGA), which includes a GWAS scaffold designed to tag both common and low frequency variants in global populations.[18] **(Extended Data Fig. 2)** Additionally, it contains enhanced tagging in exonic regions, hand-curated content to interrogate clinically relevant variants, and enriched coverage to fine-map known GWAS loci.[19] The principles used to design MEGA are currently being used to create other multi-ethnic genotyping arrays, including the Multi-Ethnic Global Array and the Global Screening Array.

Historically, analyses have been stratified by self-identified race/ethnicity to account for confounding by genetic ancestry. In PAGE, we conducted principal component analysis to evaluate population substructure and mapped self-identified racial/ethnic groups onto the estimated principal components (PCs). Most notably in Hispanics/Latinos, but evident to a lesser extent in all populations, genetic ancestry reveals greater demographic complexity compared with culturally assigned labels, appearing as a continuum and demonstrating that genetic ancestry is not categorical in diverse populations that have varying degrees of admixture (**Figure 1**). Stratifying by self-reported race/ethnicity would fail to separate groups with similar patterns of genetic ancestry and therefore would still require adjustment of PCs with reduced statistical power in a smaller sample size. For this reason, we pooled all samples in a single analysis.

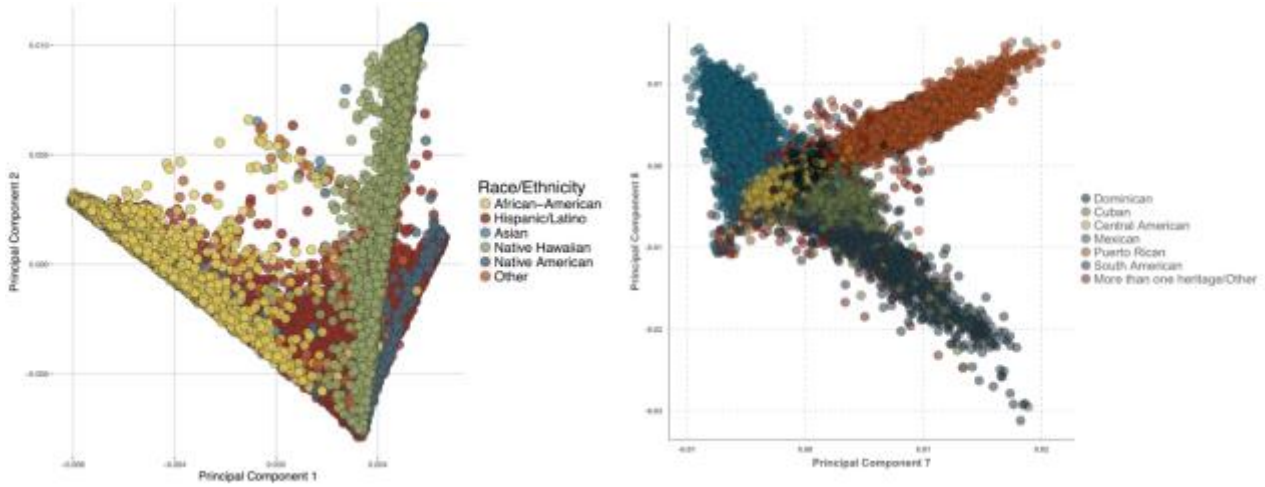

Figure 1: Principal Component Analysis of PAGE Populations.
Scatter plot of PCs for PAGE racial/ethnic groups. Each point represents one individual, color-coded by self-identified race/ethnicity. (a) Global variation (PC1 vs PC2) (b) Hispanic/Latino variation (PC7 vs PC8).

Multi-ethnic GWAS also require sophisticated statistical modeling. Known and cryptic relatedness are often concerns for studies recruiting from smaller, more isolated populations. WHI, MEC, and BioMe used population-based recruitment, whereas HCHS/SOL used a household sampling study design, which increased the inclusion of relatives. To account for relatedness within and across studies, we used two recently developed analytical methods for GWAS of related individuals from admixed populations. GENESIS [20–22] uses a linear mixed model and accounts for the correlation among genetically similar samples through a kinship matrix that estimates the known and cryptic relatedness in the presence of population structure and admixture. SUGEN [23] uses a modified version of generalized estimating equations and creates “extended” families by connecting the households who share first degree relatives. Single-variant association

testing was completed in both GENESIS and SUGEN using phenotype-specific models that were adjusted by indicators for study, self-identified race/ethnicity as a proxy for cultural background, phenotype-specific standard covariates, and the first 10 PCs. Because at the time of analysis SUGEN could analyze both continuous and binary phenotypes, while GENESIS could only analyze continuous phenotypes, we present SUGEN results below, and include GENESIS results in the Supplementary Tables. For comparison against traditional multi-ethnic approaches, we analyzed stratified by self-identified race/ethnicity, and meta-analyzed to assess heterogeneity by ancestry.

28 Novel Loci Found in 26 Phenotypes

Since the majority of GWAS have been conducted in European-ancestry populations, we hypothesized that the examination of underrepresented populations would reveal ancestry-specific associations that European-centric studies were unable to detect. Across 26 phenotypes, we discovered 28 novel loci at least 1 Mb away from a known locus that remained genome-wide significant ($P_{cond}<5x10^{-8}$) after conditioning on all previously identified variants on that chromosome (**Table 1, Supplementary Tables 2-3**). We attribute many of these discoveries to MEGA's globally diverse panel of variants and to a study population that includes ancestries where these variants are more frequent. Here, we briefly discuss two illustrative examples (**Figure 2, Extended Data Fig. 3**).

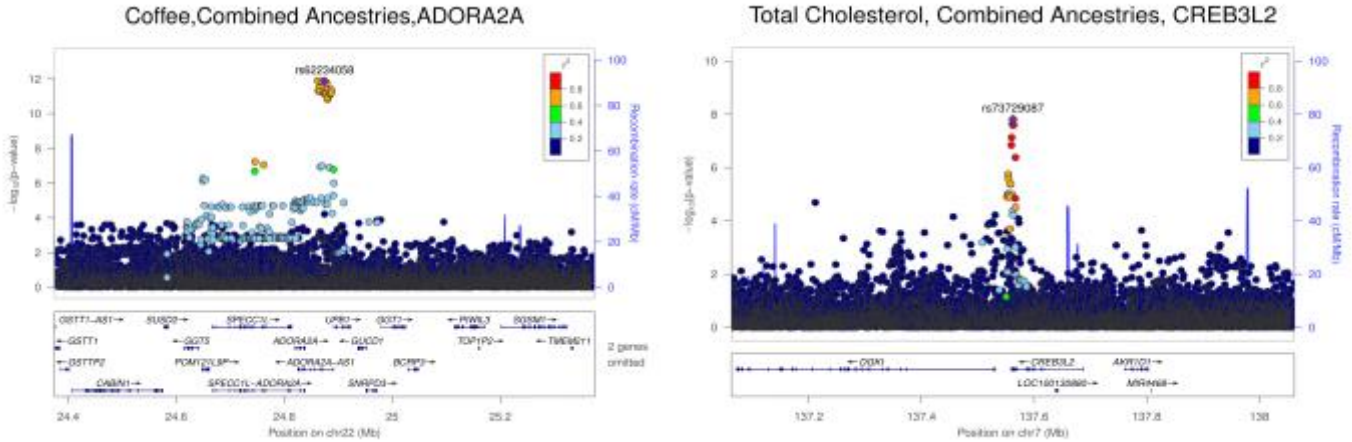

Figure 2: Exemplars of Novel Loci Identified within PAGE

LocusZoom plots for examples of novel loci are illustrated based on results from the pooled sample, specifically: coffee (cups/day)[a] with lead SNP rs62234058, and total cholesterol(mg/dl)[b] with lead SNP rs73729087.

a The association model for coffee (cups/day) was adjusted for age, sex, PC1-10, study, study center, and ancestry. Prior to analyses, a value of 1 was added to coffee intake followed by a log transformation.

b The association model for total cholesterol (mg/dl) was adjusted for age, sex, body mass index, PC1-10, study, study center, and ancestry. Intake of lipid medications was accounted for by adding a constant based on the class of lipid medication. See Methods for details.

A novel locus on chromosome 22q11 was associated with coffee intake (cups/day; **Figure 2A**) in *ADORA2A* ($P=1.33x10^{-12}$, N=35,902). The lead variant (rs62234058) is common in African Americans (coding allele frequency (CAF)=0.22) and Hispanic/Latinos (CAF=0.05), but rare in those of Asian and European ancestry (CAF<0.01). Given the rarity of the minor allele in Europeans, the discovery of this association was facilitated by our multi-ethnic study design and driven by PAGE African Americans ($P=3.70x10^{-7}$, N=11,862) and Hispanic/Latinos ($P=3.21x10^{-6}$, N=15,837). The *ADORA2A* gene is the main target of caffeine action in the central nervous system, and another SNP in this gene has previously been associated with caffeine-induced sleep disturbance (rs4822498 [24]). This finding showcases an ancestry-specific genetic trait which impacts a behavioral phenotype.

The second example describes a novel locus in *CREB3L2*/7q33 associated with total cholesterol levels (rs73729087: $P=1.52x10^{-8}$, N=33,185, CAF=0.05) (**Figure 2B**). While rare in European populations (CAF=0.005), it is more common in PAGE racial/ethnic groups, including African Americans ($P=1.77x10^{-6}$, N=10,137, CAF=0.11) and Hispanic/Latinos ($P=2.58x10^{-3}$, N=17,802, CAF=0.02). This noncoding variant is located in the 3'-UTR, possibly contributing to the regulation of *CREB3L2* expression. These examples represent just two of numerous novel findings that would not have been discovered in a European-descent study population.

Genetic Heterogeneity in the GWAS Catalog Reveals Need for Fine-Mapping

In general, GWAS identify loci where one or more tagSNPs show significant association with the trait of interest. However, GWAS do not lead directly to the identification of the functional variant (fSNP), which ideally is in strong linkage disequilibrium (LD) with the tagSNP(s) as surrogates. However, LD can vary among populations, so a tagSNP in perfect LD with the fSNP in one population may be in weak LD in a different population. This can lead to inconsistent estimates of the effect sizes among populations (and therefore effect size heterogeneity) if the tagSNP (instead of the causal fSNP) is used for effect size calculations. Because European-descent individuals are overrepresented in GWAS discovery populations and have different LD structures than other racial/ethnic groups, we hypothesized that effect size heterogeneity among populations may exist for many previously reported tagSNP associations.

To test this hypothesis, we measured the frequency of effect heterogeneity in PAGE's multi-ethnic study population of tagSNPs, primarily discovered in European populations, reported to the GWAS Catalog. We were able to replicate ($P<5x10^{-8}$) a total of 574 tagSNPs in 261 distinct genomic regions across 26 traits out of the related 3,322 unique GWAS Catalog variants **(Supplementary Table 4)**. [25] After Bonferroni correction for 574 tests, 132 tagSNPs (23.0%) showed significant evidence of effect heterogeneity by genetic ancestry (SNPxPC $P<8.71x10^{-5}$). Thus, we observe that nearly a quarter of reported GWAS Catalog tagSNPs, the preponderance of which were identified in European-based studies, show evidence of effect heterogeneity upon replication in a multi-ethnic study population. This estimate is conservative, because some of the effects that failed to replicate at $P<5x10^{-8}$ might have been underpowered to detect heterogeneous effects, especially for the less frequent alleles.

While we replicate 261 regions previously implicated in the GWAS Catalog, for most of these regions (77%) the strongest signal was not the previously reported tagSNP from the GWAS Catalog but a different tagSNP. Additionally, heterogeneity was only observed at 6% of these tagSNPs with the strongest associations within all 261 regions. This is consistent with multi-ethnic analyses fine-mapping known association signals at a majority of reported GWAS catalog loci, attributable to differential tagging of the underlying functional variation among populations, rather than that there are truly differential underlying fSNP effect sizes. These results have important implications for precision medicine, as risk prediction models based on heterogeneous GWAS Catalog tagSNPs could have poor accuracy in non-European ancestries.

42 Residual Signals in Known Loci Found in 26 Phenotypes

In addition to refining loci, multi-ethnic analysis affords an opportunity to identify independent signals (secondary variants) within known loci, further enriching our understanding of the genetic architecture of traits. To test for secondary

signals, we screened for statistical associations that remained genome-wide significant ($P_{cond}<5x10^{-8}$) after adjusting for all known tagSNPs (the "adjusted" model), identifying 42 new variants located within 1 Mb of a previously known variant (**Table 1, Supplementary Tables 2-3**). If the residual signal represents a statistically independent association, then we would expect no net change in the strength of the association between unadjusted and adjusted models and that the known tagSNPs were in weak LD with the residual SNPs. Out of the 42 residual variants, 23 and 25 in Hispanic/Latino and African-descent populations, respectively, show evidence of a secondary association independent (LD $r^2<0.2$) of previously known loci. This analysis suggests that approximately half of these known loci, from majority European-based GWAS, contain novel secondary signals in these populations.

To further illustrate the difference in mechanism between fine-mapping and secondary independent signals, we highlight two examples (**Figure 3).** The first is a refinement of the association between hexokinase 1 (*HK1*) and HbA1c. The residual signal at rs72805692 ($P_{unadj}=9.22x10^{-22}$, N=11,178, CAF=0.061) is in moderate LD in European ($r^2=0.61$) and Hispanic/Latino ($r^2=0.63$) populations with the previously implicated SNP (rs16926246) 5.7kb away. Therefore, after adjustment, the signal is greatly diminished but remains statistically significant ($P_{cond}=3.05x10^{-9}$). This represents the refinement of a known locus (fine-mapping), as the high LD present in this area results in an attenuated, but still statistically significant, signal, and may represent only one underlying fSNP. In contrast, we found a residual signal for PR interval at rs1895595, upstream of *TBX5* ($P_{unadj}=2.16x10^{-11}$, N=17,428, CAF=0.17). After adjustment for 5 known tagSNPs in this region (rs3825214, rs7312625, rs7135659, rs1895585, rs1896312), the signal remains largely unchanged ($P_{cond}=1.99x10^{-11}$). This secondary signal at rs1895595 is independent of all 5 conditioned SNPs, with extremely low LD ($r^2<0.03$) across all global populations, and therefore likely represents an independent fSNP. Both fine-mapping of primary findings and knowledge of independent, secondary alleles are important to comprehensively characterize GWAS loci, particularly in diverse populations, thereby improving genetic risk prediction.

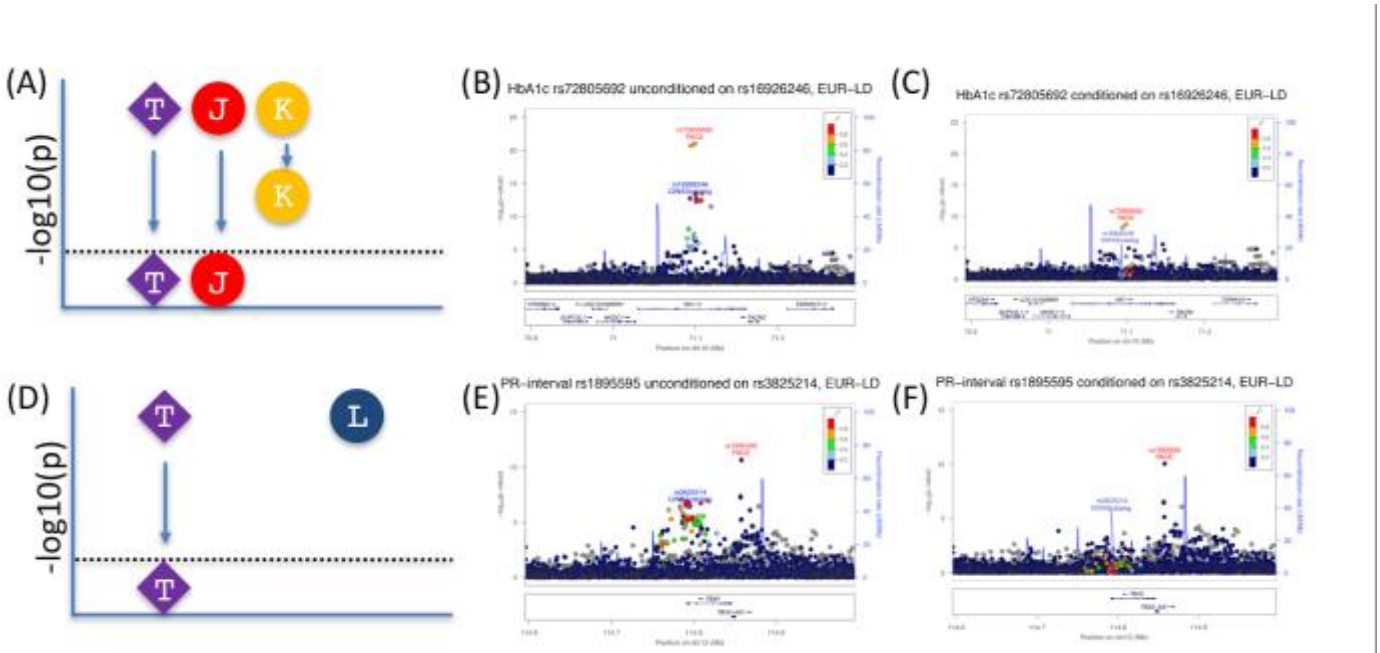

Figure 3: Residual signals can represent either refinement of signal or secondary alleles.

*(**A**) Fine-mapping: -log10 p values are plotted against position for a GWAS catalog tagSNP T, as well as two tagged SNPs: J is strongly tagged by T (r^2=1) in all populations, and K is variably tagged across populations. After adjustment, signal at T and J is no longer significant, but residual signal at K indicates that the original association has been fine-mapped. Unadjusted (**B**) and adjusted (**C**) results for trait HbA1c, showing weakened signal at residual SNP rs72805692 after adjusting for GWAS catalog tagSNP rs16926246, consistent with signal refinement. This tagSNP was first reported from a study of 46,368 Europeans[26], so LD with the tagSNP is shown from a European reference panel, illustrating how the set of strongly tagged SNPs (red/orange) is fine-mapped to the two strongest (residual) signals in the multi-ethnic population. (**D**) Secondary alleles are independent of known loci, so L is not in significant LD with T (r^2 ~ 0). After adjustment for T, signal at L is unchanged. Unadjusted (**E**) and adjusted (**F**) results for trait PR interval, showing no change in signal at residual SNP rs1895595 after adjusting for GWAS catalog tagSNP rs3825214, consistent with the residual signal being an independent secondary allele. Again, LD shown is from a European population, as the GWAS catalog report [27] was from 12,670 Europeans.*

Ancestries that Drive PAGE Findings

To tease apart the influence of specific ancestral components on the 28 novel and 42 residual loci, we calculated the correlation between the risk allele and each of the first ten PCs in the full PAGE sample (**Figure 4A**). These correlations reveal population structure underlying many of our novel and residual findings, in which there are population differences in allele frequencies for the risk alleles. Most notably, the risk allele for a novel finding for cigarettes per day among smokers on chromosome 1 (rs182996728; P=3.1x10^{-8}) was found to show significant correlation with PC4, which represents Native Hawaiian/Pacific Islander ancestry. While this variant is monomorphic or rare in most populations, it is found at 17.2% within our Native Hawaiian participants. An additional example is shown with the 5 novel and residual loci highly correlated with PC6 which are related to height and found to be at higher frequencies in 1000 Genomes within a subgroup of populations within East Asia, such as Japanese or Vietnamese. The observed variability in allele frequency for our findings will result in differential impacts across populations and must be considered when building risk prediction models. That our findings exhibit substantial variability in allele frequencies further illustrates a need for the inclusion of diverse populations disproportionately affected by disease.

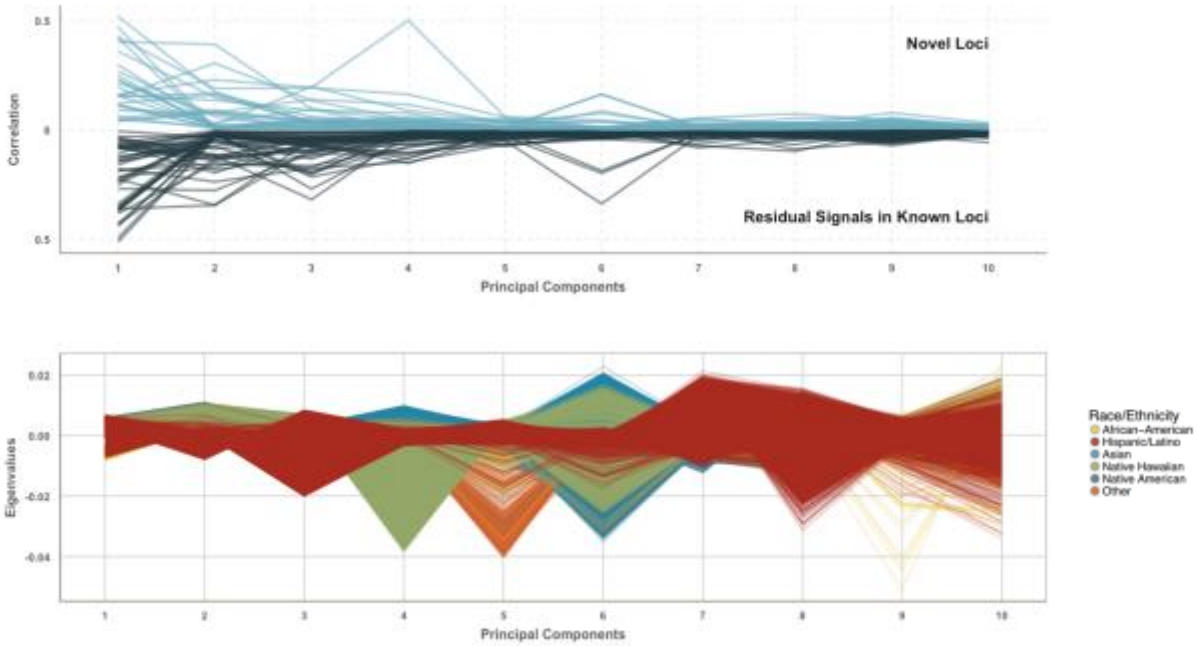

Figure 4: Correlation between SNP genotype and PC1-PC10.
A) The correlation (r^2) for each novel and residual loci calculated by obtaining the individual level data for all PAGE participants, and correlating the SNP genotype with each of the 10 PCs. The correlation for each of the 10 PCs was plotted on the y-axis, with novel loci plotted above the horizon, and residual loci plotted below. 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.

Relevance of Multi-ethnic Genetic Variation to Clinical Care

Not only has the genetic diversity of PAGE improved characterization of previously known associations and enabled the discovery of novel genetic associations, but it has also provided population-specific allele frequencies for clinically relevant variants (CRVs) that will have immediate impact on clinical care. MEGA was designed to include CRVs from well-known and frequently used knowledge bases.[19] A finding within our analyses shows an association between *HBB* (rs334) and HbA1c levels (P_{cond}=6.87x10^{-31}; N=11,178), with the majority of the association among Hispanic/Latinos (P=7.65x10^{-27}; N=10,408; Coded Allele Frequency=0.01), followed by African Americans (P=5.62x10^{-4}; N=559; CAF=0.06). The lead SNP, rs334, is a missense variant in *HBB*, which encodes the adult hemoglobin beta chain and is known for its role in sickle cell anemia. Although this association was recently reported in African Americans [28], this is the first time it has been reported in Hispanic/Latinos with admixed European, African, and Native American ancestry. Hemoglobin genetic variants are also known to affect the performance of some HbA1c assays [29–31], potentially leading practitioners to incorrectly believe that a patient has achieved glucose control. This conclusion leaves the patient more susceptible to type II diabetes (T2D) complications. Alternative long-term measures of glucose control that are not impacted by hemoglobin variants, such as the fructosamine test, should be considered for sickle cell carriers being evaluated for T2D. This result illustrates how ancestry-specific findings may be transferable to other groups that share the same genetic ancestry, such as, in this case, the African ancestry present in both African Americans and some Hispanic/Latinos.

We also investigated the *HLA-B*57:01* haplotype, which interacts with the HIV drug abacavir to trigger a potentially life-threatening immune response in 5-8% of patients. [32–34] The FDA recommends screening all patients for *HLA-B*57:01*, prior to starting abacavir treatment. [35] The rs2395029 variant in *HCP5,* a near perfect tag of *HLA-B*57:01*, is used to screen for abacavir hypersensitivity. [36] Using PAGE and Global Reference Panel samples, we show that risk allele (T) frequencies for rs2395029 rise above 5% in multiple large South Asian populations, and rise above 1% within some, but not all, admixed populations with Native American ancestry (**Figure 5**). Thus, the population attributable risk for this variant varies between continental populations and also within sub-continental regions. The allele frequencies from PAGE for clinically relevant variants, particularly polymorphisms with a medical guideline, will be available through several online databases, including ClinGen and dbSNP, to further help researchers and clinicians identify at-risk groups. PAGE allele frequencies can therefore aid in expanding the reach of precision medicine to encompass individuals of diverse ancestry.

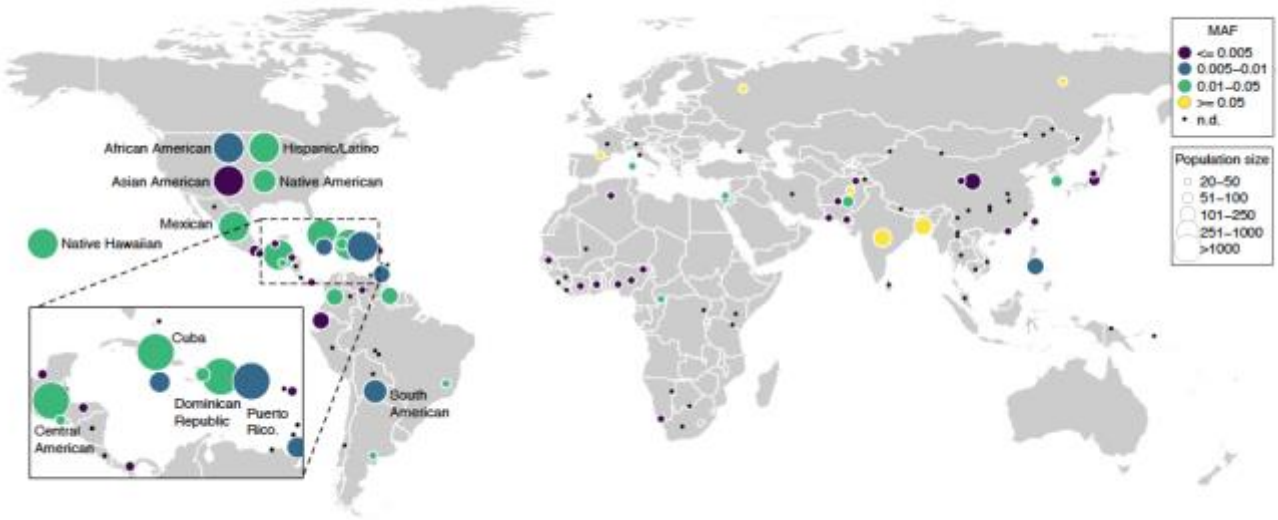

Figure 5: World map of *HLA-B*57:01* frequencies.
*The pharmacogenetic haplotype HLA-B*57:01 interacts with the HIV drug abacavir to stimulate a hypersensitivity response. A variant in a nearby gene, HCP5 rs2395029 (G allele), can be used to genotype for the star allele because it has been shown to be in linkage disequilibrium with HLA-B*57:01 [36–38]. This HCP5 SNP segregates within all continental populations of the PAGE study, providing increased resolution of the global haplotype frequency, particularly within Latin America. Above, minor allele (G) frequency is shown. Population size is indicated by the radius of the circle. Black dot (n.d.): population has less than twenty individuals or the variant is a singleton in that population.*

Discussion

Using a multi-ethnic study with the novel MEGA product and methods for analyzing admixed populations, we provide empirical evidence supporting theoretical concerns regarding the European-centric bias in GWAS. To our knowledge, this is the first time effect heterogeneity in the GWAS Catalog has formally been assessed, and the observation that a quarter of GWAS Catalog tagSNPs show evidence of effect heterogeneity by genetic ancestry has profound implications for precision medicine. Furthermore, our results suggest that a majority of GWAS catalog associations are fine-mapped in a multi-ethnic population, consistent with differential LD between tagSNP and functional variant across populations. It is imperative that clinically relevant variants are validated in diverse populations to prevent the use of imprecise genetic tags in clinical applications. Genetic tests are already being used to guide clinical decisions, and efforts to develop polygenic risk prediction models are currently underway. Researchers need to be aware of the limitations of tagSNPs that have not been replicated in non-European populations. [11]

This study also provides evidence that a significant number of novel loci (as well as independent, secondary alleles in known loci) relevant to non-European ancestries remain to be identified, many of which are undiscoverable in European-only study populations due to low allele frequencies in Europeans. Cumulatively, these results expose several shortcomings that arise from an overreliance on European GWAS.

The findings from this research demand a reevaluation of how future genetic studies are designed and implemented. As next-generation sequencing, precision medicine, and direct-to-consumer genetic testing become more common, it is critical that the genetics community takes a forward-thinking approach towards research in diverse populations. The increasing ability to identify rare variants further highlights the necessity to study genetically diverse

populations, as rare variation is more likely to be ancestry specific. 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 minorities [39]. 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 diverse [40,41], geneticists and clinicians will be required to evaluate genetic predictors of complex traits in non-Europeans. Our current genomic databases are not representative of populations with the greatest health burden or that will ultimately benefit from this work. 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. This study provides evidence and motivation to make research in diverse populations a priority in the field of genetics.

Methods

Studies. The PAGE consortium includes eligible minority participants from four studies. The Women's Health Initiative (WHI) is a long-term, prospective, multi-center cohort study investigating post-menopausal women's health in the US and recruited women from 1993-1998 at 40 centers across the US. WHI participants of European descent were excluded from this analysis. The Hispanic Community Health Study / Study of Latinos (HCHS/SOL) is a multi-center study of Hispanic/Latinos 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, CA, Chicago, IL, Bronx, NY, and Miami, FL. All SOL Hispanic/Latinos were eligible for this study. The Multiethnic Cohort (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 for MEC were included in this study. The BioMe^{TM} BioBank is managed by the Charles Bronfman Institute for Personalized Medicine at Mount Sinai Medical Center (MSMC). 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. 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. They include: White Blood Cell (WBC) count, C-Reactive Protein (CRP), Mean Corpuscular Hemoglobin Concentration (MCHC), Platelet Count (PLT), High Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), Total Cholesterol (TC), Triglycerides (TG), glycated hemoglobin (HbA1c), Fasting Insulin (FI), Fasting Glucose (FG), Type II Diabetes (T2D), Cigarettes per Day (CPD), Coffee Consumption, QT interval, QRS interval, PR interval, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Hypertension (HT), Body Mass Index (BMI), Waist-to-hip ratio (WHR), Height (HT), Chronic Kidney Disease (CKD), End-Stage Renal Disease (ESRD), and Estimated glomerular filtration rate (eGFR) by the 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 Johns Hopkins Center for Inherited Disease Research (CIDR), with 52,878 samples successfully passing CIDR's QC process. Genotyping data that passed initial quality control at CIDR were released to the Quality Assurance / Quality Control (QA/QC) analysis team at the University of Washington Genetics Coordinating Center (UWGCC). The UWGCC further cleaned the data according to previously described methods [42] , and returned genotypes for 51,520 subjects. A total of 1,705,969 SNPs were genotyped on the MEGA. Quality Control of genotyped variants was completed by filtered through various criteria, including the exclusion of (1) CIDR technical filters, (2) variants with missing call rate >= 2%, (3) variants with more than 6 discordant calls in 988 study duplicates, (4) variants with greater than 1 Mendelian errors in 282 trios and 1439 duos, (5) variants with a Hardy-Weinberg p-value less than $1x10^{-4}$, (6) SNPs with sex difference in allele frequency >= 0.2 for autosomes/XY, (7) SNPs with sex difference in heterozygosity > 0.3 for autosomes/XY, (8) positional duplicates. Sites were further restricted to chromosomes 1-22, X, or XY, and only variants with available strand information. After SNP QC, a total of 1,402,653 MEGA variants remained for further analyses.

Imputation. In order 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 [43]. Imputation was conducted at the University of Washington Genetic Analysis Center (GAC). Genotype data which passed the above quality control filters was phased with SHAPEIT2 [44] and imputed to 1000 Genomes Phase 3 reference data using IMPUTE version 2.3.2 [45]. Segments of the genome which were known to harbor gross chromosomal anomalies were filtered out of the final genotype probabilities files. Imputed sites were excluded if the IMPUTE info score was less than 0.4. A total of 39,723,562 imputed SNPs passed quality control measures. (See Supplemental Methods)

Principal Component Analysis. The selection of unrelated individuals was essential for accurate estimation of the principal components within the global study population. Kinship coefficients were estimated using PC-Relate, as implemented in the R package GENESIS [20,21]. The *SNPRelate* [46] package was implemented in R for principal components

analysis. The relevant principal components (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 within with self-identified racial/ethnic clusters. A parallel coordinate plots for the first 10 PCs was generated, where 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 info score >0.4 (n=39,723,562) were eligible for association testing in phenotype-specific models. An effective sample size (effN) was calculated for each SNP in a given phenotype-specific model, where effN = 2*MAF*(1-MAF)*N*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 SNP's IMPUTE info score. Variants with an effN less than 30 (continuous phenotypes) or 50 (binary phenotypes), were excluded from the final set of phenotype-specific results. QQ plots and $lambda_{GC}$ were used to assess genomic inflation in all phenotypes, for which lambdas 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 program [22] 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 principal component analysis 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 principal component eigenvectors, it provides robust estimates of kinship coefficients and identity-by-descent (IBD) sharing probabilities in samples with population structure, admixture, and HWE departures. It does not require additional reference population panels or prior specification of the number of ancestral subpopulations.

The SUGEN program [23] is a command-line software program developed for genetic association analysis under complex survey sampling and relatedness patterns. It implements the generalized estimating equation (GEE) method, which does not require modeling 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 analyzing 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 Extended Data Fig. 5.

Conditional Analyses. Phenotype-specific lists of previously identified "known loci" were hand-curated for each phenotype and included SNPs indexed in the GWAS Catalog or identified through non-GWAS high-throughput methods (e.g. Metabochip, Exomechip, Immunochip, etc.). The full known loci lists for each phenotype are available in the Supplementary Table 5. Conditional analyses were conducted for all phenotypes by conditioning on all previously identified known loci on a given chromosome. P-values estimated in conditional analyses are denoted by "P_{cond}" in the main text, with the SUGEN conditional results for all novel and residual findings in Supplementary Table 3.

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 (SNPxPC) interaction terms for all 10 PCs. The fit of nested models was compared using the F-statistic, where the associated interaction p-value indicated whether the inclusion of the 10 SNPxPC interaction terms improved the model fit compared to a model that lacked the interaction terms. The overall SNPxPC interaction p-values evaluated whether the additional variance explained by variant x genetic ancestry interactions was statistically significant, and represent effect modification driven by genetic ancestry. Interaction p-values for all novel and residual findings are included in Supplementary Table 3.

For comparison against more traditional (stratified) analysis strategies, all analyses were also run stratified by self-identified race/ethnicity. A minor allele count of at least 5 was required for a stratified model to be run within an ethnic group. The stratified analyses were then meta-analyzed using a fixed-effect model implemented in METAL[47]. I^2 and chi^2 heterogeneity p-values were estimated for all meta-analyzed results, and represent effect size heterogeneity driven by self-identified race/ethnicity. The race/ethnicity-specific results, I^2, and chi^2 heterogeneity p-values for all novel and

residual findings are included in Supplementary Table 3.

Assessing Single-Variant Results. SUGEN association results were used for the identification of novel and residual findings for all phenotypes. The variant with the smallest p-value in a 1Mb region was considered the "lead SNP". A lead SNP was considered to be a novel loci if it met the following criteria: 1) the lead SNP was located greater than +/- 500 Kb away from a previously known loci (per the phenotype-specific known loci list); 2) had a SUGEN p-value less than $5x10^{-8}$; 3) had a SUGEN conditional p-value less than $5x10^{-8}$ after adjustment for all previously known loci on the same chromosome; and 4) had 2 or more neighboring SNPs (within +/- 500 Kb) with a p-value less than $1x10^{-5}$. A lead SNP was considered to be a residual 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-value less than $5x10^{-8}$; and 3) had a SUGEN conditional p-value less than $5x10^{-8}$ after adjustment for all previously known loci on the same chromosome. Full results for all novel and residual findings are included in Supplementary Table 2-3.

GWAS Catalog Heterogeneity. The full GWAS Catalog database was downloaded on December 31, 2016. The data were filtered to identify results relevant to any of the 26 PAGE phenotypes, producing a subset of 3,322 unique tagSNPs that were genome-wide significant ($p<5x10^{-8}$) in the GWAS Catalog. The PAGE results for each of the 3,322 GWAS Catalog tagSNPs was examined to first identify the subset of tagSNPs that replicated ($p<5x10^{-8}$) in PAGE unconditioned models (n=574). Pairs of tagSNPs within 500,000 base pairs of each other were merged into loci, yielding 302 unique associated loci. Of the GWAS Catalog tagSNPs that were replicated in PAGE, SNPs that had a Bonferroni corrected SNPxPC interaction heterogeneity p-value ($p < 8.71x10^{-5}$, 0.05/574) were considered to have evidence of effect size heterogeneity (132/574, 23.0%). Effect heterogeneity was also assessed using PAGE's multi-ethnic study population 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 SNPxPC interaction heterogeneity p-value ($P<1.5x10^{-4}$, 0.05/333).

Allele frequency estimation. Population labels were compiled from self-identified ancestry information from the PAGE-wide sample manifest, as well as self-reported country of origin metadata from the Mount Sinai BioMe cohort. Allele frequencies were calculated in PLINK 1.90, and results were visualized in R using the ggplot2.

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(http://www.cephb.fr/en/hgdp_panel.php), or originally at http://www.ncbi.nlm.nih.gov/pubmed/11954565 and http://www.ncbi.nlm.nih.gov/pubmed/12493913, with numerous subsequent publications. Samples were filtered to include the H952 unrelated individuals as published here: http://www.ncbi.nlm.nih.gov/pubmed/17044859. Also available on the Bustamante Lab website is genotype data for the Maasai from Kinyawa, Kenya (MKK) samples maintained by the Coriell Institute for Medical Research (https://catalog.coriell.org/1/NHGRI/Collections/HapMap-Collections/Maasai-in-Kinyawa-Kenya-MKK) and genotyped as part of the International HapMap Project Phase 3(http://hapmap.ncbi.nlm.nih.gov/, http://www.sanger.ac.uk/resources/downloads/human/hapmap3.html) . We have genotyped a subset of unrelated individuals using the filters recommended in http://www.ncbi.nlm.nih.gov/pubmed/20869033.

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Author Information

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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 will also be available through ClinGen.

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	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]**	**Residual 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	5
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	3
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	2	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	28	42

Table 1: GWAS Catalog heterogeneity by Trait, including number of novel and residual findings.

[1] Only includes studies indexed in the GWAS Catalog on December 31, 2016
[2] Cases/Controls
[3] Includes pooled and sex-stratified studies / results
[4] $P<8.71 \times 10^{-5}$ for genotype:PC interaction in PAGE, adjusting for multiple tests (0.05/574)
[5] $P<1.50 \times 10^{-4}$ for genotype:PC interaction 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