Received: 22 June 2017 | Revised: 15 January 2018 | Accepted: 14 March 2018

DOI: 10.1111/ahg.12251

ORIGINAL ARTICLE

WILEY Annals of human genetics

Transethnic differences in GWAS signals: A simulation study

Daniela Zanetti[1,2] | Michael E. Weale[3]

[1]Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, CA, USA

[2]Department of Animal Biology-Anthropology, University of Barcelona, Barcelona, Spain

[3]Department of Medical & Molecular Genetics, King's College London, London, UK

Correspondence
M. E. Weale, Genomics plc, Oxford OX1 1JD, UK.
Email: m.weale@gmail.com

Funding information
Regione Autonoma della Sardegna (Master and Back Grant)

Abstract

Genome-wide association studies (GWASs) have allowed researchers to identify thousands of single nucleotide polymorphisms (SNPs) and other variants associated with particular complex traits. Previous studies have reported differences in the strength and even the direction of GWAS signals across different populations. These differences could be due to a combination of (1) lack of power, (2) allele frequency differences, (3) linkage disequilibrium (LD) differences, and (4) true differences in causal variant effect sizes.

To determine whether properties (1)–(3) on their own might be sufficient to explain the patterns previously noted in strong GWAS signals, we simulated case–control data of European, Asian and African ancestry, applying realistic allele frequencies and LD from 1000 Genomes data but enforcing equal causal effect sizes across populations. Much of the observed differences in strong GWAS signals could indeed be accounted for by allele frequency and LD differences, enhanced by the Euro-centric SNP bias and lower SNP coverage found in older GWAS panels. While we cannot rule out a role for true transethnic effect size differences, our results suggest that strong causal effects may be largely shared among human populations, motivating the use of transethnic data for fine-mapping.

KEYWORDS

Causal SNP, complex human diseases, genome-wide association studies, transethnic differences

1 | INTRODUCTION

In the past decade, through collaborative efforts and with the aid of genome-wide association studies (GWASs), the genetic basis of common complex traits has been greatly clarified (for examples, see Berndt et al., 2013; Lee et al., 2017; Morris et al., 2012; Nikpay et al., 2015; Scott et al., 2012; Timofeeva et al., 2012). Most GWASs have involved individuals of European origin [96% of all subjects according to one review (Bustamante, Burchard, & De la Vega, 2011)], but this picture is changing with increasing efforts to conduct GWASs in Asia (especially China) and Africa. Such studies are important because they allow us to redress the Euro-centric bias in GWASs and to assess whether signals found in European populations are replicable in other human populations. Transethnic replicability of GWAS signals would imply a common etiology of complex diseases, and this would have important clinical implications (Marigorta & Navarro, 2013; Visscher, Brown, McCarthy, & Yang, 2012). The portability of GWAS results would also allow for "transethnic fine-mapping" to help in the post-GWAS localization of the causal locus, by taking advantage of between-population differences in linkage disequilibrium (LD) (Rosenberg et al., 2010; Li & Keating, 2014). Conversely, a lack of transethnic replicability, if shown to be linked to true differences in causal risk allele effect sizes, would have implications for the use of genetics in complex disease medicine, both in terms of the portability of polygenic prediction algorithms among populations and in terms of the biological interpretation of GWAS signals, as some degree of population-specific genetic disease etiology would be implied.

A number of studies have compared genetic association signals across different continental populations. These have found some examples where the observed genetic effects show

consistency across ancestral groups, either in terms of effect direction or in the magnitude of the effect (Kantor et al., 2013; Marigorta & Navarro, 2013; Morris et al., 2016; N'Diaye et al., 2011; Tan et al., 2010; DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium et al., 2014), and other examples where GWAS-derived signals point to a pattern of population-specific risk effects (Wojczynski et al., 2013; Xue et al., 2013), or to a different magnitude in the association signal across populations (Thomas et al., 2012; Waters et al., 2010). More recently, Brown et al. (2016) used an infinitesimal model (which assumes all SNPs contribute to some extent to heritability) to compare transethnic GWAS datasets and presented good evidence for true differences in effect sizes between populations. From a detailed analysis of an eQTL dataset, the authors also suggested that true transethnic differences may be larger for weak genetic effects, and smaller for strong genetic effects. It is, therefore, of interest to establish to what extent signals at the top end of the effect size distribution (i.e., traditional GWAS hits) are affected by transethnic differences, and this is the question addressed in this study.

In a previous study focusing on GWAS hits, Ntzani et al. (2012) used the catalog of published GWASs previously maintained by the National Human Genome Research Institute (NHGRI), and currently maintained by the European Bioinformatics Institute (EBI) (Welter et al., 2014), to characterize the frequency and magnitude of between-population differences seen in replication studies of GWAS signals (effect sizes from replication studies were used to minimize the "Winner's Curse" bias in discovery GWAS signals). A total of 97 associations were evaluated in both European and Asian populations, 24 in both European and African populations, and 13 in all three groups. They found widespread differences in the frequency of risk alleles between Europeans, Asians, and Africans, with absolute differences >10% in 75% to 89% of the three pairwise comparisons, and they also found differences in reported risk allele effect sizes. Indeed, point estimates of effect size were opposite in direction in 18%, 21%, and 38% in the European–Asian, European–African, and Asian–African comparisons, respectively.

The transethnic differences in genetic risk effects catalogued by Ntzani et al. could be due to one or a combination of the following explanations:

(1) Between-population genetic architectures (for both risk allele *frequency* and *effect size*) are the same, but differences in power (say due to low sample sizes) prevent detection in other populations;

(2) The genetic *effect size* architectures are the same, but differences in risk allele frequency prevent detection in other populations (*in extremis*, the risk allele frequency could even be zero in a given population);

(3) The genetic *effect size* architectures are the same, but differences in LD patterns prevent detection in other populations (in cases where the "lead" or most significantly associated SNP is not the truly causal SNP); and

(4) The genetic *effect size* architectures are different—in other words, the causal SNP has a different true genetic effect size in different populations.

Note that this categorization requires one to distinguish effect size differences from allele frequency differences, and this requires one to define a frequency-independent measure of effect size. Here, we use genotypic relative risk as our measure of frequency-independent effect size, and we will restrict our simulations to diseases of low prevalence (1% in all simulations) in order to take advantage of the approximate equivalence between relative risk and odds ratios in this scenario.

Biologically, the most interesting explanation is point (4) above, as this implies there are truly different genetic risk architectures among populations. However, the relative importance of points (1)–(3) is also of interest and, in particular, point (3) is the basis for transethnic fine-mapping. It is typically not possible to distinguish between the four possible explanations based on real replications of GWASs [as in the study by Ntzani et al. (2012)]. Therefore, in the present work, we employed simulations to assess the relative importance of the four explanations listed above for generating transethnic differences in GWAS signals. We generated simulated genomic data in case–control samples of European, Asian, and sub-Saharan African origin. Random loci (SNPs) in the genome were selected to be "truly causal," and we applied equal disease-risk model parameters across the three population groups. Logistic regression analyses and statistical comparisons across the different continental populations were then performed to evaluate the level of consistency across groups, potential differences in allele frequency, and consequently the degree to which points (1)–(3) above, in the absence of point (4), could explain observed transethnic differences in GWAS signals.

2 | MATERIALS AND METHODS

To mimic a replication study following a GWAS [and thus mimic the effect sizes examined by Ntzani et al. (2012)], phased haplotypes from the 1000 Genomes Phase 1 dataset (1000 Genomes Project Consortium et al., 2012) were used as input to simulate case–control genotype data. Utah residents (from the Centre d'Etude du Polymorphisme Humain (CEPH) collection) with Northern and Western European ancestry ("CEU", $n = 85$), Finns from Finland ("FIN", $n = 93$), British samples from England and Scotland ("GBR", $n = 89$), Iberians from Spain ("IBS", $n = 14$), and Tuscans from Italy ("TSI", $n = 98$) were used as input to simulate European

samples ("EUR", $n = 379$). Han Chinese from Beijing, China ("CHB", $n = 97$); Han Chinese South ("CHS", $n = 100$); and Japanese from Tokyo, Japan ("JPT", $n = 89$) were used to simulate Asian samples ("ASN", $n = 286$). Finally, Yorubans from Ibadan, Nigeria ("YRI", $n = 88$) were used to simulate West African samples (only one population, YRI, was used for an African grouping, in recognition of the high degree of genetic heterogeneity among different African samples, making a pan-African "AFR" grouping of little relevance in simulating a typical GWAS). Simulated datasets were generated from SNPs with a global minor allele frequency (MAF) > 1% (as calculated using all samples in the 1000 Genomes Phase 1 dataset). VCFtools (Danecek et al., 2011) and Beagle (Browning & Browning, 2007) software were used to extract and transform 1000 Genomes phased data into a format suitable for GWAsimulator.

Simulations were performed via the GWAsimulator software version 2.1 (Li & Li, 2008). This program implements a moving-window algorithm to simulate case–control genotype data based on a set of phased input data. It works outwards from the nominated disease locus to generate the case and control datasets, with patterns of LD similar to the input data. A window size of 5 was used for our simulations, meaning that a haplotype of 4 SNPs was used to propose the allele of the next adjacent SNP.

To mimic a Euro-centric bias in the GWAS study forming the basis for this simulated replication study, a "true" causal disease locus was selected at random for each simulation run from the set of all autosomal SNPs in the 1000 Genomes Project Phase 1 dataset with a MAF > 5% specifically in the EUR grouping. The Genotypic Relative Risk (GRR) for this locus was set at 1.3, with a multiplicative effect, setting the alternative (nonreference) allele as the risk allele. This value was chosen to be close to the mean reported GRR of the European case–control replication studies examined by Ntzani et al. (2012) (their Supplementary Table 3, mean GRR = 1.28). Genomic regions of 500 kb were simulated, 250 kb upstream and downstream of the randomly selected disease locus. For each simulation run, 2,000 cases and 2,000 controls were created with a disease prevalence of 1%. Logistic regression analyses were performed on the simulated data from the three continental groups (EUR, ASN, and YRI), using Plink software version 1.07 (Purcell et al., 2007).

Following Ntzani et al. (2012), the following metrics were used to assess apparent transethnic differences in our simulated replications of GWAS signals among the three populations. Firstly, the Z-score, described previously by Ioannidis, Ntzani, Trikalinos, and Contopoulos-Ioannidis (2001) and by Cappelleri et al. (1996), measures the difference in estimated log-odds-ratios between the two populations divided by the estimated standard error of the difference. A "Z-score" flag was set "on" (value = 1) if the Z-score was nominally significant at the 5% level (abs(Z) > 1.96), and set "off" otherwise (value = 0). Secondly, an "opposite direction" flag was set "on" (value = 1) if the odds ratios deviated from 1 in different directions (value = 0 otherwise). Finally, a "twofold difference in same direction" flag was set "on" (value = 1) if the odds ratios were in the same direction but differed by more than twofold between the two populations (measured by their relative distance from one, after orienting both to be greater than one).

We assessed transethnic GWAS signal differences under the following "target SNP" scenarios:

(1) *Causal SNP* scenario: the causal disease SNP is assumed to be known, and so is assessed directly (mimicking replication studies following a highly powered European GWAS);

(2) *Lead SNP* scenario: The causal disease SNP is assumed not known, but the genotypes of all common SNPs are assumed known (mimicking a high-density genotyping panel, along with accurate imputation). The European lead SNP (with the lowest *P*-value in EUR) is assessed as the target SNP (mimicking a situation where the European GWAS was performed first and the European replication study contributed to identification of the lead SNP, perhaps through combined meta-analysis and fine-mapping);

(3) *Lead SNP in OmniExpress array* scenario: Imputation is not performed (mimicking an earlier GWAS study, or a study for which imputation is deemed unreliable). The European lead SNP is defined based on SNPs present on a representative medium-coverage GWAS panel (here, the Illumina Human OmniExpress Bead Chip array), and this SNP is taken forwards for assessment as the target SNP.

3 | RESULTS

A total of 1,000 simulation runs, generating case–control genotype data in populations of European, Asian, and sub-Saharan African origin, were performed in this study. Logistic associations and transethnic replications of GWAS signal comparisons were carried out on eligible simulated datasets as described below.

3.1 | Eligible simulations and allele frequencies

The Euro-centric nature of our simulations ensured that the causal SNP was polymorphic in Europeans (MAF > 1%), and this further ensured that the target SNP (in scenarios where the target SNP was not the causal SNP) was also polymorphic in Europeans. In order to allow calculation of the transethnic difference metrics devised by Ntzani et al. (2012), simulations containing monomorphic target SNPs in one of the other populations (Asians or sub-Saharan Africans) were not

TABLE 1 Eligible simulations and mean target SNP allele frequencies

	Eligible simulations/mean allele frequency (± standard deviation)			
Target SNP scenario	**N**	**EUR**	**ASN**	**AFR**
Causal SNPs	850	0.35 ± 0.24	0.36 ± 0.28	0.35 ± 0.27
Lead SNPs	799	0.39 ± 0.23	0.40 ± 0.28	0.38 ± 0.28
Lead SNPs in OmniExpress array	777	0.39 ± 0.24	0.41 ± 0.28	0.38 ± 0.27

considered eligible and were discarded. We note that simulations where the causal SNP was monomorphic in Asians or sub-Saharan Africans were permitted, provided the target SNP was polymorphic. The number of eligible simulations varied from 777 to 850 according to the target SNP scenario considered. The allele frequencies of the simulated causal SNP across the eligible simulations showed a similar average frequency in the three populations groups (Table 1). Logistic association results and allele frequencies are included in Supplementary Tables 1–3.

3.2 | Transethnic differences in GWAS signals

Table 2 summarizes the rate at which notable transethnic differences were generated in our simulation study, compared to the rates seen in the study by Ntzani et al. (2012). The "Z-score" and "opposite direction" rates are expressed as a percentage of all non-null comparisons: the "twofold difference" rates are expressed as a percentage of all same-direction comparisons.

There are some striking differences in the rate at which between-population differences were generated in our simulation study compared to those observed in the Ntzani et al. (2012) study. The rates of notable differences detected in our simulations are highly dependent on the scenario considered, and thus each scenario needs to be considered separately.

The *casual SNP* scenario shows similar effects across all ancestry pairs, and overall generates a low rate of between-population differences. Indeed, the rate of Z-score hits is consistent with that expected under the null (5%), suggesting that between-population allele frequency differences at the true causal SNP itself are insufficient on their own to generate unusual between-population differences in estimated effect sizes.

The *lead SNP* scenario results in a noticeable increase in the rate of between-population differences. We interpret this increase to be the result of the Euro-centric SNP selection process, coupled with between-population differences in LD patterns between the causal SNP and the lead SNP. However, the simulated rate of between-population differences is still considerably lower than that observed in the Ntzani et al. (2012) study, indicating that this scenario cannot on its own explain the observed results.

The *lead SNPs in OmniExpress array* scenario generates a further notable increase in the rate of between-population differences. This is sufficient to explain, in principle, the rate of observed EUR-ASN "Z-score" and "opposite direction" flags seen in the Ntzani et al. (2012) study, and much but not all of the EUR-YRI and ASN-YRI differences. However, some rates observed in the Ntzani et al. study are too large to be explained by any of our simulations.

4 | DISCUSSION

The purpose of our study was to establish whether a simple constant-effect-size model was sufficient to explain transethnic differences in strong GWAS "hits," as previously reported by Ntzani et al. (2012). We found that such a model was remarkably successful at explaining the majority of these transethnic differences, once panel design and uncertainty in causal SNP location are taken into account. If causal SNPs are known (*causal SNP* scenario), no transethnic differences are found in our simulations beyond those expected by chance. However, once uncertainty in causal SNP location is introduced (*lead SNP* scenario), this uncertainty is sufficient to induce an appreciable increase in the rate of apparent

TABLE 2 Percentage of simulations showing notable differences in effect size and/or direction of effect across populations and Ntzani et al. results

	EUR-ASN			EUR-AFR			ASN-AFR		
Reference SNPs	**Z-scores**	**Opp. Dir.**	**2-fold diff.**	**Z-scores**	**Opp. Dir.**	**2-fold diff.**	**Z-scores**	**Opp. Dir.**	**2-fold diff.**
Causal SNPs	4.82	1.29	12.40	4.71	0.94	11.52	5.18	2.24	13.96
Lead SNPs	16.67	8.52	18.08	19.77	9.14	21.63	10.40	10.64	23.95
Lead SNPs in OmniExpress array	29.21	30.12	42.73	33.46	29.47	46.90	7.72	32.82	46.17
Ntzani results	21.65	17.53	38.75	41.67	20.83	57.89	23.08	38.46	50.00

transethnic differences, even though there are no true effect size differences in our simulations. When this uncertainty is enhanced still further, by introducing older reduced-coverage GWAS panels (*lead SNPs in OmniExpress array* scenario), this further increases the rate of apparent transethnic differences, to a level where these effects on their own are enough to explain much of the transethnic GWAS data reviewed by Ntzani et al. (2012).

Some discrepancies remain unexplained, however, and these were found across all three population comparisons and using all three transethnic difference metrics. These point to a need for more complex models to fully explain the data. Our model was deliberately simplistic and was not intended to reflect reality even if it had been found to be completely sufficient. Rather, our intention was to determine the extent to which more complex models are needed in order to explain these data. Below, we consider some of the ways in which our model could be extended.

First, our model assumed a fixed strong effect size at the simulated causal locus (Genotypic Relative Risk of 1.3). This is because we were interested in explaining the transethnic patterns of early GWAS "hits" results from moderately sized datasets, as collated by Ntzani et al. (2012). Our simulated effect size was chosen to be close to the mean of the effect sizes reported in replication studies for these hits [Supplementary Table 3 of Ntzani et al. (2012)]. An extension of our work would be to consider a range of effect sizes consistent with the samples sizes and reported replication effect sizes of these earlier GWAS studies. We note that the "twofold difference" measure is particularly sensitive to the value of the true causal effect size.

Second, we could expand the remit of our study to consider weaker effect sizes, for example by exploring transethnic patterns not just of the strong GWAS "hits" reported by Ntzani et al. (2012) but also the patterns found in complete GWAS summary statistic datasets. We note that weak causal effects may display more transethnic variability than strong ones, as has been proposed by Brown et al. (2016) based on the properties of genome-wide eQTL summary statistic data.

Third, current Euro-centric GWAS arrays might create bias in imputation quality between populations. These biases might generate heterogeneity in association signals between populations, especially when non-European populations are considered. Our model could be extended to consider such issues.

Fourth, we used metrics of between-population differences in effect size, built on Genotypic Relative Risk, that were previously devised by Ntzani et al. (2012), but these are relatively simple ad hoc pair-wise metrics, and other approaches could be considered (e.g., heterogeneity among all three populations could be assayed via Cochran's Q and I^2 statistics). We note that Genotypic Relative Risk is a widely used measure of genetic risk, but it depends on an implicit assumption that effect size is independent of allele frequency and this may not be true. One limitation of these metrics is that the variant being tested must be polymorphic in the populations being compared.

Finally, our model could be extended to explicitly model transethnic differences in effect size. We note that gene–environment interactions could provide one framework for such differences (in other words, variable environmental factors among populations could induce variable effect sizes). Another interesting avenue would be to explicitly model the selection and evolution of causal alleles over time, in the context of known demographic factors such as the ancestral nature of the African population, and the Out-of-Africa bottlenecks experienced by the European and East Asian populations.

Notwithstanding the simplicity of our model, our simulations reveal the considerable effect that uncertainty in causal SNP location and LD differences has on observed transethnic signal differences, especially when older panels are used. These effects are large enough to potentially explain, on their own, much of the observed transethnic pattern of differences in strong GWAS "hits." We, therefore, make two predictions based on our study. First, we predict that the observed between-population differences in effect size will decrease as bigger GWAS studies, with more dense panels and with better imputation, are applied. Second, we predict that transethnic mapping will prove to be a viable method for fine-mapping, given that there is a case for strong causal effect sizes being largely shared between populations, and given the considerable impact that between-population differences in LD have on tag-SNP effect sizes.

ACKNOWLEDGEMENTS

Declaration of personal interests: MEW is an employee of Genomics plc, a company providing genomic analysis services to the pharmaceutical and healthcare sectors. His involvement in the conduct of this research was solely in his capacity as a Reader in Statistical Genetics at King's College London.

Declaration of funding interests: DZ was supported by the Master and Back Grant (Regione Autonoma della Sardegna).

AUTHORSHIP

Author contributions: DZ, MEW: design of the study; DZ, MEW: analysis and interpretation of data; DZ: drafting the manuscript; MEW: critical revision of the manuscript; DZ, MEW: final approval of the version to be published.

ORCID

Daniela Zanetti http://orcid.org/0000-0002-1225-1021
Michael E. Weale http://orcid.org/0000-0003-4593-1186

REFERENCES

1000 Genomes Project Consortium, Abecasis, G. R., Auton, A., Brooks, L. D., DePristo, M. A., Durbin R. M., … McVean, G. A. (2012). An integrated map of genetic variation from 1,092 human genomes. *Nature*, *491*, 56–65. https://doi.org/10.1038/nature11632

Berndt, S. I., Gustafsson, S., Mägi, R., Ganna, A., Wheeler, E., Feitosa, M. F., … Ingelsson, E. (2013). Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. *Nature Genetics*, *45*(5), 501–512. https://doi.org/10.1038/ng.2606

Brown, B. C., Asian Genetic Epidemiology Network Type 2 Diabetes Consortium, Ye, C. J., Price, A. L., & Zaitlen, N. (2016). Transethnic genetic-correlation estimates from summary statistics. *American Journal of Human Genetics*, *99*(1), 76–88. https://doi.org/10.1016/j.ajhg.2016.05.001

Browning, S. R., & Browning, B. L. (2007). Rapid and accurate haplotype phasing and missing-data inference for whole-genome association studies by use of localized haplotype clustering. *American Journal of Human Genetics*, *81*, 1084–1097. https://doi.org/10.1086/521987

Bustamante, C. D., Burchard, E. G., & De la Vega, F. M. (2011). Genomics for the world. *Nature*, *475*, 163–165. https://doi.org/10.1038/475163a

Cappelleri, J. C., Ioannidis, J. P., Schmid, C. H., de Ferranti, S. D., Aubert, M., Chalmers, T. C., & Lau, J. (1996). Large trials vs meta-analysis of smaller trials: How do their results compare? *JAMA 23–30*, *276*(16), 1332–1338. https://doi.org/10.1001/jama.1996.03540160054033

Danecek, P., Auton, A., Abecasis, G, Albers, C. A., Banks, E., DePristo, M. A., … 1000 Genomes Project Analysis Group. (2011). The variant call format and VCFtools. *Bioinformatics*, *27*, 2156–2158. https://doi.org/10.1093/bioinformatics/xbtr330

DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium, Asian Genetic Epidemiology Network Type 2 Diabetes (AGEN-T2D) Consortium, South Asian Type 2 Diabetes (SAT2D) Consortium, Mexican American Type 2 Diabetes (MAT2D) Consortium, Type 2 Diabetes Genetic Exploration by Nex-generation sequencing in multi-Ethnic Samples (T2D-GENES) Consortium, Mahajan, A., … Morris, A. P. (2014). Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. *Nature Genetics*, *46*(3), 234–244. https://doi.org/10.1038/ng.2897

Ioannidis, J. P., Ntzani, E. E., Trikalinos, T. A., & Contopoulos-Ioannidis, D. G. (2001). Replication validity of genetic association studies. *Nature Genetics*, *29*(3), 306–309. https://doi.org/10.1038/ng749

Kantor, D. B., Palmer, C. D., Young, T. R., Meng, Y., Gajdos, Z. K., Lyon, H., … Hirschhorn, J. N. (2013). Replication and fine mapping of asthma-associated loci in individuals of African ancestry. *Human Genetics*, *132*, 1039–1047. https://doi.org/10.1007/s00439-013-1310-7

Lee, J. C., Biasci, D., Roberts, R., Gearry, R. B., Mansfield, J. C., Ahmad, T., … Smith, K. G. (2017). Genome-wide association study identifies distinct genetic contributions to prognosis and susceptibility in Crohn's disease. *Nature Genetics*, *49*, 262–268. https://doi.org/10.1038/ng.3755

Li, C., & Li, M. (2008). GWAsimulator: A rapid whole-genome simulation program. *Bioinformatics*, *24*, 140–142. https://doi.org/10.1093/bioinformatics/btm549

Li, Y. R., & Keating, B. J. (2014). Trans-ethnic genome-wide association studies: Advantages and challenges of mapping in diverse populations. *Genome Medicine*, *6*(10), 91. https://https://doi.org/10.1186/s13073-014-0091-5

Marigorta, U. M., & Navarro, A. (2013). High trans-ethnic replicability of GWAS results implies common causal variants. *PLoS Genetics*, *9*(6), e1003566. https://doi.org/10.1371/journal.pgen.1003566

Morris, A. P., Voight, B. F., Teslovich, T. M., Ferreira, T., Segrè, A. V., Steinthorsdottir, V., … DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium. (2012). Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nature Genetics*, *44*, 981–990. https://doi.org/10.1038/ng.2383

Morris, D. L., Sheng, Y., Zang, Y., Wang, Y. F., Zhu, Z., Tombleson, P., … Vyse, T. J. (2016). Genome-wide association meta-analysis in Chinese and European individuals identifies ten new loci associated with systemic lupus erythematosus. *Nature Genetics*, *48*(8), 940–946. https://doi.org/10.1038/ng.3603

N'Diaye, A., Chen, G. K., Palmer, C. D., Ge, B., Tayo, B., Mathias, R. A., … Haiman, C. A. (2011). Identification, replication, and fine-mapping of loci associated with adult height in individuals of African ancestry. *PLoS Genetics*, *7*(10), e1002298. https://doi.org/10.1371/journal.pgen.1002298

Nikpay, M., Goel, A., Won, H. H., Hall, L. M., Willenborg, C., Kanoni, S., ... Farrall, M. (2015). A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nature Genetics*, *47*, 1121–1130. https://doi.org/10.1038/ng.3396

Ntzani, E. E., Liberopoulos, G., Manolio, T a, & Ioannidis, J. P. (2012). Consistency of genome-wide associations across major ancestral groups. *Human Genetics*, *131*, 1057–1071. https://doi.org/10.1007/s00439-011-1124-4

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A., Bender, D., … Sham, P. C. (2007). PLINK: A tool set for whole-genome association and population-based linkage analyses. *American Journal of Human Genetics*, *81*, 559–575. https://doi.org/10.1086/519795

Rosenberg, N. A., Huang, L., Jewett, E. M., Szpiech, Z. A., Jankovic, I., & Boehnke, M. (2010). Genome-wide association studies in diverse populations. *Nature Reviews Genetics*, *11*, 356–366. https://doi.org/10.1038/nrg2760

Scott, R. A., Lagou, V., Welch, R. P., Wheeler, E., Montasser, M. E., Luan, J., … Barroso, I. (2012). Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. *Nature Genetics*, *449*, 991–1005. https://doi.org/10.1038/ng.2385

Tan, J. T., Ng, D. P. K., Nurbaya, S., Ye, S., Lim, X. L., Leong, H., … Tai, E. S. (2010). Polymorphisms identified through genome-wide association studies and their associations with type 2 diabetes in Chinese, Malays, and Asian-Indians in Singapore. *Journal of Clinical Endocrinology and Metabolism*, *95*, 390–397. https://doi.org/10.1210/jc.2009-0688

Thomas, R., Thio, C. L., Apps, R., Qi, Y., Gao, X., Marti, D., … Carrington, M. (2012). A novel variant marking HLA-DP expression levels

predicts recovery from hepatitis B virus infection. *Journal of Virology*, *86*, 6979–6985. https://doi.org/10.1128/JVI.00406-12

Timofeeva, M. N., Hung, R. J., Rafnar, T., Christiani, D. C., Field, J. K., Bickeböller, H., … Transdisciplinary Research in Cancer of the Lung (TRICL) Research Team. et al. (2012). Influence of common genetic variation on lung cancer risk: Meta-analysis of 14 900 cases and 29 485 controls. *Human Molecular Genetics*, *21*(22), 4980–4995. https://doi.org/10.1093/hmg/dds334

Visscher, P. M., Brown, M. A., McCarthy, M. I., & Yang, J. (2012). Five years of GWAS discovery. *American Journal of Human Genetics*, *90*, 7–24. https://doi.org/10.1016/j.ajhg.2011.11.029

Waters, K. M., Stram, D. O., Hassanein, M. T., Marchand, L. L, Wilkens L. R., Maskarinec, G., … Haiman, C. A. (2010). Consistent association of type 2 diabetes risk variants found in Europeans in diverse racial and ethnic groups. *PLoS Genetics*, *6*(8), e1001078. https://doi.org/10.1371/journal.pgen.1001078

Welter, D., MacArthur, J., Morales, J., Burdett, T., Hall, P., Junkins, H., … Parkinson, H. (2014). The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. *Nucleic Acids Research*, *42*(Database issue), D1001–D1006. https://doi.org/10.1093/nar/gkt1229

Wojczynski, M. K., Li, M., Bielak, L. F., Kerr, K. F., Reiner, A. P., Wong, N. D., … Reilly, M. P. (2013). Genetics of coronary artery calcification among African Americans, a meta-analysis. *BMC Medical Genetics*, *14*, 75. https://doi.org/10.1186/1471-2350-14-75

Xue, L., Pan, C., Gu, Z., Zhao, S., Han, B., Liu, W., … Song, H. (2013). Genetic heterogeneity of susceptibility gene in different ethnic populations: Refining association study of PTPN22 for Graves' disease in a Chinese Han population. *PLoS One*, *8*(12), e84514. https://doi.org/10.1371/journal.pone.0084514

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Zanetti D, Weale ME. Transethnic differences in GWAS signals: A simulation study. *Ann Hum Genet*. 2018;1–7. https://doi.org/10.1111/ahg.12251