# Impact of limited population diversity of genome-wide association studies

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**Abstract:** The article describes the limited population diversity of genome-wide association studies and its resulting impact on the development of commercial genetic tests with restricted applicability and usefulness to certain groups, potentially increasing existing disparities. To enable development of new clinical tools applicable to all groups, much more focus is needed to engage minority communities to enroll in genetics or genomic research studies and on investigators to reach out to underrepresented communities. ***Genet Med*** **2010:12(2):81–84.**

**Key Words:** *genome-wide association studies, race, disparities*

Sequencing of the human genome, generation of haplotype maps, and advances in genotyping technology have combined to launch a gold-rush movement of genomics research for complex diseases. In particular, genome-wide association studies (GWAS) have been conducted on at least 184 traits and conditions, almost certainly an underestimate as this number includes only studies of >100,000 single-nucleotide polymorphisms with $P$ values of $<1.0 \times 10^{-5}$.[1] The value and impact of these studies to advance understanding of complex diseases remain to be seen,[2–4] but these data have already led to the development of commercial testing applications, many of which are available directly to consumers. A major shortcoming of GWAS and the subsequent commercial applications derived from these data are the limited diversity of their study populations. More effort is needed to ensure (more) diverse study populations in GWAS to yield development of clinical applications usable by all.

An analysis of GWAS publications listed in the catalog maintained by the National Human Genome Research Institute reveals the stark lack of diversity of GWA study populations.[1] As of June 16, 2009, 344 publications were listed in the catalog. After review of each publication, several data points were extracted and coded: (1) country of origin of study population(s); (2) racial or ethnicity makeup of initial study population; (3) racial or ethnicity makeup of replication study population (if any); and (4) source of study populations (newly recruited or existing cohort).

Data analysis was limited to US studies, given differences in categorization of race outside the United States. As multiple racial or ethnicity descriptors were used to characterize study populations, clustering was performed using the primary race (white, Black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian, or other Pacific Islander) and ethnicity categories (Hispanic or Latino) as defined by the Office of Management and Budget.[5] For example, populations described as white, European, European American, of European descent, of European ancestry, of European origin, non-Latino white, non-Hispanic white, and non-Hispanic white were all classified as white.

Sixty-seven of the 344 GWAS publications listed were conducted in the United States. The initial study populations of 79% of the US GWAS publications were all white; 75% of the replication sample populations were also all white (Table 1). Overall, 92% of US GWAS participants were white, followed by African-Americans (3%) (Fig. 1). Studies conducted outside the United States were concentrated mainly in Europe and Asia.

The dominance of European populations in GWA studies is of special concern because of the frequent lack of replication of initial findings in subsequent studies examining non-European populations.[6] Some such follow-up studies in non-European populations have resulted in failure to replicate a European-based association,[7–11] detection of a weaker association,[7,8,11–15] or even detection of opposite effects in the different populations.[7,16] Failure to replicate can be attributed to any number of issues, of course, including problems of study design in the original study, clinical heterogeneity, technical differences, analysis of different variants in follow-up studies and confounding environmental factors.[6,17] Failure to replicate may also be due to underlying differences in allelic architecture or linkage disequilibrium across populations. The differential effects of genetic variants identified in GWAS across populations raise serious doubt as to whether pan-ethnic clinical applications can be developed for at least some common diseases.

To explore this issue further, a review of the online descriptions of genome-based testing for 22 diseases offered by all three major companies providing testing directly to consumers (Navigenics, 23andMe, and deCODEme) was conducted. 23andMe and deCODEme indicated that testing for 16 and 11 of the 22 diseases reviewed are applicable only for individuals of European ancestry, respectively, illustrating the impact of the limited diversity of GWAS populations. deCODEme indicated that testing for nine diseases is available to individuals of Asian and/or African ancestry, although a smaller single-nucleotide polymorphism panel is offered for eight of these diseases as not all of the variants have been validated in non-European groups. For example, for African Americans, testing is only offered for 1 of 15 variants for Type 2 diabetes and 2 of 13 variants for prostate cancer. The disparities in the number or scope of testing for certain populations may engender confusion and frustration about the reasons underlying the different testing services, potentially reifying beliefs of medical exclusion or benefit for some populations.

In contrast, Navigenics did not include any information about test limitations for certain population groups in their online test descriptions. Rather, they briefly noted in their informed consent document (as does 23andMe and deCODEme) that most of their testing is based on studies of people of European ancestry

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**Table 1** Breakdown of initial and replication study samples by race or ethnicity

| | Initial sample (existing cohort) | Replication sample (existing cohort) |
|---|---|---|
| White only | 53 (42[a]) | 21 (17) |
| American Indian only | 2 (2) | 1 (1) |
| Hispanic only | 2 (2[b]) | 2 (2[b]) |
| Mixed populations | 10 (5) | 4 (2) |
| Total | 67 (51) | 28 (22) |

[a] Seventeen cohorts were from the Framingham Heart Study Original and Offspring Cohorts.
[b] The initial cohort used a subset of samples from the Insulin Resistance Atherosclerosis Study Family Study (IRASFS). The findings were then tested in the entire IRASFS cohort.

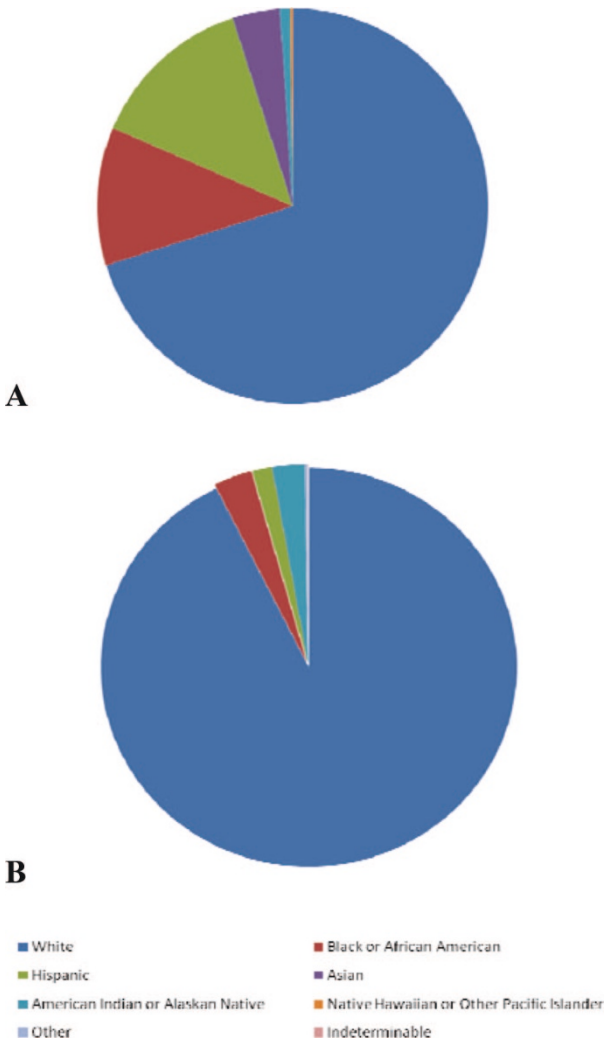


**Fig. 1.** A, Race or ethnicity of US population (American Community Survey, US Census Bureau, 2008); (B) race or ethnicity of participants in the initial and replication groups of 67 US GWA studies ($n$ = 155,705).

and, therefore, are uncertain as to whether the results are applicable to people of other backgrounds. Additional information is provided in their test report indicating that the estimated lifetime risk for most conditions were calculated based on data from European populations. As Navigenics does not opt to limit testing for individuals of certain backgrounds where data are unavailable, consumers may be confused and feel misled due to their limited understanding of genomics research.

Research in non-European populations is essential to demonstrate the analytical and clinical validity of new tests across populations. Early development of clinical applications derived from European-based study populations may result in false-positive risks for other groups. Genomic studies of African populations or isolated populations may identify rare variants because of differences in linkage disequilibirum size.[18] GWAS of diverse populations may also help elucidate the underpinnings of clinical differences observed between populations as evidenced in the recent study of differential response to interferon treatment among European and African American patients with hepatitis C,[19] potentially leading to development of a test that will be of clinical benefit to both populations.

Two major reasons may account for the lack of diversity in US GWAS populations. First, 76% (51 of 67) of US GWA studies used existing cohorts as their initial sample population (Table 1). Although convenient and likely to include detailed phenotypic data collected over a long period, the majority of these cohorts were of a single population (47 of 51), limiting the generalization of the study findings. Many of the existing cohorts may have been established before federal efforts to bolster participation of women and minorities in biomedical research.[20,21] In addition to current requirements to ensure diverse study populations, some current projects are required to use study populations that are "broadly representative of and generalizable to the US community-dwelling population" as was stipulated in one funding announcement from the US National Institutes of Health to study genetic variants associated with complex diseases.[22]

Second, challenges to the recruitment of minorities for clinical research are well documented.[23–25] Mistrust, particularly in the African American community, remains a barrier to minority recruitment in clinical studies.[26–28] Genetics or genomics research may raise additional concerns regarding the collection, storage, and use of DNA samples, leading to lower participation rates of minorities[29–35] or the perception of lack of benefit or giving back to the community.[36,37] Negative attitudes toward and perceived harms of genetic testing or screening also likely contribute to reluctance of minorities to participate in genetics or genomics research.[37–40] However, some data indicate that differences in participation rates in research by race may be minimal,[41] and that the disparity is actually due to limited access to research studies and not by refusal to participate.[25,41,42]

A number of strategies have been recommended to increase minority representation in clinical trials, although none known to specifically target genetics research.[43,44] In particular, use of strategic recruitment efforts and community engagement can bolster minority participation.[23] Setting minority recruitment goals may help ensure that investigators plan for broad-based recruitment during the study design phase.[45]

Furthermore, because many people may not be cognizant of the purpose of research,[46–48] more educational programs about biomedical research,[49–51] particularly genetics and genomics research, may help improve awareness, particularly in underrecruited populations. Additional information about the study provided at the time of recruitment may boost enrollment rates,[52] and greater dialogue with prospective participants may inform researchers of cultural sensitivities and concerns of

minority communities. Such heightened awareness may allow researchers to build trust and cultivate an enduring relationship with the community that extends beyond the boundaries of a single study.[53,54]

In addition, formal consortiums or multisite studies can enable collection of greater racial or ethnic representation. For example, the International Warfarin Pharmacogenetics Consortium, comprised of 21 research groups from 11 countries, has collected genotype and phenotype data on ~6000 patients from the 3 major racial or ethnic groups around the world.[55] Given the widespread use of the anticoagulant drug warfarin, this effort has provided much needed insight into the genetic basis of warfarin and race or ethnicity.[56] Furthermore, a number of groups have established non-European cohorts[57,58] or biobanks,[59] which may provide another resource to enhance diversity of GWA or GWA-confirmatory studies through data sharing or collaborative partnerships.[60–62]

More efforts to increase training of minority physicians and scientists should also be continued and expanded. Minority physicians play a key role in recruiting minority participants, potentially engendering greater trust, respect, and participatory decision making.[36,63] In addition, as language poses a barrier for some,[64,65] training of minority physicians born outside the United States who are bilingual can help raise awareness and understanding about participating in research in communities with a high prevalence of non–English-speaking patients. Over the past few decades, several programs have been developed to increase the number of minority scientists and health professionals such as the Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships to Promote Diversity in Health-Related Research. Additional efforts are needed to involve and educate minority physicians about clinical trials and their clinical value.[66,67]

It is unclear whether the limited population diversity of GWA studies will adversely impact uptake of commercial tests by non-white consumers given that few studies have investigated characteristics of users of these tests and their small numbers. The lack of prominence of this issue in the informational materials provided by the three companies suggests that most people would not even be aware of the limited diversity of study populations on which the test was based, and therefore, their decision to purchase the test would not likely be affected by this fact. One study reported that African Americans were least likely to express interest or sign up for a personalized genomic risk assessment (unknown if any information about validity of testing in different populations was disclosed),[68] whereas another study found comparable uptake between whites and African Americans and a significantly higher uptake among Hispanics for nutrigenomic testing.[69] Studies of attitudes toward race-based pharmacogenomics and development of race-targeted products may provide some insight about uptake of these tests. Although some African American participants appreciated the recognition of differences between groups with respect to drug response and inclusion of minorities in genetic and drug testing studies,[70,71] many expressed doubt of the efficacy of drugs developed for African Americans and concerns about racial discrimination.[70,72,73] Because of the perceived inferiority of drugs targeted to African Americans, a subset of African Americans in one study indicated they would prefer to take drugs developed for Europeans.[72]

The limited population diversity of GWA studies has resulted in restricted applicability and usefulness of new genetic tests to certain groups and poses a major barrier to widespread use of these promising clinical applications, potentially increasing existing disparities. The lack of racial or ethnic diversity in GWA studies needs to be quickly addressed by both researchers and research funders to provide a broad understanding of genetic variation across populations and to substantially reduce the development of race-limited applications.

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