Geospatial distribution and population substructure of subgroups of US ethnic minorities: implications for perpetuation of health disparities and paucity of precision medicine

Hasan Jackson
University Of Maryland, hjackso1@umd.edu

Fatimah L.C. Jackson
Howard University, fatimah.jackson@howard.edu

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Introduction

The promise of precision medicine is most real for individuals and groups that fit within the population norm for various genomic parameters. The greater the extent to which individuals and groups diverge from that norm, the less likely they are to benefit from the research on and application of precision medicine. This is because precision medicine rests upon a platform of shared ancestral background. Microethnic isolates may vary considerably from the larger population norms because of their small size, relatively endogamous state, historical isolation, economic deprivation, and sociocultural and geospatial remoteness. We have identified 40 such subgroups within U.S. ethnic minority groups that may be at greater risk for sustained health disparities and that may be more likely to be left out of the anticipated benefits of precision medicine.

A Spatial Perspective on Genetic Variation

Genetic variation has a spatial component with the potential to allow a better understanding of the underlying relationships that exist in space, as well as in time. Much like other environmental factors that vary in space (e.g., rainfall, illness, pollution), genetic variations within a population occur on different spatial scales (e.g., within a county or region, across continents) and are prone to display both subtle and abrupt differences. The most spatially relevant underlying factors are the migration and isolation of human populations.

Until recently, with the advent of commercial transportation, including travel by air, terrestrial motor vehicles, and sea, migration occurred along well-defined paths. These series of paths constituted larger migration networks that are essential to an understanding of population dynamics and the variation exhibited within and between certain populations. The paths were associated with important spatial components. Interactions with neighboring groups and the exchange of ideas and genetic information were constant drivers for variations in populations. These interactions, which add complexity to the gene pool, may be reversed to acquire a better understanding of the networks, and in some cases the specific paths, that populations use during migrations. A key component of migrations that is still evident in population dynamics today, both at the family and at the global scale, is the effect of environmental factors on genetic expression. For example, two parts of one population that migrated along two distinct paths may reconnect after many years or centuries, with varied genetic consequences. In such a case, one part of the population group may have been subjected to a stressor (e.g., pollution; limited abundance, quality, or diversity of food)

that resulted in an increased incidence of targeted deaths while the other group may have experienced more relaxed selective pressures.

Isolation is also a major component of genetic structure in a population. Population genetics are occasionally narrowly described as snapshots for a single time and location, when in fact they are constantly evolving. Continual genetic mixing provides new variations that are passed through a population. Given the genetic similarities of two populations, isolation limits new genetic material from entering a population's gene pool and eventually spreading. Like genetic migration, genetic isolation can be modeled across a space continuum. Physical environmental barriers, such as relief (e.g., high mountains, steep hills), bodies of water (e.g., oceans, major rivers), and deserts, are common examples. Another class of barriers comprises those that are societal: regulations against interethnic relationships (as in the Jim Crow South), cultural incompatibility (language, religious barriers such as those between the Palestinian and Israeli peoples), and cultural self-preference.

Human Biodiversity, Stratification, and the Challenge of Precision Medicine

Human diversity, heterogeneity, and biocultural variability present a challenge to the classic stratification models of epidemiology and public health. The quest for precision medicine rests upon a platform of accurate genomic studies coupled with sophisticated interpretations of the environmental context of genomic diversity. We need new approaches. The "race model" doesn't work, and health disparities are the end products of complex interactions that defy simplistic solutions. Precision medicine will not emerge from ahistorical recreational genetics. We need systematic approaches to understanding the structure and population biology of our species. Then, we need to fine-tune our studies to make them specific for particular subgroups of modern humans. To capture the nuances of human biodiversity, these new models must encompass the following: (1) relevant cultural/behavioral diversity, (2) genetic and genomic variation, (3) nongenetic biological differences (e.g., those induced by protracted contact with specific environments), and (4) an awareness of appropriate biological lineage histories. Figure 1 depicts the importance of understanding the ancestral foundations of an individual or group before applied genomics (as in precision medicine) can be of benefit.
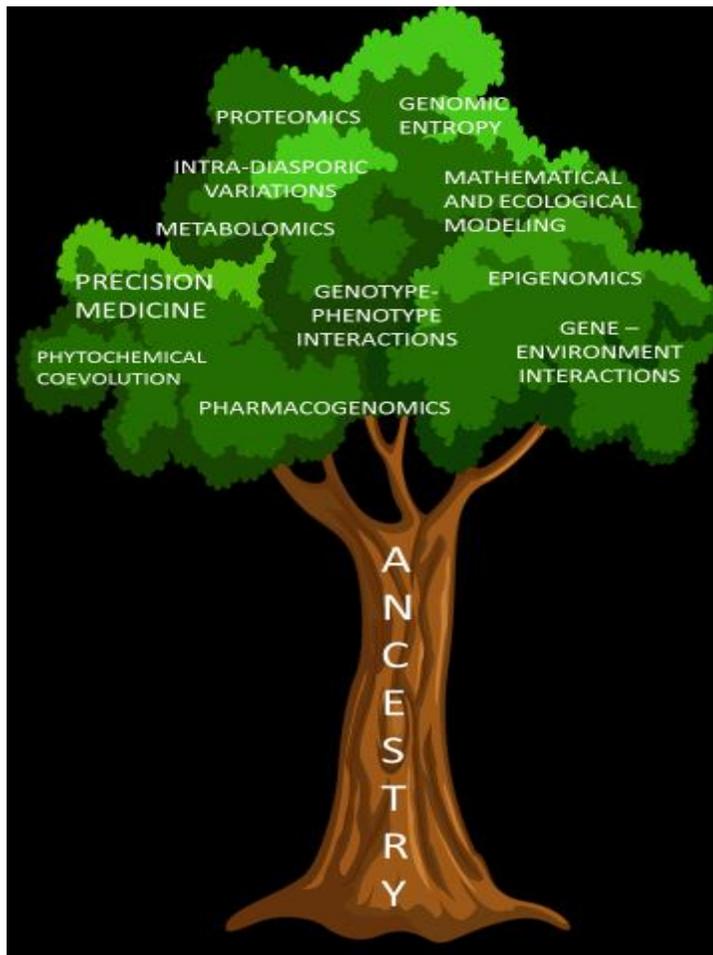
Figure 1. Foundational role of accurate and robust ancestry information in supporting a range of applied genomics interventions. Precision medicine and other expressions of sophisticated applied genomics (e.g., pharmacogenomics, proteomics, genomic entropy, gene-environment interaction studies) are only as good as the data on ancestry available for an individual or group. Without appropriate ancestry reference data, the nuances of subgroup diversity can be obscured, and the "precision" of precision (personalized) medicine is lost.

Factors That Tend to Distort Our Perceptions of Human Variability

The geographical distribution of the current world population, combined with the changing regional origins of the U.S. population, tends to distort our perceptions of human variability. Indeed, we judge the world by what is immediately around us. As a result, we tend to think that everyone is "like us" or our "neighbors" when the reality is often quite distinct. Within the United States, there is a non-uniform geospatial distribution of various ethnic subgroups, and a substructure (i.e., stratification) exists within the major macroethnic groups, such as Latinos, African Americans, and Asian Americans.

We are particularly interested in the relationships between group genetics and the environment: genes and the abiotic environment, genes and the biotic environment, and genes and the sociocultural environment. Each of these levels of interaction contributes specific variables that can influence patterns of gene expression.

An Example of Evidence for Population Substructure in African Americans

Americans of African descent tend to suffer disproportionately from hypertension. Adeyemo et al. (2009) studied a dense panel of more than 800,000 single-nucleotide polymorphisms (SNPs) in a discovery sample of 1,017 African Americans from the Washington, D.C., metropolitan region. In their study, this team identified multiple SNPs reaching genome-wide significance for systolic blood pressure in or near the following genes: *PMS1*, *SLC24A4*, *YWHA7*, *IPO7*, and *CACANA1H*. Some of the significant SNPs were also observed in a sample of West Africans. However, a few years later, Kidambi et al. (2012) conducted a non-replication study of a genome-wide association study for hypertension and blood pressure in African Americans. In a different sample of African Americans, none of the SNPs previously evaluated were convincingly associated with hypertension as a binary trait or with blood pressure level as a quantitative trait. This latter study was unable to confirm previously reported associations of *PMS1*, *SLC24A4*, *YWHA7*, *IPO7*, and *CACANA1H* with systolic and diastolic blood pressure.

Clearly, African Americans exhibit some level of population substructure that continues to befuddle our efforts at singular classification. We have developed ethnogenetic layering as a tool to help deconstruct this substructure and identify the most salient regional ancestral genetic, epigenetic, and environmental factors that may account for high levels of within-group variability (Jackson 2004, 2008, 2013). Ethnogenetic layering is a computation-based tool that is used to better

identify population subdivisions (substructure) (Jackson 2006). As ethnogenetic layering is coupled with advances in the detection and analysis of genetic variation, such as genome-wide association studies (GWAS) and bioinformatics, we may be better equipped to develop a more nuanced understanding of the relationships between genetics, the environment, and disease.

Environmental Sources of Genotype-Phenotype Discontinuity
Three types of factors are additional sources of variation in the expressed genotype (the phenotype) and modify the coded genotypic message. These are abiotic stressors (e.g., radiation, precipitation, altitude, humidity), biotic stressors (e.g., diet, subsistence, psychosocial stress), and social and cultural stressors (e.g., religion, language, ethnic identity). For example, a poor-quality diet among individuals of low socioeconomic status may partly explain the greater burden of noncommunicable disease in disadvantaged populations (de Mestral et al., 2017). In certain subgroups of African Americans who consume fish, catfish appears to contribute to elevated polychlorinated biphenyl (PCB) levels (Weintraub & Birnbaum, 2008). Class structure can also have genomic implications. For example, residing in a county with a low socioeconomic status index is associated with lower rates of survival from oropharyngeal cancer (Megwalu and Ma, 2017). So, although these stressors are not genetic, they can behave in ways in specific subgroups that influence gene expression over generations, modifying the survival value (i.e., biological fitness) of individuals and groups over time. The effect of the interaction of these stressor factors on promoting genotype-phenotype discontinuity is depicted in Figure 2.
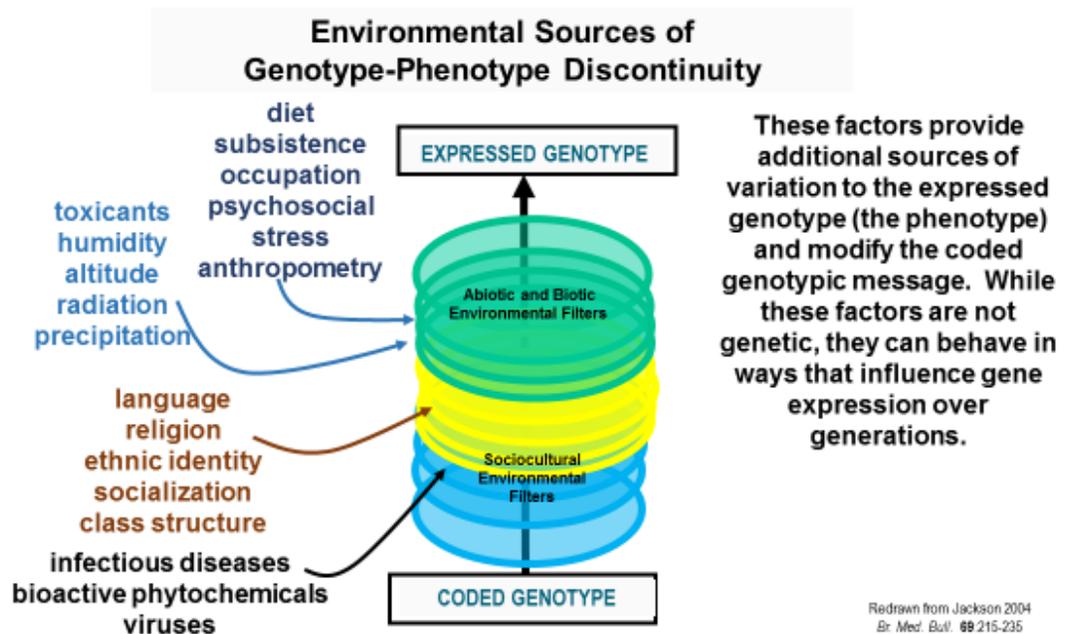
Figure 2. Environment-derived stressors that can modify the phenotype and influence gene frequencies over time.

Methods

In our studies to identify microethnic isolates, we initially focused our research on groups that lived in or had ancestral origins in one of three regions: the Chesapeake Bay area, the Carolina Coast area, and the Mississippi Delta area. We used ethnogenetic layering (Jackson 2008) as a strategy to collect and analyze geographical patterns of biological lineage data (e.g., genomic data, phenomic data) and microethnic affinity (e.g., ethnographic data) and to place all of this information within a historical contextual framework. The algorithm for ethnogenetic layering involves the following steps: collection and digitization of anthropological measures, creation of geographical maps of an area, layering of raster and vector maps, association of maps with a particular health disparity of research interest, integration of ethnogenetic and other data, and finally calculation of metadata analysis for hypothesis testing. Typically, the layers include anthropological variables, residential history, genetic ancestry, dietary patterns, clinical details, and environmental toxin exposures. Regional frequencies of significant biocultural factors that correlate with health outcomes are identified, when available, for these groups.

Results

Our research identified 40 autochthonous, isolated, endogamous microethnic subgroups in the United States with small effective population sizes and high levels of homozygosity (as a function of historical endogamy and geographical isolation). Table 1 lists these subgroups and provides additional geospatial information for each.

Many groups were found in geographically insulated regions with similar terrain (e.g., mountainous, coastal; Table 1). These regions served to separate populations from continual and widespread genetic contact with outside populations. Mountainous regions in particular were the most limiting, given the abrupt cultural and geographical variations that exist from the coastal areas to the Appalachian region. Coastal areas provided an interesting terrain because of the history of migration along coastal areas. Microethnic groups that were located in inland areas had an increased opportunity to interact with different populations, given the likelihood of improved infrastructure.

Table 1. U.S. microethnic groups identified by using the ethnogenetic layering approach (Jackson 2008). *Note:* N/A indicates that a field was not applicable (e.g., found throughout a state).

Name	County	State	Terrain	Ecoregion	Sub-ecoregion	Primary Crop
Adamstown (Upper Mattaboni) Indians	Prince William	VA	Coastal	Tropical & subtropical coniferous forest	Southeastern plains	Corn
Brandywines	Prince George's	MD	Inland coastal	Tropical & subtropical coniferous forest	Southeastern plains	Corn
Brandywines	Charles	MD	Coastal	Tropical & subtropical coniferous forest	Southeastern plains	Soybeans
Brass Ankles	Dorchester	SC	Coastal	Tropical & subtropical coniferous forest	Middle Atlantic coastal plains	Corn
Brass Ankles	Colleton	SC	Coastal	Tropical & subtropical coniferous forest	Middle Atlantic coastal plains	Corn
Brass Ankles	Berkeley	SC	Coastal	Tropical & subtropical coniferous forest	Middle Atlantic coastal plains	Corn
Brass Ankles	Orangeburg	SC	Inland	Tropical & subtropical coniferous forest	Southeastern plains	Corn
Brass Ankles	Charleston	SC	Coastal	Tropical & subtropical coniferous forest	Middle Atlantic coastal plains	Vegetables
Cajans	Mobile	AL	Coastal	Tropical & subtropical coniferous forest	Southeastern plains	Cotton

Table 1 (continued)

Name	County	State	Terrain	Ecoregion	Sub-ecoregion	Primary Crop
Cajans	Washington	AL	Coastal	Tropical and subtropical coniferous forest	Southeastern plains	Corn
Carmel Indians	Highland	OH	Mountains	Eastern temperate forest	Western Allegheny plateau	Soybeans
Carmel Indians	Magoffin	KY	Mountains	Eastern temperate forest	Interior plateau	Corn
Clifton Choctaw	Rapides Parish	LA	Inland	Tropical & subtropical coniferous forest	Southern central plains	Soybeans
Clay Eaters	N/A	GA	Inland	Tropical & subtropical coniferous forest	Piedmont	Wheat
Clay Eaters	N/A	SC	Inland	Tropical & subtropical coniferous forest	Piedmont	Wheat
Coushatta	N/A	AL	Inland	N/A	N/A	N/A
Coushatta	N/A	LA	Inland	N/A	N/A	N/A
Cros	Marlboro	SC	Inland	Tropical & subtropical coniferous forest	Southeastern plains	Soybeans
Cros	Dillon	SC	Inland	Tropical & subtropical coniferous forest	Southeastern plains	Soybeans
Cros	Marion	SC	Inland	Tropical & subtropical coniferous forest	Middle Atlantic coastal plains	Soybeans

Table 1 (continued)

Name	County	State	Terrain	Ecoregion	Sub-ecoregion	Primary Crop
Cros	Horry	SC	Inland	Tropical & subtropical coniferous forest	Southeastern plains	Soybeans
Free Moors	N/A	SC	N/A	N/A	N/A	N/A
Guineas	Barbour	WV	Mountain	Eastern temperate forest	Western Allegheny plateau	Corn
Guineas	Taylor	WV	Mountain	Eastern temperate forest	Western Allegheny plateau	Vegetables
Gullah & Geechee	N/A	SC	Coastal	Tropical and subtropical coniferous forest	Middle Atlantic coastal plain	Vegetables
Houma	N/A	LA	Coastal	Tropical and subtropical coniferous forest	Mississippi alluvial plain	Vegetables
Issues	Amherst	VA	Mountain	Eastern temperate forest	Ridge and valley	N/A
Issues	Rockbridge	VA	Mountain	Eastern temperate forest	Ridge and valley	N/A
Jackson Whites	Orange	NY	Mountain	Eastern temperate forest	Northeastern highlands	Vegetables
Jackson Whites	Rockland	NY	Mountain	Eastern temperate forest	Northern Piedmont	No preference
Jackson Whites	Bergen	NJ	Highlands	Eastern temperate forest	Northeastern highlands	Vegetables
Jackson Whites	Morris	NJ	Inland coastal	Eastern temperate forest	Northern Piedmont	Vegetables
Jackson Whites	Passaic	NJ	Inland coastal	Eastern temperate forest	Northern Piedmont	Vegetables

Table 1 (continued)

Name	County	State	Terrain	Ecoregion	Sub-ecoregion	Primary Crop
Lumbee	Robeson	NC	Inland	Tropical and subtropical coniferous forest	Southeastern plains	Soybeans
Lumbee	Bladen	NC	Inland	Tropical and subtropical coniferous forest	Southeastern plains	Corn
Lumbee	Columbus	NC	Inland	Tropical and subtropical coniferous forest	Southeastern plains	Corn
Lumbee	Cumberland	NC	Inland	Tropical and subtropical coniferous forest	Southeastern plains	Soybeans
Lumbee	Macon	NC	Inland	Eastern temperate forest	Blue Ridge	Vegetables
Lumbee	Hoke	NC	Inland	Tropical and subtropical coniferous forest	Southeastern plains	Cotton
Lumbee	Sampson	NC	Inland	Tropical and subtropical coniferous forest	Southeastern plains	Soybeans
Lumbee	Halifax	VA	Inland	Tropical and subtropical coniferous forest	Piedmont	Corn
Lumbee	Marlboro	SC	Inland	Tropical & subtropical coniferous forest	Southeastern plains	Soybeans

Table 1 (continued)

Name	County	State	Terrain	Ecoregion	Sub-ecoregion	Primary Crop
Lumbee	Dillon	SC	Inland	Tropical & subtropical coniferous forest	Southeastern plains	Soybeans
Lumbee	Marion	SC	Inland	Tropical & subtropical coniferous forest	Middle Atlantic coastal plains	Soybeans
Lumbee	Horry	SC	Inland	Tropical & subtropical coniferous forest	Southeastern plains	Soybeans
Marlboro Blues	Chesterfield	SC	Inland	Tropical & subtropical coniferous forest	Southeastern plains	Soybeans
Melungeons	Hancock	TN	Mountain	Eastern temperate forest	Ridge and valley	Vegetables
Mestees	N/A	SC	N/A	N/A	N/A	N/A
Nanticoke Moors	Sussex	DE	Coastal	Tropical & subtropical coniferous forest	Middle Atlantic coastal plains	Corn
Nanticoke Moors	Cumberland	NJ	Coastal	Eastern temperate forest	Atlantic coastal pine barrens	Soybeans
Oklahoma Choctaw	N/A	OK	N/A	Eastern temperate forest	Ouachita Mountains	Wheat
Red Bones	Richland	SC	Inland	Tropical & subtropical coniferous forest	Southeastern plains	Corn
Red Bones	Calcasieu	LA	Coastal	Great Plains	Western Gulf coastal plain	Vegetables
Red Bones	Rapides	LA	Inland	Tropical & subtropical coniferous forest	Southern central plains	Soybeans

Table 1 (continued)

Name	County	State	Terrain	Ecoregion	Sub-ecoregion	Primary Crop
Red Bones	Beauregrad	LA	Inland	Tropical & subtropical coniferous forest	Southern central plains	Soybeans
Red Bones	Vernon	LA	Inland	Tropical & subtropical coniferous forest	Southern central plains	Vegetables
Red Bones	Allen	LA	Inland	Tropical & subtropical coniferous forest	Southern central plains	Soybeans
Red Legs	Orangeburg	SC	Inland	Tropical & subtropical coniferous forest	Southeastern plains	Corn
Sabines	Terrebonne	LA	Coastal	Great Plains	Western Gulf coastal plain	No predominance
Sabines	Lafourche	LA	Coastal	Great Plains	Western Gulf coastal plain	No predominance
Sandhillers	Richland	SC	Inland	Tropical & subtropical coniferous forest	Southeastern plains	Corn
Skeetertown Indians	Suffolk	VA	Coastal	Tropical & subtropical coniferous forest	Southeastern plains	Soybeans
Turks	Sumter	SC	Inland	Tropical & subtropical coniferous forest	Southeastern plains	Soybeans
Wends	N/A	TX	Inland	Tropical & subtropical coniferous forest	Southern central plains	N/A

Examples of U.S. Microethnic Groups
Brass ankles.

The Brass Ankles, also known as Melungeons, are a multiracial group of European, African, and Native American ancestry (Schrift, 2013a). Little else is known regarding this community because the people are from an area where American Indians and Africans were enslaved and the Irish were indentured servants. Known as racial isolates of the Appalachian region, they were genetically isolated in part as a consequence of social pressures (e.g., Jim Crow segregation rules) and geography as they migrated from the low country toward the Piedmont areas of South Carolina (Henige, 1998; Wilson, 1998). The complexity of genetic diversity within the Brass Ankles was minimized because they were classified simply as mulatto or black during U.S. Census enumerations. In many respects, the Brass Ankle communities of South Carolina were derived from insular hamlets of inbred inhabitants descended from racially mixed backgrounds (Schrift, 2013b).

Gullah and geechee.

The Gullah are the descendants of enslaved Africans, reportedly from Angola and West Africa; they inhabit the low country areas of Georgia and South Carolina. Although cultural barriers have separated them from other populations of formerly enslaved Africans in the southeastern United States, it is their geographical isolation in rural coastal areas that has resulted in little genetic mixing with the inhabitants of neighboring areas. Much of their population, estimated to range from 100,000 to 300,000, resides in the Sea Islands off the coast. Historically, as newly imported enslaved Africans arrived in the southeastern coastal region, they came in continual contact with established Gullah people. Limited interaction with white farmers was due to the subtropical climate of the area, which harbored mosquitos carrying malaria and yellow fever. The Gullah have participated in some genetic research (Kamen et al., 2008); however, questions persist regarding health information and the effect of low-non-African admixture (Gribble et al., 2015) (i.e., the Gullah and Geechee maintain high proportions of African ancestry with little non-African admixture).

Lumbee.

This small Native American group in the low country of North and South Carolina, with a total population of 55,000, is one of the largest in the eastern United States (Langdon et al., 2016). The group is now a mix of Croatan Native Americans with Jewish and sub-Saharan African heritage.

Their exact heritage is unknown, and various theories of their origin exist; these include mixed-race mulatto and Native American (e.g., Cherokee, Croatan, Keyauwee, Tuscarora). As for many Native American groups in the region, information regarding health is limited; however, in the greater Carolina region, where the Lumbee reside, health disparities persist (State Center for Health and Office of Minority Health and Health Disparities, 2010; Smokowski, Evans, Cotter, & Webber, 2014). Some have noted that members are susceptible to forms of anemia, fibromyalgia, and familial Mediterranean fever. Although their exact heritage is unknown, several social (religion) and political (segregation) barriers have isolated this group from other populations. From an economic standpoint, the Lumbee reside in some of the most rural and poorest counties in North Carolina, such as Robeson County (U.S. Census Bureau, 2012)

Discussion

Families are the foundation of microethnic groups. Specifically, biological lineages tend to cluster within geographical regions, and families represent aggregates of specific interacting, genetically related biological lineages. For example, among 77 individuals self-identifying as members of the Adamstown Indians or Upper Mattaponi Band, 75% of the biological lineages are directly affiliated with the family name Adams. Other family names common in this microethnic isolate include Hincher, Mills, Dundjie, and Acree (https://www.accessgenealogy.com/native/adamstown-indians-upper-mattaponi-band.htm).

Our research suggests that U.S. microethnic isolates fall into one of two main historical demographic patterns. The first pattern is represented by groups such as the Gullah and Geechee peoples. These groups have been genetically isolated from the larger African American macroethnic population for, on average, 10 to 15 generations. Traditionally, they are highly endogamous, and barriers of physical geography have facilitated the emergence of a host of cultural and linguistic differences that further distinguish them from mainland African American groups.

The second general historical demographic pattern seen among U.S. microethnic isolates is that of extensive historical admixture followed by isolation and high rates of endogamy. The Adamstown Indians or Upper Mattaponi Band are a good example of this pattern. Aggregating them with any of their ancestral groups (e.g., Africans, Europeans, or Native Americans) would make them more vulnerable to being "missed" in the development of "race-specific" interventions focused on reducing health disparities.

The microethnic groups we have identified are generally smaller and more regionally restricted than the groups identified recently (Han et al., 2017) by using cluster analysis of 770,000 genomes. We think that the seeming invisibility of microethnic isolates in the United States reflects the reductive excessive dominance of the "racial model" in public health and epidemiology. These microethnic isolates need to be viewed as the independently stratified subgroups that they are, with their own unique genomic patterns and specific health implications.

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