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COMMENTARY

Beyond borders: A commentary on the benefit of promoting immigrant populations in genome-wide association studies

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Summary

Immigrants are an important part of many high-income nations, in that they contribute to the sociocultural tapestry, economic well-being, and demographic diversity of their receiving countries and communities. Yet, genomic studies to date have generally focused on non-immigrant, European-ancestry populations. Although this approach has proven fruitful in discovering and validating genomic loci, within the context of racially/ethnically diverse countries like the United States—wherein half of immigrants hail from Latin America and another quarter from Asia—this approach is insufficient. There is a persistent diversity gap in genomic research in terms of both current samples and genome-wide association studies, meaning that the field's understanding of genetic architecture and gene-environmental interactions is being hampered. In this commentary, I provide motivating examples of recent research developments related to the following: (1) how the increased ancestral diversity, such as seen among Latin American immigrants, improves power to discover and document genomic loci, (2) informs how environmental factors, such as immigration-related exposures, interact with genotypes to influence phenotypes, and (3) how inclusion can be promoted through community-engaged research programs and policies. I conclude that greater inclusion of immigrants in genomic research can move the field forward toward novel discoveries and interventions to address racial/ethnic health disparities.

Introduction

International migration is increasingly common; it is estimated that 1 in every 30 people is an international migrant.[1] Currently Europe and Asia harbor the greatest absolute number of international migrants (86–87 million each), followed by North America (58.7 million). As such, international migrants (henceforth referred to as immigrants) are an important part of the fabric of many high-income nations. In 2020 in North America, more than 15% of the population were immigrants, most of whom arrived through one of the major migration corridors from Latin America, the Caribbean, or Asia. This is in contrast to Europe where 19% of the population in 2020 were immigrants, but roughly half were immigrants from within the region (i.e., from other countries in Europe), and the remainder arrived through a variety of immigration corridors, including Asia, Africa, and Latin America/Caribbean among others.

Immigration is considered to be both socially determined and a social determinant of health.[2] Not all immigration is voluntary, or even legally authorized, and each of these non-traditional circumstances can lead to additional vulnerabilities. In 2018, Canada was the top resettlement destination for the largest number of refugees, followed by other destinations in the United States (US), Australia, and in Europe.[1] In the US, it is estimated that as many as 23% of all immigrants were unauthorized (undocumented) to reside in the US as of 2017.[3] The need to engage immigrant populations to bridge the gap between who is being studied in genomic research and who should be studied can be applied to many other country contexts.

I will use the US as an example throughout the remainder of the commentary, as it is home to one in five of the global stock of immigrants,[3] and it is the country context in which I do most of my own immigrant health and genomic research. Immigrants contribute to the sociocultural tapestry, economic well-being, demographic change, and the public health profile of the US[4]; in fact, the US is often referred to as a "nation of immigrants." Roughly half of all current US immigrants hail from Latin America, and another quarter arrived from Asia.[3] Although not all, most US immigrants emigrated during young adulthood and experienced many adulthood life transitions like parenthood, first within the US.[5] Previous research in the US and other high-income nations shows that over time/generations, immigrants and their children may lose many of the health advantages that first-generation immigrants enjoyed upon first arrival.[6]

At various points in this commentary, I will highlight US Hispanics/Latinos as an example of a large US immigrant population that is both notably diverse (i.e., ancestrally, culturally, linguistically, socioeconomically, etc.) and under-represented in genomic research. More than half of recent US population growth

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(2010–2020) occurred among Hispanics/Latinos[7]—who comprise the largest US racial or ethnic group at 19% of the general US population.[8]

Immigration, life stressors, and changing environments

Studying immigrants' life exposures can yield to opportunities for genomic research innovations. Immigration is considered a social determinant of health, as it can be related to many of the fundamental social factors that shape an individual's health.[2] Broadly speaking immigrants experience a complement of life stressors (e.g., xenophobia, acculturation, tenuous legal statuses, etc.) that are above and beyond what other marginalized or racialized groups living in the same country may have experienced.[9] Perhaps most importantly, these experiences change across their life course, creating the potential for mismatch between their earlier (pre-migration) and later-life environments (post-immigration) or biologically adaptative, epigenetic processes. Yet, the lack of representation of immigrants in genomic research is not recognized by most scholars, nor systematically monitored by the genome-wide association study (GWAS) Diversity Monitor.[10]

A wealth of scholarship in social epidemiology and other disciplines has pointed to the potential for stressful life experiences to become embodied (i.e., "get under the skin"), the extent of which being largely dependent on their timing in one's life course.[11] I use the broader term of embodiment, as embedding is more narrow in its reference to timing earlier in the life course and biologic consequences primarily on altered development processes.[12] There are three main life course models that shed light on how embodiment may occur to pattern the health of immigrant populations—(1) the critical period model (also referred to as sensitive period or latency models), (2) the accumulative disadvantage model (accumulation of risk, cumulative, or weathering models), and (3) the pathway model (chain-of-risk, social trajectory, or social mobility models).[13,14]

Most immigrant studies of lifestyle behaviors (e.g., smoking, diet) have yielded results consistent with the critical period model,[15] which assumes that later-life outcomes are patterned by exposures during critical periods in one's life. This body of research is supported by the epidemiologic observation of "healthy migrants" compared to other racial/ethnic groups of similar age living in the same host country.[6] The Developmental Origins of Health and Disease hypothesis posits that biological programming (or embedding) of healthier *in utero* or early-life environments may in part explain this apparent "paradox."[16] Second, the accumulative disadvantage model posits that exposures across the life course cumulatively pattern later life health. This model has been implicated with socioeconomic factors and cardiometabolic health in Latino immigrant families in our own research[17] and others' (for example in Refs.[18–20]). Third, the pathway model is less commonly studied in immigrant research, but it may be particularly useful for understanding the timing of health-related processes and the role of intermediates or "triggers" along the chain of risk.[21]

Each of these life course models presumes that an extrinsic exposure can become biologically embodied to impact one's own health.[13] However, the exact mechanisms and interdependencies have not been delineated for most health disparities. Additionally scholars note that we have to look beyond one's own life course to consider the influence of "linked lives" on health processes[22] and collective, historical, or cultural traumas.[23] Fox and colleagues have generated an intergenerational acculturation framework to explain the increase of Hispanic/Latino health disparities across generations in the US.[24] Moreover, often this body of research assumes that an immigrant's acculturation process (adaptation to a new host culture), only begins once they cross an international border, and it is not dependent on others' experiences; however, we know that this is a vast over-simplification, as transnational social ties, globalization, and family reunification may elicit emigration or hasten acculturation once an immigrant arrives to their host country.[9]

Limited diversity in GWASs: Why are immigrant populations important for genomics?

Numerous scholars have highlighted that the limited ancestral diversity in GWAS samples/studies[25,26] and in the genomics workforce are barriers to moving precision medicine forward[27,28] and may in fact exacerbate health disparities.[29] The focus on homogeneous population structures in the GWAS literature—such as seen in most European studies—convenience, healthy-volunteer, or biobank samples[25] has created a dilemma for the field. For example, as of April 2023, the GWAS Diversity Monitor recorded that <5% of all GWAS discovery samples to date are of non-European ancestry, and the availability of non-European samples and studies still varies dramatically across traits.[10] The largest growth in terms of GWAS diversity has occurred for East Asian ancestry, which now comprises 3% of GWAS discovery samples. And yet, diversity from all other ancestries remains below 2% combined. Figure 1 illustrates how both participant and study-level diversity remains low across multiple types of GWAS outcomes.

GWASs to date do not regularly report descriptive statistics on the country of birth of their sample, nor does the GWAS Diversity Monitor track this information currently.[10] Moreover, given the general focus on analyzing only relatively homogeneous populations, immigrant populations may be excluded as ancestry outliers (e.g., UK Biobank British ancestry analyses) or due to their comparatively lower samples size (statistical power). Although recent method developments have supported so-called "global" analyses of pooled samples of diverse ancestries,[26] these statistical methods are still underutilized in favor of single-group GWAS or trans-ancestral

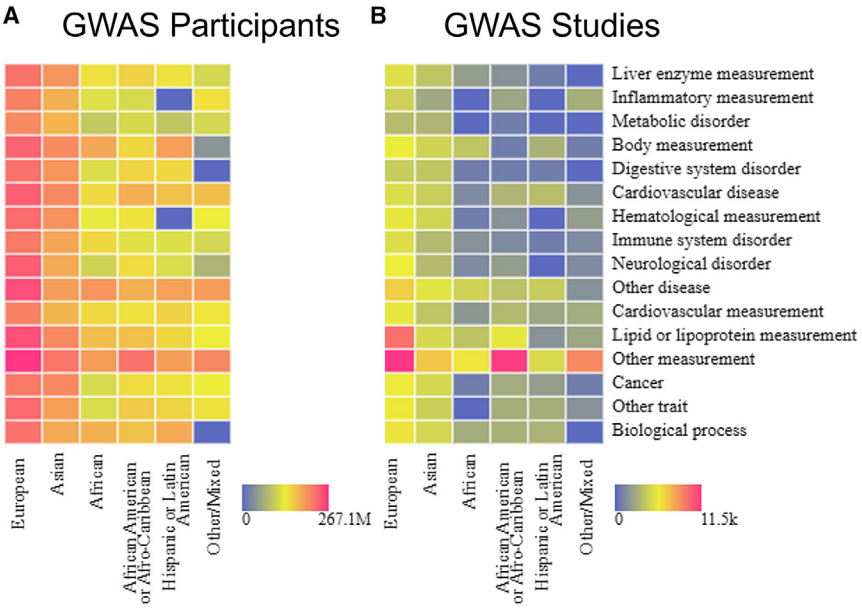

Figure 1. Heatmaps of ancestry group across traits in genome-wide association study (GWAS) discovery samples (A) and GWAS studies (B) published (www.ebi.ac.uk/gwas/) by 4/28/2022 (gwasdiversitymonitor.com, Version 1.0.0, downloaded on 4/28/2022).

meta-analyses, each of which remain European-centric due to the disparity in available samples described above.

The GWAS diversity gap is evident for many health traits and conditions including cardiovascular diseases, which are the leading cause of death in the world.[30] For example, over the last two or three decades, the highest rates of ischemic heart disease were in Central-Eastern Europe, Northern Africa, Middle East, Central Asia, and Oceania.[31] Type 2 diabetes is most common in Oceania, Latin America, and Central and Sub-Saharan Africa. Yet, populations with ancestry from each of these regions have been under-studied in GWASs to date. Again, in light of the over-representation of racial/ethnic minority individuals among those who are currently living with cardiometabolic disease in the US (e.g., Native Americans, Pacific Islanders, African Americans, or Hispanics/Latinos), the over-representation of samples and analyses of European ancestry is clearly concerning. Similar concerns have been documented for obesity, cancer, and psychiatric traits.[32–34]

GWASs supported by US-based funders (e.g., the National Institutes of Health, NIH) are legally mandated to collect and report on the inclusion of women and racial/ethnic minority populations.[35] US-based GWAS research is slightly more diverse than research from other country contexts[25]—but it still does not reflect either the racial/ethnic disparities in disease burden or the overall demographics of the US. Most recently the NIH has updated their policies to promote inclusion across the lifespan.[36] Mandated collection and reporting of other aspects of diversity could be implemented to signal their importance, promote inclusion, and benefit the literature more broadly. Country of birth does not directly indicate legal immigration status, and therefore aggregate information on the nativity of participants could be reported in such a way that maintains confidentiality. Study investigators can also seek an NIH Certificate of Confidentiality, if they collect additional immigration-related variables and are concerned about the sensitivity of this data for their participants.

Although the GWAS literature has proven fruitful at discovering common replicable loci that are associated with complex traits and diseases, they have often failed to identify causal variants or interactions with disparate environments. Previous diversity initiatives have largely been focused on either (1) forming new studies of previously under-represented populations (identified by racial or ethnic self-identification) (e.g., in body mass index GWASs[37–39]) or (2) combining across multiple race/ethnic groups using a trans-ancestral or global analysis paradigms (e.g., the Population Architecture using Genomics and Epidemiology, PAGE, Study[26]). Yet, to date these initiatives alone have not been able to keep pace or close the diversity gap in GWASs (see section on community engagement, policy change, and the social determinants of health below for more information).

Ancestral diversity strengthens genomic insights and the field's relevance to population health trends

Current demographic trends indicate that the US is becoming more ancestrally diverse.[8] Next, I will expand on US Hispanics/Latinos as a marginalized population with great ancestral diversity, rich immigrant histories, and strong transnational ties to illustrate how their greater inclusion can benefit the field of genomics. As described above, Hispanics/Latinos represent the largest racial/ethnic group in the US.[7,8] Attempts to study the genetic etiology of disease in this demographic group, in all of its diversity (i.e., ancestrally, culturally, linguistically, racially, socioeconomically, and in terms of life experiences), can benefit the knowledge base for future public health initiatives.

The diversity of US Hispanics/Latinos creates opportunities for precision medicine.[27] This ethnic group's greater ancestral diversity[40] may actually improve our power and ability to both discover and describe genomic loci. For example in the work of the Hispanic/Latino Anthropometry (HISLA) Consortium, we were able to (1) discover and generalize four novel genetic loci/signals for anthropometrics in adults of multiple ancestries (e.g., African and European) and (2) describe an additional 38 novel findings by

combining across ancestries.[39] Analyses of our trans-ancestral GWASs revealed that its greater diversity allowed us to estimate effects with better control for population stratification than if we had only analyzed the GWASs of European ancestry. The HISLA Consortium is only one of many needed initiatives to address the research gap between who is being studied and who should be benefited by genomic discoveries. Similar population-specific initiatives have bolstered what is known about the genomics of lipids, type 2 diabetes,[41] and psychiatric genetics,[42] to name a few. We also plan to expand our Hispanic/Latino GWASs to include cardiovascular outcomes in the near future.

With the spread of the obesity pandemic across the globe, many developing countries have transitioned from growth stunting and under-nutrition to pervasive obesity and over-nutrition.[43] For example, many countries in Latin America now face what is called a "double burden" of malnutrition characterized by the presence of both growth stunting and obesity, within the same community or individual. In fact, the obesity epidemic in Latin American adults is quickly approaching the epidemic seen in the US.[44] US Hispanics/Latinos face disparities in obesity and have the highest lifestyle risk of type 2 diabetes of any race/ethnic group.[45]

Nearly 60% of all US Hispanics/Latinos are of Mexican descent.[7] Projections based on Mexico imply that as few as 12% of Mexican men and 9% of Mexican women will be able to maintain a healthy weight by 2050.[46] Continued reliance on past epidemiologic observations of a "Hispanic paradox," first described in Mexican immigrant populations who immigrated decades ago,[6] is not an adequate public health approach. In fact, my own work with weight histories in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) shows that younger Mexican Americans, born in or immigrated to the US after 1980 (often considered the onset of the obesity epidemic), experience a worse trajectory of early adulthood weight gain than their co-ethnic peers.[47] Each of these lines of evidence imply that a Latino/Hispanic cardiovascular health crisis is still on the horizon.[48]

Variability in life exposures can pinpoint complex etiology of complex diseases

To date gene-by-environmental (GxE) interaction models have generally focused on interacting individual genetic with singular environmental exposures—yielding what has appeared to be small to modest interactions.[49] There has been a movement in genomics research to study all intrinsic-by-extrinsic factor interactions (IxE) instead of individual GxE interactions. Often environmental factors arise in conjunction with other factors. Environmental scientists have referred to this complex combination and layering of environmental exposures as the "exposome." Recent GxE methodologic innovations have led to the successful modeling of multiple variants, nested "layers" of environmental influence[50,51], and multiple exposures occurring at various times across the life course, but more research in this area is needed.

The exposome has been described as an alternative to a biologic "omics"-only approach, but much of its recent application has ignored the disparities in environmental exposures that are perpetuated through social or political processes.[51] Thus, a critique of the traditional exposomic approach is that it may inadvertently "molecularize" complex phenomena and therefore obscure the complexities of the social exposome or health disparities. Others have called for a "compound exposome" approach that first incorporates aspects of the social exposome, neighborhood factors, increased understanding of racial/ethnic groupings as social constructs, and then goes on to "compound" this work with community-engagement.[52]

The diversity of ancestry, allele frequencies, and linkage disequilibrium seen in many immigrant populations implies that these populations harbor a wealth of intrinsic variability. Recent immigrants should be a high priority for studies of exposomics, such as the varied IxE interactions described above.[49] The changing nature of extrinsic factors with the migration process present both opportunities for natural experiments and studies of mismatches between *in utero*, early, and later-life environments. For example, we have described what could be called IxE interaction in a recent study of polygenic score interactions on obesity in the HCHS/SOL study.[53] We found that age at immigration and diet quality each significantly interacted with polygenic scores for body mass index. By accounting for such a wide-array of environmental exposures, we were able to improve the variance explained from 10% to 16%—a 60% relative increase in variance explained.

Additional work should endeavor to assess how the nested layers of the environment interact with ancestry to increase our understanding of GxE interactions in immigrant populations. It is likely that such studies can elucidate resiliencies to be promoted in other, non-immigrant populations. For example, "shift and persist" strategies can help an individual reappraise one's stressful life events and building one's strength to endure.[54] Although these strategies were first described with children's health, they may in part explain why largely immigrant populations seem to experience lower rates of several health conditions than one would expect based on their lower socioeconomic status.[9]

To date, most research on immigrant populations has been conducted once immigrants are settled in their host countries. Additional insights could be garnered from immigration-focused study designs that compare immigrants (current, former, or intended) with non-immigrants within the same country of origin or by modeling propensity of emigration as a covariate. Longitudinal studies that track individuals across borders or use between/within-subject comparisons

(i.e., immigrant and non-immigrant; pre- versus post-immigration) are rare, even though they hold great potential for advancing the field.

Community engagement, policy change, and the social determinants of health

As we endeavor to strengthen the diversity of GWASs with respect to the inclusion of immigrants, we must also consider the ethical, legal, and social implications of the hard work ahead.[55,56] Funders and publishers should push researchers to follow best-practices for promoting inclusion in genomics, including community-engaged research programs or community partnerships,[57] and advocate for the involvement of under-represented groups in the genomics workforce and decision-making more broadly.[27] Yet, the promotion of community engagement has been slow, and information on how to translate genomic information into effective, scalable health programs still remains elusive for some community contexts.

Even though federal, state, or local immigration-related policies of the US have been consistently linked to barriers to access to care, utilization, and the health disparities faced by Hispanic/Latino populations,[58] to date there has been little progress made in terms of federal immigration policy reform.[59] Furthermore, additional barriers exist for unauthorized immigrants who are barred from participating in the health care marketplace under the Affordable Care Act as well as many other safety net programs.[56] Both funders and GWAS catalogs should begin to monitor immigrant representation to ensure the field's increasing reliance on clinical biobanks does not inadvertently exacerbate the lack of diversity with respect to immigration or ancestry.

Conclusion

Greater inclusion of immigrants holds great promise for moving the genomics field forward in terms of discovery, characterization, and GxE interactions. Additionally by considering immigration, a social determinant of health, genomics can also positivity impact precision public health, as it explores reasons for inter-individual variability in response to the same environment.[60] Not only is improving the inclusion of immigrants in genomics a matter of good science, it is also a matter of good research *citizenship*. An intentional shift must be made within the field to promote immigrant populations in genomics and rectify the diversity gap in GWASs.

Data and code availability

No data or code were generated as part of this commentary.

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Declaration of interests

The author declares no competing interests.

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