

Intersectionality and genetic ancestry: New methods to solve old problems



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Racial divisiveness is a known contributing factor to negative health outcomes such as increased chronic disease among minority populations. We need innovative studies to bridge these diversity gaps in health and a paradigm shift in our approaches. Certainly, there is strong motivation to close these gaps, but one of the reasons these problems persist is the societal construct of “race.” In practice, individuals often use the words “race,” “ethnicity,” and “ancestry” interchangeably, and science and society would benefit tremendously from more precise usage.¹ Race is a social term that is primarily defined by physical characteristics, ethnicity describes behavioural and cultural factors, whereas ancestry describes genetic lineage.¹ Unfortunately, our cultural biases cause us to prefer the terms race and ethnicity, which can reinforce harmful and prejudiced social structures. By comparison, distinctions based on ancestry use precise genomic information and represent a more unbiased clinical mechanism to bridge the health gap created by racial divisiveness. Having accurate and consistent clinical classifications of different ancestries that minimize stereotypes, over-generalizations, and other overly simplistic interpretations is a necessary first step. After we have established reasonable ancestral classifications, we need to study how our lived experiences intersect with our ancestry and how that impacts our health (Figure 1).

Chronic diseases vary in prevalence amongst non-Hispanic White, non-Hispanic Black, and Hispanic people.² The cause of these disparities may have a genetic origin, but harmful external factors (e.g., unequal and inadequate access to health care, exposure to malnutrition, and limited educational opportunities) are also associated with a higher risk of disease, and these factors disproportionately affect minorities.³ In addition to socioeconomic factors, cultural factors can heavily influence health outcomes. For instance, multiple studies

have shown that a common contributor to higher cervical cancer mortality among Muslim and Asian American women is reluctance to undergo Pap smear tests due to religious/cultural concerns of intimacy in such medical screenings.⁴ Intersectional studies such as these have become an important tool for understanding health disparities.³ Policymakers can then address health disparities by advancing social policies that improve the communication for doctors serving relevant patient groups to reduce these disparities. Other policies can reduce the pathological insults generated by substance abuse, remedy nutritional deficits, reduce exposure to poor air and water quality, or improve healthcare options that can improve the overall societal health.³ To support intersectional studies of health disparities, we need excellent data about the genetic background of the populations in question. Strong cross-sectional studies that factor in ancestry can evaluate the synergistic effects stemming from common risk factors in individuals from different geographical and social backgrounds, and differentiate the intrinsic and extrinsic determinants of health outcomes.

Although some studies have closely examined the relationship between genetic ancestry and pathology, to date most clinical cohorts with genomic data come from non-diverse study groups of mostly European ancestry and lack representation from much of the global population.⁵ Our failure to adequately represent different ancestries has distorted disease variant analysis. For example, for several cardiac diseases, the lack of diversity in genomic studies has led to misdiagnoses in African Americans.⁶ We therefore need to adequately quantify the risk that is attributable to ancestral specific genetic loci. At the same time, we need to incorporate biologically relevant and quantifiable variables derived from intersectional analysis into our experiments. Incorporation of both these elements will allow us to disassociate environmental from genetic components of an individual’s disease risk.

The 21st century has seen the advent of several technological breakthroughs that can help us quantify the risk to ancestral specific genetic loci, including stem cells, genome editing technology, and 3D organoid models, amongst others. Human-derived induced

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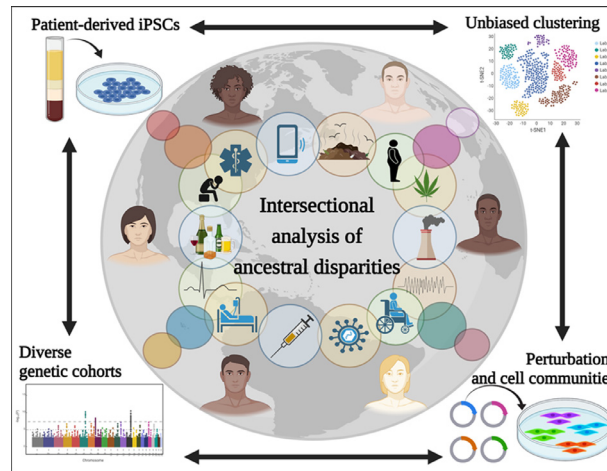


Figure 1. Researching intersectionality and ancestral differences. The combination of patient-derived iPSCs, diverse genomic cohorts, emerging genome editing technologies, and rational variables identified from intersectional studies may provide a model for testing the genetic and environmental contributions to a wide spectrum of phenotypes. Created with [Biorender.com](https://www.biorender.com)

pluripotent stem cells (iPSCs) and their differentiated cells types allow researchers to establish in vitro models of human diseases.⁷ Human iPSCs have the potential to revolutionize the care of patients by offering an individualized assessment of disease risk, including the adverse effects of different medications that may affect individuals from different genetic ancestries differently. We can also utilize stem cell lines of known ancestral origins and apply the different stressors derived from intersectional studies to characterize the genotype-phenotype relationship of pathological stimuli.⁷

A new approach to studying disease variants involves the use of genome editing technologies to rapidly study multiple variants in parallel.⁸ By systematically activating/inhibiting relevant pieces of the genome and quantifying the effects on different cellular functions, any genetic perturbation can be evaluated.⁹ The question of disease severity—how a mutation could be pathogenic in one ancestral group but not another—is one that can be readily tackled by this new method. Another new approach that promises to significantly improve our understanding of the impact of ancestral genomics on health disparities is the development of 3D organoid models for studying different genotypes and cell types. For example, a recent study took stem cell lines from ~30 individuals to create a “cell village” in which the phenotype exhibited could be traced back to specific genotypes, creating a deeper understanding of the phenotype that accounts for genomic diversity.¹⁰ Constructing artificial tissues derived from diverse individuals will allow us to understand how different alleles lead to variability in severity associated with ancestral differences.

In conclusion, to address health disparities, we need to increase the representation of traditionally marginalized individuals in all aspects of healthcare and use new

technologies available to us to better understand the interplay of individual genetics and environmental factors contributing to health disparities. In the future, we can move beyond just recognizing bio-complexity to apply new tools and more comprehensive models, which will ensure that our discoveries, treatments, and opportunities are accurate and equitable.

Contributors

CDV and MM performed the literature search, writing and designed the visualization (figure making). NKM provided conceptualization input for the text. JCW also provided concepts for the development of this manuscript as well as administrative and financial resources that contributed to its central theme. All authors read and approved the final version.

Declaration of interests

JCW is a co-founder and board member of Greenstone Biosciences and Khloris Biosciences, and a board member of Keystone Symposia and American Heart Association. The other authors declare no conflicts of interest.

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