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Editorial: Diversity in stroke omic(s) and epidemiology research: opportunities and challenges

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Editorial on the Research Topic
Diversity in stroke omic(s) and epidemiology research: opportunities and challenges

Introduction

Stroke is the leading cause of disability and second leading cause of death worldwide (GBD 2019 Stroke Collaborators, 2021; Saini et al., 2021; Feigin et al., 2022). Globally, ~15 million people suffer a stroke annually: one-third die, another third are permanently disabled (World Health Organisation, 2024). Stroke costs >$721 billion annually worldwide in healthcare and missed productivity (Feigin et al., 2022). Dramatic health disparities exist in stroke risk, treatment and outcomes, with higher incidence, complications and fatality in people of non-European ancestry and lower socioeconomic status (SES; Fukino et al., 2007; Carty et al., 2015; Carnethon et al., 2017; Kamin Mukaz et al., 2020; Chandler et al., 2021; Akam et al., 2022). Lower income countries have almost 90% of stroke deaths and disability (Feigin et al., 2022). Translating knowledge from stroke genetics is challenging in part because of the dearth of diverse studies −95% of large genomic studies and clinical trials include solely European ancestry populations (Mills and Rahal, 2020). Furthermore, there is limited genetic testing, particularly in the socioeconomic and racial groups most impacted (Carty et al., 2015; Carnethon et al., 2017; Ferrario et al., 2017; Kamin Mukaz et al., 2020; Brown et al., 2021; Prapiadou et al., 2021; Denorme et al., 2023). This Research Topic, entitled "*Diversity in stroke omic(s) and epidemiology research: opportunities and challenges*," features five original papers as examples of multifaceted approaches to exploring diversity in the populations, clinically relevant problems and techniques in stroke genomics research. They include an exploration of population needs assessments to identify potential gaps in health literacy, and a roadmap for critical community engagement necessary to translate genomic knowledge into clinical practice and social policies.

First, Brown et al. examine underrepresentation in genomic medicine, especially for stroke. Using Hawai'i and the Pacific Islands as a case study, they highlight important consequences of underrepresentation and suggest avenues to improve participation of diverse populations in stroke genomic studies. Distinguishing between racial identity, a social construct, and genetic markers of ancestry, the authors reinforce our knowledge that perpetuating current exclusionary practices (intentional or unintentional) in genomic studies will result in development of biased protocols and practices that do not apply to non-European ancestry groups, and treatments from which they do not benefit. They argue that to successfully recruit diverse participants in genomic stroke studies, investigators must seek to understand their target communities, align research goals with the community's values, engage them early in study design, and prioritize their rights.

There is no cure for stroke. Only two treatments for acute stroke exist: intravenous thrombolysis and endovascular thrombectomy. Most patients are ineligible for either because they seek medical attention too late or their causative lesion is not amenable to thrombectomy (O'Connor et al., 1999; de Los Ríos la Rosa et al., 2012). Early symptom recognition and receiving timely emergency medical care and acute treatments are critical. In their study of African American adults in South Carolina, the American state with the greatest stroke incidence and mortality, Sunmonu et al. show that two aspects of stroke literacy—knowledge of stroke signs and symptoms and intent to call emergency medical services (EMS) in the event of a stroke—were significantly lower in older adults, males, and those with high school education or less. Consistent with previous reports (Miller et al., 2007; Williams et al., 2012), greater awareness of stroke symptoms increased intent to call EMS in the event of a stroke. Encouragingly, stroke literacy and intent to call EMS were higher in stroke survivors and increased over the 18-year course of their study, highlighting the impact of stroke education on stroke survivors and perhaps the population overall. It also demonstrates population-specific opportunities to improve timely emergency room arrivals and therefore improve eligibility for acute stroke treatments.

Genomic studies can inform whether our understanding of biologic processes can be translated to different physiologic milieux. In a clinical study, Ruhl et al. show there are important nuances in different biological niches that may preclude findings from one being translated to another. For example, nitric oxide (NO) has a complex role in stroke hemodynamic regulation but overall appears to improve blood flow (Radomski et al., 1987, 1990). Alpha globin (HBA) regulates endothelial NO, and genetically deleted HBA appears to protect from kidney disease, presumably via increased NO. Since HBA copy number is variable in people of African and Asian ancestries, Ruhl et al. postulated that HBA copy number could mitigate stroke risk in these populations. However, they showed that incident ischemic stroke is independent of HBA copy number in a cohort of African ancestry individuals. Their findings reiterate that when ancestry-specific genomic information drives clinically relevant, hypothesis-driven studies, the resulting information can be quite different from that anticipated on the basis of existing studies and known physiology. This impacts the applicability of other extracranial vascular mechanisms to stroke risk.

Beyond well-known vascular risk factors (e.g., hypertension and diabetes), investigators continue searching for new clinical stroke risk factors to better define at-risk individuals. Here, Jayaraman et al. suggest pulmonary hypertension (PH) may be one such factor. In a cohort of hospitalized patients with incident stroke, most of them also had PH. Concurrent PH increased length of stay and stroke-related mortality. This effect was greater in patients who were younger, female, and Hispanic, Native American, Asian or Pacific Islander. Pulmonary hypertension and concurrent ischemic stroke occurred in Black patients almost a decade earlier than White patients. In all, their study supports PH as a risk factor for stroke, and its impact varies across populations.

Nearly one-third of strokes are recurrent events. People who suffer a recurrent stroke are more likely to become disabled or die (Skajaa et al., 2022; Aked et al., 2024). As with incident stroke, these outcomes are magnified in people of African ancestry compared with those of European ancestry (Park and Ovbiagele, 2016; Albright et al., 2018; Castello et al., 2021; Robinson et al., 2022). In a genome-wide association study (GWAS) using cohorts of diverse ancestral origin, Aldridge et al. examined the genetic risk of recurrent stroke. They discovered 18 unique genetic loci significantly associated with increased risk of recurrent stroke. These loci have known stroke biological relevance. Importantly, the authors also demonstrate that polygenic risk scores designed for incident stroke may not be applicable to recurrent stroke, suggesting that recurrent stroke may be a distinct phenotype from incident stroke.

Summary and conclusions

This Research Topic demonstrates the importance of broadly diverse participants, methodologies and clinical questions in stroke genomics specifically and stroke epidemiology in general. Genomic studies can minimize stroke disparities by identifying unique genetic profiles to predict stroke risk and even guide customized therapeutics (Mishra et al., 2022). However, lack of participant diversity in current stroke genomics research effectively excludes underrepresented populations from potential and novel therapeutic interventions based on these studies and perhaps exposes them to unnecessary risk from such derived therapies. Genetically defined factors such as ancestry are important modifiers of stroke risk and should inform overall clinical risk assessment at the individual level for better, more accurate and personalized care. Enriching the current pool of genomic data with information from multi-ancestry cohorts is an important first step in ensuring broad representation in genomic reference databases and easier identification of key genomic factors that can accelerate the development of targeted therapies with great potential to benefit the general population.

A huge knowledge gap exists in our translation of genomic predictors of stroke risk into prevention and treatments for at-risk populations. Early identification of genetically vulnerable individuals could have a seismic impact, similar to the paradigm already implemented in cancer therapeutics. Additional screening for validated genetic and genomic variants from representative populations may complement clinical stroke screening. Despite the current challenges of genomic stroke studies, opportunities abound to leverage advanced genomic technologies to investigate novel

dimensions of stroke risk in order to minimize incidence, mitigate severity and enhance recovery.

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