The Importance of Conducting Stroke Genomics Research in African Ancestry Populations

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There is a pronounced health disparity in the burden of stroke between African and European ancestry populations. Compared to European Caucasians, African ancestry populations experience an increased incidence of stroke, a younger age of onset, worse prognosis, and a stronger propensity to the hemorrhagic form of stroke. The contributors to this disparity are multifactorial, but likely include differences between populations in conventional stroke risk factors and socioeconomic factors, and the interplay between these factors and genetic background. To date, there are few large-scale genetic studies of stroke in African ancestry populations. Such studies would provide novel insights not realizable from studies of European populations. The authors describe multiple aspects of the stroke disparity between European and African ancestry populations, and summarize the rationale and caveats for including African ancestry populations in the current genomic era of stroke research.

Genome-wide association studies (GWAS) and other -omics technologies have greatly accelerated the discovery of novel susceptibility genes for a host of diseases in the hopes that some of these discoveries will reveal new biologic pathways that can be targeted to prevent disease and improve health. However, gene discovery efforts for stroke, as for many other diseases, have been carried out to date primarily in populations of European Caucasian ancestry. As outlined subsequently, the epidemiology of stroke differs substantially between populations of African and European descent, and there is potentially much to be learned by broadening the study of stroke genetics to include populations of African ancestry.

DISPARITIES IN THE BURDEN OF STROKE BETWEEN AFRICA AND WESTERNIZED COUNTRIES

Several recent studies have demonstrated that the burden of stroke in Africa is increasing [1,2], with stroke among the leading causes of morbidity and mortality throughout continental Africa. In contrast, stroke incidence in many high-income (Westernized) countries appears to be declining [3]. Although the causes of these divergent trends are not fully understood, disparities in cardiovascular risk factor control as well as lifestyles and sociodemographic factors appear to be key contributors [4]. One key limitation to understanding these trends is simply the lack of accurate stroke-related data among African populations. In a systematic review of literature on stroke in Africa published between January 1960 and June 2014, Owolabi et al. [2] reported a nearly 15% increase in ischemic stroke and nearly 30% increase in hemorrhagic stroke between the periods 1990 and 2010. Annual stroke incidence in 2010 was estimated at up to 316 cases per 100,000 individuals depending on the country evaluated. As a comparison, this rate is higher even than the previous stroke epidemic in the United States in the mid-1990s (incidence rate for first-ever and recurrent stroke of 269 per 100,000 individuals) [5], which has since seen up to a 40% incidence reduction among U.S. Medicare populations ≥65 years of age [6].

Along with an increased incidence of stroke, crude mortality rates due to stroke have also increased in sub-Saharan Africa between 1990 and 2010, again contrasting with a decline that has been observed in high-income countries [7,8]. Although communicable diseases such as HIV and lower respiratory infection remain as the top causes of death in Africa, stroke is the leading cause of death due to noncommunicable diseases in sub-Saharan Africa, accounting for 4.74% of all deaths according to a World Health Organization 2012 report [9]. Post-stroke fatality rate is also significantly higher in Africa. According to the INTERSTROKE (the study of the modifiable risk factors of acute stroke in 22 countries) study, the 1-month fatality rate after stroke was 22% in the African region compared to 4% in high-income regions [10]. Moreover, a higher disease burden due to stroke is also observed in Africa, as reflected by disability-adjusted life years. For example, in 2002, the estimated disability-adjusted life years due to stroke were 1,230 per 100,000 individuals in Angola (Africa) versus 200 per 100,000 individuals in Switzerland [2]. In summary, available data, although limited, certainly point to a high stroke incidence and worse outcomes post-stroke in Africa compared to Westernized countries. Although these trends reflect in part a limited access to health care services and support, and a relative lack of effective prevention and treatment policies in Africa, they are also likely to reflect an increases in stroke—pre-disposing conditions in Africa, such as uncontrolled hypertension, diabetes, and obesity [11].

DISPARITIES OF THE STROKE EPIDEMIC IN AFRICAN AMERICANS

The African and European disparity in stroke burden extends at least in part to African Americans (AA) and European Americans (EA) residing in the United States, thereby providing a valuable resource for the study of

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ethnic-based differences in stroke. For example, AA have a higher incidence of stroke, more hemorrhagic stroke, and higher stroke mortality as compared to their EA counterparts [12,13]. Per the 2016 American Heart Association statistics updates, 4% of adult AAs have experienced a stroke compared to 2.5% of adult EAs [14]. Age-adjusted stroke incidence rates are consistently higher in AA than in EA [15,16]. It has been further noted that the higher incidence of stroke, rather than case fatality difference, was the main driver for the substantially higher stroke mortality in AA 45 to 65 years of age compared to EA, according to data from the recent REGARDS (REasons for Geographic and Racial Differences in Stroke) study and the previous Greater Cincinnati/Northern Kentucky Stroke Study [17,18]. Additionally, the U.S. African ancestry population also appears to exhibit a poorer prognosis after stroke. A national study of inpatient rehabilitation after first stroke found that AA were younger than EA, had a higher proportion of hemorrhagic stroke, and were more disabled on admission [19]. In this study, even after adjustment for age and stroke subtype, AA had less improvement in functional status per inpatient day and had poorer functional status at discharge as compared to their EA counterparts. In another study, AA were less likely to report independence in activities of daily living and instrumental activities of daily living than EA 1 year after stroke even after controlling for stroke severity and comparable rehabilitation use [20].

The ethnic disparities in stroke incidence and prevalence are thought to be driven by a variety of factors, including a higher prevalence or severity of stroke risk factors (especially hypertension and diabetes), lower socioeconomic status among AA, or a higher susceptibility to strokes among AA due to a stronger biological or genetic vulnerability. Although all these factors are important, the higher prevalence of standard vascular risk factors among AA cannot be overemphasized, as this provides a critical intervention and stroke prevention opportunity. In the REGARDS study, traditional stroke risk factors accounted for 40% of the excess stroke risk in AA between 45 and 64 years of age, with systolic blood pressure level alone accounting for up to 20% [21]. However, it is important to note that this likely underestimates the effects of traditional risk factors, which develop at earlier ages in AAs and are difficult to account for in such analyses. The earlier onset of vascular risk factors among AA may also partially explain the observed differential impact of the same risk factors among ethnicities. For example, a 10 mm Hg increase in levels of systolic blood pressure was associated with 3 times greater increase in stroke risk in AA compared to EA (i.e., a 24% increase in AA but only an 8% increased risk in EA) [16]. In any case the excess stroke incidence among AA is multifactorial, with the development of risk factors and their subsequent sequela, namely stroke, at least partially influenced by biological and genetic ethnicity-based differences.

CHARACTERISTICS OF STROKE TYPES/SUBTYPES IN AFRICAN ANCESTRY POPULATIONS

Stroke can be classified into 2 major types: ischemic strokes, caused by blockage of vessels supplying blood to the brain, and hemorrhagic strokes, which are caused by rupture of the vessels with subsequent bleeding into the surrounding brain. The incidence of stroke types, namely ischemic and hemorrhagic, as well as their associated subtypes has also been shown to vary by ethnicity. For example, the proportion of hemorrhagic stroke in Africa ranges from 29% to 57% compared to 6% to 20% in North America [22]. The INTERSTROKE study demonstrated that hemorrhagic stroke accounted for 34% of all strokes in Africa but only 9% of all strokes in higher-income countries [10]. Given the strong association of hypertension with hemorrhagic stroke, these differences at least partly suggest a higher burden of uncontrolled hypertension in Africa as a driver of the high prevalence of hemorrhagic stroke in Africa [22,23].

Ischemic stroke can be classified based on its etiology using the TOAST (Trial of Org 10172 in Acute Stroke Treatment) study [24] or the Causative Classification of Stroke [25] classification systems into following broad categories: cardioembolic stroke, stroke due to large artery atherosclerosis, lacunar stroke (stroke due to small vessel diseases), stroke due to other mechanisms, and undetermined causes. AAs in the United States have an increased incidence of small vessel, intracranial large artery, and undetermined stroke subtypes, and a decreased incidence of cardioembolic stroke compared to European Caucasians [26-31]. For example, in the biracial Greater Cincinnati/Northern Kentucky Stroke Study population (n = 1,956) of first-ever ischemic strokes, small vessel strokes and strokes of undetermined cause were nearly twice as common among AA compared to EA and large vessel strokes were 40% more common among AA [29]. Similarly, the SLESS (South London Ethnicity and Stroke Study) study conducted in the United Kingdom reported an excess of small vessel disease (odds ratio [OR]: 2.74) and less extracranial large vessel atherosclerosis (OR: 0.59) and cardioembolic stroke (OR: 0.61) in African ancestry populations compared to EA patients with stroke [32,33]. These differences persisted even after controlling for conventional risk factors and social class, implicating unmeasured or inadequately measured risk factors or differential genetic susceptibility as potential contributors to these ethnic differences [32,33].

Ethnic disparities in stroke between AA and EA appear to be more prominent in early onset stroke. One publication reported the relative excess in deaths from stroke among AA compared with EA was most manifest in the population <65 years of age, for which the AA to EA mortality ratio was 3.7 among men 45 to 54 years of age compared to 2.2 among men 65 to 74 years of age [34]. Furthermore, in the Northern Manhattan Stroke Study AA 20 to 44 years of age were found to be 2.4 times more likely to have a stroke than were similarly aged EA [35].