Sex, Ethnicity, and CVD Among Women of African Descent

An Approach for the New Era of Genomic Research

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Cardiovascular disease (CVD) is the leading cause of death for both men and women globally, responsible for approximately 17.9 million deaths each year [1]. CVDs disproportionately affect women and men of color. Black women are more likely to succumb to CVDs than all other Americans and have high rates of other non-communicable diseases such as diabetes, obesity, chronic kidney disease, and hypertension [2-4]. These comorbid diseases significantly increase the chances of black women developing CVDs within a lifetime, adding to the disparity in this population.

Even with this disproportionate burden among women of color, there continues to be a well-documented gap in the participation of women and minorities in CVD-related clinical trials. Similarly, sex and ethnicity remain underreported and inadequately analyzed in genetics-based research. Meta-analyses performed by Cochrane Systematic Reviews revealed that women represented only 27% of participants of 258 clinical CVD trials [5]. A disconcerting disparity, considering that women carry over 53% of the disease burden [5]. Also, many CVD-related genome-wide association studies (GWAS) inadequately or completely fail to include sex as a variable in study designs and sex-specific analyses in subsequent publications [6]. Furthermore, the majority of GWAS have not focused on diverse populations [7]. Although, it is widely accepted that ethnicity, which includes culture and geographical origins of ancestry, can significantly influence disease risks between groups.

In 2015, the National Institutes of Health (NIH) launched the Precision Medicine Initiative, a strong investment toward genomics research and individualized healthcare [8]. Research that considers sex and ethnicity will strengthen precision medicine efforts and enhance dissemination and implementation of medical advancements for diverse populations. Therefore, we want to highlight important topics surrounding the study of ethnicity and sex in genetics-based research and encourage investigators to include these variables in their research study designs and evidence-based intervention strategies.

SEX AS A BIOLOGICAL VARIABLE

There are distinct biological differences between men and women that contribute to sex-based differences in CVDs. These differences manifest in several ways and may affect diagnoses, risk predictions, treatment outcomes, and management strategies [9]. Although important, sex is understudied and not well understood, contributing to a fundamental gap in knowledge. To address gaps in sex-based research, in 2015, the NIH enacted the Sex as a Biological Variable (SABV) policy [10] as a part of the efforts to enhance reproducibility through rigor and transparency [11]. Both intramural and extramural research investigators funded by the NIH are required to consider sex in their basic, preclinical, and clinical research studies. SABV policy calls for investigators to include both sexes in all vertebrate animal and human research designs, including genetics and genomics research, unless they can strongly justify a reason for studying a single sex, such as cases where a specific disease is absent in the opposite sex (e.g., cervical and prostate cancers). Appropriate implementation of this policy will improve transparency and rigor in research by challenging investigators to consider sex in study designs, while also training scientific reviewers to determine the adequacy of inclusion in grant review to influence meaningful research discussions, analyses, and outcomes. In addition to the SABV policy, earlier this year a panel of thirteen experts from 9 countries came together to create the Sex and Gender Equality in Research (SAGER) guidelines. The SAGER guidelines provide recommendations to authors and journal editors on the appropriate reporting of sex and gender in scientific manuscripts [12]. Together, these efforts highlight the gaps in research on sex and gender, and the critical need for inclusion, rigor, and transparency in research design, analyses, and reporting of results to inform practice.

ETHNIC GROUPS OF AFRICAN DESCENT

Genetic studies comprised of abundant samples of diverse ethnic populations have yielded important data related to variants linked to disease. One of the most significant genetic findings in recent history comes from the discovery of risk variants (G1 and G2) in the apolipoprotein L1 gene (ApoL1) [8]. These variants are common in people of recent African ancestry and have been identified as significant risk factors for hypertension-attributed chronic kidney disease in African American populations. A single copy of either high-risk variant (G1 or G2) offers protection against *Trypanosoma brucei* ssp. including *T. b. gambiense* and *T. b. rhodesiense*, the parasitic protozoans that cause African sleeping sickness [8]. However, inheriting 2 copies of either at risk variant increases an

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individual's chances of developing chronic kidney disease significantly, while also increasing the risk of CVD [13]. These new genetic discoveries serve as examples of the necessity of large, ethnically diverse, genetics-based participatory research studies, which can unmask the underpinnings of disease.

Until recently, participatory research studies and large GWAS efforts focused primarily on European populations. Specifically, individuals of African descent only represent 3% of all GWAS studies [7]. NIH-funded efforts including the 1000 Genomes Project and Human Heredity and Health in Africa (H3Africa) Initiative address some of this disparity by supporting large genetics research studies in African populations [14,15]. These projects serve a dual purpose by directly informing the health in African subgroups and providing insight on modern diseases affecting individuals of recent African descent. Transcontinental research efforts in Africa have helped to disentangle some of the historical evolutionary complexities of Africans and African Americans. For example, a recent study by Tishkoff et al. [16] revealed the evolutionary origins of the high-risk ApoL1 G1variant, tracing it to the Yoruba peoples of West Africa, of whom many African American individuals are descendants [17]. Studies, such as these that include significant numbers of participants of African descent, including women are critical to fully understand the effects of ethnicity on CVDs and other noncommunicable diseases such as diabetes, hypertension, and obesity, in highly susceptible groups where there are known genetic links.

CHALLENGE TO FUTURE RESEARCHERS

What we now know about health disparities in CVD has changed significantly as clinical research has diversified the populations of study through the inclusion of women, ethnic minorities, and strong global research efforts. We have made substantial strides in this area, yet there is still much work to be done. Sex and ethnicity remain underreported and inadequately analyzed in genetics-based research. A deeper understanding of risk regarding genetic predisposition is imperative for the success of personalized medicine approaches. To date, the majority of scientific research data related to CVDs are not disaggregated by both ethnicity and sex, making it difficult to develop targeted interventions and medications that can adequately and sensitively treat women of diverse subgroups.

Among black women, the risk of dying of heart disease is especially high and disturbing. Although it is well known that lifestyle behaviors, environmental factors, and socioeconomic status play an important part in this disparity, ethnicity still plays a key role even when those environmental components are considered. As we move into the promising new era of personalized medicine, investigators are encouraged to fully appreciate the inherited biological aspects of CVD along with environmental risk factors. Evolutionary risks such as those explained by the ApoL1 risk variants are likely not anomalies. Additionally, sex has already shown to affect disease in several distinct ways.

The study of sex and ethnicity in genetics-based research is sorely needed, particularly to understand disparities for chronic diseases such as CVD. Research investigators are encouraged to explore these complex variables in their research study designs to improve prevention and personalized approaches to health. Investigators are challenged to enhance the rigor of research by broadening study populations to include both male and female participants and those from significantly underrepresented groups. Investigators are also encouraged to power and to disaggregate their data by both sex and ethnicity to further our understanding of sex-based differences in disease. Guidance from the SABV policy and SAGER guidelines serve as useful tools for research investigators and may prove beneficial to future efforts in sex/gender research. Without understanding the complexities of sex and ethnicity, we are only scratching the surface of discovery from genetic-based research.

REFERENCES

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388:1459–544.
2. Robertson RM. Women and cardiovascular disease: the risks of misperception and the need for action. Circulation 2001;103:2318–20.
3. Howard G, Stafford MM, Moy CS, et al. Racial differences in the incidence of cardiovascular risk factors in older black and white adults. J Am Geriatr Soc 2016;65:83–90.
4. Mensah GA, Wei GS, Sorlie PD, et al. Decline in cardiovascular mortality: possible causes and implications. Circ Res 2017;120: 366–80.
5. Kim ES, Menon V. Status of women in cardiovascular clinical trials. Arterioscler Thromb Vasc Biol 2009;29:279–83.
6. Winham SJ, de Andrade M, Miller VM. Genetics of cardiovascular disease: Importance of sex and ethnicity. Atherosclerosis 2015;241:219–28.
7. Popejoy AB, Fullerton SM. Genomics is failing on diversity. Nature 2016;538:161–4.
8. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science 2010;329:841–5.
9. George J, Rapsomaniki E, Pujades-Rodriguez M, et al. How does cardiovascular disease first present in women and men? Incidence of 12 cardiovascular diseases in a contemporary cohort of 1,937,360 people. Circulation 2015;132:1320–8.
10. National Institutes of Health Office of Extramural Research. Consideration of sex as a biological variable in NIH-funded research (NOT-OD-15-102). Available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html. Accessed January 8, 2016.
11. National Institutes of Health & Agency for Healthcare Research and Quality. Implementing rigor and transparency in NIH & AHRQ research grant applications (NOT-OD-16e011). Available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-011.html. Accessed January 8, 2016.
12. De Castro P, Heidari S, Babor TF. Sex And Gender Equity in Research (SAGER): reporting guidelines as a framework of innovation for an

equitable approach to gender medicine. Commentary. Ann Ist Super Sanita 2016;52:154–7.
13. Tzur S, Rosset S, Shemer R, et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. Hum Genet 2010;128:345–50.
14. Adoga MP, Fatumo SA, Agwale SM. H3Africa: a tipping point for a revolution in bioinformatics, genomics and health research in Africa. Source Code Biol Med 2014;9:10.
15. 1000 Genomes Project Consortium, Abecasis GR, Auton A, et al. An integrated map of genetic variation from 1,092 human genomes. Nature 2012;491:56–65.
16. Tishkoff SA, Reed FA, Friedlaender FR, et al. The genetic structure and history of Africans and African Americans. Science 2009;324:1035–44.
17. Ko WY, Rajan P, Gomez F, et al. Identifying Darwinian selection acting on different human APOL1 variants among diverse African populations. Am J Hum Genet 2013;93:54–66.