HHS Public Access

Author manuscript

Glob Heart. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Glob Heart. 2017 June ; 12(2): 169–171. doi:10.1016/j.gheart.2017.01.008.

Genomics Research for a New Age: Examining how our shared evolutionary history is shaping our future disease outcomes

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Abstract

Cardiometabolic diseases are major contributors to mortality and morbidity, and their burden displays global and regional disparities. Gene-environment interactions contribute to the pathogenesis of cardiometabolic diseases. Population differences in genetic structure, ancient environmental pressures that shape the human genome, and early life environmental adversities (e.g., in utero conditions) all contribute to observed disparities in global cardiometabolic diseases. The genetic and socio-cultural diversity of global populations presents opportunities for discovering genomic loci that influence cardiometabolic diseases as illustrated by a few genetic, epigenetic, and population-genetic discoveries leading to notable understanding of disease mechanisms. However, African, Latin American and Hispanic, and indigenous peoples represent less than 4% of all genome-wide association study samples analyzed to date. Using examples of recent studies in African populations, we discuss the crucial importance of conducting genomic studies in ancestrally diverse populations to understand disease mechanisms and to prepare fertile ground for future delivery of precise health care to all individuals.

Genetic studies of ancestrally diverse populations are keys to discovery of new genetic variants that influence disease

Type 2 diabetes and insulin resistance are powerful predictors of cardiovascular morbidity and mortality [1] and type 2 diabetes-associated genetic variants are associated with higher all-cause mortality [2]. However, the genetic architecture and links between diabetes and cardiovascular disease (CVD) are poorly understood, particularly in populations of African

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ancestry. In the past ten years, genomic studies using genome-wide association studies (GWAS) have unraveled novel genetic loci associated with cardiometabolic diseases [3-6]. However, progress towards including ancestrally diverse individuals in genomic research, particularly individuals of African ancestry has lagged [7]. Recent reports indicate that African, Latin American and Hispanic, and native or indigenous peoples represent less than 4% of all GWAS samples analyzed to date [8].

Ancestrally diverse populations have differences in their genetic architecture that provide unique scientific opportunities for variant discovery, and for refining the resolution of susceptibility genetic loci. Missing these opportunities has direct clinical implications. For example, if pathogenicity assignment to variants used to assess risk for developing cardiovascular diseases are wrong, they are not useful and could be harmful. As an illustration, genetic variants presumed to be pathogenic and used in clinical prediction of risk of hypertrophic cardiomyopathy have recently been found to be non-pathogenic when reevaluated in diverse populations. It was found that several individuals of African ancestry received results wrongly indicating that they are at increased risk of developing hypertrophic cardiomyopathy [9]. Furthermore, recent discoveries of African ancestry-specific genetic loci associated with the metabolic syndrome [10] illustrate that ongoing efforts towards precision public health and medical care will benefit all individuals only if diverse populations are involved in the early phases of knowledge generation.

Genetic studies link old environmental pressures with current cardiometabolic diseases

Investigation of the environmental, genetic, and evolutionary factors that contributed to the rise of cardiometabolic diseases is an area of active research. It has long been hypothesized that “thrifty genotypes” that were favorable for survival of our human ancestors by enhancing energy storage during times of erratic food supply may be maladaptive in modern setting of calorie excess, and lead to development of cardiometabolic diseases [11]. Evaluation of GWAS loci associated with type 2 diabetes and obesity found no experiment-wide evidence for signatures of selection in samples of African, European, and East Asian ancestry populations [12, 13]. Although these studies did not provide supportive evidence for positive selection as a major mechanism to explain the high prevalence of these diseases, closer examination of individual loci revealed signals of selection in genetic loci associated with type 2 diabetes and obesity. For example, type 2 diabetes risk haplotypes in *IGF2BP2*, *WFS1*, and *SLC30A8* were found to be targeted by natural selection in sub-Sharan Africans and East Asians [14]. Significant selection signals were also found in African populations in known type 2 diabetes loci including *PROX1*, *GRB14*, *UEB2E2*, *IGF2BP2* and *ARAP1* [13].

We have gaps in our understanding of the specific environmental factors that exerted selective pressure in regions of the genome implicated in cardiometabolic diseases. The diversity of African populations with historical and contemporary diverse dietary and subsistence lifestyles provides a unique opportunity to study these gaps. For example, an insight in understanding the presumed selective pressure has come from studies of *APOL1*

renal risk variants associated with higher rates of end stage renal disease in west African ancestry populations and a deadly form of African sleeping sickness [15]. Evidence shows that the *APOL1* renal risk variants have increased to high frequency because their trypanolytic effect confers protection against African sleeping sickness [16]. Furthermore, significant selection signals were detected in the *PPARA* gene involved in energy metabolism and fat storage during prolonged food deficiency in a southern Ethiopian population sample but not in HapMap African population samples [17]. The selected haplotypes may inhibit PPARA expression, leading to increased carbohydrate oxidation and lipid storage, consistent with the dietary history of the Wolaita population, who depended on *Enset*, a drought-resistant food crop with high-carbohydrate and low-fat and -protein contents domesticated in Ethiopia subsequent to food deprivation 10,000 years ago [17, 18]. These findings suggest that in some African populations, the environment has influenced the genomic architecture of those individuals which has resulted in metabolically and genetically "programming" for enhanced lipid storage. In this context, a shift from a traditional agrarian lifestyle which demands significant energy expenditure, to a high calorie diet and physically less demanding lifestyle, is suggested to increase their risk for cardiometabolic disorders dramatically.

Early life genetic studies can potentially reveal pathways for timely intervention

The timing of public health intervention improves quality of life and increases cost-effectiveness of public health programs. The potential to develop early life interventions for curbing development of cardiometabolic diseases decades later has been illuminated by observational studies that found reproducible associations between early growth/development and susceptibility to cardiometabolic diseases in adulthood. Epidemiological studies of the Dutch Hunger Winter in 1944-45 and China's Great Famine in 1959-61 have enabled understanding of later life health consequences of early life severe undernutrition in European- and Asian-ancestry populations, particularly in people with Western dietary pattern [19, 20]. In contrast, paucity of long-term follow up data during and after incidents of drought and famine in Africa remains a major hurdle to conduct similar studies. Despite this limitation, a study that investigated adult cardiometabolic outcomes of fetal-infant exposure to the Biafran famine in Nigeria by comparing individuals born during and after the famine found that people exposed to the famine in early life had increased risk of hypertension, overweight, and impaired glucose tolerance [21].

The mechanisms underlying the link between early adverse environment and adult cardiometaboloic diseases are not clearly understood. Animal models that were malnourished in-utero were found to have epigenetic alterations with phenotypic consequences [22, 23]. Studies of the Dutch Hunger Winter have also found that epigenetic modulation of prenatal malnutrition may promote adverse cardiometabolic phenotypes in later life [24]. However, we know surprisingly little about the actual nutritional imbalances that induce persistent epigenetic changes with long term phenotypic outcomes. Capitalizing on the seasonal fluctuations in the dietary intake of rural Africans, a study of rural Gambian women and their offspring found that season of conception significantly influences

methylation of candidate metastable epialleles in children, and suggested that nutrients key to methyl-donor metabolic pathways play a role [25]. Further analysis in the same cohort showed that DNA methylation is influenced by periconceptional maternal plasma biomarker concentrations of key micronutrients involved in one-carbon metabolism [26].

Recently, genetic studies are providing a complementary explanation for the observed associations between early growth/development and later life cardiometabolic diseases. A study of large cohort datasets from multi-ancestry populations including those of African ancestry found that genetic factors are the major contributor to the negative covariance between birth weight and adult cardiometabolic risk including blood pressure, type 2 diabetes, and coronary artery disease [27]. Genetic determinants of blood pressure were found to be key mediators in the life-course associations between birth weight and coronary artery disease [27]. Previous studies also showed that loci associated with early growth are associated with adult cardiometabolic diseases and height, highlighting biological pathways of relevance to fetal origins of adult diseases [28]. Further research is needed to understand the functional role of these genetic variants in the mechanistic links between early growth and adult cardiometabolic diseases. Understanding the complex interaction between susceptibility genetic variants and environmental factors leading to risk differences at population- and individual-levels will be crucial to identify intervention targets.

Conclusion

Technological tools and scientific advances in genome sequencing and genome-wide studies since the publication of the Human Genome Project [29] are spearheading our understanding of the genetic diversity of global populations and the relevance of diverse ancestral population samples to discover genetic variants associated with cardiometabolic diseases. We have learnt the risks, and in some instances the mechanisms, conferred by common genetic variants associated with these conditions. Furthermore, genomic advances have started transforming medical care by facilitating inclusion of genetic variants for diagnosis and treatment. As an illustrative example, the field of pharmacogenomics is built on the promise of delivering precision care based on our understanding of genetic variants and their associated risks [30-32]. To deliver this promise to all individuals, the chasm in ancestral diversity of study participants that have remained less represented in GWAS should be addressed [8]. Lessons could be gained from recent successful initiatives that promoted genomic research in diverse global populations including the Human Heredity and Health in Africa (H3Africa), the Mexico National Institute of Genomic Medicine (INMEGEN), the 1000 Genomes Project, and the African Genome Variation Project [33-36]. Moreover, studies that aim to identify the mechanisms underlying genetic susceptibility and its interaction with environmental factors in early life and adulthood can now integrate demographic, behavioral, lifestyle, and genetic variations among populations and individuals and further refine our knowledge-base.

Acknowledgments

Conflicts of interest

F.T-.A. was supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and E.P. is a staff member of the National Heart, Lung, and Blood Institute, National Institutes of Health.

References

1. Scherer PE, Hill JA. Obesity, Diabetes, and Cardiovascular Diseases: A Compendium. Circ Res. 2016; 118(11):1703–5. [PubMed: 27230636]
2. Leong A, et al. Type 2 Diabetes Genetic Predisposition, Obesity, and All-Cause Mortality Risk in the U.S.: A Multiethnic Analysis. Diabetes Care. 2016; 39(4):539–46. [PubMed: 26884474]
3. Iotchkova V, et al. Discovery and refinement of genetic loci associated with cardiometabolic risk using dense imputation maps. Nat Genet. 2016; 48(11):1303–1312. [PubMed: 27668658]
4. Atanasovska B, et al. GWAS as a Driver of Gene Discovery in Cardiometabolic Diseases. Trends Endocrinol Metab. 2015; 26(12):722–32. [PubMed: 26596674]
5. Ligthart S, et al. Pleiotropy among common genetic loci identified for cardiometabolic disorders and C-reactive protein. PLoS One. 2015; 10(3):e0118859. [PubMed: 25768928]
6. Whitfield JB. Genetic insights into cardiometabolic risk factors. Clin Biochem Rev. 2014; 35(1):15–36. [PubMed: 24659834]
7. Peprah E, et al. Genome-wide association studies in Africans and African Americans: expanding the framework of the genomics of human traits and disease. Public Health Genomics. 2015; 18(1):40–51. [PubMed: 25427668]
8. Popejoy AB, Fullerton SM. Genomics is failing on diversity. Nature. 2016; 538(7624):161–164. [PubMed: 27734877]
9. Manrai AK, et al. Genetic Misdiagnoses and the Potential for Health Disparities. N Engl J Med. 2016; 375(7):655–65. [PubMed: 27532831]
10. Tekola-Ayele F, et al. Genome-wide association study identifies African-ancestry specific variants for metabolic syndrome. Mol Genet Metab. 2015; 116(4):305–13. [PubMed: 26507551]
11. Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet. 1962; 14:353–62. [PubMed: 13937884]
12. Southam L, et al. Is the thrifty genotype hypothesis supported by evidence based on confirmed type 2 diabetes- and obesity-susceptibility variants? Diabetologia. 2009; 52(9):1846–51. [PubMed: 19526209]
13. Ayub Q, et al. Revisiting the thrifty gene hypothesis via 65 loci associated with susceptibility to type 2 diabetes. Am J Hum Genet. 2014; 94(2):176–85. [PubMed: 24412096]
14. Klimentidis YC, et al. Natural selection at genomic regions associated with obesity and type-2 diabetes: East Asians and sub-Saharan Africans exhibit high levels of differentiation at type-2 diabetes regions. Hum Genet. 2011; 129(4):407–18. [PubMed: 21188420]
15. Parsa A, et al. APOL1 risk variants, race, and progression of chronic kidney disease. N Engl J Med. 2013; 369(23):2183–96. [PubMed: 24206458]
16. Genovese G, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010; 329(5993):841–5. [PubMed: 20647424]
17. Tekola-Ayele F, et al. Novel genomic signals of recent selection in an Ethiopian population. Eur J Hum Genet. 2015; 23(8):1085–92. [PubMed: 25370040]
18. Ehret C. On the antiquity of agriculture in Ethiopia. J Afr Hist. 1979; 20:161–177.
19. Heijmans BT, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A. 2008; 105(44):17046–9. [PubMed: 18955703]
20. Li Y, et al. Exposure to the chinese famine in early life and the risk of metabolic syndrome in adulthood. Diabetes Care. 2011; 34(4):1014–8. [PubMed: 21310886]
21. Hult M, et al. Hypertension, diabetes and overweight: looming legacies of the Biafran famine. PLoS One. 2010; 5(10):e13582. [PubMed: 21042579]
22. Reik W, Dean W, Walter J. Epigenetic reprogramming in mammalian development. Science. 2001; 293(5532):1089–93. [PubMed: 11498579]

23. Morgan HD, et al. The culture of zygotes to the blastocyst stage changes the postnatal expression of an epigentically labile allele, agouti viable yellow, in mice. Biol Reprod. 2008; 79(4):618–23. [PubMed: 18562706]
24. Tobi EW, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. Hum Mol Genet. 2009; 18(21):4046–53. [PubMed: 19656776]
25. Waterland RA, et al. Season of conception in rural gambia affects DNA methylation at putative human metastable epialleles. PLoS Genet. 2010; 6(12):e1001252. [PubMed: 21203497]
26. Dominguez-Salas P, et al. Maternal nutrition at conception modulates DNA methylation of human metastable epialleles. Nat Commun. 2014; 5:3746. [PubMed: 24781383]
27. Horikoshi M, et al. Genome-wide associations for birth weight and correlations with adult disease. Nature. 2016; 538(7624):248–252. [PubMed: 27680694]
28. Horikoshi M, et al. New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism. Nat Genet. 2013; 45(1):76–82. [PubMed: 23202124]
29. Venter JC, et al. The sequence of the human genome. Science. 2001; 291(5507):1304–51. [PubMed: 11181995]
30. Ahmed S, et al. Pharmacogenomics of Drug Metabolizing Enzymes and Transporters: Relevance to Precision Medicine. Genomics Proteomics Bioinformatics. 2016
31. Khan DA. Pharmacogenomics and adverse drug reactions: Primetime and not ready for primetime tests. J Allergy Clin Immunol. 2016; 138(4):943–955. [PubMed: 27720019]
32. Zaiou M, El Amri H. Cardiovascular pharmacogenetics: a promise for genomically-guided therapy and personalized medicine. Clin Genet. 2016
33. Consortium HA, et al. Research capacity. Enabling the genomic revolution in Africa. Science. 2014; 344(6190):1346–8. [PubMed: 24948725]
34. Moreno-Estrada A, et al. Human genetics. The genetics of Mexico recapitulates Native American substructure and affects biomedical traits. Science. 2014; 344(6189):1280–5. [PubMed: 24926019]
35. Genomes Project C, et al. A global reference for human genetic variation. Nature. 2015; 526(7571):68–74. [PubMed: 26432245]
36. Gurdasani D, et al. The African Genome Variation Project shapes medical genetics in Africa. Nature. 2015; 517(7534):327–32. [PubMed: 25470054]