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Genetic Diversity Landscape in African Population: A Review of Implications for Personalized and Precision Medicine

Olivier Sibomana

Department of General Medicine and Surgery, College of Medicine and Health Sciences, University of Rwanda, Kigali, Rwanda

Correspondence: Olivier Sibomana, Email oliviersibomana917@gmail.com

Introduction: Africa, a continent considered to be the cradle of human beings has the largest genetic diversity among its population than other continents. This review discusses the implications of this high African genetic diversity to the development of personalized and precision medicine.

Methodology: A comprehensive search across PubMed, Google Scholar, Science Direct, DOAJ, AJOL, and the Cochrane Library electronic databases and manual Google searches was conducted using key terms "genetics", "genetic diversity", "Africa", "precision medicine", and "personalized medicine". Updated original and review studies focusing on the implications of African high genetic diversity on personalized and precision medicine were included. Included studies were thematically synthesized to elucidate their positive or negative implications for personalized healthcare, aiming to foster informed clinical practice and scientific inquiry.

Results: African populations' high genetic diversity presents opportunities for personalized and precision medicine including improving pharmacogenomics, understanding gene interactions, discovering new variants, mapping disease genes, creating updated genomic reference panels, and validating biomarkers. However, challenges include underrepresentation in studies, scarcity of reference genomes, inaccuracy of genetic testing and interpretation, and ancestry misclassification. Addressing these requires the establishment of genomic research centers, increasing funding, creating biobanks and repositories, education, infrastructure, and international cooperation to enhance healthcare equity and outcomes through personalized and precision medicine.

Conclusion: High African genetic diversity presents both positive and negative implications for personalized and precision medicine. Deep further research is recommended to harness the challenges and use the opportunities to develop customized treatments.

Keywords: genetic diversity, pharmacogenomics, precision medicine, Africa

Introduction

Africa is the cradle of modern human evolution and the origin of our species' global spread. Paleontological and genetic evidence indicates that modern humans originated in Africa within the past 300 thousand years (ky) and spread across the globe within the last 100 ky. Therefore, modern humans have continuously inhabited the African continent longer than any other region.[1]

The African continent has more genetic variation than anywhere else in the world; the average African genome has nearly a million more genetic variants than the average non-African genome. Africa is also immensely culturally and ethno-linguistically diverse; while the rest of the world averages 3.2 to 4.7 ethnic groups per country, African countries have an average of greater than 8 each and account in total for 43% of the world's ethnic groups.[2,3]

Studies of protein polymorphisms, as well as studies of mtDNA, Y-chromosomal, autosomal, and X-chromosomal DNA variation, indicate that African populations are the most variable and ancestral. Phylogenetic analyses of mtDNA and Y-chromosomal haplotypes indicate that most ancestral lineages are African-specific and that all non-African lineages can be derived from a single ancestral African haplogroup, consistent with the RAO model.[4] This diversity is so extensive that genetic differences within Africans are larger than those between Africans and Eurasians, and this

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supports the "Out of Africa" model of human evolution, suggesting that the genetic diversity in Eurasians is largely a subset of that in Africans.[5]

Africa has a tremendous genetic variety that results from the complex interaction of biological, historical, environmental, and cultural elements.[3] Geographic diversity, which includes a wide range of environments from deserts to rainforests, has encouraged the emergence of unique genetic adaptations in populations living in various places.[6] Genetic mixing and diversity have been promoted by historical migratory patterns, which include the continent's function as the cradle of humanity and later waves of migration and trade. Differential selection pressures and patterns of human migration and settlement, in addition to environmental pressures like endemic diseases and a range of livelihood strategies, have further impacted genetic diversity through cultural practices and societal structures.[7]

Since African populations have demonstrated huge genetic diversity, there is a significant need for innovative interventions to overcome various African-specific health challenges.[8] The last 20 years have seen the emergence of the concepts of P4 medicine; participatory, personalized, predictive, and preventive medicine which has occurred mainly in parallel with the developments in clinical genetics, artificial intelligence, and digital technology. The concept of P4 medicine is mainly based on the use of large volumes of data, mostly biological data, especially for the case of personalized medicine, which is one of the foundations of P4 medicine.[9] Personalized medicine and precision medicine have been developed as innovative interventions to tailor treatments based on a specific individual's genetic makeup, lifestyle, and environmental factors. Indeed, precision medicine and personalized medicine are closely interrelated, with genomics playing a pivotal role in both fields.[10]

Personalized medicine is the careful tailoring of investigations and treatments to individual patients based on evidence, consideration of circumstances, and clinical skills. On the other hand, Precision medicine relies on increasingly detailed molecular characterization of disease states using the biological omics platforms to better individualize diagnostics, prognostics, and therapeutics.[11] Personalized medicine is rooted in the belief that since individuals possess nuanced and unique characteristics at the molecular, physiological, environmental exposure, and behavioral levels, they may need to have interventions provided to them for diseases they possess that are tailored to these nuanced and unique characteristics.[12] This belief has been verified to some degree through the application of emerging technologies such as DNA sequencing, proteomics, imaging protocols, and wireless health monitoring devices, which have revealed great inter-individual variation in disease processes.[12]

The pronounced genetic heterogeneity evident within African populations holds significant ramifications for medical science, particularly in the realm of disease management spanning from endemic diseases like malaria to communicable diseases such as HIV/AIDS and tuberculosis, as well as non-communicable diseases like diabetes and hypertension. Given the burgeoning prominence of personalized and precision medicine predicated upon complexity of genetic and phenotypic profiling for tailored therapeutic interventions, African genetic diversity assumes pivotal relevance, but also presents some challenges. Accordingly, this scholarly review endeavors to delineate the nuanced facets, both advantageous and challenging, of Africa's genetic multiplicity vis-à-vis its implications for personalized and precision medicine.

Methodology

Search Strategies

From June 7 to June 11 2024, a systematic exploration was conducted across PubMed, Google Scholar, Science Direct, DOAJ, AJOL, and the Cochrane Library electronic databases, utilizing predetermined search terms such as "genetics", "genetic diversity", "Africa", "precision medicine", and "personalized medicine". Complementary manual google searches were executed to complement electronic database searches. Studies meeting inclusion criteria, focusing on the implications of genetic diversity within African populations on personalized medicine, precision medicine, or individualized healthcare paradigms, underwent a thorough screening process to find relevant studies for inclusion in the current review.

Data Synthesis and Analysis

Synthesis and analysis of eligible studies were conducted employing a thematic synthesis approach to discern prevailing patterns and themes among included studies. The multifaceted implications of genetic diversity within the African population for precision and personalized medicine were scrutinized and classified into positive and negative ramifications. This review aimed to provide a comprehensive understanding and variety of insights regarding the relationship between genetic diversity and the implementation of personalized healthcare efforts within the African context. This improves informed clinical treatment and enhances scientific research in this field (Table 1).

Results and Discussion

Positive Implications of African High Genetic Diversity to Customized Medicine

African populations have a high degree of genetic variation, which has important implications for customized treatment. Opportunities to improve pharmacogenomics, better understand gene interactions and find new genetic variants are presented by this diversity. It can also help to identify genetic modifiers, validate genetic biomarkers, and create reference panels for genomic research. Moreover, it improves the prediction of disease risk and propels the progress of genomic research (Figure 1).

Substantial genetic diversity in Africa has an important role in pharmacogenomics.[13] Pharmacogenomics aims to maximize patient outcomes by creating personalized treatment plans based on an understanding of the human genome's diversity and how it affects drug response.[14] The high genetic variability in African populations is useful for pinpointing particular genetic variations that affect drug efficacy, toxicity, and metabolism.[15] This information is essential for maximizing therapeutic efficacy, minimizing side effects, and customizing medication regimens for each patient. For instance, due to genetic differences in the CYP2B6 gene, which causes HIV patients in sub-Saharan Africa (SSA) to require a lower dose of efavirenz, dose changes for this medication have been recommended.[13] Tekola-Ayele et al analyzed the genetic structure of the Wolaita ethnic group (WETH) in Southern Ethiopia by comparing genome-wide variants with HapMap populations. The study revealed that alleles linked to increased risk of adverse drug reactions for tuberculosis (NAT2), thromboembolism (VKORC1), and HIV/AIDS and solid tumors (SLC28A1) were significantly more frequent in WETH than in other African ancestry HapMap populations, underscoring the importance of validating drug dosage guidelines across genetically diverse African populations for global health diseases.[16] This shows that future drug regulations may mandate pharmacogenomics and population-specific research to assess both new and existing medications used in SSA.[13]

Africa's vast genetic diversity can enhance our understanding of gene interactions, crucial for determining disease vulnerability.[17] The interplay between genes and environmental stimuli offers unique insights into genetic and environmental contributions to health outcomes.[18,19] Comprehending this interplay is crucial for the advancement of personalized and precision medicine approaches, which seek to deliver customized therapies according to a person's genetic and environmental characteristics.[19,20]

Table 1 Summary of methodology

Steps of Methodology	Description
Electronic database searched	PubMed, Google Scholar, Science Direct, DOAJ, AJOL, Cochrane Library and manual Google search
Search date	From June 7 to June 11 2024
Key terms used in search	Genetics, genetic diversity, Africa, precision medicine, and personalized medicine
Inclusion criteria	Updated original English studies or reviews focusing on African genetic diversity and its implications to personalized or precision medicine.
Exclusion criteria	Non-English studies, case reports, conference proceedings, Obsolete studies, and studies that do not focus on African genetic diversity and its implications to personalized or precision medicine
Data synthesis and analysis	The included literature was thematically classified as positive or negative implications and discussed separately

Figure 1 Positive implications of high African genetic diversity to personalized and precision medicine.

African genetic diversity can play an important role in the mapping of disease genes through comparative genomic studies of ethnically diverse populations as well as the discovery of novel genetic variants that might be rare or not even exist in other populations.[17] For example, the identification of genetic variations associated with resistance to malaria in African populations has provided insight into potential targets for malaria treatment. As an illustration, people with sickle cell trait—who have one mutant copy of the hemoglobin gene (HbS)—are largely protected from severe malaria. Studies show that in regions where malaria is common, this mutation confers a 15.2% selective advantage.[21] Furthermore, by limiting the parasite's ability to survive inside red blood cells, G6PD deficiency—an additional genetic characteristic prevalent in African populations—also offers protection against malaria.[21] These findings would be helpful in the development of novel therapies and interventions for diseases that disproportionately impact African communities.

Validation of genetic biomarkers is another important area that can benefit from African genetic diversity. Biomarkers are useful in disease diagnosis, prognosis, monitoring as well as therapy response prediction.[22] It is more crucial than ever to have validated biomarkers to guide clinical decision-making in the current age of precision medicine.[22,23] Throughout the past few decades, genetic biomarkers including DNA mutations, DNA single nucleotide polymorphisms, and karyotypic abnormalities have been the most common types of biomarkers for detecting diseases.[24] There are 154 karyotype biomarkers and 26374 genetic biomarkers in the MarkerDB database, and around 319 diseases are associated with DNA biomarkers.[24] To guarantee biomarkers' efficacy and dependability, it is important to validate them across a range of demographics.[25] However, some studies have pointed low generatability of some biomarkers in African population. For example, Majara et al highlighted low generalizability of polygenic scores in African populations due to genetic and environmental diversity.[26] Therefore, African populations' significant genetic variety offers a unique opportunity to test and confirm these biomarkers' applicability across multiple genetic backgrounds, boosting their generalizability and utility in precision medicine.

To better understand genetic data and increase the precision of genetic risk assessment and disease prediction, reference panels are essential.[27,28] Global precision medicine is hindered by the underrepresentation of non-European populations, necessitating resources like imputing reference panels that match study populations to identify impactful low-frequency variations.[29] The lack of diversity in the current human reference genome (HRG) may cause bias in subsequent analyses. By adding a wider spectrum of genetic variations, African genetic diversity can improve the human reference genome, creating a more accurate and comprehensive genomic reference panel.[30] Creation of updated accurate panel would advance personalized and precision medicine technology and approaches to be applied to all populations including Africans.

Negative Implications of African High Genetic Diversity to Customized Medicine

Although high global genetic diversity in Africa creates a special opportunity for scientific studies and advances in medicine, it also poses several difficulties for precision and individualized care. Underrepresentation in genomic research studies and databases, scarcity of references of reference genomes, and genetic ancestry misclassification are a few of the impacts of the high African genetic diversity on the development of personalized and precision medicine on the continent (Figure 2).

First, African populations are underrepresented in genomic research studies databases.[31] In 2019, Africans made up only 3% of the genome data used for genome-wide association studies (GWAS). However, due to several factors, including politics, a lack of funding, and a lack of infrastructure and an environment that supports genomic studies, this percentage fell sharply to 1.1% in 2021.[32] Large-scale genomic research, which mostly focuses on European populations, frequently ignores African communities despite their genetic diversity.[33] The outcomes of this lack of representation are skewed, and the applicability of study findings to African populations is constrained. Therefore, discoveries and insights from these studies might not fully apply African population.

Moreover, the accuracy of genetic testing and data interpretation is severely hampered by the scarcity of complete reference genomes for a variety of African groups. Reference genomes provide a standard by which to measure genetic diversity and comprehend its consequences.[34] The reference genome sequences derived from the Human Genome Project (HGP) lack many variants from African ancestral genomes. Studies show that an African population's genome would have almost 10% more DNA than the current reference.[35] Over 3 million previously unidentified variations were discovered in 2020 through studies of the entire genome sequences of just 426 individuals from 50 ethnolinguistic groups in Africa.[36] Therefore, the effectiveness of personalized medicine approaches may be impacted by inaccurate conclusions regarding genetic markers and their relationships with diseases resulting from the absence of representative reference genomes from African populations.

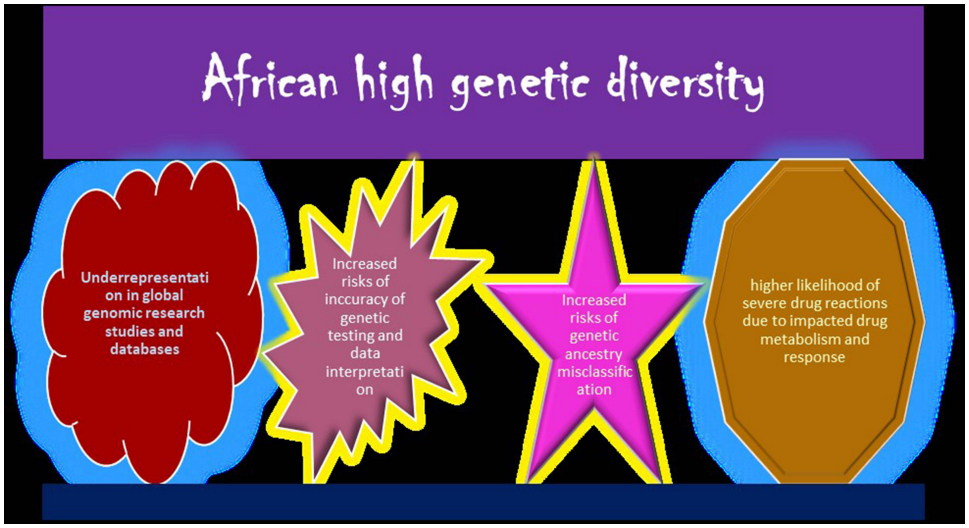

Figure 2 Negative implications of high African genetic diversity to personalized and precision medicine.

Genetic ancestry misclassification is another important concern in the African population due to high genetic diversity.[37] Ancestry data has largely superseded racial classifications in genetic investigations of health and diseases. Being more accurate than racial classifications, they enhance the identification of genetic risk factors in genome-wide studies. Polygenic risk scores, sensitive to ancestry variations, require ancestral information for accurate risk interpretation. However, determining the pathogenicity of rare variants is difficult in non-European populations due to the predominance of studies that only focused on European ancestry groups.[38–40] Genotyping arrays developed using genetic data from predominantly European ancestry populations are inefficient for analyzing African genomes, which exhibit greater genetic diversity. This diversity leads to reduced imputation accuracy for African ancestry samples due to lower linkage disequilibrium.[41] For example, genetic ancestry analysis of commonly used cancer cell lines has uncovered high rates of misclassification. As an illustration, the E006AA-hT prostate cancer cell line, originally classified as African American, was found to carry 92% European ancestry, highlighting significant discrepancies.[37]

Furthermore, there is concern about a higher likelihood of severe drug reactions in Africans due to high genetic variation that impacts drug metabolism and response. African populations exhibit genetic variations in key genes affecting drug metabolism, such as CYP2C9 and VKORC1 for warfarin, impacting dosage and adverse reactions.[42] The HLA-B*57:01 allele, more prevalent in African ancestry, was found to increase abacavir hypersensitivity risk.[43] Variants in CYP2C19 affect clopidogrel efficacy, increasing cardiovascular risks.[44] Differences in CYP2B6 and ABCB1 genes influence antiretroviral therapy outcomes as they have been associated with differences in drug efficacy and toxicity.[45] Additionally, variations in opioid metabolism genes like CYP2D6 and OPRM1 affect pain management and adverse effects.[46,47] This poses a significant challenge, but it is a simultaneous call to the need for precision and personalized medicine in Africa.

Recommendations

Africa's distinct genetic diversity and healthcare requirements necessitate a multimodal approach to the development and implementation of personalized and precision medicine. Important initiatives include establishing and empowering genomic research centers and innovation hub, increasing funding opportunities for genomic studies, establishment of African genomic biobanks and repositories, training competitive researchers, improving infrastructure and integrating available customized treatment approaches into clinical practice are essential to guarantee the effective application of customized medicine in Africa. Africa may take advantage of its genetic diversity to promote healthcare equity and better health outcomes by promoting international cooperation and creating culturally aware healthcare systems (Figure 3).

The crucial step in promoting genomics and personalized medicine research and development is the establishment of genomic research centers and innovation hubs in Africa. These research centers and hubs can act as centers of excellence,

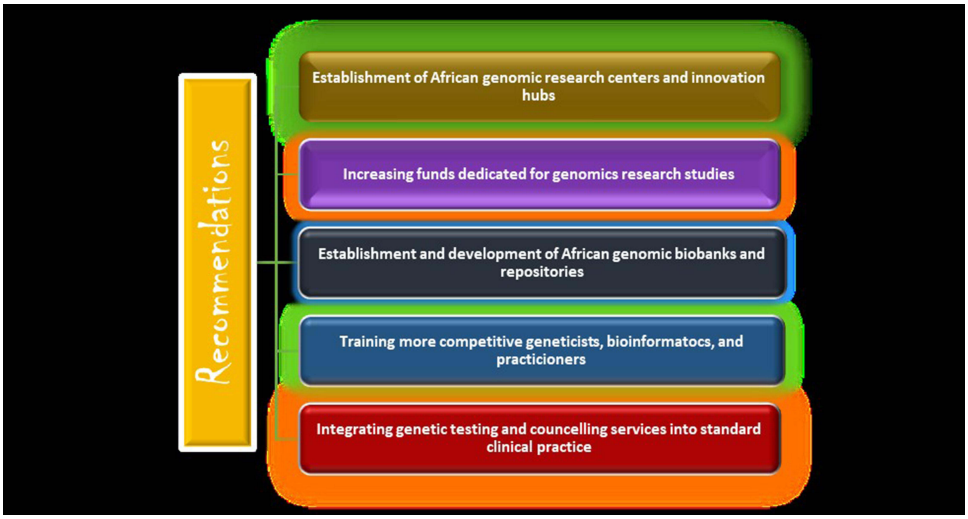

Figure 3 Recommendations for advancement of personalized and precision medicine in Africa.

bringing together professionals in the fields of research, genetics, medicine, and technology to work together on innovative projects. By focusing on common diseases in Africa such as HIV, TB, and malaria, they can use genetic knowledge to create more potent preventive and therapeutic approaches and promote the creation of innovative technologies and approaches suited to the African environment by utilizing local knowledge and resources. Additionally, they may help translate research results into workable healthcare solutions, making sure that more people can benefit from customized treatment.[32,48,49]

Recently, there has been an increase in initiatives and centers dedicated to genomics research in Africa to bridge the genomic data gap and promote personalized medicine. Important initiatives include the Human Heredity and Health in Africa (H3Africa) Initiative, which supports modern genomics research on genetic and environmental determinants of diseases,[50] and the Africa Pathogen Genomics Initiative (Africa PGI), which improves laboratory detection and surveillance of infectious diseases and antibiotic resistance.[51] Other noteworthy initiatives include the African Society of Human Genetics (AfSHG),[52] the African Centre of Excellence for Genomics of Infectious Diseases (ACEGID),[53] and the Collaborative African Genomics Network (CAfGEN).[54] Additionally, research centers such as the Centre for Epidemic Response and Innovation (CERI), the Centre for Genomics Research and Innovation (CGRI), the African Collaborative Center for Microbiome and Genomics Research (ACCME), and African Genome Education Institute (AGEI) back these initiatives. These programs are working together to increase capacity, promote cooperation, and produce significant genetic data that will help improve health outcomes throughout the continent and enable individualized treatment catered to African populations. Increasing number of these initiatives and empowering them are essential to develop personalized and precision medicine in Africa.

Inadequate funding presents major obstacles to genomic research in Africa, impeding the continent's advancement in this vital area. This leads to deficiency of infrastructure, knowledge, and resources necessary for carrying out impactful genomics research. It further fosters an environment that hinders African scientists' ability to collaborate on research projects, which delays the application of genomic research findings to real-world public health advantages. In 2015, genetics and genomics research programs in Africa received $216 million of the estimated $300 billion spent annually on medical research worldwide.[55] Increasing financing opportunities for research and development is essential to overcoming these challenges and advancing genomic research and personalized medicine projects in Africa. African nations may create enduring infrastructure, encourage partnerships, and provide significant genomic data specific to African populations by investing in genomics research, which will ultimately improve health outcomes throughout the continent.

The safe and moral handling of genetic data depends on the creation of biobanks and data repositories.[56] Biological samples and related data can be kept in these repositories, making them available for use in clinical and scientific settings. Biobanks and repositories such as H3Africa Biorepositories, South African National Biobank, MyAfroDNA, Malaria Research and Training Center (MRTC) Biobank, Kenya Medical Research Institute (KEMRI) Biobank, Egyptian National Biobank have shown an important role in collecting, processing, storing and distributing human biological samples and associated data. To guarantee that the data is used appropriately and that participants' privacy is safeguarded, appropriate governance frameworks and ethical standards must also be in place.[57,58]

To provide policymakers, researchers, and healthcare practitioners with the knowledge and abilities required to apply customized medicine, comprehensive education and training programs are required.[59–61] These programs should focus on all aspects of genomics, bioinformatics, and ethical issues surrounding genetic testing and data usage. The workforce will be ready to handle the intricacies of personalized medicine and can help to progress it if local knowledge is developed through education. South African Precision Medicine Program,[62] The African Genomic Medicine Training Initiative (AGMT),[63] Precision Medicine Program by the African Union Development Agency-NEPAD (AUDA-NEPAD)[64] are examples are programs that offer training and fellowships in genomics, bioinformatics and precision medicine. Such programs must be multiplied, nurtured, and capacitated to train many competitive practitioners, researchers, technicians, and policy implementors for the development of personalized and precision medicine.

Optimizing the healthcare system to enable genetic testing and counseling services is essential to precision medicine deployment.[65] This involves integrating genetic testing into standard clinical practice and setting up labs furnished with cutting-edge genomic technologies. Personalized treatment plans and more precise diagnoses will be possible with strengthened infrastructure.[66] Furthermore, to support patients and their families in making educated decisions and enhancing health outcomes, easily available genetic counseling services are required.[67]

Conclusion

African population has a high genetic diversity, which offers a plethora of opportunities for the advancement of precision and individualized medicine. However, challenges including underrepresentation in genomic research projects and databases, lack of complete reference genomes, and inadequate funding must be resolved. It is essential to invest in a thorough study of African genetic variation to guide the creation of customized treatment approaches. Further deep research is needed to exploit the opportunities of high African genetic diversity and transform the available challenges into opportunities to dive deep in African genomics with the intention to develop personalized and precision medicine approaches that will fit different African population groups.

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