The genetic determinants of oral diseases in Africa: The gaps should be filled

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Oral diseases are a major health concern and are among the most prevalent diseases globally. This problem is becoming more prominent in the rapidly growing populations of Africa. It is well documented that Africa exhibits the most diverse genetic make-up in the world. However, little work has been conducted to understand the genetic basis of oral diseases in Africans. Oral health is often neglected and receives low prioritisation from funders and governments. The genetic determinants of highly prevalent oral diseases such as dental caries and periodontal disease, and regionally prevalent conditions such as oral cancer and NOMA, are largely under-researched areas despite numerous articles alluding to a high burden of these diseases in African populations. Therefore, this review aims to shed light on the significant gaps in research on the genetic and genomic aspects of oral diseases in African populations and highlights the urgent need for evidence-based dentistry, in tandem with the development of the dentist/scientist workforce.

KEYWORDS
- genetics, africa, oral diseases, dental caries, periodontal disease, rare diseases

Introduction

The increase in the incidence of untreated caries of permanent teeth (1) in the 2019 Global Burden of Diseases, Injuries and Risk Factors Study (GBD) (2) is attributed to the population growth in sub-Saharan Africa. The same study reports the highest prevalence of severe periodontitis worldwide occurs in sub-Sahara Africa (3). Oral diseases and disorders (comprising dental caries, periodontal diseases, edentulism, and other oral disorders) are humankind’s most prevalent chronic conditions. Oral diseases affect about 3.48 billion people and rank third globally in incidence (2). Africa, the second largest and second most populous continent, is home to a population of 1.4 billion (4), 3,000 different ethnic groups speaking more than 2,100 different languages (5). Most genetic diversity of human populations occurs in Africans (6). The sub-Saharan African region has the highest population growth rate of 2.8% globally. This population is expected to double between 2022 and 2050 and surpass 2 billion inhabitants by the late 2040s (4).

An estimated 480 million Africans suffer from oral disease. The World Health Organisation Africa Region has identified dental caries, periodontal diseases, oral cancers, Noma, oral manifestations of HIV and AIDS, oro-facial trauma and cleft lip and/or palate as priority oral diseases (7). Oral diseases share modifiable risk factors...
with cardiovascular disease (CVD), cancer, diabetes, and chronic respiratory diseases, the four most prevalent non-communicable diseases (NCDs) (8). These risk factors include an unhealthy diet high in sugar, tobacco use, and harmful use of alcohol (9). The burden of NCDs is increasing and will eclipse communicable, maternal, neonatal and nutritional (CMNN) diseases as the leading cause of mortality in sub-Saharan Africa by 2030 (10). Despite the interrelationship between oral diseases and other prevalent non-communicable diseases, a disjuncture in management approaches has been a consistent feature of oral and medical health services (11, 12). The oral health regional strategy for Africa aims to achieve better oral health as an integral part of NCDs (13). The recent global drive toward universal health coverage (UHC) by 2030, which addressed oral diseases (14) and the WHO Oral Health Strategy release (15), provide an opportune moment to spur global political commitments for oral health.

Genetic studies and oral health

It is well documented that most genetic studies have been conducted on populations of European ancestry (16). The initiatives to characterize and understand genomic variations of human populations that followed the sequencing of human genome such as HapMap Project (17) and the 1,000 Genome Project (18), included representatives from African populations. These early initiatives further revealed the genomic complexity of African population and led to projects that focussed on sub-Saharan African such as the African Genome Variation Project (19) which revealed the influence of uncovered evidence of environment effects into the genetic susceptibility to conditions such as malaria, Lassa fever and trypanosomiasis (20). Several regional and country-based projects such as the Southern African Genome Project (21), the Ugandan Genome Resource (22) and the Nigeria 100 K Genome Project (23) also developed from these initiatives. An analysis of genome-wide association studies (GWAS) found that only 22% of the participants in these studies were of non-European origin with less than 4% of African and Latin American descent and from indigenous populations (24, 25). A study of only 16 South East Bantu speakers identified approximately 800,000 novel variants (26). Sherman et al., 2019, estimated that the African pan genome, has about 10% more abundance of DNA than the current human reference (27). In 2012, the Human Heredity and Health in Africa (H3Africa) program was launched with the aim to correct the dearth of genomics research in African continent (28). H3Africa initiative focused on capacity building through inter-continental collaborative projects, and the formation of African-based biorepositories and bioinformatics network, among other specific scientific goals (29). The Human Hereditary and Health Study in Africa (H3Africa) identified more than 3 million novel variants in a sample of 426 individuals (26, 30). In the H3Africa project, the genomics of craniofacial malformations in Africa were addressed through a multidisciplinary collaboration, the African Craniofacial Anomalies Network (AfriCRAN) (31).

Consequently, more than 100,000 participants were included in funded projects providing 50,000 genotyped samples and the identification of 26 core phenotypes. Furthermore, over 2000 workshops and meetings were held and around 700 papers were published (32).

Despite the notable achievements of H3Africa, common oral diseases are yet to be addressed in these initiatives; however, the complex genomic datasets established pave the way for projects that will ascertain the genetic determinants of prevalent oral diseases in Africa.

The paucity of studies on diverse genomes impedes our understanding of the human genome in health and disease (16), and results in the misclassification of variant pathogenicity in Africa. This situation limits the translation of genetic research into clinical practice, directly impacting patient management (18), public health policy, and ultimately exacerbates health inequalities (16). The 3 Million African Genome project (3MAG) was conceived in 2021 to sequence at least 3 million genomes carefully selected across Africa to cover ethnolinguistic and regional variation (33). The 3MAG project will improve the current situation and equip African scientists with knowledge that will enable informed approaches to a variety of public health challenges.

Explorative studies on genetic determinants of oral health and oral disease lag far behind that of other conditions. This problem is even more prominent in Africa, where only a few studies have focused on oral health and disease (34–39). The genetic determinants of highly prevalent oral diseases in African populations, such as dental caries and periodontal disease, and regionally prevailing conditions such as oral cancer and NOMA, are largely under-researched (40–42).

There are 54 countries in Africa with immense ethnic diversity. These populations differ in terms of wealth, educational accomplishment, living conditions, health systems and access to oral health services (42), hence, confirming the heterogeneity of the African population. These differences become critical as we move towards targeted healthcare (including oral health care).

This review aims at raising awareness of the genetic determinants of oral diseases and highlights research gaps in Africa. The review focuses on dental caries, periodontal disease, oral cancer, and rare diseases with craniofacial manifestations.

Dental caries

Dental caries is a complex, chronic and multifactorial disease. It is mediated by the interplay between host factors,
the microbial biofilm, a substrate that supports microbial cariogenicity and genetic influences (43, 44). The 2019 GBD report identified untreated caries of the permanent dentition, with an estimated 2 billion cases (95% uncertainty interval, 1.8 to 2.3 billion), as the most common health condition. Similarly, caries in deciduous teeth was reported as the most prevalent condition in children aged 0–14 years (1). A characterisation of the burden, trends and inequalities of untreated dental caries reported a lower prevalence of dental caries in the permanent dentition in developed countries (45). In this study, 64.6 million (95% CI, 64.4–64.9 million) and 62.9 million (62.8–63.1 million) cases of caries in the permanent and deciduous teeth, respectively, were attributed to sociodemographic inequality (44).

The incidence of untreated caries in the permanent dentition increased by 46.1% (95% uncertainty interval, 42%–50.3%) from 1990–2019 (1). It is important to note that the methodology used in the GBD studies employs spatiotemporal modelling analysis, leading to the underrepresentation of estimates from low-income settings (46).

The influence of genetic mechanisms on host factors, microbial biofilm and substrate has been suggested in different types of studies. In investigations involving twins (47), monozygotic but not dizygotic twins raised apart showed similarities in oral health status. The animal models studies involving rodents (48), suggestive quantitative locus traits (QLTs) were revealed on chromosomes 1, 2, 7 and 8. The variations in the amelogenin gene was described a factor in caries susceptibility study conducted in a Guatemalan-Mayan population (49). Recently, a genome-wide associations studies (GWAS) by Orlova et al. 2019, suggested genetic differences in caries susceptibility and in potential genetic risk factors between African-Americans and Caucasians (50).

In a review of genetic and protein interactions in dental caries, Cavallari et al. (2019) provided an overview of 27 genes and genes—protein networks associated with protection or risk of dental caries. These were PRP1, PR, PA, MG1, MG2, AMELX, ENAM, TUFT1, KLK4, HLADR4, TASI1R3, TAS2R38, MBL2, MMP20, MMP2, MMP9, MMP13, GLUT2, TAS1R2, CA-VI, DEFB1, ALOX15, VDR-TAQI, MMP3, CA6, MUC5B, VDR-FOK and are related to enamel formation, development and mineralisation, host immune response and the composition of saliva (51).

Sub-Saharan Africa has subregions with high fluoride levels in groundwater sources, causing dental and skeletal fluorosis (52). Dental fluorosis is characterised by increased surface and subsurface enamel porosity (53), and is associated with increased dental caries (54, 55). Dental fluorosis presents with differing severity in individuals exposed to similar levels of fluoride intake, suggesting the influence of genetic factors and gene-environment interactions (56).

There is a scarcity of studies on the genetic and genetic-environment interaction in the dental caries disease process in Africans. Olatosi et al. described a replication of the signals for two single nucleotide polymorphisms previously reported for childhood caries in an investigation of the role of genetics in early childhood caries in Nigeria. The study reported different size effects for two loci in the Nigerian populations compared to a previous study on an American population (36). In a similar trend, a pilot GWAS assessing genes associated with dental caries in individuals of African descent described differences in the contributions of genetic variants to caries across racial groups (50). Investigating the genetic basis of dental caries and dental fluorosis among Africans is likely to improve the understanding of caries disease processes, identify risk groups, facilitate screening, guide priority setting in health care and strengthen disease prevention.

### Periodontal diseases

Periodontitis constitutes a major health concern due to its high prevalence and significant impact on general wellbeing (42). In fact, it has been estimated that 20%–50% of the global adult population has some degree of periodontitis (57). According to the latest GBD 2019 report, the highest prevalence of severe periodontitis was reported in sub-Saharan Africa (3).

In susceptible individuals, periodontitis develops from complex interactions between the dental biofilm microbiota, host immune-inflammatory response and environmental factors (58). An individual’s susceptibility to periodontitis is dependent on their genetic background along with other risk factors such as poor oral hygiene and smoking (59). Cumulative evidence suggests that an association exists between periodontitis and different systemic diseases (60). For instance, pregnant women who are more susceptible to periodontal disease due to a hormonal surge, are more vulnerable to poor maternal and perinatal outcomes such as preeclampsia (61, 62). In addition, an association between periodontitis and chronic kidney disease has also been reported (63–65). Wahid et al. (2013) stated that published data support a bidirectional relationship between CKD and periodontal disease as patients with CKD also have a higher prevalence of periodontal disease (66).

Periodontitis, in essence, is a polygenic disease arising from variations in multiple gene loci in which each contributes to developing the clinical phenomena (67).

The genetic component of periodontitis appears to be more strongly associated with the aggressive phenotype (67). However, in the 2017 periodontal diseases classification scheme, the distinction between chronic and aggressive phenotypes is no longer justified (67). This is due to the current lack of evidence differentiating the pathophysiology between the two phenotypes (68). Therefore, periodontitis is currently classified as a single entity, “Periodontitis”, with the
incorporation of staging and grading matrix for further diagnostic description (68, 69). In which, the staging vector demonstrates the disease severity and extent, and complexity of the management. While, the disease grade reflects the biological dimension of the infection and possible adverse effects on general health (70). The application of the new classification criteria led to the assignment of some previous phenotypes to a particular representative stage or grade. For instance, the previously classified aggressive periodontitis phenotype is currently under the grade C level (71).

A wealth of data suggests that genetic variations in host genes involved in modulation of the immune-inflammatory reaction to periodontitis, have a strong effect on disease susceptibility and development (72). Genetic variants may alter the modulatory proteins or their expression, which consequently results in innate and adaptive immunity alterations and may, therefore, govern disease outcome (72). Moreover, several studies highlight the variability in genetic susceptibility among different populations (54, 55).

Single nucleotide polymorphisms (SNPs) are common across the human population (>1%), however, their frequency varies significantly among various groups (67). Single nucleotide polymorphism (SNP) is the most common genetic variation investigated in the association with susceptibility to periodontitis (67). In particular, genes encoding for mediators involved in host immunity and metabolism such as cytokines and cell-surface receptors (72). Any dysregulation in genetic expression of these mediators might result in persistent destructive inflammation of the periodontium and the development of periodontitis (73). Accordingly, the association of particular SNPs with periodontitis differs among various populations and ethnic groups (67).

For instance, the gene which encodes for interleukin-1, one of the most important inflammatory cytokines involved in periodontitis pathogenesis, has been extensively investigated for its association with periodontitis susceptibility, however, findings have been contradictory (72, 74). A positive association between IL1A -889 C/T polymorphism and chronic periodontitis was reported in Caucasian, Asian, but not in the mixed Brazilian populations in a recently conducted large scale meta-analysis (75).

In Africa, there are more than two thousand distinct ethnic groups possessing the world’s most diverse genetic makeup (76). It is likely that this genetic diversity will reflect a variation in susceptibility to periodontitis in Africa (76, 77). Nevertheless, little is known about periodontitis susceptibility among African populations (76).

**Oral cancer**

The most pivotal malignancy of the oral cavity is squamous cell carcinoma (OSCC) arising from the mucosal epithelium. More than 90% of oral cancers are SCCs (78). Oral cancer ranks as the sixth most common cancer worldwide and as third in developing nations. However, there is evident under-reporting of cases in many countries in Africa due to a lack of cancer registries, cancer control programmes, modern health infrastructure, access to healthcare, finances, educational levels and existing religious and cultural beliefs (79–81).

In instances where African databases exist for the reporting of head and neck cancers, the incidence of cancers of the lip, tongue, oral cavity, and pharynx are often combined, and the oral cavity and oropharynx are most frequently reported among head and neck squamous cell carcinomas in Sub-Saharan Africa.

It is stated that the incidence of oral cancer is escalating in eastern and southern Africa. This is the result of increasing tobacco use, increased alcohol consumption, and traditional practices like chewing khat and tobacco, which are carcinogenic (82, 83). If detected early, oral cancers can be treated more easily.

The biologic behaviour of oral cancers, such as determining which would run an indolent or aggressive course, is an area requiring genetic and genomic investigations. This would contribute to their diagnosis and management. Diverse genetic, epigenetic, and environmental factors are involved in the pathogenesis of oral SCC which has a poor prognosis (84). A systematic review assessing head and neck SCC in sub-Saharan Africa (45) found that none of the included studies reported on any genetic or genomic investigations.

The primary option for the management of oral SCC is determined by the stage of the disease and includes surgical resection, chemotherapy, radiotherapy, and immunotherapy (85). Despite advances in conventional therapy, several unfavourable consequences to therapy need to be further addressed. These include the fact that surgical resection may lead to long-term disfigurement and deformities that results in patients experiencing psychosocial stress and isolation. Radio- or chemotherapies may cause significant toxicity or treatment resistance which ultimately compromise the quality of life of patients (85, 86).

Most OSCC are considered genetically unstable (87, 88). Frequently, chromosomal loss at 3p, 8p, 9p, 17p and gains at 3q and 11q have been reported (89). When these changes extend for some distance from the clinical lesion, the clinical phenomenon of field cancerisation is described (90). Genes that have often been reported to have a role in the development of OSCC are TP53, CDKN2A, PTEN, HRAS and PIK3CA (89, 91, 92). The evidence for inherited genetic susceptibility for the development of OSCC has been difficult to source.

The effectiveness of the various current therapeutics modalities is reliant on the genetic and mutational profile of the tumour as this contributes to the oncogenic potential of the lesion. This type of targeted therapy is directed at these
genetic modifications and forms the basis of precision medicine (84, 93).

Despite considerable advancement which has been made in the management of oral cancer, its molecular heterogeneity still needs to be investigated in Africa. The molecular basis of the tumour also requires scrutiny in order to elucidate instances of resistance to therapeutic measures (84).

Rare diseases

Congenital defects and hereditary syndromes affecting the craniofacial complex are amongst the most common health problems globally (31, 94). These conditions significantly impact the quality of life of those affected and exacerbate health inequalities, particularly in low-resourced LMICs (31). Due to a lack of available data, rare diseases in Africa remain unquantified (95). Current estimates place the number of African people directly affected by rare diseases (RD) at 50 million (96, 97). The number of people indirectly affected is much higher due to the high economic and societal burden of RD (98, 99). At least 72% of RDs are believed to be of genetic origin (97).

Oral and facial clefts (OFCs) serve as a good model for studying the etiology, treatment and prevention of congenital disabilities (100). The 2022 global incidence report of cleft lip/palate (CL/P) found that CL/P prevalence is highest in Asian (∼1/500) and American populations and significantly lower in African populations (∼1/2,500) (101). There has been increasing interest in OFC studies on the continent (34, 35, 37, 38, 100). Butali et al. (2019) conducted a study on OFCs with 3,178 participants from Ghana, Nigeria and Ethiopia (37). They were able to identify two novel loci with genome-wide significance and were able to confirm previously reported loci from GWAS studies from other populations. However, the authors identified the need to perform whole genome studies to provide a more comprehensive analysis of all classes of variants, including rare variants. Identifying variants protective of OFCs may open the possibility of therapies in the future (38).

There have been few genotype-phenotype correlation studies in large cohorts of patients with RDs in Africa. The variability in phenotypic expression, high genetic heterogeneity and low mutation frequency were noted as challenges to establishing consistent genotype-phenotype correlations (96). A study in Sub-Saharan Africa found that geneticists had difficulty diagnosing Williams-Beuren Syndrome based on facial dysmorphic features (102, 103). Another study found that an artificial intelligence (AI) based tool was only able to classify 35% of Congolese participants with Down’s Syndrome compared to 80% of Belgian participants, prior to specific training (104).

Recent studies in South Africa assessed osteogenesis imperfecta (OI) type 3, which has an unusually high frequency in the Black Southern African populations (105). Out of 91 patients with a confirmed phenotypic diagnosis of OI type 3, 45% of affected individuals had a pathogenic variant of the FKBP10 gene (105). Interestingly, the individuals with a homozygous mutation in the FKBP10 gene have clinically unaffected teeth yet exhibited radiographic features of dentinogenesis imperfecta to varying degrees (106). Another study evaluating the physical features of 125 individuals with Noonan syndrome found that Black Africans had the most distinctive features (107) however, the molecular detection rate in this study was only 31.2% compared to the expected >70% using whole exome sequencing (WES). This suggests that the pathogenic variants are likely in genes that were not investigated. These studies are important as they enable a more accurate clinical diagnosis of patients, especially where molecular studies are unavailable.

Epilogue

The diverse genetic and genomic heterogeneity of Africans has been the result of ancient migration patterns and adaptive pressures on the human genome. This resulted in evolutionary events, which spilt the human population into five distinct groups: southern Khoi-San, northern Khoi-San, central African hunter-gatherers, West Africans, and East Africans. A subset migrated out of Africa and is now identified as the out-of-Africa population (108, 109). Hence, the continent of Africa can be said to be the repository of human genomic diversity and can consequently serve as the reference resource for understanding the role of genomics in human health and disease.

It is apparent that Africa is home to a huge burden of oral diseases, with limited genetic and genomic research. In the era of targeted approaches to the management of human diseases, novel discoveries in the biomedical sciences are redefining the conduct of research and improving oral health by translating these findings into clinical application (93).

It has become imperative for the African oral health fraternity to prepare and arm itself with personnel who are equipped to investigate and interpret knowledge obtained from genomics, genetic sequencing, transcriptomics and proteomics, molecular profiling and bioinformatic data. This is essential in order to improve the management of oral health diseases and disorders in the era of targeted therapy, and will facilitate the development of disease management protocols aimed at African patients and conditions (110).

Roberts et al. (2020), proposed the inclusion of adequate training in the genetics of oral diseases in undergraduate and postgraduate dental programmes for African universities. With adequate skillsets the trained dentists will have an
interest in following a career in genetic and genomic oral health research. This would enhance networking among African dental researchers and lead to improved dental research output and evidence based dentistry across the continent (111).

However, the high cost of biomedical infrastructure, laboratory set-up, project establishment and remuneration, has prevented many with an interest in biomedical research from engaging in genetic and genomic research. The genome sequencing technology is undergoing an evolutionary growth with the entry of new companies and the introduction of new techniques, which promise a significant reduction in costs (112). Joint efforts among African countries to increase funding and remuneration, as well as collaboration among institutions, will facilitate growth and prevent wasteful expenditure that may occur through duplication of these efforts.

In the current scenario where low- and middle-income countries (LMICs), most of which are in Africa, are left out of the advances in genomic technologies, The WHO Science Council proposed the establishment of a genomics committee to assist in rendering genomics for global health. This report recommends approaches based on four themes, implementation, advocacy collaboration and associated ethical legal and social issues. The WHO Science Council proposed the establishment of a genomics committee to assist in rendering genomic technology affordable in LMICs by engaging various stakeholder and commercial entities (113).

Thus, there is an urgent and pressing need for oral health researchers and policy makers to develop and participate in translational clinical research that will accelerate targeted scientific breakthroughs in the management of oral diseases in Africa.

Author contributions

SS conceptualised the idea. SS, SK, IR, MA, MC contributed equally to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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