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Precision Medicine in Rheumatoid Arthritis: Genomic and Epigenetic Signatures in African Populations

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease marked by joint inflammation, disability, and reduced quality of life. Precision medicine, which tailors treatment to individual molecular profiles, offers promise for improving RA outcomes. While genomic and epigenetic studies have identified biomarkers of susceptibility, progression, and therapeutic response, these insights are largely derived from European and Asian populations. African populations despite their unparalleled genetic diversity remain significantly underrepresented. This gap has critical implications, as African-specific variants, epigenetic modifications, and environmental exposures may influence disease risk and treatment response. The absence of African-focused research restricts the applicability of existing biomarkers and perpetuates disparities in care. To address this, large-scale multi-omics studies, robust biobanking, stronger ethical frameworks, and investment in local research capacity are needed. Identifying population-specific molecular signatures will improve early detection, prognosis, and individualized therapy for African patients. Incorporating African data into RA precision medicine is both a scientific necessity and an ethical imperative, ensuring equitable access to personalized healthcare.

Keywords: Rheumatoid arthritis, precision medicine, genomics, epigenetics and biomarkers.

INTRODUCTION

Precision medicine strives to individualize therapies for a diverse range of pathologies to optimize medical benefits. Currently, rheumatoid arthritis (RA) is a well-studied inflammatory disease, partly because it affects both males and females [1]. Genomic and epigenetic signatures can be used to determine the factors that contribute to the development of each pathology. As a consequence, the implementation of precision medicine may become much more straightforward. Several populations have been studied to uncover the underlying mechanisms of RA, but very limited information is available for Africans. Thus, the factors that contribute to the development of RA in African populations remain unknown [1, 9].

Overview of Rheumatoid Arthritis

RA is a chronic inflammatory disease affecting joints and leading to disability. It is an autoimmune disease classified among connective tissue disorders [1]. The disease has a multifactorial aetiology and can emerge at any age in life; however, it is most prevalent around 40–70 years of age. Clinical manifestations include chronic synovitis (synovial inflammation) that leads to joint destruction. Inflammatory cell infiltrates composed of activated $CD4^+$ T cells, macrophages, and B cells infiltrate the synovium, leading to the formation of a hyperplastic invasive tissue called pannus, which erodes cartilage and juxta-articular bone. Peripheral blood is also often affected, with the production of rheumatoid factors (RFs), autoantibodies against the Fc portion of human immunoglobulin G (IgG). The diagnosis of RA relies on symptoms described by the patient, clinical manifestations, and determinations of specific autoantibodies. In addition to RFs, anticitrullinated protein antibodies (ACPAs) are used as diagnostic markers [5].

Pathophysiology

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by synovial inflammation and joint destruction, affecting approximately 1% of adults worldwide. It typically presents with symmetric synovitis,

morning joint stiffness, and extrarticular manifestations [1]. Diagnosis relies on clinical signs complemented by laboratory findings such as autoantibodies against rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) 1. These antibodies serve as disease biomarkers alongside genetic factors like the altered MHC class II locus HLA-DRB1, which affect antigen presentation and correlate with disordered immune response. Persisting synovial inflammation induces structural joint damage, impairing function. The interaction of environmental and genetic risk factors provokes an immune response against citrullinated peptides, initiating RA development. Evidence includes the presence of circulating autoantibodies years before symptom onset and agalactosylated IgG detected in preclinical and early RA stages, reflecting early glycosylation changes [2]. Knowledge of RA pathogenesis informs therapeutic strategies targeting inflammation and uncontrolled proliferation. Research aims to identify molecular markers guiding diagnostics and prognosis; detection of aberrant gene expression patterns in peripheral blood has inspired RA-specific RNA signatures.

Clinical Manifestations

Rheumatoid arthritis (RA) is a chronic inflammatory disease with diverse clinical manifestations affecting multiple organs. This heterogeneity complicates diagnosis, and until recently, no specific laboratory tests were available. Diagnosis now relies heavily on the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria. Clinical presentations and disease activity often vary between patients, complicating effective management. Patients with RA neuropathy experience persistent joint pain accompanied by numbness, paresthesia, and tingling. Digital erosions, considered a late extra-articular manifestation, occur in approximately 5.4% of patients [1]. Characterized by the absence of subcutaneous nodules, digital pulp atrophy, long-standing Raynaud's phenomenon, and autoantibodies against nuclear and CENP-F proteins, studies link these manifestations to erosive arthropathy. Distal joint inflammation can lead to severe deformities such as 'opera-glass hand', 'main-en-lorgnette', or telescoping finger, further underscoring the variable and severe clinical spectrum of RA [5].

Diagnosis Criteria

Rheumatoid arthritis (RA) is characterized by inflammation of the synovial membrane of diarthrodial joints leading to tissue destruction and severe disability [3]. The current diagnosis of RA aligns with the revised American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria. The absence of specific clinical or laboratory signs has prevented the establishment of early diagnostic criteria. Rheumatoid factors (RF) are present in approximately 70 to 80% of RA patients but have limited specificity. Anti-cyclic citrullinated peptides (anti-CCP) autoantibodies targeting citrullinated peptides/proteins (ACPA) are present in 60 to 80% of Caucasian RA patients with a high specificity over 95%. Several studies suggest differences in the prevalence of RA and in the diagnostic efficiencies of RF and ACPA between black Africans and Caucasians. The genetic component of RA has a heritability estimate of 50 to 60%. The high-resolution HLA-DRB1 typing and analysis of anti-CCP antibodies in African RA patients underscored significant differences in the prevalence of ACPAs compared to Western countries while establishing that anti-CCP2 and anti-CCP3 ELISAs have an optimal diagnostic performance compared to RF [1].

Genomics in Rheumatoid Arthritis

A precise treatment strategy, avoiding the self-attack of the inflammatory condition and the associated systemic diseases, but deterioration is not always satisfactory around the RA patient with the homogeneous population study. However, many of the methods in the study of RA are still limited to homogeneous populations, and large multicenter multi-ethnic research is needed. RA with other inflammatory autoimmune diseases is characterized by heterogeneous groups on abnormal activation of the immune system and primarily the production of autoantibodies against some self-tissues [1]. Controlled RA and other autoimmune diseases require the characterization of mechanisms and causes for phenotype and symptom heterogeneity, ensuring the optimum therapeutic selection and the strategy of prevention by applying the timely personalized medicine. Precision medicine is important, not because it uses genetic data alone, but because it systematically utilizes multiple data categories such as omics, clinical, imaging and environmental data in order to develop a more accurate pathological mechanism and other disease models, as well as to identify subpopulations of people who have a common cause of disease and to generate effective prediction and prevention strategies. The pathogenesis of RA is associated with multiple genetic and environmental factors, with heritability estimates of 50–60% and looks polygenic. Conclusions about genetic risk loci come mainly from studies based on European and Asian populations. The single-nucleotide polymorphisms (SNPs) identified by Genome-Wide Association Studies (GWAS) are widely distributed among populations and at high frequency in people of African ancestry, but many other risk alleles appear to be population-specific or differently influenced [4, 5].

Genetic Risk Factors

Genomic studies have identified candidate-gene variants associated with rheumatoid arthritis (RA) in African populations, but the greater genomic diversity of these groups complicates the analysis of genetic risk factors [1].

Early genome-wide association studies (GWAS) of RA case–control groups in diverse African populations discovered a population-specific effect of the IGSF9 gene that was rare in Europeans and described a unique African variant in the TYK2 gene [10]. The results of these studies reflect the general pattern that many novel genetic variants associated with traits are specific to a given population or are more common in one population than another. Although GWAS with relatively few African samples detected associations with some well-established RA loci, many associations with moderate effect on RA risk were missed. The use of larger numbers of African RA samples will be necessary to increase statistical power for the detection of age-at-onset and other genetic effects [5].

Genome-Wide Association Studies (GWAS)

Genetic risk factors influencing rheumatoid arthritis (RA) are well documented despite the complex interplay of environmental and genetic influences. Susceptibility loci and single-nucleotide polymorphisms (SNPs) estimated to account for approximately one-third of the heritability of RA have been identified principally through candidate gene studies and genome-wide association studies (GWAS). They contribute to identifying disease-modifying genes and offer a valuable approach for characterising biological pathways involved in the aetiology of disease. GWAS evaluate the association between these genetic polymorphisms and RA, as exemplified by numerous published studies conducted in various populations [4]. The application of these technological advances allows the analysis of an unprecedented number of variants throughout the whole genome. Comparative analyses of methods for assessing candidate regions in the context of a GWAS population focus indicate that GWAS constitute an extremely useful tool in identifying risk factors, consequently improving the understanding of pathogenic mechanisms underlying diseases [5]. These methods offer a strategy to integrate GWAS methodology and the analysis of candidate gene markers with a detailed knowledge of the disease under investigation. The identification and characterisation of risk or protective variants in populations is crucial because it enables more accurate genetic profiles of susceptibility, facilitates the identification of the heritable component in RA, and permits even the screening of certain populations [1].

Role of Single Nucleotide Polymorphisms (SNPs)

SNPs represent the most prevalent form of genetic variation in human populations and consist of a change of a single nucleotide, accounting for approximately 90% of all such variants. These alterations have a crucial role in disease susceptibility and treatment response and are the most exploited variants in GWAS studies [1]. The majority of SNPs lies within non-coding regions of the genome and often exerts their regulatory functions on neighboring genes. Multiple candidate gene approaches have identified SNPs in various genes associated with RA susceptibility, offering promising leads for precision medicine yet these findings require further validation in diverse populations, including Africans. Such insights are anticipated to accelerate the identification of genomic regions linked to RA susceptibility and facilitate the discovery of novel genes and other polymorphisms broadly associated with the disease. Although several groups have discovered SNPs associated with different autoimmune disorders in diverse populations, these remain largely unexplored in African cohorts, representing a notable gap in current genomic research [1].

Epigenetics and Rheumatoid Arthritis

The three main epigenetic mechanisms that are currently under investigation with respect to rheumatoid arthritis (RA), namely, DNA methylation, histone modifications, and noncoding RNAs, are complementary and sometimes interconnected. In contrast with most cancers, candidate genes tend to be hypomethylated in RA. Other epigenetic changes, histone modifications, and abnormal expression of noncoding RNAs also contribute to RA development. The relevant epigenetic modifications may be tissue-specific, so studies should focus on cells involved in disease pathogenesis [1]. It is also important to determine whether these modifications are causes or consequences of inflammation. Some treatments may impact epigenetic modifications, and assessing these prior to therapy could help optimize responses. DNA methylation remains stable over time and could serve as a biomarker, while histone modifications change more rapidly. Epigenetic alterations are reversible and influenced by environmental factors, suggesting potential for prevention and treatment strategies. Most current studies are limited by homogeneous populations; larger, multiethnic community research is needed. Large-scale genome-wide association studies (GWASs) have considerably increased the understanding of RA aetiopathology and led to the development of genetic risk composite scores to predict disease susceptibility at a population level [1 , 2].

DNA Methylation

Phenotypic plasticity permits organisms to adapt to changing environmental conditions by activating different phenotypes based on experience or environment. Epigenetic mechanisms allow the expression of cryptic genetic variation through the transcriptional and translational regulation of genetic material. Epigenetics refers to inheritable and reversible processes that influence gene expression without changing the nucleotide sequence, including DNA methylation, histone modifications, and RNA interference. These mechanisms operate at different levels: (i) DNA methylation occurs primarily on cytosines in CpG dinucleotides, affecting chromatin structure or

transcription factor binding; (ii) histone modifications, such as acetylation or methylation, influence chromatin conformation and transcriptional activity via a histone code; and (iii) RNA interference involves short non-coding RNAs (e.g., siRNAs or miRNAs) that impact transcriptional and post-transcriptional regulation. RA patients' naive T cells share DNA methylation patterns with synoviocytes [6]. Despite the 450k BeadChip's prioritization of RefSeq genes and CpG islands, limiting coverage, differential methylation of approximately 1,000 CpGs in peripheral blood may distinguish RA cases from controls. Additional CpG sites relevant to RA could be unrepresented. An infra-red autosampler combined with gas chromatography-flame ionization detection (GC-FID) quantified the methylation levels of cytosine (Cyt) and 5-methylcytosine (MeCyt) in B and T lymphocytes. The MeCyt/Cyt ratio in B cells inversely correlates with disease activity, potentially serving as an additional RA activity biomarker [2]. Hypomethylated upstream enhancer elements activate p300 and BACH2 expression in naïve CD4+ T cells, mounting an abnormal T-cell response. Interferon-regulated genes exhibit aberrant methylation patterns, with RAP1GAP methylation flux driving inflammatory processes. Genome-wide DNA methylation patterns alongside biomarker analysis serve as powerful predictive tools for disease activity in patients or individuals at risk of developing RA. A recent meta-analysis of publicly available data identified hundreds of genes with consistent RA-associated DNA methylation profiles in peripheral blood mononuclear cells (PBMCs) or synovial fibroblasts (SF). Low-dose interleukin-6 signaling blockade reduces DNA methylation at loci linked to immune function and inflammation. RA discordant monozygotic twin studies performed in Europe and North America highlight the potential of rigorous study designs in uncovering epigenetic contributions to RA, paving the way for personalized preventive medicine [6].

Histone Modification

Histone modifications are one of the major epigenetic mechanisms influencing the pathogenesis of rheumatoid arthritis (RA). These post-translational modifications of nucleosomal histone proteins alter chromatin compaction and transcriptional accessibility [7]. The predominant histone modification studied in RA is acetylation, with increased histone acetyltransferase and decreased histone deacetylase activities observed in RA synovial cells [8]. Other critical histone marks include methylation, ubiquitination, SUMOylation, ADP-ribosylation, proline isomerisation, and citrullination. By modulating the activity of transcription factors and altering chromatin structure, histone modifications serve as an interface between environmental signals and the genome without changing the DNA sequence [2]. They can also influence both the direction and magnitude of DNA methylation effects. The chromatin structure at CpG sites controls the access of methyl-CpG-binding domain proteins to methylated DNA. This allows for DNA methylation to recruit transcriptional activating complexes rather than only repressing transcription, providing an additional layer of epigenetic regulation associated with RA [7].

Non-coding RNAs

The presence of complex epigenetic relationships between different entities involved in cellular regulatory networks remains poorly characterised, but integrative biological data analysis should allow us to reconstruct these networks more accurately than conventional approaches that analyse these entities separately. Until very recently, studies on these regulatory mechanisms remained limited because epigenetic alterations have tissue/cell specificity and the availability of relevant material has been scarce [1]. Another type of epigenetic alteration important for RA involves non-coding RNA species [2, 9]. Non-coding RNAs are molecules that can regulate gene expression at the transcriptional, post-transcriptional, and epigenetic processes. Non-coding RNAs can be divided into housekeeping and regulatory RNAs. The regulatory RNAs include microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). MicroRNAs are 18–23 nucleotides-long molecules that regulate genes at the post-transcriptional level and are well known to regulate many physiological processes. Long non-coding RNAs have diverse functions in epigenetic, transcriptional, and post-transcriptional regulation of gene expression. The involvement of non-coding RNAs in various cellular functions such as cell differentiation, proliferation, inflammatory mediation, and many other physiological roles makes them a very interesting area of research for several diseases, including RA. MicroRNAs represent the largest group of non-coding RNAs and have been widely studied in relation to RA. These are 18–23 nucleotides-long, single-stranded molecules with the capacity to regulate genes at the post-transcriptional level. It is speculated that more than 30 % of protein-coding genes are regulated by microRNAs. MicroRNAs have been shown to be critical regulators of the innate and adaptive immune systems, with many microRNAs implicated in autoimmunity and inflammatory diseases. Deregulated microRNAs may promote the excessive secretion of pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) and metalloproteases by synoviocytes and immune cells, the excessive proliferation, resistance to apoptosis, migration and invasion of synoviocytes into the cartilage, resistance to T regulatory-mediated suppression, faulty T cell selection, the promotion of Th17 differentiation, and the production of auto-antibodies. Therefore, microRNAs have the potential to be pathogenic determinants, biomarkers, and therapeutic targets in RA [2].

Current Trends in Precision Medicine

Personalized treatment aims to optimize drug regimens based on individual disease severity and pharmacological response, yielding better effectiveness with minimal adverse effects [1]. Disease progression markers predict outcomes for anti-rheumatic therapy. Matrix metalloproteinase 3 (MMP-3), a synovial biomarker, can forecast clinical remission or joint damage progression [2,7]. The precision medicine approach, therefore, aims to tailor strategies for RA therapy through disease stratification based on clinical and molecular traits.

Personalized Treatment Approaches

Precision medicine aims to deliver the right treatment to the right patient at the right time, an ambition that requires a detailed knowledge of both the disease process itself and of how the biological processes underlying it vary between patients [1]. Rheumatoid arthritis, a systemic autoimmune disorder present across all continents and ethnicities, is emblematic of disease with a complex aetiology and for which personalized approaches are being rigorously pursued. Comprehensive reviews of the disease-and its application to precision medicine-exist, albeit with little or no data on African populations.

Biomarkers for Disease Progression

Biomarkers assist with measuring disease progression. Numerous genomic and gene-expression analyses favor a precision-medicine approach and have identified markers of responsiveness to therapy, such as biologics or IL-1Ra. DNA, RNA, and protein biomarkers combine to potentially forecast the effectiveness of treatment (e.g., anti-TNF). Gene profiling also distinguishes responders to specific drugs. The development and validation of these biomarkers is essential for individualized care [9].

Ethnic Variations in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic, inflammatory, and symmetric polyarticular joint disease characterized by progressive cartilage destruction and bone erosion. RA may be induced by predisposing genetic, environmental, and epigenetic factors that trigger an inflammatory cascade, giving rise to clinical manifestations and extra-articular complications [5, 7]. The identification of new biomarkers for diagnosis and to predict disease progression is one focus of researchers. Despite the availability of several treatments, the disease still appears refractory in many patients. Because of differences in progression, prognosis, and response to treatment, the implementation of strategies such as precision medicine is required to tailor individual therapies and improve quality of life. Although Africa houses the most genetically diverse populations in the world, Americans with African ancestry have the highest prevalence of RA [1]. Diverse factors such as culture, the environment, or biogeography may play important roles in RA in African populations. Understanding associated genetic variants and epigenetic changes is therefore important to identify causal factors.

Prevalence in African Populations

African populations are likely to develop Rheumatoid Arthritis (RA), a chronic inflammatory autoimmune disorder characterized by symmetrical polyarthritis, with a predilection for the small joints of the hands and feet. Extra-articular manifestations often include pulmonary and ocular complications [10]. Cachexia, affecting approximately one-third of patients, is marked by an increased ratio of fat to lean mass due to loss of muscle mass, which can impair physical function and occur even in individuals of normal or obese body composition. The etiology of RA is multifactorial, encompassing immune, environmental, genetic, hormonal and anatomical factors while, notably, a positive family history confers an approximately threefold increased risk of developing the disease [1]. Owing to its heterogenous clinical presentation, the disease remains a significant diagnostic dilemma in the absence of specific biomarkers or tests. Consequently, the American College of Rheumatology (ACR) developed a set of diagnostic criteria in 1987 that have been universally adopted for its diagnosis. Based on findings from cross-sectional studies, RA has an urban prevalence of around 1% in Black Africans, comparable to rates in Europeans and Asians, and despite the presence of the condition, it remains uncommon in Africa as a whole. Investigations conducted in the rural settings of Uganda and Nigeria, however, suggest the possibility of a higher rural prevalence. In Africa, the onset of RA commonly occurs between 33 and 55 years of age whereas data from South Africa indicate that younger individuals, typically aged 20–30 years, are affected, thereby presenting a more aggressive form of the disease. Cultural, environmental and other socioeconomic factors are considered to play a significant role in this population.

Cultural and Environmental Influences

The frequency of rheumatoid arthritis (RA) in African populations is comparable to that on other continents. Observed differences in severity may be linked to cultural or environmental exposures that shape the epigenome. Modern technologies enable precise characterization of genome-wide epigenetic modifications, enhancing understanding of their influence on gene function and utility as biomarkers [3, 1]. African-specific epigenetic studies have documented distinct landscape variations and investigated environmental modulations of the epigenetic clock. Epigenetics holds potential as a biomarker of lifetime exposures and disease risk. Despite rapid development of epigenomic analytic approaches for complex diseases, their application in African scenarios

remains limited. Embracing this research avenue could foster novel research opportunities. As precision medicine continues to evolve, its application to single-base alterations in the microbiome and epigenome underscores the necessity for comprehensive datasets encompassing diverse populations. The African continent mandates substantial action to extend genomic and epigenomic information through collaborations aimed at expanding current datasets [1].

Genomic Studies in African Populations

The African continent represents the most genetically, environmentally, and culturally diverse region worldwide. Identifying population-specific genetic and epigenetic variants may help to understand biological processes associated with human diseases such as Rheumatoid Arthritis (RA) [1, 3]. Numerous studies on African populations have highlighted that genetic variants influencing disease susceptibility and drug response differ from those found in other populations, and that many such unique genetic variants remain undescribed. The prevalence of RA in Africa is increasing, with substantial variability across the continent and a lack of reliable epidemiological studies. At least 17 million patients are affected by RA, with a considerable population in Africa potentially untreated due to cultural and environmental differences. Genetic factors may be integrated with clinical and epidemiological information for RA patients by looking for population-specific genomic and epigenomic signatures. Preliminary research comparing RA patients and controls from Morocco with European and Asian populations showed that over 20% of certain variants mapped in RA-related loci are only present in the Moroccan population, reinforcing the hypothesis that genomic signatures from populations living in Africa may be instrumental to understand mechanisms and outcomes of RA [1].

Unique Genetic Variants

Several studies have identified unique genetic variants associated with rheumatoid arthritis (RA) in African populations that influence disease susceptibility and progression. HLA variants such as HLA-DRB1*04 remain strongly linked to RA across different ethnic groups in Africa [1]. Additional HLA variants, notably HLA-B*5801 in West Africans and analysis of the HLA-DRB1 locus within the shared epitope hypothesis in black South Africans, highlight a distinct pattern of MHC class I and II susceptibility alleles compared with Europeans. Non-HLA genetic factors also impact RA susceptibility in African populations; for example, African-specific variants of the PADI4 gene have been identified in black South Africans, although the association signals differ from those found in East Asian populations. Lower frequencies of functional PTPN22 and PTPRC variants key factors influencing RA risk in Europeans have been observed among sub-Saharan Africans. In light of the complex and multi-faceted nature of RA, generalization of European-derived data to African populations can be problematic. Instead, population-specific genomic studies remain essential to pinpoint drivers of disease onset and progression, which can aid diagnosis, improve management, and contribute to the development of tailored therapeutic regimens [1, 3, 5].

Comparative Genomics

The exploration of comparative genomics employs differences and similarities between organisms to infer purposes of strain-specific genes and generate hypotheses about lifestyle, pathogenicity, and production of molecules. Strategically, comparative genomics can compare two or more previously sequenced strains to identify the pan-genome, the core genome (genes shared) and the strain-specific genome, information critical in the development of drugs and vaccines, or in identifying markers that delineate epidemiology. Genomic studies add to the understanding of a disease's underlying disposition and pathophysiology by providing information on mechanisms relevant to treatment. Studies of molecular aberrations in RA have indicated a link between the disease and genome prediction. The genome can be screened for determining the presence of specific alterations that are known to contribute to the progression of a disease and, as a result, through determining specific genes and proteins involved in the progress of RA, a target treatment can be developed for its therapeutic management [1]. Genome-wide association studies (GWAS) and large-scale analyses of common loci associated with RA susceptibility have successfully identified several loci with disease-associated single nucleotide polymorphisms (SNPs). The relative risk of RA-associated SNPs is modest in most cases (relative risk <1.50), suggesting that individuals who harbor a certain allele or geno-type of a known variant are only modestly more likely to develop the disorder [4,5, 7].

Epigenetic Research in African Contexts

The rise of precision and systems medicine offers a promising approach to address the complex and multifactorial nature of rheumatoid arthritis (RA)[1]. Implementing this paradigm necessitates comprehensive omic studies; genomic, epigenomic, transcriptomic, and proteomic on large collections of human cohorts in a longitudinal manner. While attention has expanded towards Latin America and the Caribbean due to high prevalence and admixture of African ancestry, the African continent remains notably underrepresented. African populations boast unparalleled genetic diversity and a complex environment with genomic plasticity. Epigenetic regulation ordains genome-environment interactions and might mediate long-term effects like imprinting or "memory" of

environmental exposures generated by the rapid lifestyle transition experienced by African populations. Africa faces unprecedented socio-economic transformations, largely associated with the current epidemiological transition. The epigenome represents the first molecular level susceptible to these influences since it undergoes dynamic reprogramming in response to diverse stimuli at every stage of life [1, 3].

Environmental Epigenetics

Environmental epigenetics investigates the extent to which exposure to environmental factors influences gene expression without altering the underlying DNA sequence [2]. The association between passive smoke exposure and an elevated risk of rheumatoid arthritis (RA) underscores the importance of epigenetic mechanisms such as kynurenine biosynthesis and Toll-like receptor 10 (TLR10) methylation, which links environmental risk factors with RA development. Air pollution represents another source of environmental exposure to compounds with low water solubility that readily deposit in the lungs, diffuse into the circulation, and can incite systemic inflammation. Epigenetic mechanisms offer a plausible explanation since small gaseous molecules and ultrafine particles are unlikely to directly impact joints. Epidemiological evidence implicates an imbalance in gut microbiota as an environmental risk factor for RA. Beneficial species such as Faecalibacterium prausnitzii often display reduced abundance in RA patients, while harmful species such as Lactobacillus salivarius and Akkermansia muciniphila increase. Polysaccharide derived from Angelica sinensis, a traditional Chinese herb, has been shown to modulate the HIF–1α–glycolysis axis and reprogram the gut microbiota of collagen-induced arthritis rats, thus exerting protective effects against RA [1].

Socioeconomic Factors

In addition to traditional risk factors for rheumatoid arthritis (RA), socioeconomic factors may play an important role in disease development and progression. For example, one study found that low income is associated with increased mortality among RA patients, which may be related to poorer access to healthcare, medication adherence, or increased psychosocial stress [1]. Educational attainment, social networks, and occupation have also been linked to RA onset and prognosis; lower educational levels correlate with higher disease risk, limited social support associates with worse health outcomes, and certain occupational exposures contribute to disease pathology. However, the exact mechanisms by which socioeconomic factors influence RA remain complex and multifaceted, intersecting with many other risk determinants [1, 4].

Challenges in Research

Access to biological and clinical data is challenging for African scientists working on the genomic and epigenomic research required for precision medicine [1, 3]. Genomics and epigenetic datasets needed for these studies are scarce in public repositories; Afrocentric databases such as the Nigerian 100K Genome Project or the Southern African Human Genome Programme are just emerging. African governments should be encouraged to fund these initiatives to avoid large-scale population migration to develop precision medicine models. Regulations on ethical conduct, data privacy and assurance of data ownership are important considerations for future genomic initiatives in African populations [1].

Data Accessibility

The principal barrier to studying genomic and epigenomic markers in Africans with RA is data accessibility. African genomic databases generally lack samples from individuals with RA. Data from the Yoruba population serve as a reasonable proxy for genetic information. Access to epigenomic data for populations is equally limited, with self-controlled study designs offering an avenue for progress [1].

Ethical Considerations

Ethical considerations in precision medicine for rheumatoid arthritis (RA) encompass the responsible treatment of personal data, avoidance of discrimination, and the equitable access to preventive medicine and targeted treatments [1]. Worldwide efforts focus on developing methods for initial diagnosis and the prediction of disease progression in RA, a condition that affects approximately 1% of the population across the Americas, Europe, and Oceania. The pending Global Burden of Disease report is expected to reveal an increase in the relative prevalence of RA in developing countries from 2017 to 2027, particularly in Latin American countries such as Colombia and Peru, which may approximate the worldwide prevalence. In sub-Saharan Africa and some Asia-Pacific regions, available data indicate the possibility of lower prevalence rates. The expansion of precision medicine in African populations has the potential to influence RA diagnosis and prevention, and may identify unique individual molecular mechanisms. Various genetic and epigenetic studies conducted in European and Asian populations are likely to differ from those obtained from African populations. Additionally, a significant portion of African communities remains isolated from the shared human knowledge base, leading to limited data access for the scientific community and military establishments [1,4,7].

Future Directions in Precision Medicine

Precision medicine aims to incorporate individual characteristics to optimize therapeutic outcomes. There is limited research on genomic and epigenetic studies pertaining to African RA patients. To address this, a multi-omics approach that integrates various data types could fill current knowledge gaps by uncovering unique genomic and epigenetic signatures associated with RA in African populations [1]. Several studies have demonstrated that such an approach yields highly predictive networks and identifies novel genes closely linked to RA pathology in different populations. African cohorts constitute understudied groups capable of providing relevant information for applying precision medicine to RA treatment. Consequently, future work should prioritize exposing distinctive features resulting from the interplay of genetics, epigenetic processes, and environmental factors specific to these populations. Additionally, the clinical translation of findings derived from genomic and epigenetic analyses represents a critical step toward advancing precision medicine for RA in the African context [1,5].

Integrative Approaches

In precision medicine, population-specific differences in genomic and epigenomic signatures are exploited to guide the use of tailored molecular biomarkers of disease pathogenesis and severity of clinical phenotype. Immunopathogenic and demographic features associated with rheumatoid arthritis (RA) are population-specific and are accompanied by notable population variability in epigenomic signatures. Consequently, there is a concerted effort to identify and optimize the use of specific molecular signatures for RA prognosis and treatment response in African populations. Most ethnically-diverse genomic, epigenetic, and immunogenomic databases are Eurocentric. However, African populations exhibit higher genetic and epigenetic diversity than non-African populations. Hence, despite the lower availability of genomic studies in African populations, there is a compelling need for whole-genome investigation of the interplay between diverse molecular and immunopathogenic factors in the molecular signature and corresponding continuum of RA pathology in populations of African origin [1]. Multi-scale integrative genomic and immunogenomic models trained on datasets derived from relevant populations promise to contribute significantly to the ongoing effort to develop optimized population-specific precision medicine [1, 2].

Translational Research Opportunities

The genetic basis of RA is well established, with approximately 60% of disease risk attributed to genetics [1]. The RA locus shows strong specificity across populations, with minimal cross-ethnic overlap and distinctive effect sizes at several well-known loci such as the major histocompatibility complex (MHC) and PTPN22. These observations demonstrate the markers' ability to capture specific environmental and genomic contexts among different populations. RA exhibits pronounced differences in age of onset, severity, biomarker expression, and treatment response among various ethnic groups. African populations show the highest autoantibody prevalence, and African ancestry predicts a more severe disease outcome. The early emergence of the continental human genome project and the development of 23andMe enabled researchers to rapidly incorporate ethnically specific genomic markers into PRS, helping to identify population-specific signals. Large-scale GWAS involving Trans-National Asthma Genetic Consortium (TAGC) and the UK Biobank study identified 15 novel loci associated with asthma and other autoimmunities. Comparative analysis of effect size and allele frequency differences across these 15 loci reveals two significantly higher association signals with invariant allele frequencies in Europeans but low and variable frequencies across other groups, particularly Africans and African Americans. This challenge can be overcome by conducting more extensive GWAS studies on African cohorts or developing tailored statistical models based on WAVES analysis results [1,4,6]. The inability of GWAS summary statistics from United Kingdom (UK) Biobank European samples to predict asthma risk in African and African American populations, particularly in independent datasets, is investigated by focusing on multiple independent causal variants located within the same locus. When multiple causal variants exist, differences in linkage disequilibrium patterns between populations can lead to poor cross-population polygenic risk prediction. The diagnostic utility of candidate-gene choremes is enhanced by integrating them into a combined risk score system [1].

Case Studies

Several case studies highlight the potential of precision medicine in enhancing RA management. For instance, a drug-free remission model in RA suggested biomarkers relevant for early intervention in undifferentiated arthritis, aiding in determining treatment necessity [1]. A twin study revealed type-2-matrix-metalloproteinase (T2-MMP) as a pivotal factor in RA pathogenesis, indicating MMP-2 as a pharmacogenomic target. Moreover, a GWAS meta-analysis identified bivariate genetic components underlying RA and systemic lupus erythematosus, proposing GSZ and TRIM10/TRIM15 as novel drug targets. Such insights underscore the efficacy of precision medicine strategies. Although data on African RA cohorts are limited, studies indicate that African patients frequently experience more severe disease activity and poorer prognosis, highlighting the need for focused research. Precision Medicine therefore offers a promising, effective path toward RA management. Incorporating

genomic and epigenetic data within a systems biology framework constitutes a high-value direction for future research advances [1, 2, 3].

Successful Applications of Precision Medicine

Precision medicine combines personalized genetics, pharmacogenetics, and targeted therapies into an exceptionally potent clinical management strategy. This approach is rapidly evolving and already integrated into healthcare systems, yielding successful improvements across various medical specialties, notably in oncology and autoimmunity [3]. Rheumatoid arthritis, in particular, benefits from predictive genomic and epigenetic biomarkers that enable accurate diagnosis, refinement of patient groupings according to clinical parameters, and anticipation of disease prognosis. These advantages apply to diverse geographic areas and ethnic groups, including various African populations [1].

Lessons Learned from African Cohorts

The prevalence of autoimmune rheumatic diseases among African individuals has been increasing globally. Research on African cohorts both African Americans and native Africans offer unique insights due to their genetic and geographical links to the African continent. Analyses of various genome-wide association studies (GWASs) and intergenic transcripts consistently reveal that, although majorities of disease-associated variants overlap across populations, a considerable number of risk-associated single nucleotide polymorphisms (SNPs) remain unique to African cohorts, underscoring the value of African-focused studies [1]. Nearly half of the SNPs located on intergenic and intron markers are segregated across continental groups and countries within Africa, highlighting the extent of continental and regional genetic variation. Genome-wide DNA methylation profiling in native African populations and individuals with different ethnic backgrounds from the same country confirms the importance of environmental and cultural factors in shaping epigenetic landscapes, even within the African continent [4]. The migratory movements of African populations into Europe, as well as immigration from Asia and Europe back to Africa, have introduced additional layers of complexity to the epigenomic architecture of African populations. This dynamic demographic history emphasizes the need to investigate epigenetic alterations in relation to lifestyle changes during migration to understand mechanisms mediating cross-generation transmission of environmental effects and to characterize epigenetic changes correlating with disease susceptibility [5].

CONCLUSION

Precision medicine offers a transformative pathway for improving the management of rheumatoid arthritis. However, the exclusion of African populations from genomic and epigenetic studies undermines the universality and equity of current therapeutic approaches. Given Africa's unique genetic diversity and environmental exposures, advancing large-scale, population-specific research is critical for identifying relevant biomarkers and tailoring therapies. Strengthening local research capacity, biobanking infrastructure, and ethical frameworks will ensure sustainable progress. Ultimately, integrating African data into precision medicine is scientific necessity and a moral obligation, enabling more inclusive, effective, and equitable healthcare for patients with RA worldwide.

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