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REVIEW ARTICLE

GENETIC VARIATION AND ITS ROLE IN HEALTH AND PHARMACOLOGY: A NARRATIVE REVIEW

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Abstract

Human genetic variation plays a fundamental role in determining differences among individuals in disease susceptibility, clinical characteristics and responses to medical treatments. Advances in genomic technologies have significantly improved our ability to identify and characterize genetic differences, including single nucleotide variants, insertions and deletions, copy number variations and larger structural changes within the genome. These variations influence biological processes and contribute to both health and disease outcomes, making them essential to the development of precision medicine. This review examines the major forms of human genetic variation and their impact on disease development and pharmacological responses. It explores how genetic variants arise, their distribution across populations, and their involvement in monogenic, oligogenic and polygenic disorders. The review also highlights the importance of gene–environment interactions and epigenetic factors in shaping disease risk and progression. In addition, the paper discusses the growing field of pharmacogenomics, which investigates how genetic differences affect drug metabolism, efficacy and toxicity. Particular attention is given to clinically important variants in drug-metabolizing enzymes, transport proteins, and therapeutic targets that contribute to variability in treatment outcomes among patients. By linking disease genetics with pharmacogenomics, genetic information can be used both to predict disease risk and to guide individualized treatment strategies.

Keywords: Disease susceptibility, drug response, genetic variation, pharmacogenomics, polygenic risk scores, precision medicine.

INTRODUCTION

Human genetic variation underlies much of the observed diversity in health outcomes, disease susceptibility, and responses to pharmacological interventions. The human genome is made up of about 3.2 billion base pairs, with millions of variations separating one person from another. This genetic diversity presents itself in various ways, such as insertions and deletions (indels), copy number variations (CNVs) and major structural alterations like inversions, duplications and translocations. The most frequent of these variations are single nucleotide polymorphisms (SNPs), which can be found approximately every 300 base pairs throughout the genome[1,2].

Genetic variation arises through multiple biological mechanisms. Mutations introduce permanent changes in DNA sequence, either spontaneously during replication or due to environmental factors such as radiation or chemical exposure. Through the process of meiotic recombination, genetic material is mixed up to create new allele combinations, which increases overall population diversity. At a broader level, evolutionary factors including migration, gene flow, genetic drift and natural selection determine how these genetic variants are distributed and how their frequencies change across generations[3]. These processes collectively explain the substantial genetic diversity observed both within and between human populations.

Large-scale sequencing efforts have provided quantitative insights into the extent of human genetic diversity. In a major milestone, the 1000 Genomes Project sequenced the whole-genome and exome data of 2,504 people from 26 distinct populations worldwide. This effort successfully mapped over 88 million genetic variants, a total that features roughly 84.7 million SNPs, 3.6 million indels and upwards of 60,000 structural variants[1]. This initiative revealed that a standard human genome diverges from the reference

sequence at roughly 4 to 5 million locations. These findings highlight the widespread nature of genetic diversity, which has been continually molded by evolutionary history and population migration.

Genetic variation plays a dual role in human biology. While many variants are neutral, others may confer adaptive advantages, such as resistance to infectious diseases, or be deleterious, increasing susceptibility to inherited or complex disorders. From a health perspective, genetic diversity impacts an individual's susceptibility to disease, how a condition progresses and how their body reacts to environmental influences. Single-gene (monogenic) conditions like cystic fibrosis and sickle cell anemia are caused by highly penetrant variants that directly trigger the illness. Conversely, complex conditions such as cardiovascular diseases, diabetes and cancer stem from the collective impact of numerous genetic variants, each making a small individual contribution[4].

Genome-wide association studies (GWAS) have played a critical role in mapping genetic loci tied to complex diseases and traits. By the end of 2025, the NHGRI–EBI GWAS Catalog had documented over 7,500 studies, which collectively identify more than one million significant variant–trait correlations across a vast array of phenotypes[5,6]. While early GWAS primarily focused on common SNPs, recent methodological advances have expanded analyses to include CNVs and other structural variants, revealing contributions to disease heritability that were previously underestimated by SNP-based approaches alone[7].

Genetic variation fundamentally shapes pharmacology. Through pharmacogenomics, scientists study how inherited differences alter drug behavior inside the body (pharmacokinetics) and change drug-target interactions (pharmacodynamics). Genetic variants in receptors, transporters, and crucial drug-metabolizing enzymes like CYP2D6 and CYP2C19 ultimately explain why different patients experience vastly different drug effectiveness and toxicity levels[8]. Such variability is a major contributor to adverse drug reactions and therapeutic failure.

Efforts to translate pharmacogenomic knowledge into clinical practice have been led by initiatives such as the Clinical Pharmacogenetics Implementation Consortium (CPIC). This group publishes peer-reviewed, evidence-based recommendations that help clinicians use a patient's genetic profile to guide drug selection and dosing. As of 2025, CPIC has issued guidelines covering more than 34 genes and 164 drugs, supporting clinical decision-making to optimize dosing and drug selection[9]. Complementary resources, including the **Pharmacogenomics Knowledgebase (Pharm GKB)**, curate and disseminate pharmacogenomic data, further enabling the implementation of personalized medicine[10].

Scope and objectives of the review

This review explores the spectrum of human genetic variation and its implications for health and pharmacology. It focuses on major types and sources of genetic variants, their roles in disease susceptibility and health outcomes and their impact on drug response and safety. Additionally, it discusses population-level insights, representative clinical examples, and challenges such as inter-ethnic variability and barriers to clinical implementation. Ultimately, integrating genetic variation into healthcare offers immense potential for advancing precision medicine and optimizing therapeutic outcomes for a wide range of populations.

Background of genetic variation

Types of genetic variation

Genetic variation represents the differences in DNA sequences among individuals of the same population and is a fundamental driver of phenotypic diversity. Variants are commonly classified based on their size, frequency and molecular characteristics.

Single Nucleotide Variants (SNVs) and Single Nucleotide Polymorphisms (SNPs)

SNVs involve the replacement of a single base at a precise location in the genome. When an SNV reaches a population frequency of 1% or higher, it is classified as a single nucleotide polymorphism. These polymorphisms are the most prevalent type of genetic diversity, making up roughly 90% of all variations found in the human genome[1].

SNPs may occur in coding regions, where they can be synonymous (no amino acid change) or non synonymous, or in non-coding regulatory regions, where they can influence gene expression. Although most SNPs are functionally neutral, some significantly affect disease susceptibility and drug response. GWAS have extensively leveraged SNPs to identify genetic loci associated with complex diseases such as diabetes, cancerand cardiovascular disorders[11].

Insertions and deletions (Indels)

Insertions and deletions, collectively known as indels, refer to the gain or loss of brief DNA sequences that generally span between 1 and 50 base pairs. Indels are less frequent than SNPs but often have greater functional consequences, particularly when they occur within coding regions. Frame shift indels can disrupt the genetic reading frame. It result in premature stop codons that produce truncated or entirely nonfunctional proteins[12].

Indels play a critical role in both single-gene and complex multi-factor diseases, serving as a major cause of loss-of-function variations across the human genome. While next-generation sequencing breakthrough have significantly enhanced our ability to detect these mutations, mapping them accurately within highly repetitive DNA sequences remains difficult[13].

Copy Number Variations (CNVs)

CNVsrepresent a category of structural variants defined by the duplication or deletion of DNA segments that generally exceed 1 kilobase in size. CNVs can encompass entire genes or regulatory regions, resulting in altered gene dosage and expression levels[14].

CNVs are heavily linked to cancer, immune-related diseases and neuro developmental disorders[15]. For instance, alterations in the copy number of the *CYP2D6* gene directly dictate an individual's drug metabolism capacity, rendering CNVs a vital area of study within pharmacogenomics[16].

Structural Variants (SVs)

SVs are large-scale genomic modifications measuring 50 base pairs or more in length. These alterations encompass a variety of chromosomal changes, including deletions, duplications, insertions, inversions and translocations[17]. Although fewer in number compared to SNPs, SVs affect more base pairs per genome and can have profound functional consequences[18].

SVs contribute to genomic diversity, gene disruption, and regulatory remodeling[19]. Long-read sequencing technologies have revealed that SVs were previously underestimated due to limitations of short-read sequencing, highlighting their substantial role in both evolution and disease[20].

Tandem repeats and other variant classes

Tandem repeats which encompass both short tandem repeats (STRs) and variable number tandem repeats (VNTRs) are characterized by sequences of repeating DNA motifs[21,22]. Expansion or contraction of these repetitive segments can trigger severe health conditions, with notable examples including Huntington's disease and fragile X syndrome[23].

Other variant classes include multinucleotide variants (MNVs), which involve the simultaneous mutation of neighboring nucleotides[24] and mobile element insertions. The latter, featuring Alu or LINE-1 elements, play a significant role in driving genome plasticity and long-term evolution[25].

Detection methods for genetic variation

Breakthroughs in technology have significantly improved our capacity to identify and profile genetic diversity. Next-generation sequencing (NGS) technologies enable high throughput sequencing of DNA at unprecedented speed and resolution, allowing the identification of millions of variants in a single experiment[13,27]. NGS platforms use a variety of different approaches. For instance, whole-genome sequencing (WGS)[28], analyzes a person's entire DNA blueprint, including both coding and non-coding regions. In contrast, whole-exome sequencing (WES) [29], which focuses strictly on protein-coding regions, where most disease-causing mutations are found[30].

At the population level, genome-wide association studies (GWAS) serve as a primary tool for linking common genetic variants to complex traits and diseases. By analyzing hundreds of thousands to millions of SNPs across large patient cohorts, these studies map specific genetic loci associated with widespread conditions like diabetes, cancer and cardiovascular disorders[11]. Although GWAS have successfully identified thousands of risk loci, they primarily detect common variants and often require complementary sequencing approaches to capture rare and structural variants.

Population-level insights into genetic variation

The distribution of genetic variants differs significantly across populations due to historical, demographic, and evolutionary factors. Large-scale population genomics initiatives, most notably the 1000 Genomes Project, have generated an extensive registry of human genetic diversity across diverse ethnic backgrounds. These efforts have highlighted major discrepancies in allele frequencies among African, European, East Asian, South Asian and admixed populations[1].

African populations display the greatest degree of genetic diversity, a direct result of their more extended evolutionary history. Conversely, non-African populations exhibit markedly reduced genetic variation, stemming from severe population bottlenecks encountered during ancient migrations out of Africa. These population-specific differences have important implications for disease risk prediction and pharmacogenomics, as variants influencing drug metabolism or disease susceptibility may vary in frequency across ethnic groups[31,32].

Principles of population genetics, particularly the Hardy–Weinberg equilibrium, offer a baseline mathematical model for analyzing genotype and allele frequencies. This framework assumes ideal conditions, such as completely random mating and a total absence of evolutionary pressures like mutation or selection. Deviations from Hardy–Weinberg equilibrium may indicate selection, population stratification, mutation, or genotyping errors, and are routinely assessed in genetic studies to ensure data quality and biological relevance[3,33].

Evolutionary perspective on genetic variation

From an evolutionary perspective, genetic variation provides the fundamental substrate upon which natural selection operates. Although a large portion of variants remain selectively neutral, specific environmental pressures can render certain mutations highly advantageous[35]. A classic example is the HBB gene variant responsible for the sickle cell trait; it offers robust protection against severe malaria in heterozygous individuals. It is maintaining its elevated frequency in malaria-endemic areas despite the severe risk of sickle cell disease in homozygotes[36,37].

Conversely, genetic variation can also elevate disease susceptibility. Variants that were benign or even beneficial in ancestral environments can become maladaptive under modern living conditions. This drives the rise of chronic conditions like obesity and cardiovascular disease. This evolutionary mismatch underscores the intricate relationship between genetics, environment and health. It highlights why evolutionary perspectives are vital for decoding both disease pathology and drug responses[38,39].

Role of genetic variation in health

Genetic variation contributes to disease susceptibility through two principal genetic architectures: monogenic disorders, caused by rare variants with large effect sizes in a single gene and polygenic traits, where numerous common variants of small effect cumulatively influence disease risk[40,41]. These contrasting mechanisms explain the genetic basis of both rare inherited diseases and common complex conditions.

Genetic variation and disease susceptibility

Monogenic disorders

Monogenic disorders are caused by rare, highly penetrant genetic variants that typically adhere to Mendelian inheritance patterns. Classic illustrations include cystic fibrosis, which stems from pathogenic mutations in the CFTR gene. It also includes sickle cell disease, which is driven by a specific missense

mutation within the *HBB* gene[42,43]. These variants directly disrupt protein structure or function, leading to well-defined clinical phenotypes and making them amenable to targeted genetic screening and counseling.

Polygenic traits

In contrast, most common diseases including type 2 diabetes, coronary artery disease, obesity and many psychiatric disorders are polygenic. GWAS have identified an extensive number of risk loci associated with these conditions. As of 2025, the NHGRI-EBI GWAS Catalog reports over one million SNP–trait associations across more than 7,400 publications, underscoring the highly polygenic nature of common diseases[40].

These associations are integrated into polygenic risk scores (PRS), which weight and sum risk alleles across the genome to estimate a person's overall genetic predisposition. While their predictive accuracy fluctuates depending on the population, PRS hold significant promise for refining risk stratification in conditions like coronary artery disease and type 2 diabetes, especially when integrated with clinical and lifestyle metrics[41].

Impact of genetic variation on specific health conditions

Cancer

Inherited genetic diversity significantly influences cancer susceptibility. Pathogenic germline mutations in the tumor suppressor genes BRCA1 and BRCA2 drastically elevate the lifetime risk of developing breast and ovarian cancers, with the risk of breast cancer reaching approximately 70% in women[45]. Because these specific genes are critical for repairing DNA via homologous recombination, their impairment precipitates widespread genomic instability and subsequent oncogenesis.

Neurological disorders

Genetic variation is a key contributor to neurodegenerative diseases. One of the most important genetic factors associated with late-onset Alzheimer's disease is the APOE ε4 allele. Individuals who inherit one copy of the APOE ε4 allele have an approximately 2–3 times greater risk of developing the disease. Those who inherit two copies face a substantially higher risk, estimated to be 10–15 times greater than individuals without the allele[46,47]. APOE ε4 influences amyloid-β metabolism, neuroinflammation, and disease onset, with recent evidence linking it to shared immune-related molecular changes across neurodegenerative disorders[48].

Infectious diseases

Host genetic factors play an important role in determining susceptibility to infectious diseases and influencing their progression. Variations in human leukocyte antigen (HLA) genes affect how antigens are presented to the immune system. These genetic differences can alter immune responses and contribute to variations in disease outcomes. For example, HLA variants have been associated with differences in the severity and progression of infections such as HIV and COVID-19.

Metabolic conditions

Some genetic variants reflect evolutionary adaptations with metabolic consequences. Lactase persistence is a genetic trait that allows individuals to digest lactose beyond childhood. This trait is associated with regulatory variants located near the LCT gene, which controls the production of the lactase enzyme. It is particularly common in populations with a long history of dairy farming and milk consumption[51]. This example illustrates how genetic variation can provide nutritional advantages while shaping metabolic health.

Epigenetic and environmental interactions

Genetic susceptibility is often modified by environmental exposures through gene–environment (G×E) interactions. Lifestyle choices play a crucial role in shaping health outcomes. Factors such as dietary habits, smoking and physical activity can modify the effects of genetic predispositions. Research suggests that healthy lifestyle practices can mitigate the impact of elevated polygenic risk scores associated with obesity and cardiovascular disorders[52]. Environmental influences can alter gene activity through epigenetic processes. Key mechanisms include DNA methylation and histone modifications, which regulate gene expression without changing the underlying DNA sequence[53].

Public health implications

Advances in understanding genetic variation have important public health applications. Genetic screening programs, such as BRCA testing for hereditary cancer risk, allow early intervention and preventive strategies. However, challenges remain, including ancestry bias in GWAS data, concerns about data privacy and genetic discrimination, and unequal access to genetic testing and counselling services[54]. Addressing these issues is essential for the equitable integration of genomics into healthcare.

Together, these insights establish a strong link between genetic variation and health outcomes, providing a foundation for its application in pharmacology and precision medicine.

Role of genetic variation in pharmacology

Pharmacogenomics is the study of how genetic variation affects individual responses to medications[55]. Genetic differences among individuals can influence the way drugs are absorbed and distributed throughout the body. These variations can also affect drug metabolism and transport. In addition, genetic factors may alter how medications interact with their biological targets, leading to differences in efficacy and safety. These variations explain why the same drug and dose may be effective in some individuals but ineffective or toxic in others, forming the basis of personalized medicine[56].

Genetic differences play a key role in determining how patients respond to drugs. They primarily affect pharmacokinetics. Genetic variation can also influence pharmacodynamics by altering drug targets and cellular signaling pathways. Among the most clinically relevant genetic factors are variants in drug-metabolizing enzymes. Variants in transporters and receptors also contribute to differences in drug efficacy and safety[57].

Drug-metabolizing enzymes

The cytochrome P450 (CYP450) enzyme family serves as the central mediator of Phase I drug metabolism[58-60]. Polymorphisms in CYP genes result in different metabolizer phenotypes:

1. **Poor metabolizers (PM):** Exhibit minimal to entirely absent enzymatic activity.
2. **Intermediate metabolizers (IM):** Present with significantly reduced enzymatic function.
3. **Normal/extensive metabolizers (NM/EM):** Demonstrate standard, baseline enzymatic activity.
4. **Ultra-rapid metabolizers (UM):** Display markedly elevated enzymatic activity[61].

These phenotypes strongly influence drug plasma concentrations and clinical response[59].

Drug targets and transporters

Variants in genes encoding drug targets can alter drug sensitivity. For example, polymorphisms in VKORC1, the pharmacological target of warfarin, increase drug sensitivity and necessitate lower doses to prevent bleeding complications[63]. Genetic variation in drug transporters can influence the distribution and clearance of medications. One important example involves the SLCO1B1 gene, which encodes the hepatic transporter OATP1B1. Variants in this gene can reduce the uptake of statins into liver cells (hepatocytes). As a result, systemic drug exposure increases, leading to a higher risk of statin induced myopathy[64].

Clinically relevant pharmacogenomics examples

Cardiovascular Pharmacogenomics

- **Warfarin:** Variants in CYP2C9 (metabolism) and VKORC1 (drug target) together explain a substantial proportion of dose variability. Genotype-guided dosing reduces bleeding risk and improves anticoagulation control[63-65].
- **Clopidogrel:** Patients with CYP2C19 loss-of-function alleles produce less of the drug's active metabolite, which weakens its antiplatelet effectiveness and elevates the risk of cardiovascular events[66]. Consequently, alternative therapies like prasugrel or ticagrelor are preferred for individuals classified as intermediate or poor metabolizers[66,67].
- **Statins:** SLCO1B1 variants increase the risk of simvastatin-associated myopathy, guiding dose reduction or selection of alternative statins[64,68].

Oncology

Somatic and germline genetic variations guide targeted cancer therapy. Mutations in EGFR or ALK predict response to tyrosine kinase inhibitors, while germline variants in TPMT or NUDT15 influence thiopurine toxicity, necessitating dose adjustments[69,70].

Psychiatry and pain management

Variants in CYP2D6 and CYP2C19 affect antidepressants, antipsychotics, and opioids such as codeine[71,72]. Genotype-guided prescribing reduces adverse effects and therapeutic failure[73].

Immune-mediated adverse drug reactions

Certain human leukocyte antigen (HLA) alleles are associated with a high risk of severe drug hypersensitivity reactions. One well-known example is the *HLA-B*15:02* allele, which is strongly linked to carbamazepine induced Stevens Johnson syndrome[74-76]. This association is particularly common in Asian populations. Another important example is the HLA-*B*57:01* allele, which is associated with hypersensitivity reactions to abacavir. Identifying these genetic variants before treatment can help reduce the risk of serious adverse drug reactions[77,78].

Clinical implementation

Pharmacogenetic testing plays an important role in personalized medicine. It helps clinicians select the most appropriate medication for a patient. The testing can also guide dose optimization based on an individual's genetic profile. In addition, pharmacogenetic information can reduce the risk of adverse drug reactions[71].

The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides evidence-based prescribing guidelines to support the clinical application of pharmacogenetic testing. As of 2025, CPIC covers 34 genes and 164 drugs, facilitating routine clinical use. Many drug labels approved by regulatory agencies now include pharmacogenomic information[79,80].

Integration of genetic variation linking health and pharmacology

Genetic variation frequently plays a dual role by contributing to disease susceptibility while simultaneously influencing drug response. This convergence forms the basis of precision medicine, where genetic information is used to guide both disease risk assessment and therapeutic decision-making[81,82]. A single genetic profile can therefore inform prevention strategies, diagnosis, drug selection, and dose optimization.

Many disease-associated variants occur in genes involved in drug metabolism or drug targets[83]. Consequently, variants that increase disease risk may also modify treatment efficacy or toxicity, creating opportunities for genotype-guided interventions that address both disease pathology and pharmacological optimization[84].

Disease–drug genetic overlaps

Monogenic disorders

In rare genetic diseases, the link between pathogenic variants and a patient's response to medication is frequently straightforward[86]. For example, cystic fibrosis results from mutations in the CFTR gene, and the clinical efficacy of CFTR modulators such as ivacaftor depends on the specific mutation present[87,88]. Similarly, in Gaucher disease, pathogenic variants in the *GBA* gene influence response to enzyme replacement therapy, linking genetic etiology directly to therapeutic outcome[89].

Complex diseases

Polygenic risk scores (PRS) are widely used to predict susceptibility to complex disorders by evaluating the cumulative effects of numerous genetic variants[90]. Some of these variants lie within pharmacogenes. For example, cardiovascular PRS may account for genes that influence lipid processing and therapeutic responses to statins, including SLCO1B1[91]. Individuals with high genetic risk may benefit from early pharmacological intervention but also require dose

adjustments to minimize adverse drug reactions, such as statin-induced myopathy[92].

Precision oncology

Cancer exemplifies the integration of disease genetics and pharmacology. Both somatic and germline variants guide risk assessment and therapeutic decisions[93]. EGFR mutations increase susceptibility to certain lung cancers and predict response to tyrosine kinase inhibitors such as osimertinib[94]. Likewise, BRCA1/2 mutations increase breast and ovarian cancer risk while conferring sensitivity to PARP inhibitors, including olaparib[45]. These examples demonstrate how genetic variants inform both disease biology and targeted treatment selection.

Real-world clinical implementation

Large-scale clinical initiatives have demonstrated the feasibility of integrating genetic information into routine healthcare[96,97]. Preemptive pharmacogenomic testing programs enable genetic results to be stored within electronic health records and reused throughout a patient's lifetime[98]. Recent studies have combined polygenic risk scores with pharmacogenomic information to improve patient care. This integrated approach helps identify individuals who may be at greater risk of adverse drug reactions. Research has shown that it can enhance treatment effectiveness and overall clinical outcomes. The greatest benefits have been observed in the fields of cardiology and psychiatry[82].

Emerging directions

Gene editing technologies

Advances in CRISPR-Cas9 gene editing have enabled direct correction of pathogenic variants[99,100]. Recent approvals of CRISPR-based therapies for conditions such as sickle cell disease highlight the potential to move beyond risk prediction toward genetic cure[101,102]. These technologies also facilitate functional validation of pharmacogenomic variants.

Artificial intelligence and multi-omics integration

Machine learning approaches increasingly being used in genomic research. These methods can integrate genomic, transcriptomic and clinical data from multiple sources. This integrated analysis helps determine the potential impact of genetic variants on biological processes. As a result, researchers can better predict both disease risk and variability in drug response among individuals[103]. Artificial intelligence is accelerating variant interpretation and supporting decision making in precision medicine[104].

Overall, genetic variation serves as a unifying link between health and pharmacology. Integrating disease genetics with pharmacogenomics enables improved risk stratification, safer prescribing, and optimized therapeutic outcomes, advancing the goal of equitable and effective precision medicine[105].

Challenges, ethical issues and limitations

Despite significant advances in human genetics and pharmacogenomics, several scientific, ethical, and practical challenges continue to limit the widespread implementation of precision medicine.

Scientific and technical challenges

One major challenge lies in the complex interpretation of genetic variants. Advances in genome-wide association studies and sequencing technologies have led to the identification of a large number of variants. However, the clinical significance of many of these variants remains unclear. As a result, they are often classified as variants of uncertain significance (VUS)[106]. This limits their immediate clinical utility. Additionally, most identified variants have small effect sizes, particularly in polygenic traits, making individual risk prediction probabilistic rather than deterministic[107]. Another important limitation is the incomplete understanding of gene–gene and gene–environment interactions. Genetic effects are often influenced by external factors. Elements such as diet, lifestyle, infections and medication use can modify how genes affect health outcomes. This complexity makes disease risk assessment and treatment decisions more challenging[53].

Technical challenges continue to affect the accurate detection of genetic variants. This is particularly true for structural variants and changes located within repetitive regions of the genome. Recent advances in long-read sequencing technologies have improved variant detection capabilities. However, accurately identifying these complex variants remains a significant challenge[108,109].

Population bias and health disparities

Limited population diversity in genomic databases represents a critical obstacle to the advancement of precision medicine. Historically, the majority of genetic association and pharmacogenomic studies have focused on people of European descent. This narrow representation restricts the applicability of research findings to globally diverse populations. As a result, disease risk assessments and pharmacogenomic predictions may be less accurate for underrepresented ethnic groups[110]. This bias affects the accuracy of polygenic risk scores and pharmacogenetic guidelines, potentially exacerbating global health inequities. Genetic variation differs significantly across populations. As a result, the frequency of specific alleles can vary between ethnic groups. One example is the higher prevalence of CYP2C19 poor metabolizer alleles among Asian populations. Such differences may affect the efficacy and safety of medications. Therefore, including diverse populations in genomic studies is essential for improving the accuracy and applicability of research findings[111].

Ethical, legal and social issues

The expanding application of genetic testing has intensified discussions about ethical and legal responsibilities. Safeguarding personal genetic information and ensuring informed consent are major concerns[112]. Protecting genetic data from unauthorized access is essential to maintaining individual privacy. In some cases, this may lead to discrimination in areas such as employment and insurance, despite the existence of legal protections in certain countries[113].

Another important ethical issue is ensuring equitable access to genetic testing and personalized treatments. Access to these services is often limited by high costs and inadequate healthcare infrastructure. A shortage of trained healthcare professionals can further restrict their availability. These barriers are particularly

significant in low- and middle-income countries and may contribute to widening healthcare disparities[114].

Clinical implementation barriers

Integrating genetic information into routine clinical practice faces logistical challenges, including limited clinician training in genetics, lack of standardized testing protocols, and difficulties incorporating genetic data into electronic health record systems[115]. Moreover, reimbursement policies for pharmacogenetic testing vary widely, limiting adoption even in high-resource settings.

Limitations of study

Many pharmacogenomic associations are supported by observational studies rather than randomized controlled trials. While clinical guidelines such as those from CPIC provide evidence-based recommendations, gaps remain in long-term outcome data and cost effectiveness analyses. Furthermore, polygenic risk scores currently explain only a fraction of disease heritability. It may perform poorly outside the populations in which they were developed.

Future perspectives

Future advancements in genomic medicine are expected to address many of these limitations. Emerging technologies such as long-read sequencing, artificial intelligence-driven variant interpretation, and gene-editing platforms are likely to enhance the accuracy of variant discovery and functional characterization. These methods combine data from genomics, transcriptomics, proteomics and metabolomics. This comprehensive approach improves the understanding of disease mechanisms and their underlying molecular pathways.

CONCLUSIONS

Genetic variation plays a fundamental role in health and disease. It also contributes to differences in individual responses to medications. Modern genomic technologies have enabled the identification of diverse forms of genetic variation. These include single nucleotide variants as well as large structural changes in the genome. Understanding these variations has provided valuable insights into biological function and clinical outcomes. This review explores the contribution of genetic variants to disease susceptibility through both single gene and complex genetic mechanisms.

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AUTHOR'S CONTRIBUTIONS

Oladele FO: conceptualization, writing original draft. **Ebimo-Moko GE:** formal analysis, critical review. **Joel JD:** conceptualisation. **Sampson JE:** literature survey. **Madu WC:** data organization. Final manuscript was checked and approved by all authors.

DATA AVAILABILITY

The associated author can provide the empirical data used to support the study's conclusions upon request.

CONFLICT OF INTEREST

There are no conflicts of interest in regard to this project.

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