JOURNAL OF INTERNATIONAL CRISIS AND RISK COMMUNICATION RESEARCH
ISSN: 2576-0017
2024, VOL 7, NO S7

An Overview of Genetic Biomarkers Influencing Drug Response and Efficacy in Specific Populations

Nourah Gherman Salman Al-Amri[1], Aljohara Mohammed Hasan Halikah[2], Sharif Wusayman Lafi Alharbi[3], Mohammed Obaidallah Obaid Almatrafi[4], Ahmed Habib Aelnakhly[5], Nabial Hamadi Al Sheikh[6], Najat Khalaf Almashyakhi[7], Khaled Mohammed Hamed Alamri[8], Mahmoud Khamis Saeed Alghamdi[9], Ismaeel Mohamed Sardar[10], Abdullah Hassan Alhumrani[11], Ahmad Khalid Damanhouri[11], Rasheed Saeed Ali Alghamdi[12], Waad Hamed Alsharif[13], Abdulaziz Faihan Mashan Alotaibi[14]

1. Lab specialist , Ibn Sina Hospital
2. Lab tech , Ministry of Health
3. Laboratory technician, Wadi Al-Faraa General Hospital, Almadinah city
4. Laboratory Technician , Wadi Al-Faraa General Hospital, Madinah city
5. Laboratory, Wadi Al-Faraa General Hospital, Madinah city
6. Laboratory technician, Osfan primari health care
7. Al-Khasra General Hospital, Laboratory Specialist
8. Alfaisaliyah PHCC – Madinah, Technician-Laboratory
9. Technician Pharmacy, Umm aldoom general hospital
10. HERA Gerenal Hospital, Pharmacist
11. Executive Management of Supply Chains at Makkah Health Cluster, Pharmacy Technician
12. Haramain Railway Station health center, Technician-Pharmacy
13. Pharmacist , Hera General Hospital
14. Umm aldoom general hospital, Pharmacy technician

ABSTRACT

This review examines the role of genetic biomarkers in influencing drug response and efficacy, focusing on their impact in specific populations and the challenges in implementing pharmacogenomics in clinical practice. Genetic biomarkers, such as polymorphisms in CYP450 enzymes, HLA alleles, and TPMT, significantly affect drug metabolism, efficacy, and the risk of adverse reactions. Population-specific genetic differences, such as HLA-B15:02 in Southeast Asians and CYP2C19 variants in East Asians, highlight the importance of tailoring pharmacogenomic insights to diverse groups. While pharmacogenomics holds immense promise for personalized medicine, barriers such as limited population diversity in genomic research, high testing costs, and integration challenges hinder its widespread application. Addressing these issues through collaborative efforts and advancing equitable access to genetic testing can unlock the potential of pharmacogenomics to optimize therapeutic outcomes and reduce disparities in healthcare.

1. Introduction

Advances in precision medicine have revolutionized the way healthcare providers approach drug therapy, emphasizing the role of genetic variation in influencing individual responses to medications. Pharmacogenomics, a cornerstone of this approach, focuses on understanding how genetic differences impact drug metabolism, efficacy, and the likelihood of adverse drug reactions (ADRs). Genetic biomarkers, including specific gene polymorphisms and allelic variations, serve as vital tools in predicting drug responses, optimizing treatment regimens, and minimizing side effects. These biomarkers are particularly important in addressing variability in drug response observed across different populations, shaped by genetic ancestry, ethnicity, and environmental factors (1).

Variability in drug response remains a significant challenge in clinical practice, often resulting in suboptimal therapeutic outcomes or severe ADRs. For instance, while a drug may be effective in one individual, the same dose may result in toxicity or lack of efficacy in another due to differences in genetic makeup. This inter-individual variability is frequently driven by genetic factors, such as polymorphisms in drug-metabolizing enzymes, drug transporters, and receptors. Key examples include cytochrome P450 (CYP) enzyme polymorphisms influencing the metabolism of antidepressants and analgesics, and variations in the human leukocyte antigen (HLA) system associated with hypersensitivity reactions to specific drugs (2).

Population-specific genetic differences further compound variability in drug response. Certain genetic variants, such as HLA-B15:02 (linked to carbamazepine-induced Stevens-Johnson syndrome), are prevalent in Southeast Asian populations but rare in Europeans, underscoring the importance of incorporating population-specific pharmacogenomic insights into clinical practice. Similarly, alleles like CYP2C19 2 (a loss-of-function allele affecting clopidogrel metabolism) are more frequent in East Asians, necessitating alternative dosing strategies or drug choices in these populations. Understanding these differences is essential for delivering equitable healthcare and avoiding potential disparities in treatment outcomes (3).

Despite its promise, the integration of pharmacogenomics into routine clinical practice faces several challenges, including limited access to genetic testing, underrepresentation of diverse populations in genomic research, and insufficient clinician awareness of pharmacogenomic principles. Overcoming these barriers requires collaborative efforts across research, clinical practice, and policy-making to ensure the benefits of pharmacogenomics reach all populations equitably (3).

This review delves into the critical role of genetic biomarkers in influencing drug response and efficacy, with a focus on specific populations. It highlights key genetic markers, such as polymorphisms in CYP enzymes, HLA alleles, and transporter genes, and examines their impact on drug metabolism, efficacy, and toxicity. Additionally, it explores challenges in implementing pharmacogenomics, including disparities in research representation and the need for accessible genetic testing. By addressing these topics, the review underscores the transformative potential of pharmacogenomics in advancing personalized medicine and improving therapeutic outcomes across diverse populations.

2. Review:

1. Cytochrome P450 Enzymes (CYP450 Family)

The cytochrome P450 enzyme system plays a central role in the metabolism of nearly 70% of clinically used drugs. Genetic polymorphisms in these enzymes lead to significant inter-individual and inter-population variability in drug metabolism, influencing therapeutic efficacy and the risk of adverse drug reactions (1).

CYP2D6

- Function:

o CYP2D6 metabolizes a wide range of drugs, including antidepressants (amitriptyline, fluoxetine), opioids (codeine), and beta-blockers (metoprolol).

o It is one of the most polymorphic CYP enzymes, with over 100 identified alleles.

- Genetic Variants and Metabolizer Phenotypes:

Poor Metabolizers (PMs): Carry null alleles (CYP2D6 4, 5, 6). PMs exhibit diminished enzyme activity, leading to drug accumulation and increased risk of toxicity.

Ultra-Rapid Metabolizers (UMs): Often have gene duplications (e.g., CYP2D6 2xN), resulting in enhanced metabolism and subtherapeutic drug levels.

- Population Variability:

PMs are more prevalent in European populations (~5-10%), while UMs are more common in North African and Middle Eastern populations (~20-30%) (2). Implications: In PMs, codeine may fail to produce the desired analgesic effect because it requires CYP2D6-mediated conversion to morphine, while UMs are at higher risk of opioid toxicity.

CYP2C19

Metabolizes drugs such as clopidogrel (antiplatelet agent), omeprazole (PPI), and sertraline (antidepressant). Loss-of-function alleles (CYP2C19 2, 3) result in reduced metabolism, leading to suboptimal drug activation. Gain-of-function alleles (CYP2C19 17) enhance enzyme activity, increasing the risk of drug toxicity.

- Population Variability:

Loss-of-function alleles are more frequent in East Asians (~30%) compared to Europeans (~15%). Clinical Implications: Reduced activation of clopidogrel in poor metabolizers leads to higher rates of thrombotic events post-percutaneous coronary intervention (3).

2. Human Leukocyte Antigen (HLA) Alleles

HLA alleles mediate immune responses, including drug-induced hypersensitivity reactions. Certain alleles are strong predictive markers of severe adverse reactions.

HLA-B*57:01

- Drug Association:

Abacavir, an antiretroviral drug used in HIV treatment, is strongly linked to hypersensitivity reactions in carriers of HLA-B57:01*.

- Clinical Impact:

Hypersensitivity reaction symptoms include fever, rash, gastrointestinal distress, and respiratory complications. If untreated, these can escalate to life-threatening conditions (5).

- Population Variability:

Prevalence is ~6% in Europeans, ~3% in Africans, and <1% in East Asians. Routine genetic testing prior to abacavir prescription has virtually eliminated hypersensitivity reactions in clinical practice.

HLA-B*15:02

- Drug Association:

Carbamazepine, a widely used antiepileptic drug. Carriers of HLA-B15:02* are at a significantly increased risk of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), severe and potentially fatal skin reactions.

- Population Variability:

The allele is highly prevalent in Southeast Asian populations (e.g., ~10% in Han Chinese, Thai, and Filipino populations). It is rare in European and African populations (6). Clinical Implications: Genetic screening before carbamazepine use is now standard in high-risk populations, significantly reducing the incidence of SJS/TEN.

3. Thiopurine Methyltransferase (TPMT)

TPMT is essential for metabolizing thiopurine drugs (azathioprine, mercaptopurine, thioguanine), commonly used in autoimmune conditions and certain cancers.

Loss-of-function alleles (TPMT 2, 3A, 3C) result in reduced or absent enzyme activity. Low TPMT activity is most common in European populations (~10%) but rare in East Asians (<1%) (7). Patients with low TPMT activity are unable to effectively metabolize thiopurines, leading to drug accumulation and severe myelosuppression. Genetic testing prior to thiopurine therapy enables dose adjustments, minimizing toxicity while maintaining therapeutic efficacy.

4. Solute Carrier Organic Anion Transporter 1B1 (SLCO1B1)

SLCO1B1 encodes a hepatic transporter responsible for statin uptake and metabolism.

The SLCO1B1 5 allele reduces transporter function, increasing circulating statin levels and the risk of statin-induced myopathy. Prevalence of SLCO1B1 5 is higher in European (~15%) and South Asian populations (~20%) compared to African

(~2%) and East Asian populations (~1%) (8). Individuals with reduced-function variants are at greater risk of myopathy, especially with simvastatin. Genetic testing can guide alternative statin choices, such as atorvastatin or pravastatin, which have lower myopathy risks.

5. Challenges in Implementation

1. Population Diversity and Underrepresentation

Most pharmacogenomic research focuses on populations of European descent, limiting the generalizability of findings to other groups. Diverse populations often have unique genetic variants that remain underexplored, resulting in potential inequities in healthcare delivery (9).

2. Cost and Accessibility of Genetic Testing

Pharmacogenomic testing remains expensive and is not universally available, particularly in resource-limited settings. Limited reimbursement policies further hinder widespread adoption (10).

3. Clinical Integration and Education

Many healthcare providers lack adequate training in interpreting pharmacogenomic data. Integrating pharmacogenomic results into electronic health records (EHRs) remains a logistical and technical challenge.

4. Ethical and Privacy Concerns

Genetic testing raises concerns about data security, potential misuse, and discrimination. Transparent policies and robust patient consent processes are essential.

3. Future Directions

1. Expanding Diversity in Genomic Research

Initiatives like the All of Us Research Program aim to include diverse populations, enabling discovery of population-specific pharmacogenomic markers (11).

2. Affordable and Accessible Testing

Advances in next-generation sequencing (NGS) and cost reductions are making pharmacogenomic testing more accessible worldwide.

3. Integration with Artificial Intelligence (AI):

AI-driven algorithms can predict drug responses based on genetic data, improving precision in personalized medicine.

4. Community Engagement and Education:

Raising awareness and building trust in underserved populations can promote the equitable implementation of pharmacogenomics.

4. Conclusion

Genetic biomarkers play a pivotal role in shaping drug response, efficacy, and safety, marking a transformative shift toward personalized medicine. Variations in genes such as CYP450 enzymes, HLA alleles, TPMT, and SLCO1B1significantly influence pharmacokinetics and pharmacodynamics, underscoring the importance of integrating pharmacogenomics into clinical decision-making. For example, CYP2D6 polymorphisms affect the metabolism of opioids and antidepressants, while HLA variants like HLA-B57:01 and HLA-B15:02 are associated with hypersensitivity reactions to abacavir and carbamazepine, respectively. These genetic differences are not uniformly distributed among populations; instead, they reflect unique genetic ancestries, making population-specific insights critical for achieving equitable healthcare. East Asians, for instance, exhibit a higher prevalence of CYP2C19 loss-of-function alleles, influencing the efficacy of clopidogrel, while Southeast Asians are at greater risk of carbamazepine-induced Stevens-Johnson syndrome due to the high frequency of HLA-B15:02.

Despite its promise, the implementation of pharmacogenomics in clinical practice faces significant challenges. Limited representation of diverse populations in genomic research restricts the generalizability of findings, while accessibility and affordability of genetic testing remain barriers in many regions. Furthermore, the integration of pharmacogenomic data into clinical workflows and electronic health records requires both technical infrastructure and clinician education. Ethical considerations, including data privacy and the potential for genetic discrimination, also need to be addressed to foster trust and ensure equitable application. By addressing these challenges, pharmacogenomics has the potential to revolutionize drug therapy, enabling more precise, effective, and safer treatments tailored to individual genetic profiles. Ultimately, this approach will not only improve therapeutic outcomes but also reduce healthcare disparities, ensuring the benefits of personalized medicine are accessible to all populations.

References

Zanger UM, Schwab M. "Cytochrome P450 Enzymes in Drug Metabolism." Pharmacology & Therapeutics, 2013. DOI:10.1016/j.pharmthera.2012.10.014.

Gaedigk A, et al. "CYP2D6 Gene Duplications in Ultra-Rapid Metabolizers." Human Genetics, 2018. DOI:10.1007/s00439-018-1956-0.

Sim SC, Ingelman-Sundberg M. "CYP2C19 Polymorphisms and Drug Response." Pharmacogenomics Journal, 2010. DOI:10.1038/tpj.2010.7.

Scott SA, et al. "Pharmacogenomics of Clopidogrel in Cardiovascular Medicine." Circulation, 2013. DOI:10.1161/CIRCULATIONAHA.113.001429.

Mallal S, et al. "HLA-B*57:01 and Abacavir Hypersensitivity." Lancet, 2002. DOI:10.1016/S0140-6736(02)10995-6.

Chung WH, et al. "HLA-B*15:02 and Carbamazepine-Induced SJS/TEN." New England Journal of Medicine, 2004. DOI:10.1056/NEJMoa031884.

Weinshilboum R, et al. "Thiopurine Pharmacogenetics: TPMT and Beyond." Nature Reviews Genetics, 2011. DOI:10.1038/nrg2941.

Link E, et al. "SLCO1B1 Variants and Statin-Induced Myopathy." New England Journal of Medicine, 2008. DOI:10.1056/NEJMoa0801936.

Popejoy AB, Fullerton SM. "Genomics is Failing on Diversity." Nature, 2016. DOI:10.1038/538161a.

Relling MV, Evans WE. "Pharmacogenomics in the Clinic." Nature, 2015. DOI:10.1038/nature15817.

Thorn CF, et al. "PharmGKB: The Pharmacogenomics Knowledgebase." Clinical Pharmacology & Therapeutics, 2013. DOI:10.1038/clpt.2013.96.