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PHARMACOGENOMICS: A PERSONALIZED APPROACH TO PREVENT ADVERSE DRUG REACTIONS

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ABSTRACT
Pharmacogenomics is a fast-moving discipline that examines the intricate relationship between a patient's genetic profile and his/her response to drugs, paving the way for tailored medicine. Through the identification of genetic differences affecting drug metabolism, efficacy, and susceptibility to side effects, pharmacogenomics facilitates individualized drug therapy, ensuring maximum treatment efficacy while reducing the risks of inefficient or toxic drugs. Adverse drug reactions (ADRs) are an important and frequent cause of morbidity and mortality. ADR can be related to a variety of drugs, including anticonvulsants, anaesthetics, antibiotics, antiretroviral, anticancer, and antiarrhythmics, and can involve every organ or apparatus. The causes of ADRs are still poorly understood due to their clinical heterogeneity and complexity Adverse drug reactions (ADRs) observed during drug development have been the cause for discontinuing development of many drugs. In addition, serious but rare ADRs observed after marketing have led to withdrawal of some drugs. Genetic variants in genes coding for drug metabolism, drug transport and more recently human leukocyte antigens (HLAs) have been linked to inter-individual differences in the risk of adverse drug reactions (ADRs). Pharmacogenomics testing has already demonstrated clinical success in predicting severe toxicities associated with drugs like abacavir, carbamazepine, warfarin, and irinotecan.

Keywords: *Pharmacogenomics, efficacy, adverse drug reactions, long QT syndrome, brigade syndrome, seizure, diabetes, proarrhythmic.*

INTRODUCTION

Adverse drug reactions (ADRs) are still a major and common cause of morbidity and mortality worldwide. Despite the tremendous technical progress in molecular diagnostics, the underlying causes of ADRs are still unclear. ADRs can be caused by an enormous number of different drugs and can affect all organs and apparatuses, and several ADRs have been recently linked to specific genetic mutations. In this context, genetic susceptibility to ADRs is a growing problem, not only in anticancer chemotherapy but also in many other areas of modern medicine, such as glucose-6 phosphate dehydrogenase (G6PD) deficiency, malignant hyperthermia, epidermal tissue necrosis (Lyell's Syndrome and Stevens-Johnson Syndrome), epilepsy, thyroid disorders, porphyria, aplastic anemia, Long QT Syndrome, and Brugada Syndrome [1]. This awareness led to a well differentiated subspecialty of clinical genetics called "pharmacogenetics," defined as "the study of how variations in a few genes affect the response to medications" aimed to prevent ADRs and to optimize therapies, considering the individual variations in either pharmacokinetics or pharmacodynamics. Both pharmacokinetics, which is the complex interplay of absorption, distribution, metabolism and excretion, and pharmacodynamics, which is the physiologic consequence of the interaction between drug metabolites and receptors, are genetically encoded the family of genes called CYP encodes the vast majority of enzymes regulating both pharmacokinetics and pharmacodynamics [2]. Genetic differences are generally recognized as the most crucial factors influencing drug response, although age, diet, health status, and drug interactions also play a part. The ability to comprehend the influence of an

individual's genetic makeup on drug metabolism, transport, and mechanism of action is the central focus of the emerging new field of pharmacogenomics, which lies at the crossroads of genetics and pharmacology [3].

1. CLASSIFICATION OF ADVERSE DRUG REACTIONS

There are quite a few different ways in which adverse reactions to drugs can be classified. For the purposes of this chapter, we will be using the original classification system described by Rawlins and Thompson in 1991, which classified adverse drug reactions into two different types: type A (pharmacological) and type B (idiosyncratic). The type A reactions are an exaggeration of the known pharmacological effects of a drug, are dose-related, and, perhaps more importantly from a safety perspective, are easily reversed by the withdrawal of the drug, or even by a simple reduction in dosage. In contrast, the type B, or idiosyncratic, reactions are bizarre, cannot be anticipated from a knowledge of the pharmacological effects of the drug, are not dose-related in a simple fashion, and cannot be reproduced in animal models. The type A reactions are more common than the type B reactions (Einarson, 1993), accounting for over 80% of all reactions. While they account for a lot of morbidity, in general, type A reactions are proportionately less severe and less likely to be fatal than type B reactions [4]. Pharmacological (Type A) Adverse Drug Reactions: Pharmacological adverse drug reactions are the most frequent type of drug toxicity. They can be attributed to the primary and secondary pharmacological properties of the drug. More attention is currently given to the secondary pharmacology of new drugs during preclinical studies in order to foresee, and consequently prevent, potential difficulties that could occur after the drug is administered to humans [5]. Type B or Idiosyncratic Adverse Drug Reactions Idiosyncratic adverse reactions are less frequent than pharmacological adverse reactions, but they are as significant, if not more, since they are more severe and are responsible for most drug-related deaths. The mechanisms of idiosyncratic adverse effects. The toxic effects can involve multiple organ systems, either singularly or in combination. Type B ADRs. Have has been described as being dose independent or rather there is no simple relationship between dose and the occurrence of toxicity Of course, the assessment of patients with and without hypersensitivity to a given compound indicates very little difference in the doses received; indeed, in the patients with hypersensitivity, the doses may have been lower since the drug had to be withdrawn. Furthermore, even in the hypersensitive patients, there is little relationship between the occurrence and severity and the dose administered. However, intuitively, there must be some kind of dose-response relationship since if the patient had not received the they would not have developed the hypersensitivity

2. FACTORS EFFECTING ADVERSE DRUG REACTION

2.1Enviornmental, age and gender factors in adverse drug reactions

The influence of both environmental and age and gender variables in drug metabolism is a known phenomenon. Several studies have described the relationship between age and drug metabolism [6] Paediatric age and, more so, geriatric age at a higher risk for ADRs. Geriatric patients at a higher risk for ADRs as they are taking several drugs, with possible interaction between them in drug metabolism. Moreover, aging can result in biotransformation of several drugs, especially for decreased activity of many cytochrome enzymes. The gender factor in ADRs is often underestimated, even if gender differences in drug metabolism may be a cofactor of ADRs. Indeed, men and women have a different chromosome, translating into diverse hormonal, metabolic, structural and immunological states. In general, women are at higher risk for ADRs, in particular when treated with thyroid hormones, TNF alpha inhibitors and analeptics Also, the risk of pro-arrhythmic effect of several cardiac and non-cardiac drugs is higher in women Besides age and gender, other environmental factors may affect ADRs, particularly cigarette smoking and pollutants, which can modify CYP1A1 and CYP1A2expres. This might alter the pharmacokinetics of many drugs, such as haloperidol, propranolol and flecainide. Viral infections can likewise change the behaviour of a drug and induce an adverse drug effect, namely with ampicillin rash in infectious mononucleosis, Reye's syndrome in patients with Influenza B and Varicella Zoster viruses and multiple drugs with HIV positive patients due to their altered [7].

3. ROLE OF GENETIC CODIFICATION IN ADVERSE DRUG REACTIONS

Drug Reactions There are some findings that indicate ADRs could have a familial pattern, although in most instances, a Mendelian inheritance pattern cannot be discerned. Even in instances where mutations are recognized, these are merely markers for the potential of ADRs but not for predicting them Furthermore, ADRs can occur in individuals who have variants of uncertain forming a huge variety of proteins. Proteins are the key of-life, allowing countless activities in the cells, interacting with the environment to control and balance all aspects of cell life. Thus, the study of the genetic basis of ADR has to consider the complex interplay between the genetic information and environmental factors in a given

disease condition. Finally, it must be considered that the huge variability of genetic information is transmitted from one generation to the other, not always unaltered, inserting a further degree of variability, with great clinical "Gene "is a DNA sequence occupying precise position (called "locus") in the genomic DNA itself. Every individual has two copies of non-sexual genetic information defined as "allele," that can be considered alternative forms of a gene occurring at the same locus, each autosomes allele being inherited from either parent [8].

4.1 Role of metabolism in adverse drug reactions

Reactions Genetic mutations that influence both pharmacokinetics and pharmacodynamics can induce a susceptibility to ADR Most likely, the most common mechanism that influences drug behaviour within the body is linked to the renal and hepatic metabolism When these two mechanisms are compromised, the direct result will be an inefficient clearance of all substances that depend on renal and hepatic metabolism. Moreover, other disease conditions, such as congestive heart failure, diabetes, peripheral vascular, pulmonary, rheumatologic, and malignant diseases, are also linked to higher [9]. Moreover, other significant influencing factors that can affect the susceptibility to ADRs are the immunologic factors. There are four primary types of immunologic reactions to drugs, which include immediate hypersensitivity Ige mediated, IgG mediated, serum sickness, and delayed type cell-mediated reactions. Also, Immunological and genetic factors can also interact in the pathogenesis of ADRs, through specific alleles in HLA-genes. The issue of modulators is not in the scope of this review. It is worth mentioning that the modulating factors involved in drug metabolism can interact not only with a disease-specific mutation, but also with other environmental factors, such as age and pollutants.

4.2 Adverse drug reactions in different disease conditions

Affected drug metabolism since the identification of glucose-6-phosphate dehydrogenase (G6PD) deficiency. This is also known as "favism" because of the susceptibility of patients to haemolytic anaemia after a meal of fava beans. Over the years, links have been identified between haemolytic anaemia and the consumption of other foods (such as beans or peas), or the administration of other drugs [10]. Females, instead, have three possible genotypes: homozygous (affected), hemizygous (either affected or non-affected), and wild type (unaffected). The enzymatic deficiency can be diagnosed by the detection of enzymatic activity using different techniques. It is important to note that most people with G6PD deficiency, both male and female, do not have a particular clinical presentation throughout their lives. However, when they are exposed to either drugs or infection, they are able to experience the effects of oxidative stress, which is responsible for the depletion of NADPH, triggering an acute haemolytic crisis. In these cases, the clinical presentation may include jaundice, weakness, back or abdominal pain, and haemoglobinuria in these cases, G6PD deficiency should be considered in differential diagnosis in patients affected by acute haemolysis following exposure to known oxidative drugs. In addition to G6PD deficiency, which will be described in more detail among haemolytic anaemias, there are some other well-known genetic syndromes that are linked to adverse drug reactions, the best known being malignant hyperthermia.

- Other medications
- beta-naphthol
- chloramphenicol
- dimercaprol

Aplastic anaemia: An example of drug-induced aplastic anaemia would be in patients with Fanconi Anaemia. This is a genetic disorder, which is mostly autosomal recessive for BRCA2, BRIP1, FANCA, FANCC, FANCD2, FANCE, FANF, FANCG, and FANCI genes, but autosomal dominant for RAD51 genes, and even X-linked for FANCB genes (Mehta and Tolar, 1993). The Fanconi anaemia pathway has 19 gene products (FANCA to FANCT). In most patients' Congenital physical traits, such as short stature and skin pigmentation, aside from bone marrow failure, are the characteristics of Fanconi Syndrome. Fanconi Syndrome is the most common cause of adult-onset aplastic anaemia, which is usually preceded by chemotherapy or chemo-radiation, porphyrias: Haemoglobin and myoglobin proteins are vital for life, both having a non-protein structure called "home group" The complex metabolic process of producing hemi groups is associated with a particular enzyme pathway within liver cells Specific genes code for each enzyme participating in the hems group pathway: so far, eight enzymes have been identified. Thus, there are eight known porphyria phenotypes, each due to a particular genetic mutation: thus, porphyria is not a single disease, but a series of genetically different diseases, which share some clinical manifestations. These diseases can be caused either by variations in quantity or function of the enzyme coded by a particular gene. The genes involved are PBGD, ALAS, ALAD, UROS, UROD, CPOX, PPOX, and FECH. It is important to note that all porphyria genes are mapped in autosomes, while the only gene that maps on the X chromosome is ALAS, which is associated with a rare form of drug-induced sideroblastic. that the appearance of a This explains why the clinical features of all types of porphyria can be summarized by hematologic manifestations (anaemia), neurologic symptoms (sleep disturbances, muscle weakness, seizures, chronic back, limbs, and abdominal pain), gastrointestinal symptoms (constipation, diarrhoea, vomiting), and dermatologic symptoms (skin and mucosal ulcerations). These

symptoms and signs can be induced not only by fever, viral infections (such as C hepatitis), but also by certain drugs, particularly anaesthetics and anticonvulsive.
•Anaesthetics aptocaine bupivacaine lidocaine mepivacaine •Anticonvulsants carbamazepine malignant hyperthermia: Malignant hyperthermia can be defined as a pharmacogenetic disorder, which is most famous for its sudden adverse drug reactions. Malignant hyperthermia is essentially a metabolic muscle disorder due to heterozygous mutations in three genes to the best of knowledge. The metabolic disorder genetically determined in this disease, independent of the mutated gene, leads to an extremely rapid and uncontrolled increase of calcium ions from skeletal muscle cells It is often the case that a patient is not aware of being affected by malignant hyperthermia until the exposure to the causative drugs [11]. provides a list of drugs associated with malignant hyperthermia.
Depolarizing muscle relaxants Succinylcholine

4. PHARMACOGENOMICS BIOMARKERS IN ADVERSE DRUG REACTION

PREDICTION
Pharmacogenomic biomarkers are measurable genetic markers that predict an individual's likelihood of experiencing harmful drug side effects and responding to drugs. Over 300 gene drug pairs that have established clinical relevance are included on the FDA-approved pharmacogenomic biomarker list (FDA, 2023). [12] Abacavir hypersensitivity, or HLA-B*57:01. These markers enable easier personalization of treatment and dosage optimization. The safe and effective prescription of drugs is enabled by their clinical implementation according to standards such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) [13].

5. TECHNIQUES USED IN PHARMACOGENOMICS STUDIES

Pharmacogenomic studies employ a range of molecular and computational approaches to detect and validate the underlying genetic origins of adverse drug reactions.
Sequencing: Through the ability to identify known and unknown genetic variations that are associated with drug response, sequencing has presented a more comprehensive approach to understanding an individual's genetic makeup [14]. The field of pharmacogenomics has been revolutionized by whole-genome sequencing (WGS) and next-generation sequencing (NGS) Bioinformatics tools: For the analysis of genetic information and its application in a therapeutic context, bioinformatics tools play a crucial role. These tools are necessary for the interpretation of genetic information and its application in a therapeutic context [15].
The databases that provide gene-drug information for clinical use: Pharm: This database is used for the annotation of pharmacogenomics information, including gene-drug associations, clinical guidelines, and summaries of variants. It is a tool for healthcare professionals to make informed decisions about treatment based on pharmacogenomics information. As a tool for genetic research, bioinformatics tools are necessary for the analysis of genetic information.

6. CLINICAL IMPLEMENTATION OF PHARMACOGENOMICS

warfarin dosing: CYP2C9 and VKORC1 genotyping helps in optimizing dosing and reducing the risk of bleeding. Because of the small therapeutic index of the widely used oral anticoagulant warfarin, even a small dose variation may lead to thrombosis or bleeding. VKORC1 and CYP2C9 are two significant genetic factors that significantly influence the dose requirements and response to warfarin27. This leads to increased plasma concentrations of warfarin and an increased risk of bleeding. However, drug hypersensitivity is influenced by the VKORC1 gene, which encodes the vitamin K epoxide reductase complex subunit I (the pharmacological target of warfarin [16]. carbamazepine toxicity: Severe cutaneous reactions can be prevented by testing for the HLAB15:02* allele. In those with a genetic predisposition, the antiepileptic and mood stabilizing drug carbamazepine can cause severe cutaneous adverse reactions (SCARs), including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS).

7. CHALLENGES AND LIMITATIONS

Despite the immense progress made in the area of pharmacogenomics, there are still some challenges that exist, which hinder the application of pharmacogenomics at a wider clinical level. The underrepresentation of certain ethnic groups in pharmacogenomic studies is one of the largest concerns, as there is a lack of generalizability of results. The vast majority of the current pharmacogenomic data is from European ancestry, and therefore the precise prediction of drug response in a patient of a different genetic background cannot be ensured. It is essential to have more research to include underrepresented groups to offer equal healthcare to all.

- High Cost and Limited Access: In underdeveloped nations, genetic testing is still costly.
- Lack of Knowledge: A large number of physicians are not sufficiently trained to understand pharmacogenomic data.

8. RECENT ADVANCES AND FUTURE PERSPECTIVES

With the ability to predict ADR risk from complex data sets, current advances in artificial intelligence (AI) and machine learning are revolutionizing pharmacogenomics. Multi-gene ADR risk prediction is now feasible thanks to predictive algorithms and polygenic risk scores (PRS). Pharmacogenomics and pharmacovigilance information can enhance post-marketing safety surveillance. The tracking of ADRs is of utmost importance to detect safety signals as early as possible, particularly for those that result in rare adverse events [17]. Future pharmacogenomics studies should aim at long-term clinical outcomes, cost benefit studies, and the development of standard platforms for data sharing and interpretation. Moreover, cost-effectiveness' analyses need to be performed to evaluate the economic impact of pharmacogenomic analysis and determine whether its benefits exceed the costs of its implementation. The creation of global databases that pharmacogenomic studies encompass genetically diverse populations will improve the generalizability of findings and facilitate equal access to healthcare

9. CONCLUSION

The advent of pharmacogenomics could signal the beginning of a new era of personalized medicine. Thus, nonpreventable ADRs could become at least partially preventable, as a beginning towards optimizing pharmacotherapy using genetic knowledge. This study offers concrete proof that the application of pharmacogenomics could potentially decrease ADRs, a condition of grave importance. Our study exemplifies the wisdom, "the sum can be greater than its parts," in that how 2 bodies of literature can generate new knowledge together, and our study offers a launching pad for future studies. In the future, we might all possess a "gene chip assay report" that holds our personal genetic information that would be accessed prior to pharmacotherapy. However, the utilization of pharmacogenomics knowledge is fraught with challenges, and more basic science, clinical, and policy studies are required to define in what areas pharmacogenomics could have the most impact and how it could be implemented. Pharmacogenomics is a revolutionary innovation in personalized medicine, optimizing drug treatment by tailoring treatments based on one's genetic profile. Its application within the medical field has been very beneficial, such as in the enhanced effectiveness of treatment, reduced adverse drug reactions, and enhanced patient safety. Pharmacogenomics has made significant progress in the identification of genetic biomarkers, pharmacogenomic testing, and the development of clinical guidelines. However, challenges such as disparities in access, provider education deficits, regulatory incongruence, and ethical concerns regarding genetic privacy remain as barriers to the widespread use of pharmacogenomics.

10. AUTHOR CONTRIBUTIONS

All authors are contributed equally.

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None

12. DECLARATION COMPETING INTEREST

The authors have no conflicts of interest to declare.

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