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REVIEW ON PHARMACOGENOMICS OF ADR

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ABSTRACT

Adverse drug reactions are a leading source of morbidity and mortality in the world.Although many adverse medication reactions are thought to be unpreventable, emerging research suggests that these events could be avoided by tailoring pharmacological regimens based on genetic data.Pharmacogenomics' arrival could usher in a new era of personalised medicine. As a first step in using genetic information to optimise medication therapy, nonpreventable ADRs may become at least partially preventable. This study presents actual evidence that pharmacogenomics could potentially affects adverse drug reactions (ADRs), a serious issue.

Keywords: Pharmacogenomics, Adverse Drug reaction (ADRs), Drug-Drug Interactions (DDI), ADME, Cytochrome P450 (CYP) Enzymes, Single Nucleotide Polymorphism (SNPs), Mutation.

INTRODUCTION

Adverse drug reactions (ADRs) are a major source of worry in drug research and clinical practise, and they constitute one of the leading causes of death in Western cultures [1]. Between 1945 and 2018, 140,879 papers on ADRs and 280,473 papers on drug-drug interactions (DDIs) were published in the PubMed database. ADRs can occur as a result of improper prescribing, drug chemistry inherent toxicity, cell-specific drug toxicity, age- and sex-related anomalies in drug absorption, distribution, metabolism, and elimination (ADME), and drug-drug interactions in combination therapies or when a patient is treated with multiple drugs for concurrent disorders. [2].

The goal of pharmacogenetics is to incorporate genetic information into regular medical practise in order to reduce the impact of adverse drug reactions on both patients and the healthcare system. The full range of pharmacogenetic variants is beyond the scope of this review; rather, its goal is to provide an update on the genetic background of ADRs, as well as some red flags useful in everyday clinical practise, demonstrating how genetics can be useful for the prevention and treatment of patients with ADRs. In the future, a greater usage of genetic testing and the application of artificial intelligence. [3]

HISTORY OF PHARMACOGENOMICS

In 510 BCE, Pythagoras, a Greek philosopher and mathematician, recognised the first interindividual variability in medicine administration when he observed that certain patients got hemolytic anaemia after consuming the fava bean. Vogel invented the word pharmacogenetics in 1959, although Kalow did not define pharmacogenetics as the study of heredity and medication response until 1962. Since 1962, the word has been used to describe how genetic differences affect a person's medication reaction. [4]

The finding of a defective butyrylcholinesterase enzyme in psychiatric patients who demonstrated persistent muscular paralysis after succinylcholine injection before electroconvulsive therapy sparked interest in pharmacogenetics in the 1950s. In the 1950s, a link was discovered between the development of hemolysis and glucose-6-phosphate dehydrogenase deficit in African American males treated for malaria with primaquine.Other seminal pharmacogenetic discoveries include the identification of slow acetylators in certain ethnic groups,

such as 10% of Japanese and Eskimos, 20% of Chinese, and 60% of Caucasians, blacks, and South Indians, and the attribution of peripheral neuropathy to slow acetylation of isoniazid in some tuberculosis patients due to genetic diversity in the enzyme Nacetyltransferase.[5]

MAJOR COMPONENTS OF THE PHARMACOGENOMIC MACHINERY

The pharmacogenomic machinery is integrated by a series of genes coding for enzymes and proteins which are determinant for drug targeting and processing, as well as critical components of the epigenetic machinery responsible for the regulation of gene expression [6]. The genes involved in the pharmacogenomic response to drugs fall into five major categories: [7]

- Genes associated with disease pathogenesis;
- Genes associated with the mechanism of action of drugs (enzymes, receptors, transmitters, messengers);
- Genes associated with drug metabolism
- Genes associated with drug transporters
- Pleiotropic genes involved in multifaceted cascades and metabolic reactions

When a difference in the allele(s) responsible for the variation is prevalent, it is called a genetic polymorphism. An allele is a different version of a gene. When allelic variants exist at a constant rate of less than 1% across a population, a gene is said to be polymorphic.[6]

Mutant genes will appear more frequently in such settings along with wild-type genes In these populations, mutant genes will code for the production of mutant proteins. The mutated proteins, in turn, will interact with medications in a variety of ways, some minor, some major. The intricacy of drug metabolism cannot be explained just by monogenic features. In such cases, mutant genes will coexist with wild-type genes on a regular basis. In these populations, mutant genes will code for the production of mutant proteins. The mutated proteins, in turn, will interact with medications in a variety of ways, some minor, some major. The intricacy of drug metabolism cannot be explained solely by monogenic features.[3]

DRUG METABOLISM- AND TRANSPORT-RELATED ADRS

DifferentSingle nucleotide polymorphisms (SNPs) in Cytochromes P450 (CYP) genes may alter pharmacological efficacy and safety in 60-80 percent of people taking conventional medicines, with little age and sex-related variances. In patients receiving long-term pharmaceuticals, polypharmacy, psychiatric drugs, anti-neoplastic therapies, and treatments with a narrow therapeutic window, this is especially relevant from a practical standpoint.[8]

CENTRAL NERVOUS SYSTEM DRUGS

CYP enzymes are involved in the metabolism of most psychotropic medications (neuroleptics, antidepressants, benzodiazepines, and anti-epileptics). There have been some guidelines made for the usage of particular psychotropics. ARDs are caused by CYP2D6 polymorphisms in patients using psychotropics for bipolar illness, depression, or schizophrenia.[9]

Risperidone is metabolized via CYP2D6 and 3A4 enzymes, which affect its plasma concentrations.SNPs affect the plasma concentration of risperidone and its metabolite 9-hydroxyrisperidone in patients with schizophrenia [80]. CYP2D6 variants influence ADRs such as extrapyramidal symptoms and weight gain, and CYP2D6-PMs show more frequent ADRs and discontinuation due to ADRs [81,82]. Schizophrenic patients homozygous for the ABCB1 3435T/2677T/1236T haplotype show lower dose corrected plasma concentrations of risperidone and 9-hydroxyrisperidone than patients harboring other ABCB1 genotypes [10]

ANTINEOPLASTIC DRUGS

The majority of antineoplastic medicines generate substantial (and occasionally fatal) adverse reactions [11]. The vast majority of anti-cancer medications, regardless of their pharmacological category, have a highly complicated pharmacogenetic profile that requires pharmacogenetic assessment prior to treatment in order to maximise efficacy and avoid toxicity. Cisplatin, cyclophosphamide, docetaxel, doxorubicin, epirubicin, etoposide, fluorouracil, gemcitabine, methotrexate, paclitaxel, and tamoxifen are among the antineoplastic drugs whose pharmacogenetic profiles are summarised in [12]. Many other anticancer medications can result in life-threatening ADRs linked to certain SNPs in other genes. [13].

ANTICOAGULANTS AND ANTIPLATELETS

ADRs are frequently caused by oral anticoagulants and antiplatelet medications. To ensure that these therapies are used safely and effectively, skilled drug interaction management is required. The most regularly used antiplatelet therapies (aspirin, clopidogrel, prasugrel, ticagrelor) and anticoagulants, such as warfarin and the new generation of anticoagulant medicines, should be given special attention (dabigatran). Antiplatelet and anticoagulation therapy medication efficacy and safety are determined by a variety of genetic SNPs [14]. Warfarin (Coumadin) is a medication with a restricted therapeutic index that prevents and treats thromboembolic diseases by inhibiting the synthesis of vitamin K-dependent clotting factors.In antiplatelet therapy, aspirin is the gold standard. Aspirin suppresses the platelet cyclooxygenase (COX) pathway, which is involved in the synthesis of thromboxane A2 (TXA2). Aspirin's antiplatelet actions are ineffective in 5-45% of patients due to aspirin resistance, which is linked to several ADME gene variations [15]. There are 38 aspirin-response-related genetic variations with clinical importance, with 26% of them relating to therapeutic efficacy and 74% to drug toxicity.

ANTI-TUBERCULOSIS DRUGS

Antituberculosis treatment can result in severe ADRs linked to NAT2, CYP2E1, and GSTM1 mutations [16]. Slow acetylators in the NAT2 gene family are obvious candidates for developing ADRs in response to isoniazid [17]. Hepatotoxicity is less common in patients with homozygous mutant-type or heterozygous genotypes at the CYP2E1 RsaI polymorphism than in patients with homozygous wild-type genotype. Homozygous mutants of the CYP2E1 gene's 96-bp deletion-insertion SNP have a higher risk of hepatotoxicity [10]. In Korea, TNFA-308G/A has been linked to anti-tuberculosis drug-induced hepatitis.

OPIATES

Chronic pain is a severe health issue. An alarming increase in ADRs is being caused by the overuse of opiates or the incorrect (often indiscriminate) administration of opiates to patients with various types of pain [18]. Approximately 15-20% of the population is hypersensitive or intolerant to standard opiates doses [19]. Methadone is a long-acting opioid having two pharmacologically distinct enantiomers [(R)-methadone and (S)-methadone]. Methadone is currently used to treat people who are addicted to opiates. (R)- and (S)-methadone in high doses can have life-threatening consequences. Changes in methadone's pharmacokinetic and pharmacodynamic properties contribute to its toxicity. CYP2B6 is the enzyme that demethylates methadone in the liver, followed by CYP3A4, 2C19, 2D6, 2C18, 3A7, 2C8, 2C9, 3A5, and 1A2.

ANTI-HIV DRUGS

Understanding the pharmacogenomic profile of each drug is particularly important in combination therapies and in multimodal regimens for the treatment of HIV infection. A fixed-dose combination of darunavir (DRV), cobicistat (COBI), emtricitabine (2',3'-dideoxy-5-fluoro-3'-thiacytidine [FTC]), and tenofovir alafenamide (TAF) has been approved by the European Medicines Agency for the treatment of HIV infection. The pharmacokinetics of single compounds revealed multiple DDIs. COBI is a selective CYP3A4 inhibitor with no effect on other isoenzymes which are inhibited by RTV, such as CYP2C8 and CYP2C9. In contrast, RTV is an inducer of CYP1A2, 2C19, 2C8, 2C9, and 2B6, UGT1A4, and ABCB1. Total cholesterol: low-density-lipoprotein cholesterol and total cholesterol:high-densitylipoprotein cholesterol ratios are high in DRV-COBI-FTC-TAF versus RTV-DRV-FTC + tenofovir disoproxil fumarate [20].

STATINS

Statins are metabolised by the CYP3A4/5 enzymes, and several ABC and SLCO transporters are substrates of statins. Due to a faster metabolization of statins, CYP3A4/5-RMs show a reduced effect of statins, whereas CYP3A4/5-IMs show an improved lipid-lowering effect, as well as a significant risk of ADRs, due to a slower metabolism and elimination rate [21]. DDIs with statins are also linked to transporter malfunction, with the organic aniontransporting polypeptides (OATPs), notably OATP1B1/SLCO1B1 and OATP1B3, perhaps playing a role [22]. Hepatic transporters OATP1B1 and OATP1B3 mediate the absorption of numerous therapeutically relevant medicines, such as statins, from the blood into the liver. Reduced OATP1B1 and OATP1B3 transport function can result in clinically significant DDIs.[21]

ROLE OF GENETIC CODIFICATION IN ADVERSE DRUG REACTIONS

ADRs may run in families, according to several observations, albeit no Mendelian pattern of inheritance has been established. Even when genetic alterations are found, they are just suggestive of ADR susceptibility and cannot be predicted with accuracy. Furthermore, rather than harmful mutations or full syndromic clinical presentations, ADRs may occur in patients with variations of unknown significance (VUS). A more extensive compilation of pharmacogenetics terminology may be found in a recent publication, which includes a synthetic dictionary of the terminologies used in this review.[23]

Genetic information is stored in complex molecules, such as genomic DNA, mitochondrial DNA (mtDNA), and various kinds of RNAs. This information is organized in the genetic code, consisting of sixty-four nucleotides triplets, three stop signals, several regulatory sequences and regions interacting with both mtDNA and full RNA sets . All information stored in the genetic code specifies twenty canonical and two additional aminoacids 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. [24]

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 possible great clinical relevance. “Gene”is a DNA sequence occupying a precise position (called “locus”) in the genomic DNA itself.[25]

GENETIC DIFFERENCES IN DRUG METABOLISM

The observation that some patients had extremely low or very high drug concentrations while being given the same dose of medicine was the first indication of genetic variations in metabolism.

GENETIC POLYMORPHISM

When a difference in the allele(s) responsible for the variation is prevalent, it is called a genetic polymorphism. An allele is a different version of a gene. When allelic variants exist at a constant rate of less than 1% across a population, a gene is said to be polymorphic. [26]

Mutant genes will appear more frequently in such settings along with wild-type genes In these populations, mutant genes will code for the production of mutant proteins. The mutated proteins, in turn, will interact with medications in a variety of ways, some minor, some major. The intricacy of drug metabolism cannot be explained just by monogenic features. In such cases, mutant genes will coexist with wild-type genes on a regular basis. In these populations, mutant genes will code for the production of mutant proteins. The mutated proteins, in turn, will interact with medications in a variety of ways, some minor, some major. The intricacy of drug metabolism cannot be explained solely by monogenic features.[27]

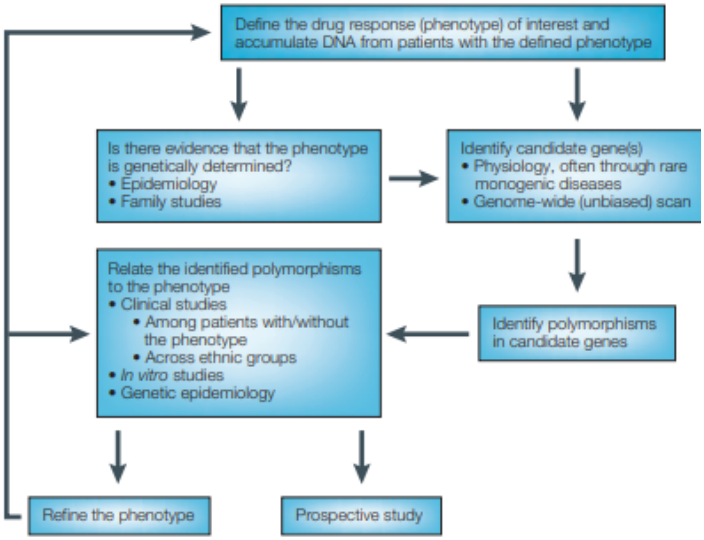

Fig 1: Algorithm for evaluating the role of genetic factors in drug actions

QUALITY ASPECTS OF PHARMACOGENOMIC ANALYSES [28]

Sample acquisition and handling:

(i) sample collection,
(ii) stability,
(iii) sample labeling,
(iv) transport to the site of analysis,
(v) tissue/sample processing and
(vi) storage,

To ensure the highest possible sample quality, should be minimised throughout the workflow. In any genomic study, procedures to assure sample adequacy and quality must be in place, especially when many centres are involved. Pre-analytical procedures, such as the extraction of DNA from snap frozen tissue, as well as the isolation of gDNA, cell-free DNA (cfDNA), and circulating tumour DNA (ctDNA) from whole venous blood, have been documented.

DNA EXTRACTION

Extraction of gDNA from various sources can be done using a variety of techniques. It is critical to choose a validated approach that result in high-quality gDNA that can be used for nucleotide variation analysis (single or array-based qPCR or end-point PCR) and sequencing (Sanger, NGS). Before proceeding with any DNA analysis, it is recommended that all DNA samples be tested for quality. The usual test compares the ratio of light absorption of the DNA solution at 260 nm to 280 nm, with an A 260/280 ratio of > 1.9.

METHODS USED FOR DETERMINATION OF NUCLEOTIDE VARIATIONS

Nucleotide variants can be determined using a variety of techniques that focus on (i) specific sequence sections or (ii) broad sequencing approaches. WES, whole gene sequencing by Sanger or NGS, including promoters, introns, and exons, on single or multiple genes, or WGS, which covers the entire genome except for specific complex loci with high sequence homology, are examples of the latter.

ALLELE SPECIFICITY

It is sometimes necessary to determine the particular allelic position of variations and a complete definition of the entire haplotype for genotyping analysis (all mutations in the gene present on one allele). It's crucial to know if two separate genetic polymorphisms inside the same gene with known functional implications are on the same allele (in cis) or segregated across the two alleles when they're found in heterozygosity in one individual (in trans). Long allele-specific PCR amplification of the region of interest, followed by NGS or Sanger sequence analyses, can be used to perform this type of analysis.

REPORTING

Nucleotide variants with confirmed functional implication should be prioritised in reporting over those whose functional implication is just hypothesised but not verified. It may be difficult to predict the functional consequences of missense (amino acid substitution) mutations. Currently, there are around 14 different functionality prediction algorithms available, each with its own set of sensitivities and specificities. The most advanced algorithms can anticipate the functional impact of 75-85% of missense mutations on the gene product in question. Physiochemical characteristics, secondary structure, protein domain models, and integrated functional residues are all different, as is how the results are interpreted.

CONCLUSIONS

Pharmacogenetics aspires to personalise pharmacological treatment in order to reduce side effects and increase efficacy. Pre-treatment predictive genetic testing aims to personalise therapy to reduce ADRs by directing medication or dose selection, and it has had a favourable impact on clinical practise, particularly with abacavir. Patients for whom regular biomarker surveillance may be indicated to reduce the risk of severe ADRs may benefit from genetic screening. There are at least three more potentially beneficial spin-offs from understanding the pharmacogenetics of ADRs, in addition to the direct patient benefit of lowering ADRs. For starters, genetic-ADR

correlations offer fresh insights into underlying pathological processes, and extrapolation of new understanding about hypersensitive reactions could have consequences for cancer, autoimmune illness, and infectious disease management. Challenges in pharmacogenetic mapping: The following are some of the difficulties that come with doing this type of study: accumulating well-characterized patient databases; identifying and accumulating adequate control group(s); statistical and methodological approaches that are still being developed; and expense. The question of whether it is worthwhile to uncover very uncommon alleles that predict rare but substantial adverse medication effects is a basic conceptual challenge that the field must address. A excellent example is thiopurine-methyltransferase deficiency, which predicts BONE MARROW APLASIA when exposed to 6-mercaptopurine, a paediatric leukaemia treatment.

THE NEED FOR COLLABORATION

Individual DNA variants that mediate both pharmacokinetic and pharmacodynamic responses are widely known, and there are now many examples of individual DNA variants that mediate both pharmacokinetic and pharmacodynamic responses. The concept, sparked by the sequencing of the human genome, of using this information to better understand the genetic basis of medication response variability is enticing, but it is fraught with difficulties. The successful implementation of this strategy will necessitate close collaboration among clinicians who see and accurately phenotype patients (and without whom the research would be impossible), industry (where well-characterized databases of patients and their drug responses are in place), industry and academic medicine researchers who identify candidate genes and pathways, and scientists who develop the technological advances required.

FUTURE DIRECTIONS

Validation or rejection of new pharmacological targets at an early stage of research could be the result. A therapeutic target with a functionally important polymorphism may be passed over in favour of one with less genetic variation. In the same way, as the molecular basis for unusual adverse drug effects, such as drug-induced arrhythmias or drug-associated hepatotoxicity, is better defined in pharmacogenetic studies, new screening algorithms could be developed to eliminate drugs that are likely to be associated with these adverse effects at an early stage of development.

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