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OVERVIEW OF GENETIC RELATED ADVERSE DRUG REACTION & CASE RELATED STUDY

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Abstract

Although the relative contributions of clinical, genetic, and environmental variables to this vulnerability vary depending on the medicine, adverse drug reaction, and ethnicity, all elements must be considered. Personalized pharmaceutical therapy is an intriguing way to reduce adverse drug reactions (ADRs) and increase efficacy since medication responses differ. With genetically driven medication and dose selection techniques, pharmacogenetics aims to make a difference.

While ADR pharmacogenetics was initially brought to light in the 1950s, it has only recently experienced a sharp rise in popularity, partly due to enhanced genotyping tools and substantial advancements in our understanding of the human genome. ADRs are categorized based on whether immune- or nonimmune-mediated processes are the predominant mechanism Several ADRs have strong correlations with human leukocyte antigen, or HLA, alleles.

The field of pharmacogenomics investigates the genetic differences in how individuals respond to various drugs, including differences in dosage needs, effectiveness, and the likelihood of adverse drug responses. With the potential to lower the frequency of ADRs and enhance patient outcomes, the use of genetic data to predict drug responses and adverse drug reactions (ADRs) is increasingly becoming used in clinical practice. Pharmacogenomic research has a lot of potential to improve medication safety and efficacy, which might eventually result in more individualized and successful therapeutic treatments.

Keyword: pharmacogenomics study, genetic related ADR

INTRODUCTION

The words "pharmacovigilance" come from the Greek term "pharmakon," which means "medicinal substance," and the Latin word "virilia," which means "to keep watch."

Pharmacovigilance (PV) is described by the WHO as the science and actions associated with the identification, evaluation, comprehension, and avoidance of side effects or any other drug-related issue.

In December 1961, thalidomide, an anti-emetic and sedative drug used in pregnant women, and severe fatal deformities (phocomelia) were linked for the first time, according to a letter written by Australian obstetrician Dr. William McBride and published in The Lancet. This marked the official introduction of PV. To centralize global data on adverse drug reactions (ADRs), the WHO launched the "Programme for International Drug Monitoring" in 1968.

The "WHO Programme" was specifically designed to find the early PV indications. A French team of pharmacologists and experts in toxicology coined the term "peripheral toxicology" (PV) in the middle of the 1970s to describe activities that promoted "The evaluation of the dangers of adverse reactions possibly associated with drug treatment."

Per WHO definition, PV is 'the pharmaceutical science related to identification, evaluation, monitoring and prevention of adverse drug reactions, including medication-related short- and long-term adverse events'. Drug-related problems that lead to drug-related injuries can be identified, measured, and documented by PV, among other functions.

Prescription drug monitoring, or PV, is primarily a post-marketing surveillance (phase 4) study. Its goals are to quantify adverse drug reactions (ADRs) that have already been identified, find unrecognized ADRs, assess how well medications work in practical settings, and reduce the death and morbidity that are linked to ADRs. Coordination of the international monitoring of drugs program (IDM) is done by the Uppsala, Sweden-based UMC. 33 associate members and 104 official members, comprising developed, developing, and underdeveloped nations, are present worldwide as of right now. There are over a billion potential drug users in India, the second most populous nation in the world.

The liver, skin, kidney, heart, and muscles are just a few of the organs that might be impacted by idiosyncratic adverse drug reactions. Certain medications may also cause more widespread hypersensitivity reactions. Most drugs that were taken off the marketplace in recent years were removed due to toxicity that either affected the heart or was hepatotoxic.

Drug-induced liver injury (DILI) is the term used to describe adverse drug reactions that affect the liver. These reactions vary in their phenotypic effects, but they are all referred to as such. When damage occurs in the biliary tree or the hepatocyte canalicular membranes, they are usually classified as cholestatic, and when the injury largely affects the hepatocyte, it is classified as hepatocellular. If liver failure is not treated with a liver transplant, as many as ten percent of those hepatotoxic adverse medication reactions can result in death.

An electrocardiogram's QT interval can lengthen when a patient takes cardiotoxic medications, indicating an interruption in cardiac repolarization. Torsade de pointes, a kind of ventricular tachycardia that can result in ventricular fibrillation and death, is associated with QT prolongation as a potential danger.

Genetic predisposition is frequently associated with severe adverse drug reactions, and there is considerable interest in the concept of creating genetic tests to identify all patients at risk of side effects prior to prescription to preserve effective medications.

The toxicity of carbamazepine and HLA-B*15:02, as well as a hypersensitivity into abacavir and HLA-B*57:01, are the two cases that are presently being transferred to the clinic.

PHARMACOVIGILANCE HISTORY

- **Pharmacovigilance Was Caused by Significant Historical Events:**

- 1785: Large and frequent doses of foxglove (Digitalis) have resulted in sickness, giddiness, vomiting, changed vision, increased motion and urine, sluggish heart rate, cool sweats, and convulsion syncope, and even death.
- 18th-century use of calomel (mercurous chloride) to treat yellow fever resulted in severe salivation, tooth loosening, and ulceration.
- 19th century: In 1880, the use of chloroform as an anaesthetic resulted in fatalities. Edward Lawrie asserted the safety of chloroform use in 1888.
- 20th Century: Pharmacopeia’s and the FDA were founded in 1906 to enforce quality standards for medication manufacture.
- 107 people died in 1937 because of sulphanilamide, which was made as an elixir with the dissolving ingredient di-ethylene glycol.
- The medicine Thalidomide, which was prescribed to pregnant women to treat morning sickness, resulted in congenital malformations in 6000–12000 newborns in 1956.

Thalidomide Tragedy:

Based on the manufacturer's safety assurances, thalidomide was first sold as an over-the-counter medication in Germany in 1957. Because the product's creators "could not identify an amount sufficient to kill a rat," they claimed that it was "completely safe" for mother and child, "even during pregnancy." Sales of thalidomide, which were sold in 46 countries by 1960, were almost identical to those of aspirin.

Sulphanilamide Tragedy:

Over a hundred people died because of this poison in fifteen states, including Virginia in the east and California in the west, between September and October of 1937. The 1938 Nutrition, Medication, or Cosmetic Act, which expanded the FDA's jurisdiction over drug regulation, was passed because of the drug and the fatalities.

ADVERSE DRUG REACTION

An adverse drug reaction is any unpleasant, unintentional, and undesirable side effect that happens at dosages used for diagnosis, treatment, or prevention. It can also refer to any adverse, dangerous side effect that follows the use of a medicine or combination of drugs that is assumed to be related to the medication.

Epidemiology;

Globally, one the main causes of mortality and morbidity is adverse medication reactions brought on by both immunological and non-immune processes.

Epidemiologic evidence substantiates the presence of variables that augment the likelihood of generic adverse medication responses, including but not limited to female gender, HIV infection, or herpes (Alvarez-Requejo et al., 1998). Use of beta blockers, systemic lupus erythematosus, and asthma are factors linked to an elevated risk of hypersensitivity meditation reactions. Despite not having a higher likelihood of medication sensitization, atopic individuals are more likely to experience severe allergic responses.

The prevalence and severity of adverse drug reactions (ADRs) are affected by both drug and patient factors, including medication type, administration route, dosage, bioavailability, comorbid illnesses, age, sex, and genetic or regional factors.

ADVERSE DRUG REACTION: CAUSES AND CONSEQUENCES

Its connection assessing is given to each drug to evaluate the likelihood of an adverse drug reaction (ADR). This is done by validating Kramer's algorithm using parameters such as prior experience with ADR, the absence of any other factors related to the underlying disease, the period that passed among the administration of the medication and its manifestation, as well as the reality that the ADR's beginning occurs immediately after drugs management (Kramer et al., 1979).

After decreasing the dosage or stopping the medication, ADR diminishes or vanishes. Recurrence following medication read ministration; not observed in any of the individuals under analysis (Hutchinson et al., 1979).

DIFFERENTIAL DRUG REACTION CLASSIFICATION

Drug Reactions: Immunologic and Non-immunologic Immunologic and non-immunologic etiologist can be used to categorize drug reactions (table1). Predictable, non-immunologic side effects account for 75–80% of adverse medication reactions. Immune-mediated side effects account for 20% to 25% of adverse medication occurrences. These consequences are unpredictable. IgE-mediated drug allergies are classified as immune-mediated reactions, which make about 5% to 10% of all medication reactions and represent real drug hypersensitivity.

TABLE: DRUG REACTIONS, BOTH IMMUNOLOGIC AND NON-IMMUNOLOGIC

CATEGORY	INSTANCE
Immunological ➢ Type I response mediated by IgE ➢ Type II response, or cytotoxicity) ➢ Type III reaction or The immunological complex, ➢ Type IV response (cell-mediated, delayed) Particular activation of T cells ➢ Rapid/rapid ligand-induced cell death ➢ Alternative	• An allergic reaction to β-lactam antibiotics Antibiotic-induced hemolytic anemia • Illness caused by anti-thymocyte globulin serum illness Topical antihistamine-induced contact dermatitis • Sulphonamide-induced morbilliform rash • The Stevens-Johnson syndrome • Necrolysis of the epidermis toxic • Drug-induced condition like lupus
NOT IMMUNE-RELATED ACCURATE ➢ Pharmacological adverse reaction ➢ A further pharmacologic side effect ➢ toxicity of drugs ➢ Interactions between drugs ➢ overdosage of drugs **Not predictable** ➢ Allergic pseudo-infection ➢ Idiosyncratic ➢ Intolerance	➢ Dry lips caused by antihistamines ➢ Thrush when using antibiotics ➢ Methotrexate-induced hepatotoxicity ➢ Theophylline-induced seizure while taking erythromycin ➢ Excessive Lidocaine (Xylocaine)-induced seizure ➢ Following primaquine treatment, hemolytic anemia for an individual with G6PD* deficiency ➢ Tinnitus following a single, modest aspirin dosage

THE INFLUENCE OF GENETIC POLYMORPHISM ON ADVERSE DRUG REACTIONS

Genetic variation and medication metabolism

CYP and ABC genes

The human body responds differently to drugs due to genetic variations. Most of the research on ADRs has focused on how pharmacokinetic factors—particularly drug metabolism—may be involved. I.e. There is increasing acknowledgment that genetic variation its pharmacological targets (pharmacodynamic factors) may also predispose to adverse drug responses (ADRs), even if research in this field is still in its infancy. (Alvarado et al.,2002).

Variations in plasma concentrations across patients receiving the same medication regimen may have a significant role in the drug response, including adverse drug reactions (ADRs). Drugs come in the form of Adenosine Triphosphate Binding Cascades (ABC) transmembrane transporter proteins and cytochrome P450, or CYP, enzyme substrates. Many CYP and ABC gene polymorphisms have been demonstrated to alter the functioning of protein products, influencing the distribution, metabolism, absorption, and excretion of a wide range of medications and being associated with several biologically significant disorders (Evans et al., 1999).

One of the most well-known and extensively researched instances of pharmacogenetic differences in drug metabolism involves the CYP2D6 gene, that is a member of this family.
More than 100 drugs, many of which are used to treat conditions related to the cardiovascular and central neurological systems, are metabolized by it (Hosking et al., 2002).
Currently, more than 75 CYP2D6 variations have been found. CYP2D6 polymorphism may be categorized into four metabolic activity types: poor, normal, rapid, or super rapid. "Probe drugs" like spartina or debrisoquine are used to do this.
Consequently, adverse drug responses (ADRs) or decreased therapeutic efficacy for multi-drug regimens may arise from medication–drug interactions.

ABC proteins, which make up the largest family for Tran's membrane proteins identified in the genome of human beings, translocate a wide range of substrates across extracellular as well as intracellular membranes, including multiple cancer treatments, cardiac glycosides (digoxin), immune-suppressive representatives, glucocorticoids, and many other medications, such as some antiretroviral medications.

ABC proteins in the gut restrict how much medication can enter the body.

As the apical membrane of numerous additional barriers forming epithelium, including circulatory system brain, blood test is, or maternal-foetal barrier, also contains specific ABC proteins. One gene that belongs to the ABC family is ABCB1. An amino acid that is encoded in exon 26 of the ABCB1 gene is not altered by the single-nucleotide polymorphism (3435C→T), which has been connected to variable production of transporter polypeptide within the duodenum. Patients who carried the ABCB1 3435-TT gene showed less than half the amount of duodenal expression of the gene compared to those with the ABC1 3435-CC genotype.

PHARMACOGENOMIC APPROACHES USED TO IDENTIFY CAUSATIVE GENES

To date, pharmacogenomic research have utilized case-control association studies utilizing either a candidate gene technique or genome-wide associations (GWA) research to identify genes that impact risk of adverse drug reactions.

Human leukocyte antigenic (HLA) variants have been implicated in susceptibility, according to compelling evidence from candidate's gene and GWA investigations on a variety of adverse medication reactions. Given that, the following paragraphs will discuss HLA genes are an overall risk factor for bad medication reactions and provide a detailed description of a few HLA linkages.

It is crucial to keep in mind that HLA genes may not be the only genetic component causing these kinds of events, and that they are unrelated to some adverse drug reactions, like muscular toxicity and cardiotoxicity.

HLA RELATIONSHIPS IN SKIN RASH, HYPERSENSITIVITY REACTIONS, AND DRUG-INDUCED LIVER DAMAGE

It has been believed in over thirty years that an individual's HLA type indicates the probability of developing adverse medication reactions. Both skin-related hypersensitivity reactions and DILI, which includes reactions that may not usually display the characteristic symptoms of a hypersensitivity reaction, have been found to have consistent and well-replicated relationships.

Currently used medications that induce DILI vary widely, and genotyping has been used to directly investigate HLA correlations with DILI instead of serotype determination. The early HLA genotyping studies consisted of candidate gene association studies on amoxicillin-clavulanate-related DILI.

The Humans Leukocytes are Antigen DRB1*15:01 allele, linked to the DR2 serotype that is examined below, was identically linked in two different potential gene association studies, even though this type of DILI usually lacks traits related to the traditional immune system.

Table 2: Associations between HLA and unfavourable medication reactions

Kind of toxicity	**Drugs**
Hypersensitivity	Abacavir
Liver injury	Amoxicillin-clavulanate
	Ximelagatran
	Ticlopidine
	Flucloxacillin
	Lumiracoxib
	Lapatinib
	Nevirapine
SJS and TEN	Carbamazepine
Different responses on the skin,	Carbamazepine
such as SJS and TEN Various skin reactions	Allopurinol

including SJS and TEN Various skin reactions	Nevirapine

HYPERSENSITIVITY AND HLA REACTIONS IMPACTING THE SKIN

Several studies have demonstrated that T-cell reactions to medications play a crucial role in immune-mediated reactions that take time to influence the skin. Because the genes which make comprise HLA code encode proteins that contribute in the transport for antigen to T cells, several studies have explored the possibility of HLA polymorphism may serve as a predictor for delayed hypersensitivity responses. HLA correlations with drug-induced skin rashes had been documented prior to the more current research demonstrating the involvement of T-cell reactions in these reactions. It was discovered that TEN along with SJS had a poor relationship with HLA class I genotype B12The A29-B12-DR7 haplotype was shown to be more closely associated with sulphonamide-induced toxicity in individuals who reacted to a particular medication.

ADVERSE DRUG REACTIONS IN NON-HLA GENETIC ASSOCIATIONS

Although idiosyncratic adverse medicine responses are commonly believed to be concentration-independent, genetic factors that affect drug concentration through their role in drug disposition also impact propensity to some bad effects of pharmaceuticals.

Additional genetic risk factors that have been found include variations in genes that shield cells from oxidative stress and those that impact the innate immune system.

The following subsections will address each of the many types of genes implicated within non-HLA genetic associations in adverse reactions to subsection fashion: genes affecting drug disposition, genes associated with oxidative stress and innate immunity, and the role of cardiovascular ion channel polymorphisms in cardio toxicity reactions.

Table 3. Adverse Drug Responses And Genes Associated With Drug Disposition

Gene	Reaction	Drug
Phase I drug metabolism		
CYP2B6	Skin rash	Nevirapine
Phase II drug metabolism		
NAT2	DILI	Isoniazid
UGT1A	DILI	Tolcapone
UGT2B7	DILI	Diclofenac
UGT1A	DILI	Various
Drug transporters		
SLCO1B1	Myopathy	Simvastatin
ABCB11	DILI	Various
ABCC2	DILI	Diclofenac
	DILI	Various
	DILI	Various

A CASE REPORT EMPHASIZING THE SIGNIFICANCE OF TDM AND GENETIC INFLUENCE IN ATAXIA & SEIZURES DESPITE PHENYTOIN

A common antiseizure medication that is prescribed and used extensively is phenytoin. Since phenytoin has a limited therapeutic range, it needs to be closely watched. Instances in which patients experience toxicity at standard therapeutic dosages (200–400 mg/day) are the main cause for concern and represent an unpredictable scenario 3. The pharmacokinetic profile of the medication is nonlinear. In addition, CYP2C9 pharmacogenetic alterations, which are critical for the metabolism of phenytoin, may possibly be responsible for the toxicity profile. The fact that CYP2C9 polymorphisms are very common within the Indian population is one of the established facts about them. In an Indian population investigation, the CYP2C9∗3 (Leu359) polymorphism was shown to exhibit significantly greater serum phenytoin levels compared to the wild variation by Chaudhary et al.

In this case study, we outline the patient's presentation due to phenytoin toxicity and stress the importance of TDM and, in practical situations, genetic testing.

A 52-year-old man was given a prescription for 200 mg of phenytoin twice a day after being diagnosed with "late onset epilepsy." He was taking medication as prescribed and experienced a seizure that was focal with reduced awareness. It was not recommended that the individual receive TDM. Following a month of therapy, he was unable to take steps and experienced frequent falls. Despite taking phenytoin, he also experienced a seizure episode.

It was marginally more than the recommended dosage (30.5 mcg/ml). The normal range for blood phenytoin levels is 10–25 mcg/ml. Ten, ataxia gradually improved after phenytoin was decreased to 100 mg BD & stopped entirely in three weeks. Next, the patient started taking 200 mg of valproate twice a day. The patient stopped having seizures after three weeks and resumed walking normally.

Discussion;

This highlights how crucial TDM or genetic testing are to the management of epileptic patients. Infusion of phenytoin may cause irritation to the vessels due to its poor solubility in water. CYP2C9 is mostly responsible for the metabolism, making up 80% of the process; CYP2C19 handle the remaining 20%. The crucial aspect in this situation is the function of CYP2C19, which takes precedence over CYP2C9's function in the event of a mutation which renders it nonfunctional.

those having variants ∗2 and ∗3 of CYP2C9 may have a 25–50% lower metabolism of PHT than those having wild-type variant ∗1 due to genetic polymorphism [6]. As a result, individuals in these population groups need to be given phenytoin with extreme caution. Physicians' ought to advocate for CYP2C9 polymorphism genetic testing whenever feasible.

Conclusion

The polymorphism CYP2C9∗3 is prevalent in a considerable fraction of the Indian population. This calls for genetic testing and the use of TDM to closely monitor patients who are taking phenytoin. One popular anti-seizure drug is phenytoin. To achieve optimal therapeutic advantages and lower the incidence of such side effects, doctors and neuro-legists need to keep in mind the underlying genetic components.

THE GENETIC OF ADVERSE DRUG OUTCOME IN TYPE 2 DIABETES

Metformin

T2D's first-line treatment is metformin. Approximately thirty percent of patients on metformin have gastrointestinal (GI) side effects, which might include bloating, diarrhoea, cramping in the abdomen, nausea, indigestion. Carrier proteins mediate the hepatic absorption, adrenal clearance, or oral absorption of metformin because it functions as an organic cation.

Three investigations have discovered a link between genetic variations in SLC22A1, the gene encoding OCT1, and GI discomfort brought on by metformin I.e. The chance of GI side effects from metformin increased by more than two times when more than two reduced functional les were present in R61C, C88R, G401S, M420del, and G465R, per a study using a GoDARTS cohort that included 1,915 metformin-tolerant and 251 metformin-intolerant people. Concurrent usage of OCT1-inhibiting medications increased this effect by a factor of four.

individuals with a recent diagnosis within the first six months of metformin therapy. Similarly, Tarasova et al. found a strong correlation between metformin's GI side effects or an 8 bp insertion (r36056065) and an SNP (rs628031) in the SLC22A1.

Dawed et al. found that in 286 severely tolerant with 1,128 tolerant patients, there is a correlation between metformin-related GI intolerance and rs3889348, an alteration that modifies intestine transcription of SLC9A4 (a gene encoding PMAT). The G allele, which lowers SLC29A4 expression, was linked to 34% increased probabilities of intolerance. Metformin transporter inhibitor medications taken concurrently worsen GI intolerance by a factor of greater than three.

The association among metformin intolerance with the low-expressing S∗ allele that arises through a combination with SERT (SLC6A4)-5-HTTLPR/rs25531 genotype was investigated, since the serotonin reuptake transporters (SERT) have a function in insulin intestine absorption.

The study found a 30% increased risk of intolerance for every S∗ allele. Dujic et al. (2016b) reported an intriguing multiplicative interaction between the genotypes of OCT1 and SERT. Carriers of less functional alleles in OCT1 were shown to have higher probabilities of being intolerant when compared with carriers of the S∗ allele vs the control population of the usual type SERT (L∗L∗) genotype.

Table-4: An Explanation Of The Gene Studies That Are Included:

Gene	Comparators
SLC29A4	Metformin-intolerant Metformin-tolerant
SLC22A1	metformin-intolerant Metformin- tolerant
SLC6A4 SLC22A1	Metformin-tolerant Metformin-intolerant
SLC22A1	Metformin-tolerant Metformin-intolerant
SLC22A1, SLC22A2, SLC47A1	Metformin-tolerant Metformin-intolerant
CYP2C9 CYP2C19 CYP2C8	Without hypoglycaemia With hypoglycaemia
POR CYP2C9 CYP2C9	Without hypoglycaemia With hypoglycaemia Without severe hypoglycaemia With severe hypoglycaemia
CYP2C9	Without severe hypoglycaemia With severe hypoglycaemia
ABCC8	Without hypoglycaemia With hypoglycaemia
SLC29A4	rs3889348G>A
SLC22A1	R61C C88R G401S M420del G465R
SLC6A4	L*L*

Dujic et al. looked at the relationship between metformin intolerance and the low-expressing S∗ allele resulting from the combination SERT (SLC6A4)-5-HTTLPR/rs25531 genotype, considering the role of reuptake of serotonin transporter (SERT) to metformin intestine absorption. Each S∗ allele in this study was linked to 30% greater probabilities of intolerance. Remarkably, Dujic et al., 2016b, found that the OCT1 and SERT variants interacted multiplicatively. Due to the standard SERT (L∗L∗) genotype, carriers of OCT1 reduced function alleles had a higher likelihood of intolerance.

Conclusion:

Adverse drug reactions are one of the variables that lead to morbidity and mortality in both people and animals. Immunological suppression, gender, and sex all raise the risk of ADR. Adverse drug reactions, which in vulnerable humans and animals show up as an apparent dose-response relationship, can be explained by the pharmacology of the medication. Since the full range of side effects is unknown, pharmaceutical companies put a lot of effort into figuring out a drug's adverse effect profile before putting it on the market. This is because efficient post-marketing surveillance is essential.

Significant progress has been achieved on learning about the genetics of adverse drug responses, as recently reported by others. Advances in understanding idiosyncratic reactions to drugs when HLA genotype is a risk factor have been made utilizing both candidate gene and GWA techniques. Clinical applications have been made of two of these relationships, which demonstrate very high levels of specificity and sensitivity between abacavir hypersensitivity and B*57:01 with cocaine cytotoxicity and B*15:02.

Despite the paucity of research on genetics or ADR with diabetes, some compelling findings are beginning to emerge. Genetic variations in the genes encoding metabolizing enzymes and drug transporters are linked to hypoglycaemia brought on by sulfonylurea and metformin-related GI side effects, respectively. More research is need to examine more recent antidiabetic medications such SGLT2i, GLP-1RA, and DPP-4i. Furthermore, racial and ethnic distinctions must be taken into consideration in pharmacogenetic investigations.

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