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Review Article

Pharmacogenomics: A Golden Science between Diagnosis and Prophylaxis

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Abstract

Pharmacogenomics pursue to dissolve the way that human genetic variation alters drug efficacy and toxicity.

Genome-wide association research and candidate gene findings submit that genetic approaches will assist select the major suitable medication and its right dose while diminishing adverse drug reactions (ADRs).

Pain is an unpleasant feeling that results from tissue injury. Pain management is a challenge. Currently, drug interaction is the first-line therapy for resolving pain. However, variations in drug efficacy among patients are common with pain analgesic medications. In addition to this, certain patients have ADRs after being treated with specific pain medications. This survey discusses the use of medications for pain management in the context of the recent pharmacogenomics researches on ADRs and drug activity.

Keywords: Pharmacogenomics; Pain Medications; Pain Management

Introduction

A proven efficient medication can fail to treat some pain cases or may cause dangerous adverse drug reactions (ADRs) [1]. Different factors may affect drug efficacy, including genetic variation which sometimes complicated drug work, modern genetic research has explained some loci which polymorphic changes can alter pharmacokinetic and pharmacodynamics of drug, Therapeutic drug monitoring (TDM) of drug concentrations in plasma, can be useful in monitoring patients who take pain medications to assure efficacy and diminish possible adverse drug reactions, TDM can be used to detect drug-related side effects and patient-reported lack of effect (e.g., tolerance).

Genetic variations be divided into two types: (1) inherited variants (i.e., germ-line genetic variants); and (2) acquired variants (i.e., somatic mutation). Germ-line variants of genes may encode drug therapeutic targets, drug-metabolizing enzymes, human-leukocyte antigen (HLA), and drug transporters could affect patient response to certain analgesic medications. Somatic variants in genes are frequently linked with cancer growth and may alter drug response of tumors that have certain mutations. This is known as targeted therapy. Precision medicine aims to illustrate how to give the "right drug" at the "right dose" for the "right patient" according personalized genetic profile [2,3].

Pharmacogenomics

Pharmacogenomics is the study of how genes affect a person's response to medications. This new field joins pharmacology (the science of drugs) and genomics (the study of gene function) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup. Currently available medications are "one size fits all," but they don't work the same mechanism for everybody. It will be complicated to predict who will profit from a medication, who will not respond at all, and who will have adverse drug reactions. Adverse drug reactions are an important cause of hospitalizations and deaths in the United States. Using research which gained from the Human Genome Project, specialists had learned how inherited variations in genes alter the body's response to medications. These genetic differences will be used to predict whether a medication will be effective for a particular person and

to help prevent adverse drug reactions. Large-scale genome wide association studies and smaller-scale studies with a candidate-gene approach, that used to study genes concerned in drug metabolism enzyme, have supported advance our understanding of the underlying mechanisms of ADRs. (figure 1) [4]. This research takes into account ancestral genetic structure, complex haplotypes, and gene- gene interactions, according to them, the United States Food and Drug Administrations (FDA) have relabeled over 100 approved drugs with genetic information [5,6].

Pharmacogenetic tests provide information about a patient's likelihood to have an adverse drug reaction (ADR) and/or a therapeutic response to a medication before prescribing pain medication. For giving the right drugs and right doses for right patients, a precise therapeutic intervention (i.e., adjust drug dosage or avoid use the drug) should be based on the information of the pharmacogenetic tests

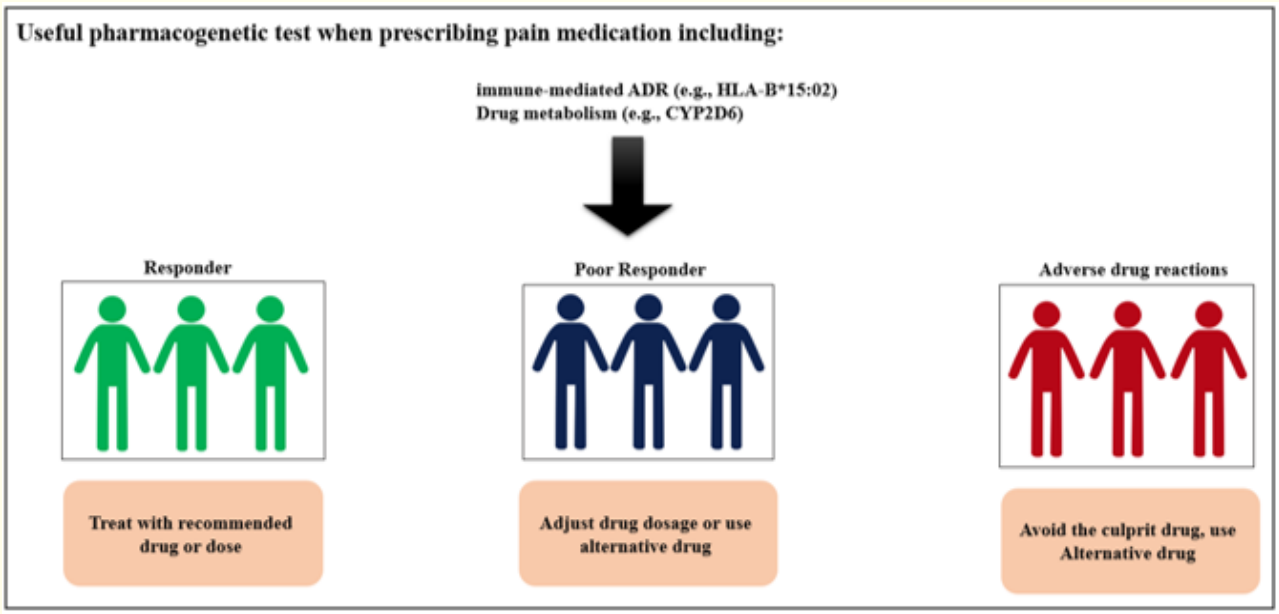

Figure 1: Pharmacogenetic testing for pain management.

Pain medication

Pharmacogenomics indicate the way that genetic variation among individuals affect patient drug responses and drug disposition [7]. With classic drug dosing, some patients will experience toxicity whilst other patients will not receive sufficient therapeutic effect. Variations in drug efficacy may differ as much as 2-10 fold or even 100-fold between members of the same family [8,9]. These variations happened due to pharmacodynamics factors, based on differences in drug target receptors and downstream signal transduction, and pharmacokinetic factors, which alter drug metabolism and elimination, changing the relationship among drug dose and steady state serum drug concentrations. Generally, genes affecting treatment can be divided into two categories: those genes affecting pharmacokinetics, and those affecting pharmacodynamics [10]. In pain management drugs, genes linked with altered pharmacokinetics include those which encode members of the cytochrome P450 family of enzymes, which are very important in glucuronidation of medications [7,10]. Genes encoding cyclooxygenase enzymes, the opioid receptors and the enzyme catecholamine methyltransferase (COMT) may alter drug pharmacodynamics [7,10].

The World Health Organization has founded a pain ladder for pain management purpose, that start with non-opioid medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), progressing to weak opioids, and culminating with strong opioids [11], another pain medication involved anticonvulsant drugs for neuralgia, adjuvant therapies which used an antidepressant medi-

cation to reduce chronic pain associated anxiety [12,13]. In Taiwan, based on the National Health Insurance Research Database, drugs that are most frequently used for pain management has been explained (Figure 2)

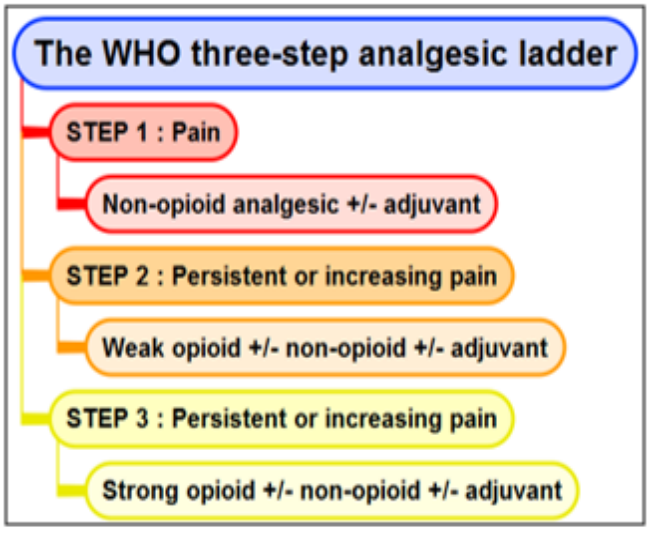

Figure 2: The WHO three-step analgesic ladder [16,17].

Drug metabolism enzymes

Drug-metabolizing enzymes are called mixed-function oxidase or monooxygenase and containing many enzymes including cytochrome P450, cytochrome b5, and NADPH-cytochrome P450 reductase and other components. The hepatic cytochrome P450s (Cyp) are enzymatic family which serves a very important role in drug metabolism and detoxification of xenobiotics with each cytochrome isozyme responding differently to exogenous chemicals that can stimulate or inhibit them. One of the most common CYPs involved in Drug metabolism is cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6).

For example, Cyp 1A1 is specifically active towards polycyclic aromatic hydrocarbons (PAHs), activating them into reactive intermediates those covalently bind to DNA, a key point in the beginning of carcinogenesis. Phase II drug-metabolizing enzymes such as glutathione S-transferase, aryl sulfatase and UDP-glucuronic transferase convert chemical carcinogens into less toxic or inactive metabolites. Several medications alter the rate of activation or detoxification of carcinogens via changing the activities of phases I and II drug-metabolizing enzymes [21].

Drugs used in pain management

NSAIDs and acetaminophen

NSAIDs, for example aspirin and ibuprofen, as well as acetaminophen, act by inhibiting the enzymes cyclooxygenase-1 and -2, which stimulate prostaglandins synthesis. The inhibition of prostaglandin synthesis results in the analgesic, anti-pyretic and anti-inflammatory properties of these drugs, with the exception of acetaminophen, which does not show anti-inflammatory affects. Because of common use of NSAIDs, they are the medications most generally associated with adverse effects, the most common of which are those involving the GI tract. Decreased prostaglandin range in the gastrointestinal mucosa reduce mucus and bicarbonate secretions, thereby reducing their protective effects against the acidic gastric environment, NSAIDs can be directly toxic to the gastric mucosa, resulting ulceration, and fatal bleeding in the end. Also, decreased prostaglandin synthesis via kidney is the reason of renal impairment. Chronic or acute toxic acetaminophen exposure may lead to liver toxicity via hepatocellular necrosis [14,15].

Opioids

Opioids are the most potent analgesics available and are the mainstay of chronic pain management in cancer and non-malignant pain patient [18,19]. To control chronic cancer pain, oral morphine is mainly administered regularly, chronic dosing can lead to pharmacological tolerance, but not to therapeutic failure. We can describe the opioid-induced tolerance pharmacologically as a "shift to the right" in the dose–response curve; that is a higher dose is required over time to preserve the same level of analgesia [20].

Opioid analgesics-codeine: CYP2D6

Codeine is vastly administered after operations and is used in drug combinations for acute and chronic pain management [22]. It is classified as a weak opioid because of less potent m-opioid receptor agonist than morphine [23]. Codeine is a prodrug and have a low affinity towards opioid receptor with low intrinsic activity at the m-opioid receptor. The initial metabolism of codeine is through glucuronidation with O-demethylation resulting in mor-

phine formation. The O-demethylation of codeine to morphine is mediated by CYP2D6 [24]. The Clinical Pharmacogenetics Implementation Consortium guidelines have provided information for presenting codeine dosing according to CYP2D6 genotypes [25]. It is proposed to consider alternative analgesics for UMs such as morphine or nonopioid. A recommended dose of 15e60 mg every 4 hours is proposed for extensive metabolizers. For the intermediate metabolizer phenotype, it is suggested to begin with 15e60 mg every 4 hours and consider alternative analgesics in cases where there is no response. For PM it is suggested to directly consider al-

Drug	Type	Response or ADR	Gene polymorphism(s)	Importance	Ethnicity
Codeine	Opioid	Respiratory depression	Metabolism: CYP2D6, CYP2B6	Ultra-rapid metabolizers (CYP2D6*1/*1 and *1/*2) should avoid usage due to potential for toxicity	Caucasian, Han Chinese, Japanese, Korean
Morphine	Opioid	Respiratory depression	Drug transporter: ABCB1 receptor interaction: OPRM1	OPRM1 c.118A>G or ABCB1 c.3435C>T genotype might be a reference for postoperative doses during the 24 h after major painful surgeries	Caucasian
Methadone	Opioid	Cardiac arrhythmia	CYP3A4, CYP2B6, and CYP2D6	CYP3A4 and CYP2B6 are the major CYP isoforms involved in methadone metabolism, with CYP2D6 contributing to a minor extent, preferentially in metabolism of the R-enantiomer	Caucasian, Han Chinese
Flurbiprofen	NSAIDs	Adverse cardiovascular, renal, and gastrointestinal events (including bleeding and ulceration)	CYP2C9	Poor metabolizers (CYP2C9*3/*3) should administrated with caution to avoid adverse cardiovascular and gastrointestinal events	Caucasian, Korean
Phenytoin	Antiepileptic drug	SJS, TEN	HLA-B*1502	Avoid usage in carriers with risk HLA genotypes to prevent SJS/TEN	Thai
Doxepin	Cyclic antidepressants	Cardiac arrhythmia, myelosuppression	CYP2D6	Poor metabolizers (CYP2D6*3/*3) should reduce dose by 60% to avoid arrhythmia and myelosuppression	Caucasian
Celecoxib	NSAIDs	Serious adverse cardiovascular events	CYP2C9	Consider starting treatment at half the lowest recommended dose in poor metabolizers (CYP2C9*3/*3) to avoid adverse cardiovascular	Caucasian

Table 1: Useful pharmacogenomics tests in predicting adverse drug reactions and dosage for pain medicine.

ternative analgesics such as morphine or a nonopioid due to lack of opioid efficacy. Thus, CYP2D6 is an example of the impact of genetic polymorphisms on pain medicine, including codeine and tramadol analgesia [26]. By contrast, the clinical rapport of CYP2D6 polymorphisms on other opioids (i.e., oxycodone, methadone, and dihydrocodeine) are still not explained [27].

Opioid analgesics: drug receptors and transporters

In addition to the combination between CYP2D6 (metabolism) and opioid response, the essential candidate genetic contributors to opioid efficacy and adverse effects are ABCB1 (drug transporter) and OPRM1 (receptor interaction) [27]. The functional study of OPRM1 revealed that the G allele (A118G) creates a novel CpG-methylation site. This methylation would prevent the growth of the OPRM1 expression rate that takes place after a prolonged opioid administration. Patients with an inhibited OPRMI allele might benefit from a k-agonist such as buprenorphine instead of m-agonist such as morphine.

Opioid analgesics-methadone: CYP3A4, CYP2B6, and CYP2D6

It is an opioid with an entirely different chemical structure to morphine and oxycodone. Actually, methadone (including R- and S-methadone) are used as second line opioids to treat cancer patients [28].

Pharmacogenomics for pain medicine: immune-mediated drug hypersensitivity

Antiepileptic drugs for neuralgia: HLA association of drug induced cutaneous ADRs

Antiepileptic drugs (AEDs) are used to monitor epilepsy or to treat certain psychiatric disorders, e.g., bipolar disorder. These medications, specially carbamazepine, Trileptal, lamotrigine, gabapentin, and topiramate, can be treated post herpetic neuralgia and fibromyalgia. However, anticonvulsants are a major reason of cutaneous ADRs (cADRs) [29]. The strong genetic association purpose an immediate participation of HLA in the pathogenesis of drug hypersensitivity. It has been shown that the HLA molecule presents an antigenic drug and effect in clonal expansion and activation of CD8þ cytotoxic T cells. A pharmacogenomic study identified an uncommon shape of granulysin excreted by these cytotoxic T lymphocytes and natural killer cells responsible for the fast and spreader keratinocyte death in SJS/TEN [30]. The elevated sensitivity and specificity of genetic biomarkers supplies a plausible basis for improving tests to determine individuals at risk for medication hypersensitivity. A wide probable research has shown that HLA-B*15:02 screening before carbamazepine treatment can effectively decrease the incidence of carbamazepine-induced SJS/TEN [31,32]. In Caucasian and Japanese populations the risk of developing hypersensitivity reactions to carbamazepine was found to be associated with another allele, HLA-A*31:01.78,79 In addition to HLA, carbamaze-

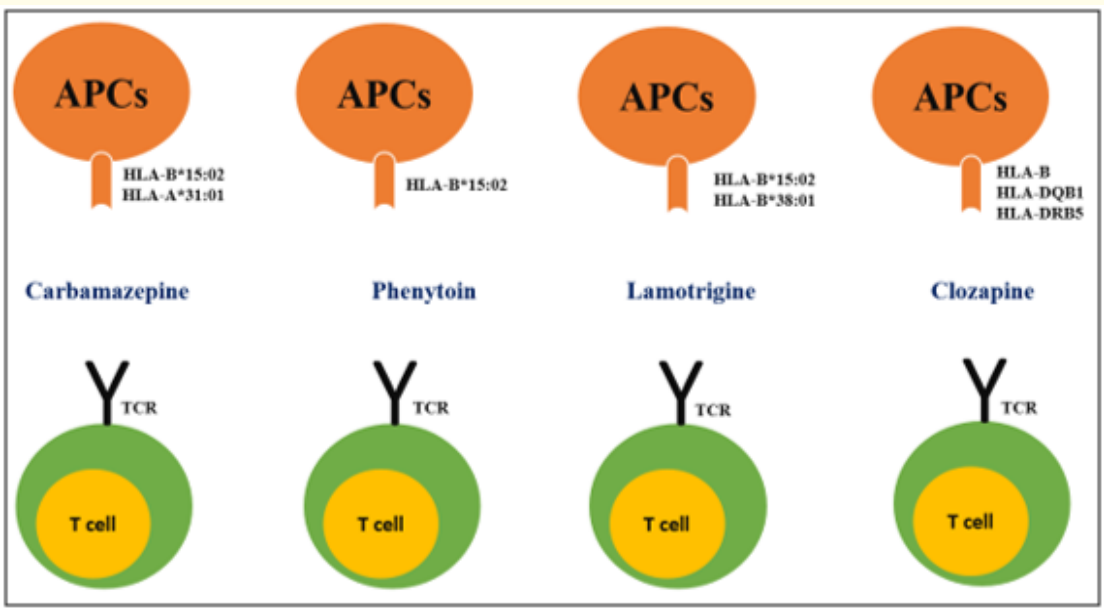

Figure 3: Severe adverse drug reactions with human leukocyte antigen (HLA) association.

The interaction of HLAeT-cell receptor (TCR) drugs is the essential event for some types of severe adverse drug reactions. Some polymorphisms of genetic variants (e.g., HLA-B*15:02) related to this critical event could be used in clinical practice. APCs ¼ antigen presenting cells.

Moving pharmacogenomic findings into medical practice for pain therapy

Prior improving pharmacogenetic tests, a trial approach for analgesics was used for decades in analgesic treatment. Available pharmacogenomics studies indicated that some of the genetic markers have potential to be used clinically to guide physicians to select a suitable analgesic medication with a correct dose for right patient. Several examples are shown in Table 1. Several tests have clinical guidelines for dose adjustment and alternative medications assembled by The Clinical Pharmacogenomics Implementation Consortium (e.g., codeine and carbamazepine). Although there have been clear advances in clinical applications of pharmacogenetics, some issues slow down the implementation of pharmacogenetic testing globally [35]. For example, turnaround time of genetic tests, limited value of genomic technologies after cost-benefit analysis, ambiguous interpretation of the pharmacogenetic test outcomes, population limitation, and limited prospective studies documenting superiority of the pharmacogenetic-guided treatment approach have to be overcome if the future of personalized medicine is to show promise or accepted for routine use.

Conclusion

The clinically beneficial pharmacogenomic tests presently available for pain therapy are those used in predicting drug toxicity or dose adjustment. More research is needed to determine genetic differences that identify drug efficacy of pain medications. This area of study is probable fast accelerating with the decreasing cost of next-generation sequencing and well established bio banking systems worldwide.

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