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Review Article

Pharmacogenomics for personalized pain medicine

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ABSTRACT

Pharmacogenomics aims to unravel the way that human genetic variation affects drug efficacy and toxicity. Genome-wide association studies and candidate gene findings suggest that genetic approaches may help choose the most appropriate drug and dosage while preventing adverse drug reactions (ADRs). Pain is an unpleasant feeling that usually results from tissue damage. The management of different types of pain (acute, chronic, inflammatory, neuropathic, or cancer) is challenging. Currently, drug intervention is the first-line therapy for resolving pain. However, differences in drug efficacy between individuals are common with pain medications. Moreover, some patients experience ADRs after being treated with specific pain drugs. This review discusses the use of drugs for pain management in the context of the recent pharmacogenomic studies on ADRs and drug efficacy.

1. Introduction

A medication with proven efficacy and safety in a series of rigorous clinical trials could still fail to work in some patients or cause serious adverse drug reactions (ADRs).[1,2] The interindividual responses to drugs are most likely affected by genetic variations, which can 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 encoding drug-metabolizing enzymes, drug transporters, drug targets, and human-leukocyte antigen (HLA) can affect individual response to medications. Somatic variants of genes are frequently associated with the development or progression of cancer, and affect the drug response of tumors that carry specific mutations, so called target therapy. Because of the impact of genetic variants on medication responses, how to give the "right drug" at the "right dose" for the "right patient" is a major goal in the era of precision medicine.[3,4]

2. Pharmacogenomics

Pharmacogenomics is the application of current technology for the precise determination of genetic variants that influence drug response, and to develop personalized strategies that maximize therapeutic efficacy and assure drug safety. Large-scale genome-wide association studies and smaller-scale studies with a candidate-gene approach, that are used to study genes involved in drug metabolism enzymes, drug transporters, drug receptors, and HLA, have helped advance our understanding of the underlying mechanisms of ADRs and drug efficacy (Figure 1). Next-generation whole-genome sequencing, which provides a diverse genome map of multiple populations, will be useful for the future of pharmacogenetic studies.[5] These studies take into account ancestral genetic structure, complex haplotypes, gene–gene interactions, and rare variants. They aim to detect and replicate novel pharmacogenetic loci of clinical significance. Based on these studies, the United States Food and Drug Administrations (FDA) have relabeled over 100 approved drugs with genetic information. A list of valid genomic biomarkers for clinical guidance can be found on the FDA website "Table of Pharmacogenomic Biomarkers in Drug Labels" (http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm). Some of these biomarkers have been implemented in medical practice.[6–8]

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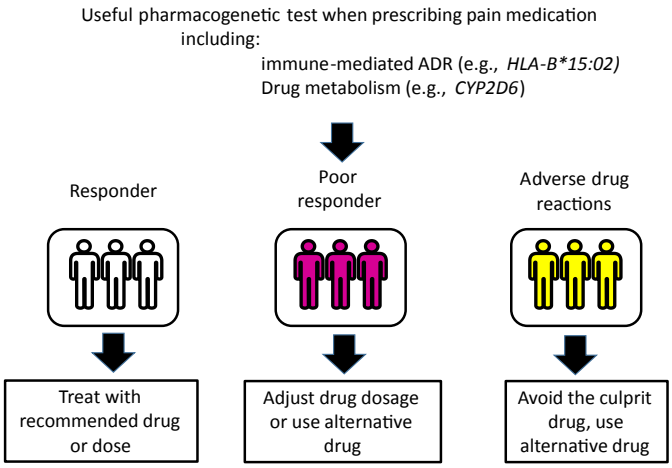

Figure 1. Pharmacogenetic testing for pain management. Pharmacogenetic tests provide information about a patient's likelihood to have an adverse drug reaction (ADR) and/or a therapeutic response to a medication before prescribing pain medication. For giving the right drugs and right doses for right patients, a precise therapeutic intervention (i.e., adjust drug dosage or avoid use the drug) should be based on the information of the pharmacogenetic tests.

3. Pain medication

Most clinical pain management options involve pharmacological interventions. Pain therapy has evolved over the years into a large specialty field. Ideal pain management approaches must provide adequate analgesia without excessive adverse effects. However, there are large interindividual differences in response to pain medications, concerning efficacy and the development of severe ADRs.[9–13] Current pain management strategies are devised using the World Health Organization pain ladder, which begins with nonopioid medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), progressing to weak opioids, and culminating with strong opioids.[9] Other pain medications include anticonvulsant drugs for neuralgia. Additionally, adjuvant therapies using antidepressant medications can aid in reducing chronic pain-associated anxiety.[14,15] In Taiwan, based on the National Health Insurance Research Database, we found the drugs that are most frequently used for pain management (Tables 1 and 2).

The field of pain medications is a valuable one to study germline variants using a pharmacogenomic approach, because of the considerable repercussions of these medications on the biological, psychological, sociological, and economical welfare of patients. Genetic studies have identified several polymorphic loci that govern the pharmacodynamics and kinetics of analgesic drugs.[16–18] The aim of this review is to highlight recent advances in the pharmacogenomics of pain medicine.

Table 1
Use of opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) in Taiwan.

Group	Main ingredient	Use (tablets/y)
Opioids	Tramadol HCL	1,512,775
Opioids	Morphine sulfate	401,810
Opioids	Meperidine HCL	349,312
Opioids	Propoxyphene HCL	308,707
Opioids	Fentanyl	74,036
Opioids	Nalbuphine hydrochloride	34,888
Opioids	Buprenorphine (hydrochloride)	13,145
NSAIDs	Diclofenac sodium (diethylammonium)	8,199,279
NSAIDs	Ibuprofen	3,398,801
NSAIDs	Glucosamine sulphate D-(crystalline)	1,850,207
NSAIDs	Acemetacin	1,754,514
NSAIDs	Celecoxib	1,081,972
NSAIDs	Flurbiprofen	657,754
NSAIDs	Etodolac	517,955
NSAIDs	Etoricoxib	253,513
NSAIDs	Fenbufen	103,317
NSAIDs	Flufenamic acid	64,139
NSAIDs	Benzydamine HCL	35,190

Table 2
Use of antidepressants and antiepileptic drugs in Taiwan.

Group	Main ingredient	Use (tablets/y)
Antidepressants	Trazodone hydrochloride	1,351,687
Antidepressants	Imipramine HCL	1,021,355
Antidepressants	Fluoxetine (HCL)	587,716
Antidepressants	Sertraline(as hydrochloride)	432,102
Antidepressants	Mirtazapine	331,711
Antidepressants	Paroxetine hydrochloride	314,050
Antidepressants	Amitriptyline HCL	253,003
Antidepressants	Escitalopram oxalate	248,157
Antidepressants	Venlafaxine	219,911
Antidepressants	Venlafaxine (HCL)	211,960
Antidepressants	Duloxetine hydrochloride	190,550
Antidepressants	Citalopram hydrobromide	156,348
Antidepressants	Doxepin (HCL)	155,567
Antidepressants	Bupropion hydrochloride	146,207
Antidepressants	Fluvoxamine maleate	114,074
Antidepressants	Moclobemide	65,511
Antidepressants	Maprotiline HCL	28,018
Antidepressants	Clomipramine HCL	9,180
Antidepressants	Dothiepin HCL	8,055
Antidepressants	Oxitriptan	672
Anticonvulsants	Clonazepam	2,807,476
Anticonvulsants	Valproate sodium	1,103,829
Anticonvulsants	Phenytoin sodium	1,057,080
Anticonvulsants	Carbamazepine	913,882
Anticonvulsants	Gabapentin	456,504
Anticonvulsants	Topiramate	284,457
Anticonvulsants	Lamotrigine	276,418
Anticonvulsants	Levetiracetam	187,679
Anticonvulsants	Phenobarbital	183,202
Anticonvulsants	Valproic acid	153,492
Anticonvulsants	Vigabatrin	57,493
Anticonvulsants	Divalproex (sodium)	44,485
Anticonvulsants	Oxcarbazepine	3161
Anticonvulsants	Phenobarbital sodium	210

3.1. Drug metabolism enzymes

The metabolism of drugs and other xenobiotics is often divided into multiple phases. Phase I enzymes are responsible for chemical modifications of the drugs. They include cytochrome P450 (CYP), cytochrome b5, and nicotinamide adenine dinucleotide phosphate-cytochrome P450 reductase. Phase II enzymes are involved in further conjugation of the active drug metabolites, some examples are glutathione S-transferases, aryl sulfatase, and uridine-glucuronosyltransferase. The hepatic CYPs are a multigene family of enzymes that play a critical role in the metabolism of many drugs, with each cytochrome isozyme displaying unique substrate specificities and susceptibility to induction and inhibition by exogenous chemicals. One of the most common CYPs involved in drug metabolism is cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6), whose metabolic rate can fluctuate by over 100-fold between the allelic variants expressed in different ethnic groups.[19] For example, approximately 10% of the Caucasian population carries an autosomal recessive trait that yields a nonfunctional variant.[20] Patients homozygous for this variant, known as poor metabolizers (PM), may have either a higher risk of adverse side effects because of drug overdose (i.e., tricyclic antidepressants or antiarrhythmics) or no drug efficacy due to poor transformation of the prodrug into its active metabolite. Conversely, in ultra-rapid