Pharmacogenomic Biomarkers in Psychiatry

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Pharmacogenomic biomarkers are potential individual genetic variations that can affect drug response influencing both pharmacokinetic parameters by causing variable activity of the systems responsible for the absorption, distribution, metabolism, and excretion of the drug and pharmacodynamic parameters like the mechanisms of action of the drug. Here, the term "pharmacogenomic biomarkers in psychiatry" means those related to a variety of psychiatric disorders, such as depression, ADHD, narcolepsy, schizophrenia, bipolar disorder, and epilepsy.

Keywords: precision medicine ; personalized medicine ; pharmacogenomics ; pharmacogenomic biomarkers ; psychiatry ; psychiatric disorders ; epilepsy

1. Introduction

The World Health Organization (WHO) estimates that about 25% of the population around the world will suffer from at least one mental disorder at some time in their lives [1][2]. Depression and anxiety are among the most common disorders, and these can affect people regardless of age, gender, ethnicity, or background. We do not fully understand what causes most cases of mental health impairment, but it is known that both genetic and environmental factors can often contribute to an individual's predisposition to a particular disorder. In other cases, serious injuries or traumatic events cause psychological symptoms that persist for a long period of time [3].

Medications can be used in order to reduce the intensity of symptoms or treat several psychiatric disorders. A patient's response to the many medications used to treat various psychiatric disorders can be highly variable [4]. Drug response is dependent on personal health risk factors (e.g., gender, age, liver and renal function, blood pressure, body fat, alcohol and drugs, and drug–drug interactions). In addition, genetic factors, i.e., individual's unique genetic makeup, can affect drug response influencing both pharmacokinetic parameters by causing variable activity of the systems that are responsible for the absorption, distribution, metabolism, and excretion of the drug and pharmacodynamic parameters, like the mechanisms of action of the drug [5][6]. Pharmacogenomics (PGx) refers to the study of drug response as it relates to potential individual genetic variations.

For an increasing number of drugs, pharmacogenomic testing is available and used to pre-screen patients and help them in selecting drug choice and drug dose accordingly [4][7]. Now, more than 10% of medications that are approved by the U.S. Food and Drug Administration (FDA) provide pharmacogenomic information (PGx information) in their drug labeling. This proportion is gradually increasing as more pharmacogenomic biomarkers (PGx biomarkers) are discovered and validated.

There are solid reasons for pharmacogenomic testing (PGx testing). Some drugs are only effective for specific genotypes and the testing can avoid unpredictable, severe, and potentially fatal drug reactions. Furthermore, for some drugs, a patient's ancestry is the essential consideration. For example, for carbamazepine, a commonly used antiepileptic drug, the FDA recommends that, if patients are descendants of genetically high-risk populations, they should take PGx testing for the presence of *HLA-B*15:02* before treatment [8][9][10]. Carriers of this variant, which is frequently found in Han Chinese descendants, are highly susceptible to the development of Stevens–Johnson syndrome and toxic epidermal necrolysis, which often lead to serious conditions, during the course of carbamazepine therapy. The *HLA-B* variant alleles are just one example of such adverse drug reactions (ADRs). In fact, there is a plethora of genetic variants that are associated with ADRs. As an evident example, carriers of a variant of MT-RNR1 (mitochondrially encoded 12S rRNA), an RNA-coding gene, are at high risk of irreversible hearing loss by a single dose of gentamicin [11][12].

For a growing number of drugs, PGx testing provide a means of optimizing the drug choice and drug dose. Drug labels include not only standard dosing information, but also guidelines for adjusting the drug dose or selecting an alternative drug, when necessary, based on a patient's genetic makeup if gene-drug interrelationships are well understood. Dosing adjustment requirements or recommendations are mostly in variants of genes that encode drug-metabolizing enzymes or

drug transporters [13]. Thus, PGx biomarkers in genetic variants that are important for interindividual variations in PK and PD have been very useful in the optimization of pharmacotherapy. Several independent institutions, including the FDA [14], the European Medicines Agency (EMA), the Clinical Pharmacogenetics Implementation Consortium (CPIC) [15], the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) [16][17], and the Dutch Pharmacogenetics Working Group (DPWG), have provided instructions on how PGx testing results can be interpreted in terms of the drug choice and the drug dose [18][19][20].

Accumulated data are then noted to FDA and its Table of Pharmacogenomic Biomarkers in Drug Labeling is widely used as a standard guideline [14]. PGx information is only included on labels when it is useful to inform clinicians of the impact of genotype on phenotype—gene–drug interrelationships—or to indicate whether a PGx test is available for a particular medication. As of now, the Table of PGx Biomarkers includes 431 drug-biomarker pairs for 298 drugs across therapeutic areas. In addition, PharmGKB provides a comprehensive resource, in which evidence-based PGx knowledges are curated and disseminated by scientific team about how our body responds to medications [21]. Pharmacogenomic information is important: it can maximize drug efficacy and reduce/avoid drug toxicity. Currently, FDA's Table of PGx Biomarkers describes PGx information for 35 psychiatric medications, as in Table 1. In addition, the Table of PGx Biomarkers includes PGx information for eight antiepileptic drugs (AEDs), as in Table 2.

Table 1. Food and Drug Administration (FDA) pharmacogenomic biomarkers in drug labeling in psychiatry.

Drug	Type	Indication	Biomarker	FDA	FDA Labeling Sections	EMA
Antidepressants						
Amitriptyline	TCA	Depression	CYP2D6	Actionable	Precautions	
Amoxapine	TCA	Depression	CYP2D6	Actionable	Precautions	
Bupropion	NDRI	Depression	CYP2D6	Informative	Clinical Pharmacology	
Citalopram	SSRI	Depression	CYP2C19	Actionable	Dosage and Administration Warnings Clinical Pharmacology	
			CYP2D6	Informative	Clinical Pharmacology	
Clomipramine	TCA	Depression	CYP2D6	Actionable	Precautions	
Desipramine	TCA	Depression	CYP2D6	Actionable	Precautions	
Desvenlafaxine	SNRI	Depression	CYP2D6	Informative	Clinical Pharmacology	
Doxepin	TCA	Depression	CYP2C19	Actionable	Clinical Pharmacology	
			CYP2D6		Clinical Pharmacology	

Duloxetine	SNRI	Depression	CYP2D6	Actionable	Drug Interactions	Actionable
Escitalopram	SSRI	Depression	CYP2C19	Actionable	Adverse Reactions	
			CYP2D6	Informative	Drug Interactions	
Fluoxetine	SSRI	Depression	CYP2D6	Informative	Precautions Clinical Pharmacology	
Fluvoxamine	SSRI	Depression	CYP2D6	Actionable	Drug Interactions	
Imipramine	TCA	Depression	CYP2D6	Actionable	Precautions	
Nefazodone	SARI	Depression	CYP2D6	Informative	Precautions	
Nortriptyline	TCA	Depression	CYP2D6	Actionable	Precautions	
Paroxetine	SSRI	Depression	CYP2D6	Informative	Drug Interactions Clinical Pharmacology	
Protriptyline	TCA	Depression	CYP2D6	Actionable	Precautions	
Trimipramine	TCA	Depression	CYP2D6	Actionable	Precautions	
Venlafaxine	SNRI	Depression	CYP2D6	Actionable	Drug Interactions Use in Specific Populations Clinical Pharmacology	
Vortioxetine	SSRI	Depression	CYP2D6	Actionable	Dosage and Administration Clinical Pharmacology	Actionable
Stimulants and non-stimulants						
Amphetamine	Stimulant	ADHD	CYP2D6	Informative	Clinical Pharmacology	

Atomoxetine	Non-stimulant	ADHD	CYP2D6	Actionable	Dosage and Administration Warnings and Precautions Adverse Reactions Drug Interactions Use in Specific Populations Clinical Pharmacology	
Modafinil	WPA	Narcolepsy	CYP2D6	Actionable	Clinical Pharmacology	
Pitolisant	H_3R antagonist	Narcolepsy	CYP2D6	Actionable	Dosage and Administration Use in Specific Populations Clinical Pharmacology	
Antipsychotics						
Aripiprazole	Atypical	Schizophrenia Bipolar disorder	CYP2D6	Actionable	Dosage and Administration Use in Specific Populations Clinical Pharmacology	Actionable
Aripiprazole lauroxil	Atypical	Schizophrenia	CYP2D6	Actionable	Dosage and Administration Use in Specific Populations Clinical Pharmacology	
Brexpiprazole	Atypical	Schizophrenia Very severe depression	CYP2D6	Actionable	Dosage and Administration Use in Specific Populations Clinical Pharmacology	Actionable

Cariprazine	Atypical	Schizophrenia Bipolar disorder	CYP2D6	Informative	Clinical Pharmacology
Clozapine	Atypical	Schizophrenia	CYP2D6	Actionable	Dosage and Administration Use in Specific Populations Clinical Pharmacology
Iloperidone	Atypical	Schizophrenia	CYP2D6	Actionable	Dosage and Administration Warnings and Precautions Drug Interactions Clinical Pharmacology
Paliperidone	Atypical	Schizophrenia	CYP2D6	Informative	Clinical Pharmacology
Perphenazine	Typical	Schizophrenia	CYP2D6	Actionable	Precautions Clinical Pharmacology
Pimozide	Typical	Tourette syndrome	CYP2D6	Testing Required	Dosage and Administration Precautions
Risperidone	Atypical	Schizophrenia Bipolar disorder	CYP2D6	Informative	Clinical Pharmacology
Thioridazine	Typical	Schizophrenia Other psychotic disorders	CYP2D6	Actionable	Contraindications Warnings Precautions

H_3R antagonist = histamine H_3 receptor antagonist; NDRI = norepinephrine-dopamine reuptake inhibitor; SARI = serotonin antagonist and reuptake inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic and tetracyclic antidepressant; WPA = wakefulness promoting agent.

Table 2. FDA pharmacogenomic biomarkers in drug labeling in epilepsy.

Drug	Type	Indication	Biomarker	FDA	FDA Labeling Sections	EMA

Brivaracetam	Inhibits synaptic vesicle SV2A protein	Epilepsy	CYP2C19	Actionable	Clinical Pharmacology	Actionable
Carbamazepine	Enhances sodium channel (rapid inactivation) Inhibits L-type calcium channel	Epilepsy Bipolar disorder	HLA-B	Testing Required	Boxed Warning Warnings Precautions	
			HLA-A	Actionable	Warnings	
Clobazam	$GABA_A$ receptor agonist	Epilepsy	CYP2C19	Actionable	Dosage and Administration Use in Specific Populations Clinical Pharmacology	
Diazepam	$GABA_A$ receptor agonist	Epilepsy	CYP2C19	Actionable	Clinical Pharmacology	
Lacosamide	Enhances sodium channel (slow inactivation)	Epilepsy	CYP2C19	Informative	Clinical Pharmacology	Informative
Oxcarbazepine	Enhances sodium channel (rapid inactivation) Inhibits N/P- and R-type calcium channel	Epilepsy Bipolar disorder	HLA-B	Testing recommended	Warnings and Precautions	
Phenytoin	Enhances sodium channel (rapid inactivation)	Epilepsy	CYP2C9		Clinical Pharmacology	
			CYP2C19	Actionable	Clinical Pharmacology	
			HLA-B		Warnings	

Valproic Acid	Inhibits voltage-dependent sodium and T-type calcium channels	Epilepsy	POLG	Testing Required	Boxed Warning Contraindications Warnings and Precautions
	Enhances GABA transmission		Nonspecific (Urea cycle disorders)	Actionable	Contraindications Warnings and Precautions

2. CYP2D6 and CYP2C9 Genes

The cytochrome P450s (CYPs) comprise a large superfamily of a variety of enzymes that serve as major workhorses for metabolizing steroid hormones, lipids, toxins, and xenobiotics. The CYP superfamily genes encode enzymes that function as monooxygenases and catalyze the modification of about 25–30% commonly used drugs [22][23]. The *CYP* genes are quite polymorphic and they can lead to increased, decreased, or completely absent drug metabolism activity. Among these genes, *CYP2D6* is particularly important and heavily studied. More than 100 *CYP2D6* variants have been reported and catalogued at the Pharmacogene Variation Consortium database [24]. In addition to large numbers of single nucleotide polymorphisms (SNPs), other types of variations—gene deletions, duplications, copy-number variants, and pseudogenes that are close to the gene—make genotyping very challenging.

Many of these variants cause the enzyme to change activity at different levels. The level of CYP2D6 activity decides how an individual responds to the substrate drugs. A standard dosage of the drug may show inadequate efficacy in some individuals and serious toxicity in others. To name a few, the drug substrates of CYP2D6 include atomoxetine (a non-stimulant for ADHD), clozapine (an antipsychotic for schizophrenia), and venlafaxine (an antidepressant), among psychiatric medications, as in Table 1 [4][25]. For these drugs, standard doses will result in higher-than-optimal active levels when individuals have absent or deficient CYP2D6 activity. Thus, the risk of ADRs increases and it may result in treatment failure.

There are substantial variations in *CYP2D6* allele frequencies among different populations [26][27]. The wild-type CYP2D6*1 allele shows normal enzyme activity and the extensive or normal metabolizer phenotype. The CYP2D6*2, -*33, and -*35 alleles also belong to this group. Other alleles contain non-functional variant(s), which produce a non-functioning enzyme (*3, *4, *5, *6, *7, and *8) or a decreased-activity enzyme (*10, *17, *29, and *41) [28]. Intermediate and poor metabolizers are individuals who carry decreased and null CYP2D6 alleles, respectively. Notably, approximately 30% of Asians and Asian descendants are intermediate metabolizers. In these populations, the *10 allele with decreased activity is very common: about 40%, when compared with about 2% in Caucasians [29]. Thus, a large proportion of Asians belong to intermediate metabolizers than Caucasians [30]. The African and African American populations also show a large proportion of CYPD6 alleles having sub-optimal activity. The frequencies of the remaining alleles vary depending on the population [30][31][32]. In Caucasians, only small proportions (less than 10%) are poor metabolizers [30]. In contrast, approximately 40% are extensive/normal metabolizers who carry two copies of *1 allele [33][34][35]. CYP2D6 poor metabolizers show higher levels of amitriptyline (as an example of drug substrates) in the plasma, when compared with extensive metabolizers, after standard doses of amitriptyline are taken [36]. When individuals carry a CYP2D6 null variant, their risk of developing ADRs becomes, at least, moderately increased [37]. Because standard dosages may cause to ADRs in poor metabolizers, it is recommended to avoid many tricyclic antidepressants (TCAs) and, instead, take an alternative option, a drug that is not a substrate of CYP2D6 [38].

Interestingly, copy-number variants were also found in *CYP2D6* genes [24]. In other words, individuals who carry more than two copies of functional CYP2D6 alleles—three to 13 copies of *CYP2D6* active allele—have been reported. These carriers are CYP2D6 ultrarapid metabolizers. In the case of 13 functional copies, the rate was up to 17 times higher than for individuals with no active CYP2D6 enzyme [39]. If the drug substrate has increased rate of metabolism, then its active form will not be available and, thus, the therapeutic response will become poor.

3. Beyond Pharmacogenomic Testing

Precision medicine targets providing the optimal diagnoses and treatments for each patient based on the categorization of biomarkers [40][41][42][43]. PGx is one of the main research areas of precision medicine. Nowadays, advances in artificial intelligence (AI), machine learning, multi-omics, and neuroimaging allow for analyzing and integrating complex genomic and clinical data in psychiatry and neurology. Artificial intelligence is the field of computing science that produces an algorithm based on available data to create predictive outcomes, even for unknown data in the future [44][45][46][47]. Particularly, state-of-the-art technology of deep learning revolutionized bioinformatics and medical imaging by yielding helpful software tools [48][49]. Whereas cancer therapy has routine clinical settings with well-established genomic data, in neuropsychiatry, the relationship between PGx data and their clinical significances has not been fully studied. Thus, the usage of artificial intelligence remains limited in the field.

AI has been used in predicting diagnosis, treatment outcome, and prognosis. As of psychiatry and neurology, multiple studies have used models, including deep learning architecture, random forest, tree-based ensemble, elastic net, and linear regression in order to evaluate and predict lithium treatment response on major depressive disorder [50]. To predict prognosis of major depressive disorder, there are algorithms, such as Gaussian process algorithm, Deep Patient, DeepCare, and Doctor AI, which utilize electronic health records. For example, Deep Patient has forecasted psychiatric disorders, including ADHD or schizophrenia with high accuracy (AUC = 0.863 and AUC = 0.853, respectively) [51]. However, the technology is still at an infancy phase and there are many obstacles and limitations to overcome in order to apply it clinically. For example, each algorithm is developed and assigned for each disease and so it is difficult to apply it to other diseases. Moreover, the sample size of each algorithm is too small to apply to public [50].

Various research efforts are ongoing in order to improve diagnosis, prognosis, and treatment in neuropsychiatry: PGx data and their treatment outcomes have been collected to support data-driven clinical decision-making for the patient. To this end, relations between genetic variation and variable drug responses to psychiatric medications should be well established [50]. The use of AI and machine learning analyses to predict individual-specific responses to psychiatric medications is challenging, but well worth pursuing [50].

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