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Bring Technology to Life

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Personalized Medication Solution for Clopidogrel/ Voriconazole/ Proton pump inhibitor/Antidepressants

BACKGROUND

Cytochrome P450 2C19 (abbreviated CYP2C19), which belongs to the CYP450 superfamily, is involved in the biotransformation and hepatic metabolism of at least 10% of commonly prescribed and clinically important drugs, such as antiplatelet agents (clopidogrel), antifungal drugs (voriconazole), some proton pump inhibitors and antidepressants. Genetic polymorphisms can have a determined influence on the in vivo enzymatic activity of CYP2C19. The most common and well-characterized variants in the CYP2C19 gene include the loss-of-function alleles of CYP2C19*2 (c.681 G>A) and CYP2C19*3 (c.636 G>A) associating with diminished enzymatic activity, and the increased-function allele of CYP2C19*17 (c.-806 C>T) with increased metabolic activity. The correlation between CYP2C19 variant diplotypes and the ability of drug metabolism has been shown in Table 1.

Clopidogrel

Clopidogrel is a P2Y inhibitor which interrupts the formation of thrombus by blocking adenosine diphosphate (ADP)-mediated platelet activation and aggregation. CYP2C19 phenotype influences the pharmacokinetics and the corresponding clinical outcomes of clopidogrel in a graded fashion, where individuals with a CYP2C19 IM or PM phenotype have significantly reduced enzymatic activity and poor treatment response; while CYP2C19 RMs and UMs with increased activity of the CYP2C19 enzyme may have increased risks of severe or moderate bleeding when receiving clopidogrel treatment[1,2].

Voriconazole

Voriconazole is a broad-spectrum antifungal agent that has been widely used for the treatment of Aspergillus species, Candida species, Scedosporium apiospermum complex and Fusarium species[3]. Standard maintenance dose of voriconazole in serum is key for treatment outcomes. Since voriconazole is primarily metabolized by the CYP2C19 enzyme, genetic variations in the CYP2C19 gene might be correlate with differentiation in interindividual drug serum concentrations, efficacy and adverse effects. It has been documented that the drug exposure of CYP2C19 PMs is approximately 4-fold higher than NMs when treated with a dose of voriconazole, resulting in increased adverse effects, such as neurotoxicity. In contrary, CYP2C19 RMs and UMs may experience treatment failure caused by inadequate serum voriconazole concentrations[3,4].

Proton pump inhibitor

Proton pump inhibitors (PPIs) are commonly used to treat a variety of acid-related disorders, including gastroesophageal reflux disease (GERD), peptic ulcer disease, and Helicobacter pylori (H. pylori) infections[5]. PPIs, especially the first-generation PPIs (omeprazole, lansoprazole, and pantoprazole) and dexlansoprazole, are predominantly cleared by CYP2C19 and polymorphisms in the CYP2C19 alleles are thus the most important pharmacogenetic parameter affecting interindividual responses towards PPI treatment. A large body of evidence have shown decreased therapeutic effectiveness of PPIs in individuals carrying CYP2C19 variants with improved PPI metabolism and clearance, such as RMs and UMs. While a higher risk of PPI-related adverse events may occur in individuals with IM or PM phenotypes, owing to increased PPI exposure and enhanced acid suppression[6].

Antidepressants

The 2015 and 2016 Clinical Pharmacogenetics Implementation Consortium Guidelines (CPIC) have updated evidence reviews between the CYP2C19 gene and selective serotonin reuptake inhibitors (SSRIs), such as citalopram, escitalopram and sertraline, as well as tricyclic antidepressants (TCAs), such as amitriptylines, imipramine and clomipramine, respectively[7,8]. As an essential pharmacokinetic parameter affecting the treatment outcomes and adverse effects of SSRIs and TCAs among populations, timely and effective access to information on the CYP2C19 genotypes is an optimal way to direct SSRI/TCA dosing and selection.

Therapeutic recommendations for individuals with different drug metabolic activities are listed in Table 2.

PERSONALIZED MEDICATION SOLUTION

Considering the close correlation between the CYP2C19 genetic polymorphisms and therapeutic efficacy and adverse effects of drugs between individuals, Tianlong Personalized Medication Solution is designed to rapidly determine the genetic polymorphism of the most common variants in the CYP2C19 gene, including CYP2C19*2 (c.681 G>A), CYP2C19*3 (c.636 G>A), CYP2C19*17 (c.-806 C>T) as well as the wild-type genotype in specimen with its exclusive pharmacogenomic reagents and the Fascan 48E multi-channel fluorescence quantitative analyzer. The results can provide genetic clues to guide rational drug dosing and to reduce adverse drug reactions for clopidogrel, voriconazole, proton pump inhibitor and antidepressants in clinical practice.

Table 1. Assignment of predicted CYP2C19 phenotype based on genotype[1].

Predicted phenotype of CYP2C19	Genotype	Examples of CYP2C19 diplotypes
Ultrarapid metabolizer (UM)	An individual carrying two increased function alleles.	*17/*17
Rapid metabolizer (RM)	An individual carrying one normal function allele and one increased function allele.	*1/*17
Normal metabolizer (NM)	An individual carrying two normal function alleles.	*1/*1
Intermediate metabolizer (IM)	An individual carrying one normal function allele and one no function allele or one increased function allele and one no function allele.	*1/*2, *1/*3, *2/*17†, *3/*17
Poor metabolizer (PM)	An individual carrying two no function alleles.	*2/*2, *2/*3, *3/*3

Note:

* 1 represents wild type with no mutations in genotype. *2, *3, *17 represent variants in the c.681 G>A, c.636 G>A and c.-806 C>T, respectively, of the CYP2C19 gene.

† The predicted phenotype of *2/*17 is temperately classified as IM, and the CYP2C19*17 allele cannot fully compensate the decreased function of CYP2C19*2.

Table 2. Therapeutic recommendation based on CYP2C19 phenotype[1,4,6,8].

CYP2C19 phenotype	Therapeutic recommendation‡*				
	Clopidogrel[1]		Voriconazole[4]	Proton pump inhibitors※[6]	Antidepressants[8]
	Cardiovascular indications	Neurovascular indications			
UM	Standard dose (75 mg/day)	None	Use an alternative CYP2C19-independent agent	Increase starting daily dose by 100%. Daily dose may be given in divided doses.Monitor for efficacy	Consider an alternative CYP2C19-independent agent. For tertiary amines, use therapeutic drug monitoring to guide dose adjustments
RM				Standard dose. Consider 50–100% increase in daily dose for Helicobacter pylori infection and erosive esophagitis treatment. Monitor for efficacy	
NM		Standard dose (75 mg/day)	Recommended starting dose		Recommended starting dose
IM	Avoid standard dose of clopidogrel if possible. Use prasugrel or ticagrelor at standard dose	Consider an alternative P2Y12 inhibitor at standar dose		Standard dose. For chronic therapy (> 12 weeks), consider 50% reduction in daily dose and monitor for continued efficacy	
PM	Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose	Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose	Consider an alternative CYP2C19-independent agent if possible. Use voriconazole at a lower dosage with therapeutic drug monitoring for certain circumstances		Avoid tertiary amine if possible. Consider an alternative CYP2C19-independent agent. For tertiary amines, consider a 50% reduction in daily dose and monitor for continued efficacy

Note:

* The examples of drugs are only for the purpose of helping to understand the detection results and do not mean the limitations on the use of drugs.

‡ Recommendations of drug use are all based on the prerequisite that there are no contraindications. For antidepressants, tricyclic antidepressants (TCAs) are used as the representative for therapeutic recommendations, please refer to instruction of Tianlong LigSeq Reagent Kit (SNP-U3) for detailed therapeutic recommendation for other classes of antidepressants.

※ Tianlong LigSeq Reagent Kit (SNP-U3) is not appropriate for therapeutic recommendations for ribeprazole and esomeprazole.

Examples of Detection Results

Gene	Gene locus	Genotype	CYP2C19 diplotypes	Medication suggestion for clopidogrel
CYP2C19	c.681 G>A	GG	*1/*1	Standard dosage of 75 mg/day
	c.636 G>A	GG		
	c.806 C>T	CC		

Clinical Significance

Suitable for patients taking clopidogrel, voriconazole, proton pump inhibitors or antidepressants, guiding rational medication to improve clinical efficacy and prevent the occurrence of adverse drug effects.

Ordering Information

Product name	Specification	Specimen	Target gene loci
LigSeq Reagent Kit (SNP-U3)	20 T/Kit	2 mL of EDTA anticoagulated whole blood	CYP2C19*1 (wild type), CYP2C19*2 (c.681 G>A), CYP2C19*3 (c.636 G>A), CYP2C19*17 (c.-806 C>T)

Features

Accurate Result

Powerful software analysis; Internal control can monitor the whole detection procedure and ensure the accuracy of the detection results reaching to over 99%.

Easy Operation

Pre-filled reagents; No need for sample extraction; No requirements for specialized equipment or techniques.

High Efficiency

Results are available in approximately 70 min after loading samples; Reports are easy to read.

Integrated Solution

Tianlong integrated solution from devices to reagents can ensure great compatibility and minimized systematic errors.

Assay Workflow

1 Sample Collection ▸▸▸ 2 Sample Detection ▸▸▸ 3 Analysis and Report

*Detection directly after sample collection and report in about 70 min.