Luminex®

Cytochrome P450 Testing: CYP2C19

An Opportunity to Improve Patient Care

xTAG® CYP2C19 Kit v3

Cytochrome P450 2C19 metabolizes 5% of the prescription drugs in use today. Some of the most commonly used and largest selling therapeutics for heart disease, depression, and fungal treatments are all metabolized by CYP2C19.[1] Understanding a patient's CYP2C19 genotype may provide insight into how they will respond to these drugs.[2]

Introduction

Adverse Drug Reactions (ADRs) are one of the leading causes of morbidity and mortality in health care. An estimated 2.2 million serious ADRs occur yearly in the United States, resulting in more than 100,000 deaths. One of the reasons attributed to the occurrence of ADRs is the prescription of more drugs, as well as an increase in the combination of drugs being used to treat patients. In the U.S., two-thirds of all patient visits result in a prescription medication accounting for more than four billion prescriptions, at a cost of nearly $320 billion.[3]

The discovery of genetic factors such as the cytochrome P450 (CYP) drug metabolizing genes and several years of subsequent clinical research have added to the understanding of the clinically relevant single nucleotide polymorphisms (SNPs) that may help predict drug response. Several genes are responsible for differences in drug metabolism and response—the cytochrome P450 (CYP) genes are among the most common. They encode the cytochrome P450 class of metabolic enzymes, found primarily in the human liver. Many of these enzymes play an instrumental role in the metabolism and clearance of clinically prescribed drugs.

Cytochrome P450 2C19 (CYP2C19) Enzyme

Drugs may be metabolized by more than one pathway involving several enzymes of the cytochrome P450 class. Cytochrome P450 enzyme 2C19 (CYP2C19) metabolizes many clinically important drugs including proton pump inhibitors, antidepressants, the antiplatelet drug clopidogrel, and the antifungal voriconazole.[4] Such drugs are considered 'substrates' of 2C19 (Table 1) and their clinical efficacy can vary based upon an individual's 2C19 genotype and corresponding phenotype.

Table 1. Common Substrates of CYP2C19[5]

Common Substrates of CYP2C19	
Proton Pump Inhibitors	• Lansoprazole/Dexlansoprazole • Omeprazole/Esomeprazole • Rabeprazole • Pantoprazole
Antiepileptics	• S-Mephenytoin • Diazepam • Phenobarbital • Phenytoin • Primidone
Antidepressants	• Amitriptyline • Citalopram • Clomipramine • Moclobemide • Imipramine • Desipramine • Sertraline
Antibiotics	• Chloramphenicol
Antifungals	• Voriconazole
Anticancer	• Nilutamide • Cyclophosphamide • Neniposide
Other	• Clopidogrel • Carisoprodol • Indomethacin • Mephobarbital • R-warfarin* • Hexobarbitol • Nelfinavir • Propranolol • Progesterone • Proguanil

*Warfarin consists of a mixture of equal parts S-warfarin and R-warfarin. S-warfarin has more potent anticoagulant activity, and is metabolized by CYP2C9.[5]

Pharmacogenetics 101[6]

The genetic variation between CYP2D6 alleles may be single nucleotide polymorphisms (SNPs), or it may be structural variations such as deletions or insertions.

Single Nucleotide Polymorphism (SNP) - Genetic variation arising from substitution of one base pair in DNA for another base pair is referred to as a SNP.

Haplotype - Combinations of several SNPs together on the same chromosome or in the same gene are called haplotype.

Alleles - Alternative forms of a gene that arise by mutations in the DNA.

Genotype - A genotype is an individual's collection of genes. The term also can refer to the two alleles inherited for a particular gene. The genotype is expressed when the information encoded in the gene is used to make protein.

Phenotype - The expression of the genotype contributes to the individual's observable traits, called the phenotype.

CYP2C19 Metabolizer Phenotypes

The CYP2C19 genotype of a patient affects the level of enzyme activity ("phenotype"). CYP2C19 phenotype can be classified into four groups:[7]

Extensive Metabolizers (EMs) have *normal* enzymatic activity

Intermediate Metabolizers (IMs) have *reduced* enzymatic activity

Poor Metabolizers (PMs) have *very low or absent* enzymatic activity

Ultra-rapid Metabolizers (UMs) have *increased* enzyme activity

The UM phenotype can cause therapeutic resistance or inefficacy at standard doses of a drug; higher doses may be required in UMs to obtain efficacy.[8] The PM phenotype is associated with reduced clearance and increased risk of adverse drug reactions.[9]

CYP2C19 variants affect metabolism of many clinically important drugs. For example, the antiplatelet drug clopidogrel is metabolized to its active metabolite by CYP2C19. Because IMs and PMs for CYP2C19 have reduced ability to produce the active metabolite, the efficacy of clopidogrel treatment is decreased, and the patient's risk for cardiovascular events increases.[10]

In 2010, the FDA added a black box warning to the label of clopidogrel stating that CYP2C19 PMs exhibit higher cardiovascular event rates following acute coronary syndrome or percutaneous coronary intervention than patients with normal CYP2C19 function. The warning also states tests are available to determine a patient's CYP2C19 genotype, and alternative treatments should be considered for CYP2C19 PMs.

The efficacy of proton pump inhibitor therapy is also affected by CYP2C19 genotype. Patients that carry one or more loss of function variants have higher plasma drug levels, increasing the efficacy of *Helicobacter pylori* eradication with therapy that includes proton pump inhibitors. However, patients with the EM or UM phenotype may have an insufficient response and may require a higher dose.[11]

Frequency of CYP2C19 Variation

The prevalence of CYP2C19 genotypes varies in the general population, with up to 45% of patients experiencing some reduced 2C19 function (Table 4). The prevalence of CYP2C19 genotypes also varies across ethnic groups. Approximately 2% of Caucasians, 4% of African Americans and 14% of Asians are poor CYP2C19 metabolizers.

Table 2: Prevalence of CYP2C19 Phenotypes in the General Population[12]

2C19 Phenotype	Percent of patients with phenotype
Extensive	35-50
Intermediate	18-45
Poor	2-15
Ultra-rapid	5-30

Conclusion

The Luminex xTAG® CYP2C19 Kit v3 assay offers a cost-effective genotyping solution with coverage of major clinically relevant CYP2C19 alleles demonstrating accurate performance across a large number of samples.[13] Pre-emptive genotyping for CYP2C19 may help identify patients at risk and act may aid clinicians in determining therapeutic strategy for drugs metabolized by the CYP2C19 gene product.

Identification of patient CYP2C19 genotypes may help

physicians tailor drug treatment to patients through the selection of appropriate therapies. These measures may improve a physician's ability to impact patient outcome by ensuring maximum drug efficacy with minimal adverse drug reactions.[14]

xTAG CYP2C19 Kit v3 (US-IVD)

Intended Use:

The xTAG CYP2C19 Kit v3 is an in vitro diagnostic test used to simultaneously detect and identify a panel of nucleotide variants found within the highly polymorphic CYP450 2C19 gene, located on chromosome 10q24, from genomic DNA extracted from EDTA or citrate anticoagulated whole blood samples. The xTAG CYP2C19 Kit v3 is a qualitative genotyping assay which can be used as an aid to clinicians in determining therapeutic strategy for the therapeutics that are metabolized by the CYP2C19 gene product, specifically *2, *3, and *17. The kit is not indicated for stand-alone diagnostic purposes. This test is not intended to be used to predict drug response or non-response.

The xTAG CYP2C19 Kit v3 is indicated for use with the Luminex® 100/200™ instrument or MAGPIX® with xPONENT® software systems.

Assay Limitations

Only alleles listed in Table 1 of the package insert for the xTAG CYP2C19 Kit v3 will be identified by this product. Other CYP2C19 alleles, which are rare, or were unknown at the time of release of this product, will not be identified by this product. These other alleles may result in either a *1 call, a no-call, or a call of a genetically related allele included in this kit. A *1 call or the call of a genetically related allele may result in a phenotype prediction that is different from the phenotype prediction that would be made if the presence of the rare allele were known. However, as with all phenotype predictions for the assay, the genetics of the 2C19 locus are only part of the phenotype prediction. The 2C19 phenotype is also affected by concomitant medications, age, body size, gender, renal and liver function, disease status, and lifestyle factors.

This test is not intended to be used to predict drug response or non-response. The results obtained using the xTAG CYP2C19 Kit v3 should be used and interpreted in the context of a full clinical evaluation. Luminex Molecular Diagnostics, Inc. is not responsible for any clinical decisions that are taken.

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