CYP2C19 Genotyping Assay: Genetics and Clinical Overview

Test Information:
CYP2C19 Genotyping Assay (CMGDL test code 4001)
For sample collection, transport and testing information refer to the CMGDL website www.medgen.med.miami.edu.
See the link for additional test ordering information such as CPT codes, test methodology and limitations.

Genetics, Epidemiology and Clinical Overview

Cytochrome P450 2C19, CYP2C19, is an isoenzyme of the cytochrome P450 super family and plays an important role in the metabolism of many commonly used drugs (Wang, 2011). Large inter-individual differences have been observed in the metabolism of these drugs in vivo, and individuals can be divided into normal (also called “extensive” metabolizer, EM), intermediate metabolizer (IM), poor metabolizers (PMs), and ultra-rapid metabolizers (UM). These differences can primarily be attributed to CYP2C19 genetic polymorphisms (de Morais et al., 1994a,b).

The CYP2C19 gene has nine exons and is located on chromosome 10. To date, more than thirty CYP2C19 Single Nucleotide Polymorphisms (SNPs), from which over twenty haplotypes were identified, are presented on the CYP2C19 allele nomenclature website (http://www.cypalleles.ki.se/cyp2c19.htm ). Genetic variations in the CYP2C19 gene are inherited in an autosomal recessive pattern of inheritance with a penetrance that is drug dependent (Mega et al., 2009; Simon et al., 2009; Nakamoto et al., 2007; Wang, 2011).

CYP2C19 mutation frequency varies among different ethnicities. The most predominant genetic defects responsible for the PM phenotype result from two SNPs, CYP2C19*2 (c.681G>A) and CYP2C19*3 (c.636G>A). In studies of PMs across global populations, these two SNPs have been proposed to explain anywhere from less than 50% to more than 90% of the PM phenotype (Nakamoto et al., 2007). The *2 allele is found in approximately 30% of Asians and 15% of Caucasians and African-Americans. The *3 allele is present in approximately 8% of Asians and is present less than 1% of Caucasians and African-Americans. A PM phenotype (ie the presence of two non-functional CYP2C19 alleles) is approximately present in 4% of Caucasians, 5% of African-Americans and 20-25% of Asians.

CYP2C19*17 (-808C>T) causes an increase in transcriptional activity, resulting in ultra-rapid metabolism of CYP2C19 substrates (Sim et al., 2006; Rudberg et al., 2008).

Genotype allelic combinations and related Phenotypes

Genetic variations in the CYP2C19 gene lead to inappropriate concentrations of drugs and drug metabolites, which may contribute to toxicity and risk of adverse drug reactions or lack of therapeutic benefit. Determining the CYP2C19 genotype can help by determining the metabolizer phenotype:

- **CYP2C19 Extensive (Normal) Metabolizer (EM):** when no mutations are detected by the genotyping assay, presence of normal *1 alleles is suggested. Normal CYP2C19 enzyme activity and normal metabolizer phenotype is expected when two normal *1 alleles are considered to be present;
- **CYP2C19 Intermediate to Normal Metabolizer:** this phenotype is suggested by the presence of one CYP2C19 allele with no function (eg *2 or *3) or one CYP2C19 allele with decreased function (eg *9);
- **CYP2C19 Intermediate Metabolizer (IM):** this phenotype is suggested by the presence of two CYP2C19 alleles with decreased function or one CYP2C19 allele with decreased function and one CYP2C19 non-functional allele;
- **CYP2C19 Poor Metabolizer (PM):** this phenotype is suggested by the presence of two CYP2C19 non-functional alleles;
- **CYP2C19 Rapid and Ultra-Rapid Metabolizer (UM):** this phenotype is suggested by the presence of one or two CYP2C19 non-functional alleles (eg *17).

Clinical Significance and Test Indications

The clinical impact of the CYP2C19 genotype is influenced by whether a drug is activated (e.g. clopidogrel, tamoxifen) or inactivated (e.g. amitryptiline, escitalopram) by the CYP2C19 enzyme.

Involvement of other metabolic pathways, and other non-genetic factors such as concurrent intake of other medications may also influence the clinical impact of the CYP2C19 genotype.

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This test is indicated in patients candidate or undergoing drug therapy with drugs metabolized by the CYP2C19 isoenzyme. The test may also be indicated for patients with personal or family history positive for adverse effects to drugs metabolized by CYP2C19. In particular, the test may be indicated if the following drugs are considered:

**Clopidogrel (Plavix®)** (instead of test code 4001, order “Clopidogrel Sensitivity CYP2C19 Genotyping assay”, test code 4101)

Clopidogrel is an antiplatelet drug used in atherothrombotic diseases, such as myocardial infarction and stroke, which is an inactive prodrug that needs to be bioactivated by the CYP2C19 enzyme.

Among persons treated with clopidogrel, carriers of CYP2C19 reduced-function alleles had significantly lower levels of the active metabolite of the drug, diminished platelet inhibition, and a higher rate of subsequent cardiovascular events than did non carriers (Mega et al., 2009; Simon et al., 2009). An increase in the daily dose is somehow a possibility although the best advice is to consider changing clopidogrel for a CYP2C19-independent drug (e.g. prasugrel or ticagrelor) (Becquemont L et al, 2011), in particular for carriers of two non-functional alleles (e.g. *2 and/or *3). Monitoring of platelet function may also be considered.

In contrast, the CYP2C19*17 allele has been significantly associated with an enhanced response to clopidogrel and an increased risk of bleeding (Sibbing et al., 2010);

Antidepressants such as Amitriptyline and Escitalopram

Determining the CYP2C19 genotype, in combination with drug monitoring once therapy is initiated, may help in titrating the medication dosage.

- If a patient carries the CYP2C19 *2 or *3 alleles higher plasma concentrations of the drug and slower clearance may be observed;
- If a patient carries the CYP2C19 *17 alleles may show lower plasma concentrations and higher clearance.

Tamoxifen

If a patient carries the CYP2C19*17 alleles higher concentrations of the active metabolite endoxifen are produced, with decreased breast cancer recurrence when treated with tamoxifen. Note that the response to tamoxifen is not expected to be affected by decrease function alleles such as the CYP2C19 *2 allele.

References

- Pharmacogenomics Knowledge Database (http://www.pharmgkb.org/)
- Home Page of the Human Cytochrome P450 (CYP) Allele Nomenclature Committee (www.cypalleles.ki.se/)
- Drug Interactions and CYP (http://medicine.iupui.edu/cinpharm/dis/) (instead of test code 4001, order “Clopidogrel Sensitivity CYP2C19 Genotyping assay”, test code 4101)

Note

The following is a list of drugs metabolized through the CYP2C19 enzyme that may be affected by these variants:

- proton pump inhibitors (lansoprazole, omeprazole, pantoprazole, and rabeprazole);
- antiepileptics (diazepam, phenytoin(O), S-mephenytoin, phenobarbital, R-mephobarbital, primidone);
- antidepressants (amitriptyline, citalopram, clomipramine, imipramine, moclobemide);
- anti-thrombotics (R-warfarin, clopidogrel); NSAIDs (indomethacin);
- antimicrobials (chloramphenicol, pentamidine);
- others (carisoprodol, cyclophosphamide, hexobarbital, nelfinavir, nilutamide, progesterone, progynan, propranolol, teniposide, Voriconazole).

Please note that this is not an all-inclusive list.