CYP2C19 genotyping (Clopidogrel pharmacogenetic testing)

CYP2C19 is an enzyme, which plays an important role in biotransformation of various medications (for example, antidepressants). Clopidogrel is one of the medications that this enzyme transforms.

Clopidogrel is a platelet aggregation inhibitor. It is a second generation thienopyridine antiplatelet medication.

Clopidogrel reduces the risk of myocardial infarction and ischemic stroke in patients with acute coronary syndrome or atherosclerotic vascular disease. Clopidogrel also reduces the risk of stent thrombosis.

Clopidogrel prevents platelet aggregation by inhibiting P2Y12 receptor of platelets.
However, clopidogrel itself is not an active form of the medication. First, it needs to be transformed into an active metabolite in order to inhibit the P2Y12 receptor. CYP2C19 is one of the important enzymes which participates in this biotransformation and it belongs to cytochrome P450 enzymes.

In some patients, treatment with clopidogrel does not achieve the desired effect and these patients remain under a higher risk of thrombosis. One of the reasons, that may be causing this, is the variation of the gene encoding CYP2C19 enzyme. CYP2C19 genotyping test is used to detect these genetic variations. This test is performed using the PCR (polymerase chain reaction) method.

CYP2C19 genotyping can show which variants of the gene are present in the individual and as a result, how they can affect clopidogrel metabolism.

CYP2C19*1 is a wild type allele and in this case, CYP2C19 normally metabolizes clopidogrel.
CYP2C19*2 and CYP2C19*3 alleles are no function alleles – they are associated with impaired metabolism of clopidogrel.
It needs to be noted, that CYP2C19*2 and CYP2C19*3 are relatively well-studied through scientific research. Other non-functional alleles, for example CYP2C19*4–*8, are less studied, however they might be affecting clopidogrel metabolism in a similar way.
On the other hand, CYP2C19*17 allele is associated with an increased activity of CYP2C19 enzyme.

Overall, the extent of clopidogrel metabolism impairment depends on the allele combination in an individual. Based on this combination, several categories of patients can be defined:

- Poor metabolizers – in these individuals both alleles are non-functional (for example, *2/*3, *2/*2, *3/*3);
- Intermediate metabolizers – these individuals have a single non-functional allele in addition to a normal or increased-function allele (for example, *1/*2, *1/*3);
- Normal metabolizers – in these individuals both alleles are normal function alleles (*1/*1);

- Rapid metabolizers – these individuals have one normal function allele and one increased function allele (*1/*17);
- Ultra-rapid metabolizers – in these individuals both alleles are increased function alleles (*17/*17).

In patients with poor or intermediate metabolism of clopidogrel, platelet inhibition by this medication is impaired. Therefore, despite treatment, these patients remain under an increased risk of stent thrombosis, myocardial infarction and ischemic stroke.

Patients with poor metabolism of clopidogrel might require alternative medications (for example, prasugrel, ticagrelor).
Clopidogrel alternatives or high dosage is needed in patients with intermediate metabolism of clopidogrel.
On the other hand, rapid and ultra-rapid metabolizers may have an increased risk of bleeding.

When interpreting the results of this test, it is essential to remember that CYP2C19 is not the only factor that might affect clopidogrel metabolism or the outcome of the treatment.

Sources:

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