CYP2C19 Gene

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Cytochrome P450 Family 2 Subfamily C Member 19

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1. Normal Function

The *CYP2C19* gene is a member of the cytochrome P450 gene family. Enzymes produced from cytochrome P450 genes are involved in the formation and breakdown (metabolism) of various molecules and chemicals within cells. The *CYP2C19* gene provides instructions for making an enzyme that is found primarily in liver cells in a cell structure called the endoplasmic reticulum, which is involved in protein processing and transport.

The CYP2C19 enzyme plays a role in the processing or metabolizing of at least 10 percent of commonly prescribed drugs, including a drug called clopidogrel (also known as Plavix). Clopidogrel is an antiplatelet drug, which means that it prevents blood cells called platelets from sticking together (aggregating) and forming blood clots. The CYP2C19 enzyme converts clopidogrel to its active form, which is necessary for the drug to function in the body. The active drug then stops (inhibits) a receptor protein known as P2RY12 that is found on the surface of platelets. During clot formation, the P2RY12 receptor protein helps platelets cluster together to form a clot in order to seal off damaged blood vessels and prevent blood loss.

2. Health Conditions Related to Genetic Changes

2.1 Clopidogrel Resistance

Multiple variations (polymorphisms) in the *CYP2C19* gene have been associated with clopidogrel resistance, a condition in which the drug clopidogrel is less effective than normal in people who are treated with it. The polymorphisms that are associated with clopidogrel resistance decrease the enzyme's ability to convert the drug to its active form.

The normal version of the gene, written as *CYP2C19*1*, provides instructions for producing a normally functioning CYP2C19 enzyme. If a person has two copies of the *CYP2C19*1* version of the gene in each cell, they are able to convert clopidogrel normally. The two most common *CYP2C19* gene polymorphisms associated with clopidogrel resistance (known as *CYP2C19*2* and *CYP2C19*3*) result in the production of a nonfunctional CYP2C19 enzyme that is unable to activate clopidogrel.

Individuals with clopidogrel resistance can be classified into two groups: intermediate metabolizers or poor metabolizers. People who have one copy of the *CYP2C19*1* version of the gene and one copy of either the *CYP2C19*2* or *CYP2C19*3* version of the gene have a reduced ability to convert clopidogrel to its active form and are classified as intermediate metabolizers. People who have the *CYP2C19*2* or *CYP2C19*3* versions of the gene for both copies of the gene can convert very little or none of the drug and are classified as poor metabolizers. Because conversion of clopidogrel to its active form is impaired in people with clopidogrel resistance, the drug is unable to inhibit P2RY12 receptor function. Without active clopidogrel to interfere, the P2RY12 receptor continues to promote platelet aggregation and blood clot formation, which can lead to heart attacks, strokes, and thromboses in individuals with a history of these conditions.

It is important to note that not all individuals with *CYP2C19* gene mutations have clopidogrel resistance. These individuals who are at increased risk for developing clopidogrel resistance may or may not have a bad reaction when treated with the drug. In addition to changes in specific genes, many other factors, including sex, age, weight, diet, and other medications, play a role in how the body reacts to clopidogrel.

2.2 Other Disorders

Polymorphisms in the *CYP2C19* gene that are associated with clopidogrel resistance (described above) can also affect the processing of other drugs. Because the CYP2C19 enzyme is involved in the metabolism of many drugs, changes to the enzyme can have wide-ranging effects. Other drugs that are affected by *CYP2C19* gene polymorphisms include proton pump inhibitors, used to treat stomach ulcers and other conditions; antidepressants, used to treat psychiatric disorders; anticonvulsants, used to treat seizure disorders; hypnotics and sedatives, used as sleep aids; antimalarial drugs, used to prevent malarial infections; and antiretroviral drugs, used to prevent viruses from replicating.

Most often, changes in the *CYP2C19* gene lead to impaired metabolism of these drugs, which reduces their effectiveness. One change in the *CYP2C19* gene (known as *CYP2C19*17*) increases the enzyme's ability to metabolize drugs. Individuals with two copies of the *CYP2C19*17* polymorphism are typically classified as ultra-rapid metabolizers.

3. Other Names for This Gene

- (R)-limonene 6-monooxygenase
- (S)-limonene 6-monooxygenase
- (S)-limonene 7-monooxygenase
- CPCJ
- CYP2C
- CYPIIC17
- CYPIIC19
- cytochrome P-450 II C
- cytochrome P450 2C19 precursor
- cytochrome P450, subfamily IIC (mephenytoin 4-hydroxylase), polypeptide 19
- cytochrome P450-11A
- cytochrome P450-254C
- flavoprotein-linked monooxygenase
- mephenytoin 4'-hydroxylase
- mephenytoin 4-hydroxylase
- microsomal monooxygenase
- P450C2C
- P450IIC19
- S-mephenytoin 4-hydroxylase
- xenobiotic monooxygenase

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