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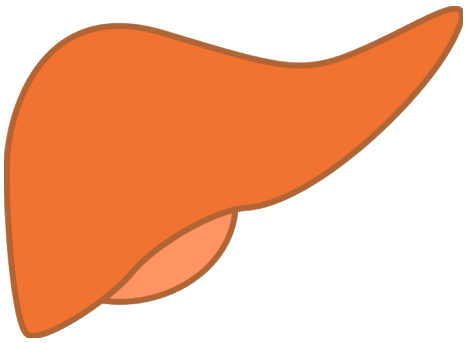
CYTOCHROME P450, FAMILY 2, SUBFAMILY C, POLYPEPTIDE 19 (CYP2C19)

A Drug Metabolism Gene

Biology Background

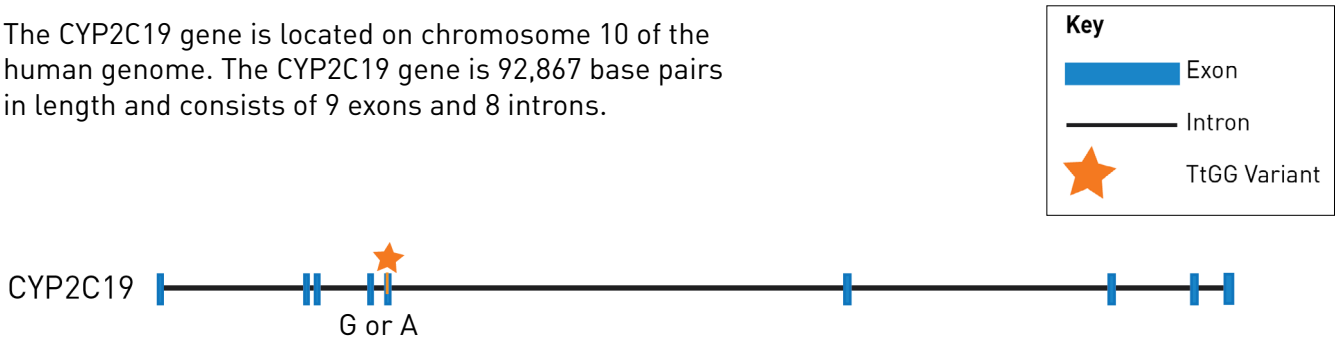
- The Cytochrome P450, family 2, subfamily C, polypeptide 19 (CYP2C19) gene produces the CYP2C19 protein. The CYP2C19 protein is an enzyme that catalyzes many reactions involved in drug metabolism and in the synthesis of cholesterol, steroids, and other lipids.
- The CYP2C19 protein is typically found on the endoplasmic reticulum within the cell.
- It is found in many cell types, notably in the liver and gastrointestinal tract.



Liver

Genomic Locus

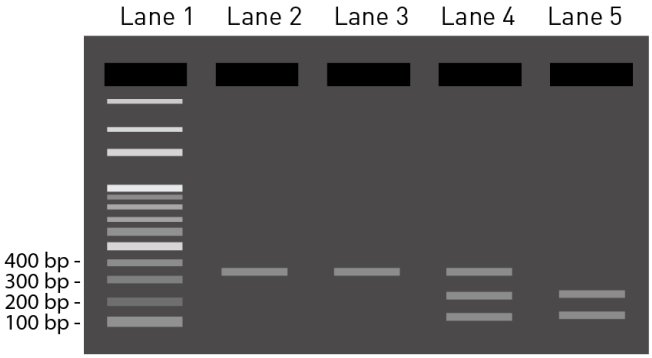
The CYP2C19 gene is located on chromosome 10 of the human genome. The CYP2C19 gene is 92,867 base pairs in length and consists of 9 exons and 8 introns.



The TtGG Variant

- In this assay, you are studying a single nucleotide polymorphism (SNP) in exon 5 of the CYP2C19 gene (see star). The nucleotide at this position is typically either a G or an A.
- The A variant produces an mRNA splice site in the middle of exon 5, removing 40 bp from the exon as compared to mRNA produced from the G allele.
- Since 40 bp is not a multiple of 3, this creates a frameshift in the mRNA produced from the A allele. The frameshift introduces a stop codon, producing a shortened protein.
- The G variant creates a site for the restriction enzyme SmaI to cut the DNA segment. Cut versus uncut DNA segments can be detected on a gel.

CYP2C19 Gel



Lane 1: DNA ladder
Lane 2: Undigested sample, 320 bp
Lane 3: Homozygous A genotype, 320 bp
Lane 4: Heterozygous GA genotype, 110 bp, 210 bp, 320 bp
Lane 5: Homozygous G genotype, 110 bp, 210 bp

Population Genetics

- Genetic variants within the CYP2C19 gene have been associated with differences in drug metabolism.
- Research has shown that the A allele, which produces a shortened protein, is the molecular explanation for a poor metabolizer phenotype for the drug mephenytoin, a medication used to control seizures.

Influence on Human Health

- Pharmacogenomics is the study of how genetic variants affect a person's drug metabolism and response.
- The goal is to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.
- The genes encoding the cytochrome P450 (CYP) enzymes have an important role in pharmacogenomics.
- By knowing which CYP variants are present in a patient's genome, researchers and physicians can better predict whether a medication will be effective and better guide prescription dosage, aiding in the prevention of adverse drug reactions.

Sources

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» Review on CYP2C19 impact on drug metabolism: Desta et al. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clinical Pharmacokinetics*. (2002)
» The Human Protein Atlas
» UCSC Genome Browser