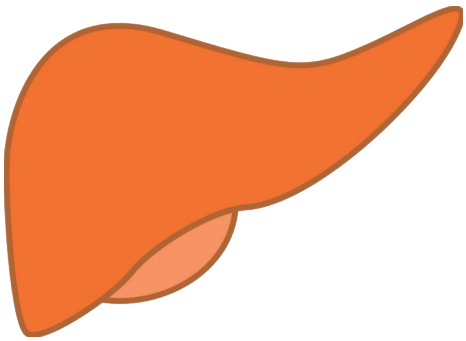
CYTOCHROME P450, FAMILY 2, SUBFAMILY C, POLYPEPTIDE 19 (CYP2C19)

A Drug Metabolism Gene

Biology Background

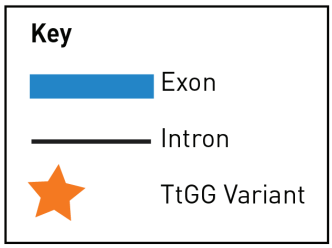
- The Cytochrome P450, family 2, subfamily C, polypeptide 19 (CYP2C19) gene produces the CYP2C19 protein, which is an enzyme that catalyzes many reactions involved in drug metabolism, synthesis of cholesterol, steroids, and other lipids.
- The CYP2C19 protein is localized on the endoplasmic reticulum within the cell.
- It is found in many cell types, notably in the liver and gastrointestinal tract (Human Protein Atlas).
- CYP2C19 is involved in the synthesis of cholesterol, steroids and other lipids by adding a hydroxyl group to an organic substrate.



Liver

Genomic Locus

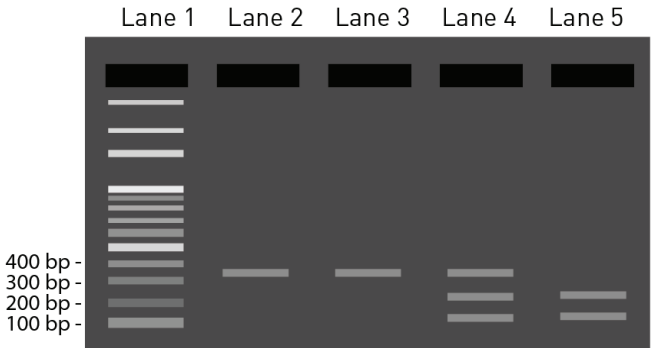
The CYP2C19 gene is located on chromosome 10 of the human genome.
The CYP2C19 gene is 90,209 base pairs consisting of 9 exons and 8 introns.



The TtGG Variant

- One common nonsense mutation is a transition (substitution) G>A at nucleotide 681 in exon 5 (see star).
- The mutation introduces an aberrant mRNA splice site in the middle of exon 5, removing an additional 40 bp from the exon.
- Since the size of this deletion is not a multiple of 3, it creates a frameshift mutation in the mRNA, introducing a downstream stop codon and results in a truncated protein.
- The G allele 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 G/A genotype, 110 bp, 210 bp, 320 bp
Lane 5: Homozygous G genotype, 110 bp, 210 bp

Population Genetics

- Genetic polymorphisms within the CYP2C19 gene have been associated with differences in drug metabolism.
- For example, the A truncated allele has been shown to be the molecular explanation for a poor metabolizer phenotype for the drug mephenytoin, an anti-convulsant 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 enzymes have an important role in pharmacogenomics.
- Knowing which variants are present can help predict whether a medication will be effective and guide prescription dosage aiding in prevention of adverse drug reactions.

Sources

-Online Mendelian Inheritance in Man (OMIM) http://omim.org/entry/124020
-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

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