

Gene Section

Mini Review

CYP2A6 (cytochrome P450, family 2, subfamily A, polypeptide 6)

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Identity

Other names: CPA6; CYP2A; CYP2A3; CYPIIA6; P450(I); P450C2A; P450PB

HGNC (Hugo): CYP2A6

Location: 19q13.2

Note: CYP2A6 plays a major role in the oxidation of nicotine, coumarin and some pharmaceuticals in human liver microsomes. Polymorphisms in the CYP2A6 gene that affect enzyme activity have been identified.

DNA/RNA

Description

9 exons. The gene sequence: 6910 bp.

Transcription

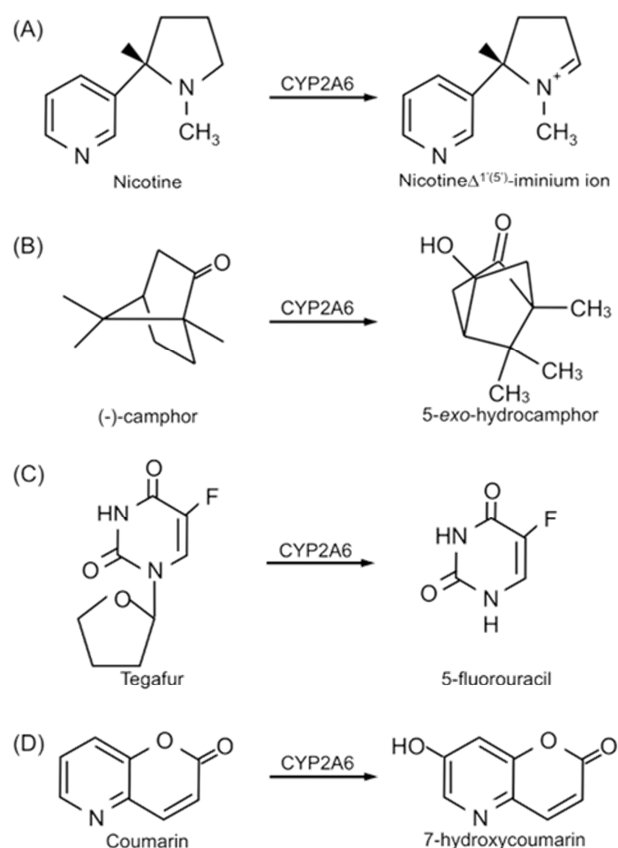
1751 base pairs.

Protein

Note

CYP2A6 is an enzyme responsible for the metabolism of clinically used pharmaceuticals such as coumarin and valproic acid, several carcinogens such as 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone and aflatoxin B1, nicotine and for the bioactivation process of tegafur to 5-FU.

The formation of 5-FU from tegafur was inhibited over 90% by a CYP2A6 selective antibody using human liver microsomes. CYP2A6 shows large interindividual and interethnic variations in its expression levels and conversion activities, which are mainly attributed to CYP2A6 genetic polymorphisms. The expression is induced by Phenobarbital and dexamethasone.



Example of CYP2A6 function.

(A) Oxidation: CYP2A6 is responsible for converting nicotine into the inactive metabolite nicotine $\Delta^{1'(5')}$ -iminium ion, cotinine. (B) Oxidation: Camphor is oxidized to 5-exo-hydroxycamphor. (C) Hydroxylation: CYP2A6 is an enzyme responsible for the metabolism of clinically used pharmaceuticals, tegafur. Tegafur is converted enzymatically to 5-FU to exert its antitumor activity. Tegafur is converted enzymatically to 5-FU to exert its antitumor activity. (D) Hydroxylation: Coumarin is hydroxylated to 7-hydroxycoumarin.

Description

494 amino acids.

Expression

Liver.

Localisation

Endoplasmic reticulum membrane, peripheral membrane protein, microsome membrane.

Function

Oxidation, reduction, coumarin 7-hydroxylase activity, electron carrier activity, heme binding, iron ion binding, oxygen binding, the hydroxylation of the anti-cancer drugs.

Homology

Belongs to the cytochrome P450 family.

Mutations**Note**

CYP2A6 shows large interindividual and interethnic variations in its expression levels and conversion activities, which are mainly attributed to CYP2A6 genetic polymorphisms. These alleles are derived from single nucleotide polymorphisms in the regulatory and coding regions, deletion mutations and conversions. Polymorphisms in the CYP2A6 gene affect enzyme activity. CYP2A6*2, a polymorphism that a single base mutation (1799T>A) cause an amino acid change from leucine at residue 160 to histidine, functionally shows no enzymatic activity in vivo and in vitro. While in Caucasian this type allele has been found in 1.1-3.0%, there is no report in Asian. CYP2A6*4C, which is a whole deleted allele for the human CYP2A6 gene, is a major mutant allele associated with decreased metabolic activity. CYP2A6*4C is relatively common in Asian populations, with estimated allele frequency of 20% in the Japanese, whereas the allele frequency is 0.5-1.0% in European. CYP2A6*7 and CYP2A6*9, a gene conversion in the 3' flanking region (6558T>C) and a point mutation in the TATA box (-48T>G), respectively, are associated with poor nicotine metabolism.

There are many alleles that have been listed by the Human CYP Allele Nomenclature Committee.

Implicated in**Lung cancer****Note**

Polymorphisms in the CYP2A6 gene that affect enzyme activity and susceptibility to lung cancer have been identified. Smoking is regarded as the main cause of lung cancer. CYP2A6 has responsible for the conversion of nicotine to inactive metabolite cotinine. A number of studies have demonstrated that CYP2A6 genetic variations are associated with nicotine kinetics

and smoking behavior. People with CYP2A6 genetic variations, poor metabolizers of CYP2A6, were less likely to be smokers and tended to smoke fewer cigarettes per day.

Disease

There is the possibility that CYP2A6 associated smoking-related cancer, such as lung cancer, esophageal, gastric and colorectal cancer.

Prognosis

Poor metabolizers of CYP2A6 were less likely to be smokers and tended to smoke fewer cigarettes.

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