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Gene Section
Review

CYP7A1 (cytochrome P450, family 7, subfamily A, polypeptide 1)

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Identity

Other names: CP7A; CYP7; CYPVII; EC 1.14.13.17; MGC126826; MGC138389

HGNC (Hugo): CYP7A1

Location: 8q12.1

Note: CYP7A1 catalyzes 7alpha-hydroxylation of cholesterol, the major rate-limiting step in bile acid biosynthesis. The enzyme also converts cholestanol and several oxysterols into their 7alpha-hydroxylated products (Norlin and Wikvall, 2007).

DNA/RNA

Description

The human CYP7A1 DNA maps to NM_000780 (Entrez Gene) and spans a region of 9.98 kb. CYP7A1 is located on chromosome 8 and consists of six exons.

Transcription

The full length CYP7A1 mRNA is 2,875 bp with an open reading frame of 1,512 bp (Noshiro and Okuda, 1990).

Pseudogene

No pseudogenes reported.

Protein

Description

The human CYP7A1 protein consists of 504 amino acids and has a molecular weight of 57,630 Da (Noshiro and Okuda, 1990). Human CYP7A1 shares 40% sequence identity with CYP7B1, the other member of the CYP7 family.

Expression

Most reports indicate exclusive liver specific expression. One study reports expression of CYP7A1 also in human prostate (Steckelbroeck et al., 2002). The expression of hepatic CYP7A1 in several species has been reported to be low in early life and to increase severalfold with age (Norlin, 2002; Massimi et al., 1998).

Localisation

CYP7A1 is an endoplasmic reticulum membrane enzyme.

Function

CYP7A1 is a cholesterol 7alpha-hydroxylase, catalyzing the first and rate-limiting step in the neutral or classic pathway for bile acid biosynthesis. Bile acid biosynthesis is the predominant pathway for cholesterol catabolism. The enzyme also 7alpha-hydroxylates 27-hydroxycholesterol and other oxysterols (Norlin et al., 2000a, b). Results supporting a role for CYP7A1 as an oxysterol 7alpha-hydroxylase are also reported by others (Dueland et al., 1992; Pandak et al., 2002). Studies on mice with a disruption in the Cyp7a1 gene (Ishibashi et al., 1996; Schwarz et al., 1996) demonstrated a crucial role for this enzyme in bile acid biosynthesis. Mice and humans with cholesterol 7alpha-hydroxylase deficiency exhibit, however, different phenotypes (Norlin and Wikvall, 2007).
Several mechanisms for regulation of CYP7A1 have been described (Chiang, 2004). Bile acids inhibit CYP7A1 gene transcription via negative feedback control. The feedback inhibition by bile acids involve several nuclear receptors such as liver receptor homolog 1 (LRH-1), hepatocyte nuclear factor 4alpha (HNF4alpha), small heterodimer partner (SHP) and the

bile acid receptor farnesyl X receptor (FXR). Also the pregnane X receptor (PXR) and the vitamin D receptor (VDR) have been identified as bile acid-activated receptors (Staudinger et al., 2001; Han and Chiang, 2009). Bile acids are also reported to suppress CYP7A1 via stimulation of inflammatory cytokines (tumor necrosis factor alpha and IL-1beta) and mitogen-activated protein kinase (MAPK) signaling pathways leading to the activation of cJun N-terminus kinase (JNK). JNK may phosphorylate and inactivate transcription factors crucial for stimulating the hepatic expression of CYP7A1 (Chiang, 2004; Gupta et al., 2004). Cholestyramine, a drug used in the treatment of hyperlipoproteinemia, induces cholesterol 7alpha-hydroxylase by binding to bile acids in the intestine and preventing their reabsorption to the liver (Brown and Boyd, 1974). Evidence for a posttranscriptional regulation of cholesterol 7alpha-hydroxylase has been reported, but most of the data available suggest that the regulation is predominantly on a transcriptional level (Chiang, 2004; Stroup and Ramsaran, 2005).

Homology

The CYP7A1 gene is conserved in many species, such as chimpanzee, dog, cow, mouse, rat, chicken, and zebrafish.

Mutations

Germinal

A metabolic disorder presenting with elevated plasma cholesterol levels caused by a homozygous deletion mutation in the CYP7A1 gene in a family of English and Celtic origin has been described (Pullinger et al., 2002). The mutation leads to a frameshift resulting in the synthesis of a truncated protein with no enzymatic activity. High levels of LDL cholesterol were seen in three homozygous subjects. The high levels of LDL cholesterol in the CYP7A1-deficient subjects were found to be resistant to treatment with hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Two male subjects had hypertriglyceridemia and premature gallstone disease. One subject had premature coronary and peripheral vascular disease. Individuals that are heterozygous for the mutation were also found to be hyperlipidemic, indicating that the disorder is inherited in a codominant fashion (Pullinger et al., 2002). The authors concluded that CYP7A1 deficiency in humans causes hypercholesterolemia. This conclusion is consistent with studies showing an association between cholesterol levels and polymorphisms at the CYP7A1 locus (Wang et al., 1998; Couture et al., 1999).

Implicated in

Gallbladder cancer

Note

CYP7A1 promoter polymorphism has been reported to be a genetic risk factor for gallbladder cancer. The association of the polymorphism with gallbladder cancer was more pronounced in female patients, and also in cancer patients who developed gallbladder cancer at advanced age (Srivastava et al., 2008).

Colorectal cancer

Note

A link between genetic polymorphism of CYP7A1 and decreased risk of colorectal adenomas has been reported (Tabata et al., 2006). Bile acids have long been implicated in colorectal carcinogenesis. The CC genotype of the CYP7A1 A-203C polymorphism was associated with a decreased risk of proximal colon adenomas. The findings provide further evidence for the role of bile acids in colorectal carcinogenesis. The polymorphism of the CYP7A1 gene probably leads to lower activity of the enzyme synthesizing bile acids (Tabata et al., 2006).

Hypercholesterolemia/hyperlipidemia

Note

Due to its important regulatory role in cholesterol catabolism, decreased CYP7A1 levels may lead to hypercholesterolemia. Indeed, high cholesterol levels were seen in subjects having a frameshift mutation in the CYP7A1 gene resulting in the synthesis of a non-functional enzyme. The hypercholesterolemia was resistant to treatment with HMG-CoA reductase inhibitors. Two of the three subjects that were homozygous for this mutation also had elevated plasma triglyceride levels. Six individuals, heterozygous for the mutation were also found to have hypercholesterolemia (Pullinger et al, 2002). An association between plasma cholesterol levels and polymorphisms at the CYP7A1 locus have been shown in some reports (Wang et al., 1998; Couture et al., 1999) whereas another study reported that common polymorphisms in the CYP7A1 gene do not contribute to variations in plasma LDL concentrations (Abrahamsson et al., 2005).

Atherosclerosis

Note

One subject with the frameshift mutation in the CYP7A1 gene (as described above) had premature coronary and peripheral vascular disease (Pullinger et al., 2002). Polymorphism in the CYP7A1 gene has

been reported to be associated with subclinical atherosclerosis including the presence of atherosclerotic plaques in postmenopausal women (Lambrinoudaki et al., 2008). CYP7A1 polymorphism has also been reported to increase the progression of atherosclerosis and the risk of new clinical events in male patients (Hofman et al., 2005).

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