bile acid receptor farnesyl X receptor (FXR). Also the pregnan 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-terminal 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).

**References**


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