

## Gene Section

### Review

# NR1H4 (nuclear receptor subfamily 1, group H, member 4)

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## Abstract

Review on NR1H4, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

## Identity

**Other names:** BAR, FXR, HRR-1, HRR1, RIP14

**HGNC (Hugo):** NR1H4

**Location:** 12q23.1

## DNA/RNA

### Description

In humans, FXR is encoded by the NR1H4 gene, consisted of 11 exons and 10 introns.

### Transcription

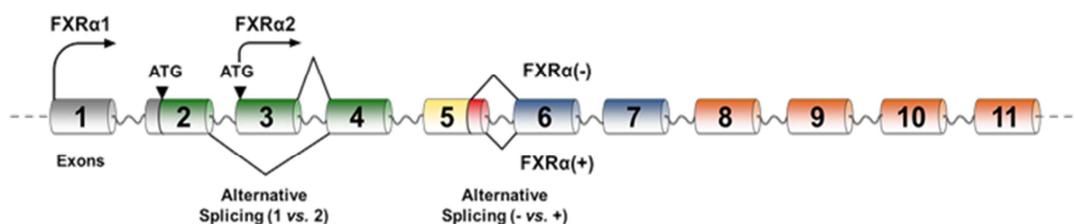
4 alternatively spliced transcript variants encoding different isoforms have been described for this gene.

Variants 3 and 4 contain an alternate 5'-terminal exon resulting in isoforms FXR $\alpha$ 2 longer than FXR $\alpha$ 1, coding by variants 2 and 5, with a distinct N-terminus due to translation initiation from an alternate in-frame start codon in the exon 3.

Use of an alternate in-frame donor splice site at exon 5 results in FXR $\alpha$ 1(-) and FXR $\alpha$ 2(-) variants that miss a 4 amino acid segment compared to FXR $\alpha$ 1(+) and FXR $\alpha$ 2(+) isoforms.

### Pseudogene

A pseudogene of FXR has been located on chromosome 1 (1p13.1-1p13.3) (Pseudogene.org).



**A. NR1H4 gene structure.** Schematic representation of the NR1H4 gene into 11 exons showing the alternative splicing and the start triplets that generate the 4 known isoforms. These have been classified according to the difference in the initial region of mRNA ( $\alpha$ 1 and  $\alpha$ 2) and the presence (+) or absence (-) of a 12-bp insert in the exon 5.

mRNA		Protein	
NM_001206979	Variant 1	NP_001193908	FXR $\alpha$ 1(+)
NM_001206977	Variant 6	NP_001193906	FXR $\alpha$ 1(+)
NM_005123	Variant 2	NP_005114	FXR $\alpha$ 1(-)
NM_001206978	Variant 5	NP_001193907	FXR $\alpha$ 1(-)
NM_001206993	Variant 3	NP_001193922	FXR $\alpha$ 2(+)
NM_001206992	Variant 4	NP_001193921	FXR $\alpha$ 2(-)

**B. NCBI reference sequences for FXR variants and isoforms.** Variants 1 and 6, and variants 2 and 5 encode the same isoforms.

## Protein

### Note

FXR is a ligand-activated transcription factor belonging to the nuclear receptor superfamily.

### Description

FXR shares the typical structure of other nuclear receptors, including the N-terminal DNA binding domain (DBD) and the C-terminal ligand binding domain (LBD) (Modica et al., 2010).

DBD contains two zinc fingers motifs involved in DNA binding and dimerization with RXR $\alpha$ .

Hinge region connects the DBD with the LBD, and contains the insert of the amino acid sequence MYTG in the FXR $\alpha$ 1/2(+) isoforms.

Ligand-independent (AF-1) and -dependent (AF-2) transactivation domains involved in the interaction with co-repressors and co-activators are located in N- and C-termini, respectively.

### Expression

FXR is expressed at high levels in the liver, small

intestine, kidney and adrenal gland (Huber et al., 2002). Lower FXR levels can be detected in other organs forming the gastrointestinal tract, pancreas, breast and endothelial cells.

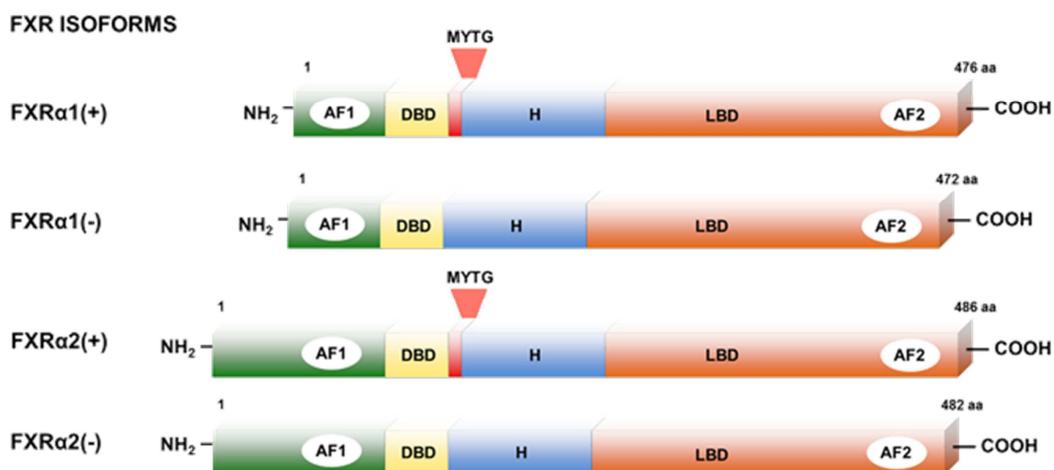
The liver predominantly expresses FXR $\alpha$ 1(+/-), whereas FXR $\alpha$ 2(+/-) are the most abundant isoforms in kidney and intestine. In all cases, the proportion of FXR $\alpha$ (1/2)(+) and FXR $\alpha$ (1/2)(-) isoforms is approximately 50% (Vaquero et al., 2013b).

### Localisation

When activated FXR translocates to the nucleus.

### Function

Binding of bile acids, the natural ligands of FXR, to the receptor leads its translocation to the cell nucleus, formation of a heterodimer RXR $\alpha$  and binding to FXR response elements on DNA, which activates the transcription of its target genes. Among FXR target genes are those encoding most of the proteins involved in bile acid metabolism and transport (Modica et al., 2010).



**FXR isoforms.** Schematic representation of FXR isoforms classified based on the presence of the exons 1 and 2 (FXR $\alpha$ 1) or 3 (FXR $\alpha$ 2) in the initial region of the mRNA and the presence (+) or the absence (-) of the amino acid sequence MYTG in exon 5. AF1 and AF2: ligand-independent and -dependent transactivation domains, respectively; DBD: DNA binding domain; H: hinge region; LBD: ligand binding domain.

Amino Acid Variation	Protein Domain	Genetic Localization	Nucleotide Variation	Reference SNP	MAF
		Intron 1	c.-190+7064C>T	rs111110390	T = 18.3%
		Intron 2	c.-189-1174G>A	rs4764980	G = 31.7%
		5'-UTR	c.-1G>T	rs56163822	T = 6.8%
M1V (FXR $\alpha$ 1)	AF-1 domain	Exon 3	c.1A>G	rs138943609	G = 0.1%
M173T (FXR $\alpha$ 1) and M183T (FXR $\alpha$ 2)	DNA binding domain	Exon 5	c.518T>C	rs61755050	C = 0.2%

**Definition, nomenclature, and allelic frequency of clinically relevant NR1H4 genetic variants.** MAF refers to the frequency at which the less common allele occurs in a given population according to the NCBI SNP database. Nucleotide positions refer to the ORF of the NM\_005123 sequence. Amino acid positions refer to the NP\_005114 (FXR $\alpha$ 1(-)) or NP\_001193921 (FXR $\alpha$ 2(-)) proteins. AF-1, ligand-independent transactivation domain.

Additional target genes have recently been described to be involved in FXR-mediated regulation of several body functions, such as prevention of hepatic and intestinal carcinogenesis, liver regeneration, intestinal barrier, attenuation of adverse effects of cholestasis, prevention of gallstone formation, and chemoprotection (Vaquero et al., 2013a). Some of the effects of FXR are mediated by the induction of the small heterodimer partner (SHP), a negative regulator encoded by the NR0B2 gene. This transcription factor interacts with other nuclear receptors blocking its activation. Glucocorticoids are able to directly activate FXR but they also antagonize the expression of FXR and its target genes (Rosales et al., 2013).

### Homology

DBD domain is a highly conserved domain, whereas LBD domain is moderately conserved in sequence and highly conserved in structure between the various nuclear receptors (Modica et al., 2010). According to sequence homology NR1H4 has been included into the liver-X-receptor-like group of genes belonging to the thyroid hormone receptor-like subfamily of nuclear receptors, together with NR1H2 (liver X receptor- $\beta$ ) and NR1H3 (liver X receptor- $\alpha$ ).

## Mutations

### Note

The presence of missense mutations in the NR1H4 gene is unusual, suggesting an important role of this gene in the maintenance of organ function and cellular homeostasis.

### Somatic

c.-1G>T is a common variation resulting in reduced translation efficiency (Marzolini et al., 2007) that might predispose to inflammatory bowel diseases (Attinkara et al., 2012) and intrahepatic cholestasis of pregnancy (Van Mil et al., 2007). c.-189-1174G>A and c.-190+7064C>T are intronic SNP that have been associated with an altered glucose

and lipid metabolism (Heni et al., 2013). c.1A>G and c.518T>C are two rare mutations in the coding sequence of FXR whose consequence is a reduction of the function of the protein. Both predispose to intrahepatic cholestasis of pregnancy (Van Mil et al., 2007). Implicated in

### Hepatocellular carcinoma and cholangiocarcinoma

#### Note

FXR is reduced in liver cancer suggesting that FXR is rather working as a tumour suppressor. Knockout mice for FXR spontaneously developed liver tumours after several months. A potential contribution of FXR in tumour suppression can be attributed to its anti-fibrogenic properties in liver. It has also been proposed a role of FXR in prevention of hepatocarcinogenesis by inhibiting the expression of gankyrin (PSMD10), which is activated in liver cancer and modifies the expression of tumour suppressor genes, including Rb, p53, C/EBP $\alpha$ , HNF4 $\alpha$ , and p16.

### Colon cancer

#### Note

Emerging evidences support an important role for FXR in intestinal carcinogenesis. FXR mRNA expression is decreased in colonic polyps, and even more pronounced in colonic adenocarcinoma. Even before carcinomas have formed, FXR loss led to extensive mucosal infiltration of neutrophils and macrophages along with increased TNF- $\alpha$  mRNA expression and nuclear  $\beta$ -catenin accumulation. FXR deficiency led to increased susceptibility to tumour development by promoting WTN- $\beta$ -catenin signalling through TNF- $\alpha$  released by infiltrated macrophages. In contrast to this indirect oncosuppressive role of FXR, by maintaining intestinal epithelium integrity, FXR also carries out a direct oncosuppressor activity. Thereby, several data suggest that FXR activation enhances apoptosis and inhibits cell proliferation by increasing the expression of proapoptotic genes

including p21, BAK1, FADD, and repressing antiapoptotic genes, such as BCL-2.

### **Chemoresistance**

#### **Note**

Ligand-dependent and independent activation of FXR and/or its signalling pathway is involved in the chemoprotective response of liver cells.

This is due in part to changes in the expression of several genes (ABCB4, TCEA2, CCL14, CCL15 and KRT13) accounting for different MOC, mainly these involved in drug efflux (MOC-1b), DNA repair (MOC-4) and cell survival (MOC-5b). Moreover, this characteristic is shared by healthy and tumour cells, and hence may play an important role in enhancing the chemoprotection of healthy hepatocytes against genotoxic compounds and reducing the response of liver tumour cells to certain pharmacological treatments.

#### **Disease**

The development of chemoresistance depends on the expression of the genes involved in a variety of mechanisms of chemoresistance (MOC), which are present in both healthy tissues, where they are involved in the defence against the chemical stress caused by potentially toxic compounds, and in cancer cells, where they account for the poor response to antitumour drugs.

### **Cholestasis**

#### **Note**

FXR has a crucial role in maintaining bile acid homeostasis, especially during cholestasis. Upon activation by enhanced bile acid levels FXR mediates responses that partially protect the hepatocyte from the deleterious effect of accumulation of toxic bile acids.

FXR inhibits bile acid synthesis in liver, through down-regulation of key enzymes in bile acid biosynthesis, such as CYP7A1 and CYP8B1. It also diminishes bile acid uptake by hepatocytes by repressing the expression of Na<sup>+</sup>-taurocholate cotransporting polypeptide or NTCP (gene symbol SLC10A1), and increases bile acid efflux by inducing the expression of ABC proteins at the canalicular membrane, such as including BSEP (ABCB11) and MDR3 (ABCB4) involved in bile acid-dependent phospholipid secretion. FXR up-regulates the phase II enzymes uridine 5'-diphosphate-glucuronosyltransferase 2B4 (UGT2B4) and sulphotransferase 2A1 (SULT2A1), which glucuronidate or sulphate bile acids to render them more hydrophilic, less biologically active, and more easily to be eliminated from the body. In the intestine FXR-induced reduction of bile acid uptake by enterocytes due to transcriptional repression of ASBT (SLC10A2), which enhances bile acid faecal loss. Moreover, FXR increases the transcription of FGF19 in the ileum, triggering a signalling pathway

that represses hepatic CYP7A1 expression, and hence down-regulation of bile acid synthesis.

#### **Disease**

Cholestasis, which is characterized by the accumulation of bile acids in liver and is associated with reduced detoxification capacity.

### **Cirrhosis**

#### **Note**

FXR is expressed in hepatic stellate cells, and its activation reduces the expression of extracellular matrix proteins by these cells, preventing liver fibrosis.

#### **Disease**

Cirrhosis is a result of advanced liver disease that is characterized by replacement of liver tissue by fibrosis and regenerative nodules, leading loss of liver function.

### **Cholelithiasis**

#### **Note**

FXR prevents gallstone formation by up-regulation of ABC proteins accounting for canalicular secretion of bile acids (BSEP) and phospholipids (MDR3), resulting in enhanced mixed micelle formation capability and, hence prevention of cholesterol crystallization in bile.

#### **Disease**

Cholelithiasis is a pathological situation characterized by presence in the gallbladder, of stones, a crystalline concretion formed by accretion of bile components.

### **Hepatic regeneration**

#### **Note**

FXR participates in bile acid-induced liver repair by promoting regeneration through regulation of the FoxM1b expression, a Forkhead Box transcription factor, which regulates cell cycle progression during liver regeneration. Moreover, FXR helps restoration of organ homeostasis.

#### **Disease**

Liver regeneration after loss of hepatic tissue is an adaptive response to repair injury consisting of induction of proliferative factors that activate the quiescent hepatocytes, followed by re-establishment of normal liver size and renewed hepatocyte quiescence.

### **Intestinal diseases**

#### **Note**

FXR plays an important role in the protection against bacterial overgrowth and the maintenance of intestinal barrier function, and it has recently been involved in the pathogenesis of idiopathic inflammatory bowel disease. FXR activation in the intestinal tract decreases the production of proinflammatory cytokines such as IL-1-β, IL-2, IL-

6, tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interferon- $\gamma$  (IFN- $\gamma$ ), thus contributing to a reduction of inflammation and epithelial permeability. In addition, intestinal FXR activation induces the expression of genes with antibacterial properties involved in enteroprotection and prevention of bacterial translocation in the intestinal tract, including angiogenin, carbonic anhydrase 12 or inducible nitric oxide synthase.

#### Disease

Intestinal bacterial proliferation and translocation, chronic diarrhoea and inflammatory bowel disease.

## Breakpoints

#### Note

NR1H4 gene is not involved in breakpoint regions.

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