

Gene Section

Review

HNF4A (Hepatocyte Nuclear Factor 4 alpha)

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Published in Atlas Database: June 2016

Online updated version : <http://AtlasGeneticsOncology.org/Genes/HNF4AID44014ch20q13.html>

Printable original version : <http://documents.irevues.inist.fr/bitstream/handle/2042/68157/06-2016-HNF4AID44014ch20q13.pdf>

DOI: 10.4267/2042/68157

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Abstract

Hepatocyte nuclear factor 4 alpha (HNF4A) also known as NR2A1 (Nuclear Receptor Subfamily 2, group A, member 1) is a member of the nuclear receptor (NR) superfamily of ligand-dependent transcription factors. The encoded protein controls the expression of several genes, especially those that play distinct roles in development,

differentiation, embryogenesis and organogenesis.

Keywords: HNF4A

Identity

HGNC (Hugo): HNF4A

Location

The human HNF4A gene is located on 20q12-q13.1

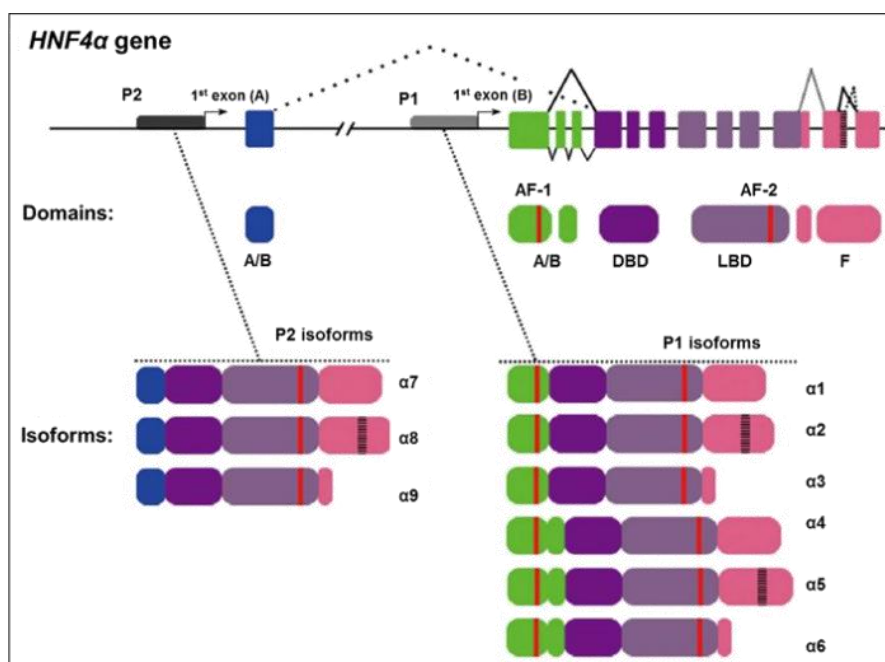


Figure 1 HNF4A transcripts. HNF4A contains two distinct promoters (P1 and P2) that drive expression of 9 known isoforms ($\alpha 1$ to $\alpha 9$) of the gene. Transcription through the P1 promoter allows transcription starting from exon 1 (B) coding for the N-terminal domain of HNF4A, designated as AF-1. Transcription through the P2 promoter allows the inclusion of exon 1 (A) but the exclusion of the exon 1 (B). Although alternative splicing of exon 1 (B) modifies only A/B domain of the P1 isoforms, F domains of both isoforms are modified by alternative splicing of the last exons. DBD: DNA binding domain; LBD: Ligand binding domain; AF-1: Activating function-1; AF-2: Activating function-2 (Modified from Babeu and Boudreau, 2014).



Figure 2 HNF4A domains. AF-1: activation function; DBD: DNA binding function; LBD: ligand binding function; F domain: repressor function that inhibits access of coactivators to NCOA5 (AF-2) which function in homodimerization and activation. H: hinge region.

DNA/RNA

Description

The human HNF4A gene spans ~77 kb.

Transcription

The HNF4A gene is composed of thirteen exons and contains two promoters, P1 and P2, which can drive the expression of many splice variants (HNF4A1-HNF4A9) that differ in the variable A/B and F domains (Harries et al., 2008). The variants derived from the P1 and P2 promoters are referred to as HNF4A1-HNF4A6 and HNF4A7-HNF4A9, respectively (Erdmann et al., 2007).

The different promoters are used in different tissues and at different times during development, and the encoded protein controls the expression of several genes. Multiple isoforms are proposed to exist in mammals and are thought to have different physiological roles in development and differentiation (Walesky and Apte, 2015).

Protein

Description

Domain structure and DNA binding

HNF4A consists of six structural domains named A-F that are responsible for specific functions: an N-terminal activation domain (AF-1, also referred to as A/B domain); a zinc finger domain that serves as the DNA-binding domain (DBD; C domain) which is highly conserved among NRs; a putative ligand binding domain (LBD; E domain); and a C-terminal domain which functions in homodimerization and activation (AF-2), and a repressor region (F domain) that inhibits access of coactivators to AF-2, and possibly to other regions (Walesky and Apte, 2015). The DBD consists of two zinc fingers, and 12 alpha helices that create a hydrophobic pocket for ligand binding (Duda et al., 2004) (Figure 2).

HNF4A binds DNA regulatory elements as a homodimer. E domain (Ligand Binding Domain-LBD) appears to be critical for homodimerization and to play a role in preventing heterodimerization with other NRs such as RXR or RAR (Bogan et al., 2000). HNF4A binds DNA response elements consisting of direct repeats. It can also bind several different co-activators (such as GRIP1, NCOA1, NCOA2, NCOA3, (SRC1, 2 and 3), CREBBP

(CBP/P300), PPARGC1A (PGC1)) (Martínez-Jiménez et al., 2006).

Expression

Multiple HNF4A isoforms exist in humans and are suggested to have different physiological roles in development and transcriptional regulation of target genes (Figure 1). HNF4A1 and 2 isoforms from the P1 promoter are expressed in the liver (hepatocytes), kidneys, small intestine and colon. HNF4A3 and 4 are expressed in human liver. P2 promoter-driven HNF4A7 and 8 are expressed in the fetal liver and adult pancreas (β -cells) and to a lesser extent in the adult liver (bile ducts), small intestine, colon and stomach. HNF4A isoforms from both the P1 and P2 promoter were also reported to be expressed in the epididymis (Tanaka et al., 2006). However, not much is known about the developmental and physiological relevance of the HNF4A isoforms (Boyd et al., 2009).

In addition to several different isoforms produced from the HNF4A gene by different promoter usage and alternative splicing, the 3'UTR of the gene was also reported to control HNF4A expression (Wirsing et al., 2011).

Localisation

Localized primarily in the nucleus.

Function

HNF4A can exist in an unliganded form, or may bind to linoleic acid (LA), an essential fatty acid (Yuan et al., 2009). Although it is not yet clear whether ligand binding affects the function of HNF4A, the HNF4A transcriptional activity is regulated at several different levels. Most prominent among the post-translational modifications of HNF4A is phosphorylation which occurs mainly at serine and to a lesser extent at threonine residues (Jiang et al., 1997). Between the kinases, PRKACA (protein kinase A, PKA) dependent phosphorylation of HNF4A was reported to inhibit recruitment to target genes (You et al., 2002). On the other hand, activation of MAP kinase pathway was shown to down-regulate HNF4A transcription (Reddy et al., 1999). AMP-activated protein kinase was also implicated in the regulation of HNF4A activity by inhibiting dimer formation and decreasing protein stability (Hong et al., 2003). p38 kinase-mediated Ser158 phosphorylation was also shown to increase DNA binding and transactivation potential of

HNF4A (Guo et al., 2006), and Ser78 phosphorylation of HNF4A by PRKCB (protein kinase C, PKC) was shown to down-regulate HNF4A protein level via the proteasome pathway (Sun et al., 2007).

Acetylation was also implicated in the regulation of HNF4A function (Soutoglou et al., 2000; Yokoyama et al., 2011). Soutoglou et al. showed that CREB-binding protein (CBP) acetylates HNF4A on lysine residues within the nuclear localization sequence, and increase nuclear retention and target gene activation by HNF4A (Soutoglou et al., 2000).

Methylation and SUMOylation are the other post-translational mechanisms that regulate HNF4A activity. Methylation of the DNA-binding domain of HNF4A by PRMT1 (Protein Arginine Methyltransferase 1), whose methylation activity on HIST4H4 (histone H4) strongly correlates with the induction of HNF4A target genes in differentiating enterocytes, increased transcriptional activity of HNF4A (Barrero and Malik, 2006). SUMOylation is the other mechanism that regulates HNF4A protein stability and potentially DNA binding activity (Zhou et al., 2012).

As a transcription factor, HNF4A was first identified to be bound to DNA sites required for the transcription of two liver-specific genes: TTR (transthyretin) and APO3 (apolipoprotein CIII) (Sladek et al., 1990). An increasing number of studies implicate a vital role of HNF4A in the development of the liver, intestine and pancreas, differentiation and homeostasis (Figure 3).

Liver

HNF4A has been shown to be required for hepatocyte differentiation and development of the liver. The expression of HNF4A mRNA in post-implantation mouse embryos was found in the primary endoderm starting at day 4.5. From day 8.5, HNF4A mRNA was detected in embryonic tissues in the liver diverticulum and the hindgut. At later times, HNF4A transcripts were found in the mesonephric tubules, pancreas, stomach, intestine, and in the metanephric tubules of the developing kidney (Duncan et al., 1994). Additionally, conditional genetic removal of HNF4A in the liver resulted in disorganization of morphological and functional differentiation in the hepatic epithelium (Parviz et al., 2003). In hepatocyte-specific knock-out model, lack of HNF4A expression in the liver caused impaired lipid metabolism and gluconeogenesis (Hayhurst et al., 2001), indicating that HNF4A controls genes involved in hepatic lipid and glucose metabolism, hereby influencing the hepatocyte metabolome (Parviz et al., 2003). On the other hand, homozygous loss of HNF4A gene resulted in embryonic lethality (Chen et al., 1994.).

HNF4A was also found to be related to epithelial cell adhesion and junction formation in the fetal liver (Battle et al., 2006). Re-expression of HNF4A was shown to induce cells to reform junctions and express hepatocyte marker genes in a dedifferentiated hepatoma cell line (Späth and Weiss, 1997; Späth and Weiss, 1998). More recently, HNF4A was implicated in the differentiation of hepatic stellate cells into hepatocyte-like cells (Liu et al., 2015). Furthermore, in non-hepatic cells, ectopic over expression of HNF4A in fibroblasts induced mesenchymal to epithelial transition (EMT), indicating that HNF4A is a dominant regulator of the morphogenetic parameters that form the epithelial phenotype (Parviz et al., 2003.).

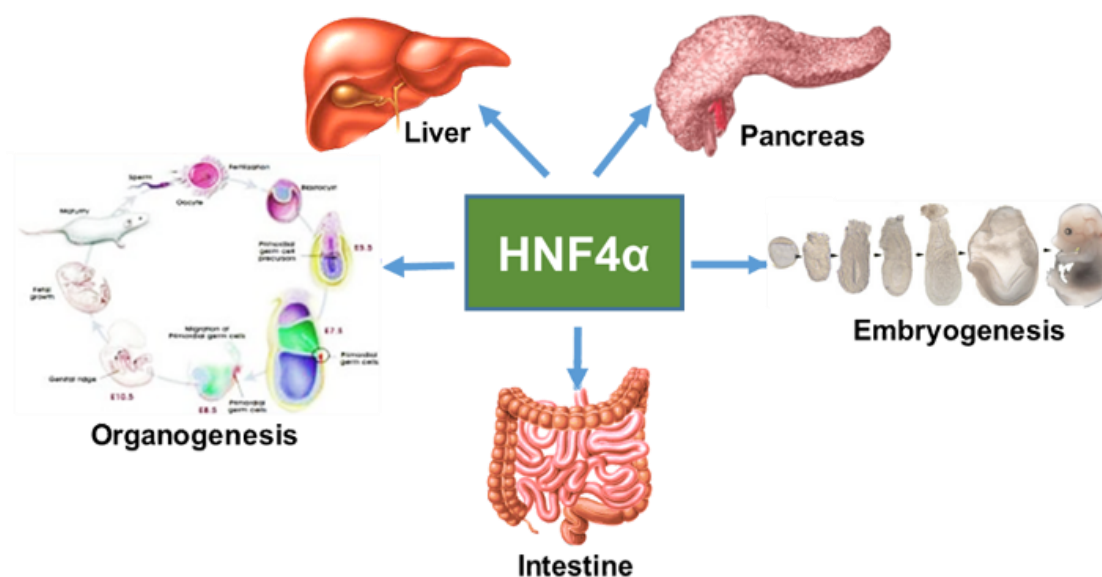
More recently, Yang et al. showed that during EMT, there is a negative feedback loop between Wnt- β -catenin signaling and HNF4A, both in vivo and in vitro. Restoring HNF4A expression was suggested as a method to inhibit invasion in hepatocellular carcinoma by preventing EMT (Yang et al., 2013).

Intestine

HNF4A plays essential roles in the intestine, particularly in epithelial cell function, differentiation and normal colon physiology (Chellappa et al., 2012).

To directly address the role of HNF4A in development of the colon, an epithelial-specific knockout model of HNF4A was created in mice by using the Cre-loxP system. Examination of the embryos revealed that HNF4A ablation disrupts development of normal crypt topology in fetal colons, and reduced goblet cell maturation (Garrison et al., 2006). In adult small intestine, HNF4A was shown to play a critical role in the homeostasis of intestinal epithelium, in the epithelial cell architecture, and in the barrier function of the intestine. Loss of intestinal HNF4A affected the Wnt/ β -catenin signaling pathway, and destabilized adherens and tight junctions (Cattin et al., 2009). Recently, Vuong et al. suggested that HNF4A isoforms play distinct roles in colon cancer, which could be caused by differential interactions with the Wnt/ β -catenin/TCF4 and AP-1 pathways (Vuong et al., 2015).

Importance of HNF4A in the formation of tight epithelial barrier to exert a selective barrier function in relation to apical-to-basal transport was also shown in a coculture system (Lussier et al., 2008). Besides nutrient metabolism (Black, 2007) and protection against pathogens (Laukoetter et al., 2006), another function of the epithelial barrier is the control of appropriate ion selectivity. Loss of this function can lead to deregulation of colonic inflammatory homeostasis and inflammatory bowel disease (IBD) (Darsigny et al., 2009).



Differentiation program in the colon

Figure 3 HNF4A can regulate different cell functions. HNF4A is an important regulator with a strong impact on endodermal development, organ differentiation and metabolism (Boyd et al., 2009).

HNF4A appears to play a protective role against IBD, an important risk factor for colorectal cancer. In patients with IBD, HNF4A expression was significantly decreased. Accordingly, intestine specific HNF4A-null mice exhibited increased susceptibility to dextran sulfate sodium (DSS) induced IBD with increased intestinal permeability, suggesting that HNF4A was required to protect the epithelium during experimental colitis (Ahn et al., 2008).

HNF4A was also addressed as a crucial transcription factor in the differentiation of intestinal cells.

Intestine specific knockout of HNF4A in the adult mouse enhanced proliferation in crypts, and increased number of mucus secreting cells (Cattin et al., 2009).

HNF4A was also shown to be involved in the regulation of genes involved in the enterocyte differentiation and in lipid metabolism (Béaslas et al., 2008; Stegmann et al. 2006; Cattin et al., 2009). To address the role of HNF4A in differentiation dependent transcription in human colonic epithelial cells, Boyd et al. performed a genome-wide identification of promoters that are occupied by HNF4A in vivo.

The analysis revealed that HNF4A was mostly associated with the promoter regions involved in transport and metabolism.

HNF4A was found to regulate differentiation dependent transcription by regulating the expression of HNF1A and CDX2, transcription factors necessary for the expression of many intestinal genes important in the development and differentiation program in the colon (Boyd et al., 2009).

Pancreas

HNF4A activity is essential for β -cell function through the regulation of several genes, including those involved in metabolism-secretion coupling, such as glucose transporter-2, L-pyruvate kinase, aldolase B, 2-oxoglutarate dehydrogenase E1 subunit, mitochondrial uncoupling protein-2 (Wang et al., 2000) and the potassium channel subunit Kir6.2 (Gupta et al., 2005), as well as the INS (insulin gene) (Wang et al., 2000; Bartoov-Shifman et al., 2002). In pancreatic β -cells, HNF4A maintains glucose homeostasis (Marcil et al., 2015; Wang et al., 2000). Gene expression analysis in type 2 diabetes (T2D) patients compared to normal glucose-tolerant controls revealed that HNF4A mRNA level decreased in pancreatic β -cells of T2D patients (Gunton et al., 2005). Moreover, HNF4A mutations were implicated in Mature-Onset Diabetes of the Young 1 (MODY1), a dominantly inherited atypical subgroup of T2D characterized by decreased glucose stimulated insulin secretion in pancreatic β -cells (Yamagata et al., 1996). More recently, it was suggested lack of HNF4A function disrupts Ca^{2+} signaling and insulin release in β -cells of patients with MODY1 through altered endoplasmic reticulum (ER) Ca^{2+} homeostasis (Moore et al., 2016).

Homology

HNF4A is highly conserved across species, with 100% amino acid conservation in the DNA binding domain of all mammalian HNF4A. HNF4A has been found in every animal organism examined thus far, including sponge and coral, and has been postulated to be the ancestor of the entire NR family (Bolotin et al., 2011) (Table 1 and Figure 4).

Species	Gene Symbol	Identity (%) Gene	Identity (%) Protein
<i>H.sapiens</i>	HNF4A		
vs. <i>P.troglodytes</i>	HNF4A	92.1	92.9
vs. <i>M.mulatta</i>	HNF4A	99.3	97.0
vs. <i>C.lupus</i>	HNF4A	98.3	92.3
vs. <i>B.taurus</i>	HNF4A	97.6	92.5
vs. <i>M.musculus</i>	Hnf4a	95.8	89.7
vs. <i>R.norvegicus</i>	Hnf4a	96.0	90.2
vs. <i>G.gallus</i>	HNF4A	87.9	82.2
vs. <i>X.tropicalis</i>	hnf4a	84.2	74.0
vs. <i>D.rerio</i>	hnf4a	82.6	72.8
vs. <i>A.gambiae</i>	AgaP_AGAP002155	64.6	65.4

Table 1 Pairwise alignment of HNF4A gene and protein sequences (in distance from human). HNF4A is highly conserved evolutionarily.











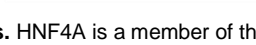
Gene	Protein	DNA-binding domain (DBD) Ligand-binding domain (LBD)
HNF4A, <i>H.sapiens</i> hepatocyte nuclear factor 4, alpha	474 aa NP_000448.3	
HNF4A, <i>P.troglodytes</i> hepatocyte nuclear factor 4, alpha	482 aa XP_514664.4	
HNF4A, <i>M.mulatta</i> hepatocyte nuclear factor 4, alpha	462 aa XP_0011110097.2	
HNF4A, <i>C.lupus</i> hepatocyte nuclear factor 4, alpha	474 aa XP_852731.1	
HNF4A, <i>B.Taurus</i> hepatocyte nuclear factor 4, alpha	455 aa NP_001015557.1	
Hnf4a, <i>M.musculus</i> hepatic nuclear factor 4, alpha	474 aa NP_032287.2	
Hnf4a, <i>R.norvegicus</i> hepatocyte nuclear factor 4, alpha	474 aa NP_071516.2	
HNF4A, <i>G.gallus</i> hepatocyte nuclear factor 4, alpha	454 aa NP_001026026.1	
hnf4a, <i>X.tropicalis</i> hepatocyte nuclear factor 4, alpha	466 aa XP_002933229.2	
hnf4a, <i>D.rerio</i> hepatocyte nuclear factor 4, alpha	454 aa NP_919349.1	
AgaP_AGAP002155, <i>A.gambiae</i> AgaP_AGAP002155	596 aa XP_308036.5	

Figure 4 HNF4A proteins and their conserved domain architectures. HNF4A is a member of the nuclear receptor (NR) family of transcription factors that use conserved DNA binding domains (DBDs) and ligand binding domains (LBDs).

Mutations

HNF4A is at the center of a complex transcriptional regulatory network and is implicated to several human diseases including diabetes (Mohlke and Boehnke, 2005), MODY1 (Ryffel, 2001), hemophilia (Reijnen et al., 1992) and hepatitis B viral infections (He et al., 2012). The HNF4A locus has been associated with high-density lipoprotein

cholesterol (HDL-C) (Teslovich et al., 2010) and metabolic dyslipidemia (Suviolahti et al., 2006). Finally, since it regulates several Phase I/II and other genes in the liver, HNF4A is suggested to play a role in drug metabolism (Hwang-Verslues and Sladek, 2010). In addition, polymorphisms (Hwang-Verslues and Sladek, 2010; Ruchat et al., 2009; Marcil et al., 2015) and mutations (Ryffel, 2001) in the human HNF4A gene are associated with altered expression and transcriptional activity.

Germinal

Diabetes mellitus, noninsulin-dependent (NIDDM):

In early disease onset, three mutations affecting HNF4A function were identified (D126Y; D126H; R154Q) (Aguilar-Salinas et al., 2001). In late onset, missense mutations were identified in the LBD (R323H) (Price et al., 2000) and the F domain (V393I); the latter resulted in a reduced transactivational activity (Hani et al., 1998). V255M mutation has also been shown to reduce transactivation, albeit modestly (Mohlke and Boehnke, 2005).

Thirteen single nucleotide polymorphisms (SNPs) in the P2 promoter, three of which were identified in Pima Indians, have also been associated with T2D (Muller et al. 2005). A 7 bp deletion in the Sp1 site of the P1 promoter was identified in type II diabetic nephropathic Caucasian patients (Price et al., 2000).

Factor VII deficiency:

Homozygous mutation for a T to G transversion at nucleotide -61 position in the factor VII promoter was shown to disrupt HNF4A binding and result in a significant reduction in factor VII promoter activity (Arbini et al., 1997).

Maturity-onset diabetes of the young, type 1 (MODY1):

Mutations in the HNF4A coding region and promoter were shown to be directly implicated in MODY1 in several different human populations (Ryffel, 2001).

Two deletion mutations (F75fsdelT and K99fsdelAA) generate truncated proteins lacking part of the zinc finger domain essential for DNA binding. An in-frame insertion mutation, V328ins, located in the LBD, was suggested to alter the highly conserved structural organization of the protein. R154X and Q268X nonsense mutants retain the DNA binding domain but lack a substantial portion of the potential ligand binding part (Ryffel, 2001). R127W and E276Q missense mutations were reported to result in a significant loss of HNF4A activity (Lausen et al., 2000). The HNF4A mutations G115S (Oxombre et al., 2004.); R127W (Furuta et al., 1997); R244Q (Hara et al., 2002.); R324H (Price et al., 2000.); IVS5-2delA (Barrio et al., 2002) have also been associated with MODY1. Of note, -146T->C in the P2 promoter region was reported to be associated with MODY1 by affecting PDX1 (IPF-1) binding to DNA (Thomas et al., 2001).

Familial Hyperinsulinism due to HNF4A deficiency (FHI-HNF4A):

Familial hyperinsulinism due to HNF4A deficiency is a form of diazoxide-sensitive diffuse hyperinsulinism (DHI), characterized by macrosomia, transient or persistent hyperinsulinemic hypoglycemia (HH), responsiveness to the diazoxide and a propensity to

develop MODY1 (Glaser, 2013). The transmission is autosomal dominant with variable penetrance (Pearson et al., 2007; Kapoor et al., 2008).

Implicated in

Gastric adenocarcinoma

HNF4A expression was seen in primary gastric adenocarcinomas and in metastases of gastric carcinoma to the breast, but was absent in primary breast carcinomas, and in metastases of breast carcinomas to the stomach (van der Post et al., 2014).

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This article should be referenced as such:

Tunçer S, Banerjee S. HNF4A (Hepatocyte Nuclear Factor 4 alpha). Atlas Genet Cytogenet Oncol Haematol. 2017; 21(2):44-51.
