

Gene Section

Review

AFP (alpha-fetoprotein)

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Published in Atlas Database: July 2012

Online updated version : <http://AtlasGeneticsOncology.org/Genes/AFPID44248ch4q13.html>
DOI: 10.4267/2042/48465

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Identity

Other names: FETA, HPAFP

HGNC (Hugo): AFP

Location: 4q13.3

Local order: AFP belongs to the family of albumin genes together with serum albumin (ALB), group-specific component/vitamin D-binding protein (GC) and afamin/alpha-albumin (AFM). All genes of this family are localized on the long arm of chromosome 4 and are proposed to originate from common predecessor. ALB, AFP and AFM located at the same chromosome locus consequently are proposed to be cooperatively regulated (Lazarevich, 2000).

Note

25037 bases. AFP was described as a major fetal serum protein absent in normal adult serum. Later dramatic increase of AFP level was revealed in serum of mice and humans with hepatocellular carcinoma, hepatoblastoma, germ cell tumors and gastrointestinal carcinomas (Abelev et al., 1963; Abelev, 1971). These findings allowed to classify AFP that is expressed in embryo, downregulated after birth and reactivated in cancer, as onco-embryonic marker. Alterations of AFP level in blood serum are widely used in diagnostics of

several types of epithelial cancers and abnormalities of prenatal development (Abelev and Eraiser, 1999).

DNA/RNA

Description

Human AFP gene consists of 15 exons and 14 introns, 15th exon is noncoding. Like other albumin genes it is proposed to originate from common predecessor that arose as a result of triplication of a primary ancestral gene. 7 kb 5'-upstream regulatory region controls stage- and tissue-specific expression of AFP.

Transcription

AFP expression is controlled mainly on the transcriptional level.

It is regulated by tissue-specific promoter, three independent enhancers, and a silencer that is at least partially responsible for AFP gene repression after birth (Spear, 1999).

AFP gene expression is regulated by complex network of transcriptional regulators such as oncogenes (c-myc, c-fos, c-jun), p53 family members, nuclear receptors (glucocorticoid and retinoid receptors, HNF4 α , FTF), hepatocyte nuclear factors (HNF1, FoxA, C/EBP families), zinc-finger repressors (Zhx2, Zbtb20) and ubiquitous factors (NF-1, Sp-1) (Lazarevich, 2000; Peterson et al., 2011).



Albumin genes cluster. S - silencer; P - promoter; E1, E2, E3 - minimal enhancers of AFP gene; E - albumin enhancer. Tissue-specific AFP enhancers located between ALB and AFP genes can modulate transcriptional activities of both promoters. Arrows indicates start and direction of transcription

Full length AFP transcript (NM_001134, 2032 bp in humans) is predominant in fetal liver. Shorter mRNAs about 1.7, 1.4, and 1.0 kb were reported in mammalian fetal or regenerating liver and carcinoma cell cultures (Lemire and Fausto, 1991).

In human hematopoietic progenitor cells the existence of two variant AFP forms originated by replacing of exon 1 with one or two alternative exons located in 5'-untranslated region is proposed (Kubota et al., 2002). AFP isoform lacking exon 1 was identified in ovarian yolk sac tumor (Fukasawa et al., 2005).

The functional role of shortened AFP transcription variants is not clear.

Pseudogene

No.

Protein

Description

AFP is translated as a major 609 amino acids precursor form (P02771) which is processed into a mature 70-kD glycoprotein consisting of 591 amino acids with 3-5% of carbohydrate residues.

AFP consists of three homologous functional domains and have characteristic pattern of cysteine residues folded into layers through disulfide bridging. Single carbohydrate chain is linked through asparagine 233.

AFP microheterogeneity is mainly due to different length and structure of carbohydrate moieties, the extent of their sialylation and fucosylation (Mizejewski, 2001). Shorter isoforms truncated at N-terminal amino acids sequence are also described (Fukasawa et al., 2005).

Based on different affinity towards several lectins (Concanavalin A, Lens culinaris agglutinin (LCA), erythroagglutinating phytohemagglutinin) AFP variants can be separated into several groups of glycoforms.

Specifically, according to LCA reactivity on affinity electrophoresis representing the degree of its fucosylation, AFP can be divided into three fractions, AFP-L1, AFP-L2, and AFP-L3. AFP-L1 that does not react with LCA is characteristics for non-malignant liver diseases, AFP-L2 (intermediate reactive) is detected in maternal serum during pregnancy and patients with yolk sac tumors, highly LCA-reactive AFP-L3 fraction is expressed by malignant liver tumors (Mizejewski, 2001; Debruyne and Delanghe, 2008).

Expression

Normally AFP is produced by visceral endoderm of yolk sac, embryonic liver and in lesser extent in fetal gut and kidney.

AFP is secreted into blood serum, reaching maximum concentration (about 3 mg/ml) at 12-16 weeks of embryonic development.

In the first weeks after birth AFP synthesis decrease dramatically.

In adults AFP levels in circulation is lower than 10-20 ng/ml. AFP reactivation in adults may result from liver regeneration, noncancerous liver diseases such as viral hepatitis or cirrhosis, primary liver or germ cell tumors and to lesser extent several forms of other epithelial malignances (Abelev and Eraiser, 1999).

Localisation

Cytoplasm, secreted.

Function

Like other proteins of albumin family AFP possesses transport function binding heavy metals, fatty acids, bilirubin, retinoids, steroids, divalent cations, various organic drugs and environmental agents (Deutsch, 1991; Mizejewski, 2001).

At least in rodents AFP demonstrate estrogen-binding properties indicating that in developing embryo circulating AFP could act as neuroprotective estrogen-neutralizing protein. Experiments on AFP knockout mice proved essential role of AFP in the control of female fertility (De Mees et al., 2006).

Compared to ALB, AFP exhibits enhanced affinity to polyunsaturated fatty acids that denotes its possible role in maternal-to-fetal circulation through the placenta.

AFP is proposed to be involved in the control of proliferation, embryonic differentiation, regulation of osmotic pressure, protection of developing fetus from maternal immune system (Mizejewski, 2001; Mizejewski, 2007).

However the precise mechanisms and universality of these functions need to be clarified by further investigations.

Homology

AFP possesses amino acid sequence homology to other members of albumin family - ALB, AFM and GC. All the albumin proteins are composed of three homologous albumin domains with similar cysteine disulfide bridge clusters (Mizejewski, 2001).

Mutations

Germinal

In AFP coding region several SNP variants with unknown clinical significance are described.

SNPs in AFP promoter region are associated with hereditary persistence of alpha-fetoprotein (HPAFP) - rare autosomal dominantly inherited benign disorder with elevated serum AFP levels (>20 ng/mL) not associated with clinical disability. HPAFP is due to 119G>A and 55C>A substitutions in distal and proximal HNF1 binding sites in AFP promoter which increase affinity of HNF1 transcription factor binding (Alj et al., 2004).

Somatic

In genome databases very rare somatic mutations of AFP with unclear clinical significance are reported.

Implicated in

Hepatocellular carcinoma (HCC)

Disease

Hepatocellular carcinoma is the most prevalent liver tumor and fifth most frequent cancer worldwide. The major risk factors for development of HCC are chronic infection with hepatitis B or C viruses, prolonged exposure to hepatocarcinogens and cirrhosis (Bosch et al., 1999). HCCs that are often diagnosed at the advanced stages and are highly resistant to conventional chemotherapy have very poor prognosis (about 7% 5-year survival).

Expression and secretion of AFP reversibly repressed in adult liver is dramatically induced in transformed hepatocytes (Abelev et al., 1963; Abelev, 1971).

Elevation of serum AFP is widely used as diagnostics marker for HCC. Sensitivity and specificity of the test depends significantly on the cut-off range (typically it varies between 20-50 ng/ml and may depend from age, geographical population and HCC etiology) (Debruyne and Delanghe, 2008).

High (>500 ng/ml) serum AFP level is described in >80% of children and about 70% of adults with HCC and distinguishes primary liver cancer from non-malignant liver disease (see below). Small highly differentiated HCCs are often AFP-negative. On the other hand, low AFP levels are also described in highly dedifferentiated anaplastic tumors (probably due to extinction of its tissue-specific transcriptional regulators). Specificity and sensitivity of HCC differentiation diagnosis can be enhanced through detection of LCA-reactive glycoform of AFP (AFP-L3) which is preferably expressed in malignant liver tumors (Debruyne and Delanghe, 2008).

Prognosis

Currently AFP serum test is conventionally used in early diagnostics of HCC especially in high risk groups. Serial measurement of serum AFP level is useful for monitoring the treatment response in HCC patients after surgical resection, chemotherapy or orthotopic liver transplantation. High proportion of LCA-reactive AFP glycoform (AFP-L3 fraction) is associated with more malignant phenotype and poor prognosis of HCC (Debruyne and Delanghe, 2008; Sturgeon et al., 2010).

Hepatoblastoma

Note

The most common type of pediatric liver cancer that phenotypically is highly similar to hepatoblasts - immature parenchymal cells of embryonic liver that give rise to hepatocytes and cholangiocytes. Like hepatoblasts, hepatoblastoma cells produce extremely high levels of AFP. In >80% of affected patients serum AFP level exceeds 1000 ng/ml (Abelev and Eraiser, 1999).

Prognosis

In majority of cases hepatoblastoma is highly sensitive to chemotherapy with cytostatic and cytotoxic drugs. Thus, combination of surgical treatment with neoadjuvant chemotherapy critically improved 5-year survival rate up to 75%.

Increase of serum AFP level in children is a sensitive marker for diagnosis and posttreatment monitoring of hepatoblastoma (Herzog et al., 2000). Correlation of pretreatment AFP level with clinical outcome is not clear.

Germ cell tumors

Disease

Germ cell tumors integrate several types of testis and ovary cancers originating from different cell types. Elevation of serum AFP levels is associated with embryonic carcinoma (derived from undifferentiated pluripotent early embryonic cells) and teratocarcinoma (tumors containing both embryonic carcinoma cells and more or less differentiated somatic tissue elements) as well as yolk sac (originating from endodermal component of fetal yolk sac) tumors. Seminoma and dysgerminoma, originating from germinal cells, as well as stromal and surface epithelium derived germ cell tumors are AFP negative (Abelev and Eraiser, 1999).

Prognosis

Due to sensitivity of germ cell tumors to cisplatin-based chemotherapy even metastatic nonseminomatous germ cell tumors are highly curable with overall cure rates >80%. Pretreatment serum concentrations of AFP, human chorionic gonadotropin (HCG, see below), and lactate dehydrogenase are approved to be independent prognostic factors for patients with metastatic nonseminomatous germ cell tumors (International Germ Cell Cancer Collaborative Group, 1997).

Oncogenesis

Yolk sac is responsible for serum protein production at the outset of embryonic development. Accordingly the forms of germ cell tumors containing embryonic and yolk sac elements (yolk sac tumors, embryonic carcinoma and teratocarcinoma) are characterized by increased AFP levels. Trophoblast elements of embryonic carcinoma and teratocarcinoma also produce elevated levels of HCG. In >80% of yolk sac tumors and embryonic carcinomas serum AFP levels are elevated up to 1000 ng/ml (Abelev and Eraiser, 1999). Combination of AFP and HCG is highly specific for differential diagnosis, choice of treatment strategy and monitoring of different forms of germ cell tumors.

Various cancer

Disease

Increase of serum AFP level was also reported in several cases of gastric, biliary tract, pancreatic, lung, breast, renal, colorectal cancer. In majority of cases serum AFP level was <50 ng/ml (Kew, 1974; Abelev

and Eraiser, 1999). No association with liver metastases was described.

Non-malignant liver diseases

Disease

Acute viral hepatitis, alcohol or drug-induced liver damage, cirrhosis, acute liver failure, states associated with liver regeneration. In the majority of hepatitis and cirrhosis cases serum AFP level is lower than 50 ng/ml while about 15% of patients demonstrate moderate AFP levels (>500 ng/ml). AFP produced by nonmalignant hepatocytes can be distinguished from that of HCC origin by its low ability to bind Lens culinaris lectin (AFP-L1 glycoform). Together with AFP elevation level this property is used for differentiation diagnosis of HCC and non-malignant liver diseases (Abelev and Eraiser, 1999).

Prognosis

In patients with acute liver failure high serum AFP concentration does not predict an improved outcome, while post-therapy rise of AFP values is associated with favourable prognosis (Schiodt et al., 2006).

Abnormalities of fetus development and pregnancy disorders

Note

During pregnancy AFP synthesized in the yolk sac of the fetus enters the amniotic fluid through placenta and reaches the maternal circulation. AFP level in maternal serum at second-trimester is used as a diagnostic marker of developmental abnormalities of fetus.

Disease

Decreased AFP levels in maternal serum or amniotic fluid signify the chromosomal abnormalities of fetus such as Down's syndrome and trisomy 18. High levels of AFP indicate increased risk for neural tube defects such as spina bifida and anencephalopathy. Abnormal AFP level can also indicate other fetal defects or obstetric complications (Mizejewski, 2007).

Hereditary disorders

Disease

Type I hereditary tyrosinemia is autosomal recessive disorder manifested in young infants by severe liver disease, renal tubular dysfunction, growth failure and rickets. Hereditary tyrosinemia results from deficiency of fumarylacetoacetate hydrolase (FAH), the last enzyme of tyrosine degradation. Severe liver disease increases the risk of HCC development. In patients newly diagnosed with hereditary tyrosinemia serum AFP levels are very high (up to 100,000 ng/ml), decreasing after treatment with nitisinone. Monitoring of AFP level is used to evaluate the risk of HCC in hereditary tyrosinemia patients.

Ataxia telangiectasia is rare, autosomal recessive disorder of childhood caused by a defect in the ATM gene encoding serine/threonine protein kinase involved

in DNA damage response and control of chromosome stability. Ataxia telangiectasia is manifested by cerebellar degeneration, dilation of the blood vessels, immunodeficiency, growth retardation, chromosomal instability, predisposition to cancer. Approximately 95% of patients with ataxia-telangiectasia demonstrate stable elevation of serum AFP in childhood increasing slowly over time. Molecular basis of this correlation is not clear.

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This article should be referenced as such:

Lazarevich NL. AFP (alpha-fetoprotein). *Atlas Genet Cytogenet Oncol Haematol*. 2013; 17(1):12-16.
