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Gene Section
Mini Review

KIAA0101 (KIAA0101)

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Identity

Other names: FLJ58702; NS5ATP9; OEATC-1; OEATC1; PAF; p15(PAF); p15PAF

HGNC (Hugo): KIAA0101

Location: 15q22.31

DNA/RNA

Note
Murine gene embryonic expression shows highly restricted expression of KIAA0101 in facial prominences, limbs, somites, brain, spinal cord and hair follicles. It has a suggested role in embryonic development (van Beuren et al., 2007).

Description

The gene is composed of 4 exons.

Transcription

One transcript. RNA was expressed as a 1.1 kb message in liver, pancreas and placenta at high levels (Yu et al., 2001). RNA profiling shows it is highly expressed in a number of tumors, specifically in esophageal tumors, anaplastic thyroid carcinomas, pancreatic cancer and non-small-cell lung cancer lines (Yu et al., 2001; Hosokawa et al., 2007). KIAA0101 was also reported to be down-regulated in colon cancer cells (Simpson et al., 2006) and human hepatocellular carcinoma (Guo et al., 2006). Nuclear protein NF-kappaB (p50) (Li et al., 2008), the Hepatitis C virus protein non-structural protein 5A (NS5A) (Shi et al., 2008) and ATF3 (Turchi et al., 2009) bind to the promoter region upstream of the KIAA0101 transcription initiation site promoting transcription in response to DNA damage.

Pseudogene

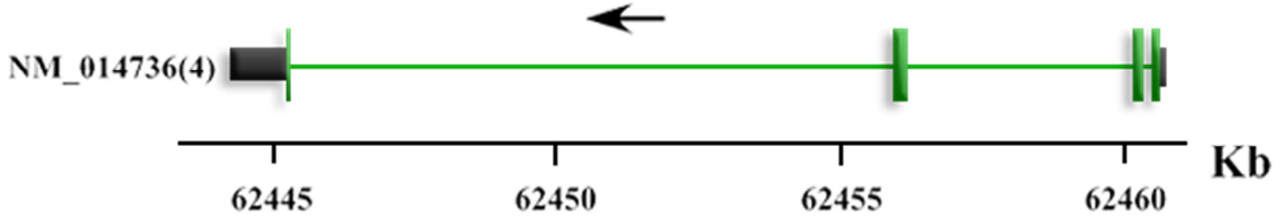
None.

Protein

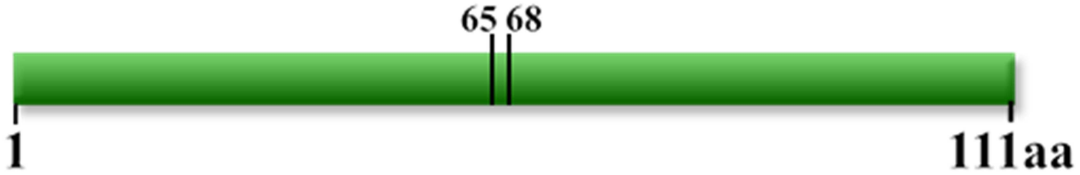
Note
NS5ATP9, Hepatitis C virus NS5A-transactivated protein 9, HCV NS5A-transactivated protein 9, Overexpressed in anaplastic thyroid carcinoma-1, OEATC-1, OEATC1, p15(PAF), L5.

Description

The KIAA0101 gene encodes for a 111 amino acid 15 kDa protein. It contains a conserved proliferating cell nuclear antigen (PCNA)-binding motif (Yu et al., 2001).



DNA diagram. KIAA0101 9768 chr: 62444265-62460755. One transcript, 4 exons.



Protein diagram. 111 aa in length, single transcript, mutation I-A at position 65 and mutation F-A at position 68 results in loss of PCNA binding.

Expression

Predominant expression in liver, pancreas and brain. Not detected in heart or liver (Yu et al., 2001). The KIAA0101 protein was down-regulated in human hepatocellular carcinoma (Guo et al., 2006; Yuan et al., 2007). Increased protein levels have been detected in pancreatic cancer cells (Hosokawa et al., 2007).

Localisation

Nucleus, mitochondrion (Yu et al., 2001; Guo et al., 2006; Simpson et al., 2006; Yuan et al., 2007).

Function

The KIAA0101 protein binds to PCNA through a conserved PCNA binding domain. PCNA is required for DNA replication or repair as a supplementary factor for DNA polymerase (Paunesku et al., 2001). Proteins bound to PCNA can prevent its binding to DNA polymerase, in turn leading to inhibition of DNA synthesis, cell cycle progression and G1 cell cycle arrest (Yuan et al., 2007). PCNA binding proteins also interact with each other to modulate this regulation. For example, KIAA0101 also interacts in a complex with p33ING1 isoform 2, another PCNA binding protein which is a potential tumor suppressor and regulator of p53 (Simpson et al., 2006). UV irradiation caused increased association of KIAA0101 with PCNA suggesting that this association occurs in response to DNA damage. KIAA0101 also competes with p21WAF for binding to PCNA (Yu et al., 2001). KIAA0101 most recently been shown to act in concert with ATF3 to control genomic integrity after UV stress (Turchi et al., 2009). KIAA0101 expression levels are also regulated by NF-kappaB, this protein family having significant roles in apoptosis, cell cycle regulation and onocgenesis (Hosokawa et al., 2007; Li et al., 2008). Together this data suggests a likely role for KIAA0101 in DNA repair and in protection from UV-induced cell death.

Mutations

Note

Experimentally mutation I-A at position 65 and F-A at position 68 result in loss of PCNA binding (Yu et al., 2001). No other mutations have been described. Screening of colon tumour samples identified a polymorphism in the intronic region just prior to the start of exon 2 (982-15delT) (Simpson et al., 2006).

Implicated in

Hepatocellular carcinoma

Disease

KIAA0101 expression was proposed to promote growth advantage and hypoxic insult resistance and be associated with promoting cell proliferation (Yuan et al., 2007). KIAA0101 overexpression was associated with concomitant p53 mutation and vascular invasion (Yuan et al., 2007). This study suggested that high expression in hepatocellular carcinoma was indicative of tumour recurrence, metastatic potential and poor prognosis (Yuan et al., 2007). KIAA0101 was also reported to be downregulated in hepatocellular carcinoma (Guo et al., 2006). This study suggested that KIAA0101 had a growth inhibitory effect.

Astrocytomas

Disease

Grade IV (glioblastoma multiforme) astrocytomas had 5 times higher expression levels when compared to Grade I (pilocytic) astrocyomas suggesting that KIAA0101 abundance correlates with malignancy grade in human astrocytes (Marie et al., 2008).

Pancreatic cancer

Disease

Pancreatic cells overexpress KIAA0101 both at cDNA and protein level. Knock down of KIAA0101 by siRNA attenuated proliferation and DNA replication whereas overexpression enhanced cell growth in pancreatic cancer cell lines (Hosokawa et al., 2007).

Anaplastic thyroid carcinoma

Disease

Anaplastic thyroid carcinoma cell lines had significant overexpression of KIAA0101. Cell growth was inhibited by silencing KIAA0101 expression using siRNA. KIAA0101 may be oncogenic or cell growth-promoting but the mechanism for this is not understood (Mizutani et al., 2005).

Follicular lymphoma

Disease

High expression of KIAA0101 (along with CCNB1 (cyclin B1), CDC2, CDKN3A, CKS1B, ANP32E) was associated with better survival/response rate in a univariate analysis following CHOP (cyclophosphamide, vincristine, doxorubicin,

prednisone) chemotherapy for follicular lymphoma treatment. Identification of these proteins aims to develop a follicular lymphoma international prognostic index to aid in informing a successful treatment strategy (Bjorck et al., 2005).

Oncogenesis

This gene is thought to be oncogenic through modulation of DNA repair pathways via interaction with PCNA.

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