

## Gene Section

### Review

# HNRNPA1 (Heterogeneous Nuclear Ribonucleoprotein A1)

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## Abstract

Heterogeneous nuclear ribonucleoprotein (HNRNPA1) gene maps to chromosome 12, plus strand and has 13 exons and 12 introns. There are three reported transcripts due to the alternative splicing.

HNRNPA1 is one of the most abundant and ubiquitously expressed nuclear proteins. HNRNPA1 is a member of RNA-binding protein family comprising of 20 members in humans (Dreyfuss, 1993; Pinol-Roma, Choi, Matunis, Dreyfuss, 1988). HNRNPA1 has diverse roles in RNA splicing, telomere length maintenance, miRNA maturation and mRNA transport from nucleus to cytoplasm.

### Keywords

HNRNPA1; RNA-binding protein; RNA splicing; telomere length maintenance; miRNA maturation; mRNA transport

## Identity

**Other names:** HNRPA1, ALS20, hnRNP A1, hnRNP-A1, IBMFPD3, UP 1, HNRPA1L3

**HGNC (Hugo):** HNRNPA1

**Location:** 12q13.13

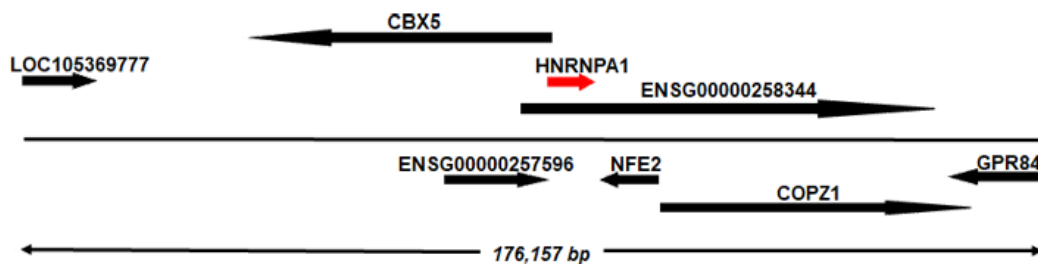
### Local order

From telomere to centromere: LOC105369777, CBX5, ENSG00000257596, HNRNPA1, NFE2, ENSG00000258344, COPZ1, GPR84

## DNA/RNA

### Note

HNRNPA1 gene consists of 13 exons and 12 introns. The gene maps to 12q13.13 and is 6399 bps long (NCBI Reference Sequence: NC\_000012.12: 54280690-54287088). Highlighted in red is the protein coding sequence from exons 1-10. (Figure 2)



Local order of HNRNPA1 together with neighboring upstream and downstream genes on chromosome 12. The direction of arrows indicates direction of transcription and arrow sizes approximate gene sizes.



HNRNPA1 gene has 13 exons and 12 introns. Numbers indicate the exons. Red exons show protein-coding regions while blue color represents untranslated regions.



HNRNPA1 has three functional regions; two RNA-recognition motifs and one Glycine-rich Prion like domain. Numbers above the bars indicate amino acids harboring the domains.

### Description

The HNRNPA1 gene is 6399 bases long and is on the plus strand. HNRNPA1 gene has 13 exons (Jean-Philippe et al., 2013).

### Transcription

HNRNPA1 produces two coding transcripts (Exon 1-11). The difference between these coding transcripts is the presence or absence of exon 8 (only longer mRNA contains exon 8). A third one was reported as a potential non-coding transcript (Mendell et al, 2004). This non-coding RNA transcript has exons 12 and 13, and it does not contain exon 8.

### Pseudogene

There are 75 pseudogenes of HNRNPA1 which are: HNRNPA1P1, HNRNPA1P10, HNRNPA1P11, HNRNPA1P12, HNRNPA1P13, HNRNPA1P14, HNRNPA1P15, HNRNPA1P16, HNRNPA1P17, HNRNPA1P18, HNRNPA1P19, HNRNPA1P2, HNRNPA1P20, HNRNPA1P21, HNRNPA1P22, HNRNPA1P23, HNRNPA1P24, HNRNPA1P25, HNRNPA1P26, HNRNPA1P27, HNRNPA1P28, HNRNPA1P29, HNRNPA1P3, HNRNPA1P30, HNRNPA1P31, HNRNPA1P32, HNRNPA1P33, HNRNPA1P35, HNRNPA1P36, HNRNPA1P37, HNRNPA1P38, HNRNPA1P39, HNRNPA1P4, HNRNPA1P40, HNRNPA1P42, HNRNPA1P43, HNRNPA1P44, HNRNPA1P45, HNRNPA1P46, HNRNPA1P47, HNRNPA1P48, HNRNPA1P49, HNRNPA1P5, HNRNPA1P50, HNRNPA1P51, HNRNPA1P52, HNRNPA1P53, HNRNPA1P54, HNRNPA1P55, HNRNPA1P56, HNRNPA1P58, HNRNPA1P59, HNRNPA1P6, HNRNPA1P60, HNRNPA1P61, HNRNPA1P62, HNRNPA1P63, HNRNPA1P64, HNRNPA1P65, HNRNPA1P66, HNRNPA1P67, HNRNPA1P68, HNRNPA1P69, HNRNPA1P7, HNRNPA1P70, HNRNPA1P71, HNRNPA1P72, HNRNPA1P74, HNRNPA1P75,

HNRNPA1P76, HNRNPA1P77, HNRNPA1P8, HNRNPA1P9, LOC100421349 and LOC100421402(NCBI,2018).

## Protein

### Note

HNRNPA1 gene encodes a 372 amino acid protein. The protein is a member of heterogeneous nuclear ribonucleoproteins (hnRNPs) and has an estimated molecular weight of 38-39 kDa (Jean-Philippe, Paz, Caputi, 2013).

### Description

HNRNPA1 has two RNA recognition motifs; RRM1 and RRM2.

These domains are known for binding to single-stranded RNAs (Dreyfuss, Swanson, Piñol-Roma, 1988).

HNRNPA1 also possesses a prion-like domain (PLD).

This domain is reported in RNA binding proteins that have been associated with neurodegenerative disorders such as Amyotrophic Lateral Sclerosis (Kim et al., 2013).

In addition, glycine-rich region mediates subcellular localization and protein-protein interactions (Han, Tang, Smith, 2010).

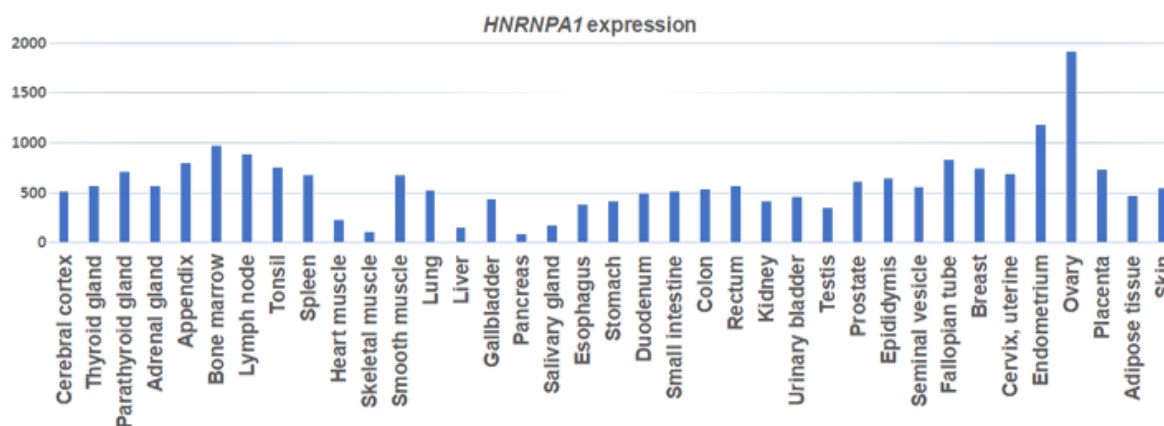
### Expression

HNRNPA1 mRNA is expressed in all human tissues including brain, skin, lung, breast and kidney (The Human Protein Atlas, 2018).

### Localisation

HNRNPA1 protein is mainly nuclear; however, under certain conditions the protein is also present in the cytosol (Roy et al., 2014).

In fact, HNRNPA1 may shuttle between nucleus and cytoplasm along with mRNAs (Jønson et al., 2007).



Expression of HNRNPA1 in different types of tissues is shown (The Human Protein Atlas, 2018).

## Function

HNRNPA1 has a very broad range of reported functions including transcriptional regulation, alternative splicing, mRNA transport, translation and miRNA processing. Most surprisingly, HNRNPA1 can interact with certain promoters and induce transcriptional repression or activation of target genes. VDR (Vitamin D receptor) (H. Chen, Hewison, Hu, Adams, 2003), FGG ( $\gamma$ -fibrinogen) (Xia, 2005) and TK1 (thymidine kinase) (Lau et al., 2000) promoters are transcriptionally repressed while APOE promoter is activated by HNRNPA1 (Campillos et al., 2003).

HNRNPA1 has an important role in mRNA splicing. The protein modulates alternative splicing of various genes including INSR (Insulin Receptor) (Talukdar et al., 2011), BRCA1 (Breast Cancer 1) (Goina, Skoko, Pagani, 2008), PKM (Pyruvate Kinase M1/2) (David, Chen, Assanah, Canoll, Manley, 2010) and its own HNRNPA1 mRNA (Hutchison, LeBel, Blanchette, Chabot, 2002). mRNA splicing is modulated by HNRNPA1 by exon skipping and splice site repression (Jean-Philippe et al., 2013).

HNRNPA1 contributes to telomere regulation by promoting telomerase activity via binding to telomeric sequences, potentially as an auxiliary factor for the telomerase enzyme (Zhang, Manche, Xu, Krainer, 2006).

HNRNPA1 has roles in mRNA transport between nucleus and cytoplasm. Although the exact mechanism is unknown, HNRNPA1 binds to poly(A) tailed mRNAs both in the nucleus and cytoplasm (Mili, Shu, Zhao, Pinol-Roma, 2001), and possibly aid their transfer through nuclear pores (Piñol-Roma Dreyfuss, 1992).

Another function attributed to HNRNPA1 is during translation. HNRNPA1 binds to internal ribosomal entry sites (IRES) that initiates 5' cap-independent translation of certain cellular and viral mRNAs (such as, MYC), CSDE1 (Upstream of NRAS), CCND1 (Cyclin D1), VEGFA (Vascular Endothelial Growth Factor), FGF2 (Fibroblast Growth Factor),

APAF1, and XIAP mRNAs (Cammass et al. 2007). In addition, the HIV-1 IRES is stimulated by hnRNPA1 (Martènez-Salas, Piñeiro, Fernández, 2012).

In addition to mRNA processing and transport, HNRNPA1 interacts directly and specifically with C-terminal region of NF- $\kappa$ B alpha inhibitory subunit via its RNA-binding domain (between residues 95 and 207) resulting in the activation of nuclear factor  $\kappa$  B (Hay, Kemp, Dargemont, Hay, 2001).

The exact mechanism of HNRNPA1 and NF- $\kappa$ B interaction is not completely understood. However, in cells lacking HNRNPA1, activation of NF- $\kappa$ B is defected. When HNRNPA1 loss is rescued, an effective NF- $\kappa$ B response to signal induction is observed only upon ligand induction.

As for the microRNA processing, HNRNPA1 binds to the terminal loop of pri-miR-18a, and facilitates MIR18A production by creating favorable cleavage site for DROSHA (Guil Cáceres, 2007). In contrast, HNRNPA1 negatively affects MIRNLET7A1 (let-7a) biogenesis. HNRNPA1 binds to terminal loop of pri-let-7a-1 and interferes with the binding of KHSRP (component of both Drosha and Dicer complexes, known to promote let-7a biogenesis); hence, inhibiting processing of pri-let-7a by Drosha (Michlewski Cáceres, 2010).

## Homology

HNRNPA1 gene has homologs across Amniota including *P. troglodytes*, *M. mulatta*, *B. taurus*, *R. norvegicus*, *G. gallus*, *M. musculus* and *H. sapiens* (NCBI HomoloGene, 2018).

There is also a well-studied HNRNPA1 homolog in *D. melanogaster* called Hrp36 (Singh Lakhota, 2012).

In total, there are 97 species including invertebrates that have genes orthologous to A1 (NCBI Ensembl, 2018).

## Mutations

### Note

Up to 106 substitution mutations were reported in the HNRNPA1 gene in 42,067 cancer patients.

Reported mutations are generally missense mutations (70 of 106). There are also 4 nonsense mutations, 30 synonymous substitutions and 2 frameshift deletions (COSMIC database, 2018). One of the frameshift deletions found in cancer patients is discovered in the Sanger Institute Cancer Genome Project (study ID :COSU652) while the other is discovered in 619 incident colorectal cancer patients in the study conducted by Giannakis et al(2016).

Yu et al. (2018) also reported a recessive frameshift mutation in HNRNPA1 leading to deregulation of cardiac transcription network and multiple signaling pathways, including Bone Morphogenetic Protein, Notch and Fibroblast growth factor signaling.

## Implicated in

### Top note

HNRNPA1 has been implicated in diverse diseases.

### **Amyotrophic Lateral Sclerosis (ALS)**

#### Note

Immunohistochemistry and immunofluorescence results showed that HNRNPA1 protein was decreased in the nuclei of neurons and the significant loss of HNRNPA1 in motor neurons with concomitant cytoplasmic aggregation in ALS cases while HNRNPA1 was mainly located in nucleus of motor neurons in normal cases (Honda et al., 2015). Mutations in prion-like domain (PrLD), enriched in uncharged polar amino acids and glycine, promote excess incorporation of HNRNPA1 into stress granules and cause the formation of cytoplasmic inclusions in animal models (H. J. Kim et al., 2013b). Whole-exome sequencing conducted by Liu et al.(2016) showed a missense mutation in HNRNPA1 in Flail-Arm ALS patients leading to cytoplasmic inclusions that co-localized with stress granules in Flail-Arm ALS.

### **Breast Cancer**

#### Note

Invasive breast cancer cells (MDA-MB-231) express the CD44v6 variants, which are regulated by HNRNPA1. Downregulation of HNRNPA1 induces a significant change in the expression levels of CD44 isoforms through alternative splicing. Silencing of HNRNPA1 significantly induced cell death and caused a decrease in cell invasion in the MDA-MB-231 cells (Loh et al., 2015). HNRNPA1 silencing through siRNAs significantly lowers the cell proliferation in MDA-MB-231 cells (Otsuka, Yamamoto, Ochiya, 2018).

#### Prognosis

In basal-like breast cancer, Kaplan-Meier survival analysis showed that patients (309 samples) showing high HNRNPA1 expression, had a distinctively

shorter relapse-free survival than patients (309 samples) expressing low level of HNRNPA1 and that patients (121 samples) showing high HNRNPA1 expression had a shorter overall survival than patients (120 samples) with low level of HNRNPA1 expression. (Otsuka, Yamamoto, Ochiya, 2018).

### **Cervical Carcinoma**

#### Note

HNRNPA1 has higher expression in cervical carcinoma compared with normal tissue samples in 32 patients with cervical cancer (Y. J. Kim et al., 2017).

HNRNPA1 expression is upregulated during differentiation of virus-infected epithelial cells in monolayer and 3D cell cultures. HNRNPA1 interacts directly with the Human papillomavirus type 16 (HPV16) late regulatory element (LRE) (which has an important role in temporally controlling virus late gene expression during epithelial differentiation) in the nucleus of differentiated W12 cells in vitro and may facilitate the alternative splicing of late transcripts of virus in differentiated epithelial cells (Cheunim, Zhang, Milligan, McPhillips, Graham, 2008).

### **Colon Cancer**

#### Note

HNRNPA1 mRNA is overexpressed in 40-78% of colon cancer stages, compared with normal colon (Ubagai, Fukuda, Tsuchiya, 2005).

A cell line based study showed HNRNPA1 to be suppressed by MIR18a in SW620 cells through autophagolysosomal degradation and thus, HNRNPA1 silencing resulted in the suppression of colon cancer cell progression (Fujiya et al., 2014).

### **Gastric Cancer (GC)**

#### Note

GC tissues have elevated levels of HNRNPA1 protein compared with normal tissues. HNRNPA1 silencing significantly prevented anchorage-dependent growth in GC cells and HNRNPA1 was important to cell growth and progression of GC. HNRNPA1 knockdown caused reduction in cell growth, invasion, migration and reversal of EMT (Epithelial to Mesenchymal Transition) in GC cells. Collectively, these results pointed out that HNRNPA1 may have a pivotal role in GC cell invasion and metastasis (Chen et al., 2018).

### **Hepatocellular Carcinoma (HCC)**

#### Note

High expression of HNRNPA1 was reported in the highly metastatic HCC cell lines and in tumor tissues of patients with recurrent HCC. HNRNPA1 silencing reduced cell invasion in highly metastatic HCC cells while overexpression of HNRNPA1 caused a significant increase in invasive behavior of



poorly metastatic HCC cells HNRNPA1 was reported to regulate the invasive capacity of HCC cells through regulating the CD44v6 expression (Zhou et al., 2013).

## Lung Cancer

### Note

The HNRNPA1 protein expression was reported to be upregulated in most tissue samples from lung cancer patients by immunohistochemistry (Boukakis, Patrino-Georgoula, Lekarakou, Valavanis, Guialis, 2010). HNRNPA1 knockdown inhibited cell viability and colony formation of lung cancer cells and arrested cells in the G0/G1 phase (Liu, Zhou, Lou, Zhong, 2016).

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