

# Gene Section

## Review

### MIR449A (microRNA 449a)

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#### Identity

**Other names:** MIRN449, MIRN449A, hsa-mir-449

**HGNC (Hugo):** MIR449A

**Location:** 5q11.2

#### DNA/RNA

##### Description

The microRNA-449 family is a group of three small, non-coding RNAs first identified in embryonic mice (Mineno et al., 2006; Wheeler et al., 2006) and highly conserved in different species.

The whole cluster consists of three members in human: miR-449a (MI0001648), miR-449b (MI0003673), and miR-449c (MI0003823), they are located in the second intron of the Cdc20b gene and they share its promoter.

Sequence miR-449a: uggcaguguauuguuagcuggu (22 bp)

Sequence miR-449b: aggcaguguauuguuagcuggc (22 bp)

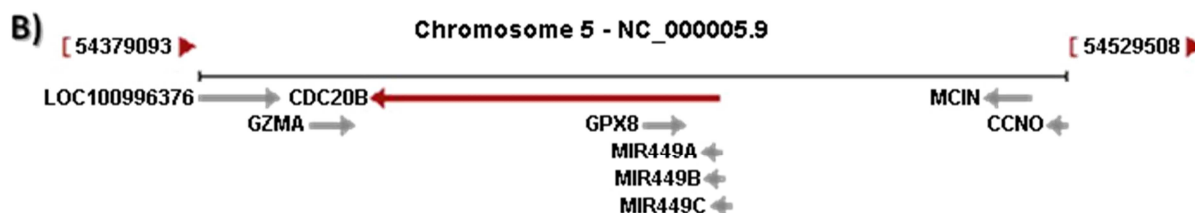
Sequence miR-449c: uaggcaguguauugcuagcggcugu (25 bp)

They regulate gene expression post-transcriptionally by mRNA degradation or translational repression (Esquela-Kerscher and Slack, 2006).

A)

	seed sequence
miR-449a	UGGCAGUGU <u>AUUGUUAGCUGGU</u>
miR-449b	AGGCAGUGU <u>AUUGUUAGCUGGC</u>
miR-449c	UAGGCAGUGU <u>AUUGCUAGCGGCUGU</u>
miR-34a	UGGCAGUGU <u>CUUAGCUGGUUGU</u>
miR-34b*	UAGGCAGUGU <u>CAUAGCUGAUUG</u>
miR-34c	AGGCAGUGU <u>AGUUAGCUGAUUGC</u>

A) Alignment of the mature sequences of the miR-34/449 family members. Modified from Lizé et al., 2010.



B) Genomic localization of miR-449 family on chromosome 5q11.2 (source: www.ncbi.nlm.nih.gov/gene/).

## Transcription

Transcription starts from chromosome 5: 54466360-54466450 [-] in human. E2F1 is a transcriptional activator of the locus (Yang et al., 2009; Lizé et al., 2010), IL-13 a repressor (Solberg et al., 2012).

The synthesis of miRNAs starts with the primary transcription by the RNA polymerase II (Lee et al., 2004) in the nucleus of a capped and polyadenylated precursor named pri-miRNA.

The pri-miRNA of miR-449a is 91 base pairs long, the one of miR-449b is 97 bp in and pri-miR-449c is 92 bp in.

The precursors are then further processed by the nucleases Drosha and Pasha, which are able to recognize and cut the stem-loop structure to generate the pre-miRNA.

Finally, these pre-miRNAs are exported into the cytoplasm and are cleaved by the ribonuclease Dicer (Lund and Dahlberg, 2006) to get the mature 22-25 bp miR-449.

The mature microRNA recognizes its target mostly via the "seed sequence", and when loaded into the RNA induced silencing complex (RISC), they lead to the degradation or the inhibition of the translation of the targeted mRNA (Hammond et al., 2000).

## Expression

miR-449 expression is strongly induced during mucociliary differentiation (Lizé et al., 2010; Marcet et al., 2011).

miR-449 is down-regulated in various cancers, most probably through epigenetic silencing (Yang et al., 2009; Noonan et al., 2009; Lizé et al., 2010; Noonan et al., 2010; Bou Kheir et al., 2011; Buurman et al., 2012; Chen et al., 2012).

miR-449 is E2F1- and DNA damage responsive and negatively regulates the E2F pathway both through the direct targeting of E2F transcription factors and indirectly through the downregulation of cyclin-dependent kinases (CDKs) either directly or through

the induction of the CDK-inhibitor p21 (Yang et al., 2009; Lizé et al., 2010). miR-449's promoter is repressed by Interleukin 13 (IL-13), leading to an increase in Notch expression and mucociliary differentiation alteration (Solberg et al., 2012). MiR-449 targets: cyclin dependent kinase 6 (CDK6), cell division cycle 25 homolog A (CDC25A); and histone deacetylase 1 (HDAC1), cyclin D1 (CCND1), cyclin E2 (CCNE2), SIRT1, Delta-like 1 (DLL1), E2F transcription factor 5 (E2F5), Geminin (GMNN), MET protooncogene (MET), v-myc avian myelocytomatosis viral related oncogene, neuroblastoma derived (N-myc), Drosophila notch homolog 1 (Notch1) (Bommer et al., 2007; Sun et al., 2008; Noonan et al., 2009; Redshaw et al., 2009; Yang et al., 2009; Lizé et al., 2010; Bou Kheir et al., 2011; Buechner et al., 2011; Lizé et al., 2011; Marcet et al., 2011).

## Localisation

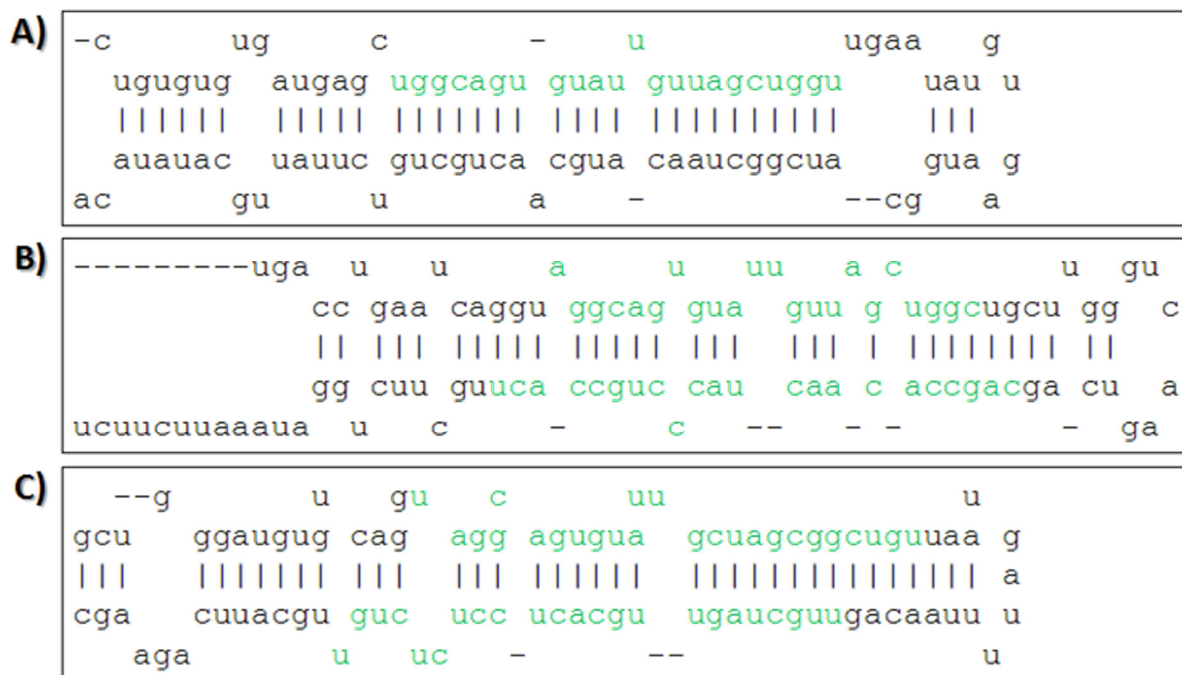
miR-449 is expressed at high levels in tissues containing ciliated cells, especially choroid plexus (Redshaw et al., 2009), lung, testis and trachea (Lizé et al., 2010; Marcet et al., 2011; Bao et al., 2012).

It is expressed specifically in multiciliated cells (Marcet et al., 2011).

## Function

miR-449 is a strong inducer of cell cycle arrest (including senescence) and apoptosis in tumor cell lines (Noonan et al., 2009; Yang et al., 2009; Lizé et al., 2010; Noonan et al., 2010; Bou Kheir et al., 2011). It is also involved in mucociliary differentiation (Lizé et al., 2010; Marcet et al., 2011).

miR-449 regulates several pathways (reviewed in Lizé et al., 2011) including Notch (Capuano et al., 2011; Marcet et al., 2011), p53 (Lizé et al., 2010), E2F-Rb (Redshaw et al., 2009; Yang et al., 2009; Lizé et al., 2010; Noonan et al., 2010; Bao et al., 2012), Wnt (Iliopoulos et al., 2009) and the cell cycle (Noonan et al., 2009; Yang et al., 2009; Lizé et al., 2010; Noonan et al., 2010; Bou Kheir et al., 2011).



**A)** Stem-loop structure of miR-449a. **B)** Stem-loop structure of miR-449b. **C)** Stem-loop structure of miR-449c. The sequence of the mature microRNAs is colored in green. (source: www.mirbase.org/).

## Protein

### Note

MicroRNAs are not translated into proteins. See DNA for further description.

## Mutations

### Note

No mutation was described.

## Implicated in

### Various cancers

#### Oncogenesis

MiR-449 functions as a tumor suppressor and is down-regulated in various cancer cells (Yang et al., 2009; Lizé et al., 2010; Ma and Tao, 2012) such as: lung adenocarcinoma and squamous cell carcinoma (Liang 2008), prostate cancer (Noonan et al., 2009), craniopharyngioma (Campanini et al., 2010), colon cancer cells (Wang et al., 2010), gastric cancer (Bou Kheir et al., 2011), hepatocellular carcinoma (Buurman et al., 2012), bladder cancer (Chen et al., 2012); while it is up-regulated in endometrioid adenocarcinoma (Wu et al., 2009).

#### Lung cancer

##### Note

In silico studies reveal that miR-449 may be down-regulated in different kinds of lung cancer such as lung adenocarcinoma and squamous cell carcinoma (Liang, 2008).

miR-449 is strongly down-regulated in the lung carcinoma cell line H1299 in comparison to normal lung tissue (Lizé et al., 2010).

#### Prostate cancer

##### Note

In prostate cancer, miR-449 has a role in cell growth regulation by repressing the histone deacetylase 1 (HDAC-1) expression. The activation of HDAC1 by the loss of miR-449 in prostate cancer cells is critical for their epigenetic evolution (Noonan et al., 2009).

#### Craniopharyngioma

##### Note

The down-regulation of miR-449 may have a role in the inhibition of the Wnt signaling pathway in craniopharyngioma (Campanini et al., 2010).

#### Gastric cancer

##### Note

miR-449 is down-regulated or even absent in mouse models of gastric cancer and in primary human gastric tumors (Wang et al., 2010; Bou Kheir et al., 2011). Although the development of gastric cancer is primarily related to *H. Pylori* infection, levels of gastrin are also involved in gastric cancer. Studies of the miR-449b expression in Gastrin knockout mice and in mice infected by *H. pylori* showed that, in both cases, the miR-449b is down-regulated compared to the control mice. Moreover, ectopic expression of miR-449b in SNU638 cells affects their proliferation and leads to apoptosis and senescence.

## Hepatocellular carcinoma

### Note

MiR-449 is down-regulated in hepatocellular carcinoma which results in high levels of histone deacetylases, leading to increased c-MET. C-Met is the receptor for hepatocyte growth factor in hepatocellular carcinoma cells (Buurman et al., 2012).

## Bladder cancer

### Note

miR-449a is downregulated in bladder cancer cells as compared to normal tissue. Reintroduction of miR-449 in the bladder cancer cell lines T24 and 5537 lead rather to cell cycle arrest than to apoptosis. The inhibition of the tumor growth by using liposome encapsulated miR-449a in vivo was successful (Chen et al., 2012).

## Endometrioid adenocarcinoma

### Note

MiR-449 is up-regulated in endometrioid adenocarcinoma cells. The expression of the estrogen receptor gene, entailed in this cancer type, could be regulated by miR-449 (Wu et al., 2009).

## Asthma

### Note

A common feature of asthma is the alteration of the airway epithelial cells. The analyses of asthmatic bronchial epithelium showed that interleukin 13 (IL-13) contributes to miR-449 repression in asthma. This leads to an increase of the Notch expression, which results in the reduction of ciliated cell and increase of mucous cells (Solberg et al., 2012).

## Primary pigmented nodular adrenocortical disease

### Note

miR-449 is up-regulated in primary pigmented nodular adrenocortical disease (PPNAD) (Iliopoulos et al., 2009).

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