

# Gene Section

## Review

### MIR191 (microRNA 191)

Sabrina Battista, Marianna Colamaio, Alfredo Fusco

Istituto di Endocrinologia e Oncologia Sperimentale / CNR, Via Pansini 5, 80131, Naples, Italy (SB, MC, AF)

Published in Atlas Database: January 2013

Online updated version : <http://AtlasGeneticsOncology.org/Genes/MIR191ID51786ch3p21.html>  
DOI: 10.4267/2042/51040

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.  
© 2013 Atlas of Genetics and Cytogenetics in Oncology and Haematology

#### Identity

**Other names:** MIRN191, miR-191

**HGNC (Hugo):** MIR191

**Location:** 3p21.31

**Local order:** Based on Mapviewer (Master Map: Genes on sequence), genes flanking miR-191, oriented from centromere to telomere on 3p21.31 are:

- WDR6: (+ strand) WD repeat domain 6
- DALRD3: (- strand) DALR anticodon binding domain containing 3
- MIR425: (- strand) microRNA 425
- **MIR191: (- strand) microRNA 191**
- NDUFAF3: (+ strand) NADH dehydrogenase (ubiquinone) complex I, assembly factor 3
- IMPDH2: (- strand) IMP (inosine 5'-monophosphate) dehydrogenase 2
- QRICH1: (- strand) glutamine-rich 1.

#### DNA/RNA

##### Description

miR-191 is located on chromosome 3, at 3p21.31 according to Entrez Gene. miR-191 is clustered together with miR-425, from which it is separated by 384 bases. miR-191 and miR-425 are intronic miRNAs, located in the intron of the DALRD3 gene, which belongs to a three-gene complex genome architecture composed by WDR6, DALRD3 and NDUFAF3. The positions of these cluster microRNAs are:

- hsa-mir-191: chr3:49058051-49058142 [-]
- has-mir-425 chr3:49057581-49057667 [-].

##### Transcription

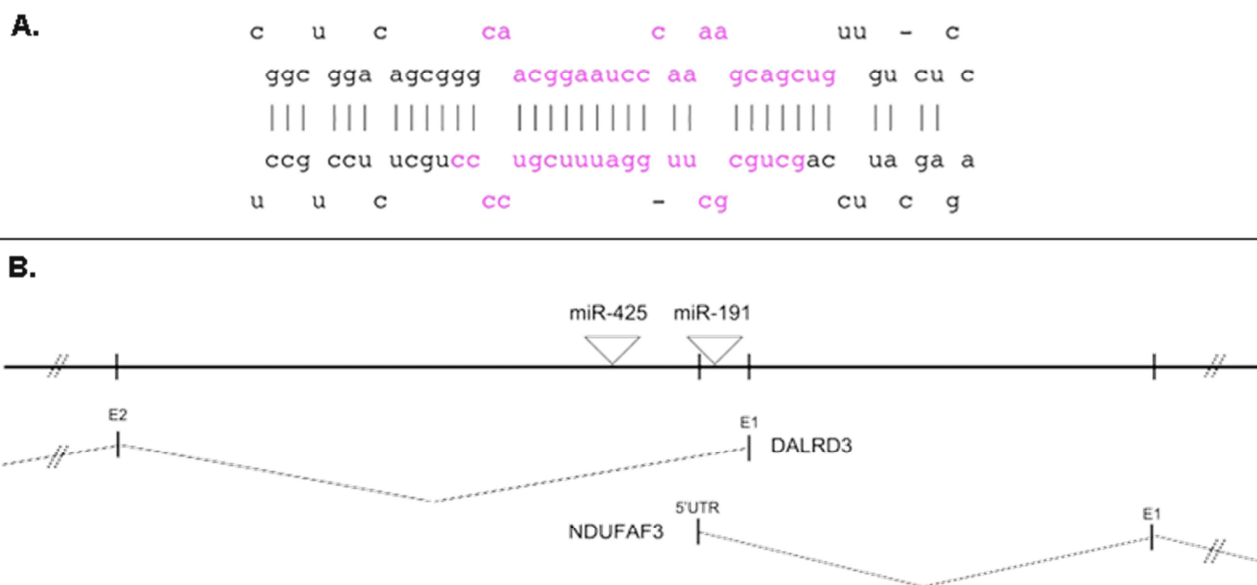
As for other miRNAs located within introns, miR-191 expression is dependent on the transcriptional regulation of its host gene (DALRD3), and tend to be transcribed into one transcript by RNA polymerase II, due to common transcription event. A CpG-rich sequence in the DALRD3 promoter and a DNA methylation signal located in this region are responsible for its transcriptional regulation. Accordingly, hypomethylation at the miR-191 locus correlates to its overexpression (and the expression of its host gene). The primary transcript (pri-miRNA), which harbors a local hairpin structure, is then cropped by a nuclear RNase III, Drosha, into ~ 70 nt precursor miRNA (pre-miRNA). The ~22 nucleotide mature miRNA sequence is excised from the precursor hairpin by the enzyme Dicer. This sequence then associates with RISC, hence triggering the cleavage of their mRNA target molecules or acting as translational repressors, by recognizing a region of homology in the 3'-UTR of the target messenger. The antisense sequence to miR-191 within the hairpin pre-miRNA is also processed as a minor sequence miRNA, named miR-191\*.

Overlapping transcripts:

- DALRD3, intron1 (sense);
- NDUFAF3, intron1 (antisense).

miR-191 is expressed in normal tissues. Down-regulation and up-regulation of miR-191 expression has been frequently described in human neoplasias.

miR-191 has also been found to be regulated by environmental factors, such as cigarette smoke and dioxin, seemingly linking miR-191 expression to a response to environmental pollutants.



**Figure 1.** Mir-191. **A.** Stem loop structure of miR-191. **B.** Model of genomic organization and transcriptional regulation of miR-191 and miR-425, associated with coexpression of NDUFAF3-DALRD3 sense-antisense gene pair.

AGGCAGGAGAGCAGGGGACGAAATCCAAGCGCAGCTGGAATGCTCTGG  
 AGACAACAGCTGCTTTTGGGATTCCGTTG**C**CCGCTGTCCAGCCG

**Figure 2.** Sequence of miR-191 gene, in which the nucleotide found mutated in familial ovarian cancers (red) is immediately downstream the sequence corresponding to the mature miRNA (bold).

**Pre-microRNA 191 (Precursor microRNA)**

- Accession: MI0000465
- Transcript length: 92 bp
- Sequence:  
 CGGCUGGACAGCGGGCAACGGAAUCCCAAAA  
 GCAGCUGUUGUCUCCAGAGCAUCCAGCUGC  
 GCUUGGAUUUCGUCCCCUGCUCUCCUGCCU

**Mature miR-191 (miR-191-5p)**

- Accession: MIMAT0000440
- Length: 23 nucleotides
- Sequence:  
 16-CAACGGAAUCCCAAAAAGCAGCUG-38

**Minor mirna sequence (hsa-miR-191-3p)**

- Previous ID: hsa-miR-191\*
- Accession: MIMAT0001618
- Length: 22 nucleotides
- Sequence:  
 58 - GCUGCGCUUGGAUUUCGUCCCC - 79

**Pseudogene**

No pseudogenes were reported for mir-191.

**Protein**

**Note**  
 MicroRNAs are not translated into aminoacids.

**Mutations**

**Note**  
 One rare variant has been found in the miR-191 gene in familial ovarian cancers. More precisely, a C to A substitution has been found in the precursor region (nucleotide 15), but not in the mature microRNA. This variant in the precursor of miR-191 slightly alters its secondary structure, hence affecting the expression of the mature miRNA.

**Germinal**

Yes.

**Implicated in**

**Acute myeloid leukemia**

**Prognosis**  
 Patients with high expression of miR-191 (and miR-199a) have significantly worse overall and event-free survival than AML patients with low expression.

**Oncogenesis**  
 miR-191 overexpression has been found in acute myeloid leukaemia (AML), where it correlates with a poor survival. miR-191 is the most overexpressed miRNA in human leukemic cell lines harboring ALL-1 rearrangements.

Its overexpression is due to All1 fusion protein mediating Drosha recruitment to the miR-191 locus and increasing pri-miRNA processing.

### **Chronic lymphocytic leukemia (CLL)**

#### **Note**

miR-191 is downregulated in CLL compared to mononuclear cells (MNC).

### **Solid tumors**

#### **Note**

miR-191 has been found dysregulated in a large number of different types of human tumor, including those of colon, lung, pancreas, prostate and stomach. CDK6 has been validated as one target of the mature miRNA, whereas the factors leading to its dysregulation in cancer cells are not known yet.

### **Ovarian cancers**

#### **Oncogenesis**

The MDM4 gene in a series of ovarian cancer cell lines and carcinomas may carry an SNP (SNP34091) in its 3'-UTR that creates a putative target site for hsa-miR-191. Biochemical evidence supports specific miR-191-dependent regulation of the MDM4-C, but not MDM4-A, variant.

### **Follicular thyroid carcinomas**

#### **Oncogenesis**

miR-191 is downregulated in thyroid follicular adenomas (FAs), follicular thyroid carcinomas (FTCs) and follicular variant of papillary thyroid carcinomas (FVPTCs). CDK6, a serine-threonine kinase involved in the control of cell cycle progression, has been identified as target of miR-191. Restoration of miR-191 expression in WRO cells reduces cell growth and migration rate on vitronectin. CDK6 overexpression, correlated with miR-191 downregulation, has been found in FAs and FTCs suggesting a role of miR-191 downregulation in the generation of these neoplasias.

### **Hepatocellular carcinomas (HCC)**

#### **Prognosis**

miR-191 is overexpressed in hepatocellular carcinomas. High miR-191 expression is associated with a poor prognosis. Inhibition of miR-191 decreases cell proliferation, induces apoptosis in vitro and significantly reduces tumor masses in vivo in an orthotopic xenograft mouse model of HCC.

#### **Oncogenesis**

Hypomethylation at the hsa-miR-191 locus was correlated to its overexpression (and the expression of its host gene) in human hepatocellular carcinomas (HCC) tissues. Hepatocellular carcinoma cell lines (Hep3B), transfected with increasing amount of anti-miR-191, exhibited a decreased proliferation compared with those transfected with a negative control.

The pathways most influenced were mitogen-activated protein kinase (MAPK) extracellular signal-regulated kinase, transforming growth factor- $\beta$  (TGF- $\beta$ ) and MAPK/c-Jun NH<sub>2</sub>-terminal kinase, which are important pathways in human hepatocarcinogenesis. Overexpression of hsa-miR-191 induces epithelial-to-mesenchymal transition into SMMC-7721 human hepatoma cells, at least in part by targeting the tissue inhibitor of metalloproteinase 3 (TIMP3).

### **Spermatogenesis**

#### **Note**

An association of miR-191, miR-425, DALRD3 and NDUFAF3 with spermatogenesis has been suggested. These genes are strongly co-expressed in sperm cells of normal individuals, whereas they are turned off in patients with teratozoospermia. These miRNAs, directly associated with co-transcription of DALRD3 and NDUFAF3, might be involved in a negative feedback loop, by targeting DICER and basonuclin (BNC2).

### **Erythropoiesis**

#### **Note**

miR-191 is abundantly expressed in colony-forming-units of erythroid lineages (CFU-Es) in which it accounts for 3,5% of all miRNAs. Down-regulation of miR-191 in committed erythroid progenitors CFU-E is essential for erythroid chromatin condensation and enucleation by up-regulating of Rik3 and Mxi1.

### **Type 1 diabetes mellitus (T1D)**

#### **Note**

MiR-191 was down-regulated (2,7-fold change) in the Tregs of diabetic patients.

#### **Disease**

T1D is a chronic autoimmune disease. Diabetes arises from a loss of tolerance to beta cells of the islets of Langerhans in the pancreas, resulting in T cell-mediated destruction of those islet cells and concomitant hyperglycaemia. T regulatory cells (Tregs) are essential for immune regulation and are involved in maintaining peripheral tolerance to autoantigens, which become altered during T1D.

### **Keratinocyte senescence**

#### **Note**

miR-191 is up-regulated in senescent human epidermal keratinocytes and has been demonstrated to have an anti-proliferative and replicative senescence-associated function in primary human keratinocytes. Its overexpression in proliferating HEK293 is sufficient per se to induce senescence, as evaluated by induction of several senescence-associated markers. Special AT-rich Binding protein 1 (SATB1) and the Cyclin Dependent Kinase 6 (CDK6) mRNAs are two miR-191 direct targets involved in this pathway.

## Toxicology of dioxin

### Note

Transcription of miR-191 has been shown to be stimulated by dioxin (TCDD), through the binding to the aryl hydrocarbon receptor (AhR)/AhR nuclear translocator (Arnt), which is able to bind a region close to the transcription start site (TSS) at the location chr3:49034919-49034937.

## Toxicology of cigarette smoke

### Note

Expression of miR-191 was demonstrated to be downregulated, together with other miRNAs, in lungs of rats exposed to environmental cigarette smoke (ECS), (a form of indoor air pollution resulting from the mixture of sidestream CS and that portion of mainstream CS that is released by actively smoking individuals into ambient air). This finding sheds light on fundamental pathogenic mechanisms involved in the damage produced by CS in its main target organ.

## Chemoprotection of nutritional bioactives against colorectal cancer

### Note

A growing number of clinical and experimental studies indicate a protective effect of dietary fish oil, containing n-3 polyunsaturated fatty acids (PUFA), with respect to colon cancer risk, especially when associated with the fiber pectin in the diet. It has been demonstrated that the colonic mucosa of azoxymethane- (AOM) injected rats shows a reduction of several miRNAs, among which miR-191, at 10 weeks, and develops colon cancers at 34 weeks, whereas in AOM-injected rats fed with pectin and fish oil, miR-191 expression was not downregulated and the number of tumors was significantly reduced. These data provide evidence that miR-191 mediates the chemoprotective role of dietary components against cancer progression.

## References

- Calin GA, Liu CG, Sevignani C, Ferracin M, Felli N, Dumitru CD, Shimizu M, Cimmino A, Zupo S, Dono M, Dell'Aquila ML, Alder H, Rassenti L, Kipps TJ, Bullrich F, Negrini M, Croce CM. MicroRNA profiling reveals distinct signatures in B cell chronic lymphocytic leukemias. *Proc Natl Acad Sci U S A*. 2004 Aug 10;101(32):11755-60
- Kasashima K, Nakamura Y, Kozu T. Altered expression profiles of microRNAs during TPA-induced differentiation of HL-60 cells. *Biochem Biophys Res Commun*. 2004 Sep 17;322(2):403-10
- Rodríguez A, Griffiths-Jones S, Ashurst JL, Bradley A. Identification of mammalian microRNA host genes and transcription units. *Genome Res*. 2004 Oct;14(10A):1902-10
- Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, Visone R, Iorio M, Roldo C, Ferracin M, Prueitt RL, Yanaihara N, Lanza G, Scarpa A, Vecchione A, Negrini M, Harris CC, Croce CM. A microRNA expression signature of human solid

tumors defines cancer gene targets. *Proc Natl Acad Sci U S A*. 2006 Feb 14;103(7):2257-61

Yanaihara N, Caplen N, Bowman E, Seike M, Kumamoto K, Yi M, Stephens RM, Okamoto A, Yokota J, Tanaka T, Calin GA, Liu CG, Croce CM, Harris CC. Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. *Cancer Cell*. 2006 Mar;9(3):189-98

Nakamura T, Canaani E, Croce CM. Oncogenic All1 fusion proteins target Drosha-mediated microRNA processing. *Proc Natl Acad Sci U S A*. 2007 Jun 26;104(26):10980-5

Garzon R, Volinia S, Liu CG, Fernandez-Cymering C, Palumbo T, Pichiorri F, Fabbri M, Coombes K, Alder H, Nakamura T, Flomenberg N, Marcucci G, Calin GA, Kornblau SM, Kantarjian H, Bloomfield CD, Andreeff M, Croce CM. MicroRNA signatures associated with cytogenetics and prognosis in acute myeloid leukemia. *Blood*. 2008 Mar 15;111(6):3183-9

Davidson LA, Wang N, Shah MS, Lupton JR, Ivanov I, Chapkin RS. n-3 Polyunsaturated fatty acids modulate carcinogen-directed non-coding microRNA signatures in rat colon. *Carcinogenesis*. 2009 Dec;30(12):2077-84

Izzotti A, Calin GA, Arrigo P, Steele VE, Croce CM, De Flora S. Downregulation of microRNA expression in the lungs of rats exposed to cigarette smoke. *FASEB J*. 2009 Mar;23(3):806-12

Elyakim E, Sitbon E, Faerman A, Tabak S, Montia E, Belanis L, Dov A, Marcusson EG, Bennett CF, Chajut A, Cohen D, Yerushalmi N. hsa-miR-191 is a candidate oncogene target for hepatocellular carcinoma therapy. *Cancer Res*. 2010 Oct 15;70(20):8077-87

Hezova R, Slaby O, Faltejskova P, Mikulkova Z, Buresova I, Raja KR, Hodek J, Ovesna J, Michalek J. microRNA-342, microRNA-191 and microRNA-510 are differentially expressed in T regulatory cells of type 1 diabetic patients. *Cell Immunol*. 2010;260(2):70-4

Wynendaale J, Böhnke A, Leucci E, Nielsen SJ, Lambertz I, Hammer S, Sbrzesny N, Kubitzka D, Wolf A, Gradhand E, Balschun K, Braicu I, Sehouli J, Darb-Esfahani S, Denkert C, Thomssen C, Hauptmann S, Lund A, Marine JC, Bartel F. An illegitimate microRNA target site within the 3' UTR of MDM4 affects ovarian cancer progression and chemosensitivity. *Cancer Res*. 2010 Dec 1;70(23):9641-9

Colamaio M, Borbone E, Russo L, Bianco M, Federico A, Califano D, Chiappetta G, Pallante P, Troncone G, Battista S, Fusco A. miR-191 down-regulation plays a role in thyroid follicular tumors through CDK6 targeting. *J Clin Endocrinol Metab*. 2011 Dec;96(12):E1915-24

He Y, Cui Y, Wang W, Gu J, Guo S, Ma K, Luo X. Hypomethylation of the hsa-miR-191 locus causes high expression of hsa-mir-191 and promotes the epithelial-to-mesenchymal transition in hepatocellular carcinoma. *Neoplasia*. 2011 Sep;13(9):841-53

Zhang L, Flygare J, Wong P, Lim B, Lodish HF. miR-191 regulates mouse erythroblast enucleation by down-regulating Rik3 and Mxi1. *Genes Dev*. 2011 Jan 15;25(2):119-24

Lena AM, Mancini M, Rivetti di Val Cervo P, Saintigny G, Mahé C, Melino G, Candì E. MicroRNA-191 triggers keratinocytes senescence by SATB1 and CDK6 downregulation. *Biochem Biophys Res Commun*. 2012 Jul 6;423(3):509-14

---

*This article should be referenced as such:*

Battista S, Colamaio M, Fusco A. MIR191 (microRNA 191). *Atlas Genet Cytogenet Oncol Haematol*. 2013; 17(7):453-456.

---