

# microARN - BIF7101

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  - microARN et séquençage à haut débit
  - Bases de données, services web et visualisation
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# Interférence par ARN

- Mécanisme de régulation post-transcriptionnelle de l'expression des gènes
- Implique des petits ARNs simple ou double brin
- Répression ou dégradation de l'ARN messager

## Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*

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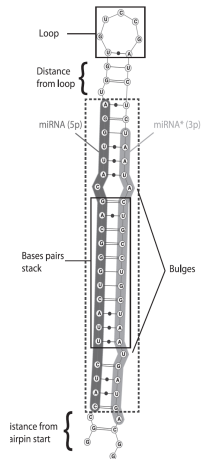
Experimental introduction of RNA into cells can be used in certain biological systems to interfere with the function of an endogenous gene<sup>1,2</sup>. Such effects have been proposed to result from a simple antisense mechanism that depends on hybridization between the injected RNA and endogenous messenger RNA transcripts. RNA interference has been used in the nematode *Caenorhabditis elegans* to manipulate gene expression<sup>3,4</sup>. Here we investigate the requirements for structure and delivery of the

# microARN - structure primaire

- Découverts chez *C. elegans* en 1993 (*lin-4*) (Lee *et al.*)
  - Nommés « microRNAs » en 2001 (Lagos-Quintana *et al.*)
- 
- Petit brin d'ARN
  - Taille de 18 nd à 25 nd
  - Issus d'une plus longue séquence d'ARN appelée pré-miARN
  - Localisés dans plusieurs régions du génome
  - Exprimés par des eucaryotes, procaryotes et virus

# microARN - structure secondaire

- pré-microARN, séquence d'une centaine de nucléotides
- Pliée en épingle cheveux (tige-boucle)
- Complémentarité imparfaite (boucle, hernies)
- Duplex microARN 5p - microARN 3p



**Figure** – Structure secondaire d'un pré-miARN (Leclercq et al., 2013)

# Biogenèse

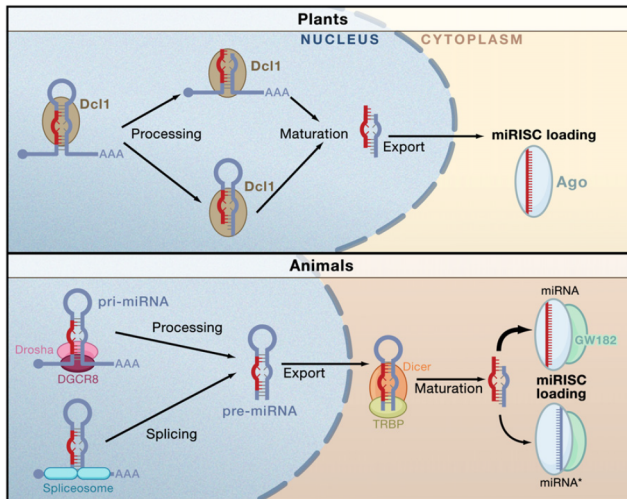


Figure – Biogenèse des microARN chez les plantes et les animaux (Carthew et Sontheimer, 2009)

# Isomirs

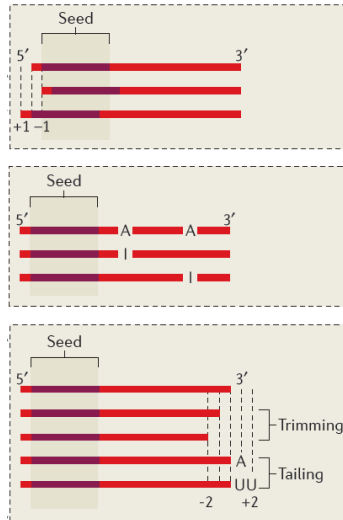


Figure – Différents types d'isomirs (isoformes) (Ameres et Zamore, 2013, modifié)

# microARNs chez les plantes et les animaux

	Plants	Animals
Number of miRNA genes present	100 < number < 200 of genes	100 < number < 500 of genes
Location within genome	Predominantly intergenic regions	Intergenic regions introns
Presence of miRNA clusters	Uncommon	Common
MiRNA biosynthesis	Dicer-like	Drosha, Dicer
Mechanism of repression	mRNA-cleavage (methylation?)	Translational repression
Location of miRNA binding motifs within target genes	Predominantly the open-reading frame	Predominantly the 3-UTR
Number of miRNA binding sites within target genes	Generally one	Generally multiple
Function of known target genes	Regulatory genes-crucial for development, enzymes	Regulatory genes-crucial for development, structural proteins, enzymes

**Table – Caractéristiques des miARNs chez les plantes et les animaux** (Millar *et al.*, 2005)



# Implications des microARNs

- Développement et croissance
- Processus biologiques
- Stress biotiques (réponses immunitaires)
- Stress abiotiques (Sécheresse, froid, salinité, etc.)
- Implication dans le cancer
- ... etc.

# Mécanismes de fonctions des microARNs

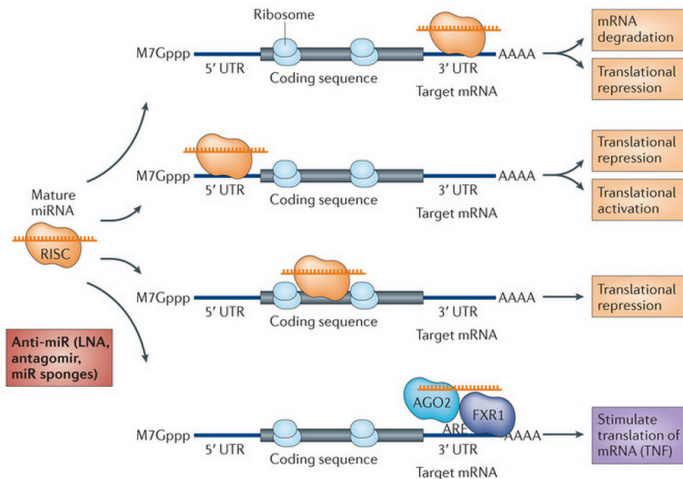


Figure – Différentes fonctions des microARNs (Ling *et al.*, 2013, modifiée)

# microARNs et bioinformatique

- Prédiction des microARNs
- Prédiction des gènes cibles
- microARN et séquençage à haut débit (NGS)
- Bases de données, services web et visualisation

# Prédiction par homologie

- Méthodes comparatives
- Conservation chez des espèces proches ou lointaines
  - Conservation de la structure secondaire
  - Conservation de la séquence
- Blast
- srnaloop (Grad *et al.*, 2003) (*C. elegans*)
- MiRscan (Lim *et al.*, 2003) (Nématodes)
- MiRseeker (Lai *et al.*, 2003) (Mouches)

# Prédiction *ab initio*

- Approches basées sur des filtres
- Approches basées sur l'apprentissage automatique (machine learning)
- Approches basées sur le duplex microARN:ARNm
- Approches intégratives traitant les données NGS

# Prédiction par filtres

- Identification de potentielles séquences en épingle à cheveux qui
  - portent des séquences inversement répétées
  - ou s'alignent avec des petits ARNs séquencés
- Filtres :
  - Taux de GC
  - Longueur du précurseur
  - Minimum Folding Energy (MFE)
  - Nombre des nucléotides non appariés dans le duplex miARN:miARN\*
  - Nombre des hernies (bulges) et des boucles internes
  - Différence de taille entre le miARN et miARN\*
- MiRscanII (Ohler *et al.*, 2004)
- MIRcheck (Jones-Rhoades et Bartel, 2004)
- MIRFINDER (Bonnet *et al.*, 2004)

# Prédiction par apprentissage automatique

- Utilisation d'un ensemble d'attributs/caractéristiques
- Entraînement des données avec deux ensembles
  - Données positives : microARNs et leurs précurseurs validés expérimentalement ou potentiellement vrais
  - Données négatives : D'autres types d'ARN (ARNr, ARNt, etc.) ou séquences génomiques extraites aléatoirement.
- ProMir (Nam *et al.*, 2005)
- Triplet-SVM (Xue *et al.*, 2005)
- miR-abela (Sewer *et al.*, 2005)
- miPred (Jiang *et al.*, 2007)
- HHMMIR (Kadri *et al.*, 2009)
- mirDup (Leclercq *et al.*, 2013)
- ... etc.

# Prédiction par apprentissage automatique

## Quelques caractéristiques

Attribut	Description
Triplets	Pourcentage de chaque triplet (Défini dans Xue et al. 2005)
Dinucléotides	Pourcentage de AA, AU, AG, AC, UA, UU, UG, UC, GA, GU, GG, GC, CA, CU, CG
Hernies	Positions, longueur et nombre de hernies dans le microARN et environs
Pairage	Nombre de paires de bases dans une fenêtre glissante de longueur 3, 5 ou 7. Présence d'une position avec un 5, 10 ou 20 mer complètement apparié.
Compositions nucléotides	Pourcentage de A, C, G et U
Types de paires de base	Pourcentage de paires de bases dans le duplexe : G-C, G-U et A-U
Boucle	miRNA dans la boucle de l'épingle
Distance du miRNA à la boucle ou au départ et fin de l'épingle	Situation du miRNA entre la boucle et le début et fin de l'épingle
G+C	Contenu GC du miRNA
MFE duplex	Energie minimale du repliement du duplexe miRNA-miRNA*
Longueur	Longueur du miRNA



# Prédiction par apprentissage automatique

## Machine à vecteurs de support (SVM)

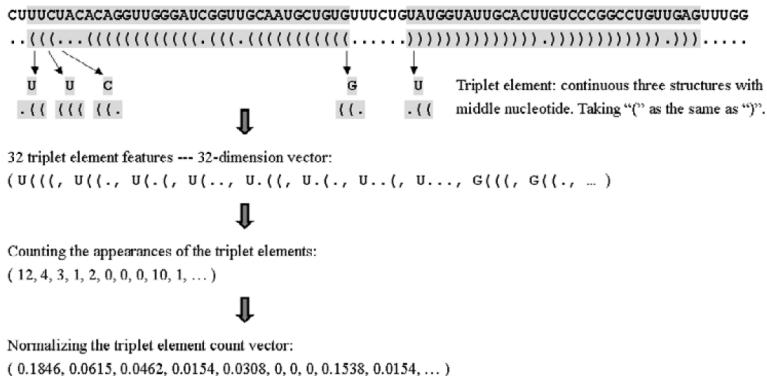


Figure – triplet-SVM (Xue *et al.*, 2005)

# Prédiction par apprentissage automatique

## Modèle de Markov caché (HMM)

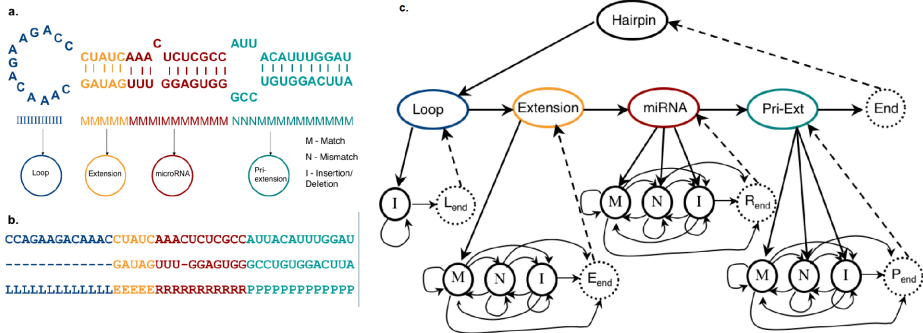
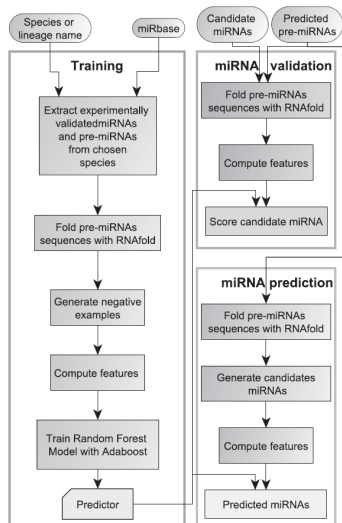


Figure – HHMMIR (Kadri *et al.*, 2009)

# Prédiction par apprentissage automatique



Random Forest avec Adaboost

Figure – mirDup (Leclercq et al., 2013)

# Prédiction basée sur le duplex microARN:ARNm

- Alignement des régions 3'-UTR de plusieurs génomes conservés
- Identification des motifs courts et conservés
- Extraction des séquences en épingle à cheveux contenant le complémentaire de ces motifs
- (Xie *et al.*, 2005)

# Approches intégratives traitant les données NGS

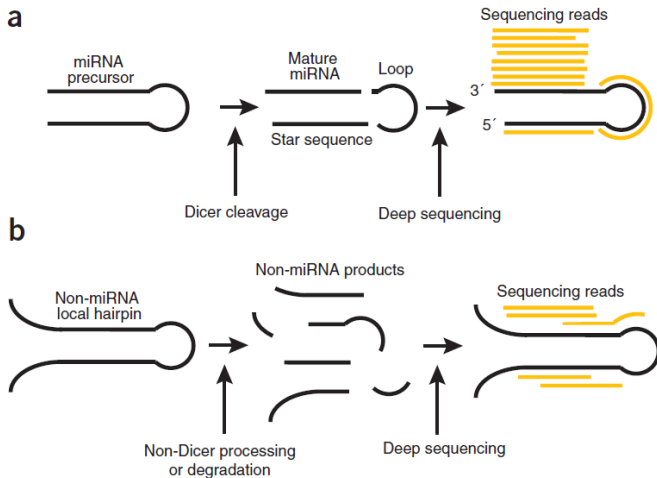


Figure – mirDeep (Friedlander *et al.*, 2008)

# Prédiction des gènes cibles

- Un microARN n'est fonctionnel que s'il cible un gène
- Animaux
  - Cible la région 3'-UTR de l'ARNm
  - Complémentarité microARN:ARNm faible (mismatches, gaps, couples G:U)
- Plantes
  - Cible n'importe quelle région de l'ARNm
  - Complémentarité microARN:ARNm presque parfaite

# Prédiction des gènes cibles

- Approches basées sur la conservation du seed 5' (nd 2 à nd 8) et la stabilité thermodynamique du microARN:ARNm
  - TargetScan (Lewis *et al.*, 2005)
  - picTar (Krek *et al.*, 2005)
  - DIANA-microT (Kiriakidou *et al.*, 2004)
- Approches basées sur l'apprentissage automatique
  - Programmation génétique : TargetBoost (Saetrom *et al.*, 2005)
  - SVM : MiTarget (Kim *et al.*, 2006)
- Services web
  - TAPIR (Bonnet *et al.*, 2010)
  - psRNATarget (Dai *et al.*, 2011)

# Pipeline d'identification à partir de données NGS

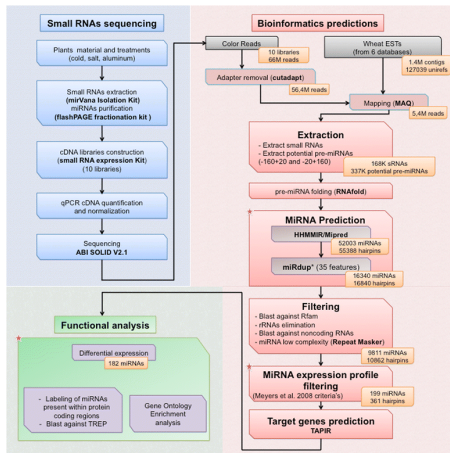


Figure – (Agharbaoui *et al.*, 2015)



# Rfam



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## Family: *mir-156* (RF00073)

Description: *mir-156* microRNA precursor

Summary

Sequences

Alignment

Secondary structure

Species

Trees

Structures

Motif matches

Database references

Curation

Jump to...

enter ID or GO

634 sequences

41 cons

0 structures

### Secondary structure

This section shows a variety of different secondary structure representations for this family. [More...](#)

You can view the secondary structure of the family using the [VARNA](#) applet. You can see more information about VARNA itself [here](#).

seqcons

bpcons

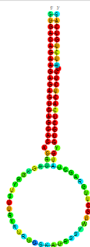
cov

ent

maxcm

norm

rbie



0.00 1.00  
Sequence Conservation

# miRBase


miRBase


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## Search miRBase

### By miRNA identifier or keyword

Enter a miRNA accession, name or keyword:

### By genomic location

Select organism, chromosome and start and end coordinates. Leave the start/end boxes blank to retrieve all miRNAs on the selected chromosome.

Choose species:  Chr:  Start:  End:

### For clusters

Select organism and the desired inter-miRNA distance.

Choose species:  Inter-miRNA distance:

### By tissue expression

Select organism and tissue.

Choose species:  Select tissue:

### By sequence

**Single sequence searches:**

Paste a sequence here to search for similarity with miRBase miRNA sequences (**max size 1000 nts**). You can choose to search against hairpin precursor sequences or mature miRNAs. This search may take a few minutes. Please note: this facility is designed to search for homologs of microRNA sequences, **not to predict their target sites**. For target site prediction, please use [the available bespoke tools](#).

**Search sequences:**

**Search method:**

Choose BLASTN to search for a miRNA homolog in a longer sequence. SSEARCH is useful for finding a short sequence within the library of miRNAs (for instance, find a short motif in a miRNA or precursor stem-loop, or find mature sequences that are related to your query).

**E-value cutoff:**

**Maximum no. of hits:**

**Show results only from specific organisms:**

Mature miRNAs

BLASTN

10

100

☐ human
 ☐ mouse
 ☐ worm
 ☐ fly
 ☐ Arabidopsis

or choose a taxonomic classification:

No species filter

**Or:** Select the sequence file you wish to use




# Next-Gen Sequence Databases

← → ↻ <https://mpss.danforthcenter.org>



**Next-Gen Sequence DBs & Web Tools**

Next-Gen DBs   miRNA Tools   Target Prediction

**SBS DATABASES**

	Organism	small RNADBs	RNA-seq DBs	PARE DBs	miRNA DGE DBs	MethylC-seq DBs	ChIP DBs
 <b>amborella</b> Next-Gen Sequence DBs	Amborella	<a href="#">link</a>		<a href="#">link</a>			
 <b>apple</b> Next-Gen Sequence DBs	Apple	<a href="#">link</a>					
 <b>arabidopsis</b> Next-Gen Sequence DBs	Arabidopsis	<a href="#">link</a> <a href="#">link-2</a>	<a href="#">link</a>	<a href="#">link</a>		<a href="#">link</a>	
 <b>brachypodium</b> Next-Gen Sequence DBs	Brachypodium	<a href="#">link</a> <a href="#">link-2</a>		<a href="#">link</a> <a href="#">link-2</a>			
 <b>gallus gallus</b> Next-Gen Sequence DBs	Chicken	<a href="#">link</a>					
 <b>grape</b> Next-Gen Sequence DBs	Grape	<a href="#">link - Affac</a> <a href="#">link - PI</a>					
 <b>magnaporthe</b> Next-Gen Sequence DBs	Magnaporthe	<a href="#">link</a>					
 <b>maize</b> Next-Gen Sequence DBs	Maize	<a href="#">link</a> <a href="#">link</a>	<a href="#">link</a> <a href="#">link</a>	<a href="#">link</a>			
 <b>legume medicago</b> Next-Gen Sequence DBs	Medicago	<a href="#">link</a>		<a href="#">link</a>			
 <b>mimulus</b> Next-Gen Sequence DBs	Mimulus	<a href="#">link</a>					
 <b>orange</b> Next-Gen Sequence DBs	Orange	<a href="#">link</a>					
 <b>papaya</b> Next-Gen Sequence DBs	Papaya	<a href="#">link</a>					
 <b>peach</b> Next-Gen Sequence DBs	Peach	<a href="#">link</a>					
 <b>poplar</b> Next-Gen Sequence DBs	Poplar	<a href="#">link</a>					
 <b>potato</b> Next-Gen Sequence DBs	Potato	<a href="#">link</a>					
 <b>rice</b> Next-Gen Sequence DBs	Rice	<a href="#">link</a> <a href="#">link-2</a> <a href="#">link-3</a>	<a href="#">link</a>	<a href="#">link</a>	<a href="#">link</a>	<a href="#">link</a>	<a href="#">link</a>
 <b>rice</b> Next-Gen Sequence DBs	Rice_glab	<a href="#">link</a>	<a href="#">link</a>				
<b>legume</b> Next-Gen Sequence DBs	Legume						

# Wheat microRNA Portal

## Wheat MicroRNA Portal

[Home/Search](#) | [Advanced Search](#) | [Data](#) | [Tools](#) | [Citations](#)

**Welcome to the UQAM Wheat microRNA Portal !**

You will find inside a total of **10 small RNA libraries** under different abiotic stress.

You will also find inside a compilation of published wheat microRNAs from different studies (**5468 wheat microRNAs** - September 2014).

Finally, you can verify your putative wheat, cereal and plant microRNAs using the web server version of **Mirdup v1.2** and **MirCheck v1.0**.

### Libraries

View the microRNAs in the investigated wheat libraries

Aerials tissues from plants in vegetative phase under normal conditions [Go](#)

### Experimental conditions

View the microRNAs by experimental conditions

Vernalisation response in winter wheat [Go](#)

### Differential microRNA expression

Searching for differential miRNA expression between different experimental conditions

e.g. MicroRNAs upregulated in vernalisation response but downregulated in aluminium response

### Searching for sequence identifiers

You can search for microRNAs by ID or Target ID

e.g. *apMir\_20602*, *Glutathione peroxidase*, or gene ontology *GO:0008152*

### Quick link

All the predicted wheat microRNAs and associated hairpins **Total 2239**

Putative miRNAs found in this database **Total 1369**

All the conserved wheat microRNAs found in this database **Total 267**

Clusters of microRNAs found in this database **Total 345**

All published wheat microRNAs included in this database **Total 5468**

### Statistics (version 1.0)

Latest update: September 2014

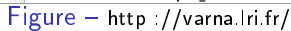
Number of validated microRNAs: **1369**

Number of associated targets: **6 841**

Number of associated ests: **4 446**

Number of small RNAs associated with ests: **168 834**

## Remita, M. A.



# Visualisation

## Représentation textuelle

```

2522 #####
2523 |
2524 # CUAUCCUCCUCCAUCCAAAUAUGAUGACUCAACUUUGUACUAAUUUUGUACAAGGUUGGCCAUCAUUUUUGGAACGGAGGGAGUAGCUAAGA
2525 & (((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((
2526 > CAUCUAUUUUUGGAACGGAGGG 100,155,21,40,57,22,84,15,15,33 ... [542] ... apMi
2527 % UCCCUCCAUUCCAAAUAAGAU 1,6,2,0,1,1,3,0,0,0 ... [14] ... apMir_39667
2528 % CCCUCCAUUCCAAAUAAGUG 13,5,1,1,0,1,6,1,3,1 ... [32] ... apMir_20989
2529 % CCUCCAUUCCAAAUAAGUGA 3,4,1,1,0,5,2,0,0,0 ... [16] ... apMir_21975
2530 % UUCCAAAUAUGAUGACUCAACUUU 1,0,0,0,0,1,1,2,0,0 ... [5] ... apMir_79710
2531 % UUCCAAAUAUGAUGACUCAAC 9,15,4,8,1,8,7,4,3,3 ... [62] ... apMir_19545
2532 % UCCAAAUAUGAUGACUCAACU 6,7,0,4,0,17,13,12,11,8 ... [78] ... apMir_20102
2533 % CCAAAUAUGAUGACUCAACUU 1,2,0,3,0,3,0,4,1,1 ... [15] ... apMir_22687
2534 % AAAUAUGAUGACUCAACUUUGU 1,4,0,0,0,0,1,0,0,0 ... [6] ... apMir_21090
2535 % AAUAUGAUGACUCAACUUUGUACUA 1,1,3,1,0,1,1,1,1,0 ... [10] ... apMir_42708
2536 % AUAGAUGACUCAACUUUGUACUAA 5,1,0,1,0,4,3,2,0,2 ... [18] ... apMir_74988
2537 % AUAGAUGACUCAACUUUGUACUA 0,2,0,0,0,3,0,0,0,2 ... [7] ... apMir_41758
2538 % GGCCAUCAUUUUUGGAACGGA 1,0,1,0,2,0,2,0,1,0,0 ... [5] ... apMir_20990
2539 % GCCAUCAUUUUUGGAACGGAG 6,1,0,4,2,1,2,1,0,4 ... [21] ... apMir_21814
2540 % CAUCUAUUUUUGGAACGGAGGGA 17,15,3,2,4,4,7,1,2,3 ... [58] ... apMir_24350
2541 % CAUCUAUUUUUGGAACGGA 1,3,0,2,0,1,1,2,3,0 ... [13] ... apMir_34735
2542 % CAUCUAUUUUUGGAACGGAGGGAGU 5,1,0,1,2,2,0,0,0,0 ... [11] ... apMir_58314
2543 % CAUCUAUUUUUGGAACGGAGG 8,10,2,0,4,0,11,1,3,2 ... [41] ... apMir_18337
2544 % CAUCUAUUUUUGGAACGGAG 1,0,0,0,2,4,1,0,0,1 ... [9] ... apMir_13964
2545 % AUCUAUUUUUGGAACGGAGGGAG 2,5,0,0,0,1,0,0,1,0 ... [9] ... apMir_23921
2546 % AUCUAUUUUUGGAACGGAGGG 2,7,0,0,1,0,3,0,1,0 ... [14] ... apMir_38531
2547 % AUCUAUUUUUGGAACGGAGGGA 6,24,4,2,6,5,1,2,3,0 ... [53] ... apMir_21967
2548 #####
2549 #####
2550 #####

```

Figure – (Agharbaoui et al., 2015)

# Visualisation

## Représentation textuelle

### Deep sequencing reads for stem-loop sequence MI0000178

Stem-loop ID	ath-MIR156a	
Confidence	Annotation confidence: high	
	Feedback: Do you believe this miRNA is real? <div><div>Yes (+39)</div><div>No (-0)</div><div>Leave comment</div></div>	
Reads	<div>ath-miR156a-5p</div> <div>.....AACUGACAGAAGAGAGUSAGCAC..... .....ACUGACAGAAGAGAGUSAGC..... .....ACUGACAGAAGAGAGUSAGCAC..... .....ACUGACAGAAGAGAGUSAGCA..... .....CUGACAGAAGAGAGUSAGCAC..... .....CUGACAGAAGAGAGUSAGCAC..... .....CUGACAGAAGAGAGUSAGCA..... .....UGACAGAAGAGAGUSAGCAC..... .....UGACAGAAGAGAGUSAGCAC..... .....UGACAGAAGAGAGUSAGCA..... .....UGACAGAAGAGAGUSAGC..... .....GACAGAAGAGAGUSAGCAC..... .....GACAGAAGAGAGUSAGCAC..... .....ACAGAAGAGAGUSAGCAC..... .....ACAGAAGAGAGUSAGCAC..... .....CAGAAGAGAGUSAGCAC.....</div>	<div>ath-miR156a-3p</div> <div>.....CUGUCACUGCUUUUCUGUCA..... .....UGUCACUGCUUUUCUGUCAG..... .....UGUCACUGCUUUUCUGUCAG..... .....UGUCACUGCUUUUCUGUC..... .....UGUCACUGCUUUUCUGUC..... .....UGUCACUGCUUUUCUGUCAG..... .....UGUCACUGCUUUUCUGUCAG..... .....UGUCACUGCUUUUCUGUC..... .....UGUCACUGCUUUUCUGUC..... .....UGUCACUGCUUUUCUGUC..... .....UGUCACUGCUUUUCUGUC..... .....UGUCACUGCUUUUCUGUC..... .....UGUCACUGCUUUUCUGUC..... .....UGUCACUGCUUUUCUGUC..... 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Figure – ath-MIR156a dans miRBase

# Exploration de la base miRBase

- [http ://www.mirbase.org/](http://www.mirbase.org/)
- Cherchez l'ensemble des microARNs chez l'homme (*homo sapiens*) en utilisant les outils *Search* et *Browse*
- Sélectionnez le précurseur **hsa-mir-15a** et extrayez toutes les informations concernant ce précurseur et ses microARNs que vous jugez utiles (séquences, fonctions, annotations, coordonnées sur le génome, etc.)
- Est-ce que la famille **miR-15** est spécifique à l'homme ?
- Avec l'outil *Search*, blastez la séquence UUUGGAUUGAAGGGAGCUCUG
  - À quel microARN cette séquence correspond-elle ?
  - Quelles sont les espèces qui expriment ce microARN ?
  - Quels sont les gènes ciblés par ce microARN ?