

False-positives in microRNA target identification: principles and implications

Hervé Seitz

December 8, 2022

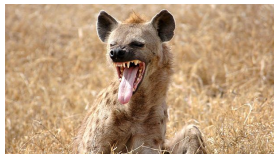
Slideshow available at:

<http://www.igh.cnrs.fr/equip/Seitz/Camb2022.pdf>

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miRNA target identification

False-positives in
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miRNA target
identification

False positives in
target prediction

Binding site
evolution after
miRNA loss

Strategy

Observed losses

Evolution of seed match
count after loss

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miRNA target identification

- Low-throughput genetics (measures *in vivo* phenotypes).

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miRNA target identification

- ▶ Low-throughput genetics (measures *in vivo* phenotypes).
- ▶ High-throughput molecular biology (finding mRNAs bound, or repressed, by a miRNA).

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miRNA target identification

- ▶ Low-throughput genetics (measures *in vivo* phenotypes).
- ▶ High-throughput molecular biology (finding mRNAs bound, or repressed, by a miRNA).
- ▶ Computational predictions.

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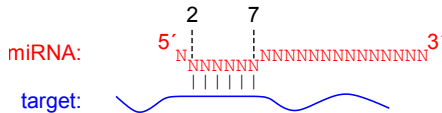
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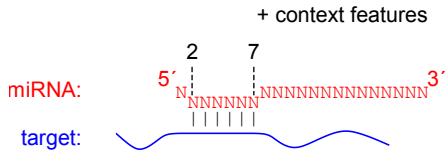
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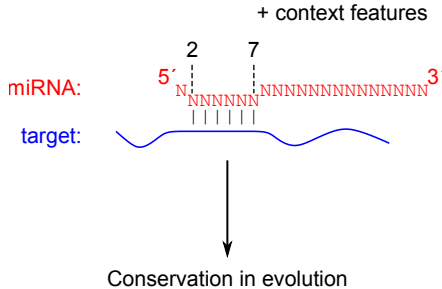
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False-positives in microRNA target identification

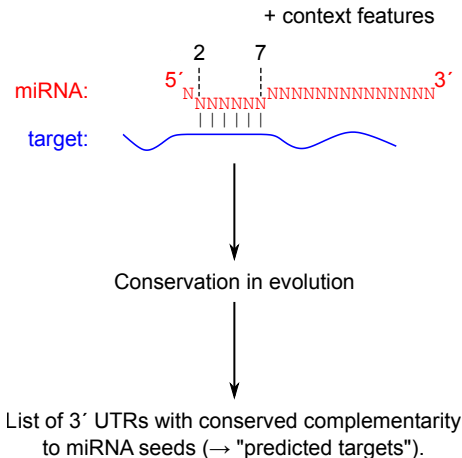
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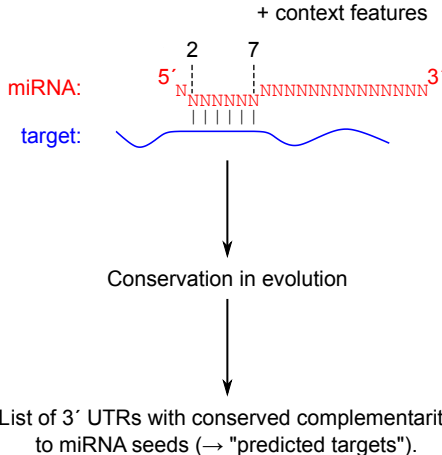
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Inconsequential interactions → even high-throughput identification needs to assess conservation.

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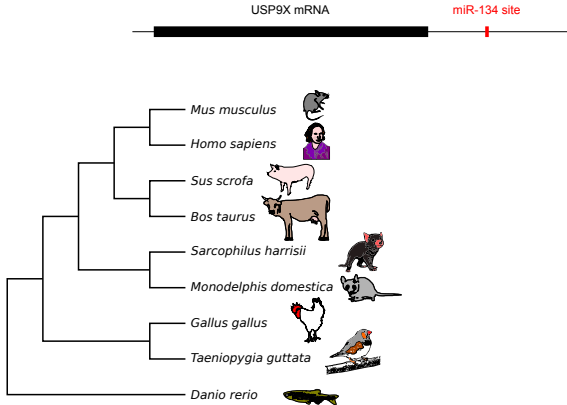
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False positives in target prediction



(Pinzón *et al.*, 2017)

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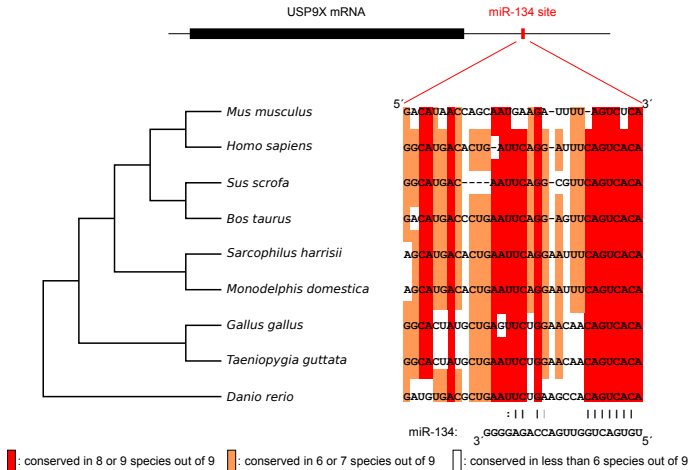
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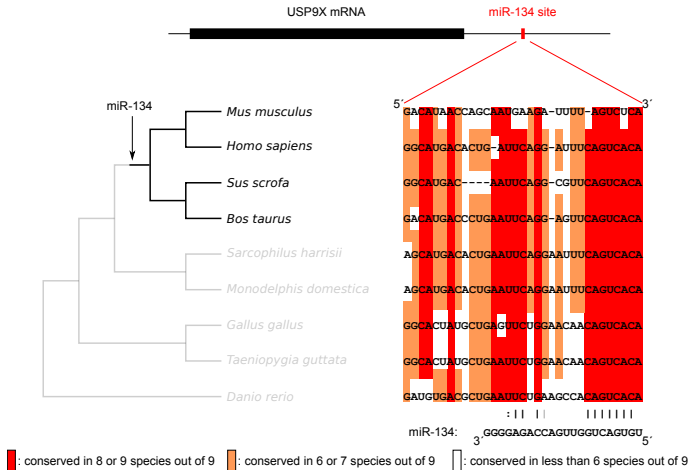
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Measuring miRNA-independent conservation with control k -mers (with same G/C content, dinucleotide composition, ...; [Friedman *et al.*, 2009](#)).

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Measuring miRNA-independent conservation with control k -mers (with same G/C content, dinucleotide composition, ...; [Friedman *et al.*, 2009](#)).

→ not submitted to the same selective pressure than actual miRNA seed matches (e.g., protein binding sites).

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Binding site evolution after miRNA loss

After loss of a *complete* miRNA family (*), how long do its seed matches persist ?

(*): family: all the miRNAs sharing the same seed sequence

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After loss of a *complete* miRNA family, how long do its seed matches persist ?

We need to be lucky: loss of complete miRNA families a long time ago (many species with miRNA loss).

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Genome List - Genomes - NCBI - Mozilla Firefox

https://www.ncbi.nlm.nih.gov/genomes/browse/overview/

National Library of Medicine
National Center for Biotechnology Information

New Genome Table
Try our new [Genome page](#) and use the feedback button to let us know what you think.

Genome > Genome Information by Organism

Organism name (common or scientific) or Accession (Assembly, BioProject) Search Download Reports from FTP site

Overview (87476) Eukaryotes (21962) Prokaryotes (378872) Viruses (47187) Plasmids (34931) Organelles (21278)

View 1 - 58 of 87,476

#	Organism Name	Organism Group	GenBank	Chromosome	Organisms	Plasmids	Assemblies
1	<i>Brassica napus</i> phytochrome	Bacteria: <i>Thermobacterium</i> group: <i>Thermobacter</i>	1,420,000	-	-	-	1
2	<i>Candida glabrata</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,270,000	-	-	-	2
3	<i>Calothrix rosea</i> venter yellow phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	1	-	1	1
4	<i>Cryptosporidium parvum</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,100,000	-	-	-	1
5	<i>Cryptosporidium parvum</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,400,000	-	-	-	1
6	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	1	-	1	1
7	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
8	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
9	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
10	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
11	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
12	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
13	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
14	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
15	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
16	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
17	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
18	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
19	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
20	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
21	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
22	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
23	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
24	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
25	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
26	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
27	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
28	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
29	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
30	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
31	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
32	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
33	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
34	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
35	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
36	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
37	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
38	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
39	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
40	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
41	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
42	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
43	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
44	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
45	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
46	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
47	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
48	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
49	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
50	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
51	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
52	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
53	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
54	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
55	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
56	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
57	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1
58	<i>Escherichia coli</i> phytochrome	Bacteria: <i>Thermobacter</i> group: <i>Thermobacter</i>	1,000,000	-	-	-	1

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- ▶ What species should we look at?
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The screenshot shows the NCBI Genome List - Genomes browser. The table displays genomic data for various bacterial species, including their names, accession numbers, and genome sizes. The table is titled "Genome List - Genomes - NCBI - Mozilla Firefox" and includes a search bar and a "New Genome Table" notification.

#	Organism Name	Accession	Genome Size (Mb)	Chromosomes	Plasmids	Annotations
1	Bacteroides fragilis	NC_010437	4.1	1	0	1
2	Bacteroides fragilis	NC_010438	4.1	1	0	1
3	Bacteroides fragilis	NC_010439	4.1	1	0	1
4	Bacteroides fragilis	NC_010440	4.1	1	0	1
5	Bacteroides fragilis	NC_010441	4.1	1	0	1
6	Bacteroides fragilis	NC_010442	4.1	1	0	1
7	Bacteroides fragilis	NC_010443	4.1	1	0	1
8	Bacteroides fragilis	NC_010444	4.1	1	0	1
9	Bacteroides fragilis	NC_010445	4.1	1	0	1
10	Bacteroides fragilis	NC_010446	4.1	1	0	1

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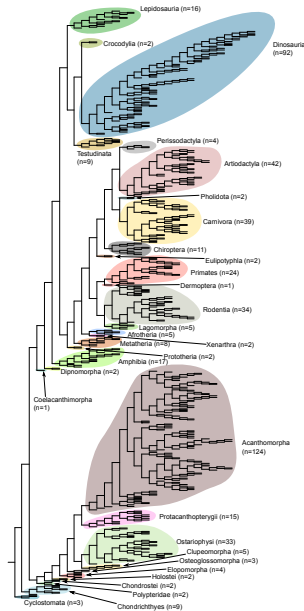
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Nov. 24, 2021: 522 vertebrates at “chromosome” level.

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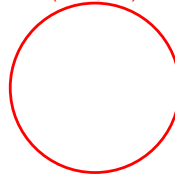
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Unique vertebrate miRNA
sequences in miRBase
(n=14,804)



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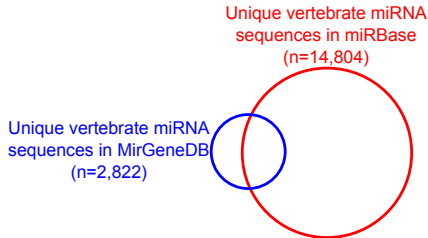
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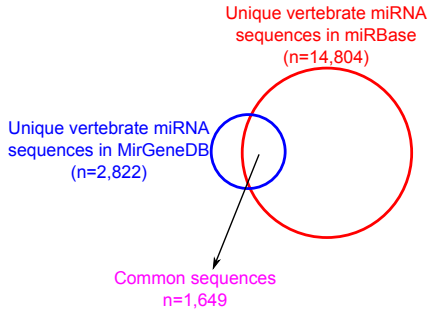
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- ▶ What species should we look at?
- ▶ What miRNAs should we look for?
- ▶ How should we qualify a loss?



False-positives in
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False positives in
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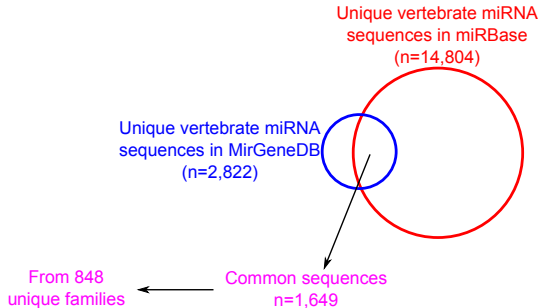
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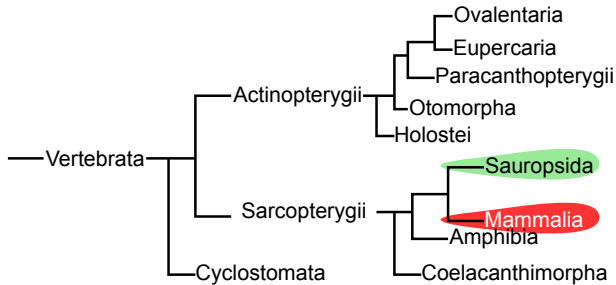
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- ▶ What species should we look at?
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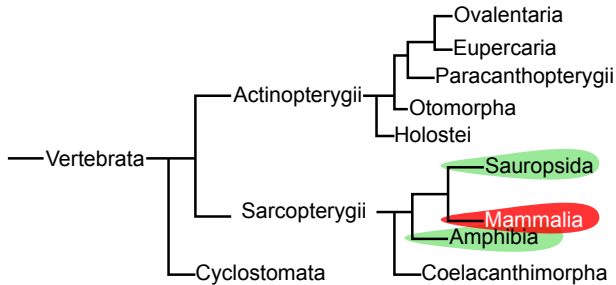
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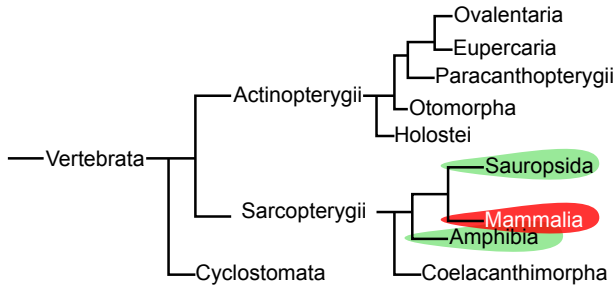
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More convincing if many species in clade of loss.

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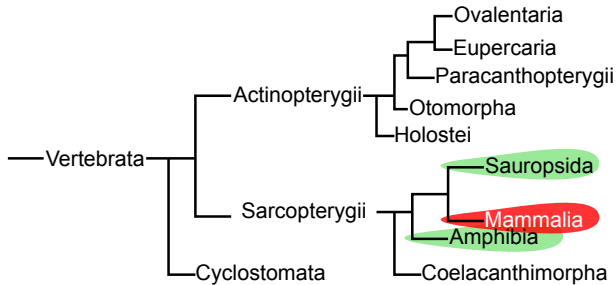
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- ▶ How should we qualify a loss?



≥ 10 species in clade of loss; presence in sister clade + 3 closest cousin clades.

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Clade	miRNA family
Feliformia	miR-541
Ferae	miR-598
Mammalia	miR-456
Eutheria	miR-2188
Myomorpha	miR-656
Mammalia	miR-460b
Feloidea	miR-676
Cervidae+Bovidae	miR-676
Whippomorpha	miR-769
Cervidae+Bovidae	miR-509
Protacanthopterygii	miR-31
Myomorpha	miR-885
Myomorpha	miR-3959
Theria	miR-458
Pinnipedia+Musteloidea	miR-297
Bovidae	miR-325-3p
Cervidae+Bovidae	miR-514

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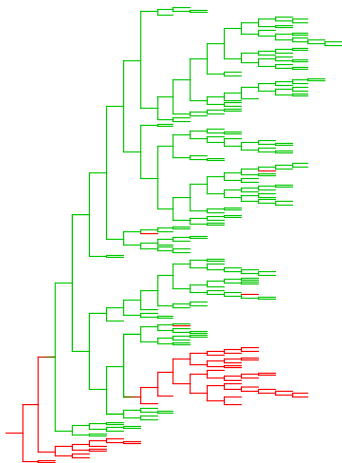
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miR-656 family:

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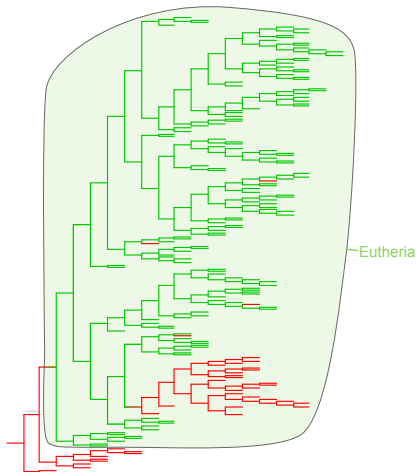
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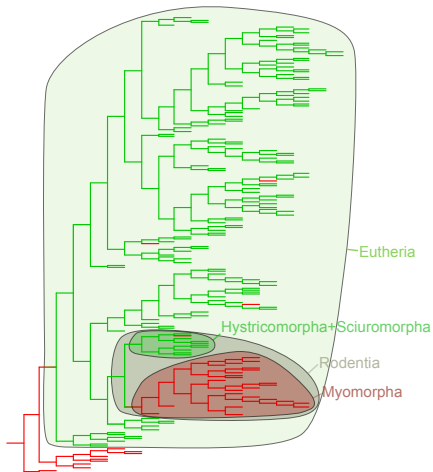
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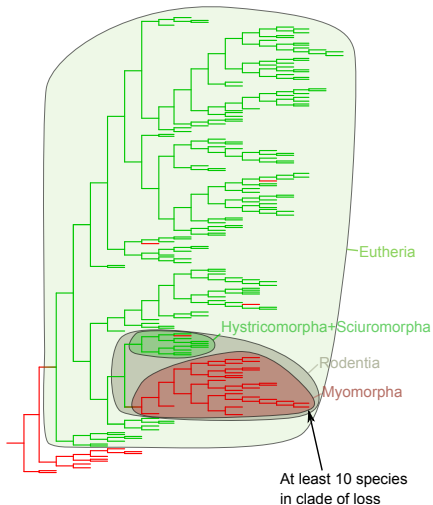
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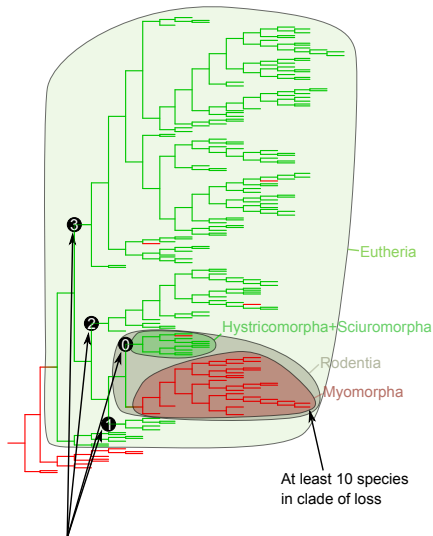
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Observed losses

miR-656 family:



At least 10 species
in clade of loss

In sister clade + at least 3 degrees of cousinhood: miRNA family
with certified presence in >50% of species at each degree

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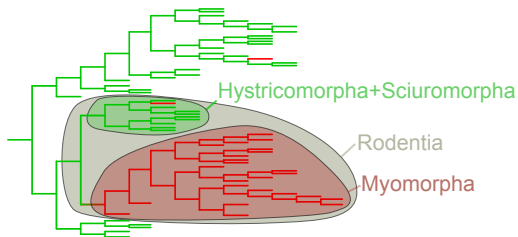
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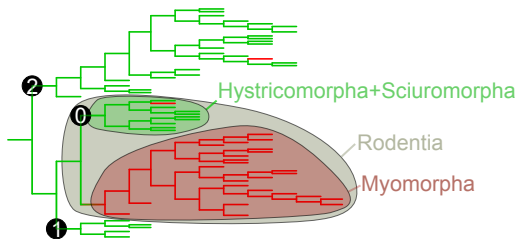
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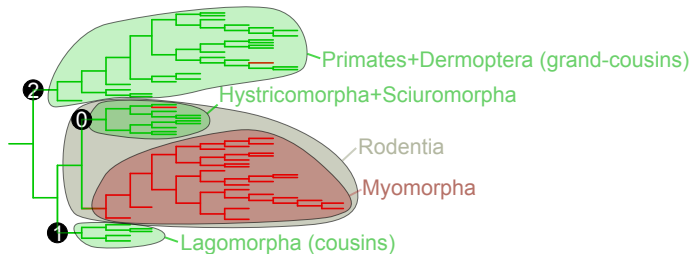
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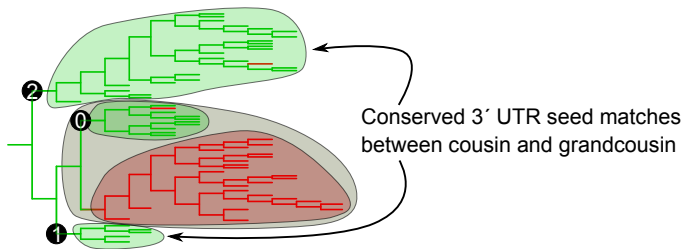
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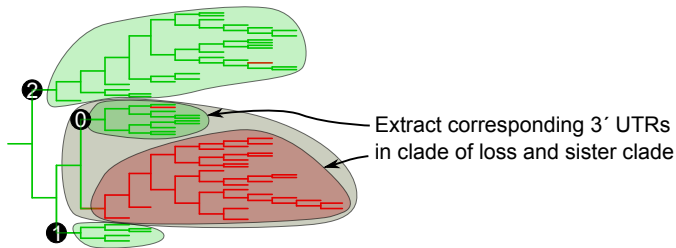
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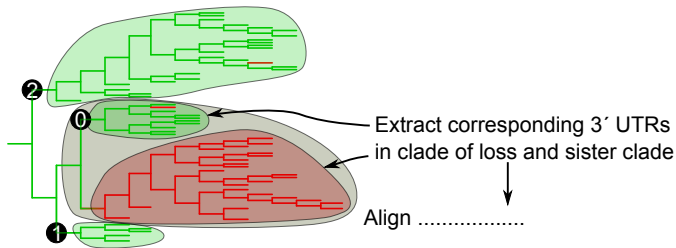
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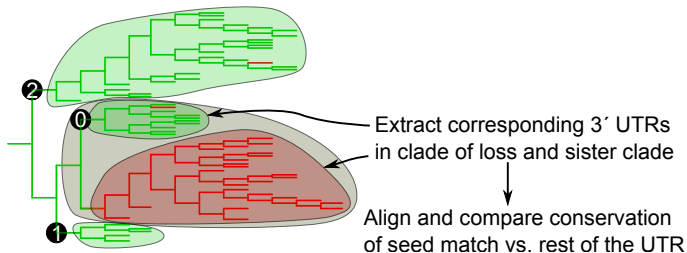
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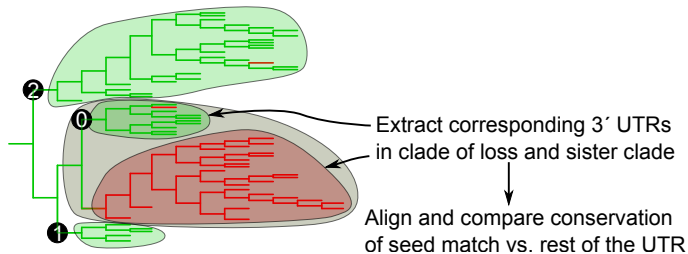
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PhyloP score: measures probability of selective conservation of seed match.

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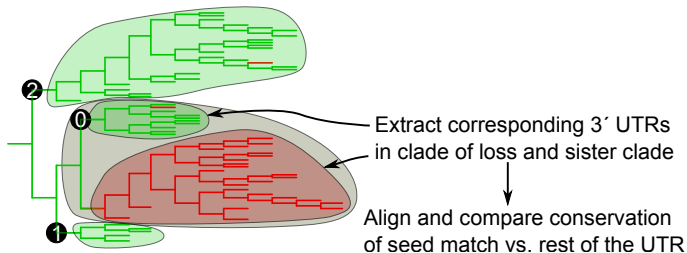
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PhyloP score: measures probability of selective conservation of seed match in a given clade vs. rest of tree.

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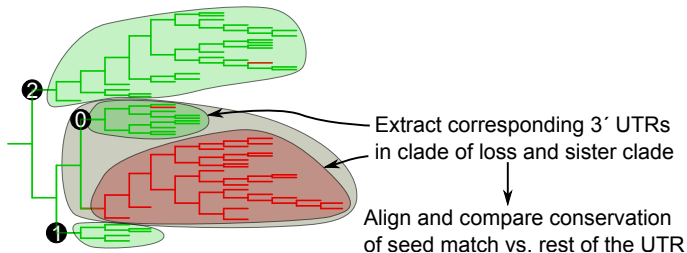
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PhyloP score: measures probability of selective conservation of seed match in a given clade vs. rest of tree.

→ Selects seed matches with selective conservation in rodents, then compare their conservation in rodent subclades (clade of loss vs. sister clade).

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After miR-656 family loss:

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After miR-656 family loss:



In Rodentia:

Site	Conservation vs. rest of UTR
	<i>p</i> -value
nt 444–449	0.00005
nt 2225–2230	0.00000

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After miR-656 family loss:



Acceleration of evolution in subclades:

Site	Clade of loss <i>p</i> -value	
nt 444–449	0.03954	
nt 2225–2230	1.00000	

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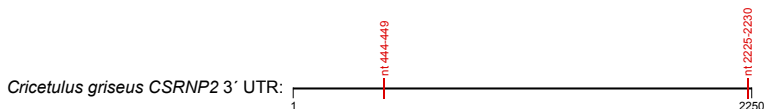
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After miR-656 family loss:



Acceleration of evolution in subclades:

Site	Clade of loss <i>p</i> -value	Sister clade <i>p</i> -value
nt 444–449	0.03954	0.50000
nt 2225–2230	1.00000	1.00000

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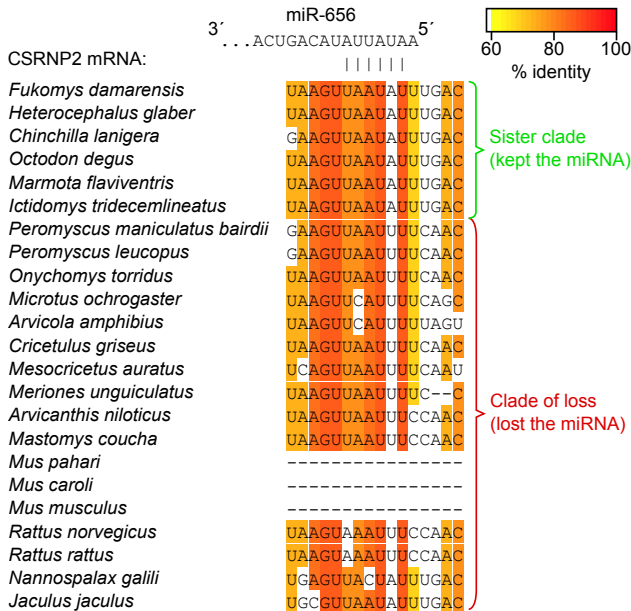
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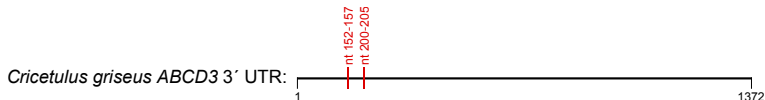
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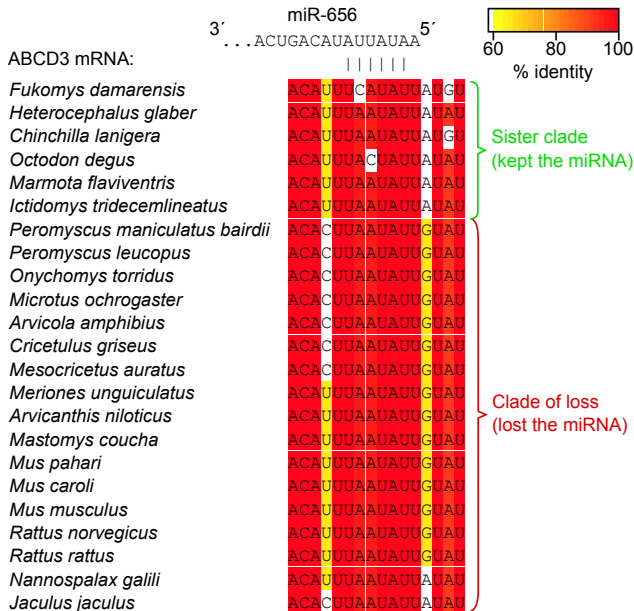
After miR-656 family loss:



Acceleration of evolution in subclades:

Site	Clade of loss <i>p</i> -value	Sister clade <i>p</i> -value
nt 152–157	1.00000	0.00583
nt 200–205	0.18718	0.50000

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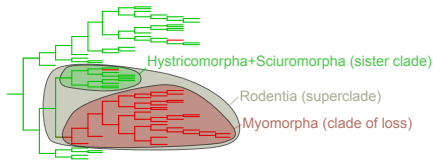
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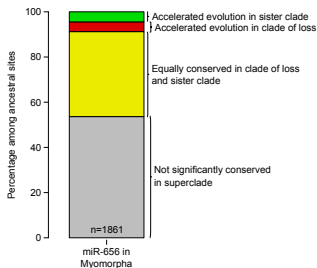
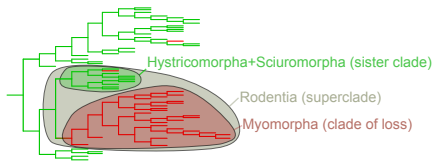
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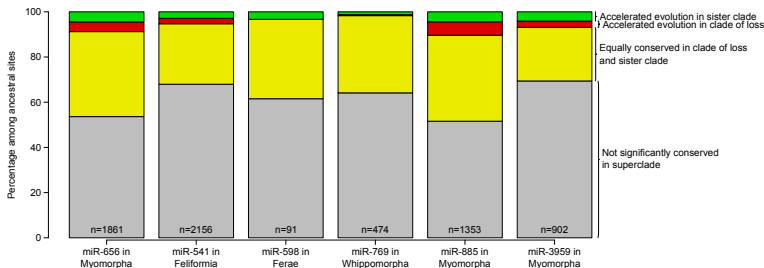
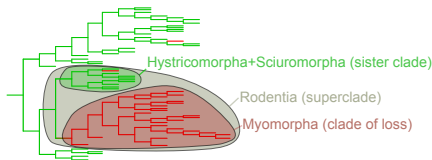
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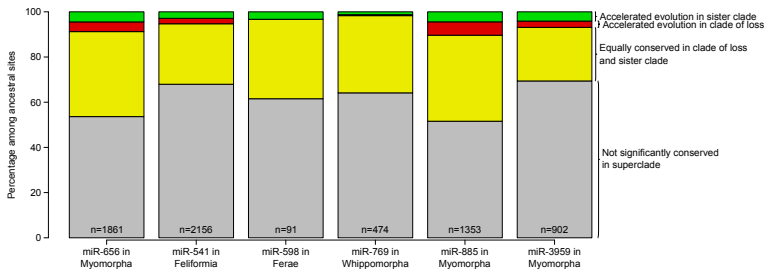
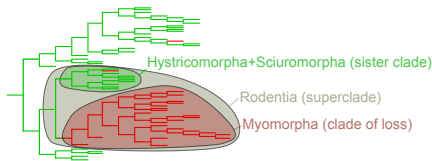
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→ Most of these seed matches are conserved in a miRNA-independent manner.

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Six analyzed family losses out of 17...

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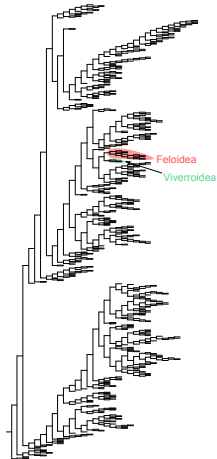
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Under-studied sister clade:



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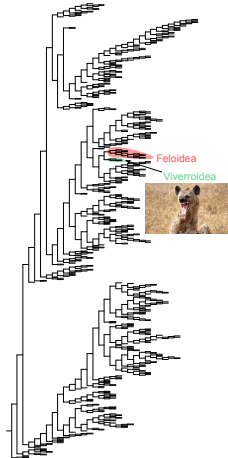
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Under-studied sister clade:



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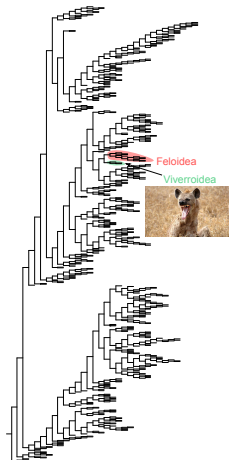
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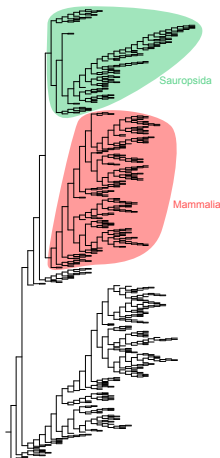
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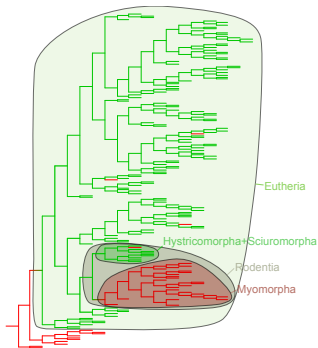
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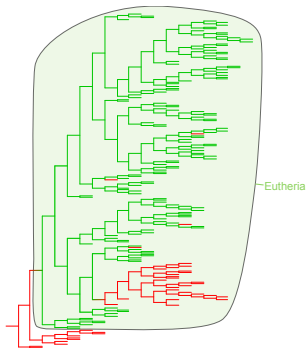
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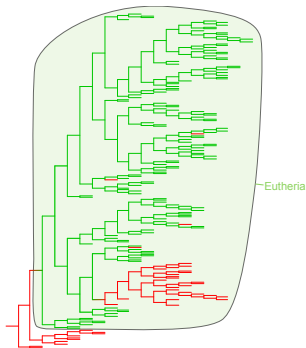
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In addition to 17 miRNA family losses: 158 miRNA family gains.



→ Searching for the appearance of conserved sites in clade of gain vs. sister clade.

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Since 2007: miR-34a, a tumor suppressor miRNA ?

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A huge corpus of molecular data suggesting tumor suppressive functions.

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A huge corpus of molecular data suggesting tumor suppressive functions.

[Mockly et al., 2022](#): anti-proliferative activity was artifactual.

Most common mistake: miRNA over-expression by transfection.

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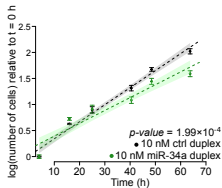
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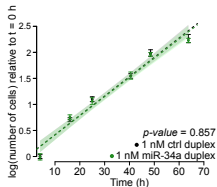
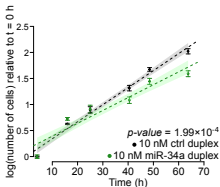
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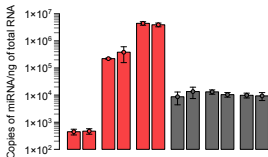
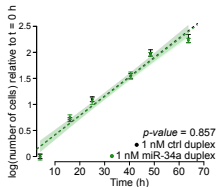
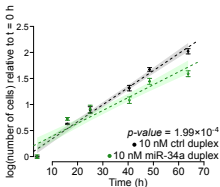
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Time post-transfection (h):	1	24	1	24	1	24	1	24	1	24	1	24
miR-34a mimic (nM):	0	1	10	0	1	10	0	1	10	0	1	10
Quantified miRNA:	miR-34a			miR-21			miR-21			miR-21		

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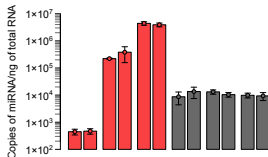
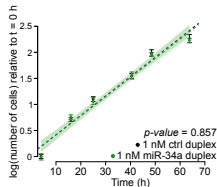
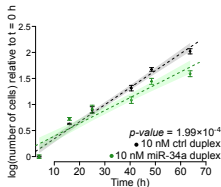
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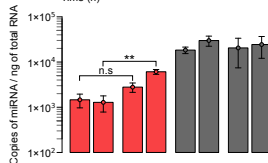
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Time post-transfection (h): 1 24 1 24 1 24 1 24 1 24

miR-34a mimic (nM): 0 1 10 0 1 10 0 1 10

Quantified miRNA: miR-34a miR-21



Treatment duration (h): 24 72 24 72 24 72 24 72

Doxorubicin treatment: - + - + - + - +

Quantified miRNA: miR-34a miR-21

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High-throughput experimental target identification captures many false positives...

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... but comparative genomics too!

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Improvement: identification of miRNA-independent conservation of binding sites.

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An iconic example: miR-34a in cancer.

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A large part of the miRNA literature probably needs a cleanup.

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Former members:

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Fondation
pour la recherche
sur le cancer



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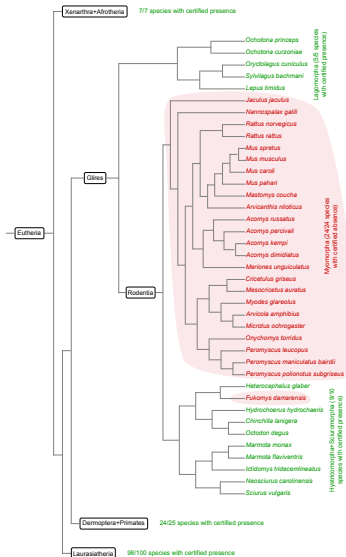
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miR-656 family:

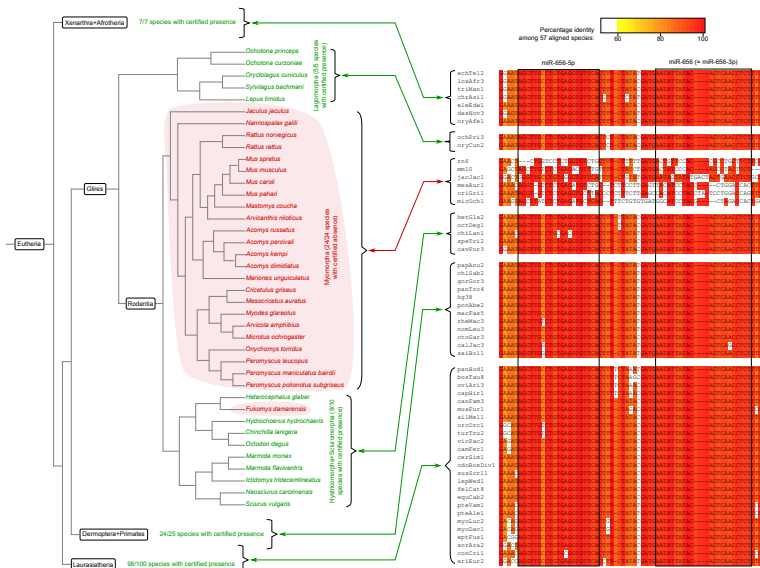


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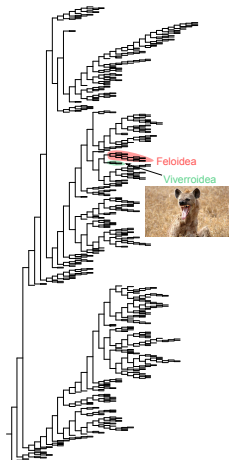
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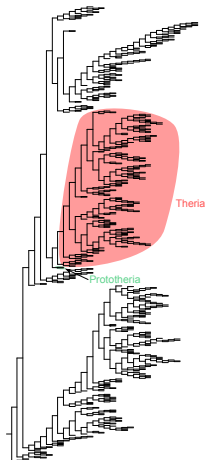
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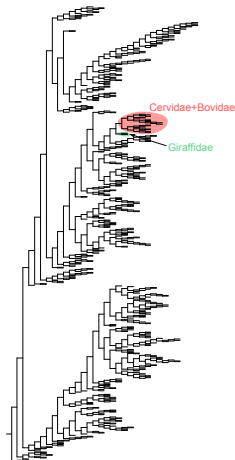
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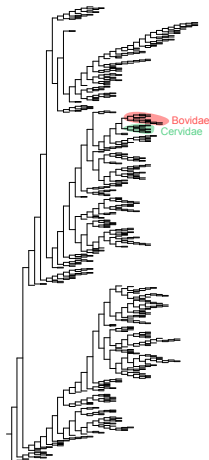
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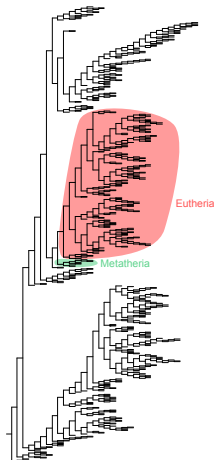
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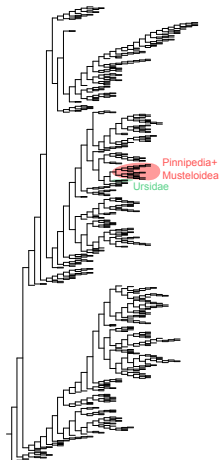
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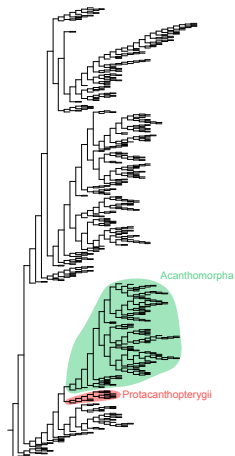
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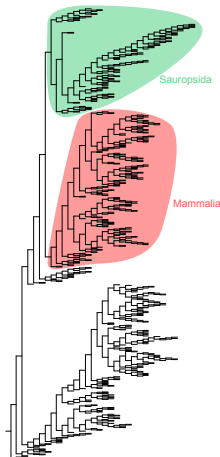
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