

The evolutionary history of vertebrate microRNA families reveals widespread microRNA-independent conservation of 3' UTR seed matches

Hervé Seitz

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Slideshow accessible for download at:

<http://www.igh.cnrs.fr/equip/Seitz/ZamoreLab24.pdf>

miRNA target
identification

False positives in
target prediction

Binding site
evolution after
miRNA loss

Strategy

Observed losses

Evolution of seed match
count after loss

Conclusion

miRNA target identification

miRNA-
independent
conservation of
3' UTR seed
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- ▶ Low-throughput genetics (measures *in vivo* phenotypes).

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Example: [Ecsedi et al., 2015](#)

miRNA target identification

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

Example: [Chi et al., 2009](#)

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- ▶ 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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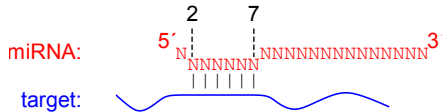
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Example: [Agarwal *et al.*, 2015](#)

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Binding site evolution after miRNA loss

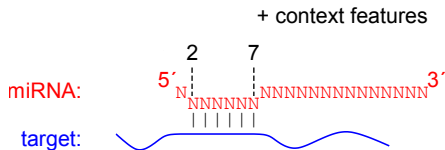
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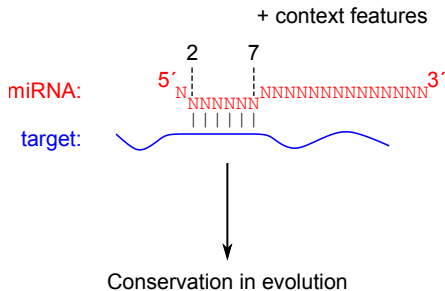
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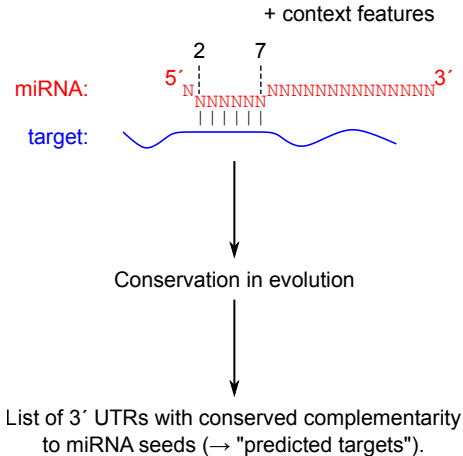
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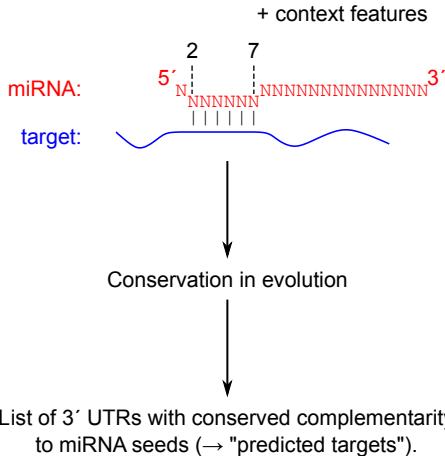
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Even high-throughput identification needs to assess conservation.

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Some 3' UTR seed matches are conserved for miRNA-independent reasons.

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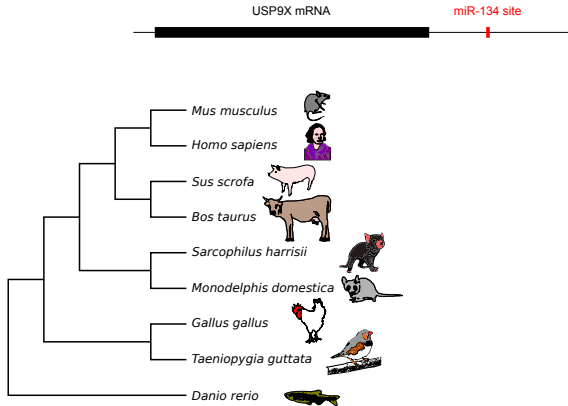
Binding site evolution after miRNA loss

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(Pinzón *et al.*, 2017)

False positives in target prediction

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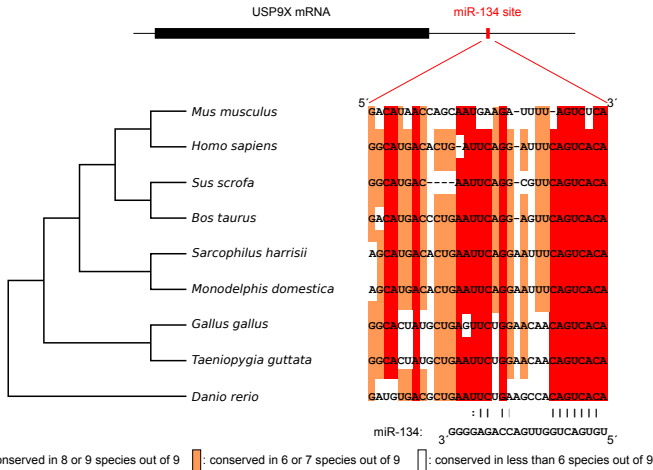
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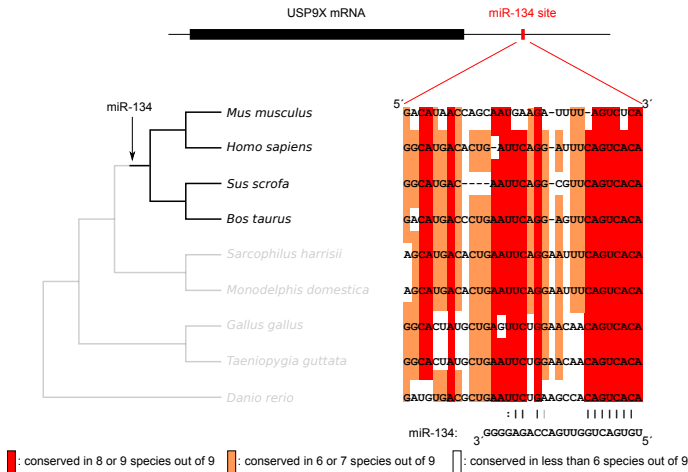
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(Pinzón *et al.*, 2017)

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Seed match “overconservation” could only be precisely measured for the most recently emerged miRNAs.

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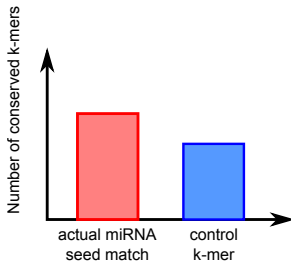
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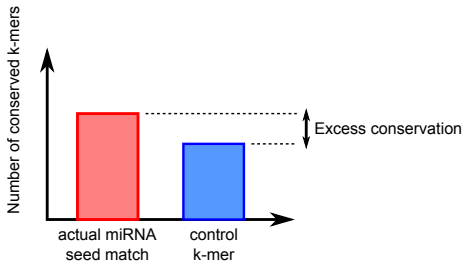
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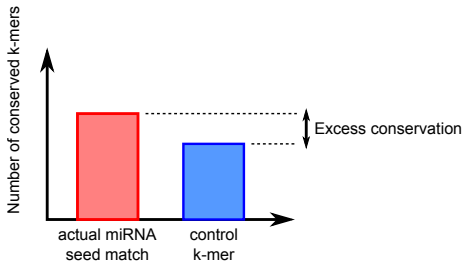
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Measuring miRNA-independent conservation with control k -mers (with same G/C content, dinucleotide composition, ...; [Friedman *et al.*, 2009](#)).

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



miRNA-independent conservation of 3' UTR seed matches

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

miRNA target
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False positives in
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(*): family: all the miRNAs sharing the same seed sequence

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

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

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

Binding site
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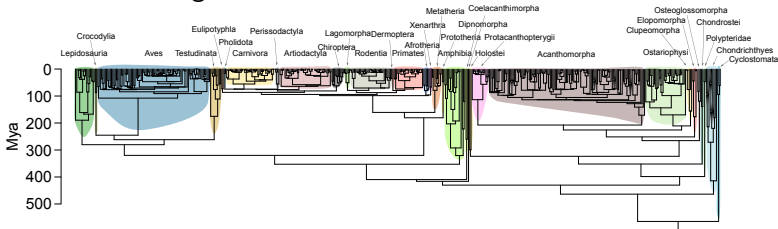
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522 vertebrate genomes:



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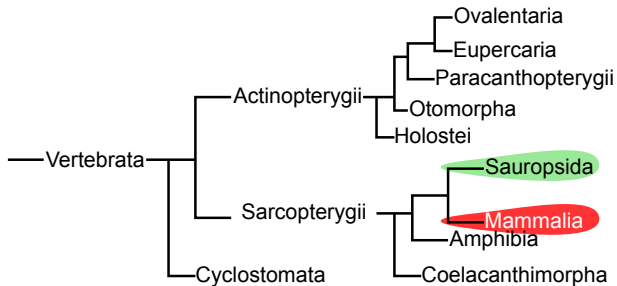
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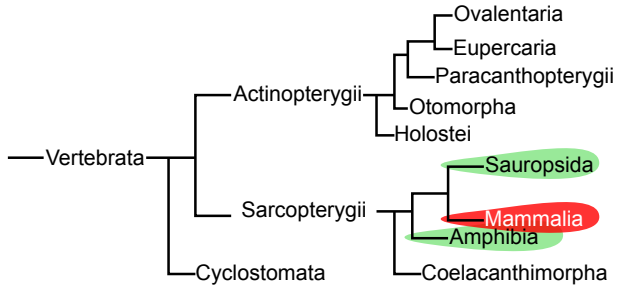
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miRNA-independent conservation of 3' UTR seed matches

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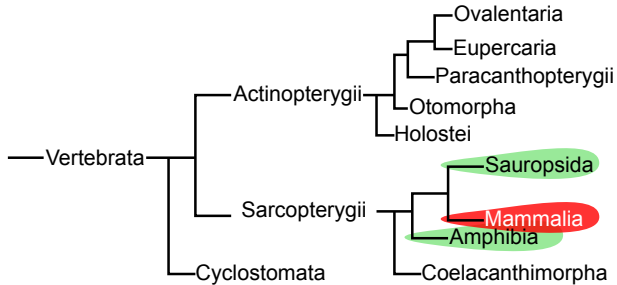
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More convincing if many species in clade of loss.

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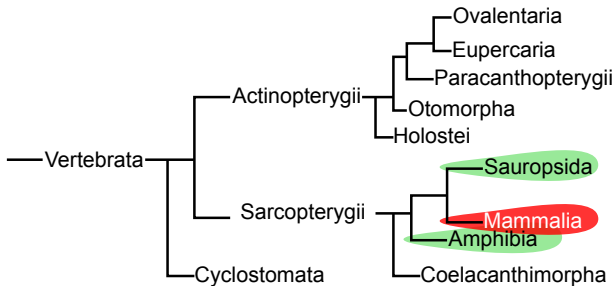
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More convincing if many species in clade of loss.
 ≥ 5 species in clade of loss; presence in sister clade + 3 closest cousin clades.

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miRNA-
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Family	Clade of loss
miR-509	Cervidae+Bovidae
miR-541	Feliformia
miR-224	Mustelidae
miR-338	Lagomorpha
miR-338	Syngnathidae
miR-460	Serpentes
miR-660	Murinae
miR-880	Deomyinae+Gerbilinae
miR-452	Mustelidae
miR-456	Balistidae+Tetraodontidae
miR-296-3p	Lagomorpha
miR-2188	Eutheria
miR-2114	Phocidae
miR-656	Myomorpha
miR-654	Delphinoida
miR-460b	Mammalia
miR-460b	Serpentes
miR-676	Cervidae+Bovidae
miR-676	Feloidea
miR-187	Serpentes
miR-769	Yangochiroptera
miR-769	Whippomorpha
miR-1185	Yangochiroptera

Family	Clade of loss
miR-451a	Paralichthyidae+Pleuronectidae
miR-509	Yangochiroptera
miR-31	Protacanthopterygii
miR-31	Lophiiformes+Tetraodontiformes
miR-885	Myomorpha
miR-296-5p	Lagomorpha
miR-296-5p	Canidae
miR-412	Lagomorpha
miR-889	Muridae+Cricetidae
miR-889	Bovinae
miR-458	Theria
miR-374	Yangochiroptera
miR-513b	Bos
miR-653	Yangochiroptera
miR-1662	Endoglyptodonta
miR-297p	Pinnipedia+Musteloidea
miR-2131	Psittaciformes
miR-122b	Paralichthyidae+Pleuronectidae
miR-325-3p	Bovidae
miR-599	Batrachia
miR-599	Corvidae+Passerides
miR-599	Galloanserae

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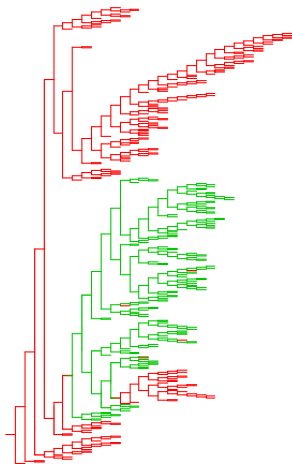
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miR-656 family:



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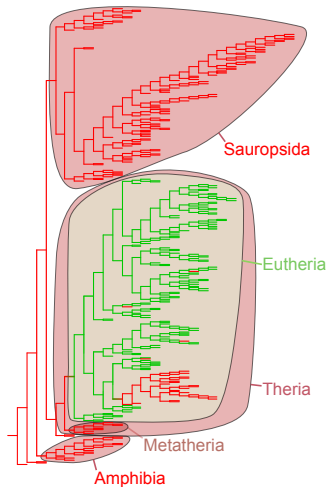
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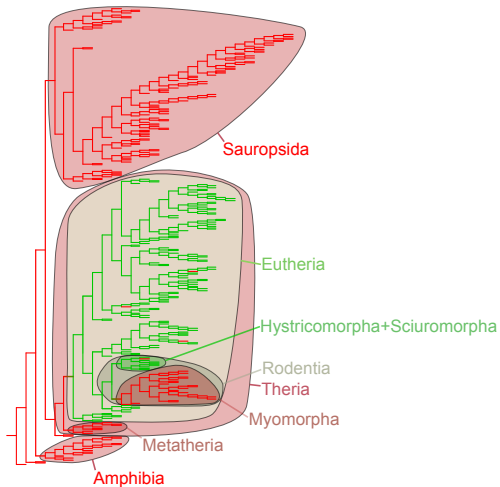
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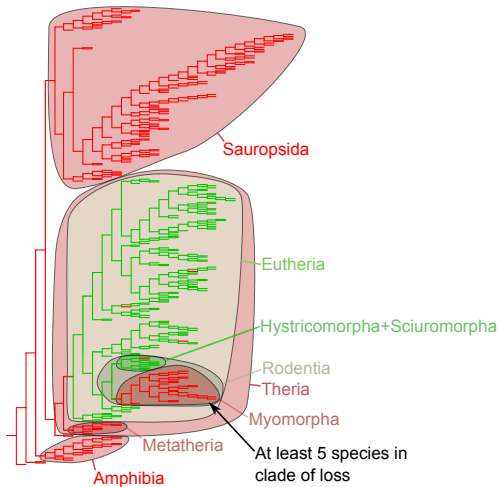
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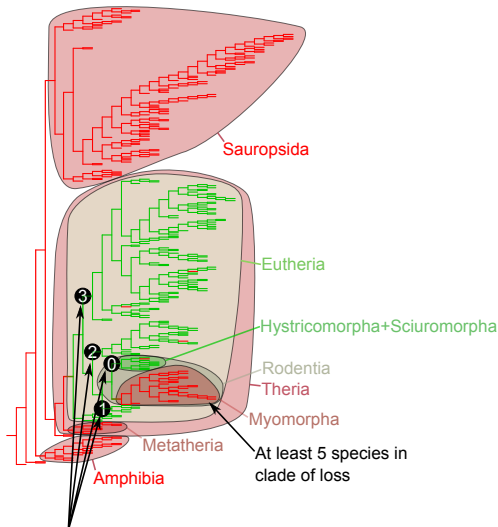
Observed losses

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miR-656 family:



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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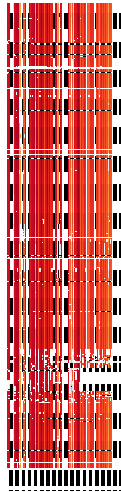
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miR-656 family:

Percentage identity among 470 mammals: 60 80 100



miRNA-independent conservation of 3' UTR seed matches

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Binding site evolution site after miRNA loss

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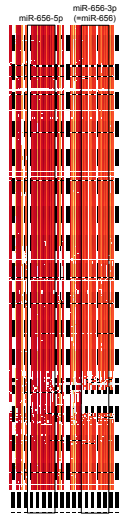
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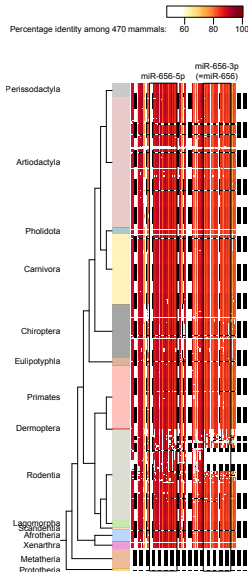
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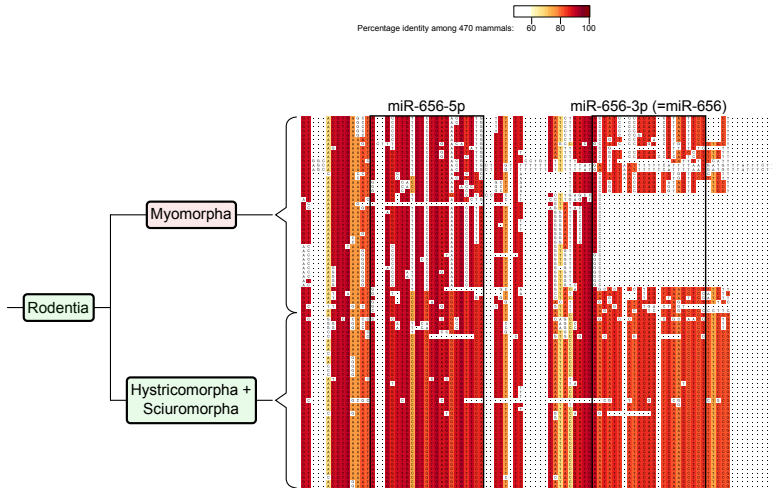
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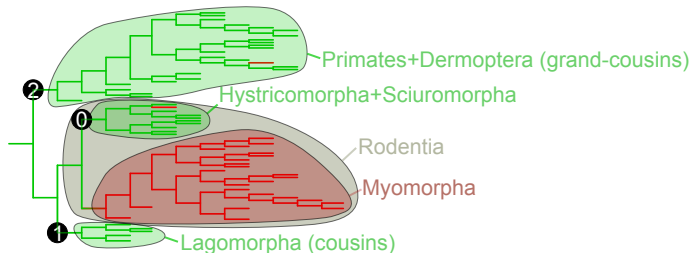
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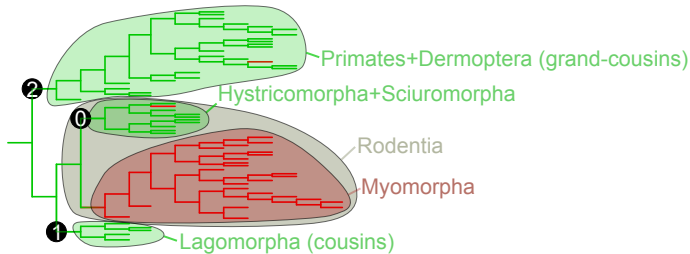
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Align 3' UTR sequences in clade of loss and sister clade.

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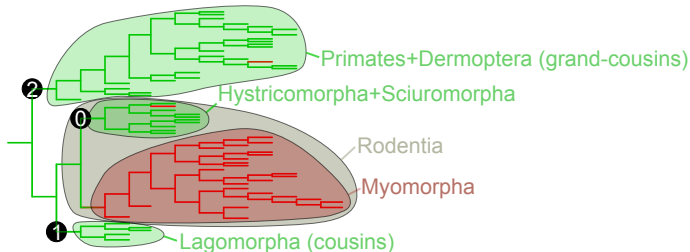
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Align 3' UTR sequences in clade of loss and sister clade.

PhyloP score: measures probability of selective conservation of seed match vs. rest of UTR.

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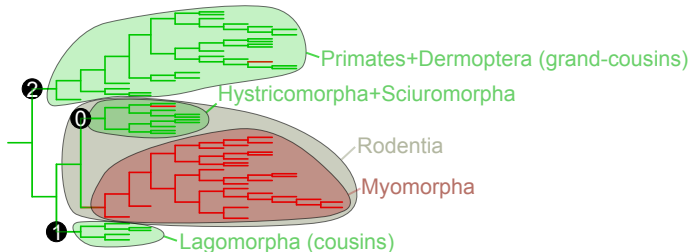
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Align 3' UTR sequences in clade of loss and sister clade.

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

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miRNA target identification

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Binding site evolution after miRNA loss

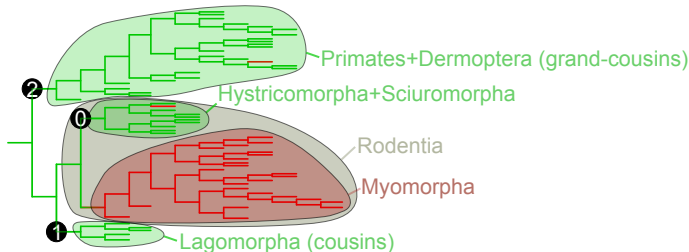
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Align 3' UTR sequences in clade of loss and sister clade.

PhyloP score: measures probability of selective conservation of seed match vs. rest of UTR in a 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).

miRNA-independent conservation of 3' UTR seed matches

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Evolution of seed match count after loss

After miR-656 family loss:

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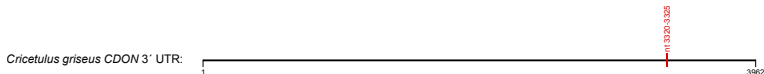
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miRNA-independent
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After miR-656 family loss:



miRNA target
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False positives in
target prediction

Binding site
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Evolution of seed match count after loss

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In Rodentia:

Site	Conservation vs. rest of UTR
	<i>p</i> -value
nt 3320–3325	0.02815

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Cricetulus griseus CDON 3' UTR:



Acceleration of evolution in subclades:

Site	Clade of loss <i>p</i> -value
nt 3320–3325	0.03585

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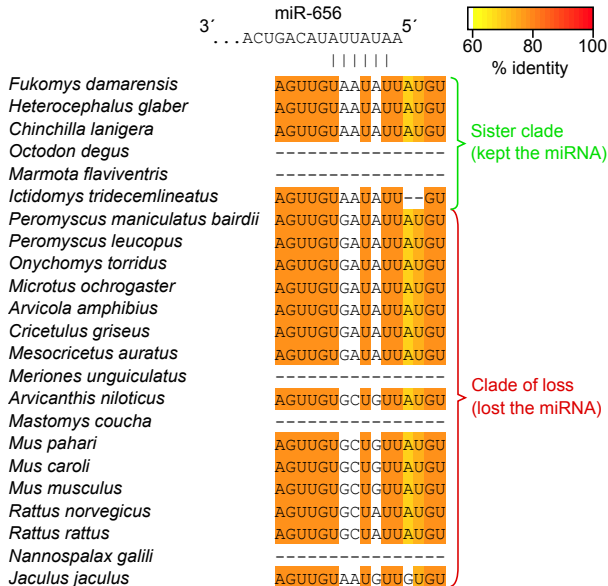
Cricetulus griseus CDON 3' UTR:



Acceleration of evolution in subclades:

Site	Clade of loss <i>p</i> -value	Sister clade <i>p</i> -value
nt 3320–3325	0.03585	0.50000

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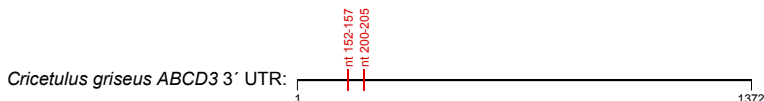
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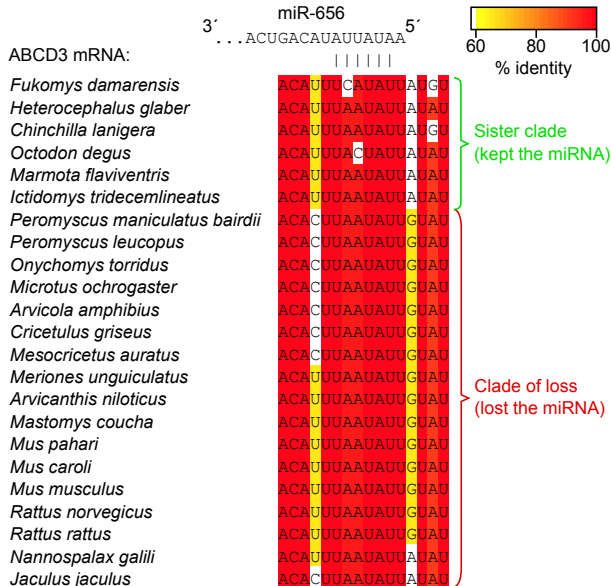
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Acceleration of evolution in subclades:

Site	Clade of loss <i>p</i> -value	Sister clade <i>p</i> -value
nt 152–157	0.50000	0.00864
nt 200-205	0.23280	0.50000

Evolution of seed match count after loss



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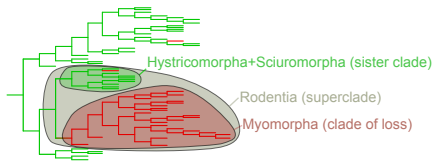
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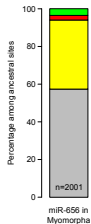
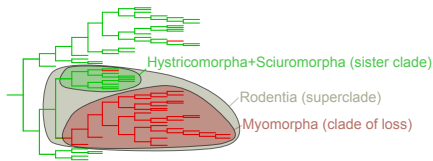
Binding site evolution after miRNA loss

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- Accelerated evolution in sister clade
- Accelerated evolution in clade of loss
- Equally conserved in clade of loss and sister clade
- Not significantly conserved in superclade

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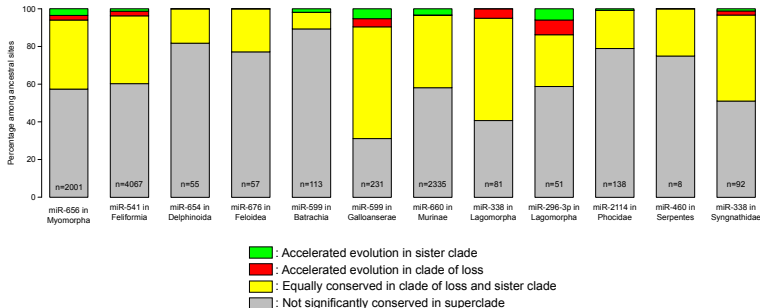
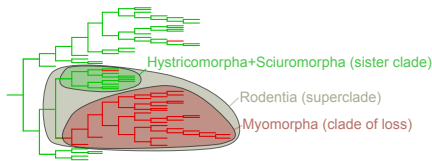
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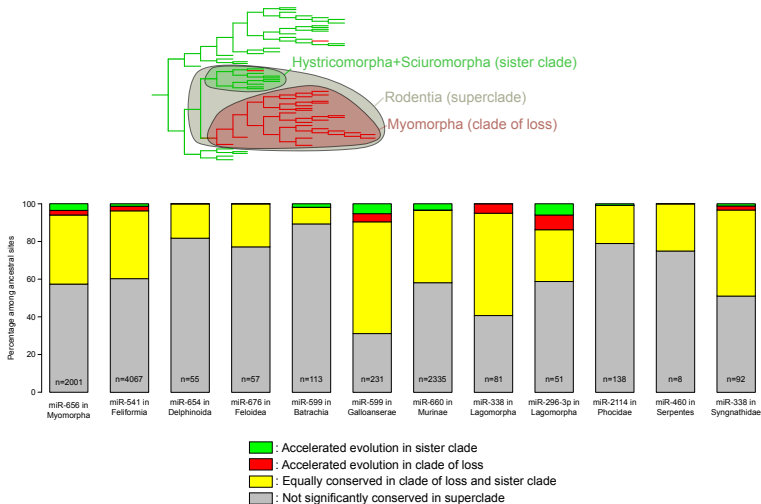
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→ Most of these seed matches are conserved in a miRNA-independent manner.

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On the analyzed examples: most conserved seed matches are not conserved because of the miRNA!

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On the analyzed examples: most conserved seed matches are not conserved because of the miRNA!

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

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May be generalized to other regulators (transcription factors, RNA-binding proteins).

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In vivo veritas: genome editing may correct a lot of false beliefs.

A natural antagonism between developmental transitions and homeostasis. Gene regulation should not only be described at the molecular scale.

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Estelle Rebecq

Élisabeth Houbbron
Pauline De Sousa

Rémy Rodriguez

Former members:

Sophie Mockly
Natalia Pinzón
Laura Martinez

Germain Busto
Blaise Li
Anna Sergeeva

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