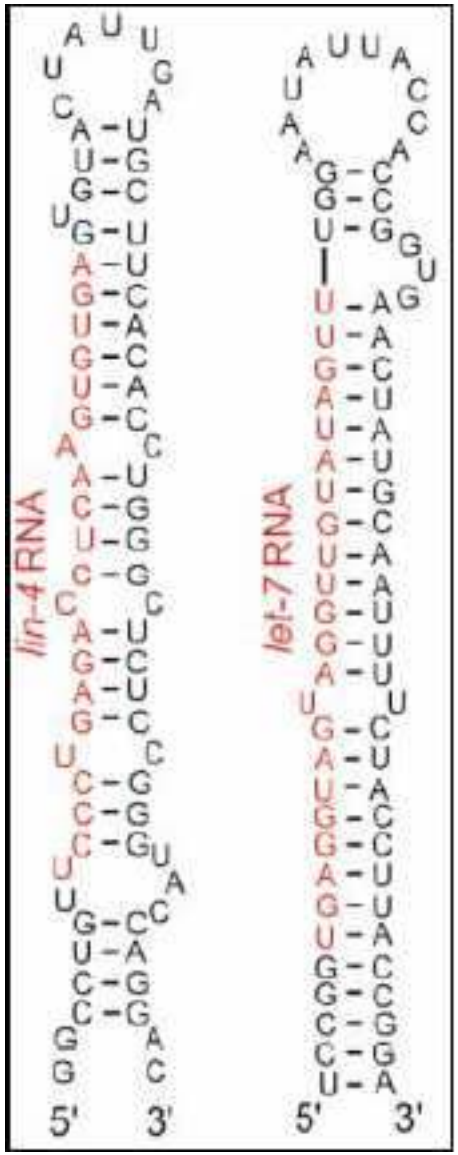
3

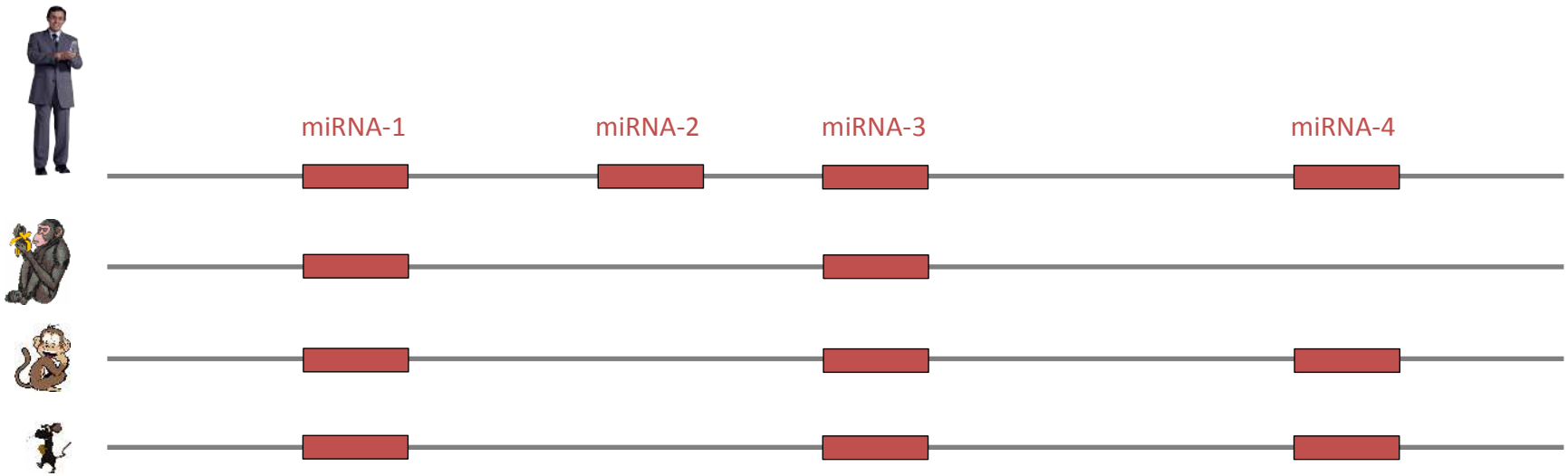
Human-specific transcripts

Human-specific transcripts | microRNA (miRNA)



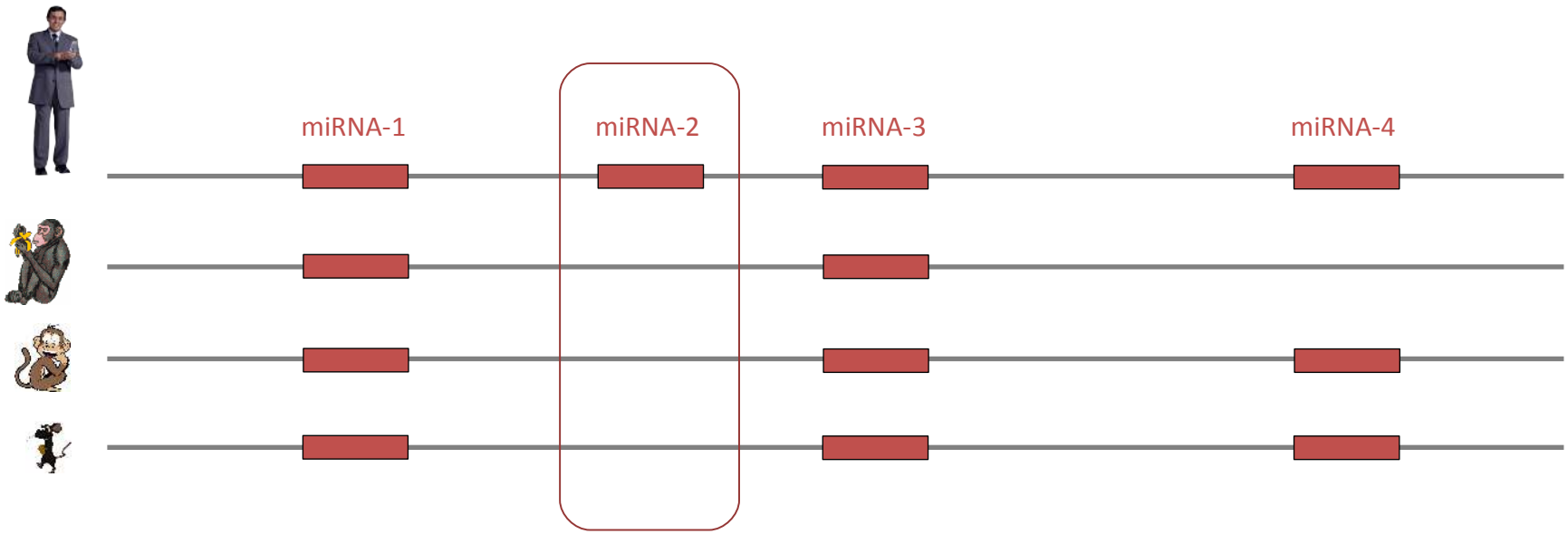
miRNA

Novel miRNA | genome analysis



+ 7 more genomes

Novel miRNA | genome analysis



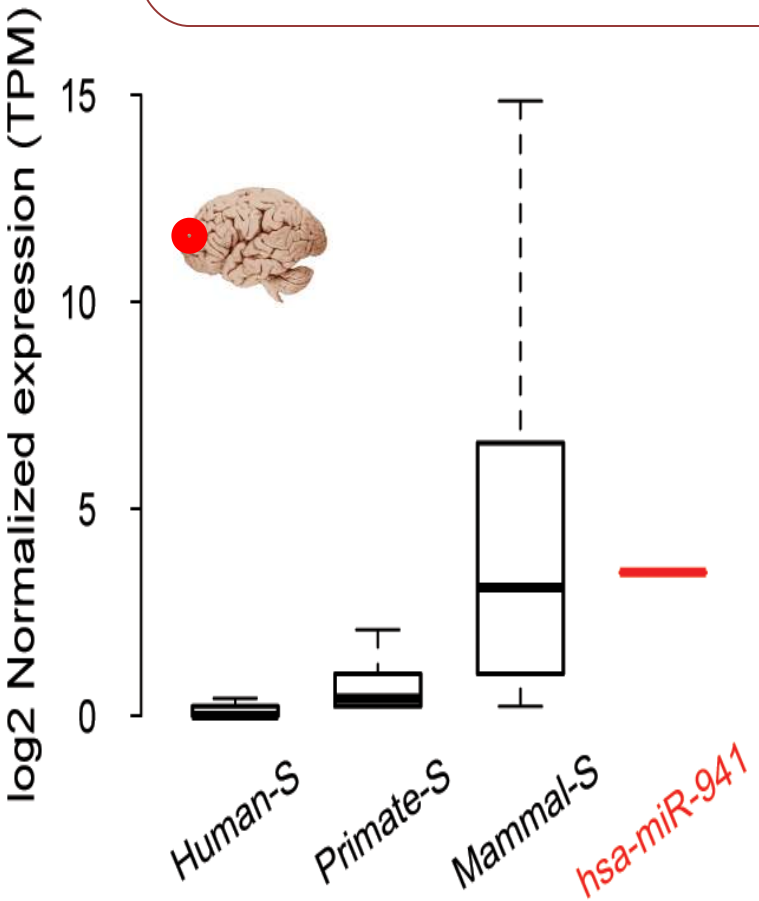
+ 7 more genomes

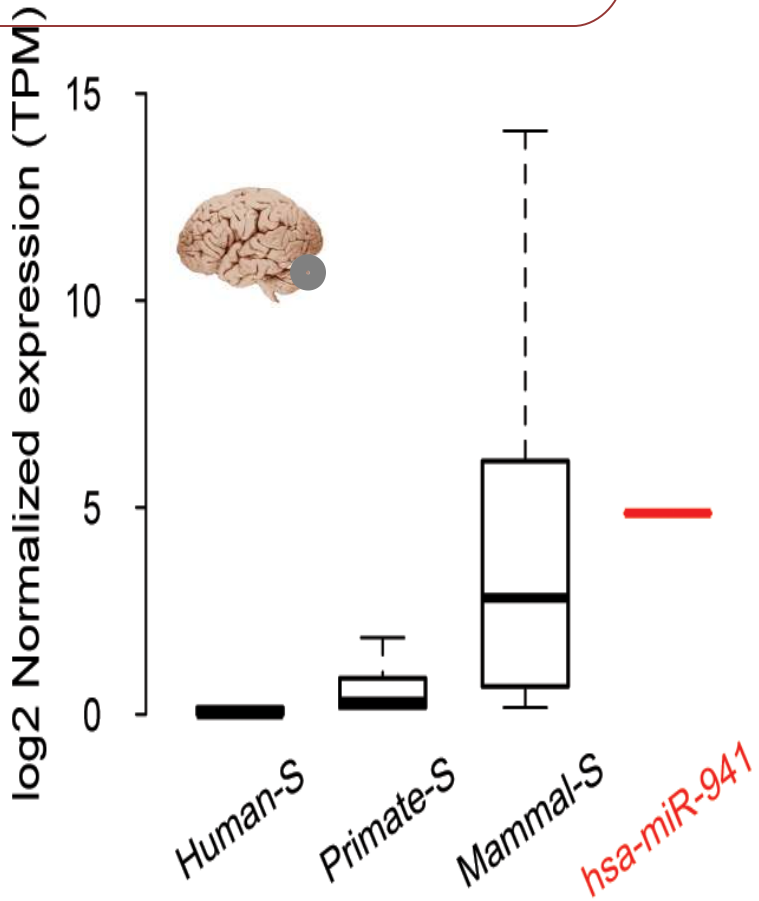
21 human-specific microRNA

1017 primate-specific microRNA

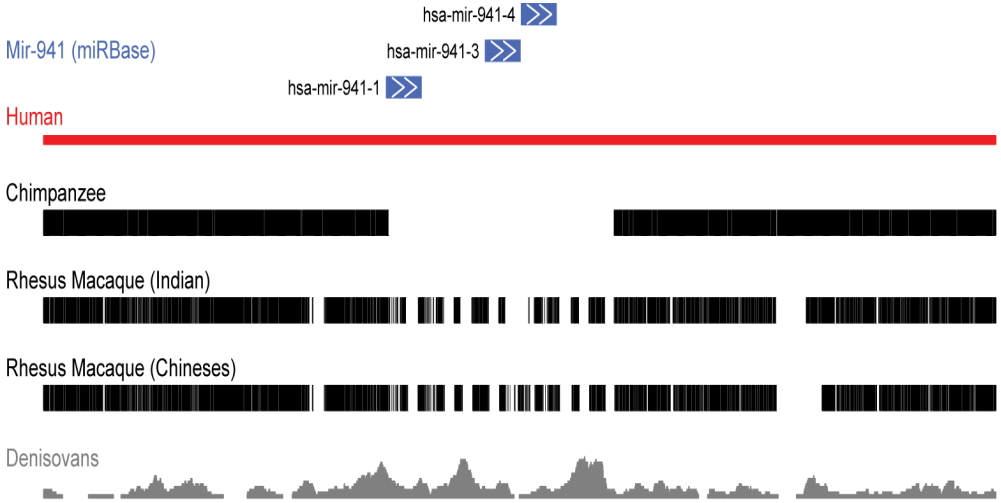
677 conserved among mammals

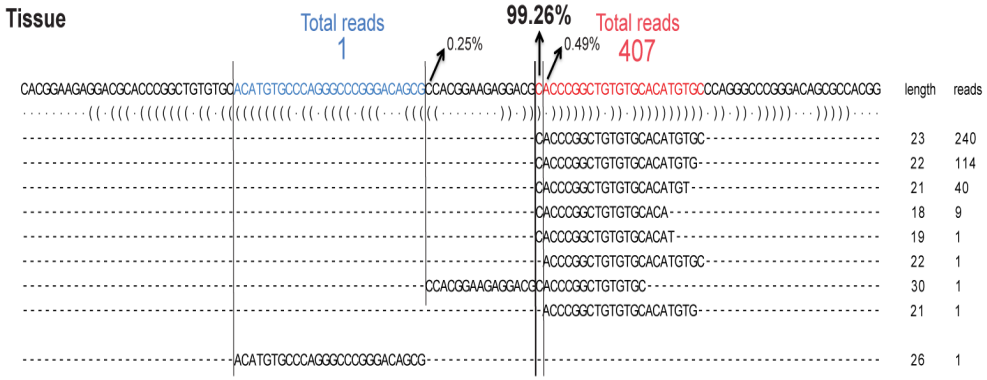
Novel miRNA | expression in brain

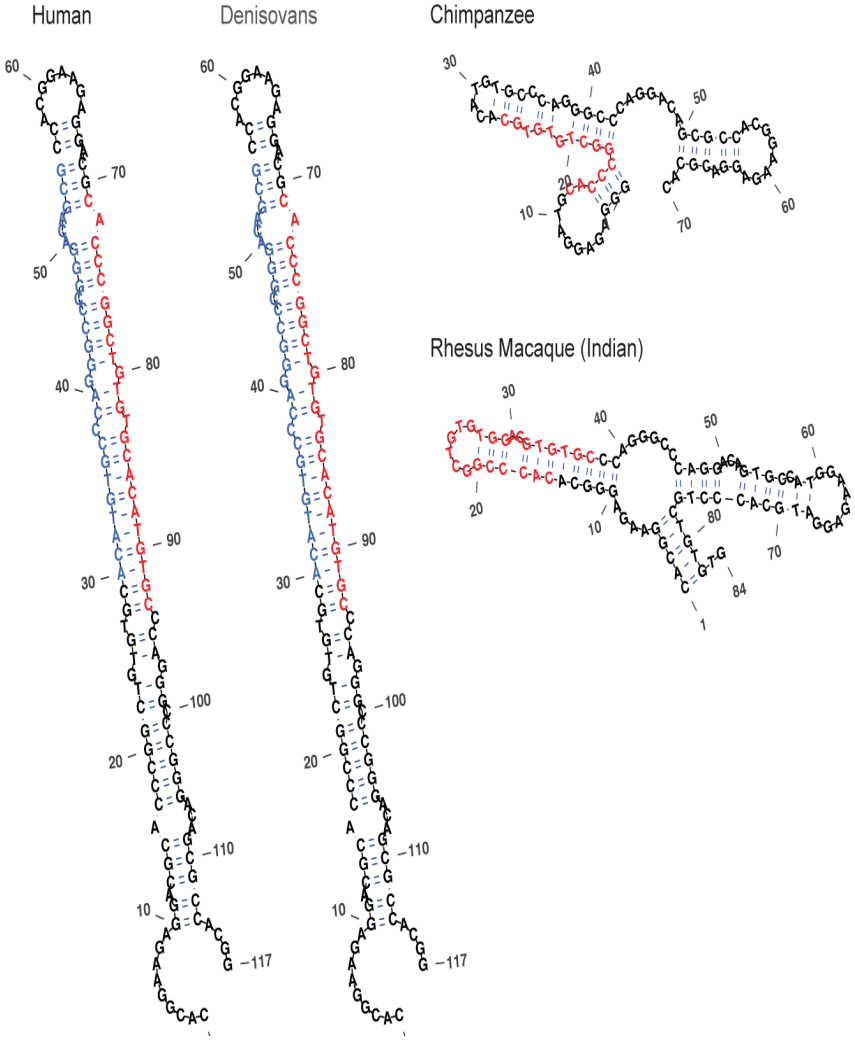




miRNA 941 | sequence evolution

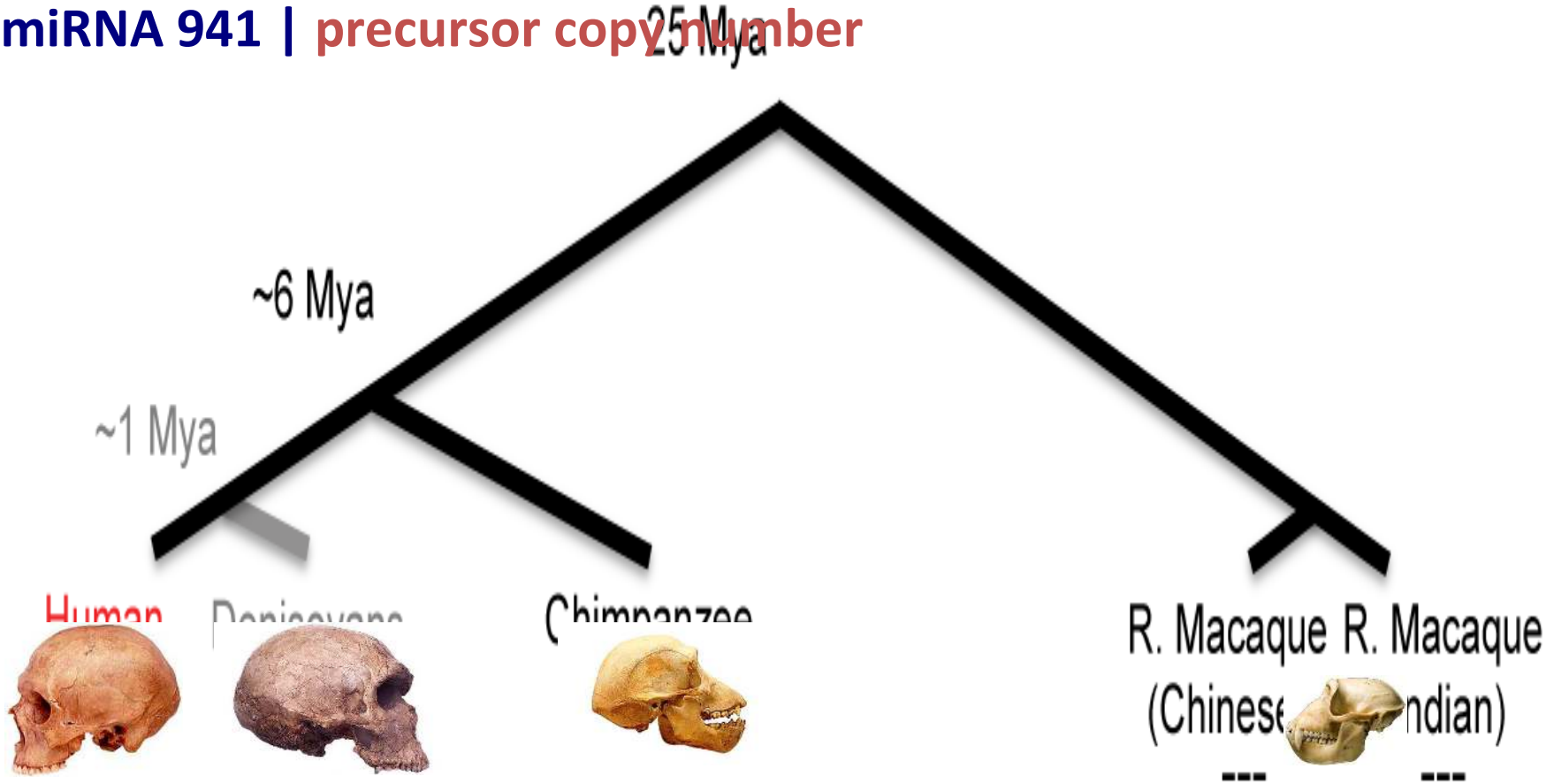






14.8.13

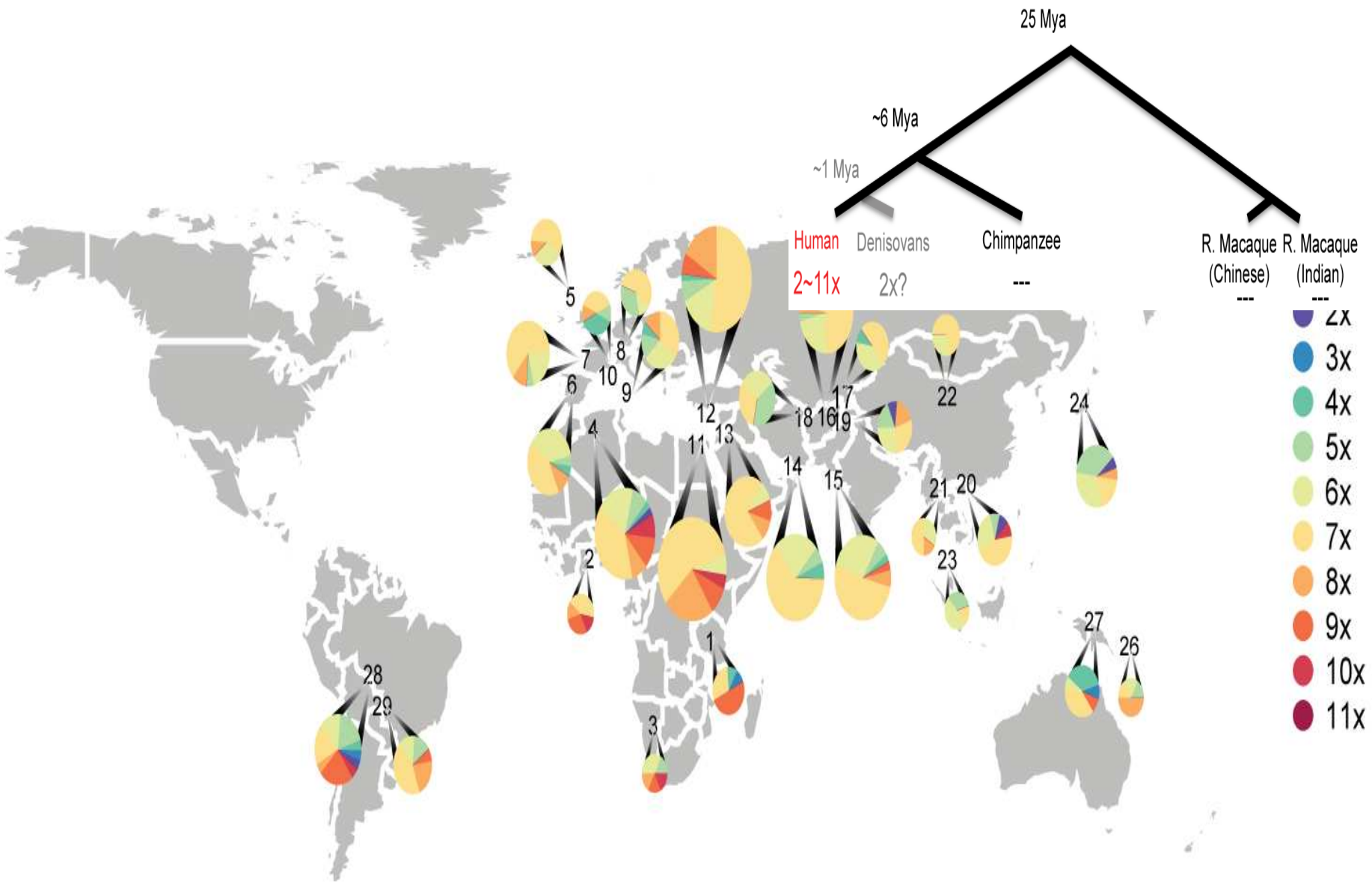
miRNA 941 | precursor copy number



14.8.13

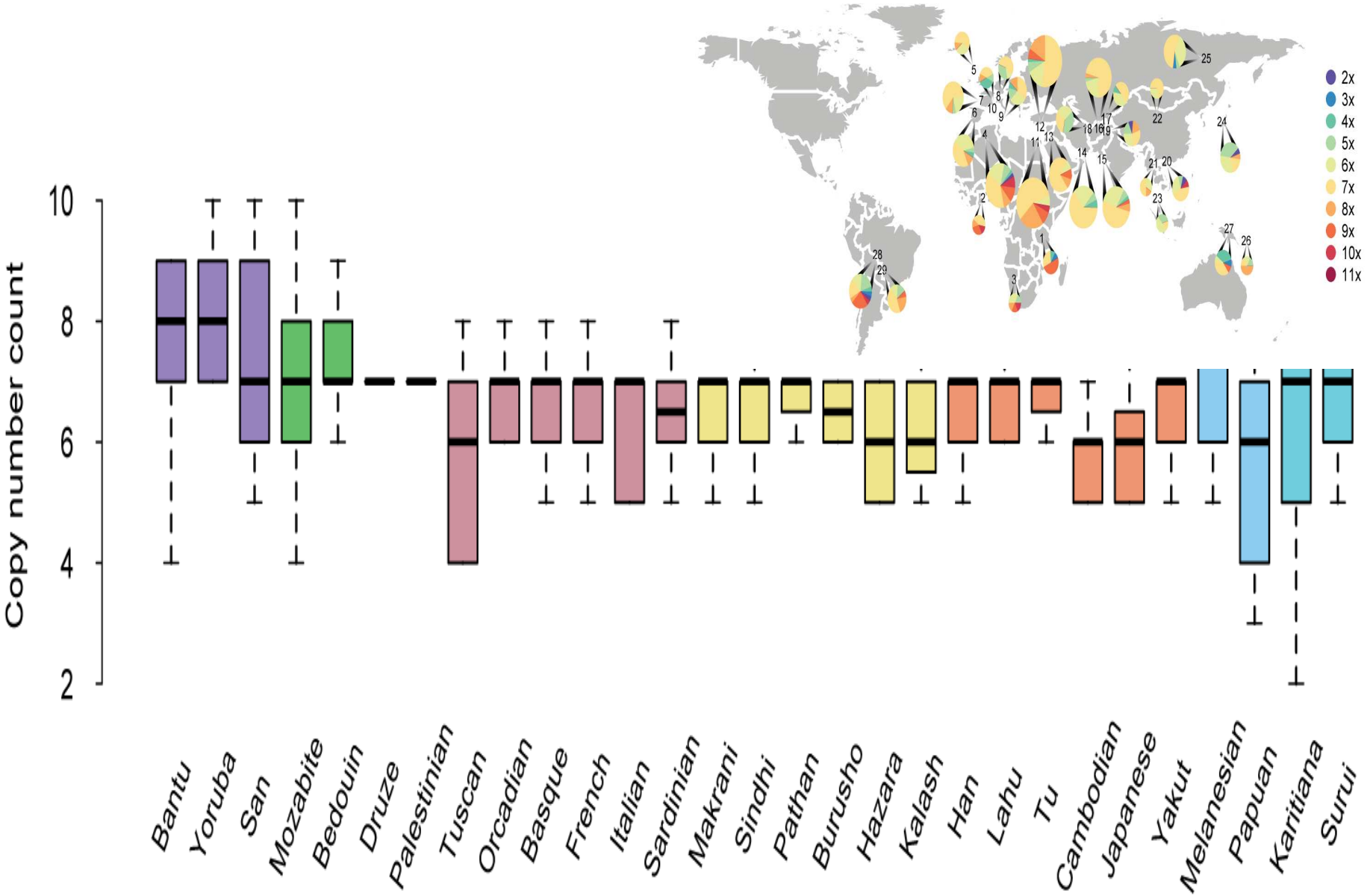
Nature Communications, 2012

miRNA 941 | copy number variation in modern humans



14.8.13

miRNA 941 | copy number variation in modern humans



miRNA 941 expression variation among populations | placenta

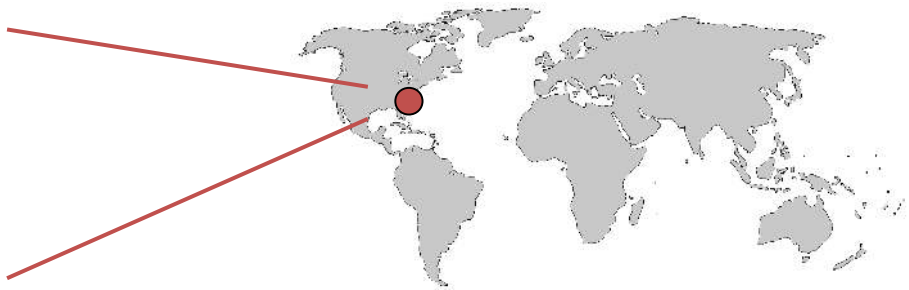
Placenta samples:

10 African (AF)

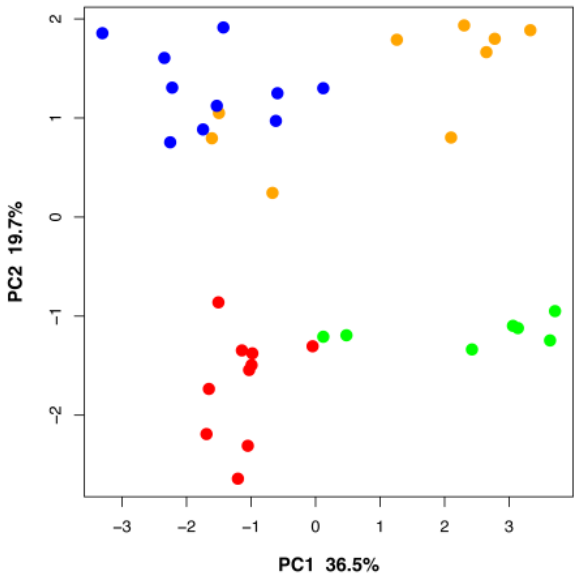
10 European (EU)

10 South Asian (SA)

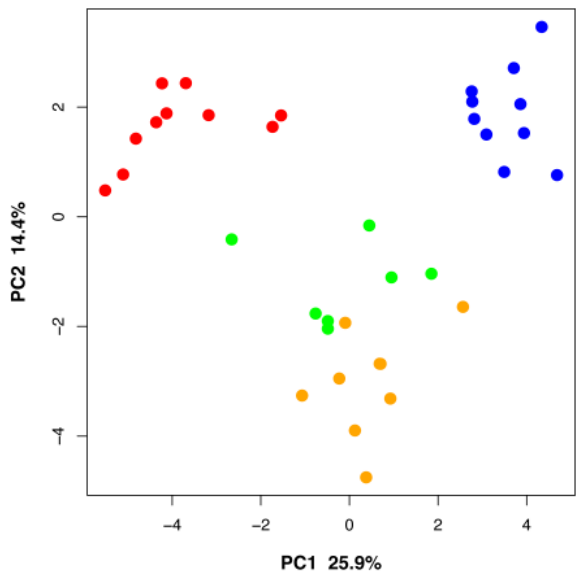
10 East Asian (EA)



40 | miRNA



127 | mRNA



African
European
South Asian
East Asian

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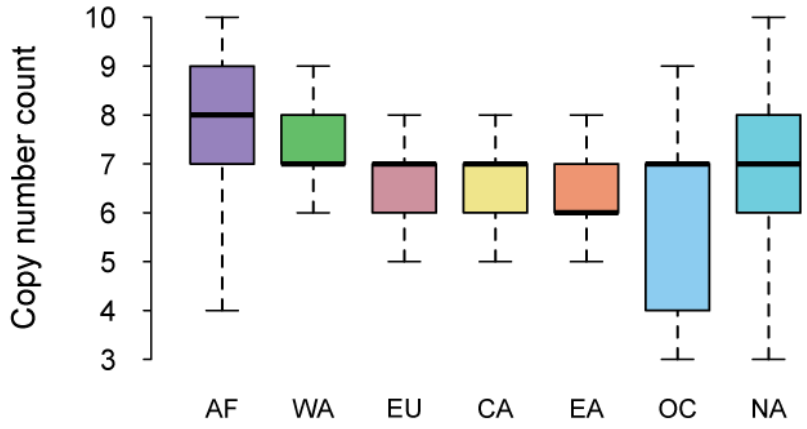
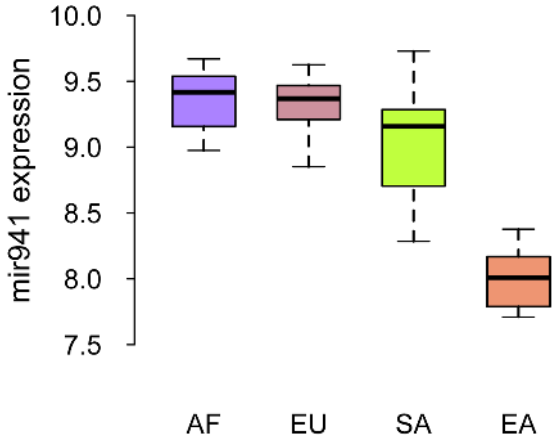
miRNA 941 expression variation among populations | placenta

miR-941 copy number



miR-941 expression



There is substantial expression variation among human populations

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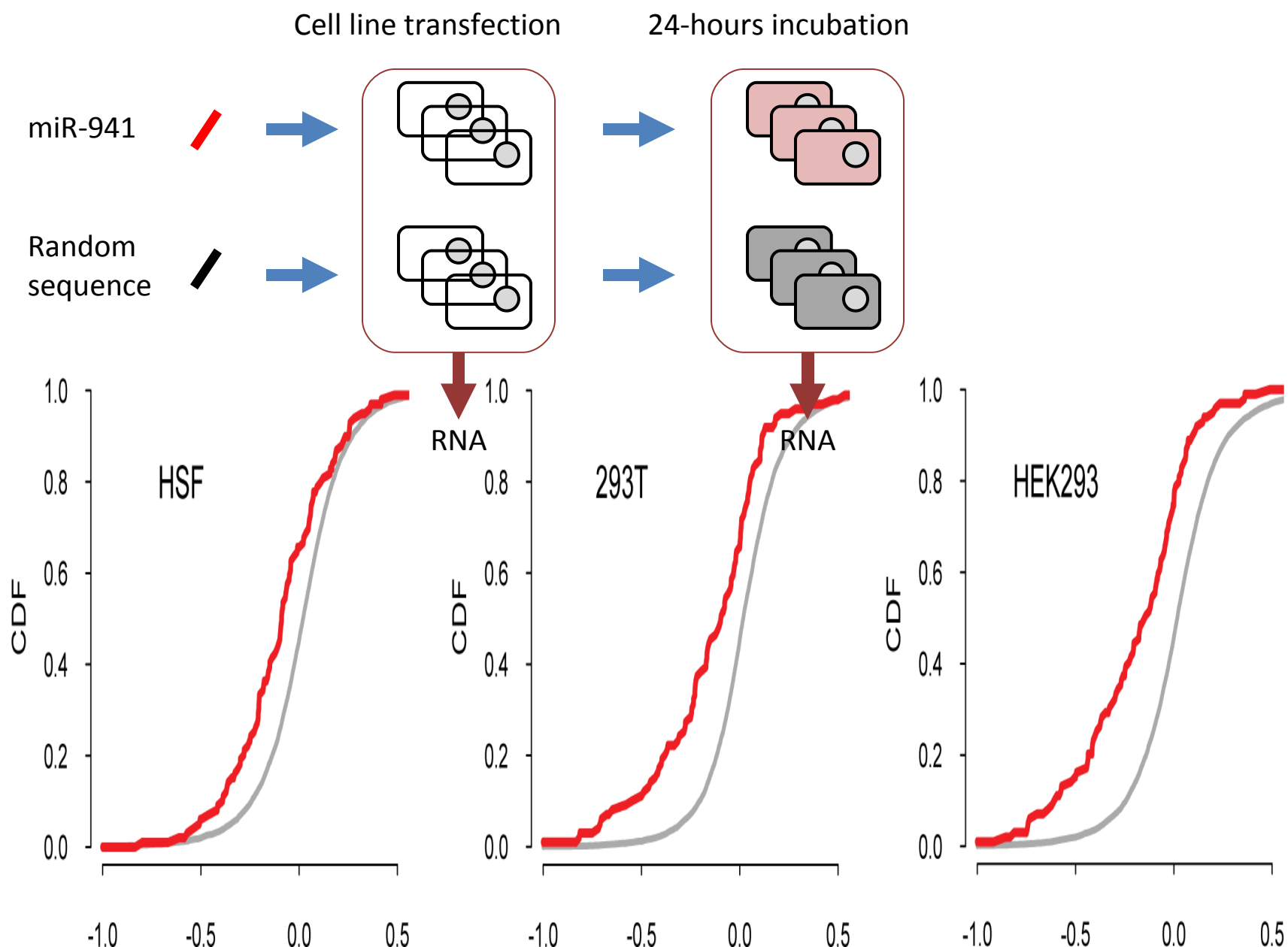
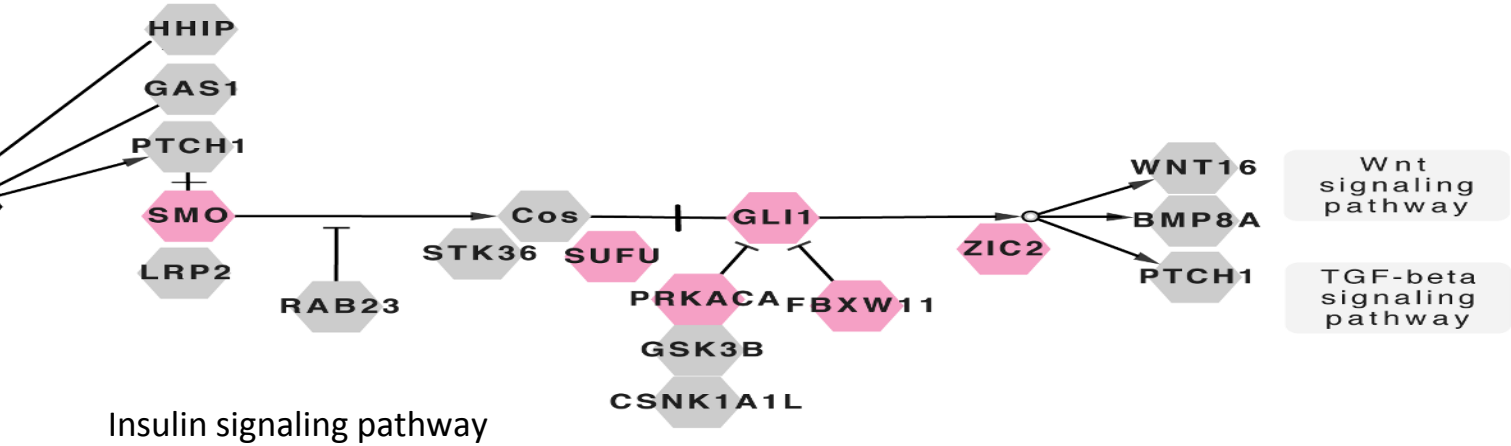
miRNA 941 | functional analysis – target genes

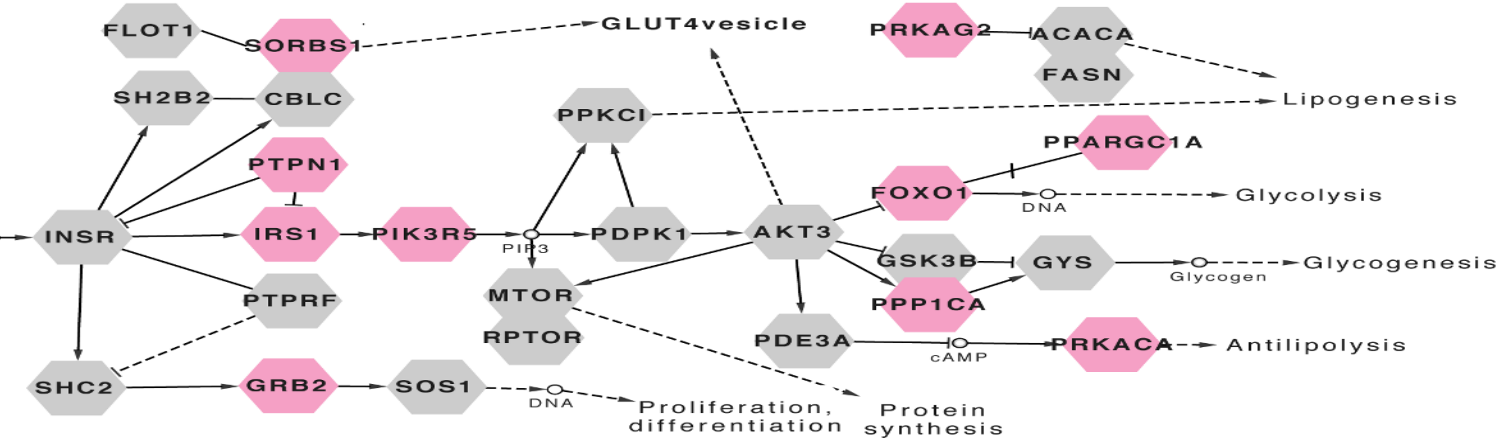


miRNA 941 | functional analysis – target pathways

Hedgehog signaling pathway



Insulin signaling pathway



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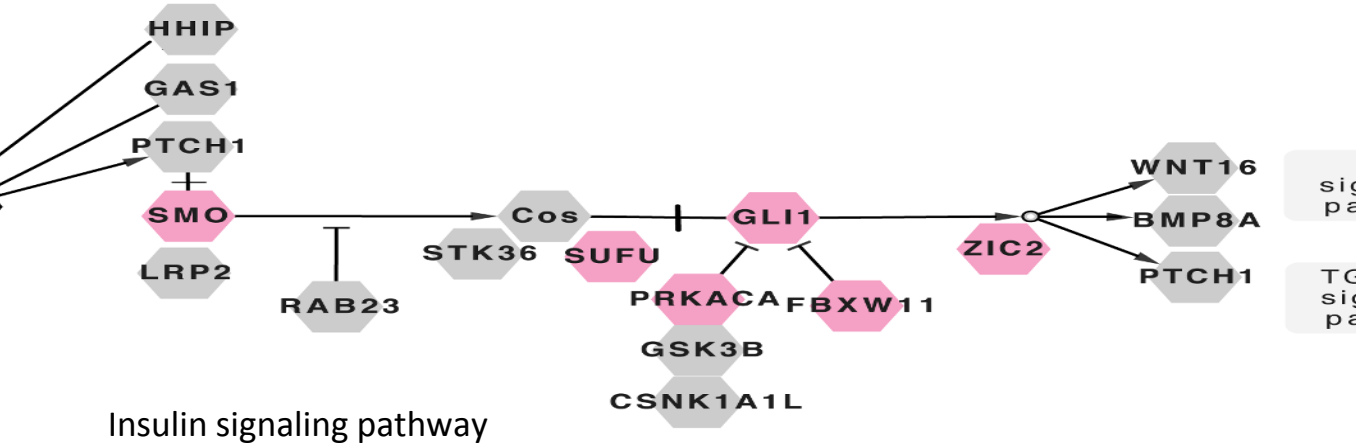
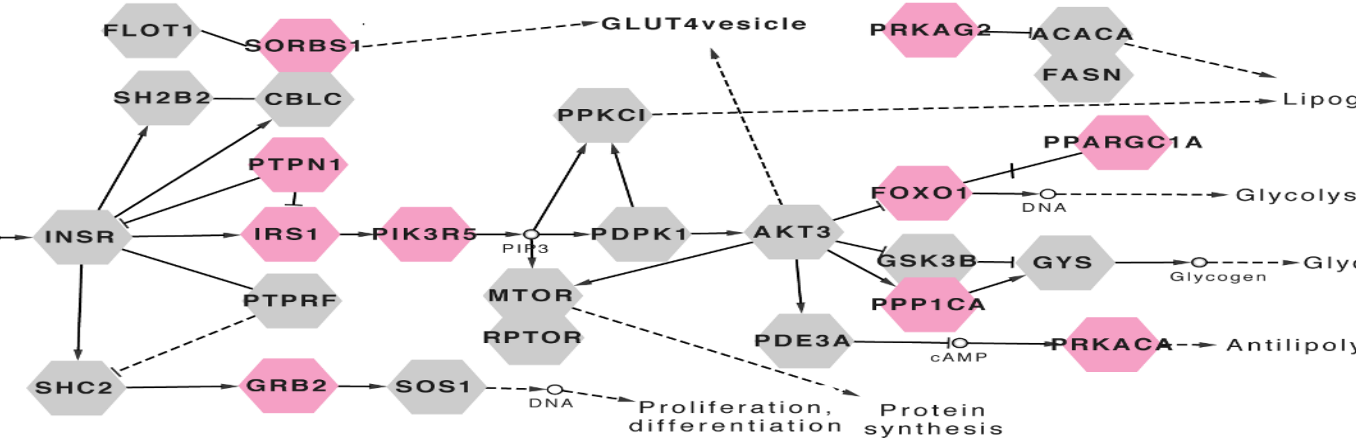
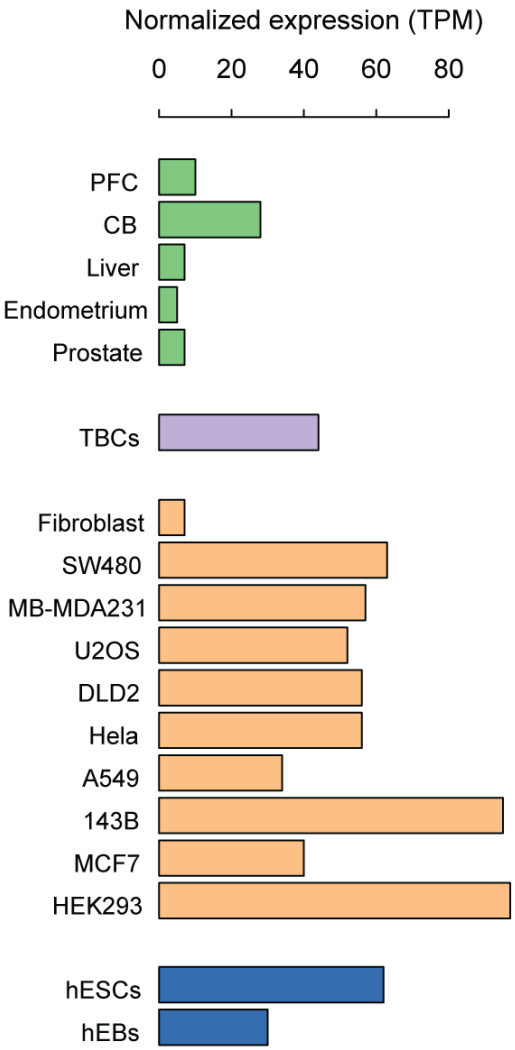
miRNA 941 | functional analysis – role in proliferation?

Hedgehog signaling pathway



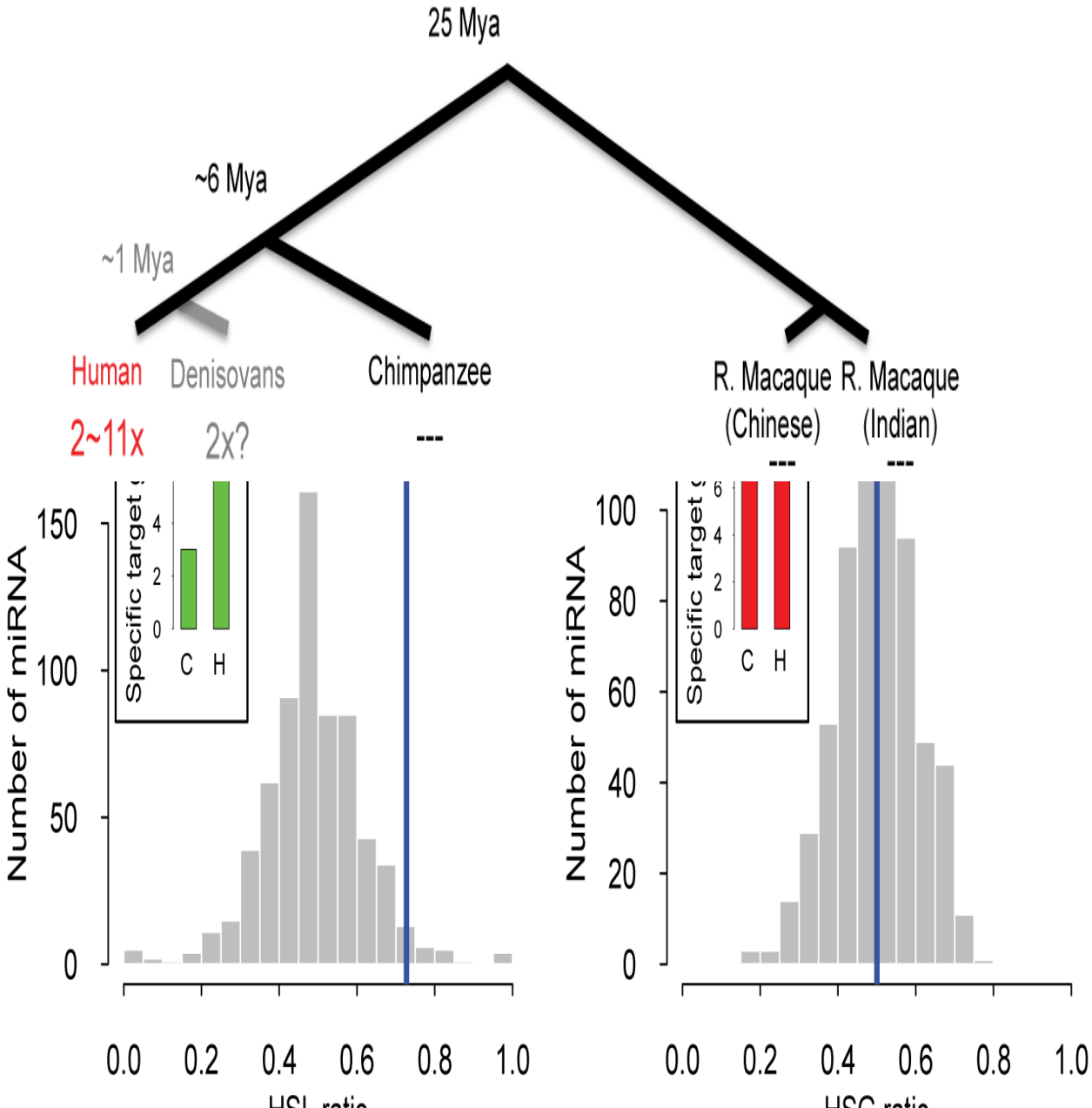
Insulin signaling pathway

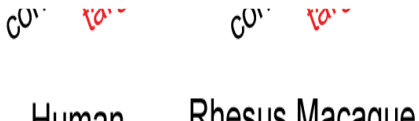




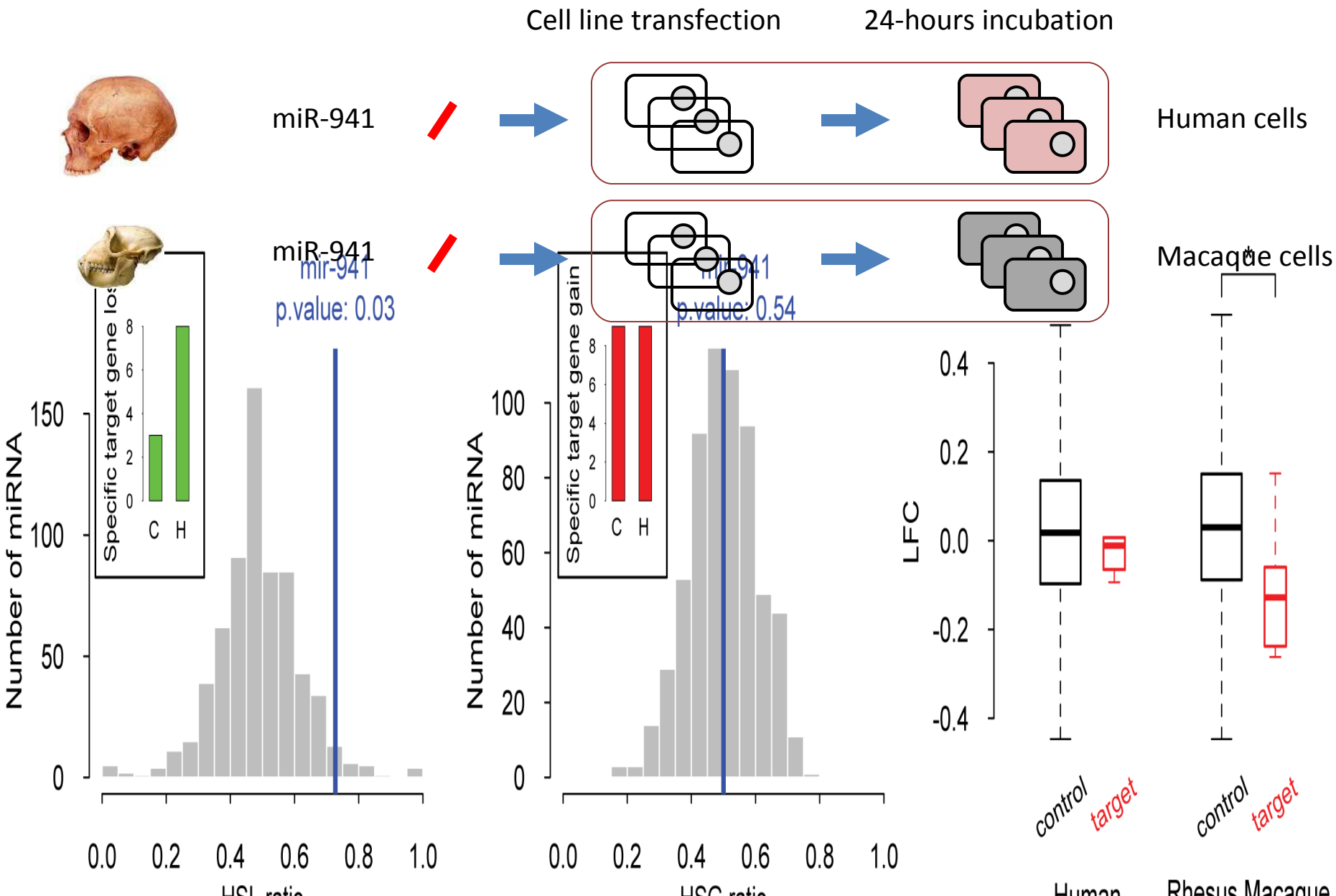
14.8.13

miRNA 941 | regulatory evolution – binding sites



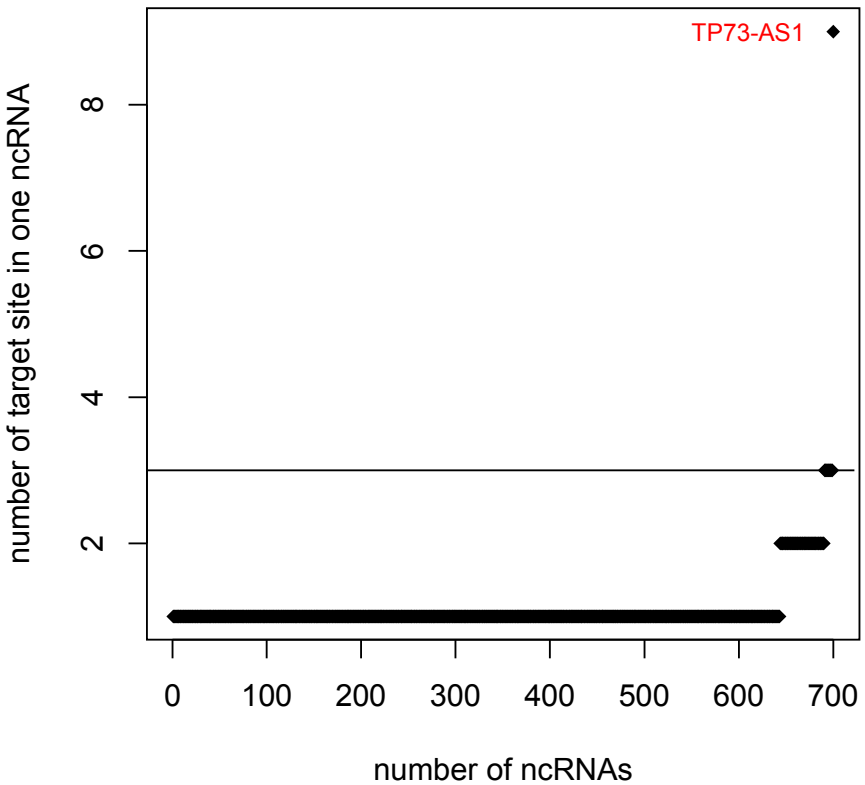


miRNA 941 | regulatory evolution – binding sites

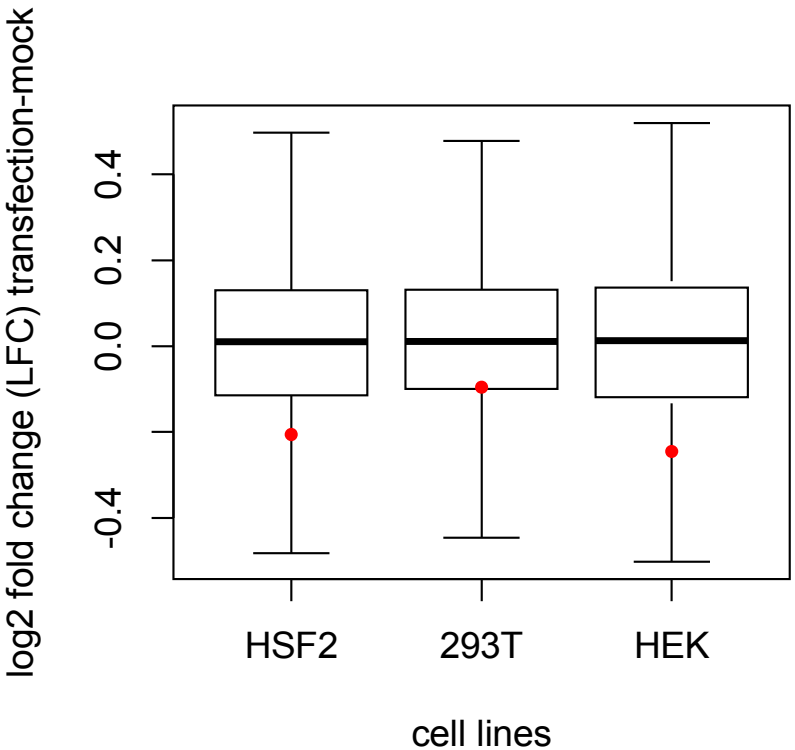


miRNA 941 | regulatory evolution – sponge

miR-941 binding sites



miR-941 inhibits sponge



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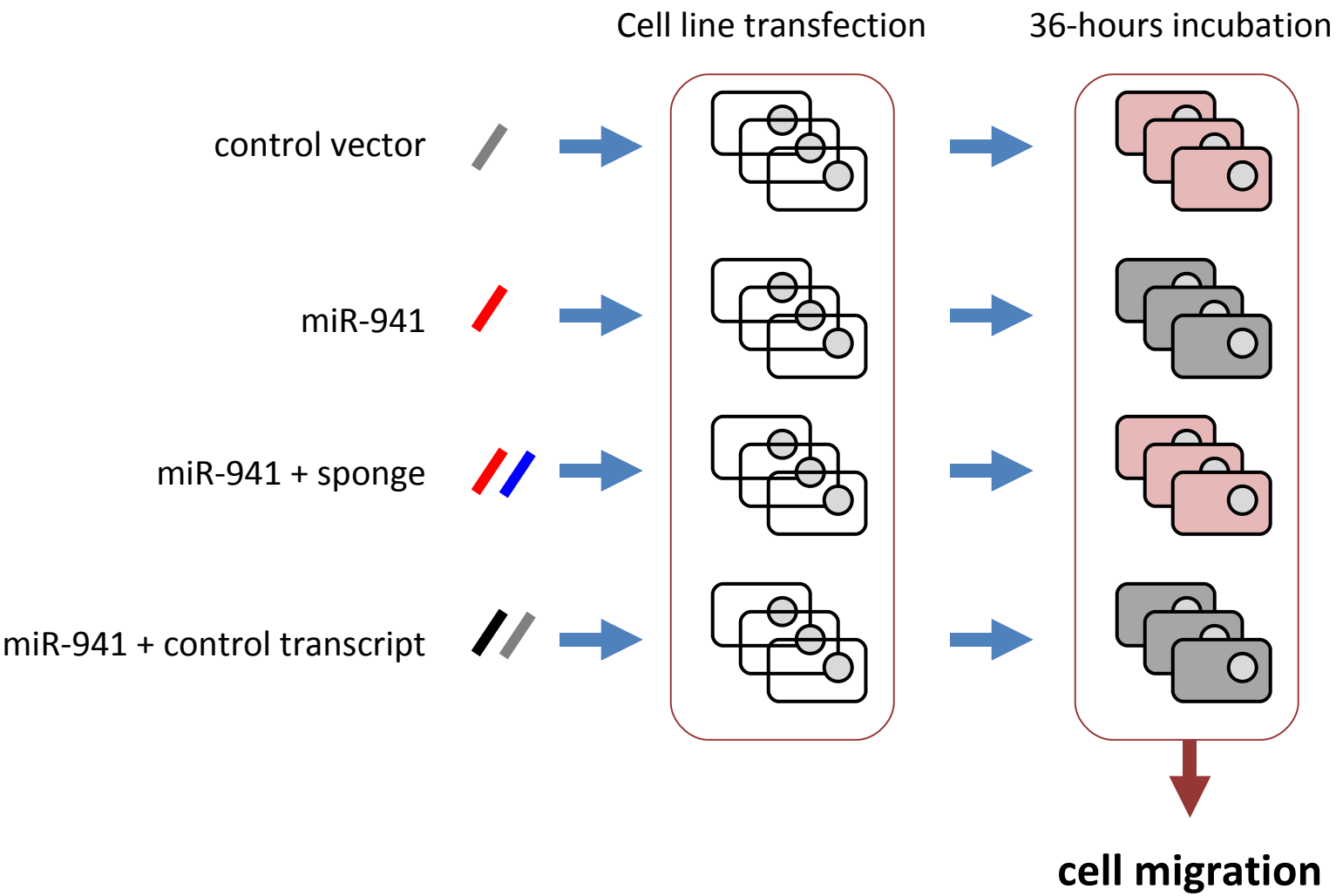
miRNA 941 | regulatory evolution – sponge



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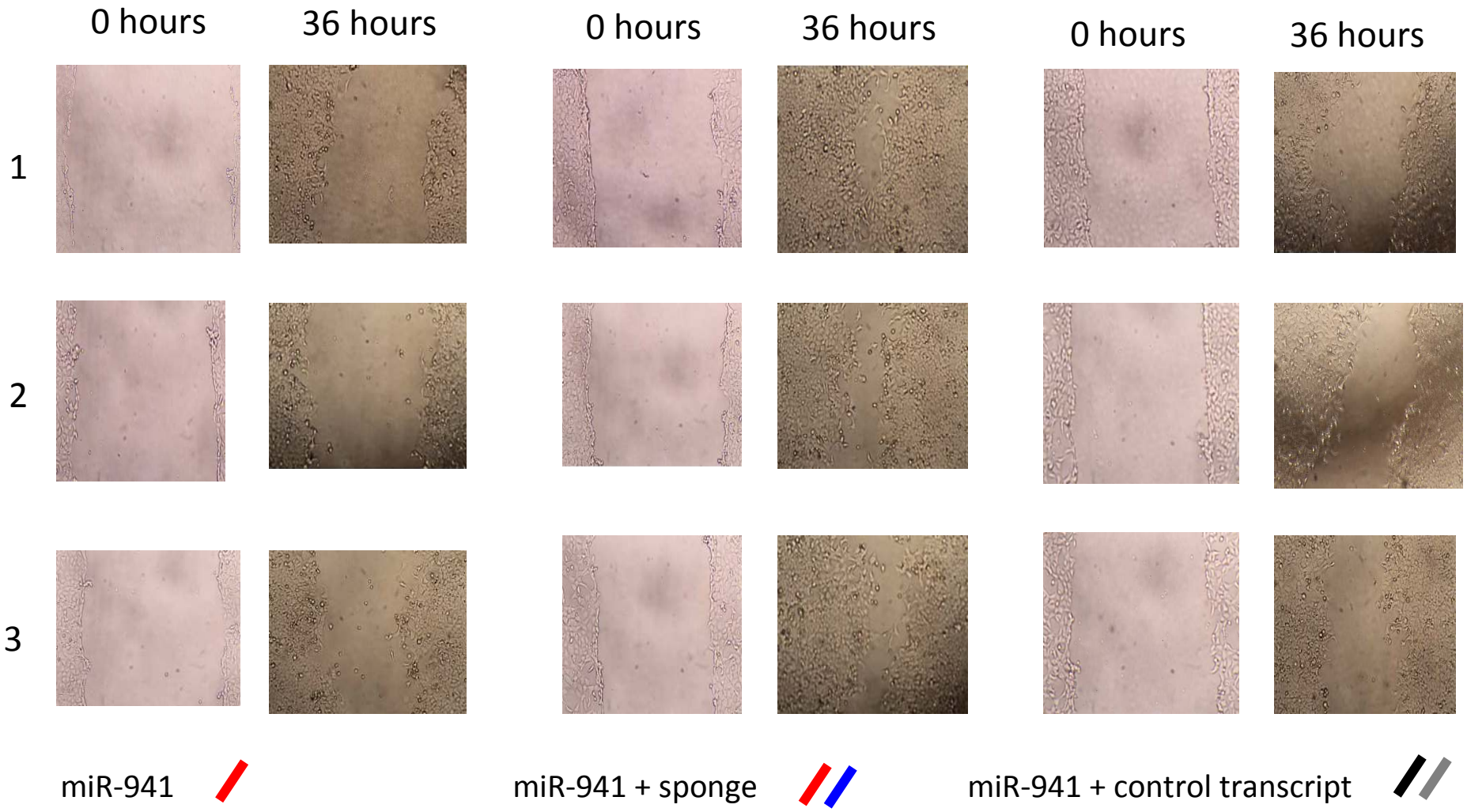
miRNA 941 | regulatory evolution – sponge

Phenotype



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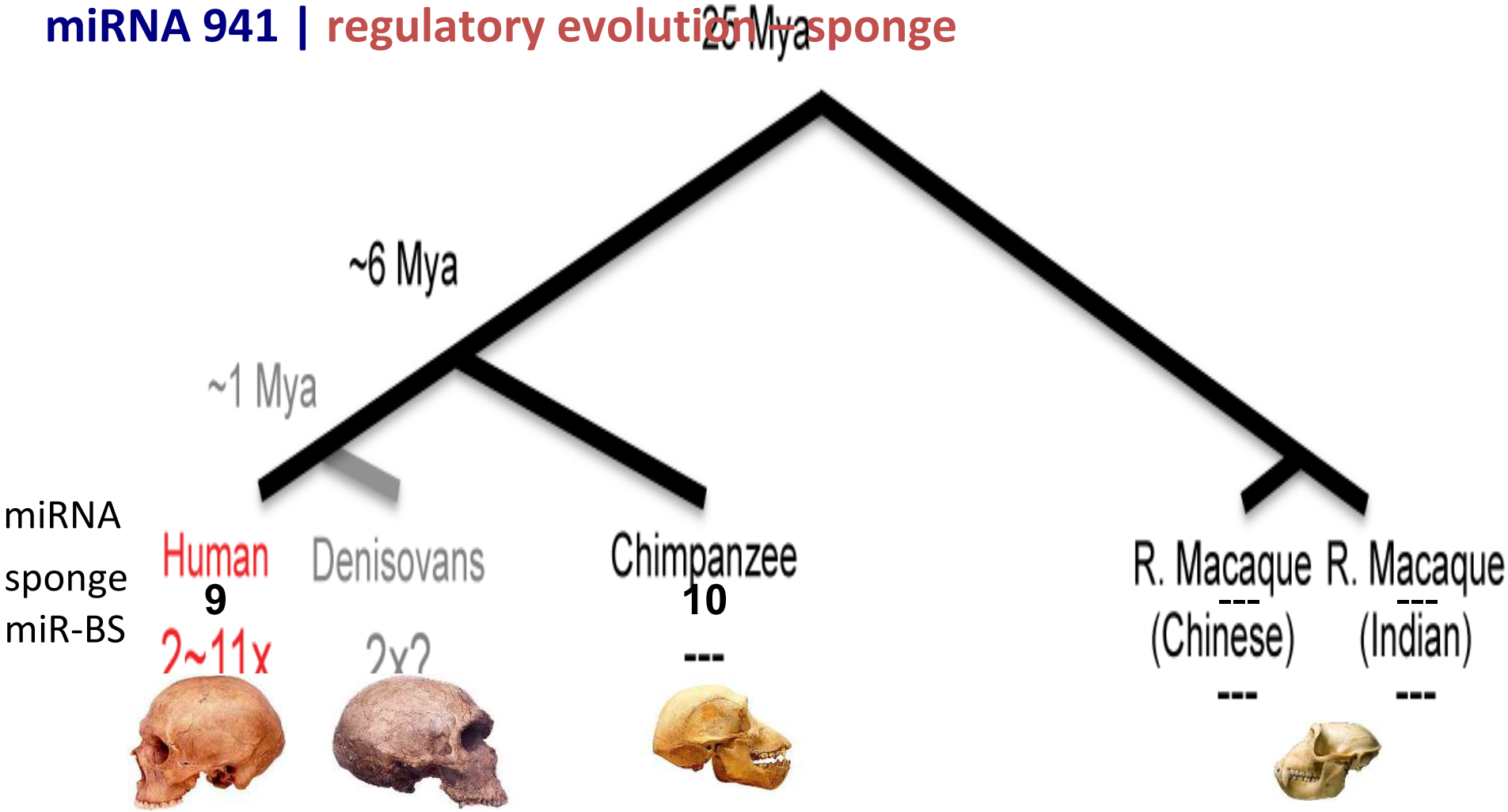
miRNA 941 | regulatory evolution – sponge



14.8.13

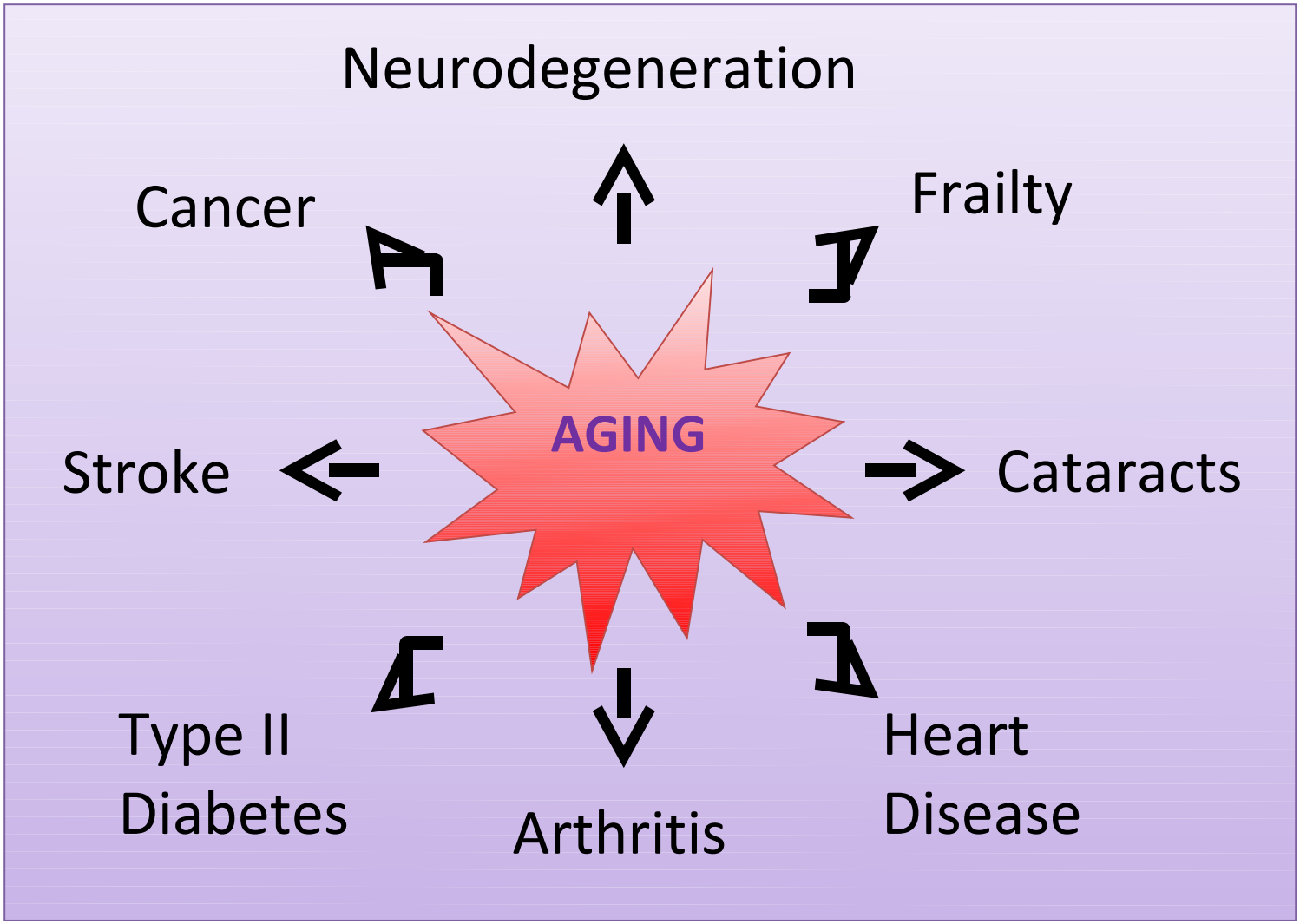
Conclusions

Transcriptome regulation driven by non-coding RNA evolves rapidly and complexly

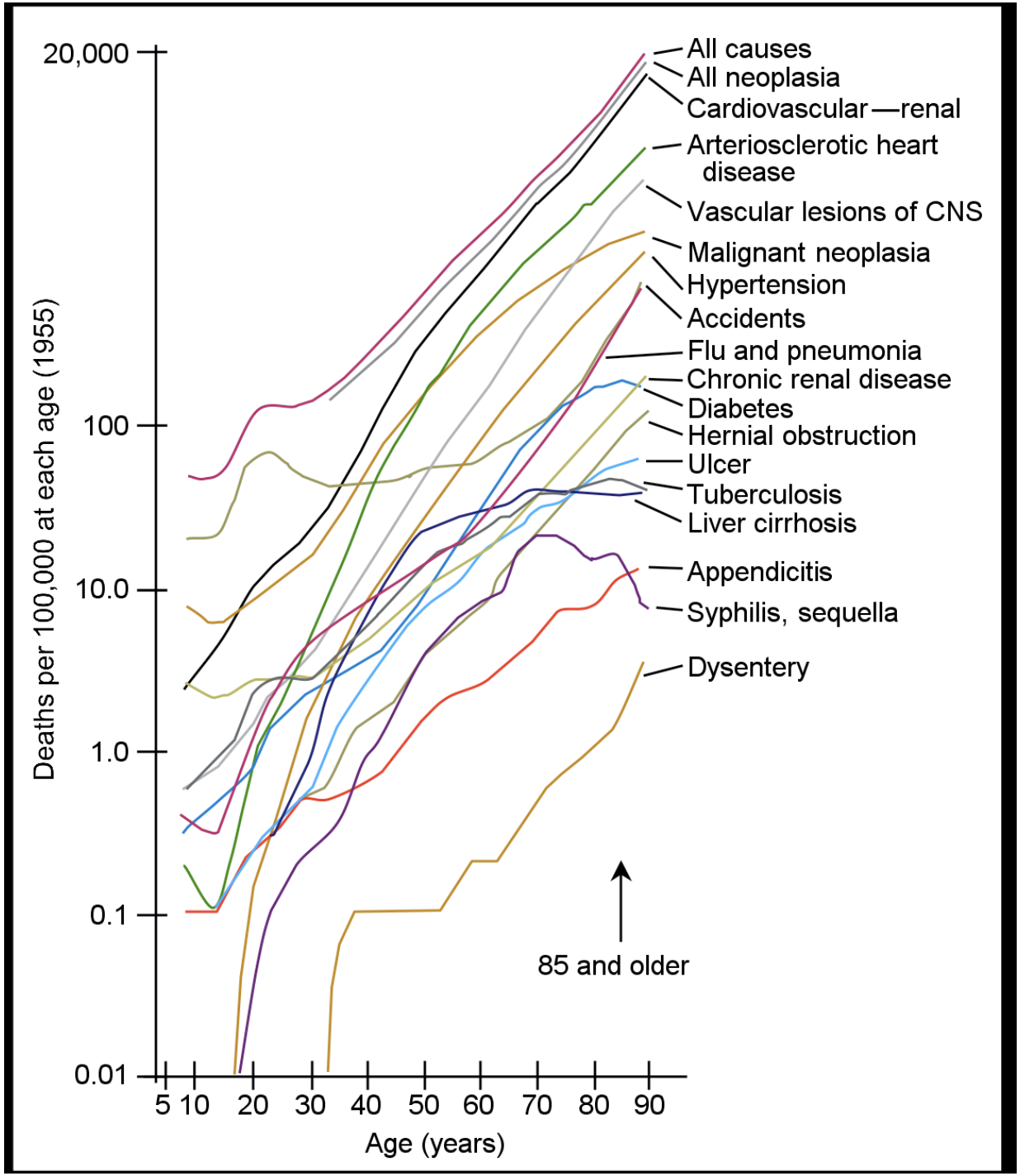
4 Brain aging

A Growing Tide of Elderly Citizens . . .

The percentage of the world's population that is age 60 and older is expected to grow steadily over the next 50 years, so that by 2050 the elderly will make up a full 25 percent of many countries' populations.

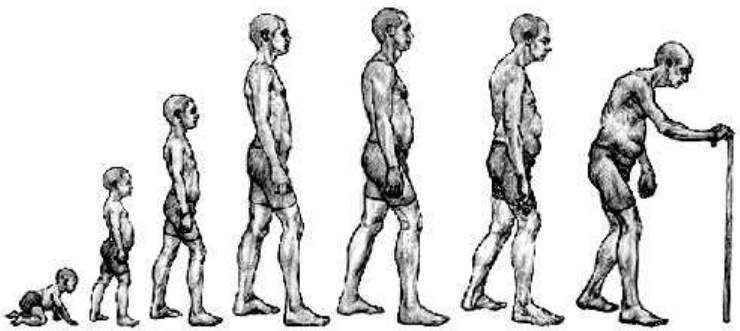

Neurodegeneration
Cancer
Frailty
AGING
Stroke
Cataracts
Type II
Diabetes
Arthritis
Heart
Disease

14.8.13

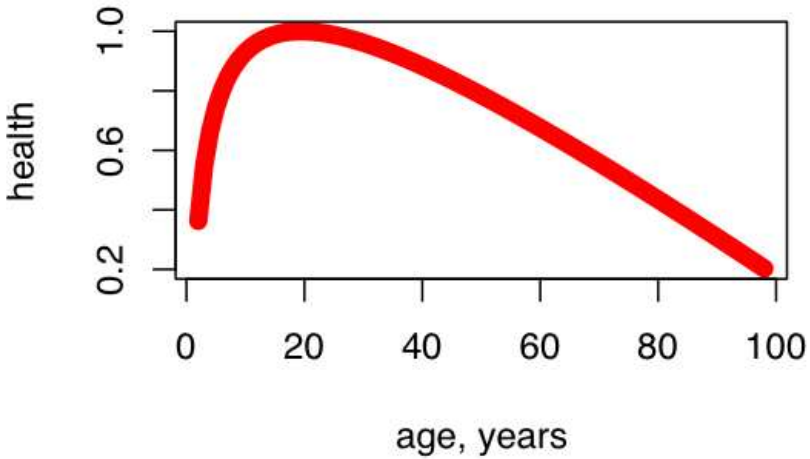

20,000
100
10.0
1.0
0.1
0.01
Deaths per 100,000 at each age (1955)
5 10 20 30 40 50 60 70 80 90
Age (years)
All causes
All neoplasia
Cardiovascular—renal
Arteriosclerotic heart disease
Vascular lesions of CNS
Malignant neoplasia
Hypertension
Accidents
Flu and pneumonia
Chronic renal disease
Diabetes
Hernial obstruction
Ulcer
Tuberculosis
Liver cirrhosis
Appendicitis
Syphilis, sequella
Dysentery
85 and older

Kohn 1978

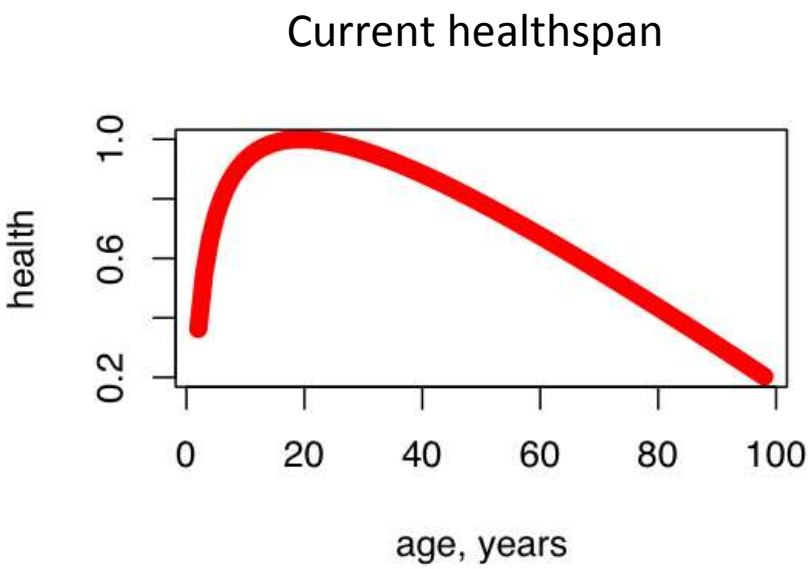
Human aging | health decrease with age

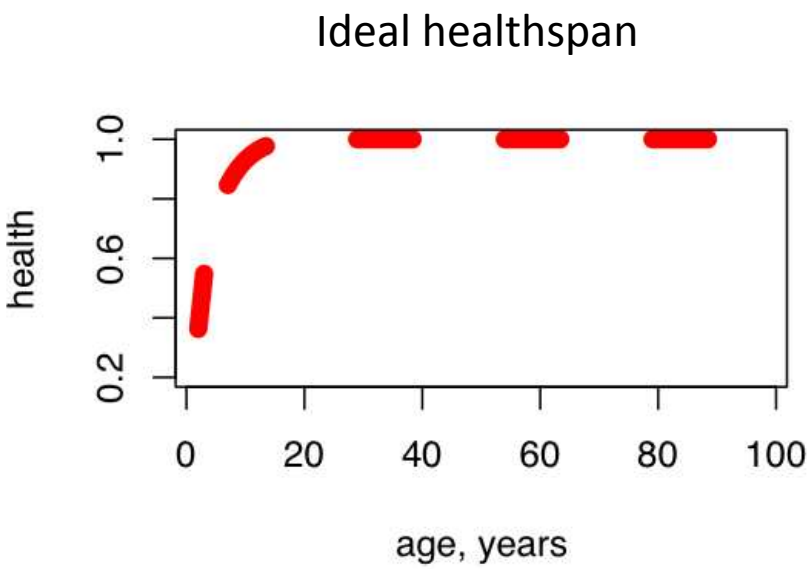


Human “healthspan”

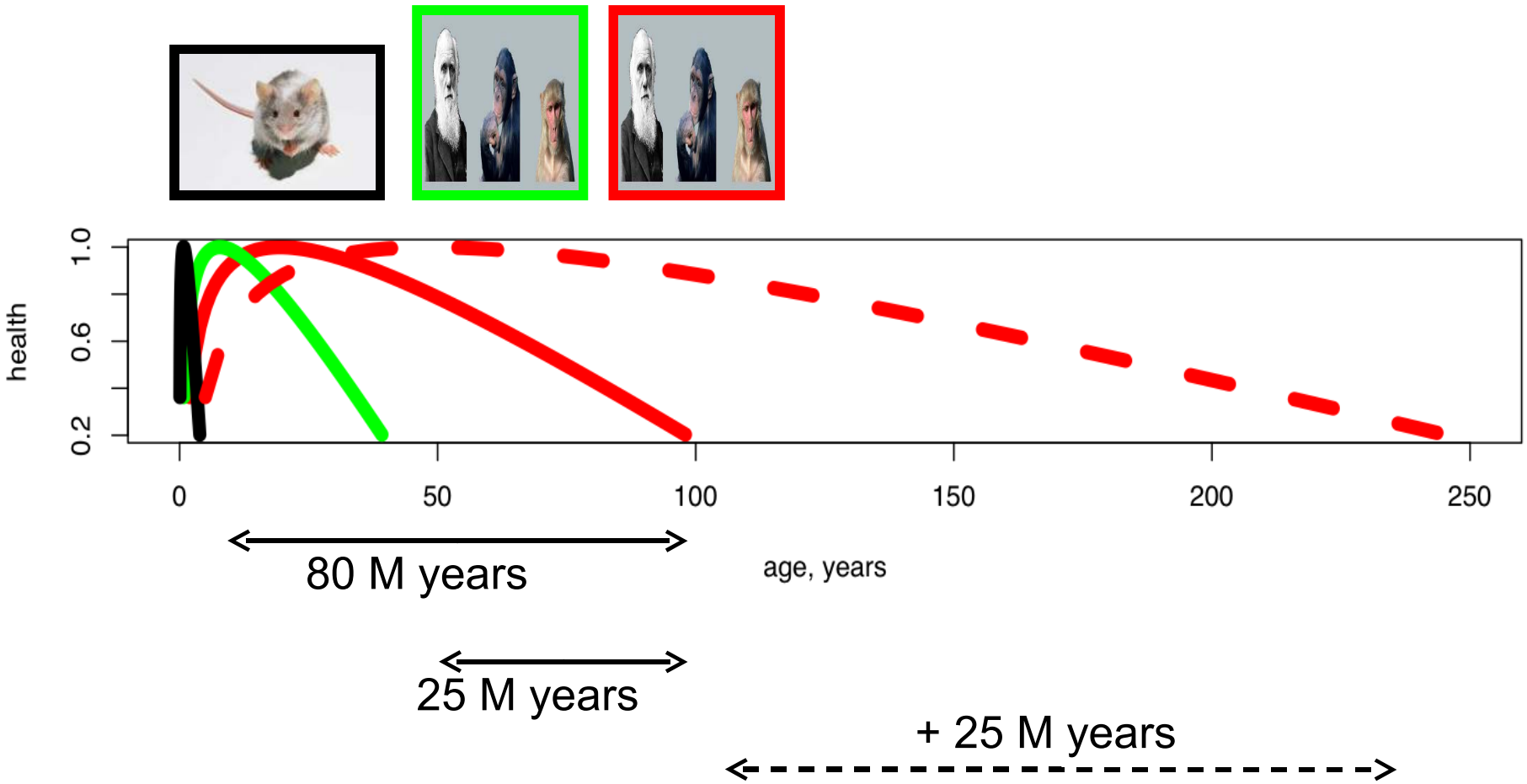


Human aging | health decrease with age



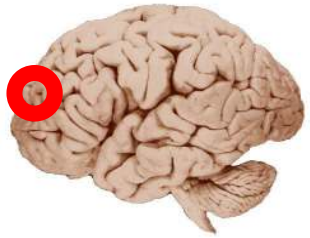


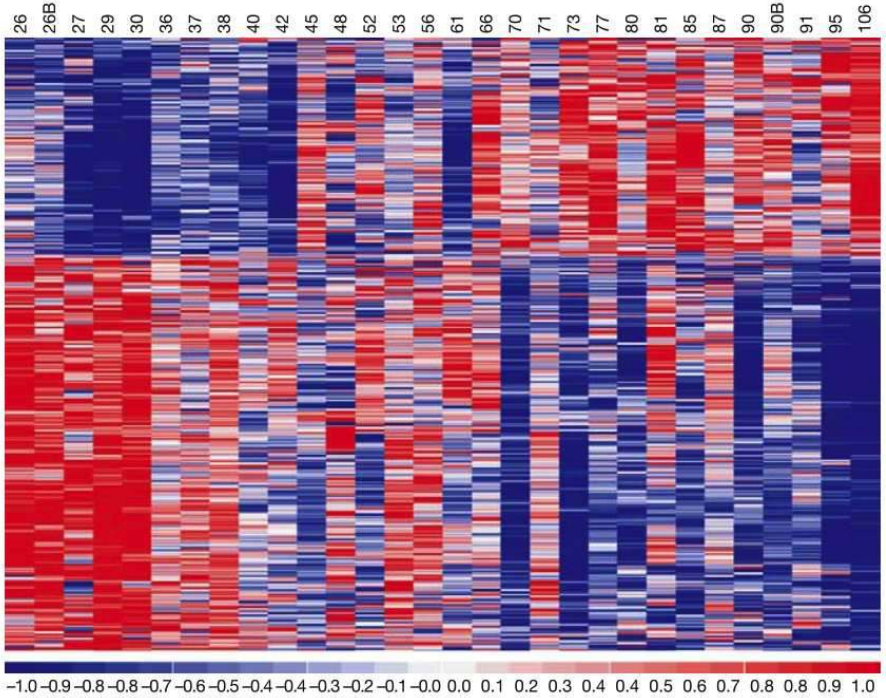
Human aging | variation among species

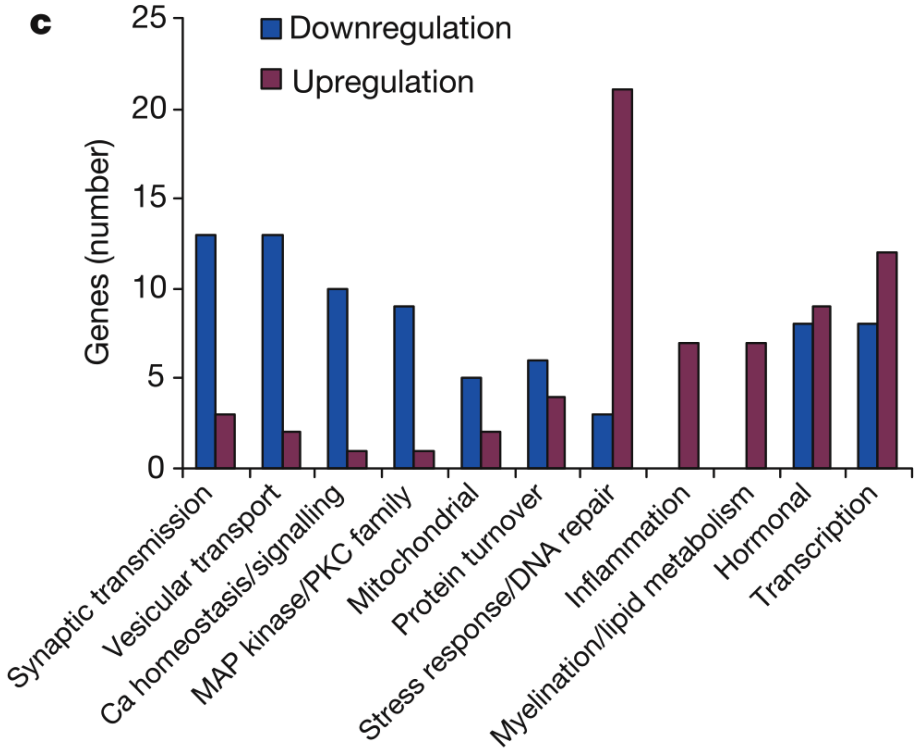


Human aging | background

mRNA







Lu et al. Nature (2004)

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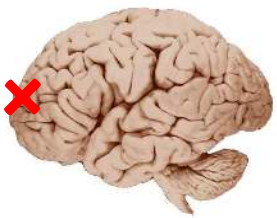
Human aging | human-macaque comparison

24 humans 0 - 98 years

24 rhesus macaques 0 - 28 years

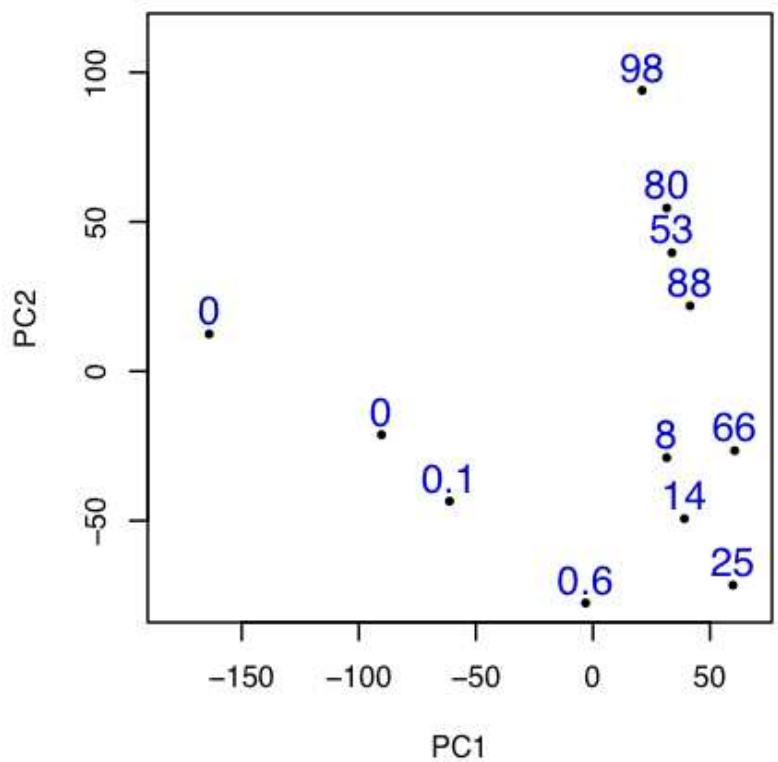


mRNA Affymetrix microarrays ~12,000 genes

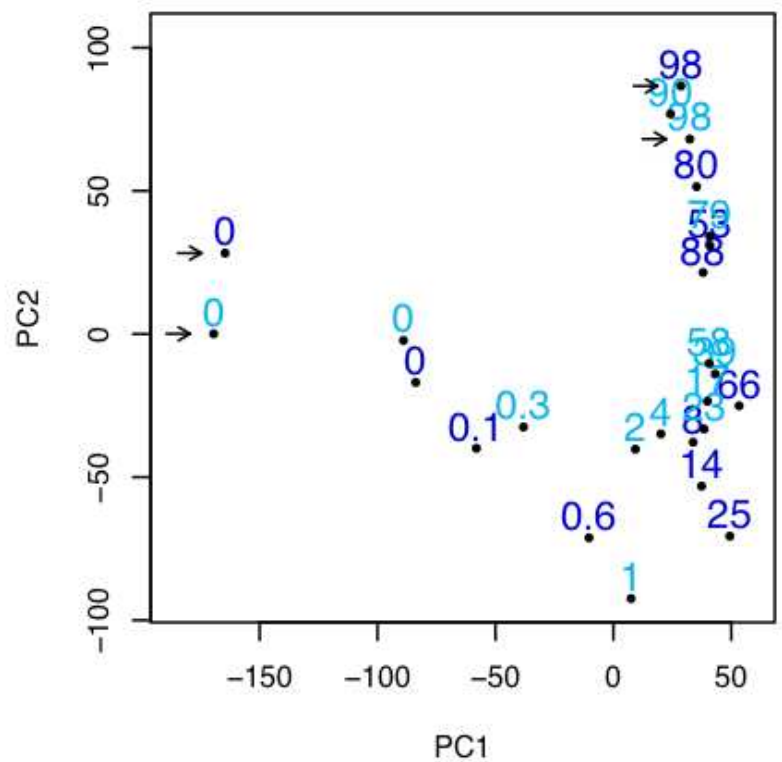
miRNA Illumina sequencing ~400 miRNAs

Human aging | expression changes with age

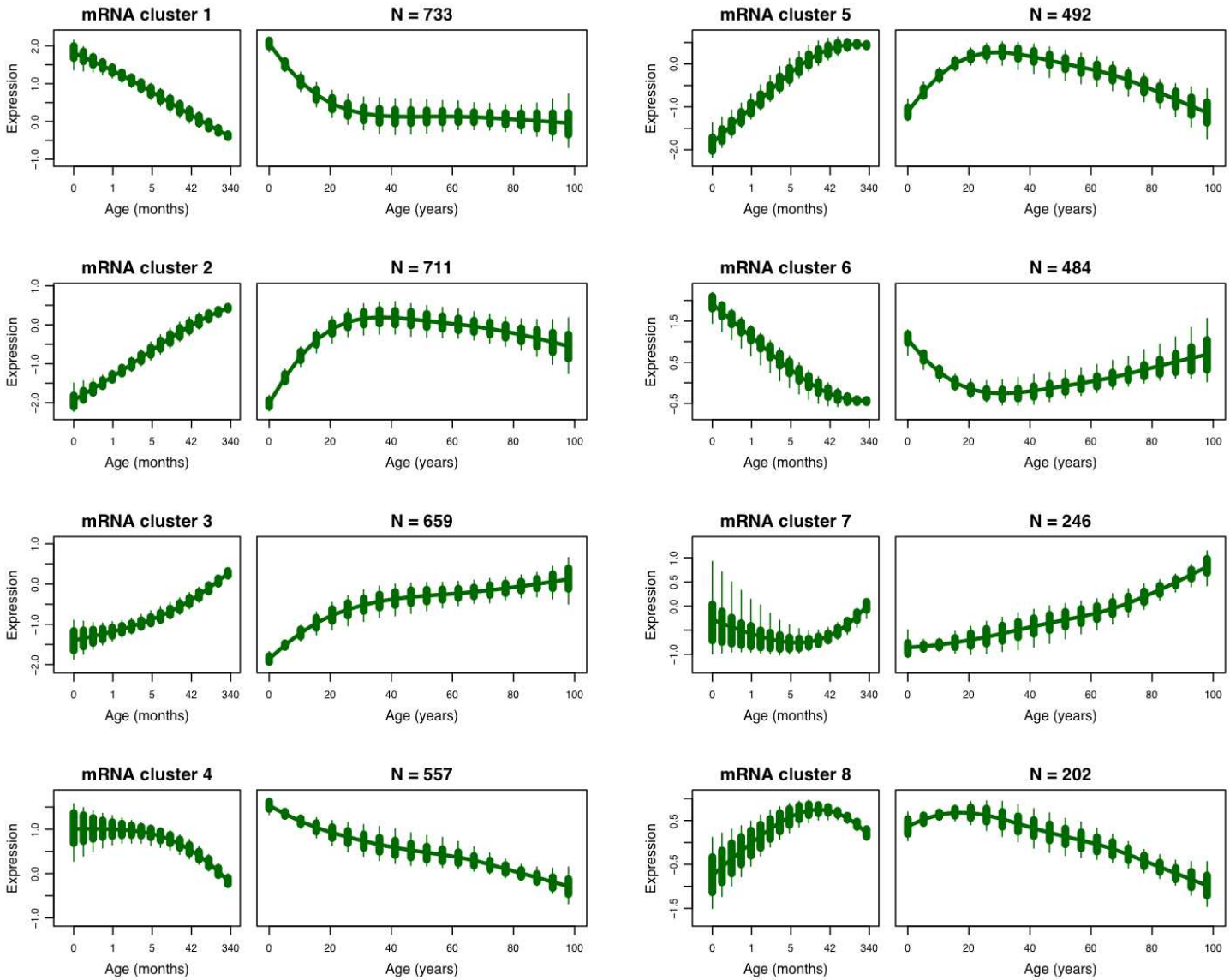
Human mRNA | set 1



Human mRNA | sets 1&2

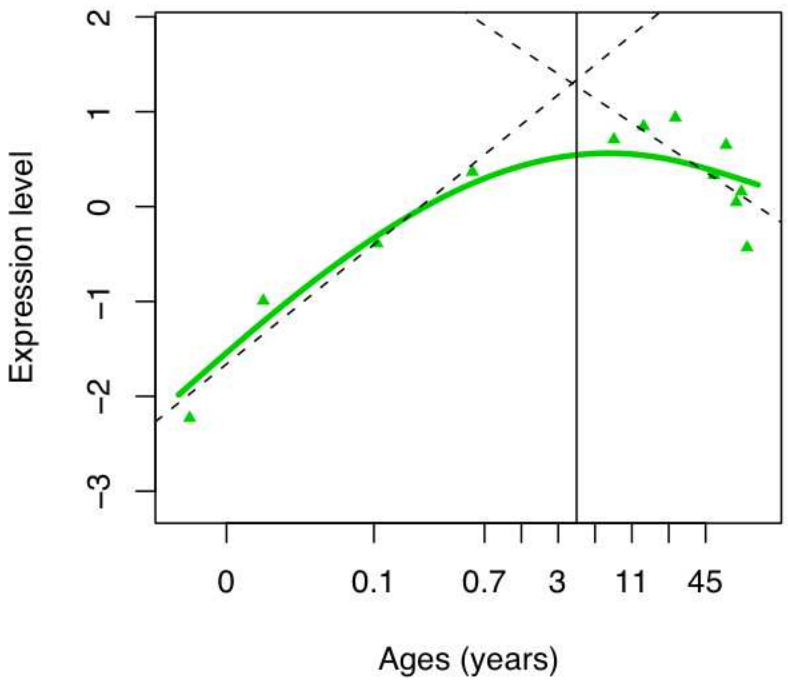


Human aging | expression patterns

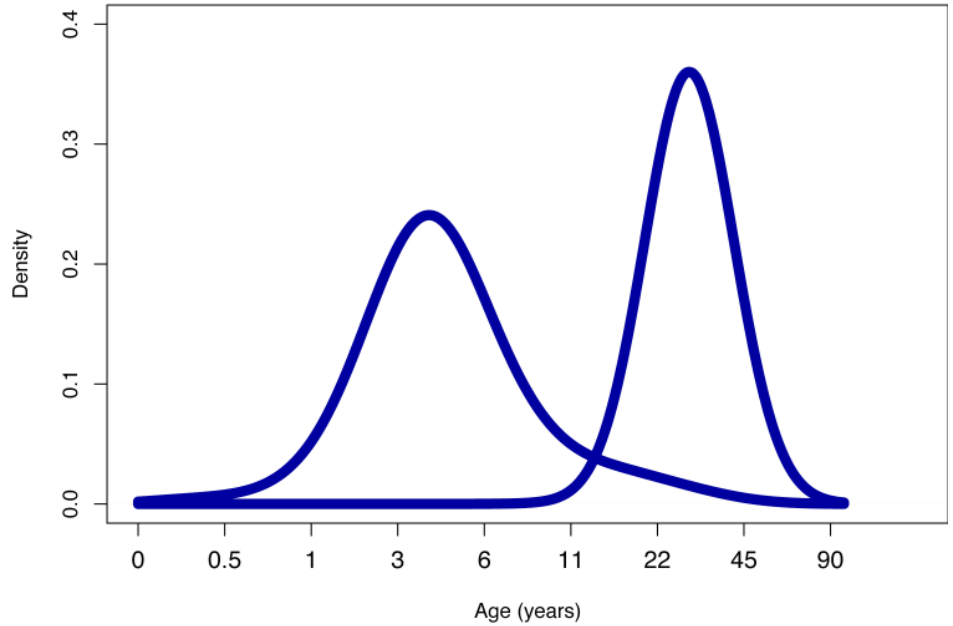


Human aging | expression "breakpoints"

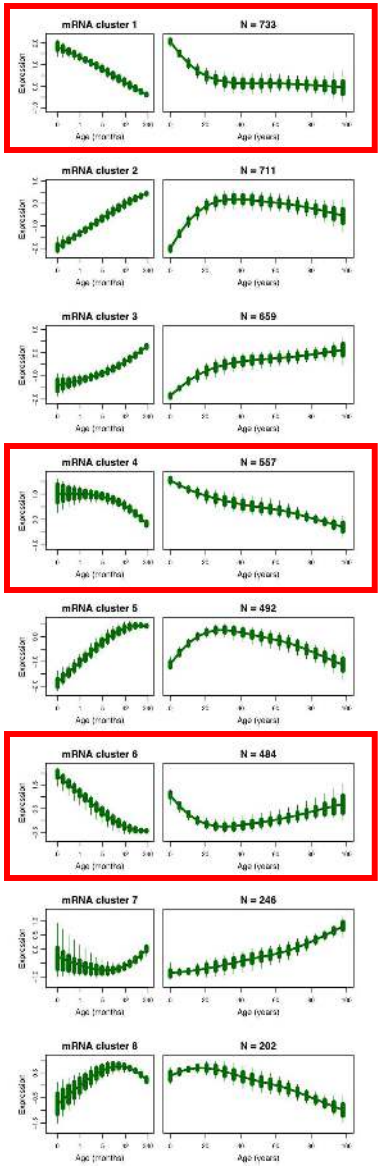
Breakpoint



Human mRNA breakpoints



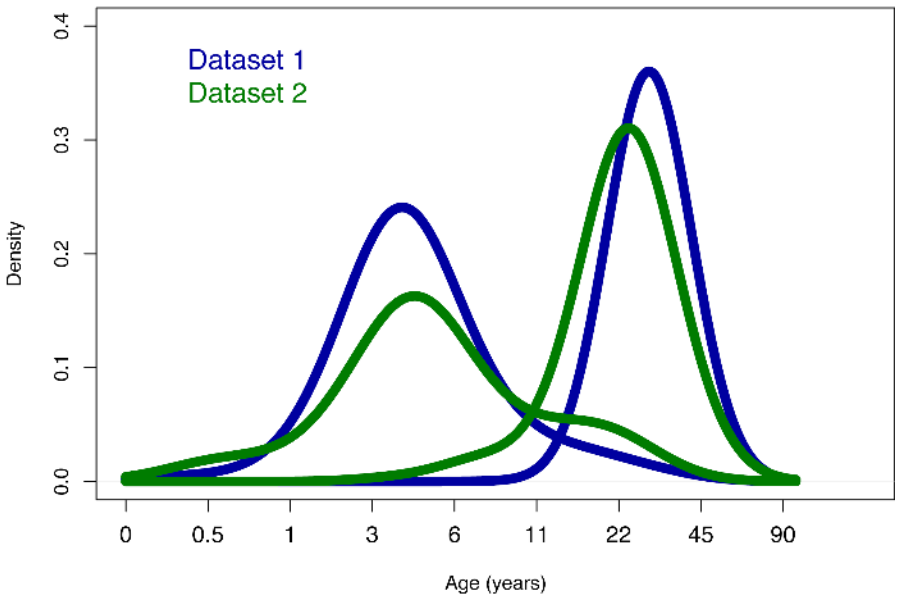
Human aging | expression “breakpoints” and gene functions



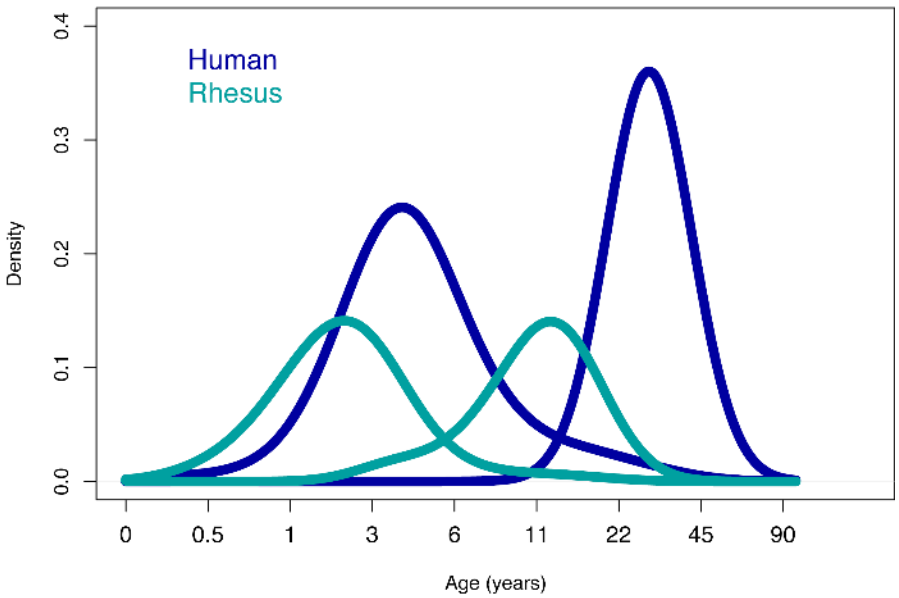
- **Nervous system development ~25 years**
- **Neuron development ~5 years**
- **Chromatin modification ~25 years**

Human aging | expression “breakpoints”

Human mRNA | two datasets



Human & Macaque mRNA



Human aging | rate of gene expression changes reflects species' lifespan

mRNA

Maximum lifespan:

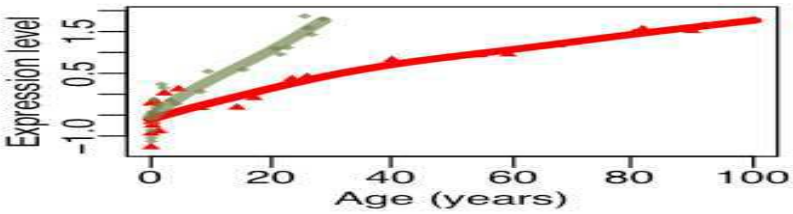
humans 120 years

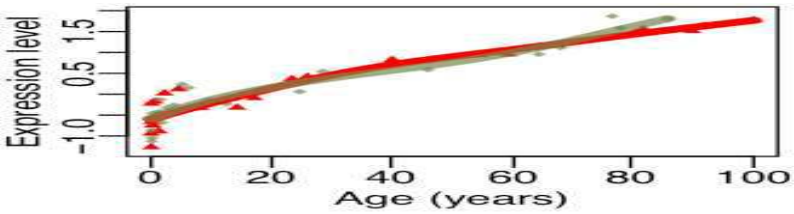
macaques 40 years

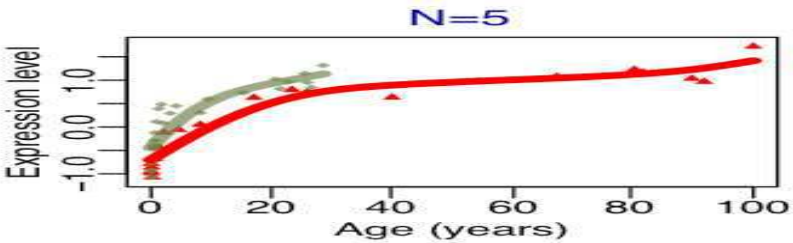
Maximum lifespan:

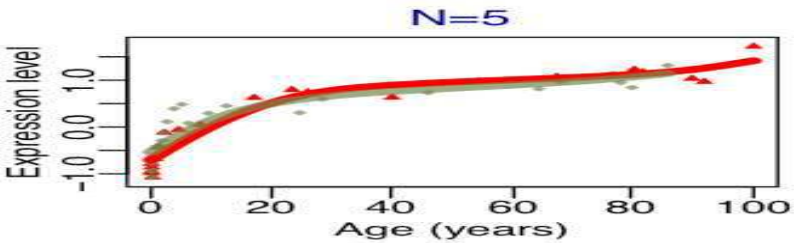
humans 120 years

macaques 120 years









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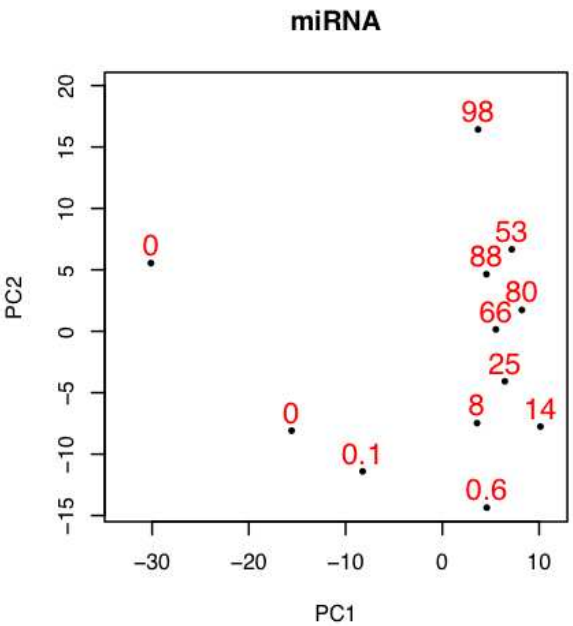
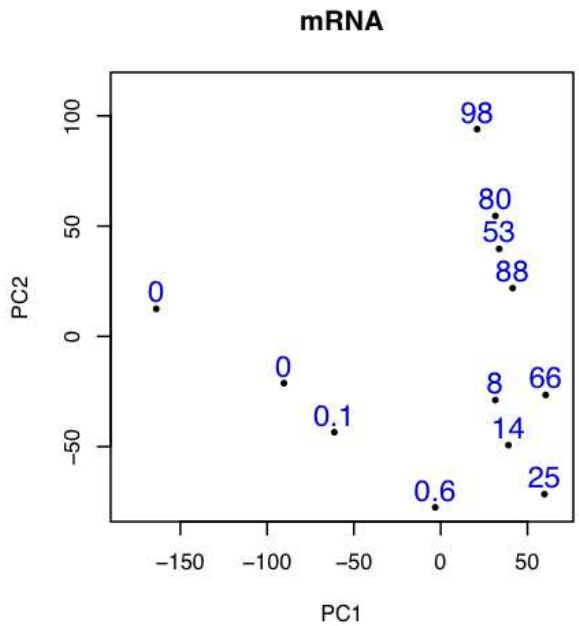
Human aging | miRNA expression

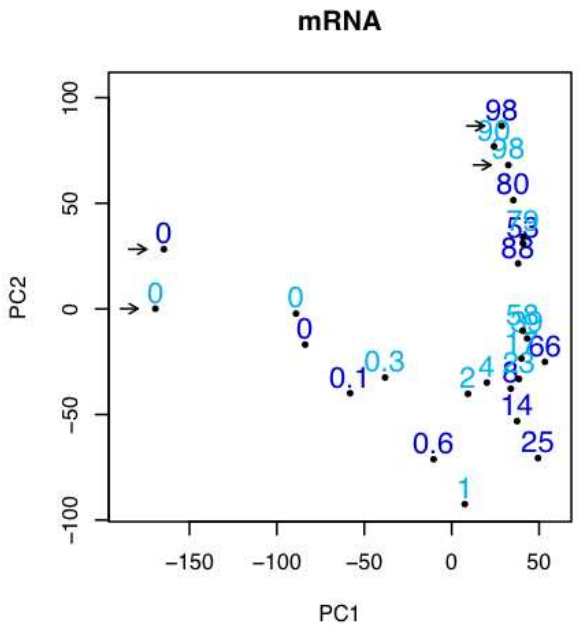
Human miRNA | 1



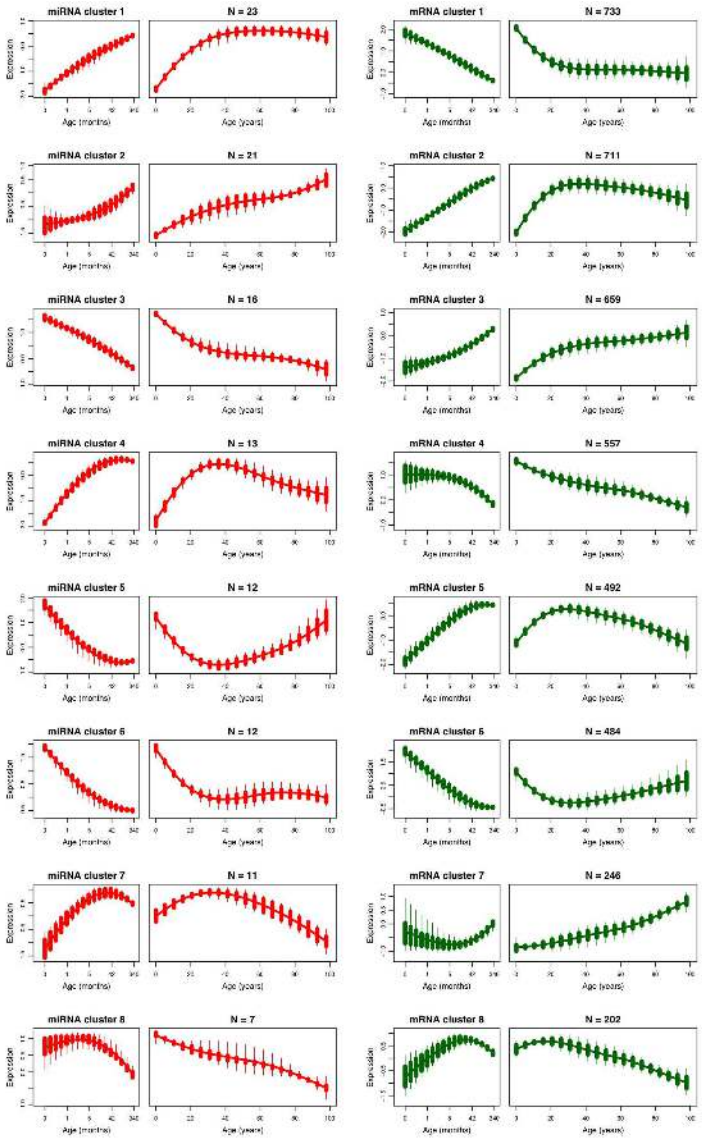
Human mRNA | 1



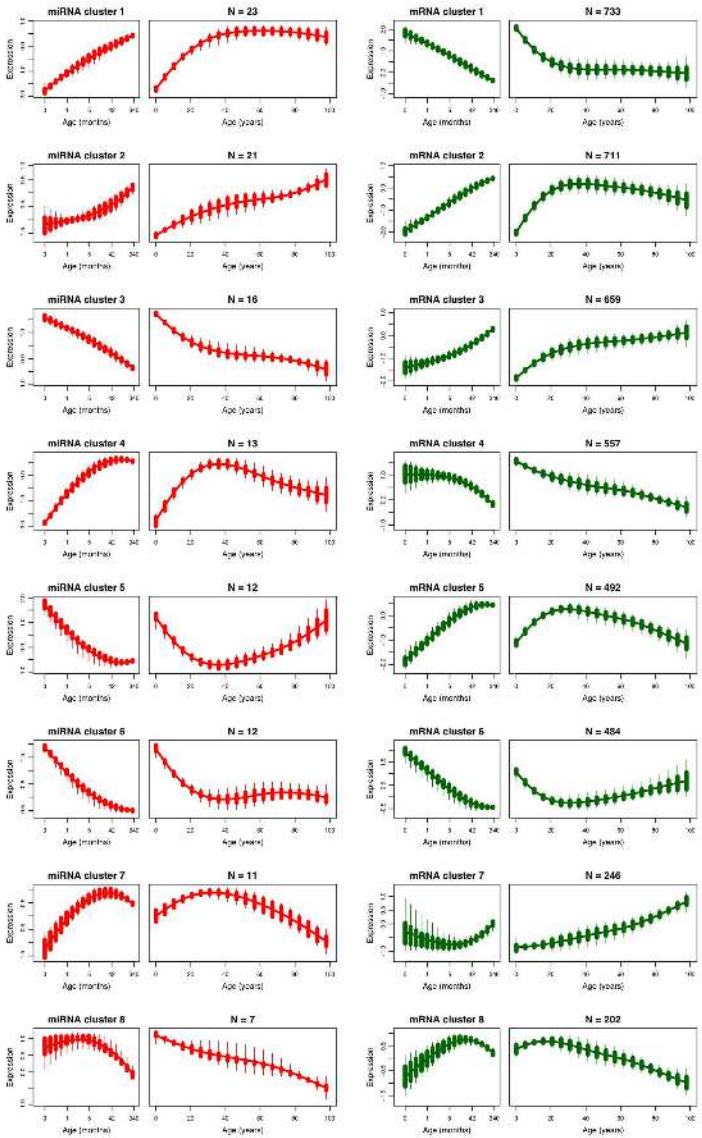
Human mRNA | 1&2



miRNA **mRNA**


miRNA cluster 1
N = 23
mRNA cluster 1
N = 733
miRNA cluster 2
N = 21
mRNA cluster 2
N = 711
miRNA cluster 3
N = 16
mRNA cluster 3
N = 659
miRNA cluster 4
N = 13
mRNA cluster 4
N = 557
miRNA cluster 5
N = 12
mRNA cluster 5
N = 492
miRNA cluster 6
N = 12
mRNA cluster 6
N = 484
miRNA cluster 7
N = 11
mRNA cluster 7
N = 246
miRNA cluster 8
N = 7
mRNA cluster 8
N = 202
Expression
Age (months)
Age (years)

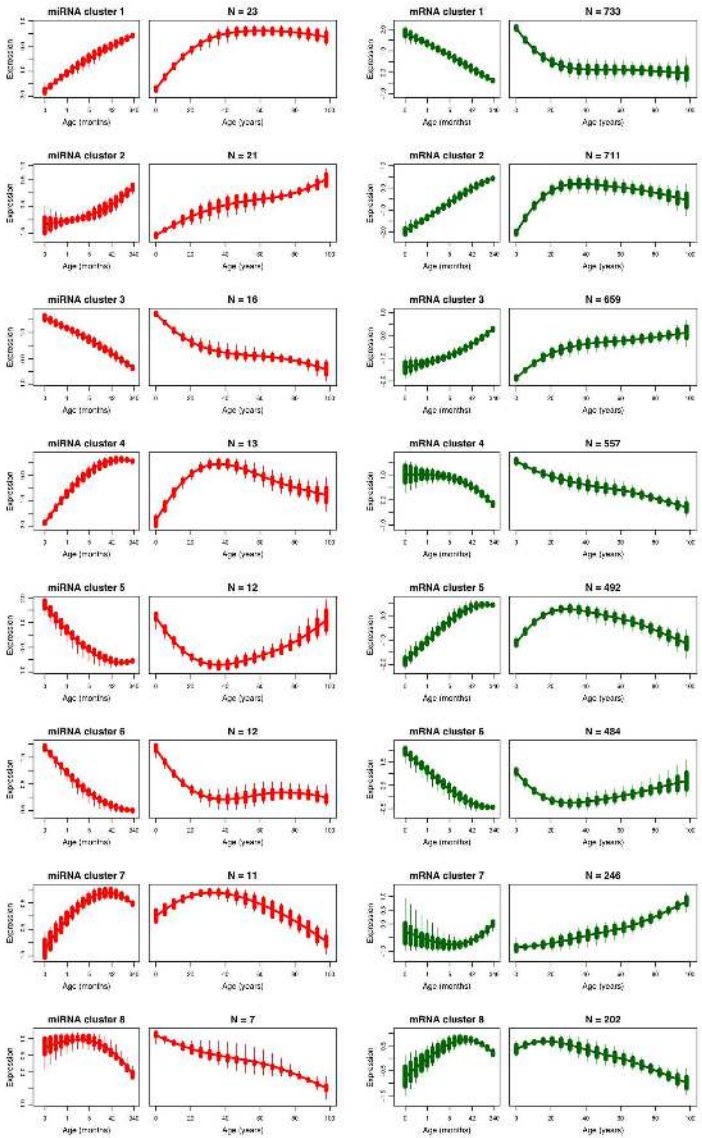
miRNA **mRNA**



? Regulation of mRNA

- **microRNA**
- **Transcription Factors**

miRNA **mRNA**

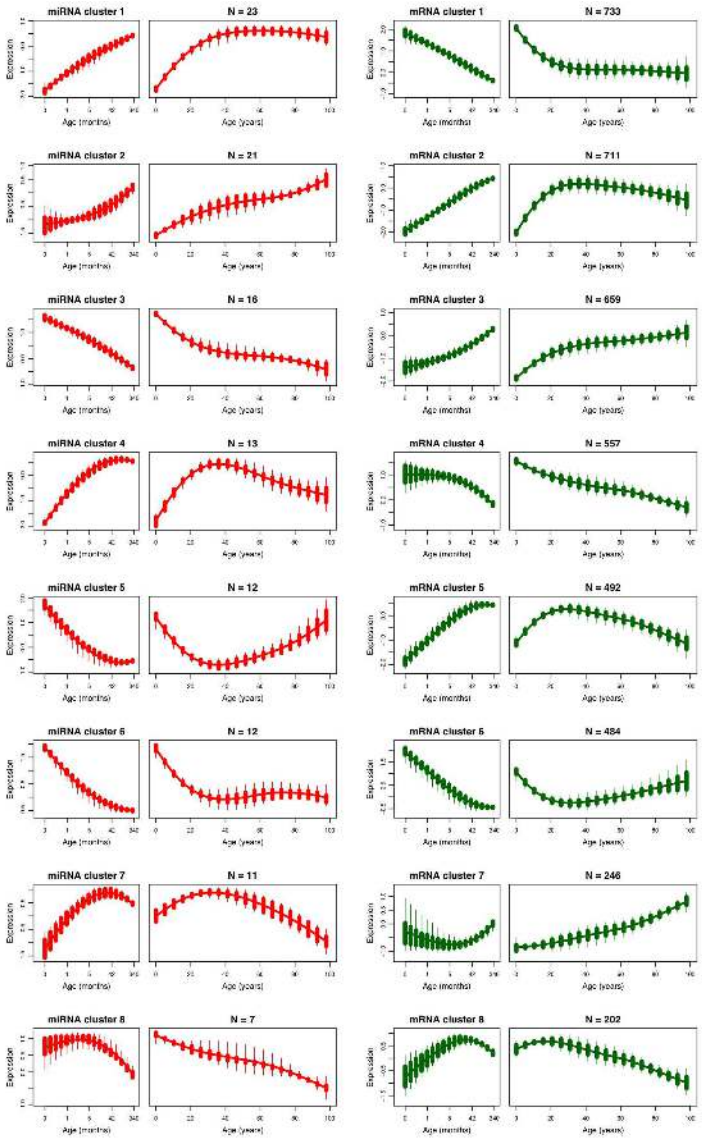


? Regulation of mRNA

- **microRNA**
- **Transcription Factors (TFs)**

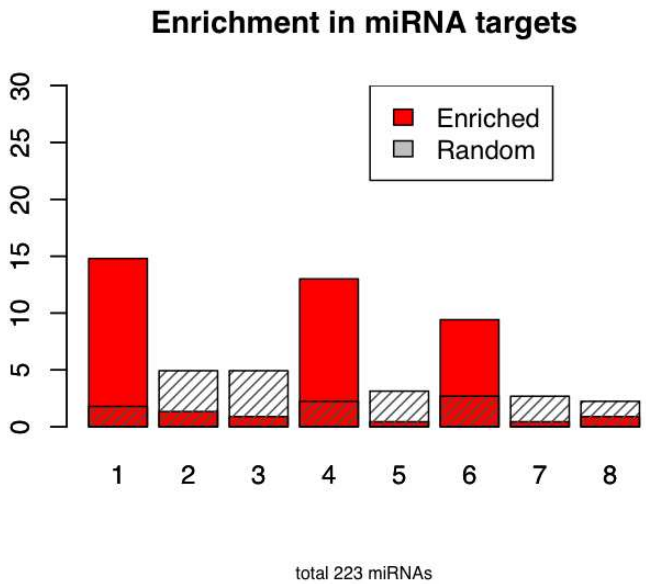
Excess of miRNA/TF target genes

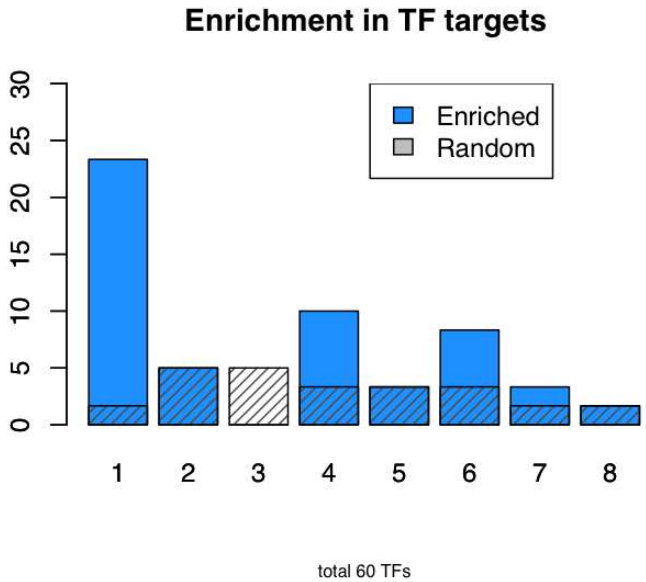
miRNA



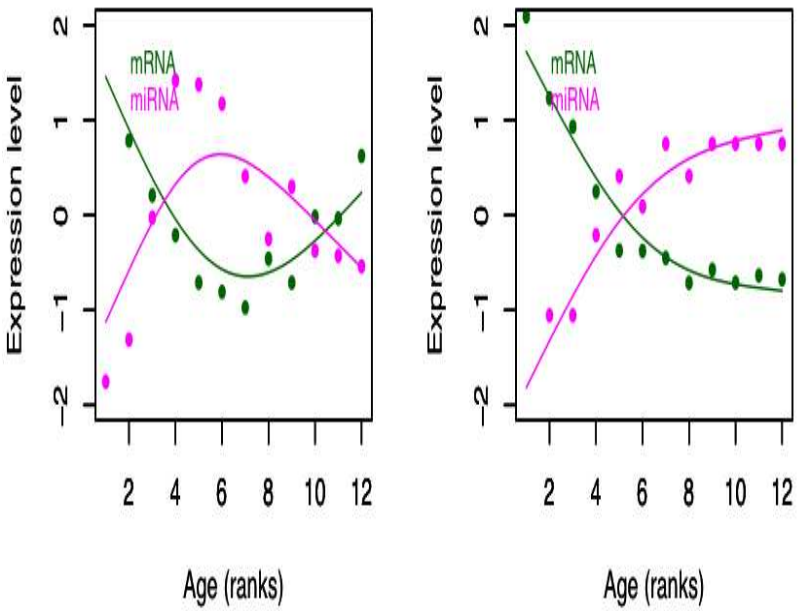
mRNA

miRNA/TF target genes

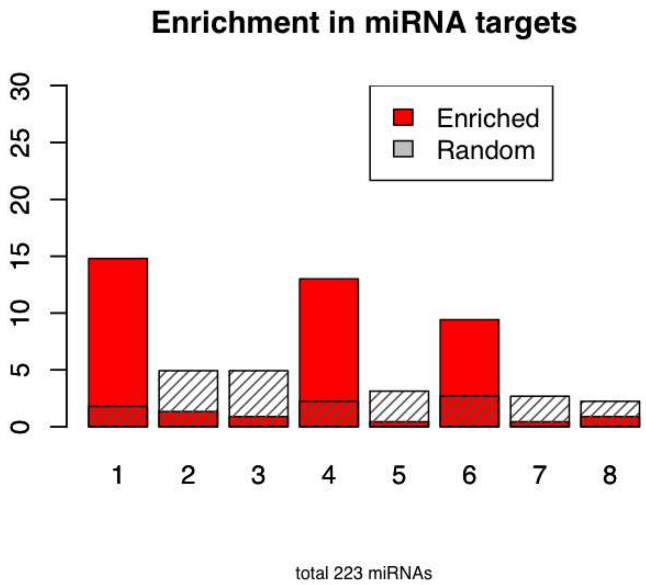


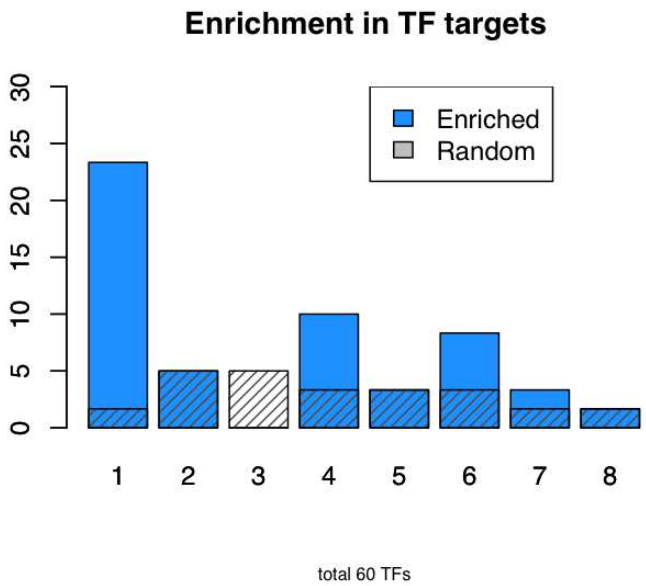


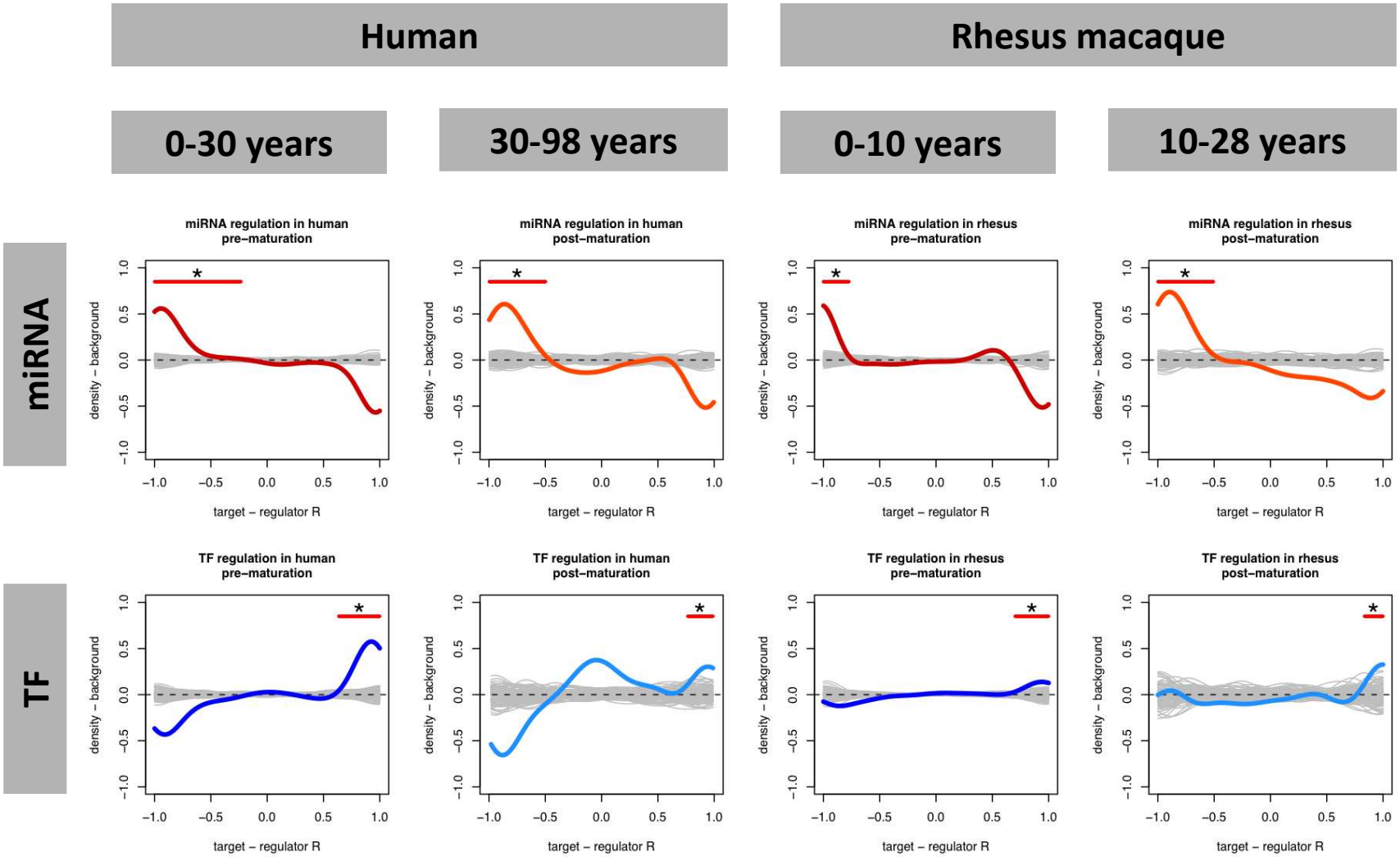
miRNA-target gene expression



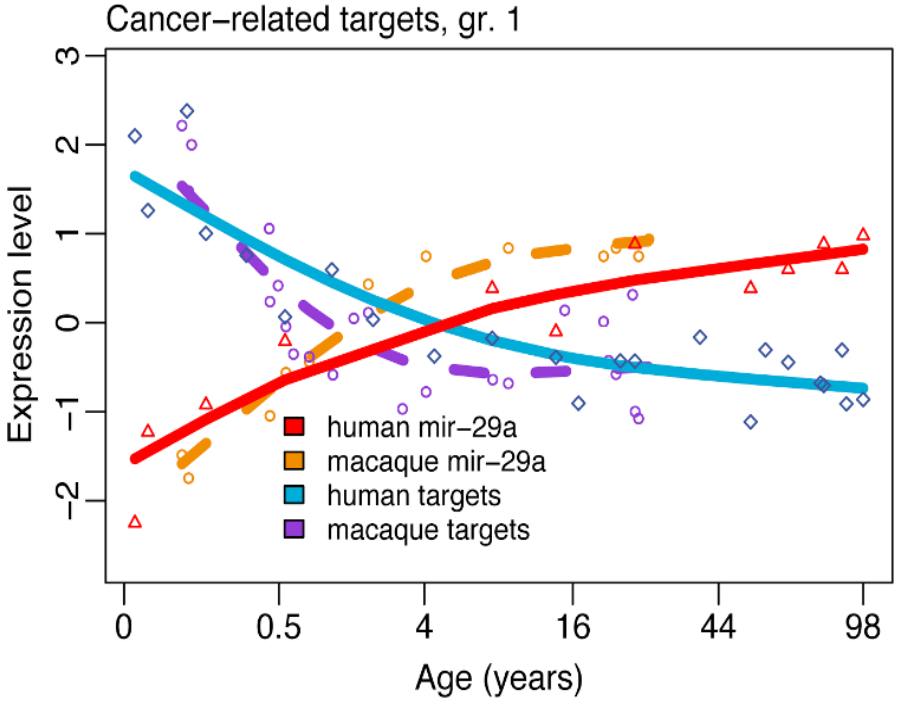
miRNA/TF target genes

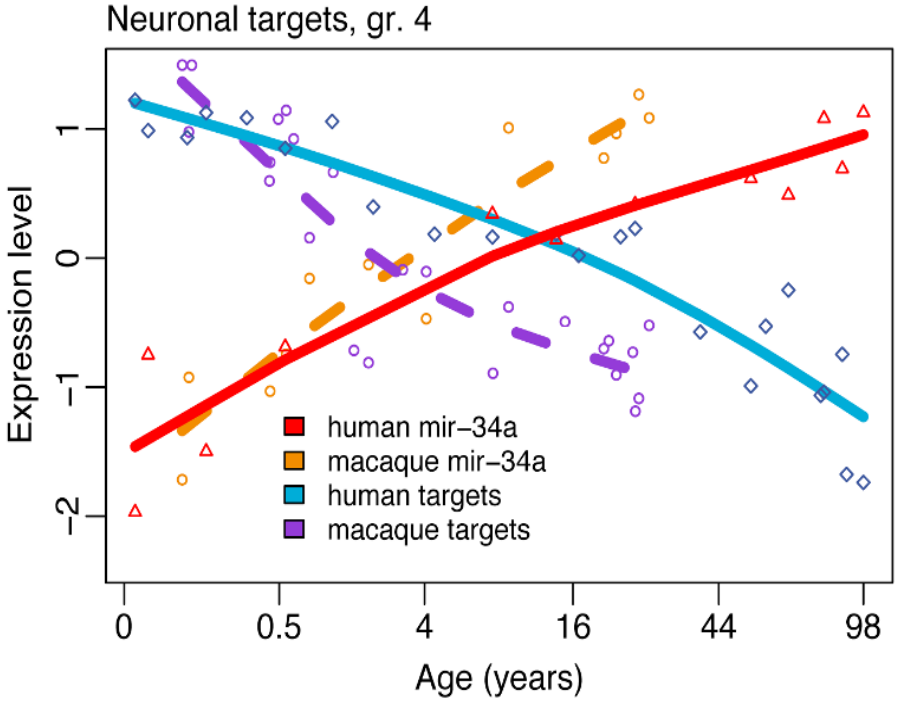


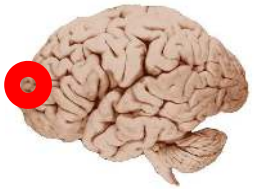



Human
Rhesus macaque
0-30 years
30-98 years
0-10 years
10-28 years
miRNA
TF
miRNA regulation in human pre−maturation
miRNA regulation in human post−maturation
miRNA regulation in rhesus pre−maturation
miRNA regulation in rhesus post−maturation
TF regulation in human pre−maturation
TF regulation in human post−maturation
TF regulation in rhesus pre−maturation
TF regulation in rhesus post−maturation
density − background
target − regulator R
−1.0
−0.5
0.0
0.5
1.0
*

Human aging | developmental regulators might drive aging







microRNA

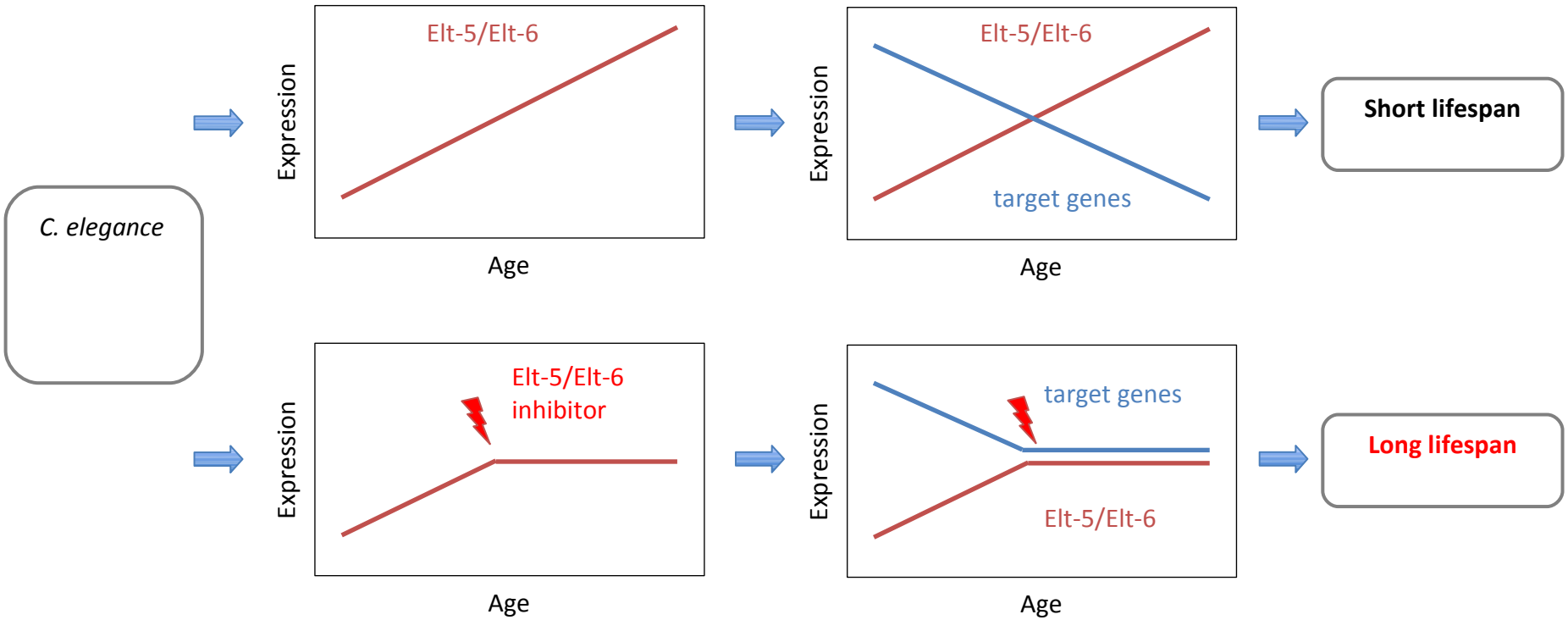
mRNA

Binding site enrichment

Expression level correlation

Aging regulation | model organisms

Experiments in *C. elegance* demonstrate that regulatory intervention during aging can extend lifespan



Budovskaya et al *Cell* 2008

Conclusions

Runaway developmental regulation may drive aging process

Main collaborations | research

short RNA

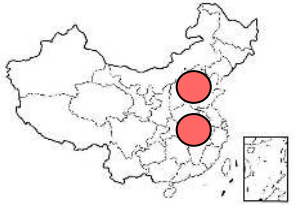
long RNA

Proteins

Metabolites

Phenotype

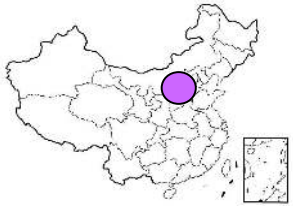
MDC Berlin



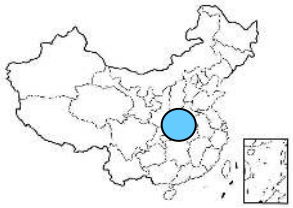
BIG

SIBS

MDC Berlin
MPI Leipzig

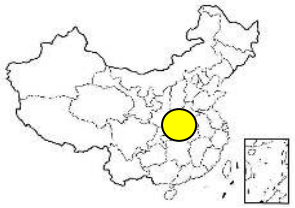


Beijing Chip Center



SIBS Proteomics Center

MPI Golm

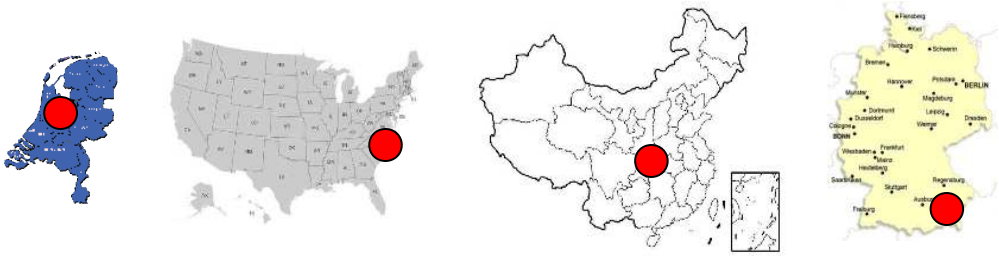


SIBS Institute of Neuroscience

Main collaborations | sample collection

> 600 individuals

Holland
USA
China
Germany

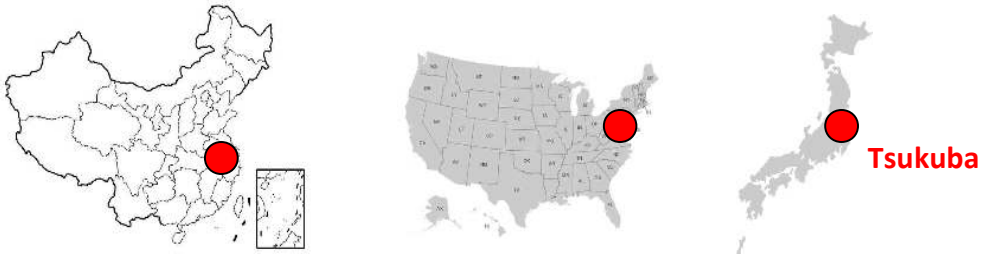


> 80 individuals

Germany
Japan
USA

> 100 individuals

China
USA
Japan



Lab members

postdocs








research assistants



students











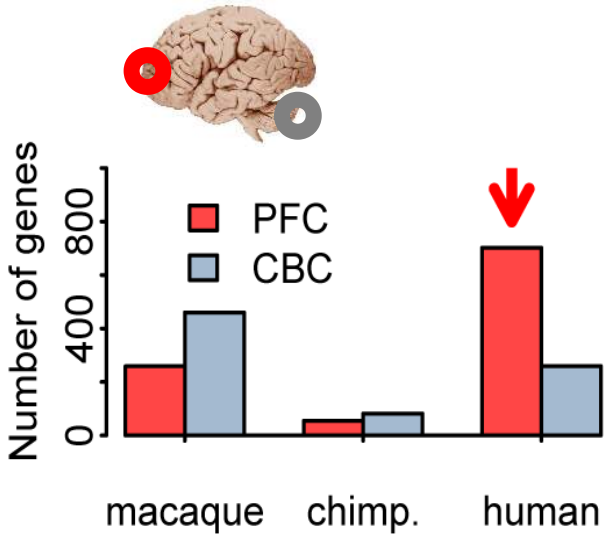

Shanghai | welcome !

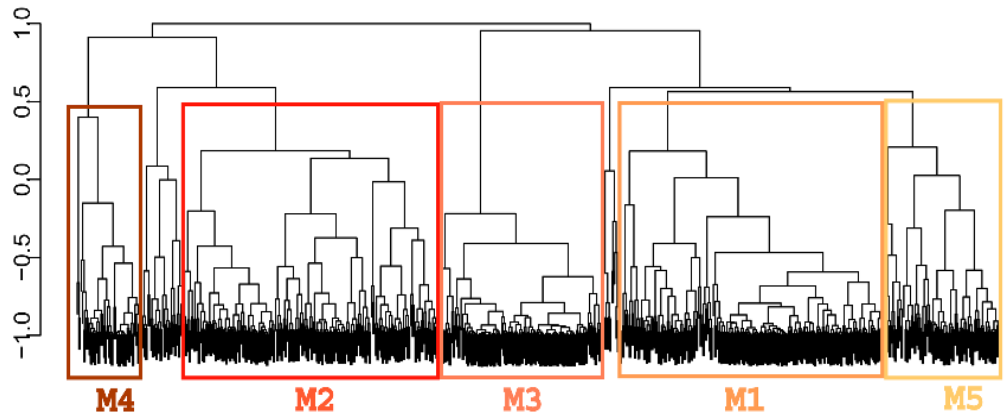
14.8.13

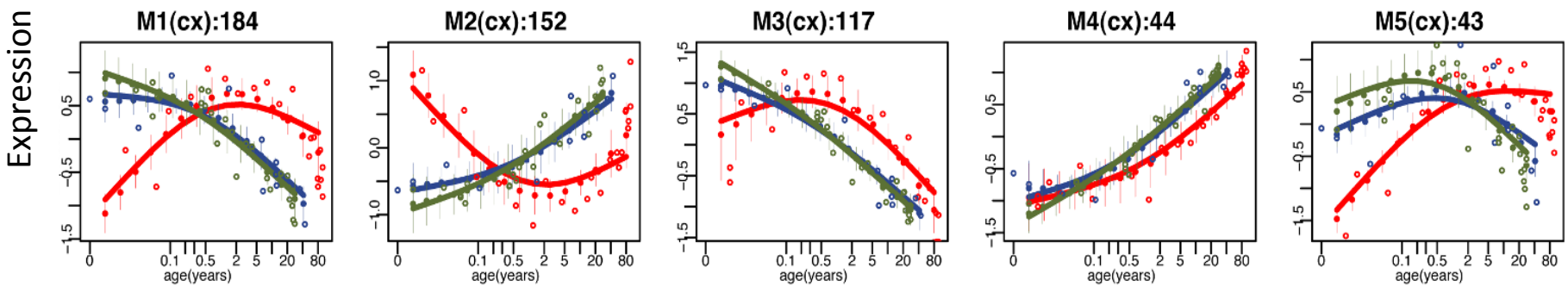
Thank you!

Human-specific expression

mRNA





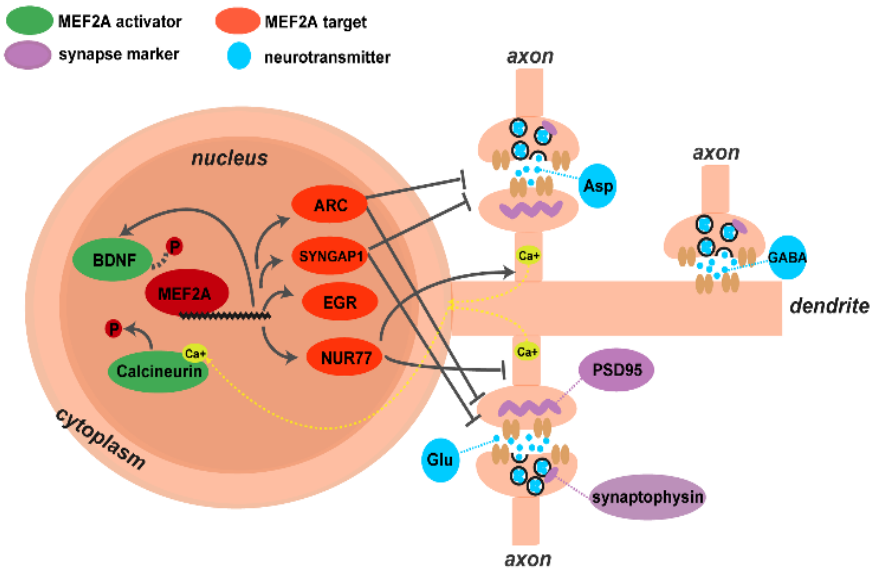


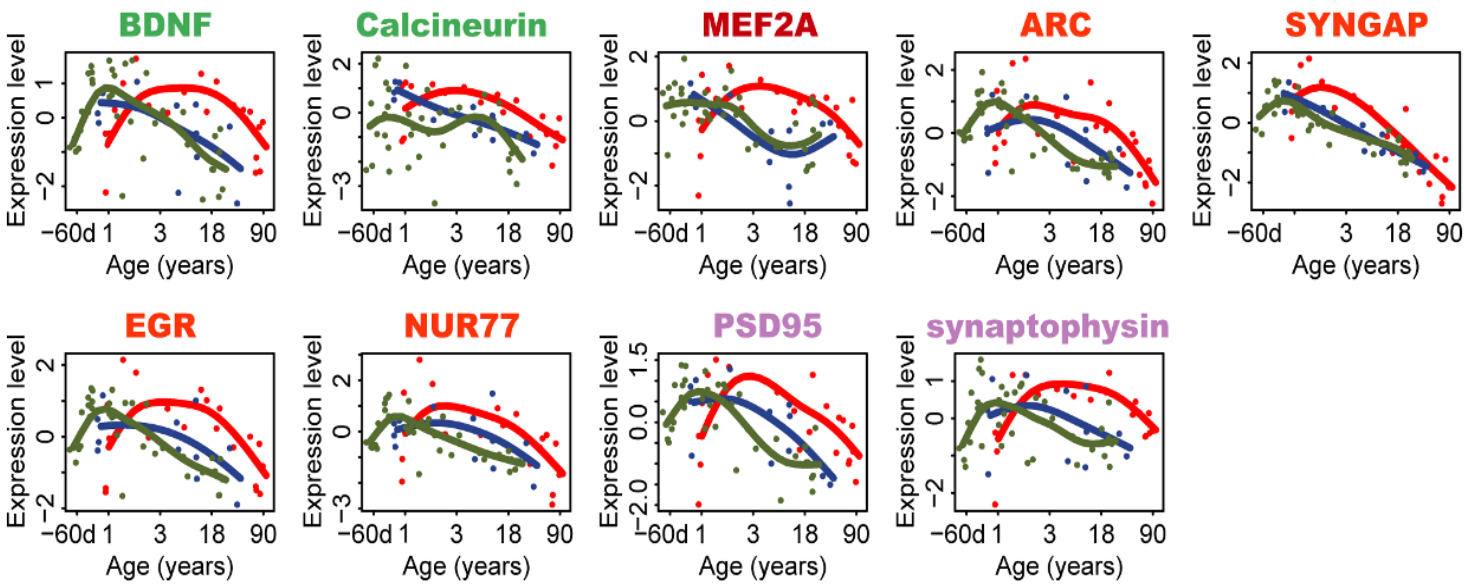
Age
(log2)

Human
Chimpanzee
Macaque

Human-specific changes | model

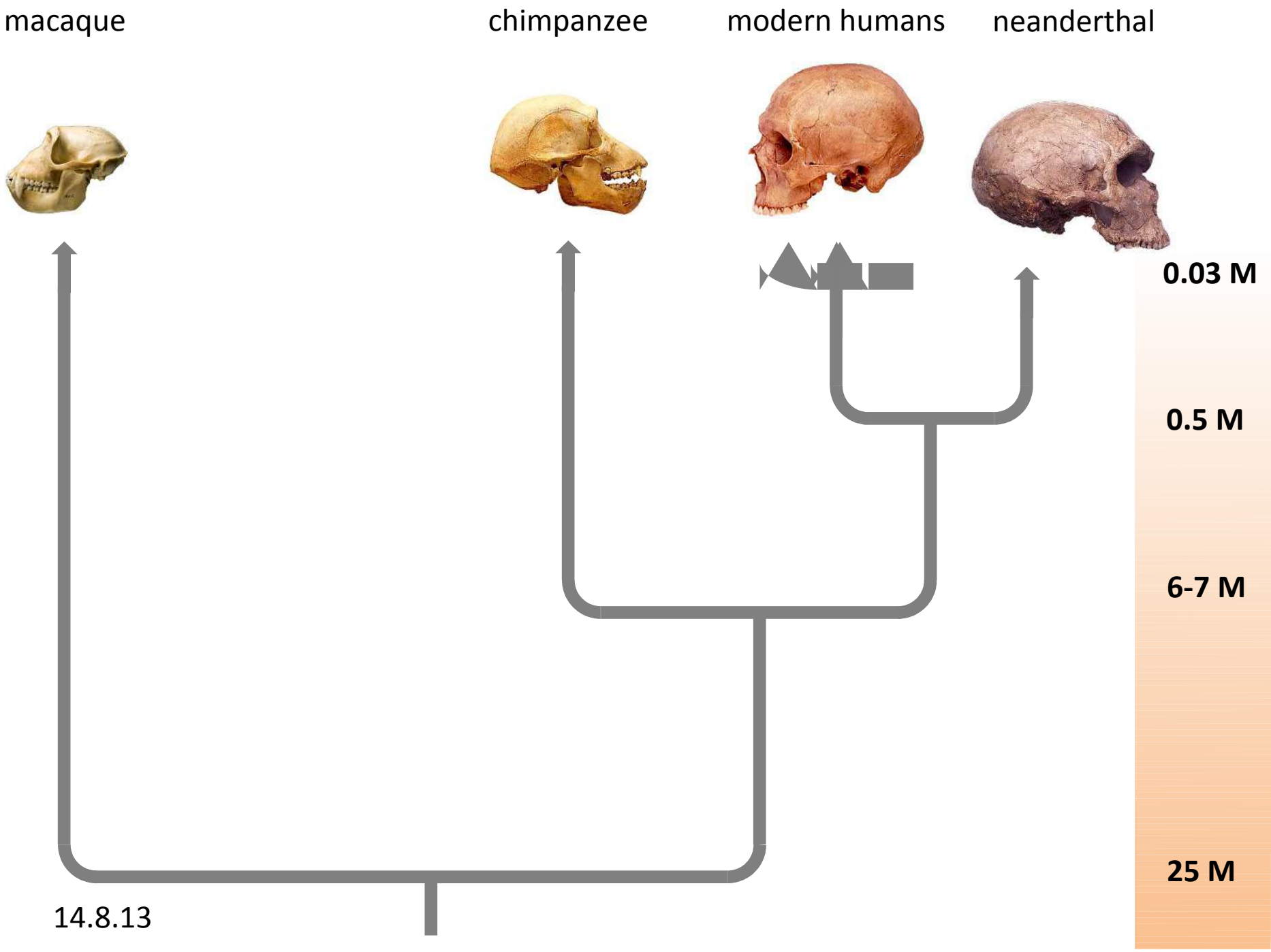
ION SIBS





Conclusions

Genetic flow from Neanderthals may have shaped contemporary human phenotypes


macaque
chimpanzee
modern humans
neanderthal
0.03 M
0.5 M
6-7 M
25 M
14.8.13

5

Long non-coding RNA in human brain

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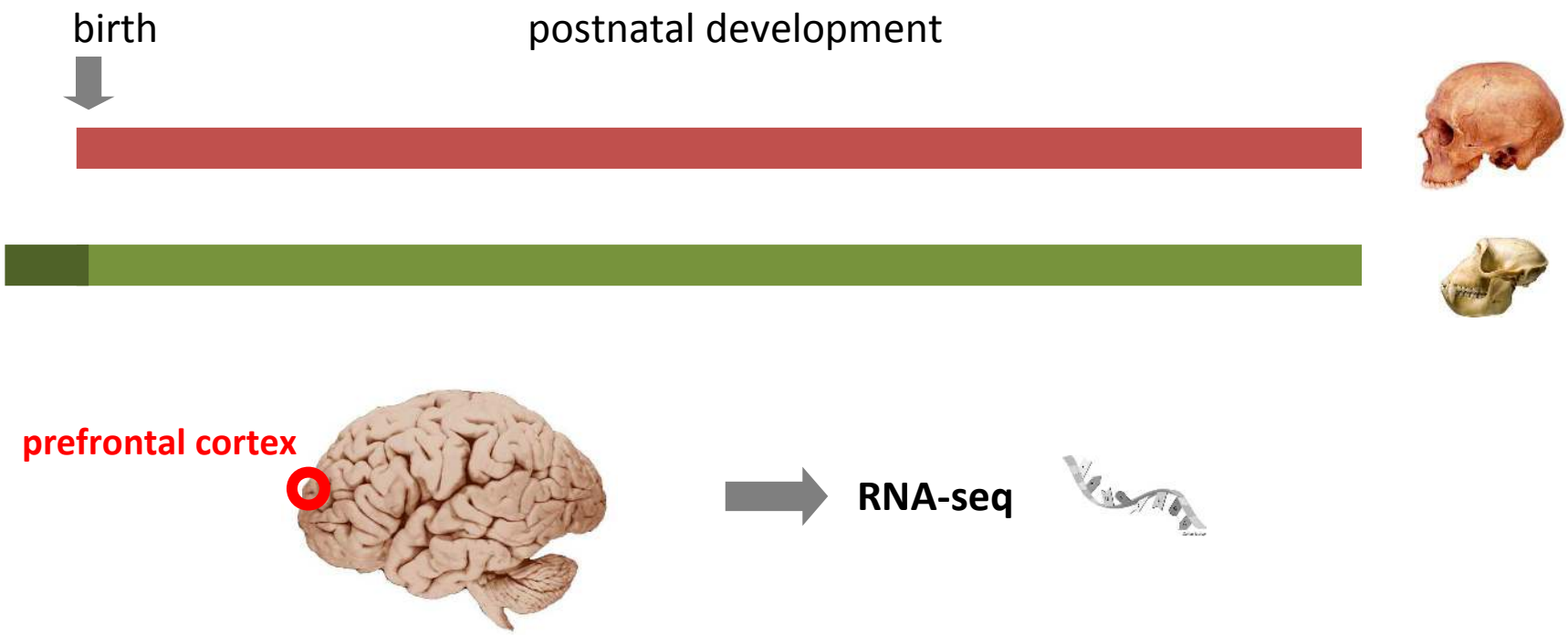
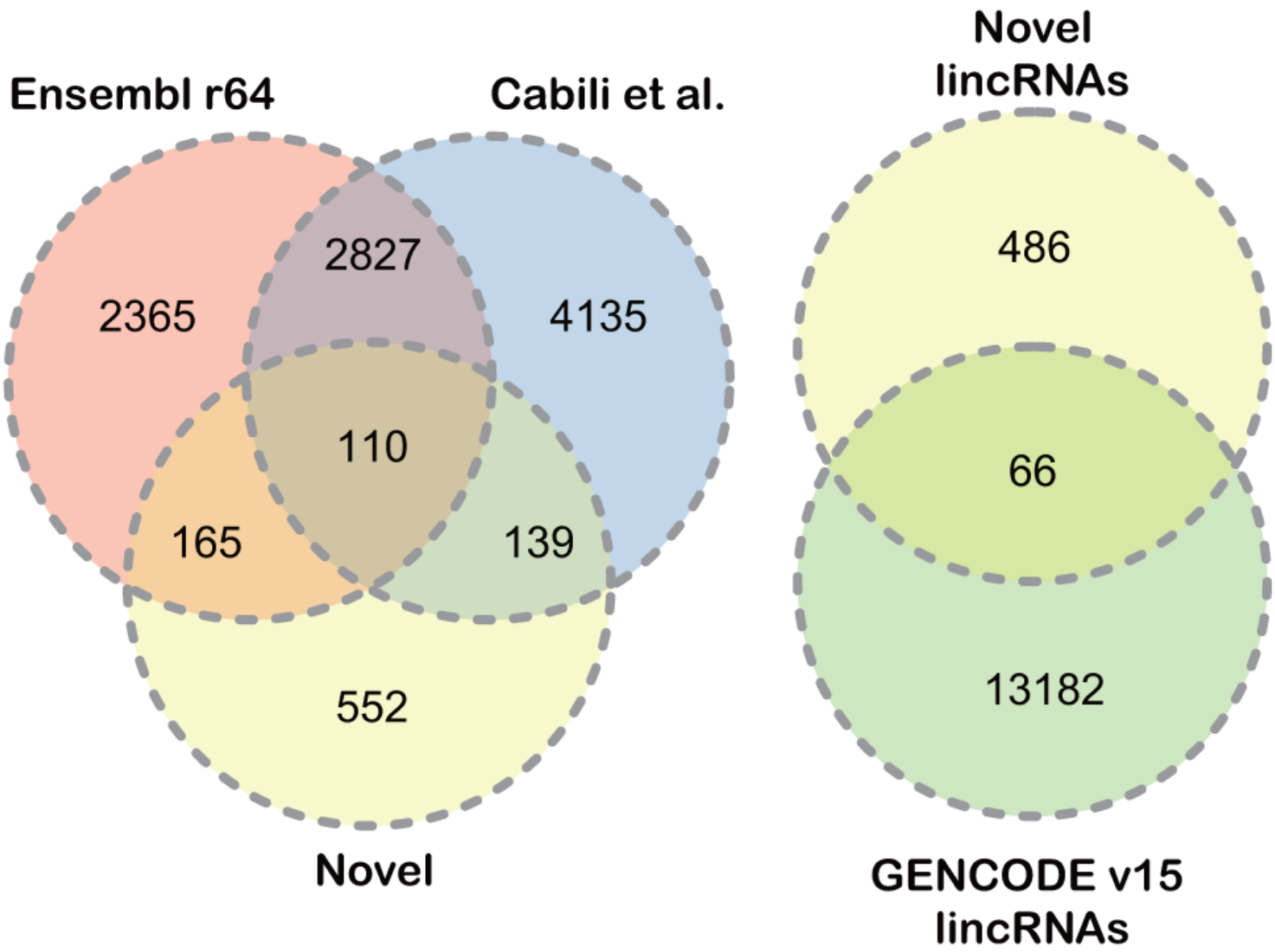
Experiment



lincRNA numbers



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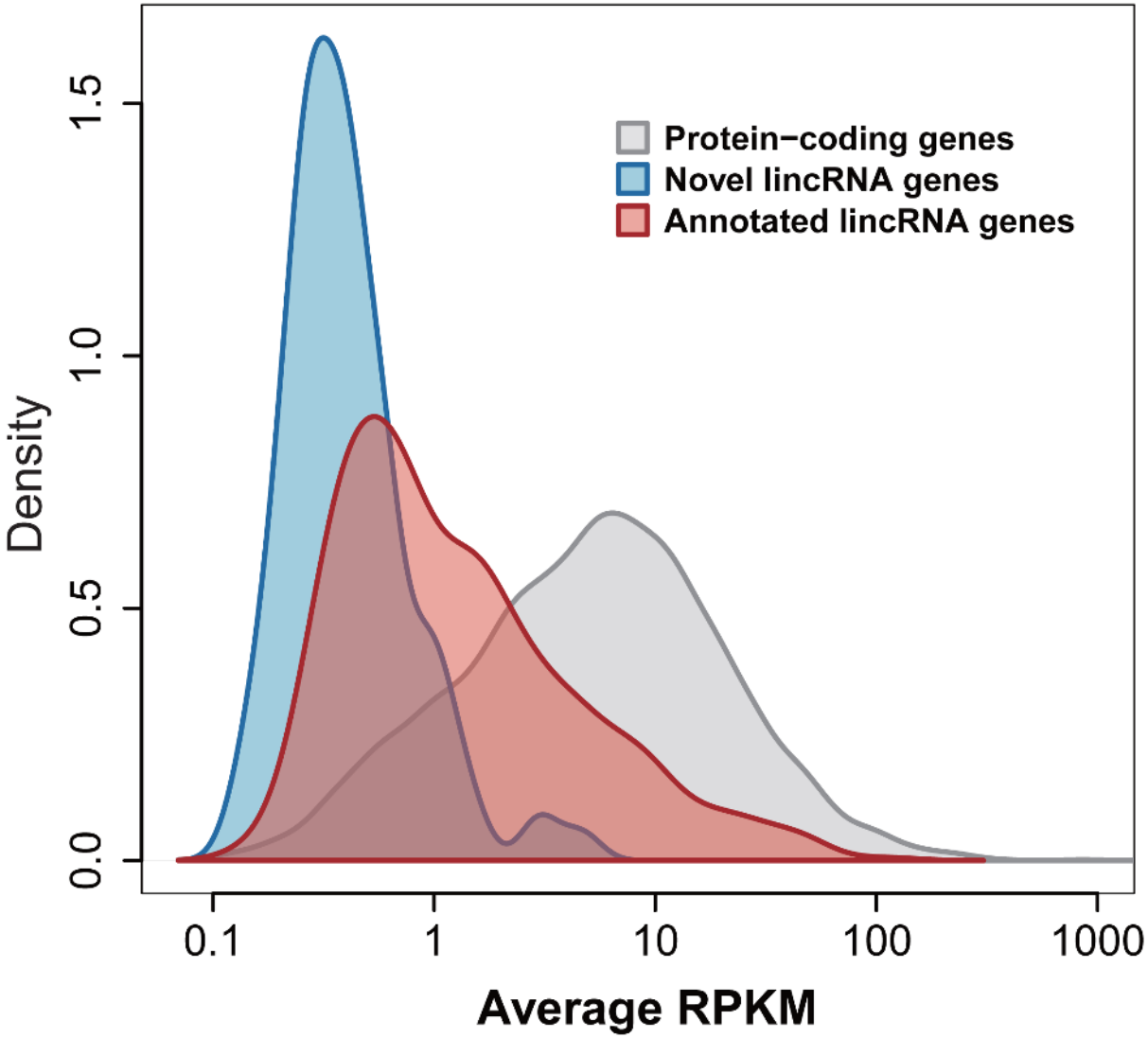
lincRNA expression levels



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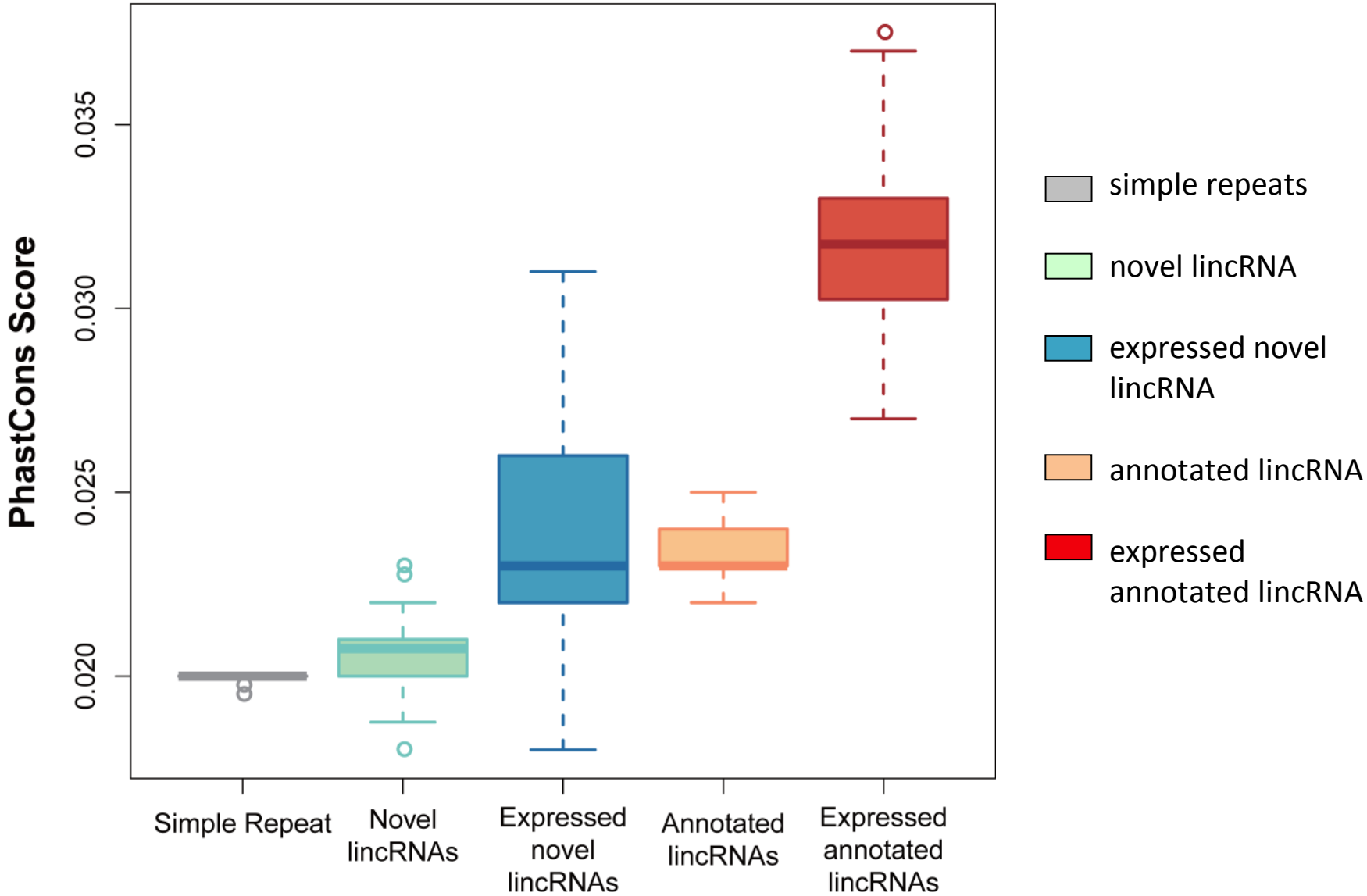
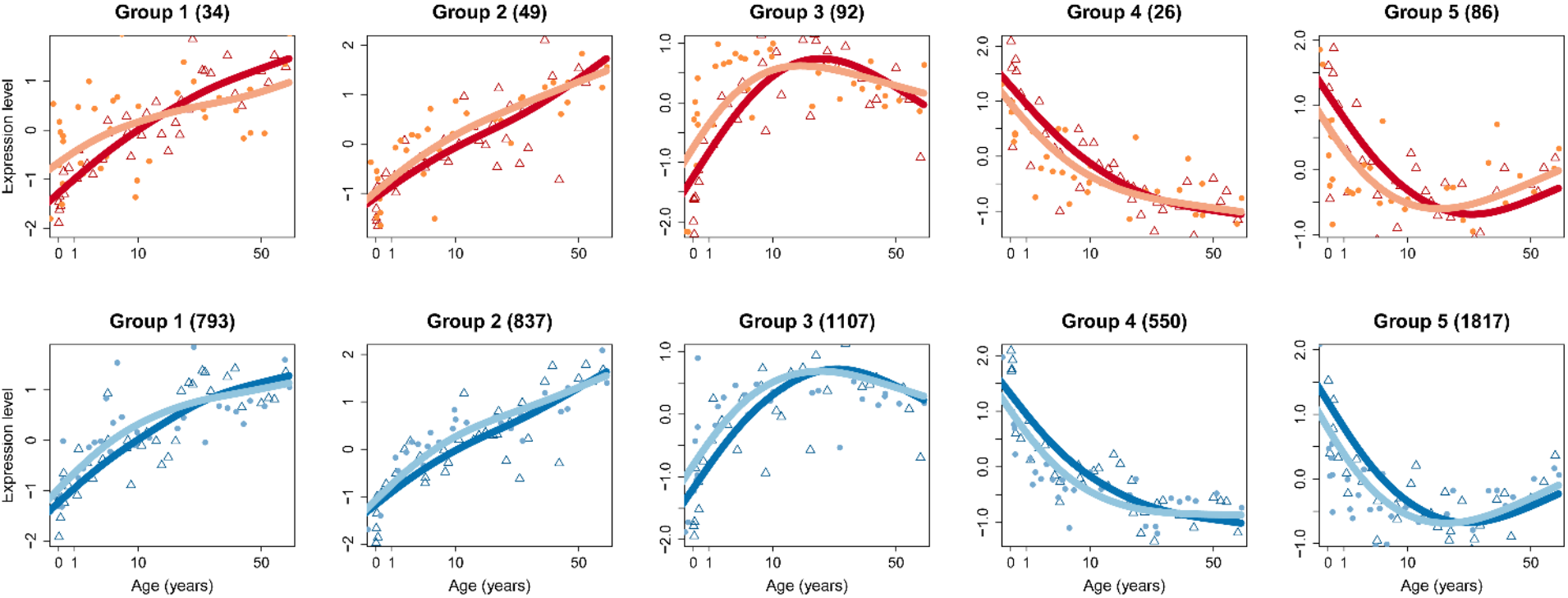
lincRNA sequence conservation



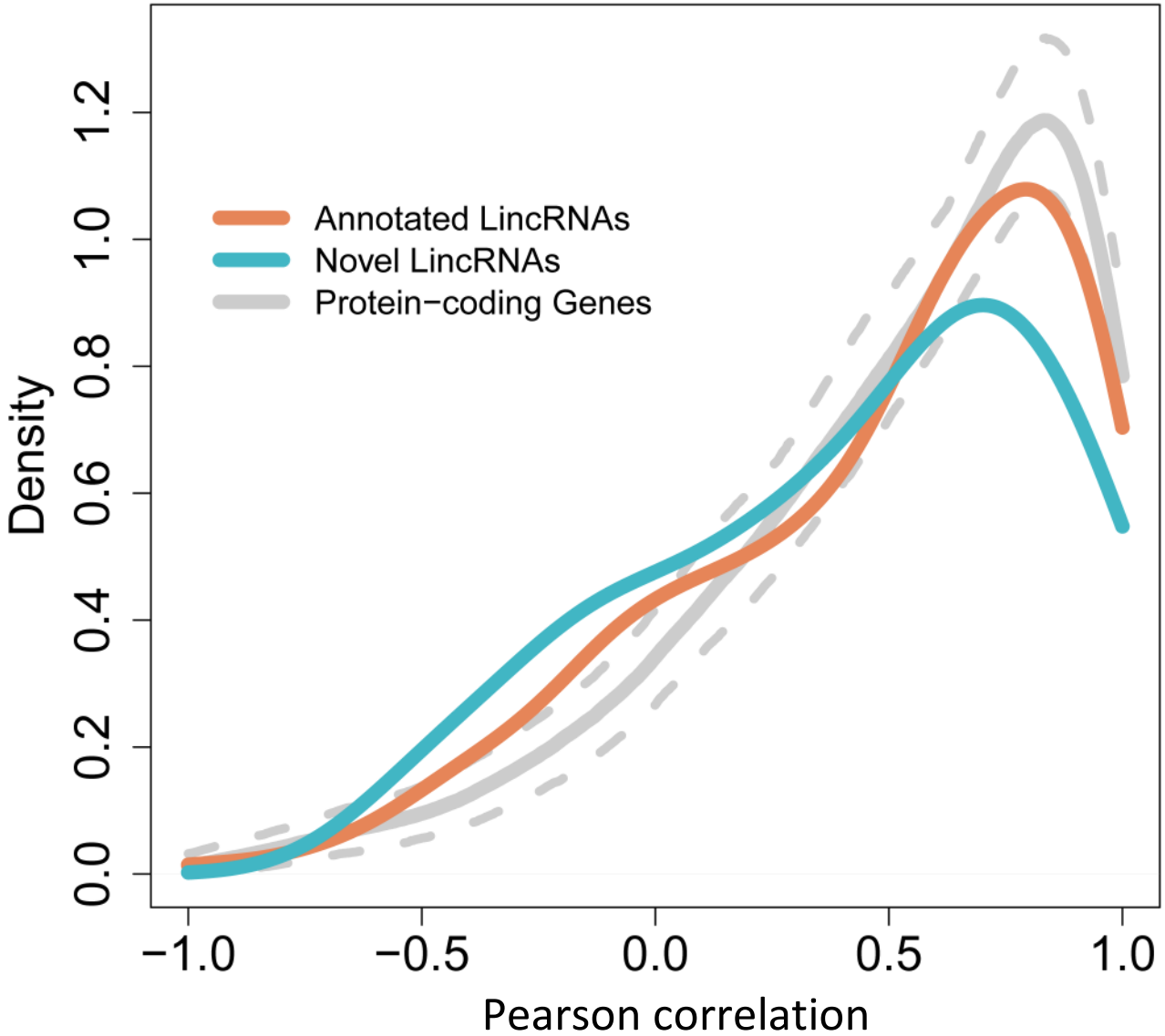
lincRNA expression conservation



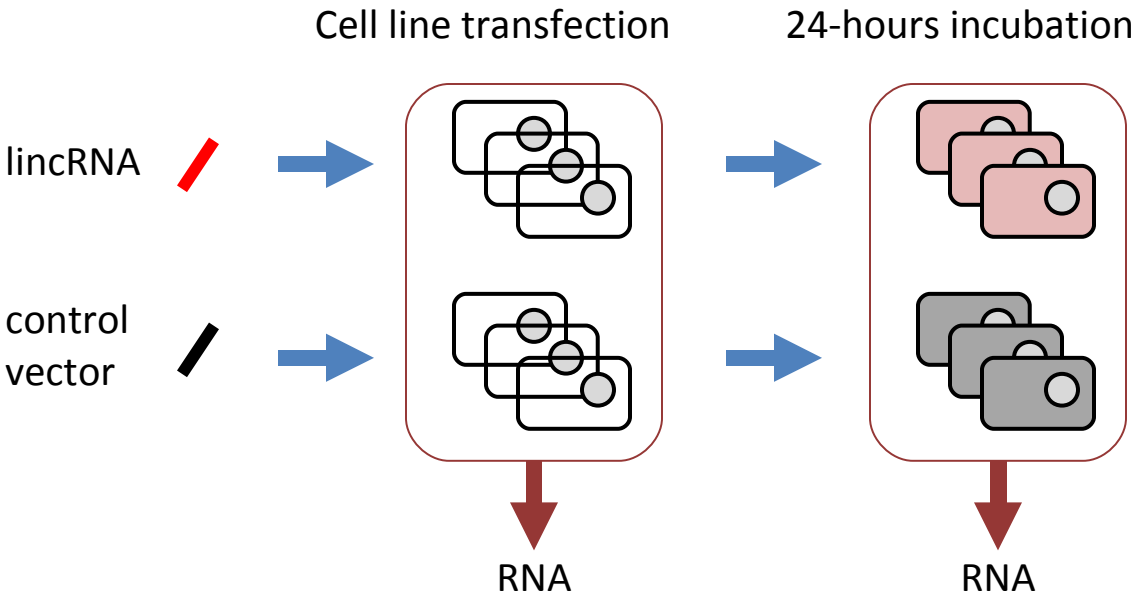
protein-coding
non-coding

protein-coding
non-coding

lincRNA expression conservation

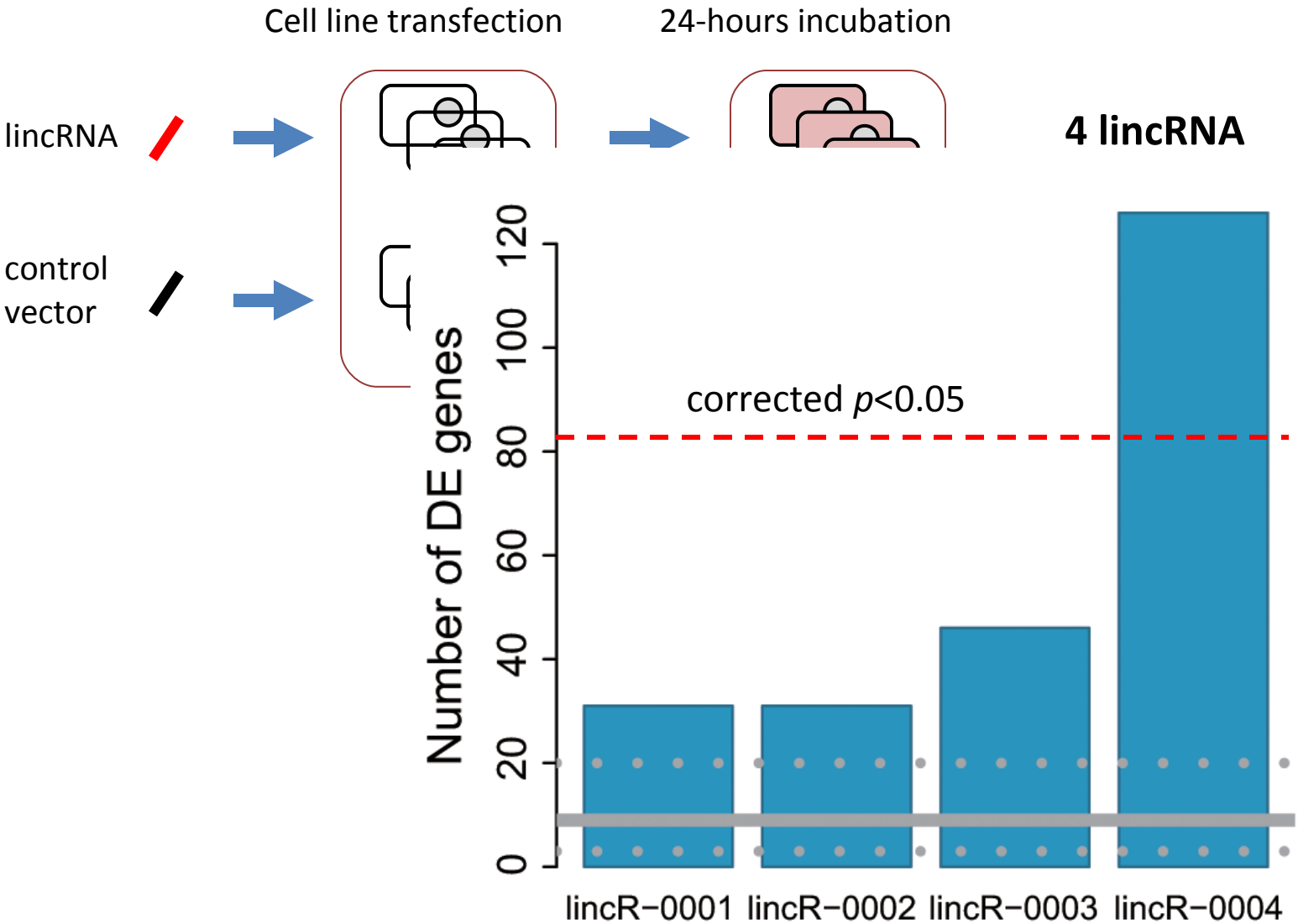


lincRNA overexpression in a cell line



4 lincRNA

lincRNA overexpression in a cell line



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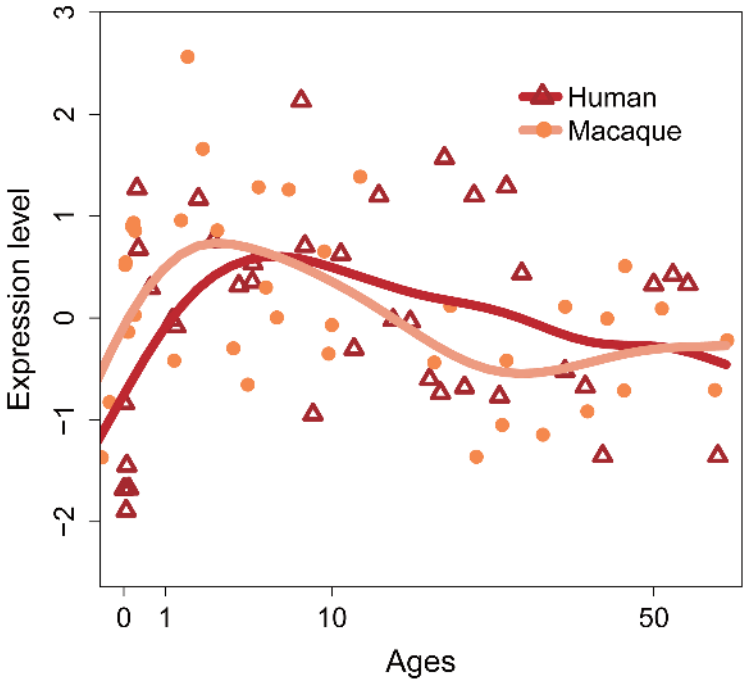
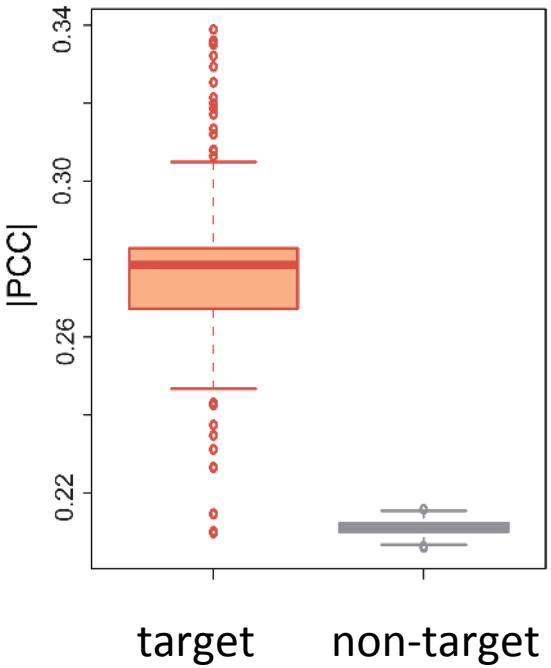
lincR-0004 targets in brain development

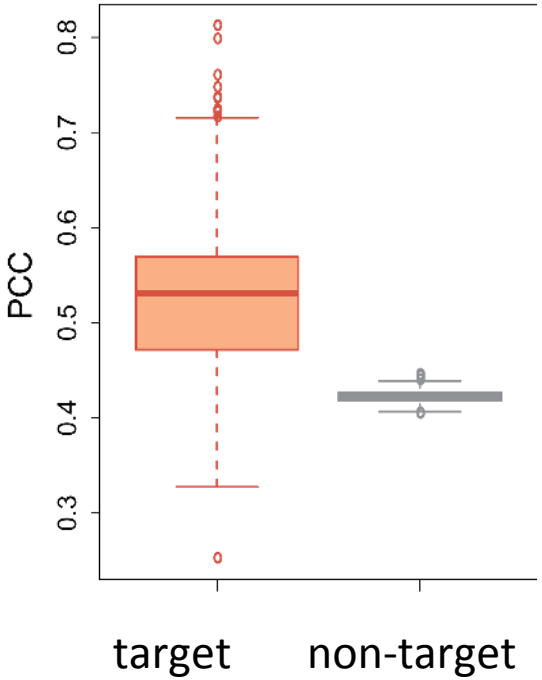
lincRNA expression



correlation with targets



expression conservation



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Conclusions

lncRNA are not conserved on the sequence level, but expression patterns in brain development are conserved

Overexpression of lncRNA not always results in [molecular]phenotype