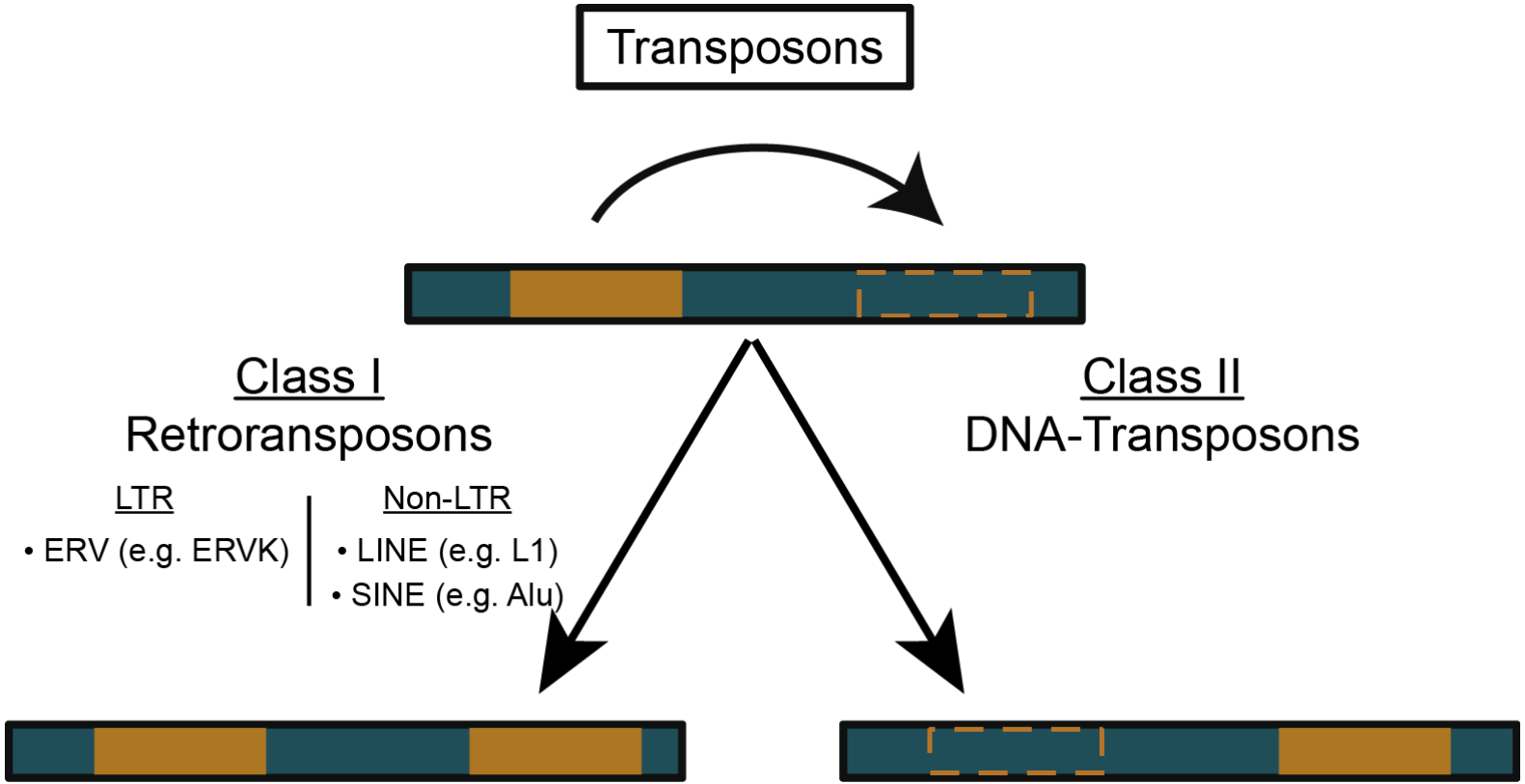
Leibniz Institute on Aging –
Fritz Lipmann Institute

Locus-specific expression analysis of Transposable Elements

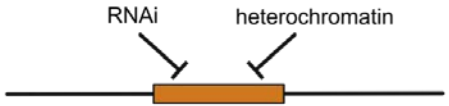
Robert Schwarz

Transposable elements

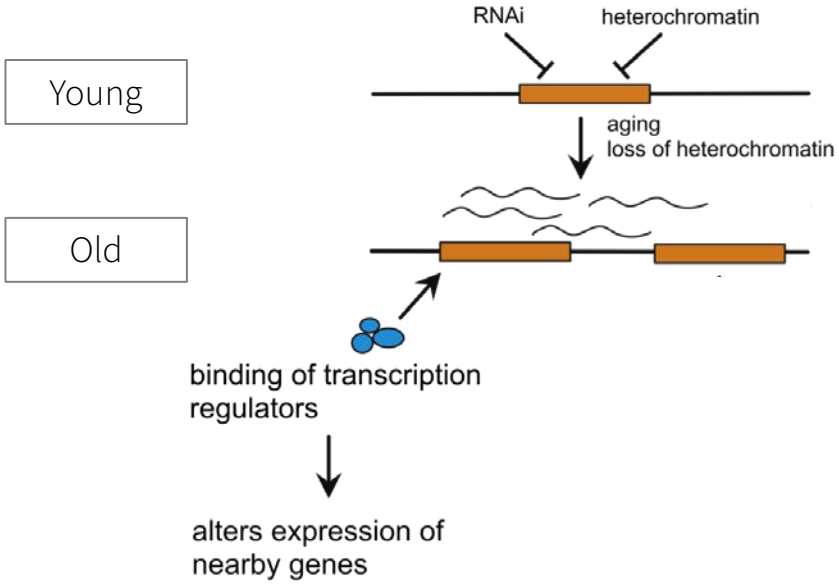


TE expression during aging and its possible consequences

Young



TE expression during aging and its possible consequences



nature COMMUNICATIONS

ARTICLE

Functional *cis*-regulatory modules encoded by mouse-specific endogenous retrovirus

Genome Biology

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Tissue-specific usage of transposable element-derived promoters in mouse development

2020

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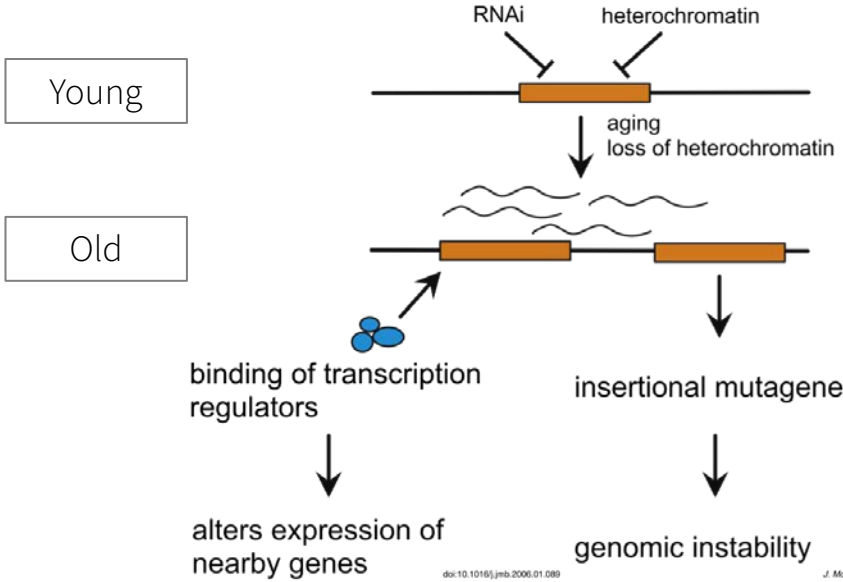

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ARTICLE

Received 12 Jul 2016 | Accepted 11 Jan 2017 | Published 28 Mar 2017 OPEN

Functional *cis*-regulatory modules encoded by mouse-specific endogenous retrovirus

Vasavi Sundaram[1,2], Mayank N.K. Choudhary[1,2], Erica Pehrsson[2], Xiaoyun Xing[2], Christopher Fiore[1,2], Manishi Pandey[1,2], Brett Maricque[1,2], Methma Udawatta[2], Duc Ngo[2], Yujie Chen[2], Asia Paguntalan[2], Tammy Ray[2], Ava Hughes[2], Barak A. Cohen[2] & Ting Wang[2]

Genome Biology

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Tissue-specific usage of transposable element-derived promoters in mouse development

Benpeng Miao[1,2], Shuhua Fu[1], Cheng Lyu[1], Paul Gontarz[1], Ting Wang[2*] and Bo Zhang[1*]

2020

doi:10.1016/j.jmb.2006.01.089 J. Mol. Biol. (2006) 357, 1383–1393

JMB Available online at www.sciencedirect.com SCIENCE DIRECT® ELSEVIER

The Human LINE-1 Retrotransposon Creates DNA Double-strand Breaks

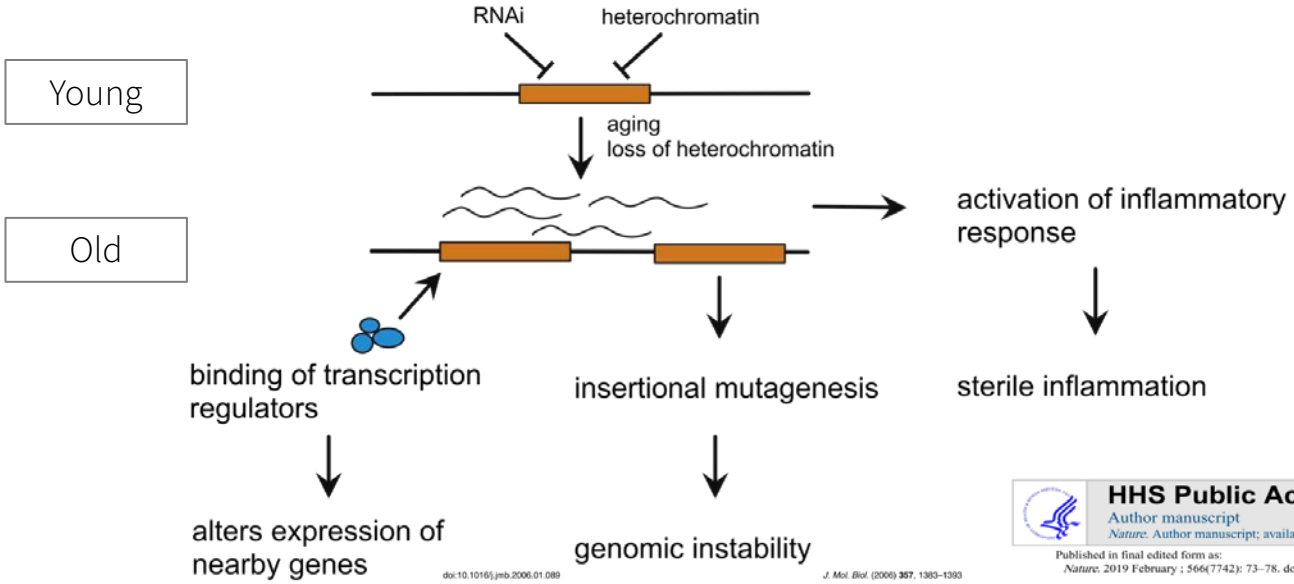
tephen L. Gasior[1], Timothy P. Wakeman[2], Bo Xu[2] nd Prescott L. Deininger[1*]

Research

A hot LI retrotransposon evades somatic repression and initiates human colorectal cancer

Emma C. Scott,[1,2,8] Eugene J. Gardner,[1,2,8] Ashiq Masood,[2,3,4,9] Nelson T. Chuang,[1,2,5] Paula M. Vertino,[6,7] and Scott E. Devine[1,2,3,4]

TE expression during aging and its possible consequences



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HHS Public Access

Author manuscript

Nature. Author manuscript; available in PMC 2019 August 06.

Published in final edited form as:

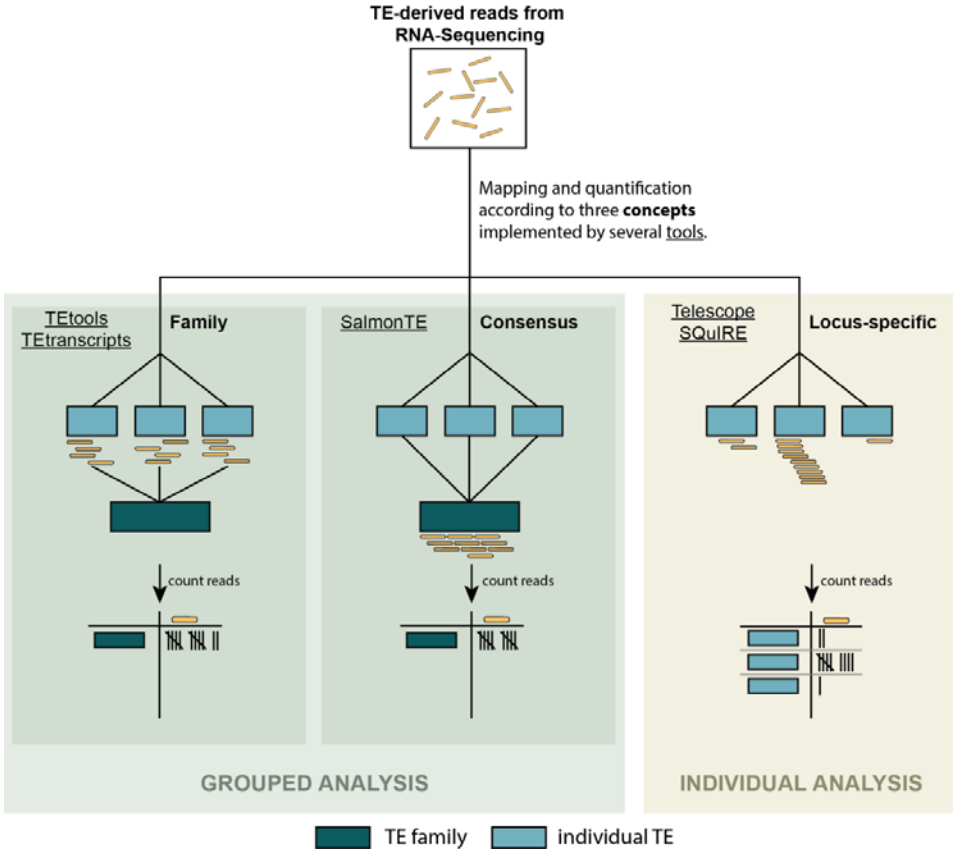
Nature. 2019 February ; 566(7742): 73–78. doi:10.1038/s41586-018-0784-9.

LINE-1 derepression in senescent cells triggers interferon and inflammaging

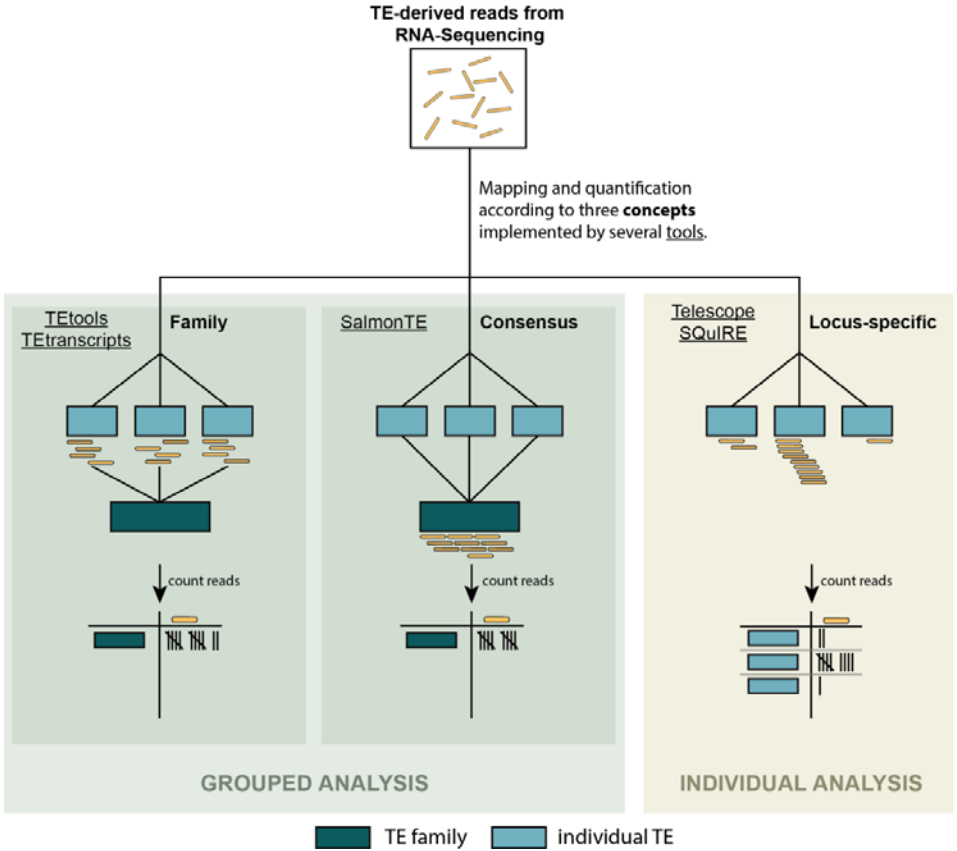
Research

A hot LI retrotransposon evades somatic repression and initiates human colorectal cancer

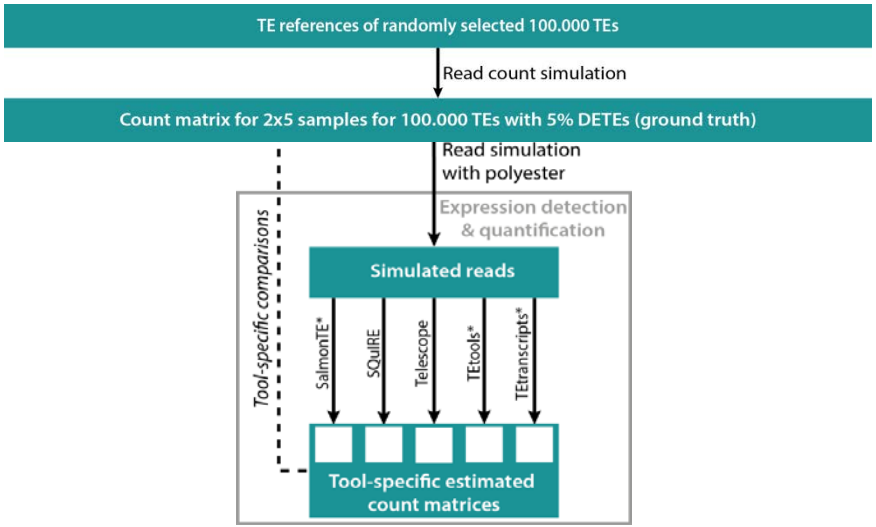
Quantification of transposable elements



Quantification of transposable elements

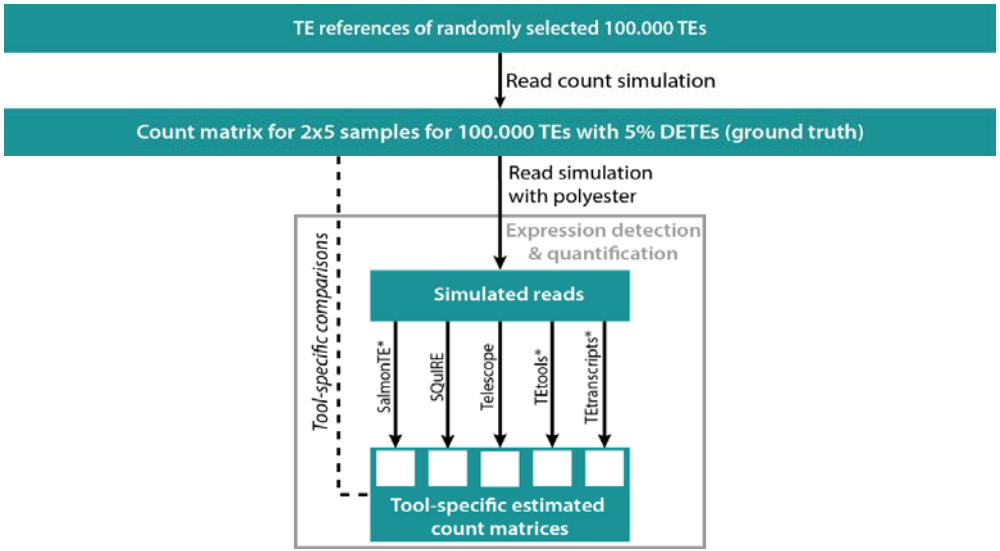


Simulation Setup

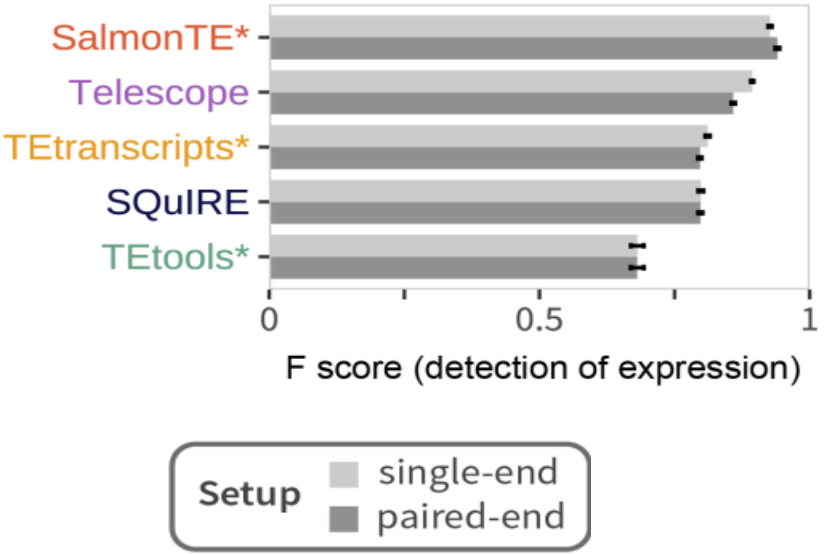


Locus-specific expression analysis of TEs

Simulation Setup



Expression detection



Locus-specific expression analysis of TEs

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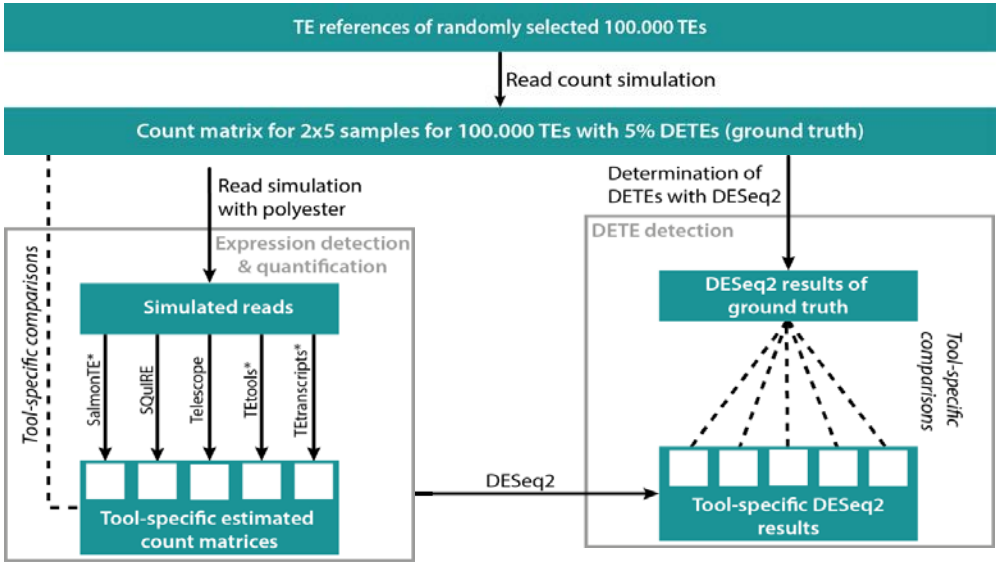
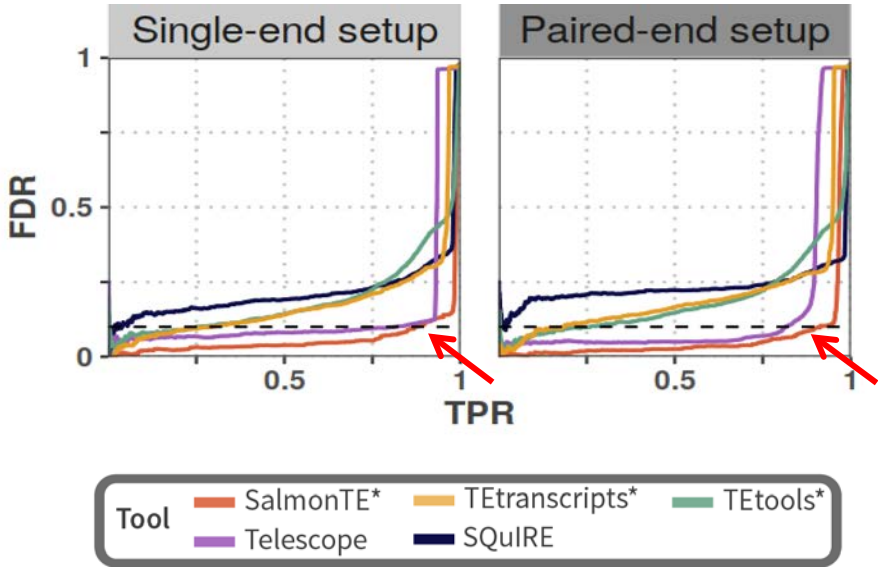


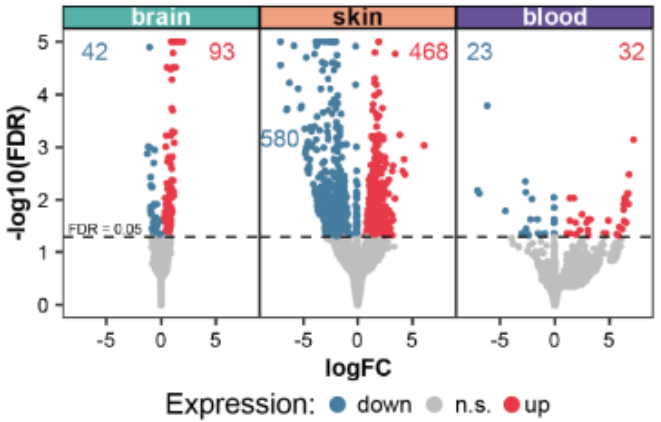
With only slight modifications to existing methods, locus-specific TE expression analysis works surprisingly well for conventional paired-end sequencing data.

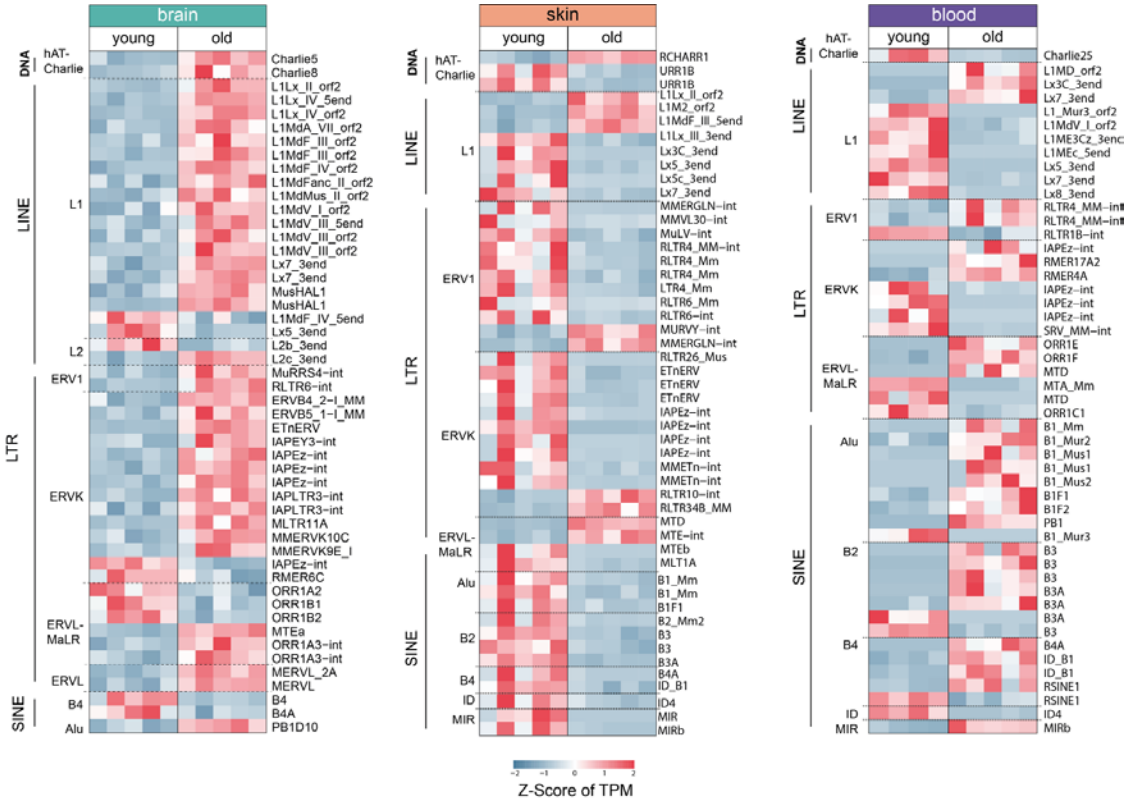
DETE detection



Genome-wide TE expression profiles in aging mice

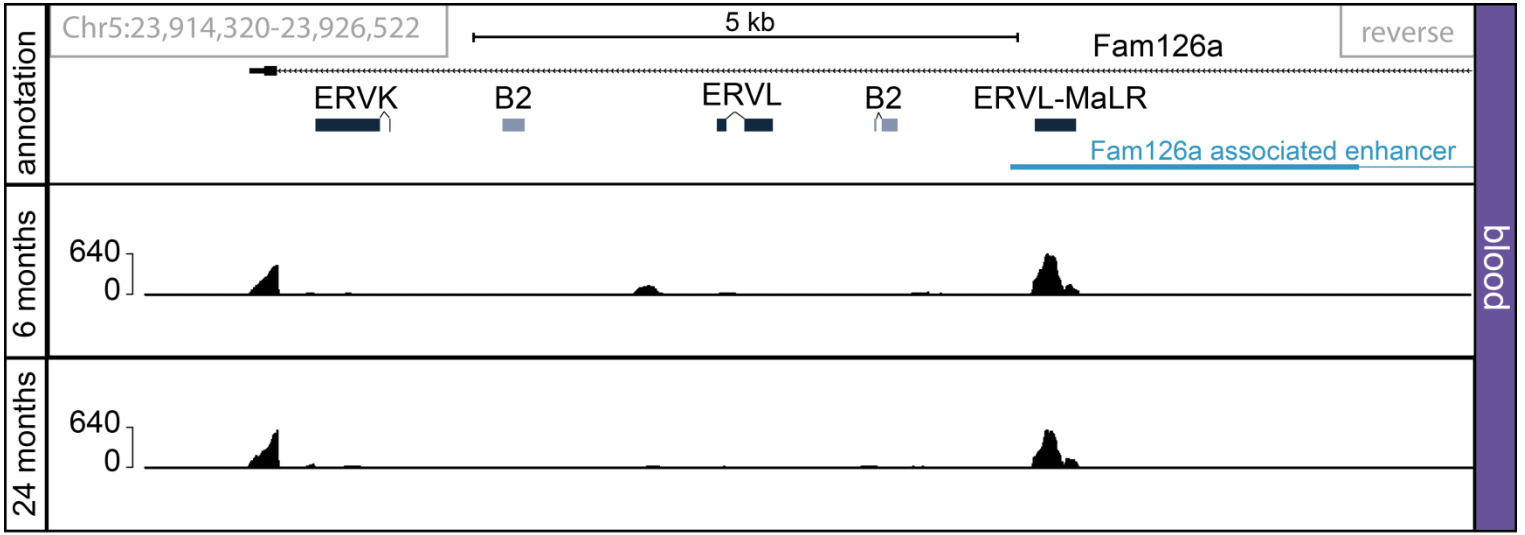
24 vs. 6 months





- Family-based analysis likely miss important dysregulation
- TE expression family-independent and tissue specific

Independently expressed?



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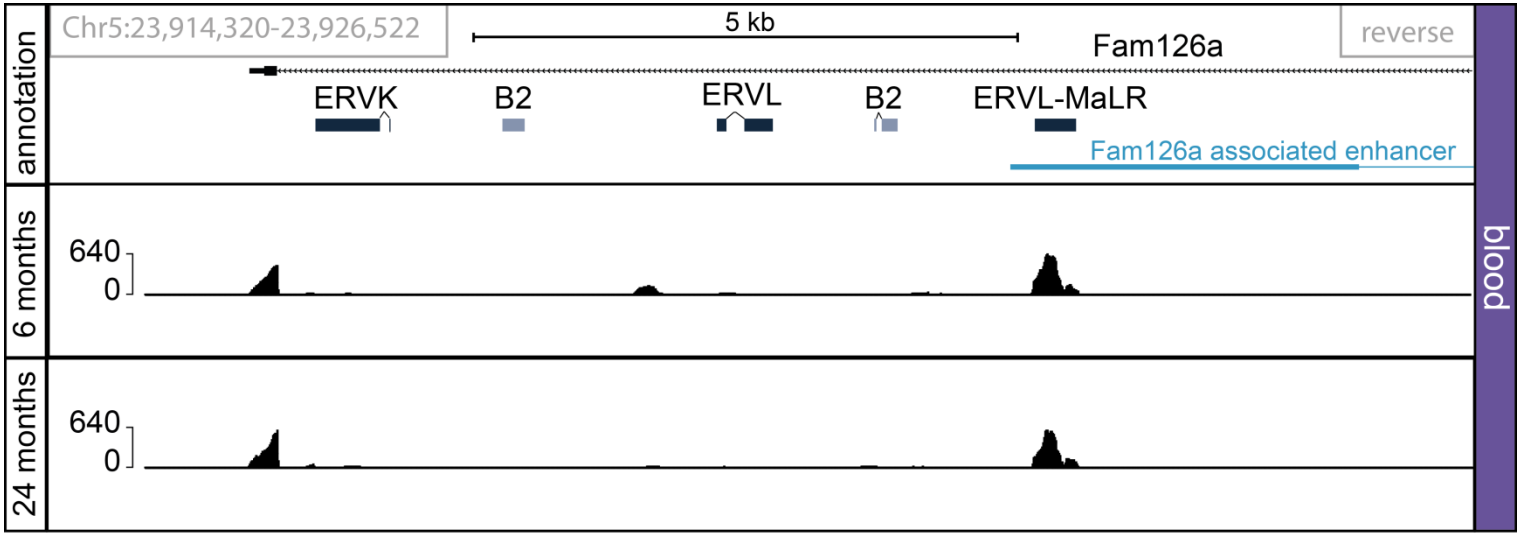
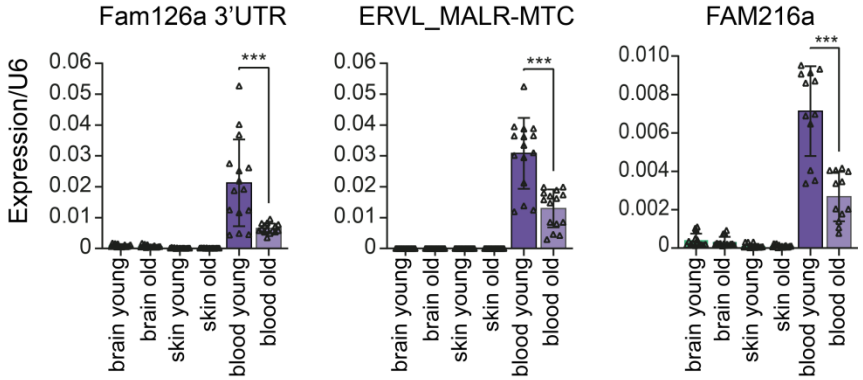
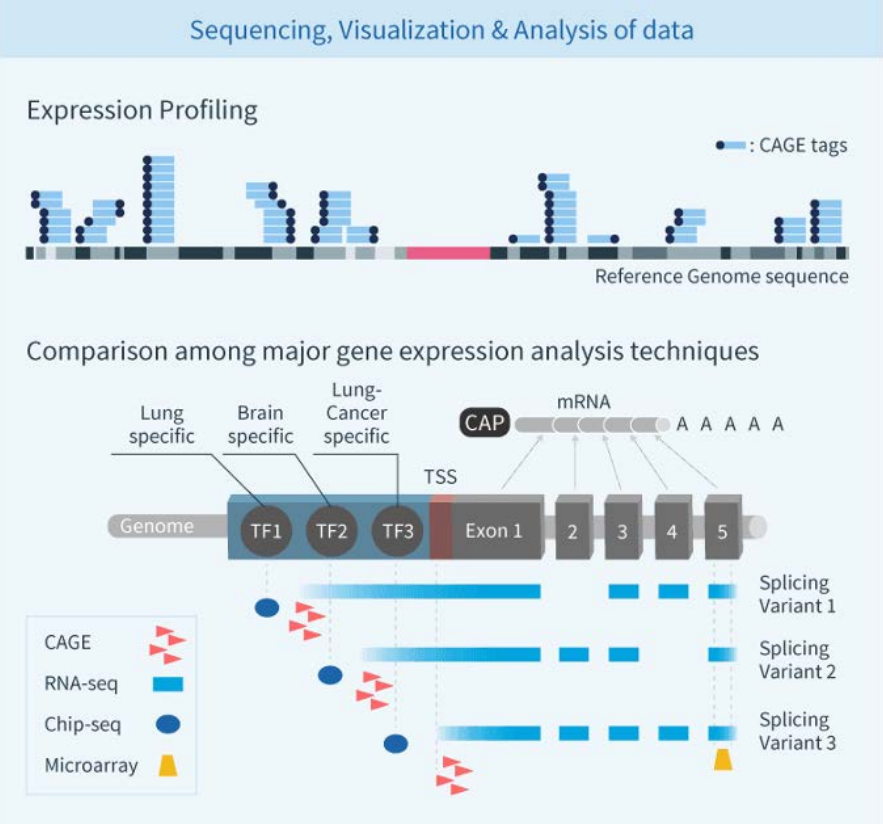




CAGE-Seq

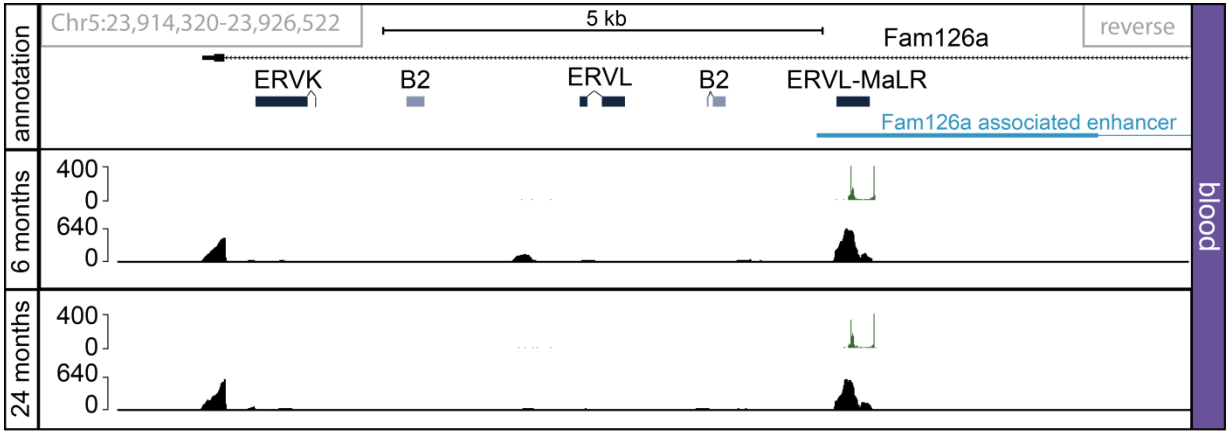


https://cage-seq.com/

- CAGE-Seq enriches Cap structure of RNAs
- CAGE tags indicate transcription start sites (TSS)
- Especially helpful to investigate transcript structures
- Established by the FANTOM consortium

→ **Identification of independent TE expression**

Detection of independently expressed TEs via CAGE-Seq



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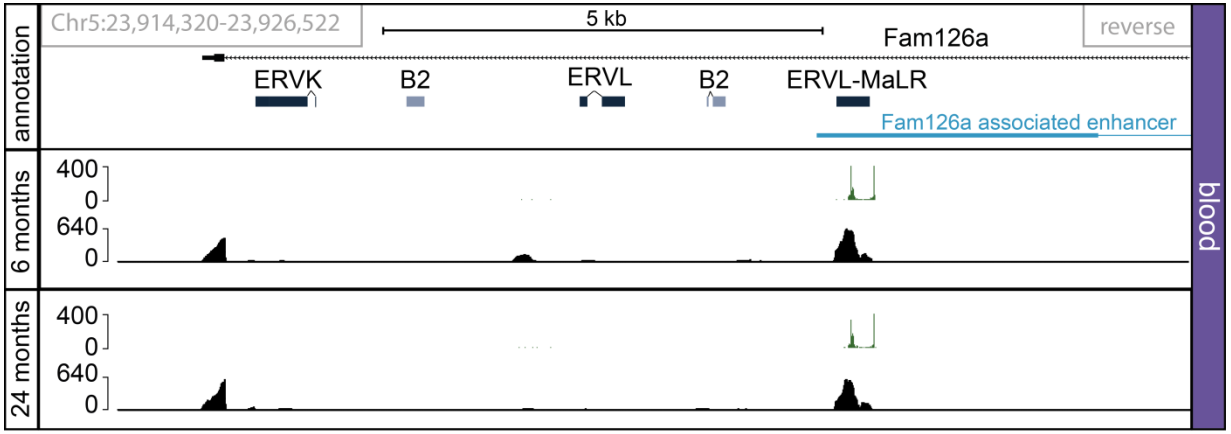
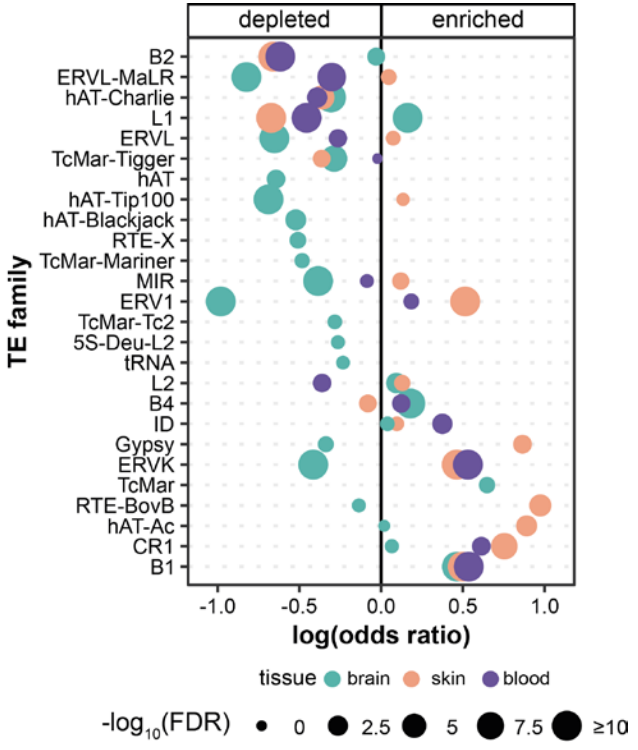
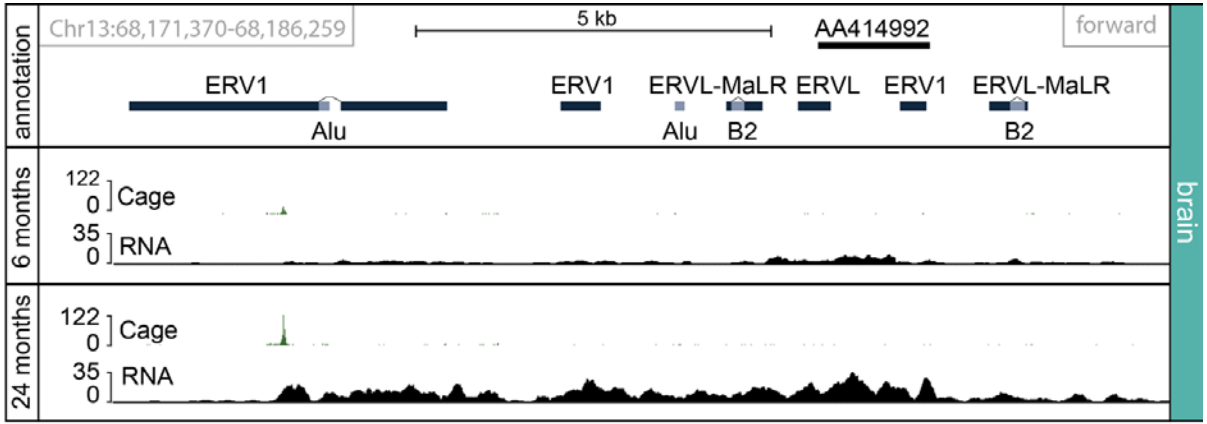


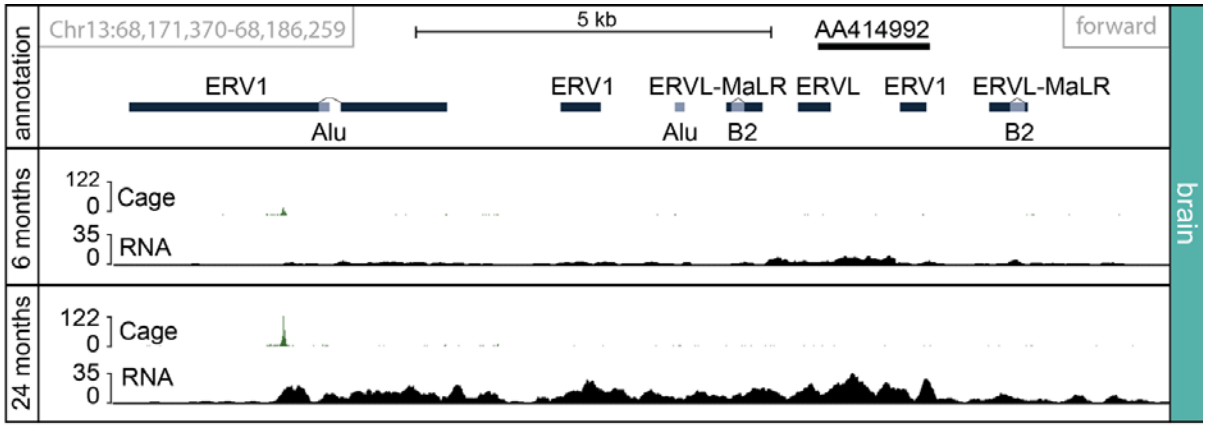


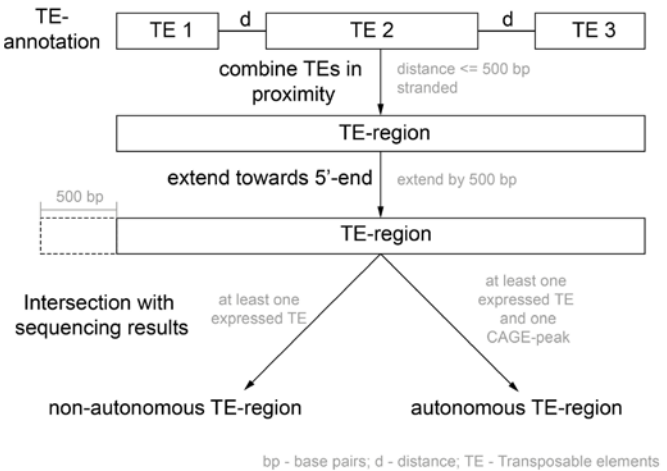
- TE-CAGE peaks are tissue-specifically enriched/depleted

Shared transcription start sites - TE regions



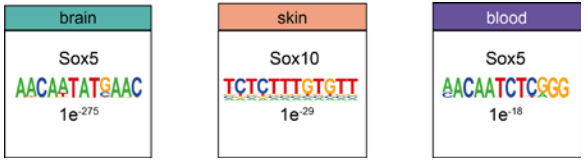
Shared transcription start sites - TE regions





bp - base pairs; d - distance; TE - Transposable elements

Where does the TE expression start?



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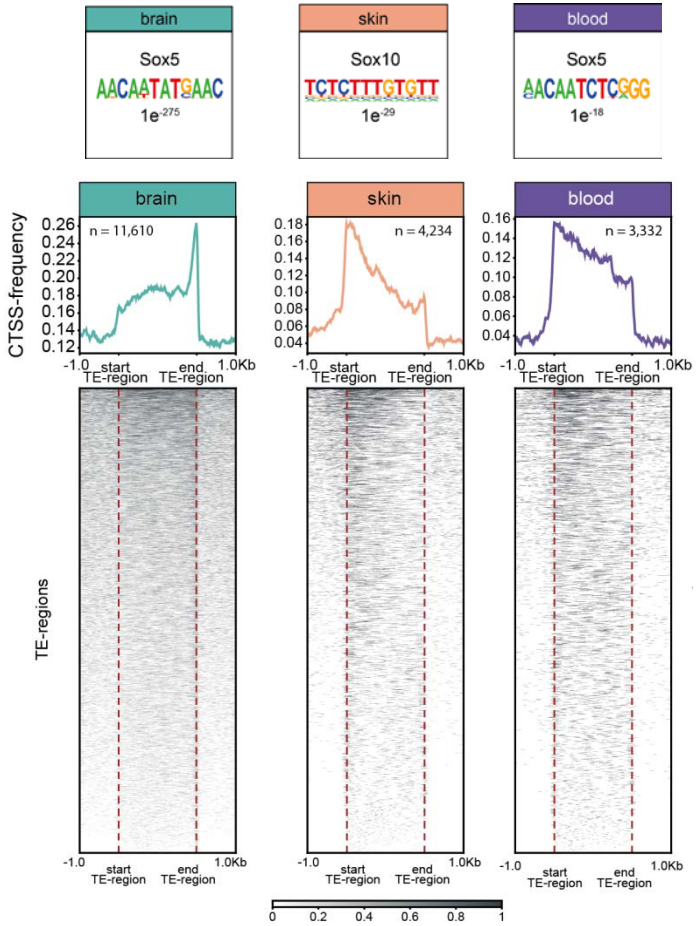

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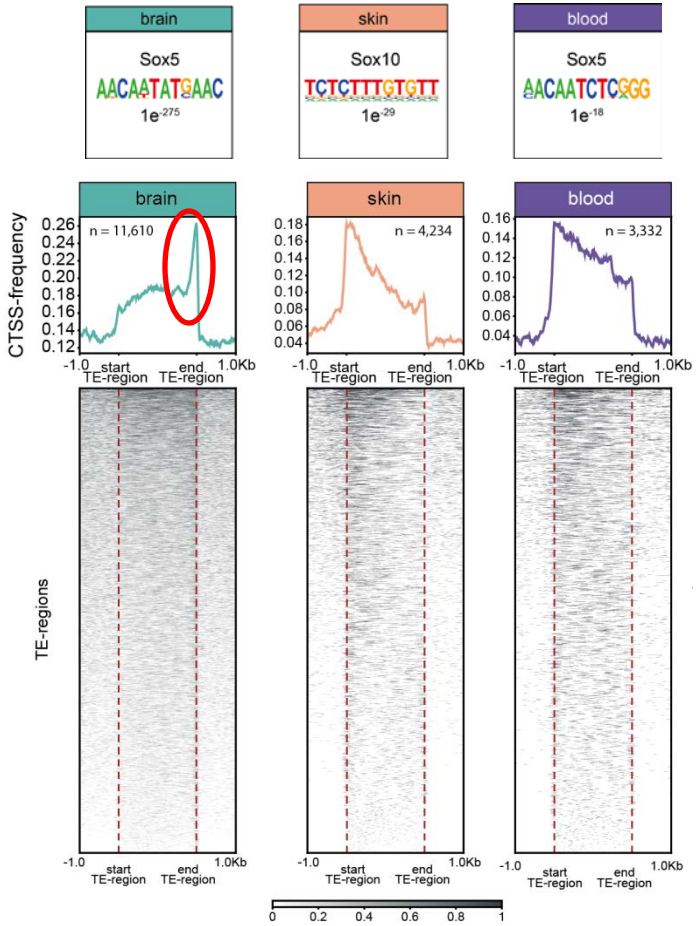

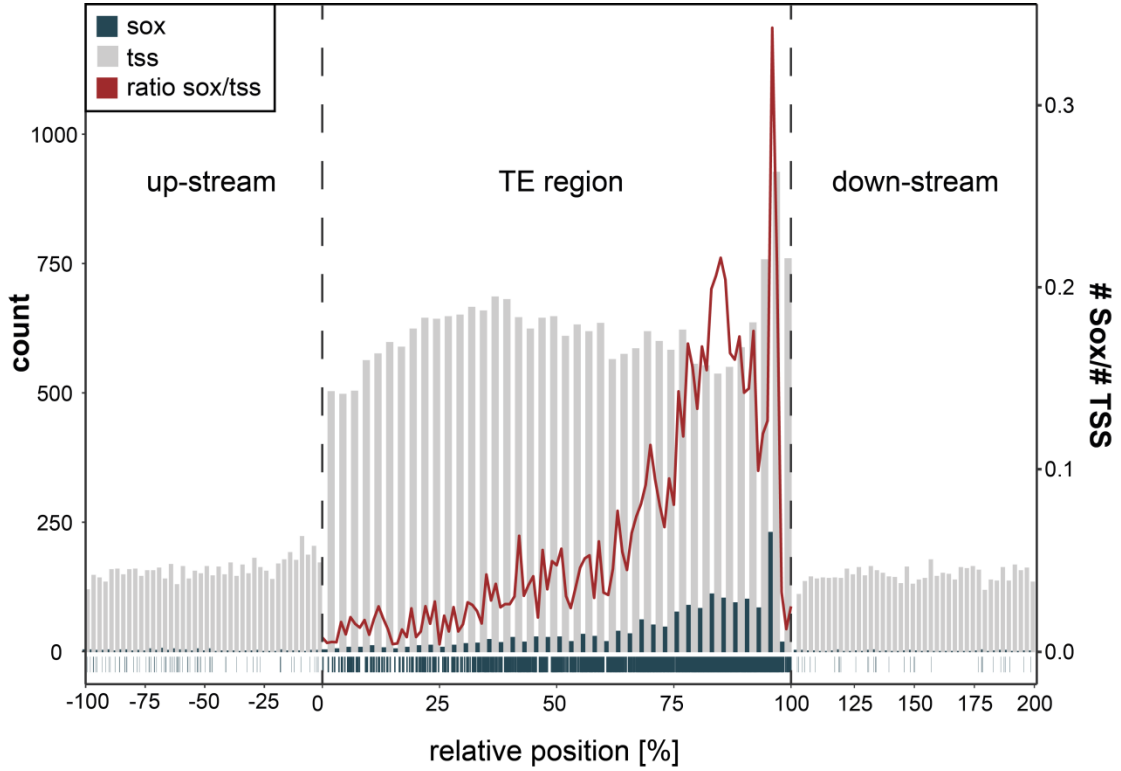

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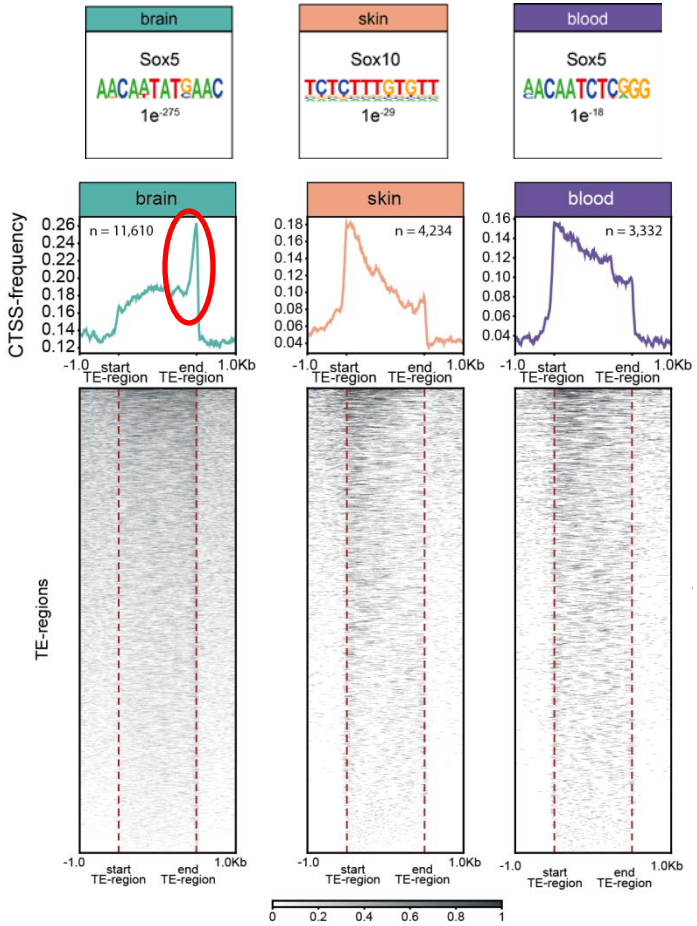
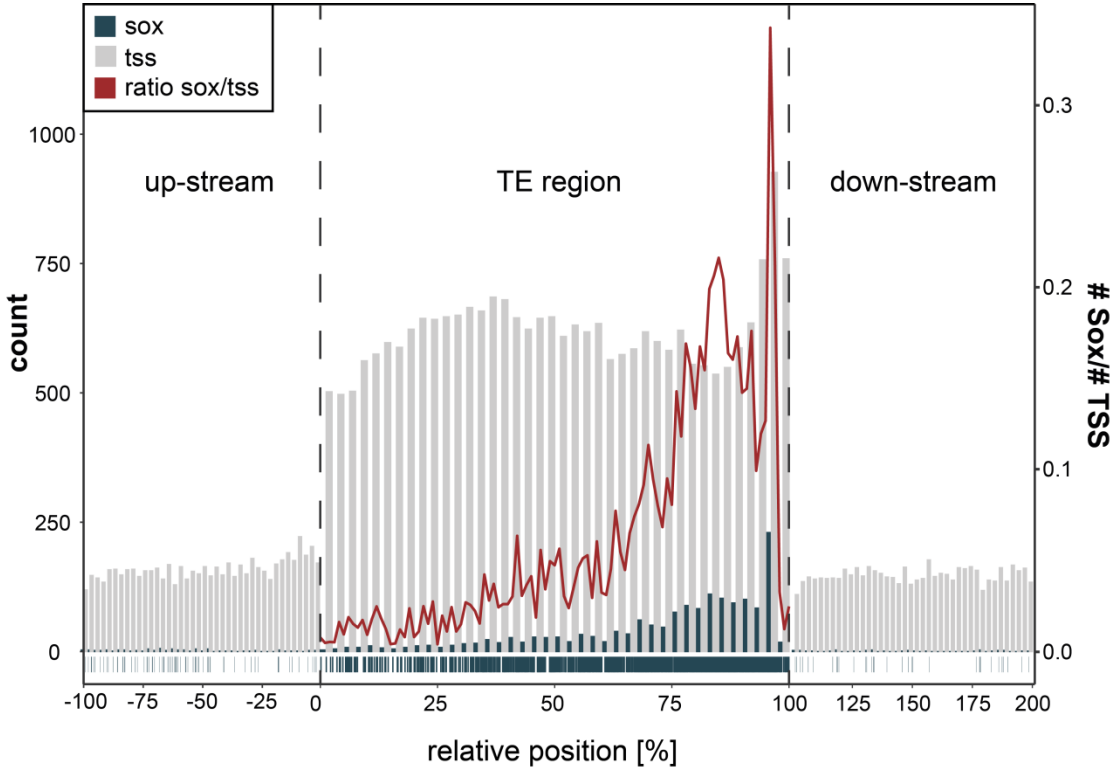
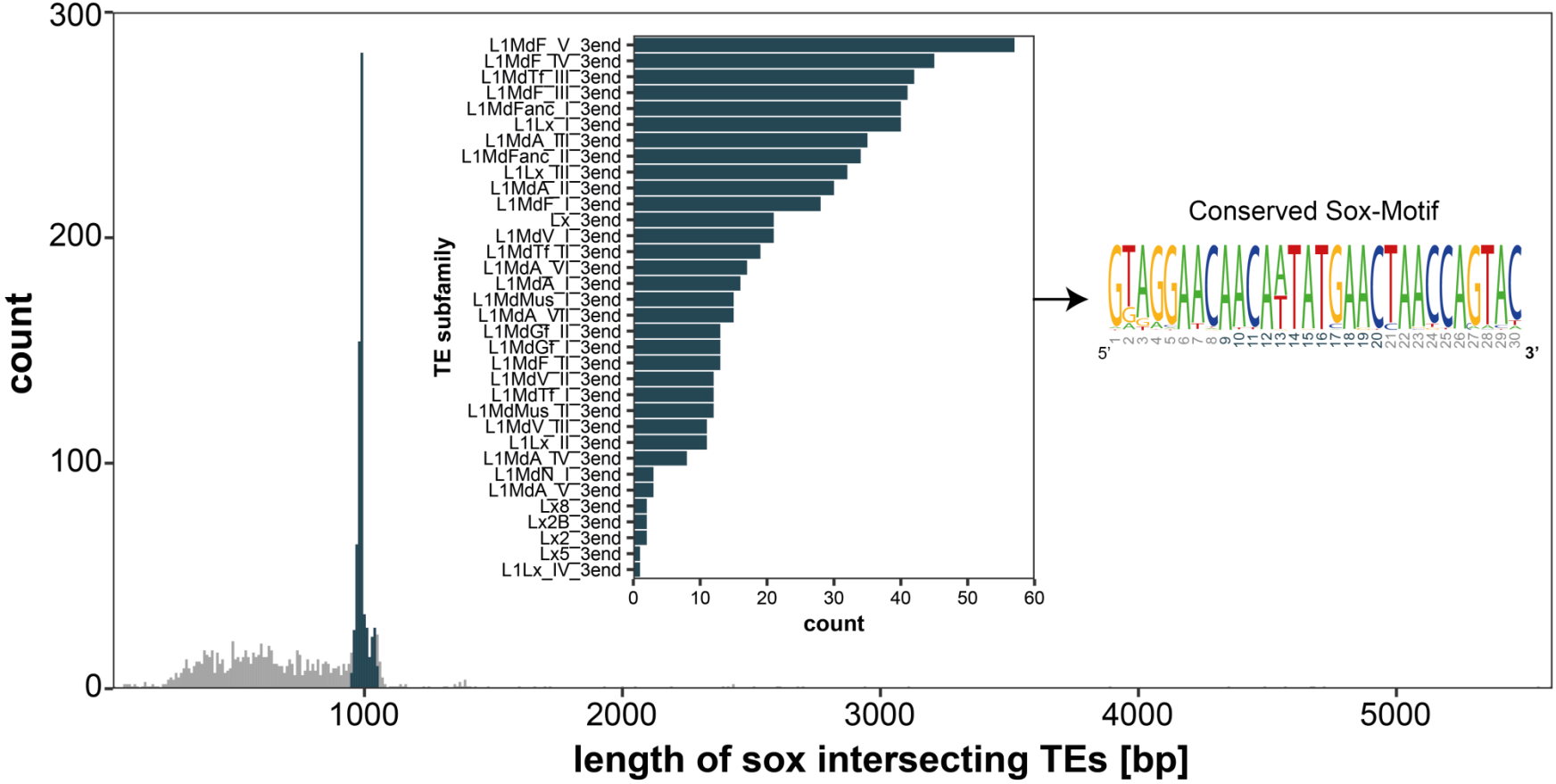


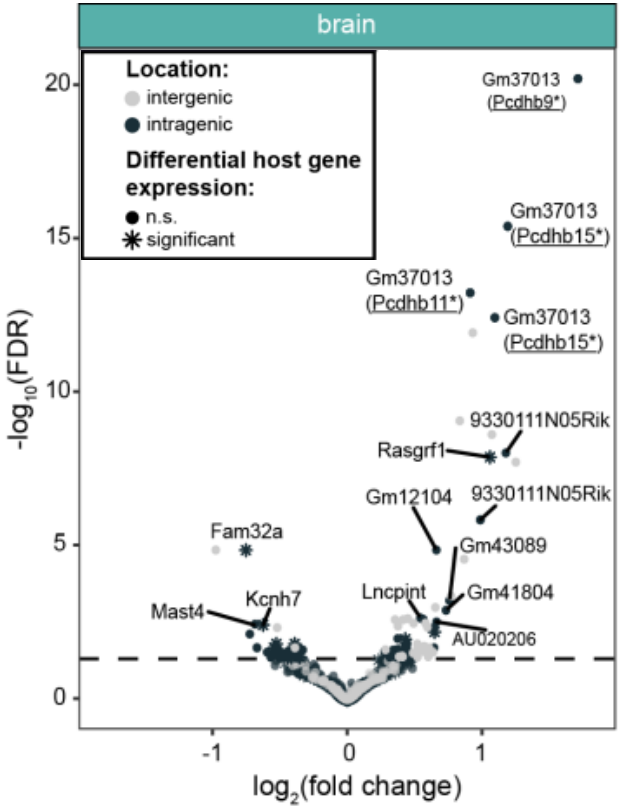


- Strong enrichment of Sox5 motif in brain
- Clear correlation of TSS occurrence with Sox5 motif

Sox5-containing TE-regions in brain



TE-associated genes in brain



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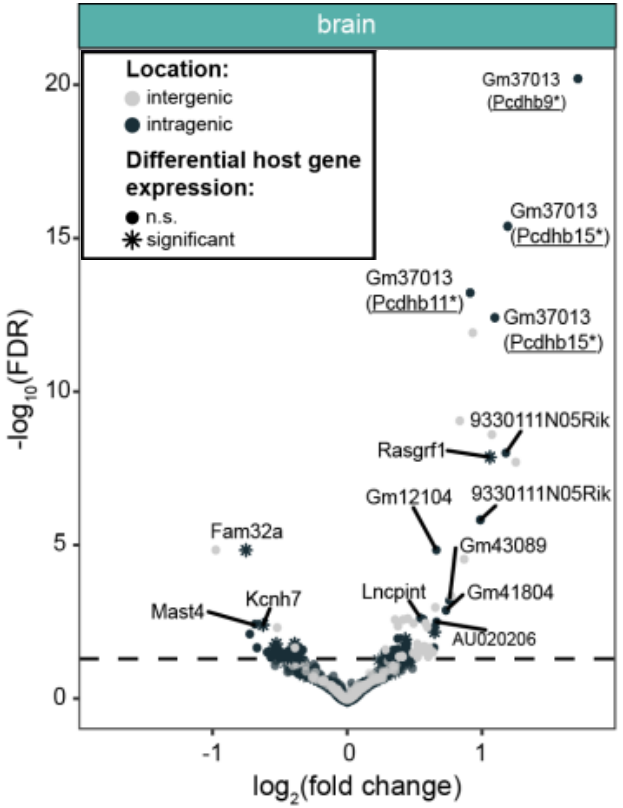
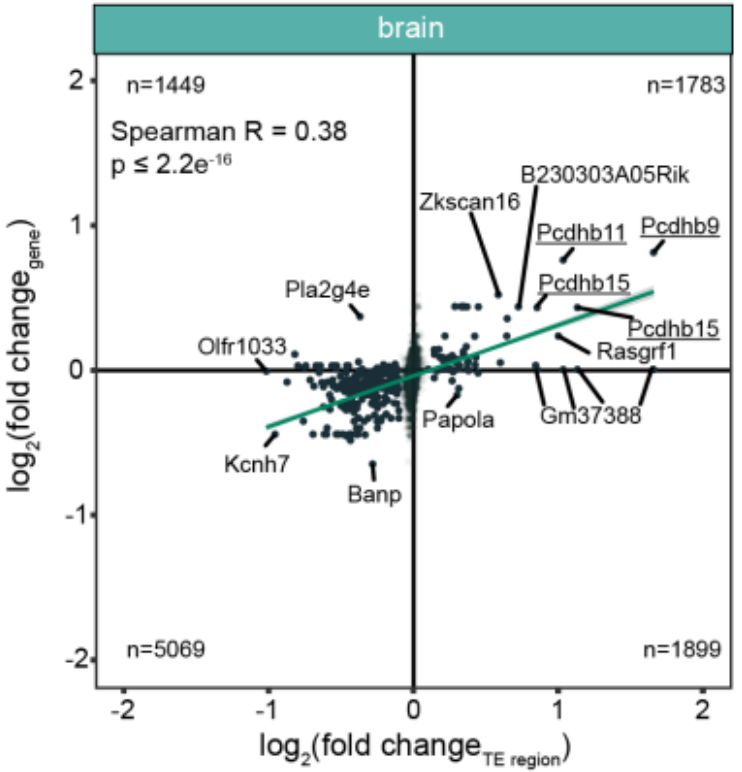
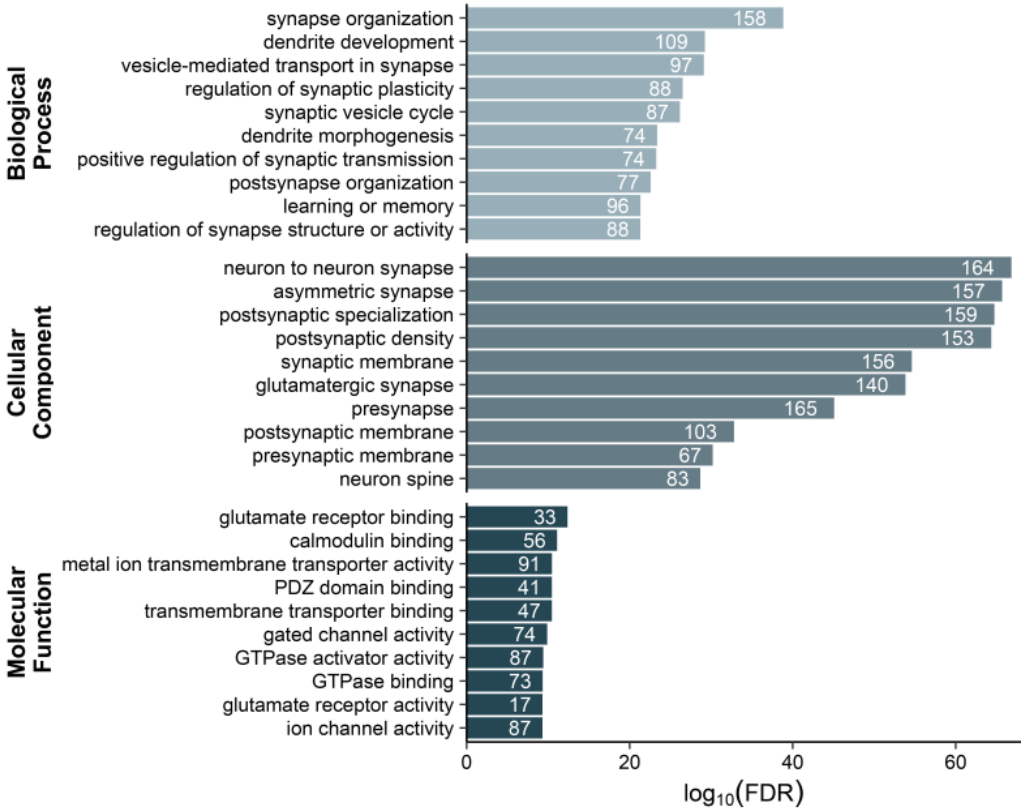
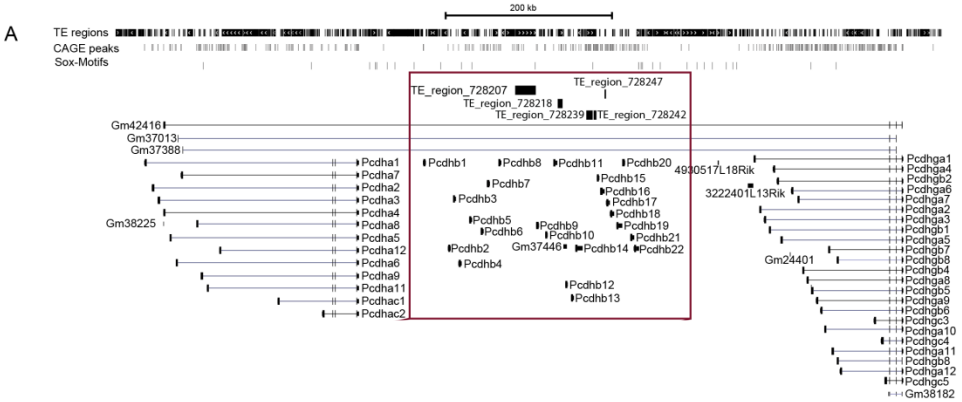




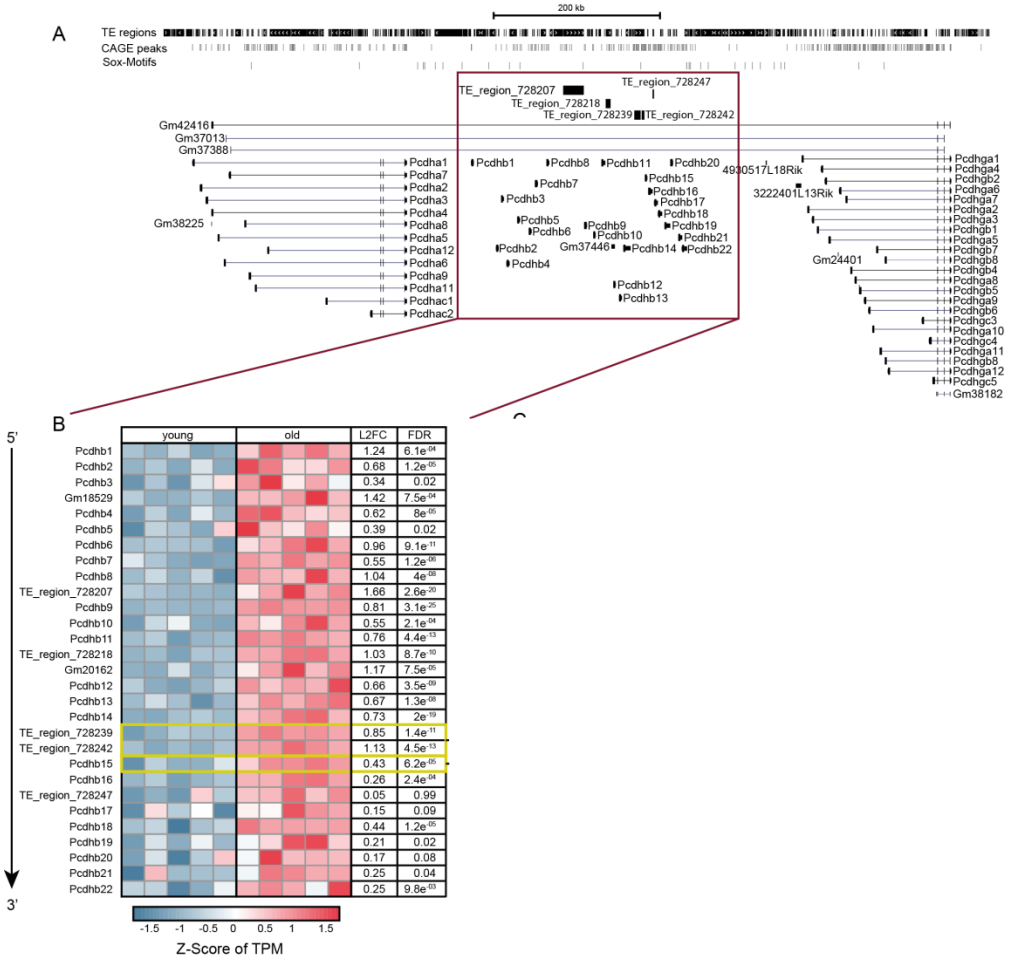
GO term analysis of TE-containing genes in brain



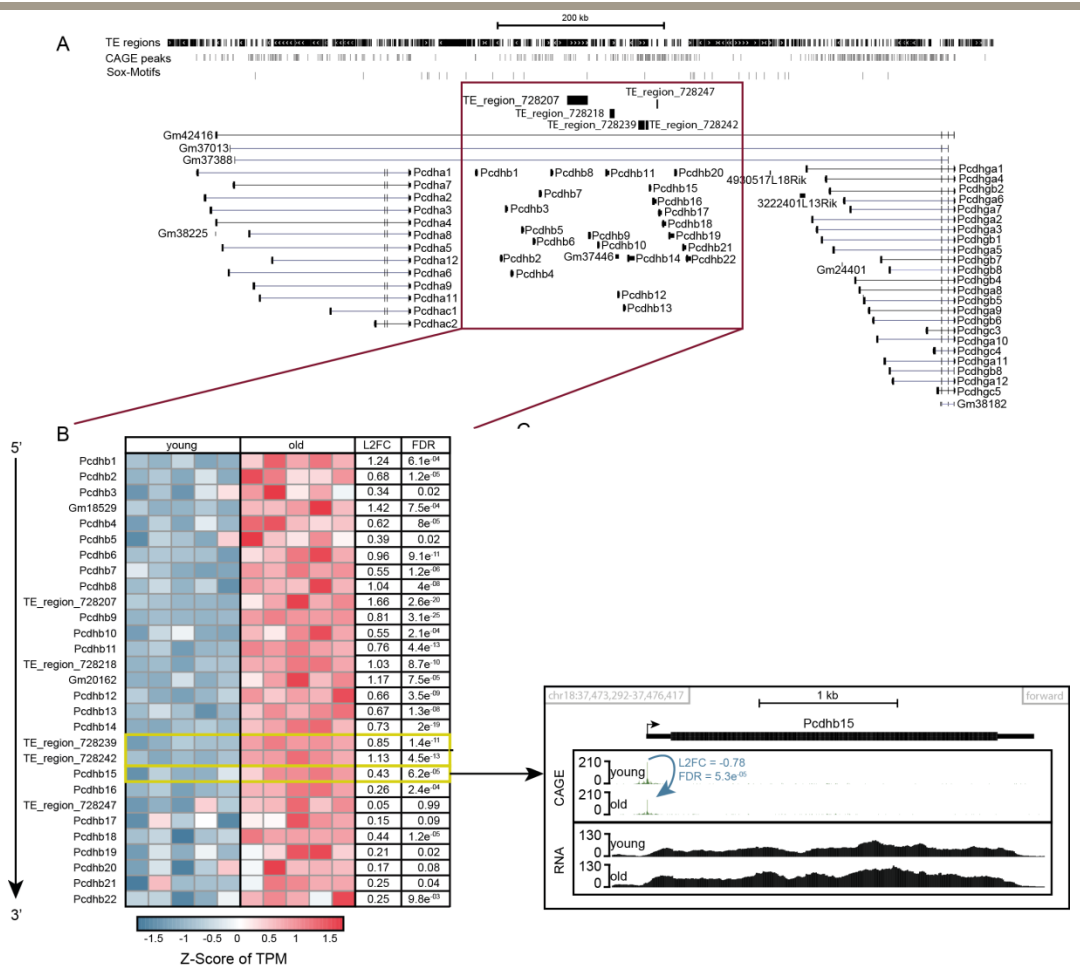
Differentially expressed TEs in Protocadherin gene cluster



Differentially expressed TEs in Protocadherin gene cluster



Differentially expressed TEs in Protocadherin gene cluster



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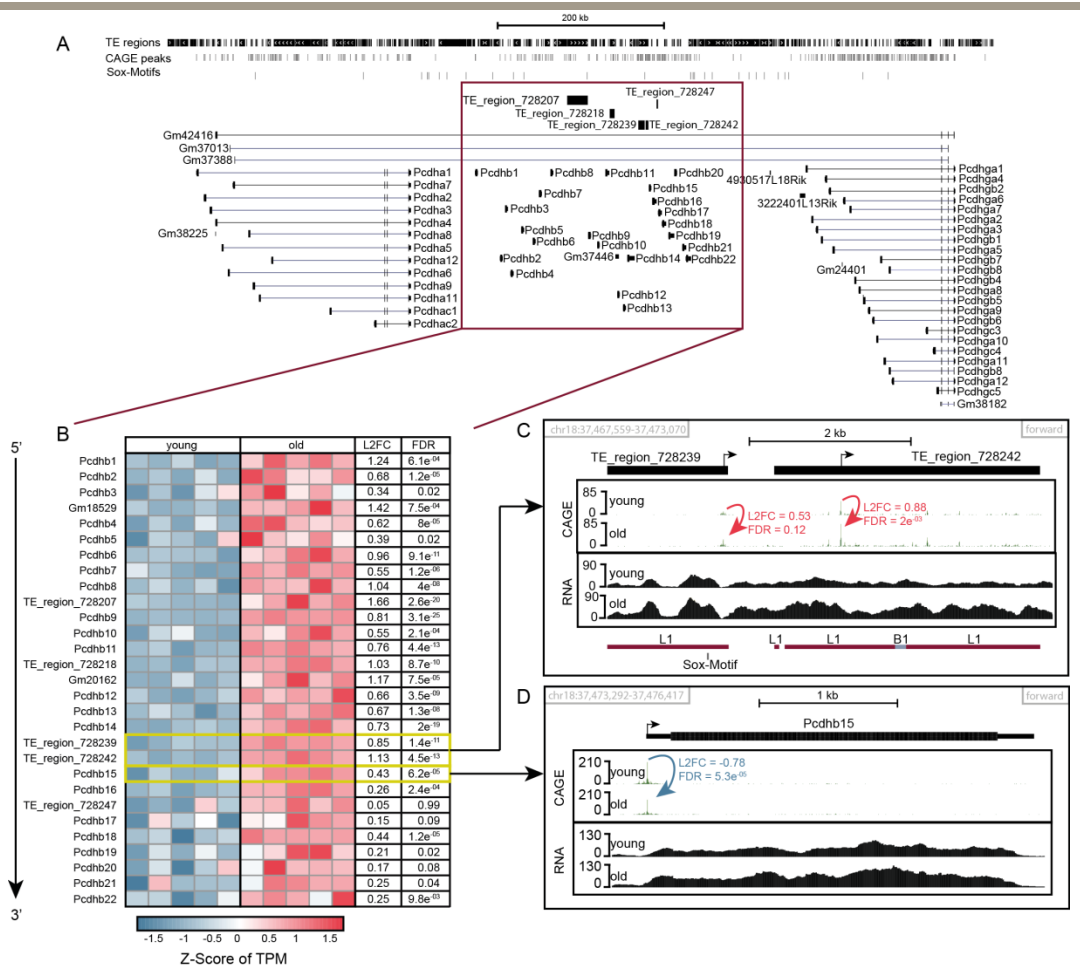

Summary

- Expression quantification of individual TEs works quite well
- Genome-wide, copy-specific TE expression signature of aging mice
- Identification of independently expressed TE regions via CAGE
- Sox5 associated TSS in 3’end of L1 subfamilies in brain
- Strong association of independent TEs with synaptic functions
- Potential effects on neuronal aging

Acknowledgement

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Martin Fischer
Maja Olecka
Konstantin Riege
Arne Sahm
Alena van Bömmel
Elina Wiechens
Katjana Schwab
Tycho Kirchner

CF Life Science Computing

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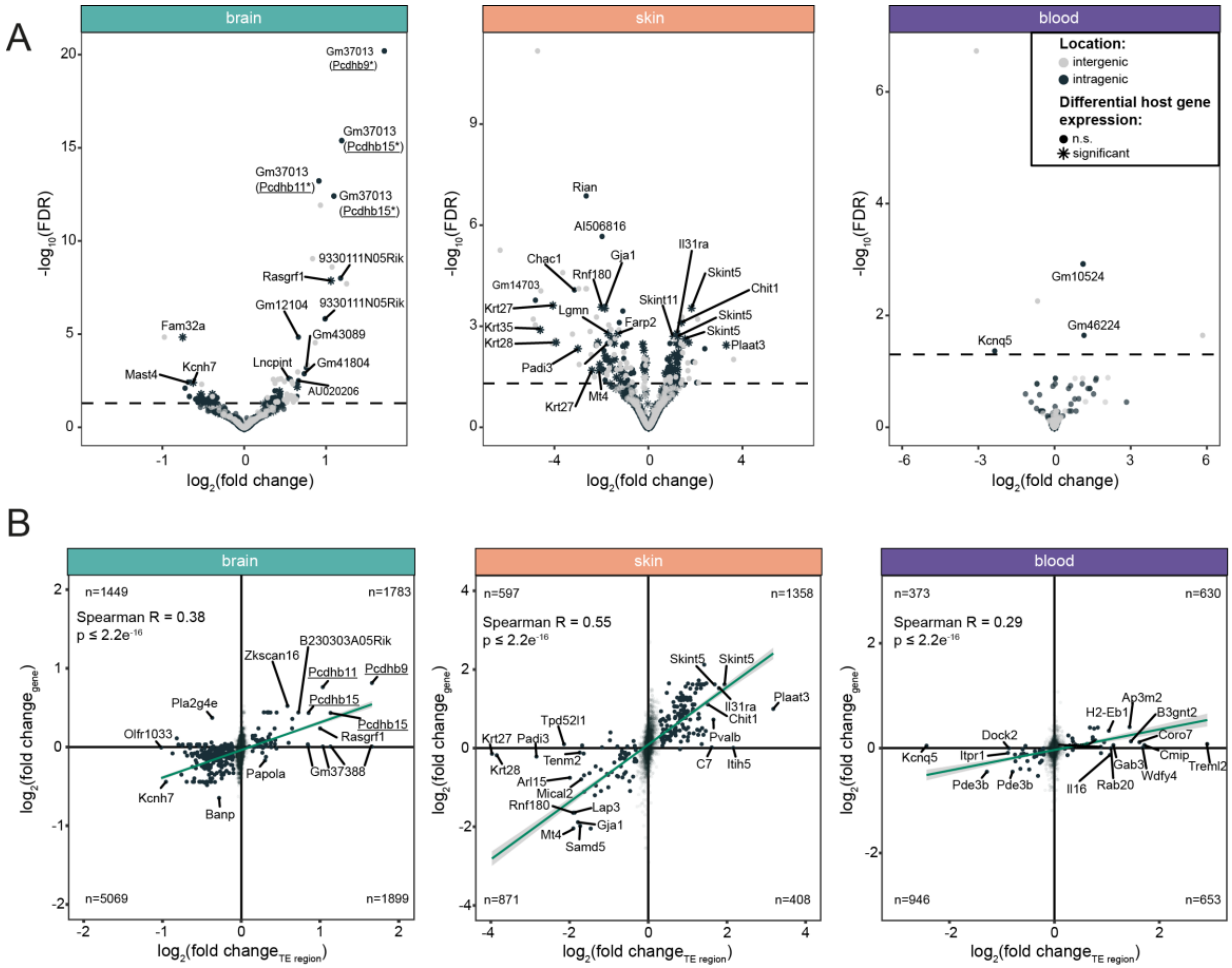
Philipp Koch
Jeanne Wilbrandt

CF DNA Sequencing

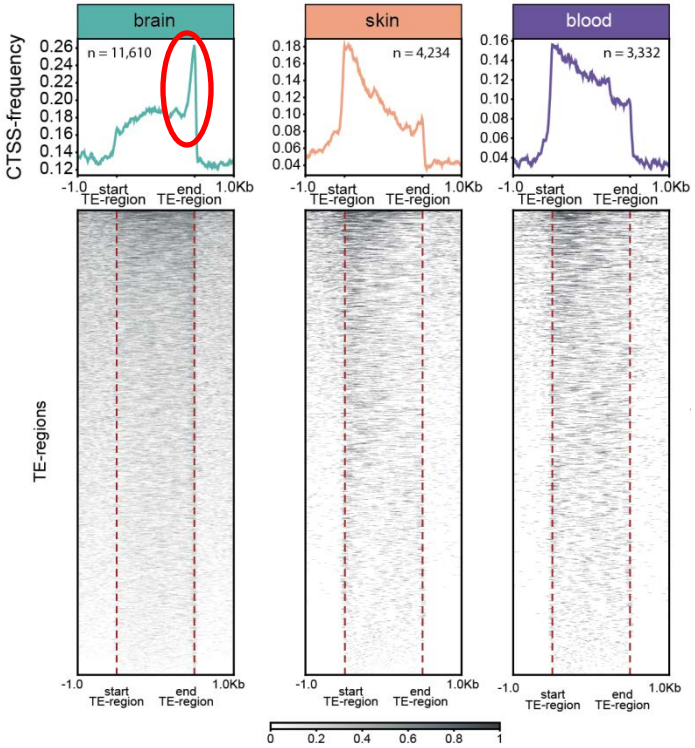
Marco Groth
Martin Bens

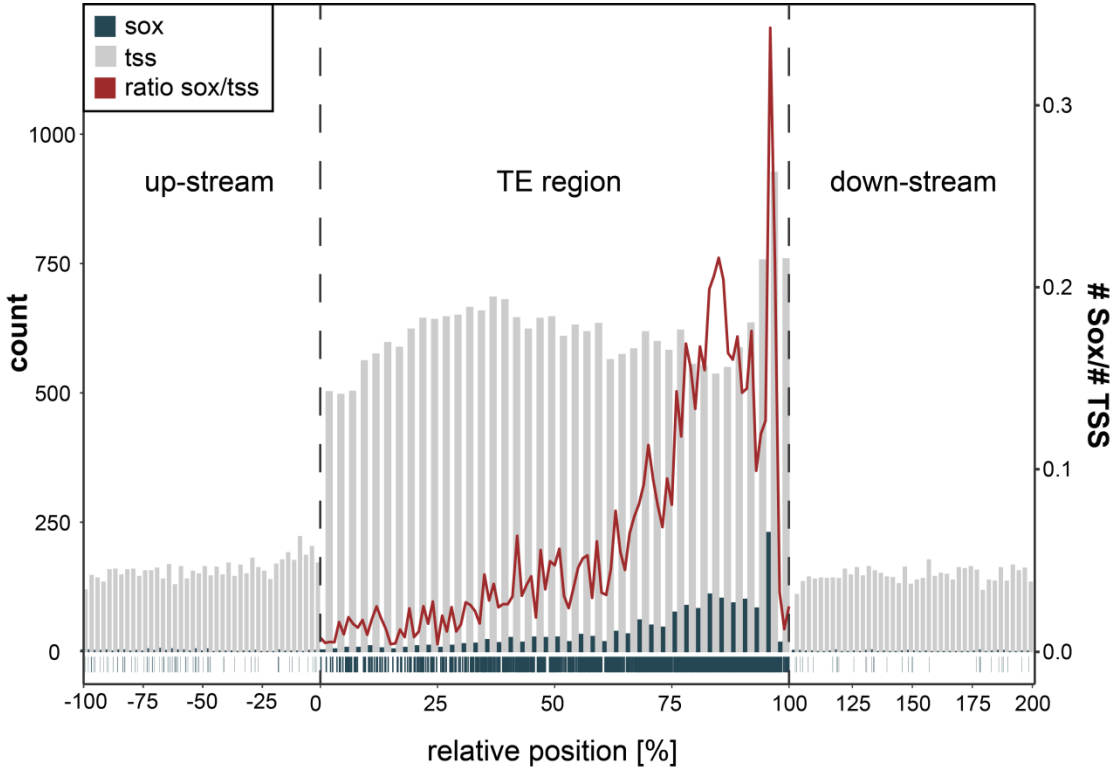
Lgsa
Leibniz Graduate School on Aging

KTS
KLAUS TSCHIRA STIFTUNG
GEMEINNÜTZIGE GMBH

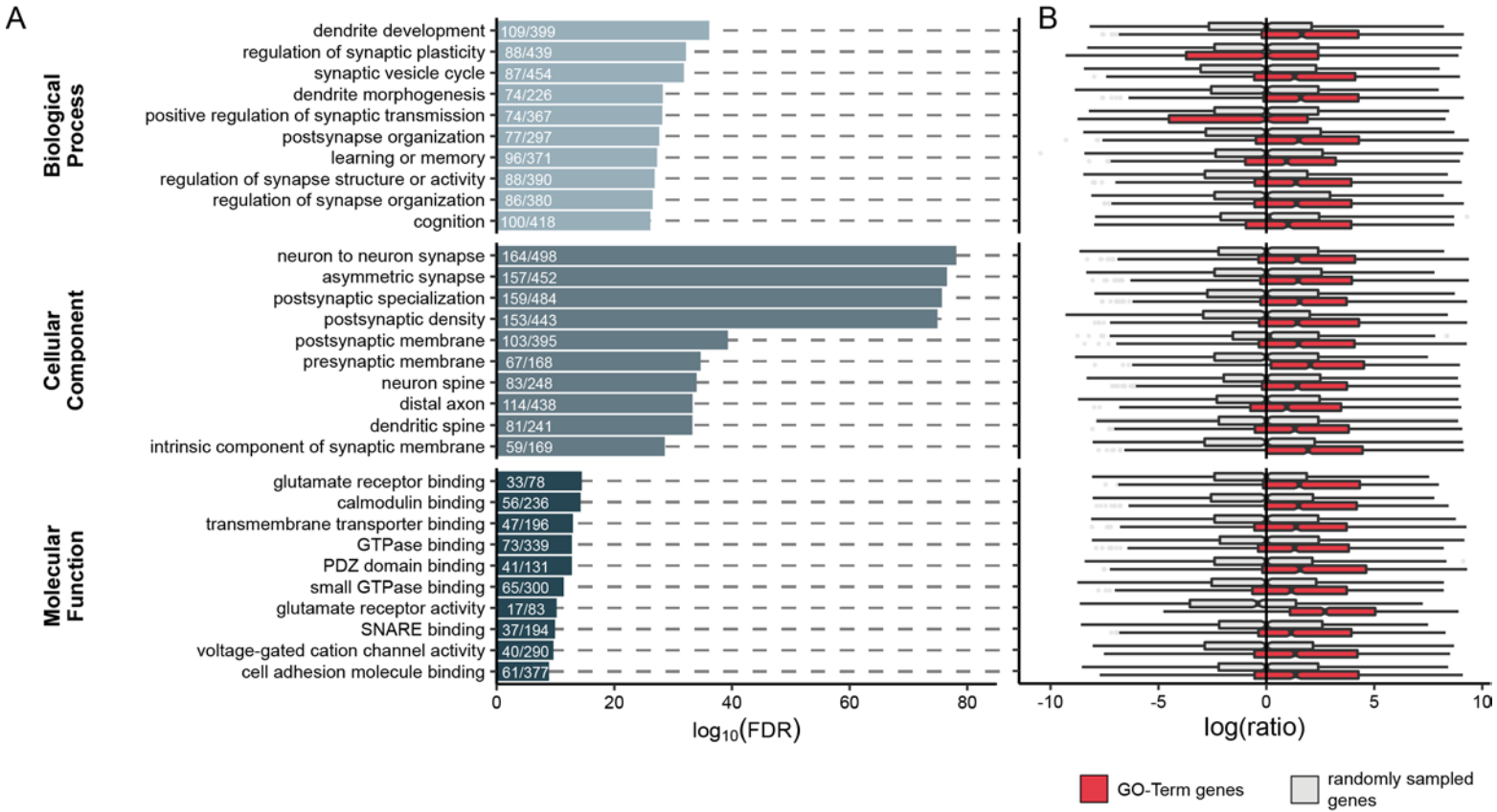

A
brain
skin
blood
-log10(FDR)
log2(fold change)
Location:
intergenic
intragenic
Differential host gene expression:
n.s.
significant
Gm37013 (Pcdhb9*)
Gm37013 (Pcdhb15*)
Gm37013 (Pcdhb11*)
Gm37013 (Pcdhb15*)
9330111N05Rik
Rasgrf1
Gm12104
9330111N05Rik
Fam32a
Gm43089
Mast4
Kcnh7
Lncpint
Gm41804
AU020206
Rian
AI506816
Il31ra
Chac1
Gja1
Rnf180
Skint5
Gm14703
Chit1
Krt27
Lgmn
Skint11
Farp2
Skint5
Krt35
Krt28
Skint5
Plaat3
Padi3
Krt27
Mt4
Gm10524
Gm46224
Kcnq5
B
brain
skin
blood
n=1449
n=1783
n=5069
n=1899
Spearman R = 0.38
p ≤ 2.2e-16
B230303A05Rik
Zkscan16
Pcdhb11
Pcdhb9
Pcdhb15
Pla2g4e
Pcdhb15
Olfr1033
Rasgrf1
Papola
Gm37388
Kcnh7
Banp
n=597
n=1358
n=871
n=408
Spearman R = 0.55
p ≤ 2.2e-16
Skint5
Skint5
Plaat3
Il31ra
Chit1
Tpd52l1
Krt27
Padi3
Pvalb
Tenm2
C7
Itih5
Krt28
Arl15
Mical2
Rnf180
Lap3
Gja1
Mt4
Samd5
n=373
n=630
n=946
n=653
Spearman R = 0.29
p ≤ 2.2e-16
Ap3m2
H2-Eb1
B3gnt2
Dock2
Coro7
Kcnq5
Itpr1
Gab3
Cmip
Treml2
Wdfy4
Pde3b
Pde3b
Il16
Rab20
log2(fold changegene)
log2(fold changeTE region)

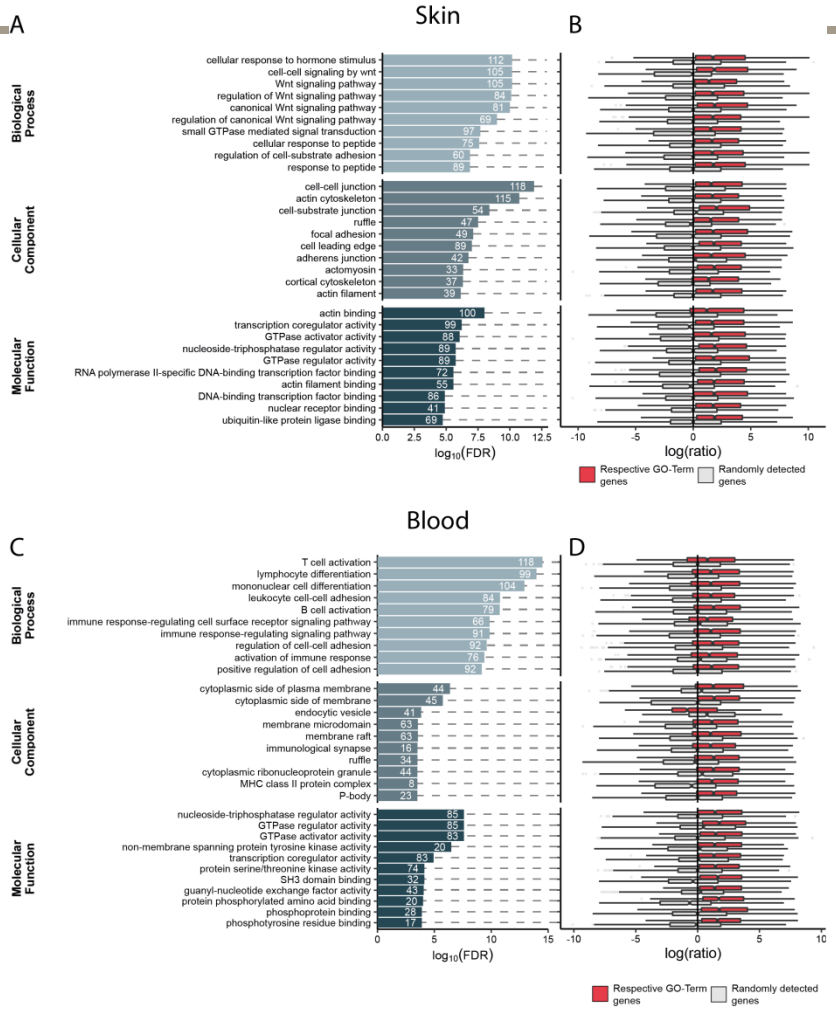
Where does the TE expression start?

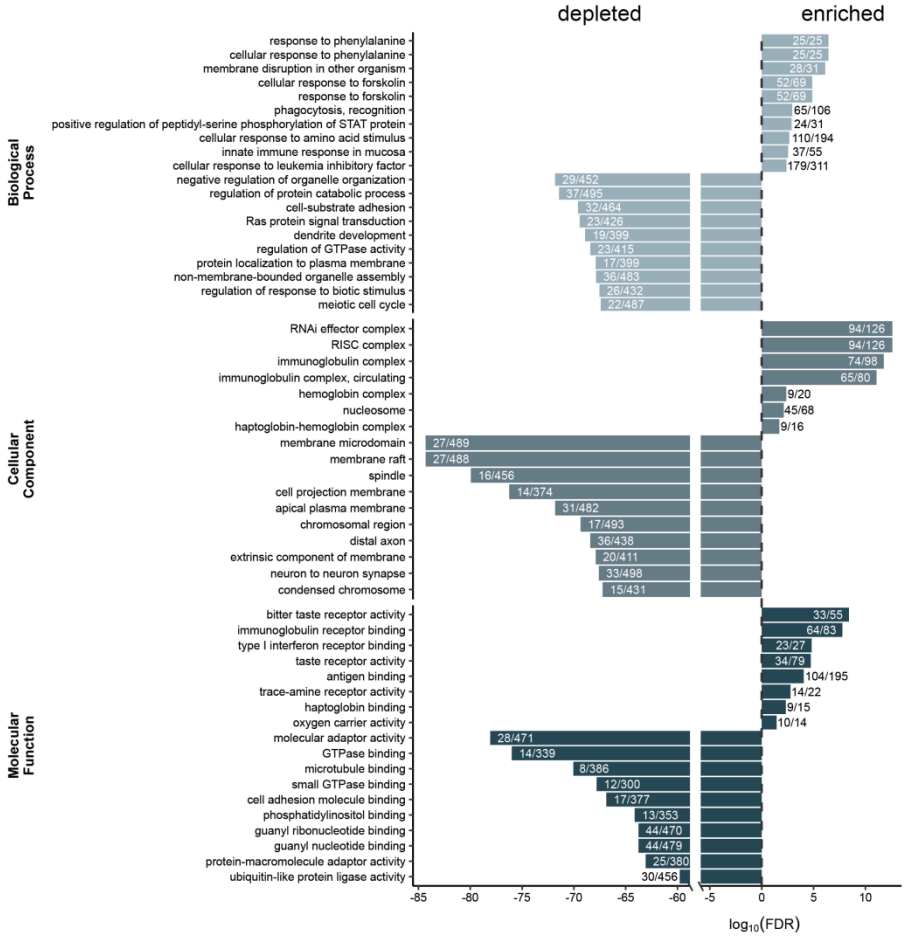




- Strong enrichment of Sox5 motif in brain
- Clear correlation of TSS occurrence with Sox5 motif


A
B
Biological Process
dendrite development 109/399
regulation of synaptic plasticity 88/439
synaptic vesicle cycle 87/454
dendrite morphogenesis 74/226
positive regulation of synaptic transmission 74/367
postsynapse organization 77/297
learning or memory 96/371
regulation of synapse structure or activity 88/390
regulation of synapse organization 86/380
cognition 100/418
Cellular Component
neuron to neuron synapse 164/498
asymmetric synapse 157/452
postsynaptic specialization 159/484
postsynaptic density 153/443
postsynaptic membrane 103/395
presynaptic membrane 67/168
neuron spine 83/248
distal axon 114/438
dendritic spine 81/241
intrinsic component of synaptic membrane 59/169
Molecular Function
glutamate receptor binding 33/78
calmodulin binding 56/236
transmembrane transporter binding 47/196
GTPase binding 73/339
PDZ domain binding 41/131
small GTPase binding 65/300
glutamate receptor activity 17/83
SNARE binding 37/194
voltage-gated cation channel activity 40/290
cell adhesion molecule binding 61/377
0
20
40
60
80
log10(FDR)
-10
-5
0
5
10
log(ratio)
GO-Term genes
randomly sampled genes


A
Skin
B
Biological Process
cellular response to hormone stimulus 112
cell-cell signaling by wnt 105
Wnt signaling pathway 105
regulation of Wnt signaling pathway 84
canonical Wnt signaling pathway 81
regulation of canonical Wnt signaling pathway 69
small GTPase mediated signal transduction 97
cellular response to peptide 75
regulation of cell-substrate adhesion 60
response to peptide 89
Cellular Component
cell-cell junction 118
actin cytoskeleton 115
cell-substrate junction 54
ruffle 47
focal adhesion 49
cell leading edge 89
adherens junction 42
actomyosin 33
cortical cytoskeleton 37
actin filament 39
Molecular Function
actin binding 100
transcription coregulator activity 99
GTPase activator activity 88
nucleoside-triphosphatase regulator activity 89
GTPase regulator activity 89
RNA polymerase II-specific DNA-binding transcription factor binding 72
actin filament binding 55
DNA-binding transcription factor binding 86
nuclear receptor binding 41
ubiquitin-like protein ligase binding 69
0.0 2.5 5.0 7.5 10.0 12.5
log10(FDR)
-10 -5 0 5 10
log(ratio)
Respective GO-Term genes
Randomly detected genes
C
Blood
D
Biological Process
T cell activation 118
lymphocyte differentiation 99
mononuclear cell differentiation 104
leukocyte cell-cell adhesion 84
B cell activation 79
immune response-regulating cell surface receptor signaling pathway 66
immune response-regulating signaling pathway 91
regulation of cell-cell adhesion 92
activation of immune response 76
positive regulation of cell adhesion 92
Cellular Component
cytoplasmic side of plasma membrane 44
cytoplasmic side of membrane 45
endocytic vesicle 41
membrane microdomain 63
membrane raft 63
immunological synapse 16
ruffle 34
cytoplasmic ribonucleoprotein granule 44
MHC class II protein complex 9
P-body 23
Molecular Function
nucleoside-triphosphatase regulator activity 85
GTPase regulator activity 85
GTPase activator activity 83
non-membrane spanning protein tyrosine kinase activity 20
transcription coregulator activity 83
protein serine/threonine kinase activity 74
SH3 domain binding 32
guanyl-nucleotide exchange factor activity 43
protein phosphorylated amino acid binding 20
phosphoprotein binding 28
phosphotyrosine residue binding 17
0 5 10 15
log10(FDR)
-10 -5 0 5 10
log(ratio)
Respective GO-Term genes
Randomly detected genes


depleted
enriched
Biological Process
response to phenylalanine
cellular response to phenylalanine
membrane disruption in other organism
cellular response to forskolin
response to forskolin
phagocytosis, recognition
positive regulation of peptidyl-serine phosphorylation of STAT protein
cellular response to amino acid stimulus
innate immune response in mucosa
cellular response to leukemia inhibitory factor
negative regulation of organelle organization
regulation of protein catabolic process
cell-substrate adhesion
Ras protein signal transduction
dendrite development
regulation of GTPase activity
protein localization to plasma membrane
non-membrane-bounded organelle assembly
regulation of response to biotic stimulus
meiotic cell cycle
25/25
25/25
28/31
52/69
52/69
65/106
24/31
110/194
37/55
179/311
29/452
37/495
32/464
23/426
19/399
23/415
17/399
36/483
26/432
22/487
Cellular Component
RNAi effector complex
RISC complex
immunoglobulin complex
immunoglobulin complex, circulating
hemoglobin complex
nucleosome
haptoglobin-hemoglobin complex
membrane microdomain
membrane raft
spindle
cell projection membrane
apical plasma membrane
chromosomal region
distal axon
extrinsic component of membrane
neuron to neuron synapse
condensed chromosome
94/126
94/126
74/98
65/80
9/20
45/68
9/16
27/489
27/488
16/456
14/374
31/482
17/493
36/438
20/411
33/498
15/431
Molecular Function
bitter taste receptor activity
immunoglobulin receptor binding
type I interferon receptor binding
taste receptor activity
antigen binding
trace-amine receptor activity
haptoglobin binding
oxygen carrier activity
molecular adaptor activity
GTPase binding
microtubule binding
small GTPase binding
cell adhesion molecule binding
phosphatidylinositol binding
guanyl ribonucleotide binding
guanyl nucleotide binding
protein-macromolecule adaptor activity
ubiquitin-like protein ligase activity
33/55
64/83
23/27
34/79
104/195
14/22
9/15
10/14
28/471
14/339
8/386
12/300
17/377
13/353
44/470
44/479
25/380
30/456
-85
-80
-75
-70
-65
-60
-5
0
5
10
log10(FDR)