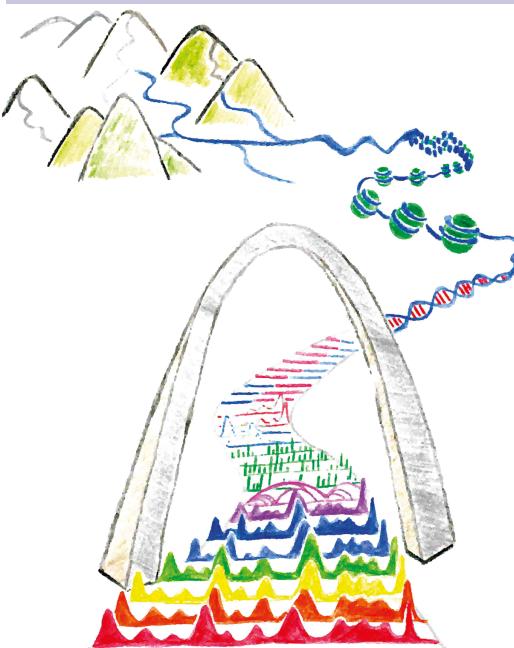


系统生物学与生物信息学
海外学者短期讲学系列课程

Current Topics in Epigenomics

表观基因组学前沿



Ting Wang
Department of Genetics
Center for Genome Sciences and Systems Biology
Washington University School of Medicine

Tsinghua University
April 15-27

The dark side of the genome: transposable elements

Outline

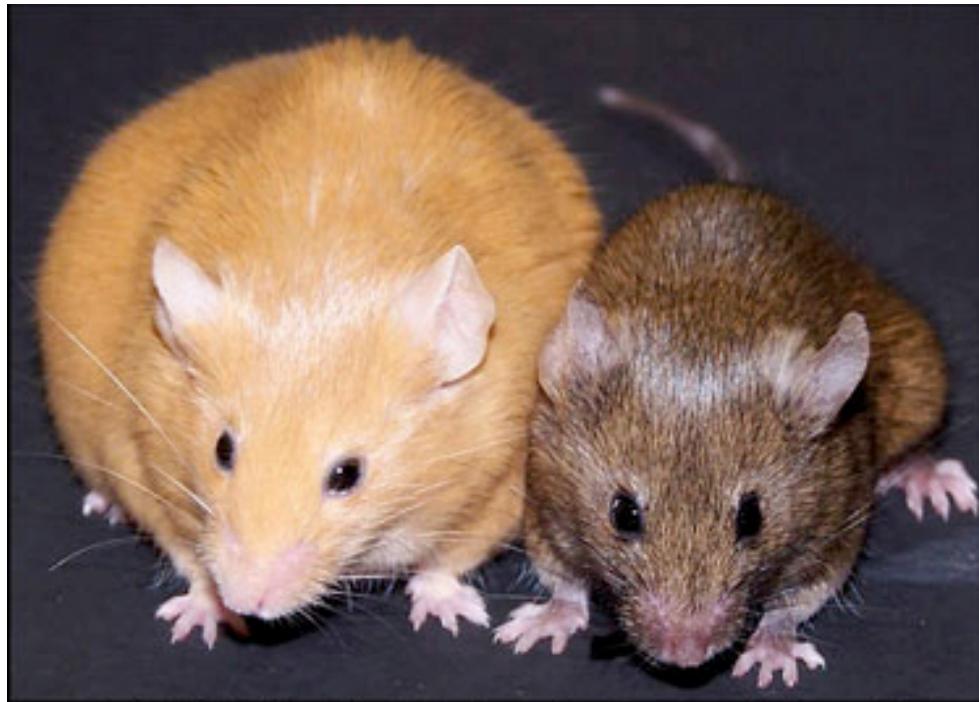
- Transposable element phenomenon
 - Pretty petunia
 - A tale of two mice
- What are transposable elements?
- Classification and mechanisms of transposition
- Transposable elements and genome evolution
- Transposable elements and biotechnology

The pretty petunia



- Why white and pink?
- Why pink stripes “pie-shaped”?
- The gene – *rt*
 - produce anthocyanin pigments
- The transposon –
dTph1
 - disrupt the *rt* locus, but get reversed from time to time

A tale of two mice



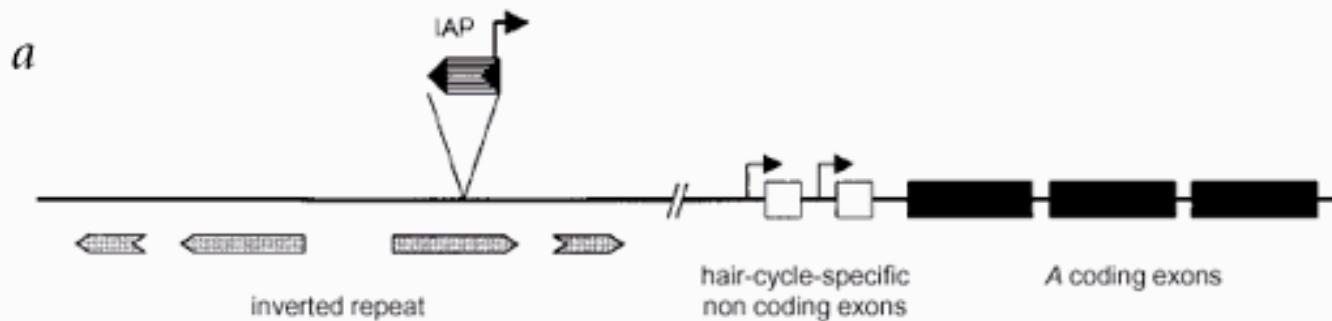
Yellow mouse

- High risk of cancer, diabetes, obesity;
- Reduced lifespan

Agouti mouse

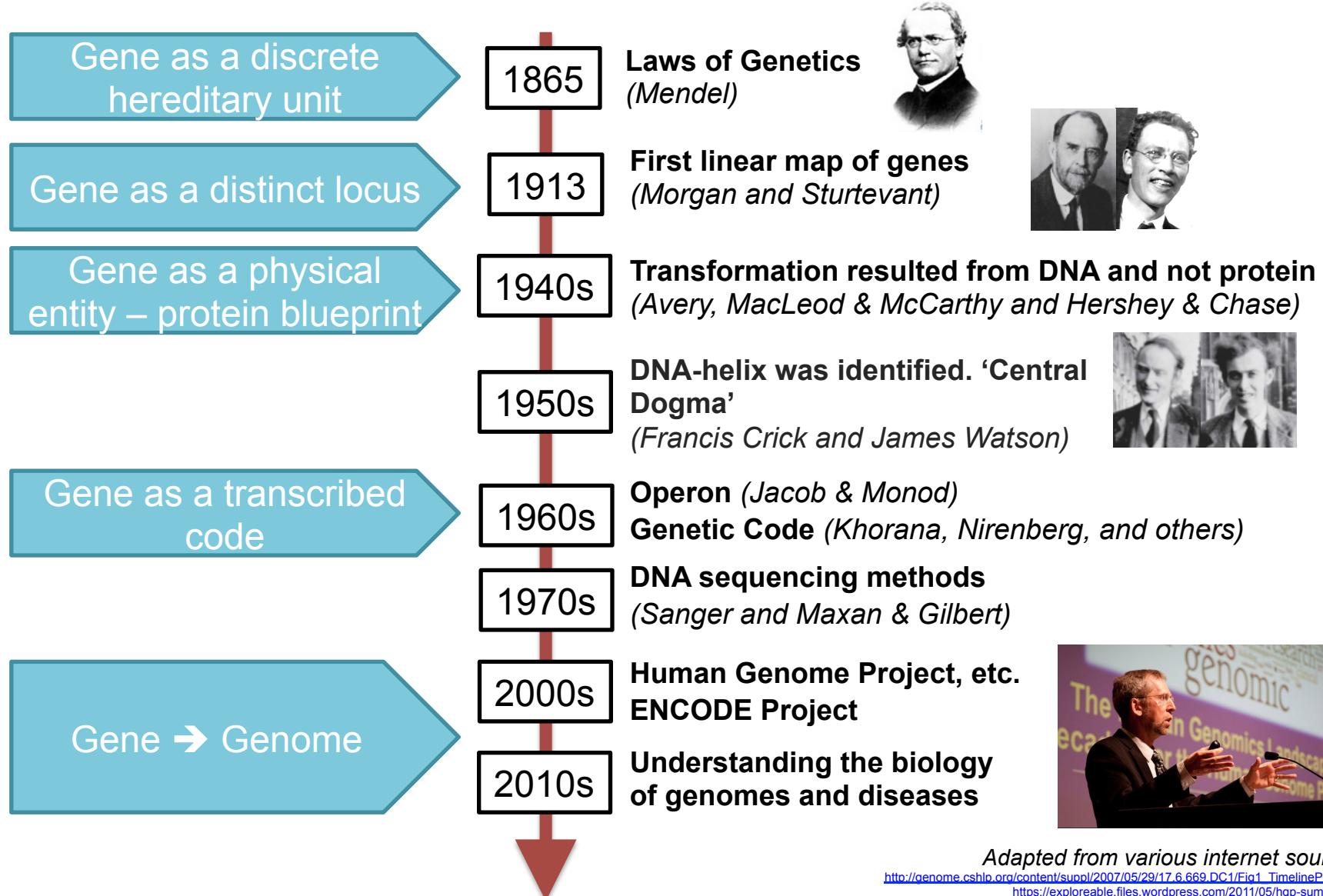
- Low risk of cancer, diabetes, obesity;
- Prolonged lifespan

Maternal supplements
with Zinc, methionine,
betaine, choline, folate,
 B_{12}

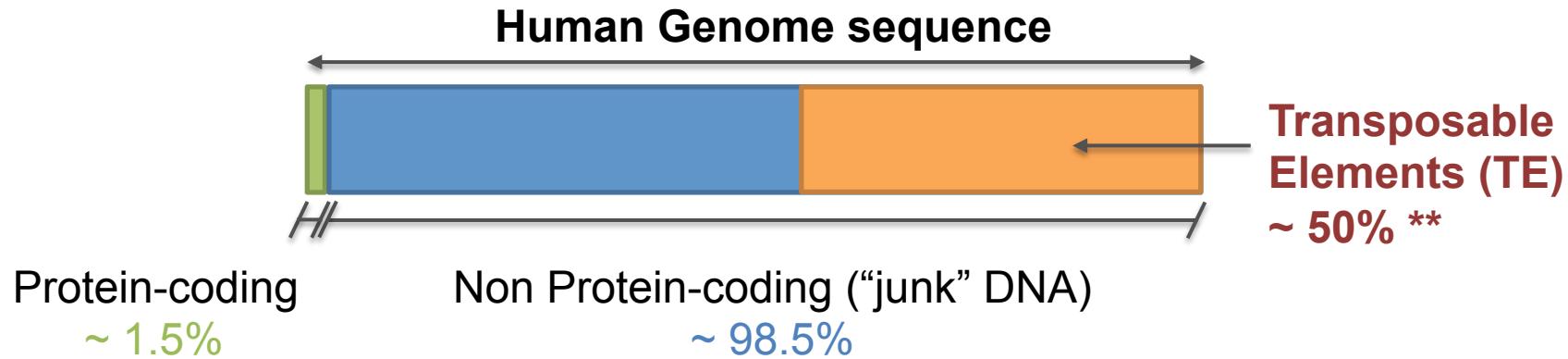


Morgan, Whitelaw,
1999
Waterland, Jirtle,
2004

The evolving concept of biology – from gene to genome



Transposable elements comprise at least half of the human genome



- TEs are **mobile genetic elements** that are inherently (i) capable of jumping to different genomic locations, and therefore (ii) are repetitive in nature.
- *** Some computational algorithms suggest that up to 70% of the human genome can be TE sequences*

**What are transposable
elements?**

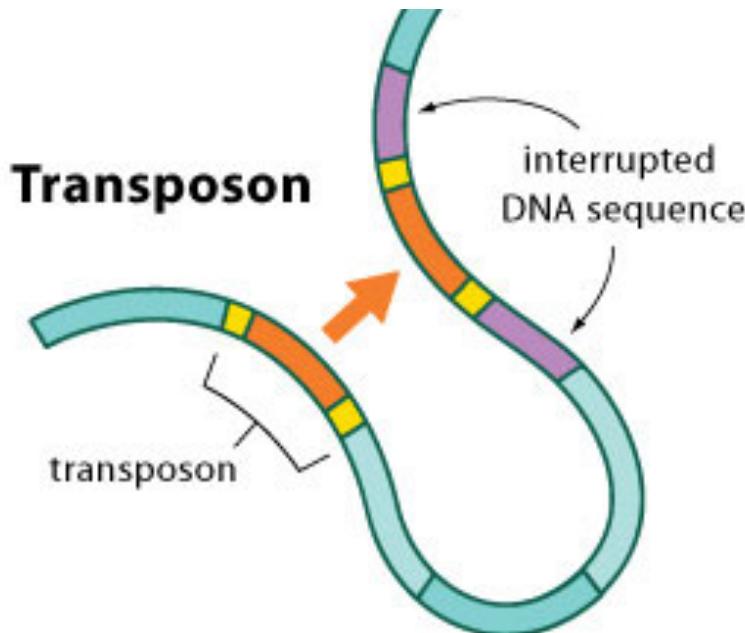
Transposable genetic elements

A transposable element is a bit of DNA that can move from place to place in an organism's genome. It is excised or copied from one site and inserted at another site.

The movement of a transposable element can generate mutations or chromosomal rearrangements and thus affect genomic architecture and expression of other genes.

-- modified from Federoff, N. 1984

Transposable Elements (TEs)



- “Jumping genes”
- Mobile genetic elements
- Controlling elements
- Transposons

Transposable elements

- “mobile genetic elements”
- comprise 45% of human chromosomal DNA
“repetitive DNA”
- contribute to spontaneous mutation, genetic rearrangements, horizontal transfer of genetic material
- aid speciation and genomic change (in bacteria transposons are often associated with antibiotic resistance genes)
- cells must depress transposition to insure genetic stability

Mobile elements

- Transposons
- Plasmid
- Bacteria phage elements
- Group II introns

Transposable elements

- Retrotransposons
- DNA transposons
- Insertion sequences

- DNA vs. RNA
- viral vs. nonviral
- replicative mechanism vs. excision mechanism

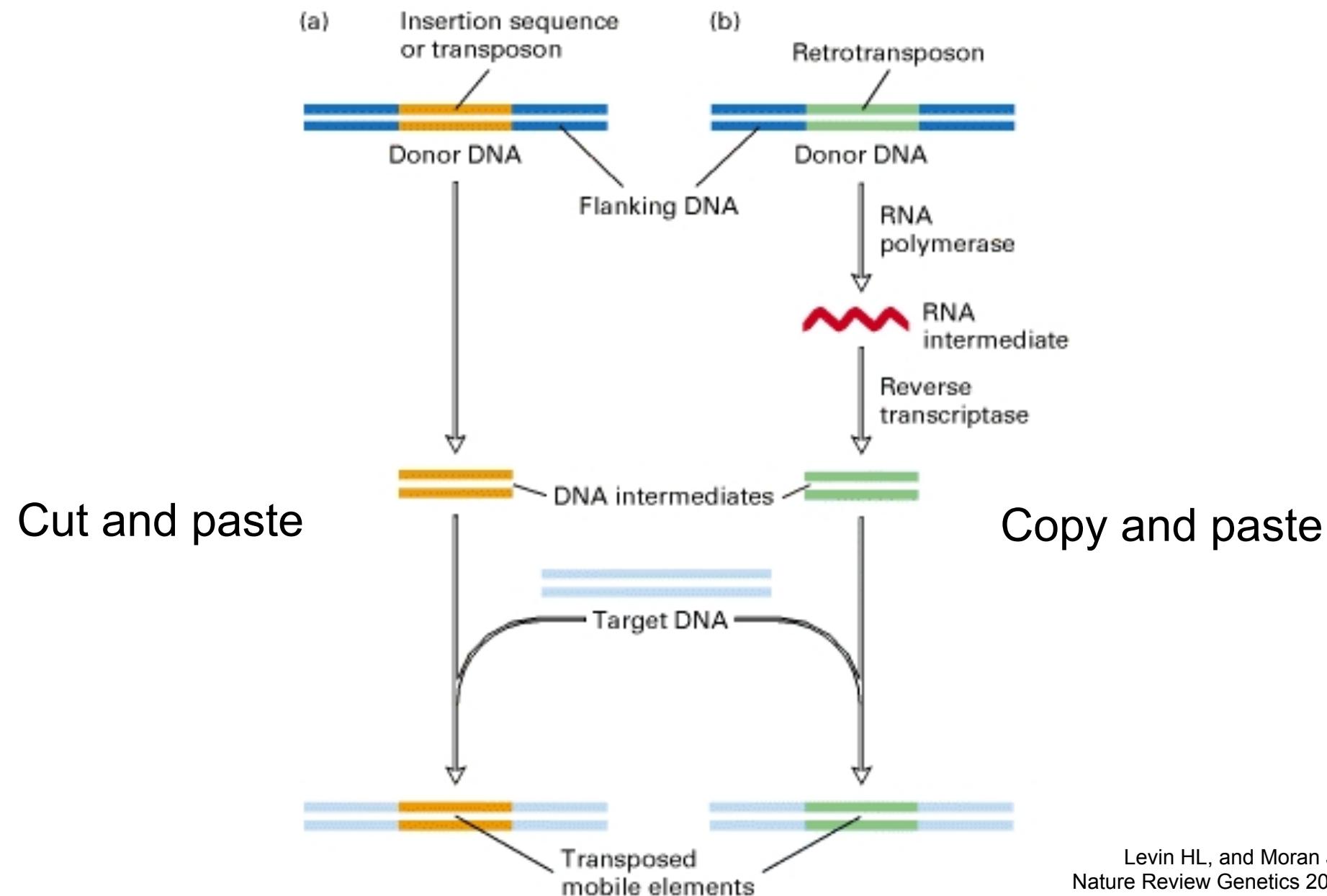
Discovery of transposons

- Barbara McClintock 1950's Ac Ds system in maize influencing kernel color
unstable elements
changing map position
promote chromosomal breaks



Classification and Mechanisms of Transposition

Classification of TEs



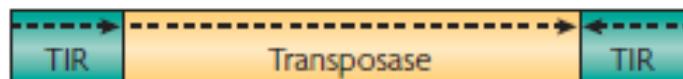
Classification of TEs

Type I — Retrotransposons



Type II — DNA transposons

Autonomous



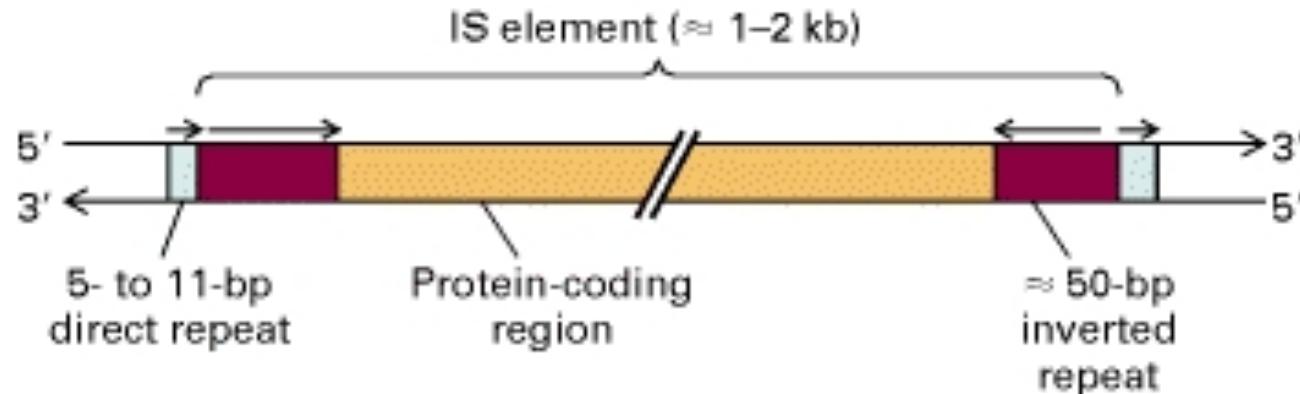
Non-autonomous



- Type I: copy-and-paste
 - Eukaryotes only

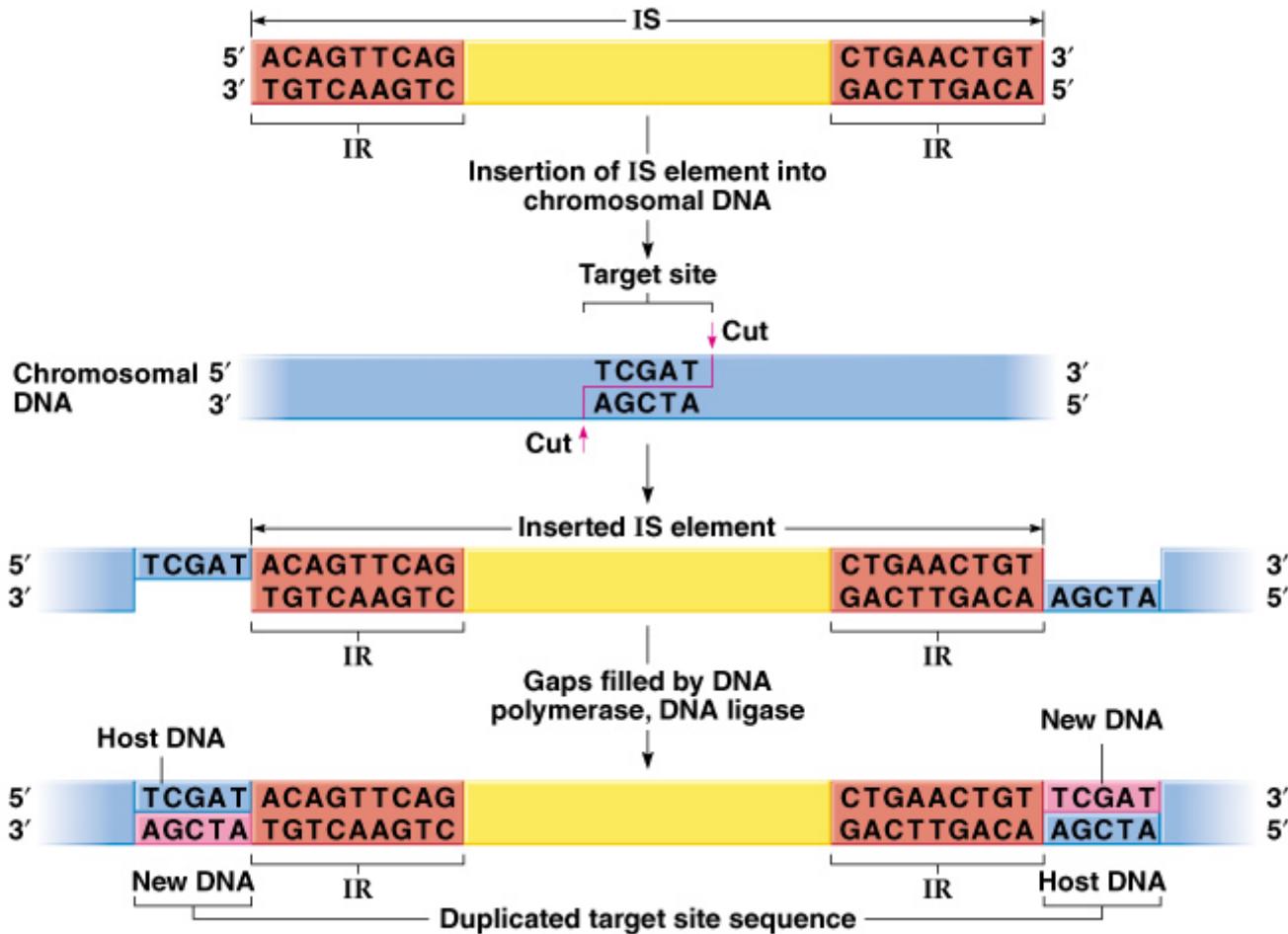
- Type II: cut-and-paste
 - Prokaryotes and eukaryotes

Bacterial transposons: IS elements



- Insertion sequences (IS elements)
- The simplest bacterial transposons
- Inverted terminal repeats
- Transposase from protein-coding region

IS elements



- Cut-and-paste transposon
- Target site duplication

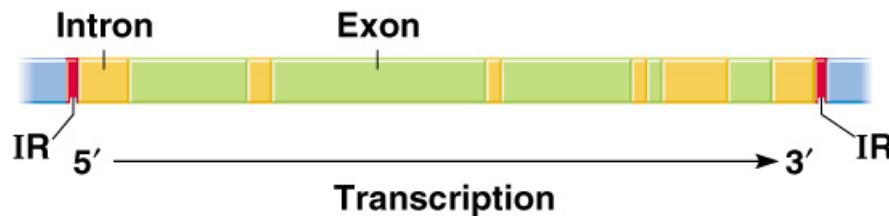
Ac and *Ds* elements in maize

- First TEs discovered in 1950s
 - Pioneering work of Barbara McClintock
- Striping and spotting of maize kernels
 - TE activities are responsible for the colorful pattern of maize kernels.

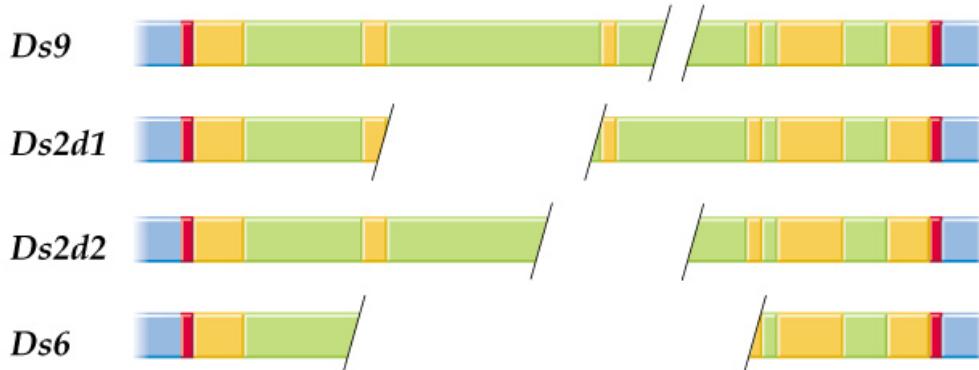


Ac and *Ds* elements in maize

a) Activator element (*Ac*)



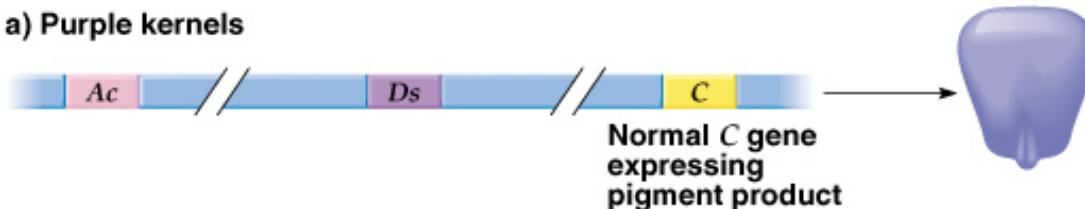
b) Dissociation elements (*Ds*)



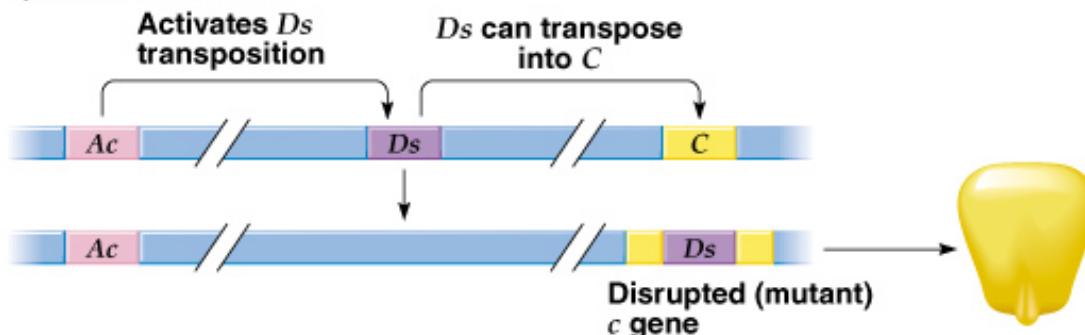
- *Ac*: activator
 - Autonomous element (cut-and-paste transposon)
- *Ds*: dissociation
 - Non-autonomous element
 - Causes chromosomal breakage

Transposon effect on kernel color

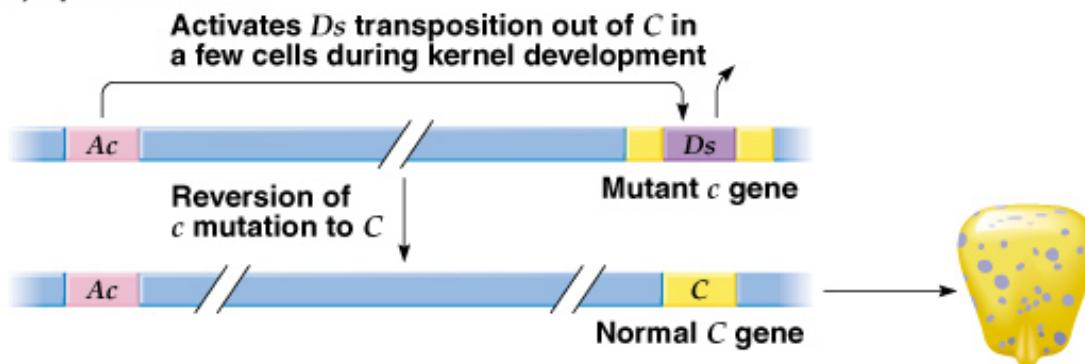
a) Purple kernels



b) Colorless kernels



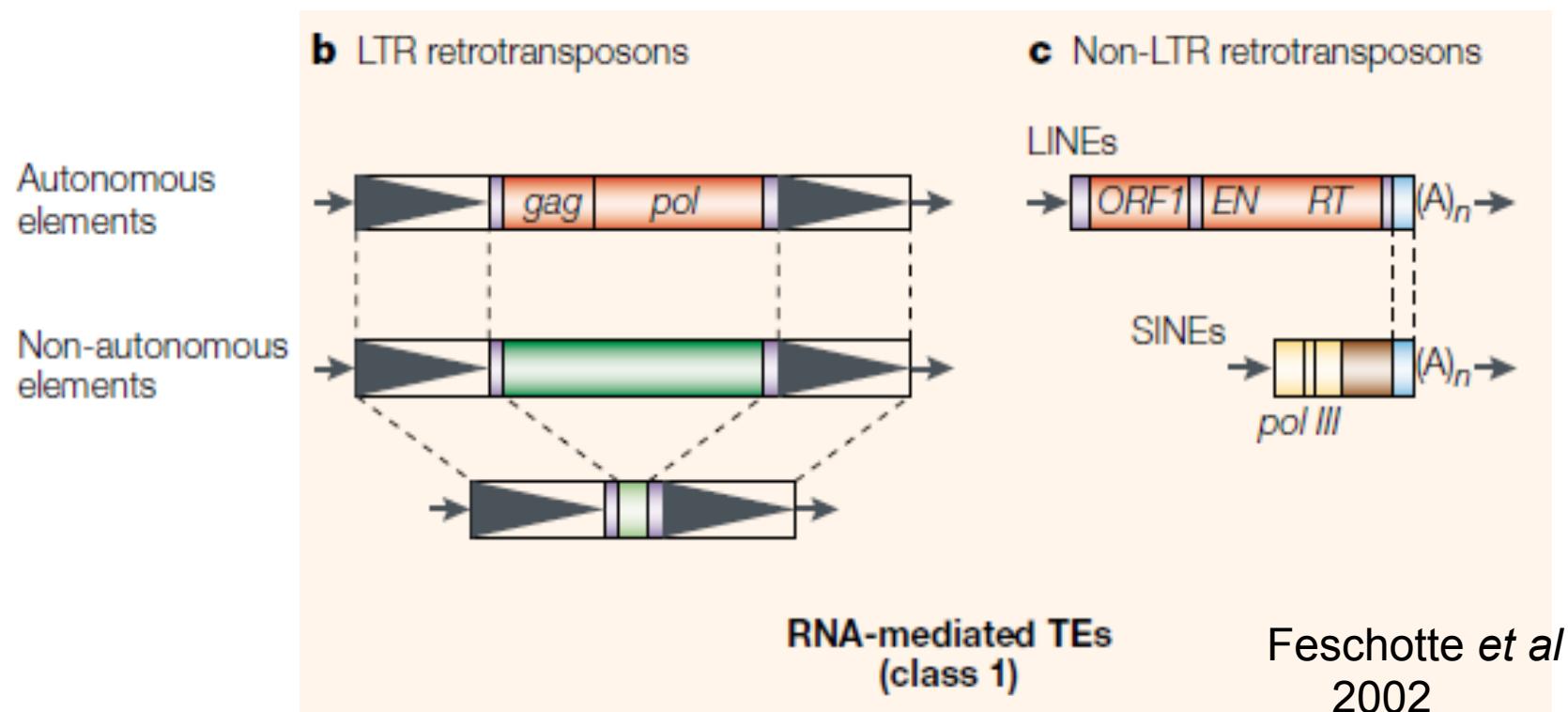
c) Spotted kernels



Other eukaryotic DNA transposons

- *P* elements in *Drosophila melanogaster*
 - P transposase and terminal inverted repeats
- *Mariner* transposon
 - An ancient and widespread transposon
 - Horizontal transfer between species

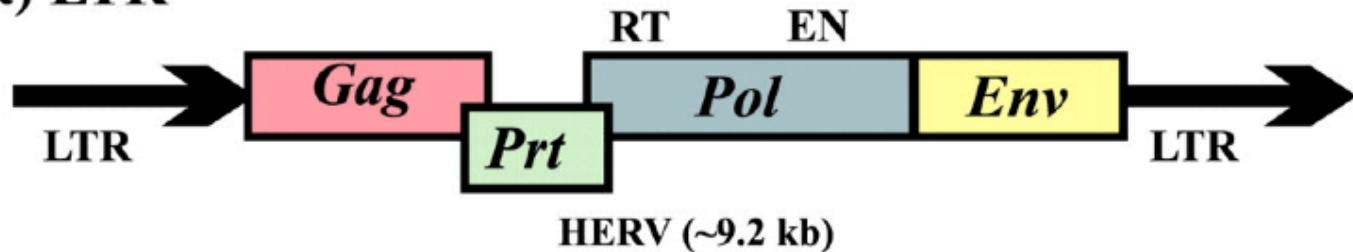
Eukaryotic retrotransposons



- All eukaryotes contain retrotransposons.
 - LTR retrotransposons: abundant in yeast and flies
 - Non-LTR: most common type in mammals

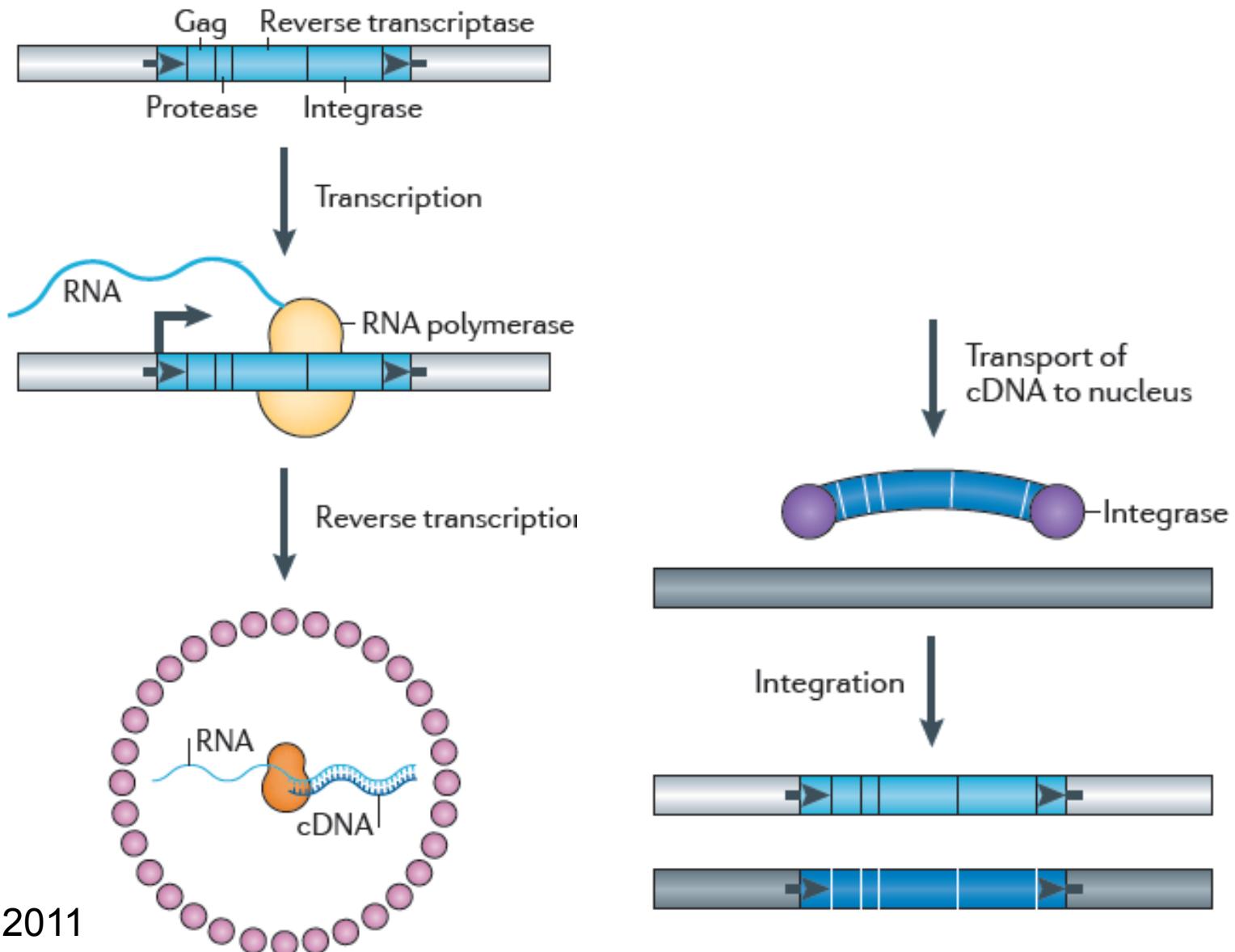
Class I LTR retrotransposon

a) LTR



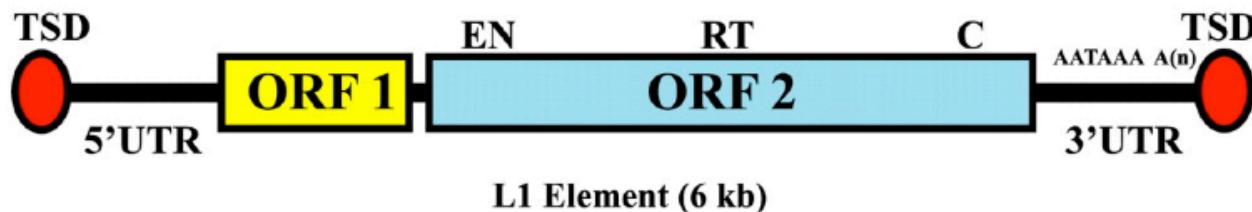
- LTR (long terminal repeats): required for replication cycle
- Genes: *gag* and *pol* (viruses have *env*)
- Pol (polyprotein): RT, IN, RH and PR1

Class I LTR retrotransposon

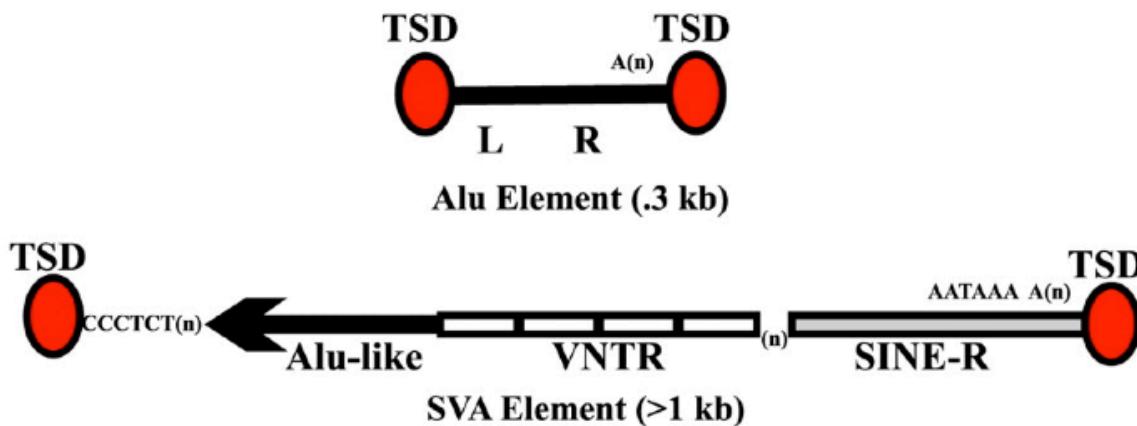


Class I non-LTR retrotransposon

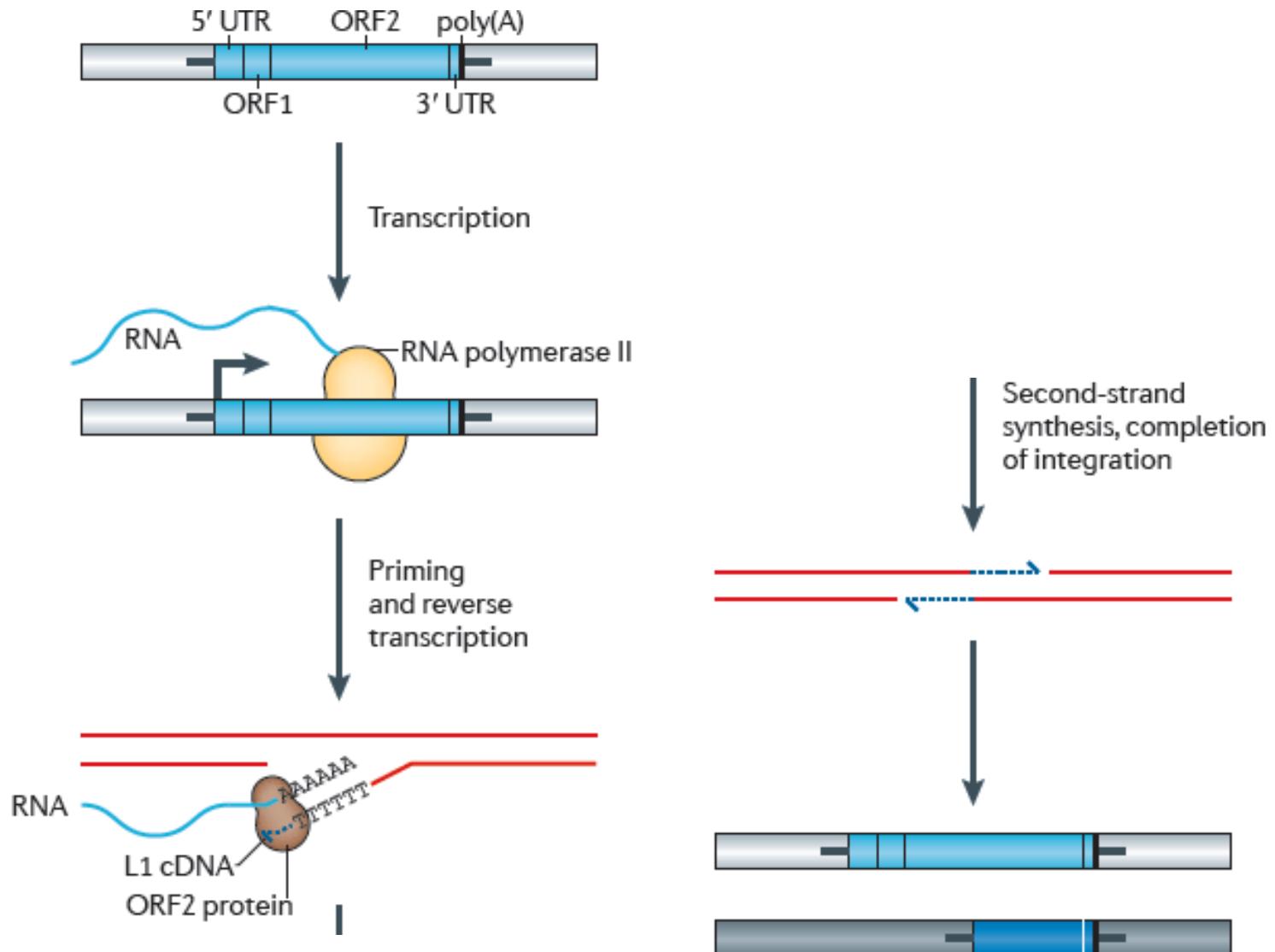
-Autonomous



-Non-Autonomous

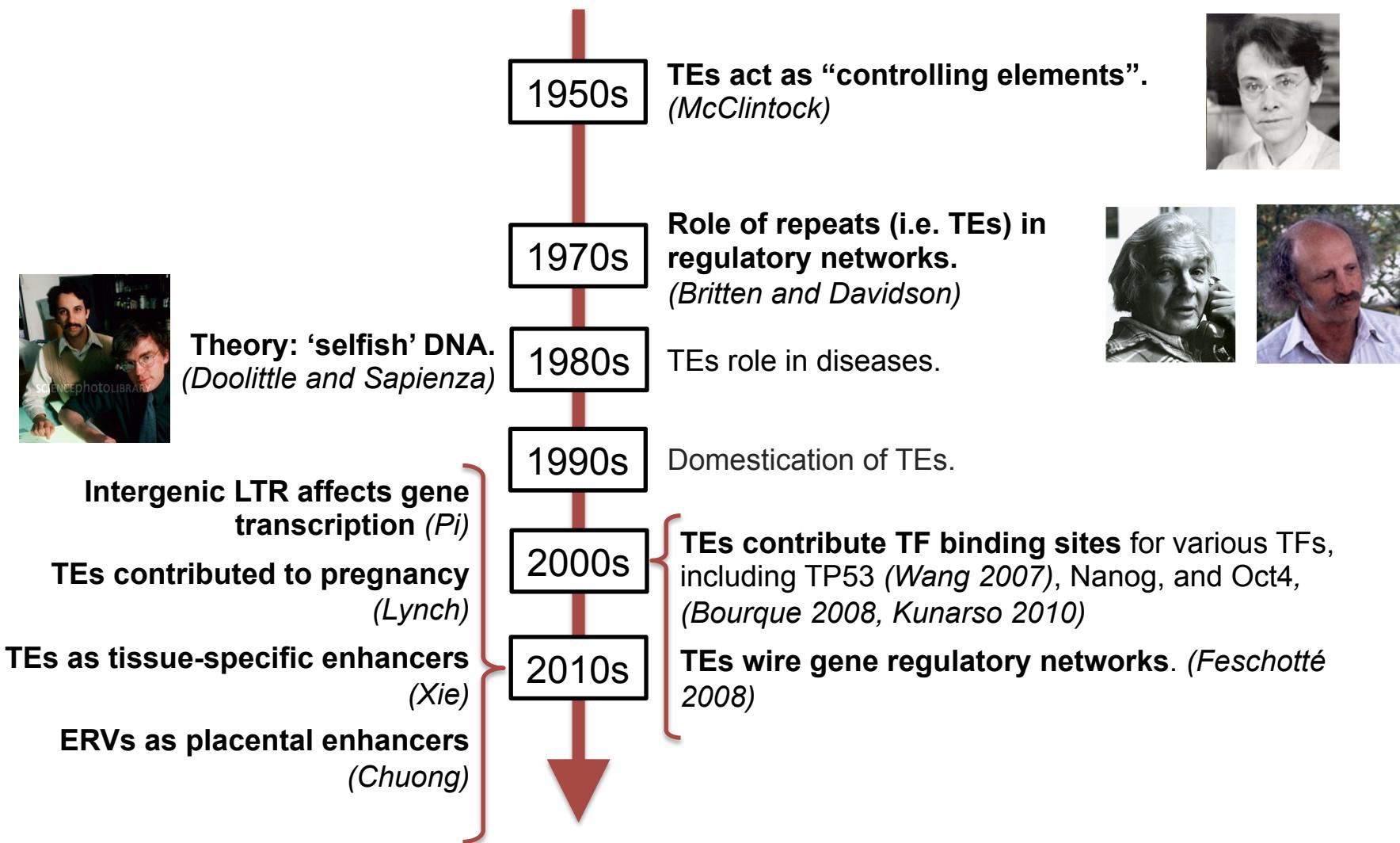


Class I non-LTR retrotransposon



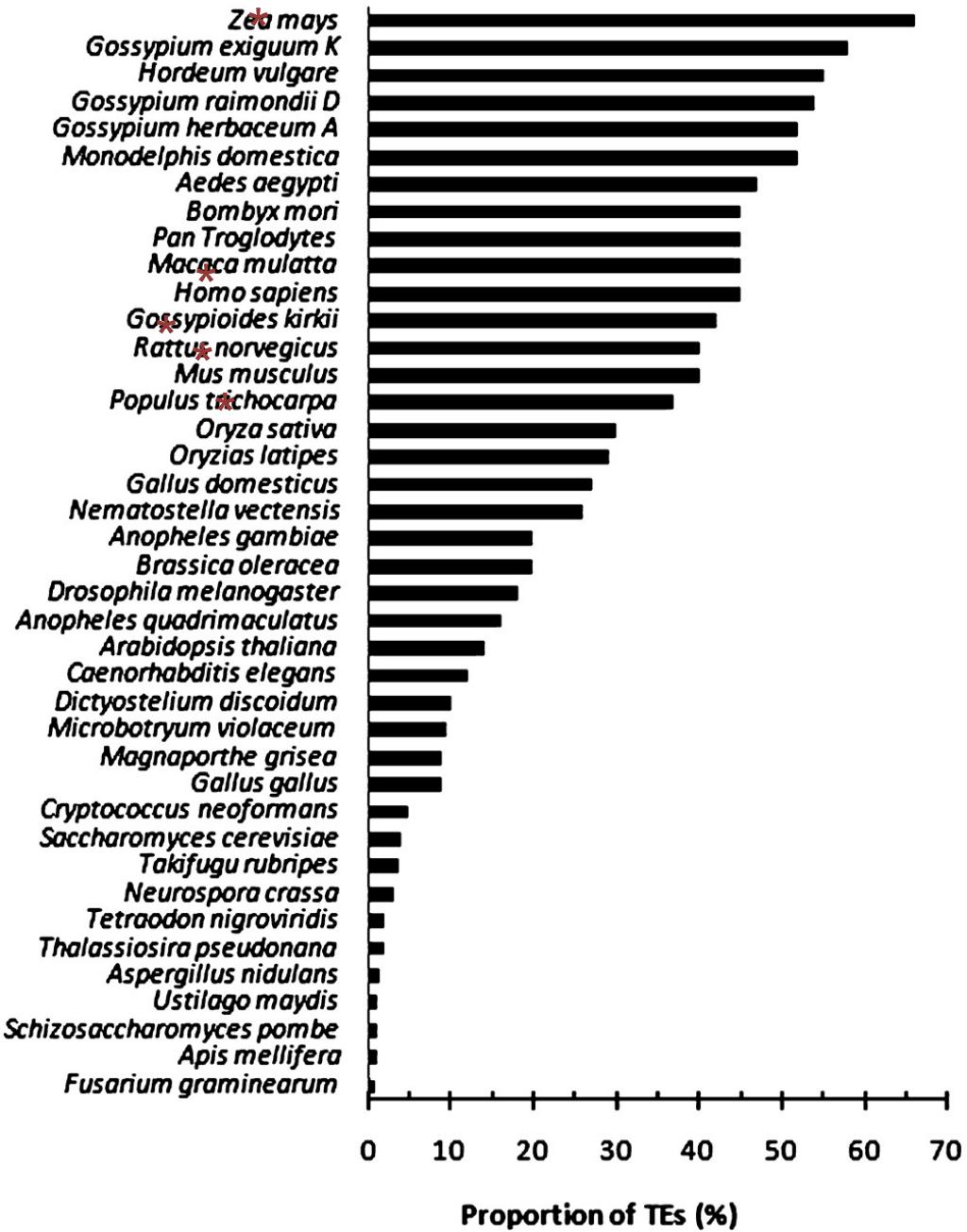
Transposable Elements and Genome Evolution

Since 2000s: ‘TEs can control gene expression’



Adapted from a Figure 1 in Rebollo et al.,
Annu. Rev. Genetics. 2012. 46:21-42

TEs are widespread and represent a range of fractions of eukaryotic genomes' sequence



TEs are prominent components of genomes

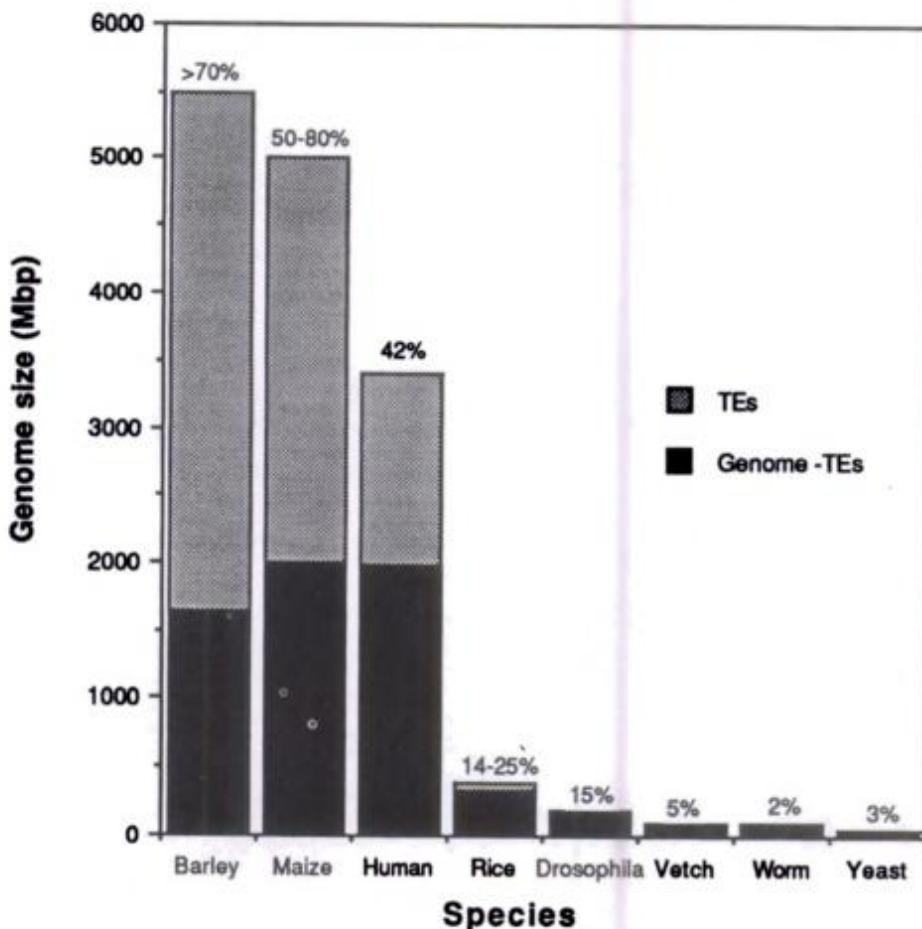


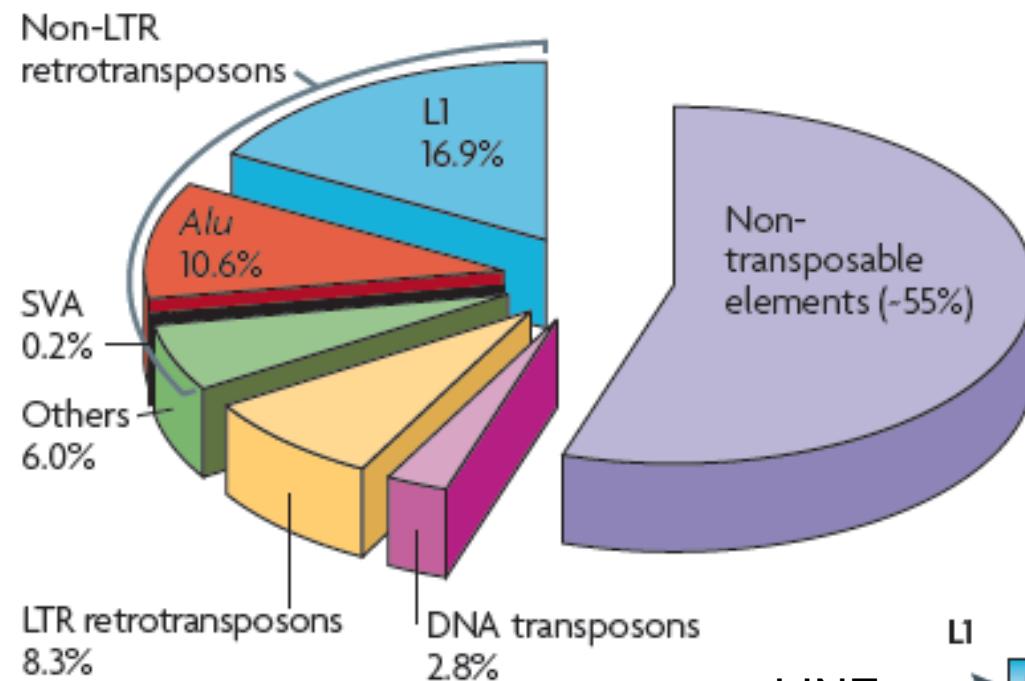
Table 1 | Genome size and transposable elements

	Genome size (picograms)	% TEs
<i>Rana esculenta</i>	5.6-8.0	77
<i>Zea mays</i>	5.0	60
<i>Homo sapiens</i>	3.5	45
<i>Mus musculus</i>	3.4	40
<i>Drosophila melanogaster</i>	0.18	15-22
<i>Caenorhabditis elegans</i>	0.1	12
<i>Saccharomyces cerevisiae</i>	0.012	3-5
<i>Escherichia coli</i>	0.0046	0.3

Biemeont et al 2006

Kidwell et al 2002

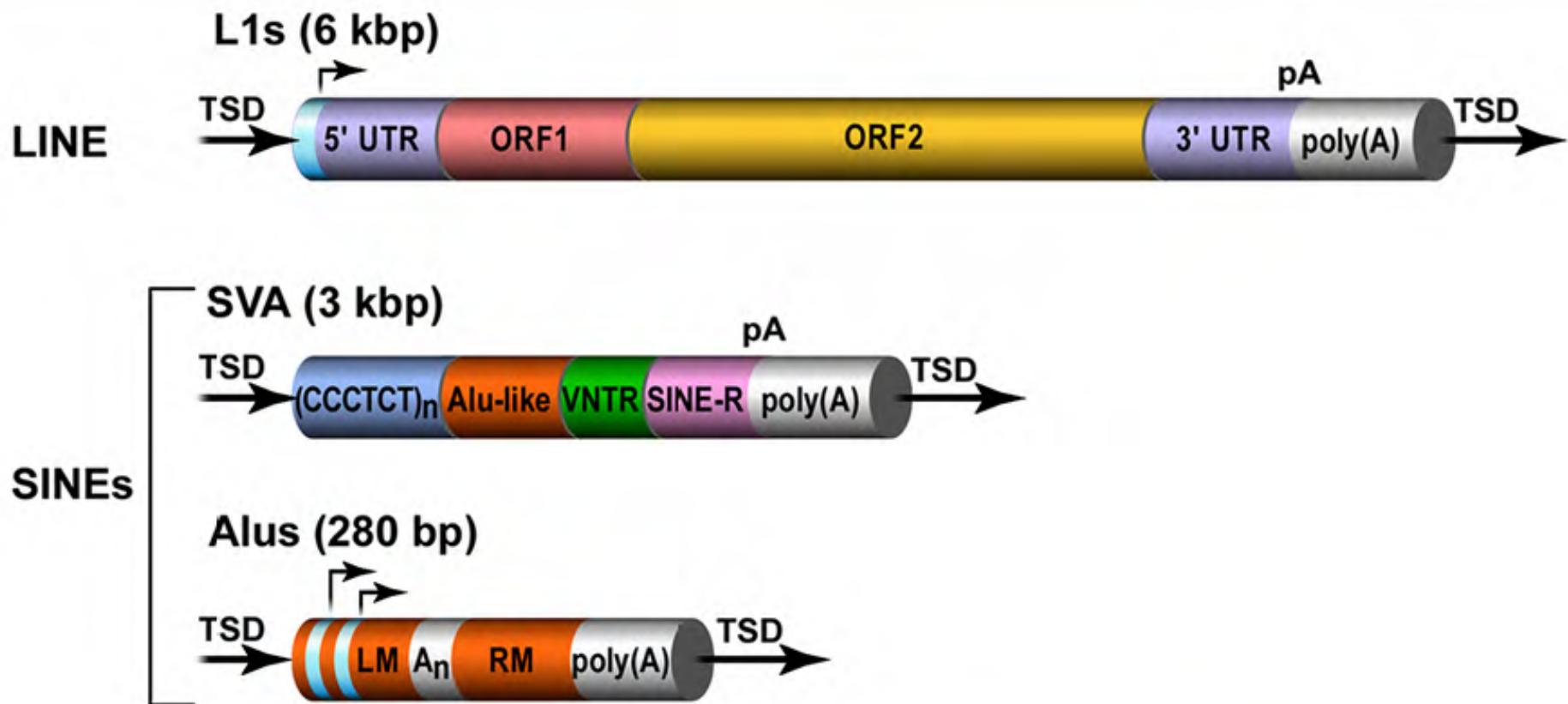
Transposable elements in human



Cordaux et al 2009

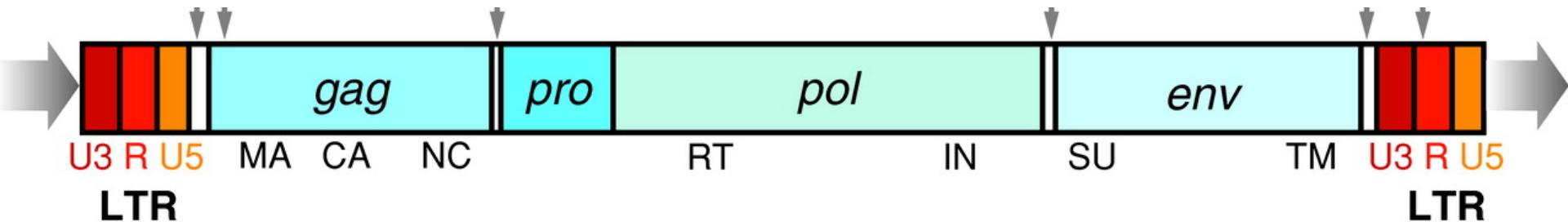


LINEs and SINEs in human

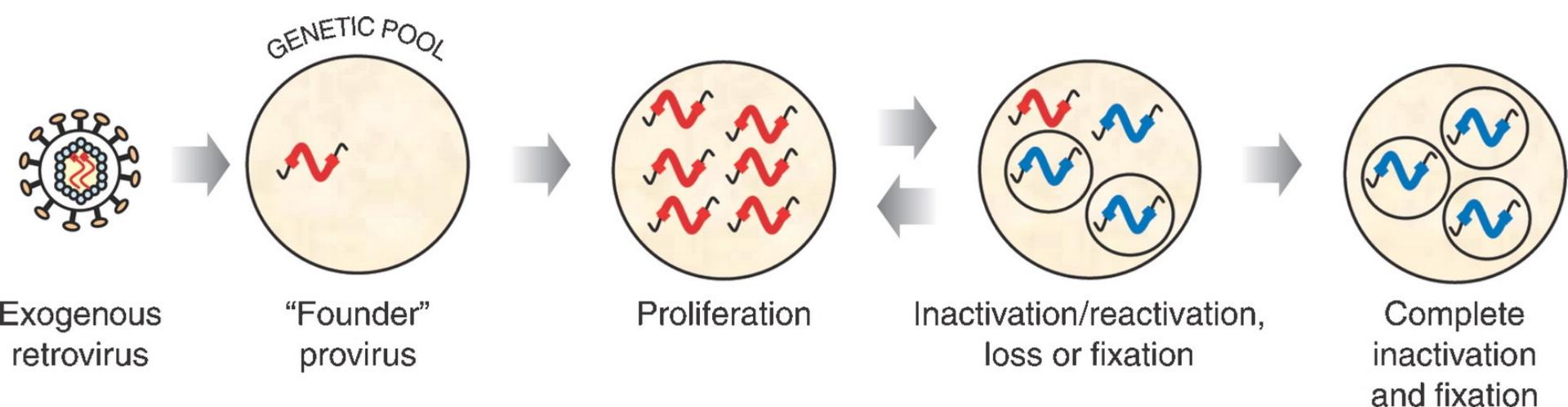


Singer *et al* 2010

Structure of a Retrovirus

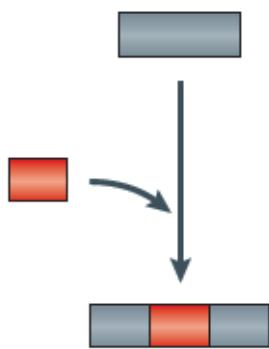


Establishment of an Endogenous Retrovirus Lineage

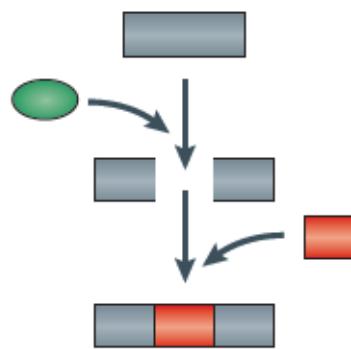


Impact of TEs on human genome structure

a Insertional mutagenesis



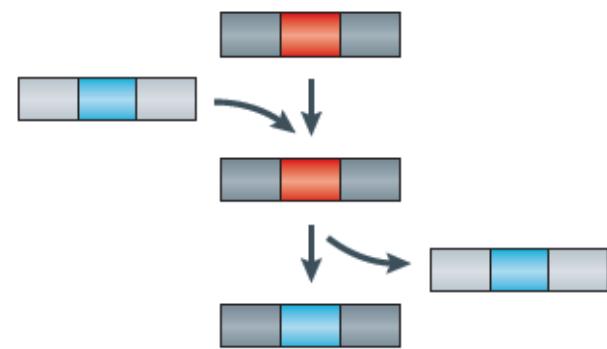
b Creating and repairing DNA double-strand breaks



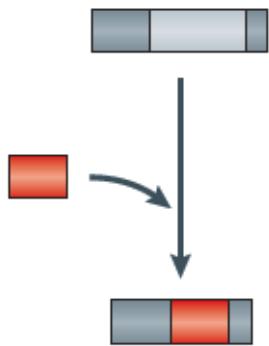
c Microsatellite seeding



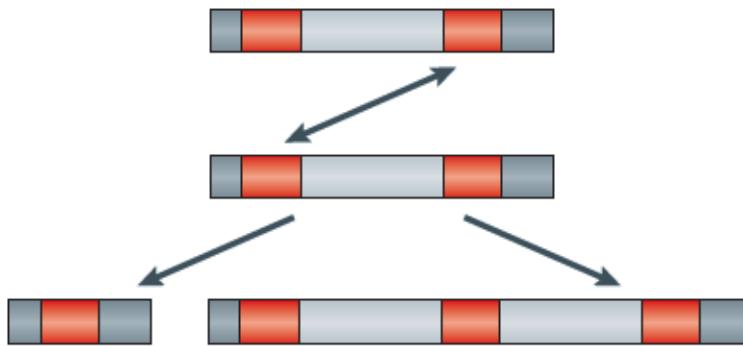
d Gene conversion



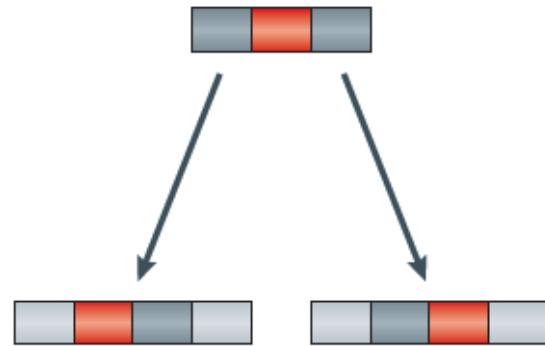
e Insertion-mediated deletions



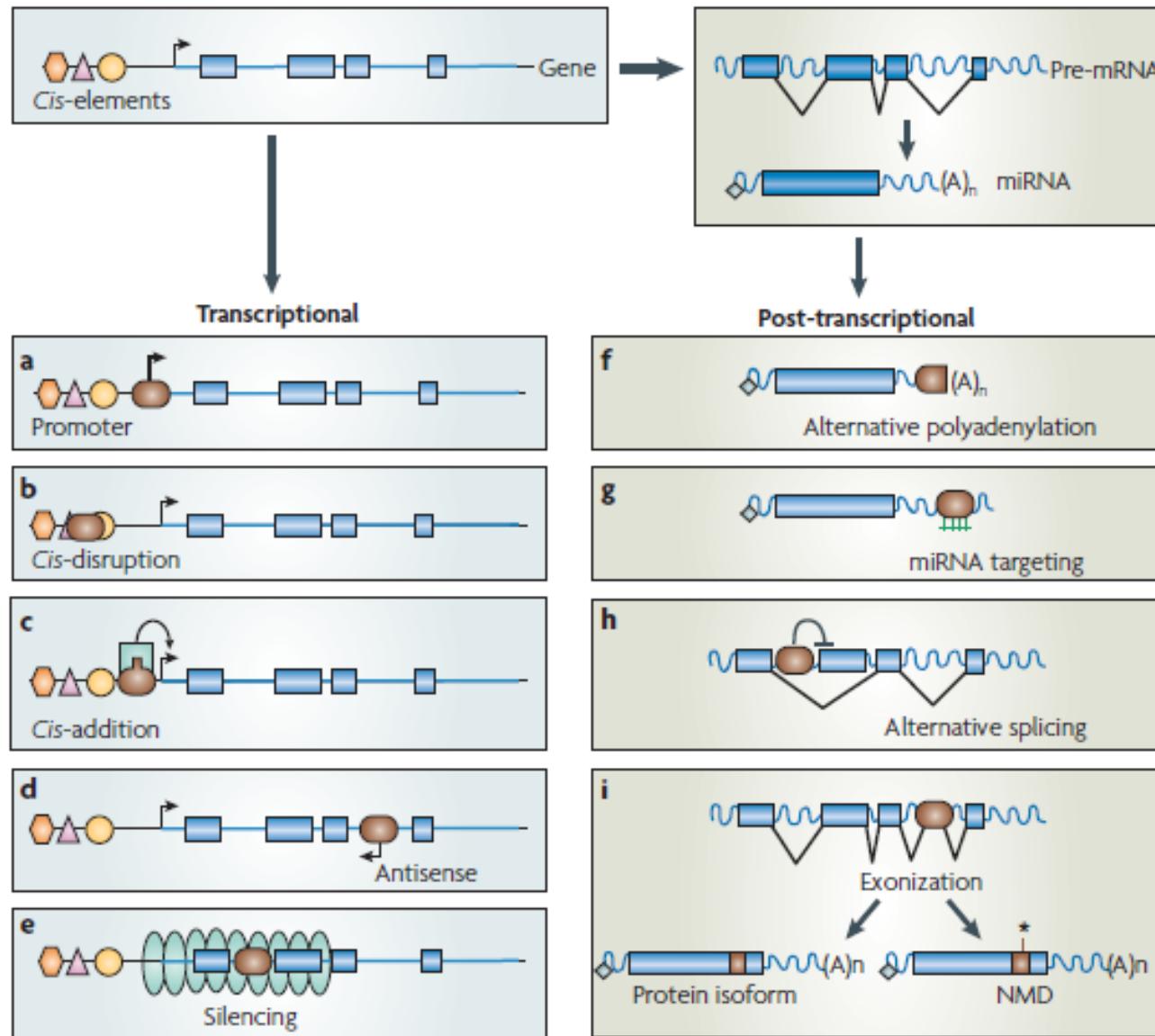
f Ectopic recombination



g Transduction

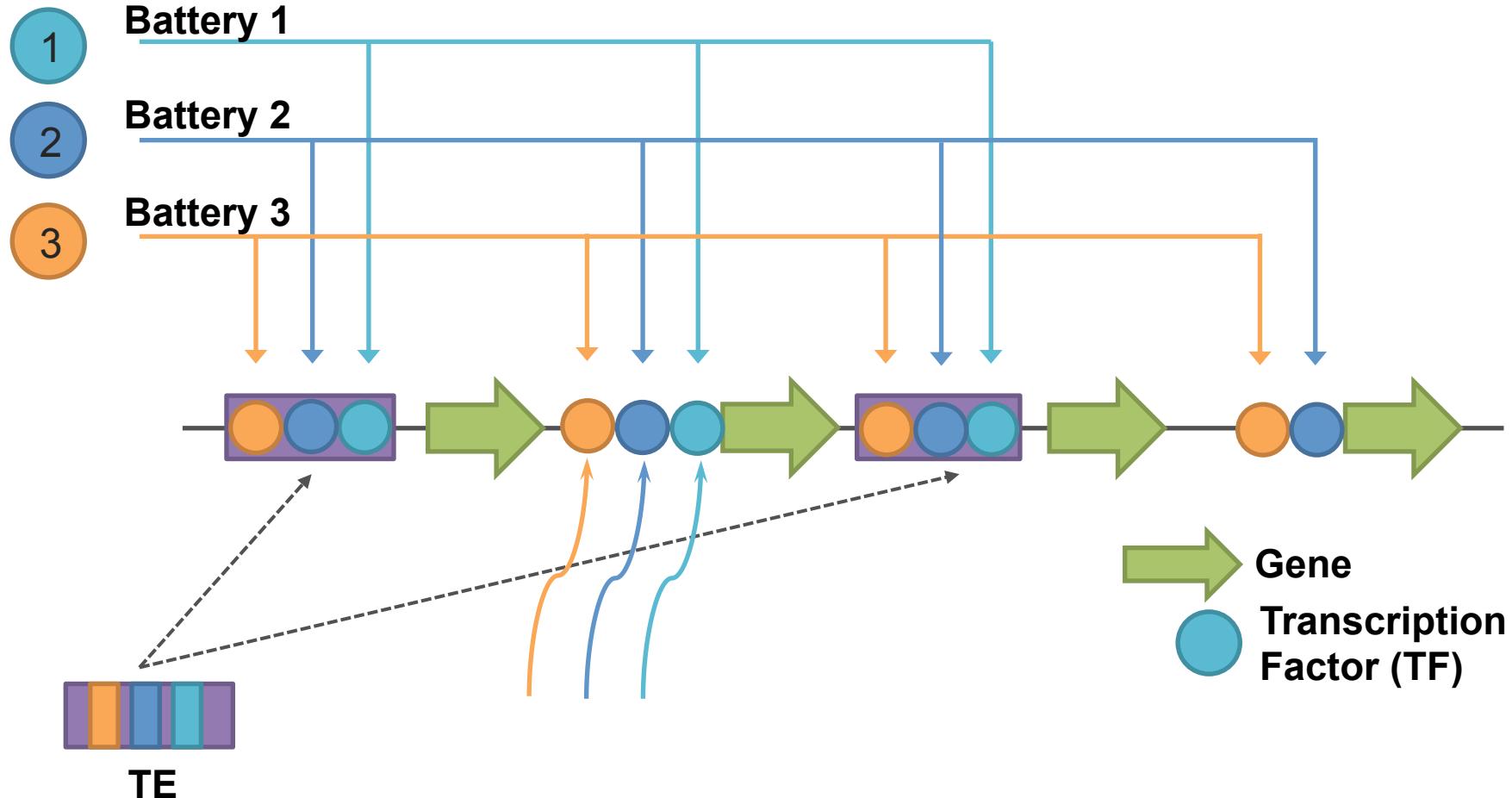


Influence of TEs on gene expression



Feschotte 2008

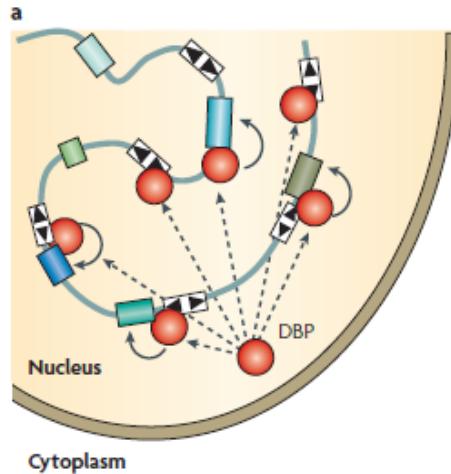
1970s: Hypothesizing TEs' role in gene regulatory networks



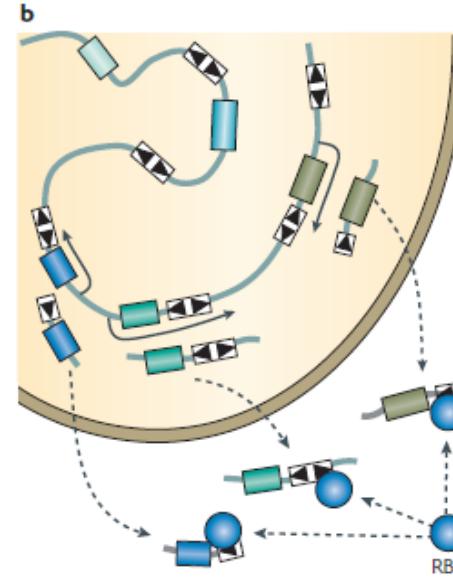
Adapted from C Feschotte *Nature Review Genetics* (2008).
AND <http://www.biology-assignment.com/gene-regulation-in-eukaryotes>

TE wiring of genetic networks

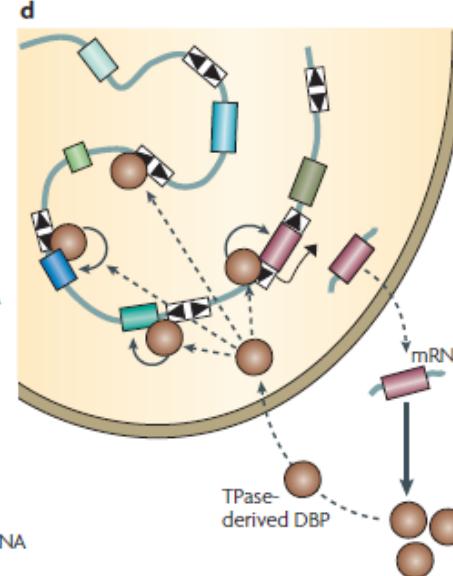
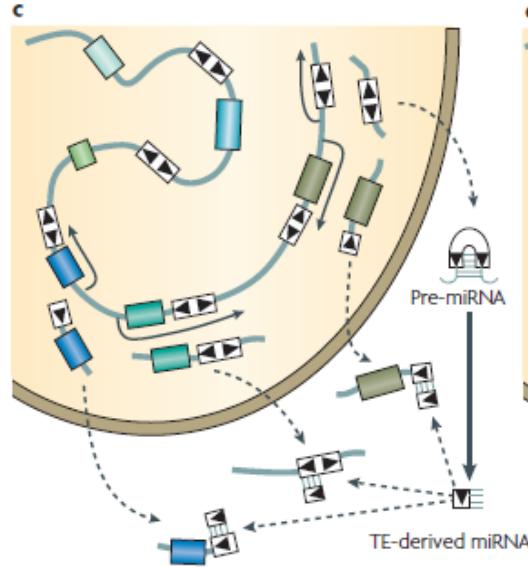
Transcriptional regulatory network



De novo assembly of miRNA network



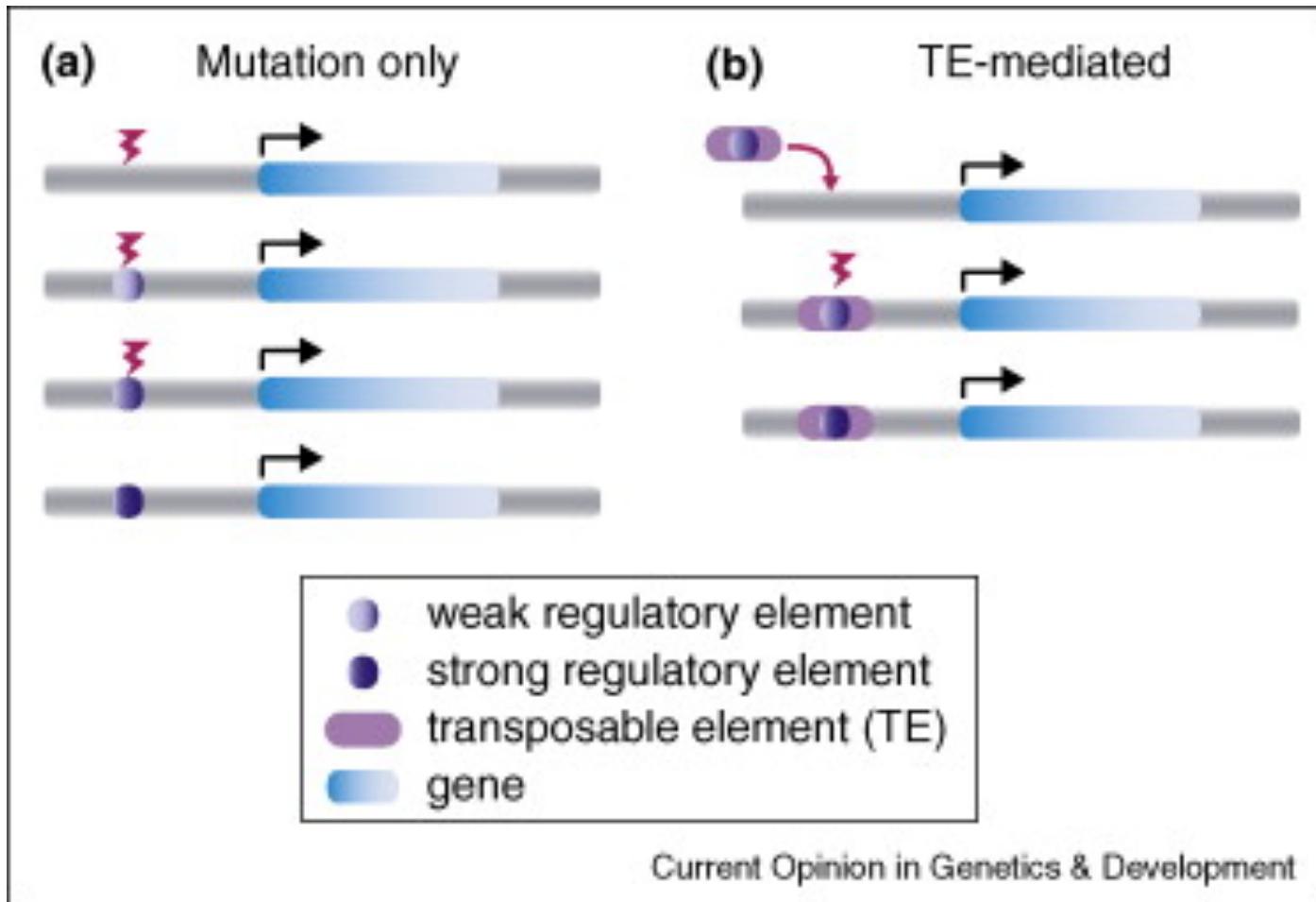
Post-Transcriptional regulatory network



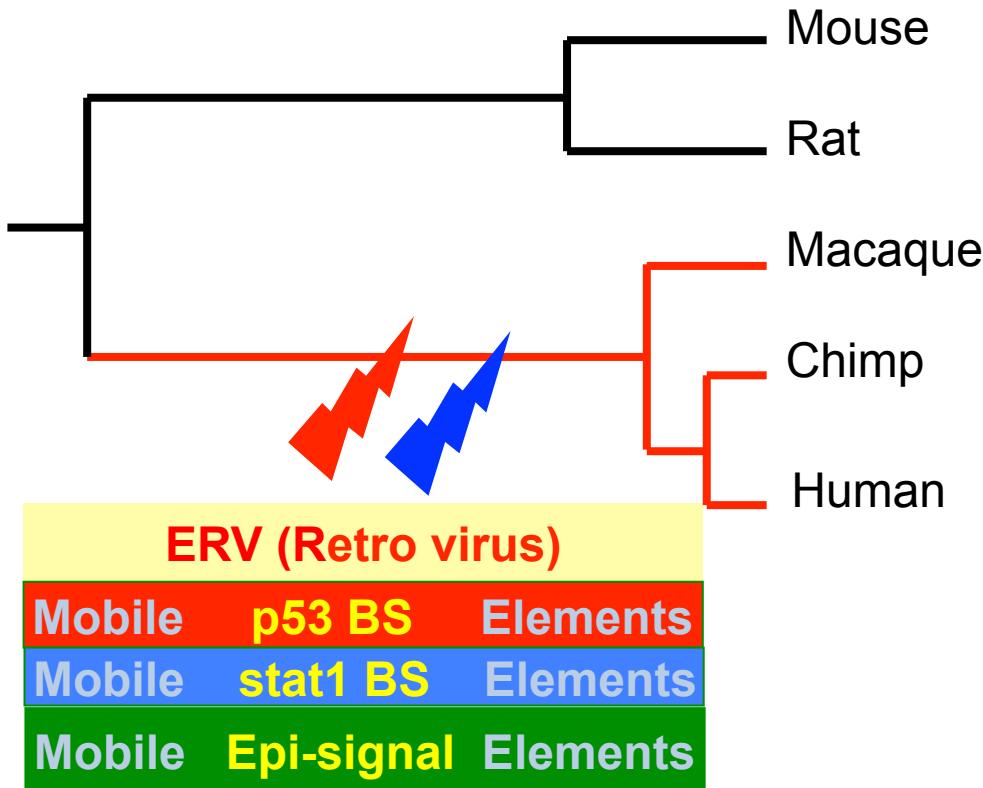
De novo assembly of cis and trans components of a transcriptional regulatory network

Feschotte 2008

TEs can be the source of new regulatory elements

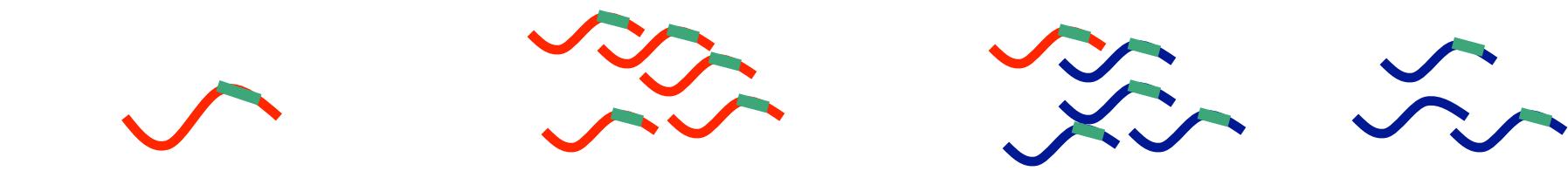
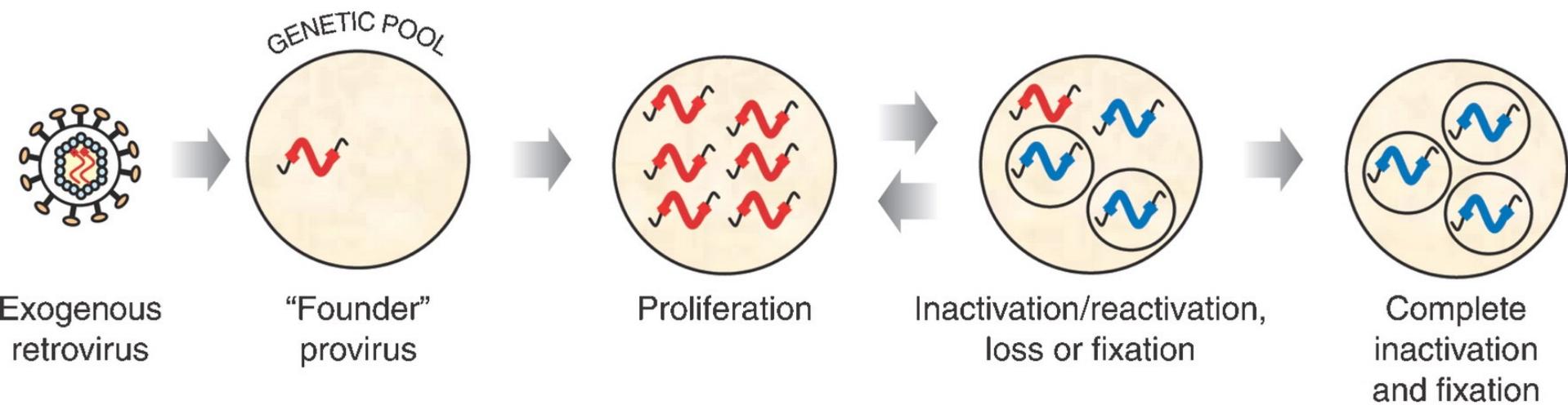


Transposable Elements Shape Regulatory Networks



- ERV insertions account for >30% of human p53 binding sites
- Transposable element dispersion created other master regulators:
Stat1, CTCF, Esr1, Oct4-Sox2

Interaction between ERV and p53 network



Gain of TF binding site

Spreading of sites

Selection

Fixation

Point mutations are responsible for creating new p53 DBS/targets

An ERV/LTR gains p53 binding sites

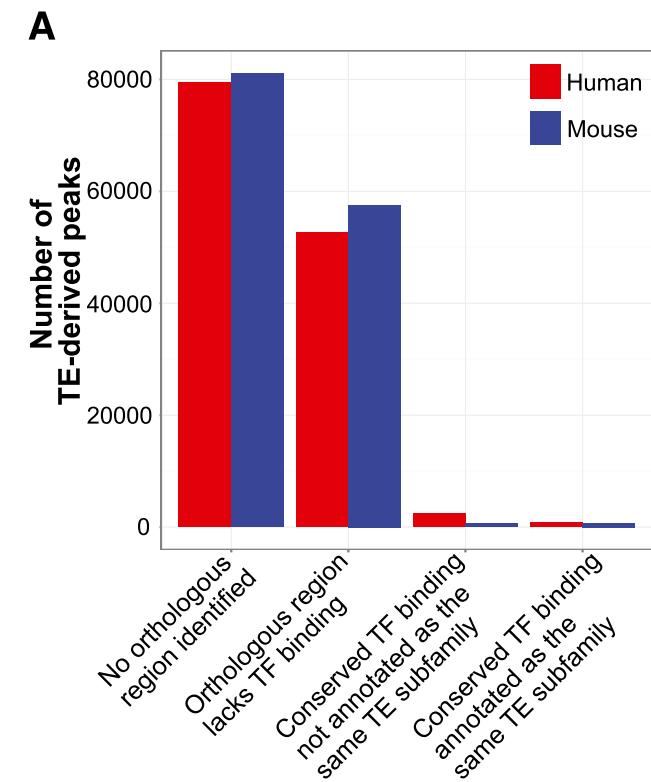
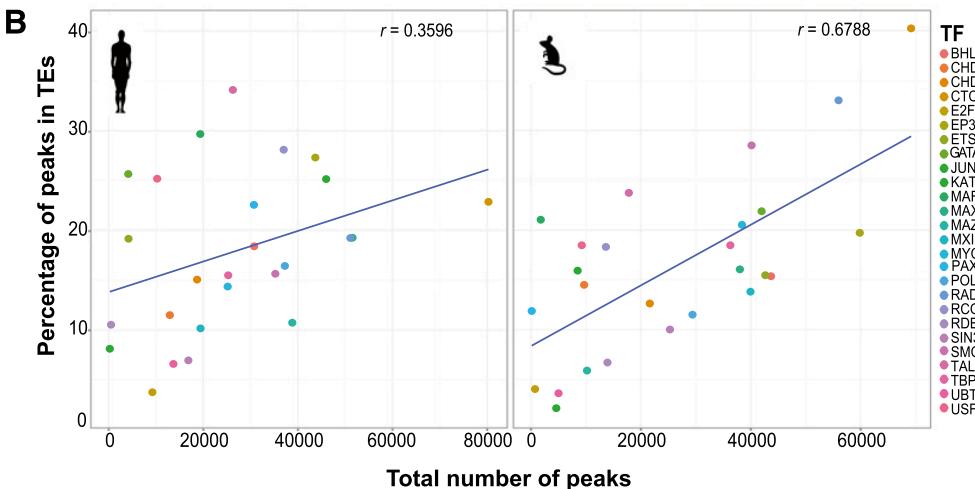
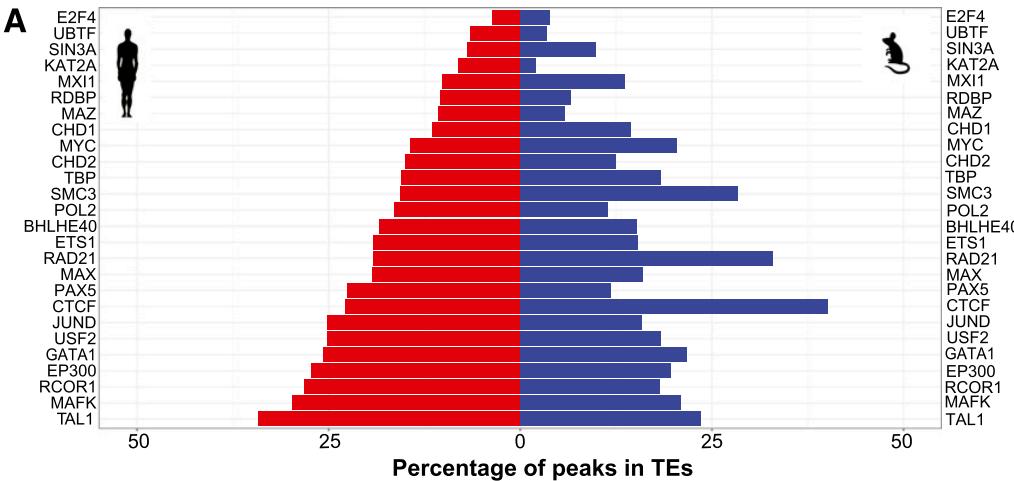
Proliferation of ERV recruits/ creates targets for p53, giving p53 a better potential to influence gene expression

Selection and modification of p53 network

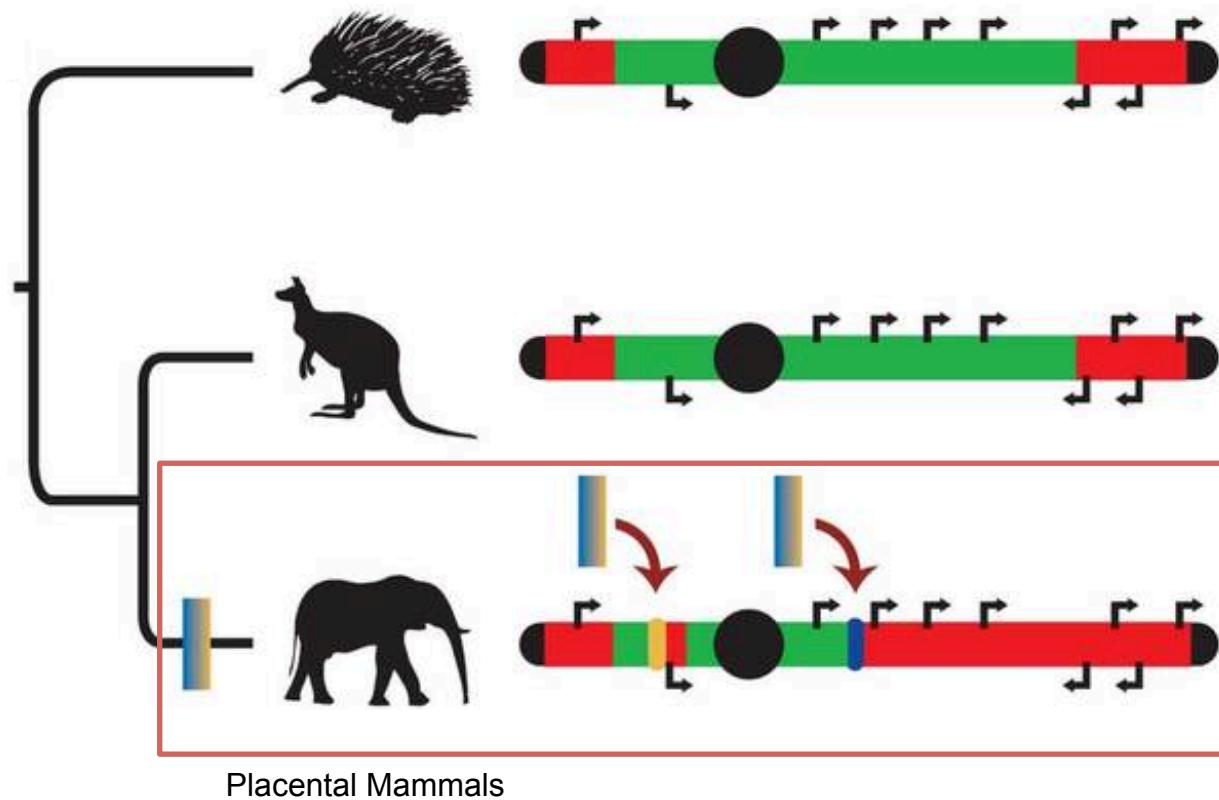
p53 becomes a master regulator

Widespread contribution of transposable elements to the innovation of gene regulatory networks

Vasavi Sundaram,^{1,4} Yong Cheng,^{2,4} Zhihai Ma,² Daofeng Li,¹ Xiaoyun Xing,¹
Peter Edge,³ Michael P. Snyder,² and Ting Wang¹

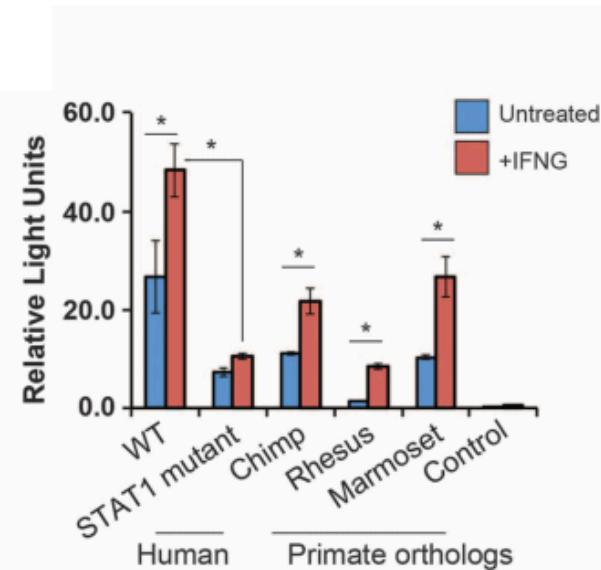
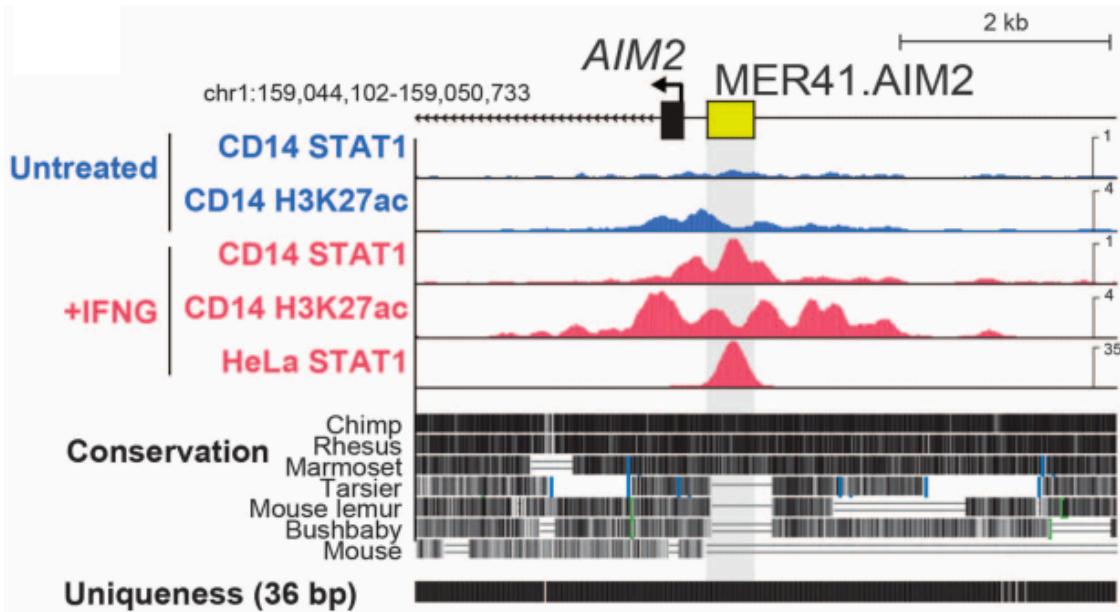


MER20 elements rewire endometrial gene expression programs involved in pregnancy

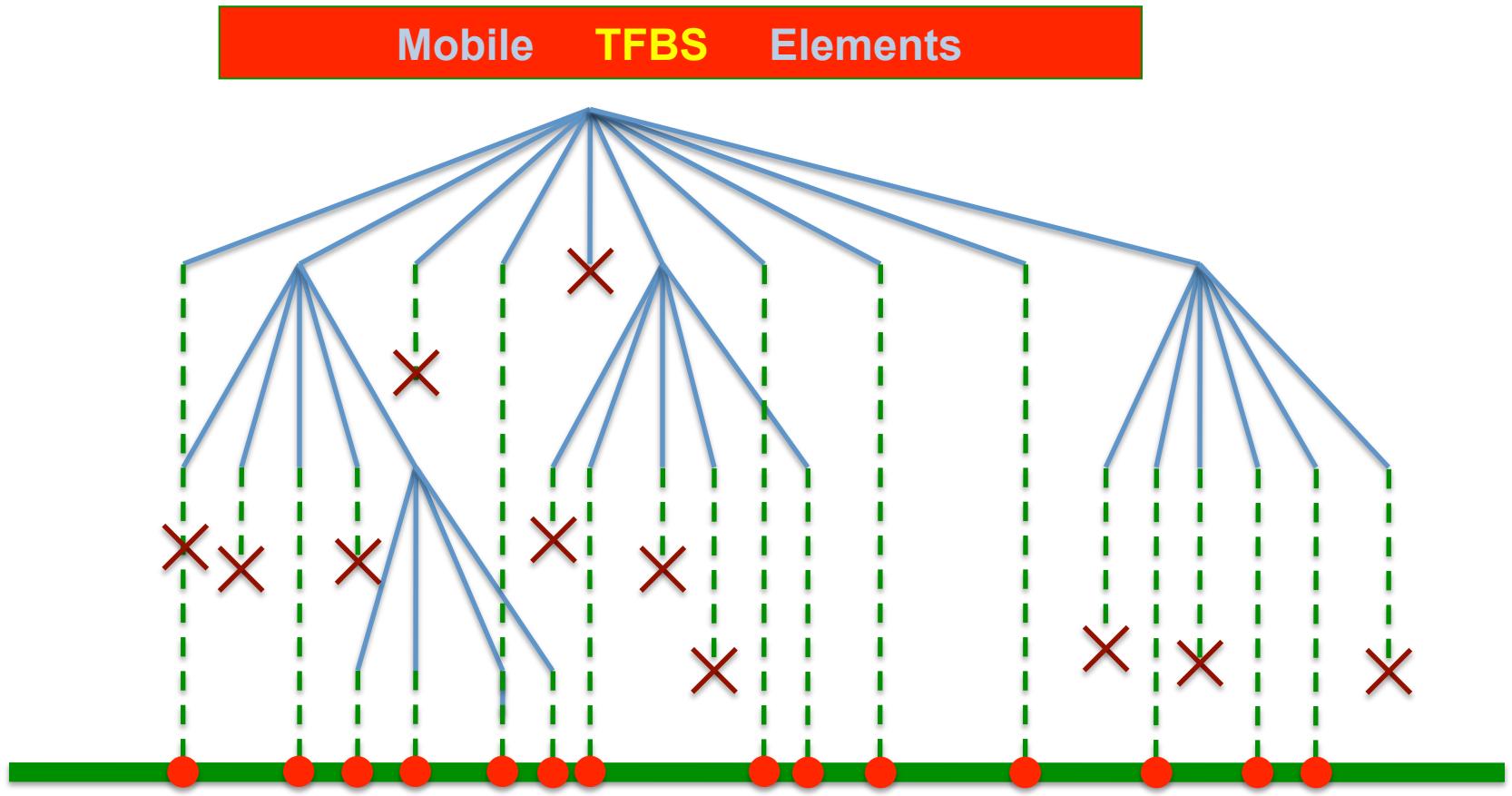


Lynch VJ, et al., Nat. Genetics, 2011

MER41 elements containing IFN-inducible enhancers have shaped the evolution of IFN response in innate immunity



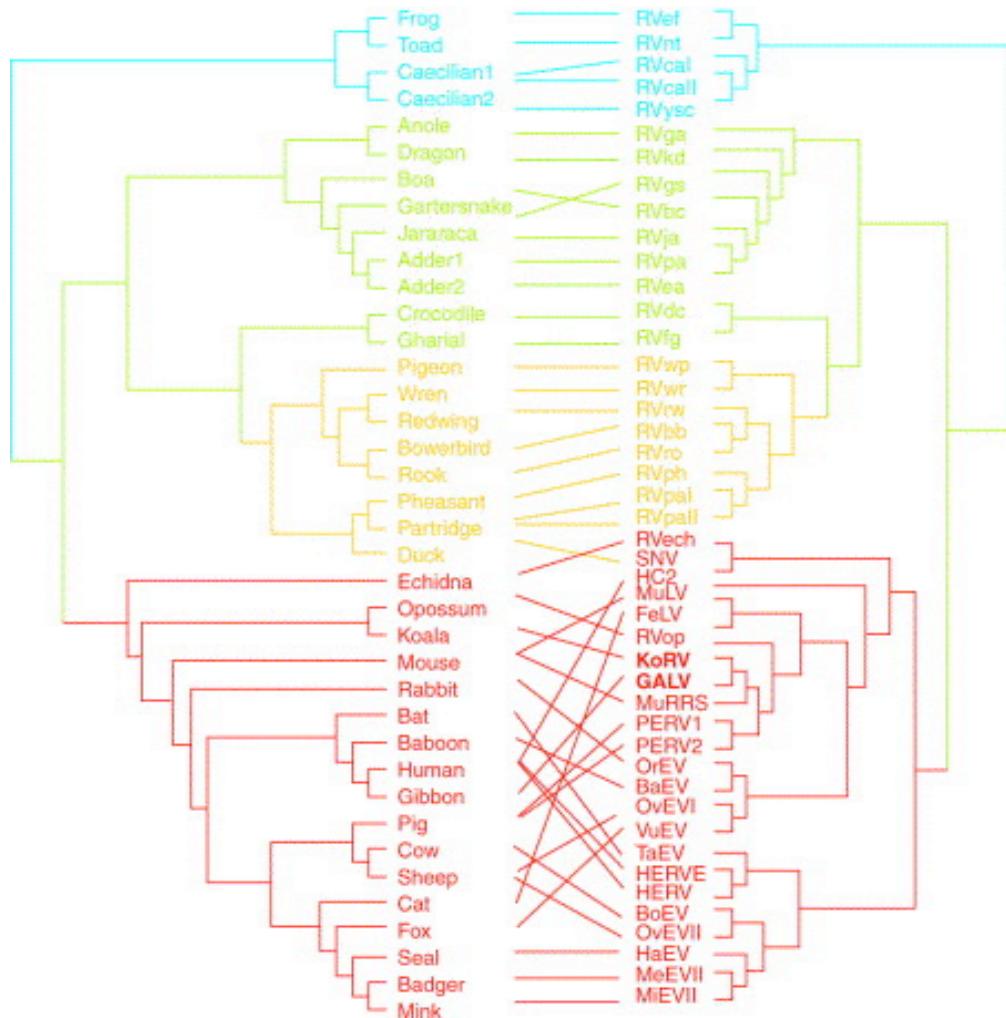
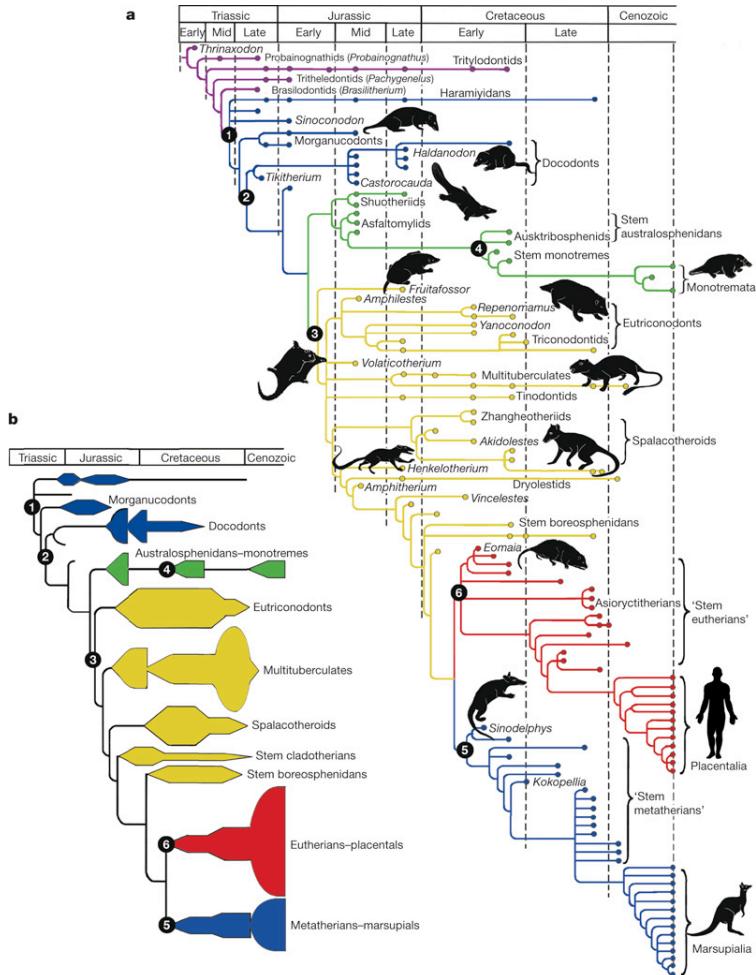
Chuong EB, et al., Science, 2016



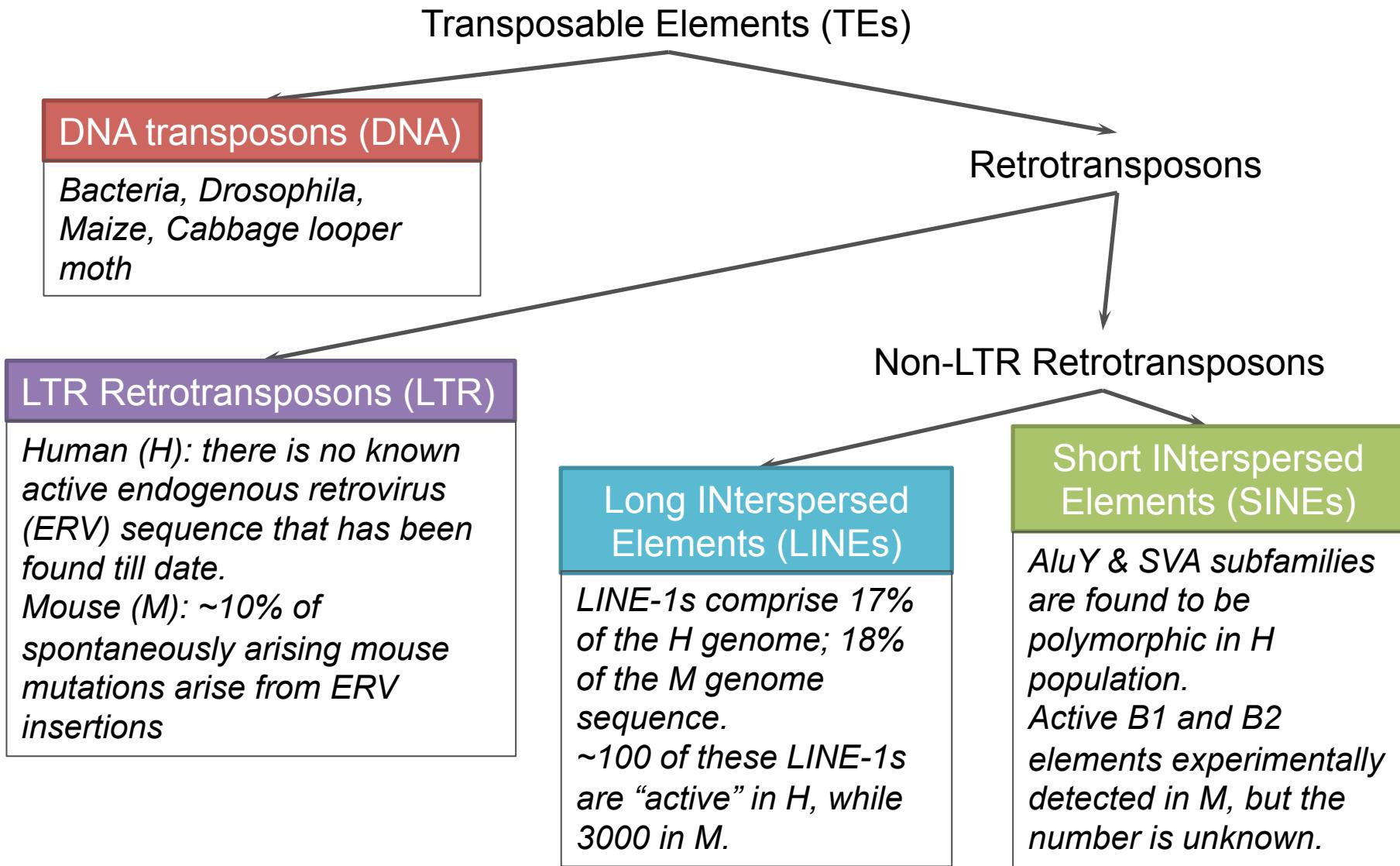
Are they all functional? How are they regulated?

Epigenetic/DNA methylation/Histone modification

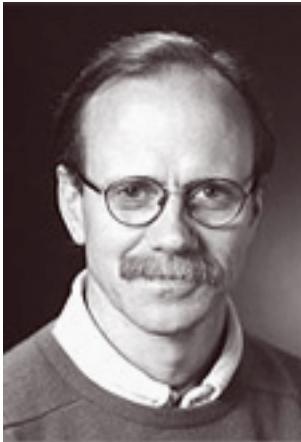
Mammalian Radiation, Gene Regulation and ERV activity



Brief overview of ‘active’ TEs



Transposable elements and somatic cell diversity



Fred Gage

Somatic mosaicism in neuronal precursor cells mediated by L1 retrotransposition

Alysson R. Muotri^{1*}, Vi T. Chu^{1*†}, Maria C. N. Marchetto¹, Wei Deng¹, John V. Moran² & Fred H. Gage¹

L1 retrotransposition in neurons is modulated by MeCP2

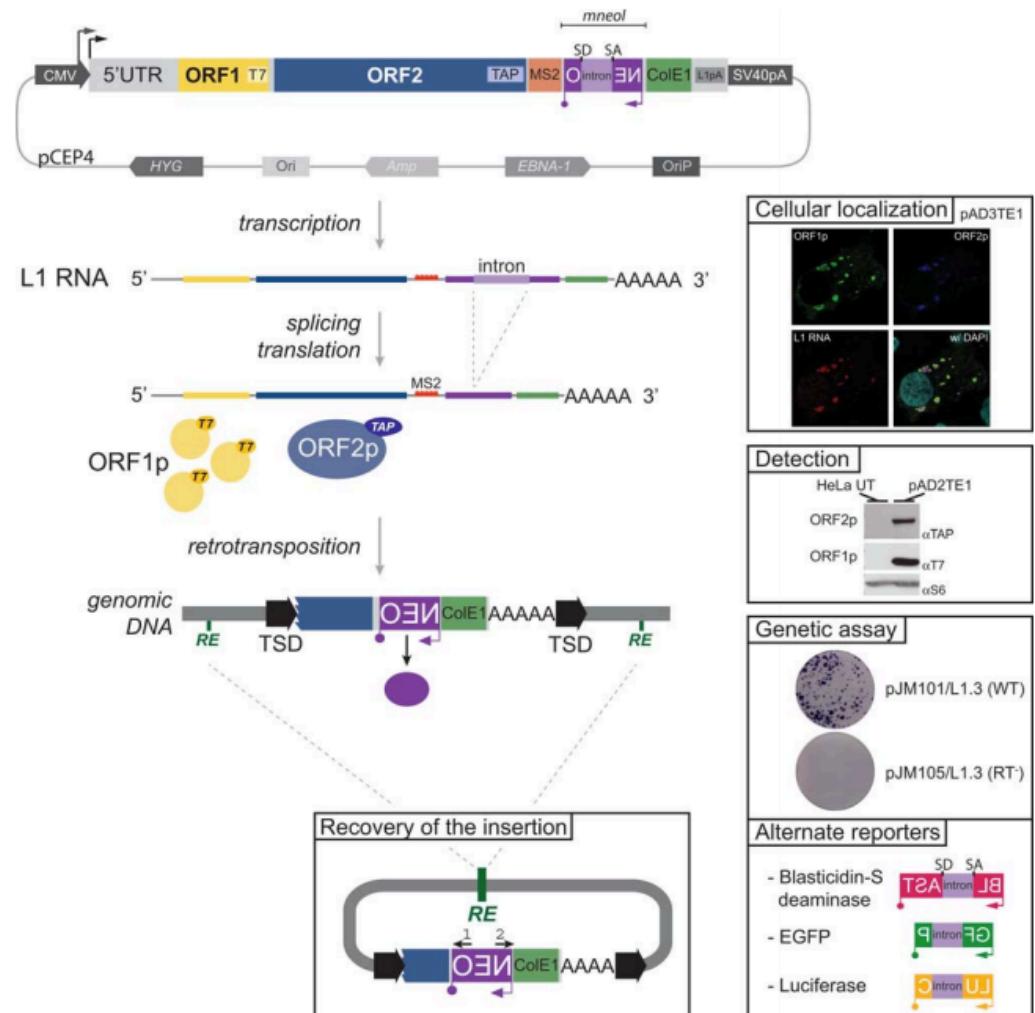
Alysson R. Muotri^{1*}, Maria C. N. Marchetto^{2*}, Nicole G. Coufal², Ruth Oefner², Gene Yeo³, Kinichi Nakashima⁴ & Fred H. Gage²

Somatic retrotransposition alters the genetic landscape of the human brain

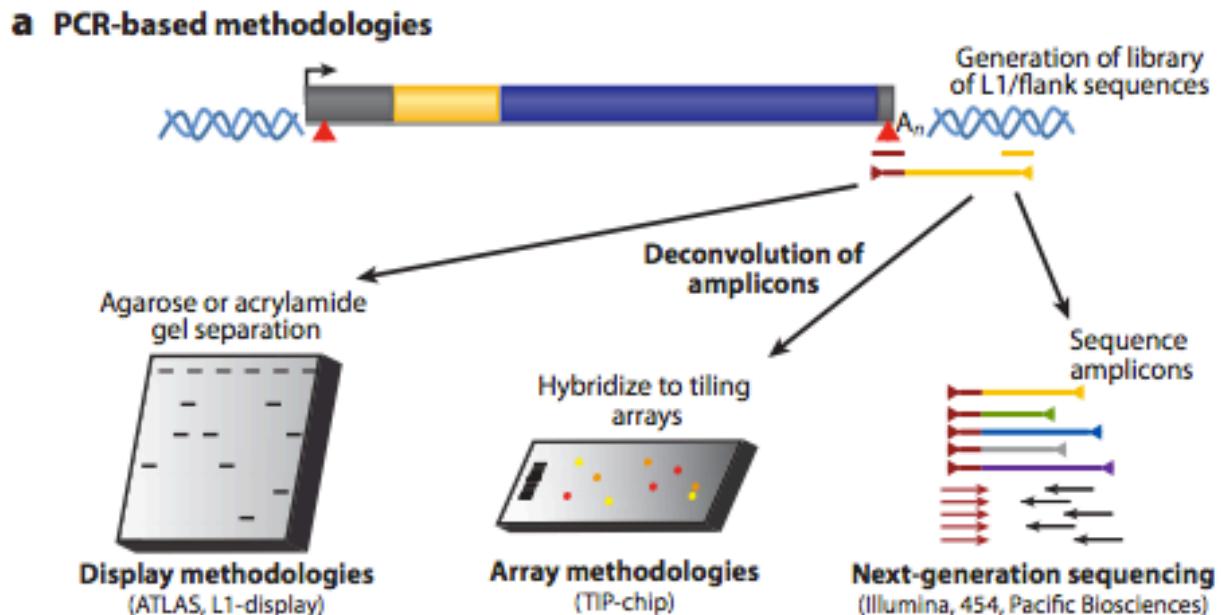
J. Kenneth Baillie^{1*}, Mark W. Barnett^{1*}, Kyle R. Upton^{1*}, Daniel J. Gerhardt², Todd A. Richmond², Fioravante De Sario¹, Paul Brennan³, Patrizia Rizzu⁴, Sarah Smith¹, Mark Fell¹, Richard T. Talbot¹, Stefano Gustincich⁵, Thomas C. Freeman¹, John S. Mattick⁶, David A. Hume¹, Peter Heutink⁴, Piero Carninci⁷, Jeffrey A. Jeddeloh² & Geoffrey J. Faulkner¹

Identifying LINE-1 mediated retrotransposition

- The assay is based on the fact that LINE-1 retrotransposes via an RNA intermediate.
- The *neo* reporter gene is disrupted by an intron in the same orientation as LINE-1's transcription.
 - Neo is expressed only when LINE-1 is successfully retrotransposed.



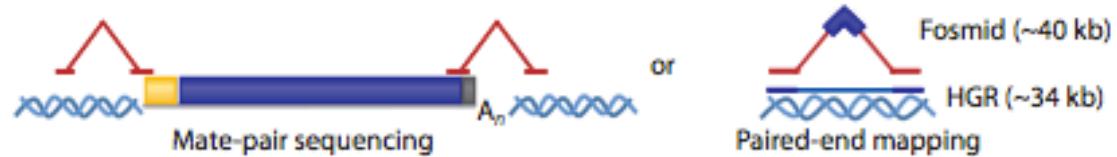
Identifying LINE-1 mediated retrotransposition



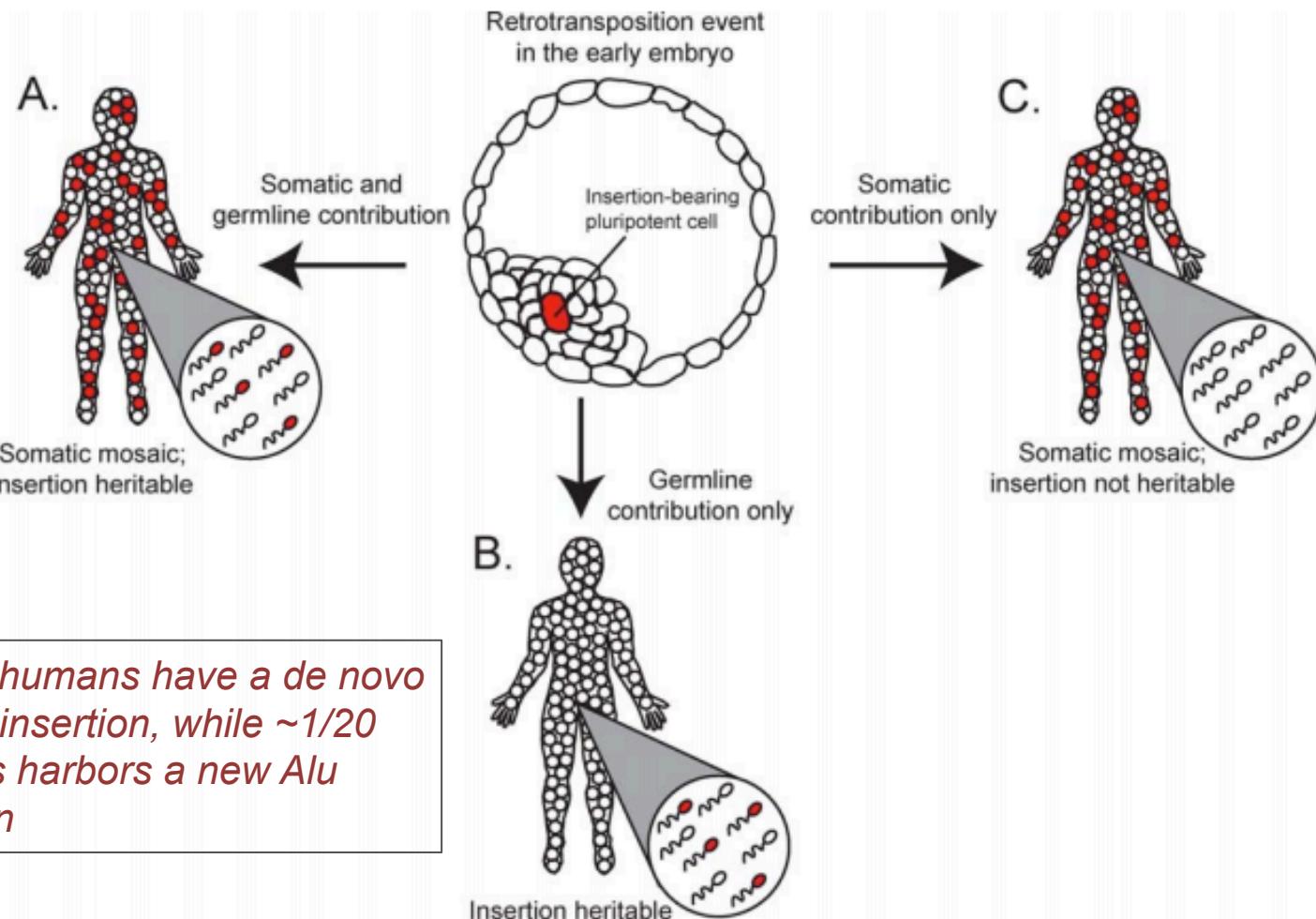
b Mining of L1s in individual genome sequences



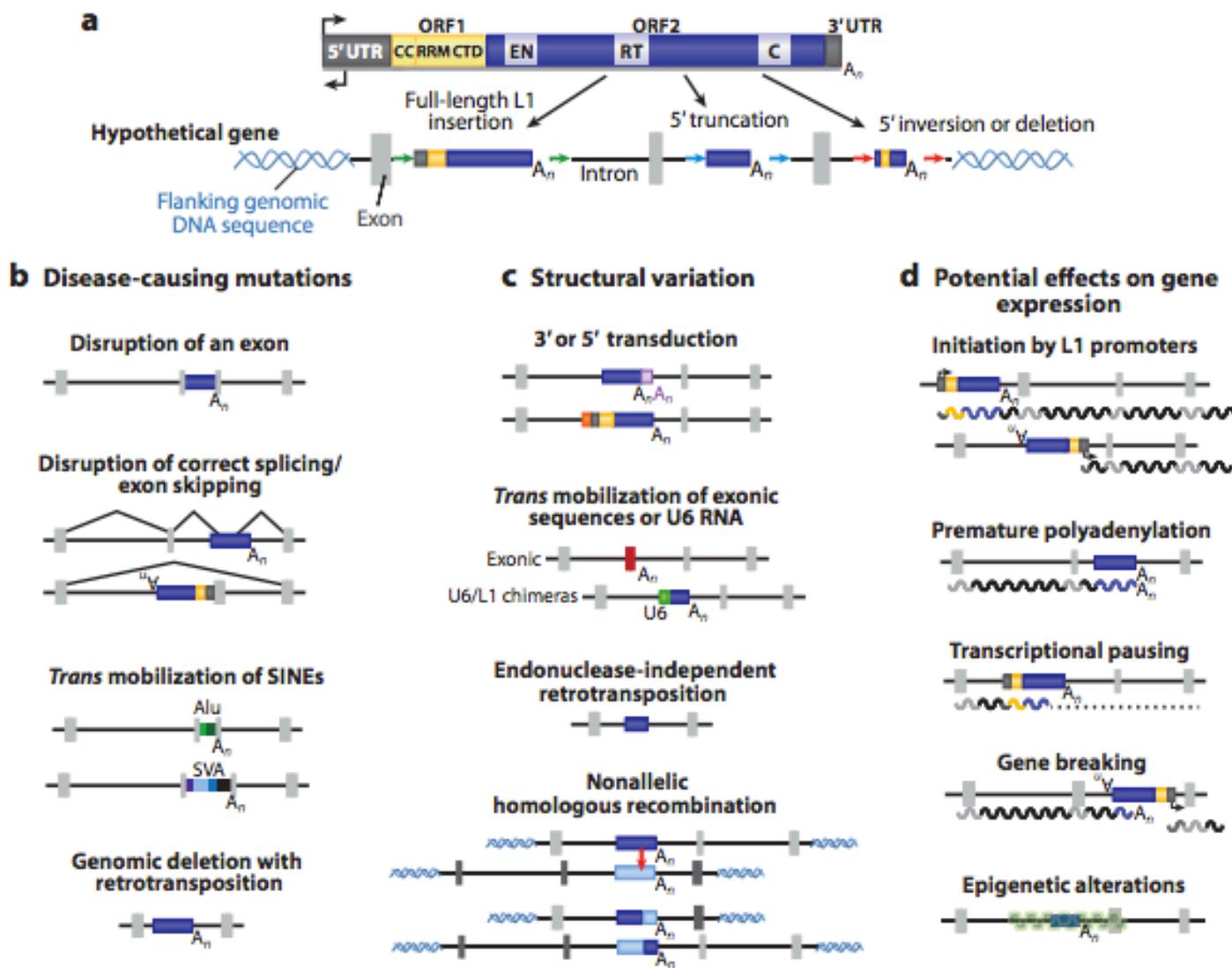
c Paired-end sequencing



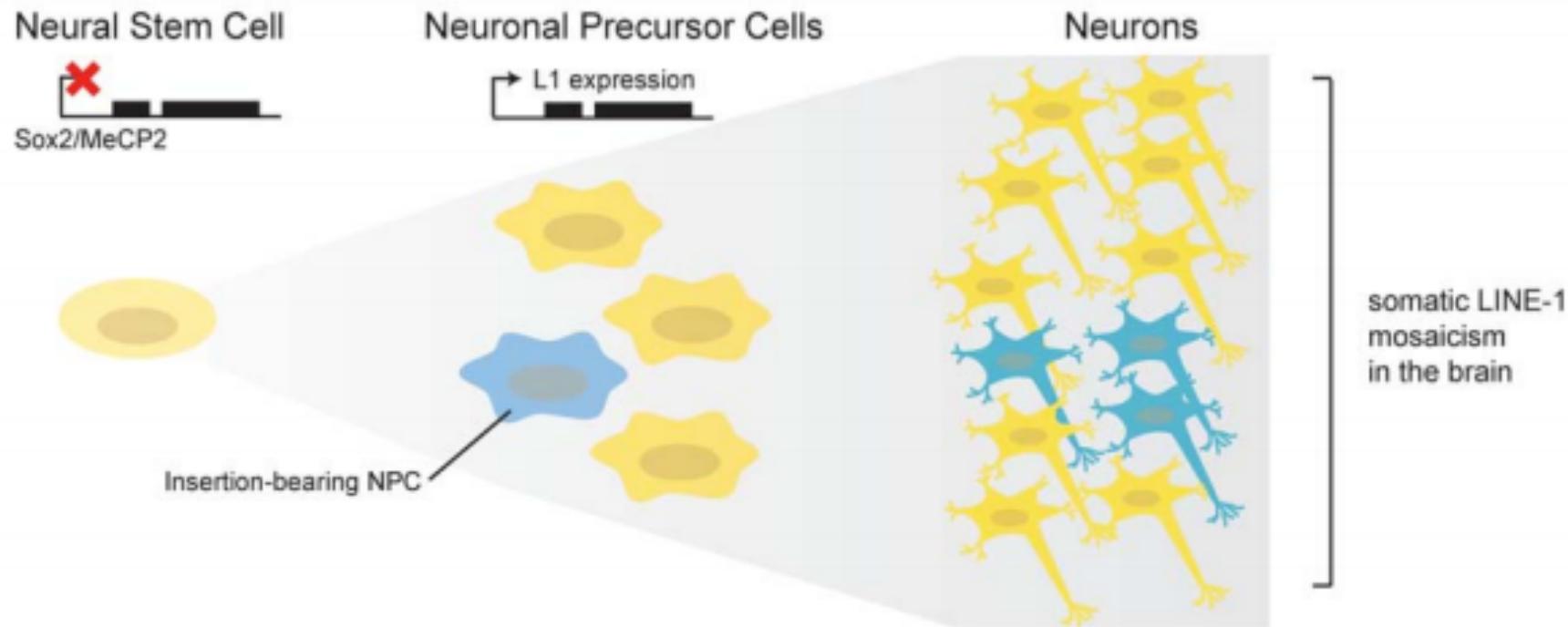
Impact of LINE-1 retrotransposition in human populations



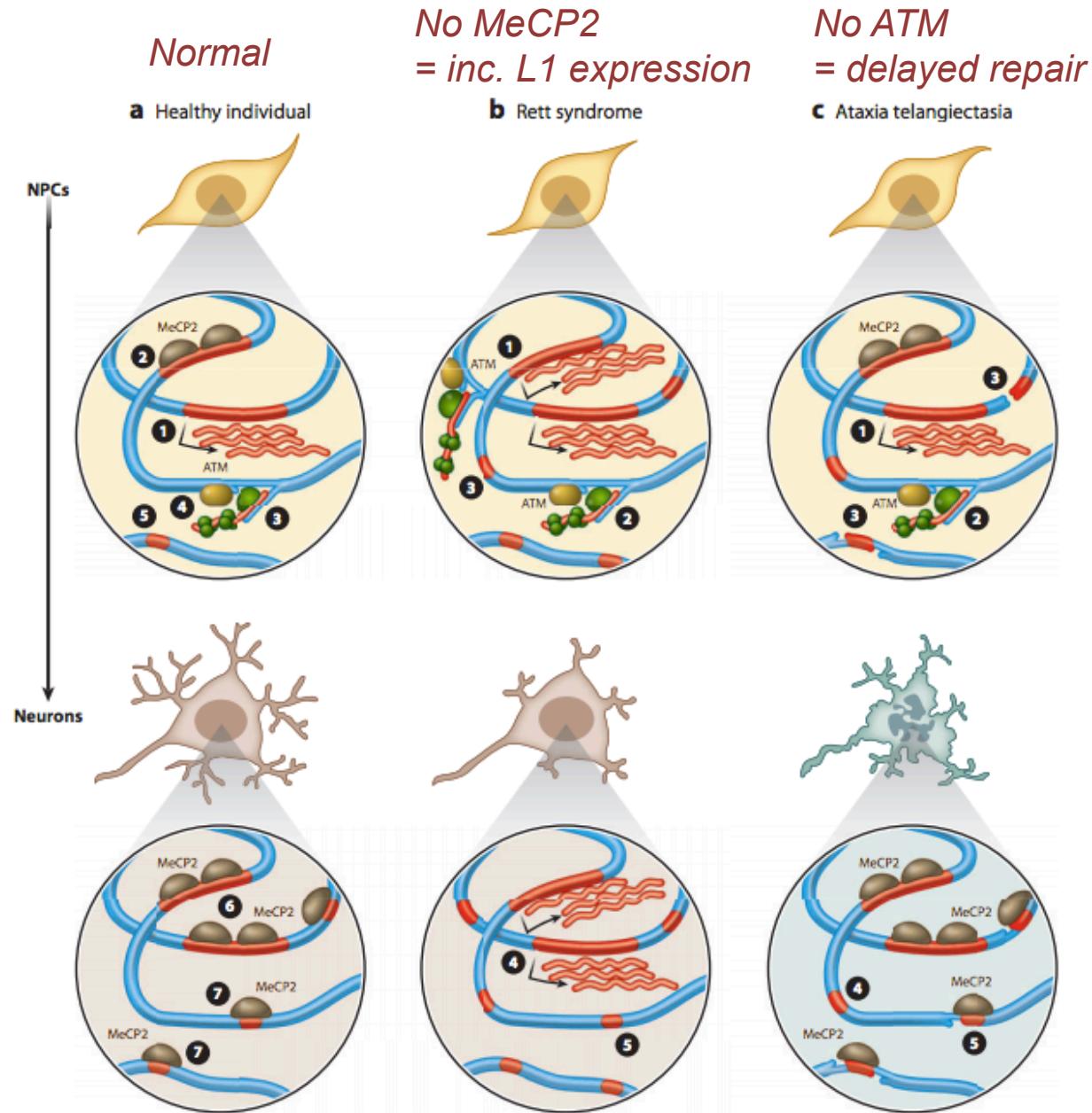
Impact of LINE-1 mobilization on the human genome



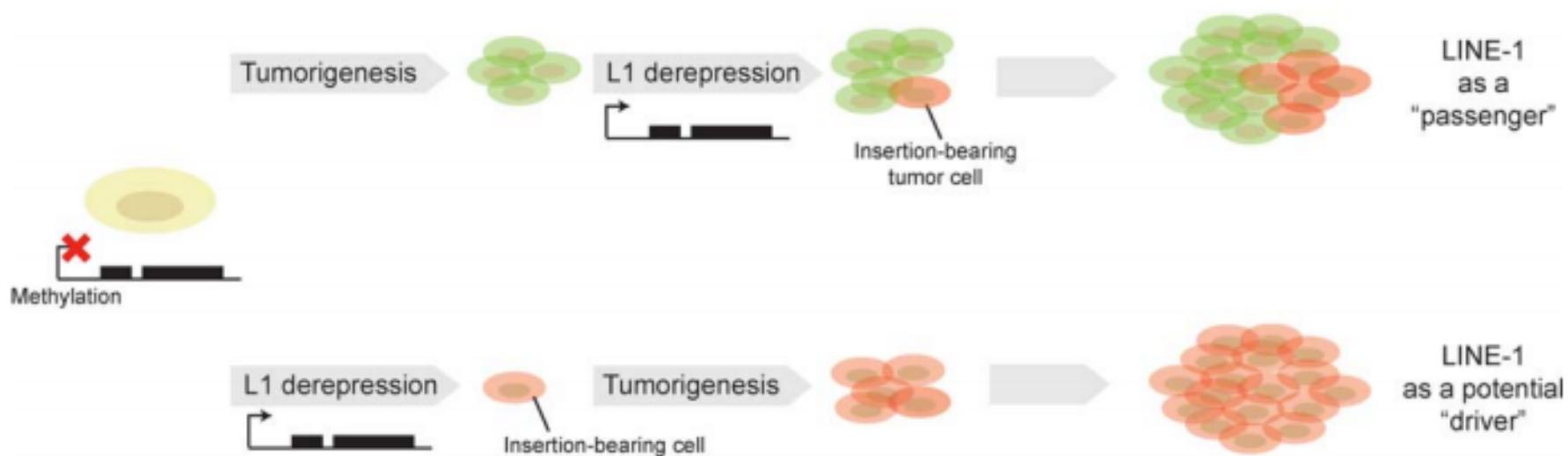
LINE-1 retrotransposition in generating somatic mosaicism



LINE-1 retro- transpositio n in healthy and diseased neurons



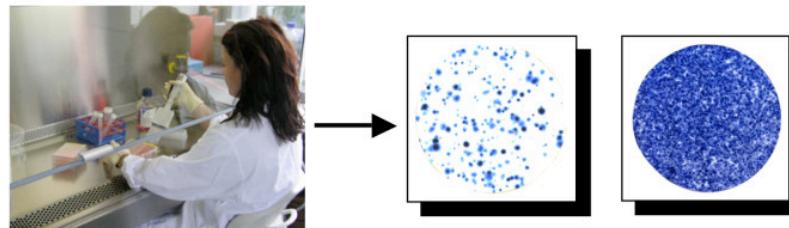
LINE-1 retrotransposition and cancer



Transposable Elements and Biotechnology

Transposons as genetic tools

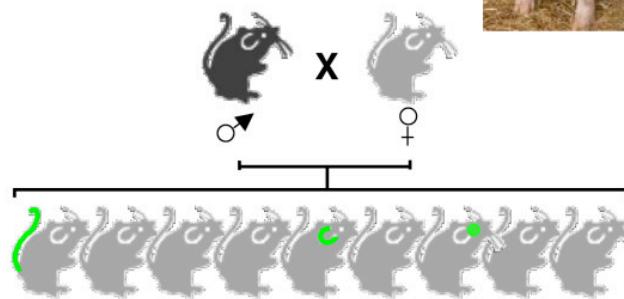
- Cell culture



- Transgenesis



- Insertional mutagenesis



© The American Society of Gene Therapy
doi:10.1038/mt...2008.169

editorial

Molecular Therapy

Sleeping Beauty Vector System Moves Toward Human Trials in the United States

In a public review of a proposed clinical gene transfer trial, the National Institutes of Health Recombinant DNA Advisory Committee (NIH)

feasibility, safety, and persistence of genetically modified T cells *in vivo* and also has several secondary objectives.

Transposons in functional genomics

