REVIEW

Mobile Elements: Drivers of Genome Evolution

Haig H. Kazazian Jr.*

Mobile elements within genomes have driven genome evolution in diverse ways. Particularly in plants and mammals, retrotransposons have accumulated to constitute a large fraction of the genome and have shaped both genes and the entire genome. Although the host can often control their numbers, massive expansions of retrotransposons have been tolerated during evolution. Now mobile elements are becoming useful tools for learning more about genome evolution and gene function.

Mobile, or transposable, elements are prevalent in the genomes of all plants and animals. Indeed, in mammals they and their recognizable remnants account for nearly half of the genome (*1*, *2*), and in some plants they constitute up to 90% of the genome (*3*). If, as many believe, the origins of life are in an "RNA world" followed by reverse transcription into DNA, then mobile elements could

Because sequence specificity of integration is limited to a small number of nucleotides—e.g., TA dinucleotides for Tc1 of *Caenorhabditis elegans*—insertions can occur at a large number of genomic sites. However, daughter insertions for most, but not all, DNA transposons occur in proximity to the parental insertion. This is called "local hopping." Active transposons encode a transposase enyme

residues, then a glutamate) and a handlike three-dimensional structure (*6*, *8*).

Although these elements generally transpose to genomic sites less than 100 kb from their original site (e.g., the *Drosophila* P element), some are able to make distant "hops" (e.g., the fish Tc1/mariner element; see below).

LTR Retrotransposons

Retrotransposons are transcribed into RNA, and then reverse transcribed and reintegrated into the genome, thereby duplicating the element. The major classes of retrotransposons either contain long terminal repeats at both ends (LTR retrotransposons) or lack LTRs and possess a polyadenylate sequence at their 3′ termini (non-LTR retrotransposons).

LTR retrotransposons and retroviruses are

Watson BM Gene Capitolo 11

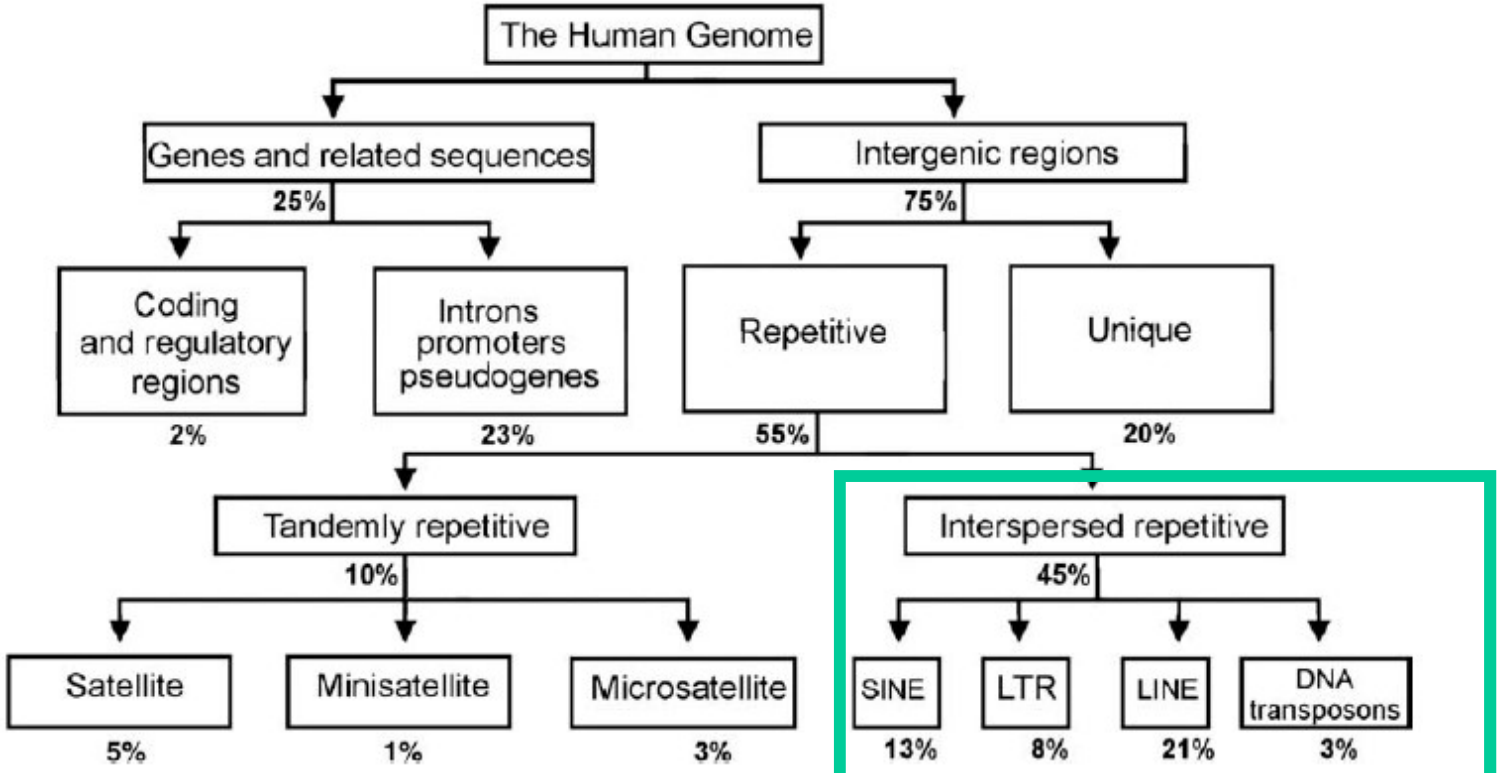
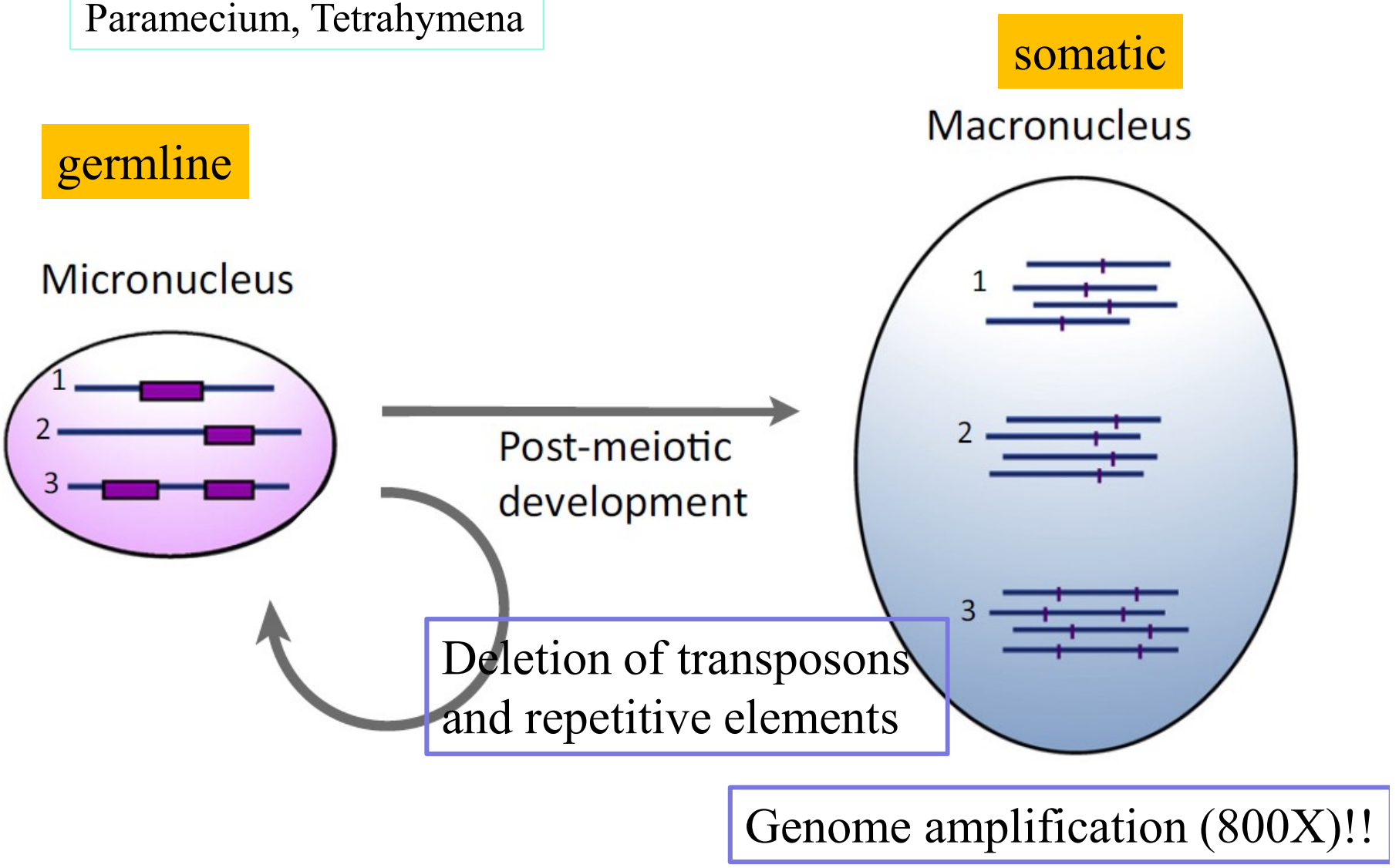
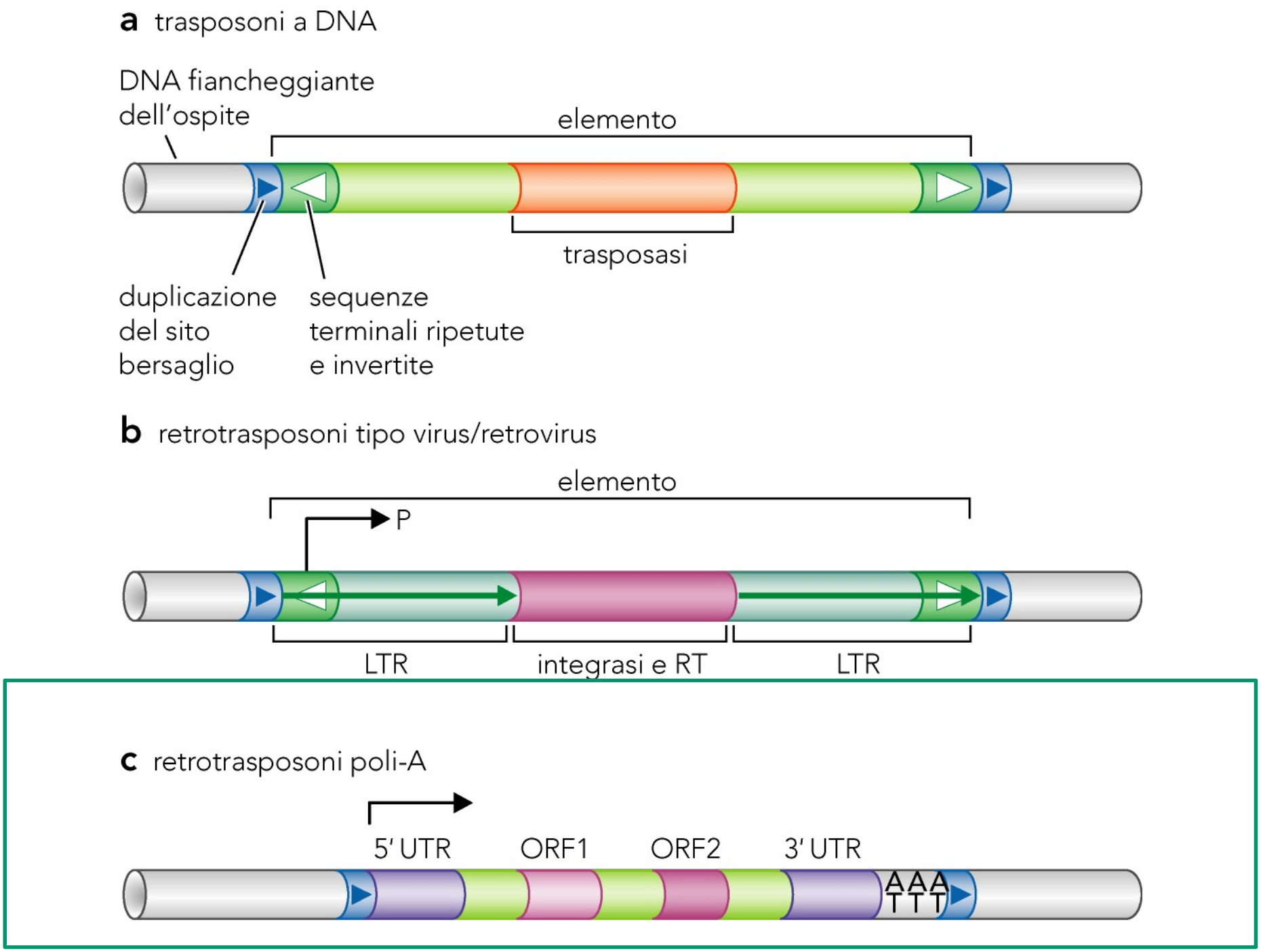


Fig. 1. Composition of the human genome. The percentage shares of various functional and non-functional sequences are shown.

Ciliates and Transposons

Paramecium, Tetrahymena




a trasposoni a DNA
DNA fiancheggiante dell'ospite
elemento
trasposasi
duplicazione del sito bersaglio
sequenze terminali ripetute e invertite
b retrotrasposoni tipo virus/retrovirus
elemento
P
LTR
integrasi e RT
LTR
c retrotrasposoni poli-A
5' UTR
ORF1
ORF2
3' UTR
AAA
TTT

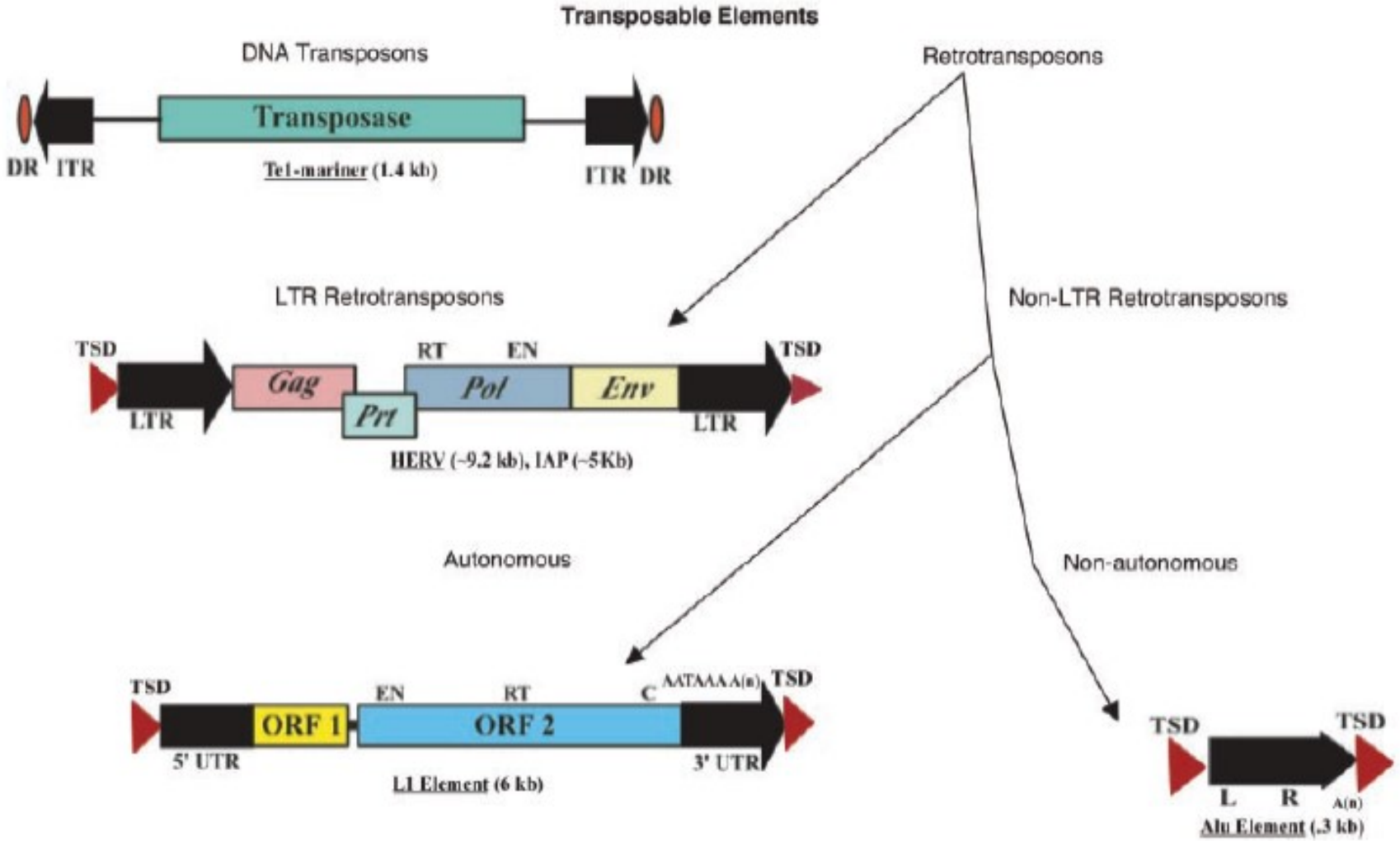
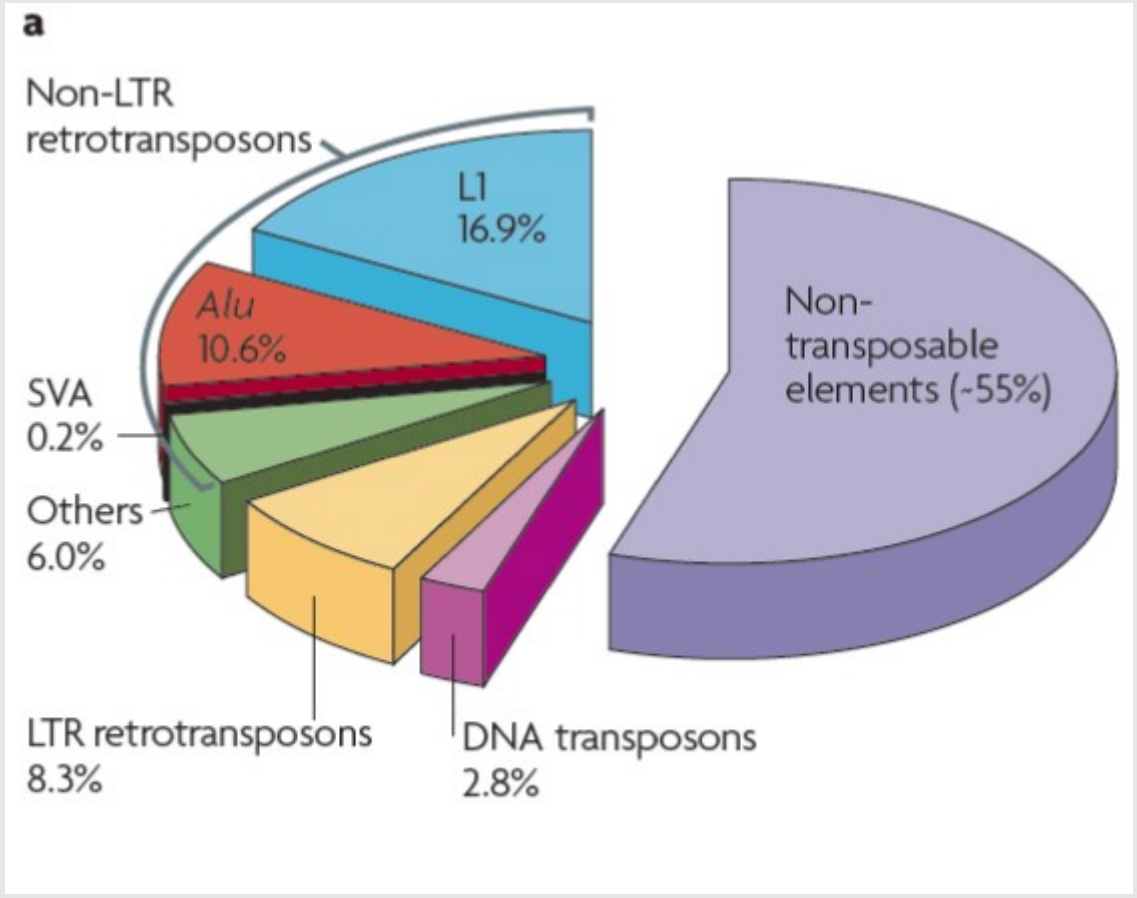


Fig. 1. Classes of mobile elements. DNA transposons, e.g., Tc-1/mariner, have inverted terminal inverted repeats (ITRs) and a single open reading frame (ORF) that encodes a transposase. They are flanked by short direct repeats (DRs). Retrotransposons are divided into autonomous and nonautonomous classes depending on whether they have ORFs that encode proteins required for retrotransposition. Common autonomous retrotransposons are (i) LTRs or (ii) non-LTRs (see text for


a
Non-LTR retrotransposons
L1 16.9%
Alu 10.6%
SVA 0.2%
Others 6.0%
LTR retrotransposons 8.3%
DNA transposons 2.8%
Non-transposable elements (~55%)

SVA

SINE-VNTR-Alu (SVA) elements are nonautonomous, hominid-specific non-LTR retrotransposons

composite mobile elements.

They represent the evolutionarily youngest, currently active family of human non-LTR retrotransposons

SINE-VNTR-Alu (SVA)

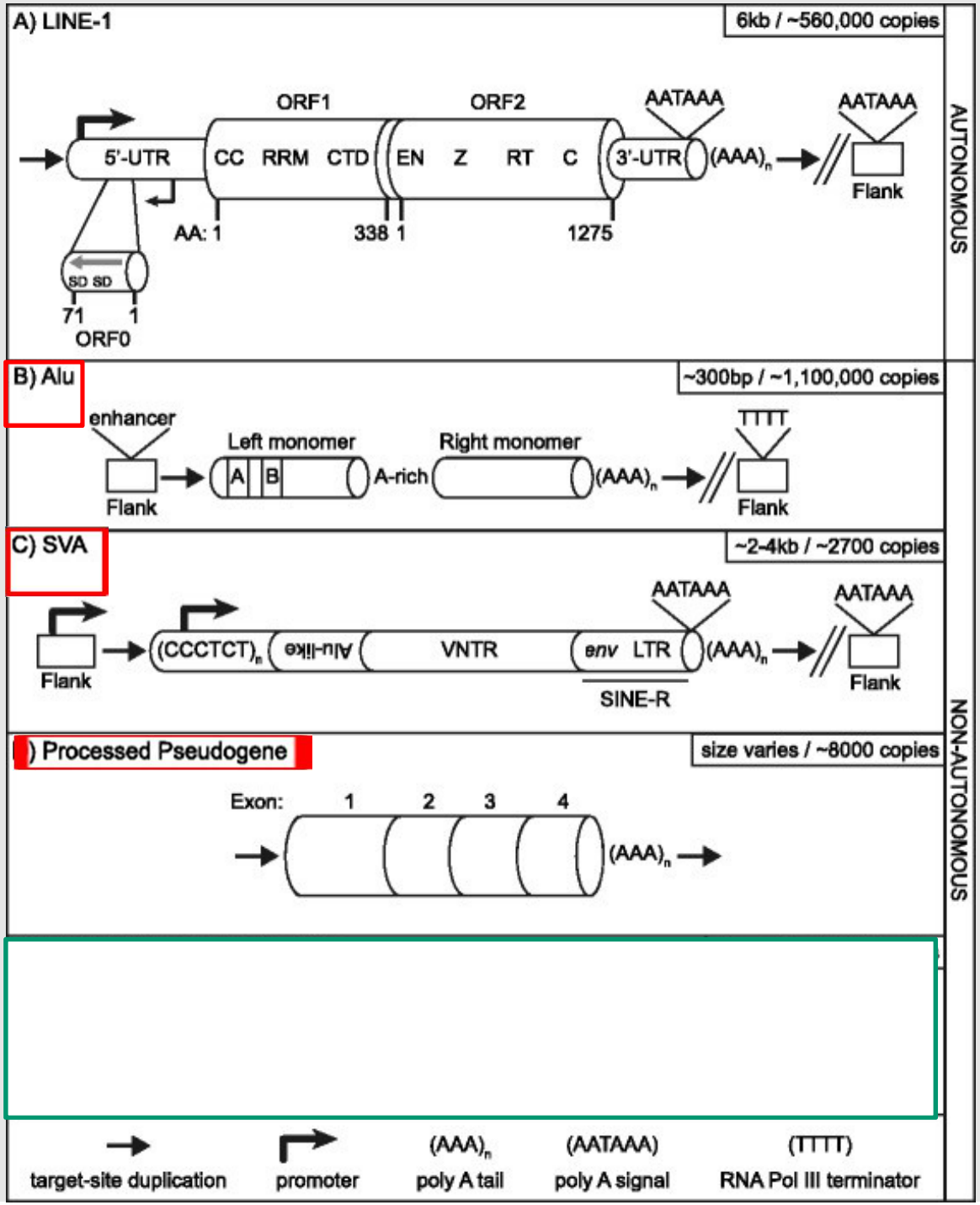
hexamer repeat region

Portion of env gene + 3′ LTR of the endogenous retrovirus HERV-K10

Roles for retrotransposon insertions in human disease

Over evolutionary time, the dynamic nature of a genome is driven, in part, by the activity of transposable elements (TE) such as retrotransposons.

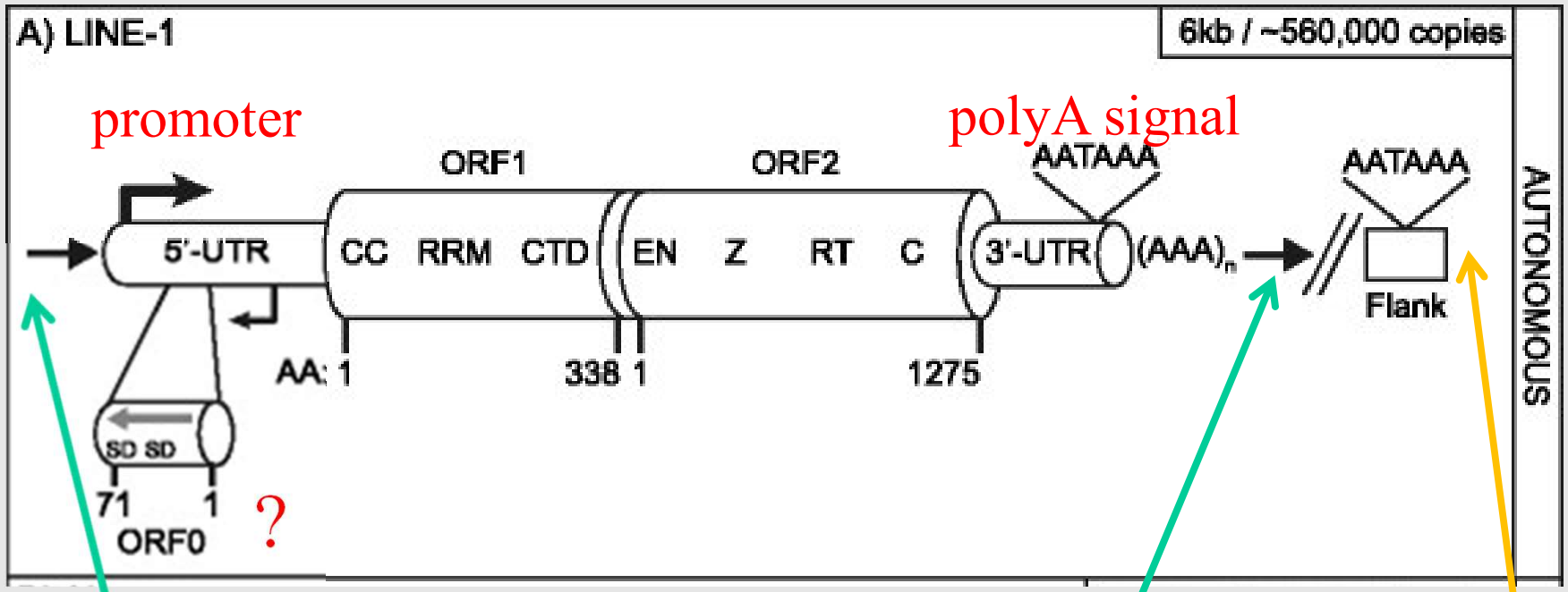
On a shorter time scale it has been established that new TE insertions can result in single-gene disease in an individual.


A) LINE-1
6kb / ~560,000 copies
ORF1
ORF2
AATAAA
AATAAA
5'-UTR
CC
RRM
CTD
EN
Z
RT
C
3'-UTR
(AAA)n
Flank
AA: 1
338 1
1275
SD SD
71
1
ORF0
AUTONOMOUS
B) Alu
~300bp / ~1,100,000 copies
enhancer
Left monomer
Right monomer
TTTT
A
B
A-rich
(AAA)n
Flank
Flank
C) SVA
~2-4kb / ~2700 copies
AATAAA
AATAAA
Flank
(CCCTCT)n
Alu-like
VNTR
env
LTR
(AAA)n
Flank
SINE-R
) Processed Pseudogene
size varies / ~8000 copies
Exon:
1
2
3
4
(AAA)n
NON-AUTONOMOUS
target-site duplication
promoter
(AAA)n
poly A tail
(AATAAA)
poly A signal
(TTTT)
RNA Pol III terminator

LINE-1

The non-LTR retrotransposon Long INterspersed Element-1 (or L1) is the only active autonomous TE.

In addition to mobilizing its own RNA to new genomic locations via a “copy-and-paste” mechanism, LINE-1 is able to retrotranspose other RNAs including Alu, SVA, and occasionally cellular RNAs.



flanking target-site duplications

LINE-1 frequently bypassed its own polyA signal in favor of a downstream one

Trascrizione L1

- RNApolymeraseII
- Transcription factors

SOX11

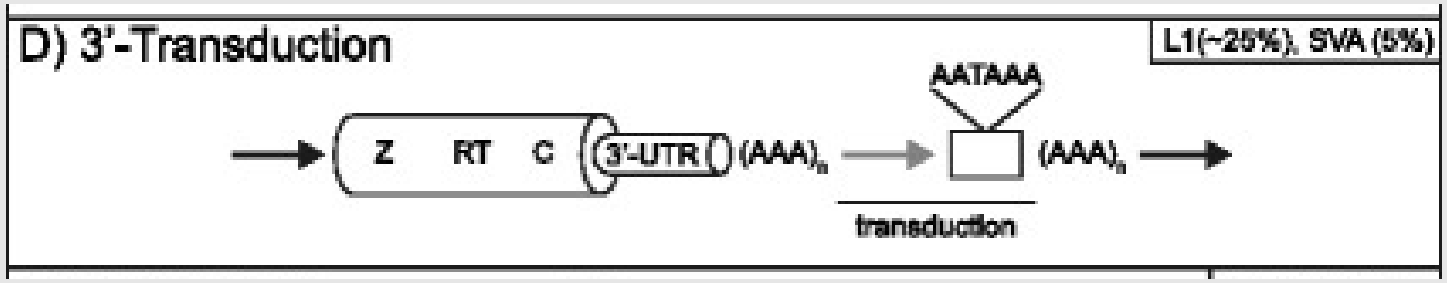
YY1

RUNX3

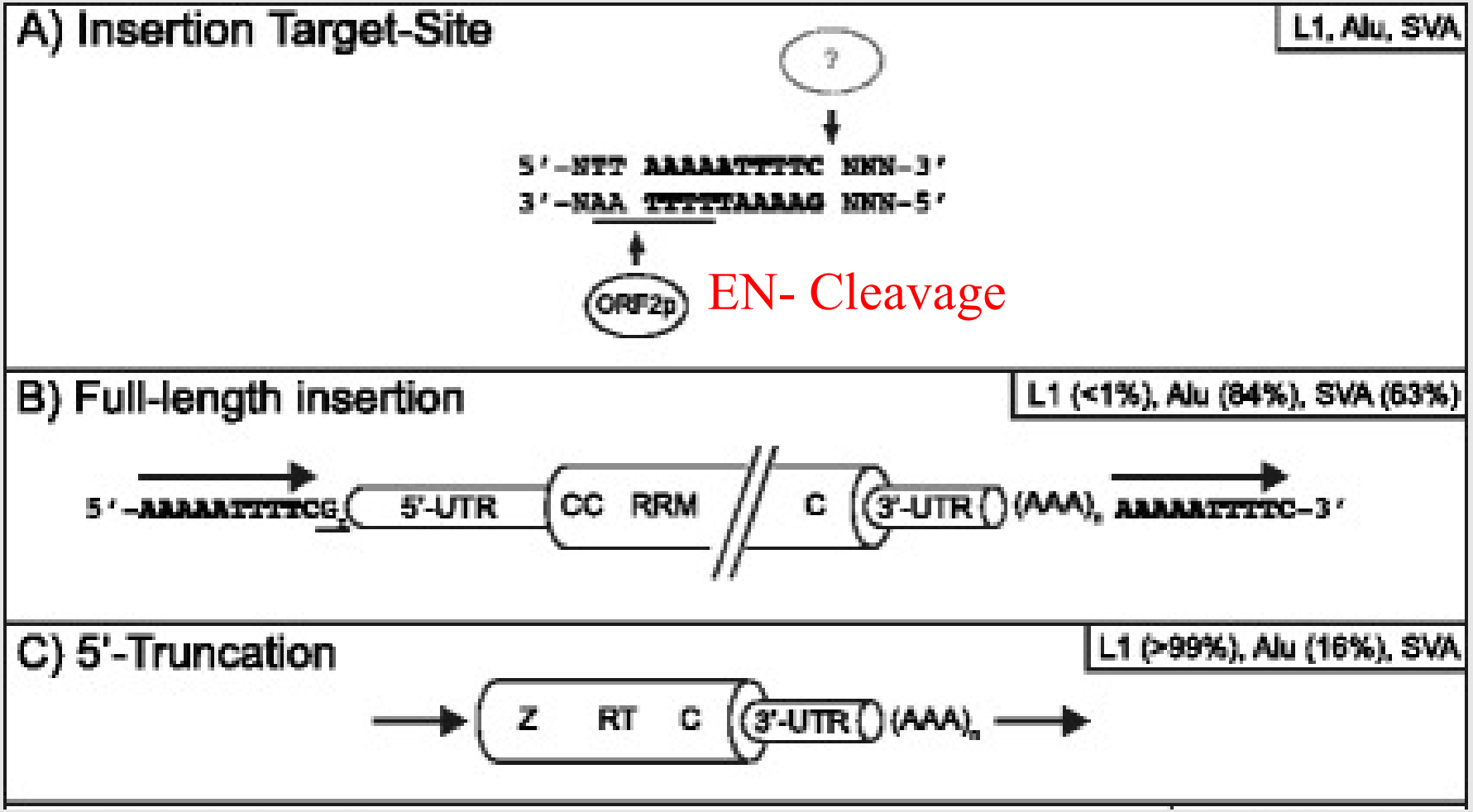
p53?

Troppa Trascrizione L1…..

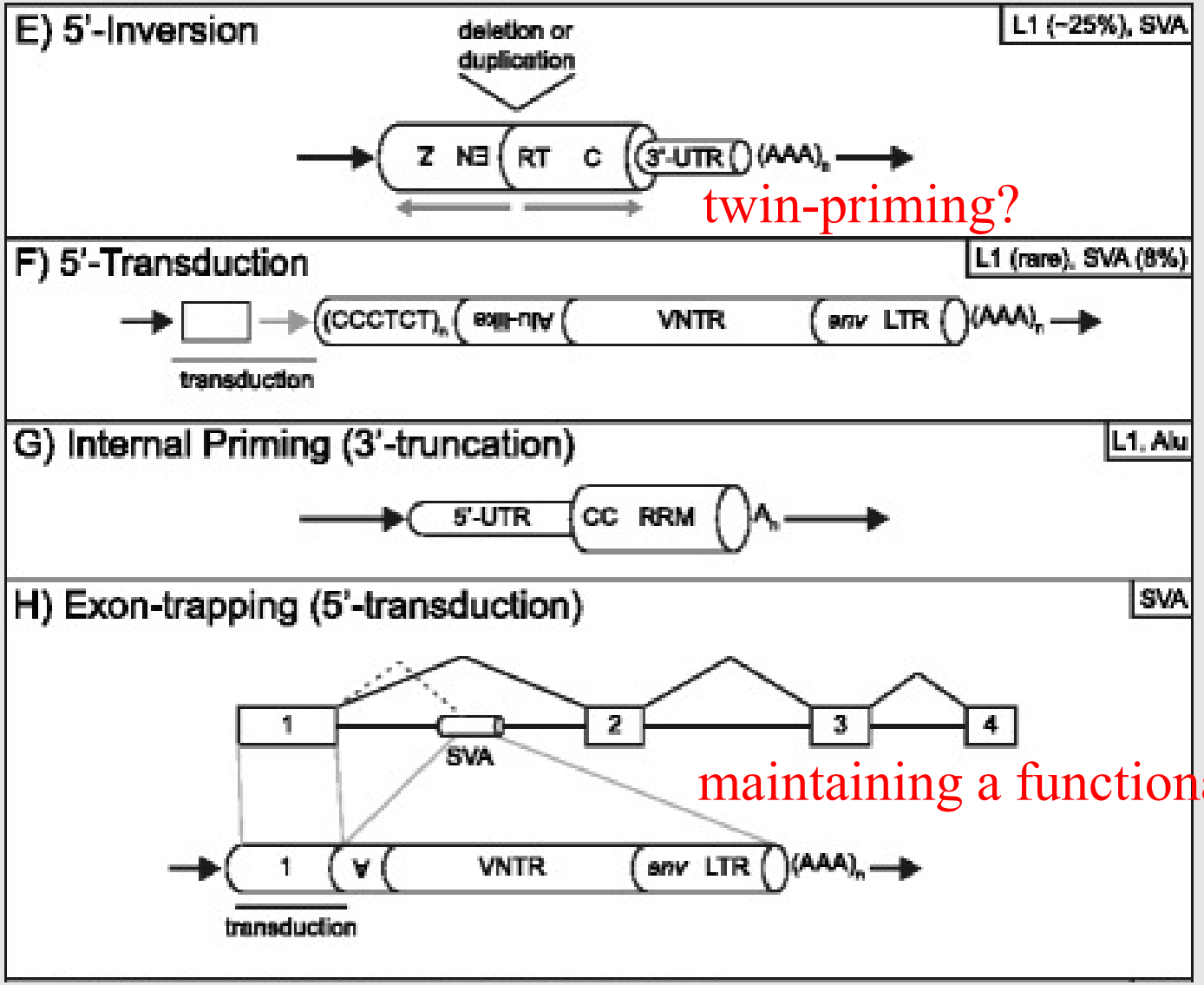
LINE-1 frequently bypassed its own polyA signal (AATAAA) in favor of a downstream one (AATAAA)



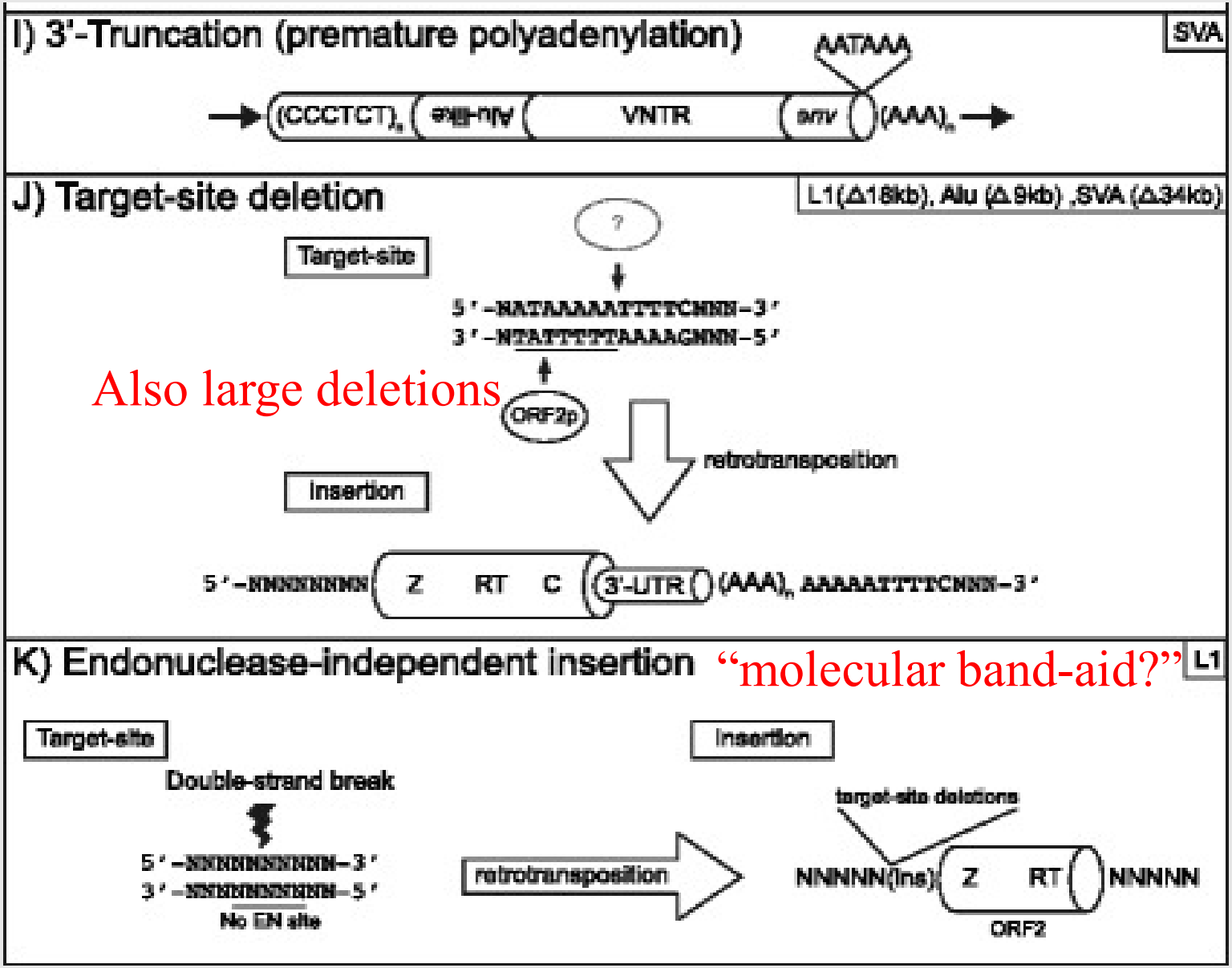
retrotransposon insertions



Numerosi altri eventi mutazionali



Numerosi altri eventi mutazionali



L1-associated genomic regions are deleted in somatic cells of the healthy human brain.

Erwin JA Nat Neurosci. 2016 Sep 12

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The healthy human brain is a mosaic of varied genomes.

Long interspersed element-1 (LINE-1 or L1) retrotransposition is known to create mosaicism by inserting L1 sequences into new locations of somatic cell genomes.

Using a single-cell sequencing approach, we discovered that somatic L1-associated variants (SLAVs) are composed of two classes:

L1 retrotransposition insertions and retrotransposition-independent L1-associated variants.

L1-associated genomic regions are deleted in somatic cells of the healthy human brain.

Erwin JA Nat Neurosci. 2016 Sep 12

A subset of SLAVs comprises somatic deletions generated by L1 endonuclease cutting activity.

Retrotransposition-independent rearrangements resulted in the deletion of proximal genomic regions.

L1-associated genomic regions are hotspots for somatic copy number variants in the brain and therefore a heritable genetic contributor to somatic mosaicism.

We demonstrate that SLAVs are present in crucial neural genes es PSD93 and affect 44-63% of cells of the cells in the healthy brain.

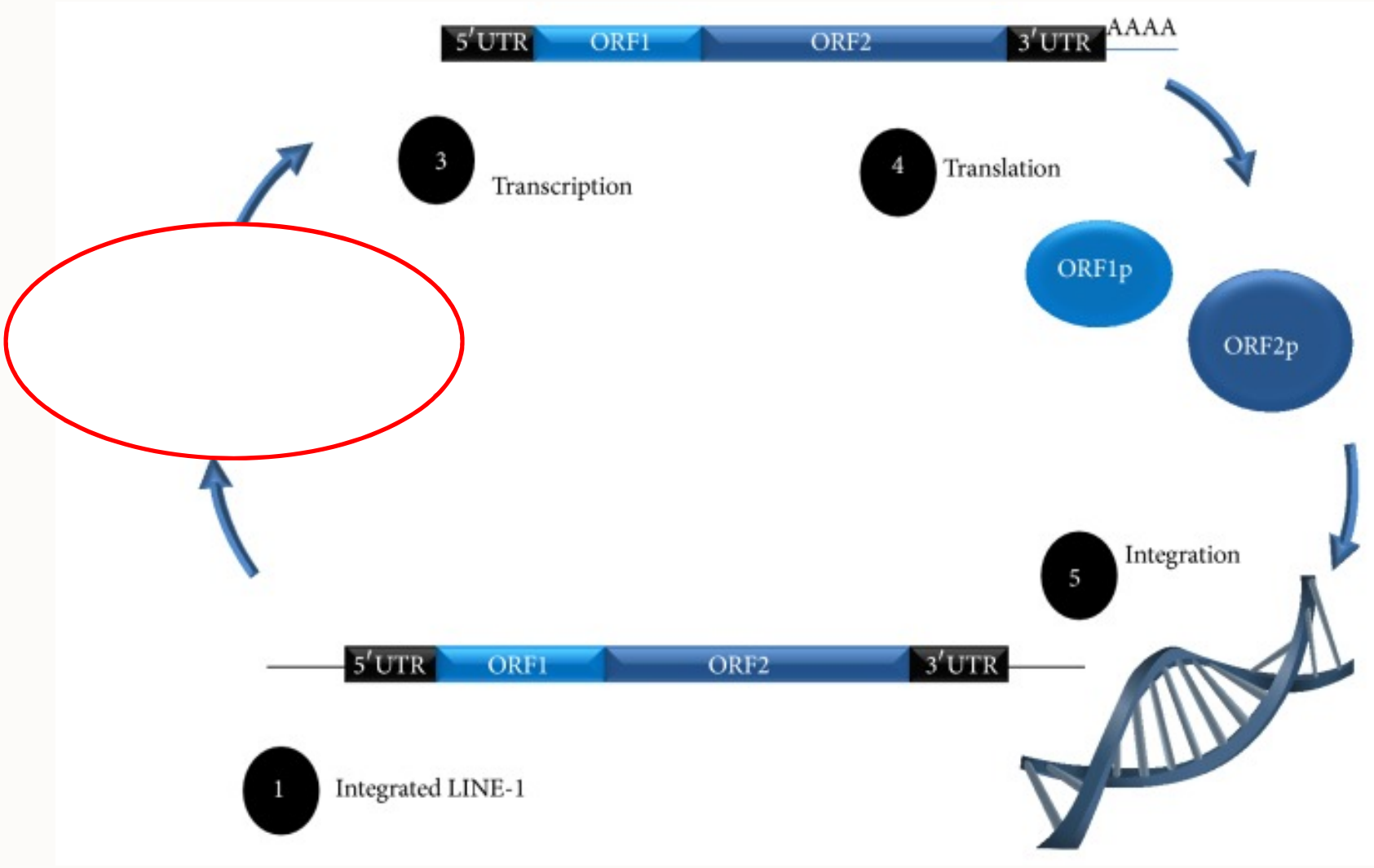
PSD93
postsynaptic density proteins

belong to a family of scaffolding proteins, the membrane-associated guanylate kinases which are highly enriched in synapses and responsible for organizing the numerous protein complexes required for synaptic development and plasticity

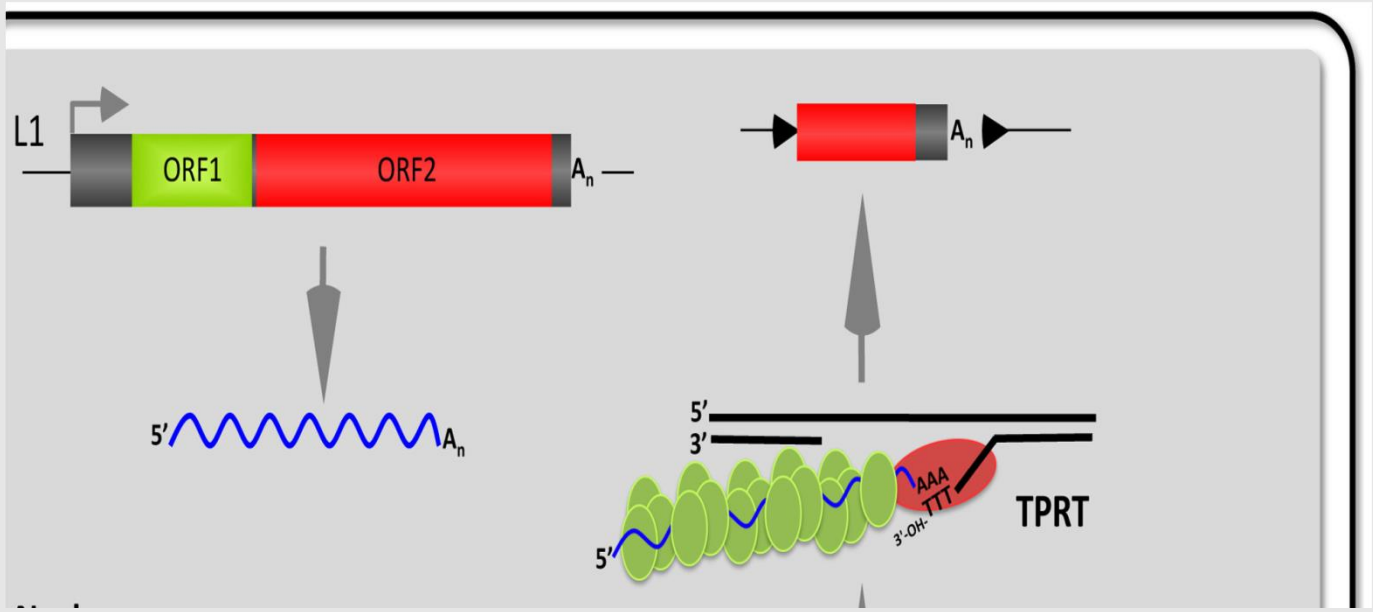
Behav Brain Res. 2017 Feb 9.

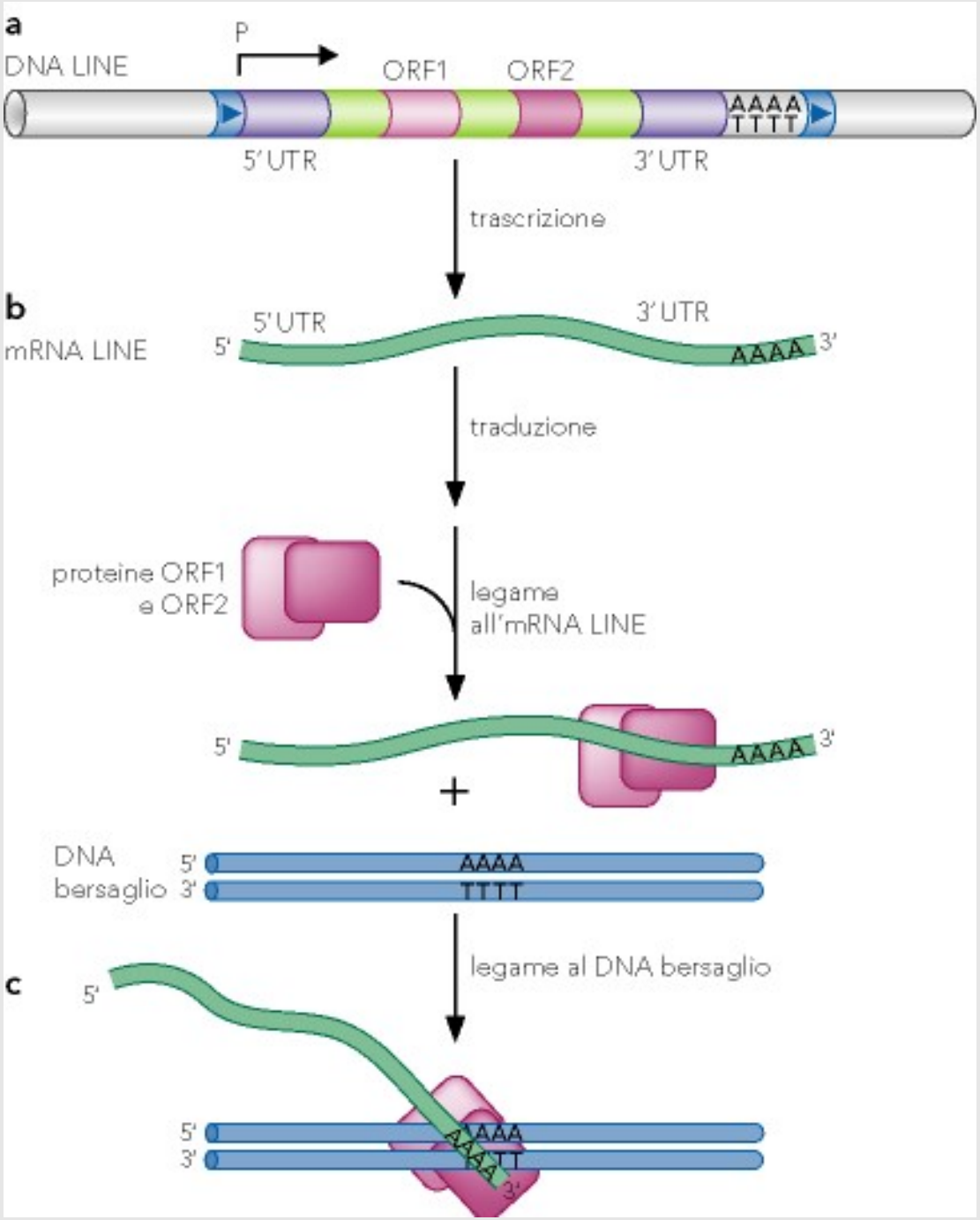
- Hypersocial behavior and biological redundancy in mice with reduced expression of PSD93

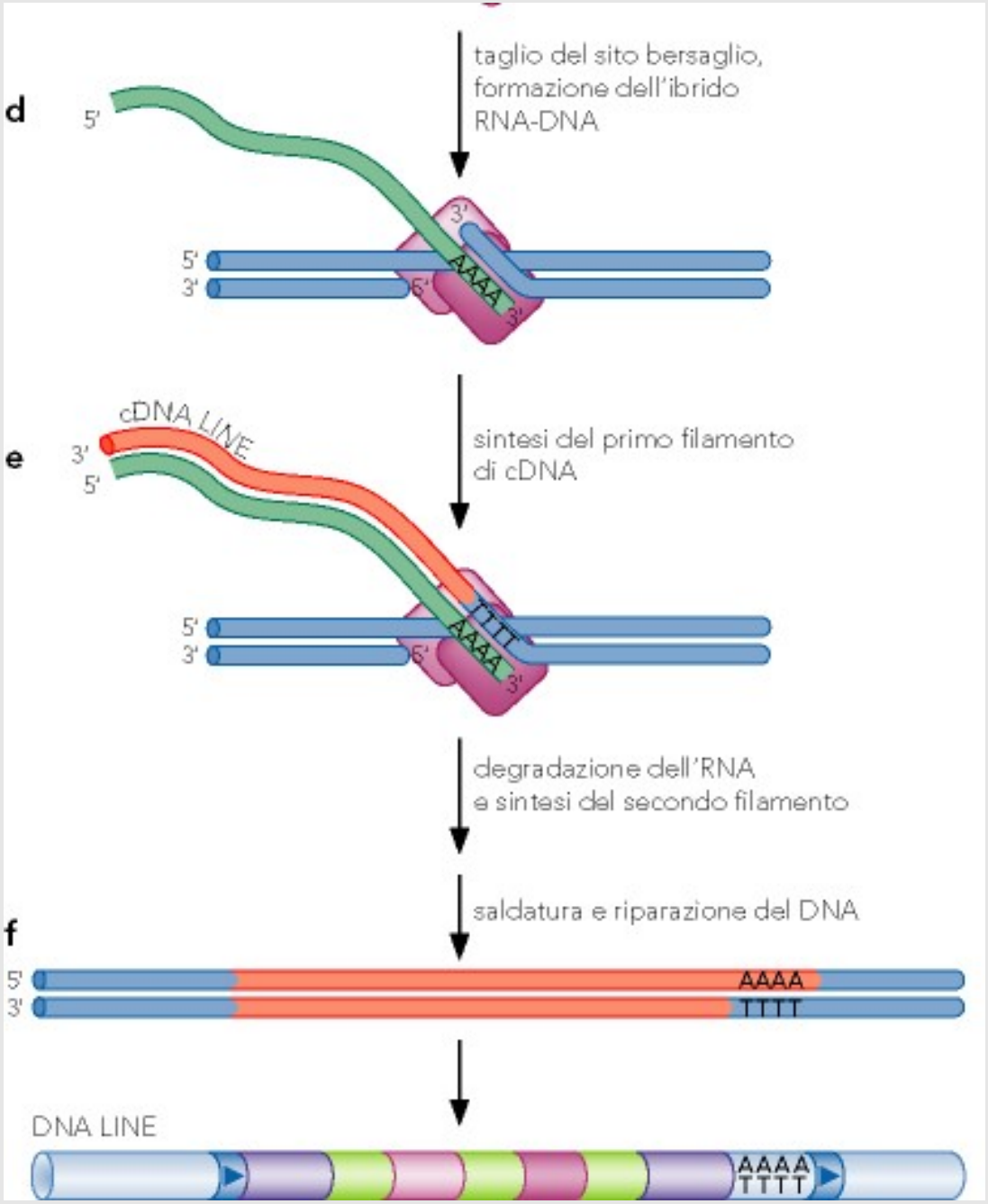
la trasposizione


5′UTR
ORF1
ORF2
3′UTR
AAAA
3
Transcription
4
Translation
ORF1p
ORF2p
5
Integration
5′UTR
ORF1
ORF2
3′UTR
1
Integrated LINE-1

target-site primed reverse transcription

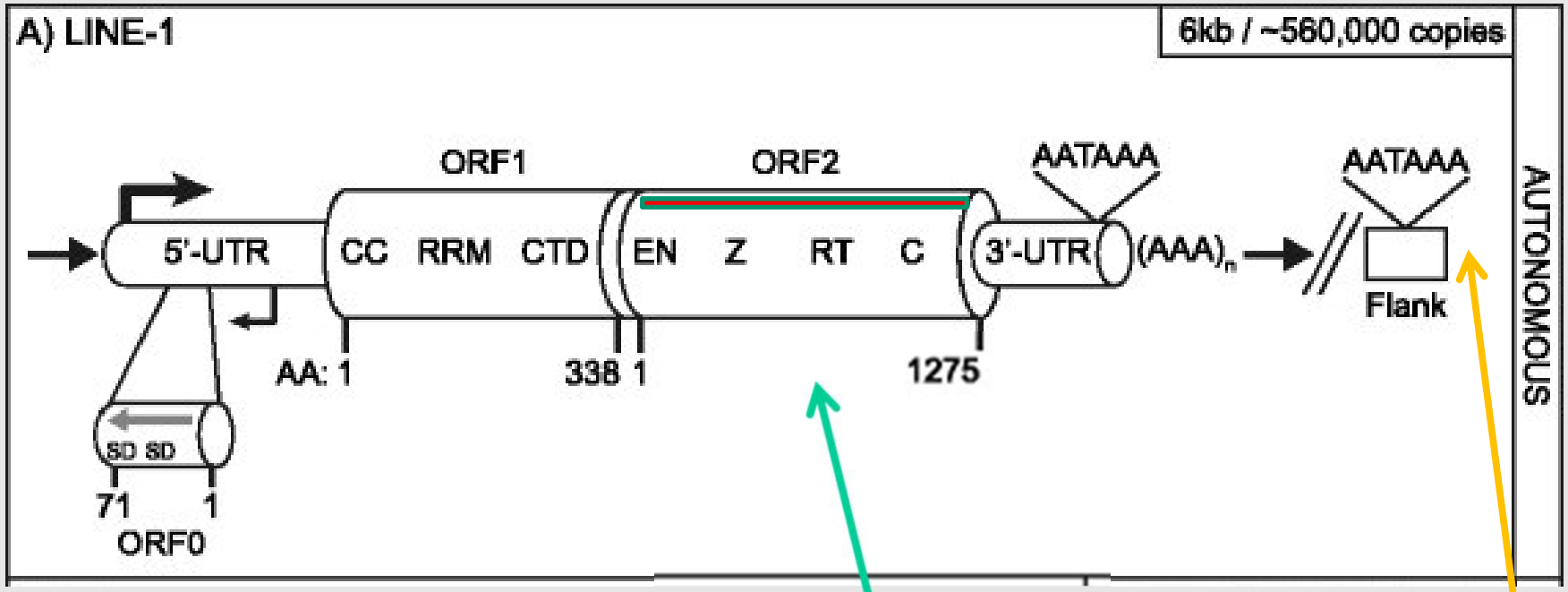



a
DNA LINE
P
ORF1
ORF2
AAAA
TTTT
5′ UTR
3′ UTR
trascrizione
b
mRNA LINE
5′ UTR
3′ UTR
5′
AAAA
3′
traduzione
proteine ORF1
e ORF2
legame
all'mRNA LINE
5′
AAAA
3′
+
DNA
bersaglio
5′
3′
AAAA
TTTT
legame al DNA bersaglio
c
5′
5′
3′
AAAA
TTTT
3′

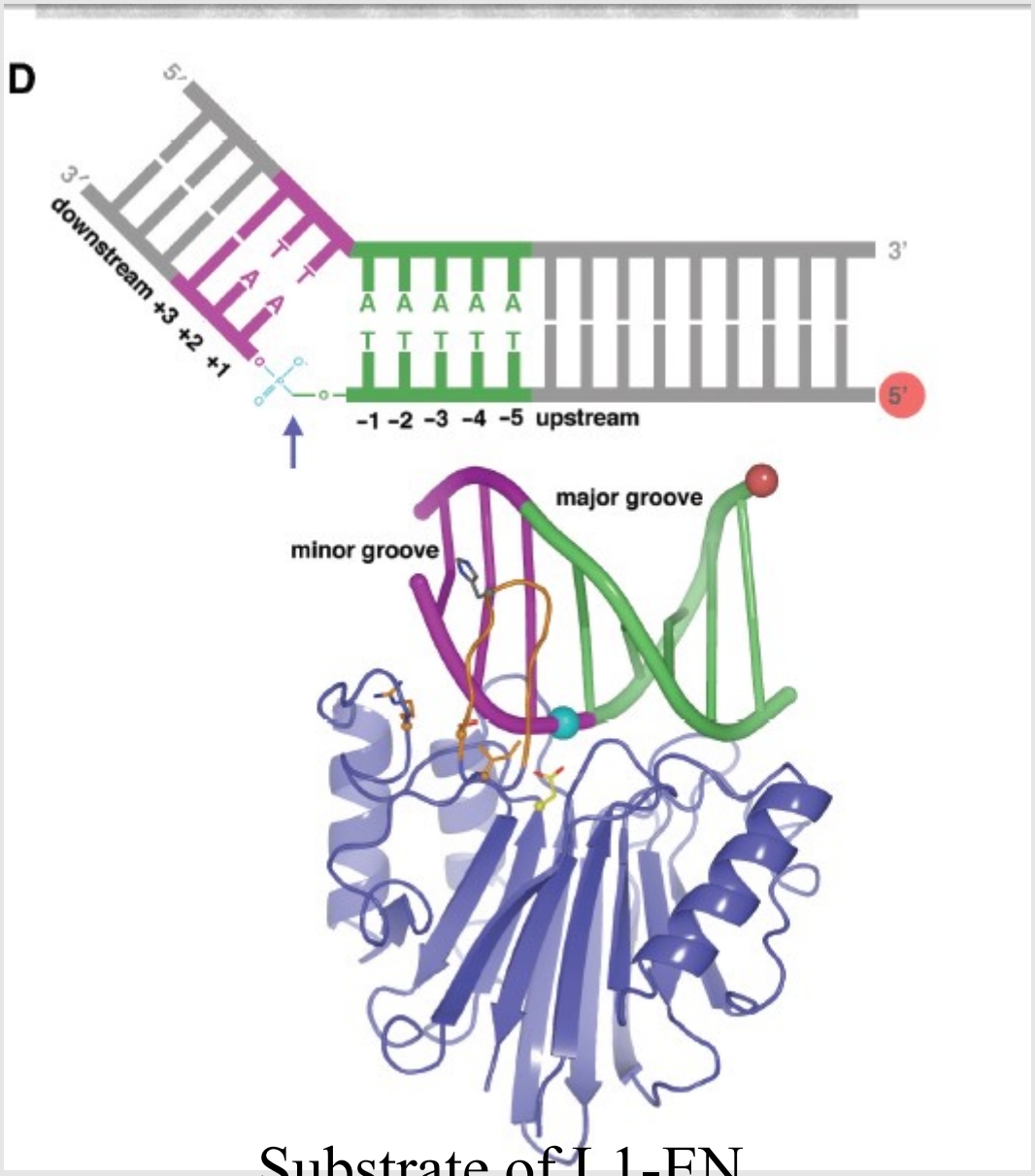


DNA damage response

Le proteine ed ENZIMI della trasposizione

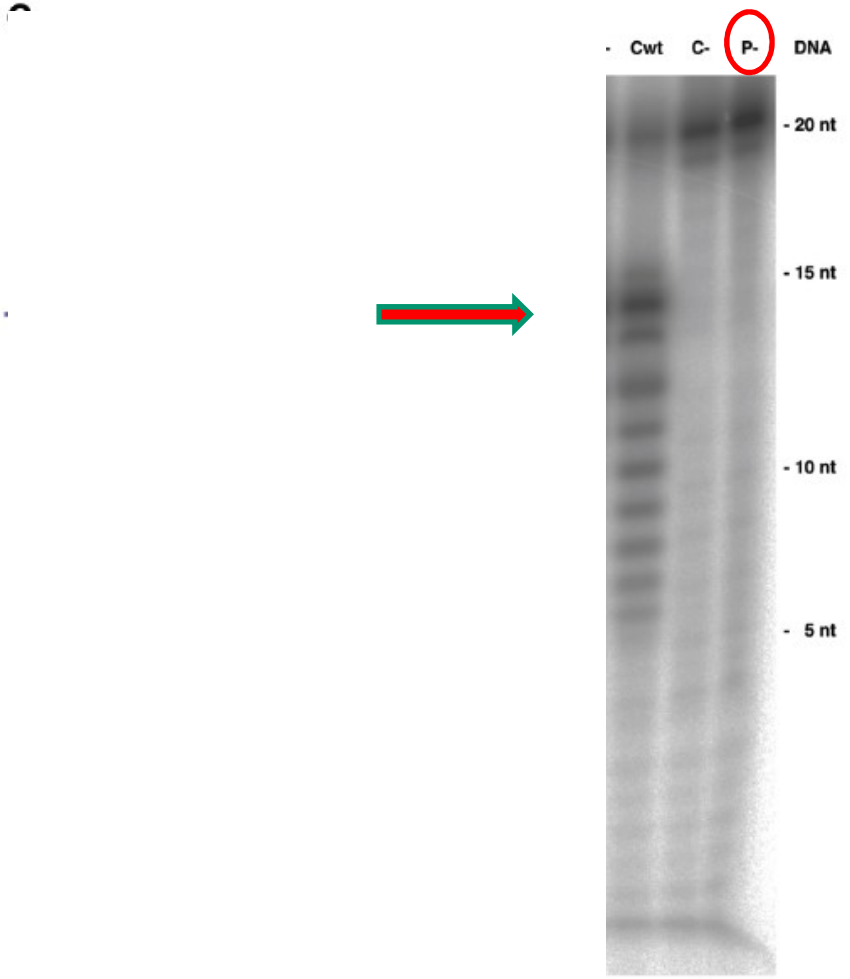


EN-endonuclease
Z domain
RT-reverse transcriptase
C-cysteine-rich.



Substrate of L1-EN

L1-EN cleavage



(P-): Cwt without L1-EN protein

Specificity of L1-EN

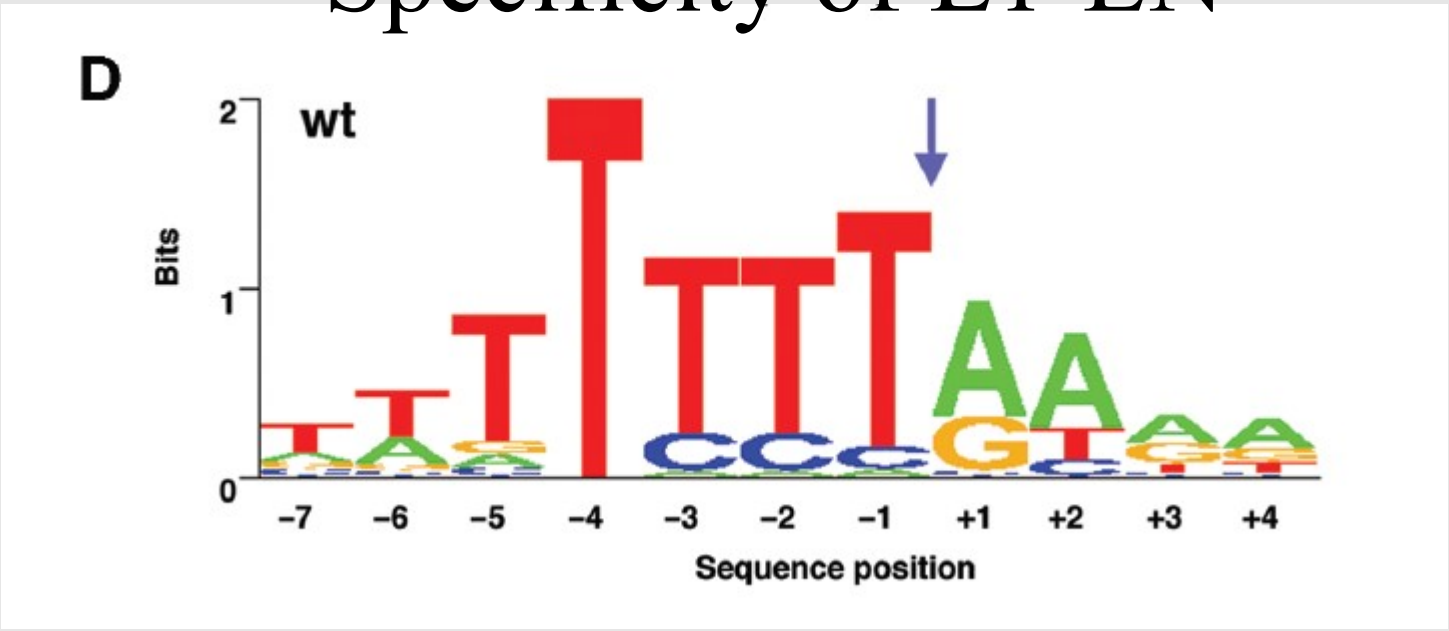
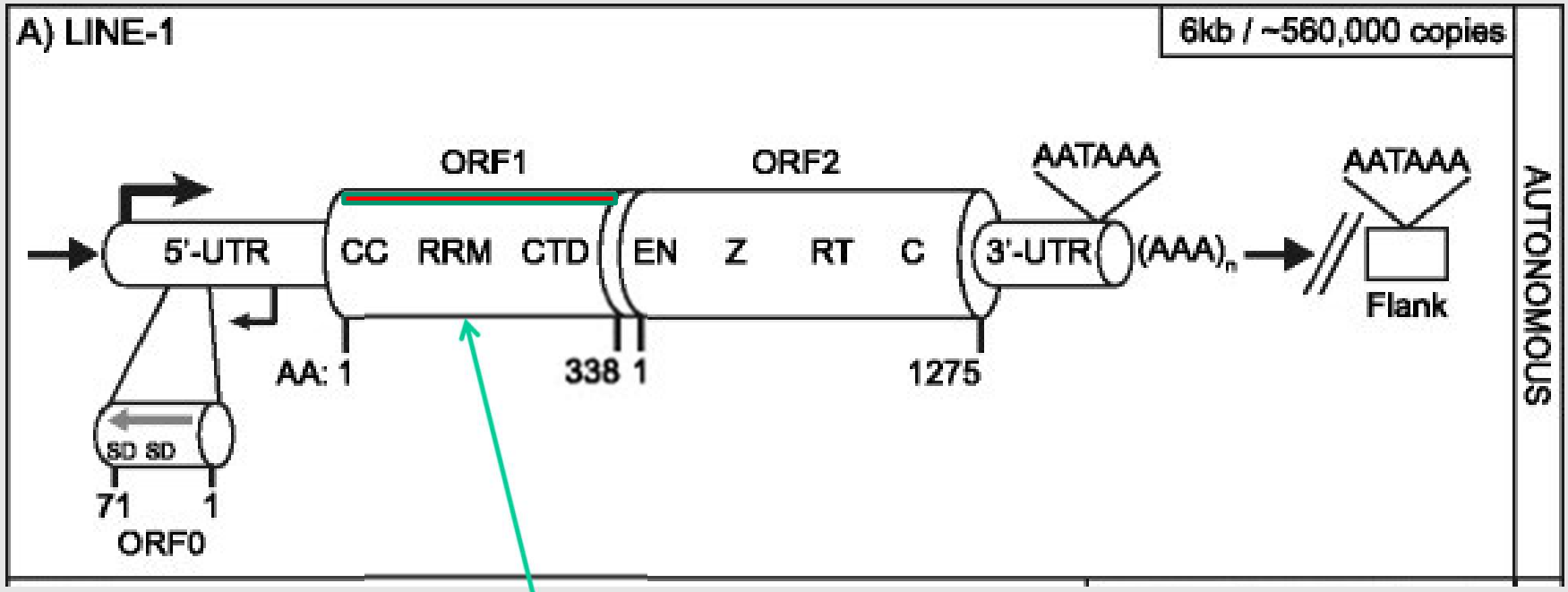


Table 1. Comparison of retrotransposition frequencies *in vivo* and plasmid nicking activities *in vitro*

L1-EN variant	Retrotransposition frequency[a], %	Plasmid nicking activity[b], %
wt	100 ± 17.1	100 ± 0.8
LTx	21 ± 2.4	29 ± 2.6
LR1	2 ± 2.3	6 ± 0.8
L3G	0 ± 2.2	10 ± 1.8
D145A	0[c]	3 ± 1.0
R155A	12 ± 3.3	19 ± 3.4
T192V	5 ± 3.0	–
S202A	32 ± 7.8	28 ± 2.2

EN mutants

Proporzionalità !!



CC-coiled coiled domain

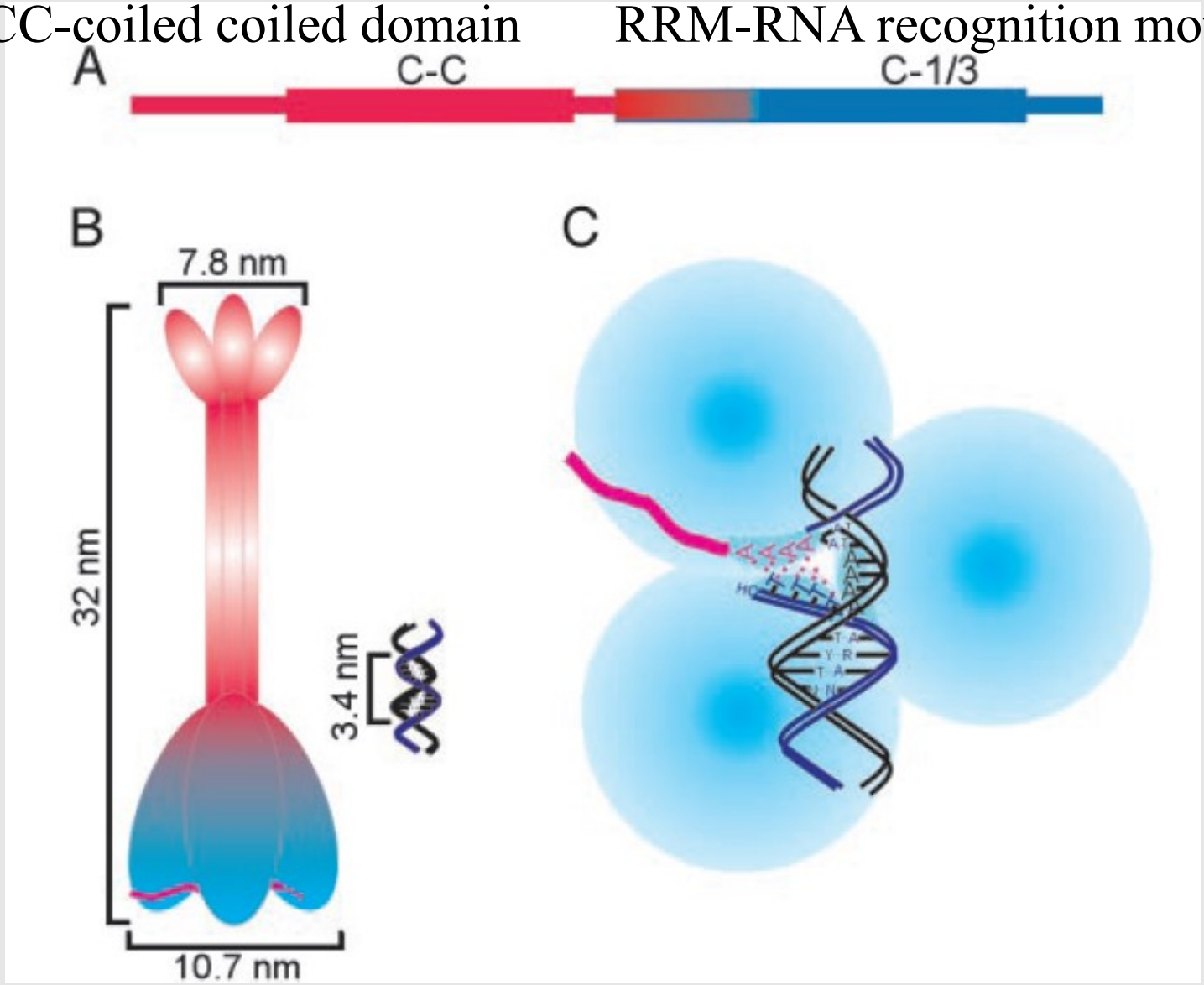
RRM-RNA recognition motif .

Trimeric structure for an essential protein in L1 retrotransposition

Sandra L. Martin*†,

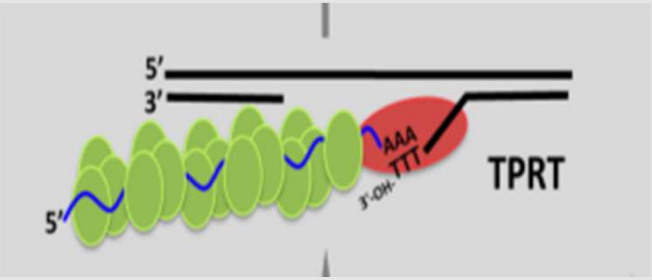
acidic(red) basic (blue)

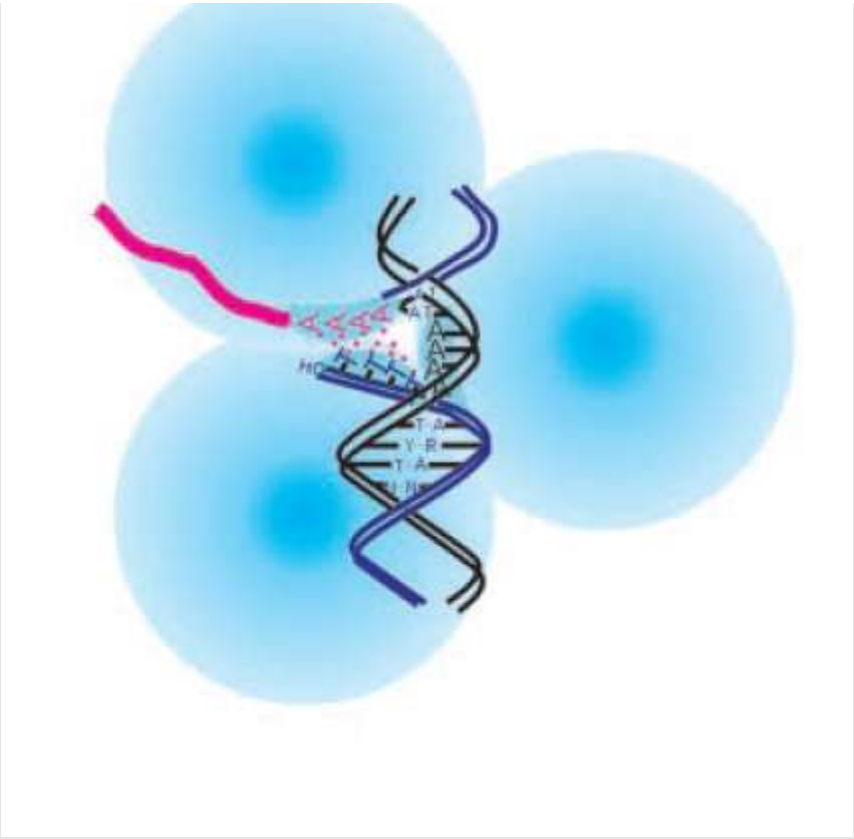
CC-coiled coiled domain RRM-RNA recognition motif



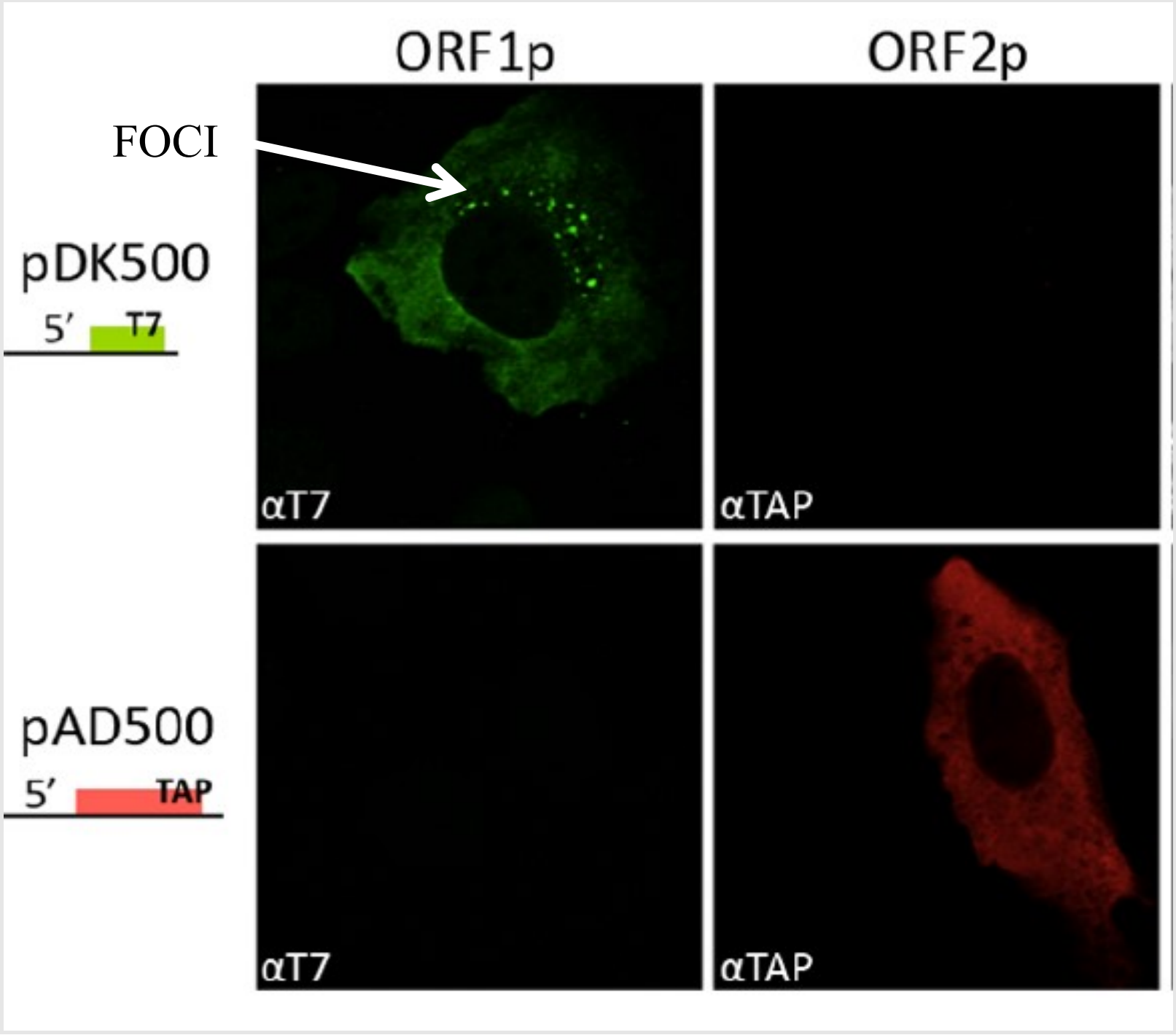
ORF1p binds single-stranded nucleic acids (L1 RNA and DNA) And functions as a nucleic acid chaperone.

1 Each subunit of the trimer contains one single-stranded nucleic acid binding interface which is bound with one of the DNA target strands or the polyA tail of the L1 RNA (red). The double-stranded regions of the target are not bound

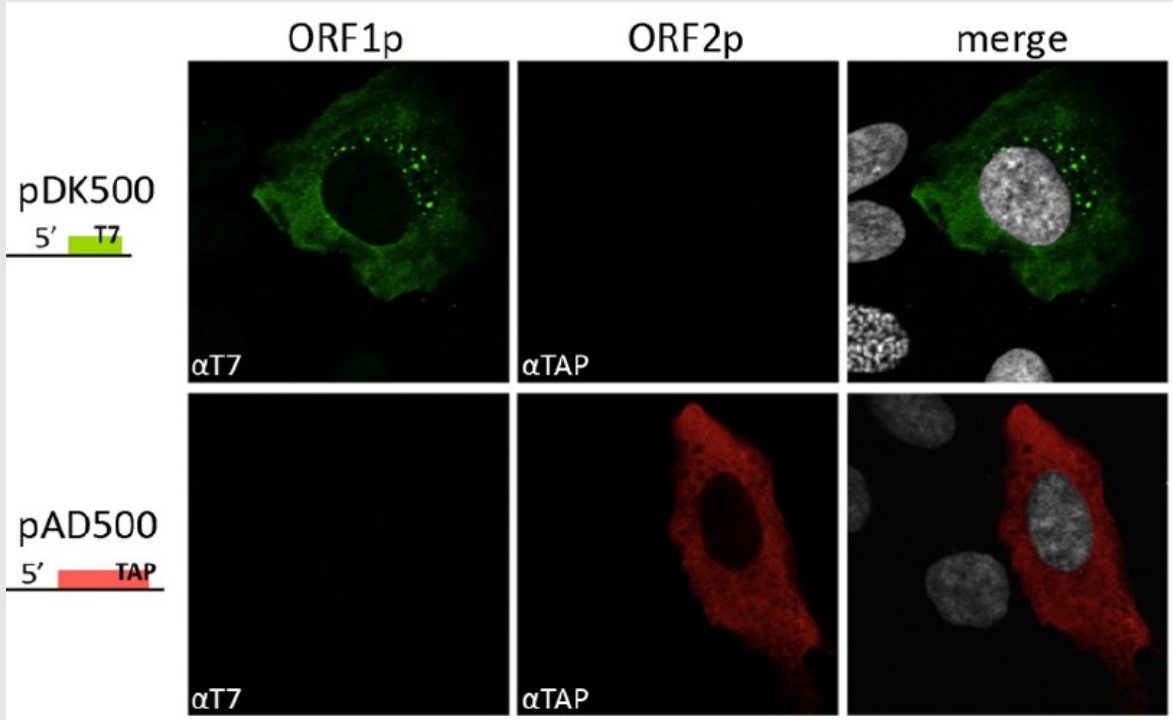


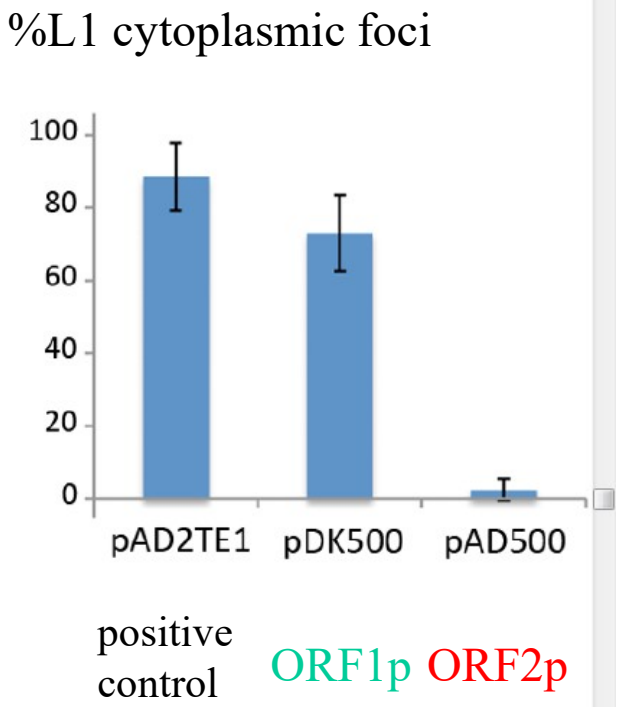


2 ORF1p coats the entire 7-kb L1 RNA to form a ribonucleoprotein particle
The nucleic acid chaperone activity of ORF1p melts the DNA and then facilitates formation of the RNA:DNA hybrid


ORF1p
ORF2p
FOCI
pDK500
5′
T7
αT7
αTAP
pAD500
5′
TAP
αT7
αTAP

ORF1p is necessary and sufficient for L1 cytoplasmic foci formation





T7-tagged ORF1p green

TAP-tagged ORF2p red;

MUTAGENESI INSERZIONALE

LINE-1

To date in humans, 124 LINE-1-mediated insertions which result in genetic diseases have been reported.

Hancks and Kazazian Mobile DNA (2016) 7:9

Disease causing LINE-1 insertions have provided a wealth of insight and the foundation for valuable tools to study these genomic parasites.

EVENTI PATOLOGICI RARI

Direct insertional mutagenesis by L1 resulted in diseases including muscular dystrophy, hemophilia, and breast cancer

POCHISSIMI ELEMENTI L1 SONO ATTIVI

it is estimated, on the basis of full-length L1 elements with preserved open reading frames and activity in in vitro retrotransposition assays, that there are 50 to 120 currently active L1 repeats in the human genome, of which a small number are highly active -“hot-L1s”