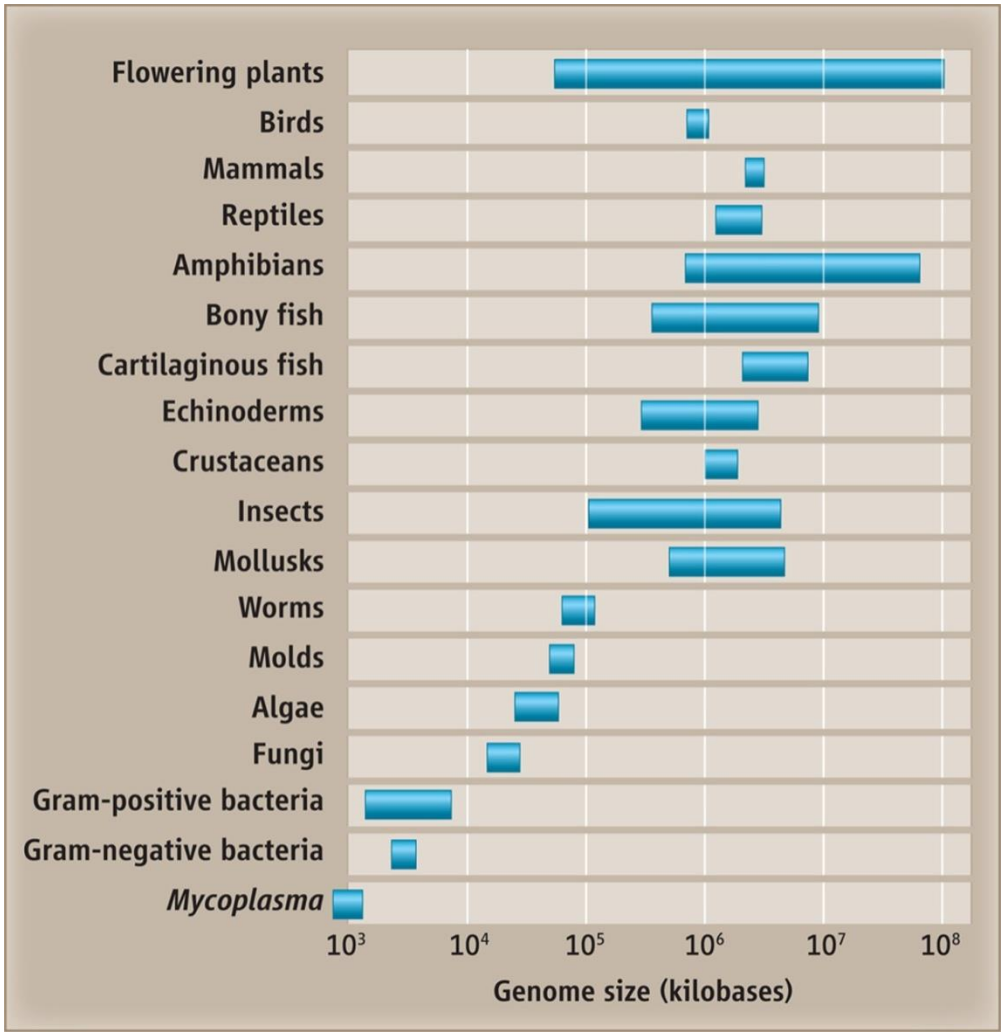
Mobilna DNA pri človeku

18. marec 2014

Paradoks C - vrednosti

Velikost genoma ni povezana z njegovo kompleksnostjo.



N V Fedoroff Science 2012;338:758-767

Nukleotidna zaporedja celih genomov

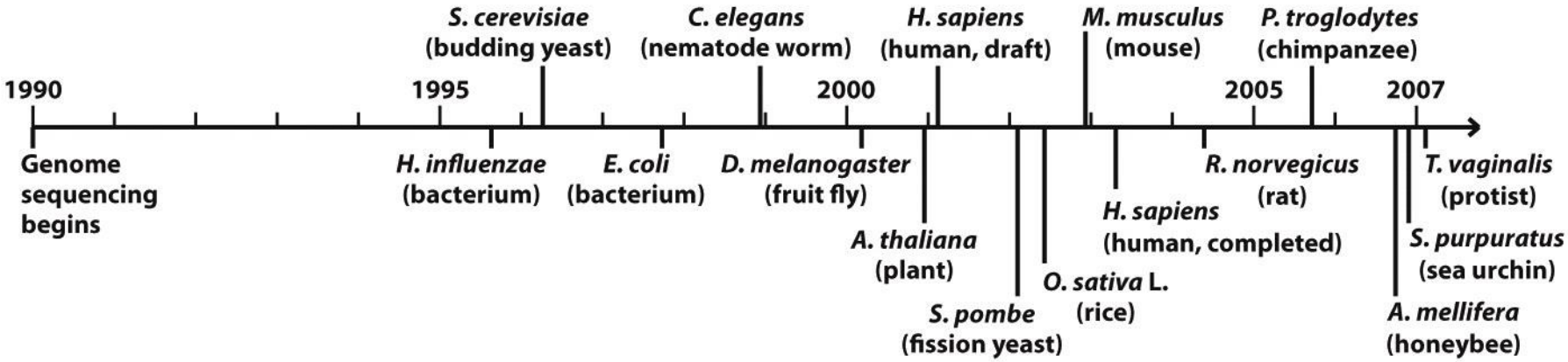


Figure 9-18
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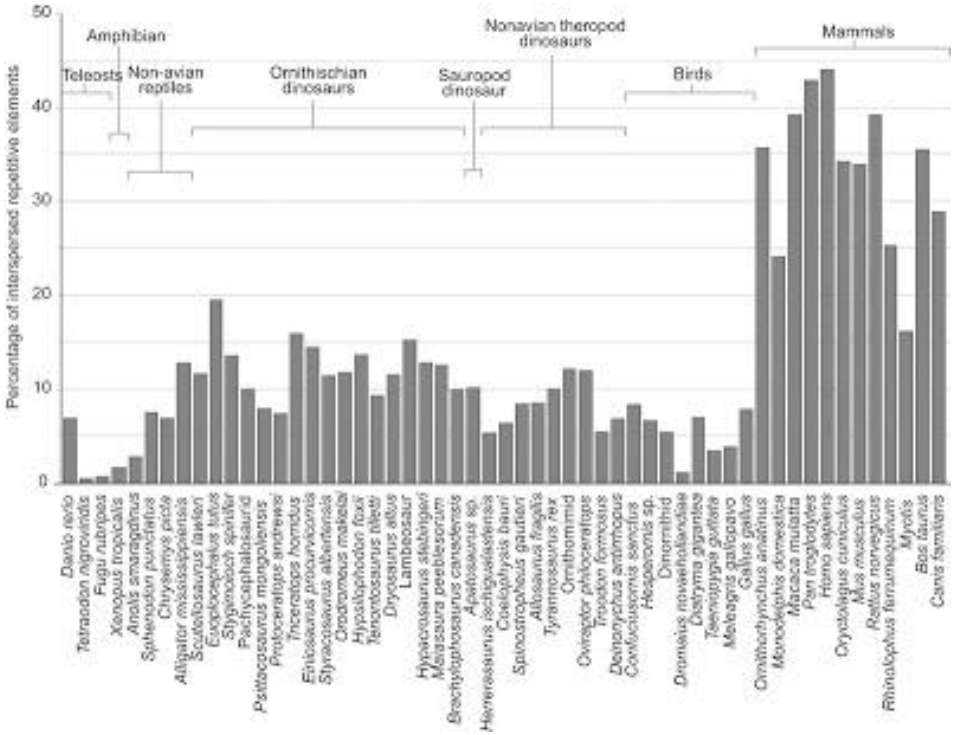
Do 17. marca 2014 je bilo določeno nukleotidno zaporedje 18830-tih genomov (Genomes OnLine Database; 3045 končanih, 15785 stalni draft).

Mobilni ali transpozicijski elementi

- Razpršena zaporedja po genomu
- Prenašajo se znotraj genoma in med genomi
- Razširjeni pri prokariontih in evkariontih
- predstavljajo velik del genoma – npr. do 70 % pri rastlinah



Človeški genom

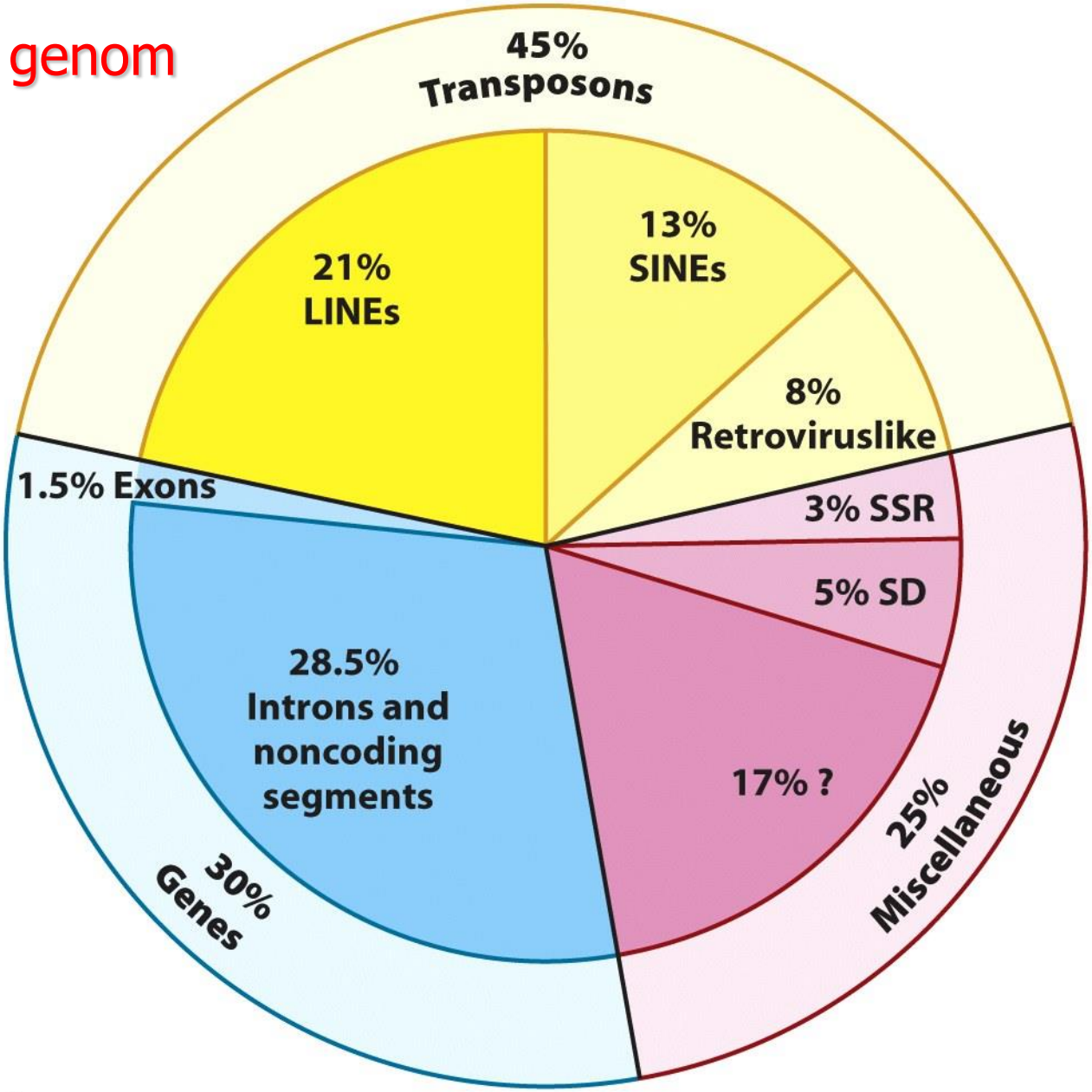


Figure 24-8
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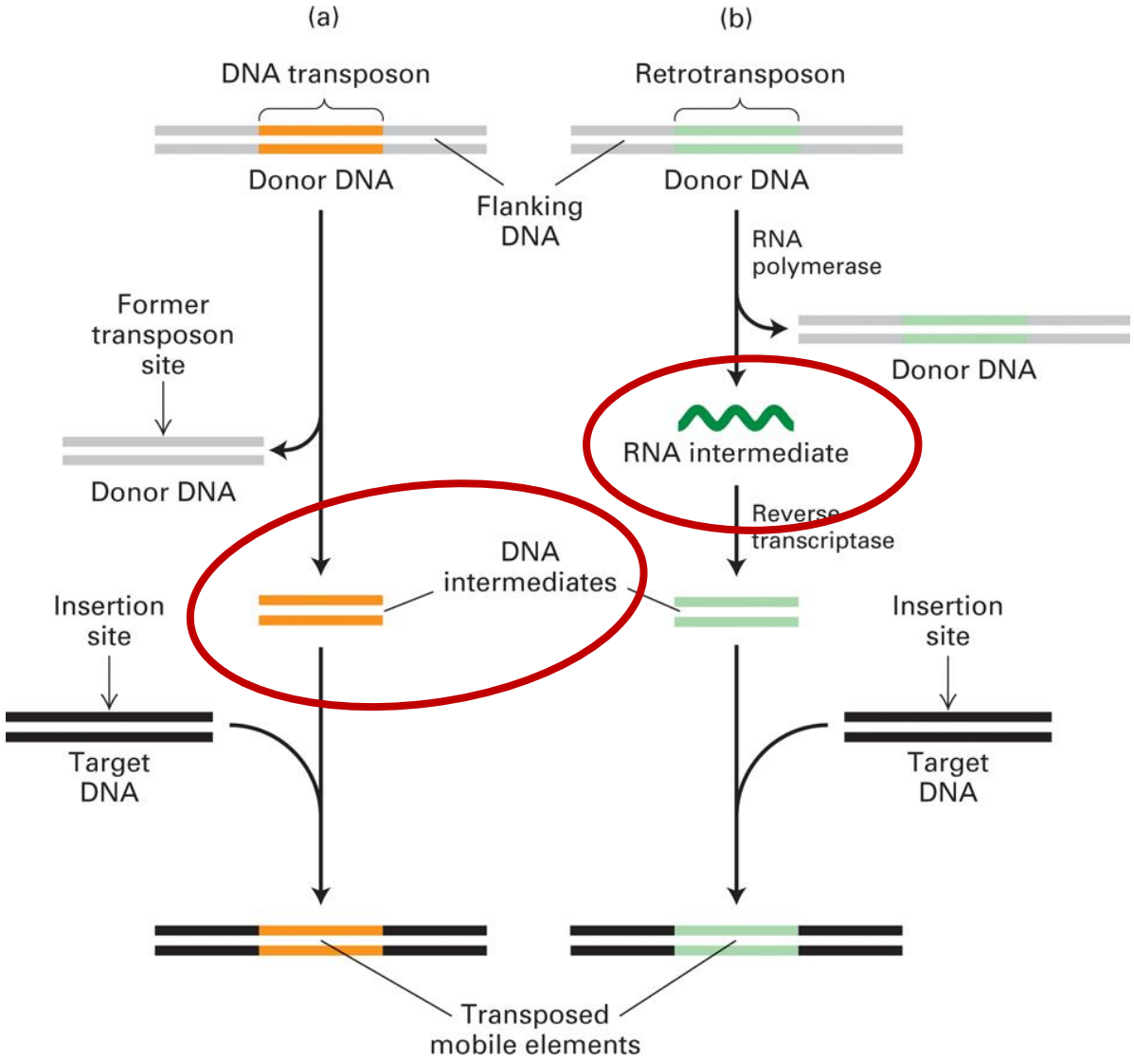
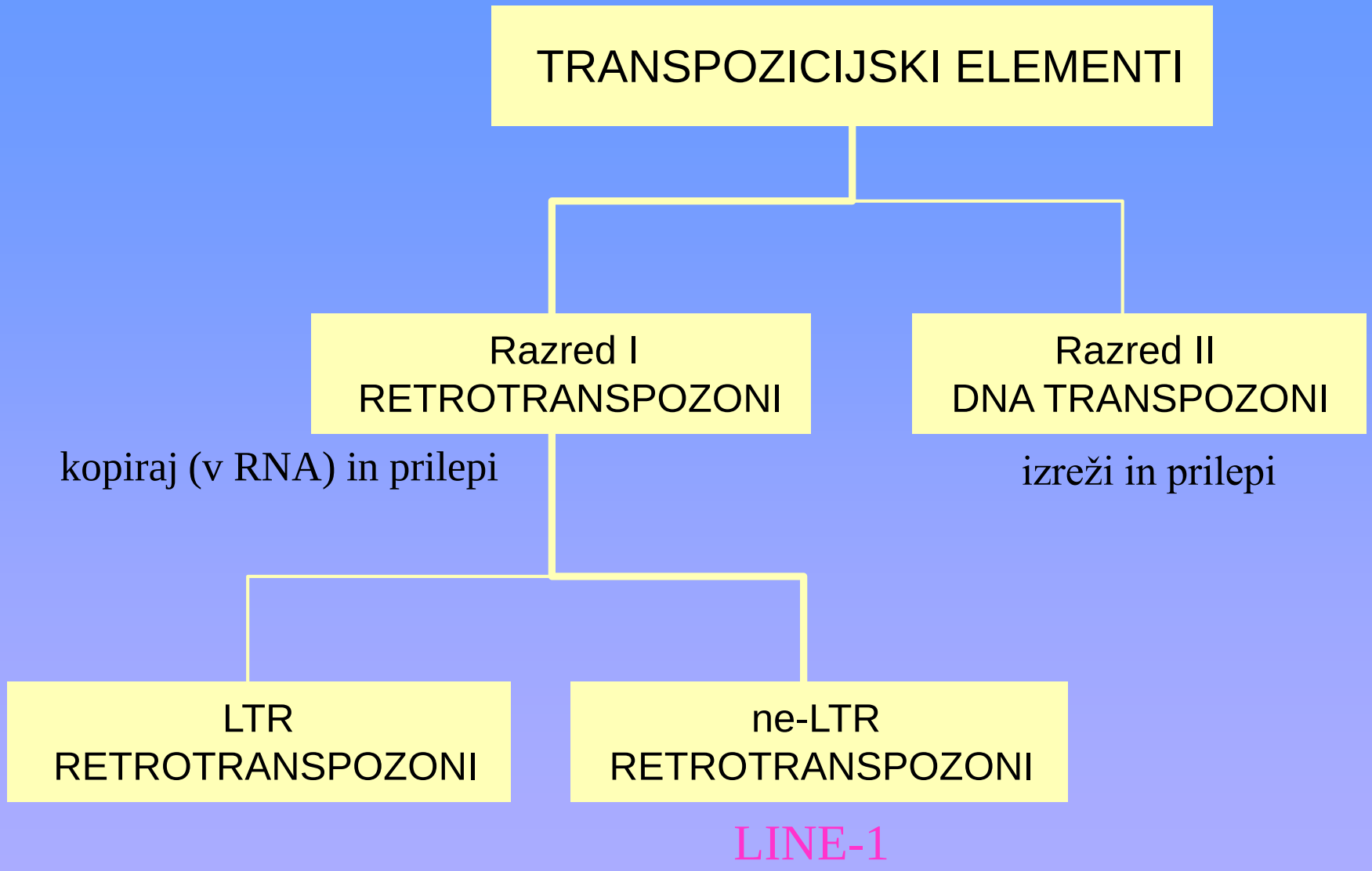
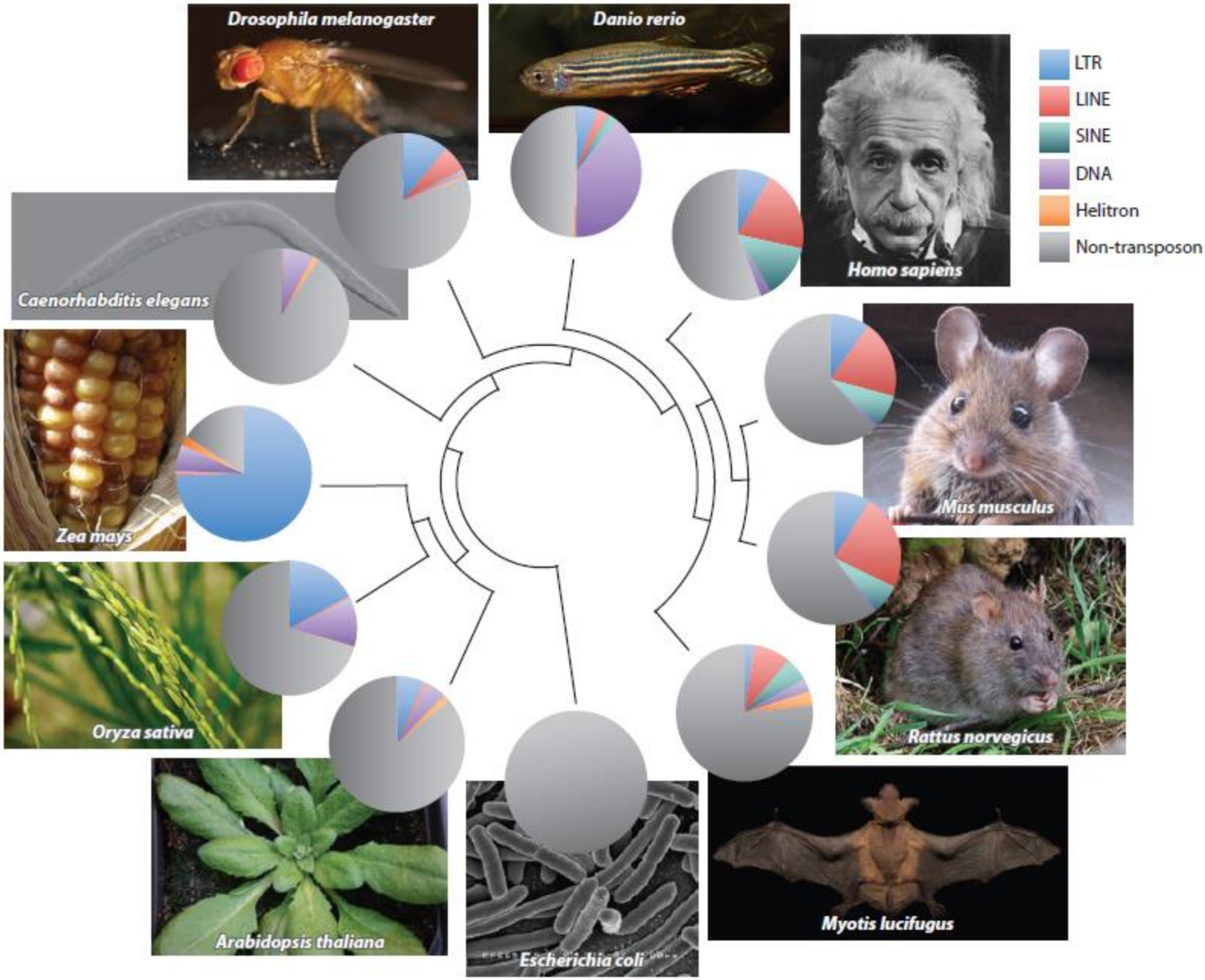
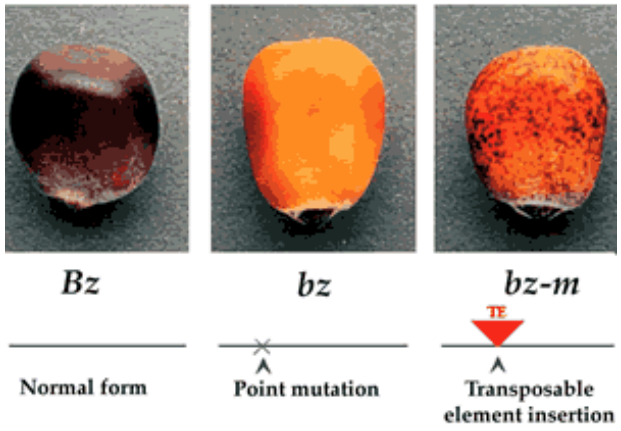
Mobilna elementi: DNA transpozoni in retrotranspozoni




TRANSPOZICIJSKI ELEMENTI
Razred I
RETROTRANSPOZONI
Razred II
DNA TRANSPOZONI
kopiraj (v RNA) in prilepi
izreži in prilepi
LTR
RETROTRANSPOZONI
ne-LTR
RETROTRANSPOZONI
LINE-1


Drosophila melanogaster
Danio rerio
Homo sapiens
LTR
LINE
SINE
DNA
Helitron
Non-transposon
Caenorhabditis elegans
Zea mays
Mus musculus
Oryza sativa
Rattus norvegicus
Arabidopsis thaliana
Escherichia coli
Myotis lucifugus



Barbara McClintock
1902–1992

Nobelova nagrada za fiziologijo ali medicino 1983

Mišljenje o mobilnih elementih

NEKOČ:

- **sebična (selfish) DNA:** molekularni paraziti, močni mutageni, ‘ugrabitelji’ celičnih mehanizmov za lastno razmnoževanje

- **junk DNA:** v najboljšem primeru benigni

DANES:

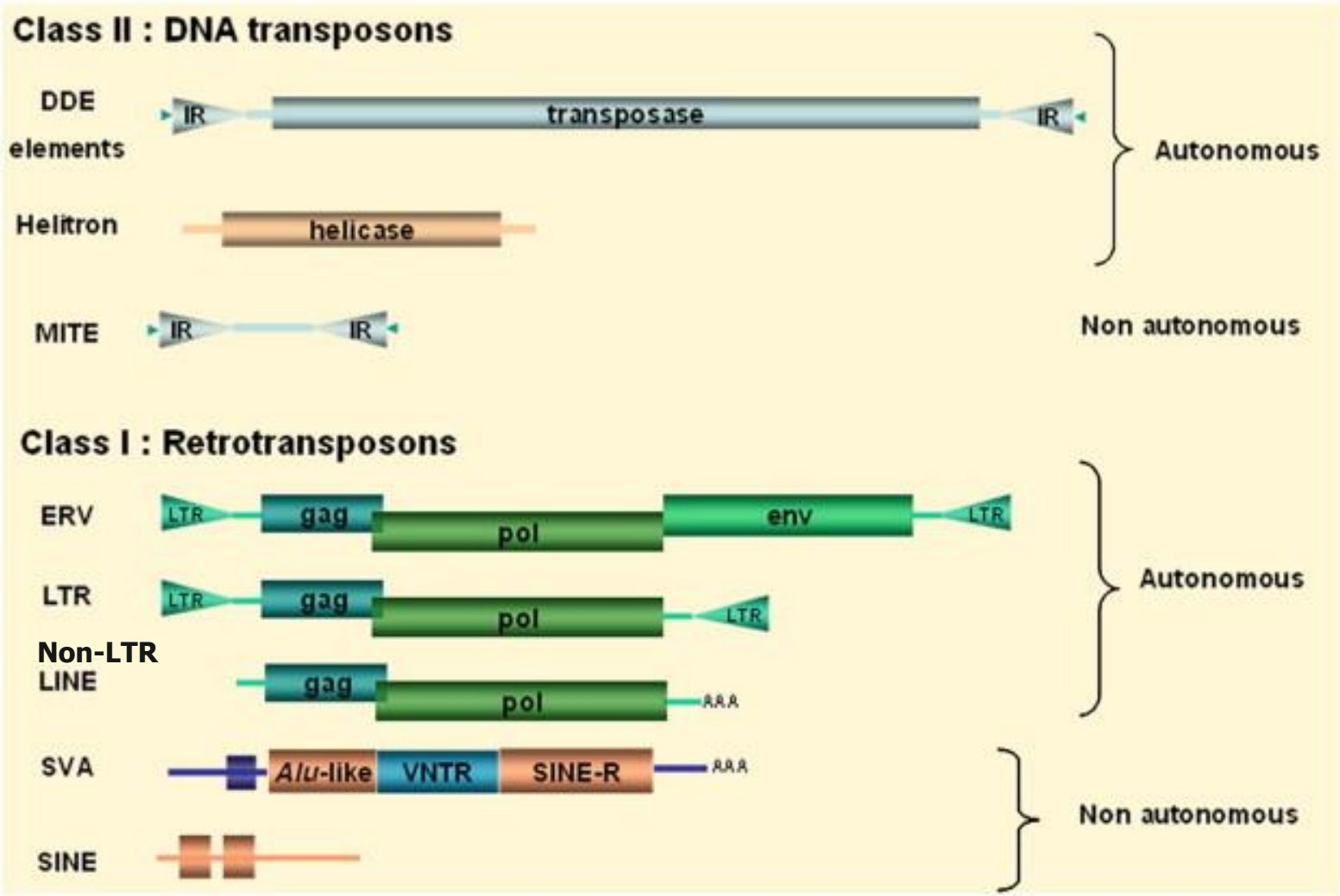
- **zaklad:** vplivajo na evolucijo genomov in izražanje genov

Evolucijska dinamika transpozicijskih elementov

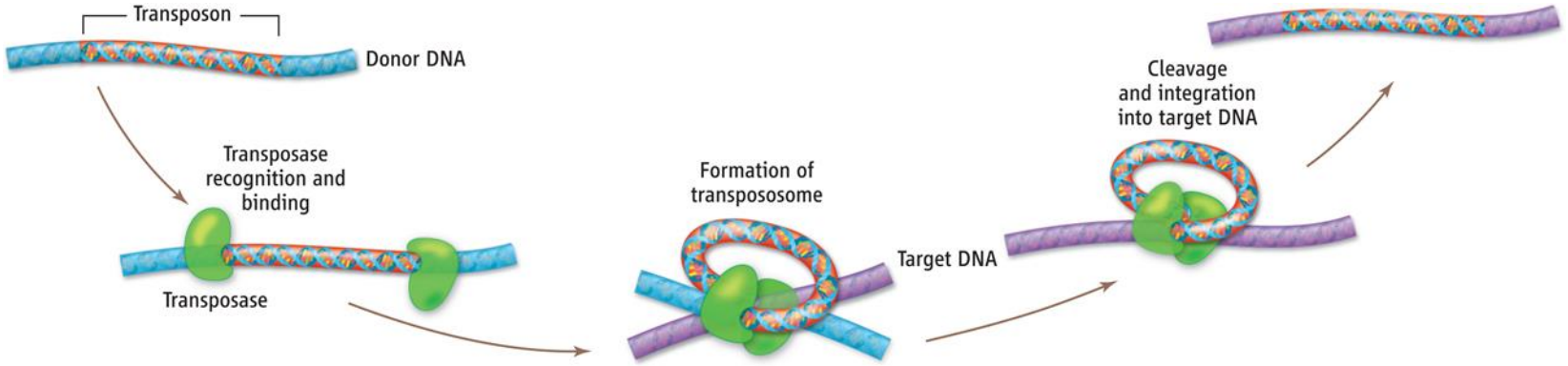
Življenski cikel TE:

- Vertikalni prenos
- Povečanje števila kopij
- Gostitelj inhibira transpozicijo
- Vertikalna inaktivacija (kopičenje mutacij) in stohastična izguba
- Ponovni vnos TE v genom s horizontalnim prenosom

Struktura in evolucija transpozicijskih elementov

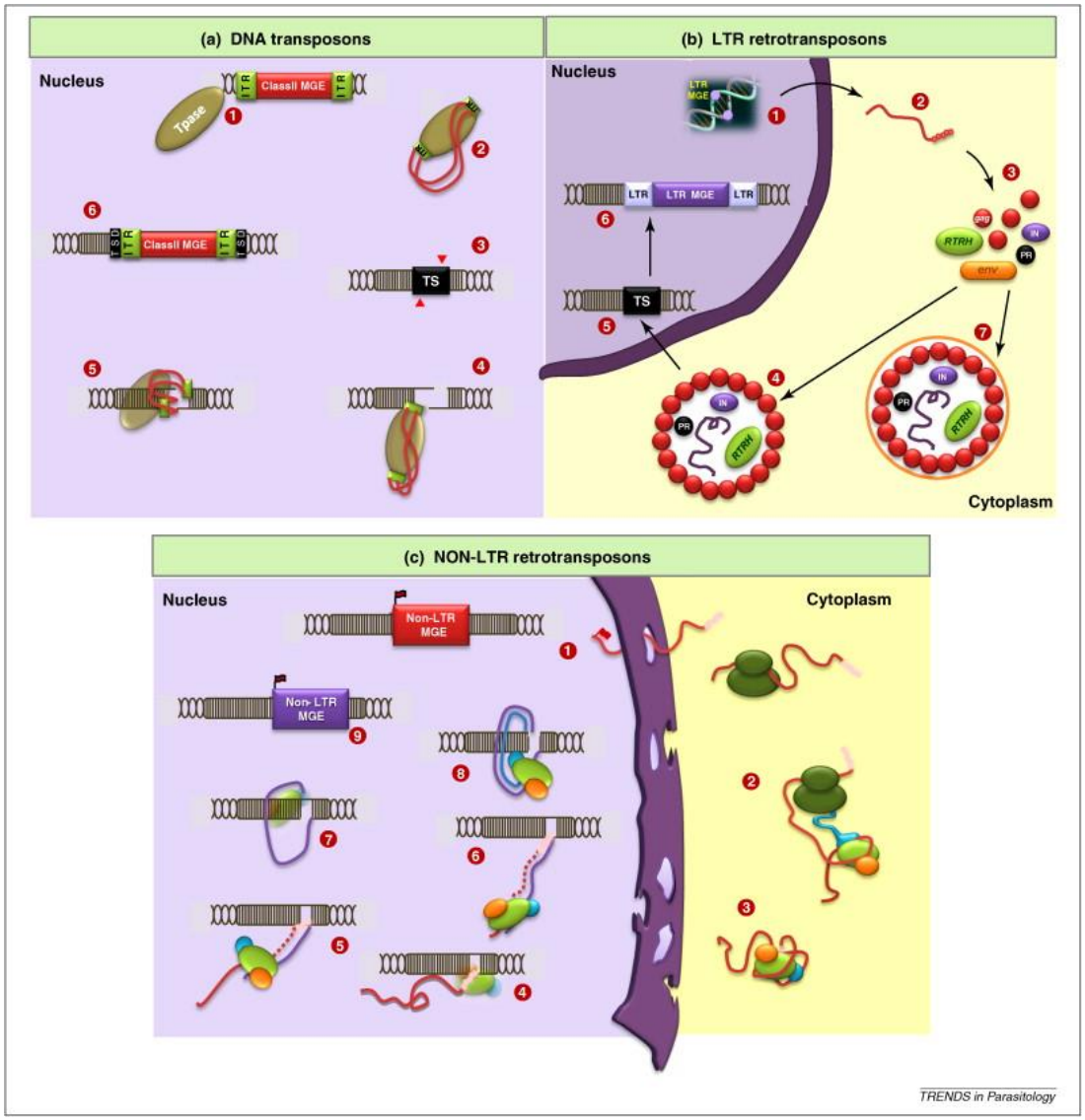


'Izreži in prilepi' mehanizem prenosa DNA transpozona



N V Fedoroff Science 2012;338:758-767

'Kopiraj in prilepi' mehanizem prenosa retrotranspozona



Ponavljajoča se zaporedja v človeškem genomu

- Tandemske ponovitve (sateliti)
- Razpršene ponovitve (mobilni ali transpozicijski elementi)
- Dva tretjini človeškega genoma sestavljajo ponovitve (de Koning et al., 2011)

TABLE 9.13 MAJOR CLASSES OF HIGH-COPY-NUMBER TANDEMLY REPEATED HUMAN DNA

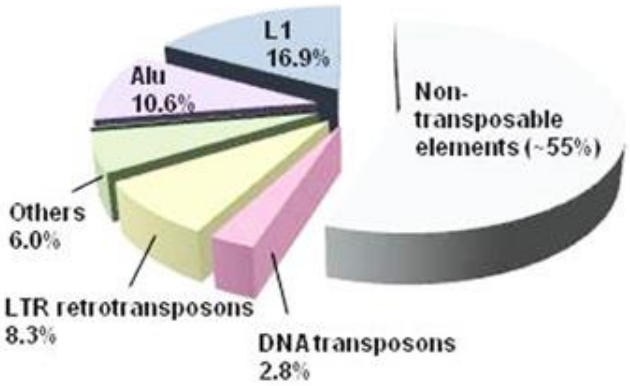
Class[a]	Total array size unit	Size or sequence of repeat unit	Major chromosomal location(s)
Satellite DNA[b]	often hundreds of kilobases		associated with heterochromatin
α (alphoid DNA)		171 bp	centromeric heterochromatin of all chromosomes
β (*Sau*3A family)		68 bp	notably the centromeric heterochromatin of 1, 9, 13, 14, 15, 21, 22, and Y
Satellite 1		25–48 bp (AT-rich)	centromeric heterochromatin of most chromosomes and other heterochromatic regions
Satellite 2		diverged forms of ATTCC/GGAAT	most, possibly all, chromosomes
Satellite 3		ATTCC/GGAAT	13p, 14p, 15p, 21p, 22p, and heterochromatin on 1q, 9q, and Yq12
DYZ19		125 bp	~400 kb at Yq11
DYZ2		AT-rich	Yq12; higher periodicity of ~2470 bp
Minisatellite DNA	0.1–20 kb		at or close to telomeres of all chromosomes
Telomeric minisatellite		TTAGGG	all telomeres
Hypervariable minisatellites		9–64 bp	all chromosomes, associated with euchromatin, notably in sub-telomeric regions
Microsatellite DNA	< 100 bp	often 1–4 bp	widely dispersed throughout all chromosomes

[a]The distinction between satellite, minisatellite, and microsatellite is made on the basis of the total array length, not the size of the repeat unit.
[b]Satellite DNA arrays that consist of simple repeat units often have base compositions that are radically different from the average 41% G+C (and so could be isolated by buoyant density gradient centrifugation, when they would be differentiated from the main DNA and appear as *satellite bands*—hence the name).

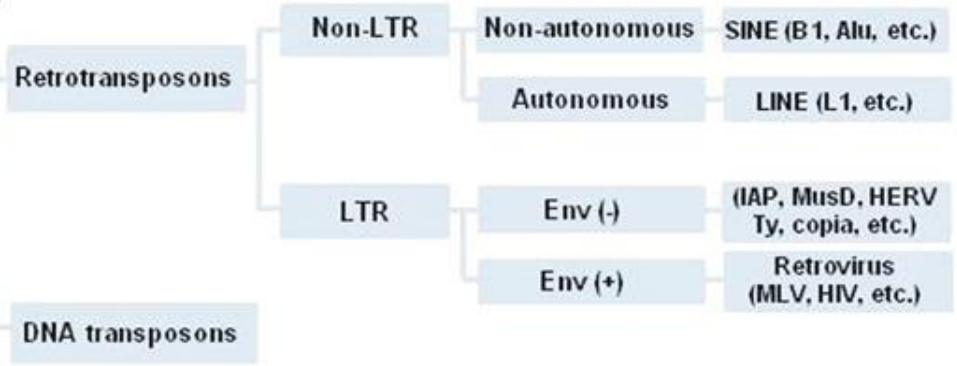
Table 9.13 Human Molecular Genetics, 4ed. (© Garland Science)

Mobilni elementi v človeškem genomu

A



B



C

			Copy no. Total	Active
Autonomous	Mouse	MERV	200,000	n.d.
		IAP	1,000	300
		MusD	100	<10
	Human	HERV	230,000	n.d.
	Mouse	L1	600,000	3,000
	Human	L1	850,000	80
Non-autonomous	Mouse	B1	500,000	
	Human	Alu	500,000~1000,000	

TABLE 6-1 Major Classes of Nuclear Eukaryotic DNA and Their Representation in the Human Genome

Class	Length	Copy Number in Human Genome	Fraction of Human Genome (%)
Protein-coding genes	0.5–2200 kb	≈25,000	≈55* (11.8)†
Tandemly repeated genes			
U2 snRNA	6.1 kb‡	≈20	<0.001
rRNAs	43 kb‡	≈300	0.4
Repetitious DNA			
Simple-sequence DNA	1–500 bp	Variable	≈6
Interspersed repeats (mobile DNA elements)			
DNA transposons	2–3 kb	300,000	3
LTR retrotransposons	6–11 kb	440,000	8
Non-LTR retrotransposons			
LINEs	6–8 kb	860,000	21
SINEs	100–400bp	1,600,000	13
Processed pseudogenes	Variable	1−≈100	≈0.4
Unclassified spacer DNA§	Variable	n.a.	≈25

*Complete transcription units including introns.
†Transcription units not including introns. Protein-coding regions (exons) total 1.1% of the genome.
‡Length of each repeat in a tandemly repeated sequence.
§Sequences between transcription units that are not repeated in the genome; n.a. = not applicable.

SOURCE: International Human Genome Sequencing Consortium, 2001, *Nature* **409**:860 and 2004, *Nature* **431**:931.

Mobilni elementi v človeškem genomu

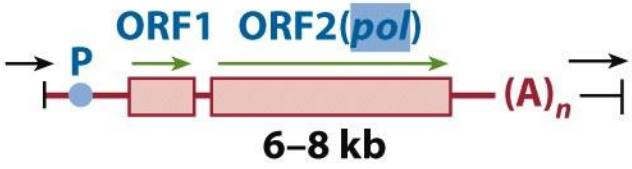
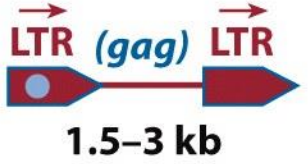
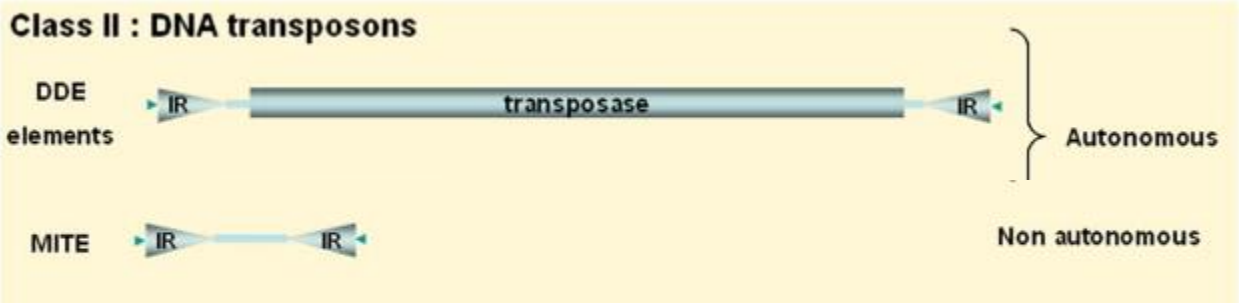
		autonomous	nonautonomous
LINEs			
LINE-1 family	~600,000		
LINE-2 family	~370,000		
LINE-3 family	~44,000		
SINEs			
Alu family	~1,200,000		
MIR	~450,000		
MIR3	~85,000		
retrovirus-like (LTR transposons)			
HERV families	~240,000		
MaLR	~285,000		
DNA transposon fossils			
MER1 (Charlie)	~213,000		
MER2 (Tigger)	~68,000		
others (including marine, etc.)	~60,000		

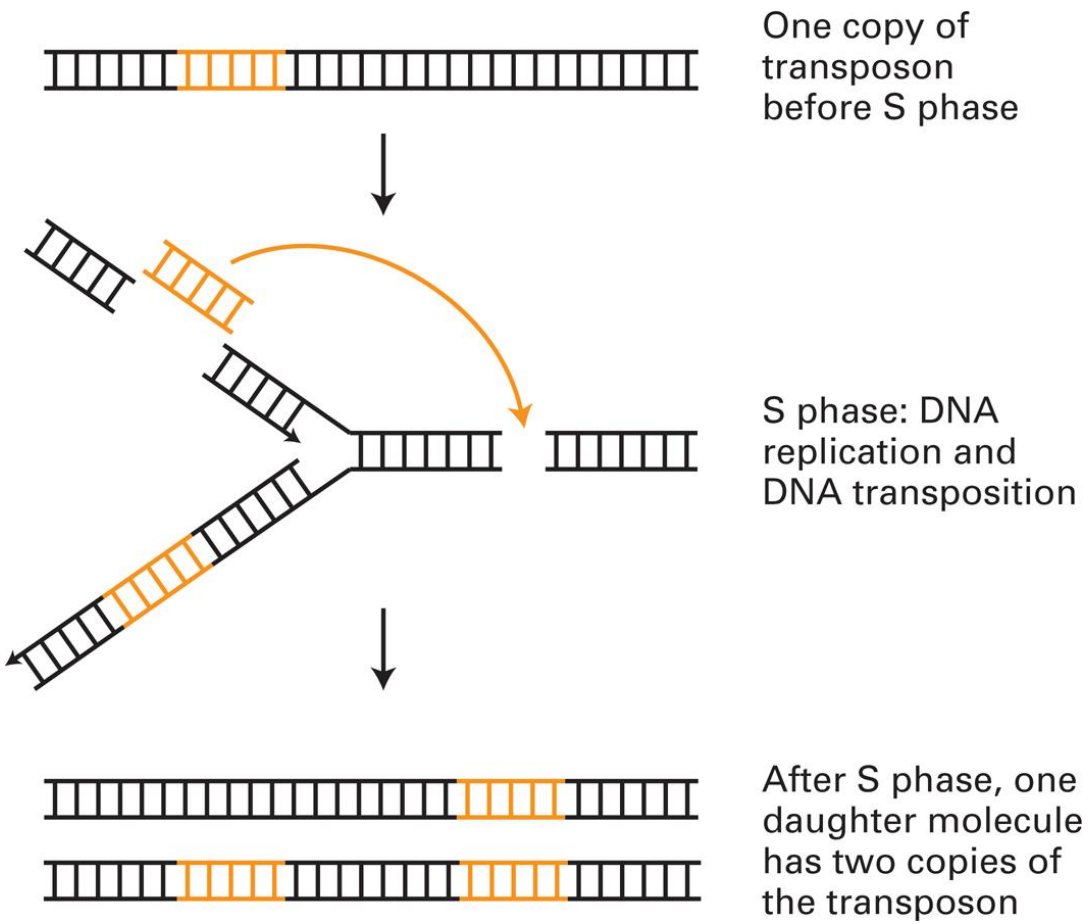
Figure 9.20 Human Molecular Genetics, 4ed. (© Garland Science)

DNA transpozoni v človeškem genomu



- 3 % genoma
- ~ 2 kb veliki
- Neaktivni so že vsaj 37 milijonov let (zgodnji primati). Izjema med sesalci so netopirji.
- Izreži in prilepi mehanizem transpozicije, helitroni (niso pri človeku) imajo replikativno transpozicijo.
- Pomnoževanje je možno med meiozo.
- Mariner, MITE (miniature inverted repeat transposable elements)

Povečanje števila kopij transpozonov med meiozo



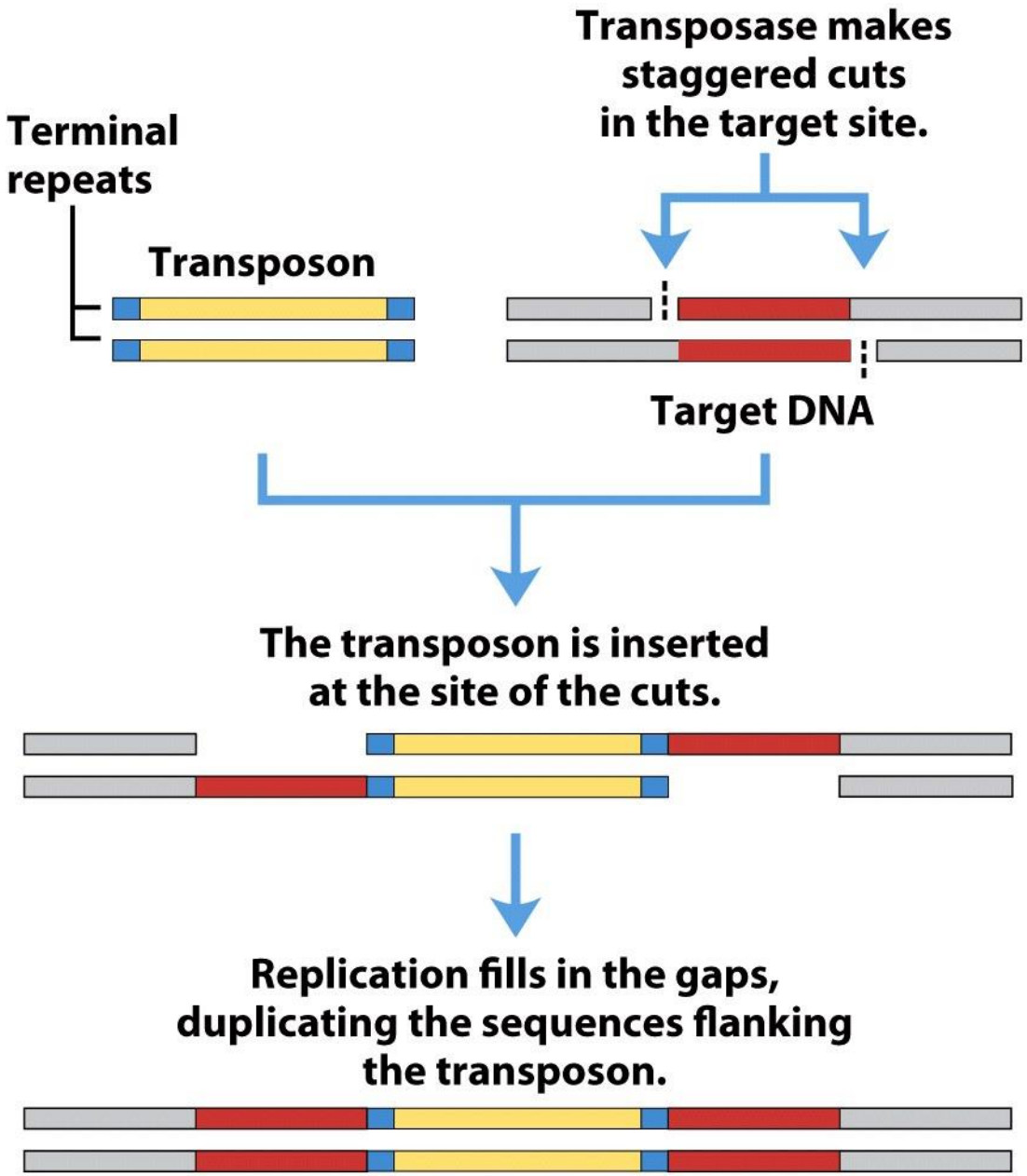


Figure 25-44

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LTR retrotranspozoni v človeškem genomu

- HERV – human endogenous retrovirus
- 8 % genoma
- Večina insercij pred približno 25 milijoni let
- Danes ni dokazov, da so aktivni
- Mehanizem retrotranspozicije je podoben virusnemu, preko RNA intermediata nastane dvojna veriga DNA, ki potuje v jedro.

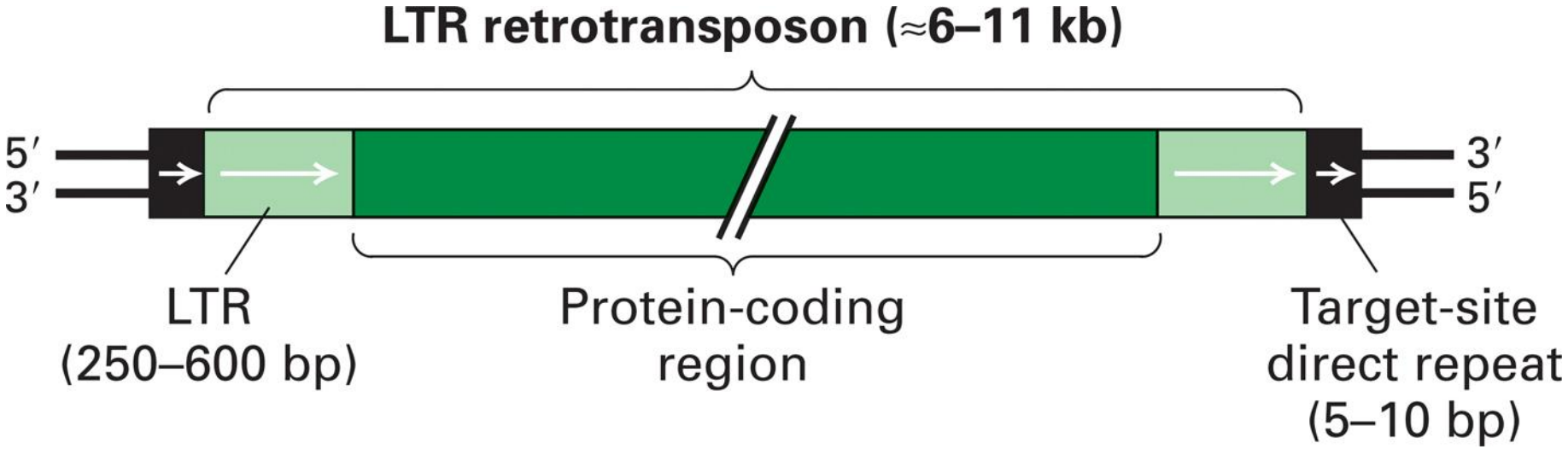

LTR retrotransposon (≈6–11 kb)
5′
3′
3′
5′
LTR
(250–600 bp)
Protein-coding
region
Target-site
direct repeat
(5–10 bp)

Figure 6.13 Generation of retroviral genomic RNA from integrated retroviral DNA.

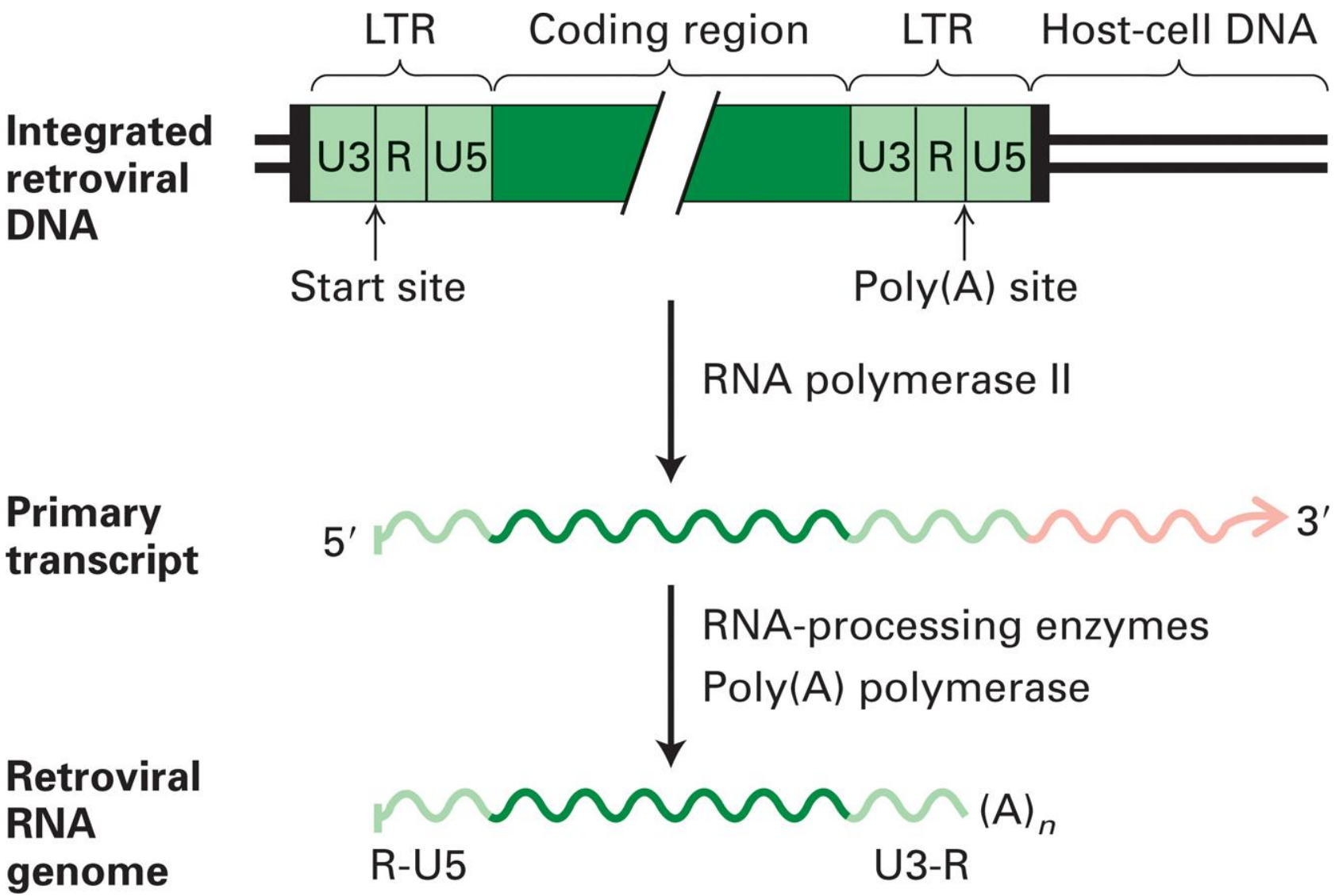
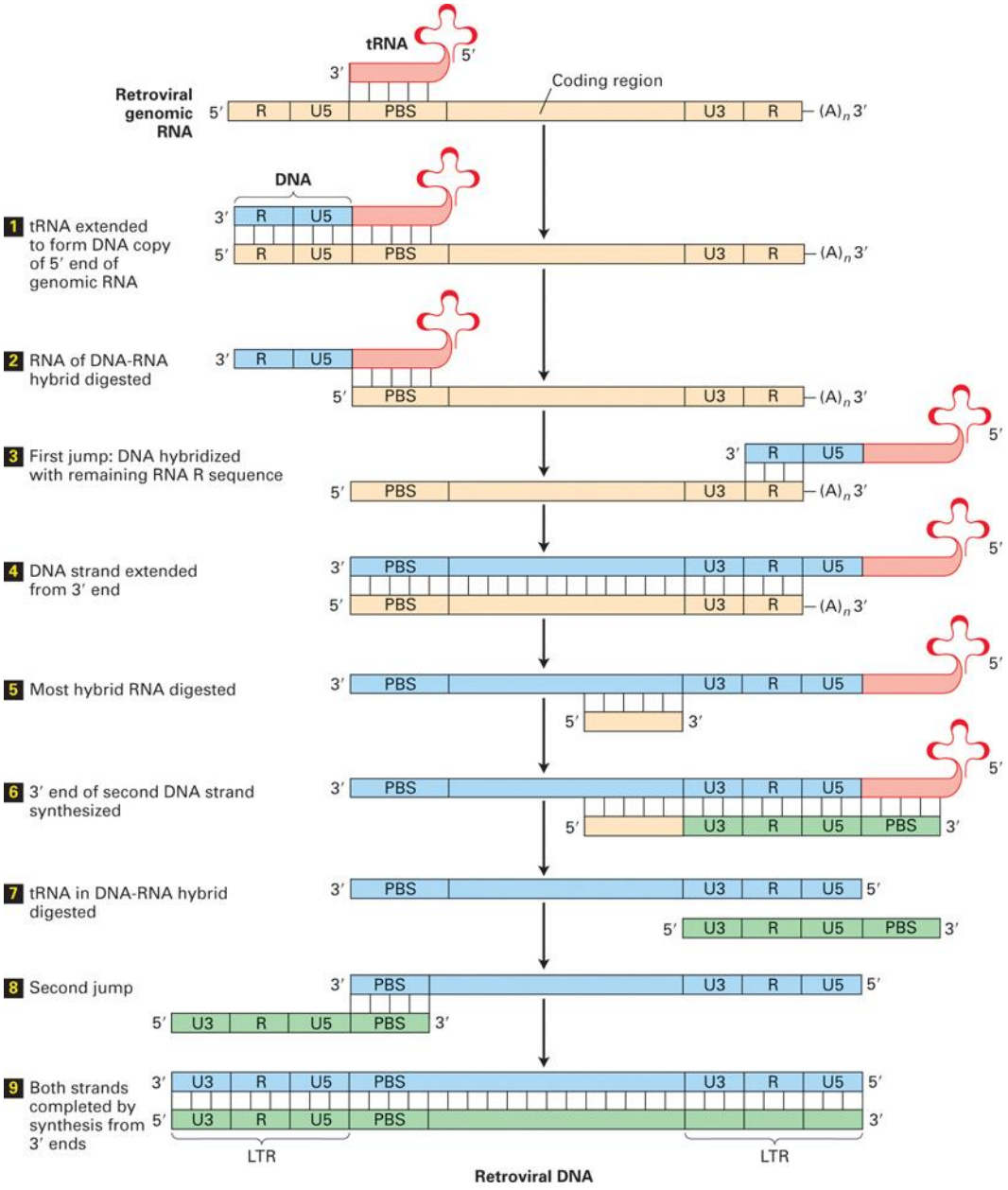
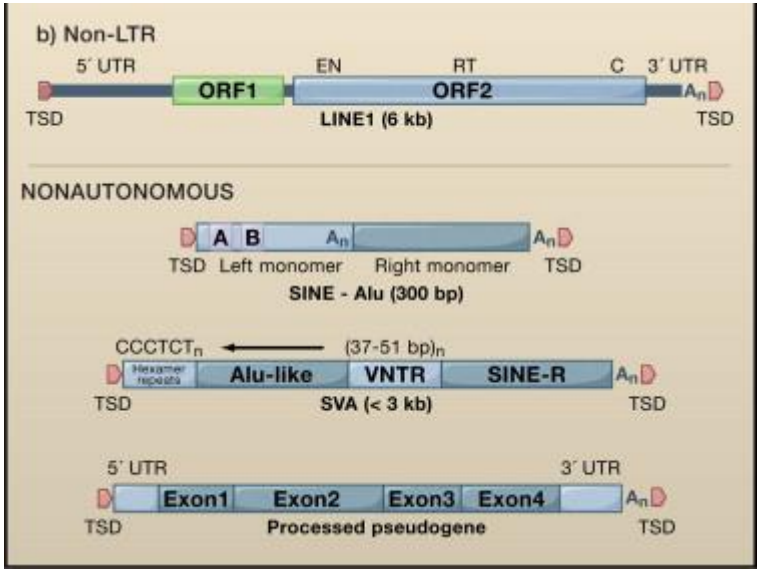


Figure 6.14 Model for reverse transcription of retroviral genomic RNA into DNA.

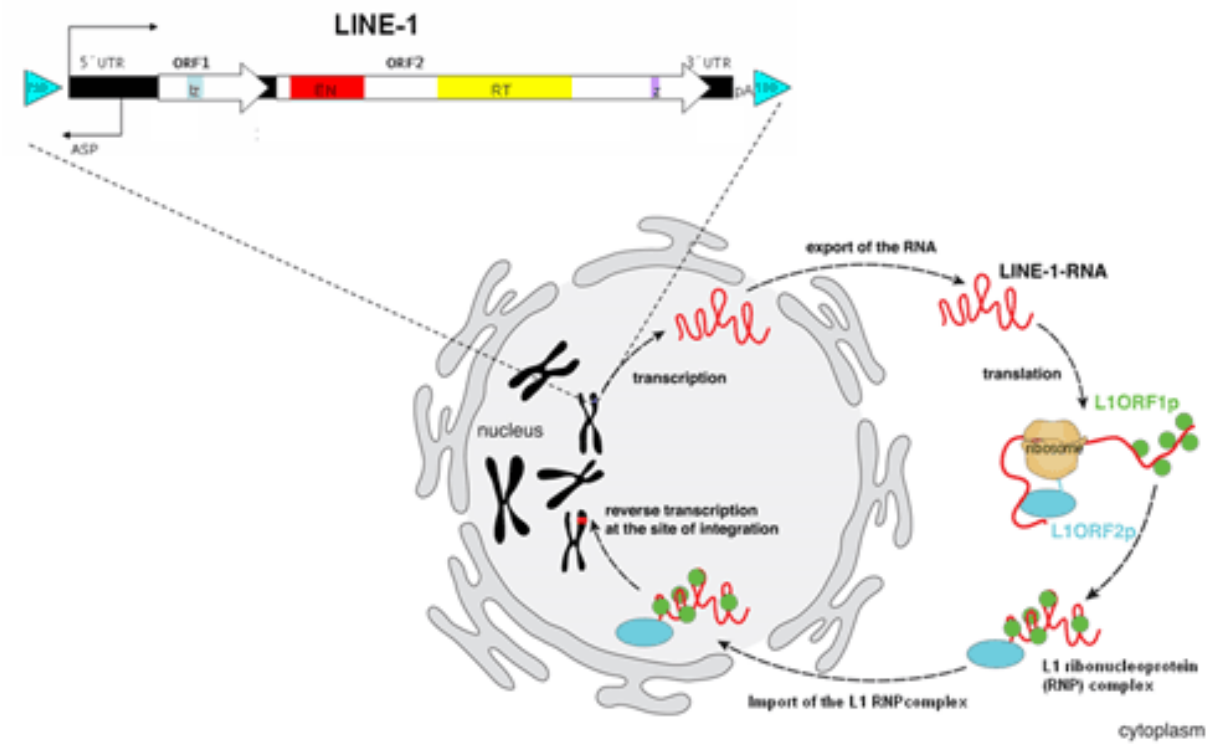


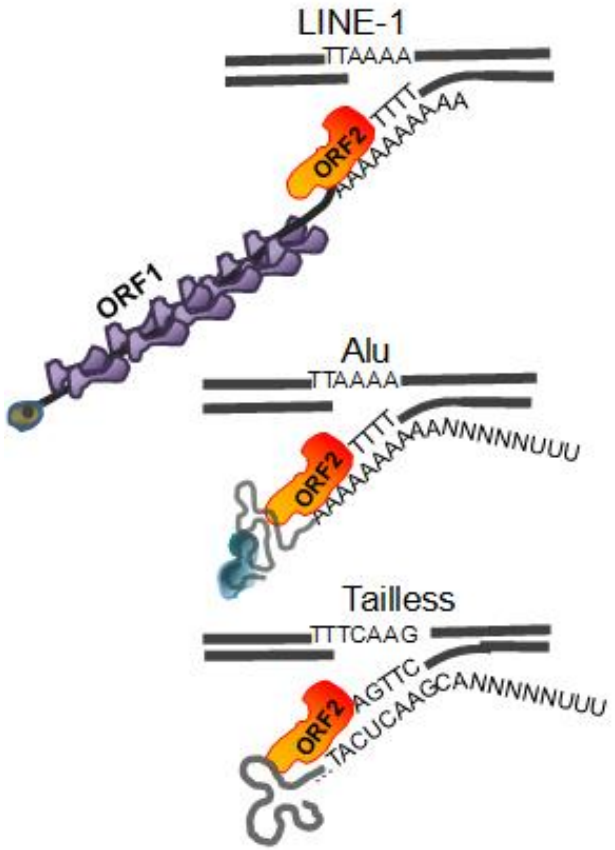
Ne-LTR retrotranspozoni v človeškem genomu

- 21 % genoma
- Aktivne 3 vrste retrotranspozov: LINE1 je avtonomen – kodira proteine, potrebne za retrotranspozicijo; Alu in SVA se prenašata *in trans* s pomočjo LINE1 proteinov
- *In trans* se prenašajo tudi procesirani psevdogeni in druge RNA

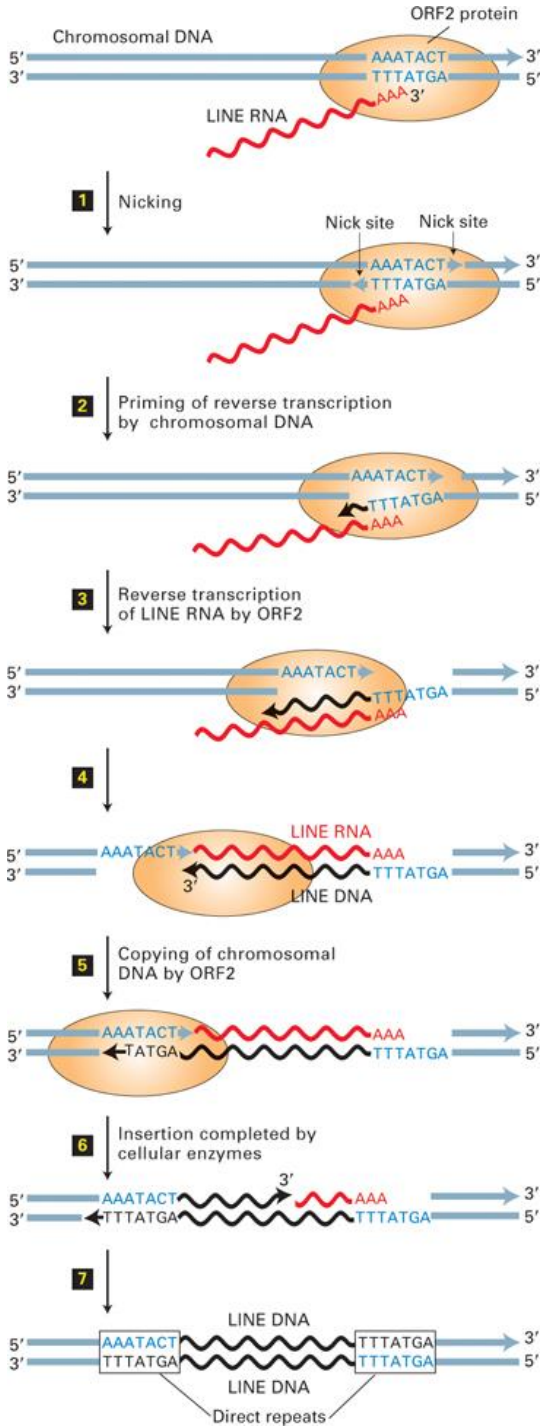


LINE se prenašajo s TPRT (target-primed-reverse-transcription)





LINE se prenašajo s TPRT



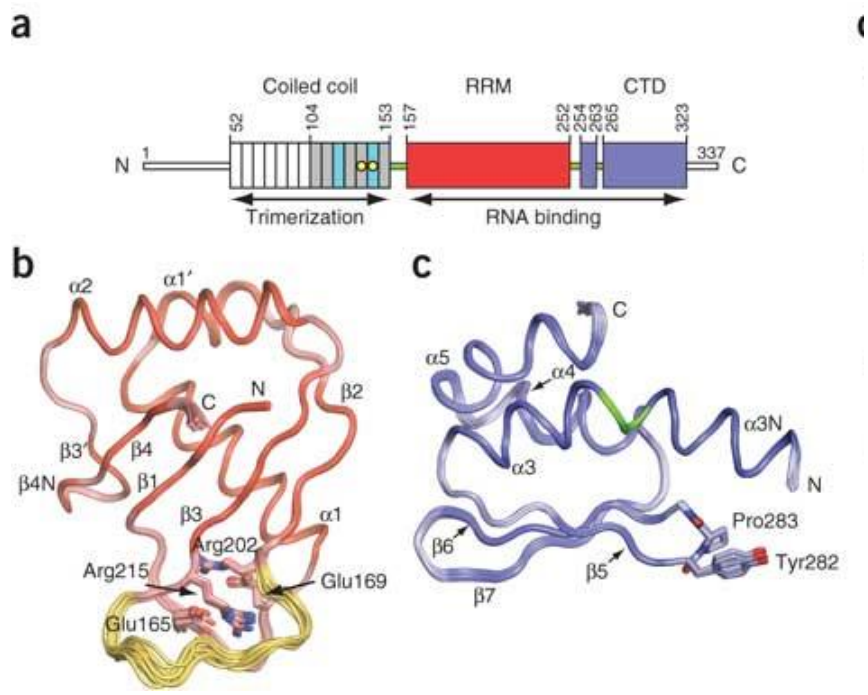
LINE1 – Long Interspersed Nuclear Element

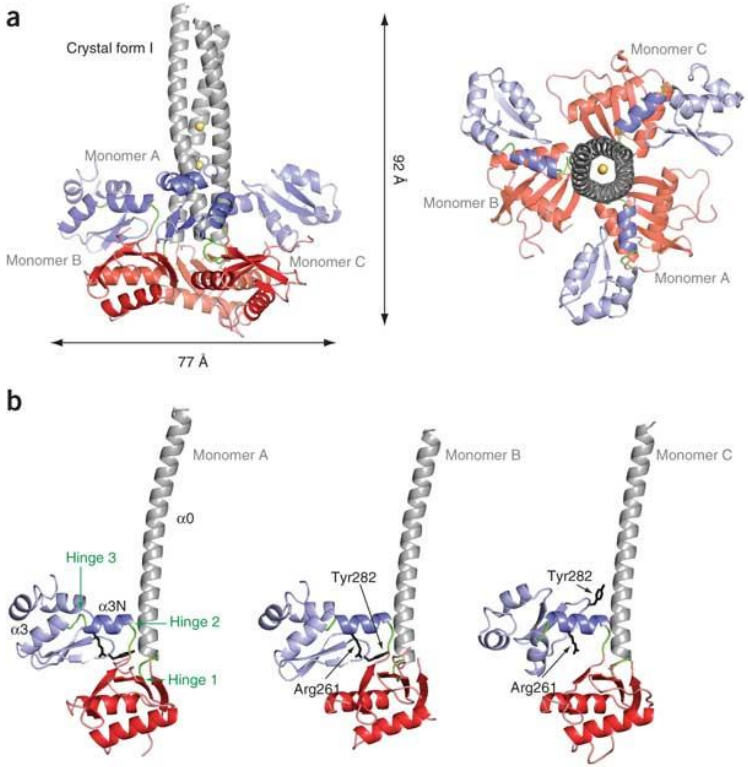
- Dolga ponavljajoča se zaporedja brez dolgih končnih ponovitev (LTR- long terminal repeats)
- > 500.000 kopij, večinoma skrajšane na 5' koncu
- Edini aktivni avtonomni TE v človeškem genomu
- Aktivni zadnjih 150 milijonov let
- 100 aktivnih kopij, od tega le nekaj 'vročih' LINE1
- 17 % genoma

LINE1 – Long Interspersed Nuclear Element

- 6 kb dolg
- Bicistronska mRNA
- 5' UTR ima interni promotor za RNA Pol II
- 3' UTR ima poliadenilacijski signal in poliA rep
- ORF1 kodira protein (40kDa), ki se veže na nukleinske kisline
- ORF2 kodira protein, ki ima endonukleazno (EN) in reverzno transkriptazno (RT) aktivnost (150kDa)

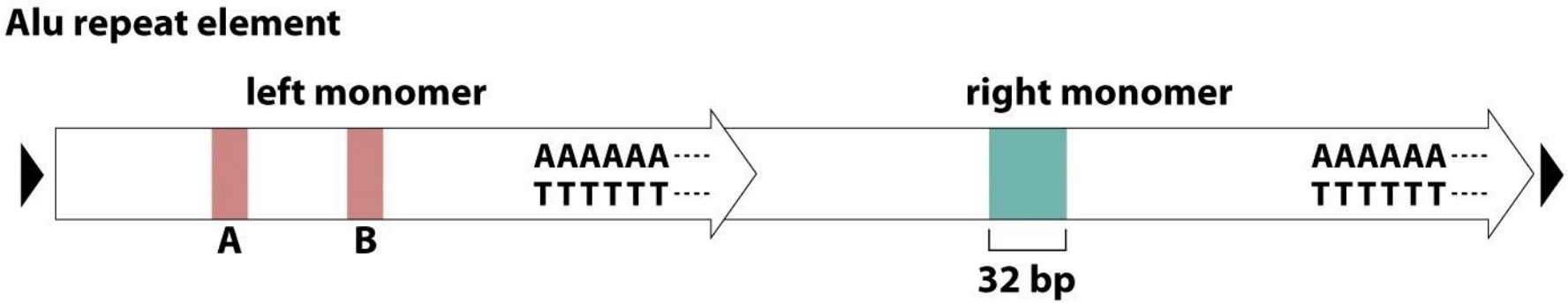
Struktura proteina ORF1p





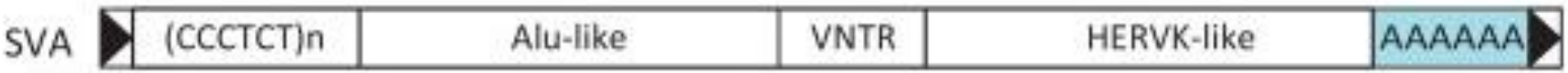
- Trimer
- RRM domena za vezavo na RNA
- LINE1 RNA se verjetno ovije okrog ORF1p

SINE – Short Interspersed Nuclear Element



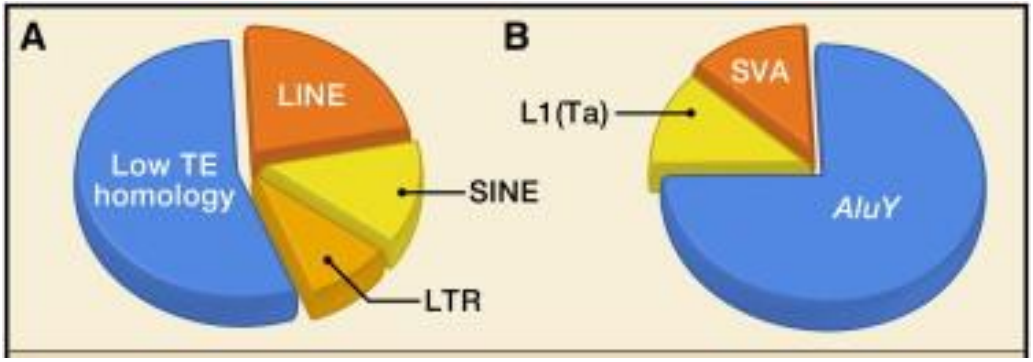
- Kratka ponavljajoča se zaporedja brez dolgih končnih ponovitev (LTR- long terminal repeats)
- V človeškem genomu prevladujejo Alu elementi (200 poddružin)
- > 1.000.000 kopij
- Neavtonomni elementi, trans mobilizirani z LINE1
- Aktivni so zadnjih 65 milijonov let
- Dolgi so ~ 300 bp
- 10 % genoma
- Izhajajo iz 7SL RNA
- V 5’ UTR ima promotor za RNA Pol III, v 3’ UTR je poliA rep.

SVA
(Short interspersed element, Variable number of tandem repeats, Alu)



- ~ 3.000 kopij
- Neavtonomni elementi
- Aktivni so zadnjih 25 milijonov let
- Dolgi so ~ 2 kb
- 0,2 % genoma
- Nimajo promotorja
- Trans mobilizirani z LINE1
- 6 družin je trenutno znanih.

Število retrotranspozicij v človeškem genomu



- Različne posledice retrotranspozicije v zarodne celice (germline) ali somatske celice
- Frekvenca retrotranspozicije v zarodnih celicah:
  - 1/21 ljudi ima novo Alu
  - 1/212 (1/108) ima LINE1
  - 1/916 ljudi ima nov SVA element

Burns in Boeke, Cell, 2012

Delež mutacij s transpozicijskimi elementi

- Drosophila: 50 % vseh mutacij povzročijo TE
- Miš: 10 %
- Človek: 0,1-0,2 %

Prva somatska mutacija pri raku črevesja - 1992

- L1 se je vgradil v APC gen (Adenomatous polyposis coli – tumorsupresorski gen, regulira β-katenin v Wnt signalni poti)
- Insercija v rakastih celicah, ne v sosednjem tkivu
- Veliko mutacij/insercij v somatskih celicah – določim z nastankom bolezni ali če primerjamo genome posameznikov
- Somatska retrotranspozicija bi lahko imela vlogo pri tumorigenezi

  - 9 tumor specifičnih insercija L1 so našli pri 20 vzorcih plučnih rakov

  - je retrotranspozicija voznik (vzrok) ali sopotnik (posledica) pri raku?

  - pri rakih so retrotranspozoni pogosto hipometilirani

Retrotranspozicija v možganih

- Retrotranspozicija L1, Alu in SVA
- Z manipuliranim L1 pokazali retrotranspozicijo v nevronski predniških celicah in hipokampusu
- Med nevrogenezo je epigenetska inhibicija transkripcije L1 nižja
- L1 mozaicizem v možganih posameznikov vpliva na lastnosti/značilnosti posameznika
- Pacienti z Rettovim sindromom (mutacije v MECP2 genu) imajo več L1 zaporedij.

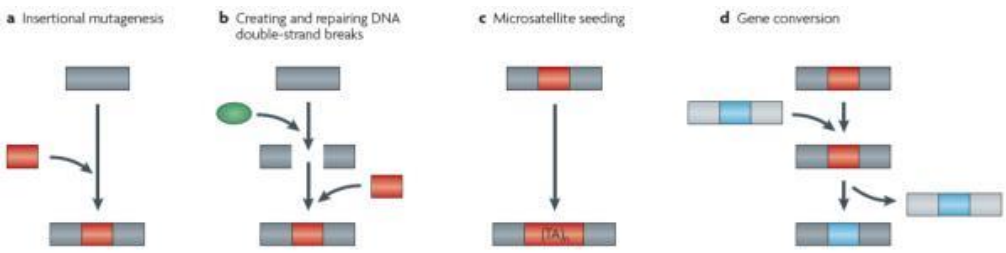
Vpliv retrotranspozicije na genom

Vpliv na evolucijo genoma:

- Hitrost pomnoževanje /retrotranspozicije (ni enakomerno skozi čas)
- Spremembe v številu kopij – poveča se velikost genoma (polimorfne insercije TE-informativno za posameznika)

Lokalna genomska nestabilnost:

- Insercijska mutageneza (v gen ali regulatorno regijo)
- dsDNA prelomi
- DSB popravljanje
- So vir satelitov (predvsem Alu)
- Genska konverzija



Cordaux in Batzer, Nat Rev Gen, 2009

Vpliv retrotranspozicije na strukturo genoma.

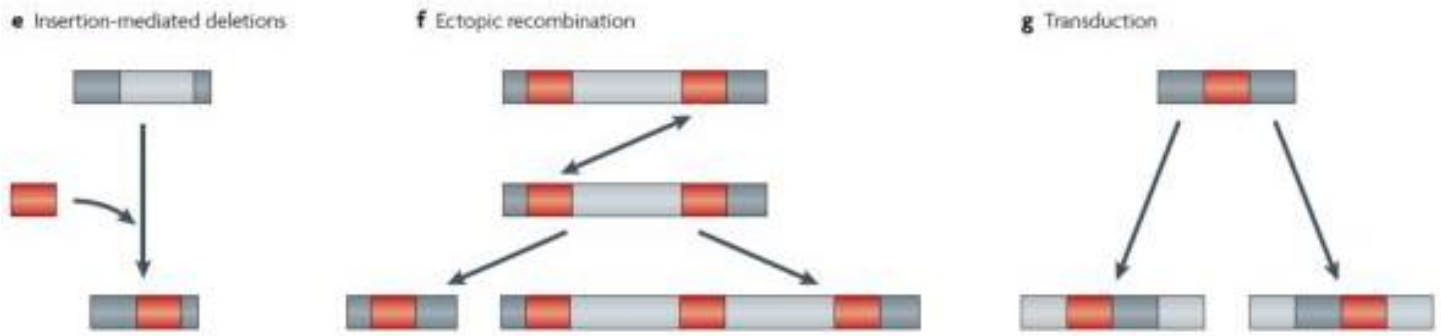
Insercijske mutageneze retrotranspozonov – 96 primerov

- Hemofilija
- Cistična fibroza
- Apertov sindrom
- Nevrofibromatoza (18: 14 Alu, 3 L1, 1 polyA)
- Duchennova mišična distrofija (Fukuyama MD, SVA v fukutin, AS-spremenjen C-konec, nepravilna lokalizacija)
- B-talasemija
- Hiperholesterolemija
- Rak na dojkah
- Črevesni rak

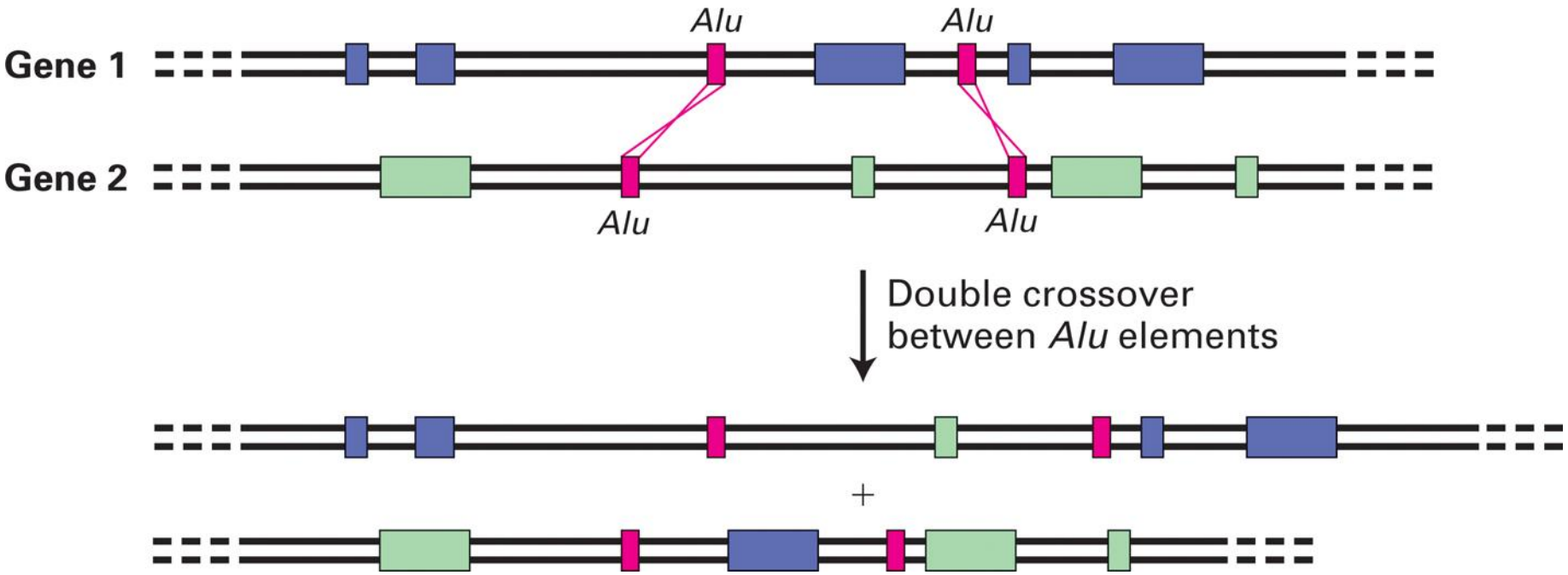
Vpliv retrotranspozicije na genom

Reorganizacije genoma:

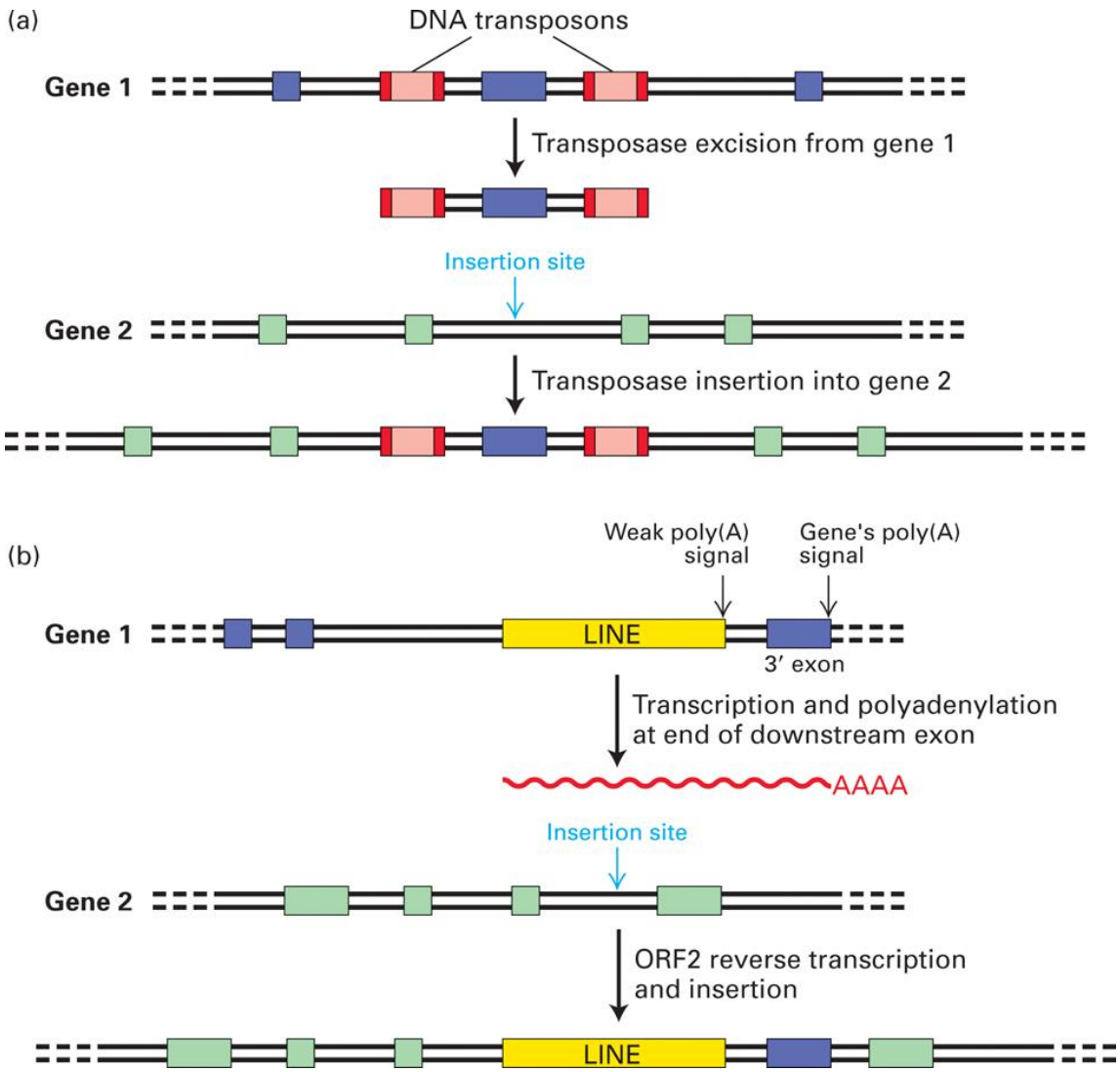
- Delecije ob inserciji
- Ektopična rekombinacija – rekombinacija med nealelnimi zaporedji, lahko starimi Alu; > 70 primerov rakov in genetskih napak; duplikacije, ki imajo na robovih Alu
- Novi geni s transdukcijo, retrotranspozicijo genov (brez retrotrotranspozona)



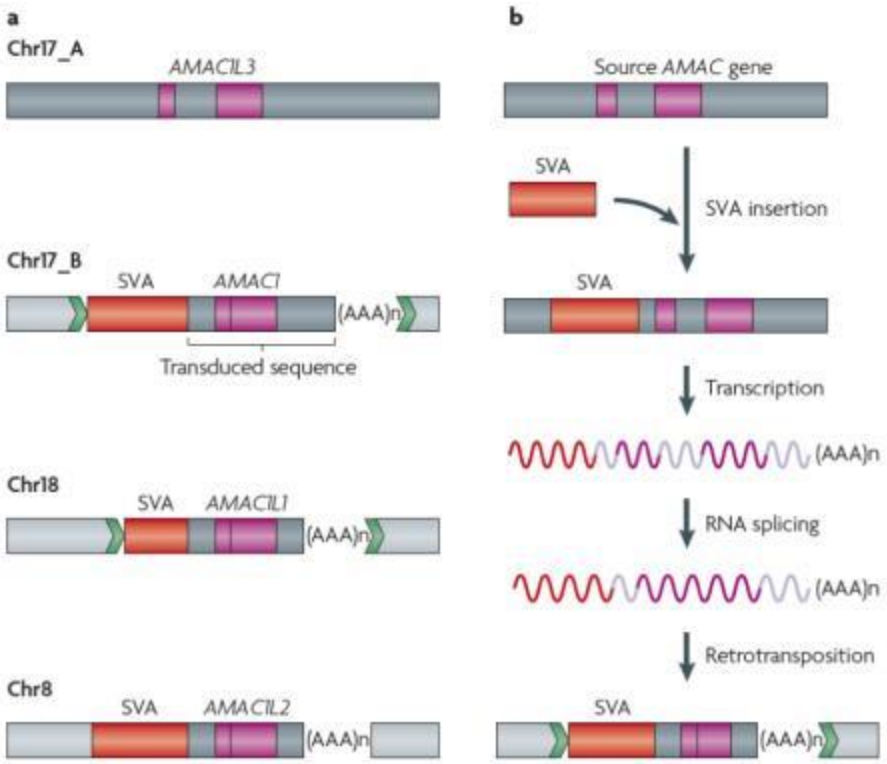
Premeščanje eksonov z rekombinacijo



Premeščanje eksonov s transpozicijo



Rojstvo nove genske družine s transdukcijo z retrotranspozi

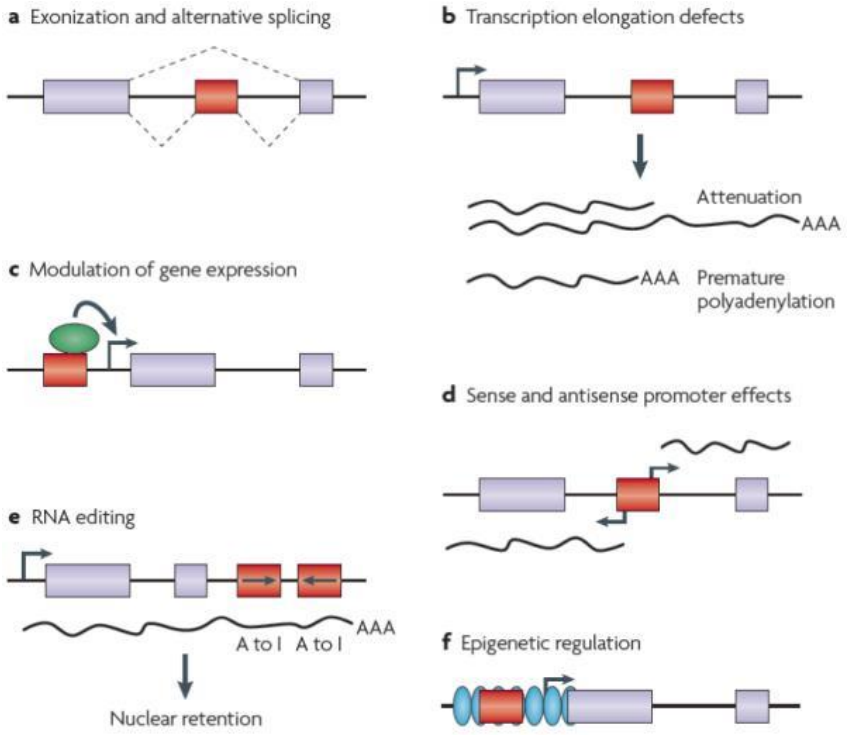


Acyl-malonyl-condensing enzyme – genska družina ima 4 člane, stara je 4-7My.

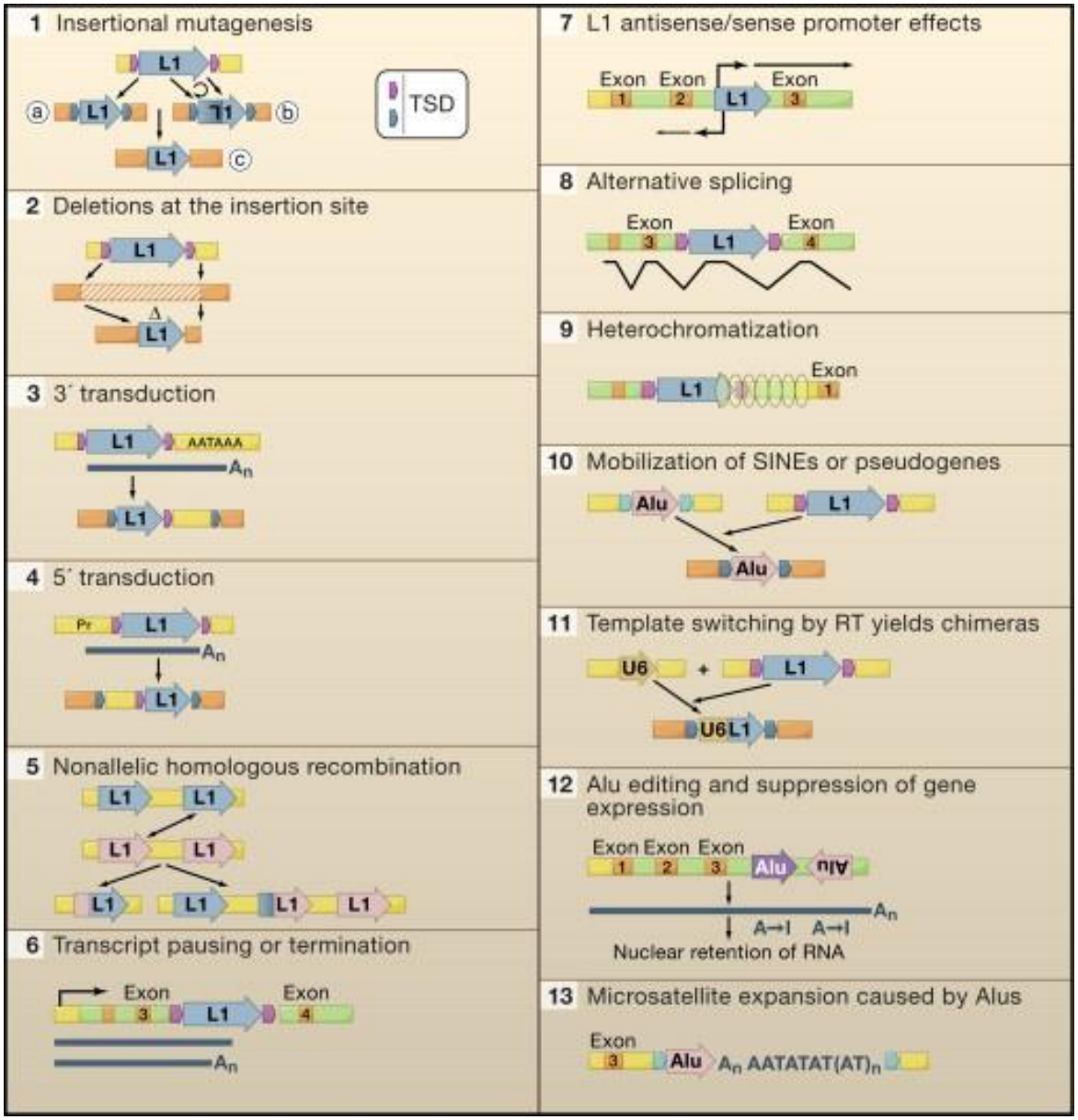
Vpliv retrotranspozicije na genom

Vpliv na izražanje genov

- nova mesta izrezovanja in lepljenja
- vpliv TE promotorja
- vpliv šibkega poliA repa
- vezava TE na regulatorne regije,
- RNA editiranje (A-I)
- epigenetska regulacija (DNA metilacija TE – promotorji in TE so bogati z GC – tvori se heterokromatin – utišajo gene, blizu katerih so TE)
- ohranjene nekodirajoče regije izvirajo iz TE (negativna selekcija – regulatorne regije)



Kako retrotranspozoni vplivajo na celico



Goodier in Kazazian, Cell, 2008

Table 2

Retrotranspositions causing single-gene disease in humans

Insertion	Gene	CHR	Reference	Disease	Subfamily	Size (nt)	PolyA tail length (nt)	Truncation	Transduction (nt)	Strand	Exon/intron/ mechanism	Target-site duplication (TSD)	L1 EN site (5′-TTTT/AA-3′)	Note
Alu	*ABCD1*	X	Kutsche *et al.* 2002	ALD	AluYb9	98	20	Y/5′TR	N	S	4.7 kb Deletion	No TSD	ATTT/GT	
Alu	*ATP7A*	X	Gu *et al.* 2007	Menkes Disease	AluYa5a2	282	89	N	N	AS	E	AAAAAGGACAGC	TTTT/AT	
Alu	*BTK*	X	Lester *et al.* 1997	XLA	AluY	N/A	N/A	N/A	N	AS	E	N/A	N/A	
Alu	*BTK*	X	Conley *et al.* 2005	XLA	AluY	281	74	N	N	S	E	AGAAATGTATGAGTAAGT	TTCT/AT	Same insertion site Conley *et al.* SVA
Alu	*CD40LG*	X	Apoil *et al.* 2007	HIGM	AluYb8	292	8	N	N	AS	E	AAAAATTTTC	TTTT/AT	
Alu	*CLCN5*	X	Claverie-Martin *et al.* 2003	Dent's Disease	AluYa5	281	50	N	N	S	E	AGAAAATGCTCGAAAGA	TTCT/AT	
Alu	*FVIII*	X	Sukarova *et al.* 2001	Hemophilia A	AluYb8	290	47	N	N	AS	3 nt Deletion	No TSD	TTTC/AT	
Alu	*FVIII*	X	Ganguly *et al.* 2003	Hemophilia A	AluYb9	288	37	N	N	AS	I/Splicing	AAAAACCAACAGG	TTTT/AT	Consensus Yb9
Alu	*FVIII*	X	Green *et al.* 2008 [125]	Hemophilia A	AluYb8	FL	N/A	N	N	AS	E	N/A		
Alu	*FIX*	X	Vidaud *et al.* 1993	Hemophilia B	AluYa5a2	244	78	Y/5′TR	N	S	E	AAGAATGGCAGATGCGA	TCTT/AA	Same insertion site as Wulff *et al.* Alu
Alu	*FIX*	X	Wulff *et al.* 2000	Hemophilia B	AluYa5a2	237	39	Y/5′TR	N	S	E	AAGAATGGCAGATGC	TCTT/AA	Same insertion site as Vidaud *et al.* Alu
Alu	*FIX*	X	Li *et al.* 2001	Hemophilia B	AluY	279	40	Y/5′TR	N	AS	E	AAGAAACTGGTCCC	TCTT/AA	
Alu	*GK*	X	Zhang *et al.* 2000	GKD	AluYc1	241	74	Y/5′TR	N	AS	I	AAAAAATAAG	TTTT/AA	
Alu	*IL2RG*	X	Lester *et al.* 1997	XSCID	AluYa5	N/A	N/A	N/A	N	AS	I	N/A	N/A	
Alu	*CRB1*	1	den Hollander *et al.* 1999	RP	AluY	244	70	Y/5′TR	N	AS	E	AAGAGTAAAGATGA	TCTT/GA	
Alu	*SERPINC1*	1	Beauchamp *et al.* 2000	Type 1 ATD	Alu	6	40	Y/5′TR	N	AS	1.4 kb Deletion	N/A	TTCT/AT	Shortest Alu insertion
Alu	*ALMS1*	2	Taşkesen *et al.* 2011 [119]	Alström syndrome	AluYa5	257	76	Y/5′TR	N	S	E	AAAAGCCTAGAGAA	TTTT/AA	
Alu	*MSH2*	2	Kloor *et al.* 2004	HNPCC	AluJ	85	40	Y/5′TR	N	S	E	N/A	N/A	Contains extra 99 nt 3′-of Alu, may be transduction or recombination
Alu	*ZFHX1B*	2	Ishihara *et al.* 2004	MWS	AluYa5	281	93	N	N	S	E	AAAATTAAAACA	TTTT/AA	
Alu	*BCHE*	3	Muratani *et al.* 1991	Cholinesterase deficiency	AluYb9	289	38	N	N	S	E	AAAAATATTTTTTCC	TTTT/AA	
Alu	*CASR*	3	Janicic *et al.* 1995	FHH and NSHPT	AluYa5	280	93	N	N	AS	E	GAAAGCGTGAGCTGC	TTTC/AA	
Alu	*HESX1*	3	Sobrier *et al.* 2005	Anterior Pituitary Aplasia	AluYb8	288	30	N	N	S	E	AGAAAATGTCTTTAGA	TTCT/AA	
Alu	*OPA1*	3	Gallus *et al.* 2010 [120]	ADOA	AluYb8	289	25	N	N	AS	I/Splicing	AAAAATTTTAAAAAGTT	TTTT/AC	
Alu	*MLVI2*	5	Economou-Pachnis and Tsichlis 1985	Associated with leukemia	AluYa5	280	26	N	N	AS	I	GAAAATGT	TTTC/AT	
Alu	*APC*	5	Halling *et al.* 1999	Hereditary desmoid disease	AluYb8	278	40	Y/5′TR	N	S	E	AAGAATAATG	TCTT/AA	Same insertion site as Miki *et al.* L1
Alu	*APC*	5	Su *et al.* 2000	FAP	AluYb9	93	60	Y/5′TR	N	AS	I/Splicing	No TSD	TTTT/AA	1.6 kb intronic deletion
Alu	*MAK*	6	Tucker *et al.* 2011, Edwin Stone, personal communication	RP	AluYb8	281	57	N	N	AS	E	AAAGAAAAAA	CTTT/AA	Identified by exome resequence
Alu	*NT5C3*	7	Manco *et al.* 2006, Leticia Ribeiro, personal communication	Chronic hemolytic anemia	Alu Ya5	281	36	N	N	S	E	AAGAATGGCAGATGG	TCTT/AA	
Alu	*CFTR*	7	Chen *et al.* 2008 [121]	Cystic Fibrosis	AluY	46	57	Y/5′TR	N	AS	E	AAGAATCCCACCTATAAT	TCTT/AA	
Alu	*CFTR*	7	Chen *et al.* 2008 [121]	Cystic Fibrosis	AluYa5	281	56	N	N	S	E	AATAGAAATGATTTTTGTC	TCTC/AT	3′-Processing of (5′-CTC-3′)
Alu	*EYA1*	8	Abdelhak *et al.* 1997	BOR syndrome	AluYa5	n/a	97.31	N/A	N	AS	E	AAAAAATAAATGTGTG	TTTT/AA	PolyA tail shortening between generations
Alu	*LPL*	8	Okubo *et al.* 2007	LPL deficiency	AluYb9	150	60	Y/5′TR	N	AS	2.2 kb Deletion	No TSD	TTTT/AA	
Alu	*CHD7*	8	Udaka *et al.* 2007	CHARGE syndrome	AluYa5/8	75	100	Y/5′TR	N	S	10 kb Deletion	No TSD	ATTT/AA	
Alu	*POMT1*	9	Bouchet *et al.* 2007	Walker Warburg syndrome	AluYa5	290	53	N	N	AS	E	AAAAAGAGATGTACTG	TTTT/AC	
Alu	*FGFR2*	10	Oldridge *et al.* 1999	Apert syndrome	AluYa5	283	69	N	N	AS	I/Splicing	AGAAAACAAGGGAAGCA	TTCT/AG	
Alu	*FGFR2*	10	Oldridge *et al.* 1999	Apert syndrome	AluYb8	288	47	N	N	AS	E	AGAATTACCCGCCAAG	TTCT/AT	

Table 2 (*Continued*)

Insertion	Gene	CHR	Reference	Disease	Subfamily	Size (nt)	PolyA tail length (nt)	Truncation	Transduction (nt)	Strand	Exon/intron/ mechanism	Target-site duplication (TSD)	L1 EN site (5′-TTTT/AA-3′)	Note
Alu	*FGFR2*	10	Bochukova *et al.* 2009	Apert syndrome	AluYk13	214	12	Y/5′TR	N	AS	E	AAAAGTTACATTCCG	TTTT/GA	
Alu	*FAS*	10	Tighe *et al.* 2002	ALPS	AluYa5	281	33	N	N	AS	I	AGAATATTCTAAATGTG	TTCT/AA	
Alu	*SERPING1*	11	Stoppa-Lyonnet *et al.* 1990	HAE	AluYc1	285	42	N	N	S	I	AAAAATACAAAAATTAG	TTTT/AG	
Alu	*HMBS*	11	Mustajoki *et al.* 1999	AIP	AluYa5	279	39	N	N	AS	E	AAGAATCTTGTCCC	TCTT/GA	
Alu	*GNPTAB*	12	Tappino *et al.* 2008	ML II	AluYa5	279	17	N	N	AS	E	AAAAACAACAACTGAG	TTTT/GA	
Alu	*BRCA2*	13	Miki *et al.* 1996	Breast Cancer	AluYc1	281	62	N	N	S	E	AATCACAGGC	GATT/AT	
Alu	*BRCA2*	13	Teugels *et al.* 2005	Breast Cancer	AluYa5	285	N/A	N	N	S	E	AAGAATCTGAACAT	TTCT/GC	3′ Processing 2 nt (5′-CT-3′)
Alu	*PMM2*	16	Schollen *et al.* 2007	CDG-Ia	AluYb8	263	10	Y/5′TR	N	AS	28 kb Deletion	No TSD	TTTT/AA	
Alu	*BRCA1*	17	Teugels *et al.* 2005	Breast Cancer	AluS	286	N/A	N	N	S	E	GAAAAAGAATCTGCTTT	TTTC/GA	
Alu	*NF1*	17	Wallace *et al.* 1991	NF1	AluYa5	282	40	N	N	AS	I/Splicing	AAAAAAAAAAACAT	TTTT/AA	First report of *de novo* Alu insertion
Alu	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	AluY	280	N/A	N	N	S	I	AAAAAATTCAG	TTTT/AA	Same insertion site as Wimmer et al.[$]
Alu	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	AluY	281	N/A	N/A	N	AS	I	N/A		
Alu	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	AluYa5	282	60	N	N	S	E	ATAAATAGCCTGGA	TTAT/AA	
Alu	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	AluYa5	284	120	N	N	AS	E	AAAAAACTTGCT	TTTT/GA	Same insertion site as Wimmer et al.[#]
Alu	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	AluYa5	281	N/A	N	N	AS	E	AAAAAACTTGCTGATGG	TTTT/GA	Same insertion site as Wimmer et al.[#]
Alu	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	AluYa5	284	110	N	N	AS	E	AATAAAACCTAAAGA	TATT/GA	
Alu	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	AluYa5	279	N/A	N	N	S	E	AAAAGAAGAACATAT	TTTT/GT	Same insertion site as Wimmer et al.[×]
Alu	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	AluYa5	264	60–85	Y/5′TR	N	AS	E	AAGAAGTGCGGTACCT	TCTT/GA	
Alu	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	AluYb8	249	121	Y/5′TR	N	S	E	AAAGCAGTGC	CTTT/AT	
Alu	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	AluYb8	288	N/A	N	N	AS	I	AAAAAAGAGAAAGACAA	TTTT/AA	Same insertion site as Wimmer et al.[$]
Alu	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	AluYb8	289	120	N	N	AS	E	AACAATGGTCTT	TGTT/AA	
Alu	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	AluYb8	288	78–178	N	N	S	E	AAACAATGATGTTA	TTTC/AA	3′ Processing of 1 nt (C)
Alu	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	AluYb8	288	118	N	N	S	E	AAAAGAAGAACATAT	TTTT/GT	Same insertion site as Wimmer et al.[×]
Alu	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	AluYb8	268	121	Y/5′TR	N	AS	I	AAAAAACAAACAAACA	TTTT/GT	
L1	*CYBB*	X	Meischl *et al.* 1998, Brouha *et al.* 2002	CGD	L1 Ta	1722	101	Y/5′TR	Y (280)	S	E	AA	TGTT/GA	Maternal Meiosis I
L1	*CYBB*	X	Meischl *et al.* 2000	CGD	L1 Ta	836	69	Y/5′TR/INV	N	S	I/Splicing	AGAAATAACTATTTAA	TTCT/AA	
L1	*CHM*	X	van den Hurk *et al.* 2003	Choroideremia	L1 Ta	6017	71	FL	Y (119/406)	AS	E	AGAAGATCAATTAG	TTCT/AA	Insertion in Early Development
L1	*DMD*	X	Musova *et al.* 2006	DMD	L1 Ta	452	41	Y/5′TR/INV	N	AS	E	AAATATCTTTATATCA	ATTT/AA	
L1	*DMD*	X	Narita *et al.* 1993	DMD	L1 Ta	608	16	Y/5′TR	N	AS	E	No TSD	TCTT/AA	2 nt deletion
L1	*DMD*	X	Holmes *et al.* 1994	DMD	L1 Ta	1400	38	Y/5′TR/INV	Y(489)	S	E	AAATCATCTGCTGCT	ATTT/AA	First Report of L1 3′-transduction
L1	*DMD*	X	Yoshida *et al.* 1998	XLDCM	L1 Ta	530	73	Y/5′TR	N	AS	5′-UTR/Loss of mRNA	AAAAAAAACCTGGTAAA	TTTT/AT	Tissue specific loss of mRNA
L1	*DMD*	X	E Bakker & G van Omenn, personal communication	DMD	N/A	878	N/A	Y/5′TR	N	S	N/A	N/A	N/A	
L1	*DMD*	X	Awano *et al.* 2010 [129], Solyom *et al.* 2011 [8]	DMD	L1 Ta	212	118	Y/5′TR	Y (212)	AS	E	GAA	TTTC/AA	Orphan 3′-transduction
L1	*FVIII*	X	Kazazian *et al.* 1988	Hemophilia A	L1 Ta	3800	54	Y/5′TR	N	S	E	AAAGACAAACAAAAC	CTTT/AA	First report of *de novo* L1 insertion
L1	*FVIII*	X	Kazazian *et al.* 1988	Hemophilia A	L1 preTa	2300	77	Y/5′TR/INV	N	AS	E	AATGTTTCCTTCTTTTC	CATT/AA	
L1	*FIX*	X	Li *et al.* 2001	Hemophilia B	L1 Ta	463	68	Y/5′TR	N	S	E	AAAAATAGTGCTGATA	TTTT/AC	
L1	*FIX*	X	Mukherjee *et al.* 2004	Hemophilia B	L1 Ta	163	125	Y/5′TR	N	S	E	GAAAAATGGATTGT	TTTC/AT	
L1	*RP2*	X	Schwahn *et al.* 1998	XLRP	L1 Ta	6000	64	FL	N	S	I/Loss of mRNA	AAGACTGTAAGGTG	TCTT/AA	Interrupted polyA
L1	*RPS6KA3*	X	Martinez-Garay *et al.* 2003	Coffin-Lowry syndrome	L1 Hs	2800	Yes	Y/5′TR/INV	N	AS	E	AAGAAAACCTGCATTT	TCTT/AG	

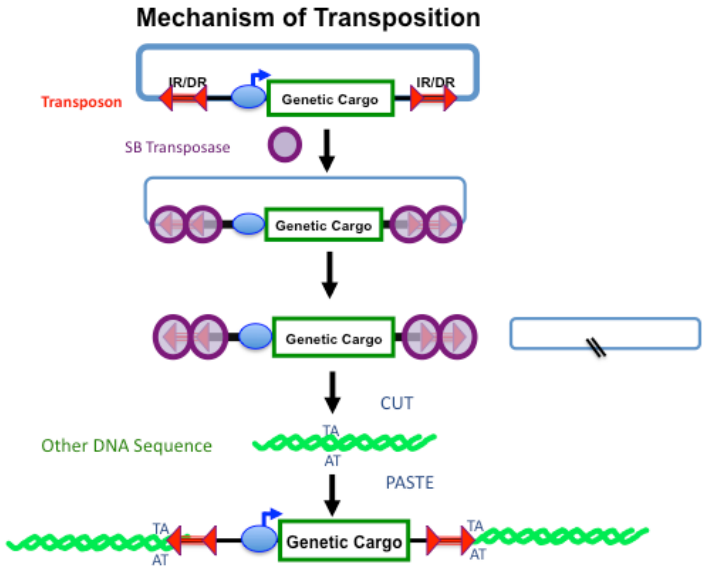
Table 2 (*Continued*)

Insertion	Gene	CHR	Reference	Disease	Subfamily	Size (nt)	PolyA tail length (nt)	Truncation	Transduction (nt)	Strand	Exon/intron/ mechanism	Target-site duplication (TSD)	L1 EN site (5′-TTTT/AA-3′)	Note
L1	*ABDH5*	3	Samuelov *et al.* 2011 [122], Eli Sprecher, personal communication	CDS	N/A	FL	N/A	N	N/A	N	I/Splicing	N/A	N/A	
L1	*APC*	5	Miki *et al.* 1992	Colon cancer	L1Ta	520	222	Y/5′TR/INV	N	S	E	AAGAATAATG	TCTT/AA	Somatic Insertion/ same insertion site as Halling *et al.* Alu
L1	*EYA1*	8	Morisada *et al.* 2010 [61•]	BOR syndrome	L1 Hs	3756	None	Y/3′TR	N	AS	17 kb Deletion	No TSD	TCTC/AG	Internal Priming
L1	*FKTN*	9	Kondo-Iida *et al.* 1999	FCMD	L1Ta	1200	59	Y/5′TR	N	S	I/Splicing/6 nt Deletion	No TSD	TTTT/AA	
L1	*SETX*	9	Bernard *et al.* 2009 [124], Christine Zühlke, personal communication	AOA2	L1 Hs	1300	42	Y/5′TR/INV	N	S	E	GGAAGAATGTGAACTGGCTA	TTCC/AG	3′-processing 2 nt (5′-CC-3′)
L1	*HBB*	11	Divoky *et al.* 1996	β-thalassemia	L1 Ta	6000	107	FL	N	AS	I	AAAATAAAAGCAGA	TTTT/AT	
L1	*PDHX*	11	Mine *et al.* 2007	PDHc deficiency	L1 Hs	6086	67	FL	N	S	46 kb Deletion	No TSD	TTTT/AT	Largest Deletion
L1	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	L1 preTa	1800	N/A	Y/5′TR	N	S	E	AAAAACGAAACTGTGT	TTTT/AT	
L1	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	L1 Ta	6000	N/A	FL	N	S	E	AAAAATCGAGGG	TTTT/AA	Untemplated 3′-T?
L1	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	N/A	2200	N/A	Y/5′TR/INV	N	AS	I/Splicing	AAGAAAATGGT	TCTT/AA	
SVA	*BTK*	X	Rohrer *et al.* 1999, Conley *et al.* 2005	XLA	N/A	251	92	Y/5′TR	N	S	E	AGAAATGTATGAGTAA	TTCT/AT	Same insertion site as Conley *et al.* Alu
SVA	*TAF1*	X	Makino *et al.* 2007	XDP	F	2627	62	FL	N	AS	I	AAAAAAAAAAAATGAAATAG	TCCT/AT	3′-Processing 3 nt (5′-CCT-3′)
SVA	*LDRAP1*	1	Wilund *et al.* 2002	ARH	E	2600	57	FL	N	S	I/Splicing	GAAACCTGTTTTCTC	TTTC/AA	
SVA	*SPTA1*	1	Hassoun *et al.* 1994, Ostertag *et al.* 2003	HE and HPP	E	632	50	Y/5′TR/INV	Y (183/599)	S	E	GAAATTTGAAGACTTCCAAGT	TTTC/AA	Orphan 3′-transduction
SVA	*HLA-A*	6	Takasu *et al.* 2007	Leukemia	F_1	2000	45	FL	N/A	AS	14 kb Deletion	N/A	CCTT/AG	Novel SVA subfamily (F_1)
SVA	*FKTN*	9	Kobayashi *et al.* 1998	FCMD	E	3023	32	FL	N	S	3′UTR/Splicing	AAGAAAAAAAAAATTGT	TCTT/AA	
SVA	*PNPLA2*	11	Akman *et al.* 2010 [123]	NLSDM	E	1800	44	Y/5′TR	N	S	E	AAAGAGGCCCGG	CTTT/AG	
pA	*COL4A6*	X	Segal *et al.* 1999	Alport syndrome	N/A	N/A	70	N/A	N/A	AS	13.4 kb Deletion	No TSD	TTCT/AT	
pA	*AGA*	4	Jalanko *et al.* 1995	AGU	N/A	N/A	37	N/A	N/A	AS	2 kb Deletion	No TSD	TTCT/AA	
pA	*BRCA2*	13	Wang *et al.* 2001	Breast Cancer	N/A	N/a	35	N/A	N/A	S	6.2 kb Deletion	No TSD	TTCT/AA	
pA	*NF1*	17	Wimmer *et al.* 2011 [53••]	NF1	N/A	130	120	N/A	N/A	AS	E	AAGAAA	TCTT/AA	

Data for this table were compiled from the primary references listed and reports before 2009 are reviewed in the following: Ostertag and Kazazian 2001 [44], Chen *et al.* 2006 [51] and Belancio *et al.* 2008 [52]. *Abbreviations*: TR = truncation, INV = inversion, E = exon, FL = full-length, I = intron. *Disease acronyms*: ADOA = Autosomal dominant optic atrophy, AGU = Aspartylglucosaminuria, AIP = Acute intermittent porphyria, ALD = Adrenoleukodystrophy, ALPS = Autoimmune lymphoproliferative syndrome, AOA2 = Ataxia with oculomotor apraxia 2, ARH = Autosomal recessive hypercholesterolemia, BOR = Branchio-oto-renal syndrome, CDG-Ia = Congenital disorders of glycosylation type Ia, CDS = Chanarin-Dorfman syndrome, CGD = Chronic granulomatous disease, DMD = Duchenne muscular dystrophy, FAP = Familial adenomatous polyposis, FCMD = Fukuyama-type congenital muscular dystrophy, FHH and NSHPT = Familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism, GKD = Glycerol kinase deficiency, HAE = Hereditary form of angioedema, HE and HPP = Hereditary elliptocytosis and hereditary pyropoikilocytosis, HIGM = Hyper-immunoglobulin M syndrome, HNPCC = Hereditary non-polyposis colorectal cancer syndrome, LPL = Lipoprotein lipase, MLII = Mucolipidosis Type II, MWS = Mowat–Wilson syndrome, NF1 = Neurofibromatosis Type I, PDHc = Pyruvate dehydrogenase complex deficiency, NLSDM = Neutral lipid storage disease with subclinical myopathy, RP = Retinitis pigmentosa, Type 1 ATD = Type 1 antithrombin deficiency, XDP = X-linked dystonia-parkinsonism, XLA = X-linked agammaglobulinemia, XLDCM = X-linked dilated cardiomyopathy, XLRP = X-linked retinitis pigmentosa, XSCID = X-linked severe combined immunodeficiency. A few insertions were left off the list as they were common polymorphisms or did not cause disease. The following websites and databases were used in the analysis: http://www.repeatmasker.org/, Repbase (http://www.girinst.org/) [109], http://dbrip.brocku.ca/ [110], The following symbols: $, *, #, indicate same insertion site in Wimmer *et al.* 2008 [53••].

Terapije z mobilnimi elementi

- *Sleeping Beauty* je sintetičen DNA transpozon, podoben Tc/Mariner transpozonu
- Iz neaktivnega elementa
- Narejen za vnos genetskega materiala v gostitelja ali za mutagenezo
- Prepozna TA mesto (200 milijonov pri človeku)
- Genska terapija (dolgotrajno izražanje transgena v T celicah, B celicah, jetrih), specifična mesta integracije



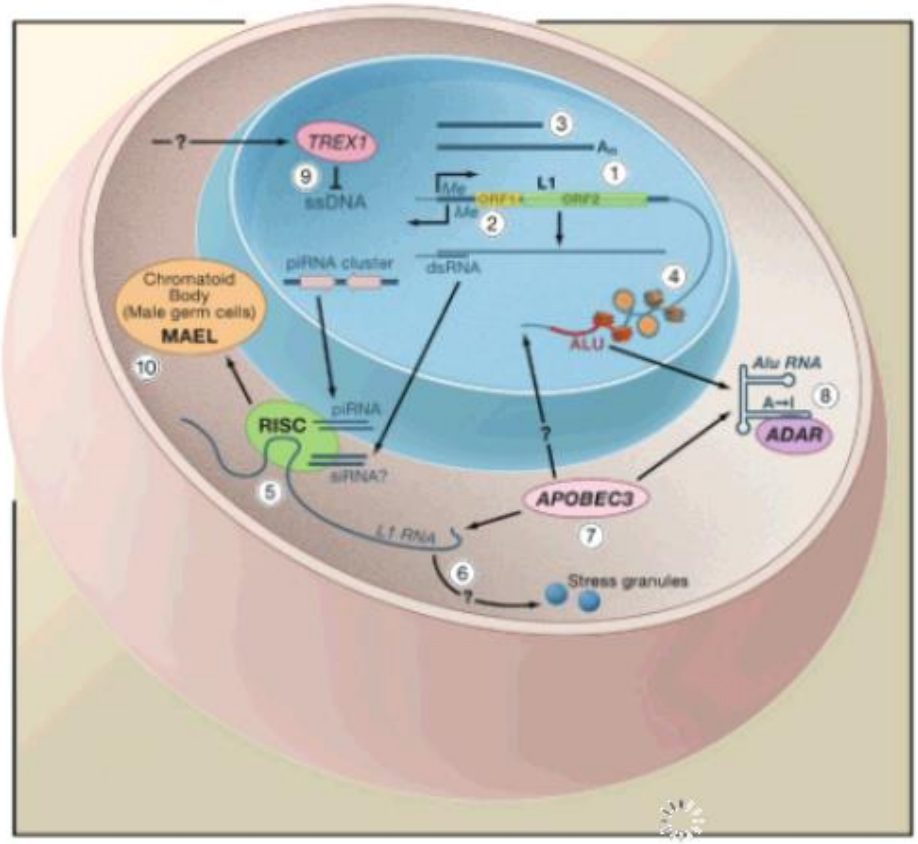
Vloga transpozicijskih elementov

- pomagajo gostitelju pri stresu
- popravljajo napake v DNA
- sodelujejo pri inaktivaciji X kromosomov
- so gonilna sila evolucije
- regulirajo izražanje genov
- sodelujejo pri nastanku novih genov

Regulacija TE v gostitelju

1. Inaktivacija L1 –skrajšanje, mutacije, preureditve
2. Inhibicija L1 z metilacijo 5'UTR
3. Pavziranje transkripcije ali prehitra terminacija
4. Heterokromatizacija ustavi izražanje L1
5. piRNA z RNAi v zarodnih celicah
6. Sekvestracija v stresna zrnca
7. Modifikacije s proteini APOBEC (G v T)
8. dsRNA editiranje z ADAR (adenozin v inozin)
9. Razgradnja ssDNA z DNA nukleazo TREX1

- Regulacija s TF



V(D)J rekombinacija

Recombination activating gene-1 in -2 sta homologa transpozaze pri Variable Diverse Joining gene rekombinaciji.

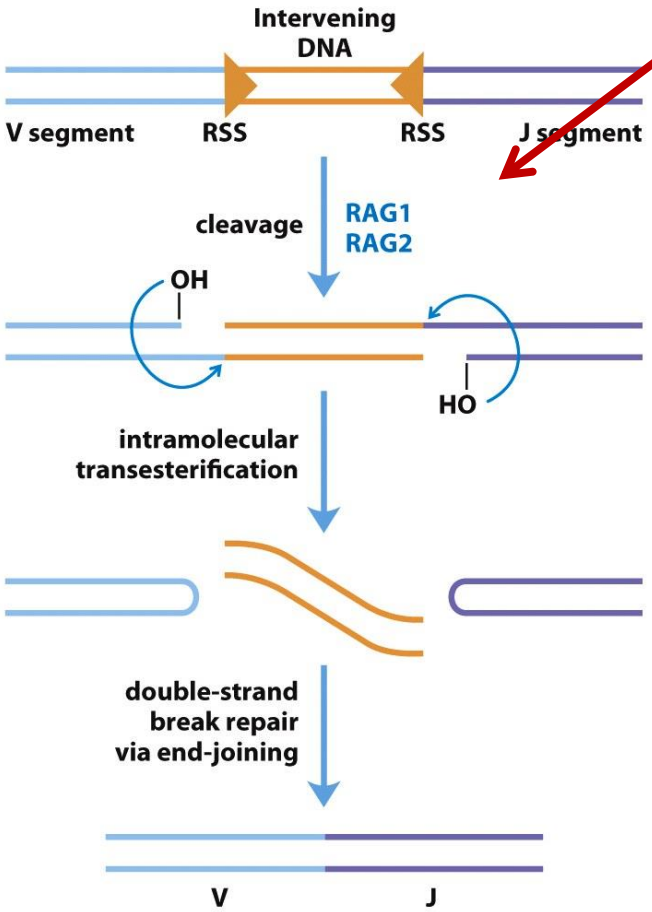


Figure 25-47
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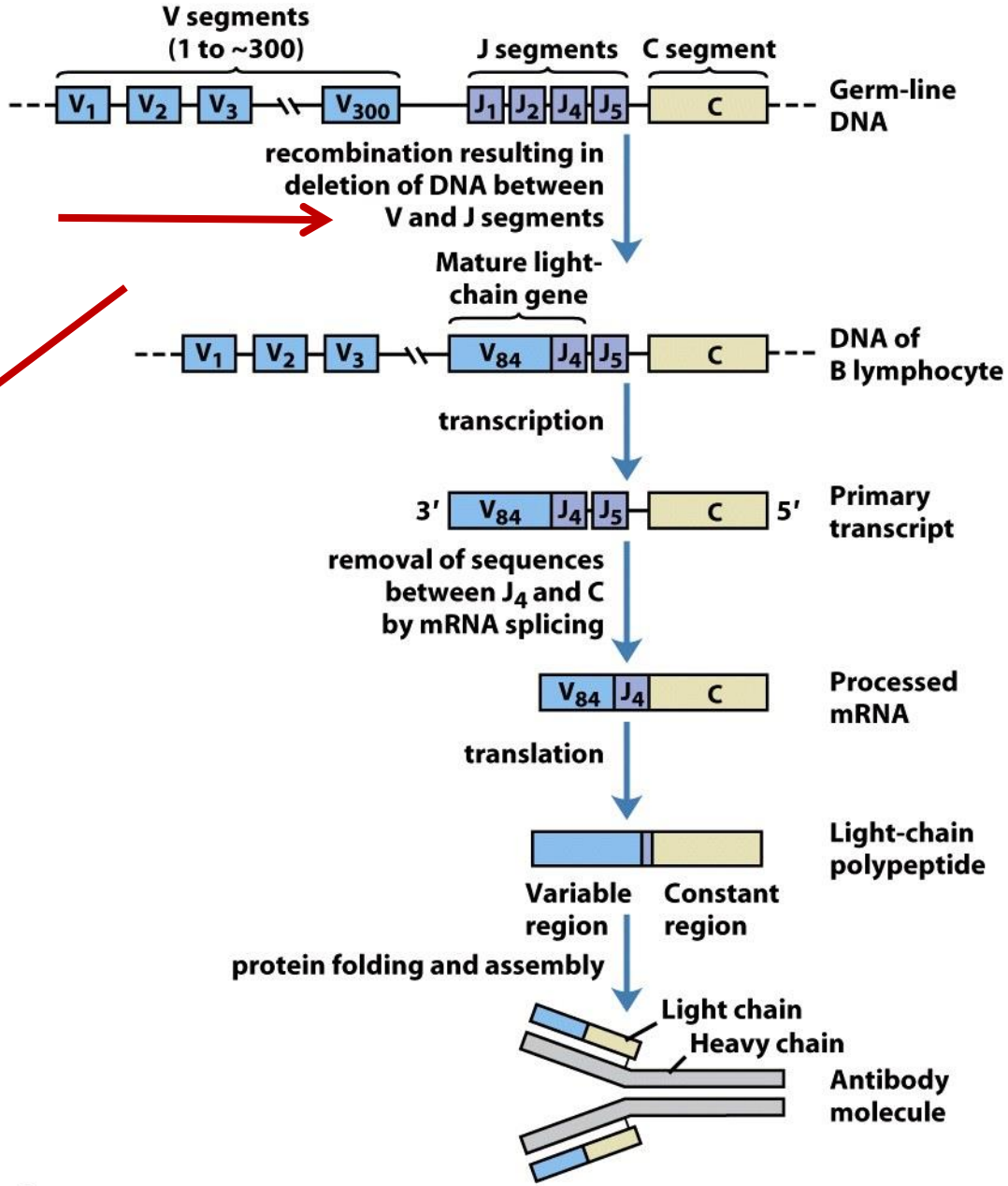

Figure 25-46
Lehninger Principles of Biochemistry, Fifth Edition

Rezistenca na antibiotike

- Transpozon pri bakterijah nosi rezistenco na antibiotik
- Vgradi se v plazmid
- Plazmid se prenaša med bakterijami