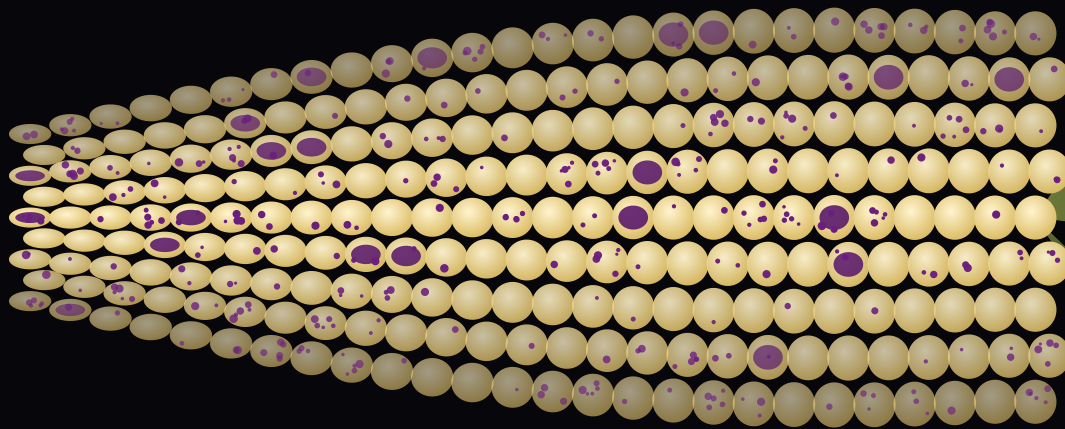


Each purple spot is a clone of cells in which Ds left the pigment gene
earlier excision → larger sector



Stylised variegated maize. The kernels are pale because a transposable element (Ds) sits inside a pigment gene; wherever it jumps out during development, the gene works again and a purple clone of cells appears.

Transposable elements

Jumping genes: DNA sequences that move from one place in the genome to another, how they do it, how cells keep them in check, and what they have built.

— DNA transposons — Retrotransposons — Repeats and target-site duplications
— Host DNA

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1. What they are

Transposable elements (TEs), or **transposons**, are DNA sequences that can move from one location in a genome to another. The process is called **transposition**. Unlike ordinary recombination, it needs little or no sequence similarity between the element and the site where it lands, and it is catalysed by enzymes the elements usually encode themselves, chiefly **transposase** or **reverse transcriptase** with an integrase or endonuclease.

Barbara McClintock discovered them in maize in the late 1940s, calling them "controlling elements". The idea that genes could move contradicted the view of the genome as a fixed string of genes, and her work was widely ignored until transposons were found in bacteria in the late 1960s. She received the **Nobel Prize in 1983**.

They are far from rare. TEs make up:

Genome	Share that is transposon-derived
Human	About 45% (LINEs ≈17–21%, SINEs ≈11–13%, LTR elements ≈8%, DNA transposons ≈3%)
Maize	About 85%, mostly LTR retrotransposons
<i>Drosophila melanogaster</i>	About 15–20%
Yeast (<i>S. cerevisiae</i>)	About 3%
<i>E. coli</i>	A few percent, as IS elements and transposons

Most of these copies are dead: mutated, truncated fragments that can no longer move. In humans only about 80–100 LINE-1 copies per genome remain capable of retrotransposition, and they also mobilise Alu and SVA elements.

Key terms

- **Autonomous element:** encodes its own transposition enzyme and can move by itself (Ac, LINE-1).
- **Non-autonomous element:** lacks a working enzyme gene but keeps the end sequences, so it moves only when an autonomous partner supplies the enzyme *in trans* (Ds, Alu).
- **Terminal inverted repeats (TIRs):** short sequences at the two ends of DNA transposons, in opposite orientation, recognised by transposase.
- **Target-site duplication (TSD):** a short direct repeat of host DNA (typically 2–20 bp) created on both sides of an element when it inserts.

- **Long terminal repeats (LTRs):** direct repeats of a few hundred base pairs at the ends of LTR retrotransposons and retroviruses.

2. Classification

Finnegan's scheme (1989) divides eukaryotic TEs by whether they move through an RNA intermediate:

Class	Mechanism	Group	Examples
Class I: retrotransposons	Copy-and-paste: DNA → RNA → cDNA	LTR retrotransposons	Ty1 (yeast), <i>copia</i> and <i>gypsy</i> (<i>Drosophila</i>), human endogenous retroviruses (HERVs)
		Non-LTR: LINEs (autonomous)	LINE-1 (L1) in mammals; I factor in <i>Drosophila</i>
		Non-LTR: SINEs (non-autonomous)	Alu (primates), B1 (mouse)
Class II: DNA transposons	Cut-and-paste: DNA → DNA	TIR transposons	Ac/Ds (maize), P element (<i>Drosophila</i>), <i>mariner</i> /Tc1, <i>piggyBac</i>
	Rolling circle	Helitrons	Abundant in plants, bats
	Self-synthesising	Mavericks (Polintons)	Large elements encoding their own DNA polymerase

In bacteria the usual groups are **insertion sequences (IS elements)**, **composite transposons**, **complex (Tn3-family) transposons** and transposing phages such as **Mu**.

3. Common structural features

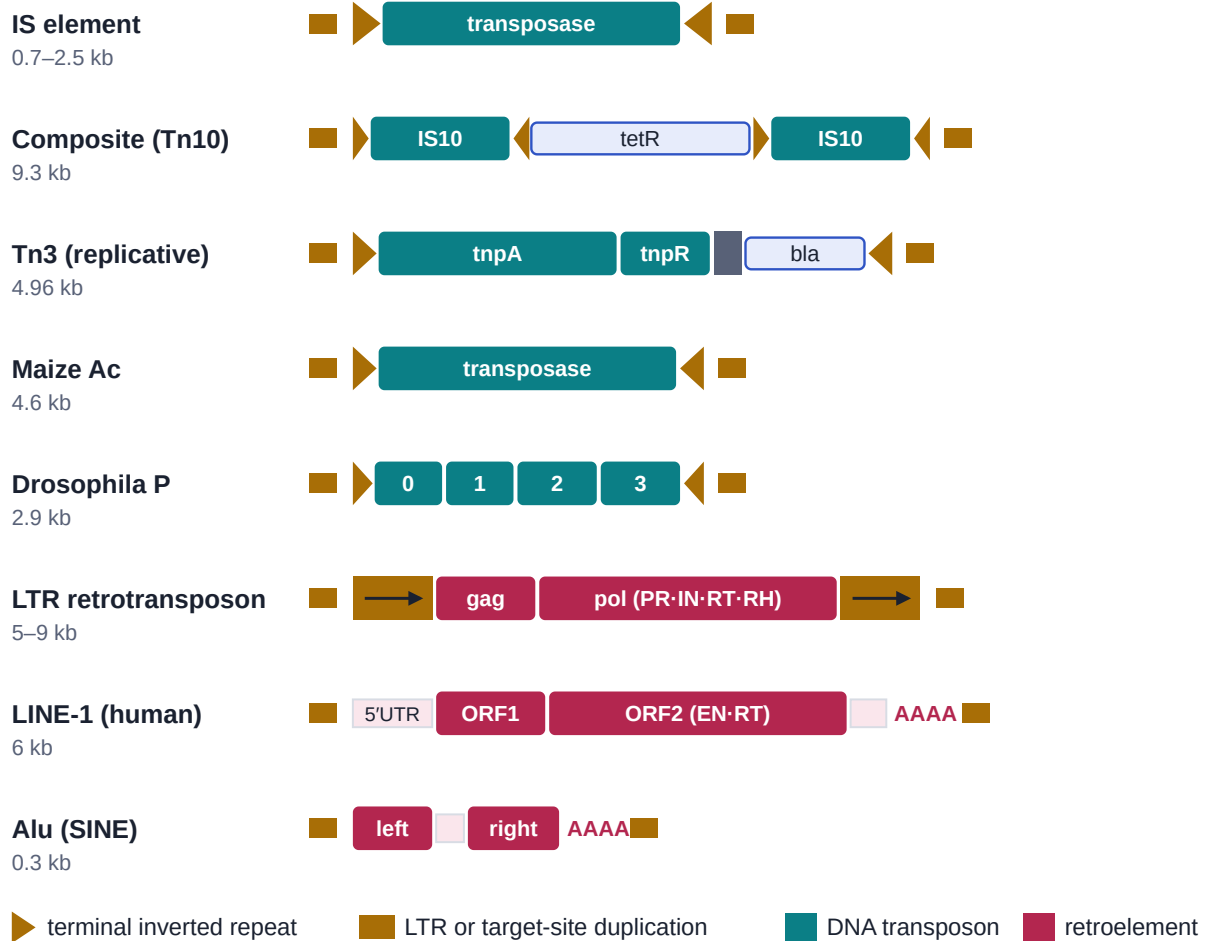


Figure 1. Structures of representative elements, not to scale. Amber blocks at each end show the target-site duplications made on insertion. DNA transposons are bounded by inverted repeats; LTR retrotransposons by long direct repeats; LINES and SINEs end in a poly(A) tail.

A target-site duplication is the fingerprint of a transposition event. It forms because the enzyme cuts the two strands of the target DNA at staggered positions; after the element is joined in, the single-stranded gaps are filled by host repair, copying the short stretch between the cuts on each side.

1. Staggered cut

5' G C A T **G T C A G** T A C 3'
3' C G T A **C A G T C** A T G 5'

transposase nicks the top strand before, and the bottom strand after, the 5 bp shown in amber

2. Insert, leaving gaps

G C A T
C G T A **C A G T C**

transposon

G T C A G T A C
A T G

3. Gap repair → duplication

G C A T **G T C A G**
C G T A **C A G T C**

transposon

G T C A G T A C
C A G T C A T G

the same 5 bp now flank the element as direct repeats

Figure 2. Formation of a target-site duplication. The TSD length is characteristic of each element: 9 bp for Tn10, 5 bp for Tn3, 8 bp for Ac and P elements, 2 bp (TA) for *mariner*, 7–20 bp for L1.

4. Mechanisms of transposition

Cut-and-paste

conservative · DNA transposons



gap repaired (may leave footprint)

copy number unchanged

Replicative

Tn3, Mu

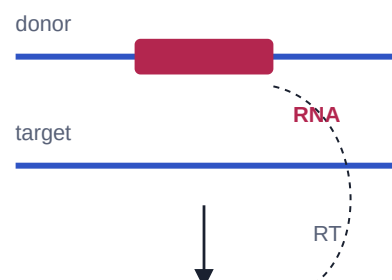


via cointegrate + resolvase

copy number +1

Copy-and-paste via RNA

retrotransposons



new cDNA copy inserted

copy number +1

Copying mechanisms are why retroelements dominate large genomes.

Figure 3. The three basic routes. Only the copying routes raise copy number directly, but cut-and-paste elements can multiply too, by moving from a replicated to an unreplicated region during S phase, or when the donor gap is repaired from the sister chromatid, which restores the element.

Conservative (cut-and-paste) transposition

1. Transposase dimers bind the TIRs and bring the two ends together (synaptic complex).
2. The element is cut out of the donor site.
3. Transposase makes a staggered cut at the target and joins the element's 3' ends to it (strand transfer).
4. Host enzymes fill the gaps, creating the TSD. The broken donor site is repaired, often leaving a small "footprint" of altered sequence.

Examples: Tn10, Tn5, Ac/Ds, P elements, *mariner*.

Replicative transposition (Shapiro model, 1979)

Transposase nicks the ends of the element and staggered-cuts the target, then joins the two. DNA replication through the element produces a **cointegrate** in which donor and target molecules are fused, with one copy of the element at each junction. A site-specific recombinase, **resolvase** (encoded by *tnpR* in Tn3), recombines between the two *res* sites to separate the molecules, each now carrying a copy. Examples: Tn3, bacteriophage Mu.

Retrotransposition

- **LTR retrotransposons** behave like retroviruses without the ability to leave the cell (most lack a working *env* gene). RNA polymerase II transcribes the element from the promoter in the 5' LTR. In the cytoplasm the RNA is packed into virus-like particles, where reverse transcriptase copies it into double-stranded cDNA. Integrase then inserts the cDNA into a new chromosomal site.
- **Non-LTR retrotransposons** (LINEs) use **target-primed reverse transcription (TPRT)**: reverse transcription happens directly at the insertion site in the nucleus.

- 1 L1 RNA with ORF1/ORF2 proteins returns to the nucleus (RNP)



- 2 ORF2 endonuclease nicks one strand at a TTTT/A site



- 3 Nicked 3'-OH anneals to the poly(A) tail and primes reverse transcription



- 4 Second-strand nick and synthesis; repair completes a new insertion, often 5'-truncated, flanked by TSDs



Figure 4. Target-primed reverse transcription by LINE-1. Reverse transcription often stops early, so most new L1 copies are 5'-truncated and lose their promoter, which is one reason almost all L1 copies are dead.

Proof that Ty moves through RNA (Boeke, Garfinkel, Styles and Fink, 1985)

An artificial intron was placed inside a yeast Ty1 element driven by an inducible promoter. After induction, new Ty1 copies appeared elsewhere in the genome, and they had lost the intron. Introns are removed only by RNA splicing, so the new copies must have been made from spliced RNA by reverse transcription. Transposition also increased when transcription was induced.

5. Bacterial transposable elements

Insertion sequences

IS elements are the simplest transposons: 0.7–2.5 kb, short TIRs (10–40 bp), and a single gene for transposase. They carry no genes useful to the host and were first recognised (Shapiro, Starlinger and Saedler, 1960s) as unusual polar mutations in the *E. coli gal* operon. Examples: IS1 (768 bp), IS10, IS50. IS elements also mediate integration of the F plasmid into the chromosome to form Hfr strains, because the same IS sequences occur in both.

Composite transposons

Two IS elements flank a central region carrying other genes, usually for antibiotic resistance. The whole unit moves when transposase acts on the outer ends of the IS elements. Examples: **Tn10** (tetracycline resistance, flanked by IS10), **Tn5** (kanamycin resistance, IS50), **Tn9** (chloramphenicol, IS1).

Complex (Tn3-family) transposons

Bounded by short TIRs (38 bp) rather than IS elements. **Tn3** carries *tnpA* (transposase), *tnpR* (resolvase and repressor of *tnpA*) and *bla* (β-lactamase, ampicillin resistance). It transposes replicatively.

Transposons and antibiotic resistance

Resistance genes on transposons can jump from chromosomes onto plasmids, and conjugative plasmids can then carry them across species. Plasmids gathering several transposons become multidrug-resistance (R) plasmids. Many also carry **integrations**, platforms that capture resistance gene cassettes. This is the main route by which resistance spreads in hospitals.

Bacteriophage Mu ("mutator") replicates by replicative transposition, inserting almost at random in the host chromosome and causing mutations in the process.

6. McClintock and the Ac/Ds system

Working on maize chromosome 9 at Cold Spring Harbor, McClintock noticed a site where chromosomes repeatedly broke. She called the element responsible **Ds** (*Dissociation*) and found it broke chromosomes only in the presence of another element, **Ac** (*Activator*). Crucially, both could change their position.

- When Ds inserts into the *C* gene, needed for purple anthocyanin in the aleurone, the kernel is colourless.
- If Ac is present, Ds can excise during kernel development. The cell in which that happens, and all its descendants, can make pigment again, forming a purple spot. Early excision gives large spots; late excision small ones.
- Without Ac, Ds is stable and the kernel stays colourless: Ds is non-autonomous.
- More copies of Ac delay the timing of excision, giving fewer, smaller spots, a dosage effect McClintock recorded carefully.

Molecular cloning (Fedoroff and others, 1980s) confirmed the model. **Ac** is 4.6 kb with 11 bp TIRs and encodes transposase; it creates 8 bp TSDs. **Ds** elements are internally deleted

versions of Ac, some only a few hundred base pairs, that keep the ends but not a working transposase gene.

Mendel's wrinkled peas

The *r* (rugosus) allele that gave Mendel wrinkled seeds is an 0.8 kb Ac/Ds-family insertion in the gene for starch-branching enzyme I (Bhattacharyya and colleagues, 1990). Without the enzyme, seeds store more sucrose, take up more water, and wrinkle as they dry.

7. P elements and hybrid dysgenesis

In the 1970s crosses between certain *Drosophila melanogaster* strains gave offspring with a syndrome called **hybrid dysgenesis**: sterility (atrophied gonads), high mutation rates, chromosome rearrangements, and recombination in males (which normally have none). The cause is the **P element**, a 2.9 kb DNA transposon with 31 bp TIRs.

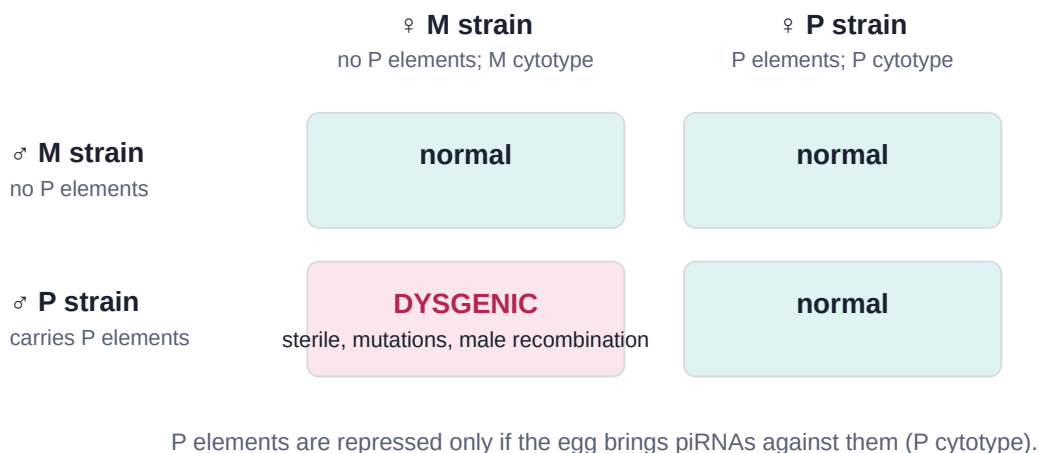


Figure 5. Hybrid dysgenesis happens only in one direction of the cross. The difference between reciprocal crosses shows that the egg's cytoplasm, not just the genes, controls P element activity.

- **P strains** carry P elements and a repressive state called the **P cytotype**. **M strains** lack P elements.
- P cytotype is maternally transmitted. It is now known to depend on **piRNAs** against P elements that the mother loads into the egg. An M-strain egg has none, so P elements brought in by sperm transpose freely in the germline of the hybrid.
- P elements move only in the **germline** because the third intron (IVS3) of the transposase transcript is spliced out only in germ cells. In somatic cells IVS3 is retained, giving a truncated protein that represses transposition.

- P elements spread through wild *D. melanogaster* populations in the mid-20th century, most likely by horizontal transfer from *D. willistoni*. Laboratory strains collected earlier are M strains.

Rubin and Spradling (1982) turned the P element into the first tool for making transgenic *Drosophila*, by injecting embryos with a P element carrying a gene of interest together with a transposase source.

8. Retrotransposons: yeast Ty and human L1 and Alu

Ty elements in yeast

Ty1 is about 5.9 kb with 334 bp LTRs (called delta sequences) and genes *TYA* (like *gag*) and *TYB* (like *pol*). It is structurally similar to a retrovirus without *env*. Single delta sequences left behind by recombination between the two LTRs of an element ("solo LTRs") are scattered through the genome.

LINE-1

Full-length human L1 is about 6 kb: a 5' UTR containing an internal promoter, **ORF1** (an RNA-binding chaperone) and **ORF2** (endonuclease plus reverse transcriptase), a 3' UTR and a poly(A) tail. About 500,000 copies make up roughly 17% of the genome, though almost all are truncated or mutated. L1 proteins act mostly on the RNA that made them ("cis preference") but also on other poly(A) RNAs, which explains the spread of Alu elements and of **processed pseudogenes**, intronless copies of ordinary genes.

Alu

Alu elements are primate-specific SINEs of about 300 bp, derived from the **7SL RNA** gene of the signal recognition particle. With over one million copies ($\approx 10\%$ of the genome), they are the most numerous element in human DNA. They are transcribed by RNA polymerase III from an internal promoter (A and B boxes), carry no protein-coding genes and depend on L1 ORF2 to move. Their name comes from the *AluI* restriction site within them.

Human disease from new insertions

Disease	Element	Note
Haemophilia A	L1 into factor VIII gene	First active human transposon to be found (Kazazian, 1988)

Disease	Element	Note
Neurofibromatosis type 1	Alu into <i>NF1</i>	New insertion in a patient, absent from the parents
Duchenne muscular dystrophy	L1 into <i>DMD</i>	Exon skipping
Hereditary breast cancer	Alu into <i>BRCA2</i>	Exon disruption
Familial hypercholesterolaemia	Alu–Alu recombination in <i>LDLR</i>	Deletions from unequal crossing over between repeats

Overall, new TE insertions account for roughly one in every few hundred human disease mutations. Somatic L1 insertions also occur in some cancers and in neurons.

9. Effects on genes and genomes

Harmful or disruptive

- **Insertional mutagenesis:** an element landing inside an exon disrupts the coding sequence; in an intron it can create a new splice site; near a gene it can add a promoter or enhancer, or break one.
- **Polar effects** in bacterial operons, because IS elements carry transcription terminators.
- **Chromosome rearrangements:** recombination between copies of an element at different sites (ectopic recombination) produces deletions, duplications, inversions and translocations.
- **Imprecise excision** leaves footprints or deletes neighbouring DNA.

Creative: raw material for evolution

- **Genome size.** Differences in genome size between related species, such as the "C-value paradox", are largely differences in TE content.
- **Exon shuffling** by L1 3' transduction, when reverse transcription reads through into downstream host sequence and carries it to a new site.
- **Regulatory rewiring.** Many enhancers, promoters and transcription factor binding sites in the human genome come from TEs.
- **Domestication** of TE genes into host functions:
 - **RAG1/RAG2**, which cut and join gene segments in V(D)J recombination of antibodies and T-cell receptors, descend from a *Transib* DNA transposon; the recombination signal

sequences are its ancient TIRs.

- **Syncytins**, which fuse placental cells into the syncytiotrophoblast, are *env* genes of endogenous retroviruses.
- **Telomerase** reverse transcriptase is related to the RTs of non-LTR retrotransposons, and *Drosophila* telomeres are maintained entirely by the retrotransposons HeT-A, TART and TAHRE.
- **CENP-B**, a centromere protein, comes from a *pogo* transposase.

Whether TEs are "selfish DNA" (Orgel and Crick; Doolittle and Sapienza, 1980) or useful to their hosts is not an either-or question. They spread because they copy themselves, and the host genome has, over time, recruited some of their parts.

10. How hosts control them

Defence	How it works
DNA methylation	Cytosine methylation silences TE promoters in plants and animals; McClintock's elements switched between active and inactive states this way
Repressive chromatin	H3K9 methylation and heterochromatin; in mammals, hundreds of KRAB zinc-finger proteins recruit KAP1 (TRIM28) to specific TE families
piRNA pathway	In the animal germline, small RNAs from TE-rich piRNA clusters guide PIWI proteins to cut TE transcripts and to silence the genes' chromatin. The "ping-pong cycle" amplifies piRNAs against active elements
siRNA / RNA-directed DNA methylation	Main defence in plants
Restriction factors	APOBEC3 enzymes mutate reverse-transcribed cDNA; SAMHD1 limits dNTPs
Self-regulation	Overproduction inhibition in <i>mariner</i> ; tissue-specific splicing of P transposase; <i>tnpR</i> repression in Tn3
Target choice	Many elements target "safe havens": Ty1 upstream of tRNA genes, Ty3 at Pol III start sites, Ty5 in heterochromatin

11. Transposons as tools

- **Transposon tagging:** genes are cloned by inserting a known element into them and using the element as a probe. The maize *bronze* gene was the first cloned this way, with Ac.
- **Insertional mutagenesis screens:** saturating a genome with insertions to find genes needed for a process. **Tn-seq** sequences millions of insertion sites in bacteria at once.
- **Transgenesis:** P elements in *Drosophila*; *piggyBac* and *Sleeping Beauty* (a Tc1/*mariner* element reconstructed in 1997 from dead fish copies) for vertebrate cells, including CAR-T cell engineering.
- **Enhancer traps and gene traps:** reporter genes on transposons that light up when they land near an active enhancer.
- **Markers:** presence or absence of Alu and L1 insertions for population and forensic studies, and for phylogeny, since an insertion is almost never lost cleanly.

12. Quick revision

Remember	Fact
Discoverer	Barbara McClintock, maize Ac/Ds, late 1940s; Nobel 1983
Two classes	Class I via RNA (copy-and-paste); Class II DNA transposons (cut-and-paste)
Hallmarks	TIRs (DNA transposons), LTRs (LTR retrotransposons), poly(A) (LINEs, SINEs), TSD for all
Replicative transposition	Tn3, Mu; cointegrate resolved by resolvase at <i>res</i>
Composite transposons	Tn10 (IS10, tet), Tn5 (IS50, kan), Tn9 (IS1, cat)
Hybrid dysgenesis	P ♂ × M ♀ only; germline IVS3 splicing; P cytotype = maternal piRNAs
RNA intermediate proof	Intron removed from Ty1 after transposition (Boeke et al., 1985)
Human genome	≈45% TE; L1 ≈17%, 6 kb, ORF1/ORF2; Alu ≈10%, 300 bp, from 7SL RNA
Non-LTR mechanism	Target-primed reverse transcription (TPRT)

Remember	Fact
Domesticated TEs	RAG1/2, syncytin, telomerase (related), CENP-B

13. End-semester question bank

Long answer (10–15 marks)

1. What are transposable elements? Classify them, with examples from prokaryotes and eukaryotes.
2. Describe the Ac/Ds system of maize and explain how it produces variegated kernels. Comment on the significance of McClintock's work.
3. Describe the structure of bacterial transposable elements (IS elements, composite and complex transposons) and their role in the spread of antibiotic resistance.
4. Explain the mechanisms of conservative and replicative transposition, with suitable diagrams.
5. Describe retrotransposons. Compare LTR and non-LTR retrotransposons, and explain target-primed reverse transcription.
6. What is hybrid dysgenesis? Explain its molecular basis in *Drosophila* and the use of P elements in genetic engineering.
7. Discuss the genetic and evolutionary significance of transposable elements, including their role in human disease and genome evolution.
8. How do host genomes control transposable elements? Describe the roles of DNA methylation and the piRNA pathway.

Short notes (5 marks)

1. Target-site duplication
2. Insertion sequences
3. Tn3 and resolvase
4. Ty elements of yeast
5. LINE-1
6. Alu elements
7. P cytotype
8. Transposon tagging

9. Bacteriophage Mu
10. Domesticated transposons

Differentiate between

1. Class I and Class II transposable elements
2. Autonomous and non-autonomous elements
3. LINEs and SINEs
4. Composite and complex transposons
5. Conservative and replicative transposition
6. Transposition and site-specific recombination

Draw and label

1. Structure of an IS element and of Tn10
2. Formation of a target-site duplication
3. Structure of a LINE-1 element
4. The replicative transposition pathway with cointegrate formation

▼ Very short answer (2 marks), with answers

1. Who discovered transposable elements? **Barbara McClintock**
2. Autonomous partner of Ds? **Ac (Activator)**
3. Enzyme that resolves the Tn3 cointegrate? **Resolvase (TnpR)**
4. Antibiotic resistance carried by Tn10? **Tetracycline**
5. RNA from which Alu is derived? **7SL RNA**
6. Two proteins encoded by LINE-1? **ORF1p (RNA-binding) and ORF2p (endonuclease/reverse transcriptase)**
7. Which intron of the P transposase gene is spliced only in the germline? **IVS3 (third intron)**
8. Percentage of the human genome derived from TEs? **About 45%**
9. Yeast LTRs are known as? **Delta (δ) sequences**
10. Small RNAs that silence TEs in the animal germline? **piRNAs**
11. Vertebrate gene-delivery transposon resurrected from fish? ***Sleeping Beauty***
12. Human immune proteins derived from a transposase? **RAG1 and RAG2**

14. Case-based MCQs

Ten hard questions that test application rather than recall. Choose an answer before opening the explanation.

Q1. A maize line has colourless kernels caused by Ds inserted in the *C* gene. When crossed to a line carrying one Ac element, the resulting kernels show purple spots. A line carrying three copies of Ac gives kernels with fewer, smaller spots. What is the best explanation?

- A. Extra Ac copies inhibit Ds transposase, so excision never occurs
- B. Ac shows a negative dosage effect: more copies delay excision to later in kernel development, so each revertant sector is smaller
- C. Ac inserts into the purple revertant cells and kills them
- D. Three Ac copies convert Ds into an autonomous element

▼ Show answer

Answer: B. McClintock observed that increasing Ac dose shifts excision later. Spot size reflects how many cell divisions occurred after the excision event, so later excision means smaller spots. Ds still depends on Ac transposase; it does not become autonomous.

Q2. Sequencing a new mutant allele reveals a 1.3 kb insertion flanked by 9 bp direct repeats of host DNA that were present only once in the wild-type allele. The 9 bp repeats most likely arose from:

- A. Recombination between two copies of the element
- B. Staggered cutting of the target by transposase and gap repair
- C. Reverse transcription of the element's RNA
- D. Unequal crossing over at meiosis

▼ Show answer

Answer: B. Short flanking direct repeats of target DNA are target-site duplications. The element's enzyme makes staggered nicks 9 bp apart; after joining, host repair fills the single-stranded gaps, copying the 9 bp on both sides. The 1.3 kb size and 9 bp TSD match IS10.

Q3. An element carrying an artificial intron is placed under an inducible promoter in yeast. After induction, new copies are found elsewhere in the genome, all lacking the intron. The best conclusion is that the element:

- A. Transposes by cut-and-paste of DNA
- B. Is a DNA transposon whose transposase also has splicing activity
- C. Transposes through an RNA intermediate that is spliced and then reverse-transcribed
- D. Is removed by the host's mismatch repair system

▼ **Show answer**

Answer: C. Introns are removed by RNA splicing. Loss of the intron in new copies means the copies were made from processed RNA by reverse transcription. This is Boeke and Fink's 1985 proof that Ty1 is a retrotransposon.

Q4. A *Drosophila* geneticist crosses males from a wild-caught strain with females from a laboratory stock established in the 1920s. Many offspring are sterile and show high mutation rates. The reciprocal cross gives normal offspring. The key reason the reciprocal cross is normal is that:

- A. P-strain eggs contain piRNAs that silence P elements introduced from either parent
- B. M-strain males carry a repressor of transposase
- C. P elements cannot be transmitted through sperm
- D. Transposase is made only in female germ cells

▼ **Show answer**

Answer: A. The wild strain is P, the old laboratory strain M. When the mother is P, her eggs carry P-element piRNAs (P cytotype), which repress transposition in the offspring's germline. When the mother is M, there are no such piRNAs, and paternally inherited P elements transpose freely, causing dysgenesis.

Q5. A P element construct is engineered with its third intron (IVS3) removed. When introduced into flies, what change in behaviour is expected?

- A. It can no longer transpose at all
- B. It transposes in somatic cells as well as in the germline
- C. It transposes only in the germline, as before
- D. It becomes a retrotransposon

▼ Show answer

Answer: B. Germline restriction depends on IVS3 being spliced only in germ cells; in somatic cells IVS3 is retained and a truncated repressor protein is made. Removing IVS3 from the gene lets functional transposase be made everywhere, so somatic transposition occurs (Laski, Rio and Rubin, 1986).

Q6. An *E. coli* strain has Tn3 on its chromosome and receives a plasmid that lacks it. During transposition to the plasmid, a large molecule is transiently seen in which the whole plasmid and chromosome are joined with two copies of Tn3. In a *tnpR* mutant, these molecules accumulate. What does this show?

- A. Tn3 moves by cut-and-paste, and TnpR is its transposase
- B. Tn3 transposes replicatively via a cointegrate, which TnpR resolves by site-specific recombination at *res*
- C. TnpR is required for reverse transcription
- D. The plasmid and chromosome recombine through homologous sequences

▼ Show answer

Answer: B. The fused molecule with duplicated Tn3 is a cointegrate, the intermediate of replicative transposition. Resolvase (TnpR) recombines the two *res* sites to separate donor and target. Without it, cointegrates cannot be resolved.

Q7. A boy with severe haemophilia A has a 3.8 kb insertion ending in a poly(A) tract within exon 14 of the factor VIII gene. Neither parent carries it. Its sequence matches the 3' end of LINE-1. Which statement is correct?

- A. The insertion arose by cut-and-paste transposition of a DNA transposon
- B. It is a new L1 retrotransposition, 5'-truncated because reverse transcription stopped early during TPRT
- C. It was produced by homologous recombination between Alu elements
- D. It must be inherited, since transposition does not occur in human germ cells

▼ **Show answer**

Answer: B. This is the case Kazazian reported in 1988. A poly(A) tail, 3'-end sequence and truncated 5' end are the hallmarks of LINE-1 insertion by target-primed reverse transcription, which often terminates before copying the whole RNA. Its absence in the parents shows it arose de novo in a germ cell or early embryo.

Q8. Alu elements have no protein-coding genes, yet over a million copies have accumulated in primate genomes. Their spread is best explained by:

- A. Their own RNA polymerase III-encoded reverse transcriptase
- B. Use of the endonuclease and reverse transcriptase encoded by ORF2 of LINE-1
- C. Integration by retroviral integrase
- D. Replication by rolling circle

▼ **Show answer**

Answer: B. Alu is a non-autonomous SINE. Its Pol III transcripts end in A-rich tails and hijack L1 ORF2 protein, which inserts them by TPRT. L1 makes the tools; Alu, with far more RNA copies, borrows them.

Q9. A composite transposon consists of a kanamycin-resistance gene flanked by two IS50 elements. A mutation inactivates the transposase gene in the left IS50 only. What is expected?

- A. The transposon can no longer move
- B. The transposon still moves, because the right IS50 supplies transposase that acts on the outer ends
- C. Only the left IS50 can move
- D. The kanamycin gene becomes unstable and is lost

▼ **Show answer**

Answer: B. In composite transposons one functional IS can supply transposase for the whole unit, because transposase acts on the outer inverted repeats. In Tn5 only the right IS50 (IS50R) makes functional transposase anyway; IS50L encodes an inactive form.

Q10. The genes RAG1 and RAG2, which cut DNA at recombination signal sequences during V(D)J recombination, are considered 'domesticated transposons'. Which observation most strongly supports this?

- A. RAG proteins are expressed only in lymphocytes
- B. RAG1/2 can carry out transposition in vitro, inserting a signal-sequence-flanked fragment into target DNA, and resemble *Transib* transposases
- C. V(D)J recombination creates antibody diversity
- D. Signal sequences contain heptamers and nonamers

▼ **Show answer**

Answer: B. Agrawal, Eastman and Schatz (1998) showed purified RAG1/2 can transpose DNA in vitro, and genome surveys found *Transib* transposons whose transposase and terminal repeats resemble RAG1 and the recombination signal sequences. Tissue specificity and antibody diversity do not show evolutionary origin.

For further reading: Griffiths et al., *Introduction to Genetic Analysis*; Snustad and Simmons, *Principles of Genetics*; Lewin's *Genes*; Alberts, *Molecular Biology of the Cell*.