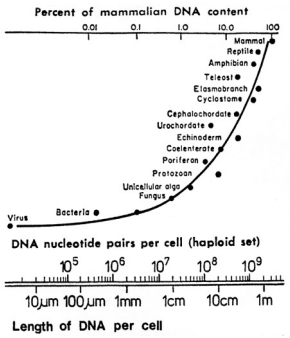
The Dilemma of Transposable Elements: Can't Live with Them, Can't Evolve without Them!

Slides assembled by
SCR Elgin, Washington University
S Parrish, McDaniel College
Genomics Education Partnership
July 5, 2022

1

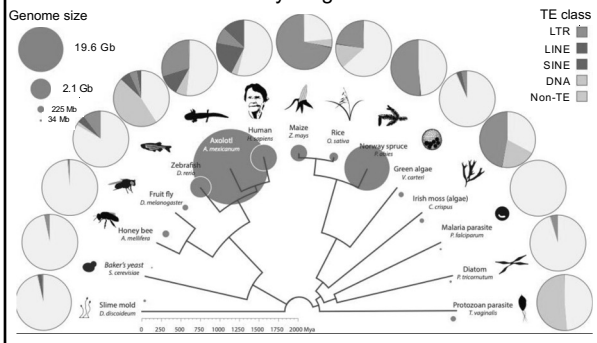
Eukaryotic genomes are surprisingly large!
Minimum haploid DNA content - the C-Value Paradox



Britten RJ, Davidson EH. Gene regulation for higher cells: a theory. Science. 1969 Jul 25;165(3891):349-57.

2

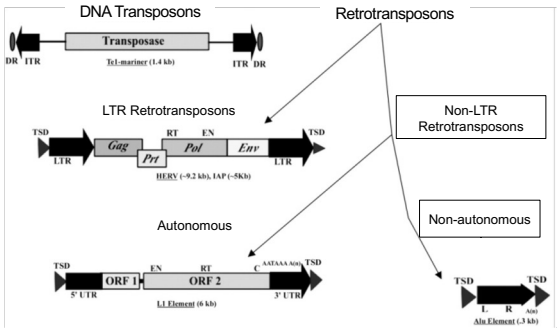
Transposable elements are major contributors to eukaryotic genomes



Wells JN, Feschotte C. A Field Guide to Eukaryotic Transposable Elements. Annu Rev Genet. 2020 Nov 23;54:539-561.

3

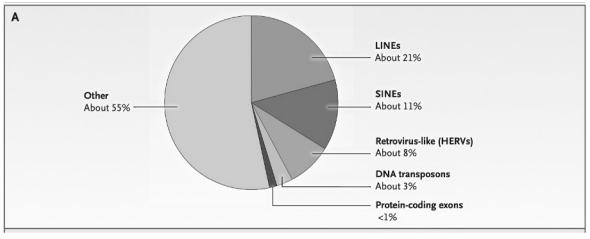
Classes of transposable elements



Kazazian HH Jr. Mobile elements: drivers of genome evolution. Science. 2004 Mar 12;303(5664):1626-32.

4

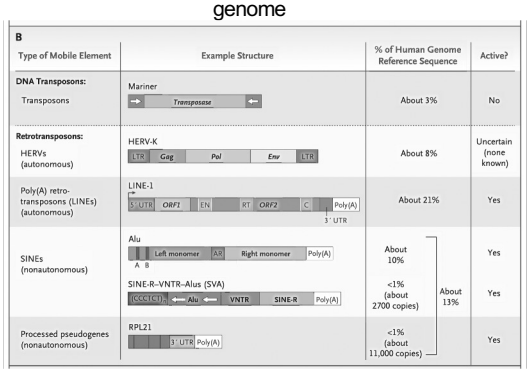
Transposable elements are major contributors to the human genome



Kazazian HH Jr, Moran JV. Mobile DNA in Health and Disease. N Engl J Med. 2017 Jul 27;377(4):361-370.

5

Transposable elements are major contributors to the human genome



Kazazian HH Jr, Moran JV. Mobile DNA in Health and Disease. N Engl J Med. 2017 Jul 27;377(4):361-370.

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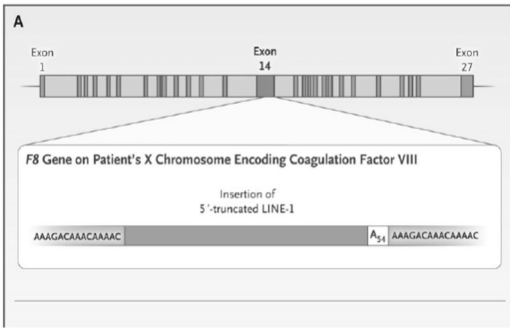
The harm that transposons can do: insertion mutations
Example: hemophilia



Kazazian HH Jr, Moran JV. Mobile DNA in Health and Disease.
N Engl J Med. 2017 Jul 27;377(4):361-370.

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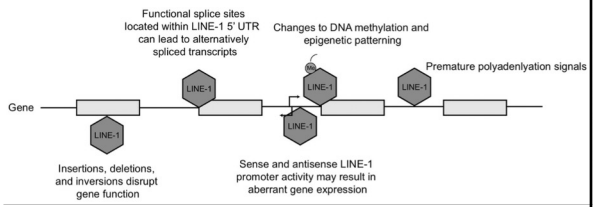
The harm that transposons can do: additional deleterious transposons effects

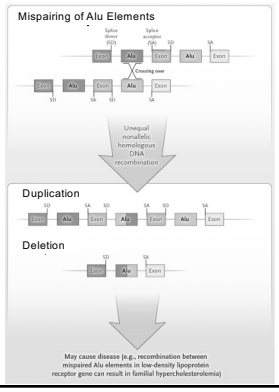
LINE-1 is clearly active in our present genome



Saleh A, Macia A, Muotri AR. Transposable Elements, Inflammation, and Neurological Disease. Front Neurol. 2019 Aug 20;10:894.

8

The harm that transposons can do: recombination events and genome instability



Kazazian HH Jr, Moran JV. Mobile DNA in Health and Disease. N Engl J Med. 2017 Jul 27;377(4):361-370.

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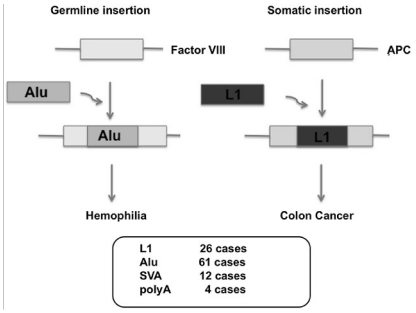
The harm that transposons can do: somatic mutations can lead to cancer



Ariumi Y. Guardian of the Human Genome: Host Defense Mechanisms against LINE-1 Retrotransposition. Front Chem. 2016 Jun 28;4:28.

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Cancer: many examples of mutations by TEs

Table 1
Examples of TE insertion and TE-mediated chromosomal rearrangements associated with cancer.

Locus and/or gene	Associated cancer	TE	Distribution
Insertion			
APC, adenomatous polyposis coli gene	Desmoids tumors	*Alu*	Germline
APC	Colon cancer	L1	Germline
APC		L1	Somatic
BRCA1, breast cancer 1 gene	Breast/ovarian cancer	*Alu*	Germline
BRCA2, breast cancer 2 gene	Breast/ovarian cancer	*Alu*	Germline
MYC, c-myc proto-oncogene	Breast carcinoma	L1	Somatic
NF1, neurofibromatosis 1 gene	Neurofibroma	*Alu*	Germline
Chromosomal deletions			
VHL, von Hippel Lindau gene	von Hippel Lindau disease	*Alu*	Germline
BRCA1	Breast/ovarian cancers	*Alu*	Germline
BRCA2	Breast/ovarian cancers	*Alu*	Germline
CDH1, cadherin 1 gene	Hereditary diffuse gastric cancer	*Alu*	Germline
CAD, caspase activated DNase gene	Hepatoma	*Alu*	Somatic
Chromosomal duplication			
MLL1, myeloid/lymphoid mixed lineage leukemia gene	Acute myeloid leukemia	*Alu*	Somatic
MYB, myb transcription factor gene	T-acute lymphoblastic lymphoma	*Alu*	Somatic
BRCA1	Breast/ovarian cancers	*Alu*	Germline
Chromosomal translocation			
EWSR1-ETV, t(5q23q31)(18q12)	Ewing sarcoma	*Alu*	Somatic
BCR-ABL, t(9;22)(q34;q11)	Chronic myeloid leukemia	*Alu*	Somatic

Chénais B. Transposable elements and human cancer: a causal relationship?
Biochim Biophys Acta. 2013 Jan;1835(1):28-35.

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The harm that transposons can do: inflammatory diseases

TABLE 1 | Disease and associated retroelements.

Disease	Retrotransposon	Mutation/Gene Referenced	Elevated Cytokines
Multiple Sclerosis (MS)	HERV-W		IFNγ, IL-6, TNF-α
Aicardi-Goutieres Syndrome (AGS)	LINE-1	TREX1, RNaseH2	TNF-α, IL-15, IFN-α
Rett Syndrome (RTT)	LINE-1	MeCP2	IL-6, IL-8
Sporadic Amyotrophic Lateral Sclerosis (ALS)	HERV-K	TDP-43	TNF-α, IL-6, IL-8, IL-1β
System Lupus Erythematosus (SLE)	HERV-E	Sgp3	IL-15, IL-10, IFN α/β, IL-6
Aging-related pathologies	LINE-1	SIRT6	IFN
Autism Spectrum Disorder (ASD)	LINE-1		IFNγ, IL-1β, IL-6

Saleh A, Macia A, Muotri AR. Transposable Elements, Inflammation, and Neurological Disease.
Front Neurol. 2019 Aug 20;10:894.

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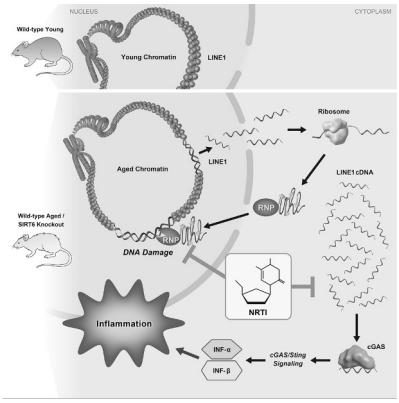

The harm that transposons can do: inflammation

Hope for bolstering defense!

NRT1 = nucleoside reverse-transcriptase inhibitors; can reduce this type I interferon response and DNA damage; they extend lifespan and improve health of SIRT6 KO mice.

Simon M, et al. LINE1 Derepression in Aged Wild-Type and SIRT6-Deficient Mice Drives Inflammation. Cell Metab. 2019 Apr 2;29(4):871-885.e5.

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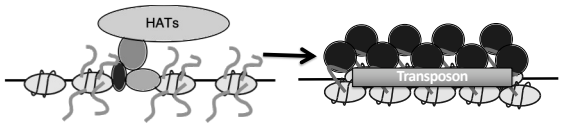
Defense! Most repetitious DNA is packaged as heterochromatin, with concomitant silencing



- Euchromatin
  - Less condensed
  - Chromosome arms
  - Unique sequences; gene rich
  - Replicated throughout S
  - Recombination during meiosis
- Heterochromatin
  - Highly condensed
  - Centromeres and telomeres
  - Repetitious sequences (e.g., TEs); gene poor
  - Replicated in late S
  - No meiotic recombination

Transcriptional activators

Heterochromatin Protein 1 complex

Hyper-acetylated histone tail

Hypo-acetylated histone tail; methylated H3/K9

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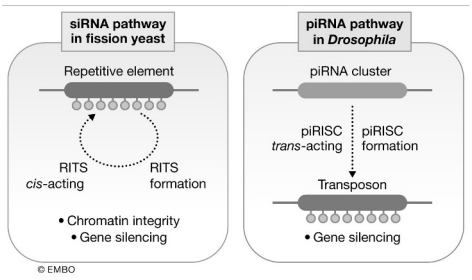
Heterochromatin formation: a defense against repeats (TEs)



Onishi, R., et al. piRNA- and siRNA-mediated transcriptional repression in Drosophila, mice, and yeast: new insights and biodiversity. EMBO Reports. 2021 22: e53062.

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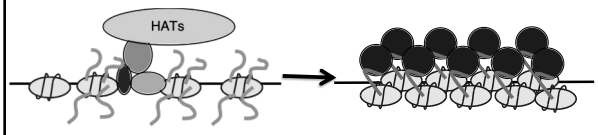
Heterochromatin formation: a defense against repeats (TEs)



- Repeats are targeted for silencing, generally by heterochromatin formation
  - Simple sequences: 2 to 20 nucleotides in tandem array; ex. $(AATAT)_n$
  - Transposable elements: retroviruses, DNA transposons, & remnants
  - Genes: rRNA genes, histone genes; foreign insertions
- Foreign repeats and endogenous duplications can both induce robust silencing
- TEs recognized by **piRNA**; organisms differ in exact mechanism.
- Protection of the germline against TE mobilization and tandem repeat instability is critical.

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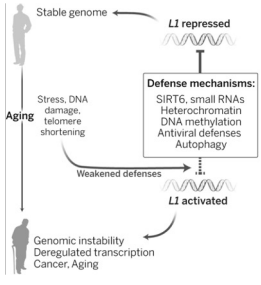
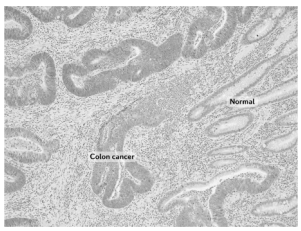
The aging problem: we appear to lose silencing as we get older



Gorbunova V, *et al.* Human Genomics. Sleeping dogs of the genome. Science. 2014 Dec 5;346(6214):1187-8.



Histological section of a colon cancer and adjacent normal epithelium. Brown stain = LINE-1 ORF1p protein; blue = cell nuclei.

Payer LM, Burns KH. Transposable elements in human genetic disease. Nat Rev Genet. 2019 Dec;20(12):760-772.

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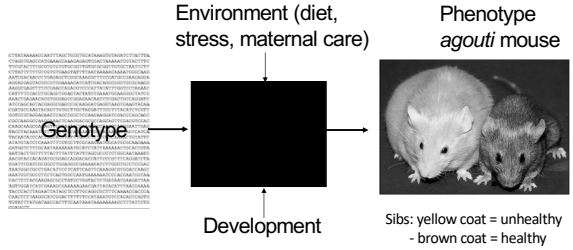
What good can transposons do? **What advantages provided by repeats/TEs have led to their persistence in genome?**



Chromatin packaging;
- essential for differential gene expression
- enables multicellular organisms with distinct cell types from common genome
- enables response to environmental changes

The need to silence TE's (by chromatin packaging) may be a key driver of evolution → chromatin system → eukaryotes

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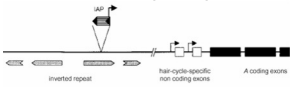
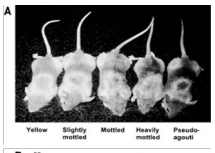
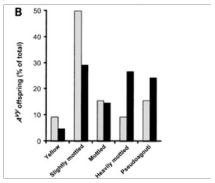
Silencing is critical: impact on the *agouti* locus, where ectopic expression is triggered by a TE







- Mothers fed **BPA** (soaks up methyl) → higher IAP expression (yellow coat)
- Mothers fed **folate** (methyl donor) → lower IAP expression (brown coat)
- Trait stable at least to the following generation (your grandparents diet could affect your epigenetics!);
- **Demonstrates selective silencing**, critical for development as well as environmental responses.

Black bars = folate feeding

Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. Mol Cell Biol. 2003 Aug;23(15):5293-300.

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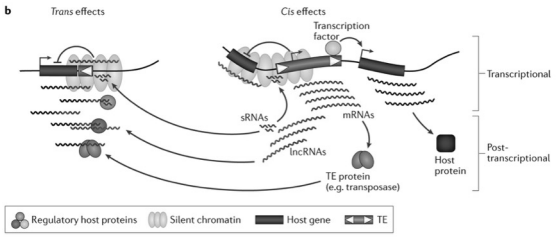
Transposable elements can function as cis- or trans-regulatory elements, creating new networks



- TEs have promoters and enhancers.
- TEs are silenced through epigenetic mechanism.
- **Exaptation:** a process where a genetic element has been co-opted for alternative function than original purpose.

Chuong EB, Elde NC, Feschotte C. Regulatory activities of transposable elements: from conflicts to benefits. Nat Rev Genet. 2017 Feb;18(2):71-86.

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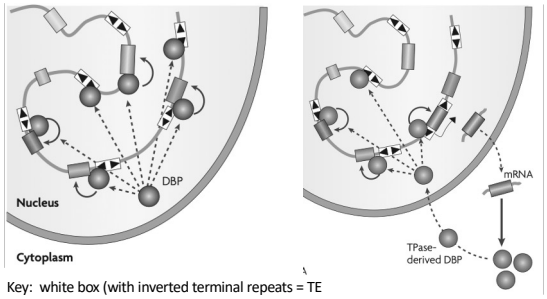
The good that transposons can do: TEs wire genetic regulatory networks & contribute regulatory proteins



Key: white box (with inverted terminal repeats = TE
colored boxes = endogenous genes
red circles = endogenous DNA binding protein; brown circles = TE-derived protein

Feschotte, C. Transposable elements and the evolution of regulatory networks. *Nat. Rev. Genet.* **9**, 397–405 (2008).

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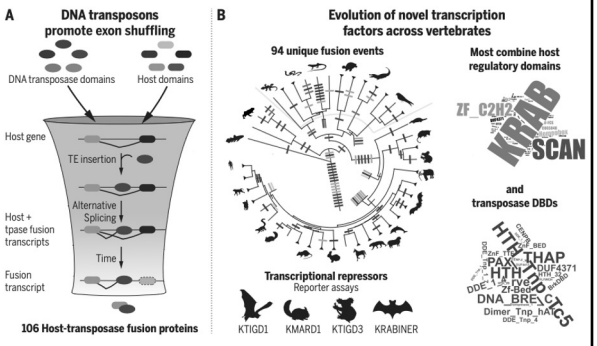
The good that transposons can do: creation of new host-transposon fusion proteins with regulatory impacts



Cosby RL, et al. Recurrent evolution of vertebrate transcription factors by transposase capture (2021) Science 371: 797.

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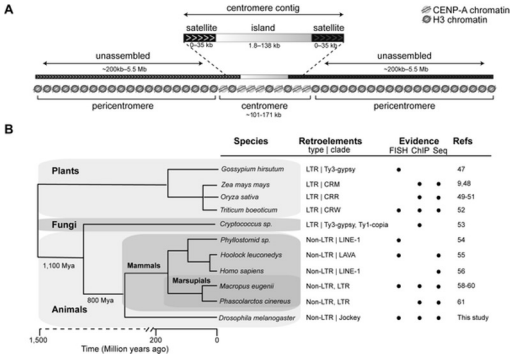
The good that transposons can do: Drosophila centromere organization based on *Jockey*



Chang CH, et al. Islands of retroelements are major components of *Drosophila* centromeres. PLoS Biol. 2019 May 14;17(5):e3000241.

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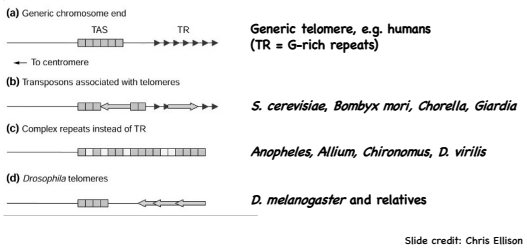
The good that transposons can do: telomeric DNA

Telomeres contain complex repetitive DNA in a variety of species



Slide credit: Chris Ellison

Louis EJ. Are *Drosophila* telomeres an exception or the rule? Genome Biol. 2002 Sep 27;3(10):REVIEWS0007.

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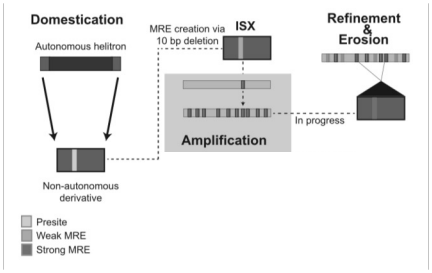
The good that transposons can do:
TEs can evolve to mark specific chromosomes (ex. sex chromosomes)



Drosophila miranda* neo-X chromosome*:
Step 1: Domestication: a mutation in a TE generates ISX, with an MRE X dosage compensation site
Step 2: Amplification: Transposition of ISX creates multiple binding sites along the chromosome arms; sites are selected for on the neo-X and against elsewhere.
Step 3: Refinement: mutations create stronger binding sites on the neo-X, weaker ones elsewhere.

Ellison CE, Bachtrog D. (2013) Dosage compensation via transposable element mediated rewiring of a regulatory network. Science 342: 846-50.

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We live in uneasy balance with our transposable elements

"Coffee Break," by Christoph Niemann

Response – Yin/Yang problem

- Silencing new TEs, maintaining silencing essential for **individual,** but TEs contribute to genome; activity essential for the **species**?
- Adaptation for **species**?
  - Fixing mutations – slow
  - Genome rearrangement, shuffling parts, shifting pattens of gene expression
  - TEs can help!
  - TEs more active when organism stressed
  - Whatever works, survives
  - Results appear more complex than logically necessary

View as of 2022 – SCR Elgin

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Alternative slides

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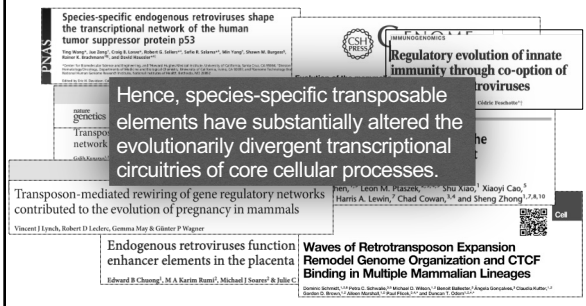
The good that transposons can do:
TEs wire genetic regulatory networks



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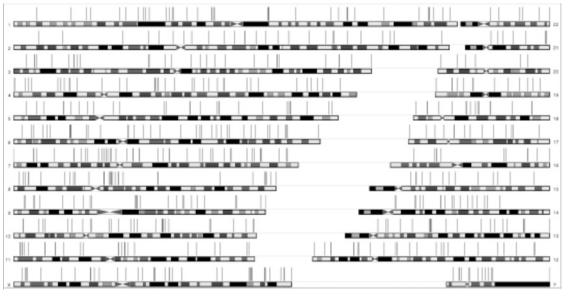
The good that transposons can do:
TEs have contributed significantly to p53 Binding Sites



Red bars = ERV sites that bind p53 (human genome)

Wang et al. 2008 PNAS 104: 18613-18618.

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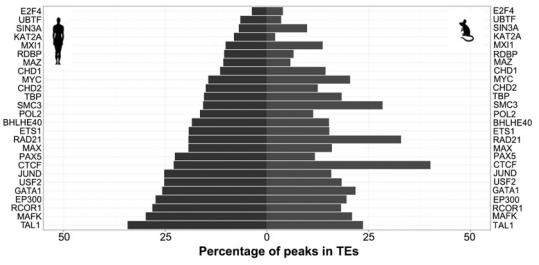
The good that transposons can do:
TEs have contributed significantly to TF Binding Sites in human and mouse genomes



Xie, Nat Genetics 2013
Sundaram, Genome Res 2014
Sundaram…Wang, Nat Comm 2017

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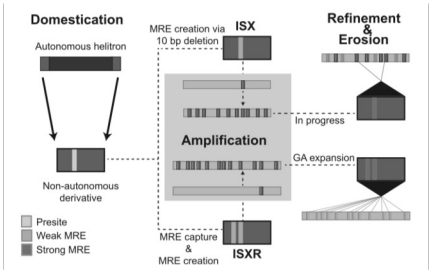
The good that transposons can do:
TEs can evolve to mark specific chromosomes (ex. sex chromosomes)



Drosophila miranda neo-X chromosome: *Step 1:* mutation of a domesticated TE generates ISX, with a binding site for the critical dosage compensation complex MSL. (Earlier mutations created ISXR on the ancestral X.) *Step 2*: Transposition of the mutated form creates multiple binding sites along the chromosome arms; these are selected for on the neo-X and against elsewhere. *Step 3*: Refinement can create stronger binding sites on the neo-X, driving it to full sex chromosome status.

Ellison CE, Bachtrog D. Dosage compensation via transposable element mediated rewiring of a regulatory network. Science. 2013 Nov 15;342(6160):846-50.

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