THE OHIO STATE UNIVERSITY

Regulation of transposable element transposition at the final layer

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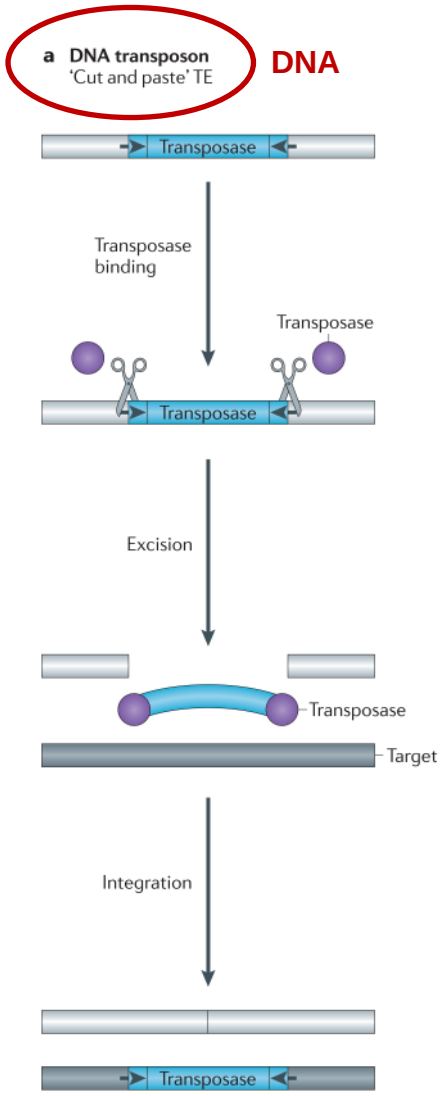
Transposable element (TE)

"Cut-Paste"



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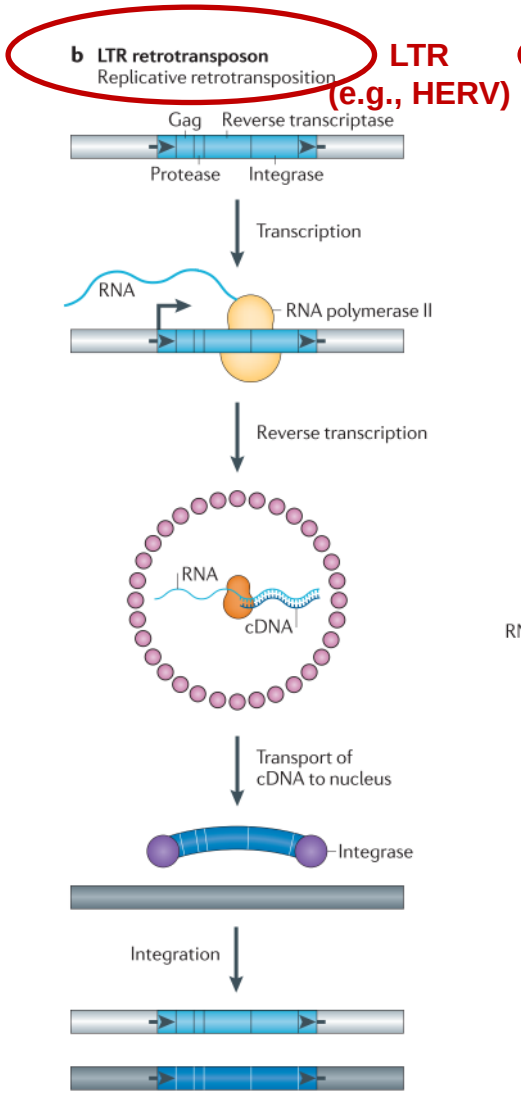

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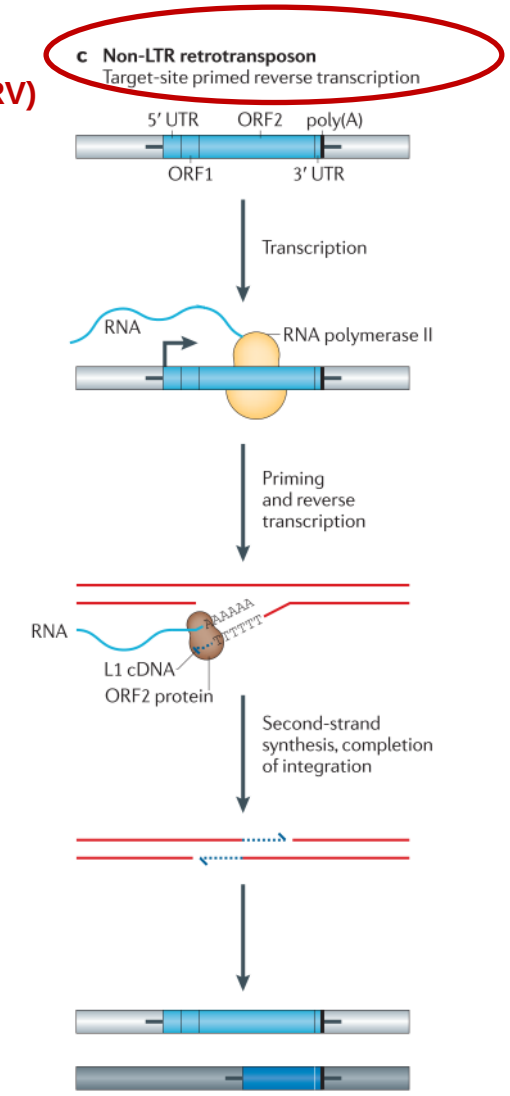
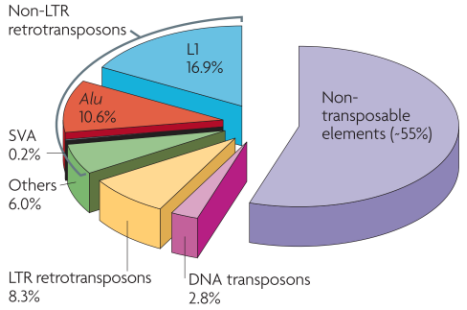


- **~45% of human genome**



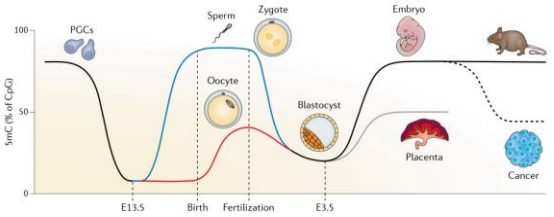
- **Active TEs**

L1 **~6 kb; >50,000 copies**

Alu **~300 bp; >1 million copies**

SVA **~2 kb; ~3,000 copies**

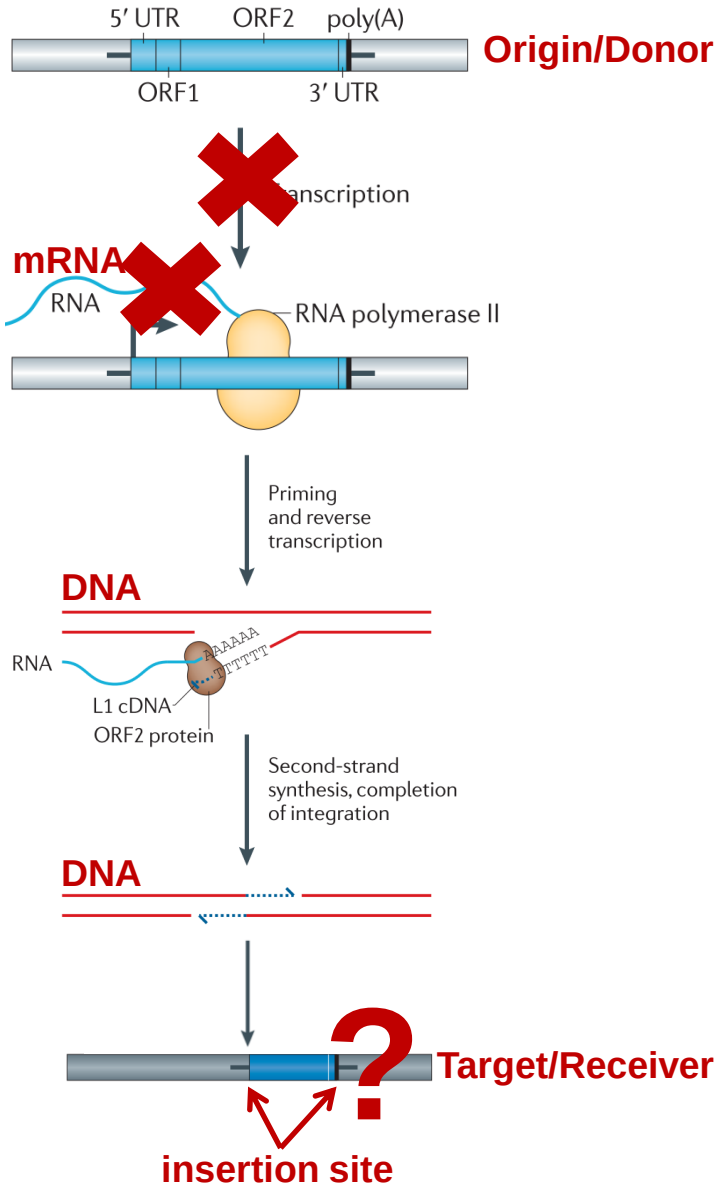
- **Transposition/mobilization**



Cordaux, et al. *Nat Rev Genet* (2009); Levin et al. *Nat Rev Genet* (2011); Deniz, et al. *Nat Rev Genet* (2019)

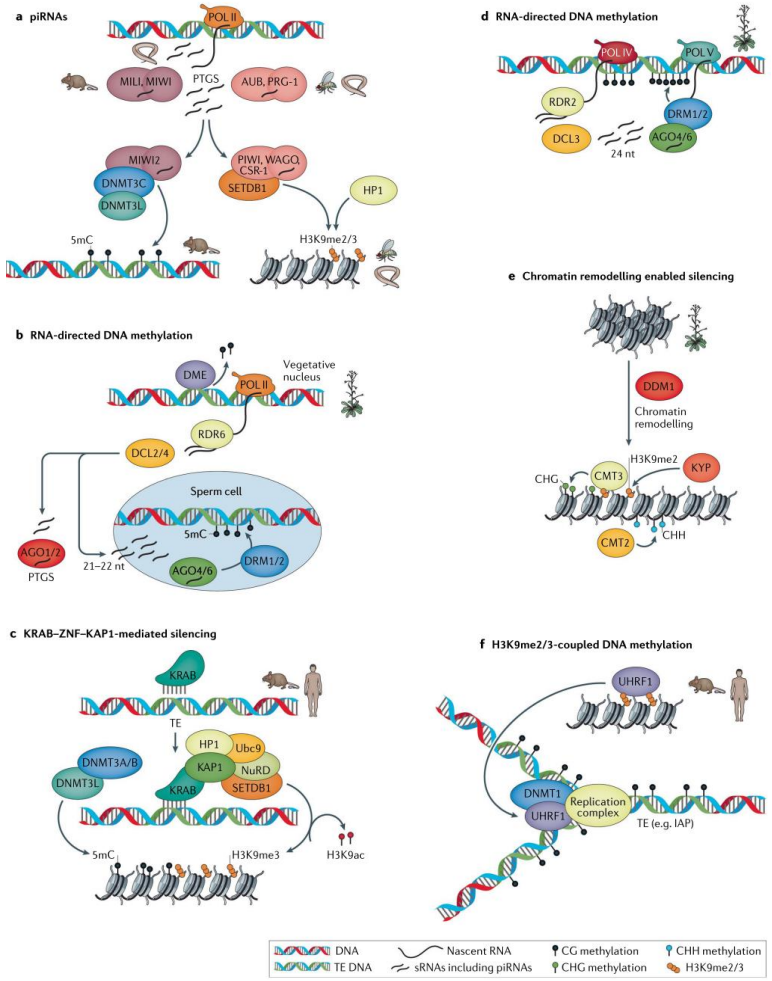
Regulation of TE activity at different layers

➢ L1 transposition process



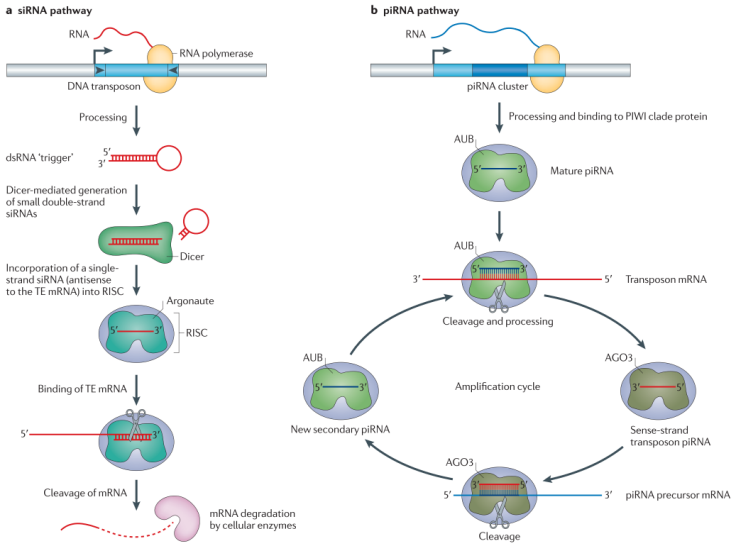
➢ First-layer defense: Transcription repression

- DNA methylation
- Histone modification
- Transcription factor



➢ Second-layer defense: mRNA degradation

- Small interfering RNA
- miRNA
- piRNA



➢ Final-layer defense: Receiver (target genomic region)

- Sequence feature
- Epigenetic status
- …

Levin et al. *Nat Rev Genet* (2011); Deniz, et al. *Nat Rev Genet* (2019)

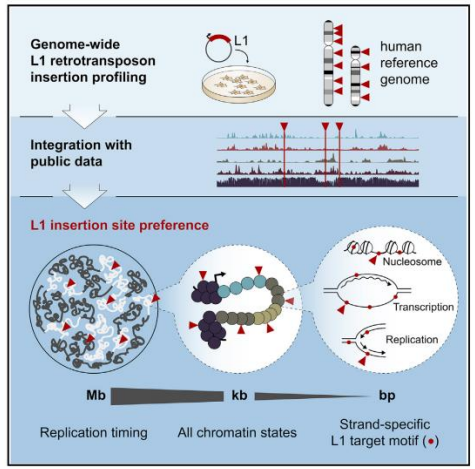
Regulation of L1 transposition at the final layer: insights from *in vitro* studies

Molecular Cell

The Landscape of L1 Retrotransposons in the Human Genome Is Shaped by Pre-insertion Sequence Biases and Post-insertion Selection

- Ion Torrent ~400 bp
- WGS
- HeLa cell line
- 1565 insertions

Graphical Abstract



Authors

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In Brief

Sultana, van Essen, et al. report the genome-wide profiling of new L1 retrotransposon insertions in cultured cells. They uncover the contribution of sequence and genomic contexts on integration site selection, its link with host DNA replication, and the role of post-integration selection in the genomic distribution of L1 elements.

Tania Sultana,[1,6,7] Dominic van Essen,[1,7] Oliver Siol,[2] Marc Bailly-Bechet,[3] Claude Philippe,[1] Amal Zine El Aabidine,[4] Léo Pioger,[4] Pilvi Nigumann,[1] Simona Saccani,[1] Jean-Christophe Andrau,[4] Nicolas Gilbert,[2,5] and Gael Cristofari[1,8,*]

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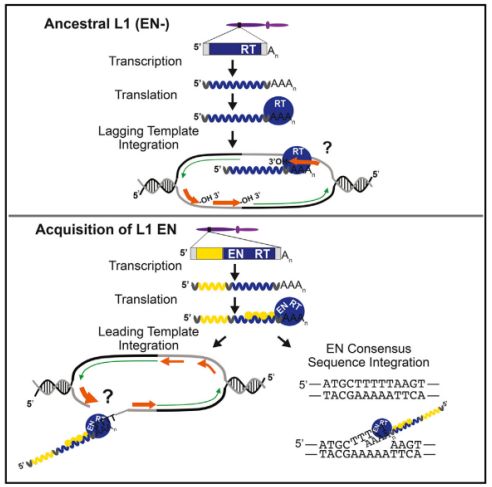
Cell

Genome-wide *de novo* L1 Retrotransposition Connects Endonuclease Activity with Replication

- PacBio
- 300-1200 bp
- Target
- 4 human cell lines
- >88,000 insertions

Graphical Abstract



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In Brief

The examination of *de novo* engineered L1 retrotransposition events in cultured human cells reveals that L1 endonuclease activity and DNA replication dictate L1 insertion preferences and promote its widespread integration throughout the human genome.

Diane A. Flasch,[1,*] Ángela Macia,[2] Laura Sánchez,[2] Mats Ljungman,[3,4] Sara R. Heras,[2] José L. García-Pérez,[2,5] Thomas E. Wilson,[1,6,*] and John V. Moran[1,7,8,*]

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Genomic/epigenomic feature of L1 insertion sites

Sample	HeLa	PA-1	NPC	hESC
# Independent Samples	7	12	9	10
PacBio CCS Read Counts	280,780	284,764	205,376	232,039
Unique L1 Insertions	**21,497**	**27,777**	**12,117**	**3,582**

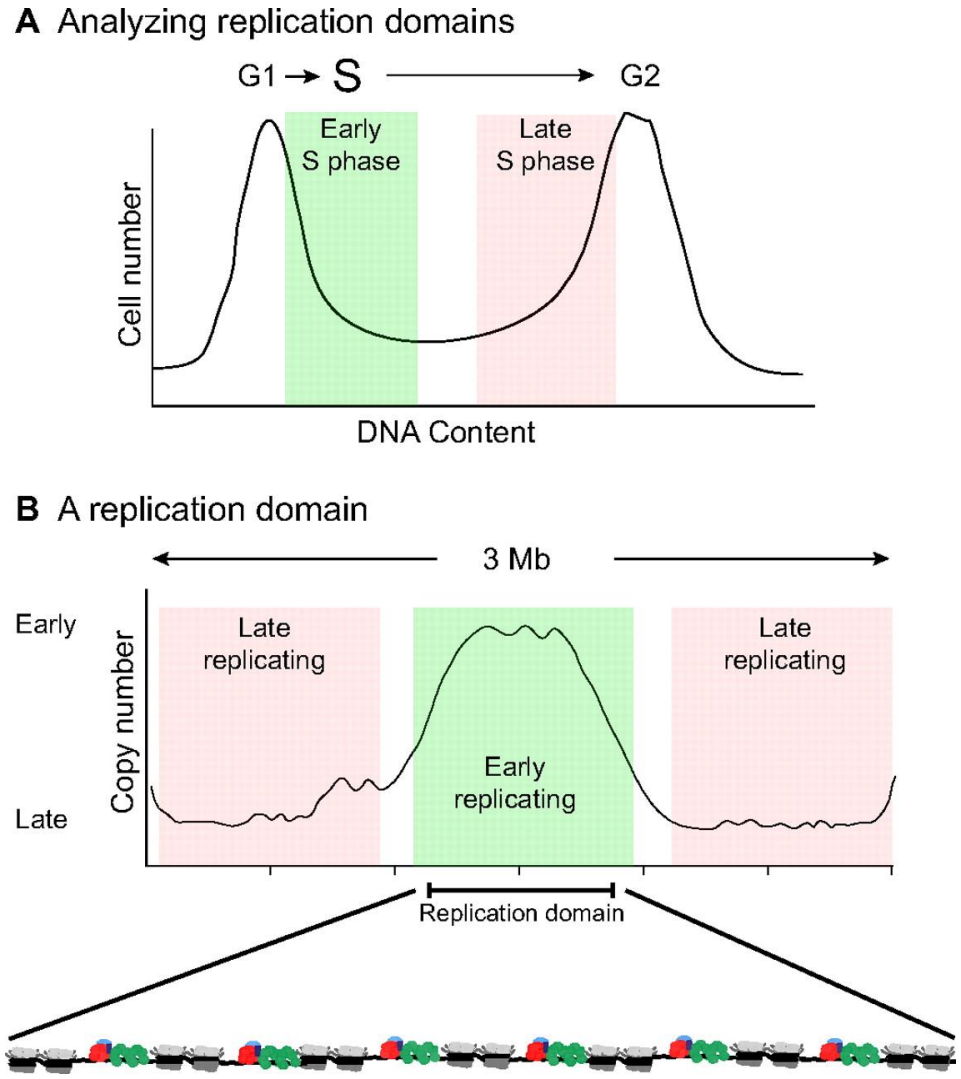
- HeLa: epithelial, adenocarcinoma
- PA-1: epithelial, teratocarcinoma
- hESC: H9 cell line
- NPC: H9-derived neural progenitor cells

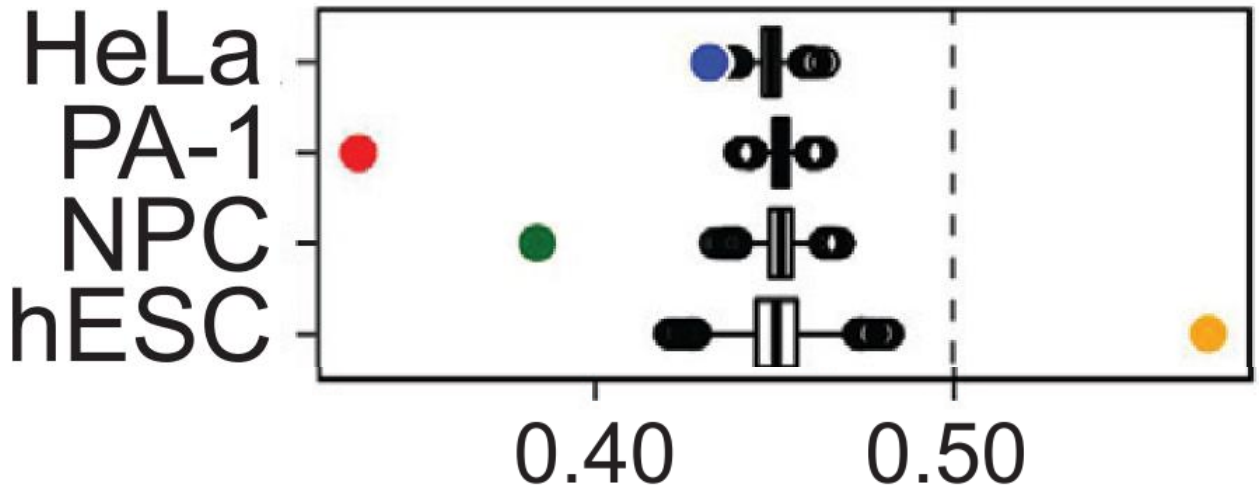
- **Sequence**

- **Homogeneous throughout the genome**
  - **Genic**
  - **Intergenic**
  - **Functional elements (enhancer, promoter)**
- **No/weak association with**
  - **Gene transcription**
  - **Histone modifications**
  - **Chromatin accessibility**

L1 insertion vs Replication timing: early (hESC) or late (PA-1) S phase of cell cycle

DNA replication





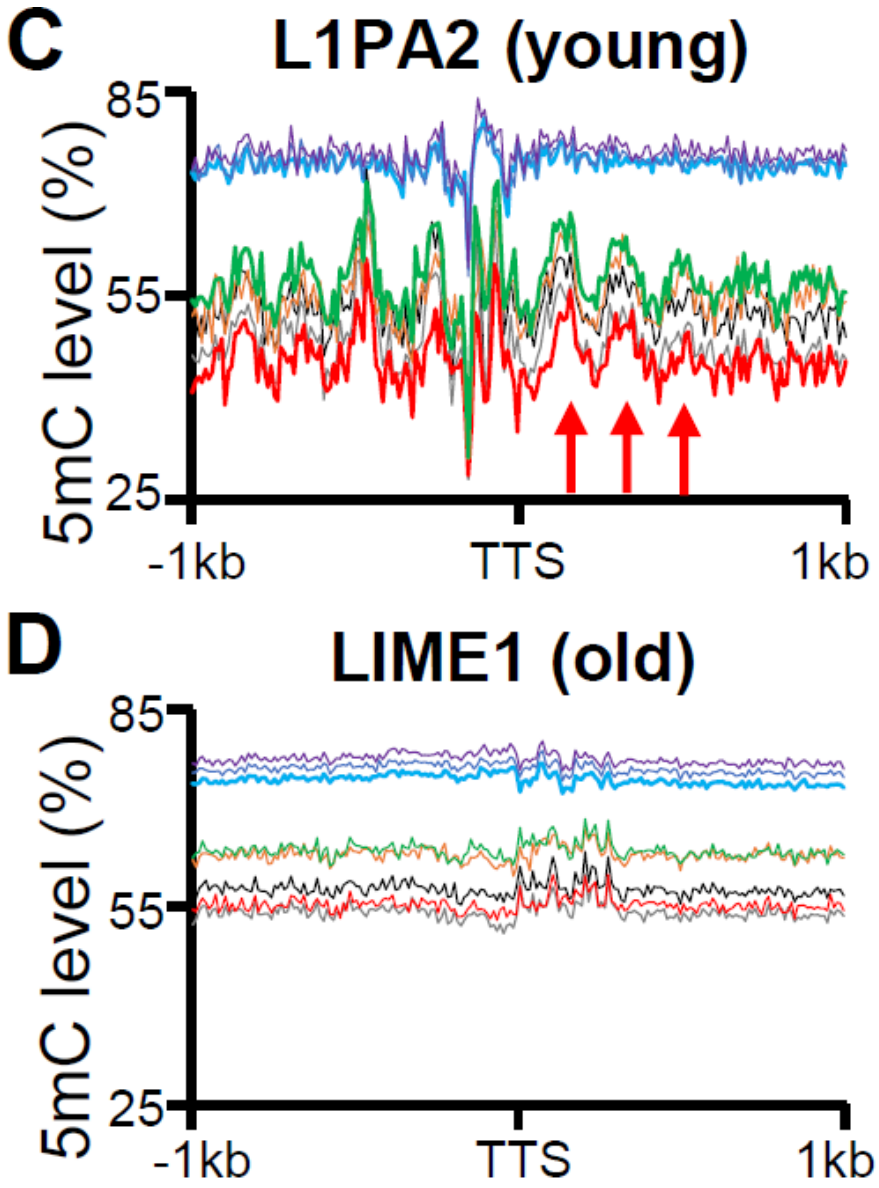
Fraction of L1 insertions at the early replication region

Differential DNA methylation pattern between cell types?

hESC
DE
AFG
HG00514
GM12878
MCF-10A
MCF-7
MDA-MB-231

- hESC: human embryo stem cell
- DE: definitive endoderm
- AFG: anterior foregut

- HG00514/GM12878: lymphocyte
- MCF-10A: epithelial, breast tissue
- MCF-7/MDA-MB-231: breast cancer

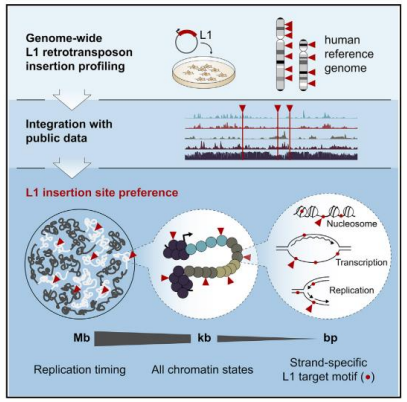


Limits and Directions

Molecular Cell

The Landscape of L1 Retrotransposons in the Human Genome Is Shaped by Pre-insertion Sequence Biases and Post-insertion Selection

Graphical Abstract



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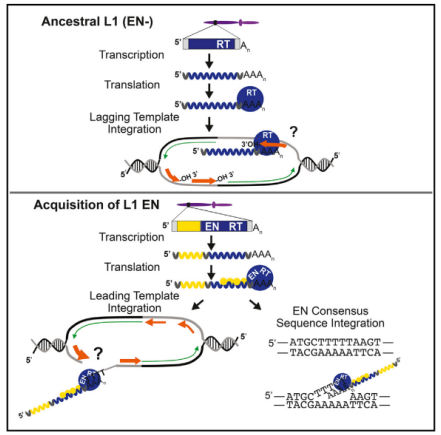

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- Blind to the full-length of L1 insertions
  - 3'end PacBio target sequencing (Cell)
  - Short-read sequencing (Mol Cell)
- No matched data for epigenetics data
  - Before and after L1 insertion
- No DNA methylation or nucleosome positioning analyses
- Association

- Full-length insight of L1 insertion
  - MeSMLR-seq
- Matched data for epigenetic markers
  - DNA methylation
  - Chromatin accessibility
  - Nucleosome positioning

MeSMLR-seq + Others

- **TE/L1 insertion**
- **DNA replication**
- **DNA methylation**
- **Nucleosome positioning**

Thanks