

Onco-Exaptation: Endogenous Retroviral LTRs as promoters for novel oncogenic transcripts

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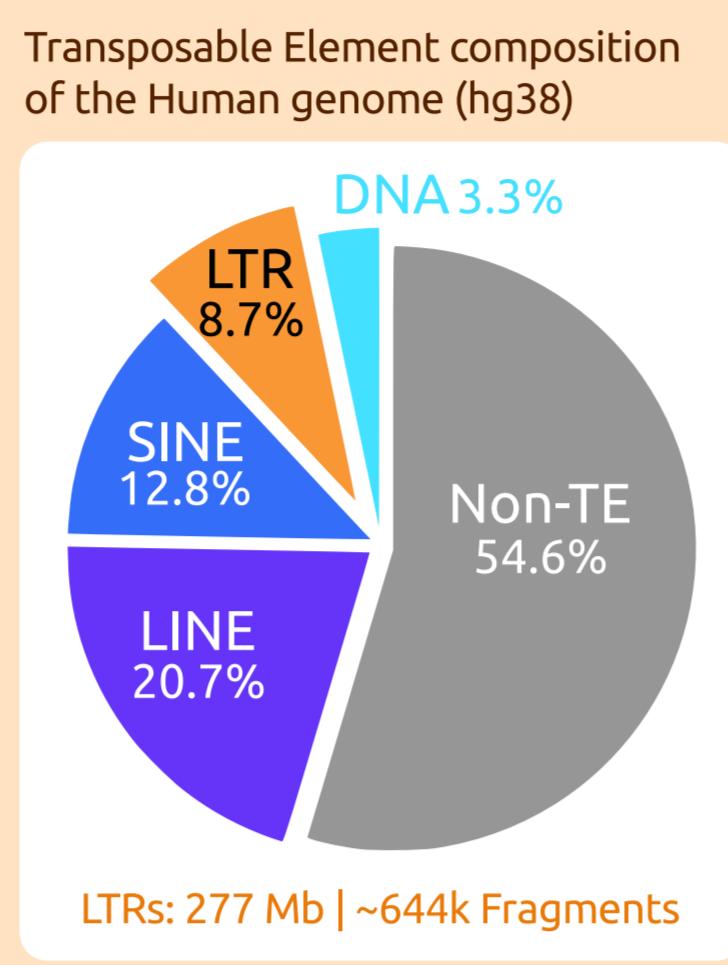
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Introduction

Exaptation is the incorporation of transposable elements (TEs) into functional, and in some cases necessary, genes or regulatory units over evolutionary time. We postulate that an analogous process occurs during oncogenesis, "onco-exaptation", where TE-derived promoters generate "noisy" transcription and novel transcripts, which can be exploited and selected for to drive cancer transcriptome evolution.



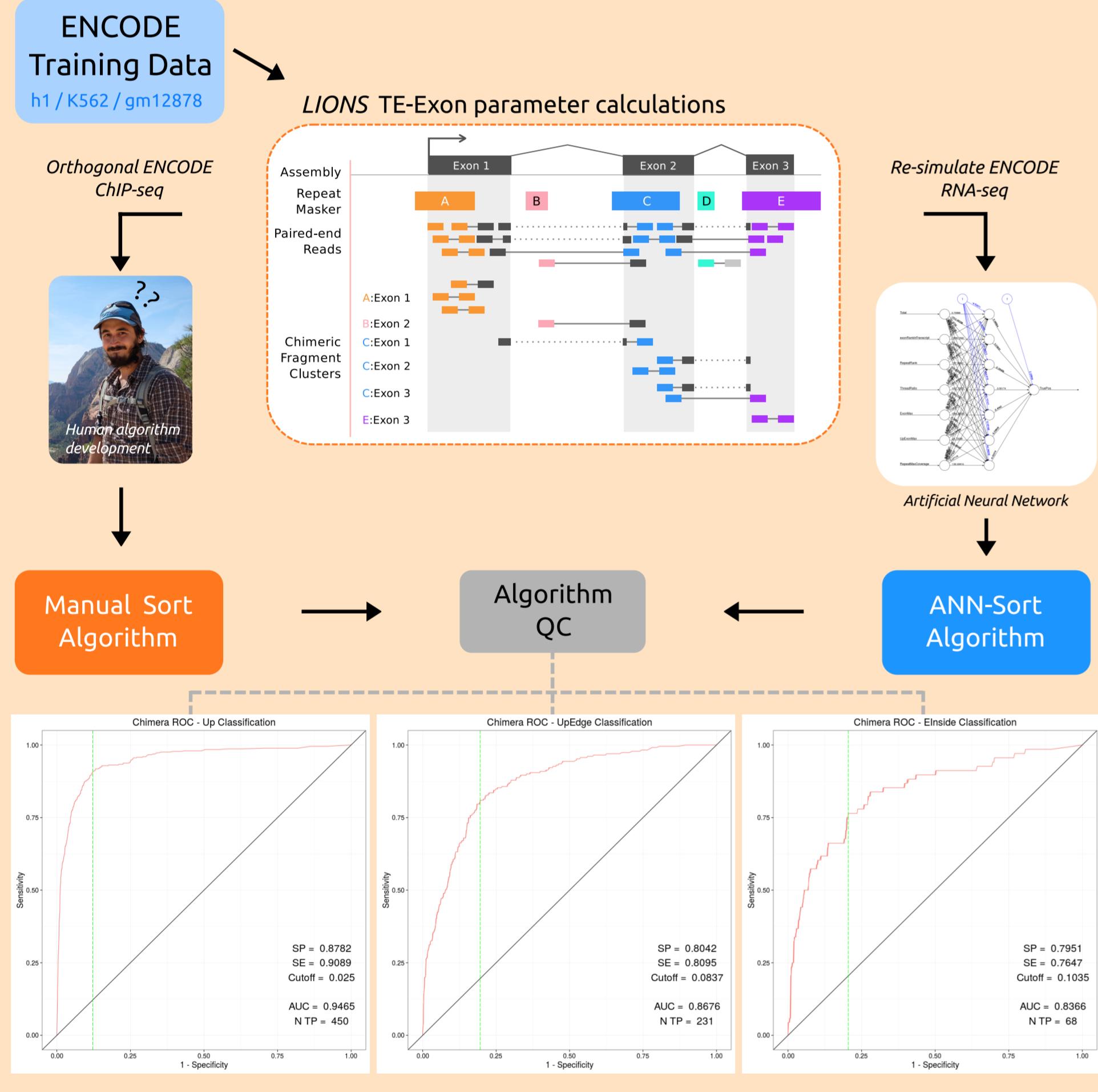
Hypothesis

(Epi)Genomic dysregulation in cancer permits transcription from TEs

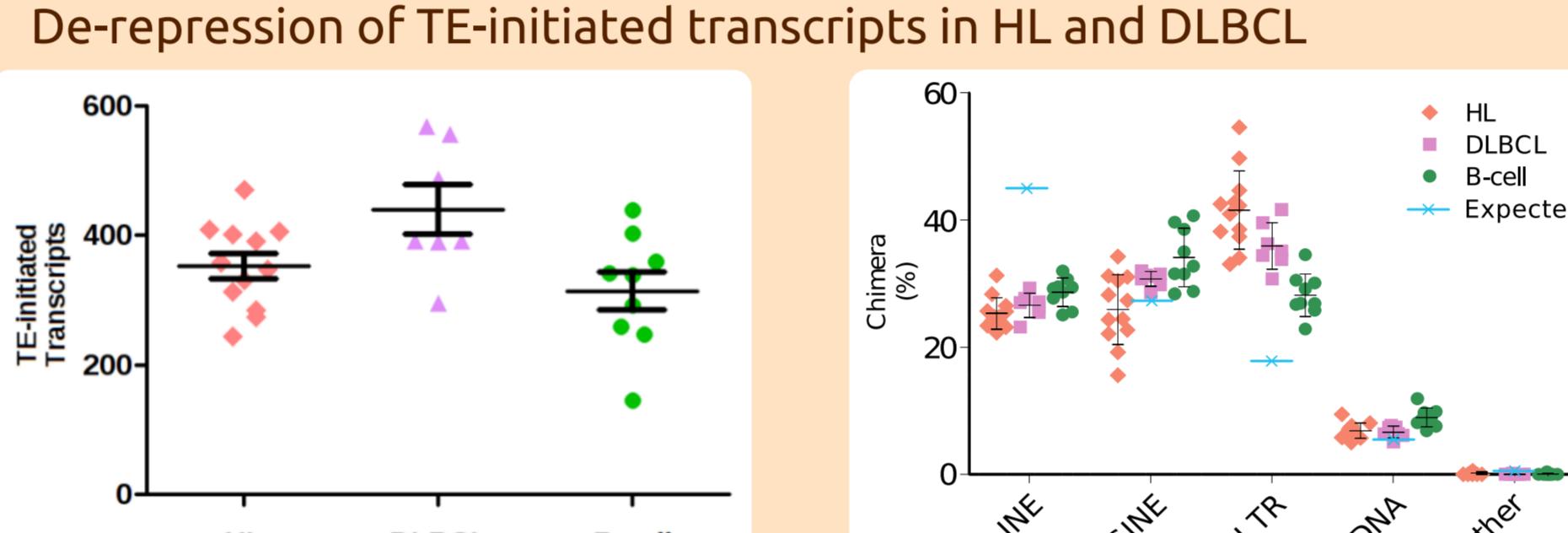
Corollary: TE initiated transcription accelerates tumorigenesis

Results

Developing a reliable detection method for TE-initiated transcription

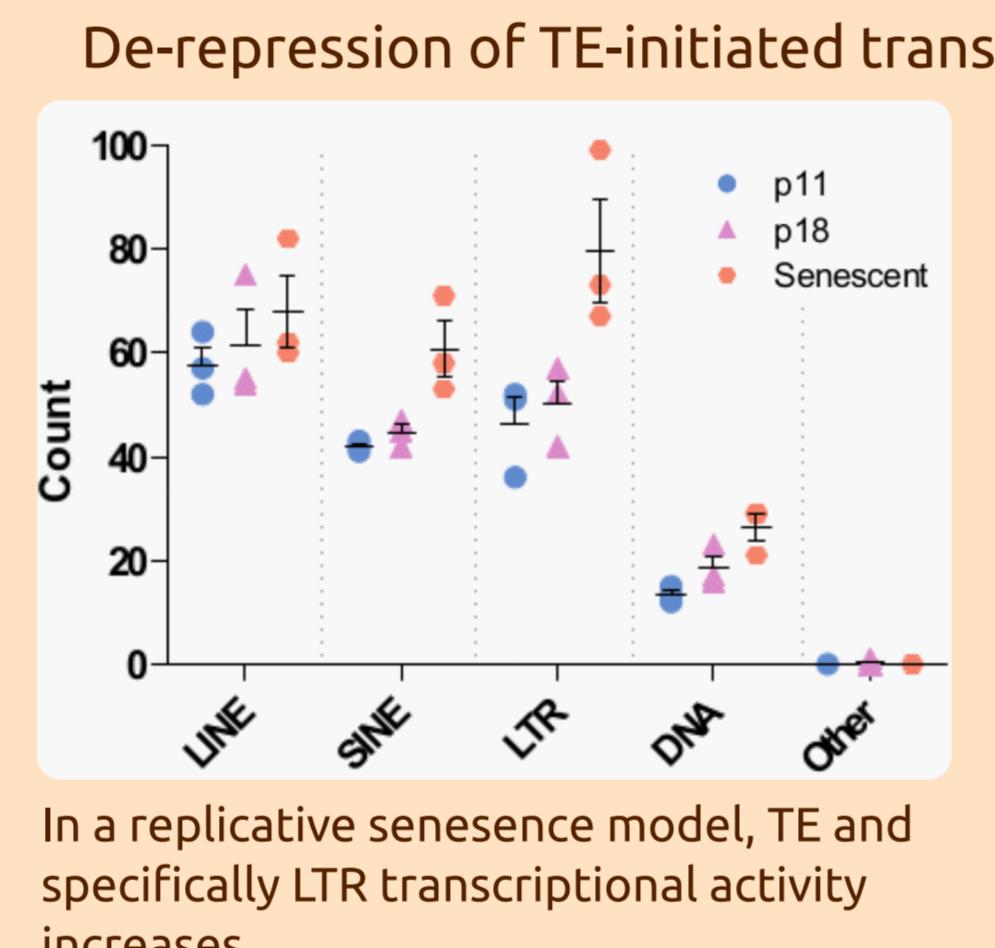


Does TE-transcription increase in cancer?



Overall, there is a modest de-repression of TE-initiated transcripts in Hodgkin Lymphoma and Diffuse Large B-cell Lymphoma relative to B-cell controls.

What's the mechanism?



In a replicative senescence model, TE and specifically LTR transcriptional activity increases.

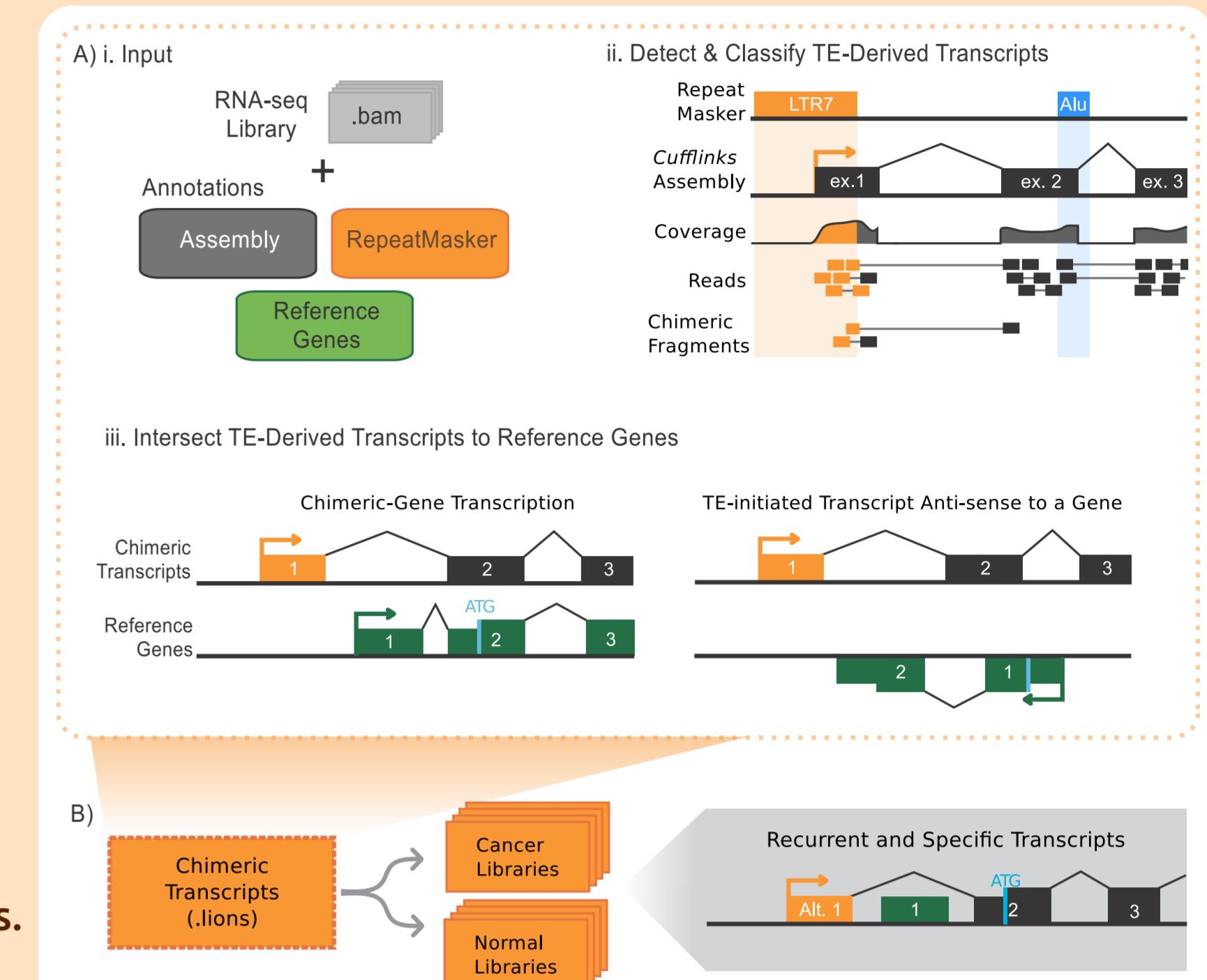
Methods

To reliably detect TE-initiated transcripts from RNA-seq data alone, we developed the LIONS suite.

Briefly, a RNA-seq library is aligned and transcripts *de novo* assembled with *Tophat2* suite. LIONS then locally analyzes 'Chimeric Fragments' (reads pairs mapping to a TE and exon) and classifies TE-initiated events using a manual algorithm and an artificial neural network classifier.

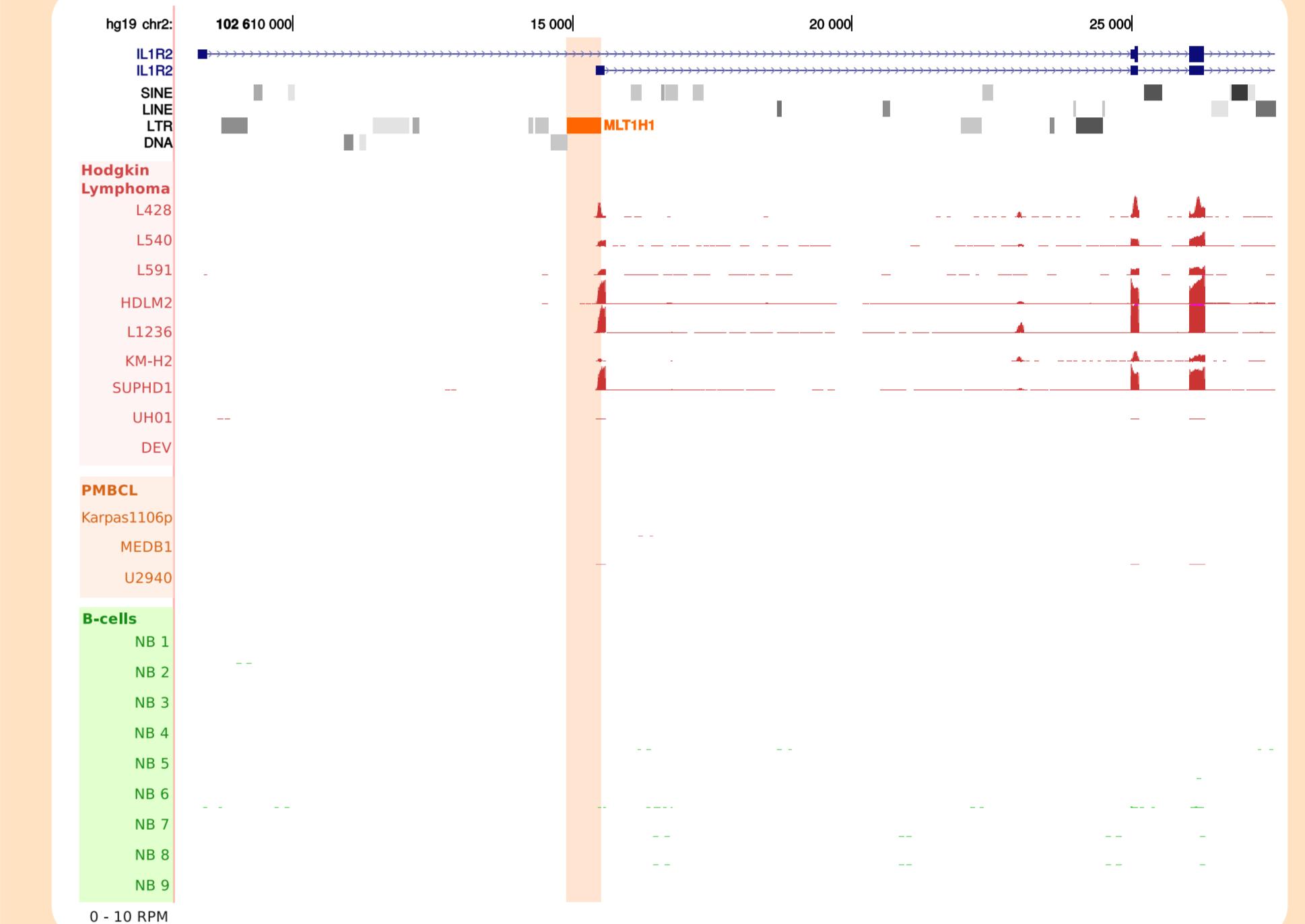
So called TE-chimeric transcripts are then quantified in each library and are further filtered to identify recurrent and cancer-specific transcripts.

LIONS pipeline



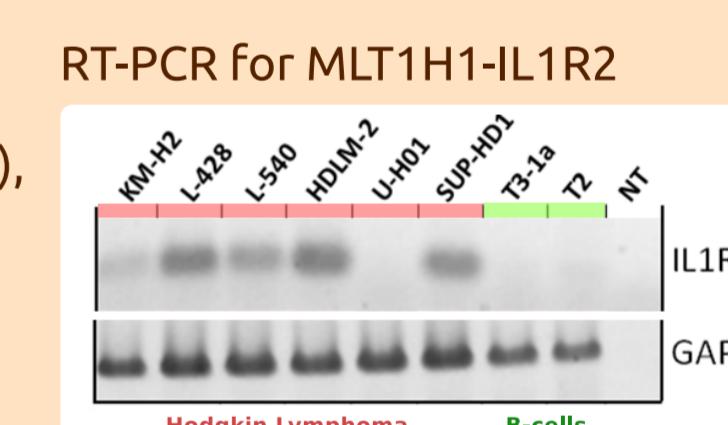
What consequences does this have?

MLT1H1-IL1R2 is a Hodgkin-specific and recurrent chimeric transcript



In 7/9 independent Hodgkin cell lines an MLT1H1 LTR element initiates cancer-specific transcription of Interleukin-1 Receptor 2 (IL1R2), one of the most differentially expressed genes in HL.

This mirrors the pattern seen for LTR driven transcription of other oncogenes in Hodgkins, THE1B-CSF1R⁺ and LOR1a-IRF5.^[2]



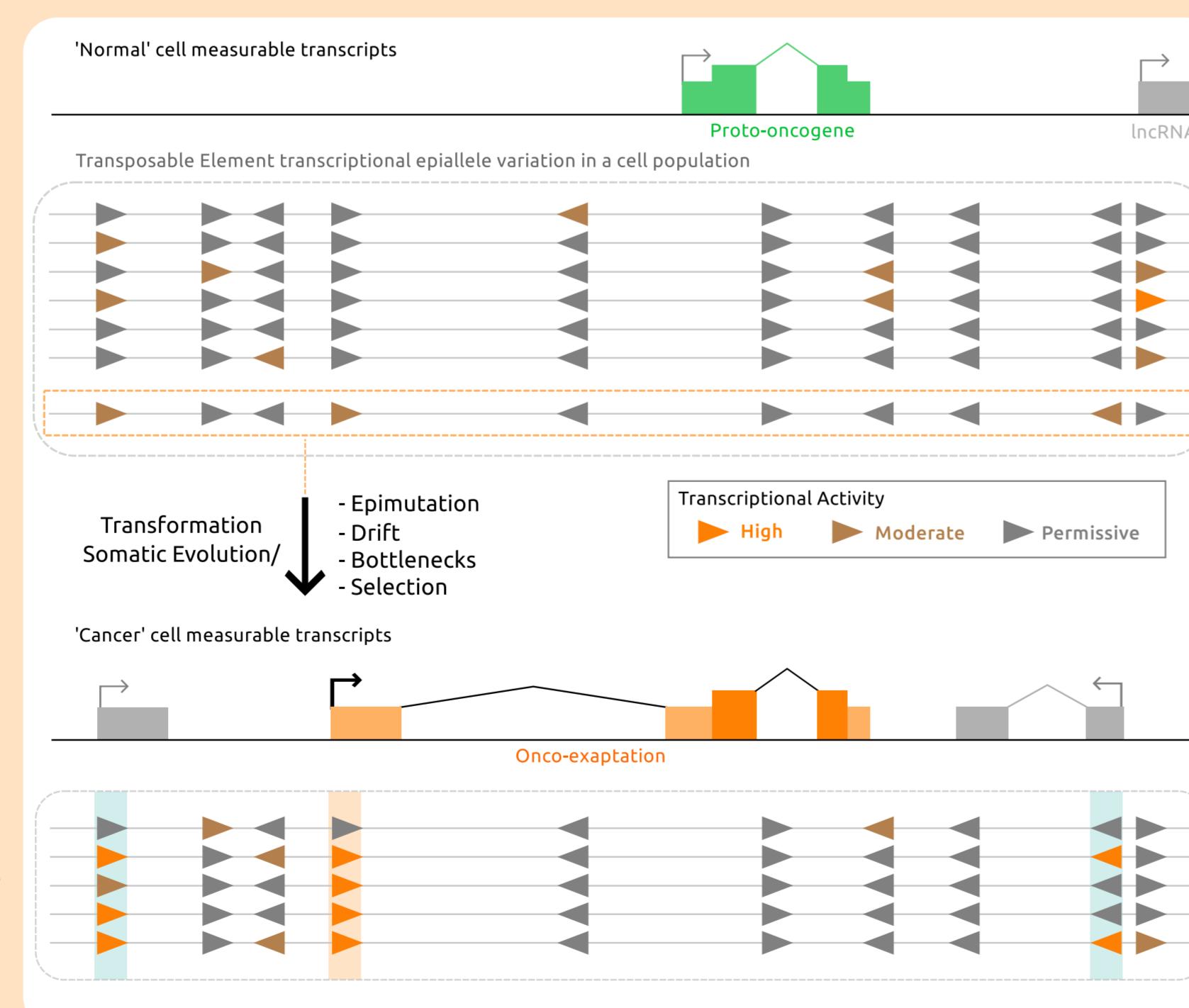
Discussion

Transposable elements are increasingly being recognized as potent catalysts for genome evolution.

We postulate that in cancer TE-initiated transcription (especially LTRs) generate a plethora of novel transcription. Then, such epigenetic variation can be selected for during cancer evolution. Thus, highly recurrent and cancer-specific transcripts may suggest that a locus is an onco-exaptation.

There are increasing reports of onco-exaptations in the literature both for protein coding genes and non-coding RNA.

An epigenetic evolution model for Onco-exaptation



Gene	Gene Function	TE-Type	Cancer	Reference (PMID)
c-MET	Tyrosine kinase receptor	(L1) L1PA2	CML	20562909
CSF1R	Tyrosine kinase receptor	(ERVL-MaLR) THE1B	Hodgkin Lymphoma	20436485
IRF5	Transcription factor	(ERV1) LOR1a	Hodgkin Lymphoma	26279299
FABP7	Fatty acid binding	(ERV1) LTR2	DLBCL	25114248
ALK	Tyrosine kinase receptor	(ERVL) LTR16B2	melanoma	26444240
SLCO1B3	Anion transporter	(ERV1) LTR7	colon, others	22326869 25611302
ERR4B	Tyrosine kinase receptor	(ERVL-MaLR) MLT1C (ERVL-MaLR) MLT1H2	ALCL	26463425

Significance

Onco-exaptation is a distinct mechanism of oncogene activation. Understanding its etiology may ultimately provide novel therapeutic avenues for treating cancer patients.

Conclusions

TE-derived transcription is a distinct mechanism of oncogene activation and can result in novel oncogenic transcripts

Endogenous Retroviral LTRs are specifically de-repressed in the HL/DLBCL and the senescent cell transcriptome

Cancer-specific and recurrently active TEs may be a marker for screening oncogenic transcripts

Acknowledgements



Further Readings

- 1. Lampricht, B. et al. Derepression of an endogenous long terminal repeat activates the CSF1R proto-oncogene in human lymphoma. *Nat. Med.* 16, 571–579, 1p following 579 (2010).
- 2. Babaian, A. et al. Onco-exaptation of an endogenous retroviral LTR drives IRF5 expression in Hodgkin lymphoma. *Oncogene* 35, 2542–2546 (2016).
- 3. Lock, F. E. et al. Distinct isoform of FABP7 revealed by screening for retroelement-activated genes in diffuse large B-cell lymphoma. *Proc. Natl. Acad. Sci. U.S.A.* 111, E3534–E3543 (2014).