

# Onco-exaptation of Endogenous Retroviral LTRs in Cancer Evolution

Artem Babaian

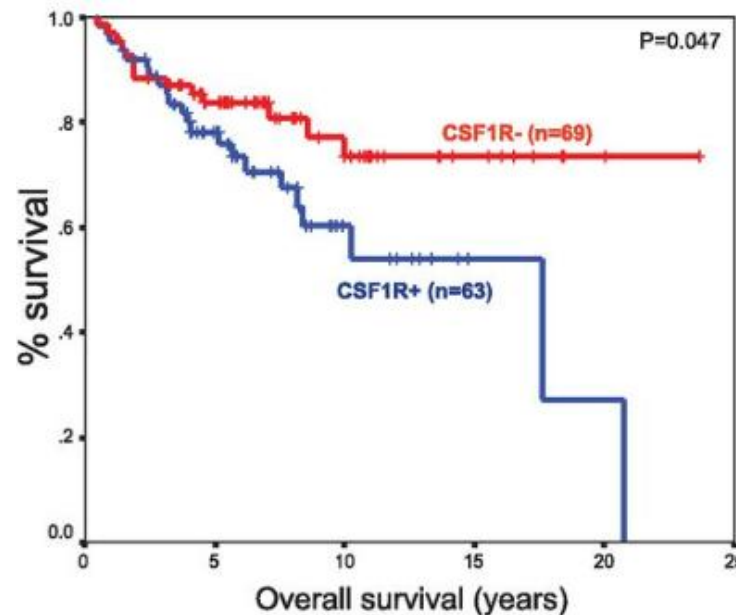
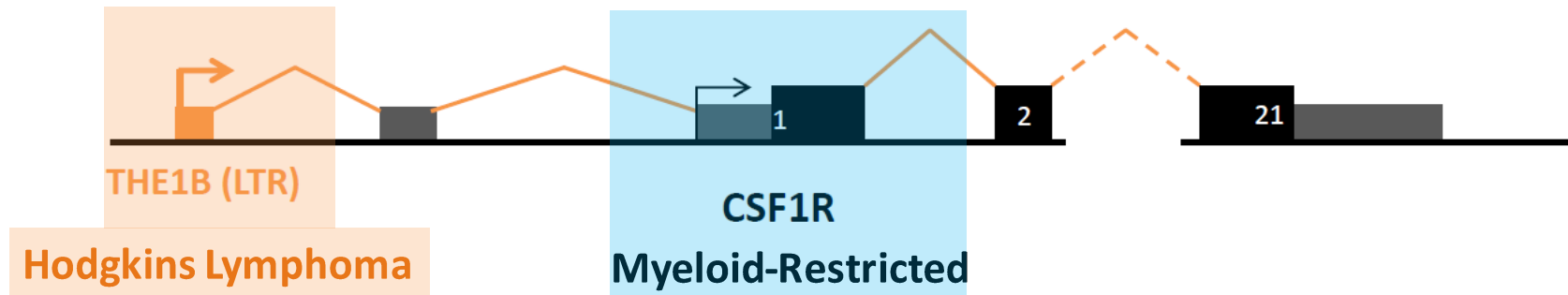


Derepression of an endogenous **long terminal repeat** activates the **CSF1R** proto-oncogene in human lymphoma.

Lamprecht B, *et al.*

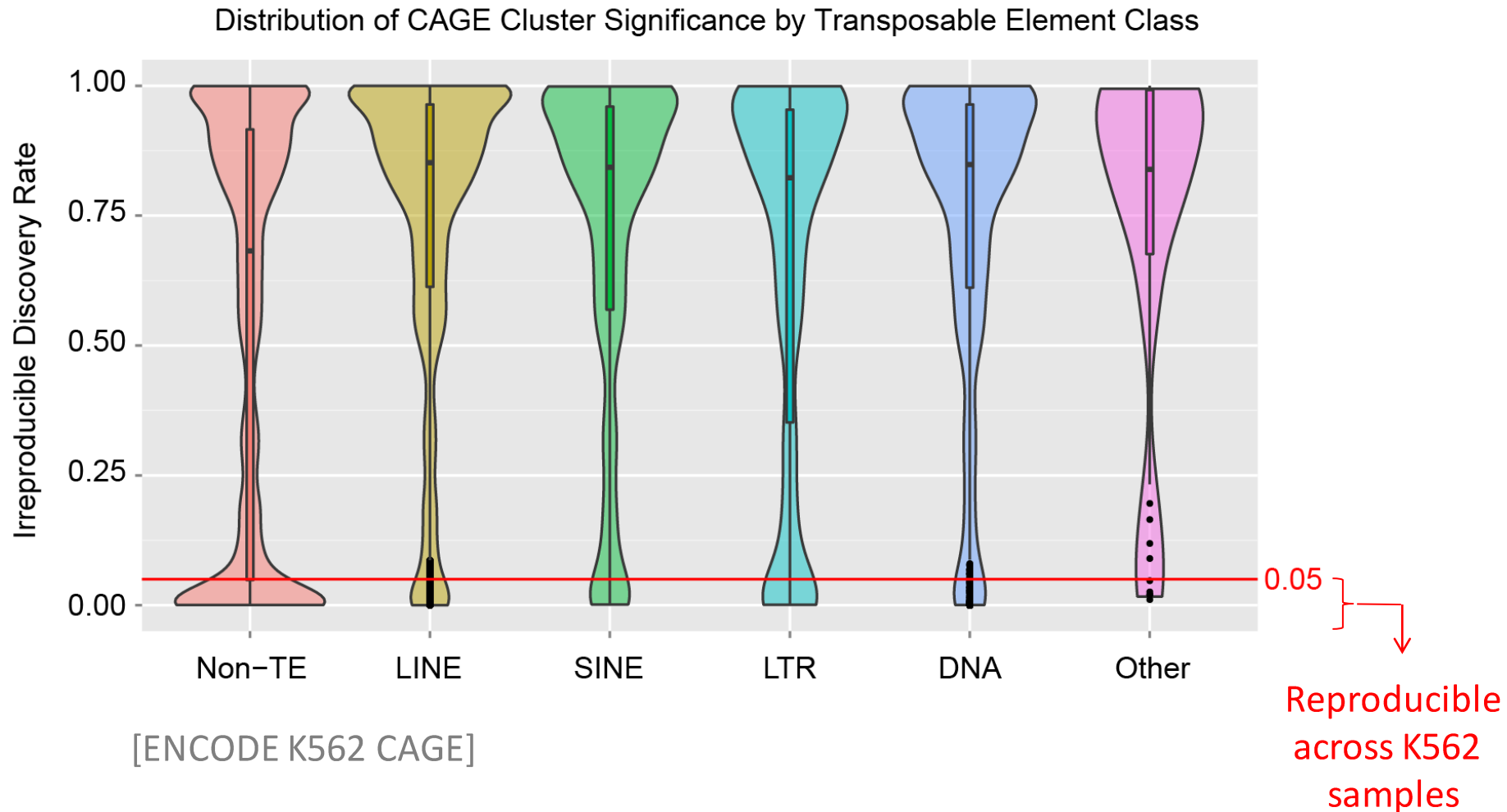
Nat Med. 2010 May;16(5):571-9, 1p following 579. doi: 10.1038/nm.2129. Epub 2010 May 2.

PMID: 20436485 [PubMed - indexed for MEDLINE]



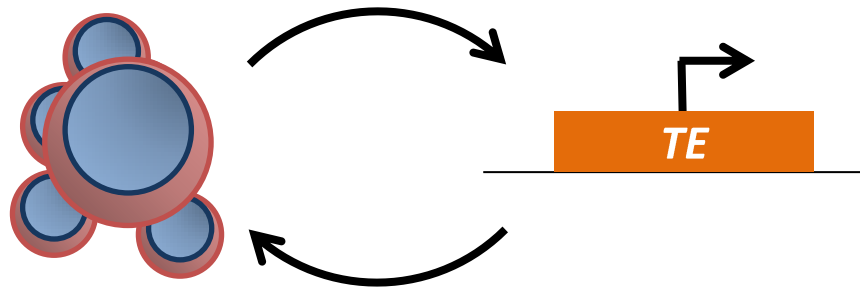
(Steidl et al., 2012)

# TEs initiate a lot of transcription



# Hypothesis

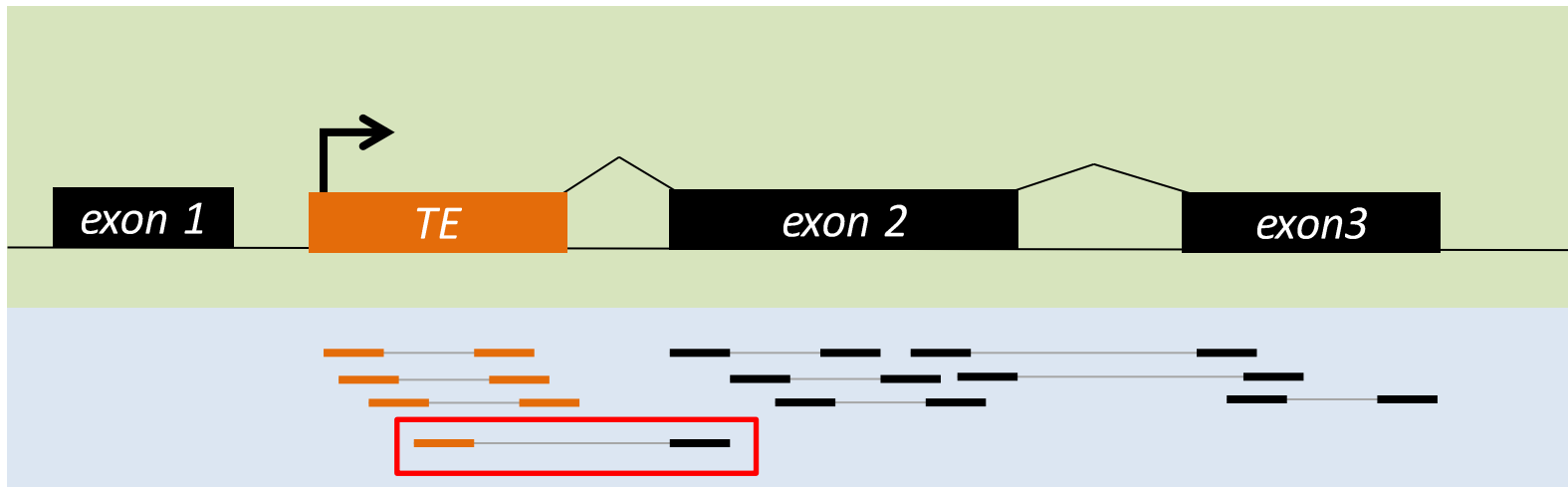
(Epi)Genomic dysregulation in cancer permits transcription of transposable elements



Corollary: TE transcription will accelerate tumourgenesis

# Screening for Chimeric Transcripts

## Transposable Element (TE) – Gene Chimera



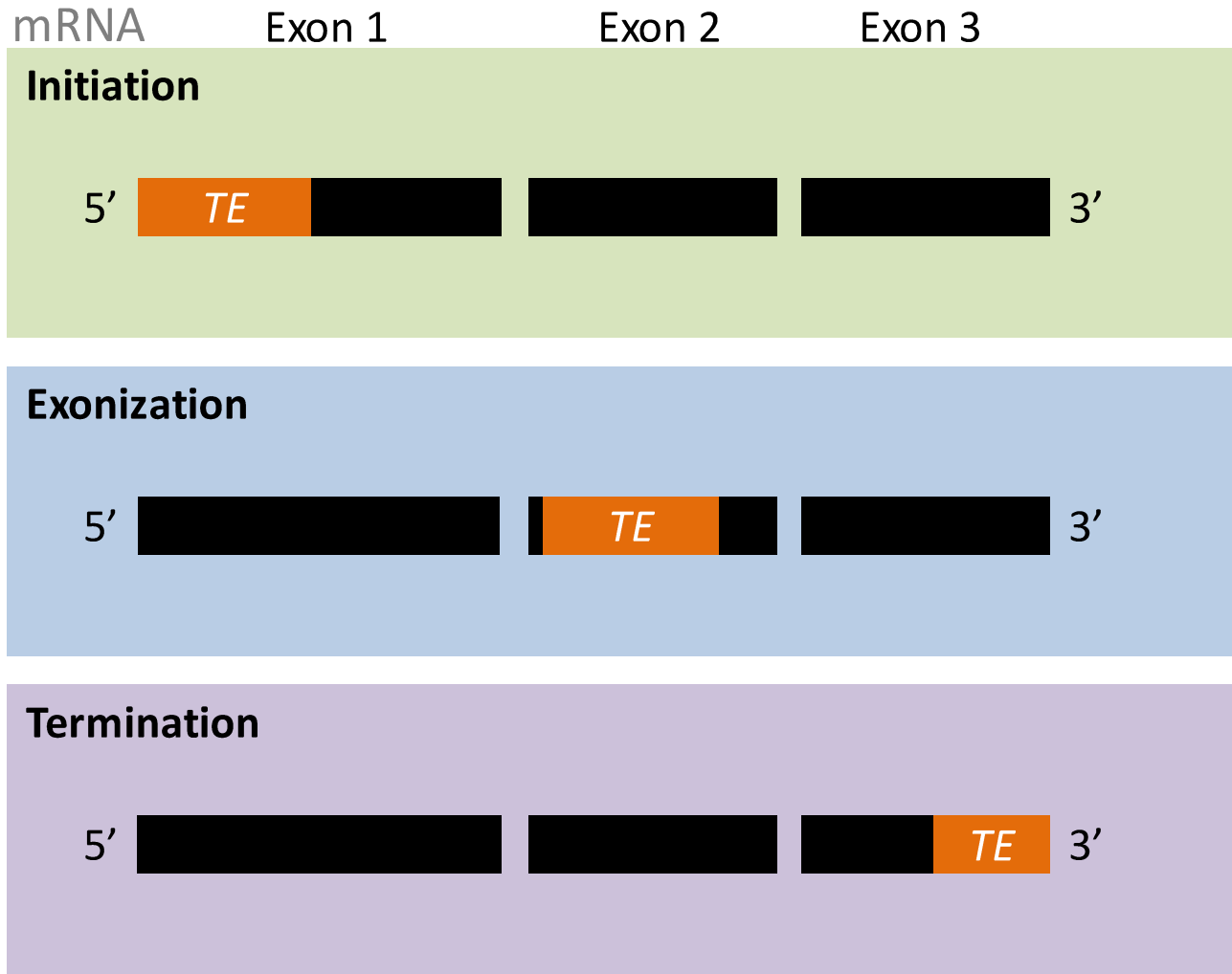
- Identify **Chimeric Fragments**



- Count Chimeric Fragments

	<i>Can</i>	<i>Norm</i>
<i>CSF1R</i>	8	0
<i>IL2RB</i>	0	0
<i>GTF3A</i>	3	2
...		

# Classification of Chimeric Reads



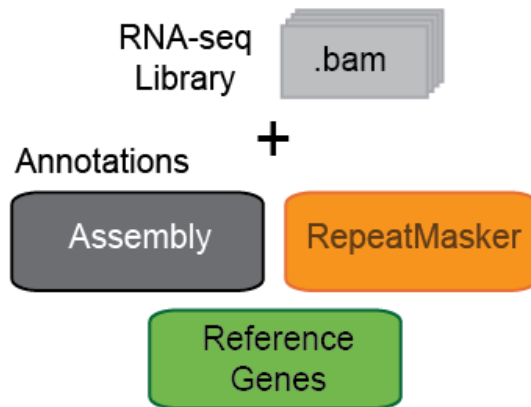
Also yields  
chimeric  
fragments

# LIONS

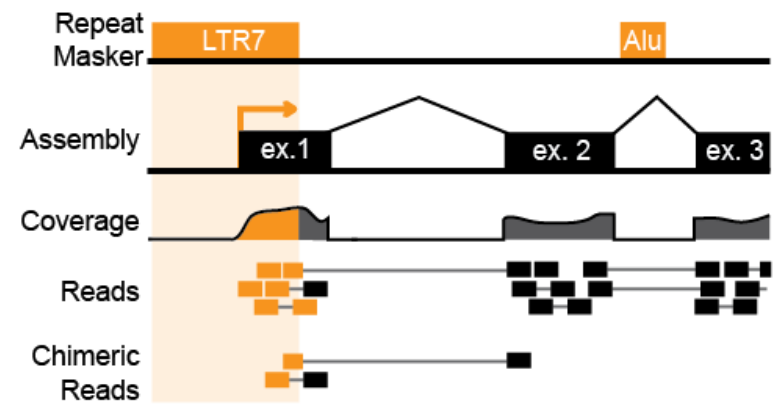
The 'Lions'



i. Input



ii. Detect & Classify TE-Derived Transcripts

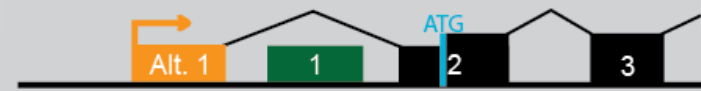


Chimeric Transcript Annotations

Cancer Libraries

Normal Libraries

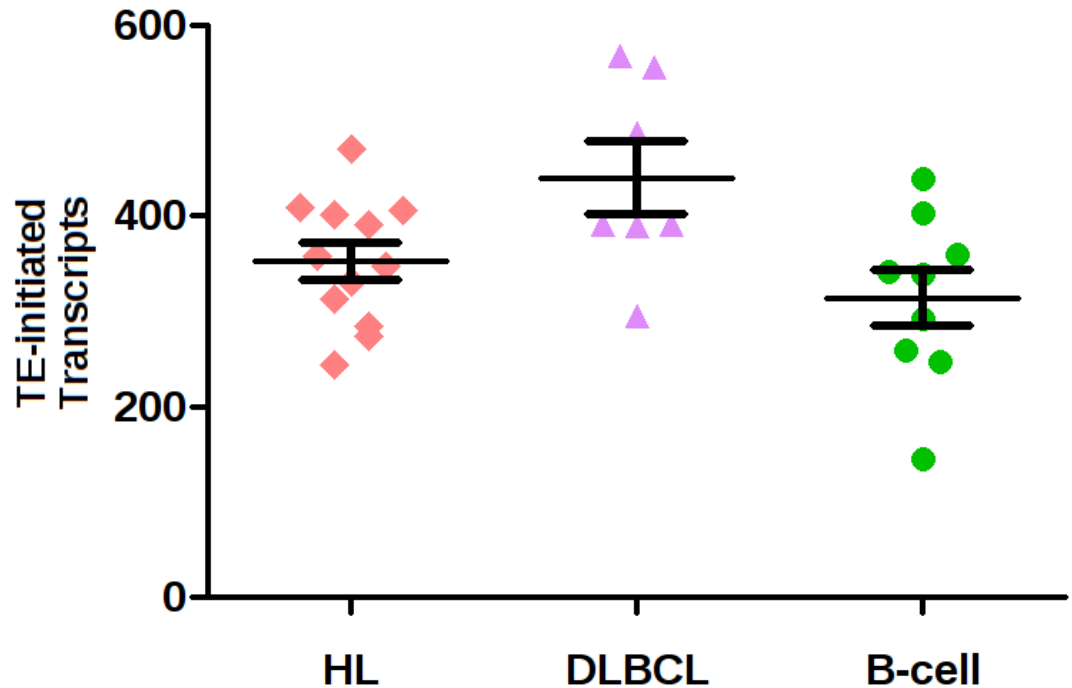
Recurrent and Cancer Specific



# Analysis of TE-initiated Transcripts

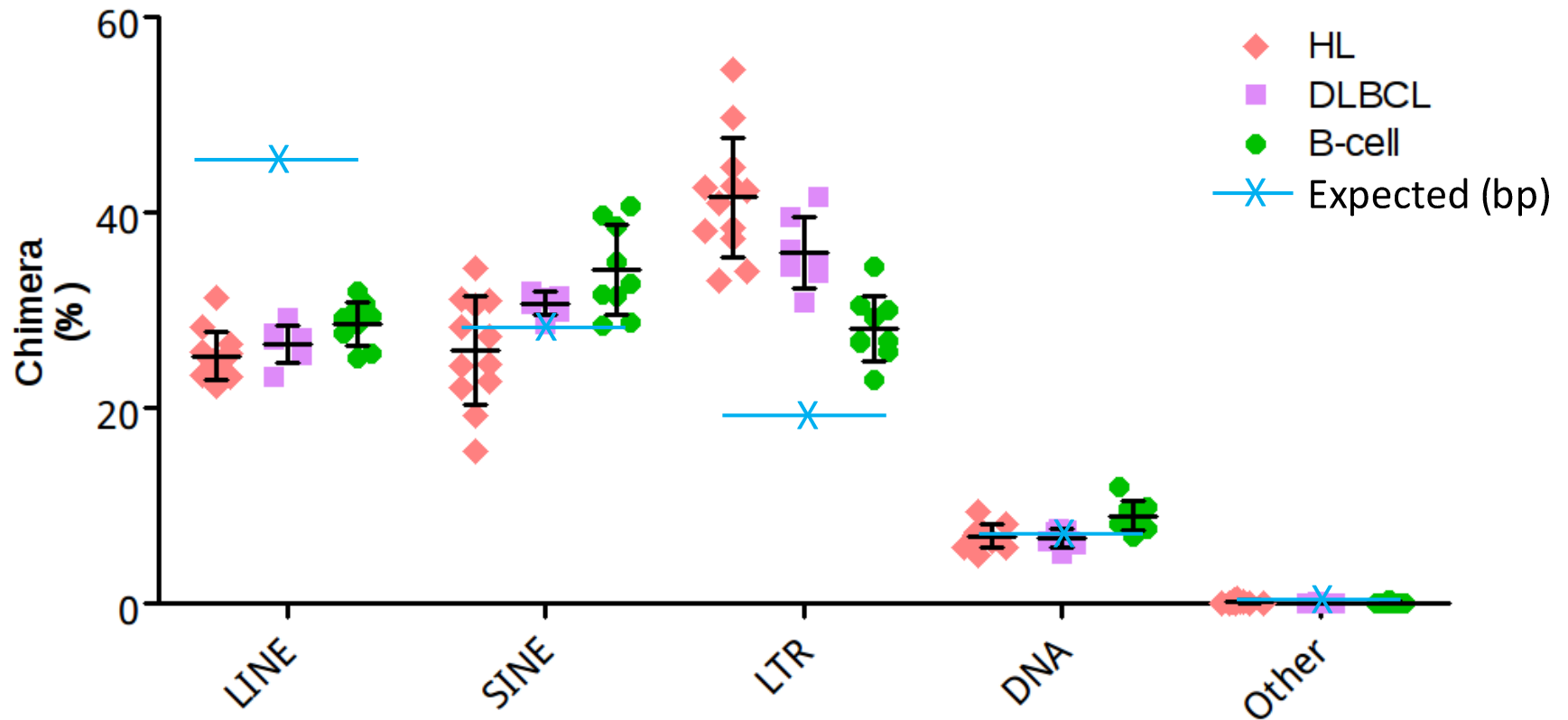
## Data Sets

- 12 Hodgkins Lymphoma cell lines
- 7 Diffuse Large B-cell Lymphoma patient samples
- 9 B-cell biopsies

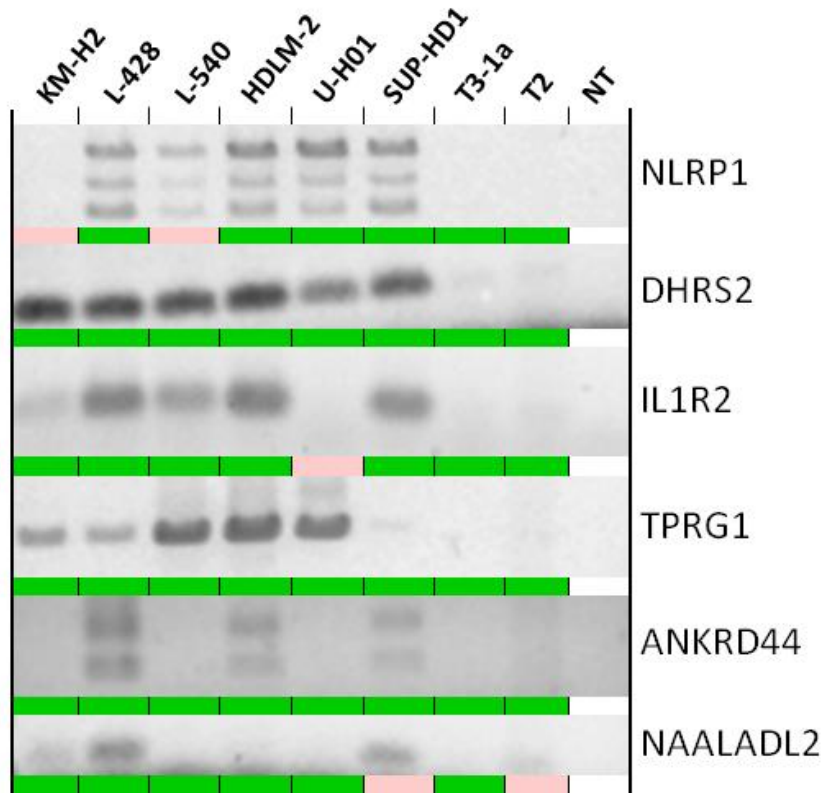




# Relative Class Distribution



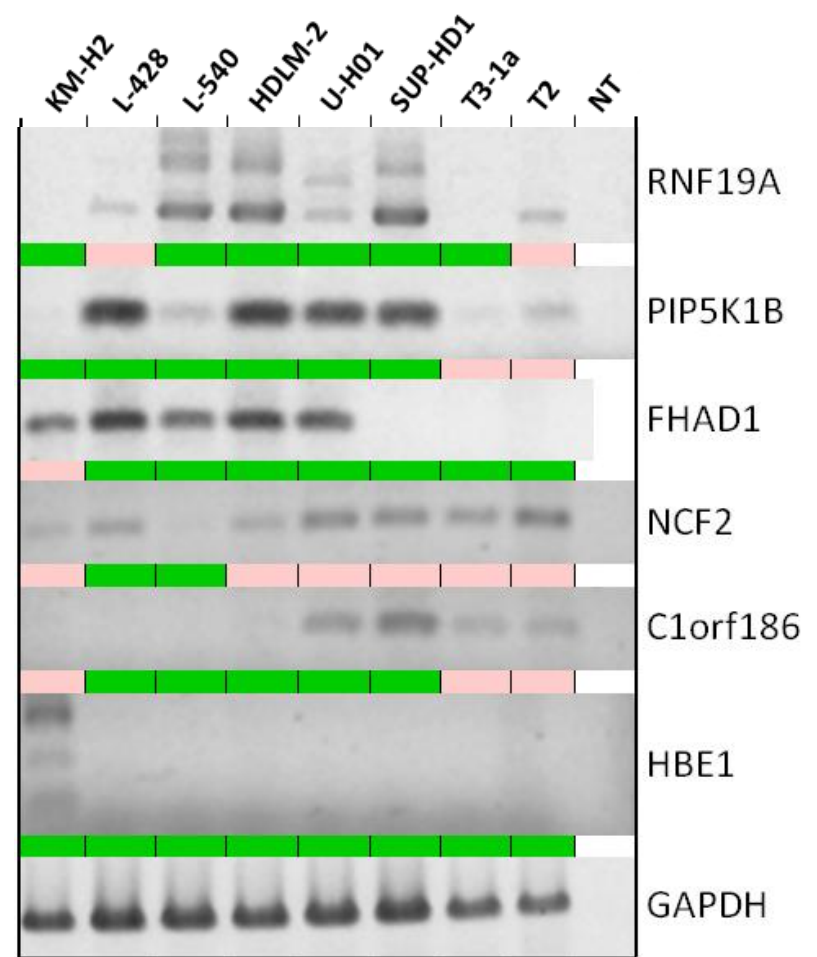
# RT-PCR Validation of LIONS



Specificity = 89.2 %

Sensitivity = 55.41 %

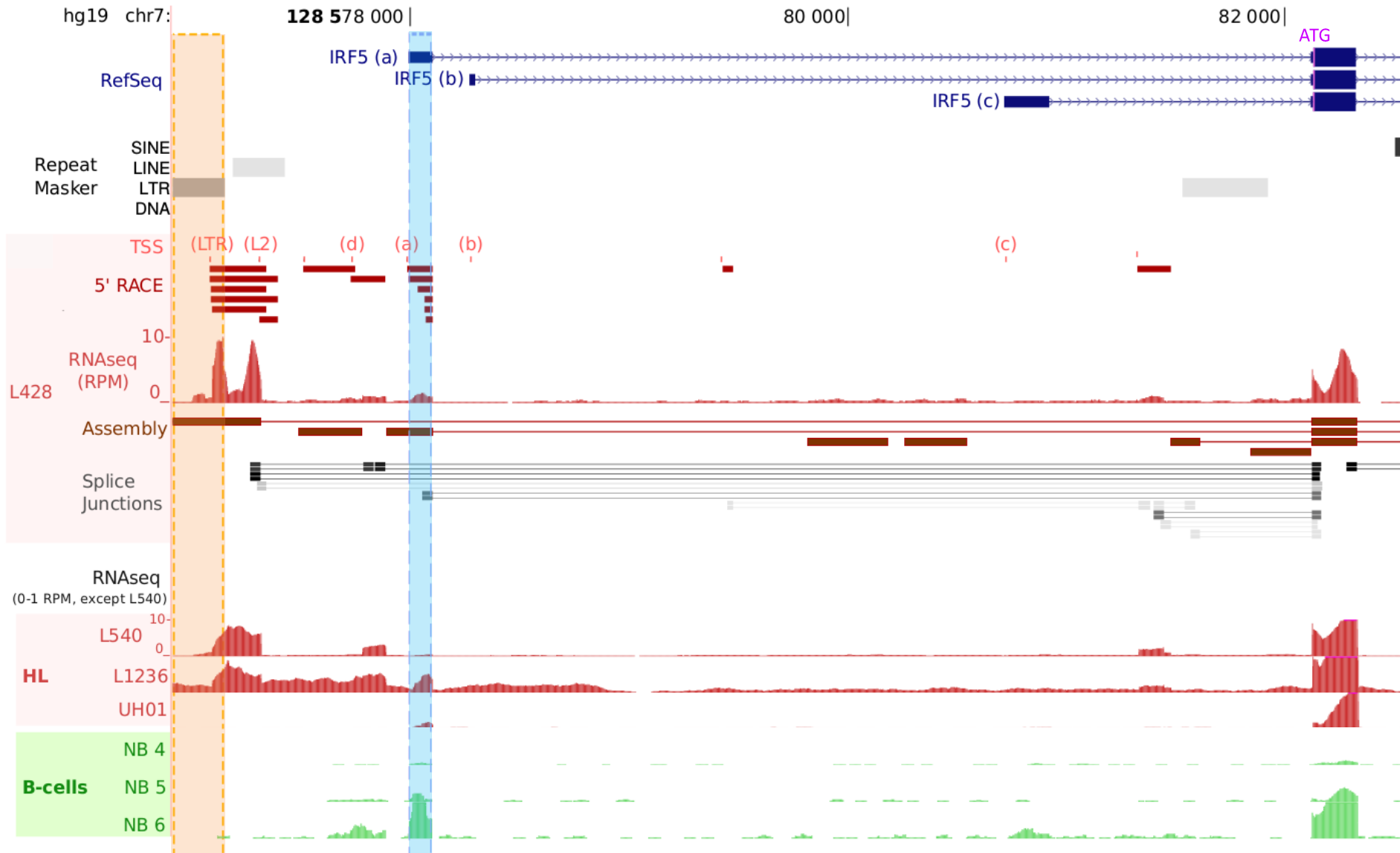
False Discovery Rate = 0.089



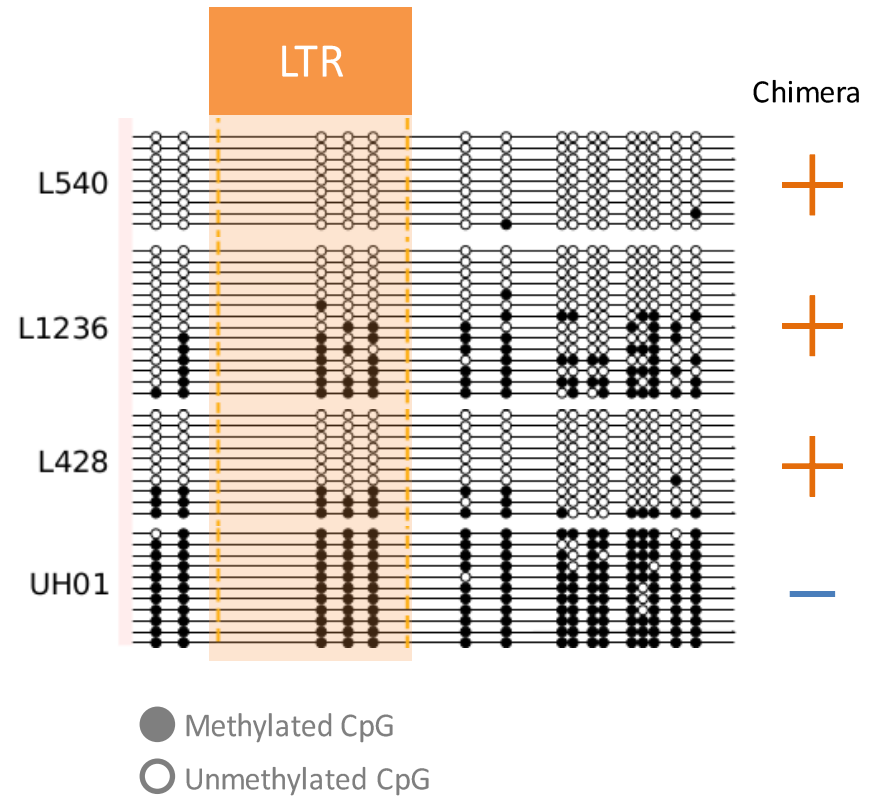
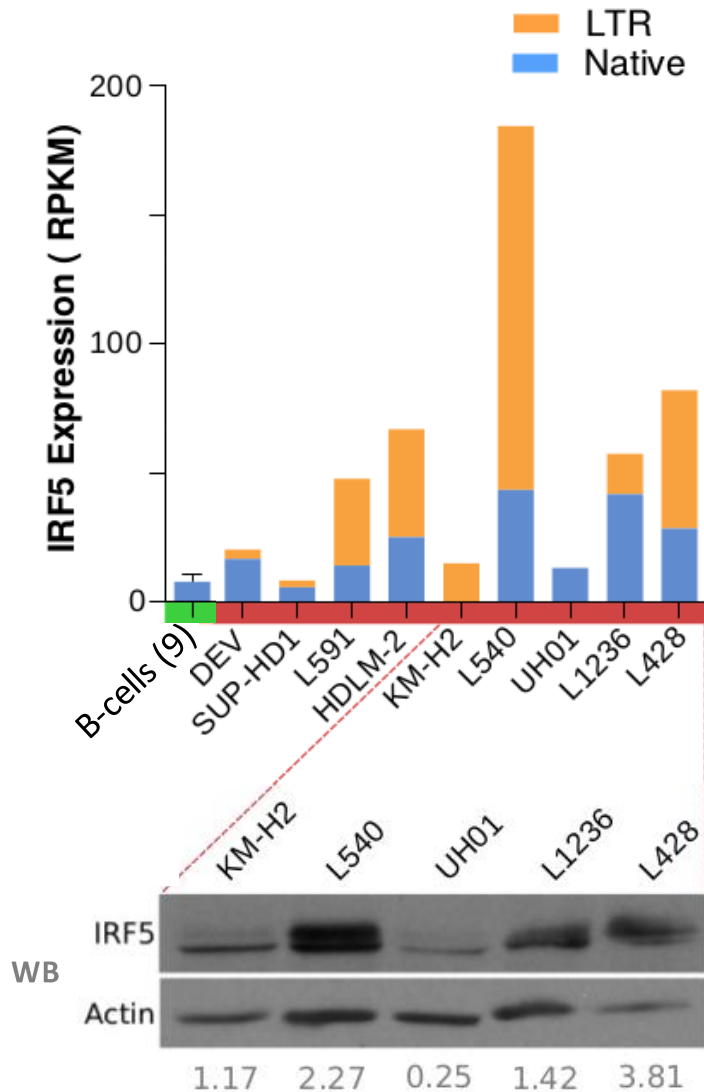
**373** Hodgkin specific + recurrent transcripts

# An LTR drives *IRF5* in HL

(Babaian et al., 2015. *In review*)

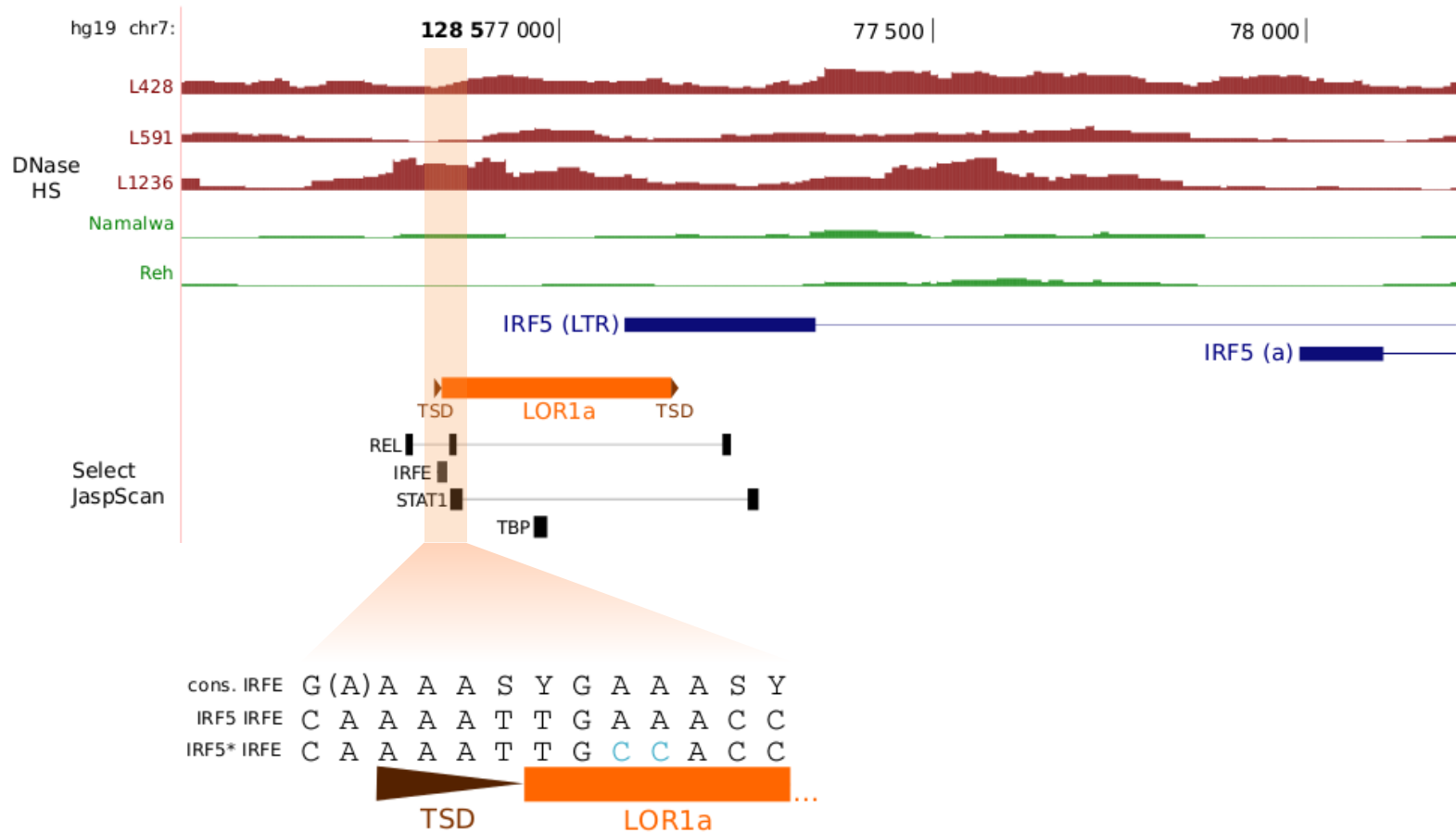


# IRF5 overexpression is LTR Driven



(Babaian et al., 2015. *In review*)

# LTR insertion created IRF5 motif

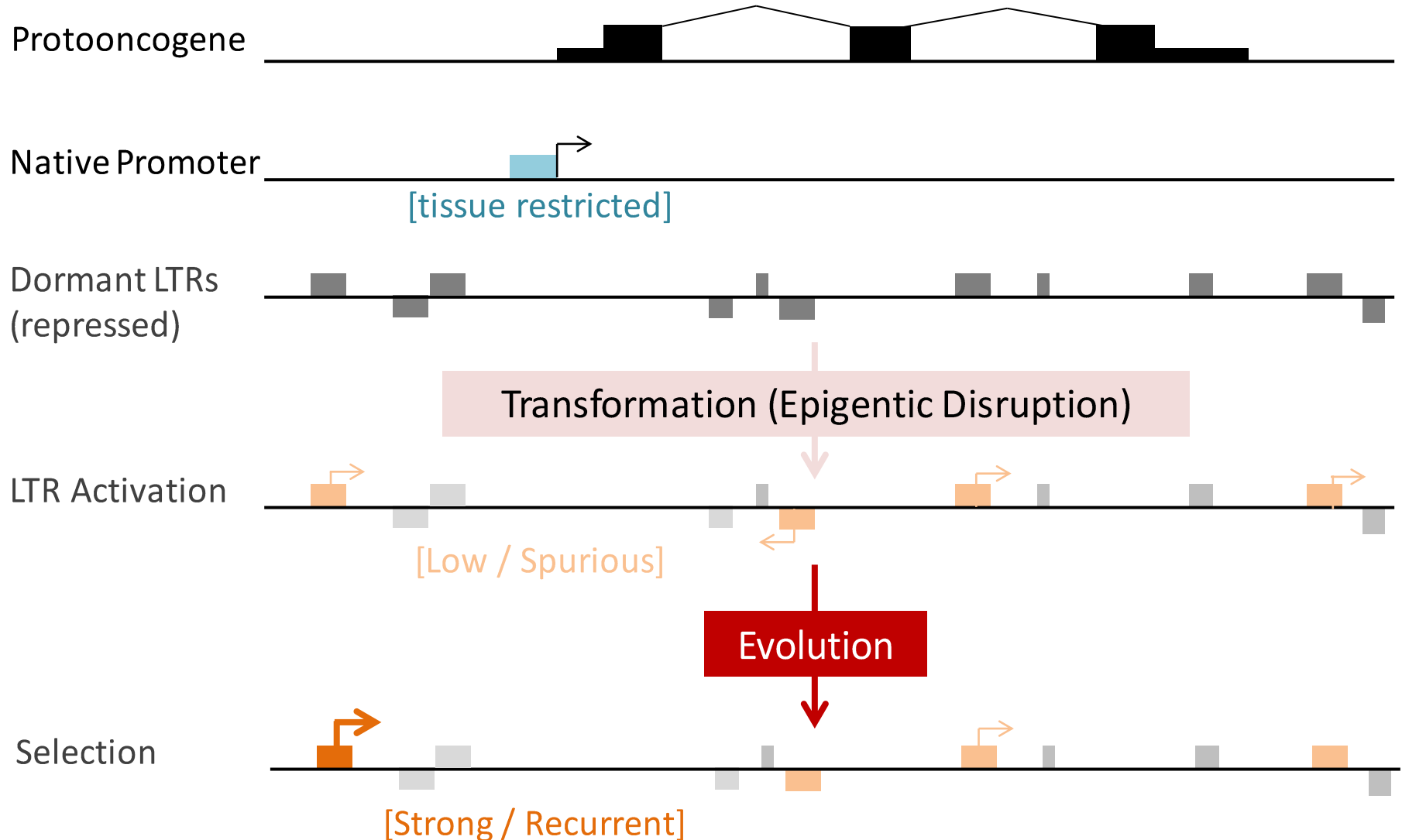


# *IRF5* as a key TF in Hodgkins Lymphoma

**Mapping of transcription factor motifs in active chromatin identifies IRF5 as key regulator in classical Hodgkin lymphoma**

Stephan Krehar *et al.*, 2014. PNAS

# Conclusion: Onco-exaptation Model



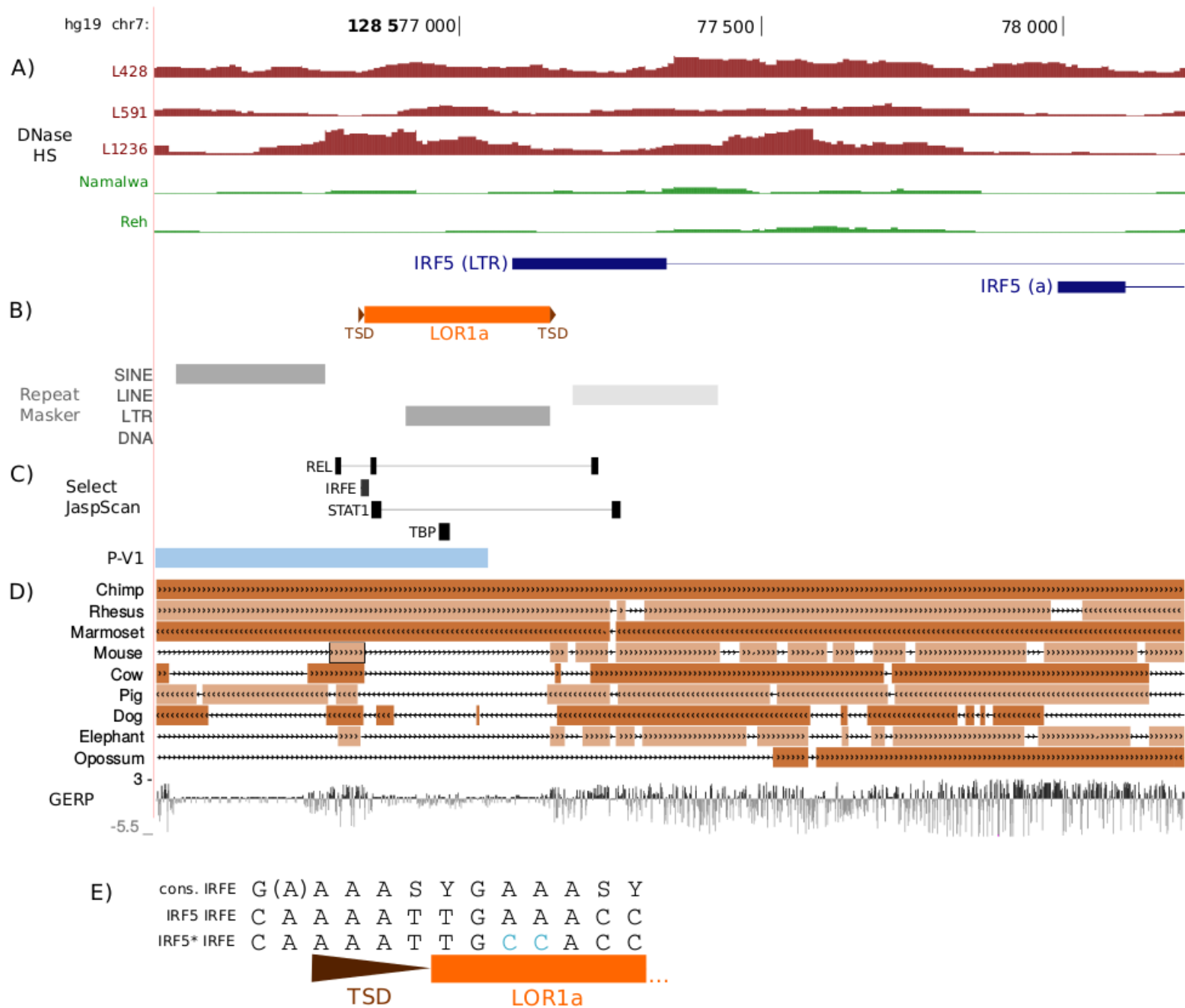


# Thanks!



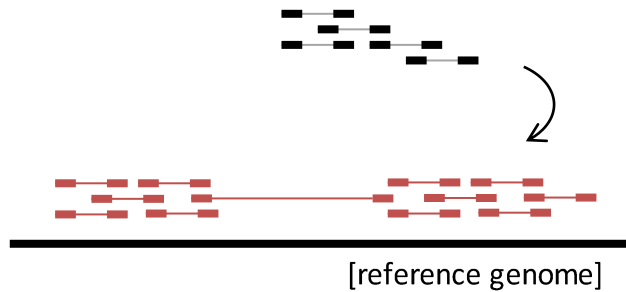
Mark Romanish  
Jake Lever  
Mehdi Karimi,  
Liane Gagnier  
Christian Steidl  
Matt Lorincz  
**Dixie Mager**





# Alignment and Assembly

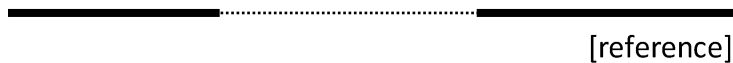
## 1) RNAseq Alignment [tophat2]



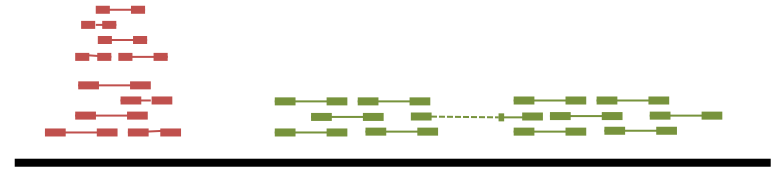
Split Read



Split Pair



## 2) Assembly [Cufflinks]



Exons



Transcripts

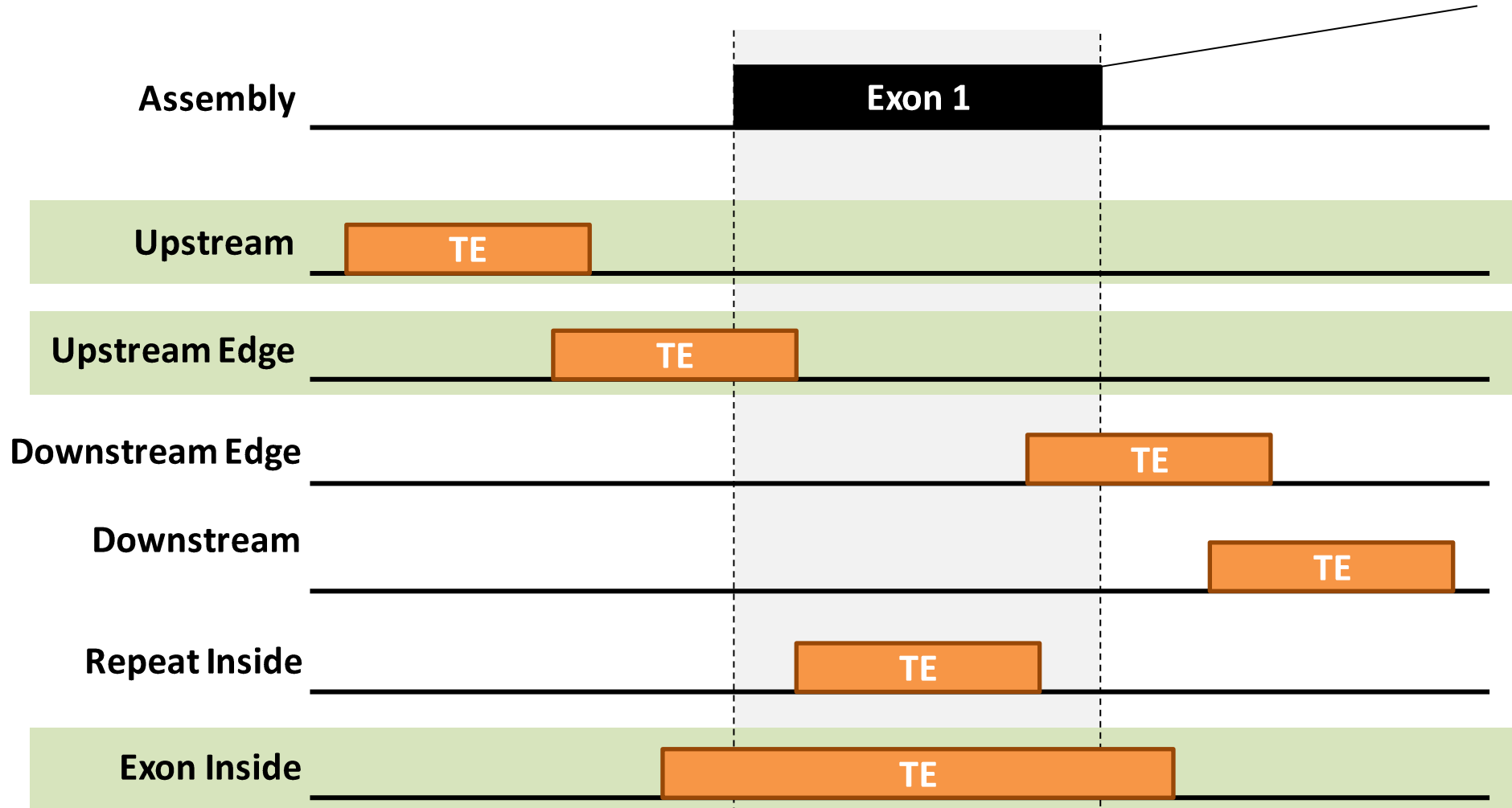


Digitize  
Expression

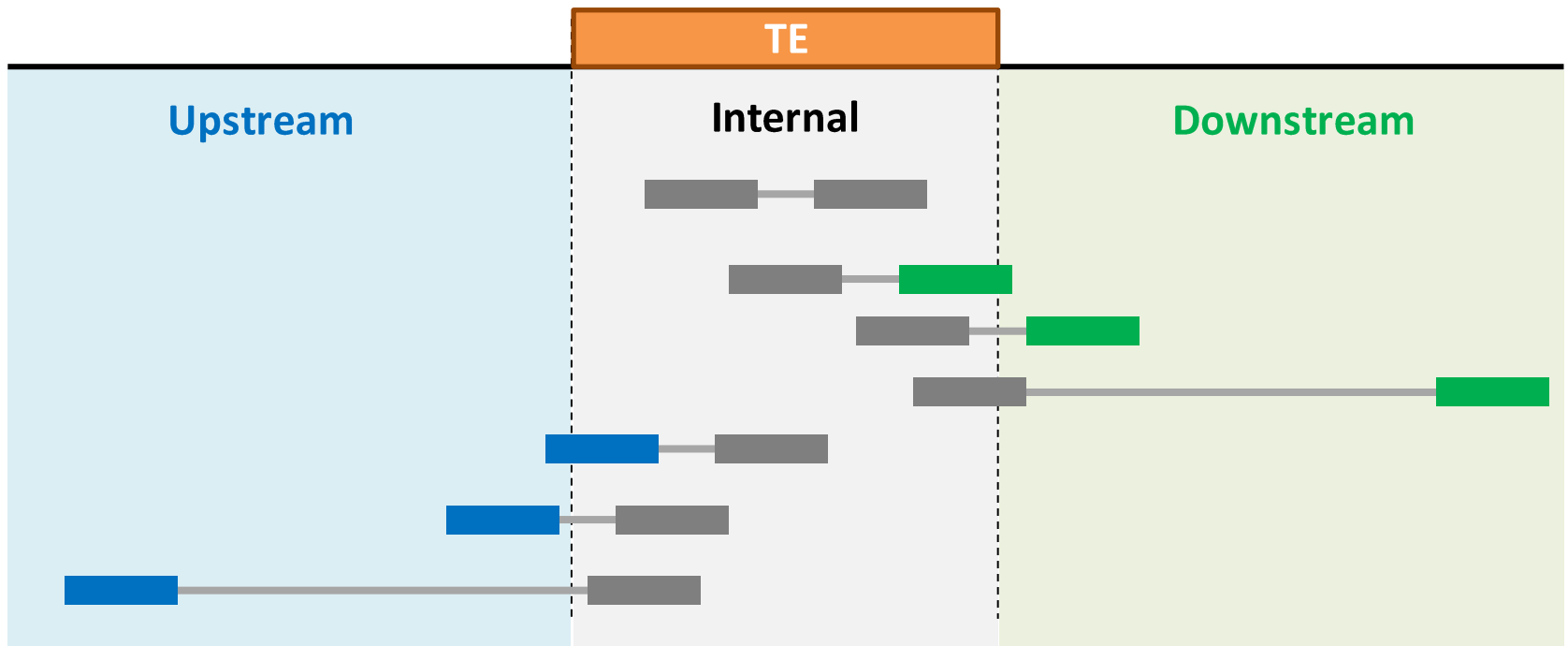


# TE / Assembly Intersection

*with Jake Lever*



# Paired-End Read Threading



$$\text{Thread Ratio} = \frac{\text{Downstream}}{\text{Upstream}}$$

# THE1B(LTR) drives oncogene CSF1R expression

