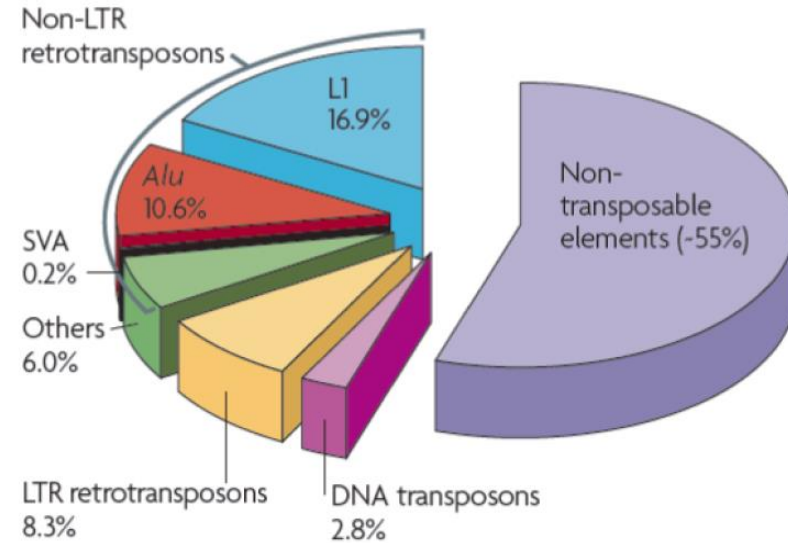


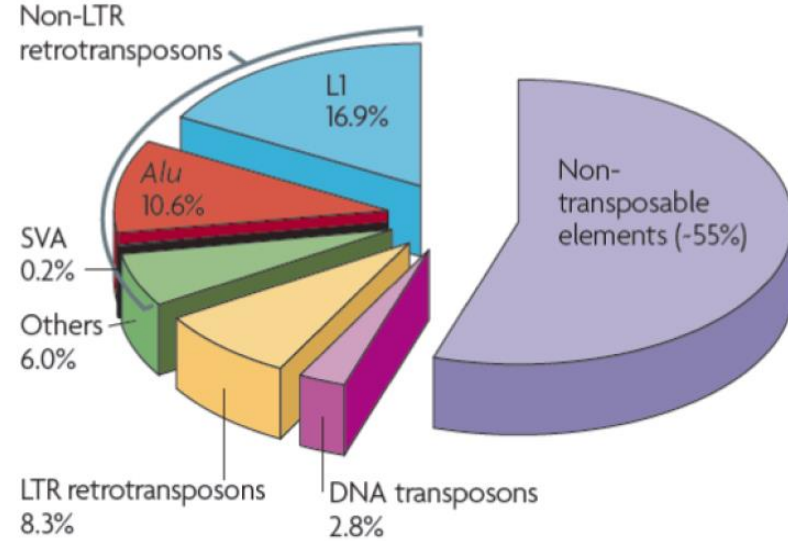
Detecting hot-activity of retrotransposons in human tumors using a novel targeted sequencing-based method

Dra. Mónica Martínez-Fernández



Cordaux *et al.* (2009) Nat Rev Genet

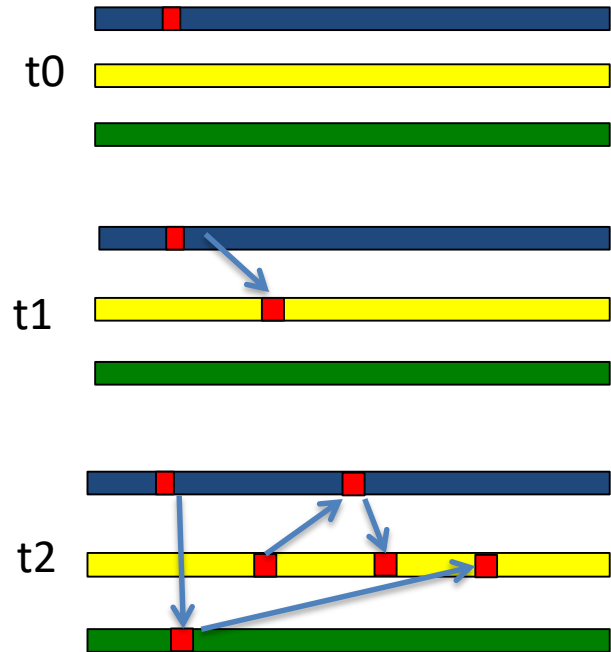
- **Retrotransposons are abundant in human genomes**

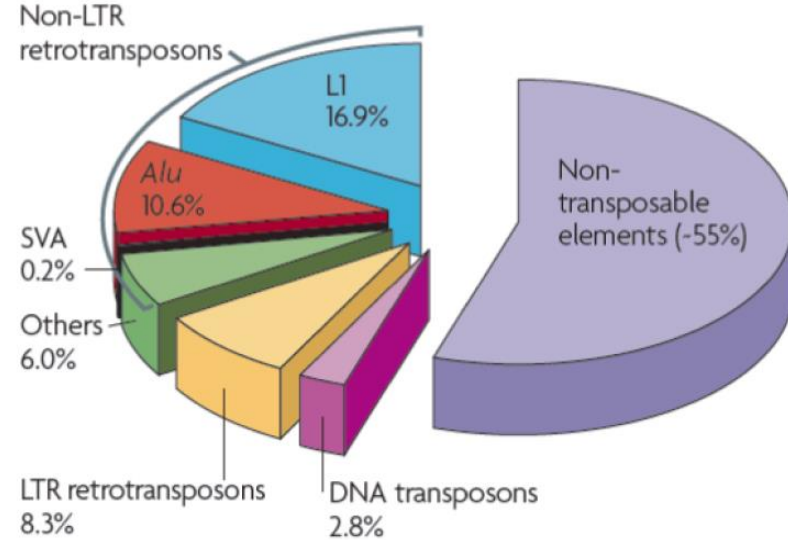


Cordaux *et al.* (2009) Nat Rev Genet

- **Retrotransposons are abundant in human genomes**

- **Retrotransposons (RT) “jump” within a genome creating genomic structural variability**

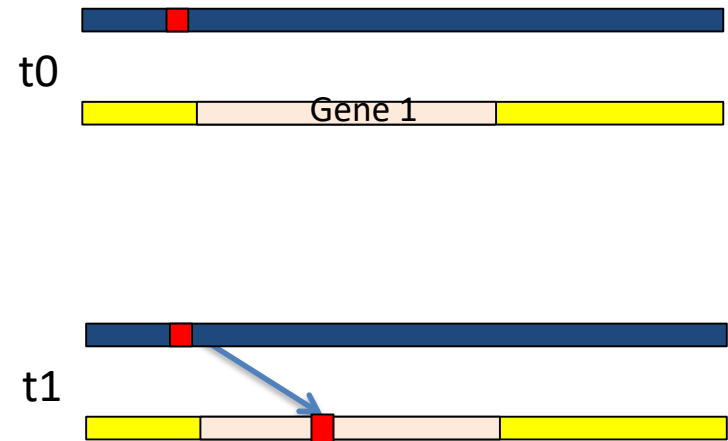




Cordaux *et al.* (2009) Nat Rev Genet

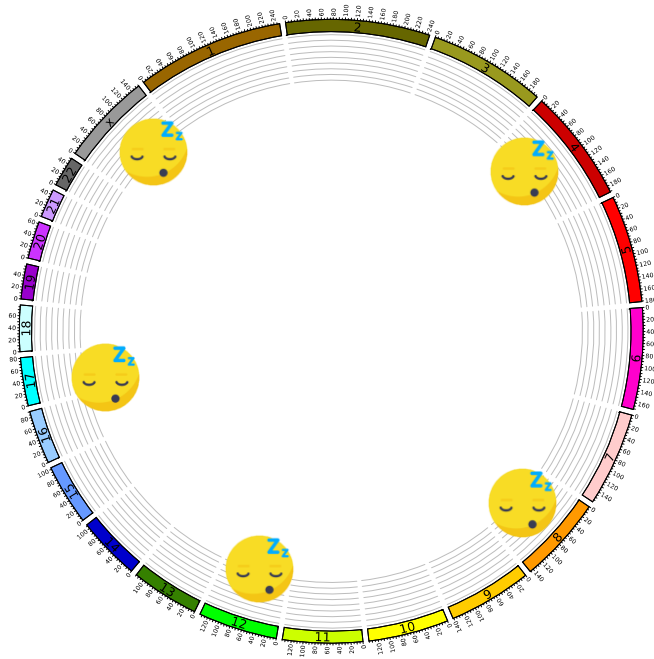
- **Retrotransposons are abundant in human genomes**

- **Retrotransposons may cause genome function alteration when they land within expressed genes**

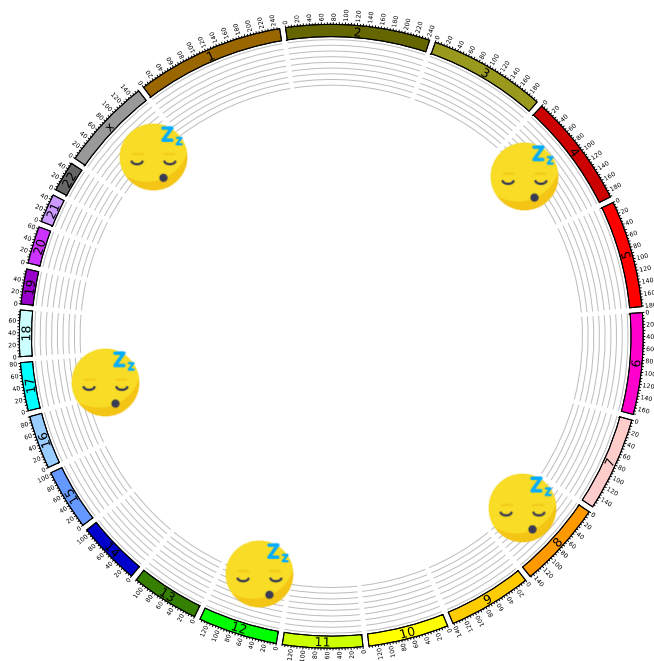


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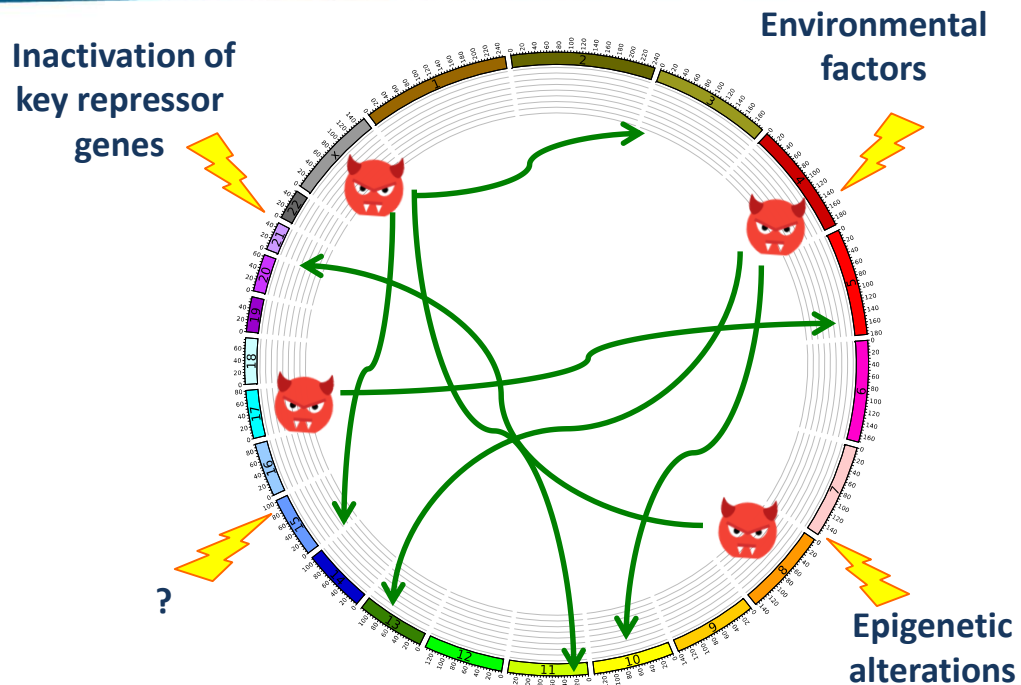
Valencia, 6th - 7th - 8th November 2018



Normal



Normal



Tumor

Is activation of retrotransposons relevant in human oncogenesis?

Landscape of Somatic Retrotransposition in Human Cancers

Eunjung Lee,^{1,2} Rebecca Iskow,³ Lixing Yang,¹ Omer Gokcumen,³ Psalm Haseley,^{1,2}
Lovelace J. Luquette III,¹ Jens G. Lohr,^{4,5} Christopher C. Harris,⁶ Li Ding,⁶ Richard K. Wilson,⁶
David A. Wheeler,⁷ Richard A. Gibbs,⁷ Raju Kucherlapati,^{2,8} Charles Lee,³ Peter V. Kharchenko,^{1,9*}
Peter J. Park,^{1,2,9*} and The Cancer Genome Atlas Research Network

Somatic retrotransposition in human cancer revealed by whole-genome and exome sequencing

Elena Helman,^{1,2} Michael S. Lawrence,² Chip Stewart,² Carrie Sougnez,² Gad Getz,^{2,3}
and Matthew Meyerson^{1,2,4,5,6}

Extensive somatic L1 retrotransposition in colorectal tumors

Szilvia Solyom,^{1,10} Adam D. Ewing,^{2,10} Eric P. Rahrman,³ Tara Doucet,^{1,4}
Heather H. Nelson,⁵ Michael B. Burns,³ Reuben S. Harris,³ David F. Sigmon,¹
Alex Casella,¹ Bracha Erlanger,⁶ Sarah Wheelan,⁶ Kyle R. Upton,⁷ Ruchi Shukla,⁸
Geoffrey J. Faulkner,^{7,8,9} David A. Largaespada,³ and Haig H. Kazazian, Jr.^{1,11}

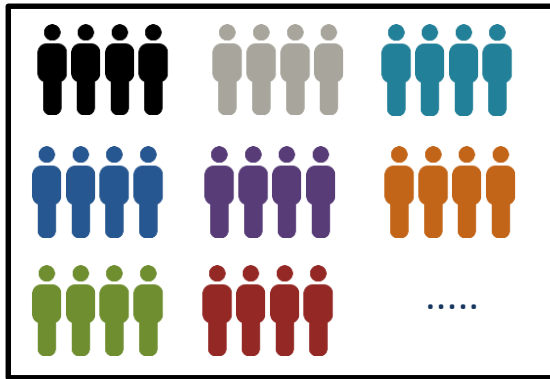
Extensive transduction of nonrepetitive DNA mediated by L1 retrotransposition in cancer genomes

Jose M. C. Tubio *et al.*

Science **345**, (2014);

DOI: 10.1126/science.1251343





TraFiC

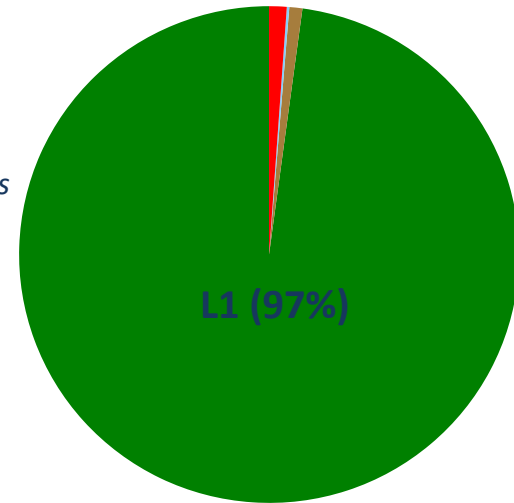
Tubio *et al.* (2014) *Science*

Rodríguez-Martín *et al.* (2018) *Nature Genetics, in press*



Somatic RT insertions

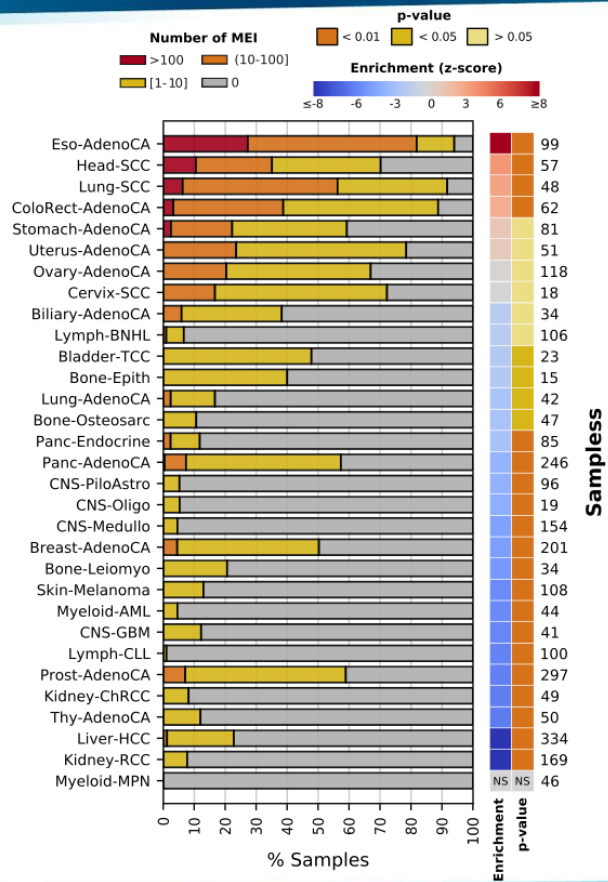
19,166 somatic RT insertions



- Around 700 researchers from around the globe.
- 2,900 cancer whole genomes (Illumina paired-end).
- 37 different tumour types.

Epithelial tumors

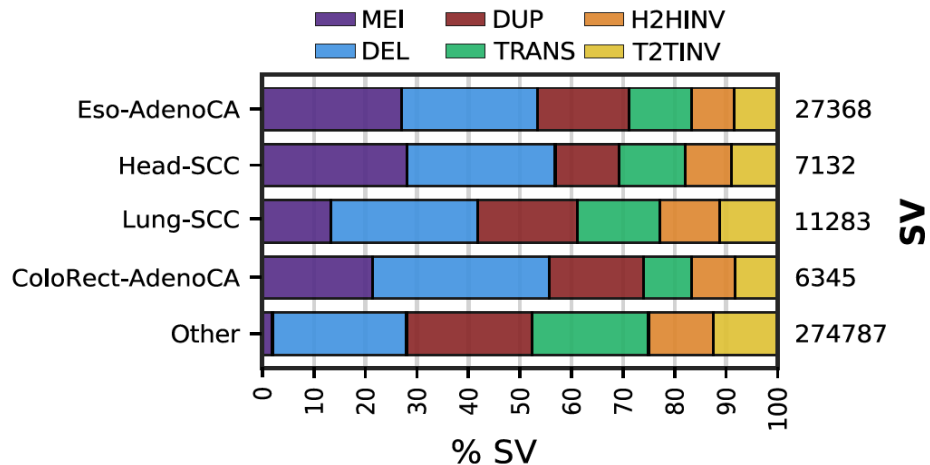
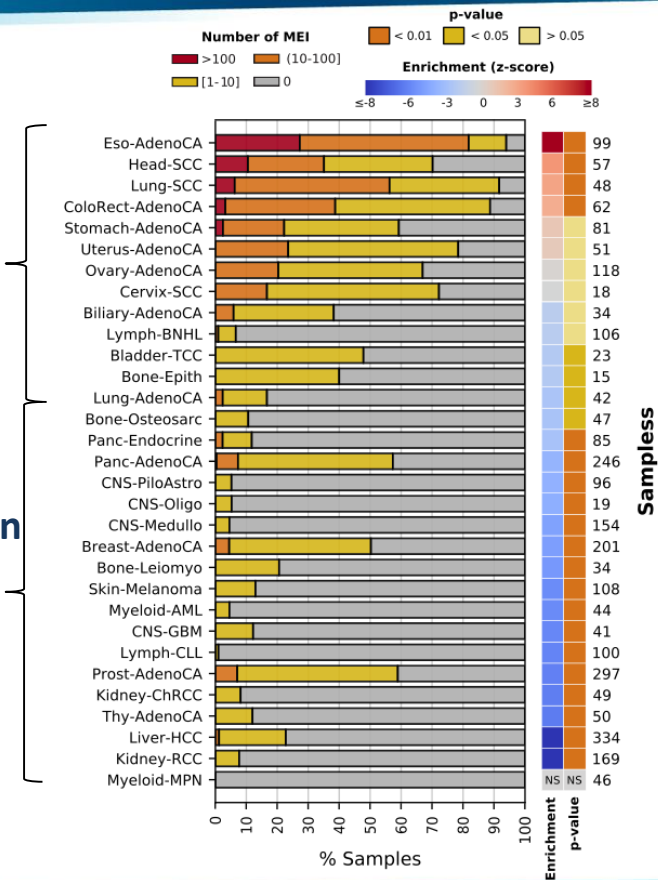
Blood, brain and bone tumors



Retrotransposition is a major player in the structural variation landscape of some tumour types

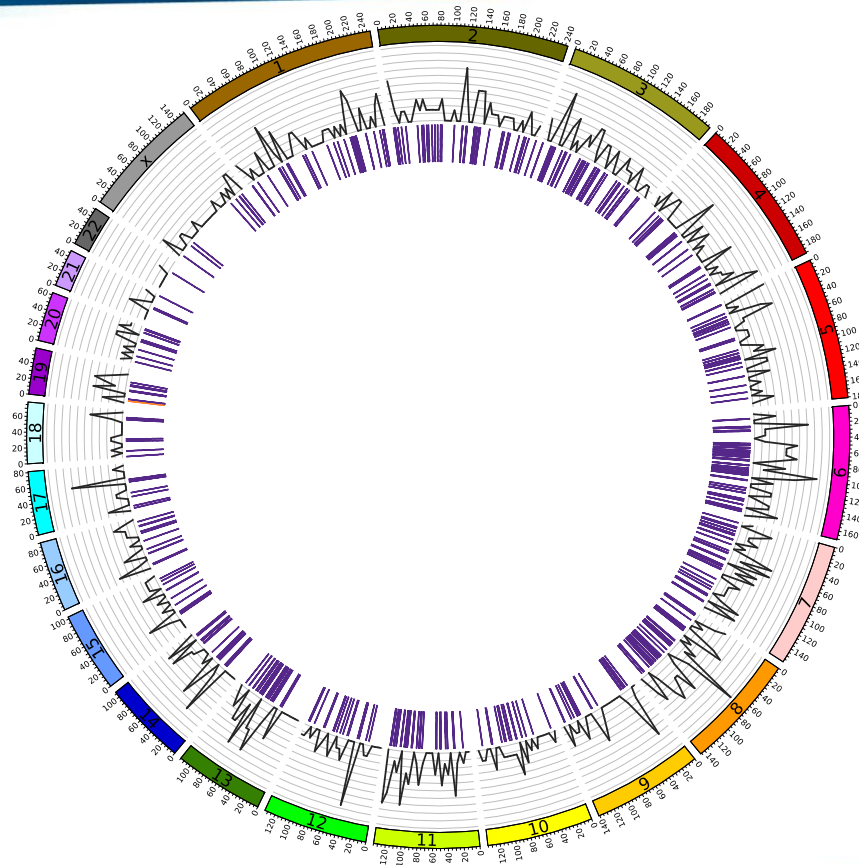
Epithelial tumors

Blood, brain and bone tumors



➤ 4 tumour types alone represent >70% of total SVs

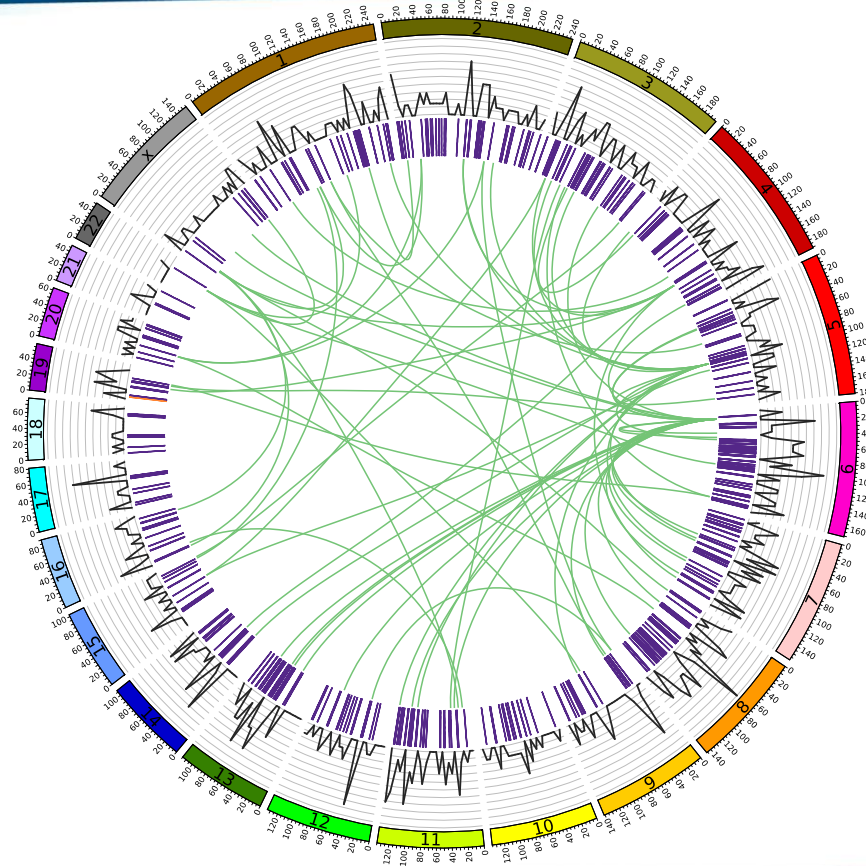
Esophageal
adenocarcinoma
tumour



— L1 integration

Some tumours exhibit a massive retrotransposition burden

Esophageal adenocarcinoma tumour

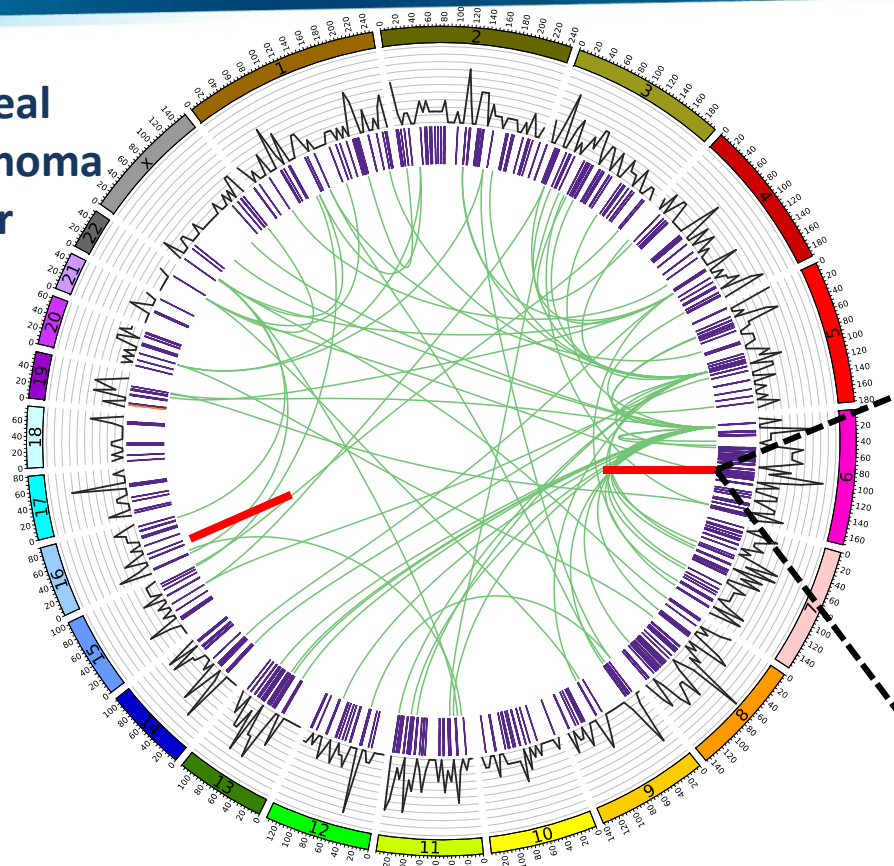


- L1 integration
- L1 3'-transduction

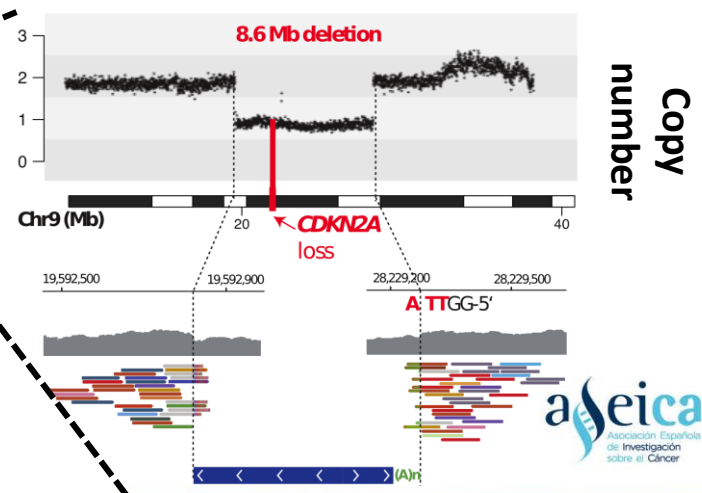
Tubio *et al.* (2014) Science

Deletion involving tumour suppressor CDKN2A (Cyclin-dependent kinase inhibitor 2A)

Esophageal
adenocarcinoma
tumour

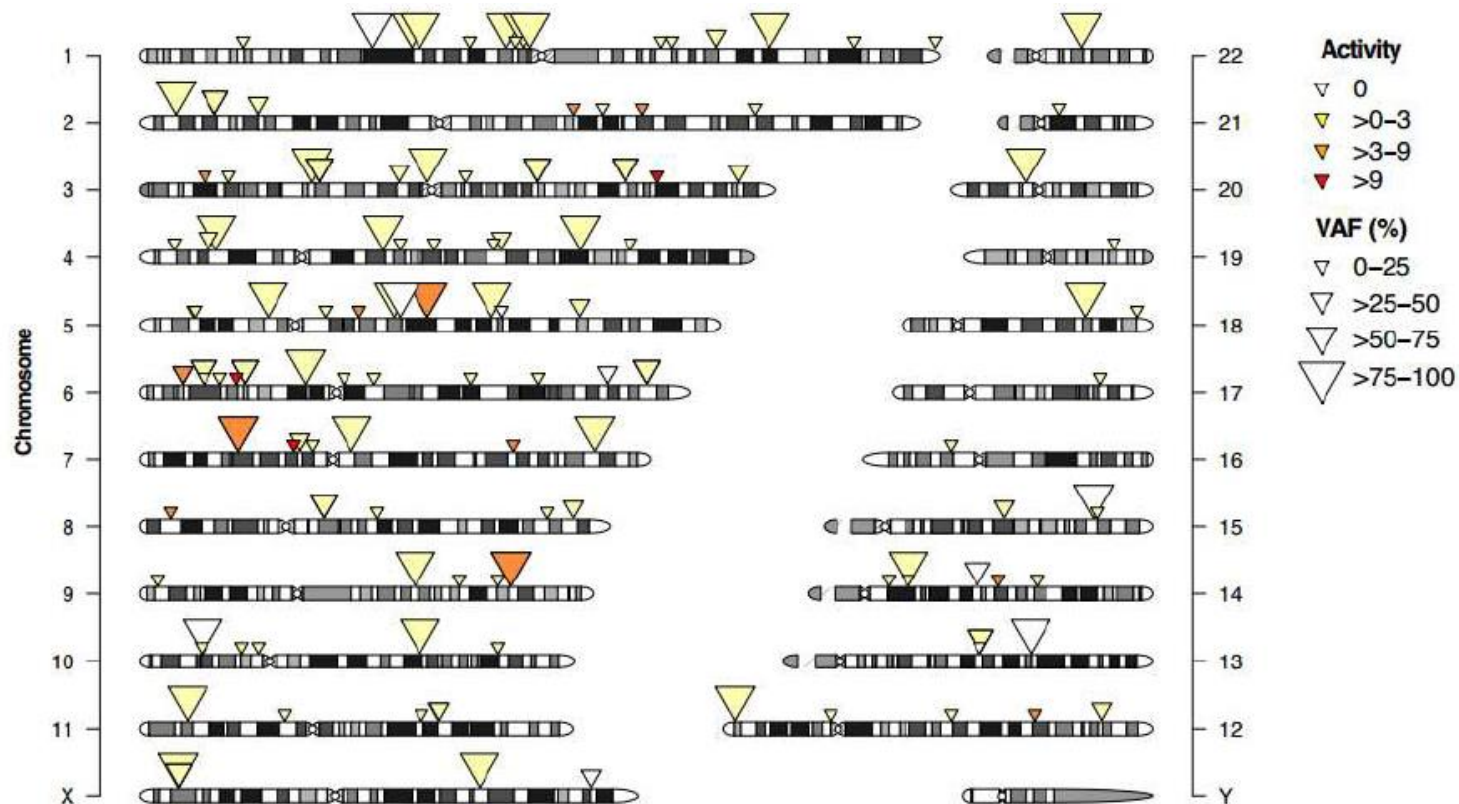


- L1 integration
 - L1 3'-transduction
 - L1-mediated deletion
- Tubio *et al.* (2014) Science
- Rodríguez-Martín *et al.* (2018) Nature Genetics



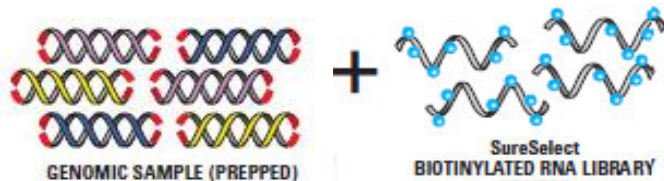
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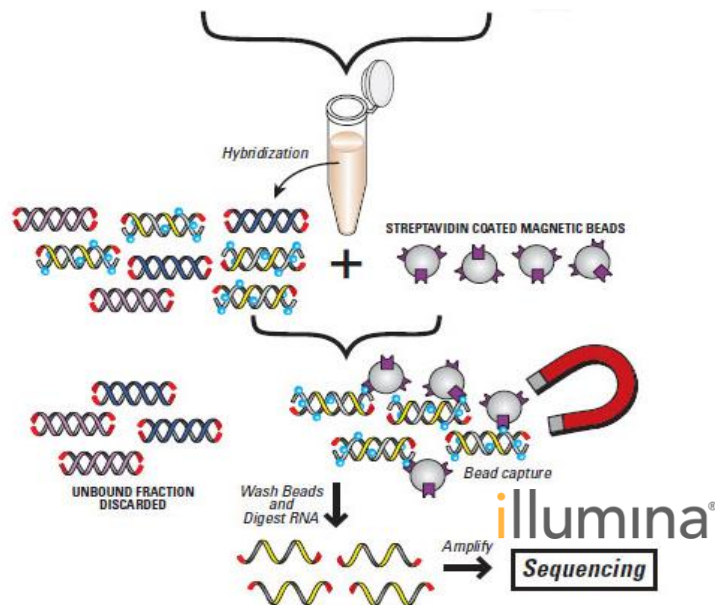




Agilent Technologies



SureSelect

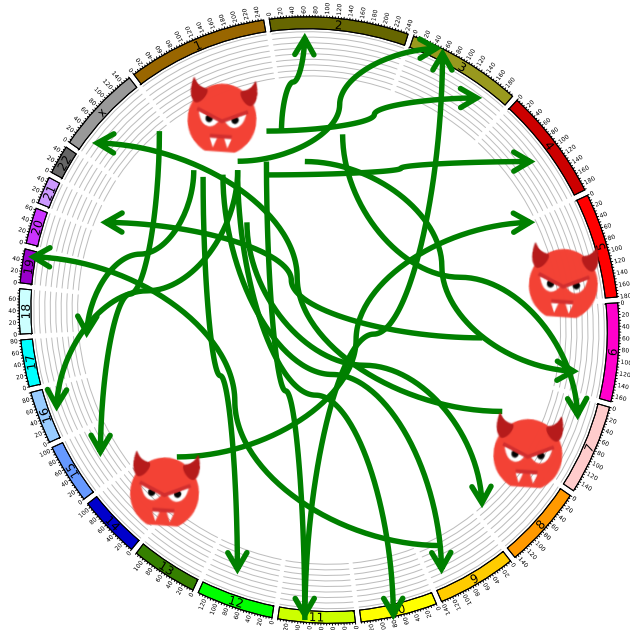


**Identification of tumor samples with high
somatic transduction rates: Traffic target**

NCI-H2087
T1 Lung Adenocarcinoma, NSCLC

NCI-BL2087
peripheral blood lymphocytes

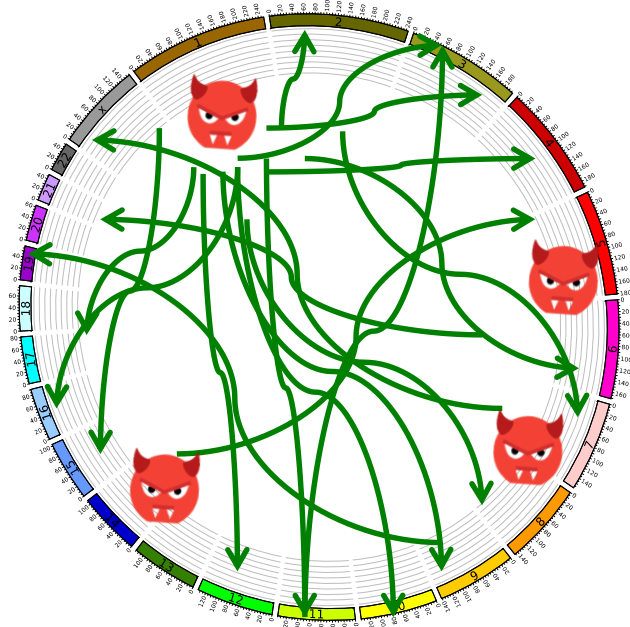
NCI-H2087
T1 Lung Adenocarcinoma, NSCLC



27 transductions

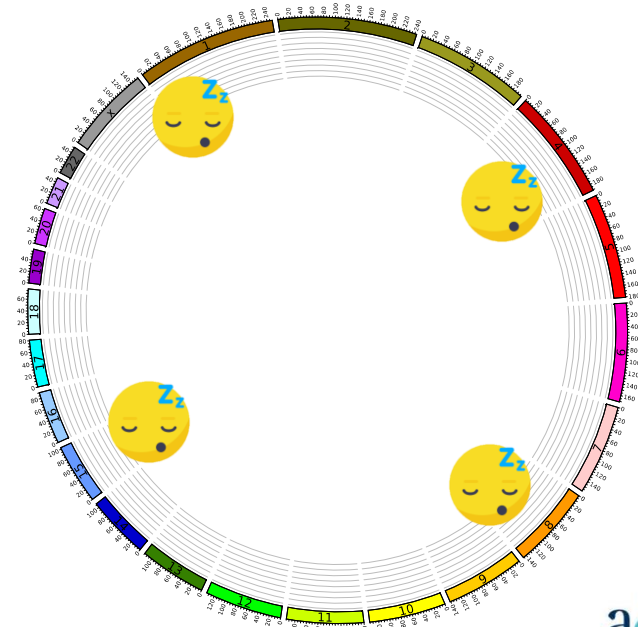
NCI-BL2087
peripheral blood lymphocytes

NCI-H2087
T1 Lung Adenocarcinoma, NSCLC



27 transductions

NCI-BL2087
peripheral blood lymphocytes



No transductions

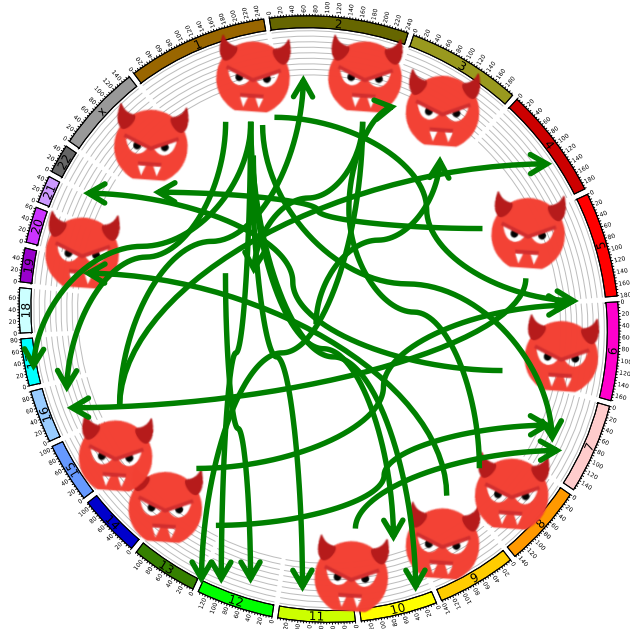
**Identification of tumor samples with high
somatic transduction rates: Traffic target**

NCI-H2009
T4 Lung Adenocarcinoma, NSCLC

NCI-BL2009
peripheral blood lymphocytes

NCI-H2009

T4 Lung Adenocarcinoma, NSCLC



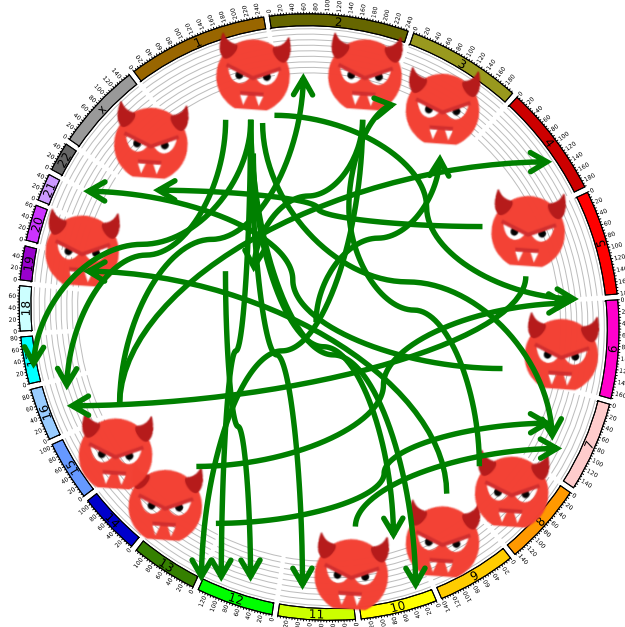
36 transductions

NCI-BL2009

peripheral blood lymphocytes

NCI-H2009

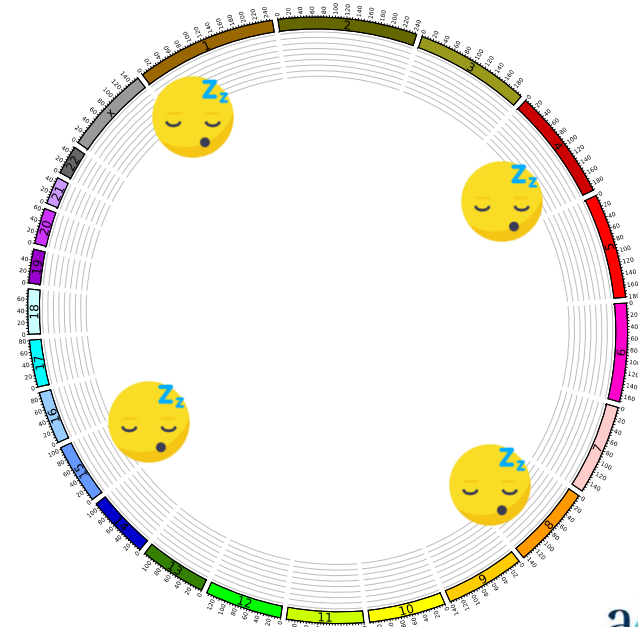
T4 Lung Adenocarcinoma, NSCLC



36 transductions

NCI-BL2009

peripheral blood lymphocytes



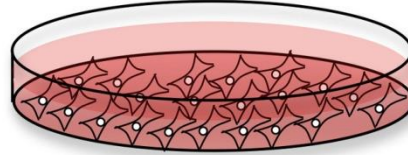
No transductions

NCI-LB771 - HEAD AND NECK CANCER

Nº transductions: 14
Nº active L1: 5
Most active element: 22q12.1, 4 transductions

NCI-LS1034 - COLORECTAL ADENOCARCINOMA

Nº transductions: 2
Nº active L1: 1
Most active element: 14q23.1, 2 transductions



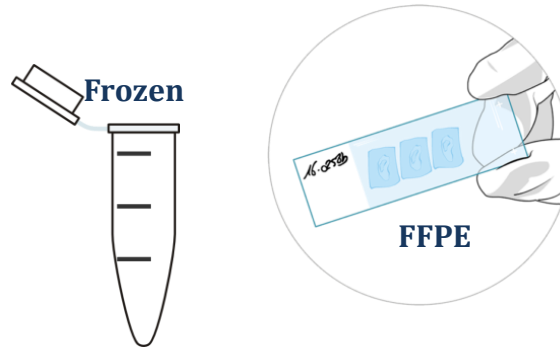
NCI-LB771PBL

Nº transductions: 0
Nº active L1: 0
Most active element: 0 transductions

NCI-LS1034PBL

Nº transductions: 0
Nº active L1: 0
Most active element: 0 transductions

Identification of tumor samples with high somatic transduction rates: Traffic target

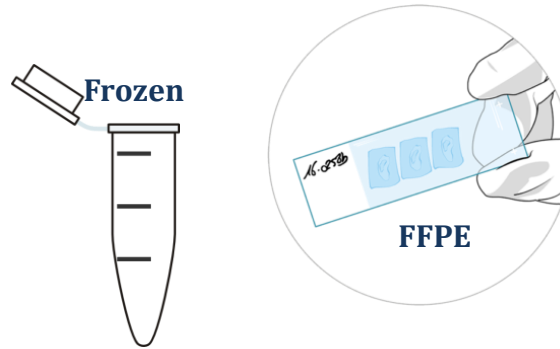


#1- **HSNCC** N° transductions: 1
N° active L1: 1

#2- **HSNCC** N° transductions: 2
N° active L1: 1

#3- **HSNCC** N° transductions: 0
N° active L1: 0

#4- **HSNCC** N° transductions: 4
N° active L1: 4



#5- **NSCLC** N° transductions: 1
N° active L1: 1

#6- **NSCLC** N° transductions: 7
N° active L1: 5

#7- **HSNCC** N° transductions: 1
N° active L1: 1

#8- **HSNCC** N° transductions: 7
N° active L1: 6

CONCLUSIONS

- Retrotransposition is one of the predominant sources of structural variation in certain tumour types
- Occasionally, retrotransposons can produce cancer driver mutations (i.e. deletion of tumour suppressor genes as CDKN2A)
- Somatic retrotransposition originates from the activation of a small set of L1 source elements, that behave as mutagenic oncogenes and potential cancer risk factors
- The present tool (Sureselect custom + Traffic target) allows the detection of active L1 source elements, opening new avenues to study the molecular consequences of L1 activation in tumor initiation and development. Its clinical application could change cancer diagnosis and help oncologists for personalized treatments

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MSc in Bioinformatics



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PhD in Biology



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PhD student



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