

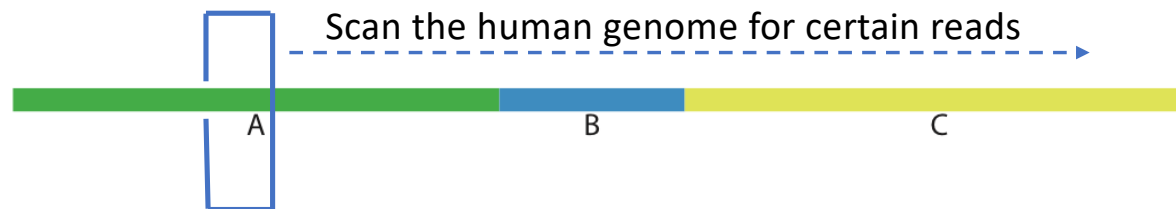
# Structural variant analysis using NGS

# Structural variation

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- Accumulated mutations over time cause cancer.
- Structural variation:
  - Genomic rearrangements of DNA.
  - Cause amplification, deletion or reordering of chromosomal regions.
  - Affect single gene/short stretches of DNA to entire chromosomes.

# Identifying structural variants



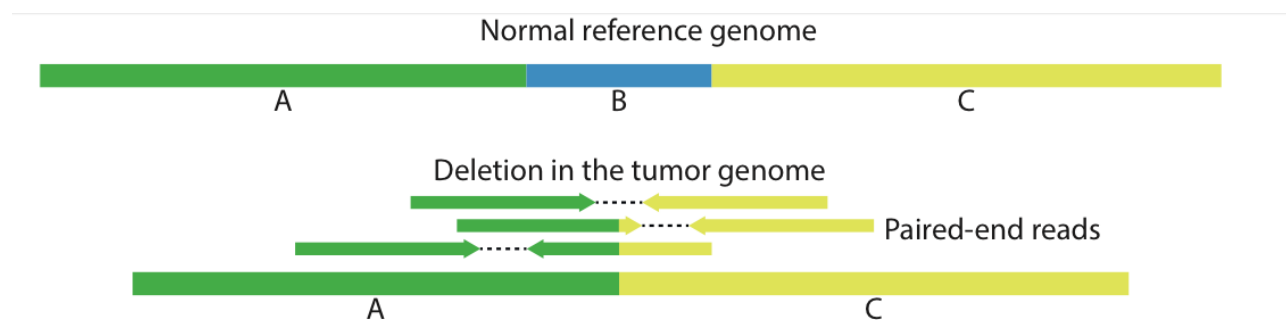
# Identifying structural variants using NGS

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# Identifying structural variants using NGS

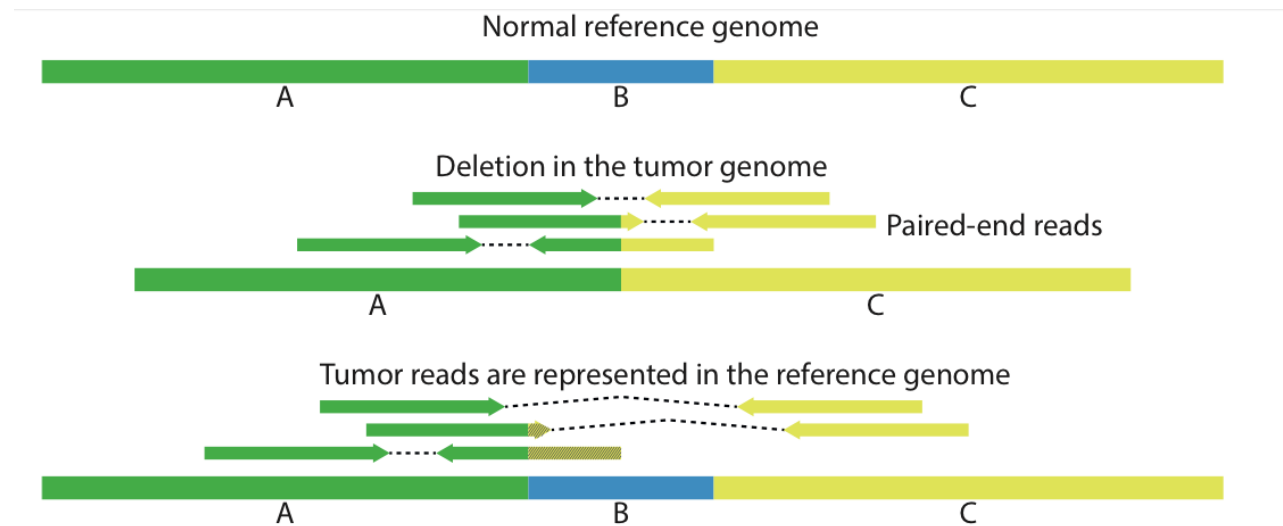
## Deletion



The sequencing data comes from the tumor genome NOT the reference genome but is mapped to the reference genome

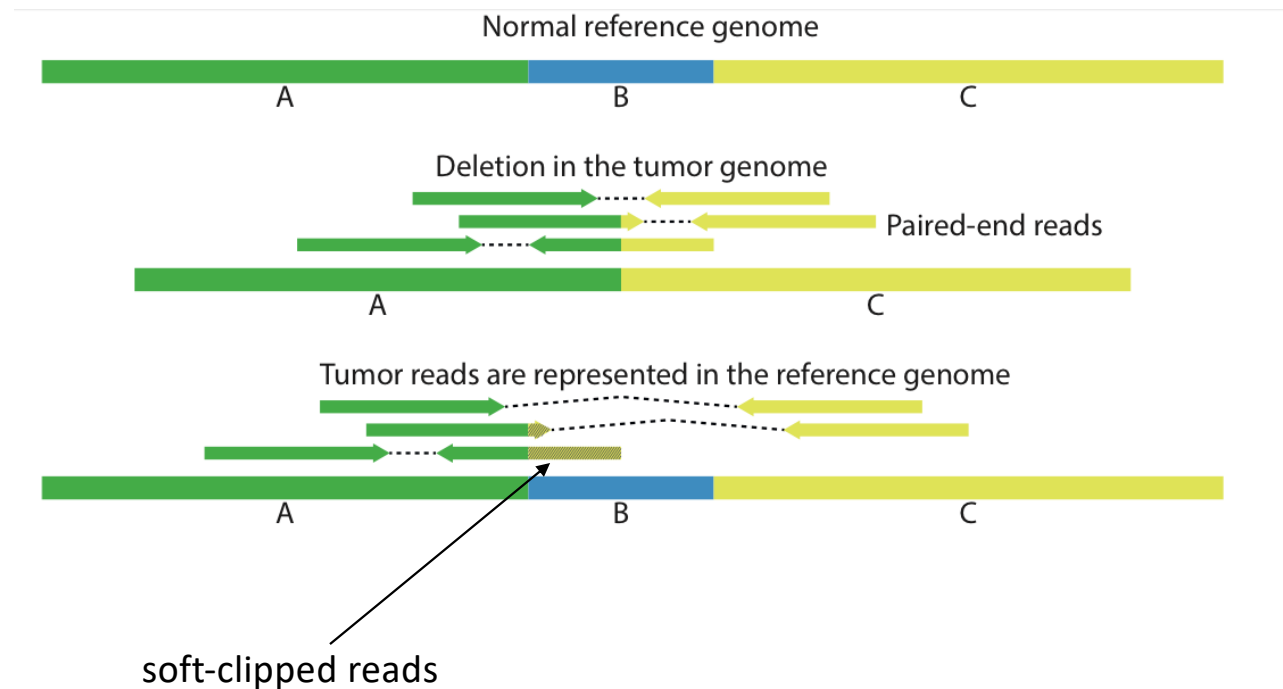
# Identifying structural variants using NGS

## Deletion



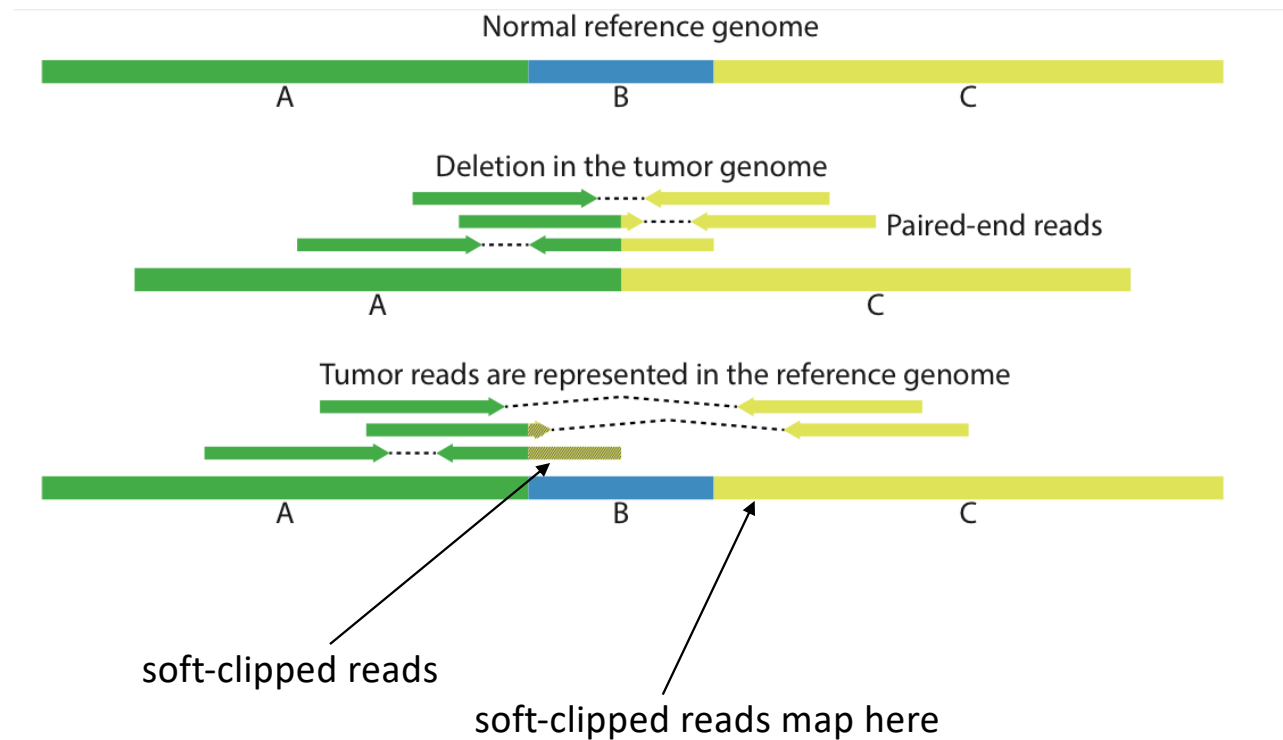
# Identifying structural variants using NGS

## Deletion



# Identifying structural variants using NGS

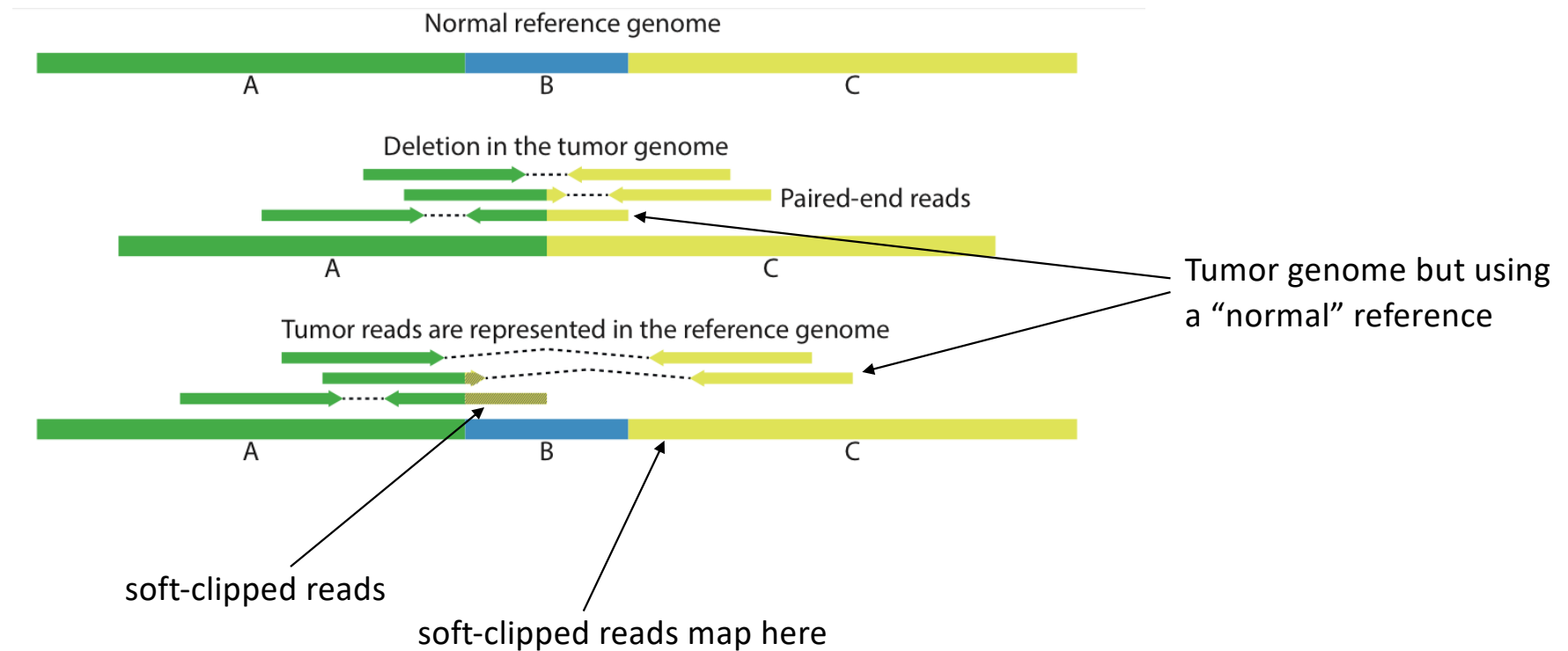
## Deletion





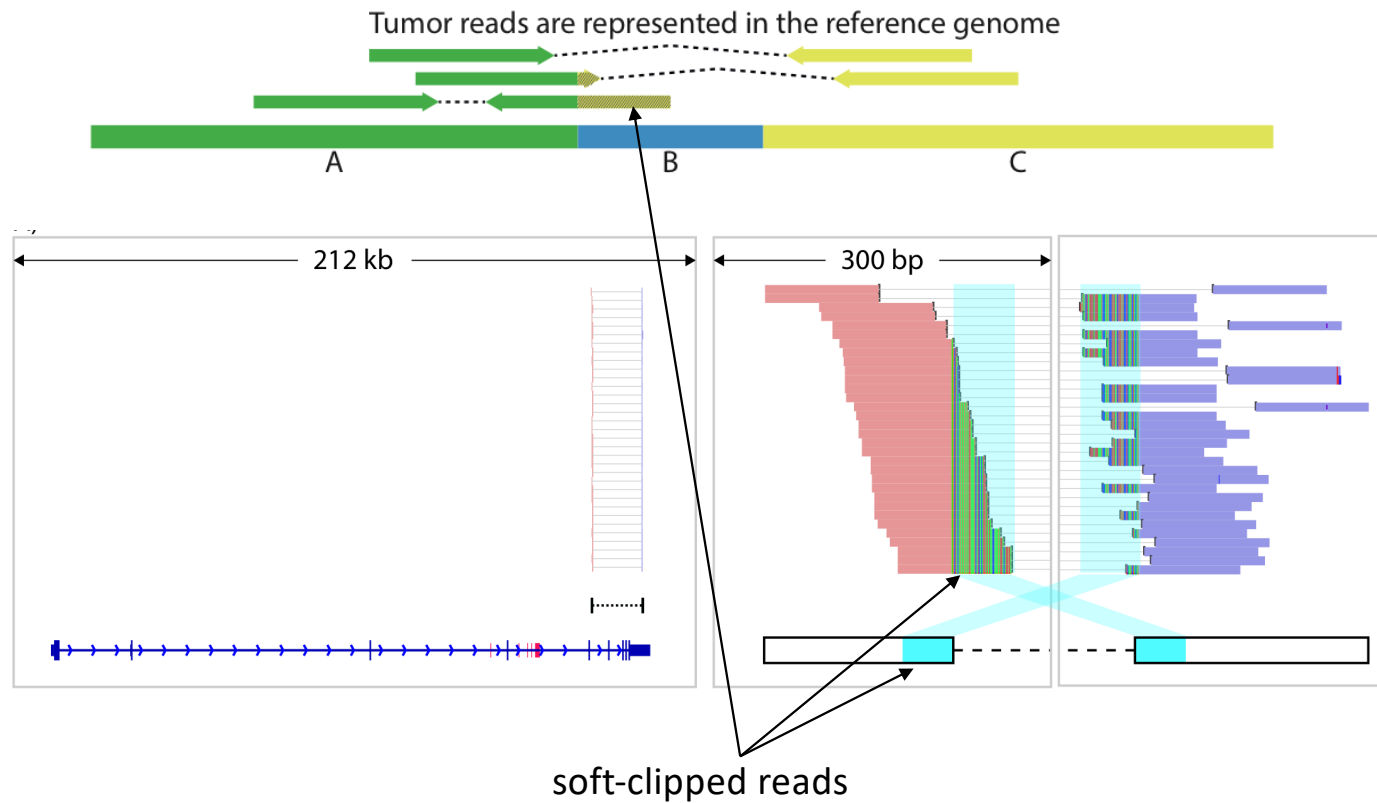
# Identifying structural variants using NGS

## Deletion



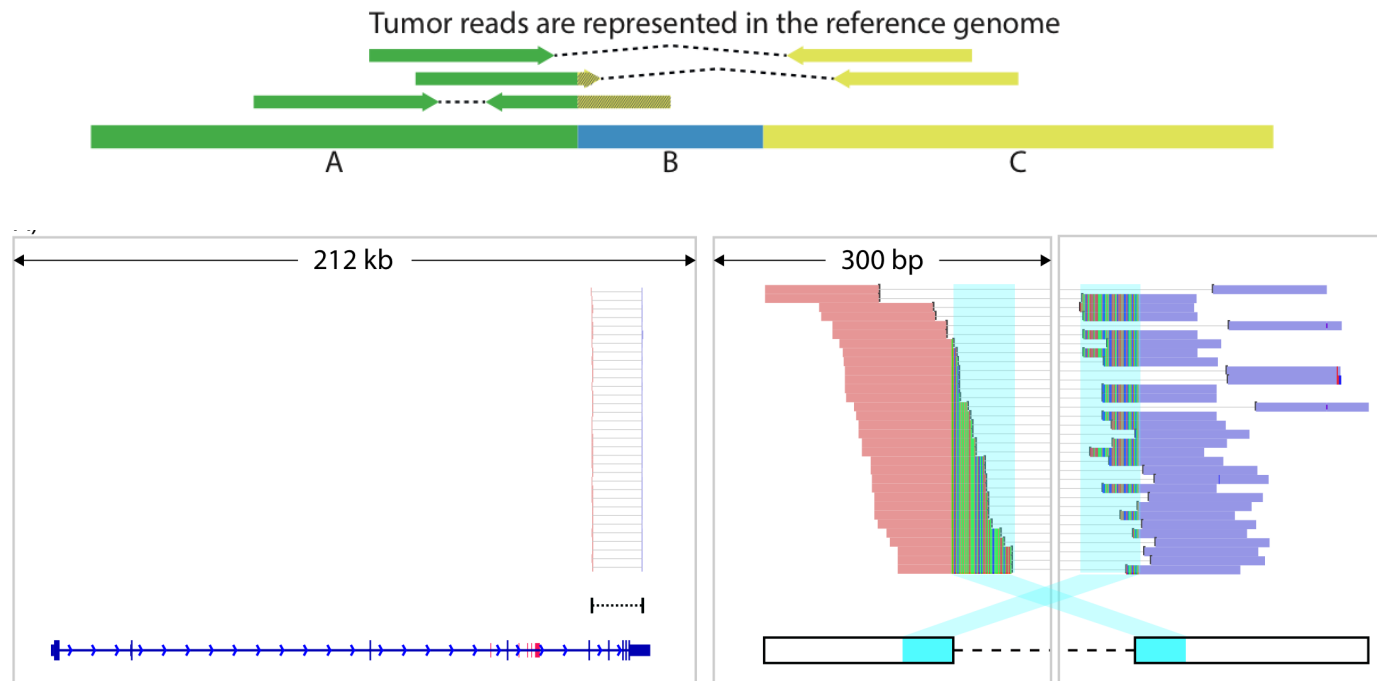
# An example, the androgen receptor in advanced prostate cancer

## Deletion



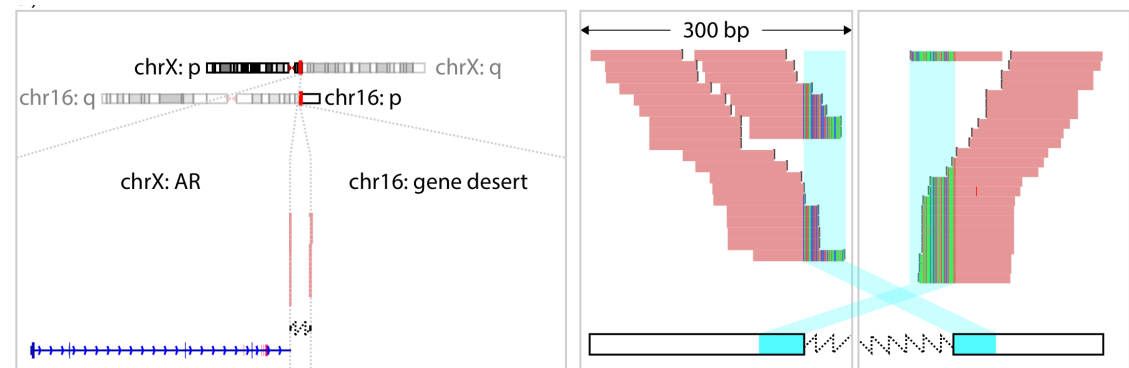
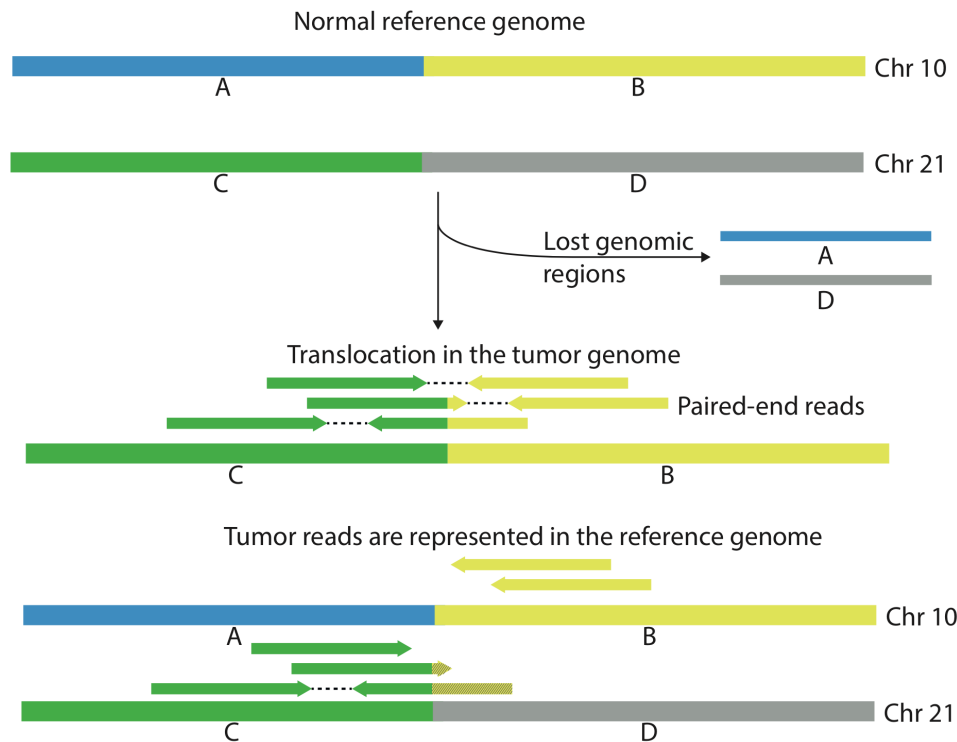
# An example, the androgen receptor in advanced prostate cancer

## Deletion



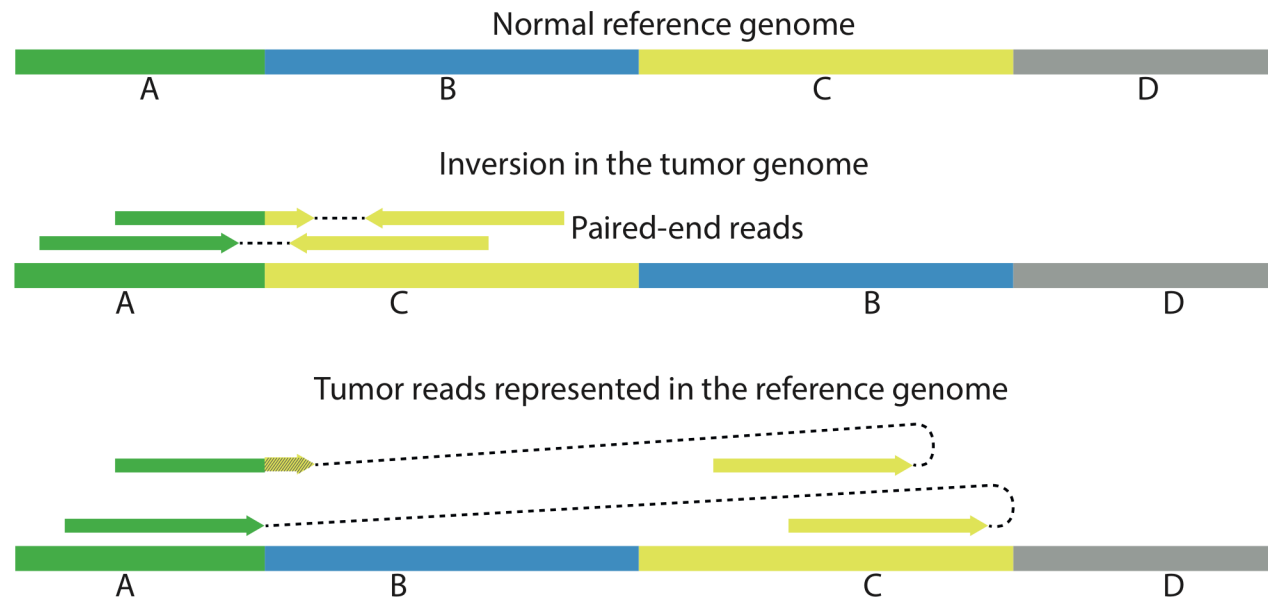
# Identifying structural variants using NGS

Translocation – similar as for deletions but on different chromosomes



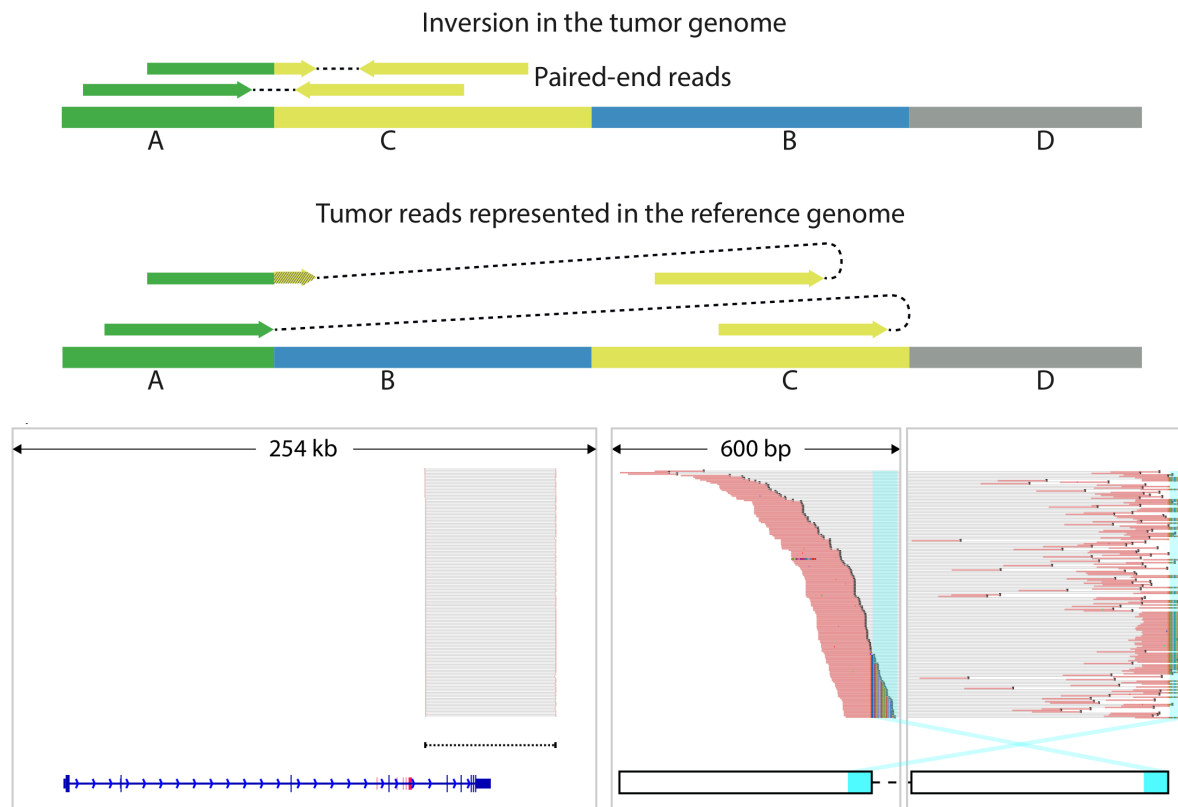
# Identifying structural variants using NGS

## Inversion



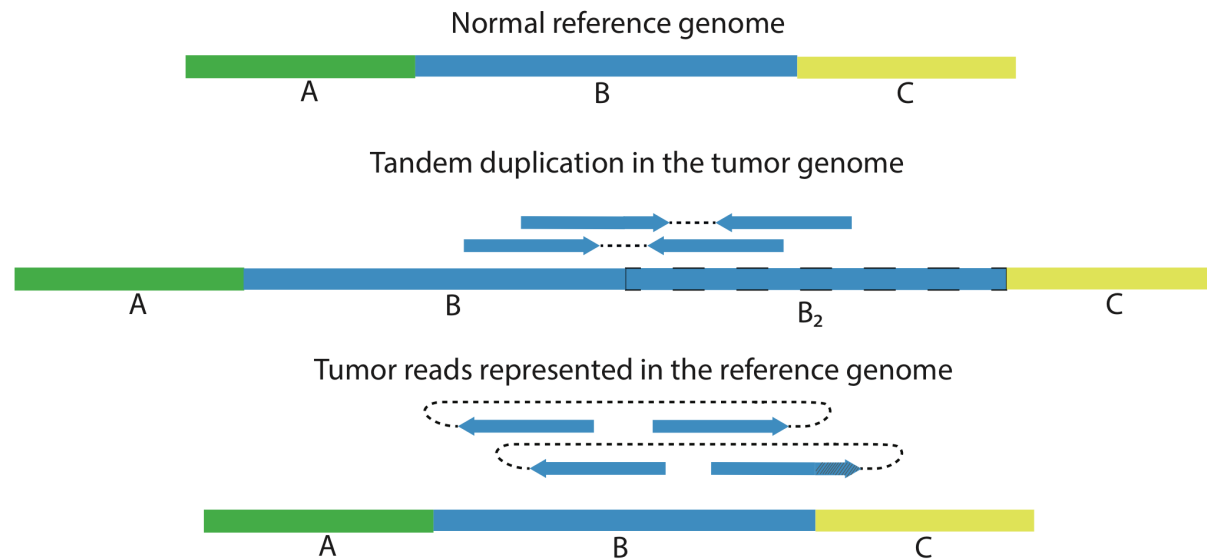
# An example, the androgen receptor in advanced prostate cancer

## Inversion



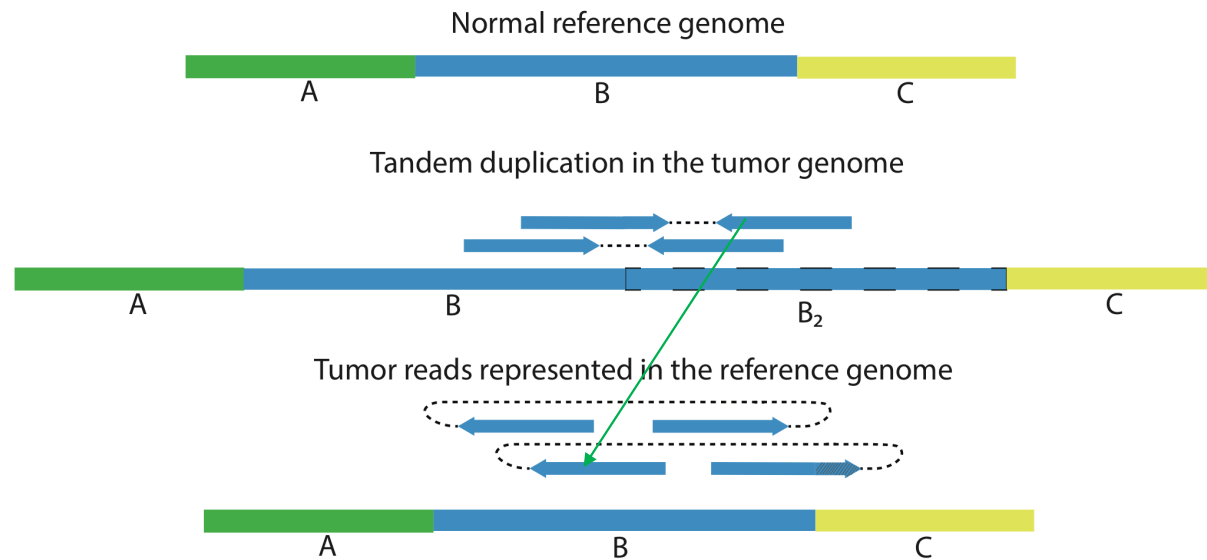
# Identifying structural variants using NGS

## Tandem duplication



# Identifying structural variants using NGS

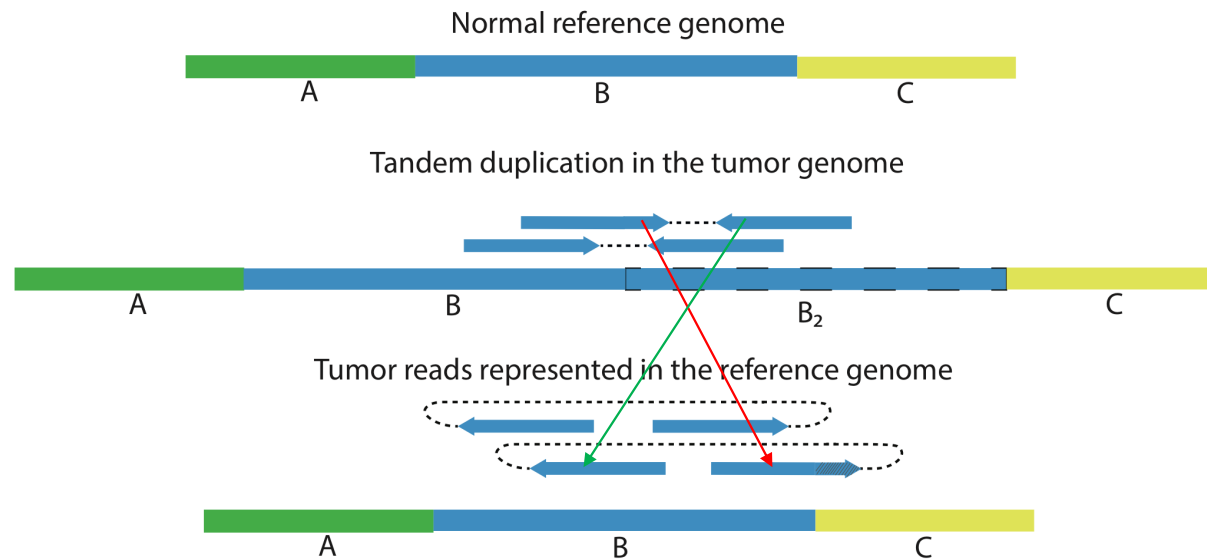
## Tandem duplication





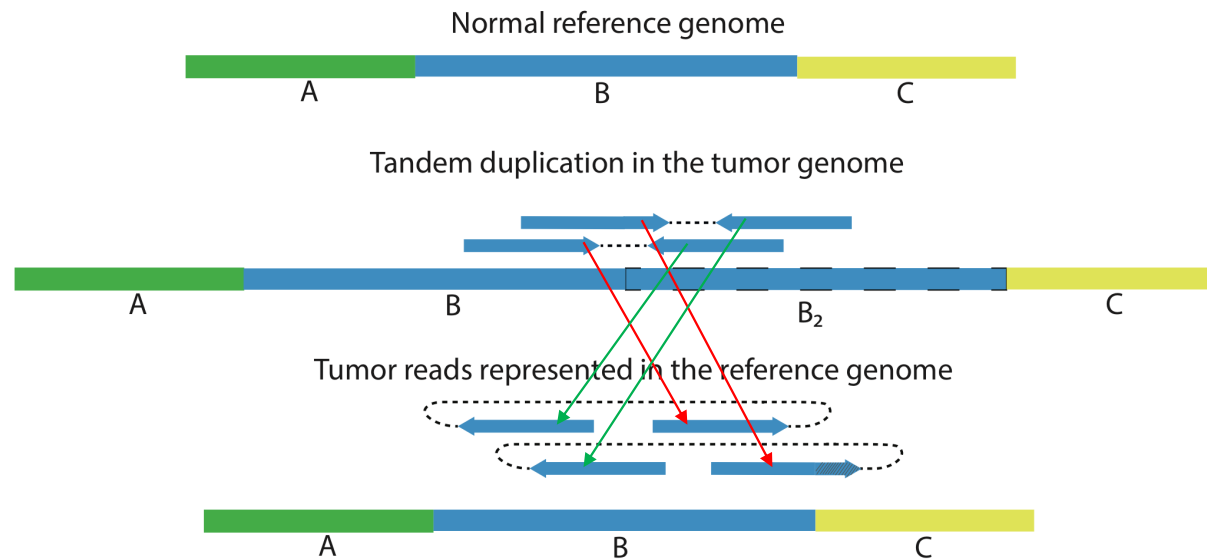
# Identifying structural variants using NGS

## Tandem duplication



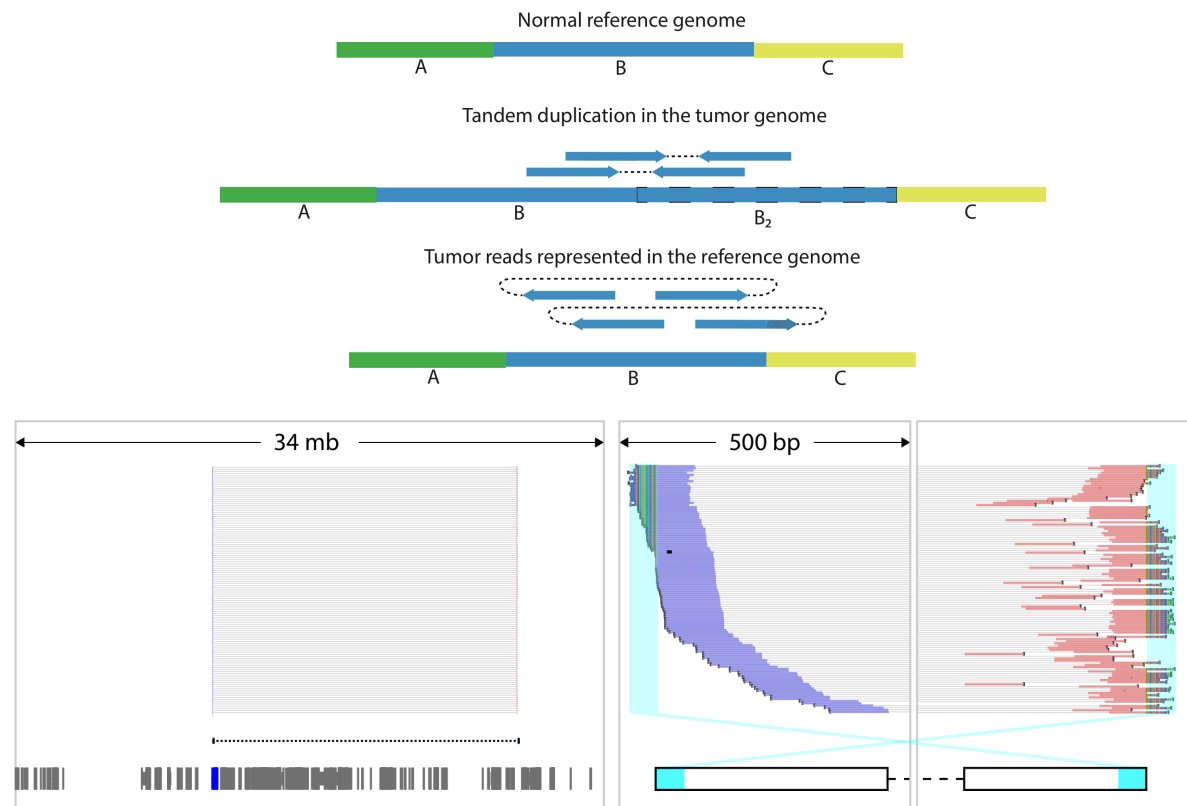
# Identifying structural variants using NGS

## Tandem duplication



# An example, the androgen receptor in advanced prostate cancer

## Tandem duplication



# Identifying structural variants

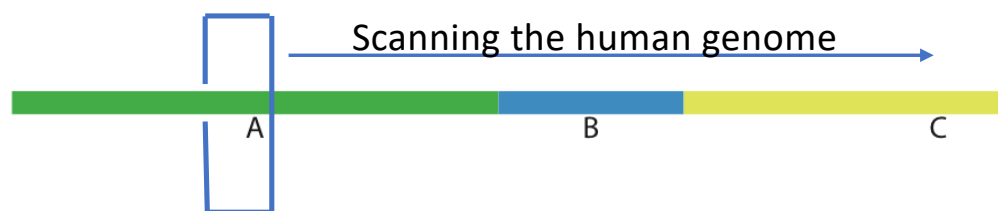
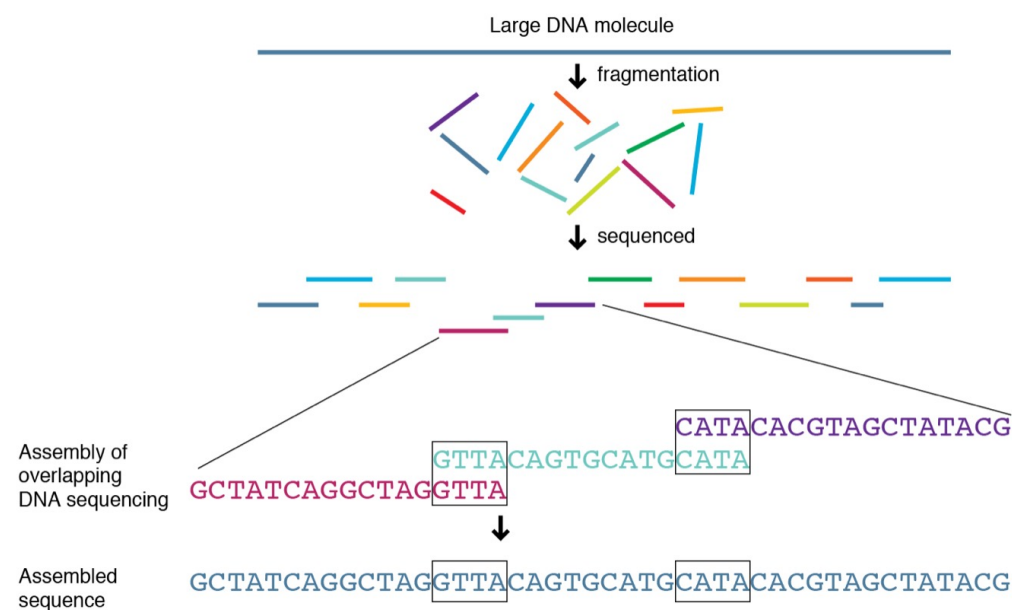


Table 1. SV detection methods and example SV callers

Method	Detection resolution	Detectable SV types	Detectable SV sizes	Example SV callers	References
Read-pair	Rough	All	Median size SV	BreakDancer	Chen et al. [14]
Split-read	Base pair	All	Small size SV	Pindel	Ye et al. [24]
Read-pair and split-read	Base pair	All	Depend on filtering/scoring	Delly	Rausch et al. [29]
Read-pair, split-read and local <b>assembly</b>	Base pair	All	Depend on filtering/scoring	Lumpy	Layer et al. [30]
				Manta	Chen et al. [33]
				GRIDSS	Cameron et al. [26]
				SvABA	Wala et al. [27]



## Structural rearrangement paper from ICGC

- WGS of 2658 cancers across 38 tumour types.
- Pattern and signature analysis of structural variants.
- Propose classification and annotation scheme.

### Article

## Patterns of somatic structural variation in human cancer genomes

<https://doi.org/10.1038/s41586-019-1913-9>

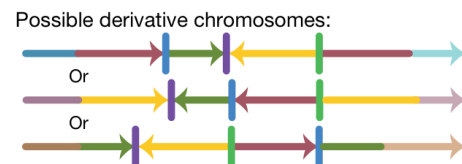
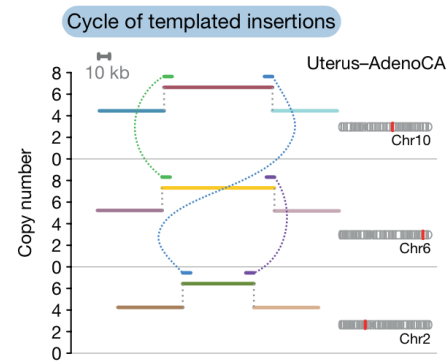
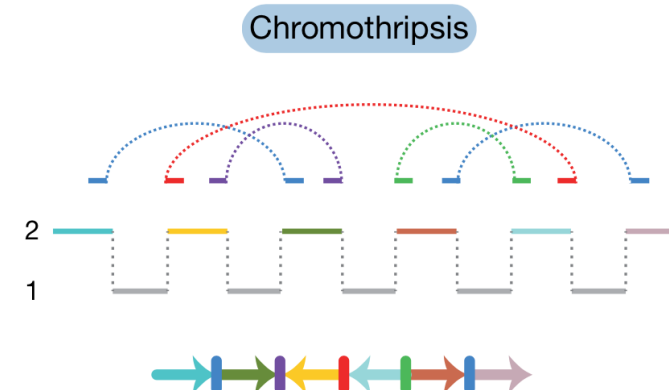
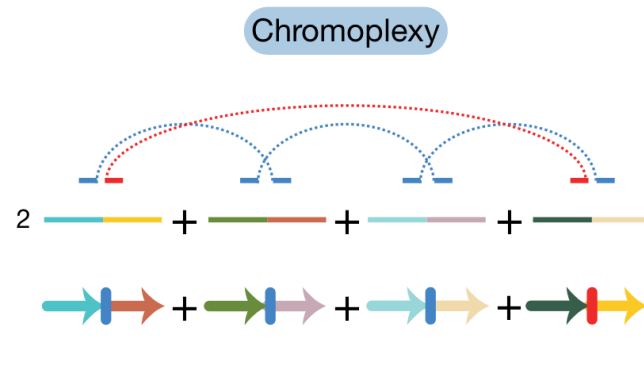
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Yilong Li<sup>1,2,14</sup>, Nicola D. Roberts<sup>1,14</sup>, Jeremiah A. Wala<sup>3,4,5,14</sup>, Ofer Shapira<sup>3,4,5,14</sup>, Steven E. Schumacher<sup>3,4,5</sup>, Kiran Kumar<sup>3,4,5</sup>, Ekta Khurana<sup>6</sup>, Sebastian Waszak<sup>7</sup>, Jan O. Korbel<sup>7</sup>, James E. Haber<sup>8</sup>, Marcin Imielinski<sup>9</sup>, PCAWG Structural Variation Working Group<sup>10</sup>, Joachim Weischenfeldt<sup>11\*</sup>, Rameen Beroukhim<sup>3,4,5\*</sup>, Peter J. Campbell<sup>11,12\*</sup> & PCAWG Consortium<sup>13</sup>

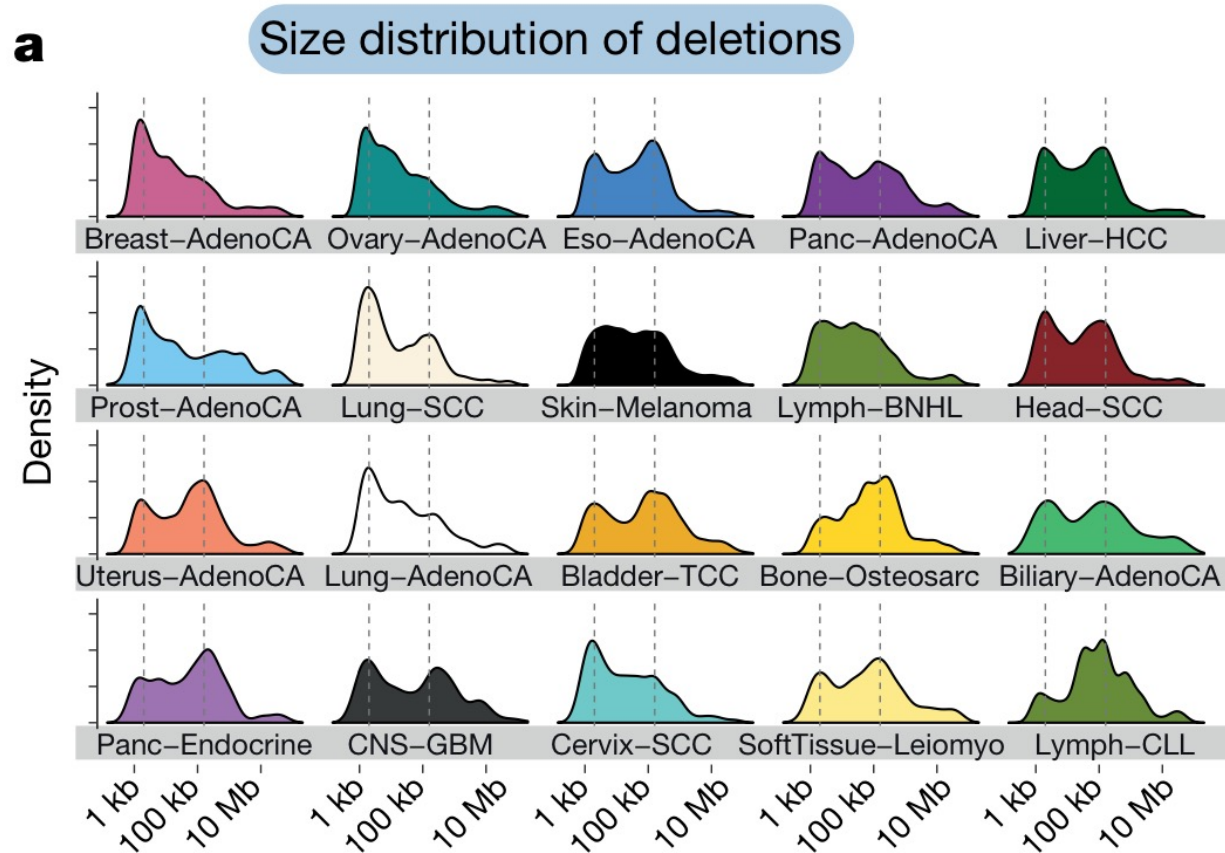
# Structural rearrangement paper from ICGC



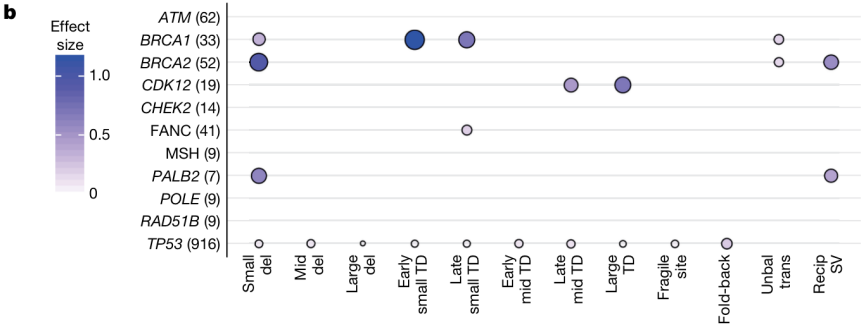
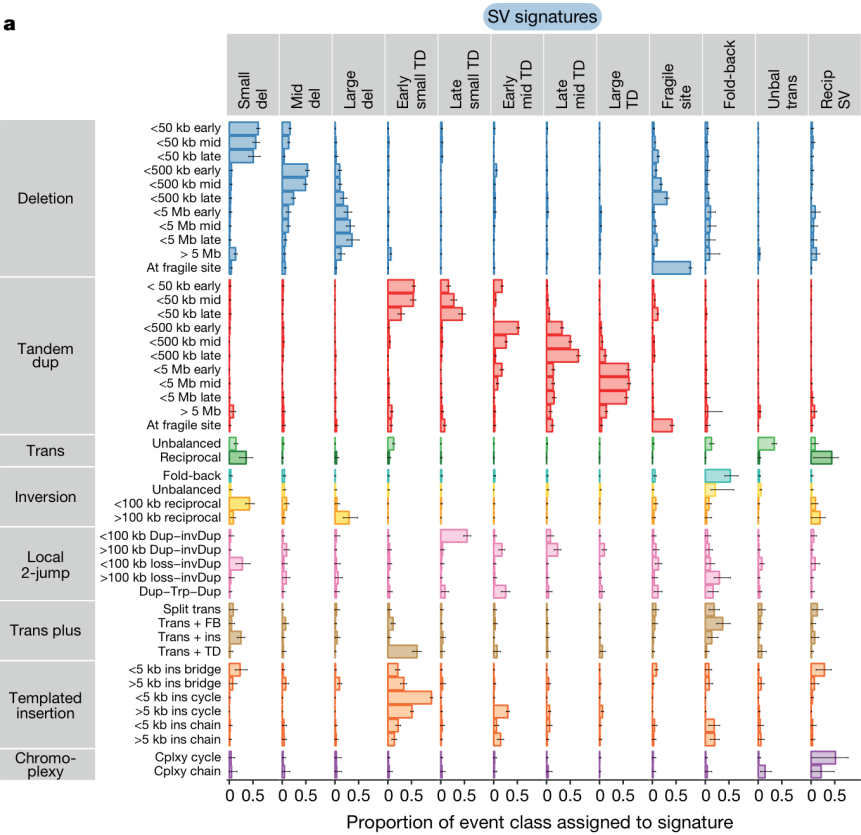
Other types as well ...

Patterns of somatic structural variation in human cancer genomes

Disturbingly many short ones ..

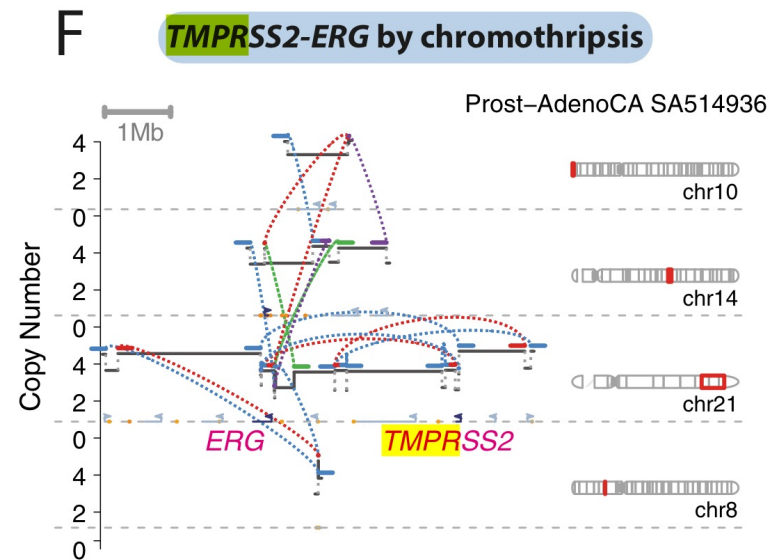
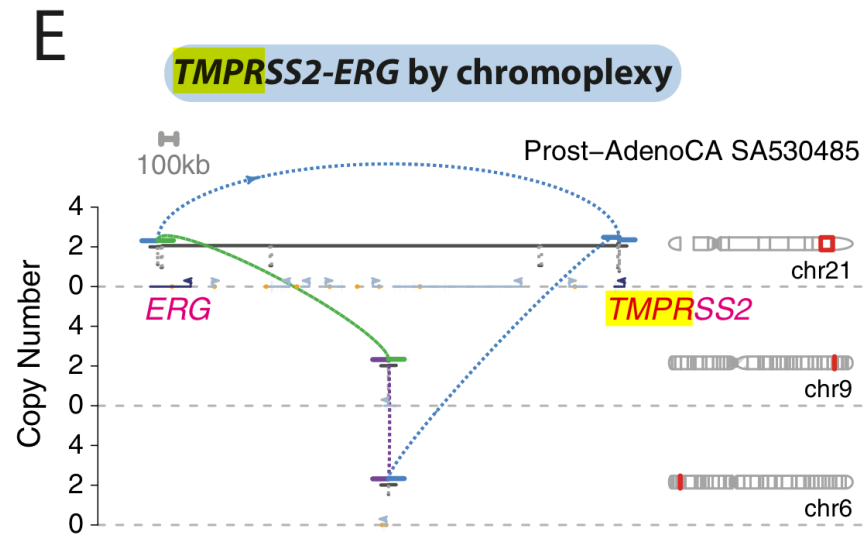


# Structural rearrangements as signatures



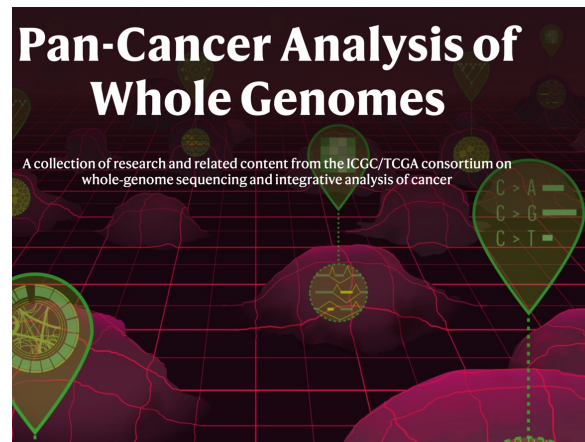


Hard to pick up with targeted sequencing!



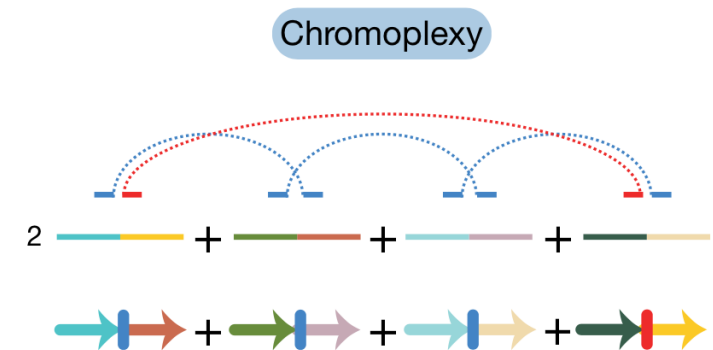
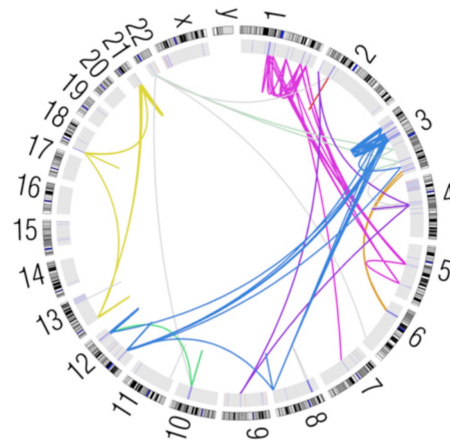
## Flagship paper from the ICGC

- Whole genome sequencing (wgs) of 2,605 primary tumours and 173 metastases or local recurrences
- RNA-sequencing data were available for 1,222 donors
- Mean age: 56 years
- Largest data set so far with “no compromises”



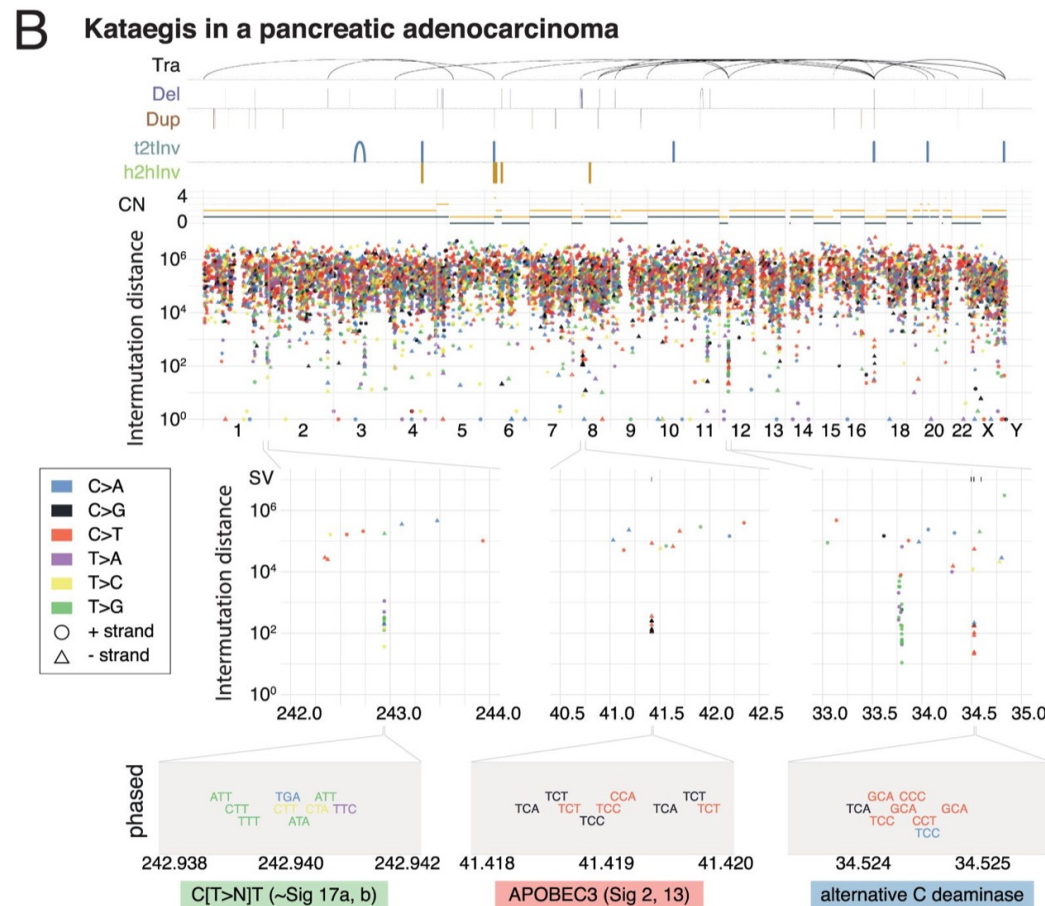
# Patterns of clustered mutations and SVs

- Chromoplexy
  - Repair of co-occurring double-stranded DNA breaks are glued together by the DNA repair machinery to create shuffled chains of rearrangements
- 17.8% of all cases



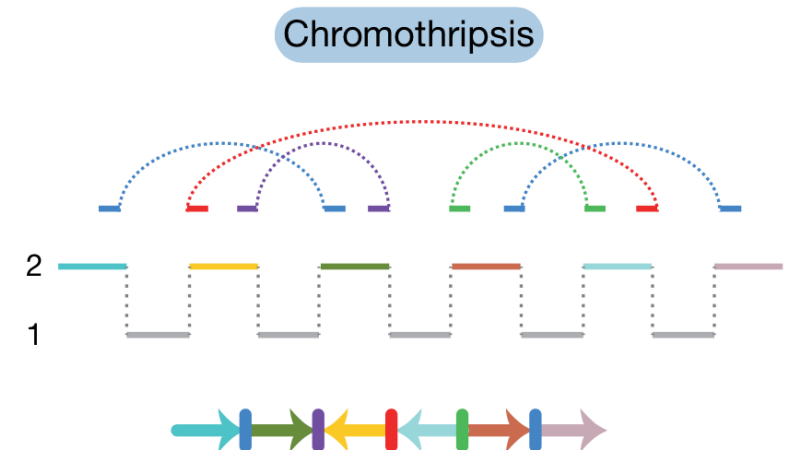
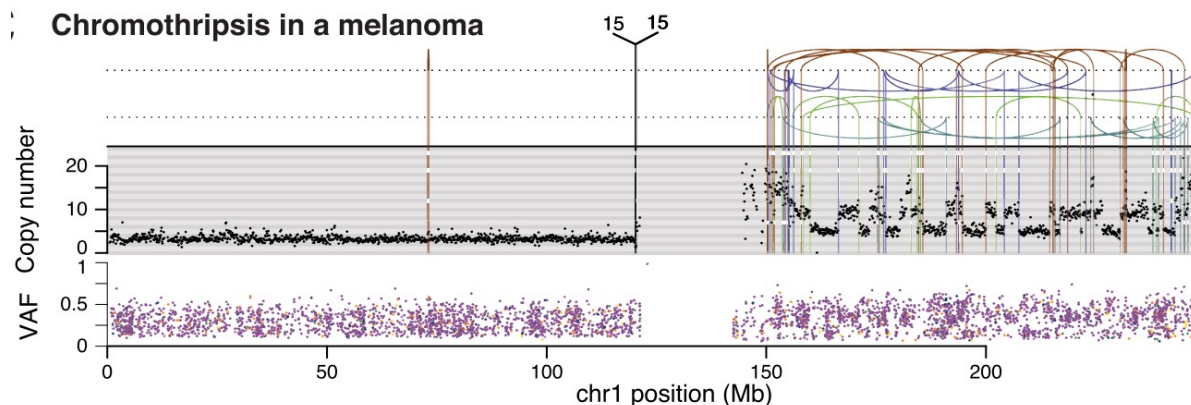
# Patterns of clustered mutations and SVs

- Kataegis
  - focal hypermutation process that leads to locally clustered nucleotide substitutions, biased towards a single DNA strand and often co-occurring with structural variants.
  - 60 % of all cases
  - APOBEC signature accounted for 81.7% of kataegis events and correlated positively with *APOBEC3B* expression levels, somatic SV burden and age at diagnosis
- Beware – can give false tumor mutational burden estimates

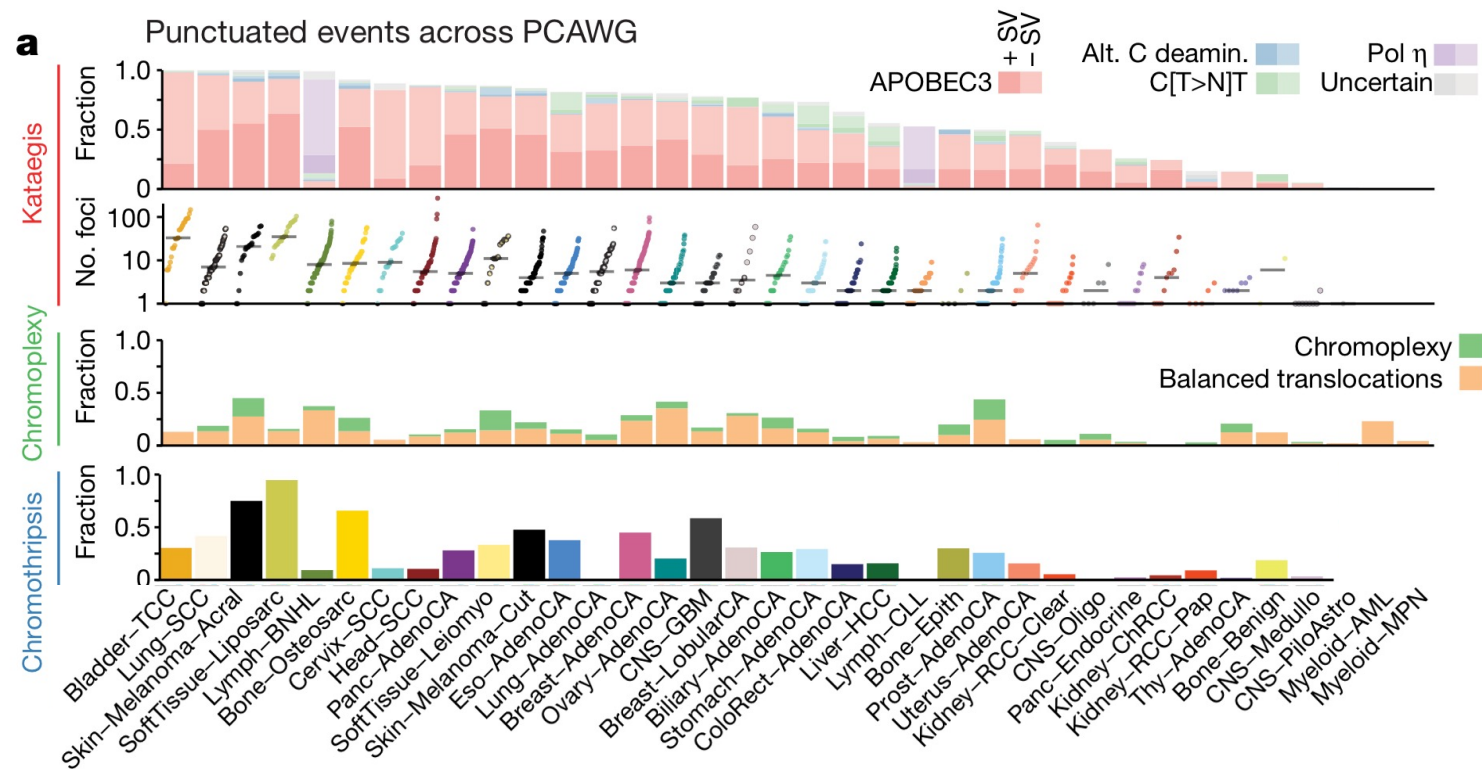


# Patterns of clustered mutations and SVs

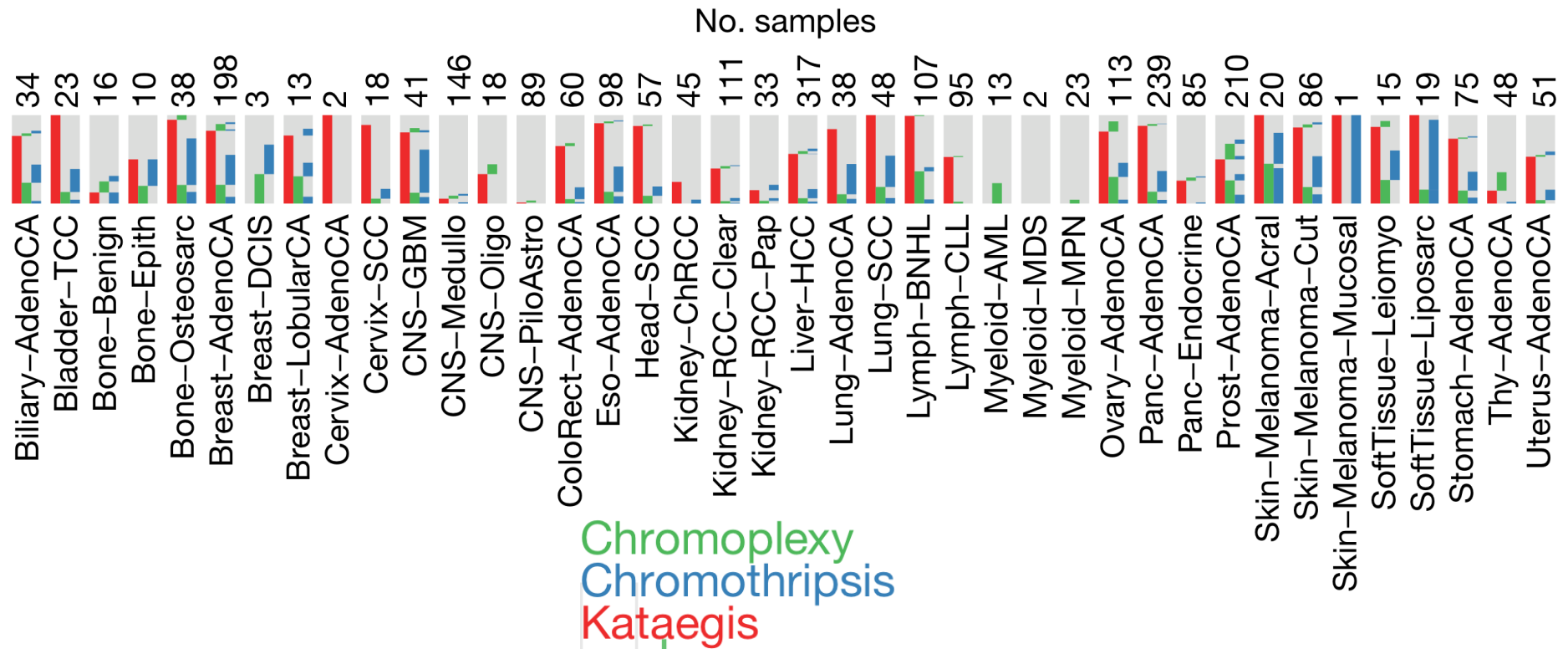
- Chromothripsis: Catastrophic event in which tens to hundreds of DNA breaks occur simultaneously and are glued back together randomly.
- 22.3% of all cases
- Correlated to whole genome duplications and TP53 alterations.
  - Pan-can OR: 3.22;  $P: 8.3 \times 10^{-35}$ ;
- Often lead to driver events



# Patterns of clustered mutations and SVs



# Co-occurrence of individual event types



# The end