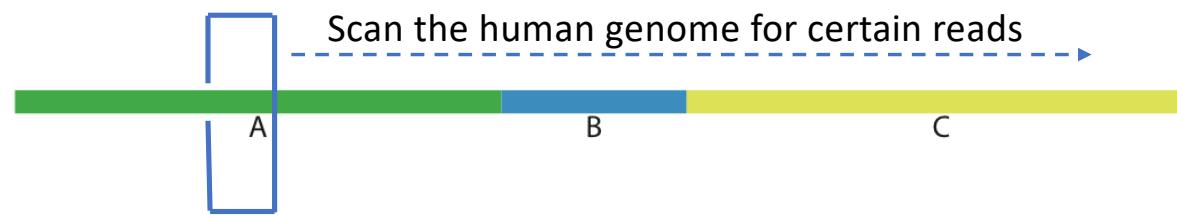
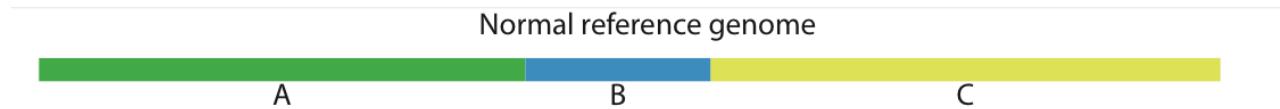


# Structural variant analysis using NGS

# Identifying structural variants

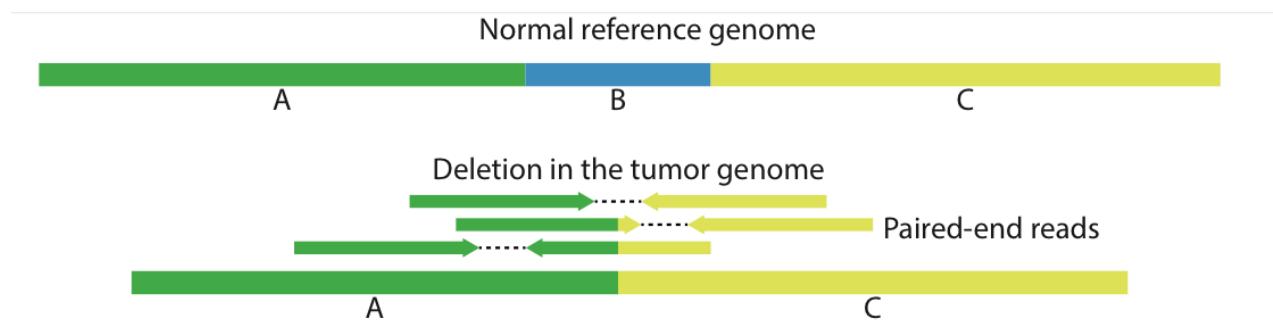


# Identifying structural variants using NGS



# Identifying structural variants using NGS

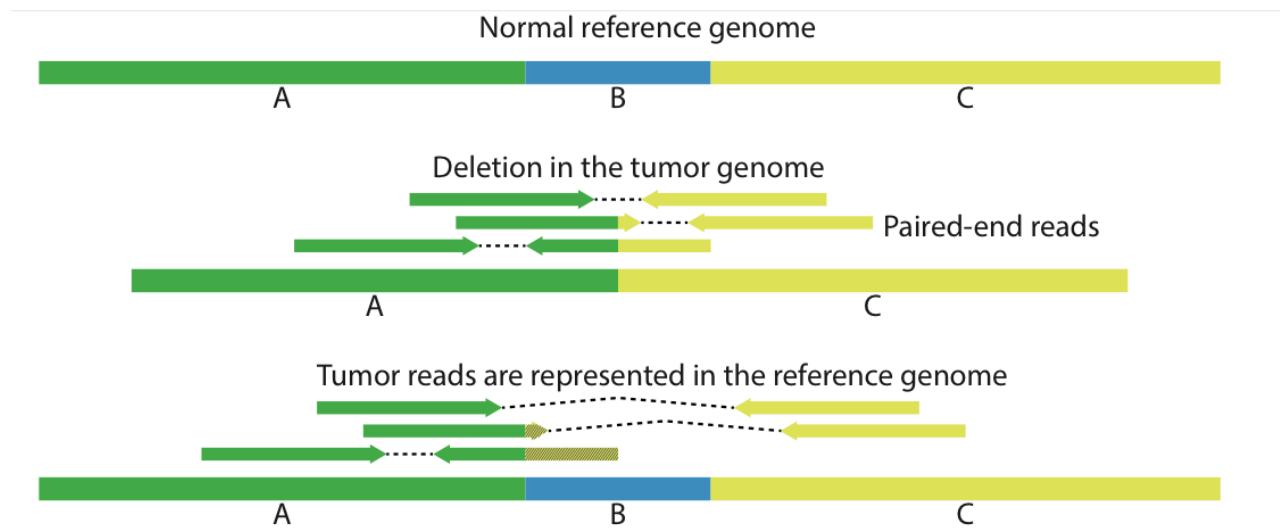
## Deletion



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

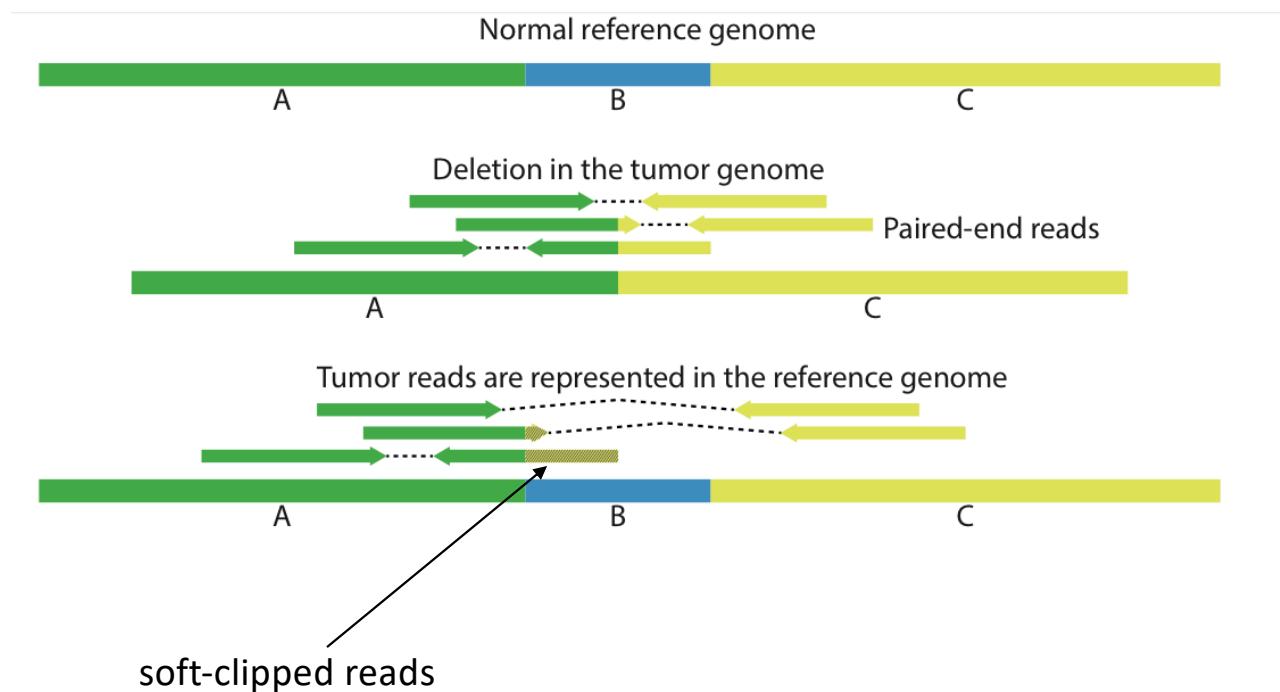
# Identifying structural variants using NGS

## Deletion



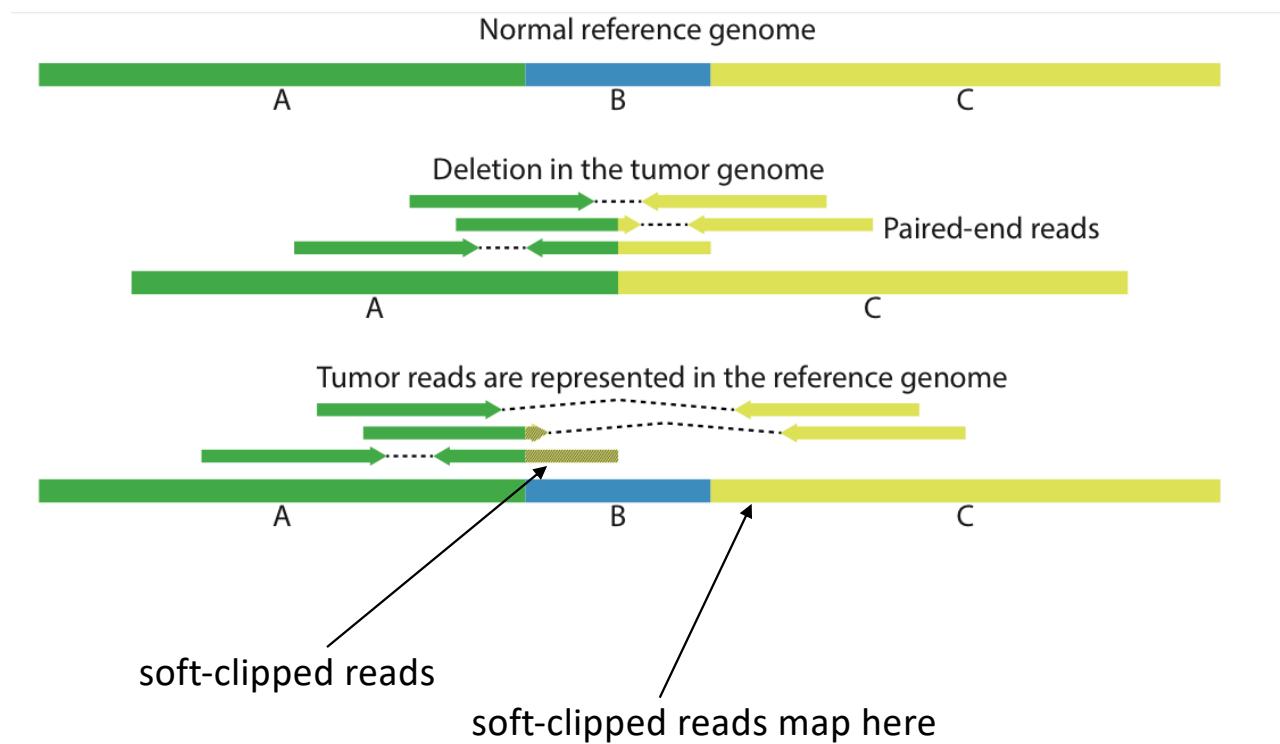
# Identifying structural variants using NGS

## Deletion



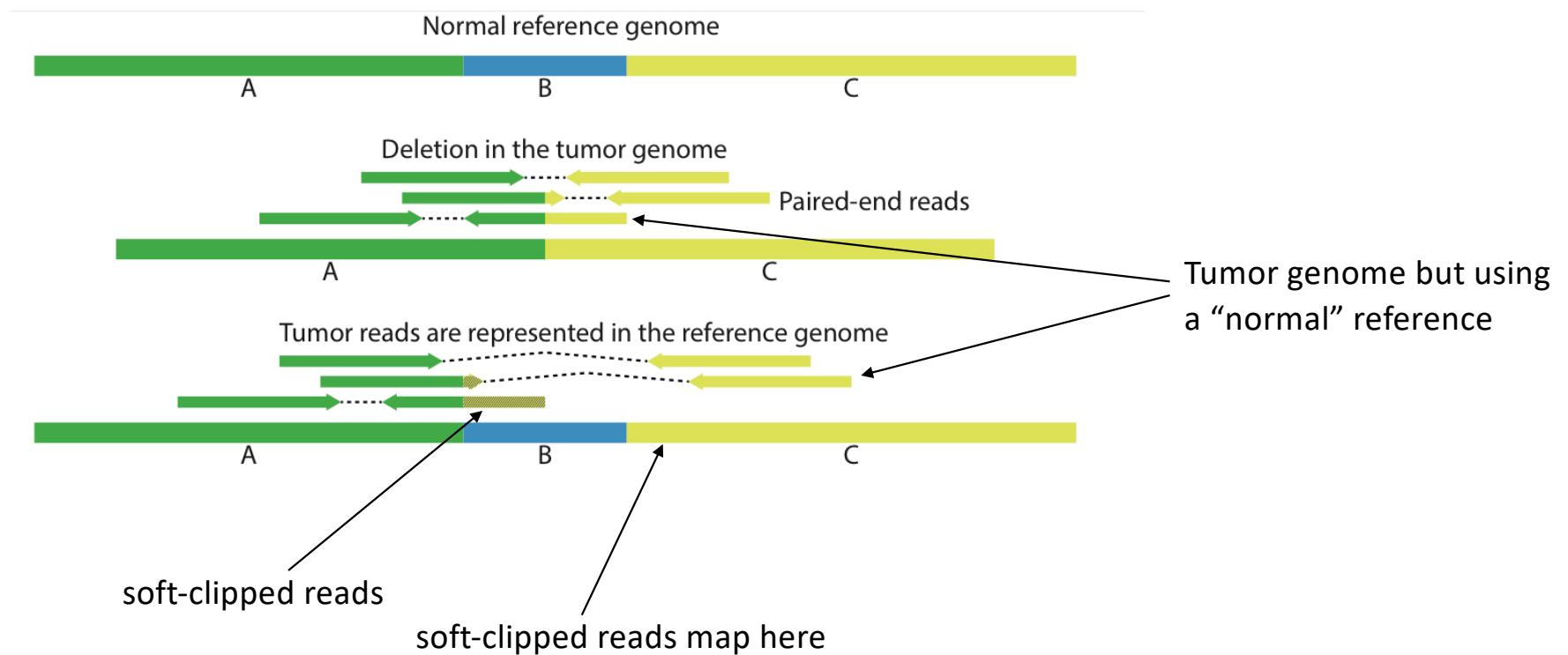
# Identifying structural variants using NGS

## Deletion



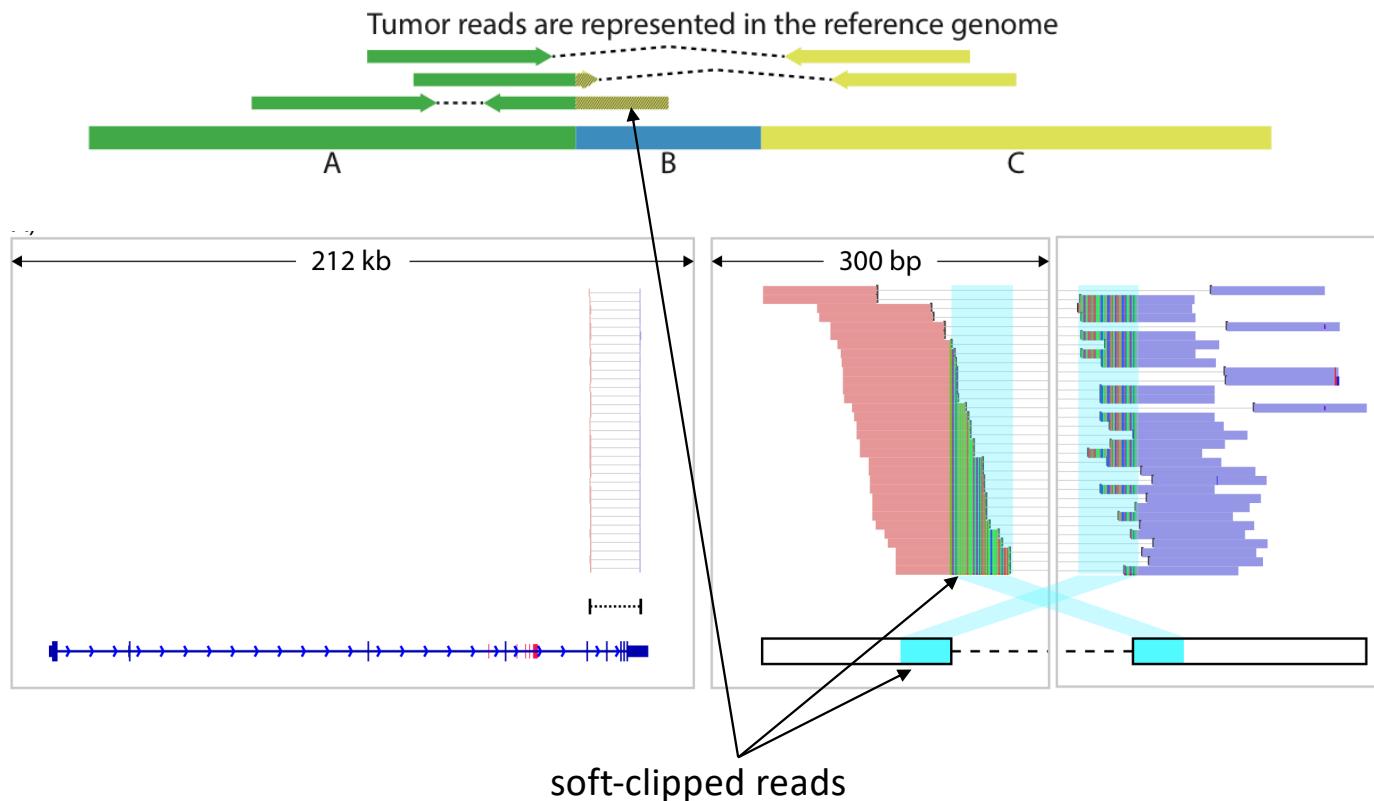
# Identifying structural variants using NGS

## Deletion



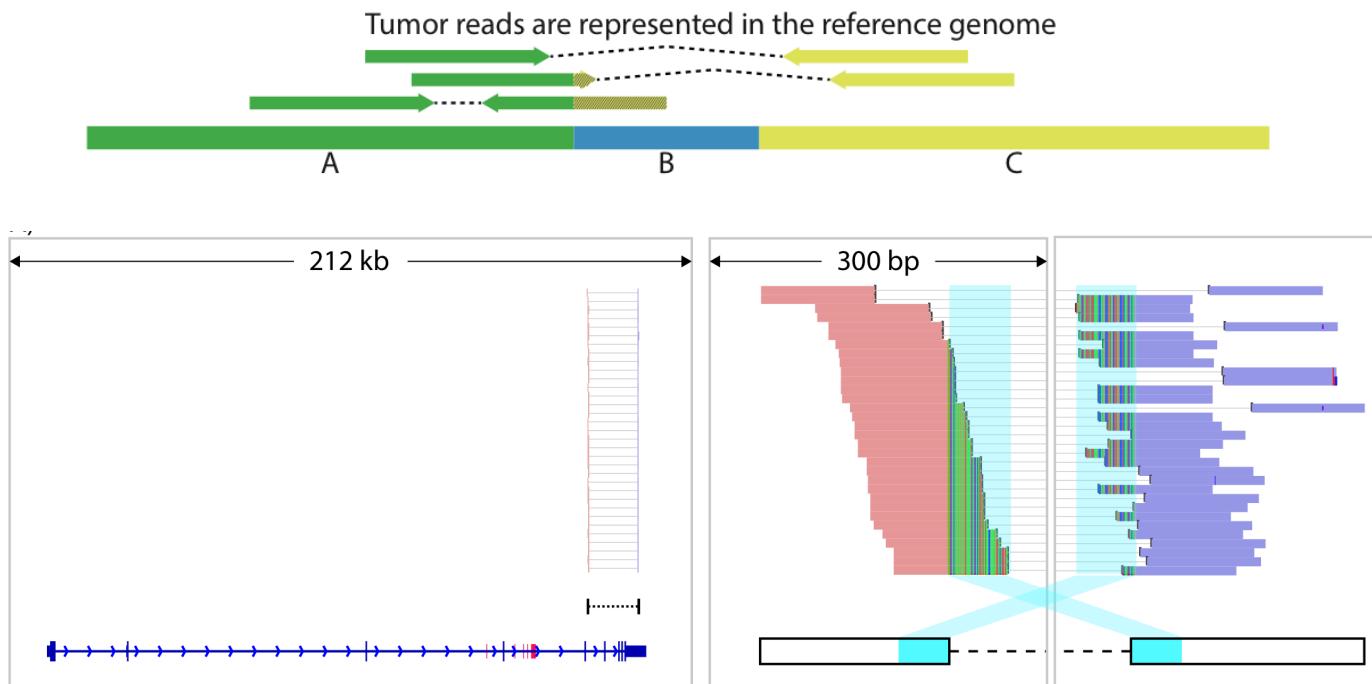
## An example, the androgen receptor in advanced prostate cancer

### Deletion



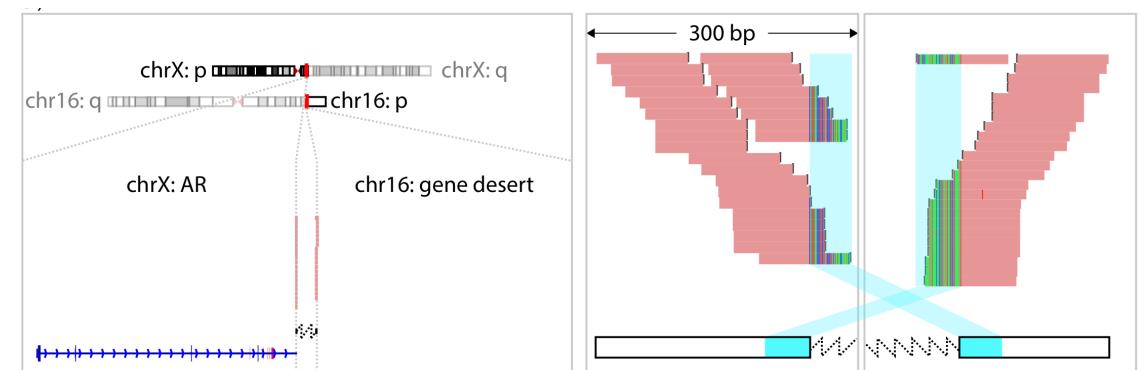
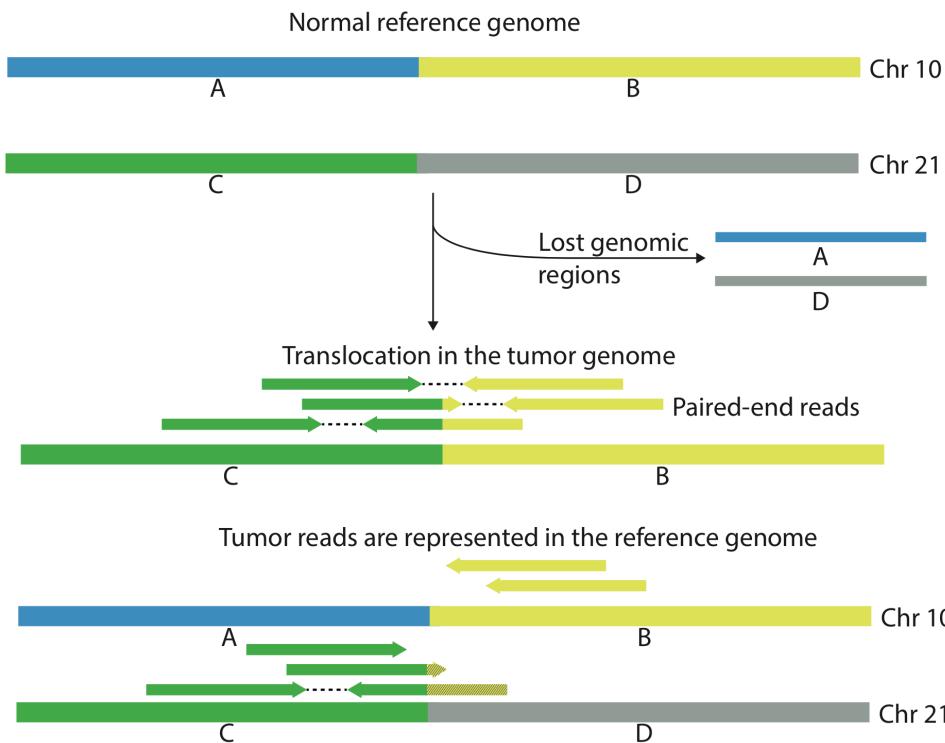
## An example, the androgen receptor in advanced prostate cancer

### Deletion



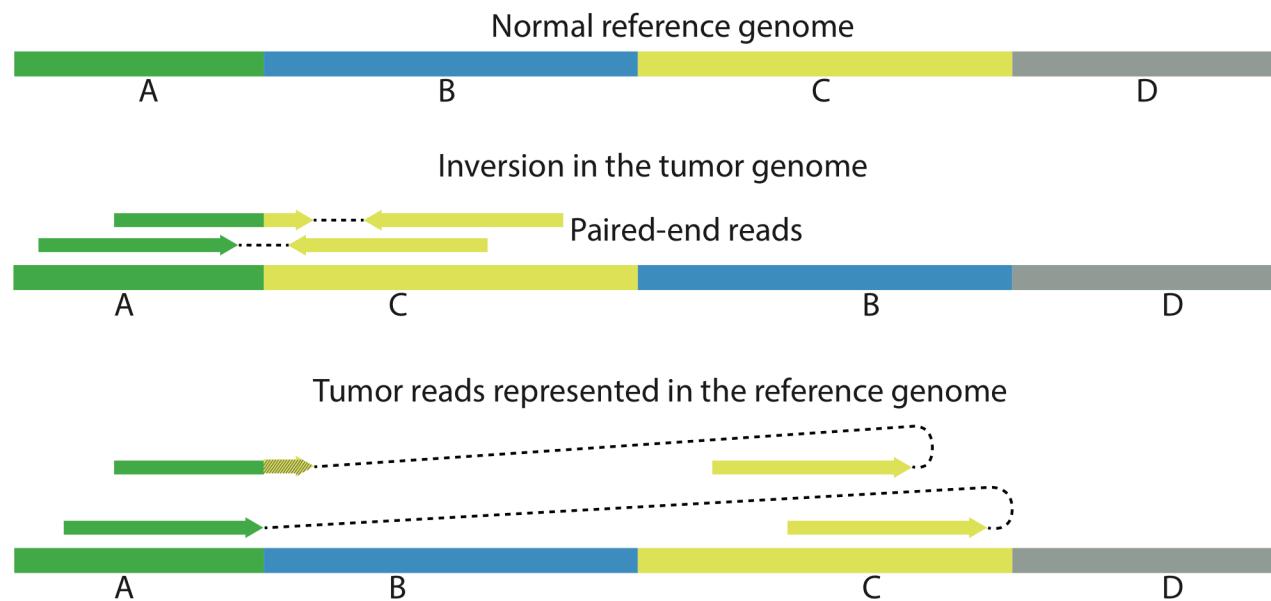
# Identifying structural variants using NGS

Translocation – similar as for deletions  
but on different chromosomes



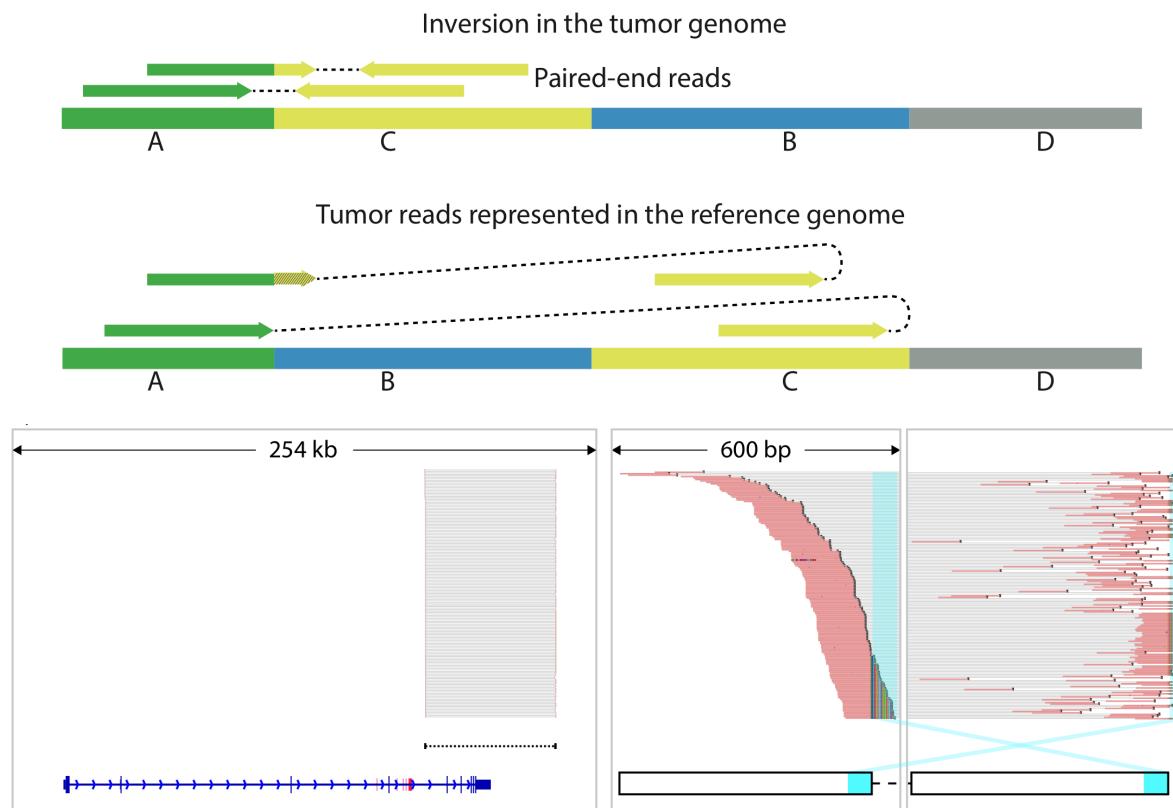
# Identifying structural variants using NGS

## Inversion



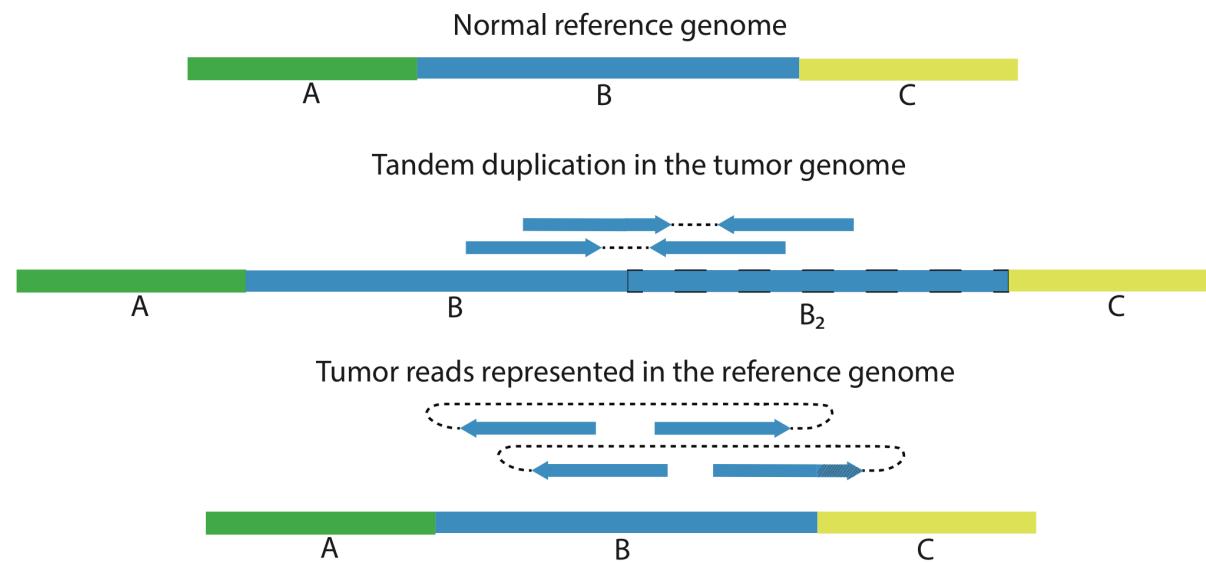
## An example, the androgen receptor in advanced prostate cancer

### Inversion



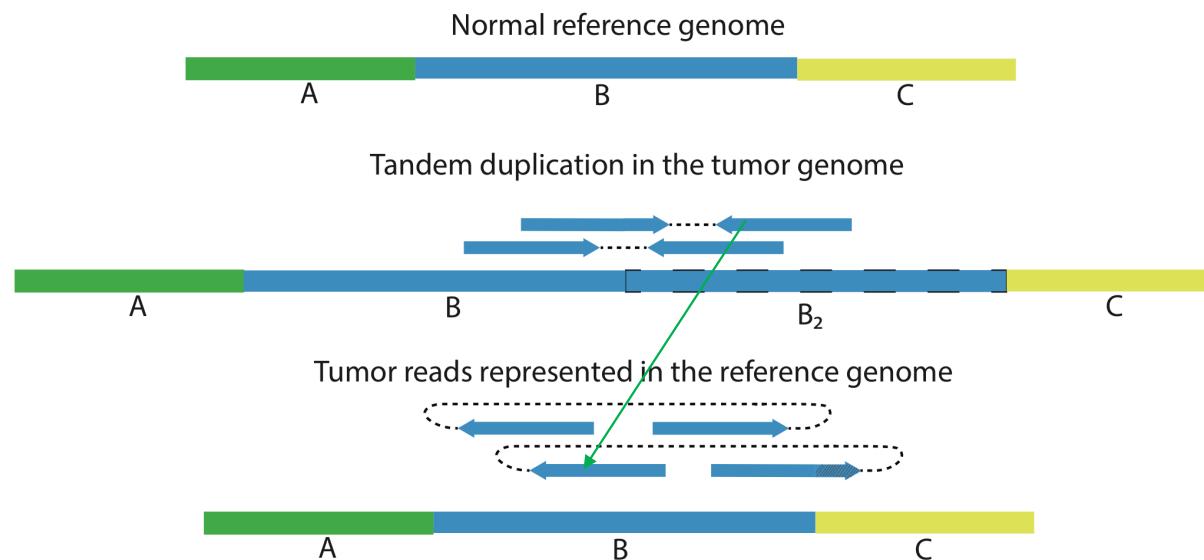
# Identifying structural variants using NGS

## Tandem duplication



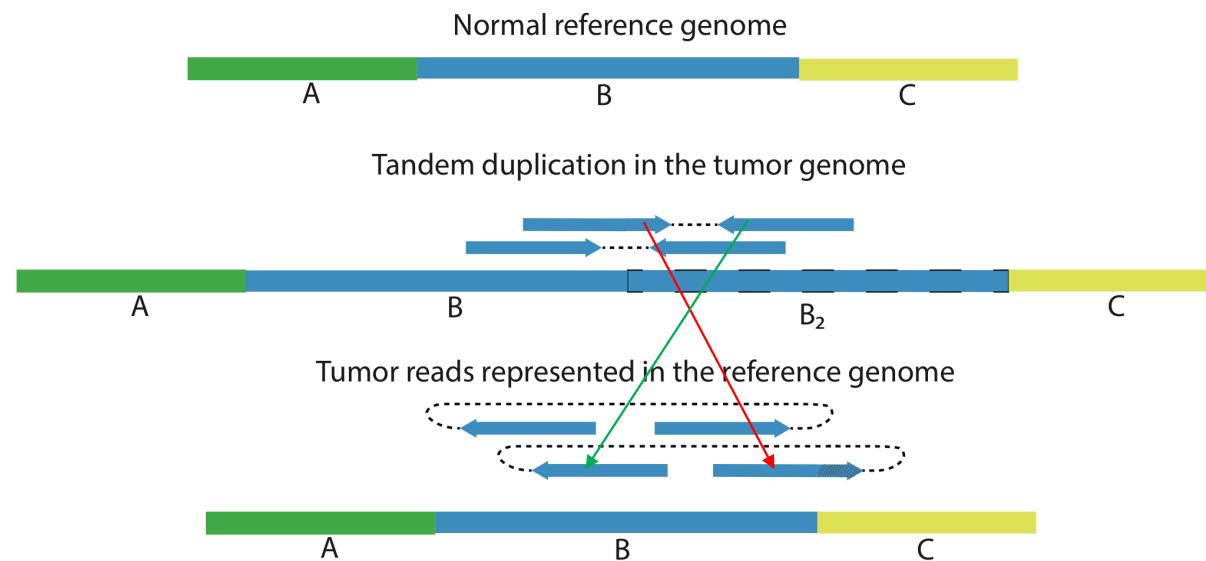
# Identifying structural variants using NGS

## Tandem duplication



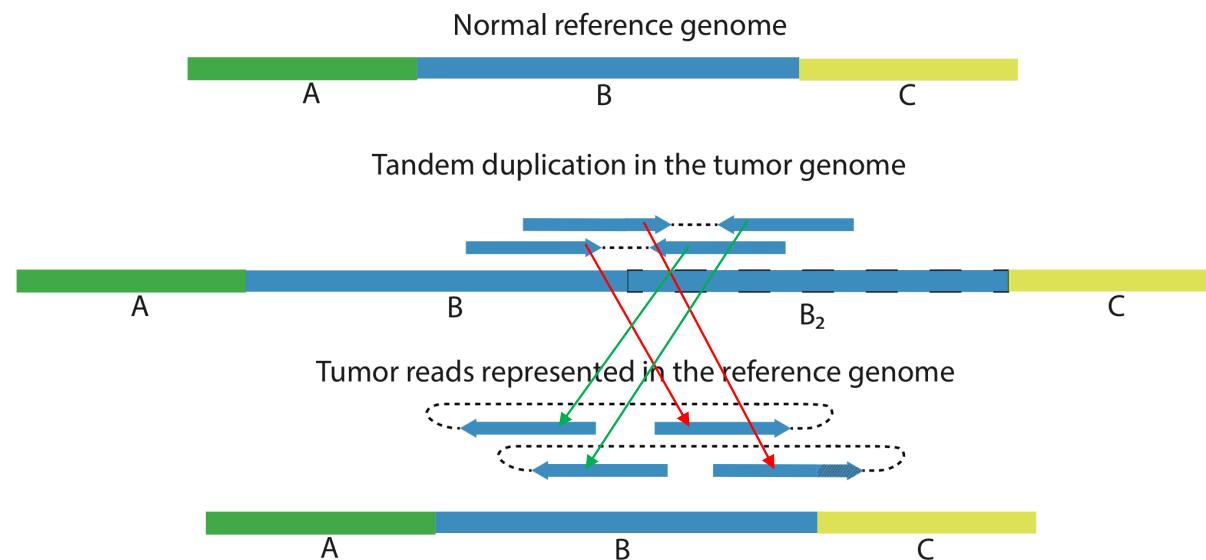
# Identifying structural variants using NGS

## Tandem duplication



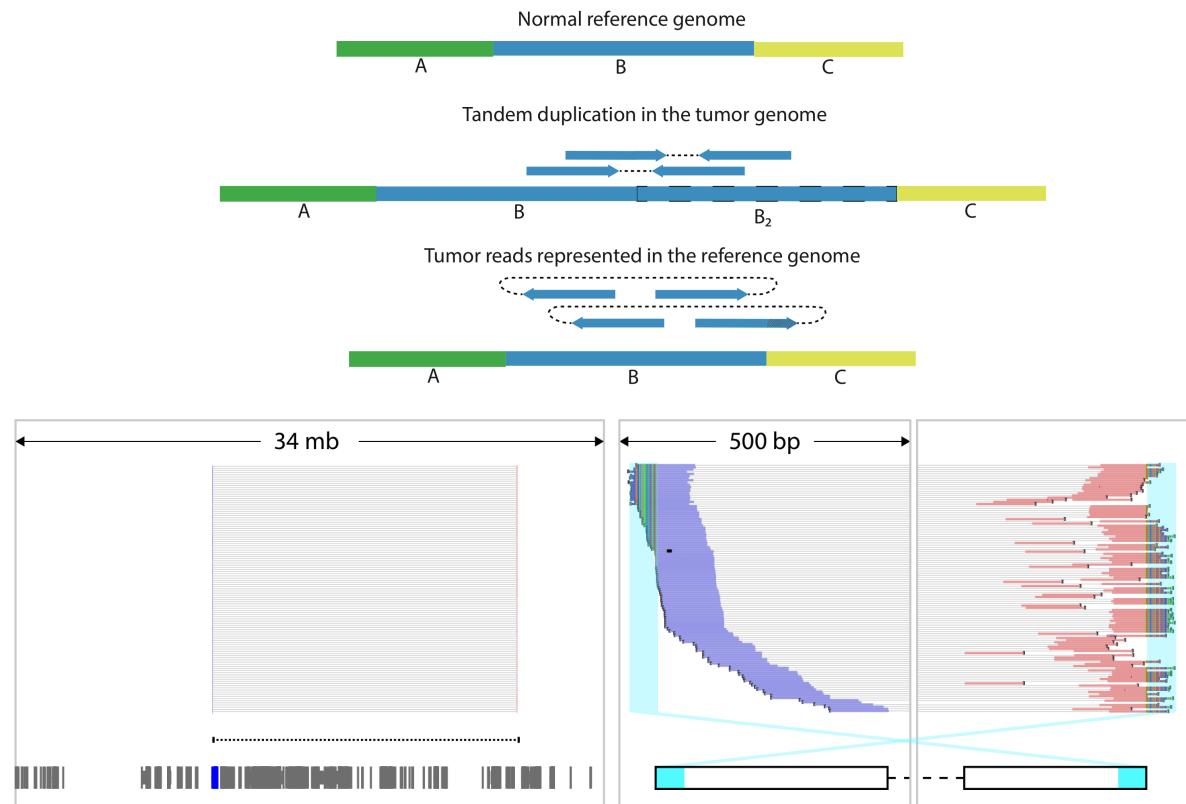
# Identifying structural variants using NGS

## Tandem duplication



An example, the androgen receptor in advanced prostate cancer

## Tandem duplication



# Identifying structural variants

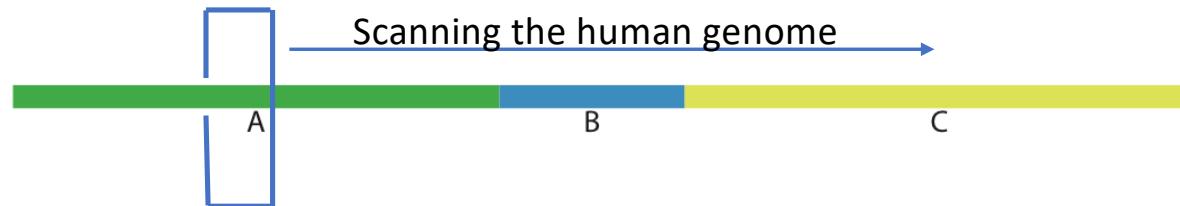
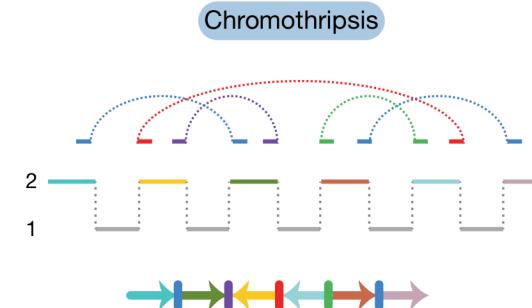
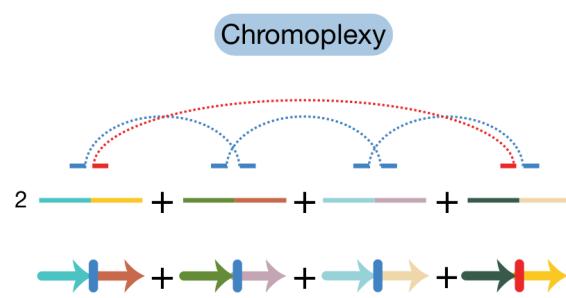


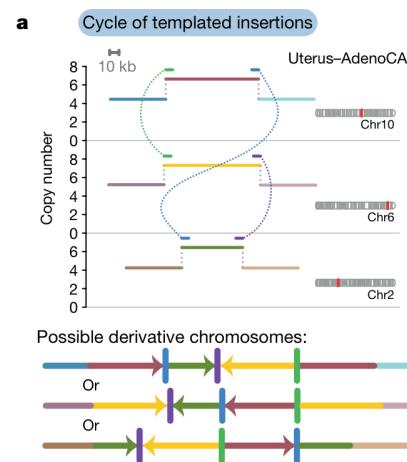
Table 1. SV detection methods and example SV callers

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-assembly	Base pair	All	Depend on filtering/scoring	Lumpy Manta GRIDSS SvABA	Layer et al. [30] Chen et al. [33] Cameron et al. [26] Wala et al. [27]

# Structural rearrangement paper from ICGC

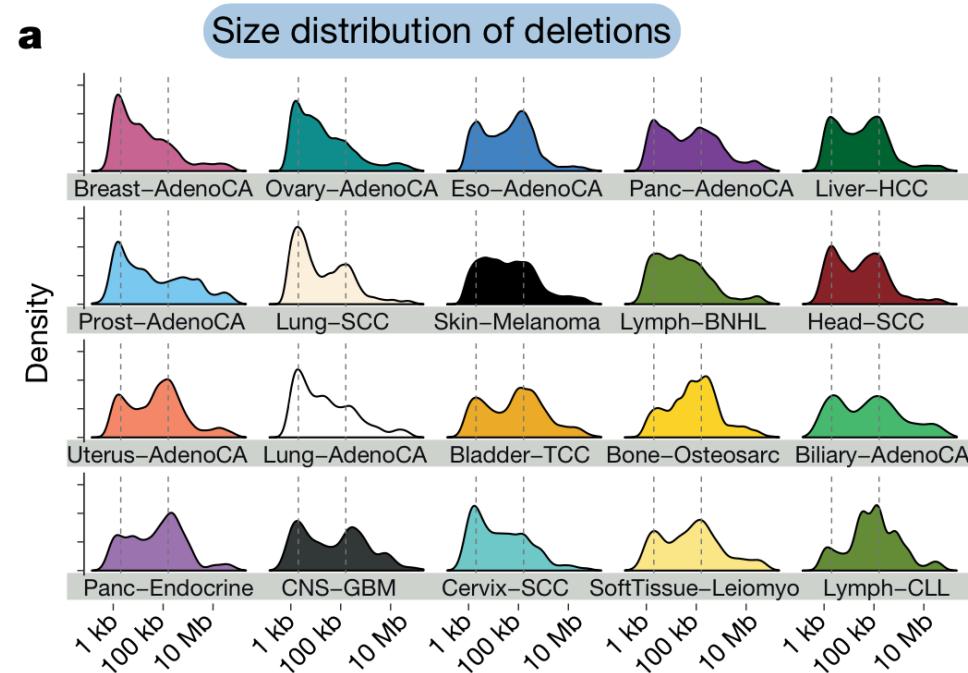


Other types as well ...

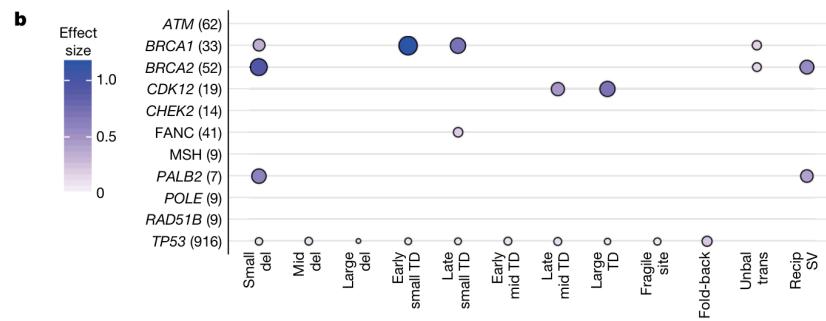
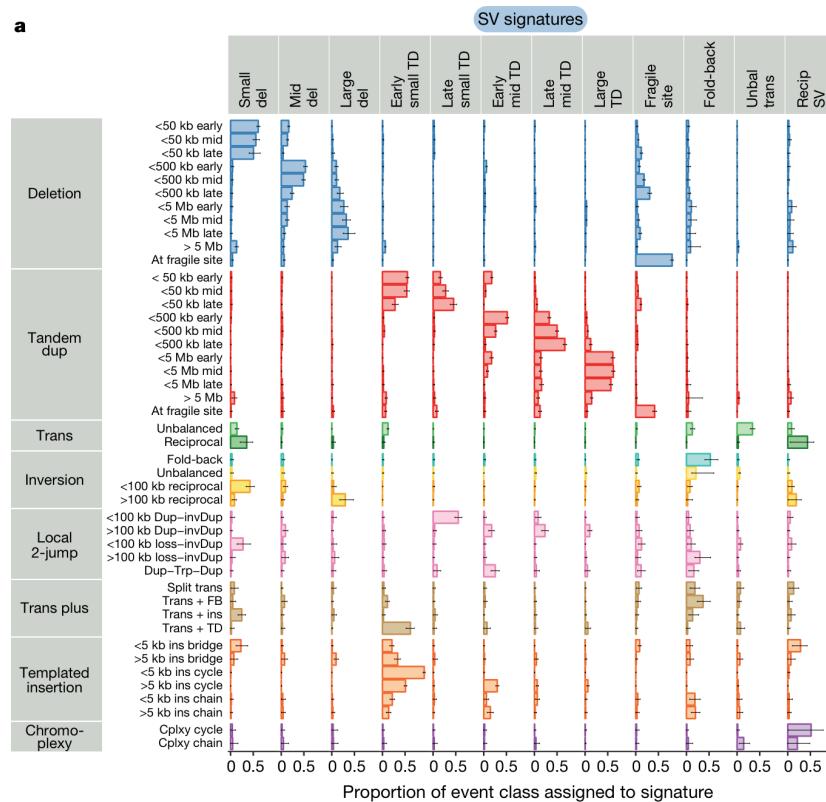


# Patterns of somatic structural variation in human cancer genomes

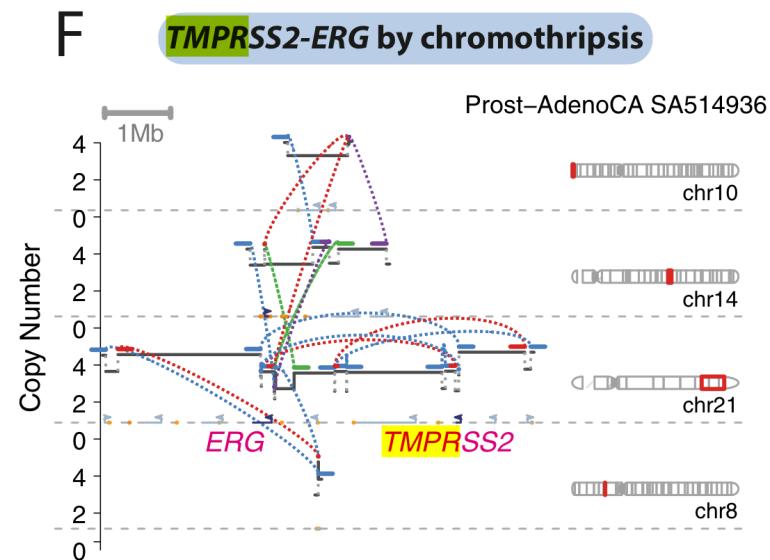
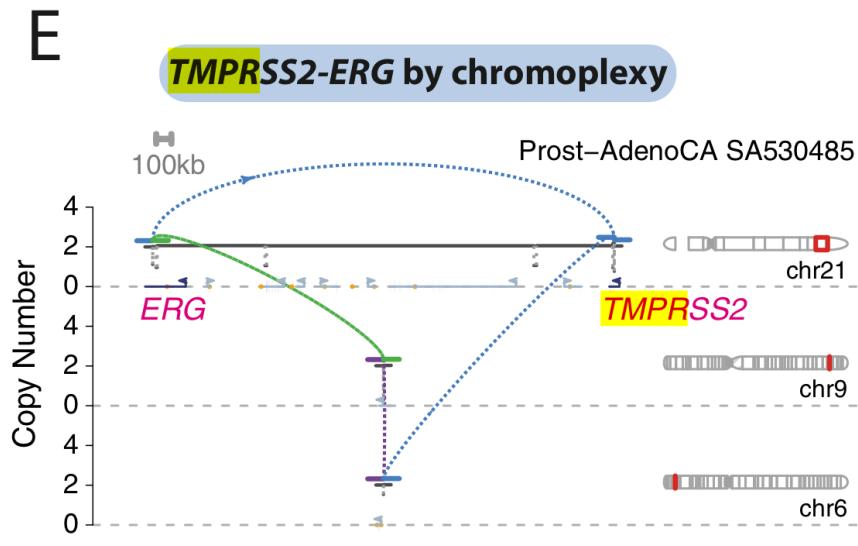
## Disturbingly many short ones ..



# Structural rearrangements as signatures

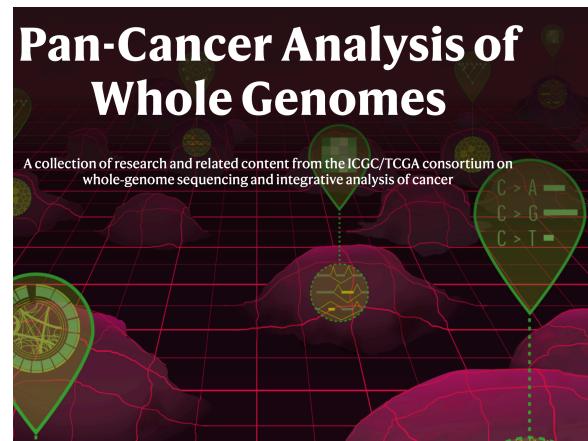


Hard to pick up with targeted sequencing!



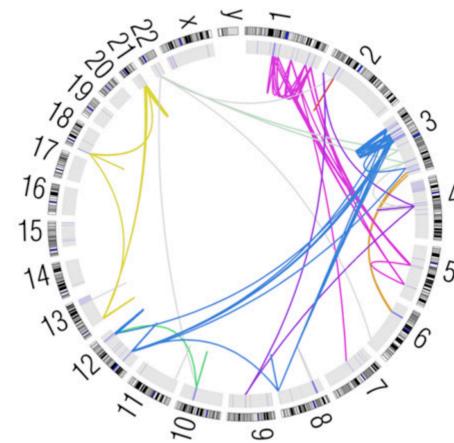
## Flagship paper from the ICGC

- 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”



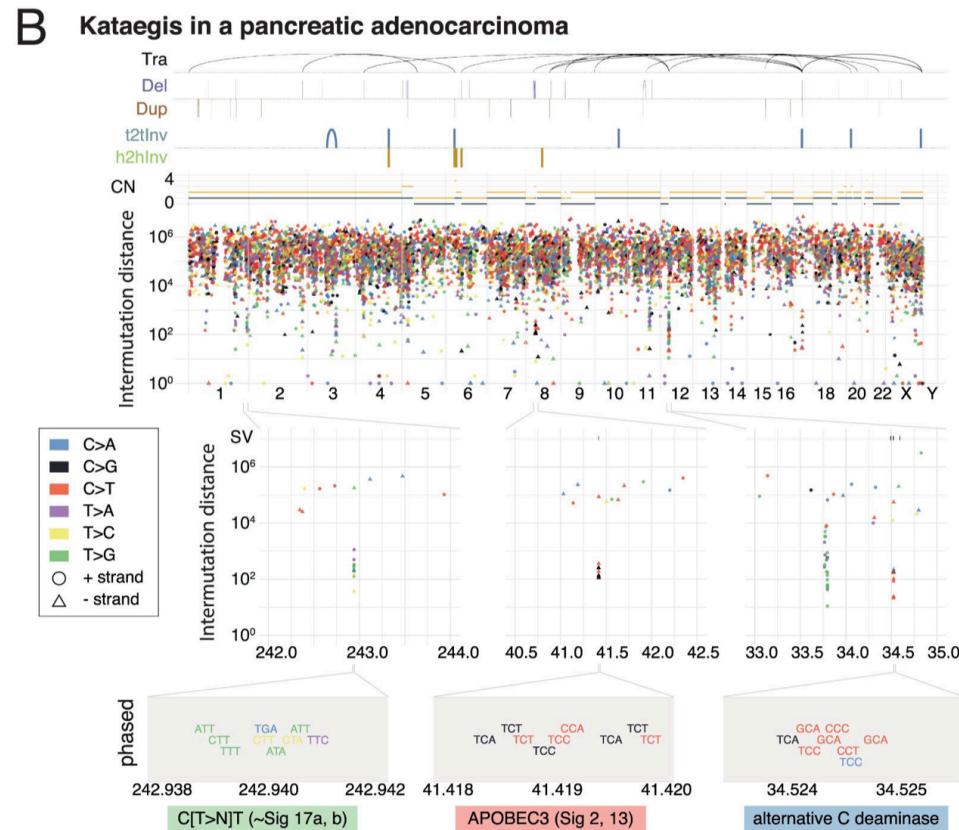
# Patterns of clustered mutations and SVs

- 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



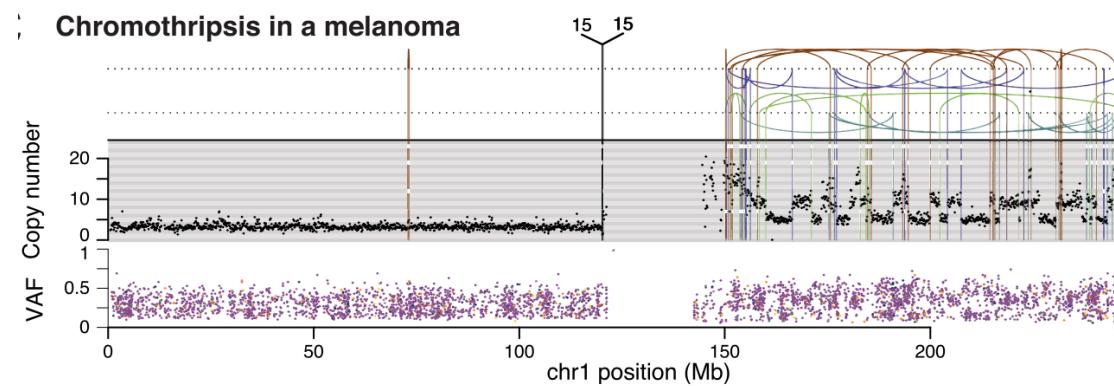
# Patterns of clustered mutations and SVs

- 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

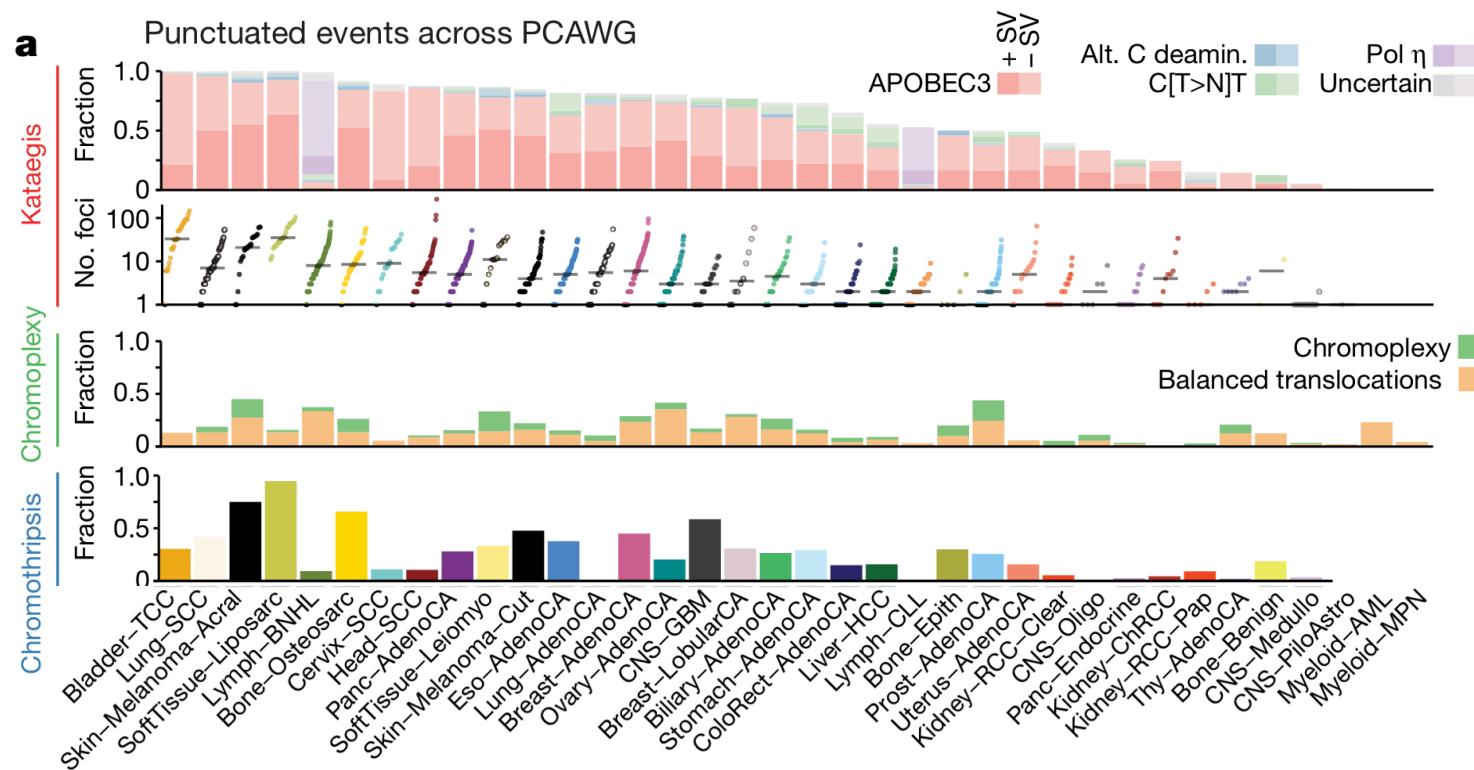


# Patterns of clustered mutations and SVs

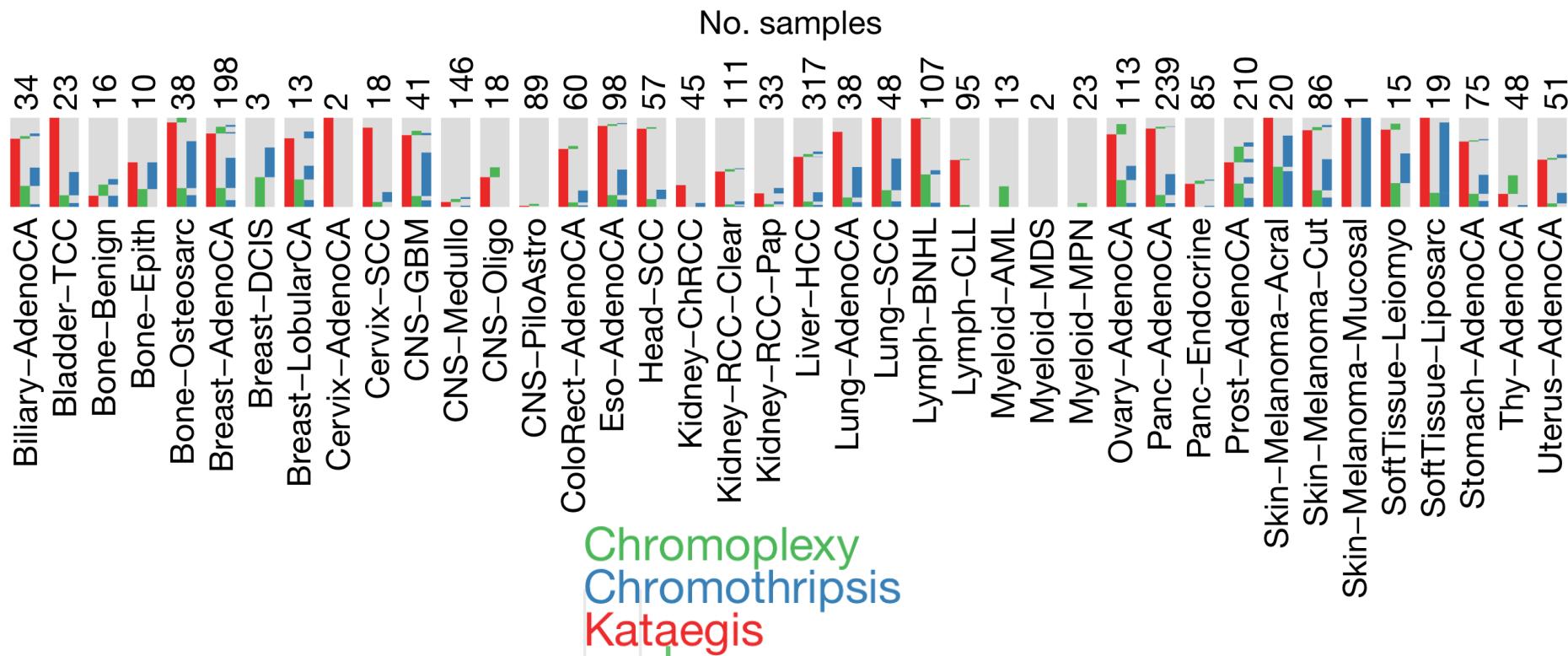
- Chromotripsy: Catastrophic event in which tens to hundreds of DNA breaks occur simultaneously and are glued back together randomly.
- 22.3% of all cases
- Correlated to whole genome duplications and TP53 alterations.
  - Pan-can OR: 3.22;  $P: 8.3 \times 10^{-35}$ ;
- Often lead to driver events



# Patterns of clustered mutations and SVs



# Co-occurrence of individual event types



# The end