Structural Variants (SVs) and Copy Number Variants (CNVs) using short-read

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Slide adapted from Dr. Tobias Rausch - EMBL

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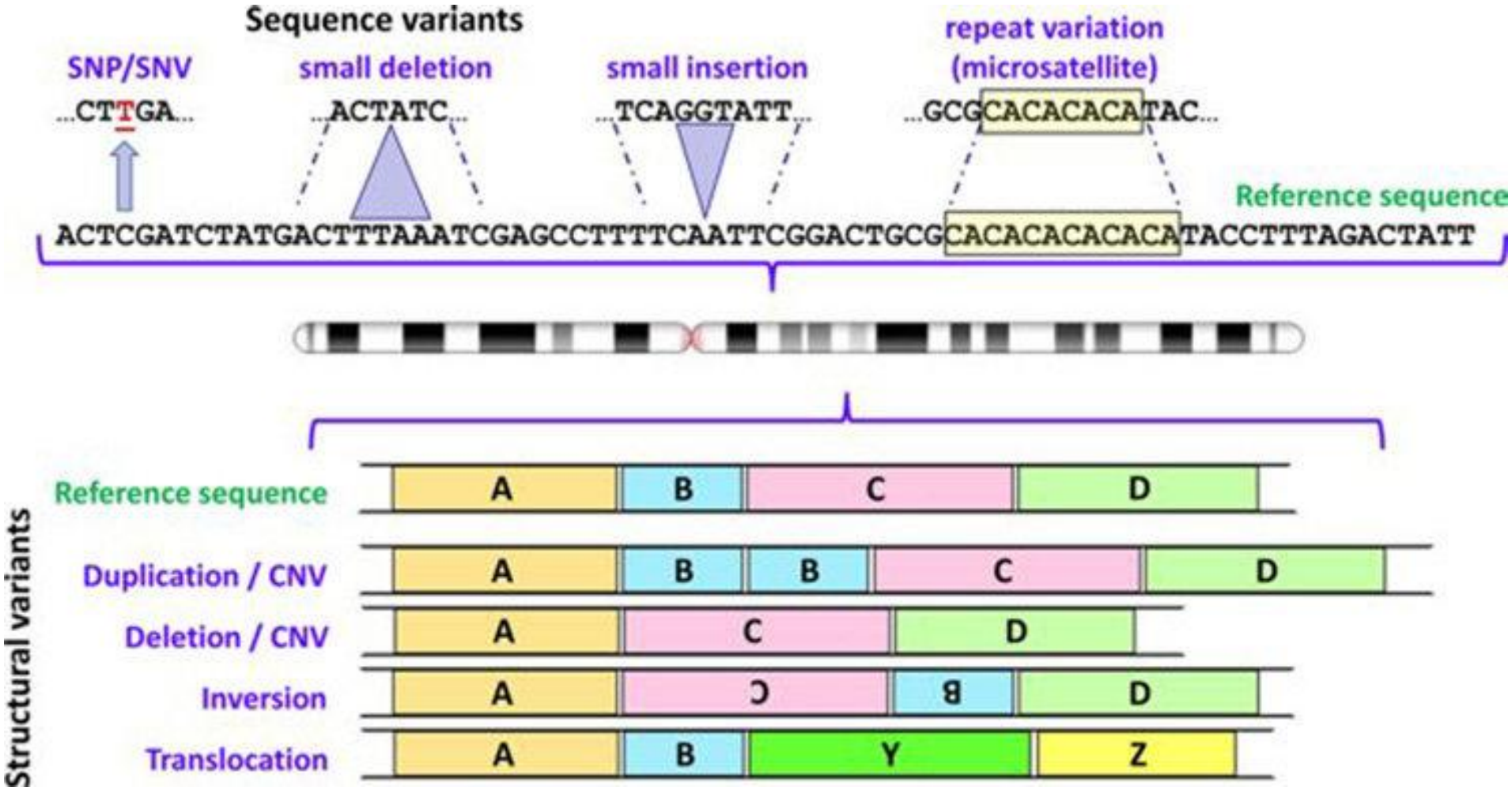
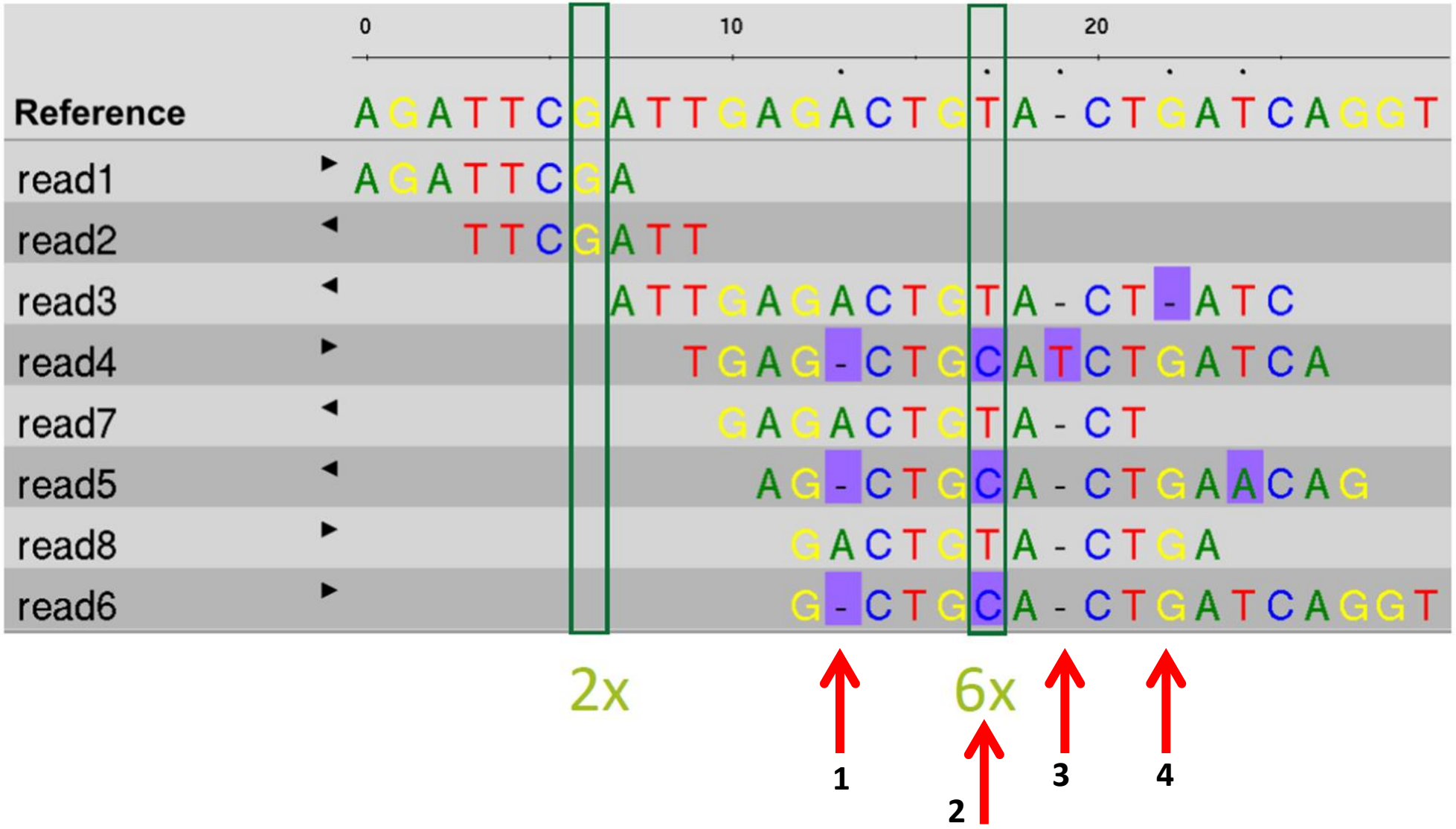
Type of variants



10.1042/EBC20170053

SNP and SNV


0
10
20
Reference
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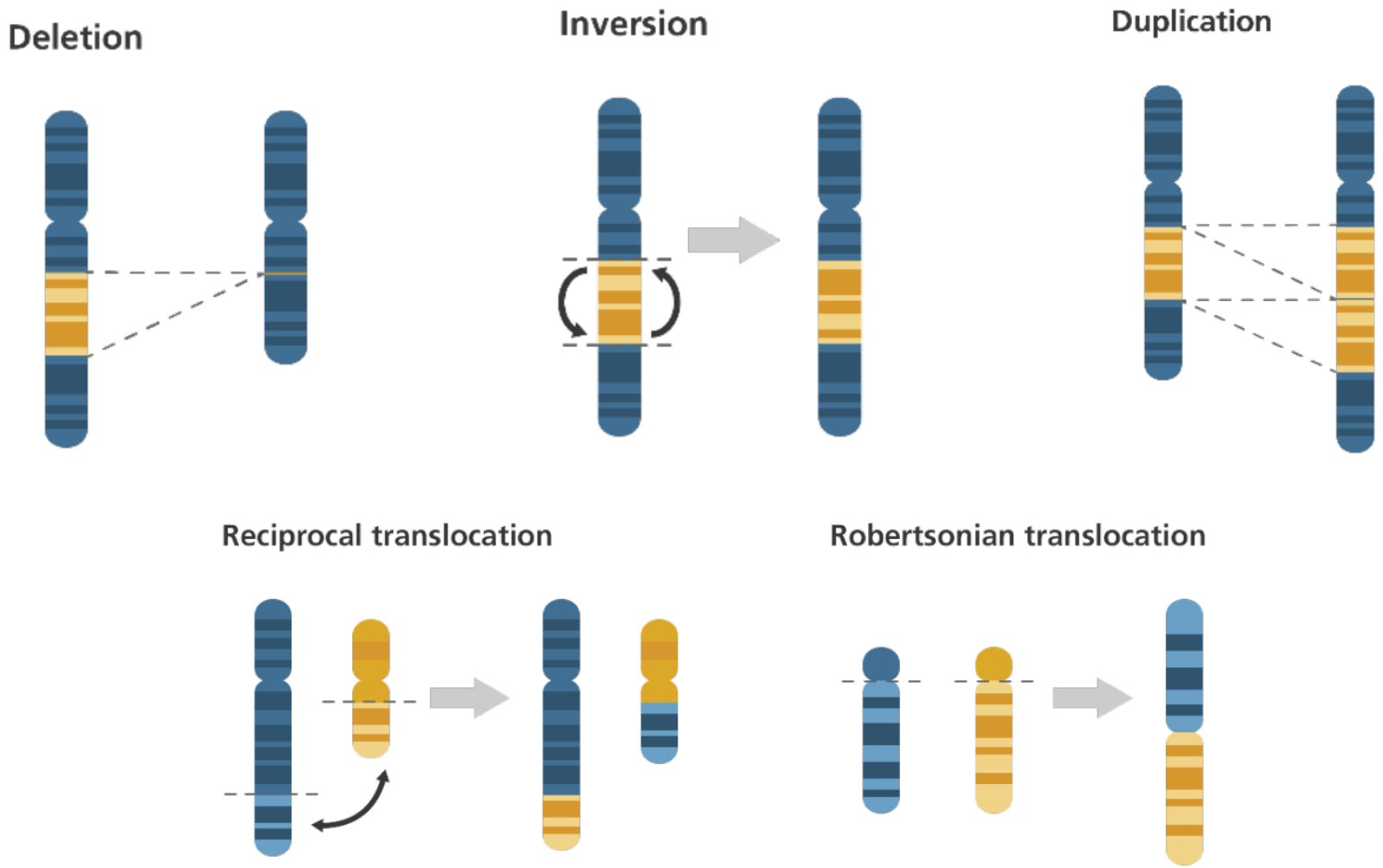
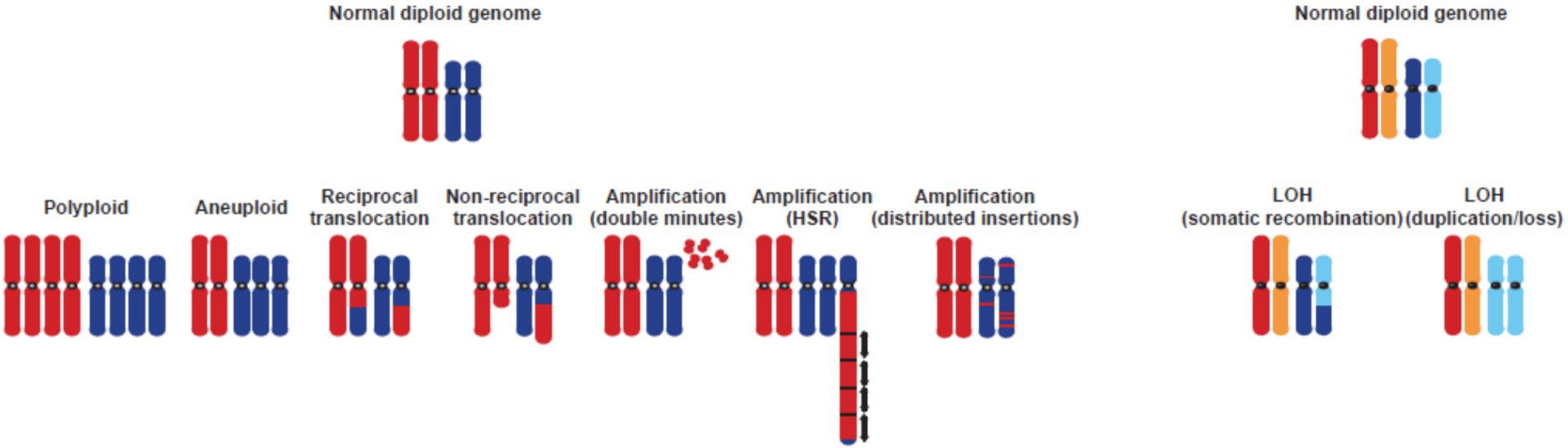
AGATTCGA
read2
TTCGATT
read3
ATTGAGACTGTA-CT-ATC
read4
TGAG-CTGCATCTGATCA
read7
GAGACTGTA-CT
read5
AG-CTGCA-CTGAACAG
read8
GACTGTA-CTGA
read6
G-CTGCA-CTGATCAGGT
2x
6x
1
2
3
4

Somatic and Germline Structural Variants (SVs)



Cancers harbour a wide Range of Chromosome Aberrations



Chromosome aberrations in solid tumors. Albertson et al., Nat Genet. 2003 Aug;34(4):369-76.

- Structural Variants (SVs)

Single-End vs Paired-End Sequencing

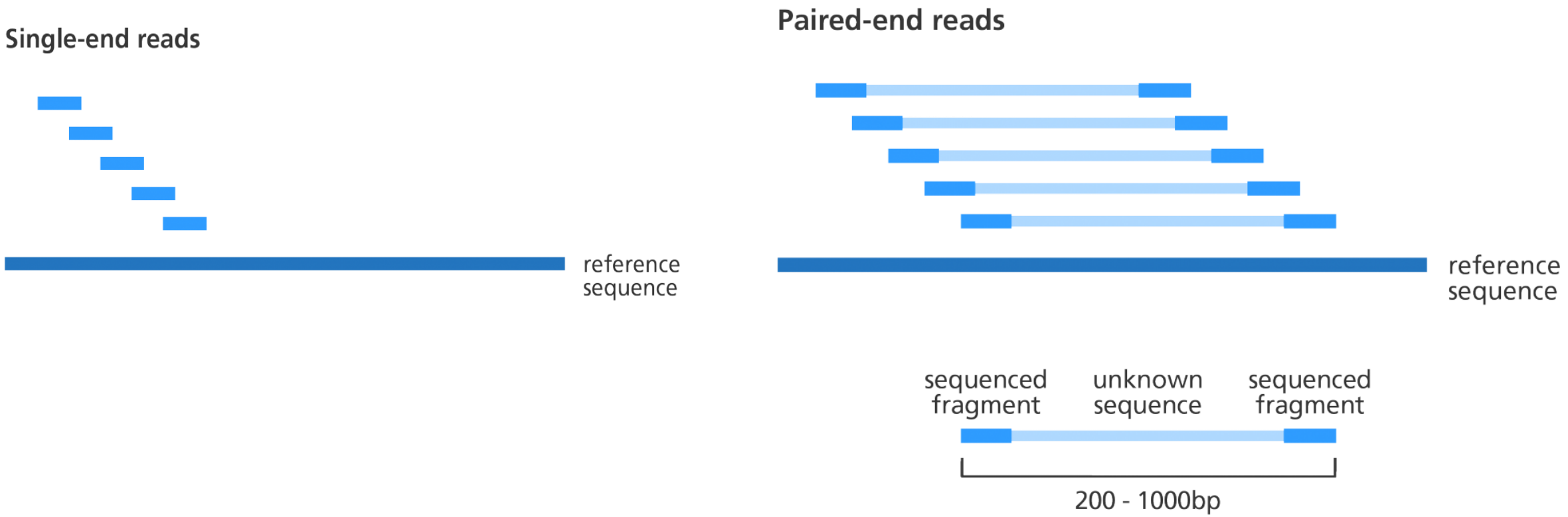
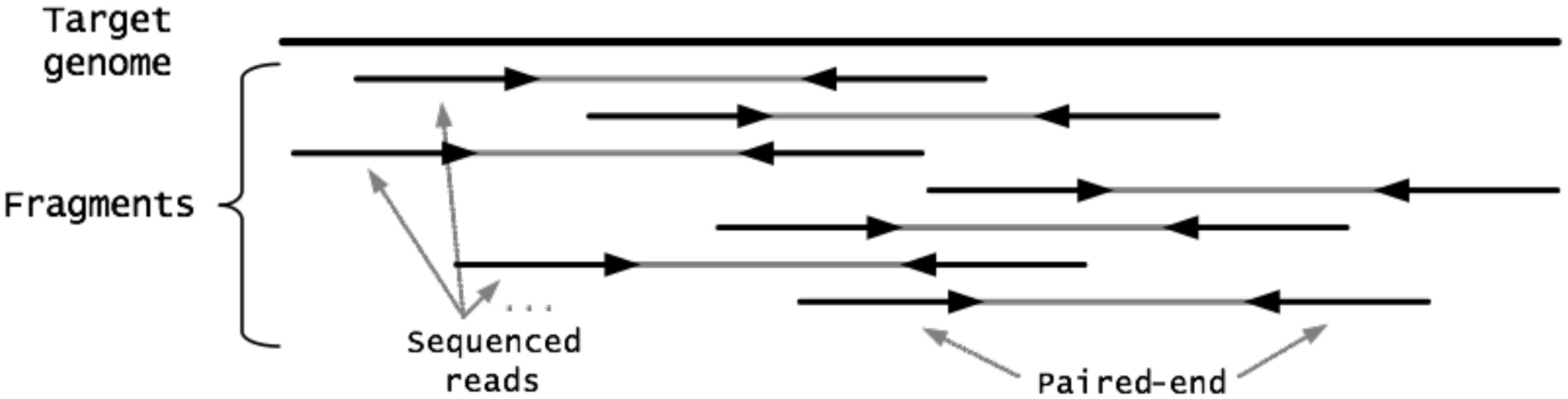
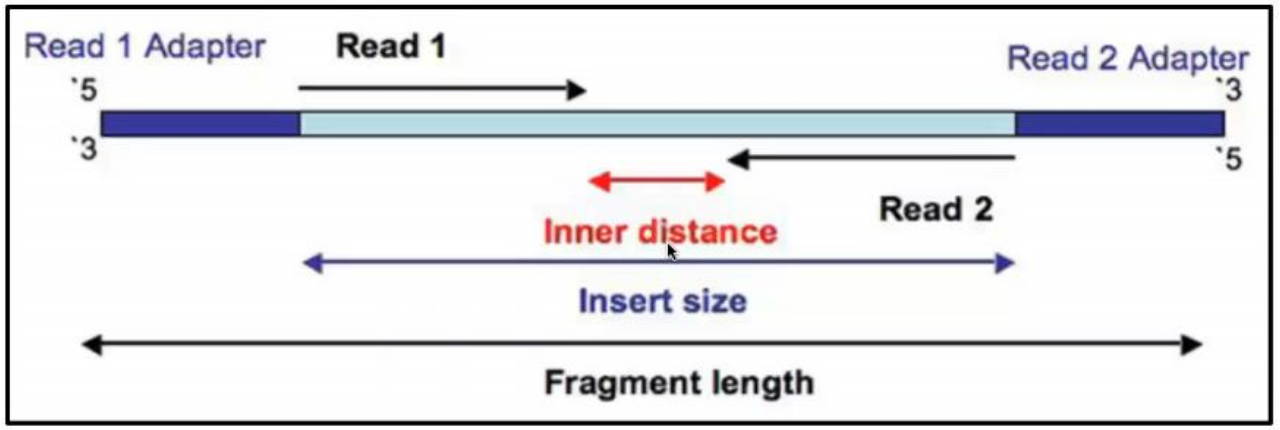


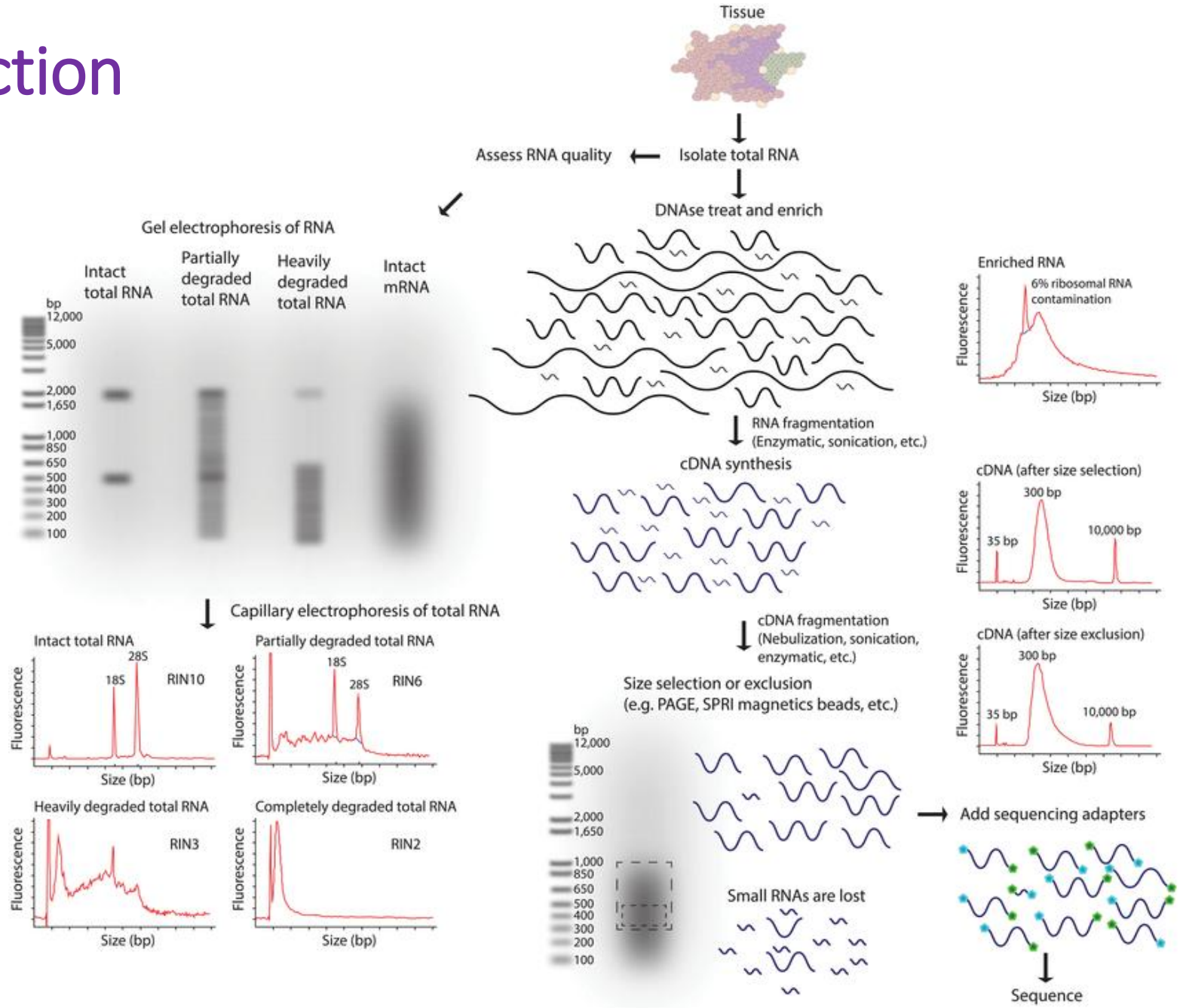
Image by Genome Research Ltd

Paired-End Sequencing



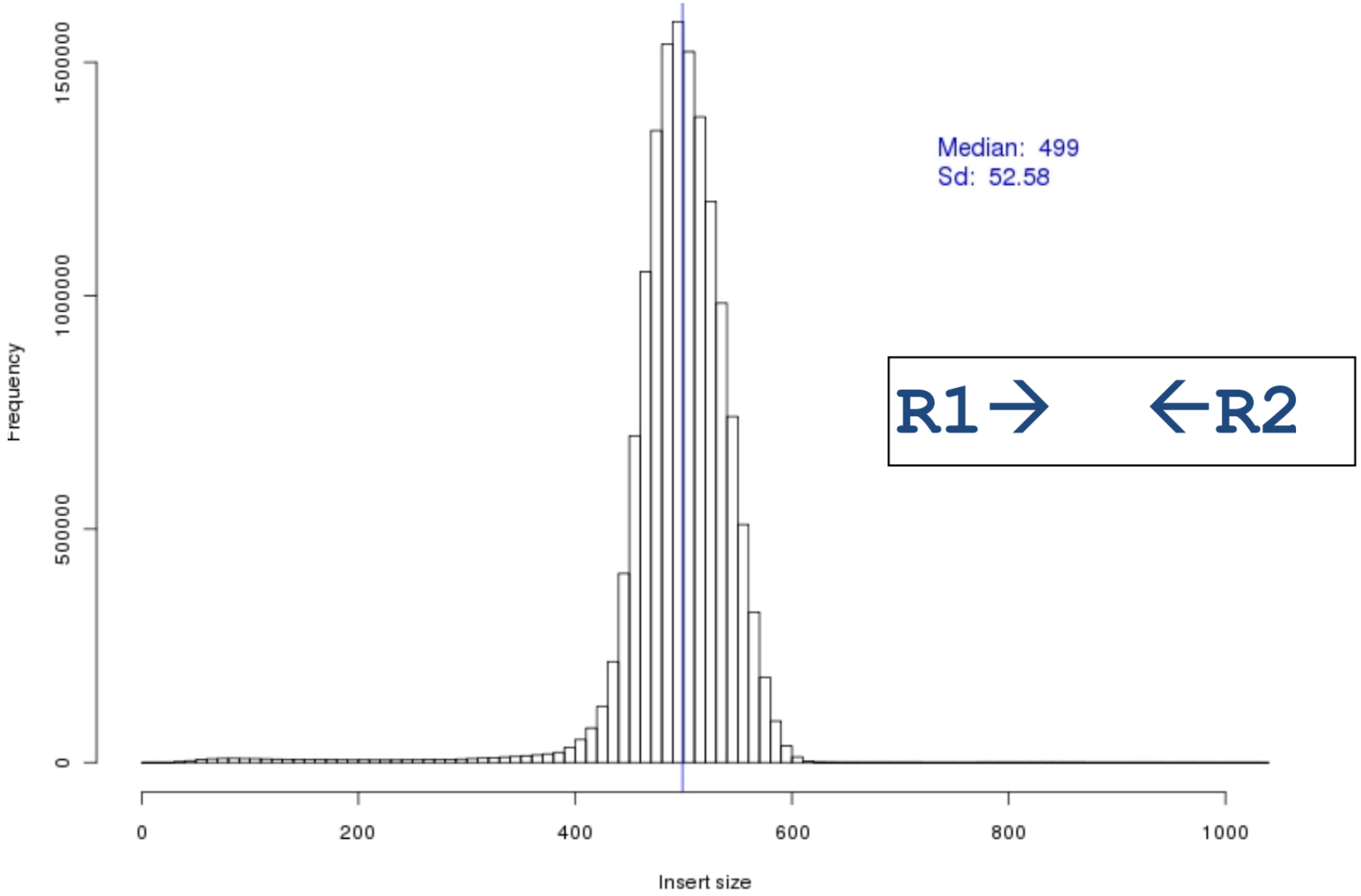


Fragment Size Selection

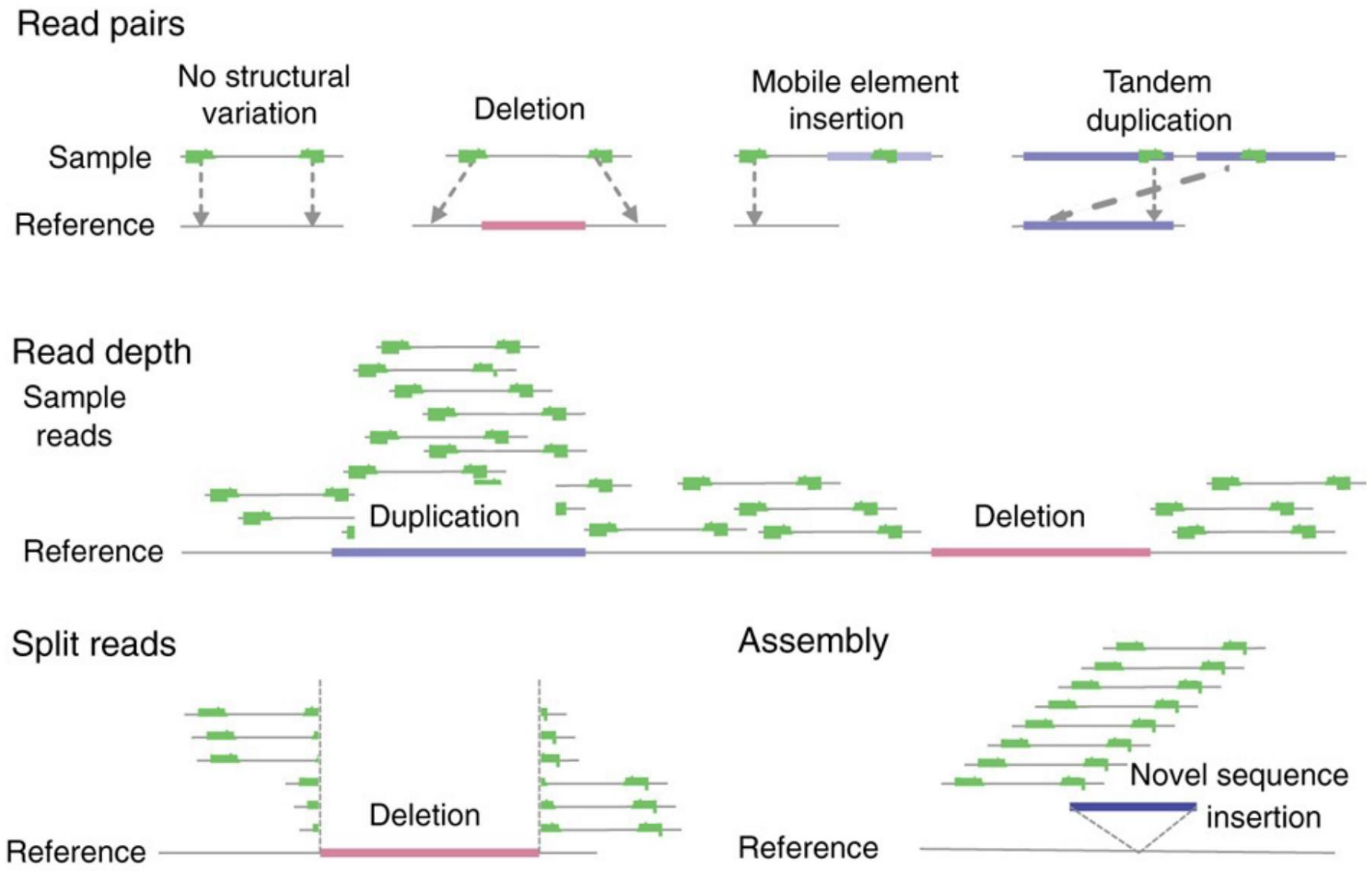


10.1371/journal.pcbi.1004393

Paired-End Libraries

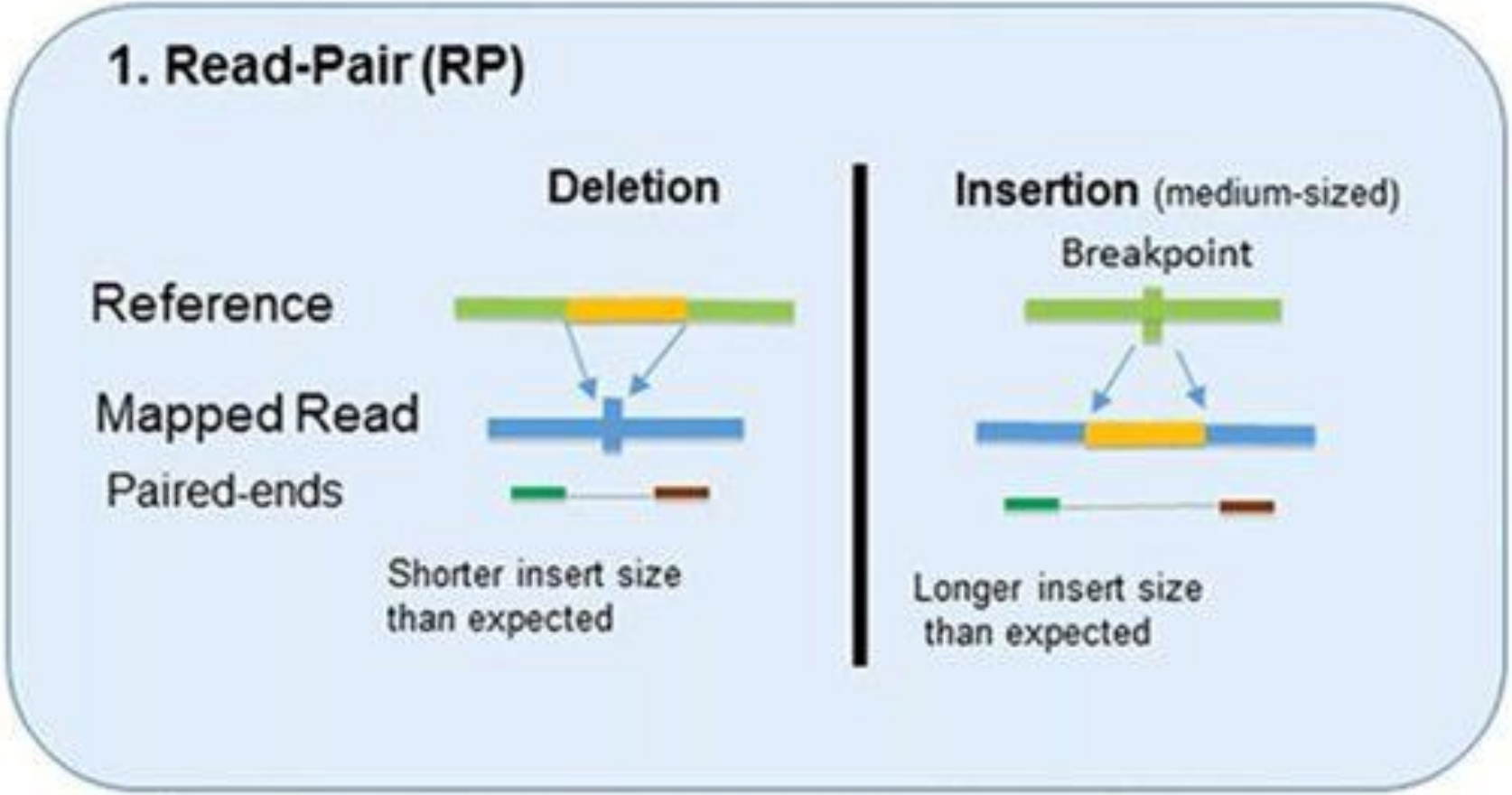


SV Discovery Approaches



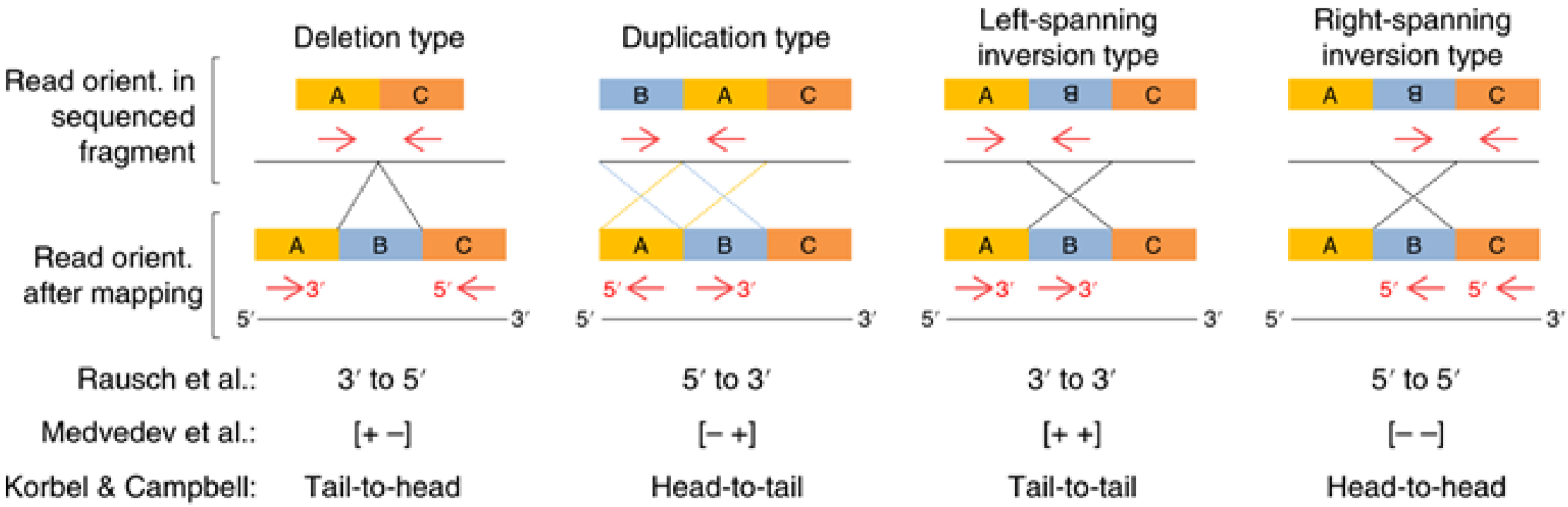
Structural variation: the genome's hidden architecture. Baker M. Nat Methods. 2012 Jan 30;9(2):133-7

Read Pairs for detection of SVs



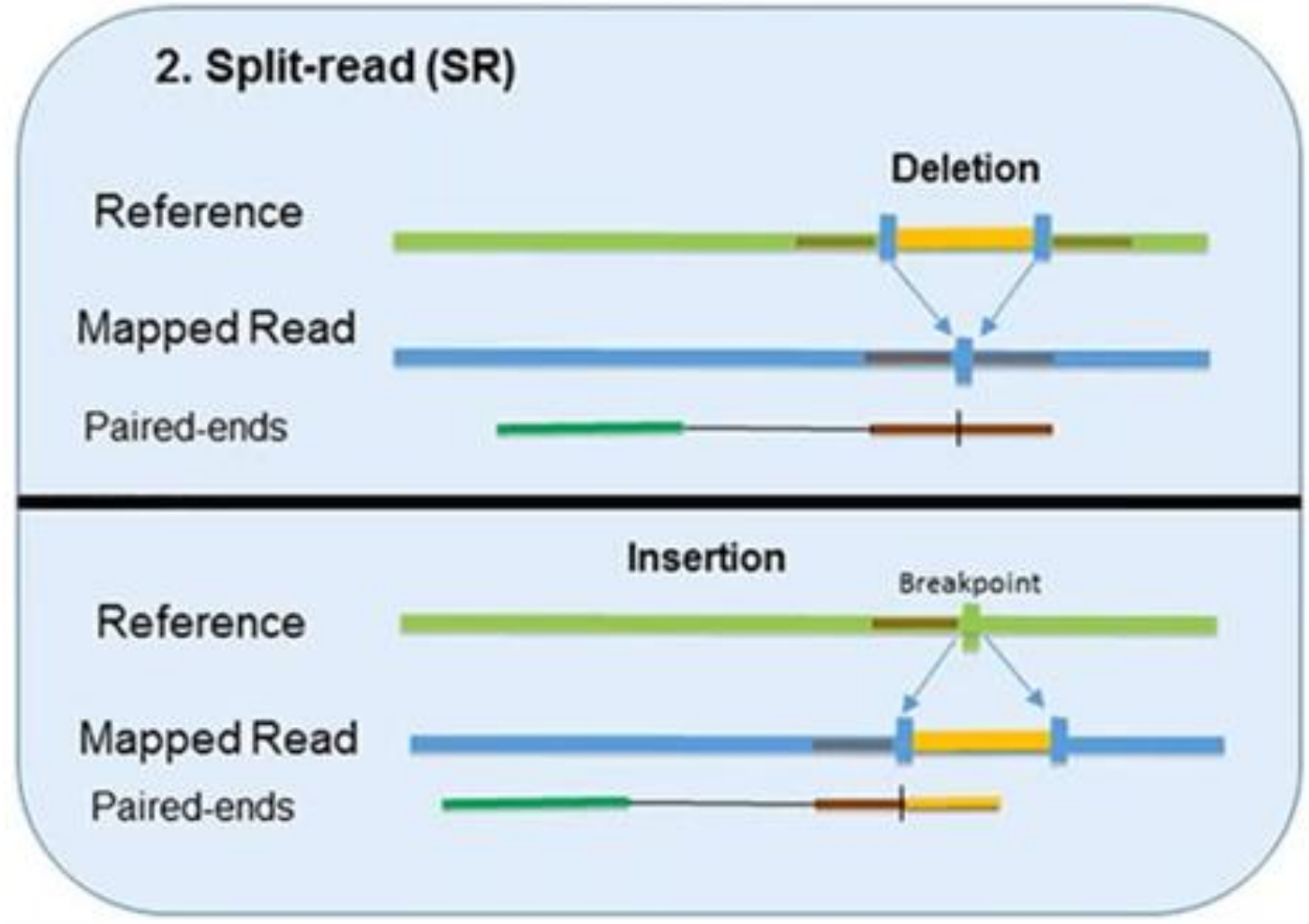
Pirooznia et al. (2015) Front. Genet

Read Pairs for detection of SVs



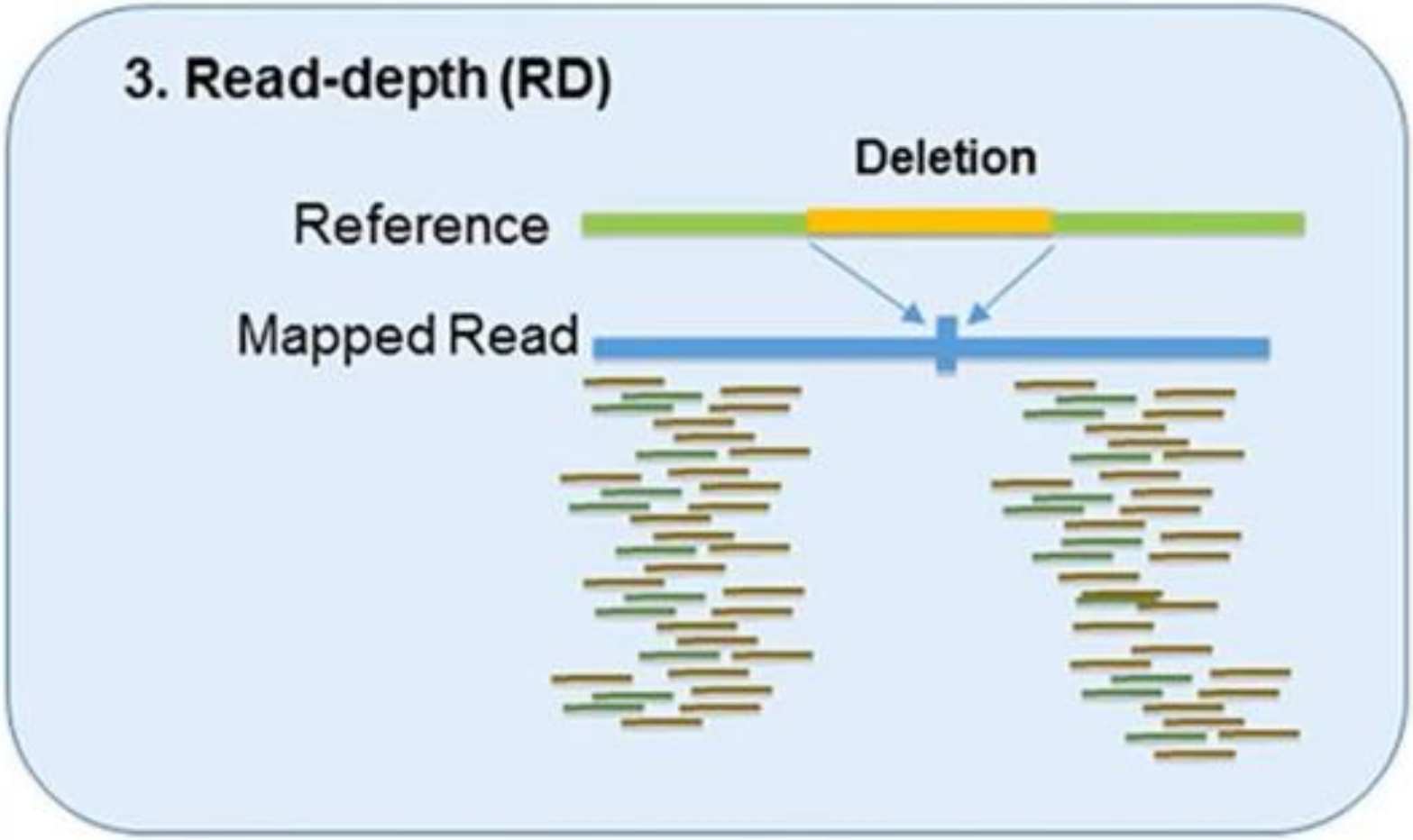
https://www.nature.com/articles/s41596-019-0234-7

Read Split for detection of SVs



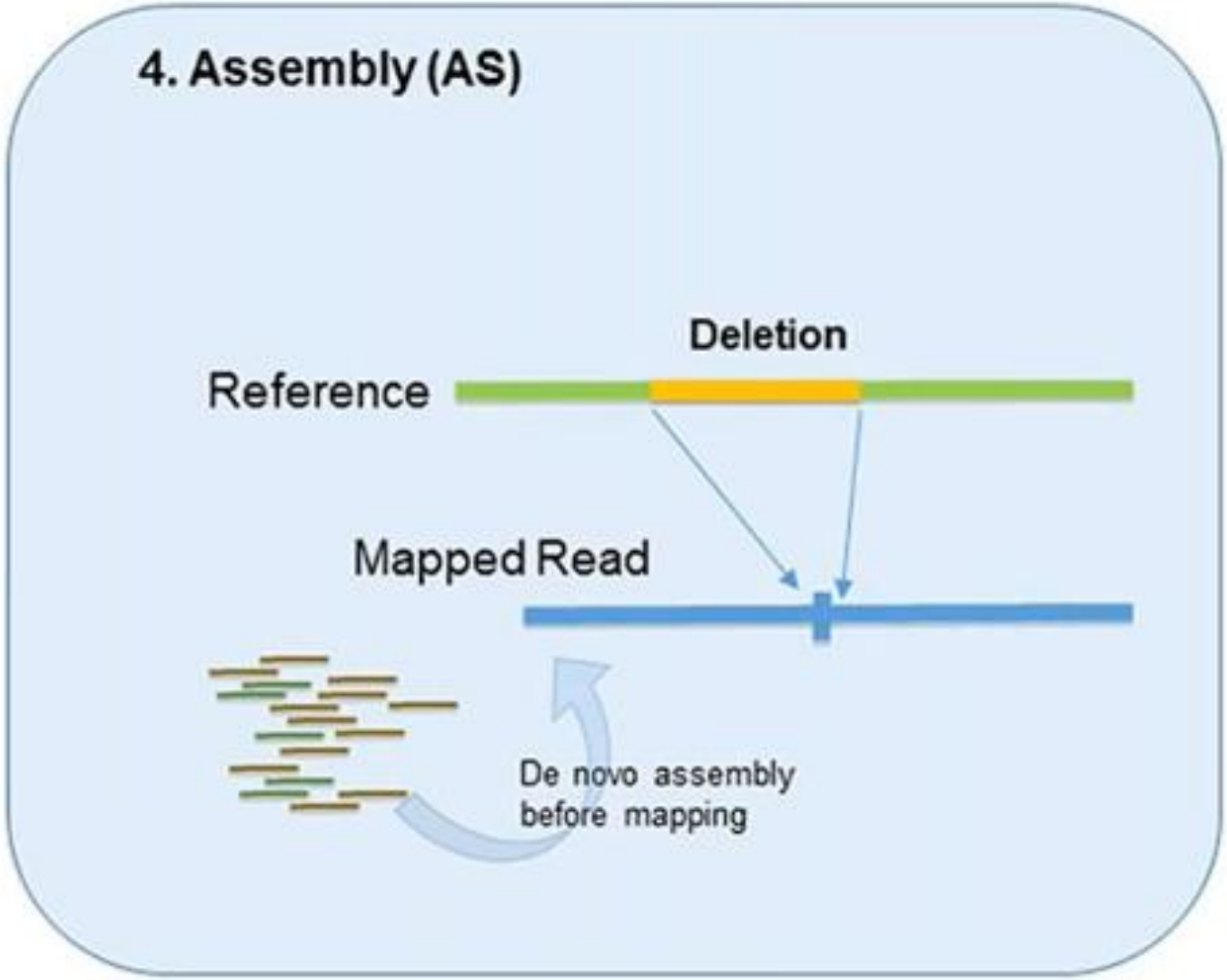
Pirooznia et al. (2015) Front. Genet

Read Depth for detection of SVs

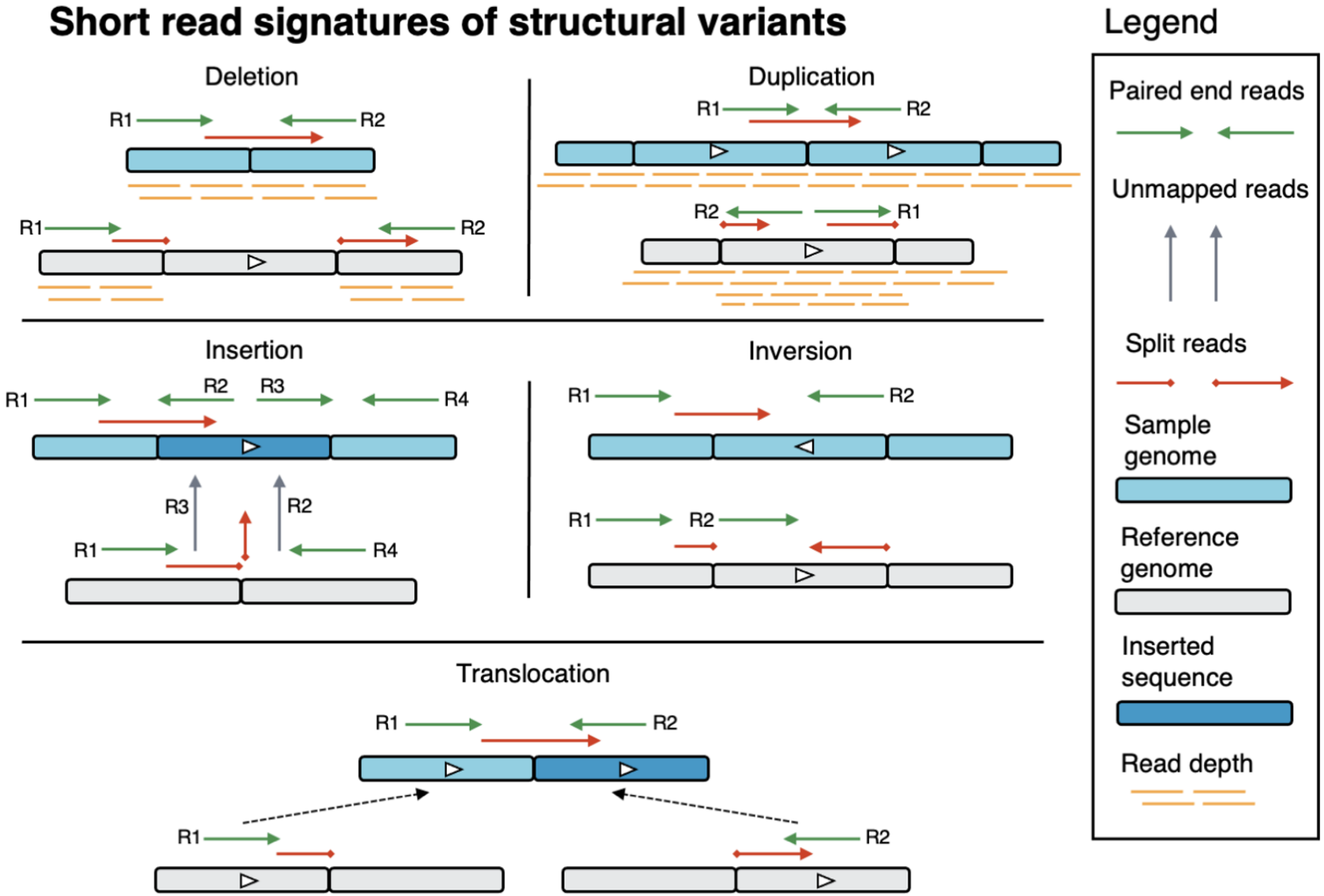


Pirooznia et al. (2015) Front. Genet

Denovo Assembly for detection of SVs

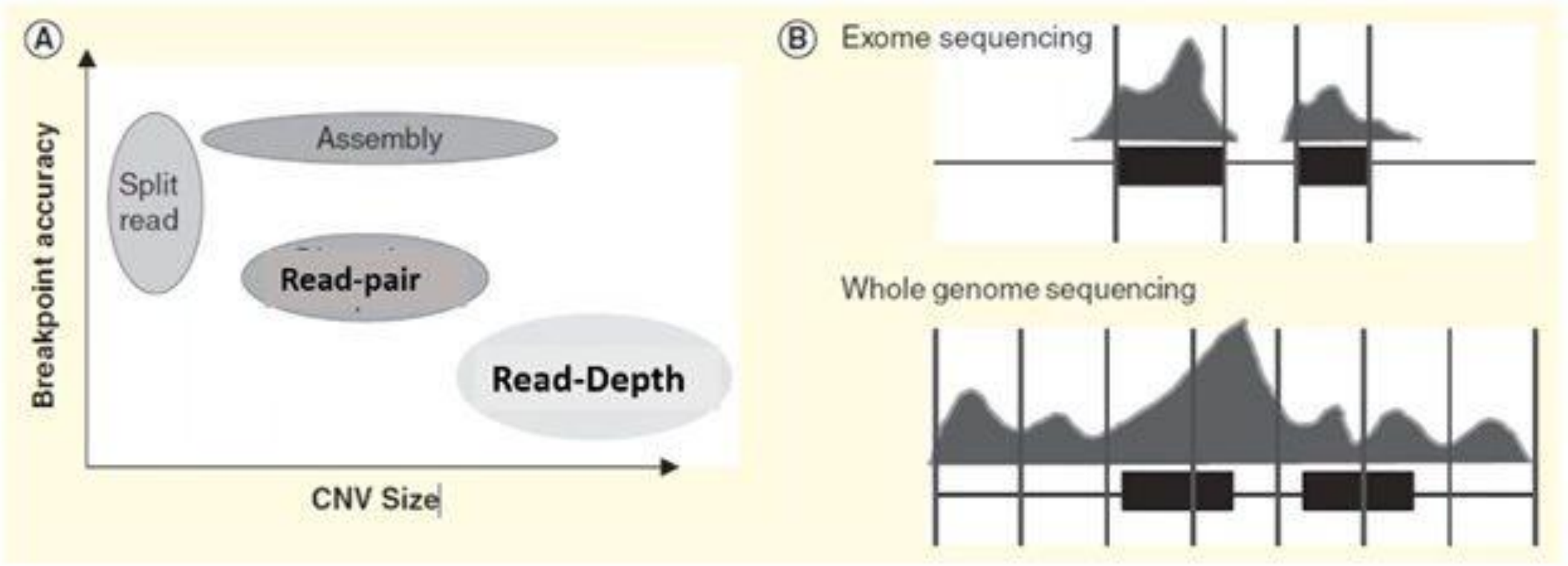


Pirooznia et al. (2015) Front. Genet



https://gatk.broadinstitute.org/hc/en-us/articles/9022476791323-Structural-Variants

Methods for detection of SVs: CNV size vs Breakpoint Accuracy

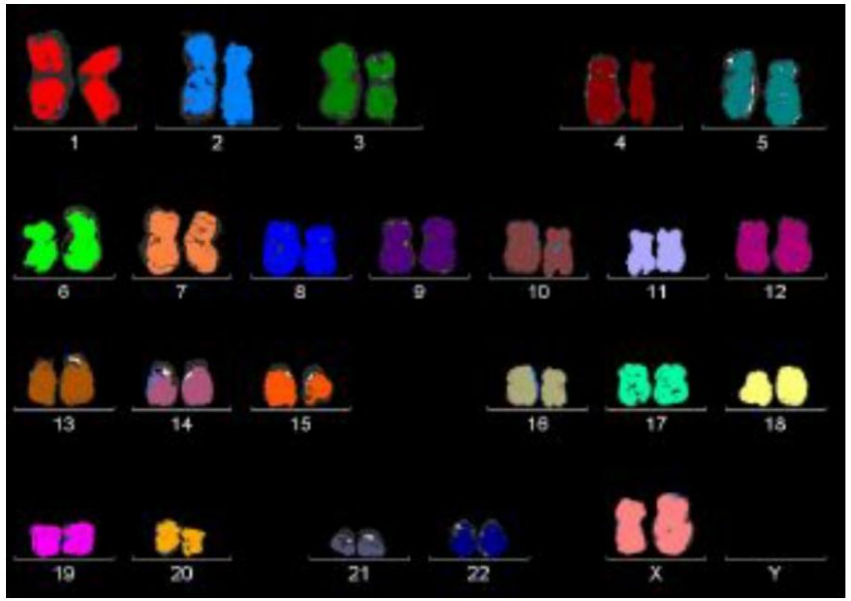


Hehir-Kwa et al. (2015) Expert Rev Mol Diagn

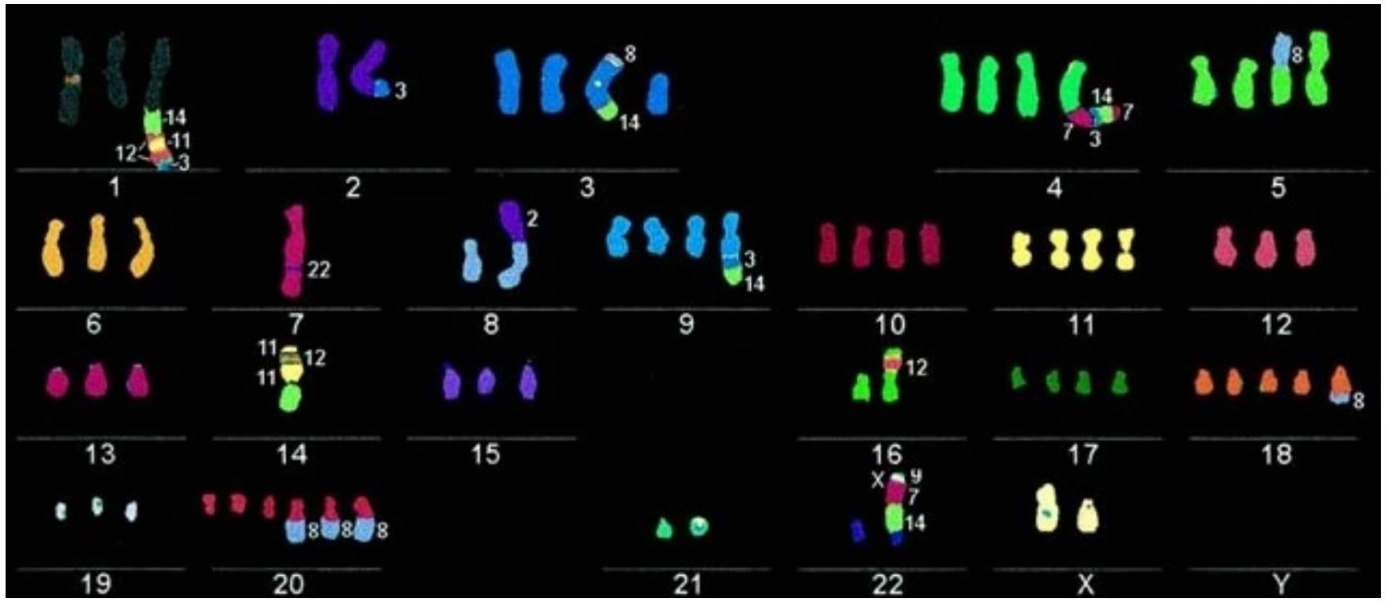
- Copy Number Variants (CNVs)

Human karyotype: Normal vs Cancer

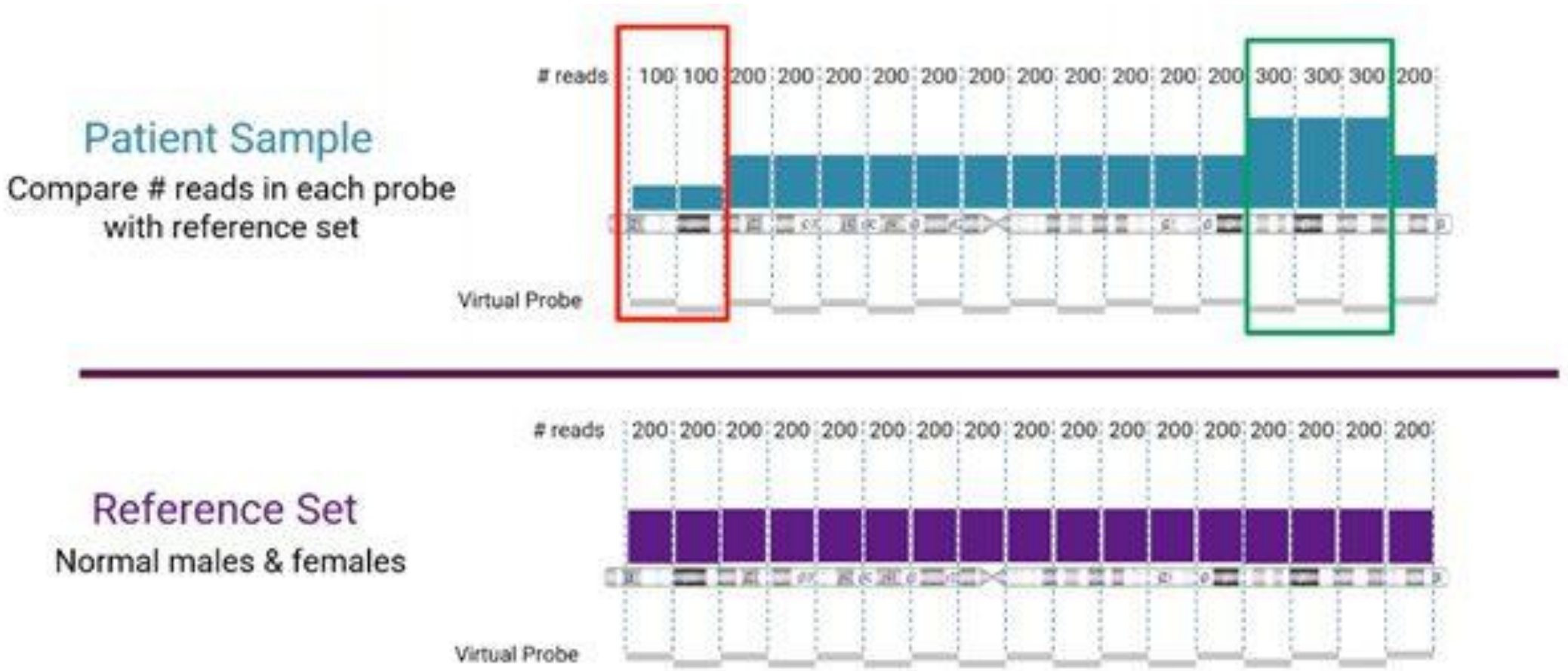
Normal Karyotype



Cancer Karyotype (NSCLC cell line D117)

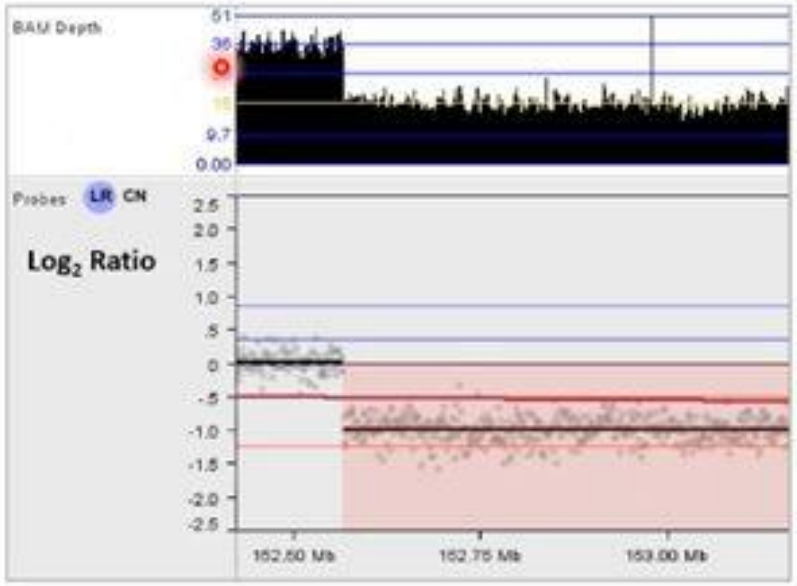


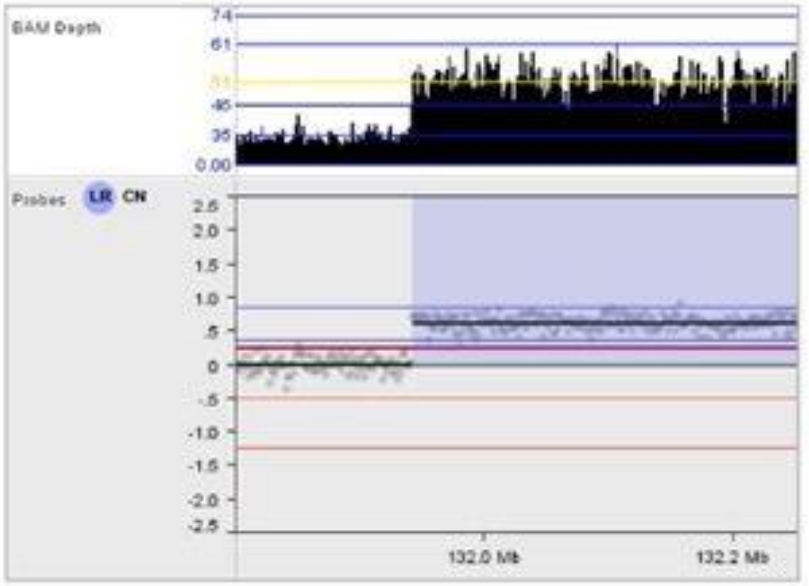
CNV detection: Normal vs Cancer



https://bionano.com/blogs/next-generation-sequencing-cnv-detection-analysis/

CNV detection: Normal vs Cancer





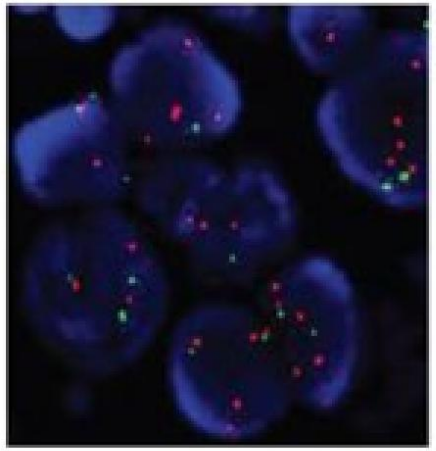
Probe Location	Patient # Reads	Reference # Reads	Ratio	Copy Number
Chr 1: Probe A	150	100	3/2	3 (dup)
Chr 1: Probe B	100	100	2/2	2 (norm)
Chr 1: Probe C	50	100	1/2	1 (del)

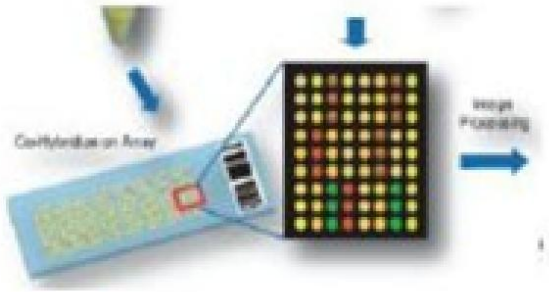
https://bionano.com/blogs/next-generation-sequencing-cnv-detection-analysis/

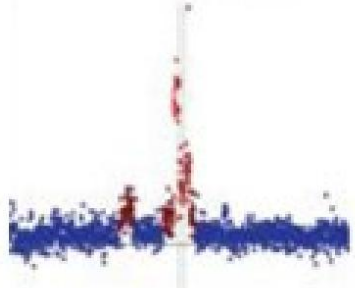
CNV detection technologies

Tech:	FISH	Array CGH	Genotype arrays	WGS
#:	<10	30-100K	100K-2M	3G!

Resolution

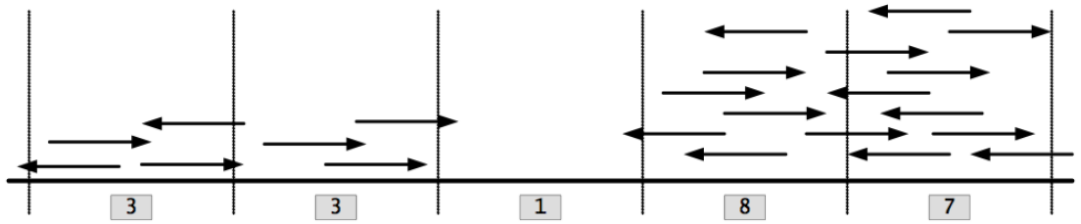






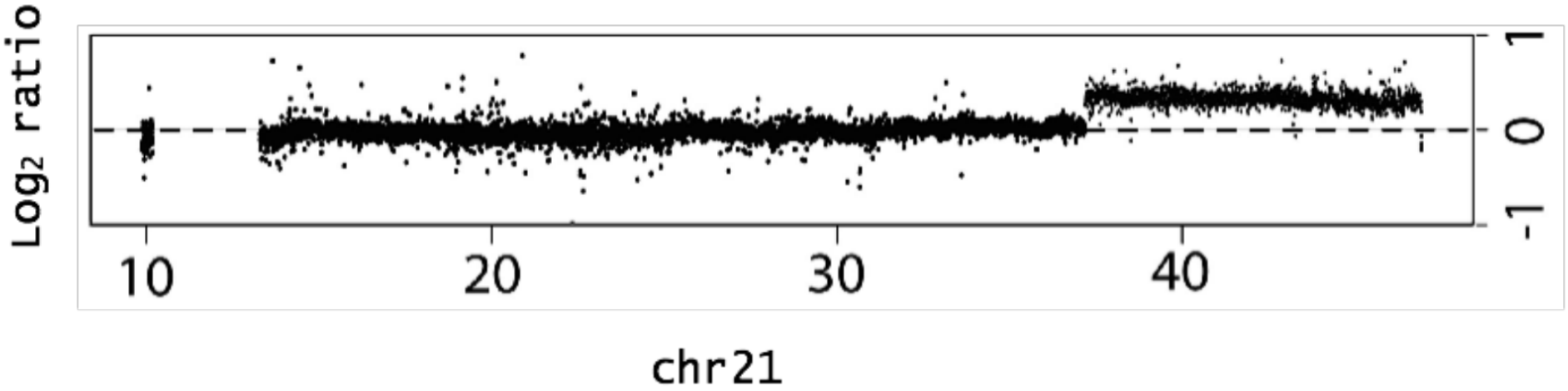
Tumor / Normal Read-Depth Ratio

- Read counting in windows for tumor and normal data



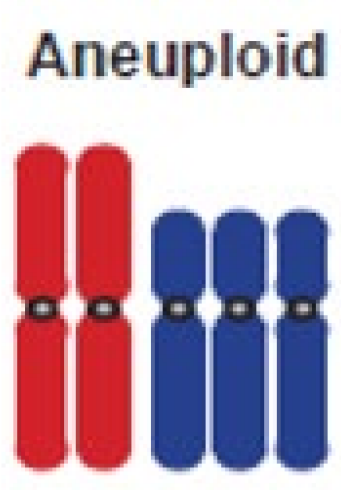
- Log2 ratio for each window
- Chromosome-wide plot

$$\log_2 \frac{\#\text{Reads}_{Disease}}{\#\text{Reads}_{Normal}}$$

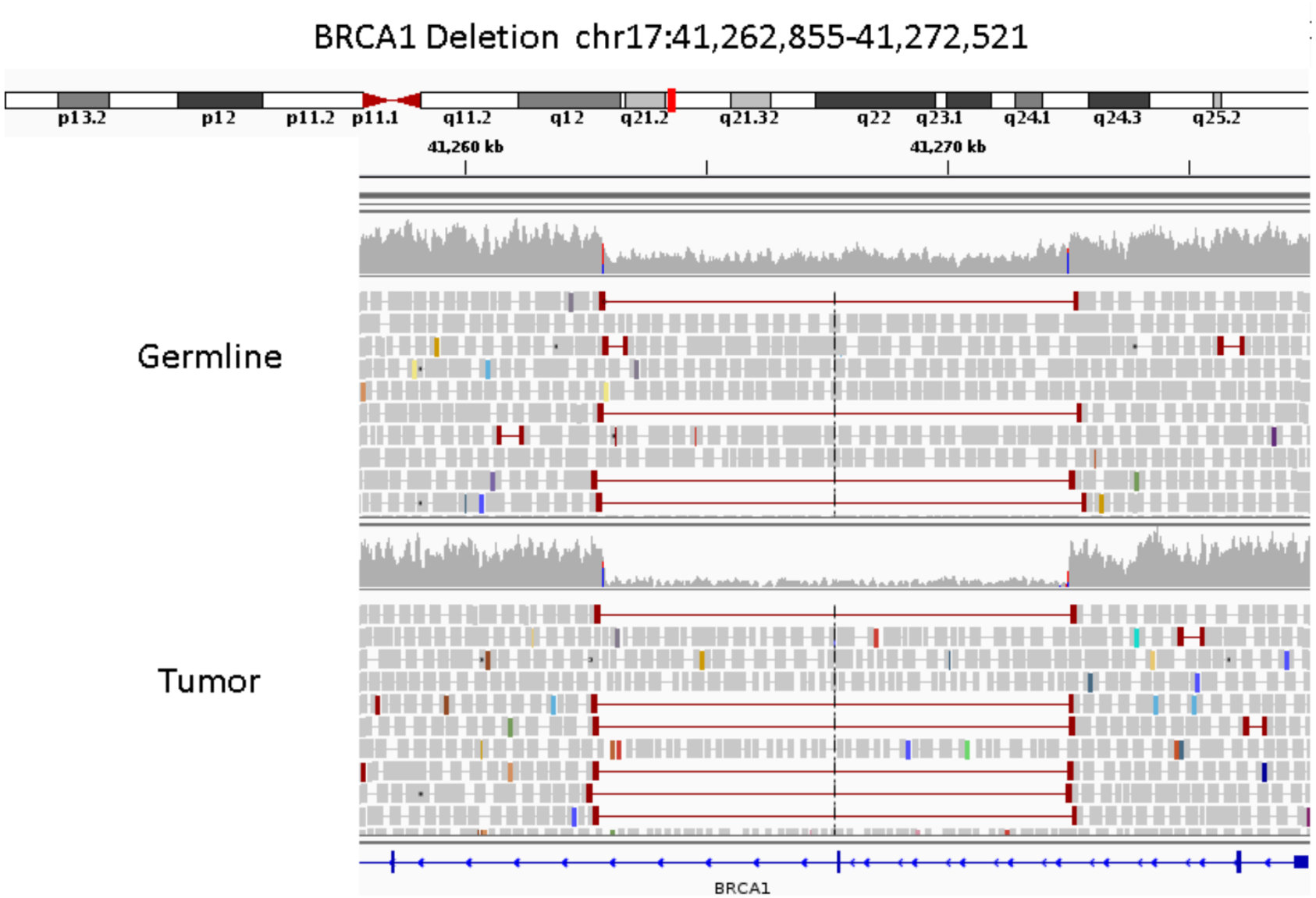


Copy Number Variants (CNVs)

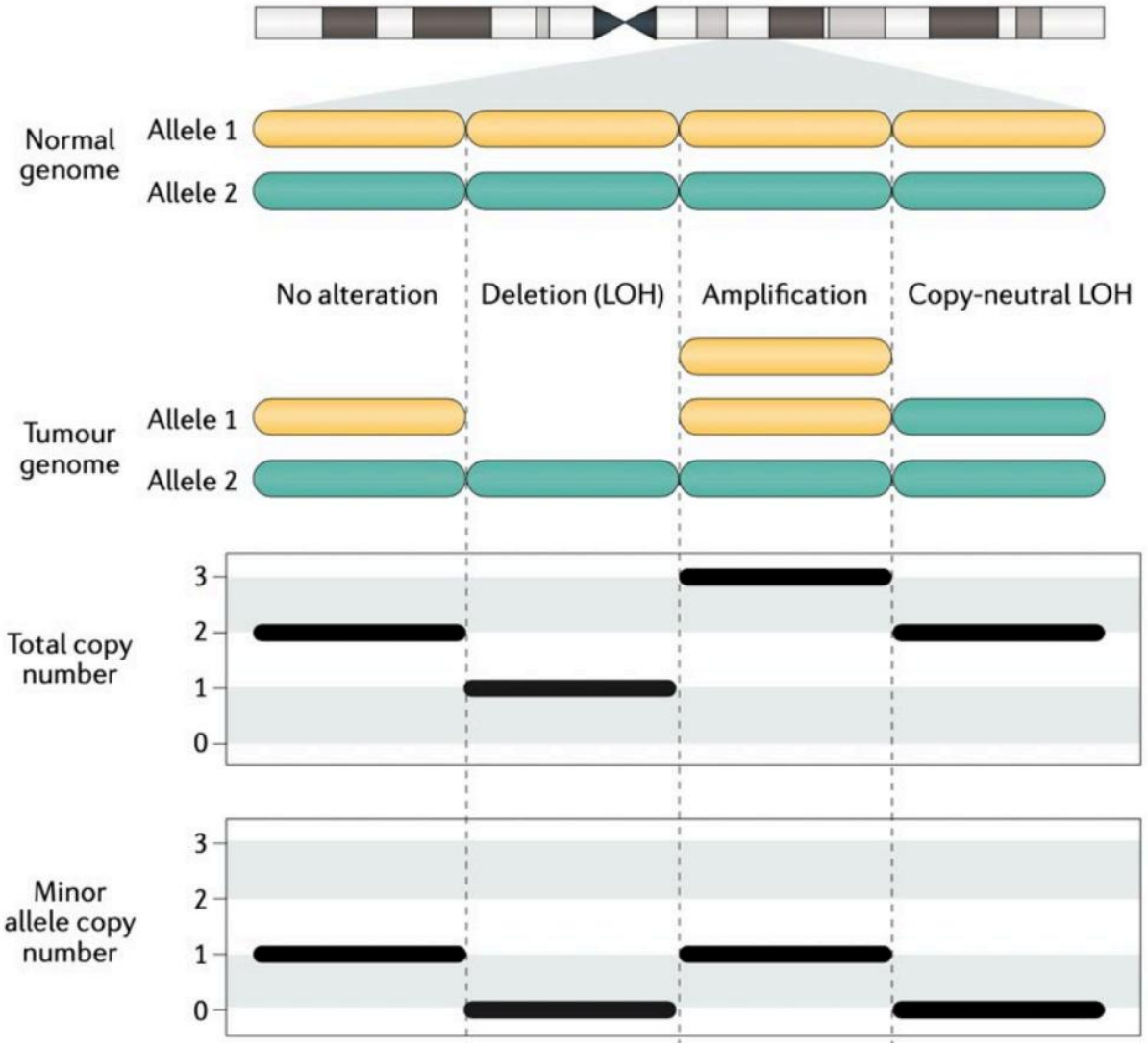
- Can vary the gene dosage of a tumor suppressor or oncogene
- Aneuploidy or non-reciprocal translocations are one form of CNV
- Rare pathogenic germline CNVs can affect known cancer predisposition genes
- Recurrent deletions or duplications indicate a selective advantage

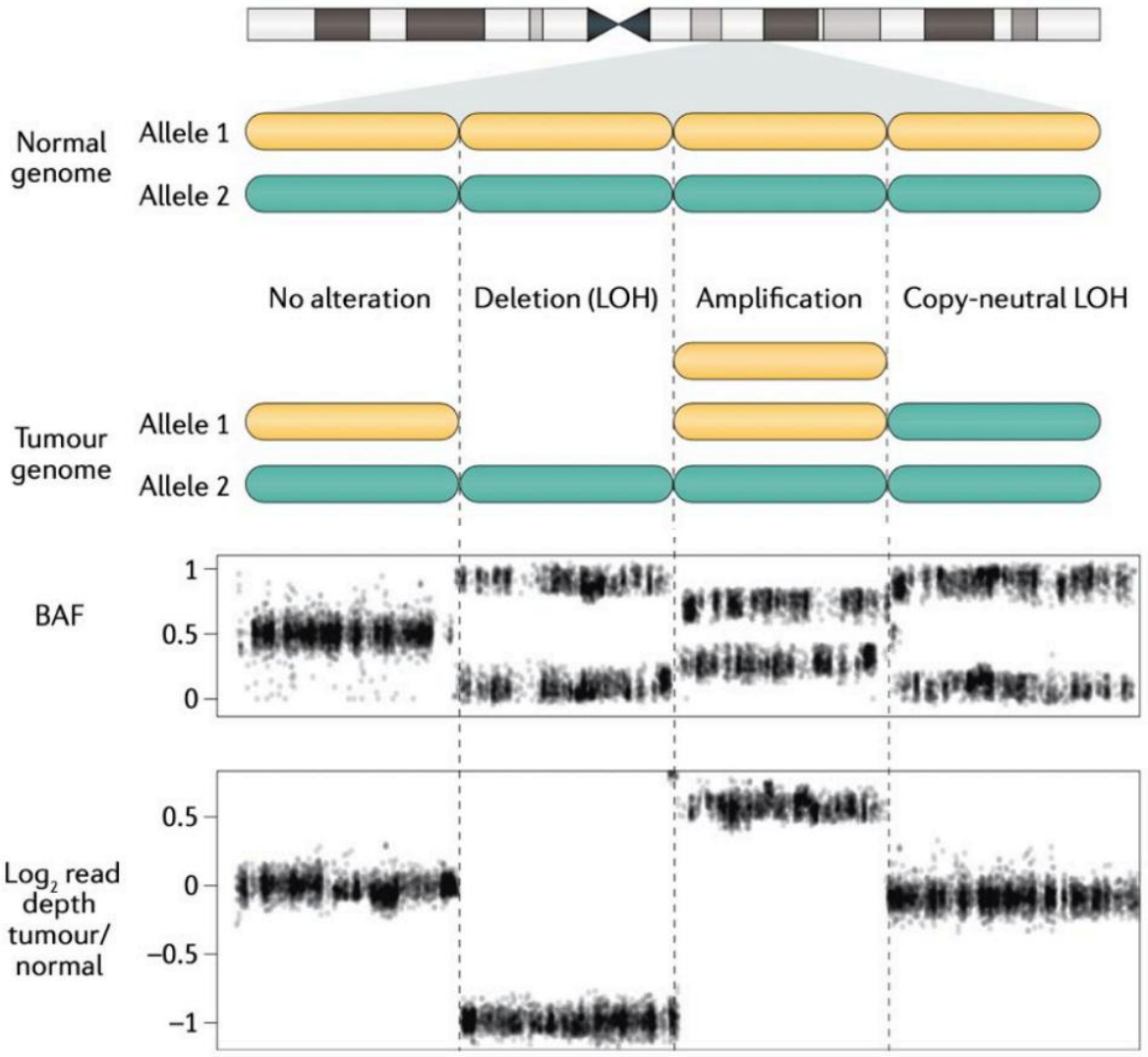


Copy Number Variants (CNVs)



Copy Number Variants (CNVs)

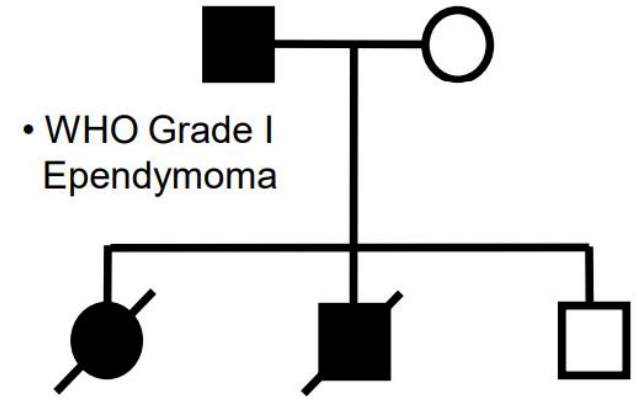


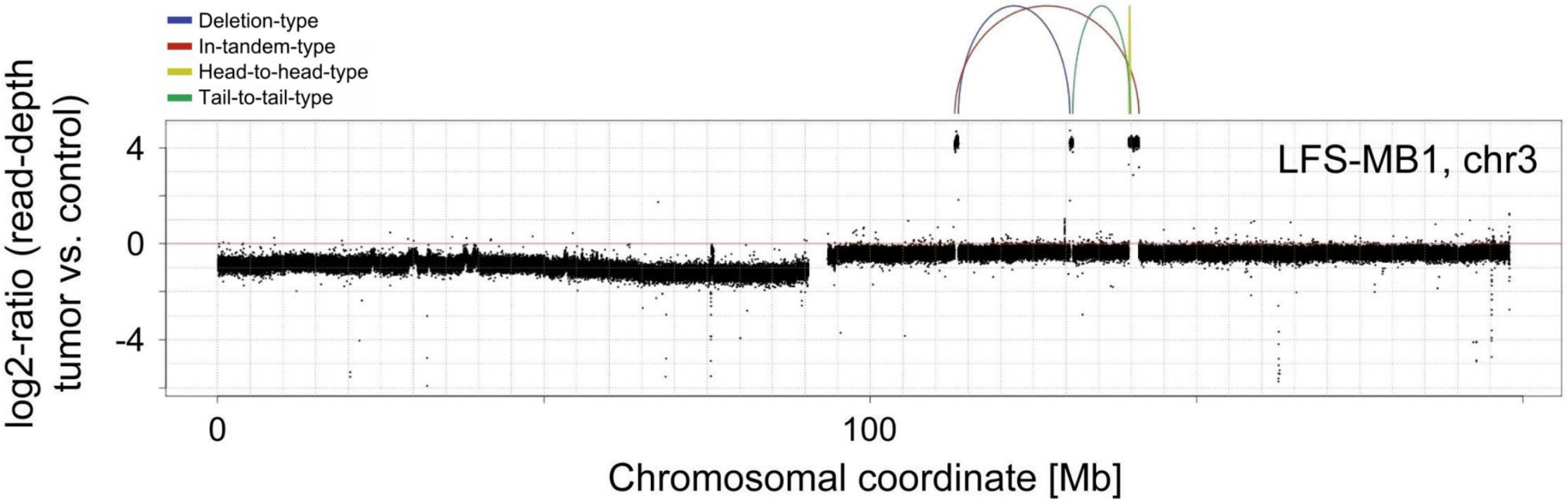


➢ Somatic Structural Variants

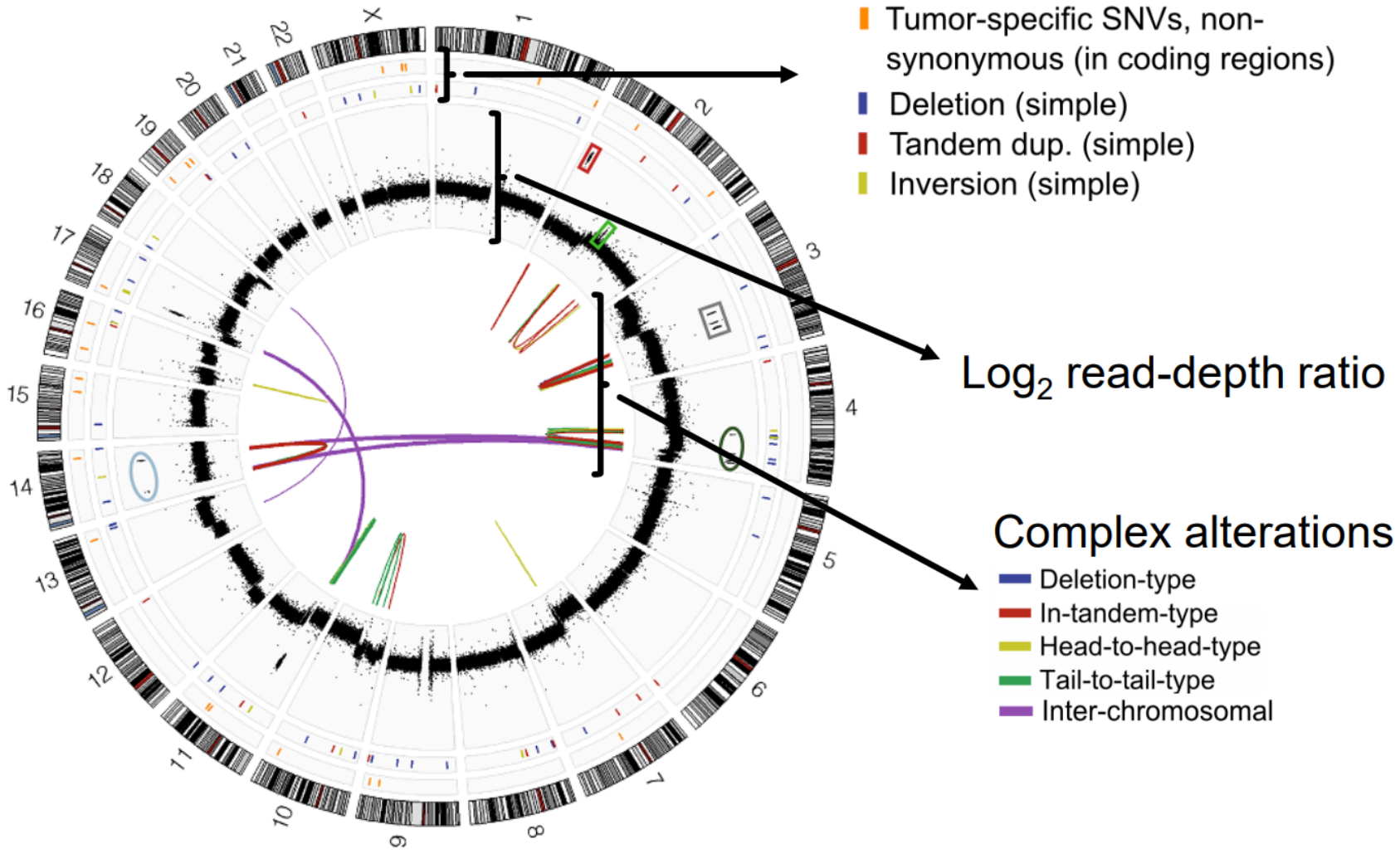
Childhood Brain Tumor Medulloblastoma

- Li-Fraumeni syndrome
  - Germline TP53 mutation



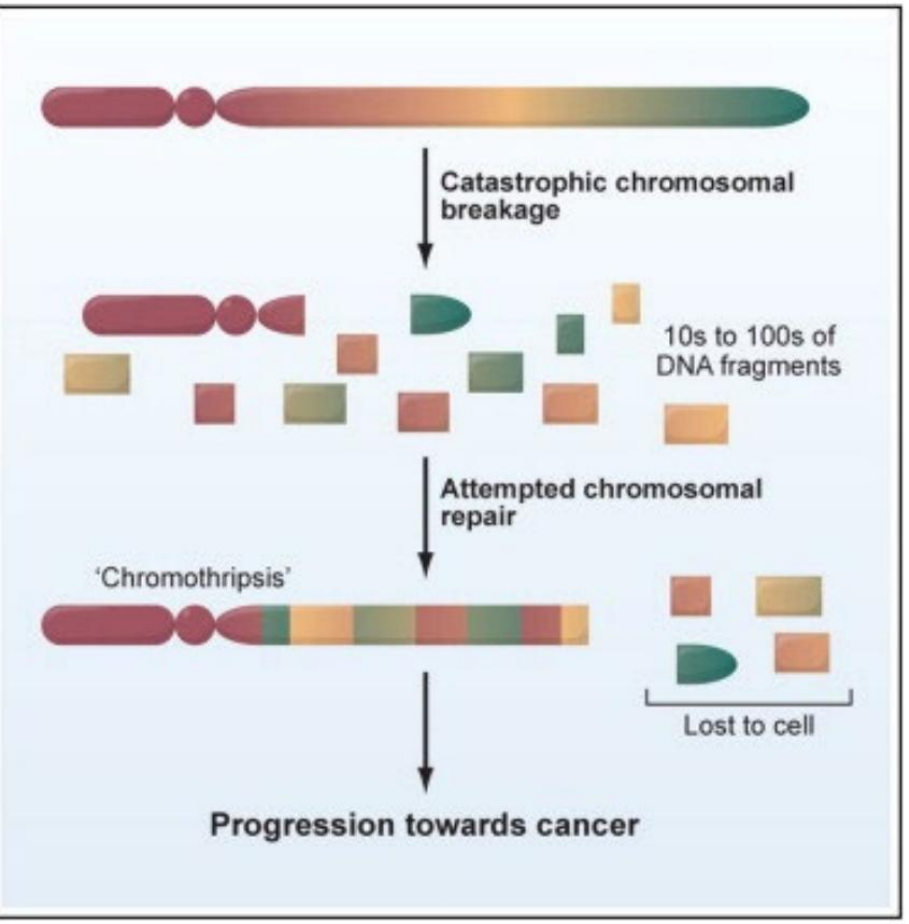


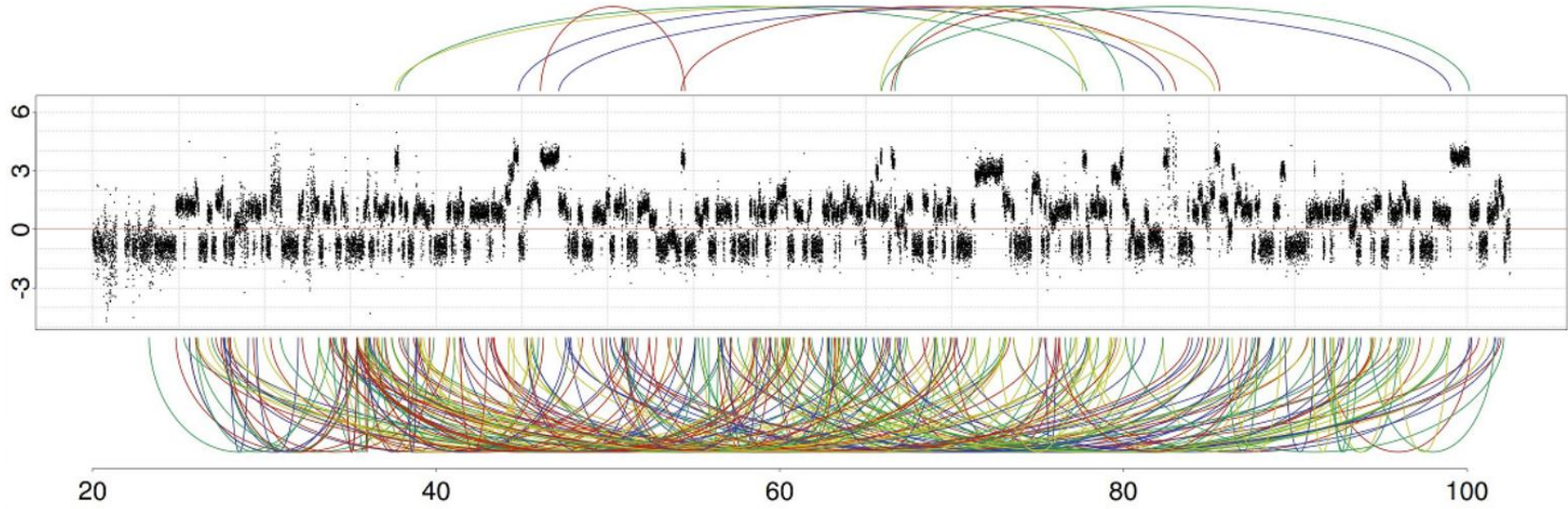
Somatic DNA alterations



Genome sequencing of pediatric medulloblastoma links catastrophic DNA rearrangements with TP53 mutations. Rausch et al., Cell. 2012 Jan 20;148(1-2):59-71.

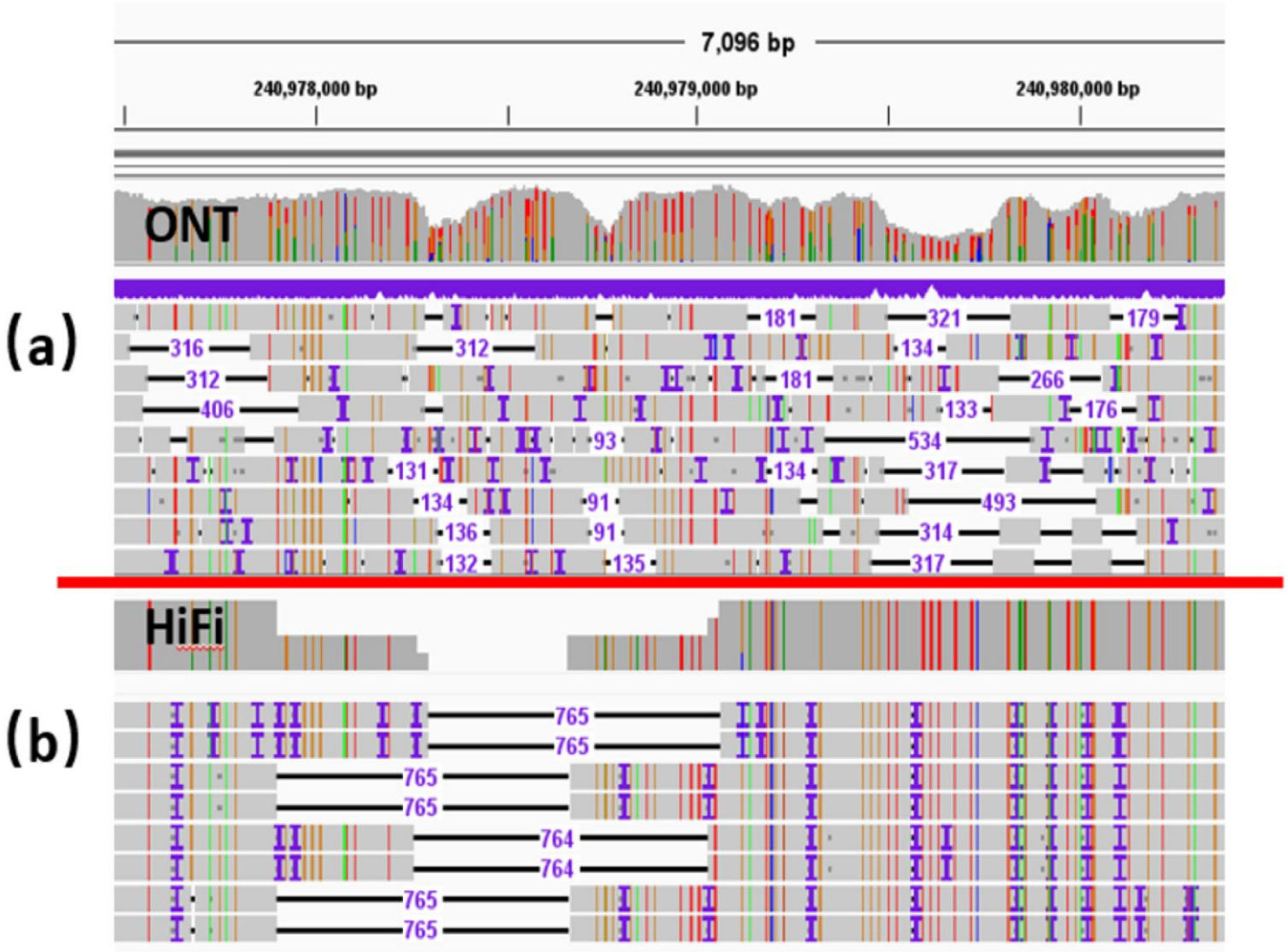
Chromothripsis





Stephens et al., Cell, 2011; Rausch et al., Cell, 2012

Pacbio vs ONT



https://www.sciencedirect.com/science/article/pii/S0010482523003086

Thank you!

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Email: Luu.p.loi@googlemail.com

Zalo: 090102182