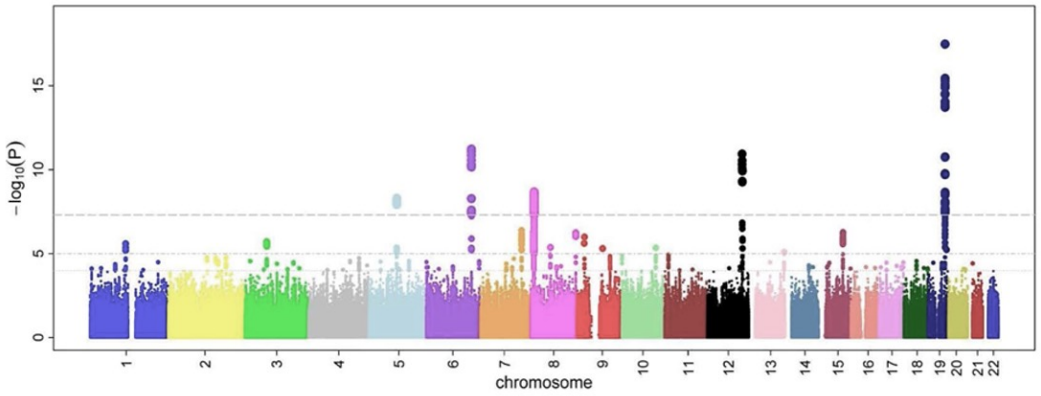
NGS – variant analysis

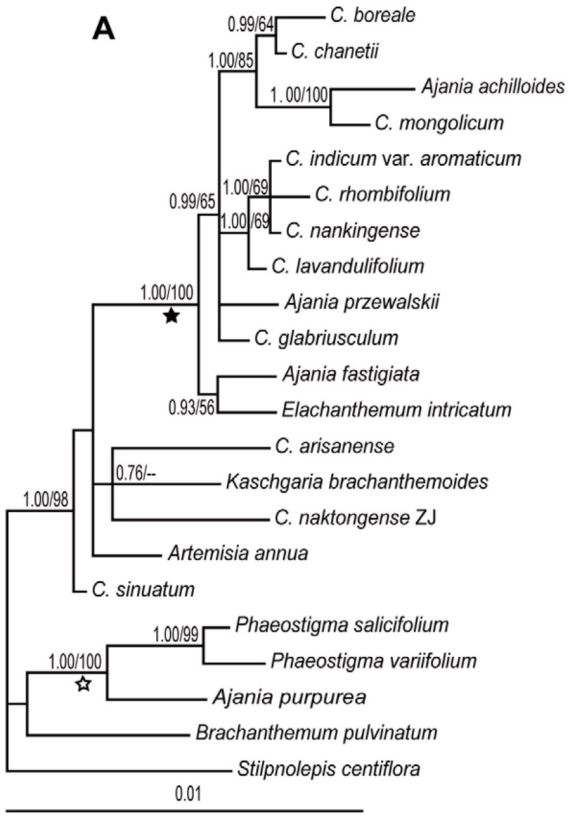
Introduction to variant analysis

Why study variants?

- Find causes for phenotypic variation
- Understand relatedness



https://en.wikipedia.org/wiki/Genome-wide_association_study

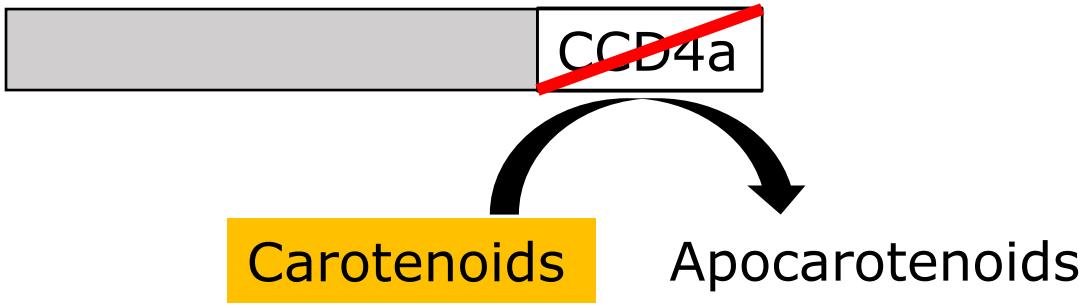


Liu PL et al. PLoS One (2012) 7:e48970

Mutation

Causes variation

Change in DNA sequence



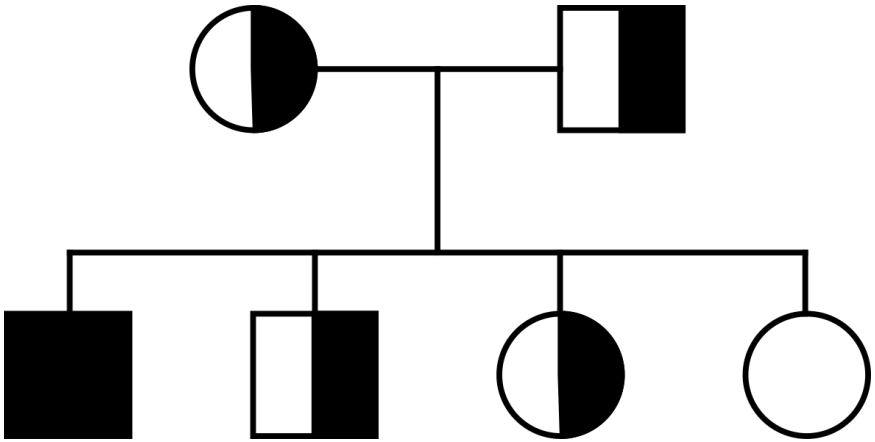
Mutations - causes

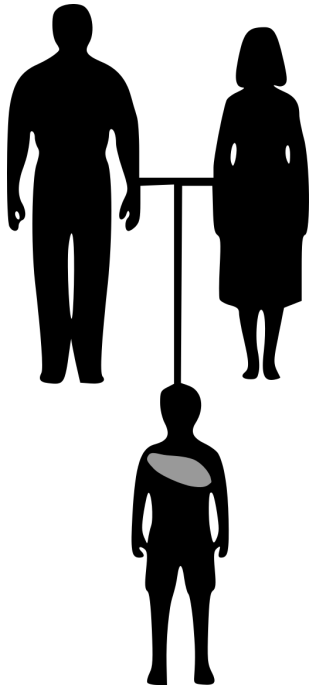
- Repair mistakes
- Unbalanced cell division
- Transposable elements

https://nl.wikipedia.org/wiki/Springend_gen

Mutations - types

- inherited – germline variant
- cells – caused by somatic mutation



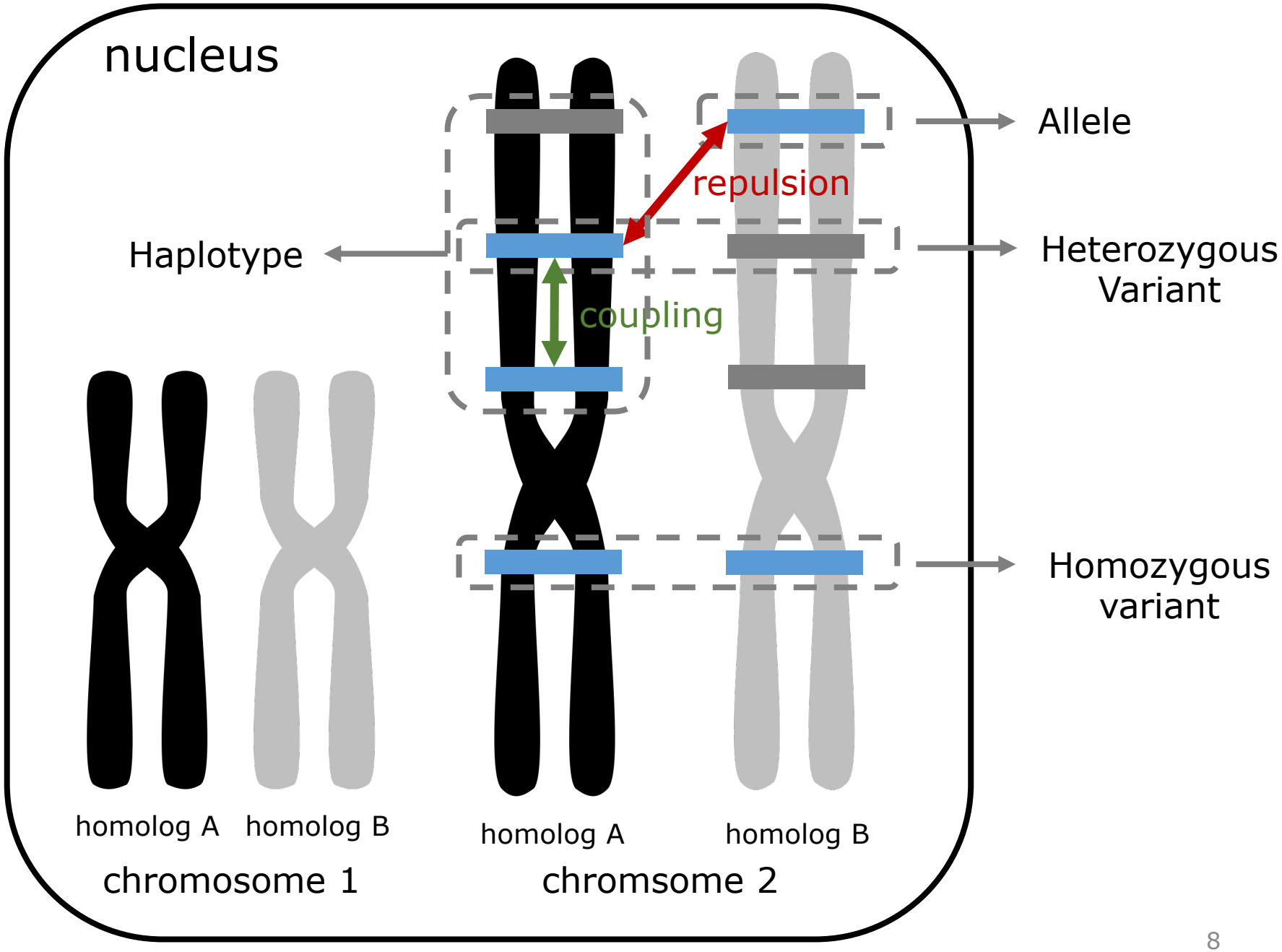



Question

Some definitions..

- **Mutation**: a change in DNA
- **Variant**: any difference that exists between any DNA
- **Polymorphism**: variation that is common in a population (often AF > 1%)

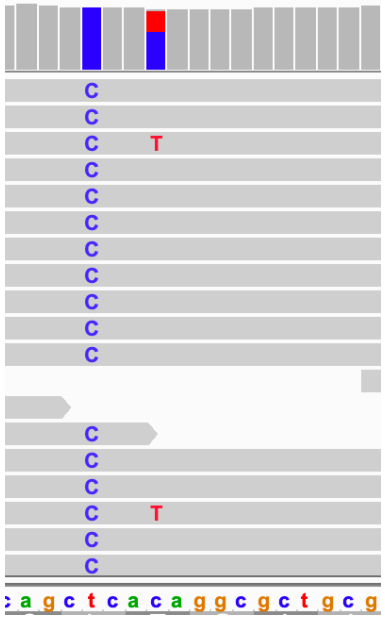
Variant vs polymorphism can be problematic: depends on the population

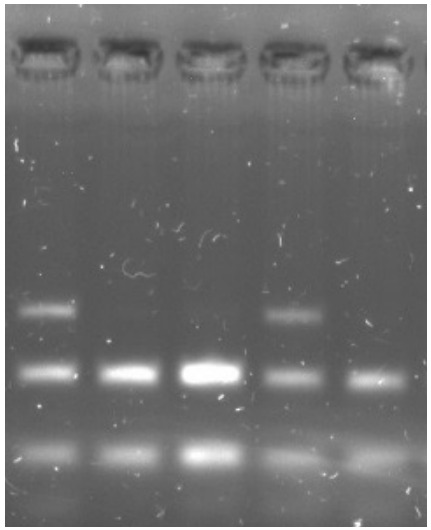

nucleus
Allele
repulsion
Haplotype
Heterozygous
Variant
coupling
Homozygous
variant
homolog A
homolog B
homolog A
homolog B
chromosome 1
chromsome 2

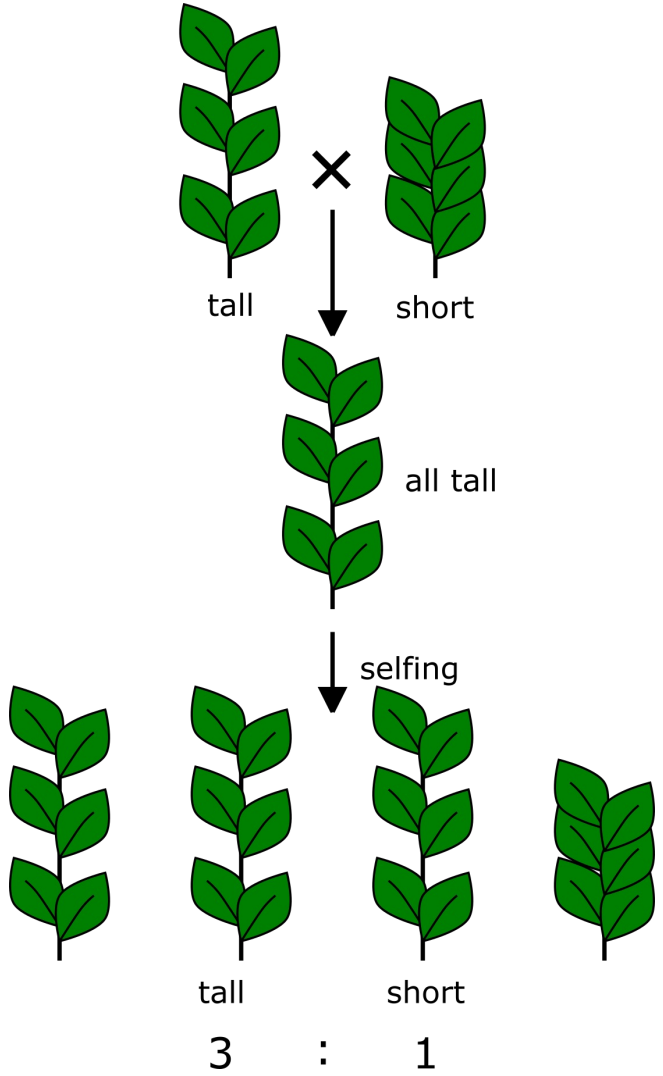
Question

Detecting variants

- Phenotypic analysis
- Molecular analysis
  - Sequencing







Small variants

- Single nucleotide variant (SNV)

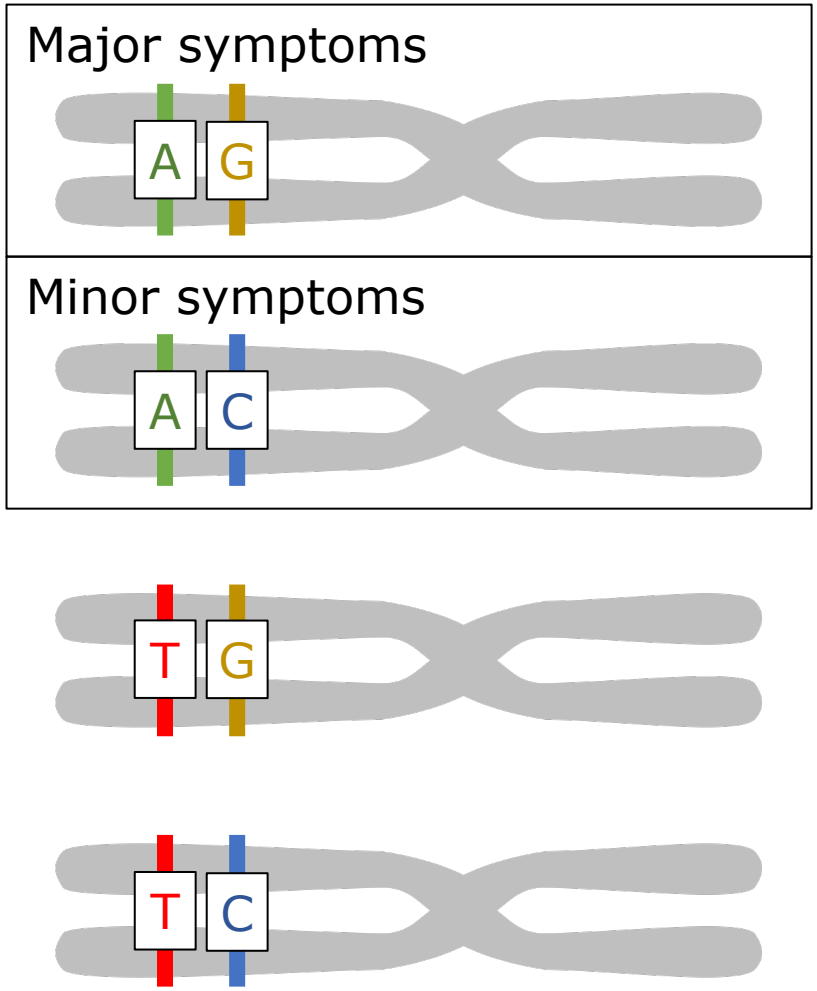
```
ATCATGACCGTCA
ATCATGTCCGTCA
```

- Insertion/deletion (INDEL)

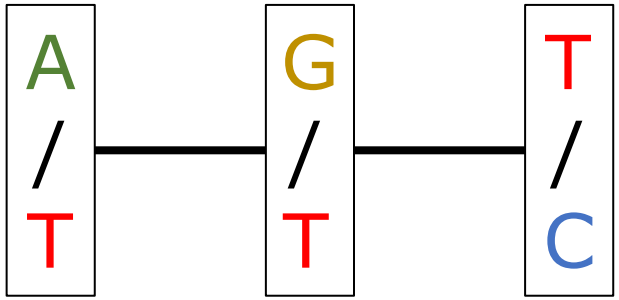
```
ATCATGACCGTCA
ATCATG---GTCA
```

Haplotypes

- NGS variants: mostly SNP
- Most SNPs are bi-allelic e.g. [A/T], [G/C]
- Genetic variation is often multi-allelic

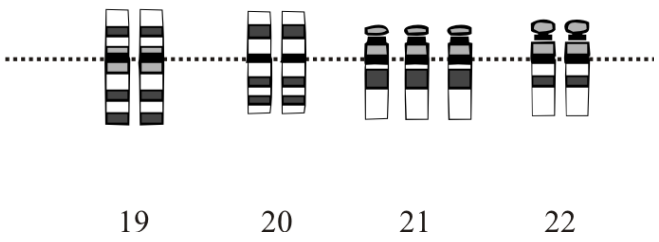


Question



Large variants

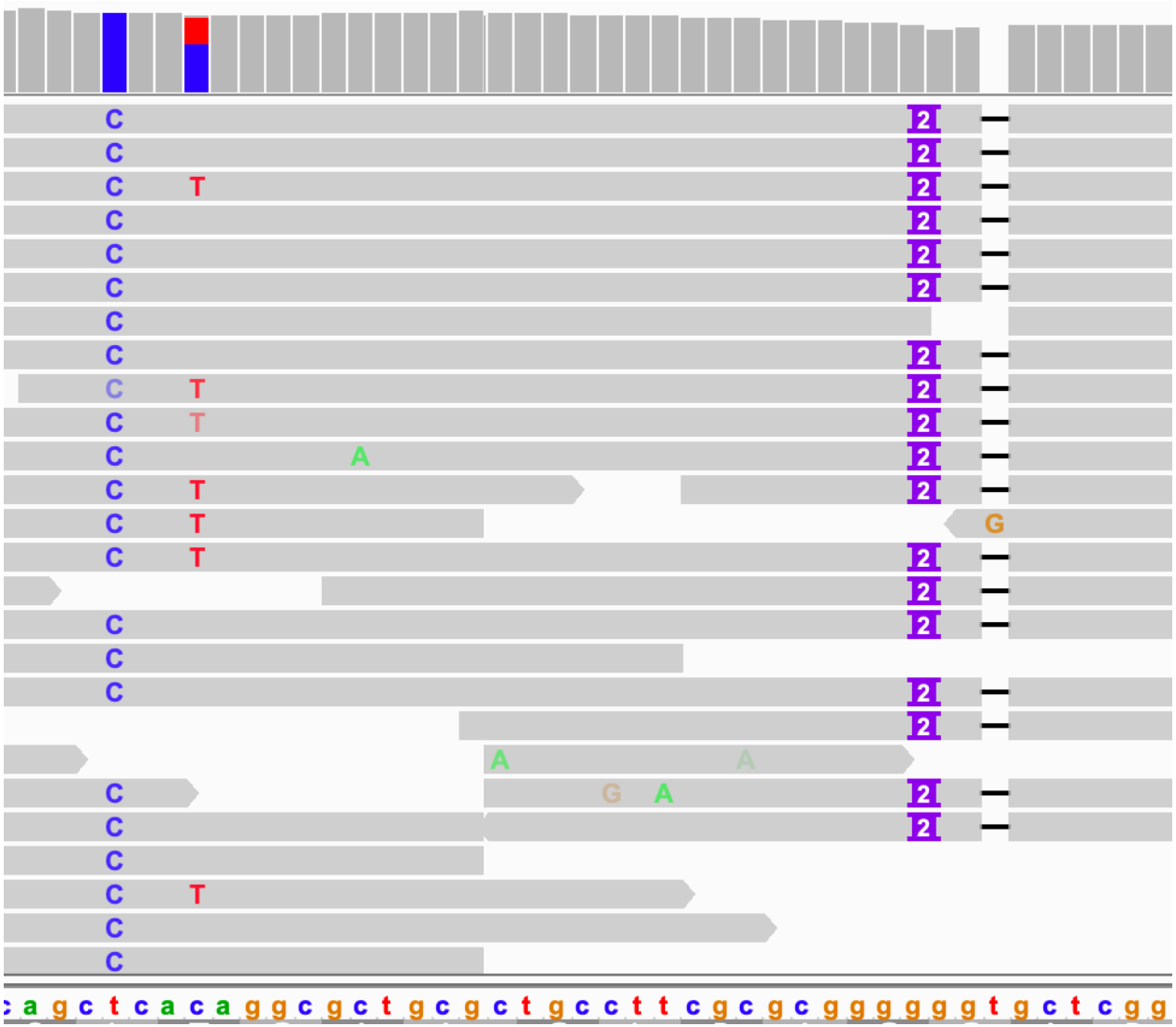
- Structural variance (> 1,000 base pairs)
  - Copy number variation
  - Translocations
  - Inversions
  - Deletions/insertions
- Chromosomal abberation



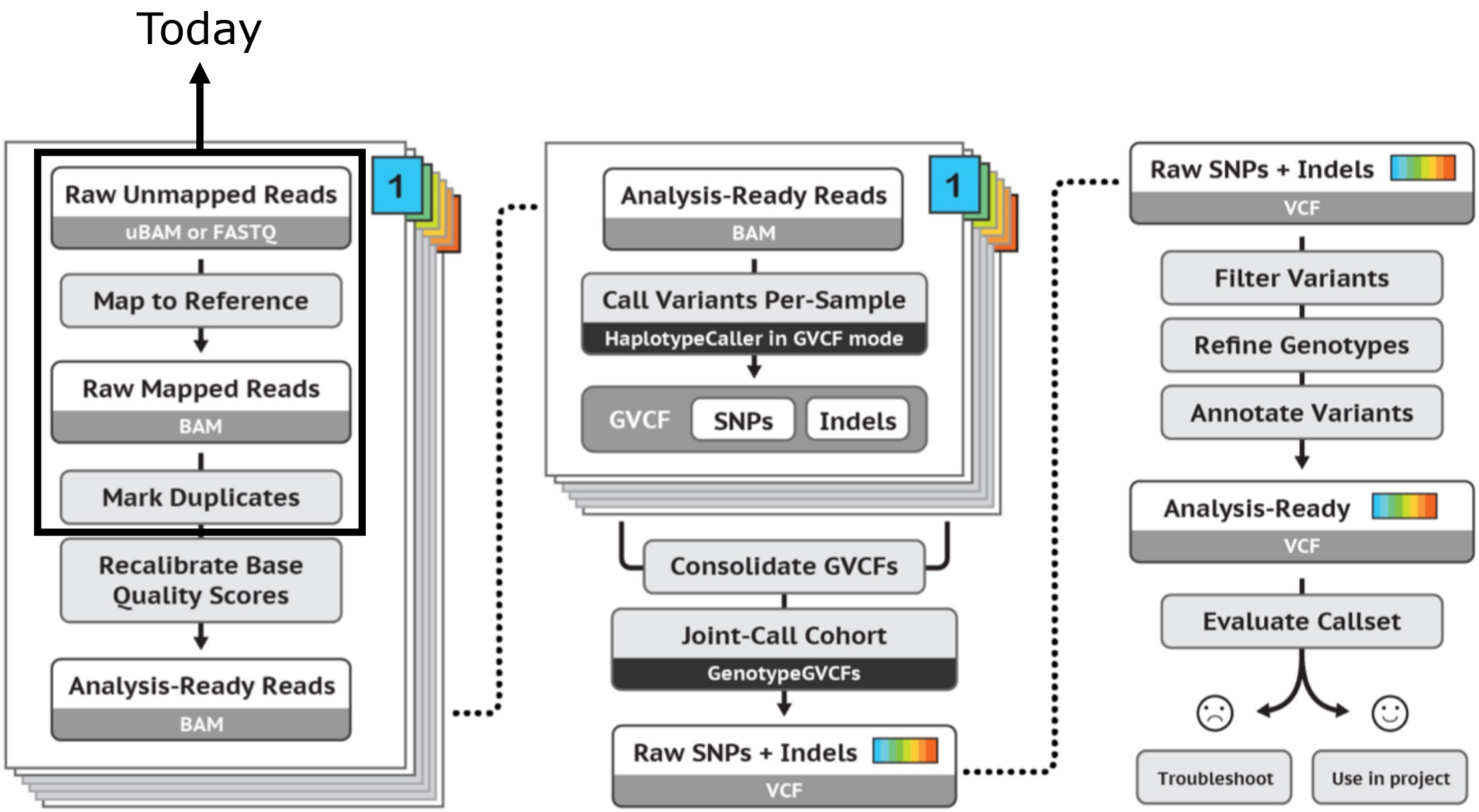
https://en.wikipedia.org/wiki/Aneuploidy

This course

- Inherited (germline) small variants
- Detection by next generation sequencing (NGS)



GATK



https://gatk.broadinstitute.org/hc/en-us/articles/360035535932-Germline-short-variant-discovery-SNPs-Indels-