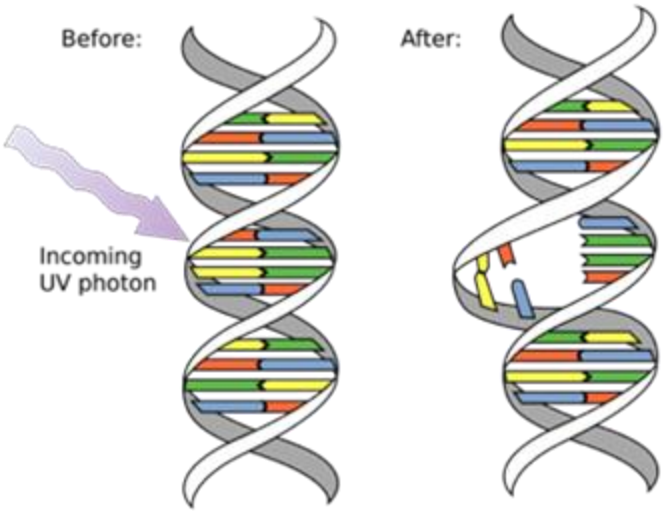
# Somatic Mutation Calling

# Cancer is a disease of the genome

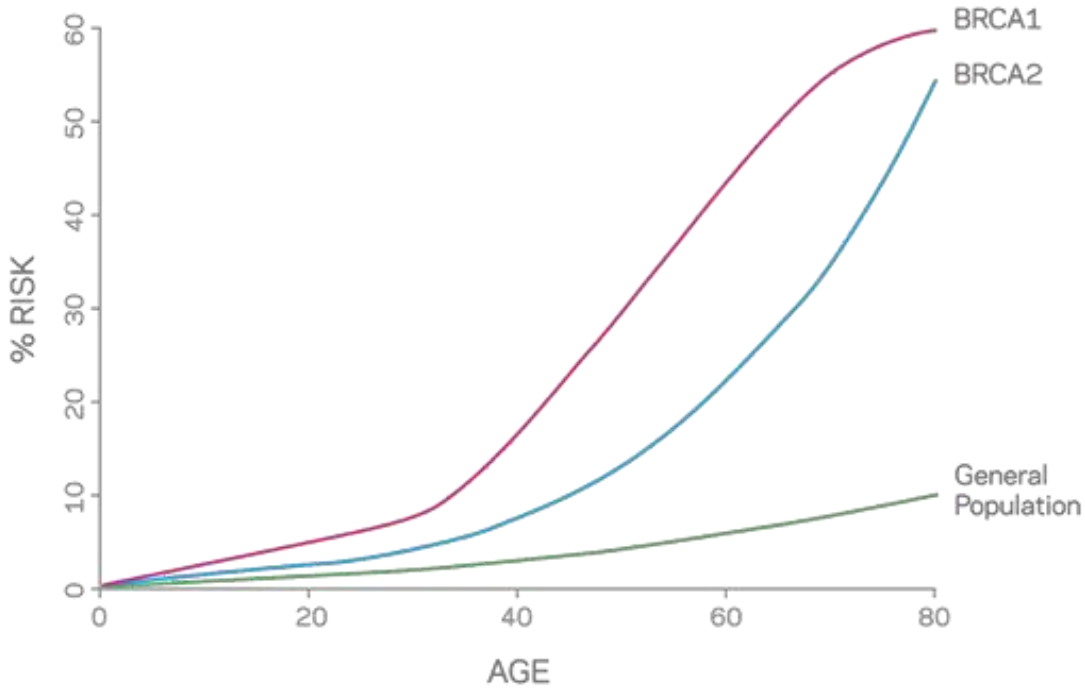
- Cancer is caused by **somatic** mutations

# Cancer is a disease of the genome

- Cancer is caused by **somatic** mutations
- These mutations are introduced into the genome of a cell (errors in DNA copying, UV light, chemicals)
- Most cancers require around 3 driver mutations



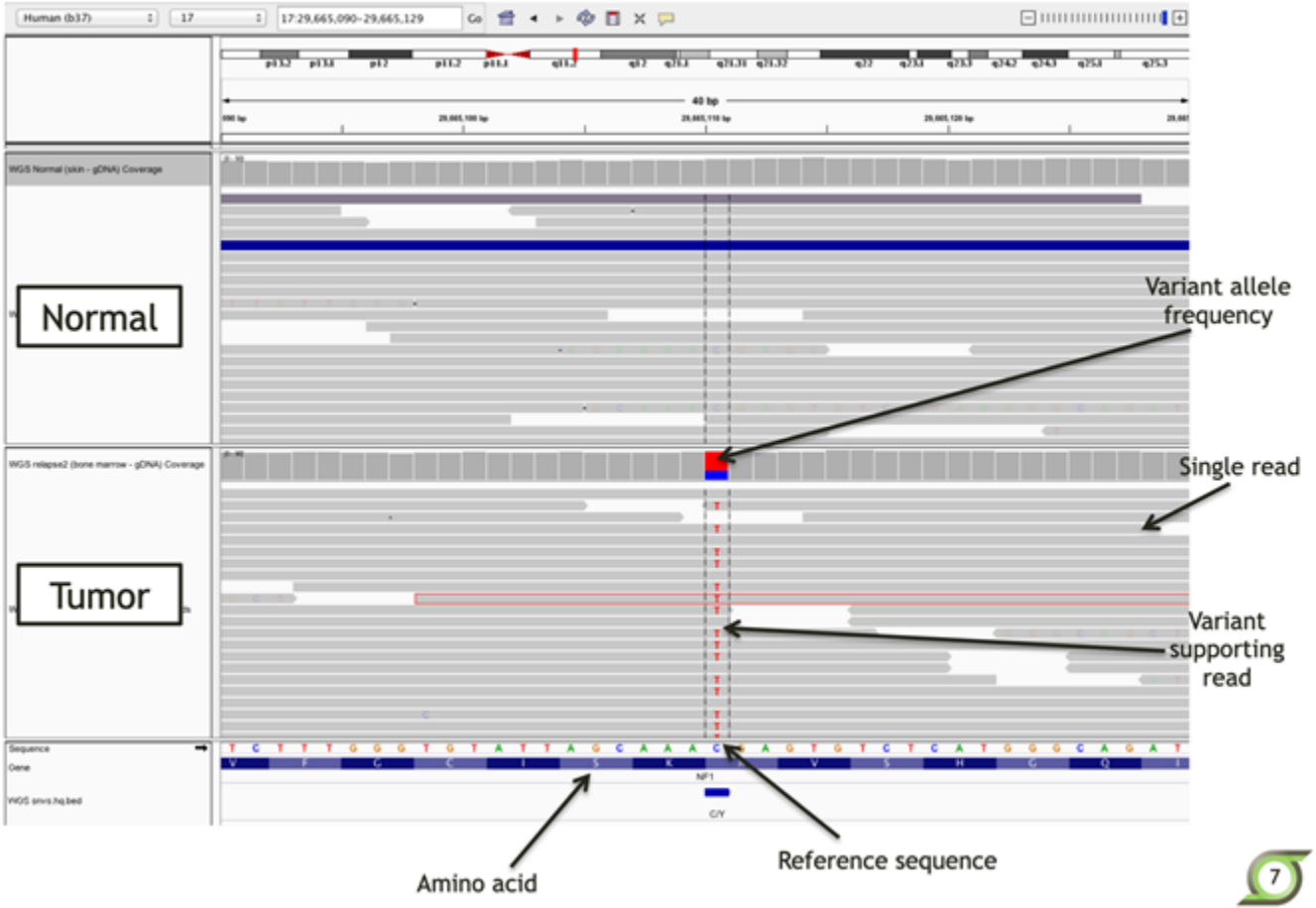
# Germline Predisposition



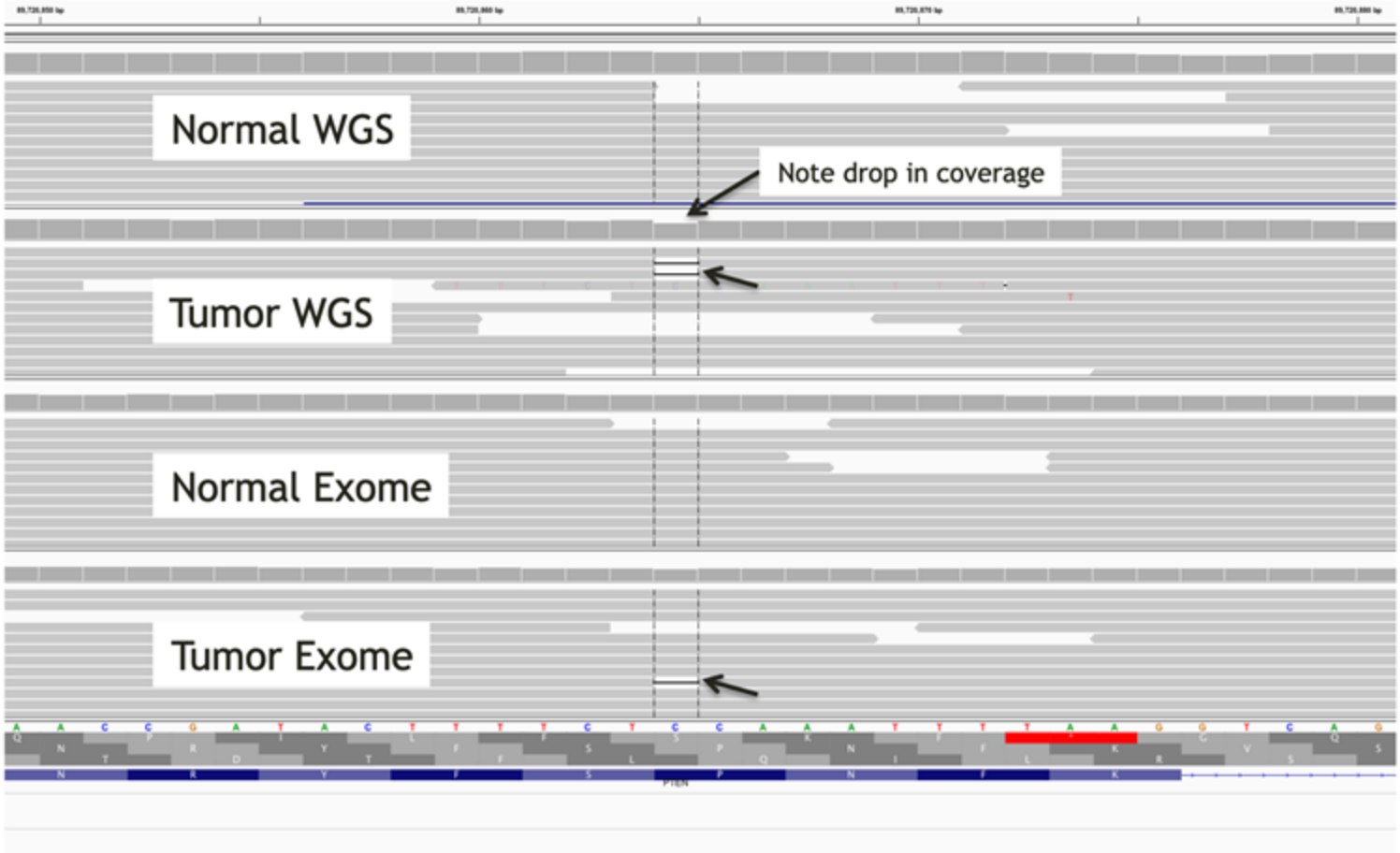
# Cancer Sequencing

- In cancer, we have to (at least) double sequencing costs
- Uses both a tumor sample and a matched normal
- We compare them to find somatic mutations

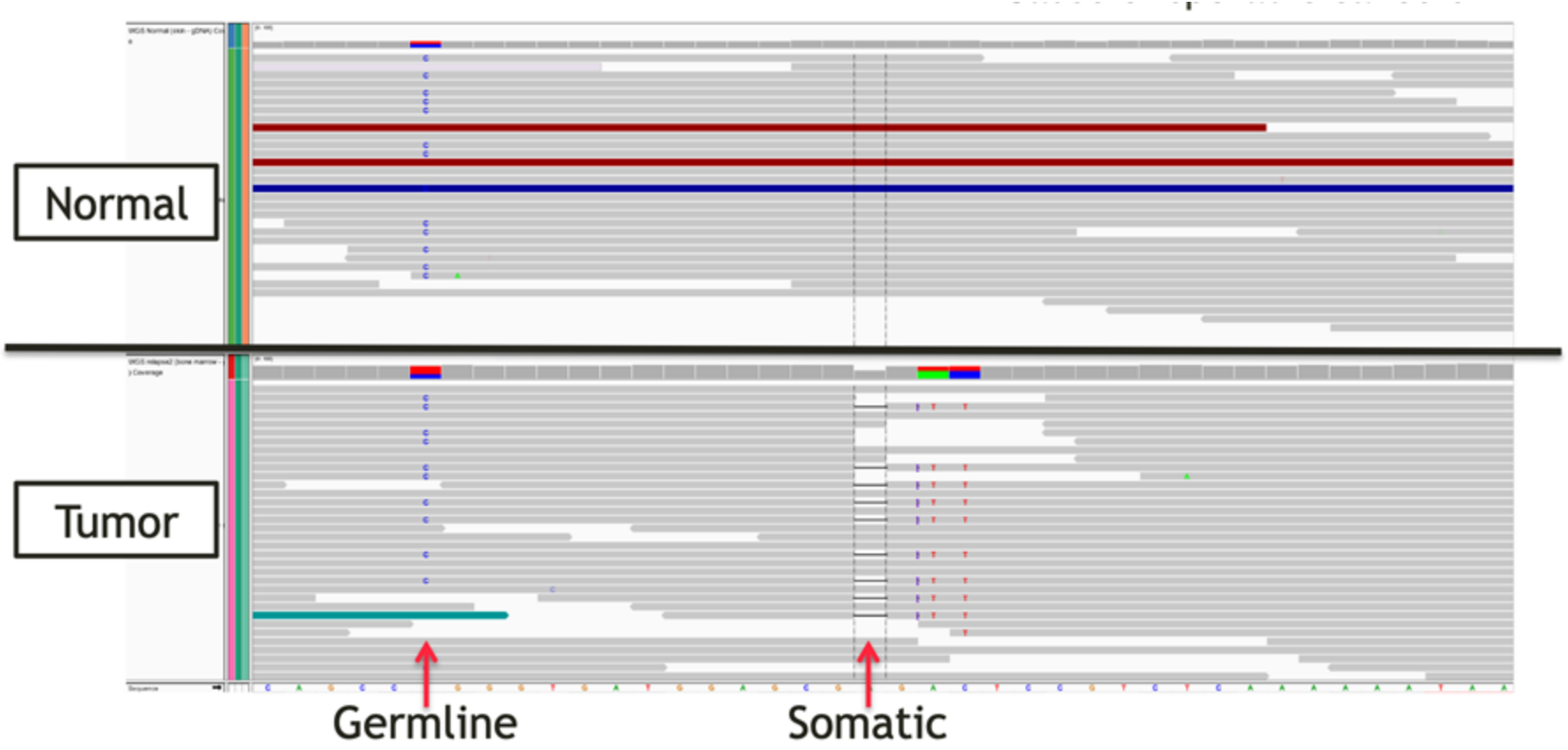
# What do somatic variants look like?



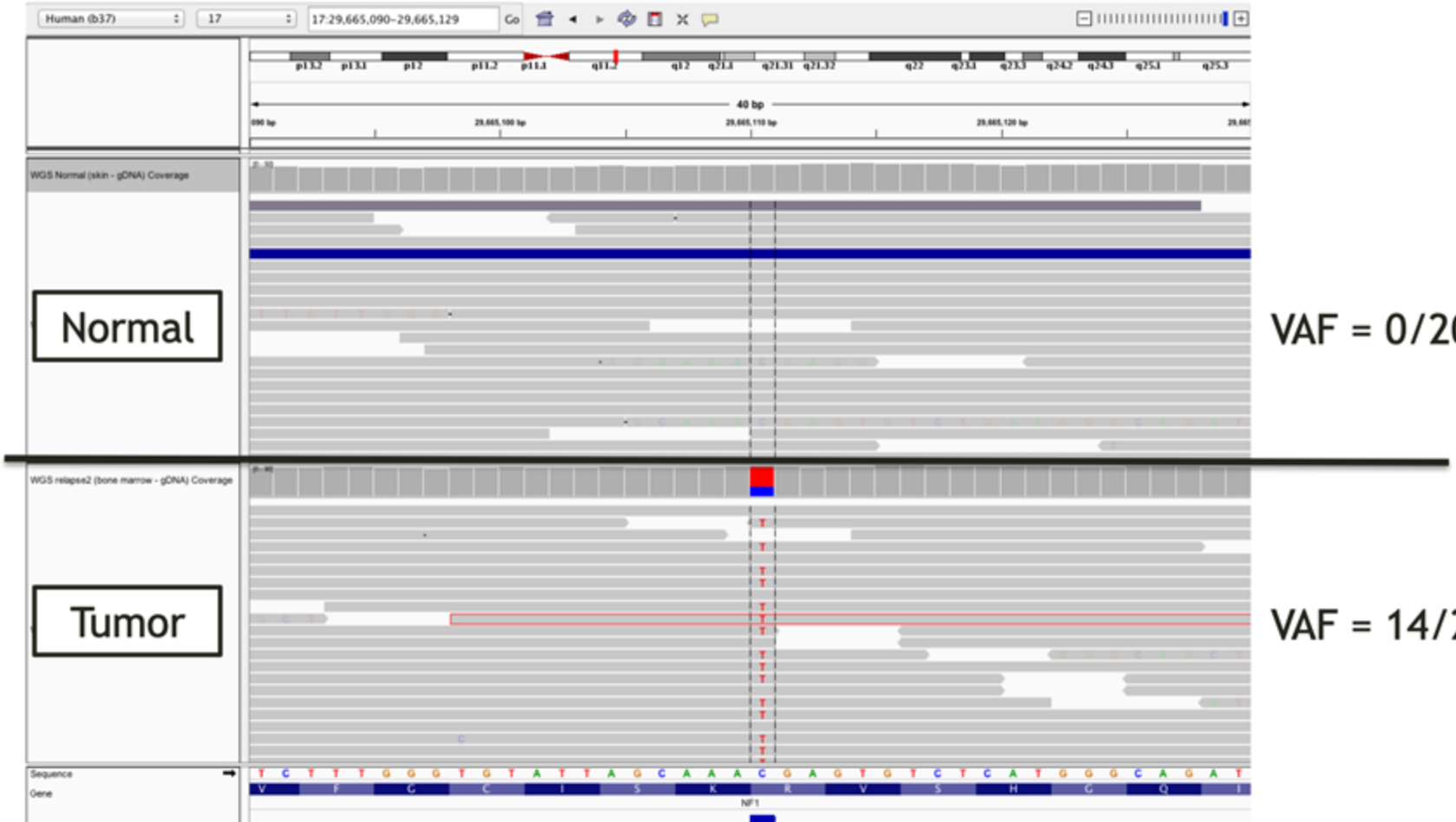
# Indels


Normal WGS
Note drop in coverage
Tumor WGS
Normal Exome
Tumor Exome
PTEN

# Germline vs Somatic



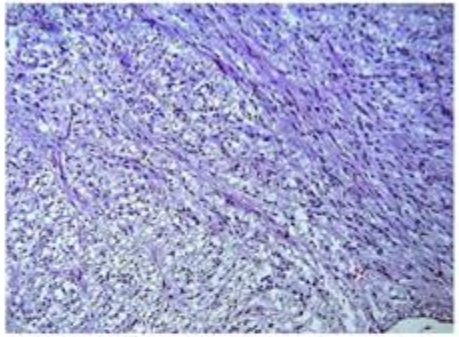
VAF = Variant reads / Total reads



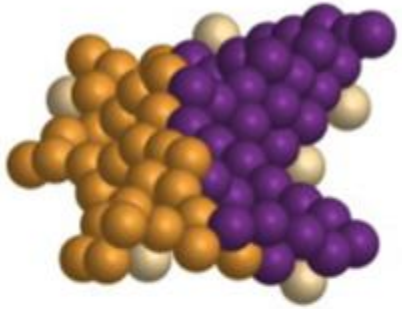

VAF = 0/20 = 0%

VAF = 14/20 = 70%

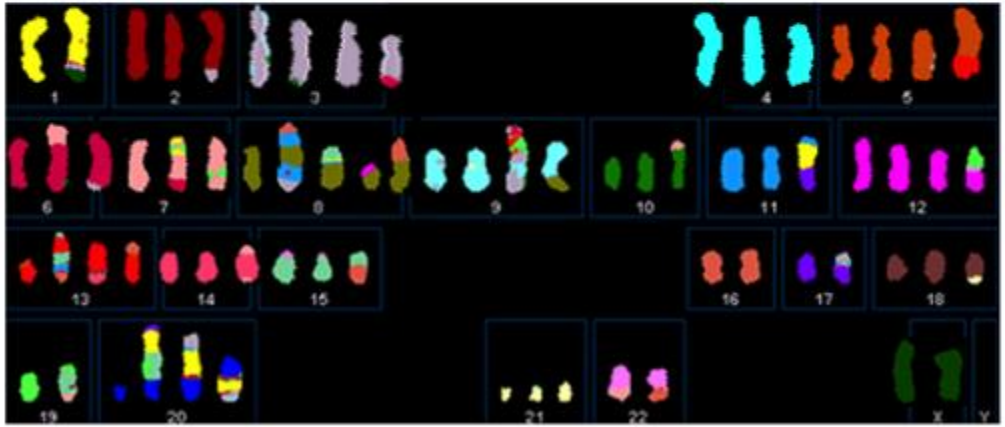
# Tumors are often impure, heterogeneous, and aneuploid



Tumors are often impure
(contain normal cells)



Tumors are often genetically
diverse collections of cells




Tumors may be aneuploid

# How does purity influence VAF?

VAF = Variant reads / Total reads


VAF = 0/20 = 0%

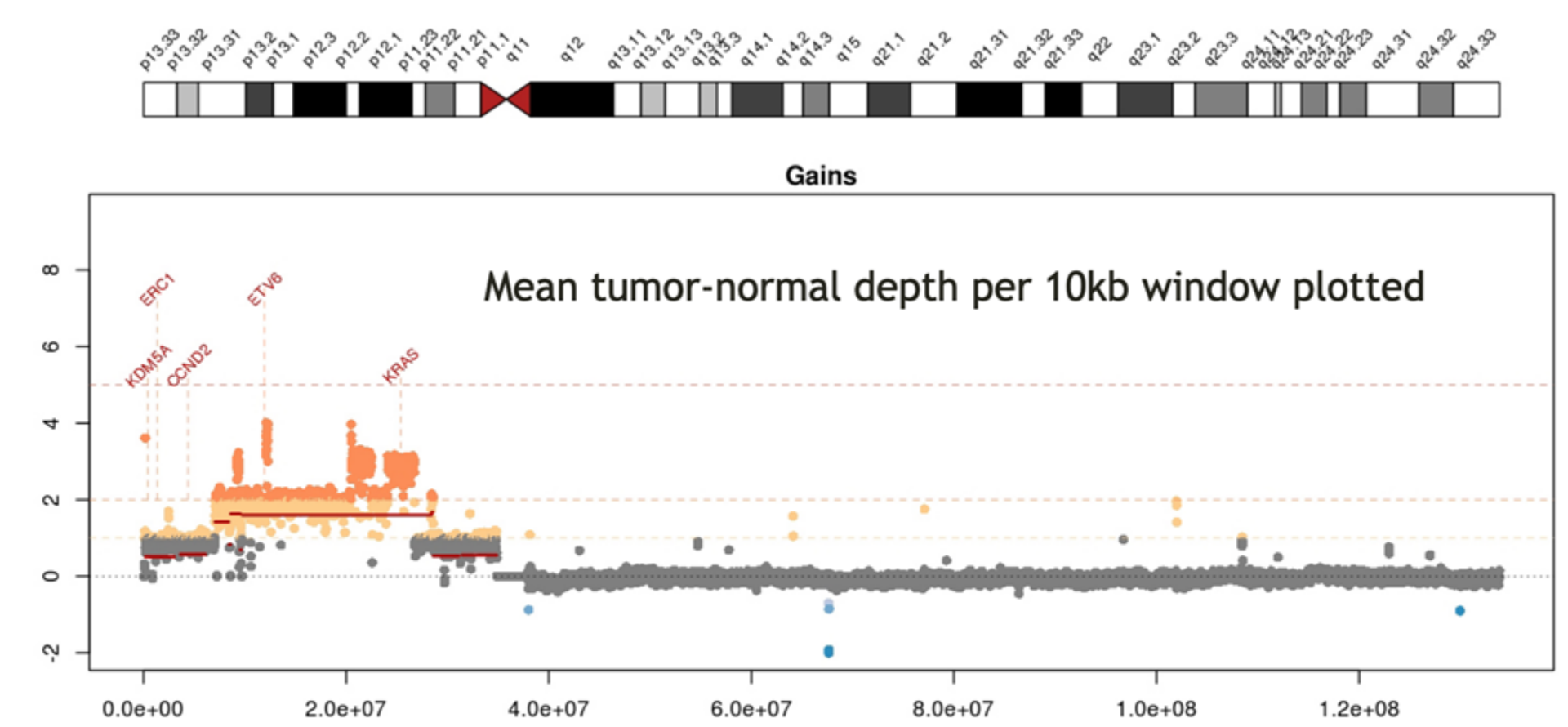
VAF = 14/20 = 70%

# How does purity influence VAF?

VAF = Variant reads / Total reads

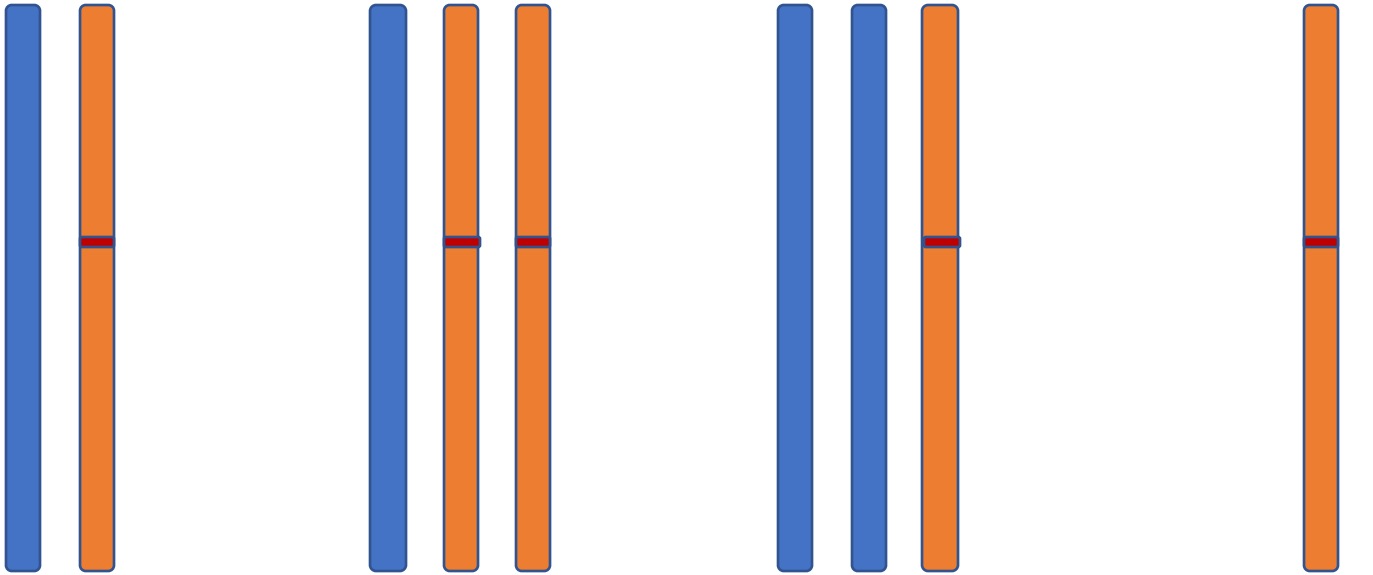

VAF = 0/20 = 0%

VAF = 5/20 = 25%




KRAS amplification in a metastatic breast cancer

# How does copy number influence VAF?



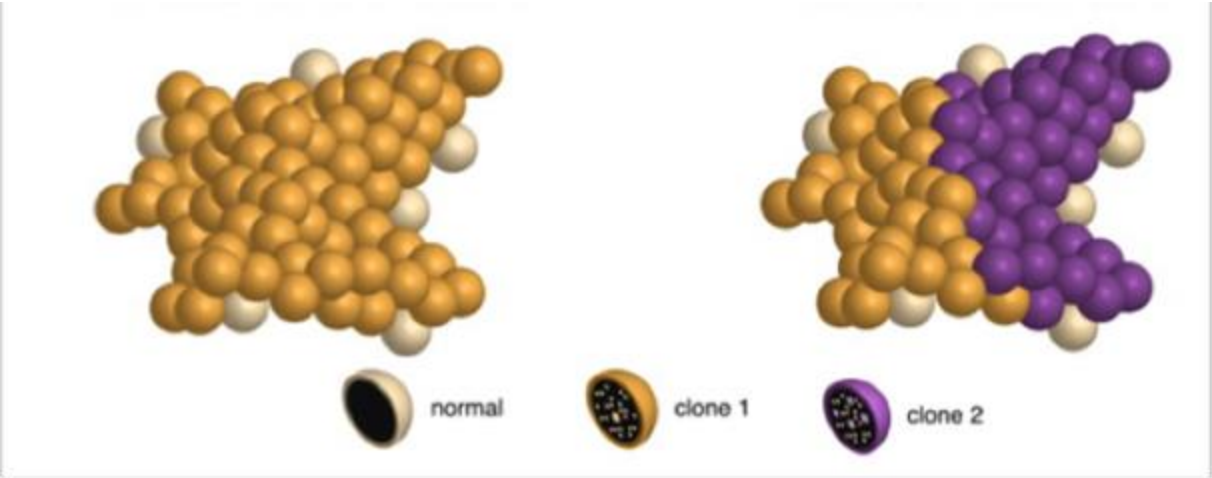
2 copies
50%
VAF

3 copies
66%
VAF

3 copies
33%
VAF

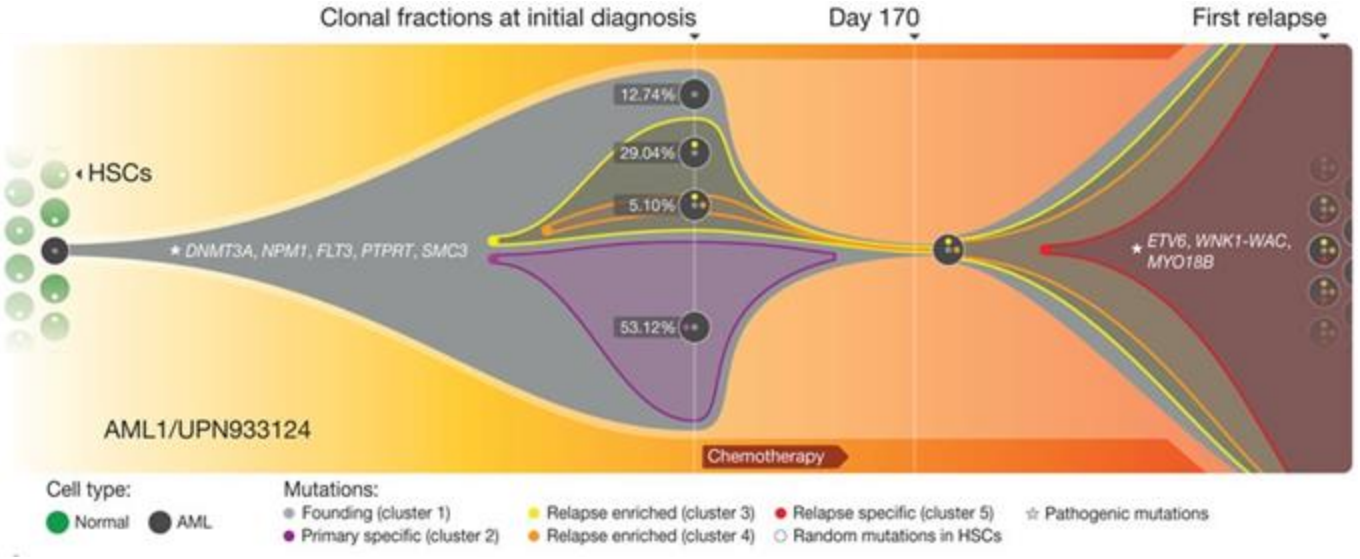
1 copy
100%
VAF

# How does clonality influence VAF?



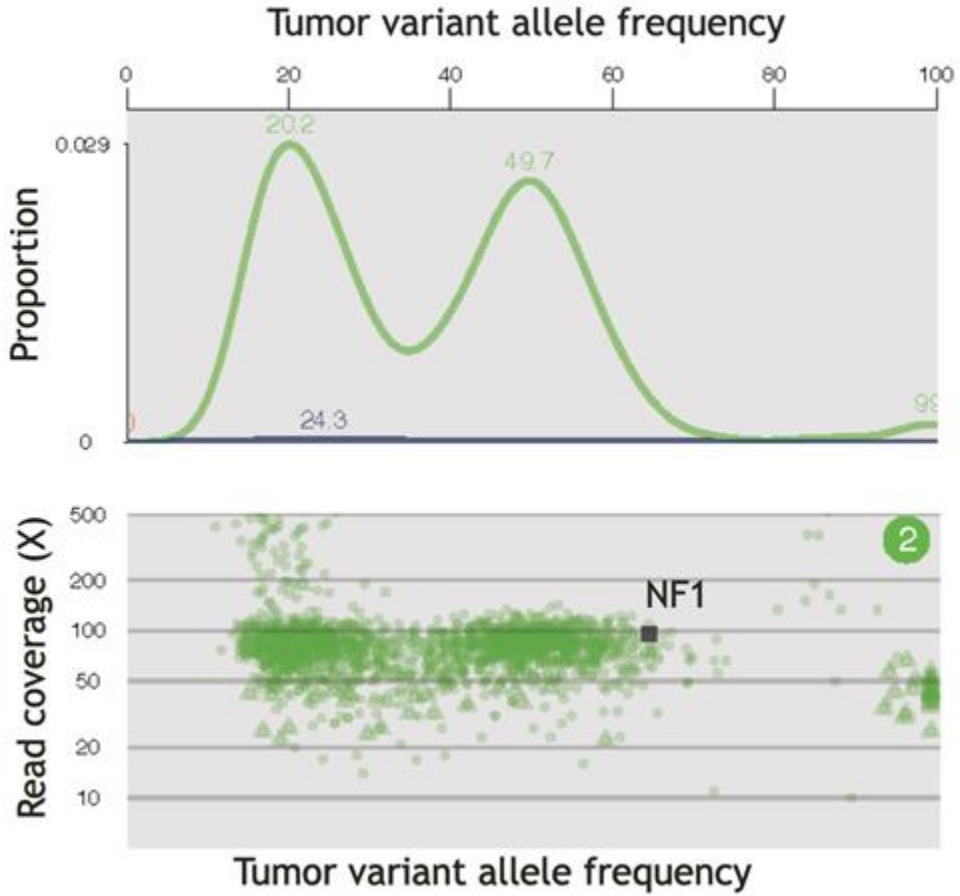

- Subclones contain genetically diverse populations of cells
- Evolution occurs at the molecular and cellular levels
- The growth rates for subclones are often different

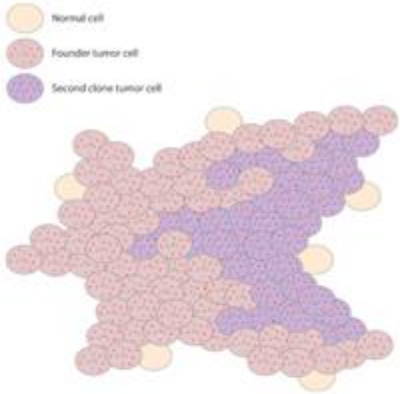
# Clonal evolution in relapsed AML




Nature 481, 506–510
doi:10.1038/nature10738

# Dominant clone vs. sub-clonal (and driver vs. passenger)




**WGS data**

# Somatic variant calling is harder

- There are more factors to consider, a wider range of possibilities, and often, more sketchy samples

# Somatic Variant detection callers

- Mutect
- Strelka
- Varscan
- Pindel
- Lancet
- Deep Somatic
- VarDict
- Seurat
- Shimmer
- more...

Lots of choices!

# Use of multiple variant callers can improve sensitivity and accuracy