Introduction to cancer genomics
Seminar series

Seminar series outline

1. Introduction to cancer genetics (June 8th)
   Graham Bignell

2. Sequencing cancer genomes (June 15th)
   Phil Stephens

3. Translation of cancer genomes (June 22nd)
   Ultan McDermott

4. Dog and devil (June 29th)
   Elizabeth Murchison

Introduction to cancer genetics

Outline

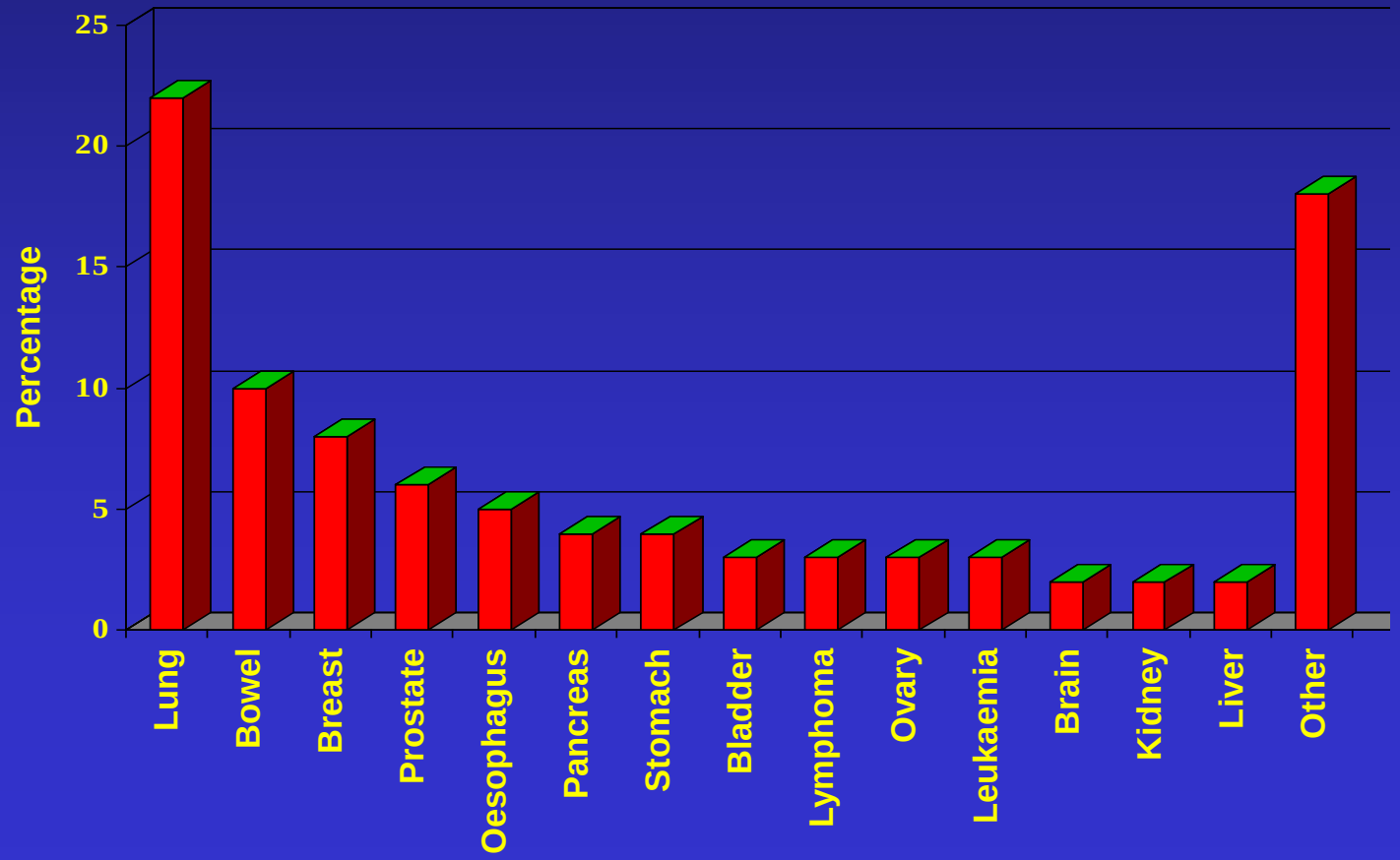
1. Cancer incidence
2. Cancer - a disease of DNA
3. Cancer genes
4. Types of mutations
5. Cancer development

Cancer incidence

One in three people in the Western world will develop cancer

One in five will die from it.

In the UK there were 153 491 cancer related deaths in 2005.



Cancer is not a single disease!

- Cancer arise in different tissues
- Result from different environmental exposures
- Respond differently to different treatments
- Have different prognosis

Cancer - a disease of DNA (1)

- An adult human is composed of ~100 million million cells
- Each cell contains a maternal and paternal copy genome
- Each copy consists of ~3 billion base pairs of DNA
- Of this 3 billion base pairs less than 5% codes for known functional elements (genes etc)

Cancer - a disease of DNA (2)

- Throughout life all cells acquire damage to their DNA
- These can arise from:-
  - chemical exposure – tobacco smoke
  - radiation – UV light exposure
  - viruses – human papillomavirus
  - normal cellular processes – DNA replication/cell division
    (error rate of DNA replication < $1x10^{-9}$ or < 6 per cell division)
- Such changes are efficiently repaired by cells
- However changes that are repaired incorrectly or missed gives rise to mutations

Are all mutations equal?

Only mutations in the relevant genomic regions help the cancer develop

These are termed driver mutations

Most mutations have no effect (termed passenger mutations)

Distinguishing driver from passenger mutations is not always straight forward!

Driver mutations

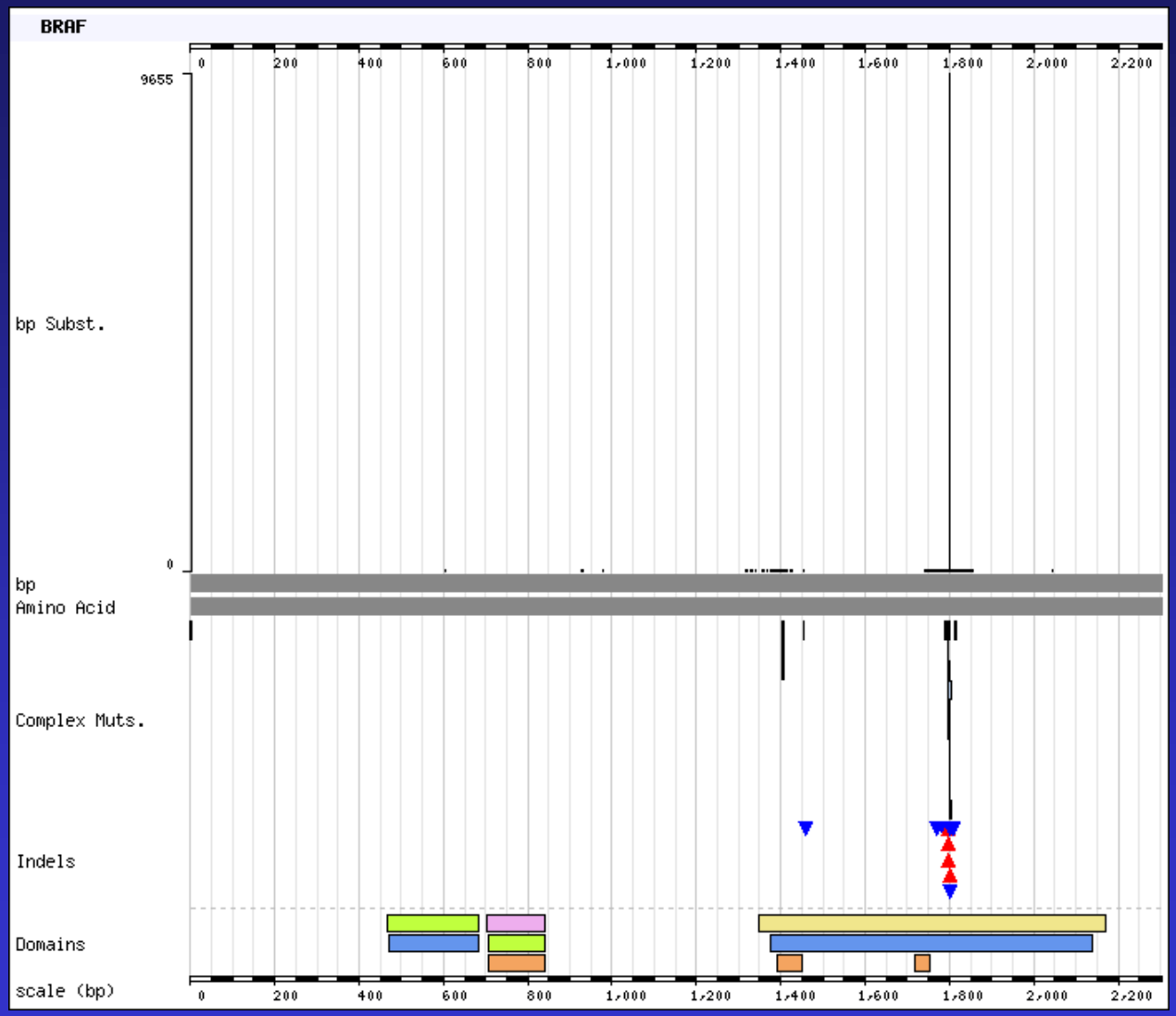
Currently driver mutations have been identified in 427 genes

These genes are termed cancer genes!
(cancer gene census)

Dominant oncogenes (338)
Require mutation of only one of the two alleles which usually results in activation of the protein

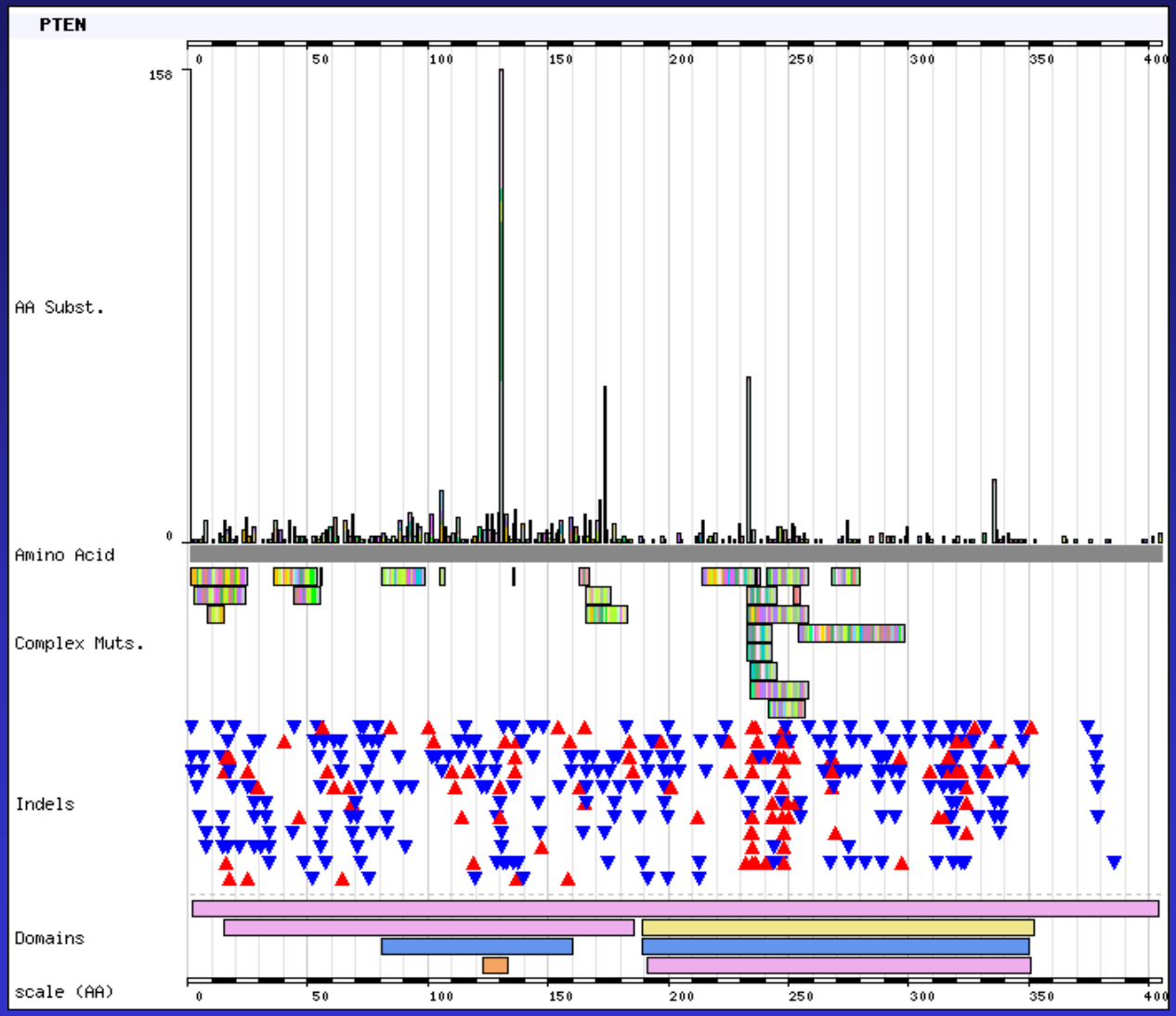
Recessive oncogenes (89)
Require mutation of both (all) alleles resulting in inactivation of protein

Dominant oncogene - BRAF



Cosmic:
13566 mutations

Recessive oncogene - PTEN



Cosmic:
1879 mutations

Types of mutations

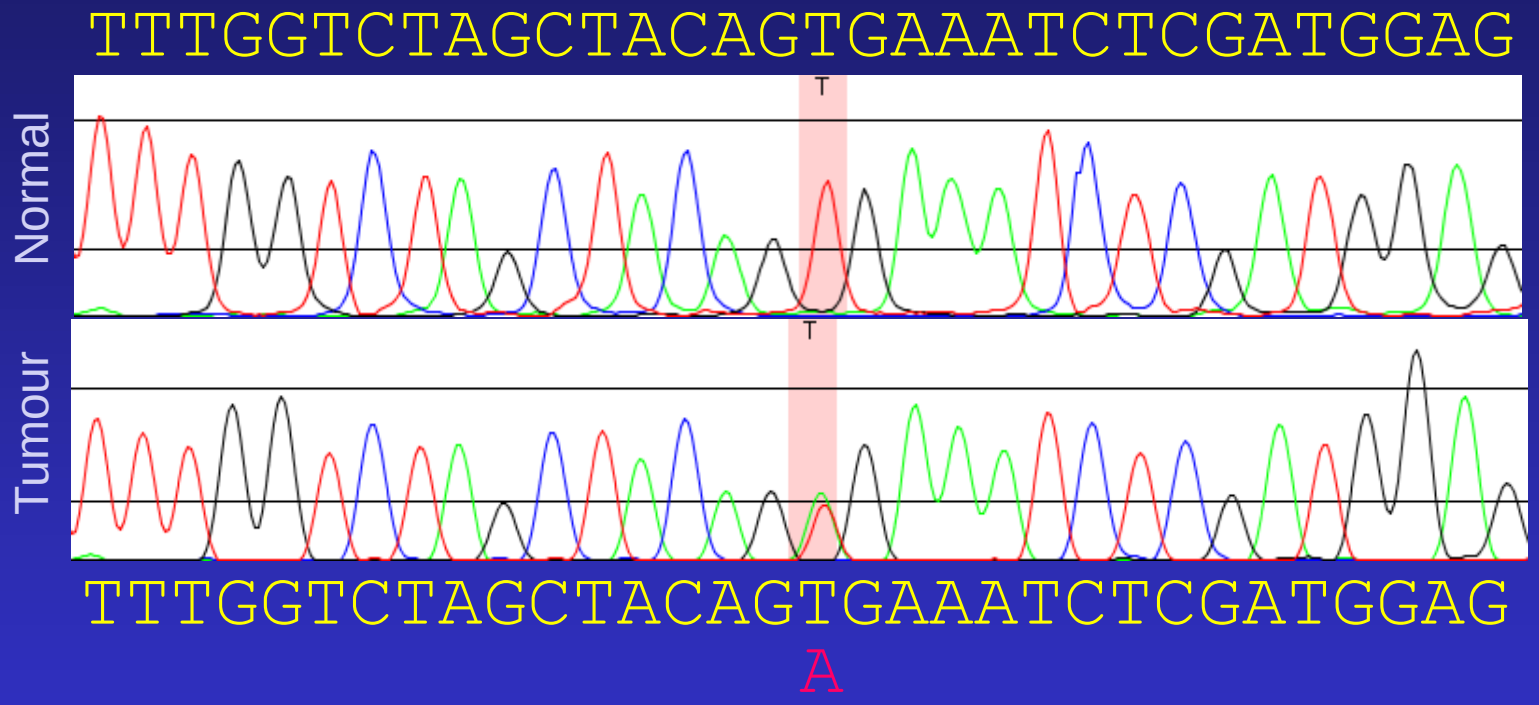
There are five mechanisms by which cancer genes can be mutated

- Intragenic mutations
- Homozygous deletions
- Rearrangements
- Amplification
- Epigenetic inactivation

Intragenic mutation

Base substitutions and small deletions/insertions of bases

BRAF

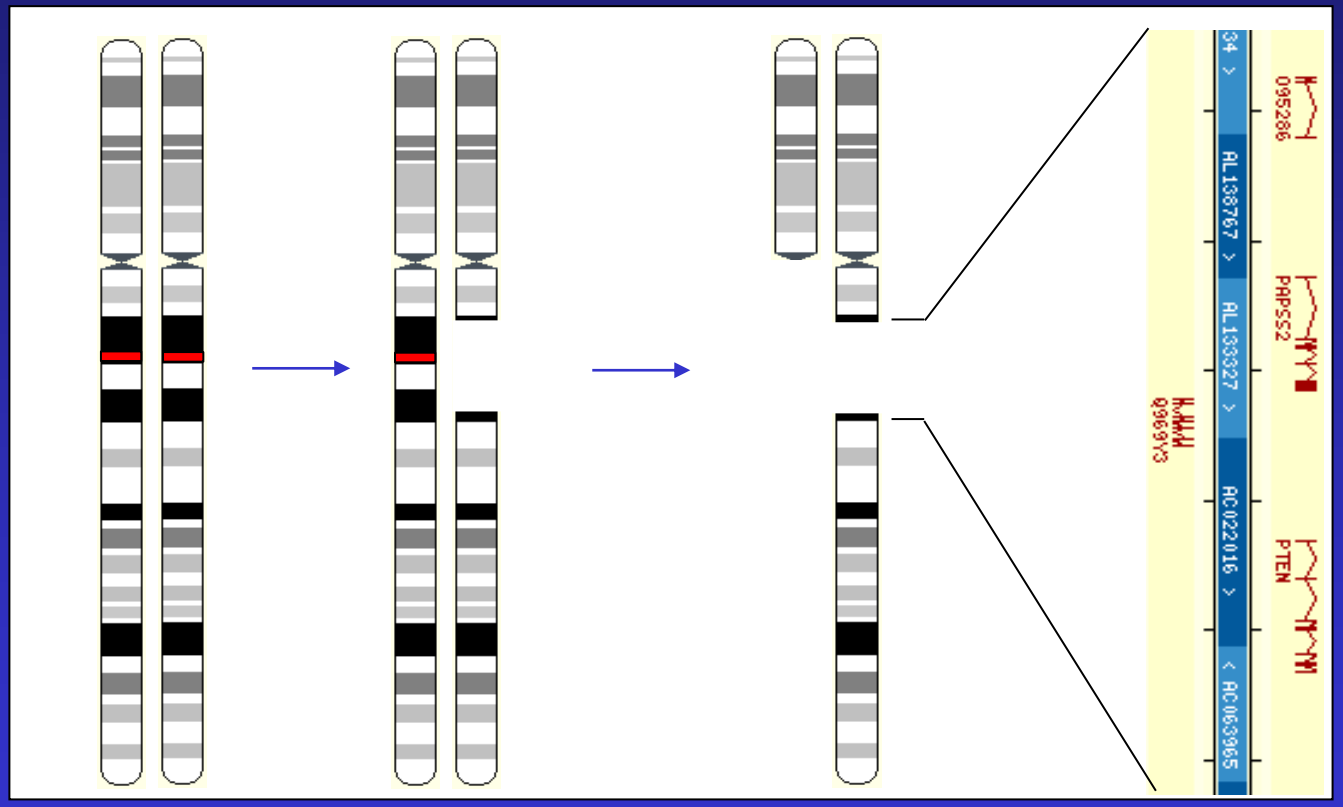


Normal	F	G	L	A	T	V	K	S	R	W	S
Tumour	F	G	L	A	T	E	K	S	R	W	S

Mutation V600E - changes one amino acid from valine to glutamic acid

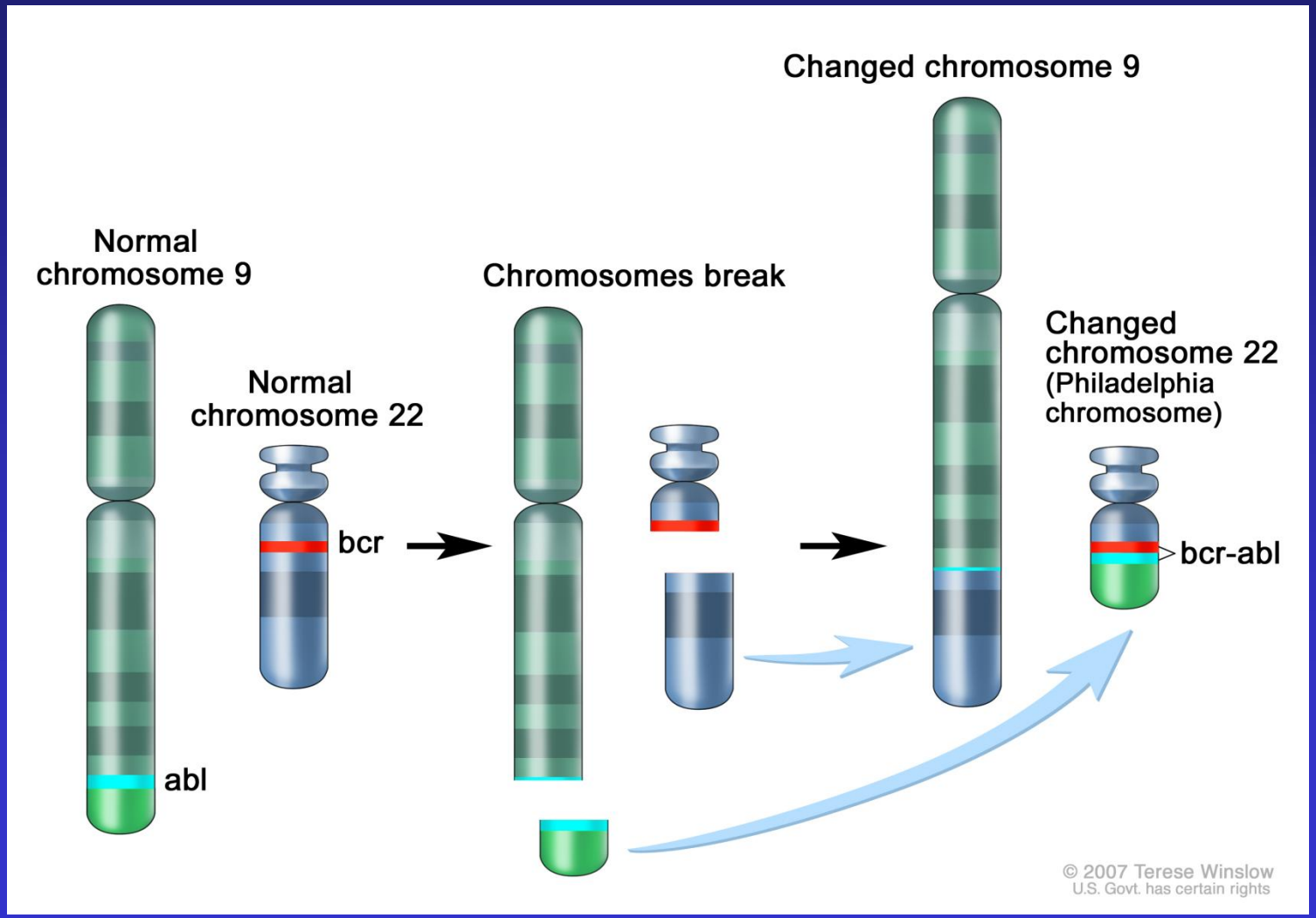
Homozygous deletion

Large scale deletions of both copies of a genomic region



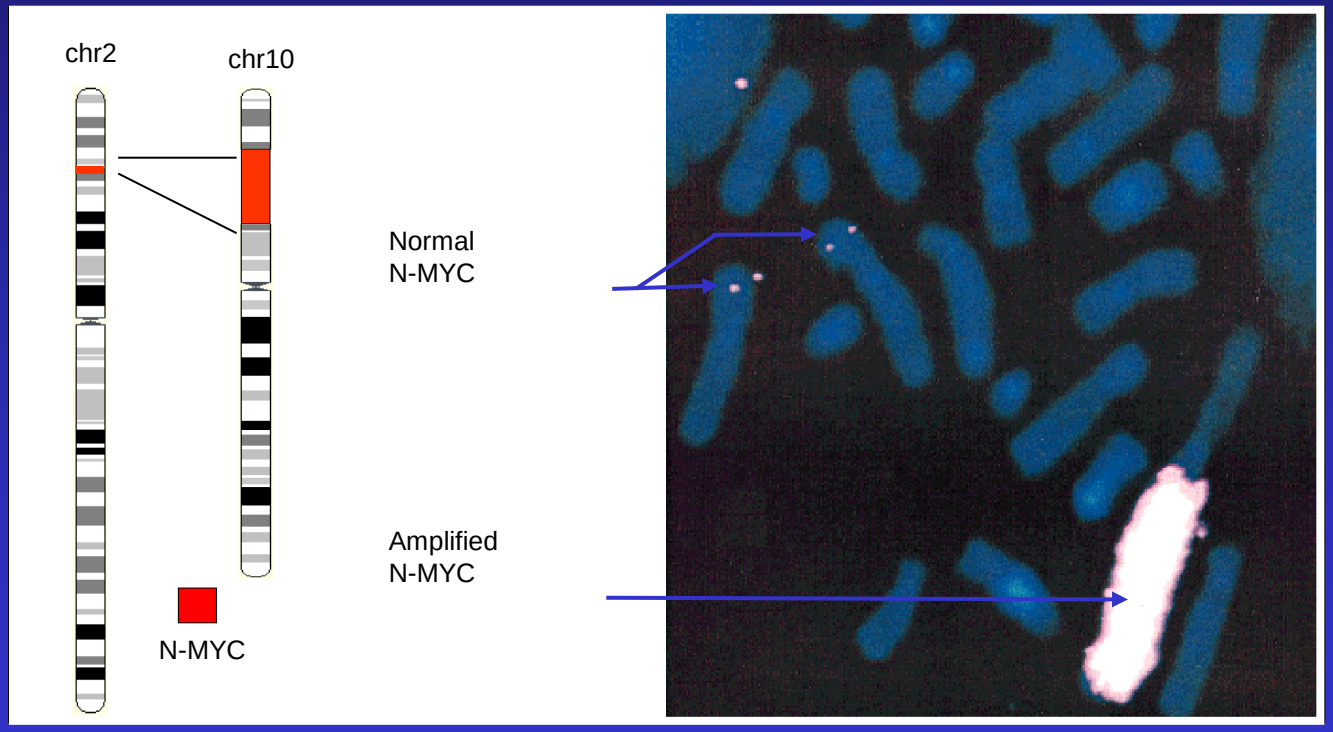
Rearrangement

Exchange of DNA between chromosomes



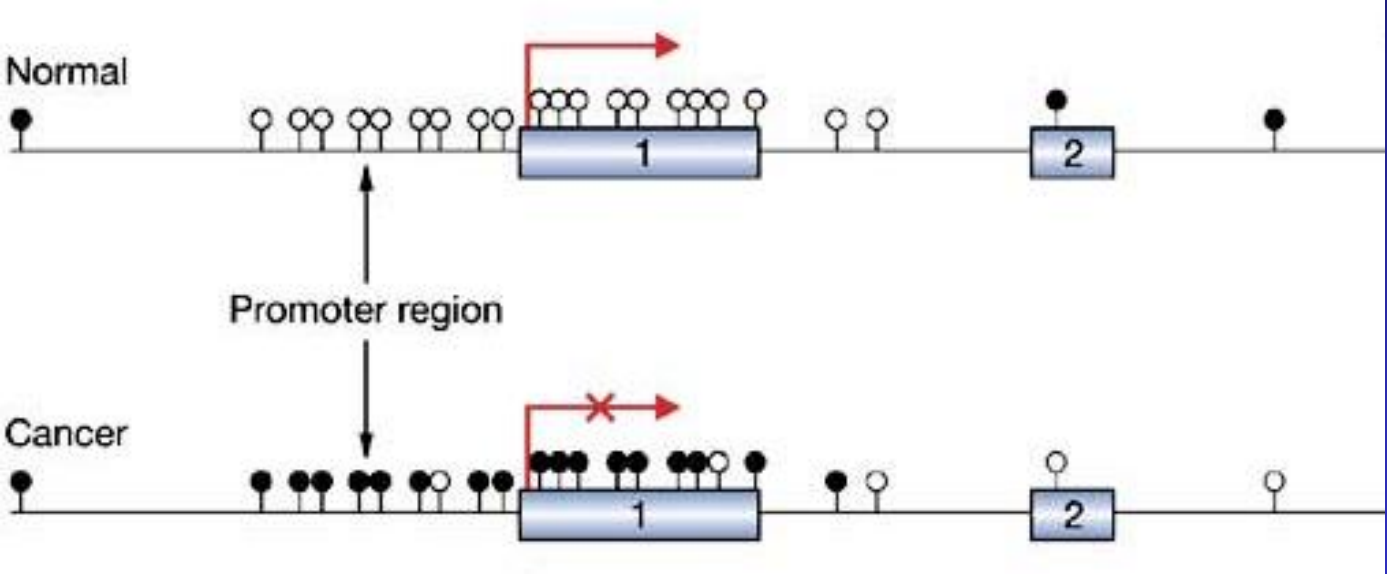
Amplification

High level increase in the number of copies of a genomic region



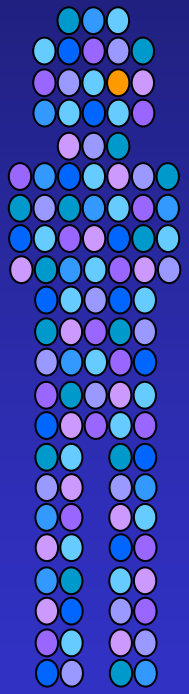
Epigenetic inactivation

Inappropriate switching off of genes



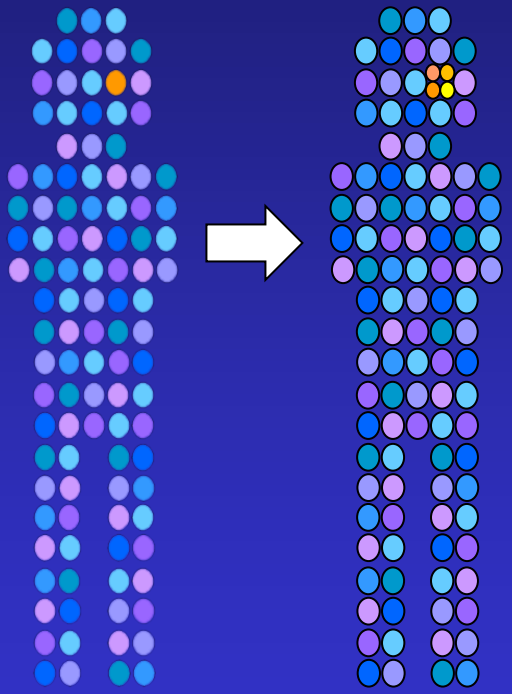
Cancer development

A cancer arises when a single cell begins to behave abnormally (dividing when it should be quiescent)



Cancer development

Benign tumour: a cell has evaded some controls on growth giving rise to a ‘clonal mass’, however they lack many of the aggressive characteristics of more advanced cancer (ie. unlimited invasive growth).



Benign tumour

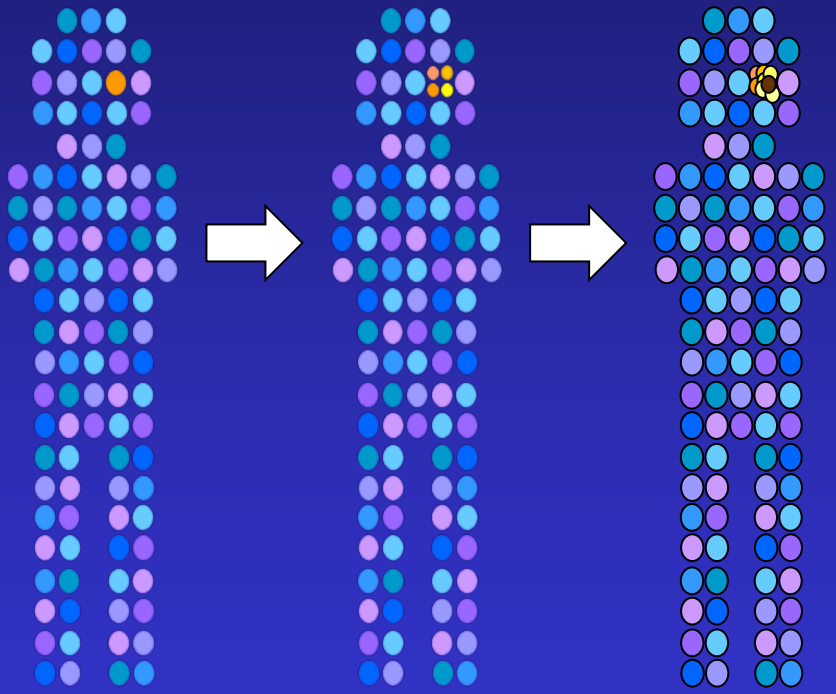
Moles (nevi) are an example of a benign tumour.

82% of nevi have a mutation of the known cancer gene *BRAF.*

BRAF mutations are thought to be the initiating event in melanoma.

Cancer development

in situ Cancer: the tumour has evaded controls on cell division and grows in a disorderly fashion.



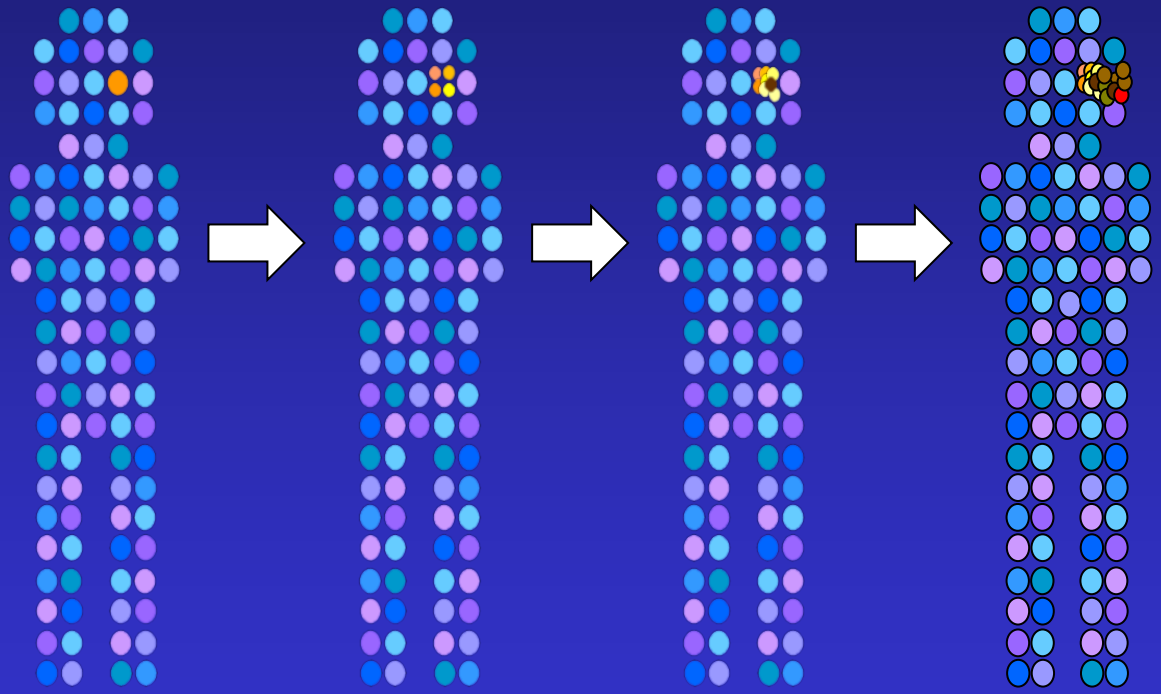
Benign tumour *In situ* cancer

"in situ" means "in its natural place".

The tumour cells are still confined to the site where they originated.

Cancer development

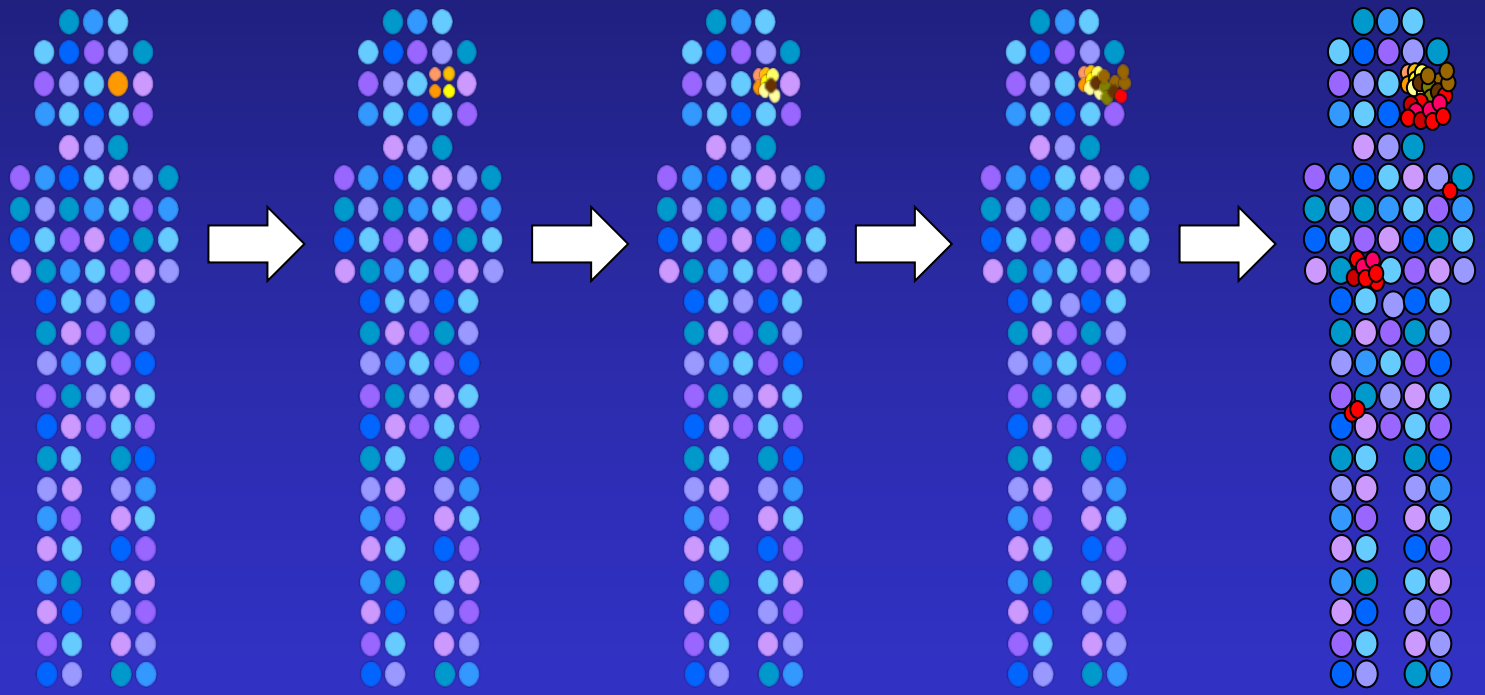
Invasive cancer: the tumour has spread beyond the layer of tissue in which it developed and is growing into surrounding, healthy tissues.



Benign tumour *In situ* cancer Invasive cancer

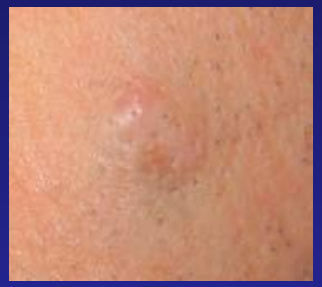
Cancer development

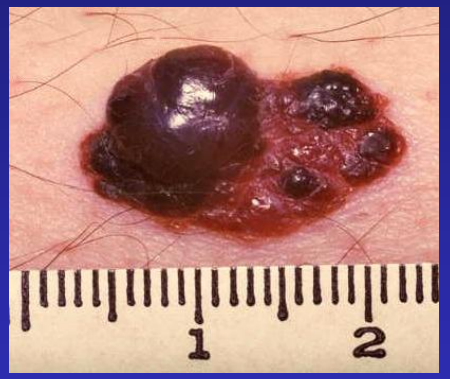
Metastatic cancer: the tumour has spread from the place where the cancer started to other parts of the body



Cancer progression

Benign nevi



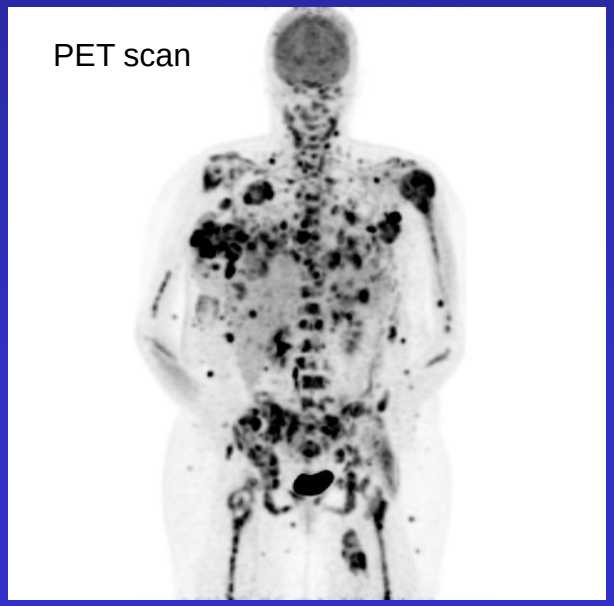


In situ cancer

?

Invasive cancer

Metastatic melanoma



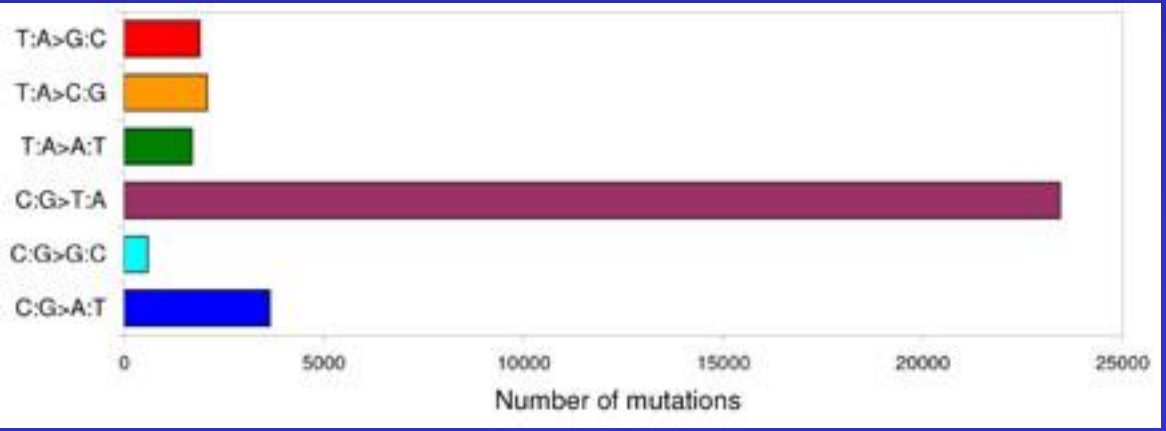
Mutational Profiles

33,558 somatic mutations

195 (0.6%) affect the encoded protein sequence

Past environmental exposures affect the patterns of mutations seen in cancer

COLO-829
Malignant
melanoma

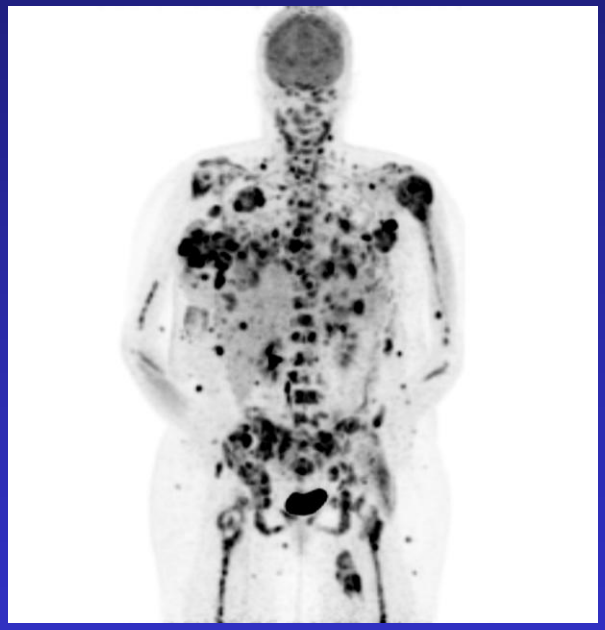


Why find the cancer genes

Understanding the genes that are mutated in cancer, their combinations and the ways in which they are mutated provides insights into:

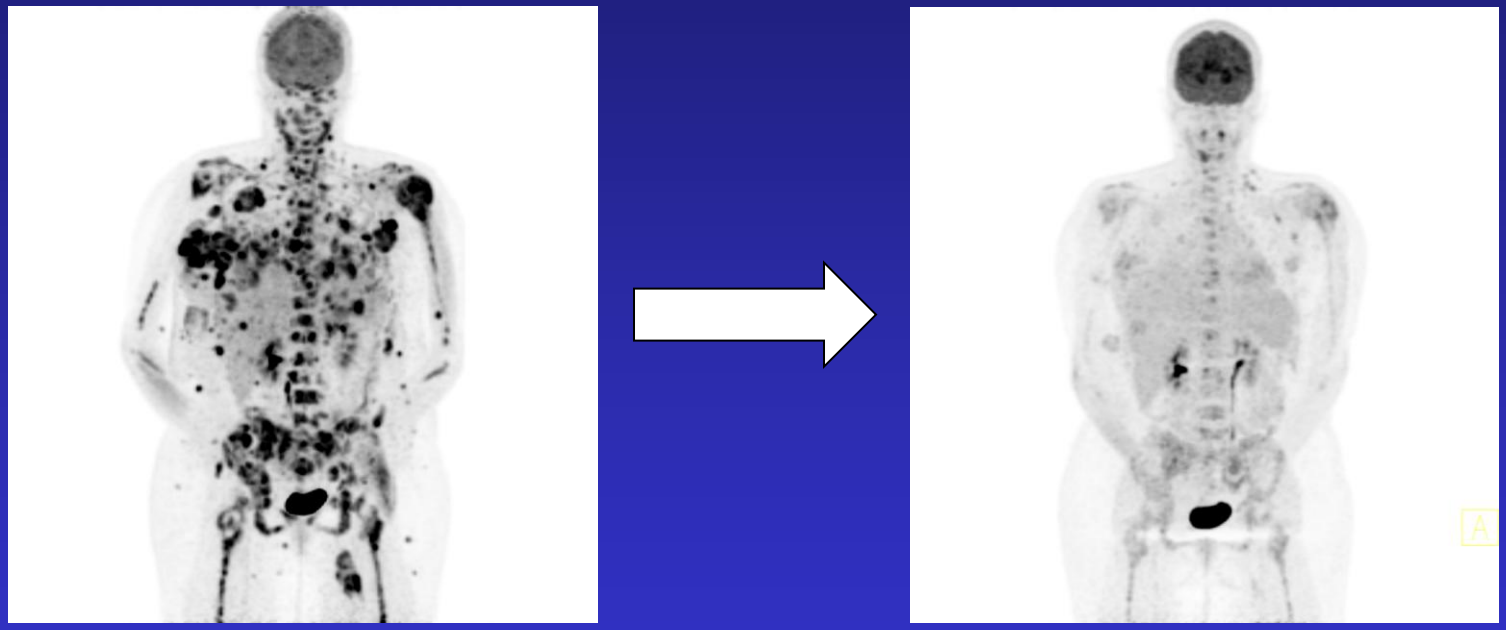
- Causes of cancer
- Classification of different cancers (aiding in accurate prognosis)
- Biological mechanisms by which cancers develop
- Appropriate therapeutic targets/treatments

BRAF – drug trials (PLX4032)



BRAF – drug trials (PLX4032)

15 days later



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