



MACQUARIE
University

BIOL3120 –Human Genetics and Evolutionary Medicine

Cancer Genetics





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Cancer Genetics

Revision

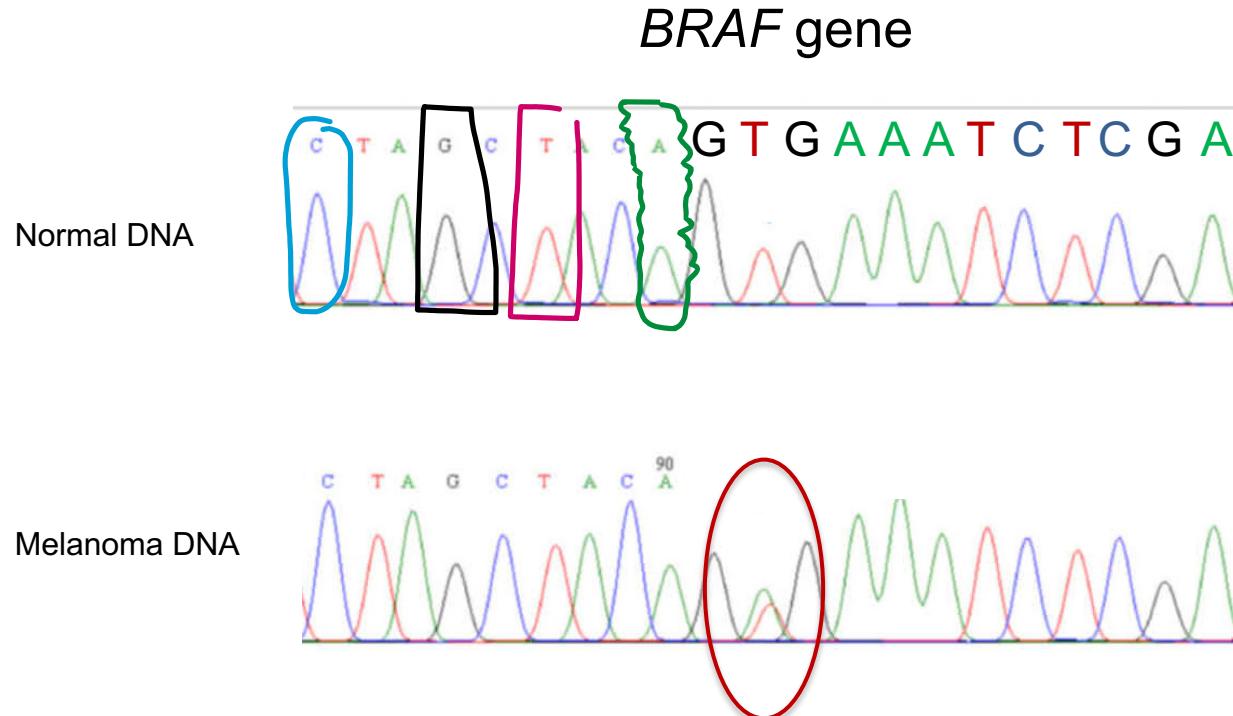
LEARNING OUTCOMES

Understand the dynamic role of mutation selection in cancer development

Analyse different types of mutations and their role in cancer development

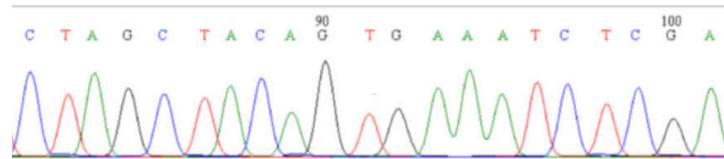
Describe the contribution of tumour suppressor genes and oncogenes in cancer

REVIEW: DNA MUTATIONS

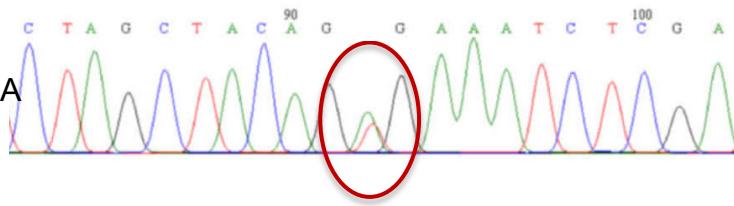


REVIEW: DNA MUTATION

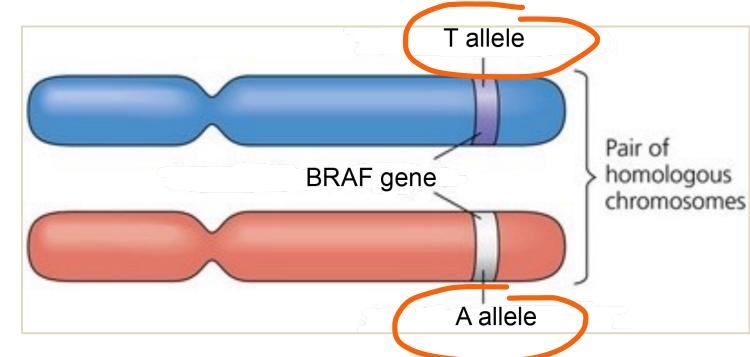
Normal DNA



Melanoma DNA



This is a heterozygous mutation



REVIEW: DNA MUTATIONS

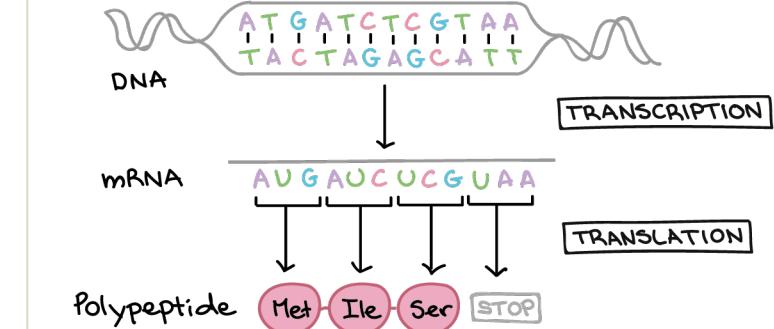
Normal DNA



Melanoma DNA

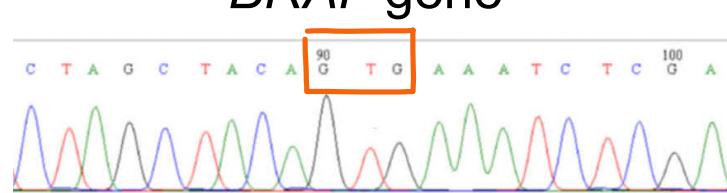


THE CENTRAL DOGMA

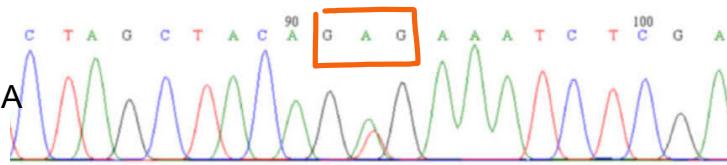


REVIEW: DNA MUTATIONS

Normal DNA



Melanoma DNA



GTG encodes Valine or V (BRAF wild type)

GAG encodes Glutamic acid or E (BRAF^{Val600Glu} or BRAF^{V600E})

This is a **missense** point mutation - single nucleotide change results in an amino acid change

	Second base			
First base	U	C	A	G
U	UUU Phenylalanine F UUC UUA Leucine L UUG	UCU Serine S UCC UCA UCG	UAU Tyrosine Y UAC UAA Stop codon UAG Stop codon	UGU Cysteine C UGC UGA Stop codon UGG Tryptophan W
C	CUU Leucine L CUC CUA CUG	CCU Proline P CCC CCA CCG	CAU Histidine H CAC CAA Glutamine Q CAG	CGU CGC Arginine R CGA CGG
A	AUU Isoleucine I AUC AUA Methionine start codon M	ACU Threonine T ACC ACA ACG	AAU Asparagine N AAC AAA Lysine K AAG	AGU Serine S AGC AGA Arginine R AGG
G	GUU Valine V GUC GUA GUG	GCU Alanine A GCC GCA GCG	GAU Aspartic D GAC GAA Glutamic E GAG	GGU Glycine G GGC GGA GGG
	UCAG	UCAG	UCAG	UCAG

Cancer Genetics

Selection and evolution



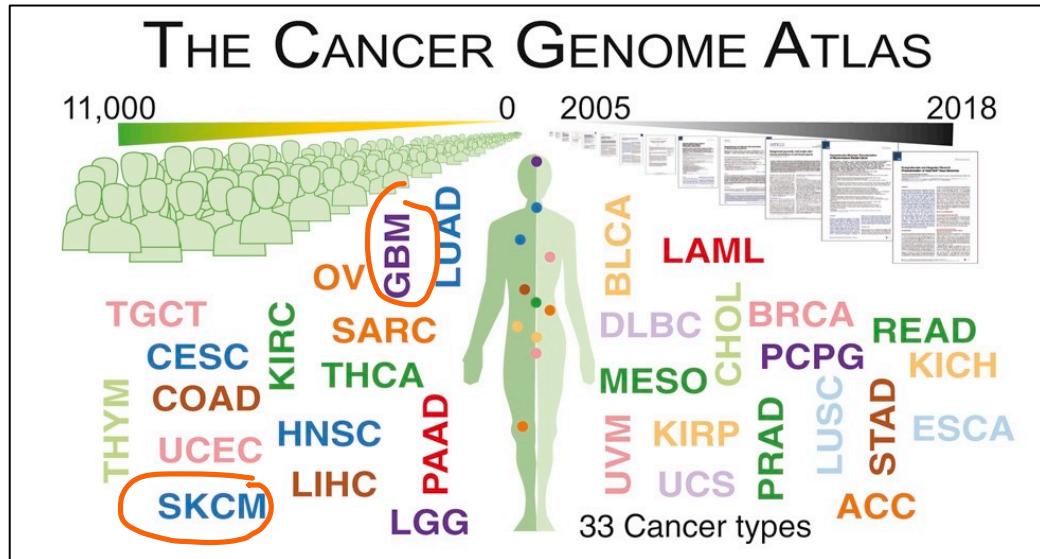
LEARNING OUTCOMES

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Describe the contribution of tumour suppressor genes and oncogenes in cancer

THE CANCER GENOME ATLAS PROGRAM



Ding et al. 2018 Cell 173: 305-320

Joint international effort, began in 2006

Molecularly characterised 33 cancer types, > 20,000 cancers and matched normal samples

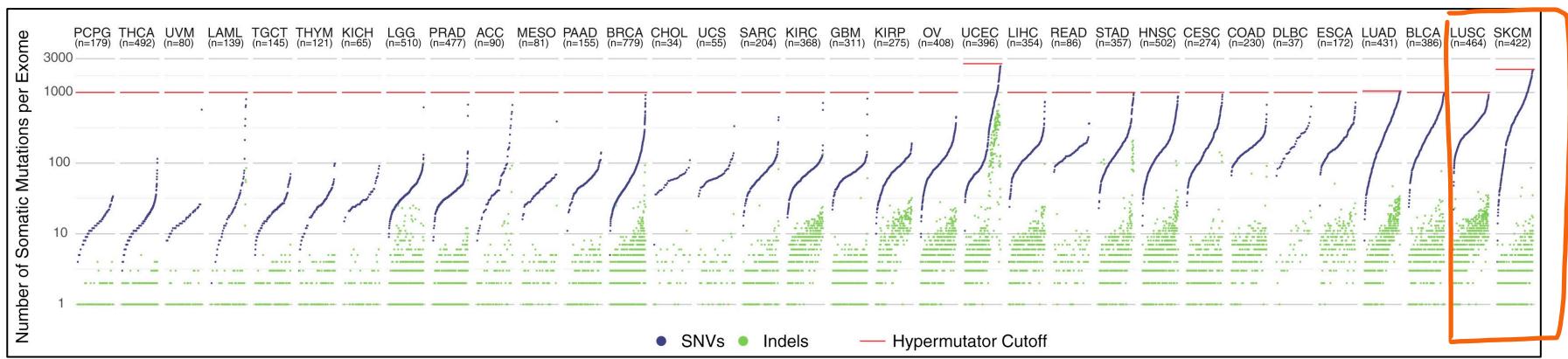
<https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga>

MUTATIONS ACCUMULATE IN HEALTHY TISSUE

- The 10^{14} cells in the human body are continuously subject to mutations 
- Mutations result primarily from replication errors or DNA damage that is not repaired
 - UV, ionizing radiation, reactive oxygen species, viruses
- There is a gradual accumulation of mutations throughout life – in healthy and cancer cells
- **Age** positively correlated with mutation load
- **Number of cell divisions** correlated with tumour load 
- Tissue exposed to **mutagens** have greater mutation load
 - Sun-exposed skin increased C>T mutations
 - Lung, oesophagus mucosa, small intestine

THE CANCER GENOME ATLAS PROGRAM

- Most cancers carry 1,000 to 20,000 somatic point mutations and a few to hundreds of insertions, deletions, and rearrangements
- Diseases known to have significant mutagen exposure, such as lung cancers (tobacco smoke; lung squamous cell carcinoma (LUSC)) and melanoma (UV; SKCM) have the highest tumour burden



Mutations are separated into single nucleotide variants (blue) and indels (green)

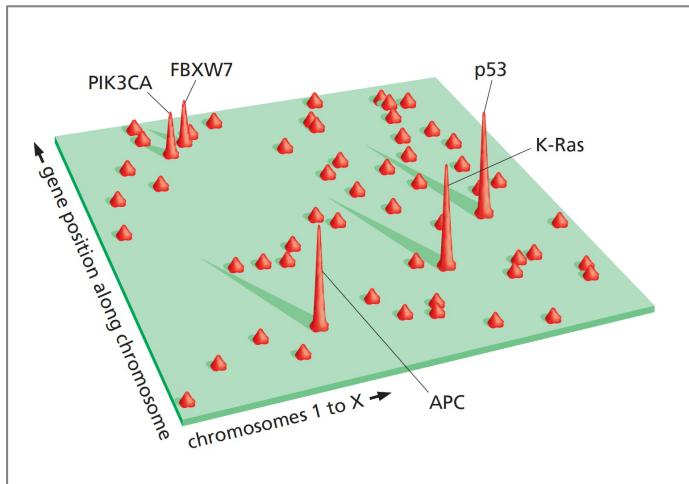
Bailey et al. 2018 Cell 173: 371-385

CANCER MUTATIONS

- Most acquired (or somatic) mutations are **neutral passenger** mutations (no direct role in cancer)
- A fraction of these mutations (**driver mutations**) confer a selective advantage to the cell – leading to growth or survival of a clone. These mutations are in **cancer genes**
- More than **500 cancer genes** have been identified so far
 - 90% are altered by somatic mutation and ~20% by germline mutations (occurs in germ cells) that predispose to cancer (familial cancers).

HOW MANY GENES ARE IMPORTANT IN CANCER

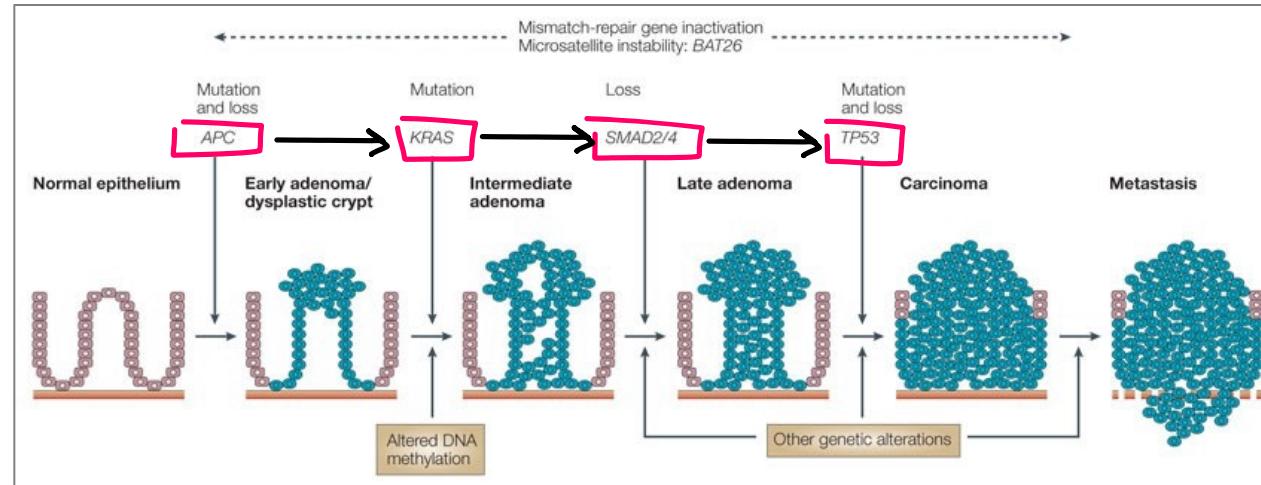
- Number of driver mutations in each cancer are in the order of **10**
- Only three genes are mutated in more than 10% of patients across the range of tumour types shown here: *TP53* (36.1%), *PIK3CA* (14.3%), and *BRAF* (10%)



A 2D map of genes mutated in colorectal cancers - few gene "mountains" are mutated in a large proportion of tumors
Wood et al. 2007 Science 318:1108-1113

CANCER EVOLUTION

Colorectal cancer

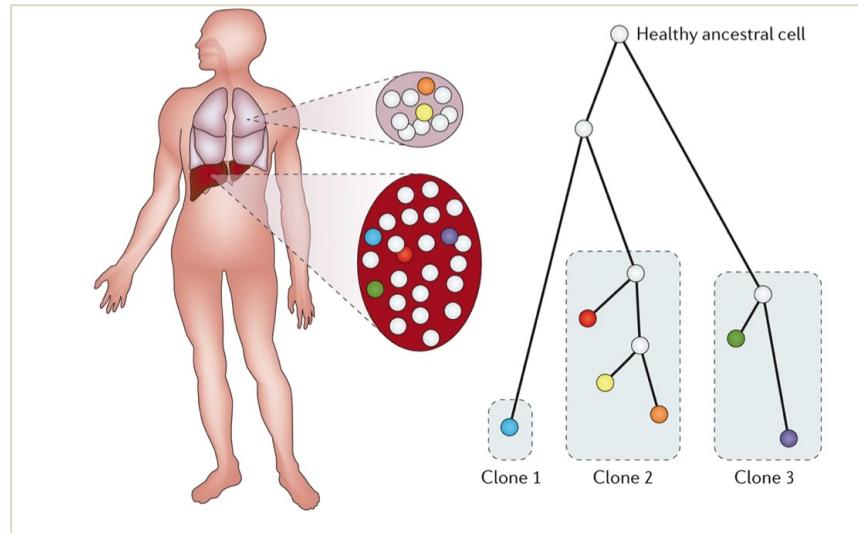


Davies et al. *Nat. Rev. Cancer* 5, 199-209 (2005)

CANCER EVOLUTION



- Dynamic selection of mutations – in response to microenvironment and therapy
- Multiple cancer subclones exists 
- Cancer show substantial intra-patient and intra-tumoural heterogeneity





SUMMARY POINTS

- TCGA has sequenced >20,000 cancer types
- Mutation burden differs with each cancer – and is highest in cancers exposed to mutagens
- Most acquired (or somatic) mutations are **neutral passenger** mutations
- ~10 **driver mutations** required to drive the development of cancer
- Cancer evolves over time with the selection of advantageous mutations – and is highly heterogeneous



Cancer Genetics

Tumour suppressors and oncogenes



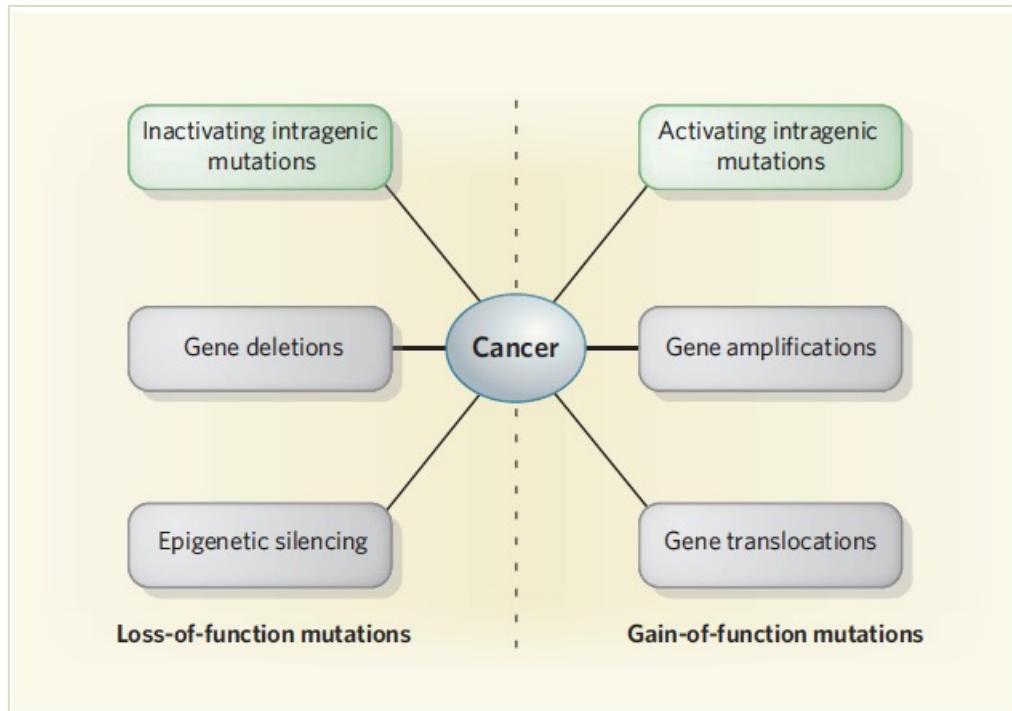
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CANCER GENES

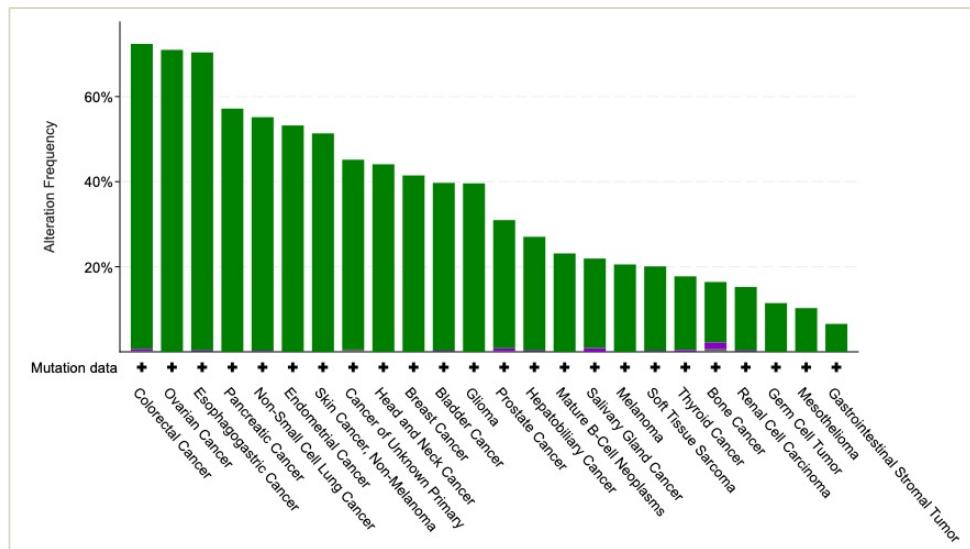


- **Loss-of-function** mutations
- **Gain-of-function** mutations

LOSS-OF-FUNCTION MUTATIONS

Tumour suppressor genes

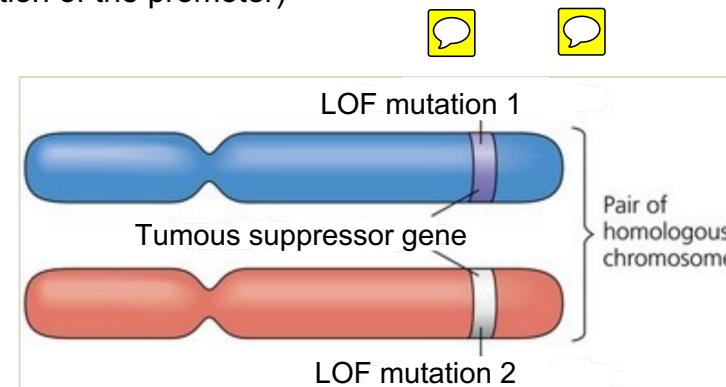
- Normally restrain cell proliferation, repair DNA or induce cell death
- Often inactivated by loss-of-function mutations



LOSS-OF-FUNCTION (LOF) MUTATIONS

Tumour suppressor genes

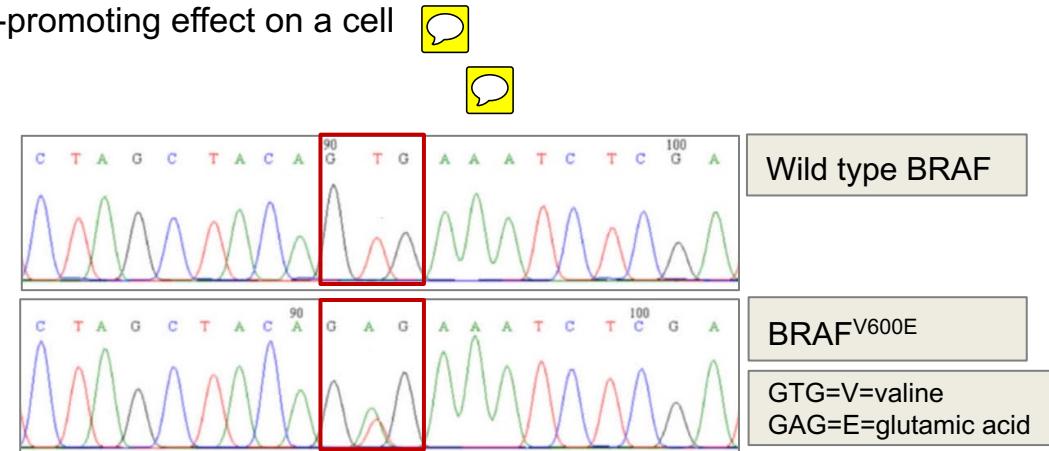
- Normally restrain cell proliferation, repair DNA or induce cell death
- Often inactivated by loss-of-function mutations
- Example loss-of-function alterations
 - Mutations, deletions, or insertions that inactivate the gene product, diminish transcription
 - Chromosomal translocation events that interrupt the tumour suppressor gene
 - Epigenetic gene silencing (eg methylation of the promoter)



GAIN-OF-FUNCTION (GOF) MUTATIONS

Proto-Oncogenes

- Normally promote cell growth and proliferation
- **Gain-of-function** mutations activate proto-oncogenes and these abnormally activated genes known as **oncogenes** – dominant, growth-promoting effect on a cell

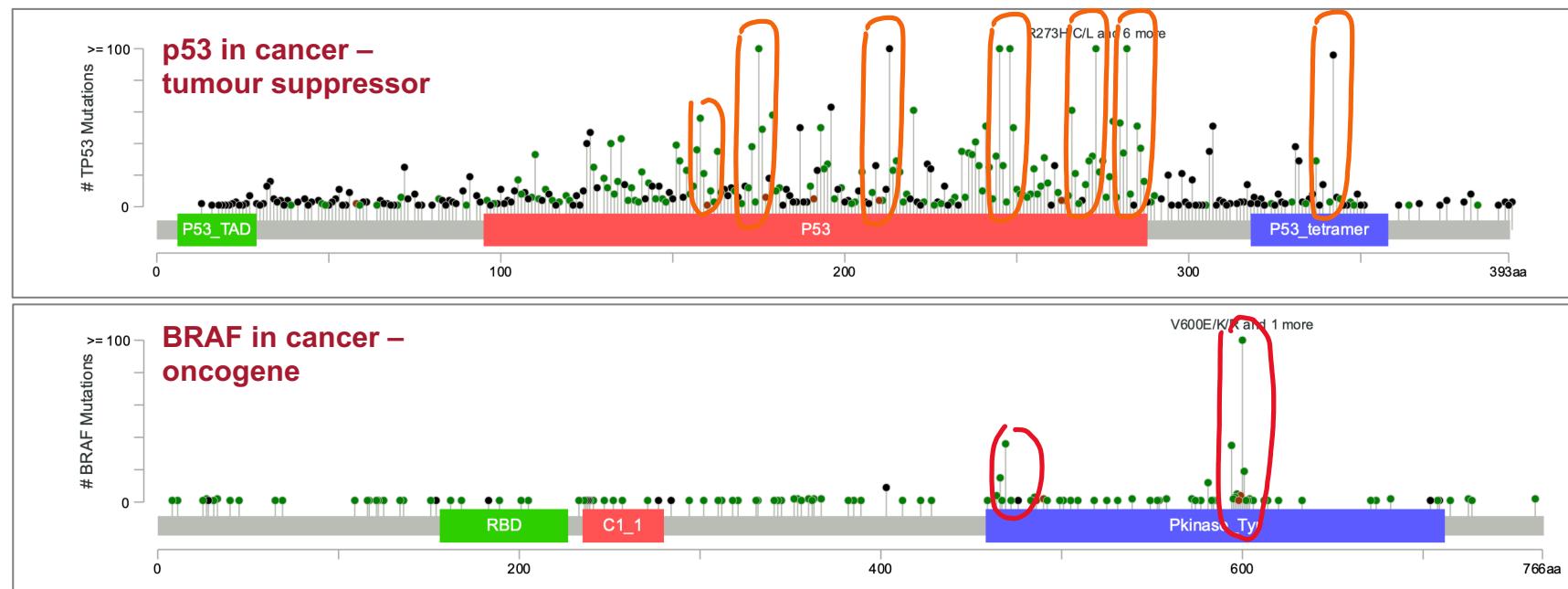


GAIN-OF-FUNCTION MUTATIONS

Proto-Oncogenes

- Normally promote cell growth and proliferation
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- Example gain-of-function alterations
 - Mutations, deletions, or insertions that activate the gene product, increase transcription
 - Gene amplification events leading to extra chromosomal copies of a proto-oncogene
 - Chromosomal translocation events that relocate a proto-oncogene to a new chromosomal site that leads to higher expression
 - Chromosomal translocations that lead to a fusion between a proto-oncogene and a second gene, which produces a fusion protein with oncogenic activity

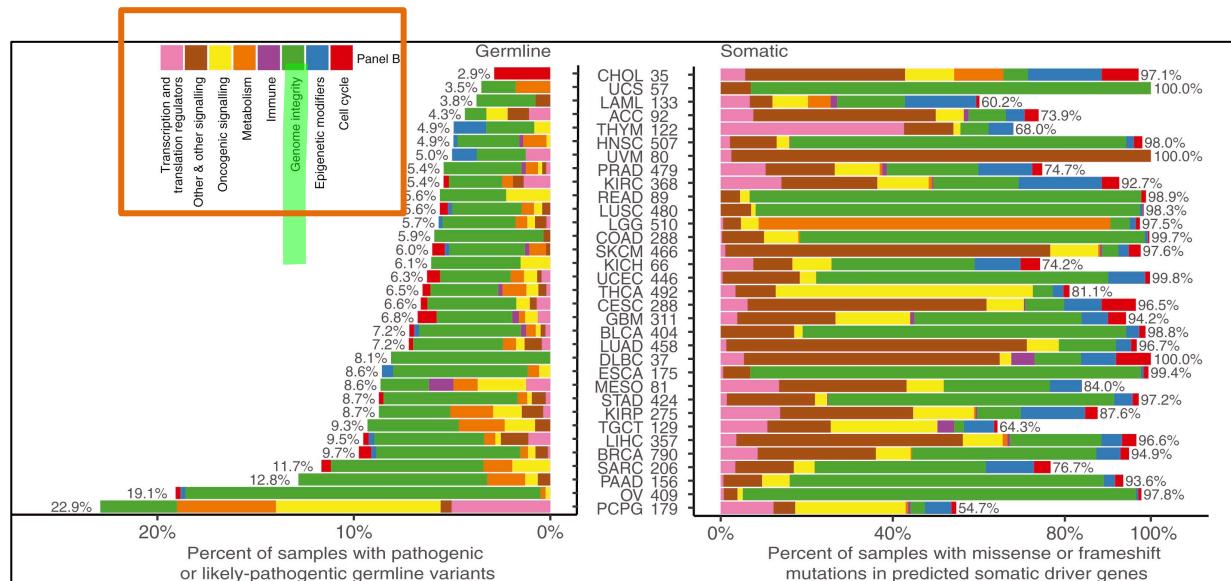
TUMOUR SUPPRESSOR GENES VS ONCOGENES



COMMON BIOLOGICAL PROCESSES

Driver genes affect a handful of key pathways/processes which are common to most cancers; often related to the hallmarks of cancer (genomic integrity, metabolism, proliferation)

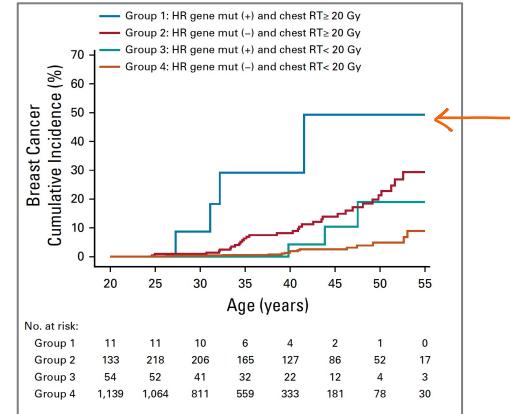
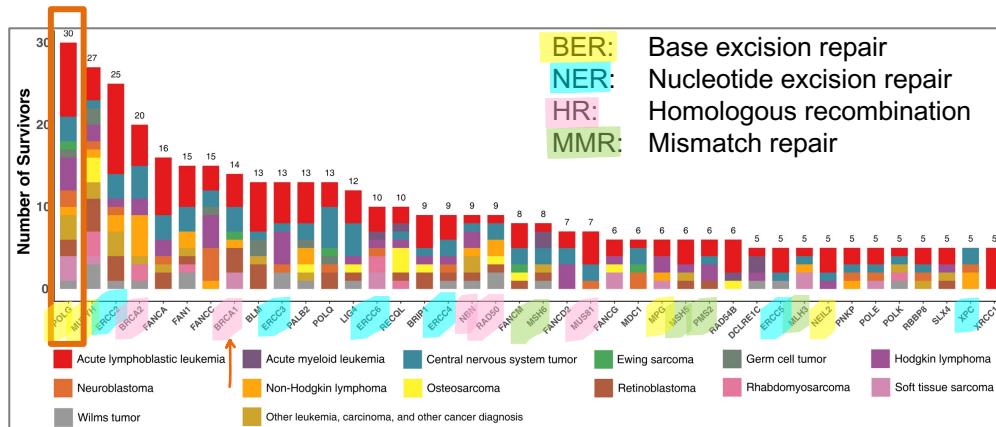
Many predisposition genes play roles in **genome integrity**



Somatic and germline driver genes grouped into eight molecular process categories *Ding et al. 2018 Cell 173: 305-320*

CHILDHOOD CANCER SURVIVORS

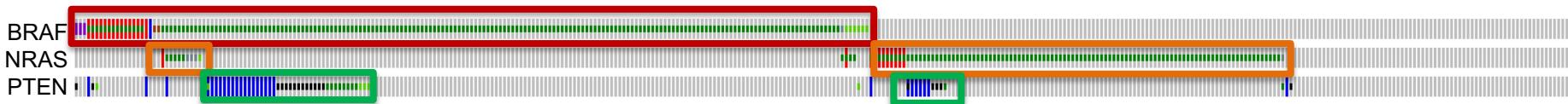
- Over 4000 childhood cancer survivors had germline DNA sequenced
 - 11.5% carried a pathogenic mutation in at least 1 DNA repair gene
 - These mutations associated with increased rates of subsequent breast cancer, sarcoma, thyroid cancer
 - Survivors with a pathogenic mutation also at elevated risk of therapy-related neoplasms – these therapies (radiotherapy and chemotherapy) cause DNA damage



Qin et al. 2020 J Clin Oncol 38:24, 2728-2740

INTERACTIONS BETWEEN DRIVER GENES

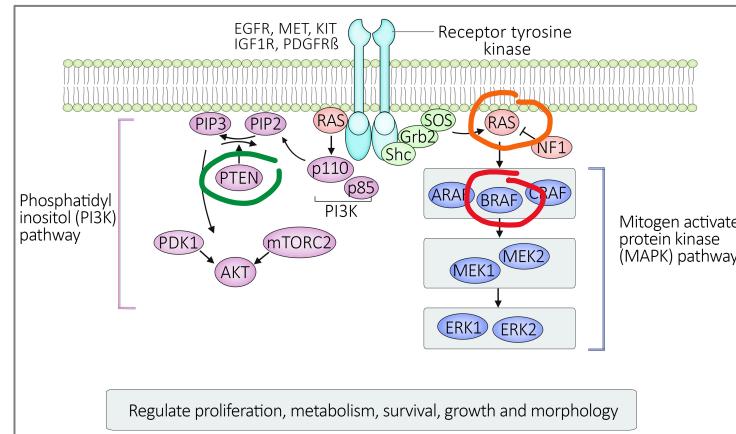
- Driver mutations can be **mutually exclusive** or **co-occur**



- BRAF and NRAS are proto-oncogenes – mutually exclusive
- PTEN is a tumour suppressor– co-occurs with NRAS and BRAF

INTERACTIONS BETWEEN DRIVER GENES

- **Co-occurrence:** indicate functional synergies – e.g they may activate distinct pathways [BRAF + PTEN]
- **Mutual exclusivity:** suggest functional redundancy – i.e a second mutation does not provide any further advantage [BRAF + NRAS], or more than one mutation creates a disadvantage to the cancer cell





SUMMARY

- Cancers evolve over time with the acquisition and selection of DNA mutations
- Gain-of-function mutations activate proto-oncogenes
- Loss-of-function mutations inactivate tumour suppressor genes
- These mutations are known as driver mutations and they affect cancer genes
- Most cancers have ~10 driver mutations in cancer genes
- Mutations can co-occur when they offer a proliferative/survival advantage
- Mutually exclusive cancer mutations indicate functional redundancy
- There is a dynamic selection of mutations, so multiple distinct cancer subclones can exist – resulting in intra-patient and intra-tumoural heterogeneity (i.e distinct cancer clones within a patient and within a lesion)