V10: Cancerogenesis (II)

- Oncogenic signaling pathways

Sanchez-Vega et al, *Cell* **173**, 321-337.e10 (2018)

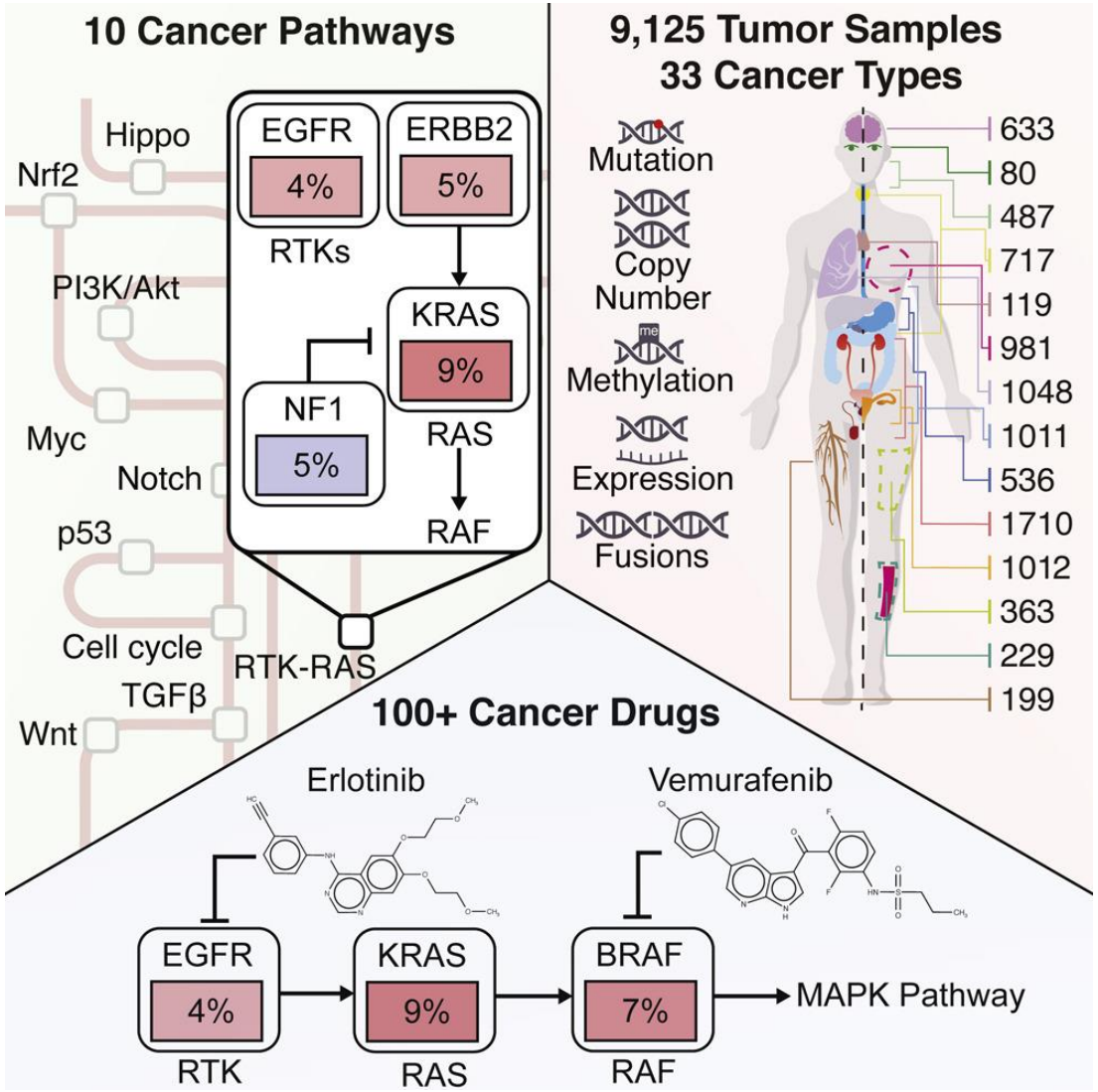
Genetic alterations in signaling pathways that control cell-cycle progression, apoptosis, and cell growth are common hallmarks of cancer.

- Cancer driver genes

Martinez-Jimenz et al, *Nature Rev Cancer* **20**, 555-572 (2020)

Cancers are diseases characterized by abnormal and uncontrolled cellular growth caused primarily by genetic mutations.
These mutations, called ‘drivers’ after their ability to drive tumorigenesis, confer on cells in a somatic tissue certain selective advantages with respect to neighboring cells.
They occur in a set of genes (called ‘cancer driver genes’).
Mutant forms of driver genes affect the homeostatic development of a set of key cellular functions.

Oncogenic Signaling Pathways in TCGA



Alteration map of 10 signaling pathways across 9,125 samples from 33 cancer types

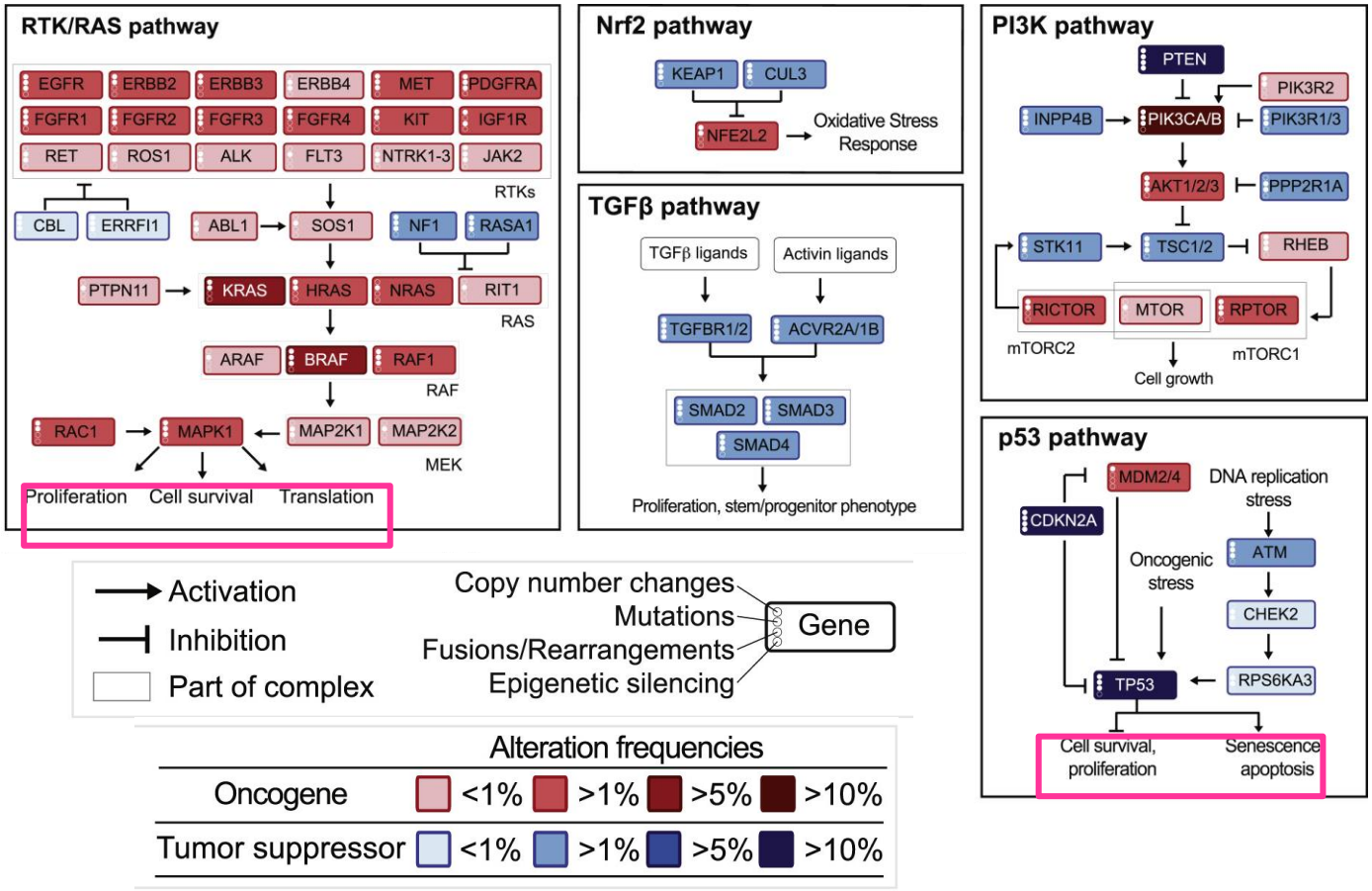
57% of tumors have at least one potentially actionable alteration in these pathways

Sanchez-Vega et al, *Cell* **173**, 321-337.e10 (2018)

10 major signalling pathways

Pathway members and interactions in the 10 selected pathways. The downstream effects of these pathways are listed.

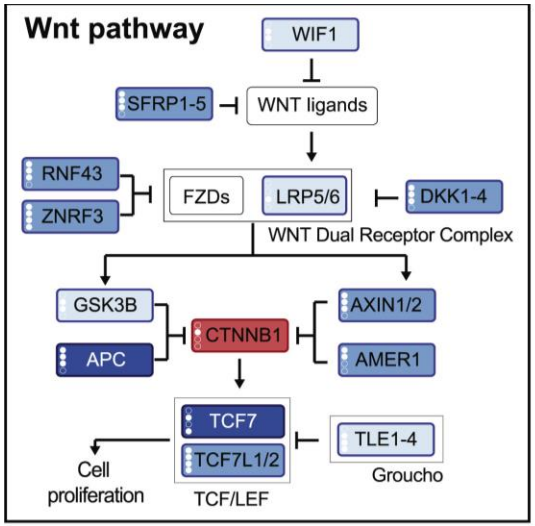
Genes are altered at different frequencies (see coloring legend) by oncogenic activations (red) and tumor suppressor inactivations (blue).

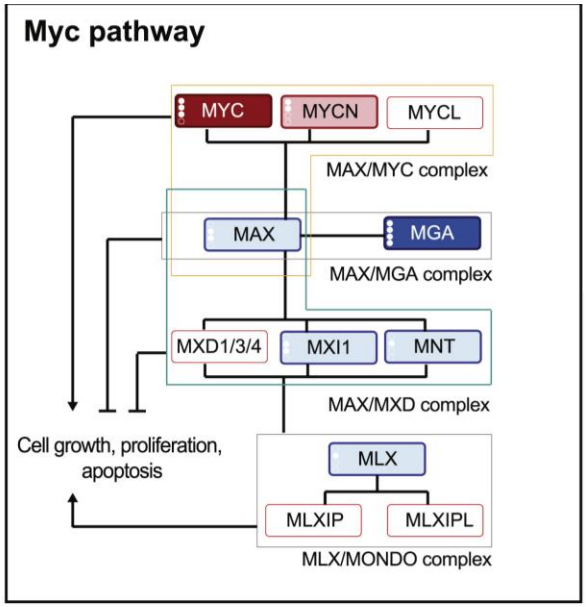


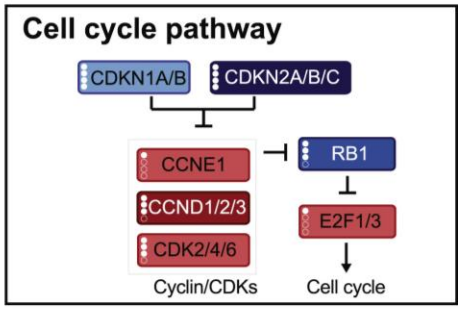
The types of somatic alteration considered for each gene (copy-number alterations, mutations, fusions or epigenetic silencing) are specified using a set of four vertical dots on the left of each gene symbol.

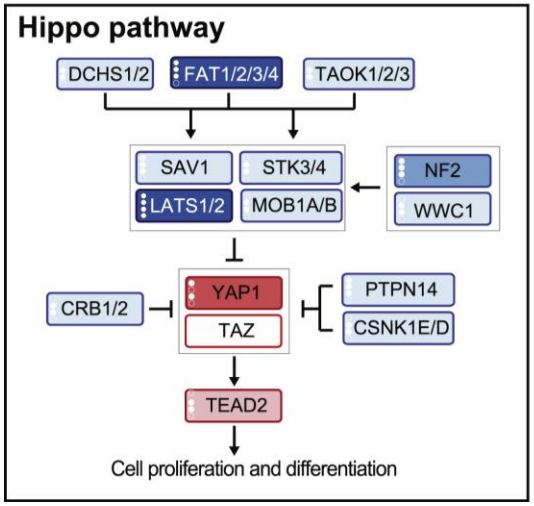
Sanchez-Vega et al, *Cell* **173**, 321-337.e10 (2018)

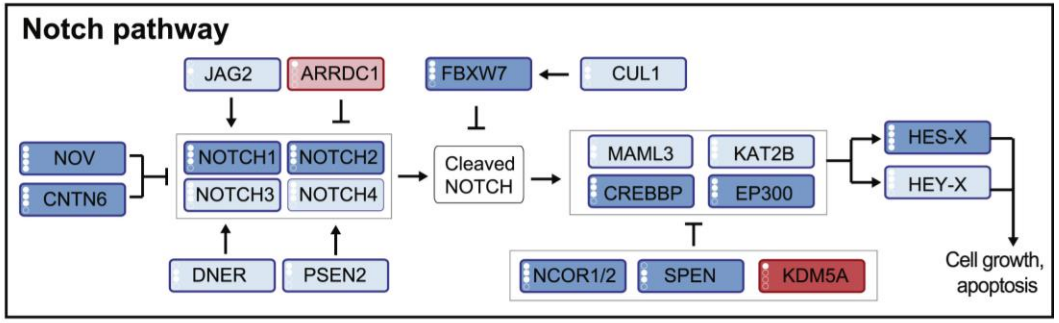
10 major signalling pathways

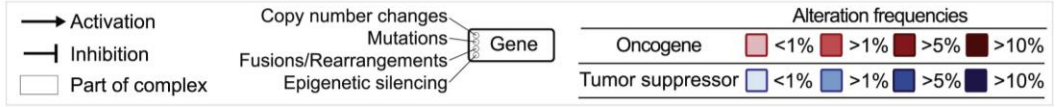






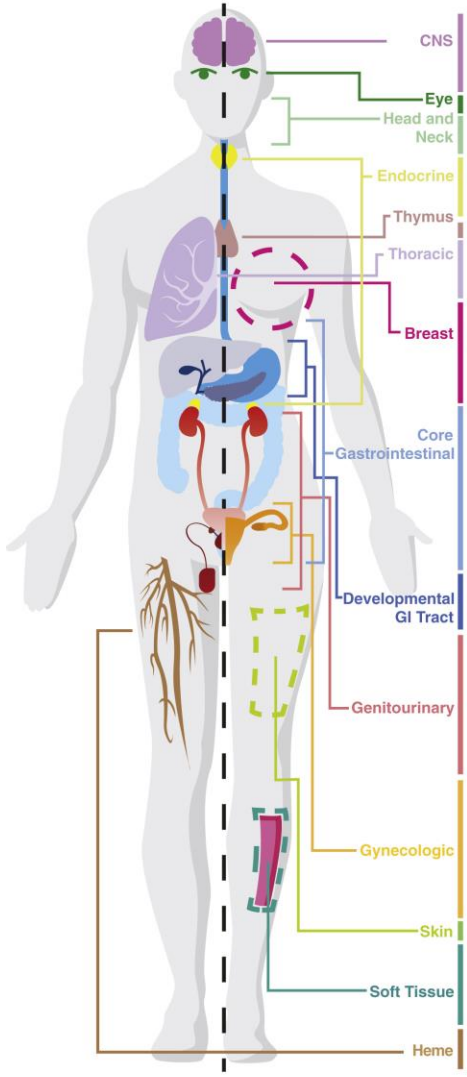






Sanchez-Vega et al, *Cell* **173**, 321-337.e10 (2018)

Pathway alteration frequencies



Sanchez-Vega et al, *Cell* **173**, 321-337.e10 (2018)

Alteration frequencies

	RTK/RAS	Cell cycle	PI3K	p53	Notch	Wnt	Myc	Hippo	TGFß	Nrf2
GBM	77	86	57	48	18	8	6	10	2	
LGG IDHwt	82	64	47	29	27	5	1	5		
LGG IDHmut-codel	9	45	22	5	26	66	3	99	50	
LGG IDHmut	19	28	15	92	24	8	10	92	21	1
UVM	6	6	4	2	10	1	2	10		1
HNSC HPV+	26	32	60	11	25	8	4	8	11	1
HNSC HPV−	45	86	39	82	36	16	20	42	13	13
THCA	84	14	4	1	4	13	2	1	2	
ACC	22	30	16	28	11	41	7	5	1	
PCPG	32	15	6	6	11	10	1	4	1	
THYM	14	9	4	7	5	7	1	7	3	2
LUAD	74	56	38	61	21	19	23	23	10	15
MESO	9	54	13	21	9	6	7	40	2	
LUSC	54	79	68	86	31	18	12	28	11	25
BRCA LumA	28	31	62	25	14	15	12	5	4	1
BRCA LumB	44	48	48	49	25	31	26	15	10	2
BRCA Her2-enriched	82	40	60	78	18	17	29	10	8	1
BRCA Basal	46	51	53	91	38	11	39	14	8	4
BRCA Normal	36	36	33	31	3	6	19	3		
STES Squamous	50	89	53	96	38	13	22	21	13	23
STES CIN	63	74	33	76	21	26	21	16	23	2
STES EBV	50	100	80	13	83	67	7	10	17	
STES GS	31	39	18	24	31	20	12	4	20	2
STES MSI-POLE	71	64	64	49	79	70	19	54	57	2
CRC MSI-POLE	99	74	68	49	74	95	52	64	55	1
CRC GS	88	45	53	19	29	90	21	10	38	5
CRC CIN	66	36	32	84	23	91	17	8	22	1
LIHC	22	69	25	37	26	43	19	12	7	7
CHOL	56	53	17	19	8	17	19	17	3	6
PAAD	78	70	19	69	14	12	14	7	41	
KIRC	14	14	17	6	8	7	5	5	3	3
KIRP	17	12	8	4	12	9	6	11	1	6
KICH	5	23	15	32	3	3	2	3	5	
BLCA	64	81	46	62	42	20	18	26	9	9
PRAD	15	28	32	21	13	35	11	5	6	1
TGCT sem	63	8	11	6	6		2			
TGCT non−sem	20	7	5	5	16	2		10	2	
OV	58	48	49	96	28	10	40	21	5	5
UCEC CN high	61	43	86	90	32	18	31	13	5	5
UCEC CN low	37	9	95	10	14	54	10	7	1	5
UCEC MSI-POLE	71	31	98	42	64	70	30	55	31	19
UCS	61	70	79	91	54	18	27	16	4	4
CESC Adeno	63	21	56	19	30	14	16	14	21	5
CESC Squamous	32	19	59	12	35	12	5	33	11	10
SKCM	94	77	33	28	27	23	10	25	7	1
SARC DDLPS	43	83	20	85	17	15	7	9	7	
SARC LMS	31	55	33	71	14	11	4	4	1	4
SARC MFS/UPS	48	74	32	68	34	20	8	21	6	4
SARC other	25	30	15	5	5	5		10		
DLBC	24	76	8	19	70	70	14	35	14	
LAML	49	17	3	9	18	11	2	3	1	1
	46	45	33	29	23	15	11	10	7	1

Cellular Programs

Fraction of altered samples per pathway and tumor subtype.

Pathways are ordered by decreasing median frequency of alterations.

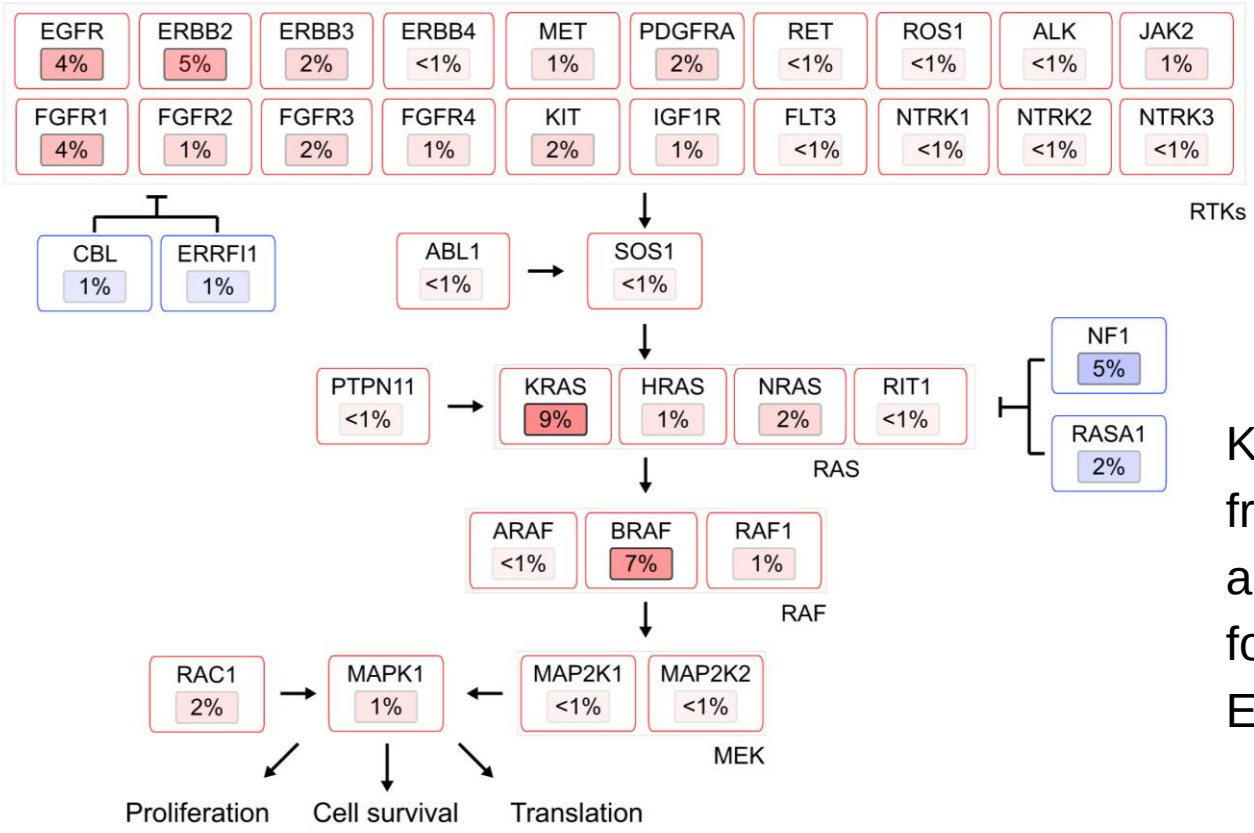
Increasing color intensities reflect higher percentages.

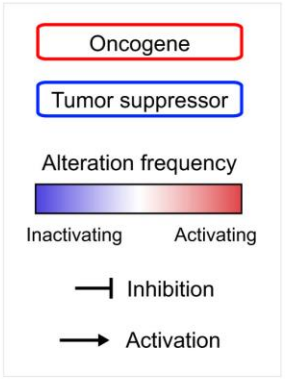
Highest mutation frequency in RTK-RAS pathway: 46% of samples contained alterations.

Alterations in the WNT pathway were most variable.

RTK-Ras pathway alterations

Altered genes and their functional relationships in the RTK-RAS pathway. Shades of red indicate frequencies of activating events (activating mutations or fusions, amplifications) and shades of blue indicate frequencies of inactivating events (inactivating mutations or fusions, homozygous losses).

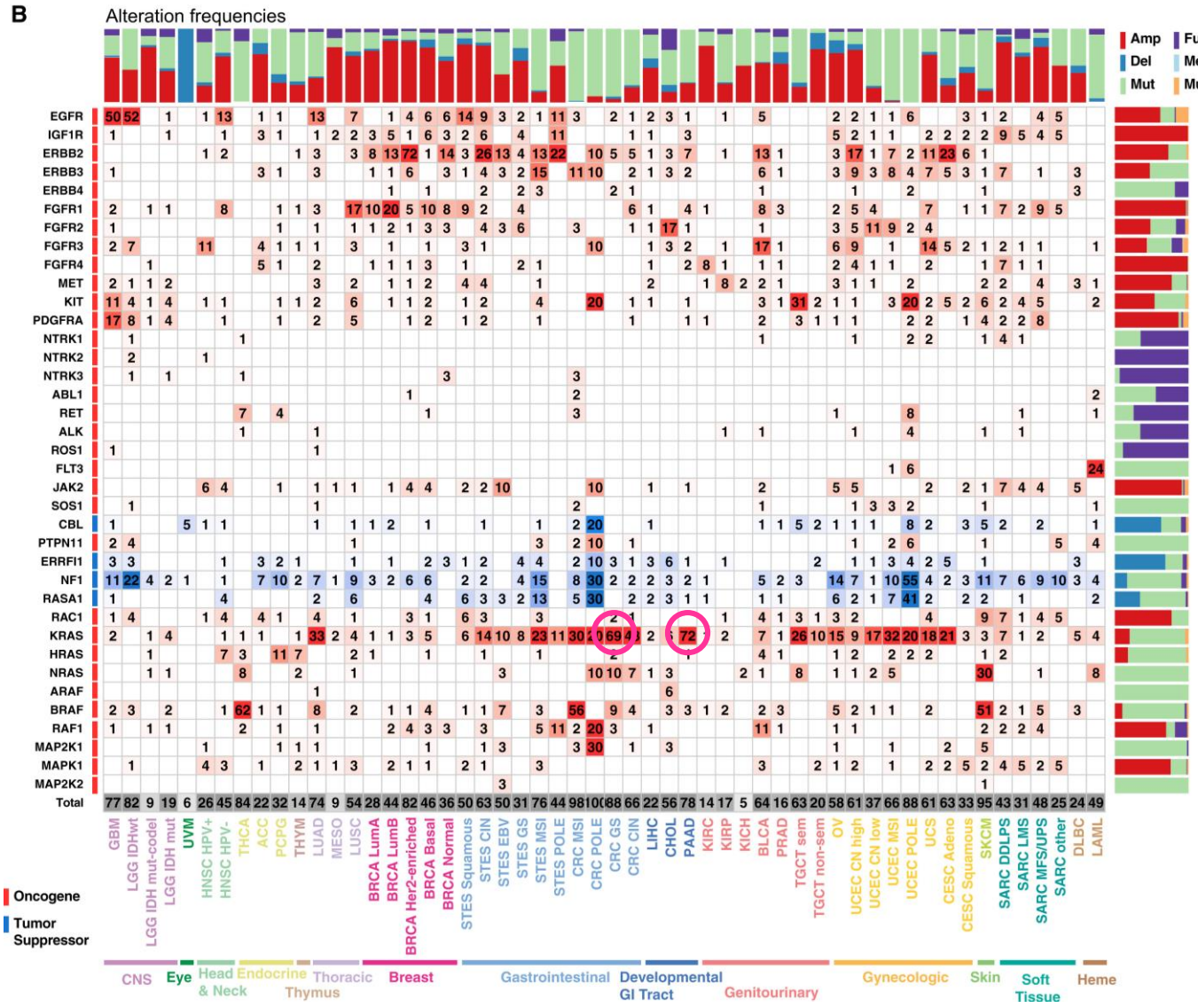




KRAS was the most frequently altered gene (9% across all samples), followed by BRAF (7%) and EGFR (4%).

Sanchez-Vega et al, *Cell* **173**, 321-337.e10 (2018)

Alterations in members of the RTK-RAS pathway



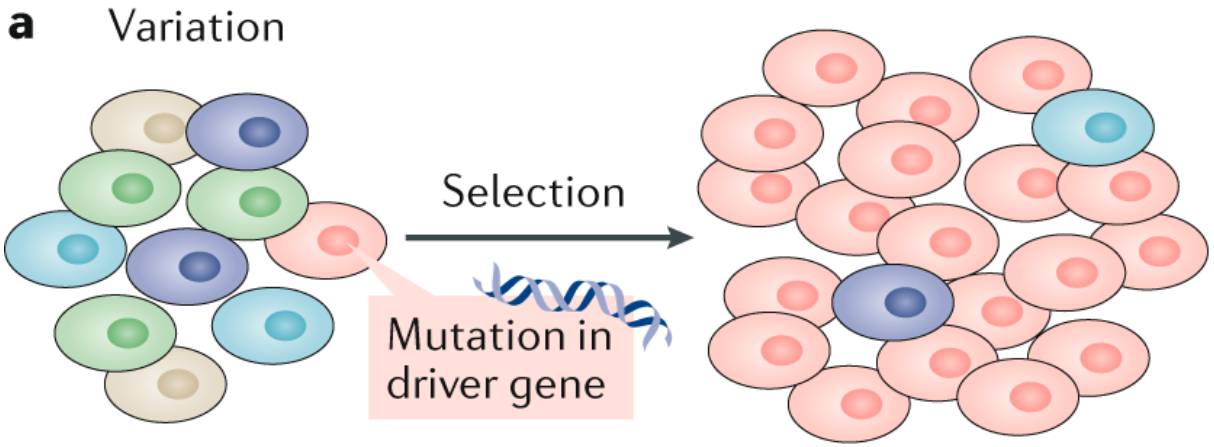
Color side bars show the fraction of samples affected by each type of somatic alteration (or a combination of them) for each pathway gene.

Top color bars show the proportion of different types of alterations for each cancer subtype.

Oncogenes are amplified; tumor suppressors are deleted.

Sanchez-Vega et al, *Cell* **173**, 321-337.e10 (2018)

Compendium of cancer driver genes



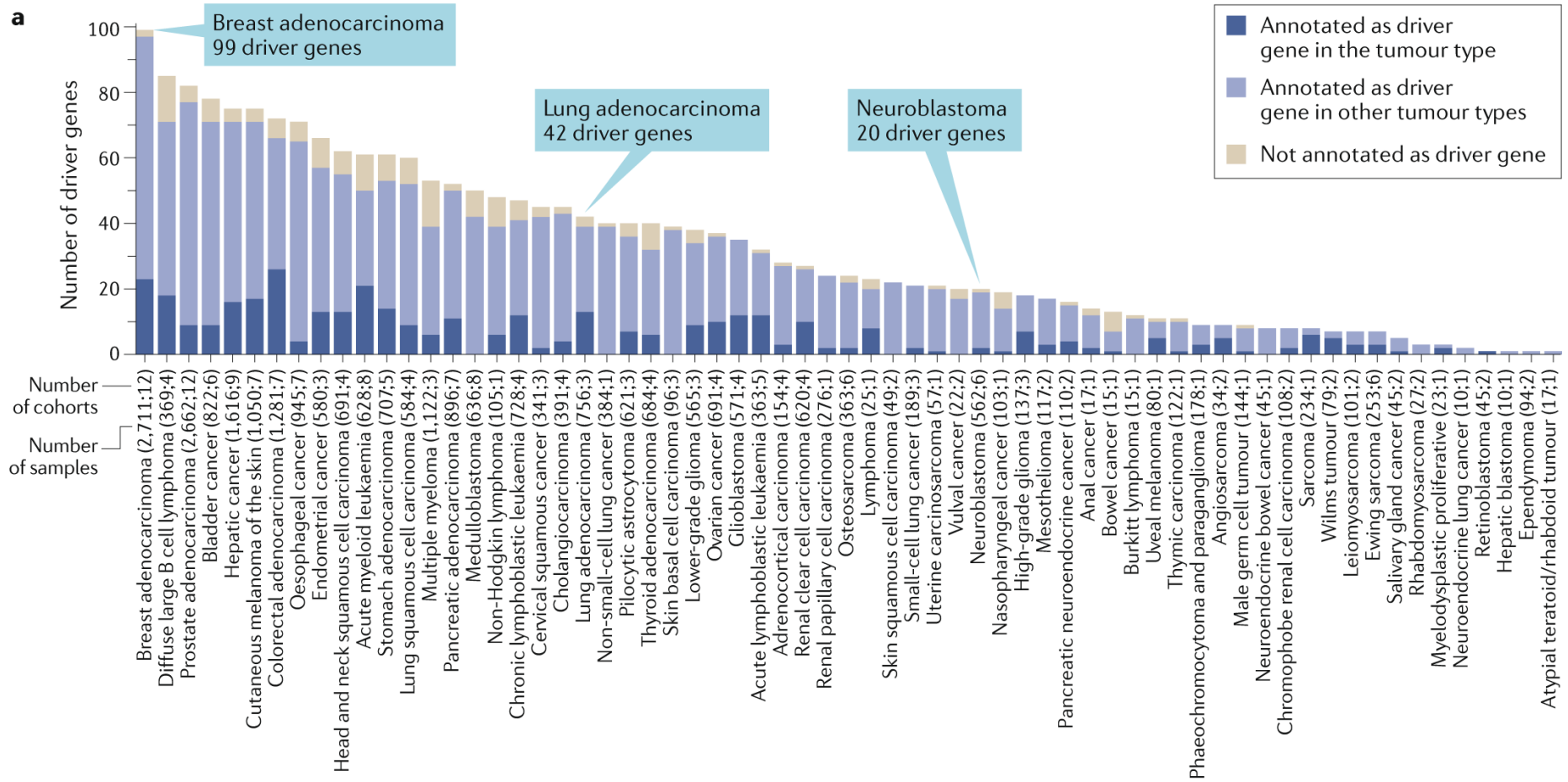
Cells in somatic tissues accumulate mutations.

Somatic mutations in certain genes provide the cell in which they occur with a selective advantage and are thus positively selected.

Following a Darwinian process, over time, a clonal expansion occurs and the cells carrying mutations in these genes become dominant within the population.

Martinez-Jimenz et al, *Nature Rev Cancer* **20**, 555-572 (2020)

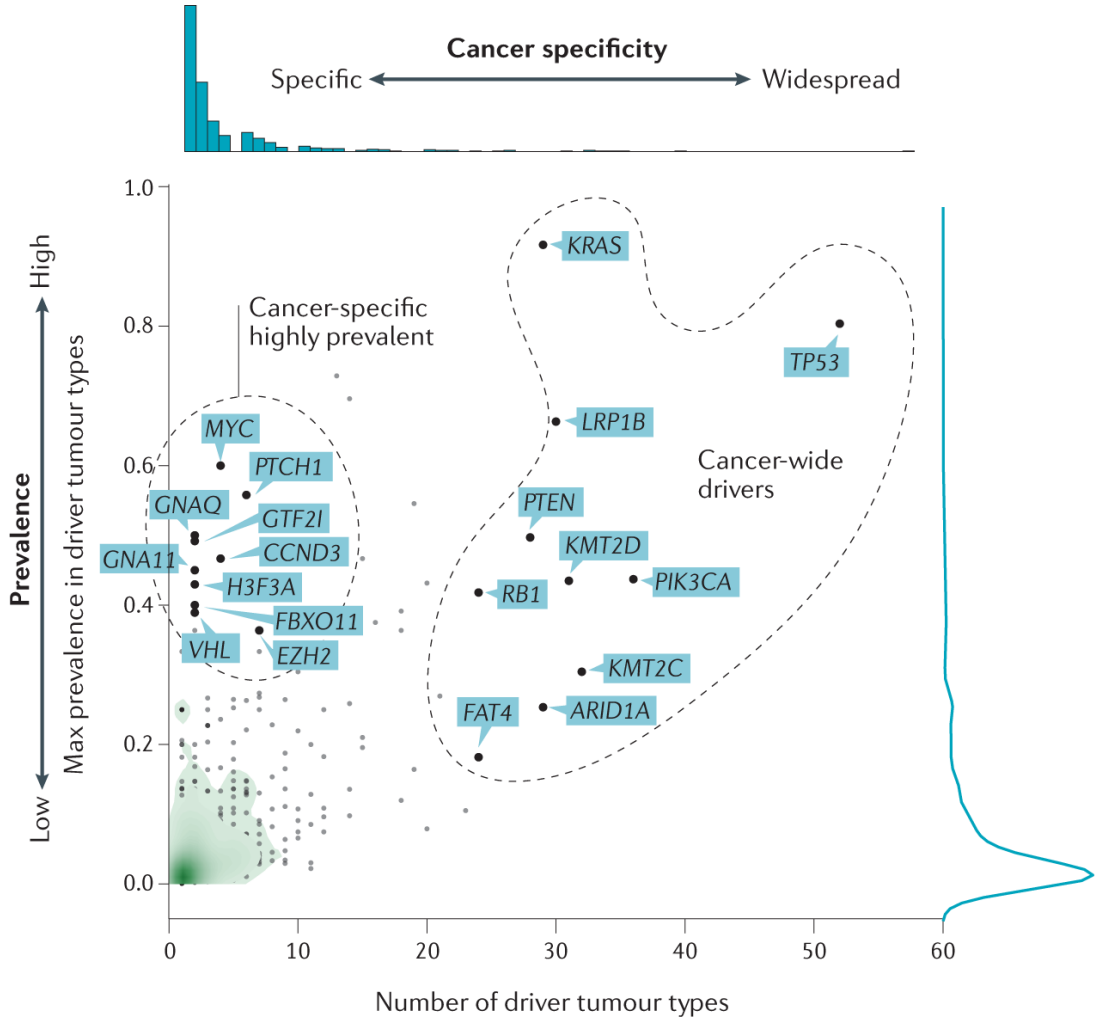
Number of cancer driver genes per tumor type

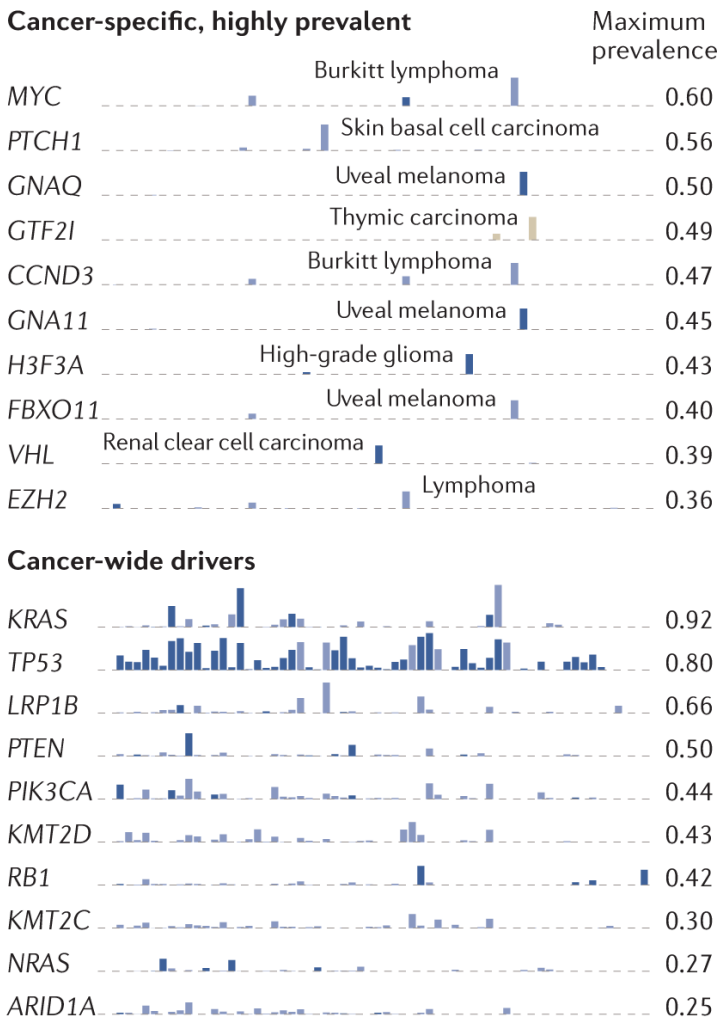


Many well-known driver genes have a widespread role across cancer types). E.g., the pattern of somatic mutations in histone-lysine *N*-methyltransferase 2C (*KMT2C*) shows signals of positive selection across 31 tumour types.

Martinez-Jimenz et al, *Nature Rev Cancer* **20**, 555-572 (2020)

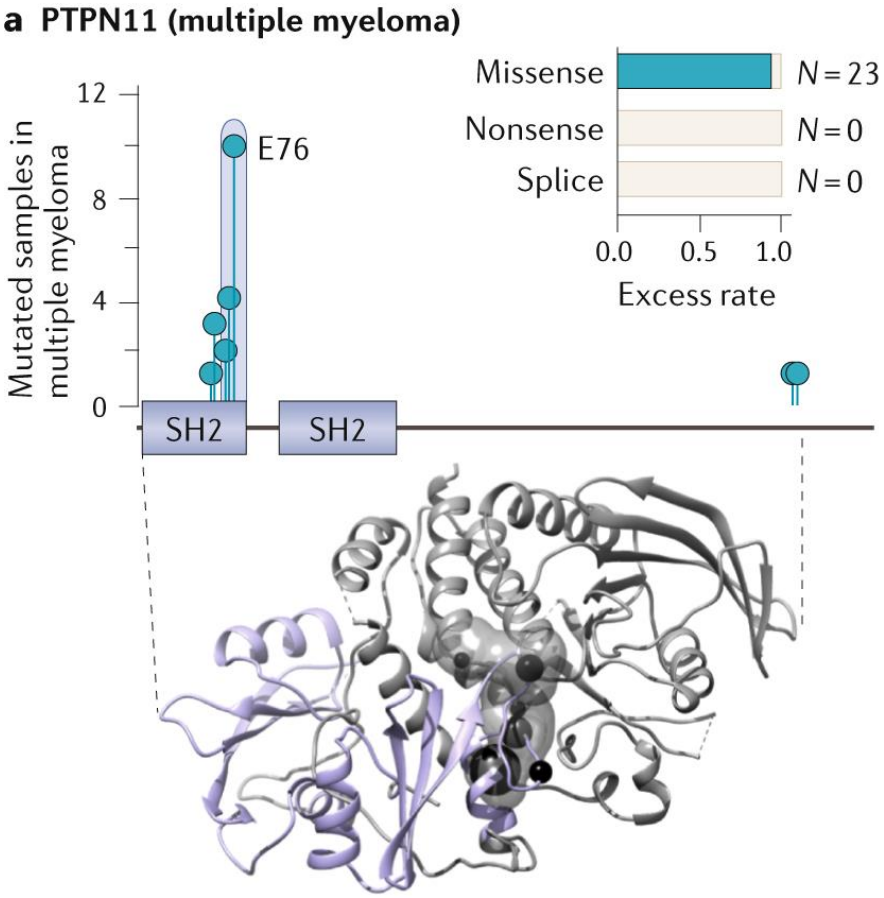
Prevalence of driver genes





Martinez-Jimenz et al, *Nature Rev Cancer* **20**, 555-572 (2020)

Interpreting mutational patterns of driver genes



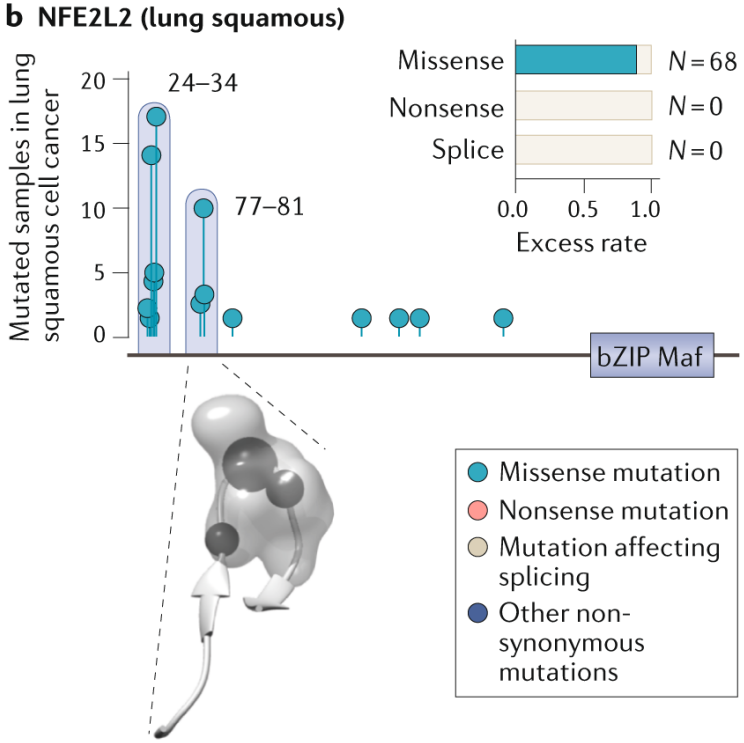
Martinez-Jimenz et al, *Nature Rev Cancer* **20**, 555-572 (2020)

The oncogene protein tyrosine phosphatase non-receptor type 11 (*PTPN11*) shows excessive missense mutations across multiple myelomas and other tumor types, which significantly cluster within the SH2 domain of its protein product.

Inhibitory contacts between this domain and the phosphatase domain are abrogated on phosphorylation by a receptor tyrosine kinase in the wild type or by mutations in the domain.

The activated PTPN11 then dephosphorylates inhibitors of several signaling pathways, such as the MAPK or AKT pathways.

Interpreting mutational patterns of driver genes

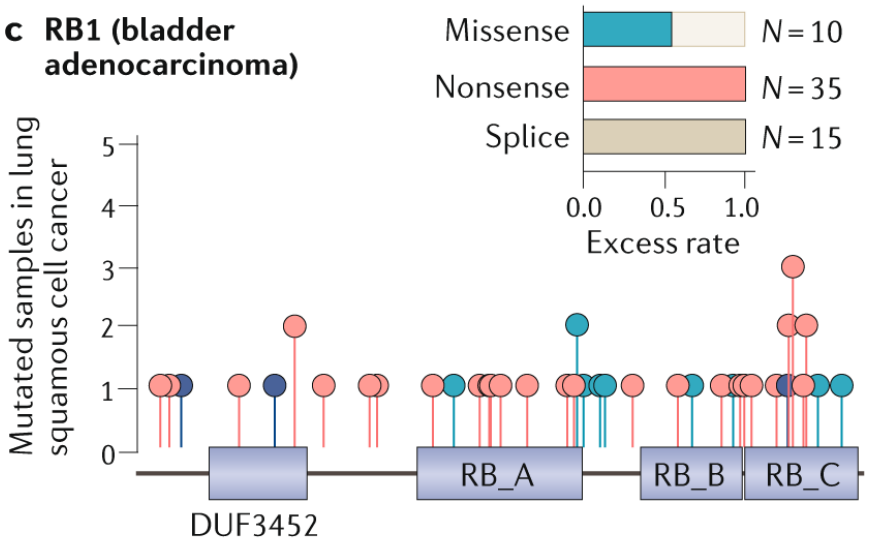


Nuclear factor erythroid 2-related factor 2 (*NFE2L2*), another classic oncogene, encodes a transcription factor that is key in the control of the redox state of the cell and its response to stress.

Across lung squamous cell carcinomas, two narrow clusters of missense mutations appear at its N-terminal portion.
These mutations affect sequences recognized by the cognate E3-ubiquitin ligase Kelch-like ECH-associated protein 1 (KEAP1), and cause the abnormal stabilization of NFE2L2, as do *KEAP1* mutations affecting the domain that recognizes the NFE2L2 degrons.
This, in turn, results in the constitutive activation of NFE2L2-regulated genes.

Martinez-Jimenz et al, *Nature Rev Cancer* **20**, 555-572 (2020)

Interpreting mutational patterns of driver genes



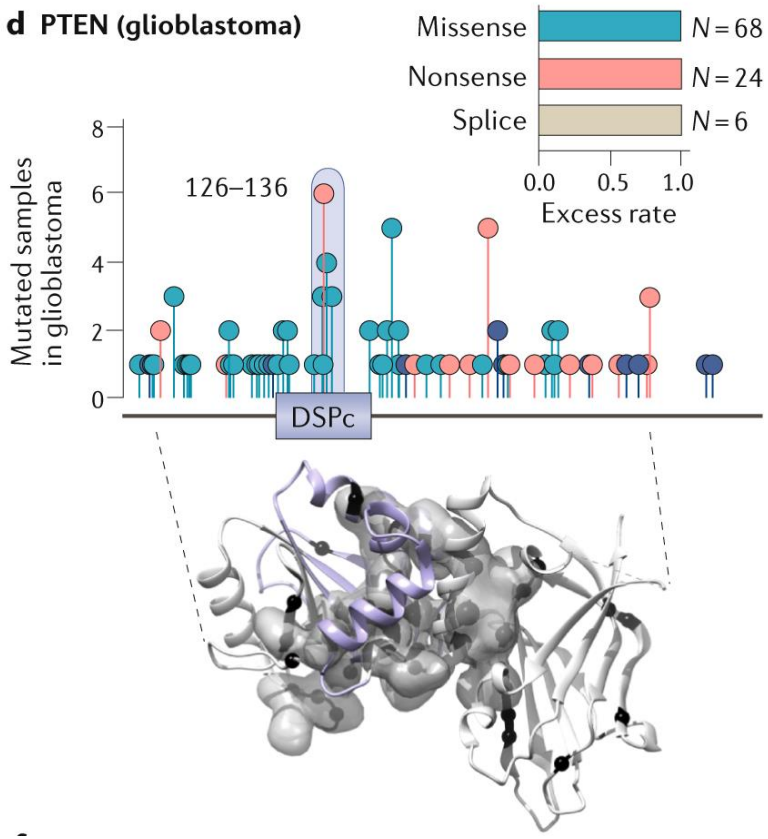
For tumor suppressors such as *RB1*, the mutational features are radically different across bladder adenocarcinomas.
There are more nonsense mutations and mutations affecting splicing than missense mutations.

Most nonsense mutations trigger nonsense-mediated decay of the *RB1* mRNA.

This causes depletion of the protein and abrogates its functions in the regulation of cell cycle progression and the cell division cycle, the response to cellular stress, differentiation, cellular senescence, programmed cell death and maintenance of chromatin structure.

Martinez-Jimenz et al, *Nature Rev Cancer* **20**, 555-572 (2020)

Interpreting mutational patterns of driver genes



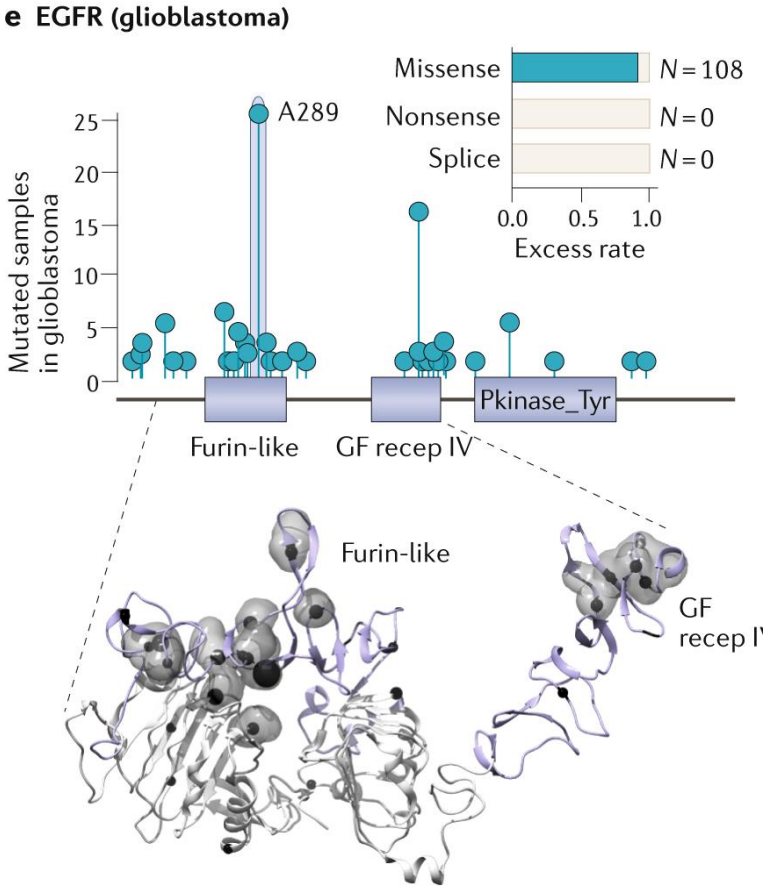
PTEN, another tumor suppressor, shows an excess of both nonsense and missense mutations across glioblastomas.

Like nonsense mutations in *RB1*, nonsense mutations in *PTEN* trigger nonsense-mediated decay. This reduces the production of a functional *PTEN* protein product, while missense mutations hinder either its enzymatic activity or its recruitment to the membrane, or increase its susceptibility to ubiquitylation for proteasome-mediated degradation.

These outcomes, in turn, interfere with its role in the regulation of a host of cellular functions, such as cell cycle progression, apoptosis and protein synthesis.

Martinez-Jimenz et al, *Nature Rev Cancer* **20**, 555-572 (2020)

Interpreting mutational patterns of driver genes: EGFR



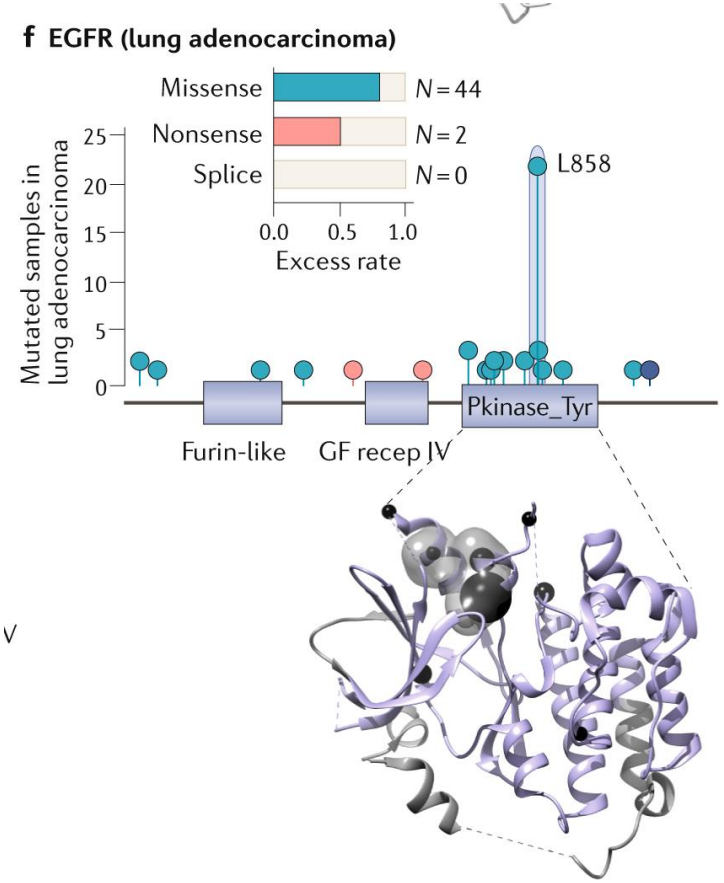
Some driver genes are affected by different tumorigenic mechanisms across tumor types.

E.g. in glioblastomas, missense mutations of *EGFR* tend to cluster in the extracellular domains of its protein product.

These act as **gain-of-function alterations**, likely through the stabilization of the open conformation of the receptor, which stimulates its autophosphorylation in the absence of a ligand.

Martinez-Jimenz et al, *Nature Rev Cancer* **20**, 555-572 (2020)

Interpreting mutational patterns of driver genes: EGFR



By contrast, across lung adenocarcinomas, missense mutations tend to cluster in the tyrosine kinase domain of the protein product of *EGFR*.

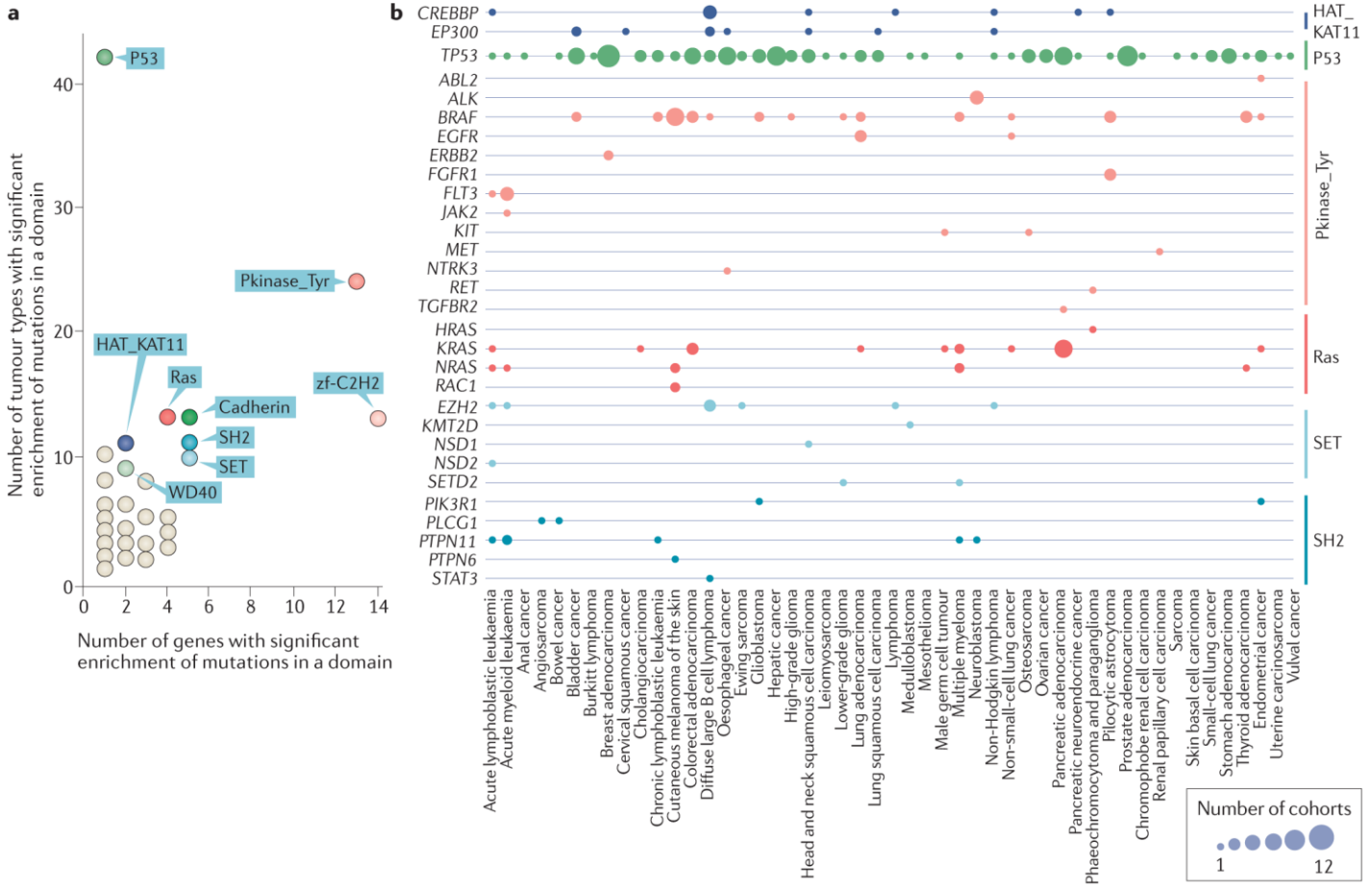
This altering its ‘on–off’ equilibrium and increases its activity at the expense of reduced affinity for ATP.

Martinez-Jimenz et al, *Nature Rev Cancer* **20**, 555-572 (2020)

Mutations in driver genes

Dots represent all domains with significant enrichment of mutations in a number of different driver genes across a number of different tumor types.

Selected domains with very significant enrichment are colored and denoted with the domain acronym, while the rest appear in light grey.



b | Genes with significant enrichment of mutations in domains of their protein products colored in part **a** across tumor types.

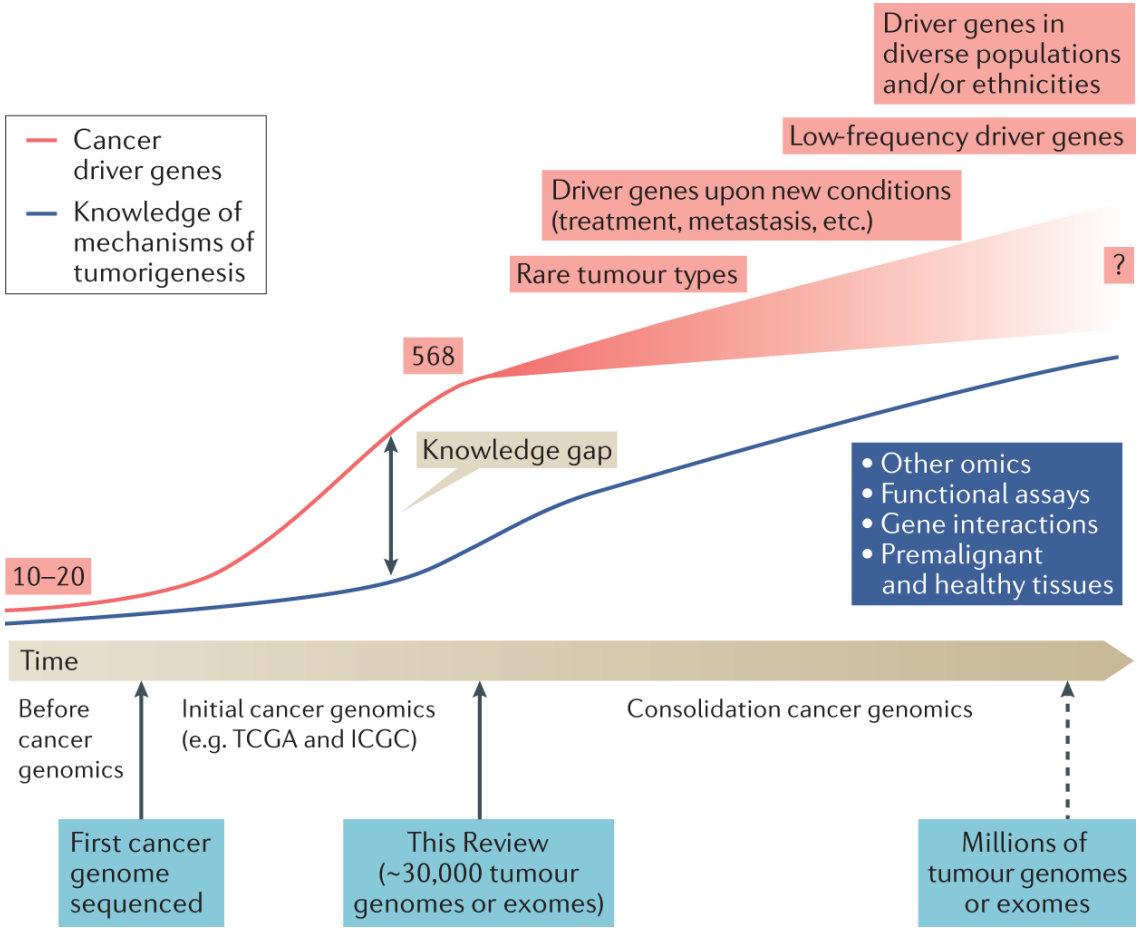
Martinez-Jimenz et al, *Nature Rev Cancer* **20**, 555-572 (2020)

Outlook

Historic look backward:
How did we get where we are today?

Outlook on the consolidation of cancer genomics and future trends in cancer genomics research.

ICGC, International Cancer Genome Consortium;
TCGA, The Cancer Genome Atlas.



Martinez-Jimenz et al, *Nature Rev Cancer* **20**, 555-572 (2020)

Paper #8

The genomic landscape of metastatic breast cancer highlights changes in mutation and signature frequencies

Lindsay Angus et al.

Nature Genetics 51, 1450–1458 (2019)

Paper presentation Jan 26, 2021

tissue biopsies from 442 patients with metastatic breast cancer:

- compared to primary breast cancer, **tumor mutational burden doubles**,
- the relative contributions of mutational signatures shift and
- the mutation frequency of six known **driver genes** increases in metastatic breast cancer.
- Significant associations with **pretreatment** are also observed.