

Driver Gene Identification

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Day 3

- Drivers: theory and detection, *Federico Abascal*
 - Exercises with `dndscv`
- Invited seminar: Cancer genomics in Latin America, *Daniela Robles*
- OncoPlots, *Patricia Basurto*
 - Introduction and exercises with `maftools`
- Discussion & Wrap-up

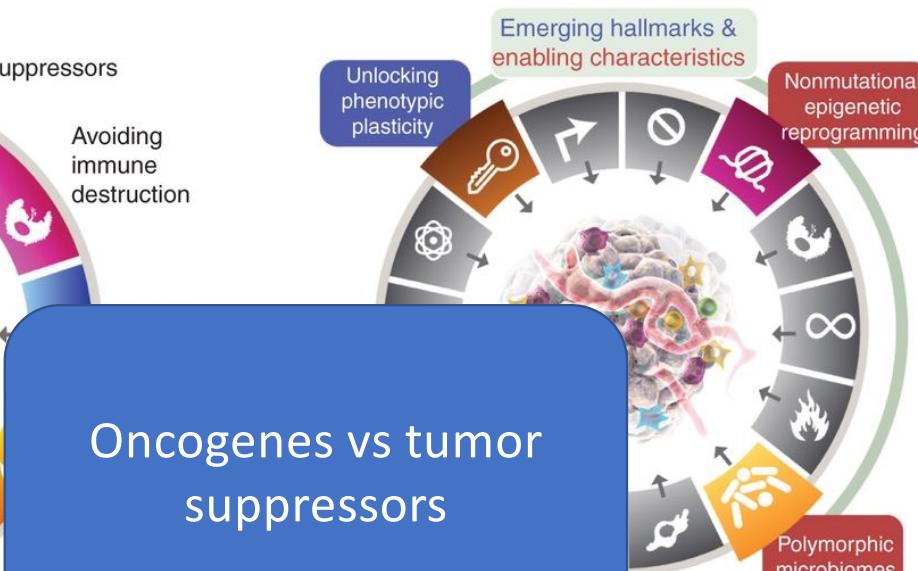
What are drivers and passengers?

- *American Journal of Traffic and Transportation Engineering*
- Drivers are **causative alterations**
 - Substitutions and small indels – point mutations:
 - Coding alterations: KRAS G12D
 - Regulatory region: *TERT* promoter
 - Structural rearrangements and copy number changes:
 - *BCR-ABL1* in leukemia, *MYC* amplification, long deletions (*TP53*)...
 - Epigenetic alterations:
 - *VHL* expression repression through promoter hypermethylation

Driver functions – hallmarks of cancer



Hanahan & Weinberg, 2011, *Cell*



Hanahan, 2022, *Cancer Discovery*

Oncogenes vs tumor
suppressors

Cancer Gene Census
<https://cancer.sanger.ac.uk/census>

Lots of info!

Tier1: 579 genes

Tier2: 154 genes

(WG < 20,000
protein-coding
genes)

Types of point mutations: substitutions and indels

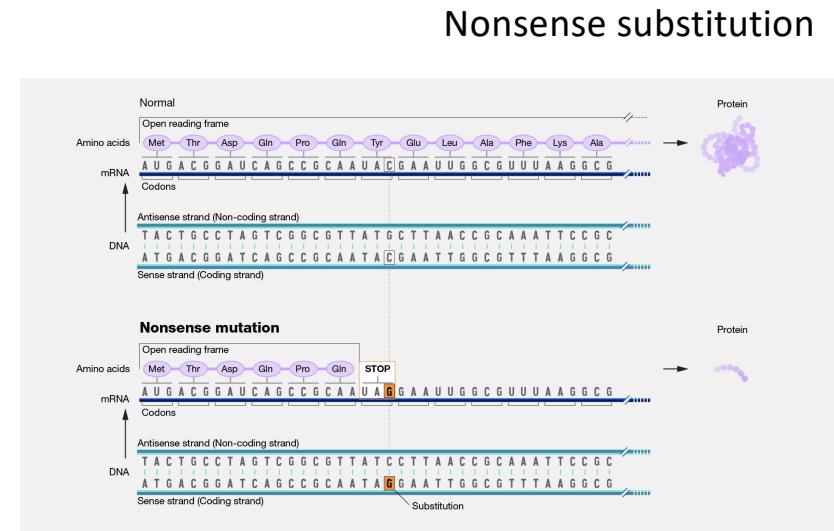
		Second letter					
		U	C	A	G		
First letter	U	UUU } Phe UUC } UUA } Leu UUG }	UCU } Ser UCC } UCA }	UAU } Tyr UAC }	UGU } Cys UGC }	UGA Stop UAG Stop UGG Trp	U C A G
	C	CUU } Leu CUC } CUA }	CCU } Pro CCC } CCA }	CAU } His CAC }	CGU } CGC }	CGA Arg CAG Gln	U C A G
	A	AUU } Ile AUC }	ACU } Thr ACC }	AAU } Asn AAC }	AGU } Ser AGC }	AGA Arg AGG Arg	U C A G
	G	GUU } Val GUC }	GCU } Ala GCC }	GAU } Asp GAC }	GGU } GGC }	GGA Gly GAG Glu	U C A G

Synonymous substitution, e.g. TAT > TAC (Tyr → Tyr)

Missense substitution, e.g. TAT > TGT (Tyr → Cys)

Nonsense substitution, e.g. TAT > TAA (Tyr → Stop*)

Indels: insertions/deletions, in frame vs out of frame

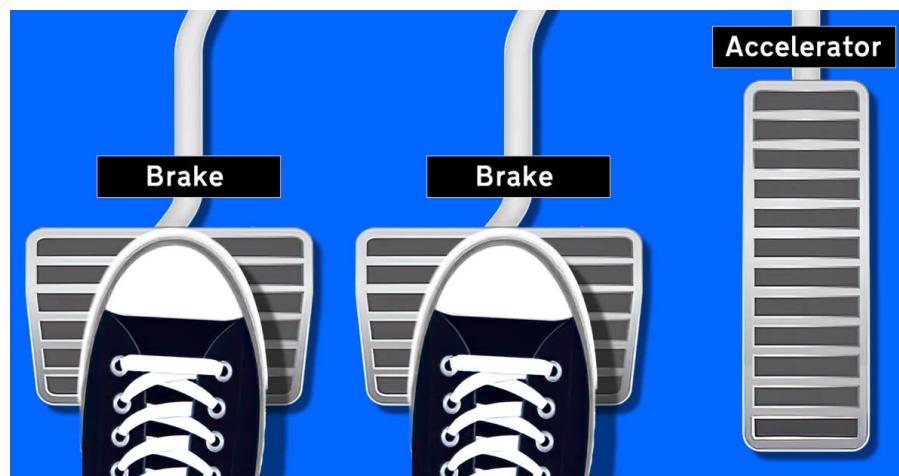


Oncogenes & tumour suppressors



Loss of function

- Double hit
- Missense, splice site, nonsense mutations
- Deletions and insertions
- Loss of loci
 - *TP53*
 - *VHL*



Gain of function

- Single hit
- Missense mutations
- Copy number gain (amplification)
 - *TERT* promoter
 - *KRAS*
 - *MYC*

How many mutations are required to develop a tumour?

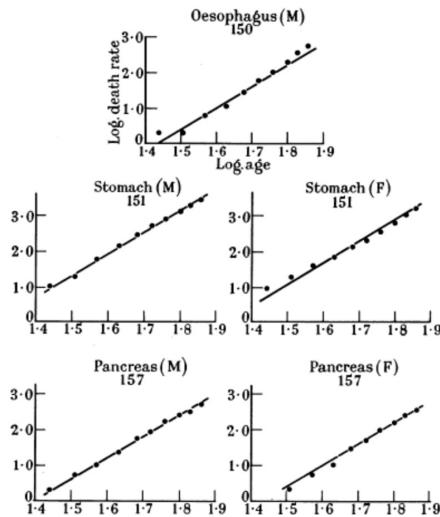
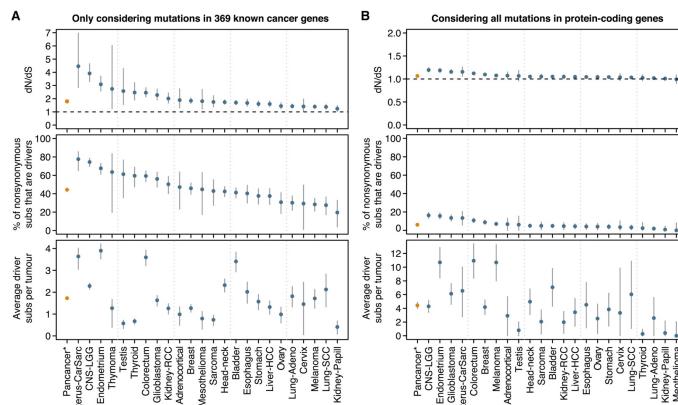


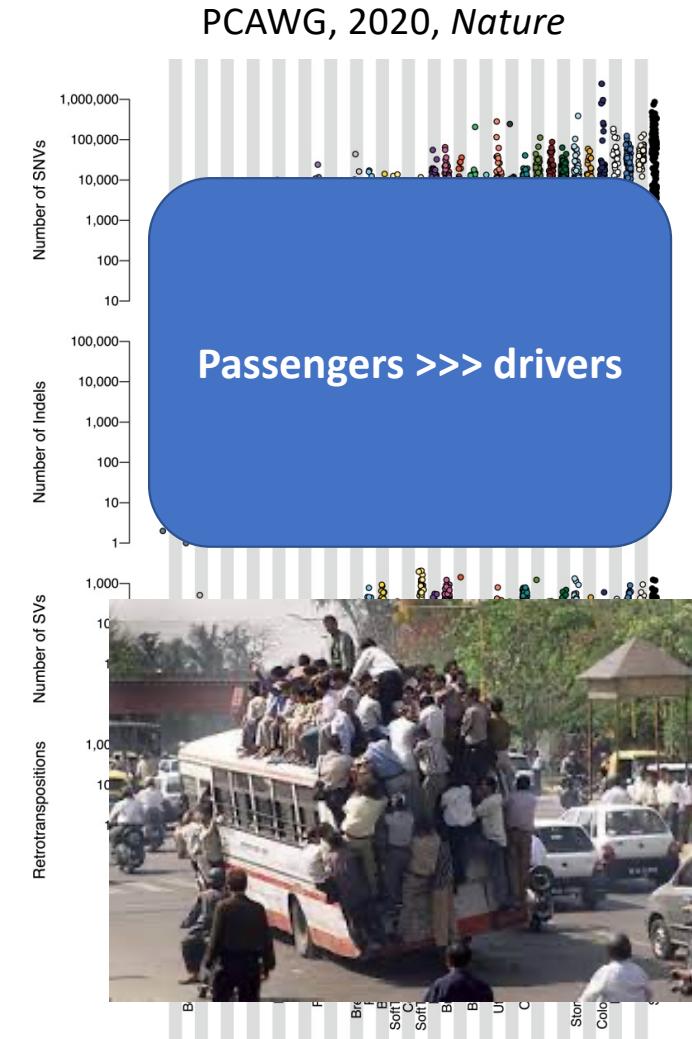
FIG. 1.—Change in mortality with age for cancer of the oesophagus, stomach and pancreas in men and for cancer of the stomach and pancreas in women shown on a double logarithmic scale, that is, the logarithm of the death rate per million persons plotted against the logarithm of the mid-point of the age group. The straight line through the points has been drawn arbitrarily to give the best fit, subject to the gradient being 6 to 1.

Armitage and Doll, 1954,
British Journal of Cancer

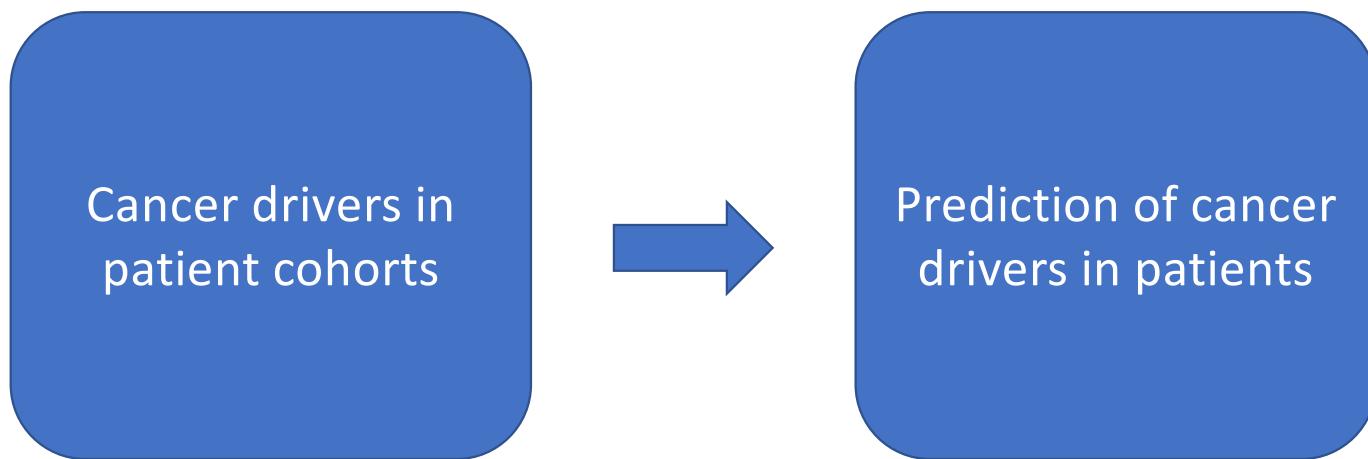


Martincorena et al, 2017, *Cell*

Typically, a handful
of drivers per
tumour



Research on cancer drivers



General Biology
Cancer Biology
New drivers
Cohort characterisation
Drug research

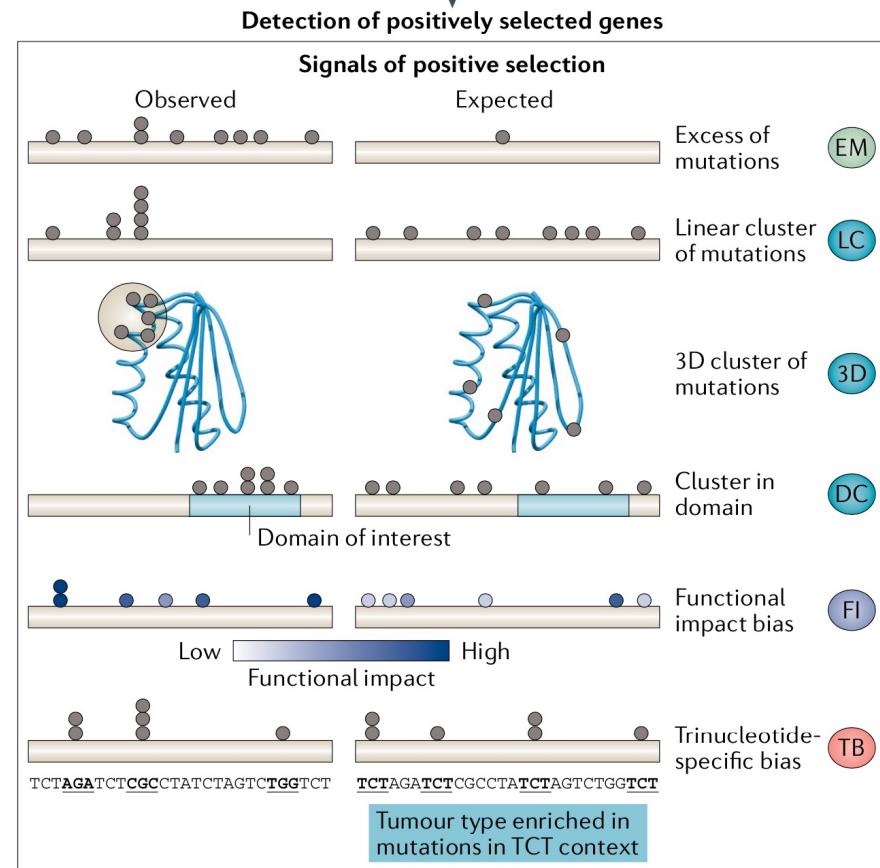
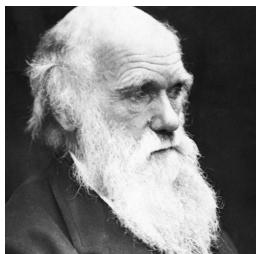
Prediction of cancer
drivers in patients

Risk prediction
Treatment

How to find drivers in cohorts?

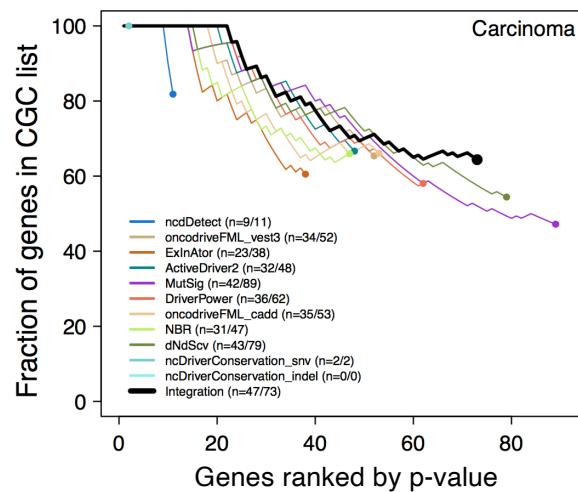


- Like finding needles in a haystack
- Recurrence – signature of positive selection
- Key – properly modelling the mutational process: null ("expected") model



Martínez-Jiménez et al, 2020, *Nature Reviews Cancer*

Methods



PCAWG Consortium – driver team

Many methods

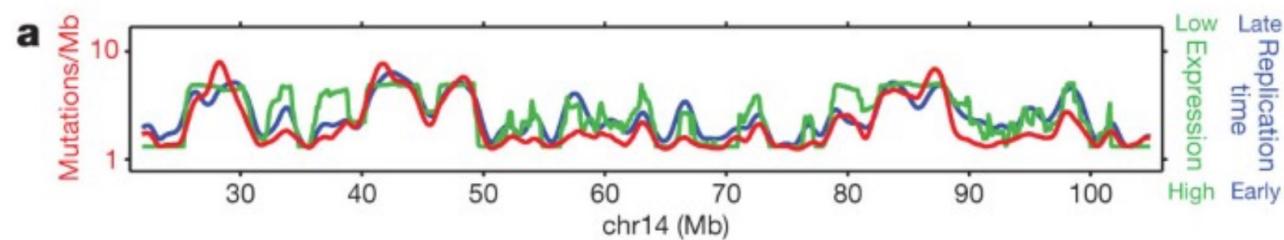
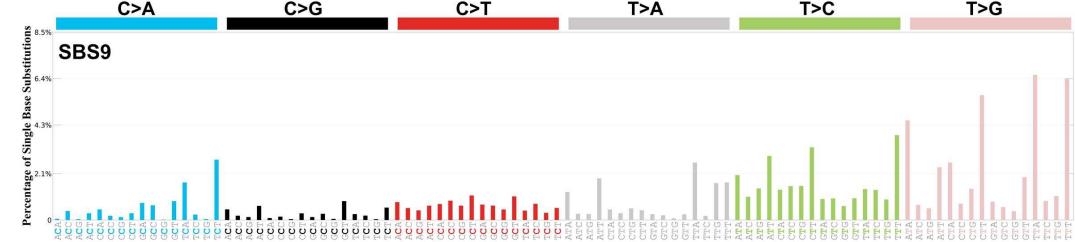
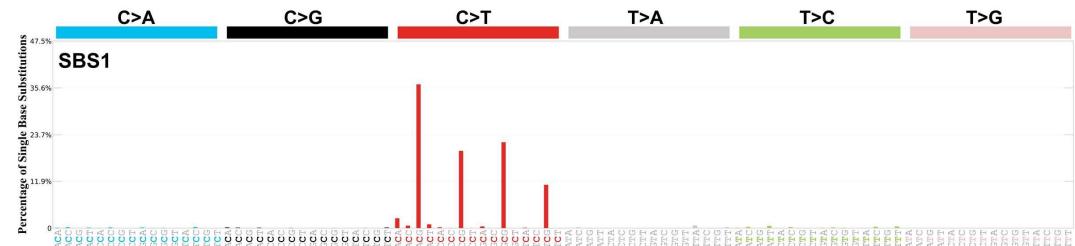
dNdScv and MutSigCV best

dNdScv easy to run & versatile

Modelling the mutational process

- Null model
- Difficult for:
 - structural variants
 - Gistic https://www.genepattern.org/modules/docs/GISTIC_2.0
 - Gene fusions, etc
 - epigenetic alterations
- Better understood for point mutations
 - substitutions
 - small indels

Most substitution mutational processes can be described using the trinucleotide context



Lawrence et al, 2013, *Nature*

Selection for substitutions in coding regions

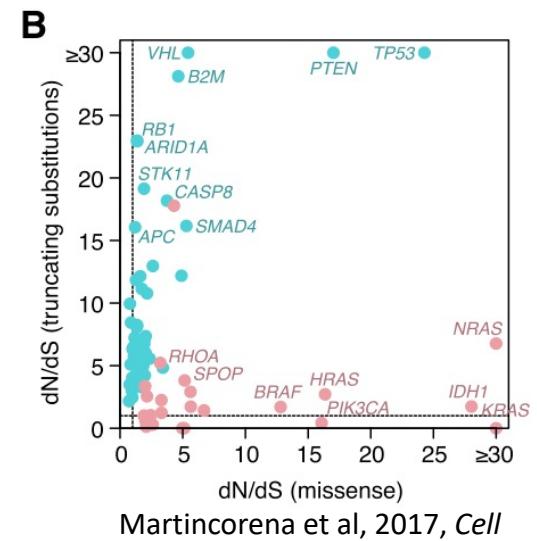
- dN/dS: a formal observed/expected test
 - Rate of non-synonymous substitutions divided by the rate of synonymous substitutions (=obs /exp under null model)
 - $dN/dS < 1$? **Negative selection**
 - $dN/dS = 1$? **Neutral evolution**
 - $dN/dS > 1$? **Positive selection!**
 - **dndscv** <https://github.com/im3sanger/dndscv>
- Non-synonymous substitutions:
 - Missense (e.g. Leu → Pro) *(OGs and TSGs)*
 - Nonsense (e.g. Ser → Stop)
• Splice sites

Truncating (TSGs)

		Second letter					
		U	C	A	G		
First letter	U	UUU } Phe UUC UUA } Leu UUG	UCU } Ser UCC UCA UCG	UAU } Tyr UAC UAA Stop UAG Stop	UGU } Cys UGC UGA Stop UGG Trp	U C A G	
	C	CUU } CUC CUA CUG } Leu	CCU } CCC CCA CCG } Pro	CAU } His CAC CAA } Gln CAG	CGU } CGC CGA CGG } Arg	U C A G	
A	A	AUU } AUC AUU } Ile AUG Met	ACU } ACC ACA ACG } Thr	AAU } Asn AAC AAA } Lys AAG	AGU } Ser AGC AGA } Arg AGG	U C A G	
G	G	GUU } GUC GUA GUG } Val	GCU } GCC GCA GCG } Ala	GAU } Asp GAC GAA } Glu GAG	GGU } GGC GGA GGG } Gly	U C A G	

Selection for point mutations in coding regions

- Oncogenes vs tumour suppressors:
 - OG: missense
 - TSG: nonsense, splice, indels, missense
- Coefficient of selection (dN/dS) interpretation
 - dN/dS of 1: all obs non-syn are exp (neutral)
 - dN/dS of 2: 50% of non-syn selected
 - dN/dS of 10: 90% of non-syn selected
 - dN/dS of 100: 99% of non-syn selected



dndscv detecting selection

- R package dndscv (Martincorena et al, *Cell* 2017)
 - dN/dS model – coef. of selection
 - Sophisticate mutational model:
 - Trinuc frequencies
 - Covariates for regional variation + data at hand
 - Overdispersion – negative binomial (equivalent of Poisson distribution)
 - User friendly
 - <https://github.com/im3sanger/dndscv>
- Selection estimates at:
 - Gene level (or domains)
 - Global
 - Sites & codons
 - Not only for cancer

dndscv gene level

- How to run:
 - dndscv function
 - panel vs no panel
 - Hypermutators
- Quick tutorial:
<http://htmlpreview.github.io/?http://github.com/im3sanger/dndscv/blob/master/vignettes/dNdScv.html>
- Outputs:

```
dout = dndscv(muts)
names(dout)
[1] "globaldnds"      "sel_cv"          "sel_loc"         "annotmuts"      "genemuts"
[6] "geneindels"       "mle_submodel"    "exclsamples"    "exclmuts"       "nbreg"
[11] "nbregind"        "poissmodel"      "wrongmuts"      "N"              "L"
```

dndscv\$sel_cv example: TCGA bladder carcinoma

gene_name	n_syn	n_mis	n_non	n_spl	n_ind	wmis_cv	wnon_cv	wspl_cv	wind_cv	qglobal_cv
TP53	5	143	35	4	24	41.0	97.7	97.7	366.9	0
PIK3CA	3	80	0	0	1	14.5	0.0	0.0	6.1	0
FGFR3	6	53	1	0	2	12.6	2.6	2.6	13.7	0
ARID1A	7	34	45	6	30	2.7	38.1	38.1	65.7	0
KDM6A	6	21	33	9	34	2.5	33.6	33.6	136.9	0
KMT2D	9	39	50	10	29	1.7	23.6	23.6	26.2	0
RB1	0	8	34	14	21	2.3	91.4	91.4	138.5	0
STAG2	8	12	22	4	14	1.3	21.8	21.8	64.8	0
ELF3	0	29	1	1	20	17.1	10.1	10.1	138.9	0
CDKN2A.p16	0	12	3	2	5	16.2	104.4	104.4	188.4	0
CDKN1A	1	5	6	0	23	5.6	51.2	51.2	389.1	0
TSC1	3	9	12	5	6	1.4	25.6	25.6	27.1	1.86E-13
ZFP36L1	0	7	3	0	18	4.1	29.5	29.5	85.4	1.54E-12
FBXW7	0	19	10	1	2	7.5	35.3	35.3	16.8	5.32E-10
EP300	2	40	16	1	7	4.5	14.4	14.4	14.1	2.90E-09

...

dndscv tutorials:

<https://drive.google.com/drive/folders/1-M4eeIzsZCyEwEnFNHFDZs2LkZAOr?usp=sharing>
<https://github.com/im3sanger/dndscv>

Other tools:

- MutSigCV: <https://www.genepattern.org/modules/docs/MutSigCV>
- IntOGen: <https://www.intogen.org/search>

w = dN/dS (coef. of selection)

(w-1)/w = fraction mutations selected

TP53 wmis = 41.0, 97.5% selected

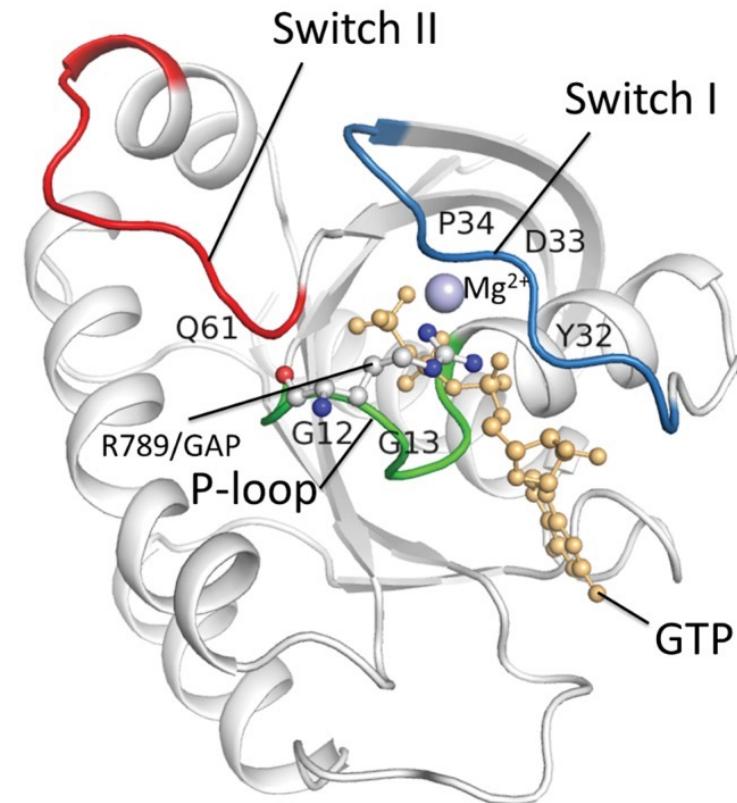
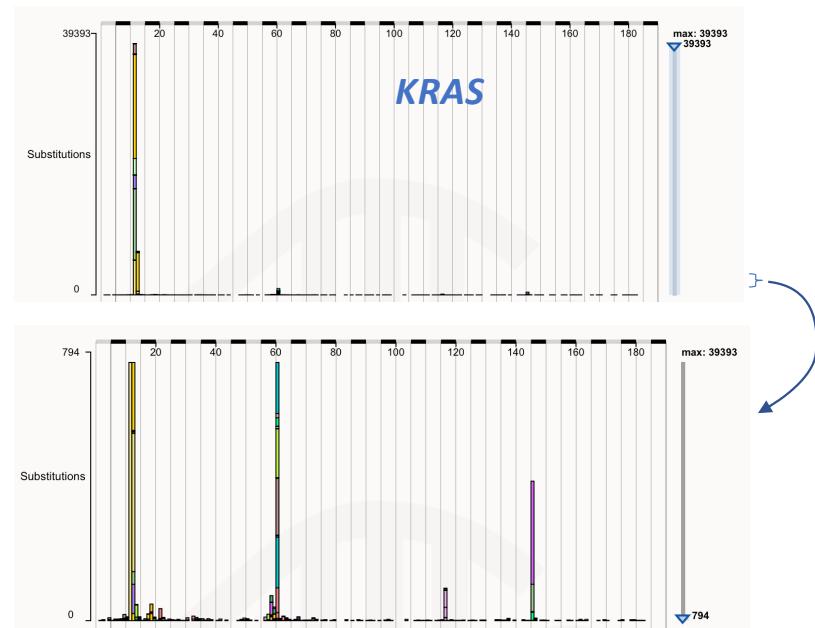
EP300 wmis = 4.5, 77.8% selected

Why are coefficients of selection important?

- Personalised medicine implications
- Hypermutators lower dN/dS

dndscv detecting selection at sites/codons

- Recurrence - hotspots
- COSMIC:



Chen et al, 2013, *PLoS one*

Hotspot analysis with dndscv: sitednds and codondnds

Site dN/dS on TCGA data

chr	pos	ref	mut	gene	aachange	impact	ref3_cod	mut3_cod	freq	mu	dnds	pval	qval
7	140453136	A	T	BRAF	V600E	Missense	GTG	GAG	408	0.002	176526.1	0	0
2	209113112	C	T	IDH1	R132H	Missense	CGT	CAT	353	0.079	4469.6	0	0
3	178952085	A	G	PIK3CA	H1047R	Missense	CAT	CGT	161	0.007	22252.8	0	0
12	25398284	C	T	KRAS	G12D	Missense	GGT	GAT	114	0.008	14578.7	6.21E-241	1.62E-233
3	178936091	G	A	PIK3CA	E545K	Missense	TGA	TAA	150	0.029	5112.8	4.94E-232	1.03E-224
12	25398284	C	A	KRAS	G12V	Missense	GGT	GTT	95	0.007	13634.6	1.26E-205	2.19E-198
1	115256529	T	C	NRAS	Q61R	Missense	CAA	CGA	72	0.003	25980.9	1.02E-184	1.51E-177
3	178936082	G	A	PIK3CA	E542K	Missense	TGA	TAA	95	0.029	3238.1	3.17E-147	4.13E-140
17	7578406	C	T	TP53	R175H	Missense	CGC	CAC	108	0.056	1938.8	2.16E-138	2.50E-131
12	25398285	C	A	KRAS	G12C	Missense	TGG	TTG	62	0.007	8299.3	1.36E-132	1.42E-125
17	7577538	C	T	TP53	R248Q	Missense	CGG	CAG	92	0.045	2025.9	9.10E-126	8.62E-119
17	7577121	G	A	TP53	R273C	Missense	GCG	GTG	90	0.056	1596.8	5.13E-115	4.46E-108
1	115256530	G	T	NRAS	Q61K	Missense	ACA	AAA	48	0.004	11185.0	2.62E-114	2.10E-107
17	7578190	T	C	TP53	Y220C	Missense	TAT	TGT	49	0.015	3290.9	2.00E-90	1.49E-83
4	1803568	C	G	FGFR3	S249C	Missense	TCC	TGC	35	0.004	8415.1	5.05E-84	3.51E-77
17	7577094	G	A	TP53	R282W	Missense	CCG	CTG	60	0.049	1216.8	3.12E-80	1.91E-73
17	7577539	G	A	TP53	R248W	Missense	CCG	CTG	60	0.049	1216.8	3.12E-80	1.91E-73
11	533874	T	C	HRAS	Q61R	Missense	CAG	CGG	29	0.002	14650.1	4.55E-79	2.63E-72
17	7577120	C	T	TP53	R273H	Missense	CGT	CAT	69	0.083	832.5	1.53E-77	8.36E-71
12	25398285	C	G	KRAS	G12R	Missense	TGG	TCG	28	0.002	14496.8	1.15E-76	5.99E-70
12	25398281	C	T	KRAS	G13D	Missense	GGC	GAC	34	0.008	4430.7	1.19E-72	5.90E-66
17	7578394	T	C	TP53	H179R	Missense	CAT	CGT	32	0.008	3808.1	3.61E-67	1.71E-60
3	178952085	A	T	PIK3CA	H1047L	Missense	CAT	CTT	26	0.003	8447.0	5.41E-66	2.45E-59

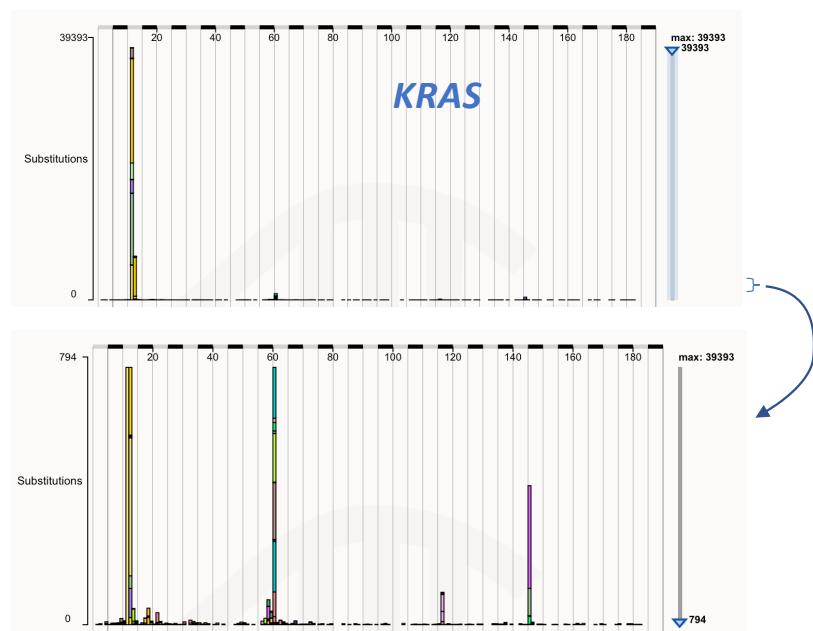
.... 565 with q<0.1

Quick tutorial: <https://rdrr.io/github/im3sanger/dndscv/f/vignettes/sitednds.Rmd>

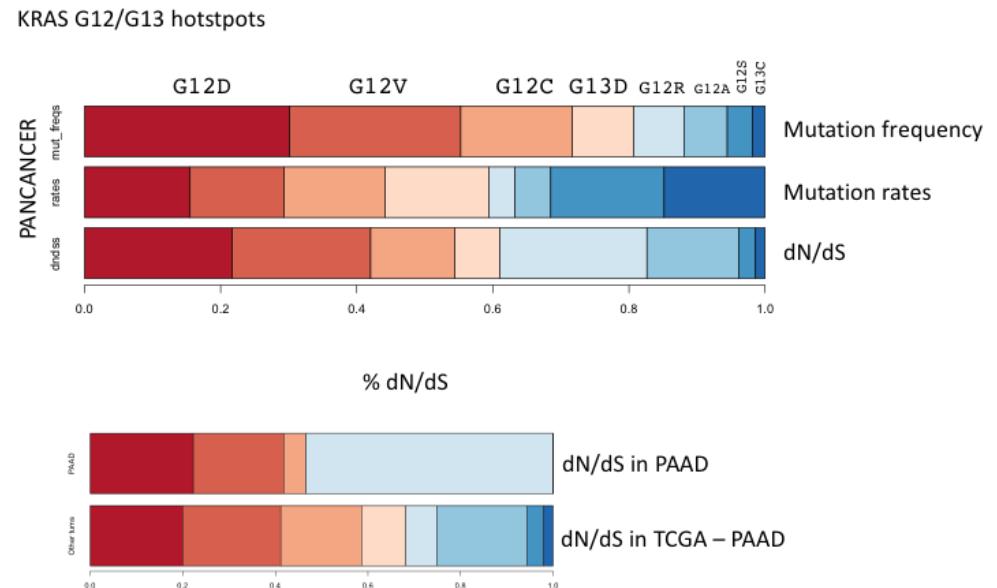
Hotspots: sitednds and codondnds

- Recurrence
- COSMIC:

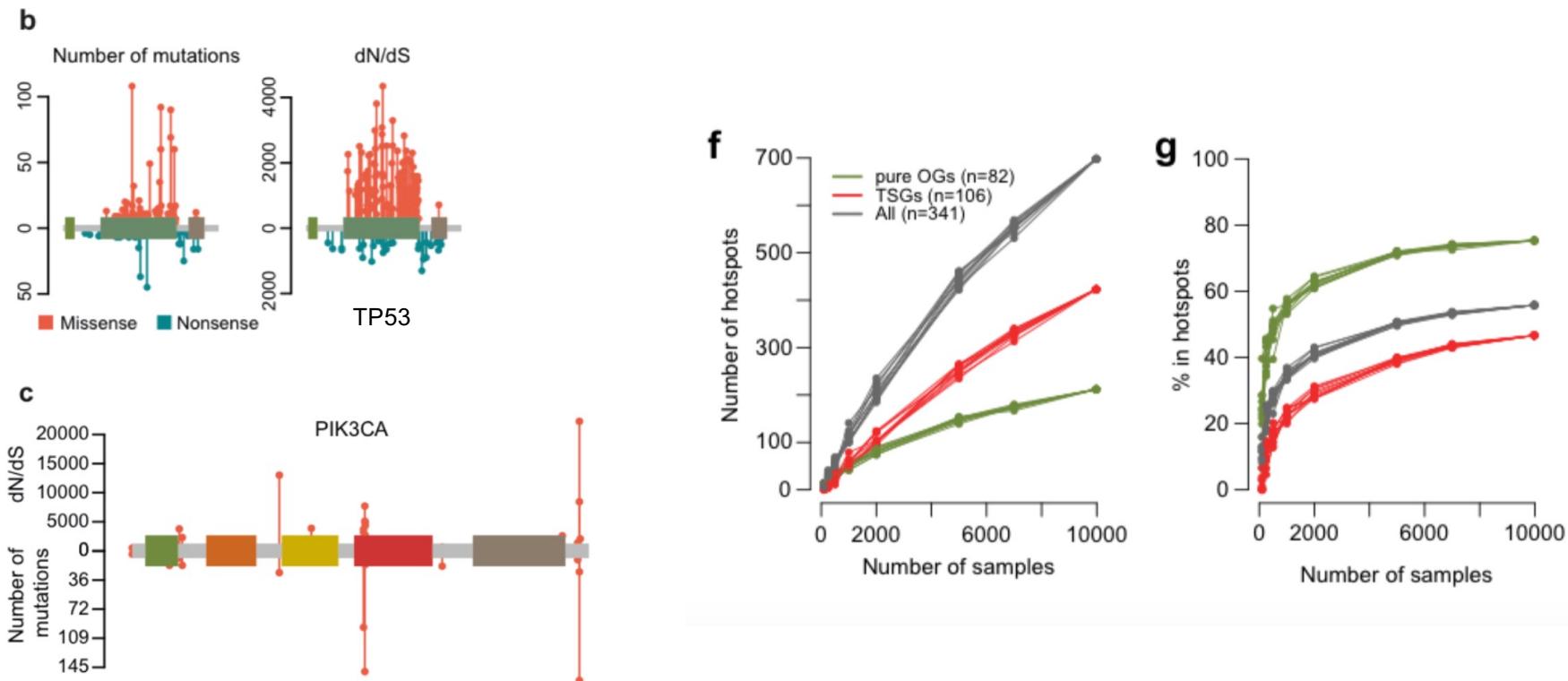
<https://cancer.sanger.ac.uk/cosmic/gene/analysis?In=KRAS>



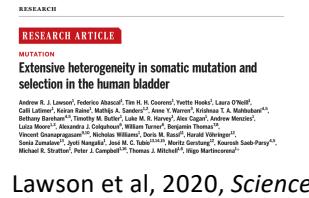
KRAS hotspots vary from tumour to tumour



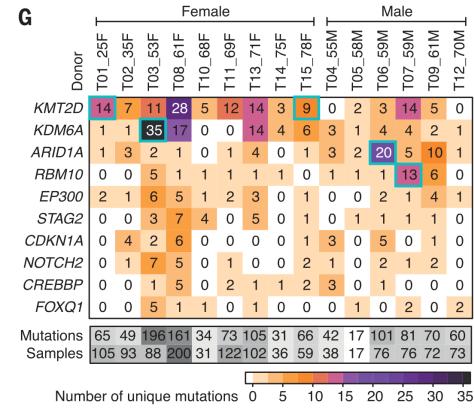
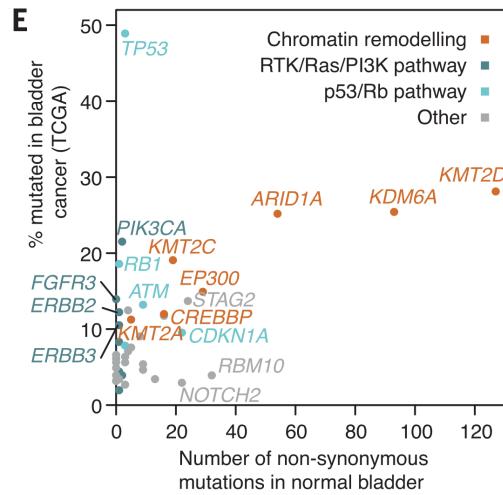
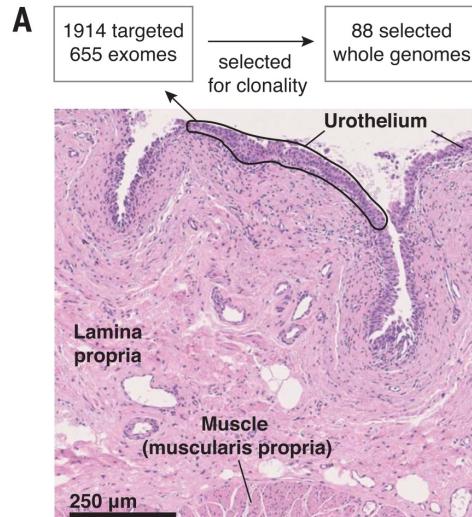
Hotspots: best for OGs



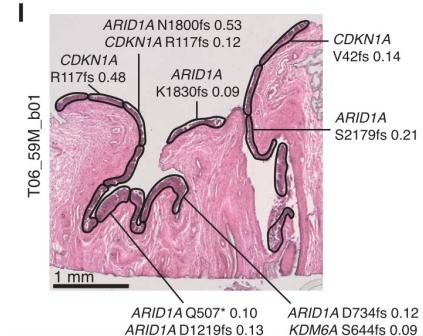
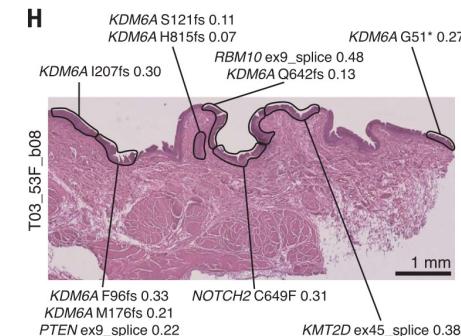
dndscv example: drivers in healthy bladder



Andrew Lawson



- Chromatin modifiers!
- TP53 early diagnosis?
- Differences between donors



dndscv\$globaldns example: healthy bladder

We can also use the output of dNdScv to evaluate the global dN/dS ratios from the targeted genes, as shown in Fig 2F.

```
global.dnds = dndscv$globaldns
print(global.dnds)

##      name     mle    cilow   cihigh
## wmis wmis 1.610909 1.323354 1.960947
## wnon wnon 7.046807 5.307025 9.356936
## wspl wspl 3.281976 2.171976 4.959248
## wtru wtru 5.575941 4.337762 7.167550
## wall wall 2.008897 1.659051 2.432514
```

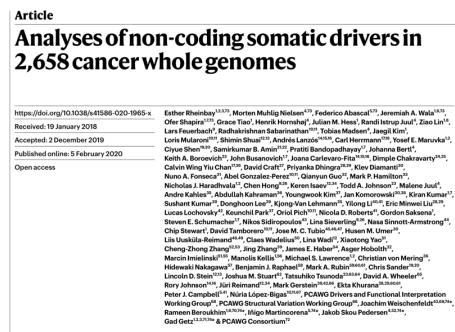
Global dN/dS ratios on the targeted genes can be used to estimate the % of nonsynonymous mutations in the targeted genes that are drivers and the estimated number of driver mutations in these microbiopsies.

```
w = as.matrix(global.dnds[,c(1,4),-1]) # Global dN/dS values wmis and wtrunc values
f = (w-1)/w # Driver fractions
n = f*c(sum(dndscv$genemuts$n_mis), sum(dndscv$genemuts$n_non+dndscv$genemuts$n_spl)) # Number of drivers
print(colSums(n)) # Estimated number of drivers
```

```
##      mle    cilow   cihigh
## 344.2974 262.7553 410.9049
```

Regulatory regions and noncoding genes

- Protein coding: 1% of the genome
 - PCAWG: 2,658 whole genomes (TCGA exomes)
 - microRNAs, lncRNAs, tRNAs...
 - Promoters, 3' and 5' UTRs, enhancers
 - Large set of driver candidates
 - *ALB*
 - lncRNAs: *NEAT1* & *MALAT1*...
 - UTRs/promoters: *WDR74*...
 - tRNAs
 - small RNAs
 - micro RNAs

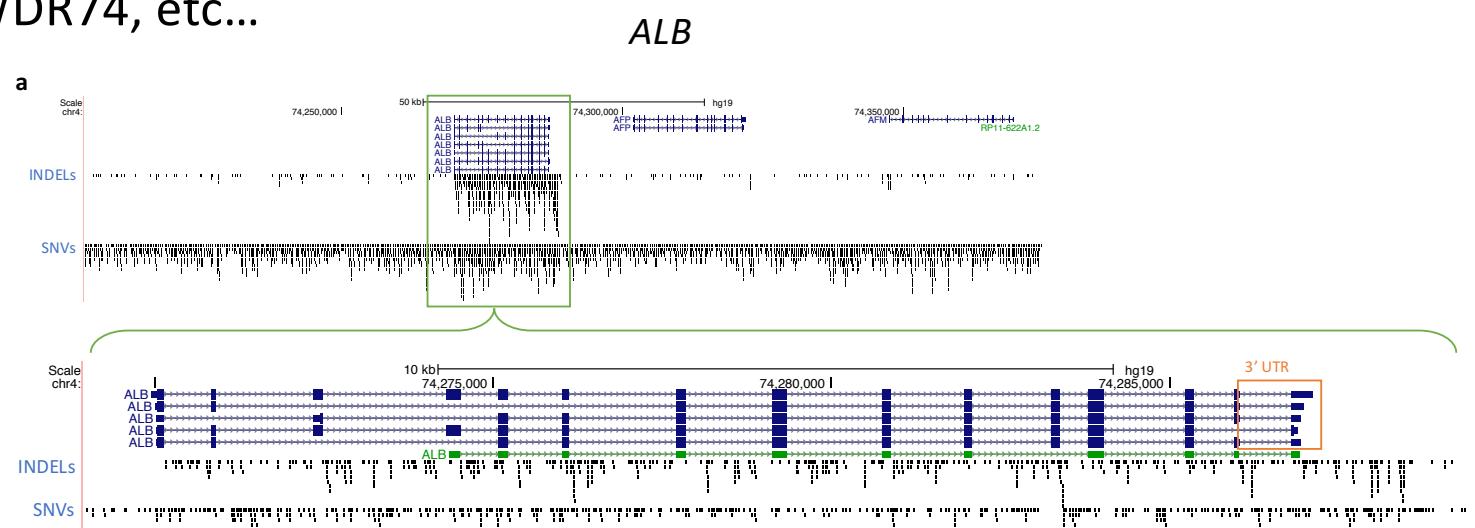


Rheinbay et al, 2020, *Nature*

Regulatory and noncoding genes

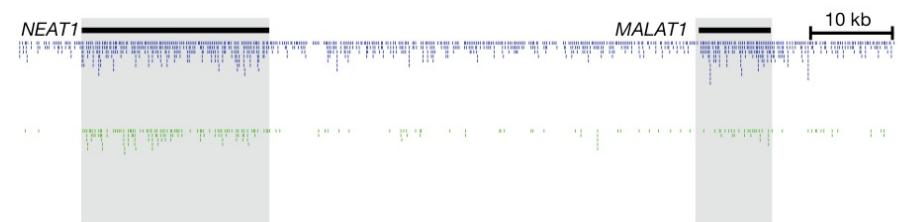
- Preliminary set of candidates

- ~~ALB~~
- lncRNAs: NEAT1 & MALAT1...
- UTRs/promoters: WDR74, etc...
- tRNAs
- small RNAs
- micro RNAs

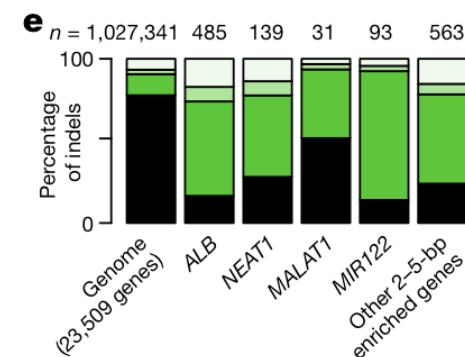


Regulatory and noncoding genes

- Preliminary set of candidates
 - *ALB*
 - lncRNAs: *NEAT1* & *MALAT1*...
 - UTRs/promoters: *WDR74*, etc...
 - tRNAs
 - small RNAs
 - micro RNAs

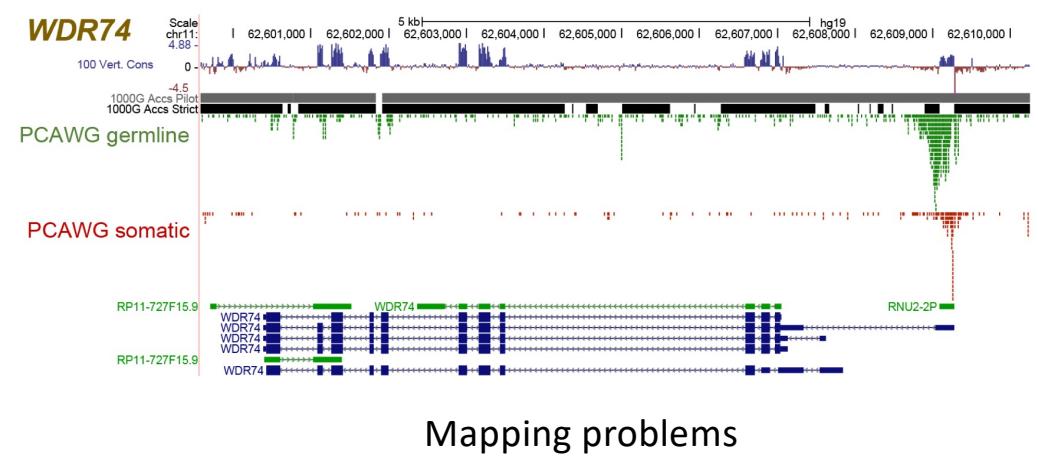


New unaccounted mutational processes
(null model violation)



Regulatory and noncoding genes

- Preliminary set of candidates
 - *ALB*
 - lncRNAs: NEAT1 & MALAT1...
 - UTRs/promoters: WDR74, etc...
 - tRNAs
 - small RNAs
 - micro RNAs



WDR74 had been reported in several publications

Regulatory regions of cancer genes: promoters and UTRs

Article

Analyses of non-coding somatic drivers in 2,658 cancer whole genomes

<https://doi.org/10.1038/s41586-020-1965-x>

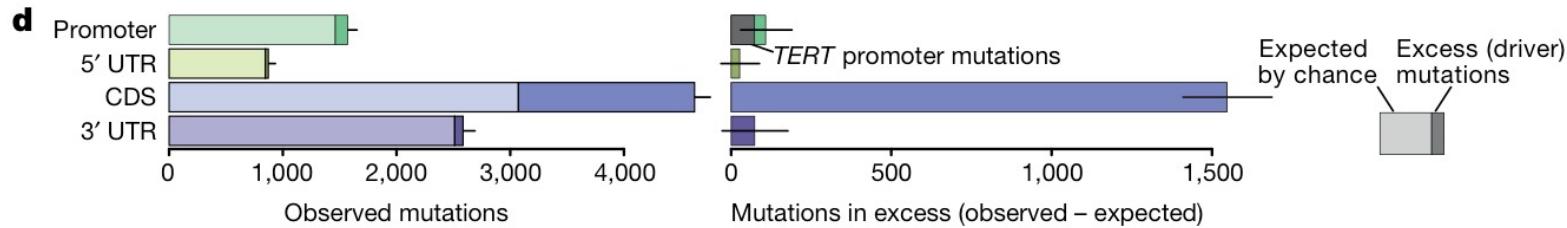
Received: 19 January 2018

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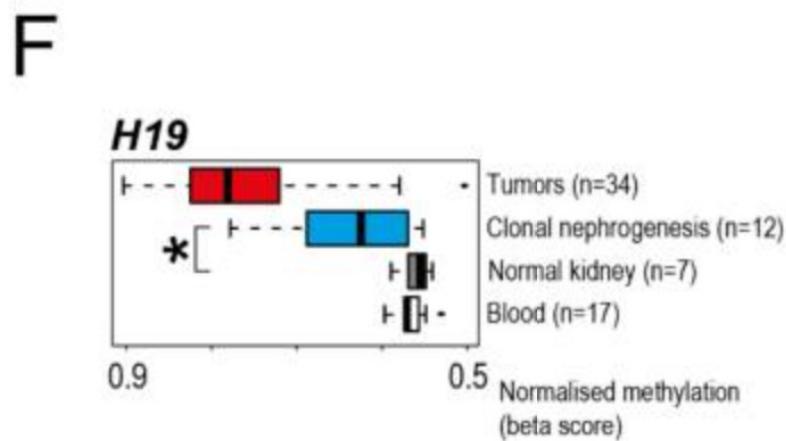
Editor: Ravi Roychowdhury^{1,2,3,4}; Horren, Marisa^{1,2,3,4}; Hedges, T.¹; Federico Alcoba^{1,2,3,4}; Hemamah A. Wala^{1,4,5}; Odile Bégin^{1,2,3,4}; Grace Yeo^{1,2,3,4}; Hélène J. Horwitz¹; Jason M. Head¹; Sébastien Boult¹; Zuo Lin¹; Lars Fougeroux¹; Radhakrishnan Subbaratnam^{1,2}; Tobias Madсен¹; Jaegil Kim¹; Loris Mularek^{1,2}; Shennin Shuai^{1,2,3,4}; Andréa Lanzo^{1,2,3,4}; Carl Hermann^{1,2,3,4}; Yosef E. Maruvka^{1,2}; Cylvia Stoeckli^{1,2,3,4}; Samirian B. Amiri^{1,2,3,4}; Prashant Dabholkar^{1,2,3,4}; Johanna P. Hart¹; Svetlana Bozovska¹; John G. Novakovich¹; Anna Carbone^{1,2,3,4}; Michael C. Chakravarthy^{1,2,3,4}; Calvin Wing Yiu Chan^{1,2,3}; David Craft¹; Priyanka Dhingra^{1,2,3,4}; Kev Diamond^{1,2}; Nuno A. Fornieira¹; Abel Gómez-Puertas¹; Qiuyun Guo^{1,2,3,4}; Mark H. Hahn^{1,2,3,4}; Andre Kalafus^{1,2}; Abdullah Kahraman¹; Youngwook Kim¹; Jan Komorowski^{1,2,3,4}; Kiran Kumar^{1,2}; Sudham Kumar¹; Donghoon Lee¹; Kyoung-Yan Lee¹; Yilong Li¹; Eric Minwei Liu^{1,2,3}; Mingming Liu^{1,2,3,4}; Daniel Loh¹; Daniel M. Lopez-Blaque^{1,2,3,4}; Natasja M. Meeuwis^{1,2,3,4}; Steven J. Schumacher¹; Nikos Sidropoulos¹; Lina Siverling^{1,2,3}; Natacha Simonetti-Amorino¹; Chi-Tsui Stewart¹; David Tamayo^{1,2,3,4}; Jose M. Vazquez^{1,2,3,4}; Luisa Wold¹; Huifen Xie¹; Chi-Lung Yu^{1,2,3,4}; Ming-Zheng Yang^{1,2,3,4}; Cheng-Zhong Zhang^{1,2,3}; Jing Zhang¹; James E. Haber^{1,2,3}; Asper Hobohm¹; Martin Hofmann-Schober¹; Androula Kalligari¹; Michael L. Lawrence^{1,2,3,4}; Christos Jon Maragis^{1,2}; Daniel Nogales^{1,2,3,4}; Barbara O’Reilly¹; Michael P. Robinson¹; Charles Sandio^{1,2,3}; Lincoln D. Stein^{1,2,3}; Joshua M. Stuett¹; Tatsuhiko Tsunoda^{1,2,3,4}; David A. Wheeler^{1,2,3,4}; Peter J. Campbell^{1,2,3}; Nuria López-Bigas^{1,2,3,4}; PCAWG Drivers and Functional Interpretation Working Group¹; PCAWG Structural Variation Working Group²; Joachim Weischenfeldt^{1,2,3,4}; Rameen Beroukhim^{1,2,3,4}; Iligo Martincicena^{1,2,3,4}; Jakob Skøl Pedersen^{1,2,3,4}; Gad Getz^{1,2,3,4,5}; & PCAWG Consortium^{1,2,3,4,5}



- Not much beyond *TERT* promoter

Epigenetic drivers

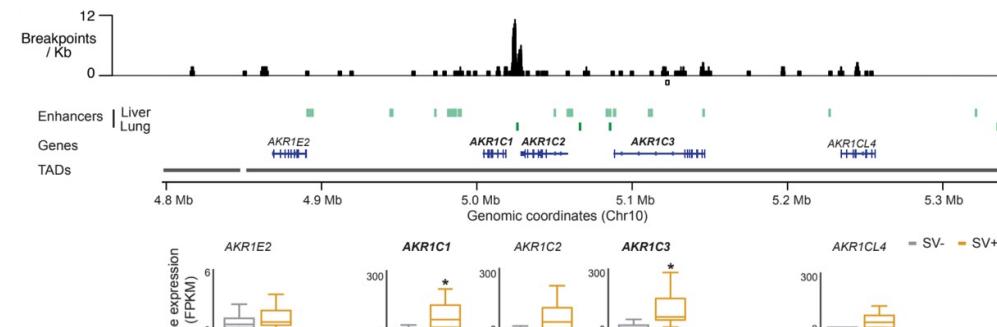
- Chromatin modifiers
- Plasticity: Δ individuals, cell types, environment → null model?
- Wilms tumour: *H19* hypermethylation.
Noncoding driver!
- *VHL* silencing through hypermethylation



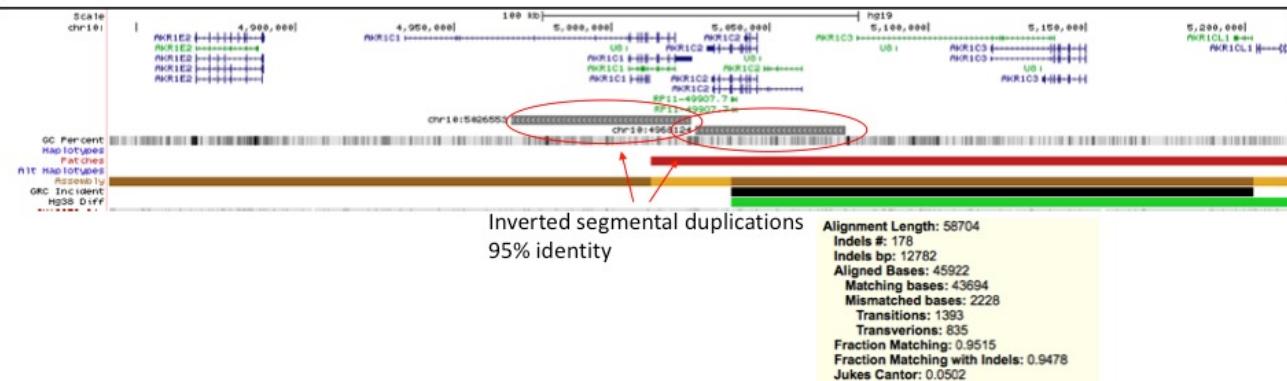
Coorens et al, 2019, *Science*

Structural drivers

- Copy number: GISTIC (Mermel et al, 2011): identifies regions of the genome that are significantly amplified or deleted across a set of samples (e.g. *MYC* oncogene amplification)
- Rearrangements:
 - Null model? Fragile sites *why?*
 - Gene fusions, enhancer hitch-hiking, copy number gain etc
 - AKR1C locus

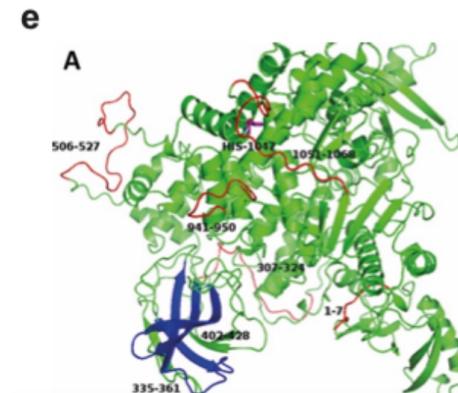
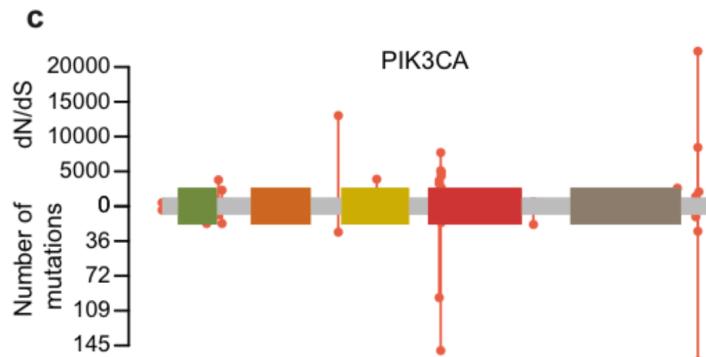


Rheinbay et al, 2020, *Nature*



Take home messages

- OG and TSG behave very differently – no B&W in Biology
- Passengers >> drivers (hypermutators particularly problematic)
- Recurrence = positive selection (obs>exp)
- Most drivers are protein-coding (+TERT) – 1% of the genome!
 - Always look into the details
- Not all non-synonymous mutations are drivers (dN/dS)
- Structural and epigenetic alterations can be drivers too



Start codon loss in OG?

Prediction of driver mutations in a given patient

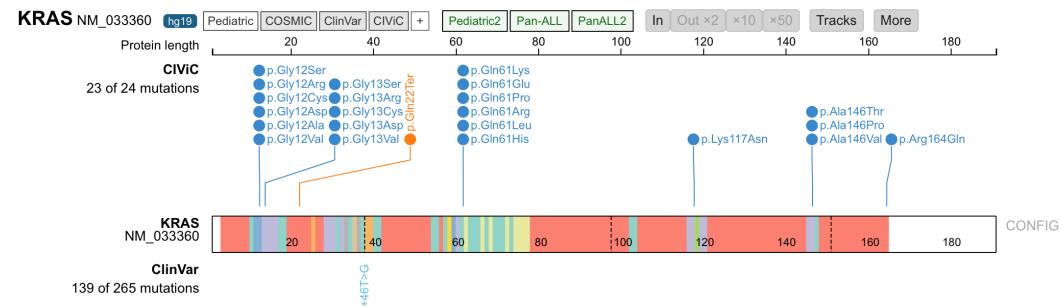
Table 1. Molecular targets for personalised cancer therapies

Cancer type	Cellular target	Targeted agent	Class of agent
Colorectal ^{16–18}	KRAS	Cetuximab	Monoclonal antibody against EGFR
Breast ^{19,20}	HER2	Trastuzumab	Monoclonal antibody against HER2/ Neu (EGFR2)
Chronic myeloid leukaemia ^{21,22}	BCR-ABL fusion protein	Imatinib	Receptor tyrosine kinase inhibitor
Gastrointestinal stromal tumours ^{23,24}	c-KIT	Imatinib	Receptor tyrosine kinase inhibitor
Non-small-cell lung cancer ^{25–28}	EGFR	Erlotinib and gefitinib	Receptor tyrosine kinase inhibitor
Non-small-cell lung cancer ^{29,30}	EML4-ALK fusion protein	Crizotinib	Receptor tyrosine kinase inhibitor
Metastatic malignant melanoma ^{31,32}	BRAF V600E	Vemurafenib	B-raf/MEK/ERK pathway inhibitor
Ovarian, breast and prostate can- cer (under investigation) ^{33,34}	BRCA1, BRCA2	Olaparib	Poly(ADP-ribose) polymerase (PARP) inhibitor

Abbreviations: APC: adenomatous polyposis coli; CML: chronic myeloid leukaemia; CRC: colorectal cancer; EGFR: epidermal growth factor receptor; EML4-ALK: echinoderm microtubule-associated protein-like 4—anaplastic lymphoma kinase fusion gene; FAP: familial adenomatous polyposis coli; GIST: gastrointestinal stromal tumour; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; PARP: poly(ADP-ribose) polymerase; TK: tyrosine kinase; TKI: tyrosine kinase inhibitor

Clinical practice

- Top genes: most mutations are drivers (*TP53*, *KRAS*, *BRAF*...)
 - Careful with hypermutators
- Hotspots: most drivers
- OGs and TSGs behave differently
- Useful tools:
 - CiVIC: <https://civicdb.org/home>
 - Cancer Genome Interpreter:
<https://www.cancergenomeinterpreter.org/home>



Cancer Genome Interpreter example



Tamborero et al, 2018,
Genome Medicine
Muiños et al, 2021,
Nature
BoostDM: CiVIC,
recurrence,
conservation, ...

This analysis will be removed after 6 months

Mutations CNAs DETAILS ⓘ

Show entries with: Mutations identified as drivers Mutations with oncogenic annotations Other mutations

Sample ID	Gene	Protein Change	Oncogenicity	Mutation	Consequence	Oncogenic annotation
TCGA-AG-3999	KRAS	G12S				2
TCGA-AG-3999	TP53	R213*				216
TCGA-AA-A00D	TP53		ALTERATIONS	PRESCRIPTIONS		
TCGA-AA-A00D	PIK3CA					
TCGA-AA-A00D	APC					
TCGA-AA-A00D	BRCA1					
TCGA-AG-3999	APC					
TCGA-AA-A00D	APC					
TCGA-AG-3999	BCL2					
TCGA-AG-3999	PTEN	TCGA-AG-3999	(M) KRAS (G12S)	KRAS (12,13)	Cetuximab (EGFR mAb inhibitor)	Colorectal adenocarcinoma
TCGA-AG-3999	PTEN	TCGA-AG-3999	(M) KRAS (G12S)	KRAS (12,13,59,61,117,146)	Panitumumab (EGFR mAb inhibitor)	Colorectal adenocarcinoma
TCGA-AG-3999	UBF1	TCGA-AG-3999	(M) KRAS (G12S)	KRAS oncogenic mutation	Panitumumab (EGFR mAb inhibitor)	Colorectal adenocarcinoma
TCGA-AG-3999	PNU-142596	TCGA-AG-3999	(M) KRAS (G12S)	KRAS oncogenic mutation	Cetuximab (EGFR mAb inhibitor)	Colorectal adenocarcinoma
TCGA-AA-A00D	C10	TCGA-AG-3999	(M) KRAS (G12S)	KRAS (D119N,G12F,F156L,G60R,F28I)	Panitumumab + Cetuximab	Colorectal adenocarcinoma
TCGA-AG-3999	DDIT3	TCGA-AG-3999	(M) KRAS (G12S)	KRAS oncogenic mutation	Trastuzumab + Lapatinib (ERBB2 mAb inhibitor + EGFR mAb inhibitor)	Colorectal adenocarcinoma
TCGA-AG-3999	TRAF3	TCGA-AG-3999	(M) KRAS (G12S)	KRAS oncogenic mutation	Cetuximab	Colorectal adenocarcinoma
TCGA-AG-3999	KCIF10	TCGA-AG-3999	(M) KRAS (G12S)	KRAS (A146T,G13D,G12C,,A146P,Q66R)	Cetuximab	Colorectal adenocarcinoma
TCGA-AA-A00D	LRFN1	TCGA-AG-3999	(M) KRAS (G12S)	KRAS oncogenic mutation	Bevacizumab	Colorectal adenocarcinoma
TCGA-AA-A00D	APC	TCGA-AA-A00D	(M) BRAF (V600E)	BRAF (V600E)	Cetuximab (EGFR mAb inhibitor)	Colorectal adenocarcinoma
play a menu 3999	CPT1	TCGA-AA-A00D	(M) PIK3CA (H1047L)	PIK3CA oncogenic mutation	Cetuximab (EGFR mAb inhibitor)	Colorectal adenocarcinoma
TCGA-AA-A00D	(M) BRAF (V600E)		BRAF (V600E)	Panitumumab (EGFR mAb inhibitor)	Colorectal adenocarcinoma	
TCGA-AA-A00D	(M) BRAF (V600E)		BRAF (.,G469A,V600E,D594G)	Cetuximab	Colorectal adenocarcinoma	
TCGA-AA-A00D	(M) BRAF (V600E)		BRAF (V600E,D594G)	Cetuximab + Panitumumab	Colorectal adenocarcinoma	
TCGA-AA-A00D	(M) BRAF (V600E)		BRAF (V600E)	Panitumumab + Cetuximab	Colorectal adenocarcinoma	
TCGA-AA-A00D	(M) BRAF (V600E)		BRAF (V600E)	Fluorouracil	Colorectal adenocarcinoma	
TCGA-AA-A00D	(M) BRAF (V600E)		BRAF (V600E)	Bevacizumab	Colorectal adenocarcinoma	
TCGA-AA-A00D	(M) BRAF (V600E)		BRAF (V600.,G596R)	Vemurafenib	Colorectal adenocarcinoma	
TCGA-AA-A00D	(M) PIK3CA (H1047L)		PIK3CA (E542K,E545K,H1047R,,)	Cetuximab	Colorectal adenocarcinoma	

play a menu 3999

Recommended readings and software

- Martincorena, Iñigo, et al. "Universal patterns of selection in cancer and somatic tissues." *Cell* 171.5 (2017): 1029-1041.
- Rheinbay, Esther, et al. "Analyses of non-coding somatic drivers in 2,658 cancer whole genomes." *Nature* 578.7793 (2020): 102-111.
- Lawson, Andrew RJ, et al. "Extensive heterogeneity in somatic mutation and selection in the human bladder." *Science* 370.6512 (2020): 75-82
- Tamborero, David, et al. "Cancer Genome Interpreter annotates the biological and clinical relevance of tumor alterations." *Genome medicine* 10.1 (2018): 1-8
- Gonzalez-Perez, Abel, et al. "IntOGen-mutations identifies cancer drivers across tumor types." *Nature methods* 10.11 (2013): 1081-1082.
- Software: [dndscv](#), [maf-tools](#), [IntOGen](#), [Cancer Genome Interpreter](#)

Thank you!