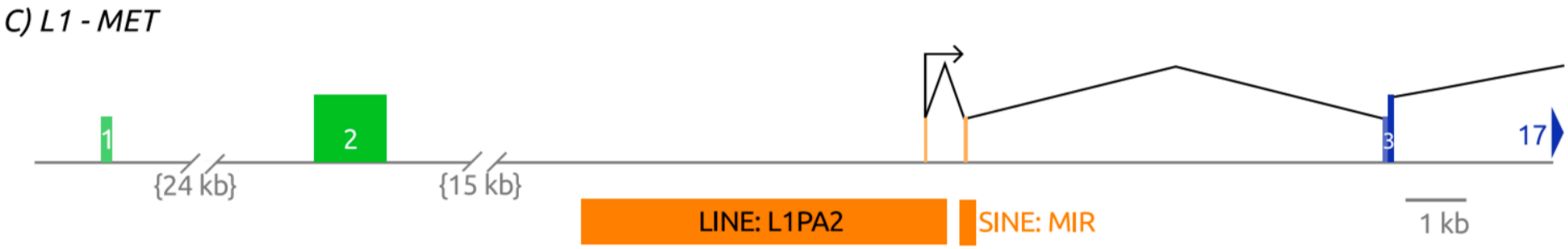
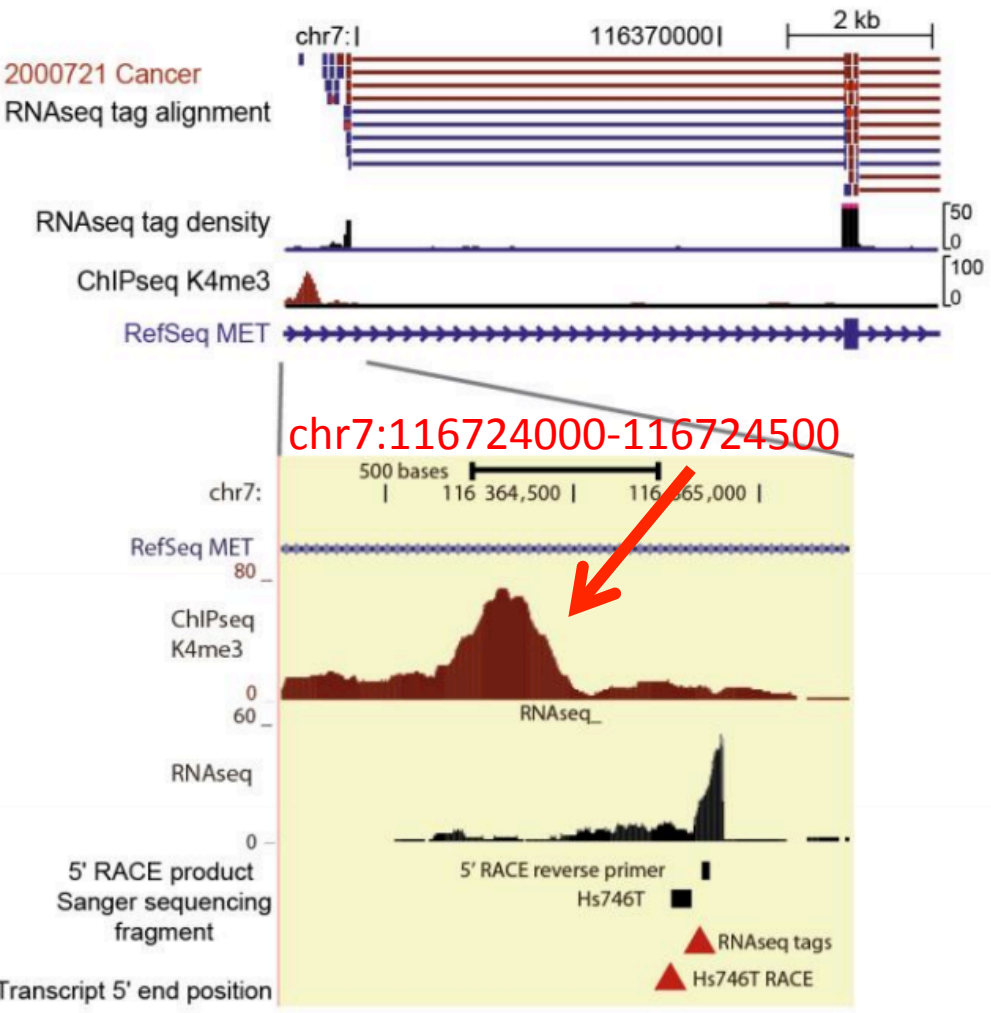
Cryptic Promoter Usage in MET

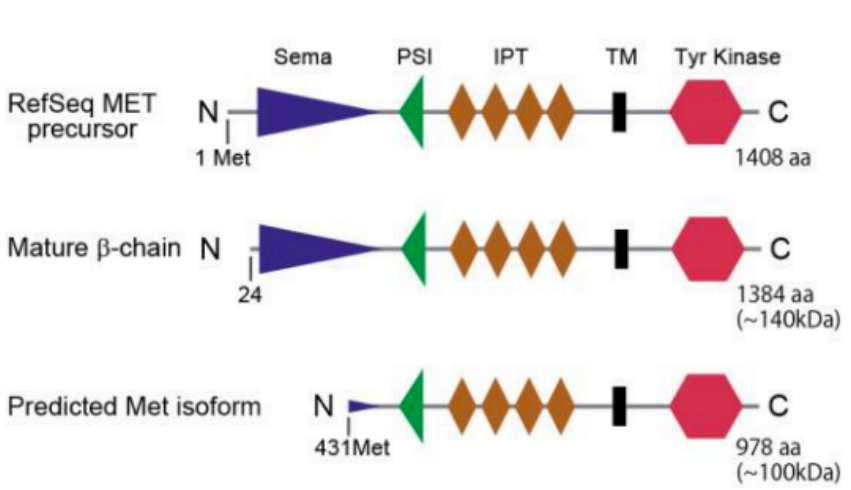
- Observed in multiple cancers for a decade
  - CML, colon, liver, bladder…

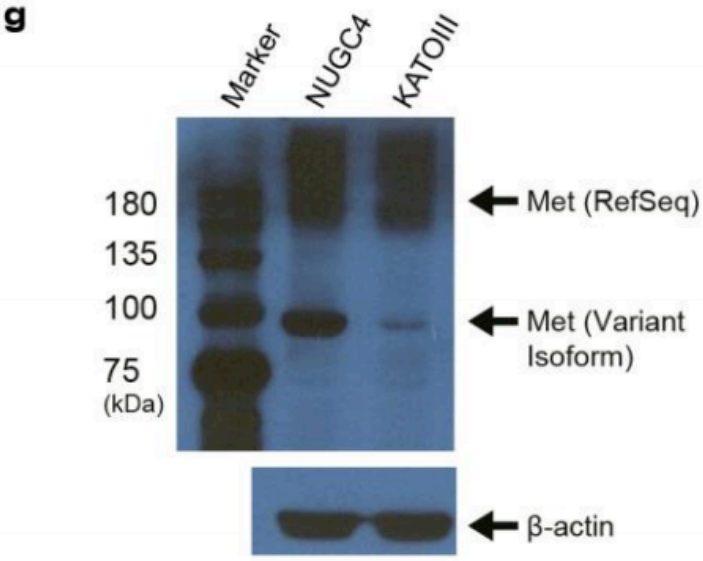


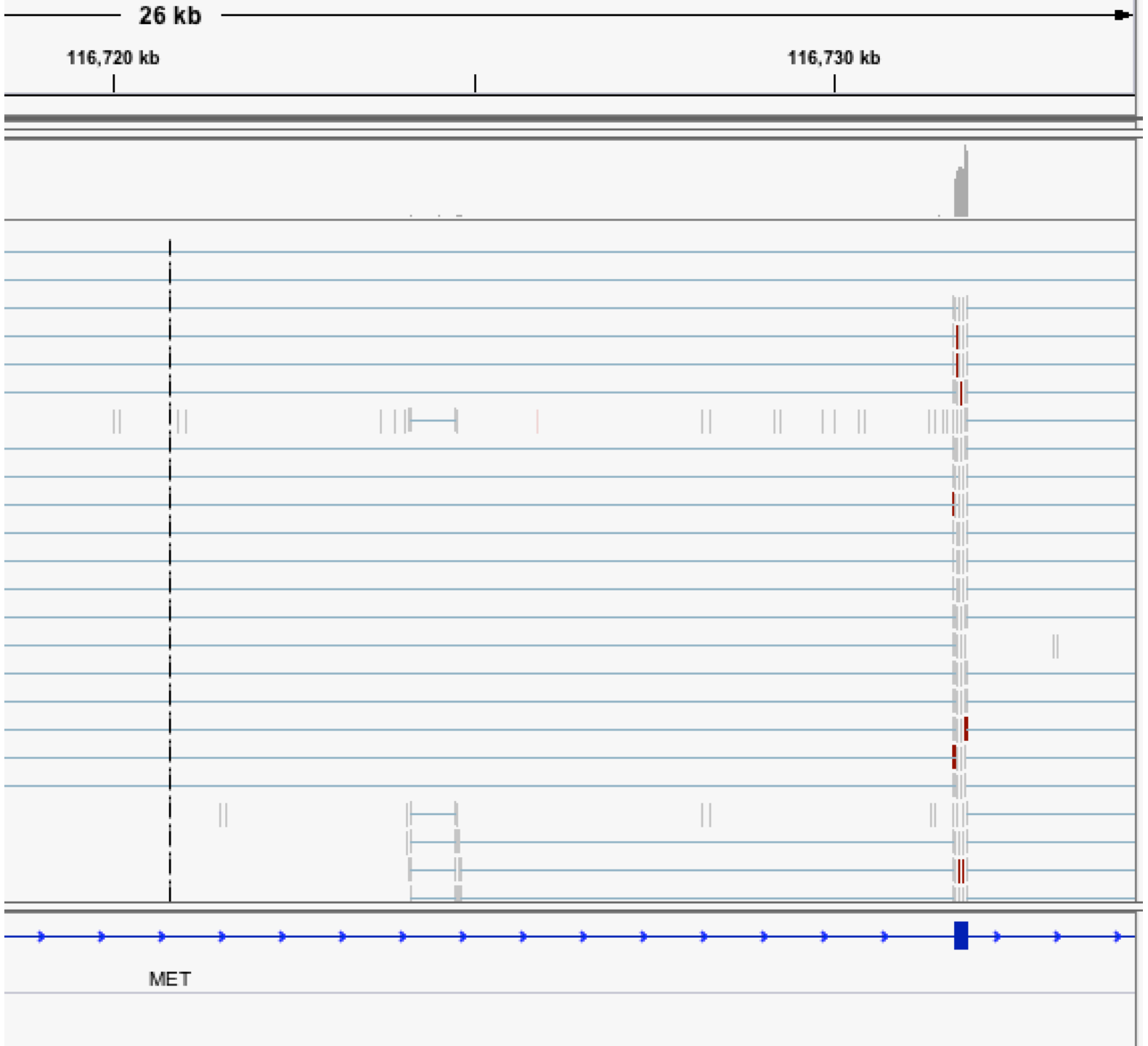
- Stable protein product in gastric CA
- Found in ~5% of KIRP samples

Translation in Gastric CA

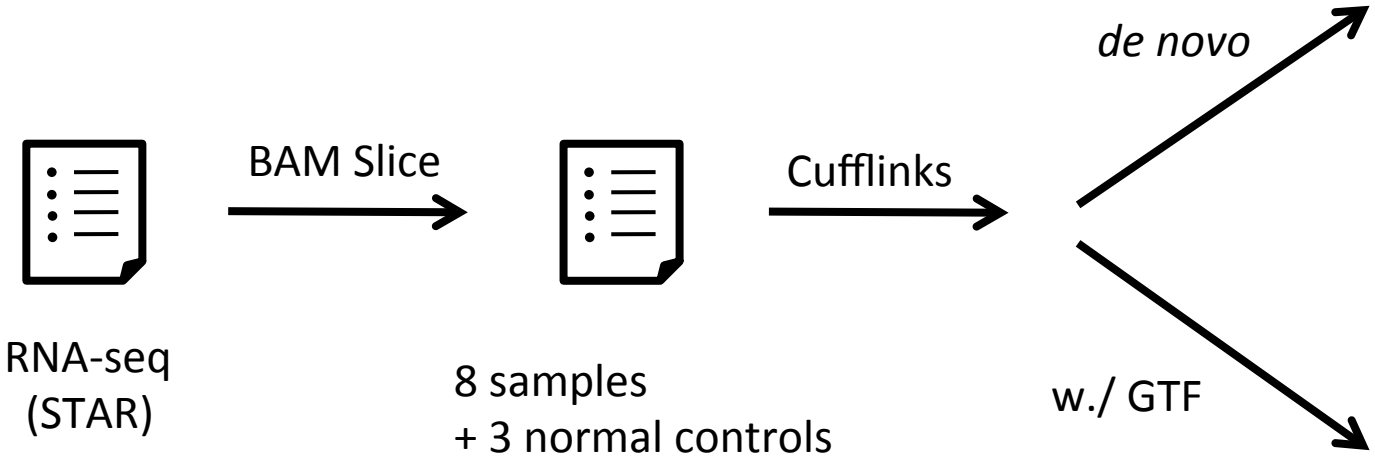


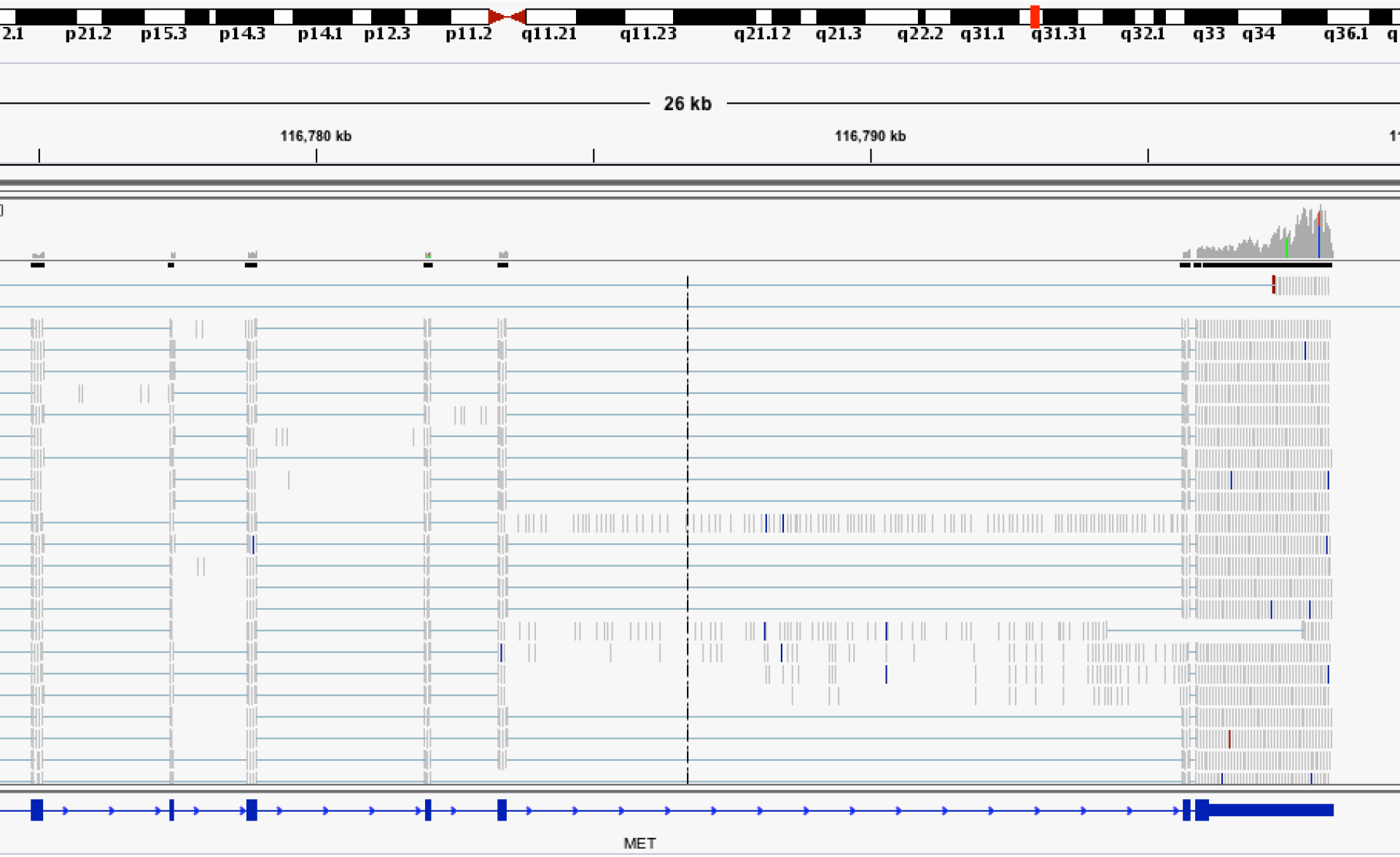





26 kb
116,720 kb
116,730 kb
MET

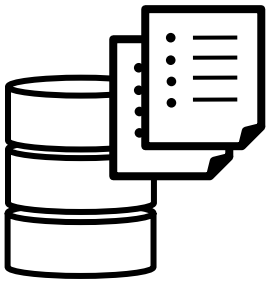
Workflow


BAM Slice
Cufflinks
de novo
w./ GTF
RNA-seq
(STAR)
8 samples
+ 3 normal controls

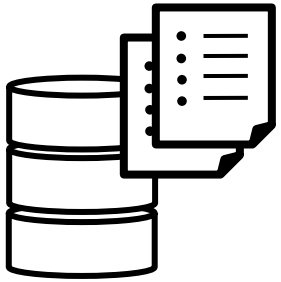

2.1
p21.2
p15.3
p14.3
p14.1
p12.3
p11.2
q11.21
q11.23
q21.12
q21.3
q22.2
q31.1
q31.31
q32.1
q33
q34
q36.1
26 kb
116,780 kb
116,790 kb
MET

Methylation

- Activation of TE is a result of loss of methylation
  - The closet probe is ~3kb downstream, marginal statistically significant (p=0.055)
- Abnormal methylation
  - Enriched in methylation cluster 2 (**hyper**meth), p=0.05
  - Enriched in C2b (basically all type2 has meth C2), $p<0.05$



ExAC



1000 Genomes

Population-specific AF ("popmax") ≤ 0.5% in *both* datasets

Scenario I

ClinVAR annotation:
- **Risk**
- **Likely pathogenic**
- **Pathogenic**

Scenario II

Scenario I
AND
Disruptive mutations:
- **Rated HIGH by Ensembl**
- **TSL1**

Scenario III

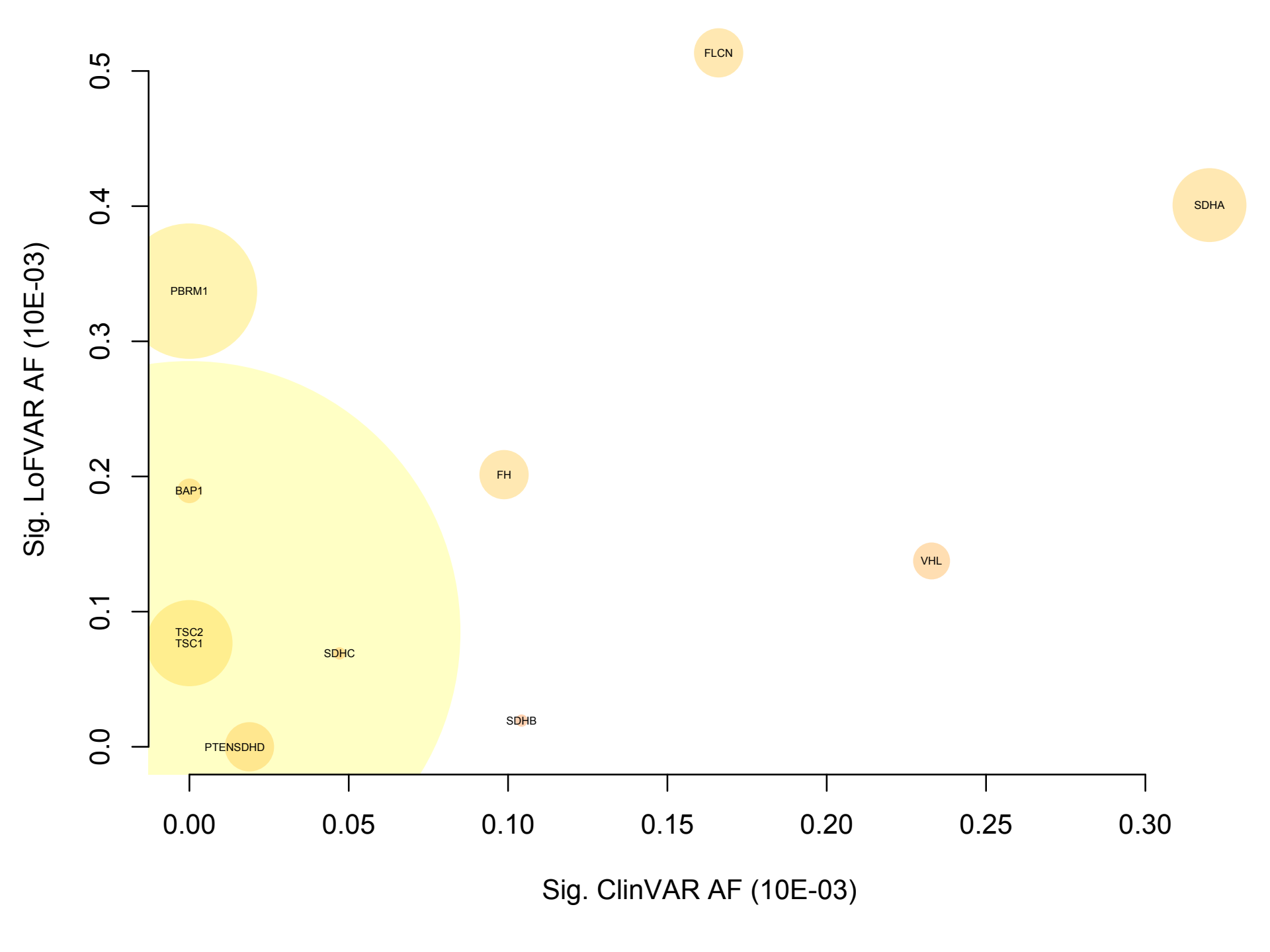
Scenario II
AND
High-impact missense:
- **Polyphen score > 0.9**
- **TSL 1, 2 & 3**

ExAC	0.7%	1.2%	4.4%
1000 Genomes	0.34%	0.42%	4.05%

Filter using 1KG

- .5% AF cutoff cross-applied to both ExAC and 1KG
  - .5% AF too restrict in sub-pop? (~1000 alleles)
  - Three SNPs has low MAFs in ExAC

	EAS	AMR	AFR	EUR	SAS		ExAC
rs554829380	0.0446	0.0375	0.0129	0.0477		0	9.06798E-05
rs45466399	0	0	0.0083	0		0	0.000408854
rs569318927	0.006	0.0058	0.0008	0.002		0	0.002291319
rs142934950	0	0.0058	0	0		0	0.000424673

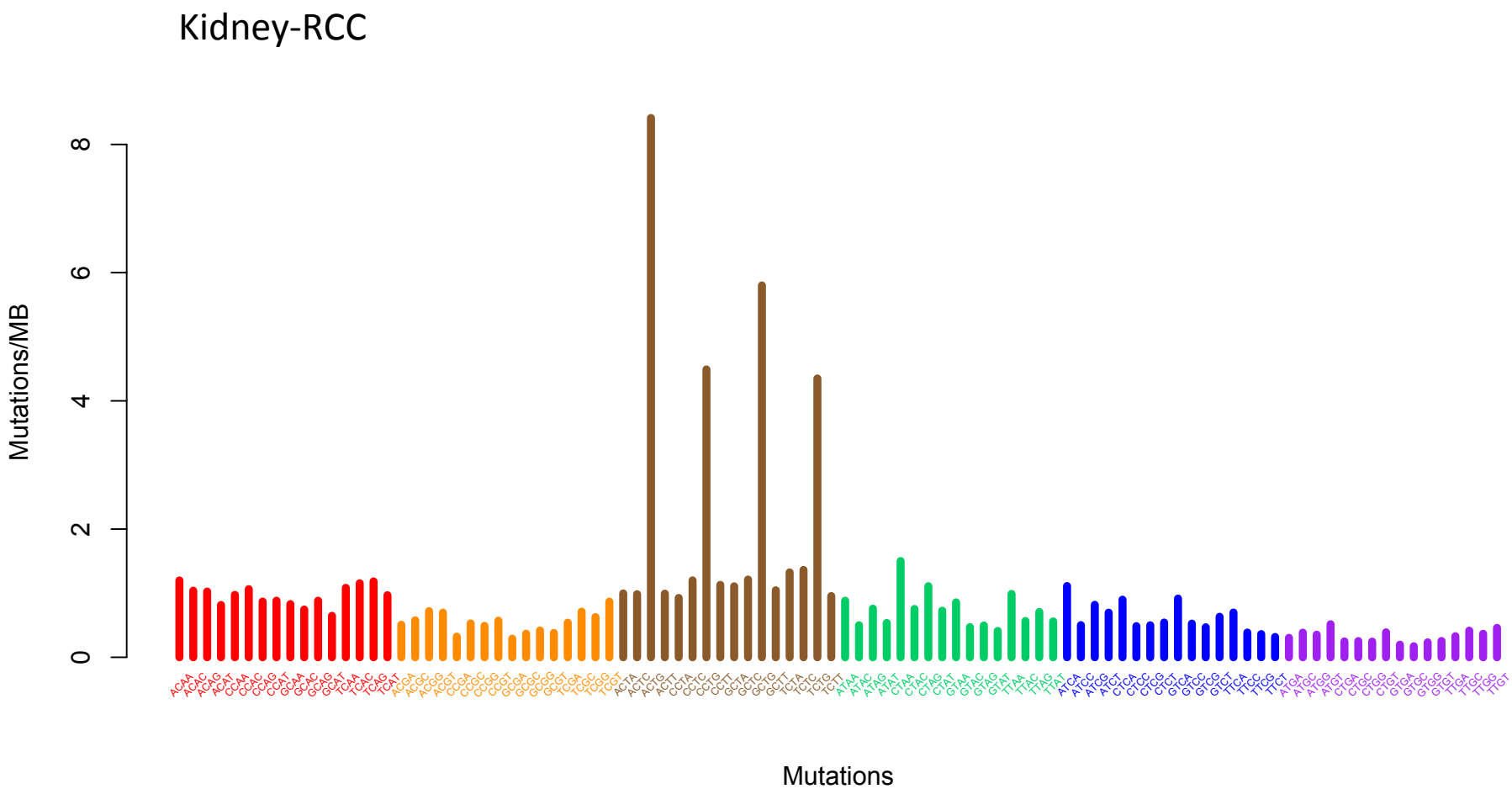

FLCN
SDHA
PBRM1
FH
BAP1
VHL
TSC2
TSC1
SDHC
SDHB
PTENSDHD
0.0
0.1
0.2
0.3
0.4
0.5
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Sig. LoFVAR AF (10E-03)
Sig. ClinVAR AF (10E-03)

Not Enriched in ExAC-TCGA

- About 12% ExAC comes from TCGA
- Need to look at RCC cohorts

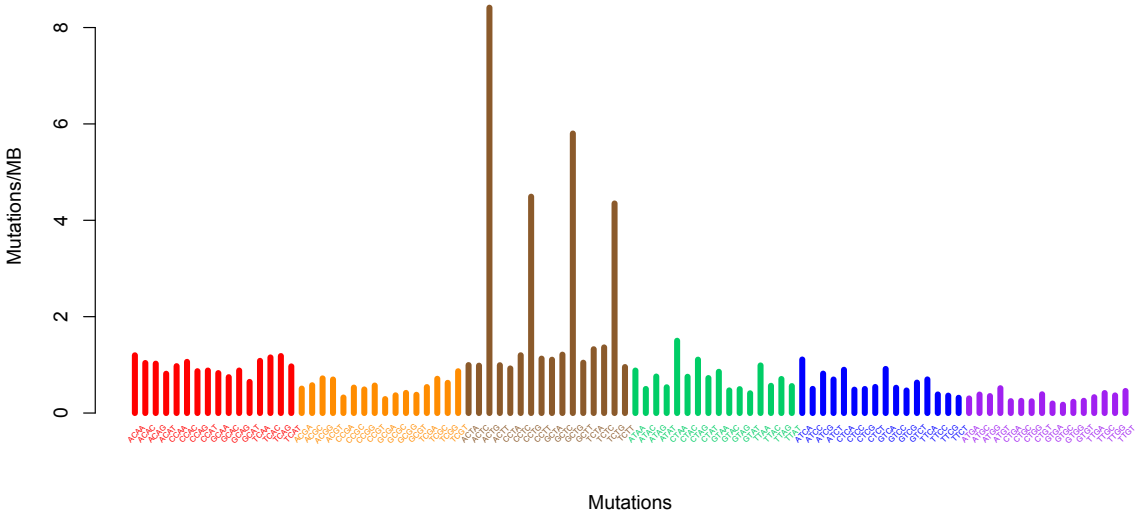
	nonTCGA	TCGA
ClinVAR	0.10%	0.07%
LoF	0.20%	0.11%
ALL	4.40%	3.85%

Signature!

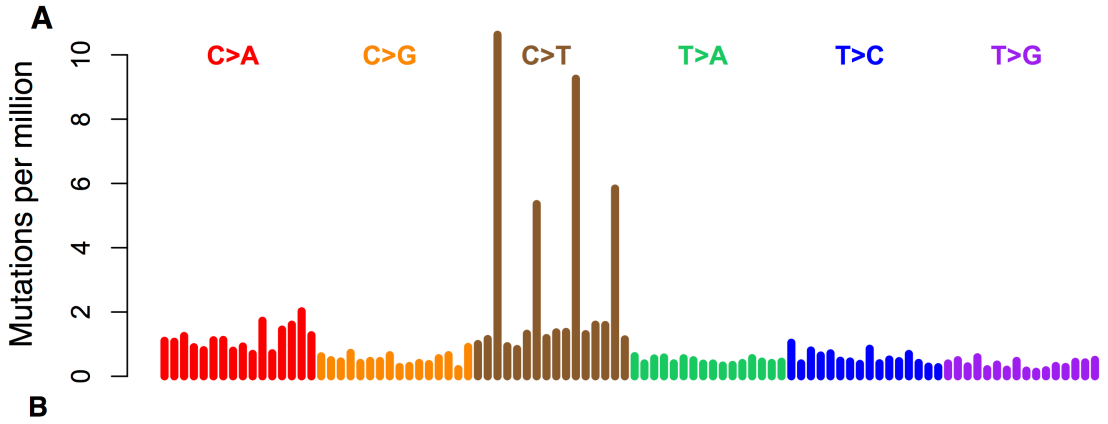


Signature!

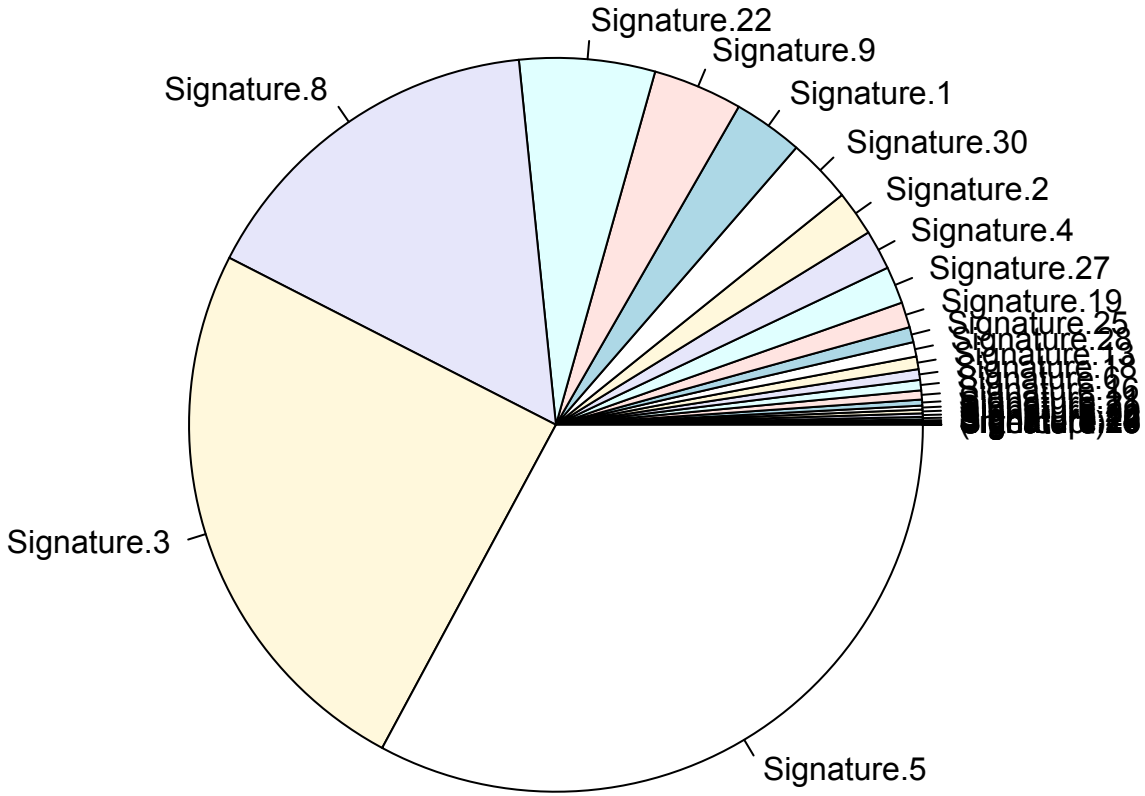
Kidney-RCC



pRCC



1,5,6,27?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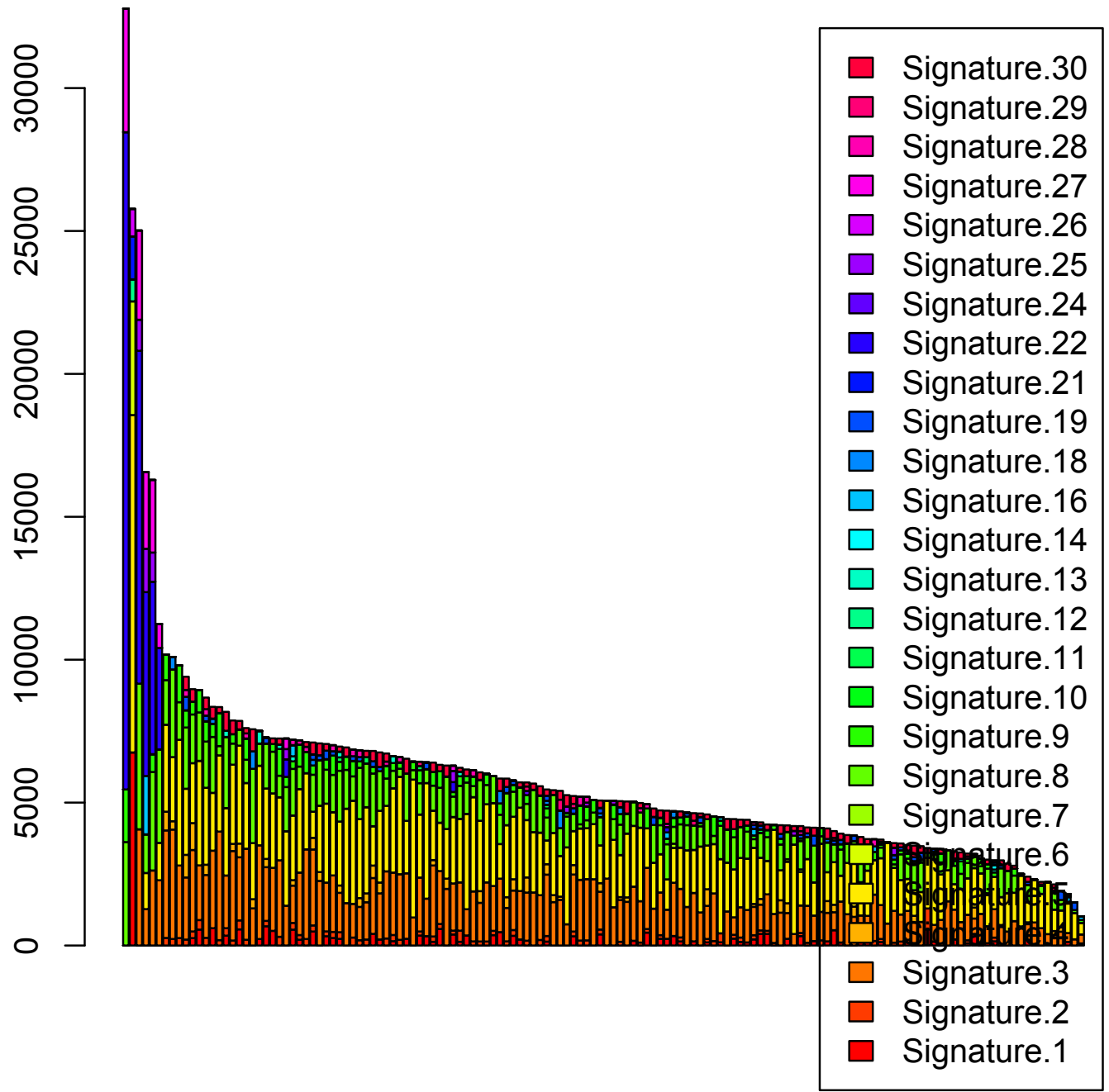
Signature.9
Signature.1
Signature.30
Signature.2
Signature.4
Signature.27
Signature.19
Signature.25
Signature.8
Signature.3
Signature.5


0
5000
10000
15000
20000
25000
30000
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Signature.28
Signature.27
Signature.26
Signature.25
Signature.24
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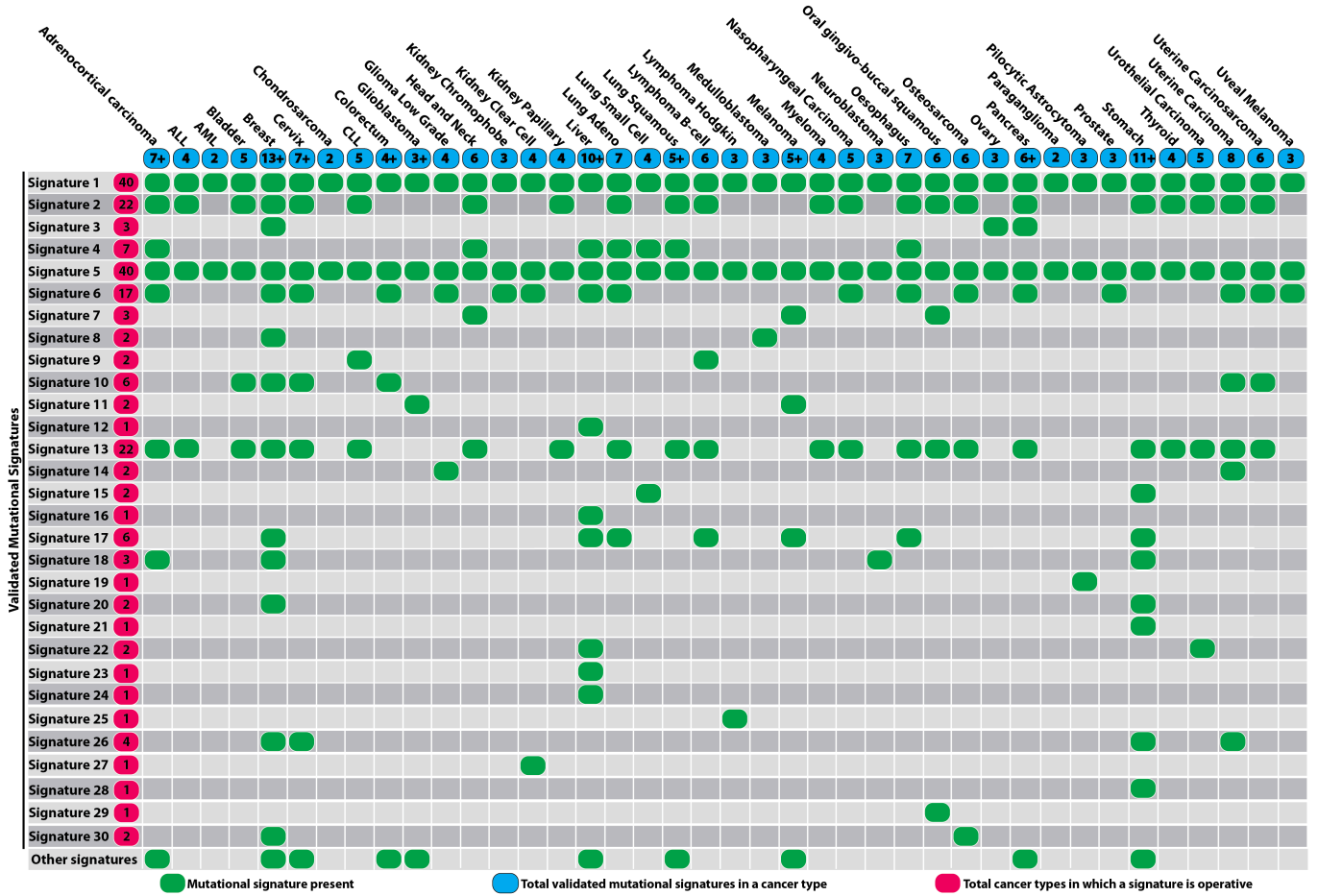
Signature.21
Signature.19
Signature.18
Signature.16
Signature.14
Signature.13
Signature.12
Signature.11
Signature.10
Signature.9
Signature.8
Signature.7
Signature.3
Signature.2
Signature.1

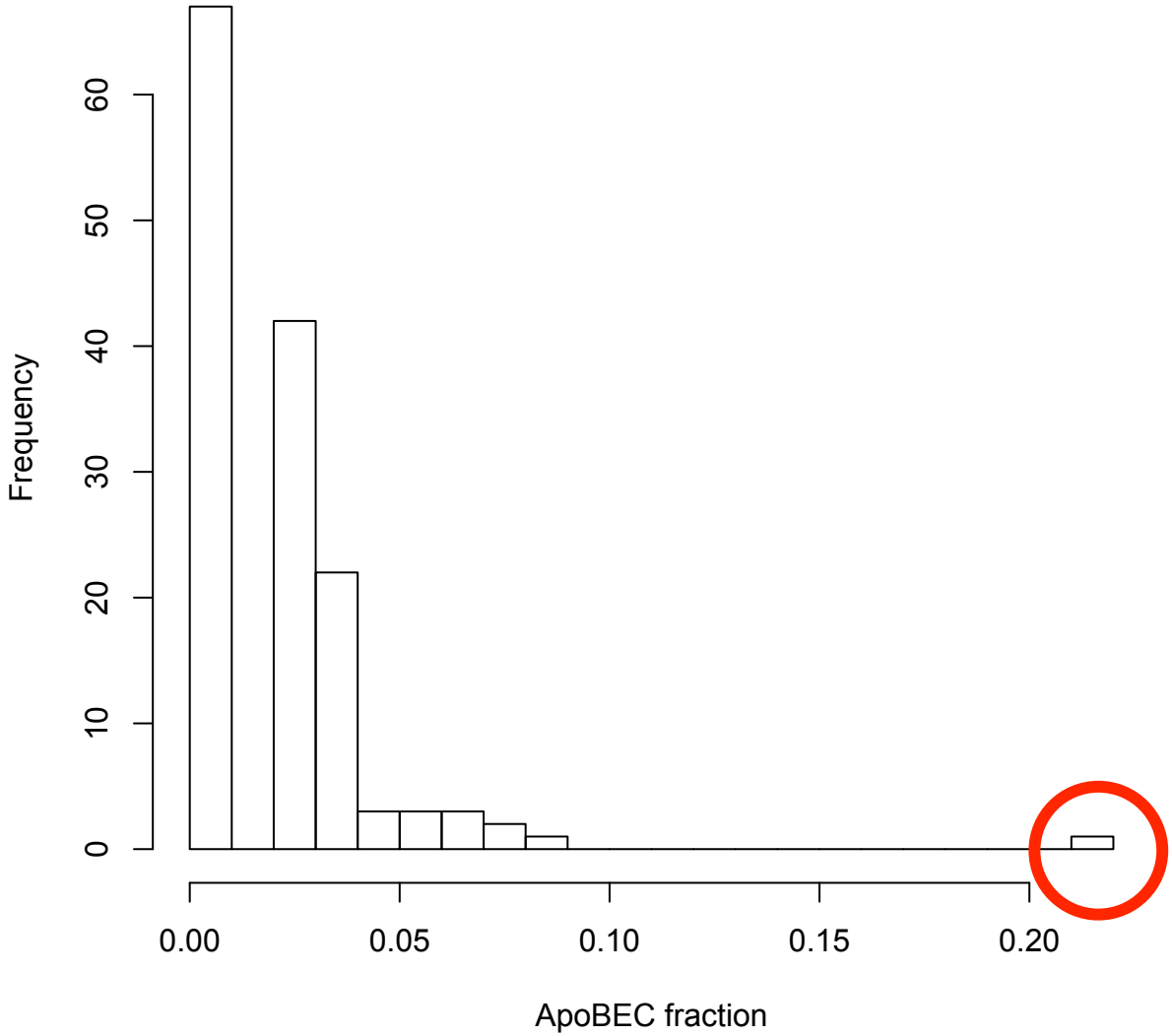
Let's Have a Pit Party

"If a blind man leads a man, both will fall into a pit"

Matthew 15:14



ApoBEC


Frequency
0
10
20
30
40
50
60
0.00
0.05
0.10
0.15
0.20
ApoBEC fraction