

Cryptic Promoter Usage in MET

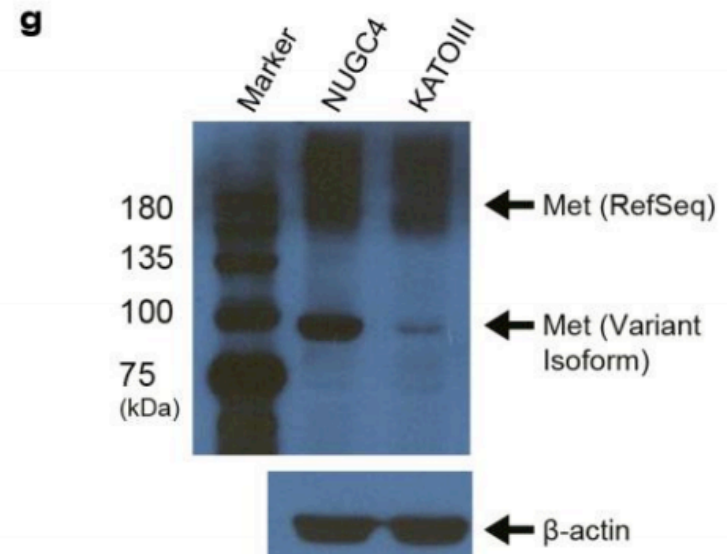
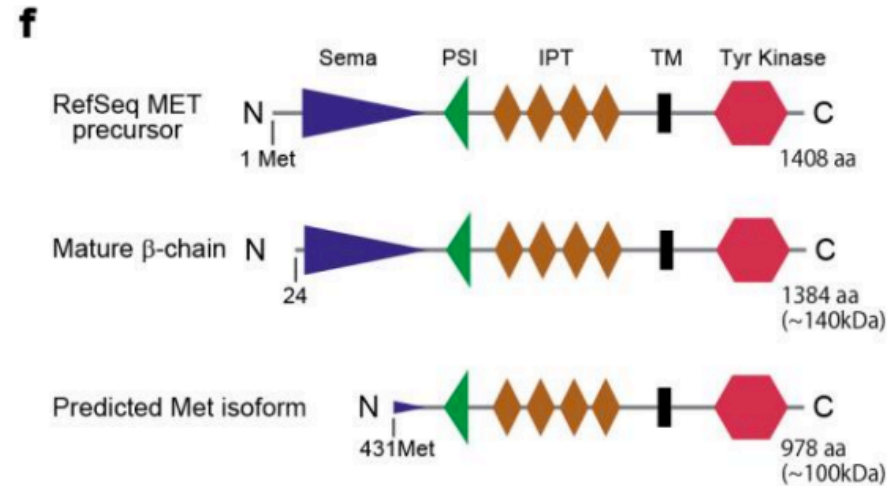
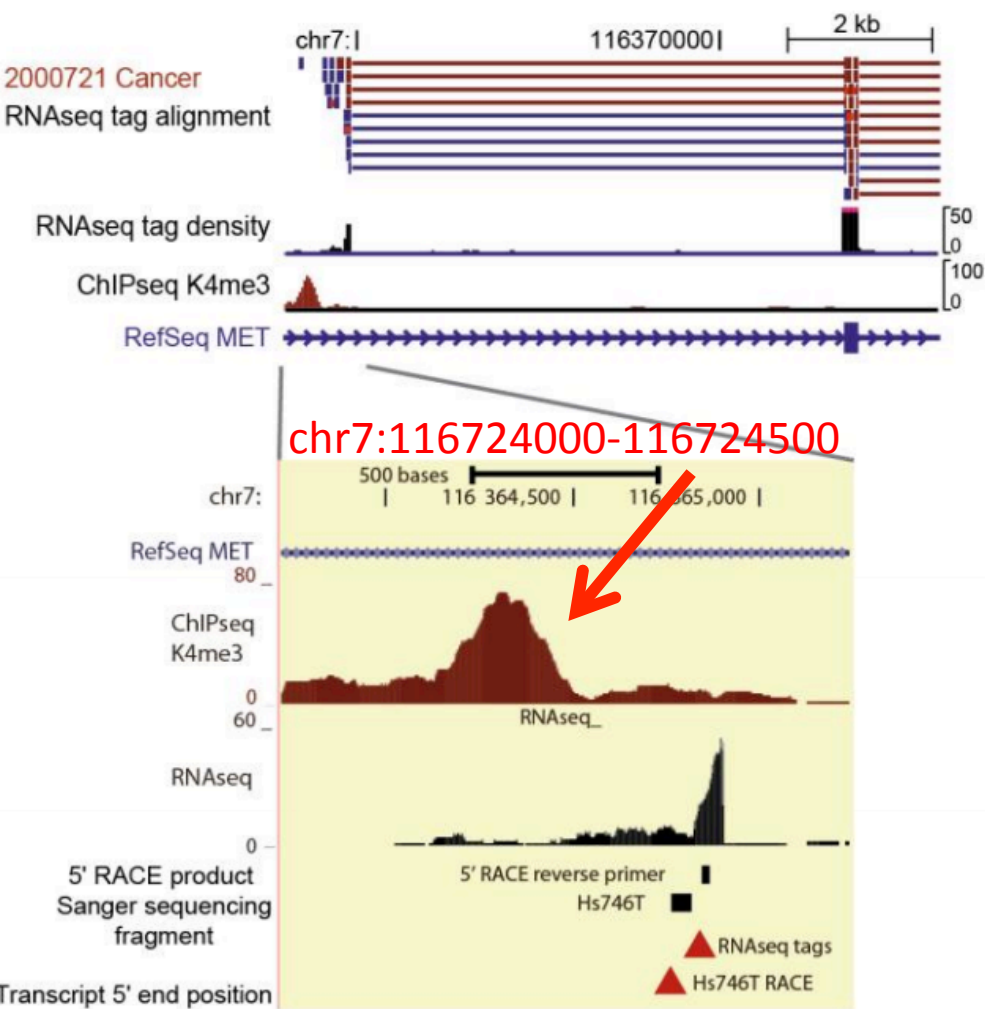
- Observed in multiple cancers for a decade
 - CML, colon, liver, bladder...

C) L1 - MET



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

Translation in Gastric CA



26 kb

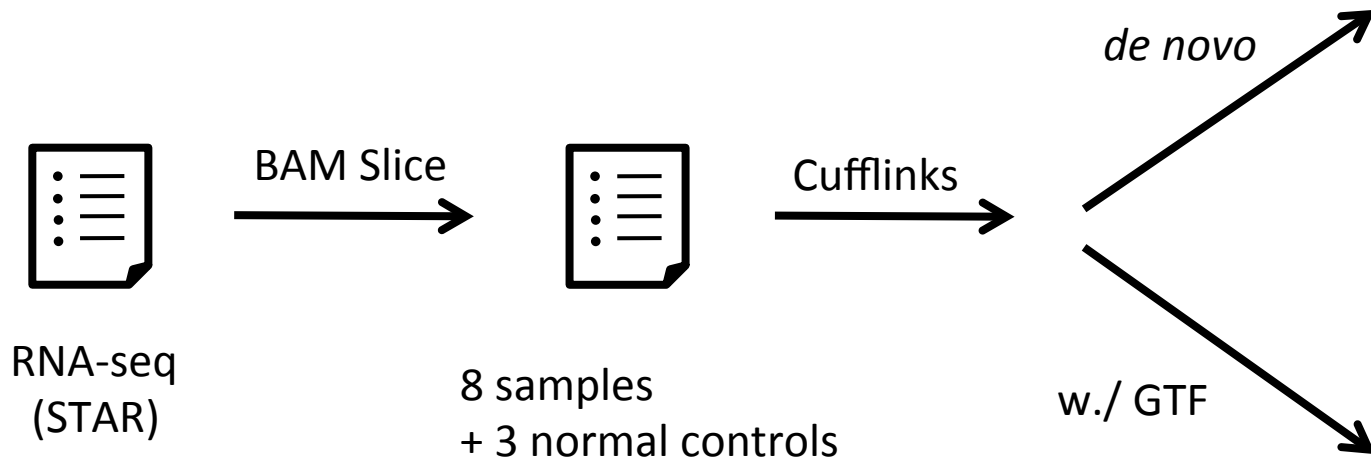
116,720 kb

116,730 kb



MET

Workflow

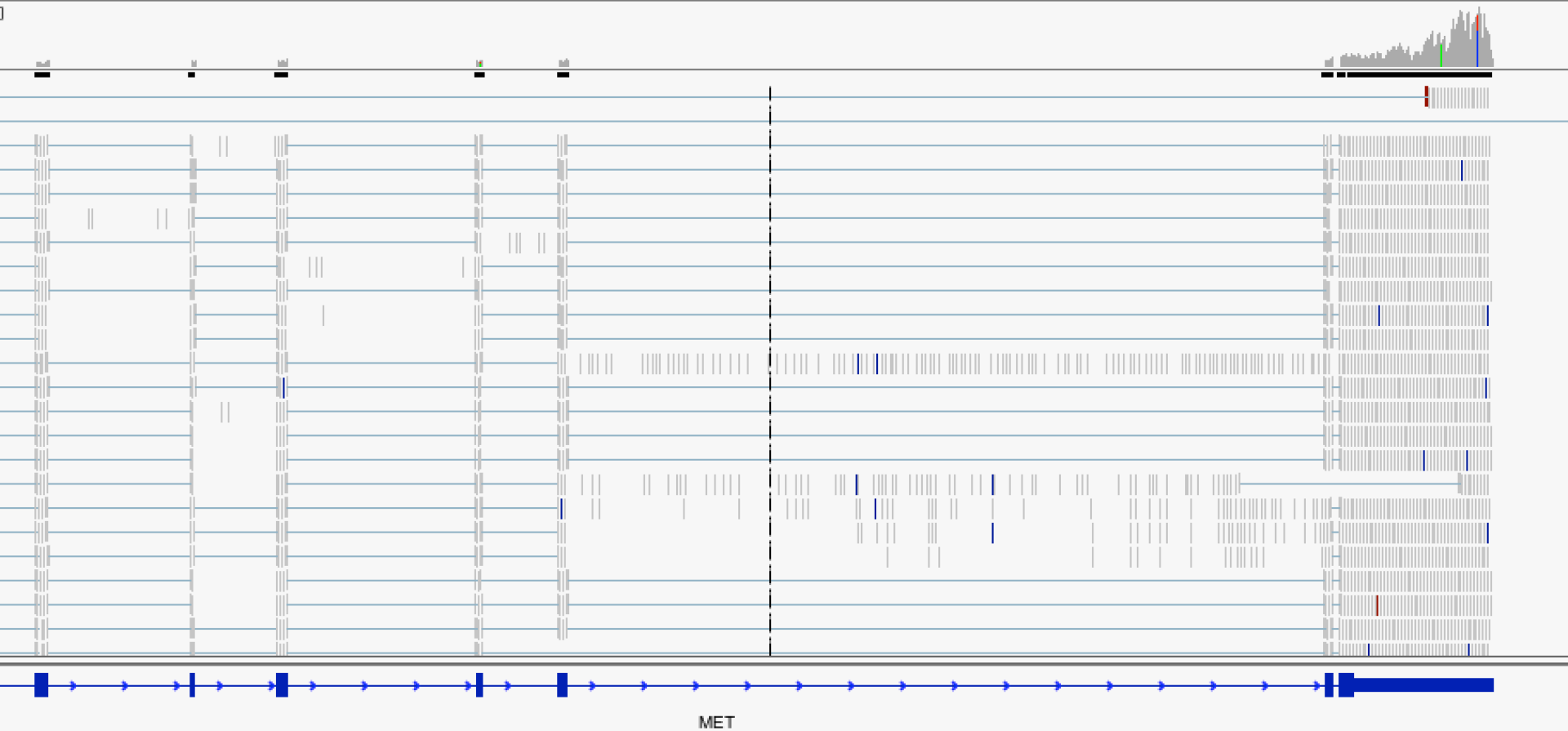


2.1 p21.2 p15.3 p14.3 p14.1 p12.3 p11.2 q11.21 q11.23 q21.12 q21.3 q22.2 q31.1 q31.31 q32.1 q33 q34 q36.1 q

26 kb

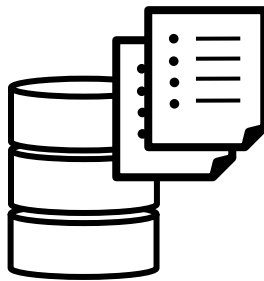
116,780 kb

116,790 kb

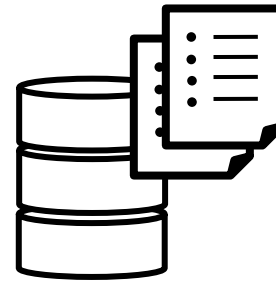


Methylation

- 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 (**hypermeth**), $p=0.05$
 - 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

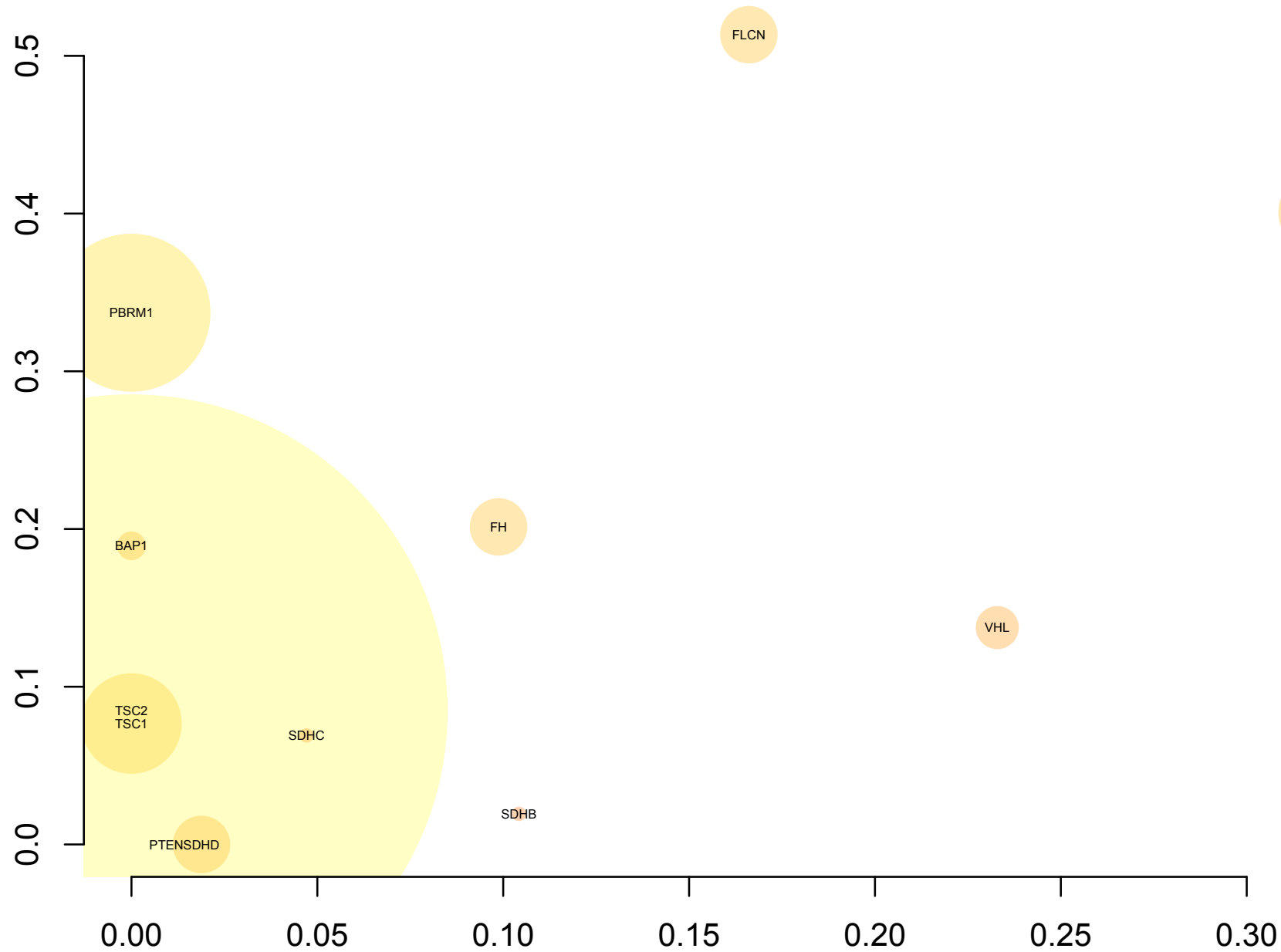
ExAC	0.7%	1.2%	4.4%
1000 Genomes	0.34%	0.42%	4.05%

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

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%