Memorial Sloan Kettering
Cancer Center

Small cell carcinoma genomics

A convergent but distinct pathogenesis

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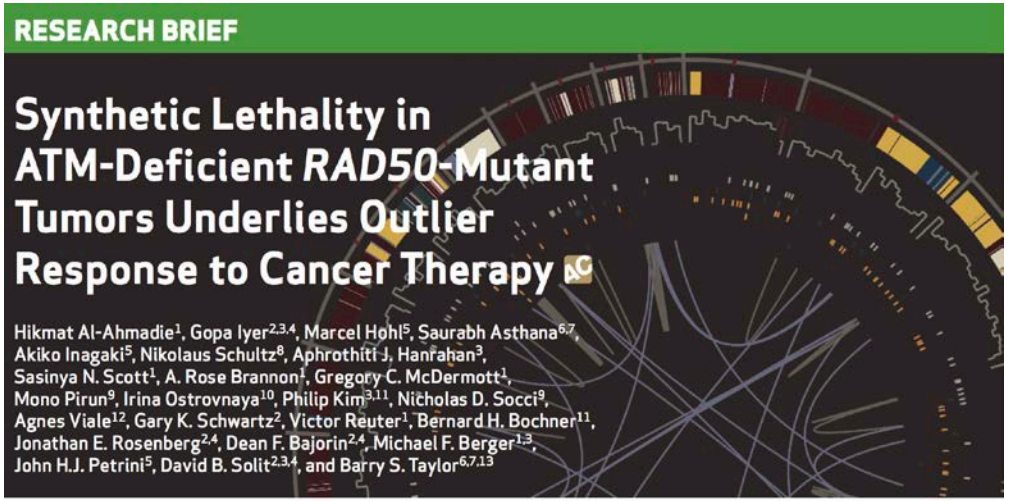
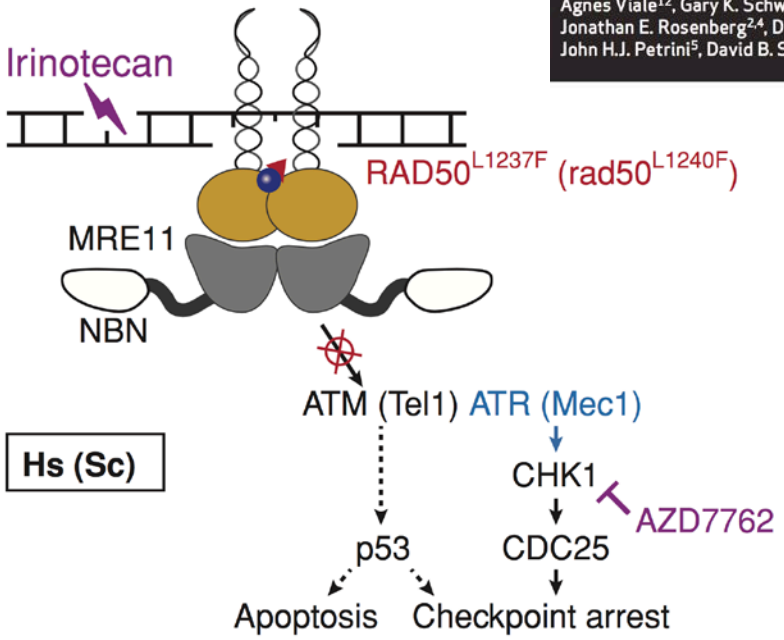
Small cell genomics by way of exceptional responders

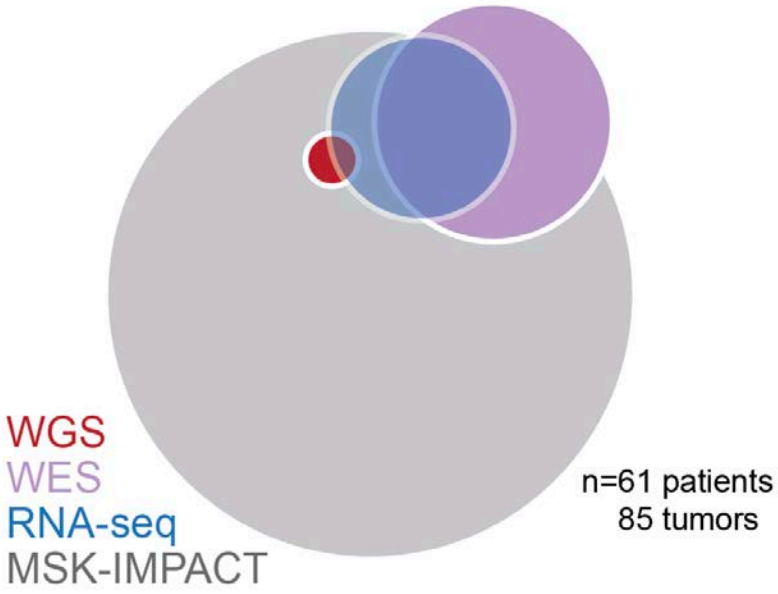




Iyer G, et al. *Science* (2012)
Al-Ahmadie H, et al. *Cancer Discov* (2014)

Bladder, cell lineage, or organ-specific differences?

Multi-modality sequencing of a rare histology



Mix of frozen and FFPE, primary untreated and post-treatment disease, patients with multi-histology disease or matched primary and metastatic specimen pairs

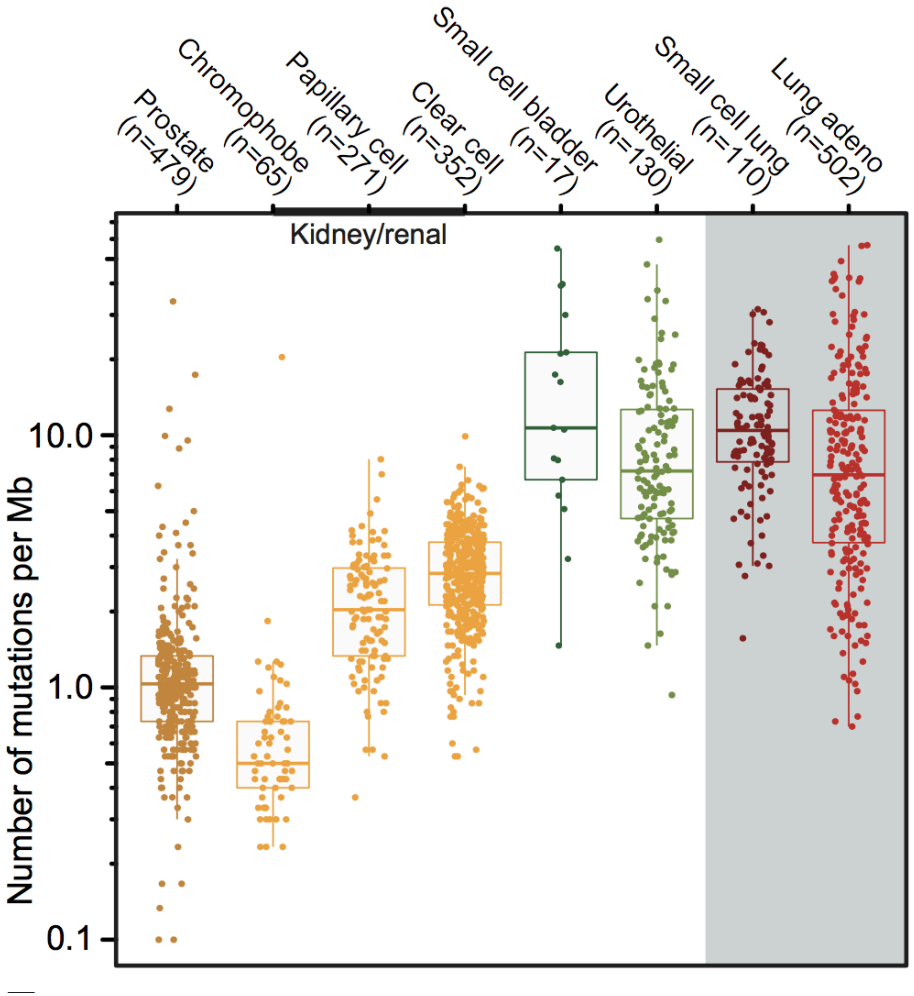
+

500 retrospectively sequenced bladder and SCLC tumors for comparative analysis

Iyer G, et al. *J Clin Oncol* (2013)
Cancer Genome Atlas Research Network, *Nature* (2014)
Al-Ahmadie H, et al. *Nat Genet* (2016)
Donahue TF, et al. *JCO Precis Oncol, in press*
Lee SH, et al. *Cell, in press*

High somatic mutational burden

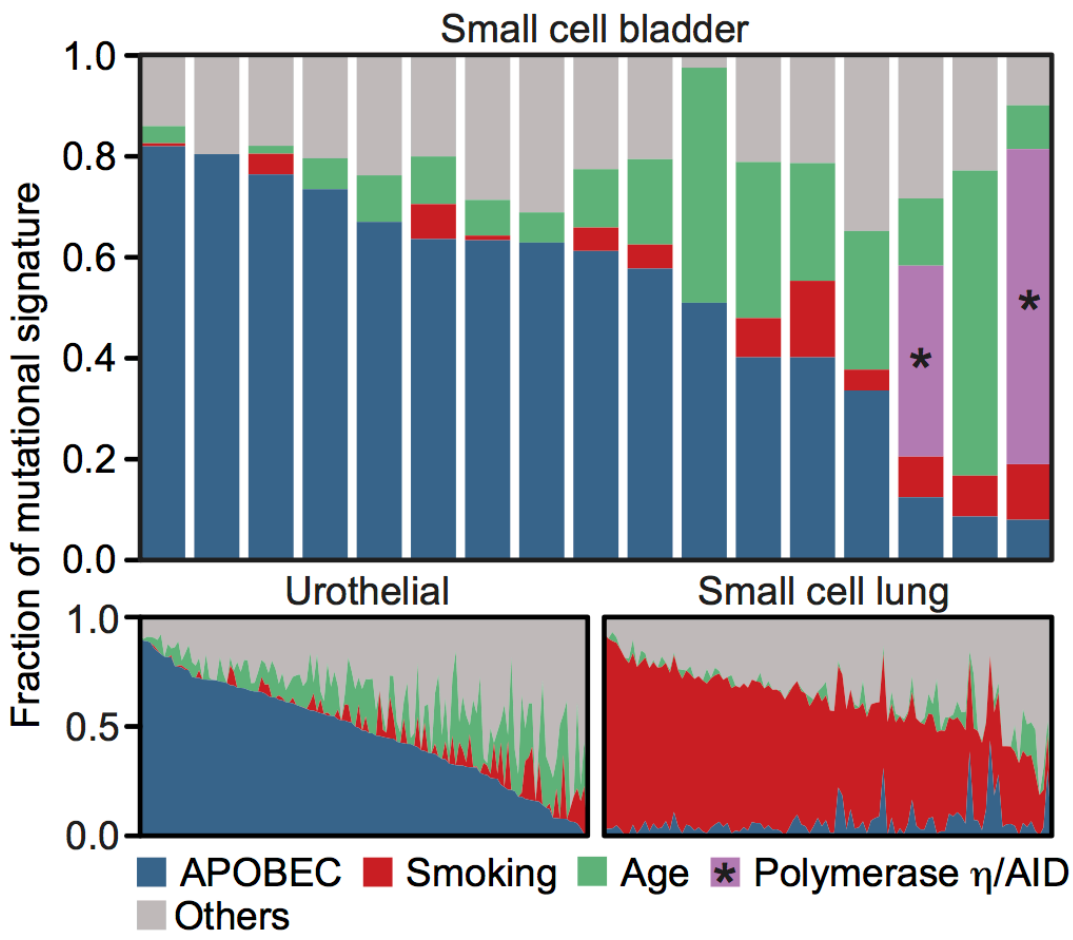
A consistent story emerging...



Chang MT, et al. *Clin Cancer Res* (2018)

APOBEC-driven

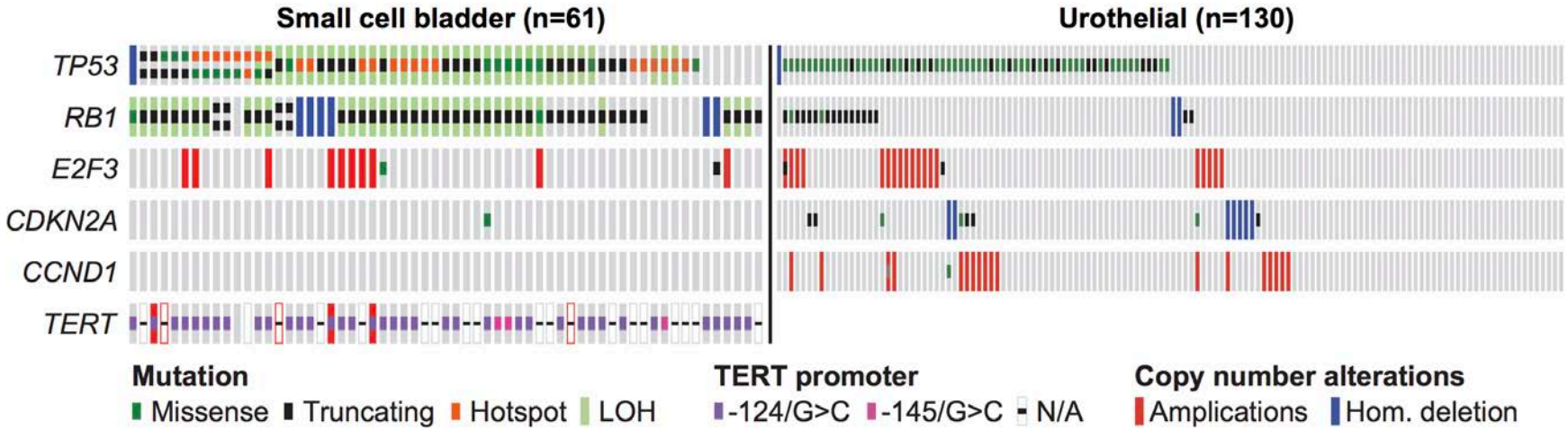
And not tobacco-associated mutagenesis



Chang MT, et al. *Clin Cancer Res* (2018)

Pattern and frequency of key lesions

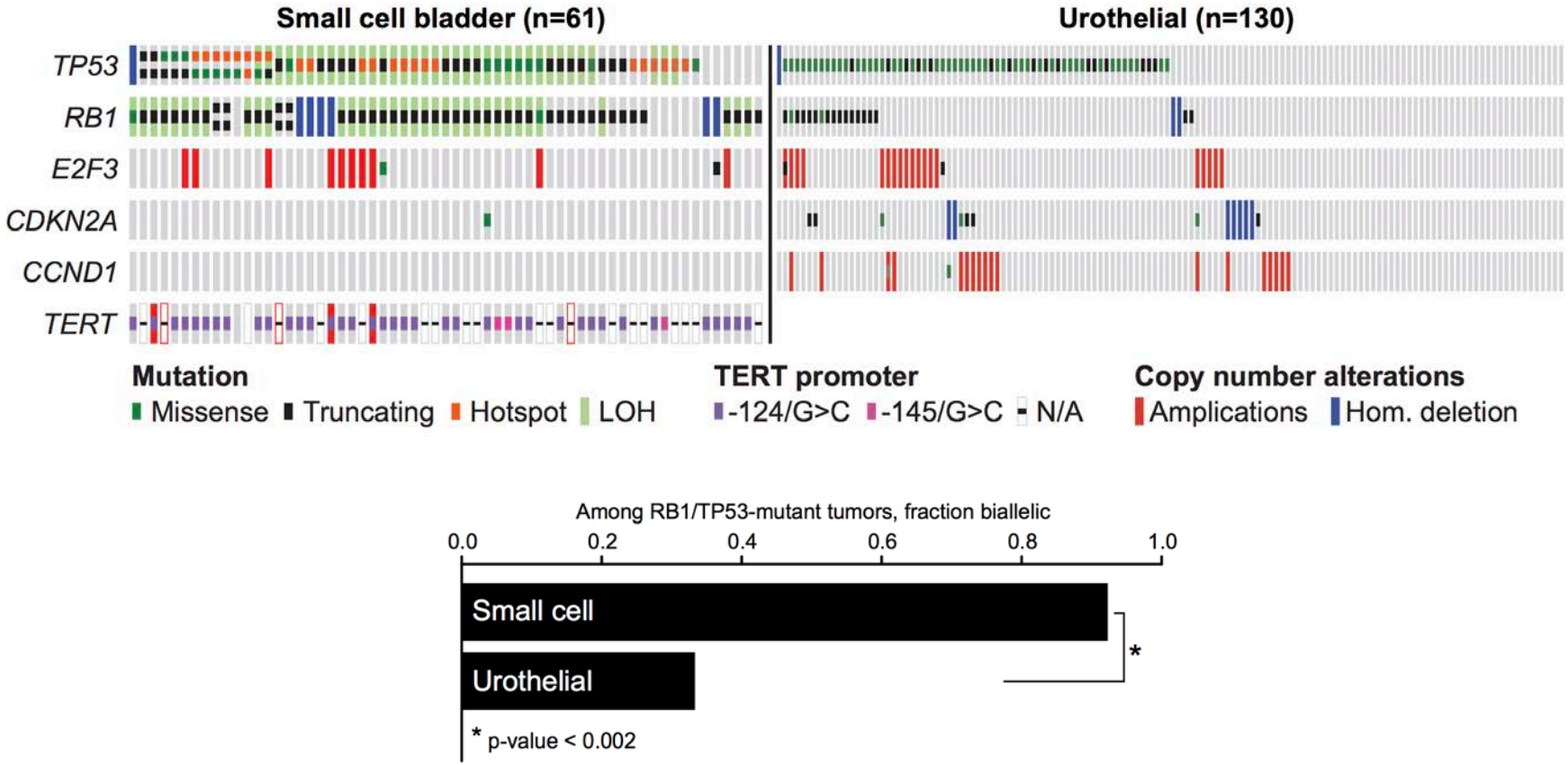
Obligate *TP53*, *RB1*, *TERT*



Chang MT, et al. *Clin Cancer Res* (2018)

Not absent but rare in urothelial

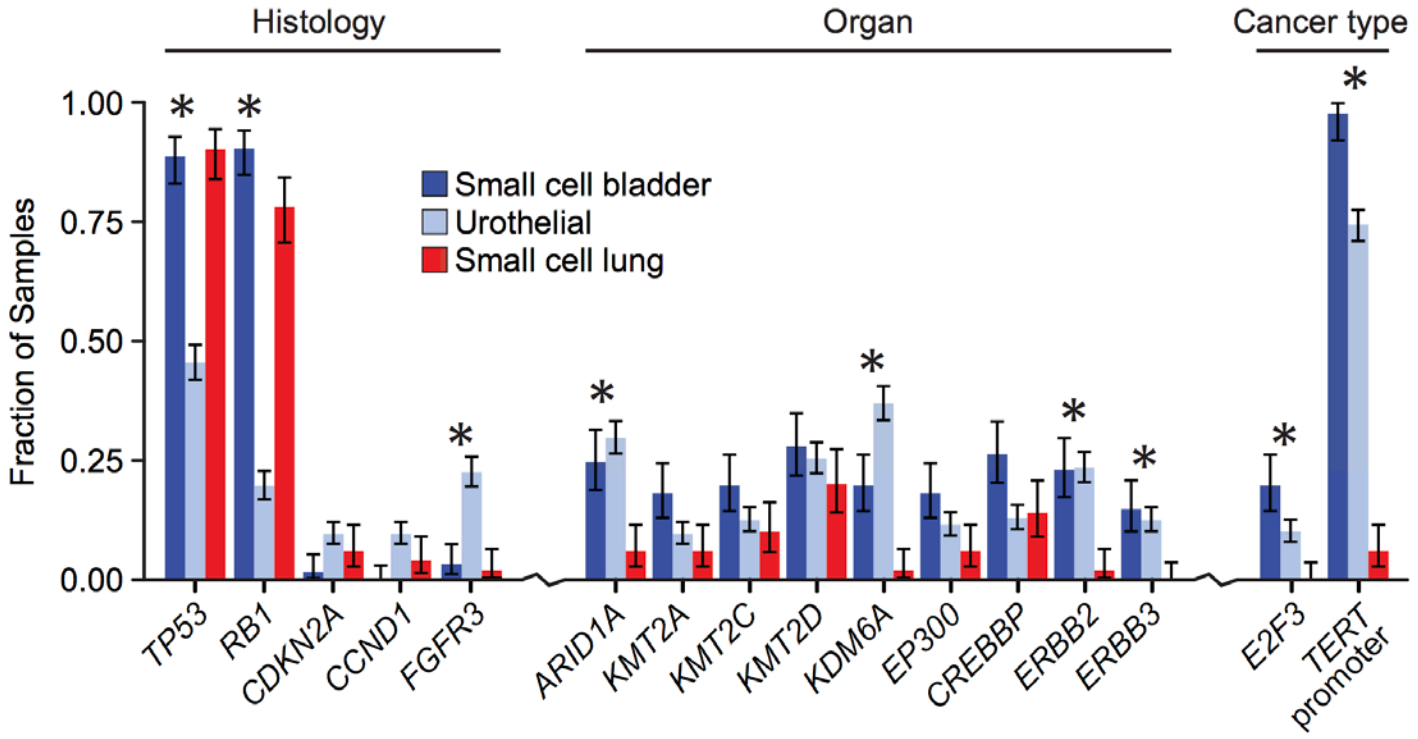
TP53+RB1



Chang MT, et al. *Clin Cancer Res* (2018)

Different differences

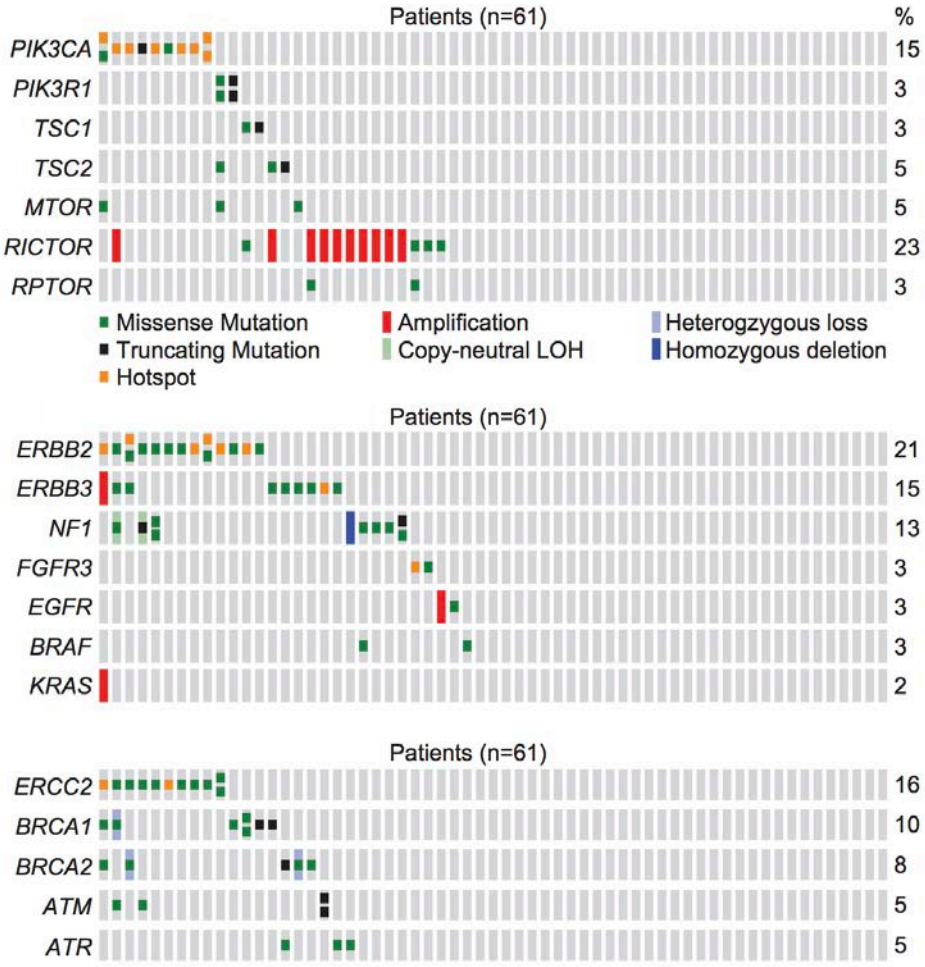
Histology, organ, and cancer type



Chang MT, et al. *Clin Cancer Res* (2018)

Potential therapeutic significance

46% of patients

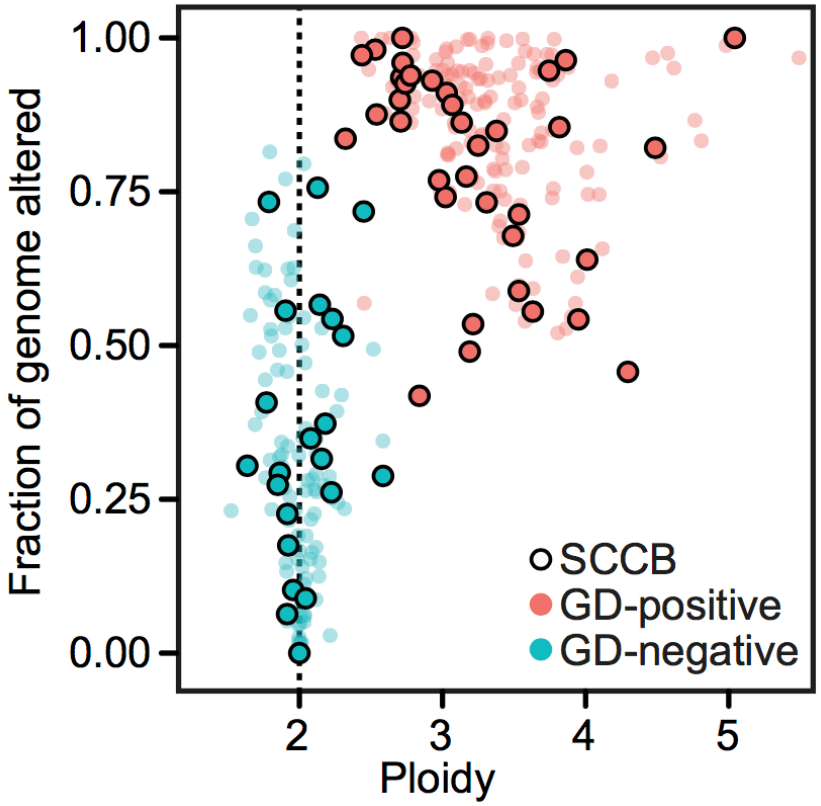


http://oncokb.org/

Chang MT, et al. *Clin Cancer Res* (2018)
Hyman DM, et al. *Nature* (2018)

High CNA burden was common

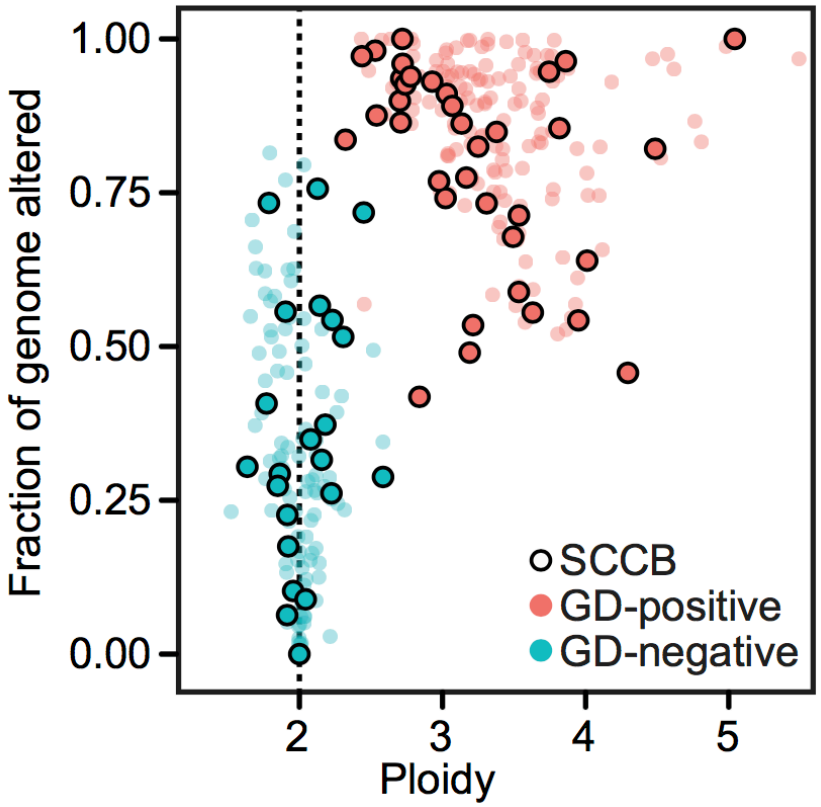
Driven by whole-genome doubling

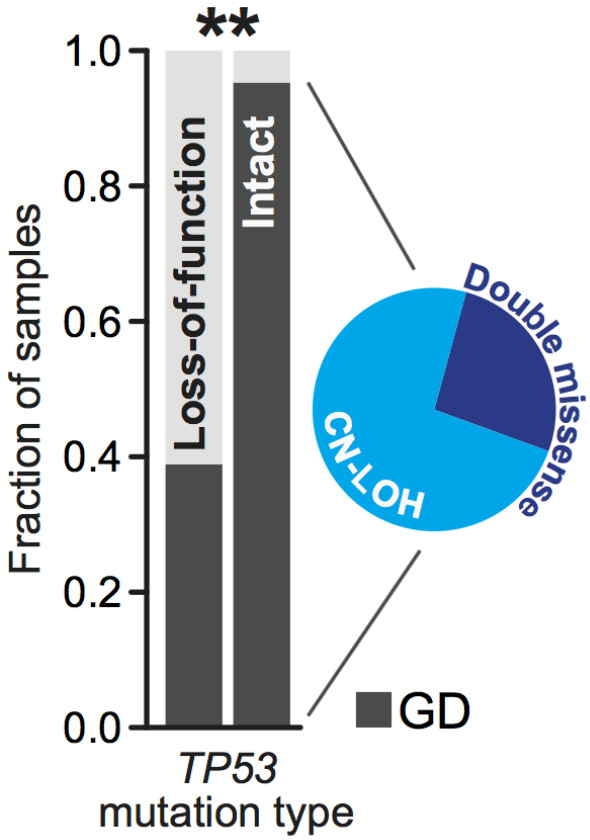


Chang MT, et al. *Clin Cancer Res* (2018)

WGD+ and biallelic missense TP53

Here, but not pan-cancer...

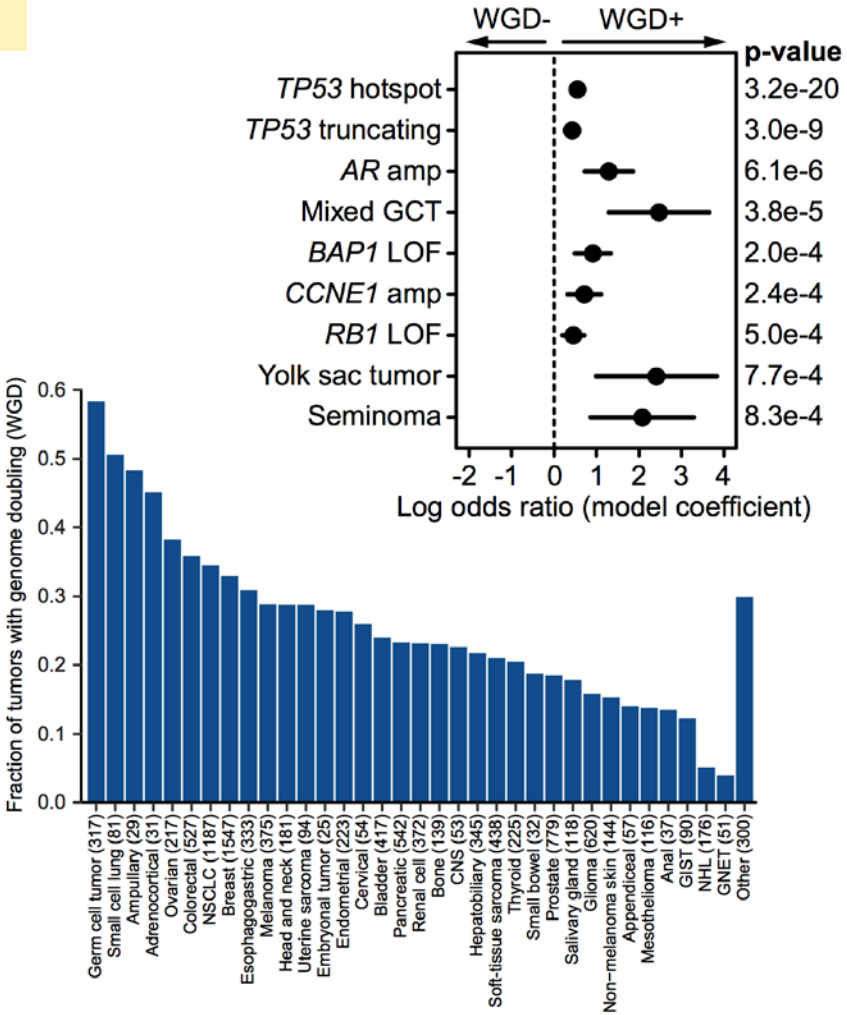


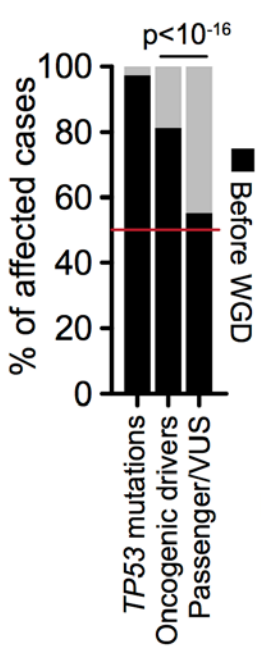


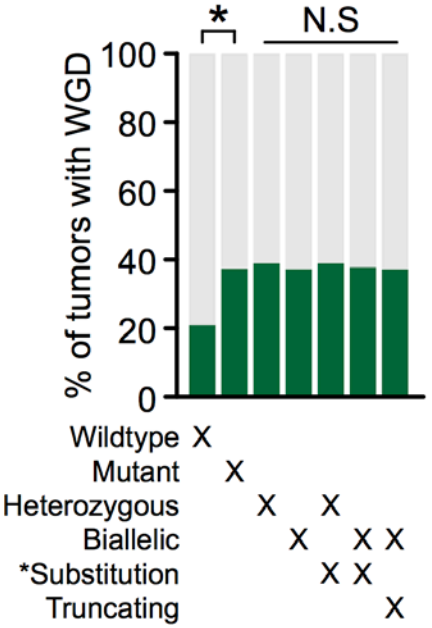
Chang MT, et al. *Clin Cancer Res* (2018)

WGD pan-cancer, a digression

Common, but 46% of WGD in cancer arise in TP53-wildtype tumors



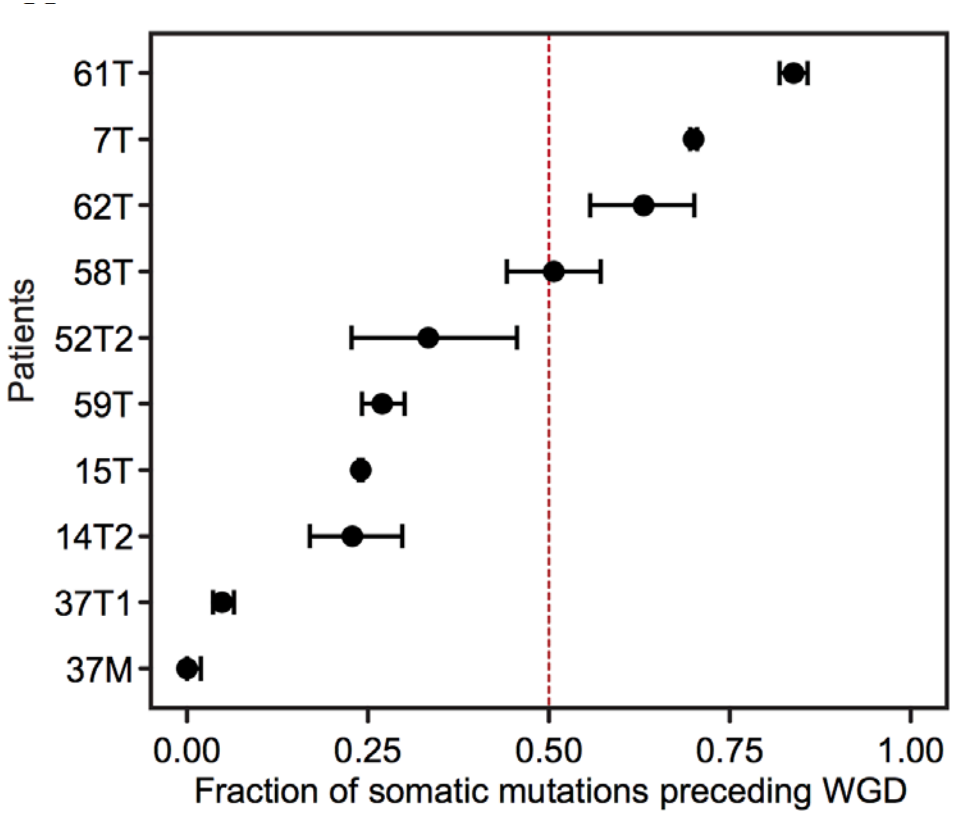




Bielski C, et al. *In revision*

Timing of WGD can vary

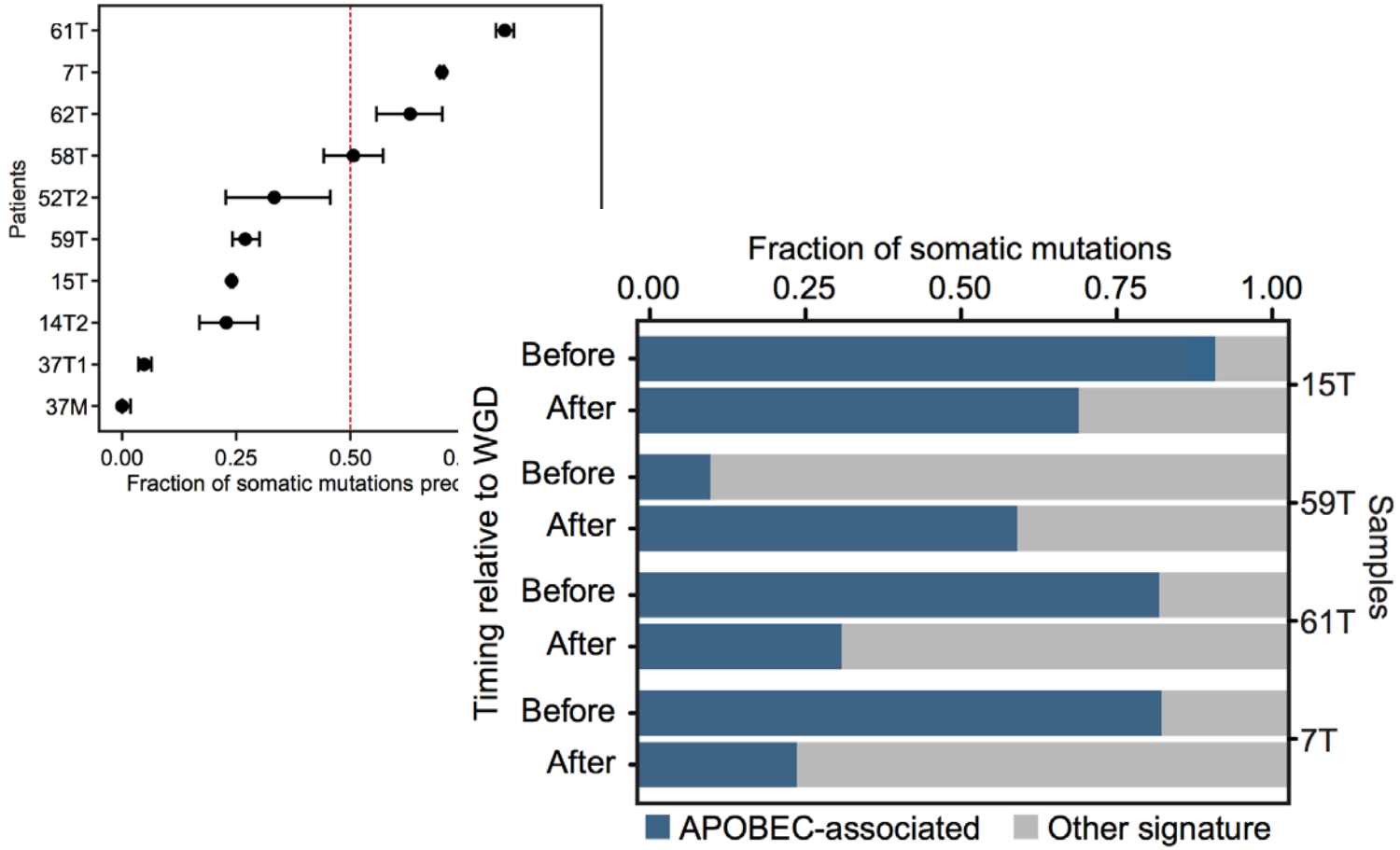
Rather than absolute timing, relative to somatic mutations...



Chang MT, et al. *Clin Cancer Res* (2018)

Waxing and waning APOBEC

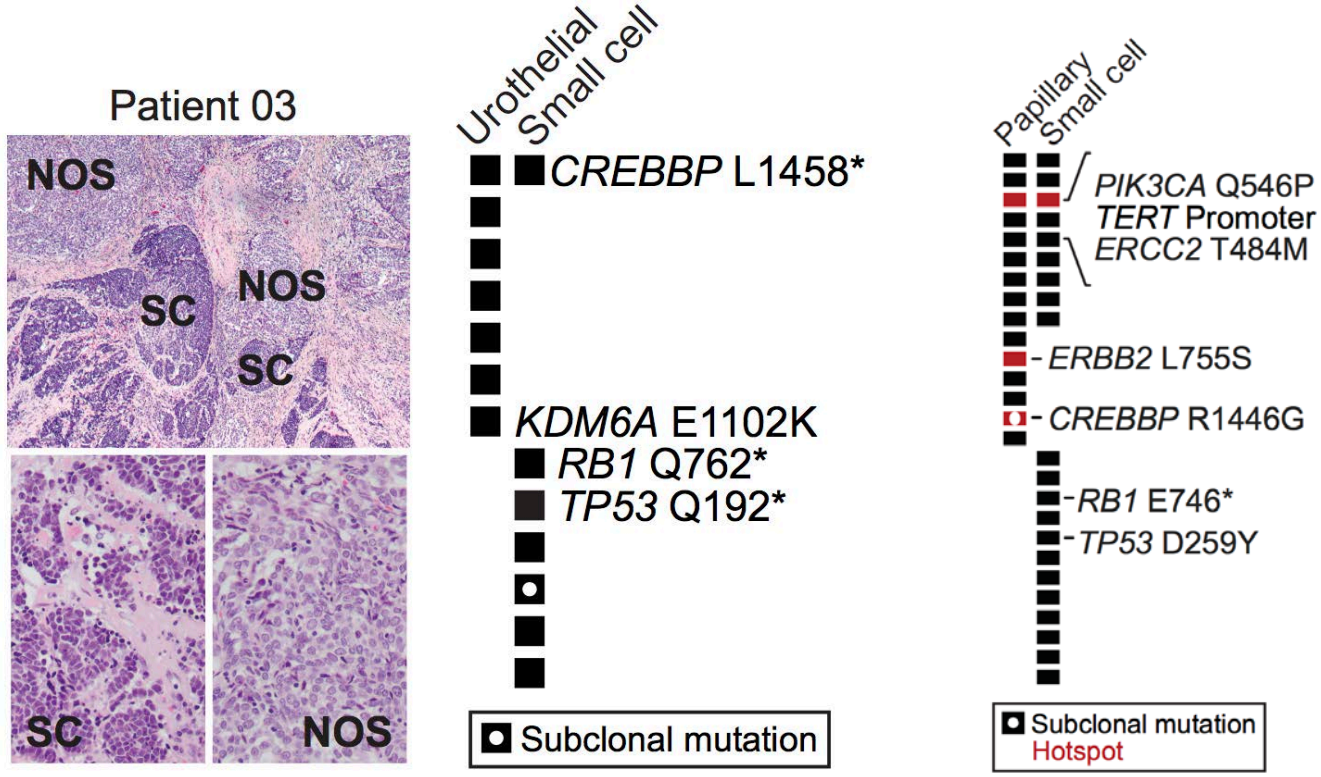
Before or after WGD



Chang MT, et al. *Clin Cancer Res* (2018)

Mixed histology tumors

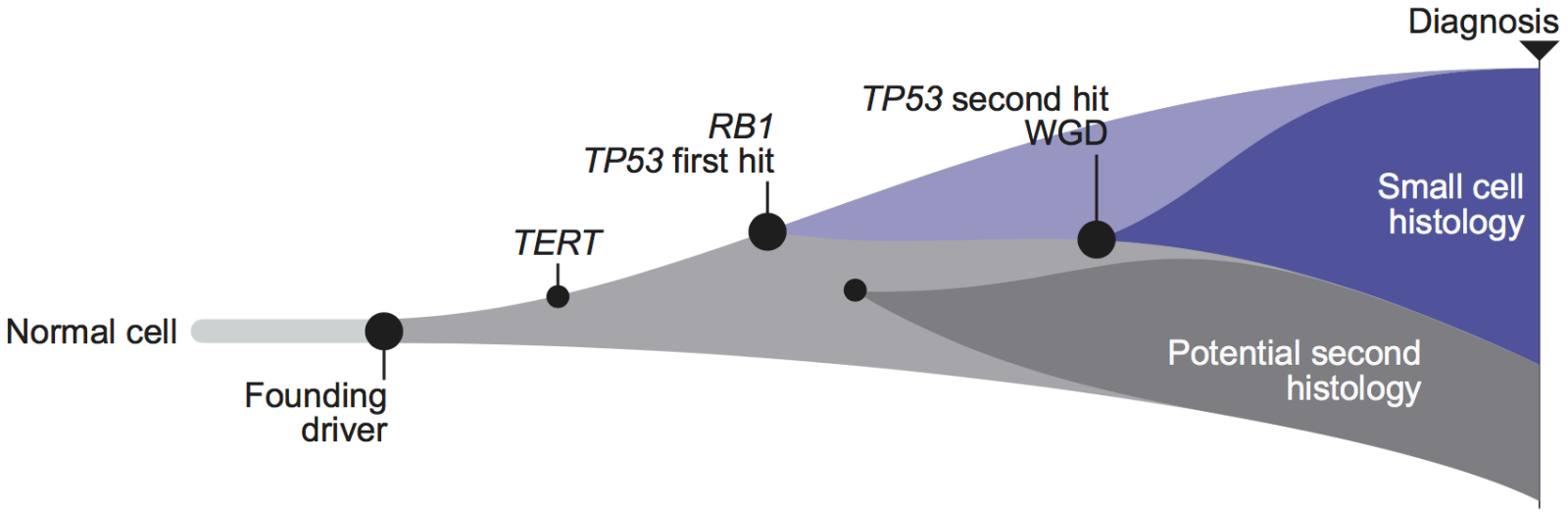
Branching evolution, RB1 and TP53 are histology-specific and come after a founding driver



Chang MT, et al. *Clin Cancer Res* (2018)

Obligate, but not the founder?

Something else initially transforms and leads to clonal outgrowth?



Chang MT, et al. *Clin Cancer Res* (2018)

Conclusions

- Small cell carcinomas of the bladder and lung have a convergent but distinct pathogenesis.

- Obligate likely early-arising lesions in *RB1* and *TP53*
  - Necessary but alone insufficient to drive small cell differentiation

- A founding driver along with other truncal driver mutations can precede histology-specific lesions in *RB1* and *TP53*.
  - Small cell and urothelial bladder cancers have a shared cellular origin where the former represents de-differentiation from UC

- Overall, aside from *RB1* and *TP53* alterations, genomic alterations present in SCCB more closely resemble UC than small cell lung cancers, indicating that most alterations contribute to oncogenesis in an organ-specific manner rather than cell type-specific manner.

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