

Metabolism, methylation and malignancy of the prostate: leveraging large scale data sets to provide insights into disease processes

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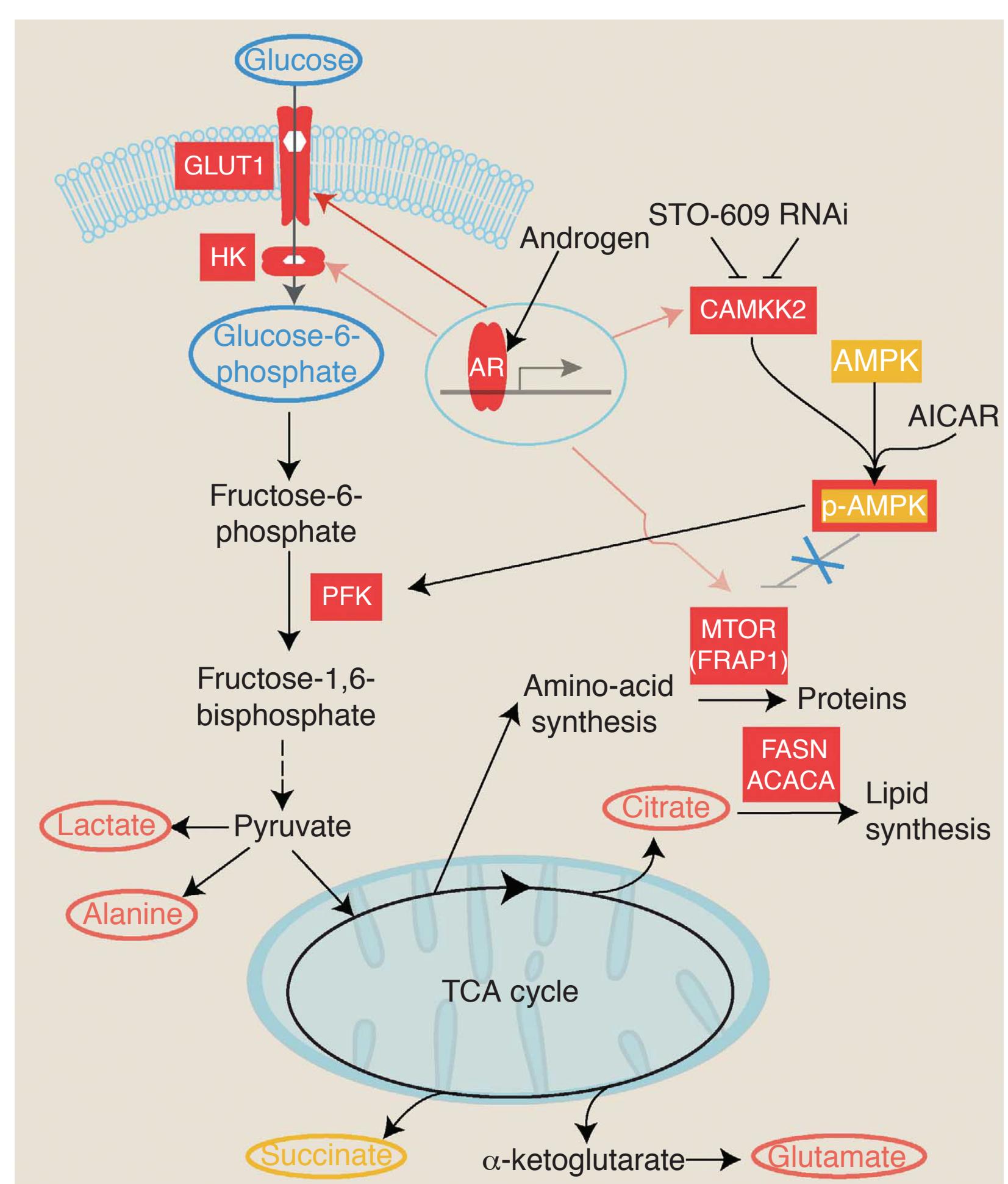
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Introduction

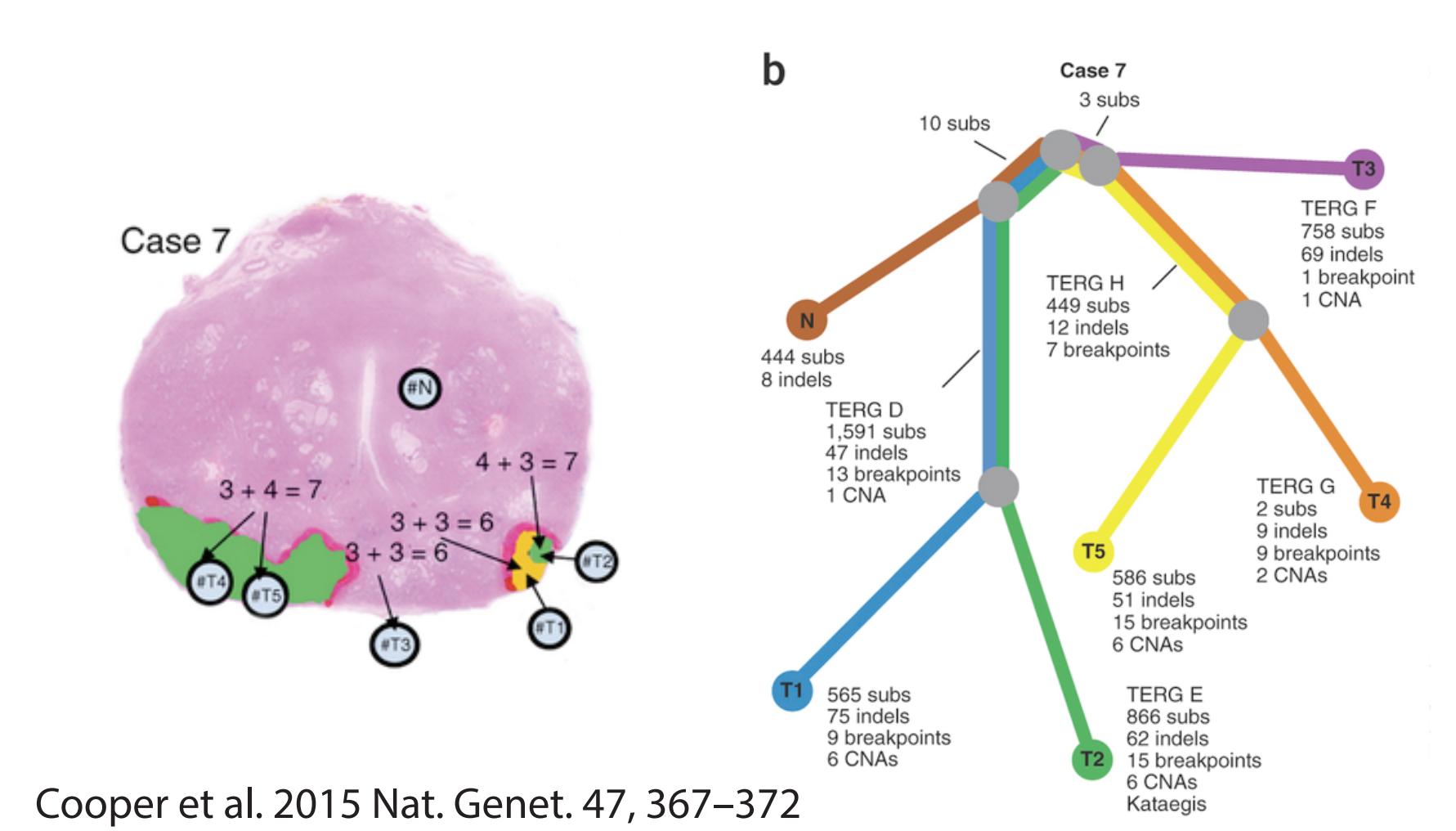
- There exist a wealth of large-scale datasets from ICGC, TCGA and other studies
- We can combine these data to obtain deeper insights into disease processes
- As an example we explore the established link between metabolic regulators and primary prostate cancer [refs. 1-3]
- Using a combination of functional genomics, gene-fusion status, epigenome and transcriptome profiling we uncover multiple convergent events regulating NPY in prostate cancer, identifying unique molecular subgroups

Mapping androgen receptor targets: AR regulation of metabolic pathways



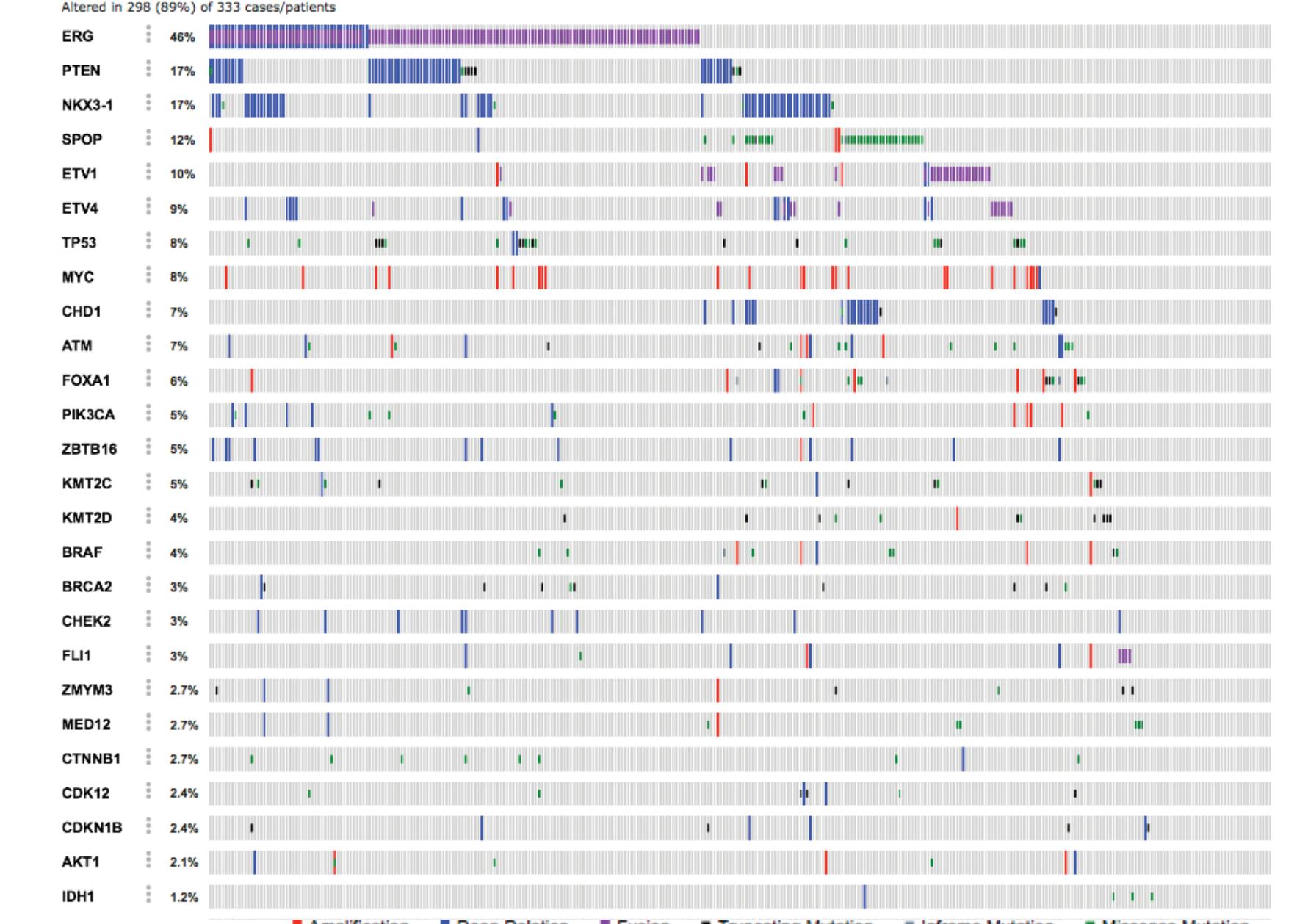
Massie et al. 2011 EMBO J. 30(13): 2719–2733

Multi-region whole genome sequencing reveals intra-tumour heterogeneity



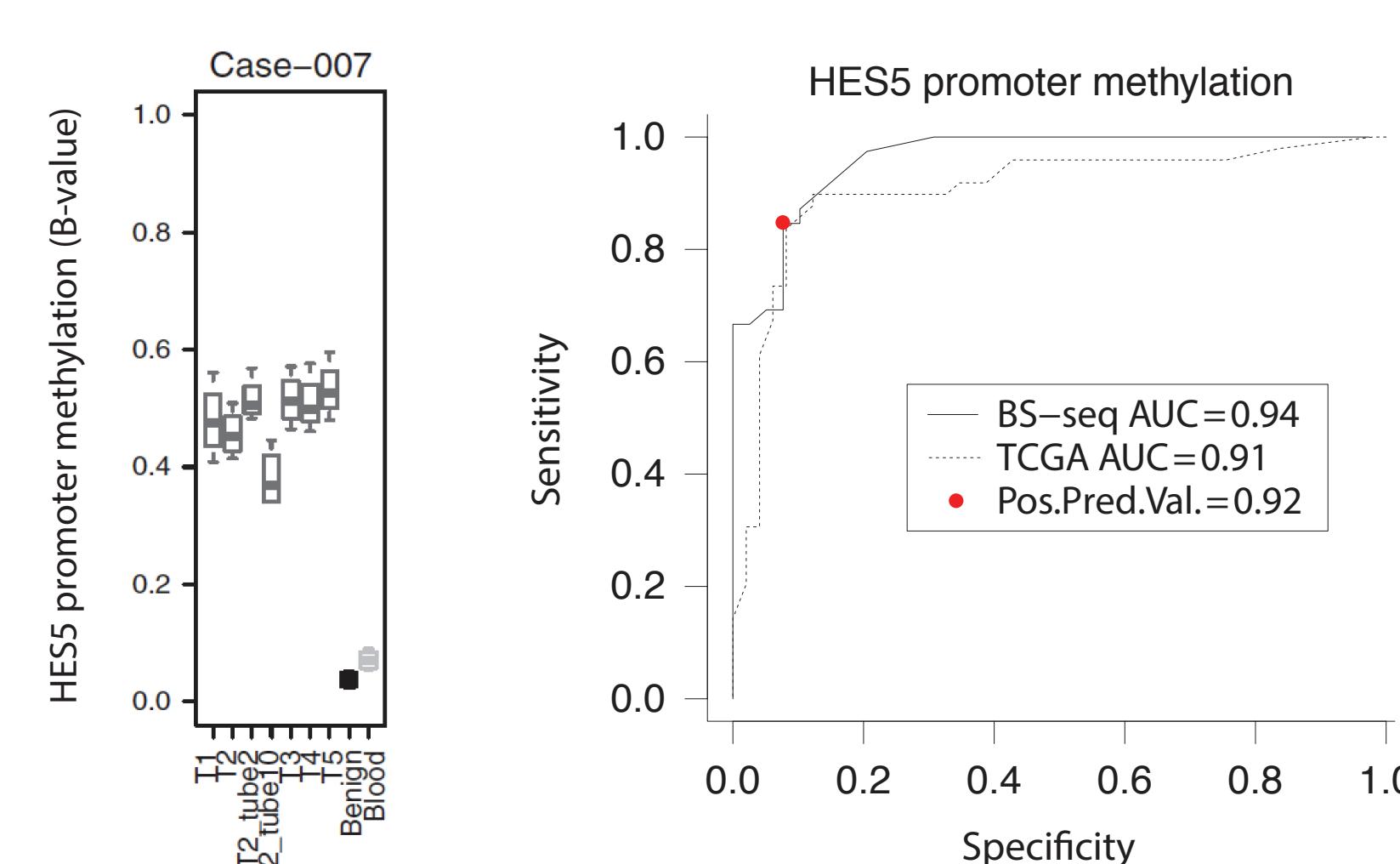
Cooper et al. 2015 Nat. Genet. 47, 367–372

Large cohort tumour genome sequencing reveals few recurrent genomic events



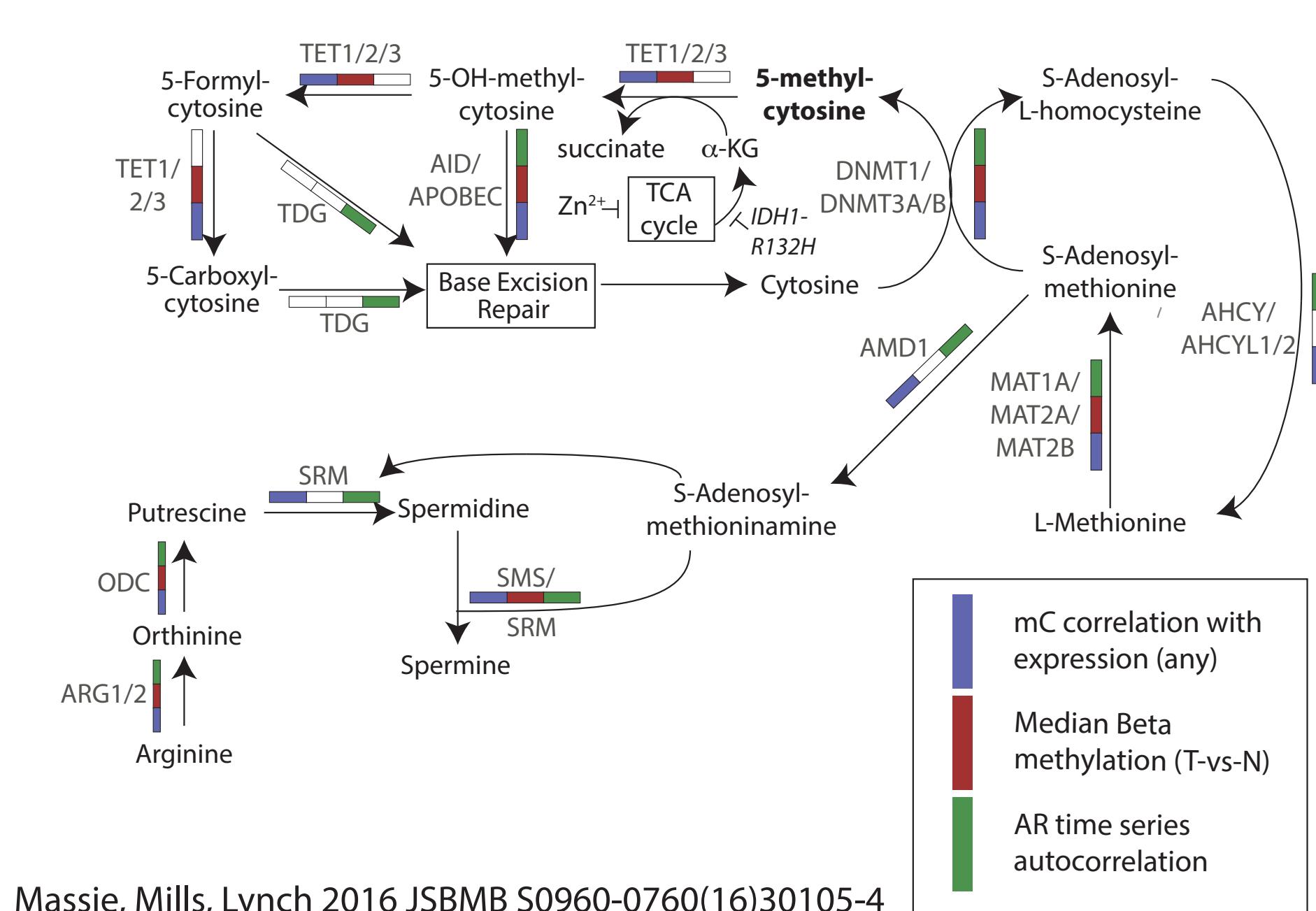
cBioPortal plot of TCGA PRAD (n=333), altered genes in rows, patients in columns

DNA methylation profiling reveals early, recurrent events



Massie et al. 2015 Endocr Relat Cancer 22(2):131–144

Convergence of AR and 5mC regulation on metabolic pathways that affect 5mC

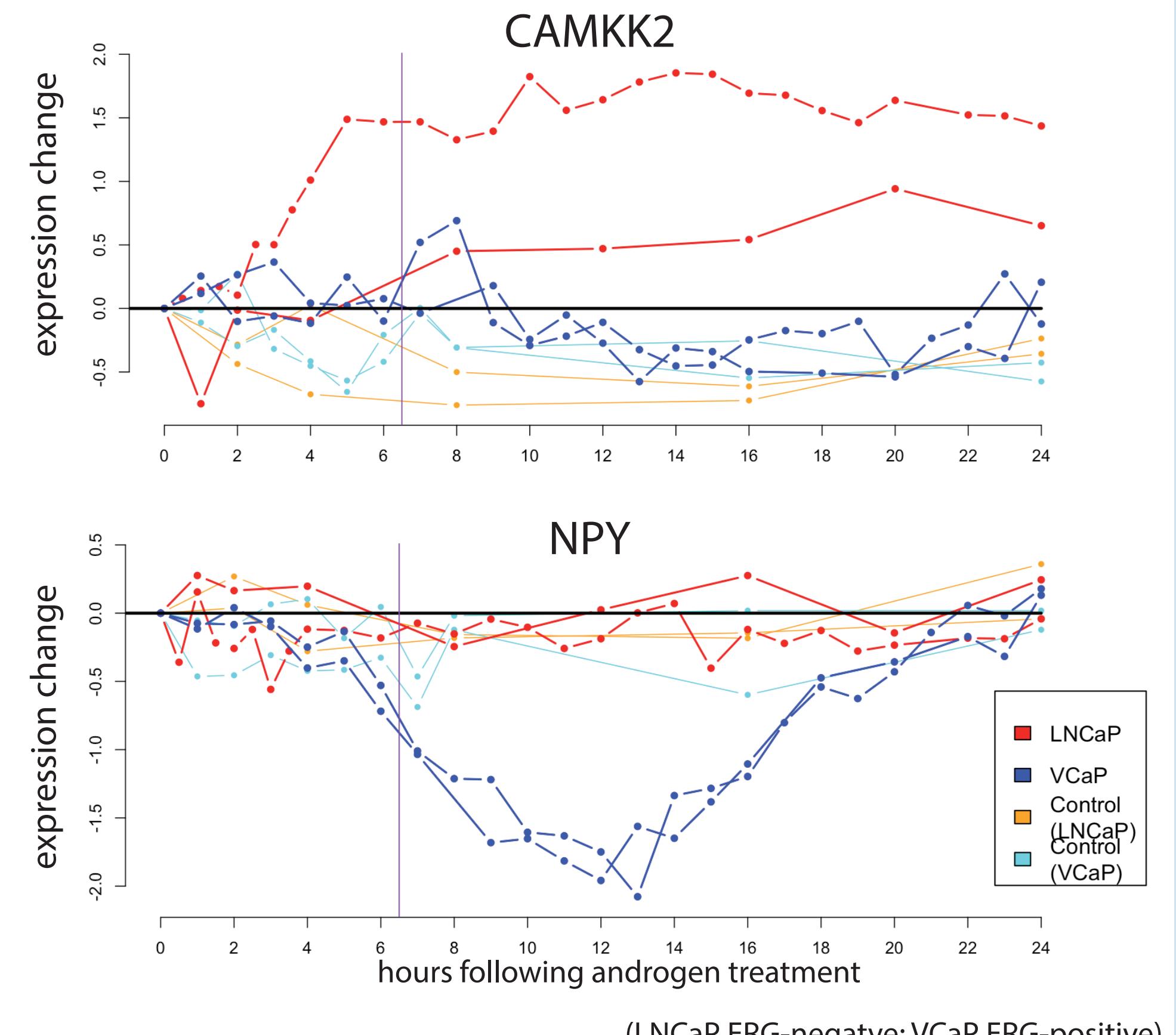


Massie, Mills, Lynch 2016 JSBMB S0960-0760(16)30105-4

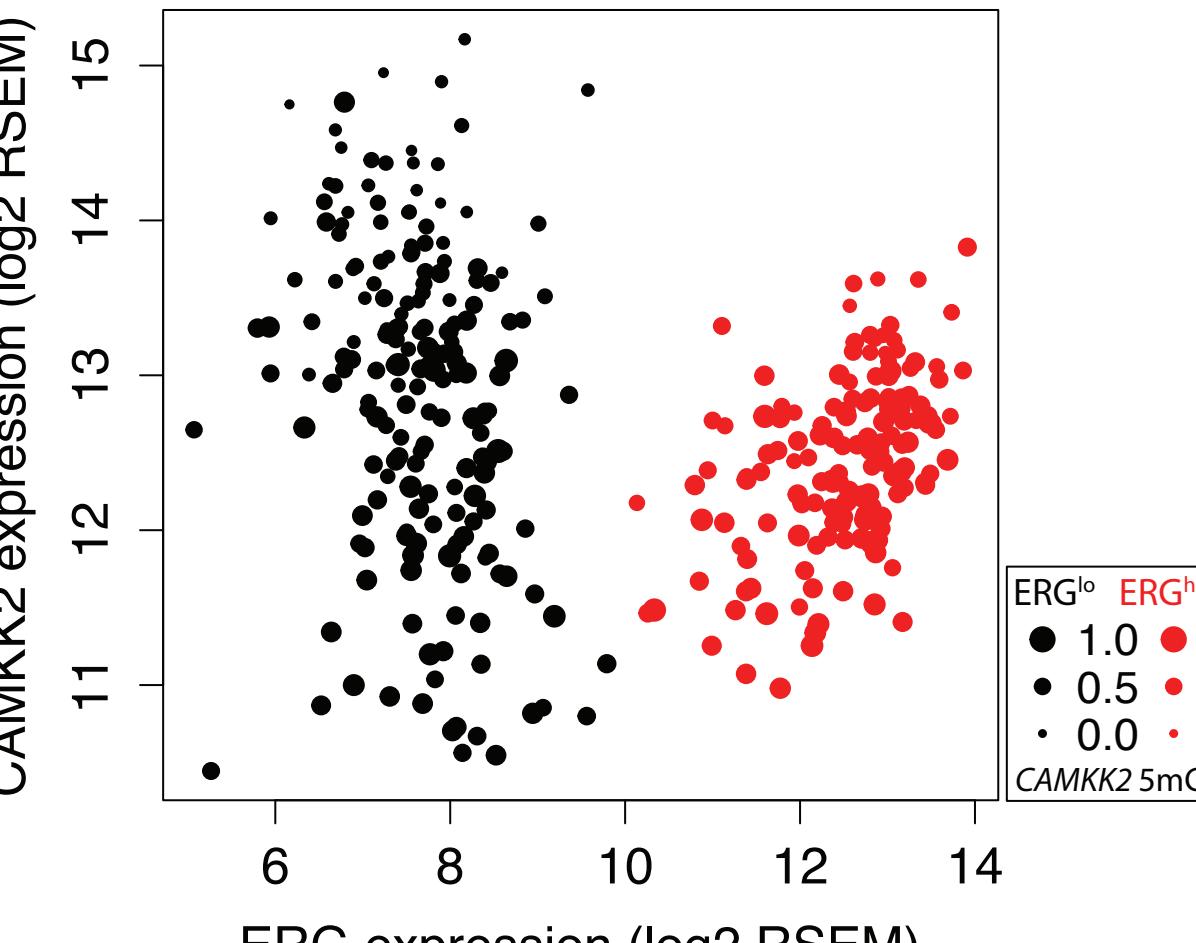
Existing models:

- In prostate cancer: AR → CAMKK2 → AMPK → anabolic metabolism [1,2]
- In the hypothalamus: Ghrelin → CAMKK2 → AMPK → NPY → increased appetite [4]
- NPY is regulated by ERG [5] and was recently identified as prognostic marker of metastasis in prostate cancer [6]

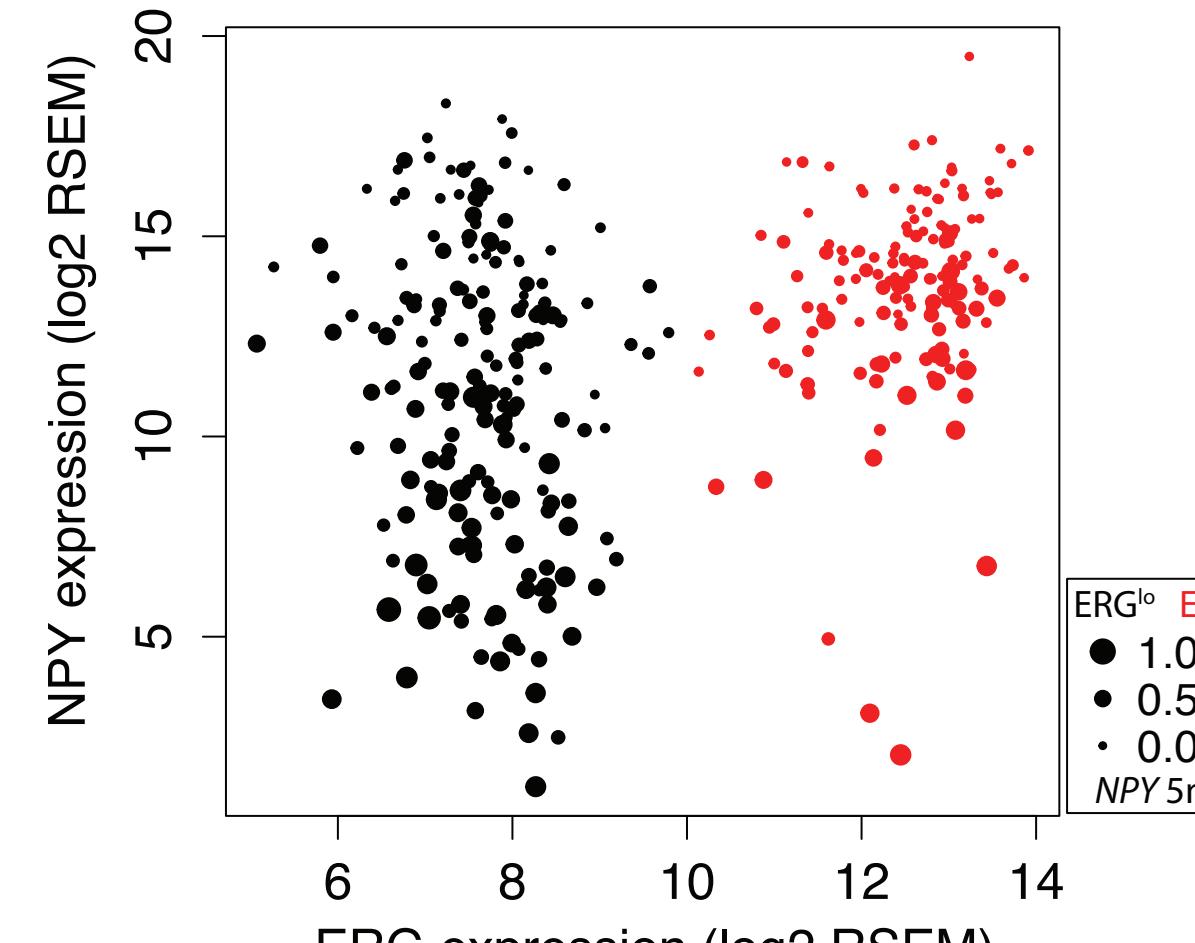
AR signaling stimulates either AR-CAMKK2 or AR-ERG-NPY in prostate cancer cell lines



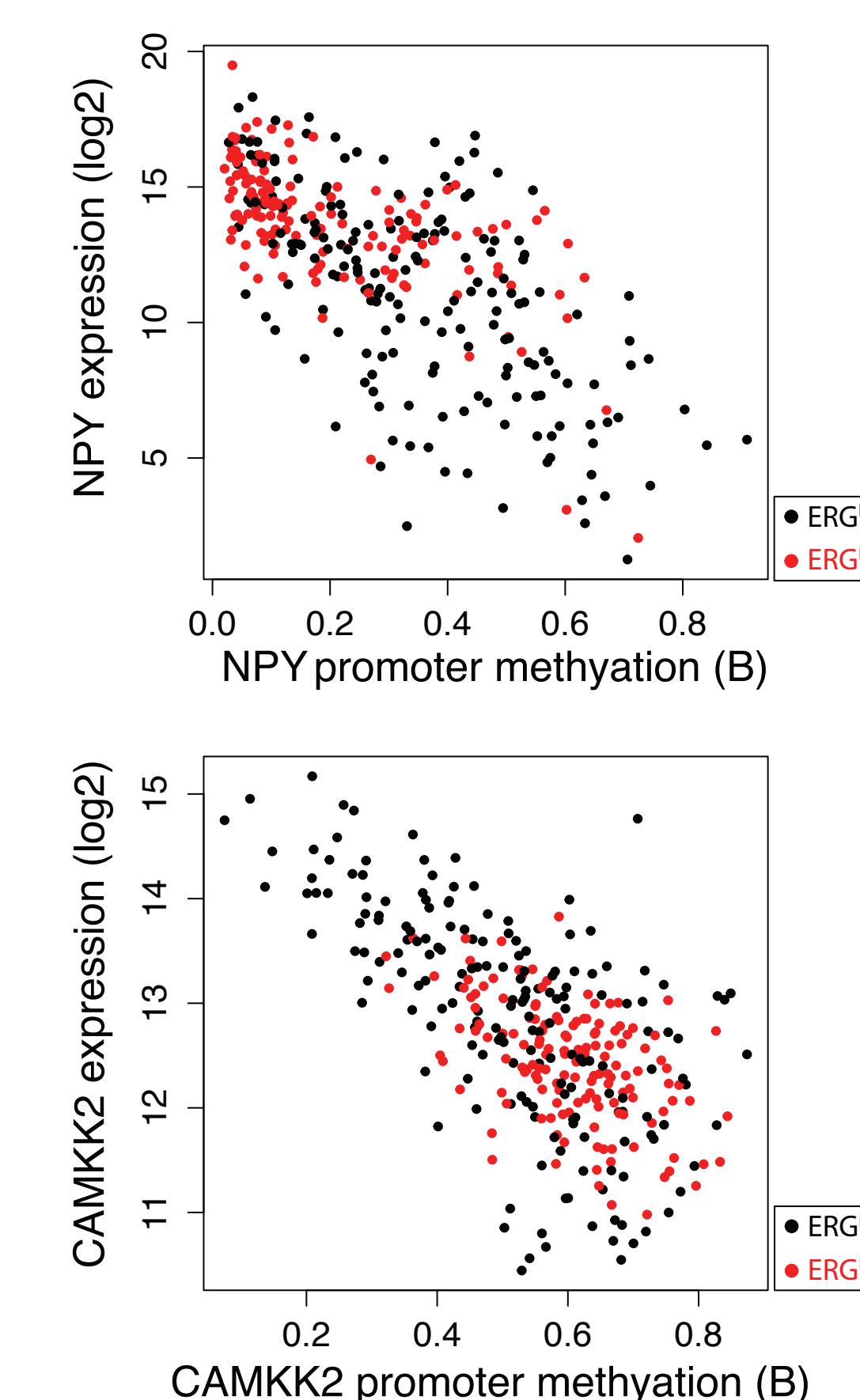
ERG^{hi} cases have low CAMKK2 ERG^{lo} cases have variable CAMKK2



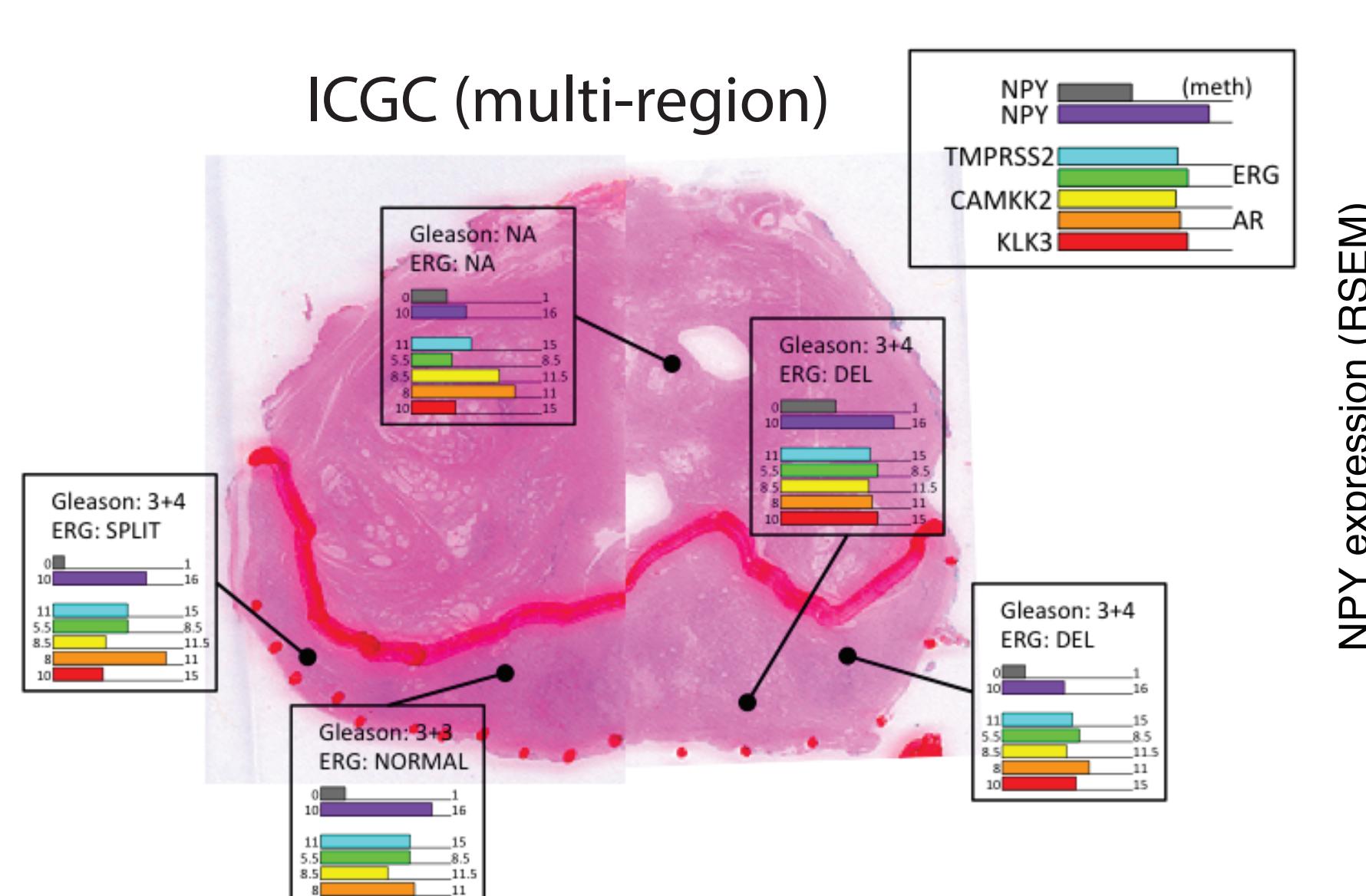
ERG^{hi} cases have high NPY ERG^{lo} cases have variable NPY



NPY and CAMKK2 promoter methylation and repression is associated with ERG status

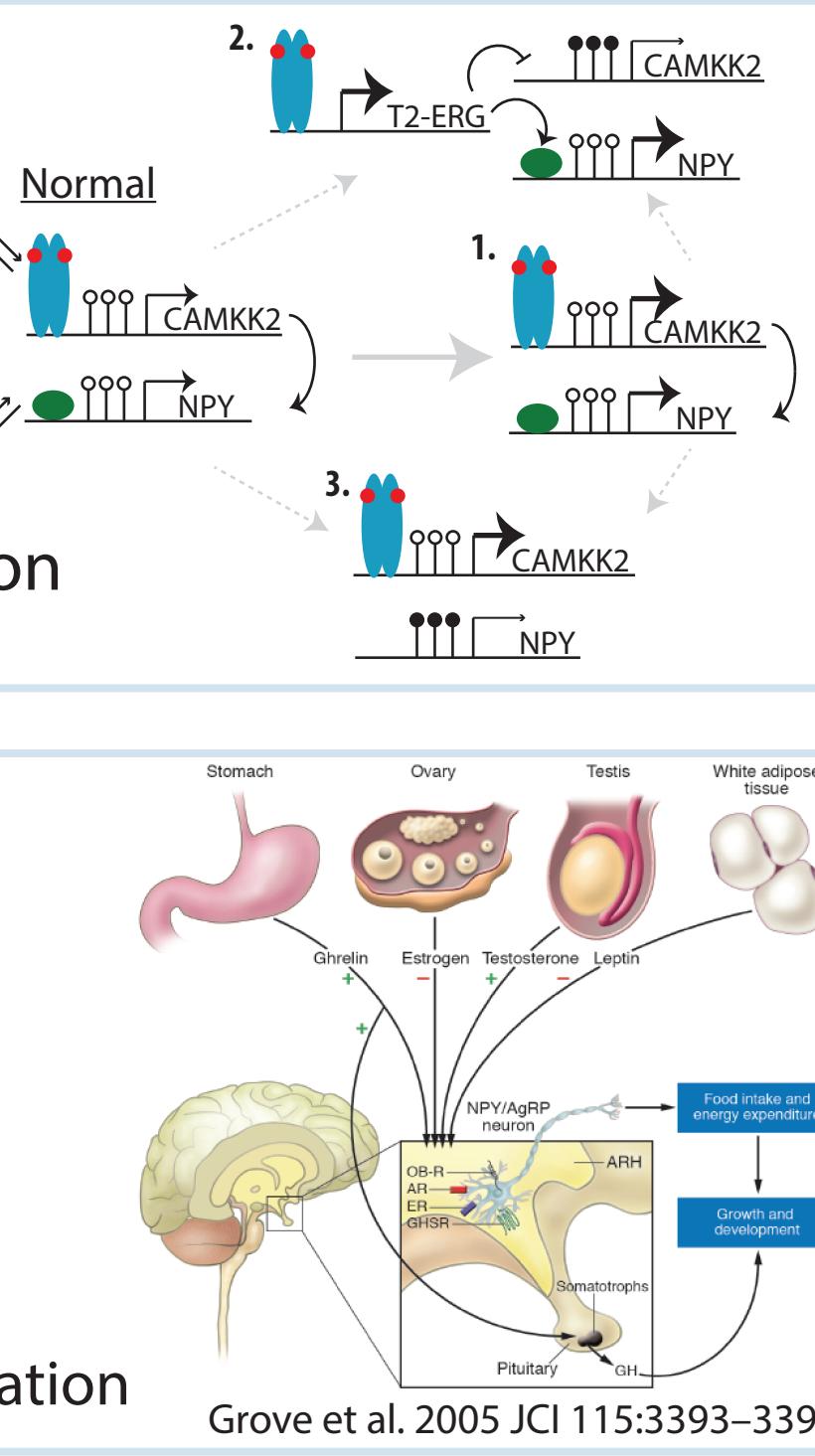


Subsets of prostate tumours: ERG-fusions and promoter methylation define NPY and CAMKK2 class



Revised PrCa model:

- Subtype-1: enhanced AR
- Subtype-2: ERG gene fusion
- Subtype-3: NPY promoter methylation



Conclusions

- Integrating large datasets can provide new insights into disease processes
- Using this approach we uncovered molecular subtypes of prostate cancers
- These subtypes suggest a fine-tuning of autocrine and systemic metabolic regulation