Epistatic effects among lung adenocarcinoma somatic mutations across oncogenesis

Jorge Alfaro-Murillo, Krishna Dasari & Jeffrey Townsend

Biostatistics Department

Yale SCHOOL OF PUBLIC HEALTH

Motivation

- *KRAS* and *TP53* are considered early drivers of LUAD but which is first?
- Smoking causes LUAD but is it just because of more mutations?
- Why is *EGFR* in so many non-smoker LUAD cases?

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- There is a constant rate at which mutations occur and are selected to high frequency (flux)
- The flux depends on the gene that will mutate as well as the current somatic genotype (previous mutations)

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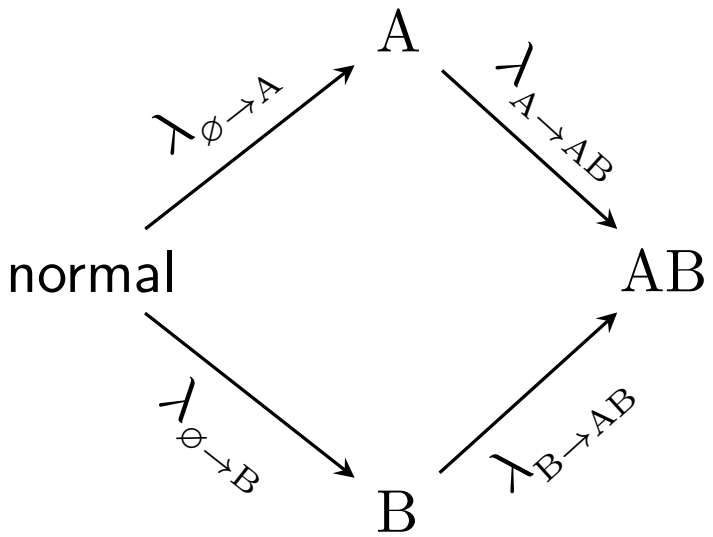

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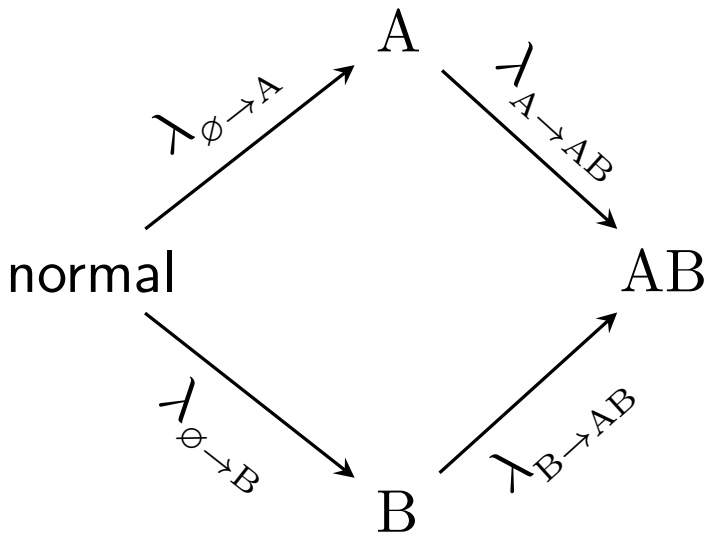

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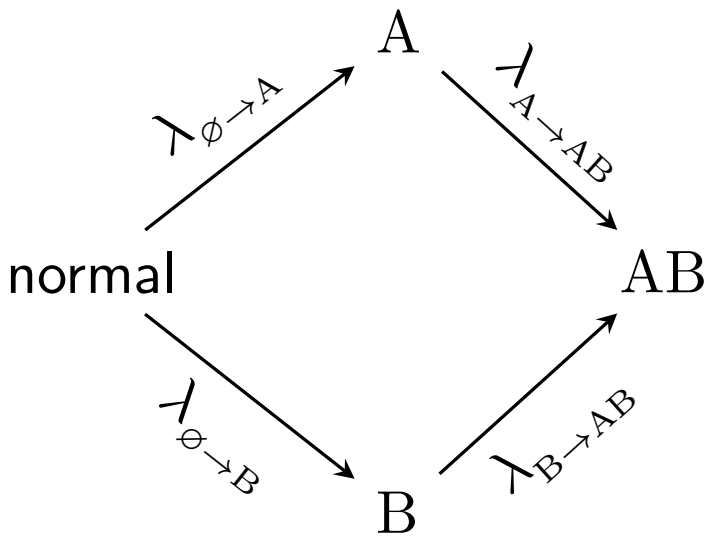

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Deconvolution of mutation and selection

- The flux is deconvolved into the mutation rate of the gene and the strength of selection on mutations of gene
- Mutation rate are obtained for each possible variant of each gene considering:
  - Molecular signatures
  - Gene expression
  - Chromatin marks
  - Replication times

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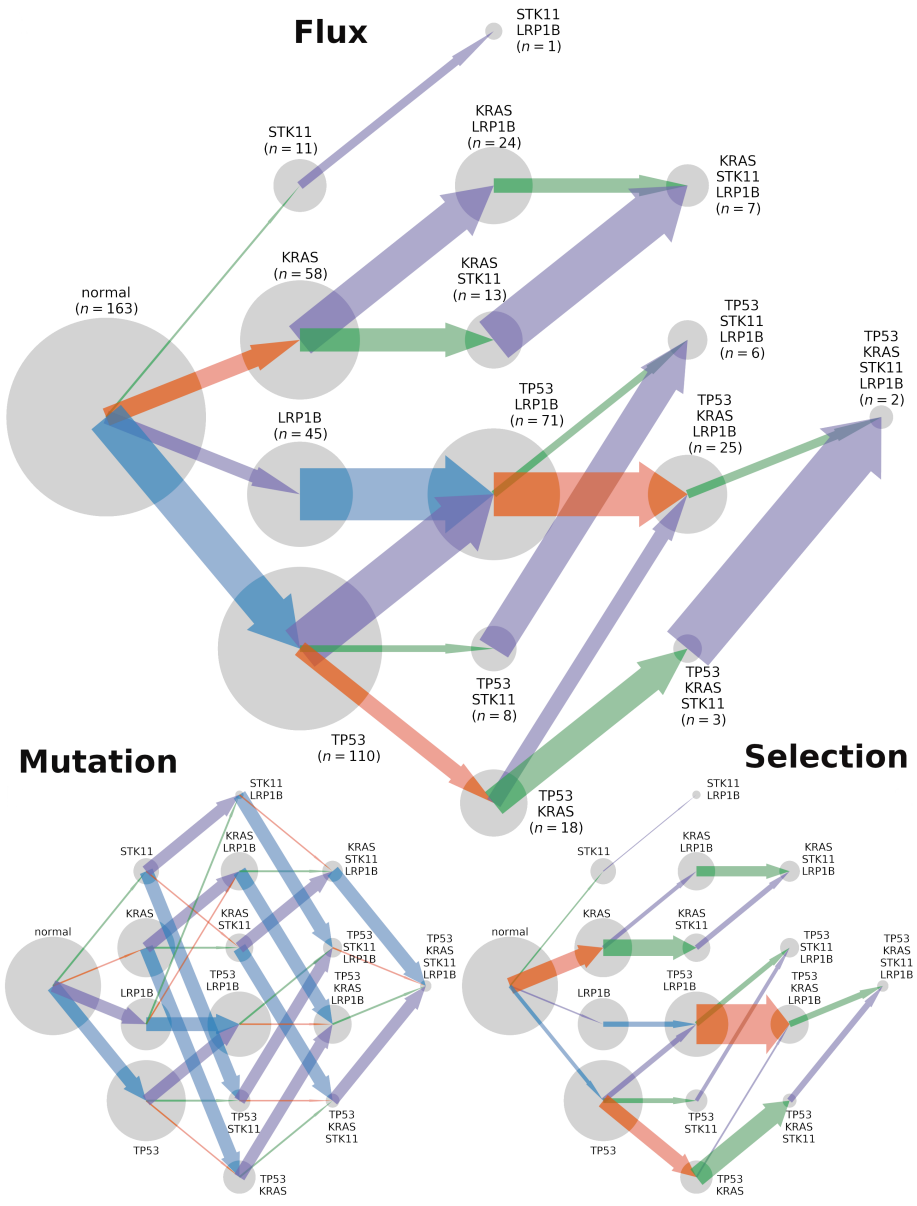
Epistasis in most commonly mutated genes in TCGA



Larger data set

- How about other genes? What is the effect of smoking?
- Aggregate multiple data
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- Classified 1,073 smokers and 447 non-smokers with clinical data and COSMIC SBS4

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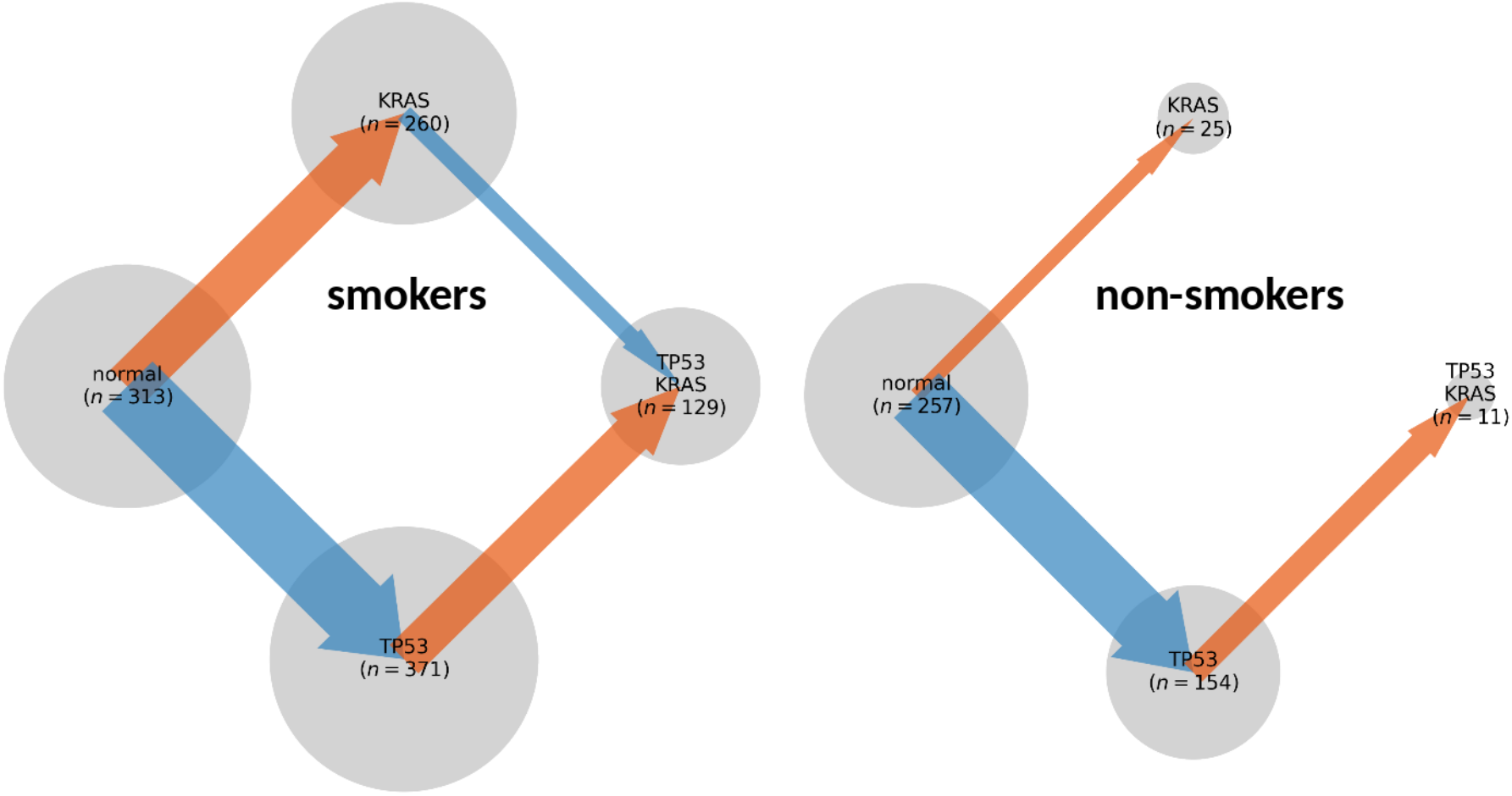
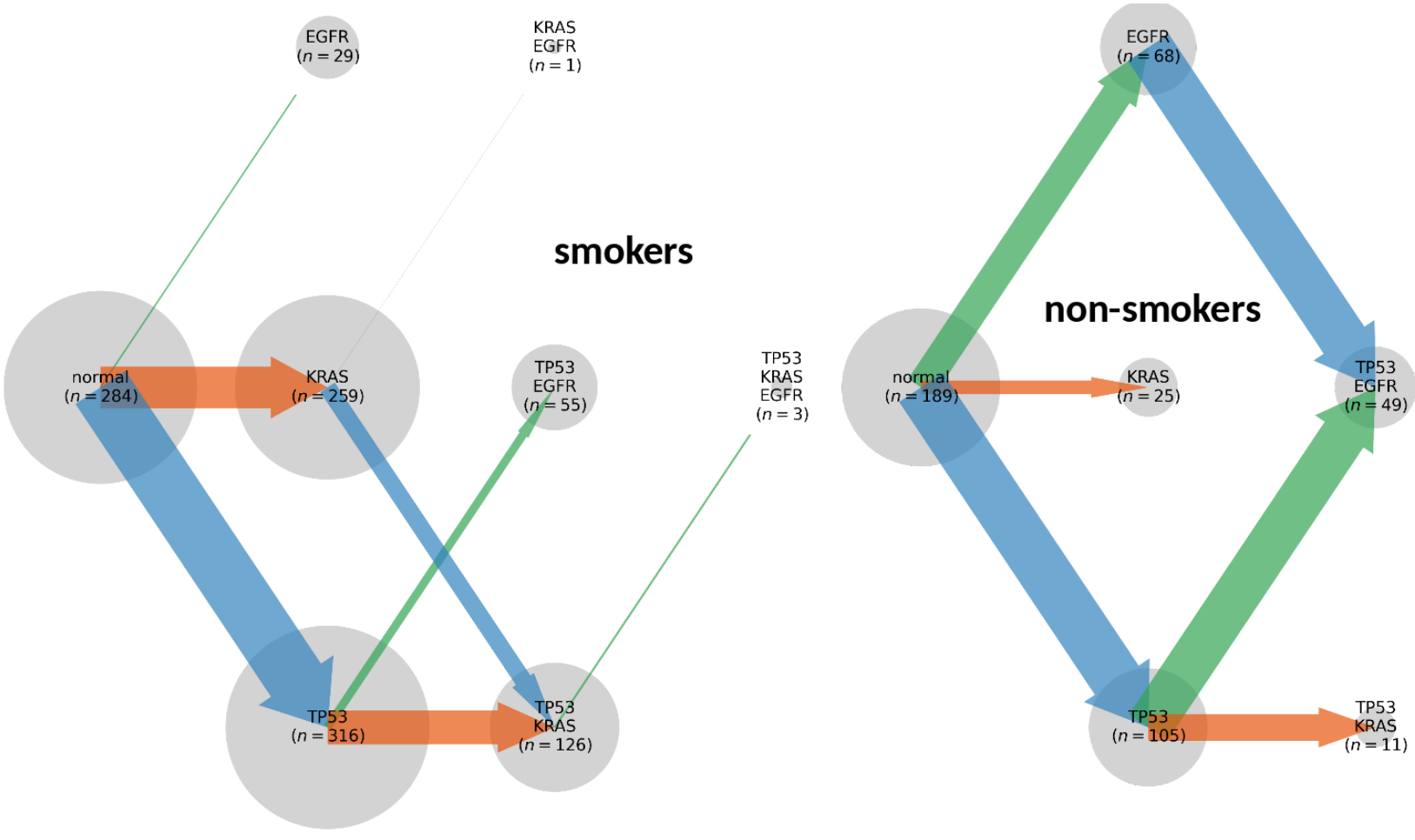
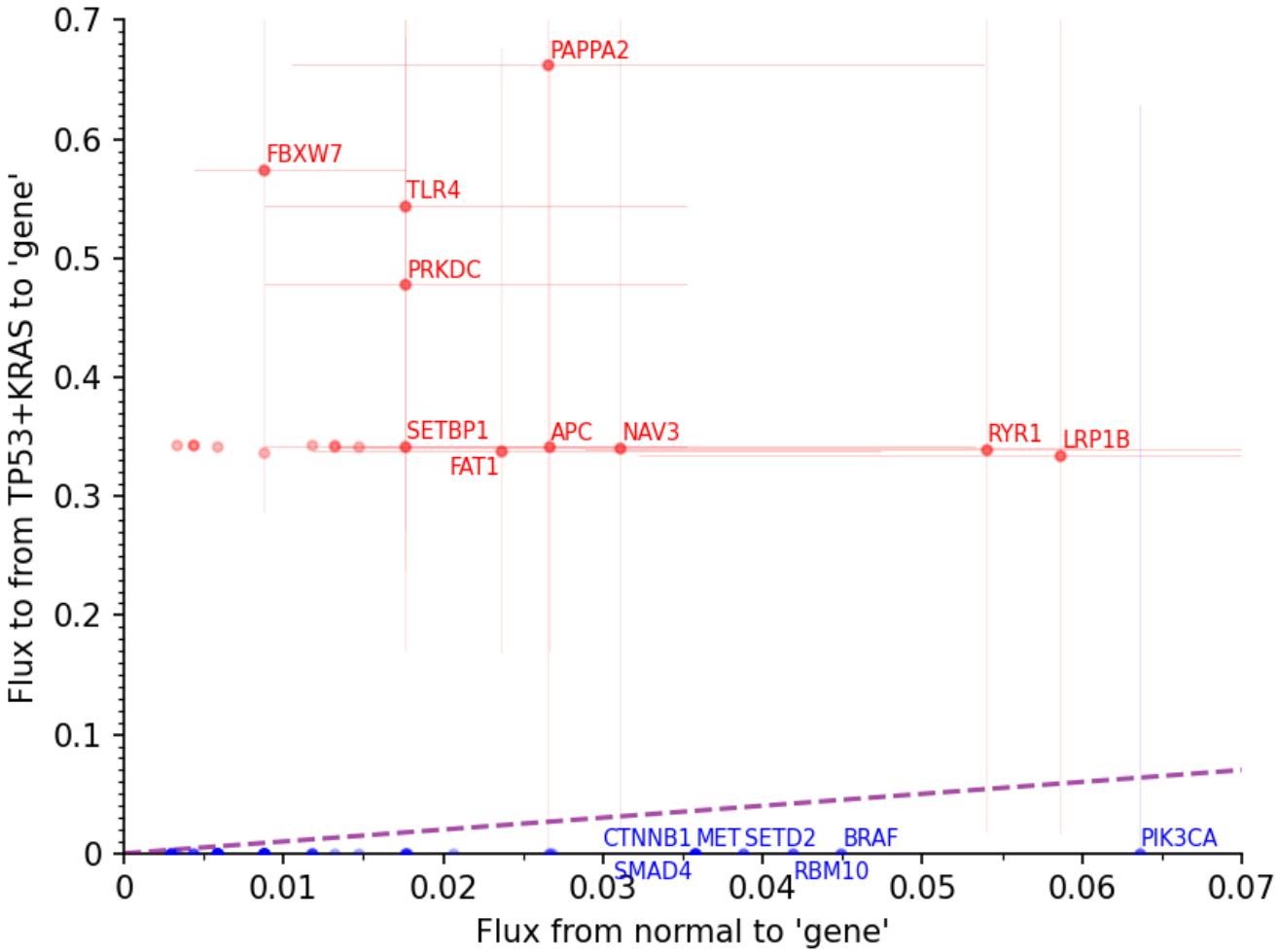


Epistasis of *TP53*, *KRAS* and *EGFR*



Epistasis other genes with *TP53+KRAS*

non-smokers



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