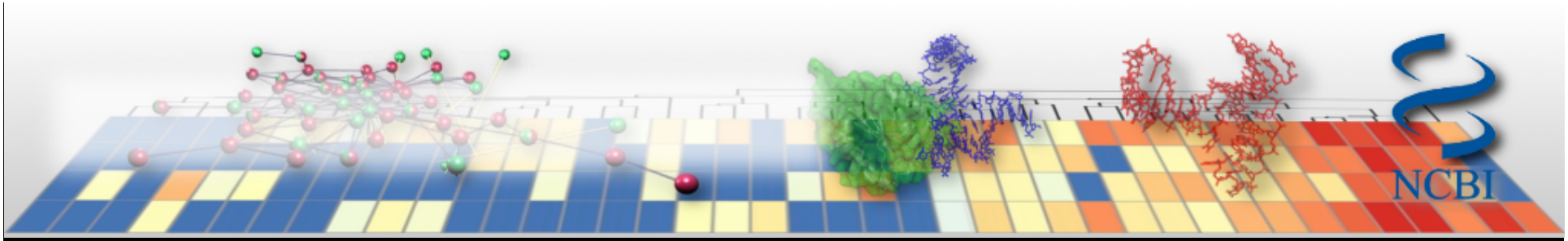


Mutual exclusivity: drivers, pathways, and beyond

Teresa Przytycka

NIH / NLM / NCBI

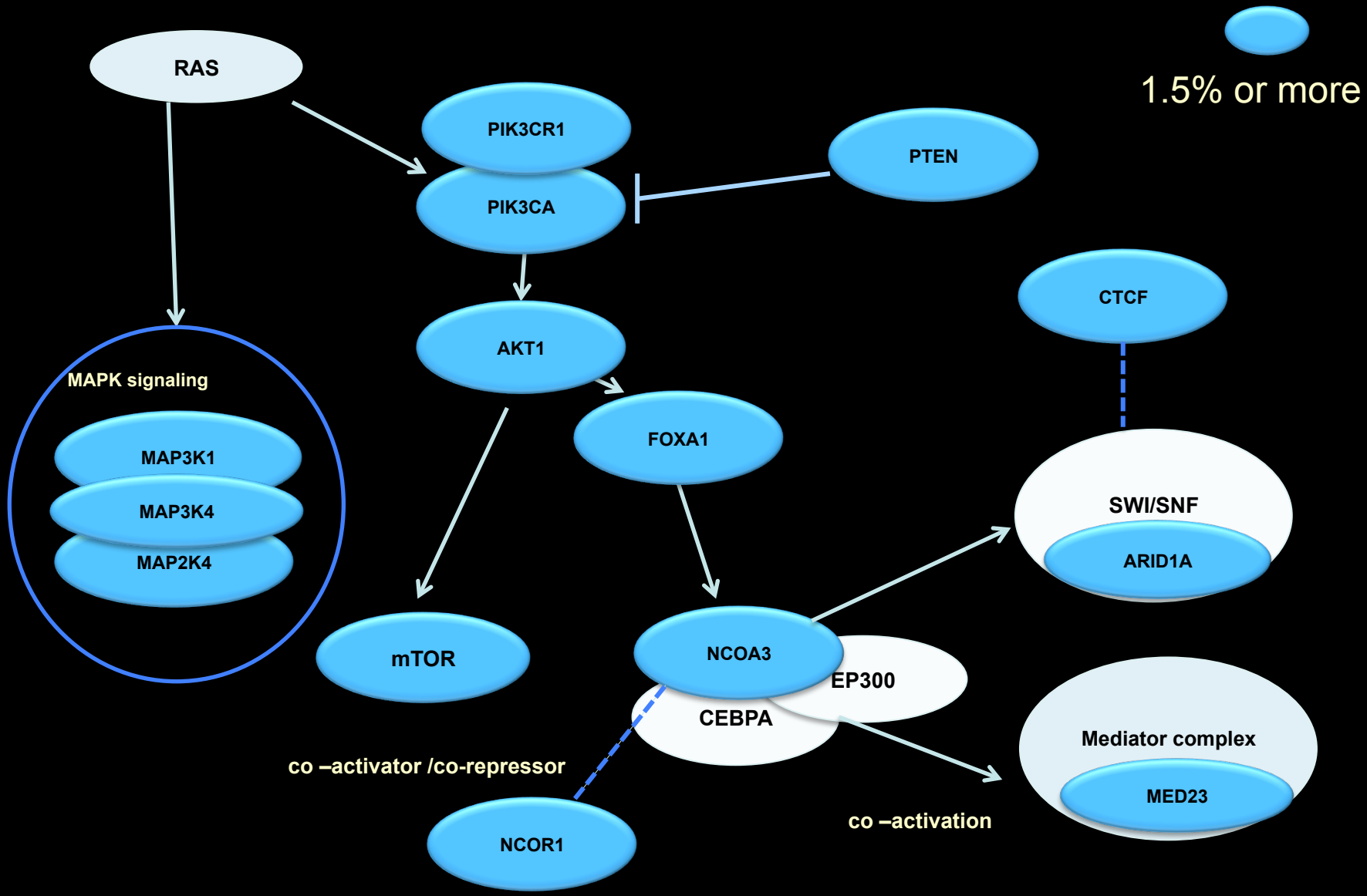
NCBI

Cancer drivers, passengers, supporting actors, witnesses

- Driver mutations /alterations– mutations contributing to cancer progression
- Passenger mutations – neutral mutations accumulating during cancer progression
- Challenges in detecting driver mutations:
  - Heterogeneity - phenotypically similar cancer cases might be caused by different sets of driver mutations
  - Rare drivers
- Best supporting actors (Igor's talk)
- Witnesses (this talk)

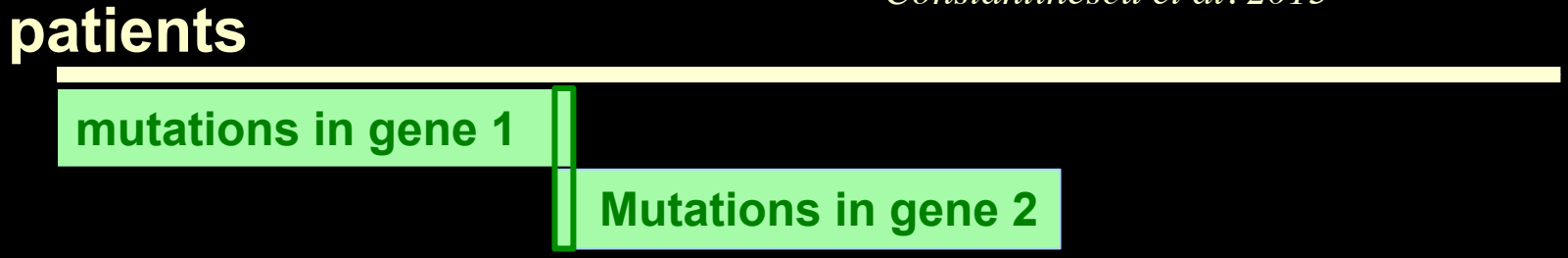
Cancer driving pathways

examples of BRCA mutated genes in their pathway context



Mutual exclusivity of cancer drivers

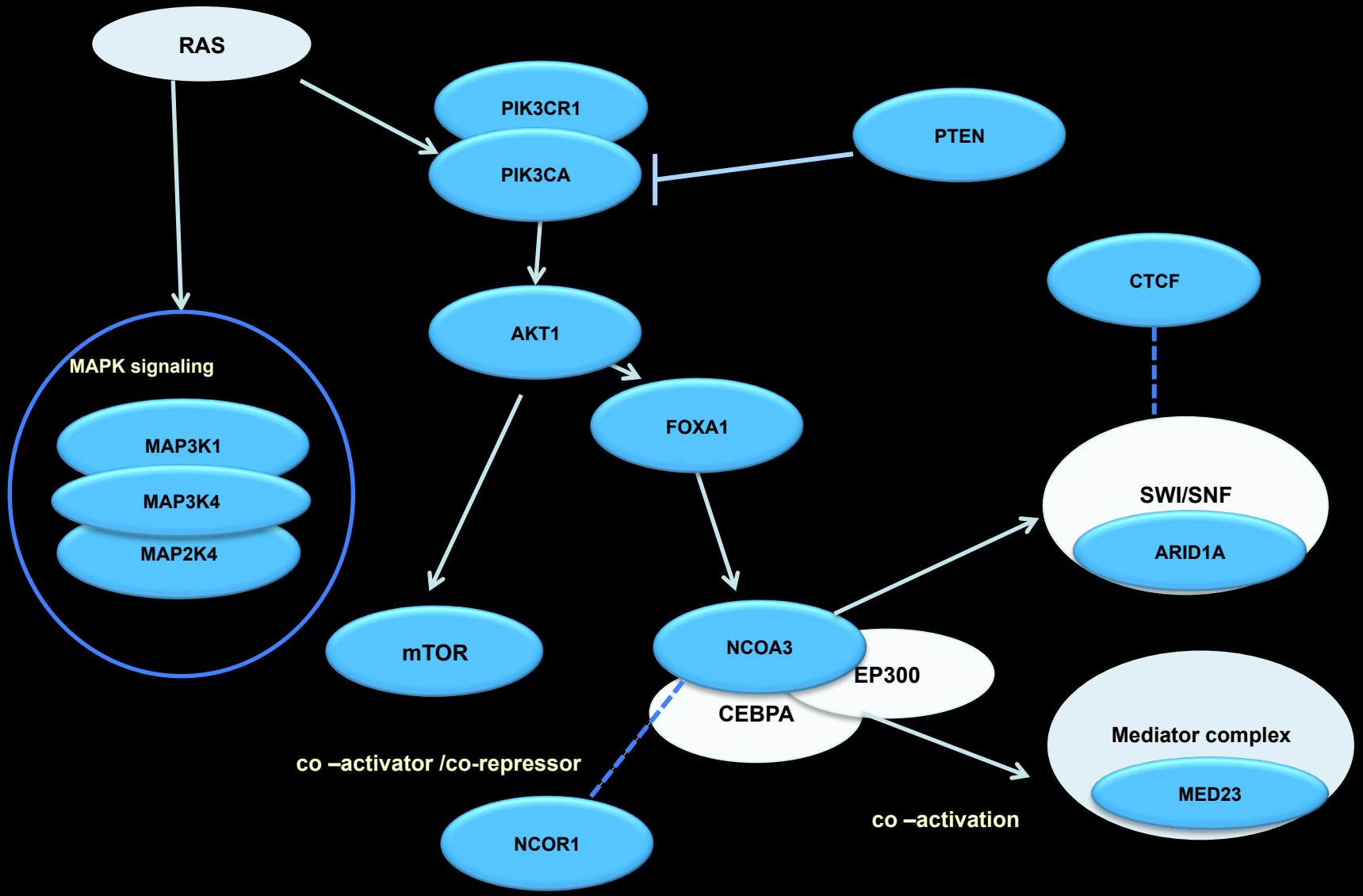
Thomas et al 2007
Ciriello, et al., 2012;
Vandin, et al., 2012;
Szczuret et.al , 2014, 2015
Leiserson, et al., Vadin et al. 2013,2014,2015;
Kim et al. 2015
Constantinescu et al. 2015



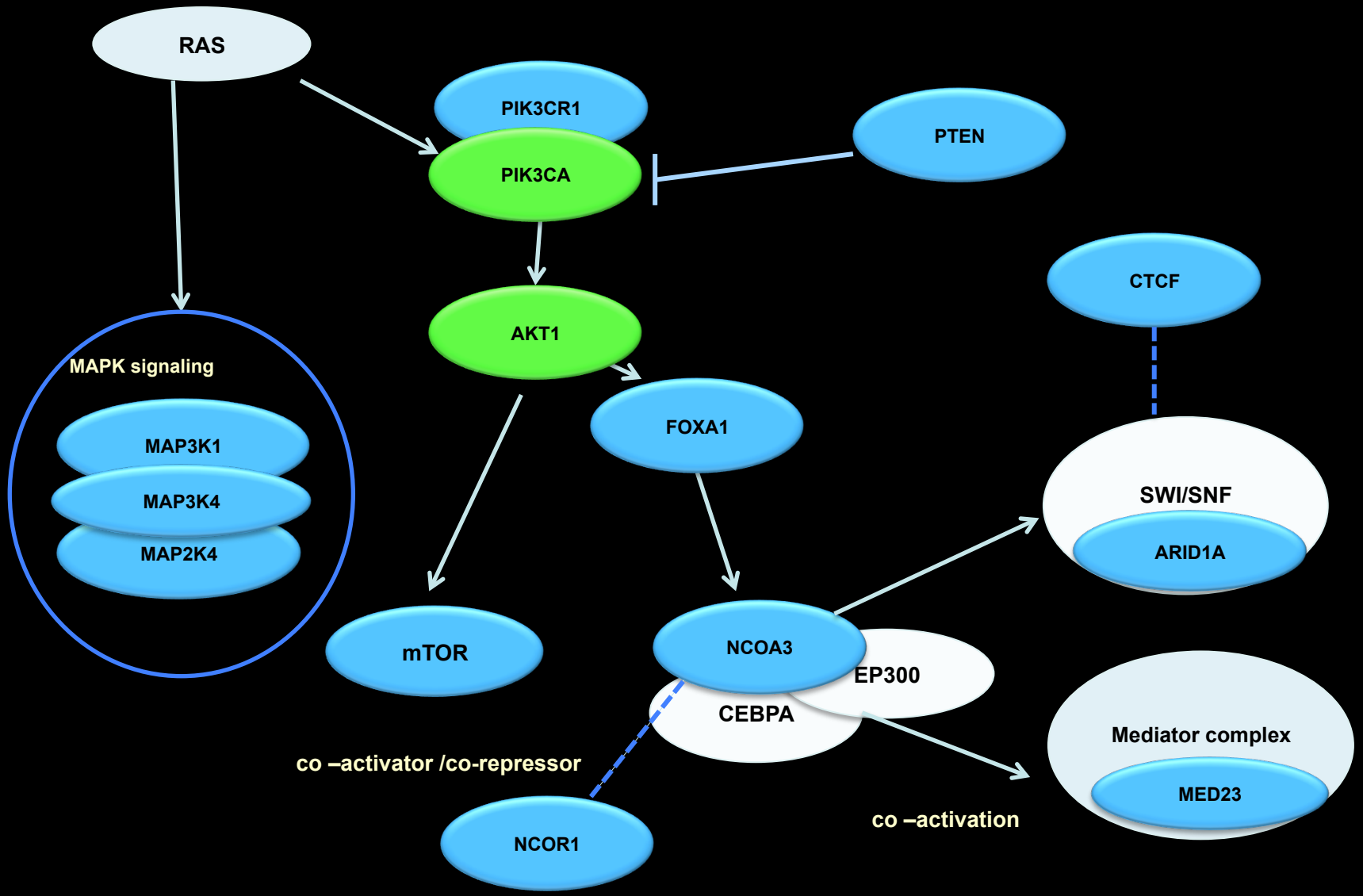
Explanations

- Two drivers dysregulating the same pathway
- Each of the drivers corresponds to of a unique cancer type or subtype
- Negative genetic interactions between drivers

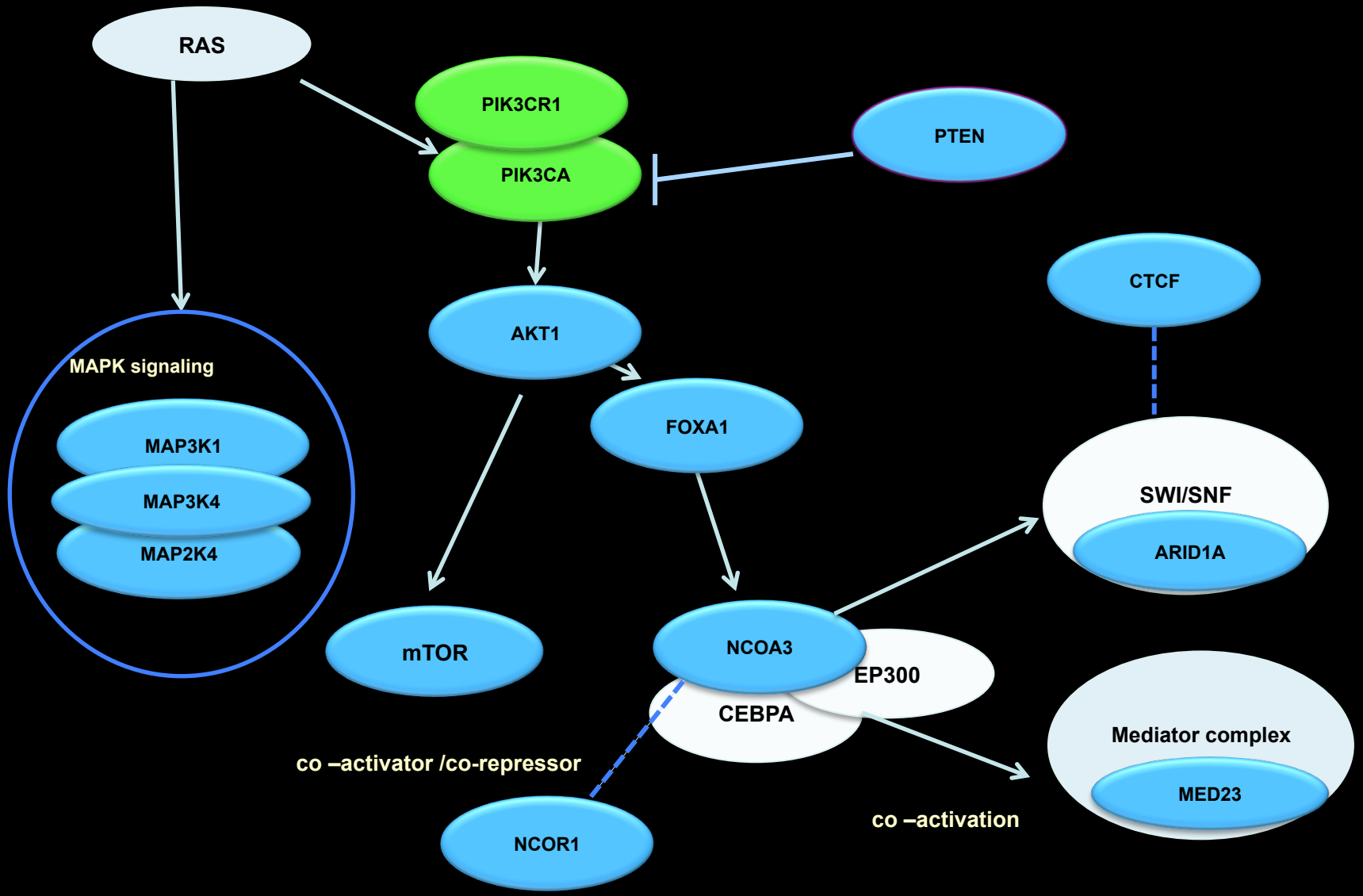
Mutually exclusive pairs often share pathways



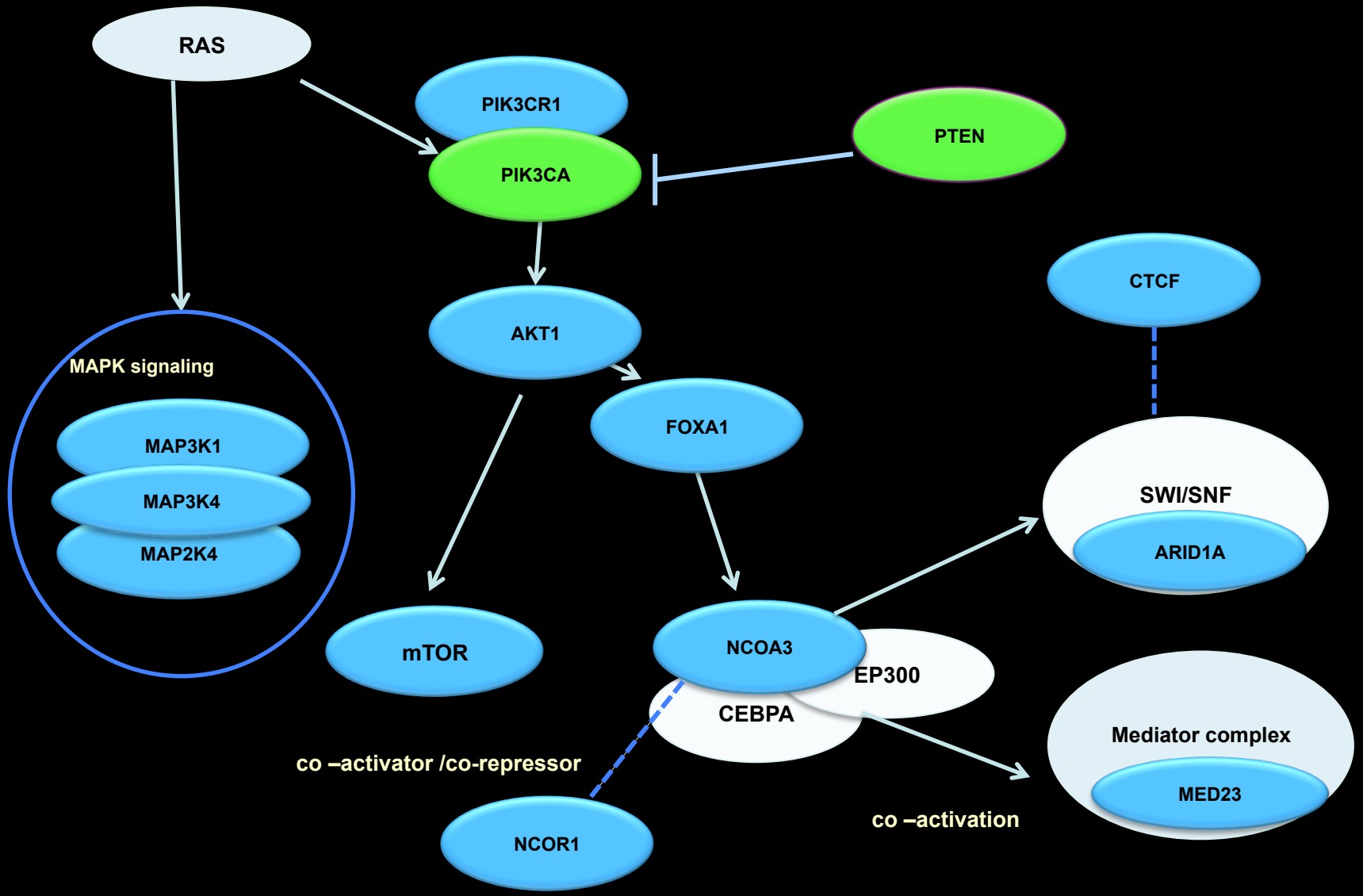
Mutually exclusive pairs often share pathways



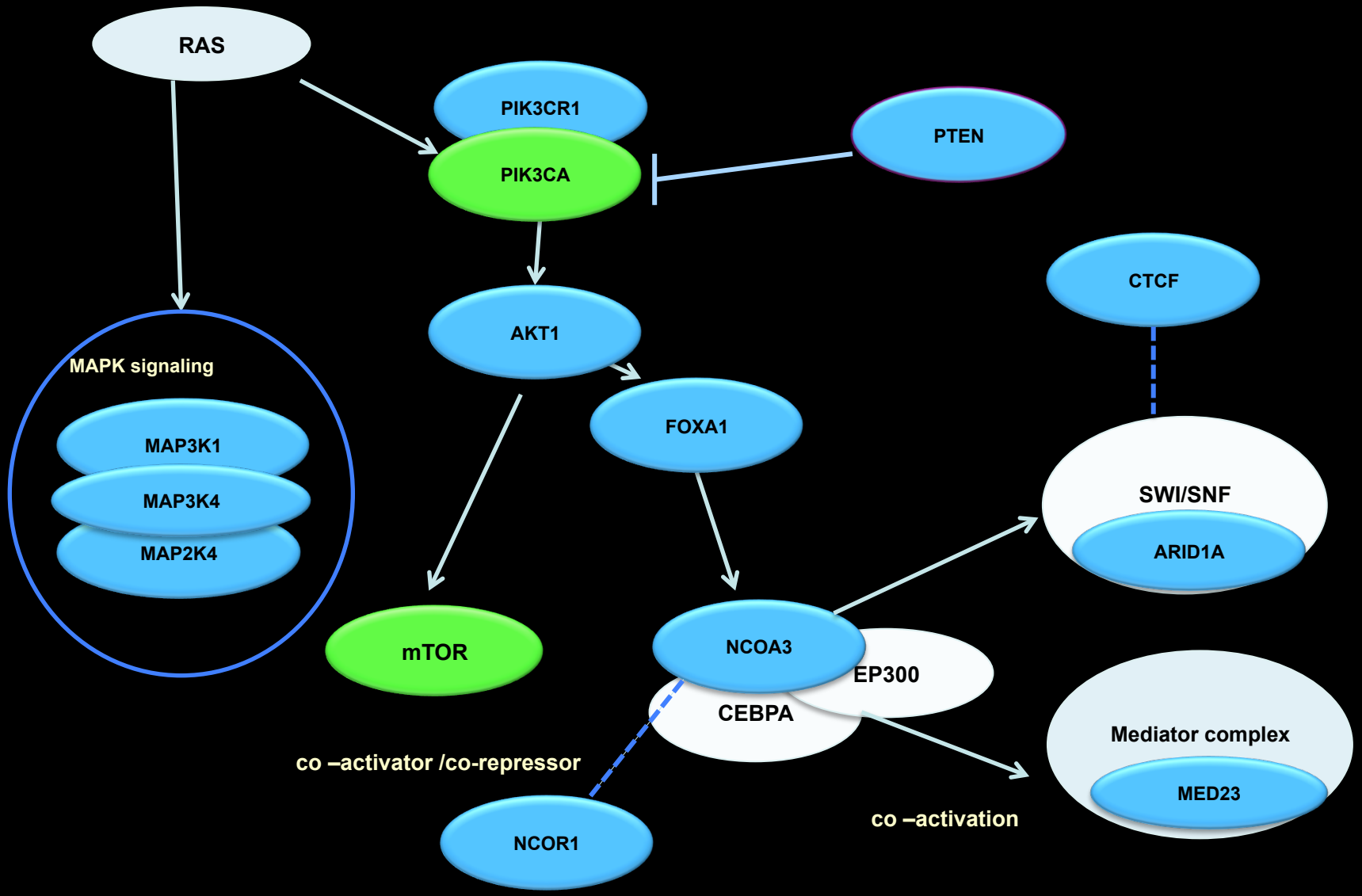
Mutually exclusive pairs often share pathways



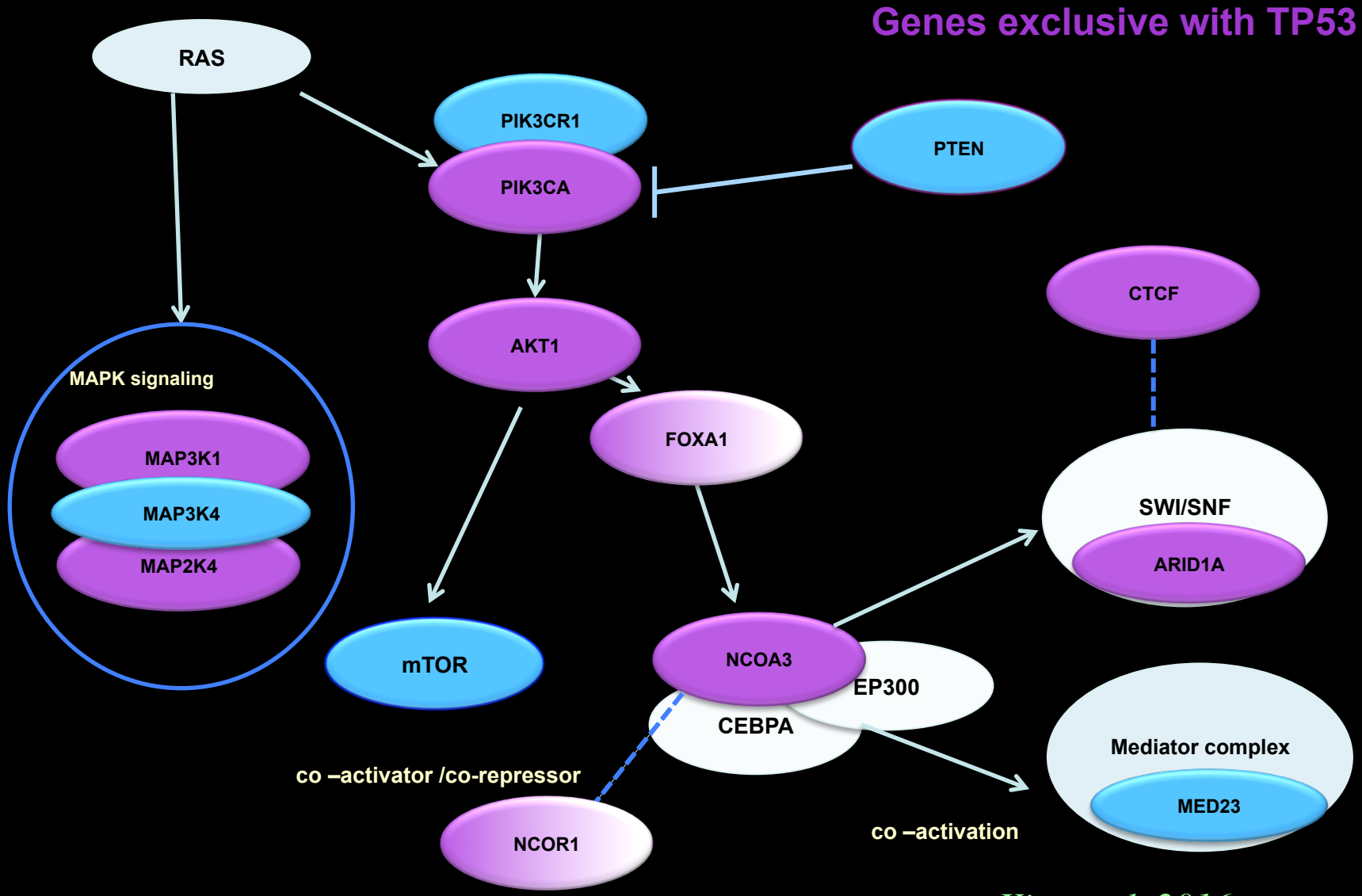
Mutually exclusive pairs often share pathways



Mutually exclusive pairs often share pathways



Mutual exclusivity relation with a gebe "outside" the pathway



Kim et al. 2016

Introducing a classification of mutual exclusivity

Motivation – distinguishing ME between drivers that:

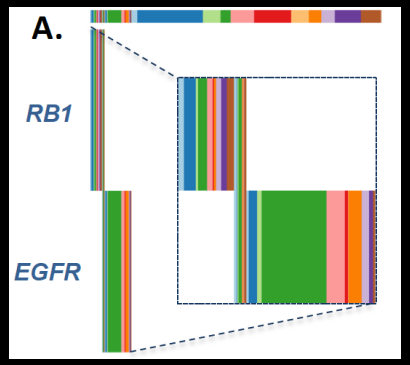
- Result in a similar phenotype (**WITHIN_ME**)
- Occur across multiple cancer types (**ACROSS_ME**)
- Between type specific drivers (**BETWEEN_ME**)

Kim et al. ISMB /Bioinformatics 2015

Mutual exclusivity classes in PanCancer context

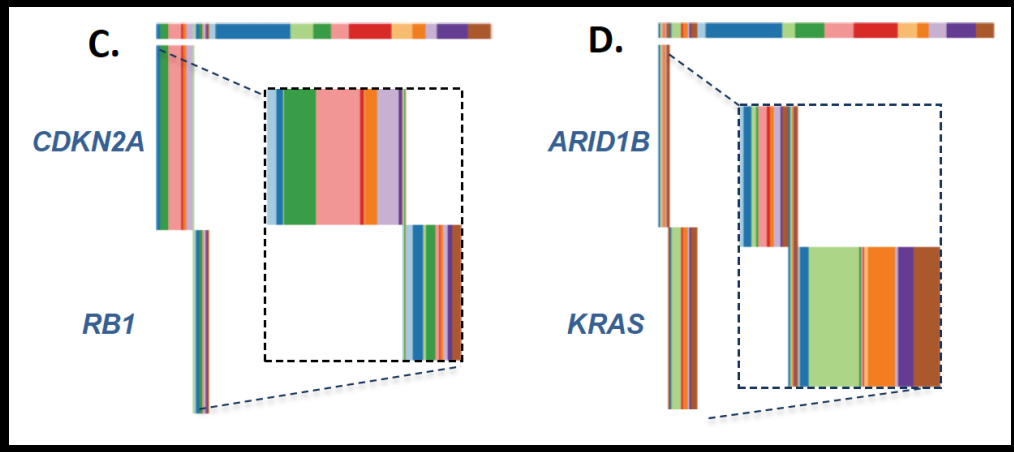
- **Within tissue exclusivity**
  WITHIN_ME

  Traditional permutation test



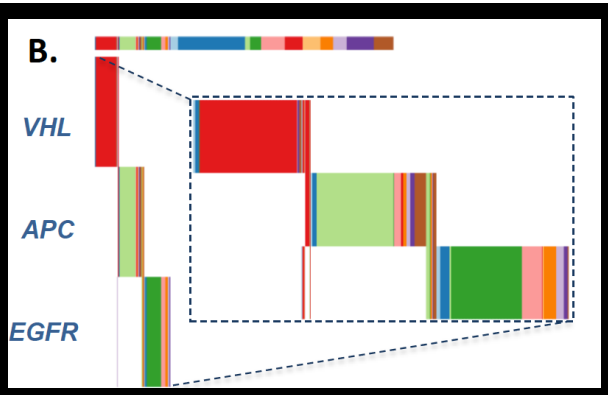
- **Across tissues exclusivity**
  ACROSS_ME

  Type-restricted permutation test



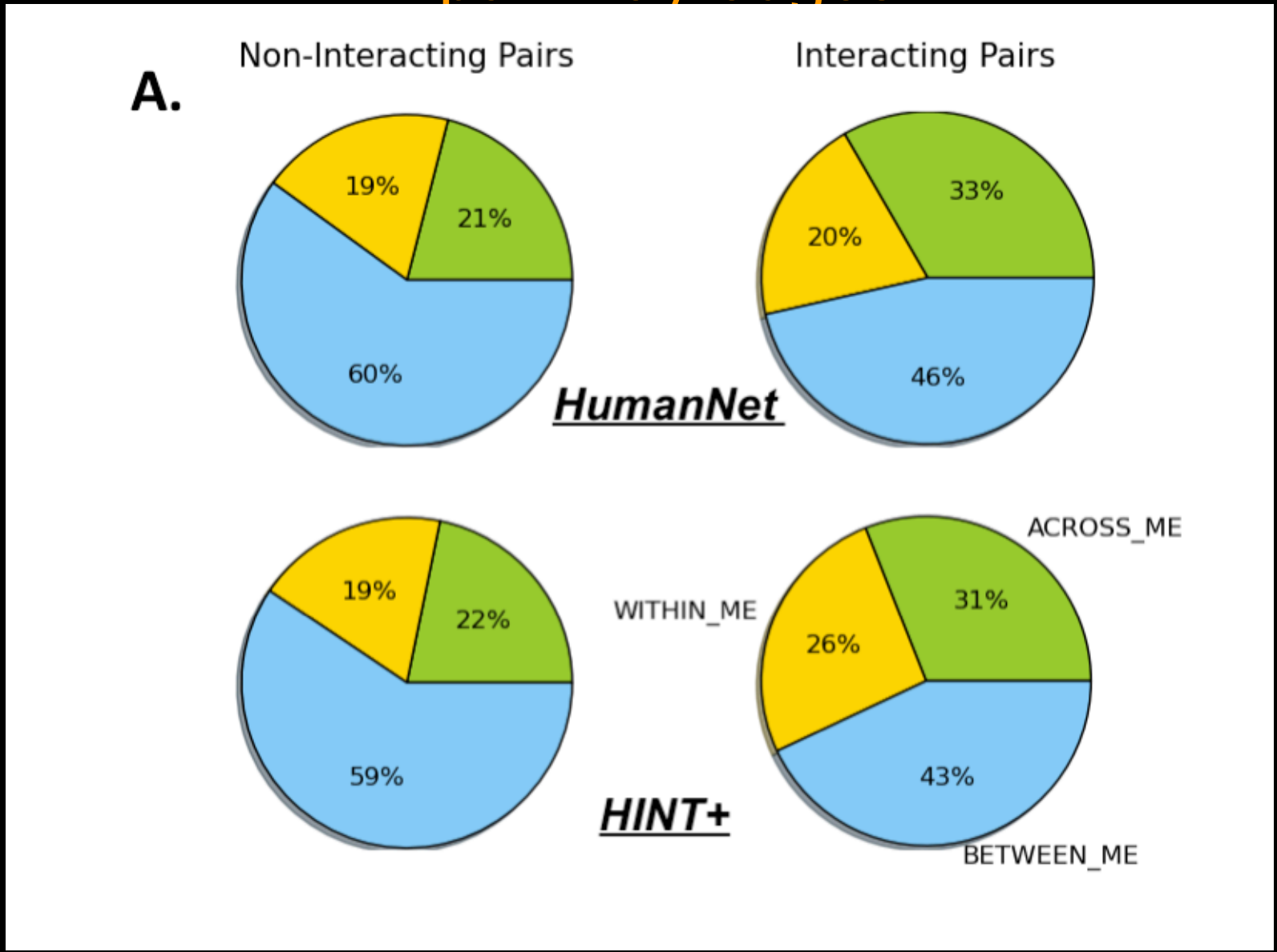
- **Between tissues exclusivity**
  BETWEEN_ME

  Traditional, type-oblivious permutation test



Kim et al. ISMB /Bioinformatics 2015

WITHIN and ACRPSS ME is biased towards pathway edges

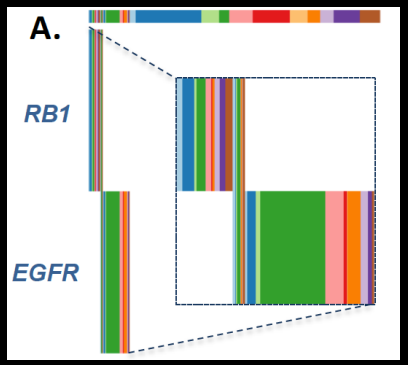


Kim et al. ISMB /Bioinformatics 2015

Finding cross-cancer dysregulated modules by combining interaction and ACROSS_ME

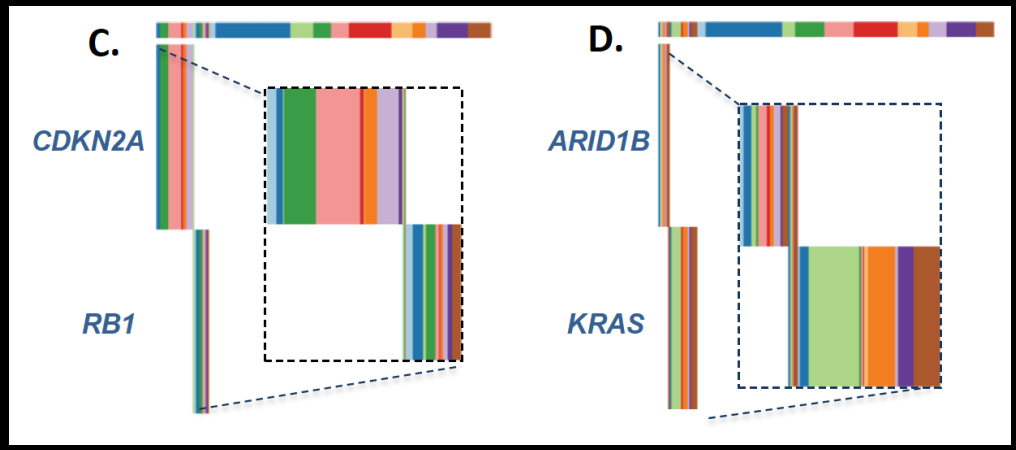
- **Within tissue exclusivity**
  WITHIN_ME

Traditional permutation test



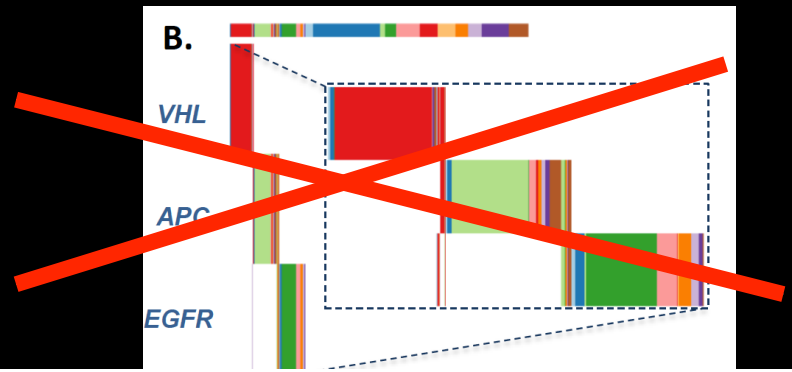
- **Across tissues exclusivity**
  ACROSS_ME

Type-restricted permutation test



- **Between tissues exclusivity**
  BETWEEN_ME

Type-oblivious permutation test



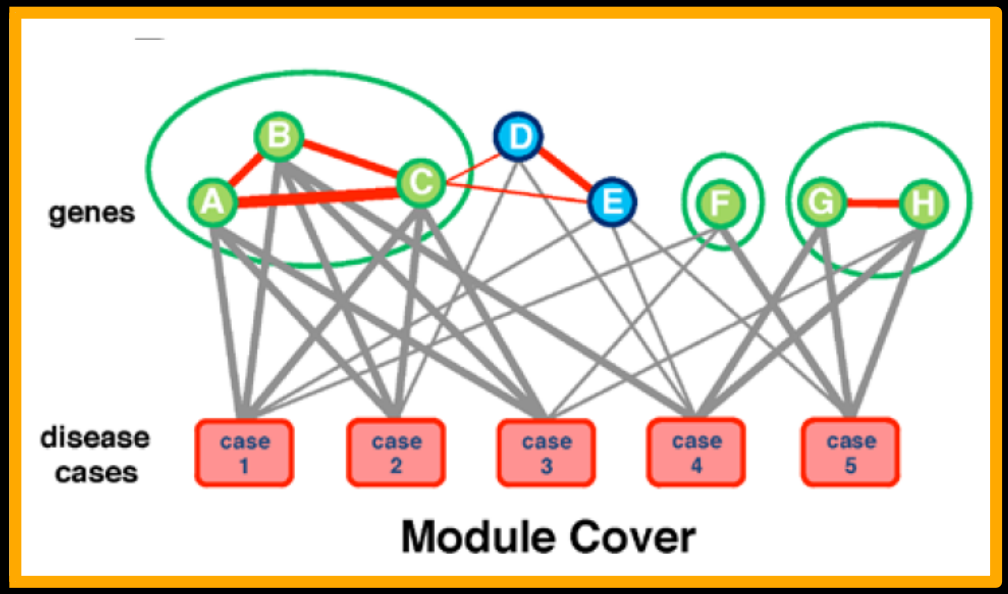
Finding PanCancer dysregulated pathway - ME Module Cover Approach

Optimization problem:

Find smallest cost set of modules so that each disease case is covered at least k times

Cost is a function of:

- ⬇ **distance in the network of genes in same module**
- ⬇ **Mutual exclusivity**
- ⬇ **Score of covering edge**
- ⬆ **unit cost per module**

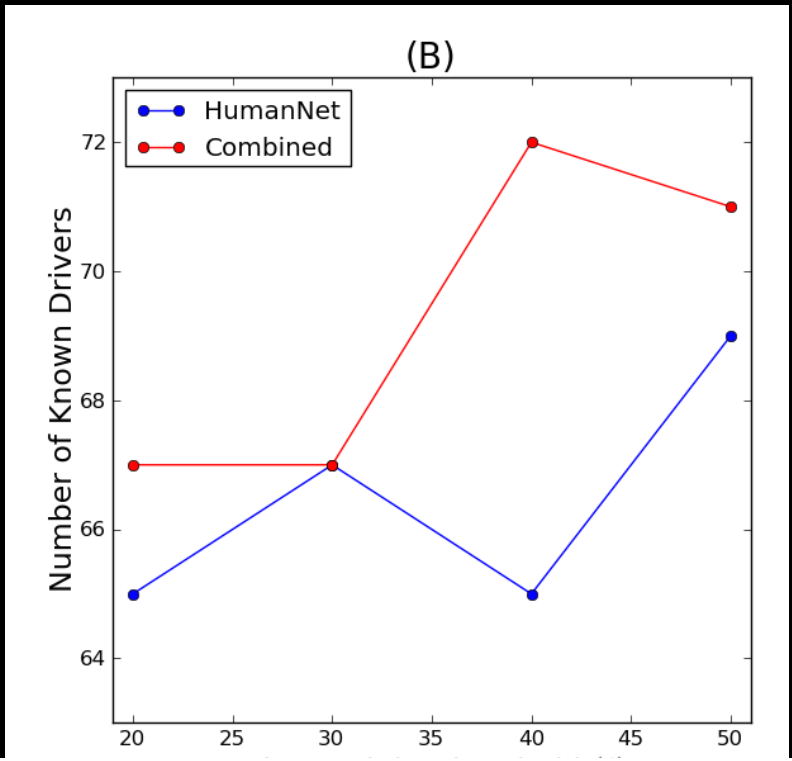


Kim et al. PSB 2013, Bioinformatics 2015

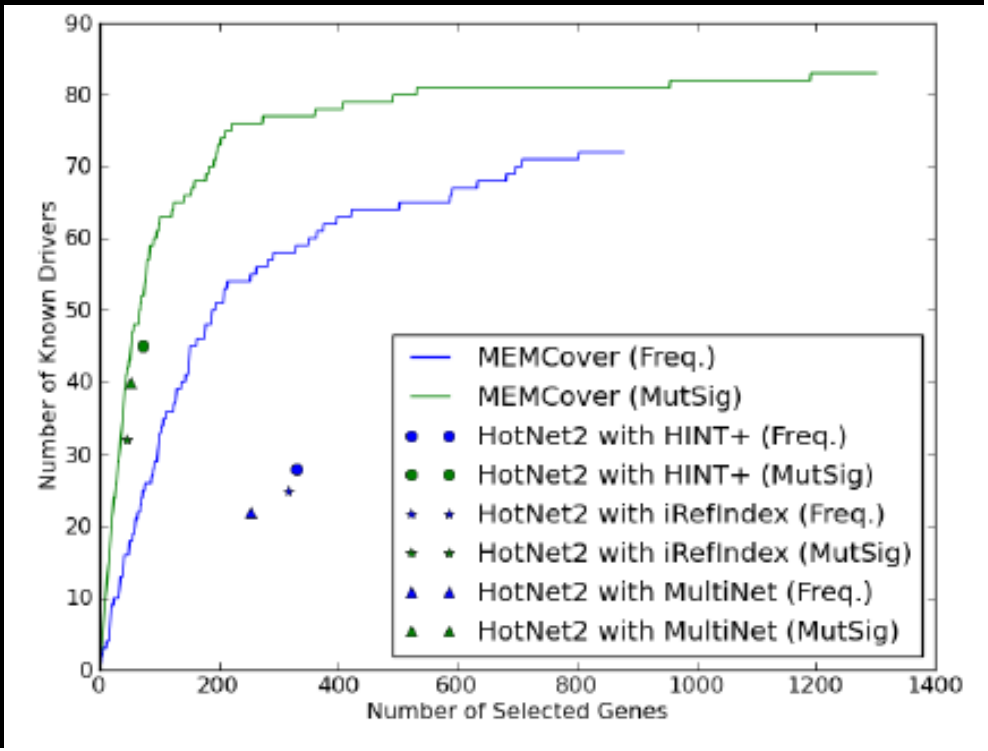
Does putting together ACROSS_ME and interaction data actually helps

MEMCover we find more cancer drivers

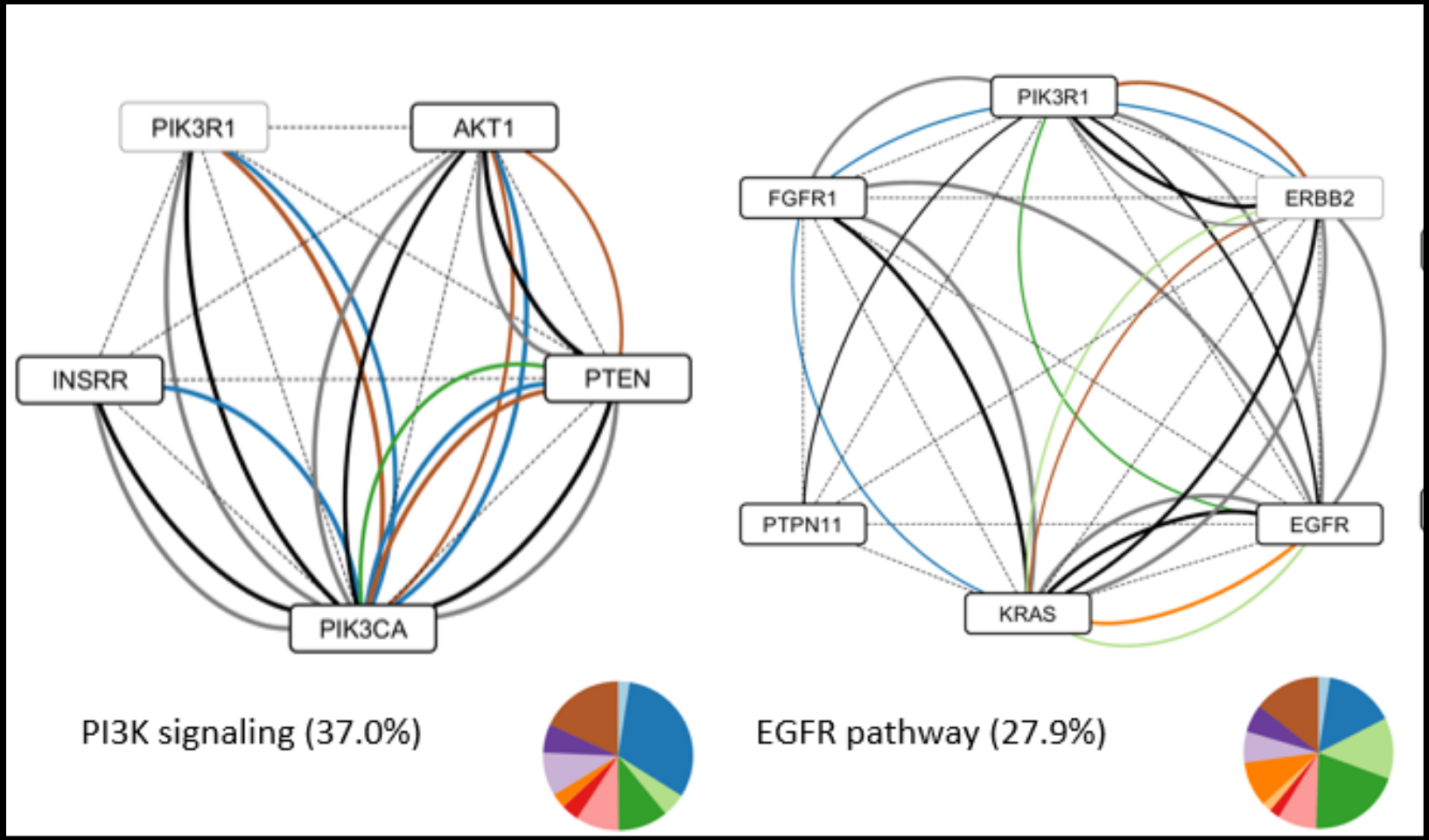
Compared to Module Cover



Compared to HotNet2

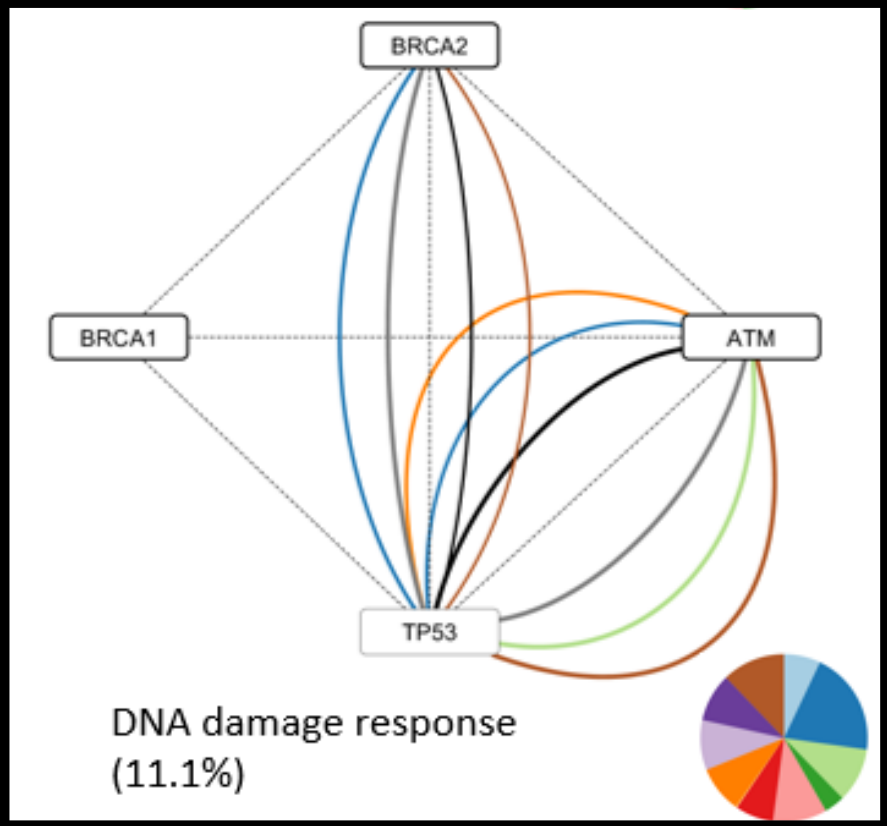


Robust mutual exclusivity within some modules

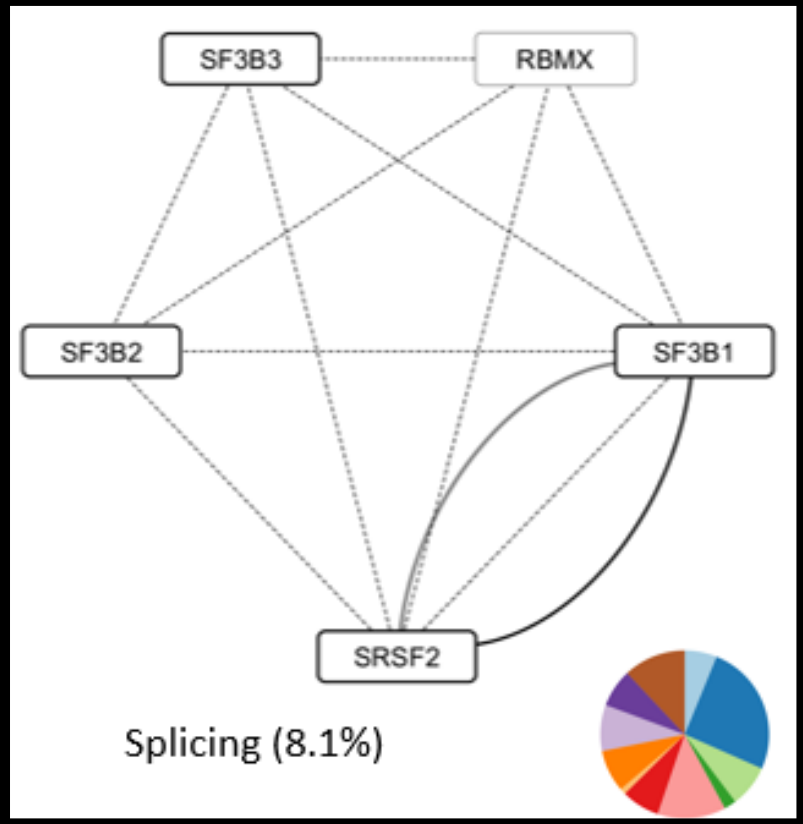


Kim et al. ISMB /Bioinformatics 2015

Hub-like ME within some modules

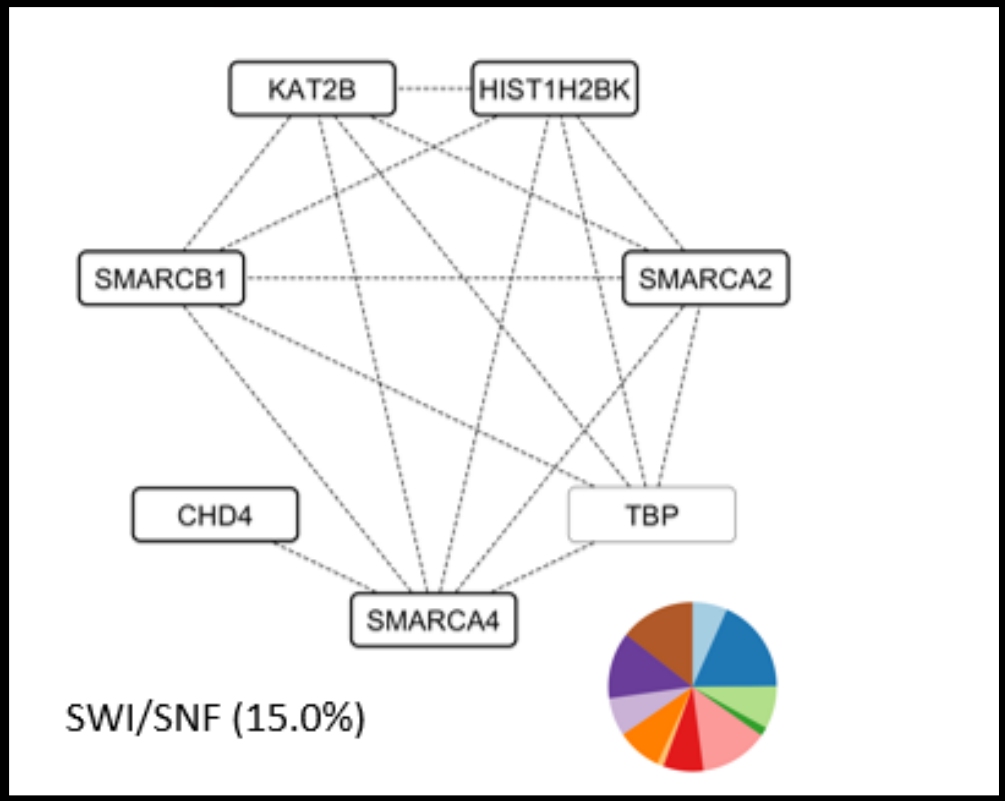


Splicing



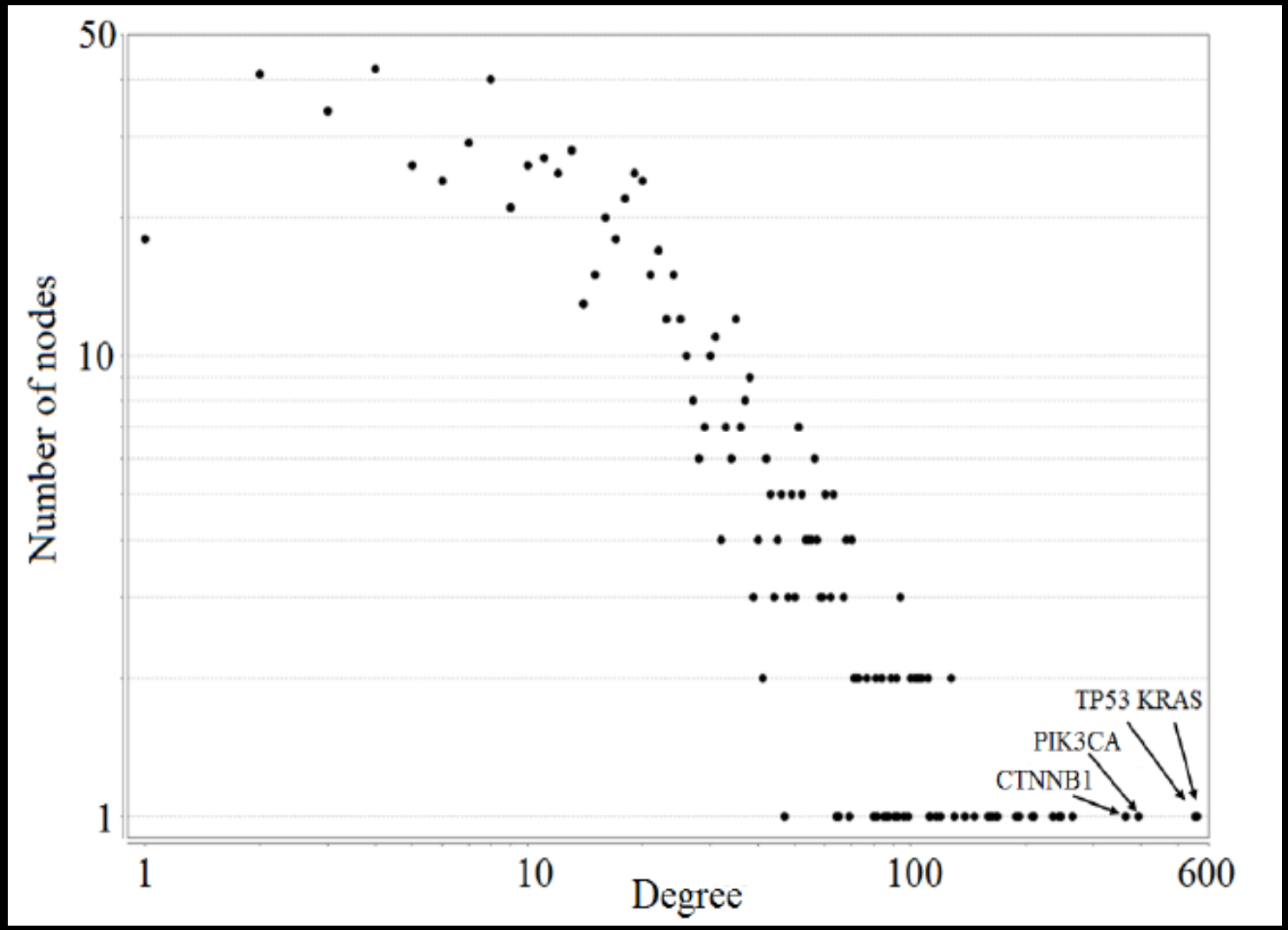
Kim et al. ISMB /Bioinformatics 2015

No ME within some modules



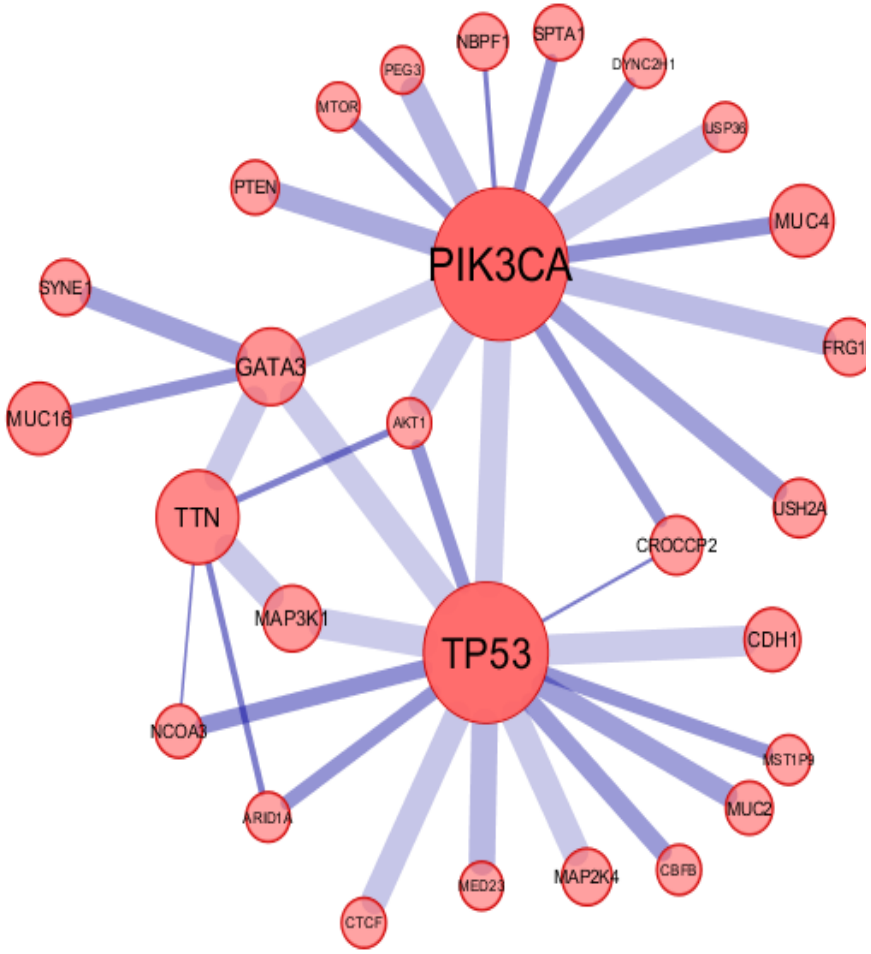
Kim et al. ISMB /Bioinformatics 2015

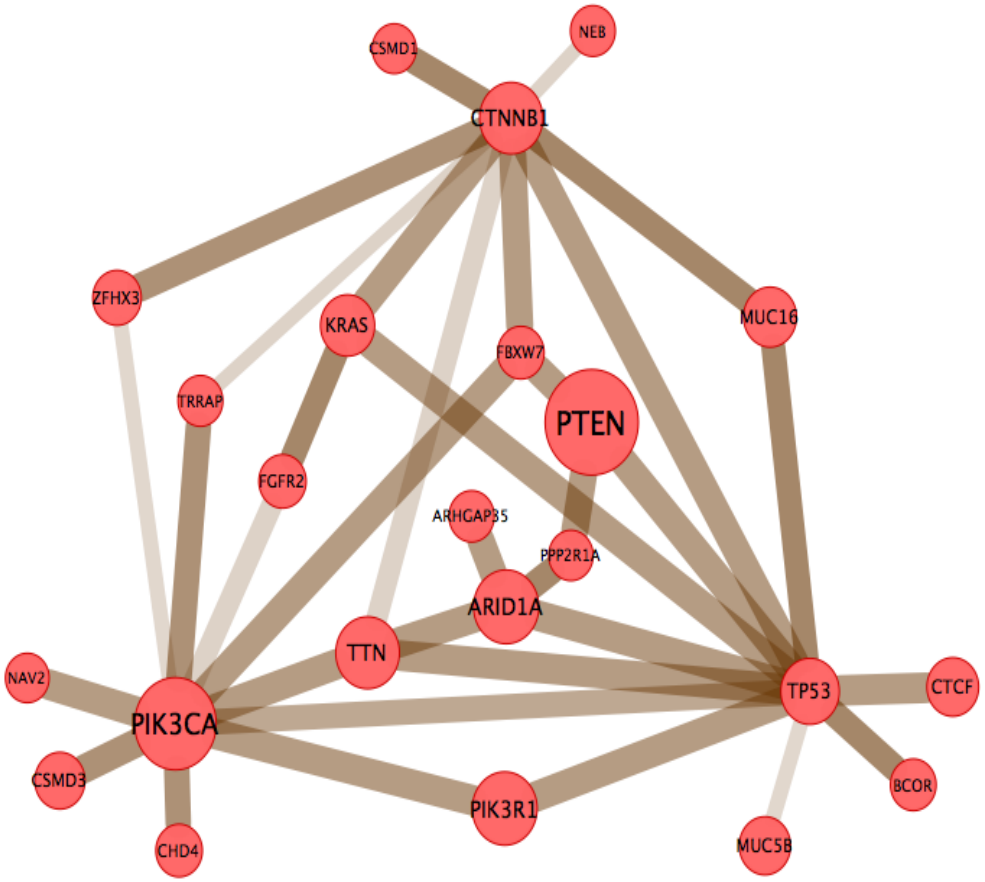
Mutual Exclusivity Hubs



Kim et al. ISMB /Bioinformatics 2015

Beyond cancer drivers



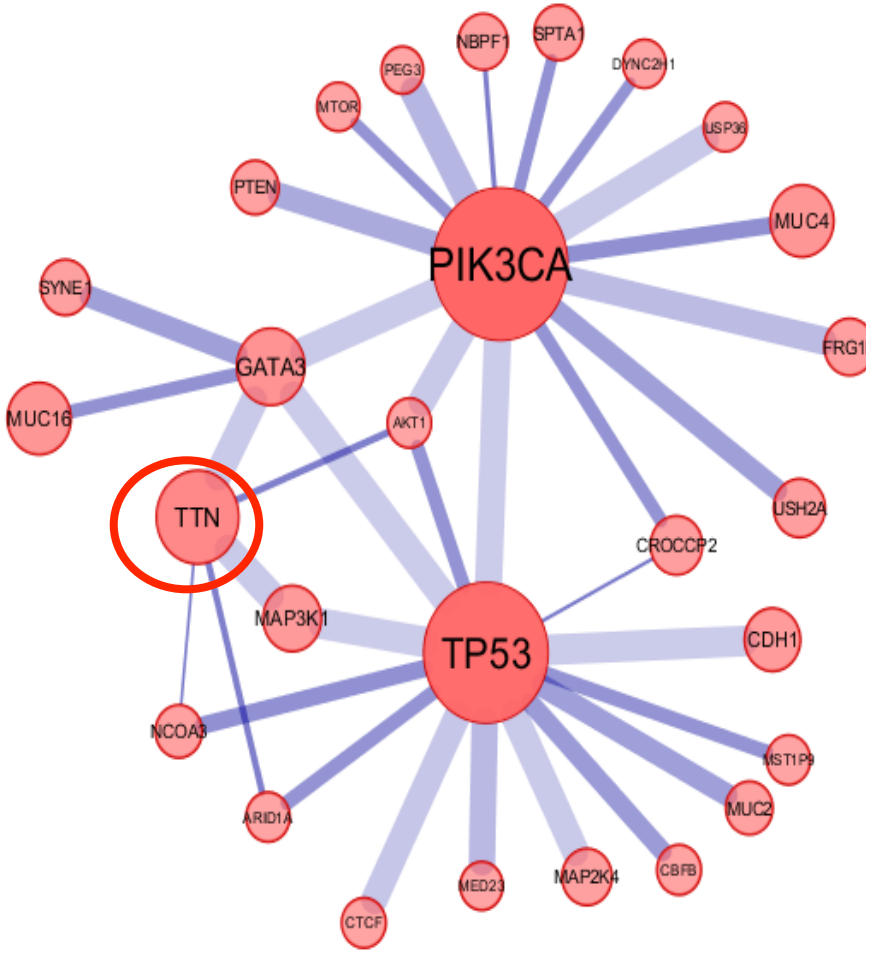


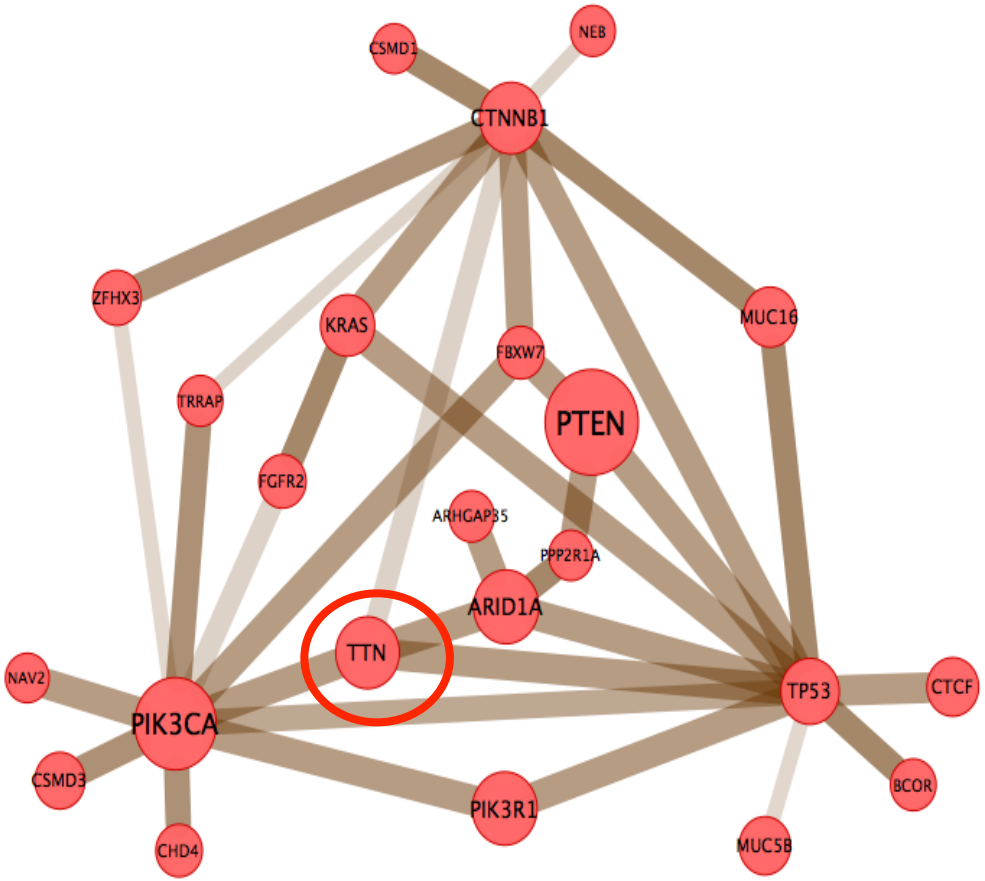
BRCA (FDR 0.0125) **UCEC (FDR 0.0025)**

(computed with our new method WeSME; width p-value; color shade FDR)

Kim et al. submitted

TTN – presumed passenger - no known role in cancer



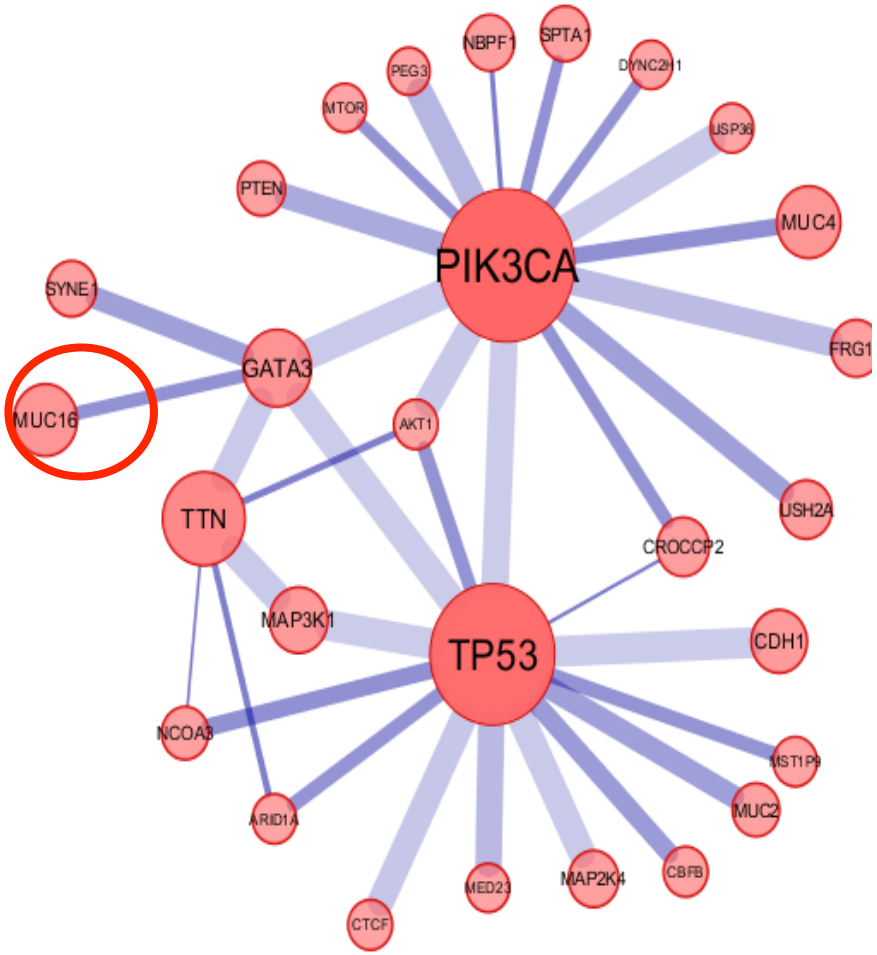


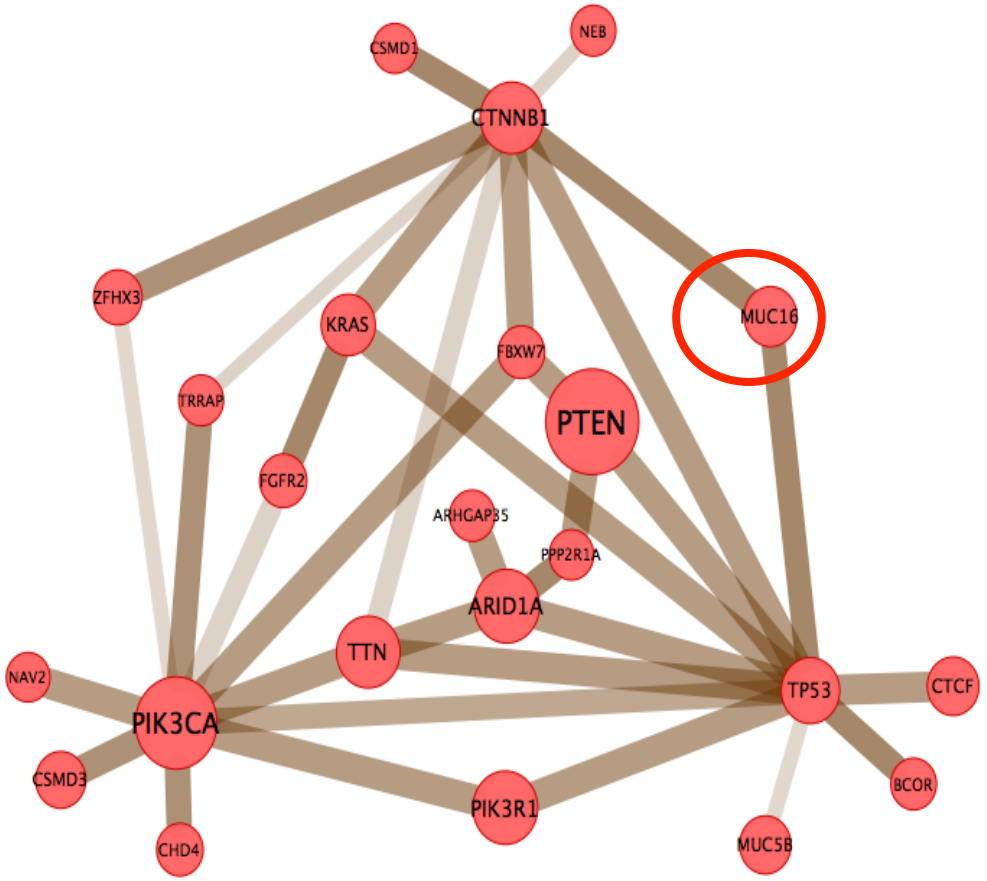
BRCA (FDR 0.0125) **UCEC (FDR 0.0025)**

(computed with our new method WeSME; width p-value; color shade FDR)

Kim et al. submitted

Presumed to be passenger mutations gene has a role in cancer



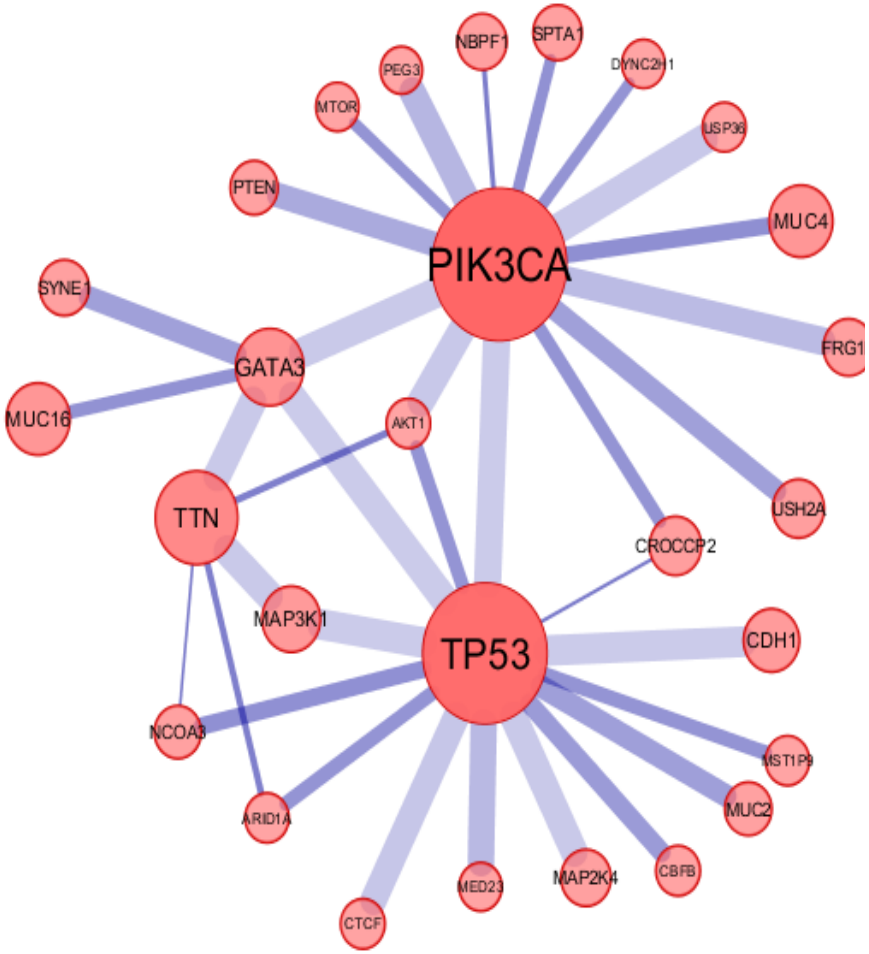


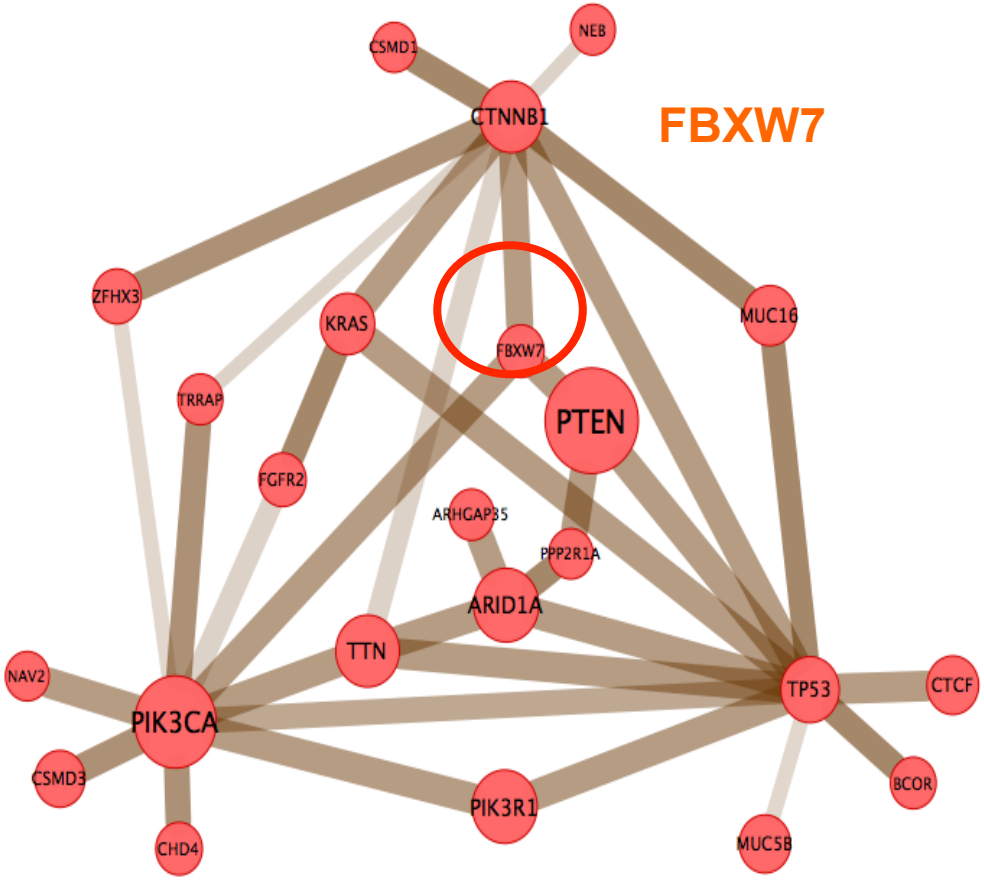
BRCA (FDR 0.0125) **UCEC (FDR 0.0025)**

(computed with our new method WeSME; width p-value; color shade FDR)

Kim et al. submitted

FBXW7 – tumor suppressor but can harbor passenger mutations



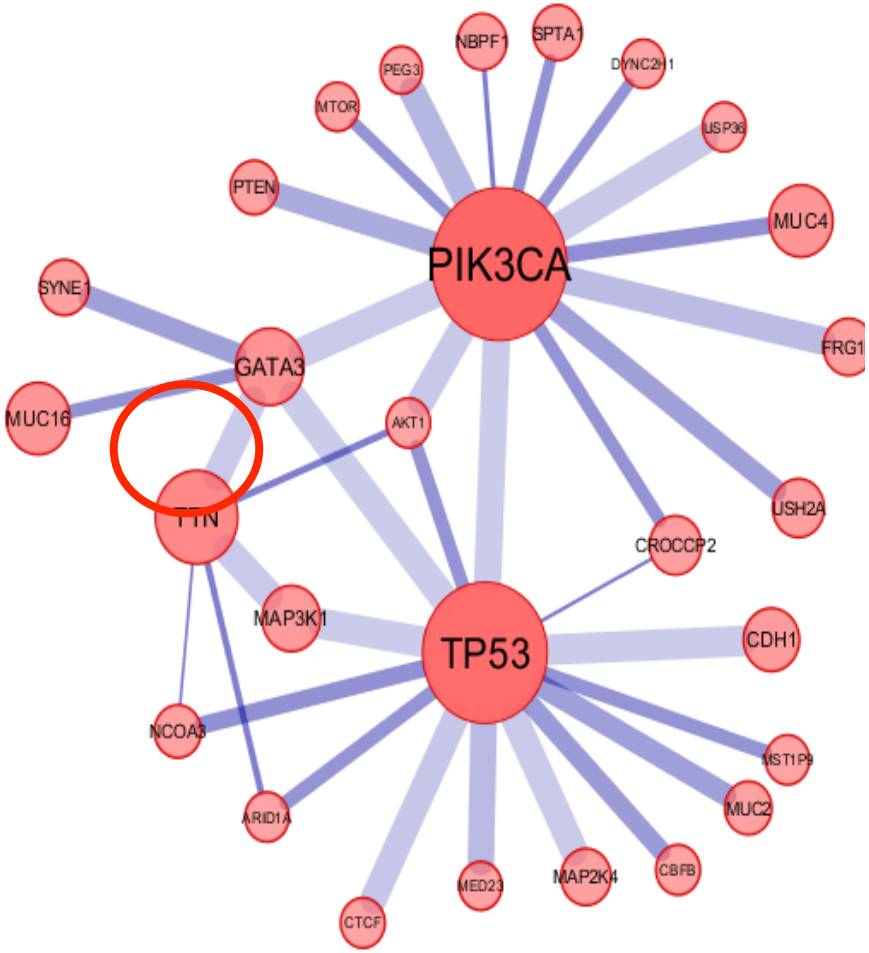


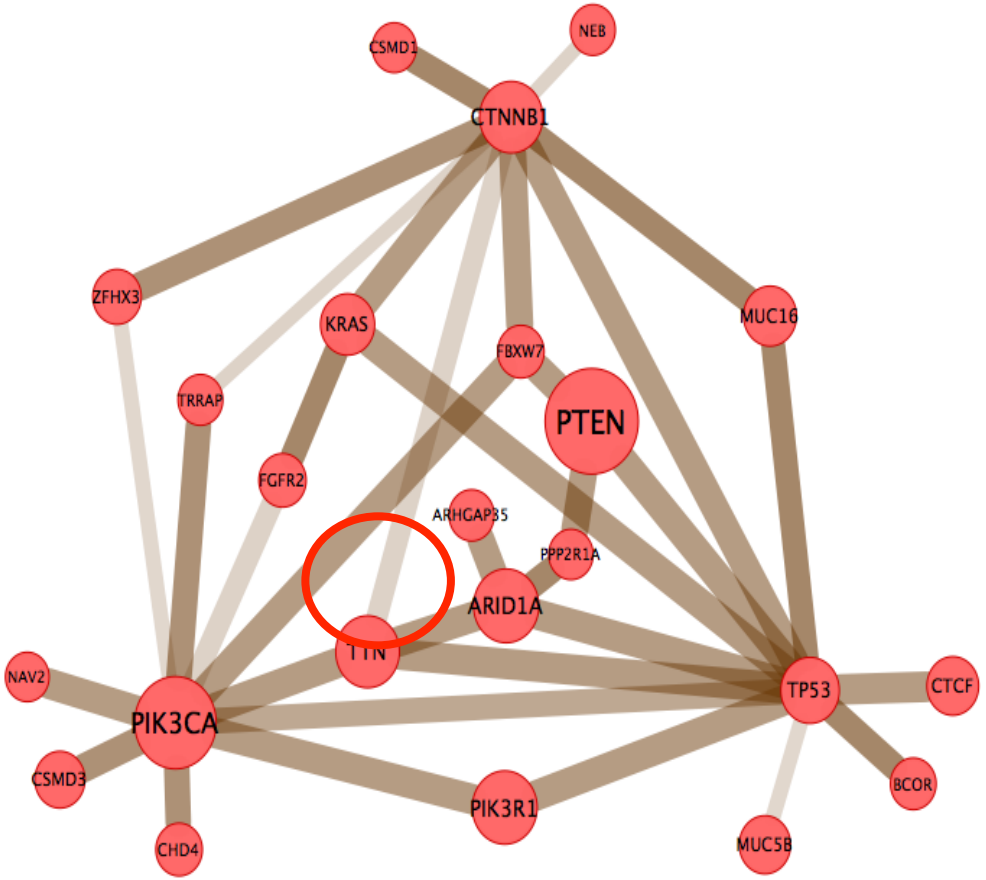
BRCA (FDR 0.0125) **UCEC (FDR 0.0025)**

(computed with our new method WeSME; width p-value; color shade FDR)

Kim et al. submitted

If TTN is a passenger that what is the train it is ridding on?





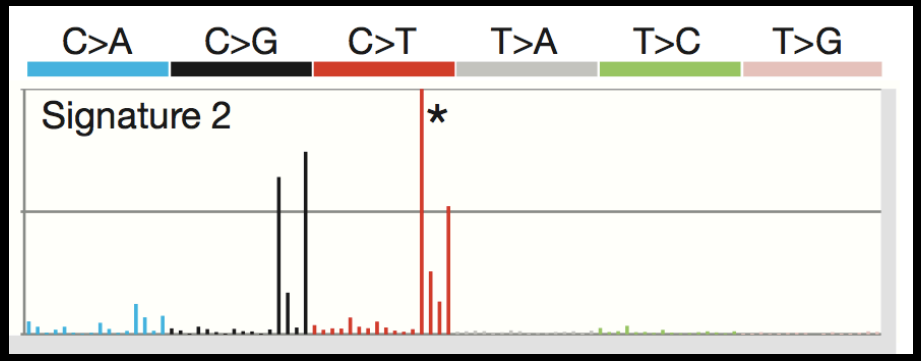
BRCA (FDR 0.0125) **UCEC (FDR 0.0025)**

(computed with our new method WeSME; width p-value; color shade FDR)

Kim et al. submitted

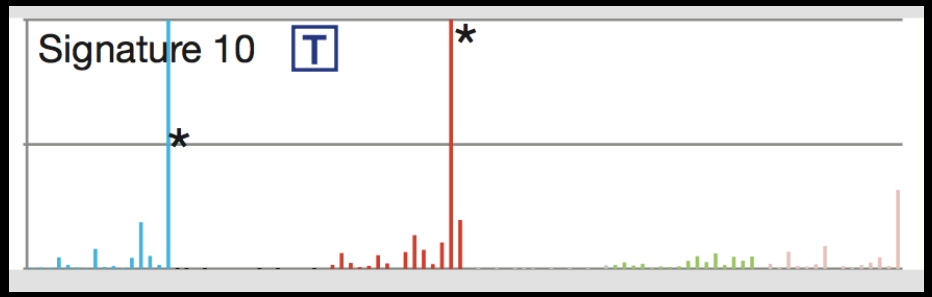
TTN carries APOBEC signature in BRCA and Pol ε signature in UCEC

From Alexandrov et al, Nature 2013



Consistent with TTN spectrum in BRCA

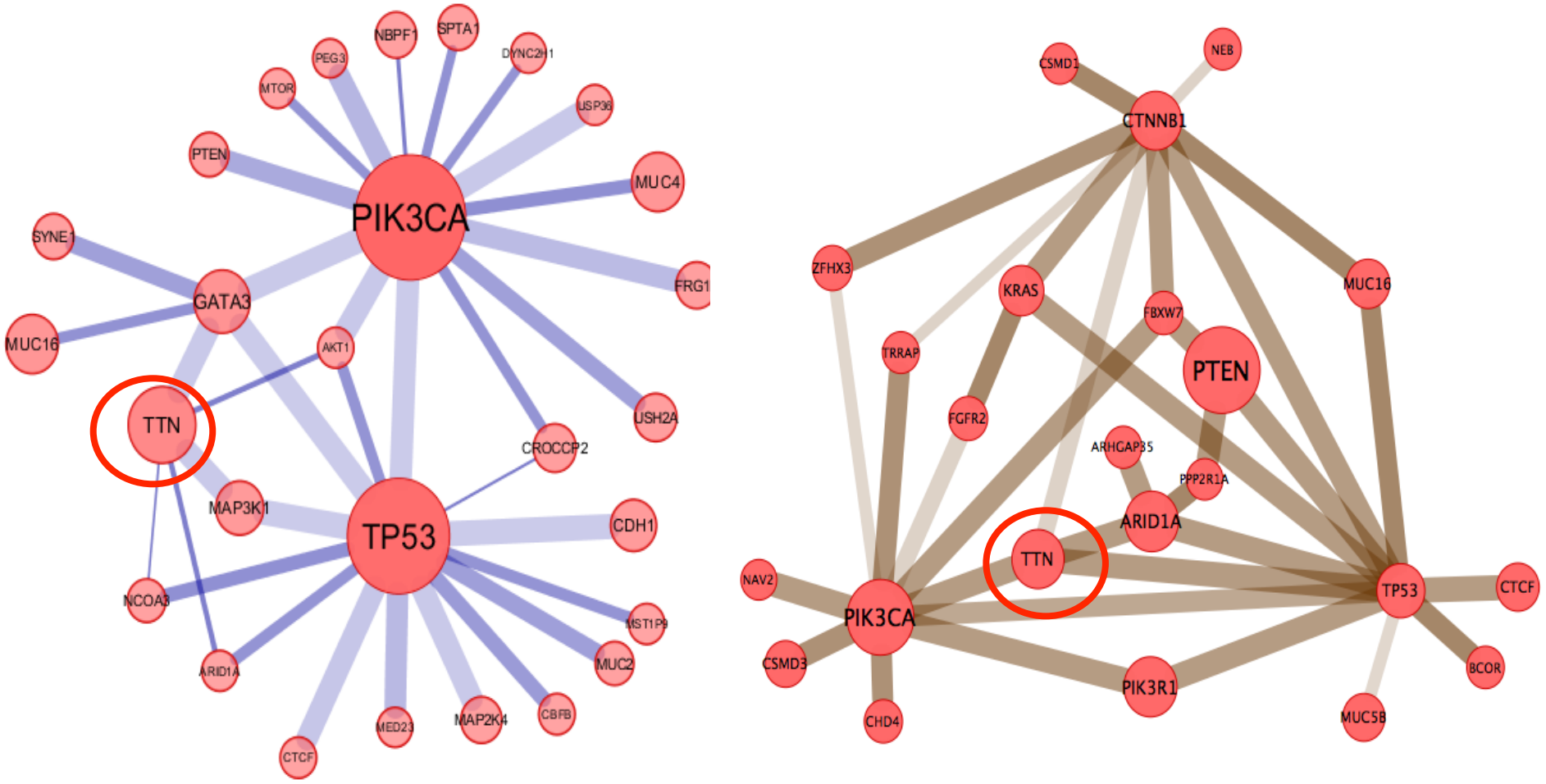
APOBEC cytidine deaminase mutational spectrum



Consistent with TTN spectrum in UCEC

Pol II ε mutation mutational spectrum

TTN and TP53 have common neighbors in BRACE

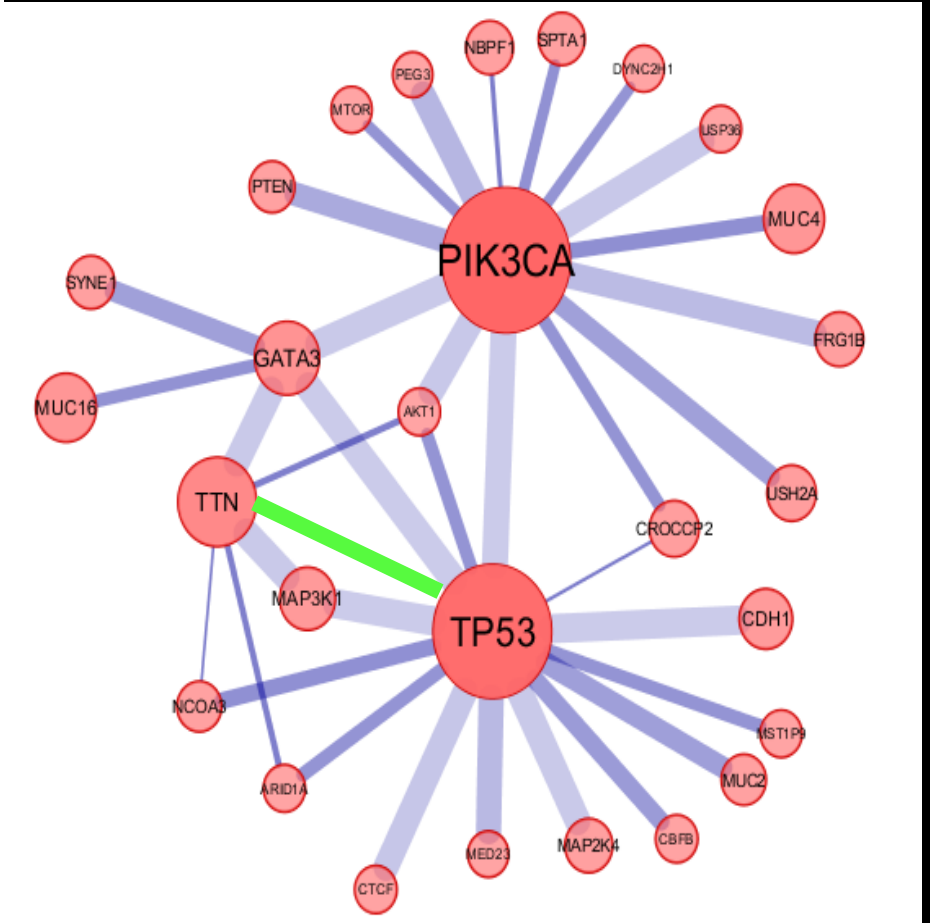


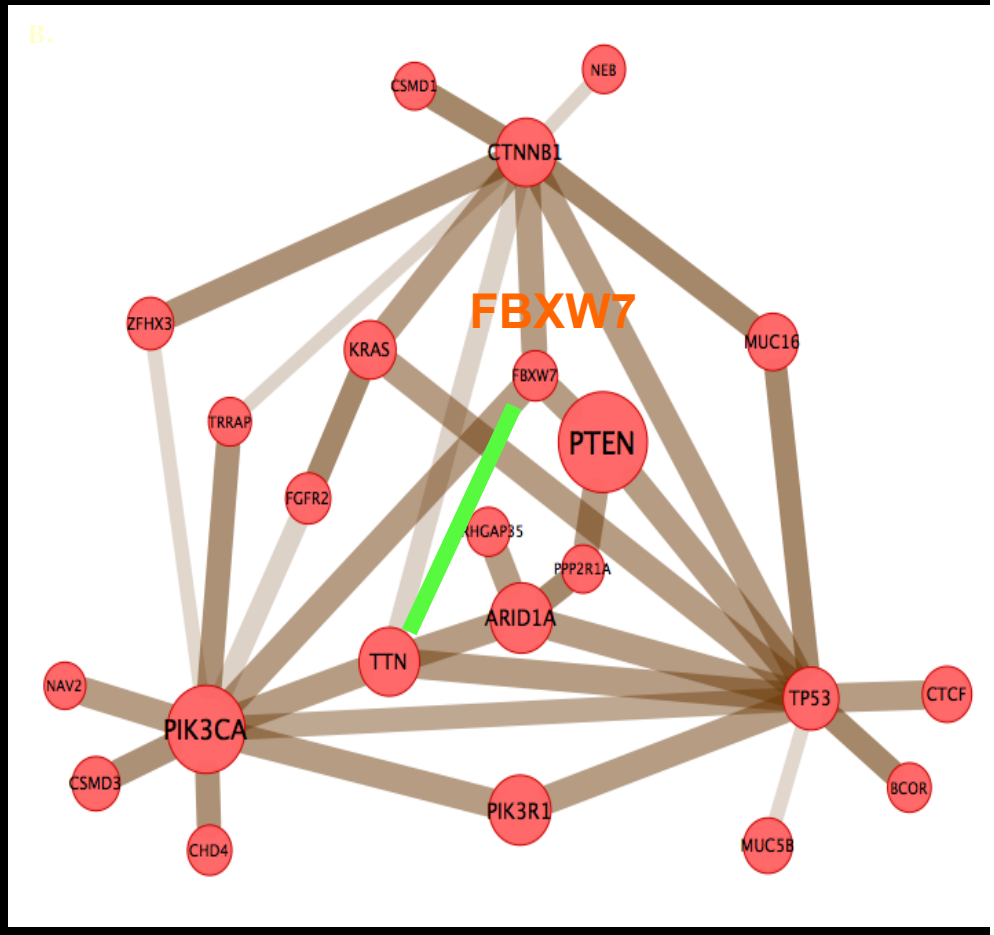
BRCA (FDR 0.0125) **UCEC (FDR 0.0025)**

(computed with our new method WeSME; width p-value; color shade FDR)

Kim et al. submitted

Co-occurrences - a causal relation or same underlying cause?





BRCA (FDR 0.0125) **UCEC (FDR 0.0025)**

(computed with our new method WeSME; width p-value; color shade FDR)

Kim et al. submitted

Can APOBEC cause TP53 mutations?

Burns *et al.*

TP53, TTN concurrence

(p-value < 0.0002, hypergeometric test).

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TP53, TTN concurrence after correcting for patients mutation frequency
p-value > 0.29

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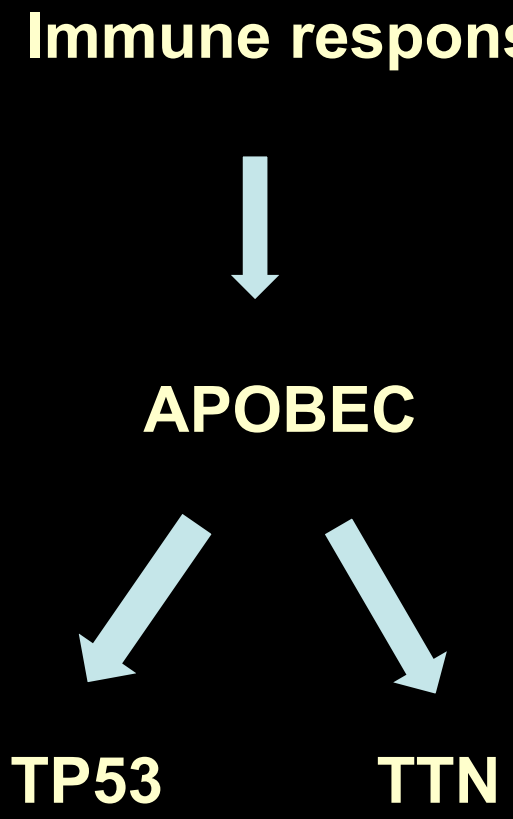
Burns *et al.*

TP53, TTN concurrence
(p-value < 0.0002, hypergeometric test).

TP53, TTN concurrence after correcting for patients mutation frequency
p-value > 0.29

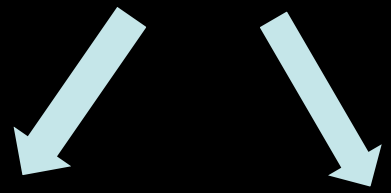


True for all TP53 mutations in BRCA?

NO

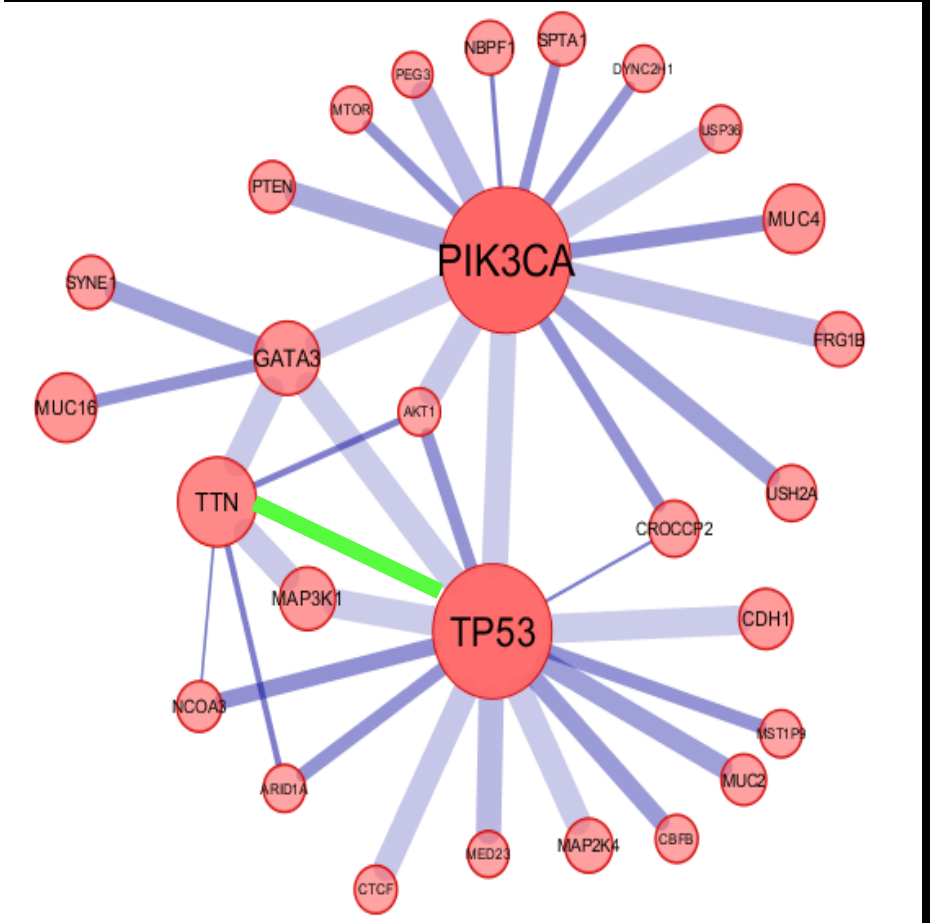
Immune response

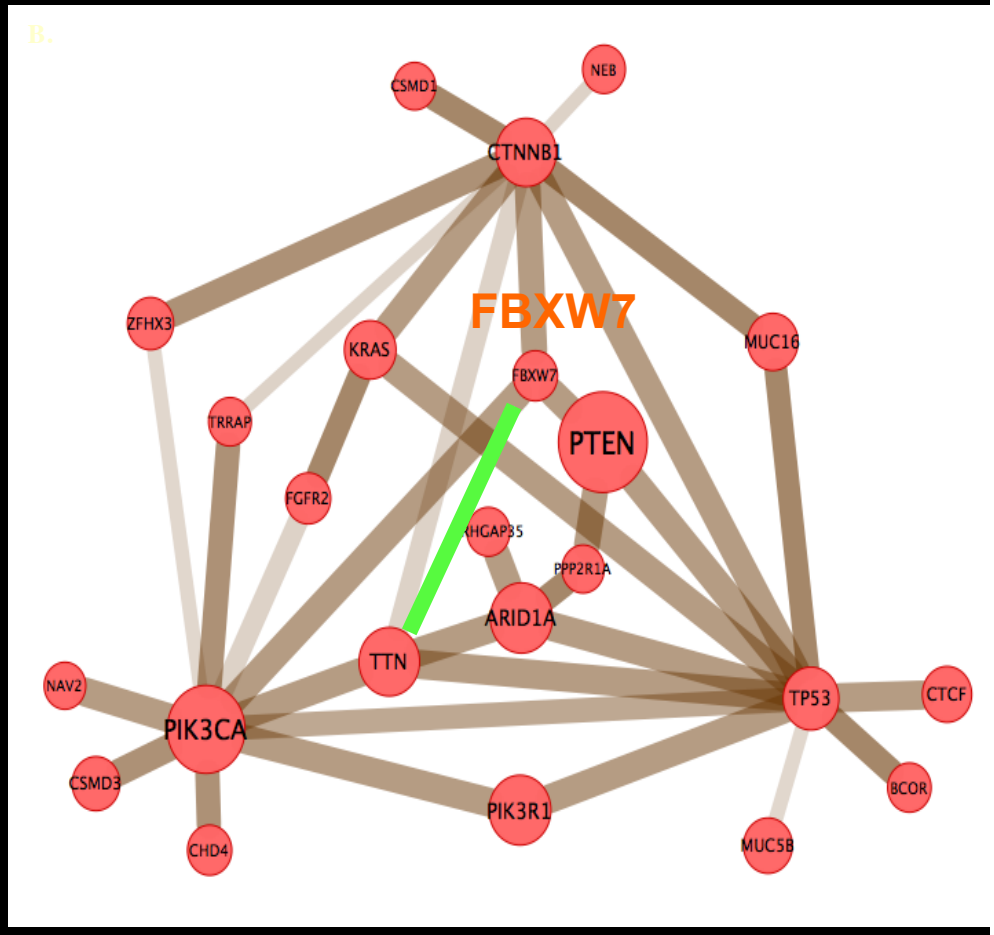
APOBEC



TP53 **TTN**

Co-occurrences - a causal relation or same underlying cause?



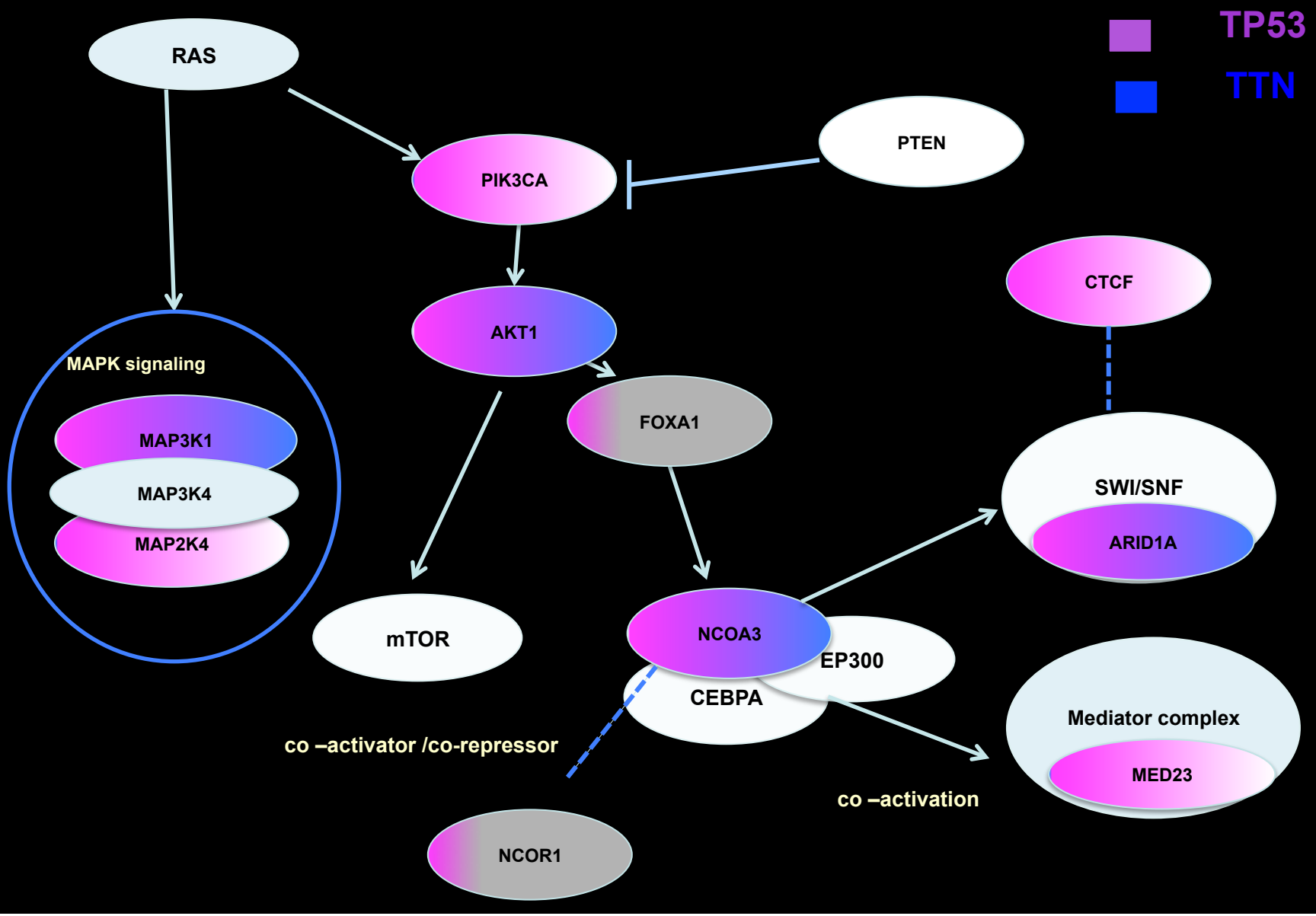


BRCA (FDR 0.0125) **UCEC (FDR 0.0025)**

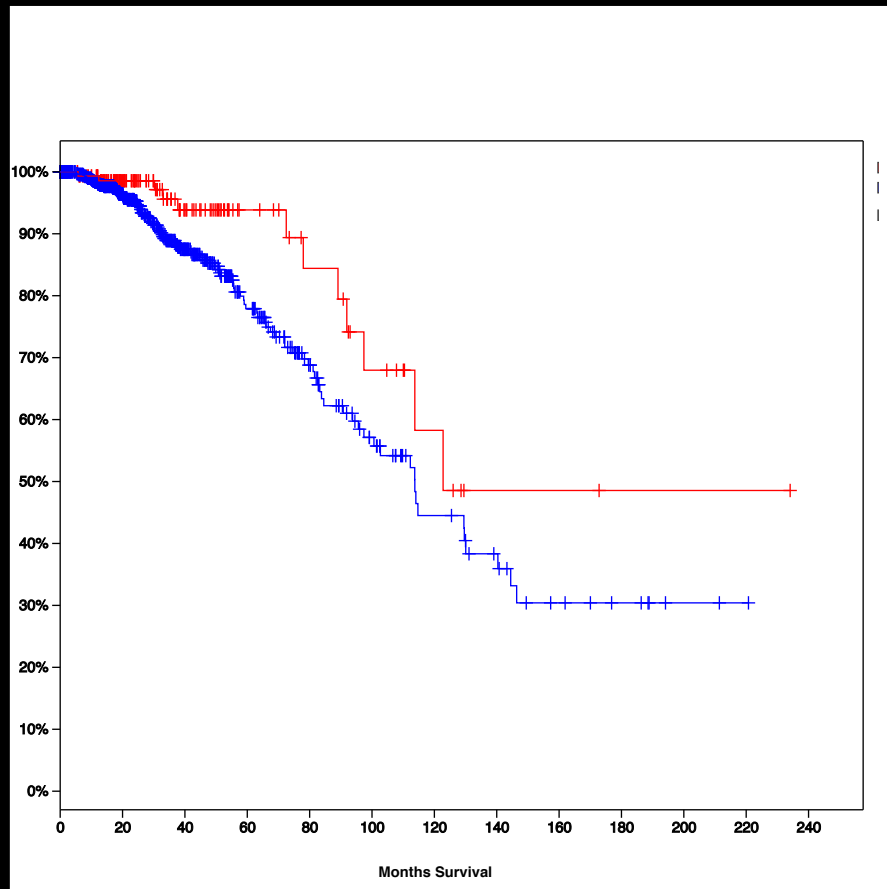
(computed with our new method WeSME; width p-value; color shade FDR)

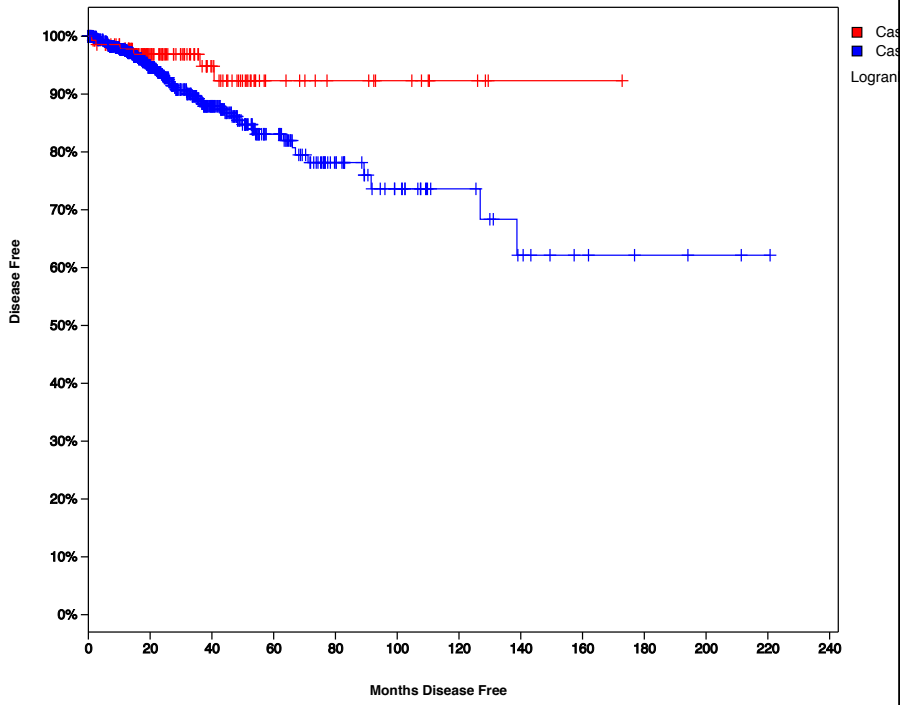
Kim et al. submitted

TTN and TP53 share exclusivity partners



Genes ME with TTN are predictors of better survival





Summary

- *Introduction of mutual exclusivity classes and their relation to interaction network*
- *Combining ME with interaction network improves identification of PanCancer dysregulated modules*
- *Mutual exclusivity and co-occurrence of passenger mutations can provide important insights into mutagenesis of cancer*

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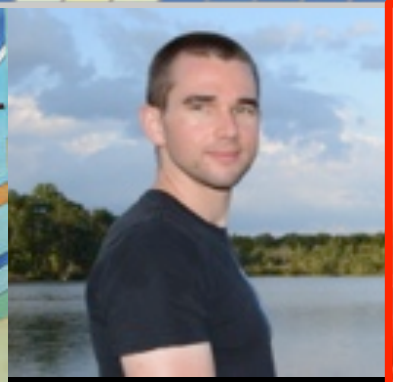
Algorithmic Methods in Computational and Systems Biology

Phung Dao



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