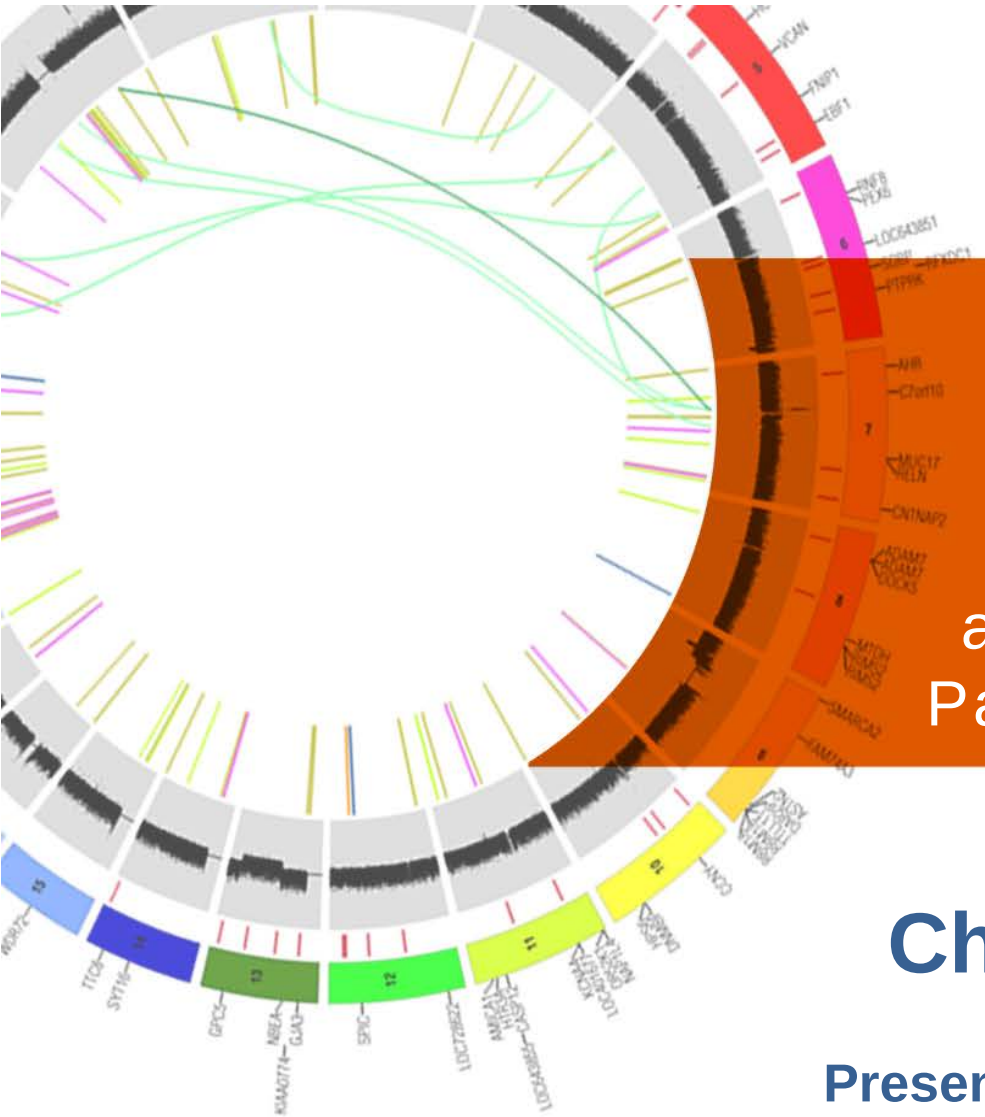

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# Domain-specific PIK3CA mutations affect different pathway activities across >3,000 TCGA Pan-Cancer-12 tumors


## Christina Yau, PhD

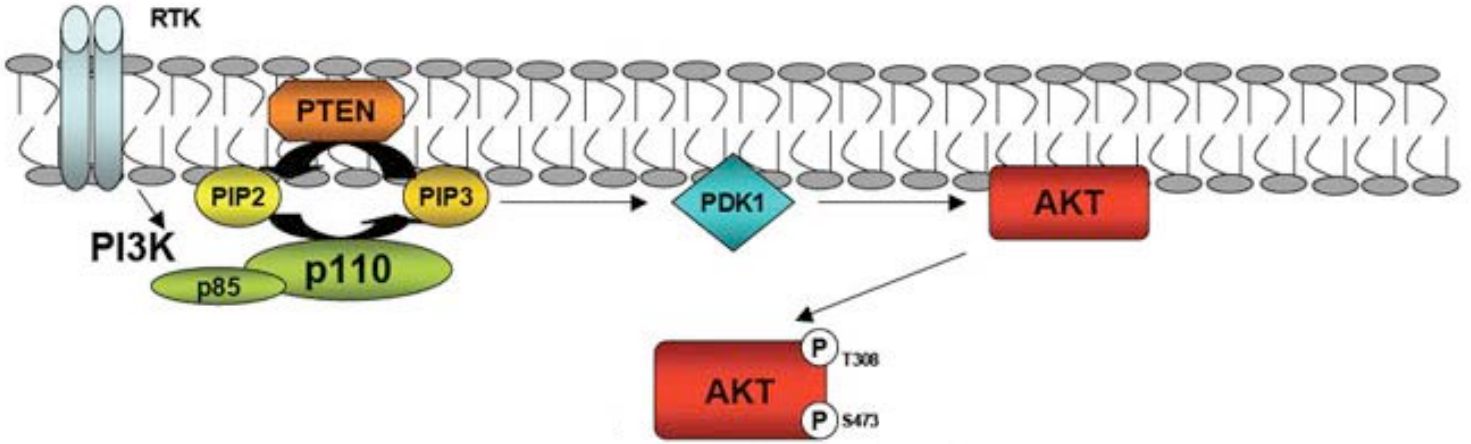
**Presented by Christopher Benz, MD**
**Buck Institute for Research on Aging**



**Pan-Can AWG (J. Stuart), *"Multi-platform analysis of 12 cancer types reveals molecular classification within and across tissues-of-origin*," accepted CELL-D-13-02496R1**

# Background

**Phosphatidylinositol 3-kinases (PI3Ks):** *3 classes, generate second messengers that control numerous cell activities*

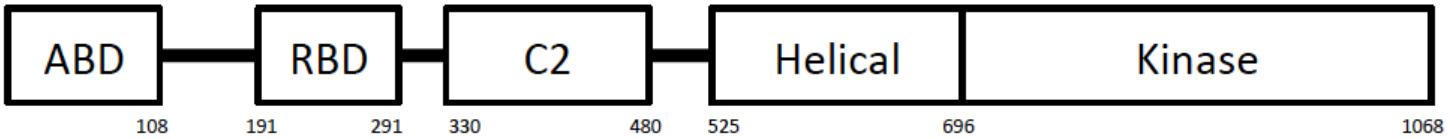



***proliferation, survival, growth, & metabolism***

**Most important in tumorigenesis: class IA heterodimeric complex**
- regulatory subunit: p85α (best studied; also p55α, p50α, p85β, p55γ)
- catalytic subunit: p110α (*PIK3CA* commonly mutated in human tumors)

# Background

**Modular protein domains encoded by *PIK3CA***

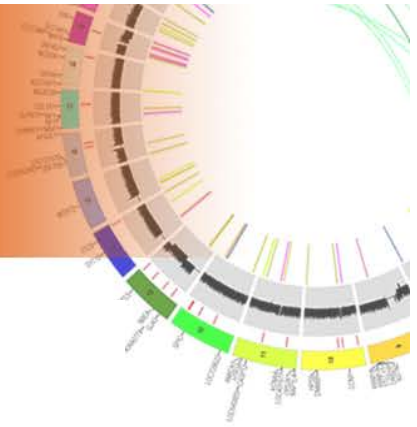



- ***PIK3CA* is frequently mutated in multiple types of cancers**
  - -- 'Hot-spot' mutations in *kinase* and *helical* domains are thought to be early and possibly initiating events in malignancies like breast cancer.
  - -- There is notable absence of mutations in Ras Binding Domain (RBD) and within conserved catalytic site of kinase domain.

- **Preclinical evidence in model systems indicates that PIK3CA mutations are activating and gain-of-function, but domain-specific mutations may have different AKT (and other pathway) activating properties and phenotypic consequences.**

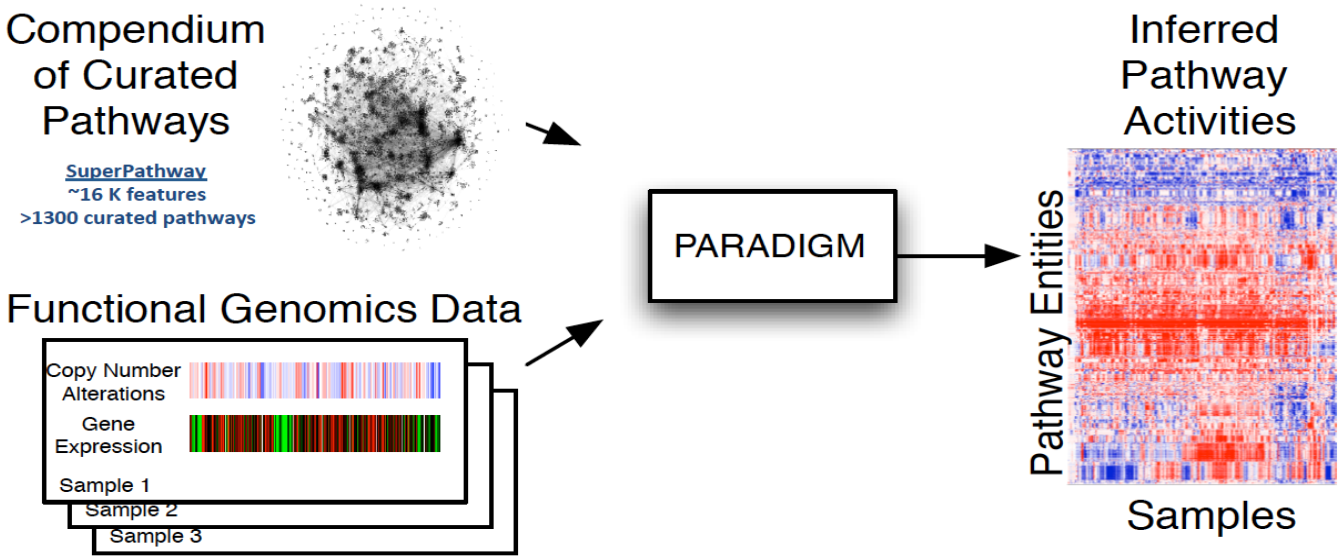
- **The TCGA Pan-Cancer dataset is big enough to offer an opportunity to ask questions about possible pathway differences linked to domain-specific PIK3CA mutations in different tumor types.**
  - Are there common domain-specific pathway activities across different tumors or are these cancer type specific?

# PARADIGM algorithm



## PARADIGM

*Infers patient-specific pathway activities from multi-dimensional cancer genomics data*




Vaske et al., Bioinformatics 26: i237-i245, 2010

**Integrates RNA gene expression and DNA copy number data onto a superimposed pathway structure to infer the activities (IPLs) of ~13K pathway features**

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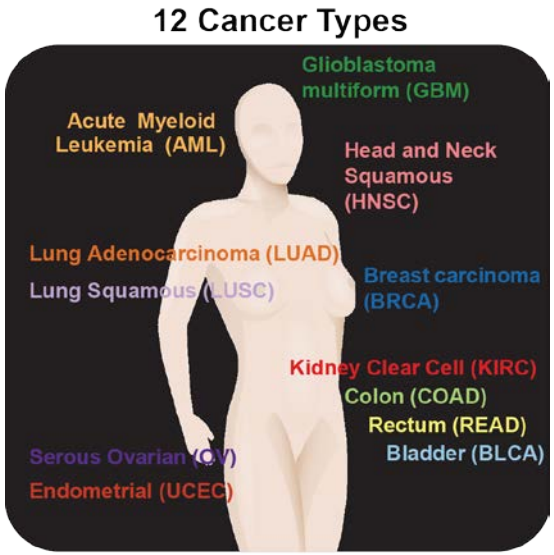
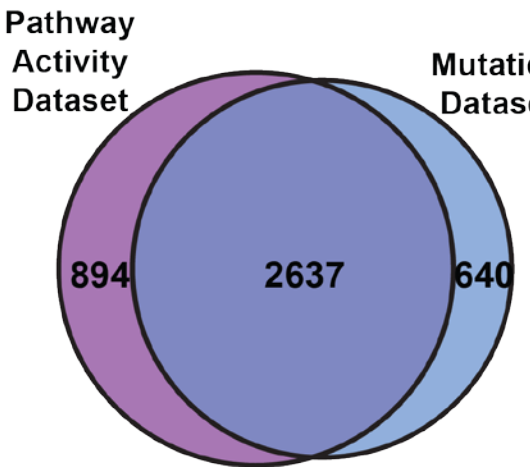
# Pan-Can-12 Dataset Characteristics

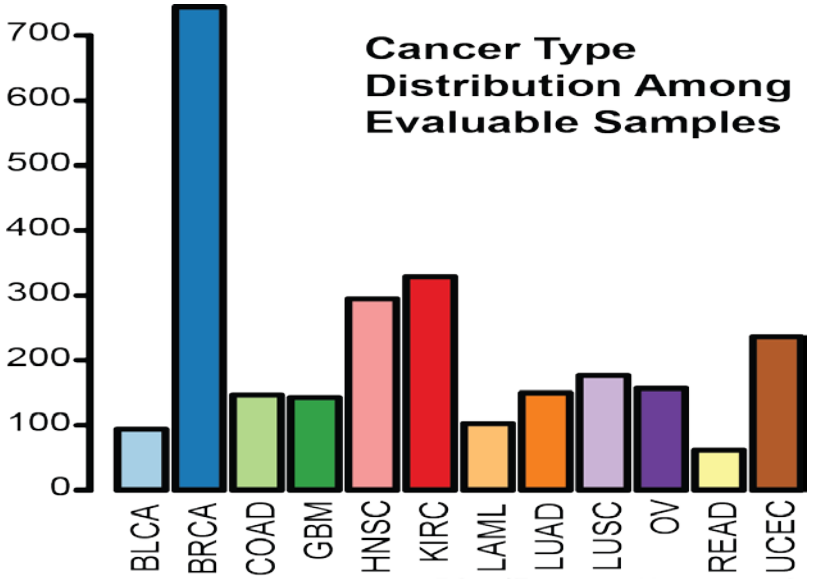



-- 3,531 samples with PARADIGM calculated integrated pathway levels (IPLs).
-- 3,277 samples with exon sequencing data.

**2,637 samples with both IPL & PIK3CA mutation data.**

**Unevenly weighted cancer type distribution in Pan-Can-12.**

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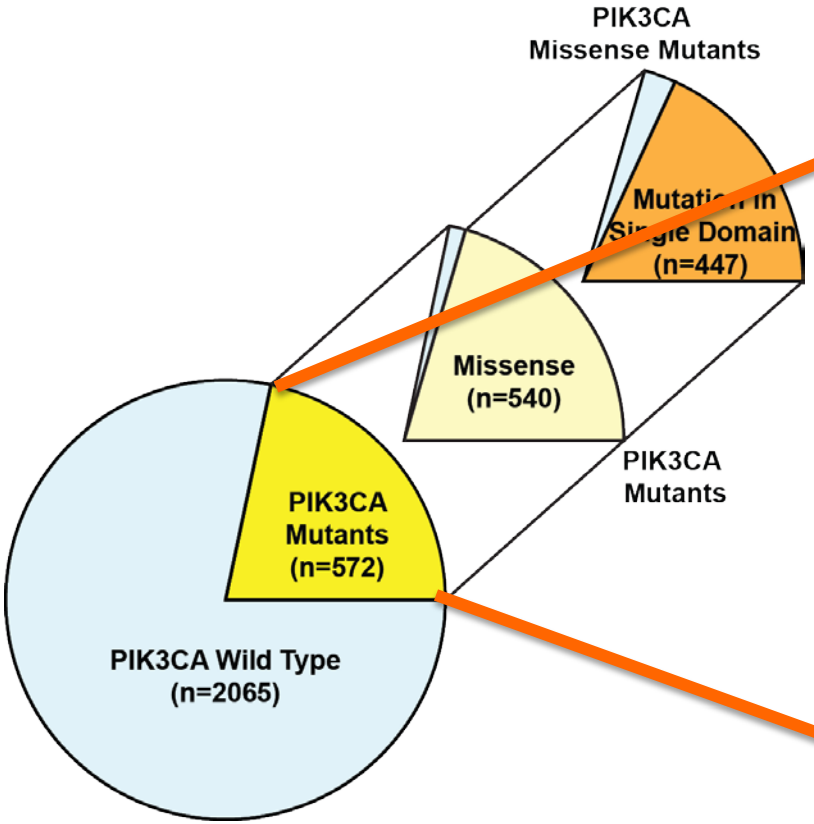
# Somatic PIK3CA mutations

**Across the evaluable Pan-Can-12 dataset:**

***PIK3CA mutation frequency = 22% (572/2637)***

***for each tumor type, varies from 0% to >50%***



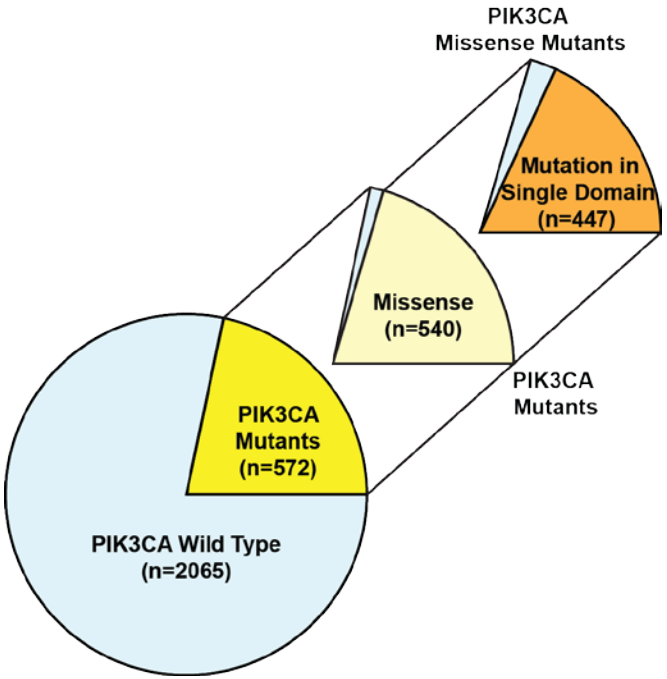

| | |
|---|---|
| Bladder (BLCA): | 20% |
| Breast (BRCA): | 35% |
| Colon (COAD): | 20% |
| Endometrial (UCEC): | 53% |
| Glioblastoma (GBM): | 8% |
| Head&Neck (HNSC): | 21% |
| Kidney (KIRC): | 3% |
| Leukemia (LAML): | 0% |
| Lung-adeno (LUAD): | 7% |
| Lung-sq cell (LUSC): | 16% |
| Ovarian (OV): | 3% |
| Rectal (READ): | 21% |

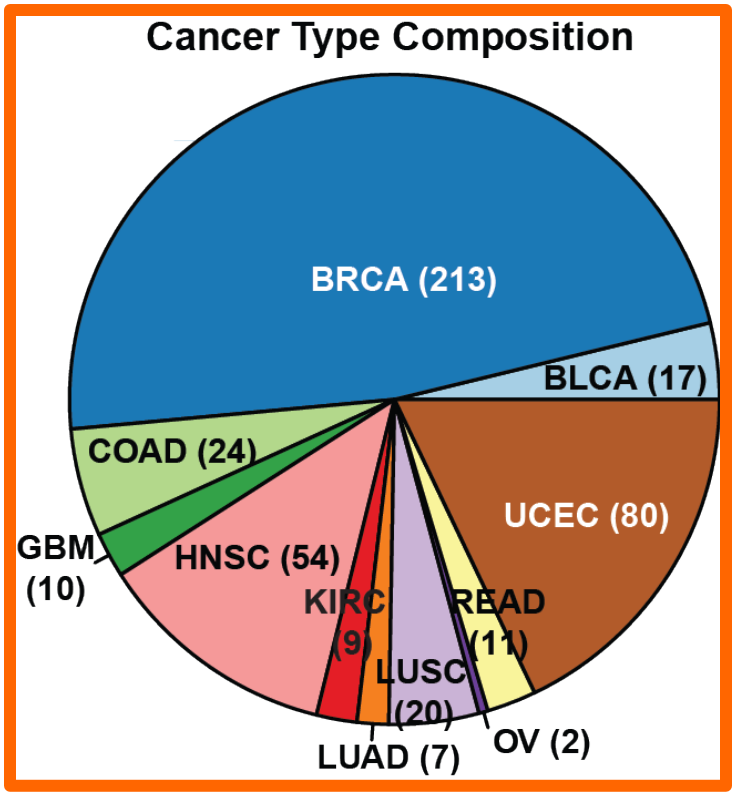
# Evaluated PIK3CA mutation cases

## Evaluable for domain-specific mutations:

***single domain, missense mutations: 447 cases***

***11 of 12 different Pan-Can tumor types***

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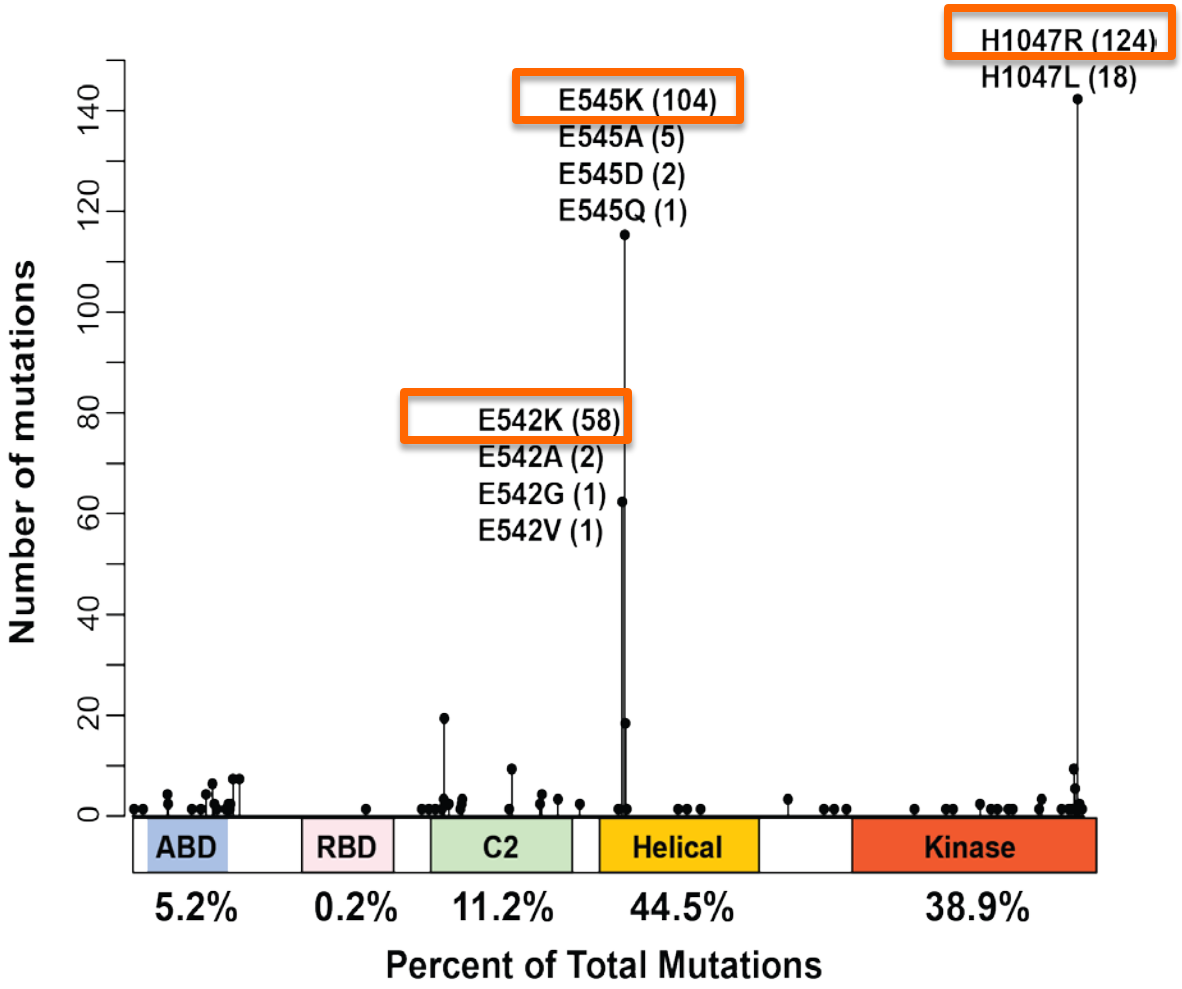
# Domain-specific PIK3CA mutations




## Domain Hot Spots:

**83% (of 447 cases) with *helical* or *kinase* domain missense mutations.**

**64% with H1047R, E545K or E542K hot spot mutations.**

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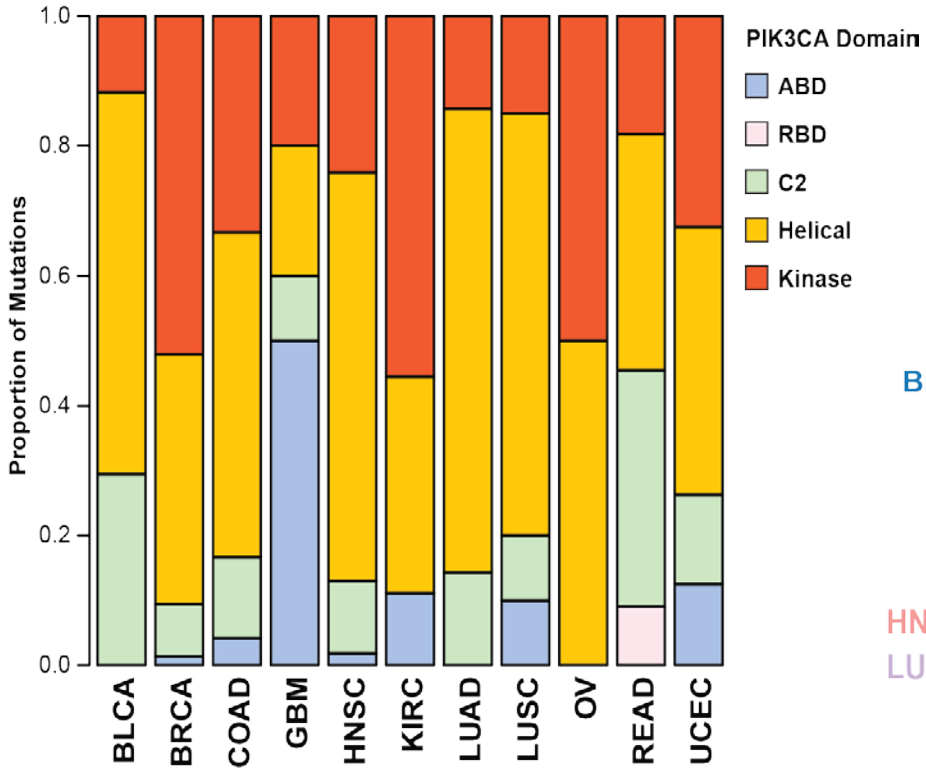
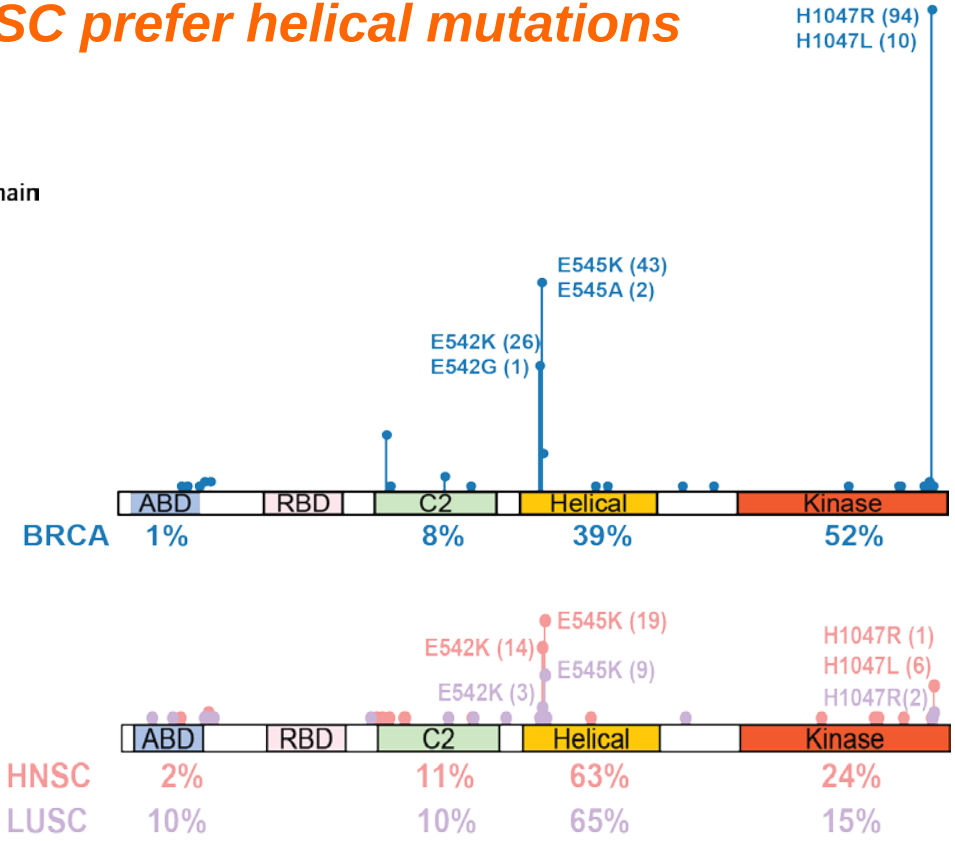
# Domain-specific PIK3CA mutations

## Domain distribution of mutations by cancer type:

***significantly different ($\chi^2$ test, $p<0.001$)***

***BRCA prefer kinase, HNSC/LUSC prefer helical mutations***

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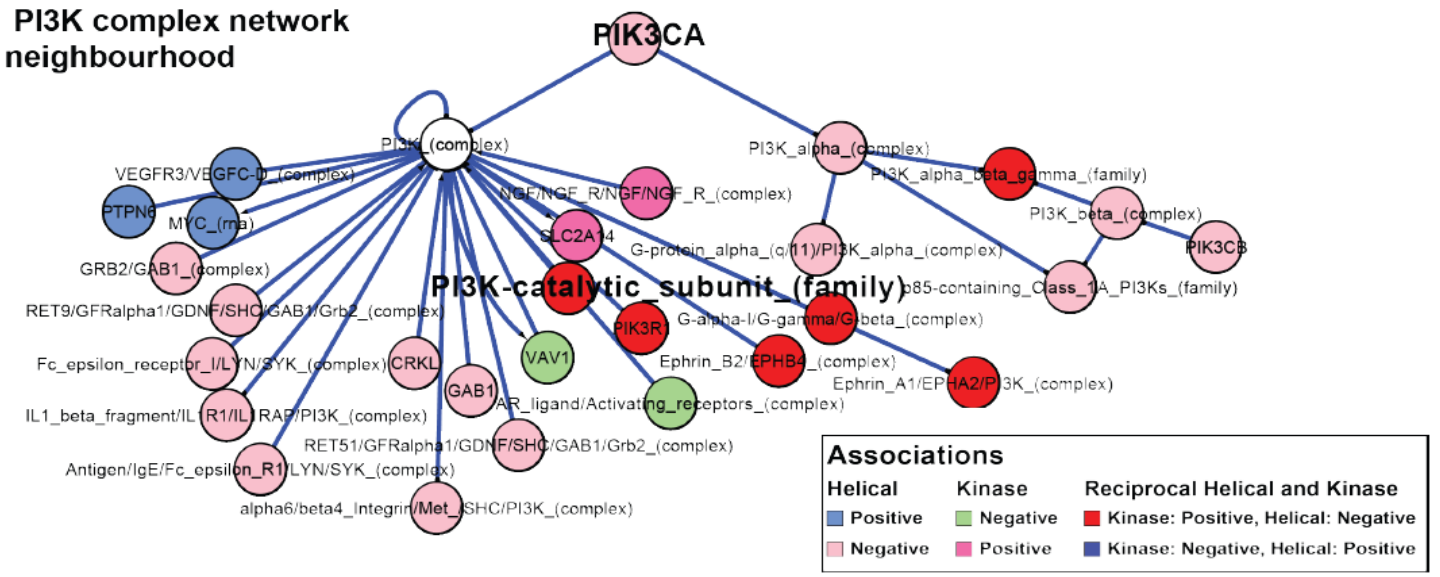
# Differential Pathway Activation

## Pathway analysis of domain-specific PARADIGM IPLs

- Identify significant IPLs for single domain mutations (vs. all others) by logistic regression, *adjusting for cancer type (Wald test p<0.05)*.
- Kinase domain = 711 IPLs, helical domain = 1,115 IPLs; unique IPL features = 1,521.
- Determine enriched pathways among significant IPLs (FDR corrected EASE score <0.05).
- Visualize by Cytoscape.




**Consistent with preclinical evidence:** *kinase domain mutations most strongly associate with superpathway hub showing PI3K catalytic subunit activation. (This hub is negatively associated with helical domain mutations.)*

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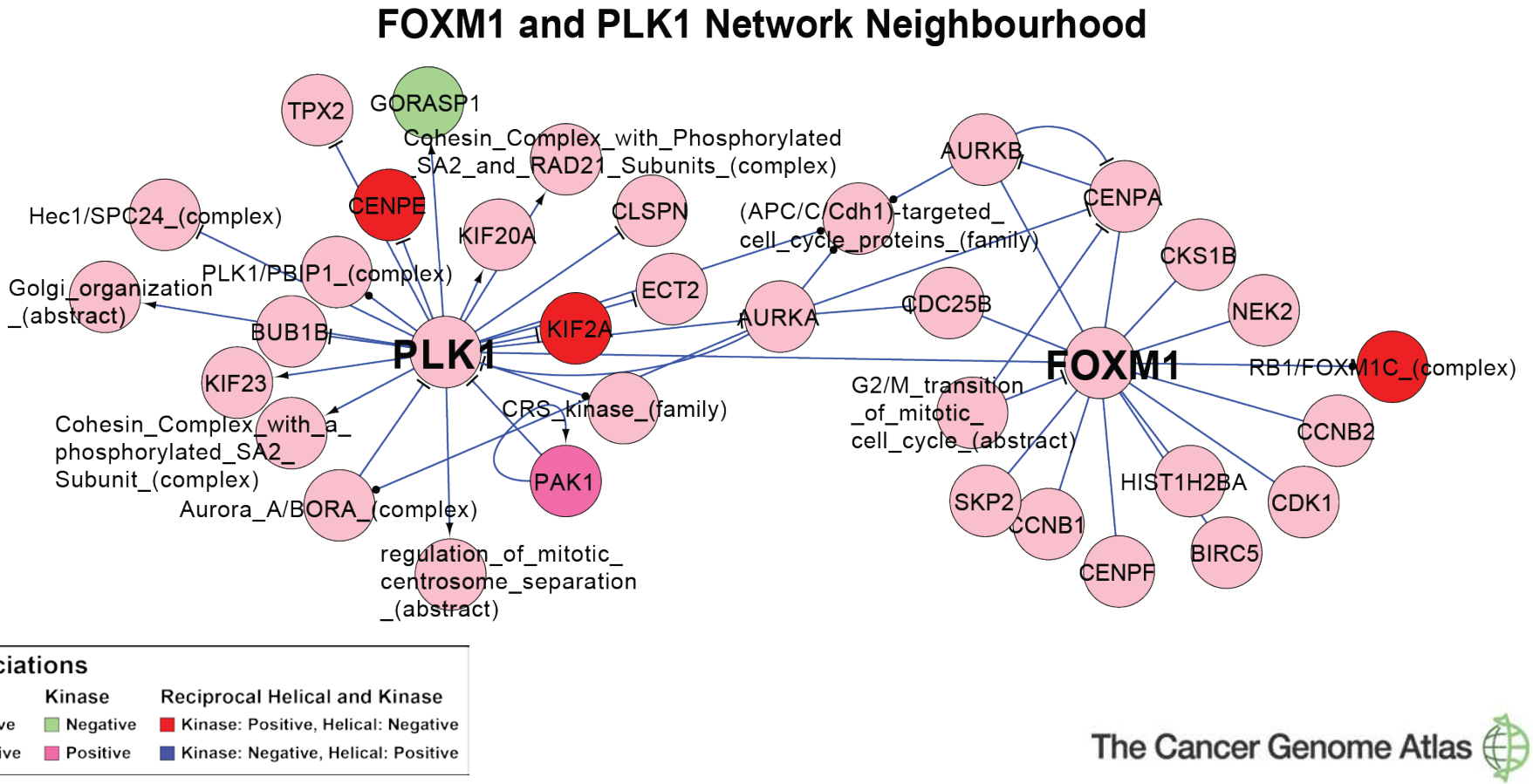
# Differential Pathway Activation

***Cell cycle and proliferation activities (e.g. PLK1, FOXM1) are most strongly associated with kinase domain mutations.***
*(These are also negatively associated with helical domain mutations.)*

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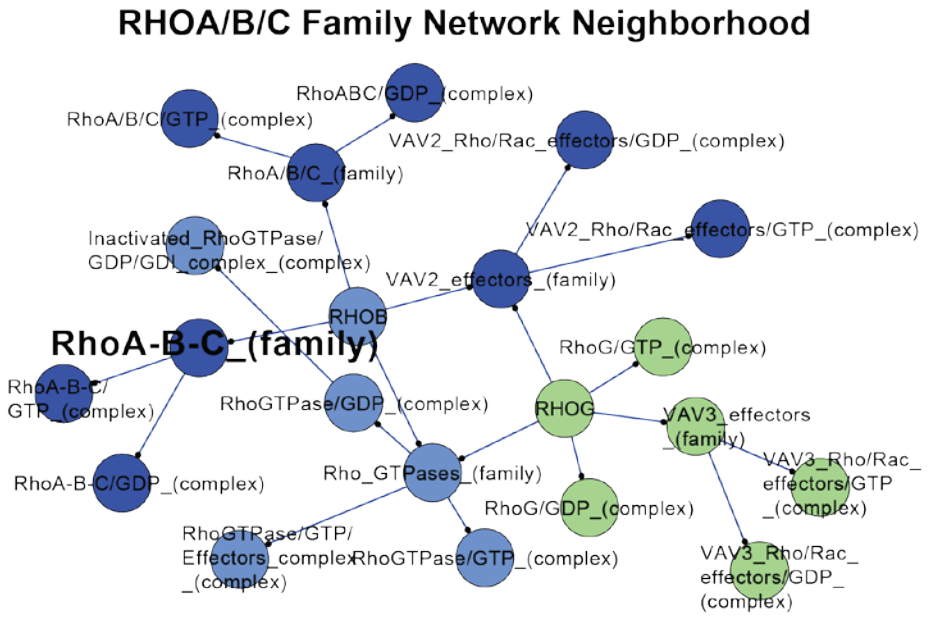
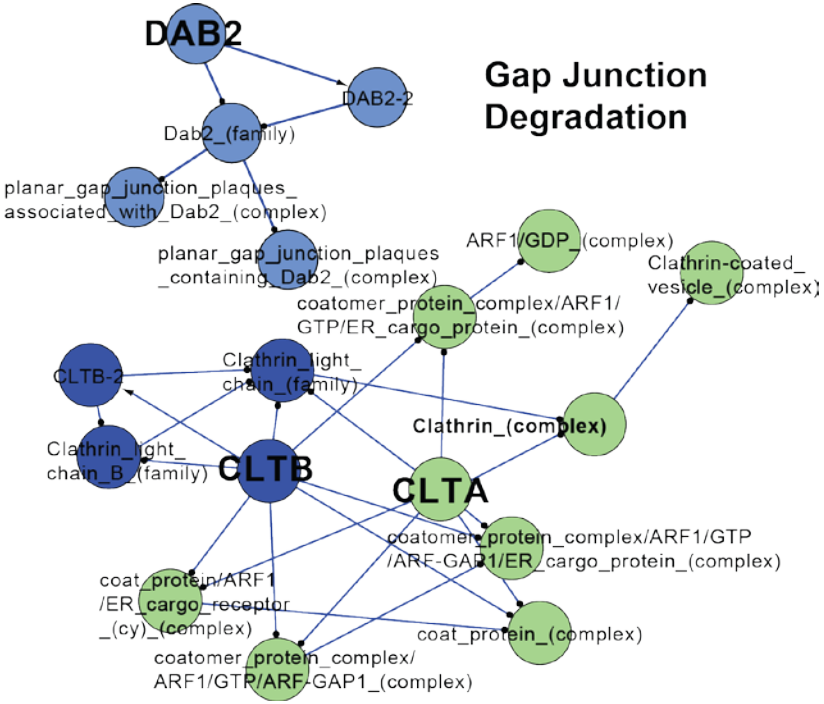
# Differential Pathway Activation

***Cell motility and disassociation activities (e.g. RHO GTPases, Gap junction degradation) are enriched and strongly associated with helical domain mutations.*** *(These are negatively associated with kinase domain mutations.)*




**Associations**

| Helical | Kinase | Reciprocal Helical and Kinase |
|---|---|---|
| Positive | Negative | Kinase: Positive, Helical: Negative |
| Negative | Positive | Kinase: Negative, Helical: Positive |

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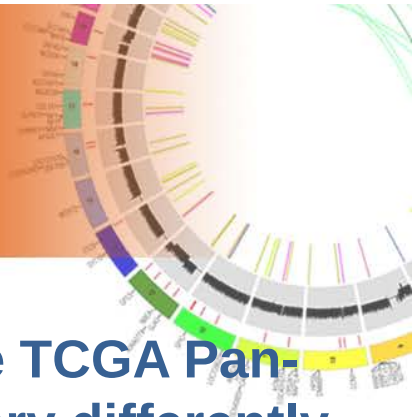
# Conclusions



- Although common across different cancer types in the TCGA Pan-Can dataset, missense PIK3CA mutations distribute very differently with respect to total mutation frequency and domain specificity (e.g. BRCA >50%, HNSC/LUSC <25% kinase mutants).
- Kinase domain mutations appear to be linked more strongly with pathway features (e.g. FOXM1, PLK1) enabling cell proliferation, while helical domain mutations are linked more strongly with features enabling cell migration & dissemination (e.g. RHO GTPases).
- Functional studies are needed to confirm these findings including the suggestion that breast cancers preferentially mutate PIK3CA to drive cell proliferation while lung and head-and-neck squamous cancers prefer helical domain mutations to drive their malignant cell motility.
- Additional comparisons are needed to identify potential tumor type-specific (context dependent) differences between kinase and helical domain pathway preferences.

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# UCSC-Buck Institute GDAC

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- Ted Goldstein

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- Christina Yau

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**Five3 Genomics**

- Steve Benz
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