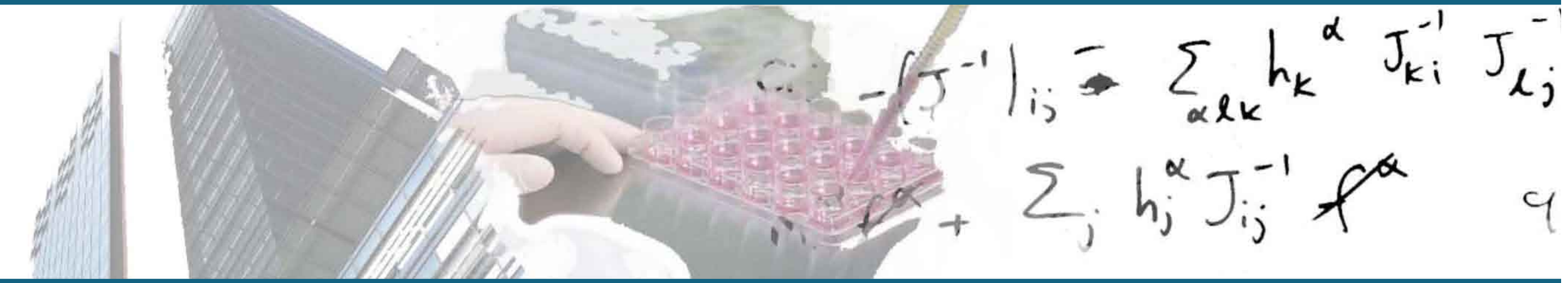
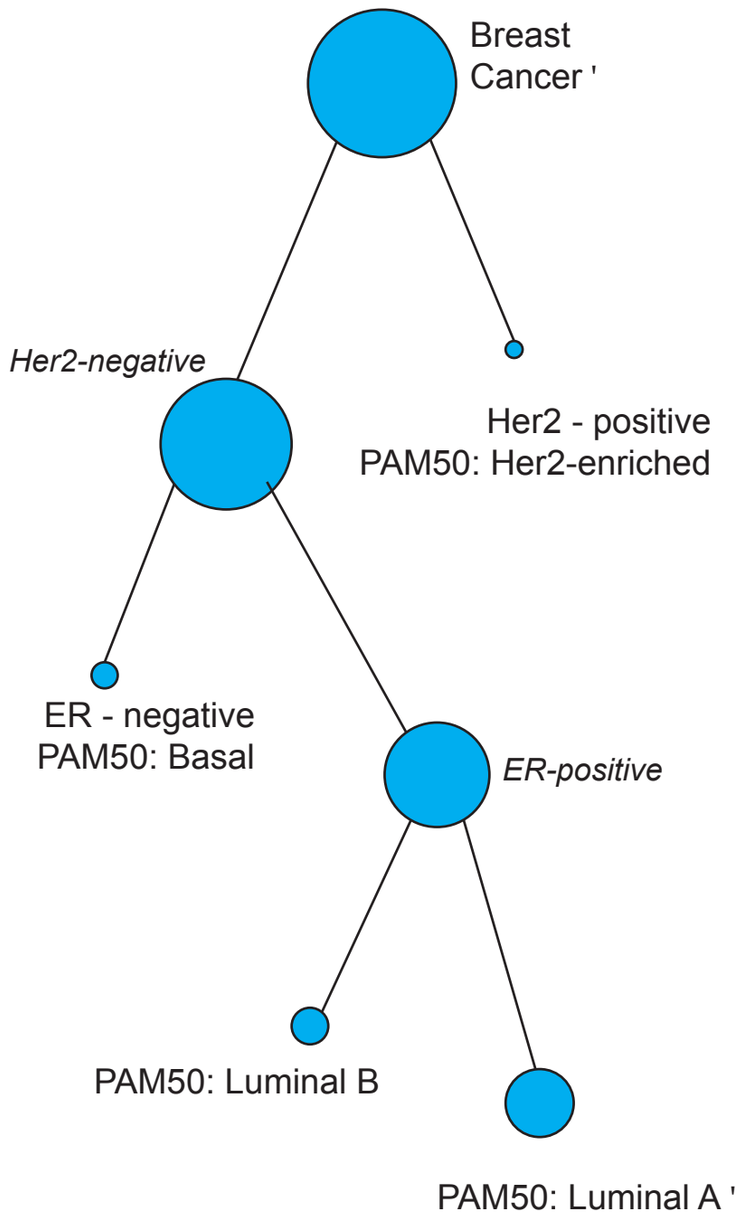


The molecular diversity of Luminal A breast tumors

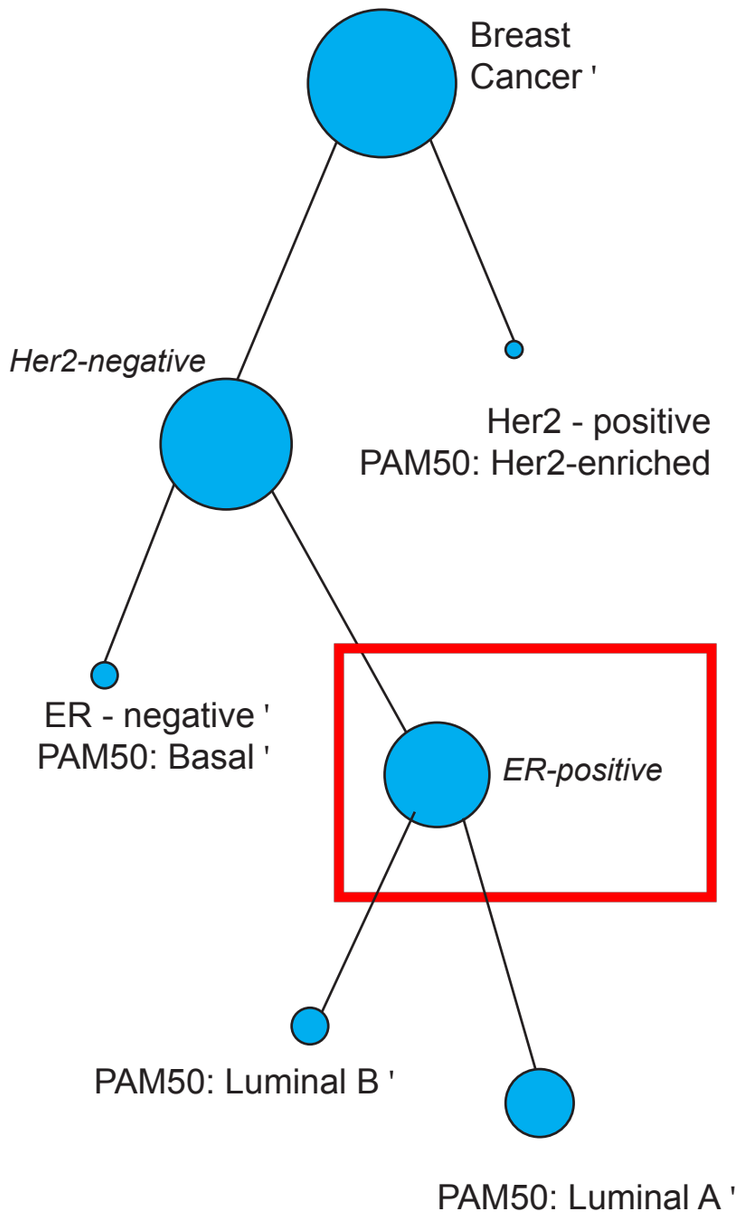
cBio

Giovanni Ciriello
Computational Biology, MSKCC
TCGA Annual Symposium
Washington DC, 2012

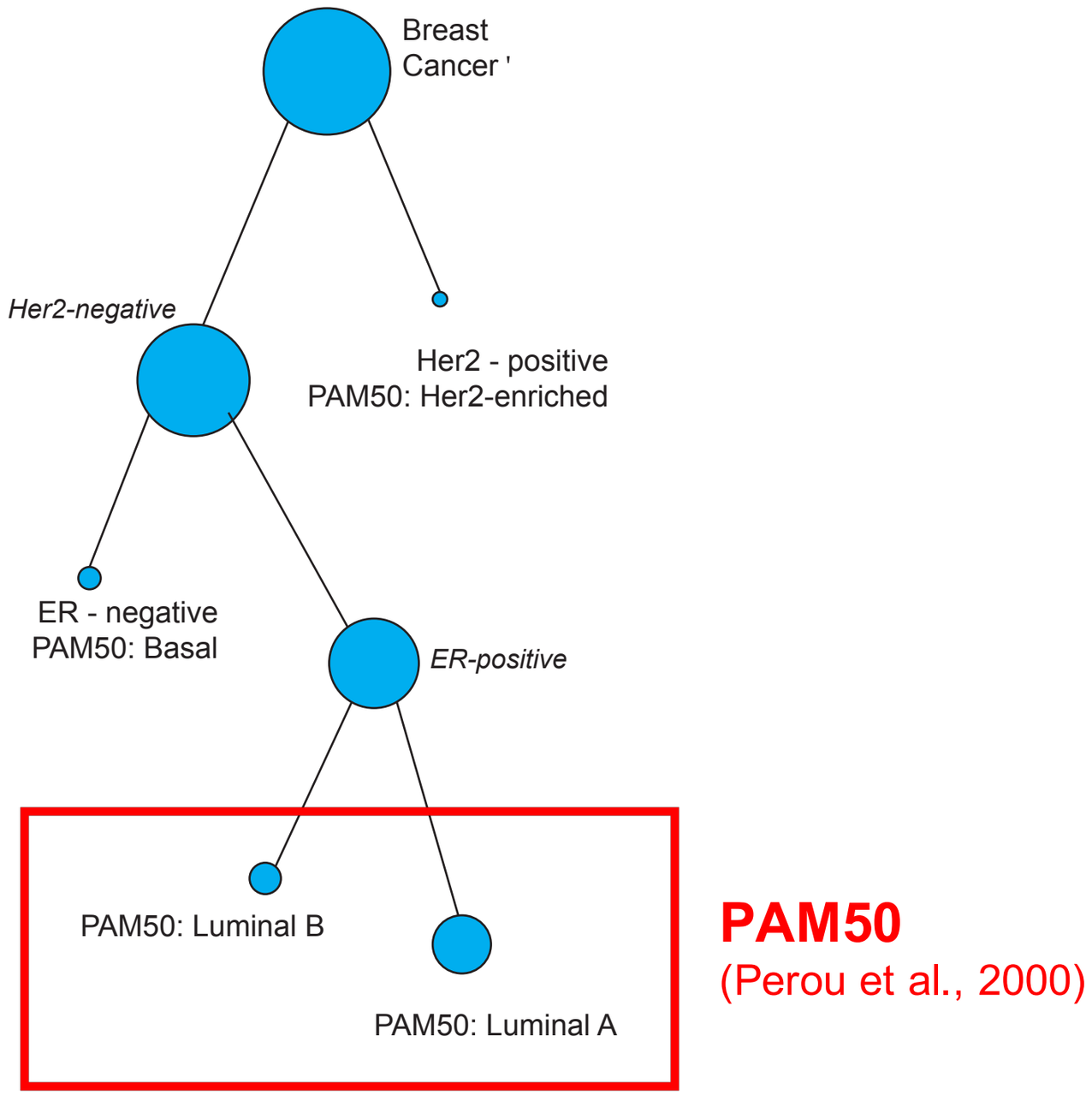
Breast Cancer Heterogeneity



Breast Cancer Heterogeneity



Breast Cancer Heterogeneity



Luminal Heterogeneity

Integrated data from:

TCGA 2012,
Ellis et al. 2012,
Banerji et al. 2012
Curtis et al. 2012
Russnes et al. 2010

~ 1500 Luminal tumors

Copy Number Alterations
Somatic Mutations
mRNA expression

Luminal Molecular Heterogeneity

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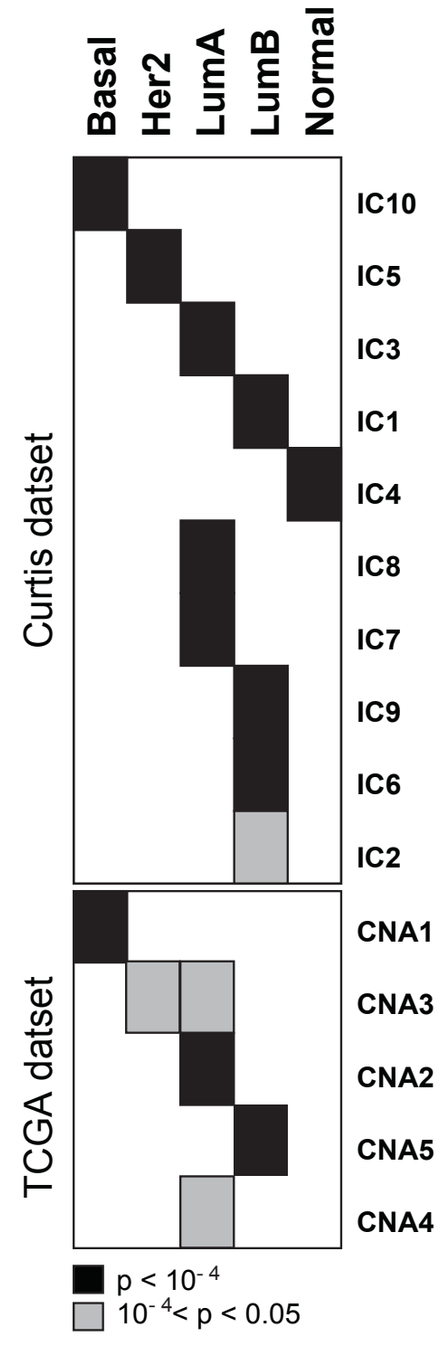
Somatic Mutations
mRNA expression

PAM50 vs CNA-clusters
(Curtis et al., TCGA)



Luminal Molecular Heterogeneity

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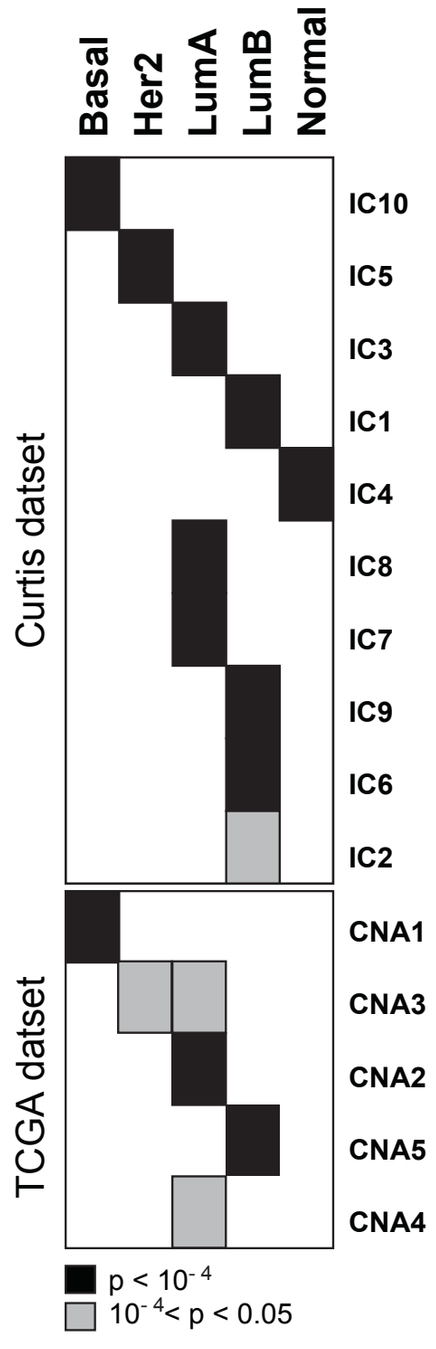
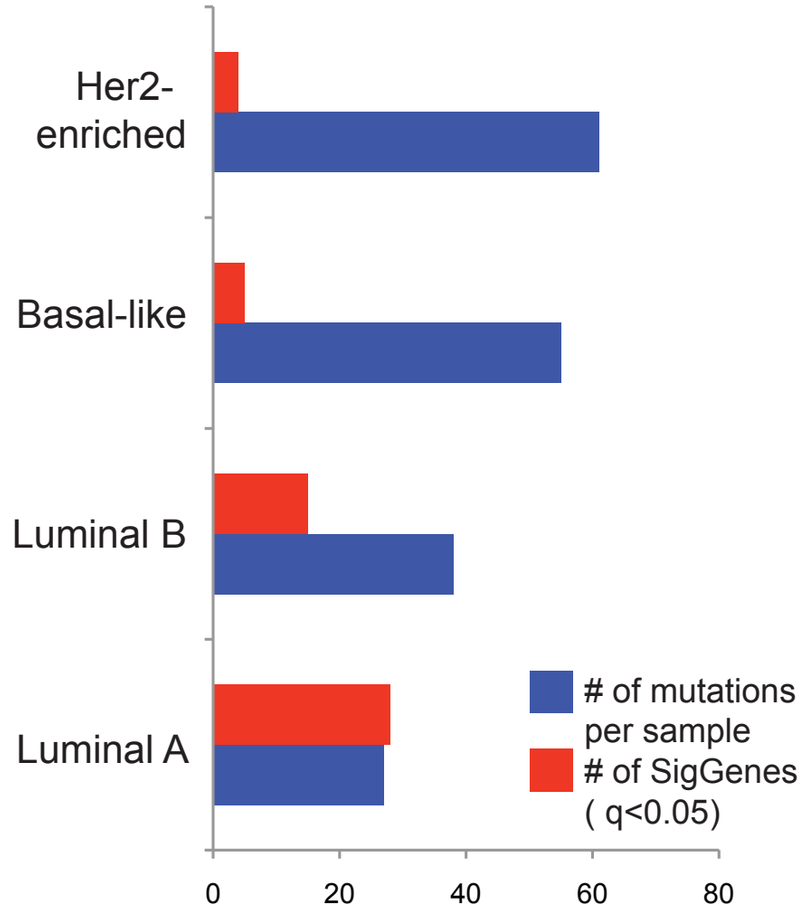
CNA-clusters
(Curtis et al., TCGA)

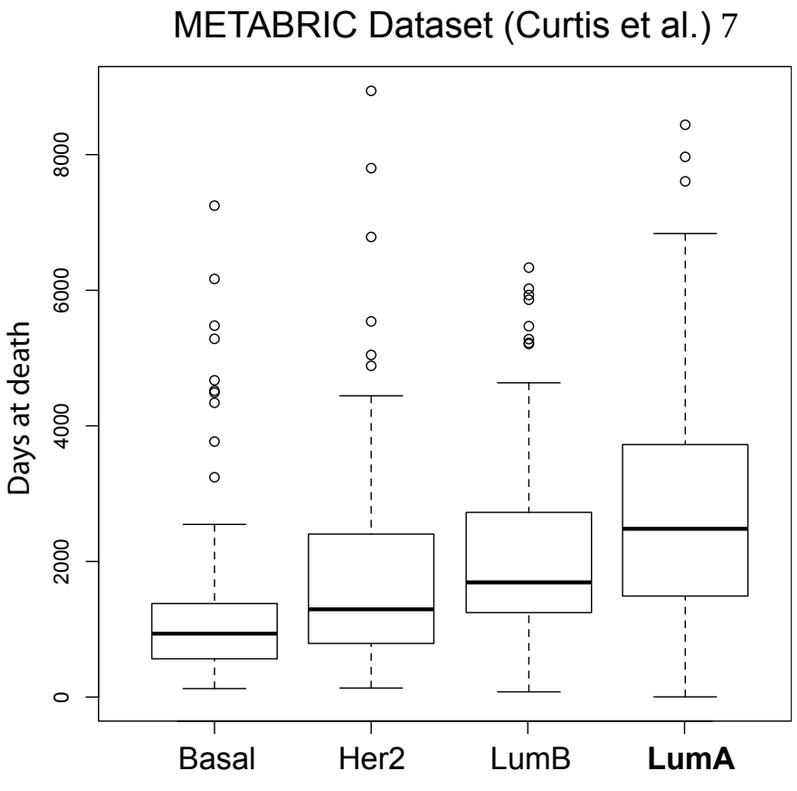


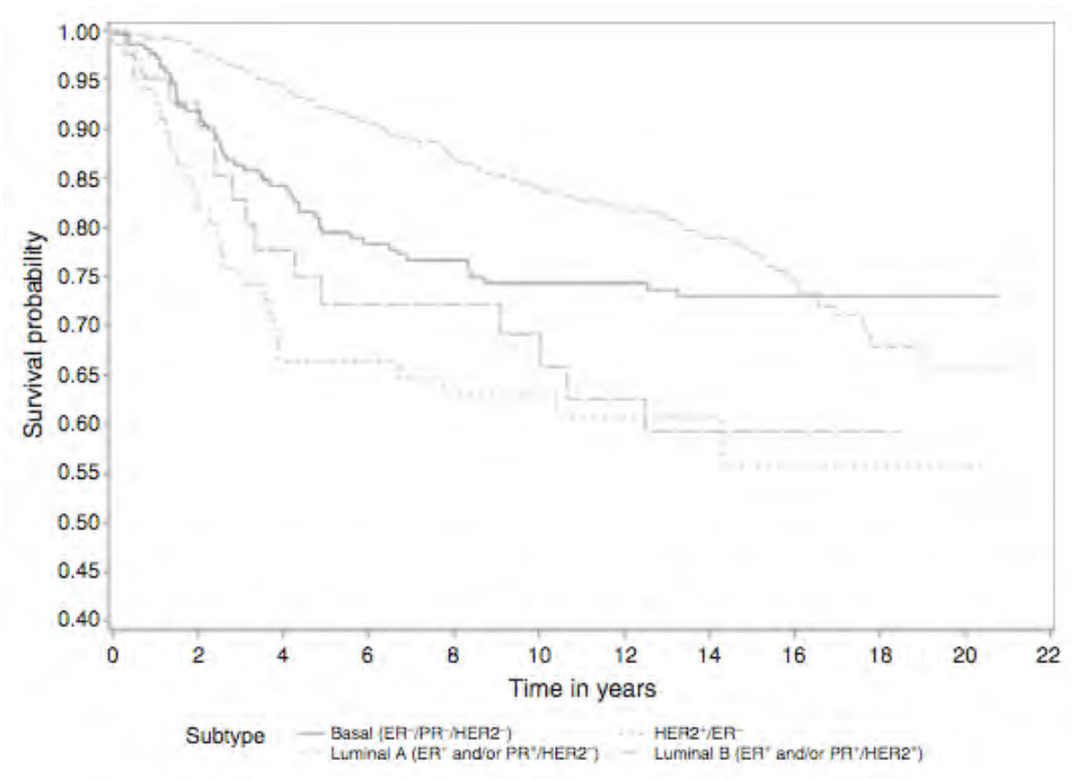
Somatic Mutations
(TCGA, Ellis et al., Banerji et al)



Luminal A Clinical Heterogeneity

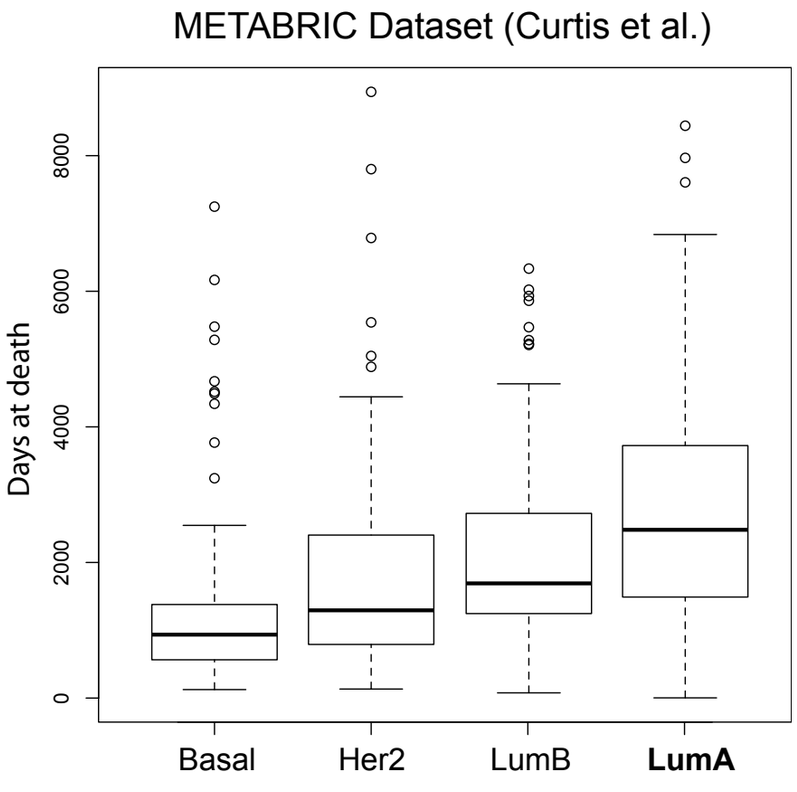
- Luminal A tumors have heterogenous outcome

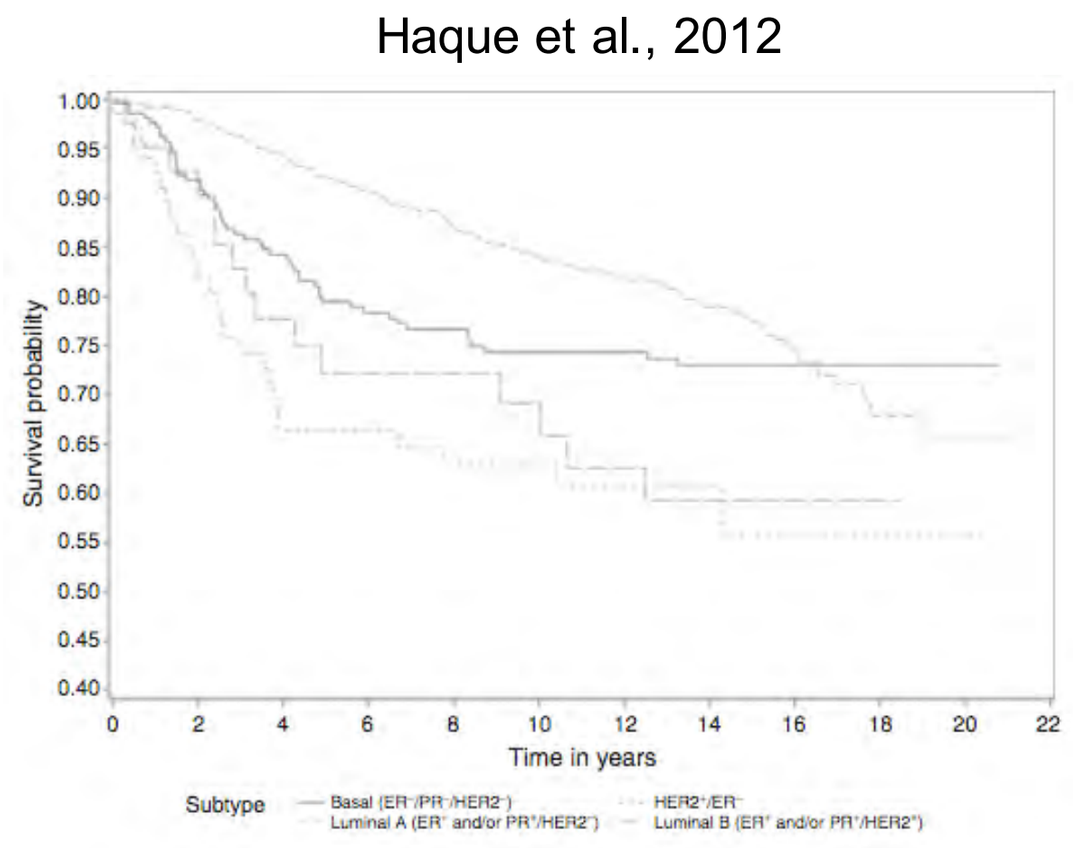




Luminal Heterogeneity

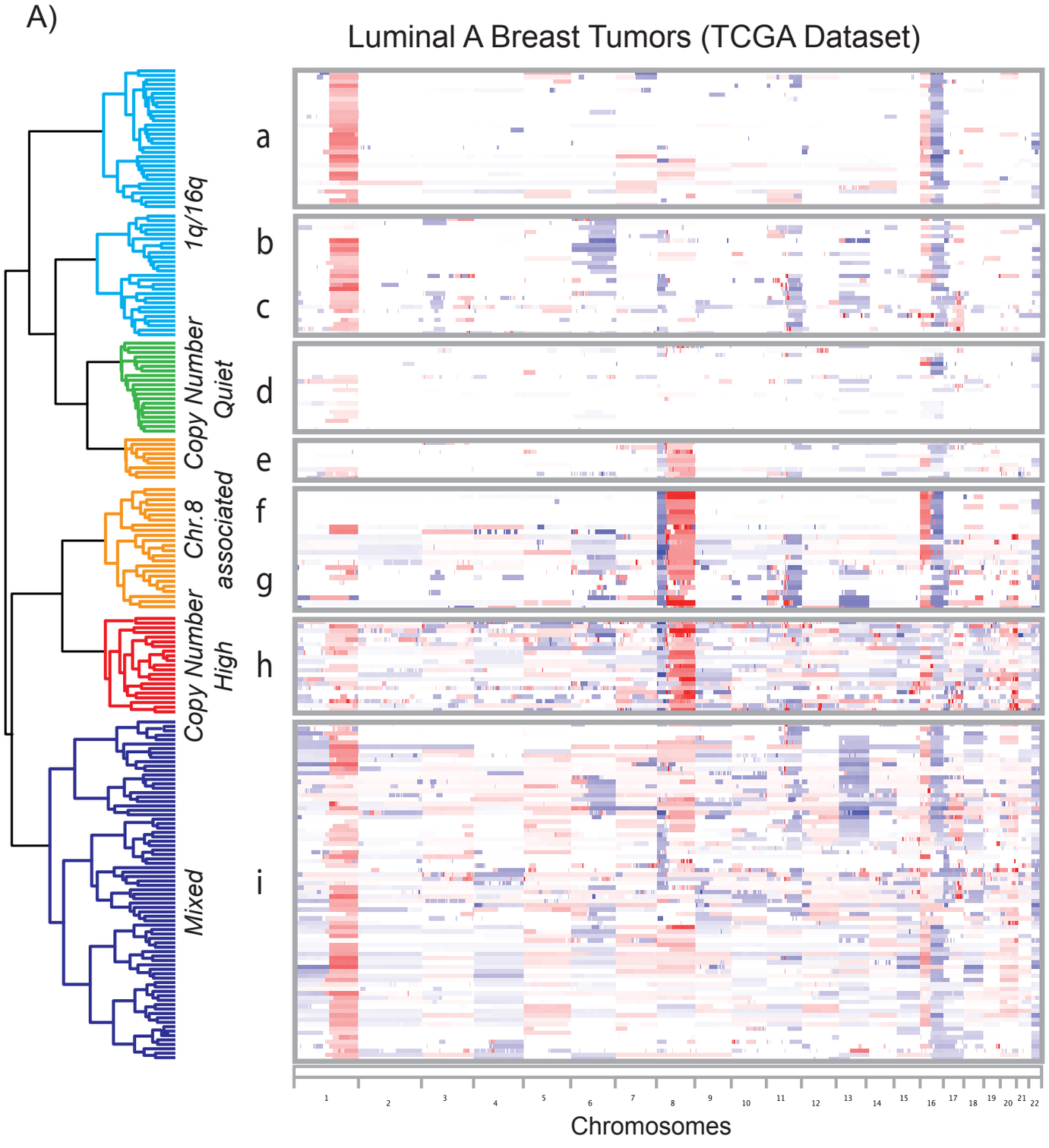
- Luminal A tumors have heterogenous outcome





Luminal A is molecularly and clinically heterogeneous
Can we link outcome variability to molecular diversity?

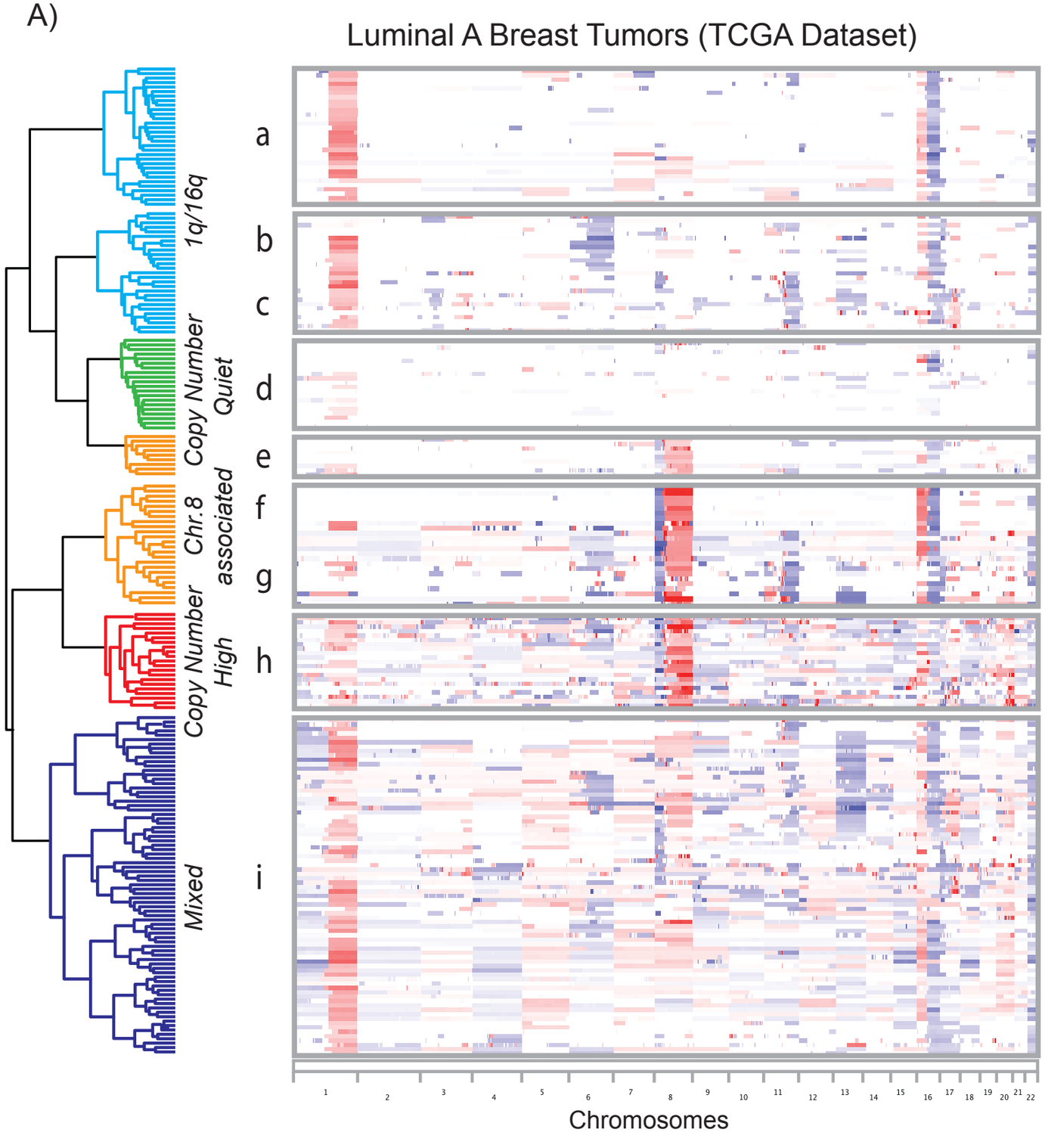
Luminal A Heterogeneity



Copy Number Alterations identify five major subgroups

Luminal A Heterogeneity

A)



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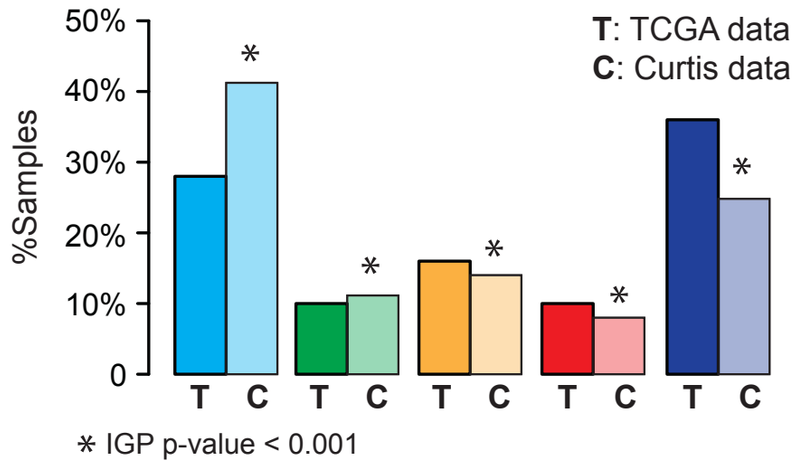
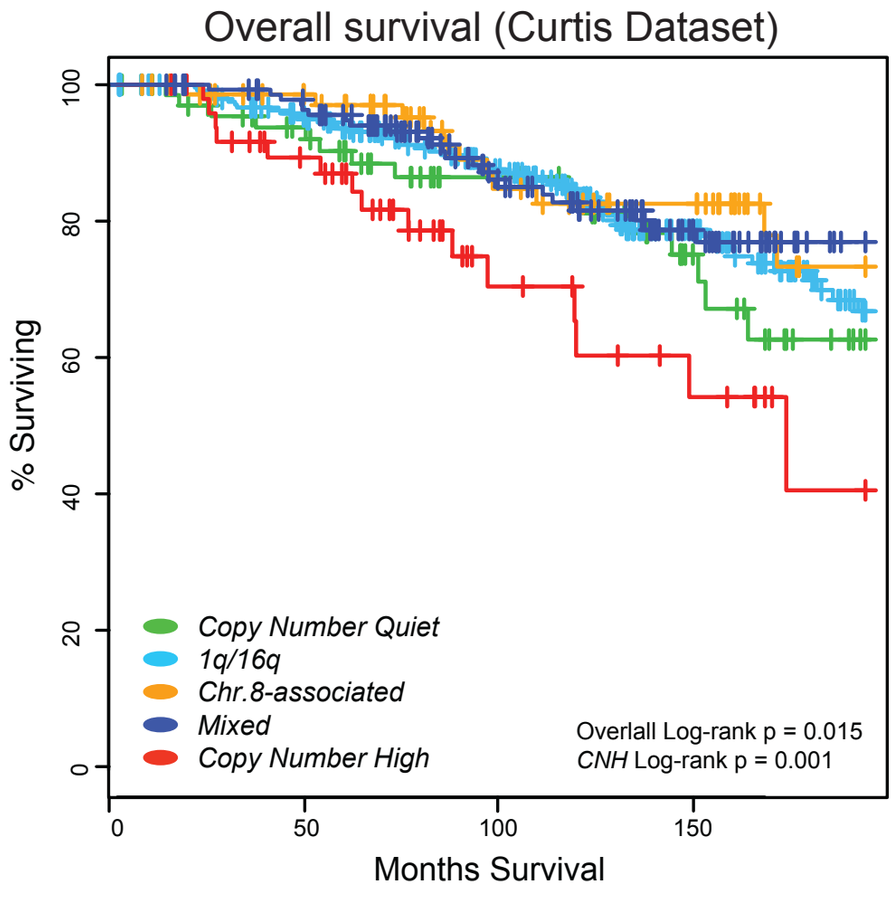
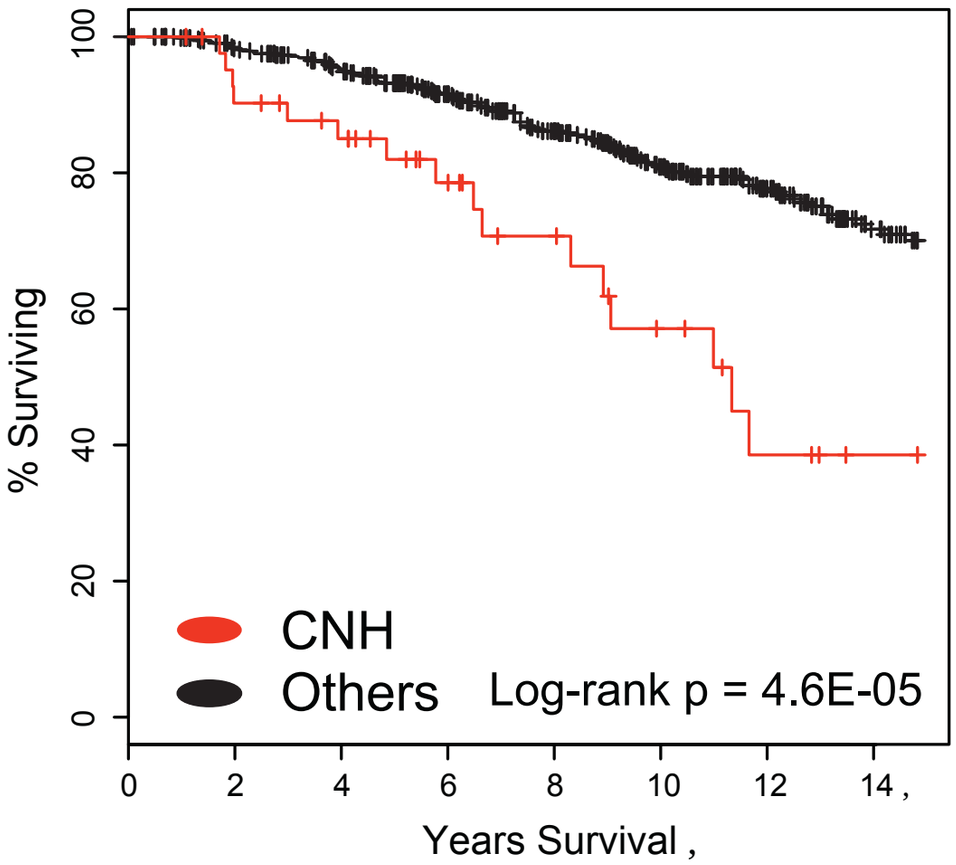


C)



Genomic Instability correlates with poor prognosis

A)



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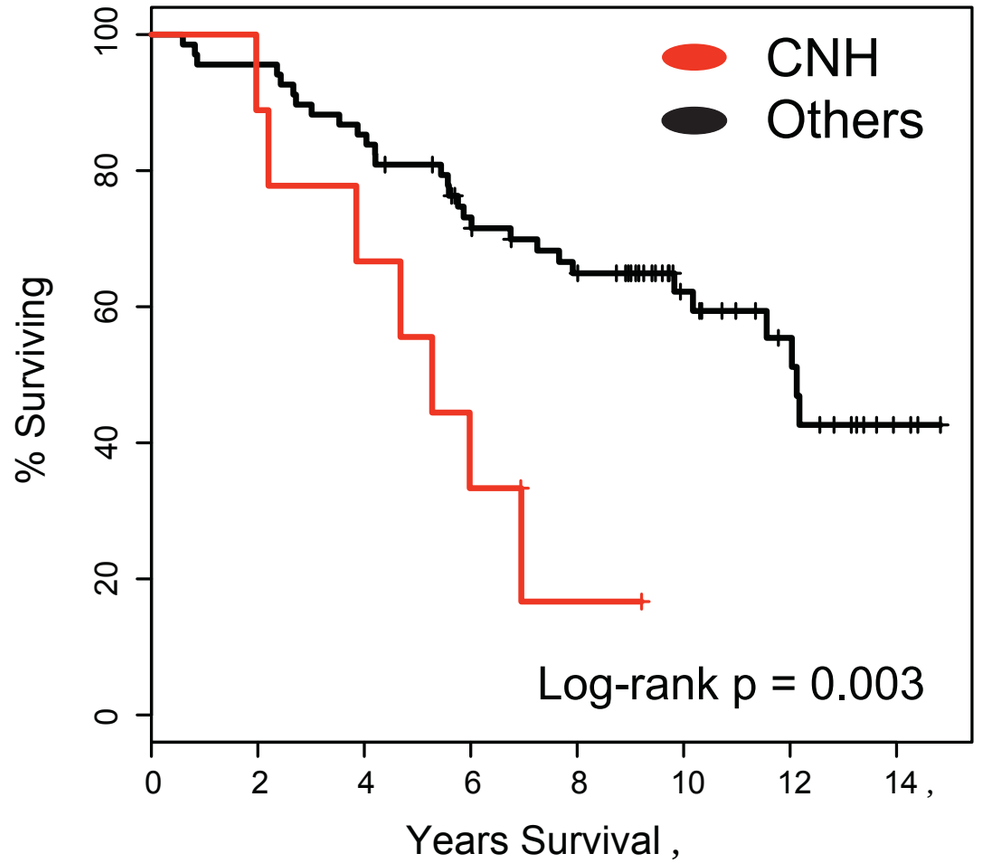

Genomic Instability correlates with poor prognosis

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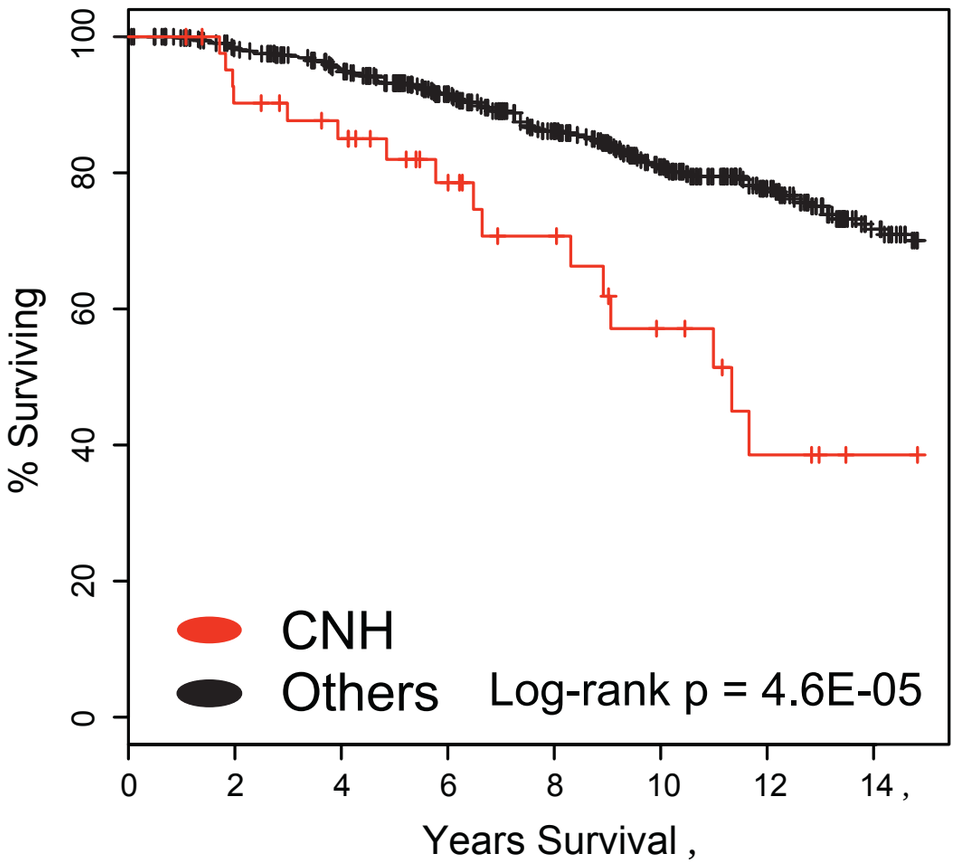

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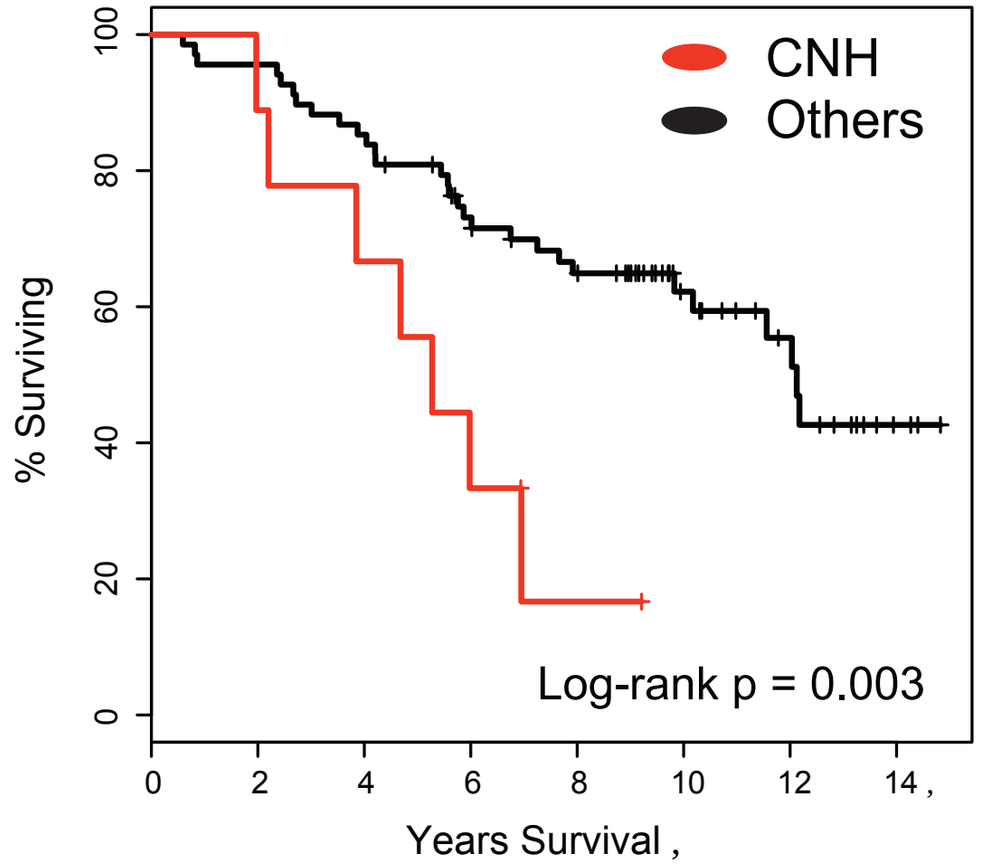
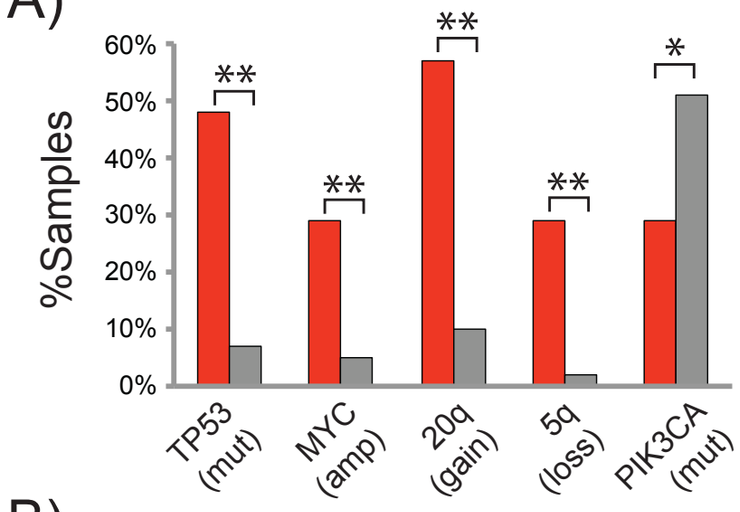


What are the molecular features of these tumors?

CNH Molecular Features

A)



Luminal A

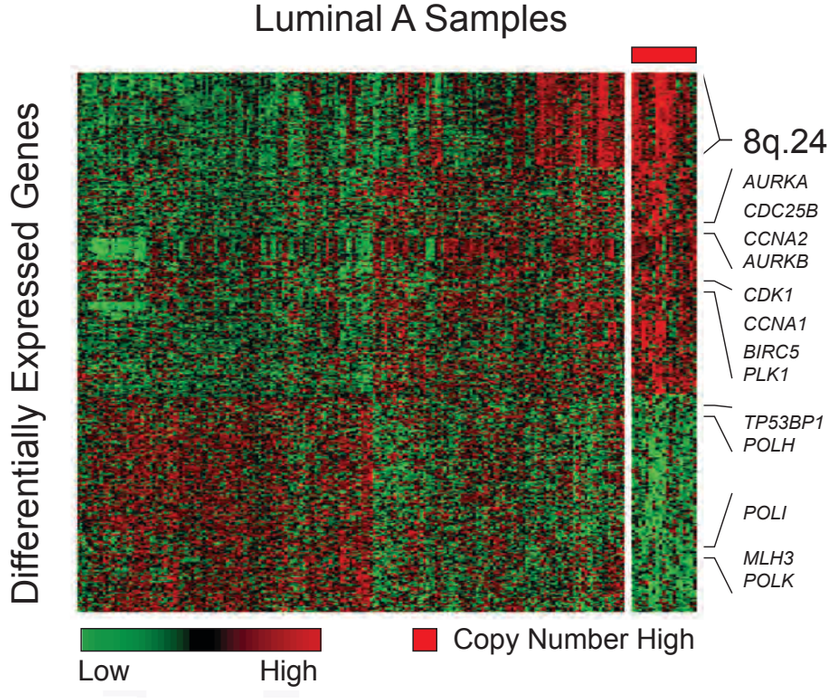
Copy Number High

Other

** p < 0.01

* p < 0.05

B)



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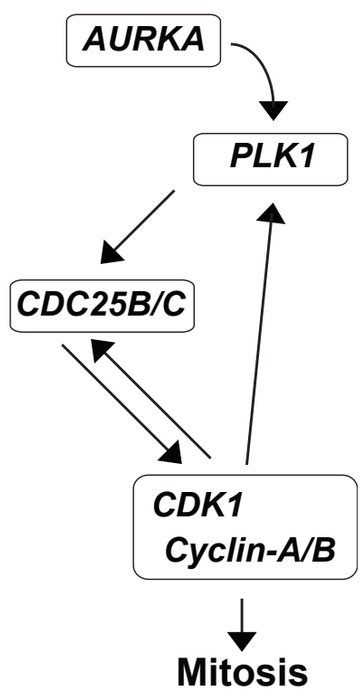
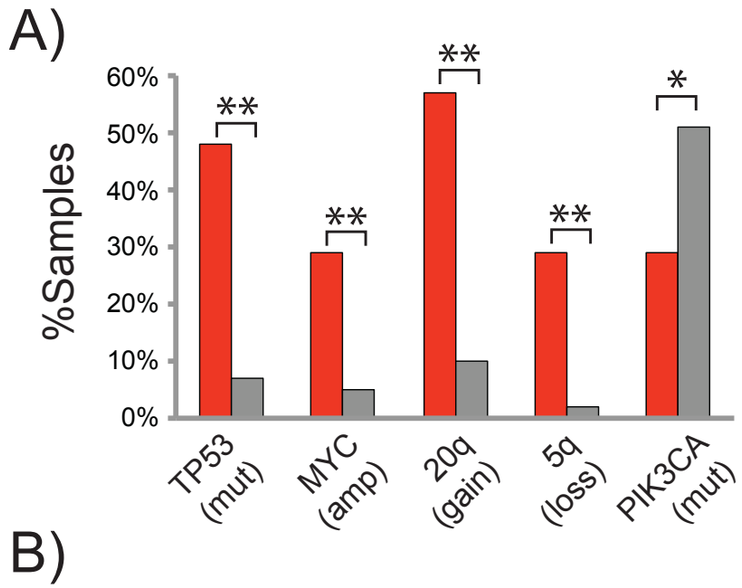
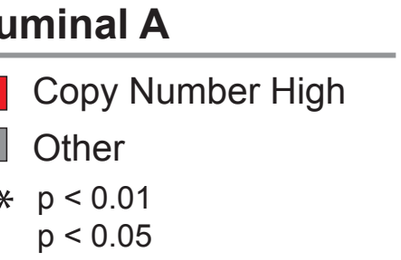
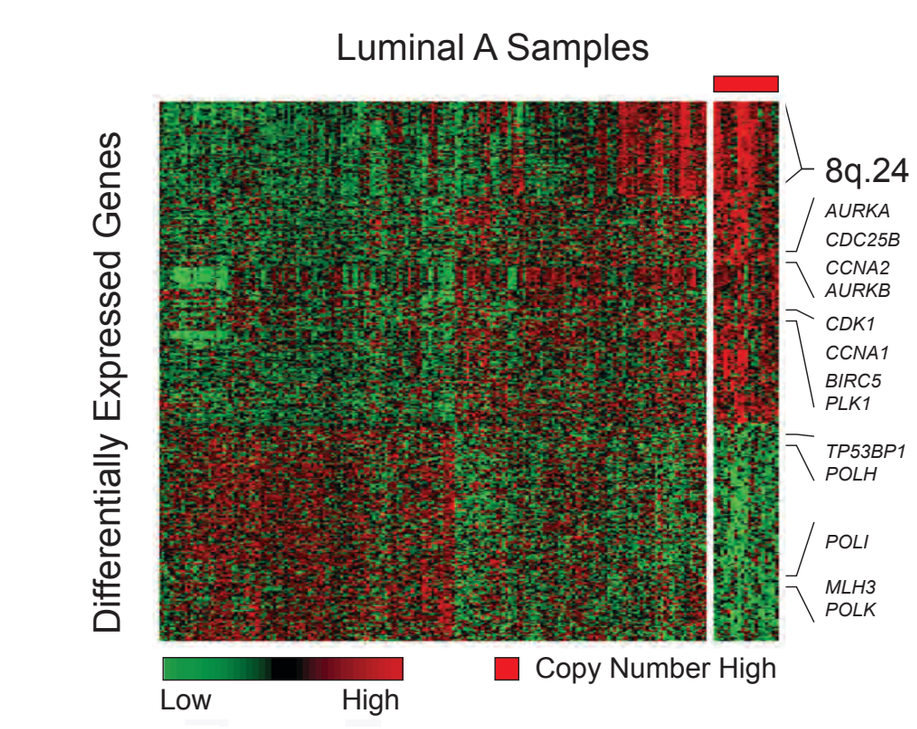
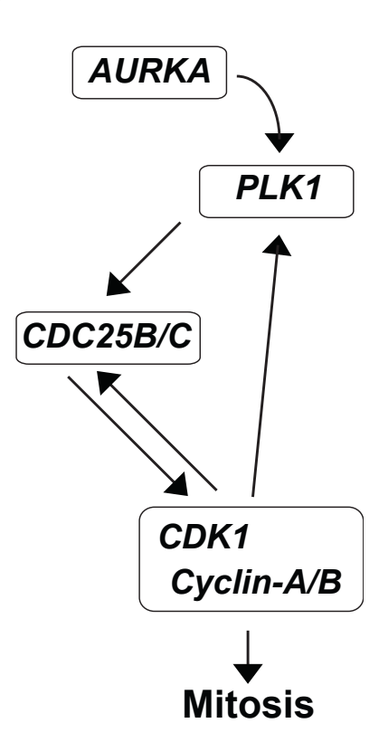


CNH Molecular Features





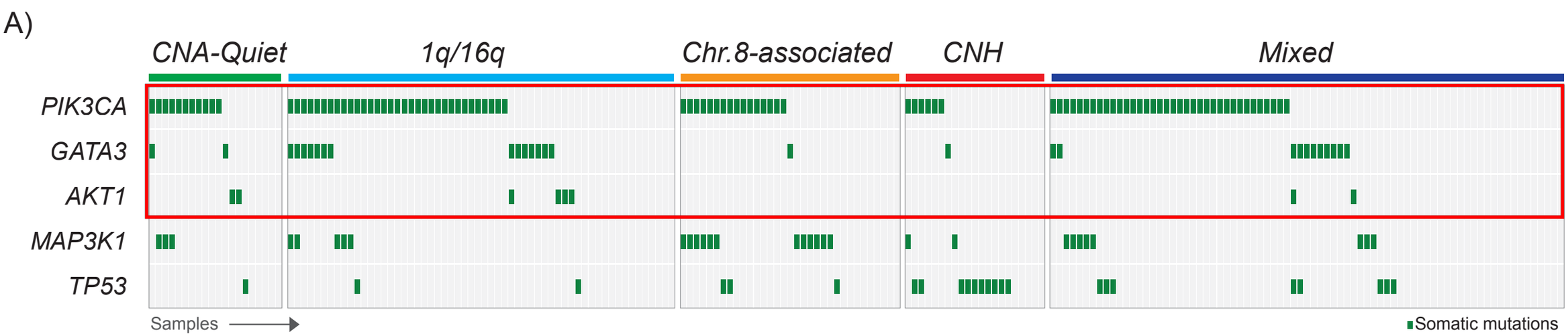




What characterizes the other Luminal A subtypes?

Luminal A Somatic Mutations

A)



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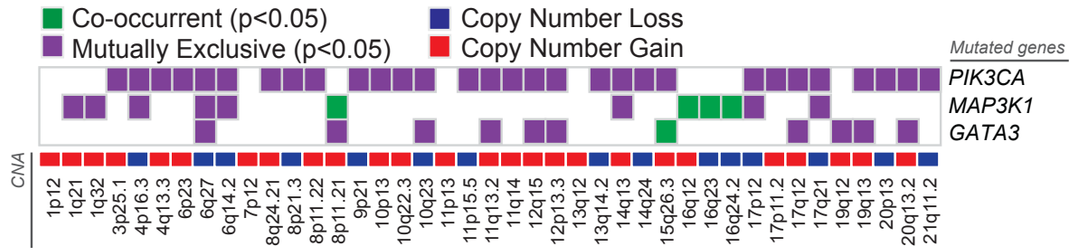

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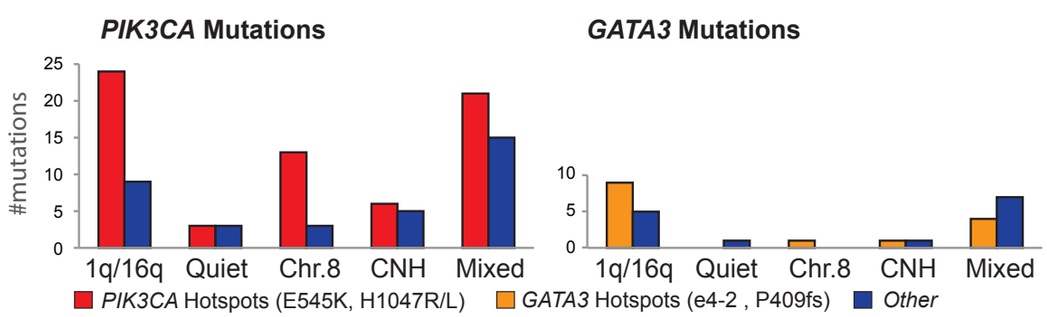
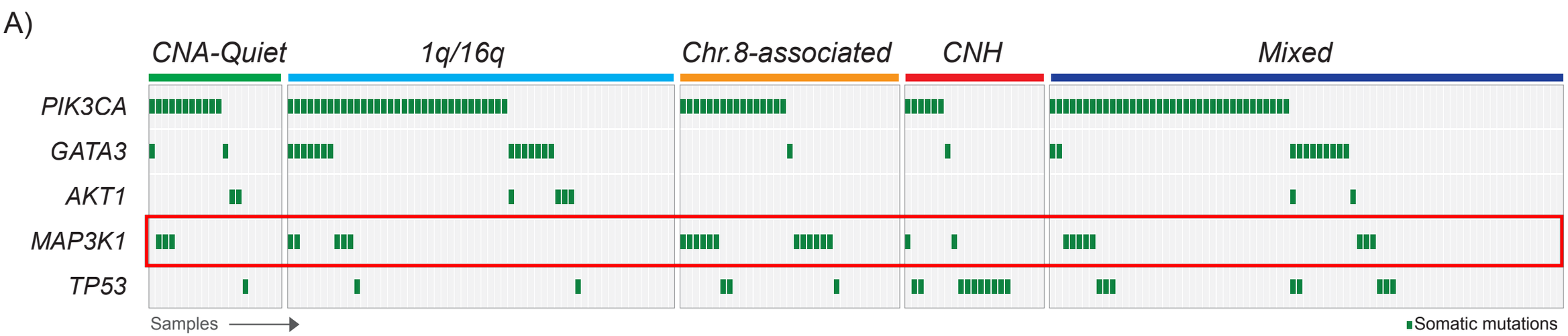
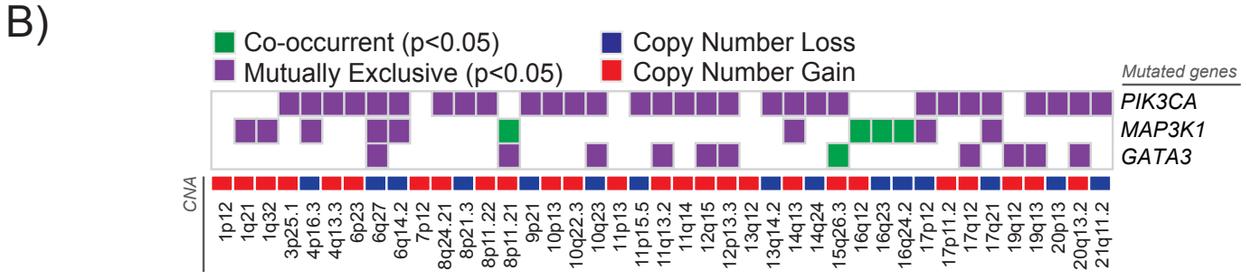
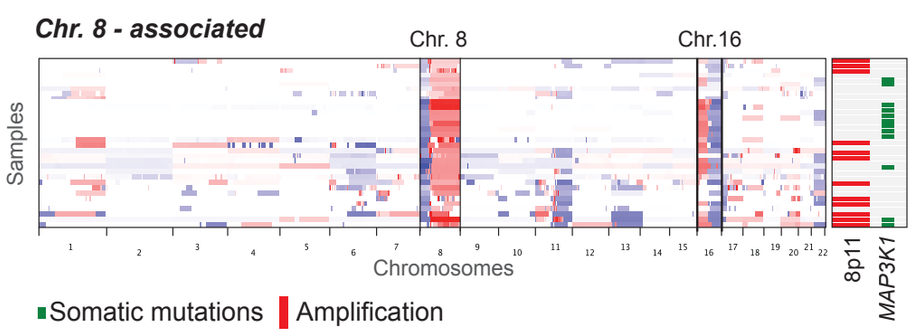
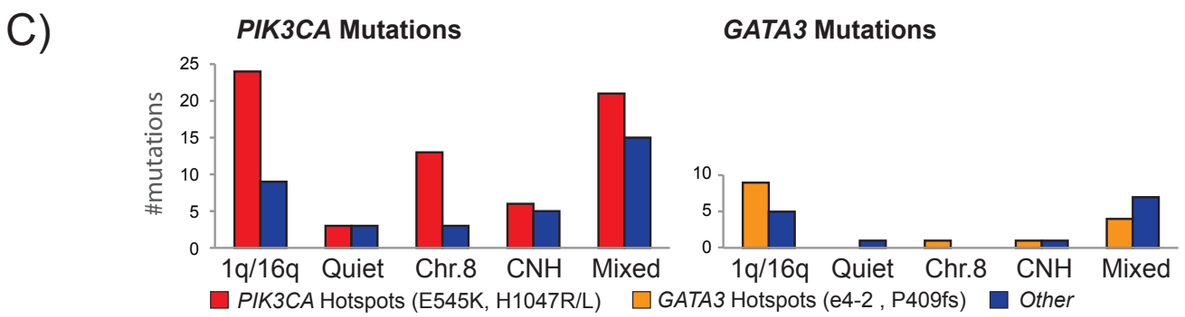


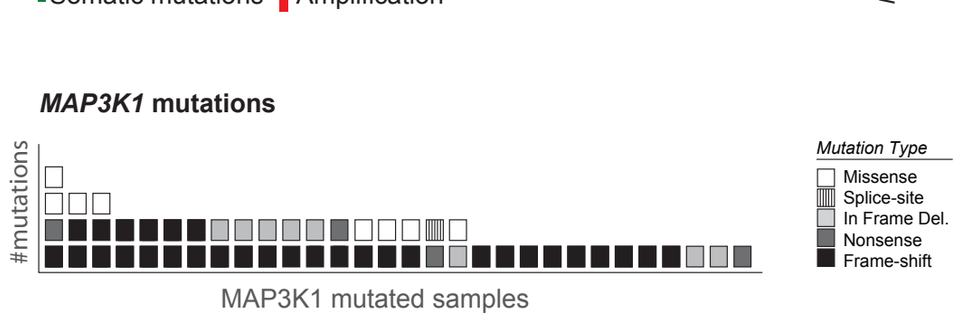
Luminal A Somatic Mutations



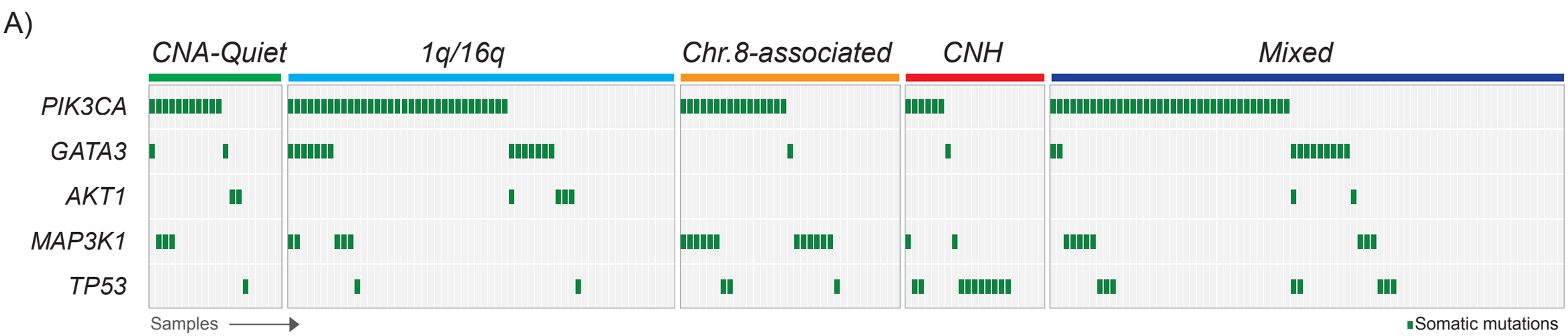


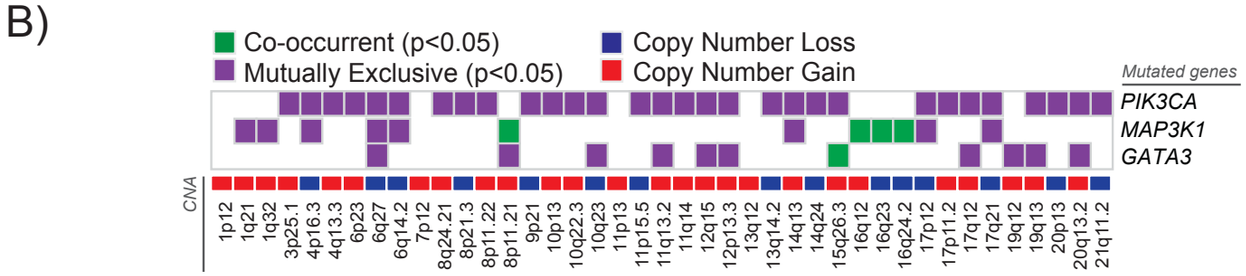


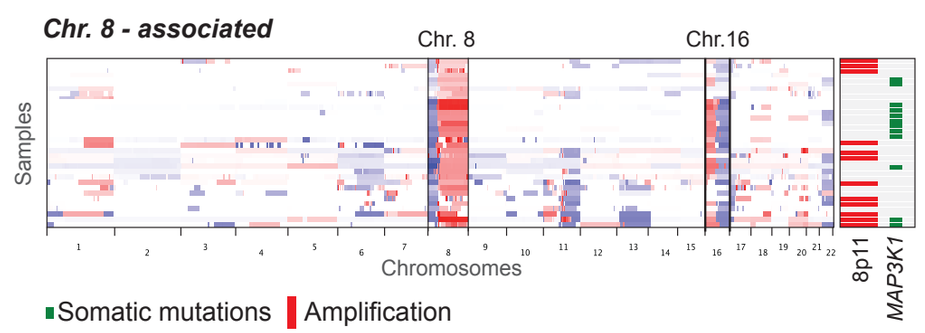


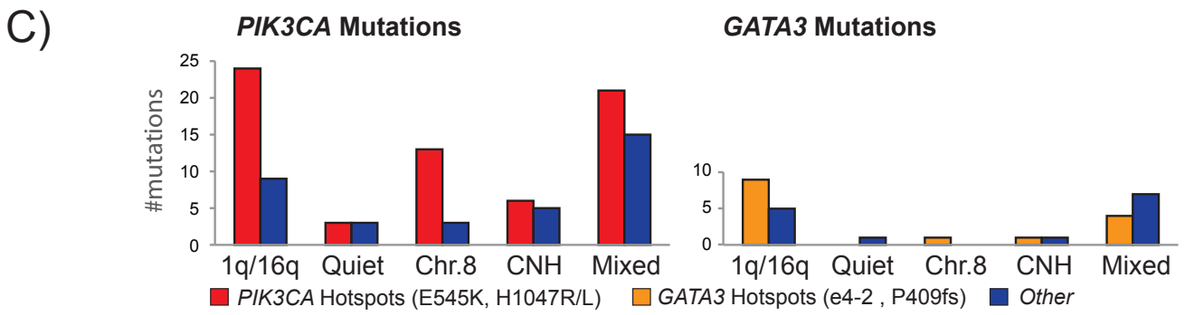


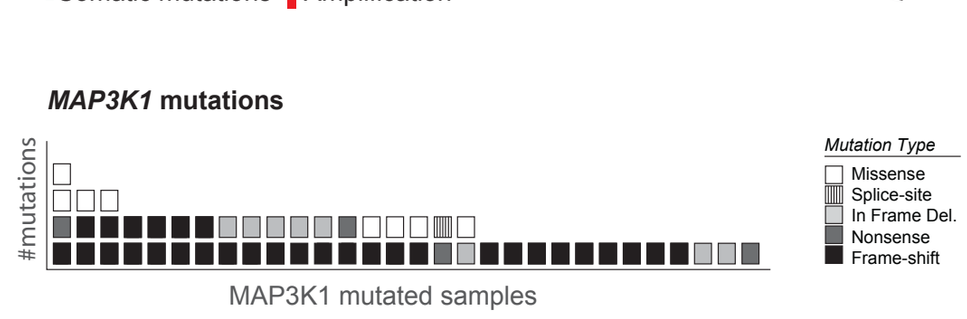
Luminal A Somatic Mutations





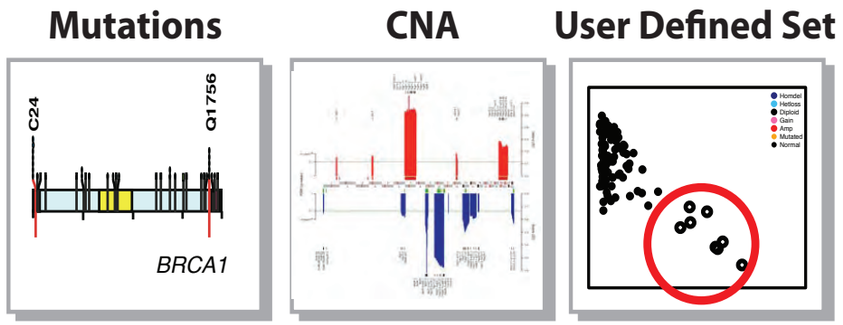


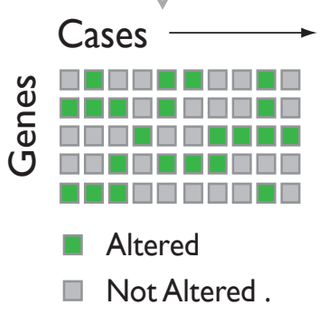


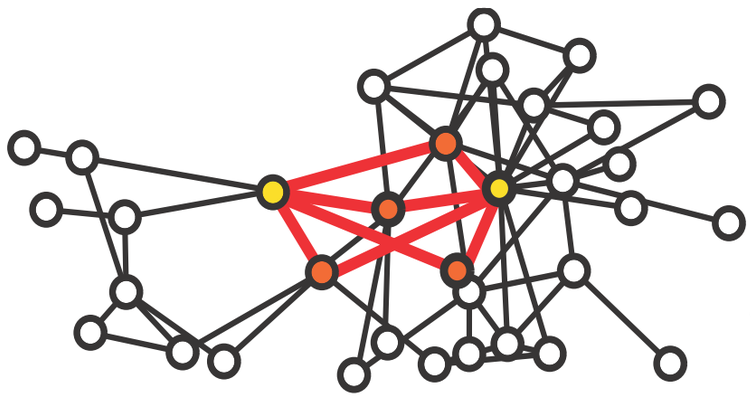


Which pathways are most de-regulated?

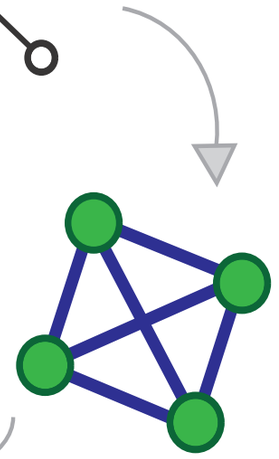
MEMo: Mutual Exclusivity Modules



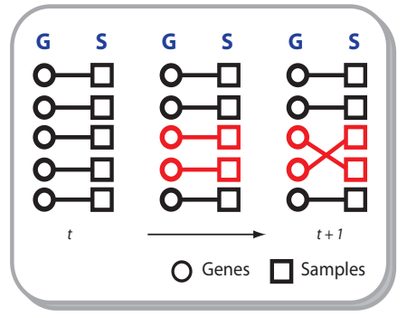




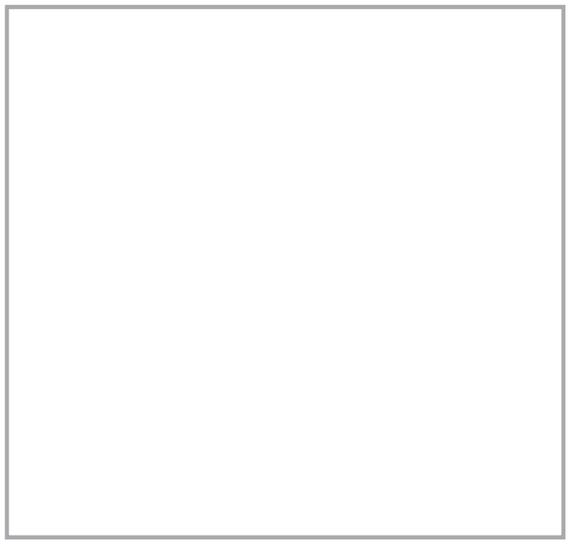
Genes connected by network proximity



Module



MCMC Switching Permutation
- preserves #alterations per sample
- preserves #alterations per gene



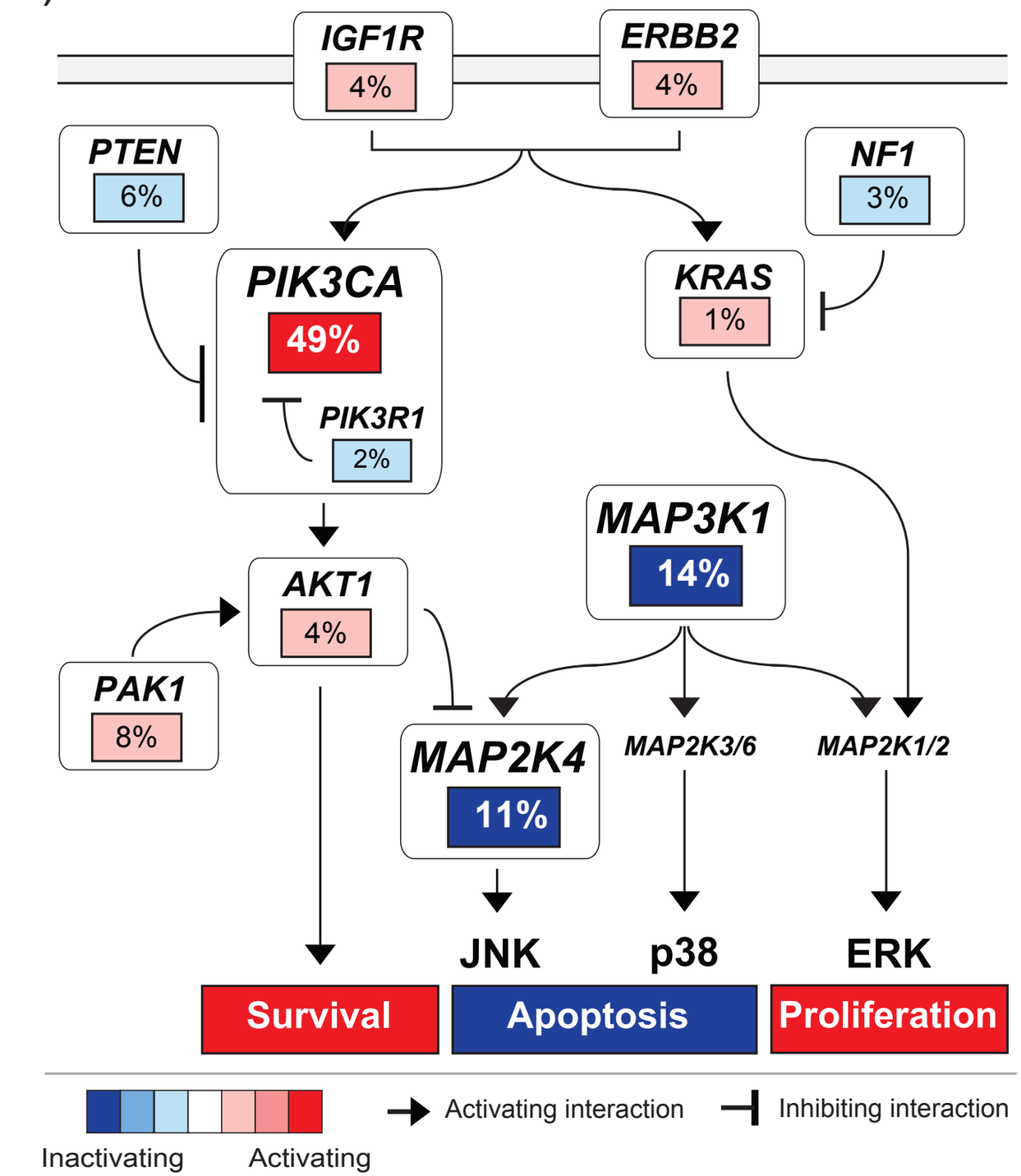
Mutual Exclusivity Module

Ciriello et al., *Genome Res.* 2012

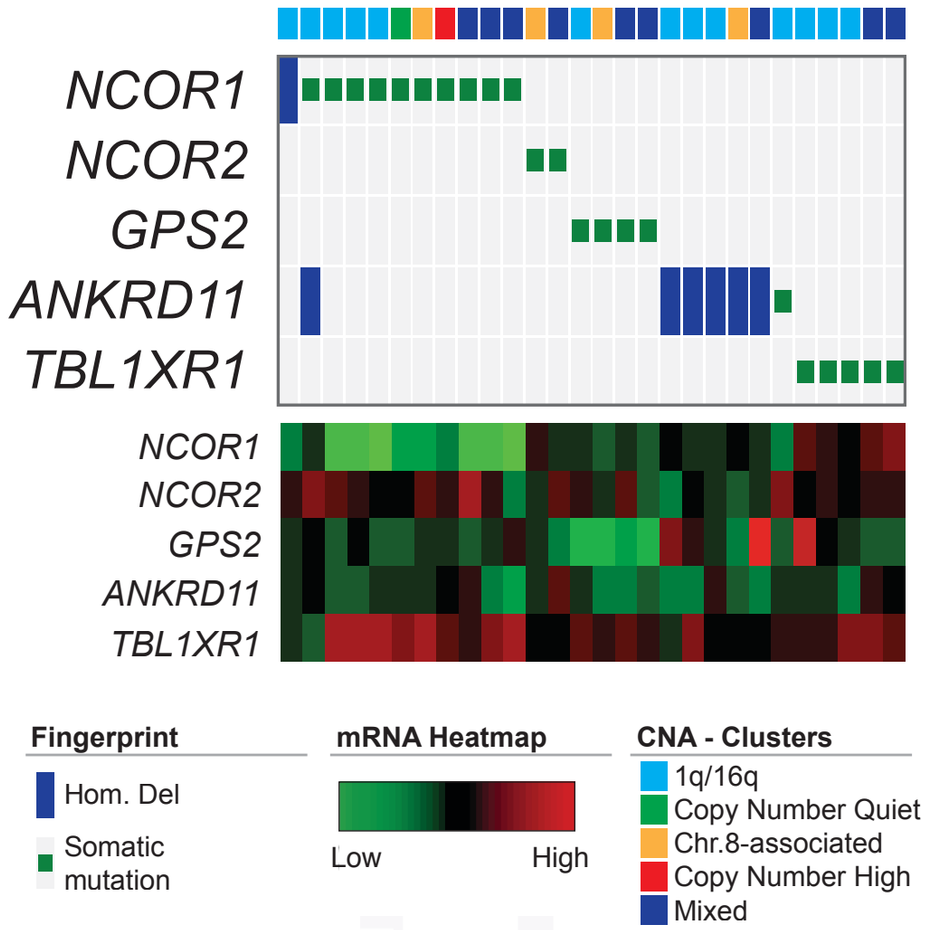
www.cbio.mskcc.org/memo

Luminal A Pathways (MEMo)

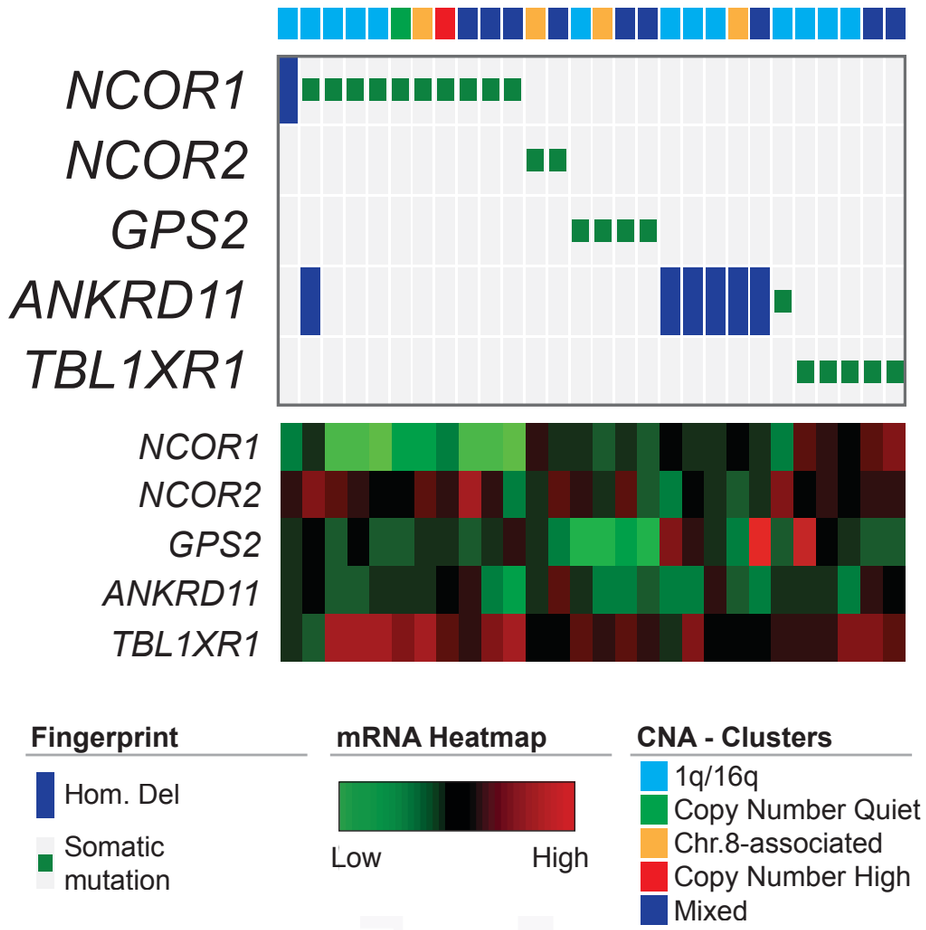
A) 2



Alterations to NCor/SMRT components

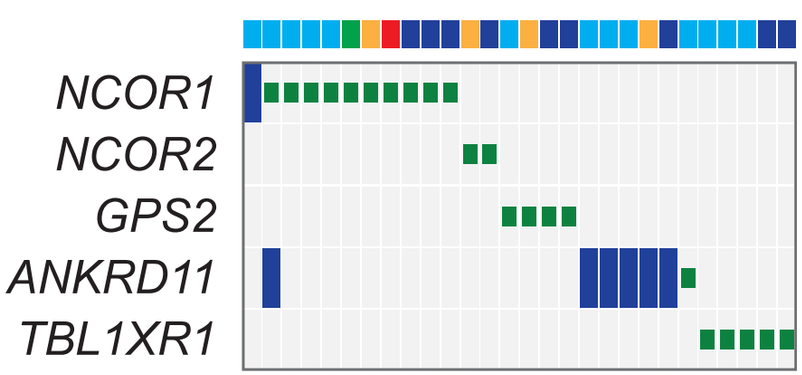


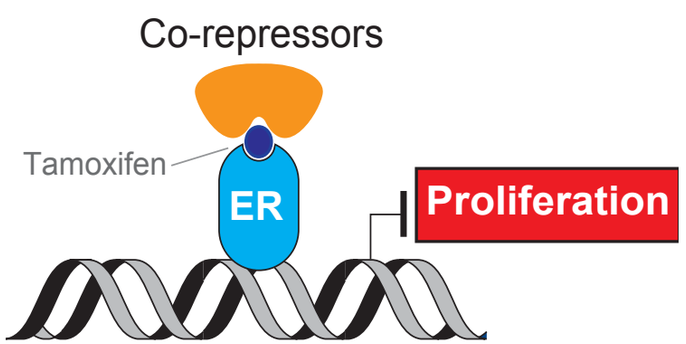
Alterations to NCor/SMRT components

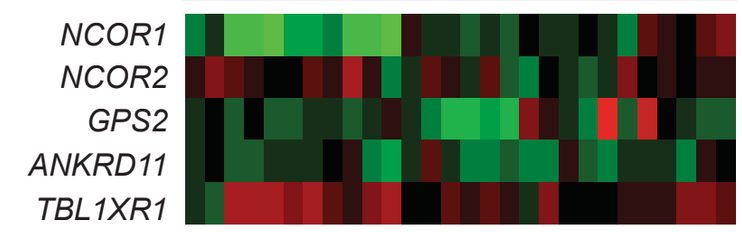


Why are co-repressor complexes important in ER+ tumors?

NCor/SMRT are required for Tamoxifen effects







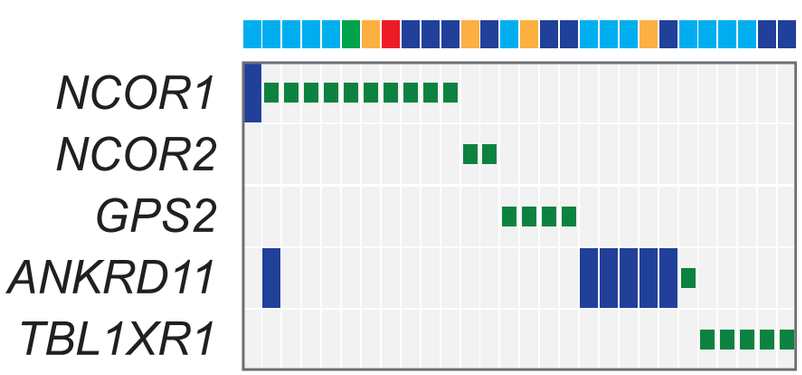
Fingerprint
- Hom. Del
- Somatic mutation

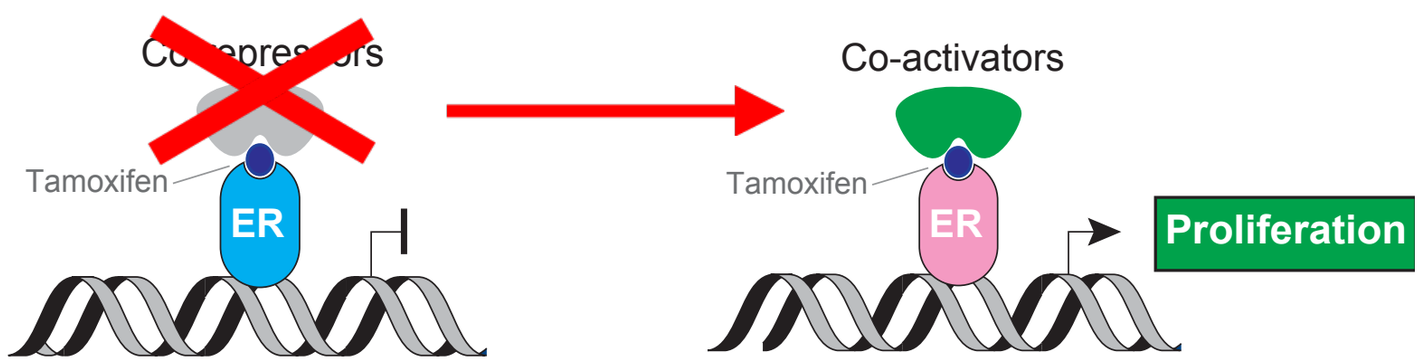
mRNA Heatmap

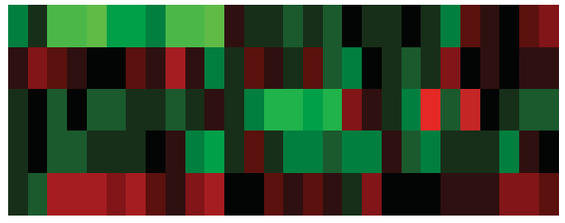
Low — High

CNA - Clusters
- 1q/16q
- Copy Number Quiet
- Chr.8-associated
- Copy Number High
- Mixed

NCor/SMRT are required for Tamoxifen effects







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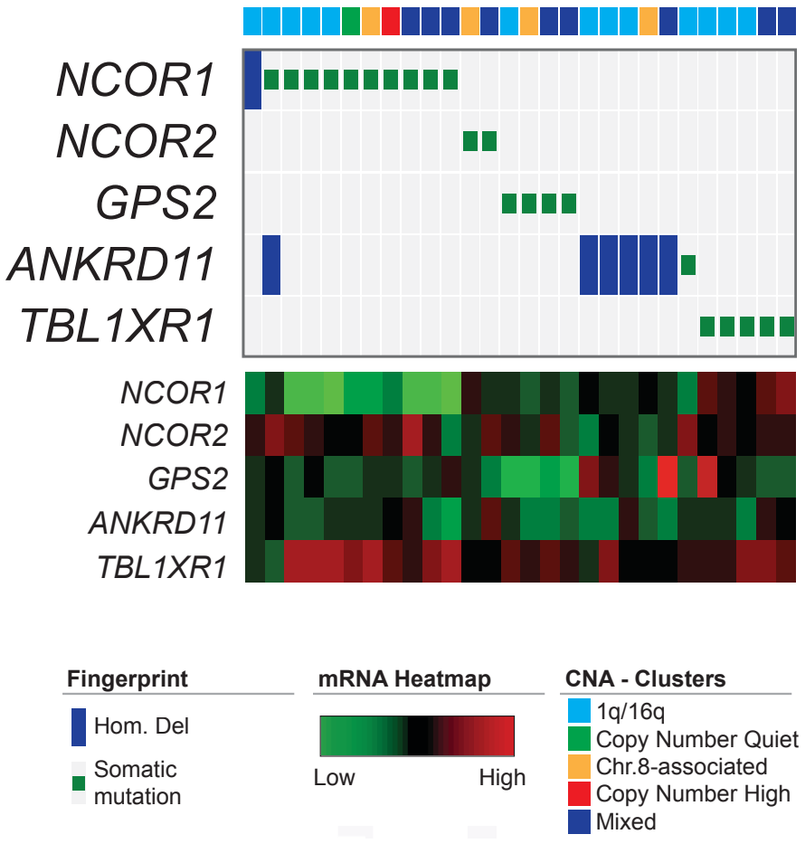
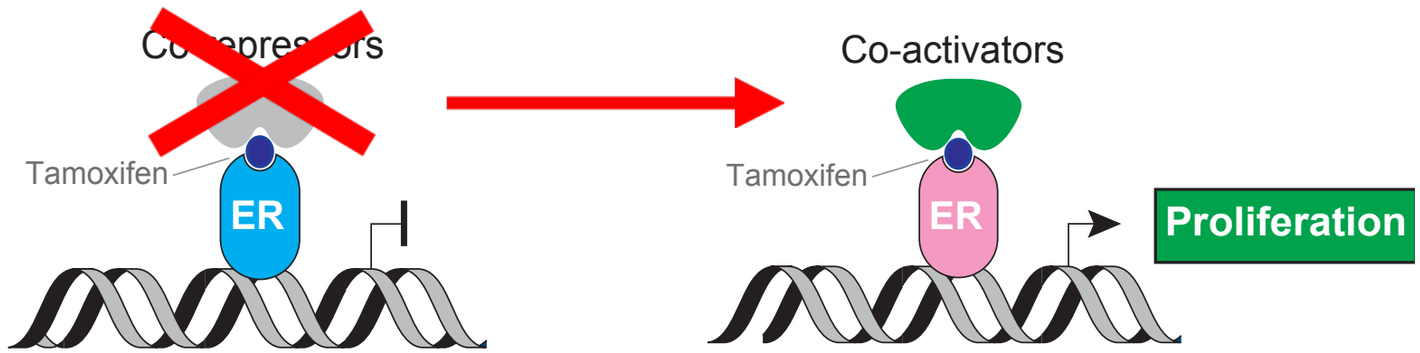
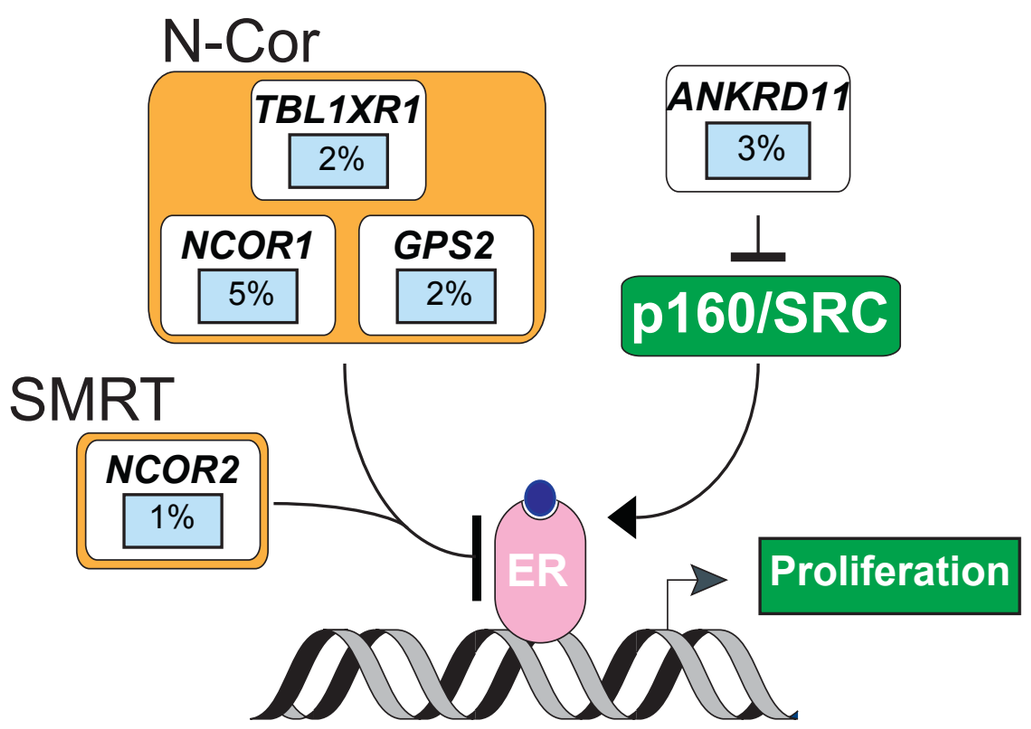
Loss of NCor/SMRT predicts resistance







Conclusions

- We dissected the genomics of **Luminal A tumors** in multiple datasets to explain their **molecular and clinical heterogeneity**
- **Four major subtypes** of Luminal A tumors
- **Atypical Luminal subtype** characterized by:
  - high genomic instability
  - p53 mutations
  - Aurora kinases up-regulation
  - poor prognosis
- Luminal A hallmark mutations are prevalent in tumors characterized by low copy number alterations
- We identified multiple rare, but mutually exclusive alterations associated with loss **NCor/SMRT**
  - These alterations may predict lack of response to endocrine therapy

Thanks!

Chris Sander
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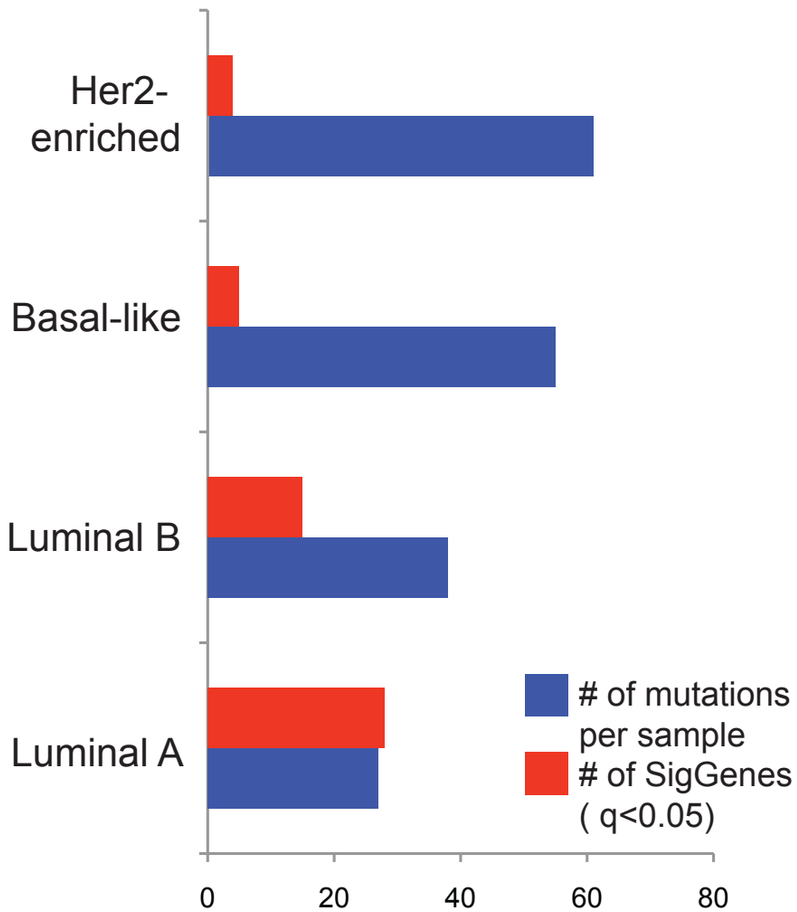
Katie Hoadley

...and the whole TCGA Breast AWG!

Appendix A

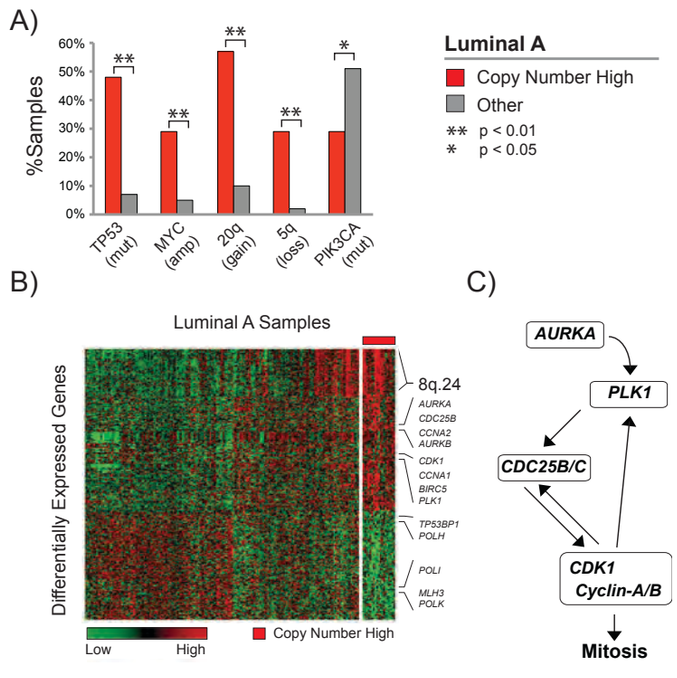
Luminal A Recurrently Mutated Genes (q < 0.05)

data from TCGA, Ellis et al., Banerji et al

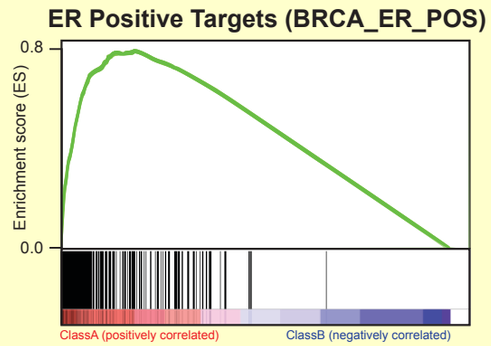


PIK3CA	*RUNX1*	*DGKG*
MAP3K1	*CTCF*	*SMCHD1*
GATA3	*CBFB*	*KRAS*
TP53	*SF3B1*	*CCND3*
CDH1	*MED23*	*NKAIN4*
MLL3	*WNT7A*	*HIST2H2BE*
MAP2K4	*TBL1XR1*	*HIST1H3B*
NCOR1	*TBX3*	*SHD*
AKT1	*GPS2*	*GPR32*
PTEN	*FOXA1*	

Appendix B

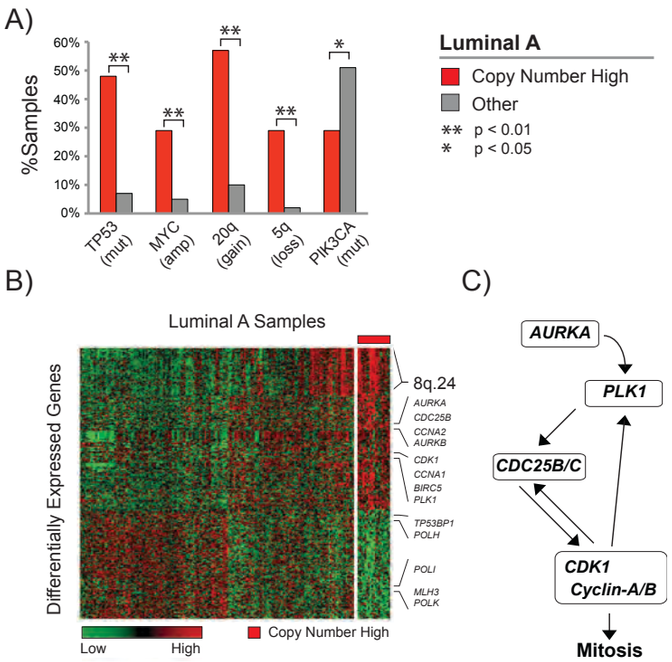


CNH tumors are ER+

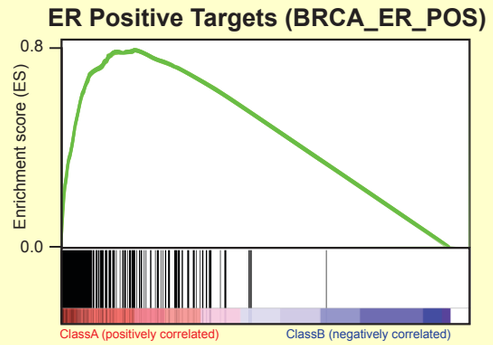


$p < 10^{-3}$, FDR = 0.03

Appendix B



CNH tumors are ER+



$p < 10^{-3}$, FDR = 0.03

Luminal B have similar subgroup