Multi-omics classification of head and neck cancer ties TP53 mutation to 3p loss

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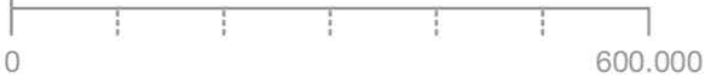
HEAD AND NECK CANCER

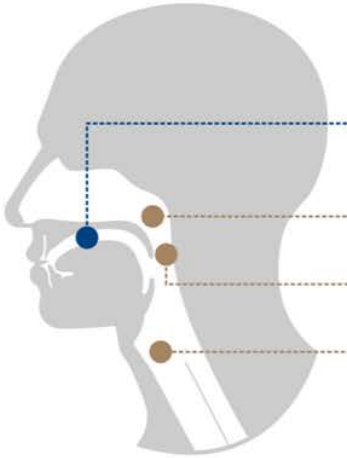
560.000[1]

NEW HEAD AND NECK CANCER CASES ANNUALLY

300.000[1]

HEAD AND NECK CANCER DEATHS ANNUALLY





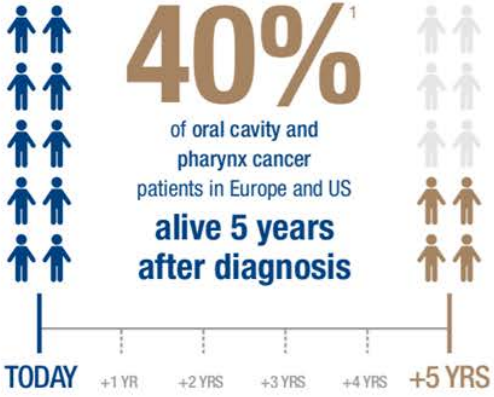
Oral Cavity[2]
the most common type

Nasopharynx

Pharynx

Larynx

At least
90%[3]
of head and neck tumours
overexpress EGFR



HPV may also be a risk factor in certain types of head and neck cancer

60%

One study found that 60% of oropharyngeal cancer patients had HPV positive tumours[4]

The number of HPV infections is increasing in developing countries which may mean a shift in demographics to a younger population with better prognosis.

Alcohol and tobacco account for

7 out of 10[1]

cases of head and neck cancer

1. Boyle P et al. *World cancer report*. International Agency for Research on Cancer 2008 Dec. **2.** Ferlay, J. *et al.* Estimates of worldwide burden of cancer in 2008:GLOBOCAN 2008. *Int. J. Cancer*: 127, 2893–2917 (2010). **3.** Sok J.C *et al. Mutant Epidermal Growth Factor Receptor (EGFRvIII) Contributes to Head and Neck Cancer Growth and Resistance to EGFR Targeting.* Clin Cancer Res 2006;12:5064–5073. **4.** Ang K.K. Harris J. Wheeler R *et al.* 2010. Human papillomavirus and survival of patients with oropharyngeal cancer. *New England Journal of Medicine*, July 1, 363(1), pp.82-84. **5.** American Cancer Society *Cancer Facts and Figures 2002* [Online] Available at: http://www.cancer.org/downloads/STT/CancerFacts&Figures2002TM.pdf [Last accessed April 2011]. | Last updated: June 2012

LET'S WORK

Boehringer Ingelheim

Study Goals

- Understand the molecular makeup of HNSCC patients
- Identify molecular subtypes within the patient cohort

Ryan Orosco

Quyen Nguyen

Study Goals

- Understand the molecular makeup of HNSCC patients
- Identify molecular subtypes within the patient cohort

Ryan Orosco

Quyen Nguyen

Trey Ideker

- Develop methods for integrating data across diverse measurement platforms
- Isolate genetic interactions in a cancer cohort

Preface

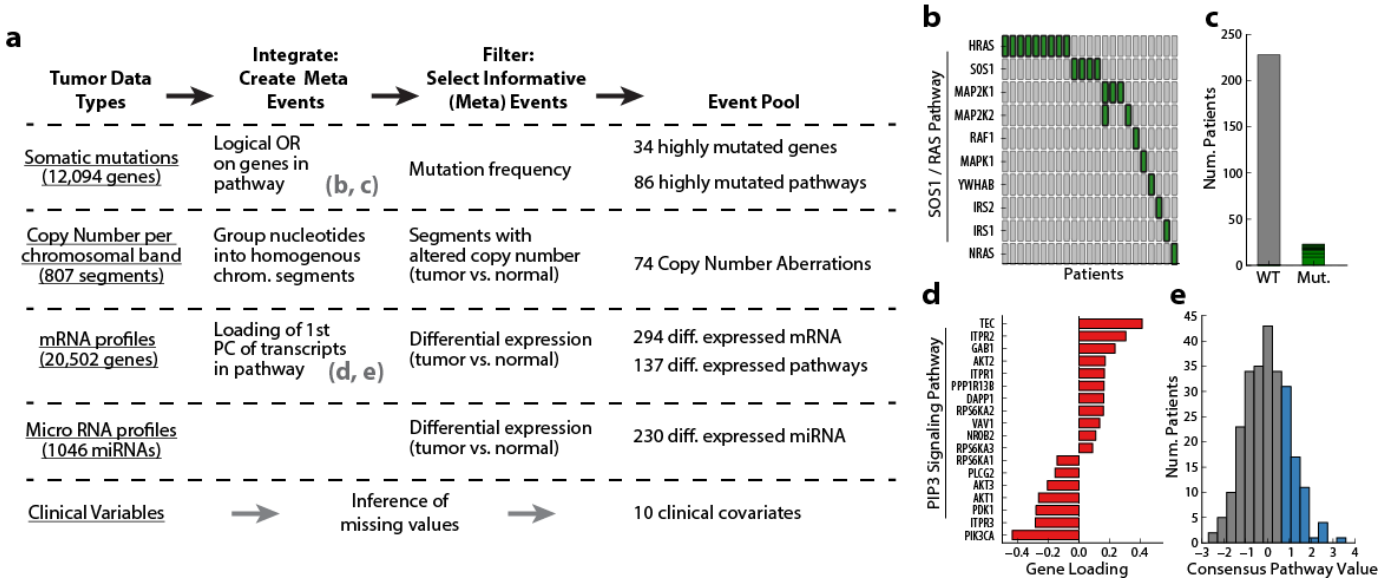
- Unpublished data, manuscript under review
- Find me tomorrow at **Poster #101**
- Reproducible analysis pipeline available soon: `github.com/theandygross/TCGA`

Selection Criteria

- Full molecular data as of January 15th Firehose Run
- Age under 85
- No HPV detected
- 251 patient discovery cohort

Study Design

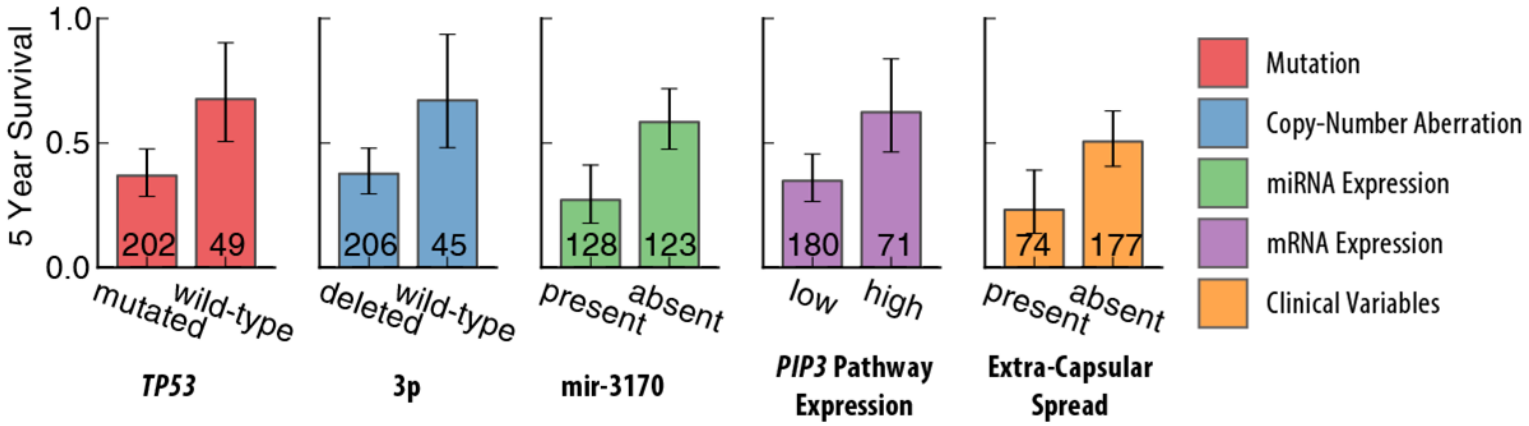
- Define a set of candidate biomarkers



Poster #101

Study Design

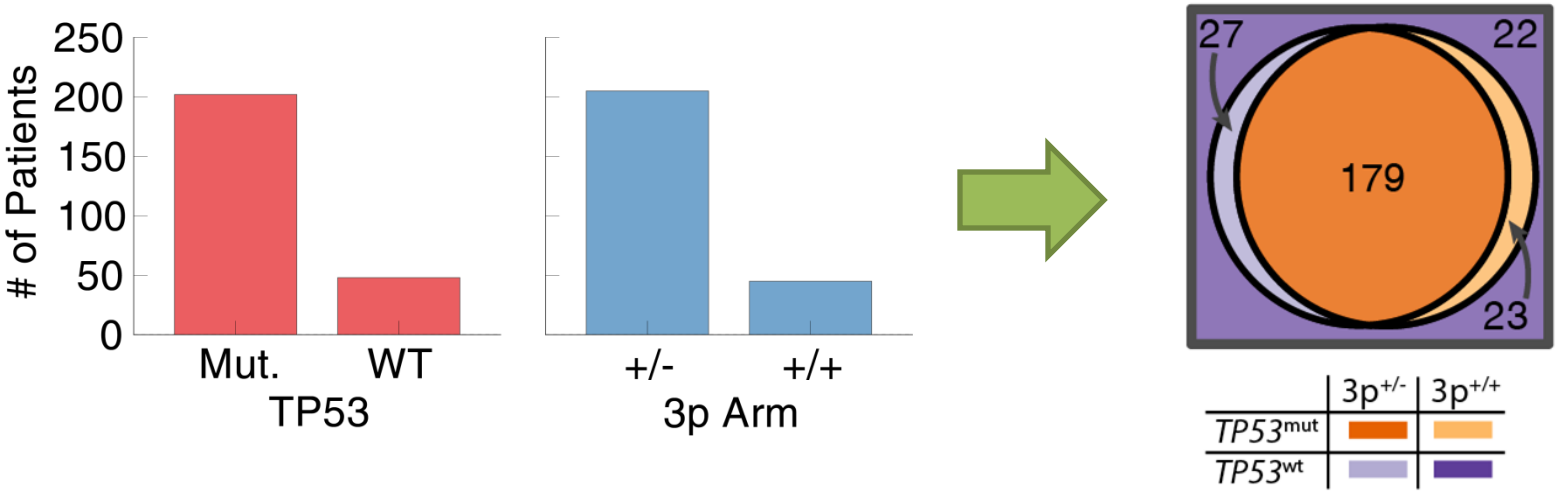
- Define a set of candidate biomarkers
- Identify biomarkers that stratify the patient cohort with respect to outcomes



Poster #101

Study Design

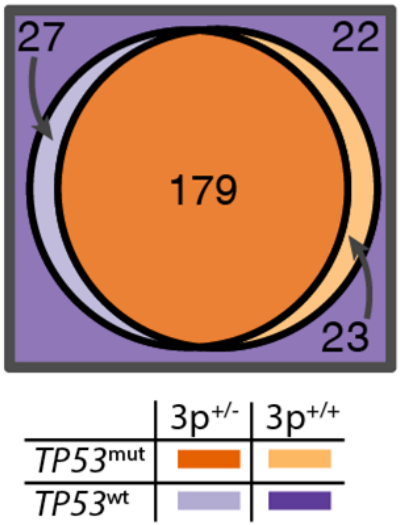
- Define a set of candidate biomarkers
- Identify biomarkers that stratify the patient cohort with respect to outcomes
- Look for associations among pairs of prognostic biomarkers



Poster #101

TP53-3p Event

- TP53 mutation and 3p deletion are highly co-occurring



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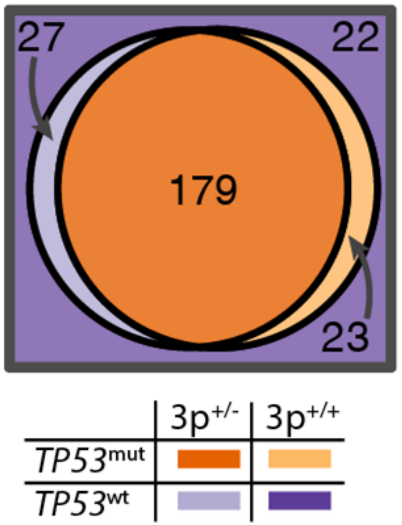
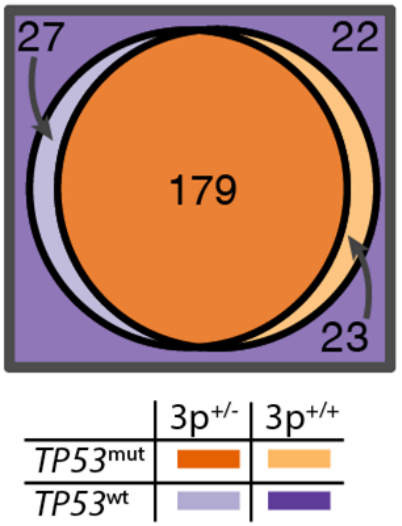


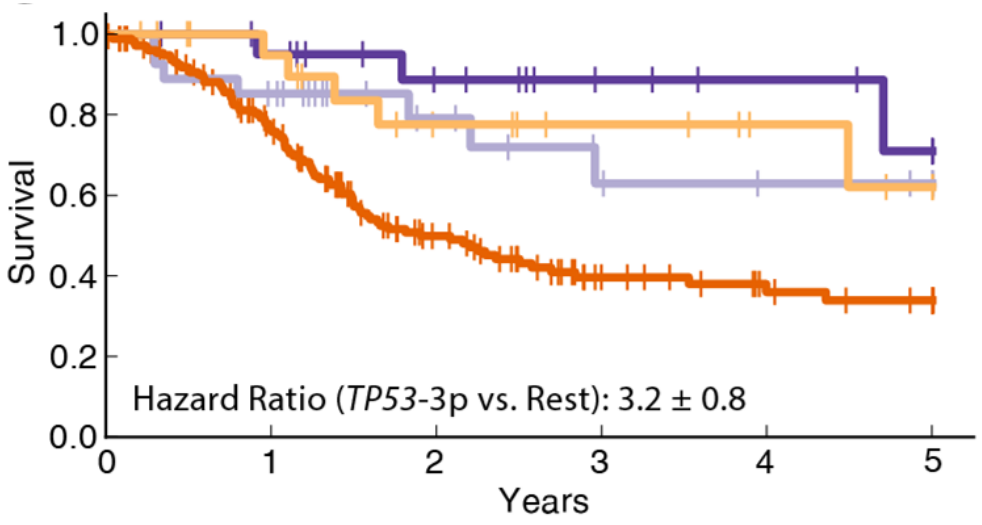
			Co-occurrence of *TP53* / 3p events	
Cohort		*n*	Odds Ratio	*p*
TCGA	Discovery	251	6.3	10^{-4*}
Recent TCGA	Validation	111	7.9	10^{-4}

* Bonferroni corrected for test space

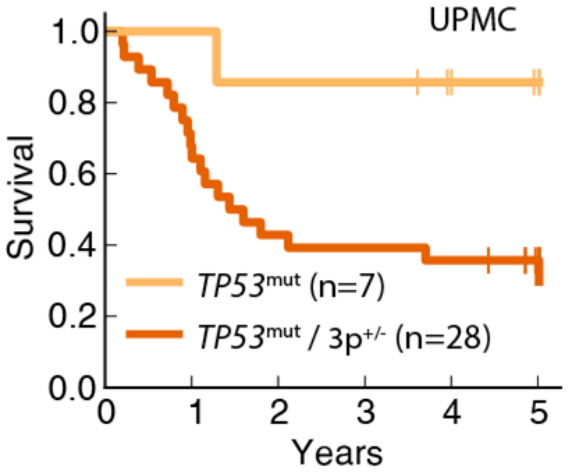
TP53-3p Event

- TP53 mutation and 3p deletion are highly co-occurring
- The adverse prognostic effect of TP53 is mediated by 3p





Independent Validation



Science. 2011 Aug 26;333(6046):1157-60. doi: 10.1126/science.1208130. Epub 2011 Jul 28.

The mutational landscape of head and neck squamous cell carcinoma.

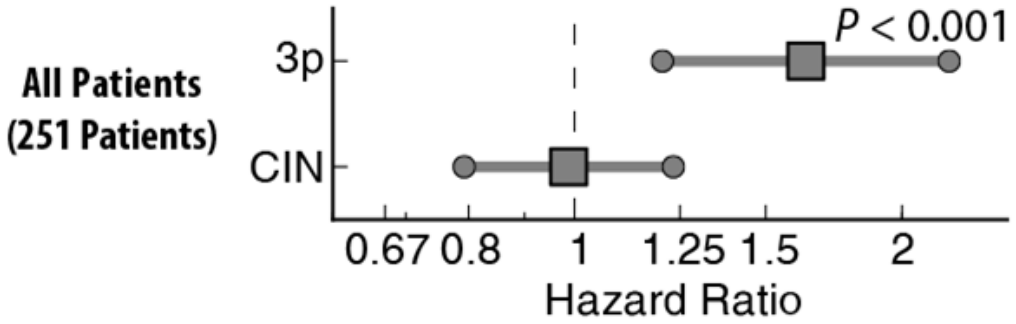
Stransky N[1], Egloff AM, Tward AD, Kostic AD, Cibulskis K, Sivachenko A, Kryukov GV, Lawrence MS, Sougnez C, McKenna A, Shefler E, Ramos AH, Stojanov P, Carter SL, Voet D, Cortés ML, Auclair D, Berger MF, Saksena G, Guiducci C, Onofrio RC, Parkin M, Romkes M, Weissfeld JL, Seethala RR, Wang L, Rangel-Escareño C, Fernandez-Lopez JC, Hidalgo-Miranda A, Melendez-Zajgla J, Winckler W, Ardlie K, Gabriel SB, Meyerson M, Lander ES, Getz G, Golub TR, Garraway LA, Grandis JR.

Jenn Grandis

Ann Marie Egloff

Are we seeing an artifact of the relationship between TP53 and Chromosomal Instability?

3p vs. Chromosomal Instability



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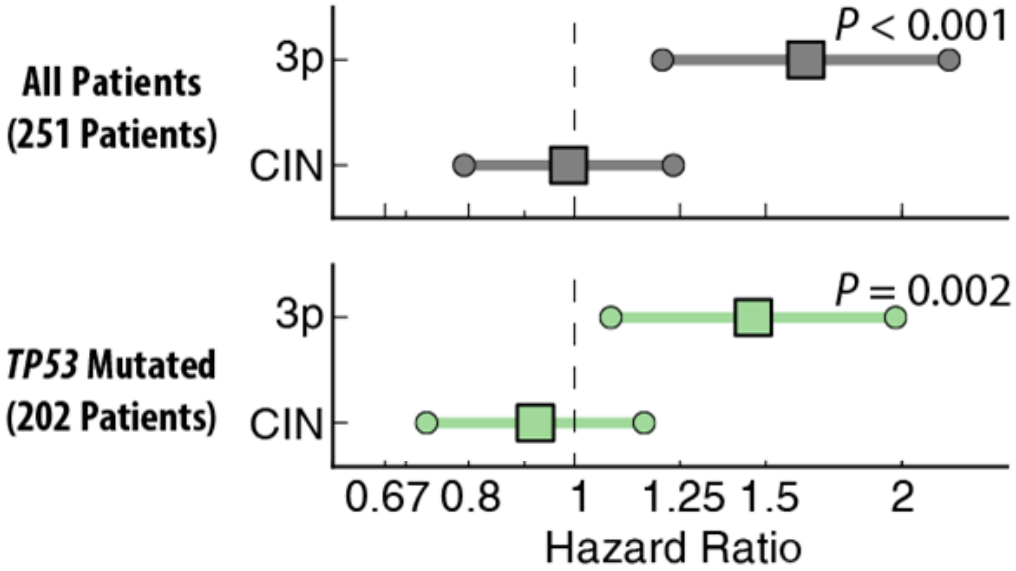

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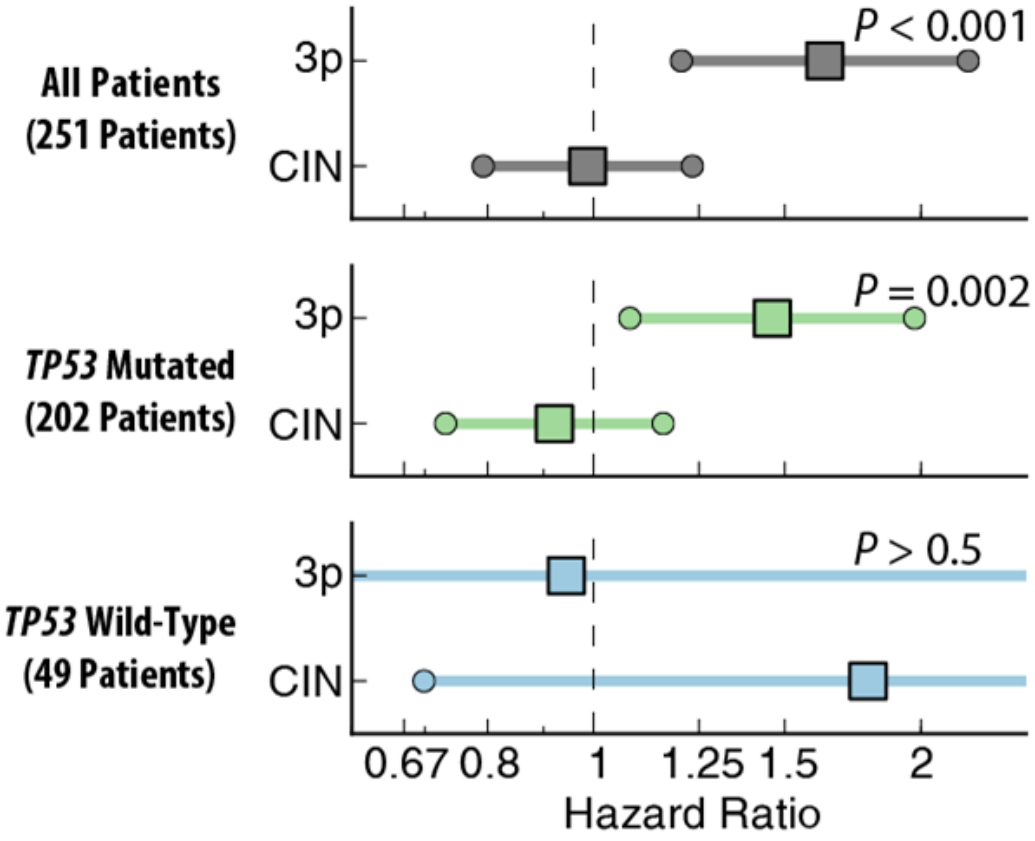
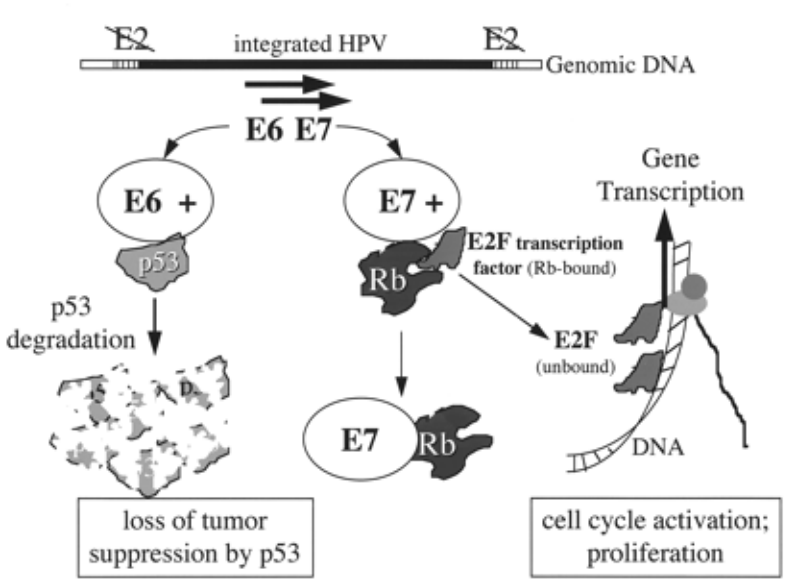


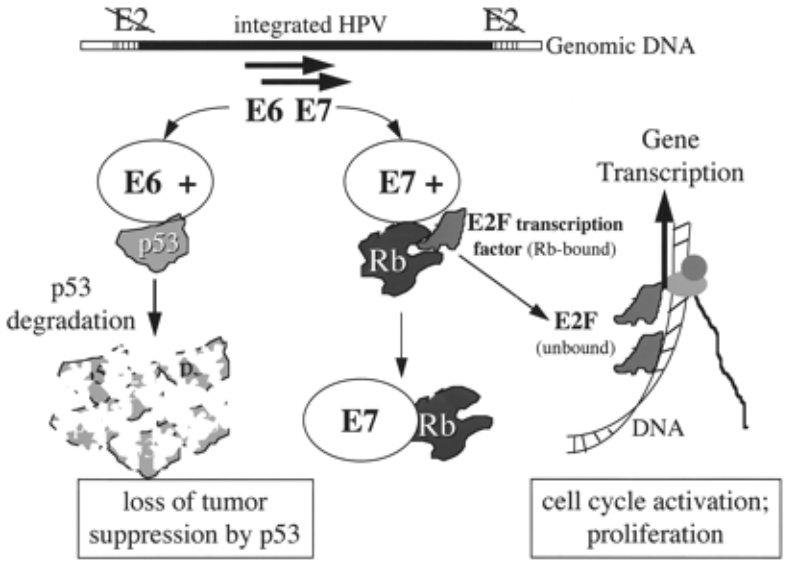
Can we see something similar in HPV+ patients?

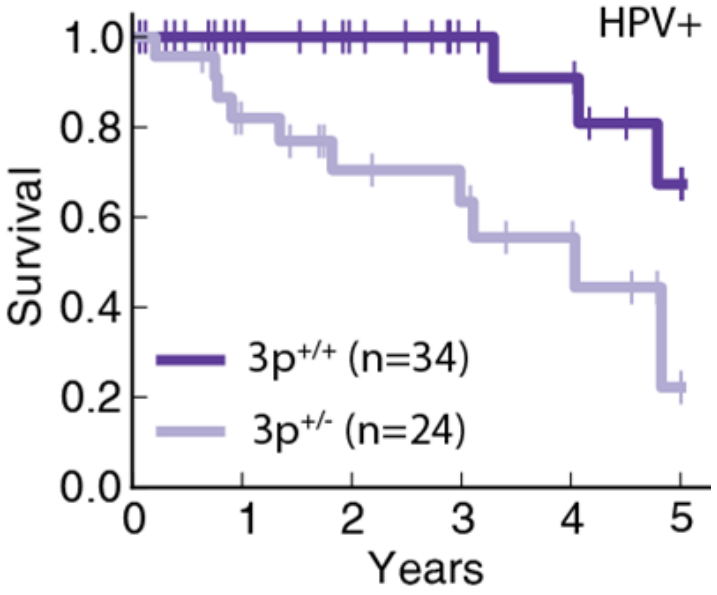
3p and HPV



M. El Mzibri, et. al (2012). DOI: 10.5772/29279.

3p and HPV

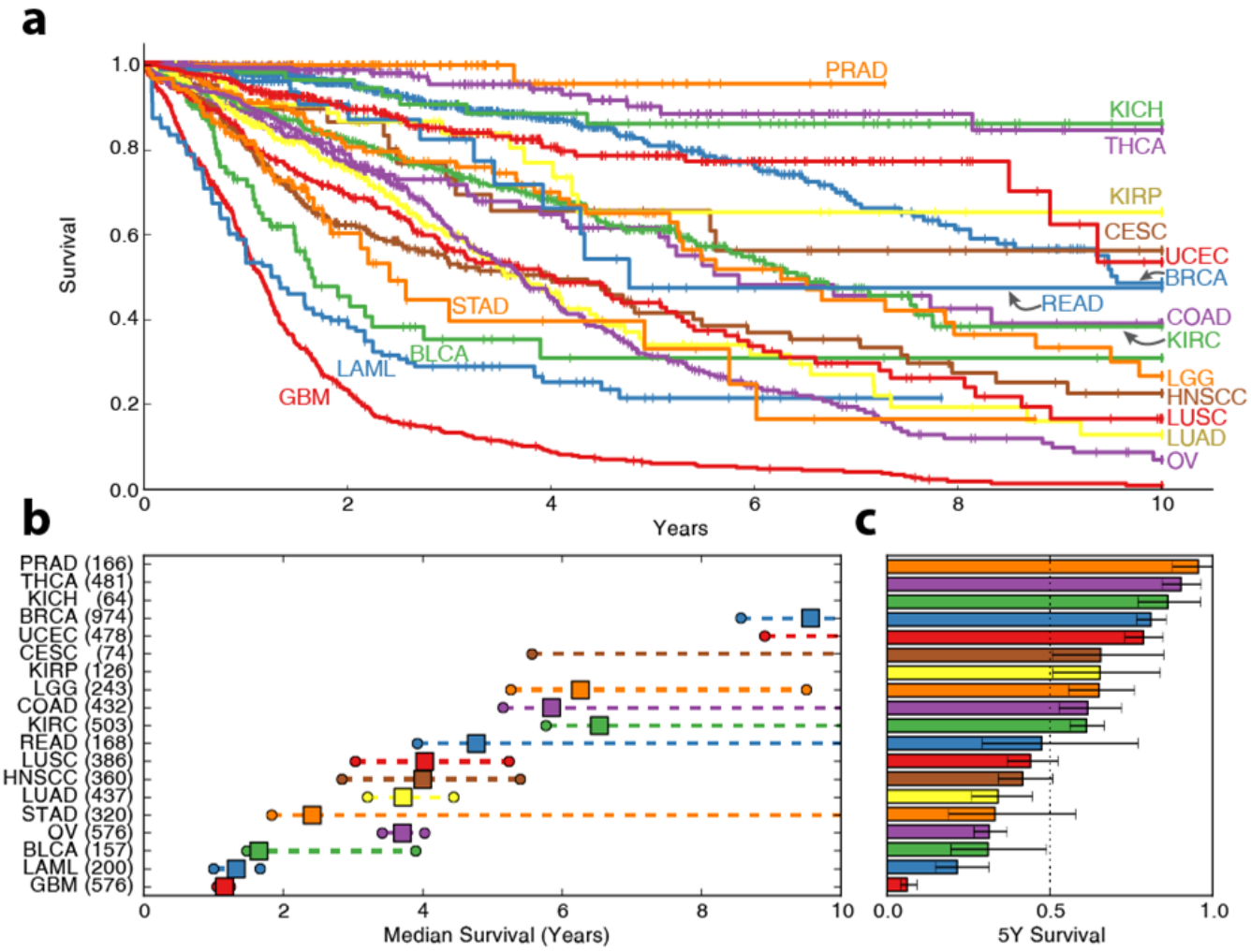




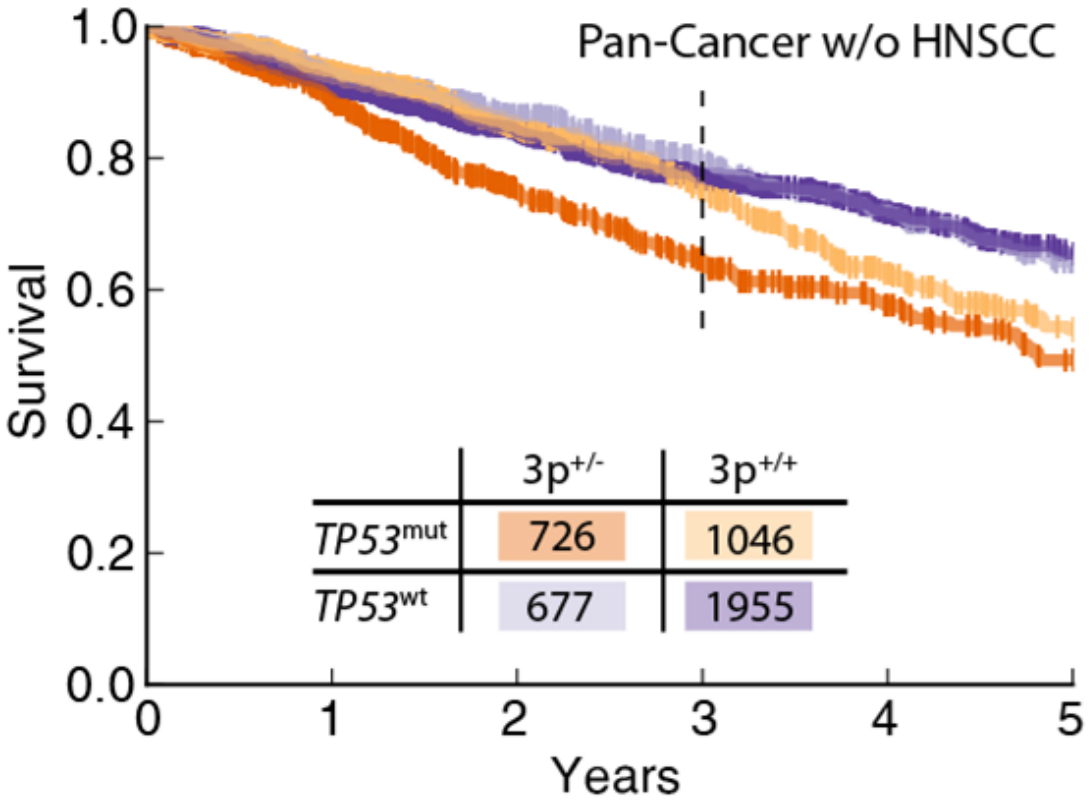
M. El Mzibri, et. al (2012). DOI: 10.5772/29279.

Does this generalize to other types of cancers?

PanCancer Analysis



PanCancer Analysis



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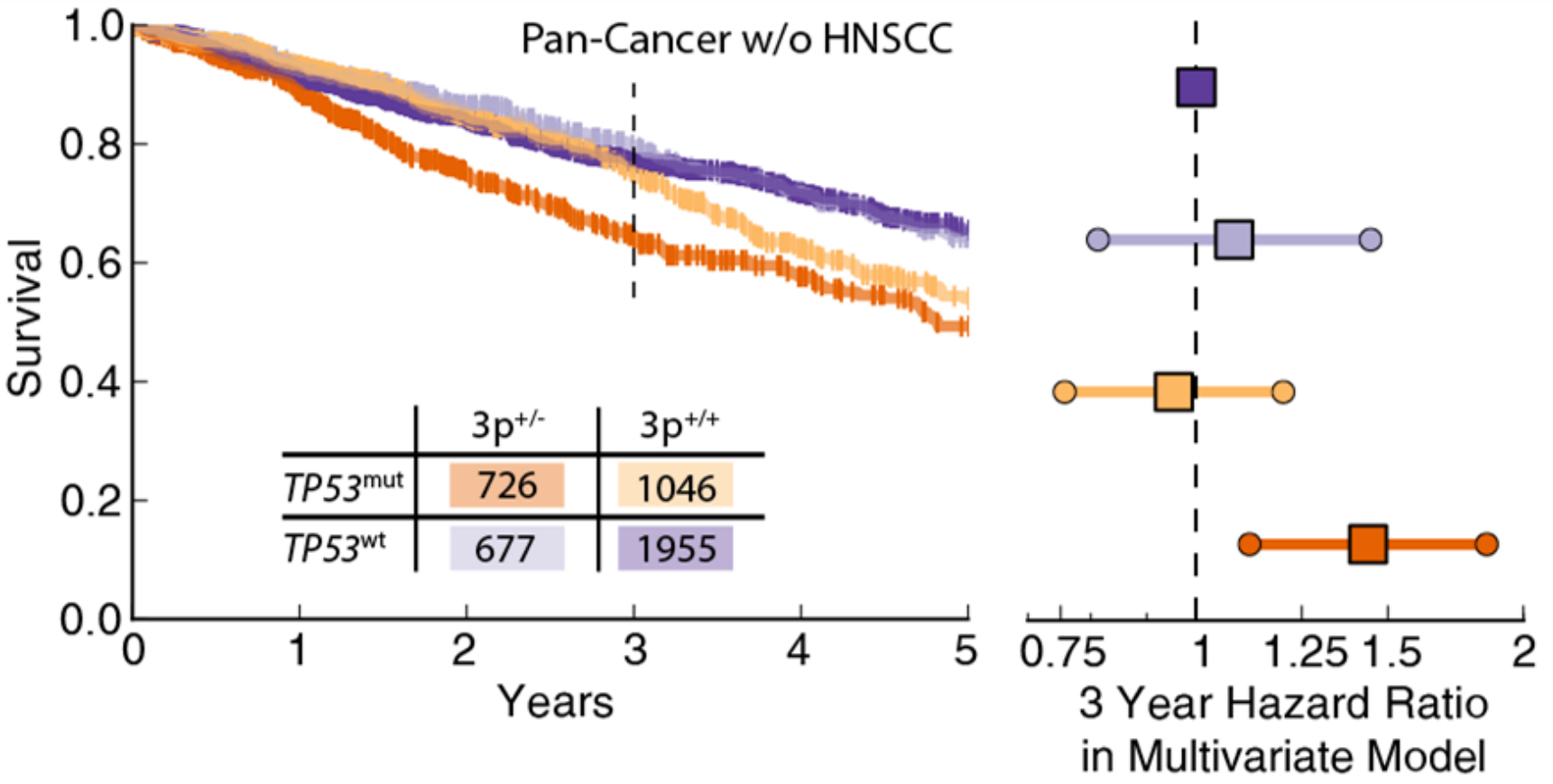

Can we further stratify the cohort?

Secondary Prognostic Screen

- 179 patients with TP53 mutation and 3p loss
- Repeat feature construction / prognostic screen

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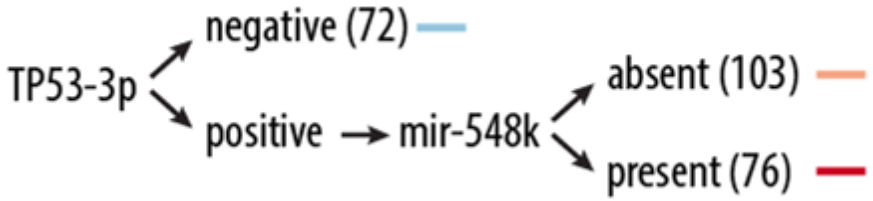
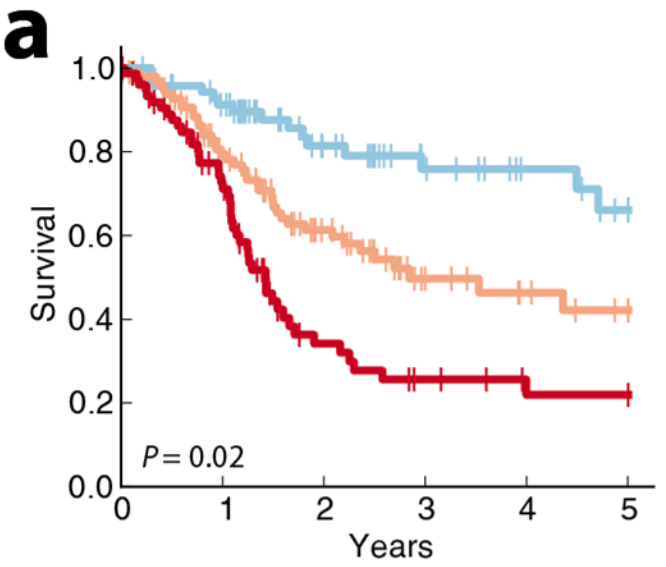
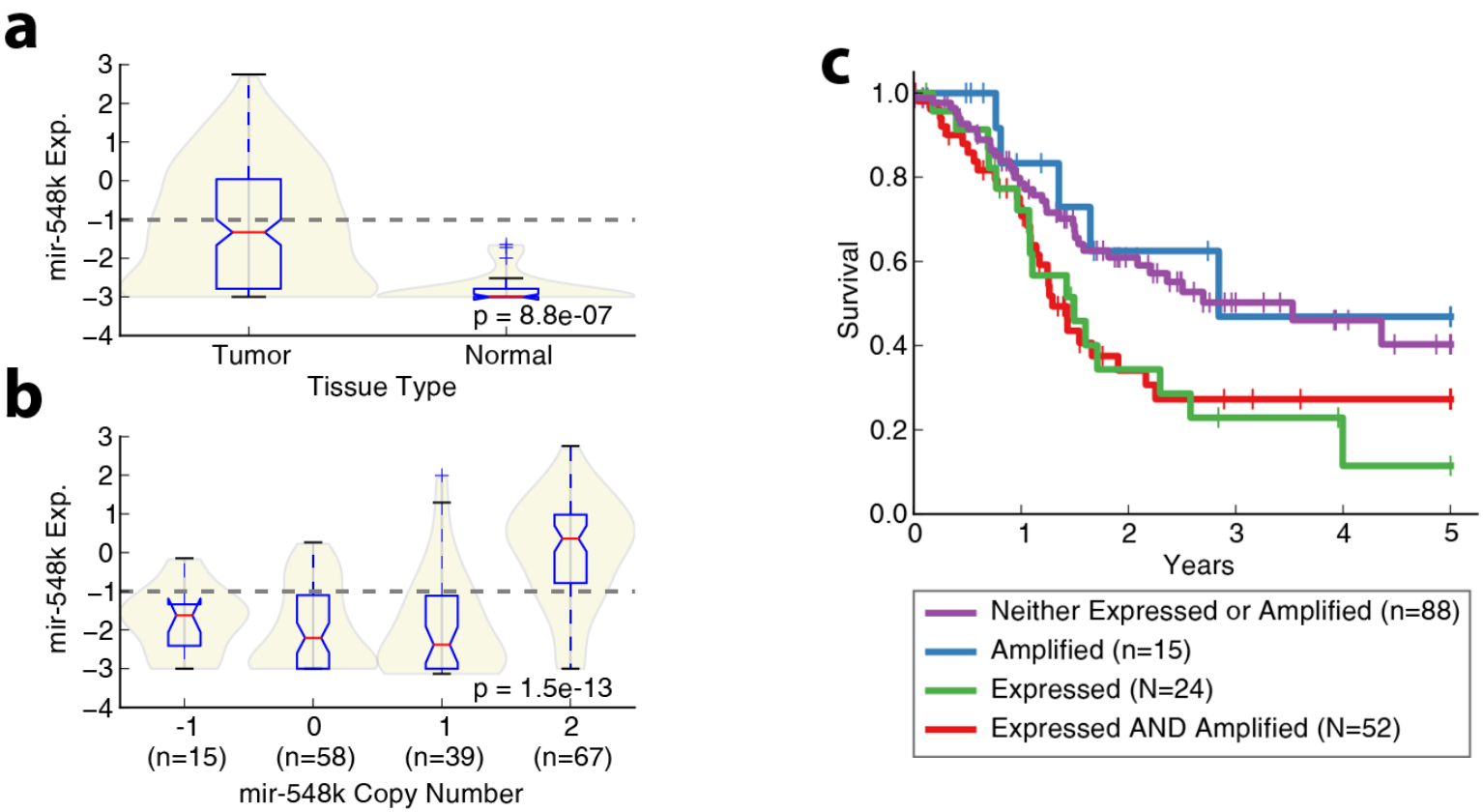
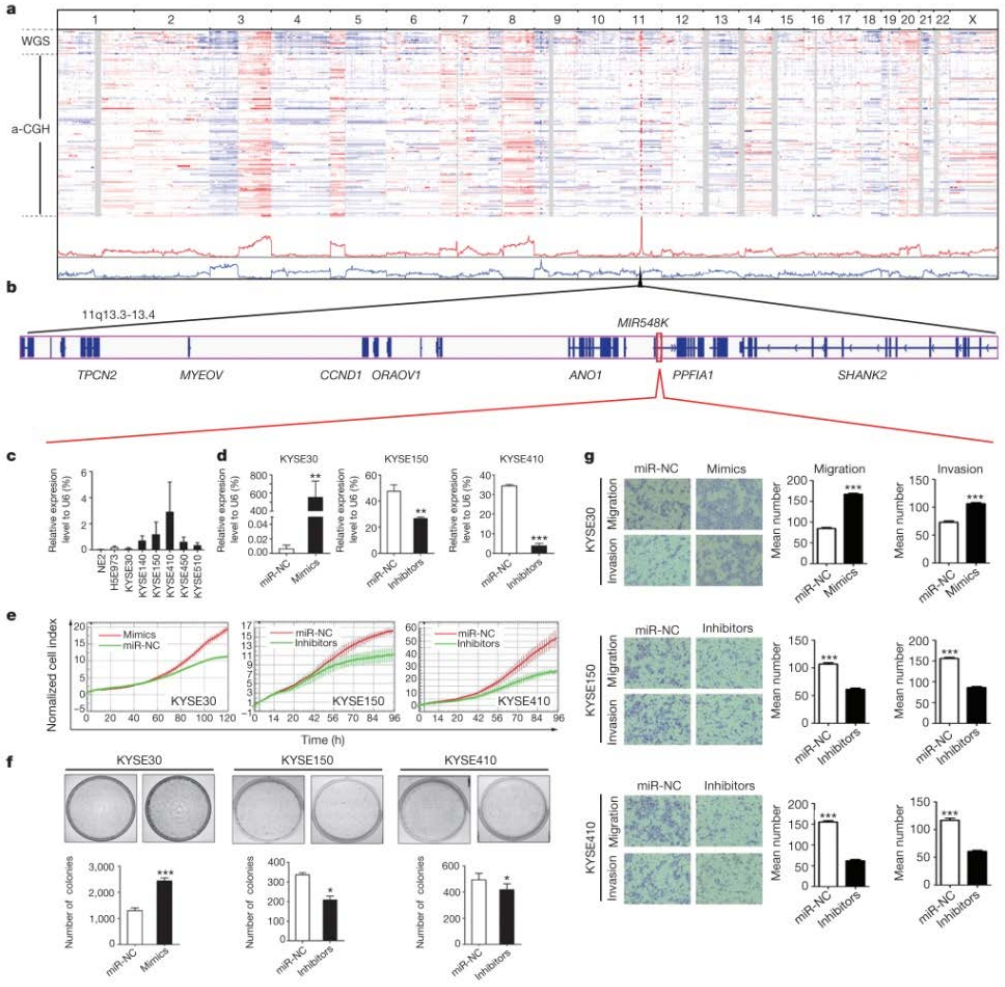




mir-548k


a
mir-548k Exp.
3
2
1
0
−1
−2
−3
−4
p = 8.8e-07
Tumor
Normal
Tissue Type
b
mir-548k Exp.
p = 1.5e-13
-1
(n=15)
0
(n=58)
1
(n=39)
2
(n=67)
mir-548k Copy Number
c
Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Years
Neither Expressed or Amplified (n=88)
Amplified (n=15)
Expressed (N=24)
Expressed AND Amplified (N=52)

Landscape of genomic copy number alterations in ESCC andoncogenic *MIR548K* identified from significantly amplified region.



Y Song *et al. Nature* **000**, 1-5 (2014) doi:10.1038/nature13176

nature

But what is going on in patients without TP53-3p?

Secondary Association Screen

- Many redundant CNA linked by chromosomal instability
- Limit features to mutation events

Secondary Association Screen

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- Limit features to mutation events

			Co-occurrence of *TP53*-3p event and *CASP8* mutation			Co-occurrence of *TP53*-3p event and *RAS* Signaling Pathway† mutation		
Cohort		*n*	*# patients mutated*	Odds Ratio	*p*	*# patients mutated*	Odds Ratio	*p*
TCGA	Discovery	251	21	0.13	3×10^{-3}*	23	0.11	4×10^{-4}*
TP53-3p positive		179	6			6		
TP53-3p negative		72	15			17		

Secondary Association Screen

- Many redundant CNA linked by chromosomal instability
- Limit features to mutation events

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TP53-3p positive		179	6			6		
TP53-3p negative		72	15			17		
Recent TCGA	Validation	111	19	0.052	2×10^{-6}	21	0.071	4×10^{-6}
TP53-3p positive		66	2			3		
TP53-3p negative		45	17			18		

† Biocarta SOS1 Mediated RAS Signaling Pathway (Reacome 524)

* Bonferroni corrected for test space of 120 gene and pathway mutation events

Conclusion

- TP53 mutation + 3p loss occurs in 70% of HNSCC patients
- In TP53-3p patients mir-548k leads to worse prognosis
- In absence of TP53-3p CASP8 and RAS signaling are important drivers

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Acknowledgments

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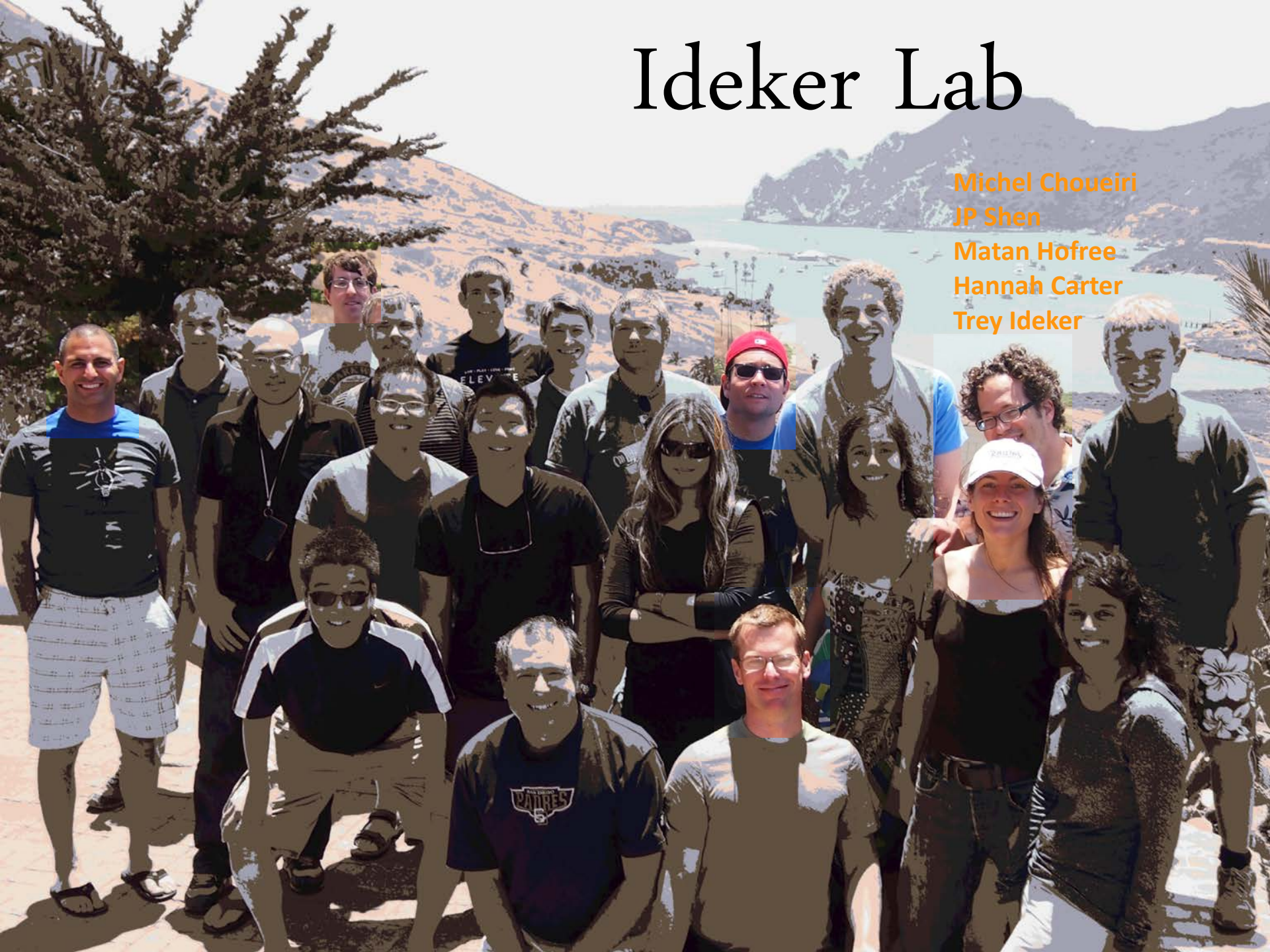
Ann Marie Egloff

UNC- Lineberger Cancer Center

Neil Hayes

Ideker Lab

Ideker Lab


Michel Choueiri
JP Shen
Matan Hofree
Hannah Carter
Trey Ideker