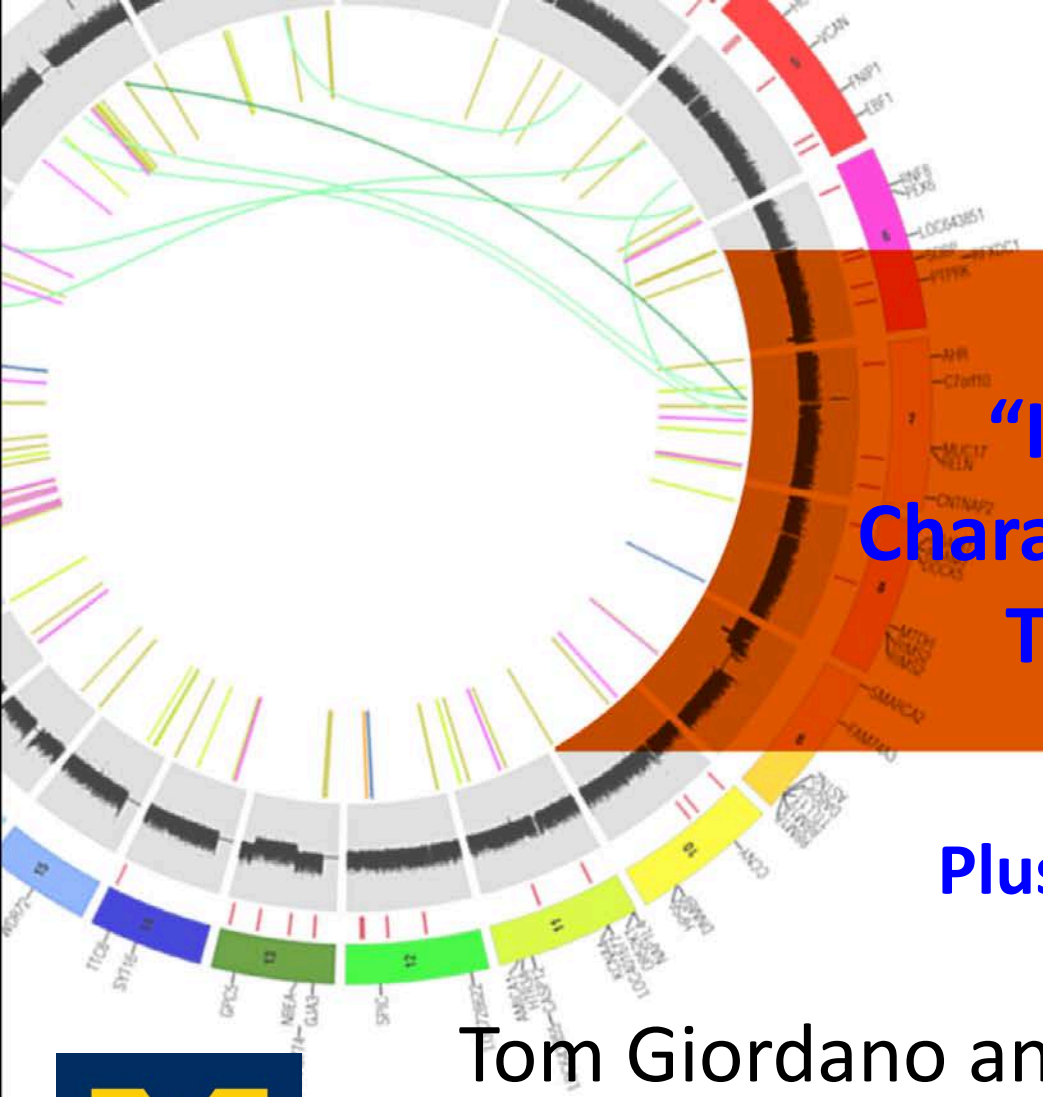


The Cancer Genome Atlas

Highlights of "Integrated Genomic Characterization of Papillary Thyroid Carcinoma"

Plus Poster #100

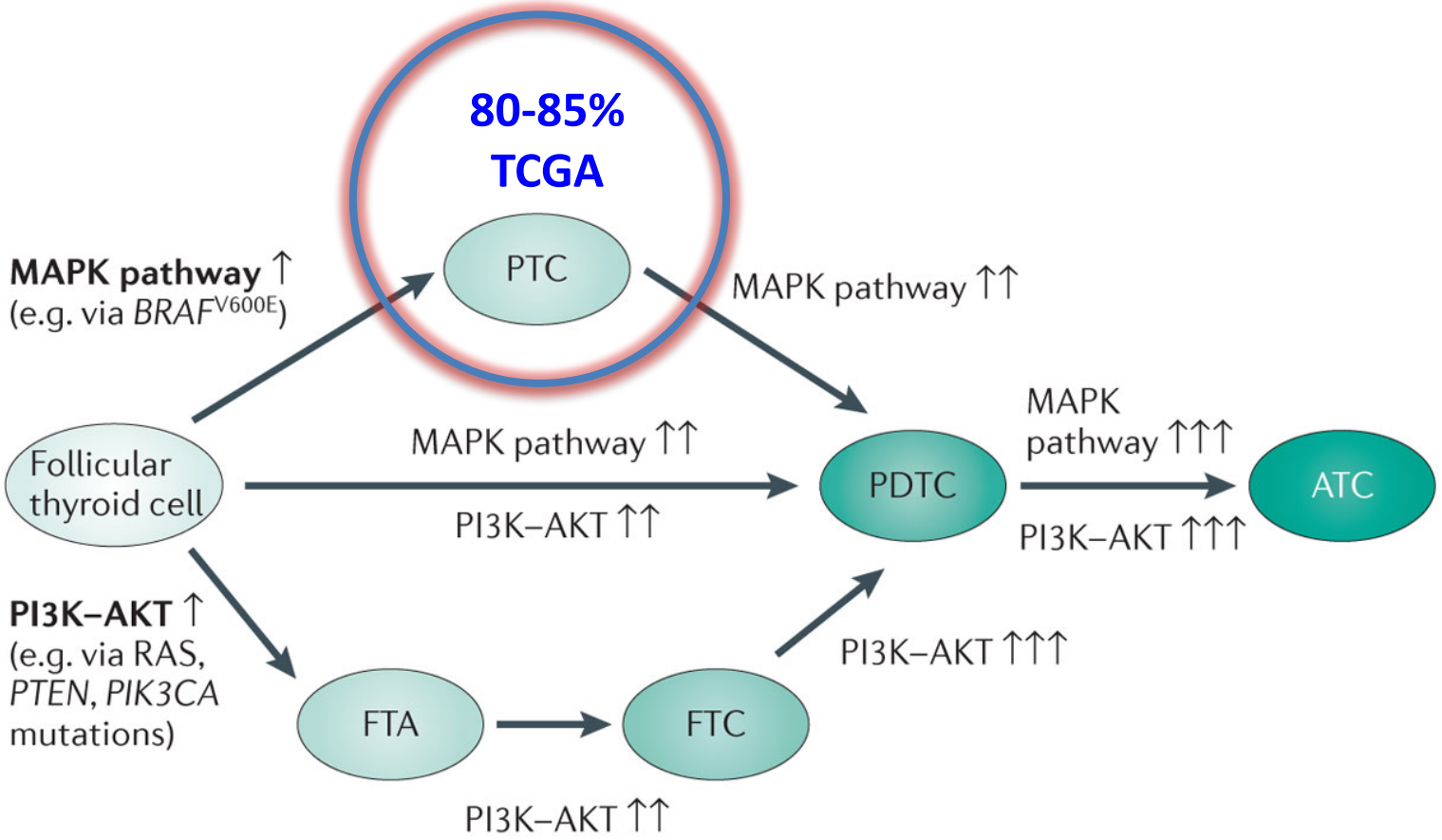
Tom Giordano and Gad Getz,
on behalf of the THCA AWG

UNIVERSITY OF MICHIGAN

VE RI TAS

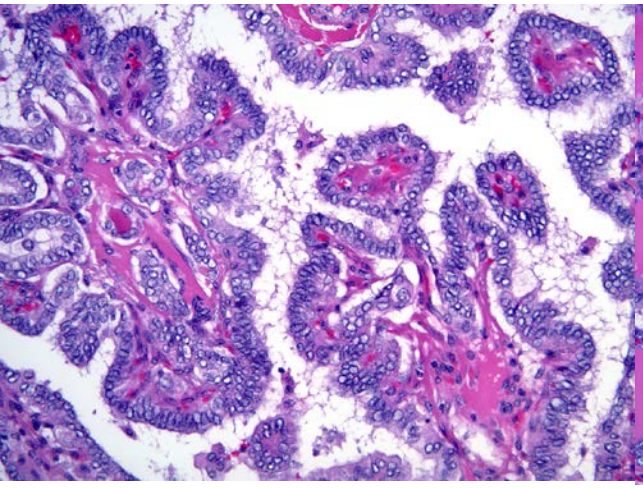
MGH 1811

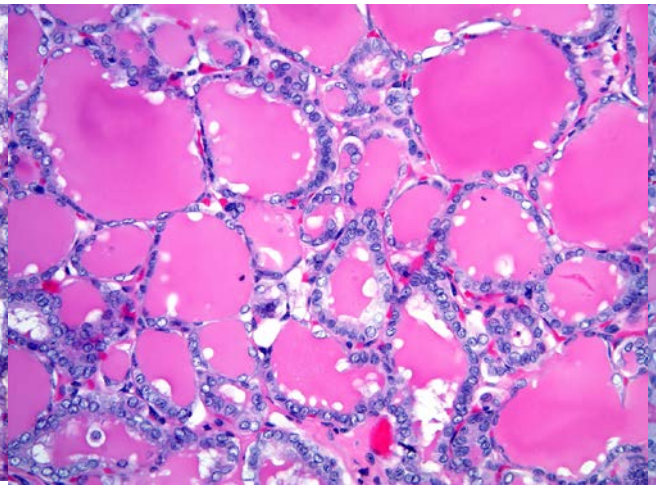
Simple model of thyroid cancer progression

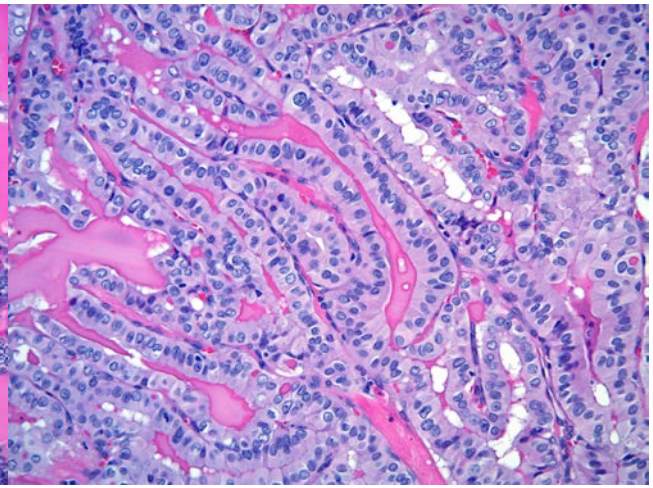


Mingzhao Xing, JHU

3 main histologic types of PTC





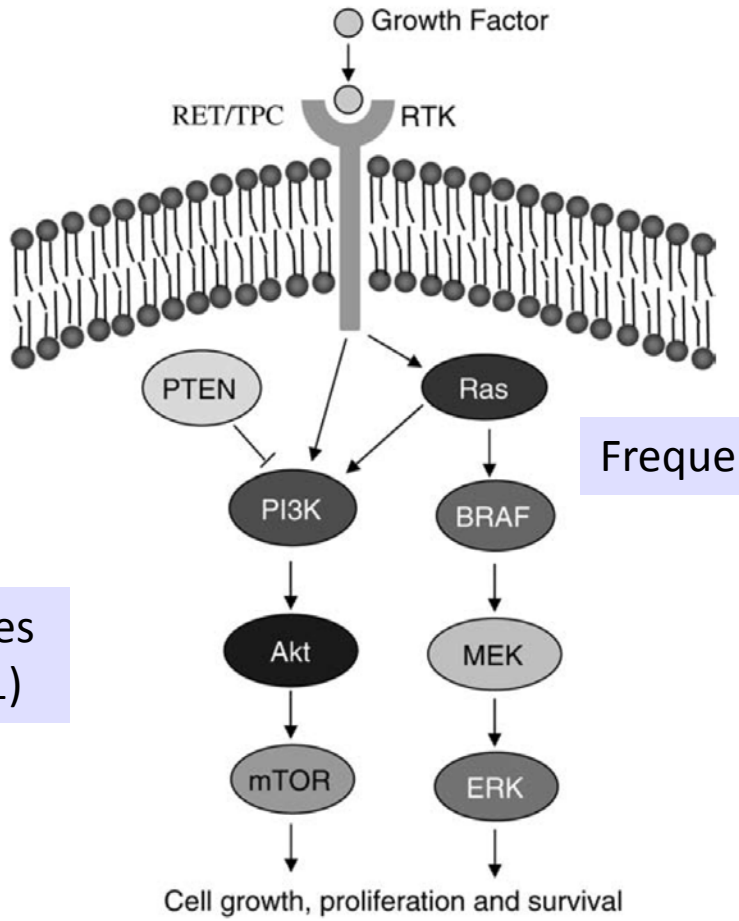


Classical	Follicular Variant	Tall Cell Variant
BRAF-V600E *RET* fusions	*RAS*	*BRAF*-V600E

Strong genotype - phenotype correlation

Cancer genes pre-TCGA

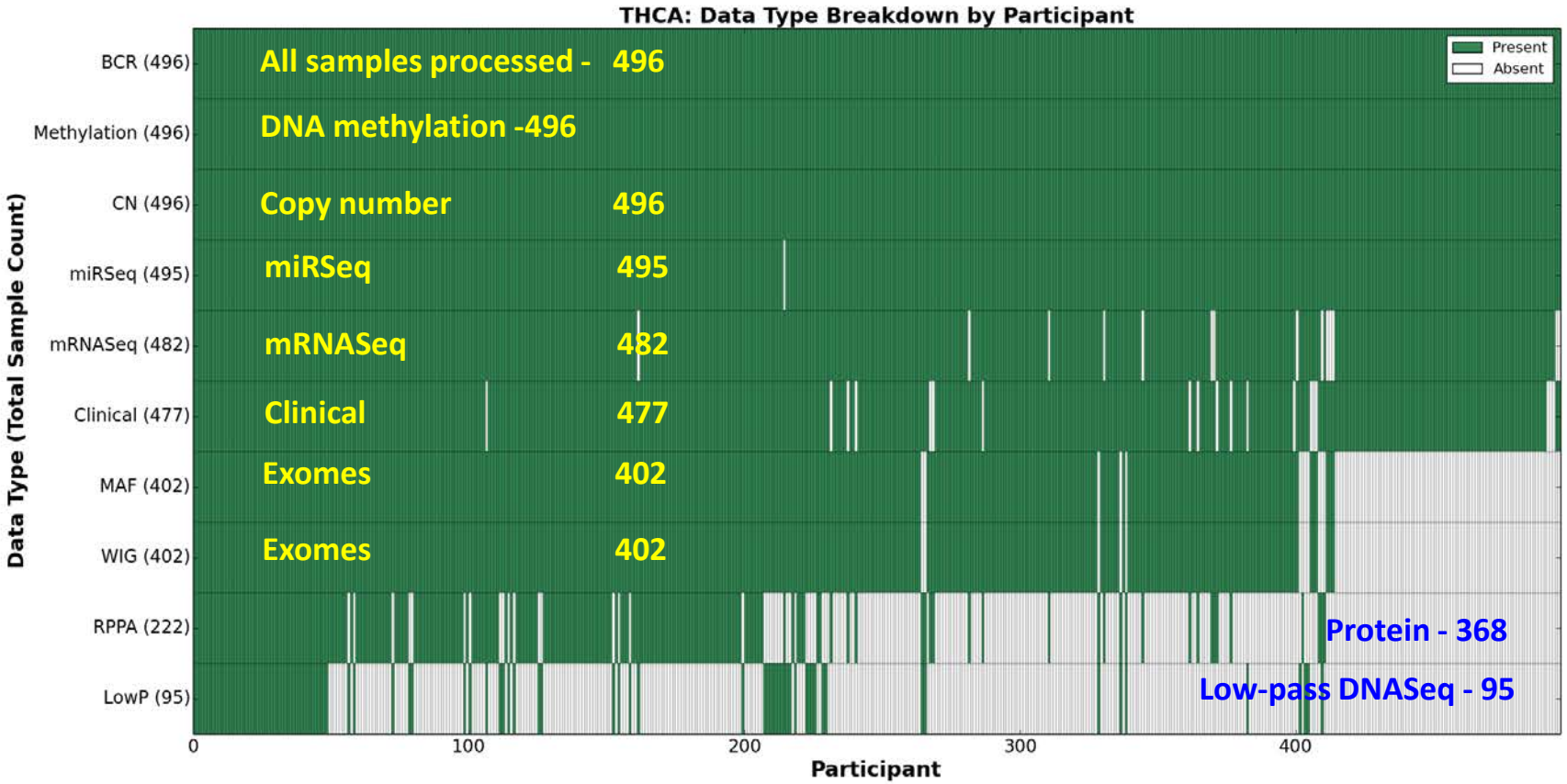
Translocations in RTKs (RET / NTRK1)



Frequent BRAF and RAS mutations

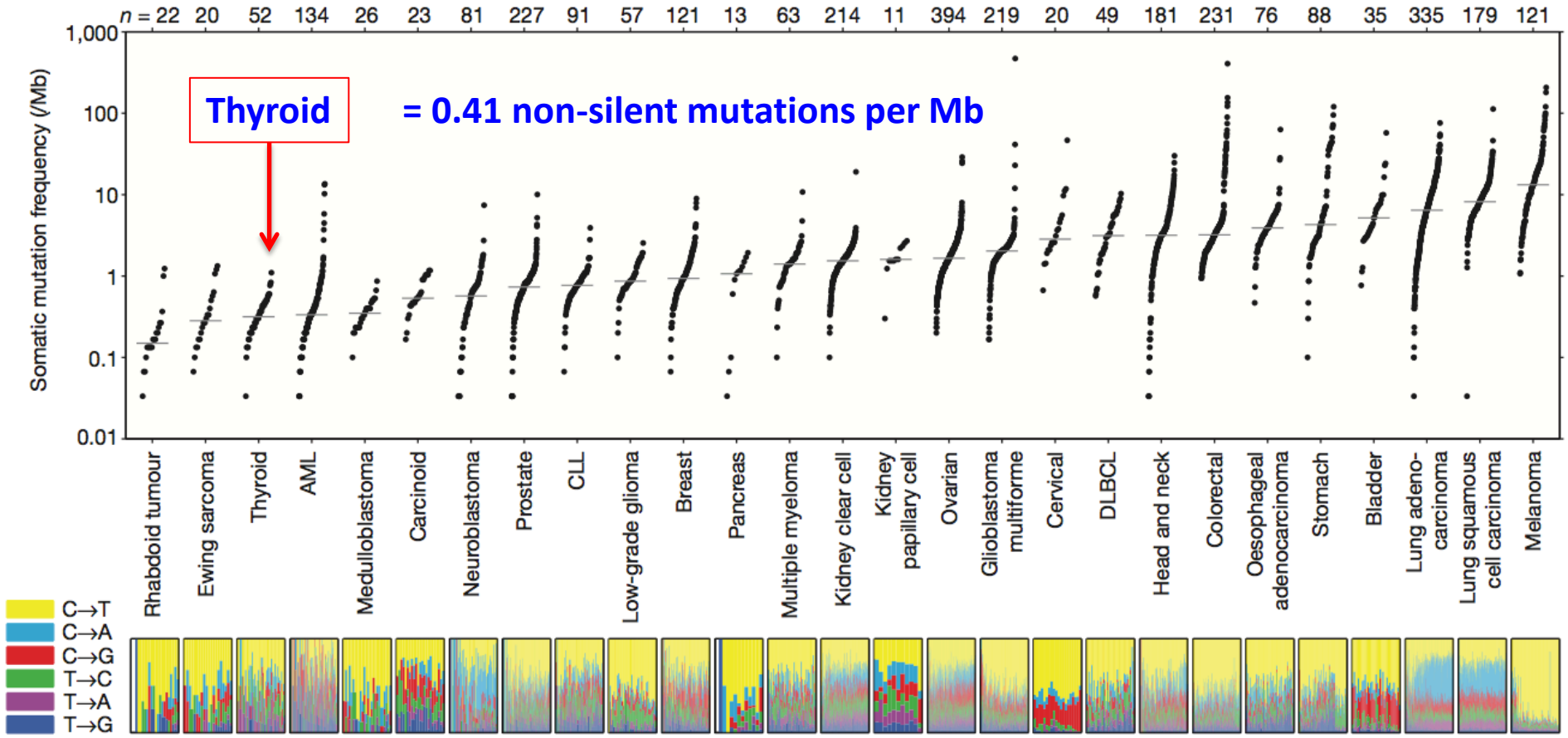
Infrequent PI3K genes
(PTEN, PIK3CA, AKT1)

496 primary PTCs
391 on all major platforms



Plus 49 whole genome sequences done with PTCs without apparent driver mutations

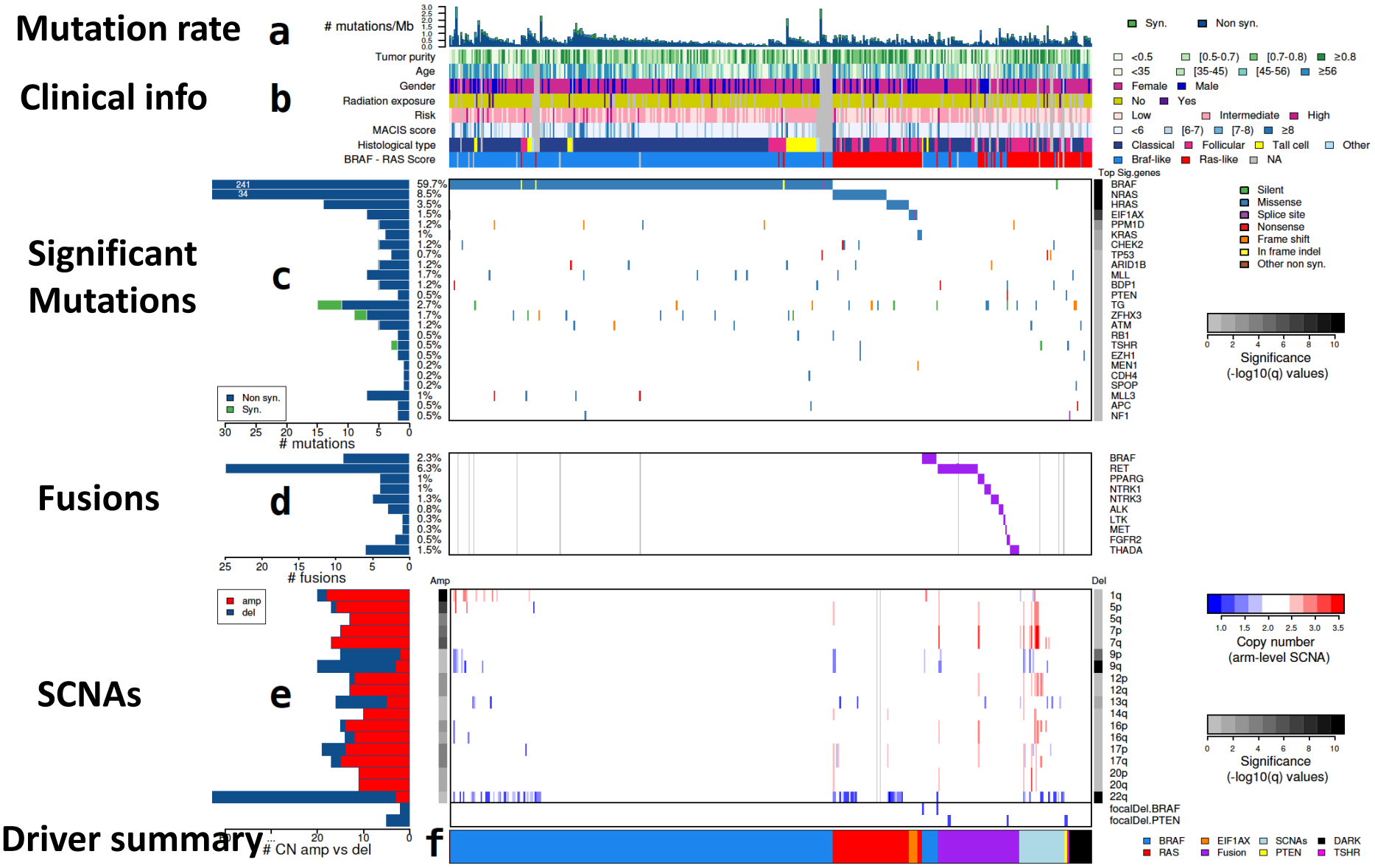
Relative mutation frequency



Somatic mutation frequencies observed in exomes from 3,083 tumor-normal pairs.

Lawrence et al. Nature 2013:499;214-218

Overview of somatic alterations



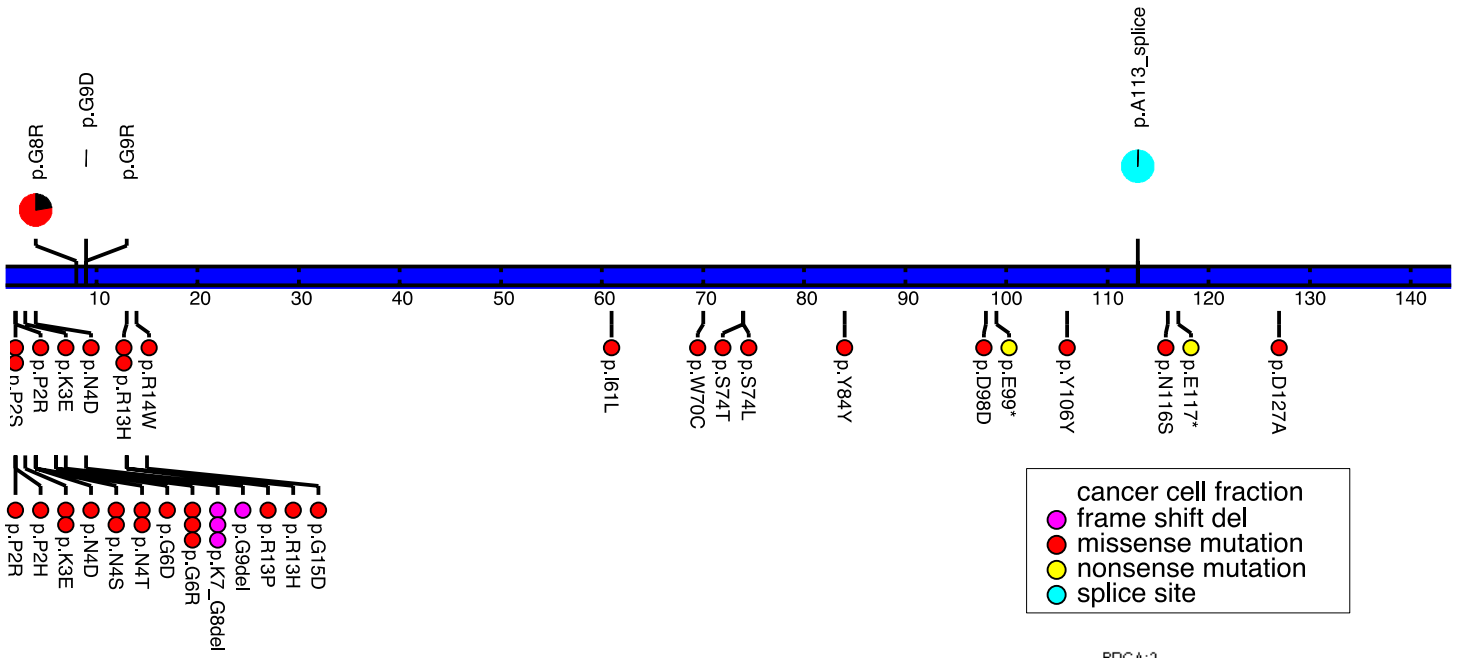
EIF1AX

Translation initiation factor 1A, X-linked

THCA:
6 mutations

COSMIC:
19 mutations
Endometrium, breast, colon, lung, esophagus, ovary and prostate

Uveal melanoma
20 mutations

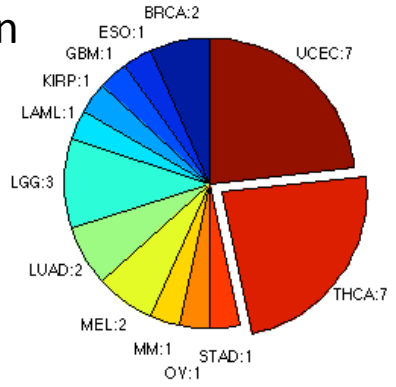


Exome sequencing identifies recurrent somatic mutations in *EIF1AX* and *SF3B1* in uveal melanoma with disomy 3

Marcel Martin[1,2], Lars Maßhöfer[3], Petra Temming[4], Sven Rahmann[1], Claudia Metz[5], Norbert Bornfeld[5], Johannes van de Nes[6], Ludger Klein-Hitpass[7], Alan G Hinnebusch[8], Bernhard Horsthemke[3], Dietmar R Lohmann[3,9] & Michael Zeschnigk[3,9]

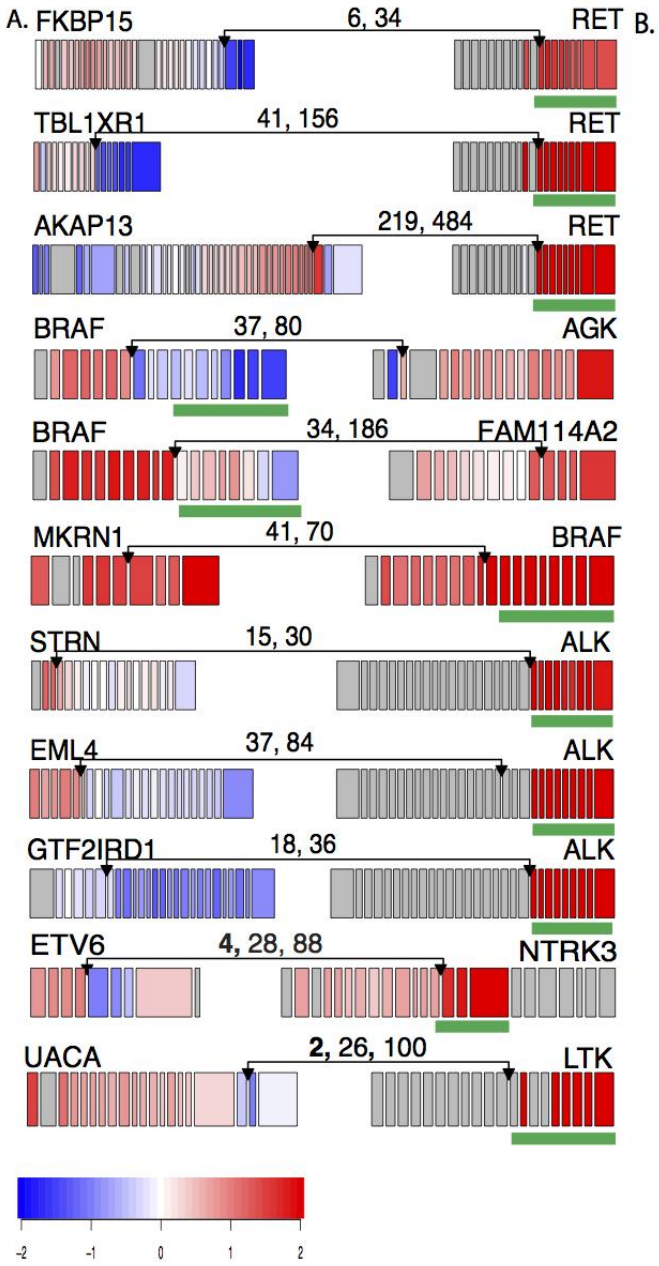
NATURE GENETICS VOLUME 45 | NUMBER 8 | AUGUST 2013

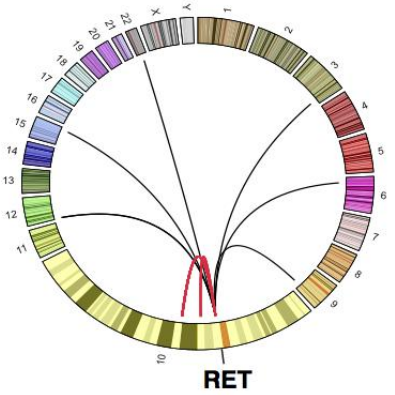
Pan-can
EIF1AX
count

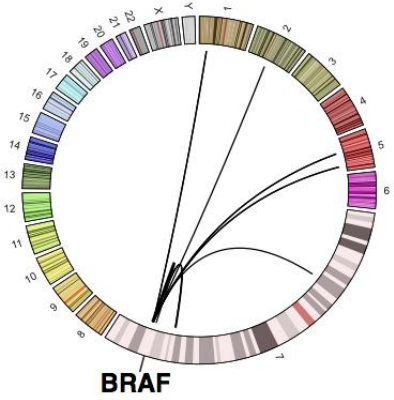


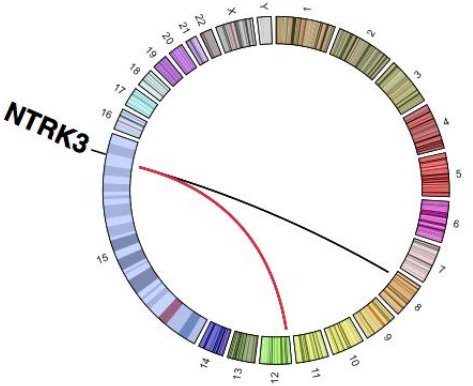
Fusions

- New *RET* partners
- Diverse *BRAF* fusions
- ALK fusions, diverse
  - (*EML4-ALK*)
- *ETV6-NTRK3*







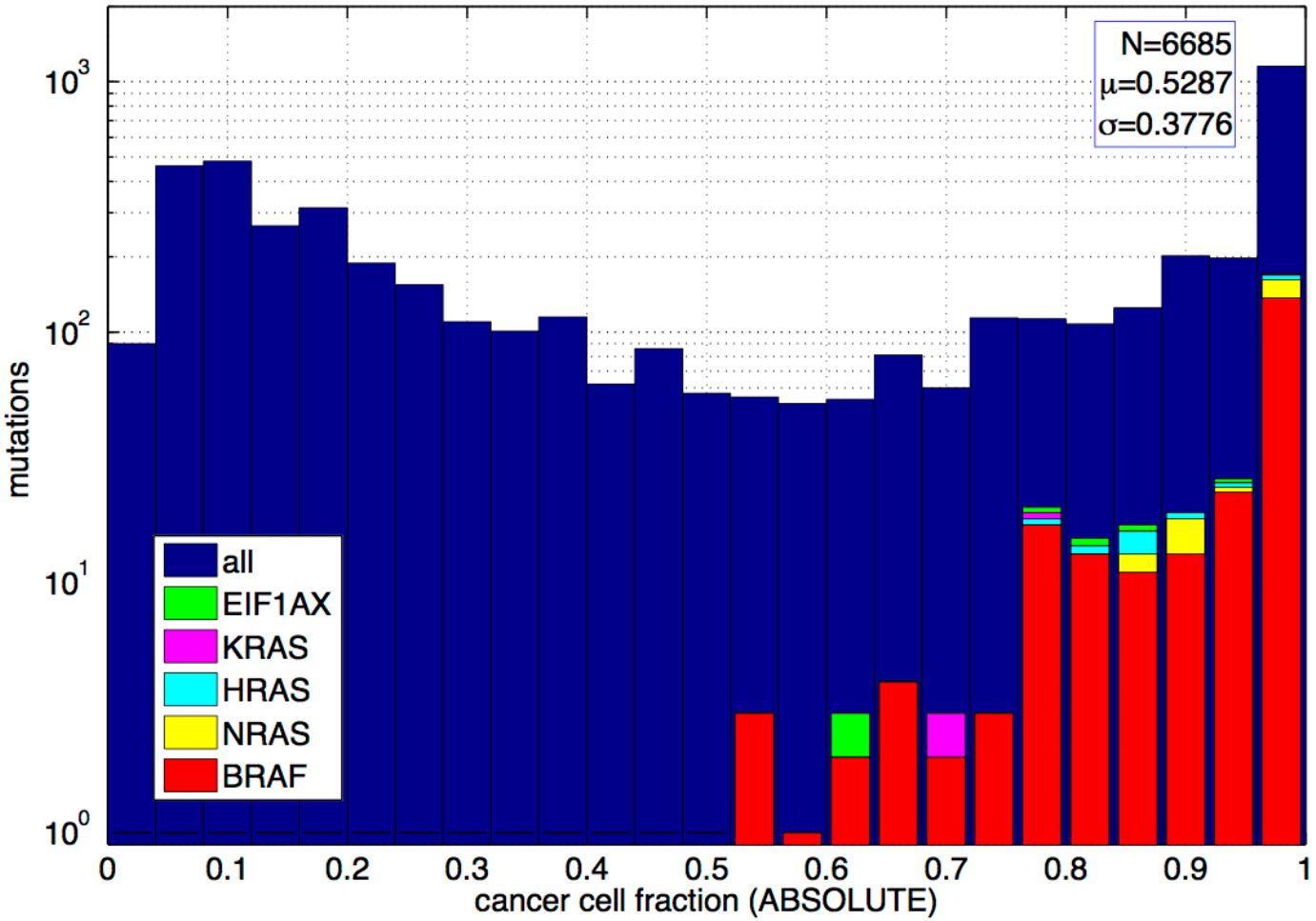


Angela Hadjipanayis, Harvard
Katie Hoadley, UNC
Chip Stewart, Broad Institute

Even remaining 14 out of 402 ‘dark matter’ samples are not entirely dark

TUMOURS	Age	Gender	Histological type	Risk	MACIS	Purity	Mutation density, non-syn	Mutation density, non-driver	BRS	TDS	T stage	N stage	M stage	Cancer gene census gene mutations	Protein Change	Somatic Rearrangments
TCGA-BJ-A191-01A	49	FEMALE	Other specify			0.95	0.816	0.544	0.464	-0.320	T1b	N0	M0			
TCGA-BJ-A28T-01A	34	FEMALE	Classical/usual	Intermediate		0.11	0.100	0.100	-0.107	1.588	T1	N1a	M0	ATM	ATM:p.L2452P:3	
TCGA-DJ-A13R-01A	50	MALE	Follicular	Intermediate	5.5	0.56	0.701	0.501	0.448	0.782	T3	N0	M0			
TCGA-E8-A416-01A	51	FEMALE	Classical/usual	Low	4.53	0.40	0.000	0.000	0.393	1.645	T1b	N0	M0			
TCGA-EL-A3CX-01A	22	FEMALE	Classical/usual	Low	4.09	1.00	0.311	0.276	0.169	-4.084	T2	N0	M0	APC	APC:p.R213*:16	
TCGA-EL-A3H1-01A	66	FEMALE	Classical/usual	Low	5.88	0.89	1.076	0.816	0.887	1.490	T1	N0	M0	CHD4	CHD4:p.V1492G:4	translocation CYCS-WARS
TCGA-EM-A1CW-01A	39	FEMALE	Follicular	Intermediate	4.45	0.50	0.549	0.377	0.863	1.576	T3	N0	MX	NF1, KDM5A	NF1:p.E244_splice:19; KDM5A:p.K1162Q	
TCGA-EM-A2CP-01A	26	FEMALE	Follicular	Low	4.06	0.04	0.236	0.169	0.558	0.510	T2	N0	MX			Antisense fusion: NFE2L2/TG; Protein fusion: out of frame: PAX8/SLA; Protein fusion: out of frame CLCA1/RPP30; Protein fusion: in frame HERC4/CLCA1; tandem_dup TG Duplication of 12 exons: in frame; Antisense fusion NFE2L2/TG; Protein fusion: in frame PAX8/NFE2L2
TCGA-EM-A2OV-01A	64	FEMALE	Follicular	Low	5.75	0.68	0.904	0.770	0.896	1.795	T2	N0	MX	EZH1	EZH1:p.Y642F:26	
TCGA-EM-A3FL-01A	63	FEMALE	Follicular	Low	5.49	0.48	0.841	0.538	0.931	1.949	T1b	NX	MX			
TCGA-EM-A3FR-01A	55	FEMALE	Classical/usual	Intermediate	5.3	0.74	0.837	0.703	0.888	0.950	T2	N1a	MX	SPOP	SPOP:p.P94R:45	
TCGA-ET-A3DV-01A	68	FEMALE	Follicular	Intermediate	7.7	1.00	0.669	0.401	0.874	1.183	T3	N0	MX			
TCGA-FK-A3SD-01A	61	FEMALE	Classical/usual	Low		0.80	1.171	0.836	0.990	1.806	T1	N0	M0	MLL, PDE4DIP, FBXO11	MLL:p.K1574R:3; PDE4DIP:p.Q2060K; FBXO11:p.Q72*	
TCGA-FY-A2QD-01A	61	FEMALE	Classical/usual	Low	6.68	0.90	0.211	0.141	0.908	1.798	T1	N0				Protein fusion: in frame NFIX/GATAD2A

Common Drivers are clonal



Chip Stewart, Broad Institute

Challenges of THCA project

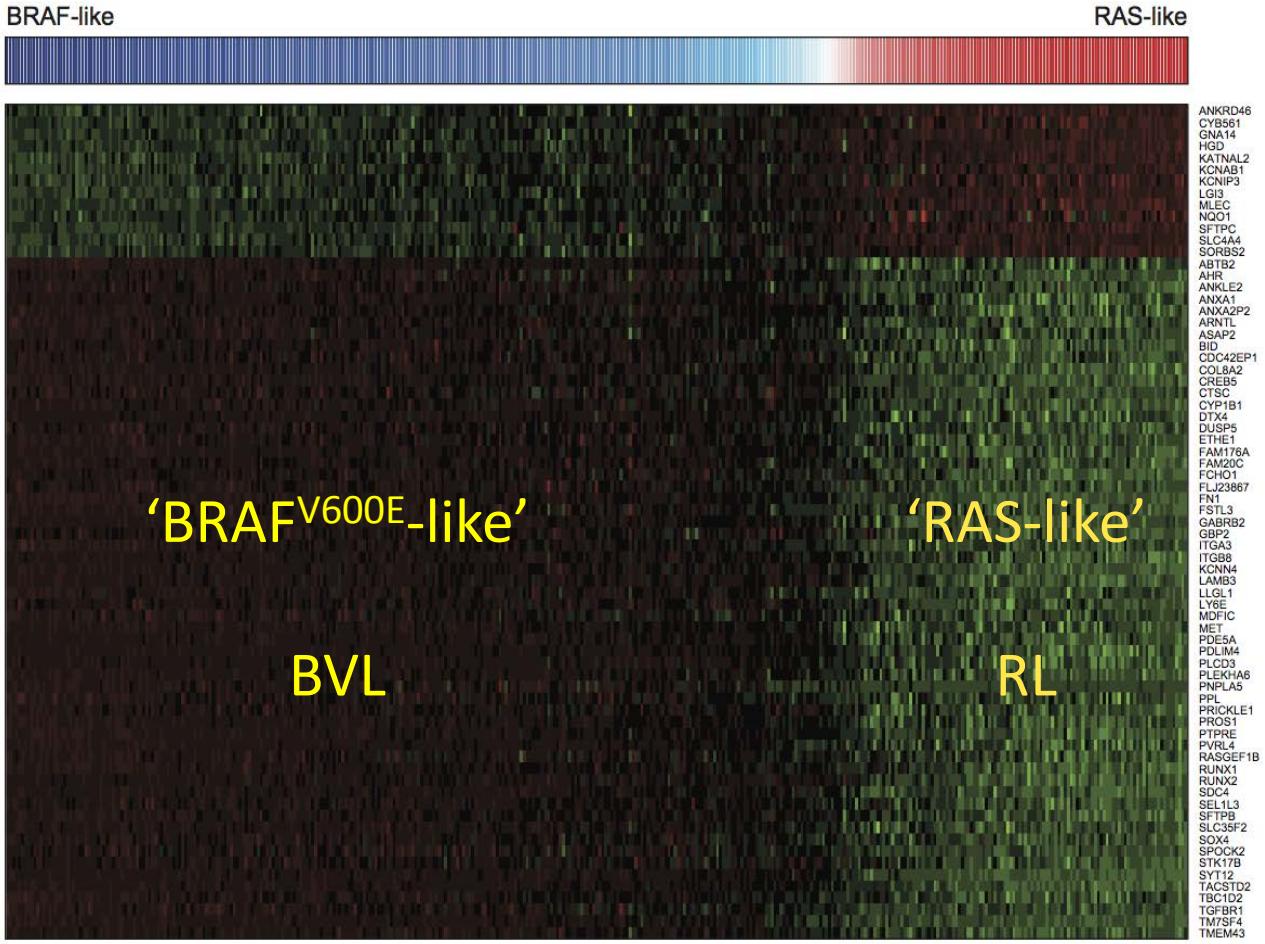
- Focused on papillary carcinoma
  - Indolent cancer type with 95% cure rate
  - No long term follow-up data (need 20 years)
- Relative low mutation density compared to other carcinomas

Two choices

- Report on a few new SSNVs, fusions, clusters, etc.

- Strive to tell a clinically-relevant story that leveraged the:
  - mutual exclusively of the drivers, *BRAF* and *RAS*
  - quiet nature of PTC genome
  - availability of multidimensional data
  - imagination of the AWG members

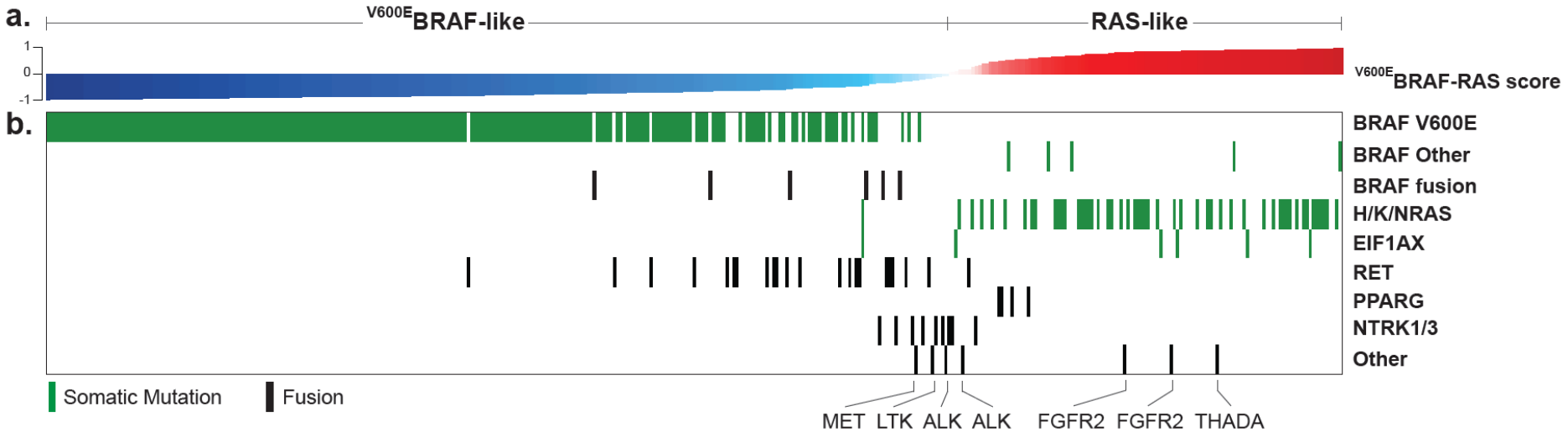
BRAF^{V600E}-*RAS* Score (BRS)



71 gene signature

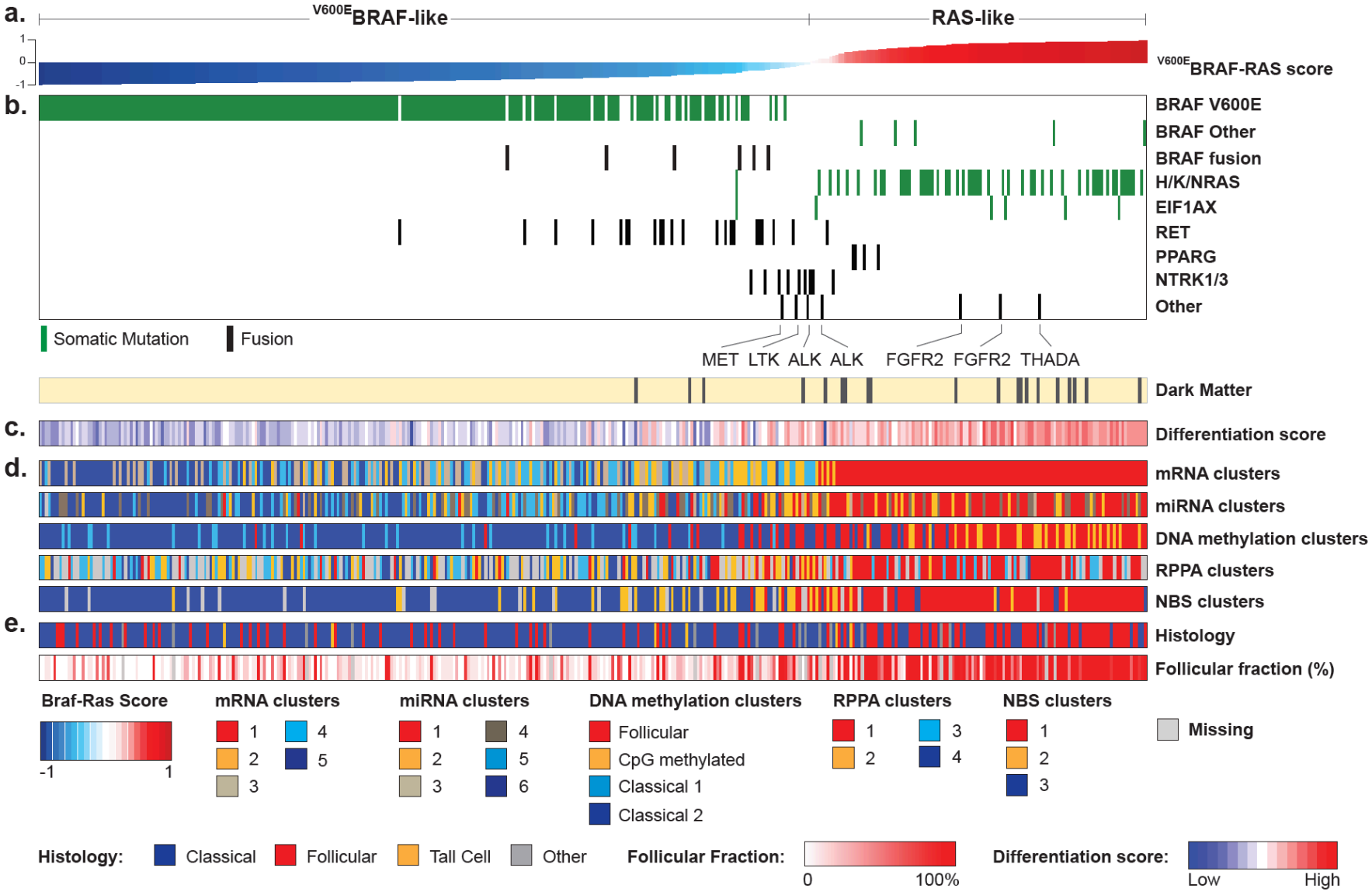
Giovanni Ciriello, Katie Hoadley, Yasin Senbagaoglu, Jim Fagin

BRAF^{V600E}-*RAS* Score (BRS) defines a gradient between two PTC classes: *BRAF*^{V600E}-like (BVL) and *RAS*-like (RL)



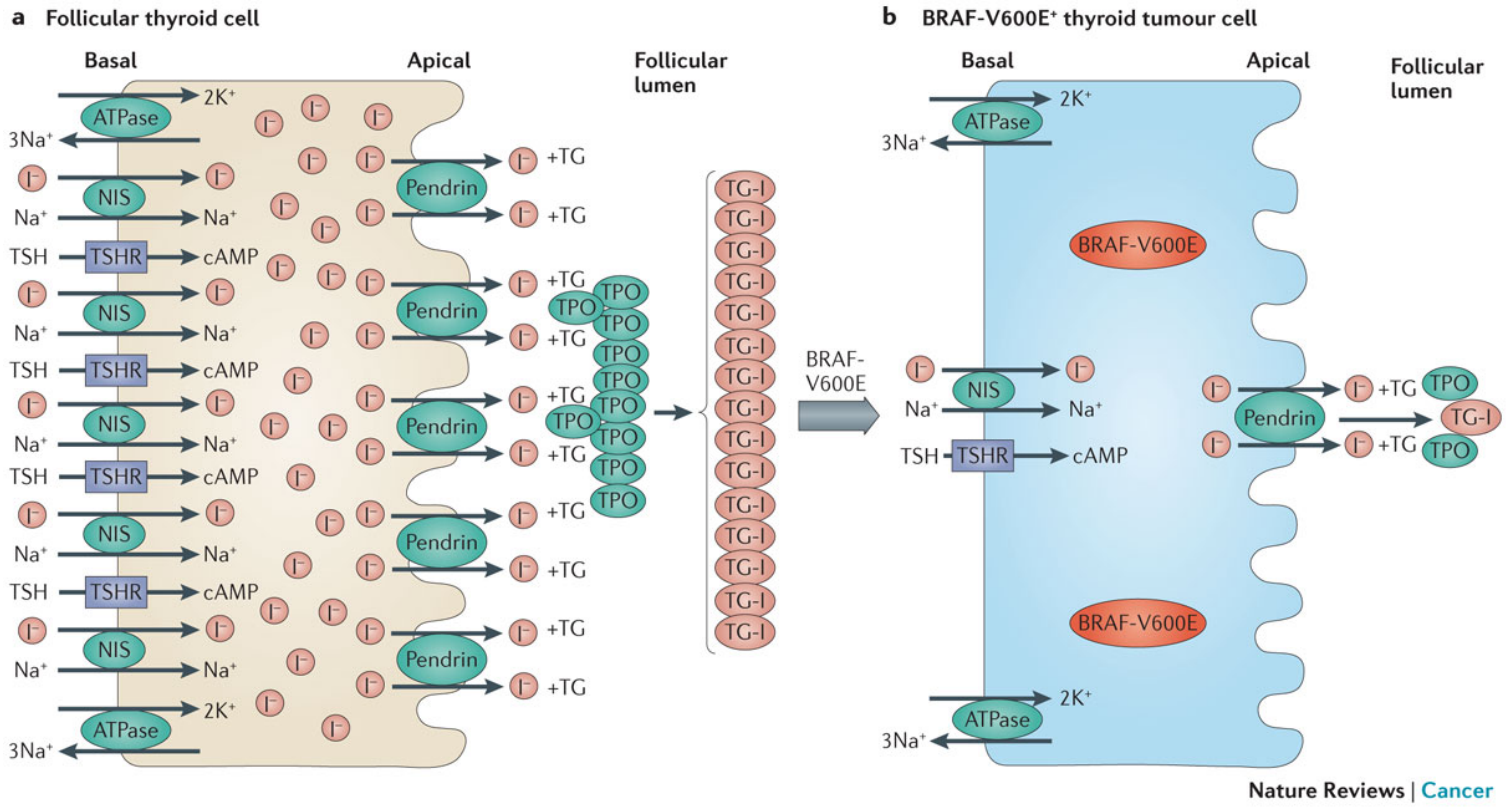
Giovanni Ciriello, Katie Hoadley, Yasin Senbagaoglu, Jim Fagin

BRAF^{V600E}-*RAS* Score (BRS)



Giovanni Ciriello, Katie Hoadley, Yasin Senbagaoglu, Jim Fagin

Silencing of iodine metabolism machinery by *BRAF*^{V600E}

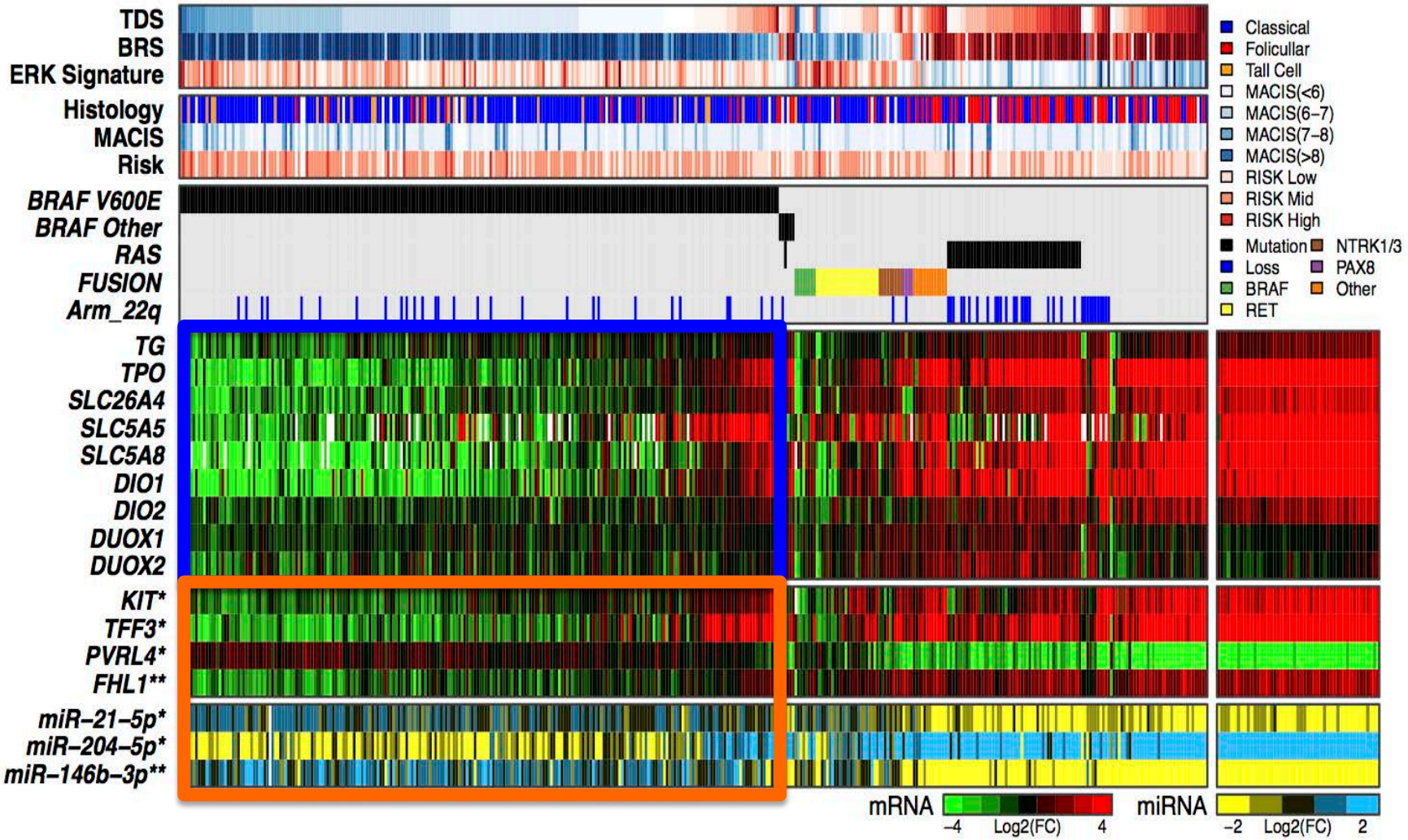


Highly differentiated follicular cell

Loss of differentiation

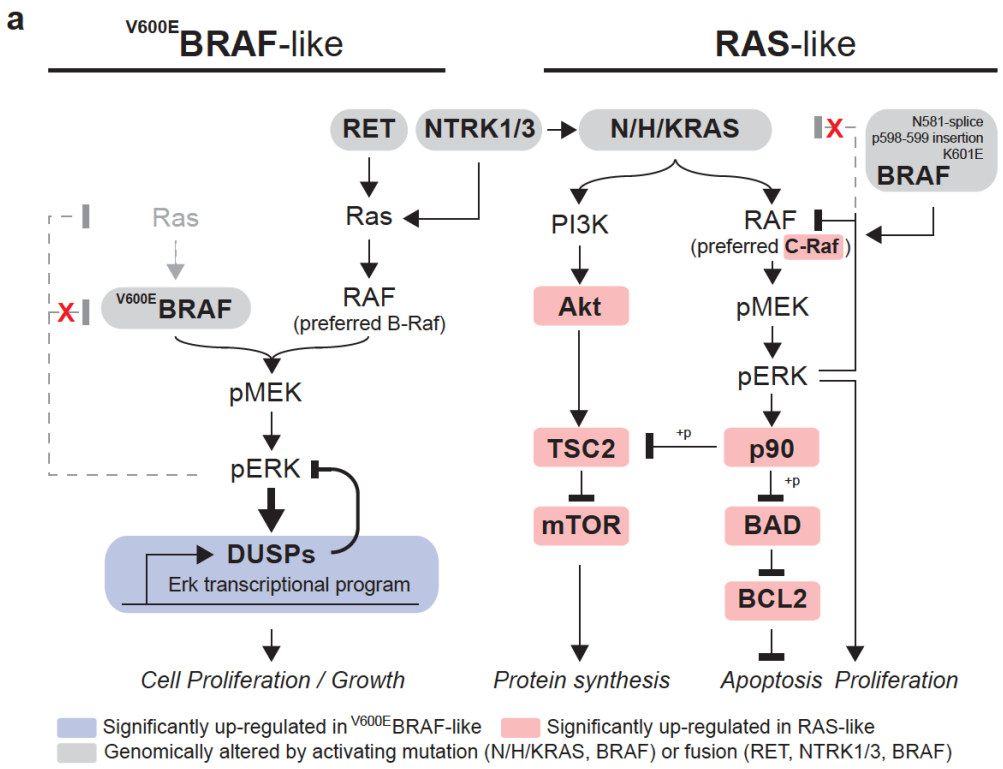
Mingzhao Xing, JHU

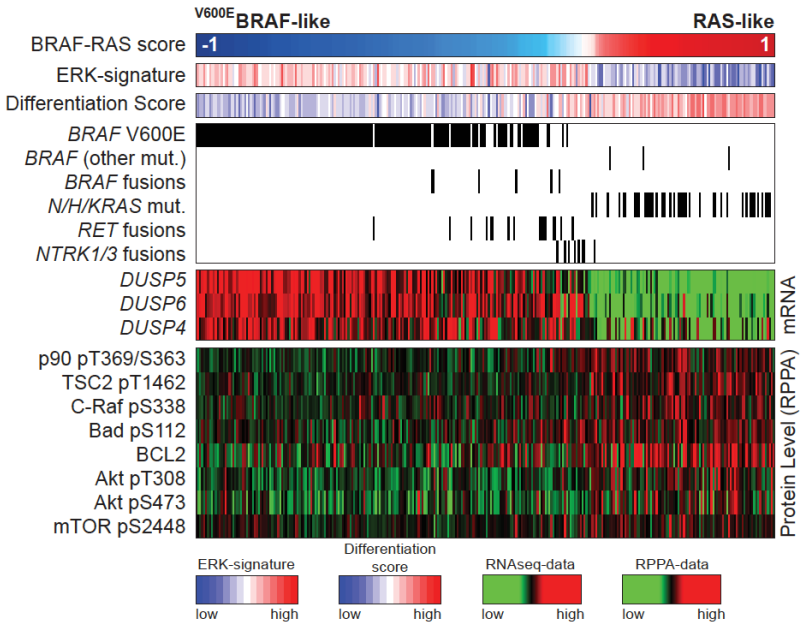
Thyroid Differentiation Score (TDS)
16 gene signature



Jaegil Kim, Gordon Robertson, Chip Stewart, Lisa Iype

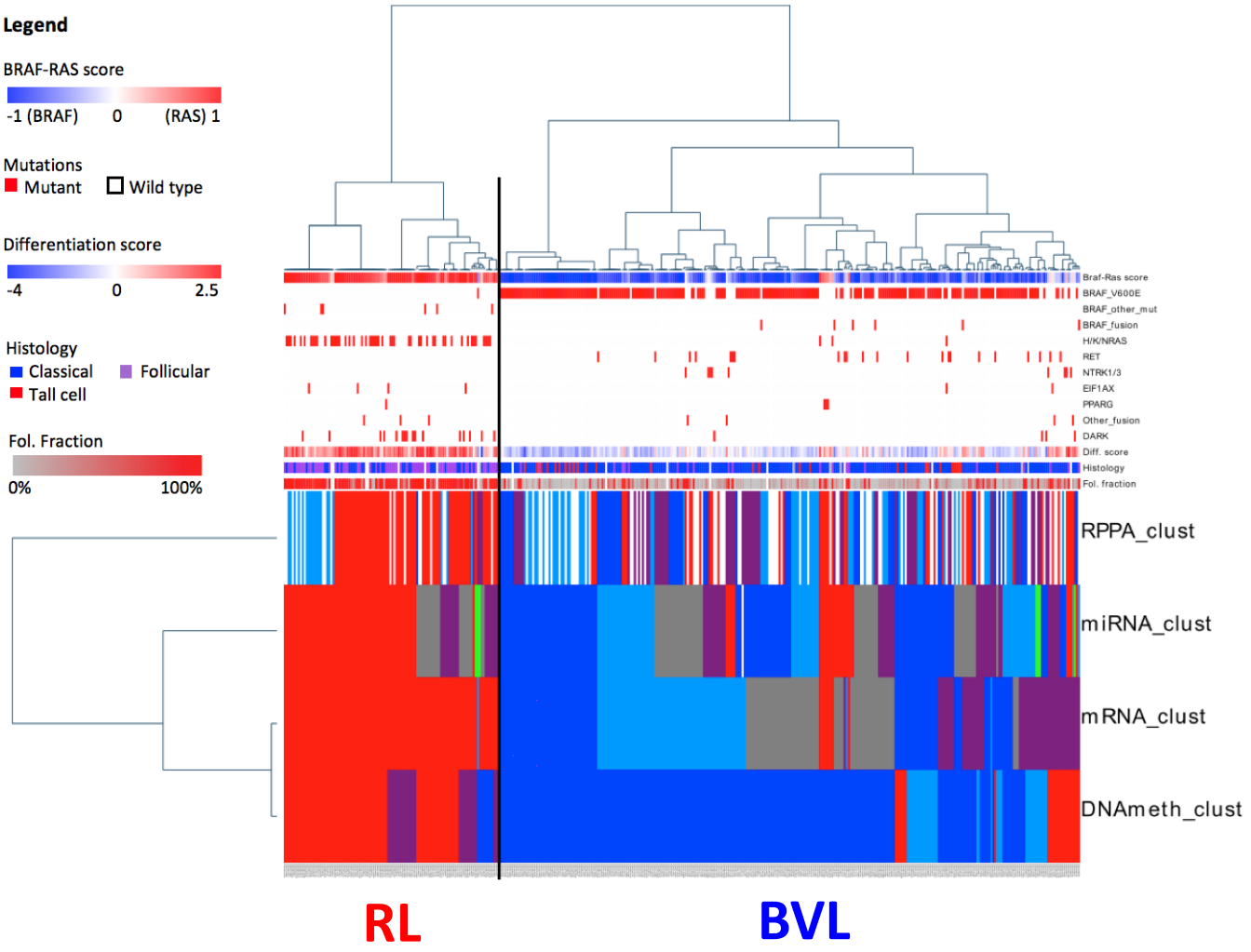
Signaling Differences between BVL and RL PTC





Giovanni Ciriello, Yasin Senbagaoglu, Jim Fagin

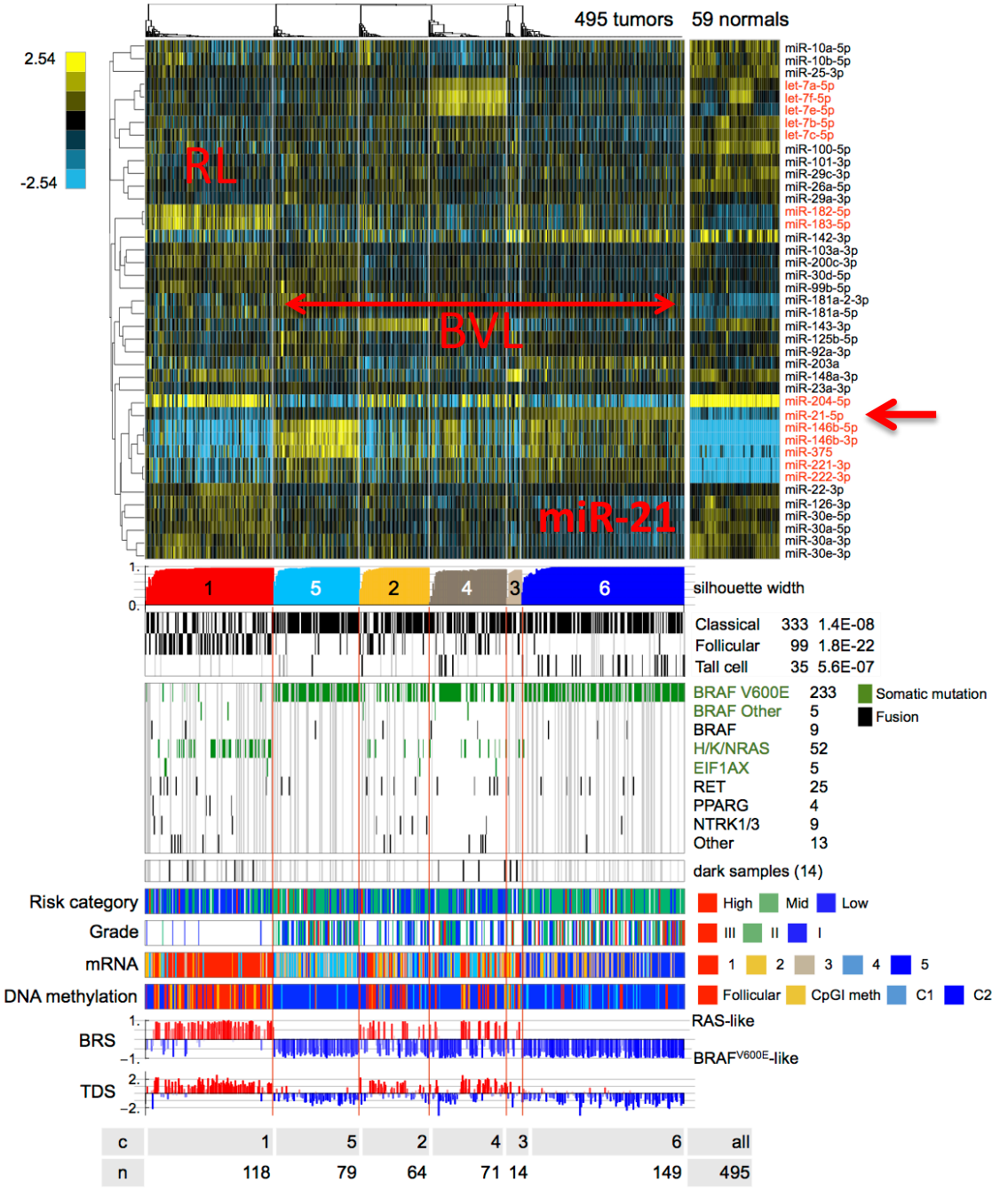
SuperCluster



Rehan Akbani

Integrated MIR story

leveraged the BRS, TDS, histologic type, and tumor grade, to demonstrate differences between clusters



Gordon Robertson, Lisa Iype, Luda Danilova,

Overarching Conclusions

- RL-PTCs and BVL-PTCs are fundamentally different in their genomic, epigenomic and proteomic profiles
- Identified clinically relevant subgroups of BVL-PTCs
  - Potential role for miRs
- Propose a reclassification of thyroid cancer that more accurately reflects the genotypic and phenotypic differences of *RAS*- and *BRAF*^{V600E}-driven

We think TCGA THCA will be a landmark study

IMPACT

- Jim Fagin working on EIF1AX biology
- Working Group on FV-PTC
  - Yuri Nikiforov, Pittsburgh
  - International group of thyroid pathologists
  - Possible NCI support (R13)
- Biomarker study
  - Martha Zeiger, Hopkins
  - Hopkins, Mayo, Michigan and Cornell
  - 238 PTCs with central compartment LN dissections
  - BRAF + miRNA expression to predict LN positivity

TCGA Thyroid Analysis Working Group

University of Michigan
Tom Giordano (co-chair)

MSKCC
Giovanni Ciriello

UCSC
Josh Stuart
Evan Paull
Matan Hofree
Trey Ideker

Brown
Ben Raphael
Fabio Vandin
Jonathon Eldridge

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Harindra Arachchi
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Mike Noble
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Luda Danilova
Justin Bishop

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Wei Zhang

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Disease experts
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Jim Fagin
Ian Ganly
Rony Ghossein
Yuri Nikiforov
Matt Ringel
Bob Smallridge
Chris Umbricht
Martha Zieger
David McFadden

TCGA and BCRs
Kenna Shaw
Margi Sheth
Brad Ozenberger
Entire TCGA Network


Thanks to TCGA
leadership,
Gaddy, Chip
and the entire
THCA AWG!