Comprehensive Molecular Characterization of Regional Metastatic Melanoma

Ian Watson

On behalf of Melanoma AWG and TCGA

Tuesday May 13th, 2014

TCGA SKCM AWG Contributors

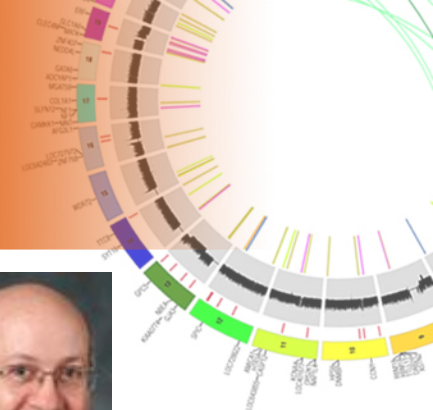**Co-Chairs:** Lynda Chin, Jeffrey Gershenwald and Ian Watson
Analysis Coordinator: Terrence Wu
Data Coordinator: Lihua Zou
Manuscript Coordinator: Ian Watson
NIH/NCI: Ina Felau, Margi Sheth, Kenna Shaw, Jean Claude Zenklusen
Broad Firehose Team: Dan Dicara, Lihua Zou, Mike Noble, Gad Getz

Clinical data: Jeffrey Gershenwald, Richard Scolyer, William Burns, Genevieve Boland, Stergios Moschos Graham Mann, John Thompson
Pathology: Richard Scolyer, Alex Lazar, Ken Tsai, Carolyn Shaiu, James Wilmott, Lauren Haydu, Jeff Gershenwald Victor Prieto
Whole exome sequencing analysis: Lihua Zou, Gad Getz, Mike Lawrence, Eran Hodis, Carrie Sougnez, Terrence Wu, Ian Watson
Copy number: Andrew Cherniack, Terrence Wu, Ian Watson
Methylation: Leslie Cope, Ludmila Danilova, James Herman
miRNAseq: Gordon Robertson, Da Yang, Andy Chu, Denise Brooks, Reanne Bowlby, Payal Sipahimalani, Andy Mungall, Yussanne Ma, Steven Jones, Marco Marra, Anders Jacobsen
RNAseq: Norman Sharpless, William Jeck, Katherine Hoadley, Stergios Moschos
LowP WGS: Raju Kucherlapati, Peter Park, Per Wu, Lixing Yang, Terrence Wu, Angela Hadjipanayis, Semin Lee, Xingzhi Song, Seth Sahil, Jianhua Zhang, Alexei Protopopov
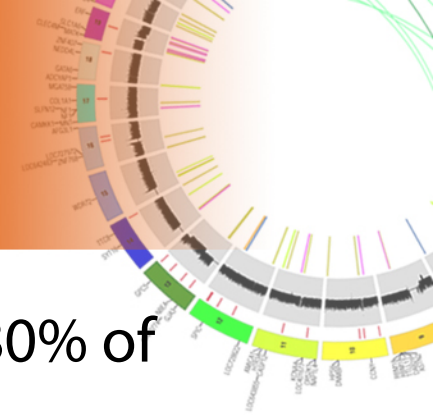**RPPA:** Gordon Mills, Scott Woodman, Jason Roszik, Mike Davies, Terrence Wu
Pathway Analysis: Chris Sander, Niki Schultz, Giovanni Ciriello, Anil Korkut, Ronglai Shen
Integrative Analysis: Sheila Reynolds

...And the rest of the **TCGA** Community
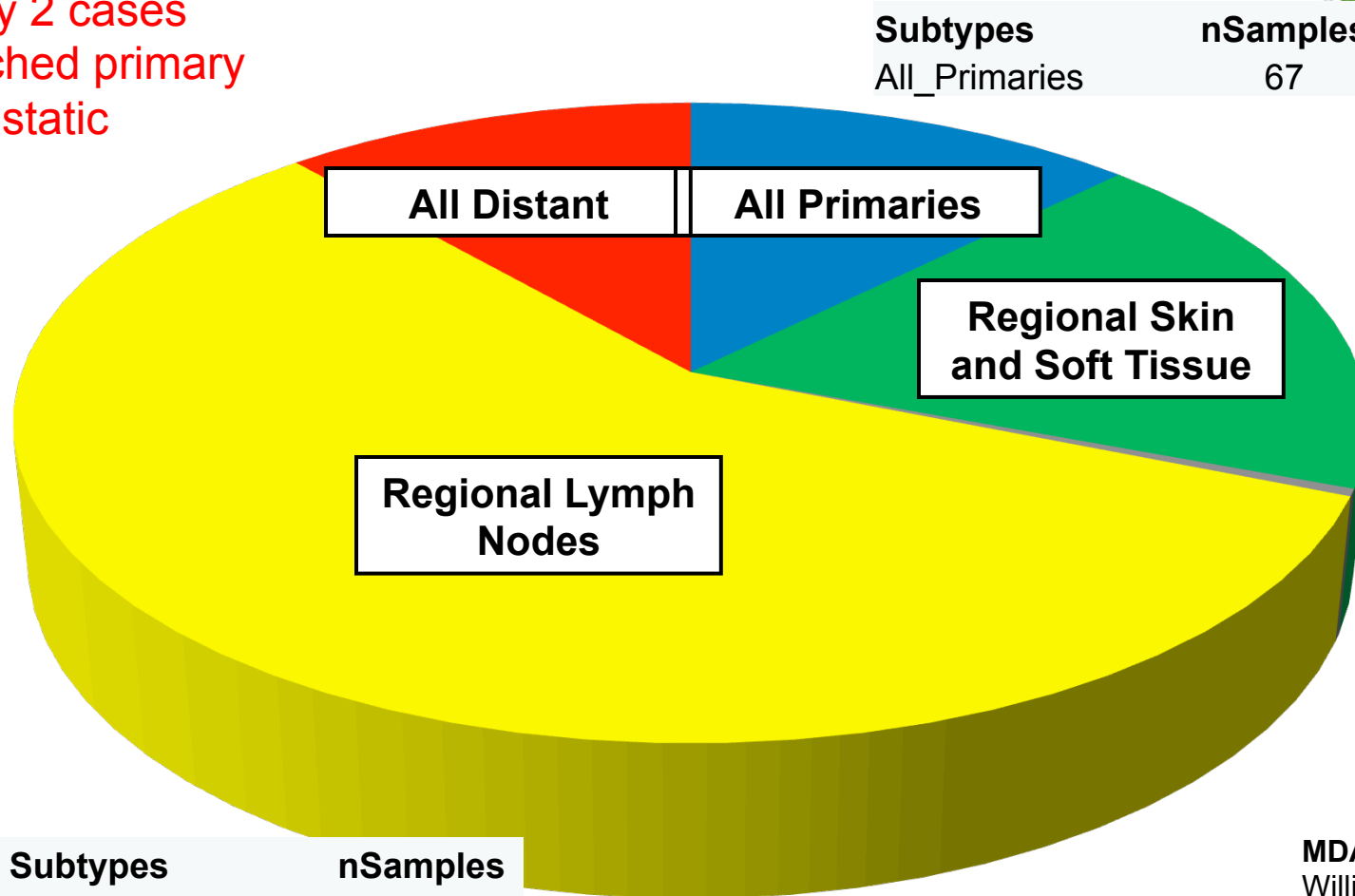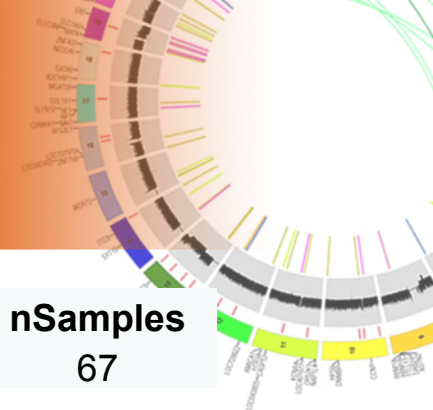… the patients

The Cancer Genome Atlas

Primary Focus: Untreated Regional Metastases

- Paradigm shift from nearly all other TCGA efforts (80% of samples analyzes are metastatic origin)

- Originating from non-glabrous skin primaries (exclude - palm of hand and soles of feet) – reduce heterogeneity

- No prior systemic treatment (exception – IFN >90 days ok)

- **<u>Rationale</u>**
  -Scarcity of frozen primary tumor tissue in sufficient quantity

  -If discovered early melanoma highly curable, however, 5-year survival rate drops to 62% for regional disease (ACS: Cancer Facts and Figures 2012)

 -Most common first site of metastasis in melanoma (lymph node and regional subcutaneous/cutaneous sites)

The Cancer Genome Atlas

TCGA Subtypes

Note: only 2 cases with matched primary and metastatic samples

Subtypes	nSamples
All_Primaries	67

All Distant

All Primaries

Regional Skin and Soft Tissue

Regional Lymph Nodes

Metastatic Subtypes	nSamples
Regional_Lymph_Node	160
Regional_Skin_or_Soft_Tissue	52
Distant_Metastases	35

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William Burns
Genevieve Boland
Jeffrey Gershenwald

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skcm: Data Type Breakdown by Participant

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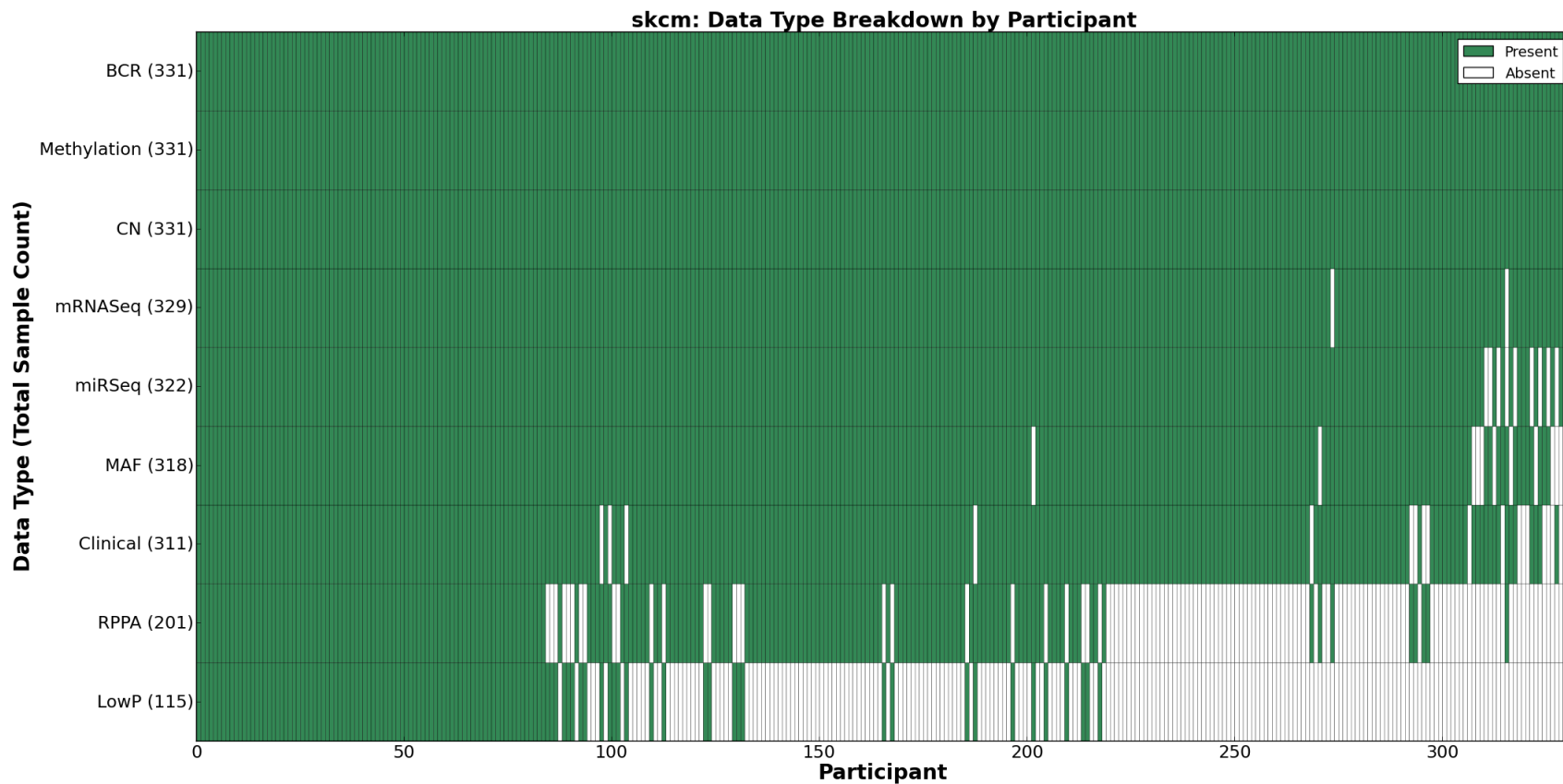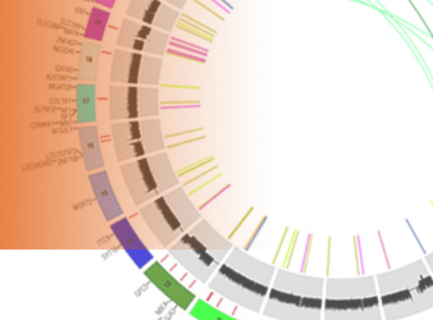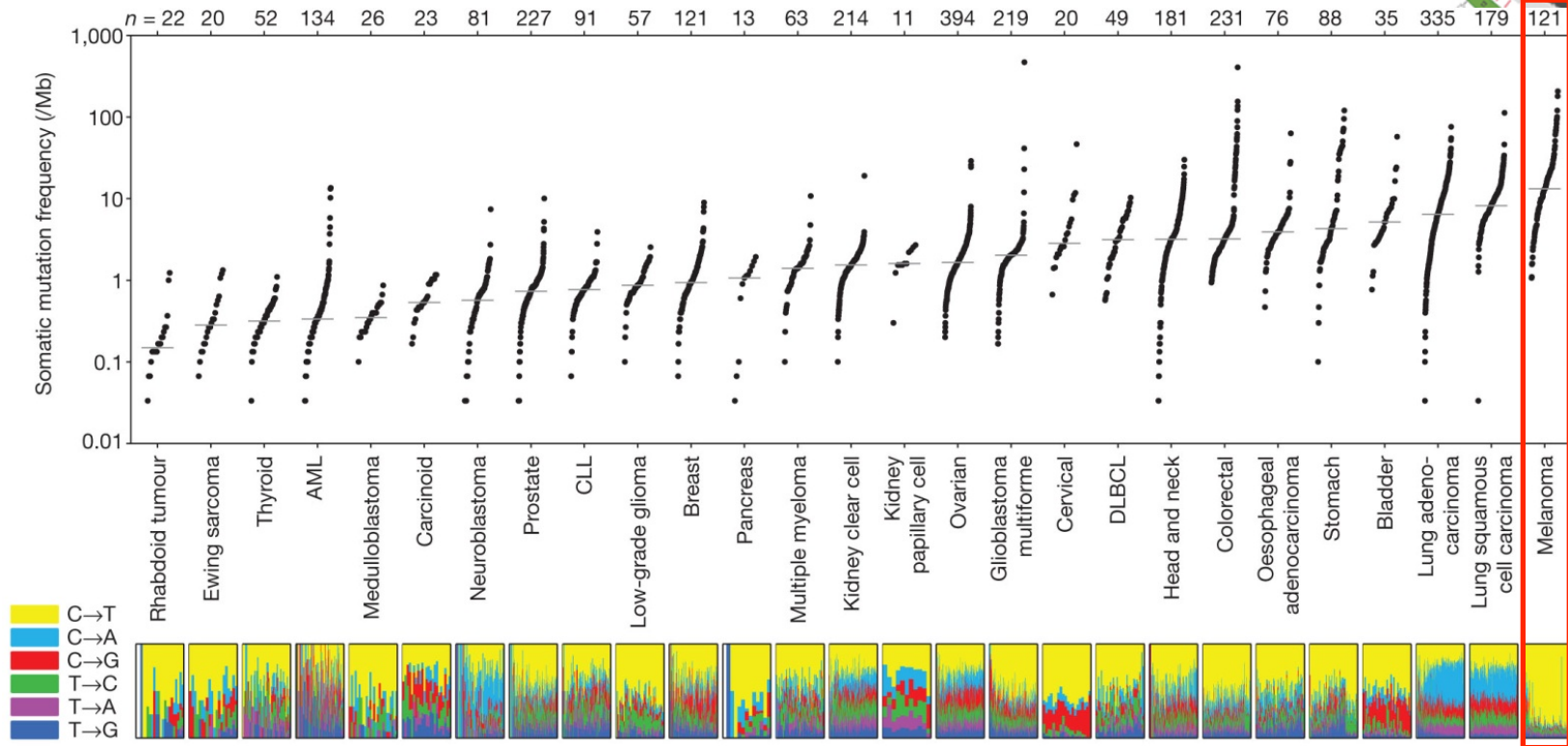
Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs.

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Mutational Landscape by WES (n=318)

SKCM-All_Samples.final_analysis_set.maf
n=218911

Legend:
- C>T (yellow)
- C>A (teal)
- C>G (red)
- A>G (green)
- A>C (blue)
- A>T (purple)
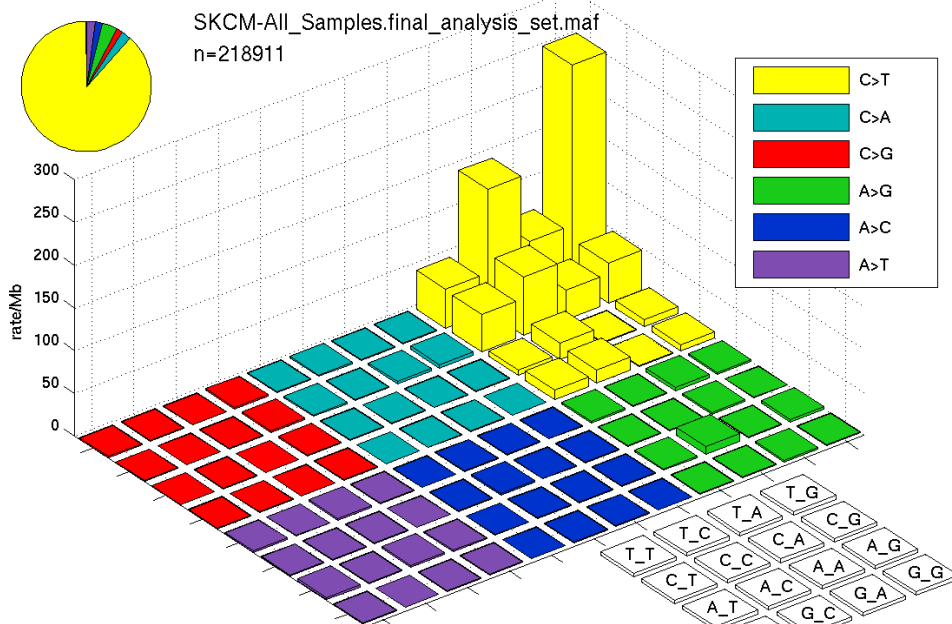
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Lihua Zou
Daniel Dicara
Mike Noble
Mike Lawrence
Gad Getz

A breakdown of mutation rates per category discovered for this individual set.

category	n	N	rate	rate_per_mb	relative_rate	exp_ns_s_ratio
(C/T)p*C->T	105743	2533131709	0.000042	42	2.5	1.6
(A/G)p*C->T	11812	2126263554	5.6e-06	5.6	0.33	1.9
A->G	5526	4496091733	1.2e-06	1.2	0.073	2.3
transver	14537	9155486996	1.6e-06	1.6	0.095	5
indel+null	15862	9155486996	1.7e-06	1.7	0.1	NaN
double_null	289	9155486996	3.2e-08	0.032	0.0019	NaN
Total	153769	9155486996	0.000017	17	1	3.5

type	count
Frame_Shift_Del	1047
Frame_Shift_Ins	270
In_Frame_Del	276
In_Frame_Ins	30
Missense_Mutation	137621
Nonsense_Mutation	8605
Nonstop_Mutation	54
Silent	75214
Splice_Site	5867
Translation_Start_Site	3
Total	228987

Significantly Mutated Genes by MutSig

Mutational heterogeneity in cancer and the search for new cancer-associated genes

Michael S. Lawrence[1]*, Petar Stojanov[1,2]*, Paz Polak[1,3,4]*, Gregory V. Kryukov[1,3,4], Kristian Cibulskis[1], Andrey Sivachenko[1], Scott L. Carter[1], Chip Stewart[1], Craig H. Mermel[1,5], Steven A. Roberts[6], Adam Kiezun[1], Peter S. Hammerman[1,2], Aaron McKenna[1,7], Yotam Drier[1,3,5,8], Lihua Zou[1], Alex H. Ramos[1], Trevor J. Pugh[1,2,3], Nicolas Stransky[1,9], Elena Helman[1,10], Jaegil Kim[1], Carrie Sougnez[1], Lauren Ambrogio[1], Elizabeth Nickerson[1], Erica Shefler[1], Maria L. Cortés[1], Daniel Auclair[1], Gordon Saksena[1], Douglas Voet[1], Michael Noble[1], Daniel DiCara[1], Pei Lin[1], Lee Lichtenstein[1], David I. Heiman[1], Timothy Fennell[1], Marcin Imielinski[1,5], Bryan Hernandez[1], Eran Hodis[1,2], Sylvan Baca[1,2], Austin M. Dulak[1,2], Jens Lohr[1,2], Dan-Avi Landau[1,2,11], Catherine J. Wu[2,3], Jorge Melendez-Zajgla[12], Alfredo Hidalgo-Miranda[12], Amnon Koren[1,3], Steven A. McCarroll[1,3], Jaume Mora[13], Ryan S. Lee[2,3,14], Brian Crompton[2,14], Robert Onofrio[1], Melissa Parkin[1], Wendy Winckler[1], Kristin Ardlie[1], Stacey B. Gabriel[1], Charles W. M. Roberts[2,3,14], Jaclyn A. Biegel[15], Kimberly Stegmaier[1,2,14], Adam J. Bass[1,2,3], Levi A. Garraway[1,2,3], Matthew Meyerson[1,2,3], Todd R. Golub[1,2,3,8], Dmitry A. Gordenin[6], Shamil Sunyaev[1,3,4], Eric S. Lander[1,3,10] & Gad Getz[1,5]

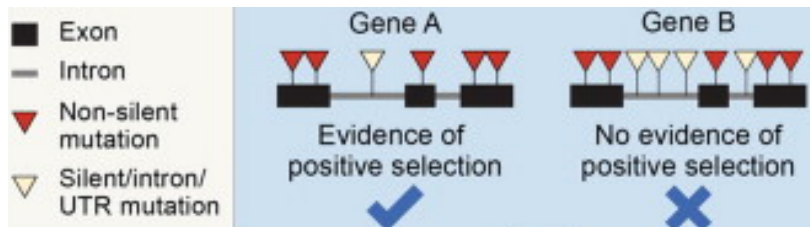-Identified 42 significantly mutated genes (Q <0.1)

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InVEx:

permutes called mutations within a gene's exons and introns (the covered region sequenced) and asks whether in the real data we observe more 'non-silent' mutations than in the permutations (which approximate what we might expect by chance)

- ■ Exon
- — Intron
- ▼ Non-silent mutation
- ▽ Silent/intron/ UTR mutation

Gene A — Evidence of positive selection ✔

Gene B — No evidence of positive selection ✘

A Landscape of Driver Mutations in Melanoma

Cell

Eran Hodis,[1,2,19] Ian R. Watson,[3,10,19] Gregory V. Kryukov,[1,2,12] Stefan T. Arold,[4] Marcin Imielinski,[1] Jean-Philippe Theurillat,[1] Elizabeth Nickerson,[1] Daniel Auclair,[1] Liren Li,[3,10] Chelsea Place,[10] Daniel DiCara,[1] Alex H. Ramos,[1,2] Michael S. Lawrence,[1] Kristian Cibulskis,[1] Andrey Sivachenko,[1] Douglas Voet,[1] Gordon Saksena,[1] Nicolas Stransky,[1] Robert C. Onofrio,[1] Wendy Winckler,[1] Kristin Ardlie,[1] Nikhil Wagle,[1,2] Jennifer Wargo,[13] Kelly Chong,[14] Donald L. Morton,[15] Katherine Stemke-Hale,[5] Guo Chen,[6] Michael Noble,[1] Matthew Meyerson,[1,2,10,11] John E. Ladbury,[4] Michael A. Davies,[5,6] Jeffrey E. Gershenwald,[7,8] Stephan N. Wagner,[16] Dave S.B. Hoon,[14] Dirk Schadendorf,[17] Eric S. Lander,[1,18] Stacey B. Gabriel,[1] Gad Getz,[1] Levi A. Garraway,[1,2,10,11,20,*] and Lynda Chin[1,2,3,9,10,20,*]

Mapping the Hallmarks of Lung Adenocarcinoma with Massively Parallel Sequencing

Marcin Imielinski,[1,2,3,5,18] Alice H. Berger,[1,5,18] Peter S. Hammerman,[1,5,18] Bryan Hernandez,[1,18] Trevor J. Pugh,[1,5,18] Eran Hodis,[1] Jeonghee Cho,[6] James Suh,[7] Marzia Capelletti,[5] Andrey Sivachenko,[1] Carrie Sougnez,[1] Daniel Auclair,[1] Michael S. Lawrence,[1] Petar Stojanov,[1,5] Kristian Cibulskis,[1] Kyusam Choi,[6] Luc de Waal,[1,5] Tanaz Sharifnia,[1,5] Angela Brooks,[1,5] Heidi Greulich,[1,5] Shantanu Banerji,[1,5] Thomas Zander,[9,11] Danila Seidel,[9] Frauke Leenders,[9] Sascha Ansén,[9] Corinna Ludwig,[9] Walburga Engel-Riedel,[9] Erich Stoelben,[9] Jürgen Wolf,[9] Chandra Goparju,[8] Kristin Thompson,[1] Wendy Winckler,[1] David Kwiatkowski,[5] Bruce E. Johnson,[5] Pasi A. Jänne,[5] Vincent A. Miller,[12] William Pao,[14] William D. Travis,[13] Harvey I. Pass,[8] Stacey B. Gabriel,[1] Eric S. Lander,[1,4,15] Roman K. Thomas,[9,10,11,16,17] Levi A. Garraway,[1,5] Gad Getz,[1] and Matthew Meyerson[1,3,5,*]

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Eran Hodis

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Landscape of Somatic Mutations

(InVEx, P. Bonferroni <0.05, Q <0.1)

(MutSig, Q <0.1, 13/42)

Fisher's exact test:
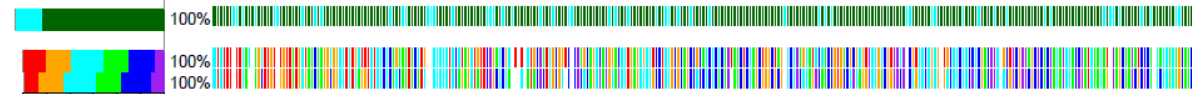- o **BRAF hotspot– NRAS: p-value = 6.461e-16**
- o   NRAS – NF1: NS
- o **BRAF hotspot- NF1: p-value = 1.888e-06**
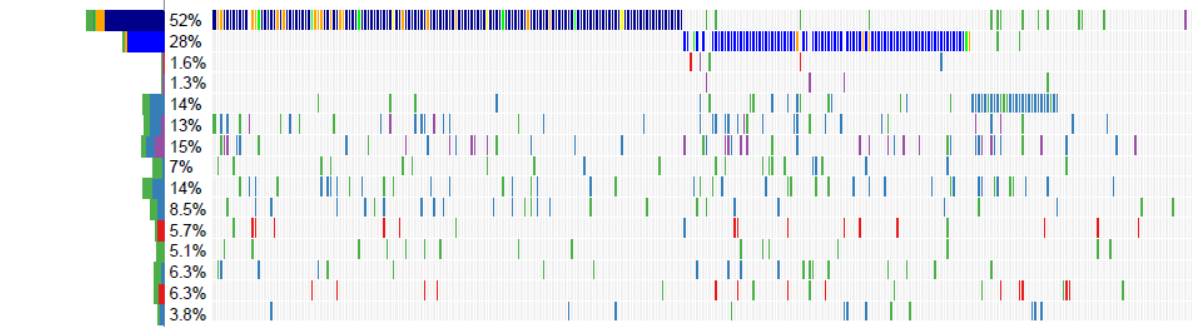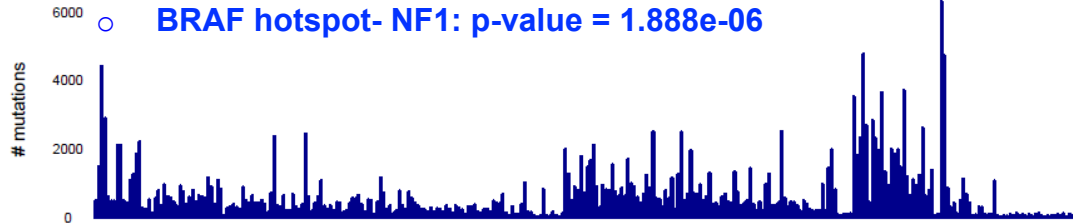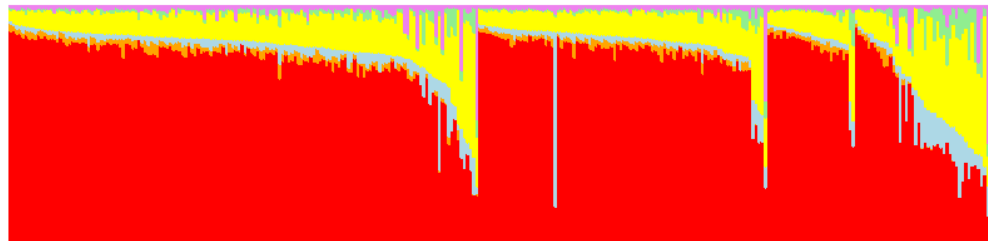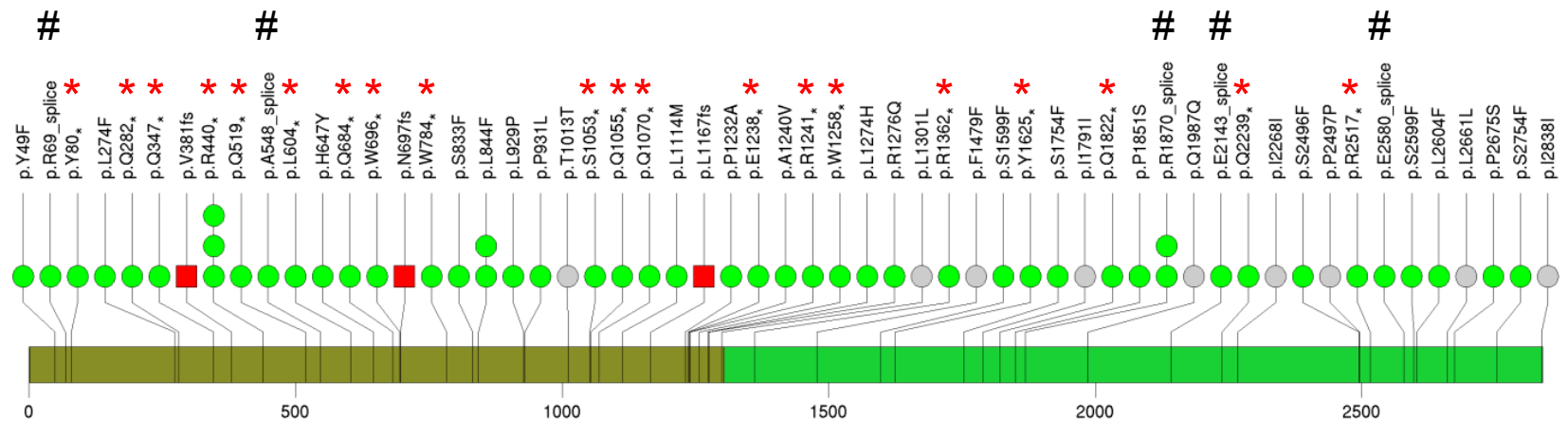
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NF1 Mutated in 14% of Samples:
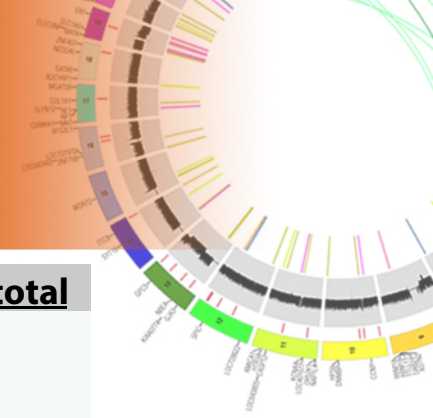
Mutation type	n_Total	% of mutation total
Nonsense	22	**36%**
Splice site	6	10%
Frame Shift Deletions	3	5%
Missense	21	**34%**
Silent	9	15%
n_Loss of Function	**31**	**51%**
n_Total:	61	

Loss of function

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Co-occurring *NF1* and *BRAF* Mutations:
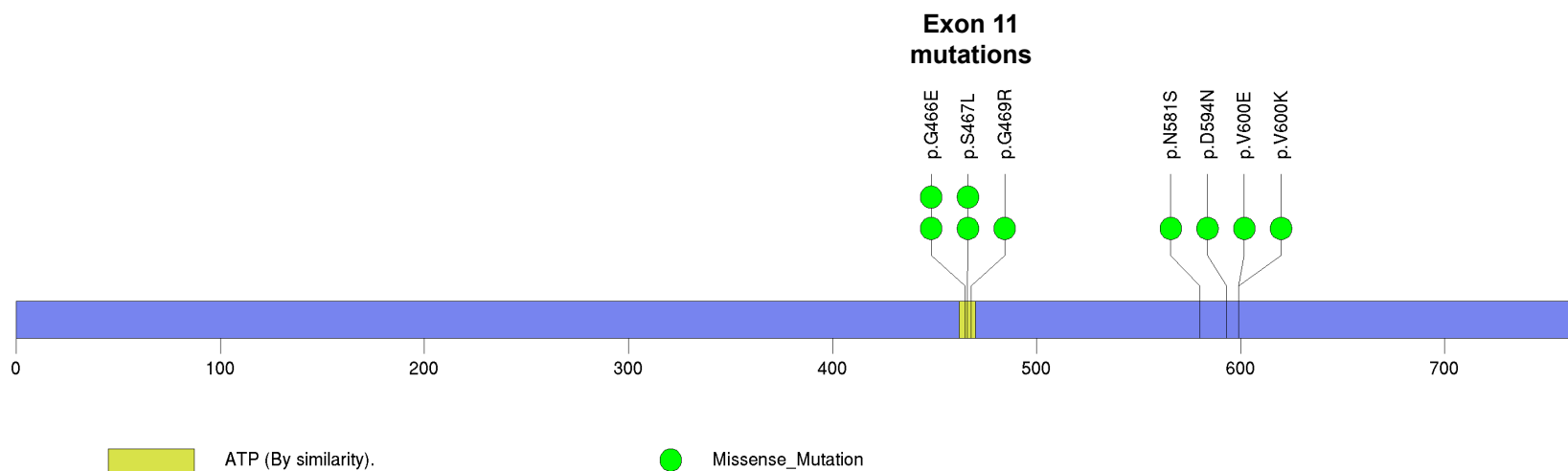
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Landscape of Somatic Mutations

(InVEx, P. Bonferroni <0.05, Q <0.1)

(MutSig, Q <0.1, 13/42)
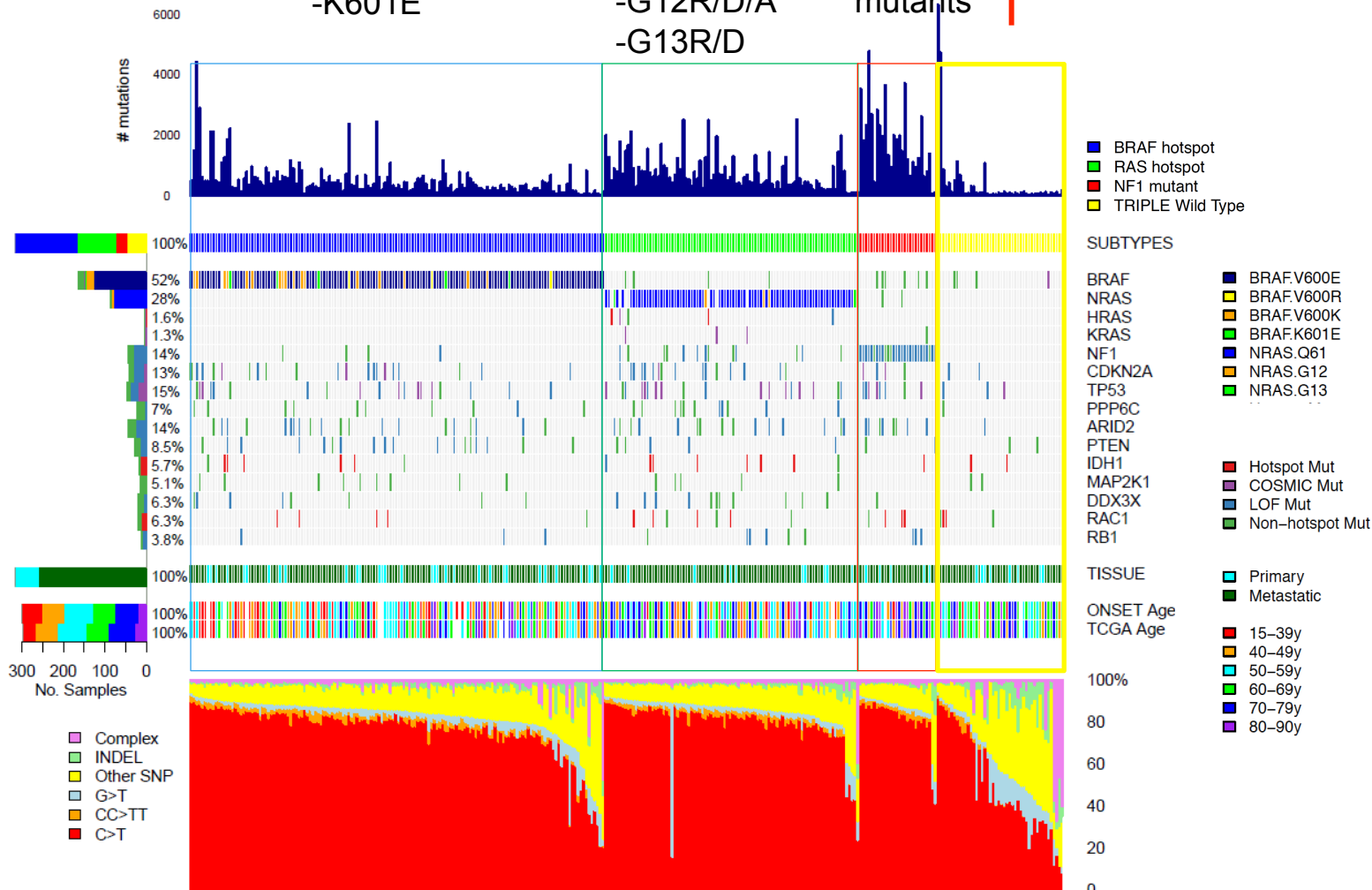

Subgroups:

1) BRAF
-V600E/R/K
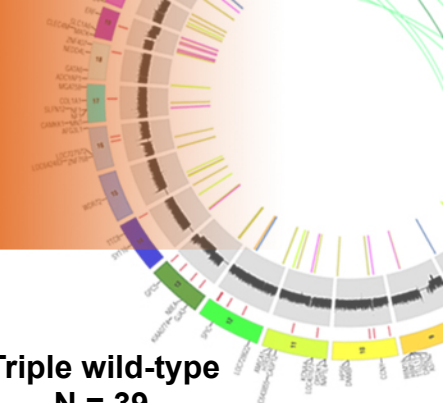-K601E

2) RAS:
-Q61R/K/L/H
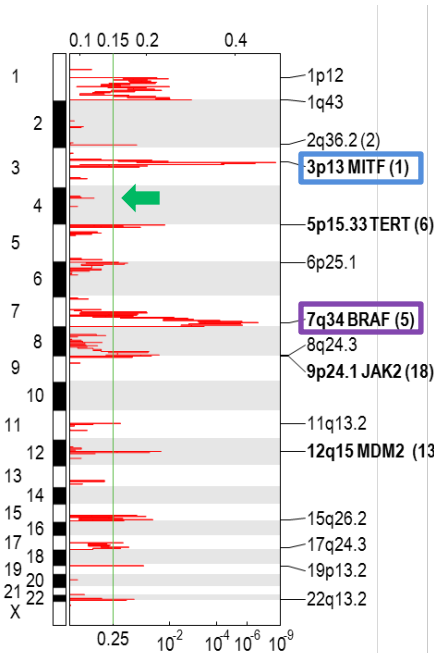-G12R/D/A
-G13R/D

3) NF1 :
-All NF1 mutants

4) Triple wild-type

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Lihua Zou
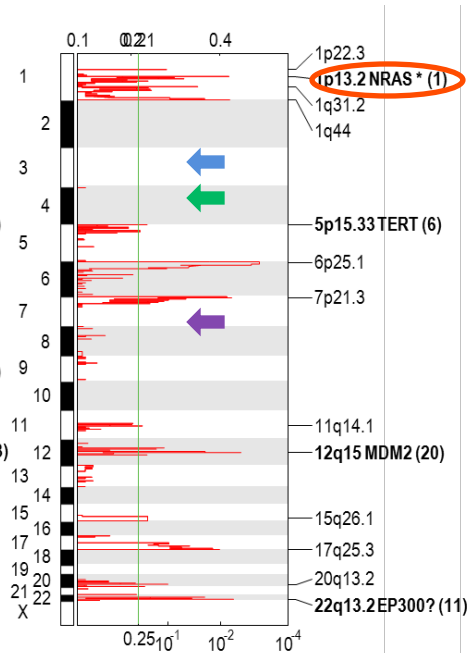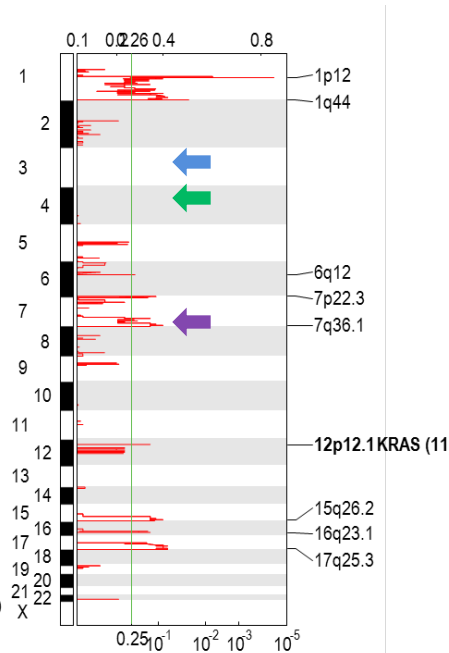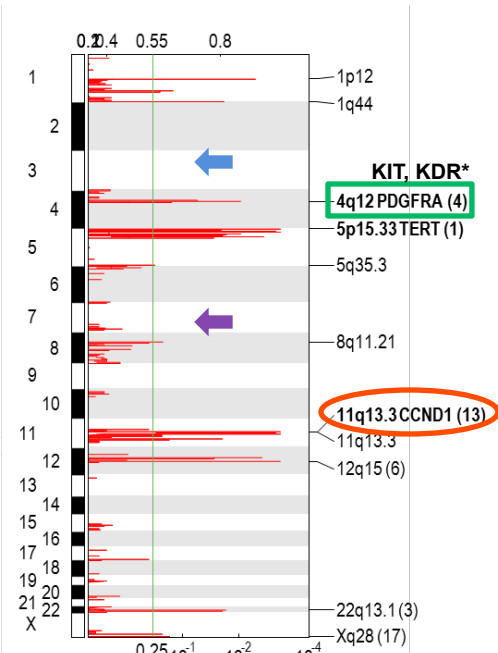
SCNAs in Each Genetic Subtype

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Lynda Chin

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Landscape of Copy Number Gains and Cosmic Mutations in Melanoma
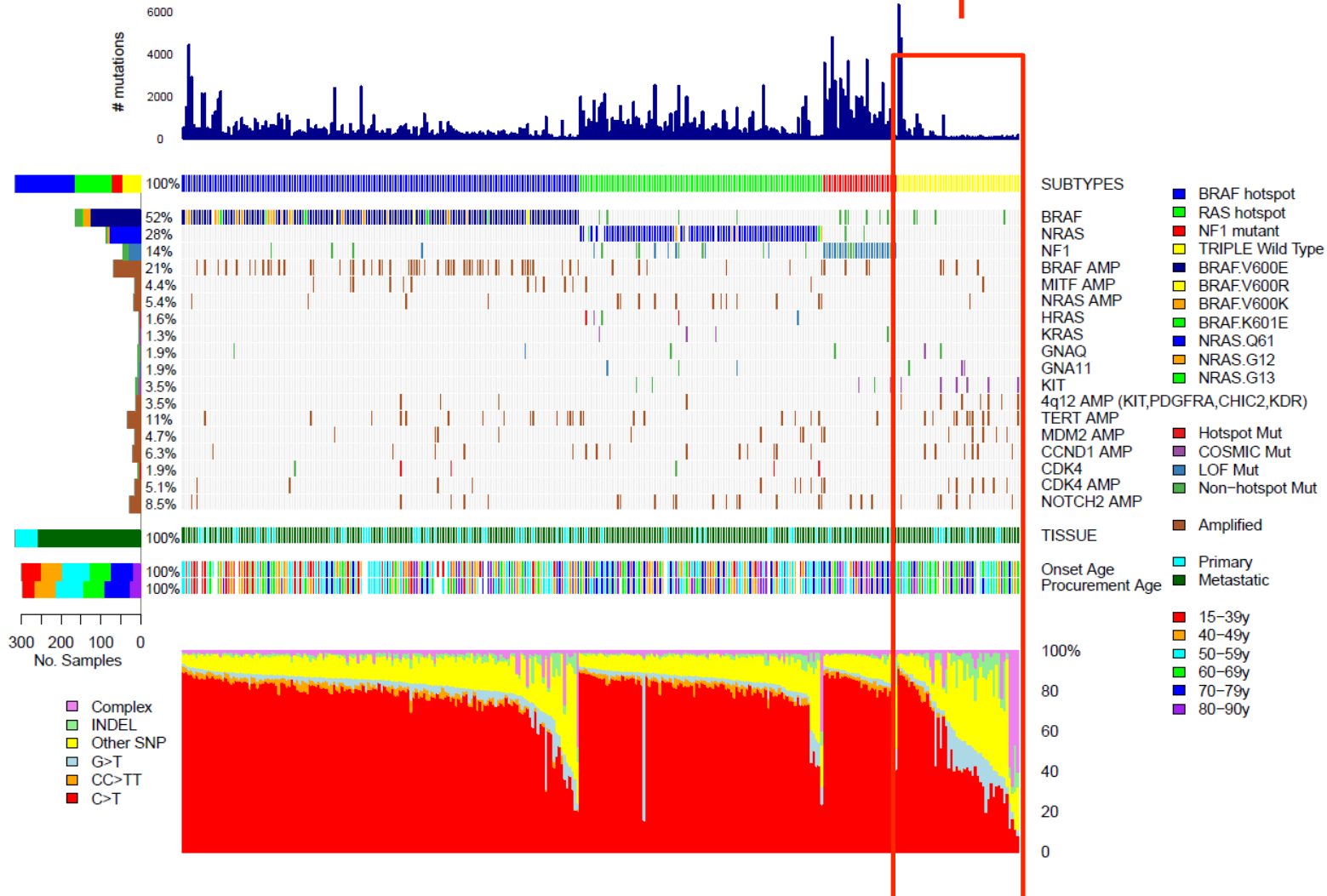
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Enriched Copy Number Gains in *BRAF/NRAS/NF1* Mutant Hotspot Samples

% of sub group (*BRAF/NRAS/NF1/ wild-type*) harboring an amplification in the indicated gene
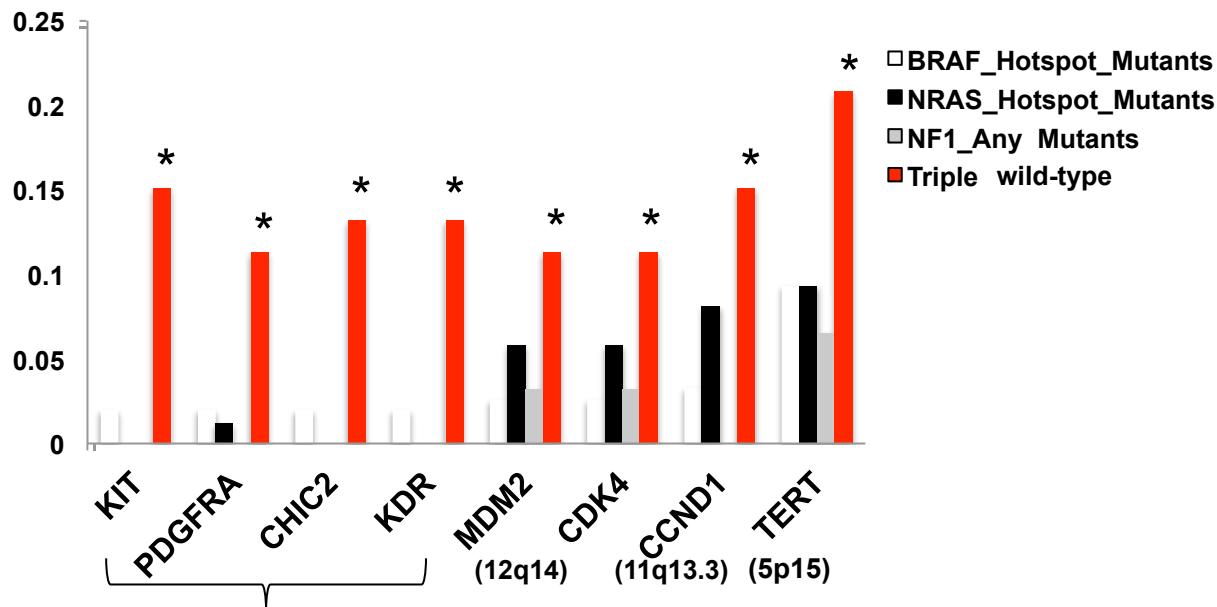
Legend:
- □ BRAF_Hotspot_Mutants
- ■ NRAS_Hotspot_Mutants
- ▨ NF1_Any Mutants
- ■ Triple wild-type

	*Fisher.P values	FDR
KIT	0.00114	0.14478
PDGFRA	0.0105	---
CHIC2	0.00354	0.44604
KDR	0.00354	0.44604
MDM2	0.0209	---
CDK4	0.0209	---
CCND1	0.00561	0.69564
TERT	0.0293	---

*Fischer's test (BRAF comparison)

Segmented value above 0.5 (no consideration for focality)

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Fusion Analysis Flowchart
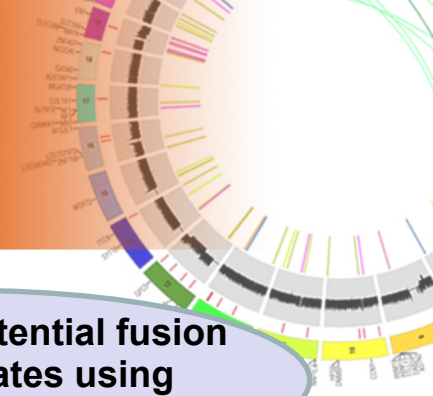
Harvard Medical School/Brigham & Women's Hospital/MD Anderson Cancer Center
Alexei Protopopov, Netty Santoso, Semin Lee, Michael Parfenov, Jianhua Zhang, Harshad S. Mahadeshwar, Jiabin Tang, Xiaojia Ren, Sahil Seth, Lixing Yang, Andrew W. Xu, Xingzhi Song, Angeliki Pantazi, Christopher A. Bristow, Ruibin Xi, Angela Hadjipanayis, **Jonathan Seidman**, **Lynda Chin**, **Peter J. Park**, **Raju Kucherlapati**

Investigate potential fusion detection rates using intragenic copy number

RNA-Seq:
1. 338 samples
2. Three callers (Mapsplice; ChimeraScan; PRADA)

DNA Deep Seq:
1. 38 samples
2. One caller (MeerKat)

Low Pass DNA Seq:
1. 119 samples
2. One callers (BreakDancer; MeerKat)

Filters:
1. 1 junction read
2. 2 discordant reads
3. Homologous filter

Integration of all potential fusions Identified by all callers

784 were detected by at least two callers

Filters for detection of drivers:
1. **Fusion centrality**
2. **Germline fusions**
3. **Fusions with function domains**

221 potential fusion drivers

Poster #63

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BRAF Fusions

Gene1	Gene2	Samples	Mutation Subtype	N of Callers	Domain_kept
ATG7	BRAF	TCGA-BF-A5EP-01	**Unknown**	2	PF00899--**PF07714**
TAX1BP1	BRAF	TCGA-D3-A2JC-06A	**Triple Wild-type**	3	**PF07714**

Note: 1.PF07714 is **Protein kinase_Tyr domain**

TCGA.D3.A2JC.06 TAX1BP1   BRAF

Exon Z-score

-2   -1   0   1   2
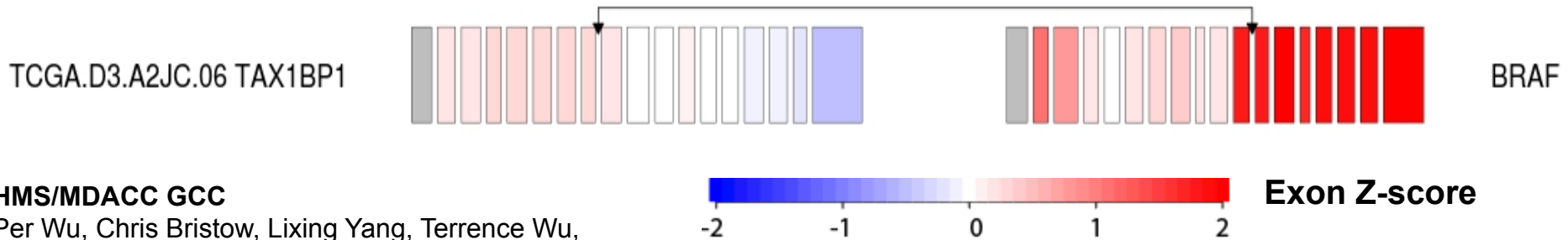
HMS/MDACC GCC
Per Wu, Chris Bristow, Lixing Yang, Terrence Wu, Angela Hadjipanayis, Semin Lee, Peter Park, Lynda Chin, Raju Kucherlapati

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Differential MAPK Signaling in Genetic Subtypes (190 antibodies on 201 cases)
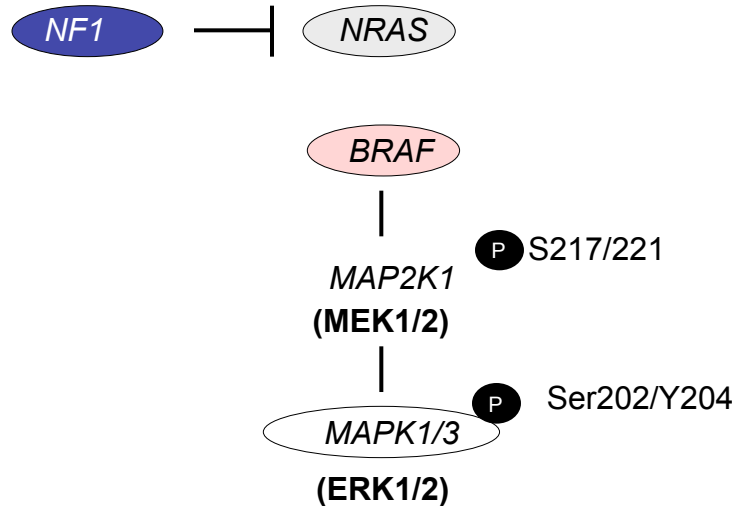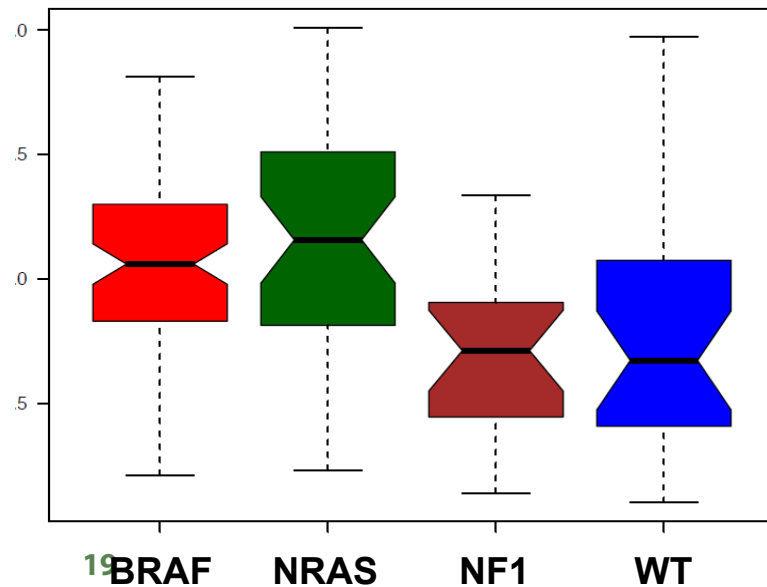
MDACC
Terrence Wu
Scott Woodman
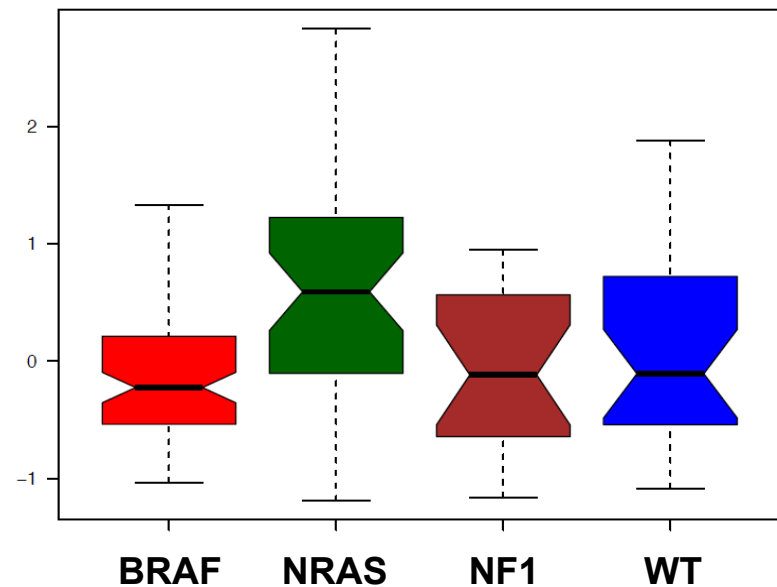Jason Roszik
Mike Davies
Gordon Mills
MSKCC
Debyani Chakravarty

MEK1 S217/221

ERK1/2 T202/Y204

- **R132C caused by C>T transition (UVB)**
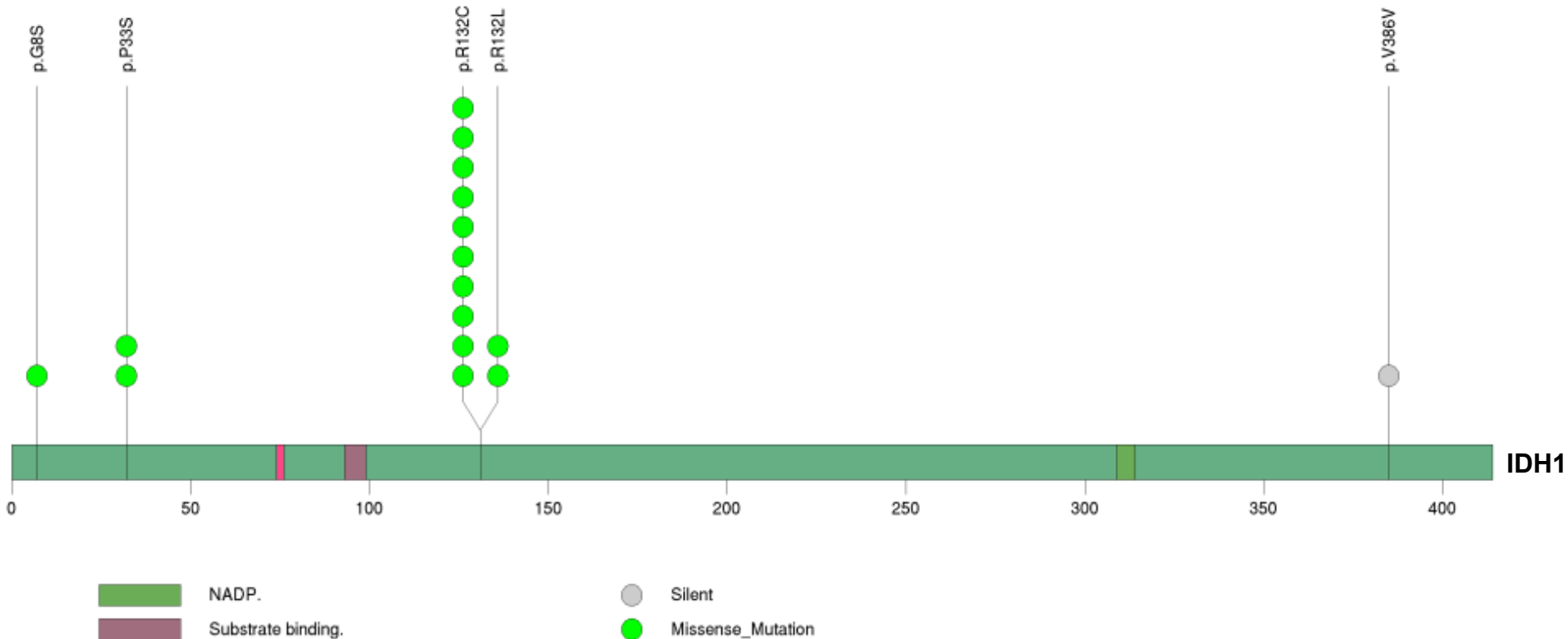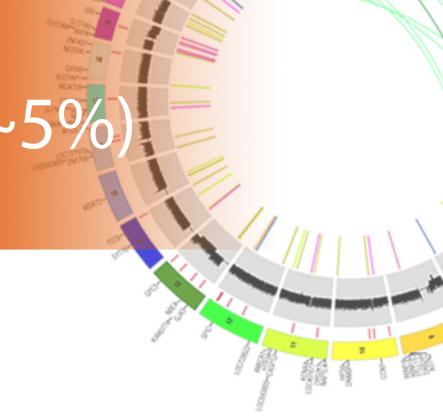
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Johns Hopkins University
Leslie Cope
Ludmila Danilova
James Herman
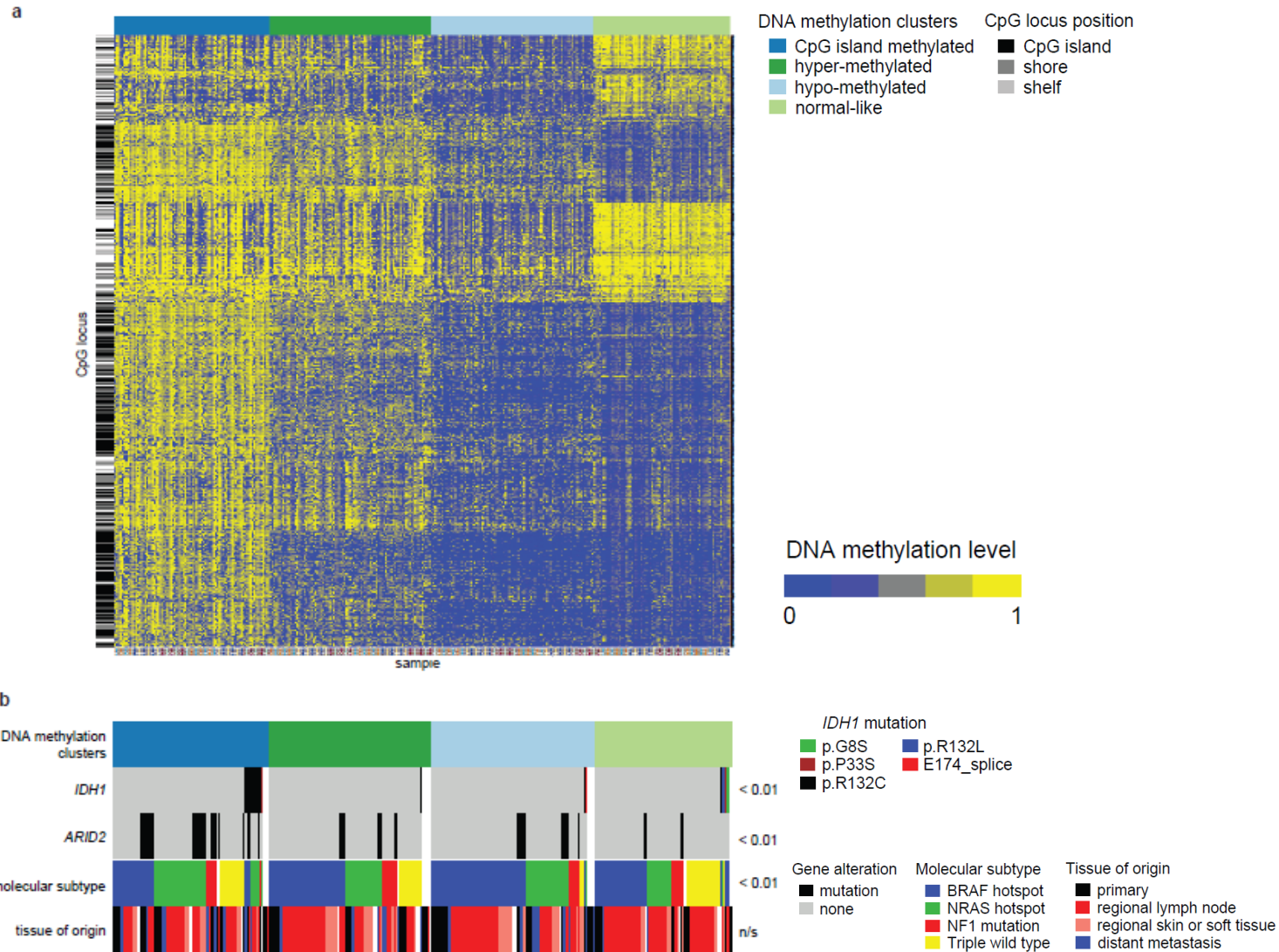
- **Days to Death/Last Follow Up**

  - **From Time of Initial Diagnosis = OS**

  - **From Time sample procurement = "TCGA survival"**
    - Difficulty is that this may be influenced by unaccounted for factors

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William Burns
Genevieve Boland
Jeffrey Gershenwald

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Hierarchical clustering identifies melanomas subgroups with elevated epithelioid, lymphocytic and MITF expression signatures not associated with mutation status

Clusters MITF-low, Keratin, Lymphoctyic
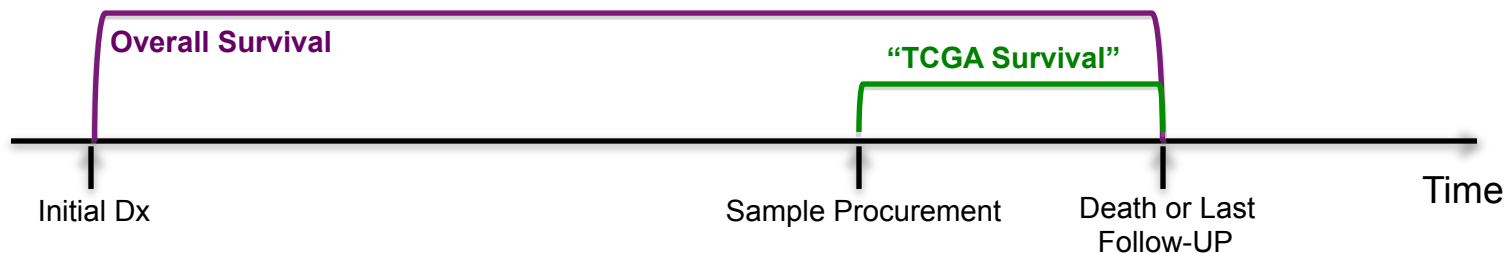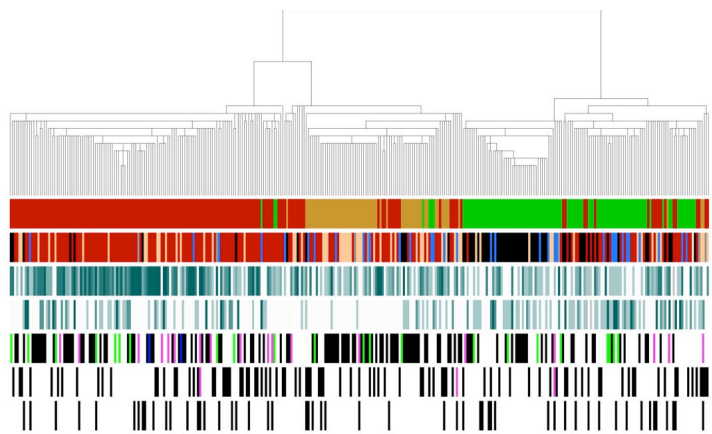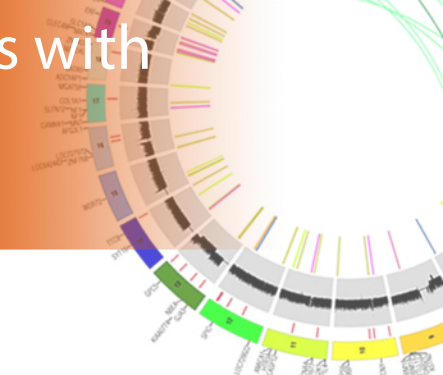Primary, Reg. Lymph Node, Reg. Subcut, Dist. met
Immune Score NA 0 1-2 3-4 5-6
Pigmentation NA 0 1 2 3
BRAFmut: V600E, V600other, K601, other
RASmut: hotspot, other
NF1mut

MITF

Keratin (epithelial) cluster

1,500 GENES

Lymphoctyic (immune) cluster

-3 0 3

University of North Carolina
Katherine Hoadley
William Jeck
Stergios Moschos
Xiaobei Zhao
Norman Sharpless

All_Regional_Meta : TCGA Survival RNACluster

Keratins (25/42)
Lymphocytic (42/117)
MITF-low (24/48)

cumulative survival rate

logrank P = 0.000394

Month
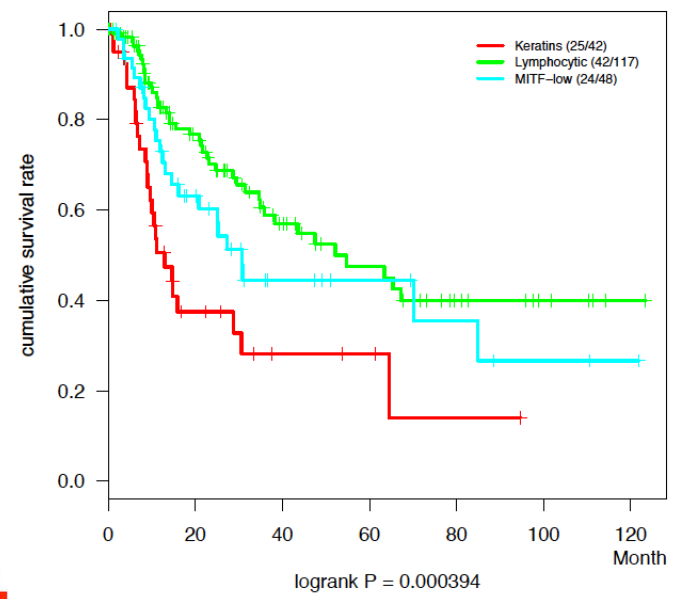
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Lymphocyte Score by Tissue Source Sites
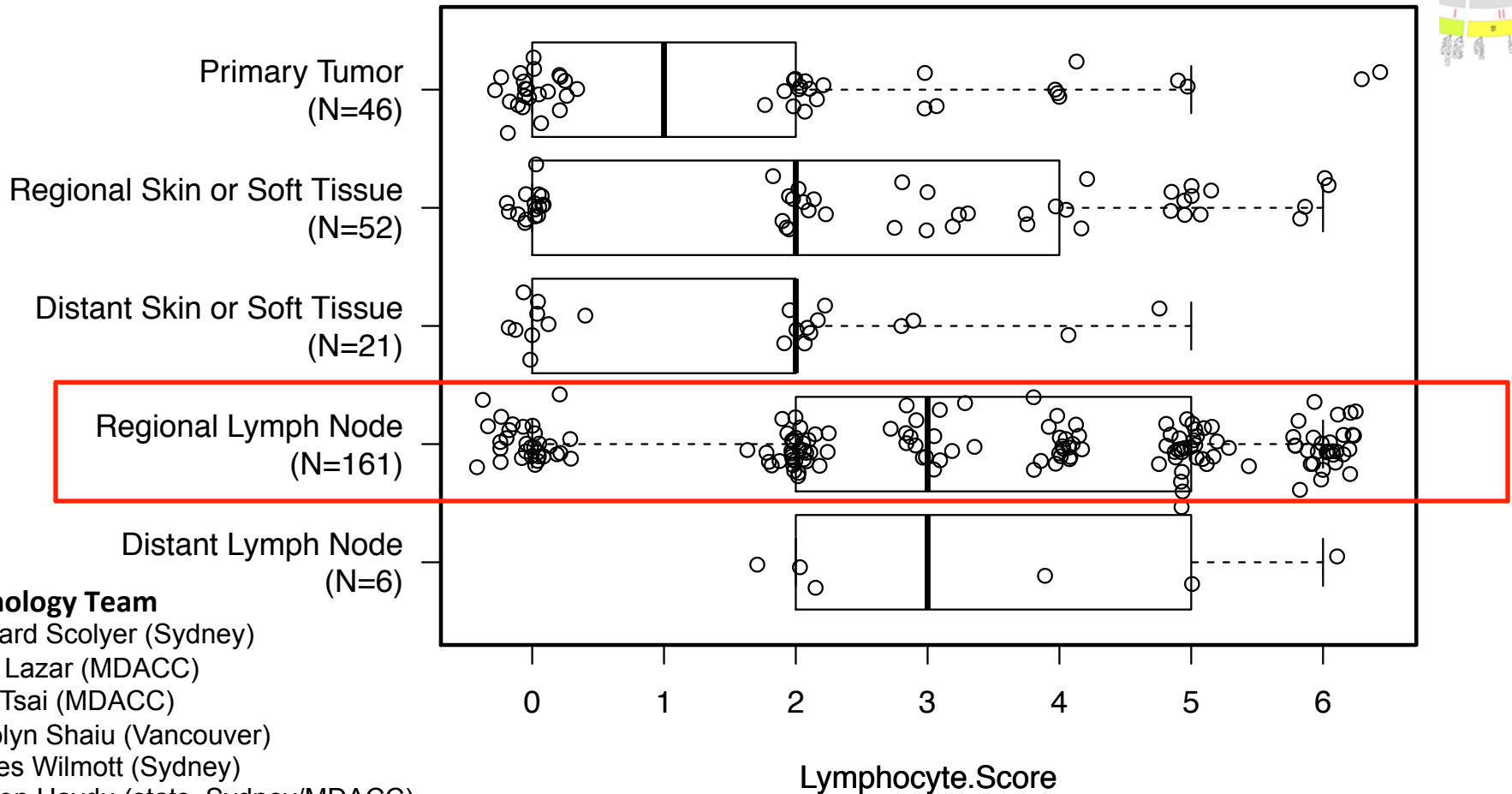
Pathology Team
Richard Scolyer (Sydney)
Alex Lazar (MDACC)
Ken Tsai (MDACC)
Carolyn Shaiu (Vancouver)
James Wilmott (Sydney)
Lauren Haydu (stats, Sydney/MDACC)
Jeff Gershenwald (MDACC)
Victor Prieto (MDACC)

Tumors from Lymph nodes have higher Lymphocyte Infiltration

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Lymphocyte Infiltration vs TCGA Survival

All_Regional_Meta : TCGA Survival Lymphocyte Score

LS:0–2 (47/91)
LS:3–6 (44/115)

logrank P=0.00778, HazardRatio=1.7, C−index=0.628

Regional Lymph Node

LScore:0-2 (34/65)
LScore:3-6 (35/93)

logrank P=0.0155, HazardRatio=1.8, C-index=0.635
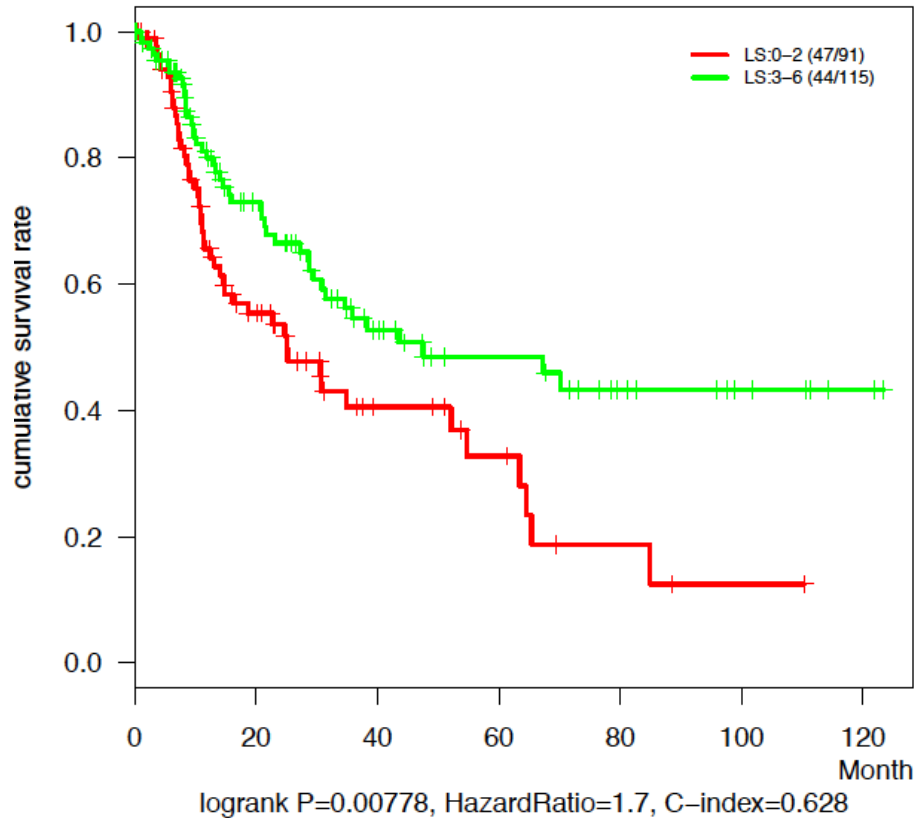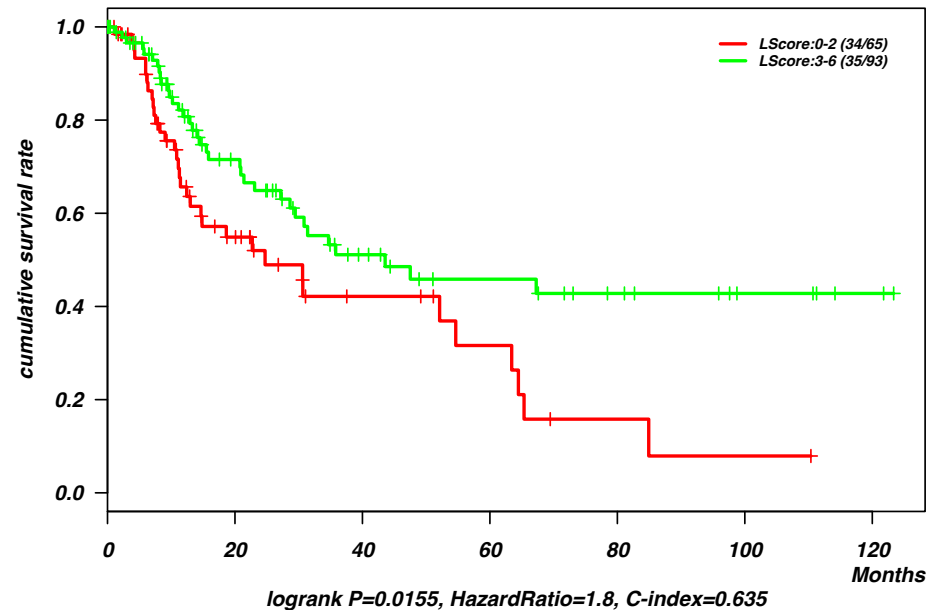
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⇧ Lymphocyte Infiltration => Longer Survival

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Highly Recurrent *TERT* Promoter Mutations in Human Melanoma

Franklin W. Huang,[1,2,3]* Eran Hodis,[1,3,4]* Mary Jue Xu,[1,3,4] Gregory V. Kryukov,[1] Lynda Chin,[5,6] Levi A. Garraway[1,2,3]†

Science 2013
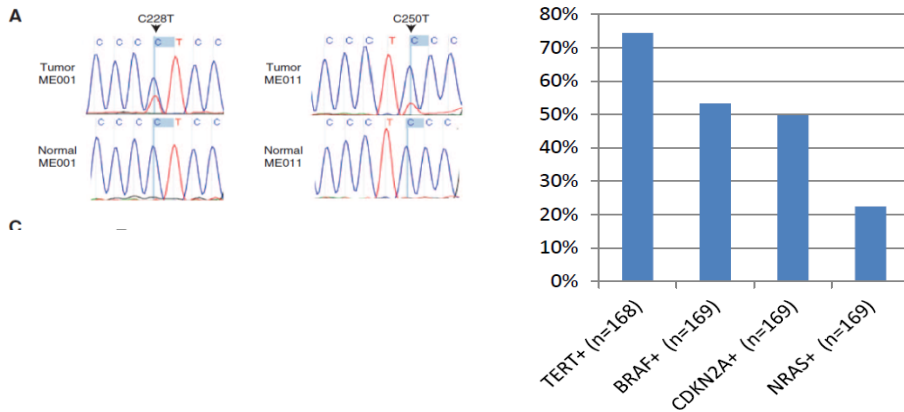
TERT Promoter Mutations in Familial and Sporadic Melanoma

Susanne Horn,[1,2] Adina Figl,[1,2] P. Sivaramakrishna Rachakonda,[1] Christine Fischer,[3] Antje Sucker,[2] Andreas Gast,[1,2] Stephanie Kadel,[1,2] Iris Moll,[2] Eduardo Nagore,[4] Kari Hemminki,[1,5] Dirk Schadendorf,[2]*† Rajiv Kumar[1]*†

Science 2013
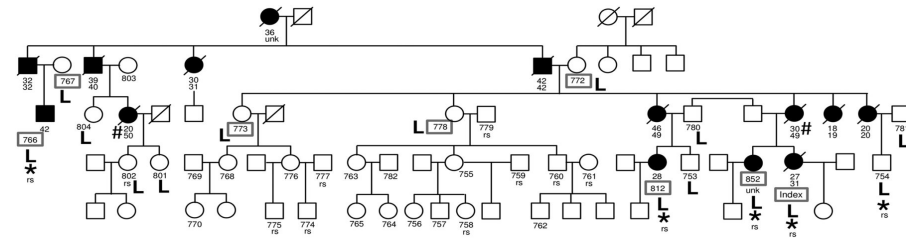
HMS/BWH/MDACC GCC
Angela Hadjipanayis, Terrence Wu, Franklin Huang, Lynda Chin, Raju Kucherlapati

- **106 TCGA melanoma tumors**

  – C228T mutation in 25 tumors (23.6%)

  – C250T mutation in 41 tumors (38.7%), mutually exclusive with C228T

  – Wild-type TERT promoter in 40 tumors (37.7%)

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Tert mRNA expression
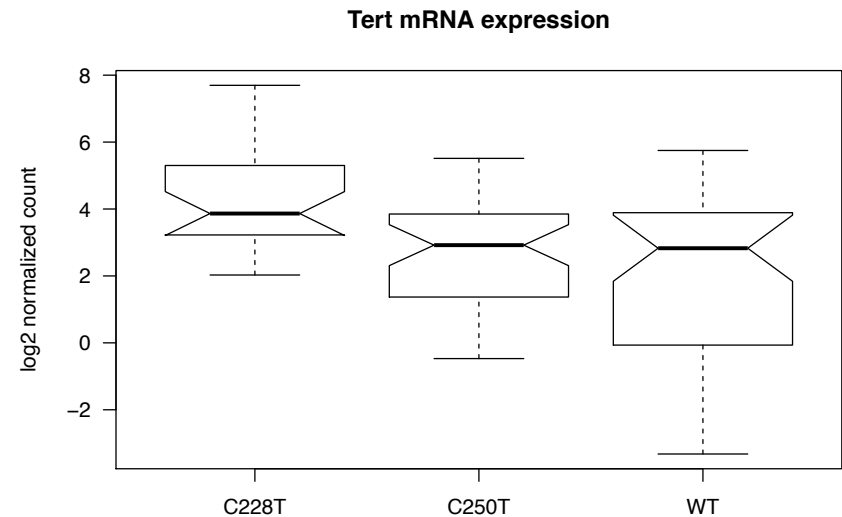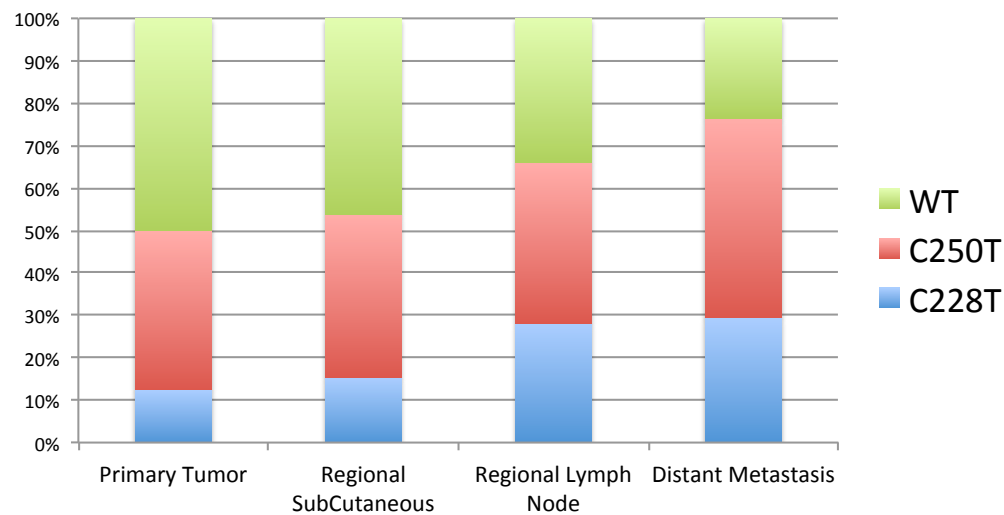
Rank-sum test: C228T >> WT, P=0.001

HMS/BWH/MDACC GCC
Terrence Wu, Angela Hadjipanayis, Franklin Huang, Lynda Chin, Raju Kucherlapati

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Pathway Analysis: Melanoma Subtypes
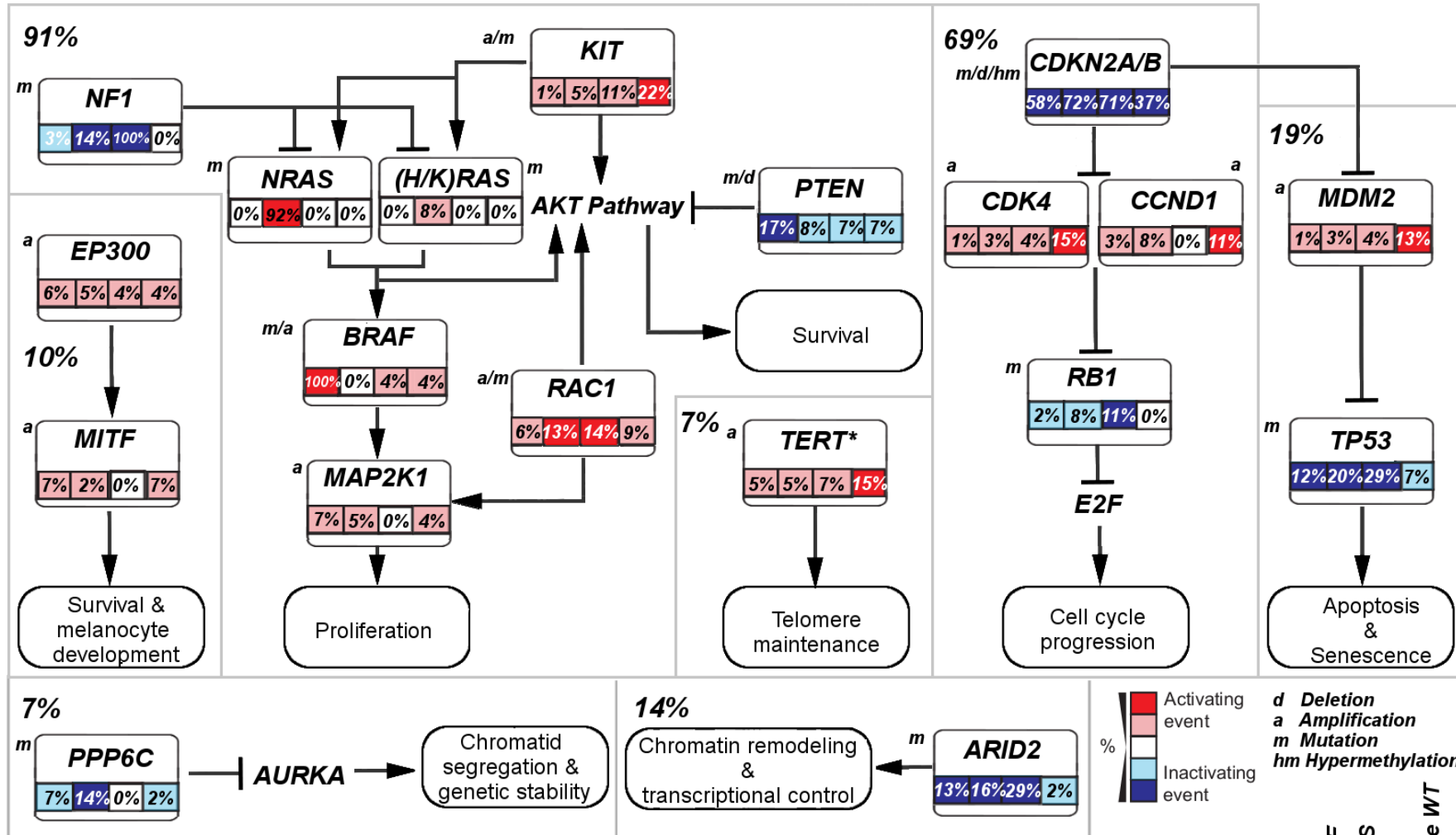
*Not including the TERT promoter mutations (65% N=120)

MSKCC

Anil Korkut, Giovanni Ciriello, Niki Schultz, Chris Sander

Summary

- Propose 4 genetically distinct subgroups of melanoma:

  - ***BRAF*** mutant (hotspot)

  - ***RAS*** mutant (hotspot)

  - ***NF1*** LoF mutations (*BRAF/NRAS WT*) with UV signature

  - ***Triple wild-type*** lacking UV signature driven by copy number alterations of known oncogenes

- Integration of other data platforms identifies differential MAPK signaling pathways altering in genetic subtypes

- Methylation clustering analysis identified a CIMP subtype enriched for IDH1 R132 mutations

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Ongoing Analysis
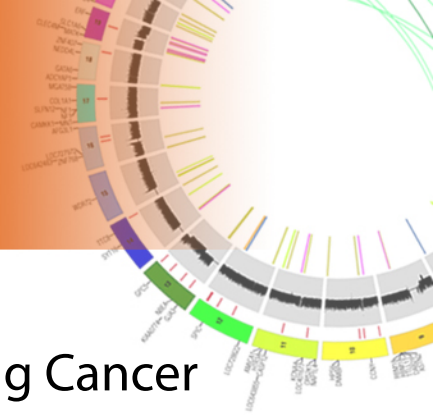
- Incorporation of Oncosign analysis (Memorial Sloan-Kettering Cancer Center)

- miRNA clustering analysis (The Genome Sciences Centre, BC Cancer Agency)

- Primary vs Metastatic comparative analyses

- Genetic determinants of lymphocytic infiltration

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…And the rest of the TCGA Community
… the patients

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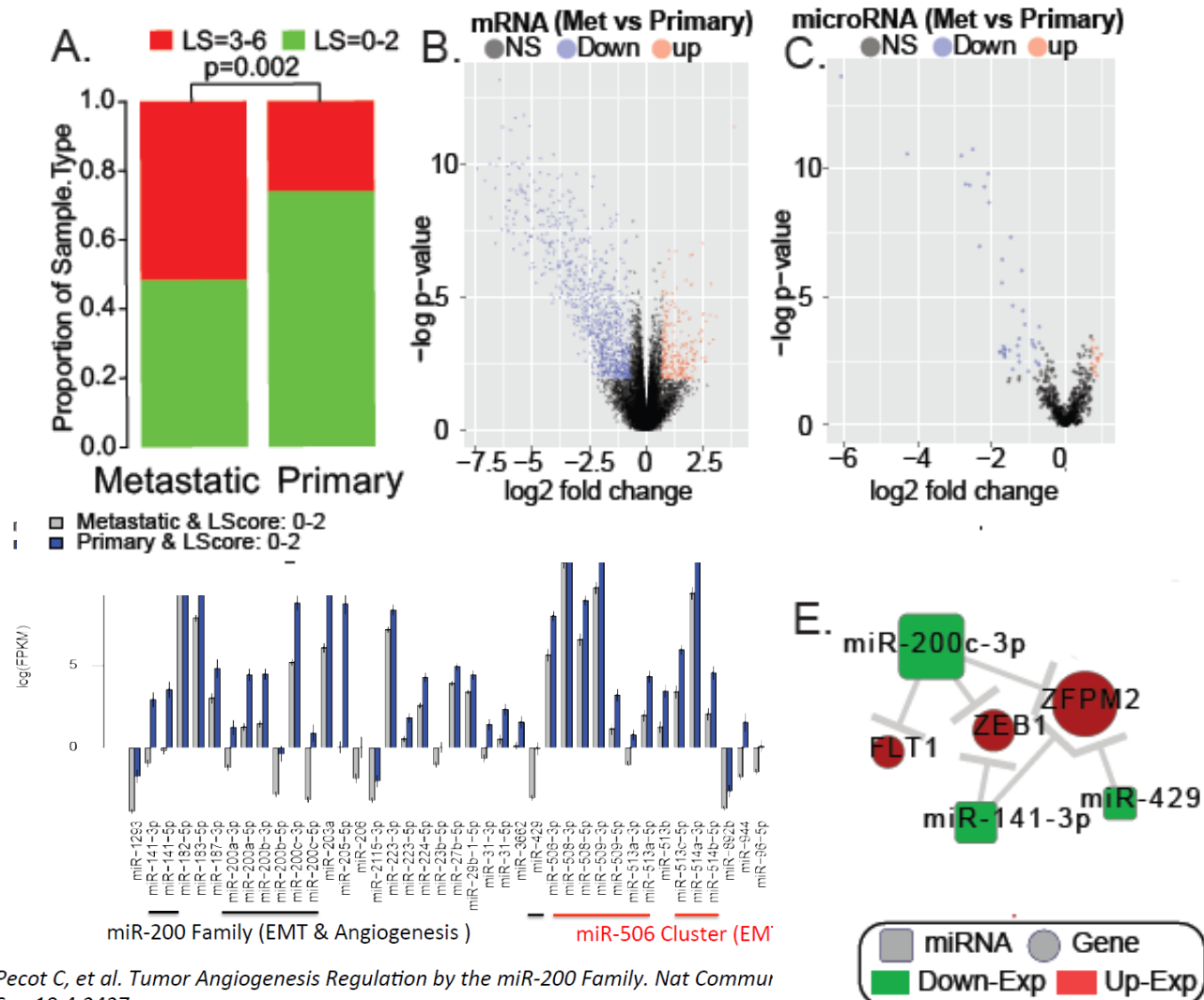
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