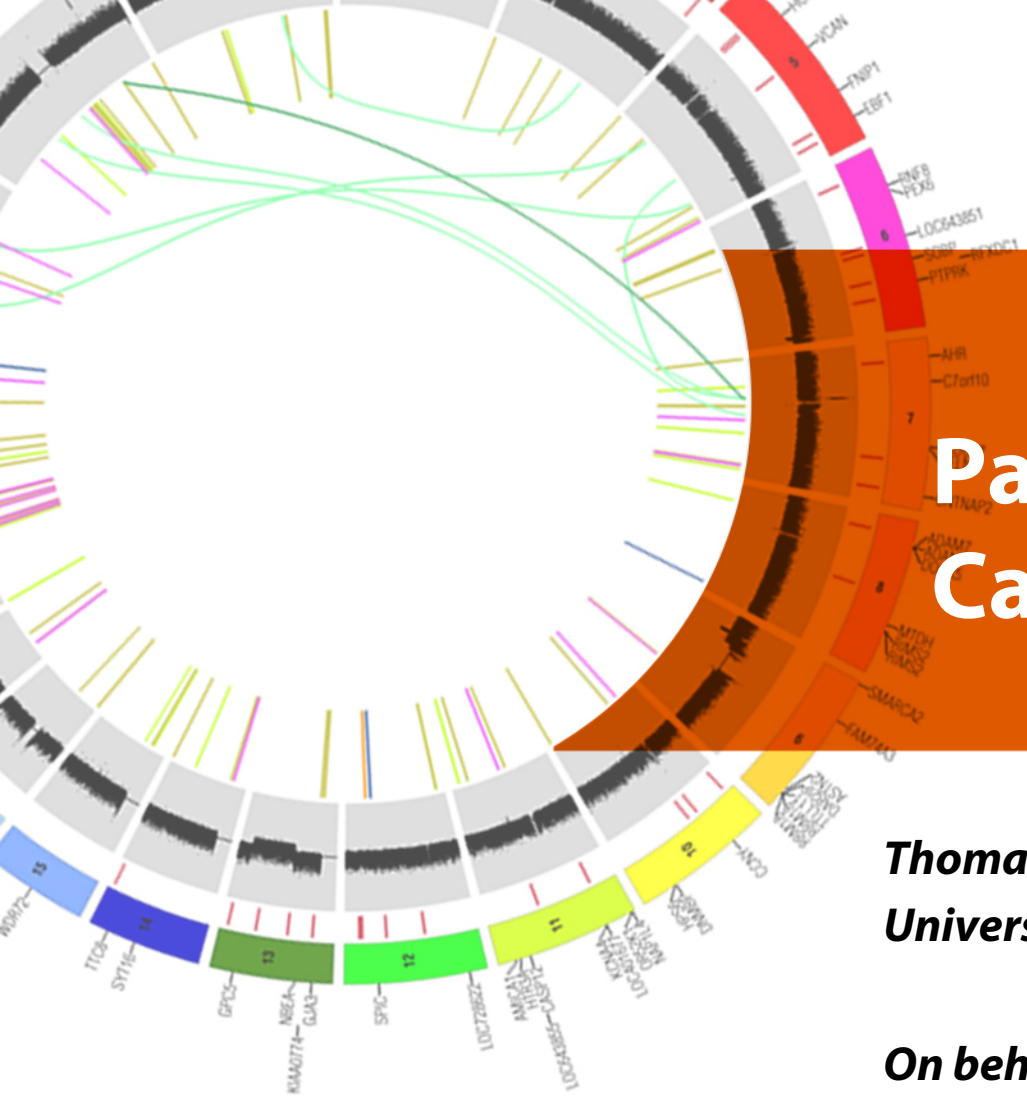


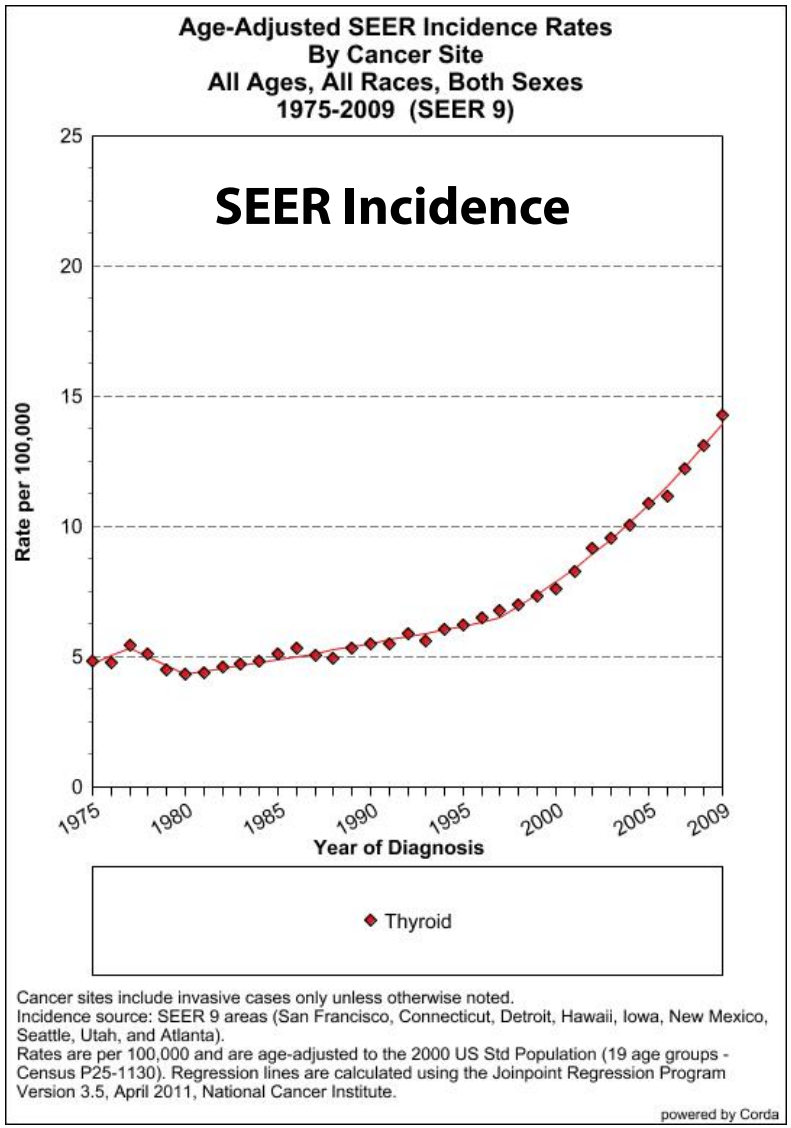
The Cancer Genome Atlas

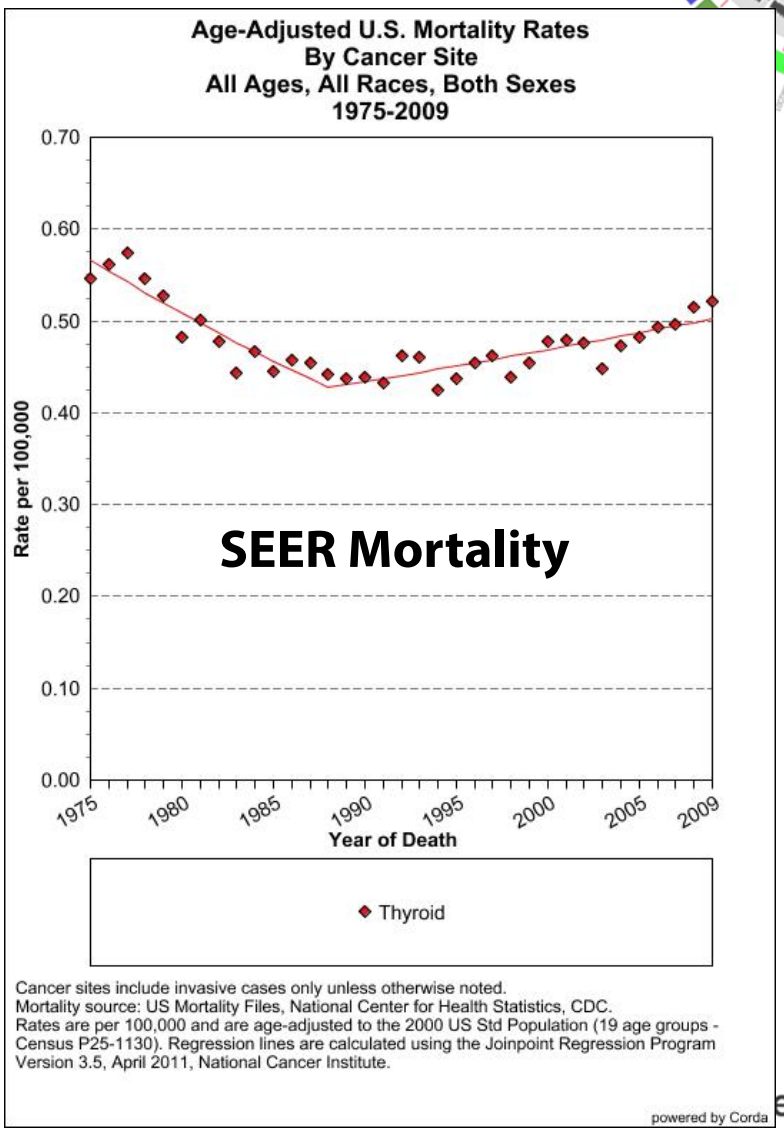
Papillary Thyroid Carcinoma Analysis

Thomas Giordano
University of Michigan

On behalf of TCGA
THCA Analysis Working Group

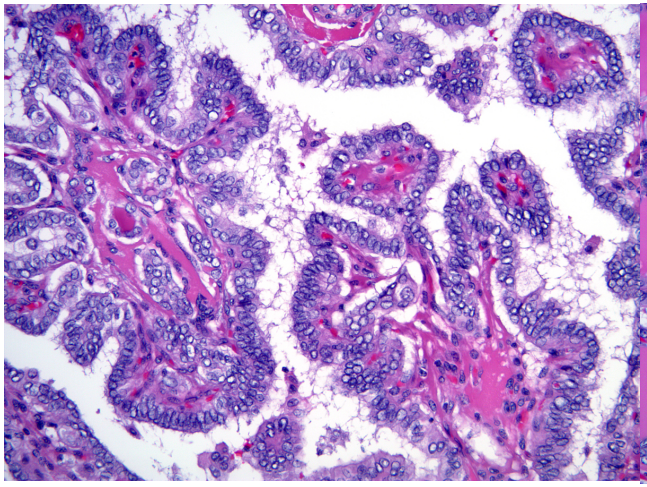
Thyroid Cancer is on the Rise



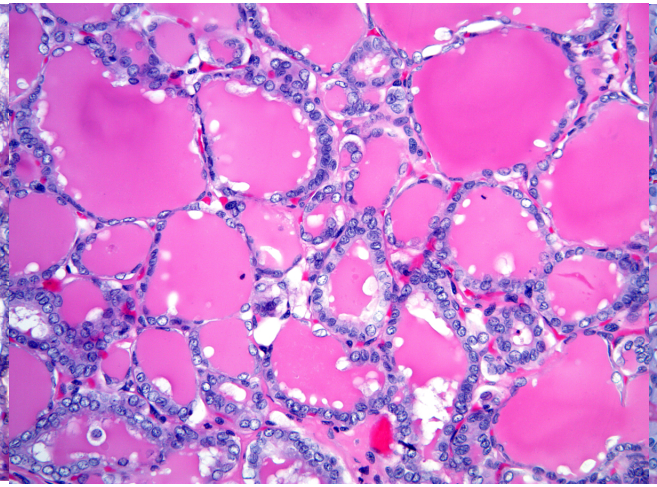


e Atlas

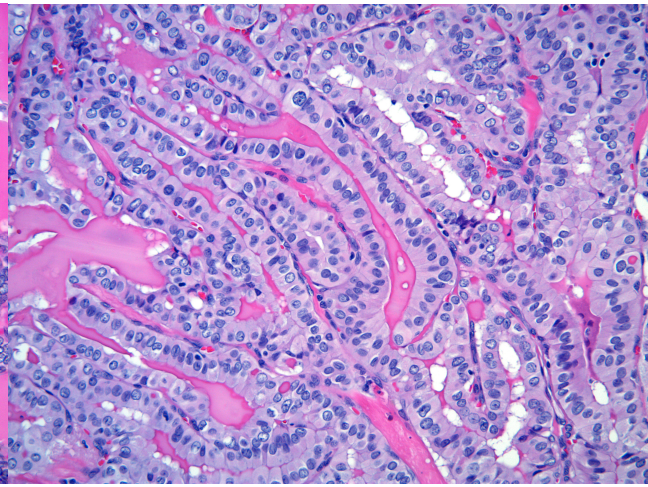
Papillary Carcinoma, 3 Main Types



Classical



Follicular Variant



Tall Cell Variant

Genetic Defects in Thyroid Cancer

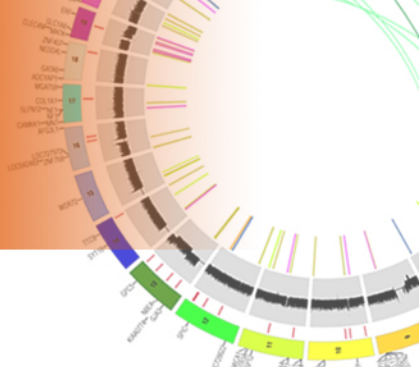


Table 2 | **Genetic defects in thyroid cancer**

Genetic alteration	Well-differentiated thyroid carcinoma		Poorly differentiated thyroid carcinoma	Undifferentiated thyroid carcinoma	Post-Chernobyl childhood thyroid cancer
	Papillary thyroid carcinoma	Follicular thyroid carcinoma			
RET rearrangement	13–43%	0%	0–13%	0%	50–90%
BRAF mutation	29–69%	0%	0–13%	10–35%	0–12%
BRAF rearrangement	1%	Unknown	Unknown	Unknown	11%
NTRK1 rearrangement	5–13%	Unknown	Unknown	Unknown	3%
Ras mutation	0–21%	40–53%	18–27%	20–60%	0%
PPARG rearrangement	0%	25–63%	0%	0%	Unknown
CTNNB1 mutation	0%	0%	0–25%	66%	Unknown
TP53 mutation	0–5%	0–9%	17–38%	67–88%	Unknown

Kondo, Ezzat and Asa. Nature Reviews Cancer 6, 292-306 (April 2006) c

BIG Issue for Thyroid

- About 25% of cases have none of the common driver mutations

- Large opportunity for TCGA project
  - Refine genotype based diagnostic assays

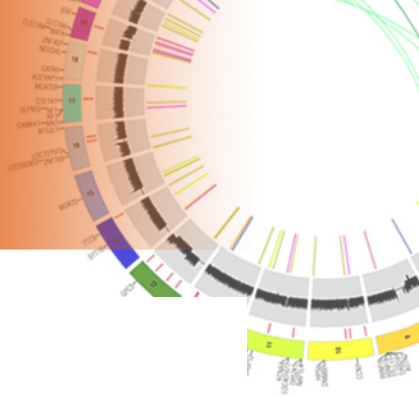
First look at the TCGA THCA Data

- Data freeze less than one month ago
- Much of the analysis generated automatically by Firehose
- Analysis really just getting started
- *Much remains to be validated*
  - Still sorting our false positive mutations

Sample Counts: Data Freeze 10/24/12

Analysis	Sample Count
Thru BCR	435
Clinical Data	218
Copy Number	330
Low Pass	94
Methylation	353
mRNAseq	254
miRseq	349
RPPA	224
MAF	323

Clinical Data Summary, n = 218



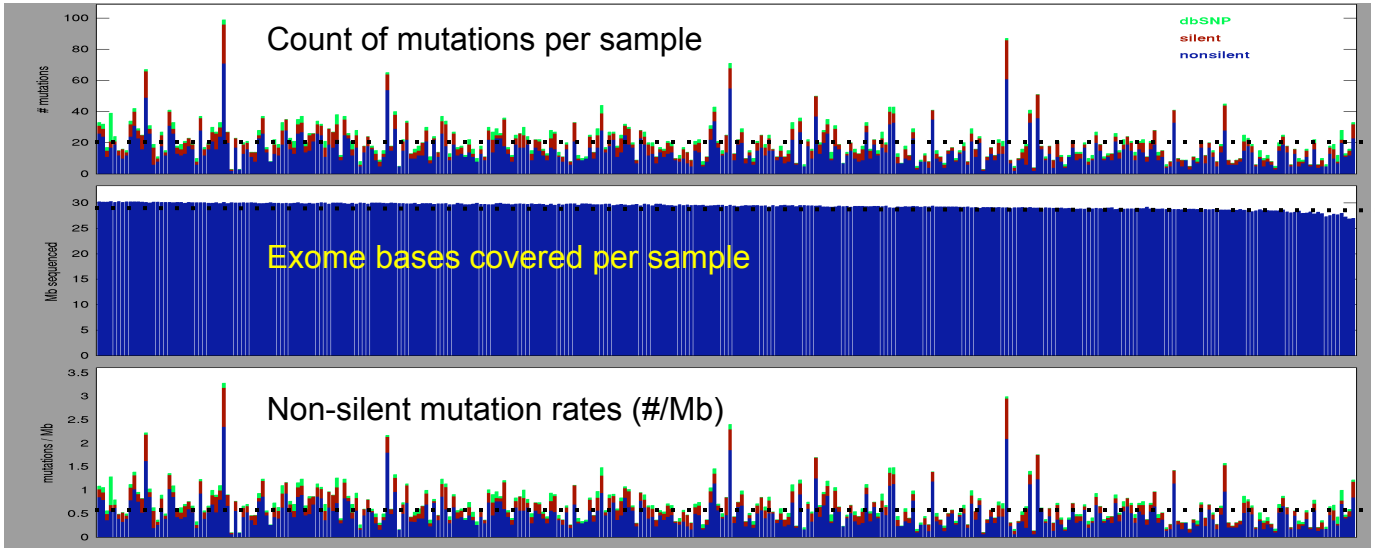
Tier 1 Data Statistics

Table 2. Statistics of selected clinical variables.

Clinical.Variable	Statistics
age	mean: 46, std: 16
vitalstatus	217 living, 1 deceased
gender	56 male, 162 female
histologicaltype	64 thyroid papillary carcinoma - follicular (>= 99% follicular patterned), 124 thyroid papillary carcinoma - classical/usual, 22 thyroid papillary carcinoma - tall cell (>= 50% tall cell features), 8 other

Papillary Carcinoma is a highly differentiated carcinoma with a low overall mutation rate

Distribution of Mutation Counts, Coverage, and Mutation Rates Across Samples



coMut (mutations, fusions, SCNAs, expression)

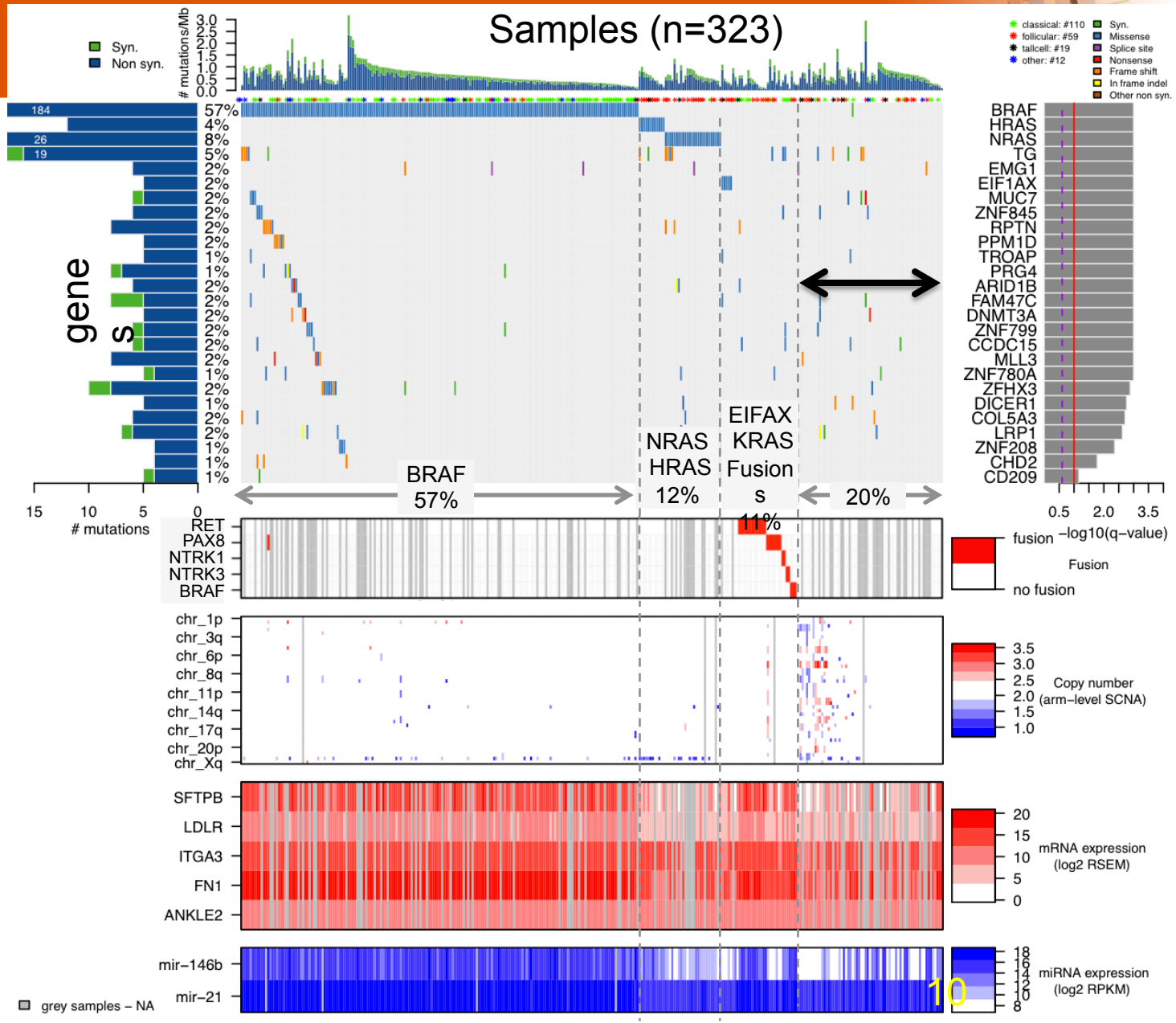
Mutations

fusions

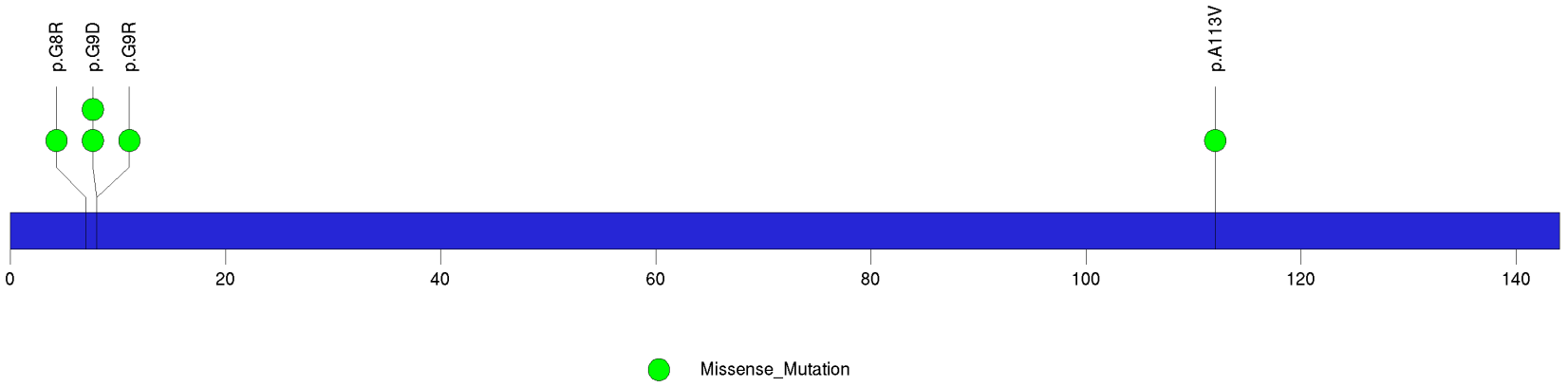
Arm-level SCNAs

mRNAseq expression

miRNAseq expression



Interesting Novel Mutation, *EIF1AX*



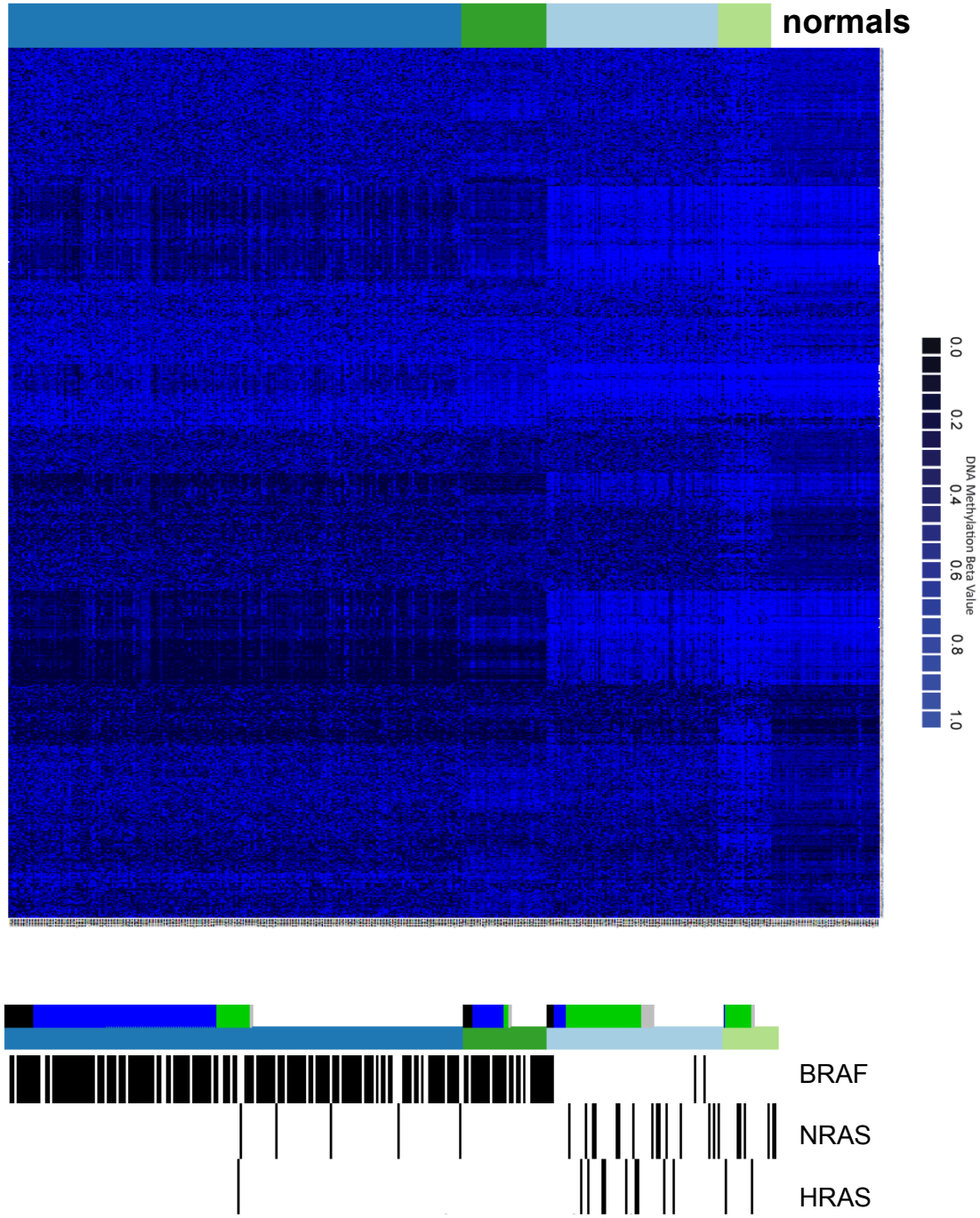
- X-linked translation initiation factor
- Essential translation factor that is required for the binding of the 43S complex to the 5' end of capped RNA
- No known role in thyroid cancer and not in any other cancer (1 synonymous mutation in COSMIC)

Other Recurrent Fusions from Low Pass WGS and RNASeq Integration

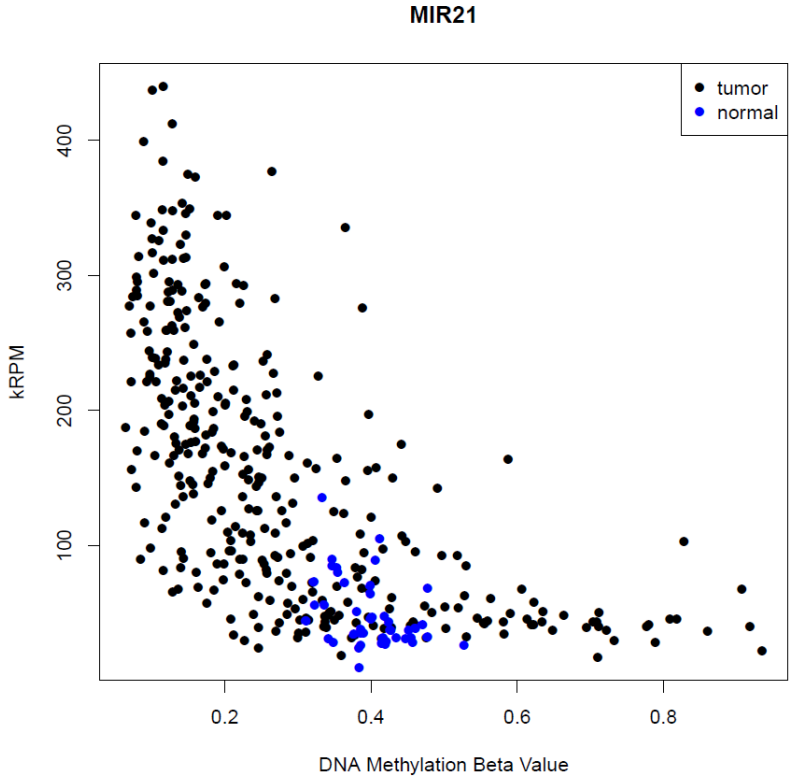
Significant List	Positive Tumor Samples
Thyroid n=95	
CCDC-RET	**9**
Intergenic-THADA	4
ETV6-NTRK3	3
PAX8-PPARG	3

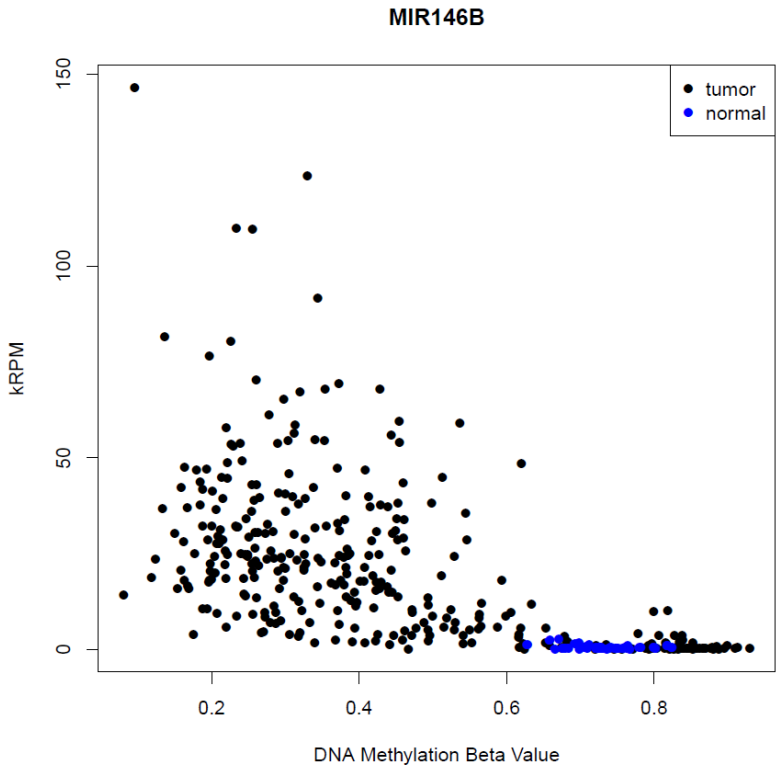
Still much to be done on fusions

DNA Methylation identifies 4 subtypes that correlate with histologic type and mutational status



miR-21 and miR-146b Expression and DNA Methylation



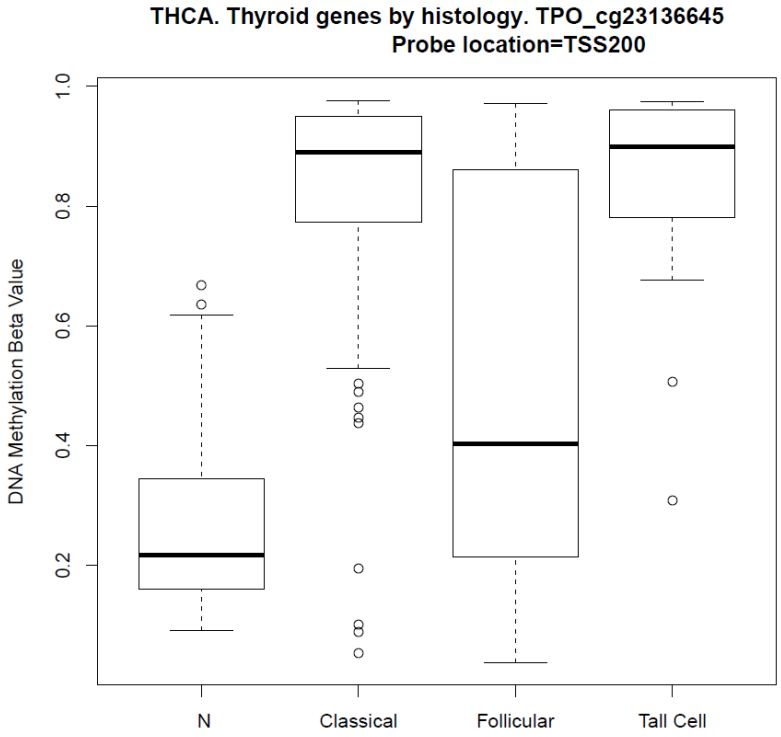


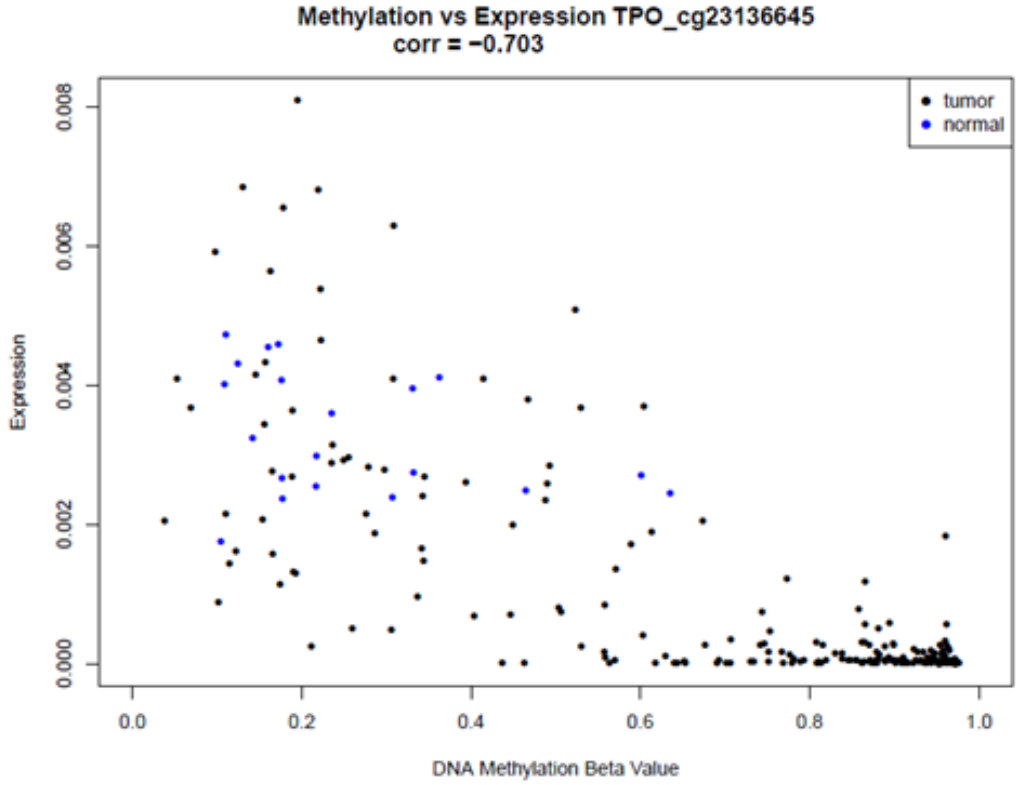
rho = -0.72

rho = -0.69

The Cancer Genome Atlas

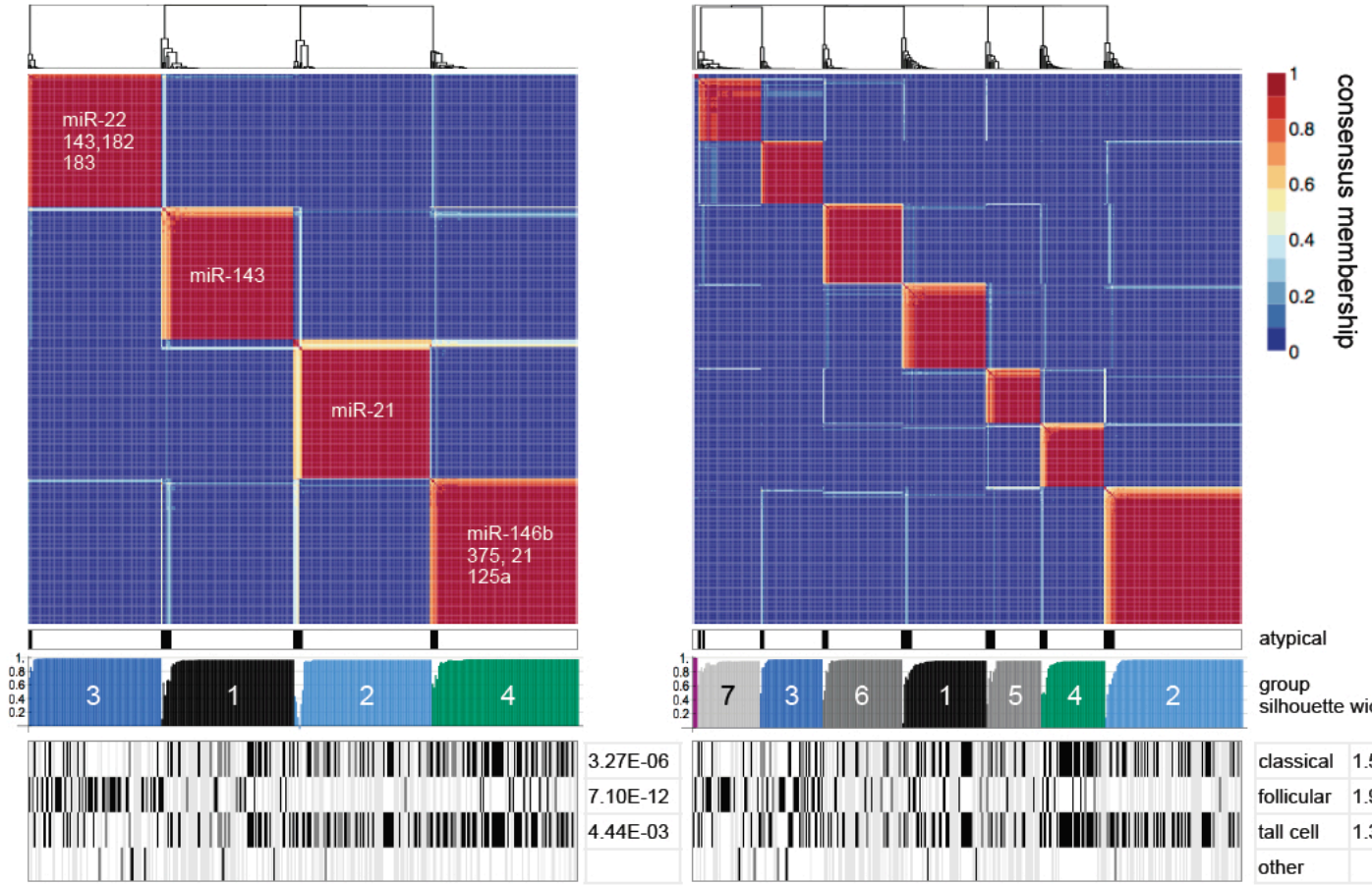
Methylation and Thyroid Genes: TPO (thyroid peroxidase)





Potentially interesting story related to tumor differentiation and response to radioiodine therapy.

MIR-based Classification



c	3	1	2	4	all
n	85	85	88	94	352
w	0.99	0.94	0.92	0.96	0.95

NMF 0.8.13, R 2.15.1

c	8	7	3	6	1	5	4	2	all
n	3	40	40	51	54	35	41	88	352
w	1.00	0.93	0.96	0.95	0.91	0.91	0.91	0.94	0.93

Thyroid (THCA) Public Clinical Data Sep-19-2012.xlsx

**	do not include c8
***	no c8; chi-sq approx may be incorrect

MIR-based Classification

BCGSC, 4 groups

Silhouette widths

c	1	4	3	2	all
n	85	85	86	93	349

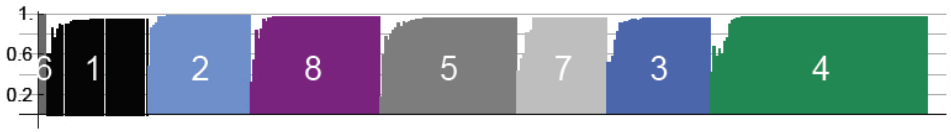
BCGSC, 6 groups

5

TCGA-BJ-A28T-01A-11R
TCGA-FE-A239-01A-11R
TCGA-BJ-A191-01A-11R
TCGA-EM-A22Q-01A-11R

c	5	2	3	1	4	6	all
n	4	62	86	83	56	58	349

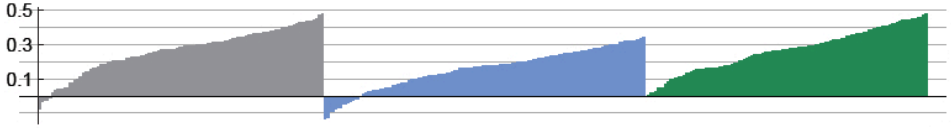
BCGSC, 8 groups



TCGA-FE-A239-01A-11R
TCGA-BJ-A191-01A-11R
TCGA-EM-A22Q-01A-11R

c	6	1	2	8	5	7	3	4	all
n	3	40	40	51	54	35	41	85	349

Firehose, 3 groups



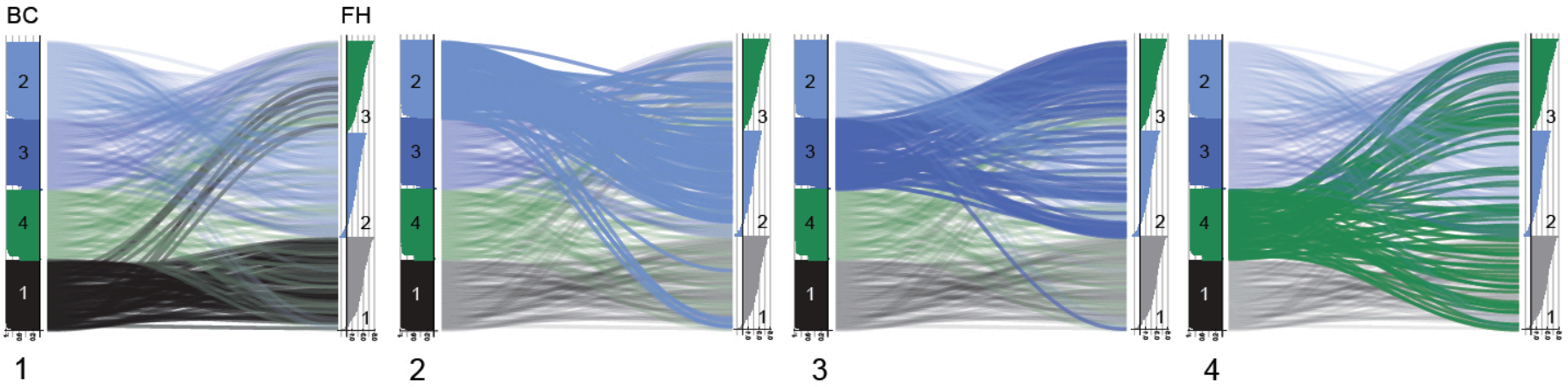
c	5	2	3	all
n	4	62	86	349

cer Genome Atlas

Comparison of MIR Clustering

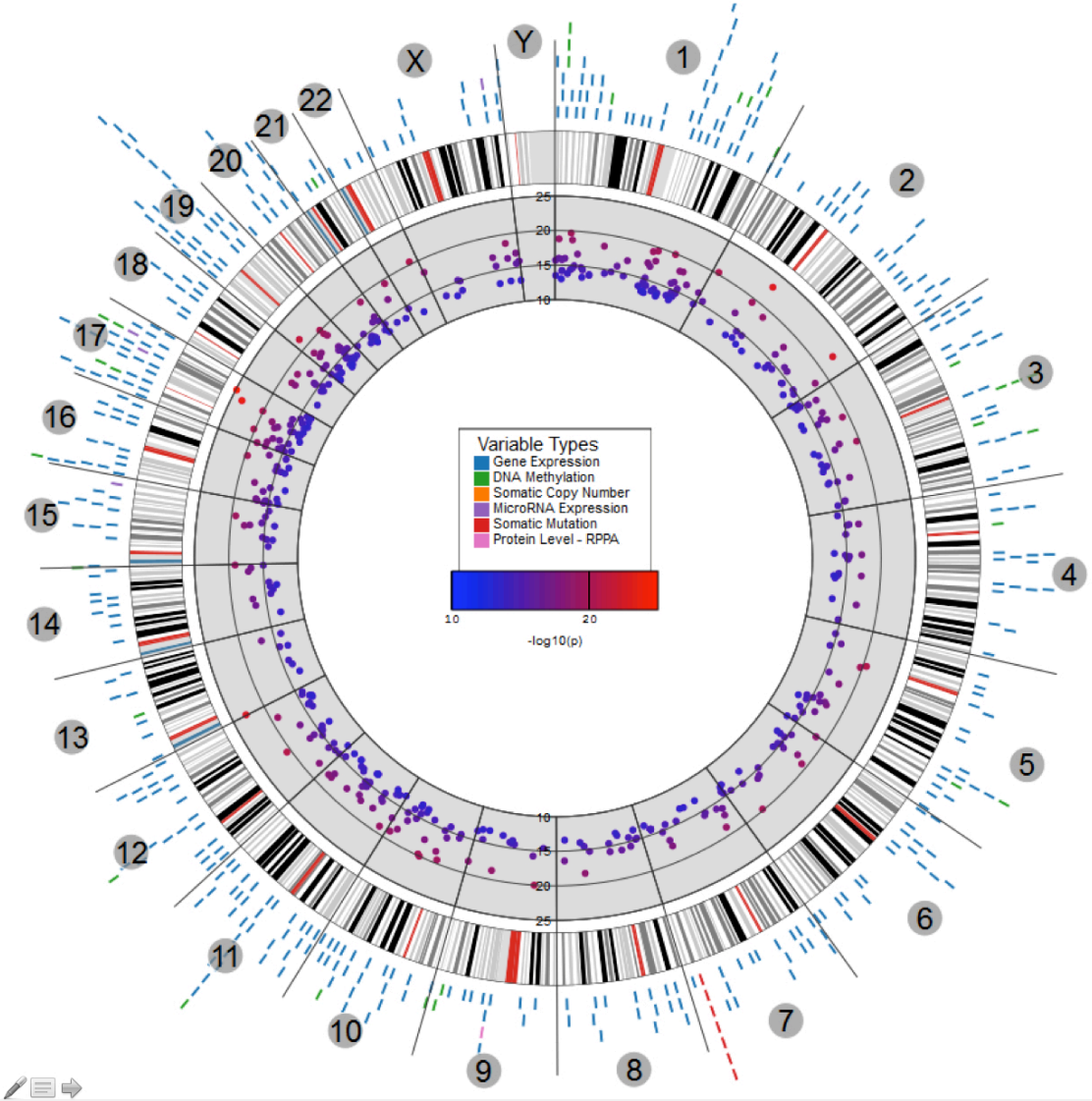
THCA miRNA-seq, 349 data freeze samples

NMF consensus clustering: compare BC (4), Firehose (3)

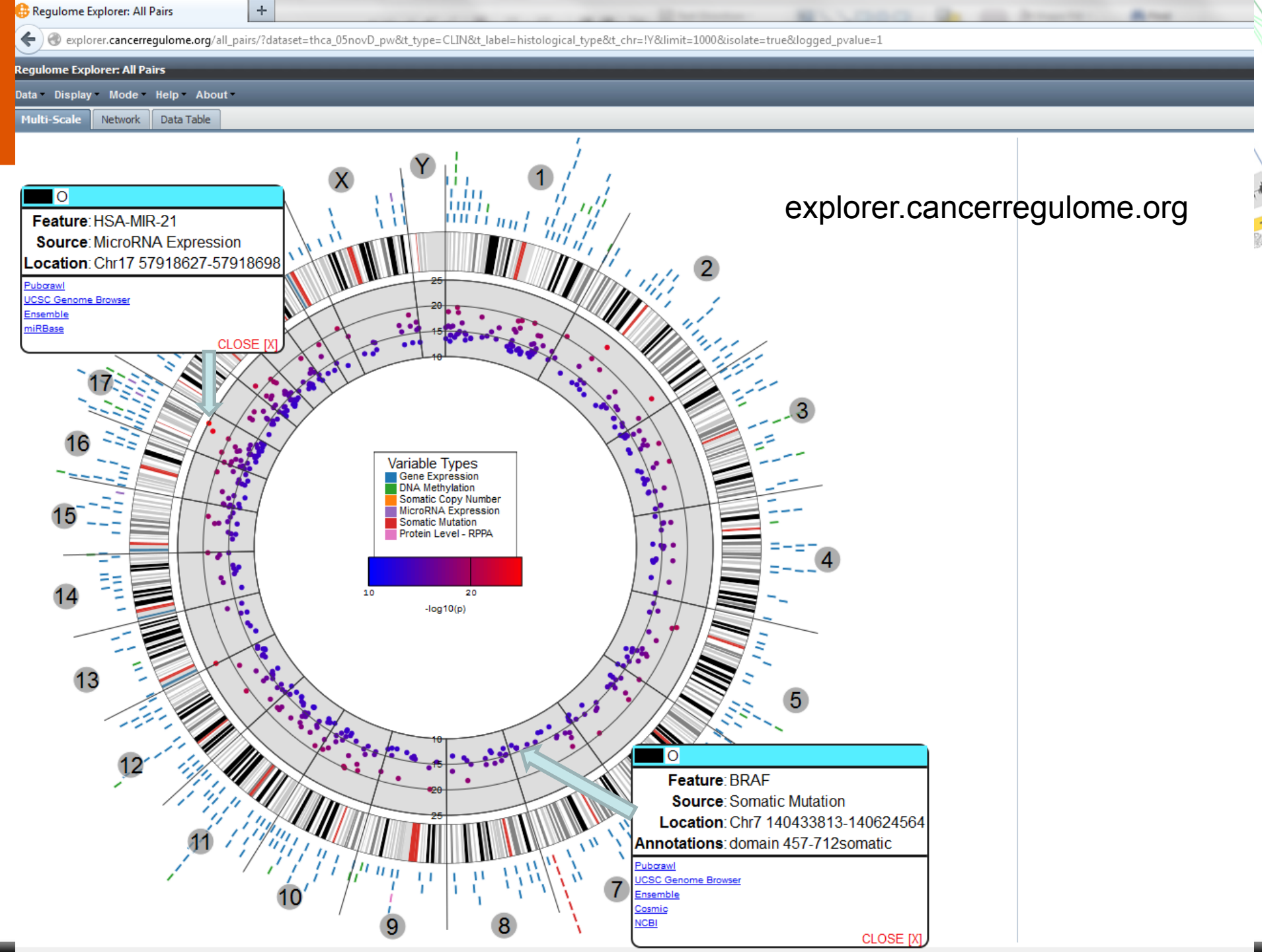


Analysis Ongoing

Cancer Regulome: Multiple Associations with Histologic Type



ancer Genome Atlas


Regulome Explorer: All Pairs
explorer.cancerregulome.org/all_pairs/?dataset=thca_05novD_pw&t_type=CLIN&t_label=histological_type&t_chr=!Y&limit=1000&isolate=true&logged_pvalue=1
Regulome Explorer: All Pairs
Data
Display
Mode
Help
About
Multi-Scale
Network
Data Table
explorer.cancerregulome.org
Feature: HSA-MIR-21
Source: MicroRNA Expression
Location: Chr17 57918627-57918698
Pubgawl
UCSC Genome Browser
Ensemble
miRBase
CLOSE [X]
Variable Types
Gene Expression
DNA Methylation
Somatic Copy Number
MicroRNA Expression
Somatic Mutation
Protein Level - RPPA
10
20
-log10(p)
Feature: BRAF
Source: Somatic Mutation
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Annotations: domain 457-712somatic
Pubgawl
UCSC Genome Browser
Ensemble
Cosmic
NCBI
CLOSE [X]

Conclusions

- THCA project is progressing as planned
- Cohort is outstanding and representative of the disease
- Overall low mutation rate with few copy number changes
- Strong associations between tumor morphology, genotype, gene expression, copy number changes and methylation status
- Many interesting leads for novel mutations and gene expression patterns
- Much to do, but on track for first paper mid-2013

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