Analysis of genomic differences between lung adenocarcinoma and squamous cell carcinoma

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Lung Cancer

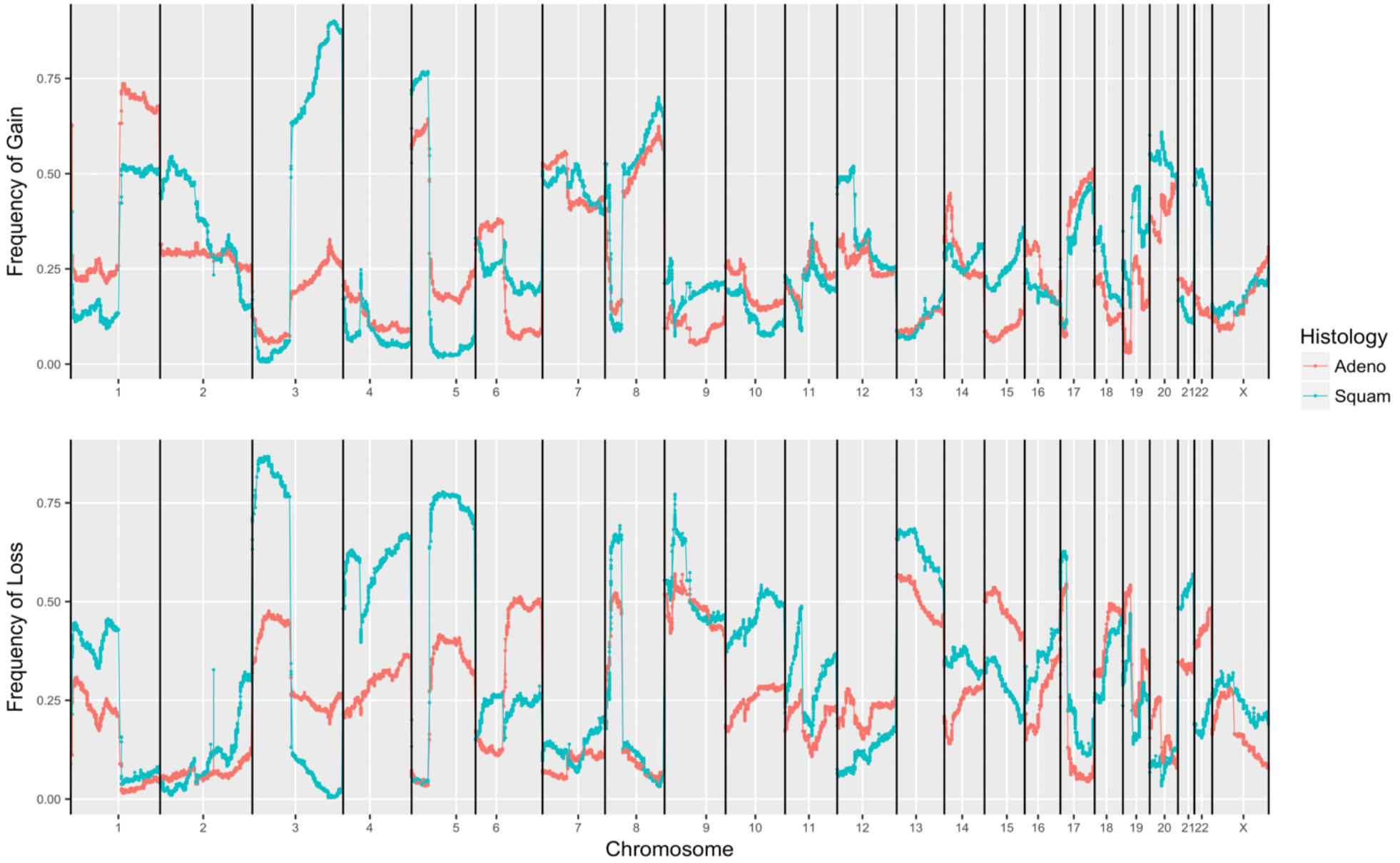
- **#1 cause of cancer-related deaths worldwide**
  - 1.8 million new cases, 1.6 million deaths every year
- **Heterogeneous disease**
  - Results from both environmental and genetic factors
- **Main global risk factor: tobacco smoking**
  - However, 10-25% of lung cancers occur in people who have never smoked

Adenocarcinoma	Squamous cell carcinoma
40% of all lung cancers	25% of all lung cancers
Located in outer edges of lungs	Located in central part of lungs
Most common lung cancer in people who have never smoked	Strongly associated with smoking

Gridelli, C. *et al.* (2015) Non-small-cell lung cancer *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.9

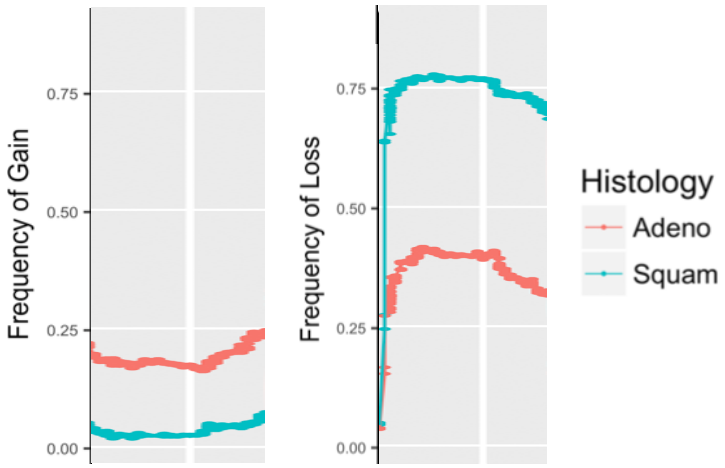
Frequency of Copy Number Variation

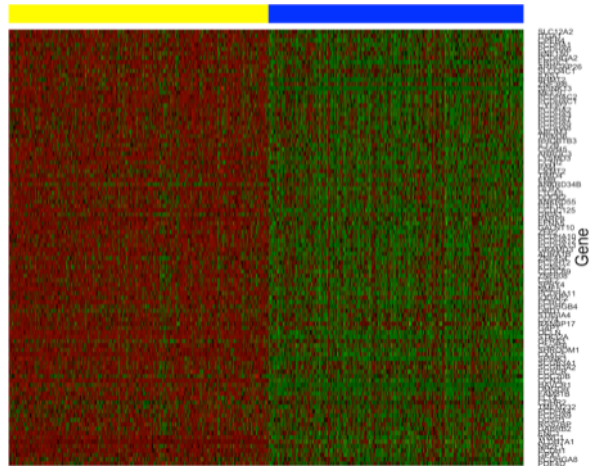
- **Copy number variation**
  - Alterations in the number of copies of specific regions of DNA, which can either be deleted or duplicated
- **TCGA samples:**
  - 516 Adeno
  - 501 Squam

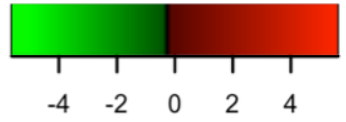


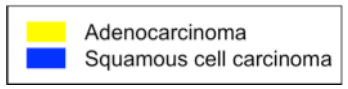
Gene Expression in Chromosomes with Significant CNV between AD and SC

Chr 5q

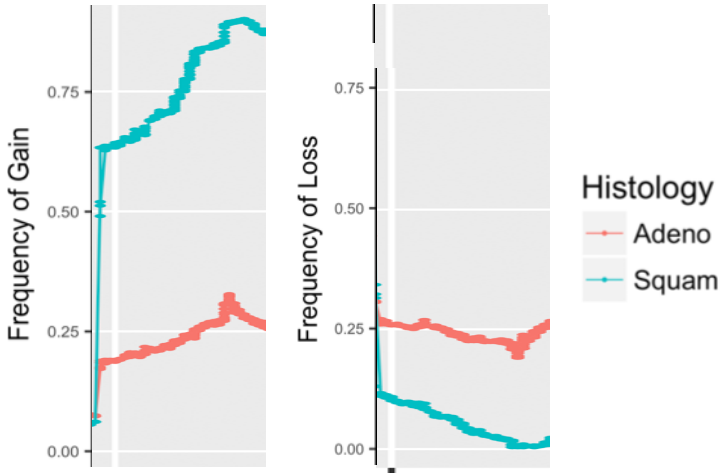


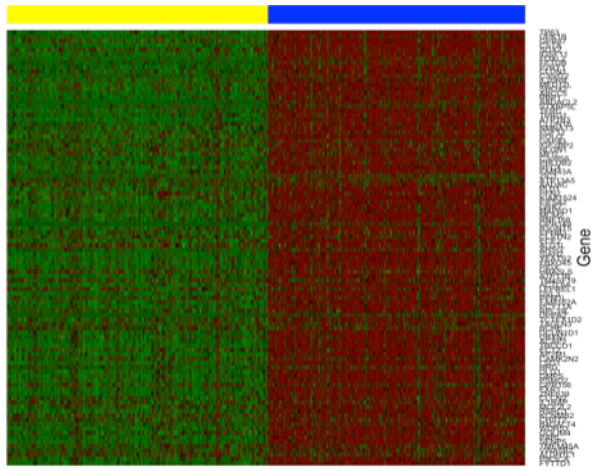


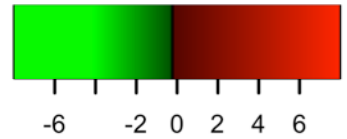


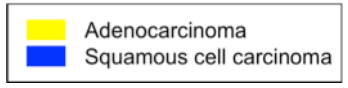


Chr 3q









Functional Enrichment Analysis (GSEA, DAVID, ToppGene)

- Differentially expressed genes with higher gene expression in adenocarcinoma on chromosomes with significant copy number variation

Significant Region	P-value	Functional Gene Set	Role in Cancer
Chr 3p	8.85E-10	• Platelet dense granule • Chemokine receptor activity • Chemotaxis • G-protein coupled receptor activity • Cytokine receptor activity	Metastasis; Tumor progression
Chr 4q	1.24E-6	• Blood coagulation • Plasminogen activation • Extracellular matrix • Platelet alpha granule • Oxidoreductase activity	Metastasis; Invasion; Tumor progression; Apoptosis
Chr 5q	1.90E-23	• Cell-cell adhesion • Calcium ion binding	Metastasis; Invasion; Apoptosis

- Differentially expressed with higher gene expression in squamous cell carcinoma on chromosomes with significant copy number variation

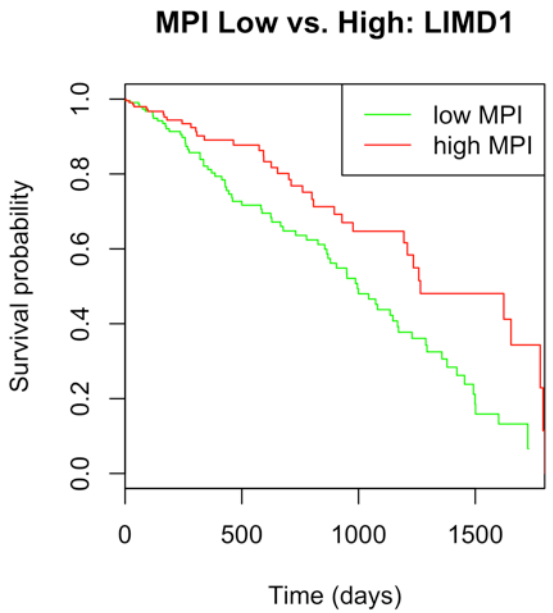
Significant Region	P-value	Functional Gene Set	Role in Cancer
Chr 3q	4.23E-42	• Nucleotide receptor activity • Nucleotide receptor signaling pathway	Proliferation; Differentiation; Apoptosis
Chr 6q	1.65E-14	• Natural Killer Cell Mediated Cytotoxicity • Natural Killer Cell Lectin-Like Receptor Binding	Proliferation

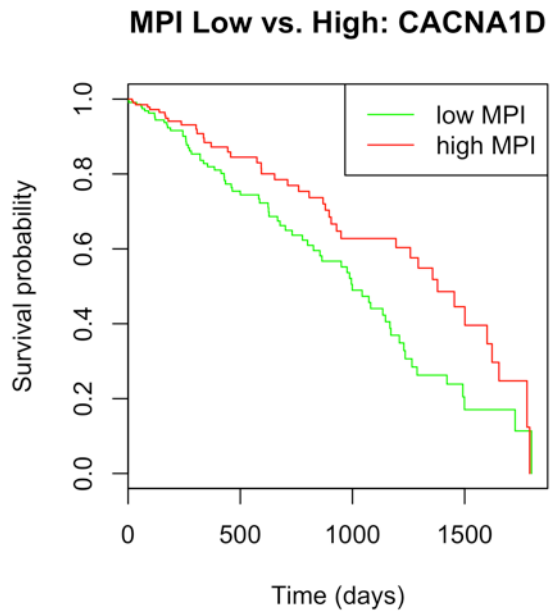
Adenocarcinoma: Metastasis and Invasion
Squamous cell carcinoma: Proliferation

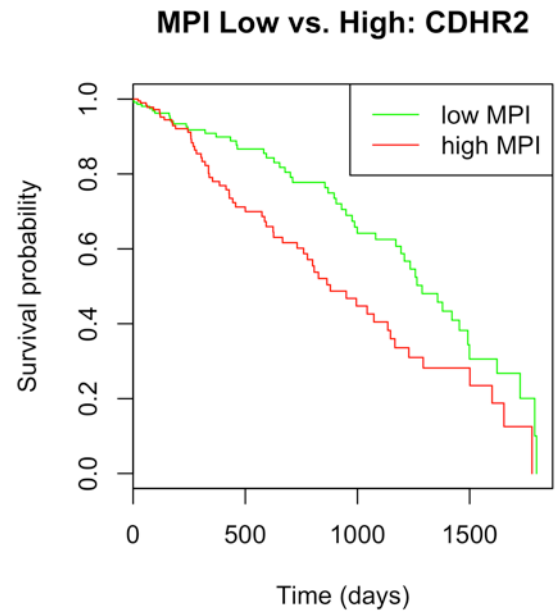
Survival Analysis (TCGA clinical data)

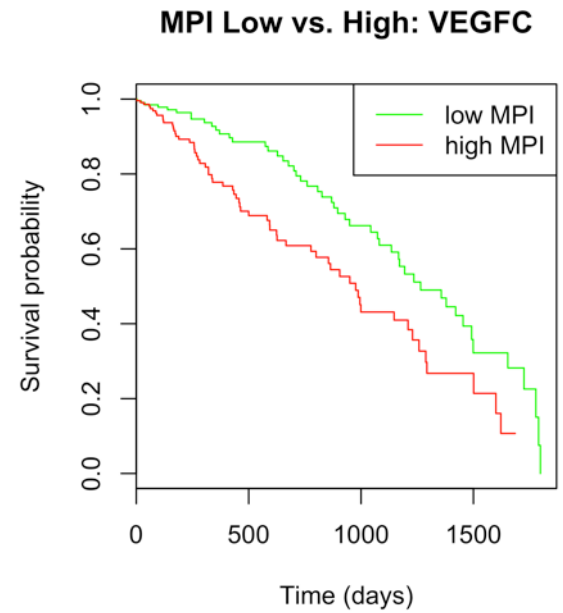
▸ 5 year survival, differentially expressed genes w/ higher expression AD

Gene	Name	Chromosome	Role in Cancer	PRECOG FDR	PRECOG Z-Score
LIMD1	LIM domains containing 1	3p	Inhibits cell proliferation	0.000619	-4.242
CACNA1D	Calcium voltage-gated channel subunit alpha1 D	3p	Cell motility, cell division, and cell death	0.00963	-3.367
CDHR2	Cadherin related family member 2	5q	Cell-cell adhesion	0.0171	3.149
VEGFC	Vascular endothelial growth factor C	4q	Angiogenesis, cell proliferation and migration	0.000121	4.698









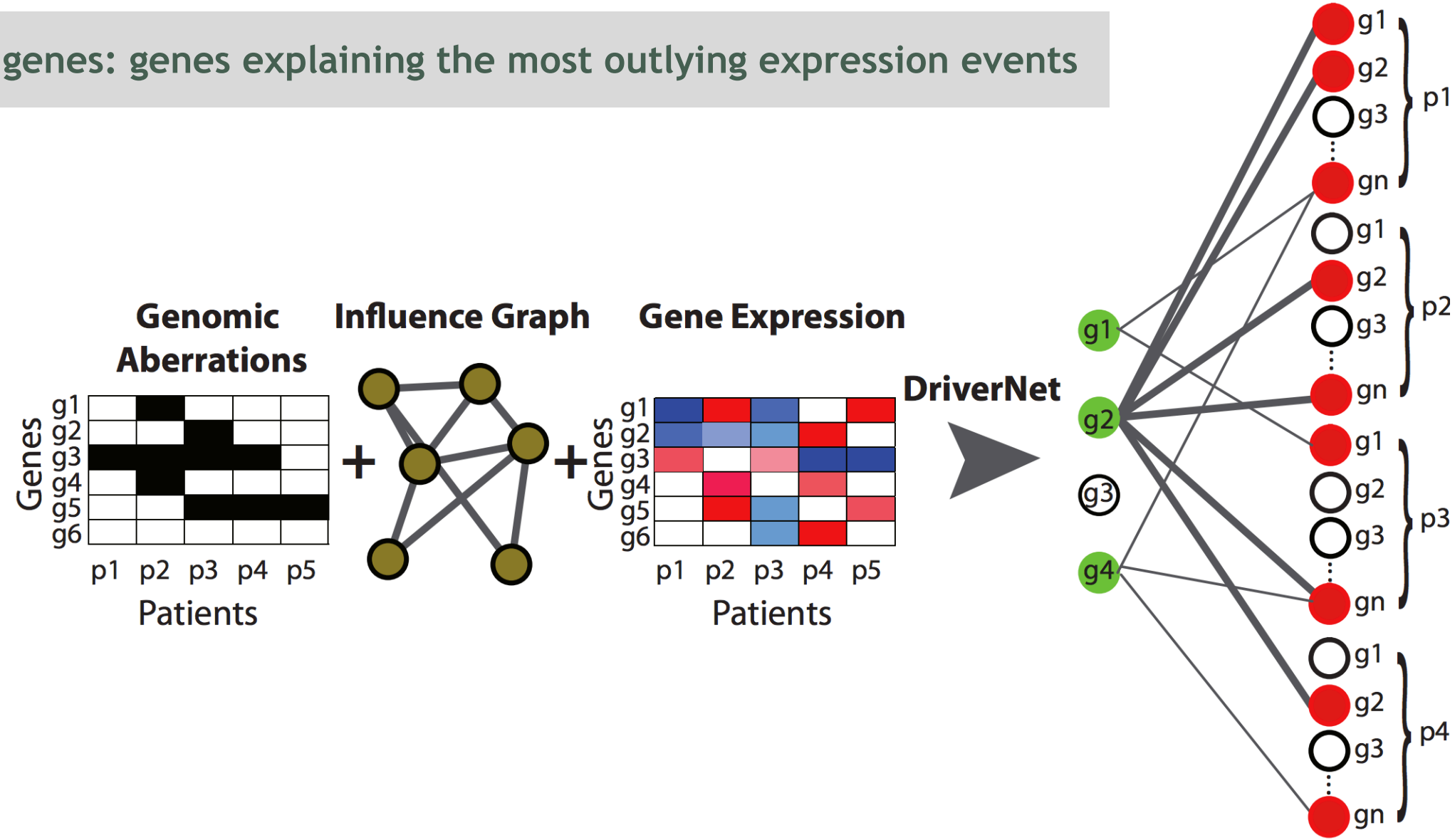
Gentles, Andrew J., et al. "The prognostic landscape of genes and infiltrating immune cells across human cancers." *Nature medicine* 21.8 (2015): 938-945.

The DriverNet Package

Predicting functionally important driver genes in lung cancer

DriverNet: Inputs and Outputs

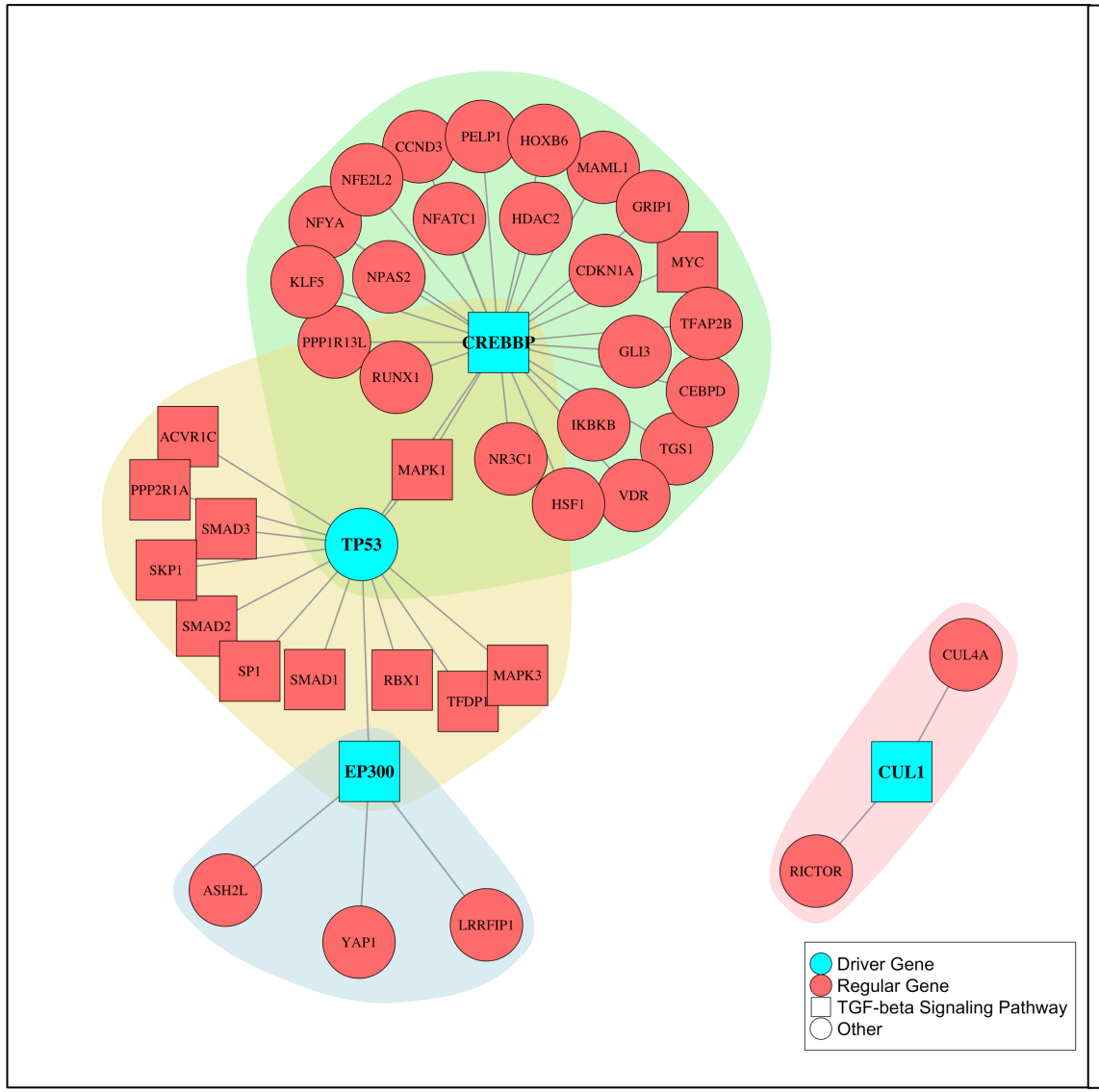
Driver genes: genes explaining the most outlying expression events



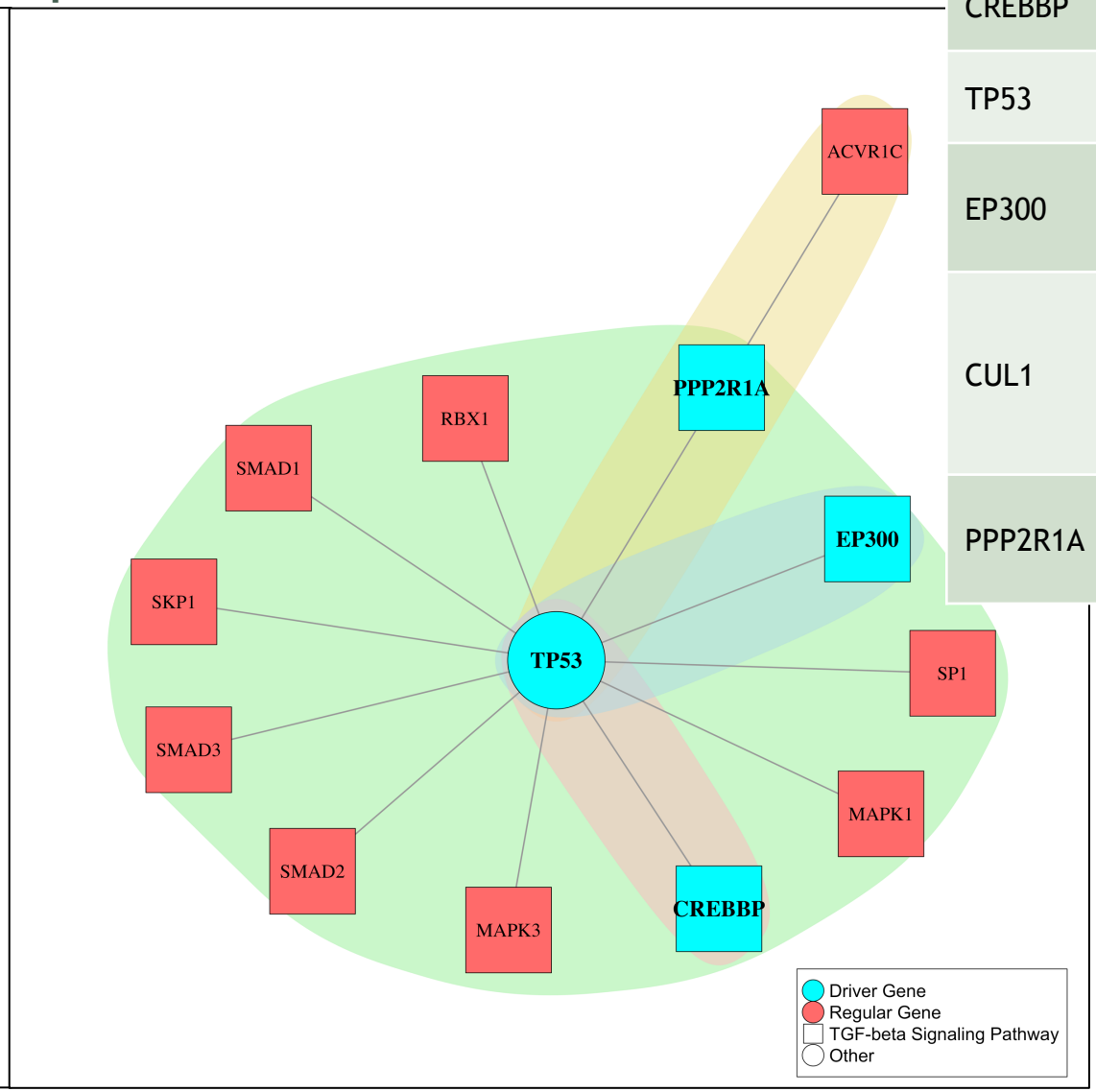
Bashashati, Ali, et al. "DriverNet: uncovering the impact of somatic driver mutations on transcriptional networks in cancer." *Genome biology* 13.12 (2012): R124.

DriverNet: TGF-beta Signaling Pathway

Adenocarcinoma



Squamous cell carcinoma



Gene	Function
CREBBP	Acetylates histones
TP53	Tumor suppressor
EP300	Histone acetyl-transferase
CUL1	Regulates proteins involved in cell cycle progression
PPP2R1A	Inhibits cell growth and division

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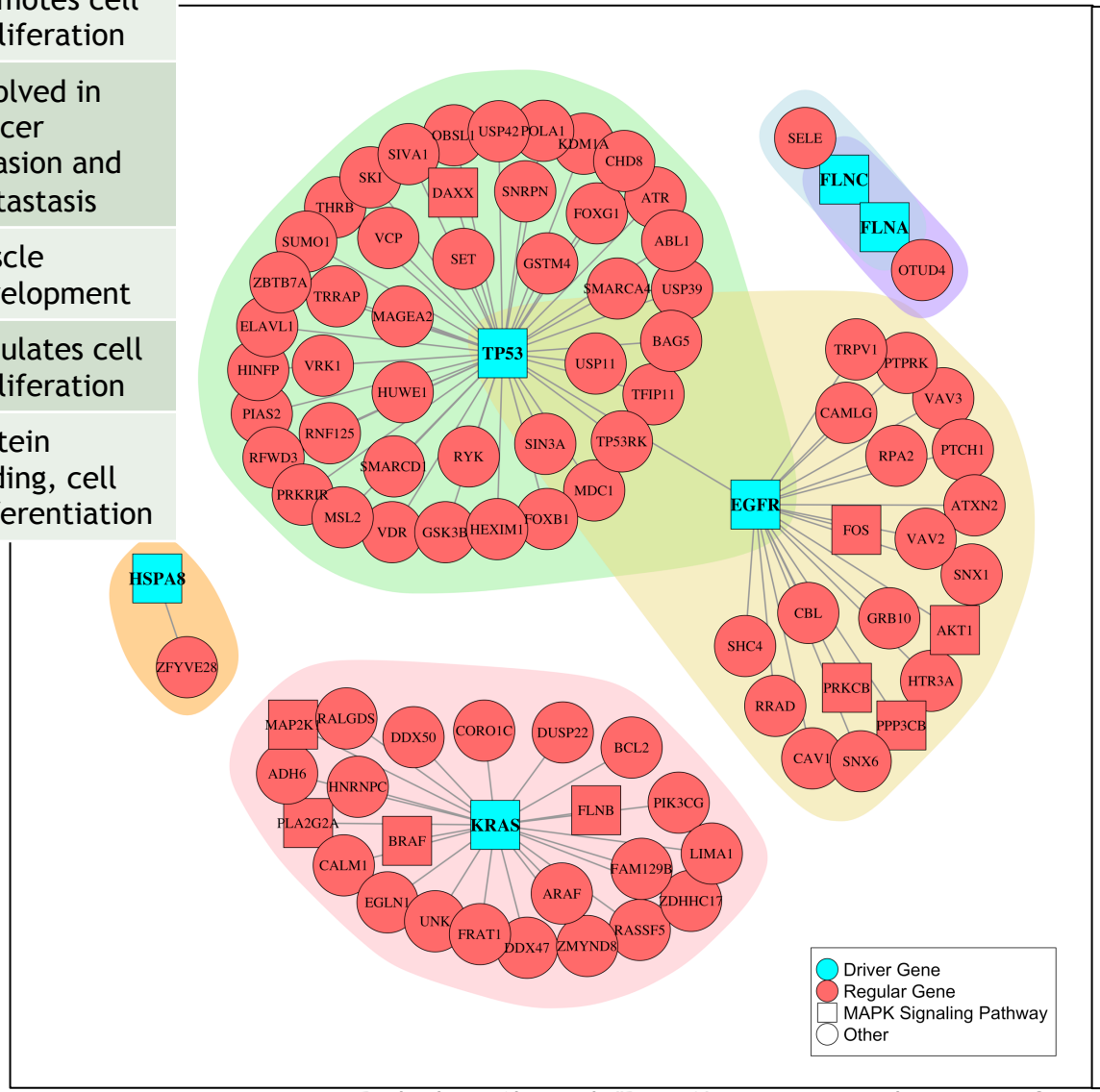
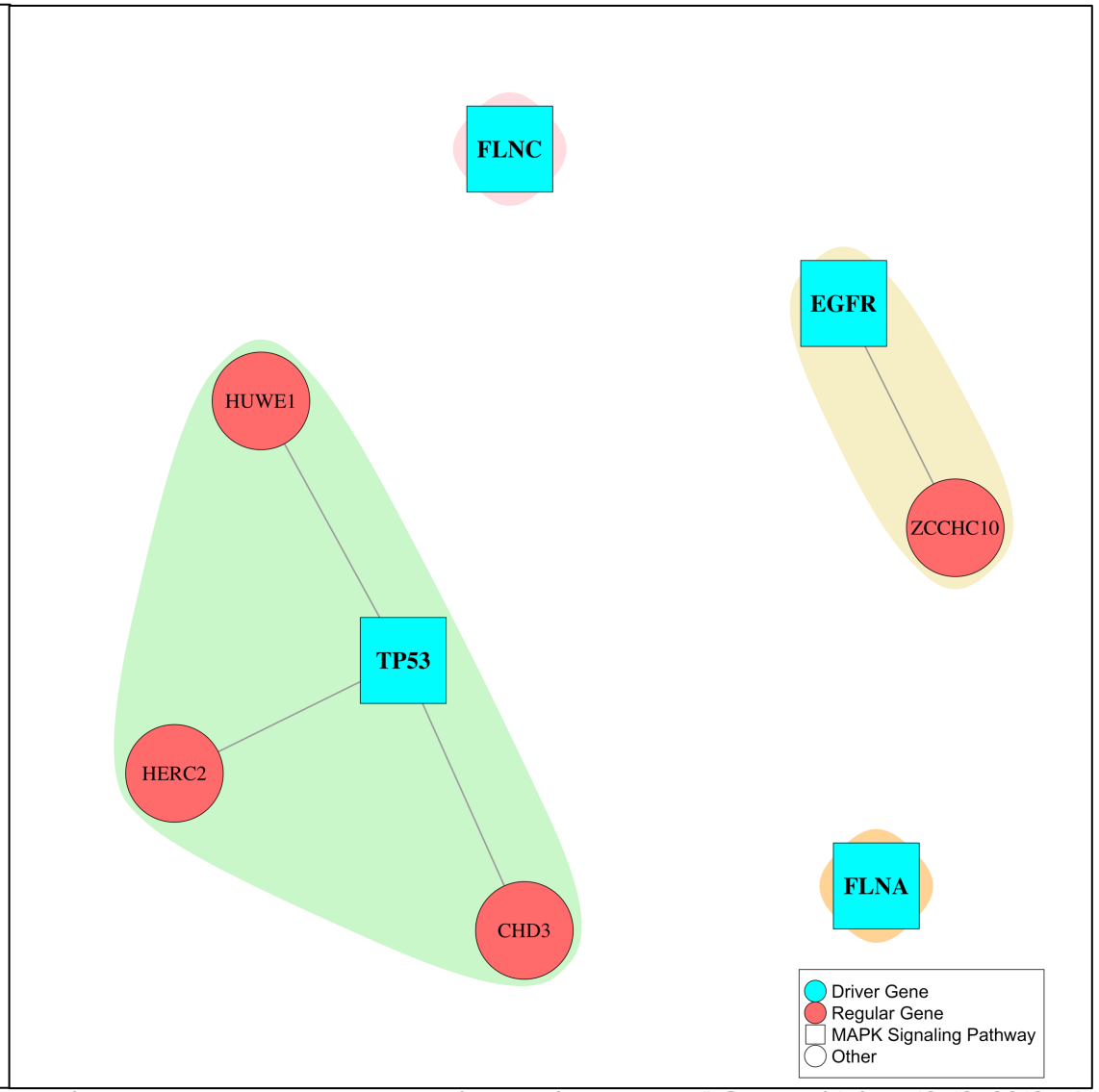
DriverNet: MAPK Signaling Pathway

Gene	Function
TP53	Tumor suppressor
EGFR	Promotes cell proliferation
FLNA	Involved in cancer invasion and metastasis
FLNC	Muscle development
KRAS	Regulates cell proliferation
HSPA8	Protein folding, cell differentiation

Adenocarcinoma



Squamous cell carcinoma



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Limitations and Future Work

- **DriverNet does not include direction**
  - Hypermethylation and hypomethylation treated the same
  - Copy number variation amplification and deletion treated the same
- **Only looked at 2 signaling pathways from the KEGG database**
  - 200 pathways in the database

Conclusions

- **Analyzed the genomic differences between adenocarcinoma and squamous cell carcinoma**
- **Need to first identify genomic differences in order to better understand how to treat them differently**
  - Often treated as the same disease (NSCLC), but are actually very different in terms of gene expression and genomic variation
  - While people are beginning to recognize that they are different, we still do not fully understand their genomic differences

Acknowledgements

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