

# Discovery of Exon Splicing Relationships Across Cancer Cell Lines

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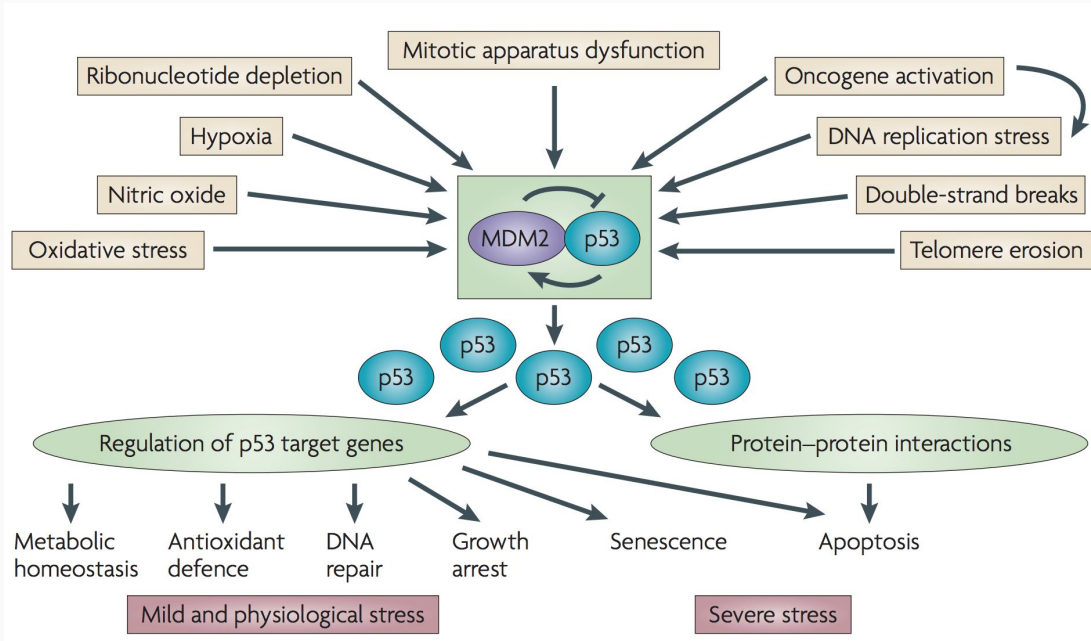
8<sup>th</sup> Annual PRIMES Conference

May 20, 2018

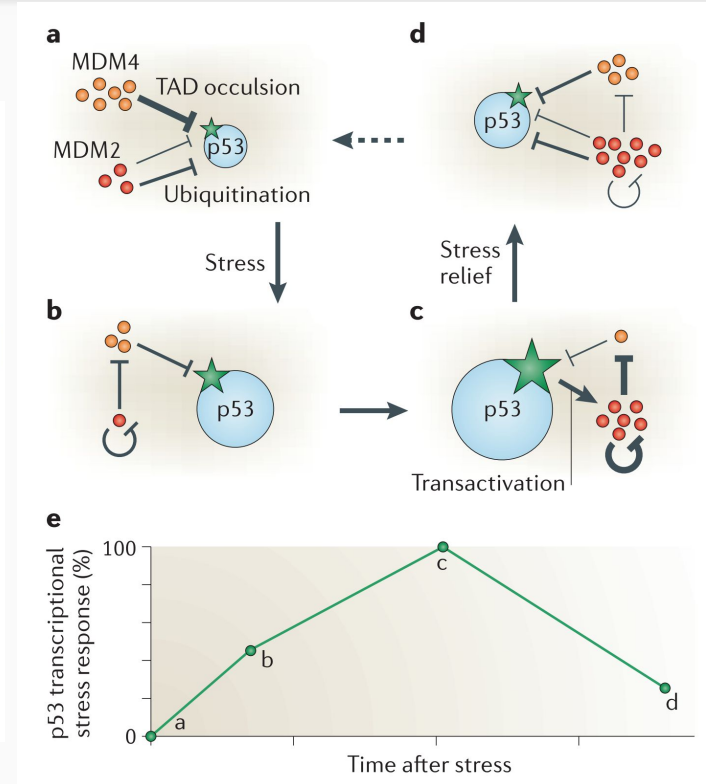
# Outline

- MDM4
  - Role in cancer
  - Alternative splicing regulation
  - Copy number effects
- Gene dependency models
  - Known confounding effects
  - Relation with exon splicing
- Future plans

# MDM4 and p53

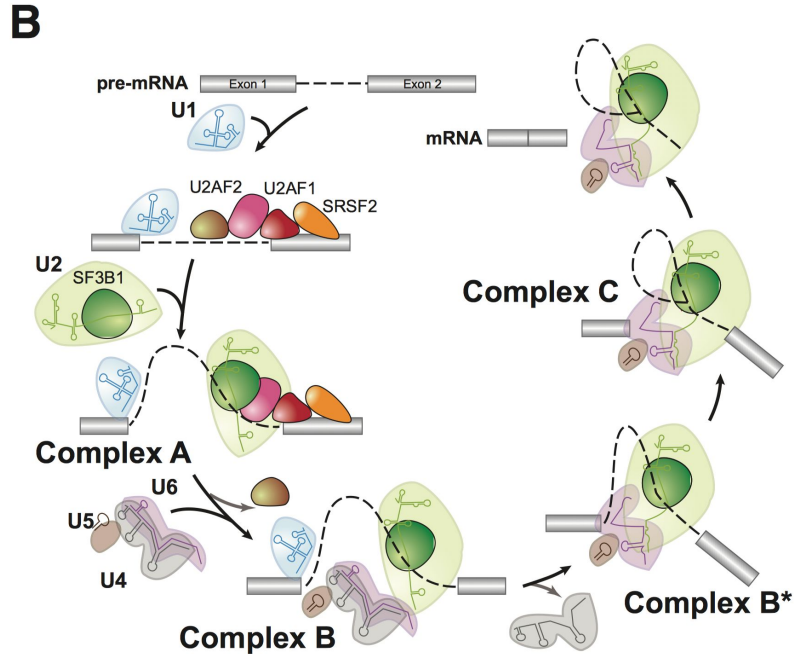


Levin and Oren. 2009, *Nature Reviews Cancer* 9: 749-758

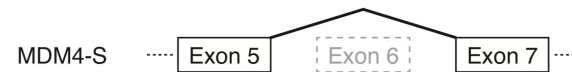
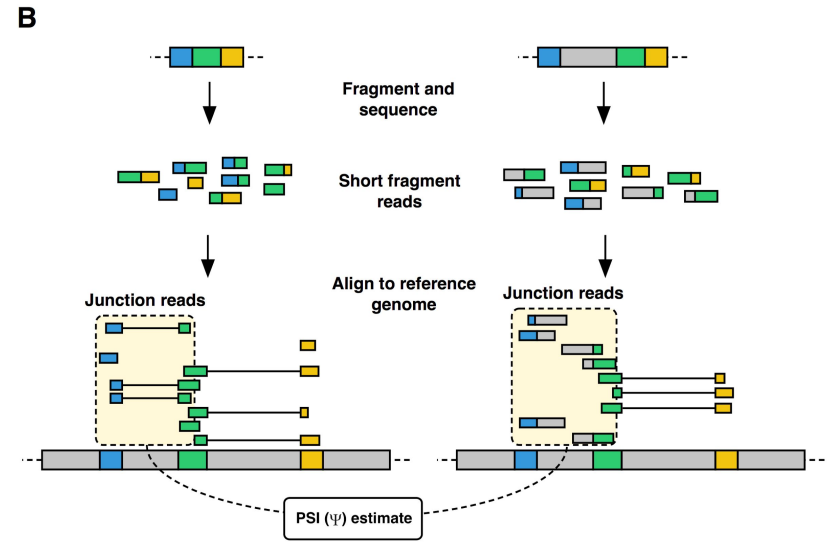


Toledo and Wahl. 2006, *Nature Reviews Cancer* 6: 909-923

# RNA splicing

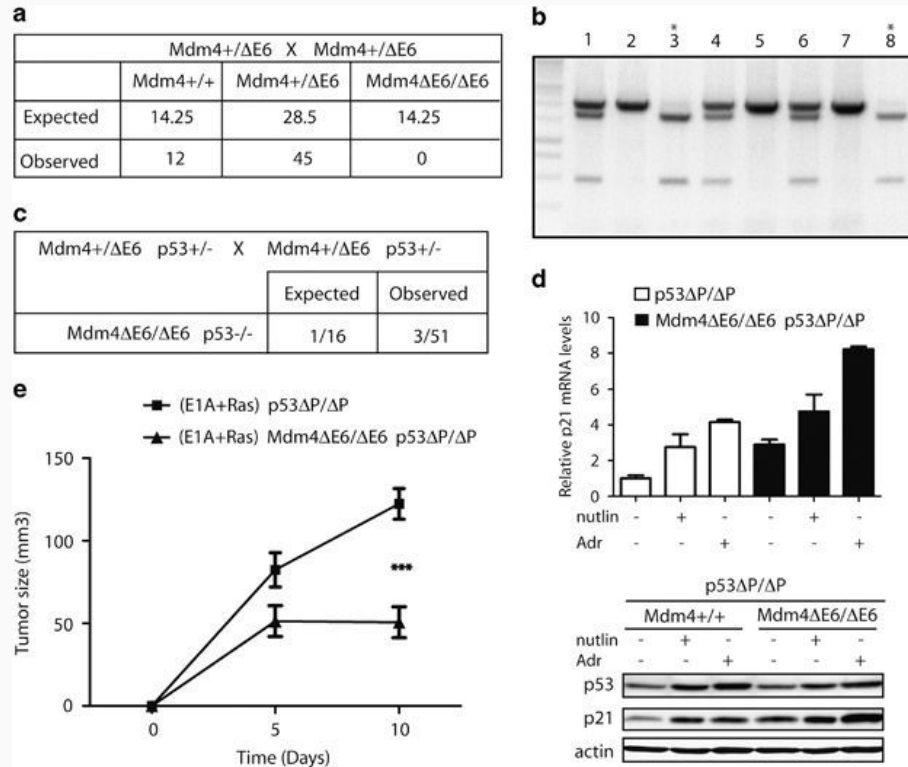


Seiler et al. 2018, *Cell Reports* **23**, 282–296

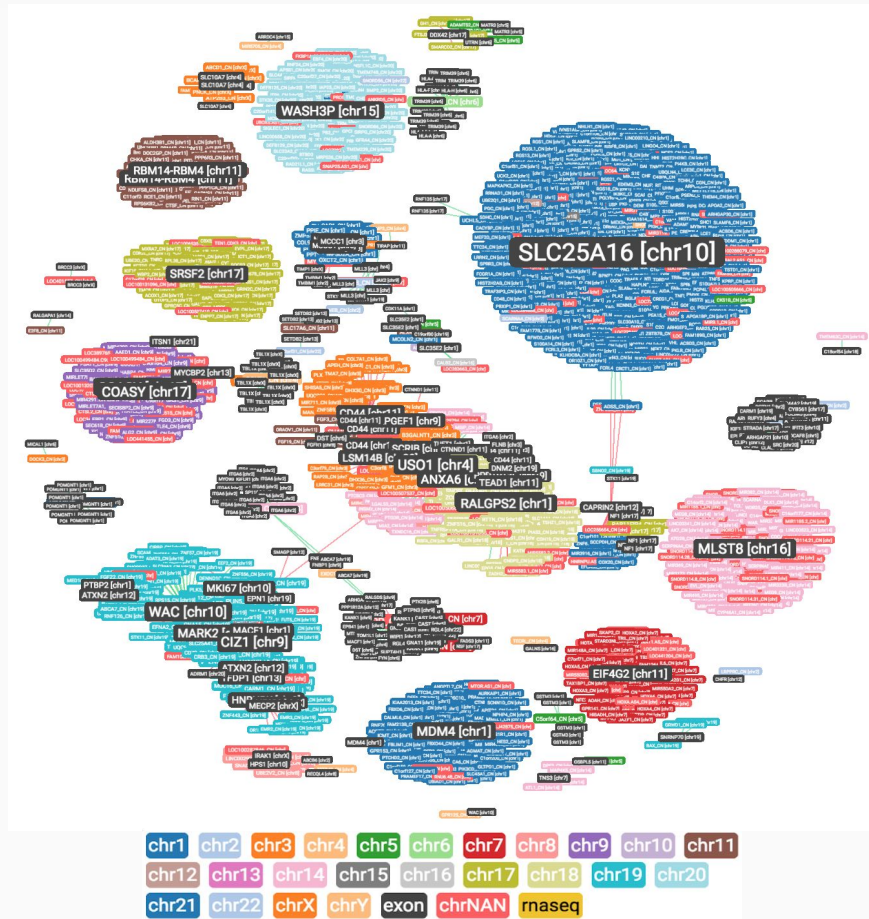


$$\text{Exon 6 inclusion} = \frac{\text{MDM4-FL}}{\text{MDM4-FL} + \text{MDM4-S}}$$

# MDM4 lacking exon 6 fails to suppress p53 activity

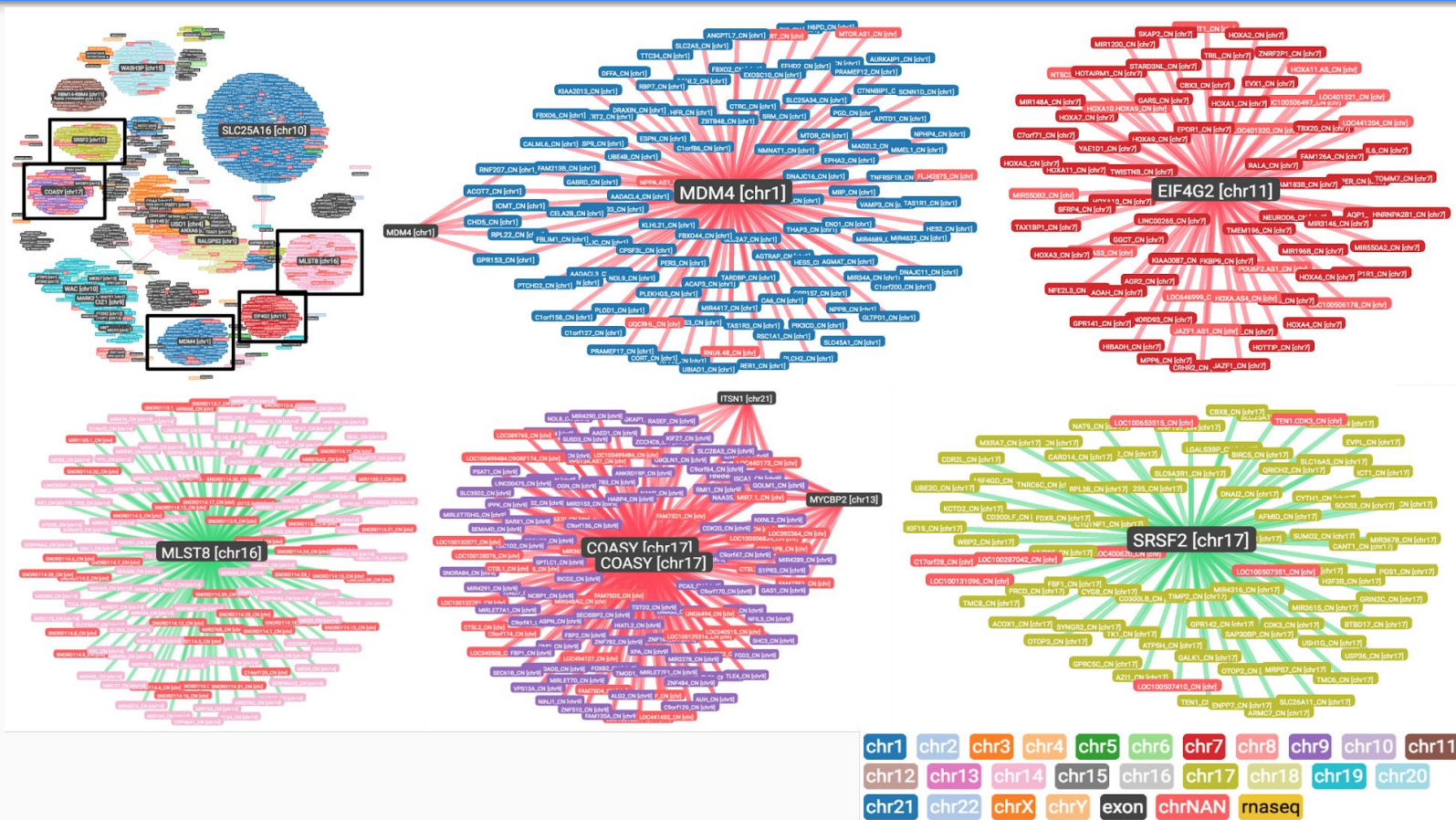


# Copy number variation - exon splicing relationships

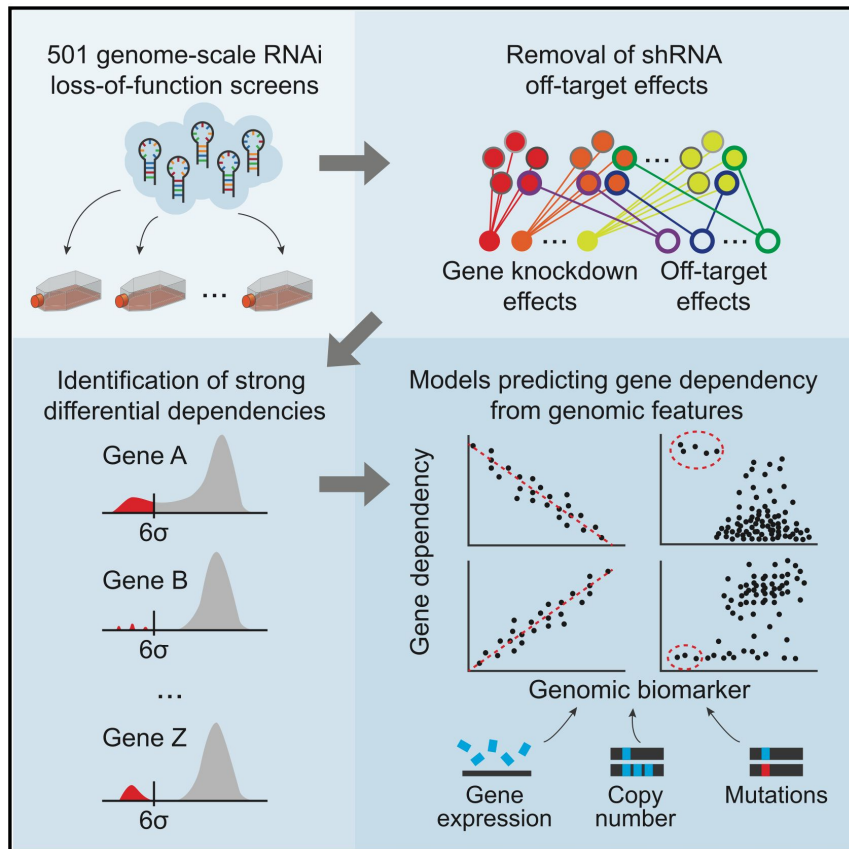




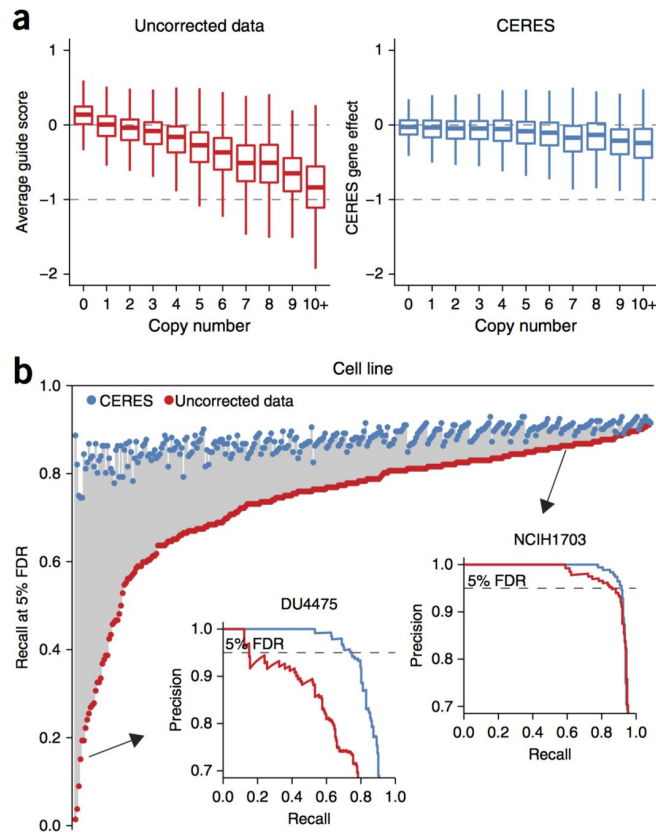
# MDM4 exon 6 splicing is partly driven by a copy number variation



# Confounding variables in gene dependency models



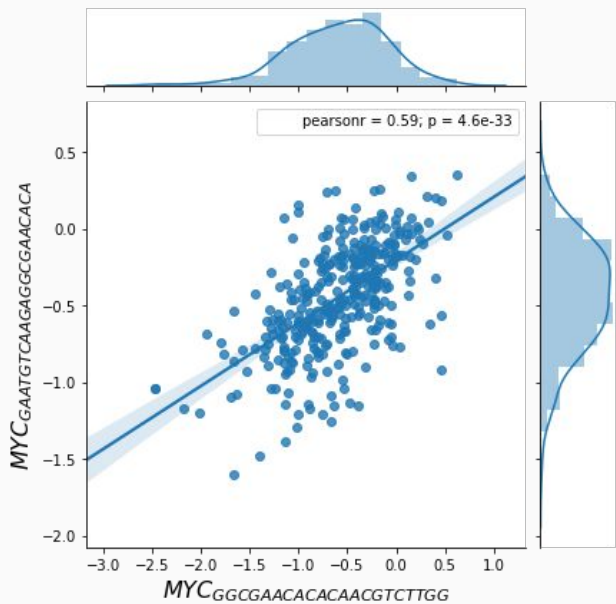
Tsherniak et al. 2017, *Cell* **170**: 564–576



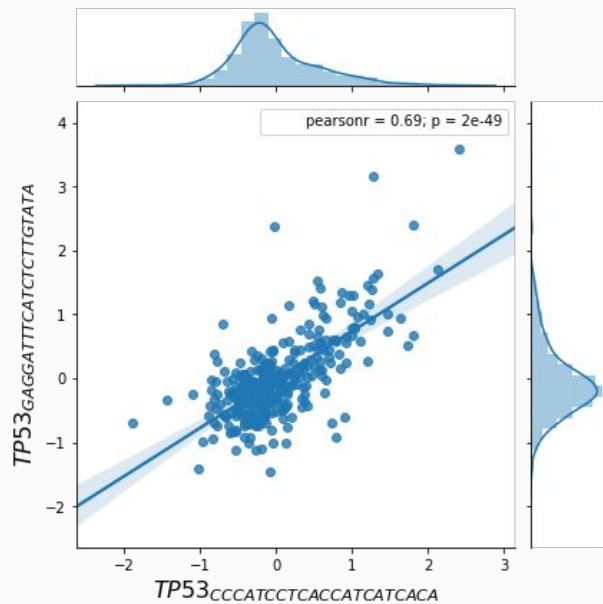
Meyers et al. 2017, *Nature Genetics* **49**: 1779-1786



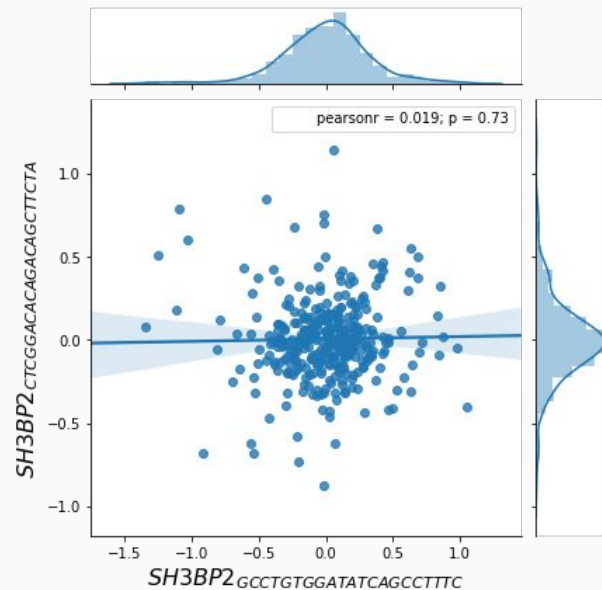
# Only differential dependency genes have exon-correlated guides



Tumor drivers/essential genes

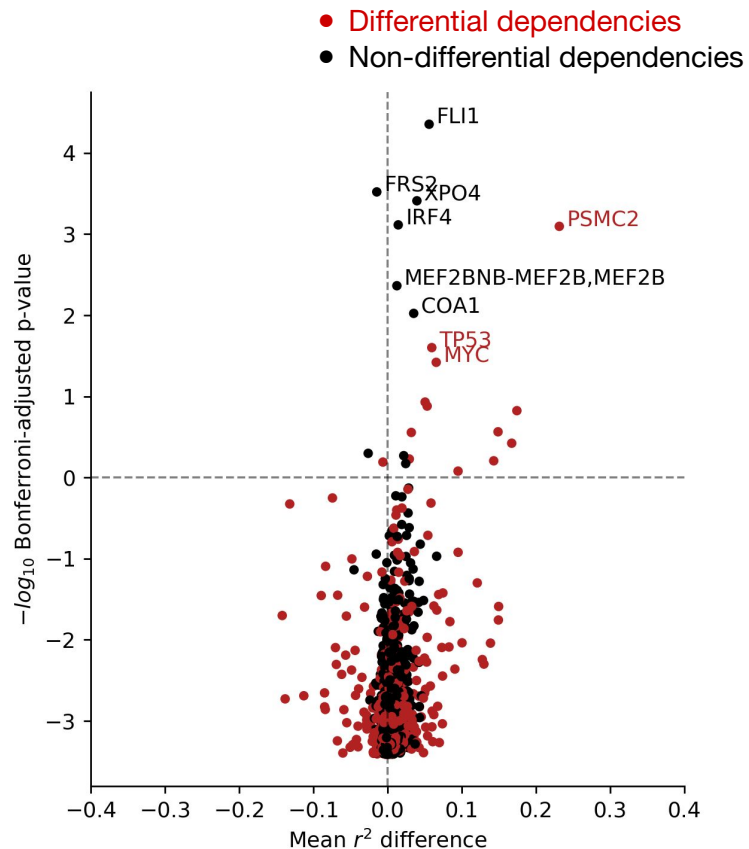
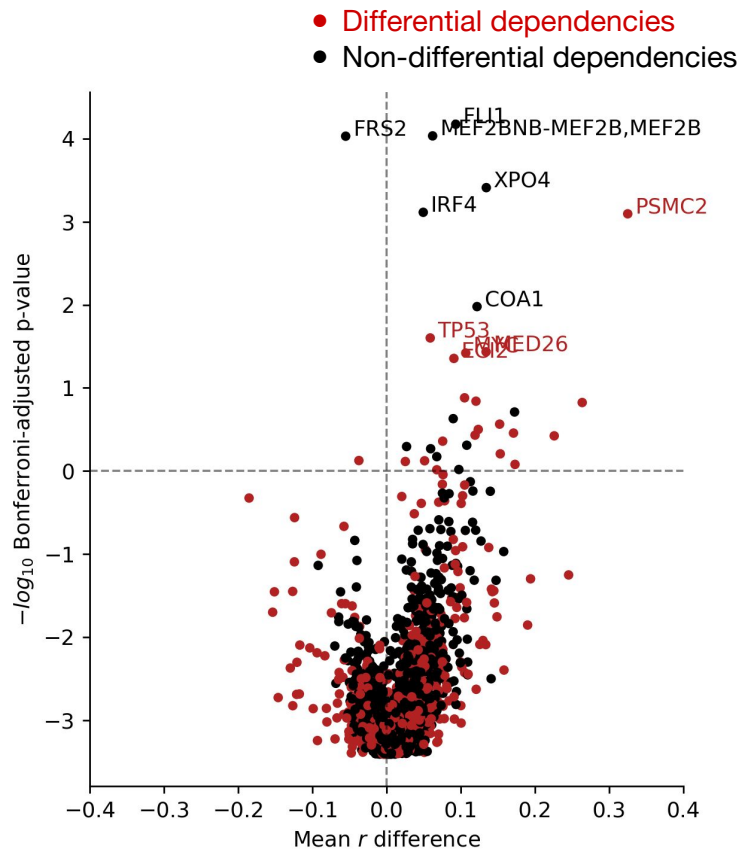


Tumor suppressors



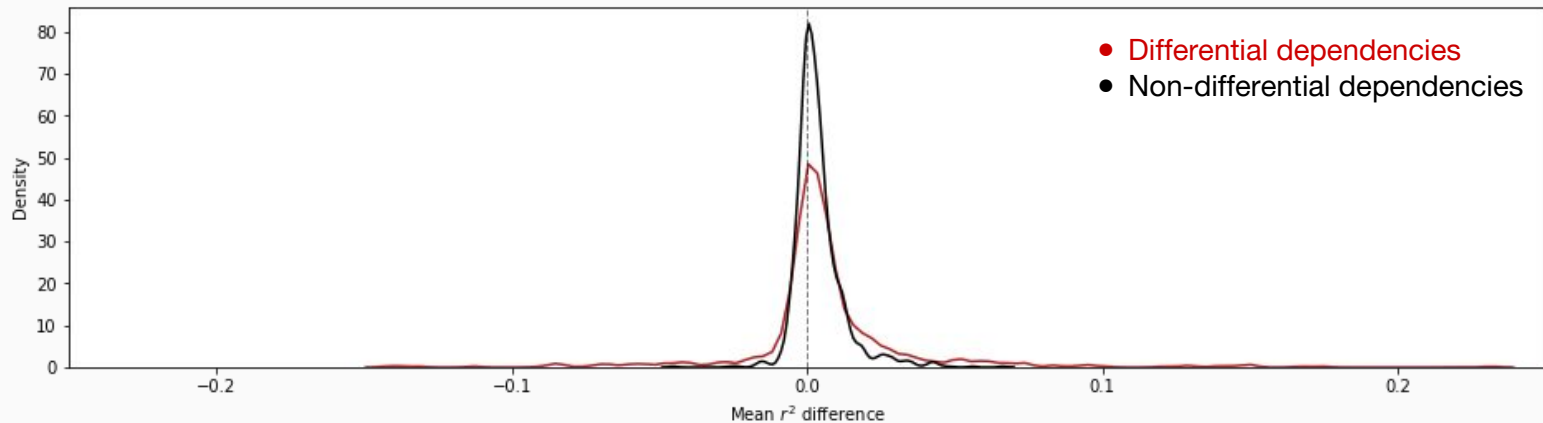
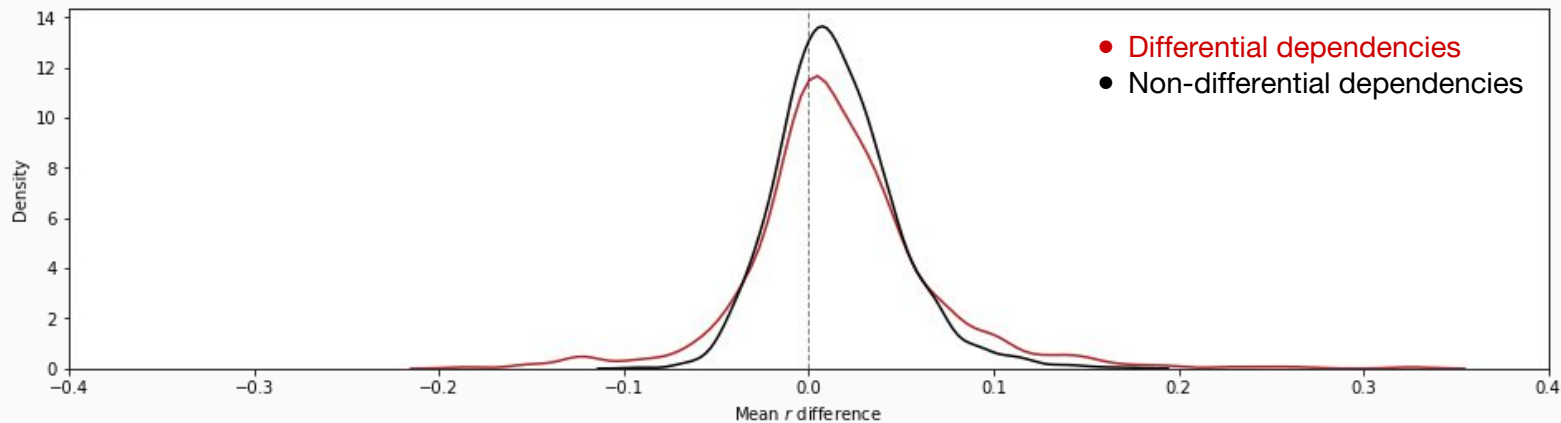
Non-differential dependency

# Does exon splicing confound shRNA gene dependency?



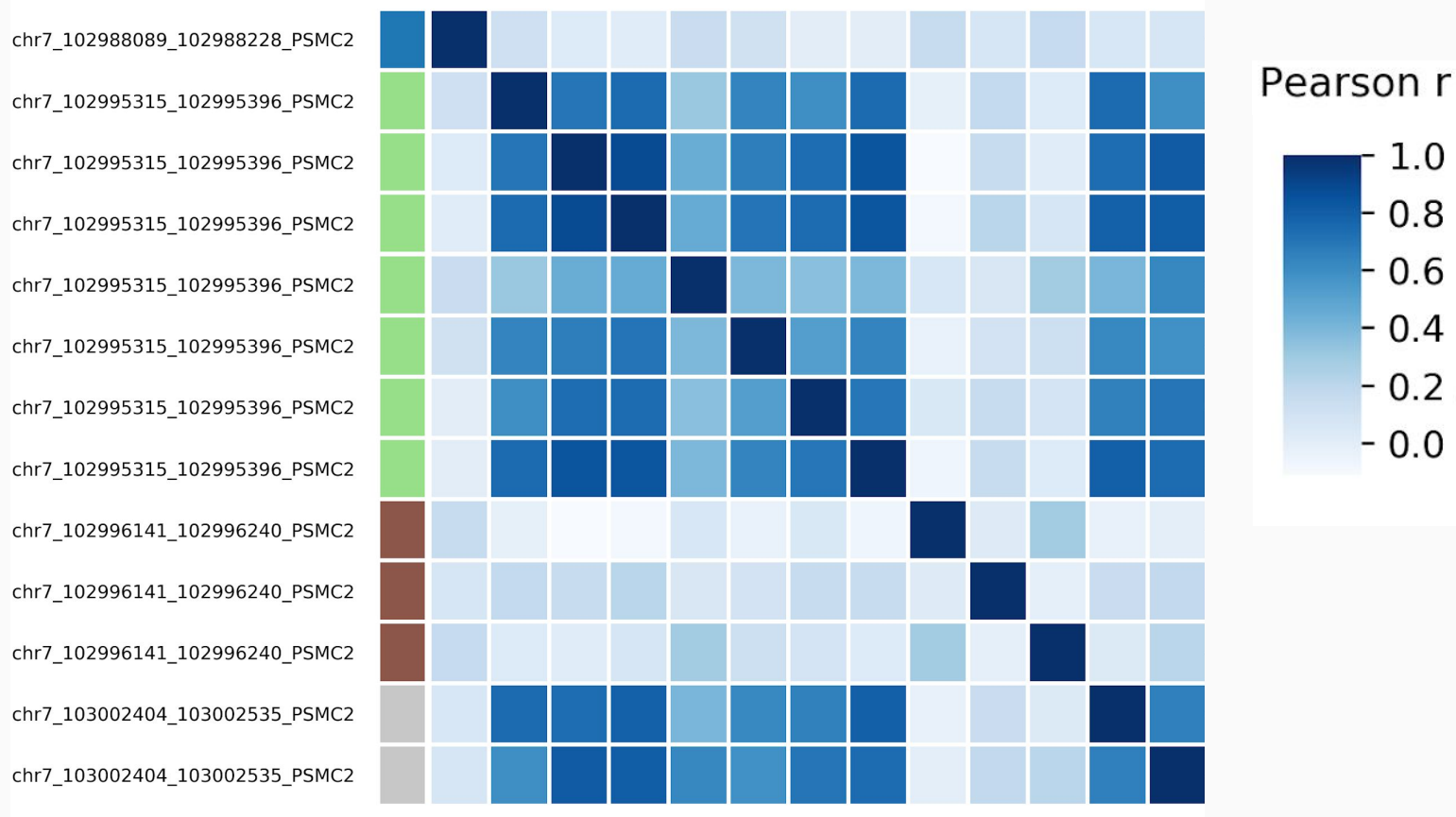
Difference in same-exon vs. different-exon correlations

# Same-exon - different-exon correlation distribution is right-skewed

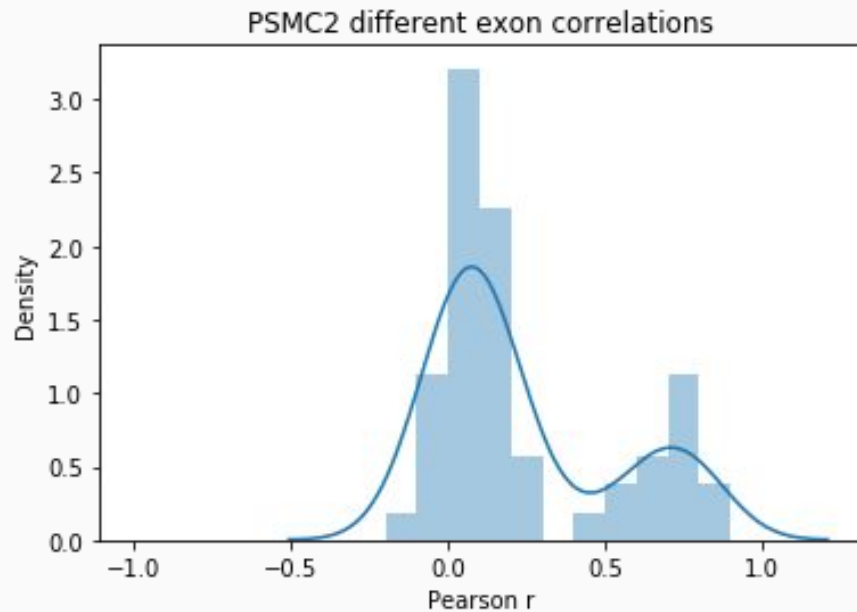
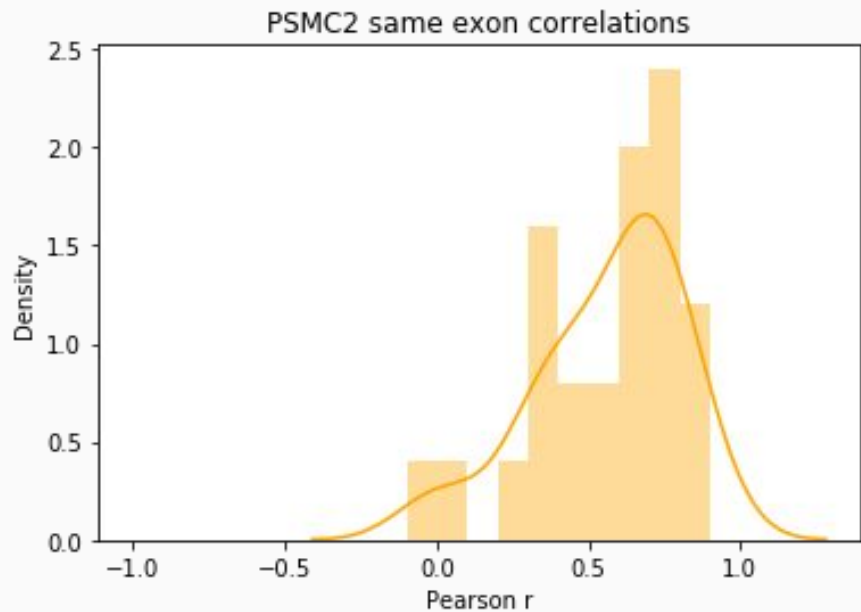


Difference in same-exon vs. different-exon correlations

# PSMC2 exon-shRNA correlations



# PSMC2 exon-shRNA correlations



# Future plans

- MDM4
  - Investigate link between copy number variation and exon 6 splicing
- Gene dependencies
  - Could same-exon correlations be due to other factors (similar target sequences, RNA folding regions)?
  - Transform exon splice levels to discrete isoform-level expression levels
  - Are differences in sgRNA/shRNA-level dependencies explained by differential exon splicing?
- Exon splicing
  - Look for other predictors of exon splicing in the CCLE (methylation, chromatin profiling, mutations)



# Thank you!

- **Dr. Mahmoud Ghandi**, for his generous guidance and support
- **MIT PRIMES**, for providing this challenging and rewarding research opportunity
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- **My parents**, for their support and encouragement