

## INTRODUCTION

TP53 variant carriers have a lifetime risk of developing cancer of about 75% in males and almost 100% in females. There is no prevention or treatment for Li-Fraumeni syndrome, so screening is important to ensure that cancer is detected early. Most of these individuals will develop common cancers associated with the condition while others will have or be at risk for developing other types of cancer. Rare TP53 germline variations are the key to understanding and discovering the incongruities of cancer predisposition in these individuals. This study conducted a focused assessment of rare TP53 variants through a whole-exome case-control study to determine how likely each cancer was to occur in individuals with the same variants and the certainty of association between variants and cancer predisposition.

## METHOD

- DNA from a total of 13,396 cases and 1,391 to 3,801 controls from the University of Texas MD Anderson Cancer Center (MDA), H. Lee Moffitt Cancer Center & Research Institute, The University of Utah School of Medicine, Duke University, and UK Biobank.
- Whole-exome sequencing was performed using Agilent SureSelect Clinical Research Exome v1/v2 and Illumina HiSeq 4000/NovaSeq 6000 to an average depth of 120-150x.
- We calculated gene-based p-values to test for associations with rare (minor allele frequency [MAF] < 0.005) TP53 protein-coding variation and each cancer using VAAST. Odds ratios (OR) and Confidence intervals for each variant category were then determined for each type of cancer.
- Meta-analysis was conducted using the published case/control counts for each study. A simple logistic regression was used to estimate the odds ratio and standard error for each study. The odds were combined using a fixed effects model.

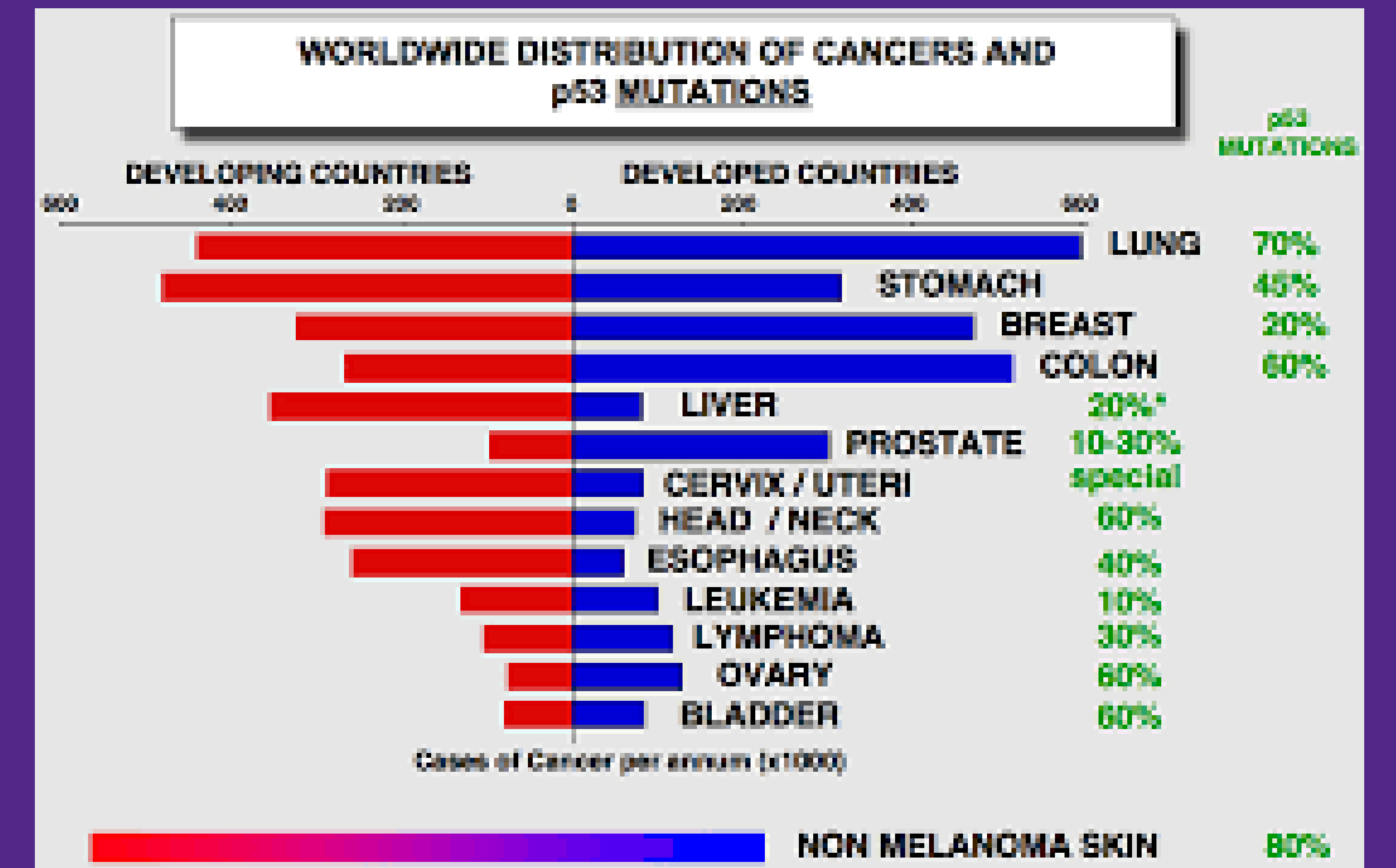
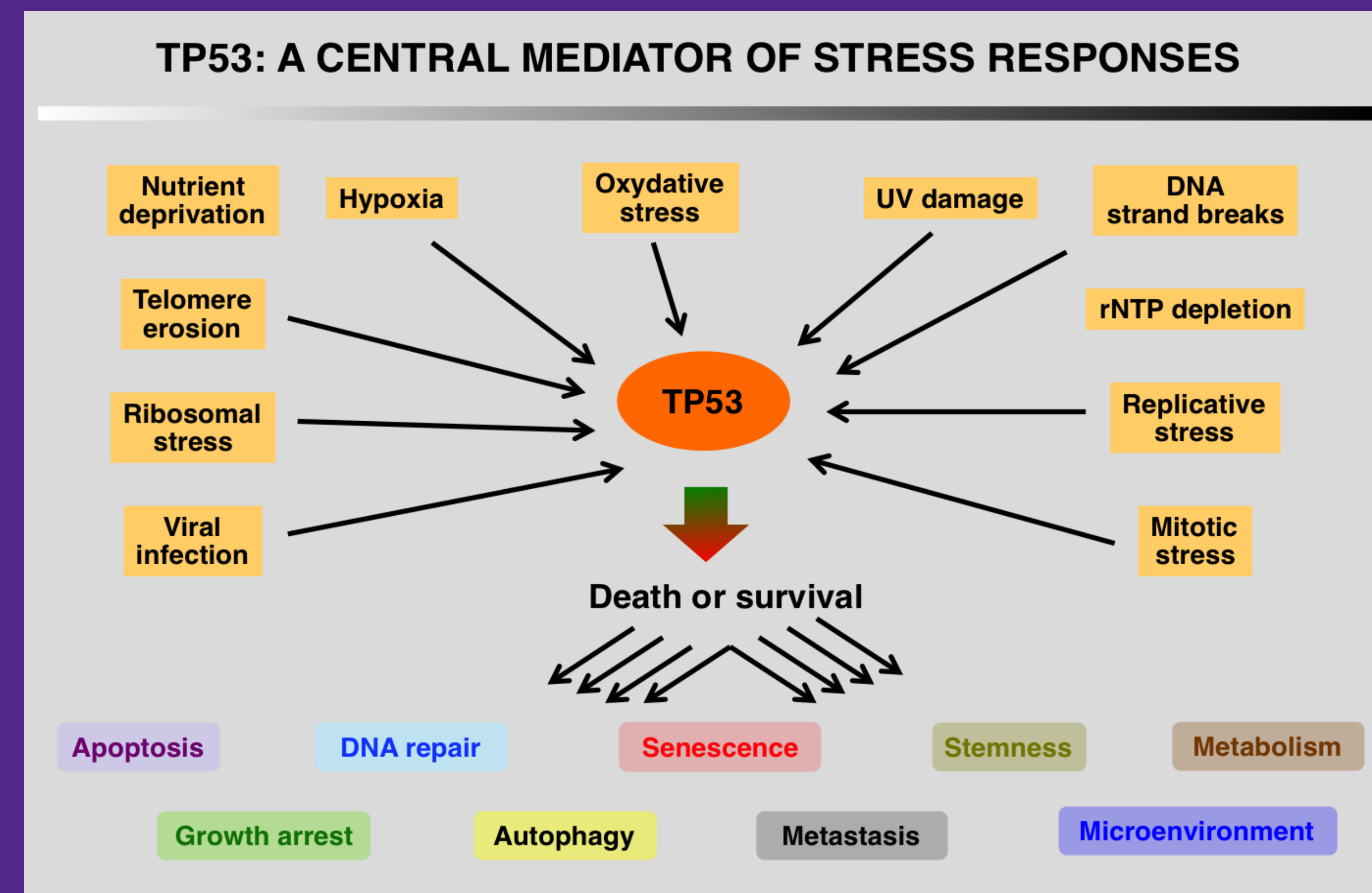
## RESULTS

We report gene-based association results for rare protein-coding variants in TP53 for each of the five cancer types. We also report OR point estimates and confidence intervals for pathogenic, VUS, and benign variants in each cancer. For pathogenic variants, we conducted a meta-analysis incorporating 1-2 additional studies for each cancer type.

## DISCUSSION

Our results provide evidence that rare TP53 protein-coding variants confer an increased risk of colorectal, melanoma, ovarian, pancreatic, and prostate cancer, in part due to missense variation which is not currently classified as pathogenic. Our meta-analysis results provide precise estimates of the risk conferred by pathogenic TP53 variants for each cancer type. Future studies will expand this analysis to other cohorts and integrate this dataset with additional controls from other sources, such as UK Biobank, to improve risk estimate precision.

# Rare TP53 Variants can predispose individuals to multiple cancers that are not Commonly Associated with Li-Fraumeni Syndrome



### Acknowledgements

- This work was supported by NIH/NCI R25CA056452 (Tatyana Childs)
- Special thanks to MD Anderson, the CPRTP program, Dr. Chad Huff, Yao Yu, Ryan Bohlender, and Michael Cao.

### References

- Guha, T., & Malkin, D. (2017). Inherited TP53 Mutations and the Li-Fraumeni Syndrome. Cold Spring Harbor perspectives in medicine, 7(4), a026187. <https://doi.org/10.1101/cshperspect.a026187>
- Lanes, M. (2022, July 6). Li-Fraumeni syndrome. NORD (National Organization for Rare Disorders). Retrieved August 3, 2022, from <https://rarediseases.org/rare-diseases/li-fraumeni-syndrome/#references>
- Malkin D. (2011). Li-fraumeni syndrome. Genes & cancer, 2(4), 475-484. <https://doi.org/10.1177/1947601911413466>
- P53 information. p53\_cancer. (n.d.). Retrieved August 5, 2022, from [http://p53.free.fr/p53\\_info/p53\\_cancer.html](http://p53.free.fr/p53_info/p53_cancer.html)
- TP53 pathways. (n.d.). Retrieved August 5, 2022, from <https://p53.fr/tp53-information/tp53-knowledge-center/26-knowledge-center/28-p53-pathways>

### Responsible Conduct of Research

- For this research project research approval was granted by MD Anderson Cancer Research Center and participants were kept anonymous, as well as data being kept confidential.