Pathway Impact of Mutations

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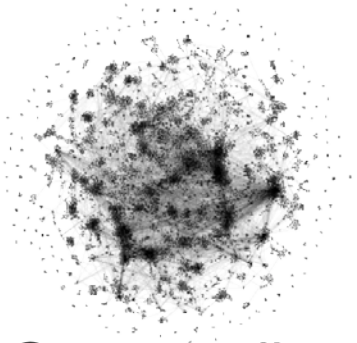
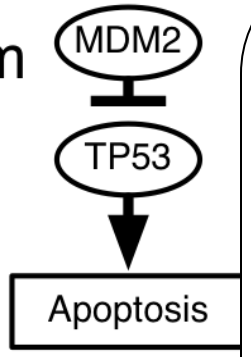
Introduction

- There are many recurrent, but low frequency mutations that are not well characterized
- The mode of action, loss-of-function or gain-of-function (LOF/GOF), of mutations can improve our understanding of disease mechanisms and treatment
- I have developed a method that utilizes functional genomic data and pathways to predict LOF or GOF
  - Complimentary to LoH, methylation, amplification, …

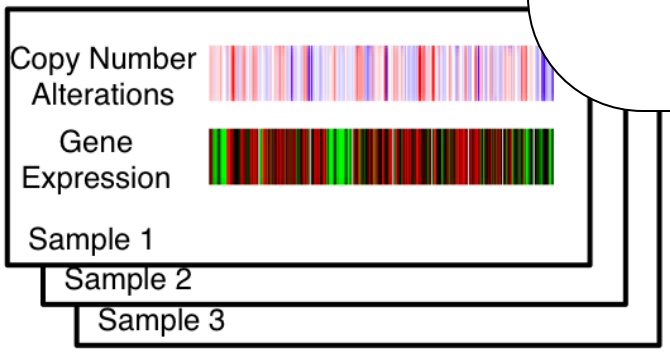
PARADIGM

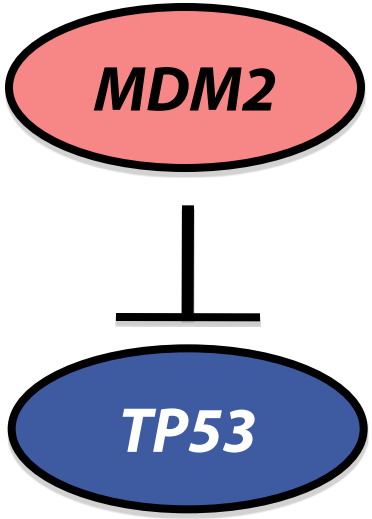


Compendium of Curated Pathways

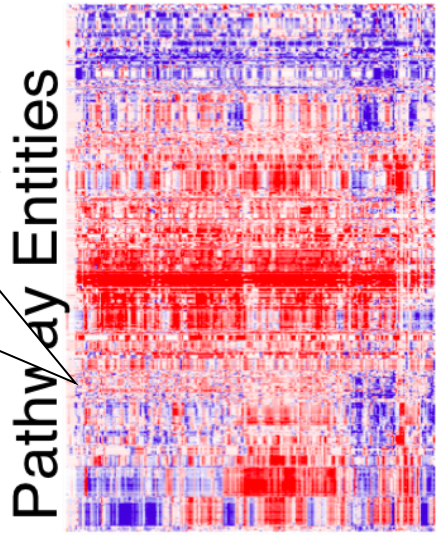


Functional Genomics

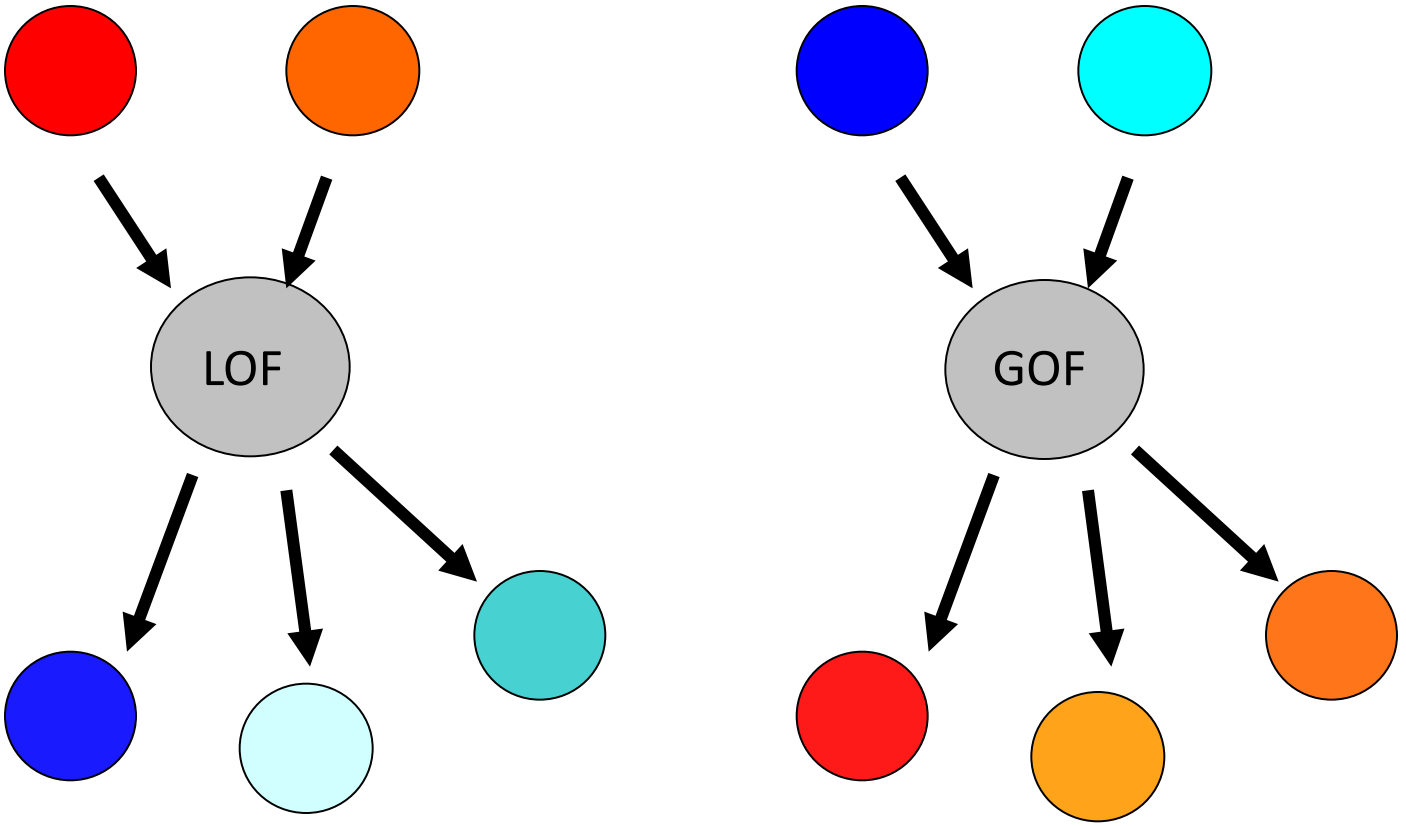




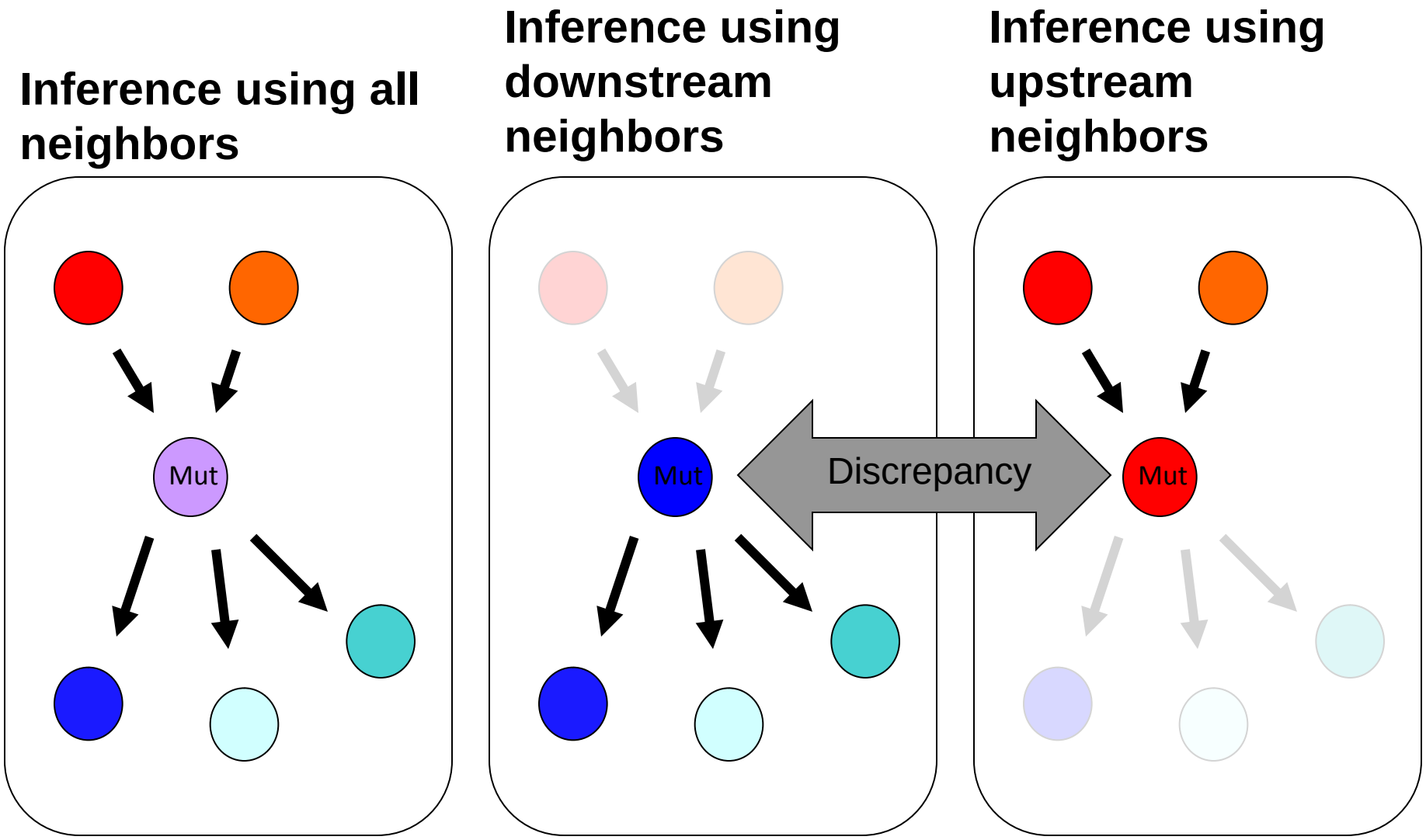
Inferred Pathway Activities



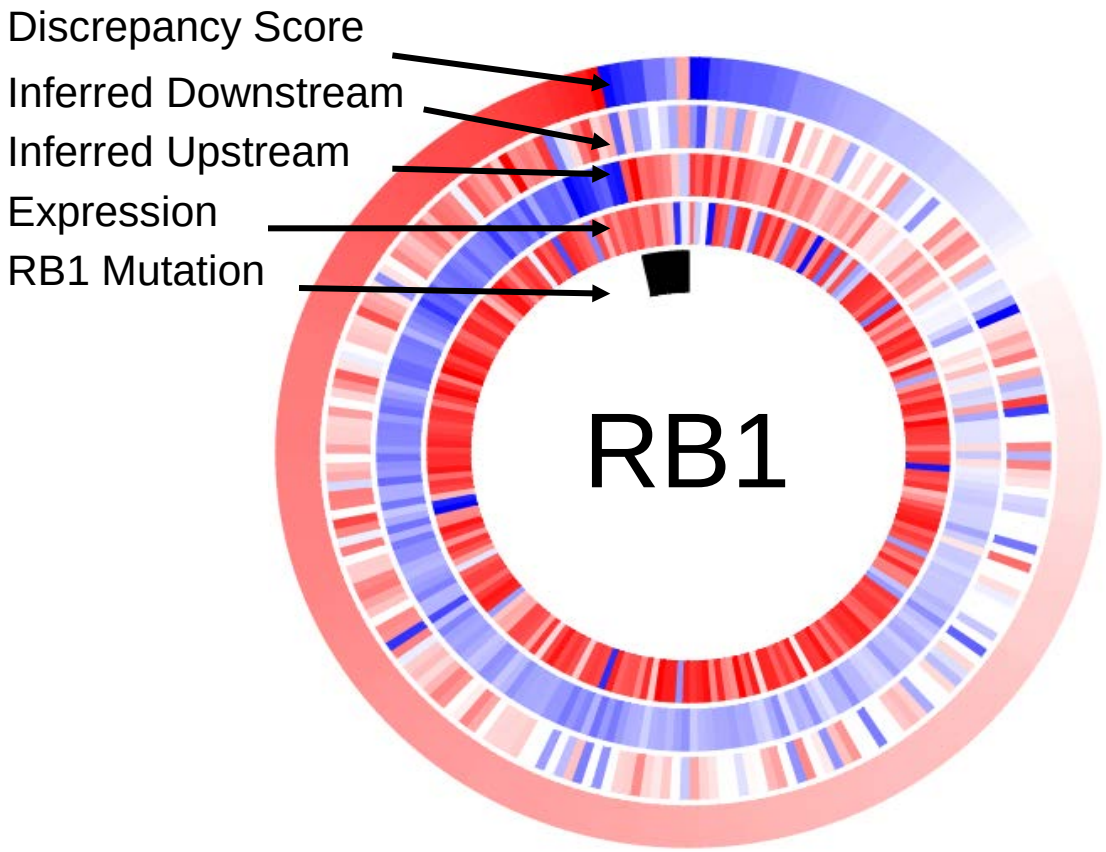
Mutations (LOF and GOF) in the context of pathways



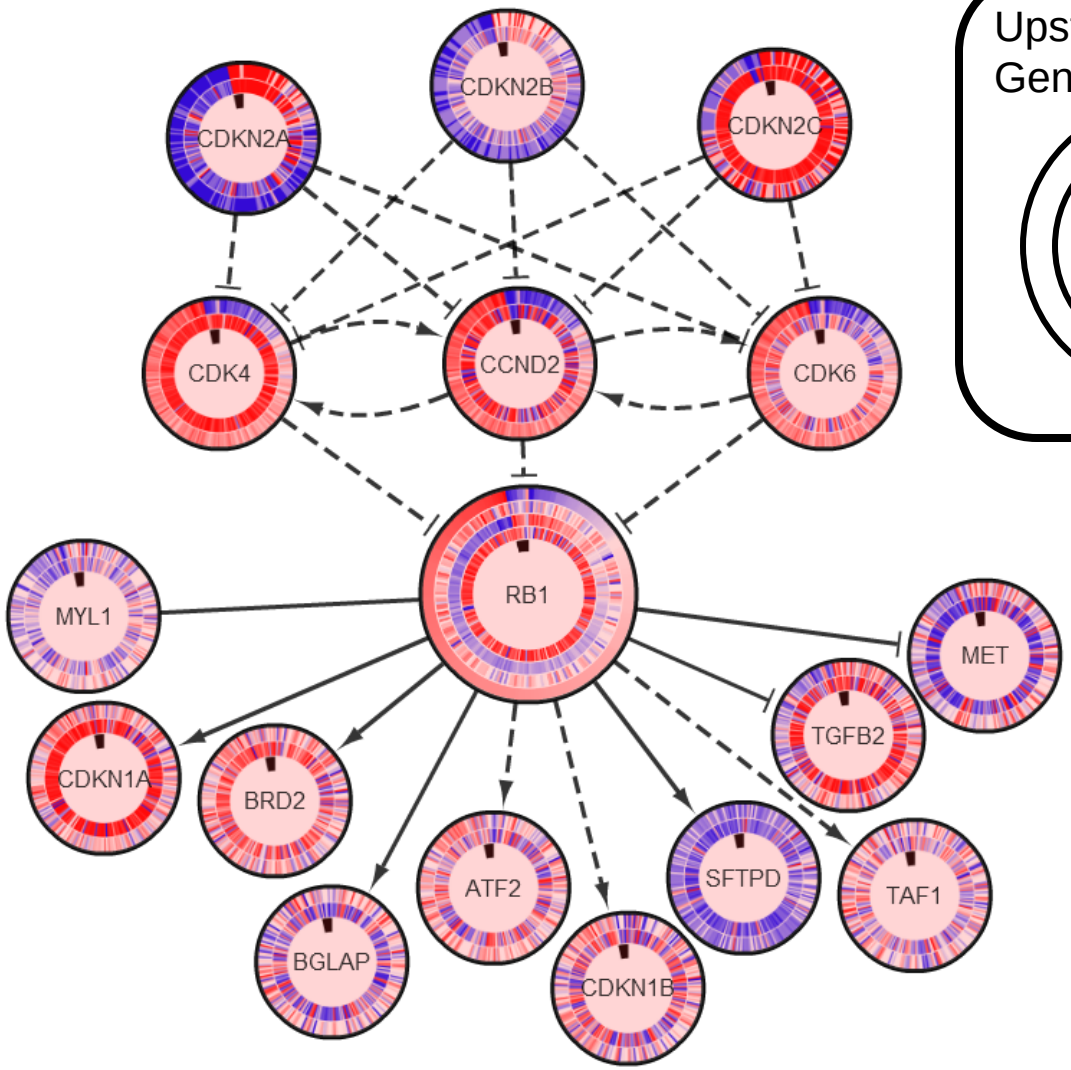
Discrepancy Analysis

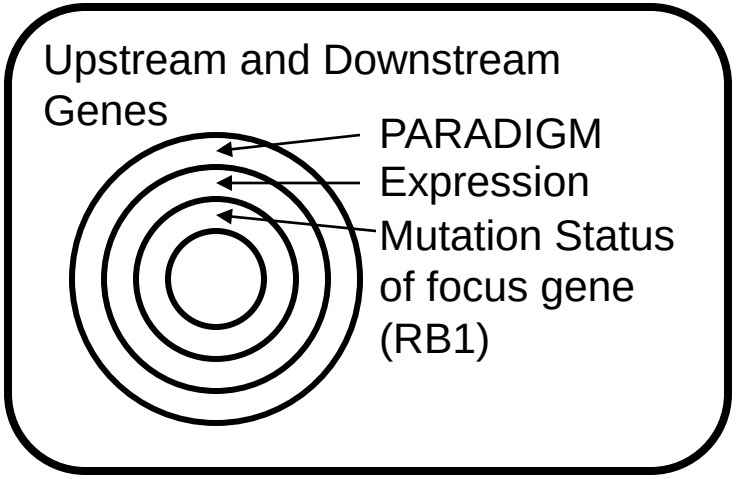


RB1 Loss-of-Function (GBM)

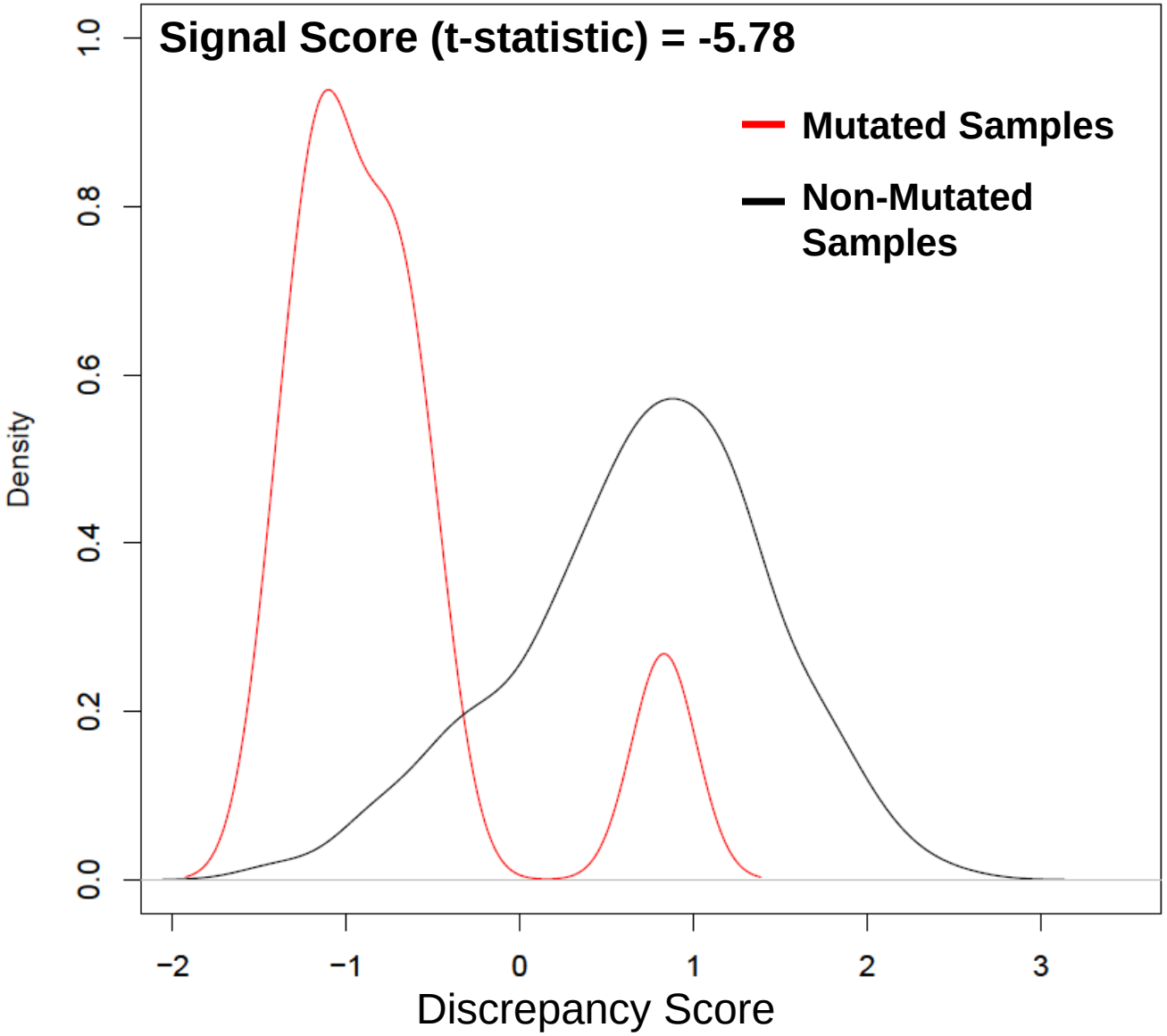


RB1 Network (GBM)



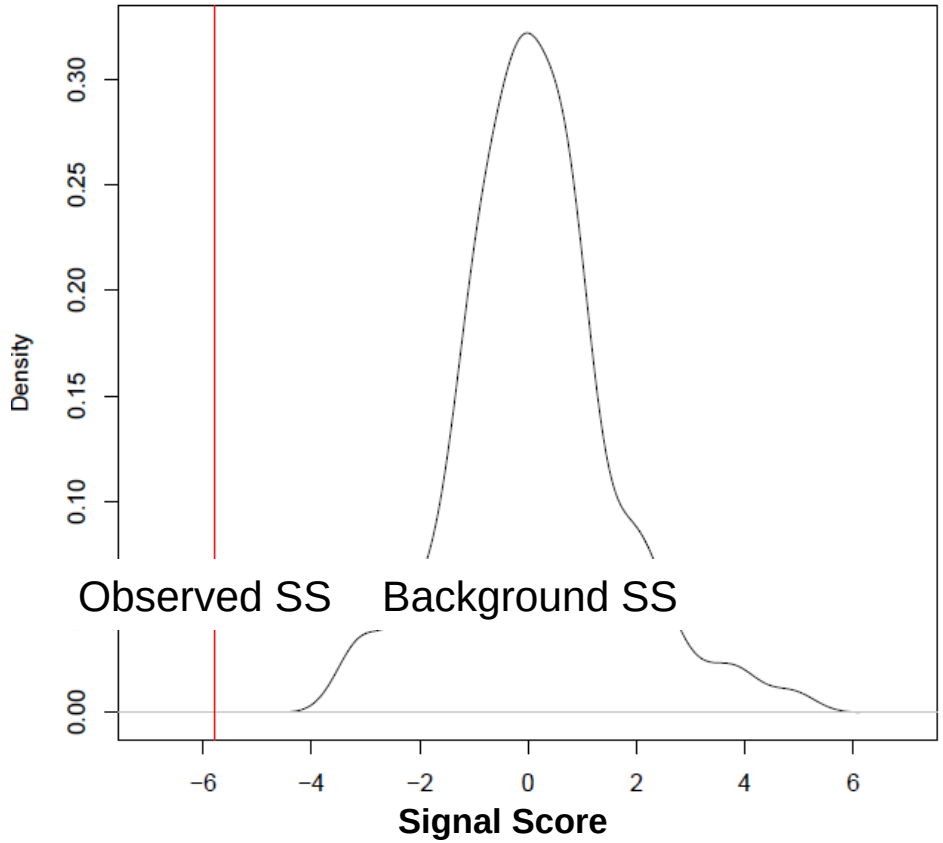


Discrepancy Scores differ in the mutated samples versus the non-mutated samples

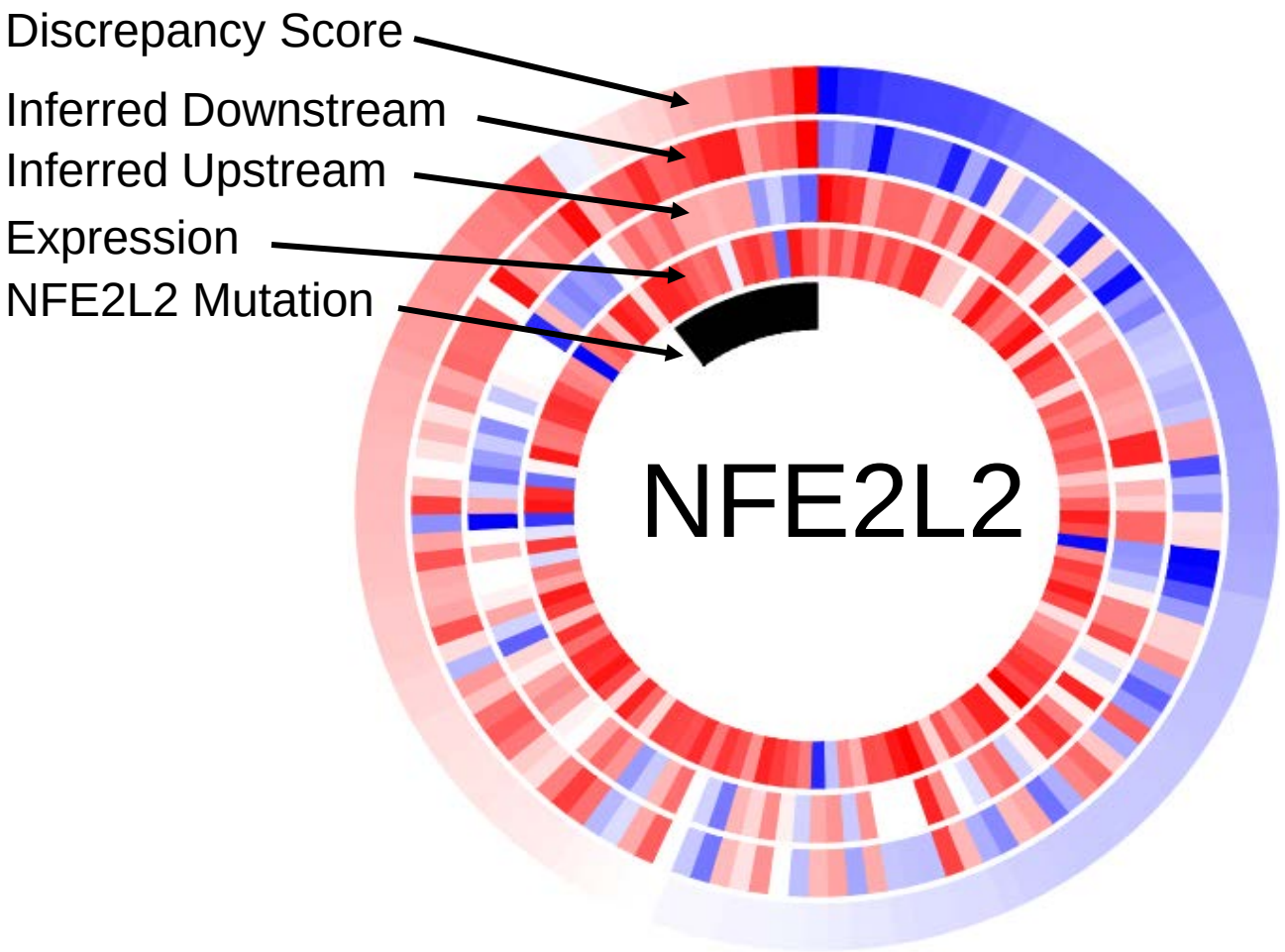


Significance Analysis

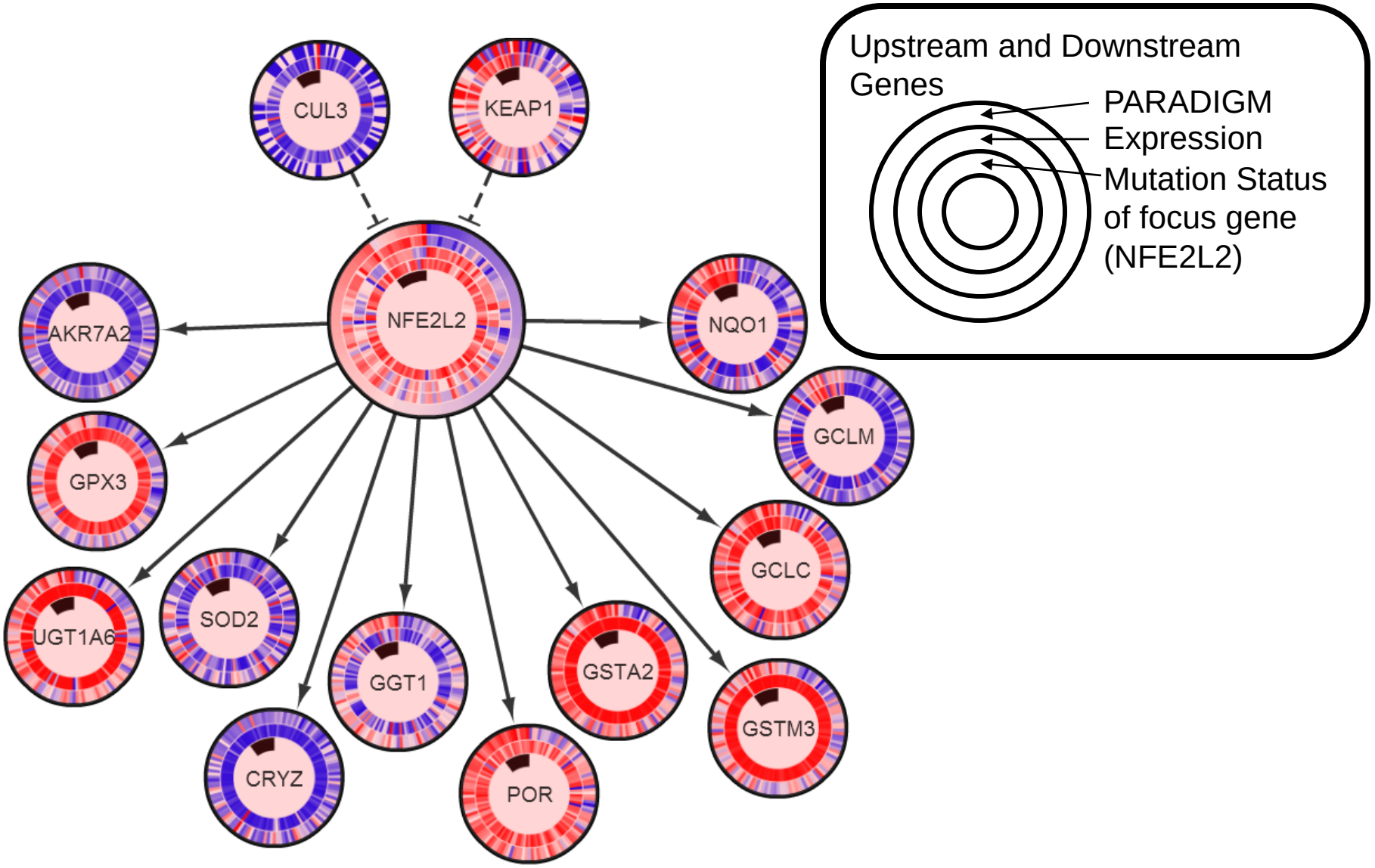
- Given the same network topology, how likely would we call a gain/loss of function
  - Background model: permute gene labels in our dataset
  - Compare observed signal score to signal scores (SS) obtained from background model



NFE2L2 Gain-of-Function (LUSC)



NFE2L2 Network



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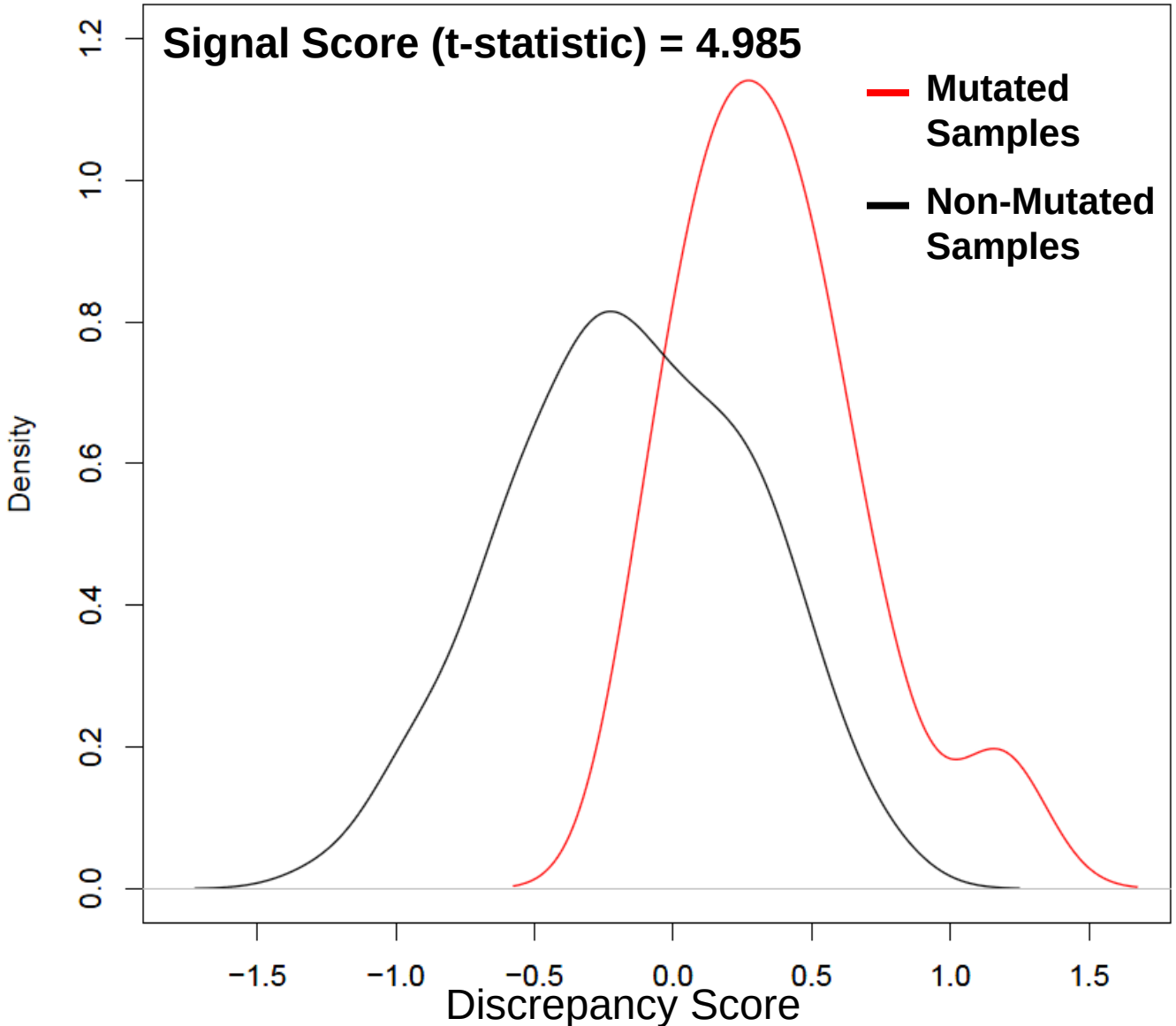
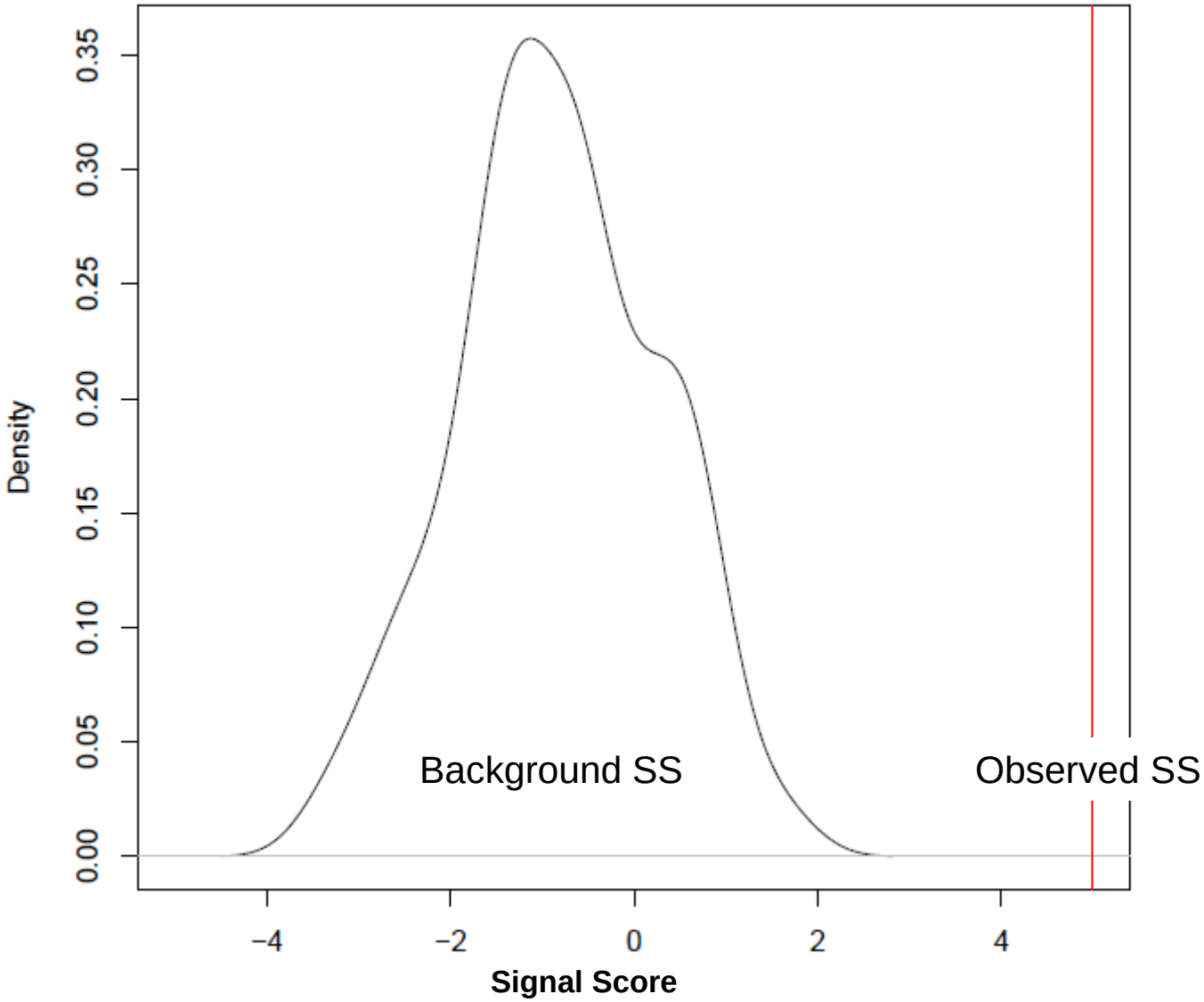
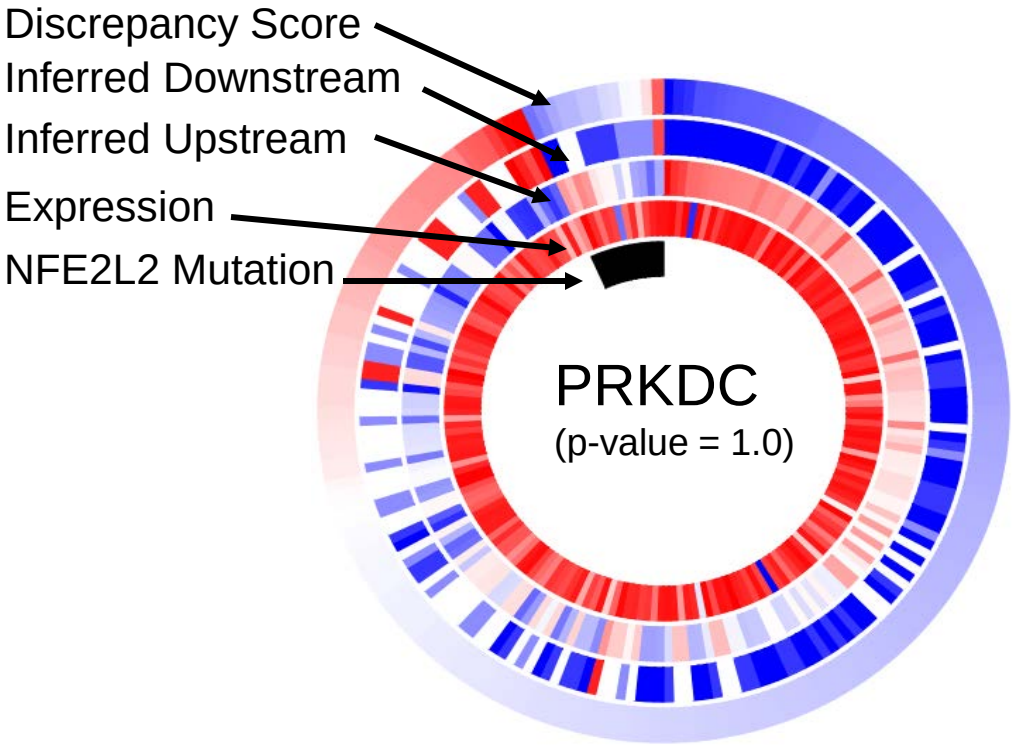


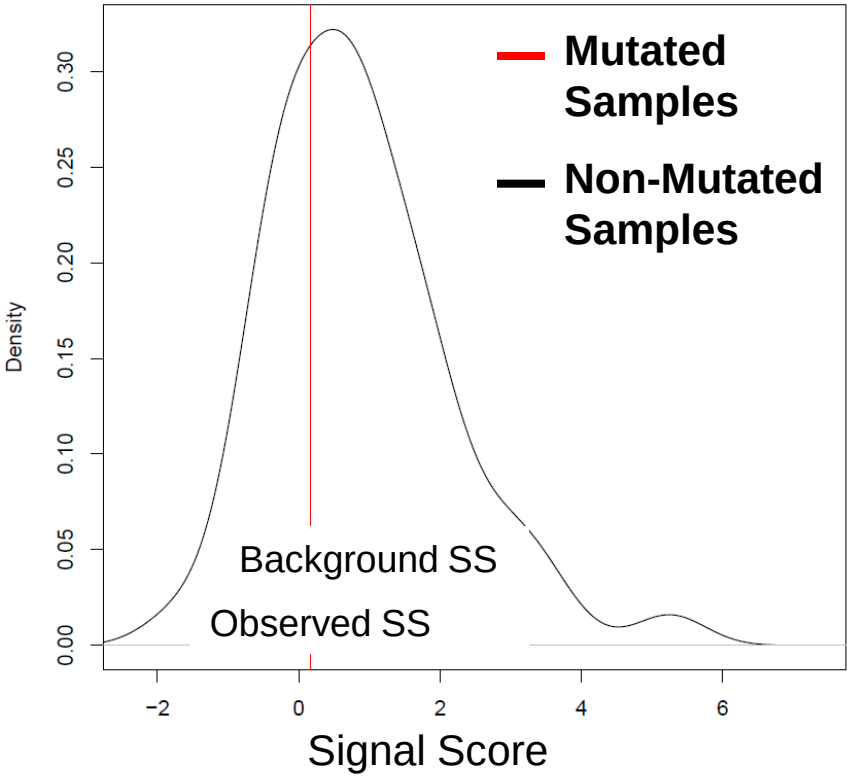
Significance Analysis



Passenger Mutations are not Discrepant

- Ran discrepancy analysis on COADREAD mutations with MutSig p-value > 0.5
  - 4 genes had enough pathway annotations to perform the analysis and were not discrepant





Summary

- Discrepancy analysis utilizes functional genomics data (such as copy number + expression) and pathway information to predict neutral, LOF, or GOF mutations
- Successfully identified RB1 LOF in GBM and NFE2L2 (NRF2) GOF in LUSC
- Discrepancy analysis is specific, did not identify discrepancies concordant with MutSig calls
- Identifying potential GOFs can reveal possible treatments to sensitive tumors or cell-lines

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