HARVARD RARE DISEASES HACKATHON 2024

Tackling FOXP1 through Amino Acid Sequence Analysis

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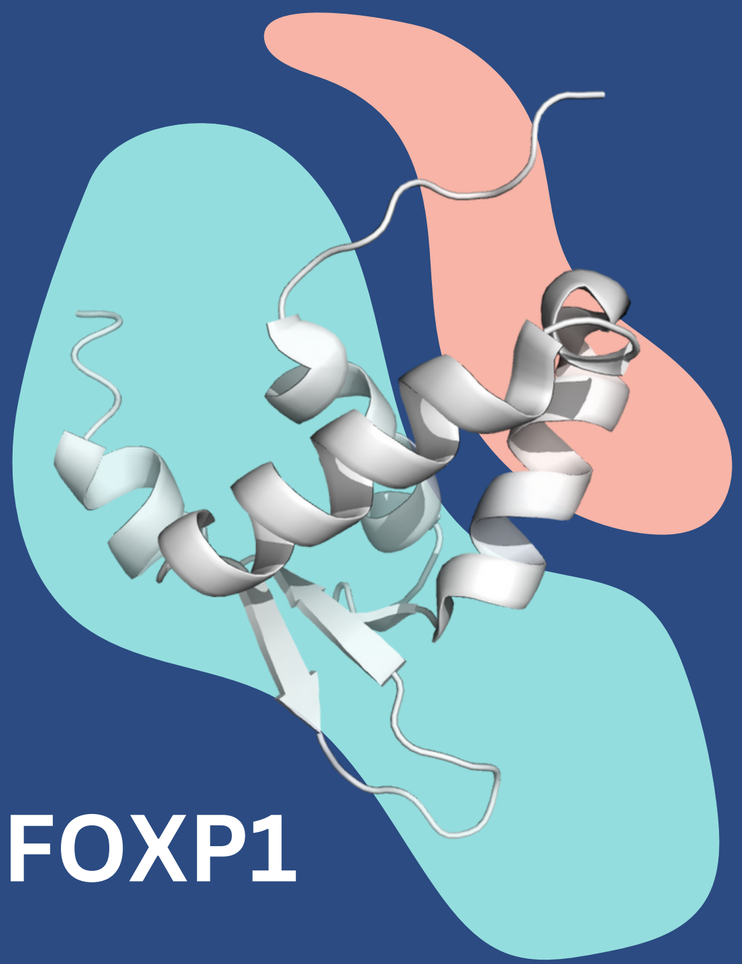


FOXP1

Problem

- FOXP1: important transcription factor for neurological functions
- Point mutations' effect on pathogenicity is poorly understood
- Analyze contributions to activity over others has not been closely analyzed.

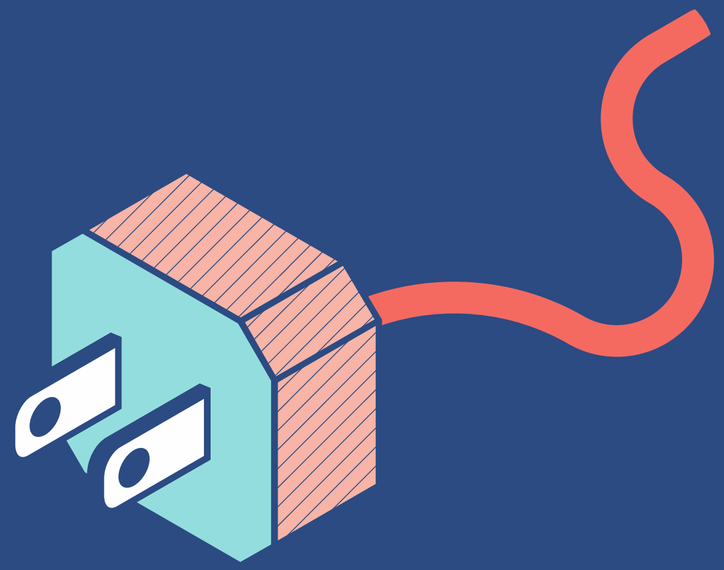
Literature

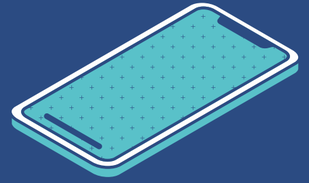
- AlphaMissense: widely cited as accurate way to predict the structural effects of mutations in the protein sequence[1].
- FOXP1 interacts with multiple binding partners + DNA --> more sites in which a mutation could be pathogenic[2].

1. Jun Cheng et al., Accurate proteome-wide missense variant effect prediction with AlphaMissense.Science381,eadg7492(2023).DOI:10.1126/science.adg7492
2. Li S, Weidenfeld J, Morrisey EE. Transcriptional and DNA binding activity of the Foxp1/2/4 family is modulated by heterotypic and homotypic protein interactions. Mol Cell Biol. 2004 Jan;24(2):809-22. doi: 10.1128/MCB.24.2.809-822.2004. PMID: 14701752; PMCID: PMC343786.

What data did our team work with?

1. Uniprot data: determine **where** FOXP1 domains were and their **functions**
2. AlphaMissense data: provided pathogenicity scores --> quickly **hone in** on certain mutants
3. UMich PEPPI tool: created **models** of mutated protein interactions with known partners as well as log(LR) **scores**





Methods/Workflow

1

STEP

Identify single point mutants from AlphaMissense. Compare these mutants against Uniprot annotations.

2

STEP

Isolate mutants with high pathogenicity.

3

STEP

Run k-mean clustering

4

STEP

Confirm destabilized interactions using PEPPI and the degree to which the mutant loses function

5

STEP

Determine the most likely downstream effects as a result of the pathogenic mutation in question

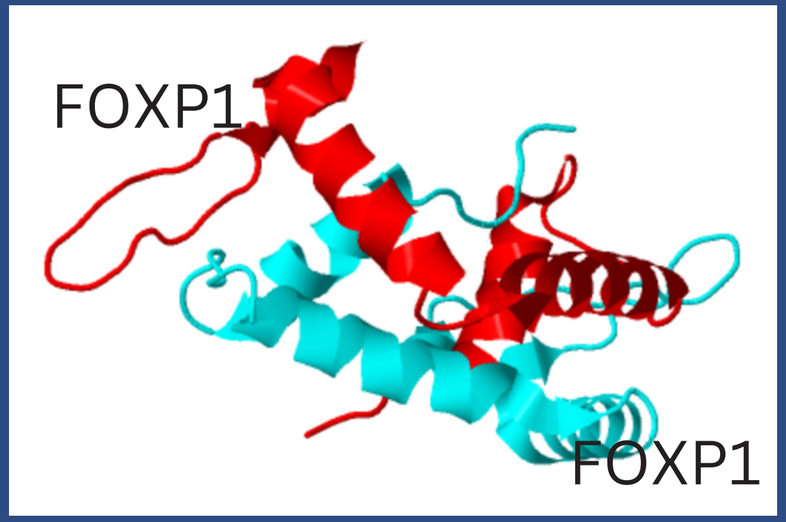
Results

PEPPI RESULTS[1]

Wild-type FOXP1-FOXP2 dimerize with LR(3.915)

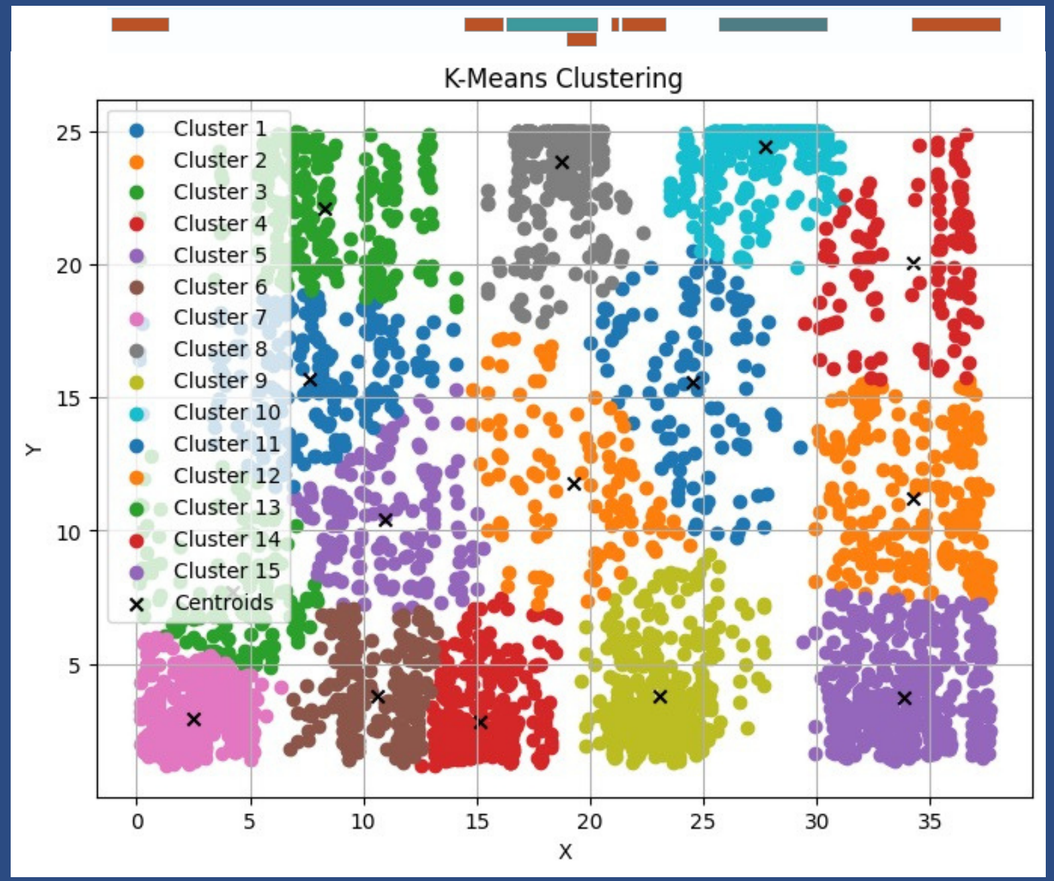
*Mutant Q142P FOXP1-FOXP2 lessen interaction with **LR(1.656)***

Mutant Q340H FOXP1-FOXP2 slightly increase interaction with LR(3.926)



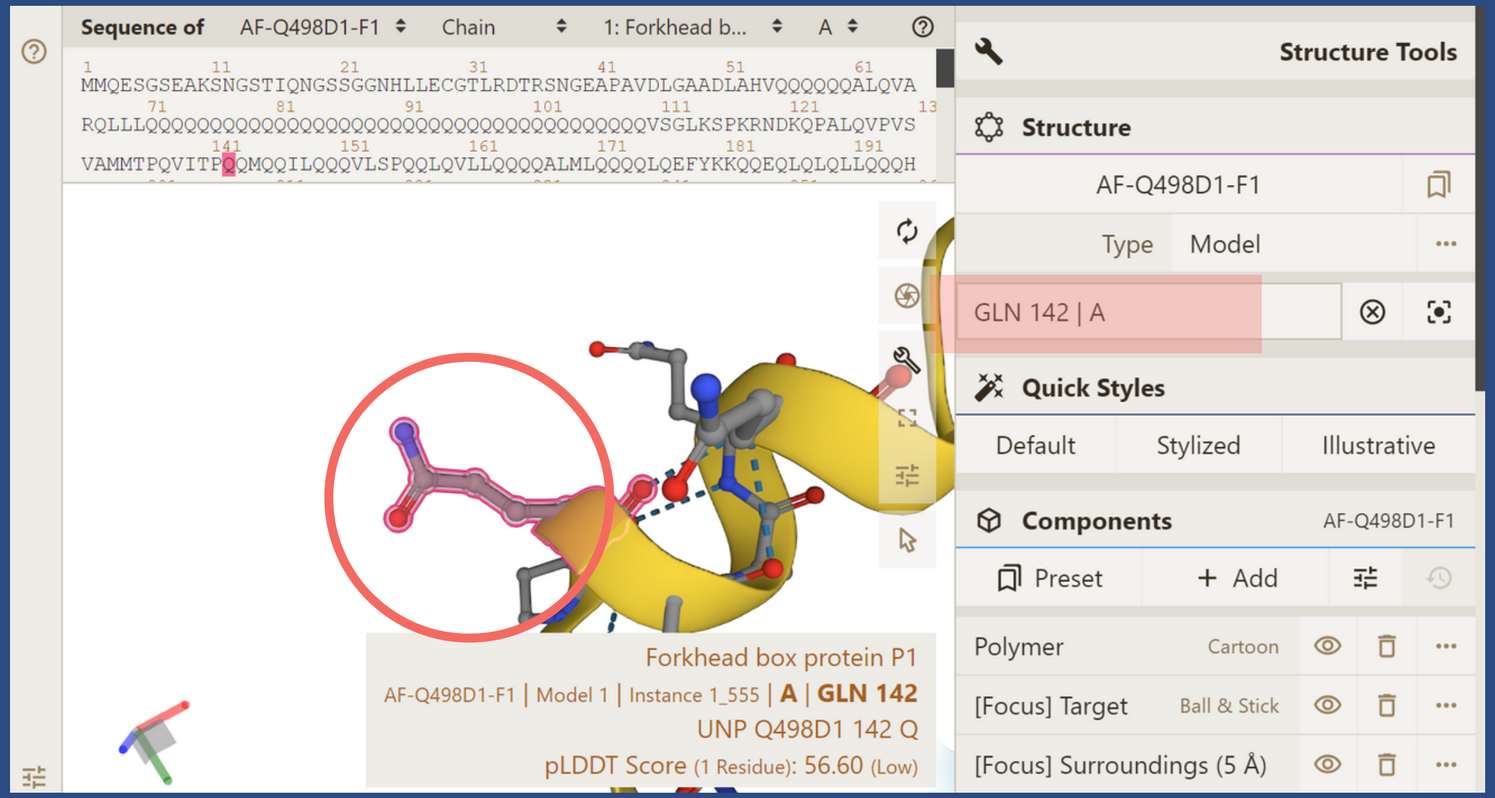
DOMAIN RESULTS

FOXP1 point mutations mapped using our k-means clustering algorithm, identifying areas of concern



1. Eric Bell, Jacob Schwartz, Peter Freddolino, Yang

Do our PEPPI results make sense?



Discussion

WHAT ARE THE IMPLICATIONS OF OUR PROJECT AND HOW CAN IT BE CARRIED FORWARD

Wholistic and Target In-Silico Mutant Analysis

Our approach takes a target protein and is able to efficiently screen and characterize mutant on the the cellular level.

Integrate a DNA-Protein Interaction Aspect for Future

For proteins like transcription factors, we hope to be able to incorporate a path of analysis that allows us to determine perturbations to the DNA binding ability of TFs.

Promote patient-specific accessibility to genetic screens

Our efficient and streamlined process can be applied to any rare genetic disease while also taking into account patient specific parameters.