Expanding mutational screens from single proteins to entire proteomes

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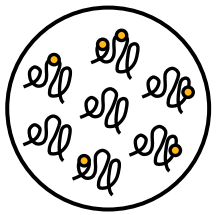
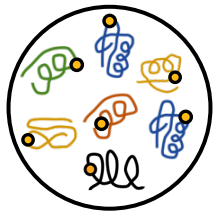
How can we accelerate variant interpretation across the proteome?

Deep mutational scanning



Many mutations in a single protein

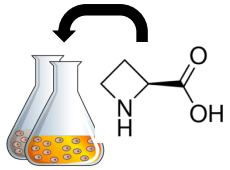
Miro



Mutations across the proteome

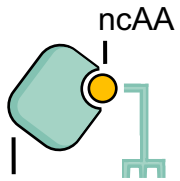
Miro: a method that measures the impact of mutations across the proteome

1. Non-canonical amino acids



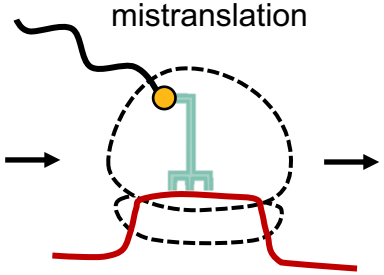
Example: Azetidine (proline analog)

2. tRNA charging

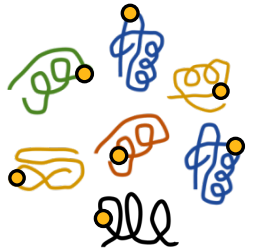


tRNA synthetase

3. Proteome-wide mistranslation



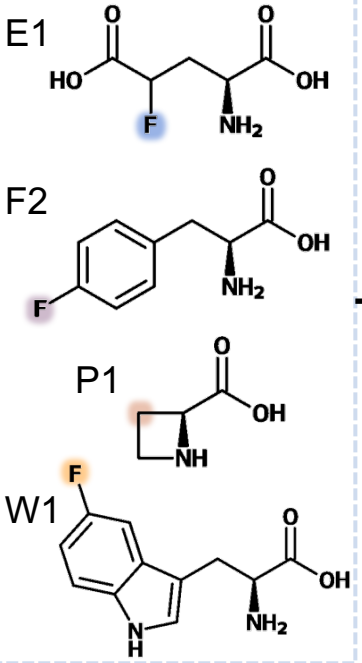
4. Collection of protein variants



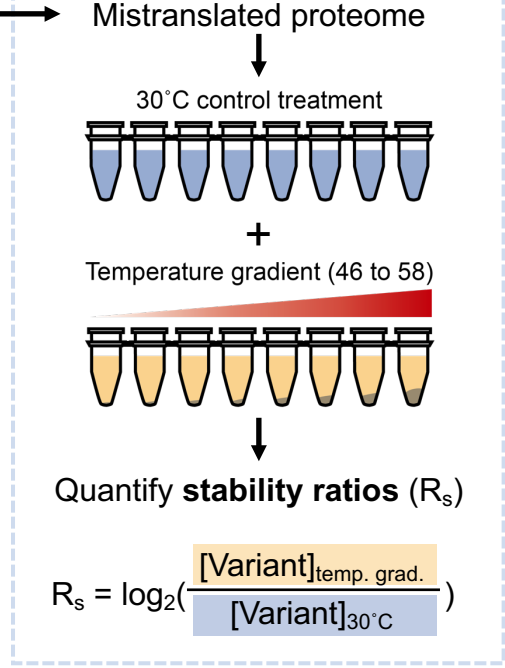
5. Biochemical selections with mass spec readout

- Thermal stability
- Solubility
- Turnover
- Enzymatic activity
- Small molecule binding
- Protein interactions

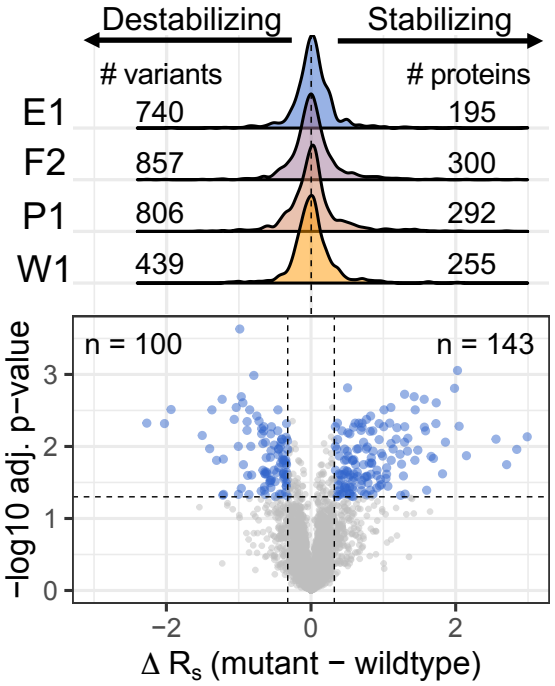
Analogs of interest



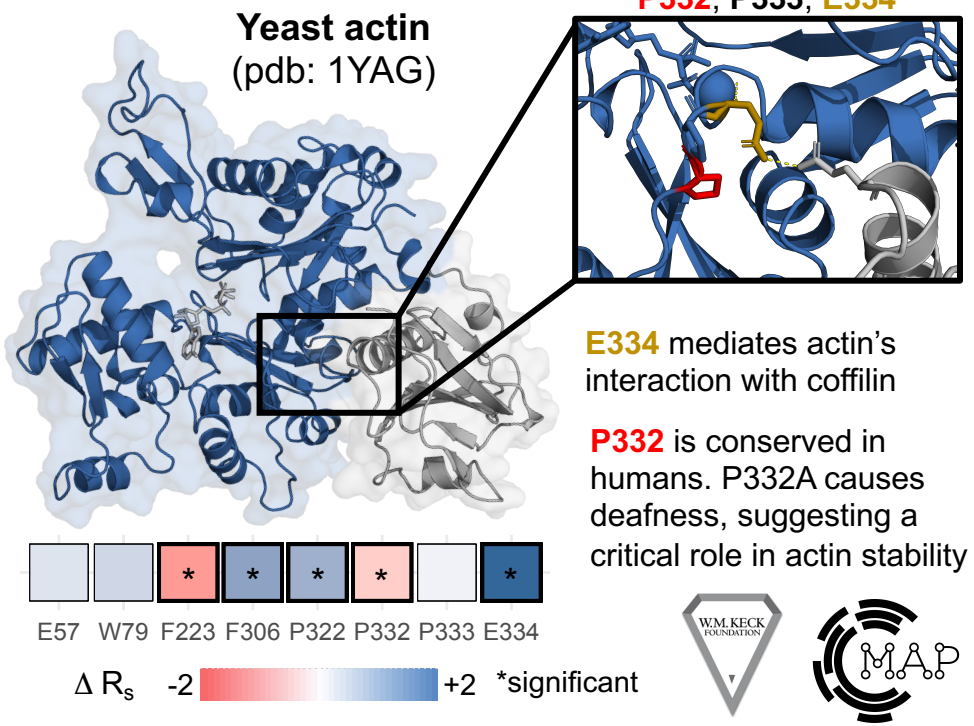
Measuring variant stability



Global impact of mistranslation



Yeast actin (pdb: 1YAG)



E334 mediates actin's interaction with coffilin

P332 is conserved in humans. P332A causes deafness, suggesting a critical role in actin stability