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Predictors of class

Using protein structure and function information to predict and understand mismatch repair variant pathogenicity

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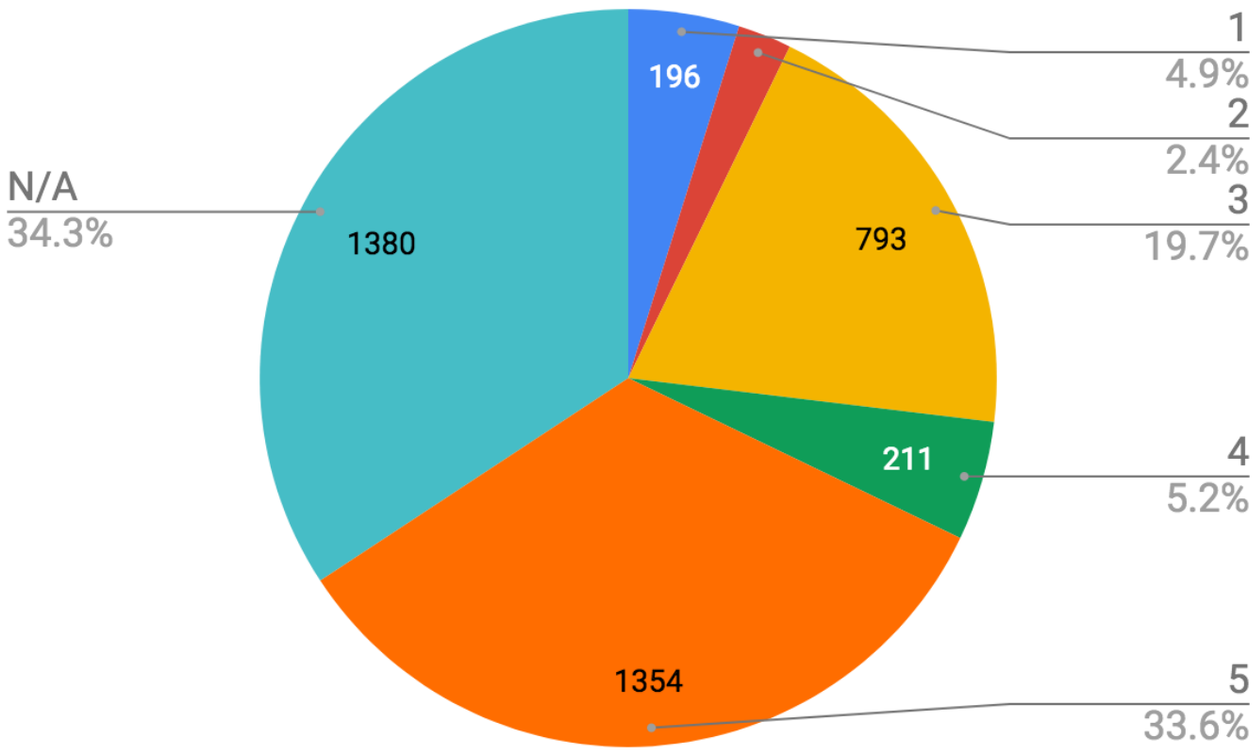
The InSiGHT database

% classifications for *MSH2, MSH6, MLH1, PMS2*



Class	Meaning
1	Not pathogenic
2	Likely not pathogenic
3	Uncertain
4	Likely Pathogenic
5	Pathogenic
N/A	Unclassified

- Class 3 and unclassified variants pose challenges for variant interpretation.
- 63% of Class 3 variants in *MSH2, MSH6, MLH1, PMS2* are missense.

Aims

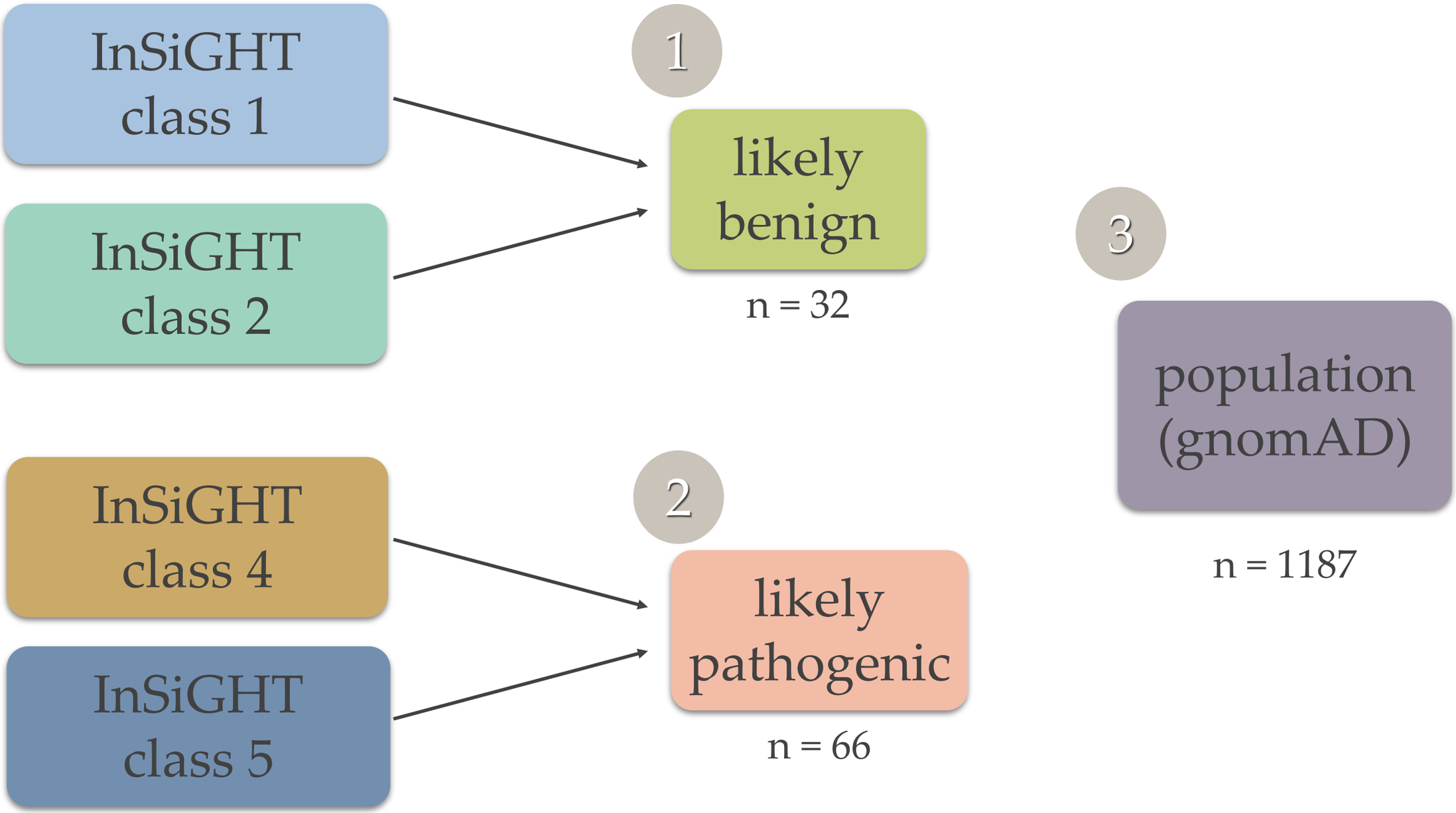
1. Predict important protein structural and functional features of missense MMR variants in *MSH2* and *MSH6*.

2. Train a machine-learning classifier on these features to distinguish pathogenic, benign and population variants.

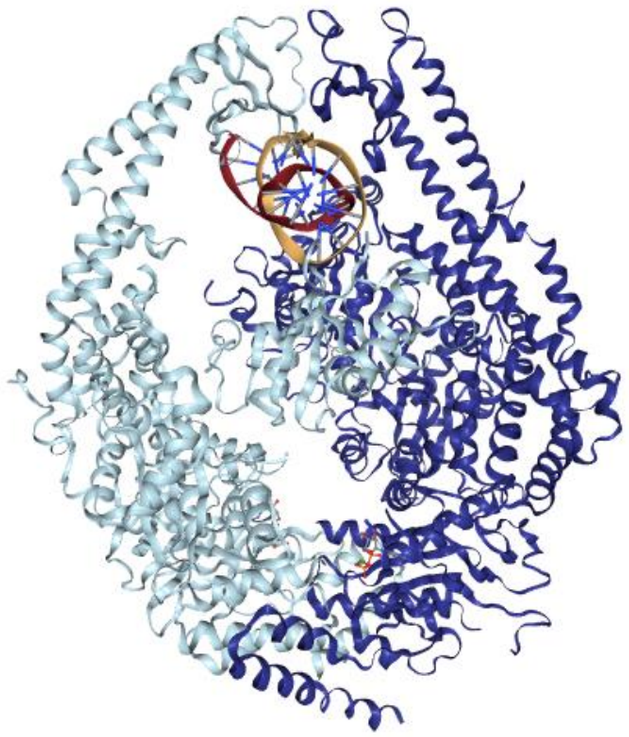
3. Apply the classifier to all *MSH2* and *MSH6* missense variants in InSiGHT.

Methods

Missense variants from *MSH2* and *MSH6* were placed into 3 independent groups



Methods



variant

mCSM suite

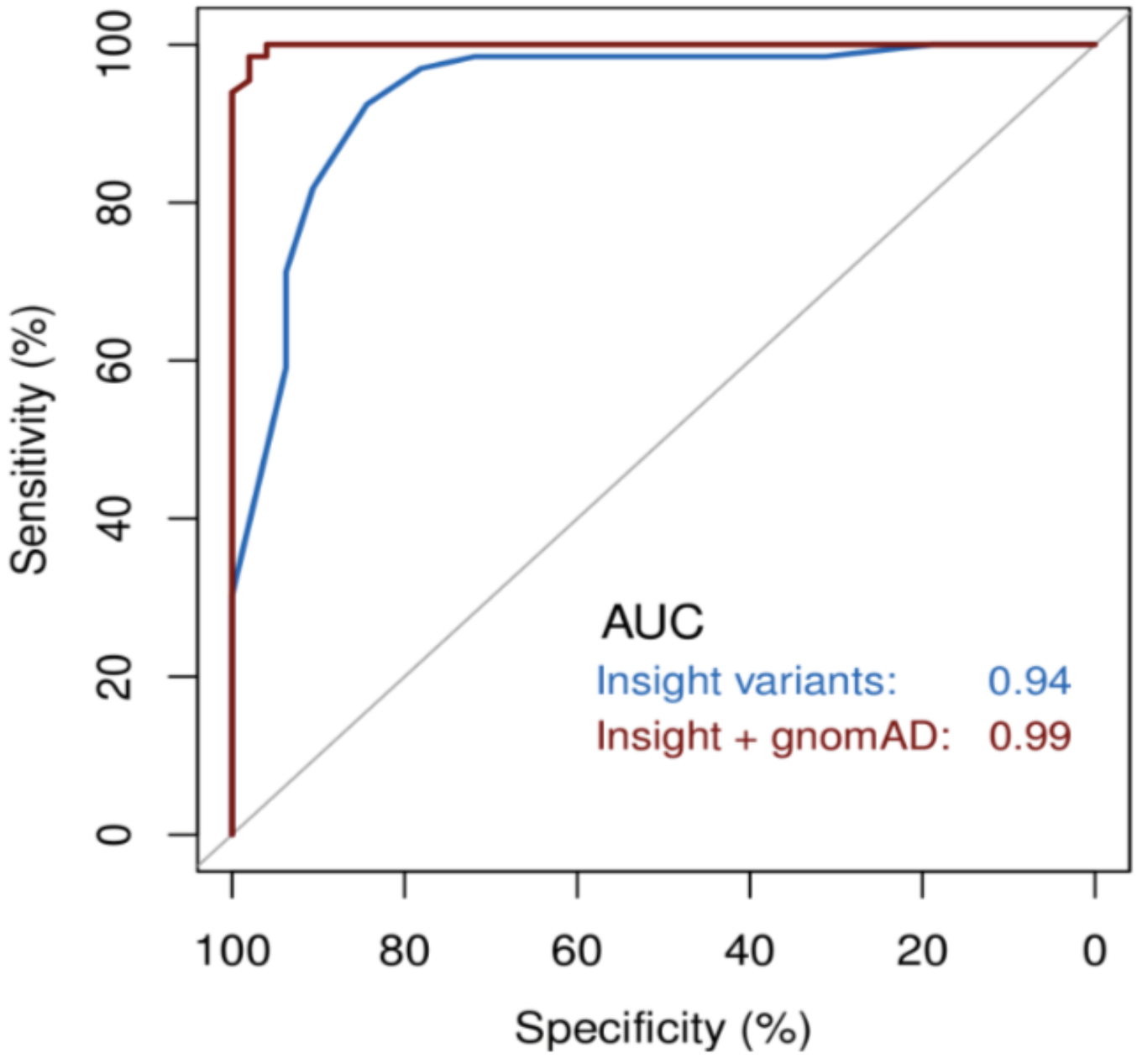
For each variant in the 3 groups:

- Map to the crystal structure for human MutS*α* (*MSH2* + *MSH6*).
- Predict protein structural and functional effects using the mCSM software suite.

Predicted Effects
protein stability
protein-protein binding
protein-DNA binding
protein-ligand binding
mutation tolerance
protein dynamics

Mutation Cutoff Scanning Matrix (mCSM)
http://biosig.unimelb.edu.au/mcsm/

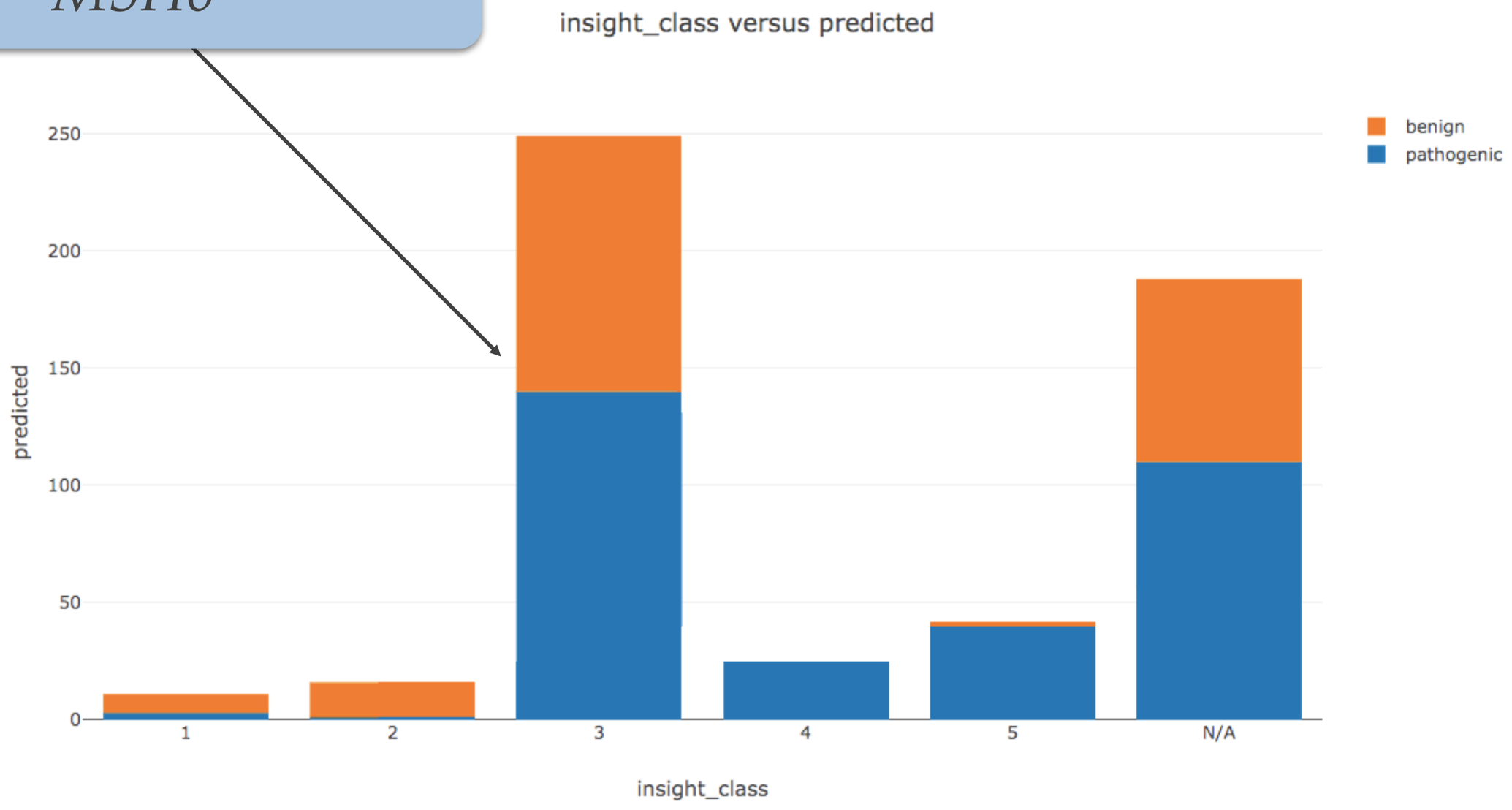
Results



- We trained a random forest classifier to distinguish between each of the 3 groups.
- Predictive performance tested using 10-fold cross validation.
  - Red = likely pathogenic *vs* population.
  - Blue = likely pathogenic vs likely benign.

Results

Re-classification of Class 3 variants in *MSH2* and *MSH6*

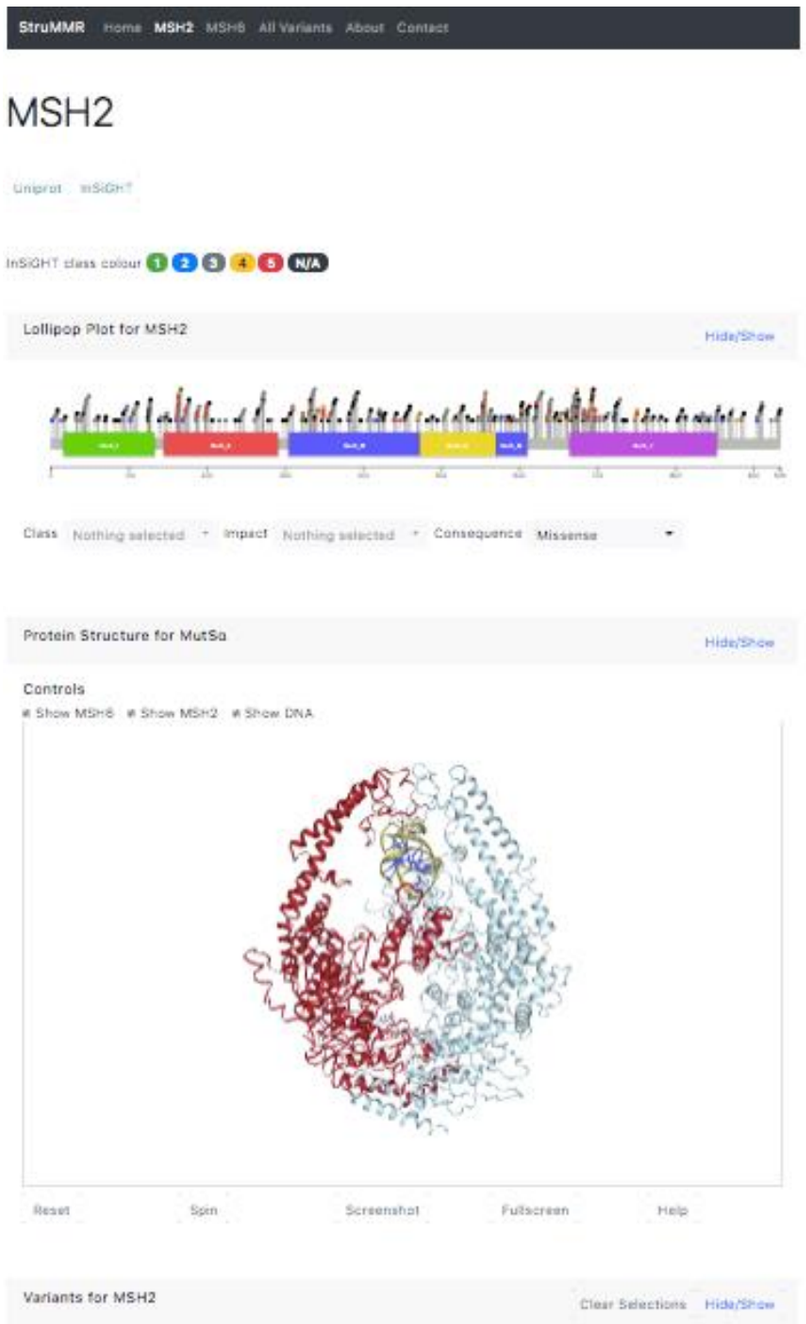


Conclusion

- Results are provided on the new interactive StruMMR website:

  http://biosig.unimelb.edu.au/strummr/

- Future work is to expand the technique to *MLH1* and *PMS2*.



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- Maurizio Genuardi
- Finlay Macrae

Extra Results

- PATH variants were situated in protein regions with lower tolerance to missense mutations compared to POP variants ($p = 0.011$)
- PATH variants were predicted to greater disrupt protein function than BEN variants ($p < 10^{-11}$) and POP variants ($p < 10^{-16}$).
- PATH variants were predicted to have a larger effect on protein stability compared to both BEN variants ($p < 10^{-6}$) and POP variants ($p < 10^{-6}$).
- Likely-pathogenic variants were also clustered closer to the ATP and Mg2+ binding sites than BEN variants ($p = 0.05$) and POP variants ($p < 0.0025$).