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L35

STRUCTURE-BASED MODELLING OF MISSENSE VARIANTS IN THE ALPHAFOLD ERA

Michael Sternberg

*Director Centre for Integrative Systems Biology and Bioinformatics Imperial College London
m.sternberg@imperial.ac.uk*

This talk will focus on the missense3D portal (missense3d.bc.ic.ac.uk) to predict the structural impact of missense variants [1,2,3].

The key features of this resource are:

- it provides a structural explanation for the prediction of the phenotypic effect of the missense variant and thus complements many other predictors including the recently-released AlphaMissense from DeepMind/Google
- it was developed to be applicable to predicted structures including by AlphaFold.

Three related web servers have been developed to model missense variants in protein tertiary structure, protein/protein interfaces and with membrane spanning reasons. The results of benchmarking the accuracy of the algorithm in both experimental structures in models predicted both by our server Phyre2 (www.sbg.bio.ic.ac.uk/~phyre2) [4] and AlphaFold.

Challenges in developing and evaluating missense variant predictors will be discussed

The talk will also introduce the web-based graphics program EzMol [5] (www.sbg.bio.ic.ac.uk/~ezmol/) designed for rapid display of protein structures for occasional users which will facilitate identifying the location of missense variants on protein structure. Finally an illustration of how structure based modelling of variants lead to

the formulation of an hypothesis about missense variant in the human protein TMPRSS2 that reduces the chances of severe Covid-19 [6].

Group publications

1. Ittisoponpisan, et al. (2019). Can predicted protein 3D structures provide reliable insights into whether missense variants are disease associated?. *Journal of molecular biology*, 431(11), 2197-2212.
2. Khanna, et al. (2021). Missense3D-DB web catalogue: an atom-based analysis and repository of 4M human protein-coding genetic variants. *Human Genetics*, 140, 805-812.
3. Khanna, et al. (2021). Missense3D-DB web catalogue: an atom-based analysis and repository of 4M human protein-coding genetic variants. *Human Genetics*, 140, 805-812.
4. Kelley, et al. (2015). The Phyre2 web portal for protein modeling, prediction and analysis. *Nature protocols*, 10(6), 845-858.
5. Reynolds, et al. (2018). EzMol: a web server wizard for the rapid visualization and image production of protein and nucleic acid structures. *Journal of molecular biology*, 430(15), 2244-2248.
6. David, et al. (2022). A common TMPRSS2 variant has a protective effect against severe COVID-19. *Current research in translational medicine*, 70(2), 103333.