PATHOGENICITY PREDICTION OF RARE VARIANTS

Predicting the pathogenic consequences of rare disease variants is a very difficult task. Computational models are of little help at the moment. American guidelines[1] suggest treating them as "weak evidence". Researchers are therefore looking for better computational methods. An article, which appeared in Am J Hum Genet[2], proposes a software, VARITY, which, according to the authors, identifies at least 10% more pathogenic variants at thresholds achieving high (90% precision) stringency. This approach, like the previous ones, is based on the data available for the human population.

A second, almost simultaneous, article published in Nature[3] uses a different and very interesting approach. The authors present a software, EVE, which investigates the consequences of the variant(s) under study in the evolutionary landscape. EVE is trained exclusively on evolutionary sequences (140,000 organisms!), thus avoiding biases present in other computational approaches. According to the authors, EVE outperforms current state-of-the-art computational methods in predicting the pathogenicity of variants.

The paper concludes with thought provoking comments, particularly relevant during the ongoing COP26: “Our analysis is one small but unusually direct demonstration of how the diversity of life on Earth benefits human health.” ... “The progressive disappearance of species is a threat to the diversity on which this work is built”.

[1] https://www.nature.com/articles/gim201530

[2] https://doi.org/10.1016/j.ajhg.2021.08.012

[3] https://www.nature.com/articles/s41586-021-04043-8