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Scientists develop an AI method to improve rare disease diagnosis

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The team under Professor Tom Lenaerts (VUB-ULB) of the IB^2 has developed an AI algorithm that makes it possible to identify combinations of genetic variants or abnormalities that cause rare diseases through computer analysis. The algorithm was developed with Prof. dr. Guillaume Smits (Center for Human Genetics of the ULB, the Erasmus Hospital and the University Children's Hospital Queen Fabiola) and was designed and built in collaboration with Yves Moreau and Jan Aerts (KU Leuven), Sonia Van Dooren (UZ Brussels) and Ann Nowé (Vrije Universiteit Brussels). The method has been named VarCoPP (Variant Combinations Pathogenicity Predictor).

Almost 80% of rare diseases are genetically determined. It is therefore important for doctors to be able to predict which genetic variants in the patient's genome may be the cause of the disease. Predicting the cause of the error is not easy but predicting whether a combination of errors in different genes has the potential to cause a rare disease is even more difficult. However, this is necessary for the better diagnoses of genetic diseases since, in many cases, only a fraction of patients can be helped.

The VarCoPP algorithm offers precisely that innovative approach: it makes it possible to simultaneously test the combinations of different variants in gene pairs and to predict their potential pathogenicity. The AI that underlies VarCoPP is driven by the database of rare diseases called DIDA, which was developed by the same researchers in 2015. The researchers successfully tested the effectiveness and reliability of the algorithm on 23 independent pathogenic gene combinations, and deliver

confidence intervals of 95% and 99% to help doctors zoom in on the most important predictions. The team is now attempting to use these results to identify the genetic causes of rare diseases in patients for whom no cause could previously be identified. The team introduces at the same time a new online diagnostic platform for researchers and clinicians, based on the algorithm. The platform is called 'ORVAL' and is described in a publication in the journal *Nucleic Acids Research* (*NAR*).

ORVAL and VarCoPP provide a novel approach to study variant combinations for rare diseases for which causal genes are known or unknown, such as for example the hundreds of autism or epilepsy genes or the 20 genes of the rare Bardet-Biedl syndrome (a genetic disorder which presents blindness, obesity and motor disorders amongst others) where different combinations of genetic variations are likely to be the cause.

More information: Sofia Papadimitriou et al, Predicting disease-causing variant combinations, *Proceedings of the National Academy of Sciences* (2019). DOI: 10.1073/pnas.1815601116

Alexandre Renaux et al. ORVAL: a novel platform for the prediction and exploration of disease-causing oligogenic variant combinations, *Nucleic Acids Research* (2019). DOI: 10.1093/nar/gkz437

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