SCIENCES & BIOENGINEERING SCIENCES

The Research Group
Artificial Intelligence Lab

has the honor to invite you to the public defence of the PhD thesis of

Barbara Gravel

to obtain the degree of Doctor of Sciences

Joint PhD with Université Libre de Bruxelles

Title of the PhD thesis:

Towards the identification of oligogenic disease variants at exome scale - from oligogenic data to a new prioritisation algorithm

Promotors:
Prof. dr. Ann Nowé (VUB)
Prof. dr. Tom Lenaerts (ULB)

The defence will take place on
Tuesday, September 24, 2024 at 5 p.m. in the Solvay Room (ULB campus de la Plaine, NO building floor 8)

The defense can also be followed through a livestream

Members of the jury

Prof. dr. Matthieu Defrance (ULB, chair)
Prof. dr. Wim Vranken (VUB, secretary)
Prof. dr. Catharina Olsen (VUB)
Prof. dr. Guillaume Smits (ULB)
Prof. dr. Yves Moreau (KULeuven)
Prof. dr. Emmanuelle Génin (INSERM/ Université de Bretagne Occidentale, FR)

Curriculum vitae

Barbara Gravel obtained her Bsc degree in Biology and Mathematics from McGill Uoniversity in 2017. She came to Brussels in 2018 to study for a master in Bioinformatics and Modelling at the ULB, which she obtained in 2020, before continuing her master's thesis work as a joint PhD student at the Interuniversity Institute of Bioinformatics in Brussels (ULB-VUB).
Her research focuses on using machine learning approaches to help predict the involvement of genetic variants in disease. During her PhD she published 4 peer-reviewed articles and presented at 3 international conferences.

Abstract of the PhD research

With the advent of high-throughput sequencing technologies, tremendous progress has been made in understanding how genetic mutations (genotypes) are linked to specific traits or diseases (phenotypes). Advances in related computational methods have enabled the development of different algorithms to help pinpoint which genetic variants might be responsible for specifc diseases. However, these algorithms are not adapted to detect more complex patterns of inheritance than the traditional "one gene - one disease" paradigm. Developping novel computational methods to identify these more complex combinations of genetic variants, known as oligogenic inheritance, is therefore essential.

This thesis work builds upon existing methods to improve the detection of pathogenic variant combinations, specifically at the whole-exome level. First, a new database is a created that collects information on all oligogenic variant combinations reported in the literature. This database not only aggregates existing knowledge but also introduces a standardized framework for assessing the pathogenicity of variant combinations. Using this database, we develop a first oligogenic priorization tool: the High-throughput oligogenic prioritizer (Hop). Hop uses machine learning to assess which variant combinations are likely to cause disease, combining this with biological network information to rank how relevant these combinations are for a particular patient's condition. This tool demonstrates superior performance to existing approaches for ranking oligogenic combinations in exomes. Finally, we investigate the usefulness of these computational tools on real patient data. We apply the Hop predictor on a cohort of patients affected with male infertility, a condition with heterogeneous genetic causes, and investigate the relevance of the prioritized combinations. This analysis validates the ability of Hop to detect oligogenic combinations that were manually identified by clinicians, and also showcases its capacity to identify novel oligogenic signatures in this disease.

In summary, this research demonstrates that it is now possible to directly detect disease causing variant combinations in whole exome sequencing data using computational approaches. By introducing a new data repository, computational tools, and analysis protocols, this research opens the way for easier detection and analysis of oligogenic signatures for genetic diseases.