Multiplex network improves diagnosis and analysis of rare diseases

The network will help understand underlying mechanisms of rare diseases and thus enables identification of causative genetic defects more accurately

Rare diseases are usually caused by a single genetic defect. Nevertheless, the search for the cause and the assessment of the effects is highly complex and difficult. Scientist Jörg Menche, Adjunct Principal Investigator at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Professor at the University of Vienna and Research Group Leader at the Max Perutz Labs (a joint venture of the University of Vienna and the Medical University of Vienna), and his team have now developed a multiplex network that maps all genes and their interactions on multiple levels and improves the identification of genetic defects and the assessment of their consequences.

(Vienna, November 09, 2021) In contrast to common diseases, which are usually characterized by a complex interaction of multiple genetic and environmental factors, rare diseases can often be traced back to a single defective gene. Targeted decoding and analysis of a gene defect and its phenotypic consequences therefore provides important information for understanding underlying mechanisms in the body and helps in choosing targeted treatment strategies. However, the individual search for the cause of disease is usually lengthy and costly. A new, systematic approach to the study of rare, uncharacterized diseases using a so-called multiplex network is now presented by the research group of network scientist Jörg Menche at CeMM and the Max Perutz Labs in their latest study, published today in the journal Nature Communications.

Three times higher probability of identifying causative genetic defect

Menche's research group has been dedicated for several years to better understanding genetic interactions using molecular network analysis to improve the diagnosis and treatment of rare diseases. For their current study, first author Pisanu Buphamalai, a CeMM PhD student in Menche's research group, built a multilayer network mapping more than 20 million gene relationships with information ranging from protein interactions to phenotypic similarities. To do this, the scientist integrated a comprehensive dataset of more than 3,700 rare diseases with a known genetic basis. Study leader Menche explains, "The multiplex network integrates different network layers that map different levels of the biological organization of our body, from the genome to the transcriptome, proteome and phenotype. By mapping protein interactions and mechanisms, we can also better characterize those proteins whose roles in diseases were previously unknown and thus track down gene defects more quickly." Pisanu Buphamalai adds, "We are guided by the interactions among proteins at both physical and functional levels. This allows us to draw conclusions

about the potential defective gene as well as associated effects. Our network approach increases the probability of finding the crucial gene aberration threefold compared to when these networks are considered separately."

Progress for network medicine: more accurate analysis, better prognosis

On the one hand, the multiplex network's modular design makes it possible to quantify the impact of a particular rare disease on a specific level of biological organization. This means determining whether certain cells, tissue forms, organs, etc. are particularly affected by a genetic defect. On the other hand, the importance of certain molecular processes for a disease can also be measured. "It is precisely because of its complexity, the linking of molecular sequences and processes, that our multiplex network is significantly more powerful and successful than looking at each network individually. It also makes it easier to make predictions about possible consequences of the genetic defect," Menche says. The network was successfully tested for functionality in collaboration with Vanja Nagy, Principal Investigator at the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases and CeMM Adjunct Principal Investigator, using data from patients with neurological diseases whose underlying genetic defect was already known. "Our study shows how a huge dataset can be used in the context of network medicine to address several practical and conceptual challenges in rare disease research to improve diagnosis and treatment for the benefit of patients," Menche says.

Attached picture: Last author Jörg Menche and first author Pisanu Buphamalai, © Laura Alvarez/CeMM;

Graphical abstract: The graphical abstract shows in the middle the multiscale maps of rare disease genes. Like geographical maps, the more information being overlaid, the more comprehensive the maps are. The scientists overlay information from various scales from genotype to phenotype, each show different patterns of connectivity among these genes. They use this to navigate our understanding of molecular causality. Furthermore, with the emergence of disease neighborhoods on these maps (glowing white dots), it's possible to inspect and predict new genes that might cause the diseases. The bottom visualization is the zooming in on particular diseases to observe how the genes (the dots) are wired and rewired across networks (different colors: red, yellow, green), reflecting their hidden underlying mechanisms. © Pisanu Buphamalai, published in Nature Communications 2021.

The study "Network analysis reveals rare disease signatures across multiple levels of biological organization" was published in the journal Nature Communications on November 09, 2021. DOI: 10.1038/s41467-021-26674-1.

Authors: Pisanu Buphamalai, Tomislav Kokotovic, Vanja Nagy, Jörg Menche;

Funding: The study was supported by the Vienna Science and Technology Fund (WWTF) through project VRG15-005.

Jörg Menche studied physics in Leipzig, Recife and Berlin. He did his PhD at the Max-Planck-Institute for Colloids and Interfaces in Potsdam (Germany), and was a postdoctoral fellow with Albert-László Barabási at Northeastern University and at the Center for Cancer Systems Biology at Dana Farber Cancer Institute in Boston. He joined CeMM in 2015 as a Principal Investigator. In September 2020, he received a joint professorship at the Max Perutz Labs and the Faculty of Mathematics of the University of Vienna, and became CeMM Adjunct PI.

The **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** is an international, independent and interdisciplinary research institution for molecular medicine under the scientific direction of Giulio Superti-Furga. CeMM is oriented towards medical needs and integrates basic research and clinical expertise to develop innovative diagnostic and therapeutic approaches for precision medicine. Research focuses on cancer, inflammation, metabolic and immune disorders, and rare diseases. The Institute's research building is located on the campus of the Medical University and the Vienna General Hospital. www.cemm.at

The **Max Perutz Labs** are a research institute established by the University of Vienna and the Medical University of Vienna to provide an environment for excellent, internationally recognized research and education in the field of Molecular Biology. Dedicated to a mechanistic understanding of fundamental biomedical processes, scientists at the Max Perutz Labs aim to link breakthroughs in basic research to advances in human health. The Max Perutz Labs are located at the Vienna BioCenter, one of Europe's hotspots for Life Sciences, and host around 45 research groups, involving more than 450 scientists and staff from 40 nations. www.maxperutzlabs.ac.at

For **further information** please contact

Anna Maria Schwendinger
Head of PR & Communications

CeMM
Research Center for Molecular Medicine
of the Austrian Academy of Sciences
Lazarettgasse 14, AKH BT 25.3
1090 Vienna, Austria
Phone +43-1/40160-70 092
aschwendinger@cemm.oeaw.ac.at
www.cemm.at

Sándor Fülöp
Junior Communications Manager

Max Perutz Labs Vienna
Dr.-Bohr-Gasse 9,

1030 Vienna, Austria
Phone +43-1/42-77 24013
communications@maxperutzlabs.ac.at
www.maxperutzlabs.ac.at