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Network-based approaches open a new avenue to classify and treat rare diseases

Scientists at CeMM, Max Perutz Labs, and St. Anna Children's Cancer Research Institute have achieved a significant advancement in the research of rare immune system disorders. Through a network-based approach, they have reclassified approximately 200 rare diseases. Initial comparisons with clinical data already demonstrate how this can enhance the prediction of treatment efficacy. Moreover, the study reveals for the first time the strong similarities between the molecular mechanisms of rare diseases and autoimmune and autoinflammatory conditions, such as chronic inflammatory bowel disorders, multiple sclerosis, and specific types of diabetes. The study has now been published in Science Advances.

(Vienna, 1 September 2023) Network-based approaches often unveil what remains concealed – this holds true in medical research as well. For several years, CeMM Adjunct Principal Investigators Kaan Boztug, Director of St. Anna Children's Cancer Research Institute, and Jörg Menche, a professor at the University of Vienna and Max Perutz Labs have been working to gain a better systemic and molecular understanding of rare diseases, congenital immune disorders, and congenital inflammatory disorders by using network-based methods. In their latest study led by the study's first author Julia Guthrie, the researchers successfully identified new molecular and mechanistic similarities between rare immune system disorders by examining the high degree of interconnectedness of molecular interactions, leading to their reclassification. By comparing their results to clinical data, the researchers demonstrated that patients with diseases within a classification group also responded to the same medications.

New classification enables more targeted therapies

For their study, the researchers examined around 200 rare immune disorders with inflammatory phenotypes. The network-based analysis of protein-protein interactions revealed similarities in the molecular mechanisms behind these diseases. Through these analyses, the diseases were reclassified, and the researchers subsequently calculated which therapies could yield the best results for each respective group. "Compared to existing clinical data, the new disease classification allows for a much better prediction of promising therapies compared to the previous approach. Network biology allows us to gain deeper insights into the intricate interplay between the immune system and diseases. This, in turn, enables us to develop more targeted and personalized approaches for diagnosis and treatment" explained co-study leader Kaan Boztug.

Similar patterns in autoimmune and autoinflammatory diseases

The results also indicate that numerous autoimmune and autoinflammatory diseases such as chronic inflammatory disorders, multiple sclerosis, systemic lupus erythematosus, and type 1 diabetes are closely linked. The study's first author Julia Guthrie explained: "We were able to identify a group of key genes and their interaction partners that are central to homeostasis. We refer to this network of key genes as 'AutoCore'. In autoimmune and autoinflammatory diseases, the AutoCore resides right at the center of the associated genes. Additionally, we identified 19 other subgroups that are intended to provide us with better insights into homeostasis and immune system deregulation."

Taking a broader perspective

While conventional approaches often categorize immune system disorders according to specific body regions and thus view them in isolation, a systemic approach aims to offer a more detailed picture of underlying mechanisms. Co-study leader Jörg Menche explained: "We increasingly recognized the conceptual and practical limitations of the traditional paradigm of 'one gene, one disease' in the research of rare diseases. This hinders our understanding of the complex molecular network through which the components of the immune system are orchestrated. Therefore, we developed a visualization in the form of a multidimensional network that depicts all currently known monogenic immune defects underlying autoimmunity and autoinflammation, as well as their molecular interactions. As a result, we can see how closely genes are interconnected in rare diseases."

The acquired data also provide a crucial foundation for identifying better treatment options for specific groups of disorders.

Images attached:
Picture: Kaan Boztug, Julia Guthrie and Jörg Menche © Piero Chiussi, CeMM
Figure 1: AutoCore Endotypes. This figure illustrates the AutoCore, the subnetwork of key genes defined by around 200 rare immune system disorders with shared phenotypes. The different colors and names highlight the 12 biggest out of 19 molecular groups identified within the AutoCore subnetwork, which can provide us with better insights into homeostasis and immune system deregulation. © Julia Guthrie
Figure 2: The AutoCore and common, polygenic autoimmune and autoinflammatory diseases. This figure illustrates the relative position of the AutoCore within the context of the network modules of common, chronic inflammatory disorders such as inflammatory bowel disease, rheumatoid arthritis and systemic lupus erythematosus. We find that the AutoCore lies at the center of these diseases connecting them through shared molecular mechanisms.
Node size reflects betweenness centrality, a measure that indicates how many times an individual disease module is a connector module between other disease modules in the network. Edge width reflects the network distance between diseases. © Julia Guthrie

The study "AutoCore: network-based definition of the core module of human autoimmunity and autoinflammation" was published on 1 September 2023 in Science Advances, DOI: 10.1126/sciadv.adg6375

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Kaan Boztug is the Scientific Director of St. Anna Children's Cancer Research Institute, Senior Physician in Pediatric Hematology and Oncology, Head of the Immunology Department at St. Anna Children's Hospital, and Professor in the Department of Pediatrics and Inflammation Research at the Medical University of Vienna. Boztug's research group focuses on congenital bone marrow failure syndromes and immune defects, as well as inherited predisposition to childhood tumors. The group aims to understand fundamental mechanisms of immune surveillance that are relevant to pediatric oncology and immunotherapy approaches. After studying medicine in Düsseldorf, Freiburg, and London, and completing his doctoral studies at the Scripps Research Institute in La Jolla, USA, Kaan Boztug underwent clinical training and postdoctoral research at the Hannover Medical School. Since 2011, he has been working as a physician and researcher at the Medical University of Vienna, serving as an Adjunct Principal Investigator at CeMM, the Research Center for Molecular Medicine of the Austrian Academy of Sciences. Additionally, Kaan Boztug is the Director of the CeRUD Vienna Center for Rare and Undiagnosed Diseases at the Medical University of Vienna.

Jörg Menche studied physics in Leipzig, Recife, and Berlin. He obtained his doctorate at the Max Planck Institute of Colloids and Interfaces in Potsdam and completed postdoctoral positions at Northeastern University and the Center for Cancer Systems Biology at the Dana Farber Cancer Institute in Boston. In 2015, he joined CeMM as a Principal Investigator. In September 2020, Jörg Menche assumed a professorship at the Institute of Mathematics at the University of Vienna, as well as the Max Perutz Labs, a joint venture between the University of Vienna and the Medical University of Vienna. At CeMM, Jörg Menche continues to serve as an Adjunct Principal Investigator.

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 toward 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, rare diseases, and aging research. The Institute's research building is located on the campus of the Medical University and the Vienna General Hospital.
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The **St. Anna Children's Cancer Research Institute (CCRI)** is an international and interdisciplinary research institution dedicated to advancing diagnostic, prognostic,

and therapeutic strategies for the treatment of children and adolescents with cancer through innovative research. Incorporating the specific characteristics of childhood tumor diseases, dedicated research groups collaborate in the fields of tumor genomics and epigenomics, immunology, molecular biology, cell biology, bioinformatics, and clinical research. Their aim is to bridge the latest scientific and experimental knowledge with the clinical needs of physicians in order to significantly improve the well-being of young patients.
ccri.at, kinderkrebsforschung.at

The **Max Perutz Labs** are a joint venture between the University of Vienna and the Medical University of Vienna. The institute conducts exceptional, internationally recognized research and education in the field of molecular biology. Scientists at the Max Perutz Labs explore fundamental mechanistic processes in biomedicine, merging innovative basic research with medically relevant inquiries. The Max Perutz Labs are an integral part of the Vienna BioCenter, a prominent hub for life sciences in Europe. The institute hosts approximately 45 research groups comprising over 450 employees from 40 different nations.
maxperutzlabs.ac.at

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