Press release

Do you speak immunology?

A new language for congenital immune disorders

(Vienna, 30.06.2021) **A detailed vocabulary to identify and explore rare, congenital immune disorders around the world? That is exactly what is now available thanks to a new study led by the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases in Vienna and the University Medical Center Groningen. Congenital immune disorders often affect only a handful of children around the world. The now published expansion of the nomenclature allows us to better analyze, identify, and treat these diseases**.

When a child in Austria falls ill with a rare immunodeficiency, their treating physician will often like to know experience with similar cases around the world. Has there ever been such a case or a similar one before? What has been the experience with treatment of the other patient? But even if a child in – for example – Japan suffers from exactly the same disease, the treating physicians probably never get to know about each other. Researchers at the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD) strive to change that. “To identify and eventually treat children with rare diseases, there needs to be a global exchange between researchers and physicians. This exchange can only be successful if everyone speaks the same language, and describes diseases in a uniform way, and if local registries are internationally interconnected,” explains Kaan Boztug, Director at the LBI-RUD and Scientific Director of the St. Anna Children’s Cancer Research Institute.

You only find what you can name

Boztug’s research group at the LBI-RUD, together with the group of Marielle van Gijn, group leader at the University Medical Center Groningen, have therefore brought together relevant partners around the world and leading medical societies in the field of immune diseases including the European Society for Immunodeficiencies (ESID) and the European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune diseases (ERN-RITA) to further develop the so-called Human Phenotype Ontology (HPO). The HPO is a kind of language, providing a standardized vocabulary for clinical changes in the human body associated with individual diseases. ”We got in touch with Peter Robinson, who originally developed HPO, and for the first time systematically expanded the vocabulary to describe immunological diseases. We have described symptoms of rare, congenital immune disorders more precisely and in greater detail to enable uniform diagnoses worldwide,” says Matthias Haimel, co-first author of the study and bioinformatician in the research group of Christoph Bock at LBI-RUD and the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences. “Until now, different terms have been applied in different countries for the same disease and its symptoms,” explains Julia Pazmandi, co-first author of the study and PhD student in Kaan Boztug’s research group. Kaan Boztug adds, “Only what you can name can be found. At the same time, an accurate description helps to discover new diseases and gene mutations.”

HPO includes 2,120 rare diseases, of which congenital immune disorders form a subgroup. For the latter, HPO has not been specific enough and therefore has hardly been used in the expert community. To change this, leading researchers and clinicians in the field have met regularly both in Vienna and virtually to revise and expand the terms of four disease groups relevant to congenital immune disorders within the

HPO. New terms such as “recurrent fever” or “unusual infections” were added. To accomplish this, selected articles were analyzed for technical terms using machine learning, which were then assigned as correct or incorrect by experts in a review process.

Top 10 ranking narrows down the diagnosis

To showcase the efficiency of their expansion of HPO terms for immune defects, the researchers analyzed 30 patients from a database. HPO terms were assigned to disease entities and based on this, the similarity to all previously revised HPO diseases was calculated. In most cases, the correct diagnosis was found in the top 10 diseases calculated for each symptom. “Artificial intelligence now makes it easier to assign certain symptoms to a rare disease. It is impossible for doctors nowadays to know about every rare disease. Further, some immune disorders are very similar to each other. Patients could thus be spared years of searching for their correct diagnosis. In this way, treatment can be initiated earlier and the outcome may be improved”, says Boztug.

Matthias Haimel adds: “In our study, we use machine learning to narrow down the selection of possible diagnoses for patients and to retrieve the full spectrum of terms from the literature at the touch of a button. The same process could be applied to unstructured clinical notes. Abnormal clinical values in medical records could thus be automatically translated into HPO codes, promoting more accurate diagnosis.”

International Collaboration – The key to rare diseases

Identifying at least a few individuals worldwide suffering from the same disease is often critical to gain insight into typical manifestations. The now expanded and reannotated HPO terms allow for a better description of symptoms and enable the creation of an electronic disease profile. Efficiently sharing such anonymized disease profiles across institutions and borders is a major challenge. Platforms facilitating this are already being used by the LBI-RUD as part of the Undiagnosed Diseases Network International (UDNI) with the ultimate goal to cure patients with rare diseases.

The present work is based on an international collaboration, led by the LBI-RUD and the University Medical Center Groningen (The Netherlands), consisting of physicians, researchers, geneticists, and bioinformaticians. In total, more than 30 experts were involved over a period of two years. The project was conducted in collaboration with three of the world’s leading medical societies in the field of immune diseases, namely the European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune diseases (ERN-RITA), the European Society for Immunodeficiencies (ESID), and the International Society for Systemic Autoinflammatory Diseases (ISSAID).

About Human Phenotype Ontology

The Human Phenotype Ontology (HPO) includes a broad vocabulary to describe diseases and serves as a tool to communicate in the field of rare diseases. The HPO currently contains approximately 200,000 annotations to describe inheritable diseases, of which 2,120 are considered rare diseases. In the area of congenital immune disorders, clear and understandable descriptions have been lacking so far. Despite ongoing efforts, there are still crucial gaps in the HPO disease ontology to describe the entire clinical picture of rare immunological diseases.

About rare diseases

In Austria alone, approximately 400,000 people suffer from a rare disease. A disease is considered rare if it affects less than one in 2,000 people. Thus, although there is a large number of people suffering from a rare disease, there are only a few with the same specific disease. This leads to an enormous delay in the diagnosis and treatment of affected patients. If one wants to study rare diseases, a worldwide search for similar cases is necessary, which is often difficult.

Foto: (from left) Julia Pazmandi, Matthias Haimel, Kaan Boztug
Credit: St. Anna Children's Cancer Research Institute

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About the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD)
LBI-RUD was founded in April 2016 in a joint effort of Ludwig Boltzmann Gesellschaft, CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Medical University of Vienna, and St. Anna Children's Cancer Research Institute. The three founding partner institutions, and CeRUD Vienna Center for Rare and Undiagnosed Diseases, constitute LBI-RUD's most important collaboration partners. Research at LBI-RUD focuses on the deciphering of rare immunological, hematopoietic, nervous, dermal, gastro-intestinal, and hepatic diseases. Those studies provide unique insights into human biology and are the basis for the development of tailored therapeutic concepts in the sense of the personalized medicine of the future. The mission of LBI-RUD is – together with its partner institutions – to sustainably develop and maintain research infrastructure integrating scientific, societal, ethical, and economical aspects of rare diseases. www.rare-diseases.at

About the St. Anna Children's Cancer Research Institute, CCRI
St. Anna CCRI is an internationally renowned multidisciplinary research institution with the aim to develop and optimize diagnostic, prognostic, and therapeutic strategies for the treatment of children and adolescents with cancer. Closely collaborating with St. Anna Children's Hospital and other institutions worldwide, St. Anna CCRI combines basic research with translational and clinical research and focuses on the specific characteristics of childhood tumor diseases in order to provide young patients with the best possible and most innovative therapies. Dedicated research groups in the fields of tumor genomics and epigenomics, immunology, molecular biology, cell biology, bioinformatics and clinical research are working together to harmonize scientific findings with the clinical needs of physicians to ultimately improve the wellbeing of our patients. Learn more: www.ccri.at & www.kinderkrebsforschung.at.

About the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences
The mission of CeMM is to achieve maximum scientific innovation in molecular medicine to improve healthcare. At CeMM, an international and creative team of scientists and medical doctors pursues free-minded basic life science research in a large and vibrant hospital environment of outstanding medical tradition and practice. CeMM's research is based on post-genomic technologies and focuses on societally important diseases, such as immune disorders and infections, cancer and metabolic disorders. CeMM operates in a unique mode of super-cooperation, connecting biology with medicine, experiments with computation, discovery with translation, and science with society and the arts. The goal of CeMM is to pioneer the science that nurtures the precise, personalized, predictive and preventive medicine of the future. CeMM trains a modern blend of biomedical scientists and is located at the campus of the General Hospital and the Medical University of Vienna.
www.cemm.at

About the Medical University of Vienna (MedUni Vienna)
MedUni Vienna is one of the most established medical education and research facilities in Europe, with a centuries-old tradition of excellence in medical research and clinical practices. With almost 8,000 students, it is the largest medical training center in the German-speaking countries. With its 30 university hospitals and two clinical institutes, 12 medical theory centers and numerous highly specialized laboratories, it is also one of Europe's leading research institutions in the biomedical sector.
www.meduniwien.ac.at