**Mutations in SYK cause severe immune disorder with cancer predisposition**

**(Vienna, March 29, 2021) Researchers have deciphered the underlying mechanism of a previously unknown immune disorder that causes severe immune dysfunction involving the intestine, skin, and nervous tissues. The international research team could demonstrate that this disorder is caused by mutations affecting the signaling molecule termed spleen tyrosine kinase (SYK). The newly discovered mutations in the corresponding gene lead to a permanent activation of SYK - resulting in aberrant immune responses, severe inflammation and a susceptibility to lymphoma. By elucidating the mechanism of this disease, it is possible that affected patients may be offered targeted (“personalized”) treatment options in the future.**

Scientists at the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD), together with an international research team, have now succeeded in finding a previously unknown genetic cause of severe multi-organ inflammation. Genetic analysis revealed mutations in the gene encoding spleen tyrosine kinase (SYK). This is a protein molecule that is instrumental in signal transduction to activate the immune system. The patients identified in this newly published study showed a similar clinical picture with recurrent inflammation, impaired immune regulation, and a clear predisposition to the development of lymphomas. Lymphomas represent a type of cancer that originates from infection-fighting cells of the immune system, called lymphocytes.

**Tendency to infection and immune defense directed against the own body**"We were able to show for the first time that mutations in the *SYK* gene are the cause of this severe immune disorder," explains Daniel Mayr, shared second author and medical student in the research group of Kaan Boztug. "SYK is a key molecule in immune regulation and thus a potential target for therapies. Its mutation-induced hyperactivity leads to an impaired immune response, and both increased infections and attacks against endogenous structures by the immune system occur," explained Boztug, co-senior author of the study and Director of LBI-RUD and Scientific Director of the St. Anna Children's Cancer Research Institute. In the individuals described in the study, SYK overactivation resulted in immune defects and inflammatory responses of varying severity in the intestines, skin, joints, liver, and nervous system.

**Tailored prevention and treatment for *SYK* mutation?**

Patients with *SYK* mutations are also at increased risk for blood cancers and therefore require regular check-ups. The six patients analyzed in this study are in different locations around the world but had similar symptoms. "This study is again an example of how fundamental knowledge can be gained in rare diseases through a global collaboration. We are particularly excited about the very productive collaboration between our institution and lab and our colleagues in Vienna and other parts of the world!" elaborates co-senior author Prof. Aleixo Muise, MD PhD from the SickKids Children’s Hospital in Toronto. The new insight that all have the same cause of disease, facilitated a productive exchange of experience between the treating centers. Given the cancer predisposition identified in this disease, patients will now be examined regularly as part of an appropriate screening program.

Although so far only six individuals are known to have a molecular disorder in the *SYK* gene, a potential targeted treatment with a SYK inhibitor is already available to them, as this drug has already been approved for other diseases. Within the study presented here, no individual has yet been treated with a SYK inhibitor. However, future studies will investigate whether such an approach can be considered as a targeted ("personalized") treatment option, particularly for severe forms of the disease that are not well controlled with other treatment options.

**From rare to the basics**

LBI-RUD scientists are convinced that new discoveries about rare diseases always have benefits beyond those currently apparent. "Rare diseases help us decipher fundamental biological principles. New knowledge and deeper understanding of how these phenomena arise that will then ideally lead us back to the clinic and personalized treatments," says Boztug.

The present results are based on an international collaboration of LBI-RUD, St. Anna Children's Cancer Research Institute, the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences and the Medical University of Vienna with leading centers worldwide: SickKids Research Institute, Toronto, Children's Hospital of Fudan University, Shanghai, East China Normal University, Shanghai and University of Oxford.