PRESS RELEASE

More clarity on hereditary colorectal cancer

Bonn researchers reclassify leading gene variants, a large proportion of them as benign

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Bonn, October 1 - The genetic confirmation of a suspected diagnosis of "hereditary colorectal cancer" is of great importance for the medical care of affected families. However, many of the variants identified in the known genes cannot yet be reliably classified in terms of their causal role in tumor formation. Under the leadership of the University Hospital Bonn (UKB) and the University of Bonn, an international team of researchers has reassessed the medical relevance of a significant number of unclear variants and thus significantly reduced their number. The results of the study have now been published in the renowned journal "American Journal of Human Genetics".

Families with hereditary tumor diseases have a high risk of developing certain cancers such as colon cancer or breast cancer. For many common hereditary tumor syndromes, there are now very effective, intensive and early cancer screening programs and other preventive measures. Timely detection and reliable diagnosis of a hereditary predisposition is therefore extremely important for the families affected.

Due to increasingly comprehensive genetic testing, however, more and more genetic variants are being found in the responsible genes whose causal significance for the development of tumors is still unclear. These are referred to as variants of uncertain significance (VUS). As a result, more than 50 percent of the variants for some genes listed in public international databases (in particular ClinVar) are now VUS. "These cannot be used for diagnosis or for testing healthy people at risk; on the other hand, they often create great uncertainty, as carriers of a VUS may have an increased tumor risk," says co-senior author Dr. Isabel Spier from the Institute of Human Genetics.

Many gene variants have no relevance for tumor formation

Researchers at the UKB's Center for Hereditary Tumor Syndromes have been working for years on identifying new genetic causes of hereditary tumor diseases. To solve the problems associated with the interpretation of VUS, special classification criteria were developed under the leadership of the Institute of Human Genetics to improve the assessment of variants in the *APC gene*. Hereditary genetic changes in this gene are responsible for familial adenomatous polyposis (FAP), one of the most common causes of hereditary colorectal cancer or hereditary polyp diseases of the gastrointestinal tract. As part of the Hereditary

Colorectal Cancer / Polyposis Variant Curation Expert Panel (VCEP), Prof. Stefan Aretz's research group is working with an international and multidisciplinary team of experts based on a collaboration between the International Society for Gastrointestinal Hereditary Tumors (InSiGHT) and the Clinical Genome Resource (ClinGen). "The gene-specific classification criteria we developed have now allowed us to reclassify a significant proportion of VUS of the *APC gene* into a medically relevant category," says Prof. Aretz, who is also a member of the Transdisciplinary Research Area (TRA) "Life & Health" at the University of Bonn.

The research team evaluated all of the more than 10,000 *APC* germline variants listed in the public databases ClinVar and LOVD. Among the variants with an initial classification as benign or pathogenic, about 95 percent remained in their original category. In contrast, 41 percent of the VUS deposited in ClinVar and 61 percent of those in LOVD were reclassified into clinically significant classes, the vast majority of them as benign. It was also shown that extensive data mining, i.e. the comprehensive search for all genetic and clinical information available worldwide on a genetic variant, contributes very effectively to a better classification. Overall, the total number of VUS was reduced by 37 percent. "Since we were able to evaluate a large proportion of VUS as harmless norm variants, all carriers of these variants worldwide are relieved," says co-senior author Prof. Aretz, who would like to emphasize the close collaboration with first author Dr. Xiaoyu Yin from Melbourne in Australia during her six-months stay as a guest scientist at the UKB. The study also demonstrates the feasibility of variant classification in large data sets, which could also serve as a generalizable model for the interpretation of variants of other genes in the future.

Publication: Xiaoyu Yin et al: Large-scale application of ClinGen-InSiGHT *APC-specific* ACMG/AMP variant classification criteria leads to substantial reduction in VUS; American Journal of Human Genetics; DOI: https://doi.org/10.1016/j.ajhg.2024.09.002

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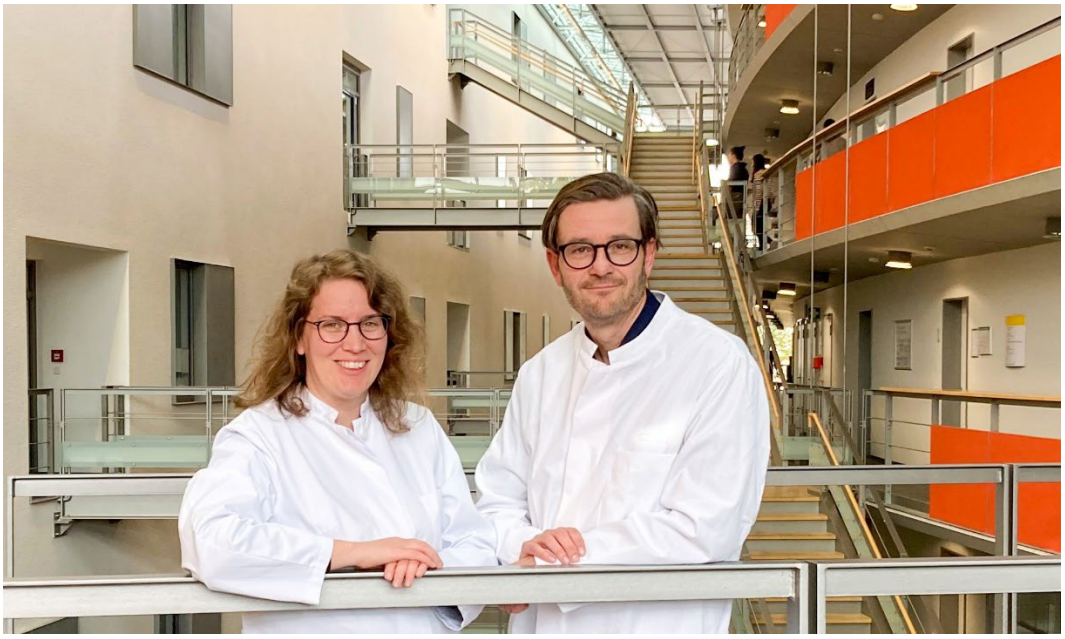

Caption: Research work led by Bonn researchers reduces gene variants of uncertain significance (VUS) in hereditary colorectal cancer: (from left) Dr. Isabel Spier and Prof. Stefan Aretz

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The Center for Integrated Oncology (CIO Bonn) is the interdisciplinary cancer center of the University Hospital Bonn and the Johanniter Hospital Bonn. All UKB clinics and institutes involved in the diagnosis, treatment and research of all oncological diseases work together under its umbrella. The CIO Bonn is part of the nationwide network of selected top oncology centers of the German Cancer Aid. Together, this network “Center for Integrated Oncology - CIO Aachen Bonn Cologne Düsseldorf” shapes cancer medicine for around 11 million people.

About Bonn University Hospital: The UKB treats around 500,000 patients per year, employs around 9,500 staff and has total assets of 1.8 billion euros. In addition to the 3,500 medical and dental students, 550 people are trained in numerous healthcare professions each year. The UKB is ranked first among university hospitals (UK) in NRW in the Focus Clinic List, had over 100 million third-party funds in research in 2023 and has the second highest case mix index (case severity) in Germany. The F.A.Z. Institute awarded the UKB first place among university hospitals in the category "Germany's Training Champions 2024".