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ERA Long-Term Research Fellowship Project

G&K

Project's key info

Title of the project	**Integrated serum and urine-omics analyses in autosomal dominant polycystic kidney disease (ADPKD) as a source of biomarkers and mechanistic insight**
Working Group involved in the project	Genes & Kidney Working Group (G&K)
Principal Investigator(s) of the project	Roman-Ulrich Müller (Germany)
Duration	12 months
Fellowship Grant	34.545,00 €
Start of the fellowship	Within 6 months after notification of the grant award to the fellow.

Receiving Institute

Name of receiving institute	University Hospital Cologne, Department for Internal Medicine Nephrology, Rheumatology, Diabetology and General Internal Medicine, Cologne, Germany
Supervisor's name	Genes & Kidney Working Group (G&K)
Supervisor's e-mail address	roman-ulrich.mueller@uk-koeln.de

Project's detailed description

Project description
In recent years, several studies have indicated the contribution of metabolic alterations to the pathogenesis of ADPKD, including the activation of aerobic glycolysis through the Warburg effect, and the reprogramming of asparagine and glutamine metabolism. These findings are potential therapeutic targets for the pathogenesis of ADPKD. Moreover, metabolic profiles aggregate external factors which could exacerbate disease progression and account for disparities in the severity of the ailment within families. Currently available prediction algorithms of outcome (e.g. Mayo Classification or PROPKD score) lack accuracy and only explain a small proportion of the individual variability in ADPKD. Interestingly, the research team has recently been able to strongly improve outcome prediction in our cohort of > 1200 patients using a novel automated mass spectrometry (MS) platform to obtain unbiased serum proteomics data (unpublished data, manuscript in preparation). Combining these datasets with metabolite abundance in an integrated analysis effort holds the promise not only to improve outcome prediction but also to provide mechanistic insight into the pathophysiology underlying rapid disease progression. To prepare this project, research team has already acquired NMRbased metabolomics data from serum and urine samples of 1000 patients. Importantly, this includes data from the recent KETO-ADPKD trial which examined ketogenic diets as a potential metabolic therapeutic approach to ADPKD (CRMEDICINE-D-23-00671_R2, Cell Reports, accepted for publication). In addition to the targeted NMR panel, these samples have now also been used for metabolite quantification employing a targeted MS-based approach in collaboration with Prof. Markus Rinschen (Aarhus, Denmark). In conjunction

with the large number of cross-sectional data from the entire cohort, these results will shed light on modifiable metabolic alterations in a dynamic and longitudinal fashion.
Goals of the project
The objective of this project is to characterize the metabolic pathways responsible for the progression of ADPKD to enhance our understanding of pathophysiology and identify potential novel therapeutic targets. Furthermore, the project aims to integrate clinical characteristics and serum proteomics obtained from the AD(H)PKD registry and predict the progression of ADPKD using data from > 1200 patients (AD(H)PKD cohort) with a follow-up of up to 8 years. This integrative computational analysis will be led and conducted in close cooperation with the computational biology department at the Cologne Center for Molecular Medicine (Dr. Philipp Antczak).

Qualifications and/or expertise required to the fellow

We welcome highly motivated candidates who have or expect to have an MD degree and further:

- Scientific publishing experience;
- High level of self-motivation, commitment, and work ethics;
- Excellent communication skills (English);
- Social competence.