Examiner's report on thesis

Name of PhD candidate **:** Kendrah Kidd

Title of thesis **:** Identification and Characterization of Individuals with Inherited Kidney Disease

The thesis of Kendrah Kidd reports new approaches to identify and characterize individuals with inherited kidney disease, specifically autosomal dominant tubulointerstitial kidney disease (ADTKD). The thesis is well-structured and written in English meeting the standards for a PhD thesis.

The introduction (Chapter 1) as well as the introductory parts of Chapters 4.1–4.5 show that the candidate is an expert in the field. The introduction includes several figures and tables which are useful for the reader to understand the background of the topic. In the thesis, five specific aims with regard to ADTKD are formulated, including prevalence (aim 1), genetic classification (aim 2), pathophysiology (aim 3), disease progression (aim 4), and identification of new *MUC1* pathogenic variants (aim 5). To address these specific aims, the PhD candidate helped develop a patient workflow to generate a rare inherited kidney disease (RIKD) registry. This workflow combined clinical and genetic data and biobanking of DNA, plasma and urine (Figure 1, page 3). The methods for this workflow as well as for the other individual studies are clearly described with sufficient details.

By using an outreach program to health care providers and directly to patients, the RIKD registry has increased to 768 families and 2079 individuals with ADTKD. This has improved the ability to better define and understand disease characteristics (Aim 1, Chapter 4.1). Three distinct subtypes of ADTKD-*REN* were identified with signal peptide variants leading to an earlier onset of disease and prosegment variants leading to an intermediate presentation (Aim 2, Chapter 4.3). A new form of ADTKD was reported, ADTKD-*APO4*, in which a mutant apolipoprotein in the circulation causes medullary amyloid deposits in the kidney (Aim 3, Chapter 4.5). Predictors for disease progression of ADTKD-*UMOD* were identified (Aim 4, Chapter 4.2), including age of first gout attack and age of patient reaching kidney failure (especially with maternal transmission) and mUMOD *in vitro* score (an *in vitro* score for the maturity of secreted *UMOD*). Finally, five novel *MUC1* pathogenic variants were found (Aim 5, Chapter 4.4) by applying a method analyzing patient urine cells for presence of MUC1-fs followed by Illumina sequencing. In the discussions related to the individual aims (Chapters 4.1–4.5), the candidate shows that she is able to critically evaluate her results, compare them to current knowledge and formulate original conclusions. The references are appropriate with good choices of original and recent articles.

There are five publications related to the dissertation which were published between 2020 and 2024. The PhD candidate is first, second or third author on these publications. The publications were in high-ranking, peer-reviewed nephrology or genetic journals.

After presenting the results and conclusions pertaining to the aims of the thesis, the PhD candidate also reflects on future research. The plans formulated include modeling of ADTKD disease progression by analyzing eGFR slopes, exploring the reasons for increased susceptibility of patients with ADTKD-*MUC1* for COVID-19, analyzing transplant outcomes of patients with ADTKD, low fat diets for *APOA4* variants and the application of new genetic strategies to explore ADTKD-*unknown.*

Summary: The presented work by Kendra Kidd is of considerable scientific and clinical importance. The thesis fulfils all the criteria for a doctoral thesis, including demonstration of independent scientific work. I therefore support awarding the candidate the academic degree of doctor (abbreviated as PhD. – after the name).

Questions

1. I would like to invite the PhD candidate to discuss her individual key contributions to the various studies in the PhD thesis. Based on my assessment, I have no doubt that she was in fact one of the investigators leading the studies and provided important intellectual contributions, but because she is embedded in a larger team ('team science') and in the publications she is not always the first author, I think it would be good to discuss this with the candidate during the defense.

2. The thesis illustrates the remaining challenges regarding the diagnosis of ADTKD-*MUC1*. Based on the work and expertise of the candidate, I would like to ask her how she envisions that the diagnosis of ADTKD-*MUC1* can be further improved in the future? Does she believe this will be through new sequencing approaches (e.g. PacBio single molecule real-time sequencing), bioinformatic approaches (e.g. Mutation Counter, Fages et al., Kidney Int Rep 2024) or does she advocate to combine genetic testing with a urinary test (staining for MUC1-fs)? How would she design a study to test the clinical performance of the proposed new strategy?

3. The obvious next step in the ADTKD field is to start testing treatments. I would like to invite the PhD candidate to provide her thoughts on this challenging next step. Which approaches would she envision? Does she think it will be possible to define 1 treatment for all forms of ADTKD or do they all require individual treatment strategies? Does she think it will be possible to deliver drugs specifically in the affected kidney tubule cells and, if so, how? Does she believe patients with ADTKD might benefit from emerging kidney-protective therapies for general CKD progression, including SGLT2-inhibitors, non-steroidal mineralocorticoid receptor antagonists and endothelin receptor antagonists?

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