Supervisor´s assessment

Doktorand:

Kendrah Kidd, MSc.

Title of thesis:

Identification and Characterization of Inherited Kidney Disease

Study program:

Molecular and Cellular Biology, Genetics and Virology

End-stage kidney disease (ESKD) is associated with high morbidity and mortality, with the cause of ESKD unknown in many cases. At least 10% of patients have a genetic cause of ESKD, with many undiagnosed. Autosomal dominant tubulointerstitial kidney disease (ADTKD) is characterized by a bland urinary sediment and chronic kidney disease (CKD) leading to ESKD at a mean age of 45y. The most common genetic causes of ADTKD are pathogenic variants in *UMOD, MUC1*, and *REN*, with an unknown cause in 15%.

The aim of Kendrah Kidd´s thesis was to identify and characterize families with ADTKD and other rare tubulo-interstitial kidney diseases, leading the way to greater understanding of the pathobiology of these diseases and opening doors for future therapies. This work has built on a long-term, highly effective collaboration between the First Faculty of Medicine, Charles University and Wake Forest School of Medicine, Winston-Salem, NC.

Within the project, Kendrah Kidd developed, the RIKD REDCap database, an interactive computer database that allowed direct contact with participants, clinicians, and researchers. This registry/biobank prospectively collects patient information, laboratory measurements, biopsy and ultrasound reports, genetic testing reports as well as biomaterials for multiple studies. Over time, the RIKD biobank has collected information on 1019 ADTK-UMOD, 930 ADTKD-MUC1 and 130 ADTKD-REN patients and received over 7000 samples. The database currently houses >1500 variables and >10000 records.

Kendrah Kidd oversaw and instituted laboratory protocols to collect and archive biologic samples, isolate nucleic acids, and prepared materials and specimens for appropriate genetic, biochemical, molecular and immunohistochemical testing. She assisted in identification, interpretation and functional characterization of genetic variation identified by whole-exome and whole-genome sequencing. She created patient surveys to assess ADTKD clinical characteristics. Since 2018, she has recruited 238 new ADTKD families, increasing our total number of families to 1100. She contributed

to identification of multiple known and new *UMOD, MUC1*, and *REN* pathogenic variants in 126, 297, and 115 individuals, respectively. She was involved in identification of *APOA4* as a new genetic cause of ADTKD. She identified an *in vitro* score of UMOD processing, gout, parental age of ESKD, and gender as factors associated with ADTKD progression. She contributed to identification of distinct subtypes of ADTKD-*REN.* Her work significantly increased our knowledge of the prevalence, characteristics, and genetic causes of ADTKD. Results of the project represent an important step forward towards future ADTKD clinical trials and provide a framework for other researchers in rare kidney diseases.

Kendrah Kidd's experimental expertise, organizational skills and professional level are best documented by her co-authorship of total of 35 research papers (with 28 of them published during her PhD program) that have been published mostly in major international journals in the field, such as Kidney International, Kidney International Reports, Nature Communication, Journal of Biological Chemistry, Proceedings of the National Academy of Sciences, American Journal of Nephrology, Genetics in Medicine, Journal of the American Society of Nephrology, Human Molecular Genetics or American Journal of Human Genetics with >650 citations and h-index 14. Kendrah Kidd played a significant role in all these studies and many of them would not have reached this level without her expertise.

Kendrah Kidd has become respected scientist coordinating research and laboratory activities internationally. She has been nominated to curate *UMOD*, *SEC61A1* and *mtRNA* genes in the ClinGen, the NIH-funded resource dedicated to build up a central resource that defines the clinical relevance of genes and variants for use in precision medicine. She has been invited and spoken internationally at the Annual ADTKD Summits at the Broad Institute of MIT and Harvard, and the MUC1 Kidney Disease Spring Retreat, Cambridge, MA, USA.

In my opinion, Kendrah Kided has certainly fulfilled the assigned topics of the dissertation and has demonstrated the ability to work independently in science.

Based on the submitted dissertation, I recommend awarding Kendrah Kidd the title of Ph.D.

Prague, 24.6.2024 Prof. Ing. Stanislav Kmoch, CSc.