Abstract

Background: 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%. **Specific Aims**: (1) To better understand ADTKD prevalence by expanding outreach. (2) To classify ADTKD families genetically and identify new genetic causes. (3) To expand existing knowledge of ADTKD pathophysiology. (4) To better characterize ADTKD clinically and identify factors associated with progression. (5) To identify novel *MUC1* pathogenic variants in undiagnosed ADTKD families. Methods: I developed an interactive computer database that allowed direct contact with participants, clinicians, and researchers. I oversaw and instituted laboratory protocols to collect samples, isolate DNA, and send for appropriate genetic testing. I assisted in interpretation of genetic variants. I created patient surveys to assess ADTKD clinical characteristics. **Results:** Since 2018, we recruited 238 new families, increasing our total number of families to 1100. We identified *UMOD, MUC1*, and *REN* pathogenic variants in 126, 297, and 115 individuals. We identified *APOA4* as a new genetic cause of ADTKD. We identified an *in vitro* score, gout, parental age of ESKD, and gender as factors associated with ADTKD progression. We identified distinct subtypes of ADTKD-*REN.* **Conclusion**: We significantly increased our knowledge of the prevalence, characteristics, and genetic causes of ADTKD. Future work will focus on identification of new therapies, based on our clinical, genetic, and pathophysiologic findings.