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Dissertation Abstract

Identification and Characterization of Inherited Kidney Disease

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Abstrakt

Úvod: Selhání ledvin (ESKD) je spojeno s vysokou morbiditou a mortalitou. Příčina ESKD je často neznámá. Asi 10 % případů ESKD je podmíněna geneticky. Autosomálně dominantní tubulointersticiální onemocnění ledvin (ADTKD) je charakterizováno chronickým onemocněním ledvin (CKD) vedoucím k ESKD ve věku okolo 45 let bez proteinurie a hematurie. Nejčastější genetickou příčinou ADTKD jsou patogenní varianty *UMOD*, *MUC1* a *REN*, asi 15% případů má neznámou genetickou příčinu. **Cíle:** (1) Zvýšení povědomí o ADTKD mezi klinickými nefrology. (2) Správná genetická klasifikace ADTKD a identifikace nových genů a jejich variant podmiňujících ADTKD. (3) Rozšíření znalostí patogenetických mechanismů ADTKD. (4) Prohloubení znalostí klinické charakterizace ADTKD a identifikace faktorů ovlivňujících progresi ADTKD. (5) Identifikace nových patogenních variant *MUC1* v rodinách s ADTKD a vyloučenou prevalentní variantou duplikace cytosinu ve VNTR *MUC1*. **Metody**: V rámci práce studentka vyvinula interaktivní databázi umožňující přímý kontakt s pacienty, lékaři a výzkumníky. Studentka zavedla laboratorní protokoly pro izolaci DNA a odběr a odesílání vzorků na příslušné genetické testování. Významně se podílela na interpretaci identifikovaných genetických variant. Dále vytvořila pacientské dotazníky pro zlepšení znalosti klinických charakteristik ADTKD. **Výsledky**: Od roku 2018 jsme rozšířili náš ADTKD registr o 238 nových rodin na celkový počet 1100. Patogenní varianty *UMOD, MUC1* a *REN* jsme identifikovali u 126, 297 resp. 115 případů. Nalezli jsme patogenní varianty *APOA4* jako nové genetické příčiny ADTKD. Identifikovali jsme faktory spojené s progresí ADTKD, což jsou typ patogenní varianty, dna, věk ESKD u rodičů a pohlaví. Definovali jsme odlišné klinické podtypy ADTKD-*REN*. **Závěr**: Zvýšili jsem schopnost nefrologů rozpoznat ADTKD a tím zlepšili správnost určení diagnózy ve skupině CKD. Dále jsme rozšířili spektrum genetických příčin ADTKD a identifikovali faktory ovlivňující progresi ADTKD.

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.

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1 Introduction

It is estimated that 10% of adults with advanced chronic kidney disease (CKD) have an inherited kidney disease (IKD) [1]. To date, there are over 380 genes associated with IKD [2].

1.1 Autosomal Dominant Tubulointerstitial Kidney Disease

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a group of rare inherited kidney diseases characterized by autosomal dominant inheritance and slowly progressive chronic kidney disease (CKD), leading to end stage kidney disease (ESKD) at a mean age of approximately 45 years (range 20-80 years)/ Patients present with no blood or protein in their urine and an elevated serum creatinine[ref]. Kidney ultrasound often shows small echogenic kidney with or without cysts. Kidney biopsy reveals nonspecific findings of tubulointerstitial fibrosis and tubular atrophy [3]. This broad phenotype makes ADTKD difficult to identify and diagnose clinically.

1.2 Genetic Heterogeneity of ADTKD

ADTKD is genetically heterogeneous. In 2002, *UMOD* was the first gene identified as a cause of ADTKD [4]. *REN, MUC1*, and *SEC61A1* were subsequently identified as causal genes [5-7].

1.2.1 ADTKD-UMOD

Individuals with ADTKD-*UMOD* have pathogenic variants in *UMOD*. The *UMOD* gene encodes the protein uromodulin, the most abundant protein in human urine [4]. UMOD is a glycoprotein exclusively produced by the thick ascending limb (TAL) of the loop of Henle [Figure 1]. While the function of uromodulin remains uncertain, recent studies suggest that it may be important in sodium reabsorption, prevention of urinary tract infections, and prevention of nephrolithiasis.. Mutations in UMOD (mUMOD) lead to aggregation within the endoplasmic reticulum (ER), leading to ER

stress and induction of the unfolded protein response (UPR) [10]. Hyperuricemia or gout may also be present in patients with ADTKD-*UMOD* [3].

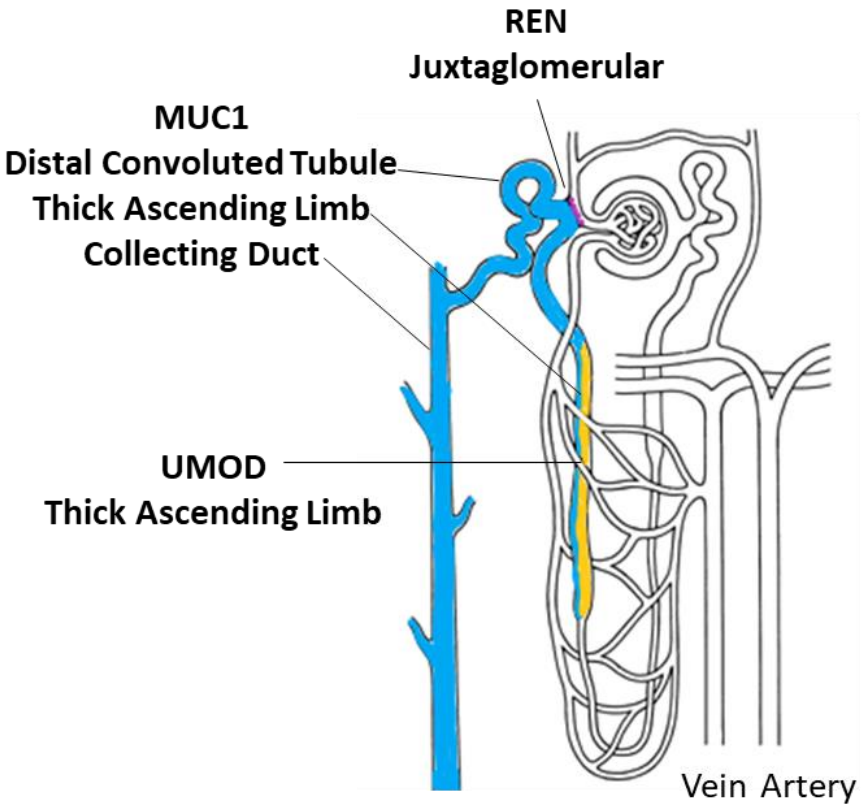

Figure 1. ADTKD gene expression in the nephron. UMOD is expressed in the thick ascending limb (yellow). MUC1 is expressed in the distal convoluted tubule, thick ascending lime and collecting duct (blue). REN is expressed in juxtaglomerular cells (purple).

1.2.2 ADTKD-REN

Individuals with ATKD-*REN* have pathogenic variants in *REN. REN* encodes REN, which is a major component of the renin-angiotensin-aldosterone system (RAAS). REN is expressed mostly by the juxtaglomerular cells of the nephron [Figure 1] [12]. REN mutations result in a marked reduction in wild-type REN production, resulting in low renin and aldosterone levels, mild hypotension, hyperkalemia, acidemia, and anemia. In addition, mutated REN is deposited intracellularly, leading to the unfolded protein response, tubular cell stress, apoptosis, tubulointerstitial scarring, and chronic kidney disease [5].

1.2.3 ADTKD-MUC1

Individuals with ADTKD-*MUC1* have a pathogenic variant in *MUC1*. *MUC1* encodes mucin-1, a membrane-bound glycoprotein mucin that is expressed in epithelial cells, including the TAL, distal convoluted tubule and collecting duct of the nephron [Figure 1]. ADTKD-*MUC1* is caused specifically by pathogenic variants that lead to a 3n+1 frameshift mutation (MUC1-fs) in the variable number of tandem repeats (VNTR) region of *MUC1* [6]. Due to the high GC content of the MUC1 gene, the presence of 20-125 repeats, and genetic variation within the VNTR repeats, *MUC1* genetic testing cannot be performed using traditional Sanger sequencing. Due to mundane clinical characteristics (chronic kidney disease and bland urinary sediment) and difficulties in genetic sequencing, diagnosis of ADTKD-*MUC1* is very difficult. [3, 11].

1.2.4 ADTKD-Unknown

Approximately 15% of families with ADTKD do not have a pathogenic variant in *UMOD*, *REN*, or *MUC1* [13]. These families either have a *MUC1* pathogenic variant that cannot be identified or an as of yet unidentified cause of kidney disease.

2 Specific Aims

To further our understanding of ADTKD, we proposed the following specific aims:

1. To more accurately determine the prevalence of ADTKD by expanding outreach to families with this condition.

2. To classify families with ADTKD genetically and to identify new genetic causes of ADTKD.

3. To expand existing knowledge of ADTKD pathophysiology.

4. To better characterize ADTKD clinically and identify factors associated with CKD progression.

5. To identify novel *MUC1* pathogenic variants in suspected ADTKD-*MUC1* families who tested negative for the +C duplication that commonly causes ADTKD-*MUC1*.

3 Methods

3.1 Research Framework

The author led the development of a research framework that would allow the following [Figure 2]:

1. Accessibility for patients, academic physicians, and private practice physicians to contact us and receive evaluation as to whether ADTKD was present.
2. Development of a registry that allows input of each new patient/family. The registry is developed in such a way that Wake Forest maintains all patient identifiers, but other groups (including the Charles University, Broad Institute, and other research organizations) have access to de-identified information

on an active basis through the Internet. Other centers can both obtain data and enter data.
3. Development of methodology for obtaining blood, plasma, and urine samples from any location within the US within 24 hours, with processing of these materials for laboratory research testing.
4. Development of methodology to receive blood or DNA shipments from anywhere in the world.
5. Email contact with patients individually or in aggregate, allowing for the sending of surveys, test results, and updated information on ADTKD.
6. Development of methods to transfer patient specimens accurately, maintaining the integrity of the samples and preventing misidentification of samples.
7. Development of methods to obtain results and provide to patients.
8. Ability to aggregate genetic results for further analysis.
9. These methods were developed to allow processing of at least 400 samples/year.
10. Development of protocols for biobanking of samples for further research.

3.2 WF-RIKD Laboratory Procedures

All patient samples are received by WF and processed according to established methods. Samples typically include blood or saliva for DNA isolation, urine, and plasma for biobanking. DNA isolation is performed utilizing standard procedures. Biobank samples are organized and stored in ultra-low temperature freezers. Urinary cell smears are prepared for MUC1fs staining as described [14]. Samples are de-identified and organized for shipments according to specific projects and analyses.

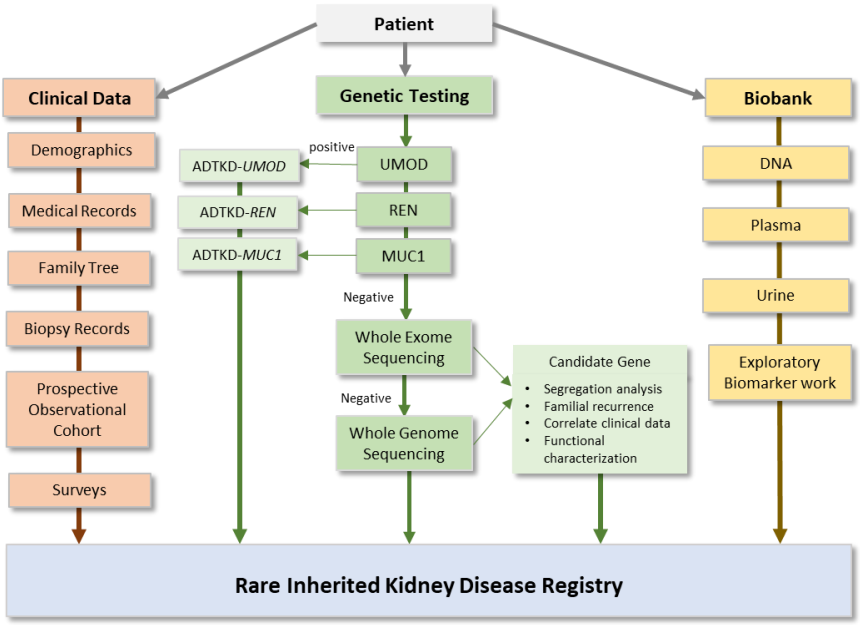

Figure 2. Charles University-Wake Forest Rare Inherited Kidney Disease (RIKD) Team Research Framework. Patients enter the study and their clinical, genetic and biobank data are integrated and stored in the inherited kidney disease (IKD) registry.

3.3 Genetic Testing

UMOD and *REN* are evaluated using standard Sanger sequencing procedures. *MUC1* samples are prepared according to protocol in association with The Broad Institute of Harvard and MIT Cambridge, MA where *MUC1* analysis is performed [15]. Whole-exome and whole-genome sequencing of ADTKD-*Unknown* families may also be performed [7, 16]. Rare pathogenic variants or families suspected of having a rare *MUC1* variant undergo PacBio single molecule real-time (SMRT) sequencing of their *MUC1* VNTR [manuscript in progress]. WF is the sole coordinating center

for The Broad's *MUC1* testing worldwide and are the only providers of *MUC1* testing in the United States.

3.4 RIKD REDCap Registry

The RIKD registry was developed, built, and curated by the author using the REDCap virtual software platform. REDCap is an NIH-supported data capture system that is HIPAA compliant [17]. The RIKD registry contains each patient's entire research record [Figure2]. Additional REDCap projects have been developed as surveys for patients to answer directly regarding topics of interest to ADTKD patients, clinicians, and researchers: comprehensive health and diet, quality of life [18], women's health [19], COVID-19 [manuscript in progress], also a prospective observational study of ADTKD patients who are pre-ESKD. The REDCap registry currently houses data on 9640 inherited kidney disease patients, with 1441 possible data elements.

3.5 Dataset Preparation and Analysis

Utilizing data captured in the RIKD REDCap registry, the author generated large datasets according to the aim of the project. Data were curated and verified with source documentation as needed. Standard statistical methods were performed: descriptive statistics, t-test, Chi-square, survival analysis, as well as univariate and multivariate analyses [11, 13, 18-21].

3.6 Development of an *UMOD in vitro* Score

Thirty-five *UMOD* pathogenic variants were identified that were prevalent in the ADTKD-*UMOD* cohort and/or were associated with a younger or older mean age of ESKD. HEK293 and/or MDCK cell lines were transfected with an expression vector for each selected variant by the laboratory of Dr. Luca Rampoldi. Cells were lysed and analyzed by Western blot. A score was developed based upon the ratio of ER retained mUMOD and mature

glycosylated UMOD in the cells. Four classes were determined with 1 having the most mature UMOD observed to 4 having the most mUMOD retained within the ER [20].

4 Results and Discussion

ADTKD is a slowly progressive kidney disease, with marked intra and inter-familial variance in disease progression. According to our registry data, the rate of decline is often not linear and may occur over 20-50 years [3]. Identification of individuals with ADTKD, paired with data organized and maintained in a consistent method, easily accessible for generation of dataset for analysis [Figure 2] has allowed our team to enhance the existing knowledge of ADTKD.

4.1 Expanding Outreach to Increase Understanding of ADTKD Prevalence

As ADTKD is a rare condition, data from each patient increases our knowledge about this condition and increases statistical power for clinical, genetic, and pathophysiological characterization. Outreach to families, clinicians and other research teams is vital to continue identifying patients with ADTKD to expand data collection and understanding of this disease.

We characterized diagnostic outcomes of individuals referred to our RIKD registry, evaluating 275 families referred with an ADTKD phenotype who underwent genetic testing. Healthcare providers (HCP) provided 73% of referrals and direct family contacts utilizing the Internet provided 27% of referrals. 171 families (62%) and 567 family members were genetically diagnosed with ADTKD. Of those diagnosed with ADTKD, 42 (25%) were families and 116 (21%) were family members resulting from direct family contact without referral from their physician. Notably patients who were self-referred had the same probability of being diagnosed with ADKTD as referrals from physicians [13].

The RIKD Team collaborates with over 130 IKD research teams throughout the Czech Republic, European Union, United States, United Kingdom, Canada, Australia, and South America. In 2018, at the start of the author's doctoral program, there were 509 families and 1541 individuals in the registry. Since 2018, there has been in ancrease to 768 families and 2079 individuals with ADTKD (Table 1), an increase of 51% in families and 35% in individuals identified with ADTKD. Our collaborative work in identifying ADTKD patients has led to publications better defining and understanding this disease [11,13,20-23].

Table 1. RIKD ADTKD Registry. Current number of individuals and families with ADTKD entered in the RIKD registry.

ADTKD-		WF-RIKD	Collaborator	Total
UMOD	Individuals	647	372	1019
	Families	245	156	401
MUC1	Individuals	449	481	930
	Families	150	180	330
REN	Individuals	28	102	130
	Families	14	23	37
Total	Individuals	1124	955	2079
	Families	409	359	768

4.2 Clinical and Genetic Predictors of Disease Progression in ADTKD-*UMOD* and -*MUC1*

We published studies describing two large cohorts of ADTKD-*UMOD* patients (n=722 and n=216), and one large cohort of ADTKD-*MUC1* patients (n=93), identifying clinical and genetic predictors of disease progression [11,20].

Clinical predictors of ADTKD-UMOD

Clinical data evaluated included: gender, weight, height,

smoking status, gout presence and age of 1st gout attack, kidney function and family history of ESKD. Body mass index (BMI), smoking status, and presence of gout were found non-significant in predicting decline to ESKD. The best clinical predictors of disease progression were: the age of first gout attack (P<0.0001), male gender (P=0.0028), familial age of ESKD (P=0.009) and age of parent reaching ESKD (P=0.0045), especially if the mother was the affected parent (P=0.0017) [11,20].

Genetic Predictors of ADTKD-UMOD

125 unique *UMOD* pathogenic variants were evaluated for association with disease progression, including position, domain location, amino acid substitution, and resultant property. No association was found with the type of pathogenic variant and progression to ESKD [20].

The rs4293393 G allele is found in the *UMOD* promoter and has an allele frequency of 19% and is associated with a 50% decrease in UMOD synthesis. We hypothesized that if the G allele was present prior to the *mUMOD* allele, affected individuals would likely produce less mUMOD and have a later age of onset of ESKD. In our analysis, we found an allele frequency of 12% in mUMOD families vs. the 19% expected, indicating a likely protective effect. Unfortunately, due to this decreased allele frequency, the study population did not meet Hardy-Weinberg equilibrium and precluded further Mendelian randomization analysis [20].

Schaffer and colleagues had noted that transport and glycosylation of mUMOD varied by mutation type [10]. With milder mutations, more mature glycosylated UMOD was secreted and less mUMOD was retained in the endoplasmic reticulum. These authors created a score from 1 to 4, with 1 having the most mature UMOD secreted and least mUMOD retained intracellularly, and a score of 4 having the most mUMOD retained within the ER and the least mature UMOD secreted. In our statistical analysis, we were able to show that a lower *in vitro* score correlated with a later age of onset of ESKD. We have applied the findings of this study to

characterize new pathogenic variants, assess whether they are benign, and help to predict the mean age of ESKD for individuals affected with *de novo* pathogenic variants [20]. Use of the *in vitro* score may also be helpful in stratifying patients in future clinical trials.

***Clinical Predictors of ADTKD*-MUC1**

Individuals with ADTKD-*MUC1* have an earlier age of kidney failure compared to ADTKD-*UMOD* (36 years vs 46 years, $P<0.0001$). Gout was present in 26% of ADTKD-*MUC1* patients, with the age of onset significantly later than that seen with ADTKD-*UMOD* (45 years vs 27 years) [11]. The lack of further clinical features, combined with the complexity of *MUC1* genetic testing, make ADTKD-*MUC1* challenging to diagnose [3]. Further examination and data modeling are required for this condition.

4.3 Identification of Three Distinct Subtypes of ADTKD-*REN*

A study of 111 individuals with ADTKD-*REN*, evaluated the clinical, genetic and pathophysiology characteristics associated with 15 pathogenic *REN* variants. The author assisted in collection of families, data analysis and interpretation, and creation of the manuscript. Pathogenic variants in the signal peptide (SP) of renin were found to be associated with early onset of disease and earlier age of ESKD. The SP mutant REN is unable to translocate to the ER for post-translational modification and accumulates in the cytoplasm. Pathogenic variants in the prosegment of renin were associated with an intermediate clinical phenotype. The prosegment mutant renin accumulates in the ER-Golgi intermediate compartments (ERGIC). Pathogenic variants in mature renin were associated with an older age of onset, often presenting similar to ADTKD-*UMOD* with gout developing in the late teenage years. The mutant mature REN accumulates in the ER, again similar to the pathophysiology seen with ADTKD-*UMOD* [21].

Identification of these three distinct subtypes based upon location of the pathogenic variant is helpful for prognosis and counseling patients with ADTKD-*REN*.

4.4 Identification and Characterization of *APOA4* as a Novel Cause of ADTKD

A large family was referred in 2015 with an ADTKD phenotype: autosomal dominant inheritance, slowly progressive CKD, and a bland urinary sediment. The proband's kidney biopsy showed tubulointerstitial fibrosis, sclerotic glomeruli and tubular atrophy. The proband tested negative for pathogenic variants in *UMOD*, *MUC1* and *REN*. Whole-genome sequencing was performed on five clinically affected family members, revealing a shared region at chromosome 11q23.2. *APOA4* was the only candidate gene for the region, with a shared missense p.Leu66Val variant among those tested. *APOA4* encodes apolipoprotein A-IV (ApoA4). ApoA4 is expressed in the small intestine, enters circulation and is filtered by the glomerulus, reabsorbed and degrade in the proximal and distal tubules [ref Kidney biopsies revealed medullary amyloid deposits, with mutant ApoA4 as the predominant amyloid fibrils [ref]. Mutant APOA4 deposition was not detected elsewhere in the body, and there were no clinical manifestations other than kidney disease [16].

Evaluation of ADTKD-*Unknown* families with whole-exome or whole-genome sequencing identified another two families with APOA4 p.Leu66Val and two families with p.Asp33Asn. Segregation analysis of the five families identified 48 genetically affected individuals; 44 individuals having lowered kidney function and all 25 individuals who had already reached ESKD [16].

This finding expands the known genetic heterogeneity of ADTKD. Patients have clinical findings consistent with ADTKD and should be genetically tested for *UMOD, MUC1*, and if negative, tested for *APOA4.* Genetic testing for these families would preclude

the need to perform kidney biopsies, which often do not include medullary tissue for amyloidosis identification.

4.5 Identification of Novel ADTKD-*MUC1* Pathogenic Variants

Due to genetic testing difficulties of the *MUC1* VNTR and the current methodology capturing the +C duplication only, our team developed to screen for non +C duplication MUC1 pathogenic variants. Patient urine cells can be stained for presence of MUC1-fs. If positive, the families underwent Illumina sequencing and six families were identified with five novel *MUC1* pathogenic variants [14].

Whole-exome sequencing does not reliably cover the entire *MUC1* VNTR for every person due the variation in repeats and high GC content [2]. However, we have two families in the RIKD registry identified by whole-exome sequencing. One family has a novel 25 base-pair duplication (3n+1) resulting in MUC1-fs [24, and another with the +C duplication was identified as a variant of uncertain significance in a large whole-exome sequencing study without further follow-up [25].

For many of the ADTKD-Unknown families, sequencing of the VNTR is critical. Our team has developed a real-time single-molecule sequencing workflow using PacBio technology. Prioritizing families for the PacBio workflow can be done by applying our MUC1-fs screening technique. We have already identified an additional 10 families with novel MUC1 variants utilizing this method [manuscript in progress].

4.6 Future Research

Since 2018, we have increased family recruitment in our ADTKD registry by 51% and individuals by 35%. This increase helps us to perform more robust natural history studies, understand

disease prevalence and will help provide patients for future clinical trials and we will continue our efforts to recruit families for identification of ADTKD. In the future we plan to increase family recruitment and further characterize ADTKD.

We will model disease progression of our ADTKD patients utilizing the over 5600 serum creatinine values housed in the RIKD registry to better understand changes in kidney function over time.

We have identified an 8-fold increased risk of COVID-19 in individuals with ADTKD-*MUC1*, and we are submitting a manuscript regarding this finding.

We plan to study transplant outcomes and the causes of death in ADTKD patients post-transplant.

We are using increasingly advanced genetic techniques as they become available to identify new genetic causes of inherited kidney disease in the undiagnosed ADTKD families.

We are evaluating potential therapeutic agents for future clinical trials. We have a prospective cohort of ADTKD-UMOD and-MUC1 patients who obtain clinical labs paired with a health survey every 3-4 months who will be well phenotyped when a trial is ready to begin.

We are planning to study low fat diets in patients with *APOA4* pathogenic variants to see if this will lower ApoA4 production and ameliorate kidney disease progression.

5. Conclusions

Within the frame of our RIKD team's long-term aims, my work resulted in and contributed to the following points:

- **We expanded our IKD registry to over 1100 family referrals.**

- We found direct family referrals comprise a significant portion of RIKD team referrals and subsequent ADTKD diagnosis.
- We identified ADTKD in 768 families and 2079 individuals.
    - ADTKD-*UMOD*: 401 families, 1019 individuals
    - ADTKD-*MUC1*: 330 families, 930 individuals
    - ADTKD-*REN*: 37 families, 130 individuals

- **We developed a robust RIKD patient registry.**
    - Using REDCap, we have developed and built a large, secure registry housing information of over 1400 data variables and 9600 IKD family members.
    - Large datasets are able to be generated for analysis with data collected in a consistent manner,
    - We are able to utilize survey studies directly to ADTKD patients to obtain information and better understand topics of concern for families:
        - Quality of Life [ref]
        - Women's health and pregnancy outcomes, which are very good for women with ADTKD and their children [ref].

- **We established a collaborative network of clinicians and IKD researchers.**
    - The RIKD team works with over 130 collaborators across the Czech Republic, European Union, United States, United Kingdom, Canada, Australia, and South America.
    - We coordinate *UMOD* and *MUC1* genetic testing for their patients, share data for evaluating ADTKD characterization, and work together to help identify

rare genes or novel causes in ADTKD-*Unknown* families.

- **We identified clinical predictors for ADTKD-*UMOD*.**
  - Hyperuricemia and gout have a high prevalence in ADTKD-*UMOD* patients.
  - Male gender, age of gout onset, family mean age of ESKD, parental age of ESKD and affected maternal age of ESKD are all significant predictors for a patient's progression to ESKD.

- **We identified genetic predictors for ADTKD-*UMOD*.**
  - Pathogenic variant position, domain, and substitution type are not significant predictors for progression to ESKD.
  - mUMOD *in vitro* score is significant in predicting severity of disease and correlates with mean age of ESKD for the pathogenic variant.

- **We better characterized ADTKD-*MUC1*.**
  - ADTKD-*MUC1* is associated with an earlier age of ESKD compared to ADTKD-*UMOD*.
  - ADTKD-*MUC1* does not have additional characteristics associated with its clinical presentation, making it difficult to diagnose and leads to underdiagnosis and underrepresentation.

- **We described three distinctive clinical, genetic, and pathophysiological subtypes in ADTKD-*REN*.**
  - Signal peptide pathogenic variants lead to an earlier onset of disease. The mutant renin is unable to enter the ER and accumulates in the cytoplasm.
  - Prosegment pathogenic variants lead to an intermediate presentation. The mutant renin accumulates within ERGIC vesicles.

- Mature renin pathogenic variants have a later onset of disease. The mutant REN accumulates in the ER, akin to ADTKD-UMOD pathophysiology.

- **We identified a novel cause in five ADKTD-*Unknown* families.**
  - *APOA4* was identified as a novel gene cause in a family with ADTKD presentation.
  - Whole-genome sequencing was used followed by evaluation of other ADTKD-*Unknown* families.
  - Five families were identified and two missense pathogenic variants.
  - 48 individuals were genetically affected, 44 with low kidney function.
  - Kidney biopsies revealed medullary amyloidosis comprised of mutant ApoA4 fibrils.
  - This increases the genetic heterogeneity of ADTKD.

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7 List of Author's Publications with Impact Factor

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