Renal transplant outcomes in patients with autosomal dominant tubulointerstitial kidney disease

Sarah Cormican1 | Claire Kennedy1,2 | Dervla M. Connaughton1,3,4 | Patrick O’Kelly1 | Susan Murray1,2 | Martina Živná5 | Stanislav Kmoch5 | Neil K. Fennelly6 | Katherine A. Benson1,2 | Eoin T. Conlon1 | Gianpiero L. Cavalleri2 | Claire Foley4,7 | Brendan Doyle6 | Anthony Dorman2,6 | Mark A. Little4,8 | Peter Lavin8 | Kendrah Kidd5,9 | Anthony J. Bleyer9 | Peter J. Conlon1,2

1Nephrology Department, Beaumont Hospital, Dublin, Ireland
2Royal College of Surgeons, Dublin, Ireland
3Department of Medicine, Boston Children’s Hospital, Harvard Medical School, Boston, MA, USA
4Trinity Health Kidney Centre, Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland
5Research Unit for Rare Diseases, Department of Pediatrics and Adolescent Medicine, First Faculty of Medicine, Charles University, Prague, Czech Republic
6Pathology Department, Beaumont Hospital, Dublin, Ireland
7Clinical Research Centre, Royal College of Surgeons, Dublin, Ireland
8Trinity Health Kidney Centre, Tallaght Hospital, Dublin, Ireland
9Section on Nephrology, Wake Forest School of Medicine, Medical Centre Blvd., Winston-Salem, NC, USA

Abstract

Introduction: Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a rare genetic cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD). We aimed to compare renal transplant outcomes in people with ESRD due to ADTKD to those with other causes of renal failure.

Methods: Patients with clinical characteristics consistent with ADTKD by the criteria outlined in the 2015 KDIGO consensus were included. We compared ADTKD transplant outcomes with those of 4633 non-ADTKD renal transplant recipients.

Results: We included 31 patients who met diagnostic criteria for ADTKD in this analysis, 23 of whom had an identified mutation (28 were categorized as definite-ADTKD and 3 as suspected ADTKD). Five patients received a second transplant during follow-up. In total, 36 grafts were included. We did not identify significant differences between groups in terms of graft or patient survival after transplantation. Twenty-five transplant biopsies were performed during follow-up, and none of these showed signs of recurrent ADTKD post-transplant.

Conclusion: In patients with ESRD due to ADTKD, we demonstrate that transplant outcomes are comparable with the general transplant population. There is no evidence that ADTKD can recur after transplantation.
1 | INTRODUCTION

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a rare genetic cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD). Due to incomplete ascertainment, the prevalence of ADTKD is not known, although some authors have suggested that it may account for up to 2% of cases of ESRD. Indeed, recent data suggest that ADTKD is one of the most common monogenic kidney diseases after autosomal dominant polycystic kidney disease. Pathogenic mutations in the gene coding for mucin (MUC1), uromodulin (UMOD), hepatocyte nuclear factor 1B (HNF1B), renin (REN), and translocon subunit alpha (SEC61A1) have been identified in individuals with ADTKD. These mutations result in production of abnormal proteins which accumulate within the tubular epithelial cell, or, in the case of SEC61A1, altered post-translational modifications, folding and sorting of secretory and transmembrane proteins. Ultimately, these processes result in cell death with tubular atrophy and surrounding interstitial fibrosis. These are the characteristic histological findings in individuals with ADTKD.

Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that a diagnosis of ADTKD be suspected in individuals with compatible clinical characteristics and a family history consistent with autosomal dominant inheritance CKD or in individuals with compatible clinical characteristics and who have a kidney biopsy with histological changes consistent with ADTKD or compatible extrarenal manifestations, for example, gout in ADTKD-UMOD or diabetes in ADTKD-HNF1B. The diagnosis can be established either when a mutation in one of the four relevant genes is identified or in individuals who have both a compatible family history and a compatible renal biopsy. Depending on the genetic mutation identified, ADTKD may be further categorized as ADTKD-MUC1, ADTKD-UMOD, ADTKD-HNF1B, ADTKD-REN, ADTKD-SEC61A1, or ADTKD-NOS (where no mutation is identified but diagnosis is made based on family history and biopsy).

At present, there is no specific disease-modifying treatment available for individuals with ADTKD. Management of other factors, for example, which expedite CKD progression, is appropriate as is treatment of extrarenal manifestations, for example, gout in individuals with mutations in the Uromodulin gene. Progressive renal impairment with ESRD occurring in middle age is the typical clinical course in individuals with ADTKD. Such individuals will have an otherwise good life expectancy and therefore require renal replacement therapy for several decades.

As in other causes of ESRD, renal transplantation is the preferred modality of renal replacement therapy due to both mortality and quality-of-life considerations. Two previous reports of renal transplant outcomes in individuals with ADTKD due to MUC1 mutations suggested that it does not recur in the allograft.

In this report, we compare outcomes of renal transplantation in individuals with ADTKD to outcomes in individuals with other causes of ESRD and reviewed any available transplant biopsy results for individuals with ADTKD who had undergone transplantation.

2 | METHODS

Ethical approval was given by the Royal College of Surgeons, Ireland (RCSI) ethics board. Irish individuals with a family history of kidney disease were identified during the Irish Kidney Gene Project (IKGP), the protocol for which has been described previously. Informed consent was given by all patients at enrollment in IKGP for survey completion, review of healthcare records, and permission to re-contact in the future.

We reviewed clinical records and kidney biopsy (both native and transplant) results for individuals identified to determine whether they met criteria for a suspected/confirmed diagnosis of ADTKD. Identified individuals were then invited to attend for enrollment in the Irish Rare Kidney Disease Registry and Biobank and genetic testing.

Written consent was given prior to collection of samples for genetic testing. Genetic testing was performed in either Wake Forest School of Medicine, Winston-Salem, NC USA, the Broad Institute of Harvard University and the Massachusetts Institute of Technology, Cambridge, MA, or Boston Children’s Hospital, Harvard Medical School, USA. These techniques have been previously described. One individual included in this report was categorized as ADTKD-MUC1 after detection of frameshift MUC1 on urinary cell smear in the First Faculty of Medicine, Charles University, Prague, as previously described.

Further individuals were recruited after referral to the renal genetics clinic in Beaumont Hospital, and two other families with a known pre-existing diagnosis of “hereditary tubulointerstitial nephritis” were included as they met KDIGO criteria for established ADTKD.

After review of clinical records, we created an access file database with clinical characteristics for all individuals included in this report. Further information regarding transplant outcomes was obtained from the Irish Kidney Transplant Registry.

All statistical analyses were conducted with the statistical software package Stata (Version 13). A P-value of <.05 was deemed significant. Graft and patient survival for the cohort of patients with ADTKD was compared with outcomes for all other Irish renal transplant recipients who received a renal transplant over a 37-year period (1982-April 2019) using a log-rank test for equality of survivor functions. This period corresponded with the timeframe within which transplants were performed.
performed in the ADKTD group. A death-censored graft survival analysis was also performed. Comparisons between baseline characteristics were made using either Mann-Whitney or Pearson chi-squared testing.

3 | RESULTS

3.1 | Patient selection

After review of clinical characteristics and biopsy reports for individuals identified during the IKGP study, individuals referred to the renal genetics clinic, and individuals from three families with a pre-existing known diagnosis of ADTKD, we identified 28 individuals with a confirmed diagnosis of ADTKD who had undergone renal transplantation. These individuals were categorized as ADTKD-MUC1 (n = 10), ADTKD-UMOD (n = 9), ADTKD-HNF1B (n = 4), or ADTKD-NOS (n = 5) and had a total of 32 grafts available for consideration.

Three further individuals were considered to have “suspected ADTKD” based on either (a) a renal biopsy demonstrating characteristic histology (n = 1) or (b) compatible clinical characteristics and a family history consistent with autosomal dominant inheritance of kidney disease (n = 2). One of these individuals had undergone two transplants meaning that a total of 36 transplants in 31 individuals were included in this study. The families, individuals, and grafts included in this report are summarized in Table 1. Mutation details have been reported elsewhere. Transplants were performed between 1980 and the present day with 15 performed before 2000 and a further 21 performed thereafter.

The comparator group was made up of 4633 renal transplant recipients with other aetiologies of ESRD from the Irish renal transplant registry who underwent renal transplantation between 1982 and 2019.

3.2 | Baseline characteristics at transplantation

We next compared the baseline clinical information at time of transplantation between this group of individuals with ADTKD and individuals included in the Irish renal transplant registry with a different etiology of renal failure. These comparisons are shown in Table 2. We did not identify any significant differences in baseline characteristics between the cohort of individuals with ADTKD and the comparator group with the exception of donor sex. Male donor sex was more common in the comparator group than the ADTKD group (58.2% vs 41.2%, P = .045). Although living donation was more common in the group with ADTKD (19.4% vs 9.9%, P = .060), this did not reach statistical significance.

3.3 | Patient and graft outcomes after transplantation

We wished to determine whether there was a significant difference between groups in terms of either patient survival or graft survival in individuals with ESRD due to ADTKD vs individuals undergoing transplantation after a different cause of renal failure. A log-rank

### Table 1

| Category     | Status of diagnosis | Criteria met | No. of individuals per family with renal transplant |
|--------------|---------------------|--------------|-----------------------------------------------------|
| 1            | ADTKD-MUC1          | C            | Bx, GT, Rel                                         | 7 |
| 2            | ADTKD-MUC1          | C            | Bx, GT, Rel                                         | 1 |
| 3            | ADTKD-MUC1          | C            | Bx, GT, Rel                                         | 1 |
| 4            | ADTKD-MUC1          | C            | Bx, GT, Rel                                         | 1 |
| 5            | ADTKD-UMOD          | C            | Bx, GT, Rel                                         | 4 |
| 6            | ADTKD-UMOD          | C            | Bx, GT, Rel                                         | 1 |
| 7            | ADTKD-UMOD          | C            | Bx, GT, Rel                                         | 2 |
| 8            | ADTKD-UMOD          | C            | Bx, GT, Rel                                         | 2 |
| 9            | ADTKD-HNF1B         | C            | Bx, GT, Rel                                         | 3 |
| 10           | ADTKD-HNF1B         | C            | Bx, GT, Rel                                         | 1 |
| 11           | ADTKD-NOS           | C            | Bx, Rel                                             | 1 |
| 12           | ADTKD-NOS           | C            | Bx, Rel                                             | 2 |
| 13           | ADTKD-NOS           | C            | Bx, Rel                                             | 2 |
| 14           | ADTKD-NOS           | S            | Bx                                                   | 1 |
| 15           | ADTKD-NOS           | S            | Rel                                                  | 1 |
| 16           | ADTKD-NOS           | S            | Rel                                                  | 1 |
| Total number |                     |              |                                                     | 31 |

Abbreviations: Bx, biopsy demonstrating changes typical of ADTKD; C, confirmed; GT, genetic test demonstrating a mutation in one of the four relevant genes; Rel, at least one first-degree relative with a history of CKD/ESRD; S, suspected.
test for equality of survivor functions did not indicate significant differences between groups for either graft survival \((P = .794)\) or patient survival \((P = .736)\) as shown by Kaplan-Meier curves in Figure 1. The reported causes of graft failure in the group with ADTKD were patient death \((n = 8)\), chronic allograft nephropathy \((n = 6)\), BK virus nephropathy \((n = 1)\), BK virus nephropathy combined with acute rejection \((n = 1)\), and acute rejection followed by chronic allograft nephropathy \((n = 1)\). Death-censored graft survival did not differ between groups \((P = .9327)\). On most recent clinical review, only 2/19 individuals with a surviving graft had significant proteinuria > 1 + on dipstick or urinary protein: creatinine ratio >30 mg/mL. These were attributed to BK virus nephropathy and advanced chronic allograft nephropathy in an individual 27 years post-transplantation.

### 3.4 | Transplant biopsy results in the ADTKD group

A total of 25 transplant biopsy results were available for 17/33 patients. These showed multiple pathologies which were not deemed related to the primary disease (acute rejection \([n = 10]\); chronic allograft nephropathy \([n = 9]\), BK virus nephropathy \([n = 2]\), calcineurin inhibitor toxicity \([n = 2]\), acute tubular necrosis \([n = 1]\), and donor-related arteriosclerosis \([n = 1]\)). Therefore, we did not identify evidence of ADTKD recurrence after transplantation in any of the individuals included in this report.

### 4 | DISCUSSION

It has previously been reported that 10%-15% of Irish patients with ESRD have an inherited cause of kidney disease. Polycystic kidney disease accounts for the majority of these patients, but there are also approximately 160 “Rare Kidney Diseases” which result from genetic mutations and frequently progress to ESRD. ADTKD is one such condition, and we have reported separately on the clinical characteristics of Irish individuals with ADTKD. Recently, the use of whole-exome sequencing has been used to evaluate Irish individuals with a suspected rare genetic cause of kidney disease.

There are, at present, no specific therapies to delay CKD progression in patients with ADTKD. Supportive management includes treating complications of CKD, treatment of gout (in patients with mutations in the UMOD gene), and preparation for ESRD. Rate of progression and age at ESRD are variable but typically occurs in middle age. These individuals will require renal replacement for the rest of their lives.

Two previous analyses of outcomes after renal transplantation in patients with Medullary Cystic Kidney Disease Type 1 (MCKD-1) (which is defined as ADTKD-MUC1 in this paper, as per KDIGO guidelines) have been published. These authors demonstrated no statistically significant difference between patients with ESRD due to MCKD-1 and other patients receiving a renal transplant. No previous analyses of transplant outcomes for patients with the unified “ADTKD” diagnosis have been published.

Our center previously published data demonstrating superior graft and patient survival for patients with ESRD due to polycystic kidney disease compared to other causes of ESRD, after adjusting for age at transplant. We did not demonstrate a statistically significant difference for patients with ADTKD, although this is may be limited by the relatively small number of patients in the ADTKD cohort.

In recent years, a number of advances have been made which increase the yield of genetic testing in individuals with suspected ADTKD.

### TABLE 2 Baseline characteristics at the time of transplantation for the group with ADTKD vs other renal transplant recipients

|                          | ADTKD        | Other       | \(P\)-value |
|--------------------------|--------------|-------------|-------------|
| Recipient age, years (median, IQR) | 44.7 (33-52) | 44 (31-56) | .94         |
| Donor age (median, IQR)   | 43 (30-49)   | 40 (24-51)  | .83         |
| Time on dialysis, months (median, IQR) | 19 (11-28) | 22 (12-38) | .25         |
| Cold ischemia time (median, IQR) | 18 (14-20) | 18 (15-22) | .32         |
| HLA mismatches (median, IQR) | 3 (2-5)     | 3 (2-4)    | .46         |
| Transplant type (% DD, n) | 80.5% (29/36)| 90.0% (4170/4633) | .06         |
| Recipient sex (% male)   | 58.3% (21/36)| 64.6% (2982/4633) | .45         |
| Donor sex (% male)       | 41.2% (14/34)| 58.2% (2567/4410) | .05         |
| Delayed graft function   | 13.0% (5/36) | 14.0% (640/4633) | .98         |
| PRA at transplantation   |              |             |             |
| 0%-10%                   | 65.7%        | 57.3%       | .79         |
| 11%-49%                  | 17.1%        | 20.4%       |             |
| 50%-84%                  | 11.4%        | 14.2%       |             |
| 85%-100%                 | 5.7%         | 8.1%        |             |

Abbreviations: ADTKD, autosomal dominant tubulointerstitial kidney disease; DD, deceased donor; HLA, human leukocyte antigen; IQR, interquartile range; PRA, percent reactive antigen.

\[9.5\]
Reliable genetic testing could allow screening of relatives wishing to become living donors prior to transplant. This would be very valuable in the management of patients with ESRD due to ADTKD.

There are a number of limitations to this work. Several of the transplants included were performed more than two decades ago, and transplantation practices have evolved over the intervening time. However, this long time period also allows us to demonstrate transplant longevity in the ADTKD population. Limiting our analysis to transplants performed after 2000 would have reduced the sample size and the length of follow-up available. The number of transplants included in this report is small although it represents a relatively large number given the rarity of ADTKD.

We have shown excellent transplant outcomes for patients with ESRD due to ADTKD who undergo renal transplantation. More than half of the patients we included in this analysis underwent a renal transplant biopsy during follow-up. It is in keeping with our understanding of the etiology of ADTKD that none of these biopsies demonstrated features of recurrence. The impact of renal transplantation on patient survival and quality of life is well established, and it is clear that transplantation should be the treatment of choice for patients with ESRD due to ADTKD.

ACKNOWLEDGEMENTS
This work was supported by funding from the Punchestown Kidney Research Fund, Beaumont Nephrology Research Fund, a Meath Foundation grant (Grant Number: 205229.13987), and SFI grant (Grant Number: 11/Y/B2093). SC is currently supported by an academic training grant under the Irish Clinical Academic Training (ICAT) Programme, supported by the Wellcome Trust and the Health Research Board (Grant Number 203930/B/16/Z); DMC is funded by the Health Research Board, Ireland (HPF-206-674), the International Pediatric Research Foundation Early Investigators' Exchange Program, and the Amgen Irish Nephrology Society.
CONFLICT OF INTEREST
None declared.

ORCID
Sarah Cormican https://orcid.org/0000-0001-7769-5152
Claire Kennedy https://orcid.org/0000-0001-7277-2171
Susan Murray https://orcid.org/0000-0002-4264-3405

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How to cite this article: Cormican S, Kennedy C, Connaughton DM, et al. Renal transplant outcomes in patients with autosomal dominant tubulointerstitial kidney disease. Clin Transplant. 2020;34:e13783. https://doi.org/10.1111/ctr.13783