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SUPPLEMENTARY MATERIAL

Supplementary File (Word)
Supplementary References.
Supplementary Methods.
Table S1. Patient characteristics, previous peritonitis, laboratories, and outcome.
Table S2. Accuracy of serum galactomannan index for differentiating fungal peritonitis at different cutoff points.

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Genetic Kidney Disease in Southern Tasmania

Gabrielle Brailsford1,2,3, Ellie Cash1, Jo Burke1,5, Geoff Kirkland1,2, Mathew Wallis1,4,5, Andrew Mallett3,4,6 and Matthew D. Jose1,2,4

1School of Medicine, The University of Tasmania, Hobart, Tasmania, Australia; 2Department of Nephrology, Royal Hobart Hospital, Hobart, Tasmania, Australia; 3Department of Renal Medicine, Royal Brisbane and Women’s Hospital, Herston, Queensland, Australia; 4KidGen Collaborative, Australian Genomics Health Alliance, Parkville, Victoria, Australia; 5Tasmanian Clinical Genetics Service, Tasmanian Health Service, Royal Hobart Hospital, Hobart, Tasmania, Australia; and 6Institute for Molecular Bioscience and Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia

Correspondence: Matthew D. Jose, Room 321 (Level 3), Hobart Clinical School, University of Tasmania, Tasmania 7001, Australia. E-mail: matthew.jose@utas.edu.au

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Evidence suggests that 1.7 million persons (10% of the Australian adult population) are living with chronic kidney disease (CKD). Within the Australian CKD population, around 10% of individuals are found to have a genetic cause for their kidney disease. As genomic sequencing technology becomes more mainstreamed, the identification of genetic kidney disease (GKD) is expected to increase. The CKD population experiences an excess of...
morbidity, engagement with health services, and mortality. In all, 1 in 7 (16%) of 2015 to 2016 hospitalizations in Australia were associated with CKD. It is yet to be clearly established whether and how individuals with CKD due to GKD differ from those with non-GKD-related CKD, and whether their disease follows the same clinical trajectory. Genetic kidney disease encompasses a vast range of complex and heterogenous conditions; thus, establishing the overall prevalence has been particularly challenging. It is most likely underestimated, particularly in areas with limited access to diagnostic tools and specialist renal services. Certain monogenic nephropathies are more commonly encountered and diagnosed, for example, autosomal dominant polycystic kidney disease (ADPKD) or Alport syndrome. There are, however, conditions that are much less frequently encountered, particularly among small populations, such as Lowe syndrome. An enhanced understanding of the genetic basis of both common and rare conditions can only lead to improved diagnosis, clinical care, therapy, and patient outcomes. The first step is to establish the prevalence, disease characteristics, and demographics.

This study sought to establish the prevalence of GKD among the CKD population that is provided clinical care by the Southern Tasmania Renal Service. We aimed to understand how GKD contributes to kidney disease in our local community, to identify unaddressed areas of clinical need, and thus to develop health care provisions accordingly. A multisource, retrospective audit involving secondary use of existing data was conducted. Patients with CKD belonging to the Southern Tasmania Renal Service were identified from AUDIT4 (Royal Hobart Hospital renal clinic database, n = 2407) and ANZDATA (Australia and New Zealand Dialysis and Transplantation Registry, n = 361). After discarding duplicates, the records of 2434 individuals referred to tertiary renal services between 1 January 2012 and 31 December 2017 were reviewed. From this population, individuals with CKD due to GKD were identified. Genetic kidney disease was defined as any condition with a known genetic etiology diagnosed in a patient on clinical or molecular grounds, in line with previous Australian prevalence studies. We compared the GKD and non-GKD populations and evaluable differences in their demographic features and clinical outcomes, including most recent kidney function and age at commencement of renal replacement therapy (RRT). To establish statistical significance, continuous variables were analyzed using the Student t test and categorical variables with the χ² test and were considered significant if P < 0.05. The study was approved by the Tasmania Health and Medical Research Human Ethics Committee (Study H0017245).

RESULTS

In Tasmania, GKD comprised 8.5% of the CKD population (208 of 2434 individuals). The GKD patients were younger than the non-GKD patients (mean age 52 years vs. 64 years, P < 0.001) and did not have a greater tendency to be either male or female. There was no significant difference in mean eGFR (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) (Table 1).

Patients with CKD more commonly developed CKD stage 5 (40% vs. 17%, P < 0.001), commenced RRT (39.4% vs. 12.3%, P < 0.001), and underwent transplantation (30.3% vs. 5%, P < 0.001). Furthermore, GKD patients who commenced RRT did so at a younger age (mean age 46 years vs. 55 years, P < 0.001) (Table 2).

Cystic kidney disease was the most common form of GKD (48%), followed by congenital anomalies of the kidney and urinary tract (CAKUT) (37%). Patients with CAKUT started RRT at younger ages than those with cystic disease (mean age 39 years vs. 55 years, P < 0.001) (Table 3). In addition, they underwent kidney transplantation at a younger age (mean age 36 years vs. 52 years, P < 0.001). Broadly speaking, patients with glomerular, tubular/metabolic, or other less common forms of GKD were more likely to be older and male. Of the 208 patients with GKD in Southern Tasmania, only 25 (12%) were known to the Tasmanian Clinical Genetics Service or had been referred for genetic testing or counseling at the time of this audit.

DISCUSSION

In Tasmania, 8.5% of the CKD population had a condition meeting our definition of GKD. This figure reflects that of other Australian subpopulations. For example, a recent Queensland-based multisite CKD registry established a GKD prevalence of 9.8% in their population. Our findings support emerging evidence that around 1 in 10 Australian patients with CKD will have an inherited cause for their disease if investigated.

Female and male individuals were represented similarly, both when comparing the GKD and non-GKD cohorts and when comparing specific types of GKD. Previous similar studies found a greater representation of females among their GKD population. Theories behind this included the presence of autosomal conditions with a higher penetrance of disease in females, or poorer survival of males with an X-linked condition. Among our study population, ADPKD and CAKUT made up 85% of our GKD population, which may explain 1 reason for our differing observation. In addition, there are records of patients in Tasmania treated by private nephrologists that were not accessed for this audit.
Our findings show that patients with GKD-related CKD among the Southern Tasmanian population experience greater morbidity at younger ages. In all, 40% (n = 84) of individuals with GKD progressed to RRT, compared to only 17% (n = 378) of the non-GKD cohort. Importantly, those with GKD commenced RRT on average 10 years younger. This reflects a pathophysiological decline in kidney function from birth, as opposed to the accumulation of kidney damage secondary to chronic disease. Arguably, identification of inherited CKD earlier may reflect motivation from families with a known history to seek specialist advice sooner. Perhaps with greater health promotion, the age at diagnosis may become even younger.

As expected, cystic kidney disease and CAKUT comprised a large majority of our GKD population. This reflects other comparable CKD cohorts in Australia. Despite the prevalence of these conditions, tailored approaches to patient management, including genetic diagnosis and counseling, remain limited. We also identified rarer inherited causes of kidney disease, for example tuberous sclerosis. This confirms that these conditions do exist within our population, albeit in small numbers. Tuberous sclerosis is a condition familiar to most nephrologists and general practitioners, and it can be diagnosed clinically. Arguably, limited clinical exposure to other rare conditions means that a proportion of Tasmanians with rare forms of GKD are currently undiagnosed, and they will require genetic evaluation and testing before a specific diagnosis can be made. By establishing a specialist renal genetics service to identify at-risk individuals and to diagnose and treat GKD, we may see a significant rise in both common and uncommon conditions.

We found that only 12% were known to the Tasmanian Clinical Genetics Service or had received genetic testing or counseling at the time of our audit. Underuse of this valuable resource creates a barrier to timely, accurate diagnosis of GKD. Patients are not accessing appropriate specialist genetic input, which means that they may be missing the opportunity for a specific diagnosis and an appreciation of the heritable nature of their condition. Creating a clear link between hospital/clinic-based management of GKD and the local genetics service facilitates early referral, accurate diagnosis, and appropriate counseling. All of these things have the potential to significantly affect the disease trajectory for affected individuals and their families.

This study confirms the considerable number of patients living with GKD in Tasmania. The prevalence of GKD among the Tasmanian CKD population reflects findings in other Australian studies. Identifying this population supports the development of a tailored renal genetics service, to aid early diagnosis and to improve clinical outcomes. Of particular value is to establish a clear link between renal and genetic services, so as to provide genetic testing, counseling, and education. A genetic result has the power to minimize diagnostic uncertainty, to inform reproductive planning, and to avoid unnecessary biopsy in certain patients. The resultant patient-centric goal is to ensure that patients and families affected by GKD receive up-to-date relevant care and are supported holistically.

**Table 1. Patient features: GKD versus non-GKD**

|                  | GKD   | Non-GKD | P value |
|------------------|-------|---------|---------|
| Age, yr          | 52    | 64      | <0.001  |
| Female sex       | 51%   | 48%     | 0.4     |
| Mean eGFR (ml/min per 1.73 m²) | 49.2 | 45      | 0.12    |

eGFR, estimated glomerular filtration rate; GKD, genetic kidney disease.

**Table 2. Clinical outcomes in patients with GKD versus non-GKD**

| Outcome           | GKD  | Non-GKD | P value |
|-------------------|------|---------|---------|
| ESKD              | 40%  | 17%     | <0.001  |
| RRT               | 38%  | 12%     | <0.001  |
| Transplant        | 30%  | 5%      | <0.001  |

ESKD, end-stage kidney disease; GKD, genetic kidney disease; RRT, renal replacement therapy.

**Table 3. Specific GKD subtypes**

| GKD subtype                          | n  | GKD cohort prevalence (%) |
|--------------------------------------|----|---------------------------|
| CAKUT                                | 76 | 37                        |
| Vesicoureteric reflux                | 57 |
| Renal agenesis/hypoplasia            | 8  |
| Abnormalities of renal pelvis or ureter | 4 |
| Horseshoe kidney                     | 3  |
| Posterior urethral valves             | 2  |
| Other                                | 2  |
| Cystic kidney disease                | 99 | 48                        |
| Polycystic kidney disease, autosomal dominant | 81 |
| Medullary cystic kidney disease       | 12 |
| Other cystic kidney disease           | 6  |
| Glomerular                           | 9  | 4                         |
| Alport syndrome                      | 9  |
| Nephrolithiasis                      | 12 | 6                         |
| Hypercalciuria                       | 10 |
| Oxalosis/cystinosis                  | 2  |
| Tubular/metabolic                    | 5  | 2                         |
| Gitelman syndrome                    | 3  |
| Fabry disease                        | 2  |
| Other                                | 7  | 3                         |
| Tuberous sclerosis complex           | 2  |
| Inherited kidney cancer syndromes    | 2  |
| Single cases (not further specified, for anonymity) | 3 |

CAKUT, congenital anomalies of the kidney and urinary tract; GKD, genetic kidney disease.

**DISCLOSURE**

All the authors declared no competing interests.

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Membranous Nephropathy With Crescents

Rasha Alawieh1, Sergey V. Brodsky2, Anjali A. Satoskar2, Tibor Nadasdy2, Samir V. Parikh1, Brad Rovin1 and Clarissa A. Cassol2

1Department of Internal Medicine, Division of Nephrology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; and 2Department of Pathology, Division of Renal Pathology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

Correspondence: Clarissa A. Cassol, The Ohio State University, 320 W. 10th Avenue, M364A Starling Loving Hall, Columbus, Ohio 43210, USA. E-mail: Clarissa.Cassol@osumc.edu; or Brad Rovin, Division of Nephrology, The Ohio State University, Wexner Medical Center, 395 West 12th Avenue, Ground Floor, Columbus, Ohio 43210, USA. E-mail: rovin.1@osu.edu

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Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults and can be primary or secondary. Primary MN is most commonly associated with anti–M-type phospholipase A2 receptor (PLA2R) antibodies and is usually IgG4 dominant, whereas secondary MN can be seen in the setting of malignancies, infections, autoimmune diseases, or as a side effect of certain medications or...