

## ACKNOWLEDGMENTS

We acknowledge the contributions of the staffs, nurses, and all investigators who work at participating Thailand PD Outcomes and Practice Patterns Study (PDOPPS) centers, including King Chulalongkorn Memorial Hospital Sunpasitthiprasong Hospital, Phayao Hospital, Pranangkla Hospital, Siriraj Hospital, Nakhon Pathom Hospital, Bangkok Metropolitan Administration General Hospital, Chao-prayayomraj Hospital, Taksin Hospital, Udon Thani Hospital, Chaiphaphum Hospital, Mukdahan Hospital, Sukhothai Hospital, Nakhonping Hospital, Sawanpracharak Hospital, Trang Hospital, Pong Hospital, Chaophraya Abhaibhubejhr Hospital, Trat Hospital, KhueangNai hospital, Amnatcharoen Hospital, and Songkhla Hospital. This study was supported by the Kidney Foundation of Thailand, Ratchadaphiseksomphot Endowment Fund (CU\_GRS\_61\_06\_30\_01), Chulalongkorn University, the National Research Council of Thailand (156/2560), Thailand Research Foundation (IRG5780017), and the 90th Anniversary of Chulalongkorn University Fund (GCUGR1125594013D).

## 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.

## REFERENCES

1. Miles R, Hawley CM, McDonald SP, et al. Predictors and outcomes of fungal peritonitis in peritoneal dialysis patients. *Kidney Int.* 2009;76:622–628.
2. Matuszkiewicz-Rowinska J. Update on fungal peritonitis and its treatment. *Perit Dial Int.* 2009;29(suppl 2):S161–S165.
3. Li PK-T, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. *Perit Dial Int.* 2016;36:481–508.
4. Nadeau-Fredette AC, Bargman JM. Characteristics and outcomes of fungal peritonitis in a modern North American cohort. *Perit Dial Int.* 2015;35:78–84.
5. Wingard JR. Have novel serum markers supplanted tissue diagnosis for invasive fungal infections in acute leukemia and transplantation? *Best Pract Res Clin Haematol.* 2012;25:487–491.
6. Marr KA, Balajee SA, McLaughlin L, et al. Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: variables that affect performance. *J Infect Dis.* 2004;190:641–649.
7. Shin B, Koh WJ, Jeong BH, et al. Serum galactomannan antigen test for the diagnosis of chronic pulmonary aspergillosis. *J Infect.* 2014;68:494–499.
8. Vaziri ND, Yuan J, Rahimi A, et al. Disintegration of colonic epithelial tight junction in uremia: a likely cause of CKD-associated inflammation. *Nephrol Dial Transplant.* 2012;27:2686–2693.
9. Swanink CMA, Meis JFGM, Rijs AJMM, et al. Specificity of a sandwich enzyme-linked immunosorbent assay for detecting *Aspergillus* galactomannan. *J Clin Microbiol.* 1997;35:257–260.

## Genetic Kidney Disease in Southern Tasmania



Gabrielle Brailsford<sup>1,2,3</sup>, Ellie Cash<sup>1</sup>, Jo Burke<sup>1,5</sup>, Geoff Kirkland<sup>1,2</sup>, Mathew Wallis<sup>1,4,5</sup>, Andrew Mallett<sup>3,4,6</sup> and Matthew D. Jose<sup>1,2,4</sup>

<sup>1</sup>School of Medicine, The University of Tasmania, Hobart, Tasmania, Australia; <sup>2</sup>Department of Nephrology, Royal Hobart Hospital, Hobart, Tasmania, Australia; <sup>3</sup>Department of Renal Medicine, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia; <sup>4</sup>KidGen Collaborative, Australian Genomics Health Alliance, Parkville, Victoria, Australia; <sup>5</sup>Tasmanian Clinical Genetics Service, Tasmanian Health Service, Royal Hobart Hospital, Hobart, Tasmania, Australia; and <sup>6</sup>Institute 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](mailto:matthew.jose@utas.edu.au)

Received 20 October 2019; revised 13 January 2020; accepted 20 January 2020; published online 30 January 2020

*Kidney Int Rep* (2020) 5, 534–537; <https://doi.org/10.1016/j.ekir.2020.01.015>

© 2020 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Evidence suggests that 1.7 million persons (10% of the Australian adult population) are living with chronic kidney disease (CKD).<sup>1</sup> Within the Australian CKD population, around 10% of individuals are found to have a

genetic cause for their kidney disease.<sup>2</sup> 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.<sup>1</sup> In all, 1 in 7 (16%) of 2015 to 2016 hospitalizations in Australia were associated with CKD.<sup>1</sup> 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 heterogeneous 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.<sup>3</sup> 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.<sup>3</sup> 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  $\chi^2$  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.<sup>2</sup> Our findings support emerging evidence that around 1 in 10 Australian patients with CKD will have an inherited cause for their disease if investigated.<sup>2</sup>

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.<sup>2</sup> 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.

**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 m <sup>2</sup> )	49.2	45	0.12

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

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.<sup>2</sup> 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<sup>4</sup> 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

**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.

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.<sup>5</sup> 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 genetic 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.

## DISCLOSURE

All the authors declared no competing interests.

## ACKNOWLEDGMENTS

This study was funded by the Royal Hobart Hospital Research Foundation and Blundstone Australia Pty Ltd.



## REFERENCES

1. Australian Institute of Health and Welfare (AIHW). Chronic kidney disease. Cat. no. CKD16. Canberra: AIHW; 2019.
2. Mallett A, Patel C, Salisbury A, et al. The prevalence and epidemiology of genetic renal disease amongst adults with chronic kidney disease in Australia. *Orphanet J Rare Dis*. 2014;9:98.
3. Devuyst O, Knoers N, Remuzzi G, et al. Rare inherited kidney diseases: challenges, opportunities, and perspectives. *Lancet*. 2014;383:1844–1855.
4. Groopman EE, Rasouly HM, Gharavi AG. Genomic medicine for kidney disease. *Nat Rev Nephrol*. 2018;14:83–104.
5. Hildebrandt F. Genetic kidney diseases. *Lancet*. 2010;375:1287–1295.

## Membranous Nephropathy With Crescents



Rasha Alawieh<sup>1</sup>, Sergey V. Brodsky<sup>2</sup>, Anjali A. Satoskar<sup>2</sup>, Tibor Nadasdy<sup>2</sup>, Samir V. Parikh<sup>1</sup>, Brad Rovin<sup>1</sup> and Clarissa A. Cassol<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Division of Nephrology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; and <sup>2</sup>Department 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](mailto: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](mailto:rovin.1@osu.edu)

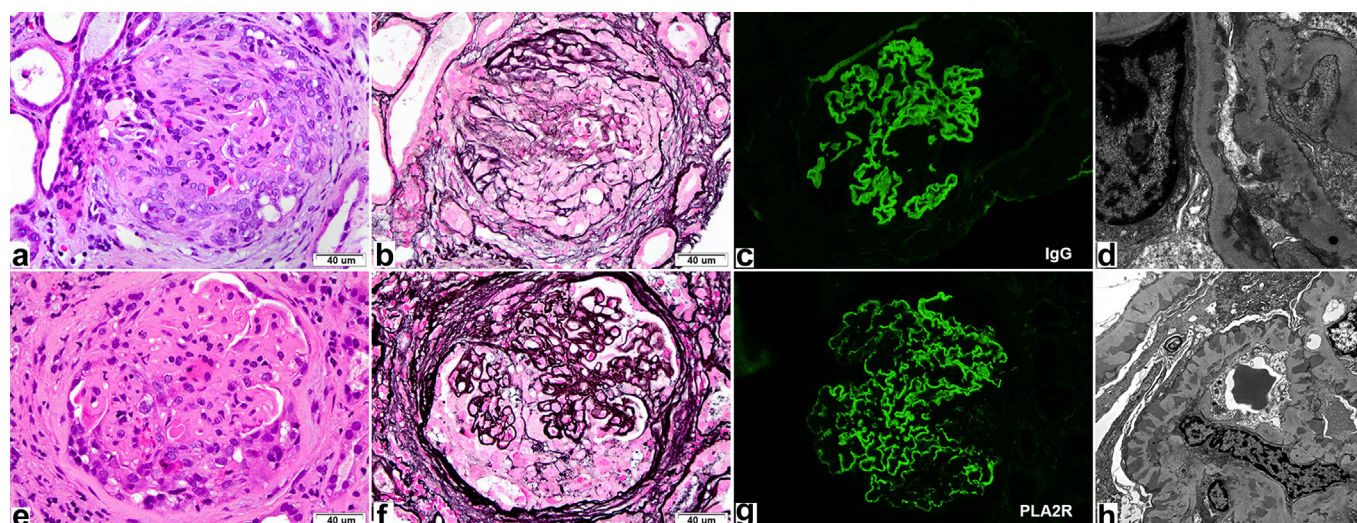
Received 14 December 2019; revised 14 January 2020; accepted 20 January 2020; published online 30 January 2020

*Kidney Int Rep* (2020) 5, 537–541; <https://doi.org/10.1016/j.ekir.2020.01.010>

© 2020 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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



**Figure 1.** Top row (a–d): a case of anti-glomerular basement membrane (GBM) disease (case 12) with segmental membranous nephropathy (MN). (a) Glomerulus with a cellular crescent (hematoxylin and eosin [H&E] stain, original magnification  $\times 400$ ). (b) Silver stain shows a compressed glomerular tuft with no obvious spikes or lucencies along the GBM (original magnification  $\times 4000$ ). (c) Linear IgG staining (immunofluorescence, original magnification  $\times 400$ ). (d) Electron microscopic image showing segmental subepithelial deposits. Bottom row (e–h): a case of PLA2R-positive MN with concomitant p-ANCA (case 8). (e) Glomerulus with a cellular crescent (H&E stain, original magnification  $\times 400$ ). (f) Silver stain highlights capillary wall irregularities (fine lucencies and spikes) in the same glomerulus that contains a cellular crescent (original magnification  $\times 400$ ). (g) An anti-PLA2R antibody shows diffuse granular positivity along the GBM (immunofluorescence, original magnification  $\times 400$ ). (h) Electron microscopy confirms diffuse subepithelial deposits.