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The Irish Kidney Gene Project – Prevalence of Family History in Patients with Kidney Disease in Ireland

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Key Words

Genetic factors · Kidney disease · Family history · Hereditary nephropathy

Abstract

Background: The prevalence of kidney disease (KD) due to inherited genetic conditions in Ireland is unknown. The aim of this study was to characterise an adult kidney disease population in Ireland and to identify familial clusters of kidney disease within the population. ***Methods:*** This was a multicenter cross-sectional study of patients with kidney disease in the Republic of Ireland, from January 2014 to September 2014, recruiting from dialysis units and out-patient renal departments. A survey was performed by collecting data on etiology of kidney disease and whether a family history of kidney disease exists. Medical records were cross-referenced to confirm the etiology of kidney disease. ***Results:*** A total of 1,840 patients were recruited with a mean age of 55.9 years (range 17–94.5) and a male predominance (n = 1,095; 59.5%). A positive family history was reported by 629 participants (34.2%). Excluding polycystic kidney disease (n = 134, 7.3%), a positive family history was reported by 495 participants (26.9%). Kidney disease due to an unknown etiology was the commonest etiology in the non-polycystic kidney disease group with a positive family history (10.6%, n = 67). Kidney diseases that are not classically associated with familial inheritance including tubulo-interstitial kidney disease, congenital abnormalities of the kidney and urinary tract and glomerulonephritis demonstrated familial clustering. ***Conclusion:*** In an Irish non-polycystic kidney disease population, 26.9% reports a positive family history. The commonest etiology of kidney disease in the positive family history cohort, excluding autosomal dominant polycystic kidney disease, was kidney disease due to unknown etiology. Examining families with kidney disease provides an opportunity to better understand disease pathogenesis and potentially identify genetic predispositions to kidney disease.

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Introduction

The population estimate, as reported by the central statistics office for Ireland, in 2014 was approximately 4.5 million [1]. The incidence rate of end-stage kidney disease (ESKD) was 88 per million people during 2013, with 3,960 patients receiving renal replacement therapy (prevalence rate of 824 per million persons) [2]. This represents a significant health service, economic and resource burden. The increasing rate of kidney disease has long been linked to the epidemic of diabetes mellitus and cardiovascular disease in Western society [3, 4]. However, despite improvements in the treatment of diabetes, hypertension and hyperlipidemia, the incidence of ESKD in Europe has increased in the last decade by a rate of 4.8% per annum [5]. In fact, studies have shown that when we adjust for risk factors such as obesity and western lifestyle, familial aggregation still persists in kidney disease [6]. This suggests that heritable genetic traits contribute to the development of kidney disease. As such, there is increasing interest in genetically inherited kidney disease. Since the 1980s, increasing numbers of Mendelian kidney diseases, resulting from single gene disorders, have been characterized. This was demonstrated in autosomal dominant polycystic kidney disease (ADPCKD) and Alport's syndrome [7]. In recent years, rarer genetically inherited defects causing kidney disease have been identified. Single gene defects in *NPHS1* (podocin) and *NPHS2* (nephrin) lead to steroid-resistant nephrotic syndrome in children [7]. More recently, the identification of the *MUC1* mutation in families with medullary cystic kidney disease has allowed for characterization and reclassification of interstitial renal diseases [8]. Analysis of these genes has allowed for establishment of definitive diagnosis, prognostication in terms of age of onset of disease and risk of progression to ESKD. Another major challenge within the ESKD population is kidney disease due to unknown or unclear etiology. Despite advances in diagnostic tools, the incidence of ESKD due to unknown or missing etiology has doubled in some European countries [5]. In Ireland, the proportion of kidney disease due to potentially inherited disorders remains unclear. In addition, Ireland may have its own specific heritable disorders. Identification of familial clusters of kidney disease, where the etiology of kidney disease is unclear, may offer a unique opportunity to study rare inherited genetic diseases. Here, we report on the prevalence of family history both in a chronic kidney disease (CKD) and ESKD population in Ireland in 2014, with the goal of identifying familial clustering of kidney disease within the population.

Subjects and Methods

This was a national, multicenter, cross-sectional study recruiting patients from dialysis units and nephrology out-patient clinics. Ethical approval was granted by the local medical ethics committee at each site. The recruitment period was from January 2014 to September 2014 and involved the selection of consecutive patients presenting to the department.

Nephrology services in Ireland are structured such that patients with CKD stage 3 (glomerular filtration rate of <60 ml/min/1.73 m^2) or higher are referred to a nephrologist for further assessment. The sites of recruitment in this study were in-centre hemodialysis units and the nephrology out-patient department of 4 hospitals. Each hospital involved in the recruitment was a tertiary referral centre with a nephrology service consisting of 3 or more nephrologists and an adjoining in-centre dialysis unit. Recruitment from further 4 satellite dialysis units took place to increase sampling numbers of the ESKD population. The total number of ESKD patients attending the above nephrology units, as of the 2013 census, was 2,586 which accounts for 65.3% of the total ESKD population in Ireland [2]. Sample size calculation for the ESKD population to detect a prevalence rate of 25% of family history of kidney disease (95% level of significance and 5% degree of precision) required the recruitment of 260 subjects. For the CKD population in Ireland, previous studies have demonstrated an estimated prevalence ranging from 11.2% for the general population [9], 11.6% for an older cohort [10] up to 17% for patients attending primary care services [11]. These results are comparable to worldwide prevalence rates of CKD which range from 8 to 16% [4]. Therefore, based on census-derived population estimates, we estimate that there were approximately 500,000 prevalent cases of CKD in Ireland at the time of sampling [12]. Therefore, in order to detect a prevalence rate of 25% for reporting a family member with kidney disease (95% level of significance and 5% degree of precision), a total of 289 subjects needed to be recruited. Written consent was obtained from each individual recruited to the study along with consent to be re-contacted in the future. Following informed consent patients were asked to complete a survey that was administered, using an iPad® device (iPad mini® 7.9-inch multi-touch display with IPS Technology, Apple Inc., Cupertino, Calif., USA). Quicktapsurvey® software (TabbleDabble Inc., Toronto, Canada) was used to collect and collate information to a central encrypted server. To ensure reliability of administration of the questionnaire, all interviewers underwent training at a centralised site using a standardised protocol. The case definition of family history of kidney disease was kidney disease requiring subjects to attend a tertiary referral out-patient nephrology clinic or an in-centre or satellite dialysis unit for renal replacement therapy. All the patients attending an adult nephrology service either as an out-patient or for dialysis were included. Patients were excluded if they were unwilling or unable to provide informed consent. The pediatric population (<17 years) were not included in this study. Patients were also excluded if they did not have kidney disease. Simple closed questions were utilized in the questionnaire with most questions having a limited range of possible answers (online supplementary section for sample of questionnaire; for online suppl. material, see www.karger.com/doi/10.1159/000436983).

The main outcome variable was a positive family history of kidney disease that was reported by the patient. A positive family history was recorded if the index patient had a history of kidney disease in either a 1st-degree relative (parent, child or sibling) or a

2nd-degree relative (grandparent, aunt, uncle, niece, nephew or cousin). Kidney disease in a relative was defined as requiring renal replacement therapy either in the form of dialysis or kidney transplant or kidney disease that warrants repeated follow-up with a nephrology service as an out-patient.

Subjects with a positive family history of kidney disease were re-contacted via telephone interview or via face-to-face interview to review both medical and family history and to establish a family pedigree. Patients who did not report a positive family history were not re-contacted.

The main predictor variable was the etiology of kidney disease. The patient-reported etiology of kidney disease was validated by cross-referencing the reported etiology of kidney disease in their medical records or kidney biopsy reports, if available. Etiology of kidney disease was categorized into 6 major categories based on the ERA-EDTA coding system [13]: familial/hereditary nephropathy, congenital anomalies of the kidney and urinary tract (including reflux nephropathy and congenital hypoplasia/dysplasia of the kidneys), glomerular disease, tubulo-interstitial kidney disease, systemic diseases affecting the kidney and miscellaneous renal disorders. Etiology of kidney disease was classified according to the physician-stated diagnosis in the patient's medical records or diagnosis as per renal biopsy report. Unknown etiology was reported in cases where no definite etiology could be attributed to the cause of kidney disease. Patients who did not know the underlying etiology of kidney disease and where the medical records and/or kidney biopsy reports were unavailable or not cross-referenced (i.e., negative family history group) were classified as 'etiology unconfirmed'.

Other variables captured using the questionnaire included age, age at diagnosis of kidney disease, sex and number of relatives with kidney disease, stage of kidney disease (CKD vs. ESKD), modality of renal replacement therapy and whether a kidney biopsy had been performed.

Statistical analysis was performed using STATA 13.1 statistical data analysis package® (StataCorp LP, College Station, Tex., USA). Baseline characteristics were tested for difference using the independent sample t test with family history of kidney disease as the outcome variable. The Pearson chi test was used to compare categorical variables and the Fisher's exact test for smaller sample sizes. ORs were calculated with family history of kidney disease as the outcome variable. Both univariate and multivariate analyses were performed, with addition adjustment for multiple comparisons using the Scheffé's method. An addition logistic regression model was included adjusting for age at diagnosis of kidney disease. Explanatory variables in the multivariate model included age at diagnosis of kidney disease, gender, stage of kidney disease, history of kidney biopsy having being performed and etiology of kidney disease. The most prevalent etiologies of kidney disease were included in the analysis with a prevalence of ≥2% within the positive family history cohort used as an arbitrary cutoff. A p valve of <0.05 was considered statistically significant.

Results

This study recruited 1,850 patients with kidney disease from January 2014 to September 2014. Seven patients (0.4%) declined to perform the survey and three patients (0.2%) withdrew consent following completion of the survey resulting in 1,840 completed surveys. The number of patients who had CKD was 728 (39.5%) whilst 1,112 (60.4%) patients had ESKD receiving either hemodialysis (n = 622, 59.5%), peritoneal dialysis (n = 60, 5.4%) or renal transplantation (n = 606, 54.5%) of which 430 (38.7%) had a functioning transplant at the time of survey (table 1). The overall prevalence of family history of kidney disease was 34.2% (95% CI 32–36.3). There was no significant difference in the prevalence of positive family history among the CKD and ESKD population; 34.6% (95% CI 31.2–38.1) in the CKD population versus 33.9% (95% CI 31.2–36.7) in the ESKD population (p = 0.753). In total, 629 patients (34.1%) reported a positive family history of kidney disease; 134 (7.3%) of whom had polycystic kidney disease as the primary etiology of kidney disease. Excluding polycystic kidney disease, the prevalence of family history of kidney disease within the cohort was 26.9% (n = 495).

The mean age of participants was 55.9 years (SD ±16.8, range 17.0–94.5 years). Persons reporting a positive family history had a significantly lower age, with a mean of 54.0 years (SD ±16.0, range 17.2–92.4 years) compared to patients with no family history of kidney disease (mean 57 years, SD ±17.1, range 17–94.5 years; p < 0.0003).

The mean age at diagnosis of kidney disease was 42.3 years (SD ±22.0, range 0–91 years). The positive family history cohort demonstrated a younger age at diagnosis of kidney disease (37.3 years, SD ±21.0 vs. 44.8 years, SD ±22.1; p < 0.0001).

The mean number of relatives reported as having kidney disease by the proband was 2.6 persons (95% CI 2.3–2.8). Of the 629 patients who reported a positive family history, 275 (43.72%) reported a 1st-degree relative with kidney disease, 159 (25.28%) a 2nd-degree relative and 195 (31%) both a 1st- and 2nd-degree relative.

Etiology of kidney disease differed among the positive and negative family history cohorts (table 2). The commonest reported etiology of kidney disease in the total cohort was diabetic nephropathy (164 of 1,840, 8.4%). Etiology of kidney disease in the positive family history cohort was confirmed with cross reference to medical records or kidney biopsy reports, if available, in 99.5% (626 of 629) of cases. In the positive family history cohort, ADPCKD accounted for 21.3% of cases (n = 134 of 629). In the non-polycystic kidney disease population with positive family history (n = 495), unknown/uncertain CKD-etiology was the commonest etiology for kidney disease (n = 67, 10.6%). Other common etiologies of kidney disease in this group included congenital abnormalities of the kidney and uri-

Table 1. Demographic and clinical details of study population

Characteristics	Negative family history		Positive family history		p value
	CKD	ESKD	CKD	ESKD	
Total, n (%)	476 (39.31)	735 (60.69)	252 (40.04)	377 (59.94)	
Age, years, mean ± SD	56.6±18.05	57.3±16.53	54.1±17.86	54.6±14.65	0.002*
Gender male	288 (60.5)	121 (48.02)	491 (66.8)	196 (51.99)	<0.0001**
ESKD		735 (60.69)		377 (59.94)	0.0041**
Hemodialysis		437 (36.09)		185 (29.41)	
Peritoneal dialysis		39 (3.22)		21 (3.32)	
Kidney transplant		370 (30.33)		236 (37.52)	
Functioning transplant		259 (23.29)		171 (27.19)	
Kidney biopsy, %	161 (33.82)	389 (52.93)	71 (28.17)	190 (50.40)	<0.0001**
Age diagnosis, years, mean ± SD	48.33±20.70	44.70±22.64	41.21±22.64	34.92±20.27	<0.0001**
Age diagnosis, years, %					
0–20	49 (11.09)	127 (17.52)	47 (20.09)	102 (27.57)	<0.0001***
21–40	112 (25.34)	222 (30.62)	77 (32.91)	125 (33.78)	
41–60	124 (28.05)	172 (23.72)	56 (23.93)	97 (26.22)	
61–80	148 (33.48)	190 (26.21)	47 (20.09)	44 (11.89)	
81–100	9 (2.04)	14 (1.93)	7 (2.99)	2 (0.54)	
Missing data	0	18 (2.48)	34 (13.4)	7 (1.86)	

* Student t test; ** Chi squared test; *** Chi squared test for linear trend.

nary tract (CAKUT; n = 65, 10.3%), diabetic nephropathy (n = 59, 9.4%), IgA nephropathy (n = 45, 7.2%) and hypertensive nephropathy (n = 37, 5.9%; table 2). On univariate analysis, disease entities associated with a positive family history of kidney disease included ADPCKD, Alport's syndrome, unspecified tubulo-interstitial kidney disease, glomerulonephritis – no histology or histology indeterminate – and CAKUT. A diagnosis of ischemic nephropathy and acquired obstructive nephropathy was associated with reduced odds of reporting a positive family history (table 3). Following adjustment for age at diagnosis of kidney disease, etiology unknown was significantly associated with a positive family history. On multivariate analysis, diabetic nephropathy, hypertensive nephropathy and IgA nephropathy also were associated with increased odds of reporting a positive family history (table 3).

Unadjusted analysis of patient characteristics demonstrated that younger age, younger age at diagnosis of kidney disease and female gender were associated with a positive family history of kidney disease (table 3). The likelihood of reporting a positive family history did not differ between those with CKD and ESKD. On univariate analysis, patients were more likely to have had a kidney transplant if they had had a positive family history (OR 1.36), however multivariate analysis failed to demonstrate significance (table 3). Adjusting for age at diagnosis of kidney disease having a positive family history of kidney disease was associated with reduced odds of having a kidney biopsy (table 3). However, excluding patients with ADPCKD, there was no difference in likelihood of having a kidney biopsy in the positive and negative family history groups (OR 0.86, 95% CI 0.69–1.07; p = 0.186).

Discussion

The prevalence of a positive family history of kidney disease in a cohort of CKD and ESKD patients in Ireland was 34.2% (n = 629). The mean number of affected relatives was 2.6. ADPCKD was the predominantly reported etiology of kidney disease; however, excluding ADPCKD, 26.9% (n = 425) of patients still report one or more relatives with kidney disease. Disease entities not classically associated with inherited kidney disease such as tubulointerstitial kidney disease, kidney disease due to unknown or unclear etiology and glomerulonephritis (histology unknown or indeterminate) were associated with a positive family history. In both the negative and positive family history disease cohorts, kidney disease due to unknown etiology remained prevalent at 8.7% and 10.6%, respectively. Patient characteristics associated with a positive family history included younger age of diagnosis and

Table 2. Confirmed etiology of kidney disease in study population

Confirmed diagnosis of proband	Total	Positive family history	Negative family history	p value
Total, n (%)	1,840 (100)	629 (34.2)	1,211 (65.8)	NA
Familial/hereditary nephropathy category				
ADPCKD	160 (8.7)	134 (21.3)	26 (2.1)	<0.0001*
Alport's syndrome/hereditary nephritis	28 (1.5)	24 (3.8)	4 (0.33)	<0.0001**
Von hipple lindau	9 (0.5)	6 (0.9)	3 (0.2)	0.070**
CAKUT category				
Including reflux nephropathy, congenital hypoplasia and dysplasia of the kidneys	155 (8.4)	65 (10.3)	90 (7.4)	0.034*
Glomerular disease category				
IgA nephropathy	126 (6.8)	45 (7.2)	81 (6.7)	0.708*
Henoch scholein purpura	6 (0.3)	3 (0.4)	3 (0.2)	0.417**
Glomerulonephritis – no histology or histology indeterminate	27 (1.5)	15 (2.4)	12 (1)	0.018*
Focal segmental glomerular sclerosis	51 (2.8)	21 (3.3)	30 (2.5)	0.286*
Mesangioprolferative glomerulonephritis	27 (1.5)	9 (1.4)	18 (1.5)	0.925*
Membranous nephropathy	20 (1.1)	5 (0.8)	15 (1.2)	0.482**
Minimal change disease	12 (0.7)	4 (0.6)	8 (0.7)	1**
Nephrotic syndrome/isolated proteinuria	13 (0.7)	4 (0.6)	9 (0.7)	1**
Thrombotic microangiopathy	21 (1.1)	9 (1.4)	12 (1)	0.488**
Lupus nephritis	14 (0.8)	6 (0.9)	8 (0.67)	0.574**
Systemic vasculitis due ANCA vasculitis/anti-GBM disease	80 (4.3)	20 (3.2)	60 (4.9)	0.077*
Systemic disease affecting kidney category				
Diabetic nephropathy	164 (8.9)	59 (9.4)	105 (8.7)	0.612*
Hypertensive nephropathy	116 (6.3)	37 (5.9)	79 (6.5)	0.591*
Ischemic nephropathy including microvascular disease, atheroembolic disease and cardiorenal syndrome	33 (1.8)	5 (0.8)	28 (2.3)	0.025**
HUS/TTP	4 (0.2)	4 (0.6)	0 (0)	0.014**
Tubulo-interstitial kidney disease category				
Unspecified tubule-interstitial kidney disease	29 (1.6)	19 (3)	10 (0.8)	<0.0001*
Secondary to kidney infections/tuberculosis	40 (2.2)	13 (2)	27 (2.2)	0.820*
Secondary to drug toxicity	37 (2)	12 (1.9)	25 (2)	0.820*
Secondary to calculus nephropathy/urolithiasis	27 (1.5)	10 (1.6)	17 (1.4)	0.753**
Acquired obstructive uropathy	22 (1.2)	2 (0.3)	20 (1.7)	0.012**
Miscellaneous renal disorders category				
CKD – etiology uncertain/unknown	173 (9.4)	67 (10.6)	106 (8.7)	0.186*
Acute kidney injury	19 (1)	3 (0.4)	16 (1.3)	0.089**
CKD caused tumour nephrectomy	20 (1)	6 (0.9)	14 (1.2)	0.815**
Etiology unconfirmed/not cross-referenced medical chart	348 (18.9)	3 (0.4)	345 (28.5)	<0.0001*
Other	59 (3.2)	19 (3)	40 (3.3)	0.744*

HUS/TTP = Hemolytic uremic syndrome/thrombotic thrombocytopenic purpura; ANCA = anti-neutrophil cytoplasmic antibody; anti-GBM = anti-glomerular basement membrane; NA = not applicable. * Chi squared test for significance; ** Fisher''s exact test for significance. p value of <0.05 considered statistically significant.

female gender whereas the stage of kidney disease or modality of renal replacement therapy did not differ between groups. When adjusted for potential confounders, a number of common kidney diseases such as diabetic nephropathy, hypertensive nephropathy, CAKUT and IgA nephropathy were associated with increased odds of reporting a positive family history.

Kidney disease is known to aggregate within families [6, 14–16]. Freedman et al. [17] studied incident dialysis patients and found a 20% prevalence in a relative with ESKD. More recently, Skrunes et al. [18] demonstrated that in a Norwegian ESKD population having a 1st-degree relative with ESKD conferred a 7-fold increase in the risk of developing kidney disease. However, few studies

Table 3. Univariate analysis, analysis adjusted for age of diagnosis of kidney disease and multivariate analysis investigating the association between positive family history of kidney disease and multiple variables

Variable	Univariate analysis OR (95% CI)	p value	Logistic regression adjusted for age at diagnosis[#] (95% CI)	p value	Multivariate analysis OR (95% CI)	p value**
Age, years	0.99 (0.98–0.99)	<0.0001*	1.01 (1.00–1.02)	0.0006*	NA	
Gender	1.77 (1.46–2.16)	<0.001*	1.74 (1.42–2.13)	<0.0001*	1.66 (1.32–2.08)	<0.0001*
Age diagnosis	0.98 (0.97–0.99)	<0.0001*	NA	NA	0.99 (0.98–0.99)	<0.001*
Kidney transplant	1.36 (1.11–1.67)	0.003*	0.96 (0.76–1.22)	0.765	0.91 (0.58–1.43)	1
Hemodialysis	0.74 (0.60–0.91)	0.004*	0.85 (0.68–1.06)	0.155	0.92 (0.61–1.39)	1
Peritoneal dialysis	1.04 (0.61–1.78)	0.892	0.97 (0.56–1.67)	0.923	0.93 (0.48–1.78)	1
Stage of kidney disease (CKD or ESKD)	0.97 (0.80–1.18)	0.753	0.88 (0.71–1.08)	0.207	0.88 (0.54–1.43)	1
Kidney biopsy	0.85 (0.70–1.04)	0.108	0.66 (0.53–0.82)	<0.0001*	1.00 (0.76–1.32)	1
Polycystic kidney disease	12.34 (8.00–19.02)	<0.0001*	11.00 (7.12–17.03)	<0.0001*	21.94 (13.54–35.70)	<0.001*
Alport's syndrome	11.97 (4.13–34.65)	<0.0001*	8.06 (2.74–23.71)	<0.0001*	23.15 (7.72–69.34)	<0.001*
Kidney disease etiology unknown	1.24 (0.90–1.72)	0.186	1.47 (1.04–2.10)	0.026*	3.52 (2.47–5.38)	<0.001*
Diabetic nephropathy	1.09 (0.78–1.52)	0.613	1.41 (0.98–2.02)	0.061	3.16 (2.09–4.78)	<0.001*
Hypertensive nephropathy	0.90 (0.60–1.34)	0.592	1.00 (0.66–1.53)	0.987	2.41 (1.52–3.80)	<0.001*
CAKUT	1.44 (1.03–2.00)	0.034*	1.06 (0.74–1.51)	0.749	2.67 (1.77–4.0)	<0.001*
IgA nephropathy	1.07 (0.73–1.57)	0.708	1.03 (0.70–1.52)	0.887	2.76 (1.80–4.30)	<0.001*
Unspecified tubulo-interstitial kidney disease	3.74 (1.72–8.09)	0.001*	3.58 (1.64–7.83)	<0.001*	8.02 (3.59–17.89)	<0.001*
Glomerulonephritis – histology unknown/indeterminate	2.44 (1.16–5.25)	0.022*	2.30 (1.04–5.08)	0.039*	6.10 (2.68–13.89)	<0.001*
Tubulo-interstitial kidney disease secondary drug toxicity	0.92 (0.46–1.85)	0.829	1.13 (0.54–2.36)	0.736	2.45 (1.15–5.24)	0.454
Ischemic nephropathy	0.34 (0.13–0.88)	0.026*	0.47 (0.18–1.25)	0.130	NA	
Acute kidney injury	0.36 (0.10–1.23)	0.104	0.57 (0.16–2.03)	0.386	NA	
Glomerulonephritis secondary ANCA/anti-GBM disease	0.63 (0.37–1.05)	0.079	0.69 (0.41–1.18)	0.175	1.65 (0.93–2.93)	0.930
Acquired obstructive nephropathy	0.19 (0.04–0.82)	0.025*	0.20 (0.45–0.86)	0.031*	NA	

ANCA = Anti-neurtophil cytoplasmic antibody; anti-GBM = anti-glomerular basement membrane; NA = not applicable.

Multivariate logistic regression analysis – explanatory variables include age of diagnosis of kidney disease, gender, stage of kidney disease, history of kidney biopsy and etiology of kidney disease. The most prevalent etiologies of kidney disease were included in the analysis with a prevalence of 2% or higher within the positive family history cohort used as an arbitrary cutoff.

* Denotes statistical significance $p < 0.05$; ** adjusted for multiple comparisons using Scheffé's method. [#] Logistic regression analysis adjusted for age at diagnosis of kidney disease.

have examined both CKD and ESKD populations. We included all the patients regardless of stage of kidney disease or modality of renal replacement therapy and found evidence of familial clustering in over a third of the population. Moreover, we have demonstrated that certain common disease entities such as diabetic nephropathy and hypertensive nephropathy are associated with reporting a positive family history. Therefore, family history of either CKD or ESKD may offer a simple additive tool in the recognition and assessment of kidney disease.

In addition, a positive family history of kidney disease was demonstrated in diseases not classically associated with familial inheritance. There was 8-fold increase in reporting a positive family history of kidney disease in patients with unspecified tubulo-interstitial kidney disease. Our study also demonstrated that CAKUT was associated with a 2-fold increase in reporting familial kidney disease with glomerulonephritis (histology unknown/indeterminate) showing a similar familial tendency. Increasingly genes are being identified for conditions which were not

previously associated with familial inheritance. Identification of the MUC1 mutation in families with medullary cystic kidney disease has helped redefine and characterize tubulo-interstitial kidney disease in cases where there were no associated features except progressive kidney disease [8, 19]. In an Irish population, a hybrid *CFHR3-1* gene has been found to be associated with familial C3 glomerulopathy [20]. With advances in molecular genetics and biological techniques, at increasingly affordable prices, genetic analysis of DNA from these families may offer the opportunity to identify causative genetic mutations or predisposing mutations that place certain families at increased risk of kidney disease. Indeed, Yang et al. [21] have demonstrated the clinical application of genetic testing where whole exome sequencing was utilized for the diagnosis of Mendelian disorders with a diagnostic yield of 25%.

In a significant number of ESKD and CKD populations, the underlying etiology of the disease remains undetermined [22]. Our group demonstrated that in a large cohort of ESKD and CKD patients in Ireland, the cause of kidney disease remains unknown in 9.4% of cases. Moreover, in our study, there was a 3-fold increase in reporting a positive family history of kidney disease in patients where the cause of kidney disease was unknown. Analysis of these familial cohorts represents an opportunity to identify inheritable genetic defects and familial risk factors that increase the risk of progression to ESKD. The hope is that this may help identify causative genetic defects prior to clinical presentation allowing for therapies that may delay deterioration leading to end-stage renal disease.

This study has limitations. Our study is reliant on the ability of a patient to self-report both the etiology of kidney disease and to correctly identify a positive family history which can be subject to reporting bias. To our knowledge, no study to date has assessed the reliability of self-reporting a positive family history of kidney disease among a kidney disease population. However, studies in patients with lymphoma demonstrate higher sensitivity and specificity among cases compared to controls for self-reporting a history of cancer in a family members (0.85, 95% CI 0.83–0.87 and 0.80, 95% CI 0.77–0.82, respectively). The sensitivity of self-reporting familial cancers by site was less specific for rare malignancies at 20% but increased to nearly 75% for more common cancers [23]. Extrapolating these findings to our cohort, it is likely that self-reporting family history of kidney disease may have similar reliability in terms of identifying affected family members. However, reporting the etiology of kidney disease, in particular rarer or more obscure causes of kidney disease, is likely to be less reliable. We, therefore, increased accuracy by confirming the etiology of kidney disease in 99.5% of patients reporting a positive family history of kidney disease and re-contacting patients to establish a family pedigree.

In addition, selection bias must be considered. Patients with a positive family history may be more likely to engage themselves with the survey. This issue was addressed by administering the survey to a large representative sample of the ESKD population in Ireland. Our sample represents 43% of the ESKD population at the various recruitment sites (n = 1,112 of 2,586) and 28.1% (n = 1,112 of 3,960) of the total ESKD population in Ireland. Our sample also demonstrates similar age distribution and distribution of modality of renal replacement therapy to the ESKD population in Ireland [2]. For the CKD population, previous studies have demonstrated an estimated prevalence ranging from 11.2% [9] to 17% in the Irish population [11]. These results are comparable to worldwide prevalence rates of approximately 8–16% [24]. Based on our initial sample size calculation, we were able to recruit sufficient numbers of patients with CKD to detect a prevalence rate of reporting a positive family history of 25%. Moreover, the reported prevalence of family history did not differ significantly between the CKD and ESKD population in our study (34.6 and 33.9%, respectively; p = 0.753). The mean age in our study was 56 years; therefore, selection bias with under-representation of younger age categories should also be considered. However, prior epidemiological studies have demonstrated that in an Irish population, prevalence rates of CKD is low in younger age groups (0.45% in the 18–39 years age group and 2.24% in the 40–59 years age group) with a sharp rise in the over 60 years age group [9]. Indeed, population-based studies in the United States have demonstrated similar low prevalence rates of CKD in younger populations [25]. This could be due to selection bias with younger age categories less likely to come into contact with medical services due to absence or milder stages of kidney disease. Alternatively, it may represent a truly low prevalence rate of CKD in younger age groups.

Despite these limitations, this paper describes the largest study to date of familial kidney disease in Ireland. The finding of a family aggregation of a kidney disease in 34.2% of a kidney disease population is significant. Few studies have assessed family history of kidney disease within the CKD population and given the scope for early intervention and therapeutic targets prior to the establishment of ESKD; this population warrants further as-

sessment and consideration. Often, it is challenging to decipher the interaction between genetics and environmental factors and their contribution to the development of kidney disease in population-based studies. Certainly, in other populations, familial aggregation of kidney disease has been demonstrated [26, 27]. In the United States, familial clustering of kidney disease has been noted in the African American population [17, 28, 29]. This elevated risk is independent of socioeconomic status [30] and prevalence of hypertension and diabetes mellitus [31, 32]. Moreover, studies in these at-risk groups have led to the identification of a number of genetic loci and candidate genes such as the *MYH9/APOL1* locus which may be responsible for kidney disease in these populations [33, 34]. Given that over one-third of this sample report a family history of kidney disease, it may offer an opportunity to study causative factors and potential genetic contribution in an Irish kidney disease population.

Transparency Declaration and Ethics

None to declare.

Disclosure Statement

The authors have no conflicts of interest to declare.

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