Published in final edited form as:

Am J Kidney Dis. 2017 October ; 70(4): 476–485. doi:10.1053/j.ajkd.2017.01.046.

PKD2-Related Autosomal Dominant Polycystic Kidney Disease: Prevalence, Clinical Presentation, Mutation Spectrum, and Prognosis

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SUPPLEMENTARY MATERIAL

Note: The supplementary material accompanying this article (<http://dx.doi.org/10.1053/j.ajkd.2017.01.046>) is available at www.ajkd.org

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Abstract

Background—*PKD2*-related autosomal dominant polycystic kidney disease (ADPKD) is widely acknowledged to be of milder severity than *PKD1*-related disease, but population-based studies depicting the exact burden of the disease are lacking. We aimed to revisit *PKD2* prevalence, clinical presentation, mutation spectrum, and prognosis through the Genkyst cohort.

Study Design—Case series, January 2010 to March 2016.

Settings & Participants—Genkyst study participants are individuals older than 18 years from 22 nephrology centers from western France with a diagnosis of ADPKD based on Pei criteria or at least 10 bilateral kidney cysts in the absence of a familial history. Publicly available whole-exome sequencing data from the ExAC database were used to provide an estimate of the genetic prevalence of the disease.

Outcomes—Molecular analysis of *PKD1* and *PKD2* genes. Renal survival, age- and sex-adjusted estimated glomerular filtration rate.

Results—The Genkyst cohort included 293 patients with *PKD2* mutations (203 pedigrees). *PKD2* patients with a nephrology follow-up corresponded to 0.63 (95% CI, 0.54–0.72)/10,000 in Brittany, while *PKD2* genetic prevalence was calculated at 1.64 (95% CI, 1.10–3.51)/10,000 inhabitants in the European population. Median age at diagnosis was 42 years. Flank pain was reported in 38.9%; macroscopic hematuria, in 31.1%; and cyst infections, in 15.3% of patients. At age 60 years, the cumulative probability of end-stage renal disease (ESRD) was 9.8% (95% CI, 5.2%–14.4%), whereas the probability of hypertension was 75.2% (95% CI, 68.5%–81.9%). Although there was no sex influence on renal survival, men had lower kidney function than women. Nontruncating mutations ($n = 36$) were associated with higher age-adjusted estimated glomerular filtration rates. Among the 18 patients with more severe outcomes (ESRD before age 60), 44% had associated conditions or nephropathies likely to account for the early progression to ESRD.

Limitations—Younger patients and patients presenting with milder forms of *PKD2*-related disease may not be diagnosed or referred to nephrology centers.

Conclusions—Patients with *PKD2*-related ADPKD typically present with mild disease. In case of accelerated degradation of kidney function, a concomitant nephropathy should be ruled out.

INDEX WORDS

Autosomal dominant polycystic kidney disease (ADPKD); *PKD2*; end-stage renal disease (ESRD); prognosis; mutation spectrum; sequencing; genetics; disease progression; disease severity; genetic prevalence; mutation detection; renal survival; kidney function; case series

Autosomal dominant polycystic kidney disease (ADPKD) is the most widespread monogenic kidney disorder worldwide. Its precise prevalence is difficult to assess, and although the theoretical lifetime risk for ADPKD has been estimated at about 10/10,000,¹ minimum point prevalences of 2.9 and 3.3/10,000 were determined in 2 population-based studies conducted in the United Kingdom and Germany, respectively.^{2–4} *PKD1* (MIM [Mendelian Inheritance in Man] 601313, located on chromosome 16p13.3)⁵ and *PKD2* (MIM 173910, located on chromosome 4q21)⁶ are the principal genes known to cause ADPKD, with an overall mutation detection rate of ~90%.^{7,8} A third gene, *GANAB*, has recently been described in 9 pedigrees, causing milder polycystic kidney disease, but in some cases severe polycystic liver disease.⁹ Mutations to *PKD1* account for the disease in 80% to 85% of mutation-positive pedigrees, whereas *PKD2* mutations are identified in the remaining 15% to 20%.^{8,10–13} A recent study suggested a higher contribution of *PKD2* mutations in ADPKD, ~30%, but the cohort was enriched in patients with milder disease.¹⁴

PKD1 encodes polycystin 1 (PC1), a multidomain glycoprotein of 4,303 amino acids that is cleaved at a G protein–coupled receptor proteolytic site. Polycystin 2 (PC2), a 968-amino-acid protein, is encoded by *PKD2* and belongs to the transient receptor potential family of calcium-regulated cation channels. The cytoplasmic carboxy-terminal coiled-coil domain of PC1 is known to interact with PC2; this interaction is determinant for PC1 maturation, trafficking to the cilia, and stability.^{15,16} Although there is considerable phenotype overlap between *PKD1*- and *PKD2*-related ADPKD, typically the latter appears to be a much less severe disorder, with end-stage renal disease (ESRD) being less frequent and occurring later in life, as underlined by the respective median ages at ESRD: about 55.6 years for truncating variants of *PKD1*, about 67.9 years for nontruncating mutations of *PKD1*, and about 79.7 years for *PKD2*.¹¹ In contrast, the severity of polycystic liver disease seems similar in patients with *PKD1* and *PKD2* mutations.¹⁷

Considerable progress in understanding pathways involved in cystogenesis has been made in the past few years^{18–20} and allowed the current development of specific therapies.^{21,22} In this context, accurate description of the ADPKD phenotype is important and represents a key step to delineate which patients should receive these new treatments. Since the discovery of both genes about 20 years ago, several studies have reported the ADPKD phenotypic spectrum, but only a few studies have focused on the population with *PKD2* mutations.^{23–25} For those studies, *PKD2* involvement was assessed mainly by linkage, and as a result, the cohorts consisted mainly of large pedigrees collected through international collaborations. Hence, small families and sporadic cases were under-represented. Another unaddressed question remains the true prevalence of *PKD2*-related ADPKD, which is difficult to evaluate given the proportion of individuals with *PKD2* mutations that remain undiagnosed until late adulthood.

Genkyst is an ongoing observational cohort, the aim of which is to include all patients with ADPKD followed up in the nephrology centers of western France, irrespective of disease severity.^{11,12} Through this population-based study, we aimed to describe the clinical presentation of *PKD2*-related ADPKD and investigate factors affecting progression to chronic kidney disease (CKD). In addition, we explored the prevalence of *PKD2* mutations

using publicly available whole-exome sequencing data and have provided, we believe for the first time, an estimate of the genetic prevalence of ADPKD.

METHODS

Patients

This study is a cross-sectional study of the Genkyst cohort, resulting from the collaboration of 22 nephrology centers in western France.^{11,12} Patients with ADPKD were recruited in January 2010 to March 2016. In individuals with a positive familial history, diagnosis of ADPKD was based on the Pei criteria: that is, at least 3 renal cysts before the age of 39 years, at least 2 cysts per kidney from age 40 to 59 years, and at least 4 cysts per kidney after the age of 60 years.²⁶ In the absence of familial history, diagnosis required the presence of at least 10 bilateral kidney cysts. The patients' clinical data obtained during medical interviews at the time of their inclusion and from medical records were entered in a standardized clinical report form. All participants provided informed consent, and the local ethics committee approved the study (CCTIRS 10.385).

Molecular Analysis

The entire coding regions of the *PKD1* and *PKD2* genes and their flanking intronic regions were screened by Sanger sequencing, as previously described.⁷ Patients with no clear pathogenic mutation detected after Sanger sequencing were screened for gross rearrangements using multiplex ligation-dependent probe amplification and array-based comparative genomic hybridization. Mutations were classified as truncating (frameshifting, indels, nonsense mutations, canonical splicing changes, and in-frame indels ≥ 5 amino acids) or nontruncating (missense, in-frame indel ≥ 4 amino acids, noncanonical splicing events, and non-stop mutations).

Prevalence Calculation

Brittany is a well-defined geographic area of 3.258 million inhabitants.²⁷ The prevalence of patients with *PKD2* mutations in Brittany followed up in nephrology centers was calculated at the midpoint of the study, March 31, 2013, as the number of patients alive at that date divided by the number of inhabitants in Brittany on January 1, 2013, closest census point. The 95% confidence intervals (CIs) for prevalence rates were computed assuming that the observed number of cases follows a Poisson distribution.

Because a significant number of patients with *PKD2* mutations may not be diagnosed or referred to a nephrology center, we estimated the genetic prevalence of *PKD2*. The Exome Aggregation Consortium (ExAC, Cambridge, MA) is a collection of exome data of 60,706 unrelated and ostensibly healthy individuals from different origins.²⁸ ExAC data were downloaded from <http://exac.broadinstitute.org> and analyzed using SNP & Variation Suit, version 7 (Golden Helix). Truncating variants (nonsense, splice, and frameshift mutations) and missense variants known to be fully penetrant were inventoried, with their respective allele counts, and entered in the calculation of the genetic prevalence. In order to confirm the results obtained by this first calculation, we also considered nonsense and splice mutations alone and evaluated the total number of pathogenic mutations by adjusting our count to the

proportion of nonsense and splice mutations in all *PKD2* single pedigrees reported in the Mayo ADPKD mutation database.²⁹

Statistical Analysis

Overview—All statistical analyses were performed using SPSS software, version 19 (IBM Corp), and JMP Pro, version 11.2.1 (SAS Institute Inc). Median values were compared using a nonparametric Mann-Whitney test or Kruskal-Wallis test, depending on the number of groups.

Analysis of Predictors of Kidney Function—Effects of sex, smoking status, number of pregnancies, mutation type, and mutation position on kidney function were individually analyzed using a linear regression taking age into account. A square-root transformation of estimated glomerular filtration rate (eGFR, calculated using CKD-EPI [CKD Epidemiology Collaboration] creatinine equation³⁰) was performed to comply with the normality required by this analysis. All variables significantly associated with age-adjusted square-root-transformed eGFR at a threshold of 0.2 were then entered in a multivariable linear regression. In order to also include patients having reached ESRD in these analyses, the last eGFR before initiating renal replacement therapy and the corresponding age were taken into account for patients with ESRD. To quantify the degree to which individuals belonging to the same pedigree or sharing the same mutation correlate with each other in regard to eGFR, we determined the intraclass correlation coefficient, adjusting for age and sex.

Analysis of Renal Survival—Renal survival (time from birth to ESRD) and hypertension-free survival (time from birth to diagnosis of hypertension) were analyzed using the Kaplan-Meier method. Differences between survival curves in male and female patients were assessed using a log rank test with a 0.05 significance level.

RESULTS

Patient Characteristics and Description of Mutation Spectrum

A *PKD2* mutation was identified in 293 patients from 203 pedigrees. *PKD2* pedigrees represented 20.2% of the 1,006 mutation-positive pedigrees registered in the Genkyst cohort as of March 2016. Characteristics of patients at inclusion are presented in Table 1. A total of 83 different mutations were reported in the 203 pedigrees (Table S1, available as online supplementary material). These mutations spanned the entire coding region of the *PKD2* gene (Fig 1) and were mainly truncating mutations (87.7% of mutations, 85.7% of pedigrees; Table S2).

Prevalence of *PKD2*-Related ADPKD

A majority of the patients with *PKD2* mutations (n = 207; 149 pedigrees) live in Brittany (a well-defined geographic area of 3.258 million inhabitants²⁷), reflecting the early involvement of these centers in the study. At the midpoint of the study period, 204 patients were alive, and the number of patients with *PKD2* mutations in Brittany included in the Genkyst cohort was hence calculated at 0.63 (95% CI, 0.54–0.72)/10,000.

However, because only a fraction of patients with *PKD2* mutations are likely to be seen in these centers, we compared these numbers with *PKD2* mutations detected in the ExAC database. A total of 11 fully penetrant variants were identified in 14 patients (Table S3). Thus, *PKD2* genetic prevalence was estimated at 2.31 (95% CI, 1.10–3.51)/10,000 in the whole ExAC population. Because some deletion or insertion mutations reported in ExAC may represent false positives due to misalignment of the exome sequences, we verified the consistency of our results taking into account only nonsense and typical splice mutations, which correspond to 60% of the pathogenic mutations reported in the 438 unique pedigrees of the ADPKD mutation database.²⁹ Considering that 8 individuals were found to have a splice or nonsense variant, we calculated that about 13.3 patients would have a mutation of *PKD2*, hence a prevalence of 2.19 (95% CI, 1.01–3.37)/10,000, consistent with our initial value. Because the ExAC database comprises patients with different ethnicities, we also considered separately the European population ($n = 36,677$), in which 6 individuals were found to have a *PKD2* mutation, corresponding to a prevalence of 1.64 (95% CI, 0.33–2.94)/10,000.

Diagnosis and Clinical Features of ADPKD in *PKD2* Patients

Diagnosis of ADPKD—Median age at diagnosis was 42 (range, 9–84.5) years ($n = 262$), and the diagnosis was made significantly earlier in women (median age at diagnosis, 40 vs 47 years; $P < 0.001$). ADPKD was diagnosed incidentally during an abdominal imaging examination prescribed for another indication in 95 (32.5%) patients, due to a familial study in 71 (24.3%), following a urologic complication in 65 (22.3%), and for exploring secondary hypertension in 31 (10.6%; Fig 2). Exact eGFRs at diagnosis were available for a minority of patients, but analysis of past eGFR values when available ($n = 226$) showed that 81.4% of patients had eGFRs > 60 mL/min/1.73 m² at diagnosis.

Hypertension—Hypertension was present in 221 (75.4%) patients, with a median age at diagnosis of 49 (range, 24–76) years. Cumulative probabilities of hypertension, obtained by study of the hypertension-free survival curve in the cohort, were 75.2% (95% CI, 68.5%–81.9%), 79.2% (95% CI, 72.7%–85.7%), and 94.3% (95% CI, 89.7%–98.9%) at age 60, 65, and 70 years, respectively. Age at diagnosis of hypertension was not influenced by sex (Fig 3A).

Urologic Events—Urologic events, including flank pain related to cysts, macroscopic hematuria or symptomatic intra-cystic hemorrhage, cyst infections, and kidney stones, were reported by 175 (59.7%) patients (see Table 2 for prevalence and median age at first occurrence). Cumulative probabilities of having had at least one of these complications were 54.6% (95% CI, 47.5%–61.7%), 60.4% (95% CI, 53.3%–67.5%), and 63.8% (95% CI, 56.3%–71.3%) at age 60, 65, and 70 years, respectively. There was no significant difference between men and women.

Kidney Function and Factors Influencing Kidney Function

Distribution of patients according to CKD stage is reported in Table 1. A majority of patients had preserved kidney function, and proportions of patients with eGFRs > 30 mL/min/1.73 m² were 97.8%, 94.2%, 73.1%, 58.8%, and 43.5% among patients younger than 40, 40 to

younger than 50, 50 to younger than 60, 60 to 70, and older than 70 years, respectively (Fig 4).

At inclusion, 66 patients had reached ESRD, as defined by the requirement of renal replacement therapy (either dialysis or kidney transplantation). Median age at ESRD obtained by Kaplan-Meier curve analysis was 77.8 (range, 41.5–84.6) years. Renal survival did not differ according to sex (Fig 3B). At age 60, 65, and 70 years, probabilities of having reached ESRD were 9.8% (95% CI, 5.2%–14.4%), 18.5% (95% CI, 12.4%–24.6%), and 38.1% (95% CI, 28.8%–47.4%), respectively.

To assess the influence of clinical and genetic factors on kidney function, we performed univariate and multivariate linear regressions. Male sex was associated with lower eGFRs (negative β value in Table 3), which is illustrated in Fig 3C. There was no influence of smoking status on eGFRs after multivariate analysis, and number of pregnancies was not associated with kidney function (Table 3). Truncating mutations were associated with lower age-adjusted eGFRs (negative β value in Table 3 and Fig 3D), and mutation position did not influence kidney function. Intrafamilial correlation analysis estimated that belonging to the same pedigree explained 34.1% of the variability in eGFRs, while sharing the same *PKD2* mutation explained only 7.1% of the variability in eGFRs. Last, we focused on a subgroup of 18 patients presenting with more severe renal involvement, defined by ESRD onset before the age of 60 years. In this subgroup, 8 patients had at least one severe associated condition or nephropathy likely to account for early progression to ESRD (listed in Table 4).

DISCUSSION

We report a detailed clinical presentation of *PKD2*-related ADPKD through a population-based study in a cohort of 293 patients from western France.

In France, most patients with ADPKD are referred to a nephrologist at an early stage of the disease. The Genkyst cohort involves all nephrologists of a single area and aims to include all consenting patients with ADPKD, irrespective of CKD stage, and is in this regard very representative of disease severity. *PKD2* represents 20% of the mutation-positive pedigrees of the Genkyst cohort, which is a little higher than previously reported^{7,8} and yet probably underestimates its true prevalence. Consistent with that point, *PKD2* genetic prevalence in Europe of 1.64/10,000, derived from the analysis of ExAC data, is almost 3 times higher than the number of the cases followed up in nephrology centers. The difference is likely due to younger individuals who are undiagnosed and patients with mild disease not followed up at a nephrology center or who remain undiagnosed in adulthood.

Use of an ExAC data set is an original way to address the much-debated question of ADPKD prevalence. Because two-thirds of *PKD1* sequence is duplicated on 6 pseudogenes, analysis of this gene region by exome capture and next-generation sequencing is not reliable. However, if we consider that patients with *PKD2* mutations represent at most about 20% to 30% of the total patients with ADPKD^{12–14} and that *PKD2* prevalence in Europe is about 1.6/10,000 (or 1/6,112), an overall prevalence of individuals with *PKD1* or *PKD2* mutation would be between 5.45 and 8.18/10,000 (or 1/1,222 and 1/1,833). This figure is consistent

with estimates of lifetime prevalence of ADPKD^{1,31,32} and higher than ADPKD point-prevalence estimates.²⁻⁴ Because the ExAC data set includes a majority of ostensibly healthy individuals, this genetic prevalence is more likely to be under- than overestimated because some patients with *PKD2* mutations may not be included.²⁸ In addition, although some missense variants of *PKD2* identified in ExAC may be pathogenic, they were not included given the lack of information on their functional consequences, which could lead to another underestimation bias.

In this study, we identified a significant number of recurrent mutations. Despite careful reanalysis of the pedigrees and discussion with patients, we were not able to link the families sharing the same mutation, but the presence of founder effect is likely for some of the mutations identified.

Taking this cohort into consideration, we can summarize the *PKD2*-related disease presentation in 3 ways. First, despite often having a positive family history, a diagnosis of *PKD2*-related ADPKD is typically made late, usually after the fourth decade. Familial investigation accounted for the diagnosis in <25% of cases and ADPKD was more often diagnosed incidentally during radiologic examination or following urologic events. Second, although a mild disease, *PKD2*-related ADPKD is far from being asymptomatic, as illustrated by the high prevalence of urologic events, with almost 40% of patients reporting flank pain, ~30% reporting macroscopic hematuria or cyst hemorrhage, and a cumulative probability of having presented with at least 1 urologic event >60% at the age of 70 years. Corresponding figures traditionally reported in the literature for the overall ADPKD population are slightly higher, with 60% of the adult population reporting flank pain and the same proportion reporting macroscopic hematuria or cyst hemorrhage.^{10,33} Hypertension was also highly penetrant, with a cumulative probability of hypertension at the age of 70 years >90%, which implies that blood pressure should be carefully monitored in at-risk individuals. As expected, median age at diagnosis of hypertension was 10 years later than reported in patients with *PKD1*-related disease.¹¹ Third, CKD progression is slow in the great majority of cases. Unlike a previous study,⁶ we did not identify a sex influence on renal survival in patients with *PKD2* mutations, probably due to the low number of them reaching ESRD, which makes group comparisons difficult. However, male patients had significantly lower eGFRs than female patients, in agreement with a recent report.¹³

The overall consistency of the *PKD2*-related disease presentation reinforces the importance of molecular genetics in the prognostic assessment of patients with ADPKD, especially at an early stage of the disease when cyst burden is still limited. Because disease severity varies in patients with *PKD2* mutations, genetic information should be considered along with clinical information, such as age at diagnosis of hypertension and age at first urologic event, using the PROPKD [Predicting Renal Outcome in Polycystic Kidney Disease] score¹² to provide prognostic information at an individual level. With the current widespread use of next-generation sequencing, the cost of molecular analysis is expected to decrease constantly.³⁴⁻³⁸ Interestingly, mutation type significantly influenced eGFR in our multivariable linear regression, with truncating mutations associated with lower eGFRs. Given the small number of patients with nontruncating mutations (n = 36), this information should still be considered with caution. It is likely that some of the nontruncating mutations

identified may correspond to hypomorphic variants. For instance, the mutation p.R322W (substitution of a tryptophan for an arginine at amino acid 322), identified in 5 patients of the cohort, has been shown to cause a significant decrease in the level of mature PC1 in vitro, but this level is still higher than in the presence of *PKD2* truncating mutation.¹⁶ This may be the case for a majority of the missense variants identified here, accounting for the apparent milder nature of the disease within this group. However, the mutation p.R322Q (substitution of a glutamine for an arginine at amino acid 322), identified in 3 patients, completely prevents PC1 maturation and surface/ciliary localization.¹⁶ In order to refine genotype-phenotype correlations within patients with *PKD2* mutations, a systematic in vitro assessment of each missense variant identified will have to be undertaken. Beyond allelic influence, additional modifier genes are probably modulating the severity of the kidney disease. This is supported because the correlation of individuals belonging to the same pedigree explained 34.1% of the variability in eGFRs, whereas the correlation of individuals sharing the same mutation explained only 7.1% of this variability.

The vasopressin 2 receptor antagonist tolvaptan is available in Canada and Japan and recently gained marketing authorizations in Europe. Several other promising therapeutic agents are currently under evaluation.²¹ The existence of these new therapeutic options will probably cause patients with ADPKD to be referred to nephrology centers more frequently and earlier in the course of the disease than presently. One burning question arises: should all patients with ADPKD be considered for those new therapies? This study shows that in patients with *PKD2* mutations, risks for reaching ESRD are 9.8% and 18.5% at the ages of 60 and 65 years, respectively. Furthermore, in almost half the patients who reached ESRD before age 60 years, a concomitant nephropathy was identified, and the absence of massive enlargement of the kidneys was suggestive of a predominant role of these cofactors in the development of kidney failure. A position statement for the use of tolvaptan in ADPKD has recently been issued by a European group of experts.³⁹ These recommendations suggest limiting tolvaptan use to adult patients aged 18 to 30 years with CKD stages 1 to 3a, aged 30 to 40 years with CKD stages 2 to 3a, and aged 40 to 50 years with CKD stage 3a who, in addition, have an eGFR decline or kidney growth suggestive of rapidly progressing disorder. In our *PKD2* cohort, only 25 patients, including 12 patients younger than 30 years, had a CKD stage and age class matching these criteria. Considering the later loss of kidney function in patients with *PKD2* mutations, the tolerance profile, and the cost of tolvaptan, it seems presently difficult to advocate for the early initiation of a long-term treatment. However, some specific situations, such as a familial history of early-onset ESRD, should raise awareness and lead to careful and regular clinical reevaluation.

This study has some limitations. Because *PKD2*-related ADPKD is probably underdiagnosed, the description of its clinical course does not reflect all individuals harboring *PKD2* mutations, but only patients who have been diagnosed. Younger patients and patients presenting with milder forms of *PKD2*-related disease may not be diagnosed or referred to nephrology centers.

In conclusion, although *PKD2*-related ADPKD is typically milder than *PKD1*-related ADPKD, it should not be considered asymptomatic. Earlier referral and careful familial investigations may enable nephrologists to provide timely symptomatic care and educate

patients about a healthy lifestyle, which may reduce environmental modulations of the phenotype. The extent to which patients with *PKD2* mutations should receive new targeted therapies presently remains uncertain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank all patients and the Genkyst Group investigators: Drs Grall, Tanquerel, Moal, Treguer, Segalen, Mesguen, Gosselin, Kersale, Hemon, and Lanfranco (Centre Hospitalier Régional Universitaire, Brest); Profs Giral, Blanco, and Fakhouri and Drs Meurette, Lino, Garandeau, Touzot, Hodemon-Corne, Allain-Launay, Cantarovich, Hristea, Couvrat, Lavainne, Vercel, Chapal, and Dufay (Centre Hospitalier Universitaire, Nantes); Prof Le Pogamp and Drs Rivalan, Morin, Laruelle, Richer, and Lorcy (Centre Hospitalier Universitaire, Rennes); Drs Merieau, Barbet, Golea, Ghouti, Gautard, Sautenet, François, Fournier, Baron, Prat, Salmon, Von Ey, Rabot, D'Halluin, Chevallier, and Moles and Profs Buchler and Halimi (Centre Hospitalier Régional Universitaire, Tours); Drs Ang,† Coulibaly, Baluta, Leonetti, Boulahrouz, and Potier (Centre Hospitalier Yves le Foll, Saint Brieuc); Drs Perrichot, Menoyo, and Pincon (Centre Hospitalier de Bretagne Atlantique, Vannes), Drs Metes and Wehbe (Centre Hospitalier de Cornouaille, Quimper); Dr Dolley-Hitze (Centre Hospitalier Broussais, Saint Malo); Drs Desport, Thierry, Belmouaz, Javaugue, Bauwens, Fride Leroy, Diolez, Colombo, and Galinier (Centre Hospitalier Universitaire, Poitiers); Drs Latif and Jousset (Centre Hospitalier du Centre Bretagne, Pontivy); Drs Guillodo, Strullu, Chaffara, and Le Mee (Association des Urémiques de Bretagne, Brest-Morlaix); Drs Goulesque and Terki (Centre de Néphrologie et de Dialysed' Armorique, Brest); Drs Besnier, Regnier-Le Coz, Blanpain, and Durault (Centre Hospitalier Georges Charpak, Saint-Nazaire); Drs Sawadogo and Guillou (Centre Hospitalier de Bretagne Sud, Lorient); Dr Le Grand (Association des urémiques de Bretagne, Lorient); Drs Benarbia, Rifaat, and Dimulescu (Association des Urémiques de Bretagne, Quimper); Drs Querard, Target, Jaulin, and Ottavioli (Centre Hospitalier Départementale de Vendée, La Roche Sur Yon); Drs Ferrier, Durand, and Menoyo-Calonge (ECHO, Vannes); Drs Lefrançois and Savoie (ECHO, Saint Herblain-Nantes); and Dr Bertheleme (Centre Héliomarin, Roscoff). We also acknowledge the clinical research team (Christelle Ratajczak, Christelle Guillerme-Regost, and Stéphanie Bouvier) and the Molecular Genetic Laboratory of Brest (Joëlle Creff, Isabelle Quéré, Caroline Benech, and Sylvia Redon).

Support: This study was conducted with the support of the National Plan for Clinical Research (PHRC regional 2010), Groupement Inter-Régional de Recherche Clinique et d'Innovation (GIRGI Grand-Ouest), the Société Française de Néphrologie, and the Institut National de la Santé et de la Recherche Médicale (INSERM). Dr Cornec-Le Gall is currently funded by an American Society of Nephrology Foundation Kidney Research Fellowship. The funders of this study did not have any role in the design or interpretation of the data.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

Contributions: Research idea and study design: ECLG, YLM, MPA, CF; data acquisition: ECLG, MPA, ER, MH, CC, EM, TF, CV, JD, PSiohan, HL, PG, LE, FB, LM, CHS, CS, PD, SG, MM, AK, GS, JFA, SM, JMC, PCH, CF, YLM; data analysis/interpretation: ECLG, MPA, PS, J-MC, PCH, CF, YLM; statistical analysis: ECLG, PSaliou; supervision or mentorship: YLM, CF. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. ECLG takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Peer Review: Evaluated by 2 external peer reviewers, a Statistical Editor, a Co-Editor, and Editor-in-Chief Levey.

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Figure 1.

Distribution of mutations identified along the *PKD2* gene. The 83 distinct *PKD2* pathogenic mutations identified in the 203 pedigrees were plotted against their respective positions within the *PKD2* coding sequence and the primary protein sequence. Note that in the figure, large rearrangements, a subclass of truncating mutations, are illustrated as an independent type of pathogenic mutation (represented as arrows if deletion boundaries are defined or lines in the opposite case), and truncating and nontruncating mutations (represented as diamonds) refer to conventional types of mutation such as point mutations, small deletions, small insertions, or small indels. Abbreviations: CC, coil-coiled domain; EF, EF hand domain; TM, transmembrane domain.

Figure 2.
Context of diagnosis in *PKD2* patients.

Figure 3.

Hypertension-free survival, renal survival, and kidney function in *PKD2* patients. (A) Kaplan survival curves represent hypertension-free survival in *PKD2* patients, showing that age at diagnosis of hypertension is not influenced by sex and that most *PKD2* patients develop hypertension. (B) Kaplan survival curves show that renal survival does not differ in male (M) and female (F) patients. (C) Age-adjusted estimated glomerular filtration rates (eGFRs) in male and female patients show that male *PKD2* patients tend to have lower eGFRs than female *PKD2* patients (nonlinear scale due to the square-root transformation of eGFR values). (D) Age-adjusted eGFRs in patients with nontruncating versus truncating mutations of *PKD2* show that patients with nontruncating variants tend to have higher eGFRs (nonlinear scale due to square-root transformation of eGFR values). Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ESRD, end-stage renal disease.

Figure 4.

Distribution of inclusion estimated glomerular filtration rate > 30 mL/min/1.73 m² according to sex and age. The given percentage is for men and women of the given age range. Number of patients in each subcategory is indicated in the bottom of each column.

Table 1

Characteristics of 293 Patients at Inclusion

Characteristic	Value
Age, y	60.7 [16.2–89.5]
Male sex	123 (42.0)
CKD stage ^a	
1	55 (18.8)
2	64 (21.8)
3a	35 (11.9)
3b	38 (13)
4	27 (9.2)
5	74 (25.3)
Undergoing RRT ^b	63 (21.5)

Note: There were 293 patients with *PKD2* mutations (203 pedigrees). Values for categorical variables are given as number (percentage); for continuous variables, as median [interquartile range].

Abbreviations: CKD, chronic kidney disease; RRT, renal replacement therapy.

^a According to estimated glomerular filtration rate (calculated using the CKD Epidemiology Collaboration creatinine equation).

^b Dialysis or kidney transplantation.

Table 2Proportion of *PKD2* Patients With Past Urologic Events and Age at First Episode

Urologic Event	Frequency of Each Event ^a	Age at First Occurrence, y ^b
Flank pains	38.9 (n = 114)	46 (16–80)
Macroscopic hematuria or intracystic hemorrhage	31.1 (n = 91)	49 (15–80)
Kidney stone	19.5 (n = 57)	41 (16–76)
Cyst infection	15.3 (n = 45)	56.5 (16–80)
1 of these complications	59.7 (n = 175)	42.5 (15–80)

^aFrequency of each event in cohort (no. of patients).^bMedian age (range).

Table 3
Effect of Clinical and Genetic Variables on Age-Adjusted Square-Root–Transformed eGFR

Variable	Univariate				Multivariate			
	β	SE	95% CI	P	β	SE	95% CI	P
Age, per 1 y older	−0.106	0.008	−0.12 to −0.09	<0.001	−0.1	0.008	−0.12 to −0.09	<0.001
Male sex	−0.41	0.11	−0.63 to −0.19	<0.001	−0.40	0.11	−0.62 to −0.18	<0.001
Mutation type, truncating vs nontruncating	−0.53	0.17	−0.84 to −0.18	0.002	−0.61	0.16	−0.94 to −0.29	<0.001
Smoking status, ever smoker vs nonsmoker	−0.29	0.12	−0.51 to −0.06	0.02	−0.21	0.12	−0.43 to 0.03	0.08
No. of pregnancies, <2 vs ≥2 births	−0.02	2.19	−0.29 to 0.26	0.9				
Mutation located within nucleotides 1–968	0.0001	0.0004	−8×10 ^{−4} to 10 ^{−3}	0.8				
Mutation position, 5′ vs 3′ of median nucleotide 484	−0.05	0.11	−0.27 to 0.17	0.7				

Note: Univariate and multivariable linear regressions.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; SE, standard error.

Table 4
Patients With Early-Onset ESRD and Associated Conditions Accounting for Early Progression to ESRD

Case	Sex	Age at ESRD, y	Factors or Associated Conditions Explaining Early Progression to ESRD	Kidney Size at ESRD, cm (L; R)	PKD2 Mutation ^a
1	M	53.2	Antiretroviral therapy—associated nephropathy	ND; ND	p.R872X
2	F	58.2	Long-term use of nonsteroidal anti-inflammatory agents	15.1; 18.3	c.1811del
3	F	52.3	Lung transplantation at age 48 y for emphysema, received calcineurin inhibitors	ND; ND	p.R807X
4	F	52.5	Severe cyst infection and cyst hemorrhage with hemodynamic instability	7; 16	p.R654X
5	F	42.4	Malignant hypertension at age 30 y; diagnosis denial and treatment rejection until initiation of hemodialysis	15.1; 15.7	del exons 10–15
6	F	54.7	Long-term severe and uncontrolled hypertension despite 4 antihypertensive medications	15; 15	p.E95X
7	M	54.4	Steroid-resistant nephrotic syndrome in childhood	ND; ND	p.K735X
8	M	56.6	Hepatitis B virus infection, suspected glomerulonephritis, proteinuria of 2 g/d despite angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker	ND; ND	c.1235dup

Note: Early-onset ESRD defined as before age 60 years. Kidney sizes at ESRD are reported when available and were measured prior to initiation of renal replacement therapy.

Abbreviations: ESRD, end-stage renal disease; L, left; ND, not documented; R, right.

^aMutations designated at the protein level (p) or coding DNA level (c). For protein-level mutations, R is arginine, X is a premature stop codon, E is glutamate, and K is lysine. For coding DNA-level mutations, del indicates deletion, whereas dup denotes duplication.