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Original Investigation

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

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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.

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Editorial, p. 456

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).