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Disquisition of Exome Sequencing of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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ABSTRACT

The Key Points *This study's target demonstrates significant genetic and phenotypic variation in ADPKD.*

Importance *The majority of research on the genetics of autosomal dominant polycystic kidney disease (ADPKD) has focused on PKD1 and PKD2 in kidney specialty cohorts. These may result in inaccurate population prevalence and phenotypic expression estimates of ADPKD-associated gene variants.*

Objective *In a large, unselected cohort, to ascertain the prevalence of ADPKD and the roles played by PKD1, PKD2, and other cystic kidney disease-related genes. Exposures Loss-of-function (LOF) variants in PKD1, PKD2, and other genes associated with cystic kidney disease (ie, ALG8, ALG9, DNAJB11, GANAB, HNF1B, IFT140, SEC61B, PKHD1, PRKCSH, SEC63); likely pathogenic missense variants in PKD1 and PKD2.*

Main Outcomes and Measures *phenotype-first analysis: presence of a rare variant in PKD1, PKD2, or other genes associated with cystic kidney disease; genotype-first analysis: ADPKD diagnosis code (Q61.2, Q61.3, 753.13, 753.12).*

INTRODUCTION

Genes associated with a particular clinical condition can be identified through studies of selected cohorts. When such associations are found, however, subsequent population-based studies are needed to more accurately determine the prevalence of pathogenic variants and their phenotypic consequences. A common observation is that, in contrast to findings based on disease-specific cohorts, there is a wider range of phenotypes, a lower disease penetrance, and a higher prevalence of putative pathogenic variants. Autosomal dominant polycystic kidney disease (ADPKD) has a clear genetic basis, and several disease-associated genes have been identified. Missense PKD1/PKD2 variants have also been associated with ADPKD, albeit with incomplete and variable disease penetrance. Protein-truncating variants that disrupt the protein-coding sequence in PKD1 or PKD2 are reported to have 100% disease penetrance.1 The Toronto Genetic Epidemiology of Polycystic Kidney Disease study reported that 55.5% of patients without family history of ADPKD did not have a detectable PKD1 or PKD2 variant. Variants in other genes, such as GANAB, DNAJB11, HNF1B, and ALG9.2-4, may be the cause of some unidentified cases. Large exome sequence databases linked to longitudinal clinical data from unselected clinical populations enable a genotype-first approach, whereby specific genotypes are associated with clinical phenotypes. This makes it possible to simultaneously examine the prevalence, penetration, and phenotypic expression of multiple genes. This study tested the hypothesis that loss-of-function (LOF) variants (i.e., early terminations, frameshift due to indels, splice site variants, large chromosomal deletions) in genes previously linked to cystic kidney or liver disease (i.e., PKD1, PKD2, ALG8, ALG9, DNAJB11, GANAB, HNF1B, IFT140, PKHD1, PRKCSH, SEC61

REVIEW OF LITERATURE

1. A meta-analysis of hypertension in autosomal dominant polycystic kidney disease

Marlai Matko T

he condition known as autosomal dominant polycystic kidney disease (ADPKD) is prevalent and has the potential to cause hypertension at some undetermined point in a child's life. However, the exact timing of this hypertension occurring in children is unknown. To determine the prevalence of excessive blood pressure in children with ADPKD, we conducted a scientific evaluation and meta-evaluation. When reporting data on the incidence of high blood pressure in children and adults younger than 21 years old with a diagnosis of ADPKD, studies chosen by authors independently. With study populations of more than 15 children, observational series were included. Articles were excluded if inadequate diagnostic standards for high blood pressure had been used. Studies with selection bias were blanketed but analyzed one after the other. Data extracted on prevalence of excessive blood pressure, proteinuria and decreased renal function the use of standardized form. Weighted suggest incidence can now be calculated through

meta-evaluation. 903 articles were retrieved from our seek; 14 research met the inclusion necessities: 1 potential randomized controlled trial; eight capability observational studies; and 5 retrospective pass-sectional research. From 928 youngsters with clinically showed ADPKD, 20% (90 five% CI 15% to 27%) were hypertensive. The anticipated prevalence of proteinuria in children with ADPKD is 20% (8 studies; 95% CI 9% to 40%) even as reduced renal characteristic occurred in eight% (5 studies; ninety 5% CI 2% to 26%).

Methodological heterogeneity was found to be quite high in the studies (I2=73.4%, 2=0.3408, p0.0001) Most studies did not use ambulatory blood strain (BP) tracking to diagnose hypertension.

In this meta-assessment we estimate 20% of children with ADPKD have high blood pressure. In the population, many kids with ADPKD are not underneath ordinary comply with-up and stay undiagnosed. We recommend that all children susceptible to ADPKD have ordinary BP size.

2. Intracranial Aneurysms in Autosomal Dominant Polycystic Kidney Disease

Arlene B. Chapman, A doctor

Autosomal dominant polycystic kidney disease is characterized by intracranial aneurysms, but the incidence of these lesions is unknown. We studied 90 two topics with autosomal dominant polycystic kidney illness who had no signs or signs and signs and signs and symptoms of any neurologic sickness. We performed high-selection computed tomography (CT) on 60 subjects, four-vessel cerebral angiography on 21 subjects, and each technique on 11 subjects to determine the prevalence of intracranial aneurysms. Intracranial aneurysms were found in four of the 88 subjects studied by radiology, compared to just one percent of the general population who were recommended for an angiographic examination (90 percent, 5 percent confidence c programming language, zero.1 to 9 percent). Three of the four topics had multiple aneurysms. Seven subjects whose CT results were suspicious underwent cerebral angiography: two had aneurysms, and five had regular vascular systems that were the cause of the tomography's suspicious results. Four topics who had everyday CT imaging research furthermore had normal angiographic examinations. In comparison to 22 of 220 manage subjects (10 percent) who did not have polycystic kidney disease, eight of the 32 subjects who underwent angiography had short complications (P 0.05). In these individuals, we were unable to identify any risk factors associated with the development of an aneurysm [20]. Asymptomatic intracranial aneurysms appear to be more frequent in people with polycystic kidney disease than in the general population, although our 95 percent confidence interval includes the possibility of no difference. We recommend high-resolution CT as a screening test for polycystic kidney disease patients because cerebral angiography is linked to increased morbidity. [N Engl J Med 1992;327: 916–20]

3. Autosomal dominant polycystic kidney disease masked as von Hippel-Lindau disease

Rupinder K. MD Chatha

The diagnostic confusion in differentiating the various causes of renal cystic diseases in adults is well documented. This confusion can include misclassifications between autosomal dominant polycystic kidney disease (ADPKD) and von Hippel-Lindau disease (VHL). We describe this kind of VHL case. A review of the literature and of the patients in our database regarding typical features of each disease, mean age of onset, and frequency of these features was undertaken to provide helpful differentiating features. Cysts in the pancreas are one distinguishing feature. In VHL, pancreatic cysts can occur in 70% of patients, often are multiple, and rarely may cause exocrine or endocrine insufficiency. Pancreatic islet cell tumors occur. Only 9% of patients with ADPKD have single, asymptomatic pancreatic cysts, are typically associated with cystic liver disease, and are not found in children or family members who are unaffected. Pancreatic malignancies do not occur with increased frequency in ADPKD. A different pattern may indicate VHL masquerading as ADPKD, particularly in patients without a strong family history. Genetic mutation screening of the VHL gene should be used in these patients.

4. Autosomal dominant polycystic kidney disease and nephrotic syndrome

Visciano, Bianca

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disorder characterized by the development and growth of cysts in the kidneys and other organs. Nephrotic range proteinuria is uncommon in ADPKD patients and must be further investigated to rule out glomerular disease. Focal segmental glomerulosclerosis is the most common nephrotic syndrome-associated ADPKD case reported anecdotally. We report the case of a 26-year-old male with ADPKD and concomitant nephrotic syndrome, in which an ultrasound (US)-guided renal biopsy showed a mesangioproliferative glomerulonephritis. Because the angiotensin-converting enzyme inhibitor/angiotensin receptor blocker association treatment

failed, we administered prednisone at a dose of one milligram per kilogram per day to the patient. His GFR remained stable and proteinuria decreased after six months of steroid treatment. This case report and other cases of the literature underline the importance of a renal biopsy in patients with ADPKD and nephrotic syndrome to make an accurate diagnosis and an appropriate treatment/prevention of renal function deterioration.

METHODS

Raw data quality control

Control of raw data quality DNA extraction, library construction, and the sequencing process itself are just a few of the processes involved in the generation of sequencing data. A thorough quality control evaluation of the raw, post-sequencing data output is required due to the fact that these procedures may produce data of insufficient quality or data that is inherently invalid.

Data preprocessing

Preprocessing of data Researchers can ascertain whether data preprocessing is required with the assistance of a comprehensive read QC report, which typically includes the aforementioned parameters. Preprocessing steps generally involve 3' end adapter removal, low-quality or redundant read filtering, and undesired sequence trimming. Several tools can be used for data preprocessing, such as Cut adapt and Trimoraic. Both PRINSEQ and QC3 are capable of preprocessing and quality control.

Sequence Alignment

Alignment of the sequence The genomic location of each fragment in the exome sequencing data can be determined by performing sequence alignment. When it comes to locating functional elements, gene structure, and exon regions, this proves to be invaluable. Moreover, sequence alignment plays a crucial role in various aspects such as detecting variants, facilitating gene expression analysis, and allowing data quality assessment.

Variant annotation

Annotation of Variants After variants are identified, they need to be annotated for better understanding disease pathogenesis. Variant annotation generally involves information about genomic coordinates, gene position, and mutation type. Non-synonymous SNVs and indels in the exome are the focus of many studies because they account for 85% of known disease-causing mutations in Mendelian disorders and a significant number of mutations in complex diseases.

Data Management

Management of Data When it comes to data storage, the enormous amount of data generated by Next Generation Sequencing (NGS) technologies might be too much for conventional storage methods. Consequently, the consideration of cloud storage services, such as Amazon S3, arises. These services offer nearly limitless storage capacity and operate on a pay-as-you-go model, accommodating usage fluctuations. Within their NGS environments, commercial service providers like Illumina also provide cloud-based data storage services, which speed up access to genomic aberrations and aid in medical diagnostics.

RESULTS

Statistical Analysis

Analyses of Statistics Characteristics between participants with and without ADPKD were compared using unpaired t tests for continuous variables and the Fisher exact test for categorical variables (Table 1). The reference group consisted of participants who did not have any LOF or rare (allele frequency 0.01) missense variants in any genes that were previously linked to cystic kidney or liver disease. Firth logistic regression was used to assess associations between carriers of LOF variants of each gene that was previously linked to cystic kidney or liver disease with an ADPKD ICD-9/10 diagnosis and, secondarily, any kidney or liver cyst diagnosis. First- and second-degree relatives in the cohort were removed in these analyses, which were adjusted for age, sex, and the first 10 genetic principal components and performed using the firthlogist Python package, version 0.5.0 (see e-Figure 4 in for flow diagram). With the Bonferroni correction for multiple comparisons, a two-sided P .05 was deemed statistically significant. A 2-sample test of proportions was used in phenotype-first analyses to compare proportions with a rare variant in one of the 11 genes related to cystic kidney or liver disease by the presence (or absence) of family history and ADPKD phenotype (typical vs. mild or atypical); patients who lacked sufficient clinical data to confirm ADPKD were excluded from these analyses. A 2-sided P.05 was considered statistically significant for phenotype-first analyses. Study Flow and Penetrance of PKD1 and PKD2 Variants

Study Flow and Penetrance of PKD1 and PKD2 Variants

Evaluation of 174 172 patients with exome sequencing revealed loss-of-function variants in PKD1 and PKD2 or in-frame deletions and missense variants in PKD1 and PKD2 classified as likely pathogenic in the Mayo PKD database.

Penetrance of PKD1 and PKD2 LOF Variants

ICD-9, International Classification of Diseases, Ninth Revision; and ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, both refer to autosomal dominant polycystic kidney disease. Penetration of LOF Variants PKD1 and PKD2 Based on ICD-9/10 code diagnoses, 2 of 2 patients (100%) with large deletions in PKD1 had ADPKD and 64 of 79 (81.0%) with PKD1 LOF variants had ADPKD. Among 66 patients with a PKD1 LOF variant and sufficient chart review data, 64 (97.0%) had ADPKD with typical ADPKD imaging findings. Two people with PKD1 LOF variants had sufficient imaging data to rule out ADPKD, but there was no ADPKD history in their families. Notably, Sanger sequencing also confirmed that the PKD1 LOF (splice donor) variant in these two patients was the same.

Table 1. Characteristics of the Study Population at the Outset

Characteristics	Participants with phenotypic ADPKD (n = 303)[a]	Participants without phenotypic ADPKD (n = 173 869)[a]	Odds ratio (95% CI)	P value
Age, median (IQR), y	61 (45-71)	60 (44-72)		
Sex, No. (%)				
Female	156 (51.4)	105 161 (60.6)		
Male	147 (48.6)	68 708 (39.4)		
Black race, No. (%)	2 (0.6)	3952 (2.3)		
Hispanic ethnicity, No. (%)	11 (3.6)	4624 (2.7)		
Ancestry, No (%)[b]				
Admixed American	7 (2.3)	2521 (1.4)		
African	5 (1.7)	5259 (3)		
East Asian	2 (0.7)	485 (0.3)		
European	286 (94.4)	161 814 (93.1)		
Southeast Asian	1 (0.3)	508 (0.3)		
Unknown	2 (0.7)	3282 (1.9)		
High-risk APOL1 genotype, No. (%)[c]	1 (0.3)	431 (0.2)		
Last eGFR, mL/min/1.73 m^2				
Mean (SD)	54 (36)	81 (27)		
<60, No. (%) (n = 162 916)	177 (58.8)	32 000 (19.6)		
First outpatient visit, median (IQR), y	2001 (1997-2009)	2003 (1998-2011)		
Last outpatient visit, median (IQR), y	2020 (2019-2021)	2021 (2019-2021)		
Follow-up time, median (IQR), y	18 (11-22)	16 (9-22)		
Comorbidities, No. (%)[d]				
Any kidney/liver cyst	303 (100)	4908 (2.8)		
Hypertension	247 (81.5)	89 398 (51.4)	4.17 (3.11-5.68)	<.001
Dyslipidemia	197 (65)	97 751 (56.2)	1.45 (1.14-1.85)	0.002
End-stage kidney disease	113 (37.3)	2567 (1.5)	39.69 (31.05-50.50)	<.001
Cerebrovascular disease	79 (26.1)	23 937 (13.8)	2.21 (1.69-2.87)	<.001
Coronary artery disease	79 (26.1)	32 973 (19.0)	1.51 (1.15-1.96)	0.003
Diabetes	79 (26.1)	38 144 (21.9)	1.25 (0.96-1.63)	0.08
Cardiac valvular abnormalities	49 (16.2)	15 560 (8.9)	1.96 (1.41-2.67)	<.001
Heart failure	48 (15.8)	13 491 (7.8)	2.24 (1.61-3.06)	<.001
Cystic liver disease	37 (12.2)	2205 (1.3)	10.83 (7.44-15.36)	<.001
Cerebral aneurysm	15 (5)	1305 (0.8)	6.89 (3.79-11.59)	<.001

Table 2. Odds Of ADPKD Or Kidney/Liver Cyst ICD-9 And ICD-10 Codes Among Participants With Lofvariants In ALG8, ALG9, DNAJB11, GANAB, HNF1B, IFT140, LRP5, PKD1, PKD2, PKHD1, PRKCSH, Or SEC63

Gene	No. of carriers	Cases, No./total (diagnosis prevalence, %)	Odds ratio (95% CI)	P value	Adjusted P value
Phenotypic ADPKD based on ICD-9/10 coding[a]					
Reference	42 485	34/42 485 (0.1)	1 [Reference]		
ALG8	159	0/159			
ALG9	25	0/25			
DNAJB11	7	0/7			
GANAB	14	1/14 (7.1)	124.87 (13.30-557.30)	<.001	0.005
HNF1B	16	1/16 (6.2)	119.85 (12.44-547.18)	<.001	0.005
IFT140	205	5/205 (2.5)	32.94 (11.78-75.89)	<.001	<.001
LRP5	1414	0/1414			
PKD1	54	42/54 (77.8)	4400.45 (2081.14-10 151.47)	<.001	<.001
PKD2	24	17/24 (70.8)	4530.34 (1655.21-14 111.73)	<.001	<.001
PKHD1	522	2/522 (1.0)	6.02 (1.23-18.08)	0.03	0.18
PRKCSH	74	0/74			
SEC63	81	0/81			
Presence of any kidney or liver cyst based on ICD-9/10 coding[a]					
Reference	42 485	2033/42 485 (4.8)	1 [Reference]		
ALG8	159	17/159 (10.7)	2.60 (1.51-4.21)	0.001	0.01
ALG9	25	4/25 (16.0)	3.09 (0.95-8.05)	0.06	0.71
DNAJB11	7	1/7 (14.3)	4.43 (0.44-23.34)	0.17	>.99
GANAB	14	3/14 (21.4)	5.51 (1.37-17.16)	0.02	0.24
HNF1B	16	3/16 (18.8)	7.02 (1.72-22.40)	0.01	0.12
IFT140	205	28/205 (13.7)	3.25 (2.12-4.81)	<.001	<.001
LRP5	1414	70/1414 (5.0)	1.15 (0.89-1.46)	0.27	>.99
PKD1	54	42/54 (77.8)	113.80 (60.69-228.45)	<.001	<.001
PKD2	24	21/24 (87.5)	185.93 (64.28-722.16)	<.001	<.001
PKHD1	522	27/522 (5.2)	1.14 (0.75-1.65)	0.52	>.99
PRKCSH	74	3/74 (4.1)	0.95 (0.26-2.44)	0.92	>.99
SEC63	81	8/81 (9.9)	2.61 (1.18-5.10)	0.02	0.25

Table 3. Genetic and Phenotypic Heterogeneity in Confirmed ADPKD Cases

C Genetic makeup of mild and atypical ADPKD phenotype cases

Gene	Variant	Category	No. with phenotype
ALG8	Asn91MetfsTer5	Truncating	1 mild
GANAB	Asp647Val	Missense with cosegregation evidence	2 mild, 2 atypical
IFT140	Arg834Ter	Truncating	1 atypical
IFT140	Trp653Ter	Truncating	1 atypical
IFT140	Ala835Val	Missense variant of uncertain significance	1 atypical
PKD1	Glu2771Lys	Missense likely pathogenic	1 atypical
PKD1	Gly2034Val	Missense with cosegregation evidence	1 atypical
PKD1	Asp1165Gly	Missense variant of uncertain significance	1 mild
PKD1	Ala1083Ser	Missense variant of uncertain significance	1 atypical
PKD1	Ala3889Ser	Missense variant of uncertain significance	1 atypical
PKD1	Pro2577His and Trp3553Arg	Missense variant of uncertain significance	1 mild
PKD1	Arg1285Gln	Missense variant of uncertain significance	1 mild
PKD1	Asp1165Gly	Missense variant of uncertain significance	1 mild
PKD2	His750IlefsTer21	Truncating	1 atypical
PKD2	Gln300Ter	Truncating	1 mild
PKD2	Arg786GlyfsTer25	Truncating	1 mild
PKD2	Ala69GlyfsTer23	Truncating	1 atypical
PKHD1	c.1836 + 1G>A	Splice donor	1 mild
PKHD1	Cys2803Arg	Missense variant of uncertain signficance	1 mild

Penetrance of Previously Described Likely Pathogenic PKD1 and PKD2 Missense Variants

Genotype-First Analysis

PKD1, PKD2, IFT140, HNF1B, and GANAB loss-of-function variants were associated with an increased risk of an ADPKD ICD-9/10 diagnosis (Bonferroni-corrected P .05 for all comparisons) (Table 2). Additionally, PKD1, PKD2, IFT140, and ALG8 were associated with any kidney or liver cyst ICD-9/10 diagnosis (Bonferroni-corrected P . However, carriers of LOF variants in IFT140 (5/205), GANAB (1/14), and HNF1B (1/16) had relatively low rates of ADPKD diagnosis.

Phenotype-First Analysis

Overall, 180 of 235 patients (76.6%) with ADPKD had a potential genetic cause, with the majority being PKD1 (127 patients) and PKD2 (34 patients); 19 of 235 (8.1%) had a rare variant in a gene associated with cystic kidney disease, including IFT140 (n = 7), GANAB (n = 4), PKHD1 (n = 3), HNF1B (n = 2), ALG8 (n = 1), and ALG9 (n = 1), as well as 1 patient with rare variants in both IFT140 and PKHD1 Genetic variants in patients with mild or atypical ADPKD included PKD1, PKD2, IFT140, PKHD1, ALG8, and GANAB.

DISCUSSION

Outcomes

The primary outcome of genotype-first analyses was the presence of at least one ADPKD diagnosis code in the ICD-9/10 codebook. Any kidney or liver cyst, which included ICD-9/10 codes for ADPKD, cystic kidney diseases (Q61.5, Q61.8, Q61.9, 753.10), congenital kidney cyst (Q61.00, Q61.01, Q61.02, 753.11, 753.19), or liver cystic disease (Q44.6, 573.8), were the secondary outcomes. For phenotype-first analyses, the primary outcome was having a rare variant (allele frequency <0.0001) in 1 of 11 genes related to cystic kidney or liver disease (ALG8, ALG9, DNAJB11, GANAB, HNF1B, IFT140, PKD1, PKD2, PKHD1, PRKCSH, SEC63). Several methods were used to determine the prevalence of ADPKD: (1) a single ADPKD ICD-9/10 diagnosis code; (2) a chart review that confirmed the ADPKD ICD-9/10 diagnosis code; (3) predicted pathogenic PKD1/PKD2 variants for each VarSome ACMG classifier; and (4) predicted pathogenic or likely pathogenic PKD1/PKD2 variants for each VarSome ACMG classifier.

Using exome sequencing in an unselected, regional health system cohort, substantial genetic and phenotypic variability in ADPKD was observed. Loss-of-function variants in PKD1 and PKD2 accounted for the majority of confirmed ADPKD cases, with additional rare variants in PKD1, PKD2, IFT140, GANAB, PKHD1, HNF1B, ALG8, and ALG9 found in other patients. There was supportive pathogenic evidence through examination of family pedigrees for several PKD1, PKD2, and GANAB variants that were previously unreported or reported as variants of uncertain significance or likely benign. However, additional data are needed to definitively classify missense variants.

Prevalence estimates of ADPKD in our cohort by phenotype matched prior literature (1.74 per 1000 for ICD-9/10 diagnosis alone; 1.35 per 1000 for ICD-9/10 diagnosis with chart review confirmation), yet were much lower than genotype-based estimated prevalence (8.64 per 1000), likely because of misclassification of missense variants. Only 31.2% of patients with PKD1 missense variants previously reported as "likely pathogenic" had ADPKD, including several PKD1 variants for which numerous carriers had no evidence of ADPKD. These results are consistent with a study of the Exome Aggregation Consortium (ExAC), which reported that the observed prevalence of previously reported pathogenic variants in PKD1 and PKD2 in ExAC was far greater than the expected prevalence (6.9 per 1000 vs 0.69 per 1000).[6] Additional work using population-based cohorts, such as this cohort, is needed to validate pathogenicity of missense variants in PKD1, PKD2, and other genes.

In this cohort, 97% of patients with LOF variants in PKD1 had ADPKD using high-quality exome

sequencing followed by confirmatory Sanger sequencing in 4 patients who did not have ADPKD on imaging. In 2 of these 4 patients, Sanger sequencing did not confirm LOF by exome sequencing. Sanger sequencing of the other 2 individuals confirmed the exome sequencing findings of a splice donor variant. While the prediction software SpliceAI predicted this variant to be disruptive, determining pathogenicity in splice variants remains notoriously challenging. Regardless, this study shows that a high-quality exome sequencing–based pipeline identifies ADPKD correctly in nearly all patients with PKD1 or PKD2 LOF variants and has important implications for genomic screening programs.

This study also demonstrates the value of including genes related to cystic kidney or liver disease in the genetic evaluation of ADPKD. In genotype-first analyses, IFT140, GANAB, and HNF1B were significantly associated with ADPKD diagnosis while ALG8 and IFT140 were also associated with a composite outcome of any kidney/liver cyst diagnosis. There was clear evidence that LOF variants in LRP5 do not cause ADPKD as no association was seen in the analysis of 1414 LRP5 LOF carriers. LRP5 was likely previously incorrectly implicated in polycystic liver disease.[7] The full extent to which variants in genes related to cystic kidney disease cause cystic kidney or liver disease requires additional study and deeper phenotyping (ie, imaging review), as has been done for ALG9. Future studies are needed to better understand the significance of mild cystic disease and whether cystic disease caused by atypical genes are responsive to therapies to slow ADPKD progression such as vasopressin receptor 2 antagonism.[8]

Currently, diagnosis of ADPKD for most patients with a family history of ADPKD is done by abdominal imaging. Genetic testing is generally only performed when ADPKD is suspected in persons without family history or with equivocal kidney imaging findings, in the setting of related kidney donation, or for family planning purposes.[10] Better knowledge of the genetic causes of ADPKD could facilitate earlier genotype-first diagnoses and enable preventive or disease-modifying actions and early treatments such as tolvaptan for ADPKD as well as potential new therapeutic options currently being evaluated in ongoing clinical trials.[11]

CONCLUSION

Among the 174 172 unselected participants in this retrospective observational study, 109 of 111 patients (98 percent) had large deletions or truncating PKD1 and PKD2 variants, while only 24 of 77 patients (31.2%) had previously described "likely pathogenic" missense PKD1 variants. Exome sequencing revealed that variants in genes other than PKD1 and PKD2 were found in 19 of the 235 patients (8 percent) clinically diagnosed with ADPKD. Of the variants listed above, 135 individuals with LOF variants or large chromosomal deletions in PKD1 or PKD2 were identified. In addition, none of the patients had LOF variants in SEC61B, but there were 3793 patients with LOF variants and 61 carriers of large chromosomal deletions in one of the genes previously linked to cystic kidney or liver disease. Results of 174 172 patients (median age, 60 years; 60.6% female; 93% of European ancestry), 303 patients had ADPKD diagnosis codes, including 235 with sufficient chart review data for confirmation. After adjusting for multiple comparisons, LOF variants in IFT140, GANAB, and HNF1B were found to be linked to the diagnosis of ADPKD in addition to PKD1 and PKD2. Among patients with LOF variants in PKD1, 66 of 68 (97%) had ADPKD; 43 of 43 patients (100%) with LOF variants in PKD2 had ADPKD. On the other hand, only 24 of the 77 patients who had a PKD1 missense variant that was previously thought to be "likely pathogenic" (31.2%) had ADPKD, indicating that they had been misclassified or that their penetrance varied. 180 of the 235 patients with an ADPKD diagnosis that was confirmed by chart review (76.6%) had a possible genetic cause; the majority of these patients had rare variants in PKD1 (127 patients) or PKD2 (34 patients); 19 of the 235 patients (8.1%) had variants in other genes that are associated with cystic kidney disease. 150 (63.8%) of these 235 patients with confirmed ADPKD had a family history of the disease. The yield for a genetic determinant of ADPKD was higher for those with a family history of ADPKD compared with those without family history (91.3% [137/150] vs 50.6% [43/85]; difference, 40.7% [95% CI, 29.2%-52.3%]; $P < .001$). Pedigree data suggested the pathogenicity of previously unreported PKD1, PKD2, and GANAB variants, and several PKD1 missense variants that had been reported as likely pathogenic appeared to be benign.

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