Bayyad *et al.*
Translational Medicine Communications (2023) 8:24
https://doi.org/10.1186/s41231-023-00157-5

Translational Medicine Communications

RESEARCH

Open Access

Exploring the clinical and genetical spectrum of ADPKD in Chile to assess ProPKD score as a risk prediction tool

Esperanza Bayyad[1], Anita Plaza[1], Jaime Klenner[2], Patricio Downey[3], Paulina Salas[4], Daniela Maragaño[1], Patricio Herrera[1], Paula Lehmann[5,6], Lily Quiroz[5,6], María Jesus Zavala[7], Karen Orostica[8], Claudio Flores[1], Leopoldo Ardiles[1], Jorge Maturana[2] and Paola Krall[1,9*]

Abstract

Background Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited condition associated primarily with *PKD1* and *PKD2* genes. However, ADPKD patients in Latin America have had limited access to comprehensive care. The ProPKD score predicts the likelihood of kidney failure before the age of 60. This study aimed to describe the clinical and genetic characteristics of Chilean ADPKD patients and assess the ProPKD score.

Methods We enrolled 40 ADPKD probands and 122 relatives from different centers. Genetic analysis of *PKD1* and *PKD2* genes was performed by combining direct and next-generation sequencing. Pathogenicity was determined using bioinformatic tools. ProPKD scores were calculated based on clinical and genetic data.

Results ADPKD probands were diagnosed at a median age of 35 years. Pathogenic, likely pathogenic, or uncertain significance variants were identified in 38/40 pedigrees, with 89% involving *PKD1* and 11% involving *PKD2* variants. Among the identified variants, 62% were novel. Patients with *PKD1* truncating variants had a more severe disease course, reaching kidney failure by a median age of 48.5 years. ProPKD scores were assessed in 72 individuals, stratifying them into high-, intermediate-, or low-risk categories and the median ages for kidney failure were 45, 49, and 52 years, respectively (log-rank $p = 0.001$).

Conclusion This study provides valuable insights into the clinical and genetic profiles of ADPKD patients in Chile. ADPKD poses a significant public health concern, warranting improvements in diagnosis and treatment. The use of the ProPKD score to predict disease progression should be further explored to enhance patient care and management.

Keywords ADPKD, Genetic analysis, End-stage renal disease, ProPKD score

*Correspondence:
Paola Krall
paola.krall@uchile.cl
Full list of author information is available at the end of the article

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the leading monogenic cause of end-stage renal disease (ESRD) [1]. The majority of ADPKD cases (80–85%) are attributed to variants in the *PKD1* gene, with *PKD2* variants accounting for 10–15% of cases. However, additional genes have been identified in patients presenting with clinical features overlapping with ADPKD [2–4].

Diagnosis of ADPKD primarily relies on imaging techniques [5]. Renal cysts typically develop early in life, often asymptomatic, but gradually enlarge and cluster, resulting in kidney enlargement. This progression can lead to symptoms such as pain, hematuria, hypertension, and a decline in renal function, eventually culminating in ESRD. Renal replacement therapies (RRT), including dialysis and transplantation, are offered to patients at this stage [6–8]. ADPKD patients account for 5–10% of individuals undergoing RRT, significantly impacting the physical and psychosocial well-being of both patients and their families [9].

Although no cure for ADPKD currently exists, ongoing experimental studies and clinical trials aim to identify effective treatments. Pharmacological therapies, such as the V2 receptor antagonist tolvaptan, have shown promise in certain patient populations. However, the use of tolvaptan varies across countries, and its approval is pending or has been restricted due to associated adverse effects [10, 11].

The relationship between specific gene variants and phenotypic features of ADPKD has been extensively studied. The *PKD1* gene is associated with a more severe phenotype compared to *PKD2*, with a median age of ESRD onset at 58.1 years and 79.7 years, respectively [12]. Furthermore, patients with *PKD1* truncating variants tend to have a more aggressive disease course, reaching ESRD at an earlier age than those with *PKD1* missense variants.

The clinical course of ADPKD can vary significantly among patients, even within the same family sharing the same underlying genetic variant. This phenotypic variability underscores the need for tools or biomarkers to estimate disease progression and assess interventions to slow down disease progression. The ProPKD score is a predictive tool developed from the GENKYST cohort, incorporating specific clinical and genetic characteristics to assign points and stratify the risk of progressing to ESRD in ADPKD patients [13]. A pilot validation study of the ProPKD score was conducted in Australian ADPKD patients, demonstrating accurate prediction of kidney function loss over a 3-year period [14]. Further studies would help validate the applicability of this tool in populations exposed to different risk factors for chronic kidney disease, ensuring equal access to research and clinical genetics in resource-limited settings [15].

Chile, as a developing nation classified as a high-income country in 2013, still faces significant income and health access inequalities, as well as disparities in quality of life [16, 17]. Therefore, the present study aimed to describe the clinical phenotype and genetic landscape of ADPKD families in Chile and evaluate the applicability of the ProPKD score in the patient population.

Patients and methods

ADPKD patients

Altogether 40 ADPKD probands were enrolled in the study between 2014 and 2020. These probands were identified and recruited by nephrologists from various public and private health centers in Chile, using previously established echographic criteria [18]. For each participant, relevant information was collected, including the location of the health center, age at ADPKD diagnosis, age at recruitment, age at initiation of RRT if applicable, and family history. To calculate the ProPKD score, we also recorded the presence of arterial hypertension and urological events occurring before the age of 35 years [13].

PKD1 and *PKD2* genetic analysis

Genomic DNA was extracted from fresh blood samples collected in EDTA tubes using the GeneJet™ Genomic DNA purification kit. The DNA concentration was measured using a spectrophotometer, and samples were diluted to a concentration of 60–70 ng/dl before being stored at -20 °C until further processing.

The analysis strategy involved two groups of patients: 19 probands underwent direct sequencing, while the remaining 21 probands were analyzed using next-generation sequencing (NGS). In the direct sequencing group, the workflow prioritized the analysis of the *PKD1* gene. Only if the results were negative or inconclusive, the analysis continued with *PKD2*. For NGS analysis, both *PKD1* and *PKD2* genes were simultaneously sequenced. Patients underwent direct sequencing or NGS as first-line analysis, according to the historical evolution of our laboratory's capabilities. During the early years of our research, we exclusively employed direct sequencing as our primary method. Subsequently, as our laboratory gained access to an NGS platform, we underwent a comprehensive validation process testing our amplicon-based NGS strategy on a subset of patients with *PKD1* variants that had been previously confirmed by direct sequencing. Once we successfully validated the accuracy and reliability of the strategy for our research objectives, we transitioned to using NGS as the primary method. We maintained a rigorous quality control approach throughout the study by cross-validating all variants identified by NGS using direct sequencing (gold standard). Hence,

direct sequencing was conducted in all patients ensuring the robustness and accuracy of our findings.

The analysis encompassed all coding exons of *PKD1* and *PKD2*, along with a minimum of 15 base pairs of surrounding intronic segments. To avoid amplification of *PKD1* pseudogenes, long-range PCR (LR-PCR) was performed in both sequencing strategies [19]. Subsequently, a nested PCR was conducted using the LR-PCR product as a template. Samples subjected to direct sequencing were analyzed using an ABI3500 Genetic Analyzer, while those selected for NGS underwent PCR amplification with custom-designed primers targeting *PKD1* and *PKD2* exons. These primers contained a 5′ overhang (5′-TCGTCGGCAGCGTCAGATGTGTATAAGAGACAG-3′ and 5′-GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAG-3′ for forward and reverse primers, respectively) that facilitated workflow on the Illumina platform with the MiSeq Reagent Kit v2 Nano (2×250 bp paired-end). Each patient was uniquely identified based on an 8-nucleotide index combination at each end.

Bioinformatic analysis

Sequence analysis obtained through direct sequencing was conducted using SeqScape v.2.5 software. The obtained sequences were aligned with reference sequences for *PKD1* (NM_001009944.3) and *PKD2* (NM_000297.4). Variants that predicted protein truncation were considered pathogenic. To assess the significance of missense variants, we utilized in silico tools such as MutationTaster, Polyphen-2, and SIFT. We classified variants as (likely) pathogenic or variants of uncertain significance (VUS) based on specific criteria. These included: 1) presence in the ADPKD database (PKDB) curated by the Mayo Clinic (https://pkdb.mayo.edu/welcome), 2) classification as (likely) pathogenic or VUS by at least two of the three predictive tools, and 3) complete segregation in at least three affected relatives.

For NGS analysis, only variants with a sequencing depth above 40× and a variant allele frequency of 0.2–0.8 were considered. These criteria were based on NGS validation assays that achieved 94.67% on-target coverage. To distinguish polymorphisms from potentially causative variants, we developed a scoring algorithm ranging from 0 to 100 that incorporated information from various databases: refGene, dbSNP (avsnp150), dbnsfp35c, clinvar, intervar, gnomad211_genome, gnomad211_exome, esp6500siv2_all, exac03, 1000G, and gnomad30_genome. Additionally, the prediction results from different tools such as Polyphen-2, MutationTaster, SIFT, LRT, Mutation Assessor, and FATHMM were taken into account to score each variant. A score of 80 was assigned to variants classified as "pathogenic," "disease causing automatic," "splicing," "stopgain," or "frameshift deletion/insertion." Additional points (0–20) were allocated based on the variant's location, with 20 points assigned if the variant affected the first codon. Variants predicted as "missense" by MutationTaster and classified as "disease_causing" received a score of 30. Variants classified as "deleterious" by LRT or SIFT received an additional 10 points each. To validate (likely) pathogenic variants and VUS detected through NGS, direct sequencing of the affected exon was performed using a novel LR-PCR. Additionally, a segregation study was conducted by direct sequencing of the affected exons in all probands with (likely) pathogenic variants or VUS.

ProPKD score

The ProPKD score was applied to ADPKD patients aged 35 years or older, or younger patients with a history of hypertension and urological events who had obtained a positive genetic result for *PKD1* or *PKD2*. The score ranged from 0 to 9 points, according to the patient's clinical and genetic characteristics. Among the 72 ADPKD individuals assessed, they were categorized as low-risk (0–3 points), intermediate-risk (4–6 points), or high-risk (7–9 points) for progression to ESRD. An alternative genetic score ranging from 0 to 4 points was proposed for patients younger than 35 years or those with missing clinical data, which provided a reasonable estimation of renal prognosis, although less accurate than the ProPKD score [13]. This approach aligns with the recommendations of the ProPKD score authors, who recognized the need for a separate scoring method for specific patients with distinct clinical characteristics and data availability.

Statistical analysis

Descriptive statistical methods were employed to analyze the clinical and genetic data. Continuous variables were described using the median and interquartile range (IQR), while qualitative variables were presented as a range or percentage. Kaplan–Meier curves were constructed to evaluate cumulative kidney survival based on specific variants and ProPKD risk. The Log-rank Mantel-Cox test was utilized to assess differences between the survival curves, with p-values less than 0.05 considered statistically significant.

Results

Basic and clinical ADPKD proband characteristics

This study included 40 ADPKD probands, with a gender distribution of 50% females. The clinical presentations consisted of familial cases ($n=37$) and sporadic cases ($n=2$). One patient, who was adopted in early childhood, did not have information about her

biological family. Recruitment took place at various health centers across the country, with a concentration in the Metropolitan region of Santiago and the Los Rios-Los Lagos regions (Fig. 1A).

The median age at clinical diagnosis of ADPKD was 35 years [30-40] years. Among the participants, 24 patients (10 males and 14 females) had already reached ESRD and required RRT at a median age of 49 years (range: 44–53 years). The time interval between ADPKD diagnosis and the onset of ESRD was 11 years (range: 5.5–17.5 years), with no significant differences observed between men and women. The enrollment workflow spanned two periods (2014–2017 and 2018–2021) during which analysis was performed through direct sequencing or targeted NGS (Fig. 1B; further details can be found in the Patients and Methods section).

Genetic testing of PKD1 and PKD2

Genetic analysis was conducted on all 40 ADPKD probands, resulting in the identification of 38 variants in a heterozygous state. Among these variants, 34 (89%) were located in the *PKD1* gene, while 4 (11%) were located in the *PKD2* gene. Two patients (ADPKD-9 and ADPKD-13) with a positive family history remained genetically unresolved. This yielded an overall detection rate of 95% (Table 1).

Among the 38 patients with positive genetic results, causative candidate variants were identified. Some of these variants were shared by two families. Four pathogenic variants were found, including three frameshift variants and one nonsense variant, which were shared by unrelated families. Two of these variants were located in *PKD1* (exons 17 and 40), and the other two were located in *PKD2* (exons 8 and 13). One *PKD2* variant and one

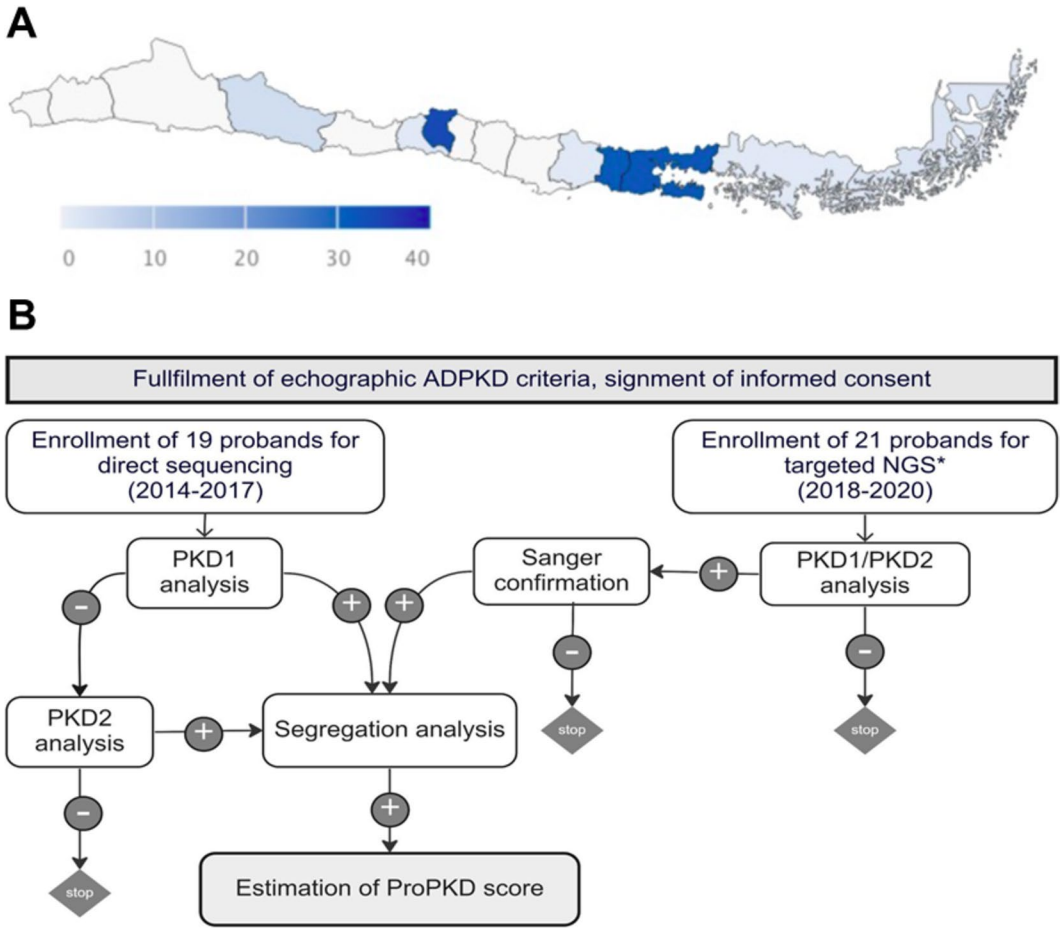

Fig. 1 **A** The geographic distribution of ADPKD patients enrolled in the study is displayed in a map, with color intensity indicating the number of patients recruited in each administrative region. This visualization provides an overview of the regional distribution of study participants and highlights the areas with higher recruitment rates. **B** The workflow of patient recruitment and DNA analysis strategies during two time periods, 2014–2017 and 2018–2020, is depicted. The diagram illustrates the step-by-step process of how patients were identified and included in the study, as well as the subsequent DNA analysis techniques employed. This visual representation explains the study's timeline and methodology, allowing for a better interpretation of the results and conclusions

Table 1 Basic, clinical and genetic characteristics of the ADPKD probands

Code (sex)	Inheritance	Deaths[a]	Age at diagnosis	Age at ESRD	Affected Gene (Exon/Intron)	Genetic change (protein prediction)	Classification	References
ADPKD-1 (F)	Fam	3	43 yrs	49 yrs	PKD1 (Ex37)	c.10907_10908delTG (p.Val3636AspfsX85)	Pathogenic	Novel
ADPKD-2 (F)	Fam	0	24 yrs	43 yrs	PKD1 (IVS25)	c.9202–2 A > G (p.Pro3067fsX182)	Pathogenic	Athena Diagnostics[b]
ADPKD-3 (M)	Fam	3	37 yrs	38 yrs	PKD1 (ex24)	c.8887insA (p.Arg2962fsX9)	Pathogenic	Novel
ADPKD-4 (M)	Fam	1	47 yrs	49 yrs	Not identified	Not identified	-	-
ADPKD-5 (M)	Fam	1	35 yrs	40yrs	PKD1 (Ex 17)	c.7126 C > T (p. Glu2376X)	Pathogenic	Rossetti et al. Kidney Int 2002 [20]
ADPKD-6 (F)	Fam	0	31 yrs	46 yrs	PKD1 (Ex 40)	c.11379_11380insG (p.Gly3793fsX22)	Pathogenic	Novel
ADPKD-7 (M)	Fam	1	29 yrs	33 yrs	PKD1 (Ex11)	c.2684 C > A (p.Ser895X)	Pathogenic	Novel
ADPKD-8 (F)	Fam	3	33 yrs	44 yrs	Not identified	Not identified	-	-
ADPKD-9 (F)	Fam	1	44 yrs	51 yrs	PKD1 (Ex29)	c.9750_9754delGGCTG (p.Glu3252AlafsX6)	Pathogenic	Novel
ADPKD-10 (F)	Fam	0	25 yrs	48 yrs	PKD1 (Ex 35)	c.10527_10528delGA (p.Glu3509AspfsX115)	Pathogenic	Yu et al. 2011 [21]; Athena Diagnostics[b]
ADPKD-11 (F)	Fam	0	30 yrs	No	PKD2 (Ex 13)	c.2465delA (Hys822LeufsX22)	Pathogenic	Novel
ADPKD-12 (M)	Fam	0	37 yrs	No	PKD1 (Ex 23)	c.8702 C > T (p.Pro2901Leu)	VUS	Athena Diagnostics[b]
ADPKD-13 (F)	Fam	1	27 yrs	47 trs	PKD1 (Ex 39)	c.11263 C > T (p.Glu3755X)	Pathogenic	Novel
ADPKD-14 (F)	Fam	1	23 yrs	52 yrs	PKD1 (Ex 17)	c.7126 C > T (p.Glu2376X)	Pathogenic	Rossetti et al. 2002 [20]
ADPKD-15 (M)	Fam	1	40 yrs	54 yrs	PKD1 (IVS 19)	c. 7703 + 1 G > A (p.Trp2498LeufsX50	Pathogenic	Audrézet et al. 2012 [22]
ADPKD-16 (F)	Fam	0	33 yrs	No	PKD1 (Ex 25)	c.9075 G > T (p.Trp3025Cys)	Likely pathogenic	Novel
ADPKD-17 (F)	Fam	0	25 yrs	No	PKD1 (Ex 40)	c.11379_11380insG (p.Gly3793fsX22)	Pathogenic	Novel
ADPKD-18 (F)	Fam	0	52 yrs	52 yrs	PKD1 (Ex 30)	c.10042 C > T (p.Arg3348Trp	Likely pathogenic	Novel
ADPKD-19 (M)	Fam	0	44 yrs	No	PKD1 (Ex 38)	c.11156 G > A (p.Arg3719Gln)	Likely pathogenic	Aguiari et al. 2000 [23]; Tsuchiya et al. 2001 [24]
ADPKD-20 (F)	Fam	0	39 yrs	45 yrs	PKD1 (Ex 38)	c.11137delG (p. Ala3713ProFsX13	Pathogenic	Novel
ADPKD-21 (F)	Fam	2	26 yrs	60 yrs	PKD1 (Ex 46)	p.12460 C > T (p.Arg4154Cys)	Likely pathogenic	Perrichot et al. 1999 [25]; Athena Diagnostics[b]
ADPKD-22 (F)	Fam	0	N/A	54 yrs	PKD1 (Ex 24)	c.8827 G > C (p.Ala2943Pro)	VUS	Novel
ADPKD-23 (M)	Fam	0	39 yrs	55 yrs	PKD1 (IVS 22)	c.8162–2 A > G (p.delGly2721_ Asp2930)	Pathogenic	Novel

Table 1 (continued)

Code (sex)	Inheritance	Deaths[a]	Age at diagnosis	Age at ESRD	Affected Gene (Exon/Intron)	Genetic change (protein prediction)	Classification	References
ADPKD-24 (M)	Fam	0	36 yrs	42 yrs	PKD1 (IVS 37)	c.11017–10 C > A (p.Arg3672fsX1)	Pathogenic	Perrichot et al. 1999 [25]; Bogdanova et al. 2000 [26]; Garcia-Gonzalez et al., 2007 [27]; Rossetti et al. 2007 [28]; Audrézet et al. 2012 [22]; Athena Diagnostics[b]
ADPKD-25 (F)	Adopted	0	36 yrs	43 yrs	PKD2 (Ex 13)	c.2465delA (p.Hys822LeufsX22)	Pathogenic	Novel
ADPKD-26 (M)	Fam	0	35 yrs	61 yrs	PKD1 (Ex 25)	c.8975 A > C (p.Hys2992Pro)	VUS	Novel
ADPKD-27 (M)	Fam	0	45 yrs	No	PKD1 (Ex 23)	c.8423 T > A (p.Ile2808Asn)	Likely pathogenic	Novel
ADPKD-28 (M)	Fam	1	36 yrs	No	PKD1 (Ex 7)	c.1598 A > G (p.Gln1533Arg)	Likely pathogenic	Novel
ADPKD-29 (M)	Fam	2	55 yrs	No	PKD1 (Ex 11)	c.2221 C > T (p.Pro741Ser)	VUS	Novel
ADPKD-30 (M)	Fam	0	NA	No	PKD2 (Ex 8)	c.1781delC (p.Asp596ThrfsX14)	Pathogenic	Novel
ADPKD-31 (F)	Fam	0	43 yrs	No	PKD2 (Ex 8)	c.1781delC (p.Asp596ThrfsX14)	Pathogenic	Novel
ADPKD-32 (M)	Fam	0	36 yrs	49 yrs	PKD1 (Ex 3)	c.325 G > T (p.Gly109X)	Pathogenic	Novel
ADPKD-33 (F)	Fam	0	35 yrs	49 yrs	PKD1 (Ex 27)	c.9404 C > T (p.Thr3135Met)	Likely pathogenic	Bataille et al. 2011 [29]; Athena Diagnostics[b]
ADPKD-34 (M)	Fam	1	56 yrs	56 yrs	PKD1 (Ex 15)	c.3447delC (p.Pro1150ArgfsX21)	Pathogenic	Novel
ADPKD-35 (M)	Spo	0	17 yrs	No	PKD1 (Ex 40)	c.11376dupG (pThr3794AspfsX22)	Pathogenic	Novel
ADPKD-36 (F)	Fam	0	12 yrs	No	PKD1 (Ex 2)	c.287 T > C (p.Leu96Pro)	Likely pathogenic	Athena Diagnostics[b]
ADPKD-37 (F)	Fam	0	35 yrs	No	PKD1 (Ex 16)	c.7061 A > G (p.Gln2354Arg)	Likely pathogenic	Athena Diagnostics[b]
ADPKD-38 (M)	Fam	0	N/A	No	PKD1 (Ex 11)	c.2429 A > G (p.Asn810Ser)	VUS	Novel
ADPKD-39 (M)	Fam	0	35 yrs	No	PKD1 (Ex 4)	c.405 G > C (p.Trp135Cys)	Likely pathogenic	Novel
ADPKD-40 (M)	Spo	0	34 yrs	No	PKD1 (Ex 15)	c.4475 G > A (p.Arg1492Hys)	VUS	Novel

F female, *M* male, *Fam* familiar, *Spo* sporadic, *N/A* not available, *VUS* variant of uncertain significance

[a] Number of deaths in the family at age < 60 yrs attributable to ESRD

[b] Variants are registered in ADPKD Mayo Clinic Database but have not been published

PKD1 variant were novel. In total, 34 different variants were identified in *PKD1* and *PKD2*, consisting of 18 nucleotide changes predicting truncating variants and 16 nucleotide changes predicting missense variants. Based on the bioinformatic analysis, these variants were classified as pathogenic ($n=18$), likely pathogenic ($n=10$), or VUS ($n=6$). Altogether 62% of these variants were considered novel, as they were not found in databases nor previous case reports (Table 1). No significant associations were found between the known/novel variants and phenotypic features such as ESRD or the development of hypertension before the age of 35.

The identified *PKD1* variants were distributed between exons 2 and 46, including four intronic

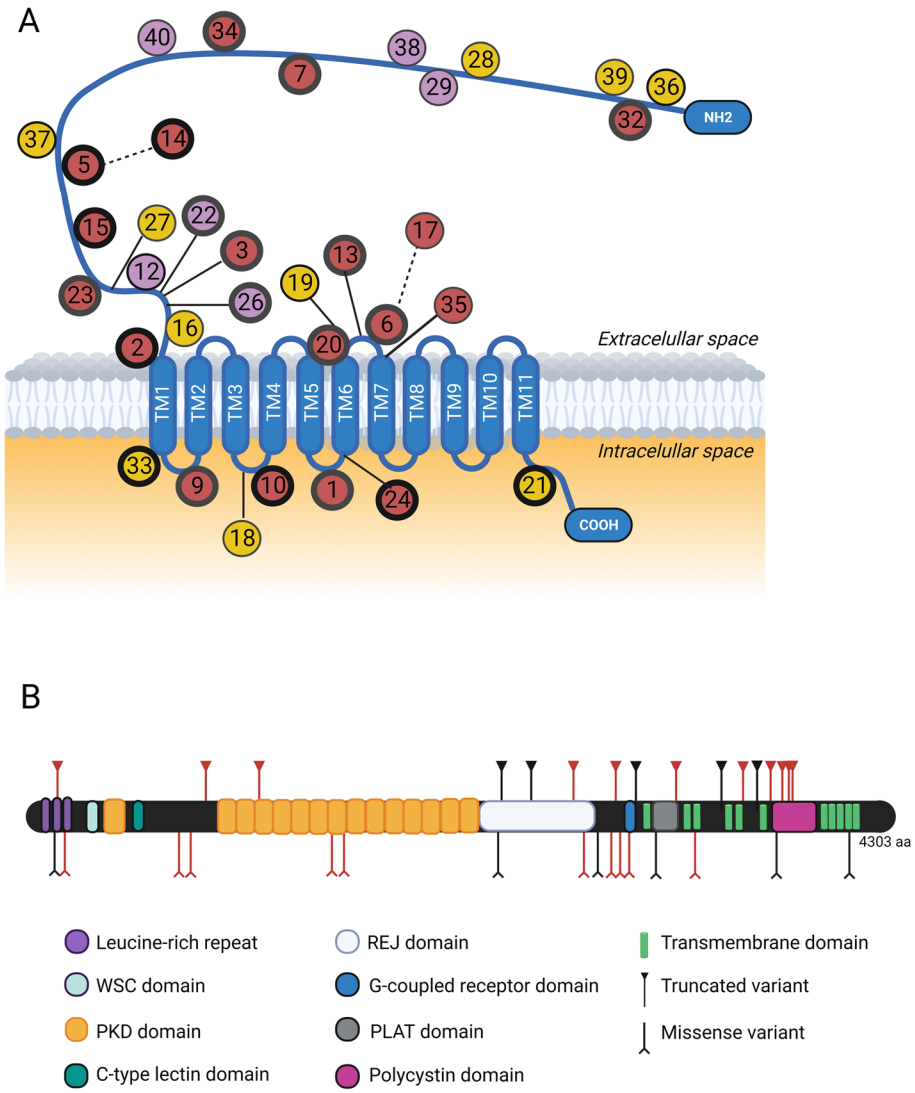

Fig. 2 **A** *PKD1* genetic landscape of ADPKD probands. The image shows the different variants identified in this study according to the bioinformatic analysis. The pathogenic variants are represented in red, likely pathogenic variants in yellow, and variants of uncertain significance (VUS) in pink circles. The variants identified in probands that had already reached end-stage renal disease (ESRD) at the time of enrolment are denoted by a bold circle border. Each number within the circle corresponds to the ADPKD family in which the variant was detected (refer to Table 1 for further details). The dashed lines connect families sharing the same variant. The elements and details in this image have been intentionally adjusted for improved interpretation and clarity. They do not necessarily reflect the precise scale or proportions and are included for a better understanding of the depicted information. **B** Localization of *PKD1* variants within protein domains. This figure illustrates the variant distribution categorized based on their position within the PKD1 protein and its associated domains, as identified using the information provided by EMBL-EBI under protein accession number P98161. The upper and lower segments depict *PKD1*-truncated and *PKD1*-missense variants, respectively. For the purposes of variant classification, any alterations that impact the splicing mechanism, cause frameshift deletions, or insertions were categorized as truncating variants. The novel variants are highlighted in red for easy identification. Created with Biorender.com

variants, and were predicted to affect different protein domains (Fig. 2A-B). The segment from exons 22 to 41, which encodes a portion between amino acids 2673 and 3846, accounted for 27% of the PKD1 protein-coding region and harbored 60% of the identified variants. *PKD2* variants, on the other hand, were only found in exons 8 and 13.

Associations between ESRD and genetic findings

During the recruitment of ADPKD probands, efforts were made to involve their relatives in the study. Among the 122 additional participants, a total of 68 individuals were confirmed to carry a *PKD1* or *PKD2* variant shared with the family proband. The median age of these individuals at the time of enrollment was 24.0 [15-30] years.

It was observed that in each family where a *PKD1* or *PKD2* variant was confirmed, ADPKD was transmitted to 67.4% of all at-risk children in the generations, which was higher than the expected 50% inheritance based on allele risk (Chi-square = 7.935, df = 1, $p = 0.0048$).

When considering both the probands and their relatives carrying a *PKD1* or *PKD2* variant, out of the 106 individuals, 38 had already reached ESRD. Individuals with *PKD1*-truncating (PKD1-T) variants exhibited the most severe progression, requiring RRT at a median age of 48.5 [44.5–52.5] years. Among these individuals, 100% had reached ESRD by the age of 60 (Fig. 3A). It was observed that male PKD1-T variant carriers tended to develop ESRD at an earlier age compared to female carriers, although this difference did not reach statistical significance (median age of 46.5 years for men vs. 49.0 years for women, $p = 0.139$). On the other hand, individuals with *PKD1*-missense (PKD1-M) variants required RRT

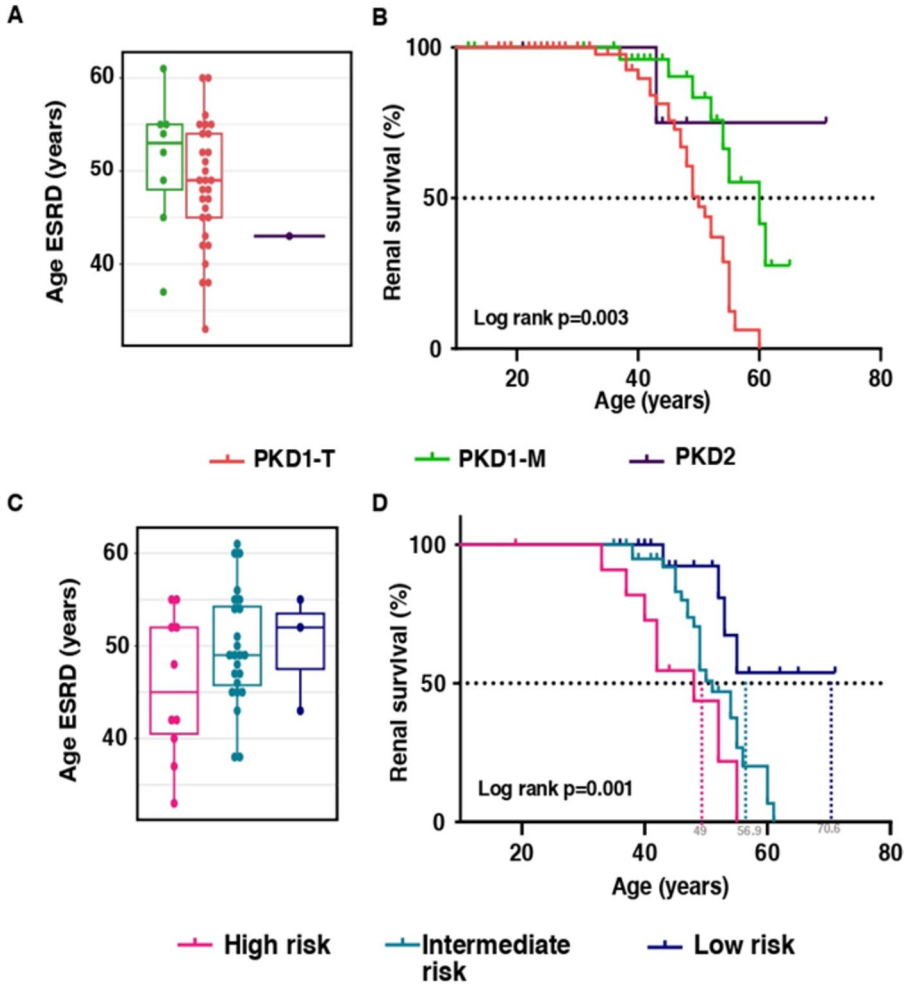

Fig. 3 **A** A boxplot is presented to compare the age at end-stage renal disease (ESRD) among patients with different types of variants in *PKD1*, specifically *PKD1*-truncating (PKD1-T) and *PKD1*-missense (PKD1-M), as well as variants in *PKD2*. The boxplot provides a visual representation of the distribution and median age at ESRD for each variant type, allowing for a comparison of disease progression among the different genetic variants. **B** Kaplan–Meier survival curves are displayed, depicting the probability of survival without reaching ESRD over time, based on the gene involved (PKD1 or PKD2) and the type of mutation. The curves are censored, meaning that the age and condition (with or without ESRD) at the time of recruitment are taken into account. This analysis provides insights into the differential risk of ESRD development based on the specific gene and mutation type, enabling the assessment of disease prognosis. **C** A boxplot is presented to compare the age at ESRD among patients stratified into high, intermediate, or low-risk categories based on the ProPKD score assessment. The ProPKD score is a risk prediction tool for CKD progression in ADPKD. The boxplot allows for a visual comparison of the age at ESRD among patients with different risk scores, providing information on the relationship between risk category and disease progression. **D** Kaplan–Meier survival curves are displayed, similar to section B, but now based on the risk stratification according to the ProPKD score. The curves depict the probability of survival without reaching ESRD over time, considering the risk categories. The analysis allows for an evaluation of the impact of risk stratification on disease prognosis and the likelihood of ESRD development

at a median age of 53 [48–56.3] years. Among the five individuals carrying *PKD2* variants, only one developed ESRD by the age of 43. Cumulative survival analysis demonstrated significant phenotypic differences in terms of the age of ESRD onset among the PKD1-T, PKD1-M, and PKD2 groups, although there were some overlapping curves (Fig. 3B). Median survival showed clinically relevant differences between the PKD1-T and PKD1-M, with a 50% chance of reaching kidney failure by 50 years for the former group and by 60 years for the latter group.

Assessment of ProPKD score in Chilean ADPKD patients

In a subset of 72 out of 106 individuals with ADPKD carrying a *PKD1* or *PKD2* variant, the ProPKD score was assessed (Supplementary Table 1). According to the results, ADPKD patients categorized as high-risk, intermediate-risk, and low-risk required RRT at median ages of 45, 49, and 52 years, respectively (Fig. 3C). Kaplan–Meier curves demonstrated significant differences among the three risk categories (Fig. 3D). The median renal survival age was 48 years for individuals with high-risk and 51 years for those with intermediate risk. All individuals in these categories required RRT by the age of 61.

For the 34 patients who were younger than 35 years or had missing clinical data, a genetic score was estimated (Supplementary Table 2). Among these patients, 33 out of 34 had a score of ≥ 2 points, reflecting that they carried a *PKD1* variant. Among the individuals with a high genetic risk score, 22 were carriers of PKD1-T variants, which conferred a high risk of ESRD by the age of 65.

Among all individuals included in the study, nine individuals between the ages of 6 and 17 years were identified with a positive genetic result. Among them, seven had undergone an echography in the past 2–5 years, which strongly suggested the presence of ADPKD in early stages. Genetic counseling was offered to the parents of these individuals both before and after the genetic analysis, even in the two cases without imaging evidence.

Discussion

This study represents the first report providing insights into the clinical and genetic characteristics of ADPKD in a Latin American population, specifically in Chile. Among the patients included in the study, we identified a total of 21 novel variants, with the majority of them located within the *PKD1* gene. This finding highlights a high mutability of the *PKD1* gene in this population. The data obtained from this study can serve as a valuable resource to support the diagnosis of ADPKD in specific cases and contribute to early and personalized clinical management. Additionally, the findings may have implications for decision-making regarding transplantation, in accordance with the laws and regulations in Chile.

In our cohort of probands, the median age at which ADPKD was clinically diagnosed was 35 years. It is noteworthy that 60% of these individuals had already progressed to ESRD at the time of recruitment and required RRT at a median age of 49 years. This observation of relatively early disease progression, compared to other reported cohorts, suggests the presence of rapid disease progression in our study population. It is important to acknowledge that there might be additional factors contributing to the more pronounced symptoms that led these individuals to seek medical attention earlier. However, it is essential to note that our initial pilot study conducted between 2014 and 2017 exhibited certain biases. ADPKD patients were predominantly recruited from local dialysis and transplant registries, which might have influenced the higher detection rate of *PKD1* variants compared to *PKD2* variants.

The majority of our ADPKD probands had a positive family history, and genetic analysis successfully identified a pathogenic, likely pathogenic variant, or VUS in 95% of them. Similar to other studies, a small subgroup of individuals did not have a family history, but genetic analysis revealed the presence of de novo *PKD1* variants [30]. One such case involved a 19-year-old patient who had been diagnosed with ADPKD two years prior and exhibited multiple risk factors, including being a male carrier of a *PKD1*-truncating variant, hypertension, and urological events.

The genetic analysis identified heterozygous variants dispersed in or adjacent to the 22/46 *PKD1* exons and 2/15 *PKD2* exons. According to public databases and reports, variants have not been localized at particular *loci*, but have been identified in untranslated regions, exons and introns. Four variants were found to be shared by two families: c.7126 C > T and c.11379_11380insG in *PKD1*, and c.1781delC and c.2465delA in *PKD2*. While some of these variants may have arisen independently because increased mutability has been described for *PKD1*, it is worth considering the possibility of a founder effect for *PKD1* c.7126 C > T and the two novel *PKD2* variants, as the families were geographically close (within 100 km) [31, 32]. Founder variants have been previously described in ADPKD, suggesting that variants that are unexpectedly frequent in specific geographic areas may have originated from a founder effect.

In this study, we observed that a significant portion of the *PKD1* variants identified were concentrated in specific segments of the protein, which are predicted to have functional relevance. Based on this finding, we suggest considering the development of an algorithm for direct sequencing or bioinformatic analysis following NGS that prioritizes this segment. This approach could help optimize cost, time, and labor in genetic analysis. However, it

is important to exercise caution and consider the potential recruitment bias in this study, as the cohort was not randomly selected.

As of January 2023, the PKDB has registered more than 2500 unique pedigrees with (likely) pathogenic variants or VUS. Earlier studies on ADPKD reported a high percentage (60% to 70%) of novel variants reflecting the limited comprehensiveness of genetic databases at the time. As these databases have expanded with the progressive incorporation of NGS sequencing, it is expected that the rate of novel variants may decrease. However, the rate of new variants identified in ADPKD is also influenced by the methods used for variant identification and the specific study population. In our cohort, we identified a total of 21 (62%) novel variants. No associations were found between novel variants and phenotype features; however, this may change over time as more patients and more clinical data are collected.

While our dataset is still limited, it serves as a valuable starting point for improving our understanding of the clinical phenotypes and genetic profiles of ADPKD in our country. This database will contribute to expanding our knowledge and prompt further research on ADPKD. Targeted NGS approaches have proven to be effective in identifying variants not only in the primary causative gene but also in other genes known to be associated with ADPKD. In addition to targeted NGS, whole-exome sequencing (WES) and whole-genome sequencing (WGS) are alternative approaches that offer a broader perspective on the genetic landscape of ADPKD. WES examines the protein-coding regions of the genome, while WGS encompasses the entire genome, including both coding and non-coding regions. These unbiased sequencing methods have the potential to identify novel genes associated with ADPKD or other genes that may play a role in the response to specific therapies, as described in other clinical contexts [4, 33]. It is worth noting that WES and WGS require more extensive sequencing and data analysis compared to targeted NGS, making them more resource-intensive. However, as technology advances and costs decrease, these comprehensive sequencing approaches might become increasingly accessible and may hold promise for further understanding the genetic complexities of ADPKD and related conditions.

Assessing the genetic profile of ADPKD in a broad manner can lead to the identification of various variants across the genome. One emerging concept in genetic research is the study of Total Mutational Burden (TMB), which refers to the total number of mutations present in a given sample. TMB has gained attention as a potential predictor of clinical outcomes and has demonstrated its utility in predicting cancer metastasis and treatment response. For example, a study focused on lung cancer utilized machine learning models to evaluate the predictive power of TMB [34]. The results showed that TMB was a significant predictor of metastasis, with the classification models demonstrating high-performance measures. Moreover, clinical studies have shown that tumors with high TMB tend to respond better to immunotherapy [35]. This suggests that TMB could be a relevant factor in predicting treatment outcomes and tailoring therapeutic approaches not only in cancer research. Consequently, it is plausible to estimate TMB in ADPKD patients to gain insights into disease progression and response to interventions.

Different biomarkers have been investigated to assess the risk of disease progression in ADPKD, including clinical, molecular, genomic, and imaging markers, featuring their advantages and disadvantages [36]. Imaging techniques such as ultrasonography, computed tomography, and magnetic resonance imaging can detect renal cysts, with monitoring of total kidney volume considered the best image-based marker for ADPKD. However, access to and affordability of these imaging methods can be limited in some countries, and accurate interpretation requires trained operators and image analysts, particularly in the early stages of the disease.

On the other hand, the cost of genetic analysis has decreased significantly over the past few decades, making it a more cost-effective option. However, genetic analysis is still not widely accessible in resource-limited settings. Nevertheless, evidence suggests that early genetic analysis can lead to substantial cost savings [37]. Genetic testing in ADPKD can provide valuable information for family planning, prenatal testing options, and clinical management decisions, as well as help evaluate future scenarios [38]. Current guidelines recommend the standard method of ADPKD genetic analysis, which involves LR-PCR followed by direct sequencing [39]. In the last decade, there have been attempts to implement NGS analysis, considering that it offers the potential to detect additional variants and somatic mosaicism. However, NGS can also result in missed variants, particularly in *PKD1* due to its gene complexity [40–42].

It is important to note that disease progression in ADPKD can vary within families, suggesting that focusing solely on the gene and type of variant may be insufficient to predict the risk of progression accurately. In our study, differences were observed in survival curves based on the type of variant and risk stratification using the ProPKD score. The ProPKD score showed better discrimination between high-, intermediate-, and low-risk groups. While the impact of genetic and clinical variables has been useful in developing the ProPKD score, until now, it has never been applied to Latin American

cohorts, which might be explained by the need for genetic testing.

Latin American countries face significant disparities, including in healthcare access. Chile, located on the southwestern coast of South America and with a population of approximately 19.5 million, is classified as a high-income country by the World Bank and an Upper-middle-income country by the sociodemographic index [43]. However, like other countries in the region, it exhibits noticeable socioeconomic variability, as evidenced by a Gini index of 0.45 in 2020. The healthcare system in Chile is served by both public (FONASA) and private providers. FONASA caters to 80% of the population and bears the cost of dialysis, a significant expenditure amounting to 253 million USD for 22,000 patients. This figure corresponds to 30% of the annual FONASA budget, not accounting for other expenses such as hospitalizations, medical visits, and medications. In our perspective, timely diagnosis of ADPKD, particularly in high-risk patients, holds the potential to propose a more individualized clinical management approach aimed at slowing down the progression of CKD and delaying the onset of ESRD. This, in turn, could contribute to reducing therapeutic costs while novel therapies for ADPKD are being developed [44, 45].

In Chile, public financial coverage of genetic testing is limited to direct sequencing, and it requires a laboratory with sanitary authorization in a clinical setting. This restriction highlights the need for cost-effective and accessible diagnostic approaches for conditions like ADPKD, given the burden imposed on the national healthcare system. It should be noted that the genetic complexity of *PKD1* may hinder widespread genetic testing in developing nations in addition to several factors including variant diversity, costs, scarcity of genetic counselors and experts in molecular genetics, patient data privacy as well as regulatory and ethical frameworks. The situation regarding genetic conditions varies from one country to another and may evolve over time as healthcare systems and resources change. Efforts to raise awareness about the ADPKD diagnosis and management could help address this issue in the future.

Our study is subject to several limitations that should be acknowledged. Firstly, the majority of our patients had received their diagnosis a long time ago, which limited our ability to obtain complete imaging records to correlate with the clinical course. Furthermore, the persistence of paper-based medical registries in certain healthcare centers posed challenges in data collection and retrieval. Although we achieved a high detection rate, it is important to note that we did not employ the multiplex-ligation probe-amplification technique to identify deletions/duplications in *PKD1* or *PKD2*. Therefore, the possibility of these genetic alterations existing within our cohort cannot be definitively ruled out. Additionally, it is important to consider that our dataset was of moderate size and initially biased toward patients registered in RRT programs. These individuals typically exhibit a more severe phenotype, increasing the likelihood of identifying pathogenic variants in *PKD1*. Consequently, the extrapolation of our findings to other ADPKD patients needs caution. Lastly, we did not conduct haplotype analysis for the few cases of unrelated families sharing variants, which could have provided insights into the presence of a founder effect within them. Despite these constraints, our study contributes valuable clinical data and insights into ADPKD in the Chilean population. Further research addressing these limitations and expanding the scope of investigation is required to enhance our understanding of the disease in this context.

This study benefits from several factors that contribute to its strengths and advantages. Chile has implemented a formal program to train clinical geneticists who can provide counseling in both public and private healthcare centers [46]. Some laboratories in Chile perform direct sequencing, which is covered by FONASA, however, *PKD1* and *PKD2* genetic testing are not included. To achieve the results presented in this study, three major research initiatives were necessary, combining direct sequencing and NGS strategies to describe the genetic profile of ADPKD patients. NGS panels offer a comprehensive option in various clinical scenarios. Chilean patient samples requiring this type of analysis are often sent to international laboratories, but *PKD1* is frequently excluded.

Since 2018, there has been a significant increase in awareness among Chilean nephrologists regarding the utility of genetic testing. This awareness stems from the ability to communicate to families the risk of inheritance and to consider living-related donors for transplantation. The ProPKD score, which assesses the risk of CKD progression in ADPKD, has emerged as a suitable risk prediction tool in the local setting. However, when comparing the age of ESRD onset in our patients with the GENKYST cohort, we observed that our patients reached this stage 2.4, 7.9, and 18.6 years earlier in the high-risk, intermediate-risk, and low-risk groups, respectively. Further studies involving larger cohorts are needed to explore the relevance of other biological and environmental factors that influence kidney decline during the disease's clinical course.

Conclusion

In summary, kidney disease poses a significant burden on the Chilean public health system, particularly for underserved patients with ADPKD. There is a pressing

need for improved diagnosis and management strategies to slow down disease progression. The integration of genetic and clinical factors through the use of a prediction tool has emerged as a promising approach to address this challenge and provide a starting point for more personalized and effective management. By combining genetic information with clinical indicators, healthcare providers can better identify high-risk patients and implement timely interventions to delay the progression of ADPKD and improve patient outcomes.

Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
PKD1	*Polycystic kidney disease-1* (POLYCYSTIN 1)
PKD2	*Polycystic kidney disease-2* (POLYCYSTIN 2)
ESRD	End-stage renal disease
ProPKD	Predicting Renal Outcome in Polycystic Kidney Disease
RRT	Renal replacement therapy
NGS	Next-generation sequencing
LR-PCR	Long-Range PCR
VUS	Variant of uncertain significance
PKDB	PKD database
TMB	Total mutational burden
CKD	Chronic kidney disease

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41231-023-00157-5.

Additional file 1: Supplementary Table 1. ProPKD score and risk categories. **Supplementary Table 2.** Genetic score.

Acknowledgements
We would like to express our sincere gratitude to all the patients and their families who participated in this study. Their willingness to contribute their time and information has been invaluable in advancing our understanding of ADPKD. We would also like to extend our appreciation to the nephrologists and nurses who provided clinical information and assistance with the sample and data collection process. Their dedication and support have been instrumental in the success of this research endeavor.

Authors' contributions
Conceptualization: EB, KO, JM, PK. Data curation, Formal analysis: EB, AP, PD, PS, DM, PH, PL, LQ, CF, LA, PK. Funding acquisition: JM, PK. Investigation, Methodology: All authors. Project administration: JM, PK. Software: AP, JK, JM, PK. Writing-original draft: EB, MJZ, LA, JM, PK. Writing-review & editing: All authors. All authors read and approved the final manuscript.

Funding
This research was supported by FONDEYCT de Iniciacion #111–40242 from the National Research Agency (ANID), by Desafio INNOVing by the Faculty of Engineering at the Universidad Austral de Chile, by the GEMINi FICR#18–77 and GEMINi-2 FICR#22–13 grants, both granted by the Gobierno Regional de Los Ríos.

Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due to confidentiality agreements but are available from the corresponding author on reasonable request subject to a non-disclosure agreement, without compromising the privacy of research participants.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Research Ethics Committee of the Health Service for Valdivia (Approval ORD#353). This study was performed following the Declaration of Helsinki, Good Clinical Practice, and Chilean Legislation (laws 20.120, 20.584, and 19.628).

Consent for publication
All participants, parents or legal guardians signed an informed consent form that included consent for the publication of their data in an anonymous manner.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Laboratory of Nephrology, Institute of Medicine, Universidad Austral de Chile, Valdivia, Chile. [2]Informatics Institute, Faculty of Engineering, Universidad Austral de Chile, Valdivia, Chile. [3]Nephrology Unit, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile. [4]Nephrology Unit, Faculty of Medicine, Hospital Exequiel González Cortés, Santiago, Chile. [5]Institute of Pediatrics, Faculty of Medicine, Universidad Austral de Chile, Valdivia, Chile. [6]Pediatrics Unit, Hospital Base Valdivia, Valdivia, Chile. [7]Neonatal Unit, Hospital Base Valdivia, Valdivia, Chile. [8]Interdisciplinary Research Institute, Vicerrectoría Académica, Universidad de Talca, Talca, Chile. [9]Department of Pediatrics and Child Surgery, Faculty of Medicine, Universidad de Chile, Santiago, Chile.

Received: 2 June 2023 Accepted: 9 October 2023
Published online: 25 October 2023

References

1. Spithoven EM, Kramer A, Meijer E, Orskov B, Wanner C, Abad JM, et al. Renal replacement therapy for autosomal dominant polycystic kidney disease (ADPKD) in Europe: prevalence and survival - An analysis of data from the ERA-EDTA Registry. Nephrol Dial Transplant. 2014;29(Suppl 4):iv15-25.
2. Harris PC, Rossetti S. Molecular diagnostics for autosomal dominant polycystic kidney disease. Nat Rev Nephrol. 2010;6(4):197–206.
3. Cornec-Le Gall E, Torres VE, Harris PC. Genetic complexity of autosomal dominant polycystic kidney and liver diseases. J Ame Soc Nephrol. 2018;29:13–23.
4. Lanktree MB, Haghighi A, Di Bari I, Song X, Pei Y. Insights into autosomal dominant polycystic kidney disease from genetic studies. Clin J Am Soc Nephrol. 2021;16(5):790–9.
5. Magistroni R, Corsi C, Martí T, Torra R. A Review of the Imaging Techniques for Measuring Kidney and Cyst Volume in Establishing Autosomal Dominant Polycystic Kidney Disease Progression. Am J Nephrol. 2018;48(1):67–78.
6. Sans-Atxer L, Torra R, Fernández-Llama P. Hypertension in autosomal-dominant polycystic kidney disease (ADPKD). Clin Kidney J. 2013;6(5):457–63.
7. Cornec-Le Gall E, Alam A, Perrone RD. Autosomal dominant polycystic kidney disease. Lancet. 2019;393(10174):919–35.
8. Montaña A, Patiño N, Larrate C, Zambrano FA, Martínez J, Lozano H, et al. Actualización en enfermedad renal poliquística. Rev Fac Med. 2018;46:107–16. Universidad Nacional de Colombia.
9. Pérez Domínguez TS, Rodríguez Pérez A, Buset Ríos N, Rodríguez Esparragón F, García Bello MA, Pérez Borges P, et al. Psiconefrología: aspectos psicológicos en la poliquistosis renal autosómica dominante. Nefrologia. 2011;31(6):716–22.
10. Chebib FT, Perrone RD, Chapman AB, Dahl NK, Harris PC, Mrug M, et al. A practical guide for treatment of rapidly progressive ADPKD with tolvaptan. J Am Soc Nephrol. 2018;29(10):2458–70.
11. Capuano I, Buonanno P, Riccio E, Amicone M, Pisani A. Therapeutic advances in ADPKD: the future awaits. J Nephrol. 2022;35:397–415. Springer.

12. Cornec-Le Gall E, Audrézet M-P, Chen JM, Hourmant M, Morin M-P, Perrichot R, et al. Type of PKD1 mutation influences renal outcome in ADPKD. J Am Soc Nephrol. 2013;24(6):1006–13.
13. Cornec-Le Gall E, Audrézet M-P, Rousseau A, Hourmant M, Renaudineau E, Charasse C, et al. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 2016;27(3):942–51.
14. Chan S, Patel C, Mallett AJ. Pilot clinical and validation study of the PROPKD score in clinical practice amongst patients with autosomal dominant polycystic kidney disease. Nephrology. 2020;25:274–5. Wiley-Blackwell.
15. Groopman EE, Rasouly HM, Gharavi AG. Genomic medicine for kidney disease. Nat Rev Nephrol. 2018;14:83–104. NIH Public Access.
16. Gallardo K, Varas L, Gallardo M. Inequality of opportunity in health: evidence from Chile. Rev Saude Publica. 2017;51:110.
17. Severino R, Espinoza M, Cabieses B. Health-related quality of life by household income in Chile: a concentration index decomposition analysis. Int J Equity Health. 2022;21(1):1–9.
18. Pei Y, Obaji J, Dupuis A, Paterson AD, Magistroni R, Dicks E, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol. 2009;20(1):205–12.
19. Tan Y-C, Michaeel A, Blumenfeld J, Donahue S, Parker T, Levine D, et al. A novel long-range PCR sequencing method for genetic analysis of the entire PKD1 gene. J Mol Diagnostics. 2012;14(4):305–13.
20. Rossetti S, Chauveau D, Walker D, Saggar-Malik A, Winearls CG, Torres VE, et al. A complete mutation screen of the ADPKD genes by DHPLC. Kidney Int. 2002;61(5):1588–99.
21. Yu C, Yang Y, Zou L, Hu Z, Li J, Liu Y, et al. Identification of novel mutations in Chinese Hans with autosomal dominant polycystic kidney disease. BMC Med Genet. 2011;12:164.
22. Audrézet MP, Cornec-Le Gall E, Chen JM, Redon S, Quéré I, Creff J, et al. Autosomal dominant polycystic kidney disease: comprehensive mutation analysis of PKD1 and PKD2 in 700 unrelated patients. Hum Mutat. 2012;33(8):1239–50.
23. Aguiari G, Savelli S, Garbo M, Bozza A, Augello G, Penolazzi L, et al. Novel splicing and missense mutations in autosomal dominant polycystic kidney disease 1 (PKD1) gene: expression of mutated genes. Hum Mutat. 2000;16(5):444–5.
24. Tsuchiya K, Komeda M, Takahashi M, Yamashita N, Cigira M, Suzuki T, et al. Mutational analysis within the 3′ region of the PKD1 gene in Japanese families. Mutat Res. 2001;458(3-4):77–84.
25. Perrichot RA, Mercier B, Simon PM, Whebe B, Cledes J, Ferec C. DGGE screening of PKD1 gene reveals novel mutations in a large cohort of 146 unrelated patients. Hum Genet. 1999;105(3):231–9.
26. Bogdanova N, McCluskey M, Sikmann K, Markoff A, Todorov V, Dimitrakov D, et al. Screening the 3′ region of the polycystic kidney disease 1 (PKD1) gene in 41 Bulgarian and Australian kindreds reveals a prevalence of protein truncating mutations. Hum Mutat. 2000;16(2):166–74.
27. Garcia-Gonzalez MA, Jones JG, Allen SK, Palatucci CM, Batish SD, Seltzer WK, et al. Evaluating the clinical utility of a molecular genetic test for polycystic kidney disease. Mol Genet Metab. 2007;92(1-2):160–7.
28. Rossetti S, Consugar MB, Chapman AB, Torres VE, Guay-Woodford LM, Grantham JJ, et al. Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 2007;18(7):2143–60.
29. Bataille S, Berland Y, Fontes M, Burtey S. High Resolution Melt analysis for mutation screening in PKD1 and PKD2. BMC Nephrol. 2011;12:57.
30. Reed B, McFann K, Kimberling WJ, Pei Y, Gabow PA, Christopher K, et al. Presence of de novo mutations in autosomal dominant polycystic kidney disease patients without family history. Am J Kidney Dis. 2008;52(6):1042–50.
31. Yu CC, Lee AF, Kohl S, Lin MY, Cheng SM, Hung CC, et al. PKD2 founder mutation is the most common mutation of polycystic kidney disease in Taiwan. NPJ Genomic Med. 2022;7(1):40.
32. Nielsen ML, Lildballe DL, Rasmussen M, Bojesen A, Birn H, Sunde L. Clinical genetic diagnostics in Danish autosomal dominant polycystic kidney disease patients reveal possible founder variants. Eur J Med Genet. 2021;64(4):104183.
33. Bergmann C, Von Bothmer J, Brüchle NO, Venghaus A, Frank V, Fehrenbach H, et al. Mutations in multiple PKD genes may explain early and severe polycystic kidney disease. J Am Soc Nephrol. 2011;22(11):2047–56.
34. Oróstica KY, Saez-Hidalgo J, de Santiago PR, Rivas S, Contreras S, Navarro G, et al. Total mutational load and clinical features as predictors of the metastatic status in lung adenocarcinoma and squamous cell carcinoma patients. J Transl Med. 2022;20(1):373.
35. Samstein RM, Lee CH, Shoushtari AN, Hellmann MD, Shen R, Janjigian YY, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet. 2019;51(2):202–6.
36. Radhakrishnan Y, Duriseti P, Chebib FT. Management of autosomal dominant polycystic kidney disease in the era of disease-modifying treatment options. Kidney Res Clin Pract. 2022;41:422–31.
37. Jayasinghe K, Wu Y, Stark Z, Kerr PG, Mallett AJ, Gaff C, et al. Cost-effectiveness of targeted exome analysis as a diagnostic test in glomerular diseases. Kidney Int Reports. 2021;6(11):2850–61.
38. Knoers N, Antignac C, Bergmann C, Dahan K, Giglio S, Heidet L, et al. Genetic testing in the diagnosis of chronic kidney disease: recommendations for clinical practice. Nephrol Dial Transplant. 2022;37(2):239–54.
39. Rangan GK, Alexander SI, Campbell KL, Dexter MAJ, Lee VW, Lopez-Vargas P, et al. KHA-CARI guideline recommendations for the diagnosis and management of autosomal dominant polycystic kidney disease. Nephrology. 2016;21(8):705–16.
40. Trujillano D, Bullich G, Ossowski S, Ballaréın J, Torra R, Estivill X, et al. Diagnosis of autosomal dominant polycystic kidney disease using efficient pkd1 and pkd2 targeted next-generation sequencing. Mol Genet Genomic Med. 2014;2(5):412–21.
41. Tan AY, Michaeel A, Liu G, Elemento O, Blumenfeld J, Donahue S, et al. Molecular diagnosis of autosomal dominant polycystic kidney disease using next-generation sequencing. J Mol Diagnostics. 2014;16(2):216–28.
42. Hopp K, Cornec-Le Gall E, Senum SR, te Paske IBAW, Raj S, Lavu S, et al. Detection and characterization of mosaicism in autosomal dominant polycystic kidney disease. Kidney Int. 2020;97(2):370–82.
43. Xie Y, Bowe B, Mokdad AH, Xian H, Yan Y, Li T, et al. Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. Kidney Int. 2018;94(3):567–81.
44. Cabrita I, Kraus A, Scholz JK, Skoczynski K, Schreiber R, Kunzelmann K, et al. Cyst growth in ADPKD is prevented by pharmacological and genetic inhibition of TMEM16A in vivo. Nat Commun. 2020;11(1):1–13.
45. Dong K, Zhang C, Tian X, Coman D, Hyder F, Ma M, et al. Renal plasticity revealed through reversal of polycystic kidney disease in mice. Nat Genet. 2021;53(12):1649–63.
46. Encina G, Castillo-Laborde C, Lecaros JA, Dubois-Camacho K, Calderón JF, Aguilera X, et al. Rare diseases in Chile: challenges and recommendations in universal health coverage context. Orphanet J Rare Dis. 2019;14(1):1–8.

Publisher's Note