# Correlation of Kidney Function, Volume and Imaging Findings, and *PKHD1* Mutations in 73 Patients with Autosomal Recessive Polycystic Kidney Disease

Meral Gunay-Aygun,* Esperanza Font-Montgomery,* Linda Lukose,* Maya Tuchman,* Jennifer Graf,† Joy C. Bryant,* Robert Kleta,* Angelica Garcia,* Hailey Edwards,* Katie Piwnica-Worms,* David Adams,* Isa Bernardini,* Roxanne E. Fischer,* Donna Krasnewich,* Neal Oden,‡ Alex Ling,† Zenaide Quezado,† Colleen Zak,§ Kailash T. Daryanani,† Baris Turkbey,‡ Peter Choyke,‡ Lisa M. Guay-Woodford,‖ and William A. Gahl*

**Medical Genetics Branch, National Human Genome Research Institute, Bethesda, Maryland; †National Institutes of Health Clinical Center, Bethesda, Maryland; ‡The EMMES Corporation, Rockville, Maryland; ‡Molecular Imaging Program, National Cancer Institute, Bethesda, Maryland; §Autosomal Recessive Polycystic Kidney Disease/Congenital Hepatic Fibrosis Alliance, Kirkwood, Pennsylvania; and ‖University of Alabama at Birmingham, Birmingham, Alabama*

**Background and objectives: Renal function and imaging findings have not been comprehensively and prospectively characterized in a broad age range of patients with molecularly confirmed autosomal recessive polycystic kidney disease (ARPKD).**

**Design, setting, participants, & measurements: Ninety potential ARPKD patients were examined at the National Institutes of Health Clinical Center. Seventy-three fulfilled clinical diagnostic criteria, had at least one *PKHD1* mutation, and were prospectively evaluated using magnetic resonance imaging (MRI), high-resolution ultrasonography (HR-USG), and measures of glomerular and tubular function.**

**Results: Among 31 perinatally symptomatic patients, 25% required renal replacement therapy by age 11 years; among 42 patients who became symptomatic beyond 1 month (nonperinatal), 25% required kidney transplantation by age 32 years. Creatinine clearance (CrCl) for nonperinatal patients (103 ± 54 ml/min/1.73 $m^2$) was greater than for perinatal patients (62 ± 33) ($P = 0.002$). Corticomedullary involvement on HR-USG was associated with a significantly worse mean CrCl (61 ± 32) in comparison with medullary involvement only (131 ± 46) ($P < 0.0001$). Among children with enlarged kidneys, volume correlated inversely with function, although with wide variability. Severity of *PKHD1* mutations did not determine kidney size or function. In 35% of patients with medullary-only abnormalities, standard ultrasound was normal and the pathology was detectable with HR-USG.**

**Conclusions: In ARPKD, perinatal presentation and corticomedullary involvement are associated with faster progression of kidney disease. Mild ARPKD is best detected by HR-USG. Considerable variability occurs that is not explained by the type of *PKHD1* mutation.**

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Autosomal recessive polycystic kidney disease (ARPKD) occurs in 1 in 20,000 births and is the most common hepatorenal fibrocystic disease of childhood (1–7). It is caused by mutations in *PKHD1*, which encodes fibrocystin/polyductin (8,9), a protein localized to the primary cilium, an organelle functioning as the cell's "sensory antenna" (10). Proteins defective in other diseases having fibrocystic pathology, such as autosomal dominant polycystic kidney disease, nephronophthisis, Bardet–Biedl, Meckel, and Joubert syndromes, also localize to the primary cilium; these disorders, along with ARPKD, comprise the "ciliopathies" (10–12).

Individuals with ARPKD have nonobstructive fusiform dilations of the renal collecting ducts, leading to progressive renal insufficiency. All ARPKD patients manifest some degree of congenital hepatic fibrosis (CHF) caused by ductal plate malformation of the developing portobiliary system; some patients also have macroscopic dilations of the intrahepatic bile ducts, a combination termed Caroli's syndrome (7,13,14). Portal hypertension complicates CHF and often results in esophageal varices and hypersplenism (15–18). Early-onset severe hypertension, often requiring multiagent therapy, occurs in most ARPKD patients (5).

Most ARPKD patients present perinatally with oligohydramnios and massively enlarged, diffusely microcystic kidneys.

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**Correspondence:** Dr. Meral Gunay-Aygun, National Human Genome Research Institute, National Institutes of Health, 10 Center Drive Building 10, Room 10C103, Bethesda, MD 20892. Phone: 301-594-4181; Fax: 301-480-7821; E-mail: mgaygun@mail.nih.gov



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Many such newborns subsequently succumb to pulmonary hypoplasia. Characterization of the clinical phenotype of ARPKD has been based primarily upon this subtype (*i.e.*, perinatally symptomatic patients) (1,4,5). Documentation of the kidney disease in patients presenting late in childhood or adulthood has been more limited (3,19,20). In this paper, we detail the clinical, biochemical, imaging, and molecular characteristics of 73 children and adults with *PKHD1* mutations and a spectrum of clinical presentations. Our data document the extent of renal glomerular and tubular dysfunction; correlate molecular, functional, and imaging findings; and provide prognostic information.

## Materials and Methods

### *Patients*

All patients were enrolled in the protocol, "Clinical Investigations into the Kidney and Liver Disease in Autosomal Recessive Polycystic Kidney Disease/Congenital Hepatic Fibrosis and other Ciliopathies" (http://www.clinicaltrials.gov, trial NCT00068224), approved by the National Human Genome Research Institute Institutional Review Board. Patients or their parents gave written informed consent. Patients who carried a clinical diagnosis of ARPKD made by a nephrologist were qualified to come to the National Institutes of Health (NIH). Diagnosis at NIH was based upon established clinical criteria (5,21), including typical kidney and liver involvement on imaging and/or biopsy and autosomal recessive inheritance. Evaluations at the NIH Clinical Center included biochemical and imaging studies and sequencing of the *PKHD1* gene. Patients who were symptomatic at birth or up to day of life 30 were classified as perinatal presenters, and those who first became symptomatic after the first month of life were classified as nonperinatals. Patients diagnosed by prenatal ultrasonography (USG) were classified as nonperinatal if they remained asymptomatic during the first month of life. When possible, parents were evaluated by ultrasound and parental DNA was analyzed.

### *Sequencing and Analysis*

For the longest open reading frame of *PKHD1*, coding exons (2 to 67) and their intronic boundaries were sequenced in two directions using a Beckman CEQ 8000 system (Beckman Coulter, Inc., Fullerton, CA) and a contract with Agencourt (Beverly, MA). DNA variant analyses were performed using Sequencher (GeneCodes, Ann Arbor, MI). The pathogenicity of missense variants was evaluated as described (22) using segregation analysis, general population frequencies, three computational prediction tools [Align GVGD (http://agvgd.iarc.fr/agvgd_input.php); PolyPhen (http://coot.embl.de/PolyPhen); and SNAP (http://cubic.bioc.columbia.edu/services/SNAP)], and the splice variant interpretation software NetGene2 Server (http://www.cbs.dtu.dk/services/NetGene2).

### *Imaging Studies*

Complete abdominal ultrasound evaluations were performed by a single technologist (K.T.D.) using standard (4 MHz) and high-resolution (7 MHz) ultrasonography (HR-USG) probes on all patients (AVI Sequoia Inc., Mountain View, CA). Magnetic resonance imaging (MRI) was performed on a 1.5- or 3-Tesla machine (Philips Medical Systems, NA, Bothell, WA; General Electric Healthcare, Waukesha, WI) without intravenous contrast media. Kidney volumes were calculated from MRI images (23,24) at the NIH Image Processing Center (A.L.) and normalized to patient surface area.

### *Laboratory Data and Demographic Studies*

Creatinine clearance (CrCl) values were based upon 24-hour urine collections. Serum-cystatin-C-based GFR was calculated using pediatric (25) and adult (26) formulas. Urine and serum osmolalities were measured on spot samples collected simultaneously while patients had *ad lib* access to fluids. Mayo Medical Laboratories measured vasopressin by RIA.

### *Statistics*

Data are presented as means ± SD. Mean differences between groups were tested with the two-tailed, two-sample *t* test. Differences between groups in times to events were investigated by Kaplan–Meier analysis and tested via the log-rank test.

## Results

### *Patient Characteristics*

Between November 2003 and January 2009, 90 potential ARPKD patients were examined at the NIH Clinical Center; 78 fulfilled clinical diagnostic criteria (5,21). The diagnosis was confirmed in 73 patients by finding at least one *PKHD1* variant judged likely to be pathogenic (22). Clinical and mutational data from these 73 patients are presented (Table 1). Twelve patients received kidney transplantation: 11 before and 1 after the NIH evaluation. In addition, renal functional and imaging data are presented for the 62 patients with native kidneys at the time of evaluation (Table 1).

One family (Table 1, family 10) contributed four siblings, six families contributed two siblings each, and one family (family 40) contributed an aunt and niece pair, leaving 63 independent families (Table 1). We identified potentially pathogenic *PKHD1* variants on both alleles in 43 families and on one allele in 20; these mutations have been previously published (22). Twenty-eight patients (25 families) had either one truncating mutation or a truncating mutation in combination with a missense variant. Forty-five patients (38 families) had nontruncating variants (Tables 1 and 2).

The patients (Table 1) included 29 males and 44 females age 1 to 56 years (13.8 ± 13.0 years; median, 9.2 years). Thirty-one patients (43%) displayed perinatal symptoms and 42 (57%) first became symptomatic between 0.1 and 43 years of age (7.0 ± 11.7 years; median, 2.9 years). Truncating and missense mutations were identified in the perinatal and nonperinatal groups (Tables 1 and 2).

Twenty-eight of 31 (90%) perinatal ARPKD patients had pregnancies complicated by oligohydramnios and 27 manifested respiratory distress at birth. Nineteen of these 27 (70%) required mechanical ventilation and 10 (37%) had pneumothorax. Oligohydramnios was noted in 1 of the 42 nonperinatal patients. Other findings at the time of diagnosis in perinatal and nonperinatal patients included hypertension ($n = 24$), enlarged hyperechoic kidneys on ultrasound ($n = 14$) or palpation ($n = 6$), splenomegaly ($n = 9$), urinary tract infection ($n = 9$), thrombocytopenia ($n = 3$), cholangitis ($n = 4$), liver cysts ($n = 2$), cardiomyopathy secondary to hypertension ($n = 2$), and esophageal variceal bleeding ($n = 1$). Seven asymptomatic siblings were diagnosed by standard-resolution screening USG.

*Table 1.* Clinical, molecular, functional, and imaging results for ARPKD patients

| Family No. | Patient No. | Gender/ Ethnicity | Age at Diagnosis[a] | Age at Diagnosis of Hypertension (years) | Presentation | Age at NIH Evaluation (years) | *PKHD1* Mutations[b] | Kidney Length (SD above Mean)[c] | Kidney Volume (ml/ 1.73 $m^2$)[d] | Kidney Findings on USG | Serum Cystatin C (mg/L) | Serum-Cystatin-C-Based GFR Estimate (ml/min/ 1.73 $m^2$) | CrCl Based on 24-Hour Urine (ml/min/ 1.73 $m^2$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | M/C | 22 weeks | 0 | Perinatal, Perinatal sibling death | 3.8 | p.Thr36Met p.Asp3230fs | Tx (2.5) | Tx | Tx | Tx | Tx | Tx |
| 2 | 2 | F/C | 22 weeks | 0 | Perinatal, Perinatal sibling death | 5.1 | p.Phe2374fs p.Gly470Val | 10.2 | NA | CM | 2.71 | 23.7 | 22 |
| 3 | 3 | F/C | 23 weeks | No hypertension | Perinatal | 2.7 | p.Phe3485fs | 5.7 | 339 | CM | 0.65 | 125.7 | NA |
| 4 | 4 | M/C | 23 weeks | 0 | Perinatal | 8.1 | IVS55 + 1G>A p.Trp2690Arg | 7.3 | 595 | CM | 1.02 | 74.2 | 82 |
| 5 | 5 | F/C | 28 weeks | 0 | Perinatal, Perinatal sibling death | 9.2 | p.Arg2573Cys | 7.5 | NA | CM | 1.57 | 44.8 | 46 |
| 6 | 6 | F/H | 28 weeks | 0.2 | Perinatal | 8.4 | p.Thr36Met p.Cys2422Arg | 4.7 | 275 | CM | 2.09 | 32.1 | 39 |
| 7 | 7.1 | M/C | 29 weeks | 0 | Perinatal | 1.2 | p.Ile222Val p.Ser3017del | 4.2 | NA | MP | 0.88 | 88.2 | 58 |
| 7 | 7.2 | M/C | 6 years | No hypertension | Nonperinatal | 8.1 | p.Ile222Val p.Ser3017del | 0.4 | 241 | MP | 0.54 | 156.2 | 109 |
| 8 | 8 | F/C | 29 weeks | 0.8 | Perinatal | 2.2 | p.Pro724Arg p.His3049Arg | 9.2 | 645 | CM | 1.36 | 53.0 | NA |
| 9 | 9 | M/H | 29 weeks | 3.5 | Perinatal | 12.3 | p.Val2798Gly p.Cys2803Arg | 1.9 | 238 | MP | 1.09 | 68.7 | 144 |
| 10 | 10.1 | F/C | 29 weeks | 1.2 | Perinatal | 18.8 | p.Thr36Met p.Ile222Val | Tx (18) | Tx | Tx | Tx | Tx | Tx |
| 10 | 10.2 | F/C | 5 years | No hypertension | Perinatal | 26.0 | p.Thr36Met p.Ile222Val | 1.4 | 179 | CM | 1.05 | 71.7 | 84 |
| 10 | 10.3 | F/C | 2 years | No hypertension | Nonperinatal | 21.0 | p.Thr36Met p.Ile222Val | 2.5 | 226 | M | 0.79 | 100.1 | 122 |
| 10 | 10.4 | M/C | 9 years | No hypertension | Nonperinatal | 28.0 | p.Thr36Met p.Ile222Val | 3.3 | 189 | M | 1.14 | 65.1 | 88 |
| 11 | 11 | F/C | 30 weeks | 0 | Perinatal, Perinatal sibling death | 11.1 | p.Ile2957Thr p.Val3546fs | Tx (2.5) | Tx | Tx | Tx | Tx | Tx |

*Table 1.* (Continued)

| Family No. | Patient No. | Gender/ Ethnicity | Age at Diagnosis[a] | Age at Diagnosis of Hypertension (years) | Presentation | Age at NIH Evaluation (years) | *PKHD1* Mutations[b] | Kidney Length (SD above Mean)[c] | Kidney Volume (ml/ 1.73 $m^2$)[d] | Kidney Findings on USG | Serum Cystatin C (mg/L) | Serum-Cystatin-C-Based GFR Estimate (ml/min/ 1.73 $m^2$) | CrCl Based on 24-Hour Urine (ml/min/ 1.73 $m^2$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 12 | 12 | M/C | 30 weeks | 0 | Perinatal | 16.7 | p.Gly2705fs<br>p.Thr36Met<br>p.Ser2861Gly | 6.3 | 333 | CM | 1.68 | 41.4 | 48 |
| 13 | 13 | F/C | 30 weeks | 0.1 | Perinatal, Perinatal sibling death | 21.0 | IVS39 + 2T>C<br>p.Trp2749Ser | Tx (15) | Tx | Tx | Tx | Tx | Tx |
| 14 | 14 | M/C | 31 weeks | 0 | Perinatal | 1.5 | p.Thr36Met<br>p.Thr36Met | 11.6 | NA | CM | 2.90 | 21.9 | 26 |
| 15 | 15 | F/C | 38 weeks | 0 | Perinatal | 1.0 | p.Leu3543fs<br>p.Ile222Val | 5.3 | NA | CM | 0.95 | 80.6 | 59 |
| 16 | 16 | F/C | 38 weeks | 0 | Perinatal, Perinatal sibling death | 9.2 | p.Ser1156Leu<br>p.Met2804Lys | 7.3 | 1089 | CM | 2.19 | 30.3 | 29 |
| 17 | 17 | F/C | 0 | 1.3 | Perinatal | 1.3 | p.Thr36Met<br>p.Ile2331Lys | 1.0 | NA | M | 0.70 | 115.3 | NA |
| 18 | 18 | M/C | 0 | 0 | Perinatal | 2.1 | p.Gln1256fs | 7.3 | NA | CM | 1.10 | 67.9 | 41 |
| 19 | 19[e] | M/C | 0 | 0 | Perinatal | 2.2 | p.Thr36Met<br>p.Trp1928Leu | 11.5 | NA | CM | 2.64 | 24.4 | NA |
| 20 | 20 | M/C | 0 | 0 | Perinatal | 3.9 | p.Arg781X<br>p.His3049Arg<br>p.Arg3957Cys | Tx (0.5) | Tx | Tx | Tx | Tx | Tx |
| 21 | 21 | M/C | 0 | 0 | Perinatal | 6.5 | p.Gly466Glu | 7.2 | 963 | CM | NA | NA | 63 |
| 22 | 22 | F/C | 0 | 0 | Perinatal | 6.7 | p.Thr36Met<br>p.Thr36Met | 2.5 | NA | CM | 2.42 | 27.0 | 61 |
| 23 | 23 | F/C | 0 | 0 | Perinatal | 6.9 | p.Gly466Glu<br>p.Val1817Gly<br>p.Met3642Ile | 7.7 | 683 | CM | 4.50 | 13.1 | 21 |
| 24 | 24 | M/C | 0 | 0 | Perinatal | 7.4 | p.Tyr255Cys | 13.6 | 1355 | CM | 1.19 | 62.0 | 49 |
| 25 | 25 | F/C | 0 | 0 | Perinatal | 13.8 | p.Thr36Met<br>p.Thr36Met | Tx (10) | Tx | Tx | Tx | Tx | Tx |
| 26 | 26.1 | M/C | 0 | 0 | Perinatal | 15.9 | p.Leu542fs<br>p.Ile2331Lys | 2.4 | 237 | CM | 0.54 | 156.2 | 134 |
| 26 | 26.2 | F/C | 13 years | No hypertension | Nonperinatal | 13.8 | p.Leu542fs<br>p.Ile2331Lys | 3.8 | 236 | MP | 0.52 | 163.2 | 192 |
| 27 | 27 | M/C | 0 | 0 | Perinatal | 26.0 | p.Ile307Thr<br>p.Gly2705fs<br>p.Ser2861Gly | 4.6 | 204 | CM | 2.05 | 32.8 | 50 |
| 28 | 28 | F/C | 0.05 years | 3 | Perinatal | 20.1 | p.Cys1249Trp<br>p.Arg1624Trp | 5.7 | NA | CM | 0.87 | 89.4 | 78 |

*Table 1.* (Continued)

| Family No. | Patient No. | Gender/ Ethnicity | Age at Diagnosis[a] | Age at Diagnosis of Hypertension (years) | Presentation | Age at NIH Evaluation (years) | *PKHD1* Mutations[b] | Kidney Length (SD above Mean)[c] | Kidney Volume (ml/ 1.73 $m^2$)[d] | Kidney Findings on USG | Serum Cystatin C (mg/L) | Serum-Cystatin-C-Based GFR Estimate (ml/min/ 1.73 $m^2$) | CrCl Based on 24-Hour Urine (ml/min/ 1.73 $m^2$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 29 | 29.1 | F/C | 0.1 years | No hypertension | Nonperinatal | 4.0 | p.Leu2106Arg | 3.7 | NA | MP | 0.54 | 156.2 | 131 |
| 29 | 29.2 | F/C | 3 years | No hypertension | Nonperinatal | 6.7 | p.Leu2106Arg | 5.5 | NA | MP | 0.42 | 209.5 | 147 |
| 30 | 30 | M/C | 0.1 years | No hypertension | Nonperinatal | 30.0 | p.Pro3652fs | 7.7 | 508 | CM | 1.38 | 52.1 | 51 |
| 31 | 31 | F/C | 0.2 years | 0.5 | Nonperinatal | 8.3 | p.Tyr486X<br>p.Ile246Thr<br>p.Tyr1136Cys | 5.6 | 646 | CM | 1.07 | 70.2 | 99 |
| 32 | 32 | F/C | 0.2 years | 0.2 | Nonperinatal | 17.2 | p.Thr36Met | 2.9 | 379 | CM | 0.91 | 84.8 | 58 |
| 33 | 33.1 | F/C | 0.3 years | 0.9 | Nonperinatal | 1.3 | p.Thr36Met<br>p.Ala3207Thr | 7.0 | NA | MP | 1.80 | 38.2 | NA |
| 33 | 33.2 | F/C | 0.4 years | 0.4 | Nonperinatal | 5.0 | p.Thr36Met<br>p.Ala3207Thr | 13.7 | NA | CM | 1.83 | 37.4 | 56 |
| 34 | 34 | M/C | 0.3 years | 0.3 | Perinatal | 2.5 | p.Ser2219Leu | 6.1 | NA | CM | 1.15 | 64.5 | 83 |
| 35 | 35 | M/C | 0.3 years | 0.3 | Perinatal | 11.1 | p.Thr36Met | 5.0 | 280 | CM | 1.47 | 48.4 | 76 |
| 36 | 36 | F/C | 0.3 years | 0.4 | Nonperinatal | 11.1 | p.Ala1254fs<br>p.Arg1624Trp | 5.0 | 886 | CM | 1.80 | 38.2 | 43 |
| 37 | 37 | M/C | 0.4 years | 0.4 | Nonperinatal | 4.1 | p.Arg496X<br>p.Gly2224Arg | 6.3 | NA | CM | 0.80 | 98.6 | 62 |
| 38 | 38 | F/AA | 0.4 years | 0.4 | Nonperinatal | 16.1 | p.Thr36Met<br>p.Arg3240Gln | Tx (15) | Tx | Tx | Tx | Tx | Tx |
| 39 | 39 | M/C | 0.5 years | 0.5 | Nonperinatal | 1.0 | p.Cys1249Trp<br>p.Gly2210Glu | 11.2 | 782 | CM | 1.19 | 62.0 | 83 |
| 40 | 40.1 | F/C | 0.7 years | 0.7 | Nonperinatal | 2.5 | pGly3378fs<br>p.Arg1624Trp | 6.0 | NA | CM | 0.68 | 119.2 | NA |
| 40 | 40.2 | F/C | 28 years | No hypertension | Nonperinatal | 30.0 | pGly3378fs<br>p.Gly1712Arg | 1.1 | 86 | M | 0.61 | 135.4 | 129 |
| 41 | 41 | F/C | 0.8 years | No hypertension | Nonperinatal | 7.9 | p.Thr3035fs<br>p.Ala293Val | 6.2 | 164 | M | 0.67 | 121.3 | 161 |
| 42 | 42 | M/C | 0.8 years | 0.8 | Nonperinatal | 8.7 | p.Thr36Met<br>p.Ile222Val | 2.7 | 462 | CM | 0.90 | 85.9 | NA |
| 43 | 43 | F/C | 0.8 years | 0.8 | Nonperinatal | 10.1 | p.Thr36Met<br>p.Ile2957Thr | 4.3 | 376 | CM | 2.39 | 27.4 | 60 |
| 44 | 44 | F/C | 1 years | No hypertension | Nonperinatal | 5.5 | p.Gly466Glu | 4.6 | 264 | MP | 0.46 | 188.4 | 190 |
| 45 | 45 | M/C | 1.1 years | 1.1 | Nonperinatal | 11.3 | p.Trp158X<br>p.Arg1624Trp | 7.4 | 650 | CM | 2.13 | 31.4 | 58 |
| 46 | 46 | F/C | 1.2 years | 1.8 | Nonperinatal | 4.1 | p.Ser2861Gly<br>p.Ile2957Thr | 10.5 | 860 | CM | NA | NA | 48 |

*Table 1.* (Continued)

| Family No. | Patient No. | Gender/ Ethnicity | Age at Diagnosis[a] | Age at Diagnosis of Hypertension (years) | Presentation | Age at NIH Evaluation (years) | *PKHD1* Mutations[b] | Kidney Length (SD above Mean)[c] | Kidney Volume (ml/ 1.73 $m^2$)[d] | Kidney Findings on USG | Serum Cystatin C (mg/L) | Serum-Cystatin-C-Based GFR Estimate (ml/min/ 1.73 $m^2$) | CrCl Based on 24-Hour Urine (ml/min/ 1.73 $m^2$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 47 | 47 | F/C | 1.8 years | 1.8 | Nonperinatal | 35.0 | p.Ala3207Thr | Tx (31) | Tx | Tx | Tx | Tx | Tx |
| 48 | 48 | F/C | 2 years | No hypertension | Nonperinatal | 13.9 | p.Tyr143Cys | 5.6 | 303 | MP | 0.68 | 119.2 | 135 |
| 49 | 49 | F/C | 2.7 years | 2.7 | Nonperinatal | 5.7 | p.Glu2431Val | 8.8 | NA | CM | 0.98 | 77.8 | 182 |
| 50 | 50 | M/C | 3 years | 3 | Nonperinatal | 6.9 | p.Thr36Met p.Gly466Glu | 7.7 | 496 | CM | 1.52 | 46.5 | 60 |
| 51 | 51.1 | M/C | 3 years | No hypertension | Nonperinatal | 8.5 | p.Arg2033Gly p.Ile2957Thr | 4.1 | 270 | MP | 0.61 | 135.4 | 178 |
| 51 | 51.2 | F/C | 3 years | No hypertension | Nonperinatal | 10.4 | p.Arg2033Gly p.Ile2957Thr | 2.2 | 181 | MP | 0.69 | 117.2 | 169 |
| 52 | 52 | F/C | 3 years | No hypertension | Nonperinatal | 9.1 | p.Arg760His p.Ala2009Thr | 2.8 | 303 | M | 0.79 | 100.1 | 108 |
| 53 | 53 | M/AA | 3 years | No hypertension | Nonperinatal | 11.0 | p.Leu1965fs | 2.3 | 205 | M | 1.06 | 70.9 | 122 |
| 54 | 54 | M/C | 3.8 years | No hypertension | Nonperinatal | 9.5 | p.Leu1965fs | 1.6 | 193 | MP | 0.72 | 111.5 | 227 |
| 55 | 55 | F/C | 4 years | No hypertension | Nonperinatal | 10.7 | p.Thr36Met p.Leu1709Phe | 5.1 | 203 | MP | 0.72 | 111.5 | 106 |
| 56 | 56 | M/C | 5 years | 5 | Nonperinatal | 37.0 | p.Arg496X p.Ile222Val | Tx (18) | Tx | Tx | Tx | Tx | Tx |
| 57 | 57 | M/C | 6 years | 6 | Nonperinatal | 12.4 | p.His686Pro | 7.6 | 549 | CM | 1.99 | 33.9 | 26 |
| 58 | 58 | F/C | 6 years | 6 | Nonperinatal | 16.2 | p.Thr36Met p.Val1741Met | 0.3 | 225 | MP | 1.07 | 70.2 | 110 |
| 59 | 59 | F/C | 6 years | 9 | Nonperinatal | 42.0 | p.Val1875Gly p.Ile2957Thr | Tx (31.5) | Tx | Tx | Tx | Tx | Tx |
| 60 | 60 | F/AA | 23 years | 23 | Nonperinatal | 40.0 | p.Leu1965fs p.Ile539Thr | Tx (36) | Tx | Tx | Tx | Tx | Tx |
| 61 | 61.1 | M/H | 28 years | No hypertension | Nonperinatal | 45.0 | p.Leu2969fs p.Arg92Trp | 0.5 | 169 | M | 0.93 | 82.7 | 57 |
| 61 | 61.2 | F/H | 39 years | No hypertension | Nonperinatal | 47.0 | p.Leu2969fs p.Arg92Trp | −1.5 | 137 | CM | 1.46 | 48.8 | 68 |
| 62 | 62 | F/C | 41 years | 15 | Nonperinatal | 52.0 | p.Ala2515fs p.Ser1862Leu | 2.7 | 257 | MP | 1.99 | 33.9 | 60 |
| 63 | 63 | F/C | 43 years | 45 | Nonperinatal | 56.0 | p.Ile222Val | −6.1 | 105 | CM | 3.88 | 15.5 | 16 |

M, male; F, female; C, Caucasian; H, Hispanic; AA, African American; CM, cystic pathology involving both cortex and medulla; M, involving all medulla but not cortex; MP, involving parts of medulla; Tx, transplanted (age at transplant/dialysis); NA, not applicable.

[a]Prenatally, in weeks gestation; postnatally, in years.

[b]Detailed description of these mutations and assessment of their pathogenicity is published elsewhere (23); mutations listed only once are heterozygous.

[c]Average of two kidneys by USG.

[d]Average of two kidneys by MRI.

[e]Patient 19 received a kidney transplantation after the NIH evaluation.

*Table 2.* Comparison of ARPKD patients with regard to time of initial presentation, extent of abnormalities on HR-USG, and *PKHD1* mutation type[a]

| | Presentation | | | Ultrasound Abnormalities | | | *PKHD1* Mutation Type | | |
|---|---|---|---|---|---|---|---|---|---|
| | Perinatal | Nonperinatal | *P* | Corticomedullary | Medullary | *P* | Truncating | Nontruncating | *P* |
| Number (percentage) of patients | 31 of 73 (42%) | 42 of 73 (58%) | – | 39 of 62 (63%) | 23 of 62 (37%) | – | 28 of 73 (38%) | 45 of 73 (62%) | – |
| Age at NIH evaluation (years) | 9.2 ± 7.4 | 17.2 ± 15.1 | 0.008 | 11.3 ± 11.9 | 14.2 ± 13.2 | 0.36 | 17.1 ± 15.2 | 11.8 ± 11.1 | 0.09 |
| Age at initial diagnosis (years) | 0.2 ± 0.9 | 7.1 ± 11.7 | 0.002 | 2.7 ± 9.1 | 7.0 ± 10.8 | 0.10 | 6.7 ± 12.6 | 2.6 ± 6.6 | 0.07 |
| Number (percentage) of patients with perinatal presentation | 31 of 31 (100%) | 0 of 42 (0%) | – | 22 of 39 (56%) | 3 of 23 (13%) | – | 12 of 28 (43%) | 19 of 45 (42%) | – |
| Number (percentage) of patients with corticomedullary involvement | 22 of 25 (88%) | 17 of 37 (46%) | – | 39 | 0 | – | 15 of 22 (68%) | 24 of 40 (60%) | – |
| Number (percentage) of patients with truncating mutations | 12 of 31 (39%) | 16 of 42 (38%) | – | 15 of 39 (39%) | 7 of 23 (30%) | – | 28 of 28 (100%) | 0 of 45 (0%) | – |
| Age at kidney transplantation (years) | 7.6 ± 6.8 | 26.3 ± 9.2 | 0.002 | NA | NA | NA | 12.4 ± 13.7 | 18.4 ± 11.0 | 0.42 |
| Cystatin-C-based GFR (ml/min/1.73 $m^2$) | 61 ± 36 | 89 ± 48 | 0.016 | 57 ± 33 | 111 ± 45 | <0.0001 | 81 ± 42 | 76 ± 48 | 0.70 |
| 24-hour urine-based CrCl (ml/min/1.73 $m^2$) | 62 ± 33 | 103 ± 54 | 0.002 | 61 ± 32 | 131 ± 46 | <0.0001 | 88 ± 55 | 87 ± 49 | 0.92 |
| Kidney volume on MRI (ml/1.73 $m^2$) | 494 ± 386 | 352 ± 224 | 0.124 | 519 ± 324 | 220 ± 53 | 0.0004 | 323 ± 236 | 449 ± 319 | 0.17 |
| SD of kidney length on USG | 6.3 ± 3.3 | 4.5 ± 3.7 | 0.050 | 6.4 ± 3.8 | 3.2 ± 1.9 | 0.0003 | 4.7 ± 2.8 | 5.5 ± 4.0 | 0.44 |

[a]Values are means ± SD.

*Kidney Involvement*

**Renal Cysts.** Standard-probe USG, HR-USG, and MRI imaging (Figure 1, A through D; Table 1) of the 62 patients with native kidneys revealed abnormalities involving the renal cortex and medulla ($n = 39$; 63%), the entire medulla only ($n = 8$; 13%), or part of the medulla only ($n = 15$; 24%). In seven patients with partial medullary involvement and in one with the entire medulla involved, the standard USG was normal and abnormalities were identified only using the HR-USG transducer. Of 25 perinatal patients with native kidneys, 3 (12%) had involvement limited to the medulla, whereas 20 of 37 nonperinatal patients (54%) had sonographic abnormalities confined to the medulla (Tables 1 and 2). The percentage of patients with corticomedullary involvement was similar among those with a truncating mutation (15 of 22, 68%) and those with nontruncating variants (24 of 40, 60%) (Tables 1 and 2).

Kidney size, a reflection of cystic changes, was evaluated by length measurements using USG (expressed as SD above the mean) and volume estimates on MRI. Kidneys with only medullary abnormalities (14.2 ± 13.2 years) were normal or only mildly enlarged (SD of length, +3.2 ± 1.9; volume, 220 ± 53 ml/1.73 m$^2$), whereas those with corticomedullary involvement (11.3 ± 11.9 years) had much greater enlargement (SD of length, +6.4 ± 3.8; volume, 519 ± 324 ml/1.73 m$^2$; Tables 1 and 2; $P < 0.001$ and $P < 0.001$) (27). Normal adult male kidney volume is 202 ± 36 ml (24); age-dependent pediatric reference values are reported (27,28).

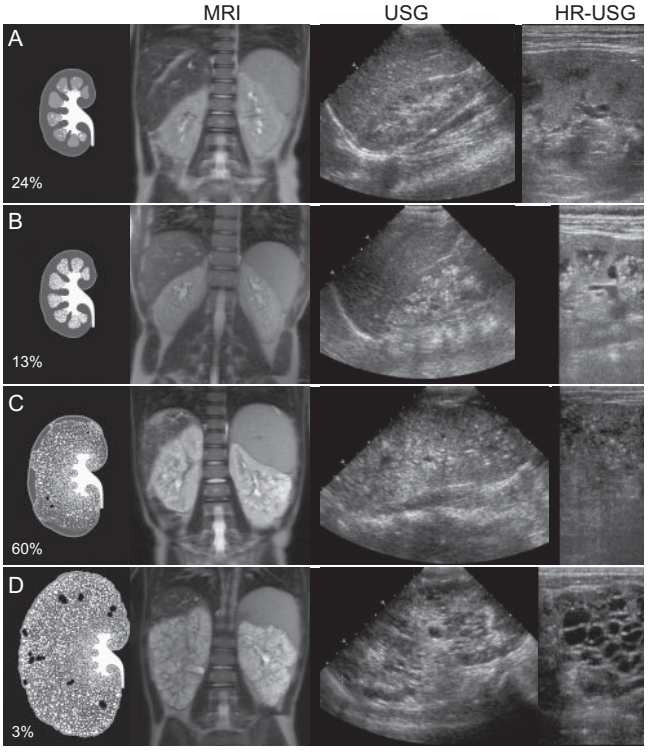


*Figure 1.* Artist's rendering, ultrasound, and MRI findings showing the spectrum of kidney abnormalities in ARPKD. Percentages refer to the frequency of each pattern within our population of 62 clinically and molecularly diagnosed pretransplant patients. (A) Normal-sized kidneys with hyperechogenicity and ductal dilations involving parts of the medulla (white dots on artist's rendering). (B) Mildly enlarged kidneys with hyperechogenicity and ductal dilations involving most of the medulla but sparing the cortex. (C) Enlarged kidneys with diffuse hyperechogenicity and ductal dilations sparing only parts of the cortex. Some macrocysts (black) are present. (D) Massively enlarged kidneys with complete involvement of medulla and cortex and numerous macrocysts.

Kidney volume corrected for body surface area did not correlate well with age (Figure 2A). This lack of correlation between kidney volume and age persisted when pediatric (<18 years) and adult patients were analyzed separately (data not shown). When corticomedullary and medullary groups were analyzed separately, kidney volume in the corticomedullary group showed some correlation with age ($y = 758.05e^{-0.037x}$, $R^2 = 0.5518$); whereas the medullary group showed no correlation ($y = 236.35e^{-0.006x}$, $R^2 = 0.0803$). Kidney length also did not correlate with age (not shown). The mean kidney size of 25 perinatally symptomatic patients (SD of length, +6.3 ± 3.3; volume, 494 ± 386 ml/1.73 m$^2$) was slightly greater than that of 37 patients diagnosed later (SD of length, +4.5 ± 3.7; volume 352 ± 224 ml/1.73 m$^2$; $P = 0.05$; 0.12) (Table 2). Mean kidney volume of patients with truncating mutations (323 ± 236 ml/1.73 m$^2$) was not significantly different from that of the nontruncating variant group (449 ± 319 ml/1.73 m$^2$; $P = 0.17$) (Table 2).

**Glomerular Function.** Seventy-five percent kidney survival was maintained for the perinatal group until approximately 11 years of age and for the nonperinatal group until age 32 years ($P = 0.003$, log-rank test) (Figure 2B). Kidney survival curves were not significantly different between the truncating and nontruncating mutation groups ($P = 0.83$, log-rank test). Twelve patients (seven perinatal and five nonperinatal) had received a renal allograft; one kidney transplant (patient 19) occurred after the NIH visit (Table 1). Age at transplantation for the perinatal group ranged from 0.5 to 18 years (7.6 ± 6.8 years) compared with 15 to 36 years (26.3 ± 9.2 years) for the nonperinatal group (Tables 1 and 2). Age at transplantation for the truncating (12.4 ± 13.7 years) and nontruncating (18.4 ± 11.0 years) mutation groups was not significantly different ($P = 0.42$) (Table 2).

Renal glomerular function was assessed in two different ways: using formulas based on serum cystatin C and using 24-hour urine creatinine plus serum creatinine. For perinatal patients (age 9.2 ± 7.4 years), the 24-hour urine-based CrCl and serum-cystatin-C-based GFR averaged 62 ± 33 and 61 ± 36 ml/min/1.73 m$^2$), respectively, compared with 103 ± 54 and 89 ± 48 ml/min/1.73 m$^2$, respectively, for 37 nonperinatal patients (age 17.2 ± 15.1 years) ($P < 0.002$, $P = 0.016$) (Tables 1 and 2). For patients with only medullary involvement (age 14.2 ± 13.2 years), the 24-hour urine-based CrCl and cystatin-C-based GFR averaged 131 ± 46 and 111 ± 45 ml/min/1.73 m$^2$, respectively. These values indicated significantly better renal function than for patients with cortical and medullary involvement (age 11.3 ± 11.9 years); that is, 61 ± 32 ($P < 0.0001$) and 57 ± 33 ml/min/1.73 m$^2$, respectively ($P < 0.0001$) (Tables 1 and 2). Twenty-four-hour urine-based CrCl and serum-cysta-

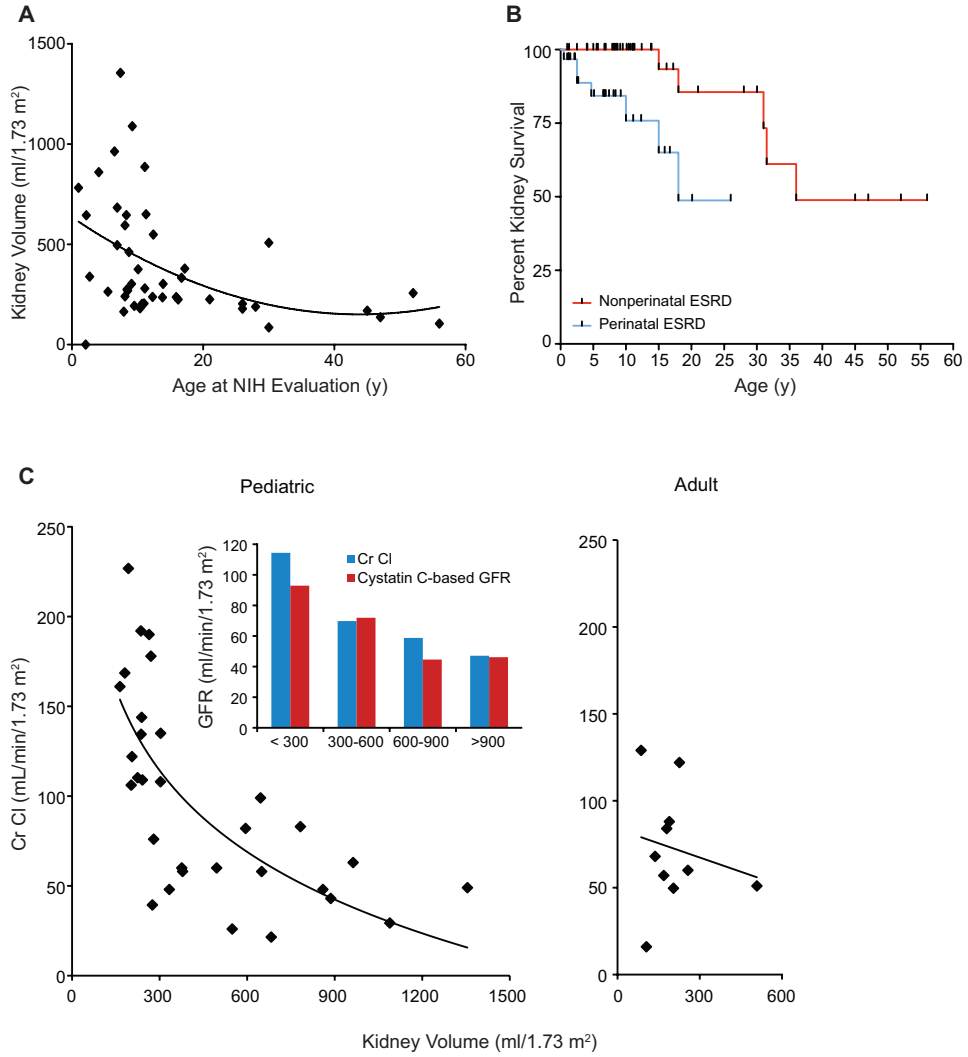


*Figure 2.* Morphometric and laboratory data. (A) Kidney volume corrected for body surface area *versus* age for 42 ARPKD patients ($y = 0.25x^2 - 22.1x + 635$, $R^2 = 0.18$). Normal adult male kidney volume is 204 ± 36 ml (24). (B) Kidney survival comparing perinatally symptomatic and nonperinatal patients ($P = 0.003$, log-rank test). (C) CrCl plotted against kidney volume corrected for body surface area in children ($y = -65.42\ln(x) + 487.42$, $R^2 = 0.51$) and adults ($y = -0.0545x + 83.706$, $R^2 = 0.04$) with ARPKD. Data for the inserted bar graph were analyzed for pediatric and adult patients together.

tin-C-based GFR (Table 2) were similar for the truncating mutation (88 ± 55 and 81 ± 42 ml/min/1.73 m$^2$, respectively) and nontruncating variant (87 ± 49 and 76 ± 48 ml/min/1.73 m$^2$, respectively) groups ($P = 0.92$ and 0.7). For the 62 nontransplanted patients, measures of glomerular function (CrCl and cystatin C) were not related to age (data not shown).

When all ages were analyzed as a whole group, the 24-hour urine-based CrCl did not correlate with kidney volume ($R^2 = 0.17$) or kidney length ($R^2 = 0.15$); similarly, serum cystatin C did not correlate with kidney volume ($R^2 = 0.13$) or length ($R^2 = 0.13$). However, when pediatric (<18 years) and adult groups were analyzed separately, there was a reverse relationship between kidney volume and function in the pediatric group ($R^2 = 0.51$), although with significant scatter (Figure 2C).

**Other Renal Manifestations.** Hypertension, noted in 52 patients, was present at diagnosis in 40 patients, including 20 with hypertension at birth (Table 1). Hypertensive patients typically required multiagent treatment, especially in early childhood (29,30).

Random urine osmolality, collected while patients had *ad lib* access to fluids and were presumed to be euvolemic, was <300 mOsm/kg in 15 patients (Table 3) and varied directly with CrCl (data not shown). A urine/plasma osmolality ratio ≤1.0, indicating dilute urine, was found in 18 of 44 patients tested; their daily urine volume was 2428 ± 920 ml/1.73 m$^2$) compared with 1662 ± 738 ml/1.73 m$^2$) for 39 patients with a urine/plasma osmolality ratio >1.0. The urine/plasma osmolality ratio averaged 2.0 ± 0.7 in 20 patients with only medullary renal involvement compared with 1.2 ± 0.5 in 36 patients who also had cortical involvement ($P < 0.0001$). Plasma vasopressin was elevated in 21 of 57 patients (Table 3), including 8 of 18 with dilute urine.

Twenty-three patients had mild proteinuria (Table 3). There was limited evidence for tubular dysfunction; glucosuria and

*Table 3.* Laboratory results for ARPKD patients with native kidneys

| | Chronic Kidney Disease Stage | Mean | SD | Range | Normal Range | No. Low | No. High |
|---|---|---|---|---|---|---|---|
| Serum sodium (mmol/L) | 1 | 138 | 2.0 | 135 to 141 | 135 to 144 | 0 of 22 | 0 of 22 |
| | 2 | 137 | 2.7 | 132 to 141 | | 5 of 18 | 0 of 18 |
| | 3 | 139 | 2.2 | 135 to 143 | | 0 of 14 | 0 of 14 |
| | 4 to 5 | 138 | 1.9 | 135 to 141 | | 0 of 9 | 0 of 9 |
| Serum magnesium (mmol/L) | 1 | 0.92 | 0.07 | 0.72 to 0.98 | 0.75 to 1.00 | 1 of 22 | 0 of 22 |
| | 2 | 0.85 | 0.10 | 0.63 to 1.01 | | 1 of 18 | 1 of 18 |
| | 3 | 0.94 | 0.09 | 0.76 to 1.07 | | 0 of 14 | 3 of 14 |
| | 4 to 5 | 0.98 | 0.16 | 0.64 to 1.21 | | 1 of 9 | 5 of 9 |
| Serum phosphate (mg/dl)[a] | 1 | 4.3 | 0.8 | 2.8 to 6.0 | 2.8 to 4.2 | 0 of 22 | 13 of 22 |
| | 2 | 4.8 | 0.9 | 3.2 to 6.2 | | 0 of 18 | 14 of 18 |
| | 3 | 5.03 | 0.8 | 3.6 to 6.2 | | 0 of 14 | 11 of 14 |
| | 4 to 5 | 5.39 | 0.7 | 4.3 to 6.8 | | 0 of 9 | 9 of 9 |
| Serum calcium (mmol/L)[a] | 1 | 2.33 | 0.17 | 2.07 to 2.56 | 2.05 to 2.50 | 0 of 22 | 1 of 22 |
| | 2 | 2.40 | 0.08 | 2.27 to 2.57 | | 0 of 18 | 2 of 18 |
| | 3 | 2.37 | 0.11 | 2.15 to 2.51 | | 0 of 14 | 1 of 14 |
| | 4 to 5 | 2.41 | 0.11 | 2.24 to 2.60 | | 0 of 9 | 2 of 9 |
| Parathyroid hormone (pg/ml)[a] | 1 | 20 | 11 | 4 to 96 | 16 to 87 | 5 of 20 | 1 of 20 |
| | 2 | 33 | 29 | 6 to 128 | | 4 of 15 | 1 of 15 |
| | 3 | 82 | 44 | 16 to 143 | | 0 of 13 | 6 of 13 |
| | 4 to 5 | 165 | 46 | 123 to 224 | | 0 of 6 | 6 of 6 |
| Urine protein ($mg/m^2$ per h) | 1 | 3.5 | 2.4 | 0 to 9.7 | <4 | NA | 7 of 20 |
| | 2 | 3.4 | 3.2 | 0 to 11 | | | 6 of 18 |
| | 3 | 5.8 | 8.3 | 0 to 30.7 | | | 5 of 13 |
| | 4 to 5 | 22.5 | 43.6 | 0 to 128 | | | 5 of 8 |
| Urine glucose (mg/d) | 1 | 73 | 53 | 14 to 251 | <500 | NA | 0 of 20 |
| | 2 | 65 | 44 | 17 to 189 | | | 0 of 17 |
| | 3 | 107 | 205 | 19 to 782 | | | 1 of 13 |
| | 4 to 5 | 135 | 106 | 23 to 308 | | | 0 of 7 |
| Urine calcium (mg/kg per d) | 1 | 2.2 | 1.9 | 0 to 7.5 | <4 | NA | 4 of 21 |
| | 2 | 1.3 | 0.7 | 0 to 2.9 | | | 0 of 18 |
| | 3 | 1.1 | 1.4 | 0 to 5.8 | | | 1 of 14 |
| | 4 to 5 | 1.2 | 1.0 | 0 to 3.4 | | | 0 of 9 |
| Urine osmolality (mOsm/kg) | 1 | 637 | 209 | 371 to 983 | 300 to 900 | 0 of 21 | 3 of 21 |
| | 2 | 356 | 137 | 125 to 758 | | 5 of 18 | 0 of 18 |
| | 3 | 305 | 30 | 258 to 348 | | 7 of 13 | 0 of 13 |
| | 4 to 5 | 291 | 45 | 206 to 336 | | 3 of 6 | 0 of 6 |
| Serum osmolality (mOsm/kg) | 1 | 289 | 5 | 282 to 302 | 278 to 298 | 0 of 21 | 1 of 21 |
| | 2 | 295 | 6 | 282 to 304 | | 0 of 18 | 3 of 18 |
| | 3 | 299 | 5 | 288 to 309 | | 0 of 14 | 8 of 14 |
| | 4 to 5 | 306 | 7 | 298 to 318 | | 0 of 9 | 8 of 9 |
| Urine volume (ml/24 h/1.73 $m^2$) | 1 | 1351 | 539 | 459 to 2407 | <2000 | NA | 2 of 20 |
| | 2 | 2263 | 1035 | 985 to 4796 | | | 8 of 18 |
| | 3 | 1936 | 550 | 1137 to 2807 | | | 5 of 13 |
| | 4 to 5 | 2425 | 803 | 1144 to 3584 | | | 5 of 8 |
| Plasma vasopressin (pg/ml) | 1 | 0.86 | 1.07 | 0.5 to 3.90 | <1.7 | NA | 4 of 21 |
| | 2 | 1.92 | 1.53 | 0.5 to 5.2 | | | 6 of 16 |
| | 3 | 5.31 | 9.89 | 0.5 to 38.0 | | | 6 of 14 |
| | 4 to 5 | 2.77 | 1.47 | 0.50 to 4.90 | | | 5 of 6 |
| TMP/GFR (mg/dl) | 1 | 4.09 | 0.89 | 1.94 to 5.63 | 2.8 to 4.4 | 1 of 21 | 6 of 21 |
| | 2 | 3.99 | 0.82 | 2.43 to 5.13 | | 2 of 17 | 6 of 17 |
| | 3 | 3.94 | 0.78 | 2.84 to 5.64 | | 0 of 13 | 2 of 13 |
| | 4 to 5 | 3.78 | 0.72 | 2.43 to 4.79 | | 1 of 9 | 1 of 8 |
| Fractional excretion of magnesium (%) | 1 | 2.9 | 0.9 | 1.8 to 4.7 | <5 | NA | 0 of 21 |
| | 2 | 4.9 | 1.7 | 2.6 to 8.4 | | | 7 of 17 |
| | 3 | 5.3 | 2.6 | 0 to 9.3 | | | 7 of 13 |
| | 4 to 5 | 8.8 | 3.5 | 4.1 to 14.8 | | | 7 of 8 |

TMP/GFR, tubular maximum phosphate reabsorption per GFR.
[a]Excludes patients on treatment for renal osteodystrophy.

hypercalciuria were rare or absent and no patient had amino aciduria. Fifteen of 59 patients had elevated tubular maximum phosphate reabsorption per GFR. The fractional excretion of magnesium was elevated in 21 of 59 patients (Table 3).

## Discussion

We present new information on the kidney disease of ARPKD by virtue of a prospective and comprehensive evaluation of 73 children and adults with *PKHD1* mutations.

Renal USG examinations of kidney-predominant, early-onset ARPKD have shown diffusely hyperechogenic kidneys with loss of corticomedullary distinction (31,32). However, kidney imaging findings in later-onset and liver-predominant ARPKD are less well defined. HR-USG and MRI imaging of a wide age range of patients with variable degrees of decline in glomerular function allowed us to determine the kidney imaging findings for the full spectrum of ARPKD patients, including those with later-onset and liver-predominant disease. In the process, we ascertained that HR-USG, performed using 7- to 9-MHz insonating frequencies, was superior to conventional USG (3 to 5 MHz) for imaging in ARPKD, especially in patients with mild kidney disease. In 35% of patients with medullary-only involvement, USG examinations of the kidney performed with a 4-MHz transducer were normal; only HR-USG probe enabled detection of the ductal dilations confined to the medulla.

In their European ARPKD cohort enriched by early-onset ARPKD patients, Bergmann *et al.* (20) reported an actuarial renal survival rate of 71% at age 10 and 66% at 15 years. Similarly, Roy *et al.* (2) found a renal survival rate of approximately 65% at age 15 years in 52 patients, 85% of which were perinatal onset. Our data on the perinatal patients reveal 75% renal survival at age 11 years, comparable to these previous results. In contrast, among our nonperinatal patients, the mean age at kidney transplantation was significantly later with 75% renal survival at age 32 years.

Correlations of our HR-USG and functional biochemical data also showed that ARPKD patients with medullary-only disease are generally asymptomatic at birth and more likely to have preserved glomerular function at older ages, whereas those with corticomedullary pathology are more likely to have respiratory distress at birth and a faster decline in glomerular function.

*PKHD1* sequencing of our patients did not reveal any patient with two truncating mutations, consistent with previous observations that ARPKD patients having two null mutations do not survive the neonatal period (20,33). When we stratified our patients on the basis of mutation types, the groups with truncating and nontruncating mutations did not differ significantly in their frequencies of perinatal presentation, corticomedullary involvement, or glomerular function. Bergmann *et al.* (20) found that the proportion of truncating mutations in patients transplanted in childhood was similar to that for patients transplanted in adulthood; that group also reported an earlier age (7.2 *versus* 10.2 years) for renal transplantation for patients with truncating mutations. Our patients with truncating mutations required renal transplant at an earlier age (12.4 ± 13.7 years) in comparison with those with nontruncating mutations (18.4 ± 11.0 years), although this was not statistically significant. Relatively small numbers of transplanted patients in each group was a limiting factor in our cohort and that of Bergmann *et al.* Future studies with a larger number of patients will likely reveal more precise predictions of age of transplant in various subgroups of ARPKD patients.

We found considerable variability in the severity of kidney disease in our ARPKD patients (Table 1). This variability was not explained by the location or type (truncating or missense) of *PKHD1* mutations (Tables 1 and 2). For example, we identified the combination of missense mutations, p.Thr36Met and p.Ile222Val, in a total of five patients, four of whom were siblings (Table 1, patients 10.1, 10.2, 10.3, 10.4, and 42). Although patient 10.1, the youngest sibling in the family, was diagnosed prenatally, had hypertension at age 1.2 years, and required kidney transplantation at 18 years, her three older siblings were doing well with normal or mildly decreased glomerular function and without hypertension at ages 21 to 28 years. Patients 10.3 and 10.4 were never symptomatic and were diagnosed by screening ultrasounds performed because of family history. Patient 42 was diagnosed at age 0.8 years when hypertension was discovered during a routine preoperative evaluation for inguinal hernia surgery. At his NIH evaluation at age 8.7 years, glomerular function was mildly decreased (Table 1).

The relationship between glomerular function and kidney volume in ARPKD was not previously explored. We identified a weak reverse correlation between kidney function and volume among ARPKD patients younger than 18 years of age, although there was significant variation. Similarly, kidney volume corrected for body surface area showed a weak reverse correlation with age. Given the cross-sectional nature of these analyses, these data do not reflect longitudinal change in kidney size of a given patient over time. There exists no report of longitudinal imaging evaluation of kidney size in ARPKD. Linear kidney measurements reported on small numbers of ARPKD patients (3,34) suggest that kidney size in ARPKD remains stable as the children get older. Therefore, it is likely that the degree of kidney enlargement in ARPKD is determined prenatally and kidney size does not change much over the lifespan of the patients. Similarly, the extent of renal pathology—whether medullary-only or corticomedullary—is likely to be largely determined prenatally and less likely to change significantly with age. The prospective portion of the NIH study, underway since 2003, may provide insights into the relationship of kidney size and function over time for individual patients with ARPKD; it may also clarify whether the extent of renal pathology remains unchanged over the lifespan of a given patient or some patients with medullary-only involvement progress to corticomedullary damage.

Most (92%) of our patients had normal 24-hour calcium excretion, suggesting that the echogenic foci identified with USG imaging of most ARPKD patients (31,32) is not related to hypercalciuria. We detected mild increases in 24-hour urine protein excretion in 39% of patients, similar to the findings of Adeva *et al.* (19). On the basis of normal levels of glucose and amino acid excretion, proximal tubular function appeared

largely intact in our ARPKD patients. We did identify mildly increased tubular maximum phosphate reabsorption per GFR values in 25% of patients; this finding seemed to be independent of the stage of CKD and its cause remains unclear. The fractional excretion of magnesium was increased in 36% of patients—primarily in those with advanced CKD, perhaps indicating a relationship between dysfunction of the distal tubule and the glomerulus. We did document a linear correlation between urine osmolality and glomerular function in ARPKD; similar observations have been made in other CKD patients.

In summary, our molecular, biochemical, and imaging data on a wide range of children and adults with ARPKD provide correlations between laboratory and imaging findings and supply prognostic information. Renal function in ARPKD does not correlate with age. There is a weak inverse correlation between kidney volume and function in children with ARPKD. Imaging evidence of abnormalities restricted to the medulla generally predicts preserved renal function, whereas corticomedullary involvement is associated with faster decline in glomerular function. Perinatal presentation is more likely to be associated with corticomedullary pathology and predicts faster decline in renal function. HR-USG is superior to standard-resolution USG, especially in diagnosis of milder patients with imaging findings confined to the renal medulla. There is wide variability in severity of renal disease among patients carrying the same *PKHD1* mutations, even within the same family, which complicates prognostic counseling and emphasizes the importance of modifying genes and potential environmental factors.

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## Disclosures

None.

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