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CLINICAL RESEARCH

High Prevalence of Kidney Cysts in Patients With CYP24A1 Deficiency

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Introduction: Loss-of-function variants in the *CYP24A1* gene cause a rare hereditary disease characterized by reduced 24-hydroxylase enzyme activity, increased serum 1,25-dihydroxycholecalciferol levels, hypercalcemia, hypercalciuria, and nephrocalcinosis and/or nephrolithiasis. Kidney cysts in patients with CYP24A1 deficiency were first reported in a single case study from our center. However, a possible association between CYP24A1 deficiency and kidney cysts has not been described.

Methods: Retrospective analysis of patients with confirmed or suspected CYP24A1 deficiency and available kidney imaging.

Results: Among 16 patients with confirmed pathogenic variants, 38% were male and 31% were children, the median age at genetic confirmation was 38 years (range 1–66), and none had a family history of cystic kidney disease. Medullary and/or corticomedullary junction cysts were present in all cases. The median age at first detected cyst was 37 years (range 3–60). The mean and median number of cysts per patient were 5.3 and 2.5 (range 1–37), respectively. Four of 5 further patients with suspected but unconfirmed pathogenic variants had cysts. The number of cysts ≥5 mm in size was above the 97.5th percentile of an age- and sex-matched control population in 55% and 67% of patients with confirmed and suspected pathogenic variants, respectively. At least 1 cyst (≥5 mm in size) was found in 80% of children with confirmed CYP24A1 deficiency.

Conclusions: These observations strongly suggest an association between CYP24A1 deficiency and kidney cysts. Further studies are needed to evaluate the role of CYP24A1, vitamin D metabolism, and/or hypercalciuria in cyst formation, and whether cysts exacerbate chronic kidney disease or modify nephrocalcinosis and stone risk.

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Deficient vitamin D 24-hydroxylase activity is a rare monogenic disorder of vitamin D and mineral metabolism that is primarily caused by biallelic pathogenic variant(s) but has occasionally been described in patients with a monoallelic gene change, often presenting with an attenuated clinical phenotype.[1] It is caused by loss-of-function variants in the *CYP24A1* gene encoding an enzyme with $25(OH)_2D$-24-hydroxylase and $1,25(OH)_2D$-24-hydroxylase activities that inactivates 25-hydroxyvitamin D ($25[OH]D_3$) and 1,25-dihydroxyvitamin D ($1,25[OH]_2D_3$) by converting them to the inert metabolites $24,25(OH)_2D_3$ and $1,24,25\text{-}(OH)_3D_3$, respectively.[2] This disorder is characterized by increased serum $1,25(OH)_2D_3$, low or undetected serum $24,25(OH)_2D_3$, hypercalcemia, suppressed intact parathyroid hormone (iPTH), hypercalciuria, nephrocalcinosis, and/or nephrolithiasis.[3] Most patients are diagnosed with CYP24A1 deficiency after presenting with kidney stones and/or hypercalcemia. Nearly all patients described to date with biallelic disease have a $25(OH)D:24,25(OH)_2D$ ratio >80, whereas unaffected patients and most monoallelic cases have a ratio <30.[4]

The association of kidney cysts with CYP24A1 deficiency was first reported in a single case study from our institution in 2012.[1] This and several additional cases[5,6] led us to systematically examine the number

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and location of kidney cysts in a cohort of patients with genetically confirmed and suspected CYP24A1 deficiency.

METHODS

Study Population

This was a retrospective observational study conducted according to the Mayo Clinic institutional review board guidelines. Mayo Clinic medical records were queried for suspected cases of CYP24A1 deficiency using characteristics of hypercalciuria, hypercalcemia, suppressed iPTH, elevated $1,25(OH)_2D_3$ level, 25(OH)D:$24,25(OH)_2D$ ratio $\geq$20 with nephrolithiasis and/or nephrocalcinosis. Demographic, clinical, laboratory, and imaging data were collected from Mayo Clinic medical records. Genetic information was obtained from Mayo Clinic medical records and by research testing (manuscript in preparation) provided by the Rare Kidney Stone Consortium CYP24A1 Deficiency Registry. Deficiency in vitamin D 24-hydroxylase activity was confirmed by pathogenic variants of the *CYP24A1* gene with an appropriate clinical phenotype. Kidney function was assessed using the full age spectrum glomerular filtration rate equation because the cohort spans age ranges from childhood to late adulthood.[7]

Imaging Review

All reviewed imaging examinations were obtained for clinical purposes using standard protocols. In most patients, these studies were mostly performed as follow-up studies, as the initial clinical presentation occurred at other medical centers. Reviewed modalities included ultrasound, computed tomography (CT) without or with i.v. contrast, and magnetic resonance imaging without and with i.v. contrast. Imaging studies were reviewed by a single board-certified radiologist with subspecialty training in genitourinary imaging. The presence or absence of cysts and cyst size were recorded for each kidney in each patient. Preference was given to the last contrast-enhanced CT or magnetic resonance image if available to assess the number of cysts and cyst size. Ultrasound examinations were also reviewed and the latest examination was used for cyst number and size if no contrast-enhanced CT or magnetic resonance imaging was available. Ultrasound examinations at our institution routinely include longitudinal cine clips through the kidney, which increases sensitivity of small cysts that may not have been captured or measured on still ultrasound images alone. Noncontrast CT was reviewed if it was the only available imaging modality for a given patient. If cysts were detected, earlier examinations were reviewed to determine the earliest date that cysts were present. To establish an association between CYP24A1 deficiency and kidney cysts, we compared the number, size, and location of kidney cysts in our cohort with a healthy, age and sex-controlled population.[8]

Table 1. Clinical characteristics of genetically confirmed CYP24A1 deficiency cohort

Clinical features	
N (male/female)	16 (6/10)
Children, *n* (%)	5 (31.3)
Reason for diagnosis, *n* (%)	
Family screening	2 (12.5)
Clinical suspicion	14 (87.5)
Age at first clinical presentation (yr)	
Mean (SD)	22.4 (16.5)
Median (range)	21 (0–59)
Clinical findings at presentation, *n* (%)	
Hypercalcemia of infancy	2 (14.2)
Hypercalcemia	2 (14.2)
Nephrolithiasis	7 (50)
Nephrocalcinosis	3 (21.4)
NL alone at diagnosis, *n* (%)	5 (31.2)
NC alone at diagnosis, *n* (%)	7 (43.8)
NL and NC at diagnosis, *n* (%)	4 (25)
Age at confirmed pathogenic variants (yr)	
Mean (SD)	32 (20.5)
Median (range)	38 (1–66)
Variants type, *n* (%)	
Monoallelic	4 (25)
Biallelic	12 (75)
Age at last follow-up (yr)	
Mean (SD)	34.1 (19.7)
Median (range)	37 (7–67)
Age at first known kidney cyst(s) (yr)	
Mean (SD)	30 (19)
Median (range)	37 (3–60)
No. of total kidney cysts per patient	
Mean (SD)	5.3 (8.6)
Median (range)	2.5 (1–37)
No. of right kidney cysts	
Mean (SD)	3.3 (5.8)
Median (range)	2 (0–24)
No. of left kidney cysts	
Mean (SD)	1.9 (3.1)
Median (range)	1 (0–13)
No. of cysts $\geq$ 5 mm	
Mean (SD)	2.8 (3.4)
Median (range)	1.5 (0–14)
Family history of cystic kidney disease, *n* (%)	
No	15 (93.8)
Yes	0 (0)
Unknown	1 (6.2)

SD, standard deviation; NL, nephrolithiasis; NC, nephrocalcinosis.

Statistical Methods

Results were expressed as mean with SD or median with full range or interquartile range (25th, 75th) for continuous variables and as percentages for categorical variables. Comparisons between groups for the continuous variables were performed with the *t*-test.

Table 2. Biochemical characteristics of genetically confirmed CYP24A1 deficiency cohort[a]

Biochemical features		*P* value
eGFR[a] (ml/min per 1.73 m^2), mean (SD)	76.5 (30)	0.01
eGFR children, mean (SD)	104.6 (32.1)	
eGFR adult, mean (SD)	66.3 (22.9)	
Serum Ca (mg/dl), mean (SD)	10.4 (1.1)	0.04
Children, mean (SD)	12.1 (2.8)	
Adult, mean (SD)	10.3 (0.5)	
Serum Pi (mg/dl), mean (SD)	3.7 (0.7)	0.11
Children, mean (SD)	4.1 (0.6)	
Adult, mean (SD)	3.5 (0.7)	
iPTH (pg/dl), mean (SD)	20.2 (15.1)	0.16
Children, mean (SD)	11 (5)	
Adult, mean (SD)	21.9 (16.2)	
$1,25(OH)_2D_3$ (pg/dl), mean (SD)	71.7 (23)	0.01
Children, mean (SD)	92 (23.3)	
Adult, mean (SD)	63 (16.9)	
$25(OH)D_3$ (ng/dl), mean (SD)	51.3 (18.4)	0.7
Children, mean (SD)	48.8 (27.6)	
Adult, mean (SD)	52.6 (13.6)	
$25(OH)D/24,25(OH)_2D$, mean (SD)	249.6 (153.4)	0.04
Children, mean (SD)	357.6 (92.9)	
Adult, mean (SD)	195.6 (154.2)	
24-h urine Ca (mg/d), adult		
Mean (SD)	292.5 (148.9)	
Median (range)	263 (67–585)	
Urinary Ca/Cr (mg/mg), children		
Mean (SD)	0.38 (0.23)	
Median (range)	0.36 (0.14–0.7)	

Ca/Cr, calcium-to-creatinine ratio; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; Pi, inorganic phosphorus; $1,25(OH)_2D_3$, 1,25-dihydroxyvitaminD; $25(OH)D_3$, 25-hydroxyvitamin D; $25(OH)D/24,25(OH)_2D$, 25-hydroxyvitamin D to 24,25-dihydroxyvitamin D ratio.
[a]Biochemical data obtained at the time of CYP24A1 deficiency evaluation.

RESULTS

Sixteen of 21 patients with suspected CYP24A1 deficiency evaluated at the Mayo Clinic or in the Rare Kidney Stone Consortium Registry had genetically confirmed pathologic variants. In the remaining 5, no sample was available for genetic testing because they were lost to follow-up.

Thirty-eight percent (6 of 16) were male, 31% (5 of 16) were children (age <18 years), 87.5% (14 of 16) were diagnosed after presenting with clinical findings, and 12.5% (2 of 16) were diagnosed by family screening. The clinical characteristics of the genetically confirmed CYP24A1 deficiency cohort are summarized in Table 1. The median age of clinical presentation was 21 years (mean 22.4, range 0–59) and at genetic confirmation was 38 years (mean 32, range 1–66). Among the 14 patients identified clinically, the initial presenting symptom was nephrolithiasis in 50% (7 of 14) and symptomatic hypercalcemia in 29% (4 of 14). Medullary nephrocalcinosis was found incidentally in the remaining 21% (3 of 14) during abdominal imaging investigation for abdominal or back pain. Table 2 displays the biochemical characteristics of the cohort. The mean estimated glomerular filtration rate ± SD (ml/min per /1.73 m^2) was higher in children compared with adults (104.6 ± 32 vs, 66.3 ± 23, $P < 0.05$). Mean serum Ca, $1,25(OH)_2D_3$, and $25(OH)D:24,25(OH)_2D$ ratio were higher, whereas mean iPTH was lower in children compared with adults ($P < 0.05$). Monoallelic or biallelic pathogenic variants were detected in 25% and 75% of the cohort, respectively (Table 3). Detailed clinical data in each patient with genetically confirmed CYP24A1 deficiency are summarized in Table 4. Thirty-one percent (5 of 16) reported receiving vitamin D supplements at the time of initial evaluation/laboratory results. Among the 5, 3 were receiving vitamin D only in the form of a daily multiple vitamin supplement. All patients were informed to avoid vitamin D supplements after their initial evaluation. Box plots (median, interquartile range, and range) of key variables (estimated glomerular filtration rate, serum Ca, $25[OH]D_3$, $1,25[OH]_2D_3$, iPTH, and $25[OH]D:24,25[OH]_2D$ ratio) are depicted in Figure 1. As expected, the median $1,25(OH)_2D_3$ and $25(OH)D:24,25(OH)_2D$ ratio levels were higher, whereas iPTH was lower in this cohort compared with the normal values.

Kidney cysts were present in all 16 patients. The median age at first available kidney imaging was 37 years (mean 30, range 3–60) and age at first kidney cyst detection was similar. Three patients with no cysts on initial imaging later developed them. The median and mean number of cysts per patient were 2.5 (range 1–37) and 5.3 (SD 8.3), respectively. The median and mean number of cysts ≥5 mm per patient were 1.5 (range 0–14) and 2.8 (SD 3.4), respectively (Table 1). All patients had normal age-adjusted kidney size, and none had a known family history of cystic kidney disease. Detailed kidney cyst characteristics based on various imaging modalities in the genetically confirmed patients are described in Table 5. Cysts were localized to the medullary and/or corticomedullary junction in all cases. The number of kidney cysts in relation to age and box plots of key variables (median, interquartile range, and range), including largest cyst size and number of cysts ≥5 mm in size, are shown in Figure 2 (a, b, c). The number of cysts ≥5 mm in diameter in 55% (6 of 11) of adult patients with confirmed deficiency was above the 97.5th percentile of an age- and sex-matched control population (Figure 2d, Table 6).[8] At least 1 cyst ≥5 mm in size was found in 80% of children with genetically confirmed CYP24A1 deficiency. Examples of the imaging modalities we used to diagnose kidney cysts (contrast-enhanced CT, MRI, and ultrasonography) are displayed in Figure 3.

Eighty percent (4 of 5) of the patients with suspected but not genetically confirmed CYP24A1 deficiency had

Table 3. CYP24A1 gene pathogenic variants identified in the cohort

ID	Pedigree number	Allelism	Sequence alteration	Amino acid alteration
1	1	Monoallelic	c.732+1G>A	p.Thr244?
2	1	Monoallelic	c.845–2A>G	p.Val282?
3	1	Monoallelic	c.845–2A>G	p.Val282?
4	2	Biallelic	c.964G>A, c.1186C>T	p.Glu322Lys, p.Arg396Trp
5	3	Biallelic	c.667A>T, c.1226T>C	p.Arg223*, p.Leu409Ser
6	4	Biallelic	c.428_430delAAG, c.1226T>C	p.Glu143del, p.Leu409Ser
7	5	Biallelic	c.1226T>C, c.1226T>C	p.Leu409Ser, p.Leu409Ser
8	6	Biallelic	c.999_1006del, c.1186C>T	p.Ser334Valfs9*, p.Arg396Trp
9	4	Biallelic	c.428_430delAAG, c.1226T>C	p.Glu143del, p.Leu409Ser
10	1	Biallelic	c.732+1G>A, c.845–2A>G	p.Thr244?, p.Val282?
11	7	Monoallelic	c.62delC	p.Pro21Argfs
12	8	Biallelic	c.469C>T, c.469C>T	p.Arg157Trp; p.Arg157Trp
13	9	Biallelic	c.1186C>T, c.428_430delAAG	p.Arg396Trp, p.Glu143del
14	10	Biallelic	c.470G>A, c.469C>T	p. Arg157Gln, p.Arg157Trp
15	11	Biallelic	c.1186C>T, c.475C>T	p.Arg396Trp, p.Arg159Trp
16	12	Biallelic	c.1186C>T, c.475C>T	p.Arg396Trp, p.Arg159Trp

medullary and/or corticomedullary junction kidney cysts. The number of cysts ≥5 mm in size in 67% (2 of 3) of adult patients was above the 97.5th percentile of an age- and sex-matched control population and at least 1 cyst ≥5 mm in size was found in 50% of children in this group (Supplementary Tables 1, 2, and 3**).**

To determine whether new cysts developed over time in this cohort, the number of cysts versus age was determined in 7 patients (all children) with confirmed or suspected CYP24A1 deficiency and serial kidney ultrasound imaging. The mean duration from the first to last ultrasound study was 4.5 years (range 1–7). New cysts (1 to 5) developed in all patients but 1, who had a short follow-up of 1 year (Figure 4).

To determine whether patients with CYP24A1 deficiency develop liver cysts, we reviewed all available hepatic imaging studies. No hepatic cysts were observed in 8 of 9 patients with adequate imaging. The remaining patient, 43 years of age at the time of imaging, had 2 possible small liver cysts via contrast-enhanced CT.

DISCUSSION

In this study, we found a strong association between CYP24A1 deficiency and medullary or corticomedullary junction simple kidney cysts with an overall prevalence of 100% in a cohort of genetically confirmed cases. Among patients with serial imaging, the number and size of cysts progressively increased in the vast majority. Hepatic cysts were not detected among those patients with available imaging except 1

Table 4. Clinical features of CYP24A1 deficiency cohort[a]

Case number	Age (yr)	Sex	Ethnicity	Age at clinical presentation (yr)	On Thiazide Diuretics/ Vit D	eGFR (ml/min/1.73 m^2)	Serum Ca mg/dl	Serum Pi mg/dl	iPTH pg/dl	25(OH) D_3 ng/dl	1,25$(OH)_2D_3$ pg/dl	25(OH)D/ 24,25$(OH)_2$D	24 h urine Ca mg/d	24 h urine Ca mg/k/d	Urine Ca/Cr mg/mg
1	10	F	W	0	no/no	>90	14.2	3.5	<1	36	66	353			>0.48
2	12	M	W	2	no/no	132	9.6	4.8	16	44	78	253			0.7
3	14	F	W	0	no/no	131	16.0	4.4	6	28	120	470		7.9	0.34
4	13	F	W	4	no/no	88	10.5	4.6	11	39	83	430			0.36
5	16	F	W	13	yes/no	67.5	10.2	3.4	<1	97	113	282		2.5	0.14
6	40	M	W	36	yes/no	64	9.7	3.3	15	31	75	148	180		
7	47	M	W	31	no/no	28	10.8	4.2	17	22	43	38	369		
8	44	F	W	37	no/yes	94	10.8	3.4	15	47	81	336	263		
9	45	F	W	34	no/yes	70	10.2	2.6	27	54	73	281	585		
10	53	M	W	38	no/no	82	11.1	4.8	6	55	77	250	325		
11	45	M	W	26	yes/yes	79	10.3	3.2	61	48	46	9	234		
12	67	F	W	59	yes/no	75	9.3	3.4	43	34	73	47	509		
13	66	M	W	19	no/no	50	10.6	3.5	14	69	70	460	207		
14	27	F	W	18	yes/yes	100	9.9	2.6	19	54	67	•	210		
15	52	F	W	18	yes/no	39	10.1	4.3	13	74	42	40	269		
16	29	F	W	23	no/yes	48	10.1	3.3	11	60	40	347	67		

eGFR, estimated glomerular filtration rate; PTHi, intact parathyroid hormone; W, white; 1,25$(OH)_2D_3$, 1,25-dihydroxyvitaminD; 25$(OH)D_3$, 25-hydroxyvitamin D; 25(OH)D/24,25$(OH)_2$D, 25-hydroxyvitamin D:24,25-dihydroxyvitamin D ratio.
[a]Laboratory data obtained at the time of CYP24A1 deficiency evaluation.

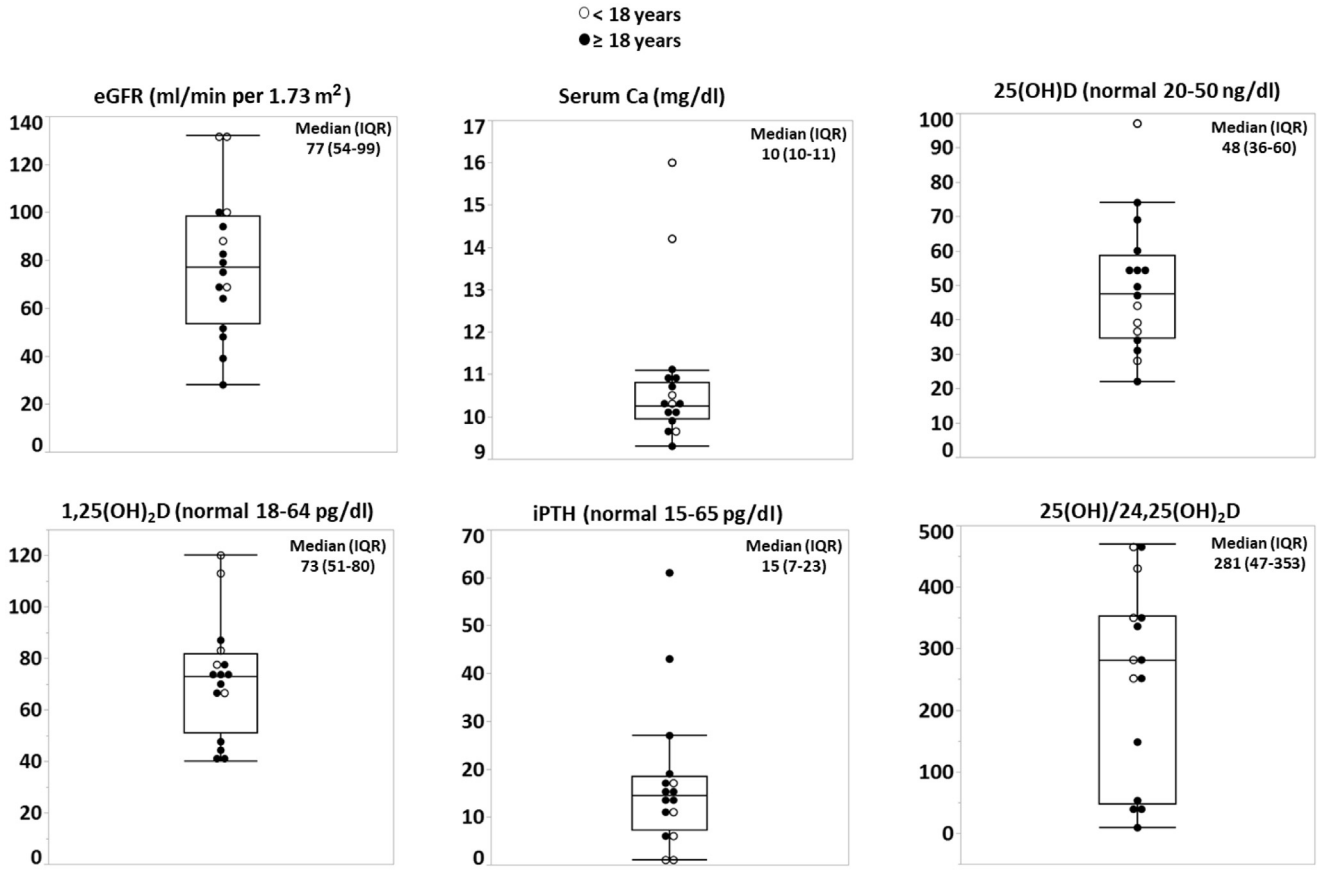

Figure 1. Box plots of key variables* in the genetically confirmed CYP24A1 deficiency cohort, including estimated glomerular filtration rate (eGFR), serum Ca, $25(OH)D_3$, $1,25(OH)_2D_3$, intact PTH, and $25(OH)D/24,25(OH)_2D$. The central rectangle spans the first quartile to the third quartile. IQR, interquartile range. *Biochemical data obtained at the time of CYP24A1 deficiency evaluation.

with possible 2 small cysts. Thus, the cysts associated with CYP24A1 deficiency appear to be limited to the kidney.

The significance of simple kidney cysts varies depending on the person's age and total number of cysts.[9] Rule *et al.*[8] described the expected number of cysts ≥5 mm in a cohort of 1948 potential adult kidney donors who had available contrast-enhanced CT data and lacked a family history of cystic kidney disease, and calculated the upper 97.5 percentile

Table 5. Kidney cyst characteristics in the CYP24A1 deficiency cohort

Case number	Age at first kidney cysts detection (yr)	Imaging modality	Age at imaging study (yr)	Total number of cysts	No. of R kidney cysts	Location of R kidney cysts	No. of L kidney cysts	Location of L kidney cysts	Smallest cyst size, mm	Largest cyst size, mm	No. of cysts ≥5 mm
1	7	US	7	1	0	n/a	1	CMJ	n/a	2	0
2	7	US	10	1	0	n/a	1	CMJ	n/a	9	1
3	3	US	12	3	2	M	1	n/a	4	10	1
4	8	US	12	2	0	n/a	2	M, CMJ	13	21	2
5	14	US	15	3	2	M	1	M	6	8	3
6	36	NCCT	36	2	1	M, CMJ	1	M, CMJ	8	17	2
7	37	NCCT	37	10	6	M	4	M	3	30	6
8	38	US	38	3	2	M, CMJ	1	M, CMJ	5	13	3
9	40	MRI	40	8	5	M	3	M	2	15	4
10	41	CECT	43	37	24	CMJ	13	CMJ	2	13	14
11	44	CECT	44	6	3	M, CMJ	3	M, CMJ	2	14	4
12	59	CECT	59	1	1	M	0	n/a	n/a	12	1
13	60	CECT	60	4	3	M	1	M	2	8	1
14	18	CECT	18	3	2	M	1	M	8	23	3
15	50	CECT	50	1	1	M	0	M	n/a	5	1
16	24	NCCT	24	1	1	M	0	n/a	n/a	8	1

CECT, contrast-enhanced computed tomography; CMJ, renal corticomedullary junction; CTU, CT urogram; M, renal medulla; MRI, magnetic resonance imaging; n/a, not applicable; NCCT, noncontrast computed tomography; US, ultrasound.

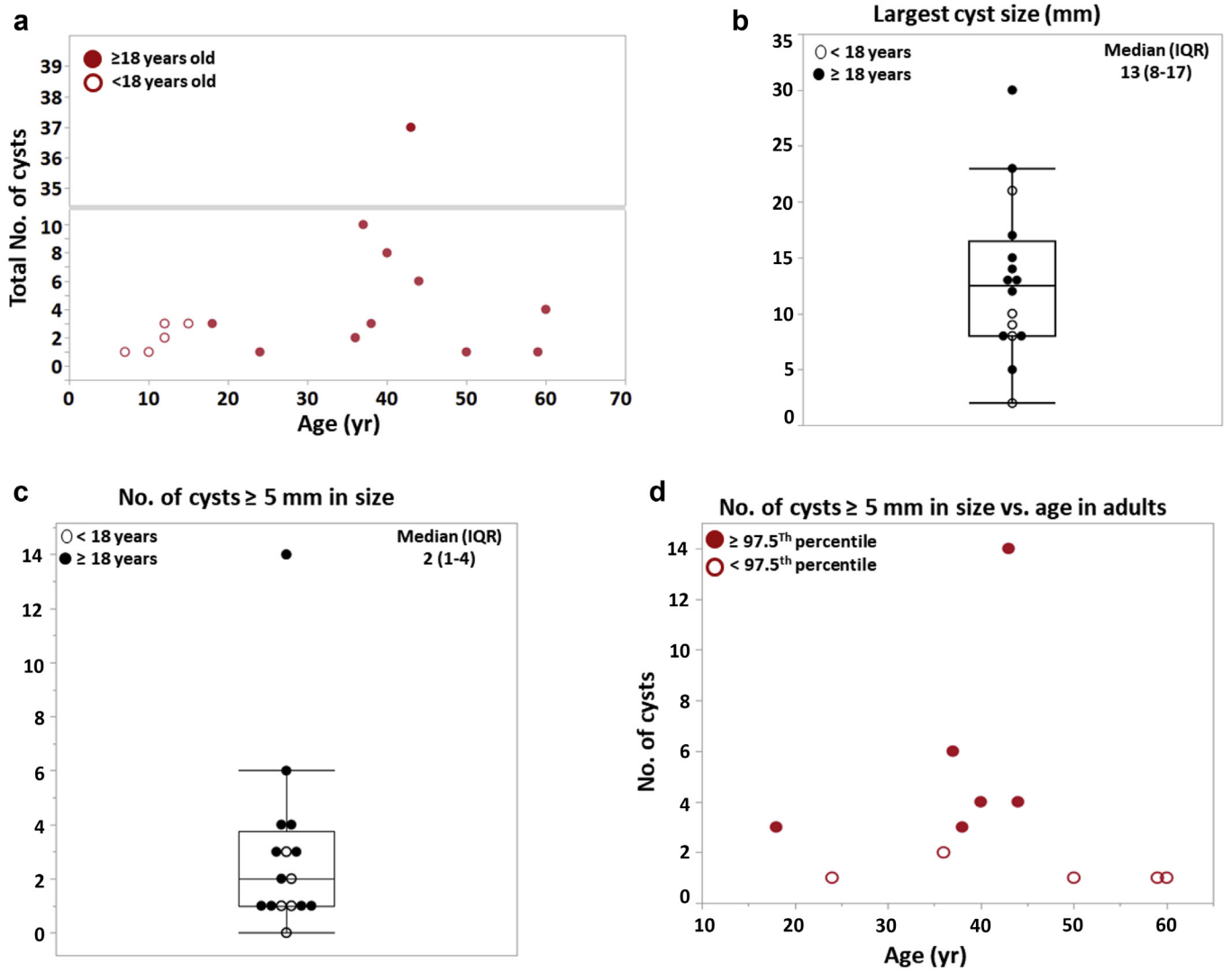

Figure 2. (a) Number of kidney cysts versus age in the genetically confirmed CYP24A1 deficiency cohort. (b) and (c) Box plots of key variables including largest cyst size in millimeters for each case, and number of cysts ≥5 mm in each case. (d) The number of cysts ≥5 mm in size in 55% (6 of 11) of adult patients with confirmed deficiency was above the 97.5th percentile of an age- and sex-matched control population. IQR, interquartile range.

of expected cysts by age and sex.[8] Using these data as an age- and sex-matched control population (Table 6), we found that 55% of the adults in our genetically confirmed CYP24A1 deficiency cohort exceeded this upper 97.5 percentile. Similar control data are not available for a healthy pediatric population, but 80% of children with confirmed CYP24A1 deficiency had at least 1 cyst ≥5 mm in size. Our data suggest a decline in kidney function over time based on estimated glomerular filtration rate calculations. There are few published data regarding the long-term implications of CYP24A1 deficiency for kidney function. Our data suggest that chronic kidney disease may be a late outcome.

Kidney cysts have been previously described in a few case reports of patients with CYP24A1 deficiency.[1,5,6] In the first report from our center, in 2012, Tebben *et al.*[1] described a 44-year-old man (case number 10 in our cohort) with small bilateral kidney cysts by abdominal CT. The second report discussed a 20-year-old pregnant woman who presented with acute pancreatitis from gestational hypercalcemia attributed

Table 6. Number of cysts (≥ 5mm in size; parapelvic cysts excluded) above the 97.5th percentile of an age- and sex-matched control adult population

	Number of cysts ≥5 mm in both kidneys	
Age group, yr	Men	Women
18–29	≥2	≥2
30–39	≥3	≥3
40–49	≥4	≥3
50–59	≥6	≥4
60–69	≥11	≥5

Adapted from Rule *et al.*[8]

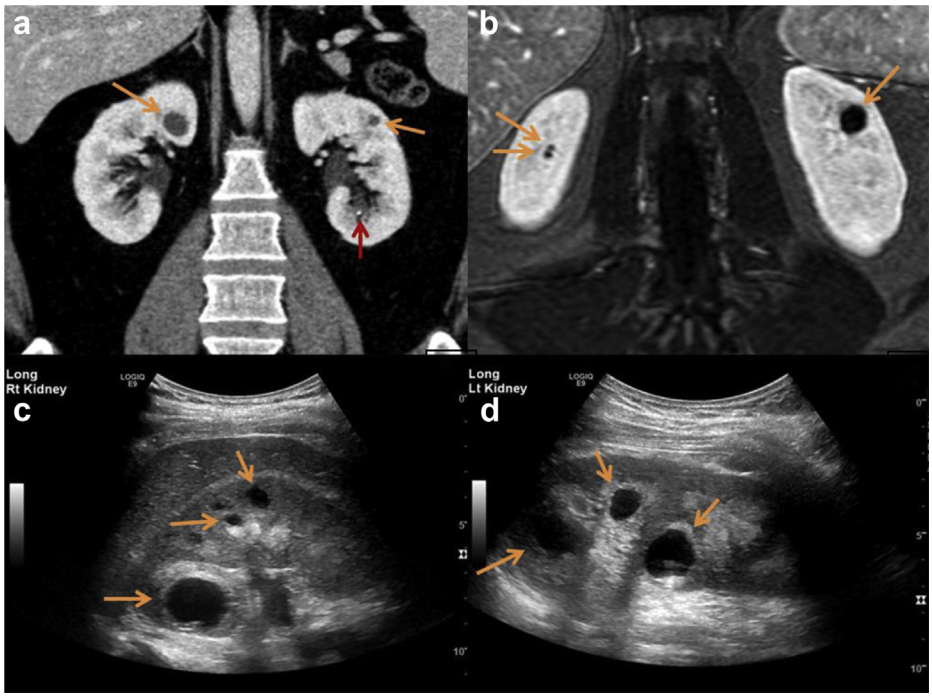

Figure 3. Characteristic kidney cysts in representative CYP24A1 deficient patients by imaging modality. (a) Contrast-enhanced computed tomography. Bilateral simple cysts at cortico-medullary junction (orange arrows), right upper pole 14 mm and left upper pole 6 mm. Small nonobstructive left lower pole calculus (red arrow). (b) Magnetic resonance image. Bilateral simple medullary cysts (orange arrows) shown post-contrast as hypo-intense smoothly marginated nonenhancing lesions, right interpolar level each 3 mm and left upper pole 15 mm. (c) and (d) Ultrasound. Bilateral medullary and corticomedullary junction simple cysts (orange arrows) and medullary nephrocalcinosis.

to her CYP24A1 deficiency. Her abdominal CT scan showed an edematous pancreas and incidental findings of bilateral kidney cysts without evidence of nephrocalcinosis. The third report described 2 patients with CYP24A1 deficiency and multiple kidney parenchymal cysts on ultrasonography.

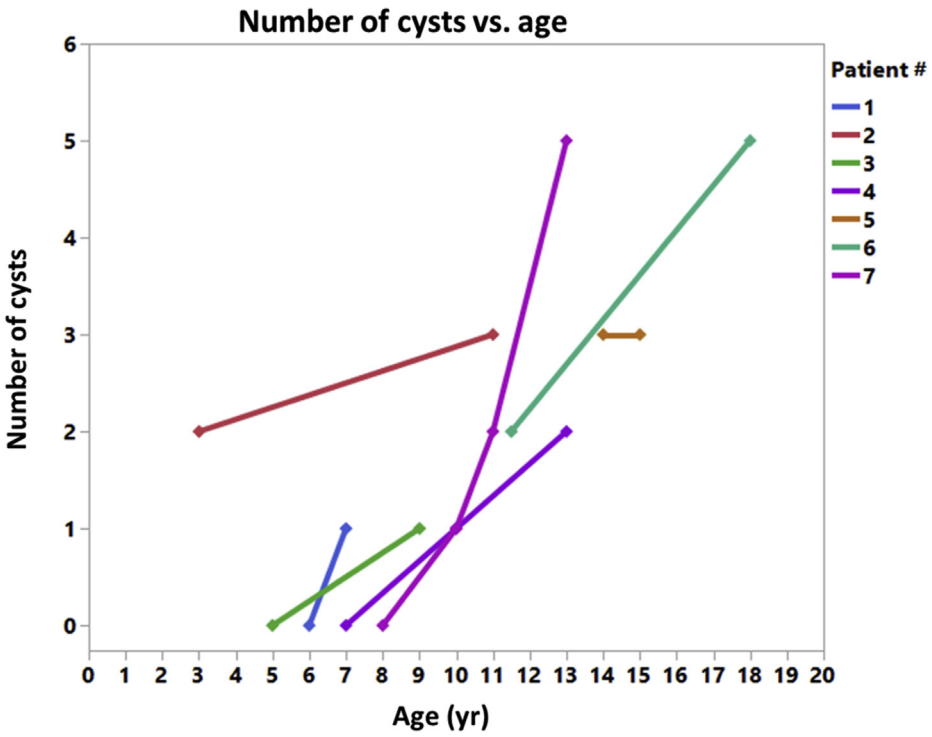

Figure 4. Kidney cyst number versus age measured from available serial kidney ultrasound imaging studies in patients with confirmed or suspected CYP24A1 deficiency during childhood period. This graph indicates that new cystogenesis (1 to 5 cysts) developed in all patients but 1 who had a short follow-up.

A recent study reported a high prevalence of simple kidney cysts in patients with primary hyperparathyroidism compared with healthy controls (34.9% vs 16.2%, $P < 0.01$).[10] The study concluded that cystogenesis might be related to the action of the elevated PTH levels on tubular epithelial cells. Our cohort PTH levels are low to low normal as expected, and thus, a high PTH level is not likely to be a contributing factor in patients with *CYP24A1* pathogenic variants. Biochemical findings shared between our cohort and primary hyperparathyroidism include hypercalcemia, hypercalciuria, and elevated $1,25(OH)_2D_3$ levels. Kidney cysts have been described in animal and human models of hereditary hypophosphatemic rickets with hypercalciuria, a rare autosomal-recessive disorder due to genetic changes in the *SLC34A3* gene that encodes the renal sodium-phosphate (Pi) cotransporter NPT2c. In this case, hypophosphatemia secondary to renal wasting leads to suppression of fibroblast growth factor 23, increased $1,25(OH)_2D_3$, and hypercalciuria.[11,12] Thus it is possible that sustained hypercalciuria or exposure to increased $1,25(OH)_2D_3$ concentration could be factors in cyst development.

Our observation suggests that the underlying mechanism of cystogenesis in CYP24A1 deficiency is renal specific. Recently, a new study suggested that calcium oxalate crystal deposition in renal tubules can trigger rapid tubular dilatation, activate polycystic kidney disease–associated signaling pathways, and thus accelerate cystogenesis in polycystic kidney disease and disease progression.[13] The authors concluded that the presence of hypercalciuria and crystal deposition could contribute to the development of kidney cysts. Additional studies will be needed to establish the relevance of this hypothesis to patients with CYP24A1 deficiency.

Our study has several strengths and some limitations. This was a retrospective analysis of clinical registry data, a voluntary data set that is inherently incomplete. Screening was not performed in all family members, and it is possible that there are patients with genetic disease who, indeed, manifest a milder phenotype.

Kidney cysts have not been widely recognized as a clinical manifestation associated with CYP24A1 deficiency. The presence of kidney cysts may provide an additional diagnostic clue, thus facilitating early recognition of CYP24A1 deficiency, early initiation of treatment, and may advance understanding of the full pathophysiology of this rare disease.

CONCLUSION

This study suggests a high prevalence of kidney cysts in patients with CYP24A1 deficiency. Further studies are needed to explore the role of CYP24A1 and vitamin D metabolism in kidney cyst formation, and whether cysts enhance chronic kidney disease risk in patients or modify nephrocalcinosis and urinary stone risk in CYP24A1 deficiency.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Clinical features of the suspected CYP24A1 deficiency cohort.

Table S2. Clinical features of the suspected CYP24A1 deficiency cohort.

Table S3. Kidney cysts characteristics in the suspected CYP24A1 deficiency cohort.

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