High Prevalence of Kidney Cysts in Patients With CYP24A1 Deficiency

Christian Hanna1, Theodora A. Potretzke2, Andrea G. Cogal3, Yaman G. Mkhaimer3, Peter J. Tebben4, Vicente E. Torres3, John C. Lieske3,5, Peter C. Harris3, David J. Sas1,5, Dawn S. Milliner1,3 and Fouad T. Chebib3

1Division of Pediatric Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA; 2Division of Radiology, Mayo Clinic, Rochester, Minnesota, USA; 3Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA; 4Division of Endocrinology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA; and 5Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

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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Correspondence: Christian Hanna, Mayo Clinic, 200 First Street SW, Rochester, Minnesota, 55905, USA. E-mail: Hanna.Christian@mayo.edu

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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. 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]D3) and 1,25-dihydroxyvitamin D (1,25[OH]2D3) by converting them to the inert metabolites 24,25(OH)2D3 and 1,24,25-(OH)3D3, respectively. This disorder is characterized by increased serum 1,25(OH)2D3, low or undetected serum 24,25(OH)2D3, hypercalcemia, suppressed intact parathyroid hormone (iPTH), hypercalciuria, nephrocalcinosis, and/or nephrolithiasis. 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.

The association of kidney cysts with CYP24A1 deficiency was first reported in a single case study from our institution in 2012. This and several additional cases led us to systematically examine the number...
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 hypercalcioria, hypercalcemia, suppressed iPTH, elevated 1,25(OH)₂D₃ level, 25(OH)D:24,25(OH)₂D ratio ≥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.

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.

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 1. Clinical characteristics of genetically confirmed CYP24A1 deficiency cohort |
|---------------------------------|------------|-------------------------------------------------|
| **Clinical features**           |            | **N (male/female)**                             |
| Age (yr)                        | 22.4 (16.5)| **Mean (SD)**                                   |
| Median (range)                  | 21 (0–59)  | **Clinical findings at presentation, n (%)**    |
| Age at first clinical presentation (yr) | 32 (20.5)  | Hypercalcemia of infancy                        |
| Mean (SD)                       | 38 (1–66)  | Hypercalcemia                                  |
| Median (range)                  | 12 (75)    | Nephrolithiasis                                |
| Age at last follow-up (yr)      | 34.1 (19.7)| Nephrocalcinosis                               |
| Mean (SD)                       | 37 (7–67)  | **No. of total kidney cysts per patient**       |
| Median (range)                  | 30 (19)    | Mean (SD)                                      |
| No. of total kidney cysts per patient | 5.3 (8.6)  | Median (range)                                 |
| No. of left kidney cysts        | 3.3 (5.8)  | No. of right kidney cysts                       |
| Mean (SD)                       | 2.5 (1–37) | Median (range)                                 |
| Median (range)                  | 3.3 (5.8)  | No. of left kidney cysts                        |
| No. of cysts ≥ 5 mm             | 1.9 (3.1)  | Mean (SD)                                      |
| Mean (SD)                       | 1.0 (0–13) | Median (range)                                 |
| Median (range)                  | 1.0 (0–13) | No                                              |
| Family history of cystic kidney disease, n (%) | 2.6 (3.4) | Median (range)                                 |
| Unknown                         | 15 (93.8)  | Family history of cystic kidney disease         |
| Yes                             | 0 (0)      | No                                              |
| Unknown                         | 1 (6.2)    | Unknown                                         |

SD, standard deviation; NL, nephrolithiasis; NC, nephrocalcinosis.
Table 2. Biochemical characteristics of genetically confirmed CYP24A1 deficiency cohort

| Biochemical features | adult (SD) | children (SD) | P value |
|----------------------|------------|---------------|---------|
| eGFR (m/min per 1.73 m²) | 76.5 (30) | 104.6 (32.1) | 0.01    |
| eGFR children, mean (SD) | 66.3 (22.9) | 10.4 (1.1) | 0.04    |
| Serum Ca (mg/dl), mean (SD) | 12.1 (2.8) | 10.3 (0.5) | 0.11    |
| Adult, mean (SD) | 3.7 (0.7) | 4.1 (0.6) | 0.16    |
| Serum Pi (mg/dl), mean (SD) | 3.5 (0.7) | 20.2 (15.1) | 0.01    |
| Children, mean (SD) | 11 (5) | 21.9 (16.2) | 0.01    |
| Adult, mean (SD) | 71.7 (23) | 92 (23.3) | 0.01    |
| 1,25(OH)2D3 (pg/dl), mean (SD) | 51.3 (18.4) | 84.8 (27.6) | 0.7     |
| Children, mean (SD) | 52.6 (13.6) | 357.8 (92.9) | 0.04    |
| Adult, mean (SD) | 249.8 (153.4) | 195.6 (154.2) | 0.01    |
| 25(OH)D3 (ng/dl), mean (SD) | 35.5 (21.6) | 35.5 (21.6) | 0.01    |
| Children, mean (SD) | 12.1 (2.8) | 12.1 (2.8) | 0.01    |
| Adult, mean (SD) | 12.1 (2.8) | 12.1 (2.8) | 0.01    |
| 25(OH)D3 (ng/dl), mean (SD) | 35.5 (21.6) | 35.5 (21.6) | 0.01    |
| Children, mean (SD) | 12.1 (2.8) | 12.1 (2.8) | 0.01    |
| Adult, mean (SD) | 12.1 (2.8) | 12.1 (2.8) | 0.01    |

Ca/Cr, calcium-to-creatinine ratio; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; Pi, inorganic phosphorus; 1,25(OH)2D3, 25-hydroxyvitamin D; 25(OH)D3, 25-hydroxyvitamin D; 25(OH)D/24,25(OH)2D, 25-hydroxyvitamin D to 24,25-dihydroxyvitamin D ratio.

*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 /1.73 m²) was higher in children compared with adults (104.6 ± 32 vs. 66.3 ± 23, P < 0.05). Mean serum Ca, 1,25(OH)2D3, 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)D3, iPTH, and 25(OH)D:24,25(OH)2D ratio) are depicted in Figure 1. As expected, the median 1,25(OH)2D3 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). 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
The number of cysts $\geq 5$ 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 $\geq 5$ 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 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 |

### Table 4. Clinical features of CYP24A1 deficiency cohort

| Case number | Age (yr) | Sex | Ethnicity | Age at clinical presentation (yr) | On Thiazide/ Diuretics/ Vit D | eGFR (ml/min/1.73 m²) | Ca mg/dl | Pi mg/dl | iPTH pg/dl | 25(OH)D3 ng/dl | 1,25(OH)2D3 pg/dl | 25(OH)D/24,25(OH)2D | 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/yes                        | 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              | 49                   | 234             |                  |
| 12          | 67      | F   | W         | 59                               | yes/yes                       | 75                    | 9.3      | 3.4    | 34       | 34            | 73              | 47                   | 509             |                  |
| 13          | 66      | M   | W         | 19                               | yes/yes                       | 50                    | 10.6     | 3.5    | 14       | 89            | 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/yes                       | 39                    | 10.1     | 4.3    | 13       | 74            | 42              | 40                   | 269             |                  |
| 16          | 29      | F   | W         | 23                               | yes/yes                       | 48                    | 10.1     | 3.3    | 11       | 60            | 40              | 347                  | 67              |                  |

eGFR, estimated glomerular filtration rate; PTH, intact parathyroid hormone; W, white; 1,25(OH)2D3, 1,25-dihydroxyvitamin D; 25(OH)D3, 25-hydroxyvitamin D; 25(OH)D/24,25(OH)2D, 25-hydroxyvitamin D:24,25-dihydroxyvitamin D ratio.

*Laboratory 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. Rule et al. 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                      | 2                      | 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                     | n/a                       | 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.
of expected cysts by age and sex.\textsuperscript{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.\textsuperscript{1,5,6} In the first report from our center, in 2012, Tebben et al.\textsuperscript{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

| Age group, yr | Number of cysts ≥5 mm in both kidneys |
|--------------|-------------------------------------|
|              | 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.\textsuperscript{8}
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 3](image)

**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 margined 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.

![Figure 4](image)

**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).12 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)2D3 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)2D3, and hypercalciuria.11,12 Thus it is possible that sustained hypercalciuria or exposure to increased 1,25(OH)2D3 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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