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# Adenine Phosphoribosyltransferase Deficiency

Synonyms: 2,8-Dihydroxyadeninuria; APRT Deficiency

Vidar Orn Edvardsson, MD,[1] Amrik Sahota, PhD,[2] and Runolfur Palsson, MD[3]

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## Summary

### Clinical characteristics

Adenine phosphoribosyltransferase (APRT) deficiency is characterized by excessive production and renal excretion of 2,8-dihydroxyadenine (DHA), which leads to kidney stone formation and crystal-induced kidney damage (i.e., DHA crystal nephropathy) causing acute kidney injury episodes and progressive chronic kidney disease (CKD). Kidney stones, the most common clinical manifestation of APRT deficiency, can occur at any age; in at least 50% of affected persons symptoms do not occur until adulthood. If adequate treatment is not provided, approximately 20%-25% of affected individuals develop end-stage renal disease (ESRD), usually in adult life.

### Diagnosis/testing

The diagnosis of APRT deficiency is established in a proband by absence of APRT enzyme activity in red cell lysates or identification of biallelic pathogenic variants in *APRT*. The detection of the characteristic round, brown DHA crystals by urine microscopy is highly suggestive of the disorder.

### Management

*Treatment of manifestations:* Treatment with the xanthine oxidoreductase inhibitors (XOR; xanthine dehydrogenase/oxidase) allopurinol or febuxostat can improve kidney function, even in individuals with advanced CKD. The prescribed dose of allopurinol and febuxostat should not routinely be reduced in affected individuals who have impaired kidney function. Ample fluid intake is advised. Surgical management of DHA nephrolithiasis is the same as for other types of kidney stones. ESRD is treated with dialysis and kidney transplantation. Even after kidney transplantation, treatment with an XOR is recommended.

*Surveillance:* Measurement of eGFR and urinary DHA excretion (or urine microscopy for assessment of DHA crystalluria) every 6-12 months; routine follow up to facilitate adherence to pharmacologic treatment at least

**Author Affiliations:** 1 Division of Pediatric Nephrology Children's Medical Center Landspítali –The National University Hospital of Iceland Reykjavik, Iceland; Email: vidare@landspitali.is. 2 Department of Genetics Rutgers University Piscataway, New Jersey; Email: sahota@biology.rutgers.edu. 3 Division of Nephrology Landspítali –The National University Hospital of Iceland University of Iceland Reykjavik, Iceland; Email: runolfur@landspitali.is.

annually; periodic renal ultrasound examination should be considered to evaluate for new asymptomatic kidney stones.

*Agents/circumstances to avoid:* Azathioprine and mercaptopurine should not be given to individuals taking either allopurinol or febuxostat.

*Evaluation of relatives at risk:* It is recommended that sibs of an affected individual undergo APRT enzyme activity measurement or molecular genetic testing (if the pathogenic variants in a family have been identified) to allow early diagnosis and treatment and improve long-term outcome.

*Pregnancy management:* The safety of allopurinol and febuxostat in human pregnancy has not been systematically studied. Some post-transplantation immunosuppressive therapies can have adverse effects on the developing fetus. Ideally a thorough discussion of the risks and benefits of maternal medication use during pregnancy should take place with an appropriate health care provider prior to conception.

## Genetic counseling

APRT deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being normal. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if the pathogenic variants in the family have been identified.

# Diagnosis

## Suggestive Findings

Adenine phosphoribosyltransferase (APRT) deficiency (also known as 2,8-dihydroxyadeninuria) **should be suspected** in individuals with the following clinical, radiographic, laboratory, and pathology findings [Balasubramaniam et al 2016, Runolfsdottir et al 2016, Garigali et al 2019, Runolfsdottir et al 2019a].

**Clinical manifestations**

- Kidney stone disease and renal colic
- Chronic kidney disease (CKD)
- Crystal nephropathy (confirmed by kidney biopsy; see **Pathology**)
- Reddish-brown diaper stain in infants and young children
- Allograft dysfunction following kidney transplantation

**Radiographic findings**

- Radiolucent kidney stones, detected by ultrasound or computed tomography (CT). Stones are not seen on a plain abdominal x-ray.
- Ultrasound examination frequently demonstrates increased echogenicity of the kidneys.

**Laboratory findings**

- **Urine microscopy.** The round and brown DHA crystals can usually be detected by urine microscopy (Figure 1A). Small and medium-sized DHA crystals display a central Maltese cross pattern when viewed by polarized light microscopy (Figure 1B), while larger crystal aggregates do not as they are impermeable to light.

  Note: (1) DHA crystals may be difficult to identify in individuals with advanced CKD, possibly due to reduced DHA clearance by the kidney [Bollée et al 2010, Edvardsson et al 2013]. (2) High urine pH in

individuals with radiolucent stones provides an additional clue to the diagnosis of APRT deficiency because uric acid stones develop in acidic urine [Edvardsson et al 2013] (see Differential Diagnosis).

- **Kidney stone analysis.** Analysis of DHA crystals and kidney stone material using infrared or ultraviolet spectrophotometry (at both acidic and alkaline pH) and/or x-ray crystallography differentiates DHA from uric acid and xanthine, which also form radiolucent stones. Although stones in persons with APRT deficiency are predominantly composed of DHA, they may contain trace amounts of other minerals.
  - Kidney stone analysis using the above techniques is dependent on skilled personnel and, thus, cannot be used to establish a diagnosis of APRT deficiency (see Establishing the Diagnosis).
  - Stone analysis employing standard chemical and thermogravimetric methods does not distinguish DHA from other purines (e.g., uric acid) and is not recommended.

**Pathology.** Renal histopathologic findings in persons with APRT deficiency and CKD or acute allograft dysfunction are characterized by diffuse tubulointerstitial DHA crystal deposits accompanied by inflammation and fibrosis (see Figure 2), which may be observed even in individuals without a history of kidney stones [Nasr et al 2010, Zaidan et al 2014, Agrawal et al 2015, Lusco et al 2017].

Note: It is important not to confuse the histopathologic manifestations of DHA crystal nephropathy with those of other crystal nephropathies, particularly those caused by oxalate (particularly primary hyperoxaluria) and uric acid deposits [Nasr et al 2010].

## Establishing the Diagnosis

The diagnosis of APRT deficiency **is established** in a proband with absent APRT enzyme activity in red cell lysates or biallelic pathogenic variants in *APRT* identified by molecular genetic testing (see Table 1). See Figure 3 for a diagnostic algorithm [Edvardsson et al 2013].

Note: Kidney stone analysis suggesting APRT deficiency is not reliable enough to establish the diagnosis.

### APRT Enzyme Activity

APRT activity measured in red cell lysates ranges from 16 to 32 nmol/hr per mg hemoglobin in healthy individuals. In almost all individuals with APRT deficiency, APRT enzyme activity measured in red cell lysates (or other cell extracts) is absent; however, exceptions do occur. For example, two enzyme isoforms resulting from the following *APRT* pathogenic variants have substantial activity in red cell lysates:

- p.Val150Phe [Deng et al 2001] (present in some individuals of northern European heritage)
- p.Met136Thr [Ikeda et al 2016] (present in >70% of Japanese, who are homozygous for this pathogenic variant)

Thus, in individuals with these two pathogenic variants, in vivo assays (e.g., uptake of adenine by intact erythrocytes or leukocytes) are required to verify APRT deficiency.

Note: (1) If enzyme activity is within normal limits or in the heterozygote range in an individual who has recently received a red cell transfusion, enzyme activity measurement should be repeated after three months. (2) Heterozygotes for an *APRT* pathogenic variant cannot be reliably identified by enzyme assay in cell extracts as the enzyme activity range in these individuals overlaps with that of controls.

### Molecular Genetic Testing

Approaches can include **single-gene testing** and use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *APRT* is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

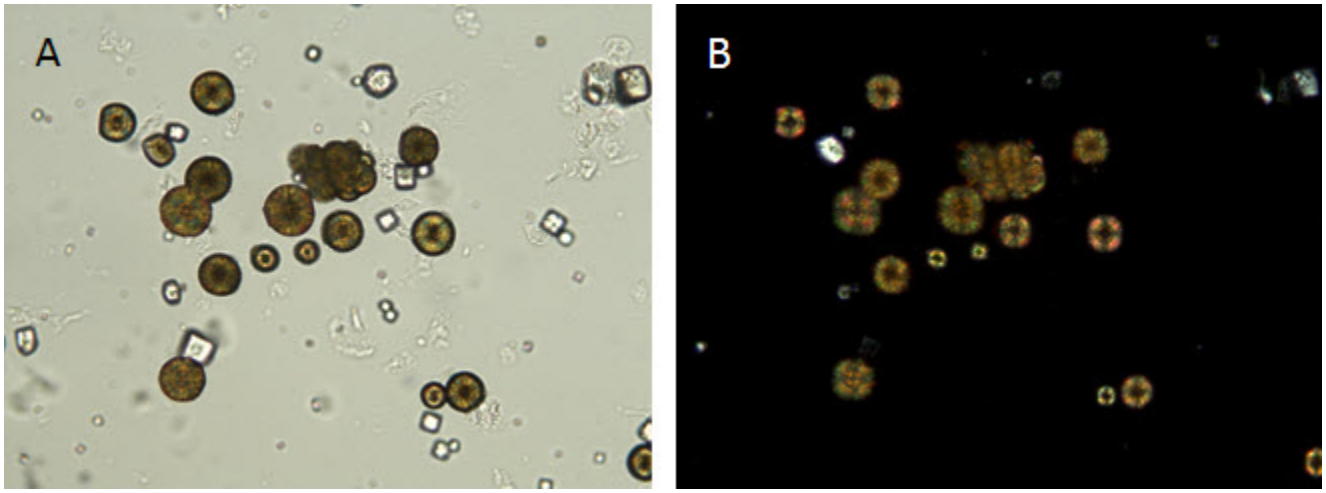



**Figure 1.** Urinary 2,8-dihydroxyadenine (DHA) crystals from an individual with adenine phosphoribosyltransferase deficiency. These crystals have a characteristic appearance and polarization pattern.

A. Conventional light microscopy shows the typical brown DHA crystals. Note the dark outline and central spicules (original magnification x 400).

B. The same field viewed with polarized light microscopy. The smaller crystals appear yellow and have a central Maltese cross pattern (original magnification x 400).

- **A multigene panel** that includes *APRT* and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

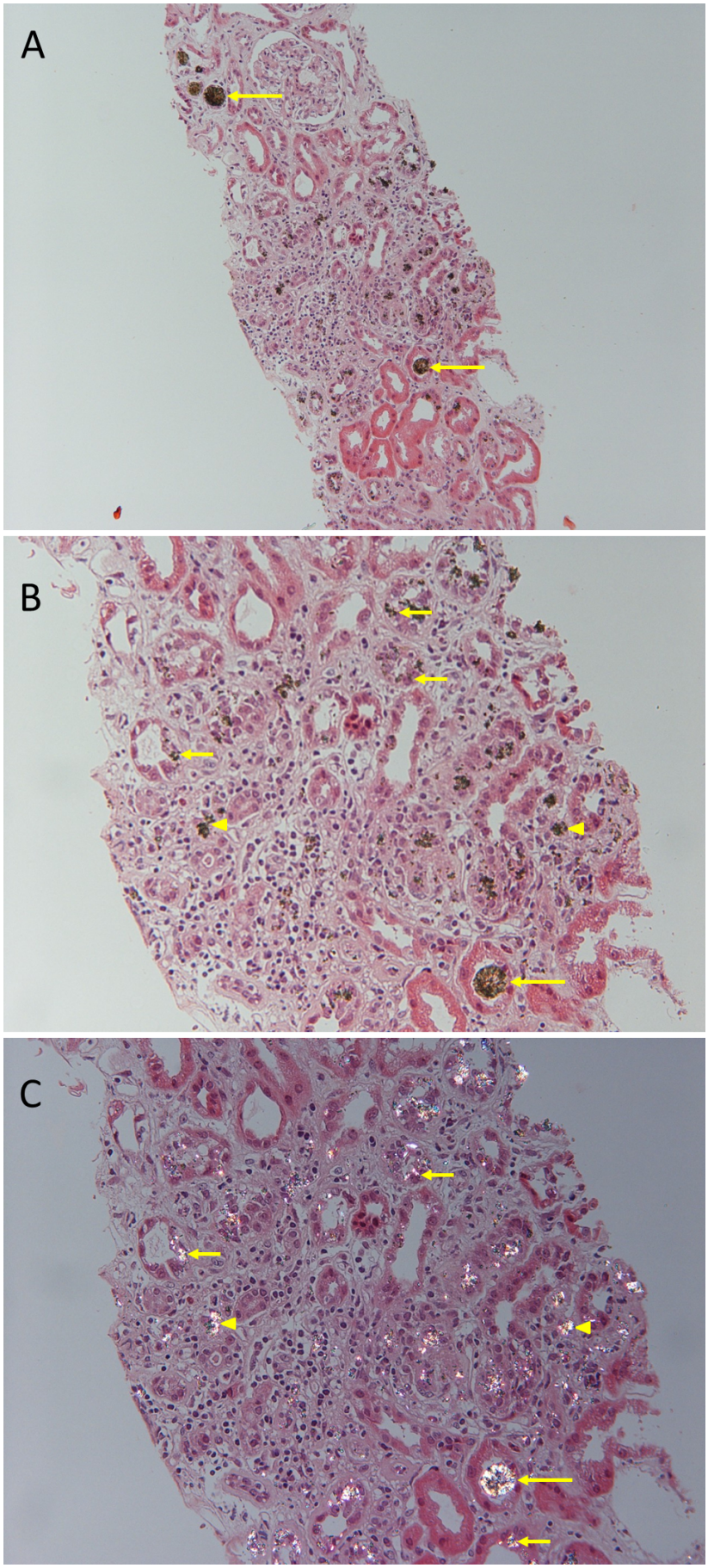


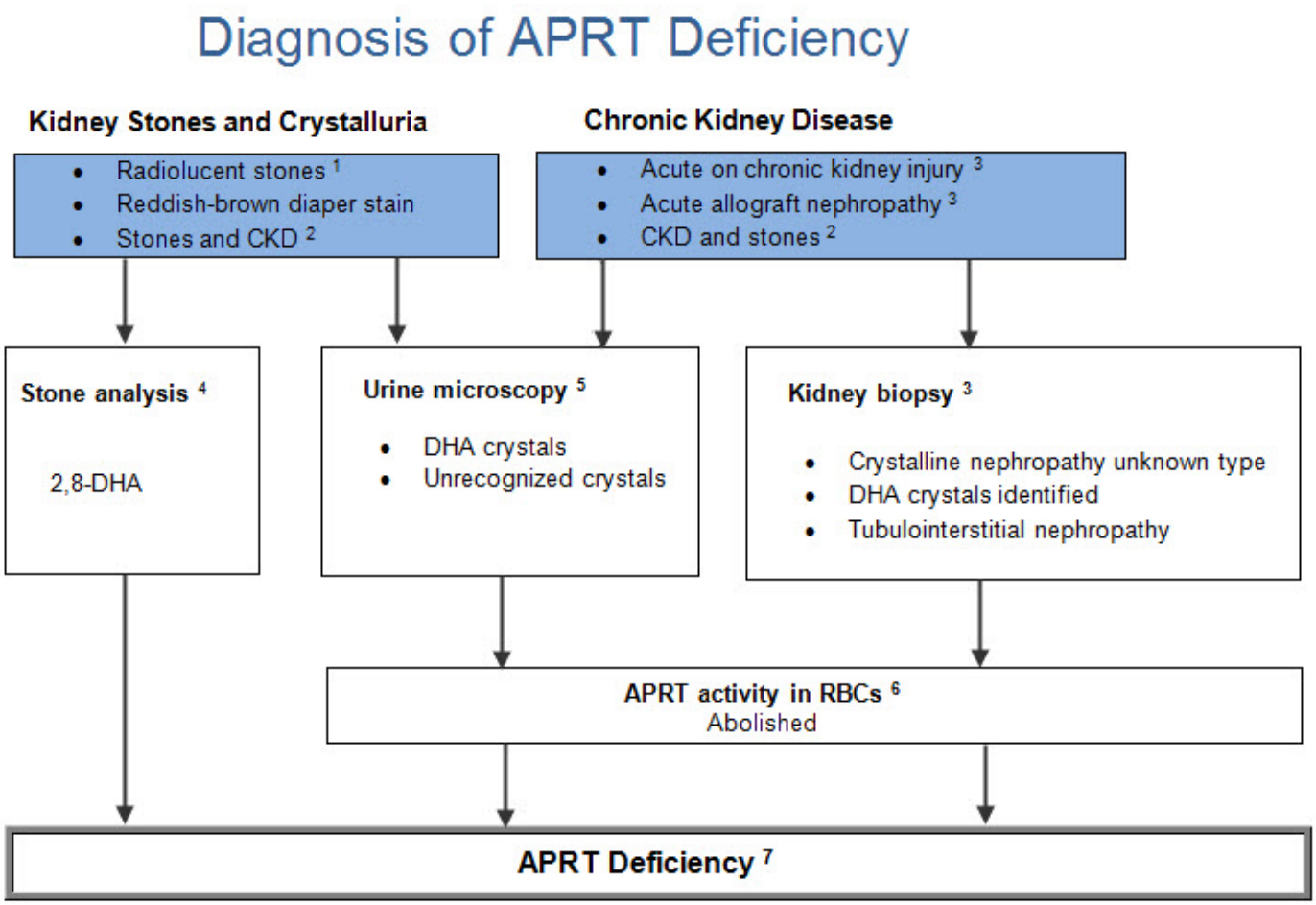

**Figure 2.** Kidney biopsy findings from an individual with adenine phosphoribosyltransferase deficiency and kidney failure due to 2,8-

dihydroxyadenine crystal nephropathy

A. 2,8-dihydroxyadenine crystals are seen within tubular lumens (arrows). Significant tubular atrophy, interstitial inflammation, and fibrosis are present (hematoxylin and eosin stain; original magnification x 100).

B. Higher magnification of the biopsy specimen shown in A. 2,8-dihydroxyadenine crystals are seen within tubular lumens (long arrow), inside tubular epithelial cells (short arrow), and in the interstitium (arrowhead) (hematoxylin and eosin stain; original magnification x 400).

C. The same microscopic field of the kidney biopsy specimen as shown in B viewed with polarized light microscopy. Crystals are seen within a tubular lumen (long arrow), inside tubular epithelial cells (short arrows), and in the interstitium (arrowheads) (hematoxylin and eosin stain; original magnification x 400).




Notes:

1. 2,8-Dihydroxyadeninuria, hyperuricosuria, and xanthinuria should be considered in the differential diagnosis of radiolucent kidney stones.

2. Individuals with radiolucent kidney stones and chronic kidney disease (CKD) should be evaluated for APRT deficiency.

3. Individuals with APRT deficiency may present with acute kidney injury (AKI), CKD or acute allograft nephropathy, even in the absence of a previous history of kidney stones. Kidney biopsy shows a variable degree of tubulointerstitial injury and features consistent with crystal nephropathy.

4. Ultraviolet spectrophotometry and/or x-ray crystallography easily differentiates 2,8-dihydroxyadenine (DHA) from uric acid and xanthine.

5. The pathognomonic round, brown urinary DHA crystals (see Figure 1) are seen in almost all individuals with the disorder. The crystals may, however, be hard to identify in affected individuals with markedly decreased renal function due to reduced crystal clearance.

6. APRT activity in red blood cell lysates ranges from 16-32 nmol/h/mg hemoglobin in healthy individuals; homozygotes and compound heterozygotes have no measurable enzyme activity and in heterozygotes the activity is approximately 25%. Recent blood transfusion may falsely elevate APRT activity.

7. Molecular genetic testing, which confirms the diagnosis when biallelic pathogenic variants in APRT are identified, may not be necessary in individuals with absent APRT activity.

**Figure 3.** Algorithm for diagnostic evaluation of adenine phosphoribosyltransferase (APRT) deficiency and 2,8-dihydroxyadeninuria
From Edvardsson et al [2013]. Used with permission.

**Table 1.** Molecular Genetic Testing Used in Adenine Phosphoribosyltransferase Deficiency

| Gene [1] | Method | Proportion of Probands with a Pathogenic Variant [2] Detectable by Method |
|---|---|---|
| *APRT* | Sequence analysis [3, 4] | ~87% [5] |
| | Gene-targeted deletion/duplication analysis [6] | Rare [7] |

*1.* See Table A. Genes and Databases for chromosome locus and protein.
*2.* See Molecular Genetics for information on allelic variants detected in this gene.
*3.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
*4.* Approximately 50 pathogenic variants have been identified in the coding region of *APRT* in >400 affected individuals from >25 countries, including at least 200 individuals from Japan (see Molecular Genetics).
*5.* DNA sequence analysis of the *APRT* coding region and intron/exon junctions from 31 affected individuals (62 chromosomes) with complete APRT deficiency failed to identify 13% of the mutated alleles [Bollée et al 2010]. It remains to be determined whether pathogenic variants occur outside of the sequenced regions or are due to epigenetic changes.
*6.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
*7.* Rare deletions of both *APRT* and *GALNS*, as well as a complex 254-bp deletion with 8-bp insertion, have been described (see Molecular Genetics).

Note that enzyme activity measurements in cell extracts alone may not be sufficient to determine the functional significance of novel variants (see APRT Enzyme Activity).

# Clinical Characteristics

## Clinical Description

More than 400 individuals with adenine phosphoribosyltransferase (APRT) deficiency have been reported in the medical literature [Bollée et al 2010, Bollée et al 2012, Harambat et al 2012, Balasubramaniam et al 2014, Zaidan et al 2014, Runolfsdottir et al 2016, Huq et al 2018, Runolfsdottir et al 2019a, Runolfsdottir et al 2019b].

**Table 2.** Presenting Renal Manifestations in APRT Deficiency

| Presenting Renal Manifestation | Approximate Frequency |
|---|---|
| Kidney stone disease [1] | 60%-90% |
| Chronic kidney disease [2, 3] | >50% |
| Acute kidney injury [4] | 30% [5] |
| End-stage renal disease | 15% |

*1.* In both children and adults
*2.* In adult life
*3.* Due to DHA crystal nephropathy
*4.* Due to urinary tract obstruction
*5.* Runolfsdottir et al [2016]

**Age at presentation.** APRT deficiency may present at any age; there is no typical age of clinical onset. However, in at least 50% of affected individuals, symptoms do not occur until adulthood.

- The age at diagnosis among individuals in the APRT Deficiency Registry of the Rare Kidney Stone Consortium (RKSC) ranged from six months to 72 years (median age: 37 years) [Runolfsdottir et al 2016].

- Approximately 35% of persons with APRT deficiency are diagnosed before age 18 years.
- In a significant number of asymptomatic individuals, a diagnosis of APRT deficiency has been suggested by the detection of DHA crystals on routine urine microscopy or through the screening of sibs of affected individuals and subsequently confirmed by enzyme activity or genetic testing.

Of note, abdominal ultrasound and CT examinations performed for other reasons may identify kidney stones in individuals with APRT deficiency who may be otherwise asymptomatic [Huq et al 2018].

**Kidney stone disease.** Between 60% and 90% of affected individuals have already developed kidney stones at diagnosis. In the absence of pharmacotherapy (see **Management,** Table 4), the majority of those untreated symptomatic persons experience stone recurrence [Runolfsdottir et al 2019a], abdominal pain, and/or lower urinary tract symptoms (e.g., straining, hesitancy, dribbling, incomplete bladder emptying).

**Chronic kidney disease (CKD)** secondary to DHA crystal nephropathy is present in more than 50% of individuals at diagnosis [Runolfsdottir et al 2016]. As many as 15% of affected individuals have progressed to end-stage renal disease (ESRD) at the time of diagnosis of APRT deficiency [Harambat et al 2012, Runolfsdottir et al 2016].

- In some of these individuals, the diagnosis was not made until after kidney transplantation had been performed.
- The relatively frequent occurrence of advanced CKD and even ESRD at the time of diagnosis is concerning and suggests a lack of familiarity with this easily treatable condition [Runolfsdottir et al 2019a].

**ESRD.** Approximately 20%-25% of affected individuals develop ESRD, usually in adult life, if adequate treatment is not provided.

- Importantly, individuals with APRT deficiency who are diagnosed and treated early with allopurinol or febuxostat have a much more favorable renal outcome [Runolfsdottir et al 2019a] (see **Management**, Table 4).
- Timely diagnosis and institution of pharmacologic therapy appears to reduce stone burden and retard or possibly prevent CKD progression to ESRD, even in severely affected individuals.

APRT deficiency is not known to affect organs other than the kidney; however, the authors and other investigators have encountered occasional individuals with APRT deficiency complaining of eye discomfort [Neetens et al 1986; Author, personal observation], which merits further study.

## Genotype-Phenotype Correlations

No genotype-phenotype correlations have been established; clinical features are known to vary greatly among individuals with the same pathogenic variants [Bollée et al 2010, Runolfsdottir et al 2016].

## Nomenclature

Originally, two types of APRT deficiency with identical clinical manifestations were described, based on the level of residual APRT activity in cell extracts (erythrocyte lysates) [Sahota et al 2001]. However, this distinction is of historical interest only, as APRT enzyme activity in intact cells has been shown to be less than 1% in both types [Kamatani et al 1985] (see APRT Enzyme Activity).

## Prevalence

The estimated heterozygote frequency in different populations ranges from 0.4% to 1.2% [Hidaka et al 1987, Sahota et al 2001], suggesting that the prevalence of a homozygous state is at least 1:50,000 to 1:100,000.

If this holds true, at least 70,000-80,000 individuals should be affected worldwide, of whom 40,000 would be expected to be in Asia, 9,000 in Europe, and 8,000 in the Americas, including at least 3,000 affected individuals in the US alone. Most of these individuals are currently unrecognized, and thus not benefitting from medical therapy.

Evidence suggests that APRT deficiency may be a seriously underrecognized cause of kidney stones and crystal nephropathy, progressing over time to ESRD in a significant proportion of untreated individuals [Zaidan et al 2014].

# Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* have been associated with pathogenic variants in *APRT*.

# Differential Diagnosis

Differential diagnosis of APRT deficiency includes other known causes of radiolucent kidney stones such as uric acid nephrolithiasis (OMIM 605990) and xanthinuria (OMIM PS278300).

The diagnosis of APRT deficiency should be considered in all individuals with chronic kidney disease or kidney failure, particularly in those with renal histopathologic features of crystal nephropathy, even in the absence of a history of nephrolithiasis. Pathologists and physicians must be aware that kidney biopsy findings in persons with APRT deficiency may have a similar appearance to and be confused with those of primary hyperoxaluria type 1, type 2, and type 3 [Bollée et al 2010, Runolfsdottir et al 2016].

# Management

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with adenine phosphoribosyltransferase (APRT) deficiency, the evaluations in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 3.** Recommended Evaluations Following Initial Diagnosis in Individuals with APRT Deficiency

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Renal** | Measurement of serum creatinine (&/or cystatin C) concentration | |
| | Urine screening for DHA crystalluria & albuminuria or proteinuria | |
| | Ultrasound or CT exam of kidneys | To assess kidney stone burden |
| | Consider kidney biopsy. | In persons w/↓ renal function &/or proteinuria |
| **Eyes** | Consider ophthalmologic consultation. | In those w/ocular or vision symptoms |
| **Miscellaneous/ Other** | Consultation w/clinical geneticist &/or genetic counselor | |

DHA = 2,8-dihydroxyadenine

## Treatment of Manifestations

**Table 4.** Targeted Treatment for Prevention/Reduction of Kidney Stones in Individuals with APRT Deficiency

| Goal | Treatment | Dosage | Considerations | Other |
|---|---|---|---|---|
| Reduction of renal DHA excretion [1] | Allopurinol [2, 3, 4] | 5-10 mg/kg/day (max dose: 800 mg/day) either 1x/day or in 2 divided doses | Allopurinol dose should not routinely be reduced in those w/impaired kidney function. | Lifelong therapy w/allopurinol or febuxostat needed for all patients, even after kidney transplantation; allopurinol or febuxostat can improve kidney function, even in those w/ advanced CKD. |
| | Febuxostat [2] | 80 mg/day [5] | May be more efficacious than allopurinol [6]. Febuxostat dose should not routinely be reduced in those w/impaired kidney function. | |
| Reduction of urine DHA supersaturation & crystallization | Ample fluid intake | NA | May provide an adjunctive benefit to pharmacologic therapy | |

CKD = chronic kidney disease; DHA = 2,8-dihydroxyadenine; NA = not applicable
*1.* There are no data to support dietary purine restriction as a treatment of this condition, particularly when treatment with allopurinol or febuxostat is used and urine DHA excretion is already very low.
*2.* Both allopurinol and febuxostat are oxidoreductase inhibitors (XOR; xanthine dehydrogenase/oxidase).
*3.* Generally effective and well tolerated
*4.* Minimizes urinary DHA excretion and crystalluria, stone formation, crystal deposition in the kidney, and development of kidney failure [Bollée et al 2010, Edvardsson et al 2018, Runolfsdottir et al 2019a]
*5.* No data are available on appropriate dosing for pediatric age groups.
*6.* A comparison between allopurinol (400 mg/day) and febuxostat (80 mg/day) on urinary DHA excretion found that febuxostat was significantly more efficacious [Edvardsson et al 2018].

**Table 5.** Treatment of Manifestations in Individuals with APRT Deficiency

| Manifestation/ Concern | Treatment | Consideration/Other |
|---|---|---|
| **DHA kidney stones [1]** | Standard surgical management | Incl extracorporeal shock wave lithotripsy |
| **CKD [2]** | Aggressive management of hypertension | Consider ACE inhibitors or angiotensin-receptor blockers in those w/ proteinuria. |
| | Standard reduction of cardiovascular risk factors | |
| **ESRD [3]** | Dialysis | It is not known if patients on dialysis benefit from allopurinol &/or febuxostat therapy, unless a kidney transplant is planned. |
| | Kidney transplant | In all patients: treatment w/allopurinol or febuxostat for ≥6 wks prior to transplantation, if possible [4]. Lifelong therapy w/allopurinol or febuxostat post transplantation is required to prevent recurrent DHA crystal nephropathy in transplanted organ. |

ACE = angiotensin-converting enzyme; CKD = chronic kidney disease; DHA = 2,8-dihydroxyadenine; ESRD = end-stage renal disease
*1.* For prevention of new kidney stone formation, see Table 4.
*2.* Including measures to relieve symptoms, control complications, and slow the progression of the disease (See the KDIGO CKD guideline.)
*3.* Management of APRT deficiency in those with ESRD
*4.* Author, unpublished observation

## Prevention of Primary Manifestations

Adequate treatment of APRT deficiency with allopurinol or febuxostat prevents kidney stone formation and the development of CKD in most, if not all, individuals with the disorder [Edvardsson et al 2001, Bollée et al 2010, Harambat et al 2012] (see Table 4).

## Surveillance

No consensus surveillance guidelines have been established.

**Table 6.** Recommended Surveillance for Individuals with APRT Deficiency

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Renal** | Measurement of eGFR derived from serum creatinine &/or serum cystatin C | Every 6-12 mos or as clinically indicated |
| | Urine microscopy for assessment of DHA crystalluria [1, 2, 3] if direct DHA measurements not available [4] | |
| | Renal ultrasound [5] | Periodically |
| **Other** | Assess medication compliance. | At least annually |

eGFR = estimated glomerular filtration rate
*1.* Using first morning void urine specimen, if possible
*2.* In those receiving pharmacotherapy
*3.* Although not optimal, the absence of DHA crystals on urine microscopy can be considered indicative of adequate treatment. A highly significant correlation between 24-hour urinary DHA excretion and DHA crystalluria has been observed [Runolfsdottir et al 2019b].
*4.* See Therapies and Assays Under Investigation for information about the UPLC-MS/MS assay for therapeutic monitoring [Thorsteinsdottir et al 2016, Edvardsson et al 2018].
*5.* To evaluate for new, asymptomatic kidney stones

## Agents/Circumstances to Avoid

Azathioprine and mercaptopurine should be avoided by individuals taking XOR inhibitors (allopurinol or febuxostat). Inhibition of xanthine oxidase may cause increased plasma concentrations of azathioprine or mercaptopurine, leading to toxicity.

## Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures. Approximately 15% of individuals with APRT deficiency may be asymptomatic [Bollée et al 2010, Runolfsdottir et al 2016]; these individuals are usually identified during family screening.

Evaluations can include the following:

- Molecular genetic testing if the pathogenic variants in the family are known. Further investigations, including assessment of renal function and urinalysis, are warranted in individuals with biallelic pathogenic variants.
- APRT enzyme activity measurements, particularly if the pathogenic variants in the family are not known

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

The safety of allopurinol and febuxostat in human pregnancy has not been systematically studied.

Animal studies using high doses of allopurinol have revealed evidence of adverse fetal effects in mice but not in rabbits or rats; it is not clear if these effects are a result of direct fetal toxicity or maternal toxicity. Thus, allopurinol should only be prescribed during pregnancy when the benefit of treatment is believed to outweigh the risk. Treatment with allopurinol during pregnancy should be considered in women with APRT deficiency who have CKD with reduced glomerular filtration rate (GFR) or who have undergone kidney transplantation.

Animal studies using high doses of febuxostat in rats and rabbits have not supported a teratogenic effect. However, very high doses in pregnant rats have been associated with neonatal loss and low pup birthweight.

Some post-transplantation immunosuppressive therapies can also have adverse effects on the developing fetus.

A thorough discussion of the risks and benefits of maternal medication use during pregnancy should ideally take place with an appropriate health care provider prior to conception.

See MotherToBaby for further information on medication use during pregnancy.

## Therapies and Assays Under Investigation

**Urinary DHA measurements.** The authors' group has recently developed a urinary DHA assay using ultra-high-performance liquid chromatography – tandem mass spectrometry (UPLC-MS/MS) [Thorsteinsdottir et al 2016], which is expected to facilitate both the clinical diagnosis and monitoring of pharmacotherapy of individuals with APRT deficiency [Edvardsson et al 2018]. Further clinical studies to examine the sensitivity and specificity of the assay are currently under way.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

# Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

## Mode of Inheritance

Adenine phosphoribosyltransferase (APRT) deficiency is inherited in an autosomal recessive manner.

## Risk to Family Members

**Parents of a proband**

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *APRT* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic. Urine microscopy does not reveal DHA crystals and they are not at risk of developing the disorder.

**Sibs of a proband**

- At conception, each sib of an affected individual has a 25% chance of inheriting two *APRT* pathogenic variants, a 50% chance of inheriting one pathogenic variant and being an asymptomatic carrier, and a 25% chance of inheriting two benign alleles.
- As many as 15%-20% of individuals who have inherited two *APRT* pathogenic variants may be asymptomatic despite their abnormal urinary DHA excretion [Edvardsson et al 2001, Bollée et al 2010]. Such individuals are usually identified during family screening.
- Heterozygotes (carriers) are asymptomatic. Urine microscopy does not reveal DHA crystals and they are not at risk of developing the disorder.

**Offspring of a proband.** Unless an individual with APRT deficiency has children with an affected individual or a carrier, his/her offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *APRT*.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of an *APRT* pathogenic variant.

## Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *APRT* pathogenic variants in the family.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

**Testing of at-risk asymptomatic sibs** of individuals with APRT deficiency is possible after molecular genetic testing has identified the specific pathogenic variants in the family. Because an effective treatment is available, this testing is appropriate to consider for at-risk sibs regardless of age. However, such testing should be performed in the context of formal genetic counseling, and is not useful in predicting age at symptom onset, type and severity of symptoms, or rate of progression in asymptomatic individuals.

**Family planning**

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling – including discussion of potential risks to offspring, the availability of effective, preventive drug treatment (see Table 4 and Prevention of Primary Manifestations), and reproductive options – to young adults who are affected, are carriers, or are at risk of being carriers.

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

## Prenatal Testing and Preimplantation Genetic Testing

Once the *APRT* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for APRT deficiency are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

# Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **APRT Deficiency Support Network**
  www.rarekidneystones.org/dha/
- **APRT Deficiency Registry of the Rare Kidney Stone Consortium**
  Landspitali - The National University Hospital of Iceland
  Iceland
  **Phone:** 00-354-543-1000
  **Fax:** 00-354-543-3021
  **Email:** rarekidneystones@landspitali.is
  APRT Deficiency Registry

# Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** Adenine Phosphoribosyltransferase Deficiency: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *APRT* | 16q24.3 | Adenine phosphoribosyltransferase | APRT database | APRT | APRT |

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

**Table B.** OMIM Entries for Adenine Phosphoribosyltransferase Deficiency (View All in OMIM)

| | |
|---|---|
| 102600 | ADENINE PHOSPHORIBOSYLTRANSFERASE; APRT |
| 614723 | ADENINE PHOSPHORIBOSYLTRANSFERASE DEFICIENCY; APRTD |

## Molecular Pathogenesis

*APRT* is a five-exon gene with a coding region of 540 bp. *APRT* encodes APRT, a cytoplasmic enzyme that catalyzes the $Mg^{++}$-dependent synthesis of 5'-adenosine monophosphate from adenine and 5-phosphoribosyl-1-pyrophosphate (PRPP) [Sahota et al 2001]. The enzyme is a homodimer [Sahota et al 2001].

The crystal structure of recombinant human APRT in complex with adenosine monophosphate (AMP) has been determined [Silva et al 2004]. The protein, which comprises nine β-strands and six α-helices, forms three domains:

- A core that includes the PRPP-binding motif
- A flexible loop besides the core region which may be involved in the catalytic function
- A variable region primarily involved in base recognition

**Mechanism of disease causation.** APRT deficiency occurs through a loss-of-function mechanism. APRT activity in red cell lysates from individuals with APRT deficiency is typically less than 1% of control values [Sahota et al 2001]. The two reported exceptions are noted in Table 7 [Deng et al 2001].

More than 50 pathogenic variants have been identified in the coding region of *APRT* in over 300 affected individuals from more than 25 countries, including at least 200 individuals from Japan.

Rarely, large deletions of both *APRT* and *GALNS*, pathogenic variants in which cause mucopolysaccharidosis type IVA, have been reported [Fukuda et al 1996, Wang et al 1999]. Of note, a complex deletion of 254 base pairs with insertion of eight base pairs has also been reported (see Table 7).

**Table 7.** APRT Deficiency: Notable *APRT* Pathogenic Variants

| Reference Sequences | DNA Nucleotide Change (Alias [1]) | Predicted Protein Change (Alias [1]) | Comment [Reference] |
|---|---|---|---|
| NM_000485.2<br>NP_000476.1 | c.294G>A<br>(1450G>A) | p.Trp98Ter | The most common pathogenic variants in affected Japanese persons; p.Met136Thr [Sahota et al 2001] has decreased affinity for the co-substrate PRPP. |
| NM_000485.2 | c.258_261dupCCGA<br>(1415_1418insCCGA) | | |
| NM_000485.2<br>NP_000476.1 | c.407T>C<br>(2066T>C) | p.Met136Thr | |
| | c.194A>T<br>(1350A>T) | p.Asp65Val | Common pathogenic variant in affected persons from Iceland, Britain, & Spain |
| | c.400+2dupT<br>(400+2insT)<br>(IVS4+2insT) | p.Ala108GlufsTer3<br>(Arg87PfsTer23) | Common pathogenic variant in European populations |
| | c.448G>T<br>(2107G>T) | p.Val150Phe | Identified compound heterozygous w/c.400+2dupT in a person of northern European heritage who had considerable residual enzyme activity in cell extracts [Deng et al 2001] |
| NM_000485.2 | del254 bp, insTTCCCGTA | | Reported in 2 families: 1 from Austria and 1 from Italy [Menardi et al 1997, Di Pietro et al 2007] |

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
*1.* Variant designation that does not conform to current naming conventions

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## Consensus Statements / Published Guidelines

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# Chapter Notes

## Author Notes

**Vidar Orn Edvardsson, MD**
Children's Medical Center, Office 21-D
Landspítali –The National University Hospital of Iceland
Hringbraut, 101 Reykjavik, Iceland
Tel: +354-543-1000; Fax: + 354-543-3021
Email: vidare@landspitali.is and rarekidneystones@landspitali.is

**Amrik Sahota, PhD, Consultant**
**APRT Deficiency Research Program**
Department of Genetics
Life Sciences Building
Rutgers University
145 Bevier Road
Piscataway, NJ 08854, USA
Tel: 732-445-7185; Fax: 732-445-1147
Email: sahota@biology.rutgers.edu

**Runolfur Palsson, MD**
Division of Nephrology, Office 14-F
Landspítali – The National University Hospital of Iceland
Hringbraut, 101 Reykjavik, Iceland
Tel: +354-543-1000; Fax: + 354-543-6467
Email: runolfur@landspitali.is and rarekidneystones@landspitali.is

The official website of the Rare Kidney Stone Consortium: rarekidneystones.org

The APRT Deficiency Research Program at Landspítali – The National University Hospital of Iceland, headed by Drs Vidar Orn Edvardsson and Runolfur Palsson, is part of the international Rare Kidney Stone Consortium (RKSC) (rarekidneystones.org) founded in 2009 with support from the National Institute of Diabetes and Digestive and Kidney Diseases and the Office of Rare Diseases Research at the US National Institutes of Health.

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