

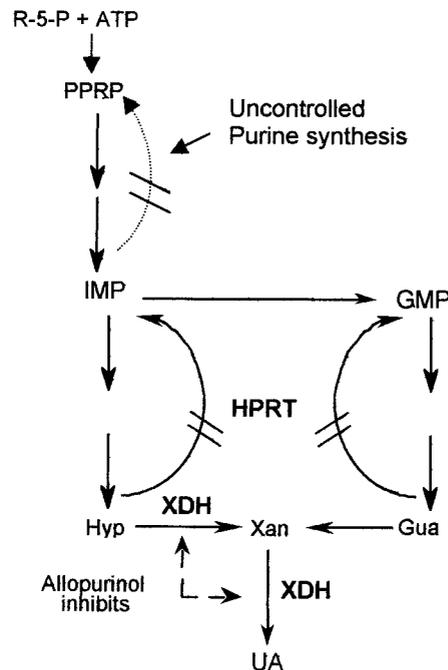
# Partial Hypoxanthine-Guanine Phosphoribosyltransferase Deficiency as the Unsuspected Cause of Renal Disease Spanning Three Generations: A Cautionary Tale

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**ABSTRACT.** Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency is an X-linked defect of purine metabolism. Clinical manifestations are usually related to the degree of enzyme deficiency: complete HPRT deficiency (Lesch-Nyhan syndrome) presenting with severe neurologic or renal symptoms, or partial HPRT deficiency (Kelley-Seegmiller syndrome) manifesting as a gout-urolithiasis syndrome. A 3-generation kindred is described in which the recognition of partial HPRT deficiency in 2 adolescent male siblings presenting with uric acid lithiasis led to the diagnosis in 2 maternal uncles already in renal failure of unknown cause. This report highlights the importance of clinical awareness leading to early diagnosis, appropriate diagnostic methodology, and therapy of a treatable inherited disorder of purine metabolism for the prevention of renal failure. *Pediatrics* 2002;109(1). URL: <http://www.pediatrics.org/cgi/content/full/109/1/e17>; *hypoxanthine-guanine phosphoribosyltransferase deficiency, renal failure*.

**ABBREVIATIONS.** HPRT, hypoxanthine-guanine phosphoribosyltransferase; LND, Lesch-Nyhan disease.

**H**ypoxanthine-guanine phosphoribosyltransferase (HPRT, EC 2.4.3.8) is an ubiquitous, cytoplasmic, housekeeping enzyme with highest activity in the brain and testes. HPRT catalyzes the transfer of the phosphoribosyl moiety of PP-ribose-P to hypoxanthine and guanine, forming inosine monophosphate and guanosine monophosphate, respectively. Inability to recycle hypoxanthine and guanine produces a lack of feedback control of synthesis accompanied by rapid catabolism of these bases to uric acid (Fig 1).<sup>1-3</sup> HPRT deficiency (McKusick #308000) is an X-linked defect (Xq26-q27.2) of purine metabolism with considerable genetic and clinical heterogeneity, the biochemical hallmark be-



**Fig 1.** Pathways for the de novo synthesis, breakdown and salvage of purine ribonucleotides. XDH = xanthine dehydrogenase; HPRT = hypoxanthine-guanine phosphoribosyltransferase; PRPP = phosphoribosylpyrophosphate. Pathologic metabolites (Hyp = hypoxanthine, Xan = xanthine) used as specific markers in differential diagnosis are shown as is the importance of functional HPRT in nucleotide feedback control of synthesis (defective in HPRT deficiency). Gua = guanine, UA = uric acid.

ing increased levels of uric acid in blood and urine.<sup>1-6</sup> Clinical manifestations are related to the degree of enzyme deficiency, complete HPRT deficiency (Lesch-Nyhan disease; LND) presenting with severe neurologic (compulsive self-injury biting, choreoathetosis), gout, and renal symptoms (kidney stones, renal failure).<sup>1-4</sup> Partial HPRT deficiency (Kelley-Seegmiller syndrome) has a broad spectrum of presentation ranging from gout and urolithiasis only, to intermediate forms characterized according to the severity of neurologic involvement.<sup>1-6</sup> Prognosis in terms of renal complications in the partial defect depends on early diagnosis. Prenatal diagnosis is possible in LND by direct enzyme assay in a chorionic villous sample, or by molecular analysis where the mutation is well-defined.<sup>1-4</sup>

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We describe a 3-generation kindred in which the diagnosis of partial HPRT deficiency in 2 adolescent male siblings presenting with urolithiasis led to the diagnosis in a maternal brother and uncle categorized as having familial renal failure of unknown cause. The objective of this report is to stress 1) the importance of clinical awareness and careful family history-taking for early diagnosis of metabolic disease; 2) the use of appropriate diagnostic methodology; and 3) early therapy of partial HPRT deficiency for the prevention of renal failure, an avoidable complication that unrecognized is costly, both to the family and to local health services.

### CASE REPORTS

The index patients (IV.1 and IV.2, Fig 2) were 2 adolescent male siblings aged 15 and 14 years, respectively, who were referred to our laboratory because of repeated episodes of renal colic and nephrolithiasis. The referral mentioned that despite the presence of hyperuricemia, urinary uric acid levels were normal to low.

Detailed history-taking revealed a positive family history of nephrolithiasis and renal failure involving a maternal brother (III.1) and uncle (II.1). The mother's brother, now aged 34 years, had suffered from renal colic and urolithiasis from the age of 20. One kidney is 20% functional. The maternal uncle, aged 65, developed renal failure at an early age, has hyperuricemia, and is now a candidate for dialysis.

Clinical examination in both siblings was normal (no signs of central nervous system involvement), but renal ultrasound revealed the presence of stones in the kidneys of both. Renal echostucture was otherwise normal, and there were no signs of hydronephrosis. Chemical and UV analysis of kidney stones of the siblings revealed uric acid. Measurement of uric acid and creatinine in 24-hour urine (after warming at 56°C) and blood drawn at the completion of the 24-hour collection revealed hyperuricemia and hyperuricosuria with an increased ratio of uric acid/creatinine. The high levels of uric acid in both plasma and urine and uric acid nephrolithiasis in male siblings, together with the similar clinical history in 2 maternal male relatives (brother/uncle), suggested an X-linked inherited defect. For this reason, purine metabolites were measured in urine and plasma, and enzymes in erythrocytes of the 2 patients, their 2 healthy siblings, and their parents. Samples were also obtained from the 2 uncles (blood only from II.1). Detailed metabolic studies, including analysis of purine

metabolites and HPRT activity, were performed as described previously. Samples were processed using anion exchange and reversed-phase, high-performance liquid chromatography systems.<sup>7</sup>

### RESULTS

The results of the purine metabolic studies in the 2 affected male adolescents, their siblings, parents, and uncles, are shown in Tables 1 and 2. The very raised plasma uric acid concentration, the increased uric acid/creatinine ratio (Table 1), the increased erythrocyte nicotinamide adenine dinucleotide, and presence of 5-amino-4-imidazole carboxamide, ribotide triphosphate (indicative of purine overproduction) apparent in the red cell nucleotide profile in Table 2, coupled with the low red cell lysate HPRT activity (Table 1) in the 2 siblings, their uncle, and great uncle, were all consistent with partial HPRT deficiency. This diagnosis was confirmed by the studies of [<sup>14</sup>C] hypoxanthine incorporation by intact red blood cells of the 4 affected males depicted in Table 1. Importantly, hypoxanthine salvage by the intact red cells was extremely high (range: 66%–97%; control: 90%–100%) indicating functional HPRT activity consistent with the lack of neurologic involvement in the affected members of this kindred. Purine metabolic studies conducted in the remaining 2 siblings of the index patients and their parents were normal.

### Therapy of the Index Cases

Elevated uric acid concentrations in HPRT deficiency may be controlled by a high fluid intake, alkali administration, a low purine diet, and allopurinol used with care (5–7.5 mg/kg/day). For this reason, allopurinol (with alkali) was administered to the 2 siblings (IV.1 and IV.2) in incremental doses until plasma uric acid levels had decreased to tolerably high normal levels. Results of monitoring of allopurinol dosage and effect on purine end products are shown in Table 3. Urine purines were monitored at

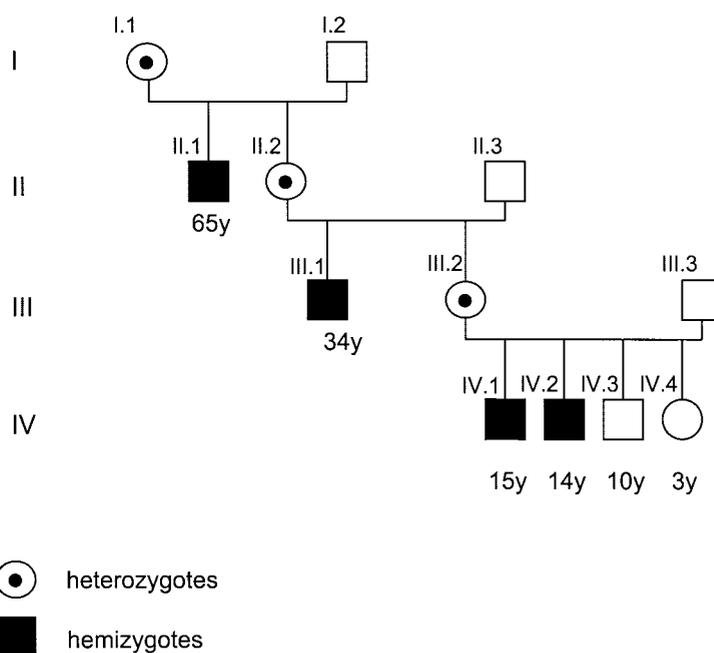


Fig 2. Pedigree of HPRT kindred.

**TABLE 1.** Results of Purine Metabolic Studies in HPRT Kindred

Patient	Age (Years)	Plasma Uric Acid mg/dL ( $\mu\text{mol/L}$ )	Urinary Uric Acid mg/24 Hours (mmol/24 Hours)	UA/Cr Ratio	Enzymes (nmol/mg/Hb/Hour)		
					Lysed RBC		*[ <sup>14</sup> C] Hyp Intact RBC
					HPRT	APRT	
IV-1	15	11.7 (695)	2330 (13.86)	0.81	4.6	34	66%
IV-2	14	8.4 (499)	2068 (12.3)	0.89	4.4	36	73%
III-1	34	4.0 (236)	1391 (8.28)	0.83	3.7	35	97%
II-1	65	8.3 (577)	ND	ND	5.3	23	91%
IV-3	10	4.7 (278)	597 (3.55)	0.46	131	27	
IV-4	3	ND	ND	ND	100	28	
III-2	38	ND	ND	ND	114	30	
III-3	41	ND	ND	ND	117	35	
Control range					80–130	16–32	90–100%
Females	3.7 $\pm$ 0.7 (222 $\pm$ 42)	454 $\pm$ 84 (2.7 $\pm$ 0.5)					
Males	4.4 $\pm$ 0.7 (261 $\pm$ 41)	504 $\pm$ 84 (3.0 $\pm$ 0.5)					

\* [<sup>14</sup>C] hypoxanthine incorporation into intact red blood cells.

UA/Cr indicates uric acid/creatinine; APRT, adenine phosphoribosyltransferase; ND, not done.

**TABLE 2.** Red Cell Nucleotide Profile in HPRT Kindred

Patient	Age (Years)	Nucleotides ( $\mu\text{mol/L}$ )											
		ATP	ADP	AMP	GTP	GDP	GMP	IMP	NAD	NADP	UDPG	ZTP	OR
IV-1	15	1530	228	16	38	15	—	—	155	58	50	22	
IV-2	14	1024	209	28	33	14	—	—	97	47	53	16	
III-1	34	1341	196	21	41	12	—	—	121	35	135	16	
II-1	65	1595	114	15	54	10	—	—	123	48	83		176
IV-3	10	1196	244	38	41	15	—	—	87	54	25		
IV-4	3	1268	268	51	36	14	—	—	95	50	48		
III-2	38	983	192	27	34	15	—	—	70	49	54		
III-3	41	1103	233	30	35	14	—	—	64	48	60		
Mean*		1570	137	13	66	17	—	—	69	54	35	—	—
$\pm$		97	34	4	10	3	—	—	15	12	8	a	b c

ATP indicates adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; GTP, guanosine triphosphate; GDP, guanosine diphosphate; GMP, guanosine monophosphate; IMP, inosine monophosphate; NAD, nicotinamide adenine dinucleotide; UDPG, uridine diphosphoglucose; ZTP, 5-amino-4-imidazole-carboxamide, ribotide triphosphate; OR, orotidine.

\* Of control range, (—) normally undetectable, (a,b,c) increased levels of components not normally present.

**TABLE 3.** Monitoring of Allopurinol Dosage and Effect on Purine Endproducts in Index Patients

	Patient IV-1 mg (mmol)	Patient IV-2 mg (mmol)
Urine		
Creatinine mg/24 h (mmol/24 h)	162.5 (14.3)	84.0 (7.4)
Endogenous purines mg/24 h (mmol/24 h)		
Uric acid	1250 (7.45)	887 (5.28)
Xanthine	359 (2.36)	260 (1.71)
Hypoxanthine	449 (3.30)	292 (2.15)
Total	(13.11)	(9.14)
Ratio total oxipurine/creatinine mmol/mmol	0.92	1.22
Drug metabolites		
Oxipurinol	90 (0.59)	39 (0.26)
Allopurinol	23 (0.17)	46 (0.34)
Allopurinol riboside	—	—
Total	113 (0.76)	40 (0.29)
Dose (%)	69% (dose 150 mg/d)	20% (dose 200 mg/d)

each increment of dosage to ensure the avoidance of xanthine uropathy, because of the fact that xanthine, unlike uric acid, is very insoluble at any pH.<sup>2,8,11</sup> The maintenance dose of allopurinol in the older sibling is 150 mg/day. Dosage in the younger sibling (IV.2) was increased to 200 mg/d because of persistently high uric acid levels in both plasma and urine. Laboratory results after the increase in dosage showed uric acid and xanthine concentrations within reported solubility limits and an acceptable ratio of uric acid to hypoxanthine and xanthine. Renal ultra-

sound repeated a year after diagnosis was normal in both siblings.

## DISCUSSION

The favorable response to therapy, after the recognition of HPRT deficiency as the basis for the urolithiasis in 2 male siblings, contrasts sharply with the unfavorable outcome in their 2 uncles already in kidney failure. This underlines the importance of early diagnosis and therapy for the prognosis of partial HPRT deficiency. Lack of awareness of this

disorder in many parts of mainland Europe is attributable to the fact that inherited defects of purine metabolism are relatively new diseases, the majority being discovered during the last 25 years. HPRT deficiency seems to be one of the most common enzyme defects of nucleotide metabolism among the 27 now described. This lack of awareness explains why it took so long for the diagnosis to be made in the uncles. Moreover, the elder, now 65, would have been 32 at the time the partial defect was first described by Kelly et al<sup>5</sup> in 1967, when presumably renal function would already have been compromised. The development of renal disease in his nephew, as in our patients with underexcreting familial gout and renal disease<sup>2,3</sup> (familial juvenile hyperuricemic nephropathy), would likewise have been attributed to familial renal disease of unknown cause.

An additional diagnostic problem in the 2 siblings was that the initial measurements of urine uric acid were misleading (and delayed the diagnosis) because falsely low values of urinary uric acid were found. Simply measuring uric acid in urine (as is usual in routine laboratories) without previous warming and thorough mixing of the entire 24-hour collection at 56°C can produce falsely low values because of uric acid precipitation postexcretion—especially if the pH is acidic.<sup>3,7,9,11,12</sup> Low urine uric acid results can also be attributable to the presence of acute renal failure, as already indicated. Equally important is the fact that normal uric acid status is age-dependent, and uric acid excretion varies throughout the day, which underlines the need to assess both plasma and 24-hour urine concentrations. The increased fractional clearance in childhood can also lead to normal plasma uric acid levels.<sup>2,3,9–11</sup> At the same time, it enhances the risk of renal failure, especially during intermittent periods of dehydration, diarrhea, or infection). Some LND patients have been institutionalized for cerebral palsy of unknown cause because only plasma uric acid was measured.<sup>4</sup> Analysis of the urine stones of our patients provided additional clues to diagnosis. Uric acid stones may be the only manifestation in some patients.<sup>2</sup> An essential factor in establishing prognosis, as well as diagnosis, is the assay of HPRT activity in intact as well as lysed cells. Because HPRT is undetectable in the majority of deficient patients, whether partial or LND, intact cell studies, in this case erythrocytes, are essential to detect functional residual activity and confirm the milder phenotype.<sup>4,7</sup>

The lessons from this report are first, that increased levels of uric acid in both plasma and urine characterize all defects of purine metabolism associated with gross purine overproduction and should be followed up by a full metabolic work-up (available in special laboratories). This entails measurement of purine metabolites in body fluids as well as enzyme assays in lysed and intact cells.<sup>2–12</sup> In addition, clinicians should be aware of the pitfalls involved when assessing uric acid status and the fact that in acute renal failure attributable to uric acid

nephropathy in HPRT deficiency, only the plasma, not the urine uric acid, may be grossly elevated.<sup>2,3,11</sup>

Second, the family history was particularly relevant in that 2 maternal uncles had a similar history suggesting an X-linked disorder. However, it is also important to be aware that although HPRT deficiency-affected patients are predominantly male (and female carriers are usually asymptomatic), HPRT deficiency has been described in a few females.<sup>1,2,13,14</sup> Thus, HPRT deficiency should be included in the differential diagnosis of genetic causes of hyperuricemia in girls together with phosphoribosylpyrophosphate synthase overactivity and familial juvenile hyperuricemic nephropathy.

To our knowledge, these 4 patients are the first diagnosed cases with partial HPRT deficiency in Greece. Their recognition is the direct result of efforts made by clinicians to increase awareness of these disorders in Europe within the structure of the European Council Program of the European Structure for the Research and Diagnosis of Inborn Errors of Purine and Pyrimidine Metabolism.

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