HPRT-related hyperuricemia with a novel p.V35M mutation in *HPRT1* presenting familial juvenile gout

Eikan Mishima¹ · Takayasu Mori³ · Yoko Nakajima⁴ · Takafumi Toyohara¹ · Koichi Kikuchi¹ · Yoshitsugu Oikawa² · Tetsuro Matsuhashi² · Yasuhiro Maeda⁵ · Takehiro Suzuki¹ · Masataka Kudo⁶ · Sadayoshi Ito⁷ · Eisei Sohara³ · Shinichi Uchida³ · Takaaki Abe^{1,8,9}

Received: 28 December 2019 / Accepted: 20 February 2020 / Published online: 3 March 2020
© Japanese Society of Nephrology 2020

Abstract

Unlike complete deficiency of hypoxanthine phosphoribosyltransferase (HPRT) (i.e., Lesch–Nyhan syndrome), partial HPRT deficiency causes HPRT-related hyperuricemia without neurological symptoms. Herein, we describe a 22-year-old man without neurological symptoms that presented gout, hyperuricemia (serum urate level, 12.2 mg/dL), multiple renal microcalculi, and a family history of juvenile gout that was exhibited by his brother and grandfather. Genetic testing revealed a novel missense mutation, c.103G>A (p.V35M), in the *HPRT1* gene, and biochemical testing (conducted using the patient's erythrocytes) showed that the patient retained only 12.4% HPRT enzymatic activity compared to that exhibited by a healthy control subject. We thus diagnosed the patient with HPRT-related hyperuricemia caused by partial HPRT deficiency. After his serum urate level was controlled via treatment with febuxostat, his gout did not recur. Thus, this study emphasizes that HPRT deficiency should be considered as a potential cause of familial juvenile gout, even in the absence of neurological symptoms.

Keywords Hyperuricemia · HPRT · Lesch–Nyhan syndrome · Familial gout · Uric acid · Febuxostat

Introduction

Hypoxanthine phosphoribosyltransferase (HPRT), which is encoded by the *HPRT1* gene, is a transferase that catalyzes the conversion of hypoxanthine to inosine monophosphate, and guanine to guanosine monophosphate. Since it plays a central role in the generation of purine nucleotides via

the purine-salvage pathway, *HPRT1* mutations cause a large clinical spectrum of X-linked disorders of purine metabolism [1]. For example, complete HPRT deficiency causes Lesch–Nyhan syndrome (OMIM #300322), which is characterized by neurological and behavioral abnormalities including self-injury, and the overproduction of uric acid, leading to hyperuricemia, gout, and urolithiasis [1]. Patients with partial HPRT enzyme function exhibit milder symptoms, including HPRT-related neurological dysfunction that presents with various degrees of neurological involvement but

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s13730-020-00459-9>) contains supplementary material, which is available to authorized users.

✉ Eikan Mishima
eikan@med.tohoku.ac.jp

✉ Takaaki Abe
takaabe@med.tohoku.ac.jp

¹ Division of Nephrology, Endocrinology, and Vascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

² Division of Pediatrics, Tohoku University Graduate School of Medicine, Sendai, Japan

³ Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

⁴ Department of Pediatrics, Fujita Health University School of Medicine, Toyoake, Japan

⁵ Center for Joint Research Facilities Support, Fujita Health University School of Medicine, Toyoake, Japan

⁶ Osaki Citizen Hospital, Osaki, Japan

⁷ Department of Medicine, Katta General Public Hospital, Shiroishi, Japan

⁸ Division of Medical Science, Tohoku University Graduate School of Biomedical Engineering, Sendai, Japan

⁹ Department of Clinical Biology and Hormonal Regulation, Tohoku University Graduate School of Medicine, Sendai, Japan

no self-injurious behaviors, and HPRT-related hyperuricemia that presents only symptoms secondary to hyperuricemia, but no neurological symptoms [2].

Herein, we report a case of HPRT-related hyperuricemia presenting familial juvenile gout without neurological symptoms. The patient was found to harbor a novel *HPRT1*

missense mutation, and partial HPRT deficiency was confirmed via biochemical analyses.

Case report

A 22-year-old man was referred to our department for the evaluation of juvenile hyperuricemia. From the age of 18, he experienced several episodes of acute pain and swelling in the foot joint. At the age of 22, he presented joint pain with swelling in his right knee, which was diagnosed as a gout attack by a finding of hyperuricemia, and by the presence of uric-acid crystals in the punctured joint fluid. He did not exhibit mental retardation, neurological symptoms, nor obesity (body mass index, 20), and reported no habitual alcohol consumption. Laboratory tests revealed hyperuricemia (serum urate level, 12.2 mg/dL) and mild renal dysfunction [serum creatinine, 0.99 mg/dL; estimated glomerular filtration rate (eGFR), 83 mL/min/1.73 m²] (Table 1). The conducted computed tomography (CT) scan and echography detected numerous microcalculi in both renal medullae (Fig. 1a, b).

Notably, the patient's brother and grandfather also reported repetitive gout attack episodes that began in late adolescence (Fig. 1c); however, no family members reported neurological symptoms nor end-stage kidney disease. This family history of juvenile gout was highly suggestive of genetic disease with urate metabolism disorder.

Table 1 Laboratory results of the patient

Laboratory data		(Normal range)
Blood		
Uric acid (mg/dL)	12.2	(3.8–7.0)
Urea nitrogen (mg/dL)	12	
Creatinine (mg/dL)	0.99	
Sodium (mmol/L)	140	
Potassium (mmol/L)	4.7	
Chloride (mmol/L)	103	
Calcium (mg/dL)	9.4	
Phosphate (mg/dL)	3.9	
Cholesterol (mg/dL)	170	
Glucose (mg/dL)	92	
Urine		
pH	5.5	
U-protein	(–)	
U-blood	(–)	
U-uric acid (g/g Cr)	0.57	

Fig. 1 Patient renal images and family pedigree. **a** Computed tomography images of patient kidneys. Arrow heads, renal microcalculi. **b** Echographic image of the right kidney (right), and echography report (left). Orange dots, renal microcalculi. Scale bar, 1 cm. **c** Patient family pedigree

To determine the cause, we screened genomic DNA isolated from the patient's peripheral blood for 166 major inherited kidney-disease genes (Supplemental Table) using a next-generation sequencer system (SPEEDI-KID) [3]. The results of this analysis revealed a novel hemizygous missense c.103G>A mutation in exon 2 of *HPRT1* (NM_000194.3), which encoded a valine-to-methionine substitution (p.V35M) (Fig. 2a, b). The mutation was confirmed by Sanger sequencing of genomic DNA and cDNA produced from patient leucocytes (Fig. 2a). The mutation site was positioned in a β -sheet motif in HPRT protein structure (Fig. 2c). The p.V35M mutation did not substantially disrupt the protein structure that was predicted by i-TASSER [4] (Fig. 2d).

The effect of the identified mutation on HPRT enzymatic activity was assessed by measuring the level of inosinic acid, which is produced from hypoxanthine by HPRT, using a sample of patient erythrocytes and a previously described method [5]. This analysis revealed that the patient retained only 12.4% HPRT enzymatic activity compared to that observed in healthy control subjects (Table 2); thus, he was diagnosed with HPRT-related hyperuricemia caused by the identified novel mutation. The patient was treated with the xanthine-oxidase inhibitor febuxostat to correct his hyperuricemia, and with sodium potassium citrate (Uralit®) to prevent progression of his uric-acid microcalculi via urine

Table 2 Analysis of HPRT activity using the patient's erythrocytes

Sample	Inosinic acid (nmol/min/mg Hb)	HPRT enzymatic activity (%)
Erythrocyte		
Control	0.18 ± 0.03	100 ± 14.6
Patient	0.023	12.8

Hb hemoglobin

Average of control was taken as 100%. Control ($n = 3$), mean ± SD

alkalization. After this, treatment achieved a normalized serum urate level (< 5 mg/dL) (Fig. 3), the gout attack did not recur, and the patient's renal function remained stable during the subsequent 2-year follow-up (serum creatinine, 0.9 mg/dL; eGFR, 89 mL/min/1.73 m²), although the number of the renal microcalculi did not decrease.

Discussion

We herein report a case of HPRT-related hyperuricemia presenting familial juvenile gout without neurological symptoms. The identified novel *HPRT1* c.103G>A (p.V35M) missense mutation caused partial HPRT deficiency that was

Fig. 2 Characteristics of the identified novel *HPRT1* c.103G>A mutation. **a** *HPRT1* gene sequence in patient genomic DNA and leukocyte cDNA, and in leukocyte cDNA from a healthy control subject. **b** Location of the identified c.103G>A (p.V35M) mutation in the *HPRT1* transcript. **c** Location of the identified p.V35M mutation

in the HPRT secondary 3D structure. Arrows, mutation sites in the *HPRT1* homotetramer. The 3D structure of the Protein Data Bank entry 1BZY is displayed (<https://www.rcsb.org/pdb>). **d** The predicted protein structure of wild-type HPRT and V35M HPRT. The models were predicted by i-Tasser

Fig. 3 Patient clinical course. Serum uric-acid (UA) levels and urinary UA excretion are shown. g Cr, g creatinine ratio

confirmed via biochemical testing. These findings emphasize that HPRT deficiency should be considered as a potential underlying cause of familial juvenile gout, even in cases that lack neurological symptoms.

HPRT deficiency is clinically classified as either Lesch–Nyhan syndrome, HPRT-related neurological dysfunction, or HPRT-related hyperuricemia¹, and its clinical severity is determined by the level of HPRT enzymatic activity that is retained by individuals carrying *HPRT1* mutations [6, 7]. Complete HPRT deficiency (< 1.5% residual HPRT activity) is associated with Lesch–Nyhan syndrome, in which involuntary movements and self-injuries emerge from less than 3 years old [7]. In contrast, partial deficiency (≥ 10% residual HPRT activity) is associated with HPRT-related hyperuricemia, which is often diagnosed via the manifestation of gout and nephrolithiasis in adolescence [6]. As shown in the present case, a retained HPRT activity level of approximately 12% induced HPRT-related hyperuricemia without neurological manifestations, which presented as gout in adolescence. Thus, our findings support previously reported genotype–phenotype correlations for *HPRT1* mutations.

More than 600 *HPRT1* mutations have been reported in individuals with HPRT deficiency, including Lesch–Nyhan syndrome [8]; however, the present mutation, c.103G>A (p. V35M), has not been previously reported in patients with HPRT deficiency, nor listed in either database of Lesch–Nyhan disease [8], the Human Gene Mutation Database [9], or ClinVar [10]. It is an extremely rare variant, as evidenced by the fact that it is not registered in minor allele frequency databases such as the 1000Genome [11], the Genome Aggregation Database (gnomAD) [12], nor the Integrative Japanese Genome Variation Database [13]. Thus,

we conclude that the *HPRT1* c.103G>A mutation is a novel causative mutation of partial HPRT deficiency.

HPRT deficiency is inherited in X-linked recessive pattern, and, therefore, occurs almost exclusively in males [1]. Consistent with this mode of inheritance, the present patient's pedigree included a brother and grandfather that exhibited a similar history of juvenile gout, which suggests that they may have harbored the same *HPRT1* c.103G>A mutation. Unfortunately, we were not able to confirm this hypothesis, because we were not able to obtain DNA samples from either the patient's brother or grandfather.

The established best management practice for uric-acid overproduction in HPRT-deficient patients is to block the conversion of xanthine and hypoxanthine into uric acid using xanthine-oxidase inhibitors, such as allopurinol or febuxostat [14]. This treatment reduces uric-acid production, and, thus, prevents both gout and uric-acid nephrolithiasis. Hyperuricosuric drugs such as probenecid are contraindicated, because they increase the risk of uric-acid nephrolithiasis. Since the present case presented renal microcalculi and gout, the patient was administered both febuxostat and sodium potassium citrate for urine alkalization. As expected, this treatment reduced uric-acid production, as indicated by his reduced urinary uric-acid level.

In conclusion, the present study emphasizes that HPRT deficiency should be suspected in cases of familial juvenile gout, even when neurological symptoms are absent, to ensure that affected patients receive appropriate treatment to control their uric-acid levels and prevent renal symptoms such as microcalculi.

Methods

The genetic test was performed in accordance with the ethical standards of Tohoku University Graduate School of Medicine and Tokyo Medical and Dental University. Isolation of genomic DNA and the creation of cDNA were performed as described previously [15–17].

Acknowledgements This work is partially supported by Tohoku University Center for Gender Equality Promotion (TUMUG) Support Project.

Compliance with ethical standards

Conflict of interest All of the authors have declared no competing interests.

Human and animal rights statement This article does not describe any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Torres RJ, Puig JG. Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency: Lesch-Nyhan syndrome. *Orphanet J Rare Dis*. 2007;2:48.
2. Jinnah HA, Ceballos-Picot I, Torres RJ, Visser JE, Schretlen DJ, Verdu A, et al. Attenuated variants of Lesch-Nyhan disease. *Brain*. 2010;133:671–89.
3. Mori T, Hosomichi K, Chiga M, Mandai S, Nakaoka H, Sohara E, et al. Comprehensive genetic testing approach for major inherited kidney diseases, using next-generation sequencing with a custom panel. *Clin Exp Nephrol*. 2017;21:63–75.
4. Yang J, Yan R, Roy A, Xu D, Poisson J, Zhang Y. The I-TASSER suite: protein structure and function prediction. *Nat Methods*. 2015;12:7–8.
5. Gordon RB, Thompson L, Emmerson BT. Erythrocyte phosphoribosylpyrophosphate concentrations in heterozygotes for hypoxanthine-guanine phosphoribosyltransferase deficiency. *Metabolism*. 1974;23:921–7.
6. Fu R, Ceballos-Picot I, Torres RJ, Larovere LE, Yamada Y, Nguyen KV, et al. Genotype-phenotype correlations in neurogenetics: Lesch-Nyhan disease as a model disorder. *Brain*. 2014;137:1282–303.
7. Madeo A, Di Rocco M, Brassier A, Bahi-Buisson N, De Lonlay P, Ceballos-Picot I. Clinical, biochemical and genetic characteristics of a cohort of 101 French and Italian patients with HPRT deficiency. *Mol Genet Metab*. 2019;127:147–57.
8. Lesch-Nyhan Disease International Study Group. <https://www.lesch-nyhan.org/> Accessed Dec 2019.
9. Stenson PD, Mort M, Ball EV, Shaw K, Phillips A, Cooper DN. The Human Gene Mutation Database: building a comprehensive mutation repository for clinical and molecular genetics, diagnostic testing and personalized genomic medicine. *Hum Genet*. 2014;133:1–9.
10. ClinVar: <https://www.ncbi.nlm.nih.gov/clinvar/> Accessed Dec 2019.
11. Genomes Project C, Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, et al. A map of human genome variation from population-scale sequencing. *Nature*. 2010;467:1061–73.
12. The Genome Aggregation Database (gnomAD) <https://www.biorxiv.org/content/10.1101/531210v3> Accessed Dec 2019.
13. Yamaguchi-Kabata Y, Nariai N, Kawai Y, Sato Y, Kojima K, Tatenno M, et al. iJGVD: an integrative Japanese genome variation database based on whole-genome sequencing. *Hum Genome Var*. 2015;2:15050.
14. Torres RJ, Puig JG, Jinnah HA. Update on the phenotypic spectrum of Lesch-Nyhan disease and its attenuated variants. *Curr Rheumatol Rep*. 2012;14:189–94.
15. Takeuchi Y, Mishima E, Shima H, Akiyama Y, Suzuki C, Suzuki T, et al. Exonic mutations in the SLC12A3 gene cause exon skipping and premature termination in Gitelman syndrome. *J Am Soc Nephrol*. 2015;26:271–9.
16. Mishima E, Mori T, Sohara E, Uchida S, Abe T, Ito S. Inherited, not acquired, Gitelman syndrome in a patient with Sjogren's syndrome: importance of genetic testing to distinguish the two forms. *CEN Case Rep*. 2017;6:180–4.
17. Mishima E, Fukuda S, Shima H, Hirayama A, Akiyama Y, Takeuchi Y, et al. Alteration of the intestinal environment by lubiprostone is associated with amelioration of adenine-induced CKD. *J Am Soc Nephrol*. 2015;26:1787–94.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.