CASE REPORT

Partial HPRT Deficiency with a Novel Mutation of the HPRT Gene in Combination with Four Previously Reported Variants Associated with Hyperuricemia

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Abstract

A 15-year-old boy was referred to our department due to gout. The laboratory findings showed hyperuricemia with a decreased erythrocyte hypoxanthine phosphoribosyl transferase (HPRT) activity. The HPRT cDNA sequence was revealed to be 206A>T, which has not been previously reported. In addition, direct sequencing of genomic DNA showed the patient to possess four variants reported to be associated with hyperuricemia. This is the first case report of partial HPRT deficiency due to a novel HPRT mutation accompanied by variants associated with hyperuricemia. Combination treatment consisting of benzbromarone and febuxostat had a significant effect in reducing the urate level in our patient.

Key words: HPRT, variant, urate, febuxostat, benzbromarone

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Introduction

Hypoxanthine-guanine phosphoribosyl transferase (HPRT) is an important enzyme that converts hypoxanthine to inosine monophosphate (IMP) as well as guanine to guanosine monophosphate (GMP) using phosphoribosyl pyrophosphate (PRPP) (1). This enzyme salvages hypoxanthine and guanine by metabolizing most of their purine bases to uric acid, which subsequently results in hyperuricemia in individuals with HPRT deficiency. Accordingly, xanthine oxidase inhibitors (XOIs), such as allopurinol, are generally used to treat hyperuricemia in patients with HPRT deficiency due to their effects in blocking the conversion of hypoxanthine to uric acid via xanthine by xanthine oxidoreductase, thus reducing uric acid production (2).

HPRT deficiency is classified into three types according to clinical hallmarks (3). Complete deficiency of HPRT, termed Lesch-Nyhan disease, is characterized by mental retardation and/or self-mutilation, as well as choreoathetosis, hyperuricemia and gout. The partial deficiency of HPRT is termed HPRT-related hyperuricemia (HRH) and is characterized by hyperuricemia and gout without neurological dysfunction. In addition to hyperuricemia, the partial deficiency of HPRT includes a phenotype of mental retardation and choreoathetosis without self-mutilation called HPRT-related neurological dysfunction.

Since the gene encoding HPRT is located on the X-chromosome, HPRT deficiency is a genetic X-linked disease (4, 5) and this genetic mutation has a critical effect on the urate level. However, recent genome-wide association studies (GWASs) have shown that various genetic loci also influence the urate levels (6-8). In a study of a general Japanese population, Takeuchi et al. reported SLC22A12 rs505802, ABCG2 rs2231142, SLC2A9 rs1014290, SLC17A1-A3 rs1165196, GCKR rs780094 and LRRC16A rs742132 to be associated with hyperuricemia (9). Of these loci, rs505802 (SLC22A12), rs2231142 (ABCG2),

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Table. Laboratory Findings.

<table>
<thead>
<tr>
<th>Blood cell counts</th>
<th>AST</th>
<th>13 IU/L</th>
<th>Urinalysis</th>
<th>pH</th>
<th>7.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 4.600 µL</td>
<td>ALT</td>
<td>11 IU/L</td>
<td>Protein (-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC 538×10⁶/µL</td>
<td>ALP</td>
<td>426 IU/L</td>
<td>Blood (-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb 16.9 g/dL</td>
<td>γ-GTP</td>
<td>20 IU/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plt 19.0×10⁶/µL</td>
<td>LDH</td>
<td>116 IU/L</td>
<td>Glucose (+)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>CK</td>
<td>10 IU/L</td>
<td></td>
<td></td>
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<tr>
<td>Blood biochemical analysis</td>
<td>Ca</td>
<td>2.45 mmol/L</td>
<td></td>
<td></td>
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<tr>
<td>Alb 6.38 µmol/L</td>
<td>IP</td>
<td>0.65 mmol/L</td>
<td></td>
<td></td>
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<tr>
<td>BUN 3.57 mmol/L</td>
<td>CRP</td>
<td>0.0 mg/L</td>
<td></td>
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<tr>
<td>Cre 72.49 µmol/L</td>
<td>T-e</td>
<td>2.90 mmol/L</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Urate 921.9 µmol/L</td>
<td>HDL-c</td>
<td>1.06 mmol/L</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Na 141 mmol/L</td>
<td>T G</td>
<td>1.79 mmol/L</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>K 4.1 mmol/L</td>
<td>FPG</td>
<td>5.5 mmol/L</td>
<td></td>
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</tr>
<tr>
<td>Cl 105 mmol/L</td>
<td>HbA1c</td>
<td>5.4%</td>
<td></td>
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<tr>
<td>T-Bil 17.1 µmol/L</td>
<td>NH₃</td>
<td>27.8 µmol/L</td>
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<td></td>
<td>Lactate</td>
<td>1.25 mmol/L</td>
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</tbody>
</table>

rs1014290 (SLC2A9) and rs1165196 (SLC17A1-A3) have been shown to have a greater effect on the serum urate level than the others.

Accordingly, we investigated rs505802 (SLC22A12), rs2231142 (ABCG2), rs1014290 (SLC2A9) and rs1165196 (SLC17A1-A3) in addition to the HPRT gene in a 15-year-old boy with partial HPRT deficiency.

Case Report

An adolescent boy experienced pain and swelling in the right metatarsophalangeal joint at 13 years of age, which spontaneously subsided within two weeks. He subsequently experienced flare-ups with the same symptoms in the right and/or left metatarsophalangeal joints once or twice a year. At 15 years of age, the frequency of these symptoms increased to one to two times per month, and he visited a local practitioner who diagnosed the disease as gout and referred him to our department for an investigation of the cause of the hyperuricemia and gout. On the initial examination at our hospital, the patient had a body weight of 56.7 kg and height of 165 cm, with no history of urinary calculi. His family history showed that his father had gout, while his mother and sisters did not. A physical examination revealed no joint swelling on arrival, neurological disorders, such as mental retardation, or history of choreoathetosis or self-mutilation. Routine laboratory findings also demonstrated no abnormal data for serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, creatinine, cholesterol, triglycerides or the complete blood cell count, whereas the level of serum urate (921.9 µmol/L) and urinary excretion of uric acid (7.35 mmol/day) were elevated (Table).

Erythrocyte HPRT, PRPP and adenine phosphoribosyl transferase activities

The erythrocyte HPRT, adenine phosphoribosyl transferase (APRT) and PRPP activities were determined using high-performance liquid chromatography (HPLC), as previously described (10).

Direct sequencing of HPRT cDNA

Direct sequencing of cDNA was performed as previously described. Total RNA was obtained from mononuclear cells using a chloroform-phenol extraction method. The forward and reverse primers for -46 to 351 of HPRT cDNA were CCCTCCTGTCGGCACC and GTTGAGAGATCATC, respectively, while those for 247 to 692 of HPRT cDNA were CTGACCTGCCTGATTACATC and ACTGGCAGATGTAAAAGAC, respectively (1).

Genotyping of rs505802 (SLC22A12), rs2231142 (ABCG2), rs1014290 (SLC2A9) and rs1165196 (SLC17A1-A3)

Genomic DNA was extracted from the patient’s blood using a DNA Quick II kit (Dainippon Pharmaceuticals, Osaka, Japan). Direct sequencing of genomic DNA was performed for genotyping of rs505802 (SLC22A12), rs2231142 (ABCG2), rs1014290 (SLC2A9) and rs1165196. The forward and reverse primers for polymerase chain reaction (PCR) were TATGTTGCTAAGGGTGAGC and TTTGCTTCAGCTTCC for rs505802, respectively, ATGGAGTTAACTGTCAAGTGGAC and CACGTTCATATTATGTAACAGGCC for rs2231142, respectively, ATCAGCTCCAGTGGA and CTCAAGTCGGAGATGGAGGAA for rs1014290, respectively, and CCATATTGGCATCTCCAGA and AAGAGCTGCGACTAGTTTCG for rs1165196, respectively.

Laboratory data

The activities of HPRT and APRT in the erythrocyte samples obtained from the patient included a hemoglobin level of 0.49 µmol/g (Hb)/min (reference value, 2.17±0.34 µmol/g Hb/min) and 0.80 µmol/g Hb/min (reference value, 0.41±0.10 µmol/g Hb/min), respectively. Based on these findings, the patient was diagnosed with a partial deficiency of HPRT.

Sequence of HPRT cDNA

The sequence analysis of the HPRT cDNA obtained from the patient demonstrated the presence of mutant HPRT.
genotypes, including a point mutation of A to T in nucleotide 206, which changed codon 69 from AAG (Lys) to ATG (Met). A sequence analysis of cells obtained from his mother, whose serum level was 392.6 μmol/L, showed the presence of both A and T bands in nucleotide 206, while that for his father showed only a normal A band in nucleotide 206. Therefore, the HPRT mutation in our patient was inherited from his mother (Figure).

Genotyping of rs505802 (SLC22A12), rs2231142 (ABCG2), rs1014290 (SLC2A9) and rs1165196 (SLC17A1-A3)

The patient had a homozygous A to G genotype at rs505802, heterozygous C to A genotype at rs2231142, heterozygous C to T genotype at rs1014290 and homozygous C to T genotype at rs1165196.

Clinical course after hospital discharge

We asked a local practitioner located near the residential address of the patient to treat the hyperuricemia due to the large distance of the patient’s home from our hospital. XOIs (febuxostat) administration was started at a dose of 10 mg/day, then increased by 10 mg every one or two months up to a dose of 60 mg/day. The urate level subsequently decreased from 921.9 to 577.0 μmol/L during xanthine oxidase inhibitor treatment, although it remained markedly above the recommended target for the management of gout noted in the Japanese guidelines (356.9 μmol/L, 6.0 mg/dL) (11). Accordingly, treatment with benzbromarone, a uric acid transporter (URAT) 1 inhibitor, was given at a dose of 50 mg/day together with a urine alkalinizing agent (potassium citrate/sodium citrate) in addition to febuxostat (60 mg/day). One month later, the urate level dramatically decreased to 107.1 μmol/L. Thereafter, the dose of febuxostat was gradually reduced to 10 mg, while that of benzbromarone remained unchanged, and the urate level was maintained between 315.0 and 340.0 μmol/L.

Discussion

This is the first case report of partial HPRT deficiency due to a novel HPRT mutation (206A>T) accompanied by variants associated with hyperuricemia. Our patient showed no signs of neurological dysfunction, including mental retardation, self-mutilation or choreoathetosis, although he had both hyperuricemia and gout. The plasma and urinary data showed an elevated level of plasma urate and urinary excretion of uric acid. Furthermore, the activity of HPRT was low, while that of APRT was high compared with their respective reference values. The elevated APRT activity may have reflected compensation for the HPRT deficiency. Accordingly, our diagnosis was partial HPRT deficiency leading to hyperuricemia and gout based on the patient’s clinical phenotypes and laboratory results (3).

More than 300 mutations throughout the coding region of the HPRT gene have been described, including deletions, insertions, duplications, abnormal splicing and point mutations (http://www.lesch-nyhan.org), all of which may induce HPRT deficiency. However, to the best of our knowledge, a point mutation of A to T in nucleotide 206 (206A>T) of the HPRT gene has not been previously reported. Previous studies have shown that genotype-phenotype correlations provide no indication of specific disease features associated with specific mutation locations (12). Accordingly, the identification of this HPRT point mutation (206A>T) with concurrent measurements of the HPRT activity confirmed our diagnosis of HPRT deficiency, which appeared to be caused by this novel HPRT point mutation.

On the other hand, recent GWASs have reported that the urate level is associated with various genetic loci, including SLC2A9, ABCG2, SLC22A11, SLC22A12, SLC16A9, GCKR, LRRC16A, the R3HDM2-INHBC region, RREB1, PDZK1, SLC2A9 and SLC17A1 (6-8). Of these loci, Yang et al. showed that the genetic urate score estimated based on the cumulative effects of loci identified in a urate meta-analysis range from -1.13 to 1.28 mg/dL, which explains the observed average serum urate variance of 6.0% (8). Another GWAS of a general Japanese population showed SLC22A12 rs505802, ABCG2 rs2231142, SLC2A9 rs1014290 and SLC17A1-A3 rs1165196 to be strongly associated with hyperuricemia (9). Direct sequencing of genomic DNA in the present case showed a homozygous A to G genotype at rs505802, heterozygous C to A genotype at rs2231142, heterozygous C to T genotype at rs1014290 and homozygous C to T genotype at rs1165196. Interestingly, each of these single nucleotide polymorphisms is associated with hyperuricemia. Takeuchi et al. showed a 2.5-fold variation in the prevalence of hyperuricemia between the lowest and highest risk groups for the combination of urate-associated loci. Therefore, the combination of variants associated with hyperuricemia, in addition to HPRT deficiency, observed in the...
present case may have influenced the urate level in our patient. 
In general, the urate level is well controlled by XOIIs, such as allopurinol, in patients with HPRT deficiency, who are characterized by urate overproduction (2). Surprisingly, the URAT 1 inhibitor used in the current case had a notable effect in reducing the patient’s serum urate level, whereas treatment with an XOI (febuxostat) had little effect. Although the mechanism underlying this phenomenon remains undetermined, our case is very interesting in terms of the therapeutic outcome, as the administration of febuxostat at a dose of 40 mg appeared to have a nearly equal hypouricosuricemic effect to that of benzbromarone at a dose of 50 mg.

In conclusion, a teenage boy suffering from gouty arthritis was diagnosed with a partial deficiency of HPRT due to a novel HPRT mutation. In addition, we found four variants associated with hyperuricemia. Interestingly, combination treatment with benzbromarone and febuxostat had a greater effect in reducing the urate level than febuxostat alone in this case. Accordingly, further examinations are needed.

The authors state that they have no Conflict of Interest (COI).

References