To the Editor: A 19-year-old Chinese male was admitted to Peking Union Medical College Hospital in November 2016, due to recurrent joints pain and swelling with hyperuricemia for 6 years. The first attack occurred in the first metatarsophalangeal joints (MTP1) of the left foot in August 2010 and was relieved gradually. The symptoms recurred in 2011. Subsequently, he was diagnosed with gouty arthritis. Then, the patient began to restrict his intake of purine-rich foods and drink excess water, but continued to suffer from recurrent attacks. Tophi were gradually found in bilateral MTP, proximal interphalangeal joint, metacarpal phalangeal joints, intertarsal joints, and auricles, successively. The recurrent renal colic appeared from 2015. In August 2016, all tophi in the extremities were enlarged and ulcerated through the skin, discharging white and sticky material. This phenomenon resulted in restricted daily activities, thereby causing to remove the tophi. Before surgery, the laboratory tests showed significantly elevated levels of serum uric acid (UA, 767 µmol/L). Imaging examination revealed bilateral multiple nephrolithiasis and bone erosions in multiple joints. He was treated with nonsteroidal anti-inflammatory drugs and 80 mg febuxostat daily. The serum UA level was lowered from 480 to 264 µmol/L. Nevertheless, the symptoms of the joints continued to worsen, and the patient could not stand or walk unaided. In addition, he had a low-grade fever due to which, he was transferred to Peking Union Medical College Hospital.

His birth and growth were without any neurological symptoms and addiction to smoking and alcohol consumption. The other family members were healthy. The physical examination at the time of admission revealed the body mass index as 16 kg/m² and blood pressure as 115/70 mmHg (1 mmHg = 0.133 kPa). Two tophi, approximately 0.5 cm in diameter, could be observed on bilateral auricles separately, as well as, in multiple joints, some of which were ulcerated. Bilateral knees were painful and presented swelling with redness on the skin and increased skin temperature.

After admission, we estimated the 24-h urinary urate clearance rate that has been identified to be associated with gout. The mutation c.477G>T was found on exon 6 of hypoxanthine-guanine phosphoribosyl transferase 1 (HPRT1) gene on X chromosome that has been identified to be associated with gout. The mutation was confirmed by Sanger sequencing. This patient was diagnosed with Kelley-Seegmiller syndrome (OMIM: 300323). The parents or sister did not present hyperuricemia; however, the mother exhibited the same abnormality with an increased urine excretion of UA. Up to the last follow-up visit in September 2017, his tophi were smaller to the last follow-up visit in September 2017, his tophi were smaller, and 420 µmol/L (December 11), 371 µmol/L (December 18), and 302 µmol/L (December 21), and the 24-h urinary clearance rate of urate and creatinine increased to 6.92 and 98.45 ml/min, separately. We insisted on the treatment of ensuring daily water intake as well as colchicine and glucocorticoids for the prevention of acute flares.

After discharge, the patient was followed up every 3 months, with serum UA level 280–330 µmol/L. The WES results revealed genetic abnormality of in this patient. Intriguingly, a mutation, c.477G>T was found on exon 6 of hypoxanthine-guanine phosphoribosyl transferase 1 (HPRT1) gene on X chromosome which was identified to be associated with gout. The mutation was confirmed by Sanger sequencing. This patient was diagnosed with Kelley-Seegmiller syndrome (OMIM: 300323). The parents or sister did not present hyperuricemia; however, the mother exhibited the same abnormality with an increased urine excretion of UA. Up to the last follow-up visit in September 2017, his tophi were smaller as assessed by physical examination and DECT [Figure 1f] and no renal calculi was found.

HPRT1 is a critical enzyme in purine salvage. The functional deficiency of HPRT1 causes excessive purines to be catabolized into UA, leading to elevated serum UA level. This phenomenon is termed as HPRT1 deficiency (OMIM: 308000), an X-linked
A complete deficiency of HPRT1 (Lesch-Nyhan syndrome) is accompanied by hyperuricemia, severe motor disability, and self-injurious behavior. The partial enzyme deficiency is presented as Kelley-Seegmiller syndrome, also known as HPRT-related gout. HPRT deficiency has a significant genetic heterogeneity, with >300 mutations on the HPRT gene locus. In our patient, WES revealed the c.477G>T mutation on exon 6 of HPRT1 gene on X chromosome from the mother. The missense mutation on this locus altered the structure of amino acids: p.K159N (NM_000194), which was in conformity with the X-linked recessive inherited Kelley-Seegmiller syndrome. Fu et al. indicated that p.K159N is one of the loci leading to this disease. Moreover, WES indicated a single heterozygous point mutation c.206G>T on exon 3 of SLC17A3 gene located on chromosome 6 in the patient, altering the amino acid, p.S69I (NM_001098486). This mutation is located on the UA Concentration, Serum, Quantitative Trait locus 4 (UAQTL4, OMIM: 612671, autosomal dominant disease), which was identified as a pathogenic variant based on the prediction of the protein function. Numerous sites of gene mutation have been reported; some patients may have two or more abnormalities on these sites that are characterized by early onset, severe clinical manifestations, organ damage, and resistance to treatment. The monogenic inherited diseases may affect the key enzymes in the pathway of UA metabolism, while single nucleotide polymorphism (SNP) may influence the activity of urate transporters and severity of inflammation in varying degrees. Each SNP has a tiny effect, while multiple SNPs may have a greater impact. Furthermore, the successful diagnosis and treatment is greatly significant to carry out the genetic analysis for such patients. Taken together, different therapeutic strategies (such as early interventions, intensive therapy like combination treatment of febuxostat and benz bromarone) could be proposed, and prognosis might be improved.

### Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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### Conflicts of interest
There are no conflicts of interest.

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