Kidney Diseases

Review Article

Kidney Dis 2024;10:313–326
DOI: 10.1159/000539516

Received: March 12, 2024
Accepted: May 16, 2024
Published online: June 17, 2024

Mutation Characteristics of Primary Hyperoxaluria in the Chinese Population and Current International Diagnosis and Treatment Status

Xingying Zhu[a] Wai W. Cheung[b] Aihua Zhang[a, c] Guixia Ding[a]

[a]Department of Nephrology, Children's Hospital of Nanjing Medical University, Nanjing, China; [b]Division of Pediatric Nephrology, Rady Children's Hospital, University of California, San Diego, CA, USA; [c]State Key Laboratory of Reproductive Medicine, Children's Hospital of Nanjing Medical University, Nanjing, China

Keywords
Primary hyperoxaluria · Primary hyperoxaluria mutations · Chinese population

Abstract
Background: Primary hyperoxaluria (PH) is a rare autosomal recessive disorder, mainly due to the increase in endogenous oxalate production, causing a series of clinical features such as kidney stones, nephrocalcinosis, progressive impairment of renal function, and systemic oxalosis. There are three common genetic causes of glycolate metabolism anomalies. Among them, PH type 1 is the most prevalent and severe type, and early end-stage renal failure often occurs. ***Summary:*** This review summarizes PH through pathophysiology, genotype, clinical manifestation, diagnosis, and treatment options. And explore the characteristics of Chinese PH patients. ***Key Messages:*** Diagnosis of this rare disease is based on clinical symptoms, urinary or blood oxalate concentrations, liver biopsy, and genetic testing. Currently, the main treatment is massive hydration, citrate inhibition of crystallization, dialysis, liver and kidney transplantation, and pyridoxine. Recently, RNA interference drugs have also been used. In addition, technologies such as gene editing and autologous liver cell transplantation are also being developed. C.815_816insGA and c.33_34insC mutation in the *AGXT* gene could be a common variant in Chinese PH1 population. Mutations at the end of exon 6 account for approximately 50% of all Chinese HOGA1 mutations. Currently, the treatment of PH in China still relies mainly on symptomatic and high-throughput dialysis, with poor prognosis (especially for PH1 patients).

Introduction

Primary hyperoxaluria (PH) is a rare autosomal recessive inherited disease, mainly caused by increased endogenous oxalate production, leading to a series of clinical features such as kidney stones, renal calcinosis, progressive renal function damage, and systemic oxalate deposition. This review mainly introduces PH through pathophysiology, genotype, prevalence, clinical manifestations, evaluation, and treatment. Meanwhile, by collecting literature, the genetic characteristics of Chinese patients with PH were summarized.

Oxalate is an insoluble product. About 60–80% of plasma oxalate is synthesized from glyoxylate in the liver,

karger@karger.com
www.karger.com/kdd

Correspondence to:
Guixia Ding, bhgyuan@163.com

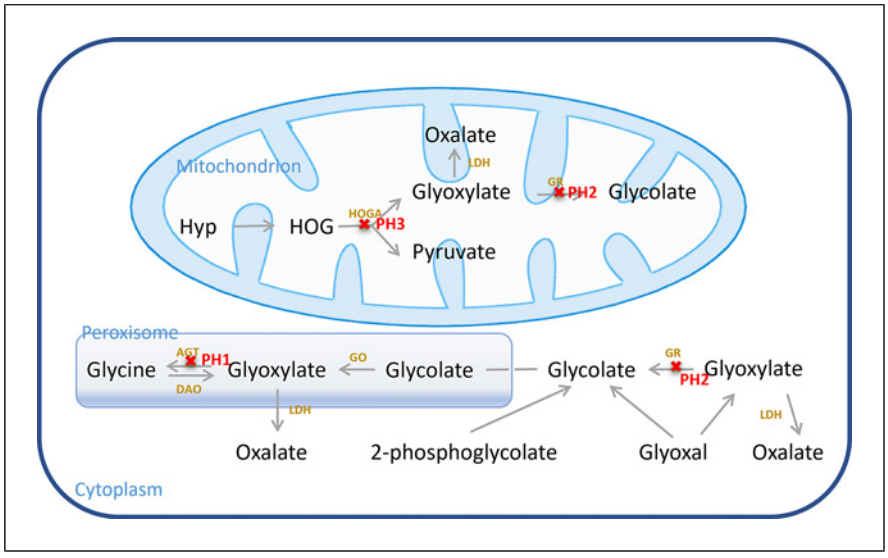

Fig. 1. Glyoxylate metabolism pathway in liver cells. Red: the type of PH caused by the affected enzyme. Hyp, hydroxyproline; HOG, 4-hydroxy-2-ketoglutarate; HOGA, 4-hydroxy-2-ketoglutarate aldolase; LDH, L-lactic dehydrogenase; GR, glyoxylate reductase/hydroxypyruvate reductase; AGT, alanine: glyoxylate aminotransferase.

and only 5–15% of dietary oxalate is normally absorbed [1]. Oxalate is almost completely discharged from the kidney. Therefore, when the excretion of oxalate in the urine is too high, hyperoxaluria will occur.

Hyperoxaluria can be divided into three forms: idiopathic, intestinal, and primary. Among them, idiopathic hyperoxaluria is the most common form, which may be induced by excessive intake of oxalate diet or oxalate precursors, or insufficient calcium diet. Intestinal hyperoxaluria is mainly exacerbated by intestinal resection or indigestion brought on by inflammatory bowel disease, resulting in increased absorption of oxalate in the intestine. The PH discussed in this review is the result of abnormal endogenous glyoxylate metabolism, caused by autosomal recessive inheritance. Therefore, when patients experience increased urinary oxalate excretion, it is necessary to exclude secondary hyperoxaluria caused by excess intake of oxalate, oxalate precursors, or alteration in intestinal microflora. This is before considering PH [2].

The Pathogenesis of PH

PH is mainly divided into three types (shown in Fig. 1). PH type 1 (PH1; OMIM 259900) is the most common and severe PH form, which accounts for about 80% of PH patients [3] and requires frequent healthcare resource use. PH1 is due to the absence of alanine: glyoxylate aminotransferase (AGT).

PH type 2 (PH2; OMIM 260000) has a lower incidence rate than PH1 (about 20% of PH) and is considered less invasive than PH1, although it occurs earlier. PH2-related mutations in the *GRHPR* gene are found in 15% of pediatric PH positive populations [4]. It lacks glyoxylate reductase/hydroxypyruvate reductase (GP/HPR) due to *GRHPR* gene mutation. Compared to PH1, PH2 patients seem to have a lower likelihood of developing CKD5 at diagnosis, and no patients have progressed to CKD5 before the age of 15 [5].

PH type 3 (PH3; OMIM 613616) is the rarest type. But PH3 is still an early onset, recurrent stone disease and PH3 have a trend toward earlier diagnosis (median 4.9 years of age) compared with PH1 (11Y) and PH2 (9.5Y), and had a median age at first symptoms of 2.7Y [6]. PH3 was previously considered the lightest form, but recently it has been found that more than 20% of PH3 patients have chronic renal dysfunction [7]. PH3 is mainly due to the lack of 4-hydroxy-2-ketoglutarate aldolase (HOGA), which is mainly expressed in liver and kidney, encoded by *HOGA1* gene.

All three types of PH often result in an increased endogenous oxalate production. Hence, if the amount of oxalate exceeds the kidney excretion capacity, oxalate could deposit in the kidney and it can cause renal function damage by inducing inflammation [8]. Recent studies have shown that CaOx crystals activate the NLRP3 inflammasome, leading to acute kidney injury (AKI) or progressive renal failure [8, 9].

Genotype of PH

Three aberrant loci have been identified in the pathogenesis of PH: AGXT (PH1), GRHPR(PH2), and HOGA1 (PH3). Only scattered PH cases have been

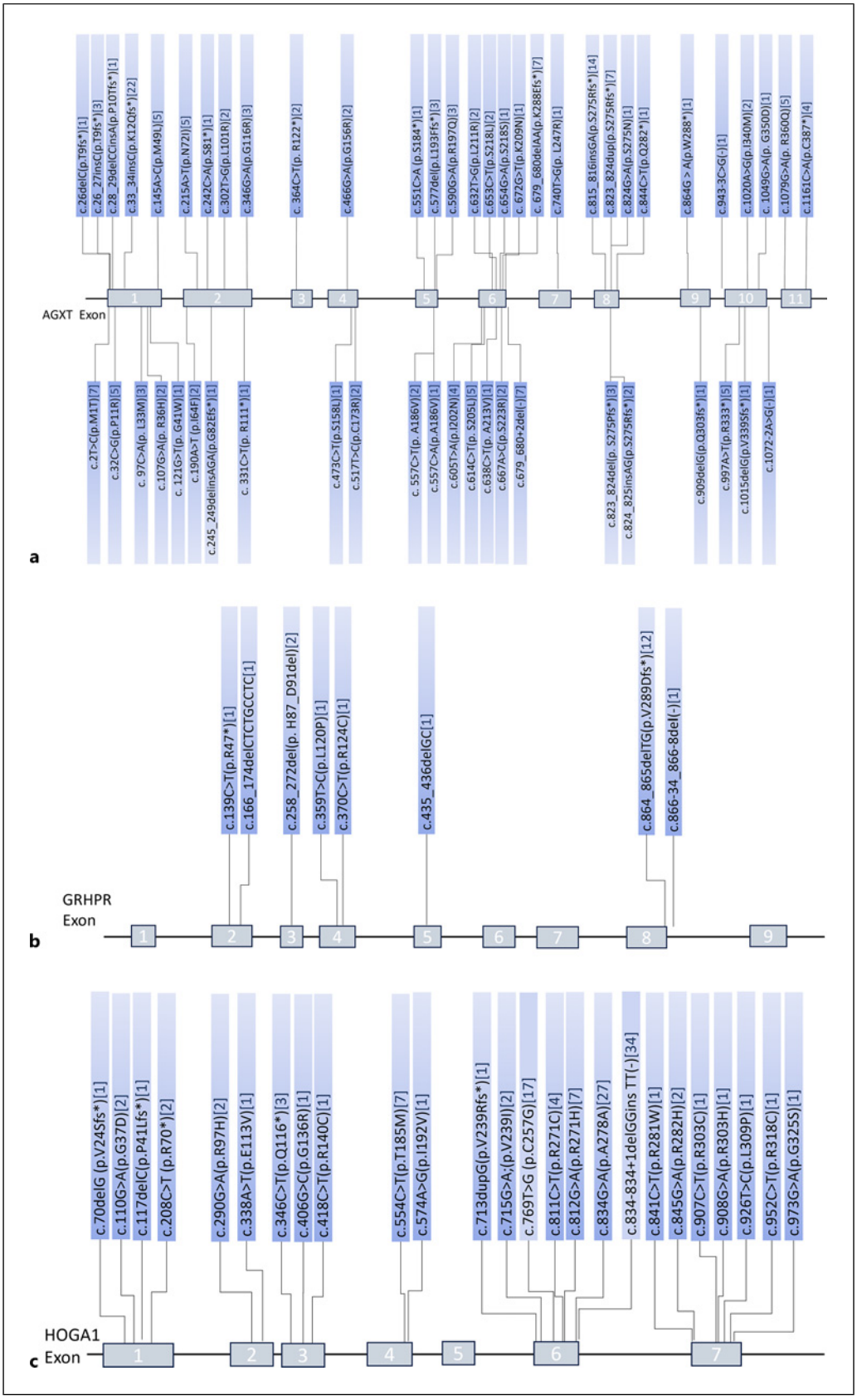

Fig. 2. Reported genetic mutations in PH patients in China. [number] represents the number of patients carrying the mutation site. **a** AGXT mutation sites in Chinese PH1 patients. **b** GRHPR mutation sites in Chinese PH2 patients. **c** HOGA1 mutation sites in Chinese PH3 patients.

reported in China, despite its large population. The PH variant spectrum in China has not been well documented. We have summarized the currently reported mutations in AGXT, GRHPR, and HOAG1 in Chinese patients with PH (shown in Fig. 2). Based on the keywords PH and Chinese, we retrieved relevant literature on genetic variations for Chinese patients with PH in the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed/) and Wanfang database [10–43] (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000539516).

Genotype of PH1

AGXT is located at 2q36-q37, which encodes AGT. At present, there are at least 285 AGXT mutants (http://www.hgmd.cf.ac.uk). Harambat et al. [44] conducted DNA analysis on 140 patients from 116 families and found three of the most common AGXT mutation alleles: p.G170R, p.I244T, and c.33dupC account for approximately 26%, 20%, and 12% of the AGXT mutation alleles, respectively. Among them, patients with mutations in the first two are mainly from Western Europe and North Africa. In Egypt, the most common mutation is p.Gly41Arg, and mutations in exons 1 and 7 account for >75% of the pathogenic variants in Egyptian patients diagnosed with PH1 [45]. In a retrospective study [46], it was found that patients with p.G170R and p.F152I variants had the lowest risk of renal failure.

Genetic Characteristics of PH1 in Chinese Patients

In China, a total of 79 PH1 patients have been reported. There is evidence that mutations c.33_34insC (22/165) and c.815_816insGA (14/165) are common among Chinese people (shown in Fig. 2a). It is worth noting that the high-risk mutation sites are mainly concentrated in the first and sixth exons, especially in multiple cytosine (C) repeat regions and guanine and adenine repeat regions, and preliminary screening can be selectively performed on exons with high incidence of mutations. Therefore, c.815_816insGA and c.33-34insC are recognized as hotspots for AGXT mutations in China, and it is worth noting that they may be associated with poor prognosis [30].

Children and adults with PH1 carrying the same mutation may experience completely different outcomes: ranging from kidney stones to end-stage kidney disease, indicating significant heterogeneity in genotypes. However, the three most common misread AGXT variants reported by Caucasians (p.G170R, p.I244T, and p.F152I) are extremely rare in the Chinese population [13] and the most common mutation in Tunisia (p.I244T) [47] has not been found in China, indicating regional differences in the AGXT mutation spectrum. On the other hand, the c.679_(IVS6+2)delAAGT mutation is considered a specific mutation in the Chinese population [48].

Genotype of PH2

So far, 75 *GRHPR* gene mutations have been found in PH2 patients. Garrefs et al. [5] performed genetic testing in 102 PH2 patients and analyzed that three major genotype groups occurred: c.103delG, c.404+3_404+6del, and c.494G>A. There may be rare mutation hotspots in Caucasians (c.494G>A, 60%); the second is intron splicing site variation (c.735-1G>A) [49]. All patients with the c.103delG mutation were Caucasian [50].

Genetic Characteristics of PH2 in Chinese Patients

Reports of PH2 patients in China are rare. A total of 10 PH2 patients with 8 types of mutations were reported (identify *GRHPR* gene mutations) (shown in Fig. 2b). Among them, mutations in exon 8 [c.864_865delTG (p.V289Dfs*)] were the most common (12/20). We believe that c.864_865delTG is a hot spot mutation of GRHPR in China.

Genotype of PH3

PH3 is caused by mutations in the 4-hydroxy-2-oxoglutarate aldolase (*HOGA1*) gene. At present, 73 mutations have been found, including two of the most common alleles (c.700+5G>T23 and p.E315del), accounting for about 70% of the HOGA1 alleles [51]. P.G287V and p.E315del account for 95% of the allele count in patients of Ashkenazi Jews ancestry [52].

Genetic Characteristics of PH3 in Chinese Patients

A total of 61 PH3 Chinese patients were collected, involving a total of 25 types of *HOGA1* gene mutations (shown in Fig.2c). Among them, missense mutations account for the vast majority (21/25). Mutations are mainly concentrated in exons 6 and 7. Splicing site mutations c.834_834+1delGGinsTT are the most common, accounting for 27.8% (34/122). The second missense mutation is c.834G>A, accounting for 22.1% (27/122). Mutations at the end of exon 6 account for approximately 50% of all Chinese HOGA1 mutations. The Chinese population may carry more HOGA1 mutations than expected.

PH Patients without Detected Genetic Mutations

Although some patients exhibit the cardinal clinical manifestations of PH, subsequent genetic screenings fail to uncover suspected genetic causes of the disease. Williams et al. [53] analyzed 28 patients with high suspicion of PH (excluding AGTX and GRHPR mutations),

and only 15 patients had *HOGA1* gene mutations. Similarly, in the study of Hopp et al. [3] 11.3% of 301 PH families had clinical phenotypes consistent with PH, but no mutations were detected in known genes.

This indicates that there are other unknown genetic defects in glyoxylate metabolism and importantly, it also implies that the prevalence of PH is higher than what is currently anticipated. It is worth noting that some patients may have mutations located in deep introns, so extended atypical splicing sites and copy number variation analysis are necessary. They can increase the diagnostic rate of typical exome sequencing analysis for PH from 26% (20/77) to 35% (27/77) [54]. In China, there may be a large number of undiagnosed PH patients, especially children and adults with renal stones.

Clinical Manifestations and Laboratory Tests

Kidney Stones and Nephrocalcinosis

In most cases, patients with PH suffer from recurrent kidney stones, which cause pain, inflammation, and hospitalization. The presence of these stones seriously affects the lives of patients. 84.0% and 81.6% of patients experienced PH1-related hospitalization and emergency/care [55]. And there is a positive correlation between urinary calcium excretion and stone events every year [6]. Even though PH3 is considered a mild type, PH3 patients have experienced recurrent stone events throughout all decades of life, similar to PH1 and PH2 [6, 56]. The progress of PH patients can be reflected in the analysis of stone load. Imaging methods usually observe the size, location, and changes of stones and nephrocalcinosis (NC) progress. However, there are no longitudinal data recording kidney stone number and size changes in PH patients. It is worth noting that when patients develop to CKD stage, the activity of renal stones may be improved. This is because less calcium and oxalate are excreted due to renal excretion decline [57]. It is worth noting that NC is an independent risk factor for renal failure [58].

In short, PH patients' progress can be reflected through kidney stone monitoring and NC. However, there are still shortcomings such as the lack of unified standards, the lack of monitoring methods, and the performance of late-stage patients cannot correctly reflect the disease condition.

Renal Function

Due to the accumulation of oxalate and local inflammation, renal function and estimated glomerular filtration rate of PH patients decrease progressively. PH patients' symptoms and age vary greatly when diagnosed, especially PH1, including patients who reached CKD in infancy and mild adult recurrent kidney stones. In a patient registration [59], 43% of PH1 patients had ESRD at the time of diagnosis, 14% of registered patients died during the period. The renal outcome in infants with PH was the worst (ESRD at visit was 80%) [60] and the mortality rate seemed to be higher (23.1%) [61]. Therefore, early screening and diagnosis of PH in children and intervention before renal function declines can effectively protect renal function.

Systemic Hyperoxalemia

When plasma oxalate exceeds 35–50 mmol/L, its physical and chemical properties are conducive to crystallization, leading to systemic calcium oxalate crystal deposition. Oxalate deposition usually occurs in the bone, eye, blood system, heart, skin, and other systems, affecting the function of the system (shown in Fig. 3). In recent years, a small number of reports have been made on the oral manifestations of PH patients, such as toothache, periodontal infections, etc. The oral manifestations are mainly described in late-stage PH and only after the onset of chronic kidney disease [62]. The patient will suffer cardiomyopathy, cardiac conduction disturbances, vasculopathy, anemia, and osteopathy (crisp pain). Assessing the oxalate load of each system through imaging and other examinations helps assess the severity of the disease. Milliner et al. [57] proposed that the use of spectral domain optical coherence tomography retinal imaging, speckle tracking echocardiography, cardiac elastography, and quantitative calcium oxalate deposition by computed tomography or magnetic resonance imaging for evaluation.

Urine Oxalate

PH patients have increased urinary oxalate. Normal oxalate excretion cannot exclude PH diagnosis in suspicious patients. Follow-up observations [63] found that the degree of hyperoxaluria at baseline was associated with renal outcome, i.e., the higher the level of uric oxalate, the increased risk of renal function damage. Sas et al. [64] found that children under the age of 5 with PH1 have relatively higher urinary oxalate excretion, which may be associated with a higher risk of PH1 renal failure in infants compared to older individuals.

Plasma Oxalate

When kidney function is gradually damaged, and GFR falls below 30–40 mL/min per 1.73 m^2, enough oxalate cannot be excreted, and plasma oxalate concentrations gradually increase. At the same time, elevated plasma oxalate levels in CKD may promote renal inflammation

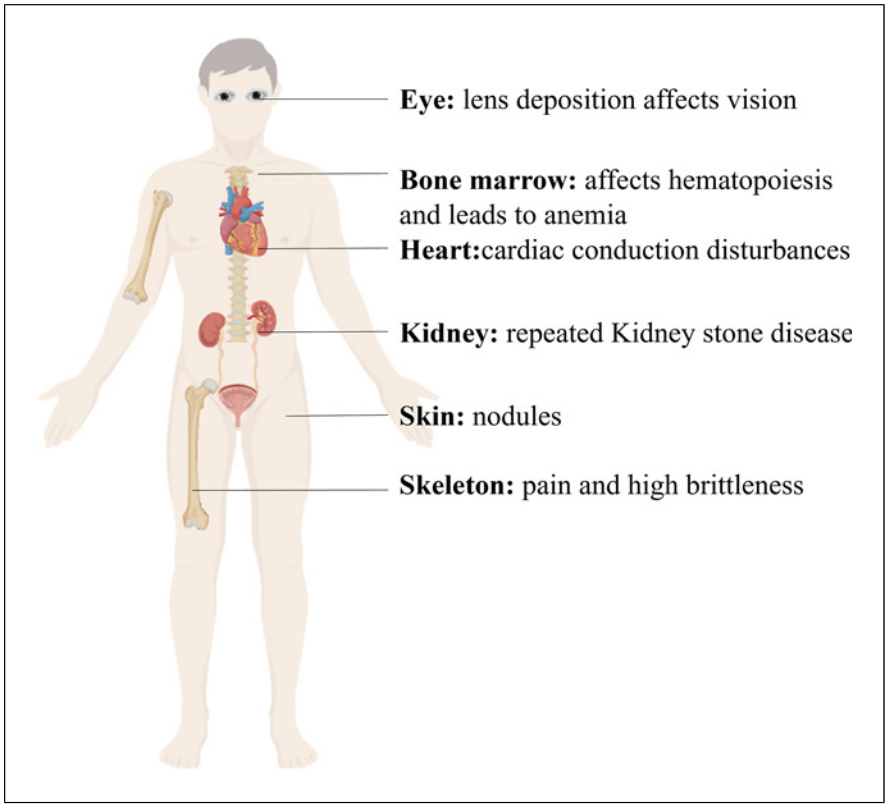

Fig. 3. When plasma oxalate exceeds 35–50 mmol/L, its physical and chemical properties are conducive to crystallization, leading to systemic calcium oxalate crystal deposition.

and accelerate CKD progression [65]. After liver transplantation, the plasma oxalate concentration decreases rapidly, indicating that plasma oxalate is a strong indicator of liver oxalate production. Meanwhile, plasma oxalic acid levels can indicate clinical endpoints, especially when patients are in CKD 3b-5 [57].

Diagnostic Biomarker

The detection of biomarkers can guide the diagnosis of PH, such as PH1 (glycolate), PH2 (glycerate), and PH3 (4OHGlu, which is the precursor to HOG in the hydroxyproline catabolic pathway) [66]. For example, in addition to the increase in urinary oxalate, urine L-neneneba glycerate in PH2 patients also increased frequently. As a result, it might be possible to detect these special biomarkers in blood or urine in order to screen for symptomatic patients and newborns with PH.

Diagnosis

Because of PH's rarity, many patients are not identified until a few years after symptoms appear. Even after kidney transplantation (KT) for ESRD, the diagnosis is made only after kidney failure again. A retrospective study of PH1 patients showed that timely diagnosis and treatment at the stage of preserving renal function may change the course of disease [44]. Therefore, early diagnosis of suspicious patients is beneficial to early intervention and reduces the damage to renal function. PH should be considered for any patient with renal failure of unknown cause, especially in the case of renal calcification or severe stone burden [67]. Children under the age of 4 years, who are individuals with complex stone problems and reduced kidney function, should be required for more frequent assessments [68]. In addition to the increase of oxalate in urine, PH2 patients are often accompanied by the increase of L-glycerate in urine [17], which is helpful for the clinical diagnosis of PH2.

PH diagnosis (shown in Fig. 4) needs to be combined with clinical and imaging studies: repeated urinary calculi, NC, and renal injury are strong evidence for a clinical diagnosis of PH. It is also necessary to conduct biochemical tests on oxalate, calcium, citrate, and sodium in the urine. Sometimes, a renal biopsy can obtain a histological diagnosis. These include calcium oxalate crystals, often best appreciated in polarized light, and sometimes features of acute inflammation not expected in

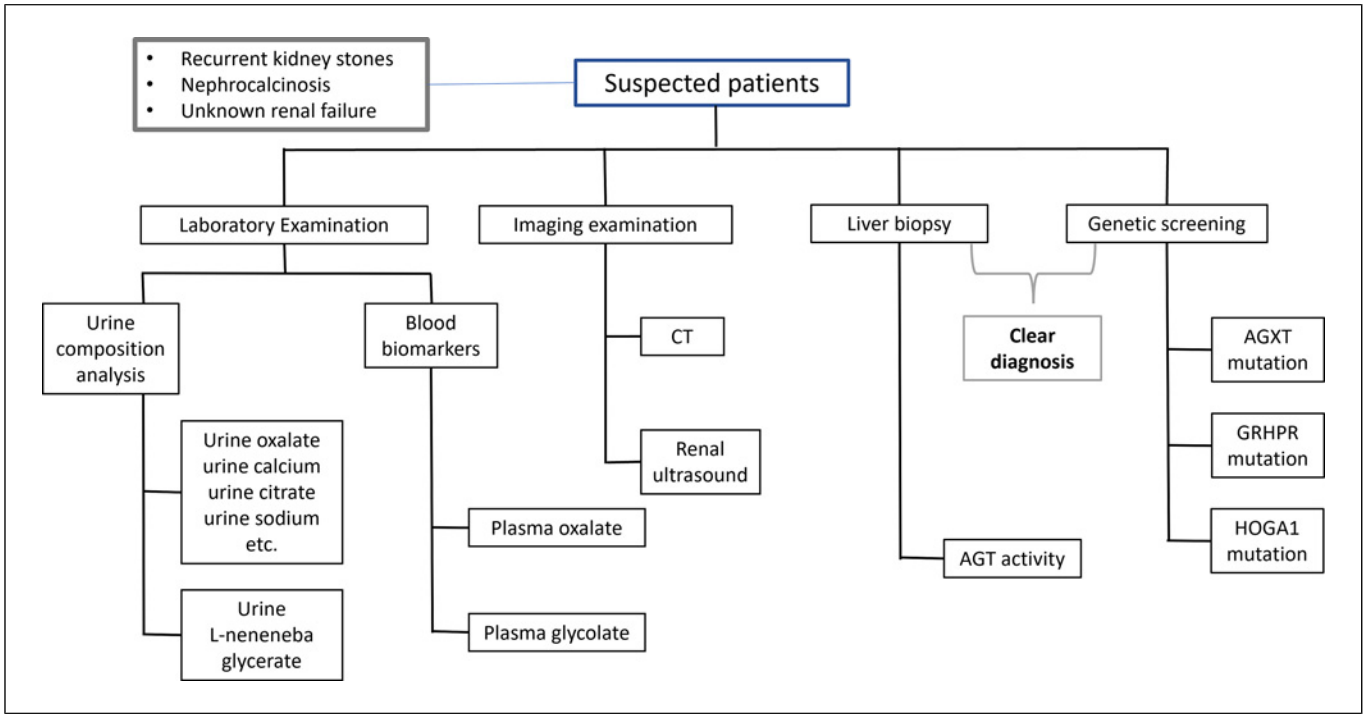

Fig. 4. Diagnostic process of PH.

cases with bland urinary sediment [69]. Recently, it has been discovered that gas chromatography-mass spectrometry is a sensitive detection method for quantifying plasma oxalate, suitable for pediatric patients [70].

However, the final diagnosis of PH mainly depends on results from liver biopsy and genetic screening. Liver biopsy proved that the lack of glycolate metabolism-related enzymes in patients was the main evidence for PH diagnosis in the past. However, with gene technology, gene detection has become necessary evidence for diagnosis. At present, genetic analysis of *AGXT* gene can replace liver biopsy as the first step and has high sensitivity. PH2 and PH3 should be considered in patients with hyperoxaluria with normal AGT activity or without AGXT mutation.

Management

Basic Support Measures

Once the patient is diagnosed with PH, supportive measures should be taken immediately to reduce oxalate crystals in the kidney. This will reduce renal function damage.

Patients need to ingest at least 2 L (even up to 3 L) of liquid per square meter of body surface area every day to promote oxalate excretion and reduce stone production. However, it is difficult to swallow a lot of liquid, especially for children. Even some patients and infants with poor compliance need gastric tubes [71]. Second, oral calcium can reduce intestinal oxalate intake and oxalate load. In addition, citrate works as a crystallization inhibitor, preventing oxalate crystallization [72].

Primary indications for surgical intervention include pain, infection, and obstruction [73]. H patients often show repeated urinary stones, which may require placement of a ureteral stent, ureteroscopic lithotripsy, shock wave lithotrips, or open nephrolithotripsy [71]. It remains to be seen whether surgical stone removal will worsen renal function, especially the effect of open and percutaneous surgery on GFR [74].

Molecular Chaperones

Pyridoxine Treatment

Most PH1-related mutations affect structural changes in protein folding efficiency and lead to various downstream effects, including an increased trend of aggregation or intracellular degradation, or AGT mistakenly targeting mitochondria with ineffective protein metabolism [75]. Pyridoxine (vitamin B6) has been shown to be effective in treating PH1 patients with specific AGXT variants and part of the reason is its action on protein

folding [76, 77]. Pyridoxine leads to a decrease in urine oxalate in ~30% of patients with PH1, particularly those with p.G170R and p.F152I genotypes [78]. However, it is used in some PH1 patients, but not in others. Isotope infusion protocols could evaluate the efficacy of new therapies by investigating pyridoxine responsiveness [79]. Considering the response of some mutations to vitamin B6, early detection and testing of vitamin B6 reactivity is of great significance.

Dequalinium Chloride Treatment

As mentioned earlier, some PH1 patients do not lack AGT enzymes, but incorrect targeting. It is therefore desirable to relocate it to the peroxisome. Dequalinium chloride (DECA) is a small molecule that inhibits mitochondrial protein translocation. Similar to Pyridoxine, DECA restores proper AGT peroxidase transport. In in vitro cell experiments, exposure to DECA can reduce oxalate accumulation, similar to pyridoxine treatment in a small proportion of PH1 patients [80].

Kidney Replacement Therapy

Dialysis

When PH patients reach the ESRD stage, they receive dialysis treatment. Patients with PH need more intensive dialysis to remove sufficient endogenous oxalate [81]. However, renal replacement therapy is still insufficient to compensate for the expected oxalate production [82]. If PH1 patients respond completely to pyridoxine and the administration of pyridoxine is not interrupted, they may respond well to lower intensity dialysis [19].

Transplantation

Longer dialysis periods result in adverse outcomes. Thus, transplantation before systemic oxalosis is imperative. Transplantation methods include simple KT, preemptive liver transplant, combined (CLKT), or sequentially performed (SLKT).

No renal replacement therapy can remove enough oxalate in PH1. After simple KT, it still produces too much oxalate, and the new graft still has a high oxalate load. Meanwhile, after KT, tissue oxalate storage is released, which can rapidly damage the allografts. So, patients with a history of NC or nephrolithiasis in both kidneys need preoperative screening for PH and appropriate treatment before KT [83].

Liver transplantation can fundamentally solve excessive oxalate production. Preemptive liver transplantation before renal failure is a better option to prevent long-term deterioration of renal function, but the timing of transplantation and posttransplant treatment is still unclear [84, 85]. The European guidelines recommend CLKT or SLKT for all PH1 CKD stage 4 and 5 patients [86]. Metry et al. [87] suggested that CLKT leads to superior kidney graft survival compared to isolated KT. Buscher et al. [88] followed up on 10 pediatric patients with PH who underwent liver and KT. Among them, 9 patients maintained stable kidney and liver function and had partial improvements in bone health and growth (no more pathological fractures and moderate catch-up growth). The liver and kidney survival rates of adolescents after 1, 10, and 15 years are 90%, 75%, and 75% [89], with good long-term outcomes. Hence, whether CLKT or SLKT is more appropriate still needs to be evaluated.

It is worth noting that pyridoxine treatment can help some PH1 patients reduce or even achieve close to normal concentrations of urinary oxalate (as described above). Therefore, pyridoxine combined with KT should be considered for PH1 patients with a homozygous G170R mutation [90, 91].

In China, an 8-month-old PH1 infant who underwent simultaneous liver and KT is currently the smallest recipient of simultaneous liver and KT in China [22]. The patient is currently 3 years old, with normal kidney function, and is still undergoing regular follow-up. This indicates that liver and KT still plays an important role in PH patients.

RNA Interference Therapeutic Agents

Another treatment option is to target the key enzymes of glycolate metabolism: substrate reduction therapy. Silence the liver-specific glycolate oxidase (GO) and lactate dehydrogenase (LDH) through RNA interference (RNAi) therapy, and then reduce the production of oxalate precursors and oxalate. Some drugs have been introduced into clinical or experimental trials. However, long-term follow-up data are needed to determine whether RNAi therapy can delay (and ideally prevent) kidney failure in PH1 patients [92]. At present, there have been no reports on the use of RNAi drugs such as Lumasiran in China.

GO Inhibitor

GO is a liver peroxidase upstream of AGT. The inhibition of GO may prevent PH1 pathological development through reducing glycolate conversion to glyoxylate. The content of nontoxic glycolate increased, while oxalate decreased due to the reduction of its precursor glyoxylate. However, in PH2 and PH3 patients, inhibition of GO cannot reduce oxalate production in the liver.

Lumasiran (ALN-GO1) is a subcutaneously administered, liver-directed RNAi therapeutic agent. It is a

N-acetylgalactosamine-coupled small interfering RNA (siRNA) and targets GO mRNA. ALN-GO1 can reduce GO and ultimately reduce oxalate production [93]. Lumasiran showed rapid urination, decreased plasma oxalate concentration, and acceptable safety in trials in children <6 years of age with PH1 [94]. On 19th of November 2020, Lumasiran received its first approval for the treatment of PH1 in all age groups in the EU [95]. In a multicenter long-term retrospective and observational study of Lumasiran in the treatment of PH1 [96], the safety of Lumasiran was once again confirmed, and it was found to effectively reduce urinary oxalate levels in patients with renal function preservation and plasma oxalate levels in HD patients without significant systemic oxalate deposition. The efficacy of early Lumasiran treatment in improving renal calcification and even normalization in infants, and starting treatment quickly without waiting for genetic confirmation, may have an impact on long-term outcomes [97].

LDH Inhibitor

LDH participates in the final step of oxalate production by catalyzing glyoxylate to oxalate in hepatocyte cytoplasm. At the same time, patients with LDH deficiency do not always show visible pathological phenotypes, signs, or syndromes. LDHA subunit is mainly expressed in muscle and liver. Therefore, the specific knockdown of LDHA can reduce LDH content in the liver. In an animal experiment [98], treatment with siRNA targeting liver LDHA resulted in a significant decrease (75%) in urine oxalate excretion in PH1 animals, while PH2 mice was relatively small (32%). Similar findings were reported by Wood et al. [99]. Results from these studies suggest that RNAi-mediated reduction of hepatic LDHA and siRNA may be an effective strategy to reduce oxalate synthesis in PH. Additional studies should also be needed to clarify whether there are alternate enzymatic pathways in the liver to create oxalate.

Nedosiran is a synthetic, double-stranded RNA oligonucleotide (siRNA) designed to target the mRNA encoding LDHA. Clinical trials have shown that nedosiran can reduce the 24-h average excretion of oxalate in PH patients and have acceptable safety and pharmacological effects in the PH for each type [100–104]. This indicates the application potential of this drug in PH patients with ESRD. Nedosiran was first approved in the UAS on September 29, 2023, to reduce urinary oxalate levels in children aged ≥9 years and adults with PH1 and relatively preserved kidney function [105]. However, whether nedosiran will inhibit LDH activity in other tissues and its potential adverse consequences await further investigation.

Restore Normal Liver Enzyme Metabolism

Combination liver and KT have some limitations, including the scarce supply of suitable organs, the significant incidence rate and mortality, and the lifelong demand for immunosuppressants. Therefore, it is desirable to use less invasive methods to change liver enzyme metabolism in patients. Normalization of only a small number of hepatocytes cannot correct excessive endogenous oxalate production because unconverted hepatocytes will continue to produce oxalate.

Hepatocyte transplantation, which is much less invasive, may provide an attractive alternative. Jiang et al. [106] reduced the proliferative potential of host hepatocytes using preparative hepatic irradiation and stimulated mitosis at the same time, so that a large number of transplanted hepatocytes could proliferate again. The results showed that hepatocyte transplantation resulted in liver re-proliferation levels sufficient to correct hyperoxaluria in PH1 mouse models.

Gene therapy is an attractive option for alternative treatments for PH. Targeted gene therapy using CRISPR/Cas9 technology for human induced pluripotent stem cells can correct abnormal liver cells in patients with PH [107]. In addition, in animal models, AAV-delivered paired *Staphylococcus aureus* nickases (D10ASaCas9) to target the *Hao1* gene has therapeutic effects on PH1 mice [108]. Nieto-Romero et al. [109] generated autologous healthy induced liver cells (iHeps) from fibroblasts derived from PH1 patients and found that the generated AGXT corrected iHeps displayed a liver gene expression profile and showed in vitro reversal of oxalate accumulation. This provides new possibilities for the implementation of liver cell replacement therapy and the establishment of personalized PH1 in vitro disease models in the future. Chen et al. [110] found that hat systemic delivery of dual adeno-associated virus encoding a split-ABE8e could artificially repair 13% of the pathogenic allele in AGXT. However, the long-term safety and efficacy of gene therapy still needs further validation.

Direct Inhibition of GO/LDH

Stiripentol (Diacomit) is an antiepileptic drug for the treatment of Dravet syndrome and has recently been shown to inhibit LDH-5 Isoenzymes and decrease oxalate synthesis by hepatocytes [111, 112]. In an ongoing phase 2 clinical trial [113], urinary oxalate concentration continued to decrease during treatment with stiripentol. At 34 months, the patient's plasma oxalate level and renal function remained normal. Therefore, treatment with stiripentol is well tolerated.

Oxalate Decarboxylase

A prospective, double-blind study showed that oxalate decarboxylase significantly decreased urine oxalate in healthy subjects on a high-oxalate diet but had no effect on creatinine clearance, urine creatinine, or other solutes related to calcium oxalate supersaturation [114]. This means that oxalate decarboxylase can reduce the excretion burden of excessive endogenous oxalate produced by PH patients and protect renal function.

Conclusion

PH is a rare autosomal recessive disorder. The increased production of endogenous oxalate can lead to repeated kidney stones, impaired renal function, renal failure, and systemic oxalate poisoning, severely affecting patients' quality of life and even their lives. Symptomatic treatment alone cannot reduce oxalate load in PH patients. Patients with PH need to fundamentally restore glyoxylate metabolism in the liver. Liver transplantation, interfering RNA, gene editing, and other treatments can be considered for patients. With the rapid development of cutting-edge technologies, genetic testing allows suspected patients to be diagnosed early. It also reduces the impact of oxalate deposition on the body's systems. In addition, gene therapy research continues to progress, which may improve the disease level and quality of life for PH patients. The gradual application of RNAi therapy can treat PH patients or be combined with simple KT to improve patient prognosis.

In China, only a small number of scattered cases of PH have been reported, and patients often delay diagnosis, even discovering renal failure again after KT. At present, there have been no reports on the use of RNAi drugs such as Lumasiran in China or the implementation of related clinical trials. Currently, the treatment of PH in China still relies mainly on symptomatic and high-throughput dialysis, with poor prognosis (especially for PH1 patients). Some patients have received KT or liver kidney combined transplantation, but long-term follow-up is unknown. Therefore, standardized statistics and follow-up can be conducted on PH patients to further clarify the genotype and phenotype correlation, treatment and prognosis of Chinese PH patients.

Acknowledgments

The relevant information is searched in the PubMed database and Wanfang database.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The funder had no role in the design, data collection, data analysis, and reporting of this study.

Author Contributions

Xingying Zhu is mainly responsible for collecting relevant literature and drafting articles. Wai W. Cheung, Aihua Zhang, and Guixia Ding made significant contributions to the concept and content modification of the article.

References

1 Demoulin N, Aydin S, Gillion V, Morelle J, Jadoul M. Pathophysiology and management of hyperoxaluria and oxalate nephropathy: a review. Am J Kidney Dis. 2022;79(5):717–27. https://doi.org/10.1053/j.ajkd.2021.07.018

2 Rumsby G, Fau Cochat P, Cochat P. Primary hyperoxaluria. New Engl J Med. 2013; 369:2162–3.

3 Hopp K, Cogal AG, Bergstralh EJ, Seide BM, Olson JB, Meek AM, et al. Rare kidney stone C: phenotype-genotype correlations and estimated carrier frequencies of primary hyperoxaluria. J Am Soc Nephrol. 2015; 26(10):2559–70. https://doi.org/10.1681/ASN.2014070698

4 Abid A, Raza A, Khan AR, Firasat S, Shahid S, Hashmi S, et al. Primary hyperoxaluria: comprehensive mutation screening of the disease causing genes and spectrum of disease-associated pathogenic variants. Clin Genet. 2023;103(1):53–66. https://doi.org/10.1111/cge.14240

5 Garrelfs SF, Rumsby G, Peters-Sengers H, Erger F, Groothoff JW, Beck BB, et al. Patients with primary hyperoxaluria type 2 have significant morbidity and require careful follow-up. Kidney Int. 2019;96(6): 1389–99. https://doi.org/10.1016/j.kint.2019.08.018

6 Singh P, Viehman JK, Mehta RA, Cogal AG, Hasadsri L, Oglesbee D, et al. Clinical characterization of primary hyperoxaluria type 3 in comparison with types 1 and 2. Nephrol Dial Transplant. 2022; 37(5):869–75. https://doi.org/10.1093/ndt/gfab027

7 Martin-Higueras C, Garrelfs SF, Groothoff JW, Jacob DE, Moochhala SH, Bacchetta J, et al. A report from the European Hyperoxaluria Consortium (OxalEurope) Registry on a large cohort of patients with primary hyperoxaluria type 3. Kidney Int. 2021;100:621–35. https://doi.org/10.1016/j.kint.2021.03.031

8 Anders HJ, Suarez-Alvarez B, Grigorescu M, Foresto-Neto O, Steiger S, Desai J, et al. The macrophage phenotype and inflammasome component NLRP3 contributes to nephrocalcinosis-related chronic kidney disease independent from IL-1-mediated tissue injury. Kidney Int. 2018;93(3):656–69. https://doi.org/10.1016/j.kint.2017.09.022

9 Darisipudi MN, Knauf F. An update on the role of the inflammasomes in the pathogenesis of kidney diseases. Pediatr Nephrol. 2016;31(4):535–44. https://doi.org/10.1007/s00467-015-3153-z
10 Chen Y, Shang D, Hao C, Zhu T. From recurrent episodes of complex urinary tract infections to diagnosis of type II primary hyperoxaluria (PH): one case report. Fudan J Med Ed. 2019;46:423–6.
11 Deng H, Zhang D, Ding J, Wang F. Two cases of hereditary kidney stones with onset in childhood and progression to end-stage renal disease in adolescence. J Kidney Dis Dial Kidney Transplant. 2019;28:521–5.
12 Cui YJ, Song CL, Cheng YB. Oliguria and acute renal dysfunction in a six-month-old infant. Zhongguo Dang Dai Er Ke Za Zhi. 2017;19(2):203–7. https://doi.org/10.7499/j.issn.1008-8830.2017.02.015
13 Du DF, Li QQ, Chen C, Shi SM, Zhao YY, Jiang JP, et al. Updated genetic testing of primary hyperoxaluria type 1 in a Chinese population: results from a single center study and a systematic review. Curr Med Sci. 2018;38(5):749–57. https://doi.org/10.1007/s11596-018-1941-y
14 Fang X, He L, Xu G, Lin H, Xu M, Geng H. Nine novel HOGA1 gene mutations identified in primary hyperoxaluria type 3 and distinct clinical and biochemical characteristics in Chinese children. Pediatr Nephrol. 2019;34(10):1785–90. https://doi.org/10.1007/s00467-019-04279-7
15 Ge Y, Liu Y, Zhan R, Zhao Z, Li J, Wang W, et al. HOGA1 variants in Chinese patients with primary hyperoxaluria type 3: genetic features and genotype-phenotype relationships. World J Urol. 2023;41(8):2141–8. https://doi.org/10.1007/s00345-023-04461-5
16 He L, Xu G, Fang X, Lin H, Xu M, Yu Y, et al. Identification of 8 novel gene variants in primary hyperoxaluria in 21 Chinese children with urinary stones. World J Urol. 2019;37:1713–21. https://doi.org/10.1007/s00345-018-2563-5
17 Lam CW, Yuen YP, Lai CK, Tong SF, Lau LK, Tong KL, et al. Novel mutation in the GRHPR gene in a Chinese patient with primary hyperoxaluria type 2 requiring renal transplantation from a living related donor. Am J Kidney Dis. 2001;38(6):1307–10. https://doi.org/10.1053/ajkd.2001.29229
18 Li GM, Xu H, Shen Q, Gong YN, Fang XY, Sun L, et al. Mutational analysis of AGXT in two Chinese families with primary hyperoxaluria type 1. BMC Nephrol. 2014;15:92. https://doi.org/10.1186/1471-2369-15-92
19 Li X, Gu J, Yang Y, Li J, Li Y. A putative mutation hotspot of the AGXT gene associated with primary hyperoxaluria type 1 in the Chinese population. Tohoku J Exp Med. 2018;246(4):233–41. https://doi.org/10.1620/tjem.246.233
20 Liao X, Li YJ, Zhong F, Chen Y, Tan M, Liao YR, et al. Clinical analysis of seven cases with primary hyperoxaluria type 1 in children. Zhonghua Er Ke Za Zhi. 2020;58(2):129–34. https://doi.org/10.3760/cma.j.issn.0578-1310.2020.02.012
21 Lu X, Chen W, Li L, Zhu X, Huang C, Liu S, et al. Two novel AGXT mutations cause the infantile form of primary hyperoxaluria type I in a Chinese family: research on missed mutation. Front Pharmacol. 2019;10:85. https://doi.org/10.3389/fphar.2019.00085
22 Ni T, Sun Z, Zhao F. A case report of invasive infantile primary hyperoxaluria type 1 and literature review. CEN Case Rep. 2023;12(2):159–63. https://doi.org/10.1007/s13730-022-00740-z
23 Wang C, Lu J, Lang Y, Liu T, Wang X, Zhao X, et al. Two novel AGXT mutations identified in primary hyperoxaluria type-1 and distinct morphological and structural difference in kidney stones. Sci Rep. 2016;6:33652. https://doi.org/10.1038/srep33652
24 Wang W, Liu Y, Kang L, He R, Song J, Li Y, et al. Mutation hot spot region in the HOGA1 gene associated with primary hyperoxaluria type 3 in the Chinese population. Kidney Blood Press Res. 2019;44(4):743–53. https://doi.org/10.1159/000501458
25 Wang X, Zhao X, Wang X, Yao J, Zhang F, Lang Y, et al. Two Novel HOGA1 splicing mutations identified in a chinese patient with primary hyperoxaluria type 3. Am J Nephrol. 2015;42(1):78–84. https://doi.org/10.1159/000439232
26 Wu J, Song J, He Y, Zhong C, Yang Q, Li Q, et al. Case series and literature review of primary hyperoxaluria type 1 in Chinese patients. Urolithiasis. 2023;51:123. https://doi.org/10.1007/s00240-023-01494-8
27 Xin Q, Dong Y, Guo W, Zhao X, Liu Z, Shi X, et al. Four novel variants identified in primary hyperoxaluria and genotypic and phenotypic analysis in 21 Chinese patients. Front Genet. 2023;14:1124745. https://doi.org/10.3389/fgene.2023.1124745
28 Xu CB, Zhou XD, Xu HE, Zhao YL, Zhao XH, Liu DH, et al. A novel nonsense variant of the AGXT identified in a Chinese family: special variant research in the Chinese reference genome. BMC Nephrol. 2021;22(1):83. https://doi.org/10.1186/s12882-021-02276-3
29 Yuen YP, Lai CK, Tong GM, Wong PN, Wong FK, Mak SK, et al. Novel mutations of the AGXT gene causing primary hyperoxaluria type 1. J Nephrol. 2004;17(3):436–40.
30 Zhao F, Li J, Tang L, Li C, Wang W, Ning C. Characteristics of the genotype and phenotype in Chinese primary hyperoxaluria type 1 populations. Urolithiasis. 2021;49:17–25. https://doi.org/10.1007/s00240-020-01201-x
31 Zhao Y, Yang Y, Zhou P, Jiang J, Chen Z, Du D. Novel mutations in response to vitamin B6 in primary hyperoxaluria type 1 after only kidney transplantation: a case report. Transl Androl Urol. 2020;9(6):2848–54. https://doi.org/10.21037/tau-20-979
32 Ji X, Liu J, Wang C, Chen J, Fang X, Shen Q, et al. A series report of 8 cases of primary hyperoxaluria type 3 and literature review. Chin J Evid Based Pediatr. 2022;17:230–4.
33 Wang X, Fu Y, Liu S, Wu S, Yu J, Gao B. One case of renal transplant failure caused by primary hyperoxaluria and literature review. Chin Exp Diagn. 2016;20:1030–1.
34 Li X, Chen S, Liu N, Huang W, Zhang G. A case of primary hyperoxaluria type 2 patient presenting with bilateral kidney stones, renal insufficiency, and decreased whole blood cells. Chin J Nephrol. 2019;35:618–20.
35 Shao L, Lang Y, Wang X, Zhang F, Wang X. Analysis of mutated genes in a family with type-primary hyperoxaluria. Chin J Nephrol. 2015;31:743–8.
36 Zhang J, Cai X, Chen Y, Deng H, Xu Z, Li Y. Clinical and AGXT gene mutation analysis of primary type 1 hyperoxaluria in children. J Clin Pediatr. 2020;38:191–5.
37 Gao Y, Zhang F, Shao L. A case of primary hyperoxaluria type I. Chin J Pediatr. 2017;55:224–5.
38 Wang W, Yan Z, Deng W, Xia R, Zeng W, Luo J, et al. Multidisciplinary comprehensive diagnosis and treatment of type I primary hyperoxaluria leading to transplant renal insufficiency after kidney transplantation. J Organ Transplant. 2021;12:77–82.
39 Zhang C, Huang Z, Li L, Mao H, Xing C. A case of primary hyperoxaluria. Chin J Nephrol. 2018;34:627–8.
40 Kuang Q, Gao C, Shi Z, Xia Z. Report of 2 cases of primary type-hyperoxaluria in children and literature review. J Clin Pediatr. 2020;38:414–7.
41 Du Y, Wang Y, Ma L, Guo Z. A case of primary hyperoxaluria type 1 in children caused by AGXT gene mutation. Int J Genet. 2023;46:150–3.
42 Shao L, Ye B, Chen M, Jiang X, Li Y, He Q. A case of primary type 1 hyperoxaluria in adults. Chin J Nephrol. 2018;34:136–8.
43 Zhou Y, Zhou Y, Liu Z, Cheng C. Multiple kidney stones, hyperoxaluria, renal insufficiency. J Kidney Dis Dial Kidney Transplant. 2015;24:395–9.
44 Harambat J, Fargue S, Acquaviva C, Gagnadoux MF, Janssen F, Liutkus A, et al. Genotype-phenotype correlation in primary hyperoxaluria type 1: the p.Gly170Arg AGXT mutation is associated with a better outcome. Kidney Int. 2010;77(5):443–9. https://doi.org/10.1038/ki.2009.435
45 Naguib S, Mansour LA, Soliman NA, El-Hanafy HM, Fahmy YA, Elmonem MA, et al. Expanding the genetic spectrum of AGXT gene variants in Egyptian patients with primary hyperoxaluria type I. Genet Test Mol Biomarkers. 2024;28(4):151–8. https://doi.org/10.1089/gtmb.2023.0525
46 Metry EL, Garrelfs SF, Deesker LJ, Acquaviva C, D'Ambrosio V, Bacchetta J, et al. Determinants of kidney failure in primary hyperoxaluria type 1: findings of the European hyperoxaluria consortium. Kidney Int Rep. 2023;8(10):2029–42. https://doi.org/10.1016/j.ekir.2023.07.025

47 Boussetta A, Fatnassi R, Jellouli M, Maamouri R, Mrad R, Gargah T, et al. Primary hyperoxaluria type 1: clinical, genetic, and evolutionary characteristics in Tunisian children. 2023.
48 Rumsby G, Williams E, Coulter-Mackie M. Evaluation of mutation screening as a first line test for the diagnosis of the primary hyperoxalurias. Kidney Int. 2004;66(3):959–63. https://doi.org/10.1111/j.1523-1755.2004.00842.x
49 Krishnasamy S, Deepthi B, Kamath N, Iyengar A, Thomas CC, Uthup S, et al. Clinical characteristics, genetic profile and short-term outcomes of children with primary hyperoxaluria type 2: a Nationwide experience. Pediatr Nephrol. 2024;39(4):1093–104. https://doi.org/10.1007/s00467-023-06200-9
50 Takayama T, Takaoka N, Nagata M, Johnin K, Okada Y, Tanaka S, et al. Ethnic differences in GRHPR mutations in patients with primary hyperoxaluria type 2. Clin Genet. 2014;86(4):342–8. https://doi.org/10.1111/cge.12292
51 M'Dimegh S, Aquaviva-Bourdain C, Omezzine A, Souche G, M'Barek I, Abidi K, et al. HOGA1 gene mutations of primary hyperoxaluria type 3 in Tunisian patients. J Clin Lab Anal. 2017;31:e22053. https://doi.org/10.1002/jcla.22053
52 Abid A. Possible ethnic associations in primary hyperoxaluria type-III-associated HOGA1 sequence variants. Mol Biol Rep. 2021;48(4):3841–4. https://doi.org/10.1007/s11033-021-06380-3
53 Williams EL, Bockenhauer D, van't Hoff WG, Johri N, Laing C, Sinha MD, et al. The enzyme 4-hydroxy-2-oxoglutarate aldolase is deficient in primary hyperoxaluria type 3. Nephrol Dial Transplant. 2012;27(8):3191–5. https://doi.org/10.1093/ndt/gfs039
54 Zhao Y, Li Y, Fang X, He L, Fan Y, Geng H, et al. Extended genetic analysis of exome sequencing for primary hyperoxaluria in pediatric urolithiasis patients with hyperoxaluria. Gene. 2022;815:146155. https://doi.org/10.1016/j.gene.2021.146155
55 Wang X, Danese D, Brown T, Baldwin J, Sajeev G, Cook EE, et al. Primary hyperoxaluria type 1 disease manifestations and healthcare utilization: a multi-country, online, chart review study. Front Med. 2021;8:703305. https://doi.org/10.3389/fmed.2021.703305
56 Arnous MG, Vaughan L, Mehta RA, Schulte PJ, Lieske JC, Milliner DS. Characterization of stone events in patients with type 3 primary hyperoxaluria. J Urol. 2023;209(6):1141–50. https://doi.org/10.1097/JU.0000000000003400
57 Milliner DS, McGregor TL, Thompson A, Dehmel B, Knight J, Rosskamp R, et al. End points for clinical trials in primary hyperoxaluria. Clin J Am Soc Nephrol. 2020;15(7):1056–65. https://doi.org/10.2215/CJN.13821119
58 Lin JA, Liao X, Wu W, Xiao L, Liu L, Qiu J. Clinical analysis of 13 children with primary hyperoxaluria type 1. Urolithiasis. 2021;49(5):425–31. https://doi.org/10.1007/s00240-021-01249-3
59 Mandrile G, van Woerden CS, Berchialla P, Beck BB, Acquaviva Bourdain C, Hulton SA, et al. Data from a large European study indicate that the outcome of primary hyperoxaluria type 1 correlates with the AGXT mutation type. Kidney Int. 2014;86(6):1197–204. https://doi.org/10.1038/ki.2014.222
60 Fadel FI, Kotb MA, Abdel MMA, Hasanin RM, Salem AM, Fathallah MG, et al. Primary hyperoxaluria type 1 in children: clinical classification, renal replacement therapy, and outcome in a single centre experience. Ther Apher Dial. 2022;26:162–70. https://doi.org/10.1111/1744-9987.13666
61 Bakkaloglu SA, Buyukkaragoz B, Pinarbasi AS, Leventoglu E, Saygili S, Comak E, et al. Comprehensive evaluation of patients with primary hyperoxaluria type 1: a nationwide study. Nephrology. 2024;29(4):201–13. https://doi.org/10.1111/nep.14273
62 Hassona Y, Hassan S, Atef A, Flaifl Y, Al-Shammas F, Abdaljaleel M. Primary hyperoxaluria: description of a new oral finding and review of literature. Spec Care Dentist. 2024. https://doi.org/10.1111/scd.12968
63 Zhao F, Bergstralh EJ, Mehta RA, Vaughan LE, Olson JB, Seide BM, et al. Investigators of rare kidney stone C: predictors of incident ESRD among patients with primary hyperoxaluria presenting prior to kidney failure. Clin J Am Soc Nephrol. 2016;11(1):119–26. https://doi.org/10.2215/CJN.02810315
64 Sas DJ, Mara K, Mehta RA, Seide BM, Banks CJ, Danese DS, et al. Natural history of urine and plasma oxalate in children with primary hyperoxaluria type 1. Pediatr Nephrol. 2024;39:141–8. https://doi.org/10.1007/s00467-023-06074-x
65 Ermer T, Eckardt KU, Aronson PS, Knauf F. Oxalate, inflammasome, and progression of kidney disease. Curr Opin Nephrol Hypertens. 2016;25(4):363–71. https://doi.org/10.1097/MNH.0000000000000229
66 Greed L, Willis F, Johnstone L, Teo S, Belostotsky R, Frishberg Y, et al. Metabolite diagnosis of primary hyperoxaluria type 3. Pediatr Nephrol. 2018;33(8):1443–6. https://doi.org/10.1007/s00467-018-3967-6
67 Stone HK, VandenHeuvel K, Bondoc A, Flores FX, Hooper DK, Varnell CD Jr. Primary hyperoxaluria diagnosed after kidney transplant: a review of the literature and case report of aggressive renal replacement therapy and lumasiran to prevent allograft loss. Am J Transplant. 2021;21(12):4061–7. https://doi.org/10.1111/ajt.16762
68 Milliner DS, Harris PC, Sas DJ, Lieske JC. Primary hyperoxaluria type 3. BTI: GeneReviews (®); 2015.
69 Moochhala SH, Worcester EM. Primary hyperoxaluria: the adult nephrologist's point of view. Clin Kidney J. 2022;15(Suppl 1):i29–32. https://doi.org/10.1093/ckj/sfac068
70 Yazdanpanah M, Cameron J, Chappel C, Yuan L. Primary hyperoxaluria screening and monitoring: quantitative measurement of plasma oxalate by gas chromatography-mass spectrometry with high sensitivity. Ann Lab Med. 2024;44(3):235–44. https://doi.org/10.3343/alm.2023.0178
71 Lawrence JE, Wattenberg DJ. Primary hyperoxaluria: the patient and caregiver perspective. Clin J Am Soc Nephrol. 2020;15(7):909–11. https://doi.org/10.2215/CJN.13831119
72 Weigert A, Martin-Higueras C, Hoppe B. Novel therapeutic approaches in primary hyperoxaluria. Expert Opin Emerg Drugs. 2018;23(4):349–57. https://doi.org/10.1080/14728214.2018.1552940
73 Ang AJS, Sharma AA, Sharma A. Nephrolithiasis: approach to diagnosis and management. Indian J Pediatr. 2020;87(9):716–25. https://doi.org/10.1007/s12098-020-03424-7
74 Cochat P, Liutkus A, Fargue S, Basmaison O, Ranchin B, Rolland MO. Primary hyperoxaluria type 1: still challenging. Pediatr Nephrol. 2006;21(8):1075–81. https://doi.org/10.1007/s00467-006-0124-4
75 Cellini B. A molecular journey on the pathogenesis of primary hyperoxaluria. Curr Opin Nephrol Hypertens. 2024;33(4):398–404. https://doi.org/10.1097/MNH.0000000000000987
76 Williams EL, Acquaviva C, Amoroso A, Chevalier F, Coulter-Mackie M, Monico CG, et al. Primary hyperoxaluria type 1: update and additional mutation analysis of the AGXT gene. Hum Mutat. 2009;30(6):910–7. https://doi.org/10.1002/humu.21021
77 Cellini B, Montioli R, Oppici E, Astegno A, Voltattorni CB. The chaperone role of the pyridoxal 5'-phosphate and its implications for rare diseases involving B6-dependent enzymes. Clin Biochem. 2014;47(3):158–65. https://doi.org/10.1016/j.clinbiochem.2013.11.021
78 Monico CG, Rossetti S, Olson JB, Milliner DS. Pyridoxine effect in type I primary hyperoxaluria is associated with the most common mutant allele. Kidney Int. 2005;67(5):1704–9. https://doi.org/10.1111/j.1523-1755.2005.00267.x
79 Garrelfs SF, van Harskamp D, Peters-Sengers H, van den Akker CHP, Wanders RJA, Wijburg FA, et al. Endogenous oxalate production in primary hyperoxaluria type 1 patients. J Am Soc Nephrol. 2021;32(12):3175–86. https://doi.org/10.1681/ASN.2021060729

80 Miyata N, Steffen J, Johnson ME, Fargue S, Danpure CJ, Koehler CM. Pharmacologic rescue of an enzyme-trafficking defect in primary hyperoxaluria 1. Proc Natl Acad Sci U S A. 2014;111(40):14406–11. https://doi.org/10.1073/pnas.1408401111
81 Hoppe B, Kemper MJ, Bokenkamp A, Portale AA, Cohn RA, Langman CB. Plasma calcium oxalate supersaturation in children with primary hyperoxaluria and end-stage renal failure. Kidney Int. 1999;56(1):268–74. https://doi.org/10.1046/j.1523-1755.1999.00546.x
82 Guillaume A, Chiodini B, Adams B, Dahan K, Deschenes G, Ismaili K. The struggling odyssey of infantile primary hyperoxaluria. Front Pediatr. 2021;9:615183. https://doi.org/10.3389/fped.2021.615183
83 Cai Z, Ding M, Chen R, Zhu J, Li L, Wu X. Primary hyperoxaluria diagnosed after kidney transplantation: a case report and literature review. BMC Nephrol. 2021;22(1):393. https://doi.org/10.1186/s12882-021-02546-0
84 Horoub R, Shamsaeefar A, Dehghani M, Nikoopour H, Entezari M, Moradi A, et al. Liver transplant for primary hyperoxaluria type 1: results of sequential, combined liver and kidney, and preemptive liver transplant. Exp Clin Transplant. 2021;19(5):445–9. https://doi.org/10.6002/ect.2019.0150
85 Perera MT, Sharif K, Lloyd C, Foster K, Hulton SA, Mirza DF, et al. Pre-emptive liver transplantation for primary hyperoxaluria (PH-I) arrests long-term renal function deterioration. Nephrol Dial Transplant. 2011;26(1):354–9. https://doi.org/10.1093/ndt/gfq353
86 Cochat P, Hulton SA, Acquaviva C, Danpure CJ, Daudon M, De Marchi M, et al. Primary hyperoxaluria Type 1: indications for screening and guidance for diagnosis and treatment. Nephrol Dial Transplant. 2012;27(5):1729–36. https://doi.org/10.1093/ndt/gfs078
87 Metry EL, van Dijk LMM, Peters-Sengers H, Oosterveld MJS, Groothoff JW, Ploeg RJ, et al. Transplantation outcomes in patients with primary hyperoxaluria: a systematic review. Pediatr Nephrol. 2021;36(8):2217–26. https://doi.org/10.1007/s00467-021-05043-6
88 Buscher R, Pape L, Buscher AK. Bone health in children with primary hyperoxaluria type 1 following liver and kidney transplantation. Front Pediatr. 2024;12:1353880. https://doi.org/10.3389/fped.2024.1353880
89 Loos S, Kemper MJ, Schmaeschke K, Herden U, Fischer L, Hoppe B, et al. Long-term outcome after combined or sequential liver and kidney transplantation in children with infantile and juvenile primary hyperoxaluria type 1. Front Pediatr. 2023;11:1157215. https://doi.org/10.3389/fped.2023.1157215
90 Lorenz EC, Lieske JC, Seide BM, Meek AM, Olson JB, Bergstralh EJ, et al. Sustained pyridoxine response in primary hyperoxaluria type 1 recipients of kidney alone transplant. Am J Transplant. 2014;14(6):1433–8. https://doi.org/10.1111/ajt.12706
91 Hoyer-Kuhn H, Kohbrok S, Volland R, Franklin J, Hero B, Beck BB, et al. Vitamin B6 in primary hyperoxaluria I: first prospective trial after 40 years of practice. Clin J Am Soc Nephrol. 2014;9(3):468–77. https://doi.org/10.2215/CJN.06820613
92 Bacchetta J, Lieske JC. Primary hyperoxaluria type 1: novel therapies at a glance. Clin Kidney J. 2022;15(Suppl 1):i17–22. https://doi.org/10.1093/ckj/sfab245
93 Liebow A, Li X, Racie T, Hettinger J, Bettencourt BR, Najafian N, et al. An investigational RNAi therapeutic targeting glycolate oxidase reduces oxalate production in models of primary hyperoxaluria. J Am Soc Nephrol. 2017;28(2):494–503. https://doi.org/10.1681/ASN.2016030338
94 Sas DJ, Magen D, Hayes W, Shasha-Lavsky H, Michael M, Schulte I, et al. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: a new RNAi therapeutic in infants and young children. Genet Med. 2022;24:654–62. https://doi.org/10.1016/j.gim.2021.10.024
95 Erger F, Beck BB. A new era of treatment for primary hyperoxaluria type 1. Nat Rev Nephrol. 2021;17(9):573–4. https://doi.org/10.1038/s41581-021-00449-9
96 Martin-Higueras C, Borghese L, Torres A, Fraga-Bilbao F, Santana-Estupinan R, Stefanidis CJ, et al. Multicenter long-term real world data on treatment with lumasiran in patients with primary hyperoxaluria type 1. Kidney Int Rep. 2024;9:114–33. https://doi.org/10.1016/j.ekir.2023.10.004
97 Kayal D, Sellier-Leclerc AL, Acquaviva-Bourdain C, de Mul A, Cabet S, Bacchetta J. Nephrocalcinosis can disappear in infants receiving early lumasiran therapy. Pediatr Nephrol. 2024;39(7):2079–82. https://doi.org/10.1007/s00467-023-06268-3
98 Lai C, Pursell N, Gierut J, Saxena U, Zhou W, Dills M, et al. Specific inhibition of hepatic lactate dehydrogenase reduces oxalate production in mouse models of primary hyperoxaluria. Mol Ther. 2018;26(8):1983–95. https://doi.org/10.1016/j.ymthe.2018.05.016
99 Wood KD, Holmes RP, Erbe D, Liebow A, Fargue S, Knight J. Reduction in urinary oxalate excretion in mouse models of primary hyperoxaluria by RNA interference inhibition of liver lactate dehydrogenase activity. Biochim Biophys Acta, Mol Basis Dis. 2019;1865(9):2203–9. https://doi.org/10.1016/j.bbadis.2019.04.017
100 Ariceta G, Barrios K, Brown BD, Hoppe B, Rosskamp R, Langman CB. Hepatic lactate dehydrogenase A: an RNA interference target for the treatment of all known types of primary hyperoxaluria. Kidney Int Rep. 2021;6(4):1088–98. https://doi.org/10.1016/j.ekir.2021.01.029
101 Hoppe B, Koch A, Cochat P, Garrelfs SF, Baum MA, Groothoff JW, et al. Safety, pharmacodynamics, and exposure-response modeling results from a first-in-human phase 1 study of nedosiran (PHYOX1) in primary hyperoxaluria. Kidney Int. 2022;101(3):626–34. https://doi.org/10.1016/j.kint.2021.08.015
102 Shee K, Ahn J, Hamouche F, Mena J, Chi T, Stoller ML. Nedosiran dramatically reduces serum oxalate in dialysis-dependent primary hyperoxaluria 1: a compassionate use case report. Urology. 2021;156:e147–9. https://doi.org/10.1016/j.urology.2021.03.014
103 Amrite A, Fuentes E, Marbury TC, Zhang S. Safety, pharmacokinetics, and exposure-response modeling of nedosiran in participants with severe chronic kidney disease. Clin Pharmacol Drug Dev. 2023;12:1164–77. https://doi.org/10.1002/cpdd.1320
104 Goldfarb DS, Lieske JC, Groothoff J, Schalk G, Russell K, Yu S, et al. Nedosiran in primary hyperoxaluria subtype 3: results from a phase I, single-dose study (PHYOX4). Urolithiasis. 2023;51(1):80. https://doi.org/10.1007/s00240-023-01453-3
105 Syed YY. Nedosiran: first approval. Drugs. 2023;83(18):1729–33. https://doi.org/10.1007/s40265-023-01976-4
106 Jiang J, Salido EC, Guha C, Wang X, Moitra R, Liu L, et al. Correction of hyperoxaluria by liver repopulation with hepatocytes in a mouse model of primary hyperoxaluria type-1. Transplantation. 2008;85(9):1253–60. https://doi.org/10.1097/TP.0b013e31816de49e
107 Esteve J, Blouin JM, Lalanne M, Azzi-Martin L, Dubus P, Bidet A, et al. Targeted gene therapy in human-induced pluripotent stem cells from a patient with primary hyperoxaluria type 1 using CRISPR/Cas9 technology. Biochem Biophys Res Commun. 2019;517(4):677–83. https://doi.org/10.1016/j.bbrc.2019.07.109
108 Torella L, Klermund J, Bilbao-Arribas M, Tamayo I, Andrieux G, Chmielewski KO, et al. Efficient and safe therapeutic use of paired Cas9-nickases for primary hyperoxaluria type 1. EMBO Mol Med. 2024;16:112–31. https://doi.org/10.1038/s44321-023-00008-8
109 Nieto-Romero V, Garcia-Torralba A, Molinos-Vicente A, Moya FJ, Rodriguez-Perales S, Garcia-Escudero R, et al. Restored glyoxylate metabolism after AGXT gene correction and direct reprogramming of primary hyperoxaluria type 1 fibroblasts. iScience. 2024;27(4):109530. https://doi.org/10.1016/j.isci.2024.109530
110 Chen Z, Zhang D, Zheng R, Yang L, Huo Y, Zhang D, et al. In vivo base editing rescues primary hyperoxaluria type 1 in rats. Kidney Int. 2024;105(3):496–507. https://doi.org/10.1016/j.kint.2023.11.029

111 Le Dudal M, Huguet L, Perez J, Vandermeersch S, Bouderlique E, Tang E, et al. Stiripentol protects against calcium oxalate nephrolithiasis and ethylene glycol poisoning. J Clin Invest. 2019;129(6):2571–7. https://doi.org/10.1172/JCI99822
112 Martin-Higueras C, Feldkotter M, Hoppe B. Is stiripentol truly effective for treating primary hyperoxaluria? Clin Kidney J. 2021;14(1):442–4. https://doi.org/10.1093/ckj/sfaa068
113 Violier P, Boyer O, Berthaud R, Dorval G. Treatment with stiripentol in a patient with primary hyperoxaluria type 1: lesson for the clinical nephrologist. J Nephrol. 2022;35(3):1049–51. https://doi.org/10.1007/s40620-021-01116-9
114 Quintero E, Bird VY, Liu H, Stevens G, Ryan AS, Buzzerd S, et al. A prospective, double-blind, randomized, placebo-controlled, crossover study using an orally administered oxalate decarboxylase (OxDC). Kidney360. 2020;1(11):1284–90. https://doi.org/10.34067/KID.0001522020