World Journal of Urology (2019) 37:1713–1721
https://doi.org/10.1007/s00345-018-2563-5

ORIGINAL ARTICLE

Identification of 8 novel gene variants in primary hyperoxaluria in 21 Chinese children with urinary stones

Lei He[1] · Guofeng Xu[1] · Xiaoliang Fang[1] · Houwei Lin[1] · Maosheng Xu[1] · Yongguo Yu[1] · Hongquan Geng[1]

Received: 16 April 2018 / Accepted: 7 November 2018 / Published online: 28 November 2018

Abstract

Purpose We analyzed primary hyperoxaluria (PH) genotype and phenotype in Chinese children. Vitamin B_6 response in the patients with genetically confirmed PH1 was also studied.

Methods We, respectively, analyzed 80 children with urinary stones. Sixty-four children were diagnosed with hyperoxaluria. Twenty-one children consented to genetic evaluation (targeted gene panel-based and whole-exome sequencing), and DNA was obtained from the children and both the parents.

Results PH accounted for 57.1% (12/21) of hyperoxaluria cases. We reported 12 PH cases, including 5 PH1, 1 PH2, and 6 PH3 cases; 2 novel mutations in *AGXT* and *GRHPR* each and 4 *HOGA1* mutations were identified. The mutations in *AGXT* and *GRHPR* were c0.1161C>A and c0.551C>A, and c0.370C>T and c0.864_865delTG, respectively. Four *HOGA1* mutations, c0.290G>A, c0.110G>A, c0.554C>T and c0.834_834 + 1delinsTT, were not reported previously. The average urine Ox 24 level in the PH patients was 0.91 mmol/1.73 m^2. Moreover, the average urine Ox 24 level in the PH1 patients (1.07 mmol/1.73 m^2) was higher than that in the PH2 and PH3 patients (0.73 mmol/1.73 m^2 and 0.71 mmol/1.73 m^2, respectively). The eGFR of the PH1 patients (76.86 mL/min) was lower than that of the PH2 and PH3 patients (132 mL/min and 136 mL/min, respectively).

Conclusions PH incidence was higher than the reported PH incidence in children with urinary stones. Hence, we suggested that genetic examination was necessary for all the children with hyperoxaluria. These novel mutations broaden the range of known gene mutations in PH.

Keywords AGXT · GRHPR · HOGA1 · Primary hyperoxaluria

✉ Yongguo Yu
Yuyongguo@xinhuamed.com.cn

✉ Hongquan Geng
Genghongquan@xinhuamed.com.cn

Lei He
Helei@xinhuamed.com.cn

Guofeng Xu
Xuguofeng@xinhuamed.com.cn

Xiaoliang Fang
Fangxiaoliang@xinhuamed.com.cn

Houwei Lin
Linhouwei@xinhuamed.com.cn

Maosheng Xu
Xumaosheng@xinhuamed.com.cn

[1] Department of Pediatric Urology, Xin Hua Hospital Affiliated To Shanghai Jiao Tong University School of Medicine, 1665 Kongjiang Road, Shanghai 200092, China

Abbreviations

PH	Primary hyperoxaluria
ESRD	End-stage renal disease
AGT	Alanine–glyoxylate aminotransferase
HOGA	4-Hydroxy-2-oxoglutarate aldolase
eGFR	Estimated glomerular filtration rate
UOx	Urinary oxalate

Introduction

Primary hyperoxaluria (PH) is a rare, autosomal recessive, inborn error of hepatic glyoxylate metabolism, which is characterized by the overproduction and increased excretion of oxalate. The estimated prevalence of PH is 1–3 per 1,000,000 individuals [1, 2]. However, it is reported that PH accounts for 1–2% of all cases of pediatric end-stage renal disease (ESRD) [3]. The oversaturation of calcium oxalate leads to recurrent urolithiasis and/or nephrocalcinosis, with

reduced renal elimination of calcium oxalate due to renal damage, which results in the deposition of oxalate in all tissues (systemic oxalosis) [4].

Primary hyperoxaluria type 1 (PH1), which is the most frequent and severe form of PH, is caused by the impaired function of alanine–glyoxylate aminotransferase (AGT), which is encoded by *AGXT* [5]. The deficiency of glyoxylate and hydroxypyruvate reductase, which is encoded by *GRHPR*, is responsible for primary hyperoxaluria type 2 (PH2) [6]. A peculiar biochemical characteristic of PH2 is the presence of increased levels of urinary L-glyceric acid. Primary hyperoxaluria type 3 (PH3) is caused by mutations in *HOGA1*, which encodes the mitochondrial enzyme, 4-hydroxy-2-oxoglutarate aldolase (HOGA) that catalyzes the final step of the catabolism of 4-hydroxy-2-oxoglutarate to glyoxylate and pyruvate [7].

To date, more than 200 mutations have been identified in patients with PH [8]. However, few patients with PH among Asians have been reported, especially Chinese children. In this article, we report 12 cases of PH including 5 cases of PH1, 1 case of PH2, and 6 cases of PH3; in addition, 2 novel *AGXT* mutations, 2 novel *GRHPR* mutations, and 4 *HOGA1* mutations were identified in 21 Chinese children. Moreover, we described the phenotype–genotype correlations between the types of PH.

Methods

Patients

We, respectively, analyzed 80 children with urinary stones who presented to our hospital (Department of Pediatric urology, Xin Hua Hospital, affiliated to the Shanghai Jiao Tong University School of Medicine) from August, 2015 to December, 2016. The median age of the patients was 3.9 ± 2.8 years, minimum–maximum, 0.6–12 years. Sixty-four patients were diagnosed with hyperoxaluria (24-h urinary oxalate level > 0.37 mmol/1.73 m^2) [9], of whom 21 patients consented to undergo genetic evaluation, and DNA was obtained from the children and both the parents. The median age of the patients was 3.7 ± 2.6 years, minimum–maximum, 0.7–10 years. Out of 21 children, 19 had stone analysis by infrared spectroscopic analysis; whewellite stone (10/19, 52.6%) was observed most frequently, followed by weddellite stone (7/19, 36.8%) and carbapatite stone (3/19, 15.8%).

Detection of mutations

Genomic DNA was isolated from whole blood treated by ethylenediaminetetraacetic acid (EDTA). All the samples were subjected to exome sequencing using the SureSelect Human All Exon V5 probe (Agilent, Santa Clara, CA, USA). Part of patients were detected by targeted gene panel-based sequencing and others were detected by whole-exome sequencing. Sanger sequencing was used to examine the cosegregation of the candidate variants. Amplified fragments were sequenced by Applied Biosystems 96-capillary 3730XL system. Mutations have been identified in various populations (refer to the Human Gene Mutation Database, HGMD professional 2018.3, https://www.hgmd.org/).

Treatment and follow-up

The intestinal absorption of oxalate is low in patients with PH compared with healthy people; therefore, dietary influence on the variability in oxalate excretion is minor. However, the patients had to avoid diets that were high in oxalate and vitamin C. In addition, the response to vitamin B_6 was studied in the patients with genetically confirmed PH1; the threshold level of the efficacy of the treatment with vitamin B_6 was defined as a relative reduction of 30% in urinary oxalate (UOx) excretion. The oral administration of vitamin B_6 was initiated at 5 mg/kg body weight/day, and increased by 5 mg/kg body weight every 6 weeks up to a final dosage of 20 mg/kg body weight/day in the 24th week. The level of UOx was measured every 6 weeks.

Prediction of the potential pathogenicity of the novel variants

To evaluate the deleterious effect of novel missense variants, the following prediction software tools were used: Polymorphism Phenotyping v2 (PolyPhen-2) (https://genetics.bwh.harvard.edu/pph2), MutationTaster (https://www.mutationtaster.org/); Swiss-Pdb Viewer version 4.1 was used to elucidate the crystallographic structure of the human steroidogenic acute regulatory protein (StAR) at a resolution of 3.40 Å (PDB: 3P0L) for homology modeling (Fig. 1).

Results

Clinical and biochemical data

The clinical features of the 21 patients are summarized in Table 1. The diagnosis of PH in patients 1–12 was genetically confirmed, including five cases of PH1, one case of PH2, and six cases of PH3. The kidney, ureter and bladder (KUB) radiographs of patients 1–12 are shown in Fig. 2. The pathogenic variants are summarized in Table 2.

The average level of urine Ox 24 in the patients with PH was 0.91 mmol/1.73 m^2, which was higher than the level of urine Ox 24 in the patients with hyperoxaluria (0.58 mmol/1.73 m^2), and no gene mutation was detected.

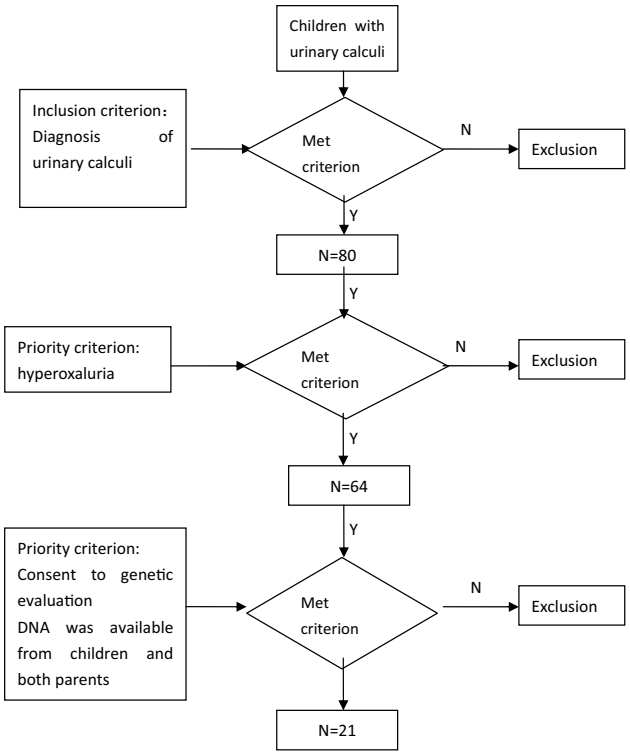


Fig. 1 Inclusion criteria for the patients

Moreover, the average level of urine Ox 24 in the patients with PH1 (1.07 mmol/1.73 m^2) was higher than those of the patients with PH2 and PH3 (0.73 mmol/1.73 m^2 and 0.71 mmol/1.73 m^2, respectively).

The estimated glomerular filtration rate (eGFR) in children and adults was calculated using the Schwartz formula and the Modification for Diet in Renal Disease Study equation, respectively. The eGFR in the patients with PH was 102.84 mL/min, which was lower than that of the patients with hyperoxaluria (127.44 mL/min), and no gene mutation was detected. Among the patients with PH, the eGFR in the patients with PH1 (76.86 mL/min) was lower than those in the patients with PH2 and PH3 (132 mL/min and 136 mL/min, respectively).

Analysis of mutations

The diagnosis of PH in 12 patients, including 5 patients with PH1, 1 with PH2 and 6 with PH3, was genetically confirmed. All the patients with PH1 carried mutations in both the alleles of *AGXT*, three of which were homozygous, and two were heterozygous, as shown in Table 2. Four mutations, namely c0.33dupC, c0.577delC, c0.823_824dupAG, and c0.1072–2A>G, have been reported previously [4, 10, 11]. Two mutations in *AGXT,* namely c0.1161C>A

Table 1 Clinical data of children with hyperoxaluria

Case number	Sex	Age	Age at first onset	Urine Ox 24 (mmol/1.73 m^2)	Urine Cit 24 (mg/1.73 m^2)	Urine Ca 24 (mg/kg)	SCr (μmol/L)	GFR (mL/min)	Urine Ox 24 after treatment with Vit. B_6 (mmol/1.73 m^2)
1	M	4 years	4 years	1.31	34.7	1.09	67	64.8	X
2	M	8 years	8 years	0.47	148.6	1.08	48	115.4	X
3	M	3 years	3 years	1.92	121.7	1.23	99	36.6	1.63
4	M	10 years	6 months	0.39	47.1	1.31	167	29.3	–
5	F	1 year	1 year	1.24	391.8	3.04	22	138.3	0.47
6	M	1 year	12 months	0.73	553.6	6.64	23	132.3	–
7	F	3 years	5 months	0.93	380.1	3.63	29	119.8	–
8	M	1 year	12 months	0.67	197.7	4.52	27	113.9	–
9	F	2 years	10 months	0.52	368.8	2.00	19	175.23	–
10	M	2	2	0.65	489.02	3.59	20	135.75	–
11	M	8 months	8 months	0.95	272.98	4.95	28	96.96	
12	M	1	1	0.59	910.66	2.23	25	133.22	–
13	M	8 years	7 years	0.73	299.33	1.09	36	136.26	
14	F	4 years	4 years	0.47	345.85	8.12	30	130.32	
15	M	6 years	1 year	0.38	278.87	1.23	33	120.67	
16	M	5 years	4 years	0.38	368.11	1.31	29	137.31	
17	F	4 years	4 years	0.94	331.64	3.04	27	128.71	
18	M	1 year	1 year	0.55	209.37	6.64	24	129.72	
19	F	6 years	6 years	0.68	460.82	3.63	33	120.67	
20	F	4 years	3 years	0.75	21.64	4.52	31	122.61	
21	F	4 years	4 years	0.39	46.99	2.00	33	120.67	

Ox 24 24-h oxalate, *Ca 24* 24-h calcium, *Cit 24* 24-h citrate

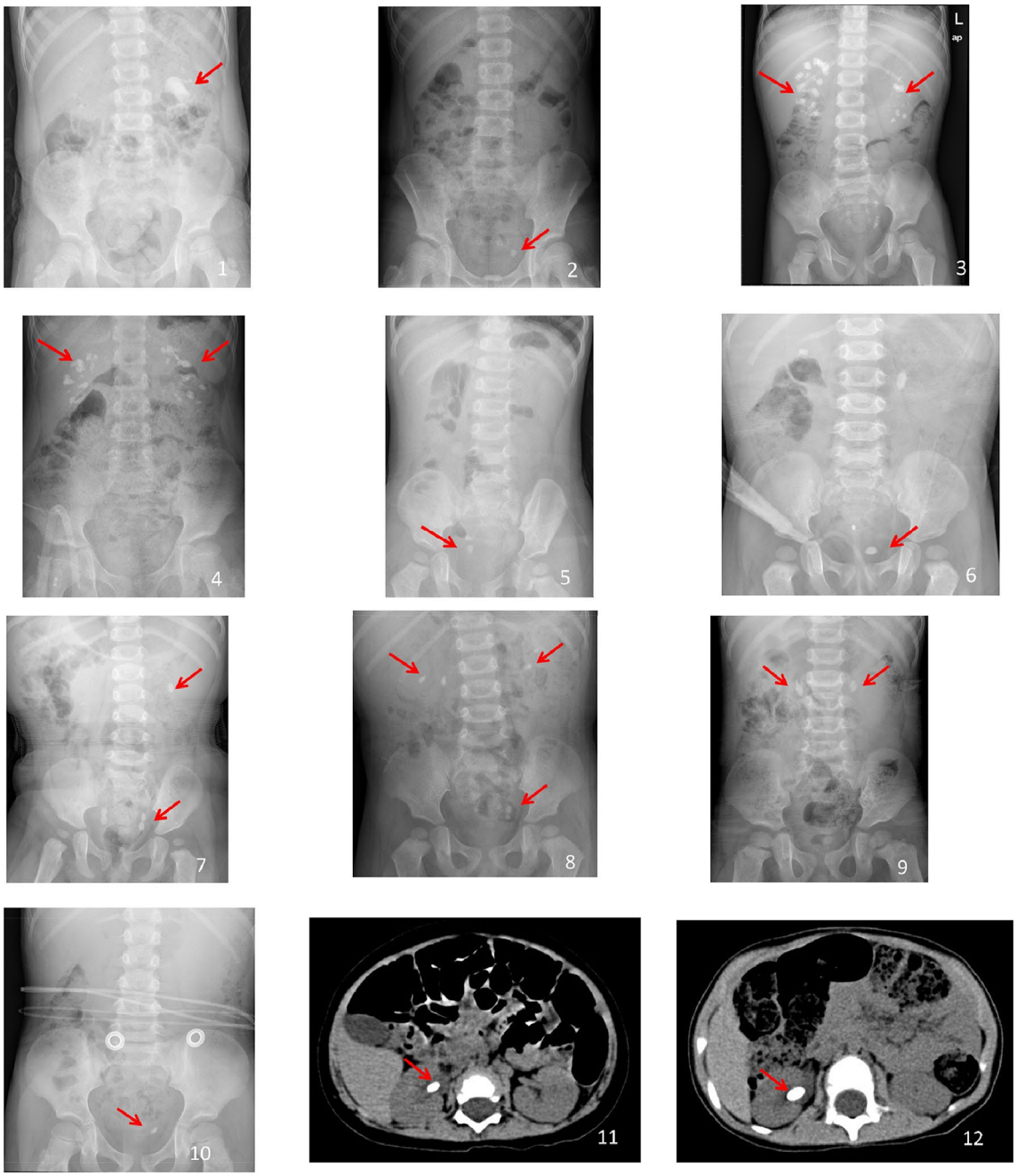


Fig. 2 Kidney, ureter and bladder (KUB) radiographs or computer tomography of patients 1–12

and c0.551C>A, have not been reported previously in the literature.

In patients with PH2, two mutations in *GR*HPR, namely c0.370C>T and c0.864_865delTG, were detected, which have not been reported previously in the literature.

Eight mutations in *HOGA1* were detected in six patients with PH3. Four mutations, namely c0.769T>G, c0.834G>A, c0.715G>A, and c0.208C>T, have been reported previously [12–14]. Four *HOGA1* mutations, c0.290G>A, c0.110G>A, c0.554C>T and c0.834_834 + 1delinsTT, were not reported previously.

The details of the prediction of the deleterious effects of the novel missense variants using the aforementioned software tools are listed in Table 3. The *GRHPR* variant c0.370C>T was predicted to be "probably damaging", with a score of 1.000 by PolyPhen-2, and was classified under the ''disease causing" class, with a score of 0.9999 using MutationTaster. The *HOGA1* variant c0.554C>T was predicted to be ''probably damaging," with a score of 0.855 by PolyPhen-2 software,

Table 2 Pathogenic variants that were identified by gene detection

No.	Gene	Zygosity	Paternal allele				Maternal allele				References
			cDNA	Protein	gnomAD MAF	ExAC MAF	cDNA	Protein	gnomAD MAF	ExAC MAF	
1	AGXT	Heter	c0.33dupC	p.Lys12Glnfs*156	0.016%	Absent	c0.577delC	p.Leu193Phefs*19	0.000%	0.001%	[10]
2	AGXT	Heter	c0.33dupC	p.Lys12Glnfs*156	0.016%	Absent	c0.577delC	p.Leu193Phefs*19	0.000%	0.001%	[10]
3	AGXT	Homo	c0.33dupC	p.Lys12Glnfs*156	0.016%	Absent	c0.33dupC	p.Lys12Glnfs*156	0.016%	Absent	[10]
4	AGXT	Heter	c0.823_824dupAG	p.Ser275Argfs*38	0.001%	0.002%	c0.1072–2A>G		Absent	Absent	[11]
5	AGXT	Heter	**c0.1161C>A**	**p.Cys387***	Absent	Absent	**c0.551C>A**	**p.Ser184**	0.003%	0.002%	
6	GRHPR	Heter	**c0.370C>T**	**p.Arg124Cys**	0.002%	0.002%	**c0.864_865delTG**	**p.Val289fs**	0.004%	0.002%	
7	HOGA1	Heter	c0.769T>G	p.Cys257Gly	0.007%	0.006%	**c0.834_834 + 1delinsTT**		Absent	Absent	[12]
8	HOGA1	Heter	**c0.290G>A**	**p.Arg97His**	0.000%	0.001%	**c0.554C>T**	**p.Thr185Met**	0.049%	0.073%	
9	HOGA1	Homo	c0.834G>A	p.Ala278Ala	0.010%	0.010%	c0.834G>A	p.Ala278Ala	0.010%	0.010%	[13]
10	HOGA1	Heter	**c0.110G>A**	**p.Gly37Asp**	0.001%	0.002%	**c0.834_834 + 1delinsTT**		Absent	Absent	
11	HOGA1	Heter	c0.715G>A; c0.834G>A	p.val239lle; p.Ala278Ala	0.060%;0.010%	0.077%; 0.010%	**c0.834_834 + 1delinsTT**		Absent	Absent	[13]
12	HOGA1	Heter	c0.208C>T	p.Arg70*	0.004%	0.003%	**c0.554C>T**	**p.Thr185Met**	0.049%	0.073%	[14]

Novel mutations are in bold type. Corresponding reference are listed in the last column

Table 3 Prediction of the potential pathogenicity of the novel variants

Gene	Variant	Mutation Taster	PolyPhen-2 (score)	Conservative prediction	gnomAD MAF (%)	ExAC MAF (%)	ACMG classification
GRHPR	c0.370C>T	0.9999	Probably damaging (1.000)	Incompletely conservative (8/9)	0.002	0.002	Likely pathogenic
HOGA1	c0.290G>A	0.9999	Benign (0.030)	Completely conservative	0.000	0.001	Uncertain significance
HOGA1	c0.554C>T	0.7774	Probably damaging (0.855)	Completely conservative	0.049	0.073	Likely pathogenic
HOGA1	c0.110G>A	0.9999	Probably damaging (1.000)	Completely conservative	0.001	0.002	Likely pathogenic

and was classified under the ''disease causing" class, with a score of 0.7774 using MutationTaster. The *HOGA1* variant c0.110G>A was predicted to be ''probably damaging," with a score of 1.000 by PolyPhen-2, and was grouped under the ''disease causing" class, with a score of 0.9999 using MutationTaster. However, the *HOGA1* variant c0.290G>A was predicted to be ''benign," with a score of 0.030 by PolyPhen-2, and was categorized under the ''disease causing" class, with a score of 0.9999 using MutationTaster. The two prediction software tools were suggestive of inconsistent results.

To investigate the potential changes in the folding and structure of the proteins, which were induced by the novel missense variants, three-dimensional (3D) structures of the mutant proteins were generated using Swiss-Pdb Viewer, and then, the structures of both the wild-type and mutant proteins were subjected to energy minimization by NOMAD-Ref. The energy-minimized 3D models are illustrated in Fig. 3. With mutations in the cDNA, the size, polarity, and hydrophobicity of the amino acids in the proteins were also altered. The disappearance of the original hydrogen bonds indicated that the interaction among the amino acid residues was altered, which may have affected the proper folding of the protein.

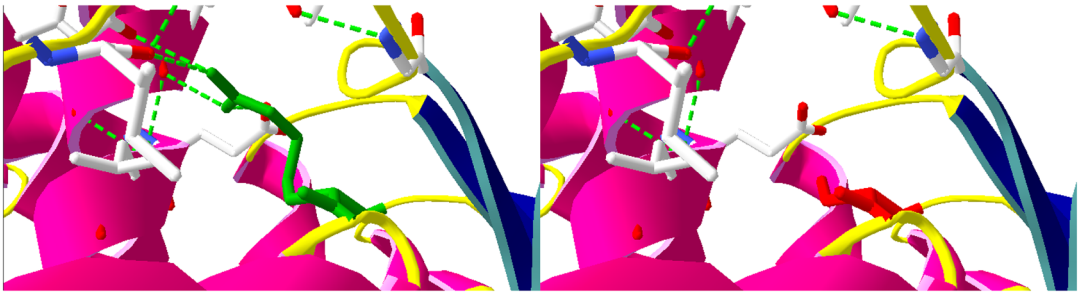
The analysis of the proteins bearing wild-type amino acid residues (left, green) and those with the mutant amino acid residues (right, red), which were encoded by the novel missense variants was performed using Swiss-Pdb Viewer (PDB: 3P0L). The black arrows indicate the differences between the wild-type and mutant models; the green dotted lines represent strong hydrogen bonds; the gray dotted lines represent the hydrogen bonds; the pink ribbons represent alpha-helices; and the blue ribbons represent beta sheets.

Discussion

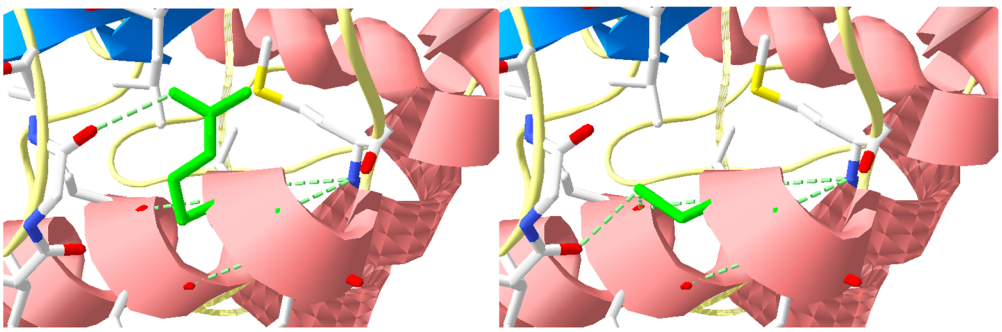
Prevalence of PH

PH is a very rare, inherited condition, whose exact prevalence is unknown. Primary hyperoxaluria type 1, which is the most common form of PH, has an estimated prevalence ranging from 1 to 3 per million individuals and an estimated incidence of ~ 1 per 100,000 live births per year, in Europe [1, 2]. There is no exact numerical value for the prevalence of PH in the patients, especially children with urinary stones and hyperoxaluria in the literature. However, in this study, through genetic detection, it was demonstrated that PH accounted for 57.1% (12/21) of the cases of hyperoxaluria, although not all the cases of hyperoxaluria were detected by whole-exome sequencing. PH accounted for at least 18.8% (12/64) of the cases of hyperoxaluria, and at least 15% (12/80) of all the cases of urinary stones, as demonstrated in this study, which was much higher than the incidence of PH in children with urinary stones, which was reported in the literature. Hopp et al. [8] arrived at the same conclusion; Hopp et al. calculated the prevalence of PH using publicly available whole-exome data. Population analyzes suggested that the degree of commonness of PH was higher than that determined from clinical cohorts (approximate prevalence, 1:58,000; approximate carrier frequency, 1:70). The estimates of the prevalence of PH1 were approximately twice the previous estimates; however, the difference was much more notable for PH3, whose observed carrier frequency in the population under consideration was higher than that of PH1; however, PH3 is sixfold less common in current clinical populations. The carrier frequency of PH2 in the population under consideration is half of that of PH1; however, it is more than sevenfold less common in clinical populations. These observations implied that cases of PH3 (and PH2) are underdiagnosed and/or incompletely penetrant. These results highlighted the role of molecular analyzes in the diagnosis and prognosis of PH, and suggest that detailed analysis of populations with idiopathic stone-forming conditions may be beneficial. Hence, we suggested that genetic examination was necessary for all the children with hyperoxaluria.

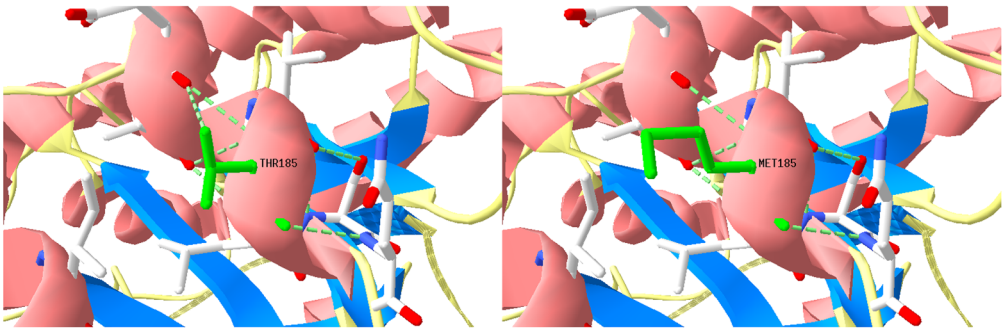
Generally, PH1 is the most severe type of PH, and patients may be affected early in life, during infancy itself, with life-threatening oxalosis. Overall, the disease is characterized by recurrent nephrolithiasis and progressive nephrocalcinosis, which lead to renal damage, and as a result, the disease



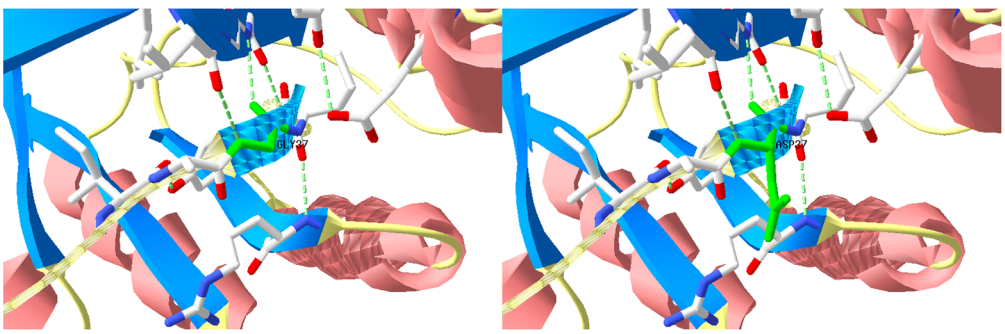
1. *GRHPR* c.370C>T



2. *HOGA1* c.290G>A p.R97H



3. *HOGA1* c.554C>T p.T185M



4. *HOGA1* c.110G>A p.G37D

Fig. 3 Predicted models of novel missense variants

progresses to ESRD during the 3rd–5th decade of life in the majority of the patients [3]. In this report, we present the complete clinical description of 12 Chinese patients with PH. Our results confirmed the high prevalence of ESRD in PH1 at the time of diagnosis; in two of five PH patients, who were 3 and 10 years old, respectively, the disease progressed to CKD stages 3b and 4, and the eGFR was 36.57 mL/min and 29.26 mL/min, respectively. In this study, no patient with PH2 and PH3 presented ESRD. In addition, the average levels of urine Ox 24 in the patients with PH1 were higher than those of the patients with PH2 and PH3, which was consistent with the reports in the literature.

Vitamin B_6 is a coenzyme of AGXT. The administration of pyridoxine hydrochloride has been shown to be associated with a decrease in the level of UOx in ~ 30% of patients with PH [4]. All the patients with PH1 should be tested for pyridoxine responsiveness, and if responsive, they should be treated until liver transplantation is performed [8]. In this study, four of the patients with PH1 received vitamin B_6 treatment (patient 4 was treated by peritoneal dialysis when the genetic diagnosis was confirmed, since the patient refused to receive vitamin B_6 treatment). Patient 5 exhibited a considerable reduction in the level of urine Ox 24 after vitamin B_6 treatment (the level of urine Ox 24 decreased from 1.24 mmol/1.73 m^2 to 0.47 mmol/1.73 m^2). The level of urine Ox 24 decreased in patient 3 after vitamin B_6 treatment; however, the relative reduction did not reach 30% (the level of urine Ox 24 decreased from 1.92 mmol/1.73 m^2 to 1.63 mmol/1.73 m^2). It was reported that the patients with homozygous p.G170R showed a survival advantage and good vitamin B_6 response [14]. However, no p.G170R mutation was detected in this study.

c0.33dupC was the most commonly observed mutation in this study. c0.33dupC is a mutation that generates a stop codon, which leads to the formation of a truncated protein, which is usually nonfunctioning [15]. This duplication has no apparent ethnic or geographic associations, and its high frequency could probably be attributed to multiple mutations in the region of eight cytosine repeat sequences where it occurs. Four novel missense variants were detected in this study. Three-fourth of the variants was predicted to be potentially pathogenic, and the analysis of one-fourth of the variants using two software tools yielded inconsistent results. These novel mutations broaden the range of known gene mutations that are implicated in PH, and further support the allelic heterogeneity of this disease.

Conclusions

In this study, the PH incidence was higher than the reported PH incidence in children with urinary stones. Hence, we suggested that genetic examination was necessary for all the children with hyperoxaluria. These novel mutations broaden the range of known gene mutations in PH, especially in Chinese children.

Author contributions LH: data collection or management, data analysis, and manuscript writing. GX: data collection or management and data analysis. XF: data collection or management. HL: data collection or management. MX: data analysis. YY: protocol development. HG: protocol development and manuscript editing

Funding This study was funded by the National Natural Science Foundation of China (Grant no. 81770702).

Compliance with ethical standards

Conflict of interest All authors declare no conflicts of interest, real or perceived, financial or nonfinancial.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

References

1. Cochat P, Deloraine A, Rotily M, Olive F, Liponski I, Deries N (1995) Epidemiology of primary hyperoxaluria type 1. Societe de Nephrologie and the Societe de Nephrologie Pediatrique. Nephrol Dial Transplant 10(Suppl 8):3–7
2. van Woerden CS, Groothoff JW, Wanders RJ, Davin JC, Wijburg FA (2003) Primary hyperoxaluria type 1 in The Netherlands: prevalence and outcome. Nephrol Dial Transplant 18(2):273–279
3. Harambat J, van Stralen KJ, Espinosa L, Groothoff JW, Hulton SA, Cerkauskiene R, Schaefer F, Verrina E, Jager KJ, Cochat P, European Society for Pediatric Nephrology/European Renal Association-European D, Transplant Association R (2012) Characteristics and outcomes of children with primary oxalosis requiring renal replacement therapy. Clin J Am Soc Nephrol CJASN 7(3):458–465. https://doi.org/10.2215/CJN.07430711
4. Williams EL, Acquaviva C, Amoroso A, Chevalier F, Coulter-Mackie M, Monico CG, Giachino D, Owen T, Robbiano A, Salido E, Waterham H, Rumsby G (2009) Primary hyperoxaluria type 1: update and additional mutation analysis of the AGXT gene. Hum Mutat 30(6):910–917. https://doi.org/10.1002/humu.21021
5. Hoppe B (2012) An update on primary hyperoxaluria. Nat Rev Nephrol 8(8):467–475. https://doi.org/10.1038/nrneph.2012.113
6. Cregeen DP, Williams EL, Hulton S, Rumsby G (2003) Molecular analysis of the glyoxylate reductase (GRHPR) gene and description of mutations underlying primary hyperoxaluria type 2. Hum Mutat 22(6):497. https://doi.org/10.1002/humu.9200
7. Monico CG, Rossetti S, Belostotsky R, Cogal AG, Herges RM, Seide BM, Olson JB, Bergstrahl EJ, Williams HJ, Haley WE, Frishberg Y, Milliner DS (2011) Primary hyperoxaluria type III gene HOGA1 (formerly DHDPSL) as a possible risk factor for idiopathic calcium oxalate urolithiasis. Clin J Am Soc Nephrol CJASN 6(9):2289–2295. https://doi.org/10.2215/CJN.02760311
8. Hopp K, Cogal AG, Bergstralh EJ, Seide BM, Olson JB, Meek AM, Lieske JC, Milliner DS, Harris PC, Rare Kidney Stone C

(2015) Phenotype-genotype correlations and estimated carrier frequencies of primary hyperoxaluria. J Am Soc Nephrol 26(10):2559–2570. https://doi.org/10.1681/ASN.2014070698
9. Ruhayel Y, Tepeler A, Dabestani S, MacLennan S, Petrik A, Sarica K, Seitz C, Skolarikos A, Straub M, Turk C, Yuan Y, Knoll T (2017) Tract sizes in miniaturized percutaneous nephrolithotomy: a systematic review from the European Association of Urology Urolithiasis Guidelines Panel. Eur Urol 72(2):220–235. https://doi.org/10.1016/j.eururo.2017.01.046
10. Williams EL, Bagg EA, Mueller M, Vandrovcova J, Aitman TJ, Rumsby G (2015) Performance evaluation of Sanger sequencing for the diagnosis of primary hyperoxaluria and comparison with targeted next generation sequencing. Mol Genet Genom Med 3(1):69–78. https://doi.org/10.1002/mgg3.118
11. Coulter-Mackie MB, Applegarth D, Toone JR, Henderson H (2004) The major allele of the alanine:glyoxylate aminotransferase gene: seven novel mutations causing primary hyperoxaluria type 1. Mol Genet Metab 82(1):64–68. https://doi.org/10.1016/j.ymgme.2004.02.001
12. Belostotsky R, Seboun E, Idelson GH, Milliner DS, Becker-Cohen R, Rinat C, Monico CG, Feinstein S, Ben-Shalom E, Magen D, Weissman I, Charon C, Frishberg Y (2010) Mutations in DHDPSL are responsible for primary hyperoxaluria type III. Am J Hum Genet 87(3):392–399. https://doi.org/10.1016/j.ajhg.2010.07.023
13. Allard L, Cochat P, Leclerc AL, Cachat F, Fichtner C, De Souza VC, Garcia CD, Camoin-Schweitzer MC, Macher MA, Acquaviva-Bourdain C, Bacchetta J (2015) Renal function can be impaired in children with primary hyperoxaluria type 3. Pediatr Nephrol 30(10):1807–1813. https://doi.org/10.1007/s00467-015-3090-x
14. Williams EL, Bockenhauer D, van't Hoff WG, Johri N, Laing C, Sinha MD, Unwin R, Viljoen A, Rumsby G (2012) The enzyme 4-hydroxy-2-oxoglutarate aldolase is deficient in primary hyperoxaluria type 3. Nephrol Dial Transplant 27(8):3191–3195. https://doi.org/10.1093/ndt/gfs039
15. Zhao F, Bergstralh EJ, Mehta RA, Vaughan LE, Olson JB, Seide BM, Meek AM, Cogal AG, Lieske JC, Milliner DS, Investigators of Rare Kidney Stone C (2016) Predictors of incident ESRD among patients with primary hyperoxaluria presenting prior to kidney failure. Clin J Am Soc Nephrol 11(1):119–126. https://doi.org/10.2215/CJN.02810315
16. Rumsby G, Cochat P (2013) Primary hyperoxaluria. N Engl J Med 369(22):2163. https://doi.org/10.1056/NEJMc1311606
17. Cochat P, Hulton SA, Acquaviva C, Danpure CJ, Daudon M, De Marchi M, Fargue S, Groothoff J, Harambat J, Hoppe B, Jamieson NV, Kemper MJ, Mandrile G, Marangella M, Picca S, Rumsby G, Salido E, Straub M, van Woerden CS, OxalEurope (2012) Primary hyperoxaluria Type 1: indications for screening and guidance for diagnosis and treatment. Nephrol Dial Transplant 27(5):1729–1736. https://doi.org/10.1093/ndt/gfs078
18. Hoyer-Kuhn H, Kohbrok S, Volland R, Franklin J, Hero B, Beck BB, Hoppe B (2014) Vitamin B6 in primary hyperoxaluria I: first prospective trial after 40 years of practice. Clin J Am Soc Nephrol CJASN 9(3):468–477. https://doi.org/10.2215/CJN.06820613
19. M'Dimegh S, Omezzine A, M'Barek I, Moussa A, Mabrouk S, Kaarout H, Souche G, Chemli J, Aloui S, Aquaviva-Bourdain C, Achour A, Abroug S, Bouslama A (2016) Mutational analysis of Agxt in tunisian population with primary hyperoxaluria type 1. Ann Hum Genet. https://doi.org/10.1111/ahg.12178