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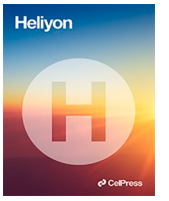

Case report

A novel variant in a Chinese boy with lysinuric protein intolerance: A case report and literature review

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ABSTRACT

We report a case of a 4-year-old boy with lysinuric protein intolerance in China. The patient presented with interstitial lung disease with obvious clubbing of the fingers and toes. During the course of diagnosis and treatment, we found he was averse to a high-protein diet, intolerant to activity, and had a history of diarrhea and fractures. Physical examination revealed hepatosplenomegaly and clubbing of the fingers and toes. Next-generation sequencing revealed compound heterozygous mutations (c.1387delG, c.958T > C) in *SLC7A7*, which was confirmed as a disease-causing gene for lysinuric protein intolerance. After a literature review, we found that c.958T > C had not been previously reported, and summarized the clinical and genetic characteristics of patients from different continents. His symptoms improved significantly after 3 months of being on a low-protein diet, supplementation with lysine, citrulline, carnitine, and trace elements, and oral corticosteroid treatment for 2 months. The patient is still under follow-up.

1. Background

Lysinuric protein intolerance (LPI) is an autosomal recessive defect in cationic amino acid (lysine, arginine, and ornithine) transport at the basolateral membrane of epithelial cells in the intestine, kidneys, and other non-epithelial cells. Thus, a typical laboratory test result involves a decrease in the levels of lysine, arginine, and ornithine in the blood and an increase in these amino acids in the urine. The clinical manifestations involve multiple systems. The common symptoms include growth restriction, vomiting, diarrhea, hyperammonemia, and coma in severe cases after the consumption of a high-protein diet. LPI is characterized by various manifestations, and genetic testing is necessary to confirm the diagnosis. Herein, we report a case of LPI in a male patient. The boy was characterized by growth restriction, inability to tolerate a high-protein diet, signs of chronic hypoxia (clubbing of the fingers and toes), hepatosplenomegaly, and interstitial lung disease on chest CT. Next-generation sequencing was performed, and compound heterozygous mutations, c.1387delG and c.958T > C, were identified. After reviewing the literature, we found that c.958T > C has not been previously reported.

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2. Case report

A 4-year-old boy was admitted to our hospital because of decreased activity tolerance for a period of 4 years, cough persisting for more than 10 days, and fever for 3 days. He was the second child of non-consanguineous parents from the same village. The boy was born at 40 weeks of gestational age with an appropriate length and weight for his gestational age and was delivered by forceps at term. There had no history of postnatal rescue. After birth, he experienced diarrhea during formula feeding, which improved after rice paste was added, with the proportion being gradually increased. At the age of 1 year, family members noticed the child's clubbed fingers. The child always felt tired and liked to be held. Over time, his activity slightly improved, but still liked to sit quietly and did not talk much. Ten days prior to admission, the patient experienced a recurrent cough that improved after receiving anti-infective treatment at another hospital. After a period of 7 days, the cough and fever occurred again, with a spike in the fever to 40 °C, which mostly occurred at night; thus, the patient was admitted to our hospital.

The patient's motor development was delayed compared with that of other children of the same age. For example, the patient could not walk without assistance until the age of 1 year and 9 months. Multiple fractures occurred before the age of 3 years. The child preferred white porridge, noodles, and other carbohydrate-rich foods over foods with high-protein content. Hereditary diseases in the family were denied and no children had died in the family. The patient's sister was noted to be healthy.

A physical examination revealed that the weight of the patient was 14 kg and height was 95 cm, which was <3rd percentile on the growth charts. Three signs of depression were observed, and rough breathing sounds and wet rales were heard in both lungs. The abdomen was flat and soft. The liver was non-tender, 3 cm below the right costal margin, with a rounded edge, and the spleen was at the costal margin. Clubbing of the fingers (toes) was evident.

After admission, laboratory examinations revealed increased procalcitonin and slightly decreased hemoglobin levels. Lactate dehydrogenase (LDH) and ferritin levels were also evaluated. In the liver function tests, the total protein and albumin levels decreased, and aspartate aminotransferase levels increased (Table 1). A plasma amino acid analysis revealed decreased lysine, arginine, and ornithine levels (Table 2). Epstein-Barr virus (EBV)-DNA was positive in the blood, and mNGS of alveolar lavage fluid suggested an influenza B virus. Chest computed tomography (CT) showed multiple inflammatory lesions (mainly infiltration) in both lungs, partial interstitial pneumonia, pleural thickening in the bilateral interlobar fissure, and multiple subpleural small cyst lesions in both lungs (Fig. 4 A). Abdominal ultrasonography revealed hepatosplenomegaly. Radiography of the left carpal and bronchoscopy revealed no abnormalities. A bronchoscopic lung biopsy revealed interstitial lung inflammation with fibrous exudative inflammation (Fig. 1 A and B). Chest CT improved after 20 days of anti-infective treatment (Fig. 4 B).

The whole-exome sequencing Trio of Beijing Genomics Institution identified compound heterozygous mutations c.1387delG and C.958T > C in exons 10 and 7 of *SLC7A7*, respectively, which were derived from his parents. The patient was finally diagnosed with lysinuric protein intolerance based on a literature review. The C.958T > C mutation is a novel mutation that has never been found in the ESP, thousand genomes, or EXAC databases (PM2). In recessive diseases, pathogenic variants have been detected at the *trans*-position (PM3). Various statistical methods can predict harmful effects on genes or gene products, including conservation prediction,

Table 1
Patient's laboratory examination.

Admission		After 1 months of treatment	After 3 months of treatment	normal
White blood cell count (/L)	4.8×10^9	7.8×10^9	11×10^9	$(8–10) \times 10^9$
Hemoglobin (g/L)	107↓	111	127	120–140
MCV (fL)	79.0	83.0	81.2	80.0–94.0
MCH (pg)	26.5	28.3	27.8	28.0–32.0
Platelets (/L)	157×10^9	356×10^9	338×10^9	(100–300) $\times 10^9$
PCT (ng/ml)	0.23↑	–	–	0–0.05
CRP (mg/dl)	0.53	0.12	–	0–0.06
Ferritin (ng/ml)	>2000↑	795.7↑	–	30–400
D dimer (ng/ml FEU)	5033↑	4382↑	1419↑	0–500
LDH (U/L)	2525.6↑	1493.9↑	874.3↑	109–255
KL-6 (U/ml)	>10000↑	>10000↑	8435↑	≤500
Blood ammonia (umol/L)	46.8 (limosis)	45.2 (limosis)	139.5↑(an hour after meal)	10–47
Blood lactic acid (mmol/L)	1.21	1.40	1.32	0.7–2.1
Cholesterol (mmol/L)	3.96	7.34↑	5.47↑	2.9–5.5
Ttriglycerides (mmol/L)	1.11	1.79↑	2.16↑	0.23–1.58
Potassium (mmol/L)	3.03↓	3.80	3.08↓	3.5–5.5
Total protein (g/L)	58.3↓	62.2↓	64.2↓	65–85
Albumin (g/L)	33.1↓	37.8	40.7	35–55
ALT (U/L)	18.3	21.4	19.4	0–40
AST (U/L)	83.5↑	66.2↑	32.8	5–40
Neuron-specific enolase (ng/ml)	148.3↑	56.03↑	–	0–16.3
Carcinoembryonic antigen (ng/ml)	5.07↑	4.10	–	0–5
Carbohydrate antigen 125 (u/ml)	77.76↑	85.47↑	–	0–35
Carbohydrate antigen 153 (u/ml)	157.6↑	165.80↑	–	0–25
Non-small cell carcinoma-associated antigen (u/ml)	8.07↑	5.86↑	–	0–3.3

Table 2
Plasma amino acid analysis results before treatment.

Amino acid	Test value	normal (umol/L)	Amino acid	Test value	normal (umol/L)
Aspartic acid	4.9	1.00–12.00	glycine	310.4	119.00–314.00
glutamate	59.9	24.00–189.00	threonine	134.8	40.00–211.00
arginine	5.4↓	11.00–69.00	citrulline	60.9↑	7.00–35.00
ornithine	11.1↓	22.00–83.00	asparagine	123.5↑	18.00–47.00
leucine	97.5	4.00–197.00	alanine	575.1↑	210.00–545.00
lysine	4.3↓	52.00–183.00	tyrosine	156.3↑	34.00–122.00
hydroxyproline	19.6↓	23.00–114.00	valine	156.3	34.00–122.00
creatine	20.7↓	23.00–189.00	methionine	29.8	5.00–34.00
proline	237.9	67.00–250.00	tryptophan	51.4	23.00–76.00
serine	235.1↑	73.00–169.00	phenylalanine	56.3	32.00–79.00
glutamine	944.7↑	249.00–579.00	isoleucine	70.6	24.00–118.00
histidine	97↑	45.00–87.00			

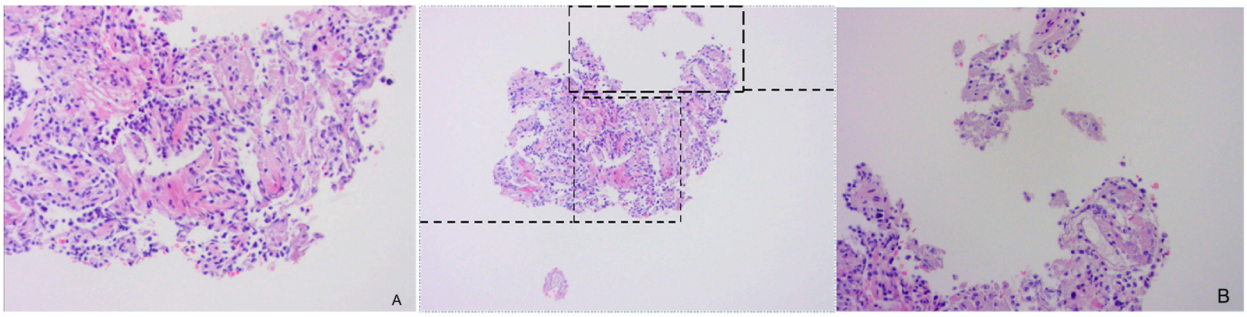

Fig. 1. Lung tissue biopsy was shown. A and B shows views of lung tissue biopsy at a magnification of 400× (H & E staining). The tissue changes were consistent with interstitial inflammation of the lung with exudative inflammation of cellulose, and infection is considered.

evolution prediction, and splice-site influence (PP3). According to the ACMG guidelines, *C.958T > C* is classified as having unknown significance (PM2+PM3+PP3) (Fig. 2).

After diagnosis, the patient was given a low-protein diet (1–1.5 g/kg/d), lysine (17 mg/kg), citrulline (60 mg/kg), and a trace element supplement. One month later, the D-dimer and lactate dehydrogenase levels decreased (Fig. 3); however, the lipid levels

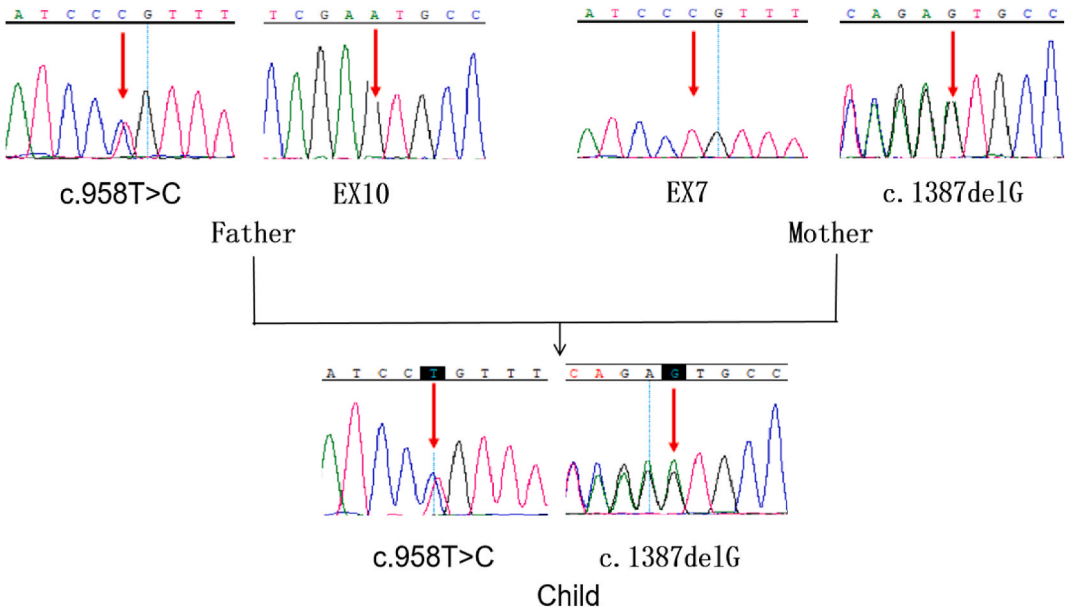

Fig. 2. Sanger sequencing of the SLC7A7 gene for the patient and his parents were shown. The mother carries the variant known to cause the disease while the variant that the father carries were of unknown significance. The child was observed to carries both variants.

increased, and chest CT indicated a slight aggravation of pneumonia (Fig. 4 C). Therefore, oral prednisone (1 mg/kg) and carnitine (35 mg/kg) were administered to prevent inflammation. Chest CT improved after 2 months of oral corticosteroid therapy (Fig. 4 D), and family members confirmed that the child's activity had significantly increased compared to the previous taciturnity. The child is still under follow-up.AT: after treatment.

2.1. Literature review

We used the keywords: "lysinuric protein intolerance" and "SLC7A7" search in PubMed and reviewed literature in English and Chinese from 1965 to 2022. Studies with clear clinical manifestations and the identified genes were included. Cases without descriptions of the clinical presentation or genetic analyses were excluded. We attempted to identify the differences by reviewing patients from different continents (Tables 3 and 4).

3. Results and discussion

Overall, 28 publications involving 108 patients with LPI were selected. Most of these cases have been reported in Europe and Asia. It is obvious that the onset of LPI occurs at an early age; therefore, most patients are observed to be pediatric cases. We infer that the relatively young age at diagnosis in Europe may be related to the fact that this disease is more common in Europe. Most patients with LPI in Europe are diagnosed by plasma amino acid analysis without genetic testing; therefore, the number of European patients included in this study is only a small fraction of the actual number. The main symptoms in Europe include a failure to thrive, skeletal anomalies, and renal disorders. Protein-rich food aversion, failure to thrive, and vomiting were the top three symptoms, whereas a loss of consciousness and cognitive delay were common in Asia. The number of cases in North America is too small to discuss the clinical features. A failure to thrive, skeletal anomalies, and symptoms of the digestive system are the primary symptoms in Africa. Hepatosplenomegaly is the most common symptom. African patients were clearly related to consanguineous parents, which was inferred from the occurrence of dominant homozygous pathogenic mutations. The clinical presentation and genes were found to have no relationship in our review, as the broad clinical spectrum was homogeneously distributed among patients with different genes.

Lysinuric protein intolerance is an autosomal recessive defect in cationic amino acid (lysine, arginine, ornithine, etc.) transport at the basolateral membrane of epithelial cells in the intestine, kidney, and other non-epithelial cells (e.g., macrophages). This concept was first described by Perheentupa, J and Visakorpi, J K [30] in 1965. The disease was first identified in Finland, with an incidence of approximately 1/60000 in the Finnish population. The disease-causing gene LPI is encoded by *SCL7A7* on chromosome 14, which results in the deficiency of the y + LAT1 protein [31]. The y + LAT1 protein transports cationic amino acids that are mainly distributed in the small intestinal mucosa and renal tubular epithelial cells. Deficiency of the y + LAT1 protein leads to malabsorption of cationic amino acids in the small intestine and excessive excretion in the kidneys. Notably, *SCL7A6* encodes the y + LAT2 protein. y + LAT2 is also expressed in tissues with high levels of y + LAT1 [32]. The tissues and cells with low transport capacity can use the y + LAT2

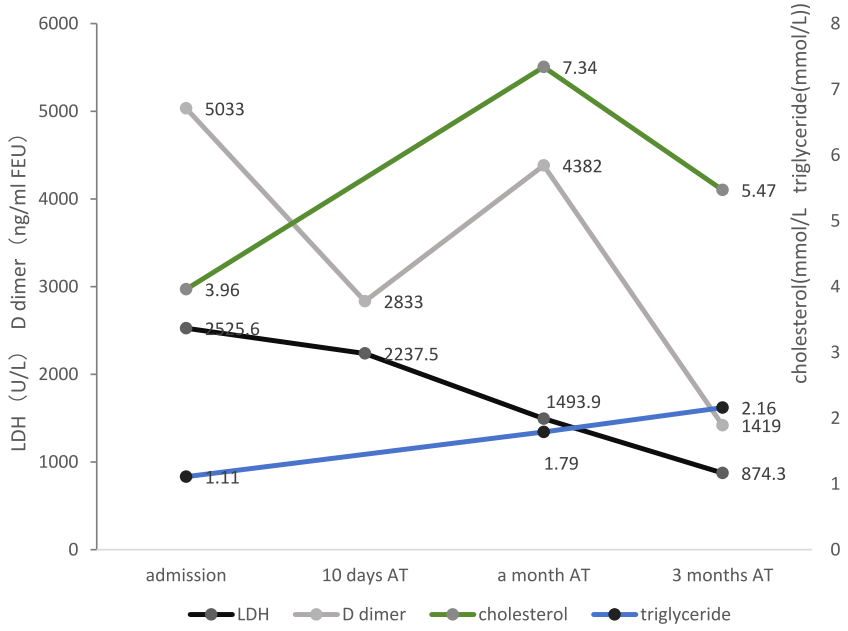

Fig. 3. Shows the trends in the LDH, D-dimer, cholesterol, and triglycerides after treatment. The cholesterol and D dimer levels increased 1 month after treatment and decreased after the addition of carnitine and oral prednisone. The LDH levels gradually declined, whereas the triglyceride levels increased slightly.

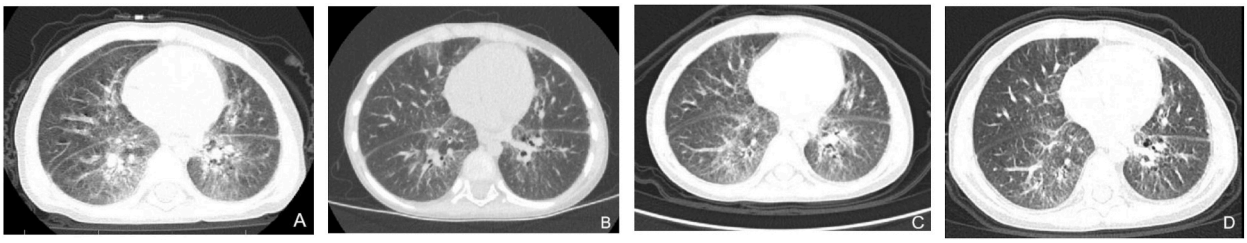

Fig. 4. A: Chest CT on admission showed multiple inflammation in both lungs, partial interstitial pneumonia. B: Chest CT improved after 20 days of anti-infective treatment. C: Chest CT after lysine and citrulline supplement showed more inflammation than B. D: Chest CT improved after oral prednisone treatment.

Table 3
Clinical characteristics of patients with lysinuric protein intolerance in different continents.

Continent	Europe [1–9]	Asia [10–23]	North America [24,25]	Africa [26–29]
Total number of people	32	67	2	8
Male	19	30	2	1
Female	13	37	–	7
Age of onset (years)	1.8 ± 2.2 (n* = 6)	4.1 ± 10.0 (n* = 43)	0.7 ± 0.6 (n* = 2)	1.1 ± 1.3 (n* = 3)
Age at diagnosis (years)	5.5 ± 5.7	10.8 ± 9.8	10.3 ± 5.7	2.9 ± 1.7
Consanguineous parents	14	9	1	7
Symptoms				
Failure to thrive	27	46	2	4
Hyperammonemia	11	5	1	–
Hepatosplenomegaly	29	18 Only Hepatomegaly: 25 Only Splenomegaly: 17	Only Hepatomegaly: 1	3 Only Hepatomegaly: 1 Only Splenomegaly: 1
Anemia	11	10	2	2
Digestive system				
Vomiting	5	28	1	3
Diarrhea	3	6	1	2
Protein-rich food aversion	12	52	1	3
Nervous system				
Loss of consciousness or coma	3	24	–	1
Seizures	4	3	–	–
Cognitive delay	11	26	–	–
Skeletal anomalies	18	15	1	4
Muscular hypotony	4	6	1	2
Respiratory system				
ILD	10	14	–	–
PAP	11	2	–	–
Renal disorder	14	27	1	1
Dysimmunity	6	13	1	–
Endocrine system	Growth hormone deficiency: 2	–	–	Hypothyroidism: 1
Asymptomatic	1	2	–	1

ILD : Interstitial lung disease; PAP : pulmonary alveolar proteinosis.
n*: refers to the number of patients included in the age of onset statistics.

protein to release cationic amino acids [33]. The study of Valeria Dall 'asta et al. [32] proved that y + LAT2 was uniformly expressed in all tissues, with the highest expression in CD3 lymphocytes. y + LAT1 was highly expressed in macrophages, intestinal cells, and kidney cells, whereas the y + LAT2 expression was low, which explained why the y + LAT protein activity in the red blood cells and fibroblasts did not change [32,34]. The clinical manifestations of LPI vary between studies. The digestive, nervous, hematological, respiratory, urinary, musculoskeletal, and immune systems may be involved, and immune and hematological complications vary. However, metabolic alterations were common to all patients with LPI. Patients with LPI are characterized by markedly elevated LDH, ferritin, and D-dimer levels. Lassila et al. [35] suggested that altered fibrin production and fibrinolysis are associated with metabolic and renal defects. In this case, lactate dehydrogenase, ferritin, and D-dimer levels were significantly decreased after a low-protein diet; supplementation with lysine, citrulline, carnitine, and trace elements; and oral corticosteroid treatment, indicating that dynamic monitoring of these indicators can help evaluate the prognosis of the disease.

The mainstay treatment for lysinuric protein intolerance consists of adequate energy and a low-protein diet (children: 0.8–1.5 g/kg/d, adults: 0.5–0.8 g/kg/d). Due to the restriction of dietary intake, the levels of calcium, iron, zinc, and vitamins are often insufficient; thus, trace elements and vitamins should be properly supplemented [36]. Second, citrulline (100 mg/kg), lysine (20–50 mg/kg/d), and carnitine should be supplemented if tolerated. Several treatments are available for various complications. For example, when nausea, vomiting, and disturbance of consciousness caused by hyperammonemia occur, an infusion of 10% glucose or a

Table 4
Genetic characteristics of patients with lysinuric protein intolerance in different continents.

Continent	Europe [1–9]	Asia [10–23]	North America [24, 25]	Africa [26–29]
Homozygous mutation	c.726G > A: 6 c.1185_1188delTTCT: 4 1001T > G: 4 c.1013G > A: 1 c.254_255delTT: 1 c.1417C > T: 1 W242X: 1 c.1228C > T: 1 c.771−848_1908 + 718 del4647 : 1 c.1371C > A in exon 10: 1 IVS6-2A > T: 1 c.1625insATCA: 1	p.R410: 24 c.1417C > T: 2 c.1099insT: 2 c.625+1G > A: 2 c.235G > A: 1 c.257G > A: 1 c.223insGTC: 1 c.344_347delTTGC: 1 c.713 C > T: 1 c.158C > T: 1 IVS4 + 1G > A: 1	c.726G > A: 1	1471delTTCT: 5 c.726G > A: 2 c.1185_1188delTTCT: 1
Compound heterozygote	c.371T > C and c.1402C > T: 2 c.753G > C and c.1185_1188delTTCT: 2 c.820dupT and c.625+1G > C: 1 c.1273T > C and c.500−4294_1908 + 1028del12136: 1	C.1387delC and IVS4+1C > T: 2 c.1387delG and c.1215G > A: 2 c.749A > T and c.749A > T: 1 c.1330dup and c.625+1G > A: 1 c.713C > T and c.625+1G > A: 1	c.475C > T and c.1001T > G: 1	–

high-concentration infusion (60–100 kcal/kg/day) should be initiated. Notably, L-arginine (100–250 mg/kg/day, intravenously) and ammonia scavengers (sodium phenylbutyrate, 450–600 mg/kg/day in patients weighing <20 kg, or 9.9–13.0 g/m^2/day in larger patients or/and sodium benzoate, 100–250 mg/kg/day, intravenously or orally) are useful. Blood purification should be initiated when the drugs are ineffective. For PAP, it is reported that whole-lung lavage and recombinant human granulocyte macrophage colony stimulating factor (GM-CSF) are reportedly useful.

The Child presented with interstitial lung disease as the dominant symptom, with symptoms of chronic hypoxia and clubbed fingers, according to the European protocols for the diagnosis and initial treatment of interstitial lung disease in children [37], we doubted whether he suffered from metabolic disease. Subsequently, metabolic examinations and genetic sequencing were performed. Plasma amino acid and urinary orotic acid analyses revealed no significant abnormalities. After finding the compound heterozygous mutations in SLCA7A, we found that lysine was not present in the result of the plasma amino acid analysis; therefore, we sent the blood to another laboratory and tested it again. The second test showed decreased levels of lysine, arginine, and ornithine, confirming a diagnosis of LPI (Table 2). There were heterozygous mutations in SLC7A7 in the young boy, c.1387delG and c.958T > C. Notably, c.958T > C has never been reported before. LPI are relatively rare in Asia, and genetic sequences play an important role in the diagnosis of rare diseases.

Ethics declarations

This case report was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University, with the approval number: no.20220514.

The patient's parents provided informed consent to participate in the study.

The patient's parents provided informed consent for the publication of their anonymised case details and images.

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Data availability

Data associated with study has not been deposited into a publicly available repository. The data will be made available on reasonable request.

CRediT authorship contribution statement

Yanhong Wang: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Hongwei Li:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Zhanhang Huang:** Data curation, Investigation. **Sen Yang:** Data curation, Investigation. **Chengyu Lu:** Data curation, Investigation. **Wei Zhang:** Data curation, Software. **Shangming Zhao:** Formal analysis, Software. **Cui Yang:** Data curation, Investigation. **Dehui Chen:** Conceptualization, Data curation, Funding acquisition, Project administration, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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