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ABOUT COVER

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The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Congenital disorder of glycosylation caused by mutation of *ATP6AP1* gene (c.1036G>A) in a Chinese infant: A case report

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Abstract

BACKGROUND

The *ATP6AP1* gene coding for the accessory protein Ac45 of the vacuolar-type adenosine triphosphatases (V-ATPase) is located on chromosome Xq28. Defects in certain subunits or accessory subunits of the V-ATPase can lead to congenital disorders of glycosylation (CDG). CDG is a group of metabolic disorders in which defective protein and lipid glycosylation processes affect multiple tissues and organs. Therefore, the clinical presentation of patients with *ATP6AP1*-CDG varies widely. In this report, we present a case of *ATP6AP1*-CDG in a Chinese infant, with clinical features and genotype.

CASE SUMMARY

An 8-mo-old boy was admitted to our hospital because unexplained hepatosplenomegaly and elevated transaminases that had been noted while he was being treated for a cough at a local hospital. A post-admission examination at our hospital revealed abnormalities in the infant's liver, brain, and immune system. Trio-based whole exome gene analysis identified a hemizygous pathogenic mutation c.1036G>A (p.E346K) in exon 9 of the *ATP6AP1* gene. This variant of the *ATP6AP1* gene has not been reported in East Asian countries until now.

CONCLUSION

Based on the infant's clinical manifestations and the results of genetic detection, he was clearly diagnosed with *ATP6AP1*-CDG. The clinical manifestations of children with CDG vary widely. Genetic testing analysis helps in the clinical diagnosis of children with CDG.

Key Words: Congenital disorders of glycosylation; *ATP6AP1* mutation; Hepatopathy;

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Core Tip: This article reports on an 8-mo-old male infant with hemizygous pathogenic mutation c.1036G>A (p.E346K) in the *ATP6AP1* gene. *ATP6AP1*-congenital disorders of glycosylation (*ATP6AP1*-CDG) is a recently identified disease and rarely occurs in Asia. If a patient shows liver, neurological, and immune deficiencies, or other multisystem abnormalities, early genetic screening is advised for a definitive diagnosis. This study expands the disease spectrum of *ATP6AP1*-CDG and improves its understanding.

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INTRODUCTION

Congenital disorders of glycosylation (CDG) are a group of monogenic genetic metabolic disorders that are caused by defects in protein and lipid glycosylation processes affecting multiple tissues and organs[1]. Vesicular- or vacuolar-type adenosine triphosphatases (V-ATPase) is a protein complex widely expressed in cell or organelle membranes. It helps to maintain the dynamic pH balance in the cellular or organelle internal environment by consuming ATP for H⁺ transport[2]. V-ATPase consists of two core structural domains (the soluble V1 domain and the intramembrane V0 domain)[3]. The pathogenic mutation in certain subunits or accessory subunits of V-ATPase may lead to CDG. In 2016, 11 patients were first detected with *ATP6AP1*-CDG. Presently, 19 patients have been diagnosed with X-linked *ATP6AP1* deficiency (*ATP6AP1*-CDG), including the case that we report here[4]. As far as we know, no East Asian cases have previously been reported. This report aims to raise awareness of the disease by describing the clinical profile of a Chinese patient with *ATP6AP1*-CDG.

CASE PRESENTATION

Chief complaints

The patient's parents reported that their baby was treated at a local hospital for a cough when he was about 8 mo old. During hospitalization, abnormal liver function and hepatosplenomegaly were detected.

History of present illness

The patient was diagnosed with bronchopneumonia and abnormal liver function at a local hospital. After 7 d of treatment with ceftazidime for anti-infection and liver protection with compound glycyrrhizin, the patient's cough stopped and the bronchopneumonia disappeared. However, the liver function indexes remained abnormal. The patient was then referred to our department for further treatment.

History of past illness

At 4 mo of age, the patient underwent an abdominal ultrasonography examination. The results showed that the mesenteric lymph nodes were enlarged, but no liver or spleen abnormalities were found at that time. When he was 7 mo and 13 d old, he had a head magnetic resonance imaging examination which showed delayed cerebral myelination. The patient subsequently had a period of brain rehabilitation treatments.

Personal and family history

The patient is the parents' first child. His mother had no history of miscarriage. At the full term of the pregnancy, the mother had a cesarean section because prenatal ultrasound examination showed "oligohydramnios". The patient was hospitalized for neonatal jaundice. He was cured and discharged a few weeks later. The mother is a hepatitis B carrier. There was no family history of hereditary diseases.

Physical examination

Upon admission, the patient's height was 71.5 cm (66th percentile) and his weight was 7.7 kg (15th percentile). No cutis laxa (CL), rash, hemorrhagic spots, petechiae, or jaundice were observed on the child's skin. The abdomen was soft. The liver was 4 cm below the right rib with a hard texture, and the spleen was 2.5 cm below the rib with a medium texture. The extremities' muscle strength was normal, and no abnormal neurological pathological reflexes were observed. The patient was lagging his peers in growth and development. He turned over at 4.5 mo, held his head upright and stable at 5 mo, and was still unable to sit at 8 mo.

Laboratory examinations

Because of the patient's young age and the predominant manifestation of elevated transaminases and liver damage, infection, congenital genetic metabolic disease, autoimmune liver disease, abnormal development of intrahepatic bile duct, and other factors could not be ruled out. Laboratory examinations showed that the hepatitis B and C viruses were negative, EB virus was negative, autoimmune liver disease antibody spectrum was normal, and T lymphocyte subsets were normal. The results of other laboratory examinations are shown in [Table 1](#).

Imaging examinations

After a liver aspiration biopsy, hematoxylin and eosin staining showed disorganized hepatic lobules with a nodular arrangement of hepatocytes, mild edema, dotted necrosis, fragmented necrosis, and bridging necrosis. The confluent area was significantly widened. There was a large amount of fibrous tissue proliferation and a division of hepatic lobules to form pseudo bullets; with more lymphocytes and individual plasma cell infiltration in the confluent area ([Figure 1A](#)). Collagen fiber staining (Masson) showed massive collagen fibrous hyperplasia and a division of hepatic lobules to form pseudo bullets ([Figure 1B](#)).

FINAL DIAGNOSIS

To find the cause of the disease, we took peripheral blood samples from the patient and his parents for trio-based whole exome gene analysis. This revealed the presence of the c.1036G>A (p.E346K) mutation in the patient's *ATP6AP1* gene. Both his parents were confirmed to be free of mutations at this locus ([Figure 2](#)). The pathogenicity of CDG caused by this site mutation has been reported in the PubMed database[4]. The patient's clinical presentation combined with the genetic sequencing conclusion resulted in a clear *ATP6AP1*-CDG diagnosis.

TREATMENT

Referring to the literature, there was no effective treatment for the disease. During hospitalization, the patient was given reduced glutathione to protect the liver. He was also given ornithine and aspartate to lower the blood ammonia symptomatically. After treatment, transaminases levels were lower than the those at the time of admission (alanine aminotransferase 120 U/L, aspartate aminotransferase 140 U/L) and the child was generally doing well, so the parents requested his discharge.

OUTCOME AND FOLLOW-UP

During the current both outpatient and telephone follow-up, the parents reported that the child showed signs of muscle weakness and had slight difficulty going upstairs. His immunoglobulin levels were consistently low. He was subsequently treated with

Table 1 Laboratory test results of the patient

Panel	Index/reference range	Result
Liver function	ALT (9-60 U/L)	213
	AST (15-45 U/L)	242
	TBIL (3.40-20.50 $\mu\text{mol/L}$)	1.60
	IBIL (3.10-14.30 $\mu\text{mol/L}$)	0.60
	TBA (0.00-10.00 $\mu\text{mol/L}$)	21.46
	TP (65.0-85.0 g/L)	62.2
	GLO (20.0-40.0 g/L)	11.3
	ALB (40.0-55.0 g/L)	50.9
	GGT (0.0-50.0 U/L)	64.0
	ALP (40-500 U/L)	557
Liver genetic metabolic index	24h-Cu (0.24-0.48 $\mu\text{mol/24 h}$)	0.03
	CER (180-450 mg/L)	133
	LACT (0.63-2.44 mmol/L)	2.79
	Blood ammonia (18-72 $\mu\text{g/dL}$)	181
Immunoglobulin	IgG (8.0-18.0 g/L)	4.20
	IgA (0.90-4.50 g/L)	1.30
	IgM (0.84-1.32 g/L)	0.54
Routine blood test	PLT ($125-350 \times 10^9/\text{L}$)	138
Blood lipids	HDL-C (1.03-2.07 mmol/L)	0.09
	LDL-C (1.0-4.4 mmol/L)	1.74
Cardiac enzymes	CK (10-174 U/L)	94
	CK-MB (0.0-25.0 U/L)	56.0
	LD (109-245 U/L)	331

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; IBIL: Indirect bilirubin; TBA: Total bile acids; TP: Total protein; GLO: Globulin; ALB: Albumin; GGT: Gamma-glutamyl transpeptidase; ALP: Alkaline phosphatase; 24h-Cu: 24-hour urine copper; CER: Ceruloplasmin; LACT: Lactic acid; PLT: Platelets; HDL-C: High-density lipoprotein; LDL-C: Low-density lipoprotein; CK: Creatine kinase; CK-MB: Creatine kinase myocardial band; LD: Lactate dehydrogenase.

gamma-globulin at a local hospital several times because of hypogammaglobulinemia. The child is now two years and one month old. Some of the laboratory tests and medications used in the clinic follow-up are summarized in Table 2. The long-term prognosis requires continued follow-up and observation.

DISCUSSION

V-ATPase is a proton pump that transports H^+ *via* active transport and provides a homeostatic pH environment for various cellular activities[5]. For example, maintaining the pH gradient from the cis to the trans Golgi apparatus ensures proper protein post-translational modifications and targeting[3,6]. V-ATPase of eukaryotes is widely distributed in the membranes of various subcellular organelles (such as Lysosomes, Golgi, clathrin-coated vesicles, platelet dense granules, and chromaffin granules) and on cell membranes[3,7]. The human V-ATPase consists of two structural domains, V0 and V1. The V0 domain is embedded in the membrane and participates in proton transportation. It is composed of a1, d1, e1, RNaseK, c, c'', and ATP6AP1 and ATP6AP2 subunits. The soluble V1 complex is responsible for catalyzing the hydrolysis of ATP and is composed of eight different subunits (A, B, C, D, E, F, G, and H)[8].

Table 2 Results of several follow-up examinations and medications for the child

Age	ALT	AST	IgG	IgA	IgM	Blood ammonia	Medication
8 mo	213	242	4.2	1.3	0.54	181	Glutathione, ursodeoxycholic acid, ornithine monohydrate
9 mo	202	332	3.5	0.1	0.16	74	Glutathione, compound glycyrrhizin
11 mo	388	515	-	-	-	-	Glutathione, compound glycyrrhizin
12 mo	167	111	3.12	0.37	0.36	142	Glutathione, compound glycyrrhizin, ornithine monohydrate
19 mo	128	196	2.16	0.32	0.09	95	Bicyclol, compound glycyrrhizin

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Ig: Immunoglobulin.

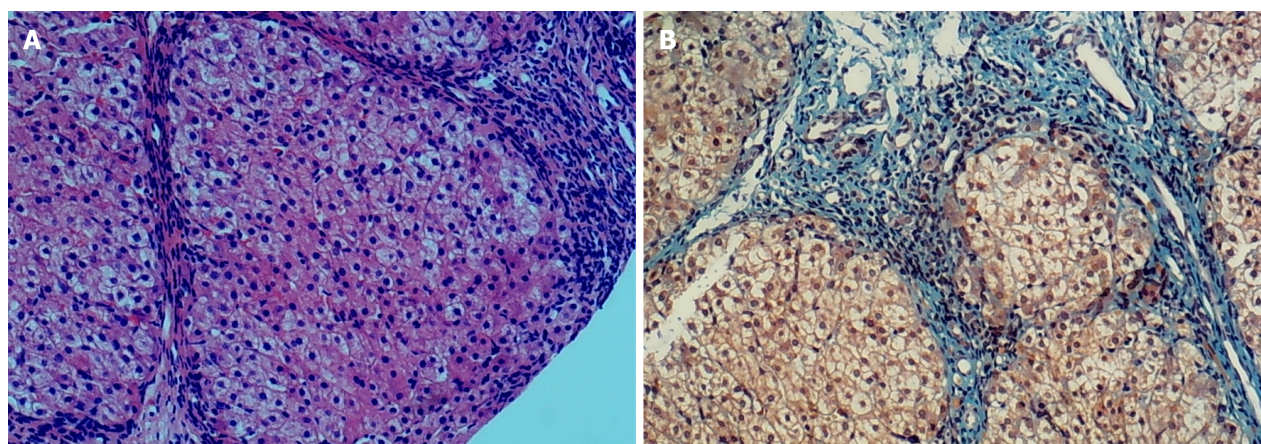


Figure 1 Liver tissue hematoxylin and eosin staining and Masson staining. A: Hematoxylin and eosin staining of liver tissue suggested the presence of pseudo lobules. Original magnification (100 ×); B: Collagen fiber staining (Masson) of liver tissue in green suggested fibrous hyperplasia. Original magnification (100 ×).

CDG is a growing group of monogenic diseases caused by disorders in the glycosylation process of proteins and lipids[9]. Glycosylation is a post-translational modification of proteins that occurs in the Golgi apparatus[10]. There are autosomal recessive, autosomal dominant, and X-linked modes of inheriting these diseases[11]. To have a better understanding of the relationship between mutations and diseases, the latest nomenclature for these diseases is "name of the mutated gene-CDG" (*e.g.*, *ATP6AP1*-CDG as reported in this article)[9].

The mechanism by which *ATP6AP1*-CDG occurs is complex. One explanation is that missense mutations in *ATP6AP1* affect the folding and assembly of V-ATPase, leading to reduced enzyme function and an inability to maintain Golgi pH homeostasis. This results in incorrect transportation of the glycosylase in the Golgi, prompting mislocalization of the enzyme. Mislocalization causes impaired glycosylation, which leads to CDG[3,8].

A total of 19 CDG patients with eight mutation types in the *ATP6AP1* gene (M248I, L144P, E346K, Y313C, Y217N, L181R, L74P, and L311E) have been reported so far[4,12-15], all with missense mutations. Five of the patients who died had mutation types L74P, L311E, and E346K[4,13,14]. This paper reports on a Chinese patient carrying one of these mutation types, E346K (c.1036G>A). The mutant locus was not included in the East Asian population of the "gnomAD" database.

Tables 3 and 4 summarize some of the reported clinical data and ancillary findings in children with *ATP6AP1*-CDG. Patients with *ATP6AP1*-CDG all showed abnormal liver function. The liver biopsy results of our patient suggested chronic hepatitis and nodular cirrhosis. The severity of liver damage varies between patients with different mutation loci. Severity ranges from minor changes in transaminases to hepatomegaly, hepatocellular steatosis, or fatty liver, to severe cirrhosis or even death from liver failure. As shown in Table 3, all children carrying the c.1036G>A (p.E346K) mutation in the *ATP6AP1* gene had more severe liver manifestations. All six children with clinical data documenting this mutation developed hepatosplenomegaly and cirrhosis, and two of them died of liver failure with a high mortality rate. Two other patients

Table 3 Comparison of reported clinical presentations of patients with *ATP6AP1*-congenital disorders of glycosylation

Family	Case	Initial diagnosis/death age	cDNA mutation	Connective tissue abnormalities	Infections	Neurological symptoms	Hepatosplenomegaly
1[4]	1.1	20 yr	c.1284G>A	Bilateral inguinal hernias	+	-	Hepatomegaly
	1.2	12 yr		Bilateral inguinal hernias	+	+/-	-
	1.3	34 yr		Bilateral inguinal hernias	+	-	-
2[4]	2	14 yr	c.431T>C	NA	+	-	-
3[4]	3.1	8 yr	c.1036G>A	NA	+	+	+
	3.2	Died 4 yr		NA	+	+	+
4[4]	4.1	23 yr	c.1036G>A	NA	+	+	+
	4.2	18 yr		NA	+	+	+
5[4]	5.1	Died 12 mo	c.1036G>A	NA	+	+	+
	5.2	3 yr		NA	+	+	Hepatomegaly
6[4]	6	4 yr	c.938A>G	NA	+	-	Hepatomegaly
7[15]	7	5 mo	c.649T>A	CL, aortic root dilation, diaphragmatic hernia	+	-	+
8[12]	8	10 yr	c.542T>G	CL, joint hypermobility	+	+/-	+
9[13]	9.1	Died 3 mo	c.221T>C	CL	-	-	+
	9.2	Died 11 mo		CL	-	-	+
10[14]	10.1	NA	c.923T>A	Ascending aorta dilation	-	-	+
	10.2	Died 4 mo		Ascending aorta dilation, atrial septal defect	-	-	Hepatomegaly
11[21]	11	1.5 yr	NA	Joint hypermobility	+	-	+
12	12	8 mo	c.1036G>A	-	+	+	+

+: Abnormal; -: Normal; NA: Not available.

with mutations in other loci also died from liver failure.

Two infants with coagulation abnormalities have been previously reported[12,14]. One patient, who could not be a liver transplant candidate, died of respiratory failure due to pulmonary hemorrhage after palliative care failed[16]. Therefore, patients with this disease should have regular liver function tests and timely assessments for coagulation abnormalities, hepatic encephalopathy, ascites, and other related complications to avoid irreversible end-stage liver disease.

Most patients had symptoms of hypogammaglobulinemia (15/19) and infections (15/19). Infections in patients with *ATP6AP1*-CDG can involve multiple tissues or organs. They can manifest as purulent otitis media, pneumonia, gastrointestinal infections, urinary tract infections, and plantar abscesses. In our case, the infant was admitted to a local hospital for a cough and was diagnosed with bronchopneumonia during his hospitalization. It is now believed that immunodeficiencies are the main cause of the *ATP6AP1*-CDG patient's susceptibility to infection or recurrent infections.

Although the protein encoded by the *ATP6AP1* gene is the Ac45 subunit of V-ATPase, cases of impaired liver function and immunodeficiency caused by genetic defects in V-ATPase itself have not been reported. The explanation for this phenomenon is that there may be tissue-specific processing of the Ac45 subunit in the liver, brain, and immune cells or that Ac45 may not only influence the pH-regulatory effects of V-ATPase[4]. Further studies are needed to investigate the mechanism of differential processing of Ac45 in different tissues.

As shown in Table 3, other abnormal clinical manifestations were connective tissue abnormalities (11/13) and neurological symptoms (9/19). Connective tissue abnormalities included CL, hernias, hyperlaxity of the joints, and aortic dilatation. No connective tissue lesions have been observed to date in the children reported in this study. Not all patients with CDG will have connective tissue abnormalities[17]. In some patients, this manifestation will gradually decrease with age[12]. All patients

Table 4 Comparison of reported ancillary tests in patients with *ATP6AP1*-congenital disorders of glycosylation

Family	Case	Abnormal liver function	Hypogammaglobulinemia	Low serum copper/ceruloplasmin	Liver biopsy
1[4]	1.1	+/-	+	+	NA
	1.2	+/-	+	+	NA
	1.3	+/-	+	NA	-
2[4]	2	+/-	+	+	Slight steatosis
3[4]	3.1	+/-	+	+	Fibrosis, steatosis, cirrhosis
	3.2	+/-	+	+	Steatosis, cirrhosis
4[4]	4.1	+	+	+	Micronodular cirrhosis
	4.2	+	+	+	Micronodular cirrhosis
5[4]	5.1	+	+	+	Fibrosis, cirrhosis, steatosis, cholestasis
	5.2	+	+	+	NA
6[4]	6	+	+	+/-	Fibrosis, cirrhosis, steatosis
7[15]	7	+	-	+	Micronodular cirrhosis, steatosis
8[12]	8	+	+	+	NA
9[13]	9.1	+	-	+	Fibrosis, steatosis, cholestasis
	9.2	+	-	+	Fibrosis, steatosis, cholestasis
10[14]	10.1	+	+	+	Fibrosis, steatosis, micronodular cirrhosis
	10.2	+	-	+	Fibrosis, steatosis, micronodular cirrhosis
11[21]	11	+	+	+	Steatosis, cirrhosis
12	12	+	+	+	Chronic hepatitis, nodular cirrhosis

+: Abnormal; -: Normal; NA: Not available.

with documented laboratory tests had a decrease in ceruloplasmin or serum copper (19/19). The mechanism of the abnormal manifestation of connective tissue in *ATP6AP1*-CDG patients has not been fully investigated. The possible reason is that the reduction of copper in the body reduces the activity of lysyl oxidase (copper-dependent enzyme), which is responsible for linking collagen and elastin of the extracellular matrix. Some of these patients showed signs of CL[12,13,18]. A previous study reporting on the skin biopsy of one CL patient showed normal quantity and quality of elastin fibers, suggesting that the phenotype of CL may not be related to the quality and quantity of elastin[15]. The exact reasons for this are to be further investigated.

Neurological abnormalities may manifest as mental retardation, epilepsy, muscle weakness, progressive hearing loss, sensorineural deafness, hyperopia, and behavioral abnormalities. The intellectual development and cognitive backwardness of the patient in this study may be attributed to delayed brain myelination.

Any patient with unexplained multisystem involvement should be suspected of having CDG and undergo isoelectric focusing electrophoresis for transferrin or apolipoprotein C-III[19]. Since some patients were found to have genetic alterations with normal transferrin electrophoresis results, glycomics was used only as a screening tool. Sequencing of the genes is still required to confirm the diagnosis of CDG[9,16]. However, studying the altered glycosylation of proteins in different cellular environments and specific glycosylation sites may be a new thought for treating patients with CDG.

There is no specific treatment for the disease. Patients can mainly consider regular check-ups, monitoring, and symptomatic supportive treatment to improve the quality of life and prolong the life. Treatments include intravenous immunoglobulin to improve hypogammaglobulinemia. However, some patients respond poorly to immunoglobulin[4,20]. One case of a successful liver transplant was reported in a child

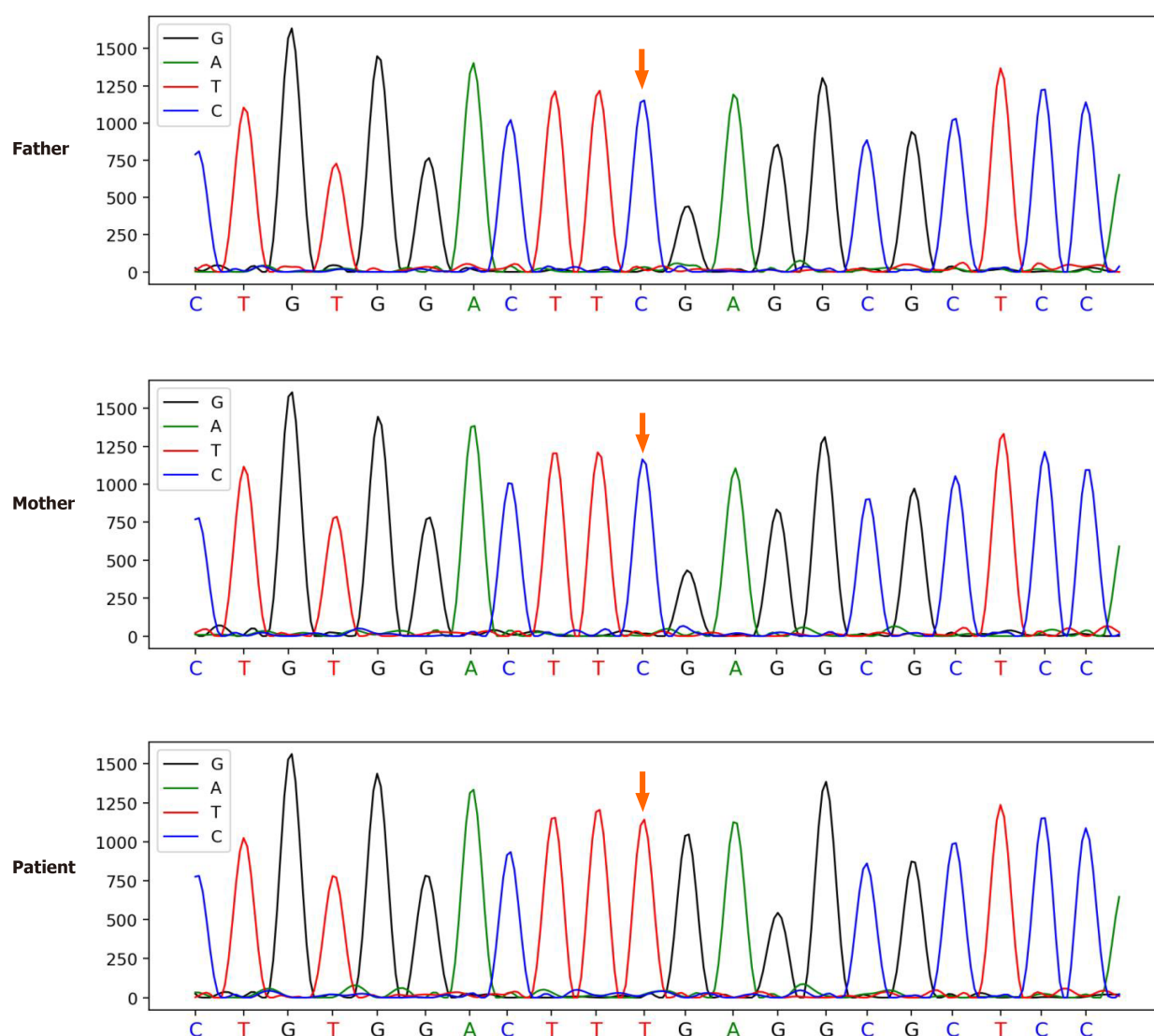


Figure 2 Genetic testing results of the family. The patient carries the c.1036G>A (p.E346K) mutation in the *ATP6AP1* gene. The red arrow refers to mutated nucleotide c.1036G>A in the patient. The genotypes of this locus in his parents were normal.

with a good postoperative status[16]. It remains to be seen whether liver transplant can be used as a treatment for this disease.

Prenatal monitoring of the mother and fetus may be an effective means to prevent the disease. In one mother and fetus, pregnancy abnormalities have been reported, including elevated maternal serum alpha-fetoprotein, elevated alpha-fetoprotein and positive acetylcholinesterase in the amniotic fluid, and abnormal prenatal ultrasound [14]. The patient's mother in this report had oligohydramnios, as did the mother of a patient diagnosed with CDG-Ih who also had the same symptoms[21]. It is not known whether these are characteristic manifestations of the disease during pregnancy, since there is a lack of data on the specific performance of the mother and fetus in the prenatal period. However, finding reliable prenatal indicators or clinical signs that can diagnose *ATP6AP1*-CDG may be needed and possible to detect the problem in time to avoid severe consequences.

CONCLUSION

In summary, 19 cases of CDG associated with *ATP6AP1* gene mutations have been reported, with detailed clinical information. The infant's clinical manifestations reported in this paper were hepatosplenomegaly, hypogammaglobulinemia, and developmental delay. All were consistent with the clinical features of previously described *ATP6AP1*-CDG cases. The diagnosis of this 8-mo-old infant with *ATP6AP1*-CDG was promptly clarified based on the clinical manifestations and trio-based whole

exome gene analysis, which has not been reported in China. It enriched the clinical phenotype spectrum of this disease. The clinical manifestations of children with *ATP6AP1*-CDG are highly variable. The mortality rate of children with some mutated loci is high. Gene sequencing can provide evidence for early diagnosis, intervention, and treatment of this disease.

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REFERENCES

- 1 Verheijen J, Tahata S, Kozicz T, Witters P, Morava E. Therapeutic approaches in Congenital Disorders of Glycosylation (CDG) involving N-linked glycosylation: an update. *Genet Med* 2020; **22**: 268-279 [PMID: 31534212 DOI: 10.1038/s41436-019-0647-2]
- 2 Beyenbach KW, Wieczorek H. The V-type H⁺ ATPase: molecular structure and function, physiological roles and regulation. *J Exp Biol* 2006; **209**: 577-589 [PMID: 16449553 DOI: 10.1242/jeb.02014]
- 3 Vasanthakumar T, Rubinstein JL. Structure and Roles of V-type ATPases. *Trends Biochem Sci* 2020; **45**: 295-307 [PMID: 32001091 DOI: 10.1016/j.tibs.2019.12.007]
- 4 Jansen EJ, Timal S, Ryan M, Ashikov A, van Scherpenzeel M, Graham LA, Mandel H, Hoischen A, Iancu TC, Raymond K, Steenbergen G, Gilissen C, Huijben K, van Bakel NH, Maeda Y, Rodenburg RJ, Adamowicz M, Crushell E, Koenen H, Adams D, Vodopitiz J, Greber-Platzer S, Müller T, Dueckers G, Morava E, Sykut-Cegielska J, Martens GJ, Wevers RA, Niehues T, Huynen MA, Veltman JA, Stevens TH, Lefeber DJ. ATP6AP1 deficiency causes an immunodeficiency with hepatopathy, cognitive impairment and abnormal protein glycosylation. *Nat Commun* 2016; **7**: 11600 [PMID: 27231034 DOI: 10.1038/ncomms11600]
- 5 Toei M, Saum R, Forgac M. Regulation and isoform function of the V-ATPases. *Biochemistry* 2010; **49**: 4715-4723 [PMID: 20450191 DOI: 10.1021/bi100397s]
- 6 Linders PTA, Peters E, Ter Beest M, Lefeber DJ, van den Bogaart G. Sugary Logistics Gone Wrong: Membrane Trafficking and Congenital Disorders of Glycosylation. *Int J Mol Sci* 2020; **21** [PMID: 32629928 DOI: 10.3390/ijms21134654]
- 7 Song Q, Meng B, Xu H, Mao Z. The emerging roles of vacuolar-type ATPase-dependent Lysosomal acidification in neurodegenerative diseases. *Transl Neurodegener* 2020; **9**: 17 [PMID: 32393395 DOI: 10.1186/s40035-020-00196-0]
- 8 Wang L, Wu D, Robinson CV, Wu H, Fu TM. Structures of a Complete Human V-ATPase Reveal Mechanisms of Its Assembly. *Mol Cell* 2020; **80**: 501-511.e3 [PMID: 33065002 DOI: 10.1016/j.molcel.2020.09.029]
- 9 Theodore M, Morava E. Congenital disorders of glycosylation: sweet news. *Curr Opin Pediatr* 2011; **23**: 581-587 [PMID: 21970833 DOI: 10.1097/MOP.0b013e3283cd693]
- 10 Ng BG, Freeze HH. Perspectives on Glycosylation and Its Congenital Disorders. *Trends Genet* 2018; **34**: 466-476 [PMID: 29606283 DOI: 10.1016/j.tig.2018.03.002]
- 11 Jaeken J, Péanne R. What is new in CDG? *J Inherit Metab Dis* 2017; **40**: 569-586 [PMID: 28484880 DOI: 10.1007/s10545-017-0050-6]
- 12 Dimitrov B, Himmelreich N, Hipgrave Ederveen AL, Lüchtenborg C, Okun JG, Breuer M, Hutter AM, Carl M, Guglielmi L, Hellwig A, Thiemann KC, Jost M, Peters V, Staufner C, Hoffmann GF, Hackenberg A, Paramasivam N, Wiemann S, Eils R, Schlesner M, Strahl S, Brügger B, Wührer M, Christoph Korenke G, Thiel C. Cutis laxa, exocrine pancreatic insufficiency and altered cellular metabolomics as additional symptoms in a new patient with ATP6AP1-CDG. *Mol Genet Metab* 2018; **123**: 364-374 [PMID: 29396028 DOI: 10.1016/j.ymgme.2018.01.008]
- 13 Ondruskova N, Honzik T, Vondrackova A, Stranecky V, Tesarova M, Zeman J, Hansikova H. Severe phenotype of ATP6AP1-CDG in two siblings with a novel mutation leading to a differential tissue-specific ATP6AP1 protein pattern, cellular oxidative stress and hepatic copper accumulation. *J Inherit Metab Dis* 2020; **43**: 694-700 [PMID: 32216104 DOI: 10.1002/jimd.12237]
- 14 Tvina A, Thomsen A, Palatnik A. Prenatal and postnatal phenotype of a pathologic variant in the ATP6AP1 gene. *Eur J Med Genet* 2020; **63**: 103881 [PMID: 32058063 DOI: 10.1016/j.ejmg.2020.103881]
- 15 Witters P, Breckpot J, Foulquier F, Preston G, Jaeken J, Morava E. Expanding the phenotype of metabolic cutis laxa with an additional disorder of N-linked protein glycosylation. *Eur J Hum Genet* 2018; **26**: 618-621 [PMID: 29192153 DOI: 10.1038/s41431-017-0044-8]
- 16 Gumm AJ, Basel DG, Thakrar P, Suchi M, Telega G. Liver failure and x-linked immunodeficiency type 47. *Pediatr Transplant* 2020; **24**: e13808 [PMID: 32790950 DOI: 10.1111/ptr.13808]
- 17 Smith-Mungo LI, Kagan HM. Lysyl oxidase: properties, regulation and multiple functions in

- biology. *Matrix Biol* 1998; **16**: 387-398 [PMID: 9524359 DOI: 10.1016/s0945-053x(98)90012-9]
- 18 **Marklová E**, Albahri Z. Screening and diagnosis of congenital disorders of glycosylation. *Clin Chim Acta* 2007; **385**: 6-20 [PMID: 17716641 DOI: 10.1016/j.cca.2007.07.002]
 - 19 **Woods AG**, Woods CW, Snow TM. Congenital disorders of glycosylation. *Adv Neonatal Care* 2012; **12**: 90-95 [PMID: 22469961 DOI: 10.1097/ANC.0b013e318241cb20]
 - 20 **Vesela K**, Honzik T, Hansikova H, Haeuptle MA, Semberova J, Stranak Z, Hennen T, Zeman J. A new case of ALG8 deficiency (CDG 1h). *J Inher Metab Dis* 2009; **32** Suppl 1 [PMID: 19688606 DOI: 10.1007/s10545-009-1203-z]
 - 21 **Quelhas D**, Martins E, Azevedo L, Bandeira A, Diogo L, Garcia P, Sequeira S, Ferreira AC, Teles EL, Rodrigues E, Fortuna AM, Mendonça C, Fernandes HC, Medeira A, Gaspar A, Janeiro P, Oliveira A, Laranjeira F, Ribeiro I, Souche E, Race V, Keldermans L, Matthijs G, Jaeken J. Congenital Disorders of Glycosylation in Portugal-Two Decades of Experience. *J Pediatr* 2021; **231**: 148-156 [PMID: 33340551 DOI: 10.1016/j.jpeds.2020.12.026]



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