Clinical Analysis and Long-term Treatment Monitoring of 3 Patients with Glycogen Storage Disease Type Ib

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Research article

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Abstract

Background To investigate the clinical and genetic characteristics of patients with glycogen storage disease type Ib (GSD Ib).

Methods Retrospectively analyzed the clinical data of 3 patients with GSD Ib admitted into our hospital, and summarized their onset characteristics, clinical manifestations, related examinations and treatment as well as mutational spectrum.

Results After gene sequencing, the diagnosis of GSD Ib was confirmed in all 3 patients. Five variants of SLC37A4 gene were detected, of which c. 572C>T was the common variant and c. 680G>A was a novel variant. The 3 cases of GSD Ib were mainly affected by liver enlargement, growth retardation, etc., and all had a history of repeated infections. At the onset, patients mainly manifested as mildly elevated alanine-aminotransferase (ALT), accompanied by decreased absolute neutrophil count (ANC), hypertriglyceridemia, and metabolic disorders (hypoglycemia, hyperlactic acidemia, metabolic acidosis, etc.). After long-term treatment by oral uncooked com starch, the abnormal liver enzymes gradually returned to normal, and metabolic abnormalities were basically controlled most of the time. With increasing age, ANC of the 3 patients decreased progressively, whereas the times of infections was reduced.

Conclusions The possibility of GSD type Ib should be kept on alert when a patient suffers recurrent infections, accompanied by hepatomegaly, elevated liver enzymes/hypoglycemia, dyslipidemia, and metabolic disorders. At present, the treatment of GSD Ib is mainly a comprehensive intervention based on diet therapy, and it is necessary to be alert to the occurrence of infectious immune diseases such as inflammatory bowel disease during follow-up.

Background

Glycogen storage disease type I (GSDI) is a group of autosomal recessive inherited metabolic disorders with varying clinical severity caused by variants in the G6PC gene (OMIM #613742) or SLC37A4 gene (OMIM # 602671), and the incidence is about 1:100,000 (1). The G6PC gene variant causes the deficiency of glucose-6-phosphatase alpha (G6Pase-α) activity, which leads to GSD type Ia (OMIM#232200), accounting for about 80% of GSDI patients, whereas the SLC37A4 gene variant causes the deficiency of glucose-6-phosphate transporter protein (G6PT), which underlies GSD type Ib (OMIM# 232220), accounting for about 20% of GSDI cases (1, 2).

Both type Ia and Ib are characterized by hepatomegaly and metabolic abnormalities such as hypoglycemia, hyperlipemia, lactic acidosis, and hyperuricemia. The SLC37A4 gene is highly expressed in hematopoietic progenitor cells, its defect has a significant effect on myeloid progenitor cells (3). At the same time, G6PT plays a role in the neutrophil homeostasis and function, endogenous glucose production is critical for neutrophil homeostasis, so the deficiency of G6PT can cause neutrophil apoptosis and neutropenia (4). Therefore, GSD Ib patients manifest neutropenia and neutrophil dysfunction, and are prone to frequent infectious diseases, such as recurrent upper respiratory tract infections, oral and intestinal mucosal ulcers, and inflammatory bowel disease (IBD), etc. Therefore, different treatment plans are needed for GSD Ib patients (2, 5).

In order to strengthen the management in GSD Ib patients, we retrospectively analyzed the clinical data of GSD Ib patients diagnosed by genetic testing, and long-term follow-up treatment in our hospital. This study is to explore the clinical indicators changes of GSD Ib patients before and after treatment, and to improve their life quality in the future.

Methods

1. Objects

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Approval number: TJ-IRB20180703). All study procedures were conducted in accordance with the tenets of the Declaration of Helsinki, and informed written consent was obtained from the parents of the patient.

Forty-nine patients with hepatic GSDs, including 3 cases with type Ib, admitted to Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology from September 2002 to July 2020, were included. The diagnostic criterion is as follows (6): (1) Hepatomegaly with or without splenomegaly, (2) Fasting hypoglycemia, (3) Growth and development delay, (4) Metabolic abnormalities: metabolic acidosis, lactic acidosis, hyperlipidemia, and hyperuricemia, (5) neutropenia, and/or (6) Liver biopsy suggesting GSDs.

As previously described(6), the following parameters were recorded: history, age of disease onset, initial symptoms, age of diagnosis, height, weight, sexual development, serum biochemical parameters (such as complete blood count, fasting glucose, liver and kidney functions, serum lipids, lactic acid, pyruvic acid, uric acid, and serum gas analysis, etc.), adrenaline test, and pathological examination of liver biopsy.

2. Genetic analysis

After obtaining the informed consents, gene sequencing (Beijing MyGenostics Inc.) was performed on the probands and their parents. Our genetic testing strategy is a GSD panel based on target gene capture technology (6), twenty GSD genes reported in OMIM database (GYS1, GYS2, G6PC, SLC37A4, GAA, AGL, GBE1, PYGM, PYGL, PFKM, PHKA2, PHKB, PHKG2, PHKA1, PGAM2, LDHA, ALDOA, ENO3, PGM1, GYG1, PRKAG2) was used for GSDs. We fragmented the genomic DNA which extracted from the sample, and the DNA probes were designed to tile along the exon regions and exon–intron boundaries of the target genes. After enrichment of DNA fragments, Illumina HiSeq X ten sequencer was used for high-throughput sequencing of the captured exon region. Sanger sequencing was finally used to verify co-segregation in the family. Suspected candidate variants were screened by comprehensively considering the genetic pattern and the clinical characteristics of the disease. The pathogenicity of variants was predicted according to the 2015-ACMG Standards and Guidelines.
Results

1. Baseline data

There were 3 patients with GSD Ib, including 1 male and 2 females (see Table 1). All patients underwent liver biopsy and showed glycogen storage as confirmed by periodic acid-Schiff staining (PAS). All patients were tested for glucose response to epinephrine stimulation after overnight fasting and the results were all positive (see Table 1).

| Clinical baseline data | Patient 1 | Patient 2 | Patient 3 |
|------------------------|-----------|-----------|-----------|
| Gender                 | Female    | Male      | Female    |
| Age of onset (years)   | 1         | 8         | 30        |
| Age at clinical diagnosis (years) | 15  | 42    | 36        |
| Course(months)         | 14        | 34        | 6         |
| Age at genetic diagnosis (years) | 12   | 13    | 11        |
| Chief complaint        | Abdominal distension | Upper respiratory tract infection, Hepatomegaly | Short stature, Hepatomegaly |
| Liver biopsy           | PAS (+)   | PAS (+)   | PAS (+)   |
| Epinephrine tolerance test | positive | positive | positive |
| Genotypes              | Base change | c.[1016G > A];[572C > T] | c.[572C > T]; [343G > A] | c.[870 + 5G > A];[680G > A] |
| Amino change           | p.[G339D];[P191L] | p.[P191L];[G115R] | splicing; W227* |
| Exon                   | 10;6      | 6;10      | 7;7       |
| Novel                  | -/-       | -/-       | -/-       |

2. Genetic test results

Five variants of SLC37A4 gene were detected in 3 patients (see Table 1), including 3 missense variants, 1 frameshift variant, and 1 splicing variant, which were c.1016G > A (p.Gly339Asp), c.572C > T (p.Pro191Leu), c.343G > A (p.Gly115Arg), c.680G > A (p.Trp227Ter) and c.870 + 5G > A, respectively. Among them, c.680G > A was a novel variant. According to the ACMG guidelines, all the above gene variants were suspected disease-associated variants. Among them, the c.572C > T variant involved 2 patients (2/3) (see Table 1 and Fig. 1).

3. Long-term follow-up

All patients were given oral uncooked cornstarch four daily doses of 1.0–2.0 g/kg (3am-9am-3 pm-9pm). According to current guidelines, follow-up is recommended every 3–6 months (adjusted by disease changes and their ages). The follow-up time were 13.75 years, 10.5 years and 8.75 years, respectively. The clinical and laboratory findings of the patients were shown in Table 2.
|                         | Patient 1 | Patient 2 | Patient 3 | Patient 1 | Patient 2 | Patient 3 | Patient 1 | Patient 2 | Patient 3 | Patient 1 | Patient 2 | Patient 3 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| **Age (years)**         | 1.25      | 12.33     | 15        | 3.5       | 13        | 14        | 3         | 10.5      | 3         | 3         | 10.5      |
| **Height (cm)**         | 72        | 141.8     | 150       | 89        | 136       | 141.6     | 90        | 137.7     | 90        | 141.6     | 137.7     |
| **Height (SDS)**        | -2.26     | -2.05     | -1.79     | -2.97     | -3.02     | -3.38     | -1.48     | -0.86     | -1.48     | -1.48     | -0.86     |
| **Growth velocity (cm/year)** | -         | 6.30      | 3.07      | -         | 4.95      | 5.6       | -         | 6.36      |           |           |           |
| **Weight (Kg)**         | 9         | 47.5      | 57.5      | 13        | 28.5      | 34        | 15        | 33.1      |           |           |           |
| **Weight (P)**          | 10–25     | 50–75     | 75–90     | 10–25     | 3         | 3         | 50–75     | 25–50     |           |           |           |
| **BMI (kg/m²)**         | 18.9      | 23.6      | 25.6      | 16.4      | 15.4      | 17.0      | 18.5      | 17.5      |           |           |           |
| **Sexual development**  | Stages of breast development | B1 | B3 | B4 | - | - | - | B1 | B2 |
|                         | Testicular volume (ml) | - | - | - | 1 | 3 | 6 | - | - |
| **Bone age (years)**    | -         | -         | -         | 1         | 3         | 6         | -         | -         |           |           |           |
| **Complete blood count**| Absolute neutrophil count (× 10⁹ / L) | 1.07 | 0.94 | 0.28 | 0.95 | 0.46 | 0.3 | 0.82 | 0.41 |
| **Liver function**      | ALT (U/L) | 75        | 10        | 25        | 50        | 37        | 30        | 37        | 28        |
|                         | AST (U/L) | 103       | 12        | 17        | 46        | 28        | 20        | 54        | 30        |
| **Blood lipids**        | TG (mmol/L) | 8.84      | 3.12      | 2.03      | 5.53      | 3.56      | 2.1       | 3.92      | 4.89      |
|                         | HDL (mmol/L) | 1.13      | 0.83      | 0.73      | 0.91      | 0.75      | 0.87      | 1.28      | 0.86      |
| **Glucose metabolism parameters** | Fasting glucose (mmol/L) | 3.7 | 2.79 | 3.1 | 3.8 | 2.49 | 4.63 | 3.48 | 3.64 |
|                         | Lactic acid (mmol/L) | 8.78 | 6.42 | 6.89 | 10.75 | 11.41 | 3.98 | 9.61 | 4.09 |
|                         | Pyruvic acid (umol/L) | 52.8 | 269.1 | 263.4 | 284.7 | 509.3 | 135.2 | 297.4 | 297.4 |
|                         | Uric acid (umol/L) | 281.9 | 674 | 419 | 499 | 537 | 366 | 519 | 522 |
| **Blood gases**         | PH        | 7.413     | 7.376     | 7.363     | 7.312     | 7.312     | 7.346     | 7.38      | 7.38      |
|                         | BE        | -8.5      | -5.8      | -6.4      | -10.9     | -10.9     | -1.1      | -1.1      | -1.1      |
| **Echocardiography**    | Liver size (cm) | 4 | 8.8 | 2 | 5 | 8 | 4.5 | 9 | 8 |
| **Kidney**              | Normal    | Normal    | Normal    | Normal    | Normal    | Normal    | Normal    | Normal    | Normal    |
| **Therapies**           | Uncooked cornstarch | - | Irregular | Irregular | - | Regular | Regular | - | Regular |
|                         | Neutropenia treatment | No | Yes | G-CSF | No | Yes | Yes | No | Yes |
|                         | Sodium Bicarbonate Tablets | No | Yes | Yes | No | Yes | No | No | No |
| **Complications**       | Number of hospitalizations (times/year) | 1 | 0.36 | 3 | 1 | 0 | 0 | 1 | 0 |
| **Inflammatory bowel disease** | No | No | Yes | No | No | No | No | No | No |

Abbreviation list: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglyceride; HDL, high-density lipoprotein; BE, base excess;

Normal range: Absolute neutrophil count > 1.5 × 10⁹ / L; ALT, 4-41 U/L; AST, 4–40 U/L; TG, 0.05–1.7 mmol/L; HDL, 1.10–1.90 mmol/L; Uric acid 202.3–416.5 umol glucose 4.11–6.05 mmol/L; Lactic acid 0.50–2.20 mmol/L; Pyruvic acid 20–100 umol/L; PH 7.35–7.45; BE -3 ~ 3.
At the first visit, the height of the 3 patients were −2.26 SDS, −2.97 SDS and −1.48 SDS, respectively. While their weight were 3-10th percentile, 10-25th percentile, and 50-75th percentile of the weight of children of the same age and sex, respectively. It is suggested that the height of the patients were more lagging behind when diagnosed, and the weight was mostly normal. After treatment, with the increase of age, the height (SDS) of two patients (patient 1 and 3) improved compared with that before treatment, while the weight of these two patients increased significantly after treatment, and the body mass index (BMI) indicated overweight. The height of patient 2 (male) has always been significantly behind, which may be related to the shorter target height (164 cm).

At the first diagnosis, abnormal laboratory findings of the 3 patients were mainly manifested as mildly elevated alanine aminotransferase (ALT), accompanied by hyperglycerideremia and metabolites abnormalities such as fasting hypoglycemia, hyperlactacidemia, and lactic acidosis. Two patients had elevated uric acid and pyruvic acid. After treatment, the liver enzymes of the 3 patients gradually returned to normal, triglycerides and lactic acid were decreased than before, but did not fall to normal levels. Pyruvic acid and uric acid decreased in 2 cases, and fasting hypoglycemia and metabolic acidosis were improved in 2 cases.

With increasing age, absolute neutrophil count (ANC) of the 3 patients decreased progressively. At the first visit, all of the 3 patients had a history of recurrent upper respiratory tract infection. Patient 2 had a history of oral ulcers, and was admitted to hospital once because of “infection”. Patient 3 had a history of upper respiratory tract infections, about once a year. As the treatment time extended, the number of infections of patients 2 and 3 was significantly reduced, only present with minor infections, such as upper respiratory tract infection or oral ulcers that did not require hospitalization. Patient 1 had an infection frequency of about 0.36 times/year before the diagnosis of genetic classification and was hospitalized for “repeated vomiting and diarrhea” 3 times in the past year, and had secondary “inflammatory bowel disease (IBD) and pancreatitis” during the last hospitalization (15 years old, course of disease 13.75 years).

**Discussion**

Glycogen storage disease (GSD) Type lb is a group of inherited metabolic disorders caused by variants in the *SLC37A4* gene, with an incidence of approximately 1/500 000. Fewer than 250 cases of type lb patients have been reported, much less than type Ia, with the most reports in China, Japan, South Korea, Iran and Serbia (7, 8).

The human *SLC37A4* gene is located on chromosome 11q23, consists of 9 exons, spans approximately 5.3 kb of genomic DNA, and is expressed ubiquitously in liver, kidney, intestine, blood and skeletal muscle (9). *SLC37A4* gene encodes G6PT, G6PT transports G6P from the cytoplasm to the lumen of the endoplasmic reticulum and delivers it to the catalytic site of G6Pase-α or G6Pase-β. G6Pase-α and G6Pase-β are G6P hydrolases in the endoplasmic reticulum membrane, which in turn hydrolyze G6P to glucose and inorganic phosphate (10). Among them, G6Pase-α and G6Pase-β are coupled functionally, rather than physically, to maintain the interendoplasmic (between meals) glucose homeostasis. A detrimental variant in the *SLC37A4* gene can cause G6PT deficiency or dysfunction, failing to complete the transport of G6P and resulting in disturbed glucose homeostasis, and then leading to hyperlactemia, lactic acidosis, hyperuricemia, and other metabolic abnormalities. Whereas G6Pase-β couples functionally with G6PT to maintain neutrophil function and homeostasis. Consequently, G6PT is essential to maintain both interand palpable glucose homeostasis and myeloid cell energy homeostasis (11). Although G6Pase-α and G6Pase-β are similar in structure and function, patients with G6Pase-β deficiency do not exhibit the metabolic phenotypes of GSD I patients. In contrast, these individuals only present with severe congenital neutropenia syndrome, reflecting the differences between the presentations of GSD Ia and GSD Ib.

So far, there are 115 pathogenic variants in the *SLC37A4* gene that have been identified, including missense variants, nonsense variants, frameshift variants, splice site variants, and deletion variants, etc. There are ethnic variability in variant types and proportions (8, 12). Previous studies have demonstrated that one of the most common types of variants is c.1042_1043del (p.Leu348Valfs* 53), which has been repeatedly reported in Germans (32%) and mixed Caucasians (27–31%) (2). In the Korean population, the most common variant is c.443C>T (p.Ala148Val), which is found in 55.6% of GSD Ib patients and 38.9% of alleles. Since it has not been reported in other races, the author speculates that the variant may be unique to Koreans (27–31%).

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The common variant type in Japanese is c.352T>C (p.Trp118Arg), accounting for 37–50% (12). No strict genotype-phenotype correlation has been determined in previous studies (13–16). In our study, 5 variant types of *SLC37A4* gene were detected in 3 patients. Among them, c.680G>A is a novel variant, the c.572C>T (p.Pro191Leu) variant is the most common and only reported in the Chinese population (17–19). We speculate that c.572C>T may be a Chinese race-specific variant.

| Patient | Mouth ulcers | Upper respiratory tract infection | Pancreatitis | Other |
|---------|--------------|----------------------------------|-------------|-------|
| Patient 1 | Yes | Yes | Yes | - |
| Patient 2 | Yes | Yes | Yes | - |
| Patient 3 | Yes | Yes | Yes | - |

**Abbreviation list:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglyceride; HDL, high-density lipoprotein; BE, base excess;

**Normal range:** Absolute neutrophil count > 1.5 × 10⁹ / L; ALT, AST, 4–41 U/L; AST, 0.5–1.7 mmol/L; HDL, 1.10–1.90 mmol/L; Uric acid, 202.3–416.5 umol glucose 4.11–6.05 mmol/L; Lactic acid 0.50–2.20 mmol/L; Pyruvic acid 20–100 umol/L; PH 7.35–7.45; BE -3 ~ 3.
The typical clinical manifestations of GSD Ib are similar to those of type Ia, including impaired glucose homeostasis such as liver enlargement and growth retardation. By contrast, neutropenia and neutrophil dysfunction are major clinical phenotypes of patients with GSD Ib. GSD Ib patients are often accompanied by neutropenia and are prone to frequent infectious diseases, such as recurrent upper respiratory tract infections, oral ulcers, enterocolitis and inflammatory bowel disease (IBD). There are also reports of GSD Ib combined with Crohn's disease (20). The exact mechanism of recurrent infections and IBD due to neutropenia and neutrophil dysfunction is still unclear. Studies have demonstrated that it may be related to impaired functions such as cell chemotaxis, calcium mobilization, respiratory burst, and leukocyte phagocytosis (21). In addition, studies have shown that patients with GSD Ib are at increased risk of autoimmune diseases (including IBD, thyroid autoimmune diseases and myasthenia gravis, etc.). Melis et al. found that this may be related to a reduced engagement in T cell glycolysis and an impaired regulatory T cell function (22). Therefore, GSD Ib caused by SLC37A4 gene variants is both a metabolic and an immune disorder (1).

A decreased number of neutrophils in peripheral blood is an important feature that distinguishes GSD Ib from GSD Ia. It is worth mentioning that not all patients diagnosed with GSD Ib based on metabolic phenotypes and genetic testing develop neutropenia, which may be related to the residual transport activity of G6PT (1). According to reports from different regions, the prevalence of neutropenia in GSD Ib patients is above 94%, and some patients may develop periodic neutropenia (1, 10, 12, 13). There are scattered reports of atypical GSD Ib patients without neutropenia or infectious diseases (23, 24). Neutropenia may also be observed in a subset of GSD Ia patients (25). Therefore, it is not possible to distinguish between type Ib and Ia based on the decrease in the number of neutrophils alone.

The current treatment of GSD Ib is mainly symptomatic. As a serious metabolic and immune multisystem disorder, if not actively treated, it may cause the patient to be fatal in adolescence. Clinically, diet therapy (raw cornstarch, etc.) can maintain the patient's glucose stability and reduce the early symptoms of the disease (10, 21). Those with poor diet control compliance often have obvious abnormalities in metabolic indicators, and death is mainly caused by metabolic disorders. Granulocyte colony stimulating factor (G-CSF) can improve neutropenia and IBD, but the underlying pathological process of the disease has not been corrected, and the specific mechanism is unknown (1, 2). For type Ib patients with both IBD and neutropenia, G-CSF and 5-aminosalicylic acid can be used in combination (1). In addition, GSD Ib patients receiving G-CSF treatment may have side effects such as splenomegaly, which is dose-dependent, and a few patients have myelodysplastic/acute myeloid leukemia (21, 26). There is also a case report of severe hypertriglyceridermia (triglyceride 80 mmol/L) in a GSD Ib infant with a significant decrease in blood lipid levels after plasma exchange (15). Another way to correct metabolic abnormalities in GSDI patients is liver transplantation or combined liver/kidney transplantation, while correction of bone marrow dysfunction in patients with GSD Ib can be achieved by bone marrow transplantation. However, many researchers believe that liver transplantation is a last resort, because the death rate associated with transplantation is higher than most other medical treatments (1). Studies have reported that bone marrow transplantation for GSD Ib patients with severe IBD and repeated infections, although their neutropenia persists, neutrophil function and IBD are improved (27). Although this is a case report, it offers hope for GSD Ib patients with severe myeloid complications. Since protein replacement therapy is not suitable for hydrophobic transmembrane proteins (such as G6PT), somatic gene therapy is a promising treatment for patients with type Ib. Effective use of gene therapy is very promising for correcting the metabolic abnormalities in GSD Ib patients, but to solve the problems of metabolic abnormalities and bone marrow complications at the same time, it may be necessary to construct either a vector with a wider range of tissue transduction specificity or a multivector approach (21).

The 3 patients in our study all had typical clinical manifestations such as elevated liver enzymes, fasting hypoglycemia, hyperlipidemia, hyperlactacidemia, lactic acidosis, and decreased neutrophil count, accompanied by hepatomegaly, growth retardation, and repeated infections. With increasing age, ANC of the 3 patients decreased progressively. Among them, the condition of patient 1 was poorly controlled, G-CSF was used irregularly, and the effect was not good, with secondary IBD and frequent hospitalizations due to infection. The other 2 patients were effectively controlled with age, and the number of infections was significantly decreased. Therefore, the clinical manifestations of patients with GSD Ib have certain heterogeneity.

Conclusion

In summary, GSD Ib patients have various gene variant types and different clinical symptoms. When recurrent upper respiratory tract infections or digestive tract symptoms are accompanied by hypoglycemia, dyslipidemia, metabolic disorders, elevated liver enzymes and/or neutropenia clinically, the possibility of GSD Ib should be vigilant. At present, the treatment is still based on diet therapy. In the long-term follow-up monitoring, it is necessary to be alert to the occurrence of infectious immune diseases such as inflammatory bowel disease.

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Declarations

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Authors' contributions

Y.L. and D.C.Q. designed and organized the study. Z.G.L., H.W., M.Z., H.M.H., C.Z., and L.X.P. cared for the patients, acquired the clinical data, and prepared the samples from the family members. Y.L. and D.C.Q. wrote the manuscript that was edited by all other authors. All authors read and approved the final
Research funding

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Availability of data and materials

The raw datasets generated and analysed during the current study are not publicly available in order to protect participant confidentiality.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Approval number: TJ-IRB20180703). All study procedures were conducted in accordance with the tenets of the Declaration of Helsinki, and informed written consent was obtained from the parents of the patient.

Consent for publication

Written informed consent to publish was obtained from each participant.

Competing interests

All authors declare that they have no conflict of interest.

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**Figures**

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A1, A2, A3, B1, B2, B3, C1, C2, C3: DNA sequencing electropherograms showing mutations (c.1016G>A, c.572C>T, c.343G>A, c.572C>T, c.870+5G>A, c.680G>A, 1016G>T, 1016G>A, 572C>T, 870+5G>A, 870+5G>A).
The exome sequencing results of the three patients and their parents. A1, patient 1 exon 10 sequencing showed variant c. 1016G>A p.Gly339Asp. A2, patient 1 exon 6 sequencing showed variant c. 572C>T p.Pro191Leu. B1, patient 2 exon 10 sequencing showed variant c. 343G>A p.Gly115Arg. B2, patient 2 exon 6 sequencing showed variant c. 572C>T p.Pro191Leu. C1, patient 3 exon 7 sequencing showed variant c. 680G>A p.Trp227Ter. C2, patient 3 exon 7 sequencing showed variant c. 870+5G>A. A3, B3, and C3 are the pedigrees of the 3 patients.