

CASE REPORT

Living Donor Liver Transplantation in a Korean Child with Glycogen Storage Disease Type IV and a GBE1 Mutation

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Glycogen storage disease type IV (GSD-IV) is an autosomal recessive disease caused by a deficient glycogen branching enzyme (GBE), encoded by the *GBE1* gene, resulting in the accumulation of abnormal glycogen deposits in the liver and other tissues. We treated a 20-month-old girl who presented with progressive liver cirrhosis and was diagnosed with GSD-IV, as confirmed by *GBE1* gene mutation analysis, and underwent living related heterozygous donor liver transplantation. Direct sequencing of the *GBE1* gene revealed that the patient was compound heterozygous for a known c.1571G>A (p.Gly264Glu) mutation and a novel c.791G>A (Arg524Gln) mutation. This is the first report of a Korean patient with GSD-IV confirmed by mutation analysis, who was treated successfully by liver transplantation. (**Gut and Liver 2009;3:60-63**)

Key Words: Glycogen storage disease type IV; *GBE1*; DNA analysis; Liver transplantation; Living donors

INTRODUCTION

Glycogen storage disease type IV (GSD-IV, Andersen disease: OMIM 232500) is a rare autosomal recessive disorder caused by deficient glycogen branching enzyme (GBE) activity.¹ This deficiency leads to the accumulation of amylopectin-like glycogen (polyglucosan), which has fewer branching points and longer outer chains than normal glycogen, and results in variable clinical presentations, including hepatic and neuromuscular forms.²

GSD-IV has been diagnosed histologically and biochemically, by measuring glycogen branching enzymes in individual tissues.³ GSD-IV is associated with mutations in *GBE1*, which encodes the glycogen branching enzyme,⁴ and several types of *GBE1* mutation have been identified.^{5,6} We describe here a 20 month-old girl with progressive liver cirrhosis associated with GSD-IV, as confirmed by *GBE1* gene analysis, who was successfully treated by liver transplantation.

CASE REPORT

A 20 month-old girl initially visited a tertiary hospital with hepatosplenomegaly. She was born at 37 weeks gestation by vaginal delivery and her birth weight was 2,470 g. On admission, her body weight was 11 kg (25th-50th percentile) and height was 79 cm (25th-50th percentile). Her blood pressure was 97/53 mmHg, heart rate 122 beats per min, respiratory rate 28 breaths per min, and body temperature was 36.5°C. On physical examination, sclera was icteric and the liver was hard and palpable by two fingerbreadth below the rib. The spleen was also palpable by two fingerbreadth below the rib, and abdomen was distended without ascites. Neurologic examination showed no definite abnormality and muscle tone was appropriate for her age. Laboratory tests showed hemoglobin 10 g/dL, white blood cell count 9,000/mm³ (neutrophils 69%, lymphocytes 23%, monocytes 7%, eosinophils 1%), platelet count 149,000/mm³, total protein 6.8 g/dL, albumin 3.2 g/dL, aspartate aminotransferase 542 IU/L,

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alanine aminotransferase 229 IU/L, total bilirubin 5 mg/dL, direct bilirubin 2.9 mg/dL, gamma-glutamyltranspeptidase 94 IU/L, alkaline phosphatase 299 IU/L, prothrombin time 47.3% (1.52 INR), and activated partial thrombin time 34.3 sec. Serologic markers for hepatitis A virus, hepatitis B virus, hepatitis C virus, Epstein-Barr virus, and cytomegalovirus were negative. A chest X-ray showed mild cardiomegaly. Hematoxylin-eosin (H&E) staining of a liver biopsy showed micronodular cirrhosis with colorless or pale eosinophilic cytoplasmic inclusions in hepatocytes and histiocytes, findings consistent with glycogen storage disease, type IV (Fig. 1A). Therapy with cornstarch was commenced but the patient showed progression of liver cirrhosis. She was therefore transferred

to the Asan Medical Center for liver transplantation. At Asan Medical Center, physical examination showed hepatosplenomegaly with distension and newly developed ascites. Echocardiography revealed mild left ventricular hypertrophy.

Molecular genetic analysis of the *GBE1* gene was performed. Direct sequencing of the 22 exons and the exon-intron boundaries of the *GBE1* gene on chromosome 3p12 using DNA isolated from peripheral blood showed that the patient was compound heterozygous for a known mutation, c.1571G>A (p.Gly264Glu), and a novel mutation c.791G>A (Arg524Gln) (Fig. 2).

At 27 months of age, she underwent living donor liver transplantation from her father, a heterozygous donor.

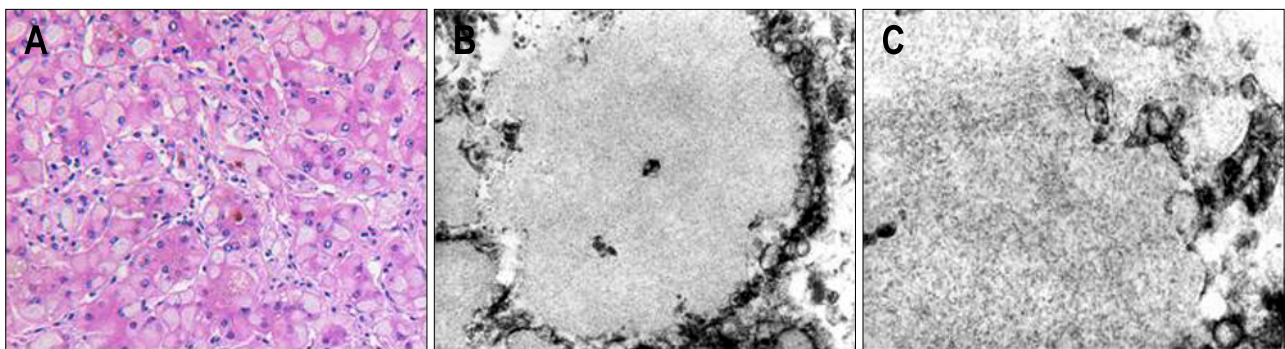


Fig. 1. Microscopic features on H&E staining (A) and electron microscopy (B, C) of a liver biopsy sample. The hepatocytes contained pale pink cytoplasmic amorphous material (H&E stain, $\times 200$) (A). These intracytoplasmic inclusions consisted of randomly oriented delicate fibrils that were up to 5 nm in diameter (B, C).

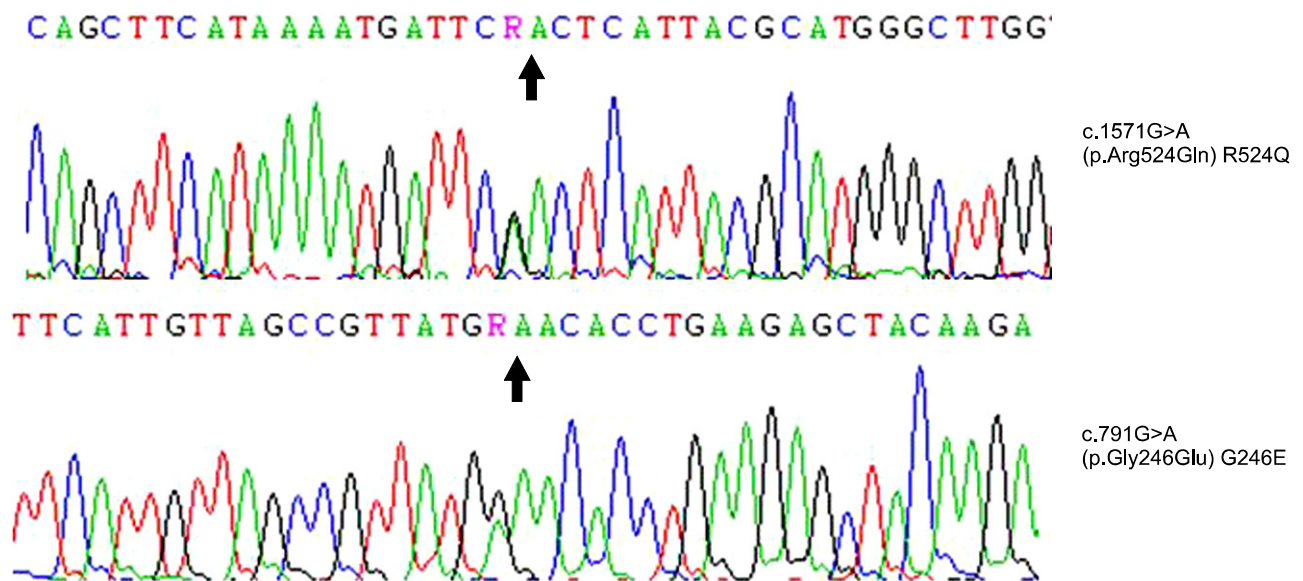


Fig. 2. *GBE1* mutations in a Korean patient with glycogen storage disease type IV. Mutations in *GBE1* are shown by sequence traces from patient DNA. Arrows indicate the exons containing mutations, which consisted of a known missense mutation (upper, c.1571G>A) in exon 12 and a novel missense mutation (bottom, c.791G>A) in exon 7.

The transplant was uneventful. The explanted liver, which measured 19×12×5.5 cm and weighed 593 gm, had a shrunken appearance and was diffusely nodular with a brownish green color. Microscopic examination revealed variable-sized regenerating nodules, supporting the diagnosis of cirrhosis. The morphologic features of the hepatocytes were identical with those observed in the previous liver biopsy (Fig. 1A). The intracytoplasmic inclusions were strongly positive on periodic acid-Schiff (PAS) staining, but were resistant to diastase, excluding other types of glycogen storage disease. Electron microscopy demonstrated that the cytoplasmic inclusions contained undulating, randomly-oriented, delicate fibrils, confirming the diagnosis of glycogen storage disease type IV (Fig. 1B, C).

Following liver transplantation, the patient was treated with standard immunosuppressive therapy. Six months after transplantation, she is well, with normal liver function, growth and development. However, mild cardiomegaly on a chest X-ray and mild left ventricular hypertrophy on echocardiography still persisted without change.

DISCUSSION

Glycogen storage diseases are over 12 types and they are classified based on the enzyme deficiency and affected tissue. In Korea, GSD-Ia was first reported in 1972 and GSD-IV was first reported in 1998.^{3,7}

Our patient presented with features typical of GSD-IV,¹ including failure to thrive, hepatosplenomegaly, and progressive liver cirrhosis, which, if left untreated, leads to death before the age of 5 years. Milder nonprogressive hepatic forms of GSD-IV have also been described, but they are less frequent.⁸ In addition to hepatic forms of GSD-IV, various neuromuscular forms are known, which differ according to age at onset and severity; these include fatal perinatal, congenital, childhood, and adult forms,⁵ which present with symptoms of myopathy, cardiopathy, and central and peripheral nervous system dysfunction. Our patient also showed mild cardiomegaly on chest X-ray and mild left ventricular hypertrophy on echocardiography, suggesting myocardial involvement.

All forms of GSD-IV result from molecular defects in *GBE1*, located on chromosome 3p12. *GBE1* mutation analysis of a variety of patients suggests a genotype/phenotype correlation, with null mutations such as deletions, insertions, or nonsense mutations being associated with a more severe clinical phenotype.^{2,5,6} However, the genotype/phenotype correlation in this disease remains unclear. Our patient showed compound heterozygosity for

the R524Q and G264E mutations. The R524Q mutation is known in patients with the milder hepatic form of GSD-IV,⁶ whereas G264E is a previously unreported mutation. This mutation clearly diminishes the GBE activity, but the pathogenic mechanism is not clear.⁹

Diagnosis of GSD-IV includes the histologic detection of abnormal glycogen storage and the biochemical measurement of deficient GBE activity, postnatally in red blood cells, leukocytes, hepatocytes, and cultured fibroblasts, and/or prenatally in amniotic fluid and chorionic villus cells.^{10,11} Although we could not measure enzyme activity to assist in diagnosis, we were able to detect abnormal glycogen storage in the liver and the *GBE1* mutations.

As there is no way to replace the deficient enzyme activity, liver transplantation is the only known treatment modality. The first successful liver transplantation for GSD-IV was performed in 1984.¹² To date, only 17 patients have been reported to receive liver transplants for this condition, and most did not develop cardiopathy or myopathy.¹³ Three of these patients received transplants from living, related, heterozygous donors, as did our patient, and no mortality or morbidity related to heterozygosity has yet been observed.¹⁴ Extrahepatic deposits of polyglucosan have been reported to be resorbed through the migration of donor cells (forming a microchimerism) from the liver allograft,¹⁵ although one patient died from cardiopathy after liver transplantation.¹⁶ Therefore, although liver transplantation was successful in our patient, long-term follow-up is necessary to guard against neuromuscular complications. Identification of the specific *GBE1* mutations will facilitate genetic diagnosis of GSD-IV, and genetic counseling for this family, should there be future pregnancies.

In conclusion, we report a patient diagnosed with GSD-IV by *GBE1* mutation analysis, who underwent successful liver transplantation from a heterozygous donor.

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