J Med Sci J Med Sci 2014;34(5):220-223
DOI: 10.4103/1011-4564.143651


CASE REPORT

# Unique Glucose-6-Phosphatase, Catalytic Subunit Mutation in a Child with Type Ia Glycogen Storage Disease in Taiwan

Chia-Ying Chang[1,2], Chien-Han Chen[3]

*[1]Department of Pediatrics, [2]Department of Medical Research, Mackay Memorial Hospital, Hsin-chu, [3]Department of Pediatrics, Min-Sheng General Hospital, Taoyuan, Taiwan, Republic of China*

The G272W mutation in the glucose-6-phosphatase, catalytic subunit (*G6PC*) gene has been reported once in mainland China, but has not been reported in Taiwan or other countries. We report a female patient with type Ia glycogen storage disease (GSD). She presented at birth with abdominal distension, shortness of breath, and nonbilious vomiting. Hyperammonemia, metabolic acidosis, hyperuricemia, and elevated liver function were noted after a subsequent survey. Tachypnea and metabolic acidosis were exacerbated whenever she was infected with croup. Abdominal and renal sonography performed at 2-year of age revealed marked hepatomegaly and nephromegaly, with increased echogenicity. The genetic survey of the patient demonstrated compound heterozygous mutations in the *G6PC* gene, including a codon 83 [c.248G >A, p.Arg83His] mutation inherited from her father, and codon 272 [c.814G >T, p.Gly272Trp] mutation inherited from her mother. Type Ia GSD was diagnosed based on the birth history, biochemistry, image study, and molecular diagnosis. After the girl was treated with cornstarch, her liver function and other abnormal biochemistry data gradually normalized. This report may facilitate clarifying the prognoses of Chinese patients with these 2 mutations of the *G6PC* gene. Furthermore, this report highlights the importance of the G272W mutation, which may be unique to the Chinese population.

Key words: Glycogen storage disease, hyperammonemia, hyperuricemia, hepatomegaly, nephromegaly

## INTRODUCTION

Glucose-6-phosphatase (G6Pase) deficiency, or Type Ia glycogen storage disease (GSD), is characterized by poor tolerance to fasting, growth retardation, and the accumulation of glycogen and fat in the liver and kidneys. G6Pase is restricted inside the endoplasmic reticulum in the liver, kidney, and intestine, and is encoded by the glucose-6-phosphatase, catalytic subunit (*G6PC*) gene on chromosome 17q21 (OMIM 232200). The symptoms of Type Ia GSD include tremors, frequent epistaxis, marked hepatomegaly, a full-cheeked round face, and enlarged kidneys.[1] Abnormal laboratory data include hypoglycemia, lactic acidosis, hyperlipidemia, hyperuricemia, and elevated liver function. We report a female patient presenting 2 genetic mutations of the *G6PC* gene. The first mutation, which was inherited from her father, is located in codon 83 [c.248G >A, p.Arg83His] and has been frequently identified in Chinese patients with Type Ia GSD.[1,2] The second mutation, which was inherited from her mother, is located in codon 272 [c.814G >T, p.Gly272Trp], and has only been reported once in mainland China,[3] but has not been reported in Taiwan or other countries.

Received: January 13, 2014; Revised: April 24, 2014; Accepted: July 14, 2014
Corresponding Author: Dr. Chien-Han Chen, Department of Pediatrics, Min-Sheng General Hospital, No. 168, Ching-Kuo Road, Taoyuan 330, Taiwan, Republic of China. Tel: +886-3-317-9599 ext. 2041; Fax: +886-3-346-8765; E-mail: chinsword@yahoo.com.tw

## CASE REPORT

An infant girl presented with abdominal distension, nonbilious vomiting, and tachypnea (60-70/min) when she was 3 days old. A physical examination indicated a weak general appearance, suprasternal and subcostal retraction, and a distended abdomen. Laboratory data revealed a high anion gap (35 mEq/L), hypoglycemia, lactic acidosis (lactate: 88 mg/dL and pyruvate: 3.22 mg/dL), and hyperammonemia (ammonia: 99 umol/L). Abnormal liver function was noted when she was 5 days old (glutamate oxaloacetate transaminase [GOT] 89 IU/L and glutamate pyruvate transaminase [GPT] 71 IU/L), and the levels elevated to GOT 298 IU/L and GPT 107 IU/L when she was 20 days old. These conditions improved after the patient underwent intravenous fluid hydration. Tachypnea and metabolic acidosis were subsequently exacerbated whenever she was infected with croup.

When the patient was 2-year-old, she was admitted to our hospital because of croup and tachypnea. A physical

examination indicated a puffy face, relatively thin limbs [Figure 1], and hepatomegaly (a liver span of approximately 6 cm). Laboratory data revealed elevated liver function (GOT: 1143 U/L; GPT: 438 U/L), metabolic acidosis (pH: 7.1; $HCO_3$: 3.1 mmol; B.E.: −26 mmol), hyperammonemia (113 ug/dL), hyperuricemia (15.7 mg/dL), and hypoglycemia (11 mg/dL). Frequent epistaxis was subsequently noted because of prolonged prothrombin time/partial thromboplastin time (14.9 s/ >120 s). In addition, hypertriglyceridemia (triglyceride: 460 mg/dL) was observed when the patient exhibited normal cholesterol levels. Sonography demonstrated marked hepatomegaly, featuring increased echogenicity and bilateral nephromegaly, grade II increased echogenicity, and fair cortex-medulla differentiation.

Based on these symptoms, GSD, and specifically type Ia GSD, was suspected. We sent blood samples for molecular diagnosis and discovered compound heterozygous mutations in the *G6PC* gene, including a codon 83 [c.248G >A, p.Arg83His] mutation that the patient inherited from her father, and a codon 272 [c.814G >T, p.Gly272Trp] mutation that she inherited from her mother [Figure 2]. Hence, type Ia GSD was diagnosed. After cornstarch supplement and vegetarian diet control were initiated, we have followed the patient for at least 2-year. Her admission rate has substantially decreased and her laboratory data, including GOT/GPT, uric acid, and lactate levels, have normalized as well, implying an acceptable prognosis.

## DISCUSSION

We report a 2-year-old girl in Taiwan with clinical manifestations indicating type Ia GSD, which was diagnosed by the presence of 2 genetic mutations of the *G6PC* gene located in codons 83 and 272.

The predominant presenting symptoms of type Ia GSD are often nonspecific and include poor feeding, lethargy, failure to thrive, respiratory distress, and abdominal distention.[4] A thorough physical examination is critical. We suggest that when hepatomegaly is noted, abdominal sonography should be arranged to determine possible hyperechogenicity of the liver caused by glycogen deposits (a notable characteristic of storage disease). Furthermore, renal sonography should be conducted to identify the presence of renal enlargement and hyperechogenicity, which are common features of type Ia GSD.[4,5] A definite diagnosis requires conducting a genetic survey. For early detection and prevention of the disease in the next pregnancy, prenatal genetic diagnosis is required to examine genetic mutations.[6]

The presented patient exhibited mutations in codon 83 [c.248G>A, p.Arg83His] and 272 [c.814G>T, p.Gly272Trp] of the *G6PC* gene. The codon R83H mutation is prevalent in Chinese patients with type Ia GSD.[2] The most large study on type Ia GSD in Taiwan indicated that R83H is the second most common mutation.[7] After summarizing all previous reports in Taiwan, including our case [Table 1],[7-11] we determined that the frequency of R83H (32.7%) mutation was similar to that of the most frequent mutation, 727G>T (34.7%); this finding indicates that the role of R83H in the pathogenesis of type Ia GSD may be as critical as that of 727G>T. According to the recently proposed 9 transmembrane helical model, the amino acid Arg83 resides on the endoplasmic reticulum lumen side[12] and is critical to glucose-6-phosphate binding and catalysis.[13] R83H is an active site mutation and patients who exhibit this mutation lack G6Pase activity.[14]

A genetic mutation in the *G6PC* gene of the case patient, the G272W mutation, is both rare and critical in the Chinese population. As shown in Table 1, G272W has not been observed in previous studies in Taiwan, although it was previously reported in mainland China.[3] Because this G272W mutation has been found in 2 distinct areas of China (Taiwan and mainland China), but has not been reported in other countries


**Figure** 1. (a) The patient exhibited a classic puffy face (b) Slim limbs were noted

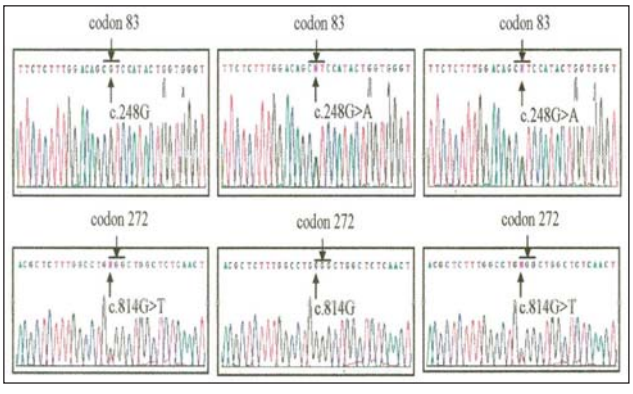


**Figure** 2. DNA sequencing indicated that the mother exhibited a c. 814G >T mutation (left), and the father exhibited a c. 248 G >A mutation (middle). The patient exhibits a combination of the compound heterozygous mutations (right)

Table 1. Summary of mutations of GSD type Ia in Taiwan

| Nucleotide changes/effect of mutations | Wong *et al*.[7] | Chiang *et al*.[8] | Lee *et al*.[9] | Shieh *et al*.[10] | Wu *et al*.[11] | Our case | Total |
|---|---|---|---|---|---|---|---|
| | *n* | *n* | *n* | *n* | *n* | *n* | *n* (%) |
| 727G >T/aberrant MRNA splice | 16[a] | | | | 1 | | 17 (34.7) |
| 327G >A/R83H, affects substrate binding | 13[a] | | 2 | | | 1 | 16 (32.7) |
| 361A >G/M121V, mild form GSD Ia | | | | 5 | | | 5 (10.2) |
| 1101 T >A/I341N, transmembrane domain | 2 | | 2 | | | | 4 (8.2) |
| 933insAA/framshift, truncated protein | 1[a] | | | | | | 1 (2.0) |
| 389C >T/Q104X, truncated protein | 1 | | | | | | 1 (2.0) |
| 435A >T/H119L, affects phophoryl-enzyme intermediate formation | 1 | | | | 1 | | 2 (4.1) |
| 814G >T/G272W | | | | | | 1 | 1 (2.0) |
| 793G >T | | 1 | | | | | 1 (2.0) |
| 341delG/frameshift, truncated protein | 1[a] | | | | | | 1 (2.0) |

[a]Mutations found in both of the studies of Wong *et al.* and Chiang *et al*; GSD = Glycogen storage disease

or populations,[15] we propose that genomes of Chinese people may be prone to this mutation, regardless of the environment, and that G272W may be unique to the Chinese population.

The exact mechanism of G272W in the pathogenesis of type Ia GSD remains unclear. One possibility is that the G272W mutant may reduce G6Pase activity. The mutant G272W is located in the transmembrane helix 7.[14] The structural integrity of transmembrane helices is critical for the correct folding, stability, and enzymatic activity of G6Pase;[14] thus, this mutation may affect the stability of G6Pase. All nearby identified mutants (N264K, L265P, G266V, G270V, G270R) in the transmembrane helix 7 have been shown to abolish or substantially reduce G6Pase activity levels.[12]

This is the first report to provide the outcome of a patient carrying the G272W mutation after follow-up for 2-year. The first report in the literature about G272W mutation did not delineate the prognosis of that patient.[3] However, the nearby G270V mutation has been found to cause a mild form of GSD1a,[16] implying that the G272W mutation in our patient may be responsible for her acceptable prognosis.

In a study of 20-year follow-up for a GSD-Ia patient who exhibited R83H mutation, cornstarch treatment had improved life quality initially during childhood but hepatocellular carcinoma and renal failure developed later after adulthood.[17] There is little evidence for a stringent genotype-phenotype relationship for each GSD-Ia gene mutation. So even our patient now has an acceptable clinical condition, long-term follow-up for late complications is still necessary.

In summation, we reported a patient exhibiting mutations in codons 83 [c.248G >A, p.Arg83His] and 272 [c.814G >T, p.Gly272Trp] of the *G6PC* gene. These compound heterozygous mutations affect binding and decrease the structural stability of the enzyme, and may explain the early onset of the disease in the newborn stage of this patient and its severe clinical expression. However, after beginning a cornstarch and vegetarian diet control, the clinical conditions and blood biochemistries of the patient gradually improved. This study highlights the rareness and importance of the G272W mutation, which may be unique to the Chinese population.

## REFERENCES


1. Froissart R, Piraud M, Boudjemline AM, Vianey-Saban C, Petit F, Hubert-Buron A, *et al.* Glucose-6-phosphatase deficiency. Orphanet J Rare Dis 2011;6:27.
2. Lei KJ, Chen YT, Chen H, Wong LJ, Liu JL, McConkie-Rosell A, *et al.* Genetic basis of glycogen storage disease type 1a: Prevalent mutations at the glucose-6-phosphatase locus. Am J Hum Genet 1995;57:766-71.
3. Xu S, Qin S, Gu X, Qiu W, Ye J, Han L, *et al.* Rapid detection of glycogen storage disease type Ia by DNA microarray. Clin Chem Lab Med 2010;48:1229-34.
4. Reitsma-Bierens WC. Renal complications in glycogen storage disease type I. Eur J Pediatr 1993;152 Suppl 1:S60-2.
5. Lin CC, Tsai JD, Lin SP, Lee HC. Renal sonographic findings of type I glycogen storage disease in infancy and early childhood. Pediatr Radiol 2005;35:786-91.
6. Lee WJ, Yang CH, Ho ES, Shih A, Lin LY, Lin WH. Prenatal diagnosis in a Chinese family with type Ia glycogen storage disease by PCR-based genetic analysis. Prenat Diagn 1996;16:1027-31.
7. Wong LJ, Hwu WL, Dai P, Chen TJ. Molecular genetics of glycogen-storage disease type 1a in Chinese patients of Taiwan. Mol Genet Metab 2001;72:175-80.

8. Chiang SC, Lee YM, Chang MH, Wang TR, Ko TM, Hwu WL. Glucose-6-phosphatase gene mutations in Taiwan Chinese patients with glycogen storage disease type Ia. J Hum Genet 2000;45:197-9.
9. Lee WJ, Lee HM, Chi CS, Shu SG, Lin LY, Lin WH. Genetic analysis of the glucose-6-phosphatase mutation of type 1a glycogen storage disease in a Chinese family. Clin Genet 1996;50:206-11.
10. Shieh JJ, Lu YH, Huang SW, Huang YH, Sun CH, Chiou HJ, *et al.* Misdiagnosis as steatohepatitis in a family with mild glycogen storage disease type 1a. Gene 2012;509:154-7.
11. Wu MC, Tsai FJ, Lee CC, Tsai CH, Wu JY. A novel missense mutation (H119L) identified in a Taiwan Chinese family with glycogen storage disease Ia (Von Gierke disease). Hum Mutat 2000;16:447.
12. Pan CJ, Lei KJ, Annabi B, Hemrika W, Chou JY. Transmembrane topology of glucose-6-phosphatase. J Biol Chem 1998;273:6144-8.
13. Lei KJ, Pan CJ, Liu JL, Shelly LL, Chou JY. Structure-function analysis of human glucose-6-phosphatase, the enzyme deficient in glycogen storage disease type 1a. J Biol Chem 1995;270:11882-6.
14. Shieh JJ, Terzioglu M, Hiraiwa H, Marsh J, Pan CJ, Chen LY, *et al.* The molecular basis of glycogen storage disease type 1a: Structure and function analysis of mutations in glucose-6-phosphatase. J Biol Chem 2002;277:5047-53.
15. Cooper DN, Ball EV, Stenson PD, Phillips AD, Shaw K, Mort ME. Human gene mutation database. Available from: http://www.hgmd.cf.ac.uk.
16. Parvari R, Isam J, Moses SW. Glycogen storage disease type 1a in three siblings with the G270V mutation. J Inherit Metab Dis 1999;22:149-54.
17. Hou JW, Wang TR. A 20-year follow-up of a male patient with type Ia glycogen storage disease. Chang Gung Med J 2003;26:283-7.