A novel mutation of the GLUT2 gene in a Turkish patient with Fanconi-Bickel syndrome

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Fanconi-Bickel syndrome is a rare inherited disorder of carbohydrate metabolism. The disease is characterized by the association of a massive hepatomegaly due to glycogen accumulation, severe hypophosphatemic rickets and marked growth retardation due to proximal renal tubular dysfunction. Fanconi-Bickel syndrome is a single gene disease and is caused by defects in the facilitative glucose transporter 2 (GLUT2) gene (SLC2A2) on chromosome 3q26.1-26.3, which encodes for the glucose transporter protein 2 expressed in hepatocytes, pancreatic beta-cells, enterocytes, and renal tubular cells. Several mutations in a gene encoding a glucose transporter have been reported in patients with Fanconi-Bickel syndrome. Here we report a Turkish child who had a novel mutation that has not been described before and we discuss the knowledge regarding genetic mutations in this rare disease.

Key words: Fanconi-Bickel syndrome, glycogen storage disease, GLUT2 gene, mutation analysis.

Fanconi-Bickel syndrome (FBS) is a rare inherited disorder of carbohydrate metabolism. The disease is characterized by the association of a massive hepatomegaly due to glycogen accumulation, severe hypophosphatemic rickets and marked growth retardation due to proximal renal tubular dysfunction. Proximal renal tubular dysfunction with glucosuria, phosphaturia, generalized aminoaciduria, bicarbonate wasting, and hypophosphatemia are characteristic laboratory findings of the disease[1,2].

Fanconi-Bickel syndrome is a single gene disease and is caused by defects in the facilitative glucose transporter 2 (GLUT2) gene (SLC2A2) on chromosome 3q26.1-26.3, which encodes for the glucose transporter protein 2 expressed in hepatocytes, pancreatic beta-cells, enterocytes, and renal tubular cells[1-3]. Since the first report of mutations in the GLUT2 gene[4], more than 30 different mutations have been identified, and most of the reported mutations are private and confined to a single family[5]. Here we report a Turkish FBS case who had a novel mutation that has not been described before and we discuss the genetic mutations in this rare disease.

Case Report

A four-year-old female child, second-born of first-degree consanguineous parents, presented with abdominal distension, X-bain deformity and failure to thrive (Fig. 1). There was no history of antenatal problems during the mother's pregnancy. It was learned that the family's first child had died at two weeks of age with an unknown etiology. The family had noticed the symptoms of our patient when she began to walk. After their application to a health facility, she was diagnosed as hypophosphatemic rickets and treatment with oral vitamin D and phosphate supplementation was commenced.

She was admitted to our hospital for evaluation of growth retardation at the age of four years. On physical examination, growth retardation (length 82 cm [-4.1 SDS], weight 12 kg

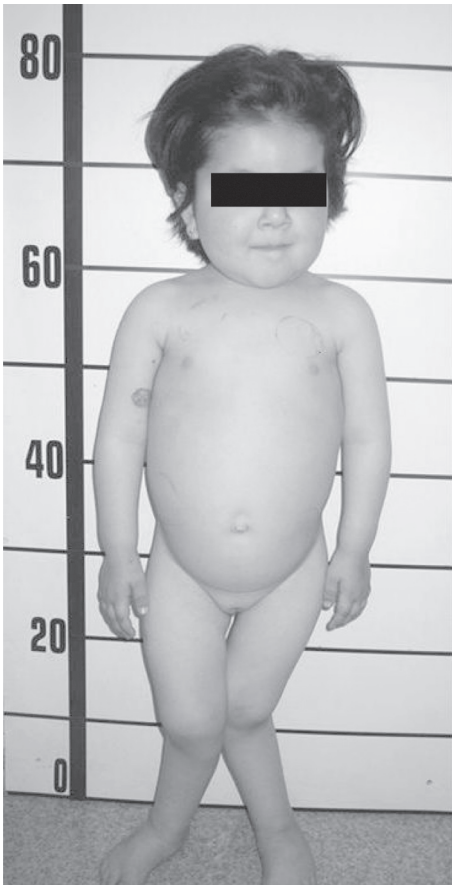

Fig. 1. Doll-like face, abdominal distension and X-bain deformity were present in the patient with Fanconi-Bickel syndrome.

[-1.7 SDS]), a "doll-like face" and clinical manifestations of rickets were recorded. Abdominal distension and hepatomegaly were noted. The liver was measured 6 cm below the right costal margin. The rest of the systemic examination was normal.

Laboratory examinations revealed normal serum calcium (9.4 mg/dl, normal: 8-10.2), reduced serum phosphorus (1.4 mg/dl, normal: 2.7-4.5), and markedly elevated serum alkaline phosphatase (1060 U/L, normal: 145-420 U/L) levels. Liver and kidney function tests were all normal. Serum triglyceride was high (168 mg/dl, normal: 32-99), whereas serum total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol levels were normal. Fasting hypoglycemia (30 mg/dl) and postprandial hyperglycemia (120 mg/dl) were recorded. Arterial blood gas analysis revealed metabolic acidosis (pH, 7.3; bicarbonate, 18 mmol/L). Urinary pH was 7 (normal: 4.5-8), with 3+ glucosuria, 2+ proteinuria and generalized aminoaciduria. The radiologic examinations demonstrated X-bain deformity on legs. Abdominal ultrasound revealed massive hepatomegaly with enlarged kidney size. Liver biopsy showed marked accumulation of glycogen in the hepatocytes (Fig. 2). On the basis of these findings, FBS was presumed and was finally confirmed by molecular analysis of the GLUT2 gene. All coding exons, including flanking introns in the GLUT2 gene, were amplified by polymerase chain reaction (PCR) from genomic DNA. The PCR products were directly sequenced using a Big Dye Primer Cycle Sequencing kit and an ABI 310 Genetic Analyzer (PE Applied Biosystems, Foster City, CA, USA). Direct sequencing revealed two-base deletion (c.835_836delGA) with a homozygous pattern in exon 6, which resulted in a creation of a premature-termination codon (p.E279KfsX6) (Fig. 3).

Symptomatic treatment with calcitriol, neutral phosphorus and Shohl solution was started and the mother was advised to feed the child by

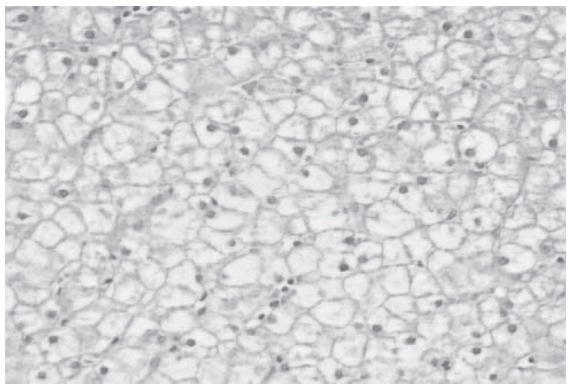

Fig. 2. The liver biopsy revealed swollen and vacuolated hepatocytes consistent with glycogenosis (hematoxylin and eosin, X100).

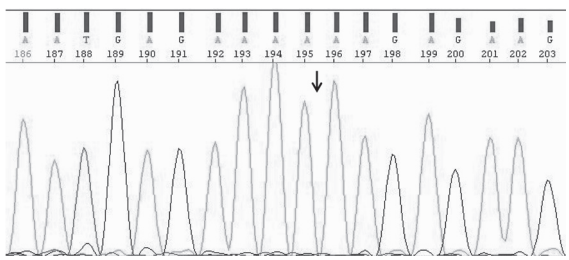

Fig. 3. Two bases were deleted with a homozygous pattern in exon 6 of the GLUT2 gene (c.835_836delGA).

frequent meals with adequate caloric intake and uncooked cornstarch before sleep. The patient has been followed to date up to five years of age and although calcium, phosphate and alkaline phosphatase levels were in normal ranges, there was no improvement in the growth retardation and other findings of FBS.

Discussion

Fanconi-Bickel syndrome is a rare but distinct clinical entity. The disorder has been reported from all parts of Europe, Turkey, Israel, Arabian countries of the Near East and North Africa, Japan, and North America. The exact frequency is not known, but consanguinity in families suggests autosomal recessive inheritance[1-2].

In the last decade, many mutations concerning the GLUT2 gene have been described for FBS. In 1997, Santer et al.[4] described the basic defect of this disease when reporting homozygosity for mutations within the gene of the GLUT2 in four patients. These mutations represented the first detection of a congenital defect within a whole family of membrane proteins, which are the facilitative glucose transporters. Later, Santer et al.[6] reported a total of 109 cases from 88 families worldwide who had been diagnosed as FBS. They report their results of mutation analysis in 49 patients from 39 families from Turkey, Europe, the Near East, North Africa, and North America. Homozygosity or compound heterozygosity for GLUT2 mutations was found in 49 patients in these cases and 23 novel mutations of the GLUT2 gene were detected. These mutations were scattered over the whole coding sequence of the GLUT2 gene and mutations have been found in all exons. None of these mutations was particularly frequent, which makes molecular genetic diagnosis laborious. It is interesting that most of the GLUT2 mutations were private and confined to a single family. Of these patients, 12 were Turkish and all had a different mutation in this reported paper[6]. Our patient's mutation is novel and not previously described in the literature. In a recent paper, three Turkish FBS patients, who had novel homozygous mutations of the GLUT2 gene, were reported, and none of them was similar to our patient's mutation[5] (Table I). There are also FBS patients reported as having no detected mutations in the protein-coding region of the GLUT2 gene[6,7]. An explanation for this situation can be that at least some of patients carry heterozygous long-range deletions not detectable with the applied PCR-based method[6].

Table I. The Reported Mutations in Turkish Fanconi-Bickel Syndrome in the Literature

No.	Author	Mutation
1	Santer et al., 2002*	793-4 ins C
2	Santer et al., 2002	793-4 ins C
3	Santer et al., 2002	449 del T
4	Santer et al., 2002	449 del T
5	Santer et al., 2002	1405C→T
6	Santer et al., 2002	1405C→T
7	Santer et al., 2002	818C→G
8	Santer et al., 2002	1562C→T
9	Santer et al., 2002	793-4 ins C
10	Santer et al., 2002	738 del 17
11	Santer et al., 2002	IVS 5+1 g→t
12	Temizel et al., 2005**	738 del 17
13	Temizel et al., 2005	818C→G
14	Temizel et al., 2005	IVS 5+1 g→t

*Santer et al. [Hum Genet 2002; 110: 21-29].
**Temizel et al. [Turk J Pediatr 2005; 47: 167-169].

Mutations reported in the literature show variations, thus the mutation detected in our patient adds additional information for FBS. It is obvious that further mutation analysis may disclose whether FBS is a single gene disease or is a syndrome derived from different gene loci.

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