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Novel compound heterozygous mutations in the fructose-1,6-bisphosphatase gene cause hypoglycemia and lactic acidosis

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Abstract

Fructose-1,6-bisphosphatase (FBPase) deficiency is an autosomal recessive disorder caused by a mutation of the fructose-1,6-bisphosphatase 1 (*FBP1*) gene and results in impaired gluconeogenesis. We describe a male patient with typical FBPase deficiency who presented with hypoglycemia and lactic acidosis. The FBPase activity in his peripheral leukocytes and liver was very low. We amplified and sequenced the entire *FBP1* coding region of the patient and his family members. Direct and allele-specific sequence analysis of the *FBP1* gene revealed that the proband had a compound heterozygote for the G164S and 838delT, which he inherited from his carrier parents. His father and mother had heterozygous 838delT and G164S mutations, respectively, without any symptoms of hypoglycemia. Gene tracking within the family revealed that his elder sister had a heterozygous G164S mutation without symptoms of hypoglycemia. A G164S mutation of *FBP1* in a heterozygous pattern (G164S and InsG960_961) has been reported previously, but the heterozygous 838delT mutation is novel. Transient transfection studies using COS-7 cells demonstrated that FBPase proteins with G164S or 838delT mutations were enzymatically inactive. In conclusion, we report a new case of molecular diagnosis of FBPase deficiency and provide evidence that impaired FBPase activity may be caused by novel compound heterozygous mutations in the *FBP1* gene.

1. Introduction

Fructose-1,6-bisphosphatase (FBPase) deficiency is an autosomal recessive inherited disorder characterized by episodic spells of hypoglycemia, ketosis, and lactic acidosis during fasting and is often lethal during the neonatal period and infancy [1-4]. Fasting and febrile infectious diseases are known to trigger these symptoms [3,5]. Fructose-1,6-bisphosphatase, which catalyzes the splitting of fructose-1,6-bisphosphate (FBP) into fructose 6-phosphate and inorganic phosphate, is a key enzyme in the regulation of gluconeogenesis [3,6]. Human FBPases are coded in 2 distinct genes, namely, *FBP1* and *FBP2* [5]. *FBP1* consists of 7 exons, spanning more than 31 kilobases at chromosome 9q22.2-q22.3, and expresses a 362–amino acid protein, mainly in the liver [3,4]. *FBP2*, which was isolated from muscle, codes 339 amino acids and shares 77% amino acid sequence identity with *FBP1* [7]. Since Kikawa et al [3] identified 3 mutations of *FBP1* responsible for FBPase deficiency in 10 Japanese patients, other *FBP1* mutations have been reported in patients with other ethnic backgrounds [8,9]. No cases of FBPase deficiency in Korea have been reported. Here, we describe a new compound-heterozygote germline mutation of the *FBP1* gene in a Korean adult male with FBPase deficiency. We performed transient transfection studies using COS-7 cells, which demonstrated that the G164S or 838delT mutation was responsible for the loss of or decrease in FBPase activity.

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2. Patients and methods

2.1. Patient profile

The proband was a 19-year-old male Korean and was born after a normal pregnancy and delivery. Other family members, including one older sister, were healthy. He suffered repeated episodes of severe hypoglycemia and acidosis during febrile illnesses in infancy and early childhood. Thereafter, he remained well until a few months before admission to our hospital, when he had become stuporous after drinking alcohol. The results of physical examination on admission were unremarkable. His height and weight were 181 cm and 75 kg, respectively. His plasma levels of glucose, insulin, and c-peptide were 30 mg/dL, 2 μIU/mL, and 0.5 ng/mL, respectively. Blood pH was 6.925, blood HCO_3^- level was 3.2 mmol/L, and serum lactate level was 67.5 mg/dL, which indicated severe lactic acidosis. As hepatomegaly was not observed on computed tomography scanning of the abdomen, an extensive evaluation was conducted; and a liver biopsy was taken. Liver glycogen content was normal (6.5%, wet weight basis; reference, 1%-6%); and hepatic glucose-6-phosphatase activity, which was measured as reported earlier [10], was within the reference range. The FBPase activities of the patient's peripheral leukocytes and liver were 0.18 nmol min^{-1} mg^{-1} protein (reference, 0.5–3.0) and 1.13 nmol min^{-1} mg^{-1} protein (reference, 25–70), respectively (Fig. 1). Fructose-1,6-bisphosphatase activity was measured using a following standard method. Liver and blood samples were obtained in accordance with protocols approved for human studies by our institutional review boards, and all the family members provided written informed consent as directed by these protocols.

2.2. FBPase activity assay

Fructose-1,6-bisphosphatase activity was measured using an nicotinamide adenine dinucleotide phosphate (NADP)-coupled spectrophotometric assay as described elsewhere [11-14]. Briefly, the assay mixture (1 mL) consisted of 20 μg protein of cell lysate, peripheral leukocytes, liver tissue, or COS-7 cells; 0.5 mmol/L NADP; 5 U/mL G6PDH; 10 U/mL glucose-6-phosphate isomerase; and ±20 μmol/L FBP, the substrate. The difference in the rate of change in absorbance per minute at 340 nm in the presence and absence of FBP was used to calculate FBPase activity. Fructose-1,6-bisphosphatase activity was expressed as nanomoles per minute per milligram protein (NADPH extinction coefficient = 6220 cm^2/mmol).

2.3. Screening for mutations in FBP1

Total RNA was prepared from peripheral lymphocytes of the family members using TRIZOL Reagent (Invitrogen, Carlsbad, CA). Double-stranded complementary DNA (cDNA) was synthesized by reverse transcription using 1.0 μg of total RNA, SuperScript II reverse transcriptase

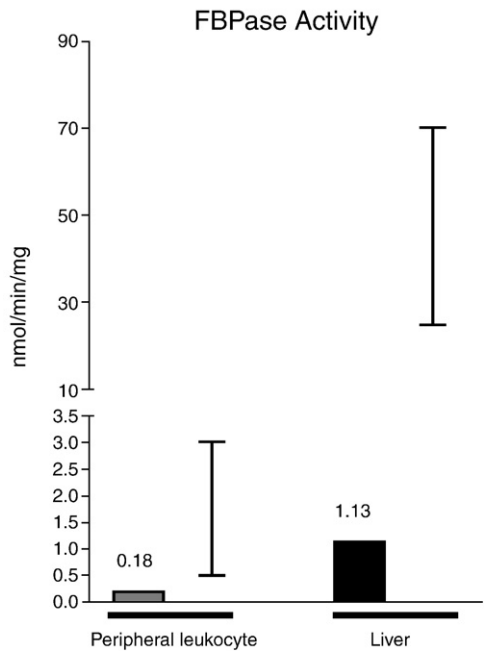

Fig. 1. Fructose-1,6-bisphosphatase activity in the patient's peripheral leukocytes and liver. The FBPase activity was measured using an NADP-coupled spectrophotometric assay. The FBPase activity of peripheral leukocytes was 0.18 nmol min^{-1} mg^{-1} protein (reference, 0.5-3.0) and that of liver was 1.13 nmol min^{-1} mg^{-1} protein (reference, 25-70). Each vertical bar indicates reference range of FBPase activity from peripheral leukocyte or liver.

(Invitrogen), and oligo (dT). The coding region of the *FBP1* gene was amplified using 3 overlapping sets of primers (Table 1). The polymerase chain reaction (PCR) conditions were as follows: first step, 2 minutes at 94°C; second step, 30 seconds at 98°C, 30 seconds at 58°C, and 30 seconds at 72°C for 30 cycles; and third step, 5 minutes at 72°C. To corroborate the sequences of the *FBP1* transcripts, we also performed genomic PCR on human *FBP1*. Genomic DNA was isolated from peripheral white blood cells using the Flexigene DNA kit (Qiagen, Hilden, Germany). Two sets of PCR primers for exons 4 and 7 were synthesized (Table 1) based on the sequence of *FBP1* (GenBank accession no. NC_000009). The PCR amplification was performed for 30 cycles of 30 seconds at 94°C, 30 seconds at 55°C, and 30 seconds at 72°C. The PCR products from FBPase cDNA and genomic DNA were separated by electrophoresis on an agarose gel and then extracted from the gel. Automated sequencing was performed using an ABI3100 Prism automatic sequencer and Big Dye terminator chemistry (Applied Biosystems, Foster City, CA). The PCR products were subcloned using a TOPO-TA cloning kit (Invitrogen), and the cloned inserts were analyzed by PCR and Big Dye terminator cycle sequencing using an ABI3100 Prism automatic sequencer. For amplification of the entire coding region of the *FBP1* wild type and the 2 mutant types, cDNA was amplified using the Expand High Fidelity PCR system (Roche Applied Science, Indianapolis, IN) according to the manufacturer's protocol. Each primer contained the *FBP1*

Table 1
Oligonucleotide primers used to amplify the 7 exons of *FBP1*

Primers	Exon no.	Size (bp)	T_m (°C)	Upstream primer	Downstream primer
FBP1 cDNA	1-3	468	56	5′-AGTGCCTACTGCCCTCTC-3′	5′-ATGTTGGAAGATCCATCAAG-3′
	2-6	496	58	5′-GAAGATAAACACGCCATCAT-3	5′-GAAATATCCCTCCGTAGACC-3′
	5-7	384	58	5′-CCCAGATAATTCAGCTCCTT-3′	5′-AGGGTACTGCTGTGTGAGAC-3
FBP1 DNA	4	390	55	5′-GAGAATGCCTCCTGTTAATG-3′	5′-CACTCTCTCTTGGTCTCCTG-3
	7	404	55	5′-ACTTTTACAGCCTCACAGGA-3	5′-GGTACTGCTGTGTGAGACAA-3
FBP1 cloning (*Hin*dIII/*Kpn*I)		1037	55	5′-GCGCAAGCTTGCCATGGCTG-ACCAGGCG-3′	5′-GCGCGGTACCCTGGGCAGAG-TGCTTCTC-3′

T_m indicates annealing temperature.

sequence and the enzyme sequence. The PCR products were subcloned into the pCR2.1-TOPO vector.

2.4. Construction of FBP1 expression vectors

For in vitro functional studies of the single T deletion at 838 base pairs (bp) from the ATG start site of the *FBP1* gene and G164S, *Hin*dIII-*Kpn*I fragments (wild type and 2 mutants) from pCR2.1 were substituted into the compatible sites of the pcDNA3 vector with a C-terminal Flag tag (Invitrogen), which was kindly donated by Dr Hyang Sook Lim (Research Institute of Molecular Genetics, Catholic Research Institute of Medical Science, The Catholic University of Korea, Seoul, Korea) (Fig. 2). The construct was used to transform DH5a bacterial competent cells. An empty vector was used as a negative control: the insert gene of the pcDNA3 with the C-terminal Flag tag was excised with *Hin*dIII and *Kpn*I, and the empty vector was purified by agarose gel electrophoresis after ligation. These constructs were used to transform DH5a bacterial competent cells. Several bacterial colonies were isolated, and their DNA was sequenced from both orientations using the vector's primers.

2.5. Cell culture and transient transfection

A COS-7 cell line was purchased from the Korean cell-line bank (Cancer Research Institute, Seoul National

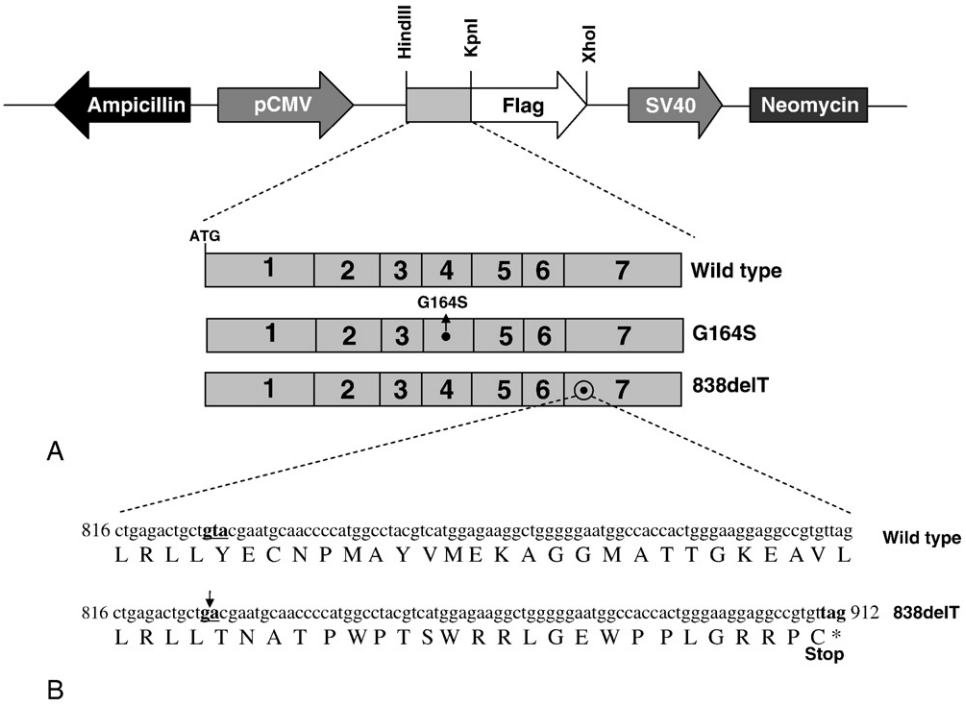

Fig. 2. Schematic diagram of the constructs used for the determination of human FBPase expression in COS-7 cells. A, The entire coding region of the 838delT, G164S, and wild-type *FBP1* cDNA was subcloned into the *Hin*dIII and *Kpn*I site of the pcDNA3 vector with a C-terminal Flag tag. The positions of restriction site and the start (ATG) and stop codons are indicated. The *Hin*dIII, *Kpn*I, and *Xho*I sites are shown. The exon numbers of the *FBP1* gene are indicated by Arabic numbers, and the mutation site (G164S or 838delT) of each construct is indicated. B, The 1-bp deletion (bp position 838; indicated by an arrow) results in a shift of the reading frame and a stop codon after 24 amino acids.

University College of Medicine, Seoul, Korea). COS-7 cells were grown in Dulbecco modified Eagle medium with 10% fetal calf serum at 37°C in a humidified 5% CO_2 incubator. COS-7 cells were plated onto 35-mm dishes for transfection. When the cells were 80% to 90% confluent, they were transfected with 2 μg of plasmid DNA complexed with 7.5 μL of Lipofectamine 2000 (Invitrogen) in 250 mL of opti-MEM I reduced serum medium (Invitrogen). Five hours after transfection, the cells were washed; and the medium was replaced with Dulbecco modified Eagle medium containing 10% fetal bovine serum. Transfected COS-7 cells were selected after treatment with 800 μg/mL of Geneticin (Invitrogen) 2 days after transfection. Geneticin-resistant COS-7 cells were analyzed for expression of FBPase by immunoblotting and immunofluorescence studies for FBPase or Flag. The COS-7 cells were also measured for FBPase activity by an NADP-coupled spectrophotometric assay.

2.6. Western blotting assay

Transfected and selected COS-7 cells were lysed with lysis buffer and centrifuged. The pellets were discarded, and supernatants were assayed for protein concentration. Aliquots containing 25 μg protein were separated using 12% acrylamide gels under denaturing conditions. After the proteins were transferred to a membrane, the membranes were first incubated with polyclonal anticytosolic FBPase antibody (Agrisera, Stockholm, Sweden) or monoclonal anti-Flag M2 antibody (Sigma-Aldrich, St Louis, MO). The membranes were then incubated with horseradish peroxidase–conjugated anti-rabbit antibody (Abcam, Cambridge, MA) or horseradish peroxidase–conjugated anti-mouse antibody (Thermo Fisher Scientific, Rockford, IL). The signals were detected using an ECL kit (Amersham, Arlington Heights, IL). β-Actin protein bands were used to assess the amount of protein that was loaded.

2.7. Immunofluorescence study

Immunofluorescence study was carried out to examine the cellular expression of wild-type and 2 mutant *FBP1* genes. Transfected and selected COS-7 cells were transferred into 6-well plates containing sterilized glass coverslips. Approximately 48 hours later, cells were fixed and treated with phosphate-buffered saline containing 0.5% Triton X-100 for permeabilization. After incubation in a blocking buffer containing normal donkey serum in phosphate-buffered saline, cells were incubated with monoclonal anti-Flag M2 antibody (Sigma-Aldrich) at 1:500 dilution. Bounded antibody was stained with Rhodamine (TRITC)-conjugated AffiniPure Donkey Anti-mouse IgG (Jackson ImmunoResearch Laboratories, West Grove, PA). Fluorescence images were obtained with a confocal laser scanning microscope (LSM Meta, Zeiss, Germany).

3. Results

3.1. Identification of novel compound heterozygous mutations in the FBP1 gene

Mutation analysis was performed on samples from the proband and his family members (Fig. 3). Mutation screening was done on peripheral lymphocyte RNA, and genomic DNA was used to corroborate the mutations detected from lymphocyte RNA. Germline DNA samples were amplified by PCR and bidirectionally sequenced for mutations across the 7 exons of *FBP1*, which encompassed the entire coding region (Table 1). The cDNA and genomic DNA from the proband and his father contained a novel germline deletion mutation (838delT) in exon 7, which should result in premature termination (Fig. 2B). A previously identified G164S mutation in exon 4 was identified in the proband, his mother, and his sister. Therefore, his father and mother had heterozygous 838delT and G164S mutations, respectively (Fig. 3). Allele-specific sequence analysis of the *FBP1* gene revealed that the proband had a compound heterozygote for the G164S and 838delT, which he inherited from his carrier parents. Subcloning and sequencing of the RT-PCR products of total RNA extracted from the leukocytes of the proband showed that the G164S mutation was located in the allele opposite the one that harbored the 838delT mutation (Fig. 4). These mutations were not present in 50 control individuals as determined by allele-specific PCR (data not shown).

3.2. FBPase protein expression and enzymatic activity of wild-type and mutant FBP1 cDNA in COS-7 cells

FBP1 cDNA constructs of the wild-type, mutant clones (G164S or 838delT) and the cotransfect (G164S plus 838delT) were overexpressed in COS-7 cells. We analyzed FBPase protein expression by Western blotting and immunofluorescence studies. Fructose-1,6-bisphosphatase expression in COS-7 cells was markedly decreased in the

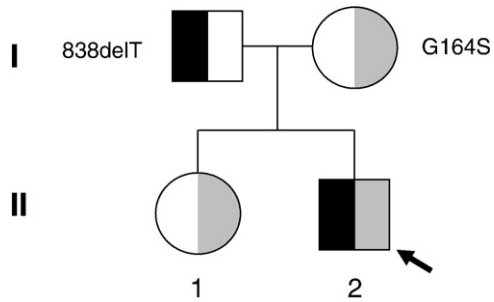

Fig. 3. Pedigree of the Korean FBPase-deficient family. Gray symbols indicate the allele of G164S. Black symbols indicate the allele of 838delT. An arrow indicates the compound-heterozygote proband with G164S mutation, which was reported previously, and the new one with the 838delT mutation. The proband inherited mutations of G164S and 838delT from his mother and father, respectively. Family members are indicated according to generation (Roman numerals) and individuals (Arabic numerals).

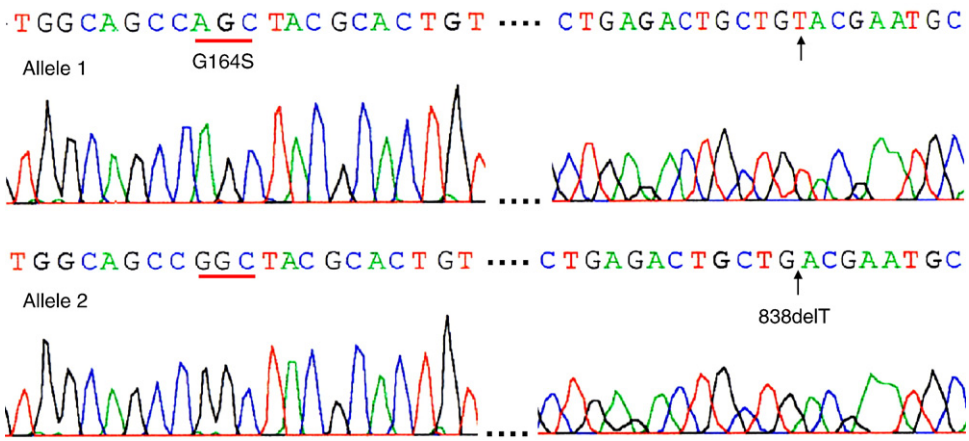

Fig. 4. *FBP1* gene mutations in a Korean family with FBPase deficiency. Allele-specific sequence analysis of the *FBP1* gene shows allele 1 harboring G164S and the corresponding allele harboring 838delT. The nucleotide sequence shows the mutations and the corresponding nonmutated sequence. Subcloning and sequencing of the reverse transcriptase PCR products of total RNA extracted from the leukocytes of the proband revealed that the G164S mutation was located in the allele opposite to that which harbored the 838delT mutation.

G164S and cotransfected constructs compared with the wild type and was undetectable in 838delT-transfected COS-7 cells (Fig. 5A, B). To confirm the FBPase activities of the G164S, 838delT, and G164S + 838delT cotransfects with that of the wild type, FBPase enzymatic activity from each overexpressed clone was tested using an NADP-coupled spectrophotometric assay. The FBPase activities of purified proteins of the G164S, 838delT, and the cotransfection

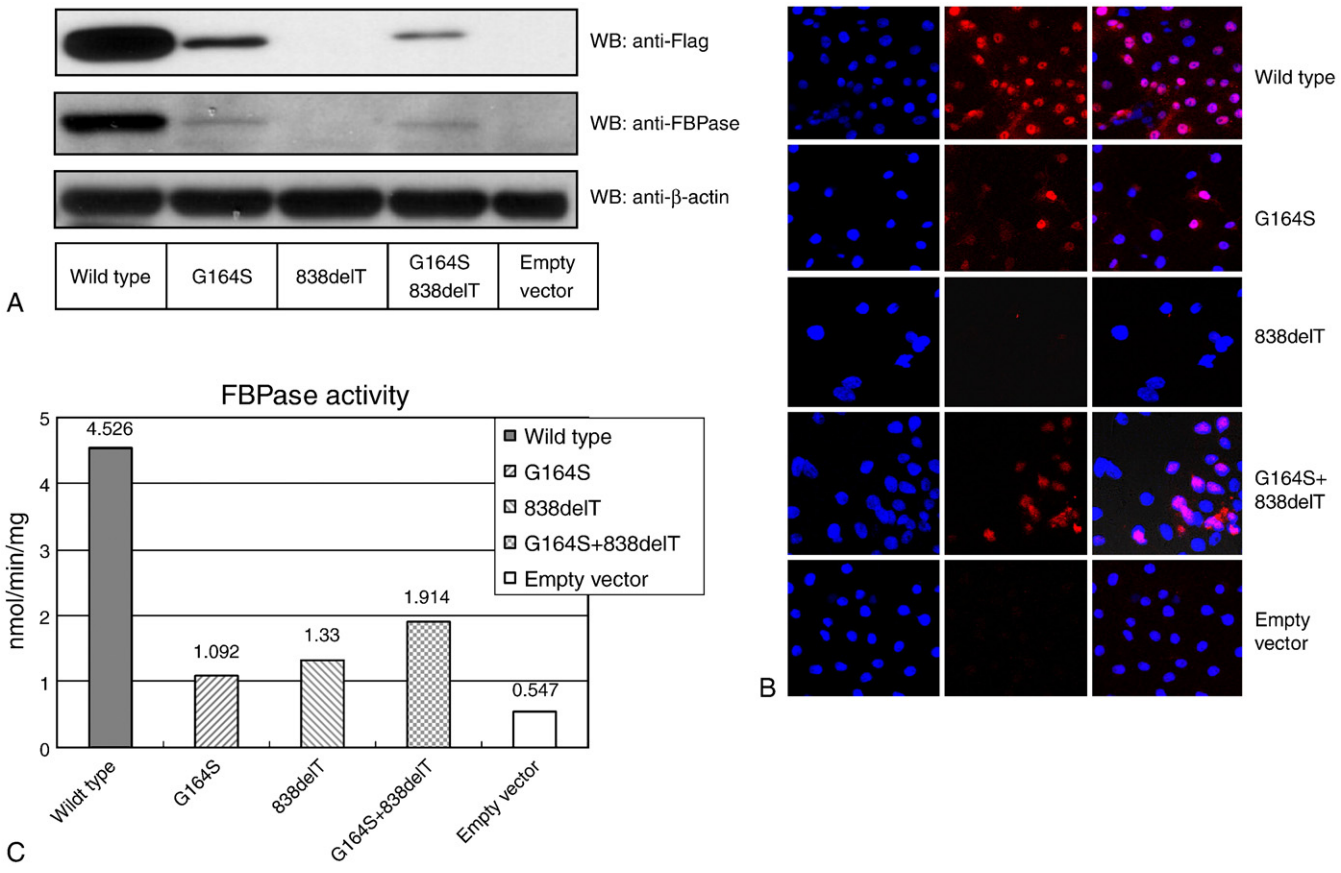

Fig. 5. Fructose-1,6-bisphosphatase protein expression and enzymatic activities of the overexpressed *FBP1* cDNAs in COS-7 cells. A and B, Analysis of FBPase proteins by Western blotting and immunofluorescence studies showing that the expression of G164S mutant *FBP1* cDNA in COS-7 cells was markedly less than that of the wild type and that *FBP1* cDNA expression of the 838delT or empty vector was undetectable. C, The FBPase activity of mutant *FBP1* cDNA was also decreased compared with that of the wild type. The data represent mean values of FBPase activities performed in duplicate. WB indicates Western blotting.

(G164S and 838delT) clones were 1.092, 1.33, and 1.914 mmol min^{-1} mg^{-1} protein, respectively. In contrast, the mean FBPase activity of wild-type purified protein was 4.526 mmol min^{-1} mg^{-1} protein (Fig. 5C). In summary, the FBPase activities of the mutant *FBP1* cDNAs were significantly decreased compared with that of the wild type.

4. Discussion

In this study, we report the first case of molecular diagnosis of FBPase deficiency in a Korean. Genetic analysis of the *FBP1* gene showed that he had a compound-heterozygote mutation involving G164S and 838delT (Figs. 3 and 4). A G164S and InsG960_961 heterozygote mutation has been characterized [3], but the G164S and 838delT heterozygote mutation is novel. Gene tracking showed that the proband's mother and elder sister had a heterozygous G164A mutation and that the father had a heterozygous 838delT mutation (Fig. 3). These results indicate that the proband inherited the G164S and 838delT mutations from each parent. Therefore, the FBPase deficiency of the proband was an autosomal recessive disorder at the molecular level. To date, 10 harmful mutations have been reported [3,5,8,9]. In this case, a G-to-A substitution at nucleotide 490 of codon 164 in exon 4 resulted in the replacement of glycine (GGC) by serine (AGC) and an 838delT mutation on the opposite allele with premature termination, which may have caused the very low FBPase activity in the proband's peripheral leukocytes and liver (Fig. 1). This possibility induced us to use COS-7 cells to identify possible pathogenic mutations of the *FBP1* gene involving FBPase expression.

The FBPase activity of purified protein from a mutant G164S cDNA construct, which was overexpressed in *Escherichia coli*, was reported to be markedly reduced [3]. We generated mutant *FBP1* cDNA expression vectors and measured their expression in COS-7 cells. We confirmed that FBPase protein expression from the mutant G164S cDNA construct, which was overexpressed in COS-7 cells, was significantly less than that of the wild-type cDNA construct and that FBPase was not expressed by the empty vector in COS-7 cells (Fig. 5A, B). It is unclear why expression of the G164S mutant was so much lower than that of the wild type. Decreased function is expected, but messenger RNA expression from the mutant alleles vs the normal allele had no detectable differences (data not shown). The FBPase activities of purified proteins from transfects with G164S and wild-type COS-7 cells were 1.092 and 4.526 mmol min^{-1} mg^{-1} protein, respectively. The FBPase activity of the mutant G164S *FBP1* cDNA, which was overexpressed in COS-7 cells, was significantly less than that of the wild type (Fig. 5C). The G164S mutation of the *FBP1* gene is expected to result in certain conformation change or protein stability because the highly hydrophilic serine substitutes for the low-hydrophilic glycine [3]. We suggest that our results agree, to some extent, with this hypothesis; but further study is needed to validate it. The deletion of one T residue in the protein-coding region of nucleotide residue 838 should result in a reading-frame shift (Fig. 2B). We examined the expression of the 838delT mutant in COS-7 cells, but FBPase protein was not detected by the anti-FBPase or anti-Flag antibodies (Fig. 5A, B). The 838delT mutation should impair protein function because of premature termination, which may have prevented downstream translation of the Flag protein. Consequently, we think that the truncated FBPase protein was not detected by anti-Flag antibody because its translation was terminated and it could not be linked to the Flag protein. We consider the 838delT to be a harmful mutation for following reasons. The amino acid sequence of FBPase is a highly conserved upstream residue in mammalian species, including humans; and several sequences in this region have been reported to be required for normal expression of FBPase activity [15]. Further studies are necessary to corroborate the finding that this novel deletion mutation of 838delT impairs FBPase activity in vitro and to determine how the truncated protein that is translated from the 838delT mutation loses its function or is degraded in the cell. The effects of the 838delT and the cotransfected G164S plus 838delT constructs were studied using COS-7 cells. The FBPase activity of 838delT *FBP1* cDNA was significantly less than that of the wild type (Fig. 5C). Therefore, amino acid residues at the C-terminal seem to be essential for normal FBPase activity. Deletion of amino acid residues at the C-terminal may affect the secondary or tertiary structure of the FBPase protein through an as yet unknown mechanism [3]. Crystallographic analysis of deleted or substituted FBPase protein may be helpful in elucidating this mechanism.

In summary, our patient was found have a compound heterozygous mutation (G164S and 838delT) and inherited the same mutant allele from each parent. This report describes the first case of molecular diagnosis of FBPase deficiency in a Korean and provides evidence that his impaired FBPase activity may be due to this novel compound heterozygous mutation of the *FBP1* gene.

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References

[1] Baker L, Winegrad AI. Fasting hypoglycaemia and metabolic acidosis associated with deficiency of hepatic fructose-1,6-diphosphatase activity. Lancet 1970;2:13-6.

[2] Gitzelmann R, Steinmann B, Van den Berghe G. Essential fructosuria, hereditary fructose intolerance, and fructose-1,6-diphosphatase deficiency. Metabolic bases of inherited disease, vol 1. New York: McGraw-Hill; 1989. p. 416-24.

[3] Kikawa Y, Inuzuka M, Jin BY, Kaji S, Koga J, Yamamoto Y, et al. Identification of genetic mutations in Japanese patients with fructose-1,6-bisphosphatase deficiency. Am J Hum Genet 1997;61:852-61.
[4] el-Maghrabi MR, Lange AJ, Jiang W, Yamagata K, Stoffel M, Takeda J, et al. Human fructose-1,6-bisphosphatase gene (FBP1): exon-intron organization, localization to chromosome bands 9q22.2-q22.3, and mutation screening in subjects with fructose-1,6-bisphosphatase deficiency. Genomics 1995;27:520-5.
[5] Matsuura T, Chinen Y, Arashiro R, Katsuren K, Tamura T, Hyakuna N, et al. Two newly identified genomic mutations in a Japanese female patient with fructose-1,6-bisphosphatase (FBPase) deficiency. Mol Genet Metab 2002;76:207-10.
[6] Pilkis SJ, el-Maghrabi MR, Claus TH. Hormonal regulation of hepatic gluconeogenesis and glycolysis. Annu Rev Biochem 1988;57:755-83.
[7] Tillmann H, Eschrich K. Isolation and characterization of an allelic cDNA for human muscle fructose-1,6-bisphosphatase. Gene 1998;212: 295-304.
[8] Herzog B, Wendel U, Morris AA, Eschrich K. Novel mutations in patients with fructose-1,6-bisphosphatase deficiency. J Inherit Metab Dis 1999;22:132-8.
[9] Herzog B, Morris AA, Saunders C, Eschrich K. Mutation spectrum in patients with fructose-1,6-bisphosphatase deficiency. J Inherit Metab Dis 2001;24:87-8.
[10] Han SH, Ki CS, Lee JE, Hong YJ, Son BK, Lee KH, et al. A novel mutation (A148V) in the glucose 6-phosphate translocase (SLC37A4) gene in a Korean patient with glycogen storage disease type 1b. J Korean Med Sci 2005;20:499-501.
[11] Kinugasa A, Kusunoki T, Iwashima A. Deficiency of glucose-6-phosphate dehydrogenase found in a case of hepatic fructose-1,6-diphosphatase deficiency. Pediatr Res 1979;13:1361-4.
[12] Baulida J, Onetti R, Bassols A. Modulation of fructose-2,6-bisphosphate metabolism by components of the extracellular matrix in cultured cells. Interaction with epidermal growth factor. FEBS Lett 1997;418:63-7.
[13] Muindi JR, Peng Y, Wilson JW, Johnson CS, Branch RA, Trump DL. Monocyte fructose 1,6-bisphosphatase and cytidine deaminase enzyme activities: potential pharmacodynamic measures of calcitriol effects in cancer patients. Cancer Chemother Pharmacol 2006;59: 97-104.
[14] Melancon SB, Nadler HL. Detection of fructose-6,-diphosphatase deficiency with use of white blood cells. N Engl J Med 1972;286: 731-2.
[15] Nomura M, Takihara Y, Yasunaga T, Shimada K. One of the retinoic acid-inducible cDNA clones in mouse embryonal carcinoma F9 cells encodes a novel isoenzyme of fructose 1,6-bisphosphatase. FEBS Lett 1994;348:201-5.