CASE REPORT

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A Novel Frameshift Mutation of the *ALDOB* Gene in a Korean Girl Presenting with Recurrent Hepatitis Diagnosed as Hereditary Fructose Intolerance

Hae-Won Choi*, Yeoun Joo Lee*, Seak Hee Oh*, Kyung Mo Kim*, Jeong-Min Ryu*, Beom Hee Lee*,†, Gu-Hwan Kim†, and Han-Wook Yoo*,†

Department of Pediatrics and †Medical Genetics Clinic and Laboratory, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Hereditary fructose intolerance is an autosomal recessive disorder that is caused by a deficiency in fructose-1-phosphate aldolase (Aldolase B). Children can present with hypoglycemia, jaundice, elevated liver enzymes and hepatomegaly after intake of dietary fructose. Long-term intake of fructose in undiagnosed patients can result in hepatic failure or renal failure. We experienced a case of hereditary fructose intolerance presenting as recurrent hepatitis-like episodes. Detailed evaluation of her dietary habits revealed her avoidance of sweetened foods and fruits. Genetic analysis of *ALDOB* revealed that she is a homozygote for a novel frameshifting mutation c[758_759insT]+[758_759insT] (p.[val253fsX24]+[val253fsX24]). This report is the first of a Korean patient diagnosed with hereditary fructose intolerance using only molecular testing without undergoing intravenous fructose tolerance test or enzyme assay. **(Gut Liver 2012;6:126-128)**

Key Words: Fructose intolerance; Aldolase B; Hepatitis; Hypoglycemia; Gene

INTRODUCTION

Hereditary fructose intolerance (HFI, OMIM# 229600) is an autosomal recessive disorder, caused by a deficiency in fructose-1-phosphate aldolase (Aldolase B) which exists in the liver, kidney, and intestines.[1] Deficiency of this enzyme causes an accumulation of fructose-1-phosphate after fructose intake, which results in toxic symptoms like vomiting, hypoglycemia, jaundice, elevated liver enzymes and hepatomegaly.[2] HFI was diagnosed traditionally by biochemical tests such as intravenous fructose tolerance test or by enzyme assay through liver or small intestine biopsy.[3] Here we report a 2-year-old girl with HFI manifesting recurrent hepatitis-like episodes, which was diagnosed by the *ALDOB* gene analysis.

CASE REPORT

A 2-year-old girl was admitted for the evaluation of recurrent episodes of aminotransferase elevation. At 6 month of age, she was first diagnosed with hepatitis at another hospital after developing fever, vomiting, and diarrhea. She showed hepatomegaly which was palpable by four finger breadth below the costal margin. Laboratory findings revealed elevated aspartate aminotransferase (AST) of 2,017 IU/L and alanine aminotransferase (ALT) of 1,242 IU/L with prothrombin time prolongation. No definite cause was found and liver enzymes were normalized after supportive care. She experienced similar episodes of aminotransferase elevation at 15-month-old and 23-month-old of age when she had symptoms of upper respiratory infections, each revealing AST of 240 IU/L, ALT of 260 IU/L and, AST of 457 IU/L, ALT of 530 IU/L. When she was admitted to our hospital at 2 years of age, her height was 115.7 cm (25th to 50th percentile), and body weight was 12.9 kg (25th to 50th percentile). Blood pressure was 116/77 mm Hg, heart rate 136/min, respiratory rate 32/min, and body temperature was 36°C and there was no abnormal findings on physical examination. She had no siblings and no family history of liver disease or genetic disease. Blood hemoglobin was 11.8 g/dL, white blood cell count 6,200/mm^3 (neutrophils 28%, lymphocytes 54%, monocytes 14%, and eosinophils 2%), platelet count 397,000/mm^3, total protein 7.0 g/dL, albumin 4.0 g/dL, AST 88 IU/L, ALT 68 IU/L, total bilirubin 0.4 mg/dL, direct bilirubin 0.1 mg/dL, gamma-glutamyltranspeptidase 23 IU/L, alkaline phospha-

Correspondence to: Kyung Mo Kim
Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Pungnap 2-dong, Songpa-gu, Seoul 138-736, Korea
Tel: +82-2-3010-3380, Fax: +82-2-473-3725, E-mail: kmkim@amc.seoul.kr
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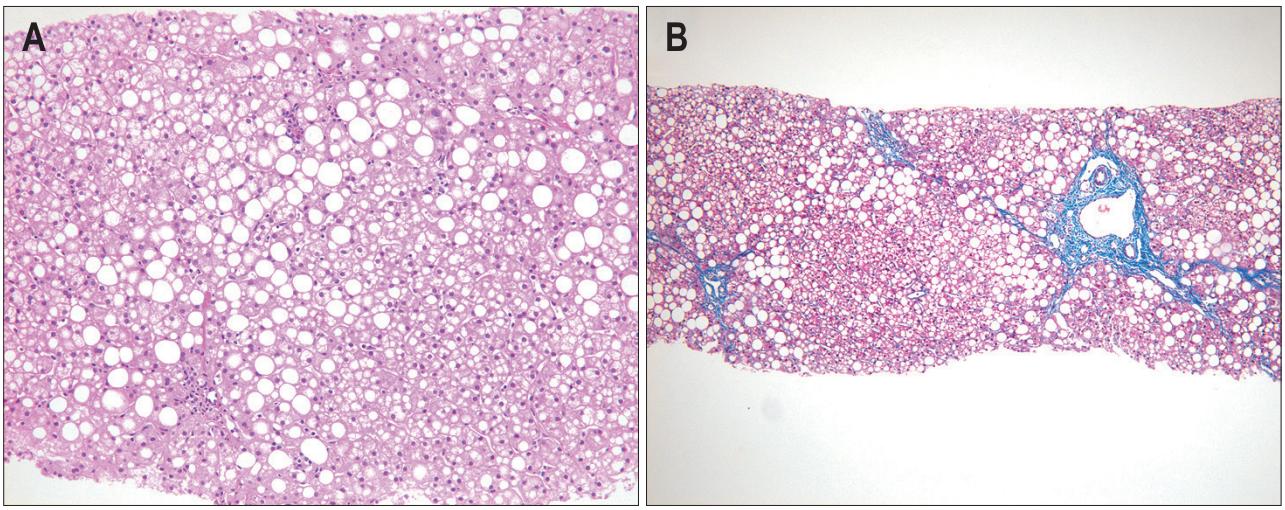

Fig. 1. Microscopic features observed on H&E staining (A) and Masson's trichome staining (B) of a liver biopsy sample. Moderate macrovesicular fatty changes (A, ×200) with periportal and perivenular fibrosis (B, ×40) suggestive of metabolic liver disease.

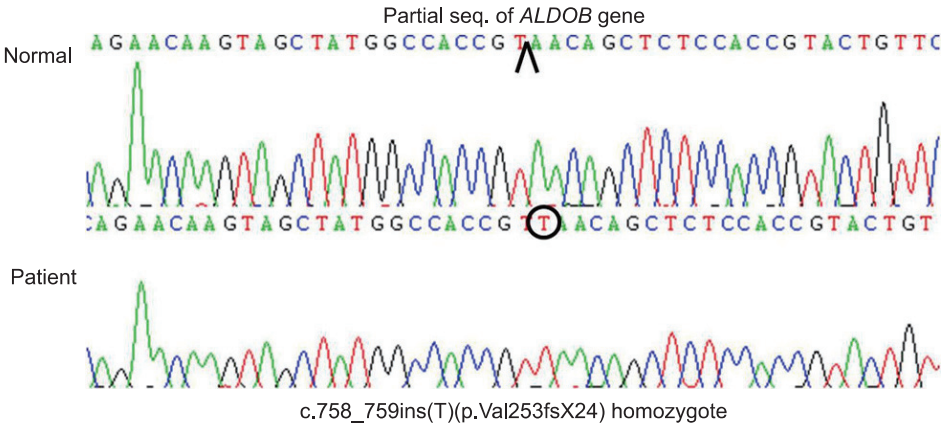

Fig. 2. Genomic DNA analysis of the *ALDOB* that the patient carries. A homozygous mutation, c.[758_759insT]+[758_759insT](p.[val253fsX24]+[val253fsX24]).

tase 187 IU/L, glucose 91 mg/dL, prothrombin time 141% (0.87 INR), and activated partial thrombin time 27.2 seconds. Serologic markers for hepatitis A virus, hepatitis B virus, hepatitis C virus, Epstein-Barr virus, and cytomegalovirus were negative and ceruloplasmin, creatine kinase, lactate dehydrogenase were normal. Liver sonogram showed hepatomegaly with diffuse increased liver parenchymal echogenicity and liver biopsy was done. On histologic examination, moderate macrovesicular fatty changes with periportal and perivenular fibrosis were noted (Fig. 1). With high suspicion of liver disease, we investigated her dietary habit, which revealed her self-avoidance of sweetened foods and fruits, indicating that she might have HFI. The molecular genetic analysis of the *ALDOB* gene was performed. Direct sequencing of the 8 exons and exon-intron boundaries of *ALDOB* gene on chromosome 9q21.3-22 using DNA isolated from peripheral blood showed that the patient is a homozygote for a novel frame-shifting mutation c.[758_759insT]+[758_759insT] (p.[val253fsX24]+[val253fsX24]) (Fig. 2). She is currently on fructose-restricted diet with no more episodes of hepatitis.

DISCUSSION

Deficiency of fructose-1-phosphate aldolase (aldolase B) causes accumulation of fructose-1-phosphate in the liver, kidney, small intestines which leads to symptoms like abdominal bloating, vomiting and elevated liver enzymes.[4] Deficiency of this enzyme also causes inhibition of other enzymes such as fructose-1,6-bisphosphate aldolase and fructokinase, resulting in impaired glycogenolysis and gluconeogenesis which can lead to fatal hypoglycemia.[5] Chronic ingestion of fructose of sucrose results in failure to thrive and repeated episodes of hypoglycemia eventually leads to fatal hepatic of renal failure.[2,6-8] Our patient presented with typical features of HFI such as vomiting, elevated liver enzymes, and hepatomegaly. Other symptoms of HFI include lethargy, convulsions, proximal tubular dysfunction which our patient didn't present. However, these manifestations can also be found in other metabolic liver diseases including galactosemia. For making the diagnosis of HFI, detailed history taking, especially for the dietary habit, is important as noted in our patient who avoided sweetened foods and fruits. Many pa-

tients with HFI develop these unpleasant symptoms and hepatic dysfunctions after ingesting fructose of sugar. Therefore, treatment of HFI mainly consists of complete elimination of fructose and sucrose from the patient's diet.

Although diagnosis of HFI was made traditionally by biochemical tests such as intravenous fructose tolerance test or by enzyme assay of Aldolase B activity through liver or small intestine biopsy, the risks of such procedures can be avoided by recent advance in molecular genetic testing.[2] The *ALDOB* gene is located on chromosome 9q22.3.[9,10] More than 50 mutations causing HFI have been reported to date, in which missense mutations are most common (http://www.hgmd.cf.ac.uk). p.A149 is the most common genotype identified along with p.A174D, p.N334K.[11-13] These three mutations account for 68% of HFI alleles worldwide but they are common mostly in northern European populations.[14] The American population shows uniquely high prevalence of two nonsense mutations, p.Δ4E4 and p.R59Op.[15] Spain also shows high prevalence of Δ4E4 surpassing p.A174D, p.N334K. New Zealand, India, Japan did not have enough published reports to define HFI alleles, indicating the existence of variability in the incidence and mutation spectrum of HFI among ethnic groups.[15] In Korea, one case of HFI has been reported in 2002, which was diagnosed by enzyme assay through intestine and liver biopsy, but not by genetic testing.[3] Therefore, our patient is the first Korean case with HFI confirmed by genetic testing. p.val253fsX24 identified in our patient is a novel mutation. This frame-shifting mutation leads to premature truncated proteins, and is expected to result in functional deterioration of the mutant protein.

The relationship between genotype and symptoms is yet uncertain.[16] Although earlier studies suggested that patients with null alleles presented with more severe phenotypes and higher incidence of death,[12,17] current reports show no difference in the severity of the symptoms between null alleles and other missense mutations.[15,18]

In conclusion, to identify more Korean patients with HFI, detailed evaluation of the dietary habit is needed when a patient is experiencing recurrent hepatitis-like episodes. The genetic testing for *ALDOB* is a valuable as well accurate method for confirming the diagnosis of HFI.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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