Identification of a Rare Mutation Causing Hereditary Tyrosinemia Type 1 in an Iranian Child Compound with Dextrocardia Phenotype

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Abstract

Different mutations in fumarylacetoacetatase (FAH) gene can lead to tyrosinemia type1 (HT1), relatively rare autosomal disorders. Nearly 50 mutations in FAH gene have been identified in different races around the world. Here we presented a boy aged 2 years and 9 months old was diagnosed with HT1 compound with dextrocardia based on his biochemical abnormality and cardio logical examinations. Screening of FAH gene exposed a heterozygous nonsense mutation R237X that was not already reported in Iranian patients. This mutation revealed a chronic progression of disease in this child.

Keywords: FAH gene; Tyrosinemia type 1; Dextrocardia; Rare nonsense mutation; Iranian patient

Introduction

Hereditary tyrosinemia type-1 (HT1;Mckusick number 276700), also known as hepatorenal tyrosinemia is an autosomal recessive aminoacidopathy disorder with a worldwide incidence of approximately 1/100,000 [1], which was the first described in 1950 [2] with the highest prevalence in the French, Canadian [3] and Scandinavian population [4]. HT1 results from the deficiency of fumarylacetoacetase enzyme which is encoded by FAH is predominantly expressed in the mammalian kidney and the liver and lesser amounts in other tissues, such as heart, stomach and lungs. The clinical spectrum of the disease is wide ranging, from chronic complications of hepatic failure to hepatocellular carcinoma, renal tubular dysfunction, renal failure and death within the first few months of life [5]. FAH is the terminal enzyme in the tyrosine catabolic pathway. In FAH deficiency, the immediate precursor, fumarylacetoacetate (FAA), is formed [6]. FAH gene is located on chromosome 15q23-q25, which contains 14 exons and spans approximately 35 kb of DNA. At present, according to the Human Gene Mutation-Database (HGMD:http://www.hgmd.cf.ac.uk), so many mutations in FAH gene have been identified in different races around the world [7]. In this report, we presented an Iranian patient with a rare mutation in the FAH gene with detailed clinical data and genetic analysis.

Materials and Methods

Patient

The boy who was 2 years and 9 months old (proband V:2 in the Figure 1) was the second child of the consanguineous healthy parent. He had a cousin with tyrosinemia deficiency that he died at the age of 12 months without confirmatory molecular study of the FAH gene. Proband(V:2) is the second child of the consanguineous healthy parent. He had a cousin (IV:3) with tyrosinemia deficiency that he died at the age of 12 months without confirmatory molecular study of the FAH gene.

Alkaline phosphate 85 U/L (0-280 U/L), alanine amino transferase 46 U/L (0-40 U/L), aspartate aminotransferase 42 U/L(0-40 U/L), and AFP 35 ng/ml (0-20 ng/ml). In plasma the level of tyrosine an SA were increased (112.2 µmol/L; reference range <83.2 µmol/L),(6.1 µmol/L; reference range 1-5 µmol/L) respectively. The level of β2-microglobuline (β2-MG) was found 1.1 mg/L (reference range 0-0.2 mg/L) in urine, but normal in plasma suggested dysfunction of the renal tubules. Abdominal ultrasound examination exposed enlarged kidneys and normal morphology and size of the spleen. A cardiovascular examination the apex was present in the 6th intercostal space (ICS) on the right side.

Mutation screening in FAH gene

Genomic DNA was obtained with informed consent from whole blood leukocytes, using a standard DNA kit method (cat no: 01376565 cinnagen company). Fourteen coding exons of FAH gene and flanking introns were amplified by polymerase chain reaction (PCR) in a 25 µl
reaction. The reaction volume containing 2.5 μl of 10X reaction buffer (15 mM MgCl2), 0.2 mM dNTPs, 20 μM of each primer, 14 of Hot start Taq polymerase (Qiagene), and 10 ng of genomic DNA. Thermo cycling consisted of an initial denaturation at 95°C for 10 min followed by 30 cycles of PCR. Each cycle of PCR consisted of denaturation at 94°C for 58 s, annealing at 60-64°C for 60 s. A final extension step of 10 min at 72°C was added. After a quality check of PCR products by electrophoresis on 1% agarose gel, bidirectional sequencing was completed on an ABI 3130 automated sequencer (XL genetic analyzer) using the Big-Dye terminator version 3.1.

Result

Sequence analysis of the FAH gene identified a rare p.R237X (C. 709 C>T) heterozygous mutation in proband child compound with Dextrocardia phenotype. This mutation leads Arg amino acid to the nonsense mutation (Figure 2).

Discussion

We reported a rare nonsense mutation (R237X) in the FAH gene identified in an Iranian child clinically diagnosed with HT1 compound with dextrocardia phenotype that had not been previously reported. The mutation of R237X was first reported in a Turkish proband with HT1. This proband carried the homozygous R237X mutation [8]. Another nine forms of HT1 patient coming from different families in Saudi Arabia were also detected with the homozygous R237X mutations [9]. In 2012, Song Fang et al. has been reported a Chinese patient with compound heterozygous mutations (R237X and L375P) in the FAH gene, leading to the HT1. Their observations revealed that the mutation of R237X could down regulate the expression of FAH mRNA [10]. R237 residue plays a very important role in maintaining the normal structure and function of FAH protein. The Iranian child with a compound clinical phenotype of dextrocardia and HT1, is a heterozygous with this mutation. Therefore, he presented with a chronic progression and slightly increased succinylacetone in the blood, compared to the acute form of HT1 with R237X homozygous reported previously [3,8]. The result of this study has application in patient screening and genetic counseling.

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References