A Novel Nonsense Mutation in The WFS1 Gene Causes The Wolfram Syndrome

Abstract: Wolfram syndrome is a rare autosomal neurodegenerative disorder usually caused by mutations in the WFS1 gene. The WFS1 gene is active in cells of body, with highly expression in the, brain, lungs, heart, inner ear, and pancreas. Within cells, WFS1 gene encodes wolframin protein that is located in a structure of endoplasmic reticulum. Endoplasmic reticulum has critical role in protein folding and material transportation within the cell or to the surface of cell. Although the actual function of wolframin protein is unknown, but based on location, defect of this protein may cause the problem in protein folding or cellular transportion. In this study DNA sequence of WFS1 gene was analyzed in a 9 years old boy, to confirm Wolfram syndrome. We found the novel pathogenic nonsense mutation in exon 4 of WFS1 gene (c.330 C>A). The heterozygosity for parents also confirmed by Sanger sequencing.

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CASE PRESENTATION

We report a 9 years old boy who was born from consanguineous parents. Due to his learning disabilities he was not able to educate in primary school. He was diagnosed with insulin depended diabetes mellitus when he was at age of 3 years. He had progressive visual deterioration without retinopathy for 6 years because of bilateral optic atrophy. Auditory evaluation detected mild bilateral sensory neural hearing loss. His medical history revealed frequent urination and symptoms of progressive nighttime enuresis from one year ago. Direct Radiouclide voiding Cystourethrography (DRNC) showed no vesicouterutral reflex, but after urodynamic tests, neurogenic bladder diagnosis was established. Fluid restriction test were performed and enabled us to diagnose central DI. In physical examination, height and weight were 128cm (25 percentile) and 30 kg (50 percentile) respectively, testis development, axillary and pubic hair was Tanner stage I. In laboratory step, fasting blood sugar (FBS), HbA1c, and urine density were 140 mg/dl (normal range 70 to 99), 8% (normal= 5.7%) and 1.064 (normal range 1.005 to 1.030) respectively. The patient was clinically diagnosed as Wolfram syndrome with these findings.

METHOD

Blood sample was collected from the patient after written consent from his parents. Genomic DNA using salting out method was extracted from blood. Genetic testing for confirmation of Wolfram syndrome was performed. Not only all exons but also exon-intron boundaries of WFS1 was amplified and sequenced by Illumina Genome Analyzer (BGI- Clinical laboratories, China). Mutant homozygote mutation in patient, also heterozygosity of parents was confirmed by Sanger sequencing of polymersome chain reaction (PCR) product. PCR was performed including 100 ng extracted DNA, 1.5um mgc22, four units of dNTPs, 1 unit TaqDNA polymerase, and specific primers for exon 4 of WFS1 gene (ABI Veriti Thermal cycler). The sequences of forward and backward primers are TGTGTTCTGATTTCCATGCATGGA and ATTTCACAACACAGCATTACCGG, respectively. The sequences of PCR products were carried out using the ABI Prism 3130 Genetic Analyzer (ABI, USA).

REFERENCES


Homozygote mutation in exon 4 of WFS1 gene (c.330 C>A) in patient, also heterozygote mutation of parents were confirmed with Sanger sequencing technique (Pars Genome laboratory, Karaj, IRAN). (Figure 1)