A novel mutation of WFS1 gene in a Japanese infant of diabetes mellitus, deafness and congenital cataract.

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Abstract

Background: Wolfram syndrome (WS) is a rare autosomal recessive disorder defined by the combination of early-onset, insulin-dependent diabetes mellitus (DM) and progressive optic atrophy (OA). Mutations of WFS1 are identified in 90% of WS patients.

Patient and Methods: We encountered a young female Japanese patient with early onset insulin-dependent DM. She was found to have a cataract at 7 months old and DM was diagnosed at 11 months. WFS1 direct sequencing and the functional consequence of the mutant WFS1 identified in this study was analysed using GPR78-luciferase vector in vitro.

Results: We identified a heterozygous twelve base deletion in exon 8 (c.973_984del12), resulting in an in-frame deletion of 3 amino acids. In vitro analysis demonstrated that the mutant WFS1 had reduced ability to protect against ER stress compared with wild type WFS1.

Conclusion: We demonstrate that a novel heterozygous mutation of WFS1 is a previously unidentified cause of WS.

Introduction

Wolfram Syndrome (WS) is a rare, autosomal recessive disorder characterized by diabetes mellitus (DM), sensorineural deafness (SD), and optic atrophy (OA). The gene for WS, WFS1 (OMIM 252320), is located on chromosome 4p16.1 and encodes the wolframin protein, a calcium-regulated endoplasmic reticulum (ER) chaperone.

Methods

Direct sequencing of WFS1 was performed. We analysed the functional consequence of the mutant WFS1 using GPR78-luciferase vector in vitro.

Case report

The Japanese female patient was admitted to our hospital for poor weight gain (Fig.1) and diabetes mellitus (DM). Her growth failure was evident at 3 months old and congenital cataract was noticed at 7 months old (Fig.2). In addition, auditory brainstem response (ABR) test revealed her severe bilateral hearing loss. Her psychomotor development was also delayed. Based on these findings, she was suspected to have WS.

Results

Sequence analysis revealed a novel heterozygous twelve base deletion in WFS1 exon 8. This deletion resulted in an in-frame deletion of four amino acids. Patient c.973_984del12, p.N325_M328del

Discussion

Our mutant (c.973_984del12, p.N325_M328del) impaired the capacity of WFS1 to suppress ER stress. This mutant is considered to be the cause of WS.

Autosomal dominant (AD) mutations of WFS1

Most WFS1 mutations in WS patients are detected on both alleles and the inheritance of WS is considered to be autosomal recessive. However, AD mutations of WFS1 have been identified recently.1,2

Dominant negative effect

WFS1 is a multimer and is likely to exist as a homotrimer of WFS1 monomers.3 Previous report suggested that the function of WFS1 is impaired through dominant negative effect.4

Conclusion

As WS is characterized by a wide spectrum of clinical features, it should be considered in the differential diagnosis of a toddler with DM and accompanying features such as hearing impairment, growth failure and cataracts.