

A Novel Compound Heterozygous Mutation in an Adolescent with Insulin-dependent Diabetes: A Case Report of Wolfram Syndrome

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Background

Wolfram syndrome (WS) is an autosomal recessive neurodegenerative disorder characterized by non-autoimmune diabetes mellitus and progressive optic atrophy. WS includes a wide spectrum of other possible disorders, such as diabetes insipidus, sensorineural deafness, genitourinary tract problems, male hypogonadism, neurological or psychiatric disorders and bowel dysfunction.

Mortality is 65% before age 35 years mainly due to central respiratory failure.

Case presentation

A 12-year-old boy presented with glycosuria and shortly developed insulin-dependent diabetes mellitus. Autoimmune markers for diabetes were negative, insulin requirement was low (ranging from 0.22 to 0.43 U/kg/day) with a good metabolic control (HbA1c range 53-59 mmol/mol).

No family history for autoimmunity or diabetes.

Genetic tests for Maturity Onset Diabetes of the Young (MODY) were performed and no mutations for GCK-MODY 2 and HNFA1-MODY 3 were found. Unexpectedly when he was sixteen, metabolic control worsened and optic atrophy was suspected during a routine eye examination and subsequently confirmed by MRI. So, Wolframin (WFS1) gene was analysed and compound heterozygosity for a missense and a frameshift mutations in exon 8 was found:

c.[2104G>A]+[2155_2168dup14]; p.[Gly702Ser]+[Phe725fs]. The missense mutation, paternally inherited, is annotated by Human Gene Mutation Database (HGMD), but no phenotype description is available. The frameshift mutation, also detected in the mother, is a 14bp duplication, not previously reported. It causes a frameshift which results in a premature stop codon, predicting a truncated protein of 25 amino acids shorter than the wild-type wolframin. No mutation was shared by the twin brother. No signs of central diabetes insipidus or any other diseases associated with WS were found. Our report of a novel inactivating mutation increases the spectrum of WFS1 defects and contributes to establish phenotype-genotype relationship.

Discussion and Conclusions

WS diagnosis is often delayed since misdiagnosed as autoimmune diabetes. The rarity of the condition and the absence of other diseases at diabetes diagnosis might make extremely challenging the recognition of WS. However the compound heterozygosity for the here reported mutations, even markedly altering the protein structure, seems to confer a mild phenotype among the spectrum of WS manifestations. A remarkable support for improving diagnosis of non-autoimmune diabetes will be hopefully provided by the new technology of Next Generation Sequencing by analyzing panel of genes instead gene by gene.

Main References:

- Aloi C et al, PLOS ONE 2012.
- López de Heredia M et al, Genetics in Medicine 2013

