A novel variant of the WFS1 gene with dominant inheritance causing Wolfram-like syndrome

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INTRODUCTION

The Wolfram syndrome (WS), also known as the DIDMOAD syndrome (Diabetes Insipidus, early-onset Diabetes Mellitus, progressive Optic Atrophy, and Deafness), is mostly associated with recessive mutations in the WFS1 gene.

However, dominant mutations in the WFS1 gene were described causing less severe Wolfram-like syndrome (WLS) lacking some of the main Wolfram syndrome features, isolated optic atrophy, isolated low-frequency sensorineural hearing loss or their combinations with or without diabetes.

Wide phenotypic variability indicates that WS is a spectrum disorder (Table 1).

Table 1: Diagnostic criteria of WS according to EURO-WAABB clinical guideline (1)

<table>
<thead>
<tr>
<th>Major features</th>
<th>Minor features</th>
<th>Variable features</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM onset &lt; 16 years</td>
<td>DM onset &gt; 16 years</td>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td>OA onset &lt; 16 years</td>
<td>OA onset &gt; 16 years</td>
<td>Cataracts</td>
</tr>
<tr>
<td>Diabetes Insipidus</td>
<td>Psychiatric disorder</td>
<td>Sensorineural hearing loss</td>
</tr>
<tr>
<td>GI disorders</td>
<td>GI disorders</td>
<td>GI disorders</td>
</tr>
<tr>
<td>Neurological (strokes, epilepsy, CI)</td>
<td></td>
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<tr>
<td>Renal tract abnormalities (structural or functional)</td>
<td></td>
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<tr>
<td>L0F mutation in WFS1/CSID2 or family history of WS</td>
<td></td>
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</tr>
<tr>
<td>Minimal criteria required for WS diagnosis:</td>
<td>2 major or</td>
<td>1 major plus 2 minor or</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>two WFS1/CSID2 mutations</td>
</tr>
<tr>
<td>Criteria required for WLS diagnosis:</td>
<td>DM or OA or deafness needs</td>
<td>At least one WFS1/CSID2 mutation</td>
</tr>
</tbody>
</table>

CASE

- Patient – 20 years old boy
  - Congenital profound hearing loss (received cochlear implant at 2.5 years)
  - Hypotonia from birth, psychomotor retardation
  - Bilateral cataracts (surgically removed lenses – aphakia)
  - Autism with autoagression diagnosed at 4 years
  - Non-autoimmune insulin-dependent diabetes mellitus diagnosed at 8 years (current FPG 7.8 mmol/l), HbA1C - 55 mmol/mol (7.2 %)
  - Epilepsy (on therapy with valproic acid)
  - Diabetic nephropathy

Fulfills criteria for WS
(1 major + 3 minor + 2 variable clinical features)

- Mother – 46 years
  - Hearing impairment – U-shaped audiogram
  - Cataracts
  - Psychiatric disorder
  - Obstipation
  - Normal glucose metabolism (current FPG 5.0 mmol/l, HbA1C - 30 mmol/mol [4.9 %])

Does not fulfill criteria for WS nor WLS

- Father is healthy

METHODS

Clinical investigation included standard biochemistry testing, urinalysis, diabetology, ophthalmological and ENT examination. Additional data were collected from available clinical files.

The DNA of the patient and his mother was extracted from peripheral blood. Genetic testing included Sanger sequencing of the WFS1 gene (promoter region and all 8 exons with exon/intron boundaries) and MLPA (SALSA P163-GB-WFS1, MRC-Holland) to identify potential deletions or duplications. Both tests were performed in the patient and his mother, DNA from father was not available.

For the differential diagnosis, the m.3243A>G variant causing MID1/MELAS syndrome was excluded using qPCR in the proband.

RESULTS

A novel heterozygous in-frame deletion NM_006005.3:c.2608_2619del, (p.870-873del) was identified in exon 8 of the WFS1 gene in the patient’s DNA. This variant was not found in the mother nor in the father.

No other rare variant was found by sequencing and no dosage defect was detected using MLPA in both the patient and his mother.

The WFS1 protein is an endoplasmic reticulum (ER) embedded protein, which functions in ER calcium homeostasis. Dysregulation of these cellular processes results in the development of ER stress, leading to apoptosis.

The deletion is localized in the cytoplasmic domain, where other pathogenic variants have been described.

Explanation

1. The patient has a novel de novo dominant WFS1 mutation and mother’s phenotype is of a different etiology. Dominant mutations in the WFS1 gene causing WLS were previously described by de Franco et al. Diabetes 2017.
2. The patient has a recessive mutation and the second mutation causing milder phenotype and inherited from the mother was not found due to technical issues (allelic dropout in PCR/sequencing, intronic/promoter mutation not covered by sequencing).
3. A mutation in another gene causing mother’s disease and may contribute to the presentation of the patient (presence of the m.3243A>G variant was excluded).

CONCLUSIONS

Identification of this novel heterozygous variant found in the patient supports the diagnosis of the Wolfram-like syndrome with dominant inheritance in the patient.

However, the suspicious phenotype of the mother keep the possibility of a second, yet unidentified genetic defect open.

Variable inheritance pattern together with the progressive character of clinical symptoms complicate the diagnosis and family genetic counseling in Wolfram syndrome.

References:
[2] Heredoa et al., Genetics in Medicine, 2013
[3] de Franco et al., Diabetes 2017

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