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 syndrom 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-WABB clinical guideline (1)

Major features	Minor features	Variable features
DM onset at < 16 years	DM onset at > 16 years	Hypogonadism
OA onset at < 16 years	OA onset at > 16 years	Cataracts
	Diabetes insipidus	Psychiatric disorder
	Sensorineural hearing loss	GI disorders
	Neurological (ataxia, epilepsy, CI)	
	Renal tract abnormalities (structural or functional)	
	LoF mutation in *WFS1/CISD2* or family history of WS	

Abbreviations: CI – cognitive impairement, DM – diabetes mellitus, GI – gastrointestinal, LoF – loss of function, OA – optic atrophy

Minimal criteria required for WS diagnosis:

2 major
OR
1 major plus 2 minor
OR
two *WFS1/CSID2* mutations

Criteria required for WLS diagnosis:

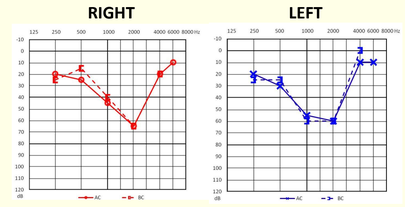
DM or OA or deafness
AND
At least one *WFS1/CSID2* mutation

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 autoaggression 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)

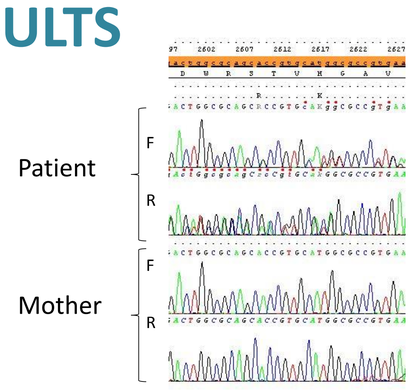
- **Mother – 46 years**
  - **Hearing impairment** – U-shaped audiogram →
  - **Cataracts**
  - **Psychiatric disorder**
  - **Obstipation**
  - Normal glucose metabolism (current FPG 5.0 mmol/l, HbA1c - 30 mmol/mol (4.9 %))



Does not fulfill criteria for WS nor WLS

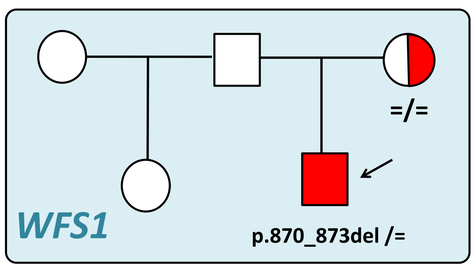
- **Father** is healthy

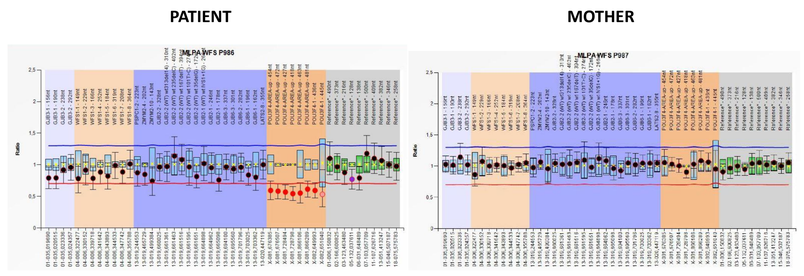
RESULTS



A novel **heterozygous** in-frame deletion **NM_006005.3: c.2608_2619del, p.(870_873del)** was identified in the exon 8 of the *WFS1* gene in the patient´s DNA.

This variant was not found in the mother nor in the father.

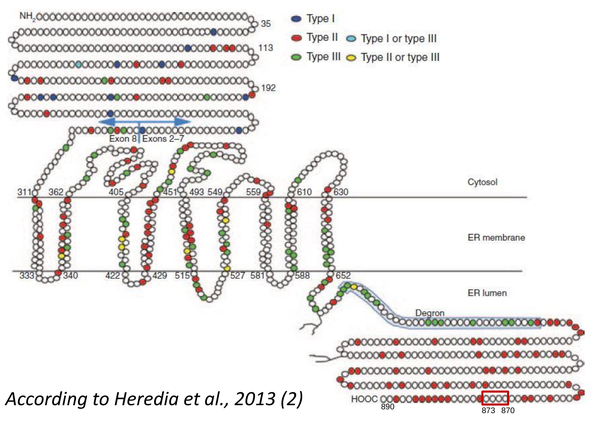




No other rare variant was found by sequencing and no dosage defect was detected using MLPA in both the patient and his mother.

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.



According to Heredia et al., 2013 (2)

Explanation

1. The patient has a **novel *de novo* dominant WSF1 mutation** and mother's phenotype is of a different etiology. Dominant mutations in the WSF1 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 droupout during PCR/sequencing, intronic/promotor 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).

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 periferal blood. Genetic testing included **Sanger sequencing** of the *WFS1* gene (promoter region and all 8 exons with exon/intron boundaries) and **MLPA** (SALSA P163-GJB-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 MIDD/MELAS syndrome was excluded using **qPCR** in the proband.

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:
[1] www.euro-wabb.org
[2] Heredia et al., *Genetics in Medicine*, 2013
[3] de Franco et al. *Diabetes* 2017

Authors certify that there is no conflict of interest with any financial organization regarding the material discussed.

SLOVAK RESEARCH AND DEVELOPMENT AGENCY

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