Intra-familial gene dosage effect of the WFS1 c.1943G>A (p.Trp648*) variant: From Wolfram-Like phenotype to Classical Wolfram Syndrome

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What Is Wolfram Syndrome?

Wolfram syndrome (OMIM #222300) — the **DIDMOAD spectrum** — is a rare progressive neurodegenerative disorder defined by **Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness**. Caused by pathogenic variants in **WFS1**, encoding the ER-resident transmembrane protein *wolframin (1)*.

- **Biallelic (recessive) variants**: classic multisystem Wolfram syndrome
- **Heterozygous (dominant) variants**: attenuated Wolfram-like phenotype — isolated optic atrophy, glaucoma, or DM

Introduction: The Wolfram Spectrum

WFS1 / Wolframin
890 aa transmembrane glycoprotein; modulates ER calcium homeostasis and UPR signalling

ER Stress Cascade
WFS1 deficiency → UPR activation → sustained ER stress → **β-cell and neuronal apoptosis**

Allelic Dosage Effect
Phenotypic severity correlates directly with residual wolframin functional capacity

Introduction: The Wolfram Spectrum

Family overview

A **father–son pair** referred for genetic evaluation following ophthalmological and metabolic workup. Clinical suspicion raised by discordant severity of visual and systemic manifestations across generations.

Inheritance pattern: Autosomal recessive — both parents obligate carriers of *WFS1* pathogenic variant

Father
Elevated IOP, glaucoma diagnosis; no diabetes; **heterozygous** carrier

Son
Progressive optic atrophy, insulin-dependent DM, multisystem involvement; **homozygous**

Methodology

Molecular genetic analysis was conducted using whole exome sequencing (**WES**).

Variant interpretation followed the American College of Medical Genetics and Genomics (**ACMG**) guidelines (4).

Segregation analysis was subsequently performed in both parents to confirm inheritance.

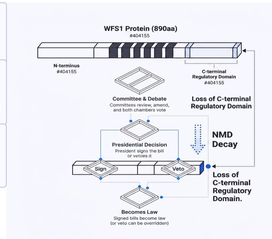
Molecular findings

VARIANT OF INTEREST

WFS1 NM_006005.3: c.1943G>A (p.Trp648*) — Nonsense / Stop-Gain Variant, Exon 8

1. **Variant Type**
   Stop-gain (nonsense): **UGG → UAA** — premature termination codon at residue 648
2. **Molecular Effect**
   Truncation of wolframin C-terminal domain; predicted **nonsense-mediated mRNA decay (NMD)** → loss-of-function
3. **ACMG Classification**
   Pathogenic — criteria met: PVS1, PM2, PP3, PP4 (co-segregation with disease)

ACMG/AMP variant classification guidelines: Richards et al., Genet Med 2015; ClinVar accession pending



Genotype–Phenotype Correlation

Allelic burden at *WFS1* directly determines phenotypic severity— a compelling demonstration of dose-dependent pathogenicity.

Parameter	Father (Heterozygous)	Son (Homozygous)
Genotype	c.1943G>A / wt — monoallelic	c.1943G>A / c.1943G>A — biallelic
Phenotype	Wolfram-like (attenuated)	Classic Wolfram Syndrome (DIDMOAD)
Ocular	Glaucoma, elevated IOP	Progressive optic atrophy (Figure)
Diabetes	Absent / uncertain	Insulin-dependent DM (early onset)
Severity	Mild, monosymptomatic	Severe, progressive multisystem disease
Residual WFS1	~50% functional wolframin	Near-complete loss of function

Heterozygous carriers retain sufficient wolframin activity to prevent classic syndrome but remain vulnerable to isolated manifestations — particularly glaucoma and optic neuropathy.

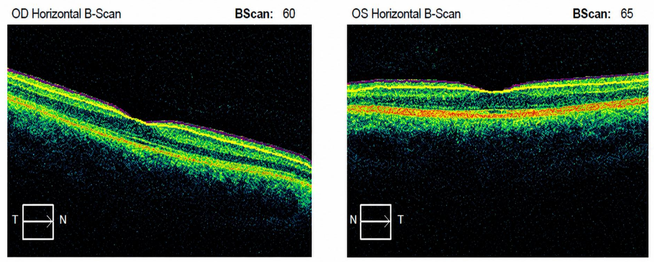


Figure. Horizontal B-scan optical coherence tomography images. Right eye (OD) shows increased central macular thickness with elevation of the neurosensory retina and disruption of the ellipsoid zone. Left eye (OS) shows a normal foveal contour and intact retinal layers. T = temporal, N = nasal.

Results

Ophthalmological manifestations

Spectrum of Ocular Involvement

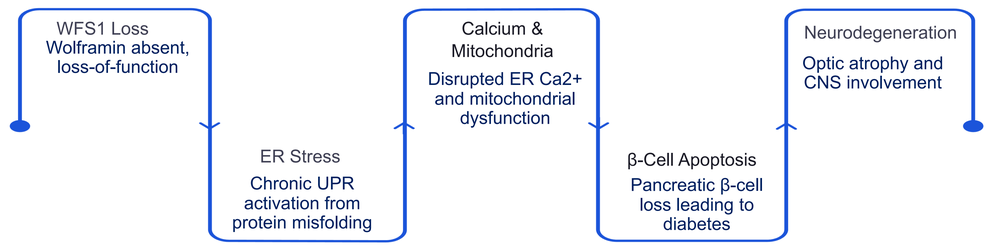
- **Optic atrophy**: bilateral, progressive; primary neurodegenerative aetiology — hallmark of classic Wolfram syndrome
- **Glaucoma**: elevated IOP with structural disc changes; observed in heterozygous carriers as partial phenotype
- **Retinal neurodegeneration**: thinning of retinal nerve fibre layer (RNFL) on OCT; reduced visual acuity
- **Progressive visual loss**: mean onset 6–8 years in homozygotes; variable in heterozygotes (7)

OCT Findings
RNFL thinning — circumferential and temporal sectors; correlates with wolframin deficiency severity

VEP Abnormalities
Prolonged P100 latency; reduced amplitude — electrophysiological marker of optic pathway dysfunction

Clinical Implication
Isolated optic atrophy or unexplained glaucoma in a child should prompt **WFS1 molecular testing**

Patophysiological mechanism



Loss of wolframin destabilises ER calcium buffering and chronically activates the **unfolded protein response (UPR)**. Sustained ER stress overwhelms adaptive capacity, triggering apoptotic cascades selectively in metabolically active cells — pancreatic β-cells and retinal ganglion/neuronal populations — producing the characteristic DIDMOAD multisystem phenotype (2).

Literature Context: WFS1 Nonsense Variants

Published Evidence

Nonsense WFS1 variants are well-documented causes of classic Wolfram syndrome in the homozygous or compound heterozygous state. **Variable expressivity** and **reduced penetrance** characterise heterozygous carriers across published series.

Dominant WFS1-related disorders (OMIM #614296) — including isolated low-frequency sensorineural hearing loss and optic atrophy — are attributed to *haploinsufficiency* or dominant-negative effects of specific missense alleles (1).

Variant	Zygosity	Phenotype	Reference
p.Gln667*	Homozygous	Classic WS	Inoue 1998
p.Arg558*	Compound het.	Classic WS	Cano 2007
p.Leu432*	Heterozygous	Optic atrophy only	Eiberg 2006
p.Trp648*	Homo/Het	WS / WS-like	**This family**

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