

WOLFRAM SYNDROME UK

Inform, Support, CURE

www.wolframsyndrome.co.uk

Parent's Pack

WOLFRAM SYNDROME UK
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This QR code will take you to the Wolfram Syndrome UK website.

This pack has been produced by Wolfram Syndrome UK in support with Birmingham Children's Hospital.

The medical information was produced with guidance by Prof Timothy Barrett Wolfram Syndrome Children's Professional at Birmingham and Dr Renuka Dias Wolfram Syndrome Children's Clinical Lead at Birmingham Children's Hospital.

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This QR code will take you to the Family Support Co-Ordinator's page on the WSUK website or you can use the link - https://wolframsyndrome.co.uk/family-support-coordinator/

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SECTION 11

Wolfram Syndrome Variants

Wolfram Syndrome Type 1

Wolfram syndrome (WS) is a rare autosomal recessive genetic disorder (the biological mother and the father must each pass one affected copy of the gene to the child) caused by mutations in the Wolfram syndrome 1 (WFS1) gene. WS is considered an ultra-rare disease and affects about 1 in 500,000 to 770,00 people in the UK. Medical experts estimate between 15,000 and 30,000 patients worldwide have this disease, including 114 - 150 in the UK.

There are currently no drug therapies or cures that exist for WS. Treatment focuses on symptom management.

The primary manifestations are insulin-dependent diabetes mellitus and optic nerve atrophy. Other common manifestations are neurodegenerative in nature and may include diabetes insipidus, sensorineural hearing loss, trigeminal neuralgia-like headaches, dysphagia (difficulty swallowing), bladder dysfunction, loss of sense of smell and taste, problems with balance and coordination, muscle spasms and seizures, gastrointestinal problems, and irregular breathing. As with other chronic disorders, patients may develop anxiety and depression. Diabetes mellitus is typically the first manifestation, usually diagnosed between the ages of 6-8, with optic nerve atrophy following between the ages of 10-12. Other manifestations tend to vary in onset.

Clinically, WS is best characterised as a spectrum of disorders, ranging in severity from mild to severe. WS patients carrying recessive and missense variants tend to have milder manifestations. The WFS1 p.R558C missense variant, for example, is associated with mild manifestations, but has a high carrier frequency (around 3%) in the Ashkenazi Jewish population. Syndrome variants include WS1, WS2, and WFS1 related disorder. The gene has also been linked to more common forms of Type 2 diabetes.

Wolfram Syndrome Type 2

Mutations in the CDGSH iron sulphur domain protein 2 (CISD2) gene have been found in a small fraction of patients with WS. Wolfram Syndrome patients carrying mutations in the CISD2 gene develop the primary features of WS, including diabetes mellitus and optic nerve atrophy, but they tend to develop other symptoms that are not typically seen in patients carrying pathogenic WFS1 variants, such as upper gastrointestinal ulceration and bleeding.

WFS1-Related Disorders (Wolfram Related Syndrome)

Some mutations in the WFS1 gene are associated with a distinct subset of patients who develop only one or a few symptoms seen in WS. Certain dominant pathogenic variants of the WFS1 gene cause deafness or diabetes alone. Other dominant WFS1 variants are associated with deafness together with mild optic nerve atrophy. It has been reported that autosomal dominant congenital cataracts are also associated with dominant variants of WFS1. Dr Urano at Washington University and Dr Hattersley at the University of Exeter have identified several dominant de novo WFS1 variants associated with a genetic syndrome of neonatal/ infancy-onset diabetes, congenital sensorineural deafness, and

congenital cataracts. These patients have WFS1-Related disorders, not Wolfram Syndrome (Figure 1).

For more information on WFS1-Related Disorders, please contact Dr Urano at urano@wustl.edu or Wolfram Syndrome UK at admin@wolframsyndrome.co.uk.

There are currently no drug therapies or cures that exist for Wolfram Syndrome.

Wolfram syndrome and WFS1-related disorders

COMMON		RARE
WFS1-related	*Wolfram Syndrome*	*WFS1*-related
1+ pathogenic *WFS1*	2 pathogenic *WFS1* or *CISD2*	1+ pathogenic *WFS1*
• Diabetes • Hearing loss • Optic Nerve Atrophy • Cataract	• Diabetes Mellitus • Diabetes Insipidus • Optic Nerve Atrophy • Hearing loss • Neurodegeneration	Hattersley & Urano, 2017 • Neonatal Diabetes • Congenital Cataracts • Sensorineural deafness • Hypotonia

Why Research Wolfram?

It is crucial that we gain a complete understanding of the complexities of Wolfram Syndrome by performing rigorous research, which will serve as the platform to discover and clinically test successful treatment options. Researchers believe that finding a treatment and cure for Wolfram Syndrome may open doors for treating diabetes and other diseases such as Parkinson's and Alzheimer's.

Normal	Wolfram Syndrome
	