Wolfram Syndrome
A guide for patients

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This booklet has been produced by the Euro-WABB project. The Euro-WABB project initiated in 2011 following an international workshop organised by Association Syndrome de Wolfram. The project aims to support efficient diagnosis, treatment, and research for Wolfram, Alström, Bardet-Biedl (WABB) and other rare syndromes. The purpose of this leaflet is to provide information and guidance on Wolfram Syndrome to Wolfram Syndrome patients and their families. We would like to sincerely thank all of the partners, clinicians and families who have contributed to this document.
Wolfram Syndrome is a genetic disorder that can cause a set of conditions including Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness as well as other possible features. It is a complex progressive neurodegenerative disease and is very rare.

**Why is it called Wolfram Syndrome?**

A syndrome is the name given to a condition where features occur in a consistent pattern, and where the cause is not understood. Wolfram Syndrome is named after a Dr Don Wolfram, who in 1938 described 4 brothers and sisters from the same family with Diabetes Mellitus and Optic Atrophy. He worked in the Mayo Clinic in North America, and since then over 300 patients have been described in the world medical literature. Wolfram Syndrome is also sometimes called DIDMOAD which is an acronym for the main features associated with the disorder (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness).

**How common is it?**

Wolfram Syndrome is very rare. It affects about 1 in 770,000 of the total UK population, or 1 in 500,000 children. A specialist physician may only see one affected individual in a professional lifetime.

**What causes Wolfram Syndrome?**

Wolfram Syndrome is an inherited genetic condition caused by a gene mutation. The gene that is usually affected is called WFS1 but other genes have also been identified including CISD2. The mutation in these genes affects the function of a protein called Wolframin. This protein is used in cells within the body including in the brain, pancreas, muscles, heart, liver and kidneys. The disruption in Wolframin is what causes the features associated with Wolfram Syndrome.
Wolfram Syndrome is very varied and presents differently for different people. The following are some of the most common features:

**Diabetes Mellitus**
Most people with Wolfram Syndrome get Diabetes Mellitus. This is when the body cannot convert glucose (sugar) to energy, because the pancreas is not making enough of a hormone called Insulin. Glucose therefore stays in the blood or is passed out in urine and is not used up by the body. Symptoms of Diabetes Mellitus include thirst, frequent passing of urine, and weight loss. Your doctor will usually be able to diagnose Diabetes Mellitus from a blood test.

**Diabetes Insipidus**
Some people, but not everybody, with Wolfram Syndrome get Diabetes Insipidus. This is when the body cannot concentrate urine because the posterior pituitary gland in the head is not making enough of a hormone called Vasopressin. Vasopressin usually regulates the amount of fluid in the body. Symptoms of Diabetes Insipidus often include being very thirsty and frequent passing of very dilute urine.

**Deafness**
Some people, but not everybody, with Wolfram Syndrome will develop some degree of deafness. This can include difficulty in hearing in a crowded room, and difficulty hearing high pitched sounds.

**Optic Atrophy**
Most people with Wolfram Syndrome will get Optic Atrophy. This is when optic fibre nerves weaken and vision is disrupted. Symptoms of Optic Atrophy often present as difficulty seeing in the classroom at school, colour-blindness or everything “going grey”. In Wolfram Syndrome the vision problems usually, but not always, get worse and some people may be registered blind within about 8 years of onset of eye problems.
Renal problems can affect some people with Wolfram Syndrome. Renal problems include urinary tract disorders and may cause difficulties with controlling bladder function (incontinence).

Neurological problems may occur in some people with Wolfram Syndrome as the nervous system is damaged. These problems can include loss of balance, sudden jerks of the muscles, depression, and breathing problems. Choking / swallowing problems may also occur in patients aged 20 onwards.

There are various other issues that can sometimes be related to Wolfram Syndrome. These can include chronic fatigue, emotional and behavioural issues, psychiatric disorders, delayed sexual development (more common in boys), and gastrointestinal or digestive disorders such as diarrhoea or constipation.

As Wolfram Syndrome is so rare not all doctors will be aware of it. Early diagnosis and management of conditions leads to better health outcomes for patients and improved quality of life. It is important that you show this information sheet to your doctor so they know what information you have. Also for further clinical information for you or your doctor, Euro-WABB have published a clinical management guideline for Wolfram Syndrome which is available on the Euro-WABB website (www.euro-wabb.org).

Most of the features of Wolfram Syndrome will exhibit during childhood. Diabetes Mellitus occurs in almost everyone with Wolfram Syndrome during childhood. The latest onset is usually about 16 years old. Optic Atrophy also occurs on average at about 10 years old and the latest onset is usually about 19 years old.

If both Diabetes Mellitus and Optic Atrophy are present by 15 years old then an individual is likely to have Wolfram Syndrome. Your doctor can take a blood sample that can be genetically tested to confirm the diagnosis of Wolfram Syndrome.
Managing Wolfram Syndrome

The current treatment for Wolfram Syndrome involves treating the various presenting symptoms separately:

- **Diabetes Mellitus** can be controlled with insulin injections. These replace the insulin in the body and allow glucose to be converted to energy for the cells to use.
- **Diabetes Insipidus** can be treated by replacing the hormone vasopressin in the body using a nasal spray or tablets. This means that the body can regulate its fluids better.
- There is unfortunately not yet a treatment for **Optic Atrophy**.
- **Deafness** can be helped with the use of a hearing aid.
- There is unfortunately not yet a treatment for **Optic Atrophy**.
- **Renal problems** can be treated by tablets; or if severe, passing a tube or catheter several times a day.
- Different Neurological disorders respond to different medicines.

Once a child has been diagnosed with Wolfram Syndrome, regular health appointments and assessments will be required. These assessments are to manage the presenting symptoms of the syndrome and also to test for the related symptoms that we know about so that they can be diagnosed and managed as early as possible.

For diabetes, diet and exercise advice will be given along with blood tests to look at average blood glucose levels over a few weeks and other treatments to manage any complications of diabetes. Yearly tests for eyesight and “Audiometry” tests for hearing are recommended for Wolfram patients to track the progress of optic atrophy and hearing loss. Regular testing for any issues with the neurological system, kidneys and digestive system are also recommended.

**Is there a cure for Wolfram Syndrome?**

Unfortunately at the moment there is no cure for Wolfram Syndrome. The current research that is taking place is to understand why mistakes in the Wolfram gene cause the syndrome. There are research groups in America, France, UK, and Japan all investigating this problem.
The chances of parents having another child affected by Wolfram Syndrome are about 25%. Wolfram Syndrome is inherited as an autosomal recessive condition; this means that both parents carry one abnormal copy of the Wolfram gene, and one normal copy. For a child to be affected, he has to inherit two abnormal copies, one from each parent. It is possible to test if an unborn child is affected during pregnancy.

For further information on Wolfram Syndrome please see:
- **Wolfram Syndrome Organisation** ([www.wolframsyndrome.org](http://www.wolframsyndrome.org))
  This website provides more information on Wolfram Syndrome. Patients and their families can register and contact other families all over the world.
- **Wolfram Syndrome UK** ([www.wolframsyndrome.co.uk](http://www.wolframsyndrome.co.uk))
  The website is run by families affected by this rare genetic disorder and the aim is to raise as much awareness of the syndrome as possible.
- **WellChild Wolfram Syndrome Family Coordinator** ([https://www.wellchild.org.uk/families-area/wolfram-families/](https://www.wellchild.org.uk/families-area/wolfram-families/))
  The WellChild WS Family Coordinator provides emotional, information and advocacy support to families with children with Wolfram Syndrome.
- **Association Syndrome de Wolfram** ([www.association-du-syndrome-de-wolfram.org](http://www.association-du-syndrome-de-wolfram.org))
  Website for the French Wolfram Association providing information and support for families.
  This article on Gene reviews provides a good review of Wolfram Syndrome.
- **Orphanet** ([www.orpha.net](http://www.orpha.net))
  Orphanet is an online database of rare diseases and related services provided through Europe. It contains information on over 5 000 conditions and lists specialised clinics, diagnostic tests, patient and organizations, research projects and clinical trials.
- **Euro–WABB** ([www.euro-wabb.org](http://www.euro-wabb.org))
  The EURO-WABB Project is a collaboration of doctors, scientists and patient support groups from all over Europe. This website provides information on Wolfram Syndrome and other rare genetic forms of diabetes.

For any queries relating to the information supplied in this guide please contact Euro-WABB at [euro-wabb@bch.nhs.uk](mailto:euro-wabb@bch.nhs.uk)

For further clinical information for you or your doctor please see the Wolfram Clinical Management Guidelines published on the Euro-WABB website.
There are a number of patient support groups and clinicians around Europe who are interested in Wolfram Syndrome. This contact sheet provides information on groups and clinicians that have been involved in the Euro-WABB project.

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<tr>
<td>Denmark</td>
<td>Dr. Lisbeth Tranebjaerg - Bispebjerg Hospital</td>
</tr>
<tr>
<td>Estonia</td>
<td>Prof. Vallo Tillman - University of Tartu</td>
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| France     | Dr Annabelle Chaussenot / Prof. Veronique Paquis – University of Nice / INSERM  
              Association Syndrome de Wolfram - [www.association-du-syndrome-de-wolfram.org](http://www.association-du-syndrome-de-wolfram.org) |
| Germany    | Dr Julia Rohayem - Munster University                                   |
| Italy      | Dr Pietro Maffei - Università degli Studi di Padova                    |
| Poland     | Dr. Wojciech Mlynarski - Medical University of Lodz                    |
| Spain      | Dr. Gema Esteban Bueno - Spanish association for the research and help of Wolfram’s syndrome  
              Dr. Virginia Nunes - IDIBELL / Miguel Lopez de Heredia (CIBERER) |
| UK         | Prof. Timothy Barrett - University of Birmingham  
              Wolfram Syndrome UK—[www.wolframsyndrome.co.uk](http://www.wolframsyndrome.co.uk)  
              Wellchild Wolfram Syndrome Family Coordinator [https://www.wellchild.org.uk/families-area/wolfram-families/](https://www.wellchild.org.uk/families-area/wolfram-families/) |

For all other countries or for information on genetic diagnostic laboratories please contact [euro-wabb@bch.nhs.uk](mailto:euro-wabb@bch.nhs.uk)