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REVIEW ARTICLE

WOLFRAM SYNDROME: A BRIEF DISCUSSION

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ABSTRACT

Wolfram syndrome is the association of juvenile onset diabetes mellitus and optic atrophy, also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness). Patients present with diabetes mellitus followed by optic atrophy in the first decade, cranial diabetes insipidus and sensorineural deafness in the second decade, dilated renal outflow tracts early in the third decade, and multiple neurological abnormalities early in the fourth decade. Other abnormalities include primary gonadal atrophy. Death occurs prematurely, often from respiratory failure associated with brainstem atrophy. A Wolfram gene has recently been mapped to chromosome 4p16.1, but there is evidence for locus heterogeneity, and it is still possible that a minority of patients may harbour a mitochondrial genome deletion. The best available diagnostic criteria are juvenile onset diabetes mellitus and optic atrophy, but there is a wide differential diagnosis which includes other causes of neurodegeneration. In families in which the causative mutations have been characterized, molecular carrier detection and prenatal diagnosis can be performed. Management is supportive and includes an annual screening for DM, vision, D, urodynamic testing, nephropathy and daily insulin injections and a controlled diet to treat DM.

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INTRODUCTION

First described in 1938 by Wolfram and Wagener, Wolfram syndrome (WFS) is a rare, complex, hereditary, neurodegenerative and genetic disorder. It manifests as a combination of young onset non-immune insulin dependent diabetes mellitus and progressive optic atrophy1 in all patients with added diabetes insipidus and sensory neural deafness in 70% of the patients, where it is referred to as DIDMOAD (Aloi *et al.,* 2012) (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness). Wolfram syndrome may also include urinary tract, neurological, reproductive and psychiatric abnormalities, limited joint mobility, cardiovascular and gastrointestinal autonomic neuropathy, as well as some types of endocrine dysfunction (Amr *et al.,* 2007). Cases of upper gastro intestinal bleeds and heart malformations have also been reported in Wolfram syndrome.

What is Wolfram syndrome

Wolfram syndrome is a condition that affects many of the body's systems. The hallmark features of Wolfram syndrome are high blood sugar levels resulting from a shortage of the hormone insulin (diabetes mellitus) and progressive vision loss due to degeneration of the nerves that carry information from the eyes to the brain (optic atrophy). People with Wolfram syndrome often also have pituitary gland dysfunction that results in the excretion of excessive amounts of urine (diabetes insipidus), hearing loss caused by changes in the inner ear (sensorineural deafness), urinary tract problems,(Chaussenot *et al.,* 2011) reduced amounts of the sex hormone testosterone in males (hypogonadism), or neurological or psychiatric disorders.

Diabetes mellitus is typically the first symptom of Wolfram syndrome, usually diagnosed around age 6. Nearly everyone with Wolfram syndrome who develops diabetes mellitus requires insulin replacement therapy. Optic atrophy is often the next symptom to appear, usually around age 11. The first signs of optic atrophy are loss of color vision and peripheral (side) vision. Over time, the vision problems get worse, and people with optic atrophy are usually blind within approximately 8 years after signs of optic atrophy first begin (Kanki, 2009). In diabetes insipidus, the pituitary gland, which is located at the base of the brain, does not function normally. This abnormality disrupts the release of a hormone called vasopressin, which helps control the body's water balance and urine production. Approximately 70 percent of people with Wolfram syndrome

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have diabetes insipidus. Pituitary gland dysfunction can also cause hypogonadism in males. The lack of testosterone that occurs with hypogonadism affects growth and sexual development. About 65 percent of people with Wolfram syndrome have sensorineural deafness that can range in severity from deafness beginning at birth to mild hearing loss beginning in adolescence that worsens over time. Sixty to 90 percent of people with Wolfram syndrome have a urinary tract problem (Kumar, 2010). Urinary tract problems include obstruction of the ducts between the kidneys and bladder (ureters), a large bladder that cannot empty normally (high-capacity atonal bladder), disrupted urination (bladder sphincter dyssynergia), and difficulty controlling the flow of urine (incontinence).

About 60 percent of people with Wolfram syndrome develop a neurological or psychiatric disorder, most commonly problems with balance and coordination (ataxia), typically beginning in early adulthood. Other neurological problems experienced by people with Wolfram syndrome include irregular breathing caused by the brain's inability to control breathing (central apnea), loss of the sense of smell, loss of the gag reflex, muscle spasms (myoclonus), seizures, reduced sensation in the lower extremities (peripheral neuropathy), and intellectual impairment. Psychiatric disorders associated with Wolfram syndrome include psychosis, episodes of severe depression, and impulsive and aggressive behavior (Rigoli, 2011). There are two types of Wolfram syndrome with many overlapping features. The two types are differentiated by their genetic cause. In addition to the usual features of Wolfram syndrome, individuals with Wolfram syndrome type 2 have stomach or intestinal ulcers and excessive bleeding after an injury. The tendency to bleed excessively combined with the ulcers typically leads to abnormal bleeding in the gastrointestinal system (Cooper, 1950). People with Wolfram syndrome type 2 do not develop diabetes insipidus. Wolfram syndrome is often fatal by mid-adulthood due to complications from the many features of the condition, such as health problems related to diabetes mellitus or neurological problems.

Background

Wolfram syndrome is a genetic condition, which is typically inherited in autosomal recessive fashion, characterized by the combination of diabetes mellitus and optic atrophy. It is along a spectrum which encompasses DIDMOAD (Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). The syndrome occurs in 1:770,000 individuals with a characteristic timeline for its clinical manifestations (Paley, 1956). There are some key features that distinguish the diabetes associated with Wolfram syndrome from Type 1 autoimmune diabetes mellitus. This syndrome is important to recognize as there are prognostic implications for those affected. The progressive loss of neuronal cell function has been implicated in the loss of ability to recognize insulin induced hypoglycemia. Severe hypoglycemia with hypoglycemic unawareness can lead to significant morbidity and mortality in diabetic patients including seizure, coma, and even death (Gunn *et al.,* 1976). Recognition that a particular patient is at increased risk for poor hypoglycemia recognition can result in changes in management of that patient to prevent further morbidity.

How common is Wolfram syndrome

The estimated prevalence of Wolfram syndrome type 1 is 1 in 500,000 people worldwide. Approximately 200 cases have been described in the scientific literature. Only a few families from Jordan have been found to have Wolfram syndrome type 2 (Blasi *et al.,* 1986).

What genes are related to Wolfram syndrome

Mutations in the *WFS1* gene cause more than 90 percent of Wolfram syndrome type 1 cases. This gene provides instructions for producing a protein called wolframin that is thought to regulate the amount of calcium in cells. A proper calcium balance is important for many different cellular functions, including cell-to-cell communication, the tensing (contraction) of muscles, and protein processing. The wolframin protein is found in many different tissues, such as the pancreas, brain, heart, bones, muscles, lung, liver, and kidneys. Within cells, wolframin is located in the membrane of a cell structure called the endoplasmic reticulum that is involved in protein production, processing, and transport (Barrett *et al.,* 1995). Wolframin's function is important in the pancreas, where the protein is thought to help process a protein called proinsulin into the mature hormone insulin. This hormone helps control blood sugar levels.

WFS1 gene mutations lead to the production of a wolframin protein that has reduced or absent function. As a result, calcium levels within cells are not regulated and the endoplasmic reticulum does not work correctly. When the endoplasmic reticulum does not have enough functional wolframin, the cell triggers its own cell death (apoptosis). The death of cells in the pancreas, specifically cells that make insulin (beta cells), causes diabetes mellitus in people with Wolfram syndrome. The gradual loss of cells along the optic nerve eventually leads to blindness in affected individuals. The death of cells in other body systems likely causes the various signs and symptoms of Wolfram syndrome type 1 (Mtanda *et al.,* 1986; Thompson *et al.,* 1989).

A certain mutation in the *CISD2* gene was found to cause Wolfram syndrome type 2. The *CISD2* gene provides instructions for making a protein that is located in the outer membrane of cell structures called mitochondria. Mitochondria are the energy-producing centers of cells. The exact function of the CISD2 protein is unknown, (Rando *et al.,* 1992) but it is thought to help keep mitochondria functioning normally. The *CISD2* gene mutation that causes Wolfram syndrome type 2 results in an abnormally small, nonfunctional CISD2 protein. As a result, mitochondria are not properly maintained, and they eventually break down. Since the mitochondria provide energy to cells, the loss of mitochondria results in decreased energy for cells. Cells that do not have enough energy to function will eventually die. Cells with high energy demands such as nerve cells in the brain, eye, or gastrointestinal tract are most susceptible to cell death due to reduced energy (Page *et al.,* 1976). It is unknown why people with *CISD2* gene mutations have ulcers and bleeding problems in addition to the usual Wolfram syndrome features.

Some people with Wolfram syndrome do not have an identified mutation in either the *WFS1* or*CISD2* gene. The cause of the condition in these individuals is unknown.

How do people inherit Wolfram syndrome

When Wolfram syndrome is caused by mutations in the *WFS1* gene, it is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Some studies have shown that people who carry one copy of a *WFS1* gene mutation are at increased risk of developing individual features of Wolfram syndrome or related features, such as type 2 diabetes, hearing loss, or psychiatric illness. However, other studies have found no increased risk in these individuals (Chu *et al.,* 1986). Wolfram syndrome caused by mutations in the *CISD2* gene is also inherited in an autosomal recessive pattern.

Symptoms

This syndrome is not an easy problem to diagnose. The majority of individuals will have this disorder for years before an accurate diagnosis is made. Some of the signs, symptoms or complaints that an individual might have or will see in their child: (Swift *et al.,* 1990; Davidson *et al.,* 1993)

- Type-1 Diabetes, normally beginning between the ages of 5 to 15
- Frequent and unusual urination in large amounts, combined with being constantly thirsty.
- Bedwetting will begin again after night training has already been successful
- Visual impairment beginning with wearing glasses but increasing rapidly
- Color blindness – socks will never match an outfit or the lawn might have many missed patches of grass after cutting.
- Reacting of the iris in the eye that is slow – even in bright lights pupils never go pinpoint
- It becomes evident that high frequency hearing loss or tonal deafness has developed
- Easy to get upset or emotionally agitated
- The challenge with this syndrome is that the symptoms are in the beginning very mild. Any one of them is not difficult to overlook or to treat as an individual abnormality. But the secondary developing complications can definitely rationalize any serious worries (Carson *et al.,* 1977). WS is a degenerative and progressive disease – meaning it will continue to get worse with time.

Causes

The cause of this disorder is a genetic mutation. The incidence of individuals who have this genetic trait in the United States is approximately one (1) %. Those individuals who have this recessive trait will not display the complete range of symptoms of WS. They are subject to an inflated rate of numerous methods of mental illness. It is merely when both parents have this trait recessively who have offspring who the WSF1 gene as a dominant affect. In these families the likelihood of getting the dominant trait is one (1) in four (4) for every birth (Karp *et al.,* 1978). Multiple cases within a single genetically predisposed family are not uncommon. In the UK it is projected that one (1) person in every 700,000 have this disorder. A United State scientist, Dr. Michael Swift, believes that the rate of individuals affected is much more common than has been reported earlier. No matter what the actual incident figures are, WS is a rare genetic disorder (Bundey *et al.,* 1992). It is currently understood to be the effect of either mitochondria or nuclear gene dysfunction. The "autosomal recessive trait" appears in both females and males with the same frequency (Barrett *et al.,* 1995).

Prognosis

The life expectancy of individuals diagnosed with this syndrome is approximately 30 years (Barrientos *et al.,* 1996).

Complications

Complications of this syndrome usually include the urinary tract as well as seizure disorders. Approximately 2/3 of individuals will experience renal problems in their 20s with a similar proportion developing neurological complications in their 30s (Barrientos *et al.,* 1996).

DIAGNOSIS

Clinical Diagnosis

WFS1-related disorders include a phenotypic spectrum ranging from Wolfram syndrome (WFS) to *WFS1*-related low-frequency sensory hearing loss (also known as DFNA6/14/38 LFSNHL).

Wolfram syndrome (WFS) is sometimes referred to as DIDMOAD diabetes insipidus, diabetes mellitus, opticatrophy, and deafness). The following are sensitive and specific for WFS (Fraser and Gunn, 1977):

- Juvenile-onset (age <16 years) diabetes mellitus
- Juvenile-onset optic atrophy (age <16 years)
- Autosomal recessive inheritance

Additional clinical features include the following: (Polymeropoulos *et al.,* 1994)

- High tone sensorineural hearing impairment (which can sometimes be congenital and severe)
- Cerebellar ataxia
- Dementia / intellectual disability (both may occur, but intellectual disability is rare)
- Psychiatric disease
- Neurogenic bladder or bladder dyssynergia
- Other endocrine findings:
- Central diabetes insipidus
- Delayed/absent puberty; hypogonadism in males
- Non-autoimmune hypothyroidism
- Growth retardation
- Cardiomyopathy and structural congenital heart defects (Collier *et al.,* 1996).

DIFFERENTIAL DIAGNOSIS

Wolfram syndrome type 2 (WFS2) (OMIM 604928), diagnosed in four Jordanian families and caused by mutations in*ZCD2* on 4q22, is characterized by juvenile-onset diabetes mellitus, optic atrophy, high-frequency sensorineural hearing impairment, urinary tract dilatation, impaired renal function, hypogonadism, and severe gastrointestinal ulcer and bleeding, but not diabetes insipidus (Ron, 2007; Rutkowski, 2007). In one family the facial features were abnormal (Haze *et al.,* 1999). The disorder is apparently very rare and may be confined to a certain ethnic background. Of note, molecular genetic testing of 377 hearing impaired probands did not reveal additional individuals with *ZCD2* mutations, indicating that mutation of *ZCD2* does not explain a substantial fraction of nonsyndromic hearing impairment.

Hearing impairment: Approximately 20% of genetic hearing impairment is inherited in an autosomal dominant manner, a small fraction of which is LFSNHL.

LFSNHL is heterogeneous (Yoshida, 2000). In addition to DFNA6/14/38, the following loci have been identified:

- DFNA1, mapped by Leon *et al*. [1992], is caused by mutations in *DIAPH1*; to date, only one family has been identified with this disorder (Ye, 2000).
- DFNA54
- DFNA11/DFNB2, caused by mutations in *MYO7A,* has been described in one family with autosomal dominant inheritance. Audiograms resembled *WFS1*-related LFSNHL, although some affected individuals had a flat audiogram (Shen *et al.,* 2002).
- Testing Strategy:

To confirm/establish the diagnosis in a proband

- The diagnosis of WFS and Wolfram-like syndrome is based on clinical findings and confirmed by findings onmolecular genetic testing.
- The diagnosis of *WFS1*-related LFSNHL is established by sequence analysis.
- If clinical suspicion is high and the sequencing analysis fails to detect a mutation(s), deletion/duplication analysis should be considered as second tier testing.

Carrier testing for relatives at risk for autosomal recessive WFS requires prior identification of the disease-causing mutations in the family (Wu *et al.,* 2007). Note: Carriers are heterozygotes for the autosomal recessive disorder WFS and are not at risk of developing WFS. Predictive testing for:

- Asymptomatic family members at risk for autosomal recessive WFS requires prior identification of the disease-causing mutations in the family;
- Asymptomatic family members at risk for autosomal dominant WFS-like disease require prior identification of the disease-causing mutation in the family (Yamamoto *et al.,* 2007).

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation(s) in the family.

Prevalence

Wolfram syndrome: More than 90 individuals from more than 60 families have been described worldwide (Hong, 2004; Takeda *et al.,* 2001; Fonseca *et al.,* 2005). A study from the UK estimated a prevalence of WFS of 1:550,000 children in the UK (Strom *et al.,* 1998). No valid estimate of prevalence is possible if atypical presentations (e.g., autosomal dominant WS-like disease, autosomal dominant LFSNHL caused by *WFS1* mutations) are included.

DFNA6/14/38 *(WFS1*-related LFSNHL)

- Mutations in *WFS1* were identified in ten of 13 families with autosomal dominant LFSNHL in whom linkagestudies either showed linkage or were compatible with linkage to chromosome 4p (Inoue *et al.,* 1998).
- In five of 30 Danish families (Lyssenko *et al.,* 2008) and three of nine Japanese families with characteristic findings on audiogram and/or a positive family history that were unsuitable for linkage analysis, molecular genetic testing showed *WFS1* mutations.

MANAGEMENT

Evaluations Following Initial Diagnosis:

To establish the extent of disease and needs in an individual diagnosed with a *WFS1*-related disorder, the following evaluations are recommended:

Wolfram syndrome and Wolfram-like syndrome (Franks *et al.,* 2008):

- Glucose tolerance test (if not already performed)
- Eye examination, including visual acuity, color vision, and visual fields
- Audiologic examination, including auditory brain stem responses (ABRs) and evoked otoacoustic emissions
- Neurologic examination
- Neuroimaging with MRI
- Developmental assessment in young children and assessment of cognitive abilities in older children and adolescents
- Baseline psychologic assessment
- Urologic consultation with imaging studies of the urinary tract and kidneys (Sandhu *et al.,* 2007)
- Test of the concentrating ability of urine to evaluate for diabetes insipidus
- Medical genetics consultation

Treatment

Diabetes mellitus is normally the symptom of WS which will require medical management first in the progress of WS. There is not any conventional advancement of this syndrome and other difficulties that may lead the start of DIABETES MELLITUS. With diabetes mellitus, the food eaten is treated by gastric fluid in the stomach into blood sugar or glucose. Blood sugar is the body's major source of energy used by the body cells to function. For these cells to be able to use this blood sugar, a hormone that is produced naturally by the pancreas, insulin, is needed. As soon as the pancreas stops

creating the precise quantity of insulin that is required for the use of blood sugar the spare blood sugar is distributed by the kidneys into urine and emptied from the body (Yamada *et al.,* 2006). Extreme blood sugar is identified as diabetic acidosis and may cause unconsciousness, coma and loss of life. The problems an individual DIABETES MELLITUS may have can include:

- Frequent thirst and urination
- Slow healing
- Weight loss or lack of weight gain or growth with children
- Itching
- Constant hunger
- Dryness of skin
- The management of DIABETES MELLITUS in WS individuals is the same as in the management of DIABETES MELLITUS in individuals who do not have WS. This includes: (Riggs *et al.,* 2005)
- Daily injections of insulin
- Diet controlled
- Exercise to use up glucose
- Frequent testing of glucose levels
- Diabetes Insipidus – Individuals who develop diabetes insipidus will drink enormous amounts of fluid and void diluted urine frequently. This leads to: (Kakiuchi *et al.,* 2006)
- Dehydration
- Weakness
- Dry mouth
- Constipation
- Dry skin

When individuals have this form of diabetes, the gland known as hypothalamus creates an abnormal quantity of hormone for anti-diuretic. DI or Diabetes insipidus doesn't have anything to do with the amount of blood sugar or insulin. This problem has also been recognized to occur in individuals with head trauma that is severe and completely unrelated to WS (Wang *et al.,* 2000). This type of diabetes is treated normally by Desmopressin Acetate nasal spray. This medication is also available in tablet as well as injectable form. In 1989 this treatment was approved by the FDA for the treatment of Diabetes Insipidus (Shen *et al.,* 2005). This medication offers heightened anti-diuretic action with minimal side effects on the blood system or the smooth muscles of individuals with Diabetes Insipidus.

Blindness/Low vision the most discernible feature of WS is iris of the eye becoming dilated. Even when in light that is bright, the iris will stay wide and respond slowly. The continuing loss of the nerves of the optic that connect the eye to the brain is what allows this to happen. This is identified as Optic Atrophy. Any eye doctor will typically see a saucer shaped void that appears white or grayish. Some reports specify that the optic nerve seems pale pink (Yu *et al.,* 1997). This can occur at any age but normally before age 12. There is no known treatment at this time for this condition.

Loss of vision in WS individuals may also be due to Diabetic Retinopathy. This is a condition of retina tissues that are light sensitive caused by continued blood sugar levels that are high. It can lead to visual damage or blindness. Blood sugar levels that are normal may help reverse changes in the small blood vessels of the eye. If blood sugar levels can be maintained in the normal range, this problem of diabetes may be evaded (Yu, 1999).

Deafness/hearing impairment is the last major symptom of WS but not automatically last to become obvious. Loss of hearing may go from the loss of those tones that are high pitch to severe sound loss. There may as well be complications such as dizziness or ataxia. This might be due to failure of nerves to properly transmit data from the ear to the brain (Hosokawa *et al.,* 2001).

Surveillance:

Wolfram syndrome: Regular evaluations including the following to detect manifestations that can occur with time: (Kaneko *et al.,* 2007; Yamamoto *et al.,* 2008; Hampton *et al.,* 1996)

- Diabetes mellitus: tests of glucose tolerance
- Optic atrophy: ophthalmologic examination
- Sensorineural hearing loss: audiologic examination including speech discrimination testing
- Neurologic deficits: neurologic examination including assessment of memory, personality changes
- Psychiatric abnormalities: assessment for signs including depression, suicidal behavior, and changes in personal appearance and social behavior
- Urologic abnormalities: urodynamic examination and assessment of ability to empty the bladder. Regular urine cultures when bladder dysfunction or other renal tract abnormality is present.
- Diabetes insipidus: assessment of concentrating ability of the urine
- Growth delay: monitoring of linear growth in children using standard growth charts
- Hypogonadism
- Puberty: monitoring for signs of onset of puberty

Conclusion

In summary, IDDM and optic atrophy are the first and essential features of Wolfram followed by development of deafness, diabetes insipidus and urinary tract abnormalities. Generally cases having IDDM and optic atrophy together need to be evaluated with respect to Wolfram. Cases with Wolfram should be followed all their lives. In these cases, rehabilitation to a normal social life is possible with good follow-up and treatment. The disorder should be kept in mind particularly in various parts of the world, where consanguinity is prevalent.

REFERENCES

Aloi, C., Salina, A., Pasquali, L., Lugani, F., Perri, K., Russo, C., Tallone, R., Ghiggeri, G. M., Lorini, R. 2012 d'Annunzio G. Wolfram syndrome: new mutations, different phenotype. PLoS One. 7(1):e29150.

Amr S., Heisey, C., Zhang, M., Xia, X. J., Shows, K. H., Ajlouni, K., Pandya, A., Satin, L. S., El-Shanti, H., Shiang,

R. 2007. A homozygous mutation in a novel zinc-finger protein, ERIS, is responsible for Wolfram syndrome 2. Am J Hum Genet. Oct; 81(4):673-83.

Barrett, T. G., Bundey, S. E., Macleod, A. F. 1995. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. *Lancet.* Dec 2;346 (8988):1458–1463.

Barrett, T. G., Poulton, K., Bundey, S. 1995. Didmoad syndrome; further studies and muscle biochemistry.*J Inherit Metab Dis.* 18(2):218–220.

Barrientos, A., Casademont, J., Saiz, A., Cardellach, F., Volpini, V., Solans, A., Tolosa, E., Urbano-Marquez, A., Estivill, X., Nunes, V. 1996. Autosomal recessive Wolfram syndrome associated with an 8.5-kb mtDNA single deletion. *Am J Hum Genet.* May;58(5):963–970.

Blasi, C., Pierelli, F., Rispoli, E., Saponara, M., Vingolo, E., Andreani, D. 1986. Wolfram's syndrome: a clinical, diagnostic, and interpretative contribution. *Diabetes Care.* Sep-Oct; 9(5):521–528.

Bundey, S., Poulton, K., Whitwell, H., Curtis, E., Brown, I. A., Fielder, A. R. 1992. Mitochondrial abnormalities in the DIDMOAD syndrome. *J Inherit Metab Dis.* 15(3):315–319.

Carson, M. J., Slager, U. T., Steinberg, R. M. 1977. Simultaneous occurrence of diabetes mellitus, diabetes insipidus, and optic atrophy in a brother and sister. *Am J Dis Child.* Dec;131(12):1382–1385.

Chaussenot, A., Bannwarth, S., Rouzier, C., Vialettes, B., Mkadem, S. A., Chabrol, B. , Cano, A., Labauge, P., Paquis-Flucklinger, V. 2011. Neurologic features and genotype-phenotype correlation in Wolfram syndrome. Ann Neurol. Mar;69(3):501-8. .

Chu P, Staff WG, Morris JA, Polak JM. DIDMOAD syndrome with megacystis and megaureter.*Postgrad Med J.* 1986 Sep;62(731):859–863.

Collier, D. A., Barrett, T. G., Curtis, D., Macleod, A., Arranz, M. J., Maassen, J. A., Bundey, S. 1996. Linkage of Wolfram syndrome to chromosome 4p16.1 and evidence for heterogeneity. *Am J Hum Genet.* Oct;59(4):855–863.

Cooper, I. S., Rynearson, E. H., Bailey, A. A., MacCarty, C. S. 1950. The relation of spinal cord diseases to gynecomastia and testicular atrophy. *Proc Staff Meet Mayo Clin.* Jun 7;25(12):320–326.

Davidson IR, McNicholl JM, O'Donnell J. Successful pregnancy in two sisters with Wolfram syndrome. *Ir Med J.* 1993 Jan;86(1):33–34.

Fonseca, S. G., *et al*. 2005. WFS1 is a novel component of the unfolded protein response and maintains homeostasis of the endoplasmic reticulum in pancreatic {beta}-cells. *J Biol Chem.* 280(47):39609–39615.

Franks, P. W., *et al*. 2008. Replication of the association between variants in WFS1 and risk of type 2 diabetes in European populations. *Diabetologia.* 51(3):458–463.

Fraser, F. C., Gunn, T. 1977. Diabetes mellitus, diabetes insipidus, and optic atrophy. An autosomal recessive syndrome? *J Med Genet.* Jun;14(3):190–193.

Gunn, T., Bortolussi, R., Little, J. M., Andermann, F., Fraser, F. C., Belmonte, M. M. 1976. Juvenile diabetes mellitus, optic atrophy, sensory nerve deafness, and diabetes insipidus--a syndrome. *J Pediatr.* Oct;89(4):565–570.

Hampton, R. Y., Gardner, R. G., Rine, J. 1996. Role of 26S proteasome and HRD genes in the degradation of 3-hydroxy-3-methylglutaryl-CoA reductase, an integral endoplasmic reticulum membrane protein. *Mol Biol Cell.* 7(12):2029–2044.

Haze, K., Yoshida, H., Yanagi, H., Yura, T., Mori, K. 1999. Mammalian transcription factor ATF6 is synthesized as a transmembrane protein and activated by proteolysis in response to endoplasmic reticulum stress. *Mol Biol Cell.* 10(11):3787–3799.

Hong, M., Li, M., Mao, C., Lee, A. S. 2004. Endoplasmic reticulum stress triggers an acute proteasome-dependent degradation of ATF6. *J Cell Biochem.* 92(4):723–732.

Hosokawa, N., *et al*. 2001. A novel ER alpha-mannosidase-like protein accelerates ER-associated degradation. *EMBO Rep.* 2(5):415–422.

Inoue, H., *et al*.1998. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). *Nat Genet.* 20(2):143–148.

Kakiuchi, C., Ishiwata, M., Hayashi, A., Kato, T. 2006. XBP1 induces WFS1 through an endoplasmic reticulum stress response element-like motif in SH-SY5Y cells. *J Neurochem.* 97(2):545–555.

Kaneko, M., *et al*. 2007. A different pathway in the endoplasmic reticulum stress-induced expression of human HRD1 and SEL1 genes. *FEBS Lett.* 581(28):5355–5360.

Kanki, T., Klionsky, D. J. 2009. Mitochondrial abnormalities drive cell death in Wolfram syndrome 2. Cell Res. Aug;19(8):922-3.

Karp, M., Laron, Z., Sanbank, U. 1978. Wolfram syndrome. *Am J Dis Child.* Aug;132(8):818–819.

Kumar, S. 2010. Wolfram syndrome: important implications for pediatricians and pediatric endocrinologists. Pediatr Diabetes. Feb;11(1):28-37.

Lyssenko, V., *et al*. 2008. Clinical risk factors, DNA variants, and the development of type 2 diabetes. *N Engl J Med.* 359(21):2220–2232.

Mtanda, A. T., Cruysberg, J. R., Pinckers, A. J. 1986. Optic atrophy in Wolfram syndrome. *Ophthalmic Paediatr Genet.* Dec; 7(3):159–165.

Page, M. M., Asmal, A. C., Edwards, C. R. 1976. Recessive inheritance of diabetes: the syndrome of diabetes insipidus, diabetes mellitus, optic atrophy and deafness. *Q J Med.* Jul; 45(179):505–520.

Paley, R. G., Tunbridge, R. E. 1956. Primary optic atrophy in diabetes mellitus. *Diabetes.* Jul-Aug;5(4):295–296.

Polymeropoulos, M. H., Swift, R. G., Swift, M.1994. Linkage of the gene for Wolfram syndrome to markers on the short arm of chromosome 4. *Nat Genet.* Sep;8(1):95–97.

Rando, T. A., Horton, J. C., Layzer, R. B. 1992. Wolfram syndrome: evidence of a diffuse neurodegenerative disease by magnetic resonance imaging. *Neurology.* Jun;42(6):1220–1224.

Riggs, A. C., *et al*. 2005. Mice conditionally lacking the Wolfram gene in pancreatic islet beta cells exhibit diabetes as a result of enhanced endoplasmic reticulum stress and apoptosis.*Diabetologia.* 48(11):2313–2321.

Rigoli, L., Lombardo, F., Di Bella, C. 2011. Wolfram syndrome and WFS1 gene. Clin Genet. Feb;79(2):103-17.

Ron, D., Walter, P. 2007 Signal integration in the endoplasmic reticulum unfolded protein response. *Nat Rev Mol Cell Biol.,* 8(7):519–529.

Rutkowski, D. T., Kaufman, R. J. 2007. That which does not kill me makes me stronger: adapting to chronic ER stress. *Trends Biochem Sci.,* 32(10):469–476.

Sandhu, M. S., *et al*. 2007. Common variants in WFS1 confer risk of type 2 diabetes. *Nat Genet.* 39(8):951–953.

Shen, J., Chen, X., Hendershot, L., Prywes, R. 2002. ER stress regulation of ATF6 localization by dissociation of BiP/GRP78 binding and unmasking of Golgi localization signals. *Dev Cell.* 3(1):99–111.

Shen, J., Snapp, E. L., Lippincott-Schwartz, J., Prywes, R. 2005. Stable binding of ATF6 to BiP in the endoplasmic reticulum stress response. *Mol Cell Biol.* 25(3):921–932.

Strom, T. M., *et al*.1998. Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) caused by mutations in a novel gene (wolframin) coding for a predicted transmembrane protein. *Hum Mol Genet.* 7(13):2021–2028.

Swift RG, Sadler DB, Swift M. Psychiatric findings in Wolfram syndrome homozygotes. *Lancet.*1990 Sep 15;336(8716):667–669.

Takeda, K., *et al*. 2001. WFS1 (Wolfram syndrome 1) gene product: predominant subcellular localization to endoplasmic reticulum in cultured cells and neuronal expression in rat brain.*Hum Mol Genet.* 10(5):477–484.

Thompson, C. J., Charlton, J., Walford, S., Baird, J., Hearnshaw, J., McCulloch, A., Kelly, W., Baylis, P. H. 1989. Vasopressin secretion in the DIDMOAD (Wolfram) syndrome. *Q J Med.* Apr;71(264):333–345.

Wang, Y., Shen, J., Arenzana, N., Tirasophon, W., Kaufman, R. J., Prywes, R. 2000. Activation of ATF6 and an ATF6 DNA binding site by the endoplasmic reticulum stress response. *J Biol Chem.* 275(35):27013–27020.

Wu, J., *et al*. 2007. ATF6alpha optimizes long-term endoplasmic reticulum function to protect cells from chronic stress. *Dev Cell.* 13(3):351–364.

Yamada, T., *et al*. 2006. WFS1-deficiency increases endoplasmic reticulum stress, impairs cell cycle progression and triggers the apoptotic pathway specifically in pancreatic beta-cells.*Hum Mol Genet.* 15(10):1600–1609.

Yamamoto, K., *et al*. 2007. Transcriptional induction of mammalian ER quality control proteins is mediated by single or combined action of ATF6alpha and XBP1. *Dev Cell.* 13(3):365–376.

Yamamoto, K., *et al*. 2008. Human HRD1 promoter carries a functional unfolded protein response element to which XBP1 but not ATF6 directly binds. *J Biochem.* 144(4):477–486.

Ye, J., *et al*. 2000. ER stress induces cleavage of membrane-bound ATF6 by the same proteases that process SREBPs. *Mol Cell.* 6(6):1355–1364.

Yoshida, H., *et al*. 2000. ATF6 activated by proteolysis binds in the presence of NF-Y (CBF) directly to the cis-acting element responsible for the mammalian unfolded protein response. *Mol Cell Biol.* 20(18):6755–6767.

Yu, H., Kaung, G., Kobayashi, S., Kopito, R. R. 1997. Cytosolic degradation of T-cell receptor alpha chains by the proteasome. *J Biol Chem.* 272(33):20800–20804.

Yu, H., Kopito, R. R. 1999. The role of multiubiquitination in dislocation and degradation of the alpha subunit of the T cell antigen receptor. *J Biol Chem.* 274(52):36852–36858.

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