

# Current Developments in Wolfram Syndrome

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## ABSTRACT

**Wolfram syndrome (WS), an infrequent cause of diabetes mellitus, derives its name from the physician who first reported the combination of juvenile-onset diabetes mellitus and optic atrophy. Also referred to as DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and deafness), it is an autosomal recessive neurodegenerative disease characterized by various clinical manifestations, such as diabetes mellitus, optic atrophy, diabetes insipidus, deafness, neurological symptoms, renal tract abnormalities, psychiatric manifestations and gonadal disorders. The condition is very rare with an estimated prevalence of one in 770,000 of the normal population, one out of 150 cases of juvenile-onset insulin-dependent diabetes mellitus, and with a carrier frequency of one in 354. This progressive neurodegenerative disease usually results in death before the age of 50 years and many patients lead a morbid life. The pathogenesis of the disorder although unknown is ascribed to mutation of a gene on chromosome 4p encoding a transmembrane protein of undetermined function called wolframin. This review summarizes the variable presentation of the disorder, its widespread complications, poor quality of life in affected individuals, and the problems in diagnosis and treatment of the syndrome.**

## KEY WORDS

DIDMOAD, Wolfram syndrome, diabetes mellitus, optic atrophy, diabetes insipidus, brainstem atrophy

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## WOLFRAM SYNDROME

This review is written for the pediatric diabetes specialist and aims to provide information on the clinical features, natural history, genetics and management of children with diabetes mellitus as part of Wolfram syndrome (WS).

WS, also known as DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and deafness), is an infrequent cause of diabetes mellitus. WS derives its name from the physician who first reported the combination of juvenile-onset diabetes mellitus and optic atrophy in four siblings<sup>1</sup>. DIDMOAD syndrome was coined with the report of two remaining components of the syndrome, diabetes insipidus and deafness. This syndrome is included among the genetic disorders associated with diabetes mellitus in the American Diabetes Association's classification. WS is an autosomal recessive neurodegenerative disease characterized by various clinical manifestations, including diabetes mellitus, optic atrophy, diabetes insipidus, deafness, neurological symptoms, renal tract abnormalities, psychiatric disorders and gonadal disorders. The most frequent of these disorders are early onset diabetes mellitus, with a low prevalence of ketoacidosis, and optic atrophy, which is considered a key diagnostic criterion in this syndrome. Diabetes insipidus usually develops later. This syndrome manifests in childhood, hampering diagnosis and treatment. The syndrome has variable presentation and complications are widespread. Full characterization of all clinical and biological features of WS is difficult because, with the exception of a few series, the number of patients in most reports is small. Morbidity and mortality are high and the quality of life is impaired due to neurological and urological complications.

The disease is rare with an estimated prevalence of one in 770,000, and a carrier frequency of one in

354<sup>2</sup>; it is believed to occur in one out of 150 patients with juvenile-onset insulin-dependent diabetes mellitus. It is classified as a progressive neurodegenerative disease and usually results in death before age 50 years<sup>3</sup>. The pathogenesis of the disease is still unknown; one candidate gene, mapped to chromosome 4p, has recently been shown to encode a transmembrane protein called wolframin whose function is not yet clearly determined<sup>4</sup>.

Juvenile diabetes mellitus and optic atrophy was found in four of eight siblings by Wolfram and Wagener in 1938<sup>1</sup>, and Tyrer in 1943 observed three of eight siblings born of a first-cousin marriage<sup>5</sup>. Review of the literature by Rose *et al.* in 1966<sup>6</sup> led to the description of seven cases including two unrelated patients; all seven patients were males. They suggested that homozygosity for a gene with pleiotropic effects may be involved and that because of clinical heterogeneity more than one locus may be involved. Shaw and Duncan<sup>7</sup> described two sisters and a niece with optic atrophy, sensorineural deafness, and diabetes mellitus, all having onset in the first year of life. Rorsman and Soderstrom<sup>8</sup> described a family in which three sisters and a brother developed diabetes mellitus at ages 9 and 5 years, and optic atrophy in their teens. In one the optic atrophy appeared before the diabetes mellitus. Wit *et al.*<sup>9</sup> documented vasopressin deficiency in a child with WS, thus confirming the central origin of the diabetes insipidus in this disorder. Salih and Tuvemo<sup>10</sup> described two Sudanese families with two affected boys in one and an affected boy and girl in the other, in whom diabetes mellitus was followed by deafness and visual failure after 3-8 years. In these three children diabetes insipidus was confirmed using a water deprivation test, and all three had severe bilateral hydronephrosis with dilated ureters and distended bladder without vesicoureteral reflux. The disease ended fatally in one case<sup>10</sup>.

In 1989 Borgna-Pignatti *et al.*<sup>11</sup> described two affected children, first cousins, who developed neutropenia, and megaloblastic and sideroblastic anemia, with borderline thrombocytopenia. In both these cases, thiamine pyrophosphate in erythrocytes and thiamine pyrophosphokinase

activity were lower than the lowest values observed in control individuals, and the hematological findings had returned to normal and insulin requirements had decreased after one month of therapy. Withdrawal of thiamine repeatedly induced relapse of the anemia and increase in insulin requirements. They proposed that an inherited abnormality of thiamine metabolism is responsible for the multisystem manifestations of DIDMOAD syndrome<sup>11</sup>.

The clinical picture of WS is highly variable and may include neurological abnormalities, such as nystagmus, mental retardation, and seizures. Swift *et al.*<sup>12</sup> found that 60% of a series of 68 homozygous patients with WS had episodes of severe depression, psychosis, or organic brain syndrome, as well as compulsive verbal and physical aggression. Heterozygous carriers of WS, estimated by Swift *et al.*<sup>13</sup> as representing approximately 1% of the United States population, are thought to be predisposed to psychiatric illness, and the risk of hospitalization for psychiatric illness or suicide is approximately eight times that of non-carriers. The manifestations of homozygous WS include hearing loss, urinary tract atony, ataxia, peripheral neuropathy, mental retardation, dementia, and psychiatric illnesses. Rando *et al.*<sup>14</sup> reported two unrelated patients who in addition to the four cardinal features had several other neurological abnormalities and in whom MRI showed widespread atrophic changes throughout the brain. Scolding *et al.*<sup>15</sup> described two pairs of affected siblings with the cardinal features of WS in addition to exhibiting neurogenic respiratory failure, startle myoclonus, Parinaud syndrome, and axial rigidity. MRI of the brain demonstrated marked brainstem atrophy<sup>15</sup>. Mathis *et al.*<sup>16</sup> report the case of a 47 year-old patient with a diagnosis of WS in view of a late neurological syndrome in association with ataxia and bilateral horizontal nystagmus. Brain resonance magnetic imaging revealed major atrophy of the brainstem and cerebellum<sup>16</sup>. The ophthalmological findings of DIDMOAD are largely dominated by optic atrophy. Through four cases and a literature review, the authors describe the ophthalmological findings in this disease and its clinical and genetic aspects.

Gabreëls *et al.*<sup>17</sup> reported a disturbance in vasopressin precursor processing in the supraoptic and paraventricular nuclei of patients with WS. In patients with diabetes insipidus, the authors detected virtually no cellular immunoreactivity for processed vasopressin in the supraoptic and paraventricular nuclei. On the other hand, a considerable number of cells immunoreactive for the vasopressin precursor were present in the paraventricular nucleus. The proprotein convertase PC2 and the molecular chaperone 7B2 were also absent. As expression of PC2 and 7B2 was detected in the nearby nucleus basalis of Meynert of one patient with WS and in the anterior lobe of the other patient with WS, the authors concluded that the absence of these two proteins in the paraventricular nucleus was not caused by mutations in their genes. They concluded that in WS patients with diabetes insipidus, not only does vasopressin neuron loss occur in the supraoptic nucleus, but there is also a defect in vasopressin precursor processing<sup>17</sup>.

Medlej *et al.*<sup>18</sup> reported 31 Lebanese patients with WS belonging to 17 families. Central diabetes insipidus was found in 87% of the patients, and sensorineural deafness confirmed by audiograms was present in 64.5%. Other less frequent features included neurological and psychiatric abnormalities, urodynamic abnormalities, limited joint motility, cardiovascular and gastrointestinal autonomic neuropathy, hypergonadotropic hypogonadism in males, and diabetic microvascular disease. New features, including heart malformations and anterior pituitary dysfunction, were recognized in some of the patients and participated in the morbidity and mortality of the disease<sup>18</sup>. El-Shanti *et al.*<sup>19</sup> found that three families linked to 4q (*WFS2*) contained several patients with profound upper gastrointestinal ulceration and bleeding. In 2006, Eiberg *et al.*<sup>20</sup> reported a 3-generation Danish family in which a Wolfram-like phenotype segregated in an autosomal dominant fashion. The four affected individuals had optic atrophy that began in childhood or middle age as well as childhood-onset progressive hearing impairment. Three of the four patients also had impaired glucose regulation: one was found to have undiagnosed diabetes mellitus and another

impaired glucose tolerance by an oral glucose tolerance test, and the third had poor pancreatic beta-cell function as evaluated by the insulinogenic index. Two additional family members had isolated congenital hearing impairment<sup>20</sup>.

Cano *et al.*<sup>21</sup>, the French Wolfram Study Group, studied 26 French diabetic patients with DIDMOAD and compared them with a population of 52 patients with type 1 diabetes mellitus matched for age at diabetes diagnosis ( $8.62 \pm 1.84$  vs  $8.27 \pm 1.30$  years;  $p = \text{NS}$ ) and diabetes duration ( $12.88 \pm 1.58$  vs  $12.87 \pm 1.13$  years;  $p = \text{NS}$ ) to study the quality of glycemic control and the incidence of microvascular complications. Glycemic control was significantly better in the DIDMOAD group than in the type 1 diabetic group ( $\text{Hb}_{\text{A1c}} 7.72 \pm 0.21$  vs  $8.99 \pm 0.25\%$ , respectively;  $p = 0.002$ ), with significant lower daily insulin requirements ( $0.71 \pm 0.07$  vs  $0.88 \pm 0.04 \text{ IU} \times \text{kg}^{-1} \times \text{day}^{-1}$ , respectively;  $p = 0.0325$ ). The prevalence of microvascular complications in the DIDMOAD group was half that observed in the type 1 diabetic group, but the difference was not significant. This better glycemic control could explain the trend to decreased microvascular diabetes complications observed in previous studies<sup>21</sup>.

Ari *et al.*<sup>22</sup> reviewed the literature and emphasized the need for careful evaluation of cases having insulin-dependent diabetes mellitus and optic atrophy. Simsek *et al.*<sup>23</sup> studied nine patients with WS evaluated by the departments of pediatrics, ophthalmology, audiology, urology and medical biology. Short stature was found in five patients, delayed puberty in two and hypergonadotropic hypogonadism in one patient. Audiography disclosed hearing loss at high frequency in all patients (100%), but only five patients had clinical subjective hearing problems. Intravenous pyelography revealed hydronephrosis in eight patients. Urodynamic study revealed a normal bladder in only one patient, and three patients had a low-capacity, low-compliance bladder, detrusor external sphincteric dyssynergia and emptying problem, while five had an atonic bladder. Ocular findings were optic atrophy, low visual acuity and color vision defects. Visual field tests revealed concentric and/or peripheral diminution in five patients. Visual evoked potentials were abnormal

(reduced amplitude to both flash and pattern stimulation) in seven patients. Cranial magnetic resonance imaging showed mild or moderate atrophy of the optic nerves, chiasm, cerebellum, basal ganglia and brainstem in six patients; there was a partially empty sella in one patient. They concluded that WS should be evaluated in a multi-disciplinary manner. Short stature is a common feature and hypogonadism may be hypogonadotropic or hypergonadotropic. A low-capacity, high-pressure bladder with sphincteric dyssynergia is also common<sup>23</sup>.

To gain further insight into the function of the *WFS1* gene encoding an endoplasmic reticulum (ER) membrane protein, Wolframin, and identify its molecular partners, Zatyaka *et al.*<sup>24</sup> used the *WFS1* C-terminal domain as bait in a yeast two-hybrid screen with a human brain cDNA library. The Na<sup>+</sup>/K<sup>+</sup> ATPase  $\beta$ 1 subunit was identified as an interacting clone. They mapped the interaction to the *WFS1* C-terminal and transmembrane domains, but not the N-terminal domain, and their mapping data suggested that the interaction most likely occurs in the ER. They confirmed the interaction by co-immunoprecipitation in mammalian cells and with endogenous proteins in JEG3 placental cells, neuroblastoma SKNAS and pancreatic MIN6 beta-cells. The Na<sup>+</sup>/K<sup>+</sup> ATPase  $\beta$ 1 subunit expression was reduced in plasma membrane fractions of human *WFS1* mutant fibroblasts and *WFS1* knockout MIN6 pancreatic beta-cells compared with wild-type cells; Na<sup>+</sup>/K<sup>+</sup> ATPase  $\alpha$ 1 subunit expression was also reduced in *WFS1*-depleted MIN6 beta-cells. Induction of ER stress in wild-type cells only partly accounted for the reduced Na<sup>+</sup>/K<sup>+</sup> ATPase  $\beta$ 1 subunit expression observed. They concluded that the interaction may be important for Na<sup>+</sup>/K<sup>+</sup> ATPase  $\beta$ 1 subunit maturation; loss of this interaction may contribute to the pathology seen in WS via reductions in sodium pump  $\alpha$ 1 and  $\beta$ 1 subunit expression in pancreatic beta-cells<sup>24</sup>.

Lou Frances *et al.*<sup>25</sup> described the clinical characteristics and outcome in three patients with WS; all three patients had antecedents of consanguinity. Genetic study revealed that one patient was homozygotic for the *WFS1* G736A mutation in exon 8 and the remaining two patients, who were

siblings, were homozygotic for the 425ins16 mutation in exon 4.

Recently, single nucleotide polymorphisms (SNPs) in *WFS1* have been reproducibly associated with type 2 diabetes mellitus. Florez *et al.*<sup>26</sup> examined the effects of genotype variants on diabetes incidence and response to interventions in the Diabetes Prevention Program (DPP), in which a lifestyle intervention or metformin treatment was compared with placebo. They genotyped the *WFS1* SNPs rs10010131, rs752854 and rs734312 (H611R) in 3,548 DPP participants and performed Cox regression analysis using genotype, intervention and their interactions as predictors of diabetes incidence. They also evaluated the effect of these SNPs on insulin resistance and beta-cell function after 1 year. Although none of the three SNPs was associated with diabetes incidence in the overall cohort, White homozygotes for the previously reported protective alleles appeared less likely to develop diabetes in the lifestyle arm. Examination of the publicly available Diabetes Genetics Initiative genome-wide association dataset revealed that rs10012946, which is in strong linkage disequilibrium with the three *WFS1* SNPs ( $r = 0.88-1.0$ ), was associated with type 2 diabetes mellitus (allelic odds ratio 0.85, 95% CI 0.75-0.97,  $p = 0.026$ ). In the DPP, they noted a trend towards increased insulin secretion in carriers of the protective variants, although for most SNPs this was seen as compensatory for diminished insulin sensitivity. They concluded that the previously reported protective effect of select *WFS1* alleles may be magnified by lifestyle intervention. These variants appear to confer an improvement in beta-cell function<sup>26</sup>.

Franks *et al.*<sup>27</sup> performed a meta-analysis of published and previously unpublished data from Sweden, Finland and France, to obtain updated summary effect estimates of polymorphisms of *WFS1*. Four *WFS1* SNPs (rs10010131, rs6446482, rs752854 and rs734312) were genotyped in a type 2 diabetes case-control study ( $n = 1,296/1,412$ ) of Swedish adults. Logistic regression was used to assess the association between each *WFS1* SNP and type 2 diabetes, following adjustment for age, sex and body mass index. The meta-analysis of 11 studies of type 2 diabetes, comprising up to 14,139

patients and 16,109 controls, was done to obtain a summary effect estimate for the *WFS1* variants. In the northern Swedish study, the minor allele at rs752854 was associated with reduced type 2 diabetes risk (odds ratio 0.85, 95% CI 0.75-0.96,  $p = 0.010$ ). Borderline statistical associations were observed for the remaining SNPs. The meta-analysis of the four independent replication studies for SNP rs10010131 and correlated variants showed evidence for statistical association (OR 0.87, 95% CI 0.82-0.93,  $p = 4.5 \times 10^{-5}$ ). In an updated meta-analysis of all 11 studies, strong evidence of statistical association was also observed (OR 0.89, 95% CI 0.86-0.92;  $p = 4.9 \times 10^{-11}$ ). They replicated the previously reported associations between SNPs at this locus and the risk of type 2 diabetes<sup>27</sup>.

Amr *et al.*<sup>28</sup> found a single missense mutation in a novel, highly conserved zinc-finger gene, *ZCD2*, in three consanguineous families of Jordanian descent with WS. It had been shown that these families did not have mutations in the *WFS1* gene, but were mapped to the *WFS2* locus at 4q22-25. A G→C transversion at nucleotide 109 predicts an amino acid change from glutamic acid to glutamine (E37Q). Although the amino acid is conserved and the mutation is non-synonymous, the pathogenesis for the disorder is because the mutation also causes aberrant splicing. The mutation was found to disrupt messenger RNA splicing by eliminating exon 2, and it results in the introduction of a premature stop codon. Mutations in *WFS1* have also been found to cause low-frequency non-syndromic hearing loss, progressive hearing loss, and isolated optic atrophy associated with hearing loss. Screening of 377 probands with hearing loss did not identify mutations in the *WFS2* gene. Wolframin is known to localize to the ER and plays a role in calcium homeostasis. The *ZCD2*-encoded protein, ERIS (endoplasmic reticulum inter-membrane small protein), is also shown to localize to the ER but does not interact directly with Wolframin. Lymphoblast cells from affected individuals show a significantly greater rise in intracellular calcium when stimulated with thapsigargin, compared with controls, although no difference was observed in resting concentrations of intracellular calcium<sup>28</sup>.

To test the influence of *WFS1* polymorphisms on medication overuse headache (MOH), a chronic headache condition related to symptomatic drug overuse, Di Lorenzo *et al.*<sup>29</sup> analyzed 82 patients with MOH for the *WFS1* His611Arg polymorphism and performed a comparison between clinical features of Arg/Arg (R/R) and non-R/R individuals. Individuals harboring the R/R genotype showed significantly higher monthly drug consumption ( $t = -3.504$ ;  $p = 0.00075$ ) and more severe depressive symptoms on the BDI questionnaire ( $t = -3.048$ ;  $p = 0.003$ ) than non-R/R. *WFS1* polymorphism emerged as the only significant predictor of drug consumption by multivariate regression analysis ( $F = 12.277$ ;  $df = 1,80$ ;  $p = 0.00075$ , adjusted  $R^2 = 0.122$ ). These results implicate *WFS1* in the clinical picture of MOH, maybe through an influence on need for drugs as in other conditions of abuse behavior<sup>29</sup>.

Sayouti *et al.*<sup>30</sup> reported two cases of WS, in a 12 year-old girl and a 13 year-old boy. In each case, there was a history of diabetes mellitus; they consulted for a progressive loss of vision. Ophthalmological examination determined that visual acuity was reduced to finger counting as well as isolated bilateral optic atrophy and constriction of the peripheral visual field.

Deletion of the *LETM1* gene correlates with the occurrence of epilepsy in patients with Wolf-Hirschhorn syndrome (WHS). The *LETM1* gene encodes a mitochondrial protein that is homologous to yeast Mdm38. Yeast Mdm38 is localized to the mitochondrial inner membrane where it was proposed to act as a  $K^+/H^+$  antiporter, or alternatively as a chaperone for selected mitochondrial inner membrane proteins. In one study authors localized the Letm1 protein to the mitochondrial inner membrane of mammalian cells, where it exists in a 550-kDa complex. They showed that Letm1 can bind to itself *in vitro*, raising the possibility that it can form higher order multimers *in vivo*. Reduced levels of Letm1 in human cells and in *C. elegans* led to swellings along the length of mitochondria, consistent with the phenotype observed in yeast. Electron micrographs show mitochondria with swollen matrices that are less electron-dense than matrices in normal mitochondria. The opposite effect is achieved by overexpression of Letm1.

Overexpression increases the electron density of the mitochondrial matrix and swelling of cristae<sup>31</sup>.

To explain the complex phenotype of a patient with WHS and features reminiscent of WS, Flipsen-ten Berg *et al.*<sup>32</sup> performed extensive clinical evaluation and classical and molecular cytogenetic (GTG banding, FISH and array-CGH) and *WFS1* gene mutation analyses. They detected an 8.3 Mb terminal deletion and an adjacent 2.6 Mb inverted duplication in the short arm of chromosome 4, which encompasses a gene associated with *WFS1*. In addition, a nonsense mutation in exon 8 of the *WFS1* gene was found on the structurally normal chromosome 4. The combination of the 4p deletion with the *WFS1* point mutation explains the complex phenotype presented by this patient. This case further illustrates that unmasking of hemizygous recessive mutations by chromosomal deletions represents an additional explanation for the phenotypic variability observed in chromosomal deletion disorders<sup>32</sup>.

While DNFA6/14/38 is characterized by low frequency sensorineural hearing loss (LFSNHL), in contrast, WS is associated with various hearing severities ranging from normal to profound hearing loss that is dissimilar to LFSNHL. To confirm whether in patients with non-syndromic hearing loss, *WFS1* mutations are found restrictively in patients with LFSNHL and to summarize the mutation spectrum of *WFS1* found in the Japanese population, Fukuoka *et al.*<sup>33</sup> screened 206 Japanese autosomal dominant and 64 autosomal recessive (sporadic) non-syndromic hearing loss probands with various severities of hearing loss. They found three independent autosomal dominant families associated with two different *WFS1* mutations, A716T and E864K, previously detected in families with European ancestry. Identification of the same mutations in independent families with different racial backgrounds suggests that both sites are likely to be mutational hot spots. All three families with *WFS1* mutations in this study showed a similar phenotype, LFSNHL, as in previous reports. In this study, one-third (three out of nine) of the families with autosomal dominant LFSNHL had mutations in the *WFS1* gene, indicating that in non-syndromic hearing loss *WFS1* is restrictively and commonly found within families with

autosomal dominant LFSNHL<sup>33</sup>. A Taiwanese family with LFSNHL was phenotypically characterized using audiological examinations and pedigree analysis. Genetic characterization was performed by direct sequencing of *WFS1* and mutation analysis. Pure tone audiometry confirmed that the family members affected with LFSNHL had bilateral sensorineural hearing loss equal to or below 2,000 Hz. The hearing loss threshold of the affected members showed no progression, a characteristic that was consistent with a mutation in the *WFS1* gene located in the DFNA6/14/38 locus. Pedigree analysis showed a hereditary autosomal dominant pattern characterized by full penetrance. Among several polymorphisms, a missense mutation Y669H (2005T>C) in exon 8 of *WFS1* was identified in members of a Taiwanese family diagnosed with LFSNHL but not in any of the control individuals<sup>34</sup>.

Cano *et al.*<sup>35</sup> described 12 patients from 11 families with WS. They reported eight novel (A214fsX285, L293fsX303, P346L, I427S, V503fsX517, R558C, S605fsX711, P838L) and seven previously reported mutations. They also looked for genotype-phenotype correlations both in patients included in this study and 19 additional patients with WS who were previously reported. Subsequently, they performed a systematic review and meta-analysis of five published clinical and molecular studies of *WFS1* for genotype-phenotype correlation, combined with their current French patient group for a total of 96 patients. The presence of two inactivating mutations was shown to predispose to an earlier age of onset of both diabetes mellitus and optic atrophy. Moreover, the clinical expression of WS was more complete and occurred earlier in patients harboring no missense mutation<sup>35</sup>. Sandhu *et al.*<sup>36</sup> studied genes involved in pancreatic beta-cell function and survival, identifying associations between SNPs in *WFS1* and diabetes risk in UK populations that were replicated in an Ashkenazi population and in additional UK studies. In a pooled analysis comprising 9,533 cases and 11,389 controls, SNPs in *WFS1* were strongly associated with diabetes risk. Rare mutations in *WFS1* cause WS; using a gene-centric approach, they showed that variation in *WFS1* also predisposes to type 2 diabetes mellitus<sup>36</sup>.

Recently it has become apparent that not all diabetes mellitus presenting in childhood is type 1. Increasingly, type 2 diabetes mellitus, secondary diabetes, maturity onset diabetes of the young, and rare syndromic forms of diabetes, such as WS and Alström syndrome, have been identified in children. Although individually rare, collectively they make up about 5% of children seen in diabetes clinics. The importance of these syndromes for children lies in the recognition of treatable complications, and for their parents, the possibility of genetic counseling. The scientific importance is enormous as they are 'experiments of nature' that reveal basic mechanisms of insulin and glucose metabolism. Scientists are now able to offer mutation analysis to correlate the clinical pattern to the genotype, and seek novel therapeutic approaches based on the developing knowledge of gene and protein functions. Although its precise functions are unknown, Wolframin deficiency increases ER stress, impairs cell cycle progression and affects calcium homeostasis.

## REFERENCES

1. Wolfram DJ, Wagener HP. Diabetes mellitus and simple optic atrophy among siblings: report of four cases. *Mayo Clin Proc* 1938; 13: 715-718.
2. Barrett TG, Bunday SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. *Lancet* 1995; 346: 1458-1463.
3. Kinsley BT, Dumont RH, Swift M, Swift RJ. Morbidity and mortality in the Wolfram syndrome. *Diabetes Care* 1995; 18: 1566-1570.
4. Inoue H, Tanizawa Y, Wasson J, Behn P, Kalidas K, Bernal-Mizrachi E, Mueckler M, Marshall H, Donis-Keller H, Crock P, Rogers D, Mikuni M, Kumashiro H, Higashi K, Sobue G, Oka Y, Permutt MA. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). *Nat Genet* 1998; 20: 143-148.
5. Tyrer JH. A case of infantilism with goitre, diabetes mellitus, mental defect and bilateral primary optic atrophy. *Med J Aust* 1943; 2: 398-401.
6. Rose FC, Fraser GR, Friedmann AI, Kohner EM. The association of juvenile diabetes mellitus and optic atrophy: clinical and genetical aspects. *Q J Med* 1966; 35: 385-405.
7. Shaw DA, Duncan LJP. Optic atrophy and nerve deafness in diabetes mellitus. *J Neurol Neurosurg Psychiatry* 1958; 21: 47-49.
8. Rorsman G, Soderstrom N. Optic atrophy and juvenile diabetes mellitus with familial occurrence. *Acta Med Scand* 1967; 182: 419-425.
9. Wit JM, Donckerwolcke RAMG, Schulpen TWJ, Deutman AF. Documented vasopressin deficiency in a child with Wolfram syndrome. *J Pediatr* 1986; 109: 493-494.
10. Salih MAM, Tuvemo T. Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD syndrome): a clinical study in two Sudanese families. *Acta Paediatr Scand* 1991; 80: 567-572.
11. Borgna-Pignatti C, Marradi P, Pinelli L, Monetti N, Patrini C. Thiamine-responsive anemia in DIDMOAD syndrome. *J Pediatr* 1989; 14: 405-410.
12. Swift RG, Perkins DO, Chase CL, Sadler DB, Swift M. Psychiatric disorders in 36 families with Wolfram syndrome. *Am J Psychiatry* 1991; 148: 775-779.
13. Swift RG, Polymeropoulos MH, Torres R, Swift M. Predisposition of Wolfram syndrome heterozygotes to psychiatric illness. *Mol Psychiatry* 1998; 3: 86-91.
14. Rando TA, Horton JC, Layzer RB. Wolfram syndrome: evidence of a diffuse neurodegenerative disease by magnetic resonance imaging. *Neurology* 1992; 42: 1220-1224.
15. Scolding NJ, Kellar-Wood HF, Shaw C, Shneerson JM, Antoun N. Wolfram syndrome: hereditary diabetes mellitus with brainstem and optic atrophy. *Ann Neurol* 1996; 39: 352-360.
16. Mathis S, Paquis V, Mesnage V, Balaboï I, Gil R, Gilbert B, Neau JP. Wolfram's syndrome presenting as a cerebellar ataxia. *Rev Neurol (Paris)* 2007; 163: 197-204.
17. Gabreëls BA, Swaab DF, de Kleijn DP, Dean A, Seidah NG, Van de Loo JW, Van de Ven WJ, Martens GJ, Van Leeuwen FW. The vasopressin precursor is not processed in the hypothalamus of Wolfram syndrome patients with diabetes insipidus: evidence for the involvement of PC2 and 7B2. *J Clin Endocrinol Metab* 1998; 83: 4026-4033.
18. Medlej R, Wasson J, Baz P, Azar S, Salti I, Loiselet J, Permutt A, Halaby G. Diabetes mellitus and optic atrophy: a study of Wolfram syndrome in the Lebanese population. *J Clin Endocrinol Metab* 2004; 89: 1656-1661.
19. El-Shanti H, Lidral AC, Jarrah N, Druhan L, Ajlouni K. Homozygosity mapping identifies an additional locus for Wolfram syndrome on chromosome 4q. *Am J Hum Genet* 2000; 66: 1229-1236.
20. Eiberg H, Hansen L, Kjer B, Hansen T, Pedersen O, Bille M, Rosenberg T, Tranebjaerg L. Autosomal dominant optic atrophy associated with hearing impairment and impaired glucose regulation caused by a missense mutation in the WFS1 gene. *J Med Genet* 2006; 43: 435-440.
21. Cano A, Molines L, Valéro R, Simonin G, Paquis-Flucklinger V, Vialettes B; French Group of Wolfram Syndrome. Microvascular diabetes complications in Wolfram syndrome (diabetes insipidus, diabetes

- mellitus, optic atrophy, and deafness [DIDMOAD]): an age- and duration-matched comparison with common type 1 diabetes. *Diabetes Care* 2007; 30: 2327-2330.
22. Ari S, Keklikçi U, Çaça I, Unlü K, Kayabaşı H. Wolfram syndrome: case report and review of the literature. *Compr Ther* 2007; 33: 18-20.
  23. Simsek E, Simsek T, Tekgül S, Hosal S, Seyrantepe V, Aktan G. Wolfram (DIDMOAD) syndrome: a multi-disciplinary clinical study in nine Turkish patients and review of the literature. *Acta Paediatr* 2003; 92: 55-61.
  24. Zatyka M, Ricketts C, da Silva Xavier G, Minton J, Fenton S, Hofmann-Thiel S, Rutter GA, Barrett TG. Sodium-potassium ATPase 1 subunit is a molecular partner of Wolframin, an endoplasmic reticulum protein involved in ER stress. *Hum Mol Genet* 2008; 17: 190-200.
  25. Lou Frances G, Soto de Ruiz S, López-Madrado Hernández MJ, Macipe Costa R, Rodríguez Rigual M. [Wolfram syndrome. Clinical and genetic study in two families - in Spanish]. *An Pediatr (Barc)* 2008; 68: 54-57.
  26. Florez JC, Jablonski KA, McAteer J, Sandhu MS, Wareham NJ, Barroso I, Franks PW, Altshuler D, Knowler WC; for the Diabetes Prevention Program Research Group. Testing of diabetes-associated WFS1 polymorphisms in the Diabetes Prevention Program. *Diabetologia* 2008; 51: 451-457.
  27. Franks PW, Rolandsson O, Debenham SL, Fawcett KA, Payne F, Dina C, Froguel P, Mohlke KL, Willer C, Olsson T, Wareham NJ, Hallmans G, Barroso I, Sandhu MS. Replication of the association between variants in WFS1 and risk of type 2 diabetes in European populations. *Diabetologia* 2008; 51: 458-463.
  28. Amr S, Heisey C, Zhang M, Xia XJ, Shows KH, Ajlouni K, Pandya A, Satin LS, El-Shanti H, Shiang R. A homozygous mutation in a novel zinc-finger protein, ERIS, is responsible for Wolfram syndrome. *Am J Hum Genet* 2007; 81: 673-683.
  29. Di Lorenzo C, Sances G, Di Lorenzo G, Rengo C, Ghiotto N, Guaschino E, Perrotta A, Santorelli FM, Grieco GS, Troisi A, Siracusano A, Pierelli F, Nappi G, Casali C. The wolframin His611Arg polymorphism influences medication overuse headache. *Neurosci Lett* 2007; 424: 179-184.
  30. Sayouti A, Benhaddou R, Khoumiri R, Gaboune L, Guelzim H, Benfdil N, Moutaoukil A. [Two cases of Wolfram syndrome - in French]. *J Fr Ophtalmol* 2007; 30: 607-609.
  31. Hasegawa A, van der Blik AM. Inverse correlation between expression of the Wolfs Hirschhorn candidate gene *Letm1* and mitochondrial volume in *C. elegans* and in mammalian cells. *Hum Mol Genet* 2007; 16: 2061-2071.
  32. Flipsen-ten Berg K, van Hasselt PM, Eleveld MJ, van der Wijst SE, Hol FA, de Vroede MA, Beemer FA, Hochstenbach PF, Poot M. Unmasking of a hemizygous WFS1 gene mutation by a chromosome 4p deletion of 8.3 Mb in a patient with Wolf-Hirschhorn syndrome. *Eur J Hum Genet* 2007; 15: 1132-1138.
  33. Fukuoka H, Kanda Y, Ohta S, Usami S. Mutations in the WFS1 gene are a frequent cause of autosomal dominant nonsyndromic low-frequency hearing loss in Japanese. *J Hum Genet* 2007; 52: 510-515.
  34. Tsai HT, Wang YP, Chung SF, Lin HC, Ho GM, Shu MT. A novel mutation in the WFS1 gene identified in a Taiwanese family with low-frequency hearing impairment. *BMC Med Genet* 2007; 8: 26.
  35. Cano A, Rouzier C, Monnot S, Chabrol B, Conrath J, Lecomte P, Delobel B, Boileau P, Valero R, Procaccio V, Paquis-Flucklinger V; French Group of Wolfram Syndrome, Vialettes B. Identification of novel mutations in WFS1 and genotype-phenotype correlation in Wolfram syndrome. *Am J Med Genet A* 2007; 143: 1605-1612.
  36. Sandhu MS, Weedon MN, Fawcett KA, Wasson J, Debenham SL, Daly A, Lango H, Frayling TM, Neumann RJ, Sherva R, Blech I, Pharoah PD, Palmer CN, Kimber C, Tavendale R, Morris AD, McCarthy MI, Walker M, Hitman G, Glaser B, Permutt MA, Hattersley AT, Wareham NJ, Barroso I. Common variants in WFS1 confer risk of type 2 diabetes. *Nat Genet* 2007; 39: 951-953.