Mammalian Genome (2024) 35:1–12
https://doi.org/10.1007/s00335-023-10028-x

# Comprehensive overview of disease models for Wolfram syndrome: toward effective treatments

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Received: 15 November 2023 / Accepted: 27 December 2023 / Published online: 13 February 2024


**Abstract**
Wolfram syndrome (OMIM 222300) is a rare autosomal recessive disease with a devastating array of symptoms, including diabetes mellitus, optic nerve atrophy, diabetes insipidus, hearing loss, and neurological dysfunction. The discovery of the causative gene, *WFS1*, has propelled research on this disease. However, a comprehensive understanding of the function of *WFS1* remains unknown, making the development of effective treatment a pressing challenge. To bridge these knowledge gaps, disease models for Wolfram syndrome are indispensable, and understanding the characteristics of each model is critical. This review will provide a summary of the current knowledge regarding WFS1 function and offer a comprehensive overview of established disease models for Wolfram syndrome, covering animal models such as mice, rats, flies, and zebrafish, along with induced pluripotent stem cell (iPSC)-derived human cellular models. These models replicate key aspects of Wolfram syndrome, contributing to a deeper understanding of its pathogenesis and providing a platform for discovering potential therapeutic approaches.

## Introduction

Wolfram Syndrome (OMIM 222300) is a rare autosomal recessive disease characterized by several symptoms, including diabetes mellitus, optic nerve atrophy, diabetes insipidus, hearing loss, and neurological dysfunction. Two types of Wolfram syndrome have been identified: type 1 and type 2, caused by pathogenic variants of *WFS1* and *CISD2*, respectively. Most Wolfram syndrome cases are classified as type 1, so we will refer to them as "Wolfram syndrome" throughout this review. Since the discovery of *WFS1* as the causative gene of Wolfram syndrome, several animal and cellular models have been established. These disease models are indispensable tools in the research on Wolfram syndrome. However, a comprehensive summary of the characteristics and phenotypes of these experimental models is lacking. Therefore, this review aims to fill this gap by providing an overview of the animal and cellular models of Wolfram syndrome established to date. In this review, we first discuss (1) the clinical symptoms of Wolfram syndrome, (2) the function of *WFS1* and the pathophysiology caused by its abnormalities, and (3) the characteristics of disease models of Wolfram syndrome.

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## Clinical features of Wolfram syndrome and the discovery of *WFS1*

This section describes the clinical features of Wolfram syndrome and the disease concept associated with the causative gene *WFS1*.

### Major symptoms of Wolfram syndrome

The first cases of Wolfram syndrome were reported by Wolfram and Wagener (1938). The report described four siblings who developed juvenile-onset diabetes mellitus and optic nerve atrophy. Subsequently, these patients also developed hearing loss and neurogenic bladder (Paley and Tunbridge 1956). In 1956, Paley and Tunbridge reported two additional cases of diabetes and optic nerve atrophy, suggesting a hereditary component (Paley and Tunbridge 1956). In 1977, a comprehensive review of 91 cases by Cremers et al. (1977) led to the official designation of this condition as "Wolfram

syndrome." Since then, numerous reports on the clinical symptoms of patients have emerged. The first nationwide survey was conducted and reported by Barrett et al. (1995), revealing a prevalence of Wolfram syndrome at 1 in 770,000. Typically, patients with Wolfram syndrome develop diabetes mellitus at a median age of 6 years and optic atrophy around 11 years. Diabetes insipidus and sensorineural hearing loss typically manifest in the second decade of life, while renal tract abnormalities and neurological complications such as cerebellar ataxia appear by the fourth decade. Neurological and urinary tract manifestations are the most common causes of morbidity and mortality (Kinsley et al. 1995). Wolfram syndrome is characterized by a reduced size of intracranial volume, particularly in the brainstem and cerebellum, leading to balance impairment (Hershey et al. 2012; Pickett et al. 2012). However, the severity of these symptoms can vary among individuals with Wolfram syndrome (De Franco et al. 2017).

## Discovery of WFS1

Wolfram syndrome was previously believed to be a mitochondrial disease due to the similarities in symptoms and the presence of mitochondrial DNA deletions in some patients (Bu and Rotter 1993; Bundey et al. 1993; Rötig et al. 1993; Vora and Lilleyman 1993). However, subsequent cases demonstrated the absence of mitochondrial DNA abnormalities, and the inheritance pattern suggested an abnormality in the nuclear genome of patients with Wolfram syndrome. Linkage analysis suggested the presence of a causative gene for Wolfram syndrome on chromosome 4p16 (Polymeropoulos et al. 1994). In 1998, Inoue et al., followed soon after by Strom et al., identified the *WFS1* gene (Inoue et al. 1998; Strom et al. 1998) (Fig. 1). Since the discovery of *WFS1*, the understanding of the pathogenesis of Wolfram syndrome has remarkably advanced. Approximately 200 *WFS1* variants associated with Wolfram syndrome have been reported, mostly found in exon 8 of *WFS1* (Smith et al. 2004). *WFS1* encodes the protein WFS1, also known as wolframin, which is an endoplasmic reticulum (ER)-membrane protein with multiple transmembrane domains comprising 890 amino acids (Strom et al. 1998; Takeda et al. 2001). WFS1 is expressed ubiquitously in various tissues, with the highest levels observed in the pancreas, heart, and brain, particularly in the hippocampus, amygdaloid area, and olfactory tubercle (Hofmann et al. 2003; Takeda et al. 2001). Recent studies have reported predominant localization of WFS1 in the ER membrane, particularly in the mitochondria-associated ER membranes, which serve as contact sites between the ER and mitochondria (Angebault et al. 2018; La Morgia et al. 2020).

## Wolfram syndrome and WFS1-related disorders

Wolfram syndrome, a rare disorder caused by recessive *WFS1* variants, is now recognized to exhibit a phenotypic spectrum. Recent findings suggest that its frequency may be higher in certain races and populations than previously assumed (Bansal et al. 2018; De Franco et al. 2017; Li et al. 2020; Marchand et al. 2021). Moreover, there are related disorders caused by a dominant inheritance form of *WFS1*, known as "*WFS1*-related disorders" or "Wolfram-like syndrome." These disorders manifest with one or more symptoms observed in Wolfram syndrome. The severity and symptoms of *WFS1*-related disorders can vary, ranging from mild diabetes mellitus, hearing loss, congenital cataracts, and optic atrophy developing independently to severe neonatal cases that exhibit all these symptoms (Kobayashi et al. 2018; Mets et al. 2010; Morikawa et al. 2017). It has also been reported that specific heterozygous *WFS1* variants can lead to nonsyndromic low-frequency sensorineural hearing loss (Bespalova et al. 2001; Cryns et al. 2002; Young et al. 2001).

## *WFS1* functions and their anomalies

Some *WFS1* variants have also been implicated in other types of diabetes. Several large-scale genome-wide association studies have reported that several single nucleotide polymorphisms (SNPs) in *WFS1* are associated with an increased genetic risk for type 2 diabetes mellitus (T2DM), irrespective of racial differences (Cheurfa et al. 2011; Elek

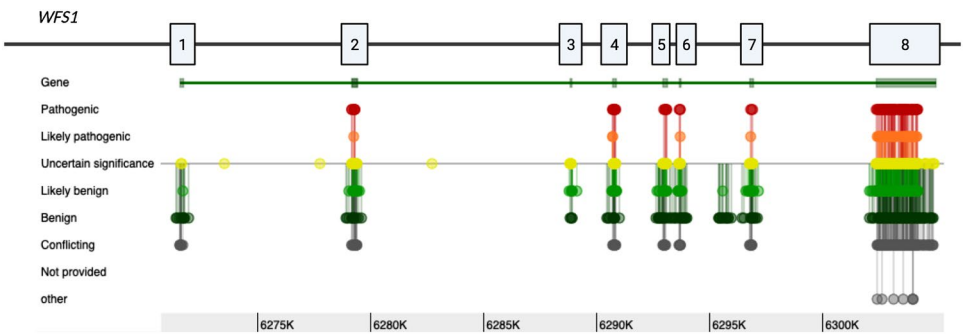


**Fig. 1** The structure of *WFS1*. *WFS1* consists of eight exons, with the largest one being exon 8. The location of reported variants is depicted in different colors. The image has been adapted from Clinvar (https://www.ncbi.nlm.nih.gov/clinvar/), and the information was accessed on July 23, 2023

et al. 2015; Heni et al. 2010; Lee et al. 2008; Long et al. 2012; Lyssenko et al. 2008; Sandhu et al. 2007; Sparsø et al. 2008; van Hoek et al. 2008; Westermark et al. 2010). However, a meta-analysis has shown that two specific *WFS1* SNPs, rs734312 and rs10010131, have a significant protective effect against the risk of developing T2DM (Cheng et al. 2013). Accordingly, understanding the pathogenesis of Wolfram syndrome and *WFS1*-related disorders may provide valuable insights into the pathogenesis of other types of diabetes, including T2DM. In this section, we describe the known physiological functions of *WFS1* and the pathological conditions that arise due to its abnormalities.

## Interaction between WFS1 and $Ca^{2+}$ channels or pumps

The ER serves as an intracellular $Ca^{2+}$ store, and WFS1 is expressed on the ER membrane. Therefore, numerous studies have explored the relationship between WFS1 and intracellular $Ca^{2+}$ homeostasis (La Morgia et al. 2020; Nguyen et al. 2020; Osman et al. 2003). The first study to demonstrate a connection between WFS1 and intracellular $Ca^{2+}$ was reported by Osman et al. (2003), who showed elevated levels of intracellular $Ca^{2+}$ in *Xenopus* oocytes overexpressing *WFS1*.

Takei et al. first revealed the relationship between $Ca^{2+}$ concentration in the ER and the expression level of WFS1 (Takei et al. 2006). They found that WFS1 regulates ER $Ca^{2+}$ storage and cytosolic $Ca^{2+}$ homeostasis by increasing the $Ca^{2+}$ uptake and store-operated $Ca^{2+}$ entry (SOCE). This regulation involves the modulation of $Ca^{2+}$ pumps and channels, such as sarcoendoplasmic reticulum ATPase (SERCA) and inositol 1,4,5-trisphosphate receptor ($IP_3R$), localized on the ER membrane (Kunnappallil and Hasan 2022). WFS1 deficiency results in upregulated SERCA expression, leading to increased $Ca^{2+}$ pumping into the ER (Zatyka et al. 2015) (Fig. 2A). Additionally, WFS1 forms a complex with neuronal calcium sensor 1 (NCS1) and $IP_3R$ to facilitate $Ca^{2+}$ transfer between the ER and mitochondria. WFS1 deficiency reduces the expression level of NCS1, followed by impaired ER-mitochondrial contact and subsequent $Ca^{2+}$ uptake into the mitochondria (Angebault et al. 2018) (Fig. 2B). Therefore, therapeutic approaches targeting intracellular $Ca^{2+}$ signaling have been explored as potential treatments for Wolfram syndrome (Abreu et al. 2021; Akiyama et al. 2009; Clark et al. 2017; Crouzier et al. 2022a; Lu et al. 2014; Nguyen et al. 2020). Apart from its interactions with $Ca^{2+}$ pumps and channels, WFS1 also interacts with the $Na^+/K^+$ ATPase beta-1 subunit, the V1A subunit of the H1 ATPase, and the voltage-dependent anion channel isoform 1 (VDAC1) (Gharanei et al. 2013; Zatyka et al. 2008; Zatyka

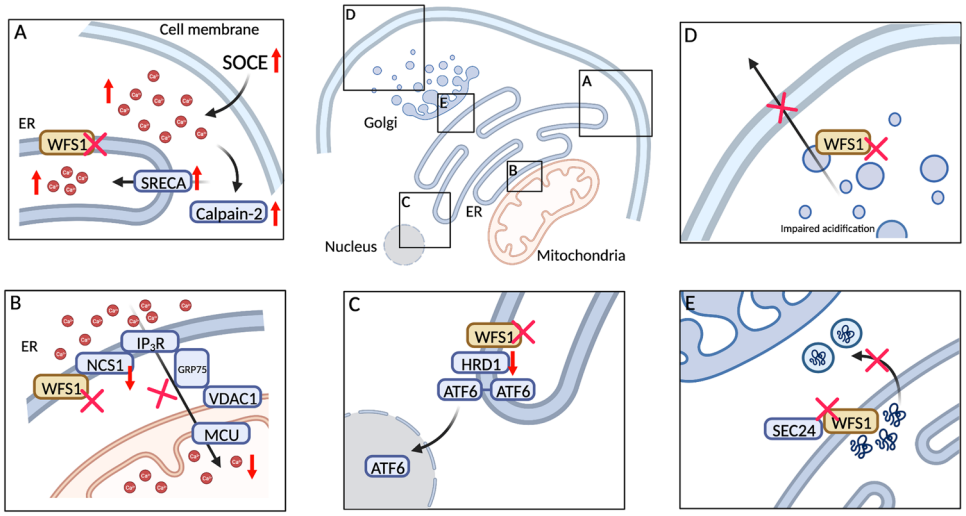


**Fig. 2** Multiple functions of WFS1. **A** WFS1 regulates $Ca^{2+}$ uptake in the ER by modulating SERCA activity. WFS1 dysfunction increases ER $Ca^{2+}$ levels and SOCE. Increased $Ca^{2+}$ concentration activates Calpain-2, leading to cell death. **B** WFS1 activates $IP_3R$ through NCS1 and stimulates $Ca^{2+}$ release from the ER. WFS1 dysfunction impairs $IP_3R$ activity, followed by decreased $Ca^{2+}$ release from the ER and $Ca^{2+}$ uptake into the mitochondria. **C** WFS1 stabilizes HRD1, an E3 ubiquitin ligase, and degrades ATF6. WFS1 abnormality induces the hyperactivation of ATF6. **D** WFS1 plays a vital role in maintaining the pH within secretory granules. WFS1 dysfunction leads to impaired granule acidification and insulin exocytosis. **E** The C-terminal of WFS1 binds to vesicular cargo proteins. The N-terminal of WFS1 is recognized by the protein transport protein SEC24, a component of coat protein complex II (COPII). WFS1 dysfunction disrupts the generation of mature COPII vesicles and hinders intercellular trafficking from the endoplasmic reticulum (ER) to the Golgi complex. *ATF6* activating transcription factor 6, *HRD1* HMG-CoA reductase degradation 1 homolog, *SERCA* sarcoendoplasmic reticulum ATPase, *SOCE* store-operated $Ca^{2+}$ entry, *$IP_3R$* 1,4,5-trisphosphate receptor, *NCS1* neuronal calcium sensor 1, *GRP75* glucose-regulated protein 75, *VDAC1* voltage-dependent anion channel 1, *MCU* mitochondrial $Ca^{2+}$ uniporter. (Created with BioRender.com)

et al. 2023). In *WFS1*-depleted cells, the H1 ATPase V1A subunit is degraded more rapidly (Gharanei et al. 2013).

### WFS1 as a component of unfolded protein response

The link between WFS1 and ER stress was first described by Ueda et al. (2005). They demonstrated that the *WFS1* expression level increased in response to ER stress. The gene expression levels of *Wfs1* are considered ER stress markers (Lipson et al. 2006) due to the presence of a conserved sequence in the promoter region similar to the ER stress response element (Kakiuchi et al. 2006). ER stress-induced *WFS1* upregulation requires the activation of inositol requiring 1 and PKR-like endoplasmic reticulum kinase, which are key regulators of the unfolded protein response (UPR) (Fonseca et al. 2005). Another UPR regulator, activating transcription factor (ATF) 6β, binds to the *Wfs1* gene promoter and induces both gene and protein expression (Odisho et al. 2015).

WFS1 has additional roles in the regulation of ER stress and protein degradation. It stabilizes the E3 ubiquitin ligase HRD1 and regulates the degradation of ATF6α by facilitating ATF6 transport to the proteasome (Fonseca et al. 2010) (Fig. 2C). This means WFS1 acts as a UPR regulator; its deficiency in pancreatic β-cells induces pathogenic ER stress, leading to impaired cell cycle and accelerated cell apoptosis (Yamada et al. 2006). However, considering their close interaction, both ER stress and intracellular $Ca^{2+}$ homeostasis may be involved in the pathogenesis of Wolfram syndrome. In fact, *WFS1* deficiency induces ER stress, resulting in $IP_3R$ dysfunction and disturbed cytosolic $Ca^{2+}$ homeostasis, which subsequently affects mitochondrial dynamics (Blackstone et al. 2016). This leads to inhibited mitochondrial fusion and trafficking, as well as augmented mitophagy, contributing to delayed neuronal development. ER stress is recognized for disrupting intracellular $Ca^{2+}$ homeostasis and inducing cellular inflammation. The concept of "sterilized inflammation," which refers to non-infectious inflammation triggered by pathogenic ER stress (Lerner et al. 2012; Oslowski et al. 2012), has recently emerged. In line with these observations, ER stress-induced sterilized inflammation caused by WFS1 dysfunction accelerates disease progression in Wolfram syndrome (Morikawa et al. 2022; Panfili et al. 2021).

### WFS1 function in intracellular trafficking

WFS1 localization extends beyond the ER to include secretory granules (Hatanaka et al. 2011). In *WFS1*-deficient pancreatic β-cells, insulin secretory granule acidification becomes impaired, leading to impaired insulin exocytosis (Hatanaka et al. 2011) (Fig. 2D). The acidification of insulin granule is necessary for efficient proinsulin processing because endopeptidase PC1/3 and PC2 activate with a low pH optimum. While the precise interaction between WFS1 expressed on the insulin granule membrane and impaired insulin granule acidification has not been elucidated, it is speculated that WFS1 regulates the activities of V-type $H^+$-ATPase and CLC-3$Cl^-$ channels expressed on the insulin granule membrane (Hatanaka et al. 2011). More recently, it was demonstrated that WFS1 serves as a vesicular cargo protein involved in intracellular trafficking (Wang et al. 2021). Specifically, the C-terminus of WFS1 directly binds to transported proteins within the ER lumen, while the N-terminus of WFS1 interacts with SEC24, a subunit of the coat protein complex II (COPII) located in the cytoplasm. This interaction allows for vesicular transport from the ER to the Golgi (Fig. 2E). This function of WFS1 has been shown to be necessary for the transportation of proteins such as proinsulin from the ER to the Golgi in pancreatic β-cells (Wang et al. 2021).

## Experimental models of Wolfram syndrome

Experimental models are indispensable tools for conducting research to understand the pathogenesis of Wolfram syndrome and to develop therapeutic strategies. Over the years, several disease models have been established to study this condition. In the 2000s, *Wfs1* knockout mice were generated as an early animal model. Subsequently, in the 2010s, disease models were extended to include rats, flies, and zebrafish. Recently, a *Wfs1* pathogenic variant knock-in mouse model has also been reported. In this section, we summarize the phenotypic characteristics observed in these Wolfram syndrome animal models and also include information on induced pluripotent stem cell (iPSC)-derived cellular models (Table 1).

### Animal models of Wolfram syndrome

The first animal model, Wolfram syndrome, was established by Ishihara et al. (2004). The whole-body *Wfs1*-deficient B6 background mice exhibited decreased pancreatic insulin content at 2 weeks old, impaired glucose homeostasis, and decreased insulin secretion around 17 weeks old. The diabetic phenotype in these mice resulted from ER stress-induced pancreatic β-cell death and was accelerated by crossing with agouti lethal yellow mice, a model that develops obesity, insulin resistance, and pancreatic β-cell hyperplasia (Akiyama et al. 2009). Similar to Wolfram syndrome patients, these mice also exhibited symptoms of central diabetes insipidus due to arginine vasopressin (AVP) deficiency (Kurimoto et al. 2021), impaired retinal functions (Bonnet Wersinger et al. 2014), and psychiatric symptoms observed in behavioral studies (Kato et al. 2008). In addition

**Table 1** Animal models of Wolfram syndrome

| Reference | Species (strain) | Specificity | Targeted region of *Wfs1* | Phenotype/onset or tested age |
|---|---|---|---|---|
| Ishihara et al. (2004) | Mouse [(129 Sv × B6) × B6] F2<br>Mouse (B6) | Whole body *Wfs1* KO | Exon 2 (replaced by neomycin-resistance gene) | Non-fasted hyperglycemia/16 weeks (Ishihara et al. 2004)<br>Decreased whole-pancreas insulin content/2 weeks old (Ishihara et al. 2004)<br>Impaired glucose homeostasis and insulin secretion on OGTT/17 weeks old (Ishihara et al. 2004)<br>Decreased AVP secretion (Kurimoto et al. 2021)<br>Alternation in emotionally triggered behavior, social interaction, and behavioral despair/34 weeks old (Kato et al. 2008)<br>Impaired photoreceptor and inner retinal functions. Elevated ER stress in the retina (Bonnet Wersinger et al. 2014) |
| Riggs et al. (2005) | Mouse (B6) | Conditional *Wfs1* KO (pancreatic β-cell) | Exon 8 | Glucose intolerance and insulin deficiency/12 weeks old |
| Luuk et al. (2008)<br>Kõks et al. (2009) | Mouse (B6) (129S6) | Whole body *Wfs1* KO | Exon 8 (replaced by *LacZ*) | Impaired glucose homeostasis/6 weeks old (Abreu et al. 2020)<br>Lower ratio of retinal thickness/longitudinal diameter (Waszczykowska et al. 2020)<br>Impaired behavioral adaptation/2–4 months old (Luuk et al. 2009)<br>Hearing loss/4 months old (Richard et al. 2023)<br>Impaired fertility (Noormets et al. 2009)<br>Reduced volume of the optic nerve, brain stem, and cortex (Blackstone et al. 2016)<br>Dopaminergic system impairment (Visnapuu et al. 2013a)<br>Increased sensitivity to the serotonin inhibitor (Visnapuu et al. 2013b)<br>Lower body mass, food intake, and serum leptin levels than wild type (Noormets et al. 2014)<br>Impaired insulin secretion in high-fat diet-fed *Wfs1* heterozygous mice (Ivask et al. 2021) |
| Richard et al. (2023) | Mouse (B6) | Whole body *Wfs1* E864K KI | Exon 8 (E864K KI) | Hearing loss/post-natal day 27–29<br>Vestibular deficits/post-natal day 21 (Richard et al. 2023) |

**Table 1** (continued)

| Reference | Species (strain) | Specificity | Targeted region of *Wfs1* | Phenotype/onset or tested age |
|---|---|---|---|---|
| Plaas et al. (2017) | Rat (Sprague–Dawley rats) | Whole body *Wfs1* KO | Exon 5 (deleted 27 amino acids (aa 212–238) and a substitution of serine to alanine at aa 239) | Impaired glucose-stimulated insulin secretion/3 months old (Plaas et al. 2017)<br>Hyperglycemia, severe body weight loss/ by 12 months old (Plaas et al. 2017)<br>Retinal gliosis, optic nerve atrophy/15 months old (Plaas et al. 2017)<br>Decreased medullary volume (Plaas et al. 2017)<br>Low-frequency, sensorineural hearing loss/6.5 months old (Jagomäe et al. 2021) |
| Sakakibara et al. (2018) | Drosophila | Conditional *wfs1* KO (neurons, glial cells) | *Drosophila wfs1* (CG4917, *WFS1* homolog) | Behavioral deficits, age-associated neurodegeneration (Sakakibara et al. 2018) |
| Kunnappallil and Hasan (2022) | Drosophila | Whole body *wfs1* KI<br>Conditional (neurons) *wfs1* KD | *Drosophila wfs1* (CG4917, *WFS1* homolog)<br>Homozygous null variant ($wfs1^{e03461}/wfs1^{e03461}$)<br>C-terminal truncated variant ($wfs1^{MI14041}$)<br>Pan- or dopaminergic-neuronal *wfs1* KD | Flight less ($wfs1^{e03461}/wfs1^{e03461}$)/5 days old (Kunnappallil and Hasan 2022)<br>Flight defect ($wfs1^{MI14041}$)/20 days old (Kunnappallil and Hasan 2022)<br>Flight defect (pan- or dopaminergic-neuronal *wfs1* KD)/5 days old (Kunnappallil and Hasan 2022) |
| Cairns et al. (2021) | Zebrafish | Whole body $wfs1a^{W692X}$ (sa10021) or $wfs1b^{W493X}$ (sa16422) | *wfs1a* or *wfs1b* (orthologues in zebrafish) | Neurodegeneration, loss of retinal ganglion cells, and visual dysfunction in zebrafish carrying $wfs1b^{W493X}$ (Cairns et al. 2021) |
| Crouzier et al. (2022b) | Zebrafish | Whole body $wfs1a^{C825X}$ (sa11465) or $wfs1b^{W493X}$ (sa16422) | *wfs1a* or *wfs1b* (orthologues in zebrafish) | Enlarged ear area and decreased rod cells in retia ($wfs1a^{C825X}$)<br>Mitochondrial dysfunction ($wfs1b^{W493X}$)<br>Decreased expression of UPR-related genes in physiological conditions and impaired visual function ($wfs1a^{C825X}$, $wfs1b^{W493X}$) (Crouzier et al. 2022b) |

*B6* C57 BL/6, *KO* knock out, *KI* knock-in, *OGTT* oral glucose tolerance test, *KD* knockdown, *UPR* unfolded protein response

to the B6 strain, another whole-body *Wfs1* knockout mouse model on the 129S6 background was developed (Kõks et al. 2009; Luuk et al. 2008). These 129S6 mice, in which LacZ replaces exon 8 of *Wfs1*, showed an earlier onset of diabetes compared to the B6 strain (Abreu et al. 2020). Interestingly, males were found to be at higher risk of developing diabetes than females (Noormets et al. 2011). The phenotype of this 129S6-background mouse model is well studied, and besides the diabetic phenotype, this mouse model recapitulates many of the symptoms observed in patients with Wolfram syndrome (Blackstone et al. 2016; Ivask et al. 2021; Luuk et al. 2009; Noormets et al. 2009, 2014; Richard et al. 2023; Visnapuu et al. 2013a, b; Waszczykowska et al. 2020). The only *Wfs1*-conditional knockout mouse model was reported by Riggs et al. These B6 background mice, with specifically knocked out *Wfs1* in pancreatic β-cells, develop glucose intolerance and insulin deficiency by 12 weeks of age (Riggs et al. 2005). Most recently, a *Wfs1* E864K knock-in mouse model was reported (Richard et al. 2023). These *Wfs1* E864K knock-in mice develop an early onset of severe vestibular dysfunction besides hearing loss. Human patients with Wolfram syndrome carrying the *WFS1* p.E864K variant develop low-frequency sensorineural hearing loss, optic atrophy, and impaired glucose tolerance. However, no vestibular neuropathy has been reported. These facts suggest that the role of *WFS1* in the human vestibular system may not be as crucial as in rodents.

Besides the mouse model, the *Wfs1*-deficient rat is a well-established animal model for Wolfram syndrome (Plaas et al. 2017). This model involves whole-body *Wfs1* knockout in Sprague–Dawley background rats, which show impaired glucose homeostasis starting at 3 months of age. At 15 months of age, these rats exhibit retinal gliosis, optic nerve atrophy, and reduced medullary volume. Although the onset age of each symptom is older than that in the mouse models, the larger body size of rats makes it advantageous for conducting therapeutic interventions and sample collection. Recently, the drosophila and zebrafish models with *WFS1* homolog knockout have been reported as additional models for Wolfram syndrome. Optical transparency of the zebrafish embryo enables the observation of neural development in vivo. Drosophila has a short generation time and a small body size, making it possible to test many potential therapeutic molecules. Using these Wolfram syndrome zebrafish and Drosophila models, phenotypes caused by *WFS1* deficiency, including neurodegeneration, visual dysfunction, and mitochondrial dysfunction, have been well studied (Cairns et al. 2021; Crouzier et al. 2022b; Kunnappallil and Hasan 2022; Sakakibara et al. 2018).

The pursuit of novel therapeutic approaches to combat Wolfram syndrome is actively underway. One promising strategy involves repurposing existing diabetic medications for the treatment of Wolfram syndrome, such as GLP1 receptor agonists (Panfili et al. 2023). Notably, exenatide and dulaglutide have been reported to improve glucose tolerance in Wolfram syndrome mouse models (Gorgogietas et al. 2023; Kondo et al. 2018; Sedman et al. 2016). Similarly, another GLP-1 receptor agonist, liraglutide, was found to prevent the development of glucose intolerance, reduce neuroinflammation, protect against retinal ganglion cell death, and delay the progression of hearing and vision loss in *Wfs1* mutant rat models (Jagomäe et al. 2021; Seppa et al. 2019, 2021; Toots et al. 2018).

## iPSC-derived models of Wolfram syndrome

The first successfully developed insulin-producing cells from patients with Wolfram syndrome were reported by Shang et al. (2014). In their study, the authors generated insulin-producing cells from skin fibroblast-derived iPSCs of Wolfram syndrome patients. These patient-derived insulin-producing cells showed lower insulin content and reduced tolerance to ER stress compared to controls. This cellular model provided crucial insights into ER stress-related diseases derived from human patients. Maxwell et al. improved the differential protocol for iPSC-derived β-cells (SC-β-cells) and used CRISPR/Cas9 techniques to explore the potential of gene therapy and personalized cell therapy for Wolfram syndrome (Maxwell et al. 2020). In their study, they successfully restored insulin secretion in patient-derived SC-β-cells through the correction of *WFS1*. Transplanting the gene-edited SC-β-cells into diabetic mice resulted in improved blood glucose profile. In addition, they found that SC-β-cells differentiated from Wolfram syndrome patients with mild *WFS1* variants retained their insulin secretory capacity (Kitamura et al. 2022). This indicates that these SC-β-cell models exhibit phenotypes consistent with the symptoms observed in patients. Using these SC-β-cell models, a combination treatment of 4-phenylbutyric acid and tauroursodeoxycholic acid has been demonstrated to effectively address the diabetic phenotype in Wolfram syndrome patients with the *WFS1* p.R558C variant (Kitamura et al. 2022). Besides pancreatic β-cells, neural cells have also been developed as a disease model from Wolfram syndrome patient iPSCs. Impaired neurite outgrowth was observed in neurons derived from Wolfram syndrome patients, and this morphological change was prevented by treatment with valproic acid (Pourtoy-Brasselet et al. 2021). Valproic acid has been reported to reduce ER stress and act as a histone deacetylase inhibitor for neurons. It is not clear how valproic acid promotes neurite outgrowth in the neuronal cell model of Wolfram syndrome. However, valproic acid may exert neuroprotective effects by reducing ER stress and through pleiotropic mechanisms. Zatyka et al. demonstrated that the interaction between WFS1 and VDAC1 is essential for mitochondrial function and dynamics in iPSC-derived neural

cells (Zatyka et al. 2023). These models could prove useful for studying the pathogenesis of brainstem atrophy and neurodegeneration observed in Wolfram syndrome.

## Future expectations

Numerous clinical and basic studies have significantly contributed to understanding the function of *WFS1* and advancing toward a cure for Wolfram syndrome. In future, further research is expected to uncover the unknown pathogenesis, particularly regarding the development of optic nerve atrophy and neurological symptoms associated with *WFS1* dysfunction. Furthermore, the development of therapeutic agents against Wolfram syndrome necessitates the use of patient-derived disease models. In addition to pancreatic β-cells and neural cells, the development of retinal ganglion, inner ear, and AVP-producing neural cells is important. These patient-derived cellular models can serve as invaluable tools for developing preclinical and personalized therapeutic reagents against visual impairment, hearing loss, and central diabetes insipidus in Wolfram syndrome. Research on Wolfram syndrome, including the development of various disease models, continues to serve as a prototype for studying ER stress-related diseases.

**Acknowledgements** SM thanks Dr. Fumihiko Urano (Washington University School of Medicine in St. Louis), Dr. Toshihiro Tajima (Department of Pediatrics, Jichi Medical University), and Dr. Atsushi Manabe (Department of Pediatrics, Hokkaido University Graduate School of Medicine) for their mentorship and Sachiko Nakayama, Yui Sakurai, Ryoko Miyoshi, Kaoru Yokoki, and Miki Kaiho (Department of Pediatrics, Hokkaido University) for their invaluable secretarial assistance.

**Author contributions** SM performed the literature search and wrote the draft. SM, KT, NK, NH, and AK critically reviewed the manuscript. All authors approved the final version of the manuscript to be published.

**Funding** SM received funding from The Japanese Society for Pediatric Endocrinology Future Development Grant, which is supported by Novo Nordisk Pharma Ltd. KT received funding from Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan (23K08011).

**Data availability** Data sharing not applicable – no new data generated.

## Declarations

**Conflict of interest** The authors have no conflict of interest to declare.

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