



WFS1 Spectrum Disorder

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Summary

Clinical characteristics

WFS1 spectrum disorder (*WFS1*-SD) comprises classic *WFS1* spectrum disorder and nonclassic *WFS1* spectrum disorder.

- **Classic *WFS1*-SD**, a progressive neurodegenerative disorder, is characterized by onset of diabetes mellitus and optic atrophy before age 16 years. Additional complications may include one or more of the following: variable hearing impairment / deafness, diabetes insipidus, neurologic abnormalities, neurogenic bladder, and psychiatric abnormalities.
- **Nonclassic *WFS1*-SD** is less common than classic *WFS1*-SD. Phenotypes that appear to be milder than classic *WFS1*-SD include: optic atrophy and hearing impairment; neonatal diabetes, profound congenital deafness, and cataracts; isolated diabetes mellitus; isolated congenital cataracts; and isolated congenital, slowly progressive, and low-frequency (<2000 Hz) sensorineural hearing loss.

Diagnosis/testing

- **Classic *WFS1*-SD.** The diagnosis is established in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *WFS1* identified by molecular genetic testing.

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- **Nonclassic WFS1-SD.** The diagnosis is established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant identified by molecular genetic testing.

Management

There is no cure for WFS1-SD.

Treatment of manifestations: Supportive care (based on the manifestations of classic or nonclassic WFS1-SD) is often provided by multidisciplinary specialists in diabetic care, endocrinology, ophthalmology and low vision, audiology, speech-language therapy, neurology, pulmonology, psychiatry / psychology / mental health, urology, gastroenterology, social work, and medical genetics.

Surveillance: For both classic and nonclassic WFS1-SD, regular monitoring of existing manifestations, the response of an individual to supportive care, and the emergence of new manifestations is recommended.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives in order to identify as early as possible those who would benefit from prompt initiation of treatment for the earliest manifestations of WFS1-SD: diabetes mellitus, optic atrophy, and sensorineural hearing loss.

Pregnancy management: Pregnant women with insulin-dependent diabetes mellitus, a characteristic of both classic and nonclassic WFS1-SD, have a two- to eightfold higher risk of having a child with a birth defect or a pattern of birth defects (diabetic embryopathy) than women who do not have diabetes. Optimizing glucose control before and during pregnancy can reduce – but not eliminate – the risk for diabetic embryopathy. Because women with classic WFS1-SD may develop diabetes insipidus during pregnancy, monitoring for diabetes insipidus during pregnancy is warranted. Consultation with a maternal fetal medicine specialist during pregnancy should be considered for all women with WFS1-SD.

Genetic counseling

- **Classic WFS1-SD** is caused by biallelic WFS1 pathogenic variants and is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a WFS1 pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- **Nonclassic WFS1-SD** is caused by a heterozygous pathogenic variant and can either be inherited in an autosomal dominant manner from an affected parent or result from a *de novo* WFS1 pathogenic variant. If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to sibs of inheriting the pathogenic variant is 50%. If the WFS1 pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism.
- **Both classic and nonclassic WFS1-SD.** Once the WFS1 pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for classic and nonclassic WFS1-SD are possible.

GeneReview Scope

This *GeneReview* encompasses the current understanding of the spectrum of WFS1 pathogenic variants and associated WFS1 spectrum disorder phenotypes. The intent of this chapter is to alert clinicians to the need to:

- Evaluate an individual with one or two WFS1 pathogenic variants for medically actionable manifestations in the associated WFS1 spectrum disorder phenotypes (regardless of the clinical findings that prompted molecular genetic testing);
- Provide genetic counseling based on each family's genetic finding.

GeneReview Scope: WFS1 Spectrum Disorder

Number of WFS1 Pathogenic Variants	Mode of Inheritance	Phenotypic Spectrum	Previous Phenotypic Designations
Two (i.e., biallelic) pathogenic variants	AR	Classic WFS1 spectrum disorder	<ul style="list-style-type: none"> • Wolfram syndrome type 1 • DIDMOAD (<i>diabetes insipidus, diabetes mellitus, optic atrophy, & deafness</i>)
One (i.e., heterozygous) pathogenic variant	AD (inherited or <i>de novo</i>)	Nonclassic WFS1 spectrum disorder (i.e., one isolated or several related findings) ¹	Wolfram syndrome-like disease

AD = autosomal dominant; AR = autosomal recessive

1. Includes isolated autosomal dominant WFS1-related nonsyndromic low-frequency sensorineural hearing loss (DFNA6/14/38).

Diagnosis

Suggestive Findings – Classic WFS1 Spectrum Disorder

Classic WFS1-SD **should be suspected** in individuals with any of the following clinical findings and family history.

Major clinical findings [Barrett et al 1995, Urano 2016]:

- Diabetes mellitus (onset age usually <16 years)
- Optic atrophy (onset age usually <16 years)

Additional clinical findings may include one or more of the following:

- High-tone sensorineural hearing impairment
- Cerebellar ataxia
- Psychiatric illness
- Neurogenic bladder (overactive or underactive)
- Other endocrine findings:
 - Central diabetes insipidus
 - Delayed puberty, particularly in males, associated with hypogonadism
 - Non-autoimmune hypothyroidism
- Structural congenital heart defects

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Suggestive Findings – Nonclassic WFS1 Spectrum Disorder

Nonclassic WFS1-SD **should be suspected** in individuals with any or the following clinical findings and family history.

Clinical findings (one or more) [Urano 2016]:

- Diabetes mellitus (onset age usually >16 years)
- Optic atrophy (onset age usually >16 years)
- Low-tone sensorineural hearing impairment including profound hearing loss in infancy
- Neonatal diabetes, congenital deafness, and/or cataracts

Family history may suggest autosomal dominant inheritance (e.g., affected males and females in more than one generation) or the proband may have a *de novo* pathogenic variant and be the only affected family member. Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis of *WFS1* Spectrum Disorder

The diagnosis of **classic *WFS1* spectrum disorder is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *WFS1* identified by molecular genetic testing (see Table 1).

The diagnosis of **nonclassic *WFS1* spectrum disorder is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

- **A deafness, retinal dystrophy, or monogenic diabetes multigene panel** that includes *WFS1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

Table 1. Molecular Genetic Testing Used in *WFS1* Spectrum Disorder

Gene ¹	Method	Proportion of Pathogenic Variants ² Identified by Method
<i>WFS1</i>	Sequence analysis ³	>95% ⁴
	Gene-targeted deletion/duplication analysis ⁵	3 reported ⁶

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Hardy et al [1999], Chaussonot et al [2015], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020] and Leiden Open Variation Database [Astuti et al 2017]

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. Three intragenic deletions of one or more exons have been described [Chaussonot et al 2015]. Structural rearrangements have also been described [Elli et al 2012].

Clinical Characteristics

Clinical Description – Classic *WFS1* Spectrum Disorder

Classic *WFS1* spectrum disorder (*WFS1*-SD) is characterized by childhood-onset diabetes mellitus and progressive optic atrophy, with variable hearing impairment / deafness, diabetes insipidus, neurologic abnormalities, and psychiatric abnormalities (see Table 2).

Table 2. Select Features Associated with Classic *WFS1* Spectrum Disorder

Feature	Common	Uncommon	Increases w/Age
Diabetes mellitus, childhood onset	●		
Diabetes mellitus, neonatal onset or adult onset		●	
Optic atrophy	●		
Sensorineural hearing impairment	●		
Cataracts		●	
Cerebellar ataxia			●
Autonomic dysfunction		●	
Bulbar dysfunction			●
Respiratory issues		●	
Developmental delay (in young children)		●	
Intellectual disability (in older children & adults)		●	
Psychiatric disorders	●		
Urinary tract issues ¹	●		
Bowel dysfunction	●		
Seizures		●	

Table 2. continued from previous page.

Feature	Common	Uncommon	Increases w/Age
Other endocrine findings	Central diabetes insipidus	●	
	Hypogonadism	●	
	Hypothyroidism		●
	Growth restriction		●

Based on data from Barrett et al [1995], Hardy et al [1999], Eiberg et al [2006], Plantinga et al [2008], Berry et al [2013], Haghghi et al [2013], De Franco et al [2017], and Lusk et al [2020]

1. Both functional (neurogenic bladder) and structural (upper urinary tract dilatation)

A comprehensive review of classic *WFS1*-SD, genotype-phenotype correlations, pathophysiology, and therapeutic strategies is available [Mishra et al 2021].

Classic *WFS1*-SD is a progressive neurodegenerative disorder characterized by onset of diabetes mellitus and optic atrophy before age 16 years, and frequently associated with sensorineural hearing loss, progressive neurologic abnormalities, and other endocrine abnormalities. Several organ systems may be affected; however, because only a minority of published cases have had extensive clinical workup, the natural history of these multiorgan findings in classic *WFS1*-SD is largely unknown.

The natural history of classic *WFS1*-SD was described in 45 individuals in 29 families in the United Kingdom [Barrett et al 1995]. Hearing impairment was present in 64% by age 20 years. Sixty percent of all individuals studied (mean age: 16 years, range: 5-32 years) had one or more of the following: cerebellar ataxia, peripheral neuropathy, intellectual disability, dementia, psychiatric illness, and urinary tract atony. In the families of British, Pakistani, and mixed Arab/African origin, *WFS1* pathogenic variants were subsequently identified in 17 of 19 probands [Hardy et al 1999].

Diabetes mellitus (DM). Median age of onset of DM was before age ten years (age range: <1-17 years). Almost all individuals with DM were insulin dependent. DM may present with ketoacidosis; however, the overall course is milder than that seen in isolated DM, with lower prevalence of microvascular complications.

Optic atrophy (OA) occurs eventually in all known individuals with classic *WFS1*-SD. OA is progressive; the median age of onset is before ten years. Note: Visual acuity of 6/60, signifying that the tested person sees at six meters that which an average person sees at 60 meters, is the definition of "registered vision impaired" in the United Kingdom and "legally blind" in the United States. Most individuals with classic *WFS1*-SD gradually progress to severe vision impairment (visual acuity of 3/60) over years.

Very rarely, *WFS1* pathogenic variants may be associated with isolated optic atrophy with autosomal recessive inheritance [Grenier et al 2016].

Sensorineural hearing impairment, present in about 66% of individuals with classic *WFS1*-SD, ranges from congenital deafness to a milder, sometimes progressive sensorineural hearing impairment. Median age of onset in one report was 12.5 years [Barrett et al 1995]. A multicenter study confirmed the preferential involvement of high frequencies and the slowly progressive rate of hearing loss, but did not confirm any sex differences in degree of hearing loss [Plantinga et al 2008].

A longitudinal study of 40 individuals showed that high-frequency hearing loss worsened and speech intelligibility index worsened over time, but the change over one year was subclinical, suggesting gradual progression over years [Karzon et al 2018].

Neurologic abnormalities were present in 62% of the individuals (mean age: 30 years, range: 5-44 years) studied by Barrett et al [1995] before molecular confirmation of the diagnosis was possible. However, very limited data are available regarding the frequency of the types of neurologic abnormalities.

Current experience indicates the presence of symptomatic neurologic findings by the fourth decade, with presymptomatic onset typically between the first and second decades.

Neurologic findings were progressive and resulted from general brain atrophy with brain stem and cranial nerve involvement [Barrett et al 1995, Chausseot et al 2015]. Abnormal cerebral MRIs found in eight of 45 affected individuals typically showed generalized brain atrophy most prominently of the cerebellum, medulla, and pons; and reduced signal intensity of the optic nerves and the posterior of the hypothalamus [Barrett et al 1995].

- Truncal or gait ataxia was found in 15 of 45 individuals [Barrett et al 1995].
- Episodes of central apnea, a serious manifestation, occurred in five of 45 individuals [Barrett et al 1995].
- A significantly increased risk of psychiatric illness including suicidal behavior has been reported [Eiberg et al 2006, Astuti et al 2017], as has dementia, occasionally seen as part of the wider neurodegeneration.
- Intellectual disability is not a common feature.

Brain MRI findings in 30 individuals with classic *WFS1*-SD followed for a median of five years [Samara et al 2020] include:

- Absent or diminished posterior pituitary bright spot (first visit, 53%; last visit, 70%)
- T₁-/T₂-weighted pons signal abnormalities (first visit, 53%; last visit, 67%)
- Optic nerve atrophy (first visit, 30%; last visit, 80%)
- White matter T₂-weighted hyperintensities (first visit, 27%; last visit, 35%)
- Cerebellar atrophy (first visit, 23%; last visit, 70%)

Other endocrine findings

- **Diabetes insipidus** of central origin occurred in 72% of affected individuals, with a median age of onset of 15.5 years. The range in age of onset was broad, possibly because of delays in establishing the correct diagnosis.
- **Hypogonadism** is more prevalent in males than in females. It can be either hypogonadotropic (i.e., central) or hypergonadotropic (i.e., secondary to gonadal failure). The underlying pathology of either type is not understood. Females usually retain their ability to become pregnant; about six successful pregnancies are described in the literature. One female had absence of the uterus [L Tranebjærg, personal observation]. Fertility is reduced, more severely in males than in females [Haghighi et al 2013].
- **Hypothyroidism.** Frequency is not known.
- **Growth restriction.** Most affected individuals achieve an adult height in the normal range.

Urinary tract. Dilated renal outflow tracts (hydroureter), urinary incontinence, and recurrent infections are common signs of neurogenic bladder. Sixteen of 29 affected individuals had such signs, with a median age of onset of 22 years (age range: 10-44 years) [Barrett et al 1995]. Urodynamic examinations showed incomplete bladder emptying or complete bladder atony, progressing to megacystis and potentially acute urinary outflow obstruction [Wragg et al 2018].

Gastrointestinal dysmotility and celiac disease. Constipation, chronic diarrhea, and other bowel dysfunction is reported in up to 25% of individuals with classic *WFS1*-SD.

Prognosis. Ten of the 45 individuals with classic *WFS1*-SD reported in Barrett et al [1995] had died at the time of that report. The causes of death included hypoglycemic coma, status epilepticus, end-stage kidney disease from recurrent urinary tract infection, central respiratory failure associated with brain stem atrophy, and suicide. However, the median age of death is now recognized to be much older than that reported in Barrett et al [1995]. In a national specialist multidisciplinary team clinic for 40 affected adults, the median age in the clinic was 37 years, and the oldest individual was 65 years [B Wright, personal communication].

Clinical Description – Nonclassic *WFS1* Spectrum Disorder

Nonclassic *WFS1*-SD is less common than classic *WFS1*-SD. At least 14 families with nonclassic *WFS1*-SD have been reported to date [Eiberg et al 2006, Hogewind et al 2010, Rendtorff et al 2011, Berry et al 2013, Bonnycastle et al 2013, De Franco et al 2017]. In a multidisciplinary clinical service in the UK, only about 15 of more than 100 individuals with *WFS1* pathogenic variants presented with nonclassic *WFS1*-SD [T Barrett, D Williams, B Wright, personal observation].

Most affected individuals have isolated optic atrophy and congenital deafness. Some families also have diabetes mellitus that is isolated or in combination with optic atrophy and deafness. Although published data on follow up are limited, the findings appear to be non-progressive, with a milder phenotype than classic *WFS1*-SD. Furthermore, affected individuals do not appear to develop progressive neurodegeneration, and no brain MRI findings have been reported to date.

Additionally, five probands were reported with neonatal diabetes mellitus, congenital cataracts, and sensorineural deafness [De Franco et al 2017]; no follow-up data have been reported.

Autosomal dominant optic atrophy and hearing impairment. Autosomal dominantly inherited optic atrophy and hearing impairment was first described in a three-generation Danish family, followed for more than 30 years [Eiberg et al 2006]. Four family members had childhood-onset optic atrophy but retained color vision and useful visual acuity into their seventh decade. In addition, they had moderately severe hearing impairment, present since childhood. Audiograms showed a flat or U-shaped pattern. Although one individual had diabetes mellitus and one had impaired glucose tolerance at ages 70 and 67 years, respectively, this may have been coincidental, as type 2 diabetes is common in the elderly.

In a family of Dutch origin, three affected members from two generations had childhood-onset optic atrophy and hearing impairment [Hogewind et al 2010]. They had vision impairment, partial loss of color vision, and abnormal visual evoked potentials. Audiograms showed a relatively flat pattern of hearing loss across all frequencies in the two older individuals, and low-tone loss in the youngest. No other features of classic *WFS1*-SD (including diabetes mellitus, diabetes insipidus, kidney abnormalities, or psychiatric issues) were identified.

Eight families from the UK, US, and Sweden also had autosomal dominantly inherited optic atrophy and sensorineural deafness. Optic atrophy, which presented in childhood or adulthood, was very slowly progressive. Early-childhood-onset sensorineural hearing loss was profound; several family members required cochlear implants.

Autosomal dominant diabetes mellitus was reported in a four-generation family from Finland in which eight members had adult-onset diabetes mellitus (diagnosed between ages 18 and 51 years) [Bonnycastle et al 2013]. Diabetes mellitus did not present with diabetic ketoacidosis; seven of the eight individuals were insulin dependent, and six were of normal weight. Detailed clinical examination of the family members with diabetes did not reveal any other features of classic *WFS1*-SD, including hearing impairment in audiograms, optic atrophy or vision impairment in annual ophthalmologic examinations, or diabetes insipidus.

Autosomal dominant nuclear cataracts. In a four-generation Irish family, 11 family members were affected without other ocular or systemic features [Berry et al 2013].

Autosomal dominant low-frequency sensorineural hearing loss (DFNA6/14/38; see [Genetic Hearing Loss Overview](#)) has been reported in individuals without ocular or other systemic features. Because hearing loss in these individuals is congenital, slowly progressive, and low frequency (<2000 Hz), it is often not diagnosed until after language is acquired. (Note: It is unknown why hearing loss is high frequency in classic *WFS1*-SD and low frequency in DFNA6/14/38.) Unlike classic *WFS1*-SD, the decline in speech recognition scores in DFNA6/14/38 correlates to the level of hearing impairment.

Neonatal diabetes, profound congenital deafness, and cataracts. This phenotype was reported in five probands who represented simplex cases (i.e., a single occurrence in a family) and had *de novo* *WFS1* pathogenic variants [De Franco et al 2017]. To date no long-term outcome data are available on these children.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified for classic *WFS1*-SD or nonclassic *WFS1*-SD.

Prevalence

Classic *WFS1*-SD. A study prior to the availability of molecular genetic testing estimated a prevalence of classic *WFS1*-SD of 1:550,000 children in the UK [Barrett et al 1995].

Recent epidemiologic studies based on molecularly confirmed classic *WFS1*-SD reviewed in Mishra et al [2021] estimated a prevalence of:

- 1:54,478 in the Messina district of northeast Sicily [Lombardo et al 2014];
- 1:1,351,000 in Italy [Rigoli et al 2020];
- 1:805,000 in northern India [Ganie et al 2011].

Nonclassic *WFS1*-SD. There are no prevalence figures for nonclassic *WFS1*-SD. However, in the authors' experience of leading a highly specialized multidisciplinary clinic in the UK for more than ten years, of 100 individuals seen with *WFS1* pathogenic variants, 15 had nonclassic *WFS1*-SD [T Barrett, D Williams, B Wright, personal observation].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *WFS1*.

Differential Diagnosis

Wolfram syndrome type 2 (WS2) (OMIM 604928) is an autosomal recessive disorder caused by biallelic pathogenic variants in *CISD2*. Like classic *WFS1* spectrum disorder (*WFS1*-SD), WS2 presents as a continuum of clinical features; however, the full clinical spectrum of WS2 abnormalities has not yet been fully established because so few affected individuals have been described. To date, the following clinical features have been reported in individuals with WS2:

- Families of Palestinian Arab origin have been described with juvenile-onset diabetes mellitus, optic atrophy, high-frequency sensorineural hearing impairment, urinary tract dilatation, impaired kidney function, hypogonadism, and severe gastrointestinal ulcer and bleeding [al-Sheyyab et al 2001, Amr et al 2007]; abnormal facial features were described in one family [Amr et al 2007].
- Diabetes insipidus, psychiatric abnormalities, and variable degrees of optic atrophy have been reported in individuals from Italy and Morocco [Mozzillo et al 2014, Rondinelli et al 2015, Rouzier et al 2017]. Peptic ulcers, mucocutaneous bleeding, and defective platelet aggregation were also described in a subset of these individuals.

Note: A novel *CISD2* pathogenic variant (c.215A>G; p.Asn72Ser) was identified in an individual with clinical findings suggestive of classic *WFS1*-SD who did not have *WFS1* pathogenic variants [Rouzier et al 2017].

Other Genetic Causes of Features Seen in *WFS1* Spectrum Disorder

Hearing impairment. See [Genetic Hearing Loss Overview](#).

Monogenic diabetes syndromes. See Table 3.

Table 3. Monogenic Diabetes Syndromes in the Differential Diagnosis of *WFS1* Spectrum Disorder

Gene(s) / Genetic Mechanism	Differential Disorder	MOI	Selected Features of Differential Disorder			
			Endocrine abnormalities	Eye findings	Hearing loss	Neurologic abnormalities
<i>ALMS1</i>	Alström syndrome	AR	Insulin resistance / type 2 DM often presents in 2nd decade. Other endocrine abnormalities incl hypogonadotropic hypogonadism in boys, polycystic ovaries in girls, & hypothyroidism. Obesity common, leading to non-alcoholic fatty liver disease.	Cone-rod dystrophy presents as progressive visual impairment, photophobia, & nystagmus starting between birth & age 15 mos; no light perception by age 20 yrs in many persons.	Progressive SNHL begins in 1st decade in ~70% of persons. Hearing loss may become moderate to severe (40-70 dB) by end of 1st-2nd decade.	Detrusor-urethral dyssynergia in females in late 2nd decade
<i>BBS1</i> <i>BBS2</i> <i>BBS4</i> <i>BBS7</i> <i>BBS9</i> <i>BBS10</i> <i>BBS12</i> <i>MKKS</i> <i>MKS1</i> <i>TTC8</i> ¹	Bardet-Biedl syndrome	AR	Insulin resistance / type 2 DM in adolescence or adulthood; male hypogonadotropic hypogonadism. Obesity is common.	Cone-rod dystrophy; night blindness usually evident by age 7-8 yrs; mean age of legal blindness is 15.5 yrs.	~50% of adults develop subclinical SNHL only detectable by audiometry.	Significant (moderate) learning difficulties in majority of persons; severe impairment on IQ testing in minority
<i>DMPK</i>	Myotonic dystrophy type 1 (DM1)	AD	DM is common in mild & classic DM1.	Cataracts in mild & classic DM1	No data available	Mild myotonia (sustained muscle contraction) in mild DM1; muscle weakness/wasting & myotonia in classic DM1
<i>FXN</i>	Friedreich ataxia	AR	30% have DM.	Optic nerve atrophy, often asymptomatic, occurs in ~25%. Progressive diminution of contrast acuity is typical w/ disease progression.	SNHL in 13% of persons	Slowly progressive ataxia w/mean onset age 10-15 yrs (usually <25 yrs); dysarthria, muscle weakness, spasticity in lower limbs, scoliosis, bladder dysfunction, absent lower limb reflexes, loss of position & vibration sense
mtDNA deletion	Kearns-Sayre syndrome (See Mitochondrial DNA Deletion Syndromes.)	Mat	DM, hypoparathyroidism, & growth hormone deficiency	Pigmentary retinopathy & progressive external ophthalmoplegia w/ onset age <20 yrs	SNHL in some persons	Cerebellar ataxia; impaired intellect (ID &/or dementia)

Table 3. continued from previous page.

Gene(s) / Genetic Mechanism	Differential Disorder	MOI	Selected Features of Differential Disorder			
			Endocrine abnormalities	Eye findings	Hearing loss	Neurologic abnormalities
<i>SLC19A2</i>	Thiamine-responsive megaloblastic anemia syndrome	AR	DM; non-type 1 in nature w/age of onset from infancy to adolescence; may be thiamine responsive in childhood.	OA (when commented on in case reports)	Progressive SNHL w/ generally early onset; can be detected in toddlers. SNHL is irreversible & not prevented by thiamine treatment.	Significant neurologic deficit incl stroke & focal or generalized epilepsy reported in early childhood in 27% of persons.

AD = autosomal dominant; AR = autosomal recessive; DM = diabetes mellitus; DM1 = myotonic dystrophy type 1; ID = intellectual disability; Mat = maternal; MOI = mode of inheritance; mtDNA = mitochondrial DNA; OA = optic atrophy; SNHL = sensorineural hearing loss

1. Listed genes represent the more commonly associated genes; at least 26 genes are associated with Bardet-Biedl syndrome (see [Bardet-Biedl Syndrome Overview](#)).

Optic atrophy associated with hearing impairment. See Table 4.

Table 4. Disorders with Optic Atrophy Associated with Hearing Impairment in the Differential Diagnosis of WFS1 Spectrum Disorder

Gene	Differential Disorder	MOI	Selected Features of Differential Disorder		
			Eye findings	Hearing loss	Neurologic abnormalities
<i>OPA1</i>	Optic atrophy type 1 (OMIM 165500)	AD	Bilateral & symmetric optic nerve pallor assoc w/insidious ↓ in visual acuity usually age 4-6 yrs; visual field defects; color vision defects. Visual impairment is usually moderate (6/10-2/10), but ranges from mild or even insignificant to severe (legal blindness w/acuity <1/20).	Auditory neuropathy → SNHL ranging from severe & congenital to subclinical ¹	~20% have assoc additional clinical features, esp neurologic signs.
<i>PRPS1</i>	Charcot-Marie-Tooth neuropathy X type 5 (See Phosphoribosylpyrophosphate Synthetase Deficiency .)	XL	Optic neuropathy in males; onset of visual impairment at age 7-20 yrs	Early-onset (prelingual) bilateral profound SNHL in males	Peripheral neuropathy in males w/onset age 5-12 yrs

Table 4. continued from previous page.

Gene	Differential Disorder	MOI	Selected Features of Differential Disorder		
			Eye findings	Hearing loss	Neurologic abnormalities
<i>TIMM8A</i> ²	Deafness-dystonia-optic neuropathy syndrome	XL	Slowly progressive ↓ in visual acuity from OA beginning at ~20 yrs in males	Prelingual or postlingual SNHL in early childhood in males; females may have mild hearing impairment.	Slowly progressive dystonia or ataxia in 2nd decade; dementia beginning at age ~40 yrs; psychiatric symptoms (e.g., personality change, paranoia) may appear in childhood & progress. Females may have focal dystonia.

AD = autosomal dominant; MOI = mode of inheritance; OA = optic atrophy; SNHL = sensorineural hearing loss; XL = X-linked

1. Identified by specific audiologic testing only

2. The diagnosis of deafness-dystonia-optic neuropathy syndrome is established in either a male proband with a hemizygous *TIMM8A* pathogenic variant, or a female proband with a heterozygous *TIMM8A* pathogenic variant or a contiguous gene deletion of Xq22.1 involving *TIMM8A*.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with classic or nonclassic *WFS1* spectrum disorder (*WFS1*-SD), the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

See also [Wolfram Syndrome Clinical Management Guidelines](#), page 5, for recommended baseline investigations.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Classic or Nonclassic *WFS1* Spectrum Disorder

System/Concern	Evaluation	Comment
Diabetes mellitus	By diabetologist	
Optic atrophy	Ophthalmologic eval	<ul style="list-style-type: none"> Assess extraocular movement, best corrected visual acuity, visual evoked potentials. Perform color vision testing, visual field testing, optical coherence tomography, fundus exam.
	Optometry &/or low-vision clinic	Assess for low-vision aids.
Sensorineural hearing impairment	<ul style="list-style-type: none"> Audiologic exam Eval by speech-language therapist 	Incl: <ul style="list-style-type: none"> Auditory brain stem responses to confirm pathology & provide baseline Evoked otoacoustic emissions to identify type of hearing impairment Audiogram Speech discrimination tests Assessment for hearing aids; children w/ profound infancy-onset deafness may require cochlear implant.

Table 5. continued from previous page.

System/Concern	Evaluation	Comment	
Neurologic dysfunction	Neurologic exam incl brain MRI (if not performed previously)	Evaluate for: <ul style="list-style-type: none"> • Motor system: coordination, balance, ataxia • Sensory system: peripheral neuropathy • Cranial nerves: anosmia, ability to taste, dysarthria, swallowing/choking difficulties, apneic episodes • Autonomic system: hypotensive episodes, abnormal temperature regulation &/or sweating episodes Consider speech-language therapy, OT, PT assessments.	
Respiratory function	Polysomnography	<ul style="list-style-type: none"> • Central apnea can occur secondary to brain stem atrophy. • Sleep disturbance is common & multicausal. 	
Psychiatric	Neuropsychiatric eval	<ul style="list-style-type: none"> • Consider anxiety, depression eval. Although reported, psychoses are rare. 	
Neurogenic bladder	History of: urgency, frequency, difficulty voiding, urinary incontinence, recurrent infections	<ul style="list-style-type: none"> • Refer to urologist. • Consider urodynamic eval, imaging of urinary tract & kidneys for dilated ureters, & assessment of kidney function. 	
Bowel dysfunction	History of: constipation, urgency, accidents		
Other endocrine findings	Diabetes insipidus	Assess concentrating ability of urine.	Paired early morning urine & fasting plasma osmolality & sodium concentrations after nocturnal & morning euglycemia
	Hypogonadism	Evaluate for absent or delayed puberty &/or infertility	Refer for assessment for primary gonadal failure &/or hypogonadotropic hypogonadism.
	Hypothyroidism	Thyroid function tests	May be non-autoimmune
	Growth restriction	Plot height, weight, & head circumference on standard growth charts.	To identify growth failure &/or provide baseline
Genetic counseling	By medical genetics health care professionals ¹	To inform affected persons & families re nature, MOI, & implications of WFS1-SD	
Family support & resources	<ul style="list-style-type: none"> • Contact w/patient advocacy organization • Assess need for social work involvement for caregiver support. • Assess need for help coordinating multidisciplinary care. • Assess need for community resources & support/advocacy organizations (e.g., Parent to Parent). 		

MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; WFS1-SD = WFS1 spectrum disorder

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for WFS1-SD.

Management is focused on supportive care, often provided by multidisciplinary specialists in diabetic care, endocrinology, ophthalmology and low-vision clinics, audiology, speech-language therapy, neurology,

pulmonology, psychiatry / psychology / mental health, urology, gastroenterology, social work, and medical genetics (see Table 6).

See also [Wolfram Syndrome Clinical Management Guidelines](#), pages 6-12, for management recommendations.

Table 6. Treatment of Manifestations in Individuals with Classic or Nonclassic *WFS1* Spectrum Disorder

Manifestation/Concern	Treatment	Considerations/Other
Diabetes mellitus	Routine practice for insulin-dependent DM	<ul style="list-style-type: none"> • Diabetic ketoacidosis is rare. • Because episodes of severe hypoglycemia are common, ¹ insulin is given as multiple daily injections or continuous infusion by insulin pump. • Continuous glucose monitoring w/hypoglycemia alarm is recommended due to risk for hypoglycemic episodes. • Other hypoglycemic agents are not licensed for use in <i>WFS1</i>-SD (due to insufficient evidence for efficacy or safety).
Optic atrophy	Correction of refractive error	
	Low-vision services	<ul style="list-style-type: none"> • Evaluate for visual aids. • Community vision services through early intervention or school district
Sensorineural hearing impairment	Treatment of SNHL depends on degree of hearing impairment. ²	
Activities of daily living	Vision impairment support	Communication training (e.g., Braille), walking aids
	Occupational therapist	<ul style="list-style-type: none"> • To support tasks incl mobility & ADL • To assist w/household modifications if needed
Dysphagia	Speech-language therapist	<ul style="list-style-type: none"> • Determine exact cause of swallowing malfunction. • Modify food types & consistency, head positioning during swallowing, & exercises to ensure safe swallow.
	Dentist/dental hygienist	Attention to oral hygiene & dental care
Dysarthria	Speech-language pathologist	Help maintain vocal control, improve speech, teach breathing techniques, & assist communication in general.
Central apnea	Respiratory team	Options incl overnight noninvasive ventilatory support.
Psychiatric	Per standard treatment by psychiatric professional (psychiatrist, psychologist, neuropsychologist) as needed	Pharmacologic & non-pharmacologic therapies available.
Neurogenic bladder	<ul style="list-style-type: none"> • Anticholinergic drugs • Clean intermittent self-catheterization or indwelling catheter • Treatment of recurrent urinary tract infections 	<ul style="list-style-type: none"> • Detrusor muscle dyssynergia may require pharmacologic relaxants or stimulants at different stages. • Ensure central diabetes insipidus is screened for & treated.
Bowel dysfunction	Dietary mgmt	In conjunction w/bladder dysfunction

Table 6. continued from previous page.

Manifestation/Concern		Treatment	Considerations/Other
Other endocrine findings	Diabetes insipidus	Per standard treatment	Care w/arginine vasopressin replacement to avoid hyper-/hyponatremia
	Hypogonadism		Hormone replacement therapy
	Hypothyroidism		Thyroid hormone replacement
	Growth restriction		Evaluate for growth hormone supplementation according to national guidelines for growth hormone therapy.
Transition of care to adult service providers		Assess understanding of illness, capacity for independent life skills	<ul style="list-style-type: none"> Start from early in 2nd decade. Involve young person as well as care providers in planned transfer to adult services.
Family/Community		<ul style="list-style-type: none"> Ensure appropriate social services involvement to connect families w/ local resources, respite, & support. Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies. 	Consider support w/adaptive sports, higher education, & employment opportunities.

ADL = activities of daily living; DM = diabetes mellitus; SNHL = sensorineural hearing loss; WFS1-SD = WFS1 spectrum disorder

1. Rohayem et al [2011]

2. See [Genetic Hearing Loss Overview](#) for details about treatment options.

Individualized education plan in the US (Education, Health and Care plan in the UK)

- An individualized education plan (IEP) provides specially designed instruction and related services to children who qualify.
- IEP services will be reviewed annually to determine whether any changes are needed.
- Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
- Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
- PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
- As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- In the US, families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Social/behavioral concerns. Consultation with a developmental or community pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Surveillance

See also [Wolfram Syndrome Clinical Management Guidelines](#), pages 6-12, for surveillance recommendations.

Classic *WFS1* Spectrum Disorder

To monitor existing manifestations, the response of an individual with classic *WFS1*-SD to supportive care, and the emergence of new manifestations, the evaluations in Table 7 are recommended.

Table 7. Recommended Surveillance for Individuals with Classic *WFS1* Spectrum Disorder

System/Concern	Evaluation	Frequency
Diabetes mellitus	Glycemic control	Every 3 mos
Complications of diabetes mellitus	Nephropathy	Annual screening starting at age 12 yrs
	Retinopathy	In those w/duration of diabetes ≥ 5 yrs: annual screening
	Neuropathy	Annual screening for parathesias
	Dyslipidemia screen	Annually
	Hypertension	At least annually
Optic atrophy	<ul style="list-style-type: none"> Eye exam (visual acuity, color vision testing, slit lamp exam for cataracts, funduscopy, visual fields) Need for low-vision aids 	Annually
Sensorineural hearing impairment	Audiogram incl assessment of speech discrimination	Every 1-2 yrs
Neurologic	Neurologic exam incl assessment of cerebellar ataxia as well as memory, personality changes	
Activities of daily living & mobility	Physical medicine, OT/PT assessment of mobility, self-help skills	Per treating clinicians
Dysphagia	For those w/o this concern previously: obtain history of swallowing/choking episodes & refer to speech-language therapist as needed.	Annually
	For those known to have this concern	Per treating speech-language therapist
Dysarthria	For those w/o this concern previously: obtain history of speech difficulties & refer to speech-language therapist as needed.	Annually
	For those known to have this concern	Per treating speech-language therapist
Development in young children	Monitor educational needs.	Annually in childhood
Cognitive decline / Intellectual disability	Per treating clinician	As clinically indicated
Psychiatric/Behavioral	Assess for symptoms of depression, suicidal behavior, & changes in personal appearance & social behavior	Per treating clinician
Neurogenic bladder	<ul style="list-style-type: none"> Urodynamic exam & assessment of bladder emptying Routine urine cultures when there is bladder dysfunction &/or other urinary tract abnormality 	Annually

Table 7. continued from previous page.

System/Concern		Evaluation	Frequency
Other endocrine findings	Diabetes insipidus	Assess concentrating ability of urine.	Per treating clinician
	Hypogonadism	Monitor for signs of onset of puberty.	
	Hypothyroidism	Monitor linear growth in children using standard growth charts.	
	Growth restriction		
Family/Community		<ul style="list-style-type: none"> • Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies. • Assess need for follow-up genetic counseling if new questions arise (e.g., family planning). 	

OT = occupational therapy; PT = physical therapy

Nonclassic WFS1 Spectrum Disorder

To monitor existing manifestations, the response of an individual with nonclassic WFS1-SD to supportive care, and the emergence of new manifestations, the evaluations in Table 8 are recommended.

Table 8. Recommended Surveillance for Individuals with Nonclassic WFS1 Spectrum Disorder

System/Concern	Evaluation	Frequency
Diabetes mellitus	Glycemic control	Annually until diagnosis; then every 3 mos
Optic atrophy	<ul style="list-style-type: none"> • Eye exam (visual acuity, color vision testing, slit lamp exam for cataracts, funduscopy, visual fields) • Need for low-vision aids 	Annually
Sensorineural hearing impairment	Audiogram incl assessment of speech discrimination & need for hearing aids or cochlear implants	
Family/Community	<ul style="list-style-type: none"> • Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies. • Assess need for follow-up genetic counseling if new questions arise (e.g., family planning). 	

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic relatives at risk in order to identify as early as possible those who would benefit from prompt initiation of treatment for the earliest manifestations of WFS1-SD: diabetes mellitus, optic atrophy, and sensorineural hearing loss.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnant women with insulin-dependent diabetes mellitus, a characteristic of both classic and nonclassic WFS1-SD, have a two- to eightfold higher risk than pregnant women without diabetes of having a child with a birth defect or a pattern of birth defects (diabetic embryopathy). These defects can involve the craniofacial, cardiovascular, gastrointestinal, urogenital, musculoskeletal, and central nervous systems. Optimizing glucose

control before and during pregnancy can reduce but does not eliminate the risk for diabetic embryopathy. High-resolution fetal ultrasonography and fetal echocardiogram are recommended to screen for congenital anomalies during pregnancy. Consultation with a maternal fetal medicine specialist during pregnancy should also be considered.

Because women with classic *WFS1*-SD may develop diabetes insipidus during pregnancy [Rugolo et al 2002], monitoring for diabetes insipidus during pregnancy is warranted.

See [MotherToBaby](#) for further information on medication use during pregnancy.

Therapies Under Investigation

For a review of current and future therapeutic strategies, see Mishra et al [2021].

Classic *WFS1*-SD. An ongoing multicenter randomized double-blind controlled pivotal clinical trial is evaluating the use of sodium valproate to slow the progression of neurodegeneration ([EudraCT Number 2017-001215-37](#)).

Search [ClinicalTrials.gov](#) in the US and [EU Clinical Trials Register](#) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Classic *WFS1* spectrum disorder (*WFS1*-SD) is caused by biallelic pathogenic variants and inherited in an autosomal recessive manner.

Nonclassic *WFS1*-SD is caused by heterozygous pathogenic variants and inherited in an autosomal dominant manner.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child with classic *WFS1*-SD are presumed to be heterozygous for a *WFS1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *WFS1* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
 - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;

- Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- There is no conclusive evidence that the heterozygous parents of a child with *WFS1*-SD caused by biallelic *WFS1* pathogenic variants are at any increased risk for components of *WFS1*-SD.

Sibs of a proband

- If both parents are known to be heterozygous for a *WFS1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- The clinical course of classic *WFS1*-SD is highly variable (even between sibs with the same biallelic pathogenic variants) and is not predictable from the type or location of the familial pathogenic variants.
- There is no conclusive evidence that the heterozygous sibs of a proband with *WFS1*-SD caused by biallelic *WFS1* pathogenic variants are at any increased risk for components of *WFS1*-SD.

Offspring of a proband. The offspring of an individual with *WFS1*-SD caused by biallelic pathogenic variants are obligate heterozygotes for a pathogenic variant in *WFS1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *WFS1* pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *WFS1* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with nonclassic *WFS1*-SD have the disorder as the result of a *de novo* *WFS1* pathogenic variant.
 - Some individuals diagnosed with nonclassic *WFS1*-SD have an affected parent.
 - If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
 - If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
 - The proband has a *de novo* pathogenic variant.
 - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- * A parent with somatic and germline mosaicism for a *WFS1* pathogenic variant may be mildly/minimally affected.
- The family history of some individuals diagnosed with nonclassic *WFS1*-SD may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Clinical variability may be observed between affected family members with the same *WFS1* pathogenic variant [Eiberg et al 2006].
- If the *WFS1* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *WFS1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs are still presumed to be at increased risk for nonclassic *WFS1*-SD because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with nonclassic *WFS1*-SD caused by a heterozygous pathogenic variant has a 50% chance of inheriting the *WFS1* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *WFS1* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults with *WFS1*-SD and to young adults who are at risk of having *WFS1* pathogenic variant(s).

Prenatal Testing and Preimplantation Genetic Testing

Once the *WFS1* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for classic and nonclassic *WFS1*-SD are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **Association Syndrome de Wolfram**
France
Phone: 09 63 07 32 22
www.association-du-syndrome-de-wolfram.org

- **MedlinePlus**
[Wolfram syndrome](#)
- **Wolfram Syndrome UK**
United Kingdom
Phone: 01903 211358
www.wolframsyndrome.co.uk
- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**
Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)
Fax: 202-337-8314
Email: info@agbell.org
[Listening and Spoken Language Knowledge Center](#)
- **American Diabetes Association**
Phone: 800-DIABETES (800-342-2383)
Email: AskADA@diabetes.org
diabetes.org
- **American Society for Deaf Children**
Phone: 800-942-2732 (ASDC)
Email: info@deafchildren.org
deafchildren.org
- **Diabetes UK**
United Kingdom
Phone: 0345 123 2399
Email: helpline@diabetes.org.uk
www.diabetes.org.uk
- **International Foundation for Optic Nerve Disease (IFOND)**
NY
Phone: 845-534-8606
Email: ifond@aol.com
www.ifond.org
- **National Association of the Deaf**
Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
Fax: 301-587-1791
Email: nad.info@nad.org
nad.org
- **National Federation of the Blind**
Phone: 410-659-9314
Email: nfb@nfb.org
www.nfb.org
- **Wolfram Syndrome International Registry and Clinical Study**
Phone: 314-362-8683
Email: urano@wustl.edu
www.wolframsyndrome.dom.wustl.edu

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. WFS1 Spectrum Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
WFS1	4p16.1	Wolframin	Hereditary Hearing Loss Homepage (WFS1) CCHMC - Human Genetics Mutation Database (WFS1)	WFS1	WFS1

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B. OMIM Entries for WFS1 Spectrum Disorder ([View All in OMIM](#))

116400	CATARACT 41; CTRCT41
125853	TYPE 2 DIABETES MELLITUS; T2D
222300	WOLFRAM SYNDROME 1; WFS1
600965	DEAFNESS, AUTOSOMAL DOMINANT 6; DFNA6
606201	WOLFRAMIN ER TRANSMEMBRANE GLYCOPROTEIN; WFS1
614296	WOLFRAM-LIKE SYNDROME, AUTOSOMAL DOMINANT; WFSL

Molecular Pathogenesis

WFS1 spectrum disorder (*WFS1*-SD) is considered a prototype of endoplasmic reticulum (ER) disease [Mishra et al 2021]. *WFS1* encodes wolframin, an endoglycosidase H-sensitive ER transmembrane glycoprotein. The precise function of wolframin has not been established, but deficiency is thought to lead to ER stress, impair cell cycle progression, and affect calcium homeostasis. There is no direct interaction between wolframin and the ER intermembrane small protein encoded by *CISD2*, pathogenic variants of which cause WFS2 (see Differential Diagnosis) [Amr et al 2007].

Wolframin is widely expressed, including in retinal ganglion cells and optic nerve glia in monkeys.

There is some in vitro evidence that *WFS1* pathogenic variants are associated with systemic inflammation, opening up a new avenue for therapeutic strategies [Panfili et al 2021].

Mechanism of disease causation. Pathogenic variants in *WFS1* result in loss of wolframin function.

Chapter Notes

Author Notes

Professor Timothy Barrett is based at the Institute of Cancer and Genomic Sciences, University of Birmingham, and Honorary Consultant in Pædiatric Endocrinology and Diabetes at Birmingham Women's and Children's Hospital. He has published more than 200 research papers in scientific journals as well as reviews and book chapters in the fields of pediatrics, diabetes, and genetics of childhood diabetes syndromes. His research interests include functional genetics, rare diabetes syndromes, and translational research to early-phase clinical trials in rare disease.

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