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WARS2 Deficiency

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Summary

Clinical characteristics

The current (but limited) understanding of the WARS2 deficiency phenotypic spectrum, based on 29 individuals from 24 families reported to date, can be viewed as a clustering of hallmark features within the broad phenotypes of epilepsy and movement disorder.

The epilepsy spectrum encompasses neonatal- or infantile-onset developmental and epileptic encephalopathy (DEE) and other less well described seizure types. DEE manifests mostly in the neonatal period or within the first year of life. Seizures are generally difficult to control and may lead to status epilepticus and death. Over time the following become evident: global developmental delay, mild-to-severe intellectual disability, speech impairment (slurred and slow speech, dysarthria or no speech production but preserved receptive speech), weakness and muscle atrophy, motor hyperactivity with athetosis, and neuropsychiatric manifestations including aggressiveness and sleep disorders.

The movement disorder spectrum encompasses the overlapping phenotypes of levodopa-responsive parkinsonism/dystonia and progressive myoclonus-ataxia/hyperkinetic movement disorder and is primarily associated with childhood or early adulthood onset.

Of note, the continua within and between the epilepsy spectrum and the movement disorder spectrum remain to be determined pending reporting of more individuals with WARS2 deficiency.

Diagnosis/testing

The diagnosis of WARS2 deficiency is established in a proband with suggestive findings and biallelic pathogenic variants in *WARS2* identified by molecular genetic testing. Of note, to date all individuals with a childhood- or early adulthood-onset movement disorder have the hypomorphic *WARS2* variant c.37T>G (p.Trp13Gly) in *trans* with a *WARS2* pathogenic variant.

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Management

Treatment of manifestations: There is no known cure for WARS2 deficiency. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. Supportive treatment of *WARS2*-related DEE ideally involves multidisciplinary care by specialists in child neurology (treatment of seizures), nutrition/feeding, pulmonology, physical therapy, developmental pediatrics, social work, medical ethics, and medical genetics. Supportive treatment of *WARS2*-related movement disorders ideally involves multidisciplinary care by specialists in neurology (treatment of movement disorders), physiatry, physical therapy, occupational therapy, speech-language pathology (including consideration of augmentative and alternative communication), developmental pediatrics, mental health, social work, and medical genetics. Of note, individuals with parkinsonism show an overall good response to dopaminergic therapy, mostly to levodopa (alternatively, dopamine receptor agonists).

Surveillance: Because most infants and young children with *WARS2*-related DEE are severely affected and may be hospitalized for prolonged periods, it is recommended that they be reviewed regularly by senior clinical specialists when hospitalized. For individuals with a *WARS2*-related movement disorder, it is recommended that monitoring of existing manifestations, the individual's response to supportive care, and the emergence of new manifestations follow the recommendations of the treating specialists.

Agents/circumstances to avoid: Valproic acid has caused severe hepatopathy and neurologic deterioration in one individual with *WARS2*-related DEE.

Genetic counseling

WARS2 deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *WARS2* pathogenic variant or hypomorphic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic variants, a 50% chance of inheriting one variant, and a 25% chance of inheriting neither of the familial *WARS2* variants. Sibs who inherit:

- Biallelic loss-of-function pathogenic variants are likely to have *WARS2*-related epilepsy;
- A *WARS2* loss-of-function pathogenic variant in *trans* with the hypomorphic *WARS2* variant are likely to have a *WARS2*-related movement disorder;
- One variant (either a pathogenic variant or a hypomorphic variant) are asymptomatic and are not at risk of developing WARS2 deficiency;
- Neither of the familial *WARS2* variants are unaffected and not carriers.

Once the WARS2 deficiency-related variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

GeneReview Scope

WARS2 Deficiency: Phenotypic Spectrum outlines the current (but limited) understanding of the clustering of distinctive features in the two broad phenotypic spectra (epilepsy and movement disorder) and their associated genotype-phenotype correlations. Of note, the continua within and between these two major phenotypic spectra remain to be determined pending reporting of more individuals with WARS2 deficiency.

WARS2 Deficiency: Phenotypic Spectrum

Phenotype	Typical Onset	Genotype
Epilepsy [1, 2]	Neonatal or infantile onset	Biallelic *WARS2* pathogenic variants

WARS2 Deficiency: Phenotypic continued from previous page.

Phenotype	Typical Onset	Genotype
Movement disorder [3]	Childhood or early adulthood onset	Hypomorphic *WARS2* variant c.37T>G (p.Trp13Gly) in *trans* w/*WARS2* pathogenic variant [4]

1. Including developmental and epileptic encephalopathy (DEE) and other seizure types
2. WARS2-related epilepsy has also been referred to as NEMMLAS (*ne*urodevelopmental disorder, *m*itochondrial, w/abnormal *m*ovements and *l*actic *a*cidosis, with or without *s*eizures) (see Nomenclature).
3. Primarily levodopa-responsive parkinsonism/dystonia and progressive myoclonus-ataxia/hyperkinetic movement disorder
4. The *WARS2* variant c.37T>G (p.Trp13Gly) is a hypomorphic variant that is disease causing only when in *trans* with a *WARS2* loss-of-function variant (see Molecular Genetics, **Special technical laboratory considerations**).

Diagnosis

No consensus clinical diagnostic criteria for WARS2 deficiency have been published.

Suggestive Findings

WARS2 deficiency **should be considered** in a proband with the following clinical, laboratory and imaging findings, and family history.

Epilepsy Spectrum – Neonatal or Infantile Onset

Clinical findings

- Initial manifestations:
  - Seizures ranging from developmental and epileptic encephalopathy (DEE) to other seizure types.

    Note: For the purposes of this *GeneReview*, DEE is defined as severe seizure onset shortly after birth (often called infantile epileptic spasms syndrome).
  - Hypotonia with or without peripheral spasticity
  - Global developmental delay
  - Poor suck
- Manifestations over time:
  - Intellectual disability
  - Speech impairment (no speech, slurred and slow speech) with receptive language relatively spared
  - Often movement disorder (e.g., mild ataxia, dystonia, athetosis) and/or neuropsychiatric findings

Laboratory findings. Lactic acidosis may be present in early life, and serum lactate can reach 31 mmol/L [Wortmann et al 2017]. However, lactate can also be normal.

Brain MRI. Nonspecific findings can include:

- Cerebral and cerebellar volume loss
- White matter abnormalities (including absent myelination, nonspecific periventricular signal changes)
- Thin corpus callosum
- Hypoplastic cerebellar vermis, cerebellar peduncles, and brain stem
- Hypoxemic-ischemic basal ganglia lesions

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.

Movement Disorder Spectrum – Childhood or Early Adulthood Onset

Clinical findings

- Initial manifestations:
  - Action tremor of the hand, unilateral leg tremor, occasional jerks
  - Tremor
  - Distal limb myoclonus
  - Ataxia
  - Ballistic and dystonic movements
  - Axial hypotonia with trunk instability
  - Developmental delay
- Manifestations over time:
  - Movement disorders, such as parkinsonism (rigidity, bradykinesia, akinesia, dysarthria, dysphagia, hypomimia); other movement disorders such as dystonia, myoclonus, ataxia, tremor (resting, action, and postural), and chorea; and ocular disorders such as oculogyric crisis (spasmodic movements of the eyeballs into a fixed position, usually upward), ptosis, supranuclear gaze palsy, and exotropia
  - Mild-to-moderate developmental delay / intellectual disability
  - Versive seizures (a forced and involuntary turning of the head and eyes in one direction with an associated neck extension resulting in a sustained unnatural position of both)
  - Neuropsychiatric manifestations such as social phobia, anxiety, depression, aggressive behavior, psychosis, and apathy
  - Spasticity, peripheral hypertonia

Neuroimaging

- **Brain MRI.** Often normal; in some individuals, patchy or nonspecific periventricular T_2 hyperintensities, cerebellar atrophy, and variable global brain atrophy can be seen. In one individual pallidal T_2 hyperintensity was described.
- **DaTscan®** (specific type of single-photon emission computed tomography). Abnormalities of the dopaminergic striatal pathways are seen.

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.

Establishing the Diagnosis

The diagnosis of WARS2 deficiency **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *WARS2* 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 section is understood to include likely pathogenic variants. (2) Identification of biallelic *WARS2* variants of uncertain significance (or of one known *WARS2* pathogenic variant and one *WARS2* variant of uncertain significance) does not establish or rule out the diagnosis. (3) The common *WARS2* variant c.37T>G (p.Trp13Gly) is a hypomorphic variant that is disease causing only when in *trans* with a *WARS2* loss-of-function variant. This variant is **not** disease causing in the homozygous state.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that

the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Note: Single-gene testing (sequence analysis of *WARS2*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Option 1

A mitochondrial, intellectual disability, genetic epilepsy syndrome, or inborn error of metabolism multigene panel that includes *WARS2* 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.

Option 2

Comprehensive genomic testing does not require the clinician to determine which genes is 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 WARS2 Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
WARS2	Sequence analysis [3]	100% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None reported [4, 7]

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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Includes the hypomorphic variant c.37T>G (p.Trp13Gly), which is only disease causing when present in *trans* with loss-of-function pathogenic variants [Ilinca et al 2022, Skorvanek et al 2022]. Of note, the p.Trp13Gly variant is typically not detected by standard filtering criteria of exome sequencing. Therefore, if another pathogenic *WARS2* variant is detected in the heterozygous state, using additional and/or modified filters to specifically confirm/exclude the presence of the p.Trp13Gly hypomorphic variant in *trans* is recommended (see Molecular Genetics).
6. 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.
7. One individual with a 36-kb deletion including exon 2 of *WARS2* had a severe fatal neonatal form of disease that might also be explained by the presence of another variant (p.Val349Leu) with a more significant deleterious effect and possibly other modifiers. Additionally, two sibs with levodopa-responsive parkinsonism had the p.Trp13Gly variant in compound heterozygosity with an exon 2 deletion. Deletion of exon 2 is predicted to result in an in-frame deletion of 86 amino acids (p.Lys31_Q116del), consistent with a loss-of-function effect [Wortmann et al 2017, Skorvanek et al 2022].

Clinical Characteristics

Clinical Description

The current (but limited) understanding of the WARS2 deficiency phenotypic spectrum can be viewed as a clustering of hallmark features within the broad phenotypes of epilepsy and movement disorder. The epilepsy spectrum encompasses neonatal- or infantile-onset developmental and epileptic encephalopathy (DEE) and other seizure types. The movement disorder spectrum encompasses levodopa-responsive parkinsonism/dystonia and progressive myoclonus-ataxia/hyperkinetic movement disorder. Of note, the continua within and between the epilepsy spectrum and the movement disorder spectrum remain to be determined pending reporting of more individuals with WARS2 deficiency.

To date, 29 individuals from 24 families with biallelic variants in *WARS2* have been reported [Bowling et al 2017, Musante et al 2017, Theisen et al 2017, Wortmann et al 2017, Burke et al 2018, Vantroys et al 2018, Hübers et al 2019, Maffezzini et al 2019, Nogueira et al 2019, Virdee at al 2019, Martinelli et al 2020, Ilinca et al 2022, Skorvanek et al 2022, Pauly et al 2023].

Epilepsy Spectrum

Developmental and epileptic encephalopathy (DEE) has been reported in the medical literature in 13 individuals [Bowling et al 2017, Musante et al 2017, Theisen et al 2017, Wortmann et al 2017, Vantroys et al 2018, Maffezzini et al 2019, Nogueira et al 2019, Virdee at al 2019]. Epilepsy was described in 6/13 individuals, with infantile spasms syndrome (previously termed West syndrome) described in two of the six individuals [Musante et al 2017]. However, information on other types of seizures observed is limited. In one individual seizures were described as long lasting with decreased awareness, lateral eye deviation, and eyelid twitching [Vantroys et al 2018].

DEE manifests mostly in the neonatal period or within the first year of life. Seizures are generally difficult to control and may lead to status epilepticus and death.

Evolution of manifestations over time include global developmental delay, mild-to-severe intellectual disability, speech impairment (slurred and slow speech, dysarthria, or no speech production but preserved receptive speech), muscle weakness, muscle atrophy, motor hyperactivity with athetosis, and neuropsychiatric manifestations including aggressiveness and sleep disorders. Other findings are dysmorphic features.

Developmental delay and intellectual disability were observed in 12/13 individuals with *WARS2*-related DEE. One neonate died at age three weeks; therefore, developmental delay could not be evaluated.

In early childhood, delay is especially in expressive language, whereas receptive language is relatively spared. Some individuals never speak [Theisen et al 2017]; in some individuals speech is slurred and slow [Musante et al 2017].

Global motor delay, especially in the first year of life, has been reported [Wortmann et al 2017, Maffezzini et al 2019]. Children, however, usually achieve independent ambulation. One child did not acquire motor abilities until age 7.5 years [Wortmann et al 2017]. Another individual was not able to walk [Theisen et al 2017].

Intellectual disability ranges from mild to severe, usually in the moderate-to-severe range. Except for information that one child attended a special school [Maffezzini et al 2019], no data are available about the level of independence in other older individuals.

Hypotonia (7/13) was axial. Additional findings were brisk reflexes, upgoing toes, and limb spasticity [Theisen et al 2017, Wortmann et al 2017, Vantroys et al 2018, Maffezzini et al 2019].

Movement disorders in *WARS2*-related DEE are usually milder than in those observed in the movement disorder spectrum and do not interfere with daily activities. The common movement disorders are ataxia (5/13) and dystonia (4/13). Ataxia is rarely severe and, in most instances, mild [Musante et al 2017, Theisen et al 2017, Wortmann et al 2017, Maffezzini et al 2019]. Although reported, choreiform movements, tremor, and athethosis are rare [Musante et al 2017, Vantroys et al 2018].

Neuropsychiatric manifestations, including aggressive behavior and sleep disorders, were described in 4/13 individuals [Musante et al 2017, Maffezzini et al 2019].

Other findings

- **Gastrointestinal manifestations** seen in *WARS2*-related DEE include intestinal pseudo-obstruction and obstipation [Wortmann et al 2017, Maffezzini et al 2019]. Pseudo-obstruction was reported in one neonate who required an ileostomy [Wortmann et al 2017].

  One child developed acute hepatopathy at age 6.5 years after the administration of valproic acid [Vantroys et al 2018], and one had an episode of severe liver failure at age four months [Bowling et al 2017].

- **Hypoglycemia** was reported in three neonates [Theisen et al 2017, Wortmann et al 2017] and one child at age six years [Vantroys et al 2018].

- **Dysmorphic and musculoskeletal features** can include long philtrum, thin upper lip, low-set ears, broad nasal bridge, hypertelorism, narrow and high-arched palate, and equinus foot [Musante et al 2017, Vantroys et al 2018]. Clench fist was also described.

- **Ocular involvement** can include optic nerve atrophy, visual impairment, retinitis pigmentosa, strabismus, nystagmus, and amblyopia [Bowling et al 2017, Wortmann et al 2017, Maffezzini et al 2019, Skorvanek et al 2022].

- **Cardiac involvement** is rare. One individual with *WARS2*-related DEE had mild cardiomyopathy [Wortmann et al 2017].

Prognosis. To date, at least seven of 13 children with *WARS2*-related DEE have died in the neonatal period or early childhood due to epileptic seizures [Theisen et al 2017, Wortmann et al 2017], respiratory insufficiency following infection, or multiorgan failure [Bowling et al 2017, Wortmann et al 2017].

Movement Disorder Spectrum

The movement disorder spectrum is primarily comprised of an early-onset levodopa-responsive parkinsonism/dystonia phenotype (12/16 individuals) [Burke et al 2018, Nogueira et al 2019, Virdee et al 2019, Martinelli et al 2020, Ilinca et al 2022, Skorvanek et al 2022, Pauly et al 2023]; however, a few (4/16) individuals do not have parkinsonism and instead have progressive myoclonus-ataxia/hyperkinetic movement disorder (4/16) [Hübers et al 2019, Skorvanek et al 2022].

Onset. Onset can be as early as in the first year of life but is more commonly in childhood [Skorvanek et al 2022].

Parkinsonism. Most individuals with *WARS2*-related movement disorder have parkinsonism (11/16) that may include moderate-to-severe bradykinesia or akinesia that is often – but not always – associated with rigidity [Burke et al 2018, Martinelli et al 2020, Skorvanek et al 2022]. Further manifestations may include dysarthria, dysphagia, and hypomimia. Parkinsonism has not been reported in individuals with myoclonus-ataxia/hyperkinetic movement disorder.

Tremor can be seen in almost all individuals (15/16). At disease onset asymmetric action tremor of the hand is seen; it can be exacerbated by excitement and physical activity. Tremor can further progress to bilateral resting

and postural tremor. In one individual, unilateral leg tremor was the first manifestation, which progressed to the other limbs during the disease course [Burke et al 2018]. Tremor was levodopa responsive in all individuals [Burke et al 2018, Skorvanek et al 2022].

Dystonia is common (10/16) and can be focal-cervical, axial, in the upper limb, or generalized [Skorvanek et al 2022].

Myoclonus was observed in 7/16 individuals, four of whom had levodopa-responsive parkinsonism/dystonia and three of whom had progressive myoclonus-ataxia/hyperkinetic movement disorder. Myoclonus typically involves the distal limbs, is severe, and increases with action and intention, as well as during excitement or fever. It is slowly progressive and can progress to continuous myoclonus [Skorvanek et al 2022].

Occasional myoclonic limb jerks have also been reported [Skorvanek et al 2022, Pauly et al 2023].

Ataxia, described in 5/16 individuals with both movement disorder phenotypes, is mild and is not present at disease onset but develops later in the disease course [Skorvanek et al 2022].

Other movement disorders

- Choreiform movements are rare but have been described [Skorvanek et al 2022].
- A hyperkinetic movement disorder with uncontrollable ballistic and dystonic movements and loss of already acquired skills has been described in one individual to date [Hübers et al 2019].

Developmental delay (DD) and intellectual disability (ID). Individuals with *WARS2*-related movement disorder have mostly mildly impaired intellect (7/16); however, details are limited [Skorvanek et al 2022, Pauly et al 2023].

Neuropsychiatric manifestations (5/16 individuals) include anxiety, depression, aggressive behavior, psychosis, apathy, social phobia, and unsociable character [Skorvanek et al 2022, Pauly et al 2023].

Other findings

- **Seizures** were reported in two individuals with *WARS2*-related movement disorder: one with versive seizures with paroxysmal epileptic alterations in the frontal lobe [Martinelli et al 2020] and the other with neonatal seizures followed by persistent generalized and complex partial seizures [Ilinca et al 2022].
- **Ocular involvement** can include ptosis, slow saccades, and exotropia [Bowling et al 2017, Wortmann et al 2017, Maffezzini et al 2019, Skorvanek et al 2022].
- **Cardiac involvement** is rare. Sinus tachycardia was documented in one individual with *WARS2*-related movement disorder [Skorvanek et al 2022].
- **Increased limb tone.** No details provided [Skorvanek et al 2022, Pauly et al 2023].

Genotype-Phenotype Correlations

Several genotype-phenotype correlations have been observed.

Biallelic loss-of-function *WARS2* pathogenic variants are typically associated with neonatal- or infantile-onset DEE. However, at least two individuals with biallelic loss-of-function *WARS2* variants had levodopa-responsive parkinsonism/dystonia [Virdee et al 2019, Ilinca et al 2022].

p.Trp13Gly. Evidence suggests that the common *WARS2* variant c.37T>G (p.Trp13Gly) is a hypomorphic variant that is disease causing only when in *trans* with a loss-of-function variant. While individuals with the hypomorphic p.Trp13Gly variant in *trans* with a loss-of-function variant typically have the milder childhood- or early adulthood-onset movement disorder phenotype, this genotype has also been identified in at least one individual with infantile-onset DEE (between age six and nine months) [Martinelli et al 2020].

In general, clinically significant intrafamilial clinical variability has not observed among sibs who have the same biallelic *WARS2* variants [Musante et al 2017, Wortmann et al 2017, Maffezzini et al 2019, Skorvanek et al 2022]. However, in one family with early-onset levodopa-responsive parkinsonism/dystonia, a sister had less severe manifestations than her affected brother. She had slowly progressive distal myoclonus and borderline intellectual ability, whereas her brother had severe distal myoclonus, intermittent cervical and axial dystonia, and mild-to-moderate intellectual disability [Skorvanek et al 2022].

Nomenclature

The title of this *GeneReview*, WARS2 deficiency, encompasses the full phenotypic spectrum reported in individuals with pathogenic *WARS2* genotypes – that is, individuals with *WARS2*-related epilepsy, typically caused by biallelic *WARS2* pathogenic variants, and individuals with *WARS2*-related movement disorder, typically caused by compound heterozygosity for a *WARS2* pathogenic variant in *trans* with the hypomorphic variant c.37T>G (p.Trp13Gly).

Other designations used in the literature to refer to individuals with phenotypes within the WARS2 deficiency spectrum include:

- NEMMLAS (*ne*urodevelopmental disorder, *m*itochondrial, with abnormal *m*ovements and *l*actic *a*cidosis, with or without *s*eizures) (OMIM 617710)
- Childhood-onset parkinsonism-dystonia 3 (OMIM 619738)

Prevalence

To date, 29 individuals from 24 families have been identified with WARS2 deficiency (see Clinical Description).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *WARS2*.

Differential Diagnosis

Epilepsy Spectrum

Developmental and epileptic encephalopathy (DEE). Because the phenotype of *WARS2*-related DEE is indistinguishable from many other inherited disorders with neonatal- or infantile-onset encephalopathy, all neurodevelopmental disorders, epileptic encephalopathy syndromes, and mitochondrial disorders should be considered in the differential diagnosis. See the Primary Mitochondrial Disorders Overview and the following OMIM Phenotypic Series:

- Intellectual disability without other distinctive findings: OMIM Autosomal Dominant, Autosomal Recessive, and Syndromic X-linked Intellectual Developmental Disorder Phenotypic Series.
- DEE: OMIM Developmental and Epileptic Encephalopathy Phenotypic Series

Additionally, the infantile-onset disorders in Table 2a have overlapping phenotypic features with *WARS2*-related DEE, including increased serum lactate, developmental delay, intellectual disability, seizures, and muscle involvement.

Table 2a. Selected Genes of Interest in the Differential Diagnosis of *WARS2*-Related Developmental and Epileptic Encephalopathy

Gene	Disorder	MOI	Features of This Disorder	
			Key features	Distinguishing this disorder from *WARS2*-related DEE
GNB1	*GNB1* encephalopathy	AD	ID/DD, behavioral issues, seizures, abnormal muscle tone, movement disorders, GI findings	• Movement disorders less common • Macrocephaly • Infantile-onset hypotonia that develops into hypertonia & spasticity
GNAO1	*GNAO1*-related disorder	AD	• Severe seizure onset shortly after birth • May be assoc w/prominent movement disorder • No distinguishing brain MRI findings • Central hypotonia, global DD, severe ID	• Movement disorder may be severe; most persons show mixed pattern of permanent or paroxysmal hyperkinetic & hypertonic movements that affect the whole body. • Overlap between movement disorders & epilepsy in most affected persons
LIAS	*LIAS*-related hyperglycinemia, lactic acidosis, & seizures (OMIM 614462)	AR	• Hypotonia & seizures assoc w/↑ serum glycine & lactate in 1st days of life • DD • Death in childhood	Hyperglycinemia
LRPPRC	Mitochondrial complex IV deficiency, nuclear type 5 (OMIM 220111)	AR	• ID/DD w/speech delay, hypotonia, ataxia, seizures • ↑ serum lactate	Lesions in brain stem & basal ganglia in brain imaging
MECP2	*MECP2*-related severe neonatal encephalopathy (See *MECP2* Disorders.)	XL	• ID, seizures, rigidity, muscle hypotonia, microcephaly • Early death due to respiratory failure	• Muscle hypotonia • Microcephaly • Bilateral polymicrogyria • Not reported in females

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; GI = gastrointestinal; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

Other seizure types. All genetic epilepsy syndromes without other distinctive findings should be considered in the differential diagnosis.

Movement Disorder Spectrum

Table 2b. Genes of Interest in the Differential Diagnosis of *WARS2*-Related Movement Disorders

Gene	Disorder	MOI	Features of This Disorder	
			Key features	Distinguishing from *WARS2*-related movement disorders
ATP13A2	Kufor-Rakeb syndrome (See Neurodegeneration with Brain Iron Accumulation Disorders Overview.)	AR	Juvenile onset w/supranuclear gaze palsy, spasticity, & dementia	• Juvenile onset • Atypical parkinsonism • Iron deposition in basal ganglia on brain MRI
DNAJC6 [1]	PARK-*DNAJC6*	AR	• ID/DD, seizures, movement disorders (dystonia, spasticity, myoclonus) • Neuropsychiatric features	• Onset of parkinsonism is between 2nd & 4th decade • Nonresponsive to levodopa • Loss of ambulation

Table 2b. continued from previous page.

Gene	Disorder	MOI	Features of This Disorder	
			Key features	Distinguishing from *WARS2*-related movement disorders
FBXO7	PARK-*FBXO7* (See Parkinson Disease Overview.)	AR	• Tremor, rigidity, akinesia, scissor gait, hyperreflexia • Mostly good responsiveness to levodopa	No neuropsychiatric symptoms
PARK7 (*DJ1*)	PARK-*DJ1* (See Parkinson Disease Overview.)	AR	• Early-onset parkinsonism w/ tremor, bradykinesia, loss of postural reflexes; asymmetric onset of symptoms • Neuropsychiatric symptoms	• Age of onset is typically older than in *WARS2*-related movement disorders. • Absence of multisystem involvement
PINK1	PARK-*PINK1*	AR	• Rigidity, bradykinesia, postural instability, resting tremor, frozen gait, dystonia hyperreflexia w/asymmetric onset • Favorable response to levodopa	• Very slow disease progression • Postural instability • Neuropsychiatric symptoms are not common.
PLA2G6	*PLA2G6*-related dystonia-parkinsonism (See *PLA2G6*-Assoc Neurodegeneration.)	AR	Extrapyramidal symptoms, balance problems, neuropsychiatric features, dystonia, myoclonus, cerebellar signs	• Often iron deposition is seen on brain imaging. • Onset is mostly in young adulthood/adulthood.
PRKN	PARK-Parkin	AR	Bradykinesia, resting tremor, rigidity, dystonia	• Slow disease progression • No neuropsychiatric features
SGCE	*SGCE* myoclonus-dystonia	AD	• Myoclonus of proximal limbs, dystonia (torticollis or writer's cramp), often responding to alcohol • Psychiatric features	• Responsive to alcohol • Dystonia can be only manifestation.
SLC18A2	Infantile-onset parkinsonism-dystonia 2 (OMIM 618049)	AR	• Infantile-onset parkinsonism w/dystonia, poor fine motor skills, ataxia, limb hypertonia, autonomic dysfunction • Variable DD	• Normal brain imaging • ↑ levels of neurotransmitter metabolites & ↓ levels of norepinephrine & dopamine in urine analysis • Exacerbation of symptoms under levodopa, but symptom control under dopamine receptor agonists
SYNJ1	PARK-*SYNJ1* (See Parkinson Disease Overview.)	AR	• Rigidity, tremor, dystonia, staring gaze, supranuclear gaze palsy • Seizures • Cognitive impairment	No neuropsychiatric symptoms

Table 2b. continued from previous page.

Gene	Disorder	MOI	Features of This Disorder	
			Key features	Distinguishing from *WARS2*-related movement disorders
TPP1	Neuronal ceroid lipofuscinosis 2 (OMIM 204500)	AR	• Seizures, mental deterioration, ataxia, myoclonus • Vision loss	• Late infantile onset w/rapid deterioration • Multiple seizure types, refractory to treatment • EEG w/photoparoxysmal response at low-frequency photic stimulation • Cerebellar & cortical atrophy of predominantly the posterior region on brain MRI
VPS13C	PARK-*VPS13C* (See Parkinson Disease Overview.)	AR	• Akineto-rigid syndrome, resting tremor • Dysautonomia • Cognitive impairment	No neuropsychiatric symptoms

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; PARK = Parkinson disease
1. Papandreou et al [2020]

For a general review of the clinical characteristics and causes of monogenic Parkinson disease, see Parkinson Disease Overview.

Myoclonus-ataxia predominate phenotypes should further be differentiated from:

- Myoclonus epilepsy syndromes (See Progressive Myoclonic Epilepsy Type 1.)
- Neuraminidase deficiency (OMIM 256550)
- DRPLA
- Neuronal ceroid lipofuscinosis (OMIM Phenotypic Series: Ceroid lipofuscinoses)

Management

No clinical practice guidelines for WARS2 deficiency have been published.

Evaluations Following Initial Diagnosis

The evaluations recommended to determine the extent of disease and needs of an individual diagnosed with *WARS2*-related epilepsy are summarized in Table 3a and of an individual with *WARS2*-related movement disorder in Table 3b. Note: It is often not necessary to repeat evaluations performed as part of the evaluation that led to the diagnosis.

Table 3a. *WARS2*-Related Epilepsy: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measure length, weight, head circumference	Plot these measurements serially on growth charts.

Table 3a. continued from previous page.

System/Concern	Evaluation	Comment
Neuromuscular	By pediatric neurologist	• Assess functional neurologic status. • Brain imaging • EEG if seizures are suspected
	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Equinovarus foot deformity, contractures, scoliosis if present • Need for adaptive devices
	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Respiratory	Referral to pediatric pulmonologist for children w/evidence of ↓ respiratory function	Assessment may incl consideration of tracheostomy & artificial ventilation (see **Ethics consultation**).
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval for GI dysmotility, aspiration risk, & nutritional status • Consider eval for gastrostomy tube placement to manage dysphagia &/or increased risk of aspiration.
Ophthalmologic	Pediatric ophthalmologist	To incl eval for: • Ptosis & strabismus • Visual acuity • Evidence of optic atrophy/pigmentary retinal changes Consider obtaining baseline photographs to document ptosis.
Cardiovascular	Eval for cardiomyopathy	
Psychiatric/ Psychologic	Assessment of emotional, behavioral, & social development	Indicated if signs of neuropsychiatric manifestations are present such as aggressiveness &/or sleep disturbance
Genetic counseling	By genetics professionals [1]	To inform families re nature, MOI, & implications of WARS2 deficiency to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community resources & support/ advocacy organizations (e.g., Parent to Parent); • Social work involvement for parental support; • Home nursing referral.	
Ethics consultation	Clinical ethics services	• Assess health care decisions in the context of the best interest of the child & the values & preferences of the family. • For difficult life-prolonging decisions or for clarification of treatment options, consider seeking further opinions from independent clinical teams. [2]

GI = gastrointestinal; MOI = mode of inheritance

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

2. Linney et al [2019]

Table 3b. *WARS2*-Related Movement Disorder: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Assessment by neurologist for cerebellar motor dysfunction (gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades, & smooth pursuit)	Use standardized scale to establish baseline for ataxia (e.g., SARA).
	Assess for parkinsonism.	Use UPDRS.
	Assess for myoclonus incl myoclonus at rest, w/ action, & in response to stimuli.	Use standardized UMRS.
Musculoskeletal / Activities of Daily Living	By physical medicine & rehab / OT & PT	To assess gross motor & fine motor skills, gait, ambulation, need for adaptive devices, need for ongoing PT/OT
Ophthalmologic	Complete eye exam	• Assess for best corrected visual acuity, nystagmus, & ptosis. • Consider referral for corrective measures incl prisms &/or surgery.
Dysarthria	Eval by speech-language pathologist	To determine need for speech-language therapy &/or alternative means of communication
Feeding	For those w/frequent choking or severe dysphagia, assess nutritional status & aspiration risk.	Consider involving a gastroenterology / nutrition / feeding team, incl formal swallowing eval.
Cognitive	By psychologist	Cognitive eval to establish baseline
Psychiatric	By mental health professional or psychiatrist	Evaluate as needed for depression & supportive therapy.
Educational assessment	Eval for IEP	Performed by educational institution
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of WARS2 deficiency to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources; • Social work involvement for parental support; • Home nursing referral.	To facilitate peer support for affected persons & their families

IEP = individual educational plan; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia; UMRS = Unified Myoclonus Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

To date, there is no known cure for WARS2 deficiency.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4a for *WARS2*-related epilepsy; see Table 4b for *WARS2*-related movement disorder).

Table 4a. *WARS2*-Related Epilepsy: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Nutrition/Feeding	Nasogastric tube, gastrostomy tube	By feeding team, incl nutritionist, gastroenterologist

Table 4a. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Respiratory insufficiency	Per treating pulmonologist	May incl consideration of tracheostomy & artificial ventilation
Neuromuscular	Physical therapy	• To maintain muscle strength & mobility & to prevent contractures • Consider need for adaptive positioning devices.
Seizures	Standard treatment w/ASM by experienced neurologist based on seizure semiology	• Certain ASMs need monitoring of levels. • Avoid use of valproate. [1] • Education of parents/caregivers [2]
Ophthalmologic involvement	By ophthalmologist	For early detection of optic nerve atrophy & visual impairment [1]
	Low vision services	For children: through early intervention programs &/or school district
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Neuropsychiatric symptoms	Standard treatment as indicated by psychologist/ psychiatrist	
Other	Aggressive mgmt of fever & infection	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Ongoing assessment of need for palliative care involvement &/or home nursing for those w/ complex medical issues

ASM = anti-seizure medication
1. See Vantroys et al [2018] and Agents/Circumstances to Avoid.
2. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Table 4b. *WARS2*-Related Movement Disorder: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Cerebellar ataxia / Activities of daily living	• Physical & occupational therapy • Self-directed exercise	• PT (balance exercises, gait training, muscle strengthening) to maintain mobility & function • OT to optimize ADL (incl use of adaptive devices, e.g., weighted eating utensils & dressing hooks) • Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, motorized chairs). • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats) & improve mobility (e.g., ramps to accommodate motorized chairs)
Parkinsonism	Pharmacologic treatment	Levodopa (alternatively, dopamine receptor agonists); propranolol for tremor control [1, 2]
Dystonia	Botulin toxin injections	One person w/cervical dystonia showed good response to botulinum toxin injections. [3]
Hyperkinetic movements	Pharmacologic treatment	Tiapridhydrochloride [4]

Table 4b. continued from previous page.

Manifestation/Concern		Treatment	Considerations/Other
Action myoclonus	**Pharmacologic**	Valproic acid	• 1st drug of choice; diminishes myoclonus & frequency of generalized seizures • Should be given in low doses while monitoring liver enzymes, as a hepatopathy after use of valproic acid has been described. [5]
		Clonazepam	FDA approved for treatment of myoclonic seizures; used as add-on therapy [6]
		High-dose piracetam	Useful in treatment of myoclonus [7]
		Levetiracetam, brivaracetam, [8] perampanel [9]	Seem to be effective for both myoclonic jerks of non-epileptic origin & generalized seizures
		Topiramate & zonisamide	May be used as add-on therapies
		N-acetylcysteine	Variable results [10]
	Other	Vagus nerve stimulation	Reduces seizures & significantly improves cerebellar function on neurologic exam [11]
		Avoid extreme stimuli (lights, noises, stress).	
Dysarthria		Speech-language therapy	Consider alternative communication methods as needed (e.g., writing pads & digital devices).
Dysphagia		Feeding therapy programs to improve nutrition & dysphagia & reduce aspiration risk	• Video esophagram may help define best food consistency. • Education re strategies to mitigate aspiration
Developmental delay / Intellectual disability		See Developmental Delay / Intellectual Disability Management Issues.	
Cognitive/Psychiatric		Pharmacologic treatment	Standard treatment for psychiatric manifestations (e.g., depression, anxiety, & psychosis)
		Psychotherapy / neuropsychological rehab	Consider cognitive & behavioral therapy.
Social support		Social work referral	To assist in identifying sources for in-home &/or local community support

ADL = activities of daily living; OT = occupational therapy; PT = physical therapy

1. Tremor cannot be completely controlled by the dopaminergic treatment; a jerky dystonic hand tremor persists despite satisfactory control of the extrapyramidal manifestations [Skorvanek et al 2022].

2. In individuals with parkinsonism, side effects of the dopaminergic therapy can occur over time, with wearing-off phenomenon, "on-off" fluctuations, peak-dose dyskinesia, and retrocolic dystonic spasms.

3. Skorvanek et al [2022]

4. Hübers et al [2019]

5. Vantroys et al [2018]

6. Shahwan et al [2005]

7. Koskiniemi et al [1998]

8. Kälviäinen et al [2016]

9. Crespel et al [2017]

10. Edwards et al [2002]

11. Smith et al [2000]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for school-age individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- Individualized education plan (IEP) services:
  - An 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.
  - As required by special education law, children should be in the least restrictive environment feasible at school and included in general education as much as possible and when appropriate.
  - Vision 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.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Surveillance

Because most infants and young children with *WARS2*-related developmental and epileptic encephalopathy are severely affected and may be hospitalized for prolonged periods from the onset of disease manifestations, they should be reviewed regularly by senior clinical specialists if they are hospitalized.

The recommendations regarding frequency of follow up in Table 5a (for *WARS2*-related epilepsy) and Table 5b (for *WARS2*-related movement disorder) pertain to outpatient visits only.

Table 5a. *WARS2*-Related Epilepsy: Recommended Surveillance

System/Concern	Evaluation	Suggested Frequency of Outpatient Surveillance After Initial Assessment
Neurologic status incl possible seizures / subclinical status epilepticus	• Eval of seizure status by pediatric neurologist; to incl EEG & video EEG monitoring • Without seizure correlates, routine EEG is not indicated. • Assess for new manifestations, e.g., seizures, changes in tone, movement disorders.	At each visit (or per treating clinician)

Table 5a. continued from previous page.

System/Concern	Evaluation	Suggested Frequency of Outpatient Surveillance After Initial Assessment
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, need for adaptive devises	
Development	Monitor developmental progress & educational needs.	
Gastrointestinal	• Assessment of feeding • Monitoring of stool frequency • Dietary assessment to maintain adequate nutrition & growth	
Growth	Assessment of nutritional status, height, weight, & body mass index	
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

OT = occupational therapy; PT = physical therapy

Table 5b. *WARS2*-Related Movement Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Cerebellar involvement	Clinical eval (using standardized scores, e.g., SARA) recommended	At each visit
Parkinsonism	Clinical eval using UPDRS	
Action myoclonus	Assess severity of myoclonus using UMRS.	
Dysarthria	Assess need for alternative communication method or speech therapy.	
Activities of daily living	Eval of rehab plan	
School performance	Interview	
Cognitive/Psychiatric	Evaluate mood, signs of psychosis, & cognitive complaints to identify need for pharmacologic & psychotherapeutic interventions.	
Family support & resources	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

SARA = Scale for the Assessment and Rating of Ataxia; UMRS = Unified Myoclonus Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale

Agents/Circumstances to Avoid

Valproic acid can cause severe hepatopathy and neurologic deterioration, as reported in one individual with *WARS2*-related DEE [Vantroys et al 2018].

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

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

WARS2 deficiency is inherited in an autosomal recessive manner. To date:

- Most individuals with *WARS2*-related epilepsy have the disorder as the result of biallelic *WARS2* loss-of-function pathogenic variants;
- Most individuals with *WARS2*-related movement disorder have the disorder as the result of compound heterozygosity for a *WARS2* loss-of-function pathogenic variant in *trans* with the hypomorphic *WARS2* variant c.37T>G (p.Trp13Gly).

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *WARS2* pathogenic variant or hypomorphic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *WARS2* pathogenic variant or hypomorphic variant and to allow reliable recurrence risk assessment..
- If a pathogenic variant or hypomorphic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *WARS2* pathogenic variant or hypomorphic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic variants, a 50% chance of inheriting one variant, and a 25% chance of inheriting neither of the familial *WARS2* variants. Sibs who inherit:
  - Biallelic loss-of-function pathogenic variants are likely to have *WARS2*-related epilepsy;
  - A *WARS2* loss-of-function pathogenic variant in *trans* with the hypomorphic *WARS2* variant are likely to have *WARS2*-related movement disorder;
  - One variant (either a pathogenic variant or a hypomorphic variant) are asymptomatic and are not at risk of developing WARS2 deficiency;
  - Neither of the familial *WARS2* variants are unaffected and not carriers.

- In all but one family, clinically significant intrafamilial clinical variability has not been observed among sibs who have the same biallelic *WARS2* variants [Musante et al 2017, Wortmann et al 2017, Maffezzini et al 2019, Skorvanek et al 2022] (see Genotype-Phenotype Correlations).
- Note: Individuals who are homozygous for the hypomorphic *WARS2* variant are predicted to be asymptomatic [Ilinca et al 2022, Skorvanek et al 2022].

Offspring of a proband

- To date, individuals with *WARS2*-related developmental and epileptic encephalopathy are not known to reproduce.
- The offspring of an individual with a *WARS2*-related movement disorder are obligate heterozygotes (carriers) for either a *WARS2* pathogenic variant or the *WARS2* hypomorphic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a WARS2 deficiency-related variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the WARS2 deficiency-related variants in the family.

Related Genetic Counseling Issues

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 who are affected, are carriers, or are at risk of being carriers.
- Carrier testing for reproductive partners of individuals known to be carriers should be considered, particularly if consanguinity is likely and/or if both partners are of the same ethnic background.

Prenatal Testing and Preimplantation Genetic Testing

Once the WARS2 deficiency-related variants have been identified in an affected family member, prenatal and preimplantation genetic testing 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.

- **American Parkinson Disease Association (APDA)**
  Phone: 800-223-2732
  Fax: 718-981-4399
  Email: apda@apdaparkinson.org
  www.apdaparkinson.org
- **Fox Trial Finder**
  foxtrialfinder.michaeljfox.org

- **MedlinePlus**
  Parkinson disease
- **Michael J. Fox Foundation for Parkinson's Research**
  Phone: 800-708-7644 (toll-free)
  Email: info@michaeljfox.org
  www.michaeljfox.org
- **Mito Foundation**
  Australia
  Phone: 61-1-300-977-180
  Email: info@mito.org.au
  www.mito.org.au
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Parkinson's Disease Information Page
- **Parkinson's Disease Society (UK)**
  United Kingdom
  Phone: 0808 800 0303
  Email: hello@parkinsons.org.uk
  www.parkinsons.org.uk
- **Parkinson's Foundation**
  Phone: 800-4PD-INFO (473-4636)
  Email: contact@parkinson.org
  www.parkinson.org
- **The Charlie Gard Foundation**
  United Kingdom
  Email: hello@thecharliegardfoundation.org
  www.thecharliegardfoundation.org
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org
- **RDCRN Patient Contact Registry: North American Mitochondrial Disease Consortium**
  Patient Contact Registry

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. WARS2 Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
WARS2	1p12	Tryptophan--tRNA ligase, mitochondrial	WARS2 @ LOVD	WARS2	WARS2

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 WARS2 Deficiency (View All in OMIM)

604733	TRYPTOPHANYL-tRNA SYNTHETASE 2; WARS2
617710	NEURODEVELOPMENTAL DISORDER, MITOCHONDRIAL, WITH ABNORMAL MOVEMENTS AND LACTIC ACIDOSIS, WITH OR WITHOUT SEIZURES; NEMMLAS
619738	PARKINSONISM-DYSTONIA 3, CHILDHOOD-ONSET; PKDYS3

Molecular Pathogenesis

Aminoacyl-tRNA synthetases are nucleus-encoded mitochondrial enzymes involved in a broad range of cellular processes. Pathogenic variants involving aminoacyl-tRNA synthetases can affect several cellular mechanisms, mainly in tissues with a high energy demand such as the central nervous system (CNS). Accordingly, pathogenic variants in 17 of the 19 aminoacyl-tRNA synthetases have been associated with diseases of the CNS [Lott et al 2013, Moulinier et al 2017, Sissler et al 2017].

WARS2 encodes a ubiquitously expressed mitochondrial tryptophanyl-tRNA synthetase, which has a cytoplasmic (WAR) and a mitochondrial (WARS2) form vital for mitochondrial translation. Pathogenic variants in *WARS2* cause different structural and kinetic changes in mitochondrial tryptophanyl-tRNA synthetase that in turn affect one or more steps in the process of transferring/charging tryptophan to its cognate tRNA in the mitochondria, thus affecting mitochondrial protein synthesis. Investigation of aminoacylation of *WARS2* variants showed a clear decrease in charged mitochondrial tryptophanyl-tRNA synthetase in the fibroblasts of affected individuals, while total mitochondrial tryptophanyl-tRNA synthetase levels appeared normal, indicating that the defect in WARS2 deficiency causes improper aminoacylation of tryptophanyl-tRNA, leading to abnormalities in mitochondrial oxidative phosphorylation protein biosynthesis [Wortmann et al 2017].

Functional data show that the hypomorphic p.Trp13Gly variant diminishes (but does not abolish) transport of WARS2 protein into mitochondria [Ilinca et al 2022, Skorvanek et al 2022]. Of particular note, individuals homozygous for the hypomorphic p.Trp13Gly variant are predicted to be asymptomatic (see ***WARS2*-specific laboratory technical considerations**).

Mechanism of disease causation. Loss of function

***WARS2*-specific laboratory technical considerations.** Evidence to date suggests that the common *WARS2* variant p.Trp13Gly is a hypomorphic variant that is disease-causing only when in *trans* with a loss-of-function pathogenic *WARS2* variant. The presence of the p.Trp13Gly variant at a relatively high frequency (922 alleles [0.33%], including six homozygotes in all populations in gnomAD v2.1.1) supports the idea that this variant is not disease causing in the homozygous state. Based on the assumption that individuals in reference databases such as gnomAD are not affected by rare severe neurologic disorders, standard algorithms used in clinical diagnostic laboratories are likely to filter out variants that are present at a high frequency in the homozygous state. Therefore, diagnostic laboratories offering testing for *WARS2* need to take into consideration the relative high frequency of this hypomorphic variant and its relevance to disease causation, especially if another pathogenic *WARS2* variant is detected in the heterozygous state, in which case using additional and/or modified filters to specifically confirm/exclude the presence of the p.Trp13Gly hypomorphic variant in *trans* is recommended [Ilinca et al 2022, Skorvanek et al 2022].

Table 6. *WARS2* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_015836.4 NP_056651.1	c.37T>G	p.Trp13Gly	Hypomorphic variant that is not disease causing if homozygous but is disease causing when in *trans* w/loss-of-function pathogenic variant [Ilinca et al 2022, Skorvanek et al 2022] (See Genotype-Phenotype Correlations.)

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Contact Professor Henry Houlden (h.houlden@ucl.ac.uk) or Sara Nagy, MD, Msc (s.nagy@ucl.ac.uk) to inquire about review of *WARS2* variants of uncertain significance.

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