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TARDBP-Related Amyotrophic Lateral Sclerosis-Frontotemporal Dementia

Synonyms: *TARDBP*-ALS-FTD, TDP-43 Proteinopathy, TDP-43-Linked ALS-FTD

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Summary

Clinical characteristics

In this *GeneReview*, *TARDBP* amyotrophic lateral sclerosis-frontotemporal dementia (*TARDBP*-ALS-FTD) refers to the spectrum of phenotypes caused by pathogenic variants in *TARDBP*, the gene encoding TDP-43. The phenotypic spectrum encompasses pure (i.e., without other neurologic findings) amyotrophic lateral sclerosis (ALS; most common), pure (i.e., without other neurologic findings) frontotemporal dementia (FTD; rare), a combination of ALS and FTD, and atypical neurologic phenotypes (very rare). Individuals with the same *TARDBP* pathogenic variant (even within the same family) may have clinical features that vary in both type and severity. Common manifestations are dysarthria and dysphagia; less common manifestations can include parkinsonism, cognitive deterioration, and behavioral and psychological manifestations of dementia. Life expectancy for *TARDBP*-ALS is highly variable and mainly associated with an individual's clinical features; overall disease duration averages three to five years. For *TARDBP*-FTD, disease duration averages one to 16 years.

Diagnosis/testing

The diagnosis of *TARDBP*-ALS-FTD is established in a proband with suggestive findings and most commonly a heterozygous pathogenic (or likely pathogenic) variant in *TARDBP* identified by molecular genetic testing. Rarely, homozygous pathogenic (or likely pathogenic) variants in *TARDBP* have been reported.

Management

Treatment of manifestations: There is no cure for *TARDBP*-ALS-FTD. Individuals benefit from multidisciplinary supportive care to improve quality of life, maximize function, and reduce complications. This can include care by

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specialists in neurology, physiotherapy, occupational therapy, speech-language therapy, nutrition, respiratory therapy, pulmonology, psychology, social work, genetic counselling, palliative care, and special nursing.

Surveillance: Frequent monitoring of existing manifestations, the individual's response to supportive care, and the emergence of new manifestations by the treating clinicians is recommended.

Genetic counseling

TARDBP-ALS-FTD is inherited in an autosomal dominant manner. About half of individuals diagnosed with *TARDBP*-ALS-FTD have an affected parent. Each child of an individual with *TARDBP*-ALS-FTD has a 50% chance of inheriting the *TARDBP* pathogenic variant. Once a *TARDBP* pathogenic variant has been identified in an affected family member, predictive testing for at-risk relatives and prenatal and preimplantation genetic testing for the presence of the *TARDBP* pathogenic variant are possible. (Note: Because the clinical presentation of *TARDBP*-ALS-FTD may differ among heterozygous family members, accurate prediction of future possible clinical manifestations in an individual found to have a familial *TARDBP* pathogenic variant is not possible.)

GeneReview Scope

With the current widespread use of multigene panels and comprehensive genomic testing, it has become apparent that heterozygous *TARDBP* pathogenic variants are associated with:

- A phenotypic spectrum encompassing pure (i.e., without other neurologic findings) amyotrophic lateral sclerosis (ALS; most common), pure (i.e., without other neurologic findings) frontotemporal dementia (FTD; rare), a combination of ALS and FTD, and atypical neurologic phenotypes;
- Variable expressivity such that individuals with the same *TARDBP* pathogenic variant (even within the same family) may have clinical features that vary in both type and severity.

Because *TARDBP* pathogenic variants are associated with both a broad phenotypic spectrum and variable expressivity, individuals found to have a *TARDBP* pathogenic variant need to be evaluated for medically actionable motor and psychiatric manifestations in the entire *TARDBP*-ALS-FTD spectrum regardless of the clinical findings that prompted molecular genetic testing. In addition, relatives at risk of inheriting a *TARDBP* pathogenic variant need to be counseled regarding the marked variation in clinical findings that can be seen even among affected family members.

Diagnosis

In this *GeneReview*, *TARDBP* amyotrophic lateral sclerosis-frontotemporal dementia (*TARDBP*-ALS-FTD) refers to the spectrum of phenotypes caused by pathogenic variants in *TARDBP*, the gene encoding TDP-43.

No consensus clinical diagnostic criteria for *TARDBP*-ALS-FTD have been published.

Suggestive Findings

TARDBP-ALS-FTD **should be suspected** in probands with the following clinical and neuroimaging findings and family history.

Clinical findings

- **Age at onset** ranges from 22 to 80 years, with a mean of 53 ± 10-12 years [Newell et al 2019, Sprovieri et al 2019].
- **Amyotrophic lateral sclerosis (ALS),** the most common clinical presentation of *TARDBP*-ALS-FTD, is characterized by progressive degeneration of both upper and lower motor neurons resulting in muscle weakness and paralysis.

- **Frontotemporal dementia (FTD),** the second most common presentation, includes behavior and/or language dysfunction. Of the three FTD clinical syndromes, behavioral FTD (bvFTD) is more widespread than the two language variants, semantic variant PPA (svPPA) and nonfluent variant PPA (nfvPPA), which are collectively identified as primary progressive aphasia (PPA) [Jo et al 2020].

Brain MRI

- **ALS.** Although conventional structural MRI scans are usually normal in individuals with the ALS phenotype, corticospinal tract high signal intensity may be seen. Of note, research studies demonstrate widespread volumetric changes beyond the frontotemporal and motor regions.
- **FTD.** Although frontotemporal atrophy is prominent, these findings are general features of ALS/FTD of all causes. There are no systematic MRI studies of *TARDBP*-ALS-FTD.

Family history. Because *TARDBP*-ALS-FTD can be associated with significant intrafamilial clinical variability, a thorough family history should be taken with a high index of suspicion for both motor and psychiatric signs regardless of the presenting features in the proband. The family history may be positive and consistent with autosomal dominant inheritance (e.g., males and females in multiple generations with ALS and/or FTD) or the family history may be negative (i.e., the proband represents a simplex case). Absence of a known family history does not preclude the diagnosis.

Note: Simplex cases (i.e., a single occurrence of the disorder in a family) are sometimes referred to as "sporadic cases"; however, because the term "sporadic" can imply a non-recurring (non-genetic) cause, the term "simplex" is preferred.

Establishing the Diagnosis

The diagnosis of *TARDBP*-ALS-FTD **is established** in a proband with suggestive findings and most commonly a heterozygous pathogenic (or likely pathogenic) variant in *TARDBP* identified by molecular genetic testing (see Table 1). Rarely, homozygous pathogenic (or likely pathogenic) variants in *TARDBP* have been reported (see Molecular Genetics, ***TARDBP*-specific laboratory technical considerations**).

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

Because *TARDBP*-ALS-FTD is clinically indistinguishable from ALS/FTD due to other causes, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

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

- **An ALS multigene panel** that includes *TARDBP* 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. (5) Because some ALS panels may

be limited to the most frequently associated genes (e.g., *C9orf72* and *SOD1* [see ALS Overview]), care needs to be taken to choose a multigene panel that includes *TARDBP*.

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 is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is increasingly performed.

  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 *TARDBP*-Related Amyotrophic Lateral Sclerosis-Frontotemporal Dementia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TARDBP	Sequence analysis [3]	~100% [4]
	Gene-targeted deletion/duplication analysis [5]	None 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 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. 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. Since the proposed mechanism that leads to *TARDBP*-ALS-FTD is gain of function of *TARDBP*, it is unlikely that copy number variants in *TARDBP* will comprise a significant number of variants.

Clinical Characteristics

Clinical Description

Most individuals with *TARDBP*-related amyotrophic lateral sclerosis-frontotemporal dementia (*TARDBP*-ALS-FTD) present with manifestations of amyotrophic lateral sclerosis (ALS) with upper and lower motor neuron disease (MND). Rarely, affected individuals present with pure (i.e., without other neurologic findings) frontotemporal dementia (FTD), a combination of ALS and FTD, or an atypical neurologic phenotype such as FTD with supranuclear palsy. Additional manifestations within the *TARDBP*-ALS-FTD phenotypic spectrum may appear during the disease course [Van Deerlin et al 2008, Yokoseki et al 2008] (see Table 2).

Of note, the clinical presentation of *TARDBP*-ALS-FTD may differ between and within families, causing an unpredictable pattern and age of onset of clinical manifestations.

Table 2. *TARDBP*-Related Amyotrophic Lateral Sclerosis-Frontotemporal Dementia: Frequency of Disease Features

Feature	Frequency			Comment
	Nearly all	Common [1]	Infrequent	
Motor findings				
Upper motor neuron disease	●			Weakness, spasticity, altered muscle tone
Lower motor neuron disease	●			Weakness, fasciculations, atrophy

Table 2. continued from previous page.

Feature		Frequency			Comment
		Nearly all	Common [1]	Infrequent	
Bulbar involvement	Dysarthria		●		Motor language deficit
	Dysphagia		●		Problems swallowing food &/or liquids
Parkinsonism				●	Extrapyramidal findings such as resting tremor, rigidity, akinesia
Cognitive deterioration					
Executive dysfunction				●	Issues w/planning, problem solving, organizing
Memory impairment				●	Amnesia, mostly recent memory
Language impairment				●	Deficits in speech production or comprehension
Apraxia				●	Impaired execution of learned motor tasks
Dyscalculia				●	Diminished mathematical reasoning
Behavioral & psychological manifestations of dementia					
Disinhibition				●	Impulsivity, socially unacceptable behavior, risk taking
Apathy				●	Indifference, lack of interest
Delusions/hallucinations				●	Often bizarre delusions, mostly visual hallucinations
Psychosis				●	Psychosis, often as initial symptom
Anxiety				●	Generalized stress & apprehension
Repetitive, compulsive behavior				●	Often complex, ritualistic behaviors mimicking obsessive-compulsive disorder
Preference for sweet food				●	↑ craving for sweet foods

1. Features are ranked as common if present >33%, if frequency was mentioned.

ALS. The entire clinical spectrum of ALS (which includes abnormal muscle tone and tendon reflexes, fasciculations, muscle cramps, and gait disturbances) may be present. In one study, spinal onset (involving limb muscles) occurred in 62.5% of affected individuals, bulbar onset (including involvement of swallowing and speech) in 10%, and both bulbar and spinal onset in ~27% [Lattante et al 2013]. Some early cognitive impairment may be present even in individuals previously diagnosed with pure ALS [Gregory et al 2020].

FTD. The three main FTD clinical syndromes are behavioral variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA), and nonfluent/agrammatic variant primary progressive aphasia (nfvPPA). Studies of the rare instances of pure *TARDBP*-FTD show that affected individuals usually present with bvFTD with common behavioral features such as irritability, repetitive behavior, aggressiveness, and delusions that worsen progressively. These behavioral features can overlap with executive dysfunction, memory deficits, and changes in eating habits. Some individuals also manifest primary progressive aphasia (PPA) with language impairment resembling semantic dementia [Floris et al 2015].

Parkinsonism. Heterozygous *TARDBP* pathogenic variants have also been associated with parkinsonism. The manifestations include Parkinson-like weakness in the legs, overlapping with bvFTD, hallucinations, REM sleep behavior disorder, and mild cognitive impairment [Rayaprolu et al 2013].

Life expectancy for *TARDBP*-ALS is highly variable and mainly associated with an individual's clinical features. Overall disease duration averages three to five years from onset with a steady rate of decline.

For *TARDBP*-FTD, disease duration averages one to 16 years from onset, depending on the cohort [Floris et al 2015]. As expected, survival in FTD is markedly compromised when ALS manifestations become apparent [Geser et al 2009].

Genotype-Phenotype Correlations

Since most *TARDBP* pathogenic variants have incomplete age-related penetrance, identifying genotype-phenotype correlations becomes difficult. No clear genotype-phenotype correlations have been identified.

However, of note:

- Three *TARDBP* variants occurring at lysine residues, c.527A>T (p.Lys176Ile) [Chen et al 2021], c.541A>G (p.Lys181Glu) [Chen et al 2019], and c.787A>G (p. Lys263Glu) [Kovacs et al 2009], have been associated with FTD phenotypes including cognitive deficits and personality and behavioral changes such as apathy and lack of motivation (see Table 6). Nevertheless, these associations cannot be made conclusively without additional reports.
- Phenotypic manifestations of *TARDBP* variants can vary by ethnicity [Acosta-Uribe et al 2022].
- In a Sardinian population with FTD caused by *TARDBP* variant c.1144G>A (p.Ala382Thr), most affected individuals had a bvFTD phenotype with temporal lobe atrophy [Floris et al 2015].

Penetrance

While there is intra- and interfamilial variability in the age of onset and clinical presentation, the pathogenicity of missense variants shows high penetrance and males and females are similarly affected [Hardiman et al 2022].

Prevalence

Dedicated online databases provide detailed information on geographic prevalence of *TARDBP* pathogenic variants [Pinto et al 2011, Cruts et al 2012, Abel et al 2013].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Family history. The frequency of *TARDBP* pathogenic variants is about twice as high in individuals with a family history of amyotrophic lateral sclerosis (ALS) and/or frontotemporal dementia (FTD) (3%-4%) compared to those without a family history of these disorders (~1.5%) [Mackenzie et al 2010, Lattante et al 2013].

Differential diagnosis for *TARDBP*-ALS-FTD

- **Isolated upper motor signs.** Compressive (cervical) myelopathy, hereditary spastic paraplegia, adrenomyeloneuropathy (see X-Linked Adrenoleukodystrophy), and cerebrotendinous xanthomatosis in individuals with isolated manifestations of upper motor involvement
- **Lower motor signs.** Plexopathy, chronic inflammatory polyradiculoneuropathy, and multifocal motor, toxic, infectious, or metabolic neuropathies or myopathies such as inclusion body myositis (see Inclusion Body Myopathy with Paget Disease of Bone and/or FTD) or polymyositis can mimic lower motor signs [Masrori and Van Damme 2020].
- **Other forms of upper and/or lower motor neuron disorders.** Spinal muscular atrophy IV (See ALS Overview, Differential Diagnosis.)

- **Psychiatric disorders.** Especially in *TARDBP*-bvFTD with prominent behavioral manifestations, often in young individuals, a psychiatric diagnosis such as depression, obsessive-compulsive disorder, bipolar disorder, and schizophrenia may be considered. Diagnostic workup and longitudinal clinical follow up are likely to distinguish between psychiatric disorders and FTD; however, they may exist concomitantly.
- A rare ALS/FTD variant of prion disease [Vicente-Pascual et al 2018]

Management

No clinical practice guidelines specifically for *TARDBP*-related amyotrophic lateral sclerosis-frontotemporal dementia (*TARDBP*-ALS-FTD) have been published. Guidance provided in this section is for amyotrophic lateral sclerosis (ALS) and/or frontotemporal dementia (FTD) more generally.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *TARDBP*-ALS-FTD, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *TARDBP*-Related Amyotrophic Lateral Sclerosis-Frontotemporal Dementia

System/Concern	Evaluation	Comment
Neurologic	Complete neurologic exam	• UMN involvement: assess spasticity, Babinski signs, hyperreflexia • LMN involvement: assess weakness, amyotrophy, fasciculations; perform EMG
Cognitive function	Neuropsychological exam	Evaluate extent & profile of cognitive disturbance
Musculoskeletal/ADL	Orthopedics / physical medicine & rehab / PT eval	To incl assessment of: • Muscle tone; joint range of motion; posture; mobility; strength, coordination, & endurance; pain; bedsores • Need for adaptive devices • Footwear needs • Physical therapy needs • Need for assistive walking devices (e.g., cane, walker, walker w/wheels, walker w/seat, wheelchair)
	OT eval	To assess: • Fine motor function (e.g., hands, feet, face, fingers, & toes) • Home adaptations for ADL & safety
	Eval of driving safety	In case of cognitive impairment & impaired judgement, driving safety should be evaluated.
Psychiatric illness	History of psychiatric illness [1]	• Attention to possible alcohol or drug abuse • Referral for psychiatric eval as needed
Dysarthria	For those w/dysarthria: eval by speech-language pathologist	Referral to speech-language pathologist as needed
Dysphagia	For those w/frequent choking or severe dysphagia, assess nutritional status & aspiration risk	Consider involving a gastroenterologist, nutritionist, feeding team, &/or speech-language pathologist, incl formal swallowing eval.
Respiratory function	By pulmonologist	Assess respiratory function & need for respiratory support.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of *TARDBP*-ALS-FTD 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.	• Early discussion of advanced care planning • The affected person's perspective & burden must be taken into account for clinical decision making. • The presence of cognitive impairment may raise ethical concerns.

ADL = activities of daily living; LMN = lower motor neuron; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; UMN = upper motor neuron

1. Devenney et al [2014], Piguet et al [2017], Oskarsson et al [2018], Masrori & Van Damme [2020]

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

Treatment of Manifestations

There is no cure for *TARDBP*-ALS-FTD.

Individuals with *TARDBP*-ALS-FTD benefit from supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by a neurologist, physiotherapist, occupational therapist, speech-language therapist, dietitian, respiratory therapist, pulmonologist, psychologist, social worker, genetic counsellor, palliative care physician, and specially trained nurses (see Table 4).

Table 4. Treatment of Manifestations in Individuals with *TARDBP*-Related Amyotrophic Lateral Sclerosis-Frontotemporal Dementia

Manifestation/Concern	Treatment	Considerations/Other
ADL	Physical medicine & rehab / PT & OT	Ankle-foot braces, walkers, wheelchairs, hospital beds, toileting equipment, lifts to improve functionality
UMN involvement / LMN involvement	Riluzole	
	Edaravone	Edaravone is not approved worldwide.
Spasticity	Baclofen, tizanidine, cannabinoids, & muscle stretching	
Muscle cramps	Magnesium supplements, quinine sulfate, gabapentin, or carbamazepine	
Parkinsonism	PT, levodopa trial	Because of psychiatric levodopa side effects, use only when functional impairment is significant.
Cognitive function	Cognitive rehab	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Psychiatric/ behavioral manifestations	Environmental, behavioral, & physical interventions	To minimize occurrence & consequences of undesired behaviors
	Counseling	For those w/affective disorders or to support affected person &/or caretaker(s)
	SSRIs	For those w/affective disorders or disinhibition & challenging behaviors, the first-line approach is pharmacologic therapy.
	Venlafaxine	Used when apathy is prominent
	Atypical antipsychotics	• When severe manifestations (agitation, aggressiveness, psychosis) are refractory to SSRIs • Often a temporizing measure until individuals become more apathetic. • Risk of iatrogenic extrapyramidal syndrome
Pseudobulbar affect	Dextromethorphan/quinidine	
Dysarthria	Per speech-language therapist	Use of augmentative communication devices
Dysphagia	Continuous eval & therapy	Safe swallowing techniques, diet modifications, gastrostomy tube
Sialorrhea	Anticholinergic medications, salivary gland botulinum toxin injections, or radiotherapy	Anticholinergic medication can affect cognition.
Respiratory function	Assisted ventilation	Noninvasive at first, proceeding to tracheostomy if necessary
Bladder dysfunction	Anticholinergics & intravesical botulinum toxin	Anticholinergic medication can affect cognition.
Family/caregiver support & resources	Psychosocial support & education via caregiver & patient support groups	To reduce stress & burden on caregivers

ADL = activities of daily living; LMN = lower motor neuron; OT = occupational therapy; PT = physical therapy; SSRI = selective serotonin reuptake inhibitor; UMN = upper motor neuron
Based on Andersen et al [2012], Siuda et al [2014], Piguet et al [2017],Oskarsson et al [2018], Masrori & Van Damme [2020]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, see Table 5 for recommended evaluations.

Table 5. Recommended Surveillance for Individuals with *TARDBP*-Related Amyotrophic Lateral Sclerosis-Frontotemporal Dementia

System/Concern	Evaluation	Frequency	
		ALS	FTD
Neurologic	Neurologic exam for new manifestations &/or response to medications	Every 2-3 mos	Undefined; depends on disease progression & presenting manifestations
Mobility/ADL	Physical medicine & rehab / PT & OT		
Cognitive function	Rapid screening tools, incl tests of verbal fluency		
Psychiatric/behavioral manifestations	Medical history, neurologic exam		
Pseudobulbar affect	Medical history		NA
Dysarthria	Eval by speech-language therapist	Every 3-6 mos	Undefined; depends on disease progression & presenting manifestations
Dysphagia	Medical history	Every 2-3 mos	NA
Sialorrhea			
Respiratory function	Medical history, clinical exam, additional testing (e.g., forced vital capacity, vital capacity)		
Bladder function	Medical history		
Family/caregiver support & resources	Medical history; assess need for additional support.		Undefined; depends on disease progression & presenting manifestations

ADL = activities of daily living; NA = not applicable; OT = occupational therapy; PT = physical therapy
Based on Andersen et al [2012], Piguet et al [2017]

Evaluation of Relatives at Risk

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

Pregnancy Management

Incidences of ALS complicating pregnancy are rare, since the disease shows a low prevalence in women of reproductive age. Pregnancy of women with ALS is largely complicated by impaired respiratory function due to underlying weakness of the diaphragm and costal muscles and the increased respiratory and weight-bearing demands of pregnancy [Lupo et al 1993]. However, the influence of pregnancy on ALS disease progression itself remains speculative.

Maternal ALS is not particularly associated with poorer neonatal outcomes and does not appear to cause obstetric complications. However, the method and timing of delivery may be influenced by the severity of the disease. Although natural delivery is possible because ALS does not affect the motor and sensory nerves of the uterus [Chiò et al 2003], cæsarean delivery may be required due to restricted mobility and the increased respiratory demands of labor [Sarafov et al 2009, Pathiraja & Ranaraja 2020].

Riluzole can safely be used during pregnancy, although its effects on fetal growth remain unclear. Low birth weight has previously been reported when used during pregnancy [Scalco et al 2012].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Unlike *SOD1*-ALS-FTD (see ALS Overview), for which tofersen has recently been approved by the FDA, there are no approved antisense oligonucleotide therapies for *TARDBP*-ALS-FTD.

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

TARDBP-related amyotrophic lateral sclerosis-frontotemporal dementia (*TARDBP*-ALS-FTD) is inherited in an autosomal dominant manner.

Note: Rarely, homozygous pathogenic (or likely pathogenic) variants in *TARDBP* have been reported (see Molecular Genetics, ***TARDBP*-specific laboratory technical considerations**). Genetic counseling for individuals homozygous for a *TARDBP* pathogenic and their family members is not discussed in this chapter.

Risk to Family Members (Autosomal Dominant Inheritance)

Parents of a proband

- About half of individuals diagnosed with *TARDBP*-ALS-FTD have an affected parent.
- About half of individuals diagnosed with *TARDBP*-ALS-FTD represent simplex cases (i.e., the only family member known to have *TARDBP*-ALS-FTD.
- 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.
- The family history of some individuals diagnosed with *TARDBP*-ALS-FTD may appear to be negative because of failure to recognize the disorder in family members, 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%.
- The clinical presentation of *TARDBP*-ALS-FTD may differ among family members who are heterozygous for the same pathogenic variant, causing an unpredictable pattern and age of onset of clinical manifestations (see Penetrance).
- If the *TARDBP* 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 both parents are clinically unaffected but their genetic status is unknown, sibs are still at increased risk for *TARDBP*-ALS-FTD because of the possibility of age-related penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *TARDBP*-ALS-FTD has a 50% chance of inheriting the *TARDBP* 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 *TARDBP* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *TARDBP* pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.
- Predictive testing may facilitate recruitment into future gene-specific clinical trials (see Therapies Under Investigation).

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of *TARDBP*-ALS-FTD, it is appropriate to consider testing of symptomatic individuals regardless of age.

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 or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *TARDBP* pathogenic variant or, rarely, pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Note: Accurate prediction of future possible clinical manifestations in a fetus found to have a familial *TARDBP* pathogenic variant is not 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. For more information, see the National Society of Genetic Counselors position statement on prenatal testing in adult-onset conditions.

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.

- **ALS Association**
  Phone: 800-782-4747
  Email: alsinfo@alsa-national.org
  www.alsa.org
- **Amyotrophic Lateral Sclerosis Society of Canada**
  Canada
  Phone: 800-267-4257 (toll-free); 416-497-2267
  Email: communityservices@als.ca
  www.als.ca
- **Les Turner ALS Foundation**
  Phone: 847-679-3311
  Email: info@lesturnerals.org
  www.lesturnerals.org
- **MedlinePlus**
  Amyotrophic lateral sclerosis
- **NCBI Genes and Disease**
  Amyotrophic lateral sclerosis
- **Association for Frontotemporal Degeneration (AFTD)**
  Phone: 866-507-7222
  Email: info@theaftd.org
  www.theaftd.org
- **Motor Neurone Disease Association**
  United Kingdom
  Phone: 01604 250505
  Fax: 01604 624726/638289
  Email: enquiries@mndassociation.org
  www.mndassociation.org
- **Muscular Dystrophy Association - Amyotrophic Lateral Sclerosis**
  Phone: 800-572-1717

Email: ResourceCenter@mdausa.org
www.mda.org/disease/amyotrophic-lateral-sclerosis

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. TARDBP-Related Amyotrophic Lateral Sclerosis-Frontotemporal Dementia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TARDBP	1p36.22	TAR DNA-binding protein 43	TARDBP database	TARDBP	TARDBP

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 TARDBP-Related Amyotrophic Lateral Sclerosis-Frontotemporal Dementia (View All in OMIM)

605078	TAR DNA-BINDING PROTEIN; TARDBP
612069	AMYOTROPHIC LATERAL SCLEROSIS 10 WITH OR WITHOUT FRONTOTEMPORAL DEMENTIA; ALS10

Molecular Pathogenesis

TARDBP encodes the TAR DNA-binding protein 43 (TDP-43). As a ubiquitously expressed protein, TDP-43 regulates many aspects of RNA metabolism, including alternative splicing, microRNA processing, RNA transport, and local translation. Although predominantly nuclear, TDP-43 shuttles into the cytoplasm. A prominent feature of *TARDBP*-related amyotrophic lateral sclerosis-frontotemporal dementia (*TARDBP*-ALS-FTD) is the loss of TDP-43 from the nucleus and its deposition in the cytoplasm, where it forms hyperphosphorylated and ubiquitinated aggregates [Arai et al 2006, Neumann et al 2006]. This abnormal redistribution of TDP-43 suggests a loss of normal nuclear function and a toxic gain of function in the cytoplasm. These proposed disease mechanisms are not mutually exclusive and may occur at the same time.

Most pathogenic variants are found in exon 6, which encodes for the glycine-rich C-terminal region of TDP-43 [LOVD].

Mechanism of disease causation. Importantly, TDP-43 regulates its own expression by binding to its transcript and triggering alternative splicing of intron 7 within its 3' untranslated region (UTR), leading to the destruction of its mRNA. The existence of 3' UTR variants associated with amyotrophic lateral sclerosis, and the discovery that one of these variants leads to increased transcript expression, suggests that perturbed autoregulation may result in disease [Gitcho et al 2009]. Recent findings point to the importance of TDP-43 liquid-liquid phase separation in mediating autoregulation, as disease-associated variants may lead to defects in self-regulation by modulating TDP-43 condensation properties [Hallegger et al 2021, Koehler et al 2022].

***TARDBP*-specific laboratory technical considerations.** Two variants in *TARDBP* (c.881G>T; p.Gly294Val and c.1144G>A; p.Ala382Thr) have been reported in the homozygous state in individuals with ALS-FTD [Borghero et al 2011, Mosca et al 2012, Corrado et al 2020]. Therefore, these variants can cause disease when heterozygous (most common) or homozygous.

Table 6. Notable *TARDBP* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_007375.4 NP_031401.1	c.800A>G	p.Asn267Ser	Common variant [Borroni et al 2009]
	c.859G>A	p.Gly287Ser	Common variant [Morgan et al 2017]
	c.881G>T	p.Gly294Val	Common variant [Sun et al 2014]; reported in homozygous state in person w/ALS [Corrado et al 2020]
	c.883G>A	p.Gly295Ser	Common variant [Floris et al 2015]
	c.892G>A	p.Gly298Ser	ALS founder variant in southern China [Xu et al 2022]
	c.943G>A	p.Ala315Thr	Common variant [Corcia et al 2021]
	c.1009A>G	p.Met337Val	Common variant [Sreedharan et al 2008, Pang et al 2017]
	c.1122T>G	p.Tyr374Term	Atypical TDP-43 expression in person w/ALS [Cooper-Knock et al 2022]
	c.1144G>A	p.Ala382Thr	Common variant in Sardinia [Floris et al 2016]; reported in homozygous state in 2 families in which 1 member had ALS-FTD & another family member had either (1) no neurologic disease [Mosca et al 2012] or (2) ALS-FTD [Borghero et al 2011]
	c.527A>T	p.Lys176Ile	Mutated lysine residue assoc w/FTD phenotypes [Chen et al 2021]
	c.541A>G	p.Lys181Glu	Mutated lysine residue assoc w/FTD phenotypes [Chen et al 2019]
	c.787A>G	p.Lys263Glu	Mutated lysine residue assoc w/FTD phenotypes [Kovacs et al 2009]

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.

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