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CSF1R-Related Disorder

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Summary

Clinical characteristics

The spectrum of *CSF1R*-related disorder ranges from early-onset disease (age <18 years) to late-onset disease (age ≥18 years). Early-onset disease is associated with hypotonia, delayed acquisition of developmental milestones, and non-neurologic manifestations (such as skeletal abnormalities); both early- and late-onset disease have similar neurodegenerative involvement. Most affected individuals eventually become bedridden with spasticity, rigidity, and loss of the ability to walk. They lose speech and voluntary movement and appear to be generally unaware of their surroundings. The last stage of disease progresses to a vegetative state with presence of primitive reflexes, such as visual and tactile grasp, mouth-opening reflex, and sucking reflex. Death most commonly results from pneumonia or other infections. About 500 individuals with *CSF1R*-related disorder have been reported to date.

Diagnosis/testing

The diagnosis of *CSF1R*-related disorder is established in a proband with suggestive findings and a heterozygous *CSF1R* pathogenic variant or biallelic *CSF1R* pathogenic variants identified by molecular genetic testing.

Management

Treatment of manifestations: Multidisciplinary care by specialists in neurology, psychotherapy, neuropsychological rehabilitation, physical therapy, occupational therapy, speech-language therapy, social services for family support, and genetic counseling.

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Surveillance: Monitoring of existing manifestations, the individual's response to supportive care, and the emergence of new manifestations as specified by the multidisciplinary care providers.

Agents/circumstances to avoid: For individuals with gait problems and cognitive decline, sedatives, antipsychotics, and other medications that may decrease alertness and increase the risk of falling should be used cautiously.

Genetic counseling

Early-onset *CSF1R*-related disorder is typically caused by biallelic pathogenic variants and inherited in an autosomal recessive manner; rarely, early-onset *CSF1R*-related disorder may be caused by a heterozygous pathogenic variant. Late-onset *CSF1R*-related disorder is typically caused by a heterozygous pathogenic variant and inherited in an autosomal dominant manner; rarely, late-onset *CSF1R*-related disorder may be caused by biallelic *CSF1R* pathogenic variants. While biallelic pathogenic variants are usually associated with early-onset disease and heterozygous pathogenic variants are usually associated with late-onset disease, definitive prediction of phenotype based on *CSF1R* genotype is not possible at this time.

Autosomal recessive inheritance: The parents of an individual with *CSF1R*-related disorder caused by biallelic pathogenic variants are presumed to be heterozygous for a *CSF1R* pathogenic variant. If both parents are known to be heterozygous for a pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial *CSF1R* pathogenic variants. Sibs who inherit the same biallelic *CSF1R* pathogenic variants do not necessarily have the same clinical manifestations early in the disease course; however, in the end stage, all individuals with *CSF1R*-related disorder typically have devastating neurologic involvement. The heterozygous sibs of an individual with *CSF1R*-related disorder caused by biallelic pathogenic variants are typically asymptomatic.

Autosomal dominant inheritance: Many individuals with *CSF1R*-related disorder caused by a heterozygous pathogenic variant have an affected parent. Some individuals with *CSF1R*-related disorder caused by a heterozygous pathogenic variant represent a simplex case; such individuals may have the disorder as the result of a pathogenic variant that occurred *de novo* in the proband; a pathogenic variant inherited from a mosaic parent; or a pathogenic variant inherited from an asymptomatic heterozygous parent. Each child of an individual with a heterozygous *CSF1R* pathogenic variant has a 50% chance of inheriting the pathogenic variant. Family members who are heterozygous for the same *CSF1R* pathogenic variant do not necessarily have the same clinical manifestations early in the disease course; however, in the end stage, all individuals with *CSF1R*-related disorder typically have devastating neurologic involvement.

Once the *CSF1R* pathogenic variant(s) have been identified in an affected family member, predictive testing for at-risk relatives and prenatal and preimplantation genetic testing for *CSF1R*-related disorder are possible.

GeneReview Scope

***CSF1R*-Related Disorder: Phenotypic Continuum**

Proposed Terminology [1]	*CSF1R* Genotype		Manifestations	Encompassed Terminology [2]
	Biallelic PVs	Monoallelic PV		
Early-onset *CSF1R*-related disorder (age <18 yrs)	Typical	Rare	• Neurologic manifestations • Skeletal abnormalities • Nonspecific dysmorphic facial features • Congenital brain abnormalities	Brain abnormalities, neurodegeneration, & dysosteosclerosis (BANDDOS)

CSF1R-Related Disorder: Phenotypic continued from previous page.

Proposed Terminology [1]	*CSF1R* Genotype		Manifestations	Encompassed Terminology [2]
	Biallelic PVs	Monoallelic PV		
Late-onset *CSF1R*-related disorder (age ≥18 yrs)	Rare	Typical	Typically limited to neurologic manifestations (progressive neurologic decline)	• Adult-onset leukoencephalopathy w/axonal spheroids & pigmented glia (ALSP) • Pigmentary orthochromatic leukodystrophy (POLD) • *CSF1R*-related leukoencephalopathy • Hereditary diffuse leukoencephalopathy w/ spheroids (HDLS) [3]

Adapted from Dulski et al [2024], Table 1
PV = pathogenic variant
1. Dulski et al [2024]
2. See Nomenclature.
3. The original Swedish family with HDLS had a heterozygous pathogenic variant in *AARS1* (see Differential Diagnosis).

Diagnosis

Suggestive Findings

CSF1R-related disorder should be suspected in a proband with the following clinical and neuroimaging findings (that present in an age-dependent manner) and family history [Konno et al 2017, Dulski et al 2023c, Dulski et al 2024].

Early Onset (age <18 years)

Clinical findings. Most common neurologic manifestations include:

- Speech disturbances
- Developmental delay and/or cognitive decline
- Spasticity with abnormal reflexes and other pyramidal signs
- Parkinsonism
- Dysphagia
- Seizures

Radiographic features [Guo et al 2019]

- Diffuse osteosclerosis of the craniofacial bones, most prominent in the skull base
- Platyspondyly and sclerosis of the vertebral bodies
- Sclerotic pelvic bones most prominent in the iliac bodies, sclerosis of proximal femora
- Tubular bones: diaphyseal sclerosis and metaphyseal radiolucency with metaphyseal undermodeling

Neuroimaging findings. The spectrum of brain abnormalities include the following [Monies et al 2017, Guo et al 2019, Oosterhof et al 2019, Breningstall & Asis 2020, Tamhankar et al 2020, Kındış et al 2021, Sriram at al 2022, Dulski et al 2023c]:

- Progressive bilateral white matter lesions that are hyperintense on T_2-weighted and FLAIR images, and hypointense on T_1-weighted images in the deep, subcortical, and periventricular areas that are often asymmetric, especially early in the disease course. Early lesions are patchy and focal but with time become

confluent. T_2-weighted and FLAIR hyperintensities are present in other areas, including the corpus callosum and corticospinal tracts.

- Calcifications

  Note: Calcifications are poorly visible or not at all on conventional (1.5- or 3-Tesla) brain MRI; however, they may be appreciated on 7-Tesla brain MRI, which to date has limited availability. Calcifications are also detectable by thin-slice brain computed tomography (CT), which is available in routine clinical settings. Calcifications may be better visualized by 1 mm sections together with sagittal reconstructions.

- Cerebral atrophy
- Ventriculomegaly
- Agenesis or thinning of the corpus callosum
- Dandy-Walker malformation
- Malformations of cortical development (thinning of the cortex with poor white-gray distinction and underdeveloped gyration)

Late Onset (age ≥18 years)

Clinical findings

- Progressive neurologic decline beginning at mean age of 40±10 years in women and 47±11 years in men
- Neurologic manifestations
  - Speech disturbances
  - Cognitive decline
  - Neurobehavioral/psychiatric manifestations (behavioral and personality changes)
  - Spasticity
  - Parkinsonism
  - Seizures

Neuroimaging findings. Typical brain abnormalities on imaging include the following [Van Gerpen et al 2008, Sundal et al 2012, Bender et al 2014, Konno et al 2014, Konno et al 2017, Dulski et al 2022b, Mickeviciute et al 2022]:

- Progressive bilateral white matter lesions that are hyperintense on T_2-weighted and FLAIR images, and hypointense on T_1-weighted images in the deep, subcortical, and periventricular areas that are often asymmetric, especially early in the disease course. Early lesions are patchy and focal but with time become confluent. T_2-weighted and FLAIR hyperintensities are present in other areas, including the corpus callosum and corticospinal tracts.
- Cerebral atrophy, including thinning of the corpus callosum
- Calcifications are observed in the white matter in up to half of affected individuals, and frequently have a characteristic "stepping-stone appearance" in the frontal pericallosal area and punctate appearance in the frontal white matter (adjacent to the anterior horns of the lateral ventricles) and the parietal subcortical white matter [Konno et al 2017].

  Note: Calcifications are poorly visible or not at all on conventional (1.5- or 3-Tesla) brain MRI; however, they may be appreciated on 7-Tesla brain MRI, which to date has limited availability. Calcifications are also detectable by thin-slice brain computed tomography (CT), which is available in routine clinical settings. Calcifications may be better visualized by 1 mm sections together with sagittal reconstructions.

Laboratory Findings

In both early- and late-onset *CSF1R*-related disorder, cerebrospinal fluid (CSF) is unremarkable (i.e., normal cell count, glucose concentration, and proteins; no inflammatory cells; typically, normal isoelectric focusing and no oligoclonal bands). CSF studies are primarily used to evaluate for other diseases [Saitoh et al 2019].

Family History

Family history for early- and late-onset *CSF1R*-related disorder may suggest autosomal dominant inheritance (e.g., affected males and females in multiple generations), autosomal recessive inheritance, or the proband may represent a simplex case (i.e., the only family member known to be affected). A positive family history is more likely to be seen in probands with late-onset disease (i.e., age ≥18 years). The absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *CSF1R*-related disorder **is established** in a proband with suggestive findings and a heterozygous *CSF1R* pathogenic (or likely pathogenic) variant or biallelic *CSF1R* pathogenic (or likely pathogenic) variants identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous or biallelic *CSF1R* variant(s) of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). 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 *CSF1R*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Option 1

A multigene panel that includes *CSF1R* and other genes of interest (in probands with early or late onset, a leukodystrophy and leukoencephalopathy or Parkinson disease and parkinsonism panel; in probands with early onset specifically, a skeletal disorders or brain malformations panel; in probands with late onset specifically, a movement disorders or dementia panel; 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 gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of *CSF1R* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing. Of note, several splicing variants beyond the canonical splice site have been identified [Rademakers et al 2011, Konno et al 2017, Wu et al 2022] that may be detected by genome sequencing.

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 *CSF1R*-Related Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
CSF1R	Sequence analysis [3]	>95%% [4]
	Copy number & gene-targeted deletion/ duplication analysis [5]	<5% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Several intronic variants outside of the canonical splice junction typically included by standard sequencing have been reported [Rademakers et al 2011, Konno et al 2017, Wu et al 2022]. These and other deep intronic variants may be detected by genome sequencing.
5. 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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Ishiguro et al [2023]) may not be detected by these methods. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. To date, a few large intragenic deletions have been reported in individuals with *CSF1R*-related disorder [Ishiguro et al 2023].

Clinical Characteristics

Clinical Description

The spectrum of *CSF1R*-related disorder ranges from early-onset disease (age <18 years) to late-onset disease (age ≥18 years). Early-onset disease is more often associated with non-neurologic manifestations (such as skeletal abnormalities), whereas both early- and late-onset disease have similar neurodegenerative involvement.

Information on about 500 affected individuals has been reported to date. The following description of the phenotypic features associated with *CSF1R*-related disorder is based on reports of about 150 individuals (most of whom have late-onset disease) [Konno et al 2017, Dulski et al 2023c, Dulski et al 2024]. See Table 2 for a summary of the frequency of select features by age of onset.

Table 2. *CSF1R*-Related Disorder: Frequency of Select Features by Age of Onset

Feature	Early Onset (n=19) [1]	Late Onset (n=122) (% of affected) [2]
Neurologic manifestations	15/17	100%
Infantile-onset hypotonia	3/11	Not reported
Developmental delay	7/14	Not reported

Table 2. continued from previous page.

Feature	Early Onset (n=19) [1]	Late Onset (n=122) (% of affected) [2]
Speech abnormalities	13/15	52%
Cognitive impairment	12/14	94%
Parkinsonism	12/15 [3]	74%
Pyramidal signs	12/15	57%
Seizures	9/16	32%
Dysphagia	9/12	17%
Optic nerve atrophy	2/7	<1% [4]
Brain imaging abnormalities	19/19	100%
White matter abnormalities	19/19	81%
Calcifications	15/18	75%
Brain atrophy	See footnote 5.	64%-92%
Callosal abnormalities	12/16 [6]	49% [7]
Ventriculomegaly	13/19	100%
Dandy-Walker malformations	7/19	See footnote 8.
Malformations of cortical development	4/10	<1% [4]
Skeletal abnormalities (clinical and/or radiographic)	13/17	<1% [4]
Dysmorphic features	7/17	<1% [4]

1. Dulski et al [2023c]
2. Konno et al [2017], Dulski et al [2024]
3. Rigidity; no data on other parkinsonian features
4. Reported in a few individuals
5. Brain atrophy was evidenced both on neuroimaging and pathologic examination [Oosterhof et al 2019, [Sriram et al 2022]. Of note, data to date are limited in young persons, as it is difficult to differentiate atrophy from hypoplasia, especially when neuroimaging has been performed just once.
6. Agenesis
7. Atrophy [Guo et al 2019]
8. Arnold-Chiari malformation, another posterior fossa malformation, has been reported [Guo et al 2019].

Findings Unique to Early-Onset *CSF1R*-Related Disorder

Infantile-onset hypotonia ("floppy baby syndrome") is characterized by decreased muscle tone, frequently accompanied by developmental delay, hyperextensibility of the joints, and postural disturbances [Kaler et al 2020]. It may disappear in adolescence.

Developmental delay may be observed from birth with delayed reaching of milestones, or begin in childhood with the loss of previously acquired milestones or regression in development [Dulski et. al 2023c].

Skeletal abnormalities, reported in limited detail, include bone fragility and susceptibility to fracture beginning in childhood, short extremities or proportionate short stature usually of variable severity, and bone sclerosis (which, when involving the skull, has been associated with narrowing of the optic foramen and secondary optic atrophy) [Guo et al 2019, Oosterhof et al 2019]. Radiographs can show pelvic bone sclerosis, vertebral sclerosis, platyspondyly, undermodeling of the tubular bones with widened metaphysis, radiolucent metaphysis, constricted diaphysis, and sclerotic diaphysis).

Dysmorphic features, reported in limited detail, may include abnormal size and shape of the skull (macrocephaly, bony prominences), epicanthus, ptosis, bulbous nose, high-arched palate, and chest deformities (bell shaped, pectus carinatum) [Dulski et al 2023c].

Findings Shared by Early- and Late-Onset *CSF1R*-Related Disorder

Speech abnormalities usually include dysarthria and/or aphasia. Of note, not infrequently, dysarthria co-occurs with aphasia.

Dysarthria denotes slurring of speech and affects more than 50% of individuals [Konno et al 2017, Dulski et al 2023c, Wu et al 2024]. It is most often of mixed type, including spastic, hypokinetic with cerebellar features that may manifest as a strained voice, hypophonia (soft speech), slow rate of speech, monotonicity, excessive or reduced stress on syllables, or inappropriate variation in pitch.

Aphasia refers to disturbances of language production (motor or non-fluent aphasia) or comprehension (sensory or fluent aphasia). Although there are no systematic studies on the subtypes of aphasia in *CSF1R*-related disorder, limited evidence suggests the motor subtype is more common [Lee et al 2015, Daida et al 2017, Konno et al 2017, Jiang et al 2022].

Cognitive impairment occurs to some extent in virtually all individuals and may be the first manifestation or appear later in the disease course. The major components of cognitive decline are processing speed, executive function, word retrieval, and visual problem solving [Rush et al 2023]. These progressive findings are the primary cause of loss of independence in activities of daily living [Konno et al 2017, Konno et al 2018, Dulski et al 2023c, Rush et al 2023].

Pyramidal signs include spasticity, hyperreflexia, extensor plantar response, hemiparesis, and/or quadriparesis.

Extrapyramidal signs

- Parkinsonism (hypomimia, rigidity, bradykinesia, shuffling gait, postural instability, resting and/or kinetic tremor) is common and most often of the non-tremor dominant subtype [Sundal et al 2013].
- Dystonia may be isolated to one body part, one side of the body, or generalized. It may be a part of a corticobasal syndrome [Baba et al 2006, Sundal et al 2013].
- Myoclonus may resemble tremor in individuals with polymyoclonus (repetitive low-amplitude myoclonus).
- Dyskinesia and chorea may also be observed in some individuals [van der Knaap et al 2000, Baba et al 2006, Sundal et al 2013].

Cerebellar involvement can include ataxia (lack of coordination), dysmetria (imprecise movement control), cerebellar tremor (involuntary shaking during movement), dysdiadochokinesia (difficulty with rapid alternating movements), scanning speech (abnormal speech pattern), and nystagmus (involuntary eye movement) [Wu et al 2024].

Notably, in most individuals motor signs may occur in varying combinations (e.g., pyramidal and extrapyramidal signs). For instance, it is common to observe increased muscle tone of mixed spastic-rigid type.

Dysphagia (swallowing disturbances) is more common in individuals with severe neurologic deficits [Konno et al 2017, Dulski et al 2023c]. It may encompass difficulty initiating swallowing, sensation of food sticking in the throat or chest, regurgitation, coughing or choking during meals, recurrent pneumonia (due to aspiration), unintentional weight loss, and malnutrition or dehydration.

Sensory deficits include impairment of vibration, position, touch, and pain perception as well as impairment of higher integrative sensory functions such as graphesthesia, stereognosis, and sensory neglect on double stimulation.

Apraxia (inability to perform certain voluntary purposeful movements despite preserved ability to use the affected body part) may occur in up to one third of individuals [Konno et al 2017].

Astereognosis (inability to identify objects by touch) and agraphesthesia are common. Disturbance of right-left body side recognition, a characteristic feature, is most likely due to involvement of the corpus callosum.

Visual disturbances include homonymous quadrantanopsia or hemianopsia. These manifestations may be due to optic nerve atrophy, for which the pathophysiologic underpinnings are not understood [Shu et al 2016, Dulski et al 2023c].

Seizures. Initial seizure types vary. Generalized seizures seem the most common and tend to occur more frequently in individuals with more severe neurologic deficits. Occasionally, they may be the first manifestation of the disease [Konno et al 2017, Dulski et al 2023c].

Neurobehavioral/psychiatric manifestations. Many individuals report anxiety and symptoms of depression [Rush et al 2023]. There are some reports of findings reminiscent of the behavioral variant of frontotemporal dementia, with personality changes, executive dysfunction, and loss of judgment and insight [Rush et al 2023].

Pseudobulbar affect (i.e., uncontrolled crying or laughing disproportionate to the individual's emotional state) has been reported occasionally [Ahmed & Simmons 2013, Robinson et al 2015, Rosenstein et al 2022, Sriram et al 2022].

Other. On average, women develop the first manifestations of late-onset *CSF1R*-related disorder earlier (age 40 years) than men (age 47 years) [Konno et al 2017].

Intrafamilial variability. Individuals from the same family who have the same *CSF1R* pathogenic variant(s) do not necessarily have the same clinical manifestations early in the disease course; however, in the end stage, all individuals with *CSF1R*-related disorder typically have devastating neurologic involvement.

Prognosis. Presence of malformations of cortical development, skeletal deformities, and cognitive impairment as the initial and predominant presentation is usually associated with a worse prognosis, with faster disease progression and earlier disability [Dulski et al 2022a, Dulski et al 2023c, Dulski et al 2024].

Most affected individuals eventually become bedridden with spasticity and rigidity. They lose speech and voluntary movement, and appear to be generally unaware of their surroundings. In the last stage of disease progression, individuals lose their ability to walk and progress to a vegetative state. Primitive reflexes, such as visual and tactile grasp, mouth-opening reflex, and sucking reflex, are present. Death most commonly results from pneumonia or other infections.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified to date.

Penetrance

Penetrance is estimated to be high but incomplete [Karle et al 2013, Sundal et al 2015, Konno et al 2017].

Nomenclature

Pathology-based terminology. Prior to the molecular characterization of *CSF1R*-related disorder, pathology-based terminology – pigmentary orthochromatic leukodystrophy (POLD) and hereditary diffuse leukoencephalopathy with spheroids (HDLS) – was used to describe what appeared to be distinct disorders [Dulski et al 2024]. These terms were later consolidated under a single pathology-based designation, adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP).

Gene-based terminology. The molecular characterization of *CSF1R* allowed gene-based terminology to be established, i.e., *CSF1R*-related leukoencephalopathy/leukodystrophy and *CSF1R*-related ALSP.

Unified terminology. In recognition of the shared molecular etiology and significant phenotype overlap between *CSF1R*-related leukoencephalopathy and brain abnormalities, neurodegeneration, and dysosteosclerosis (BANDDOS), Dulski et al [2024] proposed the designation *CSF1R*-related disorder – subdivided into early onset (age <18 years) and late onset (age ≥18 years) – as a unifying diagnostic term encompassing both entities.

Prevalence

Based on a few screening studies in cohorts with leukoencephalopathies/leukodystrophies, the total worldwide prevalence of *CSF1R*-related disorder to date is estimated to be 0.5-1.5:100,000 [Papapetropoulos et al 2022].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CSF1R*.

Differential Diagnosis

CSF1R-related disorder may present with a range of non-motor and motor features, which may be nonspecific and overlap with other neurodegenerative genetic disorders and conditions that are often of unknown cause (e.g., multiple sclerosis and atypical parkinsonism, including corticobasal degeneration, multiple system atrophy, progressive supranuclear palsy, and frontotemporal lobal degeneration [Baba et al 2006, Sundal et al 2013]). At present, there are several other clinical, radiologic, and pathologic mimics of *CSF1R*-related disorder, including those described below and in Table 3.

Early-Onset *CSF1R*-Related Disorder

Hereditary disorders that primarily affect the central nervous system and manifest with glial and/or myelin abnormalities may mimic early-onset *CSF1R*-related disorder (see Table 3) [Sarret 2020, Davies et al 2023, Jańczewska et al 2023].

Late-Onset *CSF1R*-Related Disorder

Primary progressive multiple sclerosis. Before the discovery of the molecular genetic cause of the disorder, *CSF1R*-related disorder was frequently misdiagnosed as multiple sclerosis, particularly primary progressive multiple sclerosis (PPMS). There is significant clinical overlap between PPMS (average age of onset: 32 years) and late-onset *CSF1R*-related disorder [Tutuncu et al 2013, Aharony et al 2017, Saitoh et al 2019]. White matter lesions are seen in both PPMS and *CSF1R*-related disorder; however, confluent white matter lesions in frontoparietal areas are more consistent with *CSF1R*-related disorder than with PPMS [Sundal et al 2015]. PPMS is also associated with callosomarginal lesions and later onset of cognitive decline than *CSF1R*-related disorder. Incontinence appears later in the disease course and correlates with the overall disability in PPMS [Aharony et al 2017]. In contrast to *CSF1R*-related disorder, oligoclonal bands are often present in PPMS and can be used as a discriminative marker [Saitoh et al 2019].

Genetic disorders. *CSF1R*-related disorder may also phenotypically mimic genetic motor neuron disease and other neurodegenerative disorders featuring spasticity, parkinsonism, ataxia, and cognitive decline [Baba et al 2006, Aharony et al 2017, Souza et al 2020]. These disorders can be distinguished by brain MRI findings characterized mainly by cerebral atrophy without the characteristic white matter lesions found in *CSF1R*-related disorder. However, molecular genetic testing or neuropathologic examination are needed to make the ultimate distinction.

- *AARS1*-related leukoencephalopathy or Swedish hereditary diffuse leukoencephalopathy with spheroids (HDLS) is an adult-onset autosomal dominant progressive neurodegenerative disorder that clinically and pathologically mimics the late-onset form of *CSF1R*-related disorder [Sundal et al 2019]. However, affected individuals show a unique neuroimaging pattern, with a centrifugally expanding rim of decreased diffusion evidenced by MRI diffusion-weighted/tensor imaging through the white matter around anterior ventricular horns [Sundal et al 2014, Sundal et al 2019].
- *AARS2*-related leukoencephalopathy is an autosomal recessive progressive neurodegenerative disease with cognitive decline, neurobehavioral/psychiatric manifestations, cerebellar ataxia, and pyramidal and extrapyramidal features. In addition, most affected women develop premature ovarian insufficiency. The age of onset usually occurs between the second and fifth decades of life. Compared to *CSF1R*-related disorder, *AARS2*-related leukoencephalopathy has less corpus callosum involvement and usually no brain calcifications [Papapetropoulos et al 2022, Muthusamy et al 2023].
- A *CSF1R*-related disorder mimic with an autosomal dominant pattern of inheritance of unknown genetic cause was reported in a single family with typical clinical, radiologic, and neuropathologic features of late-onset *CSF1R*-related disorder, but without pathogenic variants in *CSF1R, AARS1*, *AARS2*, or other genes known to be associated with neurodegenerative disorders [Dulski et al 2023b].

Table 3. Genetic Disorders to Consider in the Differential Diagnosis of *CSF1R*-Related Disorder

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/*CSF1R*-related disorder	Distinguishing from *CSF1R*-related disorder
Disorders of interest in the differential diagnosis of early-onset *CSF1R*-related disorder				
ABCD1	X-linked adrenoleukodystrophy	XL	• Cognitive decline, dementia • Spastic paraparesis	• Neuropathy & slowly spastic paraparesis • WML are contrast enhancing. • Corticospinal tracts are involved from cranial to medulla.
ADAR *IFIH1* *RNASEH2A* *RNASEH2B* *RNASEH2C* *SAMHD1* *TREX1*	Aicardi-Goutières syndrome	AD AR	Neurodegeneration	Chilblain skin lesions
AQP4 *GPRC5B* *HEPACAM* *MLC1*	Megalencephalic leukoencephalopathy w/ subcortical cysts	AD AR	Neurodegeneration	Subcortical cysts on neuroimaging
ARSA	Adult metachromatic leukodystrophy (See Arylsulfatase A Deficiency.)	AR	• Executive dysfunction, personality changes, memory issues • Pyramidal signs, seizures	• Peripheral neuropathy • Spread of WML into the cerebellar region & WM myelin breakdown w/low-density tigroid stripes
ASPA	Canavan disease	AR	• Neurodegeneration • Macrocephaly	Rostrocaudal progression of myelin loss on serial imaging studies
ATP7A	Menkes disease (See *ATP7A*-Related Copper Transport Disorders.)	XL	Neurodegeneration	• Neuropathy • "Occipital horns"
C9orf72	*C9orf72* frontotemporal dementia &/or amyotrophic lateral sclerosis	AD	Neurodegeneration	Frontal &/or temporal atrophy w/far fewer WML

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/*CSF1R*-related disorder	Distinguishing from *CSF1R*-related disorder
CHMP2B	*CHMP2B* frontotemporal dementia	AD	Neurodegeneration	Frontal &/or temporal atrophy w/far fewer WML
CLN3 *CLN5* *CLN6* *CLN8* *CTSD* *CTSF* *DNAJC5* *GRN* *KCTD7* *MFSD8* *PPT1* *TPP1*	Neuronal ceroid lipofuscinoses (OMIM PS256730)	AR AD [1]	Neurodegeneration	Retinal degeneration
DARS2	Leukoencephalopathy w/brain stem & spinal cord involvement & lactate elevation	AR	• Slowly progressive pyramidal, cerebellar, & dorsal column dysfunction • Deterioration of motor skills	• Peripheral neuropathy • WML are either non-homogeneous/spotty or homogeneous & confluent. • Signal abnormalities are evident in the medullary pyramids, dorsal columns, & lateral corticospinal tracts.
EIF2B1 *EIF2B2* *EIF2B3* *EIF2B4* *EIF2B5*	Childhood ataxia w/central nervous system hypomyelination / vanishing white matter	AR	• Cognitive decline • Spastic paraparesis • Cerebellar ataxia	• Stress-induced deterioration w/ minor trauma or infections • More widespread & diffuse WM changes & atrophy than in *CSF1R*-related disorder • Cystic breakdown of WM
ERCC6 *ERCC8*	Cockayne syndrome	AR	Neurodegeneration	• Peripheral neuropathy • Progressive microcephaly
GALC	Krabbe disease	AR	Pyramidal signs, developing into para- or tetraparesis	• Peripheral neuropathy • MRI shows predominance in posterior part of WM • MRI detects demyelination in brain stem & cerebellum • T_2-weighted value is progressively prolonged in occipital deep WM & posterior part of central semiovale in late-onset disease.
GCDH	Glutaric acidemia type 1	AR	Neurodegeneration	• Progressive macrocephaly • Acute exacerbations of neurologic deficits
GFAP	Alexander disease	AD	Neurodegeneration	• Palatal myoclonus • Cognitive function in adults is frequently normal. • Infratentorial atrophy on MRI
GLA	Fabry disease	XL	WML	Gray matter pathology

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/*CSF1R*-related disorder	Distinguishing from *CSF1R*-related disorder
GLB1 *GM2A*	GM1 & GM2 gangliosidoses (See *GLB1*-Related Disorders and GM2 Activator Deficiency.)	AR	Neurodegeneration	• Skin & eye changes • Hepatosplenomegaly
GRN	*GRN* frontotemporal dementia	AD	Neurodegeneration	Frontal &/or temporal atrophy w/far fewer WML
LMNB1	*LMNB1*-related autosomal dominant leukodystrophy	AD	• Cognitive impairment • Pyramidal & cerebellar signs	• Early autonomic dysfunction • Periventricular normal rim on MRI
MAPT	*MAPT*-related frontotemporal dementia	AD	Progresses over a few yrs into profound dementia w/mutism	Frontal &/or temporal atrophy w/far fewer WML
NOTCH3	CADASIL	AD	• Frontal lobe syndrome • WML	• Stroke-like clinical signs • Multiple cerebral infarcts & WML incl characteristic temporal pools
NPC1 *NPC2*	Niemann-Pick disease type C	AR	Neurodegeneration	Visceral manifestations
PLP1	Pelizaeus-Merzbacher disease (See *PLP1* Disorders.)	XL	Clinical & neuroimaging findings	
POLR1C *POLR3A* *POLR3B*	POLR3-related leukodystrophy	AR	• Neurologic deficits • Abnormal dentition	• Endocrine abnormalities • Progressive myopia
SUMF1	Multiple sulfatase deficiency (Austin disease)	AR	Neurodegeneration	Organomegaly
TREM2 *TYROBP*	Polycystic lipomembranous osteodysplasia w/sclerosing leukoencephalopathy (Nasu-Hakola disease)	AR	• Insidious personality changes, frontal lobe syndrome • Motor impairments • Dementia & progression to vegetative state	• Pain/tenderness of feet/wrists • Polycystic osseous lesions, pathologic fractures • U-fibers partially affected
>350 genes [2]	Primary mitochondrial disorders	AD AR Mat XL	• Neurodegeneration • Brain calcifications	• Skin photosensitivity • Distinct physical appearance
Disorders of interest in the differential diagnosis of late-onset *CSF1R*-related disorder				
AARS1	*AARS1*-related leukoencephalopathy (Swedish hereditary diffuse leukoencephalopathy with spheroids) (OMIM 619661)	AD	Phenotypic mimic of late-onset *CSF1R*-related disorder	Neuroimaging pattern w/centrifugally expanding rim of ↓ diffusion (evidenced on MRI diffusion-weighted/tensor imaging) through WM around anterior ventricular horns
AARS2	*AARS2*-related leukoencephalopathy (OMIM 615889)	AR	Phenotypic mimic of late-onset *CSF1R*-related disorder	• Premature ovarian insufficiency in all females • WM demonstrates rarefaction.

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/*CSF1R*-related disorder	Distinguishing from *CSF1R*-related disorder
APP *PSEN1* *PSEN2*	Early-onset familial Alzheimer disease (See Alzheimer Disease Overview.)	AD	• Executive dysfunction, personality changes • Similar age of onset	• Episodic memory loss • WM changes are present but much less pronounced.

AD = autosomal dominant; AR = autosomal recessive; CADASIL = *c*erebral *a*utosomal *d*ominant *a*rteriopathy with *s*ubcortical *i*nfarcts and *l*eukoencephalopathy; MOI = mode of inheritance; Mat = maternal; WM = white matter; WML = white matter lesions; XL = X-linked

2. Except for *DNAJC5*-related neuronal ceroid lipofuscinosis (which is inherited in an autosomal dominant manner), neuronal ceroid lipofuscinoses are inherited in an autosomal recessive manner.

3. McCormick et al [2018]

Management

No clinical practice guidelines for *CSF1R*-related disorder have been published. Therefore, the following considerations are based on the authors' experience managing individuals with this disorder and should be viewed as personal opinions rather than recommendations.

Note that the care of individuals with early-onset *CSF1R*-related disorder requires addressing issues of developmental delay and skeletal abnormalities that are typically addressed by developmental pediatricians and pediatricians and thus are not discussed further in this chapter. Rather, the assessment and management of the manifestations of neurodegeneration observed in all individuals with *CSF1R*-related disorder are discussed in detail.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *CSF1R*-related disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *CSF1R*-Related Disorder: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic deficits	Complete neurologic assessment	• Incl screening for cognitive impairment • Assessment for motor impairment incl gait, bradykinesia, rigidity, & tremor; sensory deficits; & bulbar signs • When seizures are suspected, an EEG or video EEG is recommended
Cognitive abilities & neurobehavioral/ psychiatric manifestations	Referral to psychologist &/or neuropsychologist as needed	• Assessment of cognitive function (executive function, language processing, visuospatial/visuoconstructional skills) • Assessment for anxiety, depression, apathy, indifference, abulia, disinhibition, distraction, & other behavioral or personality changes
Dysarthria	Speech-language pathologist eval	• Assessment of need for speech therapy • Consider need for alternative & augmentative communication.
Dysphagia	Gastrointestinal &/or feeding therapist eval	• Incl nutritional assessment, safety of oral feedings • Consider need for gastrostomy tube placement.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal/ADL	Primary care / orthopedics / physical medicine & rehab / PT eval	Incl assessment of: • Skeletal system (incl radiographs) • Muscle tone; joint range of motion; posture; mobility; strength, coordination, & endurance; pain; & bedsores • Need for adaptive devices • Footwear needs • PT needs
	OT	• To assess small motor function • To assess ADL
Gastrointestinal issues	Primary care physician &/or gastroenterologist	To assess for constipation, incontinence
Vision deficits	Ophthalmologic eval	Detailed ophthalmologic eval, incl assessment of visual acuity, visual fields, & intraocular pressure
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *CSF1R*-related disorder to facilitate medical & personal decision making
Family support & resources	Assessment of family & social structure to determine availability of adequate support systems	• Direct families / affected persons to community or online resources. • Social work involvement for parental support • Home nursing referral

ADL = activities of daily living; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

The limited data available to date suggest that hematopoietic stem cell transplantation (HSCT) could modify disease progression in symptomatic individuals with early neurologic findings of *CSF1R*-related disorder [Tipton et al 2021, Dulski et al 2022a, Dulski et al 2024] and could be more beneficial in individuals with motor involvement (i.e., gait problems) as the initial and predominant disease manifestation, in contrast to individuals initially experiencing non-motor manifestations (i.e., cognitive impairment) [Dulski et al 2022a]. However, before conclusions can be drawn about the role of HSCT in the treatment of individuals with *CSF1R*-related disorder, more data are needed.

Supportive treatment is recommended to improve quality of life, maximize function, and reduce complications. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. *CSF1R*-Related Disorder: Symptomatic Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Cognitive decline / Dementia	• Cognitive behavioral therapy • Psychotherapy & psychoeducational interventions	

Table 5. continued from previous page.

Manifestation/Concern		Treatment	Considerations/Other
Neuropsychiatric manifestations		Psychotherapy / neuropsychological rehab	• To date, standard treatment for psychiatric manifestations (e.g., depression, suicidal tendencies, anxiety, & psychosis) have not had long-term benefit. • Antipsychotics are not recommended in general due to extrapyramidal side effects but may be used in persons who have issues with aggression.
Motor dysfunction	**Pyramidal signs**	Botulinum toxin for spasticity	
	Parkinsonism	Levodopa or other dopaminergic therapies	Most persons do not benefit from levodopa. 1 However, a trial with slowly titrated dose up to 1,000 mg/day is warranted to determine individual response.
Musculoskeletal/ADL		PT	• Transfers (e.g., from bed to wheelchair, wheelchair to car) • Training on fall techniques to minimize risk of injury
		OT	• To accomplish tasks such as mobility, washing, dressing, eating, cooking, & grooming • To assist w/household modifications to meet special needs
Dysarthria		Speech-language therapy	Consider alternative means of communication.
Dysphagia		Per treating feeding team	To assure adequate nutrition & minimize risk of aspiration
Seizures		ASM	Many ASMs may be effective; none has been demonstrated effective specifically for this disorder.
General & recurrent infections		Use of antibiotics to treat general & recurrent infections such as pneumonia &/or urinary tract infections	
Family/Community		Education	• Social issues (unemployment, divorce, financial challenges, &/or alcohol addiction) & suicidal tendencies are often assoc w/progression of disease. • Some of the social consequences may be avoided if family members are informed early re nature of disorder.

ADL = activities of daily living; ASM = anti-seizure medications; OT = occupational therapy; PT = physical therapy
1. Sundal et al [2013]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. *CSF1R*-Related Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic & neuropsychiatric deficits	By neurologist & neuropsychologist for ↑ severity / new manifestations [1]	Symptomatic persons: every 6 mos or as needed
	By specialist in physical medicine & rehab / PT	
	Brain MRI (preferably 3 or 7 Tesla)	Every 12 mos or as needed
Feeding/Nutrition (esp difficulty w/swallowing &/or weight loss & need to consider gastrostomy tube placement)	By feeding team	Per treating feeding team
Gastrointestinal issues	By primary care doctor	Every 12 mos or as needed
Vision problems	By ophthalmologist	Per treating ophthalmologist
Musculoskeletal/ADL (including development of contractures &/or changes in mobility)	By PT/OT	Per treating PT/OT
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).	

ADL = activities of daily living; OT = occupational therapist; PT = physical therapist
1. Recommended frequency of these evaluations depends on the age of the asymptomatic family member and the average age of disease onset in the family: (a) annually for individuals twenty or more years younger than the average age of disease onset in their family and (b) every six months for individuals approaching the age of expected symptomatic disease onset [Authors, unpublished observations].

Agents/Circumstances to Avoid

As many individuals with *CSF1R*-related disorder have gait problems and cognitive decline, sedatives, antipsychotics, and other medications that may decrease alertness and increase the risk of falling should be used cautiously.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

In a retrospective cohort study, it was observed that glucocorticoids might protect against symptomatic disease onset in individuals at risk for late-onset *CSF1R*-related disorder (i.e., asymptomatic individuals with a heterozygous *CSF1R* pathogenic variant) [Dulski et al 2023a]. This effect was also observed in a mouse model of the disease [Chitu et al 2023]. For a detailed discussion on the optimal dose, route of administration, type of glucocorticoid, and timing of therapy, see Dulski et al [2023d]. Note that glucocorticoids are not beneficial in individuals with advanced disease [Dulski et al 2023d].

Currently, one interventional clinical trial is in progress, enrolling individuals age 18 years and older with the late-onset *CSF1R*-related disorder commonly known as adult-onset leukoencephalopathy w/axonal spheroids & pigmented glia (ALSP) (NCT05677659). It is a Phase II multicenter, open-label study investigating the safety and tolerability of VGL101 (Vigil Neuroscience, Inc), a humanized monoclonal antibody acting as an agonist for the triggering receptor expressed on myeloid cells 2 (TREM2) receptor. Since TREM2 and macrophage colony-

stimulating factor 1 receptor (CSF1R; encoded by *CSF1R*) share common signaling pathways, it is hypothesized that activation of TREM2 may compensate for deficiency in CSF1R.

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

Genetic Counseling

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

Mode of Inheritance

Early-onset *CSF1R*-related disorder is typically caused by biallelic pathogenic variants and inherited in an autosomal recessive manner. Rarely, early-onset *CSF1R*-related disorder may be caused by a heterozygous pathogenic variant [Breningstall & Asis 2020; Sriram et al 2022; Dulski et al 2024; J Dulski, unpublished data].

Late-onset *CSF1R*-related disorder is typically caused by a heterozygous pathogenic variant and inherited in an autosomal dominant manner. Rarely, late-onset *CSF1R*-related disorder may be caused by biallelic *CSF1R* pathogenic variants [Guo et al 2019; Dulski et al 2024; J Dulski, unpublished data].

Note: While biallelic pathogenic variants are typically associated with early-onset disease and heterozygous pathogenic variants are typically associated with late-onset disease, definitive prediction of phenotype based on *CSF1R* genotype is not possible at this time [Dulski et al 2024].

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an individual with *CSF1R*-related disorder caused by biallelic *CSF1R* pathogenic variants are presumed to be heterozygous for a *CSF1R* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *CSF1R* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent. 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.
- The heterozygous parents of an individual with early-onset *CSF1R*-related disorder caused by biallelic pathogenic variants are typically asymptomatic; however, definitive prediction of phenotype based on *CSF1R* genotype is not possible at this time [Dulski et al 2024].

Sibs of a proband

- If both parents are known to be heterozygous for a *CSF1R* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial *CSF1R* pathogenic variants.
- Sibs who inherit the same biallelic *CSF1R* pathogenic variants do not necessarily have the same clinical manifestations early in the disease course; however, in the end stage, all individuals with *CSF1R*-related disorder typically have devastating neurologic involvement.
- The heterozygous sibs of an individual with *CSF1R*-related disorder caused by biallelic pathogenic variants are typically asymptomatic; however, definitive prediction of phenotype based on *CSF1R* genotype is not possible at this time [Dulski et al 2024].

Offspring of a proband. The offspring of an individual with biallelic *CSF1R* pathogenic variants are obligate heterozygotes for a pathogenic variant in *CSF1R*.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for a *CSF1R* pathogenic variant.

Heterozygote detection. Heterozygote testing for at-risk relatives requires prior identification of the *CSF1R* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Many individuals with *CSF1R*-related disorder caused by a heterozygous *CSF1R* pathogenic variant have an affected parent [Rademakers et al 2011, Kinoshita et al 2012, Stabile et al 2016, Dulski et al 2024].
- Some individuals with *CSF1R*-related disorder caused by a heterozygous *CSF1R* pathogenic variant represent a simplex case (i.e., the only family member known to be affected). Such individuals may have the disorder as the result of:
  - A pathogenic variant that occurred *de novo* in the proband;
  - A pathogenic variant inherited from a mosaic parent; or
  - A pathogenic variant inherited from an asymptomatic heterozygous parent. (The penetrance of *CSF1R*-related disorder is estimated to be high but incomplete [Karle et al 2013, Sundal et al 2015, Konno et al 2017].)
- If the proband appears to be the only affected family member, molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status, inform recurrence risk assessment, and provide insight into familial genotype-phenotype correlations.
- 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.* Somatic and germline mosaicism has been reported in an unaffected mother of four sibs with late-onset *CSF1R*-related disorder [Eichler et al 2016]. 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 (gonadal) cells only.

    * Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

- The family history of some individuals diagnosed with *CSF1R*-related disorder 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, late onset of the disease in the affected parent, or incomplete penetrance [Dulski et al 2024]. Therefore, a negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent has the pathogenic variant identified in the proband.

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

- If a parent of the proband is known to be heterozygous for the *CSF1R* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
  - Sibs who are heterozygous for the same *CSF1R* pathogenic variant do not necessarily have the same clinical manifestations early in the disease course; however, in the end stage, all individuals with *CSF1R*-related disorder typically have devastating neurologic involvement.
  - On average, women develop the first manifestations of late-onset *CSF1R*-related disorder earlier (age 40 years) than men (age 47 years).
- If the *CSF1R* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Eichler et al 2016].
- If the parents have not been tested for the *CSF1R* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for *CSF1R*-related disorder because of possible incomplete penetrance in a parent and the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with a heterozygous *CSF1R* pathogenic variant has a 50% chance of inheriting the 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 *CSF1R* 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 causative *CSF1R* pathogenic variant(s) have been identified in an affected family member. Such testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals.
- 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 in minors (i.e., testing of asymptomatic at-risk individuals age <18 years)

- Predictive testing of minors for adult-onset disorders for which no treatment exists is not considered appropriate. Such testing 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 *CSF1R*-related disorder, it is appropriate to consider testing 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 *CSF1R* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for *CSF1R*-related disorder are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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.

- **Sisters' Hope Foundation**
  Email: info@sistershopefoundation.org
  sistershopefoundation.org
- **Alex, The Leukodystrophy Charity**
  United Kingdom
  Phone: 020 7701 4388
  Email: info@alextlc.org
  alextlc.org
- **European Leukodystrophy Association (ELA)**
  Phone: 03 83 30 93 34
  www.ela-asso.com
- **Leukodystrophy Australia**
  Australia
  Phone: 1800-141-400
  Email: info@leuko.org.au
  www.leuko.org.au
- **United Leukodystrophy Foundation**
  Phone: 800-SAV-LIVE; 815-748-3211
  Email: office@ulf.org
  www.ulf.org
- **Myelin Disorders Bioregistry Project**
  Phone: 215-590-1719
  Email: sherbinio@chop.edu

Myelin Disorders Bioregistry Project

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. CSF1R-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
CSF1R	5q32	Macrophage colony-stimulating factor 1 receptor	CSF1R	CSF1R

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 CSF1R-Related Disorder (View All in OMIM)

164770	COLONY-STIMULATING FACTOR 1 RECEPTOR; CSF1R
221820	LEUKOENCEPHALOPATHY, HEREDITARY DIFFUSE, WITH SPHEROIDS 1; HDLS1

Molecular Pathogenesis

CSF1R encodes macrophage colony-stimulating factor 1 receptor (CSF1R), a cell surface receptor primarily for cytokine colony-stimulating factor 1 (CSF-1) that regulates the survival, proliferation, differentiation, and function of mononuclear phagocytic cells, including microglia of the central nervous system . CSF1R comprises a highly glycosylated extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain. Binding of CSF-1 to its receptor, CSF1R, results in the formation of receptor homodimers and subsequent autophosphorylation of several important proteins, including the phosphatase SHP-1 and the kinases Src, PLC-γ, PI(3)K, Akt, and Erk [Rademakers et al 2011]. In the brain, CSF1R is predominately expressed in microglial cells [Papapetropoulos et al 2022].

To date, most reported *CSF1R* pathogenic variants that cause *CSF1R*-related disorder affect kinase activity and potentially phosphorylation of downstream targets. However, the mechanisms of neuronal/glial dysfunction underlying *CSF1R*-related disorder remain to be fully elucidated [Papapetropoulos et al 2022].

Mechanism of disease causation. The mechanisms of disease causation are not fully understood and likely differ depending on the *CSF1R* pathogenic variant(s) and possible interplay with other genetic and non-genetic factors [Dulski et al 2024].

***CSF1R*-specific laboratory technical considerations.** While most pathogenic variants underlying *CSF1R*-related disorder are within coding or canonical splice site regions, several splicing variants beyond the canonical splice site have been identified that may be detected by genome sequencing [Rademakers et al 2011, Konno et al 2017, Wu et al 2022].

Chapter Notes

Author Notes

Dr Wszolek (wszolek.zbigniew@mayo.edu) and Dr Dulski (dulski.jaroslaw@mayo.edu; jaroslaw.dulski@gumed.edu.pl) are actively involved in clinical research regarding individuals with *CSF1R*-related disorder. They would be happy to communicate with patients and their families, patient organizations, and clinicians treating patients with the disorder.

Contact Drs Wszolek and Dulski to inquire about review of *CSF1R* variants of uncertain significance.

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References

Literature Cited

Aharony SM, Lam O, Corcos J. Evaluation of lower urinary tract symptoms in multiple sclerosis patients: review of the literature and current guidelines. Can Urol Assoc J. 2017;11:61-4. PubMed PMID: 28443147.

Ahmed A, Simmons Z. Pseudobulbar affect: prevalence and management. Ther Clin Risk Manag. 2013;9:483-9. PubMed PMID: 24348042.

Baba Y, Ghetti B, Baker MC, Uitti RJ, Hutton ML, Yamaguchi K, Bird T, Lin W, DeLucia MW, Dickson DW, Wszolek ZK. Hereditary diffuse leukoencephalopathy with spheroids: clinical, pathologic and genetic studies of a new kindred. Acta Neuropathol. 2006;111:300-11. PubMed PMID: 16523341.

Bender B, Klose U, Lindig T, Biskup S, Nägele T, Schöls L, Karle KN. Imaging features in conventional MRI, spectroscopy and diffusion weighted images of hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS). J Neurol. 2014;261:2351-9. PubMed PMID: 25239393.

Breningstall GN, Asis M. Bone disease associated with hereditary diffuse leukoencephalopathy with spheroids. Pediatr Neurol. 2020;112:44-6. PubMed PMID: 32911262.

Chitu V, Biundo F, Oppong-Asare J, Gökhan Ş, Aguilan JT, Dulski J, Wszolek ZK, Sidoli S, Stanley ER. Prophylactic effect of chronic immunosuppression in a mouse model of CSF-1 receptor-related leukoencephalopathy. Glia. 2023;71:2664-78. PubMed PMID: 37519044.

Daida K, Nishioka K, Li Y, Nakajima S, Tanaka R, Hattori N. CSF1R mutation p.G589R and the distribution pattern of brain calcification. Intern Med. 2017;56:2507-12. PubMed PMID: 28824062.

Davies A, Tolliday A, Craven I, Connolly DJA. An approach to reporting paediatric leukoencephalopathy and leukodystrophies. Clin Radiol. 2023;78:401-11. PubMed PMID: 36990927.

Dulski J, Heckman MG, Nowak JM, Wszolek ZK. Protective effect of glucocorticoids against symptomatic disease in CSF1R variant carriers. Mov Disord. 2023a;38:1545-9. PubMed PMID: 37309919.

Dulski J, Heckman MG, White LJ, Żur-Wyrozumska K, Lund TC, Wszolek ZK. Hematopoietic stem cell transplantation in CSF1R-related leukoencephalopathy: retrospective study on predictors of outcomes. Pharmaceutics. 2022a;14:2778. PubMed PMID: 36559271.

Dulski J, Koga S, Dickson DW, Wszolek ZK. Report of a family with adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) without mutations in CSF1R, AARS1 or AARS2. Mov Disord Clin Pract. 2023b;10:307-12. PubMed PMID: 36825047.

Dulski J, Middlebrooks EH, Wszolek ZK. Novel application of 7T MRI in CSF1R-related leukoencephalopathy. Neurology. 2022b;99:1110-1111. PubMed PMID: 36180242.

Dulski J, Muthusamy K, Lund T, Wszolek Z. CSF1R-related disorder: state of the art, challenges, and proposition of a new terminology. Parkinsonism Relat Disord. 2024;121:105894. PubMed PMID: 37839910.

Dulski J, Souza J, Santos ML, Wszolek ZK. Brain abnormalities, neurodegeneration, and dysosteosclerosis (BANDDOS): new cases, systematic literature review, and associations with CSF1R-ALSP. Orphanet J Rare Dis. 2023c;18:160. PubMed PMID: 37349768.

Dulski J, Stanley ER, Chitu V, Wszolek ZK. Potential use of glucocorticosteroids in CSF1R mutation carriers - current evidence and future directions. Neurol Neurochir Pol. 2023d;57:444-9. PubMed PMID: 37889001.

Eichler FS, Li J, Guo Y, Caruso PA, Bjonnes AC, Pan J, Booker JK, Lane JM, Tare A, Vlasac I, Hakonarson H, Gusella JF, Zhang J, Keating BJ, Saxena R. CSF1R mosaicism in a family with hereditary diffuse leukoencephalopathy with spheroids. Brain. 2016;139:1666-72. PubMed PMID: 27190017.

Guo L, Bertola DR, Takanohashi A, Saito A, Segawa Y, Yokota T, Ishibashi S, Nishida Y, Yamamoto GL, Franco J, Honjo RS, Kim CA, Musso CM, Timmons M, Pizzino A, Taft RJ, Lajoie B, Knight MA, Fischbeck KH, Singleton AB, Ferreira CR, Wang Z, Yan L, Garbern JY, Simsek-Kiper PO, Ohashi H, Robey PG, Boyde A, Matsumoto N, Miyake N, Spranger J, Schiffmann R, Vanderver A, Nishimura G, Passos-Bueno M, Simons C, Ishikawa K, Ikegawa S. Bi-allelic CSF1R mutations cause skeletal dysplasia of dysosteosclerosis-pyle disease spectrum and degenerative encephalopathy with brain malformation. Am J Hum Genet. 2019;104:925-35. PubMed PMID: 30982609.

Ishiguro T, Konno T, Hara N, Zhu B, Okada S, Shibata M, Saika R, Kitano T, Toko M, Nezu T, Hama Y, Kawazoe T, Takahashi-Iwata I, Yabe I, Sato K, Takeda H, Toda S, Nishimiya J, Teduka T, Nozaki H, Kasuga K, Miyashita A, Onodera O, Ikeuchi T. Novel partial deletions, frameshift and missense mutations of CSF1R in patents with CSF1R-related leukoencephalopathy. Eur J Neurol. 2023;30:1861-70. PubMed PMID: 36943150.

Jańczewska I, Preis-Orlikowska J, Domżalska-Popadiuk I, Preis K, Jańczewska A. Children with corpus callosum anomalies: clinical characteristics and developmental outcomes. Neurol Neurochir Pol. 2023;57:269-81. PubMed PMID: 37078131.

Jiang J, Li W, Wang X, Du Z, Chen J, Liu Y, Li W, Lu Z, Wang Y, Xu J. Two novel intronic mutations in the CSF1R gene in two families with CSF1R-microglial encephalopathy. Front Cell Dev Biol. 2022;10:902067. PubMed PMID: 35721475.

Kaler J, Hussain A, Patel S, Majhi S. Neuromuscular junction disorders and floppy infant syndrome: a comprehensive review. Cureus. 2020;12:e6922. PubMed PMID: 32071826.

Karle KN, Biskup S, Schüle R, Schweitzer KJ, Krüger R, Bauer P, Bender B, Nägele T, Schöls L. De novo mutations in hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS). Neurology 2013;81:2039-44. PubMed PMID: 24198292.

Kındış E, Simsek-Kiper P, Koşukcu C, Taşkıran EZ, Göçmen R, Utine E, Haliloğlu G, Boduroğlu K, Alikaşifoğlu M. Further expanding the mutational spectrum of brain abnormalities, neurodegeneration, and dysosteosclerosis: a rare disorder with neurologic regression and skeletal features. Am J Med Genet Part A. 2021;185:1888–96. PubMed PMID: 33749994.

Kinoshita M, Yoshida K, Oyanagi K, Hashimoto T, Ikeda S. Hereditary diffuse leukoencephalopathy with axonal spheroids caused by R782H mutation in CSF1R: case report. J Neurol Sci. 2012;318:115–8. PubMed PMID: 22503135.

Konno T, Tada M, Tada M, Koyama A, Nozaki H, Harigaya Y, Nishimiya J, Matsunaga A, Yoshikura N, Ishihara K, Arakawa M, Isami A, Okazaki K, Yokoo H, Itoh K, Yoneda M, Kawamura M, Inuzuka T, Takahashi H, Nishizawa M, Onodera O, Kakita A, Ikeuchi T. Haploinsufficiency of CSF-1R and clinicopathologic characterization in patients with HDLS. Neurology. 2014;82:139-48. PubMed PMID: 24336230.

Konno T, Yoshida K, Mizuno T, Kawarai T, Tada M, Nozaki H, Ikeda SI, Nishizawa M, Onodera O, Wszolek ZK, Ikeuchi T. Clinical and genetic characterization of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia associated with CSF1R mutation. Eur J Neurol. 2017;24:37-45. PubMed PMID: 27680516.

Konno T, Yoshida K, Mizuta I, Mizuno T, Kawarai T, Tada M, Nozaki H, Ikeda SI, Onodera O, Wszolek ZK, Ikeuchi T. Diagnostic criteria for adult-onset leukoencephalopathy with axonal spheroids and pigmented glia due to CSF1R mutation. Eur J Neurol. 2018;25:142-7. PubMed PMID: 28921817.

Lee D, Yun JY, Jeong JH, Yoshida K, Nagasaki S, Ahn TB. Clinical evolution, neuroimaging, and volumetric analysis of a patient with a CSF1R mutation who presented with progressive nonfluent aphasia. Parkinsonism Relat Disord. 2015;21:817-20. PubMed PMID: 25934184.

McCormick EM, Zolkipli-Cunningham Z, Falk MJ. Mitochondrial disease genetics update: recent insights into the molecular diagnosis and expanding phenotype of primary mitochondrial disease. Curr Opin Pediatr. 2018;30:714-24. PubMed PMID: 30199403.

Mickeviciute GC, Valiuskyte M, Plattén M, Wszolek ZK, Andersen O, Danylaité Karrenbauer V, Ineichen BV, Granberg T. Neuroimaging phenotypes of CSF1R-related leukoencephalopathy: Systematic review, meta-analysis, and imaging recommendations. J Intern Med. 2022;291:269-82. PubMed PMID: 34875121.

Monies D, Maddirevula S, Kurdi W, Alanazy MH, Alkhalidi H, Al-Owain M, Sulaiman RA, Faqeih E, Goljan E, Ibrahim N, Abdulwahab F, Hashem M, Abouelhoda M, Shaheen R, Arold ST, Alkuraya FS. Autozygosity reveals recessive mutations and novel mechanisms in dominant genes: implications in variant interpretation. Genet Med. 2017;19:1144–50. PubMed PMID: 28383543.

Muthusamy K, Sivadasan A, Dixon L, Sudhakar S, Thomas M, Danda S, Wszolek ZK, Wierenga K, Dhamija R, Gavrilova R. Adult-onset leukodystrophies: a practical guide, recent treatment updates, and future directions. Front Neurol. 2023;14:1219324. PubMed PMID: 37564735.

Oosterhof N, Chang IJ, Karimiani EG, Kuil LE, Jensen DM, Daza R, Young E, Astle L, van der Linde HC, Shivaram GM, Demmers J, Latimer CS, Keene CD, Loter E, Maroofian R, van Ham TJ, Hevner RF, Bennett JT. Homozygous mutations in CSF1R cause a pediatric-onset leukoencephalopathy and can result in congenital absence of microglia. Am J Hum Genet. 2019;104:936-47. PubMed PMID: 30982608.

Papapetropoulos S, Pontius A, Finger E, Karrenbauer V, Lynch DS, Brennan M, Zappia S, Koehler W, Schoels L, Hayer SN, Konno T, Ikeuchi T, Lund T, Orthmann-Murphy J, Eichler F, Wszolek ZK. Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia: review of clinical manifestations as foundations for therapeutic development. Front Neurol. 2022;12:788168. PubMed PMID: 35185751.

Rademakers R, Baker M, Nicholson AM, Rutherford NJ, Finch N, Soto-Ortolaza A, Lash J, Wider C, Wojtas A, DeJesus-Hernandez M, Adamson J, Kouri N, Sundal C, Shuster EA, Aasly J, MacKenzie J, Roeber S, Kretzschmar HA, Boeve BF, Knopman DS, Petersen RC, Cairns NJ, Ghetti B, Spina S, Garbern J, Tselis AC, Uitti R, Das P, Van Gerpen JA, Meschia JF, Levy S, Broderick DF, Graff-Radford N, Ross OA, Miller BB, Swerdlow RH, Dickson DW, Wszolek ZK. Mutations in the colony stimulating factor 1 receptor (CSF1R) gene cause hereditary diffuse leukoencephalopathy with spheroids. Nat Genet. 2011;44:200-5. PubMed PMID: 22197934.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Robinson JL, Suh E, Wood EM, Lee EB, Coslett HB, Raible K, Lee VMY, Trojanowski JQ, Van Deerlin VM. Common neuropathological features underlie distinct clinical presentations in three siblings with hereditary diffuse leukoencephalopathy with spheroids caused by CSF1R p.Arg782His. Acta Neuropathologica Communications. 2015;3:42. PubMed PMID: 26141825.

Rosenstein I, Andersen O, Victor D, Englund E, Granberg T, Hedberg-Oldfors C, Jood K, Fitrah YA, Ikeuchi T, Danylaité Karrenbauer V. Four Swedish cases of CSF1R-related leukoencephalopathy: visualization of clinical phenotypes. Acta Neurol Scand. 2022;145:599-609. PubMed PMID: 35119108.

Rush BK, Tipton PW, Strongosky A, Wszolek ZK. Neuropsychological profile of CSF1R-related leukoencephalopathy. Front Neurol. 2023;14:1155387. PubMed PMID: 37333006.

Saitoh BY, Yamasaki R, Hiwatashi A, Matsushita T, Hayashi S, Mitsunaga Y, Maeda Y, Isobe N, Yoshida K, Ikeda SI, Kira JI. Discriminative clinical and neuroimaging features of motor-predominant hereditary diffuse leukoencephalopathy with axonal spheroids and primary progressive multiple sclerosis: a preliminary cross-sectional study. Mult Scler Relat Disord. 2019;31:22-31. PubMed PMID: 30901701.

Sarret C. Leukodystrophies and genetic leukoencephalopathies in children. Revue Neurologique. 2020;176:10-9. PubMed PMID: 31174885.

Shu Y, Long L, Liao S, Yang J, Li J, Qiu W, Yang Y, Bao J, Wu A, Hu X, Lu Z. Involvement of the optic nerve in mutated CSF1R-induced hereditary diffuse leukoencephalopathy with axonal spheroids. BMC Neurology. 2016;16:171. PubMed PMID: 27619214.

Souza PVS, Badia BML, Silva LHL, Farias IB, Pinto W, Oliveira ASB. Motor neuron disease with leukodystrophy due to CSF1R mutation. Rev Neurol (Paris). 2020;176:219-21. PubMed PMID: 31522743.

Sriram N, Padmanabha H, Chandra SR, Mahale R, Nandeesh B, Bhat MD, Christopher R, Gupta M, Udupi GA, Mailankody P, Mathuranath PS. CSF1R related leukoencephalopathy - rare childhood presentation of an autosomal dominant microgliopathy! Ann Indian Acad Neurol. 2022;25:311-4. PubMed PMID: 35693676.

Stabile C, Taglia I, Battisti C, Bianchi S, Federico A. Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS): update on molecular genetics. Neurol Sci. 2016;37:1565-9. PubMed PMID: 27338940.

Sundal C, Baker M, Karrenbauer V, Gustavsen M, Bedri S, Glaser A, Myhr KM, Haugarvoll K, Zetterberg H, Harbo H, Kockum I, Hillert J, Wszolek Z, Rademakers R, Andersen O. Hereditary diffuse leukoencephalopathy with spheroids with phenotype of primary progressive multiple sclerosis. Eur J Neurol. 2015;22:328-33. PubMed PMID: 25311247.

Sundal C, Carmona S, Yhr M, Almström O, Ljungberg M, Hardy J, Hedberg-Oldfors C, Fred Å, Brás J, Oldfors A, Andersen O, Guerreiro R. An AARS variant as the likely cause of Swedish type hereditary diffuse leukoencephalopathy with spheroids. Acta Neuropathol Commun. 2019;7:188. PubMed PMID: 31775912.

Sundal C, Fujioka S, Van Gerpen JA, Wider C, Nicholson AM, Baker M, Shuster EA, Aasly J, Spina S, Ghetti B, Roeber S, Garbern J, Tselis A, Swerdlow RH, Miller BB, Borjesson-Hanson A, Uitti RJ, Ross OA, Stoessl AJ, Rademakers R, Josephs KA, Dickson DW, Broderick D, Wszolek ZK. Parkinsonian features in hereditary

diffuse leukoencephalopathy with spheroids (HDLS) and CSF1R mutations. Parkinsonism Relat Disord. 2013;19:869-77. PubMed PMID: 23787135.

Sundal C, Jönsson L, Ljungberg M, Zhong J, Tian W, Zhu T, Linden T, Börjesson-Hanson A, Andersen O, Ekholm S. Different stages of white matter changes in the original HDLS family revealed by advanced MRI techniques. J Neuroimaging. 2014;24:444-52. PubMed PMID: 23751174.

Sundal C, Van Gerpen JA, Nicholson AM, Wider C, Shuster EA, Aasly J, Spina S, Ghetti B, Roeber S, Garbern J, Borjesson-Hanson A, Tselis A, Swerdlow RH, Miller BB, Fujioka S, Heckman MG, Uitti RJ, Josephs KA, Baker M, Andersen O, Rademakers R, Dickson DW, Broderick D, Wszolek ZK. MRI characteristics and scoring in HDLS due to CSF1R gene mutations. Neurology. 2012;79:566–74. PubMed PMID: 22843259.

Tamhankar PM, Zhu B, Tamhankar VP, Mithbawkar S, Seabra L, Livingston JH, Ikeuchi T, Crow YJ. A novel hypomorphic CSF1R gene mutation in the biallelic state leading to fatal childhood neurodegeneration. Neuropediatrics. 2020;51:302–6. PubMed PMID: 32464672.

Tipton PW, Kenney-Jung D, Rush BK, Middlebrooks EH, Nascene D, Singh B, Holtan S, Ayala E, Broderick DF, Lund T, Wszolek ZK. Treatment of CSF1R-related leukoencephalopathy: breaking new ground. Mov Disord. 2021;36:2901-9. PubMed PMID: 34329526.

Tutuncu M, Tang J, Zeid NA, Kale N, Crusan DJ, Atkinson EJ, Siva A, Pittock SJ, Pirko I, Keegan BM, Lucchinetti CF, Noseworthy JH, Rodriguez M, Weinshenker BG, Kantarci OH. Onset of progressive phase is an age-dependent clinical milestone in multiple sclerosis. Mult Scler. 2013;19:188-98. PubMed PMID: 22736750.

van der Knaap MS, Naidu S, Kleinschmidt-Demasters BK, Kamphorst W, Weinstein HC. Autosomal dominant diffuse leukoencephalopathy with neuroaxonal spheroids. Neurology. 2000;54:463-8. PubMed PMID: 10668715.

Van Gerpen JA, Wider C, Broderick DF, Dickson DW, Brown LA, Wszolek ZK. Insights into the dynamics of hereditary diffuse leukoencephalopathy with axonal spheroids. Neurology. 2008;71:925–9. PubMed PMID: 18794495.

Wu J, Cheng X, Ji D, Niu H, Yao S, Lv X, Wang J, Li Z, Zheng H, Cao Y, Zhan F, Zhang M, Tian W, Huang X, Luan X, Cao L. The phenotypic and genotypic spectrum of CSF1R-related disorder in China. Mov Disord. 2024. Epub ahead of print. PubMed PMID: 38465843.

Wu X, Sun C, Wang X, Liu Y, Wu W, Jia G. Identification of a de novo splicing mutation in the CSF1R gene in a Chinese patient with hereditary diffuse leukoencephalopathy with spheroids. Neurol Sci. 2022;43:3265-72. PubMed PMID: 34791569.

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