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NLM Citation: Beaudin M, Gamache PL, Gros-Louis F, et al. SYNE1 Deficiency. 2007 Feb 23 [Updated 2018 Dec 6]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

SYNE1 Deficiency

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Created: February 23, 2007; Updated: December 6, 2018.

Summary

Clinical characteristics

SYNE1 deficiency comprises a phenotypic spectrum that ranges from autosomal recessive cerebellar ataxia at the mild end to arthrogryposis multiplex congenita (AMC) at the severe end. SYNE1-deficient cerebellar ataxia, the most commonly recognized manifestation of SYNE1 deficiency to date, is a slowly progressive disorder typically beginning in adulthood (age range 6-45 years). While some individuals have a pure cerebellar syndrome (i.e., cerebellar ataxia, dysarthria, dysmetria, abnormalities in ocular saccades and smooth pursuit), many also have upper motor neuron dysfunction (spasticity, hyperreflexia, Babinski sign) and/or lower motor neuron dysfunction (amyotrophy, reduced reflexes, fasciculations). Most individuals develop features of the cerebellar cognitive and affective syndrome (i.e., significant deficits in attention, executive functioning, verbal working memory, and visuospatial/visuoconstructional skills). The two less common phenotypes are SYNE1-deficient childhood-onset multisystem disease (ataxia, upper and lower motor neuron dysfunction, muscle weakness and wasting, intellectual disability) and SYNE1-deficient arthrogryposis multiplex congenita (decreased fetal movements and severe neonatal hypotonia associated with multiple congenital joint contractures including clubfoot).

Diagnosis/testing

The diagnosis of SYNE1 deficiency is established in a proband with suggestive findings and biallelic *SYNE1* pathogenic variants identified by molecular genetic testing.

Management

Treatment of manifestations: There is no specific treatment for SYNE1 deficiency. The goals of treatment are to maximize function and reduce complications. Each affected individual should be managed by a multidisciplinary team of relevant specialists including neurologists, occupational therapists, physical therapists,

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physiatrists, orthopedists, nutritionists, speech therapists, respiratory therapists, and psychologists depending on the clinical manifestations.

Surveillance: Annual (or more often as needed) neurologic examination; assessment of mobility and self-help skills (as they relate to ataxia, spasticity, weakness), dysarthria, dysphagia, cognition, and psychiatric manifestations.

Genetic counseling

SYNE1 deficiency is inherited in an autosomal recessive manner. The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *SYNE1* pathogenic variant). At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *SYNE1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal diagnosis for a pregnancy at increased risk, and preimplantation genetic testing are possible.

GeneReview Scope

SYNE1 Deficiency: Included Phenotypes [1]
• *SYNE1* cerebellar ataxia (autosomal recessive cerebellar ataxia 1 [ARCA1]) • SYNE1-deficient arthrogryposis multiplex congenita (AMC)

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

SYNE1 deficiency comprises a phenotypic spectrum that ranges from autosomal recessive cerebellar ataxia to arthrogryposis multiplex congenita (AMC).

Suggestive Findings

SYNE1 deficiency **should be suspected** in individuals with a combination of the following clinical features and/or clinical syndrome based on age of onset.

Clinical features

- Cerebellar ataxia
  - Progressive ataxia of gait
  - Clumsiness of hands
  - Dysmetria
  - Dysarthria
  - Abnormalities in ocular saccades and smooth pursuit
- Upper and/or lower motor neuron involvement
  - Spasticity, hyperactive deep tendon reflexes, extensor plantar response
  - Muscle atrophy, diminished deep tendon reflexes, fasciculations
- Cognitive impairment
  - Delayed motor milestones in infancy
  - Intellectual disability
  - Cognitive dysfunction typical of the cerebellar cognitive and affective syndrome (deficits in executive functioning, language, visuospatial/visuoconstructional skills)
- Skeletal involvement

- Scoliosis or kyphosis
- Pes cavus
- Arthrogryposis with distal joint contractures

Clinical syndrome, defined according to age at onset:

- **Neonatal onset.** Arthrogryposis multiplex congenita (AMC); neonatal hypotonia with decreased fetal movements resulting in distal joint contractures (including bilateral clubfoot, adducted thumbs, flexion contractures of fingers) followed by delayed motor milestones and progressive motor decline after the first decade [Attali et al 2009, Baumann et al 2017]
- **Childhood onset.** Multisystem phenotype; childhood-onset ataxia with upper and lower motor neuron dysfunction, elevation of serum CK concentration, pes cavus, other skeletal and soft tissue anomalies, intellectual disability, followed by respiratory insufficiency in adolescence [Synofzik & Schüle 2017]
- **Adult onset.** Cerebellar ataxia (ARCA1); cerebellar ataxia, frequent upper and/or lower motor neuron involvement, and cognitive impairment typical of the cerebellar cognitive and affective syndrome [Dupré et al 2007, Synofzik et al 2016]

Electrophysiologic Studies

Cerebellar ataxia

- **Nerve conduction studies.** Usually normal; may occasionally show an axonal neuropathy [Synofzik et al 2016, Yucesan et al 2017]
- **Electromyography (EMG).** Usually normal; may occasionally show acute or chronic neurogenic changes in individuals with clinical evidence of motor neuron dysfunction [Izumi et al 2013, Synofzik et al 2016]

AMC

- **Nerve conduction studies and EMG (in newborns).** May be normal [Baumann et al 2017]
- **EMG (later onset).** Includes mild chronic neurogenic findings [Attali et al 2009]

Brain Imaging

Brain MRI in individuals with childhood-onset multisystem disease or adult-onset ataxia usually shows marked diffuse cerebellar atrophy with no other abnormalities (Figure 1).

- Brain stem atrophy has been reported in one individual with childhood-onset multisystem disease [Izumi et al 2013].
- White matter abnormalities in the brain and spinal cord that mimicked findings in multiple sclerosis have been reported in two individuals with adult-onset ataxia [Algahtani et al 2017].

^{18}F-FDG-PET imaging shows marked homogeneous hypometabolism in the cerebellar hemispheres. Pontine brain stem hypometabolism has been reported in one individual with motor neuron involvement [Synofzik et al 2016].

Establishing the Diagnosis

The diagnosis of SYNE1 deficiency **is established** in a proband with suggestive findings and biallelic *SYNE1* pathogenic variants identified by molecular genetic testing (see Table 1).

Because the phenotype of SYNE1 deficiency is indistinguishable from many other inherited disorders with similar complex neurologic and neuromuscular phenotypes, molecular genetic testing approaches include **comprehensive genomic testing** or use of a **multigene panel** [Dupré et al 2007, Baumann et al 2017, Coutelier et al 2018, Sun et al 2019].

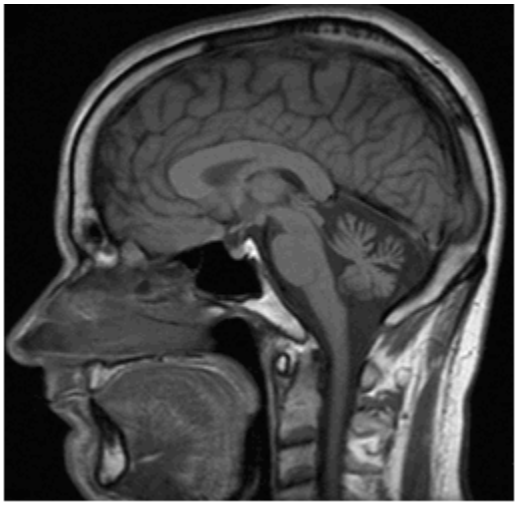

Figure 1. MRI of a female age 29 years with *SYNE1* adult-onset cerebellar ataxia. Sagittal T_1-weighted imaging shows marked diffuse cerebellar atrophy with no atrophy of the cerebral cortex, midbrain, pons, or medulla.

Note: Single-gene testing (sequence analysis of *SYNE1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

- **A multigene panel** that includes *SYNE1* and other genes of interest (see Differential Diagnosis) may be considered 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.

Table 1. Molecular Genetic Testing Used in SYNE1 Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SYNE1	Sequence analysis [3]	~100% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown (no data on gene-targeted del/dup analysis are available)

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. Dupré et al [2007], Mademan et al [2016], Synofzik et al [2016], Baumann et al [2017], Coutelier et al [2018], Sun et al [2019]
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.

Clinical Characteristics

Clinical Description

The phenotype and severity of SYNE1 deficiency vary widely and span a spectrum ranging from adult-onset cerebellar ataxia at the milder end to childhood-onset multisystem disease and prenatal-onset arthrogryposis multiplex congenita at the more severe end.

SYNE1 Adult-Onset Cerebellar Ataxia

SYNE1-deficient cerebellar ataxia, also known as autosomal recessive cerebellar ataxia 1 (ARCA1), typically begins in adulthood (mean age at onset: 31.6 years [Dupré et al 2007]; range 6 to 45 years in reported series).

The initial description of ARCA1 was that of a pure cerebellar syndrome characterized by cerebellar ataxia, dysarthria, dysmetria, and abnormalities in ocular saccades and smooth pursuit [Dupré et al 2007]. In individuals from the original series, 33% had brisk reflexes and 6% had positive Babinski signs and/or ankle clonus, suggesting mild upper motor neuron involvement. Subsequently, Synofzik et al [2016] reported motor neuron dysfunction in as many as 58% of affected individuals, comprising 31% with pure upper motor neuron dysfunction (spasticity, positive bilateral Babinski signs), 19% with combined upper and lower motor neuron dysfunction, and 8% with pure lower motor neuron dysfunction (amyotrophy, reduced reflexes, fasciculations, or neurogenic changes on EMG). Slow saccades have been reported along with other oculomotor abnormalities, including square wave jerks, ophthalmoparesis, and strabismus. Skeletal involvement with scoliosis and pes cavus is an associated finding in some individuals. Reduced sense of vibration, polyneuropathy, and urge incontinence are rare occurrences [Synofzik et al 2016]. There is no evidence of muscle disease, and creatine kinase values are normal.

Individuals with SYNE1-deficient cerebellar ataxia show typical findings of the cerebellar cognitive and affective syndrome: significant deficits in attention, executive functioning, verbal working memory, and visuospatial/visuoconstructional skills [Laforce et al 2010, Mademan et al 2016].

The disease course is usually slowly progressive, resulting in a moderate degree of disability but normal life expectancy [Dupré et al 2007].

SYNE1 Childhood-Onset Multisystem Disease

A rarer phenotype is childhood-onset complex and severe multisystem disease with ataxia, upper and lower motor neuron dysfunction, pes cavus, intellectual disability, and findings suggestive of muscle disease (weakness, muscle wasting, elevated creatine kinase values, respiratory insufficiency) [Synofzik et al 2016]. Involvement of bulbar muscles may be prominent with tongue fasciculations and atrophy as well as slurred speech, and the clinical picture may mimic amyotrophic lateral sclerosis [Izumi et al 2013]. Respiratory insufficiency may present with respiratory distress or restrictive lung disease and may require noninvasive or mechanical ventilation. The reported broad range of skeletal and soft tissue abnormalities includes sacral cysts, pseudoarthrosis clavicula, hyperlaxity of joints, Achilles tendon contractures, kyphosis, scoliosis, pes cavus, cataract, and hypertelorism.

One individual had developmental abnormalities of the visceral organs (i.e., malrotation of the colon and unilateral position of both kidneys) [Mademan et al 2016, Synofzik et al 2016].

Brain MRI may show brain stem atrophy in addition to cerebellar atrophy [Izumi et al 2013].

Death between ages 36 and 44 years has been reported in a few individuals [Izumi et al 2013, Synofzik et al 2016].

SYNE1 Arthrogryposis Multiplex Congenita

SYNE1-deficient arthrogryposis multiplex congenita is characterized by decreased fetal movements in the absence of polyhydramnios, intrauterine growth restriction, or associated malformations [Attali et al 2009, Baumann et al 2017]. Neonates have severe hypotonia presenting as "floppy infant" with bilateral clubfeet, distal joint contractures with adducted thumbs and flexion contractures of fingers, and cryptorchidism in males (see Baumann et al [2017], Figure 1). Proximal weakness, facial weakness, and decreased or absent deep tendon reflexes have been reported. Motor milestones are delayed, followed by progressive motor decline after the first decade. Affected individuals use the Gower maneuver when arising from a squatting position and have limited ability to ambulate independently and to alternate their feet when climbing stairs. Flexion contractures of the proximal interphalangeal joints of the third and fourth fingers may persist despite adequate management.

Cerebellar involvement and pyramidal signs have not been reported. Intellectual development is borderline to normal. Growth deficiency worsens with advancing age despite adequate weight gain. Hyperopia with intermittent strabismus has been reported.

Early death has been reported in two individuals: one age 22 years with severe kyphoscoliosis and restrictive lung disease who died of pneumonia and sepsis [Attali et al 2009], and an infant age four months who presented with severe neonatal hypotonia and respiratory failure. Note that the infant did not undergo genetic testing but had a sib with confirmed SYNE1 deficiency [Baumann et al 2017].

In SYNE1-deficient AMC, muscle biopsy may show variations in the size of muscle fibers without increased number of muscle fibers with central nuclei. Creatine kinase values are normal.

Genotype-Phenotype Correlations

Most pathogenic variants associated with the ARCA1 phenotype are nonsense or frameshift and are localized throughout the gene, excluding the KASH domain. Most – but not all – *SYNE1* pathogenic variants associated with motor neuron involvement are located toward the 3' end of the gene [Yoshinaga et al 2017].

SYNE1 pathogenic variants associated with arthrogryposis multiplex congenita (AMC) are distal truncating variants that are expected to lead to a truncated Nesprin1α (or Nesprin1α2) isoform, which is muscle and retina specific [Duong et al 2014, Potter et al 2017].

Nomenclature

In this *GeneReview*, the term "SYNE1 deficiency" refers to the full neurologic and neuromuscular phenotypic spectrum of biallelic *SYNE1* pathogenic variants: from autosomal recessive cerebellar ataxia 1 (ARCA1) at the mild end of the continuum to SYNE1-AMC at the most severe end of the continuum.

Note: Autosomal recessive cerebellar ataxia 1 (ARCA1) has also been referred to as "recessive ataxia of Beauce" and "spinocerebellar ataxia recessive 8" (SCAR8).

Most recently, the International Parkinson and Movement Disorder Society Task Force on Classification and Nomenclature of Genetic Movement Disorders suggested the term "ATX-SYNE1" [Rossi et al 2018].

Prevalence

ARCA1, initially described in the French Canadian population, has now been reported worldwide, notably in Japan, Europe, the Middle East, and Brazil. Although its exact prevalence is not known, it is highly prevalent in the French Canadian population, which is a homogeneous founder population [Dupré et al 2007].

When Friedreich ataxia has been excluded, SYNE1 deficiency represents 5.3%-6% of unexplained early-onset (i.e., age <40 years) autosomal recessive ataxias [Mademan et al 2016, Synofzik et al 2016].

The prevalence of SYNE1-deficient arthrogryposis multiplex congenita cannot be evaluated as it has only been reported in a few families to date.

Genetically Related (Allelic) Disorders

Heterozygous *SYNE1* pathogenic variants are also an uncommon cause of Emery-Dreifuss muscular dystrophy type 4 (EDMD4) or Emery-Dreifuss muscular dystrophy-like, characterized by early joint contractures, progressive muscular atrophy, and muscle weakness, with cardiomyopathy in EDMD [Zhang et al 2007] or without cardiac involvement in EDMD-like [Chen et al 2017]. Typically, affected individuals manifest the following: (1) early contractures of the Achilles tendons, elbows, and posterior cervical muscles (progression of which eventually severely limits anterior spinal flexion); (2) progressive skeletal muscle weakness and wasting; and (3) severe cardiomyopathy with ventricular and supraventricular arrhythmias, chamber dilatation, and heart failure as a consequence of myocardial cell replacement by fibrosis and adipose tissue [Chen et al 2017]. Heart transplantation may be required.

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of SYNE1 Deficiency

MOI	Disorder	Gene [1]	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/SYNE1 Deficiency	Distinguishing from SYNE1 Deficiency
AR	SCA-AR, 10 (SCAR10; ARCA3) (See Hereditary Ataxia Overview.)	*ANO10*	• Very similar clinically • Pure cerebellar ataxia w/ occasional UMN signs • Cognitive impairment • Absence of polyneuropathy • Marked cerebellar atrophy	Seen mainly in Europe (whereas SYNE1 deficiency is seen worldwide)
	Primary coenzyme Q_{10} deficiency (SCAR9; ARCA2)	*COQ8A*	Often a pure cerebellar ataxia phenotype w/cognitive impairment & cerebellar atrophy	• Exercise intolerance • Epilepsy • Myoclonus • Occasional stroke-like cerebral lesions • Absence of UMN &/or LMN signs

Table 2. continued from previous page.

MOI	Disorder	Gene [1]	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/SYNE1 Deficiency	Distinguishing from SYNE1 Deficiency
	Friedreich ataxia	*FXN*	• Cerebellar ataxia • Positive Babinski signs	• Sensory involvement w/spinal cord atrophy • Abolished reflexes • Square-wave jerks • Hypertrophic cardiomyopathy • Childhood to teenage onset • Absence of cerebellar atrophy
	Boucher-Neuhäuser syndrome & *PNPLA6*-related Gordon Holmes syndrome (See *PNPLA6*-Related Disorders.)	*PNPLA6*	• Cerebellar ataxia • Spasticity • Hyperreflexia	• Hypogonadotropic hypogonadism • Chorioretinal dystrophy • Childhood onset • Pontine atrophy
	ARSACS (AR spastic ataxia of Charlevoix-Saguenay)	*SACS*	• Ataxia • Dysarthria • Eye movement abnormalities • UMN signs • Seen worldwide but high prevalence in French Canadians	• Infantile or childhood onset • Sensorimotor neuropathy • Retinal striation • Frequent mitral valve prolapse
	Spastic paraplegia 7	*SPG7*	• Pyramidal signs w/spasticity • Cerebellar ataxia w/cerebellar atrophy	• Spastic paraparesis more predominant • Optic neuropathy • Ptosis
AD	SCA3	*ATXN3*	• Cerebellar ataxia • UMN signs w/occasional amyotrophy & fasciculations • Cognitive impairment	• Extrapyramidal features w/dystonia, rigidity, parkinsonism • Progressive external ophthalmoparesis
	SCA6	*CACNA1A*	• Cerebellar ataxia w/adult onset & slow progression • Occasional UMN signs	Extrapyramidal features w/dystonia & blepharospasm
XL	Fragile X-associated tremor/ataxia syndrome (FXTAS) (See *FMR1*-Related Disorders.)	*FMR1*	• Cerebellar ataxia of adult onset • Cognitive impairment	• Predominant tremor • Parkinsonism • MRI: White matter lesions in cerebellar peduncles & brain stem

AD = autosomal dominant; AR = autosomal recessive; LMN = lower motor neuron; MOI = mode of inheritance; SCA = spinocerebellar ataxia; UMN = upper motor neuron; XL = X-linked

1. Within a MOI, genes are in alphabetic order.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with SYNE1 deficiency, the evaluations summarized in this section (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 SYNE1-Deficient Cerebellar Ataxia

System/Concern	Evaluation	Comment
Neurologic	Assessment by neurologist for: • Cerebellar motor dysfunction (gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades & smooth pursuit) • UMN &/or LMN dysfunction (weakness, spasticity, Babinski signs, hyperrefflexia, amyotrophy, fasciculations) • Vibration loss or polyneuropathy based on clinical findings	• Use standardized scale to establish baseline for ataxia (SARA, ICARS, or BARS). [1] • Consider electrophysiologic studies (EMG & NCS) to detect neurogenic changes or signs of neuropathy. • Brain MRI to evaluate presence & severity of cerebellar atrophy
	Refer to neuromuscular clinic (OT/PT/rehabilitation specialist).	To assess gross motor & fine motor skills, ambulation, & need for adaptive devices & PT
Speech	For those w/dysarthria: speech/language evaluation	
Feeding	For those w/frequent choking or severe dysphagia, assess: • Nutritional status • Aspiration risk	Consider involving a gastroenterology/ nutrition/feeding team.
Respiratory	For those w/respiratory symptoms or muscular involvement: obtain pulmonary function tests	Consider involving pulmonary specialist / respiratory therapist
Cognitive/ Psychiatric	Assess for cognitive dysfunction assoc w/cerebellar cognitive & affective syndrome (executive function, language processing, visuospatial/visuoconstructional skills, emotion regulation)	Consider use of: • CCAS scale [2] to evaluate cognitive & emotional involvement • Psychiatrist, psychologist, neuropsychologist if needed
Musculoskeletal	Assess for skeletal involvement, mainly scoliosis & pes cavus.	
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

BARS = Brief Ataxia Rating Scale; CCAS = cerebellar cognitive affective syndrome; EMG = electromyogram; ICARS = International Co-operative Ataxia Rating Scale; LMN = lower motor neuron; NCS = nerve conduction study; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia; UMN = upper motor neuron
1. Bürk & Sival [2018]
2. Hoche et al [2018]

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with SYNE1-Deficient Arthrogryposis Multiplex Congenita

System/Concern	Evaluation	Comment
Neurologic	Assessment by neurologist of: • Tone, primitive reflexes, deep tendon reflexes • Progression of motor milestones • Muscular involvement (e.g., proximal weakness, facial weakness)	Consider EMG, which may show neurogenic changes.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	Multidisciplinary neuromuscular clinic assessment by orthopedist, physiatrist, OT/PT	To include assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • Need for adaptive devices • Need for PT (for improving gross motor skills) &/or OT (for improving fine motor skills)
Feeding	Assess: • Nutritional status • Aspiration risk	Consider involving: • Gastroenterologist • Nutritionist • Feeding team
Speech	Speech/language evaluation	
Respiratory	• Involve pulmonary specialist / respiratory therapist • Assess for pulmonary insufficiency	
Neurodevelopmental	Developmental assessment	• To include motor, speech/language evaluation, & general cognitive skills • Evaluation for early intervention / special education
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

OT = occupational therapy/therapist; PT = physical therapy/therapist
1. Baumann et al [2017]

Treatment of Manifestations

There is no specific treatment for SYNE1 deficiency. The goals of treatment are to maximize function and reduce complications. Each affected individual should be managed by a multidisciplinary team of relevant specialists such as neurologists, occupational therapists (OT), physical therapists (PT), physiatrists, orthopedists, nutritionists, speech therapists, respiratory therapists, and psychologists depending on the clinical manifestations.

Table 5. Treatment of Manifestations in Individuals with SYNE1-Deficient Cerebellar Ataxia

Manifestation/Concern	Treatment	Considerations/Other
Ataxia	Care by physiatrist, OT/PT	• Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, ramps to accommodate motorized chairs), feeding (e.g., weighted eating utensils), dressing (e.g., dressing hooks) • PT (balance exercises, gait training, muscle strengthening) to maintain mobility & function [1] • OT to optimize ADL • Inpatient rehabilitation w/OT/PT may improve ataxia & functional abilities in those w/degenerative ataxias. [2, 3] • Weight control to avoid obesity • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats)
	Pharmacologic treatment	Consider Riluzole (100 mg/d [3]), the only drug shown to improve ataxia symptoms in persons w/ataxia of mixed etiologies; use requires monitoring of liver enzymes.
	Transcranial magnetic stimulation	Consider transcranial magnetic stimulation over the cerebellum, [2] which possibly improves cerebellar motor signs after 21 daily treatments (tested in patients w/various causes of spinocerebellar degeneration).
Upper motor neuron involvement (spasticity)	Pharmacologic treatment	Baclofen, tizanidine, or dantrolene may relieve muscle spasms & spasticity; however, there are no specific guidelines for SYNE1 deficiency.
Dysarthria	Speech & language therapy	Consider alternative communication methods as needed (e.g., writing pads & digital devices).
Dysphagia	Modify food consistency to reduce aspiration risk.	Video esophagram may help define best consistency.
Poor weight gain	Nutrition assessment	Consider nutritional & vitamin supplementation to meet dietary needs.
Scoliosis / Skeletal involvement	Surgical treatment	Refer to orthopedic surgeon when required.
Cognitive/ Psychiatric	Pharmacologic treatment	Standard treatment for psychiatric manifestations (e.g., depression, anxiety, & psychosis)
	Psychotherapy / neuropsychological rehabilitation	Consider cognitive & behavioral therapy, including Goal Management Training®. [4]

ADL = activities of daily living; OT = occupational therapy/therapist; PT = physical therapy/therapist
1. Martineau et al [2014]
2. Zesiewicz et al [2018]
3. van de Warrenburg et al [2014]
4. Ruffieux et al [2017]

Table 6. Treatment of Manifestations in Individuals with SYNE1-Deficient Arthrogryposis Multiplex Congenita

Manifestation/Concern	Treatment	Considerations/Other
Musculoskeletal	Multidisciplinary neuromuscular clinic, physiatry, OT/PT	Maximize gross motor & fine motor skills through PT/OT & use of adaptive devices. Alternative casting/splinting & stretching.
	Orthopedics	Manage contractures, clubfoot, & scoliosis w/bracing &/or surgical intervention.

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Feeding/Dysphagia	Gastroenterology / nutrition / feeding team	Modify food consistency to reduce aspiration risk &/or consider NG feeding & gastrostomy.
Speech	Speech/language evaluation	Consider involving speech therapist & OT to improve communication skills.
Respiratory	Manage pulmonary complications; treat respiratory infections.	
Neurodevelopmental	Early intervention / individual education program based on needs	

NG = nasogastric; OT = occupational therapy; PT = physical therapy
Haliloglu & Topaloglu [2013]

Surveillance

There are no published surveillance guidelines for individuals with SYNE1 deficiency or for degenerative ataxias in general.

Table 7. Recommended Surveillance for Individuals with SYNE1 Deficient Cerebellar Ataxia

System/Concern	Evaluation	Frequency
Neurologic	• Neurologic assessment for progression of ataxia; UMN or LMN signs • Monitor ataxia progression w/standardized scale (SARA, ICARS, or BARS) [1]	Annually; more often for an acute exacerbation
	Physiatry, OT/PT assessment of mobility, self-help skills as they relate to ataxia, spasticity, weakness	
Dysarthria	Need for alternative communication method or speech therapy	Per symptom progression
Dysphagia	Assess aspiration risk & feeding methods	
Cognitive/ Psychiatric	Evaluate mood, signs of psychosis, cognitive complaints to identify need for pharmacologic & psychotherapeutic interventions.	Per symptom progression & development of psychiatric symptoms

BARS = Brief Ataxia Rating Scale; ICARS = International Co-operative Ataxia Rating Scale; LMN = lower motor neuron; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia; UMN = upper motor neuron
1. Bürk & Sival [2018]

Table 8. Recommended Surveillance for Individuals with SYNE1-Deficient Arthrogryposis Multiplex Congenita

System/Concern	Evaluation	Frequency
Neurologic	Neurologic assessment	Annually; more often for an acute exacerbation
	Physiatry, OT/PT assessment of mobility, self-help skills	
Musculoskeletal	Assess for: • Progression of kyphoscoliosis • Clubfoot relapse • Other complications that limit function	Annually or more often according to specific complaints

Table 8. continued from previous page.

System/Concern	Evaluation	Frequency
Speech	Assess for: • Speech & language development; • Need for alternative communication method.	Individualized according to specific needs & potential for progression
Feeding	Assess: • Aspiration risk; • Nutritional status.	As neurologic function improves consider advancing food consistency & diet.
Respiratory	Attention to possible respiratory insufficiency	As needed
Neurodevelopmental	Educational placement & school support	Annually
Social/Behavioral	Assess age-related social/maturation issues.	Annually or more often according to specific needs

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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

SYNE1 deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *SYNE1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with SYNE1 deficiency are obligate heterozygotes (carriers) for a *SYNE1* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *SYNE1* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *SYNE1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SYNE1* pathogenic variants have been identified in an affected family member, prenatal diagnosis for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

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

- **AMCSI: Arthrogryposis Multiplex Congenita Support, Inc.**
  P.O. Box 6291
  Spartanburg SC 29304
  Phone: 805-55-AMCSI (1-805-552-6274)
  Email: bod@amcsupport.org
  www.amcsupport.org
- **Ataxia UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  www.ataxia.org.uk
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: lporter@ataxia.org.uk
  www.euroataxia.org

- **National Ataxia Foundation**
  Phone: 763-553-0020
  Fax: 763-553-0167
  Email: naf@ataxia.org
  www.ataxia.org
- **NCBI Genes and Disease**
  Spinocerebellar ataxia
- **CoRDS Registry**
  Sanford Research
  Phone: 605-312-6300
  CoRDS Registry

Molecular Genetics

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

Table A. SYNE1 Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SYNE1	6q25.2	Nesprin-1	SYNE1 homepage - Leiden Muscular Dystrophy pages	SYNE1	SYNE1

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 SYNE1 Deficiency (View All in OMIM)

608441	SPECTRIN REPEAT-CONTAINING NUCLEAR ENVELOPE PROTEIN 1; SYNE1
610743	SPINOCEREBELLAR ATAXIA, AUTOSOMAL RECESSIVE 8; SCAR8

Molecular Pathogenesis

Gene structure. *SYNE1* is one of the largest genes in the human genome with 0.5 Mb of genomic DNA. Alternatively spliced transcript variants encoding different protein isoforms have been described. The longest transcript NM_182961.3 (27,748 bp; variant 1) has 146 exons, of which exons 1 and 2 are noncoding. A shorter transcript variant NM_033071.3 (27,439 bp; variant 2) has 146 exons with exon 1 noncoding; this variant has multiple differences in the coding region but maintains the same reading frame as transcript variant 1.

See Table A, **Gene** for a detailed summary of gene, transcripts, and protein isoforms.

Pathogenic variants. Most pathogenic variants associated with the ARCA1 phenotype are nonsense or frameshift and are localized throughout the gene, excluding the KASH domain [Yoshinaga et al 2017]. Pathogenic variants associated with arthrogryposis multiplex congenita (AMC) are distal truncating variants that are expected to lead to a truncated Nesprin1α (or Nesprin1α2) isoform, which is muscle and retina specific [Duong et al 2014, Potter et al 2017].

Normal gene product. *SYNE1* encodes a multi-isomeric protein called nesprin1, a scaffold protein involved in the binding of the nuclear membrane and the cytoskeleton. Nesprin-1 localizes at the outer nuclear membrane, where it interacts with SUN proteins located at the inner nuclear membrane to form the linker of the nucleoskeleton and cytoskeleton (LINC) complex [Sosa et al 2012]. The longest transcript variant NM_182961.3 encodes a 8,797-amino-acid protein (>1000 kd) known as the nesprin-1 giant isoform (Nes1g or isoform-1 or enaptin) (NP_892006.3) [Gros-Louis et al 2007]. The nesprin-1 giant protein contains two N-terminal paired calponin homology domains that bind cytoskeletal actin, a transmembrane domain, multiple spectrin repeats that mediate anchoring and interaction with other proteins and organelles, and a C-terminal KASH domain that localizes the protein to the nuclear envelope. Transcript variant NM_033071.3 encodes an 8,749-amino-acid protein known as KLNes1g (or nesprin-1 isoform 2) (NP_149062.1) [Razafsky & Hodzic 2015]. The shorter KLNes1g isoform lacks the C-terminal KASH domain.

Two isoforms of the proteins are specifically expressed in the central nervous system when compared with other isoforms and with the related Nesprin2 protein: Nes1g is particularly expressed in CNS tissues along with its KLNes1g, which is abundantly expressed in the cerebellum [Gros-Louis et al 2007, Duong et al 2014, Razafsky & Hodzic 2015].

SYNE1 has multiple alternative start and termination sites that allow for multiple isoforms lacking certain specific domains [Rajgor et al 2012; see also Razafsky & Hodzic 2015, Yoshinaga et al 2017, Potter et al 2018, and references therein]. These isoforms are present in multiple subcellular locations beyond the nuclear envelope and serve to link these structures to the actin skeleton [Zhang et al 2007]. Specific isoforms appear to have a tissue-specific transcription, and this transcription is highly adaptable according to cell needs for maintaining homeostasis [Rajgor et al 2012].

Abnormal gene product. Most pathogenic variants associated with the ARCA1 phenotype are nonsense or frameshift and are localized throughout the gene, excluding the KASH domain [Yoshinaga et al 2017]. Hence, these pathogenic variants are expected to affect the structure of the KLNes1g isoform, whose loss of function is thought to lead to ARCA1 [Razafsky & Hodzic 2015]. Indeed, the KLNes1g isoform is abundantly expressed in the cerebellum, where it localizes to essential synapses between mossy fibers and cerebellar granule neurons within the granule cell layer [Potter et al 2018]. Analyses in murine models suggest that this isoform is involved in vesicular trafficking and dendritic membrane structural organization, which indicates that defective synaptic transmission may underlie ARCA1 pathology; however, this remains to be confirmed [Razafsky & Hodzic 2015]. Pathogenic variants that alter the more C-terminal region of the protein have the potential to also alter the ubiquitously expressed Nesprin1β isoform, which may underlie the more complex multisystem phenotype observed in some individuals [Potter et al 2018].

Pathogenic variants associated with arthrogryposis multiplex congenita (AMC) are distal truncating variants that are expected to lead to a truncated Nesprin1α (or Nesprin1α2) isoform, which is muscle and retina specific [Duong et al 2014, Potter et al 2017]. There is mounting evidence that Nesprin1α is involved in skeletal muscle function: Nesprin1α is upregulated during myogenic differentiation and is required for the recruitment of centrosomal proteins to the nuclear envelope, which ensures proper nuclear positioning [Gimpel et al 2017]. Aberrant nuclear positioning is associated with other muscular diseases, suggesting that proper nuclear localization is essential for skeletal muscle function [Stroud et al 2017]. In murine studies of different Nesprin1 isoforms, loss of Nesprin1α2 led to severe nuclear mispositioning and postnatal lethality, suggesting that this is the isoform essential for skeletal muscle function [Stroud et al 2017]. Hence, loss of the Nesprin1α isoform may underlie muscular involvement in SYNE1 deficiency.

All *SYNE1* pathogenic variants would also affect the Nesprin1 giant (Nes1g) isoform, which is predominantly expressed in the central nervous system at the nuclear envelope of Bergmann glia and at ciliary rootlets of ependymal cells [Baumann et al 2017, Potter et al 2018]. Mouse models with loss of Nes1g did not show any cerebellar phenotype but presented ventricular enlargement potentially reflecting cilia dysfunction [Potter et al

2018]. Of interest, scoliosis, respiratory insufficiency, and cognitive impairment are all clinical findings that have been reported in association with other ciliopathies, suggesting that loss of the Nes1g isoform may underlie some non-cerebellar and non-muscular features of the phenotype [Potter et al 2018].

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Revision History

- 6 December 2018 (bp) Comprehensive update posted live
- 13 October 2011 (cd) Revision: cognitive changes associated with this disorder as reported by Laforce et al [2010]
- 18 August 2011 (cd) Revision: mutation scanning of select exons and prenatal testing clinically available
- 14 July 2011 (me) Comprehensive update posted live
- 15 September 2009 (cd) Revision: sequence analysis and targeted mutation analysis available clinically
- 23 February 2007 (me) Review posted live
- 6 February 2007 (nd) Original submission

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