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DRPLA

Synonym: Dentatorubral-Pallidoluysian Atrophy

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Summary

Clinical characteristics

DRPLA (dentatorubral-pallidoluysian atrophy) is a progressive neurologic disorder characterized by five cardinal features (irrespective of the age of onset): ataxia, cognitive decline, myoclonus, chorea, epilepsy, and psychiatric manifestations. Onset ranges from infancy to late adulthood (range: age 0-72 years; mean: age 31.5 years). The clinical presentation varies by age of onset: individuals with juvenile onset (before age 20 years) have myoclonus, epilepsy, and progressive intellectual deterioration, whereas individuals with adult onset (after age 20 years) have ataxia, choreoathetosis, and dementia or neuropsychiatric changes. Disease duration is on average eight years (range: 0-35 years) and age at death is on average 49 years (range: age 18-80 years).

Diagnosis/testing

The diagnosis of DRPLA is established in a proband with suggestive clinical findings and a heterozygous pathogenic CAG trinucleotide expansion in *ATN1* identified by molecular genetic testing.

Management

Treatment of manifestations: Standard anti-seizure medications (ASMs) for seizures; appropriate psychotropic medications for psychiatric manifestations; symptomatic treatment of ataxia with riluzole and rehabilitation therapy; adaptation of environment and care to the level of dementia; appropriate educational programs for children.

Agents/circumstances to avoid: General anesthesia can increase the risk of intra- and postoperative seizures.

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Pregnancy management: Because the use of ASMs during pregnancy may have an effect on the fetus, discussion of the risks and benefits of using an ASM during pregnancy should ideally occur prior to conception when transition to a lower-risk medication may be possible. The use of riluzole during pregnancy has not been well studied in humans.

Genetic counseling

DRPLA is inherited in an autosomal dominant manner. The risk to the children of an affected individual of inheriting an expanded CAG repeat is 50%. The size of the repeat transmitted to the offspring depends on the size of the parent's repeat and the sex of the transmitting parent. Once an abnormal CAG repeat expansion in *ATN1* has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for DRPLA (dentatorubral-pallidoluysian atrophy) have been published.

Suggestive Findings

DRPLA **should be suspected** in a proband with the following clinical features by age, brain MRI findings, and family history.

Clinical features (by age)

- **Juvenile onset (before age 20 years).** Ataxia, myoclonus, seizures, progressive intellectual deterioration
- **Adult onset (after age 20 years).** Ataxia, choreoathetosis, dementia, psychiatric disturbance

Brain MRI findings. Cerebellar and brain stem atrophy; white matter lesions [Tsuji 2012, Sugiyama et al 2020]

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations) and Japanese familial origin. DRPLA is extremely rare outside of Japanese populations [Tsuji 2012]. Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of DRPLA **is established** in a proband with a heterozygous abnormal CAG repeat expansion in *ATN1* identified by molecular genetic testing (see Table 1).

Note: Pathogenic CAG repeat expansions in *ATN1* **cannot be reliably detected** by standard next-generation sequencing-based methods, including multigene panels or exome sequencing.

Repeat sizes

- **Normal.** 6 to 35 CAG repeats [Koide et al 1994, Nagafuchi et al 1994, Ikeuchi et al 1995a, Ikeuchi et al 1995c]
- **Intermediate.** 35 to 47 CAG repeats are incompletely penetrant and are usually associated with a milder clinical phenotype [Chaudhry et al 2021]. Intermediate alleles are unstable and can expand on transmission, resulting in full-penetrance alleles in the next generation; this is a very rare event. The unaffected Japanese population has a greater number of individuals with 20-35 CAG repeats than populations of European and African origin [Yanagisawa et al 1996, Takano et al 1998]. There is a report of a normal expanded allele with 42 CAG repeats in a family of Italian ancestry [Grimaldi et al 2019].
- **Pathogenic (full penetrance).** 48 to 93 CAG repeats [Shimojo et al 2001, Maruyama et al 2012]. For exceptions see Penetrance.

Molecular genetic testing has traditionally relied on targeted analysis to characterize the number of *ATN1* CAG repeats. However, genome sequencing-based tools for the detection of nucleotide repeat expansions have been developed [Ibañez et al 2022]. Such testing may be able to detect an expanded *ATN1* CAG repeat but may not be able to accurately determine the number of repeats, depending on the method and analytical tools used by the genetic testing laboratory.

Table 1. Molecular Genetic Testing Used in DRPLA

Gene [1]	Method [2, 3]	Proportion of Probands with a Pathogenic Variant Detectable by Method
ATN1	Targeted analysis for CAG expansions	100%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics, ***ATN1* technical considerations**, for specific methods to characterize the number of CAG repeats in *ATN1*.
3. Note: To date, standard sequence-based multigene panels and exome sequencing cannot reliably detect pathogenic CAG repeat expansions in this gene.

Clinical Characteristics

Clinical Description

DRPLA (dentatorubral-pallidoluysian atrophy) is a progressive neurologic disorder characterized by five cardinal features (irrespective of the age of onset): ataxia, cognitive decline, myoclonus, chorea, epilepsy, and psychiatric manifestations [Ikeuchi et al 1995b, Kanazawa 1998]. Clinical manifestations vary by age of onset, which is inversely related to *ATN1* CAG repeat size [Ikeuchi et al 1995b, Komure et al 1995].

Onset ranges from infancy to late adulthood (range: age 0-72 years; mean: age 31.5 years). Juvenile onset (before age 20 years) is characterized by myoclonus, epilepsy, and progressive intellectual deterioration, whereas adult onset (after age 20 years) is characterized by ataxia, choreoathetosis, and dementia or neuropsychiatric changes. Disease duration is on average eight years (range: 0-35 years) and age at death is on average 49 years (range: age 18-80 years) [Hasegawa et al 2010].

Juvenile Onset (Before Age 20 Years)

Juvenile-onset (also referred to as childhood- or early-onset) DRPLA is generally associated with ≥65 CAG repeats. Juvenile onset is typically characterized by developmental delay, progressive intellectual disability, myoclonus, and epilepsy, often referred to as a progressive myoclonic epilepsy (PME) phenotype [Kanazawa 1998, Hasegawa et al 2010, Maruyama et al 2012, Carroll et al 2018].

Developmental delay and intellectual disability are the most common initial manifestations, with a mean age of onset of 7.1 ± 4.8 (range: 2-18) years [Egawa et al 2008, Maruyama et al 2012]. Variable findings are developmental regression, attention-deficit/hyperactivity disorder, autism spectrum disorder, and microcephaly [Licht & Lynch 2002, Shahwan et al 2005].

Seizure types vary and are frequently resistant to anti-seizure medication [Koide et al 1994, Ikeuchi et al 1995b, Egawa et al 2008]. Clinical-electrographic focal-onset seizures with altered alertness are frequently seen, with higher prevalence when epilepsy onset is before age 10 years [Egawa et al 2008]. Seizure types may evolve over time. Partial seizures and brief generalized seizures (atypical absence and myoclonic seizures) may be seen earlier and generalized tonic-clonic seizures later in the disease course [Egawa et al 2008]. Common findings are photosensitivity with reflex seizures triggered by visual stimuli and EEG photoparoxysmal response to intermittent photic stimulation.

Ataxia may occur early in the disease course or develop later. Eventually, chorea and psychiatric manifestations may also develop [Hasegawa et al 2010, Maruyama et al 2012].

Adult Onset (After Age 20 Years)

Adult-onset (also referred to as late-onset) DRPLA is generally associated with <65 CAG repeats. In one series, the mean age of onset was 48 years [Hasegawa et al 2010]. The most prominent clinical features are ataxia and/or choreoathetosis, combined with personality changes with or without cognitive decline [Kanazawa 1998]. In some individuals, involuntary movements and dementia may mask the presence of ataxia.

Behavioral impairment is characterized by delusions, hallucinations, depressed mood, apathy, loss of inhibitory control, poor judgment, impulsivity, irritability, and aggression [Adachi et al 2001, Grimaldi et al 2019]. This clinical picture may cause psychiatric hospitalization and complicate the differential diagnosis, particularly in younger adults. Cognitive decline is characterized by deterioration of attention and executive functions, semantic fluency, and visuoconstructive abilities; memory is relatively preserved in all its components [Lindsay & Storey 2017, Grimaldi et al 2019].

Rarely, seizures may be present in individuals with disease onset between ages 20 and 40 years. Older individuals (especially those older than age 60 years in one series) may present with isolated ataxia and/or ataxia combined with dementia [Sugiyama et al 2018].

The severity and frequency of sleep disturbances in DRPLA are probably underestimated. Insomnia, excessive daytime sleepiness, and circadian rhythm disturbance can occur. In a case report by Kim et al [2018], a family with DRPLA presented with REM sleep behavior disorders (RBD) in the absence of more common sleep-related respiratory issues such as sleep apnea or hypopnea. In some members of this family, RBD appeared before the classic clinical manifestations of DRPLA.

Other clinical manifestations that may be present in adult-onset DRPLA irrespective of the actual age of onset include choreoathetosis, dystonia, myoclonus, oculomotor impairments, postural instability, corneal endothelial degeneration, and optic atrophy [Warner et al 1995, Destée et al 2000, Ito et al 2002, Hatano et al 2003, Wardle et al 2008, Vale et al 2010, Silver et al 2015, Grimaldi et al 2019].

Dysphagia is frequently seen in the late stages of disease [Hasegawa et al 2010].

Other clinical manifestations rarely reported include parkinsonism, tremors, hyperreflexia, and posterior column sensory loss [Shimojo et al 2001, Licht & Lynch 2002, Rajput 2011].

All Ages

Neuroimaging. Typical MRI findings include atrophic changes in the cerebellum and brain stem, in particular the pontine tegmentum. Quantitative analyses reveal that both the age at MRI and the size of the expanded CAG repeat correlate with the atrophic changes.

Cerebellar white matter lesions are also described in individuals with late adult-onset and elderly-onset disease, often in the paravermal areas (medial part of the cerebellar hemispheres adjacent to the vermis) and present as high-intensity signals in MRI FLAIR images. Although paravermal lesions are considered typical of DRPLA and lacking in other autosomal dominant spinocerebellar ataxias, they are not specific to DRPLA and can be present in adult-onset neuronal intranuclear inclusion disease and fragile X-associated tremor/ataxia syndrome [Sugiyama et al 2018, Sugiyama et al 2020].

Diffuse high-intensity areas deep in the white matter are often observed on T_2-weighted MRI in individuals with adult-onset DRPLA of long duration [Koide et al 1997].

Using ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET), bistriatal glucose hypometabolism was reported in two affected individuals with juvenile-onset DRPLA; this was not present in individuals with adult onset [Sone et al 2016].

Neuropathology. The major neuropathologic changes are combined degeneration of the dentatorubral and pallidoluysian systems. Also described are cerebral white matter damage, including diffuse myelin pallor, axonal preservation, and reactive astrogliosis with only mild atherosclerotic changes [Muñoz et al 2004].

Histologically, as in other polyglutamine diseases, neurons show intranuclear inclusions [Mori et al 2012a, Mori et al 2012b].

Genotype-Phenotype Correlations

Heterozygotes. In general, an inverse correlation exists between the age at onset and the size of the expanded *ATN1* CAG repeat [Koide et al 1994, Ikeuchi et al 1995b] (see Table 2).

Note: *ATN1* CAG repeat ranges overlap and the distinctions are not clearly defined.

Table 2. Correlation between Age at Onset and Size of *ATN1* Repeat

Age at Onset	*ATN1* CAG Repeat Range
<21 years	63-79
21-40 years	61-69
>40 years	48-67

Adapted from Koide et al [1994], Ikeuchi et al [1995b]

Because juvenile onset (before age 20 years) is associated with the progressive myoclonus epilepsy (PME) phenotype and adult onset (after age 20 years) with the non-PME phenotype, the clinical presentation is strongly correlated with the size of expanded CAG repeats. The frequency of signs and symptoms in affected individuals with <65 CAG repeats and those with ≥65 CAG repeats were summarized by Hasegawa et al [2010].

Severe infantile onset with an extreme *ATN1* CAG expansion of 90-93 CAG repeats (c.1462CAG[90_93]) has been reported [Shimojo et al 2001].

Homozygotes

- An individual with relatively small biallelic expanded *ATN1* CAG repeat expansions had symptom onset at age 14 years, indicating a possible dosage effect [Sato et al 1995].
- An individual of Japanese ancestry homozygous for a 57-CAG repeat expansion was born to consanguineous parents. Early onset (around age 18 years) and more severe manifestations were observed [Ikeuchi et al 1995b].

Penetrance

Pathogenic (full-penetrance) CAG repeats (i.e., 48-93 CAG repeats) are fully penetrant, except for one individual with 51 CAG repeats who was asymptomatic at age 81 years [Hattori et al 1999].

Anticipation

The marked expansion of the *ATN1* CAG repeat on transmission to offspring results in onset of manifestations 26 to 29 years earlier than affected fathers and 14 to 15 years earlier than affected mothers [Koide et al 1994, Nagafuchi et al 1994, Ikeuchi et al 1995a, Ikeuchi et al 1995b, Ikeuchi et al 1995c, Hattori et al 1999, Vinton et al 2005].

Nomenclature

DRPLA may also be referred to as:

- Naito-Oyanagi disease [Kanazawa 1998];
- Haw River syndrome [Burke et al 1994a, Burke et al 1994b];
- *ATN1*-related dentatorubral-pallidoluysian atrophy (based on the dyadic naming approach proposed by Biesecker et al [2021] to delineate mendelian genetic disorders).

Prevalence

DRPLA is more prevalent in populations of Japanese ancestry, where it affects 0.2-0.7 in 100,000 people [Takano et al 1998, Tsuji et al 2008]. The Japanese population has a greater number of individuals with 20-35 CAG repeats than populations of European origin [Takano et al 1998]. A nationwide epidemiologic study showed that DRPLA is the third most common autosomal dominant ataxia, accounting for 9.7% of cases in Japan [Tsuji et al 2008]. In another Japanese study, DRPLA was the most common cause of childhood-onset cerebellar ataxia [Ono et al 2019].

DRPLA is thought to occur at much lower rates in non-Japanese populations; however, it has also been reported in North America, South America, Europe, and Australia (for a summary of all cases reported see Chaudhry et al [2021]). The frequency of DRPLA has been estimated in cohorts with mostly cerebellar ataxia of unknown cause, typically with a pattern of autosomal dominant inheritance, in the following countries/regions:

- Brazil: 0.2%-0.92% [Braga-Neto et al 2017, Pinto et al 2021]
- China: 1% [Lee et al 2001]
- France: 0.25% [Le Ber et al 2003]
- Italy: 1% [Filla et al 2000]. A study of the largest northern European DRPLA pedigree, originating in Italy in the 1500s with a founder couple, demonstrated that DRPLA can be observed over time in certain geographic areas [Grimaldi et al 2019], suggesting that prevalence could be higher than expected in non-Asian populations.
- Korea: 3.4% [Jin et al 1999]
- Portugal: 2%-11.2% [Silveira et al 2002, Vale et al 2010]. In the Portuguese population, the prevalence of DRPLA was estimated at 0.33 in 100,000 people, ranking as the second most frequent autosomal dominant ataxia [Coutinho et al 2013]. The prevalence in Portugal is almost comparable to Japan, and is higher than that described for the rest of Europe. The Portuguese families with DRPLA share the same haplotype as in Japan [Martins et al 2003], which could explain the higher prevalence in this country.
- Singapore: 3.4% [Zhao et al 2002]
- South Wales: 11.4% [Wardle et al 2008]. In South Wales the theory of a founder effect only accounted for some but not all of the high prevalence of DRPLA, as the Japanese haplotype was only detected in three out of four families [Wardle et al 2008]. These findings suggested that DRPLA prevalence can also be influenced by spontaneous repeat expansions in families with high-normal repeats.
- Spain: 1.4%-3.3% [Pujana et al 1999, Infante et al 2005]
- Venezuela: 3.1% [Paradisi et al 2016]

Genetically Related (Allelic) Disorders

***ATN1*-related neurodevelopmental disorder** (*ATN1*-NDD) is characterized by developmental delay / intellectual disability. Other neurologic findings can include infantile hypotonia, brain malformations, epilepsy, cortical visual impairment, and hearing loss. Distinctive facial features and hand and foot differences are common. *ATN1*-NDD is caused by a heterozygous pathogenic variant in a 16-amino-acid sequence of exon 7 in *ATN1*. All probands reported to date with *ATN1*-NDD whose parents have undergone molecular genetic testing have the condition as a result of a *de novo ATN1* pathogenic variant.

Pallister-Killian syndrome (PKS) (OMIM 601803). Tissue-limited mosaicism of tetrasomy of the short arm of chromosome 12, including *ATN1*, is associated with PKS. Of note, the identification of mosaic tetrasomy of 12p

requires chromosome analysis of specific tissues; thus, routine molecular genetic testing of a blood sample would not be expected to suggest a diagnosis of PKS.

Differential Diagnosis

Adult onset. For individuals with adult-onset DRPLA (dentatorubral-pallidoluysian atrophy) who exhibit ataxia, dementia, or choreoathetosis (the non-PME phenotype), the differential diagnosis includes the autosomal dominant disorders summarized in Table 3.

Table 3. Selected Genes in the Differential Diagnosis of Adult-Onset DRPLA

Gene(s)	Disorder	Comment
HTT	Huntington disease (HD)	The presence of ataxia is important for differentiating DRPLA from HD. Some persons w/the non-PME phenotype of DRPLA may initially be diagnosed as having HD, as the main clinical features in these persons are involuntary movements & dementia, symptoms that often mask the presence of ataxia. The history of ataxia as an early symptom as well as atrophy of the cerebellum and brain stem (particularly pontine tegmentum) on imaging study is important in the differential diagnosis. Atrophy of the caudate nucleus favors the diagnosis of HD. It is frequently necessary to do molecular genetic testing for Huntington disease, Huntington disease-like phenotypes, and DRPLA in persons w/unexplained progressive dementia & involuntary movements.
JPH3	Huntington disease-like 2	
PRNP	Genetic prion disease	
~40 genes incl: *ATXN1* *ATXN2* *ATXN3* *ATXN7* *ATXN8* *ATXN10* *CACNA1A* *TBP*	Autosomal dominant cerebellar ataxias (See Hereditary Ataxia Overview.)	Persons w/DRPLA who have mildly expanded CAG repeats (c.1462CAG[49_55]) tend to exhibit, particularly in early stages, pure cerebellar symptoms such as ataxia w/o dementia, choreoathetosis, or character changes, making the clinical diagnosis of DRPLA difficult. Such persons need to be distinguished from those w/ataxia of other etiologies.

Juvenile onset. For those with early-onset DRPLA (age <20 years) who exhibit progressive intellectual deterioration, myoclonus, and epilepsy (the PME phenotype), the differential diagnosis includes the disorders summarized in Table 4 (see also Malek et al [2015]).

Table 4. Selected Genes in the Differential Diagnosis of Early-Onset DRPLA

Gene(s)	Disorder	MOI
CLN3 *CLN5* *CLN6* *CLN8* *CTSD* *CTSF* *DNAJC5* *GRN* *KCTD7* *MFSD8* *PPT1* *TPP1*	Neuronal ceroid lipofuscinosis (OMIM PS256730)	AR (AD) [1]

Table 4. continued from previous page.

Gene(s)	Disorder	MOI
CNTN2 *MARCHF6* *RAPGEF2* *SAMD12* *STARD7* *TNRC6A* *YEATS2*	Benign adult familial myoclonus epilepsy (OMIM PS601068)	AD
CSTB	EPM1 (Unverricht-Lundborg disease)	AR
EPM2A *NHLRC1*	Progressive myoclonus epilepsy, Lafora type	AR
FTL	Neuroferritinopathy	AD
GBA1 (*GBA*)	Gaucher disease type 3 (primary neurologic disease)	AR
GOSR2	EPM6 (OMIM 614018)	AR
HEXA	Late-onset Tay-Sachs disease (See *HEXA* Disorders.)	AR
MT-TF *MT-TH* *MT-TI* *MT-TK* *MT-TL1* *MT-TP* *MT-TS1* *MT-TS2*	MERRF (myoclonus epilepsy associated with ragged red fibers)	Mat
NEU1	Neuraminidase deficiency (OMIM 256550)	AR
PANK2	Pantothenate kinase-associated neurodegeneration	AR
PLA2G6	Infantile neuroaxonal dystrophy (See *PLA2G6*-Associated Neurodegeneration.)	AR
PRICKLE1	Progressive myoclonic epilepsy with ataxia (EPM1B) (See *PRICKLE1*-Related Disorders.)	AR
SCARB2	*SCARB2*-related action myoclonus – renal failure syndrome (EPM4)	AR

AD = autosomal dominant; AR = autosomal recessive; EPM = epilepsy, progressive myoclonic; Mat = maternal; MOI = mode of inheritance

1. Neuronal ceroid lipofuscinosis (NCL) is inherited in an autosomal recessive manner with the exception of *DNAJC5*-related NCL, which is inherited in an autosomal dominant manner.

Management

No clinical practice guidelines for DRPLA (dentatorubral-pallidoluysian atrophy) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with DRPLA, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. DRPLA: Recommended Evaluations Following Initial Diagnosis by Age of Onset

System/Concern	Evaluation	Comment
Juvenile onset (before age 20 years)		

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Neurologist assessment for myoclonus incl at rest, w/action, & in response to stimuli	Use standardized UMRS.
	Seizure: type & frequency	Obtain baseline EEG before initiation of ASM (when EEG is most characteristic).
	Neurologist assessment for cerebellar motor dysfunction (gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades, & smooth pursuit)	Use standardized scale to establish baseline for ataxia (SARA, ICARS, or BARS). [1]
	Neurologist assessment for chorea	Chorea is rare in juvenile-onset DPRLA.
Intellectual disability	Neuropsychologist assessment	Cognitive eval to establish baseline
Development / School performance	Developmental assessment	• To incl motor, adaptive, & cognitive • Eval for IEP
Psychiatric	Psychiatrist assessment for ADHD, ASD, etc.	Evaluate as needed for therapy.
Musculoskeletal/ADL	By physical medicine & rehab / OT & PT	To assess gross motor & fine motor skills, gait, ambulation, need for adaptive devices, & need for ongoing PT/OT
Sleep disturbances	Sleep study	To assess for obstructive sleep apnea
Adult onset (after age 20 years)		
Neurologic	Neurologist assessment for cerebellar motor dysfunction (gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades, & smooth pursuit)	Use standardized scale to establish baseline for ataxia (SARA, ICARS, or BARS). [1]
	Neurologist assessment for extrapyramidal features (e.g., parkinsonism, choreoathetosis, dystonia, etc.), pyramidal manifestations (e.g., spasticity, Babinski sign, etc.)	Use standardized scales to establish baseline (e.g. MDS-UPDRS for parkinsonism). [2]
	Seizures	• Rare after age 40 years • EEG
Cognitive/ Psychiatric	Assess for cognitive dysfunction assoc w/ cerebellar cognitive affective syndrome (executive function, language processing, visuospatial/visuoconstructional skills, emotion regulation), behavioral impairment (e.g., loss of inhibitory control, hallucinations, etc.), depressed mood	• Refer to psychiatrist, psychologist, &/or neuropsychologist as needed. • Use neuropsychological tests to establish baseline for cognitive decline. • Consider that behavioral impairment & affective disturbances are often reported by caregiver.
Sleep disturbances	Sleep study	Assessment for insomnia, REM sleep behavior disorders, etc.
Speech	For those w/dysarthria: eval by SLP	Consider need for alternative means of communication.
Vision	Eye exam	To assess for corneal endothelial degeneration & optic atrophy
	Assess need for low vision services.	

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Feeding	For persons w/frequent choking or severe dysphagia, assess nutritional status & aspiration risk.	Consider involving gastroenterology / nutrition / feeding team, incl formal swallowing eval.
All ages of onset		
Genetic counseling	By genetics professionals [3]	To inform affected persons & their families re nature, MOI, & implications of DRPLA to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources; • Social work involvement for parental support for children; • Home nursing referral.	

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; ASM = anti-seizure medication; BARS = Brief Ataxia Rating Scale; ICARS = International Cooperative Ataxia Rating Scale; IEP = individualized education program; MDS-UPDRS = Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MOI = mode of inheritance; SARA = Scale for the Assessment and Rating of Ataxia; SLP = speech-language pathologist; UMRS = Unified Myoclonus Rating Scale

1. Bürk & Sival [2018]

2. Goetz et al [2008]

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

Treatment of Manifestations

There is no cure for DRPLA.

Few publications regarding symptomatic treatment for DRPLA are available in the literature. Thus, many manifestations of DRPLA are treated in a standard way in clinical practice.

The supportive care for individuals with juvenile-onset (before age 20 years) DRPLA is summarized in Table 6 and for individuals with adult-onset (after age 20 years) DRPLA in Table 7.

Table 6. Juvenile-Onset DRPLA: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Myoclonus	Pharmacologic treatment	• Carbamazepine, phenytoin [1] • Levetiracetam [2] • All standard drugs
	Other	Avoid extreme stimuli (lights, noises, stress).
Epilepsy	ASM	• Generalized seizures: sodium valproate, perampanel, zonisamide [1] • Standard medications

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Cerebellar ataxia	PT & OT	• PT (balance exercises, gait training, muscle strengthening) to maintain mobility & function [3] • OT to optimize ADL (incl use of adaptive devices, e.g., weighted eating utensils & dressing hooks) • Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, motorized chairs). • Inpatient rehab w/OT/PT may improve ataxia & functional abilities in affected persons w/degenerative ataxias. [4] • Weight control to avoid obesity • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats) & improve mobility (e.g., ramps to accommodate motorized chairs) • Although neither exercise nor PT slows progression of incoordination or muscle weakness, affected persons should maintain activity.
ADL	PT & OT	• Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, motorized chairs). • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats) & improve mobility (e.g., ramps to accommodate motorized chairs)
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Dysarthria	Speech & language therapy	Consider alternative communication methods as needed (e.g., writing pads & digital devices).
Dysphagia	Feeding therapy programs to improve nutrition & dysphagia & reduce aspiration risk	• Video esophagram may help define best food consistency. • Education re strategies to mitigate aspiration • PEG tube in advanced cases
Psychiatric comorbidity	Pharmacologic & psychological therapy	Use psychotropic medications in standard manner.
Weight	Nutrition assessment	• Consider nutritional & vitamin supplementation to meet dietary needs. • Avoid obesity, which can exacerbate difficulties w/ ambulation & mobility.
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Ongoing assessment of need for palliative care involvement &/or home nursing

ADL = activities of daily living; ASM = anti-seizure medication; OT = occupational therapy; PEG = percutaneous endoscopic gastrostomy; PT = physical therapy

1. Carroll et al [2018]

2. Kobayashi et al [2012], Hamada et al [2014]

3. Shahwan et al [2005]

4. Ilg et al [2009], Miyai et al [2012], van de Warrenburg et al [2014], Zesiewicz et al [2018]

Table 7. Adult-Onset DRPLA: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Cerebellar ataxia	• PT & OT • Self-directed exercise	• PT (balance exercises, gait training, muscle strengthening) to maintain mobility & function [1] • OT to optimize ADL (incl use of adaptive devices, e.g., weighted eating utensils & dressing hooks) • Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, motorized chairs) • Inpatient rehab w/OT/PT may improve ataxia & functional abilities in affected persons w/degenerative ataxias. [2, 3] • Weight control to avoid obesity • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats) & improve mobility (e.g., ramps to accommodate motorized chairs) • Although neither exercise nor PT slows progression of incoordination or muscle weakness, affected persons should maintain activity.
	Pharmacologic treatment	Riluzole [2] may be beneficial for ataxia
Choreoathetoid & dystonic movements	Pharmacologic treatment	Tetrabenazine, risperidone, bromazepam, gabapentin [4]
Dystonia	Pharmacologic treatment	Use standard medications
Dysarthria	Therapy by SLP	Consider alternative communication methods as needed (e.g., writing pads & digital devices).
Dysphagia	Feeding therapy programs to improve nutrition & dysphagia & reduce aspiration risk	• Video esophagram may help define best food consistency. • Education re strategies to mitigate aspiration
Weight	Nutrition assessment	• Consider nutritional & vitamin supplementation to meet dietary needs. • Avoid obesity, which can exacerbate difficulties w/ ambulation & mobility.
Cognitive/ Psychiatric	Pharmacologic treatment	• Use standard treatments for psychiatric manifestations. • Quetiapine may be beneficial for psychosis. [5]
	Psychotherapy / neuropsychological rehab	Consider cognitive & behavioral therapy. [6]
Family/Community	• Ensure appropriate social work involvement to connect families or care providers w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Ongoing assessment of need for palliative care involvement &/or home nursing

ADL = activities of daily living; OT = occupational therapy; PT = physical therapy; SLP = speech-language pathologist

1. Martineau et al [2014]
2. Ilg et al [2009], Miyai et al [2012], Zesiewicz et al [2018]
3. van de Warrenburg et al [2014]
4. Carroll et al [2018]
5. Narita & Sumiyoshi [2018]
6. Ruffieux et al [2017]

Developmental Delay / Intellectual Disability Management Issues

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

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

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

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 8 (for individuals with juvenile onset) and Table 9 (for individuals with adult onset) are recommended.

Table 8. Juvenile-Onset DRPLA: Recommended Surveillance

System/Concern	Evaluation	Frequency
Myoclonus	Severity of myoclonus using UMRS	Per treating neurologist based on symptom progression
Epilepsy	Response of seizure type & frequency to therapy	Per treating neurologist
Cerebellar involvement	Clinical eval	
Dysarthria	Assessment of need for alternative communication method or speech therapy	Per treating SLP
Dysphagia	Assess aspiration risk & feeding methods.	Per treating feeding specialists

Table 8. continued from previous page.

System/Concern	Evaluation	Frequency
Weight / Nutritional status	• Monitor BMI • Consult nutritionist • High-calorie supplementation	Annually; more often if disease progresses
ADL	By treating PT & OT to evaluate rehab plan	1-2x per yr
Development	Monitor developmental progress & educational needs.	At each visit
Cognitive/ Psychiatric	Evaluate mood, signs of psychosis, cognitive complaints to identify need for pharmacologic & psychotherapeutic interventions.	Per treating mental health specialist based on response to therapy & symptom progression
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).	Annually

ADL = activities of daily living; OT = occupational therapist; PT = physical therapist; SLP = speech-language pathologist; UMRS = Unified Myoclonus Rating Scale

Table 9. Adult-Onset DRPLA: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	Neurologic assessment for ataxia progression w/standardized scale (SARA, ICARS, or BARS) [1] & signs of movement disorder	Annually; more often for acute exacerbation
ADL/Musculoskeletal	Physiatry, OT/PT assessment of mobility, self-help skills	
Dysarthria	By SLP re need for alternative communication method or speech therapy	Per symptom progression
Dysphagia	Assess aspiration risk & feeding methods.	
Weight / Nutritional status	• Monitor BMI. • Consult nutritionist re need for high-calorie supplementation.	Annually; more often if the disease progresses
Cognitive/ Psychiatric	Evaluate mood, signs of psychosis, & cognitive function to identify need for pharmacologic &/or psychotherapeutic interventions.	Per symptom progression & development of psychiatric symptoms
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).	Annually

BARS = Brief Ataxia Rating Scale; ICARS = International Co-operative Ataxia Rating Scale; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia; SLP = speech-language pathologist

1. Bürk & Sival [2018]

Agents/Circumstances to Avoid

General anesthesia can increase the risk of intra- and postoperative seizures [Takayama et al 2002].

Evaluation of Relatives at Risk

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

Pregnancy Management

In general, women with epilepsy from any cause are at greater risk for mortality during pregnancy than pregnant women without epilepsy; use of anti-seizure medications (ASMs) during pregnancy reduces this risk. However, exposure to ASMs may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and

the stage of pregnancy at which the medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from medication exposure is often less than that associated with exposure to an untreated maternal seizure disorder. Therefore, use of ASMs during pregnancy is typically recommended. Discussion of the risks and benefits of using a given ASM during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible [Sarma et al 2016].

The medications carbamazepine, phenytoin, and levetiracetam, discussed in Treatment of Manifestations, Table 6, are considered ASMs, even when they are used for an indication other than seizures (such as myoclonus). Care must be taken when weighing the fetal risk of adverse effects versus the benefit to the pregnant woman when one of these medications is being taken for an indication other than for seizure control.

There is little to no human data on potential adverse fetal effects when piracetam, brivaracetam, or perampanel is taken during pregnancy.

Limited data about the use of N-acetylcysteine during human pregnancy has been reassuring, without an appreciable increased risk of fetal malformations.

The use of riluzole during pregnancy has not been well studied in humans. One woman took riluzole throughout her pregnancy and delivered a healthy term infant, whereas another woman delivered an infant with growth restriction [Kawamichi et al 2010, Scalco et al 2012].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

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

Mode of Inheritance

DRPLA (dentatorubral-pallidoluysian atrophy) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with DRPLA have an affected parent.
- In some families, an asymptomatic father of an affected individual has a mildly expanded CAG repeat and paternal transmission results in intergenerational increase in the size of the expanded CAG repeats. Examples include:
  - A proband with no family history of DRPLA whose father had 59 CAG repeats and was asymptomatic at age 65 years [Ikeuchi et al 1995b];
  - A proband with no family history of DRPLA whose father had 51 CAG repeats and was asymptomatic at 81 years [Hattori et al 1999].

- If neither of the parents of the proband is known to have DRPLA, recommendations for the evaluation of parents include physical examination and consideration of targeted analysis for an *ATN1* CAG expansion.
- The family history of some individuals diagnosed with DRPLA may also appear to be negative because of failure to recognize the disorder in family members or early death of the parent before the onset of symptoms. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for an expanded *ATN1* CAG repeat.

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

- If a parent of the proband has an abnormal *ATN1* CAG expansion, the risk to the sibs of inheriting an expansion is 50%. The clinical features expected in the sib depend on the size of the repeat transmitted to the sib, which in turn depends on the size of the parent's repeat and the sex of the transmitting parent.
- The marked expansion of the *ATN1* CAG repeat on transmission to offspring results in onset of manifestations 26 to 29 years earlier than affected fathers and 14 to 15 years earlier than affected mothers [Koide et al 1994, Nagafuchi et al 1994, Ikeuchi et al 1995a, Ikeuchi et al 1995b, Ikeuchi et al 1995c, Hattori et al 1999, Vinton et al 2005].
- In general, an inverse correlation exists between the age at onset and the size of the expanded *ATN1* CAG repeat (see Genotype-Phenotype Correlations).

Offspring of a proband

- The risk to the children of an affected individual of inheriting an expanded CAG repeat is 50%. The size of the repeat transmitted to the offspring depends on the size of the parent's repeat and the sex of the transmitting parent.
- DRPLA exhibits significant anticipation, particularly when transmitted paternally (see Anticipation).

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected and/or is known to have an *ATN1* CAG expansion, the parent's family members are at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and availability of prenatal/preimplantation genetic testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made 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.

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

- Testing of at-risk adults for DRPLA in the presence of nonspecific or equivocal symptoms is predictive testing, not diagnostic testing.
- Predictive testing for at-risk relatives is possible once the *ATN1* CAG expansion has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

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

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

It is appropriate to consider testing symptomatic individuals regardless of age in a family with an established diagnosis of DRPLA.

Prenatal Testing and Preimplantation Genetic Testing

Once an abnormal CAG repeat expansion in *ATN1* has been identified in an affected family member, prenatal and preimplantation genetic testing for DRPLA are possible.

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

Resources

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

- **CureDRPLA**
  Email: info@cureDRPLA.org
  CureDRPLA
- **Ataxia UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  ataxia.org.uk
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: ageorgousis@ataxia.org.uk
  euroataxia.org
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Email: naf@ataxia.org
  ataxia.org
- **Parent to Parent**
  Phone: 484-272-7368
  www.p2pusa.org
- **Spanish Ataxia Federation (FEDAES)**

Spain
Phone: 601 037 982
Email: info@fedaes.org
fedaes.org

- **CoRDS Registry**
  Sanford Research
  Phone: 605-312-6300
  CoRDS Registry
- **CureDRPLA Global Patient Registry**
  Email: drplaregistry@ataxia.org.uk
  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. DRPLA: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ATN1	12p13.31	Atrophin-1	ATN1 database	ATN1	ATN1

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 DRPLA (View All in OMIM)

125370	DENTATORUBRAL-PALLIDOLUYSIAN ATROPHY; DRPLA
607462	ATROPHIN 1; ATN1

Molecular Pathogenesis

Expression of truncated proteins encoded by *ATN1* with expanded polyglutamine stretches result in frequent formation of peri- and intranuclear aggregates and apoptotic cell death, suggesting that processed expanded proteins are more toxic to cells than full-length proteins [Igarashi et al 1998, Shimohata et al 2002].

As in other polyglutamine disorders, the disease-causing CAG expansion in *ATN1* lead to the identification of neuronal intranuclear protein aggregates, or intranuclear inclusions (NIIs), in the brains of affected individuals [Hayashi et al 1998, Igarashi et al 1998, Mori et al 2012a, Mori et al 2012b]. Accumulation of abnormal atrophin-1, the protein encoded by *ATN1*, in the neuronal nuclei is the predominant neuropathologic finding. Of note, NIIs are observed in central nervous system regions far beyond the systems previously reported to be affected on conventional neuropathologic findings. It has been suggested that NIIs are responsible for clinical features such as dementia and epilepsy [Yamada et al 2000, Yamada et al 2001, Yamada et al 2002].

Mechanism of disease causation. Gain of function

***ATN1* technical considerations**

- Molecular genetic testing approaches have until recently involved **targeted testing**. Testing is typically performed by PCR amplification of the *ATN1* trinucleotide repeat region followed by gel or capillary electrophoresis. Note: In CAG repeat disorders in general, highly expanded alleles (usually >100 CAG repeats) may not be detectable by the PCR-based assay, and additional testing (e.g., Southern blot analysis

or triplet repeat-primed [TP] PCR [Warner et al 1996]) is indicated to detect a highly expanded repeat in individuals who are apparently homozygotes by PCR analysis.
- Genome sequencing-based tools have been developed for the detection of triplet repeat expansions [Ibañez et al 2022].
- Variants detectable by sequencing have not been associated with DRPLA, but are associated with *ATN1*-related neurodevelopmental disorder.

Table 10. *ATN1* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Repeat Range
NM_001007026.1 NP_001007027.1	c.1462CAG[6_35]	Normal
	c.1462CAG[35_47]	Intermediate
	c.1462CAG[48_93]	Pathogenic (full penetrance)

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

Chapter Notes

Author Notes

Silvia Prades, PhD, is actively involved in managing research projects regarding individuals with DRPLA and peer support groups. She would be happy to communicate with persons who have any questions regarding diagnosis of DRPLA or other considerations.

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