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DRPLA

Synonym: Dentatorubral-Pallidoluysian Atrophy

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Summary

Clinical characteristics

Dentatorubral-pallidoluysian atrophy (DRPLA) is a progressive disorder of ataxia, myoclonus, epilepsy, and progressive intellectual deterioration in children and ataxia, choreoathetosis, and dementia or character changes in adults. Onset ranges from before age one year to age 72 years; mean age of onset is 31.5 years. The clinical presentation varies depending on the age of onset. The cardinal features in adults are ataxia, choreoathetosis, and dementia. Cardinal features in children are progressive intellectual deterioration, behavioral changes, myoclonus, and epilepsy.

Diagnosis/testing

The diagnosis of DRPLA is established in a proband with suggestive clinical findings and a family history of DRPLA or by the identification of a heterozygous pathogenic CAG trinucleotide expansion in *ATN1* by molecular genetic testing. The CAG repeat length in individuals with DRPLA ranges from 48 to 93.

Management

Treatment of manifestations: Standard anti-seizure medication 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.

Pregnancy management. The use of anti-seizure medication during pregnancy may have an effect on the fetus. Discussion of the risks and benefits of using a given anti-seizure medication during pregnancy should ideally take place prior to conception; transition to a lower-risk medication may be possible. The use of riluzole during pregnancy has not been well studied in humans.

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Genetic counseling

DRPLA is inherited in an autosomal dominant manner. The risk to the offspring 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. Prenatal testing for a pregnancy at increased risk is possible using molecular genetic testing if the diagnosis in the family has been confirmed.

Diagnosis

No formal clinical diagnostic criteria are available for DRPLA.

Suggestive Findings

Dentatorubral-pallidoluysian atrophy (DRPLA) **should be suspected** in individuals with the following clinical features (by age), brain MRI findings, and family history:

- **Clinical features (by age)**
  - **Age <20 years.** Ataxia, myoclonus, seizures, progressive intellectual deterioration
  - **Age >20 years.** Ataxia, choreoathetosis, dementia, psychiatric disturbance
- **Brain MRI findings.** Cerebellar and brain stem atrophy [Tsuji 2012]
- **Family history.** Consistent with autosomal dominant inheritance and Asiatic (mainly Japanese) familial origin

Note: (1) Absence of a family history of DRPLA does not preclude the diagnosis. (2) DRPLA is extremely rare outside of Asiatic populations [Tsuji 2012].

Establishing the Diagnosis

The diagnosis of DRPLA **is established** in a proband with suggestive clinical findings and a family history of DRPLA **or** by the identification of a heterozygous pathogenic CAG trinucleotide expansion in *ATN1* by molecular genetic testing (see Table 1).

Note: Comprehensive testing strategies for the diagnosis of ataxic disorders can be found in van de Warrenburg et al [2014] and the Hereditary Ataxia Overview.

Allele sizes

- **Normal alleles.** 6-35 CAG repeats
- **Mutable normal alleles.** Mutable normal alleles are not associated with symptoms but are unstable and can expand on transmission resulting in occurrence of symptoms in the next generation; this is a very rare event. The normal Japanese population has a greater number of individuals with 20-35 CAG repeats than are found in populations of European origin [Takano et al 1998].
- **Full-penetrance alleles.** ≥48 CAG repeats. The largest full-penetrance allele reported to date is 93 [Shimojo et al 2001, Maruyama et al 2012].

Molecular testing approaches typically involve **targeted testing**. Testing is typically performed by PCR amplification of the *ATN1* trinucleotide repeat region followed by gel or capillary electrophoresis.

Note: (1) 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 allele in individuals who are apparently homozygotes by PCR analysis. (2) Variants detectable by sequencing analysis have not been associated with DRPLA.

Table 1. Molecular Genetic Testing Used in DRPLA

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ATN1	Targeted analysis for pathogenic variants	100%

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.

Clinical Characteristics

Clinical Description

Dentatorubral-pallidoluysian atrophy (DRPLA) is a progressive disorder of ataxia, myoclonus, epilepsy, and progressive intellectual deterioration in children and ataxia, choreoathetosis, and dementia or character changes in adults. The onset of DRPLA ranges from infancy to late adulthood (range: 0-72 years; mean: 31.5 years) [Hasegawa et al 2010]. Disease duration is on average eight years (range 0-35 years) and age at death is on average 49 years (range 18-80 years) [Hasegawa et al 2010]. The clinical presentation varies depending on the age of onset. The cardinal features in children are ataxia, intellectual disability, behavioral changes, myoclonus, and epilepsy; cardinal features in adults are ataxia, choreoathetosis, and dementia [Tsuji 2012].

Studies have shown that ataxia and cognitive impairment are cardinal features irrespective of the age of onset [Ikeuchi et al 1995b].

Individuals with onset before age 20 years usually have a progressive myoclonus epilepsy (PME) phenotype characterized by myoclonus, seizures, ataxia, and progressive intellectual deterioration [Naito & Oyanagi 1982, Ikeuchi et al 1995b, Tsuji 2012]. Various forms of generalized seizures (including tonic, atonic, clonic, or tonic-clonic seizures) are also observed [Tsuji 2012].

Seizures are less frequent in individuals with onset between ages 20 and 40 years. Seizures are rare in individuals with onset after age 40 years and a CAG repeat size lower than 65 [Hasegawa et al 2010, Tsuji 2012].

Individuals with onset of DRPLA after age 20 years tend to develop cerebellar ataxia, choreoathetosis, dementia, and psychiatric disturbances (non-PME phenotype). In some individuals, involuntary movements and dementia mask the presence of ataxia. Psychosis may sometimes be a presenting feature [Adachi et al 2001].

Cervical dystonia was the presenting feature in one family [Hatano et al 2003].

Neuroimaging. Atrophic changes in the cerebellum and brain stem, in particular the pontine tegmentum, are the typical MRI findings of DRPLA. Quantitative analyses revealed that both the age at MRI and the size of the expanded CAG repeat correlate with the atrophic changes.

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 (18F-FDG-PET), bistriatal glucose hypometabolism was reported in two affected individuals with preadolescent-onset disease; this was not present in individuals with later-onset disease [Sone et al 2016].

Neuropathology. The major neuropathologic changes are relatively simple and consist of combined degeneration of the dentatorubral and pallidoluysian systems. Cerebral white matter damage, including diffuse myelin pallor, axonal preservation, and reactive astrogliosis with only mild atherosclerotic changes, has been described at autopsy [Muñoz et al 2004]. Histologically, as in other polyglutamine diseases, neurons show intranuclear inclusions [Mori et al 2012a, Mori et al 2012b].

See Molecular Pathogenesis for further information on the pathogenesis of DRPLA.

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 Size	
	Range	Median
<21 years	63-79	68
21-40 years	61-69	64
>40 years	48-67	63

Because onset before age 20 years is associated with the progressive myoclonus epilepsy (PME) phenotype and an older age of onset 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 fewer than 65 CAG repeats and those with 65 or more CAG repeats are summarized in Hasegawa et al [2010].

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

Homozygotes. A single individual who had relatively small biallelic expanded *ATN1* CAG repeat alleles is reported to have had symptom onset at 14 years, indicating a possible dosage effect [Sato et al 1995].

Penetrance

Expanded alleles are fully penetrant except for one individual with a mildly expanded number of CAG repeats (51 repeats) who was asmptomatic at age 81 years [Hattori et al 1999].

Anticipation

The marked expansion of the CAG repeat during transmission of pathogenic *ATN1* alleles from parent to child results in prominent anticipation. Affected offspring typically have symptoms 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, after the individuals who first observed the age-dependent onset of symptoms and the robust heritability of the condition [Kanazawa 1998]. DRPLA in a large African American family in North Carolina was referred to as Haw River syndrome [Burke et al 1994a, Burke et al 1994b].

Prevalence

The prevalence of DRPLA in the Japanese population is estimated at 0.48:100,000 based on the nationwide study [Tsuji et al 2008]. Analysis of the distribution of normal *ATN1* alleles by size has demonstrated that CAG repeats larger than 17 repeats are significantly more frequent in the Japanese population than in populations of European origin, which is in accordance with the observation that DRPLA is relatively more common among the Japanese than other ethnic populations [Takano et al 1998].

Although DRPLA has been reported to occur predominantly in the Japanese, individuals with molecularly confirmed DRPLA have been identified in other populations including European and North and South American [Burke et al 1994b, Le Ber et al 2003, Martins et al 2003, Wardle et al 2009, Paradisi et al 2016]. Analyses of some Italian families with DRPLA show that the haplotype associated with DRPLA is very similar to the Japanese and Portuguese haplotype, suggesting a founder effect [Veneziano et al 2014].

Although rare in the US, DRPLA has been identified in a large African American family in North Carolina [Burke et al 1994a, Burke et al 1994b] and in a second African American family [Licht & Lynch 2002].

Genetically Related (Allelic) Disorders

***ATN1*-related neurodevelopmental disorder.** Heterozygous *de novo* pathogenic variants in exon 7 of *ATN1* are associated with a neurodevelopmental disorder (also referred to as CHEDDA) characterized by congenital hypotonia, epilepsy, developmental delay, and digit abnormalities [Palmer et al 2021].

Differential Diagnosis

For individuals with adult-onset dentatorubral-pallidoluysian atrophy (DRPLA) who exhibit ataxia, dementia, or choreoathetosis (the non-PME phenotype), the differential diagnosis includes the following.

Huntington disease and Huntington disease-like phenotypes including Huntington disease-like 1 (see Genetic Prion Disease) and Huntington disease-like 2. The presence of ataxia is important for differentiating DRPLA from Huntington disease. Some affected individuals with the non-PME phenotype of DRPLA may initially be diagnosed as having Huntington disease, as the main clinical features in these individuals are involuntary movements and 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 Huntington disease. It is frequently necessary to do molecular genetic testing for Huntington disease, Huntington disease-like phenotypes, and DRPLA in individuals with unexplained progressive dementia and involuntary movements.

Ataxia. Individuals with DRPLA who have mildly expanded CAG repeats [c.1462CAG(49-55)] tend to exhibit, particularly in early stages, pure cerebellar symptoms such as ataxia without dementia, choreoathetosis, or character changes, making the clinical diagnosis of DRPLA difficult. Such individuals need to be distinguished from those with ataxia of other etiologies including the dominantly inherited ataxias for which the involved genes are known (e.g., SCA1, SCA2, Machado-Joseph disease [SCA3], SCA6, SCA7, SCA17) and other dominant SCAs (see Hereditary Ataxia Overview).

Progressive intellectual deterioration, myoclonus, and epilepsy. For those with early-onset DRPLA (age <20 years), the differential diagnosis includes the following (see also Malek et al [2015]):

- Benign adult familial myoclonus epilepsy (also called familial essential myoclonus and epilepsy). See Familial adult myoclonic epilepsy: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.
- Gaucher disease
- Hexosaminidase A deficiency
- Infantile neuroaxonal dystrophy
- MERRF (myoclonus epilepsy associated with ragged-red fibers)
- Neuroferritinopathy
- Neuronal ceroid-lipofuscinosis
- Pantothenate kinase associated neurodegeneration

- Progressive myoclonic epilepsy type 4, 5, 6
- Progressive myoclonus epilepsy, Lafora type
- Sialidosis (OMIM 256550)
- Unverricht-Lundborg disease

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with dentatorubral-pallidoluysian atrophy (DRPLA), the following evaluations are recommended:

- EEG in the presence of seizures
- Head MRI to monitor progression of the disease
- Neuropsychological testing for evidence of dementia and psychiatric disturbance
- Consultation with a clinical geneticist and/or genetic counselor
- Consultation with a rehabilitation therapist

Treatment of Manifestations

The following are appropriate:

- Treatment of seizures with anti-seizure medication in a standard manner
- Treatment of psychiatric problems with appropriate psychotropic medications
- Symptomatic treatment of ataxia using riluzole and rehabilitation therapy [van de Warrenburg et al 2014, Romano et al 2015]
- Adaptation of environment and care to the level of dementia
- For affected children, adaptation of educational programming to abilities

Surveillance

Surveillance is individualized based on disease progression.

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 or a seizure disorder from any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of anti-seizure medication during pregnancy reduces this risk. However, exposure to anti-seizure medication 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 anti-seizure medication during pregnancy is typically recommended. Discussion of the risks and benefits of using a given anti-seizure drug 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 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.org 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 is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with DRPLA have an affected parent.
- It is appropriate to evaluate both parents of an affected individual with molecular genetic testing even if they are asymptomatic.
- In some cases, 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].
- The family history of an affected individual may also appear to be negative because of failure to recognize the disorder in family members [Ikeuchi et al 1995b] or early death of the parent before the onset of symptoms.

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 a full-penetrance allele, the risk to the sibs 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.
- If a parent has a mutable normal allele, the risk of a full penetrance allele in a sib is presumably lower than 50%. However, because the finding of a mutable normal allele in a parent of an individual with DRPLA has not been reported to date, no precise estimate can be calculated.

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. See Anticipation.

Other family members of a proband. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected or has a mutable normal or full-penetrance allele, 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.

Testing of at-risk adult relatives

- Testing of at-risk adults for DRPLA in the presence of nonspecific or equivocal symptoms is predictive testing, not diagnostic testing. When testing at-risk individuals for DRPLA, it is helpful to first test for the *ATN1* (*DRPLA*) CAG expansion in an affected family member to confirm the molecular diagnosis in the family.
- Testing of asymptomatic, healthy at-risk adults for DRPLA can be performed, taking into consideration their autonomy of choice and right to privacy.

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

- Predictive testing for at-risk relatives is possible once the *ATN1* (*DRPLA*) 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 adult-onset disorders for which no treatment exists is not considered appropriate. Such testing negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- See also 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 the *ATN1* (*DRPLA*) CAG trinucleotide repeat expansion has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for DRPLA are possible.

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
  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
- **Parent to Parent**
  Phone: 484-272-7368
  www.p2pusa.org
- **Spanish Ataxia Federation (FEDAES)**
  Spain
  Phone: 34 983 278 029; 34 985 097 152; 34 634 597 503
  Email: sede.valladolid@fedaes.org; sede.gijon@fedaes.org; sede.bilbao@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

As in other polyglutamine disorders, the disease-causing CAG expansion in *DRPLA* (*ATN1*) led 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 DRPLA protein (atrophin-1) 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].

Animal models. Studies of mouse models suggest that neuronal dysfunction without neuronal death is the essential pathophysiologic process and that age-dependent neuronal intranuclear accumulation (NIA) underlies the neuronal dysfunction in DRPLA.

Mouse models for DRPLA expressing full-length human *ATN1* with CAG expansion have been created [Sato et al 1999b, Sato et al 2009].

Mice expressing 76 CAG repeats exhibited intergenerational instability of CAG repeats (as similarly observed in families with DRPLA), but no obvious neurologic phenotypes. Mice with 129 CAG repeats exhibited devastating progressive neurologic phenotypes similar to individuals with juvenile-onset DRPLA. Neurologic dysfunction of the globus pallidus (GP) and cerebellum was observed, as well as progressive shrinkage of distal dendrites of Purkinje cells (PCs) and progressive brain atrophy, but no obvious neuronal loss. Neuronal abnormalities are associated with massive NIIs. Abnormalities in individual neurons including reductions in the number and size of spines as well as in the area of perikarya and diameter of dendrites were also observed. These abnormalities probably explain the brain atrophy and neuronal dysfunction in this disease [Sakai et al 2006, Sato et al 2009, Suzuki et al 2012, Suzuki et al 2013].

Recently lysine-specific demethylase 1 (LSD1) and its target ATN1 were shown to be responsible for neuronal progenitor cell maintenance during cortical development in vivo [Zhang et al 2014].

Gene structure. *ATN1* comprises ten exons spanning 20 kb; it is alternatively spliced resulting in two transcript variants (NM_001007026.1 and NM_001940.3) that encode the same protein with differences only in their untranslated exons (NP_001007027.1 and NP_001931.2). For a detailed summary of gene and protein information, see Table A, **Gene.**

Benign variants. The CAG repeat in *ATN1* is located in exon 5, 1,462 bp downstream from the putative methionine initiation codon, and is predicted to code for a polyglutamine stretch. The CAG repeats in normal individuals range from six to 35 repeat units [Koide et al 1994, Nagafuchi et al 1994, Ikeuchi et al 1995a, Ikeuchi et al 1995c].

Mutable normal alleles. Mutable normal alleles may exist; Takano et al [1998] have shown that the normal Japanese population has a greater number of individuals with 20-35 CAG repeats than are found in populations of European origin. Mutable normal alleles are not associated with symptoms but are hypothetically unstable and could expand on transmission resulting in occurrence of symptoms in the next generation. However, no case of a mutable allele expanding or contracting in the subsequent generation has been reported.

Pathogenic variants. The CAG repeats in individuals with DRPLA range from 48 to 93 repeat units [Koide et al 1994, Nagafuchi et al 1994, Ikeuchi et al 1995a, Ikeuchi et al 1995b, Ikeuchi et al 1995c, Alford et al 1997, Shimojo et al 2001] (for more information, see Table A).

Table 3. Selected *ATN1* Variants

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Benign	c.1462CAG(6_35) (CAG 6-35 repeats)	See footnote 1.	NM_001007026.1 NP_001007027.1
Pathogenic	c.1462CAG(49_55) [2]	See footnote 2.	
	c.1462CAG(48_93) (CAG 48-93 repeats)	See footnote 1.	
	c.1462CAG(90_93) [3] (CAG 90-93 repeats)	See footnote 1.	

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.
1. Each CAG repeat results in the addition of a glutamine residue to the polymorphic polyglutamine repeat.
2. See Differential Diagnosis.
3. See Genotype-Phenotype Correlations.

Normal gene product. The *ATN1* cDNA is predicted to code for 1,190 amino acids. Atrophin-1 is a nuclear protein with putative nuclear localizing signals [Sato et al 1999a, Nucifora et al 2003]. Several studies have suggested that the *Drosophila* ortholog of atrophin-1 (DRPLA protein) functions as a transcriptional co-regulator in diverse developmental processes [Wood et al 2000, Zhang et al 2002, Charroux et al 2006, Shen et al 2007].

Abnormal gene product. 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]. Expanded polyglutamine stretches have been shown to interact with TATA-binding protein (TBP)-associated factors (TAFII130) or cAMP response element-binding protein (CREB)-binding protein (CBP), resulting in the suppression of CREB-dependent transcriptional activation that is vital for neuronal survival and plasticity [Shimohata et al 2000, Nucifora et al 2001, Shimohata et al 2005].

Chapter Notes

Author Notes

Ataxia Study Group (ASG)

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The Ataxia Study Group (ASG) is an international consortium of scientific investigators from academic and research centers who are committed to the cooperative planning, implementation, and performance of clinical trials and other research studies in ataxia disorders. The ASG was founded on the 14 Jan 2008 in Strasbourg (France) and has the legal form of a European Economic Interest Grouping (EEIG). It is open to clinicians and scientists who are experienced in management of ataxia patients, who have performed or participated in clinical studies of ataxia patients, or who have made other important contributions to the field of ataxia research.

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References

Published Guidelines / Consensus Statements

Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 8-30-22.

National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2019. Accessed 8-30-22.

EFNS/ENS Consensus on the diagnosis and management of chronic ataxias in adulthood. Eur J Neurol. 2014;21:552–62. PubMed PMID: 24418350.

Literature Cited

Adachi N, Arima K, Asada T, Kato M, Minami N. Goto Yi, Onuma T, Ikeuchi T, Tsuji S, Hayashi M, Fukutani Y. Dentatorubral-pallidoluysian atrophy (DRPLA) presenting with psychosis. J Neuropsychiatry Clin Neurosci. 2001;13:258–60. PubMed PMID: 11449034.

Alford RL, Margolis RL, Ross CA, Richards CS. Southern analysis for detection of CAG repeat expansions associated with dentatorubral pallidoluysian atrophy. Hum Genet. 1997;99:354–6. PubMed PMID: 9050922.

Burke JR, Ikeuchi T, Koide R, Tsuji S, Yamada M, Pericak-Vance MA, Vance JM. Dentatorubral-pallidoluysian atrophy and Haw River syndrome. Lancet. 1994a;344:1711–2. [letter]. PubMed PMID: 7996992.

Burke JR, Wingfield MS, Lewis KE, Roses AD, Lee JE, Hulette C, Pericak-Vance MA, Vance JM. The Haw River syndrome: dentatorubropallidoluysian atrophy (DRPLA) in an African-American family. Nat Genet. 1994b;7:521–4. PubMed PMID: 7951323.

Charroux B, Freeman M, Kerridge S, Baonza A. Atrophin contributes to the negative regulation of epidermal growth factor receptor signaling in Drosophila. Dev Biol. 2006;291:278–90. PubMed PMID: 16445904.

Hasegawa A, Ikeuchi T, Koike R, Matsubara N, Tsuchiya M, Nozaki H, Homma A, Idezuka J, Nishizawa M, Onodera O. Long-term disability and prognosis in dentatorubral-pallidoluysian atrophy: a correlation with CAG repeat length. Mov Disord. 2010;25:1694–700. PubMed PMID: 20589872.

Hatano T, Okuma Y, Iijima M, Fujishima K, Goto K, Mizuno Y. Cervical dystonia in dentatorubral-pallidoluysian atrophy. Acta Neurol Scand. 2003;108:287–9. PubMed PMID: 12956864.

Hattori M, Yuasa H, Takada K, Yamada T, Yamada K, Kamimoto K, Uchida M. Genetic analysis of a dentatorubral-pallidoluysian atrophy family: relevance to apparent sporadic cases. Intern Med. 1999;38:287–9. PubMed PMID: 10337944.

Hayashi Y, Kakita A, Yamada M, Egawa S, Oyanagi S, Naito H, Tsuji S, Takahashi H. Hereditary dentatorubral-pallidoluysian atrophy: ubiquitinated filamentous inclusions in the cerebellar dentate nucleus neurons. Acta Neuropathol (Berl). 1998;95:479–82. PubMed PMID: 9600594.

Igarashi S, Koide R, Shimohata T, Yamada M, Hayashi Y, Takano H, Date H, Oyake M, Sato T, Sato A, Egawa S, Ikeuchi T, Tanaka H, Nakano R, Tanaka K, Hozumi I, Inuzuka T, Takahashi H, Tsuji S. Suppression of aggregate formation and apoptosis by transglutaminase inhibitors in cells expressing truncated DRPLA protein with an expanded polyglutamine stretch. Nat Genet. 1998;18:111–7. PubMed PMID: 9462738.

Ikeuchi T, Koide R, Onodera O, Tanaka H, Oyake M, Takano H, Tsuji S. Dentatorubral-pallidoluysian atrophy (DRPLA). Molecular basis for wide clinical features of DRPLA. Clin Neurosci. 1995a;3:23–7. PubMed PMID: 7614090.

Ikeuchi T, Koide R, Tanaka H, Onodera O, Igarashi S, Takahashi H, Kondo R, Ishikawa A, Tomoda A, Miike T, Sata K, Ihara Y, Hayabara T, Isa F, Tanabe H, Tokiguchi S, Yayashi M, Shimizu N, Ikuta F, Naito H, Tsuji S. Dentatorubral-pallidoluysian atrophy: clinical features are closely related to unstable expansions of trinucleotide (CAG) repeat. Ann Neurol. 1995b;37:769–75. PubMed PMID: 7778850.

Ikeuchi T, Onodera O, Oyake M, Koide R, Tanaka H, Tsuji S. Dentatorubral-pallidoluysian atrophy (DRPLA): close correlation of CAG repeat expansions with the wide spectrum of clinical presentations and prominent anticipation. Semin Cell Biol. 1995c;6:37–44. PubMed PMID: 7620120.

Kanazawa I. Dentatorubral-pallidoluysian atrophy or Naito-Oyanagi disease. Neurogenetics. 1998;2:1–17. PubMed PMID: 9933295.

Kawamichi Y, Makino Y, Matsuda Y, Miyazaki K, Uchiyama S, Ohta H. Riluzole use during pregnancy in a patient with amyotrophic lateral sclerosis: a case report. J Int Med Res. 2010;38:720–6. PubMed PMID: 20515588.

Koide R, Ikeuchi T, Onodera O, Tanaka H, Igarashi S, Endo K, Takahashi H, Kondo R, Ishikawa A, Hayashi T, Saito M, Tomoda A, Miike T, Naito H, Ikuta F, Tsuji S. Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA). Nat Genet. 1994;6:9–13. PubMed PMID: 8136840.

Koide R, Onodera O, Ikeuchi T, Kondo R, Tanaka H, Tokiguchi S, Tomoda A, Miike T, Isa F, Beppu H, Shimizu N, Watanabe Y, Horikawa Y, Shimohata T, Hirota K, Ishikawa A, Tsuji S. Atrophy of the cerebellum and brainstem in dentatorubral pallidoluysian atrophy. Influence of CAG repeat size on MRI findings. Neurology. 1997;49:1605–12. PubMed PMID: 9409354.

Le Ber I, Camuzat A, Castelnovo G, Azulay JP, Genton P, Gastaut JL, Broglin D, Labauge P, Brice A, Durr A. Prevalence of dentatorubral-pallidoluysian atrophy in a large series of white patients with cerebellar ataxia. Arch Neurol. 2003;60:1097–9. PubMed PMID: 12925365.

Licht DJ, Lynch DR. Juvenile dentatorubral-pallidoluysian atrophy: new clinical features. Pediatr Neurol. 2002;26:51–4. PubMed PMID: 11814736.

Malek N, Stewart W, Greene J. The progressive myoclonic epilepsies. Pract Neurol. 2015;15:164–71. PubMed PMID: 25720773.

Martins S, Matama T, Guimaraes L, Vale J, Guimaraes J, Ramos L, Coutinho P, Sequeiros J, Silveira I. Portuguese families with dentatorubropallidoluysian atrophy (DRPLA) share a common haplotype of Asian origin. Eur J Hum Genet. 2003;11:808–11. PubMed PMID: 14512972.

Maruyama S, Saito Y, Nakagawa E, Saito T, Komaki H, Sugai K, Sasaki M, Kumada S, Saito Y, Tanaka H, Minami N, Goto Y. Importance of CAG repeat length in childhood-onset dentatorubral-pallidoluysian atrophy. J Neurol. 2012;259:2329–34. PubMed PMID: 22527233.

Mori F, Tanji K, Odagiri S, Toyoshima Y, Yoshida M, Kakita A, Takahashi H, Wakabayashi K. Autophagy-related proteins (p62, NBR1 and LC3) in intranuclear inclusions in neurodegenerative diseases. Neurosci Lett. 2012a;522:134–8. PubMed PMID: 22728060.

Mori F, Tanji K, Toyoshima Y, Yoshida M, Kakita A, Takahashi H, Wakabayashi K. Optineurin immunoreactivity in neuronal nuclear inclusions of polyglutamine diseases (Huntington's, DRPLA, SCA2, SCA3) and intranuclear inclusion body disease. Acta Neuropathol. 2012b;123:747–9. PubMed PMID: 22318854.

Muñoz E, Campdelacreu J, Ferrer I, Rey MJ, Cardozo A, Gómez B, Tolosa E. Severe cerebral white matter involvement in a case of dentatorubropallidoluysian atrophy studied at autopsy. Arch Neurol. 2004;61:946–9. PubMed PMID: 15210537.

Nagafuchi S, Yanagisawa H, Sato K, Shirayama T, Ohsaki E, Bundo M, Takeda T, Tadokoro K, Kondo I, Murayama N, Tanaka Y, Kikushima H, Umino K, Kurosawa H, Furkawa T, Nihei K, Inoue T, Sana A, Komure O, Takahashi M, Yoshizawa T, Kanazawa I, Yamada M. Dentatorubral and pallidoluysian atrophy expansion of an unstable CAG trinucleotide on chromosome 12p. Nat Genet. 1994;6:14–8. PubMed PMID: 8136826.

Naito H, Oyanagi S. Familial myoclonus epilepsy and choreoathetosis: hereditary dentatorubral-pallidoluysian atrophy. Neurology. 1982;32:798–807. PubMed PMID: 6808417.

Nucifora FC Jr, Ellerby LM, Wellington CL, Wood JD, Herring WJ, Sawa A, Hayden MR, Dawson VL, Dawson TM, Ross CA. Nuclear localization of a non-caspase truncation product of atrophin-1, with an expanded polyglutamine repeat, increases cellular toxicity. J Biol Chem. 2003;278:13047–55. PubMed PMID: 12464607.

Nucifora FC Jr, Sasaki M, Peters MF, Huang H, Cooper JK, Yamada M, Takahashi H, Tsuji S, Troncoso J, Dawson VL, Dawson TM, Ross CA. Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. Science. 2001;291:2423–8. PubMed PMID: 11264541.

Palmer EE, Whitton C, Hashem MO, Clark RD, Ramanathan S, Starr LJ, Velasco D, De Dios JK, Singh E, Cormier-Daire V, Chopra M, Rodan LH, Nellaker C, Lakhani S, Mallack EJ, Panzer K, Sidhu A, Wentzensen IM, Lacombe D, Michaud V, Alkuraya FS. CHEDDA syndrome is an underrecognized neurodevelopmental disorder with a highly restricted ATN1 mutation spectrum. Clin Genet. 2021;100:468–77. PubMed PMID: 34212383.

Paradisi I, Ikonomu V, Arias S. Spinocerebellar ataxias in Venezuela: genetic epidemiology and their most likely ethnic descent. J Hum Genet. 2016;61:215–22. PubMed PMID: 26538302.

Romano S, Coarelli G, Marcotulli C, Leonardi L, Piccolo F, Spadaro M, Frontali M, Ferraldeschi M, Vulpiani MC, Ponzelli F, Salvetti M, Orzi F, Petrucci A, Vanacore N, Casali C, Ristori G. Riluzole in patients with hereditary cerebellar ataxia: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2015;14:985–91. PubMed PMID: 26321318.

Sakai K, Yamada M, Sato T, Yamada M, Tsuji S, Takahashi H. Neuronal atrophy and synaptic alteration in a mouse model of dentatorubral-pallidoluysian atrophy. Brain. 2006;129:2353–62. PubMed PMID: 16891319.

Sarma AK, Khandker N, Kurczewski L, Brophy GM. Medical management of epileptic seizures: challenges and solutions. Neuropsychiatr Dis Treat. 2016;12:467–85. PubMed PMID: 26966367.

Sato A, Shimohata T, Koide R, Takano H, Sato T, Oyake M, Igarashi S, Tanaka K, Inuzuka T, Nawa H, Tsuji S. Adenovirus-mediated expression of mutant DRPLA proteins with expanded polyglutamine stretches in neuronally differentiated PC12 cells. Preferential intranuclear aggregate formation and apoptosis. Hum Mol Genet. 1999a;8:997–1006. PubMed PMID: 10332031.

Sato K, Kashihara K, Okada S, Ikeuchi T, Tsuji S, Shomori T, Morimoto K, Hayabara T. Does homozygosity advance the onset of dentatorubral-pallidoluysian atrophy? Neurology. 1995;45:1934–6. PubMed PMID: 7477999.

Sato T, Oyake M, Nakamura K, Nakao K, Fukusima Y, Onodera O, Igarashi S, Takano H, Kikugawa K, Ishida Y, Shimohata T, Koide R, Ikeuchi T, Tanaka H, Futamura N, Matsumura R, Takayanagi T, Tanaka F, Sobue G, Komure O, Takahashi M, Sano A, Ichikawa Y, Goto J, Kanazawa I, Katsuki M, Shoji T. Transgenic mice harboring a full-length human mutant DRPLA gene exhibit age-dependent intergenerational and somatic instabilities of CAG repeats comparable with those in DRPLA patients. Hum Mol Genet. 1999b;8:99–106. PubMed PMID: 9887337.

Sato T, Miura M, Yamada M, Yoshida T, Wood JD, Yazawa I, Masuda M, Suzuki S, Shin R-M, Yau H-J, Liu F-C, Shimohata T, Onodera O, Ross CA, Katsuki M, Takahashi H, Kano M, Aosaki T, Tsuji S. Severe neurological phenotypes of Q129 DRPLA transgenic mice serendipitously created by en masse expansion of CAG repeats in Q76 DRPLA mice. Hum. Mol. Genet. 2009;18:723–36. PubMed PMID: 19039037.

Scalco RS, Vieira MC, da Cunha Filho EV, Lago EG, da Silva IG, Becker J. Amyotrophic lateral sclerosis and riluzole use during pregnancy: a case report. Amyotroph Lateral Scler. 2012;13:471–2. PubMed PMID: 22670879.

Shen Y, Lee G, Choe Y, Zoltewicz JS, Peterson AS. Functional architecture of atrophins. J Biol Chem. 2007;282:5037–44. PubMed PMID: 17150957.

Shimohata M, Shimohata T, Igarashi S, Naruse S, Tsuji S. Interference of CREB-dependent transcriptional activation by expanded polyglutamine stretches--augmentation of transcriptional activation as a potential therapeutic strategy for polyglutamine diseases. J Neurochem. 2005;93:654–63. PubMed PMID: 15836624.

Shimohata T, Nakajima T, Yamada M, Uchida C, Onodera O, Naruse S, Kimura T, Koide R, Nozaki K, Sano Y, Ishiguro H, Sakoe K, Ooshima T, Sato A, Ikeuchi T, Oyake M, Sato T, Aoyagi Y, Hozumi I, Nagatsu T, Takiyama Y, Nishizawa M, Goto J, Kanazawa I, Davidson I, Tanese N, Takahashi H, Tsuji S. Expanded polyglutamine stretches interact with TAFII130, interfering with CREB-dependent transcription. Nat Genet. 2000;26:29–36. PubMed PMID: 10973244.

Shimohata T, Sato A, Burke JR, Strittmatter WJ, Tsuji S, Onodera O. Expanded polyglutamine stretches form an 'aggresome'. Neurosci Lett. 2002;323:215–8. PubMed PMID: 11959423.

Shimojo Y, Osawa Y, Fukumizu M, Hanaoka S, Tanaka H, Ogata F, Sasaki M, Sugai K. Severe infantile dentatorubral pallidoluysian atrophy with extreme expansion of CAG repeats. Neurology. 2001;56:277–8. PubMed PMID: 11160976.

Sone D, Sato N, Yokoyama K, Sumida K, Kanai M, Imabayashi E, Saito Y, Matsuda H. Striatal glucose hypometabolism in preadolescent-onset dentatorubral-pallidoluysian atrophy. J Neurol Sci. 2016;360:121–4. PubMed PMID: 26723987.

Suzuki K, Sato T, Yamada M, Takahashi H, Tsuji S. DRPLA: recent advances in research using transgenic mouse models. Methods Mol Biol. 2013;1010:277–92. PubMed PMID: 23754232.

Suzuki K, Zhou J, Sato T, Takao K, Miyagawa T, Oyake M, Yamada M, Takahashi H, Takahashi Y, Goto J, Tsuji S. DRPLA transgenic mouse substrains carrying single copy of full-length mutant human DRPLA gene with variable sizes of expanded CAG repeats exhibit CAG repeat length- and age-dependent changes in

behavioral abnormalities and gene expression profiles. Neurobiol Dis. 2012;46:336–50. PubMed PMID: 22342974.

Takano H, Cancel G, Ikeuchi T, Lorenzetti D, Mawad R, Stevanin G, Didierjean O, Durr A, Oyake M, Shimohata T, Sasaki R, Koide R, Igarashi S, Hayashi S, Takiyama Y, Nishizawa M, Tanaka H, Zoghbi H, Brice A, Tsuji S. Close associations between prevalences of dominantly inherited spinocerebellar ataxias with CAG-repeat expansions and frequencies of large normal CAG alleles in Japanese and Caucasian populations. Am J Hum Genet. 1998;63:1060–6. PubMed PMID: 9758625.

Takayama N, Iwase Y, Sakio H. Anesthetic management of a patient with dentato-rubro-pallido-luysian atrophy. Masui. 2002;51:902–3. PubMed PMID: 12229143.

Tsuji S, Onodera O, Goto J, Nishizawa M, et al. Sporadic ataxias in Japan--a population-based epidemiological study. Cerebellum. 2008;7:189–97. PubMed PMID: 18418674.

Tsuji S. Dentatorubral-pallidoluysian atrophy. Handb Clin Neurol. 2012;103:587–94. PubMed PMID: 21827919.

van de Warrenburg BP, van Gaalen J, Boesch S, Burgunder JM, Durr A, Giunti P, Klockgether T, Mariotti C, Pandolfo M, Riess O. EFNS/ENS Consensus on the diagnosis and management of chronic ataxias in adulthood. Eur J Neurol. 2014;21:552–62. PubMed PMID: 24418350.

Veneziano L, Mantuano E, Catalli C, Gellera C, Durr A, Romano S, Spadaro M, Frontali M, Novelletto A. A shared haplotype for dentatorubropallidoluysian atrophy (DRPLA) in Italian families testifies of the recent introduction of the mutation. J Hum Genet. 2014;59:153–7. PubMed PMID: 24401908.

Vinton A, Fahey MC, O'Brien TJ, Shaw J, Storey E, Gardner RJ, Mitchell PJ, Du Sart D, King JO. Dentatorubral-pallidoluysian atrophy in three generations, with clinical courses from nearly asymptomatic elderly to severe juvenile, in an Australian family of Macedonian descent. Am J Med Genet A. 2005;136:201–4. PubMed PMID: 15948186.

Wardle M, Morris HR, Robertson NP. Clinical and genetic characteristics of non-Asian dentatorubral-pallidoluysian atrophy: A systematic review. Mov Disord. 2009;24:1636–40. PubMed PMID: 19514013.

Warner JP, Barron LH, Goudie D, Kelly K, Dow D, Fitzpatrick DR, Brock DJ. A general method for the detection of large CAG repeat expansions by fluorescent PCR. J Med Genet. 1996;33:1022–6. PubMed PMID: 9004136.

Wood JD, Nucifora FC, Duan K, Zhang C, Wang J, Kim Y, Schilling G, Sacchi N, Liu JM, Ross CA. Atrophin-1, the dentato-rubral and pallido-luysian atrophy gene product, Interacts with ETO/MTG8 in the nuclear matrix and represses transcription. J Cell Biol. 2000;150:939–48. PubMed PMID: 10973986.

Yamada M, Piao YS, Toyoshima Y, Tsuji S, Takahashi H. Ubiquitinated filamentous inclusions in cerebellar dentate nucleus neurons in dentatorubral-pallidoluysian atrophy contain expanded polyglutamine stretches. Acta Neuropathol (Berl). 2000;99:615–8. PubMed PMID: 10867794.

Yamada M, Tsuji S, Takahashi H. Genotype-phenotype correlation in CAG-repeat diseases. Neuropathology. 2002;22:317–22. PubMed PMID: 12564773.

Yamada M, Wood JD, Shimohata T, Hayashi S, Tsuji S, Ross CA, Takahashi H. Widespread occurrence of intranuclear atrophin-1 accumulation in the central nervous system neurons of patients with dentatorubral-pallidoluysian atrophy. Ann Neurol. 2001;49:14–23. PubMed PMID: 11198291.

Zhang F, Xu D, Yuan L, Sun Y, Xu Z (2014) Epigenetic regulation of Atrophin1 by lysine-specific demethylase 1 is required for cortical progenitor maintenance. Nat Commun. 18;5:5815

Zhang S, Xu L, Lee J, Xu T. Drosophila atrophin homolog functions as a transcriptional corepressor in multiple developmental processes. Cell. 2002;108:45–56. PubMed PMID: 11792320.

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