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ATP1A3-Related Neurologic Disorders

Allison Brashear, MD,[1] Kathleen J Sweadner, PhD,[2] Jared F Cook, MA,[3] Kathryn J Swoboda, MD,[4] and Laurie Ozelius, PhD[5]

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Summary

Clinical characteristics

ATP1A3-related neurologic disorders represent a clinical continuum in which at least three distinct phenotypes have been delineated: rapid-onset dystonia-parkinsonism (RDP); alternating hemiplegia of childhood (ACH); and cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS). However, some affected individuals have intermediate phenotypes or only a few features that do not fit well into one of these major phenotypes.

- RDP has been characterized by: abrupt onset of dystonia over days to weeks with parkinsonism (primarily bradykinesia and postural instability); common bulbar involvement; and absence or minimal response to an adequate trial of L-dopa therapy, with few exceptions. Often fever, physiologic stress, or alcoholic binges trigger the onset of symptoms. After their initial appearance, symptoms often stabilize with little improvement; occasionally second episodes occur with abrupt worsening of symptoms. Rarely, affected individuals have reported a more gradual onset of symptoms over weeks to months. Anxiety, depression, and seizures have been reported. Age of onset ranges from four to 55 years, although a childhood variation of RDP with onset between ages nine and 14 months has been reported.
- AHC is a complex neurodevelopmental syndrome most frequently manifesting in infancy or early childhood with paroxysmal episodic neurologic dysfunction including alternating hemiparesis or dystonia, quadriparesis, seizure-like episodes, and oculomotor abnormalities. Episodes can last for minutes, hours, days, or even weeks. Remission of symptoms occurs with sleep and immediately after awakening. Over time, persistent neurologic deficits including oculomotor apraxia, ataxia, choreoathetosis, dystonia, parkinsonism, and cognitive and behavioral dysfunction develop in the

Author Affiliations: 1 Professor and Chair, Department of Neurology Wake Forest School of Medicine Winston-Salem, North Carolina; Email: abrashea@wakehealth.edu. 2 Associate Professor of Cellular and Molecular Physiology, Department of Surgery Massachusetts General Hospital Boston, Massachusetts; Email: sweadner@helix.mgh.harvard.edu. 3 Project Manager, Department of Neurology Wake Forest University School of Medicine Winston-Salem, North Carolina; Email: jarcook@wakehealth.edu. 4 Director, Neurogenetics Unit Center for Genomic Medicine Department of Neurology Massachusetts General Hospital Boston, Massachusetts; Email: kswoboda@mgh.harvard.edu. 5 Associate Neuroscientist, Department of Neurology Massachusetts General Hospital Boston, Massachusetts; Email: lozelius@partners.org.

majority of those affected; more than 50% develop epilepsy in addition to their episodic movement disorder phenotype.
- CAPOS (*c*erebellar ataxia, *a*reflexia, pes cavus, *o*ptic atrophy, and *s*ensorineural hearing loss) syndrome is characterized by episodes of ataxic encephalopathy and/or weakness during and after a febrile illness. Onset is between ages six months and four years. Some acute symptoms resolve; progression of sensory losses and severity vary.

Diagnosis/testing

Diagnosis of an *ATP1A3*-related neurologic disorder is established in an individual with the clinical features of RDP, AHC, or CAPOS syndrome and/or by the identification of a heterozygous pathogenic variant in *ATP1A3*.

Management

Treatment of manifestations: Standard treatment of visual disturbance, hearing loss, seizure disorders, cardiac arrhythmia, and cardiomyopathy. Consideration of CPAP or BiPAP for those with sleep apnea. Those with severe dysphagia may require a gastrostomy tube. Physical therapy, occupational therapy, and speech therapy for motor dysfunction, ataxia, and dysarthria. Acute spasms may respond to chloral hydrate or other medication that induces sleep. Dystonia can be treated with benzodiazepines, dopamine agonists, or levo-dopa. Psychotherapy and standard pharmacotherapy for those with mood disorder or psychosis. Early referral for developmental support / special education.

Prevention of primary manifestations: Prophylaxis for AHC episodes may include flunarizine, topiramate, a ketogenic diet, and sleep. A trial of high-dose benzodiazepines may be considered in individuals with RDP and AHC. Triggers that lead to acute attacks should be avoided.

Prevention of secondary complications: When dystonia is present, physical therapy to prevent contractures in the hands and feet.

Surveillance. Affected individuals should be monitored for the development of dysphagia (RDP and CAPOS syndrome), seizures (RDP and AHC), and psychiatric symptoms (RDP).

Agents/circumstances to avoid:

- RDP. Triggers including alcohol, fever, psychological stress (e.g., childbirth), excessive exercise.
- AHC. Triggers including psychological stress / excitement; environmental stressors (e.g., bright light, excessive heat or cold, excessive sound, crowds); water exposure (e.g., bathing, swimming); certain foods or odors (e.g., chocolate, food dyes); missed meals; excessive or atypically strenuous exercise; illness; irregular sleep (missing a nap, delayed bedtime).
- CAPOS syndrome. Febrile illness, pregnancy.

Pregnancy management: Affected pregnant women should be monitored for the development of symptoms of RDP. The number of pregnant women with RDP is small, but several reports of childbirth as a trigger have been noted. Exposure to anti-seizure medication may increase the risk to the fetus of adverse outcome; that risk, however, is often less than the risk to the fetus associated with exposure to an untreated maternal seizure disorder. Discussion of the risks and benefits of using a given anti-seizure medication during pregnancy should ideally take place before conception.

Genetic counseling

ATP1A3-related neurologic disorders are inherited in an autosomal dominant manner. *ATP1A3* pathogenic variants may be inherited or occur *de novo*. In contrast to initial reports a familial history is not required for a diagnosis of RDP. In AHC, pathogenic variants are more commonly *de novo* than inherited; in both RDP and

CAPOS syndrome both inherited and *de novo* pathogenic variants have been observed. Each child of an individual with an *ATP1A3*-related neurologic disorder has a 50% chance of inheriting the *ATP1A3* pathogenic variant. Prenatal testing for pregnancies at increased risk is possible if the *ATP1A3* pathogenic variant in the family is known. The variability of presentation within a family with a known *ATP1A3* pathogenic variant further complicates genetic counseling. Lifelong asymptomatic individuals who harbor a heterozygous *ATP1A3* pathogenic variant have been reported in families with RDP.

GeneReview Scope

ATP1A3-Related Neurologic Disorders: Included Phenotypes [1]
• Rapid-onset dystonia-parkinsonism (RDP) • Alternating hemiplegia of childhood (AHC) • Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS) syndrome

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

Diagnosis

ATP1A3-related neurologic disorders represent a clinical continuum in which at least three distinct phenotypes have been delineated: rapid-onset dystonia-parkionsonism (RDP); alternating hemiplegia of childhood (ACH); and CAPOS (*c*erebellar ataxia, *a*reflexia, *p*es cavus, *o*ptic atrophy, and *s*ensorineural hearing loss) syndrome (see Clinical Description). Some affected individuals have intermediate phenotypes or only a few features that do not fit well into one of these major phenotypes. Clinical diagnostic criteria for the three major *ATP1A3*-related neurologic phenotypes have been published [Rosewich et al 2017].

Suggestive Findings

ATP1A3-related neurologic disorders **should be suspected** in individuals with the following clinical features (by age) and neuroimaging findings [Rosewich et al 2017].

Clinical Features

Infancy and early childhood

- Alternating hemiparesis, hemiplegia, or dystonia
- Paroxysmal episodes of monocular nystagmus with or without other motor signs or symptoms
- Paroxysmal conjugate or dysconjugate ocular movement abnormalities
- Acute flaccid quadriparesis persisting for hours to days
- Recurrent paroxysmal tonic or dystonic seizure-like episodes

Child or adult

- Paroxysmal onset of ataxia, which becomes fixed or remains episodic
- Paroxysmal dystonia or hemidystonia
- Acute, fluctuating motor function deficits persisting for hours to days, which may include ataxia, chorea, hemiplegia, or paresis
- Paroxysmal episodes of motor signs with EEG monitoring documenting the absence of epileptiform activity
- Episodes clinically consistent with generalized or focal epilepsy (with or without ictal EEG)

Any age

- Asymmetric paroxysmal onset of hemiplegia or paresis, quadriplegia or paresis, spasticity, dystonia, and dyskinesia, with or without the subsequent appearance of fixed neurologic deficits
- Rostrocaudal gradient (topographic, not temporal) of fixed or fluctuating motor involvement
- Multiple environmental triggers including physical exertion, extremes of temperature, emotional stimuli, and chemicals
- Seizure-like paroxysmal tremor affecting one or more limbs or inclusive of whole-body tremors
- Paroxysmal bulbar symptoms with or without resolution over hours to days
- Suspected epileptic event with normal EEG recording during a typical spell, especially if associated with tonic or dystonic posturing or migratory paresis

Neuroimaging Findings

Brain MRI is normal in the setting of either acute onset of new neurologic symptoms or recurrent episodes of neurologic impairment.

Note: Later in the disease course in a small number of individuals with the AHC phenotype, more subtle abnormalities (including diffuse cerebral atrophy and/or isolated cerebellar atrophy, or mesial temporal sclerosis) have been described [Sweney et al 2009, Sasaki et al 2014a].

Establishing the Diagnosis

The diagnosis of an *ATP1A3*-related neurologic disorder **is established** in a proband with classic clinical features of RDP, AHC, or CAPOS syndrome (see Clinical Description) and/or by the identification of a heterozygous pathogenic (or likely pathogenic) variant in *ATP1A3* by molecular genetic testing (Table 1).

Note: Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants.

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, or **comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *ATP1A3* is performed.
- **A multigene panel** that includes *ATP1A3* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **Comprehensive genomic testing** (when available) including exome and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

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

Table 1. Molecular Genetic Testing Used in *ATP1A3*-Related Neurologic Disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ATP1A3	Sequence analysis [3]	~80%-90% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Panagiotakaki et al [2015], Viollet et al [2015], Duat Rodriguez et al [2017]
5. All reported individuals with CAPOS syndrome have the same heterozygous c.2452G>A pathogenic missense variant [Rosewich et al 2014c, Duat Rodriguez et al 2017], although some affected individuals had symptoms that also overlapped with the AHC phenotype.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. No data on gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

ATP1A3-related neurologic disorders represent a clinical continuum in which three main phenotypes have been described: rapid-onset dystonia-parkinsonism (RDP), alternating hemiplegia of childhood (AHC), and cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS). Individuals with intermediate phenotypes or with only a few features have also been described (see Genotype-Phenotype Correlations).

Rapid-Onset Dystonia-Parkinsonism (RDP)

Clinical diagnostic criteria for RDP include the following [Rosewich et al 2017]:

- Abrupt onset of dystonia with or without features of parkinsonism over a few minutes to 30 days
- A clear rostrocaudal gradient of involvement (face > arm > leg)
- Prominent bulbar findings

  Note: Absence of prominent bulbar findings does not preclude the diagnosis.
- Absent or minimal response to an adequate trial of L-dopa therapy [Termsarasab et al 2015]
- Family history consistent with autosomal dominant inheritance

  Note: Absence of a family history of RDP does not preclude the diagnosis.

Additional features may include the following:

- Appearance of symptoms after triggering events such as running, childbirth, emotional stress, or alcoholic binges
- Stability of the phenotype with little improvement after its initial appearance
- Low concentration of dopamine metabolites in cerebrospinal fluid in some (not all) affected individuals

- Absence of other parkinsonian features including pill-rolling tremor and diurnal fluctuation; minimal or no response to standard medications for parkinsonism

The study of the clinical manifestations of RDP has focused primarily on dystonia/parkinsonism [Anselm et al 2009, Blanco-Arias et al 2009, Svetel et al 2010, Tarsy et al 2010]. Age at onset is extremely variable, typically ranging from four to 55 years, although onset at age nine months and after age 60 years has been reported.

Motor findings. The clinical stages of RDP may include mild antecedent dystonic symptoms, primary onset, and occasional second episodes of worsening.

- **Antecedent symptoms** have included nonspecific symptoms of dystonia, usually in the hands and arms. Some individuals reported mild limb cramping, most often involving the hands, prior to development of typical RDP following a physiologic stressor. While minimal or no tremor is typically present at onset, one individual initially had one year of parkinsonism, not dystonia, followed by abrupt onset of oromandibular dystonia with dysarthria. At least two affected individuals had fluctuating symptoms before the deficit became permanent; this has also been described in infants with an RDP-like presentation.
- **Primary onset** is usually paroxysmal or abrupt over hours to several weeks. In all affected individuals in two large US families, progression stopped at or before one month after onset. Many reported specific triggers consisting of either physical or psychological stress. Alcohol was a trigger in many but not all. The bulbar and arm symptoms rarely improve after the primary onset, although four individuals reported mild improvement in leg symptoms.
- **Occasional second episodes of worsening** have been reported in a few individuals who experienced episodes of abrupt worsening of symptoms one to nine years after the initial onset. Because only a few affected individuals have been reexamined over an extended time, documentation of second events is incomplete. The second events resemble the primary onset, with worsening of bulbar, arm, and leg symptoms over a similar time course. Except for these second events, little change is reported over many years in those affected individuals for whom such information is available, although the number of known affected individuals is small and lack of progression of symptoms requires further longitudinal study.

Non-motor features include mood disorders, substance abuse, and psychosis (see also Genotype-Phenotype Correlations). Although anxiety is also prevalent among persons with RDP, rates of anxiety did not significantly differ from family-matched controls without RDP [Brashear et al 2012b]. Cognitive impairment including difficulty with memory and learning, psychomotor speed, attention, and executive functioning has also been reported [Cook et al 2014]. Seizures have been reported in children and adults [Brashear et al 2007, Brashear et al 2012b], often after the appearance of motor symptoms.

Alternating Hemiplegia of Childhood (AHC)

AHC is a complex neurodevelopmental syndrome that most frequently manifests in infancy or early childhood with paroxysmal neurologic symptoms that can last for minutes to hours to even days and sometimes weeks, with remission of symptoms only during sleep and the immediate period post awakening.

Clinical diagnostic criteria for AHC include some constellation of the following (see Note) [Rosewich et al 2017]:

- Onset of symptoms before age 18 months
- Paroxysmal disturbances including tonic or dystonic spells (either unilaterally of one or more limbs or generalized), oculomotor abnormalities (monocular or binocular nystagmus, intermittent eso- or exotropia, skew deviation, ocular bobbing, ocular flutter), and autonomic phenomena (unilateral or bilateral pupillary dilatation, flushing, pallor affecting one limb or hemibody) during hemiplegic episodes or in isolation
- Repeated attacks of hemiplegia involving either side of the body and alternating in laterality

- Episodes of quadriparesis or hemi-/quadriplegia as a separate attack or as generalization of a hemiplegic episode
- Immediate disappearance of symptoms upon sleeping (symptoms may later resume after waking)
- Evidence of developmental delay (speech and language delay, cognitive deficits) and neurologic abnormalities including choreoathetosis, dystonia, and/or ataxia

Note: Diagnostic criteria assume that (1) initial diagnostic workup has not shown evidence of an alternative etiology (e.g., treatable metabolic disorder); (2) brain MRI is normal or with nonspecific features not identifying an alternative pathophysiology (e.g., vascular disease such as moyamoya); and (3) EEG during prolonged episodes of hemiplegia or dystonia does not provide an alternative explanation for episodes.

While neonates and young infants often present with seizure-like episodes, eye movement abnormalities, and autonomic manifestations, they can also present with episodes of flaccid quadriparesis. Paroxysmal episodic neurologic dysfunction is the predominant feature early in the disease course. As affected children age, interictal persistent neurologic dysfunction (including oculomotor apraxia, ataxia, dystonia, parkinsonism, and cognitive and behavioral dysfunction) increases.

More than 50% of children with AHC manifest clinical seizure activity by early childhood. Status epilepticus and status dystonicus can be life-threatening complications in some. For reviews, see Sweney et al [2009], Panagiotakaki et al [2010], Kansagra et al [2013], Sasaki et al [2014b], Heinzen et al [2014], and Rosewich et al [2017].

Additional paroxysmal neurologic symptoms include the following:

- More complex dyskinesias
- Headache
- Epilepsy (focal, partial, or generalized tonic-clonic)
- Status epilepticus or status dystonicus

Persistent, interictal neurologic symptoms that become increasingly evident with age include the following:

- Ataxia
- Oculomotor apraxia
- Strabismus
- Hypotonia or rigidity
- Choreoathetosis
- Impaired articulation or bulbar function
- Generalized or focal dystonia
- Areflexia or hyperreflexia

Non-motor interictal neurologic symptoms include the following:

- Behavioral outbursts, impulsivity
- Aggression
- Mood disorders

Other associated features in some individuals with AHC include the following:

- Tremor
- Recurrent apnea
- Respiratory distress
- Oxygen desaturation during episodes of neurologic dysfunction

- Consistent facial features [Gurrieri et al 2016], including a high forehead, thin eyebrows, hypotonic appearance to the face, an exaggerated Cupid's bow of the upper lip, an everted vermillion of the lower lip, and downturned corners of the mouth
- Cardiac conduction abnormalities (T wave abnormalities and intraventricular conduction delay) with increased risk for potential fatal arrhythmia and acquired cardiomyopathy [Jaffer et al 2015, Rosewich et al 2017]

CAPOS Syndrome

CAPOS syndrome presents in infancy or childhood with cerebellar ataxia after a fever and eventually a characteristic set of symptoms including the following [Rosewich et al 2017]:

- Cerebellar ataxia
- Areflexia
- Pes cavus (not present in all affected individuals)
- Progressive optic atrophy
- Progressive sensorineural hearing loss

In addition to ataxia, symptoms during the acute febrile encephalopathy may include hypotonia, flaccidity, nystagmus, strabismus, dysarthria, anarthria, lethargy, loss of consciousness, and even coma. There is usually considerable recovery within days to weeks, but persistence of some ataxia and other symptoms is typical. Additional features seen in one or more affected individuals include abnormal eye movements, dysphagia, autistic traits, brief seizures during acute illness, dystonia, and cognitive dysfunction [Nicolaides et al 1996, Demos et al 2014, Heimer et al 2015, Potic et al 2015, Maas et al 2016, Duat Rodriguez et al 2017].

This condition has been described in nine families and in three individuals who have an apparently *de novo* pathogenic variant in *ATP1A3* [Demos et al 2014, Duat Rodriguez et al 2017]. Onset and progression of optic atrophy and sensorineural hearing loss are not well characterized. While the course and severity of deficits can vary considerably, there appears to be progression over time.

Pathophysiology

Neuropathology specimens from persons with RDP show changes in neuronal pathways, suggesting involvement of cerebral and cerebellar connections necessary for motor control [Oblak et al 2014].

Genotype-Phenotype Correlations

Review of published studies has shown that the same pathogenic variant may lead to different phenotypes (e.g., RDP in one family but AHC in another), suggesting that *ATP1A3*-related disorders truly represent a continuum of phenotypes [de Carvalho Aguiar et al 2004, Zanotti-Fregonara et al 2008, Heinzen et al 2012, Roubergue et al 2013, Boelman et al 2014, Rosewich et al 2014b, Yang et al 2014, Viollet et al 2015].

AHC. Individuals with AHC and the pathogenic variant p.Glu815Lys may have earlier onset of symptoms and greater motor and cognitive impairment, and more often experience status epilepticus and respiratory paralysis [Sasaki et al 2014b, Yang et al 2014, Panagiotakaki et al 2015, Viollet et al 2015].

Intermediate and atypical phenotypes

- Intermediate phenotypes, often with onset in the childhood years, have also been reported in individuals with the following pathogenic variants: p.Gly358Asp, p.Arg756His, p.Gly867Asp, p.Asp923Asn, and p.Glu951Lys [Anselm et al 2009, Brashear et al 2012b, Roubergue et al 2013, Rosewich et al 2014a, Sasaki et al 2014a, Panagiotakaki et al 2015, Pereira et al 2015, Termsarasab et al 2015, Jaffer et al 2017].

- Childhood-onset schizophrenia with long-standing mild motor delays, selective mutism, and aggression was reported in a child age six years who was heterozygous for the p.Val129Met variant [Smedemark-Margulies et al 2016].
- One individual with catastrophic infantile-onset epileptic encephalopathy who died at age 16 months had a novel heterozygous p.Gly358Val variant in *ATP1A3*. Another individual with epilepsy, episodic prolonged apnea, postnatal microcephaly, and severe developmental delays had a novel heterozygous p.Ile363Asn variant in *ATP1A3* [Paciorkowski et al 2015].
- Rapid-adult-onset ataxia with profound dysarthria and progressive cerebellar degeneration was reported in a single individual with a *de novo* heterozygous p.Gly316Ser pathogenic variant [Sweadner at al 2016].
- Approximately 12 individuals with different pathogenic variants in the amino acid residue p.Arg756 [Yano et al 2017] have atypical features that may represent a definable phenotype that is distinct from RDP, AHC, and CAPOS:
    - All affected individuals had an episodic course with fever-induced encephalopathy as a key defining feature. Varying associated motor deficits including hypotonia, paresis, weakness, ataxia, dystonia, and dysphagia were described.
    - For those with more prominent ataxia, the name "relapsing encephalopathy with cerebellar ataxia" (designated RECA) has been proposed [Dard et al 2015, Hully et al 2017].
    - Those whose primary feature is weakness have been given the designation of FIPWE: fever-induced paroxysmal weakness and encephalopathy [Yano et al 2017].

Penetrance

RDP. Penetrance is incomplete. The small number of families with RDP studied to date limits the estimate of penetrance; however, several members of the larger reported families have had a heterozygous *ATP1A3* pathogenic variant but no symptoms [Kramer et al 1999, de Carvalho Aguiar et al 2004, Brashear et al 2007].

AHC. Penetrance is even more uncertain, as most *ATP1A3* pathogenic variants reported to date have occurred *de novo*.

CAPOS syndrome. There is no evidence of incomplete penetrance in the families/individuals reported to date [Demos et al 2014, Maas et al 2016, Duat Rodriguez et al 2017].

Nomenclature

The nomenclature of all three well-described phenotypes, based on early clinical categorization, is useful for highlighting symptoms that provide a starting point for diagnosis.

Rapid-onset dystonia-parkinsonism (RDP) was first recognized and named by Dobyns et al [1993] in a girl age 15 years with an abrupt onset of dystonia with severe bulbar symptoms and some signs of parkinsonism (postural instability with bradykinesia). Cerebrospinal fluid levels of dopamine metabolites were low; thus, the term "RDP" was used to describe what later came to be known as "DYT12 caused by pathogenic variants in *ATP1A3*" (DYT12 is also referred to as DYT-ATP1A3; see Dystonia Overview). Because classic signs of Parkinson disease, such as tremor, are unusual in individuals with RDP, the term "parkinsonism" in the designation "RDP" represents a subset of parkinsonian symptoms, and the disorder is classified as combined dystonia (previously called dystonia-plus) [Albanese et al 2013].

Alternating hemiplegia of childhood (AHC) was named for its most striking and diagnostic motor symptom; however, the range of manifestations show it to be a CNS disorder affecting function broadly in various brain circuits, and the disease evolves with age.

***C*erebellar ataxia, *a*reflexia, *p*es cavus, *o*ptic atrophy, and *s*ensorineural hearing loss (CAPOS) syndrome** was named for a unique cluster of symptoms. It is now recognized to share characteristics with RDP and AHC;

however, the fact that to date the same *ATP1A3* pathogenic variant has been observed in the nine unrelated families/individuals, some of whom have a *de novo* pathogenic variant, supports the continued use of the term.

Prevalence

RDP. The prevalence is not known. RDP has been described in individuals and families from the US, Europe, and Asia, and in individuals of African descent [Webb et al 1999, de Carvalho Aguiar et al 2004, Brashear et al 2007, Lee et al 2007, Blanco-Arias et al 2009, Tarsy et al 2010, de Gusmao et al 2016].

AHC. The prevalence has been estimated at 1:1,000,000.

CAPOS syndrome. The prevalence is not known.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are currently reported to be associated with pathogenic variants in *ATP1A3*.

Differential Diagnosis

Rapid-Onset Dystonia-Parkinsonism (RDP)

The physician needs to exclude more common and treatable forms of dystonia-parkinsonism (see Dystonia Overview and Parkinson Disease Overview). Evaluations should include brain MRI and assessment for Wilson disease. Additionally administration of L-dopa should be trialed. In RDP, the MRI is normal and the response to L-dopa is usually minimal or none, with only one reported exception [Termsarasab et al 2015].

The differential diagnosis of RDP includes the following:

- **Dopa-responsive dystonia (DRD)** differs from RDP in the response to L-dopa, which is minimal in those with RDP [Bressman et al 2002, Kabakci et al 2005, Geyer & Bressman 2006], with only one exception [Termsarasab et al 2015]. Furthermore, DRD typically presents in the leg and, in some reports, has been confused with cerebral palsy [Nygaard et al 1994]. "DRD" refers to the following disease entities: autosomal dominant GTPCH1-deficient DRD, autosomal recessive TH-deficient DRD, and autosomal recessive sepiapterin reductase-deficient DRD.
- **DYT1 dystonia**, unlike RDP, has a more caudal to rostral gradient. Onset of DYT1 dystonia in older individuals is rare, whereas RDP may present abruptly after age 30 years.
- **Young-onset parkinsonism.** Individuals with young-onset parkinsonism may have limb dystonia as an early manifestation; however, unlike persons with RDP, they should have a significant and sustained response to L-dopa. Other genetic forms of Parkinson disease including *PINK1* type of young-onset Parkinson disease and parkin type of early-onset Parkinson disease (both inherited in an autosomal recessive manner) should be considered.
- **Possible locus heterogeneity.** Although no other genes or loci are known to be associated with RDP, not all individuals with a phenotype consistent with RDP have an *ATP1A3* pathogenic variant; therefore, it is possible that pathogenic variants in another gene or genes cause RDP.

  A clinical diagnosis of RDP in a kindred of eight individuals who have neither a pathogenic variant in *ATP1A3* nor linkage to chromosome 19q in the DYT12 region is apparently a phenocopy [Kabakci et al 2005]. The proband presented at age six years with overnight onset of dysphonia, dysphagia, orofacial dystonia, and dystonia of all four limbs, findings that meet the diagnostic criteria for RDP. However, five of

the eight affected individuals had renal disease consisting of renal hypoplasia, renal cysts, and/or end-stage kidney disease, which has not been observed in individuals with RDP and *ATP1A3* pathogenic variants.

Alternating Hemiplegia of Childhood (AHC)

Given the early onset and protean neurologic symptoms in affected infants and young children, the differential diagnosis of AHC is unavoidably broad.

It is particularly important early in the diagnostic evaluation of an individual suspected of having AHC to exclude metabolic disorders or vascular syndromes that could benefit from specific therapeutic approaches including: moyamoya disease (OMIM PS252350); mitochondrial disorders such as pyruvate dehydrogenase deficiency (in which spells are typically accompanied by lactic acidosis; see Primary Pyruvate Dehydrogenase Complex Deficiency Overview); and glucose transporter type 1 deficiency syndrome (Glut1-DS), which responds to a ketogenic diet.

The often prolonged episodes of hemiparesis, dystonia, or quadriplegia observed early in the course of AHC are typically not associated with epileptiform activity on EEG – a finding that can help to distinguish AHC from infantile-onset epileptic encephalopathy syndromes (OMIM PS308350).

The paroxysmal nature of symptoms in AHC can mimic inborn errors of neurotransmitter biosynthesis and metabolism such as aromatic L-amino acid decarboxylase deficiency and tyrosine hydroxylase deficiency. Studies of CSF neurotransmitters are necessary to exclude this group of disorders, and ideally should be performed as part of the diagnostic workup early in the clinical course (and prior to *ATP1A3* molecular genetic testing), since alternative treatments for these disorders (e.g., neurotransmitter precursors and pyridoxine or dopamine receptor agonist therapy) are available.

Specific disorders and alternative genetic etiologies to consider include the following:

- Pyruvate dehydrogenase deficiency (OMIM PS312170), MELAS, and other mitochondrial disorders
- Glut1-DS
- Inborn errors of neurotransmitter biosynthesis and metabolism [Sweney et al 2009], especially disorders with deficient dopamine biosynthesis including aromatic L-amino acid decarboxylase deficiency, tyrosine hydroxylase deficiency, dihydropteridine reductase deficiency (OMIM 261630), and 6-pyruvoyl-tetrahydrobiopterin synthase deficiency (OMIM 261640).
- *ATP1A2*-related disorders. Three neurologic diseases associated with pathogenic variants in the homologous gene *ATP1A2* have some overlapping clinical manifestations: infantile seizures, familial hemiplegic migraine (FHM2), and familial common migraine [De Fusco et al 2003, Vanmolkot et al 2003, Bassi et al 2004, Kaunisto et al 2004, Swoboda et al 2004, Ambrosini et al 2005, Todt et al 2005]. Despite the related genes and manifestations of hemiplegia and seizure, *ATP1A2* is expressed mainly in astrocytes instead of neurons [McGrail et al 1991], and the underlying pathophysiology is likely to be different from that of *ATP1A3*-related disorders [Swoboda et al 2004, Jen et al 2007].
- *CACNA1A*-related disorders (familial hemiplegic migraine 1, episodic ataxia 2 (OMIM 108500), and spinocerebellar ataxia type 6)
- SLC1A3 glutamate transporter-related disorders [Jen et al 2005] (episodic ataxia 6; see Hereditary Ataxia Overview)
- *SCN1A*-related disorders [Kim et al 2013, Weller et al 2014] (*SCN1A*-related seizure disorders and familial hemiplegic migraine 3)
- *ADCY5*-related disorders [Westenberger et al 2017], which include familial dyskinesia with facial myokymia (OMIM 606703)

Locus heterogeneity in AHC is strongly suggested by the identification of infants and children with a phenotype meeting the classic clinical criteria for AHC but in whom no apparent pathogenic variant involving *ATP1A3* or its locus have been identified.

In several large studies of individuals with features of AHC [Panagiotakaki et al 2015, Viollet et al 2015], 82%-85% had pathogenic variants in *ATP1A3*, suggesting a different (unknown) genetic cause for disease in approximately 15%-20% of individuals in these cohorts.

CAPOS Syndrome

CAPOS syndrome is unique, and each of its major symptoms has multiple etiologies as separate conditions. The combination of features, particularly sensorineural hearing loss in association with pes cavus deformity, elicits a rather broad differential diagnosis including mitochondrial and peroxisomal disorders.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with an *ATP1A3*-related neurologic disorder, the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 2. Recommended Evaluations Following Initial Diagnosis of *ATP1A3*-Related Neurologic Disorders

System/Concern	Evaluation	Comment
Eyes	Ophthalmologist consultation & OCT for eval of optic atrophy	For persons w/CAPOS
Ears	Hearing specialist consultation & audiogram to evaluate for sensorineural hearing loss	For persons w/CAPOS
Cardiovascular	EKG & echocardiogram to evaluate for cardiac conduction abnormalities & cardiomyopathy; consider referral to cardiologist.	For persons w/AHC
Musculoskeletal	Assessment for pes cavus	For persons w/CAPOS
Neurologic	EEG if seizures are suspected	For persons w/RDP & AHC
	Sleep apnea	Baseline polysomnogram
Miscellaneous/ Other	Neuropsychological testing to evaluate cognitive or memory problems	For persons w/RDP & AHC. Questionnaires to prompt treating clinicians to elicit history & observations relevant to disease symptoms & mgmt are available; see Resources.
	Consultation w/clinical geneticist &/or genetic counselor	All phenotypes

AHC = alternating hemiplegia of childhood; CAPOS = *c*erebellar ataxia, *a*reflexia, *p*es cavus, optic atrophy, and *s*ensorineural hearing loss; OCT = optical coherence tomography; RDP = rapid-onset dystonia-parkinsonism

Treatment of Manifestations

Table 3. Treatment of Manifestations in Individuals with *ATP1A3*-Related Neurologic Disorders

Manifestation/Concern	Treatment	Considerations/Other
Optic atrophy	Visual aids	Referral to ophthalmologist
Sensorineural hearing loss	Standard treatment	See Hereditary Hearing Loss and Deafness Overview.

Table 3. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Sleep apnea	CPAP or BiPAP; ENT eval for tonsillectomy/ adenoidectomy	
Cardiac arrhythmia &/or cardiomyopathy	Standard treatment	Referral to cardiologist
Feeding difficulties or dysphagia	Standard therapy; gastrostomy tube if required for severe dysphagia	Persons w/RDP
Motor dysfunction	PT &/or OT eval	All phenotypes
Dysarthria	Speech therapy	
Seizure disorder	Standard treatment	All phenotypes. Seizure care plan (w/provision of rescue therapy for prolonged seizures if indicated) strongly recommended
Acute spasms or attacks	Chloral hydrate or other sleep-inducing medication (persons w/AHC)	For either recurrent brief or more prolonged tonic or dystonic episodes associated w/ alterations in consciousness; low threshold for suspicion of seizure activity
Dystonia	Benzodiazepines, dopamine agonists, or levo-dopa may be helpful.	All phenotypes; may be severe
Ataxia	Physical therapy	All phenotypes
Mood disorder, substance abuse, &/or psychosis	Psychotherapy & standard pharmacotherapy	Persons w/RDP
Developmental delay	Early referral for developmental support / special education; may incl PT, OT, speech therapy, &/or cognitive therapy	Consider referral to neurodevelopmental specialist.

AHC = alternating hemiplegia of childhood; OT = occupational therapy; PT = physical therapy; RDP = rapid-onset dystonia-parkinsonism

Prevention of Primary Manifestations

Note: Pallidal deep brain stimulation has not been effective [Deutschländer et al 2005; Kamm et al 2008; Brücke et al 2014; Brashear A, personal communication].

Prevention of Secondary Complications

Table 4. Prevention of Primary Manifestations in Individuals with *ATP1A3*-Related Neurologic Disorders

Manifestation/Concern	Prevention	Considerations/Other
Spasms or attacks	Trial of high-dose benzodiazepines persons w/RDP & AHC)	No systematic study of benzodiazepine therapy has been published.
	Flunarizine (persons w/AHC) [1, 2]	Abrupt withdrawal of flunarizine has been assoc w/deterioration in clinical status. [3]
	Topiramate [4] (persons w/AHC)	
	Ketogenic diet (persons w/AHC)	3 persons responded to a ketogenic diet. [5]
	Sleep (persons w/AHC)	Adult: place in a quiet, dark room. Child: put down for a nap.

Table 4. continued from previous page.

Manifestation/Concern	Prevention	Considerations/Other
Avoidance of triggers	See Agents/Circumstances to Avoid.	

1. Flunarizine has been examined in a few small series of affected individuals and is reported to decrease the frequency and/or severity of the episodic dystonic and/or plegic episodes [Silver & Andermann 1993, Sasaki 2001, Pisciotta et al 2017].
2. Flunarizine has remained the most commonly prescribed therapy for prophylaxis of episodic neurologic dysfunction in AHC for more than two decades.
3. Sweney et al [2009], Sasaki et al [2014a]
4. Jiang et al [2006], Chi et al [2012]
5. Ulate-Campos et al [2014], Vila-Pueyo et al [2014], Roubergue et al [2015], Pisciotta et al [2017]

When dystonia is present, physical therapy to prevent contractures in the hands and feet is appropriate.

Surveillance

RDP. Monitor for evidence of the following:

- Dysphagia, which (rarely) requires use of a feeding tube
- Psychiatric symptoms
- Seizures, which are reported in some individuals following acute onset of RDP

AHC. Monitor for evidence of seizures, which occur over time in a large proportion of affected individuals.

CAPOS syndrome. Monitor for evidence of swallow dysfunction to reduce the risk of aspiration.

Agents/Circumstances to Avoid

At-risk family members and asymptomatic individuals with an *ATP1A3* pathogenic variant are cautioned to avoid alcohol and excessive exercise.

Infections and fever are also common triggers; while practical preventive strategies are lacking, unnecessary exposure should be avoided. There is no known reason to avoid vaccinations.

RDP. Triggers associated with the abrupt onset of RDP that should be avoided include (but are not limited to) the following:

- Alcohol
- Fever
- Psychological stress (e.g., childbirth)
- Excessive exercise (e.g., running track)

AHC. Triggers associated with inducing paroxysmal episodes in AHC [Sweney et al 2009] include the following:

- Psychological stress
- Emotional excitement
- Environmental stressors: bright light (sunlight or fluorescent lighting), excessive heat or cold, situations associated with excessive noise, crowds
- Water exposure in the form of bathing, swimming, shampooing
- Certain foods or odors: chocolate, food dyes
- Missed meals
- Excessive or atypically strenuous exercise (e.g., walking farther than usual, use of a playground swing)
- Illness
- Irregular sleep, missing a nap, delayed bedtime

CAPOS syndrome. Febrile illness can trigger an episode of ataxic encephalopathy and/or weakness. Pregnancy can also trigger worsening of symptoms in women with CAPOS syndrome [Chang et al 2018].

Evaluation of Relatives at Risk

It is appropriate to evaluate the at-risk family members of an affected individual in order to identify as early as possible those who should avoid triggers such as alcohol and excessive exercise (see Agents/Circumstances to Avoid).

Evaluations can include the following:

- Molecular genetic testing if the pathogenic variant in the family is known
- Neurologic evaluation if the pathogenic variant in the family is not known

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

Pregnancy Management

The pregnancy of a woman should be monitored for symptoms of RDP, onset of which has followed childbirth in some (not all) women who are heterozygous for an *ATP1A3* pathogenic variant.

In principle, abortion or cesarean section could be sufficiently stressful to trigger an episode.

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

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 information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Levodopa and dopamine agonists usually provide little benefit, but are an important part of the diagnostic evaluation.

There is no known way to prevent the abrupt onset of symptoms in RDP. During the abrupt onset, no acute treatment other than symptomatic relief of dystonia is available.

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

ATP1A3-related neurologic disorders are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- A proband with an *ATP1A3*-related neurologic disorder may have an affected parent.
  - Many individuals diagnosed with a relatively less severe *ATP1A3*-related neurologic disorder (e.g., RDP or CAPOS) inherited an *ATP1A3* pathogenic variant from an affected parent [de Carvalho Aguiar et al 2004, Demos et al 2014]. In some families, an affected individual may inherit an *ATP1A3* pathogenic variant from a heterozygous, asymptomatic parent; this is more frequently observed when the affected individual has RDP.
  - Very rarely, an individual with a more severe *ATP1A3*-related neurologic disorder (e.g., AHC) inherited an *ATP1A3* pathogenic variant from an affected parent.
- A proband with an *ATP1A3*-related neurologic disorder may have the disorder as the result of a *de novo* pathogenic variant (i.e., neither parent is heterozygous for the *ATP1A3* pathogenic variant).
  - *De novo* pathogenic variants are common in RDP.
  - CAPOS syndrome is known to have resulted from a *de novo* pathogenic variant in at least three individuals [Demos et al 2014, Rosewich et al 2014a, Maas et al 2016].
  - AHC is usually the result of a *de novo* pathogenic variant.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant (i.e., neither parent is known to be affected with an *ATP1A3*-related neurologic disorder) include obtaining a detailed medical and family history, examination by a movement disorder specialist, and molecular genetic testing of both parents for the *ATP1A3* pathogenic variant identified in the proband.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (germline mosaicism has been reported [Hully et al 2017]).
- Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation or reduced penetrance (reduced penetrance is seen in RDP but has not been reported in CAPOS syndrome; penetrance in AHC is currently unknown). Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations and genetic testing have been performed.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of a proband is affected and/or has an *ATP1A3* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. Sibs who inherit the *ATP1A3* pathogenic variant typically share the same phenotypic features as the proband; however, reduced penetrance (see Penetrance) and intrafamilial variability have been observed. In one family, affected individuals were described as having typical and atypical AHC (i.e., intermediate phenotypes between AHC and RDP) [Roubergue et al 2013]. The occurrence of both mild and severe forms of *ATP1A3*-related neurologic disorders have been reported in the same family.

- If the parents have not been tested for the *ATP1A3* pathogenic variant but are clinically unaffected, sibs of a proband are still at increased risk for an *ATP1A3*-related neurologic disorder because of the possibility of reduced penetrance in a heterozygous parent (see Penetrance) or the possibility of parental germline mosaicism (germline mosaicism has been reported [Hully et al 2017]).

Offspring of a proband. Each child of an individual with RDP, AHC, or CAPOS syndrome has a 50% chance of inheriting the *ATP1A3* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *ATP1A3* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the *ATP1A3* pathogenic variant in the family.

Issues unique to RDP. Because of the sudden onset of RDP, at-risk individuals may become hypervigilant about symptoms. Serious psychological issues have been observed in families [Brashear et al 2012a].

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

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

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *ATP1A3* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. 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.

- **Alternating Hemiplegia of Childhood Foundation (AHCF)**
  Phone: 313-663-7772
  Email: AHCFoundation@ahckids.org

www.ahckids.org

- **Cure AHC**
  Phone: 919-488-4217
  Email: info@cureahc.org
  www.cureahc.org
- **Dystonia Medical Research Foundation**
  Phone: 312-755-0198; 800-377-DYST (3978)
  Fax: 312-803-0138
  Email: dystonia@dystonia-foundation.org
  Rapid-Onset Dystonia Parkinsonism
- **American Parkinson Disease Association (APDA)**
  Phone: 800-223-2732
  Fax: 718-981-4399
  Email: apda@apdaparkinson.org
  www.apdaparkinson.org
- **Parkinson's Foundation**
  Phone: 800-4PD-INFO (473-4636)
  Email: contact@parkinson.org
  www.parkinson.org
- **Alternating Hemiplegia of Childhood Registry**
  Phone: 617-726-4878
  Fax: 617-724-9620
  AHC Clinical Research Registry
- **Global Dystonia Registry**
  www.globaldystoniaregistry.org

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. ATP1A3-Related Neurologic Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ATP1A3	19q13.2	Sodium/potassium-transporting ATPase subunit alpha-3	ATP1A3 database	ATP1A3	ATP1A3

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 ATP1A3-Related Neurologic Disorders (View All in OMIM)

128235	DYSTONIA 12; DYT12
182350	ATPase, Na+/K+ TRANSPORTING, ALPHA-3 POLYPEPTIDE; ATP1A3
601338	CEREBELLAR ATAXIA, AREFLEXIA, PES CAVUS, OPTIC ATROPHY, AND SENSORINEURAL HEARING LOSS; CAPOS
614820	ALTERNATING HEMIPLEGIA OF CHILDHOOD 2; AHC2

Molecular Pathogenesis

Virtually all pathogenic variants that have been studied experimentally make one-residue changes to the protein and reduce activity, Na^+ affinity, or the stability of the protein. There is a tendency for high inhibition with stable protein to manifest as AHC, while pathogenic variants associated with RDP retain some activity or result in poor protein expression [reviewed in Heinzen et al 2014].

The Na,K-ATPases convert metabolic energy by moving Na^+ ions out of the cell and K^+ ions into the cell, restoring the ion gradients reduced by the activity of ion channels and Na^+-dependent carriers. In the central nervous system (CNS), the Na,K-ATPase is harnessed for reuptake of glutamate and other transmitters, extracellular K^+ buffering, extrusion of Ca^{2+} by Na^+:Ca^{2+} exchange, and the regulation of cell volume. Because it transports three Na^+ ions out of the cell for every two K^+ ions transported in, it is electrogenic and makes a small direct hyperpolarizing contribution to membrane potential.

Na,K-ATPase has three types of subunits (alpha, beta, and FXYD), and each subunit has multiple isoforms.

- The catalytic alpha subunit has three isoforms (alpha 1, 2, and 3) that are expressed in the CNS by three distinct genes [Moseley et al 2003]. Although it is found in a few peripheral cell types, the alpha 3 isoform is expressed exclusively in neurons in the CNS [McGrail et al 1991].
- Three beta subunits required for Na,K-ATPase function are also expressed in the CNS.
- The FXYD subunit regulates and modifies the properties of the complex; at least three FXYD subunits are expressed in the CNS.

A review [Heinzen et al 2014] includes information on animal models of rapid-onset dystonia-parkinsonism.

Gene structure. *ATP1A3* comprises 23 exons; NM_152296.4 is the predominant transcript. Additional transcripts have been described; for a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Several common coding SNPs are reported in dbSNP.

Pathogenic variants

- **RDP.** To date, at least 20 missense or small indel variants have been described as causative of RDP in both familial cases and simplex cases (resulting from a *de novo* pathogenic variant) [Heinzen et al 2014, Rosewich et al 2014b]. The variant most frequently reported in RDP is p.Thr613Met (~26% both *de novo* and familial occurrence) [de Carvalho Aguiar et al 2004, Brashear et al 2007, Lee et al 2007, McKeon et al 2007, Barbano et al 2012].
- **AHC.** To date, pathogenic variants reported in individuals with the classic AHC phenotype are largely different from those reported with RDP; however, some overlap exists.

  More than 85 pathogenic variants have been reported to result in an AHC phenotype. Most affected individuals have a *de novo* pathogenic variant; however, at least two familial cases with autosomal dominant inheritance have been reported as well as affected identical twins. Three pathogenic variants – p.Asp801Asn (~40%), p.Glu815Lys (~20%), and p.Gly947Arg (~10%) – account for more than two thirds of the *de novo* pathogenic variants observed to date [Panagiotakaki et al 2015, Viollet et al 2015].
- **CAPOS syndrome.** All reported families and individuals with CAPOS syndrome have the same unique missense variant, p.Glu818Lys [Duat Rodriguez et al 2017].

Table 5. *ATP1A3* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.385G>A	p.Val129Met	NM_152296.4 NP_689509.1
c.946G>A	p.Gly316Ser	

Table 5. continued from previous page.

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1073G>T	p.Gly358Val	
c.1073G>A	p.Gly358Asp	
c.1088T>A	p.Ile363Asn	
c.1838C>T	p.Thr613Met	
c.2266C>T	p.Arg756Cys	
c.2267G>A	p.Arg756His	
c.2267G>T	p.Arg756Leu	
c.2401G>A	p.Asp801Asn	
c.2443G>A	p.Glu815Lys	
c.2452G>A	p.Glu818Lys	
c.2600G>A	p.Gly867Asp	
c.2767G>A	p.Asp923Asn	
c.2839G>A or C	p.Gly947Arg	
c.2851G>A	p.Glu951Lys	

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.

Normal gene product. *ATP1A3* encodes the alpha 3 subunit of the sodium/potassium-transporting ATPase (Na,K-ATPase), which comprises 1,013 amino acid residues.

Abnormal gene product. Both functional studies and structural analysis of the alpha 3 subunit of the Na,K-ATPase suggest that missense variants impair enzyme activity or stability [de Carvalho Aguiar et al 2004, Heinzen et al 2012]; however, it is not known whether this loss of function occurs by haploinsufficiency or dominant-negative effects.

Functional biochemical studies with several pathogenic variants associated with the RDP phenotype all show reduced Na^+ affinity suggesting that defects in the handling of Na^+ may be a major factor in the development and pathology of RDP [Rodacker et al 2006, Blanco-Arias et al 2009, Einholm et al 2010].

Chapter Notes

Author Notes

Wake Forest School of Medicine: Rapid-Onset Dystonia-Parkinsonism

To obtain up-to-date help, a report of possible diagnosis should be made to one of the AHC or RDP organizations listed in Resources. There, contacts with experienced clinicians can be found as well as information about known pathogenic variants, and novel pathogenic variants can be considered. For AHC, parent organizations in several countries provide advice and support, raise funding for research, and hold family meetings.

Novel variants and novel symptoms associated with *ATP1A3* variants should also be reported to these organizations. The identification of non-pathogenic genetic variants is also possible in patients with other disease etiologies, and is important to arrive at a correct diagnosis. Equally important are reports of patients with

typical manifestations but without a pathogenic variant in *ATP1A3*, who might have a pathogenic variant in a second causative gene.

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- 22 February 2018 (ma) Comprehensive update posted live
- 6 November 2014 (me) Comprehensive update posted live; title changed
- 13 September 2012 (ab/tb) Revision: alternating hemiplegia of childhood added as a genetically related disorder
- 25 August 2011 (me) Comprehensive update posted live
- 19 March 2009 (cd) Revision: sequence analysis available clinically
- 7 February 2008 (me) Review posted live
- 5 October 2007 (ab) Original submission

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