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Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016.

ATP1A3-Related Neurologic Disorders

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Initial Posting: February 7, 2008; Last Update: November 6, 2014.

Summary

Clinical characteristics. The spectrum of *ATP1A3*-related neurologic disorders includes rapid-onset dystonia-parkinsonism (RDP), alternating hemiplegia of childhood (AHC), and *c*erebellar ataxia, *a*reflexia, *p*es cavus, *o*ptic atrophy, and sensorineural hearing loss (CAPOS) syndrome. While early reports emphasized the distinctness of RDP and AHC, it is increasingly evident that these conditions represent a spectrum related to mutation of *ATP1A3*. Because only ten individuals from three families and one individual with a *de novo* mutation have been described with CAPOS syndrome to date, its phenotype is less defined; however, some features overlap with RDP and AHC as well.

- RDP is characterized by abrupt onset of dystonia with parkinsonism (primarily bradykinesia and postural instability); a clear rostrocaudal (face>arm>leg) topological gradient of involvement; bulbar involvement; and absence of response to an adequate trial of L-dopa therapy. 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. Anxiety, depression, and seizures have been reported. Age of onset is four to 55 years.
- 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 develop in the majority of those affected, including oculomotor apraxia, ataxia, choreoathetosis, dystonia, parkinsonism, and cognitive and behavioral dysfunction; more than 50% develop epilepsy in addition to their episodic movement disorder phenotype.

- CAPOS syndrome (a mnemonic for cerebellar ataxia, areflexia, optic atrophy, and sensorineural hearing loss) is characterized by episodes of ataxic encephalopathy and/or weakness after a febrile illness. Onset is between ages six months and five years. Some acute symptoms resolve; disease progression and severity vary.

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

Management. *Treatment of manifestations:*

- RDP. High-dose benzodiazepines in some, and standard treatment for seizures, dysphagia, and depression and anxiety.
- AHC. Avoiding triggers; reducing the frequency and/or severity of recurrent paroxysmal episodes with medication (e.g., flunarizine, topiramate) or by sleep (either natural or induced with medications such as benzodiazepines or chloral hydrate). Standard treatment of seizures.
- CAPOS syndrome. Treatment of manifestations apart from hearing and visual aids has not been reported. Management includes physical therapy to prevent contractures and monitoring of swallow function to reduce the risk for aspiration.

Agents/circumstances to avoid:

- RDP. Triggers including alcohol, fever, psychological stress, 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

Genetic counseling. *ATP1A3*-related neurologic disorders are inherited in an autosomal dominant manner. *ATP1A3* mutations may be inherited or *de novo*. In AHC, *de novo* mutations are more common than inherited; in both RDP and CAPOS syndrome both inherited and *de novo* mutations 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.

GeneReview Scope

***ATP1A3*-Related Neurologic Disorders: Included Disorders** [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. Disorders associated with genes other than *ATP1A3* are not addressed in this *GeneReview*.

Diagnosis

Suggestive Findings

Rapid-onset dystonia-parkinsonism (RDP) should be considered in individuals with the following clinical features [Brashear et al 2007]:

- Abrupt onset of dystonia with features of parkinsonism over a few minutes to 30 days [Dobyns et al 1993]
- A clear rostrocaudal (face>arm>leg) topological gradient of involvement
- Prominent bulbar findings on examination
- Absence of response to an adequate trial of L-dopa therapy (e.g., carbidopa/levodopa 25/100 one pill 3x/day)
- Family history consistent with autosomal dominant inheritance, although *de novo* mutations are common [Anselm et al 2009, Blanco-Arias et al 2009, Tarsy et al 2010].

Additional features that suggest RDP:

- Minimal or no tremor at onset
- Occasional mild limb dystonia prior to the abrupt onset of dystonia
- Triggers (e.g., running, childbirth, emotional stress, or alcoholic binges) associated with the abrupt onset of symptoms
- Stabilization of symptoms within a month
- Rare "second onsets" or abrupt worsening of symptoms later in life
- Minimal improvement overall, but with limited improvement in gait

Non-motor features of RDP:

- Cognitive impairment [Cook et al 2014]
- Psychiatric illnesses including psychosis [Brashear et al 2012a]

Although most people with RDP present with at least some of these typical features, exceptions have included:

- Onset in infancy
- Onset over age 60 years
- Onset of seizures after appearance of motor symptoms

Alternating hemiplegia of childhood (AHC). Diagnostic criteria for a clinically definite diagnosis of AHC (see Note):

- Onset of symptoms before age 18 months
- Paroxysmal disturbances including tonic or dystonic spells, oculomotor abnormalities, and autonomic phenomena during hemiplegic episodes or in isolation
- Repeated attacks of hemiplegia involving either side of the body
- Episodes of bilateral hemiplegia or quadriplegia either at the onset or as generalization of a hemiplegic episode
- Immediate disappearance of symptoms upon sleeping (symptoms may later resume after waking)
- Evidence of developmental delay 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 Moya-moya); and (3) EEG during prolonged episodes of hemiplegia or dystonia does not provide an alternative explanation for episodes.

Other associated features in some individuals with AHC:

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

CAPOS syndrome. Suggestive findings:

- Episodes of ataxic encephalopathy and/or weakness after a febrile illness
- Onset in infancy or childhood
- Cerebellar ataxia
- Areflexia
- Progressive optic atrophy
- Progressive sensorineural hearing loss

Other associated features in some individuals with CAPOS syndrome:

- Abnormal eye movements
- Pes cavus
- Dysphagia
- Autistic traits
- Seizures
- Dystonia
- Cognitive dysfunction

Establishing the Diagnosis

The diagnosis of an *ATP1A3*-related neurologic disorder is established when a heterozygous pathogenic variant is detected in *ATP1A3* (encoding the alpha 3 subunit of the Na,K-ATPase) (Table 1).

- One genetic testing strategy is sequence analysis of *ATP1A3.*
- An alternative genetic testing strategy is use of a multi-gene panel that includes *ATP1A3* and other genes of interest (see Differential Diagnosis). Note: The genes included and the methods used in multi-gene panels vary by laboratory and over time.

Table 1.

Summary of Molecular Genetic Testing Used in *ATP1A3*-Related Neurologic Disorders

Gene [1]	Test Method	Proportion of Probands with a Pathogenic Variant Detectable by This Method		
		RDP	**AHC**	**CAPOS**
ATP1A3	Sequence analysis of the coding region [2]	20/53 [3]	~80%	4/4
	Deletion/duplication analysis [4]	Not tested [5]	Not tested [5]	Not tested [5]

1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants detected in this gene.
2. Sequence analysis detects variants that are benign, likely benign, of unknown significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exonic or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
3. Sequence analysis identified pathogenic variants in 20 of 53 families referred with "possible" RDP, including 14 cases with *de novo* mutation [Brashear, personal observation].
4. Testing that identifies exonic or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
5. To date there have been no reports of exonic or whole-gene deletions/duplications as a cause of *ATP1A3*-related neurologic disorders.

Clinical Characteristics

Clinical Description

Rapid-Onset Dystonia-Parkinsonism (RDP)

The study of the clinical manifestations of RDP has focused on dystonia/parkinsonism [Dobyns et al 1993, Brashear et al 1996, Brashear et al 1997, Brashear et al 1998b, Kramer et al 1999, Pittock et al 2000, Linazasoro et al 2002, de Carvalho Aguiar et al 2004, Zaremba et al 2004, Kamphuis et al 2006, Lee et al 2007, McKeon et al 2007, Kamm et al 2008, Zanotti-Fregonara et al 2008, Anselm et al 2009, Blanco-Arias et al 2009, Svetel et al 2010, Tarsy et al 2010].

The clinical presentation of RDP includes the following:

- Rapid onset of dystonia with parkinsonism (primarily bradykinesia and postural instability) over hours to days to weeks
- 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) patients
- Absence of other features including pill-rolling tremor, diurnal fluctuation, and responsiveness to standard medications for parkinsonism

To date, all known affected individuals have sought medical attention after developing motor symptoms. Of those with

motor symptoms and an *ATP1A3* mutation, most presented with a rostrocaudal topological gradient, rapid onset in less than 30 days, and no response to dopaminergic medications. Many had an identifiable trigger, such as fever, physiologic stress, or alcohol consumption. One individual had antecedent parkinsonism; at least two had fluctuating symptoms before the deficit became permanent.

Motor findings. The clinical stages of RDP include: antecedent 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. One individual initially had one year of parkinsonism, not dystonia, followed by abrupt onset of oromandibular dystonia with dysarthria.

Primary onset in individuals with an identified *ATP1A3* mutation 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; however, 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 re-examined 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.

Non-motor features include mood disorders, substance abuse, and psychosis. 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 1998b, Brashear et al 2012b].

Alternating Hemiplegia of Childhood (AHC)

Initial descriptions of AHC emphasized the characteristic paroxysmal motor manifestations and noted its similarity to migraine in terms of specific triggers and response to sleep [Verret & Steele 1971, Krägeloh & Aicardi 1980].

AHC is a complex neurodevelopmental syndrome which 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.

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], and Heinzen et al [2014].

Paroxysmal neurologic symptoms include the following:

- Ocular movement abnormalities (monocular or binocular nystagmus, intermittent eso- or exotropia, skew deviation, ocular bobbing, ocular flutter)
- Hemiparesis or hemiplegia which can alternate from side to side
- Quadriparesis or quadriplegia
- Unilateral tonic or dystonic posturing of one or more limbs, or generalized dystonic posturing
- Autonomic manifestations including unilateral or bilateral pupillary dilatation, flushing, pallor affecting one limb or hemibody
- 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:

- 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:

- Speech and language delay
- Behavioral outbursts, impulsivity
- Aggression
- Cognitive delay or intellectual disabilities
- Mood disorders

CAPOS Syndrome

CAPOS syndrome has been described to date in three families and one individual with a *de novo* mutation. It presents in infancy or childhood with cerebellar ataxia after a fever, and eventually a characteristic set of symptoms. Symptoms during the acute febrile encephalopathy have included 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. Other features include areflexia, pes cavus, progressive sensorineural hearing loss, and optic atrophy [Nicolaides et al 1996, Demos et al 2014].

Features common to all known patients with CAPOS include cerebellar ataxia, areflexia, progressive optic atrophy,

and sensorineural hearing loss. Features seen in one or more affected individuals include abnormal eye movements (n=5), pes cavus (n=3), dysphagia (n=2), autistic traits (n=2), brief seizures during acute illness (n=1), dystonia (n=1), and cognitive dysfunction (n=1) [Demos et al 2014].

Onset and progression of optic atrophy and sensorineural hearing loss are not well characterized but appear to progress over time. Only three of the affected individuals examined to date were older than age 22 years. Motor impairment ranged from mild difficulties with balance to severely ataxic gait.

CNS Studies in the *ATP1A3*-Related Neurologic Disorders

Brain imaging (MRI, CT)

- **RDP.** Normal
- **AHC.** Early in the course of the disease, typically normal. Later in the disease course, more subtle abnormalities (including diffuse cerebral atrophy and/or isolated cerebellar atrophy, or mesial temporal sclerosis) described in a small number of patients [Sweney et al 2009, Sasaki et al 2014a].
- **CAPOS syndrome.** Normal [Nicolaides et al 1996, Demos et al 2014]

Brain function studies

- **RDP**
  - Position emission tomography(PET) studies using the dopamine transporter imaging agent [^{11}C]β-CFT did not show a decrease in dopamine reuptake sites [Brashear et al 1999].
  - Striatal [123I]-FP-CIT uptake in one individual with RDP with a previously undescribed *ATP1A3* mutation was just within the normal range. [99mTc]-HMPAO scan was also normal [Zanotti-Fregonara et al 2008].
  - Transcranial sonography in an individual with a previously undescribed *ATP1A3* mutation revealed bilateral hyperechogenicity of the substantia nigra, the significance of which is unknown [Svetel et al 2010].
- **AHC.** SPECT scans performed during prolonged episodes of hemiplegia typically demonstrate hypometabolism on the hemisphere opposite the side of paralysis, in contrast to the hyperperfusion seen associated with epileptic activity [Dangond et al 1997].

Cerebral blood flow

- **RDP.** Cerebral blood flow was similar in persons with RDP when compared with age-matched controls [Brashear et al 1999].
- **AHC.** Magnetic resonance angiography (MRA) studies examining cerebral blood flow in the setting of acute hemiplegic episodes have failed to demonstrate significant vascular flow abnormalities [Sweney et al 2009].

CSF neurotransmitter studies

- **RDP.** Cerebrospinal fluid (CSF) concentration of the dopamine metabolite homovanillic acid (HVA) which was low in one symptomatic individual with an *ATP1A3* mutation increased after L-dopa treatment, but not in another individual with the same mutation, and did not correlate with clinical improvement. In addition, an asymptomatic individual who was heterozygous for an *ATP1A3* pathogenic variant also had low CSF HVA levels. Thus, based on data currently available, CSF HVA levels are not diagnostic [Brashear et al 1998a].

- **AHC.** CSF studies including neurotransmitter metabolite studies are usually normal.
- **CAPOS syndrome**. CSF concentration of neurotransmitter metabolites has not been reported.

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

Genotype-phenotype correlations for the three identified phenotypes (RDP, AHC, and CAPOS syndrome) are complex.

- 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 pathogenic variant c.2767G>A (encoding p.Asp923Asn) is the only variant reported in both RDP and AHC [Roubergue et al 2013].
- One study found that patients 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].
- The same heterozygous *ATP1A3* missense mutation c.2452G>A (p.Glu818Lys) was reported in all individuals with CAPOS syndrome (3 unrelated families and 1 individual with a *de novo* mutation) [Rosewich et al 2014c].
- Intermediate phenotypes have also been reported [Anselm et al 2009, Brashear et al 2012b, Rosewich et al 2014a, Sasaki et al 2014a], consistent with the spectrum of phenotypes observed to date.

Genotype-phenotype correlations with RDP were reported by Brashear et al [2007] based on *ATP1A3* sequence analysis in 49 persons from 21 families referred with "possible" RDP; see Table 2 (pdf). Pathogenic variants were identified in 36 persons from ten families, including three that were *de novo* and one in a single individual whose family members were not tested. No pathogenic variants were found in 13 persons from 11 families. Several additional individuals with similar clinical features are also included in Table 2.

Comparison of onset, topological gradient (i.e., rostrocaudal or vice versa), and presence of bulbar symptoms, tremor, and pain in individuals with and without pathogenic variants in *ATP1A3* revealed the following:

- All 36 individuals with rapid-onset ($p=0.002$), rostrocaudal topological gradient ($p<0.001$) and bulbar symptoms ($p<0.001$) had a pathogenic variant. Note: These three findings also characterized one of 13 persons who did not have a pathogenic variant. Unlike the 36 individuals in whom a pathogenic variant was found, this individual responded to anticholinergic therapy, making it likely that the findings in this case represent a phenocopy.
- None of the 36 individuals with a pathogenic variant reported tremor ($p=0.003$) or severe pain ($p=0.051$).
- Four of the 13 individuals who did not have a pathogenic variant reported tremor at onset; two of 11 reported pain (data available on 9 only). The presence of pain and tremor in an affected individual appears to signal decreased likelihood of a pathogenic variant in *ATP1A3*. Note: It is not clear if this is an absolute distinction, as tremor was reported later in life in a small number of affected individuals with pathogenic variants from two families.

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 were asymptomatic [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 three families reported to date [Demos et al 2014].

Nomenclature

The nomenclature of all three disorders, 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 15-year-old girl 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 mutation of *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 dystonia-plus (combined dystonia).

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 three unrelated families and one individual with a *de novo* mutation 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 Korea, and in an individual of African-Caribbean descent [Webb et al 1999, de Carvalho Aguiar et al 2004, Zaremba et al 2004, Brashear et al 2007, Lee et al 2007, Kamm et al 2008, Zanotti-Fregonara et al 2008, Anselm et al 2009, Blanco-Arias et al 2009, Svetel et al 2010, Tarsy et al 2010, Pekmezovic et al 2009].

AHC. The prevalence of the classic AHC phenotype has been estimated at 1 in 1,000,000.

CAPOS syndrome. The prevalence of CAPOS syndrome is not known

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Possible alternative loci. It is unclear whether mutation of genes at other loci is also causative of the classically described rapid-onset dystonia-parkinsonism (RDP) or alternating hemiplegia of childhood (AHC) phenotypes, but it is highly probable.

- **RDP.** 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* mutation; therefore, it is possible that mutation of another gene or genes causes RDP. For example, in a German family in which eight members had RDP, none had a mutation in *ATP1A3* and none showed linkage to the *ATP1A3* locus on chromosome 19, suggesting the presence of at least one additional locus for RDP [Kabakci et al 2005]. Of note, five of the eight affected members had concurrent renal disease, which has not been seen in individuals with an *ATP1A3* mutation.
- **AHC.** 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 within whom no apparent mutation involving the ATP1A3 gene or locus have been identified.

Locus heterogeneity is unknown for *c*erebellar ataxia, *a*reflexia, *p*es cavus, *o*ptic atrophy, and *s*ensorineural hearing loss (CAPOS) syndrome.

Three neurologic diseases associated with mutations 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 diseases.

RDP. The presence of tremor at onset of symptoms, a reversed rostrocaudal topological gradient, and significant limb pain exclude the diagnosis of rapid-onset dystonia-parkinsonism (RDP) [Brashear et al 2007].

The physician needs to exclude more common and treatable forms of dystonia-parkinsonism (see Dystonia Overview and Parkinson Disease Overview). Testing should include brain MRI, a trial of L-dopa, *TOR1A* (*DYT1*) testing, and evaluation for Wilson disease. In RDP, the MRI is normal and the response to L-dopa is minimal or none.

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]. Furthermore, DRD typically presents in the leg and, in some reports, has been confused with cerebral palsy [Nygaard et al 1994].
- **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 recently described genetic forms of Parkinson disease including *PINK1* type of young-onset Parkinson disease and parkin type of juvenile Parkinson disease should be considered.
- **Other.** A kindred of eight individuals with RDP who have neither mutation in *ATP1A3* nor linkage to chromosome 19q in the DYT12 region is an apparent 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 which 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 renal disease, which has not been observed in individuals with RDP and *ATP1A3* mutations.

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, such as

moya-moya disease, mitochondrial disorders including pyruvate dehydrogenase deficiency (in which spells are typically accompanied by lactic acidosis), and GLUT1 deficiency, 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, which can help to distinguish AHC from infantile-onset epileptic encephalopathy syndromes.

The paroxysmal nature of symptoms in AHC can mimic inborn errors of neurotransmitter biosynthesis and metabolism such as aromatic L-amino acid decarboxylase (AADC) deficiency and tyrosine hydroxylase (TH) 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:

- Pyruvate dehydrogenase deficiency, MELAS, and other mitochondrial disorders
- Glut1 deficiency syndromes [Rotstein et al 2009]
- Inborn errors of neurotransmitter biosynthesis and metabolism [Sweney et al 2009], especially disorders with deficient dopamine biosynthesis including AADC, TH, DHPR or PPTS deficiency
- *ATP1A2*-related disorders [Swoboda et al 2004, Jen et al 2007]
- *CACNA1A*-related disorders : familial hemiplegic migraine 1, episodic ataxia 2, and spinocerebellar ataxia type 6 (SCA6)
- SLC1A3 glutamate transporter-related disorders [Jen et al 2005] (episodic ataxia 6)
- *SCN1A*-related disorders [Kim et al 2013, Weller et al 2014] (*SCN1A*-related seizure disorders and familial hemiplegic migraine 3)

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 a known *ATP1A3*-related neurologic disorder, the following evaluations are recommended:

Rapid-onset dystonia-parkinsonism (RDP)

- Brain imaging to exclude stroke
- EEG to evaluate possibility of seizures
- Neuropsychological testing to evaluate cognitive or memory problems
  Note: Questionnaires to prompt treating clinicians to elicit history and observations relevant to disease symptoms and management may be obtained from organizations included in Resources.

Alternating hemiplegia of childhood (AHC)

- Brain imaging to exclude stroke
- EEG to evaluate possibility of seizures
  Note: Questionnaires to prompt treating clinicians to elicit history and observations relevant to disease symptoms and management may be obtained from organizations included in Resources.

Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS) syndrome

- Brain imaging to evaluate the cerebellum
- EMG for areflexia and assessment for pes cavus to evaluate for peripheral neuropathy
- Ophthalmology consult and OCT (optical coherence tomography) for evaluation of optic atrophy
- Audiogram and hearing specialist consultation to evaluate sensorineural hearing loss

Treatment of Manifestations

For all phenotypes

- Critical care: standard management of manifestations such as seizure or apnea
  Note: A seizure care plan, with provision of rescue therapy for prolonged seizures if indicated, is strongly recommended for those in whom epilepsy has been confirmed by either electrodiagnostic testing or highly suggestive clinical features.
- Occupational therapy to maximize motor function
- Speech therapy for dysarthria

RDP. In a few patients with RDP decreased spasms have been noted with high-dose benzodiazepines. Dosing should be judged by the physician on an individual basis.

Standard therapies for the following are appropriate:

- Seizures
- Dysphagia
- Psychotherapy for mood disorder (such as depression and anxiety), substance abuse, and/or psychosis

Two individuals treated with deep brain stimulation [Kamm et al 2008] did not show marked improvement [A Brashear, personal communication].

AHC. Medical treatment generally involves the following [Neville & Ninan 2007]:

- **Episode prophylaxis** (avoiding triggers; reducing the frequency and/or severity of recurrent paroxysmal episodes by sleep – either natural or induced with daily prophylactic medications):
  - **Prophylactic medications**
    - Flunarizine. Symptomatic benefit in reducing the frequency and/or severity of the recurrent paroxysmal episodes of neurologic dysfunction has been reported with flunarizine [Silver & Andermann 1993, Sasaki 2001]. Flunarizine has been examined in a few small series of patients, and is reported to decrease the frequency and/or severity of the episodic dystonic and/or plegic episodes. In spite of the lack of well-designed placebo-controlled trials, flunarizine has remained the most commonly prescribed therapy for prophylaxis of episodic neurologic dysfunction in AHC for more than two decades. Note that abrupt withdrawal of the medication has been associated with

deterioration in clinical status [Sweney et al 2009, Sasaki et al 2014a].

- Topiramate is another commonly prescribed agent for prophylaxis [Jiang et al 2006, Chi et al 2012].

- **Sleep.** Placing the affected individual in a quiet, dark room or putting a child down for a nap can help alleviate severe episodes and/or promote an earlier recovery.

- **Acute attack management** with use of various rescue medications including:
  - Benzodiazepines, which are commonly used and reported to be of some benefit in increasingly the tolerability of episodes, especially for severe or prolonged dystonic episodes
  - Chloral hydrate
  - Other sleep inducers

A low threshold for suspicion of seizure activity is critical, particularly in the setting of either recurrent brief or more prolonged tonic or dystonic episodes associated with alterations in consciousness or apparent awareness of their environment. Epilepsy management utilizes existing anticonvulsants.

Recently, two separate reports described patients with AHC who responded to a ketogenic diet [Roubergue et al 2014, Ulate-Campos et al 2014].

CAPOS syndrome. Symptomatic treatment includes hearing and visual aids.

Prevention of Secondary Complications

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

Surveillance

Patients with RDP need to be monitored for evidence of:

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

Patients with AHC need to be monitored for evidence of seizures which occur over time in a large proportion of affected individuals.

Patients with CAPOS syndrome need to be monitored for evidence of swallow dysfunction in order 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 or excessive exercise.

Infections and fever also are common triggers, and although practical prevention 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
- Excessive exercise (such as 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, or situations associated with excessive sound, 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.

Evaluation of Relatives at Risk

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 caesarean section could be sufficiently stressful to also be a trigger.

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

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

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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face 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

- Many individuals diagnosed with RDP or CAPOS syndrome have an affected parent.
- A proband with an *ATP1A3*-related neurologic disorder may have the disorder as the result of *de novo* mutation.
    - *De novo* mutations are common in RDP: RDP resulted from *de novo* mutation in eight of seventeen reported probands [Brashear et al 2007, Kamm et al 2008, Anselm et al 2009, Blanco-Arias et al 2009, Tarsy et al 2010].
    - AHC is usually the result of *de novo* mutation.
    - CAPOS syndrome is known to have resulted from *de novo* mutation in one of the three reported families (no samples were available to test for *de novo* mutation in the other 2 families) and the simplex case [Demos et al 2014, Rosewich et al 2014a].
- Recommendations for the evaluation of parents of a proband with apparent *de novo* mutation 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.
- 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, s/he 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 or has an *ATP1A3* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%; however, the actual risk of being affected may be lower due to reduced penetrance in RDP and variable expressivity in CAPOS syndrome.
- Affected sibs usually share the same phenotypic features, although in one family reported, affected individuals were described as having typical and atypical AHC (i.e., intermediate phenotypes between AHC and RDP) [Roubergue et al 2013]. No families have been reported with typical AHC and typical RDP in different individuals have been reported.
- The sibs of a proband with clinically unaffected parents are still at increased risk for the disorder because of the possibility of reduced penetrance in a parent (RDP) and variable expressivity (CAPOS syndrome). Parents who are clinically unaffected should undergo molecular testing to determine if they have the *ATP1A3* pathogenic variant identified in the proband.

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 identified in the proband.

Other family members of a proband

- The risk to other family members depends on the status of the proband's parents.
- If a parent is affected or has an *ATP1A3* pathogenic variant, his or her 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 apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant, the variant is likely *de novo*. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

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

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration can be given to banking DNA of affected individuals.

Prenatal Testing

If the *ATP1A3* pathogenic variant has been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing of this gene or custom prenatal testing.

Requests for prenatal testing for conditions such as *ATP1A3*-related neurologic disorders are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be an option for some families in which the *ATP1A3* pathogenic variant has been identified.

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)**
  2000 Town Center
  Suite 1900
  Southfield MI 48075
  Phone: 650-796-1910

Fax: 650-365-5798
Email: lynn@ahckids.org
ahckids.org

- **Alternating Hemiplegia of Childhood International Alliance**
  ahcia.org
- **Dystonia Medical Research Foundation**
  One East Wacker Drive
  Suite 2810
  Chicago IL 60601-1905
  Phone: 800-377-3978 (toll-free); 312-755-0198
  Fax: 312-803-0138
  Email: dystonia@dystonia-foundation.org
  Rapid-Onset Dystonia Parkinsonism
- **American Parkinson Disease Association (APDA)**
  135 Parkinson Avenue
  Staten Island NY 10305
  Phone: 800-223-2732 (toll-free); 718-981-8001
  Fax: 718-981-4399
  Email: apda@apdaparkinson.org
  www.apdaparkinson.org
- **National Parkinson Foundation**
  1501 Northwest 9th Avenue
  Bob Hope Road
  Miami FL 33136-1494
  Phone: 800-327-4545 (toll-free); 305-243-6666
  Fax: 305-243-6073
  Email: contact@parkinson.org
  www.parkinson.org
- **Global Dystonia Registry**
  www.globaldystoniaregistry.org
- **US-International Alternating Hemiplegia of Childhood Registry**
  Email: sharon@ahckids.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	HGMD
ATP1A3	19q13.2	Sodium/potassium-transporting ATPase subunit alpha-3	ATP1A3 database	ATP1A3

Data are compiled from the following standard references: gene from HGNC; chromosome locus, locus name, critical region,

complementation group from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD) 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 Genetic Pathogenesis

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

Gene structure. *ATP1A3* comprises 23 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

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

Pathogenic allelic variants

- **RDP.** To date, 14 missense or small indel variants have been described as causative of RDP in both familial cases and simplex cases (resulting from *de novo* mutation) [reviewed in Heinzen 2014, Rosewich et al 2014b]. See Table 2 (pdf) for additional information.
- The variant c.2767G>A encoding p.Asp923Asn is the only pathogenic variant reported in both RDP and AHC. In one family, individuals with either AHC or RDP have been reported [Roubergue et al 2013].
- **AHC.** To date, mutations reported in individuals with the classic AHC phenotype are largely different from those reported with RDP; however, some overlap exists.

More than 30 pathogenic variants have been reported to result in an AHC phenotype in more than 150 individuals. Most affected individuals have *de novo* mutation; however, at least two familial cases with autosomal dominant inheritance have been reported as well as affected identical twins. Three pathogenic variants account for more than two thirds of the *de novo* mutations observed to date [Heinzen et al 2012, Rosewich et al 2012, Ishii et al 2013, Roubergue et al 2013, Hoei-Hansen et al 2014, Sasaki et al 2014a, Ulate-Campos et al 2014]. See Table 2 for additional information.

- **CAPOS syndrome.** The ten individuals from three families with CAPOS syndrome and the single case resulting from *de novo* mutation all have the same unique *ATP1A3* missense variant, p.Glu818Lys [Demos et al 2014, Rosewich et al 2014c].

Normal gene product. *ATP1A3* encodes the alpha 3 subunit of the sodium/potassium-transporting ATPase (Na,K-ATPase), which comprises 1013 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 mutations impair enzyme activity or stability [de Carvalho Aguiar et al 2004]; however, it is not known whether this loss of function occurs by haploinsufficiency or dominant-negative effects.

Functional biochemical studies with several pathogenic mutations 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].

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Chapter Notes

Author Notes

RDP Study

To obtain up-to-date help, a report of possible diagnosis should be made to one of the AHC or RDP organizations listed above under Resources. There, contacts with experienced clinicians can be found as well as information about known mutations, and novel mutations can be considered. For AHC, there are parent organizations in several countries that 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 mutation in *ATP1A3*, who might have a mutation in a second causative gene.

Acknowledgments

The authors would like to thank Dr. William B Dobyns for his contributions to this research and all of the families and patients who participated in this research.

Revision History

- 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 to live Web site
- 5 October 2007 (ab) Original submission

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