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The Expanding Spectrum of Neurological Phenotypes in Children With *ATP1A3* Mutations, Alternating Hemiplegia of Childhood, Rapid-onset Dystonia-Parkinsonism, CAPOS and Beyond

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Abstract

BACKGROUND—*ATP1A3* mutations have now been recognized in infants and children presenting with a diverse group of neurological phenotypes, including Rapid-onset Dystonia-Parkinsonism (RDP), Alternating Hemiplegia of Childhood (AHC), and most recently, Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy, and Sensorineural hearing loss (CAPOS) syndrome.

METHODS—Existing literature on *ATP1A3*-related disorders in the pediatric population were reviewed, with attention to clinical features and associated genotypes among those with RDP, AHC, or CAPOS syndrome phenotypes.

RESULTS—While classically defined phenotypes associated with AHC, RDP, and CAPOS syndromes are distinct, common elements among *ATP1A3*-related neurological disorders include characteristic episodic neurological symptoms and signs that vary in severity, duration, and frequency of occurrence. Affected children typically present in the context of an acute onset of paroxysmal, episodic neurological symptoms ranging from oculomotor abnormalities, hypotonia, paralysis, dystonia, ataxia, seizure-like episodes, or encephalopathy. Neurodevelopmental delays or persistence of dystonia, chorea, or ataxia after resolution of an initial episode are common, providing important clues for diagnosis.

CONCLUSIONS—The phenotypic spectrum of *ATP1A3*-related neurological disorders continues to expand beyond the distinct yet overlapping phenotypes in patients with AHC, RDP, and CAPOS syndromes. *ATP1A3* mutation analysis is appropriate to consider in the diagnostic algorithm for any child presenting with episodic or fluctuating ataxia, weakness or dystonia whether they manifest persistence of neurological symptoms between episodes. Additional work is needed to better identify and classify affected patients and develop targeted treatment approaches.

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alternating hemiplegia of childhood; rapid-onset dystonia-Parkinsonism; CAPOS syndrome; ataxia; dystonia; hemiplegia; *ATP1A3*; sodium potassium ATPases

Introduction

Na^+,K^+-adenosine triphosphatases (ATPases, sodium/potassium pumps) are P-type cation transport proteins that play a critical role in maintaining electrochemical gradients for Na^+ and K^+ across the plasma membrane. The energy for transporting ions is derived from hydrolysis of ATP, exchanging three molecules of Na^+ for every two molecules of K^+. The alpha subunit is the catalytic subunit, and three of the four alpha isoforms (alpha1, 2, and 3) are expressed in the nervous system.[1] Mutations of the alpha2 subunit (*ATP1A2*), expressed predominantly in astrocytes, are associated with familial hemiplegic migraine (FHM) type 2.[2] Mutations affecting the alpha3 subunit, *ATP1A3*, expressed in neurons, are associated with an expanding phenotypic spectrum of distinct yet overlapping neurological phenotypes, including rapid-onset dystonia Parkinsonism (RDP), alternating hemiplegia of childhood (AHC), and cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS) syndromes. The purpose of this review is to explore the recently expanding and diverse range of phenotypes associated with mutations in *ATP1A3*, to review phenotype-genotype associations, and to consider how new observations can help guide diagnostic and treatment approaches in the infant or child presenting with an acute onset of paroxysmal and fluctuating neurological symptoms and signs ranging from paralysis to ataxia to dystonia and beyond.

Dobyns et al.[3] provided the first evidence of a role for *ATP1A3* in human disease pathogenesis. They described a single large family with dominant transmission of a syndrome they called RDP.[4] Affected individuals manifested acute or subacute onset of rapidly evolving dystonia and Parkinsonism in adolescence or adulthood after a provocative stressor. Although acute progression of dystonia and bradykinesia were the initial manifestations of the disease, a more variable, slower decline in function was sometimes observed.[5] RDP was initially identified in its familial form, but sporadic cases have been increasingly identified.[6]

AHC is a unique and complex neurodevelopmental syndrome first described by Verret and Steele in 1971. It was initially thought to be a migraine variant because of the unique features of stimulus sensitivity-induced paroxysmal alternating hemiplegia in association with other paroxysmal neurological and autonomic symptoms.[7,8] The underlying pathophysiologic mechanism remained elusive until recently, when de novo mutations in *ATP1A3* proved causative in most cases.[9–12] After the discovery that mutations in *ATP1A3* were a frequent cause of AHC, and that AHC and RDP were in fact allelic disorders, an increasing number of patients with intermediate, nonclassic phenotypes have been described. However, AHC and RDP in their classic forms have, to date, almost exclusively nonoverlapping mutations in *ATP1A3*.

Another unique disorder recently associated with a mutation in *ATP1A3* is CAPOS syndrome (OMIM #601338). In 1996, Nicolaides et al.[13] described a mother and two children with relapsing, early onset cerebellar ataxia in association with areflexia, pes cavus deformity, optic atrophy, and sensorineural hearing loss, features for which the syndrome was ultimately named. However, they also observed an abrupt onset of neurological symptoms, predominantly hypotonia and ataxia, in association with a stressor such as a febrile illness, with onset of first episodes ranging from 9 to 16 months. Recently, three additional families were described with a single, identical *ATP1A3* missense mutation.[14]

In the following, we review the classical clinical presentations and neurological features of each disorder and relevant data on genotype-phenotype correlations. We compare and contrast onset and evolution (including nonmotor features), pathophysiologic mechanisms, differential diagnostic considerations, and current therapeutic approaches.

Clinical features

Alternating hemiplegia of childhood

Verret and Steele initially described a series of eight children with onset of intermittent episodes of alternating hemiplegia in association with a variety of other characteristic but more variable neurological features including developmental delay, choreoathetosis, and dystonia.[7] Diagnostic criteria were subsequently refined[8,15] and are listed in the following. Table 1 compares and contrasts key features of classically defined AHC and RDP.

Classic diagnostic criteria:

1. Onset of symptoms before 18 months of age
2. Paroxysmal disturbances including tonic or dystonic spells, oculomotor abnormalities, and autonomic phenomena during hemiplegic episodes or in isolation
3. Repeated attacks of hemiplegia involving either side of the body
4. Episodes of bilateral hemiplegia or quadriplegia as generalization of a hemiplegic episode or bilateral from the beginning
5. Immediate disappearance of symptoms upon sleeping, which later may resume after waking
6. Evidence of developmental delay and neurological abnormalities including choreoathetosis, dystonia, or ataxia

In reports summarizing series of patients with AHC diagnosed using classic criteria,[16–18] age of onset for both dystonic and hemiplegic episodes occurred in the majority in the first year of life. The frequency, duration, and severity of episodes are highly variable, occurring from multiple times per day to every few days and lasting from minutes to days or even weeks with a waxing and waning course.[16] Abnormal eye movements, including monocular nystagmus,[19] frequently occur in association with other types of episodes or in isolation and in some instances may be the first manifestations of the disease.[16]

A hallmark of the disorder, aside from the pathognomonic, often migratory, uni- and bi-lateral plegic episodes, is a pronounced sensitivity to environmental and physiologic triggers. Provocative factors have included physical activity, specific foods, light sensitivity, water exposure, and medications.[16] Cessation, or significant improvement, of paroxysmal neurological deficits occurs with sleep, although at times only transiently.[17] Anecdotally, this feature often serves as the only window during which families can provide food, water, and medications for affected children, because bulbar and respiratory function can be impaired during episodes, making oral intake unsafe. Additional persistent neurological comorbidities are frequently present and are increasingly penetrant with age, including gross and fine motor delay, cognitive and intellectual deficits, dysarthria, ataxia, chorea, and dysautonomia.[16,17,20]

Before the identification of mutations in *ATP1A3*, diagnostic studies performed to identify a specific biomarker or metabolic abnormality in AHC proved unrevealing or inconsistent.[21–25] Neuroimaging studies are usually normal, at least early in the course of the disease, although nonspecific cortical atrophy, mesial temporal sclerosis, or cerebellar atrophy are present in some patients, and the presence of such abnormalities may depend on age and phenotypic severity. Single-photon emission computed tomography or fludeoxyglucose positron emission tomography scans performed during a hemiplegic episode have demonstrated hypometabolism in the contralateral hemisphere. Computed tomography or magnetic resonance imaging-based angiograms are generally normal.

Evolution of paroxysmal neurological symptoms and signs over time is typical, with a waxing and waning quality; infants and young children may demonstrate a predominance of hypotonic and plegic episodes. Spell types may evolve over time to become more tonic or dystonic in nature. Epilepsy is increasingly penetrant with age and is ultimately diagnosed in about 50% of patients. An epilepsy diagnosis is ultimately often made on the basis of characteristic clinical manifestations, that is, episodic generalized tonic-clonic convulsions, partial complex seizures, or status epilepticus. However, a delay in diagnosis often occurs because clinicians as well as parents initially discount that novel spells may represent seizure activity because most children had previously had extensive evaluation to exclude epileptiform activity in association with a variety of paroxysmal neurological, ocular, and autonomic abnormalities. Early on, brief tonic or dystonic episodes in infancy may be indistinguishable from observed epileptic events in disorders such as Dravet syndrome; older patients may suffer from recurrent, at times severe episodes of status epilepticus. Recent investigation into genotype-phenotype correlations among patients with AHC[26] has provided some evidence that certain mutations may be more frequently associated with severe adverse outcomes, including status epilepticus, cognitive impairment, and persistent severe motor disability.

Although paroxysmal and fluctuating motor symptoms and signs are often the earliest and most severe neurological manifestation in children with AHC, impaired cognition, executive function, and mood and behavioral issues become increasingly evident with age. As they reach adolescence, episodic hemiplegia, dystonia, and abnormal eye movements sometimes wane in frequency and severity, whereas concerns regarding behavior and autonomy become increasingly significant.[27] Unfortunately, only a few published studies to date help

clarify specific details regarding the range and severity of neuropsychologic deficients in patients with AHC,[28] although multiple studies cite the nearly universal co-occurrence of both motor and cognitive developmental delay in children meeting clinical diagnostic criteria for the syndrome.[16–18,20]

Rapid-onset dystonia Parkinsonism

Dobyns et al.[3] were the first to report on a large family with 12 affected individuals, with acute or subacute onset of dystonia and Parkinsonism ranging in age from 15 to 45 years. Initial symptoms evolve over hours to days, often ultimately including symptoms such as postural instability and bradykinesia.[5] Paroxysmal oculomotor abnormalities were also described within the family, including oculogyric crisis. In all instances, cognition remained normal.

As awareness of RDP has increased, the phenotypic spectrum has expanded.[29] RDP, also known as DYT12, is an autosomal dominant disorder with variable penetrance (and some reports of de novo mutations), typically with onset in the second to third decade of life after a physiologic stressor.[29] Dystonia remains the hallmark feature, often manifesting with significant, early bulbar involvement (dysarthria and hypophonia), that progresses in a rostrocaudal, frequently asymmetric fashion.[29] Subsequent stabilization typically occurs after the initial, acute progression, but “secondary onset” with later recurrence of rapid functional loss, has been observed.[29] Tremor is generally absent in RDP.[29]

Core diagnostic criteria:

1. Abrupt onset of dystonia with features of Parkinsonism over a few minutes to 30 days
2. A clear rostrocaudal (face > arm > leg) gradient of involvement
3. Prominent bulbar findings on examination
4. Absence of response to an adequate trial of L-dopa therapy
5. Family history consistent with autosomal dominant inheritance and more recently via de novo mutations

Additional helpful features:

1. Minimal or no tremor at onset
2. Occasional mild limb dystonia before the abrupt onset of dystonia
3. Triggers (e.g., running, childbirth, emotional stress, or alcoholic binges) associated with the abrupt onset of symptoms
4. Stabilization of symptoms within a month
5. Rare “second onsets” or abrupt worsening of symptoms later in life
6. Minimal improvement overall, but with limited improvement in gait

The true burden of RDP as a distinct syndrome in the pediatric population is uncertain. In one instance, a previously well 4-year-old infant suffered mild head trauma followed rapidly

by eye movement abnormalities, mutism, prominent hypotonia, and subsequent persistent but fluctuating dystonia.[30] Over time, unprovoked episodes of whole body flaccidity and/or stiffness and bulbar impairment were observed. In an Irish family with RDP, one family member was observed to have recurrent attacks of provoked hemidystonia from the age of 4 years that continued well into adulthood.[31] However, in an increasing number of cases, the distinction between AHC and RDP phenotypes is less clear, with earlier onset and a broader range of paroxysmal neurological symptoms blurring the distinction between the two disorders. For instance, in a family with two affected siblings reported by Brashear et al.[32] in 2012, one child had onset of fluctuating and episodic hypotonia, dysphagia, mutism, dystonia, and ataxia at 9 months of age, whereas the other exhibited early hypotonia and motor delays followed by episodic slurred speech, ataxia, drooling, and dysarthria.

The cognitive and nonmotor aspects of RDP in adults have been the focus of recent investigation.[33–35] In the same Irish family observed previously, features of social phobia, anxiety, depression, and schizoid tendencies were prominent.[31] In a review of 23 patients with RDP, higher prevalence of mood disorders and psychosis were observed.[33] A separate study with 29 patients with RDP showed consistent impairment in attention, verbal fluency, coding tasks, visual memory, and verbal learning tasks compared with controls, suggesting cognitive impairment as part of the RDP phenotype.[34] Published studies to date assessing detailed cognitive function in AHC are limited, but cognitive impairment is virtually universal among cohorts.

CAPOS syndrome

Nicolaides et al.[13] were the first to report on three patients from a single family in which relapsing, early-onset cerebellar ataxia associated with progressive optic atrophy and sensorineural deafness were shared features. Additionally, all patients had varying degrees of areflexia and pes cavus deformity, ultimately leading to the acronym of CAPOS. More recently, Demos et al.[14] reported on additional families with similar syndromic features, during which a novel mutation in *ATP1A3* was identified. Additional clinical features were described in this limited series of patients and are reviewed in more detail in later sections.

ATP1A3 pathophysiology

Na,K-ATPase is a ubiquitous integral plasma membrane protein which actively exports three Na^+ ions and imports two K^+ ions for each ATP hydrolyzed. It is responsible for maintenance of the transmembrane Na^+ gradient and is also a major determinant of neuronal resting membrane potential. The alpha subunit of the Na/K-ATPase has several isoforms that are expressed in a cell type- and tissue-dependent manner. In adult vertebrates, although kidney cells express mostly alpha1, muscle and glial cells express alpha1 and alpha2 isoforms of Na/K-ATPase. Neurons may express alpha1, alpha2, alpha3, or any combination of these isoforms, and evidence suggests that neuronal type (e.g., neocortical, hippocampal, cerebellar, and so forth) is the determining factor.[36] Neurons of the central and peripheral nervous systems use up to 50% of the energy of ATP hydrolysis just to maintain the operation of this enzyme and transporter.[36]

The specific role of *ATP1A3* gene and its alpha3 isomer in neurophysiologic function continues to be investigated, although it appears to be exclusively expressed in neurons.[37,38] Several studies looking at the regional distribution of the isomer within the brain have shown prominent involvement in the Purkinje cell layer and molecular layer interneurons of the cerebellar cortex,[37,39] ventral horn neurons and interneurons of the spinal cord,[40] and basal ganglia structures,[37] among others. Additionally, *ATP1A3* function is implicated importantly in hippocampal function and memory mechanisms[41] as well as spatial learning, motor activity, and anxiety[42] in mouse models.

The underlying mechanisms of stress sensitivity in both AHC and RDP are unknown. Critical function in maintaining ionic homeostasis has stage-specific developmental impact[43]; however, the role of stress in protein expression and function is unclear. Other channelopathies have similar associations of disrupted membrane function with provoking stimulus, as in variants of FHM.[44] In a study of *ATP1A3* mutant mice, “restraint stress” was found to induce significant deficits in motor coordination and balance, as well as decreased thermal sensitivity and alterations in monoamine metabolism.[38] An impact on function or expression of the cardiac-specific alpha3 isomer[45] could provide an alternative explanation for autonomic dysfunction.

Altered alpha3 subunit expression may play a vital role in the pathogenesis of seizure activity by failing to re-establish resting membrane potential after repetitive action potentials or excitatory synaptic activity.[46–48] This has been posited as an additional explanation as to the underlying cause of abrupt paroxysmal symptoms including dystonia and hemiplegia.[47] The relative infrequency of seizures reported in RDP and the variable epilepsy burden in AHC further highlights the likely contribution of age and developmentally specific protein expression.[43]

Genotype/phenotype correlations

Alternating hemiplegia of childhood

Heterozygous de novo mutations in *ATP1A3* are present in most patients clinically diagnosed with AHC in the initially reported series of patients, ranging from 74% in a mixed European Caucasian cohort to nearly 100% in a Japanese cohort.[9,10,12] The correlation of genotypes with phenotypes across the spectrum of *ATP1A3*-related neurological syndromes, including RDP, AHC, and CAPOS, are listed in Table 2. To date, mutations in AHC, RDP, and CAPOS are largely distinct, with rare exceptions, in part because of the carefully defined clinical criteria differentiating these syndromes. More than three dozen unique mutations have been associated with an AHC phenotype; however, there are clearly “hot spots” for de novo mutations resulting in AHC, because more than 50% of patients reported to date have one of two common mutations, *D801N* or *E815K*. A third mutation, *G947R*, is fairly frequent in European Caucasian cohorts, wherein the same amino acid change is associated with two different missense mutations (Table 2). In addition, two groups have published data supporting that the *E815K* mutation is associated with a more severe phenotype characterized by a neonatal presentation, status epilepticus, more severe delays/deficits in gross motor function, more severe intellectual disability/cognitive impairment, and frequent respiratory failure.[12,26] The observations by Sasaki et al[26] in a Japanese cohort

seem to indicate a more consistently severe phenotype than has been evident in AHC patients with European ancestry, raising questions about the influence of additional modifiers or genetic background and its influence on phenotype. Further studies on ongoing to better characterize these preliminary genotype/phenotype correlations, given the relatively small numbers of subjects.

RDP syndrome

No distinct genotypic influence is clearly evident as yet regarding presentation of RDP symptoms in childhood versus adulthood, although case reports have observed episodic flaccidity in infancy and early childhood as a prodrome to more typical RDP features.[32] This suggests that the type of neurological symptoms may be influenced by developmental maturation of the affected individual at the time of onset. As yet, no novel mutations have been described in children that had not previously been identified, but may change quickly, given that this phenotype was only recently recognized in children.

ATP1A3 is the only gene in which mutations are known to cause RDP[3,29]; however, evidence of locus heterogeneity has been reported in a German family with clinical features of RDP, as well as concurrent renal disease, but no mutation.[6] To date, 12 mutations have been associated with either familial (dominant) or sporadic RDP cases (Table 2).

In all instances in which ATP1A3 mutations have been identified, rapid-onset, rostrocaudal gradient of progression, and bulbar symptoms were reported,[29] whereas in mutation-negative individuals, tremor and pain were more commonly reported at onset.[29] No consistent clinical differences were seen between patients carrying different mutations and patients within a family or across families with the same mutation exhibited variable expressivity.[29]

CAPOS syndrome

A single mutation in *ATP1A3*, c.2452G>A (p.Glu818Lys) has been identified in three unrelated families with CAPOS syndrome.[14] In all three families, onset of symptoms was associated with a febrile illness.[13,14] Age of onset varied between 6 months and 5 years of age.[13,14] All affected individuals had cerebellar ataxia, areflexia, optic atrophy, and sensorineural hearing loss at the most recent examination.[14] Three of ten individuals had pes cavus at the most recent examination.[14] Five of 10 individuals had abnormal eye movements during episodes of ataxia associated with encephalopathy and weakness.[14] Two individuals reported dysphagia during an episode.[14] One individual reported seizures during an episode.[14] Other symptoms either reported or present on examination included dystonia in one individual, urinary symptoms in one individual, cognitive dysfunction in one individual, cardiac arrhythmia in one individual, and autistic traits in two individuals.[14]

The mutation in *ATP1A3* associated with CAPOS syndrome appears to be a recurring de novo mutation in the three families so far identified and is fully penetrant. There have been no reports of asymptomatic carriers. Additional individuals with CAPOS syndrome without a mutation in ATP1A3 have not been reported.[14]

Differential diagnosis

Alternating hemiplegia of childhood

Because of the variable presentation of complex neurological symptoms in AHC, a number of other syndromes must be considered in the differential diagnosis, including FHM syndromes, the episodic ataxias, glutamate transporter disorders, metabolic defects including mitochondrial disorders and pyruvate dehydrogenase deficiency, glucose transporter defects, infantile-onset epileptic encephalopathies, vascular disorders such as moyamoya disease and others.[16,17] Normal neuroimaging and the lack of epileptiform activity on electroencephalography in association with characteristic plegic or tonic episodes early in the course of the disease can help to exclude some of these disorders, along with the absence of characteristic metabolic abnormalities such as elevated plasma lactate or abnormal cerebrospinal fluid to plasma glucose ratio that would support an alternative diagnosis.

The pathognomonic features of alternating hemiplegia in AHC have long been recognized to be similar in phenomenology with the episodic neurological dysfunction reported in FHM type 1 and 2 associated with mutations in *CACNA1A* and *ATP1A2*, albeit with earlier onset, more frequent recurrence and much higher prevalence of additional neurological signs and symptoms. Phenotypes associated with the FHM syndromes have increasingly expanded over the past few years to include episodic encephalopathy, epilepsy, and persistent neurological deficits including intellectual disability and ataxia in some affected individuals and families.[50–53] *ATP1A2* mutations have also been demonstrated in familial epilepsy and hemiplegic migraine syndromes.[54] Patients with mutations in *CACNA1A* have an increasingly broad spectrum of phenotypes, including reports of acute onset of hemiplegic episodes after minor head trauma.[55]

Jen et al.[56] reported a de novo mutation in *SLC1A3* encoding the glutamate transporter EAAT1 in a child reported to have had onset of episodic hypotonia after breast feeding. He subsequently manifested developmental delays, incoordination and episodic ataxia, recurrent hemiplegic episodes associated with headache, and seizures.

Glucose transporter 1 (Glut1) deficiency syndrome is a disorder marked by epilepsy, episodic weakness, delays in psychomotor development, intermittent ataxia, and hypoglycorrhachia and often has paroxysmal and nonparoxysmal symptoms that can substantially overlap with those observed in infants with AHC. Glut1 deficiency is associated with mutations in the *SLC2A1* gene.[57] Studies have demonstrated that mutations in *SLC2A1* are rare in patients presenting in infancy with a more classic AHC phenotype.[58] However, because patients with Glut1 deficiency can improve significantly with treatment with a ketogenic diet, this disorder should always be considered.

SCN1A mutations are frequently identified in instances of severe myoclonic epilepsy of infancy (Dravet syndrome). Early manifestations of hemiclonic/tonic seizures in the setting of a febrile illness may mimic unilateral dystonic episodes of AHC. Electroencephalography is critical in differentiating between the two entities. Recently, *SCN1A* mutations have also been identified in FHM, with onset of hemiplegic episodes as early as 11 years of age in one family.[59]

Benign nocturnal AHC is a disorder characterized by transient and recurrent attacks of hemiplegia without other paroxysmal neurological disorders arising from sleep.[60,61] The occurrence of episodes in sleep, and the lack of more serious comorbid developmental impairments, is usually sufficient to help distinguish this disorder from AHC.

Rapid-onset dystonia Parkinsonism

To date, RDP appears to represent a unique diagnostic entity in adults, as no other disorder shares the specific constellation of features. However, in pediatric patients, disorders associated with dopa-responsive dystonia phenotypes must be considered because phenotypes are highly variable. Exclusion of inborn errors of metabolism, such as Wilson disease, or other early-onset Parkinsonism syndromes, in which limb dystonia may be an early manifestation, is also important because alternative treatments are available.[62] DYT1 dystonia, or early-onset primary dystonia, may share some overlapping features with some of the childhood-onset RDP cases reported to date, although DYT1 typically has a more caudal to rostral gradient of involvement.[63] One should also consider dopa-responsive dystonia syndromes associated with mutations in *GCH1* (Segawa disease), tyrosine hydroxylase deficiency, and sepiapterin reductase deficiency because patients with these disorders may be missed on newborn screening because of the absence of elevated phenylalanine levels. However, paroxysmal onset of symptoms is not typical in these disorders unless patients are exposed to precipitating anti-dopaminergic medications.

Treatment

Alternating hemiplegia of childhood

Therapeutic options in AHC have proved of limited success to date. A variety of treatment strategies targeted toward episode prophylaxis can be helpful in some individuals, including avoidance of specific stressors or triggers, using daily prophylactic medications such as flunarizine or topiramate, or implementing strategies to induce sleep as a management tactic. Medications variably useful in acute attack management include benzodiazepines (administered orally, rectally, or via nasal administration), chloral hydrate, phenobarbitol and other sleep inducers, and antiepileptic agents if appropriate in children with concomitant epilepsy.[64] Behavioral and mood disturbances become increasingly prevalent in later childhood and adolescence, and antipsychotic agents and mood stabilizing medications may be of value. Epilepsy is often reasonably managed with standard antiepileptic agents; however, it is important to try to distinguish nonepileptic from epileptic episodes and treat appropriately.

In children with AHC, flunarizine remains a mainstay of prophylactic therapy,[65,66] although it is not currently Food and Drug Administration approved in the United States and has never been adequately tested in a sufficiently powered placebo-controlled trial; nonetheless, anecdotal reports of benefit are compelling in a disorder with limited treatment options.[16–18] No definitive mechanistic explanation for potential efficacy has been proven, although flunarizine has been demonstrated to block voltage-dependent Na^+- and Ca^{2+}-dependent channels and alters synaptic transmission,[67] and the utility of flunarizine in epilepsy and migraine has been previously documented.[68] A recently published cohort of Japanese

patients suggests a potential protective benefit of the medication in severe cases of AHC, and these investigators have previously reported an abrupt deterioration in the setting of withdrawal of flunarizine in some patients.[26]

A second prophylactic agent increasingly used in AHC is topiramate.[69,70] Like flunarizine, reports of benefit have been largely anecdotal.[16] It too blocks voltage-dependent Na^+ channels; in addition, it is an antagonist of non-N-methyl D-aspartate glutamate and calcium channel receptors and is a carbonic anhydrase inhibitor.

More recently, a case study citing the potential benefit of the ketogenic diet with AHC[71] has been published. However, the utility of this therapy, as well as other non-pharmaceutical interventions (e.g., vagus nerve stimulation, deep brain stimulation), has not been formally studied.

Rapid-onset dystonia Parkinsonism

Therapeutic options in RDP remain limited, and the dystonia has proved markedly resistant to established therapies. Symptomatic treatment of dystonia with benzodiazepines, often at relatively high doses, provides symptomatic relief in some patients. In spite of the observation of a low cerebrospinal fluid level of homovanillic acid in one patient, treatment with L-dopa/carbidopa demonstrated little or no benefit in symptoms, in spite of documented normalization of homovanillic acid levels.[26] Neuro-stimulation via deep brain stimulation has been proposed to be potentially beneficial, but a report of bilateral pallidal stimulation in one patient proved ineffective.[72,73]

Conclusions

The recent discovery that *ATP1A3* mutations are causative in an increasingly diverse group of neurological disorders has shifted our focus to shared features, which may provide further insights into the mechanisms by which the disruption of ATP expression and function causes neurological dysfunction.[49] In AHC and RDP, the mechanisms contributing to the sudden and often stepwise deterioration seen in both disorders remains poorly understood. In AHC, multifaceted neurological symptoms and signs fluctuate more dramatically, and with a wider range of symptoms and signs than in those with RDP, yet shared features of the additional neurological comorbidities, including cognitive impairment, mood and behavioral disorders, dystonia, and bulbar involvement (especially dysarthria), are compelling. Epilepsy, ataxia, and oculomotor apraxia are prevalent in AHC and relatively infrequent in RDP, and this may reflect differences in severity of channel dysfunction or expression, or relate in part to the onset of neurological dysfunction during a period of critical nervous system maturation and development. Genotype phenotype observations can help to facilitate earlier diagnosis and more accurate prognosis for these conditions and allow more carefully designed and thoughtfully conceived treatment trials. However, it is clear that these disorders represent points on a continuum that will continue to expand as new cases are identified. Improved therapeutic options will ultimately arise from an increased understanding of how mutations in *ATP1A3* cause neurological dysfunction and the united efforts of the scientists and clinicians pursuing new and more effective therapies.

References

1. McGrail KM, Phillips JM, Sweadner KJ. Immunofluorescent localization of three Na,K-ATPase isozymes in the rat central nervous system: both neurons and glia can express more than one Na,K-ATPase. J Neurosci. 1991; 11:381–391. [PubMed: 1846906]
2. Benarroch EE. Na+, K+-ATPase: functions in the nervous system and involvement in neurologic disease. Neurology. 2011; 76:287–293. [PubMed: 21242497]
3. Dobyns WB, Ozelius LJ, Kramer PL, et al. Rapid-onset dystonia-parkinsonism. Neurology. 1993; 43:2596–2602. [PubMed: 8255463]
4. de Carvalho Aguiar P, Sweadner KJ, Penniston JT, et al. Mutations in the Na+/K+-ATPase alpha3 gene ATP1A3 are associated with rapid-onset dystonia parkinsonism. Neuron. 2004; 43:169–175. [PubMed: 15260953]
5. Brashear A, Farlow MR, Butler IJ, Kasarskis EJ, Dobyns WB. Variable phenotype of rapid-onset dystonia-parkinsonism. Mov Disord. 1996; 11:151–156. [PubMed: 8684384]
6. Kabakci K, Isbruch K, Schilling K, et al. Genetic heterogeneity in rapid onset dystonia-parkinsonism: description of a new family. J Neurol Neurosurg Psychiatry. 2005; 76:860–862. [PubMed: 15897512]
7. Verret S, Steele JC. Alternating hemiplegia in childhood: a report of eight patients with complicated migraine beginning in infancy. Pediatrics. 1971; 47:675–680. [PubMed: 5089756]
8. Bourgeois M, Aicardi J, Goutieres F. Alternating hemiplegia of childhood. J Pediatr. 1993; 122:673–679. [PubMed: 8496742]
9. Heinzen EL, Swoboda KJ, Hitomi Y, et al. De novo mutations in ATP1A3 cause alternating hemiplegia of childhood. Nat Genet. 2012; 44:1030–1034. [PubMed: 22842232]
10. Rosewich H, Thiele H, Ohlenbusch A, et al. Heterozygous de-novo mutations in ATP1A3 in patients with alternating hemiplegia of childhood: a whole-exome sequencing gene-identification study. Lancet Neurol. 2012; 11:764–773. [PubMed: 22850527]
11. Hoei-Hansen CE, Dali CI, Lyngbye TJ, Duno M, Uldall P. Alternating hemiplegia of childhood in Denmark: clinical manifestations and ATP1A3 mutation status. European J Paediatr Neurol. 2014; 18:50–54. [PubMed: 24100174]
12. Ishii A, Saito Y, Mitsui J, et al. Identification of ATP1A3 mutations by exome sequencing as the cause of alternating hemiplegia of childhood in Japanese patients. PloS One. 2013; 8:e56120. [PubMed: 23409136]
13. Nicolaides P, Appleton RE, Fryer A. Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss: a new syndrome. J Med Genet. 1996; 33:419–421. [PubMed: 8733056]
14. Demos MK, van Karnebeek CD, Ross CJ, et al. A novel recurrent mutation in ATP1A3 causes CAPOS syndrome. Orphanet J Rare Dis. 2014; 9:15. [PubMed: 24468074]
15. Krageloh I, Aicardi J. Alternating hemiplegia in infants: report of five cases. Dev Med Child Neurol. 1980; 22:784–791. [PubMed: 7450304]
16. Sweney MT, Silver K, Gerard-Blanluet M, et al. Alternating hemiplegia of childhood: early characteristics and evolution of a neurodevelopmental syndrome. Pediatrics. 2009; 123:e534–541. [PubMed: 19254988]
17. Mikati MA, Kramer U, Zupanc ML, Shanahan RJ. Alternating hemiplegia of childhood: clinical manifestations and long-term outcome. Pediatr Neurol. 2000; 23:134–141. [PubMed: 11020638]
18. Sakuragawa N. Alternating hemiplegia in childhood: 23 cases in Japan. Brain Dev. 1992; 14:283–288. [PubMed: 1456380]
19. Egan RA. Ocular motor features of alternating hemiplegia of childhood. J Neuroophthalmol. 2002; 22:99–101. [PubMed: 12131468]
20. Panagiotakaki E, Gobbi G, Neville B, et al. Evidence of a non-progressive course of alternating hemiplegia of childhood: study of a large cohort of children and adults. Brain. 2010; 133:3598–3610. [PubMed: 20974617]
21. Kemp GJ, Taylor DJ, Barnes PR, Wilson J, Radda GK. Skeletal muscle mitochondrial dysfunction in alternating hemiplegia of childhood. Ann Neurol. 1995; 38:681–684. [PubMed: 7574469]

22. Kyriakides T, Drousiotou A. No structural or biochemical evidence for mitochondrial cytopathy in a case of alternating hemiplegia of childhood. Ann Neurol. 1994; 36:805–806. [PubMed: 7979233]
23. Nevsimalova S, Dittrich J, Havlova M, et al. Alternating hemiplegia in childhood: a cross-sectional study. Brain Dev. 1994; 16:189–194. [PubMed: 7943602]
24. Wong V, Ho GC, Yeung HW, Ma KM. Alternating hemiplegia syndrome: electroencephalogram, brain mapping, and brain perfusion SPECT scan study in a Chinese girl. J Child Neurol. 1993; 8:221–226. [PubMed: 8409262]
25. Fons C, Campistol J, Panagiotakaki E, et al. Alternating hemiplegia of childhood: metabolic studies in the largest European series of patients. Eur J Paediatr Neurol. 2012; 16:10–14. [PubMed: 21945173]
26. Sasaki M, Ishii A, Saito Y, et al. Genotype-phenotype correlations in alternating hemiplegia of childhood. Neurology. 2014; 82:482–490. [PubMed: 24431296]
27. Save J, Poncelin D, Auvin S. Caregiver's burden and psychosocial issues in alternating hemiplegia of childhood. Eur J Paediatr Neurol. 2013; 17:515–521. [PubMed: 23672836]
28. Shafer ME, Mayfield JW, McDonald F. Alternating hemiplegia of childhood: a study of neuropsychological functioning. Appl Neuropsychol. 2005; 12:49–56. [PubMed: 15788223]
29. Brashear A, Dobyns WB, de Carvalho Aguiar P, et al. The phenotypic spectrum of rapid-onset dystonia-parkinsonism (RDP) and mutations in the ATP1A3 gene. Brain. 2007; 130:828–835. [PubMed: 17282997]
30. Anselm IA. Rapid-onset dystonia-parkinsonism in a child with a novel ATP1A3 gene mutation. Neurology. 2009; 73:400–401. [PubMed: 19652145]
31. Pittock SJ, Joyce C, O'Keane V, et al. Rapid-onset dystonia-parkinsonism: a clinical and genetic analysis of a new kindred. Neurology. 2000; 55:991–995. [PubMed: 11061257]
32. Brashear A, Mink JW, Hill DF, et al. ATP1A3 mutations in infants: a new rapid-onset dystonia-Parkinsonism phenotype characterized by motor delay and ataxia. Dev Med Child Neurol. 2012; 54:1065–1067. [PubMed: 22924536]
33. Brashear A, Cook JF, Hill DF, et al. Psychiatric disorders in rapid-onset dystonia-parkinsonism. Neurology. 2012; 79:1168–1173. [PubMed: 22933743]
34. Cook JF, Hill DF, Snively BM, et al. Cognitive impairment in rapid-onset dystonia-parkinsonism. Mov Disord. 2014; 29(Suppl 3):344–350. [PubMed: 24436111]
35. Barbano RL, Hill DF, Snively BM, et al. New triggers and non-motor findings in a family with rapid-onset dystonia-parkinsonism. Parkinsonism Relat Disord. 2012; 18:737–741. [PubMed: 22534615]
36. Dobretsov M, Stimers JR. Neuronal function and alpha3 isoform of the Na/K-ATPase. Front Biosci. 2005; 10:2373–2396. [PubMed: 15970502]
37. Bottger P, Tracz Z, Heuck A, Nissen P, Romero-Ramos M, Lykke-Hartmann K. Distribution of Na/K-ATPase alpha 3 isoform, a sodium-potassium P-type pump associated with rapid-onset of dystonia parkinsonism (RDP) in the adult mouse brain. J Comp Neurol. 2011; 519:376–404. [PubMed: 21165980]
38. DeAndrade MP, Yokoi F, van Groen T, Lingrel JB, Li Y. Characterization of Atp1a3 mutant mice as a model of rapid-onset dystonia with parkinsonism. Behav Brain Res. 2011; 216:659–665. [PubMed: 20850480]
39. Ikeda K, Satake S, Onaka T, et al. Enhanced inhibitory neurotransmission in the cerebellar cortex of Atp1a3-deficient heterozygous mice. J Physiol. 2013; 591:3433–3449. [PubMed: 23652595]
40. Edwards IJ, Bruce G, Lawrenson C, et al. Na+/K+ ATPase alpha1 and alpha3 isoforms are differentially expressed in alpha- and gamma-motoneurons. J Neurosci. 2013; 33:9913–9919. [PubMed: 23761886]
41. Heo S, Csaszar E, Jung G, Beuk T, Hoger H, Lubec G. Hippocampal levels and activity of the sodium/potassium transporting ATPase subunit alpha-3 (AT1A3) are paralleling memory training in the multiple T-maze in the C57BL/6J mouse. Neurochem Int. 2012; 61:702–712. [PubMed: 22797008]

42. Moseley AE, Williams MT, Schaefer TL, et al. Deficiency in Na,K-ATPase alpha isoform genes alters spatial learning, motor activity, and anxiety in mice. J Neurosci. 2007; 27:616–626. [PubMed: 17234593]
43. Doganli C, Beck HC, Ribera AB, Oxvig C, Lykke-Hartmann K. alpha3Na+/K+-ATPase deficiency causes brain ventricle dilation and abrupt embryonic motility in zebrafish. J Biol Chem. 2013; 288:8862–8874. [PubMed: 23400780]
44. Asghar SJ, Milesi-Halle A, Kaushik C, Glasier C, Sharp GB. Variable manifestations of familial hemiplegic migraine associated with reversible cerebral edema in children. Pediatr Neurol. 2012; 47:201–204. [PubMed: 22883286]
45. Hilgenberg LG, Pham B, Ortega M, et al. Agrin regulation of alpha3 sodium-potassium ATPase activity modulates cardiac myocyte contraction. J Biol Chem. 2009; 284:16956–16965. [PubMed: 19376779]
46. Chu Y, Parada I, Prince DA. Temporal and topographic alterations in expression of the alpha3 isoform of Na+, K(+)-ATPase in the rat freeze lesion model of microgyria and epileptogenesis. Neuroscience. 2009; 162:339–348. [PubMed: 19362129]
47. Azarias G, Kruusmagi M, Connor S, et al. A specific and essential role for Na,K-ATPase alpha3 in neurons co-expressing alpha1 and alpha3. J Biol Chem. 2013; 288:2734–2743. [PubMed: 23195960]
48. Clapcote SJ, Duffy S, Xie G, et al. Mutation I810N in the alpha3 isoform of Na+,K+-ATPase causes impairments in the sodium pump and hyperexcitability in the CNS. Proc Natl Acad Sci U S A. 2009; 106:14085–14090. [PubMed: 19666602]
49. Rosewich H. The expanding clinical and genetic spectrum of ATP1A3-related disorders. Neurology. 2014; 82:945–955. [PubMed: 24523486]
50. Ducros A, Denier C, Joutel A, et al. The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. N Engl J Med. 2001; 345:17–24. [PubMed: 11439943]
51. de Vries B, Stam AH, Beker F, et al. CACNA1A mutation linking hemiplegic migraine and alternating hemiplegia of childhood. Cephalalgia. 2008; 28:887–891. [PubMed: 18498393]
52. Takahashi T, Arai N, Shimamura M, et al. Autopsy case of acute encephalopathy linked to familial hemiplegic migraine with cerebellar atrophy and mental retardation. Neuropathology. 2005; 25:228–234. [PubMed: 16193840]
53. Swoboda KJ, Kanavakis E, Xaidara A, et al. Alternating hemiplegia of childhood or familial hemiplegic migraine? A novel ATP1A2 mutation. Ann Neurol. 2004; 55:884–887. [PubMed: 15174025]
54. Roth C, Freilinger T, Kirovski G, et al. Clinical spectrum in three families with familial hemiplegic migraine type 2 including a novel mutation in the ATP1A2 gene. Cephalalgia. 2014; 34:183–190. [PubMed: 24096472]
55. García Segarra N, Gautschi I, Mittaz-Crettol L, et al. Congenital ataxia and hemiplegic migraine with cerebral edema associated with a novel gain of function mutation in the calcium channel CACNA1A. J Neurol Sci. 2014; 342:69–78. [PubMed: 24836863]
56. Jen JC, Wan J, Palos TP, Howard BD, Baloh RW. Mutation in the glutamate transporter EAAT1 causes episodic ataxia, hemiplegia, and seizures. Neurology. 2005; 65:529–534. [PubMed: 16116111]
57. Rotstein M, Doran J, Yang H, Ullner PM, Engelstad K, De Vivo DC. Glut1 deficiency and alternating hemiplegia of childhood. Neurology. 2009; 73:2042–2044. [PubMed: 19996082]
58. De Grandis E, Stagnaro M, Biancheri R, et al. Lack of SLC2A1 (glucose transporter 1) mutations in 30 Italian patients with alternating hemiplegia of childhood. J Child Neurol. 2013; 28:863–866. [PubMed: 22899793]
59. Weller CM, Pelzer N, de Vries B, et al. Two novel SCN1A mutations identified in families with familial hemiplegic migraine. Cephalalgia. 2014; 34:1062–1069. [PubMed: 24707016]
60. Mangano S, Fontana A, Spitaleri C, Mangano GR. Benign nocturnal alternating hemiplegia of childhood: a new case with unusual findings. Brain Dev. 2013; 36:408–410. [PubMed: 23820111]
61. Wagener-Schimmel LJ, Nicolai J. Child neurology: benign nocturnal alternating hemiplegia of childhood. Neurology. 2012; 79:e161–163. [PubMed: 23109658]

62. Puschmann A. Monogenic Parkinson's disease and parkinsonism: clinical phenotypes and frequencies of known mutations. Parkinsonism Relat Disord. 2013; 19:407–415. [PubMed: 23462481]
63. Fuchs T, Ozelius LJ. Genetics of dystonia. Semin Neurol. 2011; 31:441–448. [PubMed: 22266882]
64. Neville BG, Ninan M. The treatment and management of alternating hemiplegia of childhood. Dev Med Child Neurol. 2007; 49:777–780. [PubMed: 17880649]
65. Silver K, Andermann F. Alternating hemiplegia of childhood: a study of 10 patients and results of flunarizine treatment. Neurology. 1993; 43:36–41. [PubMed: 8423908]
66. Sasaki M. Long-term effect of flunarizine on patients with alternating hemiplegia of childhood in Japan. Brain Dev. 2001; 23:303–305. [PubMed: 11504600]
67. Golumbek PT, Rho JM, Spain WJ, van Brederode JF. Effects of flunarizine on spontaneous synaptic currents in rat neocortex. Naunyn Schmiedebergs Arch Pharmacol. 2004; 370:176–182. [PubMed: 15340775]
68. Pledger GW, Sackellares JC, Treiman DM, et al. Flunarizine for treatment of partial seizures: results of a concentration-controlled trial. Neurology. 1994; 44:1830–1836. [PubMed: 7936231]
69. Jiang W, Chi Z, Ma L, et al. Topiramate: a new agent for patients with alternating hemiplegia of childhood. Neuropediatrics. 2006; 37:229–233. [PubMed: 17177149]
70. Chi LY, Zhao XH, Liu XW, Jiang WJ, Chi ZF, Wang SJ. Alternating hemiplegia of childhood in Chinese following long-term treatment with flunarizine or topiramate. Int J Neurosci. 2012; 122:506–510. [PubMed: 22494152]
71. Roubergue A, Philibert B, Gautier A, et al. Excellent response to a ketogenic diet in a patient with alternating hemiplegia of childhood. JIMD Rep. 2014
72. Calderon DP, Fremont R, Kraenzlin F, Khodakhah K. The neural substrates of rapid-onset dystonia-parkinsonism. Nat Neurosci. 2011; 14:357–365. [PubMed: 21297628]
73. Deutschlander A, Asmus F, Gasser T, Steude U, Botzel K. Sporadic rapid-onset dystonia-parkinsonism syndrome: failure of bilateral pallidal stimulation. Mov Disord. 2005; 20:254–257. [PubMed: 15455448]

TABLE 1

Unique and Shared Features Between AHC and RDP Phenotypes

RDP	AHC	Shared Features
Onset >18 mo	Onset <18 mo, often in neonates, young infants	Virtually no overlap in age of onset in classic forms
Abrupt onset	Abrupt onset	Yes, not as evident in AHC due to onset in young infants
Fluctuating neurological symptoms/signs: dystonia	Fluctuating neurological symptoms/signs: more frequent and diverse spell types including tonic, dystonic, hemiplegic and oculomotor abnormalities	Yes, but hypotonia, hemiplegia, and ataxia common in AHC and children often demonstrate age-dependent evolution in spell types
Persistent neurological deficits: dystonia, bulbar dysfunction, Parkinsonism	Persistent neurological deficits: chorea, bulbar dysfunction, hypotonia, ataxia, oculomotor apraxia, dystonia	Overlapping, yet distinct—varies with age and severity in AHC
Epilepsy (infrequent)	Epilepsy (common) with age-dependent penetrance	Yes, more severe and prevalent in AHC
Cognitive impairment infrequent	Cognitive impairment nearly universal	Yes, more severe and prevalent in AHC
Mood disorders	Mood/behavioral disorders	Yes, often severe in AHC—increasing prevalence with age
Triggers: physical or emotional stressors, i.e., boot camp, binge drinking, childbirth	Triggers: excitement or other strong emotions, sleep deprivation, illness, excessive environmental stimuli—lights, water, sounds	Somewhat broader range of stressors identified, because AHC presents more episodically early in the clinical course; triggers persist in AHC

Abbreviations:

AHC = Alternating hemiplegia of childhood

RDP = Rapid-onset dystonia Parkinsonism

TABLE 2

ATP1A3 Genotypes as They Correlate With RDP, AHC, and CAPOS Phenotypes

Nucleotide Change	Protein Change	Phenotype	Inheritance	Recurrent (Yes/No), Frequency
410C>A	S137Y	AHC	Sporadic	Yes, infrequent
410C>T	S137F	AHC	Sporadic	No
419A>T	Q140L	AHC	Sporadic	No
821T>A	I274N	AHC	Sporadic and familial (dominant)	Yes, infrequent
821T>C	I274T	RDP	Sporadic	No
829G>A	E277K	RDP	Sporadic	Yes, infrequent
965T>A	V322D	AHC	Sporadic	Yes, infrequent
979_981delCTG	L327del	RDP	Sporadic	No
998G>T	C333F	AHC	Sporadic	Yes, infrequent
1003A>C	T335P	AHC	Sporadic	No
1072G>T	G358C	AHC	Sporadic	No
1112T>C	L371P	AHC	Sporadic	No
1838C>T	**T613M***	RDP	Sporadic, familial (dominant)	Yes, most frequent recurrence in RDP, n = 6
2051C>T	S684F	RDP	Sporadic	No
2264G>C	G755A	AHC	Sporadic	No
2263G>A	G755S	AHC	Sporadic	Yes, infrequent
2263G>T	G755C	AHC	Sporadic	Yes, infrequent
2267G>A	R756H	RDP	Sporadic	No
2270T>C	L757P	AHC	Sporadic	No
2273T>G	I758S	RDP	Familial (dominant)	No
2312C>A	T771N	AHC	Sporadic	No
2316C>A	S772R	AHC	Sporadic	No
2318A>G	N773S	AHC	Sporadic	No
2318A>T	N773I	AHC	Sporadic	No
2338T>C	F780L	RDP	Familial (dominant)	No
N/A	D801E	AHC	Sporadic/familial	No (twins)
2401G>A	**D801N**	AHC	Sporadic	Yes, frequent in AHC, n >60 reported
2401G>T	D801Y	RDP	Familial	No

Nucleotide Change	Protein Change	Phenotype	Inheritance	Recurrent (Yes/No), Frequency
2411C>T	T804I	AHC	Sporadic	Yes, infrequent
2415C>G	D805E	AHC	Sporadic	No
2417T>G	M806R	AHC	Sporadic	No
2428A>T	I810F	AHC	Sporadic	No
2429T>G	I810S	AHC	Sporadic	No
2431T>C	S811P	AHC	Sporadic	Yes, infrequent
2443G>A	**E815K**	AHC	Sporadic	Yes, frequent in AHC, n >40 reported
2452G>A	E818K	Capos	Familial (dominant)	Yes, 100% so far
2542+1G>A	Splice site	AHC	Sporadic	Yes, infrequent
2600G>A	G867N	RDP/AHC		No
2755_2757delGTC	V919del	AHC	Sporadic	No
2767G>A	D923N	AHC/RDP	Familial (AHC), sporadic and familial (RDP)	Yes, low frequency, n = 5
2767G>T	D923T	AHC	Sporadic	No
2780G>A	C927Y	AHC	Sporadic	No
2780G>T	C927F	AHC	Sporadic	Yes, infrequent
2781C>G		AHC	Sporadic	No
2839G>A	**G947R**	AHC	Sporadic	Yes, third most frequent for AHC in European Caucasian cohorts, n >10
2839G>C	G947R	AHC	Sporadic	Yes, low frequency, n = 4
2864C>A	A955D	AHC	Sporadic	No
2974G>T	D992Y	AHC	Sporadic	Yes, infrequent
3038_3040dupACT	Y1013dup	RDP	Sporadic	No

Abbreviations:

AHC = Alternating hemiplegia of childhood

CAPOS = Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss

RDP = Rapid-onset dystonia Parkinsonism

* Most frequent recurrent mutations in RDP; most frequent recurrent mutations in AHC; last updated May 4, 2014.