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Episodic Ataxia Type 1

Synonym: EA1

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Summary

Clinical characteristics

Episodic ataxia type 1 (EA1) is a potassium channelopathy characterized by constant myokymia and dramatic episodes of spastic contractions of the skeletal muscles of the head, arms, and legs with loss of both motor coordination and balance. During attacks individuals may experience a number of variable symptoms including vertigo, blurred vision, diplopia, nausea, headache, diaphoresis, clumsiness, stiffening of the body, dysarthric speech, and difficulty in breathing, among others. EA1 may be associated with epilepsy. Other possible associations include delayed motor development, cognitive disability, choreoathetosis, and carpal spasm. Usually, onset is in childhood or early adolescence.

Diagnosis/testing

Diagnosis is based on clinical findings, an electrophysiologic test of axonal superexcitability and threshold electrotonus, and/or the identification of a heterozygous pathogenic variant in *KCNA1* by molecular genetic testing.

Management

Treatment of manifestations: Acetazolamide, a carbonic-anhydrase inhibitor, may reduce the frequency and severity of attacks in some but not all affected individuals. Anti-seizure medication may significantly reduce the frequency of attacks in some individuals. Supportive therapies, such as physical therapy, may reduce the risk of later-onset orthopedic complications. Routine treatment of seizure disorders, scoliosis, and developmental disabilities.

Prevention of primary manifestations: In addition to pharmacologic treatments, behavioral measures including avoidance of stress, abrupt movements, loud noises, and caffeine may be used to reduce disease manifestations in both symptomatic and asymptomatic individuals.

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Prevention of secondary complications: Joint contractures can be prevented by appropriate physiotherapy.

Surveillance: Annual neurologic examination.

Agents/circumstances to avoid: Triggers of attacks, including physical exertion, emotional stress, and changes in environmental temperature; marked generalized myokymia has been reported during induction of anesthesia.

Pregnancy management: Affected women should be made aware that pregnancy may trigger attacks; possible loss of balance and falls could endanger the fetus. Several stressors that trigger attacks may cause breathing difficulties; thus, delivery by C-section should be considered.

Genetic counseling

EA1 is inherited in an autosomal dominant manner. Most individuals diagnosed with EA1 have an affected parent; however, *de novo* pathogenic variants have been reported. Each child of an individual with EA1 has a 50% chance of inheriting the *KCNA1* pathogenic variant. Prenatal testing for a pregnancy at increased risk is possible if the pathogenic variant has been identified in an affected family member.

Diagnosis

No consensus diagnostic criteria for episodic ataxia type 1 (EA1) have been published.

Suggestive Findings

Episodic ataxia type 1 (EA1) **should be suspected** in individuals with the following clinical, imaging, and laboratory findings.

Clinical manifestations

- Episodic attacks of:
  - Generalized ataxia, loss of balance, and jerking movements of the head, arms, and legs
  - Dysarthria
  - Incoordination of hands
  - Weakness
  - Tremors
  - Muscle twitching/stiffening
  - Dizziness
  - Stiffening of the body
  - Blurred vision, diplopia
  - Nausea, headache, and vomiting
- Neuromyotonia (muscle cramps and stiffness)
- Myokymia (muscle twitching with a rippling appearance) occurring in the limbs or especially in the muscles of the face or hands
- Childhood or early-adolescent disease onset (average age of onset: ~8 years)

Imaging and laboratory findings

- Normal brain MRI
- Routine laboratory blood tests including serum concentration of creatine kinase and electrolytes
- EMG that displays a pattern of either rhythmically or arrhythmically occurring singlets, duplets, or multiplets

Note: In some individuals myokymic activity on the EMG becomes apparent after the application of regional ischemia.

- To evaluate for interictal motor activity (neuromyotonia/myokymia): surface or needle EMG recordings are performed before, during, and after the application of regional ischemia (e.g., using an inflated sphygmomanometer cuff applied around the upper or lower arm for up to 15 minutes).
- In specialized centers, electrophysiologic assessments of axonal superexcitability and threshold electrotonus performed according to the TRONDHM protocol (using Qtrac© software; UCL Institute of Neurology [Kiernan et al 2000]) differentiate individuals with EA1 from normal controls with high sensitivity and specificity [Tomlinson et al 2010].

Family history is consistent with autosomal dominant inheritance.

Note: (1) Lack of a family history of EA1 does not preclude the diagnosis. (2) Muscle biopsy is usually not helpful in establishing the diagnosis, although bilateral calf hypertrophy, enlargement of type 1 and type 2 gastrocnemius muscle fibers, abnormal mitochondria, and variable glycogen depletion have been observed [VanDyke et al 1975, Kinali et al 2004, Demos et al 2009, Brownstein et al 2016]. Nevertheless, these changes have not been consistently reported among individuals with EA1.

Establishing the Diagnosis

The diagnosis of EA1 **is established** in a proband by means of electrophysiology assessments and/or by identification of a heterozygous pathogenic (or likely pathogenic) variant in *KCNA1* by molecular genetic testing (see Table 1).

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

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of EA1 is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of EA1 has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of EA1 molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *KCNA1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. Although deletions of *KCNA1* have not as yet been reported to cause EA1, it is theoretically possible that such deletions may occur. Therefore, gene-targeted deletion/duplication analysis of *KCNA1* may be considered if sequence analysis does not identify a pathogenic variant.

- **A multigene panel** that includes *KCNA1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of EA1 is not considered because an individual has atypical or complex phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option [Tacik et al 2015]. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in Episodic Ataxia Type 1

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
KCNA1	Sequence analysis [3]	>90% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. All affected individuals described thus far are heterozygous for *KCNA1* pathogenic variants at amino acid residues highly conserved among the voltage-dependent K^+ channel superfamily.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No deletions or duplications of *KCNA1* have been reported to cause EA1.

Interpretation of test results. For *KCNA1* sequence variants, publications on in vitro assessment of channel function may be useful [D'Adamo et al 1998, D'Adamo et al 1999, Imbrici et al 2008, D'Adamo et al 2015b, Hasan et al 2017, Imbrici et al 2017]. Channel function assays are not offered on a clinical testing basis.

Clinical Characteristics

Clinical Description

Episodic ataxia type 1 (EA1), first described by VanDyke et al [1975], is a potassium channelopathy characterized by constant myokymia and dramatic episodes of spastic contractions of the skeletal muscles of the head, arms, and legs with loss of both motor coordination and balance.

Typical attacks in individuals with EA1. In addition to the features noted in Suggestive Findings, **Clinical manifestations**, individuals may experience the following symptoms:

- Vertigo
- Diaphoresis
- Clumsiness
- Difficulty in breathing, which can occur during ataxic episodes or as isolated episodes [Shook et al 2008]

The duration of the attacks is brief, lasting seconds to minutes, although prolonged attacks lasting hours have been described [Lee et al 2004a, D'Adamo et al 2015a]. Episode occurrence is variable, with some individuals experiencing severe ataxia more than 15 times per day and others experiencing attacks less often than once a month.

The first symptoms typically manifest in the first or second decade of life.

Less common symptoms during attacks

- Choreoathetosis
- Carpal spasm
- Clenching of the fists
- Mild lower limb sensory impairment
- Isolated neuromyotonia
- Nystagmus [Hasan et al 2017]
- Hyperthermia [D'Adamo et al 2015a, Mestre et al 2016]
- Hypothermia, which led to the death of an individual with EA1 as a result of exposure to anesthesia [Mestre et al 2016]

  Note: Anesthetic agents have an inhibitory effect on kv1.1 channels.

Triggers. A specific traumatic event, physical or emotional, may determine the onset and worsening of the disease [Imbrici et al 2008]. Attacks may be brought on by the following stimuli:

- Stress or anxiety
- Intercurrent illness or fever
- Excitement or emotional upset
- Fatigue
- Menstruation or pregnancy
- Environmental temperature, including hot baths or use of a hairdryer [Eunson et al 2000]
- Startle response
- Abrupt movements or sudden postural changes (kinesigenic stimulation), including riding a merry-go-round
- Vestibular stimulation (turning head from side to side while standing still; sitting still on a rotating chair; instillation of cold water [i.e., ≤30° C] into either external auditory canal)
- Exercise, such as repeat knee bends
- Ingestion of the following:
  - Caffeine
  - Alcohol
  - Foods rich in salt
  - Bitter oranges

- Chocolate

Interictal ataxia has not been reported to date in individuals with EA1.

Myokymia manifests clinically during and between attacks as fine twitching of groups of muscles and intermittent cramps and stiffness. The severity of some symptoms may either improve or worsen with age [Imbrici et al 2008].

- Myokymia is typically evident as a fine rippling in the perioral or periorbital muscles and by lateral finger movements when the hands are held in a relaxed, prone position.
- Exposure of the forearm to warm or cold temperatures may increase or decrease, respectively, the spontaneous activity recorded from a hand muscle.
- Rarely, episodes of intense myokymic activity during attacks without either ataxia or other neurologic deficits may be observed.
- Myokymic activity is continuous and present in almost all affected individuals [Lee et al 2004b, D'Adamo et al 2015a].

Cognitive dysfunction includes the following:

- Severe receptive and expressive language delay
- Inability to learn to ride a bicycle
- The need for life-skill programs or schools for children with mild to moderate learning difficulties [Zuberi et al 1999, Demos et al 2009]

Neuromuscular findings

- Moderate muscle hypertrophy with generalized increase in muscle tone and bilateral calf hypertrophy are observed.
- Increased muscle tone can cause the following:
  - Unusual hypercontracted posture
  - Abdominal wall muscle contraction
  - Elbow, hip, and knee contractures
  - Shortened Achilles tendons that may result in tiptoe walking

Seizures. Tonic-clonic and partial seizures, an isolated episode consisting of photosensitive epilepsy [Imbrici et al 2008], as well as head-turning and eyes deviating to the same side, flickering eyelids, lip-smacking, apnea, and cyanosis have been reported [Zuberi et al 1999]. Prolonged episodes (more than 30 minutes) have been reported in an individual with severe early-onset epilepsy, albeit without the typical ataxia [Rogers et al 2018].

Other anomalies [Kinali et al 2004, Klein et al 2004]

- Scoliosis
- Kyphoscoliosis
- High-arched palate
- Minor craniofacial dysmorphism

Electroencephalogram (EEG) abnormalities have been observed in persons with EA1 [VanDyke et al 1975, Zuberi et al 1999, Lee et al 2004a].

- EEG may be characterized by intermittent and generalized slow activity, frequently intermingled with spikes.
- Zuberi et al [1999] described a boy age three years who presented with an ictal EEG with rhythmic slow-wave activity over the right hemisphere, becoming spike-and-wave complexes that subsequently spread to the left hemisphere.

Compound muscle action potentials (CMAP) from electromyography (EMG) showed presence of repetitive components of CMAP in ulnar as well as in tibial nerves. They were evident both on routine motor studies and on F-wave studies, making F-waves unrecognizable [Hasan et al 2017].

- Sensory conduction test results were normal.
- Abnormal neuromuscular transmission was reported from Hasan et al [2017] after a train of stimuli at 20 Hz or 50 Hz that resulted in a decrement of the amplitude of the first CMAP elicited followed by an increment of the second CMAP amplitude elicited (decrement-increment phenomenon), similar to what is usually observed in organophosphate intoxication.

Brain MRI is usually normal; however, rare findings include the following:

- Cerebellar atrophy in one family [Demos et al 2009]
- Mild vermian hypoplasia [Tacik et al 2015]
- Small right subcortical frontal gliosis [Brownstein et al 2016]

Genotype-Phenotype Correlations

Because of significant inter- and intrafamilial phenotypic variability, reliable genotype-phenotype correlations have been extremely difficult to establish. It is now apparent that phenotypic differences exist not only across families, but also among affected individuals within a family. Indeed, differences in severity and frequency of EA1 attacks have been reported even in monozygotic twins [Graves et al 2010].

Penetrance

Most individuals harboring a *KCNA1* pathogenic variant exhibit features of EA1; however, penetrance is incomplete.

Nomenclature

EA1 has also been known as:

- Acetazolamide-responsive periodic ataxia
- Continuous muscle fiber activity
- Episodic ataxia with myokymia
- Familial paroxysmal kinesigenic ataxia and continuous myokymia
- Isaacs-Mertens syndrome
- Hereditary paroxysmal ataxia with neuromyotonia

Prevalence

EA1 is a rare disease and the prevalence can be estimated only roughly. Several families from Australia, Brazil, Canada, Germany, Italy, Russia, Spain, the Netherlands, United Kingdom, and the United States have been described. Based on limited data, a disease prevalence of 1:500,000 has been proposed. Actual prevalence may well be considerably higher, as the disorder may remain either unrecognized in many families or be incorrectly diagnosed.

The populations that are more or less at risk are also unknown.

Genetically Related (Allelic) Disorders

It is unclear whether the following truly represent unique phenotypes associated with a pathogenic variant in *KCNA1* or fall within the phenotypic spectrum of episodic ataxia type 1 (EA1). While episodic onset of neurologic features remains a key feature in individuals with a pathogenic variant in *KCNA1*, ataxia may not be present. Whether episodic "ataxia" is a misnomer, as suggested by Brownstein et al [2016], will be revealed as more individuals undergo genomic evaluation.

- Eunson et al [2000] reported isolated neuromyotonia without episodes of ataxia.
- Brownstein et al [2016] reported cataplexy triggered by sudden physical exertion in multiple individuals of a three-generation family, and muscle spasms with rigidity in another family.
- D'Adamo et al [2015a] reported a unique phenotype characterized by episodes of long-lasting attacks with hyperthermia, short sleep duration, and severe migraine.
- Hypomagnesemia with accompanying recurrent muscle cramps, tetanic episodes, tremor, and limb muscle weakness has been described in a large Brazilian family harboring a *KCNA1* pathogenic variant [Glaudemans et al 2009].
- Tristán-Clavijo et al [2016] reported a Spanish family with migraine and tremor without ataxia.
- Set et al [2017] reported an individual with episodes of bilateral stiffening of the lower extremities lasting for two to 12 hours, with no ataxia or myokymia.
- Rogers et al [2018] reported early-onset epileptic encephalopathy and cognitive impairment without ataxia.

Differential Diagnosis

Episodic ataxia can occur sporadically or in a number of hereditary or acquired disorders.

Table 2. Disorders to Consider in the Differential Diagnosis of Episodic Ataxia Type 1

Disorder	Gene	MOI	Clinical Features	Onset	Frequency of Attacks	Attack Triggers	Treatment	Interictal Findings
EA2 [1] (OMIM 108500)	*CACNA1A*	AD	• Paroxysmal attacks of ataxia, vertigo, nausea lasting minutes to days; can be assoc w/ dysarthria, diplopia, tinnitus, dystonia, hemiplegia, & headache (migraine in ~50%) • Atrophy of cerebellar vermis on MRI	Typically childhood or early adolescence (range: 2-32 yrs)	Range: 1-2/yr to 3-4/wk	• Stress • Exertion • Caffeine • Alcohol • Fever • Heat • Phenytoin	Acetazolamide can stop or ↓ attack frequency/ severity.	Initially asymptomatic; may develop interictal findings incl nystagmus & ataxia
EA3 [2] (OMIM 606554)	Unknown	AD	• Vestibular ataxia • Vertigo • Tinnitus	Variable				Myokymia

Table 2. continued from previous page.

Disorder	Gene	MOI	Clinical Features	Onset	Frequency of Attacks	Attack Triggers	Treatment	Interictal Findings
EA4 [3, 4, 5] (OMIM 606552)	Unknown		• Recurrent attacks of vertigo, tinnitus, diplopia, & ataxia • Abnormal eye movements (incl abnormal smooth pursuit, nystagmus, & abnormal vestibuloocular reflex) • Slowly progressive cerebellar ataxia in some	Early adulthood (range: 3rd-6th decade)			No response to acetazolamide	Absence of interictal myokymia
EA5 (OMIM 613855)	*CACNB4* [6]	AD	Recurrent episodes of vertigo & ataxia lasting several hours [6]				Acetazolamide prevented attacks.	Spontaneous downbeat & gaze-evoked nystagmus, mild dysarthria, & truncal ataxia
EA6 (OMIM 612656)	*SLC1A3* [7]	AD	• Attacks of ataxia precipitated by fever • Subclinical seizures • Slurred speech followed by headache • Bouts of arm jerking w/ concomitant confusion • Alternating hemiplegia			• Stress • Fatigue • Caffeine • Alcohol		Gaze-evoked nystagmus
EA7 (OMIM 611907)	Unknown [8]	AD	Attacks assoc w/ weakness, vertigo, & dysarthria lasting hrs to days	Before age 20 years	Range: 1/mo to 1/yr; frequency tends to ↓ w/age.	• Exercise • Excitement		
EA8 [9] (OMIM 616055)	Unknown	AD	• Unsteady gait, generalized weakness, & slurred speech lasting mins to hrs • In 2 women: improvement	2nd year of life	Range: 2/day to 2/mo		Clonazepam was effective.	

Table 2. continued from previous page.

Disorder	Gene	MOI	Clinical Features	Onset	Frequency of Attacks	Attack Triggers	Treatment	Interictal Findings
			during pregnancy; in others: ↓ frequency & severity of attacks w/age • Twitching around eyes, nystagmus, myokymia, mild dysarthria, & persistent intention tremor in some • Migraine headache w/o aura reported in 2 individuals • Epilepsy not reported					
Spastic ataxia 1 (OMIM 108600)	*VAMP1*	AD	Initially, progressive leg spasticity of variable degree followed by ataxia (involuntary head jerk, dysarthria, dysphagia, & ocular movement abnormalities)	Early childhood - early 20s				
Familial paroxysmal kinesigenic dyskinesia [10]	*PRRT2*	AD	• Unilateral or bilateral involuntary movements • Attacks usually last a few secs to 5 mins but can last several hrs & incl dystonia, choreoathetosis, &/or ballism • May be preceded by aura, & do not involve loss of consciousness • Severity & combinations of symptoms vary • Predominantly seen in males	Typically childhood & adolescence (range 4 mos - 57 yrs)	Range: 100/day to as few as 1/mo	Sudden movements (e.g., standing up from sitting position, being startled, or changes in velocity)	Phenytoin or carbamezepine can ↓ frequency of (or prevent) attacks.	
Familial paroxysmal nonkinesigenic dyskinesia	*PNKD*	AD	• Unilateral or bilateral involuntary movements	Typically in childhood or early teens; can	A few times/day	Attacks are spontaneous or precipitated by: • Alcohol		

Table 2. continued from previous page.

Disorder	Gene	MOI	Clinical Features	Onset	Frequency of Attacks	Attack Triggers	Treatment	Interictal Findings
			• Attacks lasting mins to hrs: dystonic posturing w/ choreic & ballistic movements; may be preceded by aura; occur while awake; are not associated w/seizures • Frequency, duration, severity, & combinations of symptoms vary w/in & among families	be as late as age 50 yrs		• Caffeine • Excitement • Stress • Fatigue • Chocolate		
Isaac syndrome (acquired neuromyotonia, NMT) [11]	NA	NA	• Rare neuromuscular disorder • Hyperexcitability of motor nerve → continuously contracting or twitching muscles (myokymia) & muscle hypertrophy • Cramping, ↑ sweating, & delayed muscle relaxation • Stiffness most prominent in limb & trunk muscles • A few persons report sleep disorders, anxiety, & memory loss	15-60 years		Symptoms not usually triggered by exercise; occur even during sleep or under general anesthesia		

Table 2. continued from previous page.

Disorder	Gene	MOI	Clinical Features	Onset	Frequency of Attacks	Attack Triggers	Treatment	Interictal Findings
			(Morvan syndrome)					

AD = autosomal dominant: MOI = mode of inheritance; NA = not applicable
See Episodic Ataxia: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.
1. EA2 is allelic to SCA6 and familial hemiplegic migraine type 1.
2. EA3 has been described in a large Canadian kindred of Mennonite heritage [Steckley et al 2001].
3. EA4 (also referred to as periodic vestibulocerebellar ataxia) has been described in families from North Carolina of northern European origin by Farmer & Mustian [1963] and Vance et al [1984].
4. Steckley et al [2001]
5. EA4 does not link to loci identified with EA1, EA2, or spinocerebellar ataxia types 1, 2, 3, 4, and 5 [Damji et al 1996].
6. EA5 can result from pathogenic variants in *CACNB4* as described in a French-Canadian family [Escayg et al 2000]. EA5 is allelic with susceptibility to juvenile myoclonic epilepsy 6 (EJM6, OMIM 607682); the semiology of seizures in EA5 is similar to EJM6.
7. EA6 can result from pathogenic variants in *SLC1A3*, which encodes the excitatory amino acid transporter 1. In cells expressing mutated proteins, glutamate uptake is reduced, suggesting that glutamate transporter dysfunction underlies the disease [Jen et al 2005, de Vries et al 2009].
8. EA7 has been described in a four-generation family whose affected individuals showed episodic ataxia [Kerber et al 2007]. A candidate region on chromosome 19q13, termed the EA7 locus, has been identified [Kerber et al 2007].
9. Genome-wide linkage analysis found linkage to an 18.5-Mb locus on chromosome 1p36.13-p34.3 [Conroy et al 2014].
10. The phenotype of paroxysmal kinesigenic dyskinesia can include benign familial infantile epilepsy (BFIE), infantile convulsions and choreoathetosis (ICCA), hemiplegic migraine, migraine with and without aura, and episodic ataxia.
11. The acquired form of Isaac's syndrome occasionally develops in association with peripheral neuropathies or after radiation treatment. Twenty percent of affected individuals have an associated thymoma. Antibodies that involve K+ channels have been detected in approximately 40% of affected individuals [Hart et al 2002]. Several of these auto-antibodies do not bind directly with Kv1.1, Kv1.2, or Kv1.6 channels, as previously believed, but rather to associated proteins such as leucine-rich glioma-inactivated protein 1, contactin-associated protein-like 2, contactin-2, or others as yet unidentified [Irani et al 2010, Lai et al 2010, Lancaster et al 2011].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and therapeutic needs in an individual diagnosed with episodic ataxia type 1, the evaluations summarized in Table 3 (if not already completed) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Episodic Ataxia Type 1

System/Concern	Evaluation	Comment
Neurologic	Neurologic exam	Incl initiation (& observation) of attacks by either mild exercise or vestibular stimuli (see Clinical Description, **Triggers**)
	Electromyogram	To confirm presence of myokymia if it is not visible on exam
	Electroencephalogram	To evaluate for epilepsy [1]
Other	Consultation w/clinical geneticist &/or genetic counselor	

1. Zuberi et al [1999], Eunson et al [2000], Chen et al [2007]

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Episodic Ataxia Type 1

Manifestation/ Concern	Treatment	Considerations/Other
Typical attacks [1]	Acetazolamide [2]: 125 mg orally 1x/day starting dose; in those w/good renal function, ↑ daily doses may be required: 8-30 mg/kg/day in 1-4 divided doses (max dose: 1 g/day)	Acetazolamide should not be prescribed to patients w/liver, renal, or adrenal insufficiency.
	Phenytoin 3.7 mg/kg/day may improve muscle stiffness & motor performance. [3, 4]	In some cases, phenytoin but not acetazolamide has shown effectiveness for both ataxia & dyskinesia. [5, 6]
	Sulthiame 50-200 mg daily may ↓ attack rate.	During this treatment abortive attacks lasting a few secs were still observed; troublesome side effects incl paresthesias & intermittent carpal spasm.
	Carbamazepine has been prescribed in doses up to 1,600 mg/day. [7]	Significant ↓ in frequency, severity, & duration of symptoms observed [8]
	Lamotrigine has been proposed as an alternative treatment.	Attacks ameliorated in some patients [9]
Seizures	Diphenylhydantoin 150-300 mg/day	Resulted in reasonable control of seizures in some
	Other anti-seizure meds may be required to control seizures in some. [10]	Consider referral to neurologist.
Scoliosis	Routine treatment per orthopedist	

1. Several drugs variably improve EA1 symptoms, but with the lack of clinical trials comparing the efficacy of these drugs, no single medication has been proven to be very effective.
2. Chronic treatment with acetazolamide may result in side effects including neuropsychiatric manifestations, tiredness, paresthesias, rash, and formation of renal calculi, necessitating discontinuation of therapy [Graves et al 2014, D'Adamo et al 2015a].
3. Kinali et al [2004]
4. Phenytoin should be used with caution in young patients, as it may cause permanent cerebellar dysfunction and atrophy [De Marcos et al 2003].
5. Dressler & Benecke [2005]
6. Phenytoin is most often a second-line drug for typical attacks [McTague et al 2018].
7. The dose needs to be adjusted according to factors including age, weight, the particular carbamazepine product being used, responsiveness of the individual, and other medications being taken.
8. Imbrici et al [2017]
9. Graves et al [2014]
10. Graves et al [2010]

Developmental Delay / Intellectual Disability Management Issues

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

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.

- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

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

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction. Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Prevention of Primary Manifestations

In addition to the pharmacologic treatments mentioned above, behavioral measures such as avoidance of stress, abrupt movements, loud noises, and caffeine may be implemented to reduce disease manifestations in either a symptomatic or an asymptomatic person.

Prevention of Secondary Complications

Contractures occur in a small proportion of individuals and can be prevented by appropriate physiotherapy.

Surveillance

Surveillance should include annual neurologic examination.

Agents/Circumstances to Avoid

Known triggers of attacks (see Clinical Description, **Triggers**) should be avoided; physical exertion, emotional stress, and changes in environmental temperature are the most common triggers.

Marked generalized myokymia has been reported during induction of anesthesia [Kinali et al 2004].

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic at-risk relatives in order to identify as early as possible those who would benefit from behavioral measures and avoidance of caffeine intake. If the pathogenic variant in the family is known, molecular genetic testing can be used to clarify the genetic status of at-risk relatives.

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

Pregnancy Management

No published literature addresses management of the pregnancy of an affected mother or the effect of maternal EA1 on a fetus. However, affected women should be made aware that pregnancy may trigger attacks [Graves et al 2014] and the possible loss of balance and fall could endanger the fetus's life. Moreover, several stressors that trigger attacks may cause breathing difficulties, thus, delivery by C-section should be considered.

In general, women with epilepsy or a seizure disorder from any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of anti-seizure medication during pregnancy reduces this risk. However, exposure to anti-seizure medication may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from anti-seizure medication exposure is often less than that associated with exposure to an untreated maternal seizure disorder. Therefore, use of anti-seizure medication to treat a maternal seizure disorder during pregnancy is typically recommended. Discussion of the risks and benefits of using a given anti-seizure drug during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible [Sarma et al 2016].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

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

Other

Morphologic studies on lateral gastrocnemius (LG) muscles derived from a mouse model of EA1 did not reveal changes in muscle mass, fiber type composition, or vascularization [Brunetti et al 2012].

Homozygous Val408Ala/Val408Ala pathogenic variants are embryonically lethal in an animal model of EA1 [Herson et al 2003], although this has not been reported in humans.

Genetic Counseling

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

Mode of Inheritance

Episodic ataxia type 1 (EA1) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with EA1 have an affected parent.
- A proband with EA1 may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is unknown.

- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include neurologic evaluation and molecular genetic testing for the *KCNA1* pathogenic variant identified in the proband.
- If the *KCNA1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (though theoretically possible, no instances of germline mosaicism have been reported).
- The family history of some individuals diagnosed with EA1 may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate neurologic evaluation and molecular genetic testing have been performed on the parents of the proband.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the pathogenic 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 the proband is affected, the risk to the sibs is 50%.
- If the *KCNA1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism.
- If the parents have not been tested for the *KCNA1* pathogenic variant but are clinically unaffected, sibs are still at increased risk for EA1 because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with EA1 has a 50% chance of inheriting the *KCNA1* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is heterozygous for a *KCNA1* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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

Family planning

- The optimal time for determination of genetic risk is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of being affected.

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *KCNA1* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible.

Resources

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

- **Ataxia UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  www.ataxia.org.uk

- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: lporter@ataxia.org.uk
  www.euroataxia.org

- **National Ataxia Foundation**
  Phone: 763-553-0020
  Fax: 763-553-0167
  Email: naf@ataxia.org
  www.ataxia.org

- **CoRDS Registry**
  Sanford Research
  Phone: 605-312-6300
  CoRDS Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Episodic Ataxia Type 1: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
KCNA1	12p13.32	Potassium voltage-gated channel subfamily A member 1	KCNA1 database	KCNA1	KCNA1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Episodic Ataxia Type 1 (View All in OMIM)

160120	EPISODIC ATAXIA, TYPE 1; EA1
176260	POTASSIUM CHANNEL, VOLTAGE-GATED, SHAKER-RELATED SUBFAMILY, MEMBER 1; KCNA1

Molecular Pathogenesis

KCNA1 encodes the potassium voltage-gated channel subfamily A member 1, commonly known as the α-subunit of the voltage-gated delayed-rectifier potassium channel Kv1.1. Voltage-gated potassium channels (Kv) play key roles in neurotransmission and nerve cell physiology. They shorten the duration of action potentials, modulate the release of neurotransmitters, and control the excitability, electrical properties, and firing pattern of central and peripheral neurons [Pessia 2004]. In particular, Kv1.1 channels regulate neuromuscular transmission and control the release of β-aminobutyric acid (GABA) from cerebellar basket cells onto Purkinje cells [Herson et al 2003]. The Kv1.1 channel opens upon membrane depolarization, after which potassium flow results in a hyperpolarizing effect that is necessary to limit neuronal excitability [Pessia 2004]. The channel is known for its role in controlling the excitability of cerebellar, hippocampal, cortical, and peripheral nervous system neurons [Brunetti et al 2012, D'Adamo et al 2015a].

Functional studies have shown that pathogenic missense variants in *KCNA1* (the only gene currently known to be associated with EA1) result in loss of function of the channel. Kv1.1 channel function in EA1 is impaired by altering the channel's gating kinetics, voltage dependence, assembly, and trafficking [Imbrici et al 2006, Hasan et al 2017; for a review see D'Adamo et al 2015b].

Homomeric Kv1.1 channels are tetrameric structures composed of four identical α-subunit monomers. Each monomer is encoded by *KCNA1*. However, potassium channel diversity is greatly enhanced by the ability of Kv1.1 to co-assemble with α-subunits of other members of the Kv1 family to form heterotetrameric channels with properties different from the parental homomeric channels. Kv1.1 is mostly found co-assembled with Kv1.2 subunits; they are expressed together at cerebellar basket cell terminals and at the juxtaparanodal region of motor axons. A pathogenic variant in Kv1.1 affects the function of the Kv1.1/1.2 heteromeric channel to which they contribute [Hasan et al 2017]. D'Adamo et al first demonstrated that proteins encoded by *KCNA1* pathogenic variants associated with EA1 alter the expression and gating properties of heteromeric channels composed of human Kv1.2 and Kv1.1 subunits [D'Adamo et al 1999, Rea et al 2002].

Kv1.1 channels possess a slow process of inactivation, which has been named C-type or P-type depending on the structural determinants of this process that have been located within the C-terminus and pore region. Kv channels may also exhibit fast *N-type* inactivation that is caused by a "ball-and-chain" mechanism of pore occlusion. Fast inactivation may be conferred to non-inactivating channels by auxiliary subunits such as Kvβ1.1 and Kvβ1.2. Four β subunits participate in the ion channel complex and provide four inactivation particles; notable example: channels composed of Kv1.1, Kv1.4, and Kvβ1.1 subunits that are expressed in hippocampal mossy fiber boutons [Geiger & Jonas 2000]. Proteins encoded by *KCNA1* pathogenic variants also impair the function of hetero-oligomeric complexes comprising Kv1.1, Kv1.4, and Kvβ1.x subunits in distinct ways [Imbrici et al 2006, Imbrici et al 2011]. These studies raised the question as to whether other allelic variations, whose gene products may or may not form hetero-oligomeric complexes with Kv1.1 subunits, may underlie a similar channelopathy.

Gene structure. *KCNA1* has a transcript of 7,983 nucleotides with a coding region of 1,488. There are two exons, but the coding region is located entirely within exon 2. The reference sequences in Table 5 include the correction of a sequence error (see Table 5, footnote 1). For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. In 5% of control chromosomes analyzed by Zuberi et al [1999], two silent changes in the coding sequence were observed.

Pathogenic variants. To date, more than 30 *KCNA1* pathogenic variants have been identified by sequence analysis (see Figure 1). Most are missense variants that are distributed throughout the gene; however, nonsense variants and small deletions have also been identified [Eunson et al 2000, Shook et al 2008].

Interestingly, four different variants of the highly conserved threonine 226 residue, located within the second transmembrane segment, have been identified [Rajakulendran et al 2007]. In particular, the amino acid change p.Thr226Arg is associated with epilepsy, infantile contractures, postural abnormalities, and skeletal deformities. Although the defects caused by the p.Thr226Ala, p.Thr226Arg, and p.Thr226Met amino acid changes on channel functions are virtually identical, they lead to diverse phenotypes.

Table 5. *KCNA1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.676A>G	p.Thr226Ala	NM_000217.2 [1] NP_000208.2
c.677C>G	p.Thr226Arg	
c.677C>T	p.Thr226Met	
c.1223T>C	p.Val408Ala	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Reference sequences include the correction of a sequence error published by Ramaswami et al [1990] and reported by Browne et al [1994] and Zuberi et al [1999].

Normal gene product. *KCNA1* encodes the voltage-gated K^+ channel Kv1.1. The predicted 496-amino-acid Kv1.1 protein contains six hydrophobic segments with the N- and C-termini residing inside the cell. The S4 segment of each Kv1.1 subunit comprises the main voltage sensor that opens the channel by undergoing a conformational rearrangement on membrane depolarization. The S5-S6 loop (H5 region) contributes to the ion-conducting pore. The GYG residues, residing within this loop, control the K^+ selectivity of the channel.

Abnormal gene product. The molecular mechanisms underlying episodic ataxia type 1 have been established by determining the functional properties of wild type and several mutant channels in *Xenopus* oocytes or mammalian cell lines [Adelman et al 1995, D'Adamo et al 1998, Zerr et al 1998, D'Adamo et al 1999, Zuberi et al 1999, Eunson et al 2000, Manganas et al 2001, Imbrici et al 2003, Cusimano et al 2004, Imbrici et al 2006, Imbrici et al 2007, Imbrici et al 2008, Imbrici et al 2009, Imbrici et al 2011, D'Adamo et al 2015a]. Overall, these studies have shown that allelic variations underlying EA1 impair channel function and reduce the outward K^+ flux through the channel, although with highly variable effects on aspects of channel expression and gating.

Regarding channel gating, *KCNA1* pathogenic variants may alter the protein structure and affect the kinetics of opening and closing, voltage dependence, and N- and C-type inactivation [D'Adamo et al 1998, D'Adamo et al 1999, Maylie et al 2002, Imbrici et al 2006, Imbrici et al 2009, Imbrici et al 2011, D'Adamo et al 2015b, Hasan et al 2017].

Individuals with EA1 are heterozygous for a *KCNA1* pathogenic variant, possessing a normal and a mutated allele, which may be equally expressed. Therefore, channels composed of wild type and mutated subunits may be formed. Co-expression systems, which mimic the heterozygous condition, have shown that some mutated subunits exert dominant negative effects on wild type subunits, resulting in less than half the normal current, whereas others have virtually no effect on surface expression. It has been shown that *KCNA1* allelic variations also alter the function of heteromeric channels containing different subunits, demonstrating that pathogenic variants in a single gene disrupt the functions of other closely related proteins [D'Adamo et al 1999, Rea et al 2002, Imbrici et al 2006, Hasan et al 2017]. Based on these findings, a model accounting for the cerebellar symptoms of EA1 was proposed by D'Adamo and colleagues (see Figure 2).

A mouse model of EA1 has been generated by introducing a pathogenic variant analogous to the human p.Val408Ala EA1 pathogenic variant into the murine ortholog, *Kcna1*. These animals showed impaired motor performance and altered cerebellar GABAergic transmission from the basket cells to the Purkinje cells [Herson et al 2003]. Such *Kv1.1* knock-in ataxic mice also exhibited spontaneous myokymic activity exacerbated by fatigue, ischemia, and low temperature [Brunetti et al 2012]. Spontaneous myokymic discharges were present despite motor nerve axotomy, suggesting that the motor nerve is an important generator of myokymic activity. This study also showed that altered Ca^{2+} homeostasis in motor axons of mutated animals may contribute to spontaneous myokymic activity [Brunetti et al 2012].

The causes that trigger the paroxysms of ataxia remain elusive, although a phenomenon akin to spreading acidification of the cerebellar cortex has been suggested [Chen et al 2005].

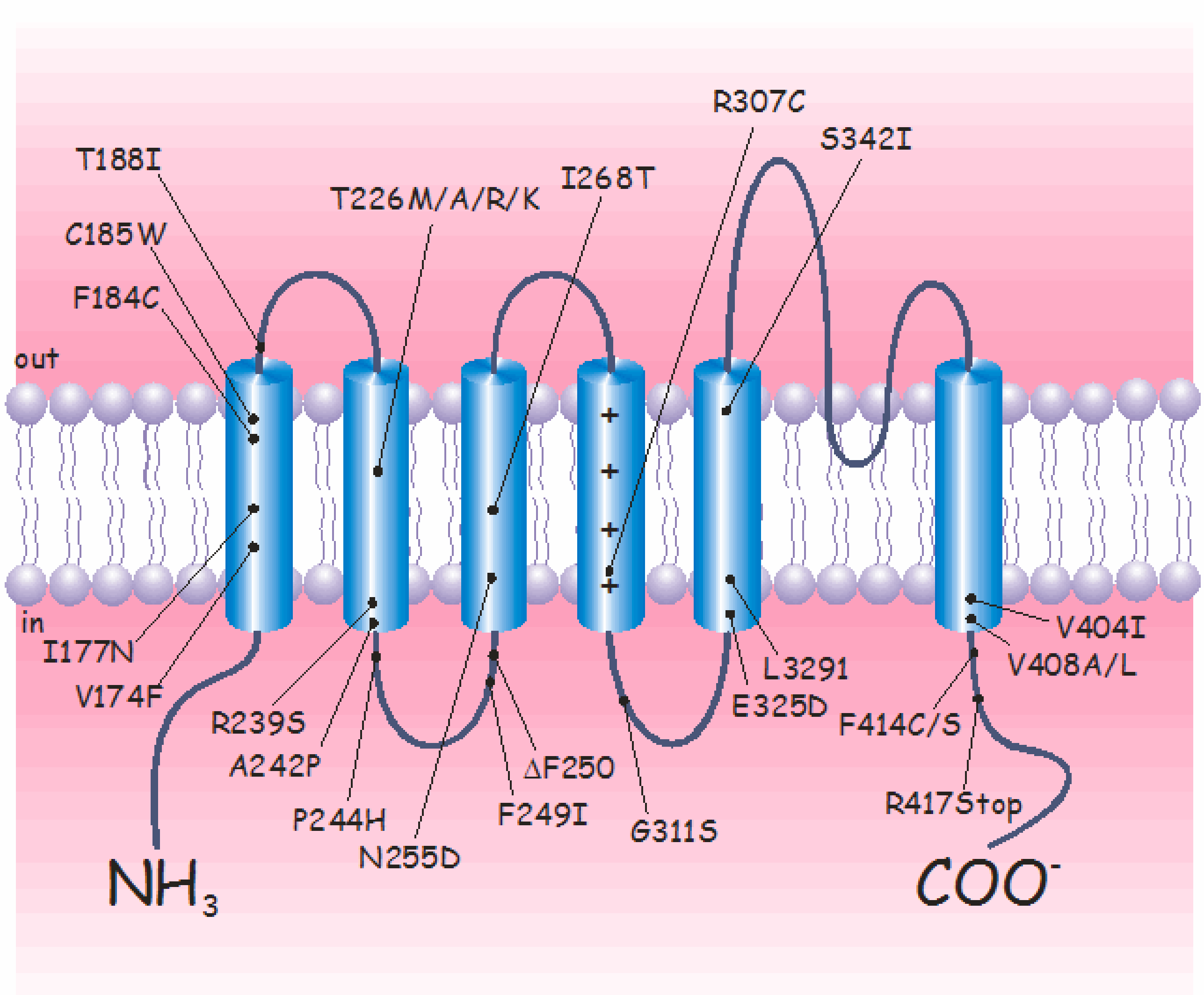

Figure 1. Schematic drawing of the conventional membrane topology of a human Kv1.1 subunit. Four such subunits comprise a functional homotetrameric channel. Different subunits belonging to the Kv1 subfamily may form heterotetrameric channels. The positions of pathogenic variants identified to date in individuals with EA1 are indicated.

Modified from D'Adamo et al [2012]; used by permission of Nova Science Publishers, Inc.

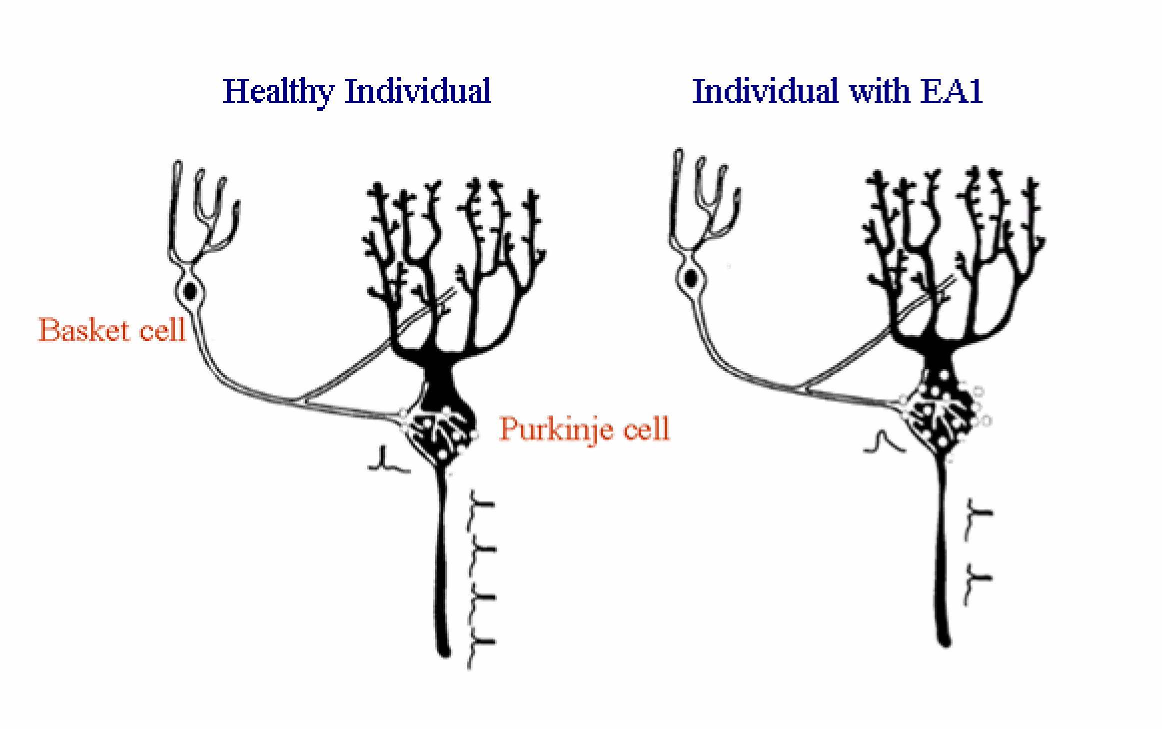

Figure 2. Proposed effects of EA1-causing pathogenic variants on basket cell and Purkinje cell inhibitory outputs

The diagram shows a basket cell that has synapses on the initial segment and soma of a number of Purkinje cells from the cerebellar cortex of an unaffected individual (*left*) compared to an individual with EA1 (*right*). The reduced delayed rectifier function of EA1 heteromeric channels comprising Kv1.1 and Kv1.2 subunits, which are expressed at the presynaptic level of basket cells, may increase the membrane excitability, prolong their action potential duration, and enhance Ca^{2+} ion influx. Larger amounts of γ-aminobutyric acid (GABA) may be released from basket cell terminals reducing the inhibitory outputs of the relevant Purkinje cells. As a result, the output of the entire cerebellum to the rest of the brain may be markedly altered leading to the cerebellar symptoms characteristic of EA1 (see D'Adamo et al 1999, Figure 7).

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Chapter Notes

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