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Episodic Ataxia Type 1

Synonyms: EA1, Episodic Ataxia with Myokymia, Hereditary Cerebellar Ataxia with Neuromyotonia

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Summary

Disease 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 some individuals may experience vertigo, blurred vision, diplopia, nausea, headache, diaphoresis, clumsiness, stiffening of the body, dysarthric speech, and difficulty in breathing. EA1 is associated with an increase incidence of epilepsy. Other findings can include delayed motor development, cognitive disability, choreoathetosis, and carpal spasm. Onset is in childhood or early adolescence.

Diagnosis/testing. Diagnosis is based on clinical findings and molecular genetic testing of *KCNA1,* the only gene in which mutations are known to cause EA1.

Management. *Treatment of manifestations:* Acetazolamide (ACTZ), a carbonic-anhydrase (CA) inhibitor, may reduce the frequency and severity of the attacks in some but not all affected individuals. Antiepileptic drugs (AEDs) may significantly reduce the frequency of the attacks in some individuals.

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

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

Surveillance: Annual neurologic examination.

Agents/circumstances to avoid: General anesthetics have occasionally been reported to precipitate or aggravate neuromyotonia

Genetic counseling. EA1 is inherited in an autosomal dominant manner. Most individuals diagnosed with EA1 have an affected parent; to date, only one *de novo* mutation has been reported. Each child of an individual with EA1 has a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

Episodic ataxia type 1 (EA1), a neurologic disease resulting from alterations in the voltage-gated potassium channel (Kv1.1), is suspected in individuals with the following clinical findings:

- **Attacks** of: generalized ataxia with jerking movements of head, arms, and legs; stiffening of the body; loss of balance; dizziness; blurred vision; dysarthria; and diplopia. These episodes may occur several times a month, may last seconds to

minutes, and can be precipitated by anxiety, emotional stress, fatigue, startle response, and sudden postural changes (kinesigenic stimulation). Mild exercise, kinesigenic stimulation, and vestibular caloric stimulation may be used to induc attacks.

- **Neuromyotonia** (muscle cramps and stiffness) and **myokymia** (muscle twitching with a rippling appearance) may occur in the limbs or especially in the muscles of the face or the hands. Evidence of myokymia, detected by electromyography (EMG), is found in nearly all individuals with EA1 regardless of clinical findings. The EMG 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.
- **Childhood** or **early-adolescent disease onset**
- **Family history** consistent with **autosomal dominant inheritance**

Testing

Axonal superexcitability and threshold electrotonus may be investigated by means of a simple and rapid electrophysiologic test that can differentiate individuals with EA1 from normal controls with high sensitivity and specificity [Tomlinson et al 2010].

Brain MRI and routine laboratory blood tests, including serum concentration of creatine kinase and electrolytes, are generally normal.

Muscle biopsy is usually not helpful in establishing the diagnosis, although bilateral calf hypertrophy, enlargement of type 1 anc type 2 gastrocnemius muscle fibers, and variable glycogen depletion have been reported [Van Dyke et al 1975, Kinali et al 2004, Demos et al 2009]. Nevertheless, these changes have not been consistently reported among individuals with EA1.

Molecular Genetic Testing

Gene. *KCNA1* is the only gene in which mutations are known to cause episodic ataxia type 1.

Clinical testing

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

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method [1]	Test Availability
KCNA1	Sequence analysis	Sequence variants [2]	>90% [3]	Clinical Testing
	Deletion / duplication analysis	Deletions / duplications [4]	Unknown; none reported [5]	

Test Availability refers to availability in the GeneTests™ Laboratory Directory. *GeneReviews* designates a molecular genetic test as clinically available only if the test is listed in the GeneTests™ Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.

1. The ability of the test method used to detect a mutation that is present in the indicated gene

2. Examples of mutations detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site mutations; typically, exonic or whole gene deletions/duplications are not detected.

3. All affected individuals described thus far are heterozygous for *KCNA1* mutations at amino acid residues highly conserved among the voltage-dependent K^+ channel superfamily.

4. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment. See CMA.

5. No deletions or duplications involving *KCNA1* have been reported to cause episodic ataxia type 1.

Interpretation of test results

- For issues to consider in interpretation of sequence analysis results, click here.
- For *KCNA1* sequence variants, publications on in vitro assessment of channel function may be useful [Imbrici et al 2008] Channel function assays are not offered on a clinical testing basis.

Information on specific allelic variants may be available in Molecular Genetics (see Table A. Genes and Databases and/or **Pathologic allelic variants**).

Testing Strategy

To confirm/establish the diagnosis in a proband

- To induce attacks:
  - Mild exercise (knee bends; running up a staircase quickly; arising from a chair quickly)

- Vestibular stimulation (head turning 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)
- Sudden and unexpected tactile or acoustic stimuli causing a startle response (rising quickly after a loud handclap)

- To evaluate for interictal motor activity (neuromyotonia/myokymia) in individuals who report characteristic episodes: 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).
- Usually, sequence analysis of *KCNA1* is recommended as a confirmatory diagnostic test.
- Although no deletions of *KCNA1* have been reported to cause EA1, it is theoretically possible that such mutations exist. Therefore, deletion/duplication analysis may be useful in individuals displaying EA1 symptoms if sequence analysis does not identify a disease-causing *KCNA1* mutation.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Note: It is the policy of *GeneReviews* to include in *GeneReviews*™ chapters any clinical uses of testing available from laboratories listed in the GeneTests™ Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Genetically Related (Allelic) Disorders

Eunson et al [2000] reported a unique phenotype characterized by isolated neuromyotonia without episodes of ataxia in association with a mutation in *KCNA1*. It is unclear whether this truly represents a unique phenotype or falls within the phenotypic spectrum of episodic ataxia type 1.

Hypomagnesemia with accompanying recurrent muscle cramps, tetanic episodes, tremor, and limb muscle weakness has been described in a large Brazilian family harboring a *KCNA1* mutation [Glaudemans et al 2009].

Clinical Description

Natural History

Episodic ataxia type 1 (EA1), first described in 1975 by Van Dyke et al, 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 some individuals may experience vertigo, blurred vision, diplopia, nausea, headache, diaphoresis, clumsiness, stiffening of the body, dysarthric speech, and difficulty in breathing [Van Dyke et al1975].

The duration of the attacks is brief, lasting seconds to minutes, although prolonged attacks of five to 12 hours have been described [Lee et al 2004a]. Some individuals experience severe ataxia more than 15 times per day, whereas others experience attacks less often than once a month [Van Dyke et al 1975].

The first symptoms typically manifest during childhood (1st or 2nd decade of life). A specific traumatic physical or emotional event may determine the onset and worsening of the disease [Imbrici et al 2008]. Attacks may be brought on by stimuli including fever, startle response, abrupt movements, emotional stress, anxiety, repeat knee bends, exercise, ingestion of caffeine and riding a merry-go-round. Attacks may occur, for example, when the individual has had to suddenly alter course to avoid falling or potential collision. High temperatures that occur after a hot bath or during use of a hairdryer may also precipitate attacks [Eunson et al 2000]. Whether interictal ataxia develops in individuals with EA1 has not been clearly reported to date.

Myokymia manifests clinically during and between attacks as fine twitching of groups of muscles and intermittent cramps and stiffness. Usually, it is evident as a fine rippling in perioral or periorbital muscles and by lateral finger movements when the hands are held in a relaxed, prone position.

Rarely, episodes of intense myokymic activity during attacks without either ataxia or other neurologic deficits are observed. Myokymic activity is continuous.

The exposure of the forearm to warm or cold temperatures may increase or decrease, respectively, the spontaneous activity recorded from a hand muscle.

The severity of some symptoms may either improve or worsen with age [Imbrici et al 2008].

Since the first description of EA1 by Van Dyke et al [1975] and the identification and characterization of mutations in *KCNA1*, th phenotypic spectrum of EA1 has widened considerably, indicating that it is not a purely cerebellar syndrome. Affected individuals may display delayed motor development, choreoathetosis, carpal spasm, clenching of the fists, and isolated neuromyotonia.

Cognitive dysfunction described in EA1 includes severe receptive and expressive language delay; inability to learn to ride a bicycle; and the need for life-skill programs or schools for children with mild to moderate learning difficulties [Zuberi et al 1999 Demos et al 2009].

Moderate muscle hypertrophy with generalized increase in muscle tone and bilateral calf hypertrophy are observed. Neuromuscular findings secondary to the increased tone include unusual hypercontracted posture; abdominal wall muscle contraction; elbow, hip, and knee contractures; and shortened Achilles tendons that may result in tiptoe walking.

Some individuals display attacks of difficulty in breathing, which can occur during ataxic episodes or as isolated episodes of an inability to inhale without wheezing [Shook et al 2008].

Skeletal deformities including scoliosis, kyphoscoliosis, high-arched palate, and minor craniofacial dysmorphism have been

described [Kinali et al 2004, Klein et al 2004]. It is now apparent that phenotypic differences exist not only between families, but also between individuals of the same family.

Tonic-clonic and partial seizures, an isolated episode consisting of photo-sensitive 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].

Abnormal electroencephalograms (EEG) have been observed in persons with EA1 [Van Dyke 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 three-year-old boy 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.

Neuromimaging with MRI is usually normal; however, Demos et al [2009] reported a family with cerebellar atrophy.

Genotype-Phenotype Correlations

Due to significant interfamilial and intrafamilial phenotypic variability, reliable genotype-phenotype correlations have been extremely difficult to establish. 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* mutation exhibit features of EA1; however, penetrance is incomplete.

Nomenclature

EA1 has also been known as:

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

Prevalence

EA1 is a rare disease and the prevalence can be estimated only roughly. At present, several families from the United States, Brazil, United Kingdom, The Netherlands, Australia, Italy, Spain, and Russia 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.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Table 2. Episodic Ataxia: OMIM Phenotypic Series

Phenotype	Phenotype MIM number	Gene/Locus	Gene/Locus MIM number
Episodic ataxia/myokymia syndrome	160120	*KCNA1, AEMK, EA1*	176260
Episodic ataxia, type 2	108500	*CACNA1A, CACNL1A4, SCA6*	601011
Episodic ataxia, type 3	606554	*EA3*	606554
Episodic ataxia, type 4	606552	*EA4, PATX*	606552
Episodic ataxia, type 5	613855	*CACNB4, EJM6, EA5, EIG9*	601949
Episodic ataxia, type 6	612656	*SLC1A3, EAAT1, EA6*	600111
Episodic ataxia, type 7	611907	*EA7*	611907

Data from Online Mendelian Inheritance in Man

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

- **Episodic ataxia type 2 (EA2)** is characterized by paroxysmal attacks of ataxia, vertigo, and nausea typically lasting minutes to days in duration. Stress, exertion, caffeine, and alcohol may trigger attacks that can be associated with dysarthria, diplopia, tinnitus, dystonia, hemiplegia, and headache. Approximately 50% of individuals with EA2 have migraine headaches. Onset is typically in childhood or early adolescence. MRI can demonstrate atrophy of the cerebellar vermis. EA2 is inherited in an autosomal dominant manner. Mutations in *CACNA1A*, which encodes for a voltage-dependent Ca^{2+} channel alpha subunit, can cause this disease.

- **Episodic ataxia type 3 (EA3)** [OMIM 606554] has been described in two families of northern European origin from rural North Carolina by Farmer & Mustian [1963] and Vance et al [1984]. A relationship between the two kindreds is suspected but has not been established. EA3 is characterized by attacks of vertigo, diplopia, and ataxia beginning in early adulthood. In some individuals, slowly progressive cerebellar ataxia occurs. This condition does not link to loci identified with EA1, EA2, or spinocerebellar ataxia types 1, 2, 3, 4, and 5 [Damji et al 1996]. A candidate region on chromosome 1q42 has been identified [Cader et al 2005].
- **Episodic ataxia type 4 (EA4)** [OMIM 606552] has been described in a large Canadian Mennonite family [Steckley et a 2001]. EA4 is also known as familial periodic vestibulocerebellar ataxia and is characterized by brief acetazolamide-responsive attacks of vestibular ataxia, vertigo, tinnitus, and interictal myokymia. Interictal nystagmus and ataxia were not identified. The age of onset is variable. The gene defect that underlies EA4 is not known; EA4 does not link to the loci for EA1 or EA2.
- **Episodic ataxia type 5 (EA5)** [OMIM 601949] can result from a mutation in *CACNB4*, encoding the beta-4 isoform of the regulatory beta subunit of voltage-activated Ca(2+) channels. A c.311G>T (p.Cys104Phe; reference sequences NM_000726.3; NP_000717.2) mutation has been described in a French-Canadian family [Escayg et al 2000]. The phenotype was characterized by recurrent episodes of vertigo and ataxia that lasted for several hours. Interictal examination showed spontaneous downbeat and gaze-evoked nystagmus and mild dysarthria and truncal ataxia. Acetazolamide prevented the attacks. EA5 is allelic with juvenile myoclonic epilepsy (JME); the semiology of seizures in EA5 is similar to JME.
- **Episodic ataxia type 6 (EA6)** [OMIM 612656] is characterized by attacks of ataxia precipitated by fever, subclinical seizures, slurred speech followed by headache, and bouts of arm jerking with concomitant confusion and alternating hemiplegia. EA6 can result from mutations in *SLC1A3*, which encodes the excitatory amino acid transporter 1 (EAAT1). 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].
- **Episodic ataxia type 7 (EA7)** [OMIM 611907] has been described in a four-generation family whose affected individuals showed episodic ataxia before age 20 years [Kerber et al 2007]. The disease is characterized by attacks associated with weakness, vertigo, and dysarthria lasting hours to days. Attacks may be brought about by exercise and excitement. A candidate region on chromosome 19q13, termed the EA7 locus, has been identified [Kerber et al 2007].
- **Autosomal dominant spastic ataxia (ADSA)** [OMIM 108600]. Affected individuals initially show progressive leg spasticity of variable degree followed by ataxia in the form of involuntary head jerk, dysarthria, dysphagia, and ocular movement abnormalities. The age at onset is from early childhood to early twenties. Linkage studies identified a locus on 12p13, termed SAX1 [Meijer et al 2002].
- **Familial paroxysmal kinesigenic dyskinesia (PKD)** is characterized by attacks of dystonia, choreoathetosis, and ballism that last seconds to hours and are sometimes preceded by an aura and precipitated by sudden movements, cold, hyperventilation, and mental tension. Attacks can be as frequent as 100 per day to as few as one per month. Age of onset is typically in childhood [Bruno et al 2004]. Familial PKD is inherited in an autosomal dominant manner; the gene(s) associated with PKD have not been identified. Linkage of familial PKD to 16q11.2-q22.1 has been established in several families with PKD [Tomita et al 1999, Bennett et al 2000, Valente et al 2000].
- **Familial paroxysmal nonkinesigenic dyskinesia (PNKD)** is characterized by attacks of dystonia, chorea, ballismus or athetosis provoked by alcohol, caffeine, excitement, stress, or fatigue. Attacks are not typically triggered by movement, may be accompanied by a preceding aura, last minutes to hours, and rarely occur more than once per day. Age of onset is typically in childhood or early teens. Familial PNKD is inherited in an autosomal dominant manner; *PNKD*, encoding myofibrillogenesis regulator 1, is the only gene known to be associated with this disease [Lee et al 2004b, Rainier et al 2004, Chen et al 2005a]. A second locus for familial PNKD has been identified on chromosome 2q31 in a Canadian family of European descent [Spacey et al 2006].
- **Isaacs syndrome** (acquired neuromyotonia, NMT) is a rare neuromuscular disorder characterized by hyperexcitability of the motor nerve that results in continuously contracting or twitching muscles (myokymia) and muscle hypertrophy. Individuals also experience cramping, increased sweating, and delayed muscle relaxation. Stiffness is most prominent in limb and trunk muscles. Symptoms are not usually triggered by exercise and occur even during sleep or when individuals are under general anesthesia. A few affected individuals report sleep disorders, anxiety, and memory loss (Morvan syndrome). Onset is between ages 15 and 60 years. The acquired form occasionally develops in association with peripher neuropathies or after radiation treatment. Twenty percent of affected individuals have an associated thymoma. Antibodie to voltage-gated potassium channels are detected in approximately 40% of affected individuals [Hart et al 2002]. It has been shown that antibodies bind variably to the Kv1.1- and 1.2-containing juxtaparanodes of peripheral and central myelinated axons [Kleopa et al 2006].

Note to clinicians: For a patient-specific 'simultaneous consult' related to this disorder, go to SimulConsult®, an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with episodic ataxia type 1, the following evaluations are recommended:

- Detailed medical history of the individual

- Neurologic examination
- Initiation (and observation) of attacks of ataxia by either mild exercise or vestibular stimuli
- EMG to confirm the presence of myokymia, particularly if it is not visible on examination
- EEG to look for epilepsy [Zuberi et al 1999, Eunson et al 2000, Chen et al 2007]
- Medical genetics consultation

Treatment of Manifestations

Acetazolamide (ACTZ), a carbonic-anhydrase (CA) inhibitor, may reduce the frequency and severity of the attacks in some but not all affected individuals. The mechanism by which ACTZ reduces the frequency and severity of the attacks is unclear. The recommended starting dosage is 125 mg once a day, given orally. However, individuals with good renal function may require higher daily doses, ranging from 8 to 30 mg/kg/day in one to four divided doses (not to exceed 1 g/day). ACTZ should not be prescribed to individuals with liver, renal, or adrenal insufficiency.

Chronic treatment with ACTZ may result in side effects including paresthesias, rash, and formation of renal calculi.

Antiepileptic drugs (AEDs) may significantly reduce the frequency of the attacks in responsive individuals; however, the response is heterogeneous as some individuals are particularly resistant to drugs [Eunson et al 2000].

- **Diphenylhydantoin** treatment at a dose of 150-300 mg daily resulted in reasonable control of seizures in some individuals [Van Dyke et al 1975]. In particular, phenytoin treatment at a dose of 3.7 mg/kg/day may improve muscle stiffness and motor performance [Kinali et al 2004]. Nevertheless, phenytoin should be used with caution in young individuals, as it may cause permanent cerebellar dysfunction and atrophy [De Marco et al 2003].
- **Sulthiame** 50-200 mg daily may reduce the attack rate. During this treatment abortive attacks were still noticed lasting few seconds and troublesome side effects were paresthesias and intermittent carpal spasm.
- **Carbamazepine** up to 1600 mg daily [Eunson et al 2000]. However, the dose needs to be adjusted according to differen factors including, age, weight, the particular carbamazepine product being used, responsiveness of the individual, and other medications being taken.

Prevention of Primary Manifestations

In addition to the pharmacologic treatments mentioned above behavioral measures, such as avoidance of stress, abrupt movements, loud noises or caffeine intake may be used 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

General anesthetics have occasionally been reported to precipitate or aggravate neuromyotonia [Eunson et al 2000].

Evaluation of Relatives at Risk

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, the mother should be made aware that during attacks, loss of balance and falls could endanger the fetus's life. Several stressors trigger attacks that may cause breathing difficulties, thus, delivery by C-section should be considered.

Therapies Under Investigation

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

Other

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 *V408A/V408A* mutations are embryonically lethal in an animal model of EA1 [Herson et al 2003], although this has not been reported in humans.

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available

consumer-oriented resources. See the GeneTests Clinic Directory.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with episodic ataxia type 1 have an affected parent.
- A proband with episodic ataxia type 1 may have the disorder as the result of a new gene mutation. To date, only one *de novo* mutation has been identified [Demos et al 2009].
- If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include accurate neurologic evaluation and sequence analysis of *KCNA1*. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: (1) Although most individuals diagnosed with episodic ataxia type 1 have an affected parent, the family history 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. (2) If the parent is the individual in whom the mutation first occurred s/he may have somatic mosaicism for the mutation 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%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- The sibs of a proband with clinically unaffected parents are still at increased risk for the disorder because of the possibility of reduced penetrance in a parent.
- If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, the risk to sibs is low, but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Each child of an individual with episodic ataxia type 1 has a 50% chance of inheriting the mutation.

Other family members. The risk to other family members depends on the status of the proband's parents. If a parent is affected, his or her family members may be at risk.

Related Genetic Counseling Issues

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

Family planning

- The optimal time for determination of genetic risk 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 is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by

amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximatel ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified in the family before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period o by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

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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**
  Lincoln House
  1-3 Brixton Road
  London SW9 6DE
  United Kingdom
  Phone: 0845 644 0606 (helpline); 020 7582 1444 (office); +44 (0) 20 7582 1444 (from abroad)
  Email: helpline@ataxia.org.uk; office@ataxia.org.uk
  www.ataxia.org.uk
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  Ataxia UK
  9 Winchester House
  Kennington Park
  London SW9 6EJ
  United Kingdom
  Phone: +44 (0) 207 582 1444
  Email: marco.meinders@euro-ataxia.eu
  www.euro-ataxia.eu
- **International Network of Ataxia Friends (INTERNAF)**
  Email: internaf-owner@yahoogroups.com
  www.internaf.org
- **National Ataxia Foundation**
  2600 Fernbrook Lane
  Suite 119
  Minneapolis MN 55447
  Phone: 763-553-0020
  Email: naf@ataxia.org
  www.ataxia.org
- **WE MOVE: Worldwide Education and Awareness for Movement Disorders**
  204 West 84th Street
  New York NY 10024
  Phone: 866-546-3136 (toll-free)
  Fax: 212-875-8389
  Email: wemove@wemove.org
  www.wemove.org
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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 Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
KCNA1	12p13.32	Potassium voltage-gated channel subfamily A member 1	KCNA1 homepage - Mendelian genes	KCNA1

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) 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 Genetic Pathogenesis

Voltage-gated potassium channels (Kv) play key roles in neurotransmission and nerve cell physiology. Kv channels 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 [Hille 2001, Pessia 2004]. In particular, Kv1.1 channels (encoded by *KCNA1*) regulate neuromuscular transmission, control the release of β-aminobutyric acid (GABA) from cerebellar basket cells onto Purkinje cells [Herson et al 2003], and modulate synaptic transmission in hippocampus [Geiger & Jonas 2000].

Nomenclature of Kv channels is organized by subfamilies based on sequence relatedness by using the abbreviation Kvy.x whereby the prefix specifies both the permeating ion (K^+) and the voltage-dependence of the channel (v). According to this standardized nomenclature Shaker-related channels have been classified in the subfamily Kv1.x and each member numbered Kv1.1 through Kv1.9. The same criteria have been used to classify auxiliary subunits (Kvβ1.1 and Kvβ1.2) and channels related to the subfamilies Shab (Kv2.1 and Kv2.2), Shaw (Kv3.1 to 3.4) and Shal (Kv4.1 to Kv4.3).

Functional homomeric Kv1.1 channels are tetrameric structures composed of four identical monomers. Each monomer is encoded by *KCNA1*.

However, potassium channel diversity is greatly enhanced by the ability of different types of pore-forming subunits to heteropolymerize and to form channels with properties different from the parental homomeric channels. Kv channels may 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 to the ion channel complex and provide four inactivation particles. Notable examples:

- Heteromeric channels composed of Kv1.1 and Kv1.2 that are expressed at cerebellar basket cell terminals and at the juxtaparanodal region of motor axons
- Channels composed of Kv1.1, Kv1.4, and, Kvβ1.1 subunits that are expressed in hippocampal mossy fiber boutons

Kv1.1 channels possess a slower 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.

D'Adamo et al first demonstrated that *KCNA1* mutations 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]. Successively, it has been shown that *KCNA1* mutations also impair the function of hetero-oligomeric complexes comprising Kv1.1, Kv1.4, and Kvβ1.1 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.

Normal allelic variants. *KCNA1* has a transcript of 7983 nucleotides with a coding region of 1488. There are two exons, but the coding region is located entirely within exon 2. In 5% of control chromosomes analyzed by Zuberi et al [1999] two silent changes in the coding sequence were observed, c.684T>C and c.804G>C (see Table 3). The reference sequences in Table 3 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].

Pathologic allelic variants. To date, 23 *KCNA1* mutations have been identified by sequence analysis (see Figure 1). Most are missense mutations that are distributed throughout the gene; however, nonsense and small deletion mutations have also been identified [Eunson et al 2000, Shook et al 2008].

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

Table 3. Selected *KCNA1* Allelic Variants

Class of Variant Allele	DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change	Reference Sequences
Normal	c.684T>C (C684T)	p.= [2]	NM_000217.2 NP_000208.2
	c.804G>C (C804G)	p.= [2]	
Pathologic	c.676A>G	p.Thr226Ala	
	c.677C>G	p.Thr226Arg	
	c.677C>T	p.Thr226Met	
	c.1222G>T	p.Val408Leu	
	c.1241T>G	p.Phe414Cys	
	c.1249C>T	p.Arg417X	
	c.748_750delTTC	p.Phe250del	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Variant designation that does not conform to current naming conventions

2. p.= designates that protein has not been analyzed, but no change is expected.

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 upon 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 (see also Molecular Genetic Pathogenesis).

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]. 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* mutations 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].

Individuals with EA1 are heterozygous for a *KCNA1* disease-causing mutation, 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 mutant 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 mutations in a single gene disrupt the functions of other closely related proteins [D'Adamo et al 1999, Rea e al 2002, Imbrici et al 2006]. 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 mutation analogous to the human p.Val408Ala mutation 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 mutant animals may contribute to spontaneou 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 2005b].

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page PubMed

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Chapter Notes

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- 21 April 2009 (mp) Initial submission

Figures

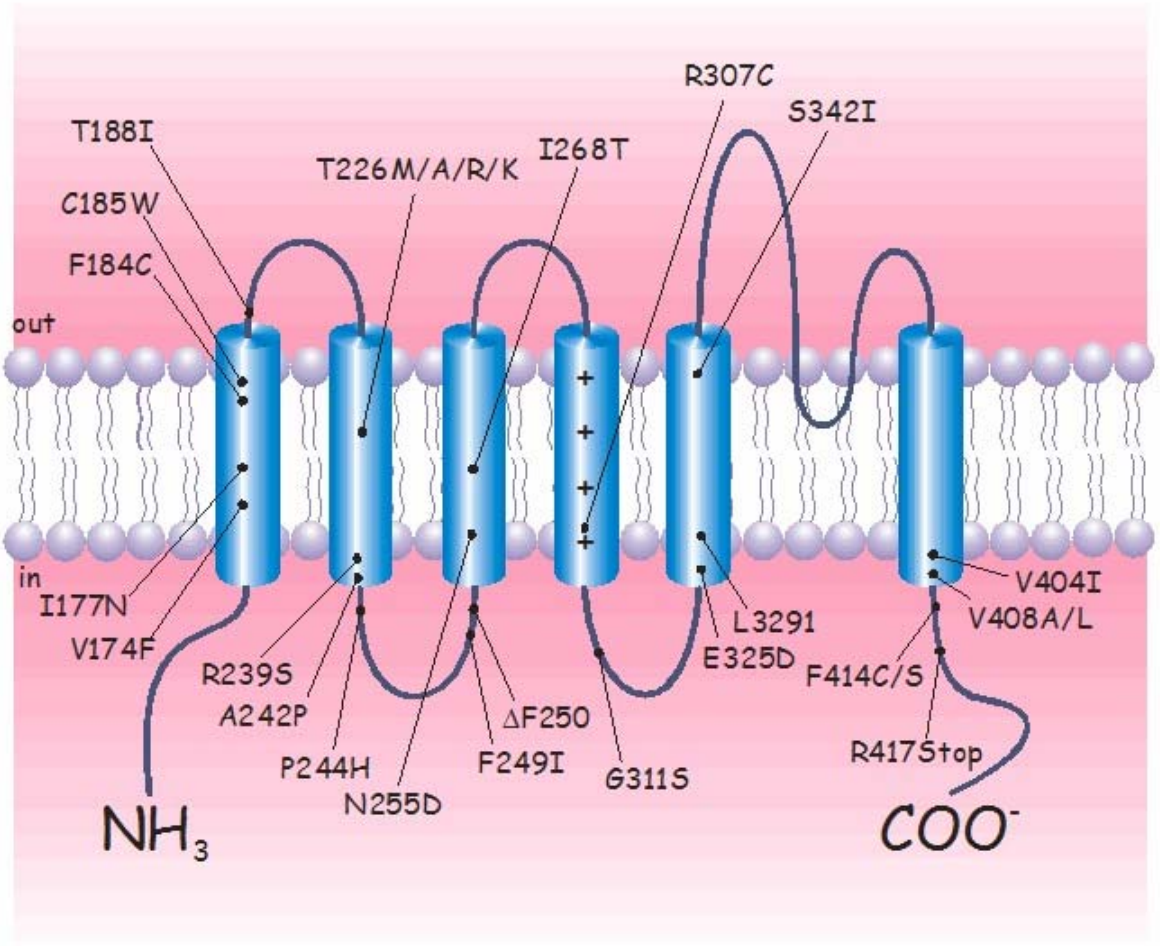

Figure 1. Schematic drawing of the conventional membrane topology of a human Kv1.1 subunit. Four such subunits comprise a functional homotetrameric channel. Different subunits belonging to the Kv1 subfamily may form heterotetrameric channels. The positions of mutations identified to date in individuals with EA1 are indicated [D'Adamo et al 2012].

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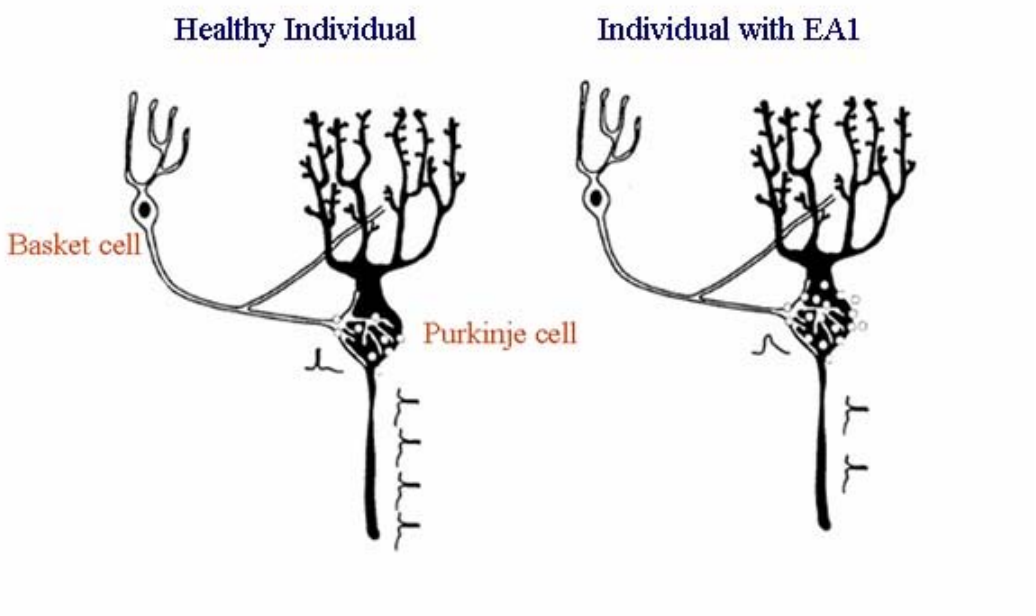

Figure 2. Proposed effects of EA1-causing mutations on basket cell and Purkinje cell inhibitory outputs.

The diagram shows a basket cell which has synapses on the initial segment and soma of a number of Purkinje cells from the cerebellar cortex of a normal 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 syndrome (see D'Adamo et al 1999, Figure 7).

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