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REVIEW ARTICLE

Primary episodic ataxias: diagnosis, pathogenesis and treatment

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Primary episodic ataxias are autosomal dominant channelopathies that manifest as attacks of imbalance and incoordination. Mutations in two genes, *KCNA1* and *CACNA1A*, cause the best characterized and account for the majority of identified cases of episodic ataxia. We summarize current knowledge of clinical and genetic diagnosis, genotype–phenotype correlations, pathophysiology and treatment of episodic ataxia syndromes. We focus on unresolved issues including phenotypic and genetic heterogeneity, lessons from animal models and technological advancement, rationale and feasibility of various treatment strategies, and shared mechanisms underlying episodic ataxia and other far more prevalent paroxysmal conditions such as epilepsy and migraine.

Keywords: episodic ataxia; channelopathies; review

Abbreviations: CSD = cortical spreading depression; EA = episodic ataxia; IPSCs = inhibitory post-synaptic currents

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Introduction

Episodic ataxias are rare neurological conditions characterized by spells of incoordination and imbalance, often with associated progressive ataxia. The genes lesioned in episodic ataxia of early onset include neuronal voltage-gated potassium and calcium channels, which are widely distributed in the nervous system but are particularly abundant in the cerebellum. The genetic identification of these genes broadened the clinical spectrum of episodic ataxia, now known to be variably associated with epilepsy, dystonia, hemiplegic migraine, myasthenia and even intermittent coma. How mutations in these ion channel genes cause a broad spectrum of paroxysmal neurological symptoms and lead to progressive neurodegeneration is not understood. Furthermore, there is much variation regarding clinical manifestations and response to medications even among patients with the same mutations, suggesting that other factors modulate the phenotypic expression of disease-causing mutations. Episodic ataxia is clinically and genetically heterogeneous (Table 1); many patients with episodic ataxia, especially those with onset after early adulthood (Julien *et al.*, 2001) or no interictal signs, await further genetic characterization and mutation identification.

The major symptoms and disability of episodic ataxia are episodic ataxia and progressive, inter-attack weakness, dystonia and ataxia. The symptoms are mainly cerebellar in origin. The cerebellum does not initiate movement, but it compares what the cortex wished to accomplish and what the spinal cord actually executed to modulate cortical activities and orchestrate the timing of contraction and relaxation of the agonist and antagonist muscles to perform complex motor tasks. At the core of the cerebellar computational circuitry are the Purkinje cells, which integrate cortical and sensory excitatory and inhibitory inputs, encode relevant information in their firing rate, then relay the information to the deep cerebellar nuclei for the final output of the cerebellum. There is an enormous convergence of synaptic activity onto each Purkinje cell, with input from mossy fibres, parallel fibres, climbing fibres and noradrenergic fibres. In principle, defects in any of these components can result in cerebellar dysfunction and ataxia.

Table 1 Clinical features of the primary episodic ataxia syndromes

	EA1	EA2	EA3	PATX/EA4	EA5	EA6	Other EAs
OMIM	160120	108500	606554	606552	601949	600111	Unassigned
Attack duration	sec–min	hours	1min–6hr	brief	hours	hours–days	hours–days
Age of onset	2–15	2–20	1–42	23–60	3-teen	5	after 30
Myokymia	usual	no	usual	no	no	No	No
Nystagmus	no	usual	occasional	usual	usual	No	Usual
Epilepsy	occasional	infrequent	occasional	occasional	usual	Yes	No
Tinnitus	infrequent	no	usual	occasional	no	No	No
Acetazolamide	occasional	usual	usual	no	transient	No	Occasional
Inheritance	AD	AD	AD	AD	AD	Sporadic	Multiple
chr locus	12q13	19p13	1q42	unknown	2q22-q23	5p	Unknown
Mutated gene	*KCNA1*	*CACNA1A*	unknown	unknown	*CACNB4*	*SLC1A3*	Unknown
Mutant protein	Kv1.1	Cav2.1	unknown	unknown	Cav2.1	EAAT1	Unknown

At least six episodic ataxia (EA) syndromes have been described, but only EA1 and EA2 have been documented in multiple families. Recent genetic discoveries are providing insight into the molecular mechanisms of these dramatic clinical disorders (Table 1). The incidence of episodic ataxia is likely to be less than 1/100 000, based on the cases seen by experts in regional centres.

EA1

Clinical features

Autosomal dominant episodic ataxia type 1 (EA1) is characterized by brief episodes of ataxia (seconds to minutes) and interictal myokymia (also termed neuromyotonia) (Browne *et al.*, 1994). The onset is typically in early childhood. The episodes of ataxia, which can be associated with dysarthria and a coarse tremor, are typically precipitated by physical and emotional stress, startle or sudden movements (Brunt and Van Weerden, 1990). Aura-like symptoms, including a feeling of falling or weakness, may also occur. The interictal myokymia may be detected clinically or may only be apparent by surface or needle electromyography (EMG). Phenotypic variants such as the combination with partial epilepsy, shortening of the Achilles tendon in children, transient postural abnormalities in infancy, peripheral weakness and neuromyotonia without episodes of ataxia have also been reported (Zuberi *et al.*, 1999; Eunson *et al.*, 2000; Klein *et al.*, 2004). Although the typical duration of attacks is seconds to minutes, recurring up to 30 times a day, atypical variants with prolonged attacks lasting 5 to 12 h have also been described (Lee *et al.*, 2004).

Genetic characteristics

The EA1 locus was mapped to chromosome 12q near a cluster of three potassium channel genes (Litt *et al.*, 1994). Missense mutations in *KCNA1* were discovered in multiple EA1 pedigrees (Browne *et al.*, 1994, 1995). These were the first report of mutations in a human potassium channel gene and the first known ion channel mutations involving the brain.

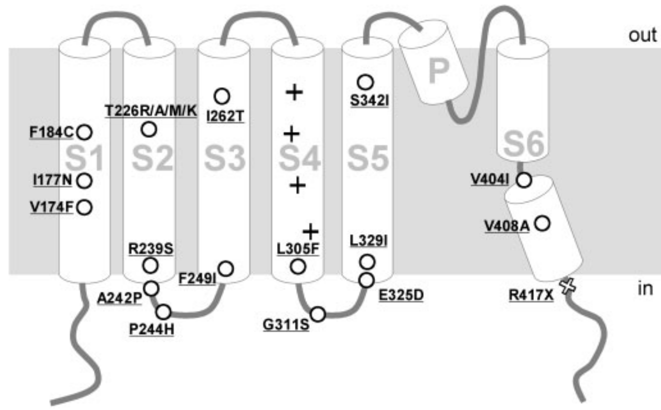

Fig. 1 EA1 mutations in Kv1.1 represented in two dimensions. The predicted structure includes six transmembrane segments (S1–S6). Four such subunits come together to form a functional voltage-gated potassium channel. S4 with regularly spaced positively charged residues is the main voltage sensor. S5, S6 and the re-entrant P loop form the pore with selectivity for K^+. Circles represent missense mutations; the cross represents a nonsense mutation.

Genotype–phenotype correlations

To date, 19 missense mutations and one truncation mutation in *KCNA1* have been reported (Browne *et al.*, 1994, 1995; Comu *et al.*, 1996; Scheffer *et al.*, 1998; Zerr *et al.*, 1998; Bretschneider *et al.*, 1999; Zuberi *et al.*, 1999; Eunson *et al.*, 2000; Knight *et al.*, 2000; Kinali *et al.*, 2004; Klein *et al.*, 2004; Lee *et al.*, 2004; Chen *et al.*, 2006; Poujois *et al.*, 2006) (Fig. 1). The mutations are distributed throughout Kv1.1. *In vitro* expression studies indicate that all mutations impair Kv1.1 function, predicting increased neuronal excitability (Adelman *et al.*, 1995; Bretschneider *et al.*, 1999; Eunson *et al.*, 2000; Rea *et al.*, 2002). The degree and nature of the potassium channel dysfunction appears to explain the phenotypic diversity observed.

Mutations associated with relatively severe phenotypes poorly responsive to medications or associated with seizures tend to show profound reductions in potassium currents when compared to wild type. On the other hand, mutations associated with neuromyotonia alone without ataxia do not alter current amplitude and have only subtle effects on voltage threshold and time course of activation. Mutations associated with the more typical EA1 phenotype show an intermediate pattern; the current amplitude is unaffected but the voltage threshold for activation is significantly increased.

Pathophysiology

Kv1.1 is a human homolog of the *Shaker* channel in Drosophila (Papazian *et al.*, 1987) and is abundantly expressed in the cerebellum and perinodally along motor axons (Wang *et al.*, 1994). Most of the mutations involve the transmembrane segments of the Kv1.1 subunit altering channel dynamics. Well-known triggers for episodes of ataxia include stress, caffeine, hormonal changes and fatigue. The mechanism by which these triggers initiate attacks is largely unknown.

Animal models

The *KCNA1* knockout mouse, which lacks Kv1.1 channels, suffers from epileptic seizures but not episodic ataxia (Smart *et al.*, 1998). More recently, a knockin mouse model bearing the human EA1 mutation V408A was created by homologous recombination. (Herson *et al.*, 2003). In contrast to the *KCNA1* null mutation, the V408A mutation is embryonic lethal in the homozygous state. In contrast, heterozygous V408A/+ mice exhibit stress-induced loss of motor coordination that is ameliorated by acetazolamide, similar to human patients with EA1. Consistent with the Kv1.1 localization in GABAergic cells in the cerebellum, recordings of spontaneous inhibitory post-synaptic currents (IPSCs) in Purkinje cells from cerebellar slices of V408A knockin mice reveal an increased frequency and amplitude of IPSCs compared to wild-type littermates; neither the amplitude or frequency of miniature IPSCs nor the frequency of basket cell firing was different. These electrophysiologic data suggest that the behavioural changes are linked to changes in GABA release in the cerebellum. Consistent with Kv1.1 localization in the hippocampus, knockin EA1 mice exhibit impaired spatial learning and memory and a reduced induction of synaptic plasticity in *KCNA1*-expressing neurons.

EA2 and allelic disorders

Clinical features

Episodic ataxia type 2 (EA2) is characterized by longer episodes of ataxia (hours) with interictal nystagmus and mildly progressive baseline ataxia (Baloh *et al.*, 1997; Jen *et al.*, 2004a). As with EA1, episodes are commonly triggered by physical and emotional stress. The attacks can be dramatically responsive to acetazolamide. EA2 is by far the most common episodic ataxia syndrome. Like EA1, the onset of EA2 is typically early in life. There has only been one report of EA2 with onset after age 60 years (Imbrici *et al.*, 2005). Episodes can vary from a pure ataxia to combinations of symptoms suggesting involvement of the cerebellum and brainstem and even occasionally the cerebral cortex. Vertigo, nausea and vomiting are the most commonly associated symptoms, occurring in more than 50% of patients. About half of the patients report headaches that meet the International Headache Society (IHS) criteria for migraine. On examination during an acute episode of ataxia, patients typically exhibit a spontaneous nystagmus not seen during the interictal examination. Between episodes, the most common finding is a gaze-evoked nystagmus with features typical of rebound nystagmus. Spontaneous vertical nystagmus, particularly downbeat nystagmus, is seen in about one-third of cases. This may begin with a positional downbeat nystagmus in the head-hanging position that over time becomes a spontaneous downbeating nystagmus.

EA2 is allelic with familial hemiplegic migraine type 1 (FHM1) (Ophoff *et al.*, 1996) and, in some families, episodes of both ataxia and hemiplegic migraine occur in the same patients (Jen *et al.*, 1999; Ducros *et al.*, 2001). EA2 patients can also have progressive ataxia (Yue *et al.*, 1997; Denier *et al.*, 1999), fluctuating weakness (Jen *et al.*, 2001), epileptic seizures (Jouvenceau *et al.*, 2001; Jen *et al.*, 2004a; Kors *et al.*, 2004) and dystonia (Spacey *et al.*, 2005).

Genetic characteristics

The disease locus of EA2 was mapped to chromosome 19p (Kramer *et al.*, 1995; Vahedi *et al.*, 1995; von Berderlow *et al.*, 1995) in the same region as the disease locus for FHM1 (Joutel *et al.*, 1993). A calcium channel gene *CACNA1A* mapped to this locus on chromosome 19p. Ophoff and colleagues (1996) characterized the genomic structure of *CACNA1A* and identified missense mutations in FHM1 and truncation (frameshift and splice site) mutations in EA2.

The gene *CACNA1A* is extensively alternatively spliced that additional exons have since been identified (Zhuchenko *et al.*, 1997; Bourinet *et al.*, 1999; Soong *et al.*, 2002). A polymorphic stretch of CAG repeats thought to be in the 3′ untranslated region was in fact translated in a longer splice variant that may be the predominant form in the human cerebellum (Ishikawa *et al.*, 1999). Glutamine-encoding CAG-repeat expansion in *CACNA1A* causes spinocerebellar ataxia type 6 (SCA6), a dominantly inherited pure cerebellar ataxia syndrome of late onset (Zhuchenko *et al.*, 1997). Thus, EA2, FHM1 and SCA6 are allelic disorders, all caused by mutations in *CACNA1A*.

Genotype–phenotype correlations

A wide range of phenotypes have been associated with mutations in *CACNA1A* (Fig. 2; Table 2). There is much

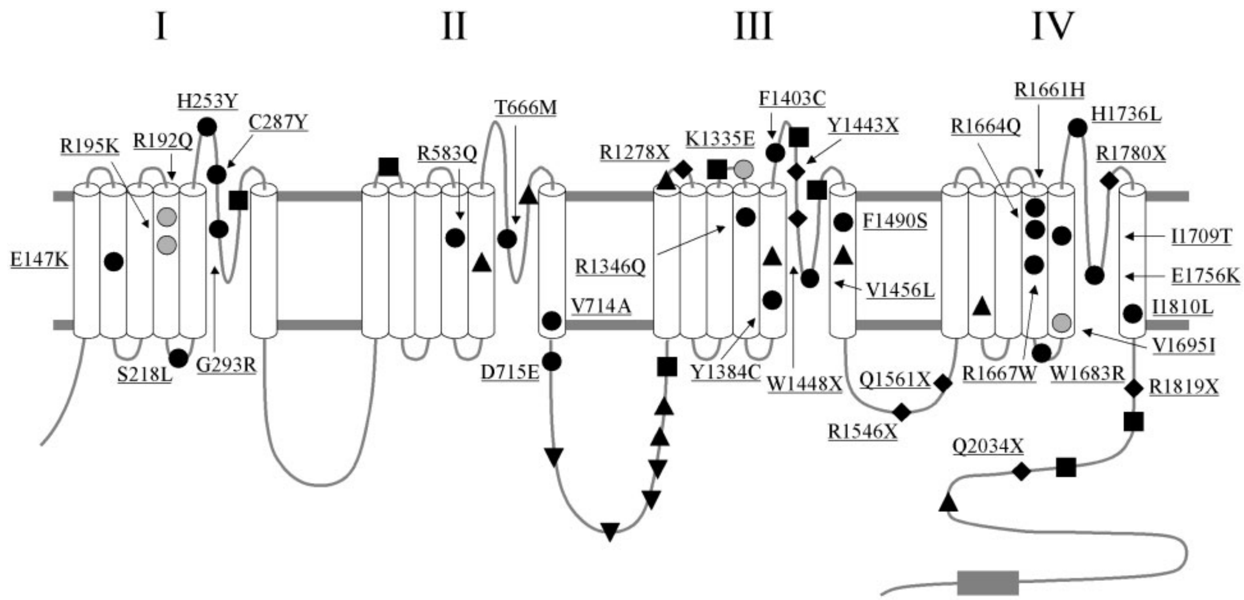

Fig. 2 EA2 mutations in Cav2.1 represented in two dimensions. The predicted structure includes four homologous domains (I–IV), each with six transmembrane segments (SI–S6). Symbols denote mutations: circles—missense; diamond—nonsense; upward triangles—nucleotide deletions; downward triangles—nucleotide insertions; squares—aberrant splicing; rectangle—polyQ in SCA6. Grey symbols represent mutations with pure hemiplegic migraine without cerebellar features. The amino acid residues are numbered according to RefSeq NM_023035, which is the long isoform that includes the polyglutamine tract in the C-terminal.

Table 2 Currently identified phenotypes associated with mutations in *CACNA1A*

Phenotype	Type of mutation
Familial hemiplegic migraine (FHMI)	Missense, usually S4–S6 regions
Episodic ataxia type 2 (EA2)	Usually interrupts reading frame, can be missense
Severe progressive ataxia with episodic features	Missense in pore region
Cerebral oedema and coma after trauma	Missense in I S-4–S5 link
Spinocerebellar ataxia type 6 (SCA6)	CAG repeat expansion in carboxy terminus
Late-onset episodic ataxia	In-frame insertion

clinical overlap among EA2, FHM1 and SCA6. The majority of patients with FHM1 have cerebellar symptoms and signs (Ducros *et al.*, 2001). Over half of the EA2 patients have migraine (Jen *et al.*, 2004a). Although SCA6 is characterized by progressive ataxia, patients with SCA6 can present with fluctuating ataxia similar to EA2 (Baloh *et al.*, 1997; Geschwind *et al.*, 1997; Jodice *et al.*, 1997). On the other hand, some members of an EA2 family presented with prominent progressive ataxia (Yue *et al.*, 1997) reminiscent of SCA6.

As a general rule, all FHM1 mutations are missense mutations and most, but not all, EA2 mutations disrupt the open reading frame, likely subject to nonsense mediated mRNA decay or rapid degradation of truncated protein products. The location and type of mutation are important but are not the only determining factors. Ducros *et al.* (2001) reported results of their studies on the clinical manifestations associated with mutations in *CACNA1A* in 28 families with FHM1. Overall, they found nine mutations in *CACNA1A*, all of which were missense mutations. Eighty-nine percent of subjects with mutations had attacks of hemiplegic migraine. Six mutations were associated with hemiplegic migraine and cerebellar signs and 83% of the subjects with these six mutations had nystagmus, ataxia or both. Only three mutations were associated with pure hemiplegic migraine. Jen *et al.* (2004a) found a wide range of mutations associated with the EA2 phenotype. Most commonly, mutations predicted premature termination of the open reading frame, with a range of truncation sites from the shortest having only domain 1 intact, to the longest having all four domains intact with only a truncation of the C terminus. Missense mutations typically involved the pore loop region of the protein. Functional studies of the mutated channel in EA2 have shown a marked reduction in current expression and deficiencies in plasma membrane targeting (Guida *et al.*, 2001; Wan *et al.*, 2005b). As with EA1, more severe mutations are generally associated with more severe functional effects, both with regard to current expression and plasma membrane targeting.

Pathophysiology

CACNA1A encodes the pore-forming and voltage-sensing subunit Cav2.1 of the P/Q type voltage-gated calcium channels. These channels are abundantly expressed in the cerebellum and presynaptically at the neuromuscular junction (Mori *et al*., 1991; Ludwig *et al*., 1997). Genetic analysis in EA2 families have revealed over 50 mutations in *CACNA1A* with more than two-thirds predicting a premature stop owing to nonsense mutations or defects in splice sites (Denier *et al*., 1999; Jen *et al*., 2004a; Wan *et al*., 2005a; Eunson *et al*., 2005). Cav2.1 is highly expressed at the neuromuscular junction, where calcium entry through P-type calcium channels triggers acetylcholine release at motor nerve terminals. Unlike the cerebellum, which is inaccessible for *in vivo* electrophysiological investigation, the neuromuscular junction is easily accessible and has proven informative in unraveling not only the peripheral manifestations but also synaptic remodelling in the periphery. Although EA2 patients complain of fluctuating weakness but typically do not manifest weakness at baseline, electromyographic studies demonstrate a reduced safety factor of neuromuscular transmission and increased jitter and blocking on voluntary single fibre electromyography (Jen *et al*., 2001). *In vitro* microelectrode studies in patients with genetically characterized EA2 showed marked reduction of end plate potential quantal content, confirming a presynaptic defect in neuromuscular transmission (Maselli *et al*., 2003). Interestingly, the end plate potentials showed high sensitivity to N-type blockade with omega conotoxin not seen in controls. The finding of impaired neuromuscular transmission in EA2 patients is consistent with a loss-of-function mechanism for EA2 mutations. The presence of N-type calcium channels in the neuromuscular junction of EA2 patients reflects a possible compensatory mechanism to restore normal activity both at the neuromuscular junction and at central neuronal synapses.

As in the case of EA1, the mechanism for the episodic features with EA2 is largely unknown. Understanding the mechanism of these rare episodic neurological disorders should provide insight into understanding the pathophysiology of the more common episodic neurological disorders such as epilepsy and migraine. Although channelopathies underlie several neurological disorders characterized by episodic symptoms, mutations in genes that do not encode ion channels have been found to cause recurrent episodic symptoms, emphasizing indirect ways by which neuronal excitability can be modulated. For example, a mutation in casein kinase 1-δ (CK1δT44A) which causes a familial form of advanced sleep phase syndrome (FASPS) also causes migraine with aura (Xu *et al*., 2005). Cortical spreading depression (CSD) is thought to be the pathophysiologic mechanism underlying migraine with aura and a lower threshold for CSD could be a common mechanism for episodic neurological dysfunction. Mice transgenic for human CK1δT44A were found to have a significantly decreased threshold for CSD compared to controls and a significantly increased number of CSD events per level of stimulus compared to controls. Mutations in ion channels can also lead to a decreased threshold for CSD and spontaneous neuronal discharge (see later).

Animal models

The recessive mouse models *tottering*, *leaner*, *rolling Nagoya* and *rocker* harbouring mutations in murine *Cacna1a* have epilepsy, dystonia and ataxia (Fletcher *et al*., 1997; Mori *et al*., 2000; Zwingman *et al*., 2001). In *tottering* mice, the attacks of dyskinesia are triggered by clinically relevant precipitants such as stress and caffeine (Fureman *et al*., 2002). Function studies in *tottering* mice show reduced current density from Cav2.1 channels, which are expressed abundantly in cerebellar Purkinje and granule cells. This would result in a general reduction in Purkinje cell firing rates and a loss of inhibition of deep cerebellar nuclei. These mouse models are consistent with the loss-of-function hypothesis for Cav2.1, as has been proposed for its human EA2 mutations.

A mutant mouse model harbouring a human FHM1 mutation R192Q (with no associated cerebellar symptoms in human) complicates the quandary of whether these mutations lead to a gain- versus a loss-of-function (van den Maagdenberg *et al*., 2004). Early expression studies of R192Q in HEK293 cells demonstrated a gain of channel function, with increased channel density and open probability, which differed from other FHM1 mutations that demonstrated impaired channel function (Hans *et al*., 1999). In contrast, when expressed in cerebellar granule cells isolated from mice lacking Cav2.1, the same R192Q mutant channel was found to show a reduced channel density but enhanced (estimated) single channel calcium influx, which appeared to be a shared feature among several FHM1 mutants (Tottene et al., 2002). In the mouse model harbouring R192Q, there was an overall gain-of-function, with increased mutant channel density, increased neurotransmission at the neuromuscular junction and enhanced cortical glutamate release. In addition, the threshold for eliciting CSD was reduced in R192Q mice, and the propagation velocity of CSD was increased. By comparison, Cav2.1 null mice show a higher threshold and slower propagation speed of CSD (Pietrobon, 2005).

An alternative hypothesis links migraine with loss-of-function Cav2.1 mutations and weakened neurotransmission. Cao and Tsien (2005) observed a reduction in both channel density as well as calcium influx when they expressed FHM1 mutant constructs in hippocampal neurons from a Cav2.1-knockout mouse model. In the presence of endogenous Cav2.1 channels, the mutant Cav2.1 (P/Q type) channels interfered with the wild type in mediating both excitatory and inhibitory synaptic transmission (Cao *et al*., 2004; Cao and Tsien, 2005). Furthermore, there was a compensatory increase in the contribution to synaptic transmission from N-type channels, with potentially increased sensitivity to G-protein-mediated presynaptic inhibition (Cao and Tsien, 2005). This disease model of migraine allows for trigger-driven neuromodulation and further impairment of already defective mutant-expressing synapses.

Emerging data also point to alterations in the intrinsic properties of Purkinje neurons in addition to synaptic dysfunction caused by mutations in the P/Q type voltage-gated calcium channels (Bond *et al*., 2005). Irregular Purkinje firing has been observed in mouse models *tottering, leaner* and *lethargic* (Hoebeek *et al*., 2005; Walter *et al*., 2006). This loss in the precision of Purkinje pacemaking was demonstrated to be a direct consequence of mutant calcium channels and could be rescued by increasing the activity of small-conductance calcium-dependent potassium channels (K_{Ca}) (Walter *et al*., 2006). Chronic *in vivo* perfusion of K_{Ca} agonists into these mutant mice markedly reduced the frequency and severity of intermittent dystonic posturing and improved motor performance (Walter *et al*., 2006).

EA3–EA6

Online Mendelian Inheritance of Man (OMIM) currently records six episodic ataxia clinical phenotypes, each with distinctive genetic features (Table 1). EA3 was described in a single large Canadian family with episodic vertigo, tinnitus and ataxia with episodes typically lasting minutes (Steckley *et al*., 2001). The disease locus was distinct from EA1 and EA2 and mapped to chromosome 1q42 (Cader *et al*., 2005). Interestingly, there is clear overlap in clinical features between EA3 and migraine-associated vertigo. Currently it is unclear whether this syndrome represents a distinct episodic ataxia or a migraine-vertigo syndrome.

EA4, also called periodic vestibulocerebellar ataxia, was described in two North Carolina kindreds with late-onset vertigo and ataxia as well as interictal nystagmus (Farmer and Mustian, 1963; Damji *et al*., 1996). The attacks typically last hours and are not relieved by acetazolamide. Linkage analysis ruled out EA1 and EA2 loci, but so far no genome-wide scan has been reported.

EA5 was identified when a series of families with episodic ataxia were screened for mutations in the calcium channel β4 subunit *CACNB4*, on chromosome 2q (Escayg *et al*., 2000). This family had clinical features similar to EA2 but mutations in *CACNA1A* were ruled out. Complicating matters, the same mutation was found in a German family with generalized epilepsy (but no ataxia) and functional studies showed only subtle changes in calcium channel function.

EA6 was identified in a single child with episodic and progressive ataxia, episodes of hemiplegia and seizures. Through a candidate gene approach, a *de novo* mutation was identified from a screen of the candidate gene *SLC1A3*, a glutamate transporter localized to astrocytes (Jen *et al*., 2005). The mutation altered a strictly conserved amino acid residue, and functional studies of the mutated protein showed an almost complete loss-of-function with a dominant negative effect on the wild type allele.

There is a clear pattern to the genetic mutations associated with episodic ataxia and hemiplegic migraine.

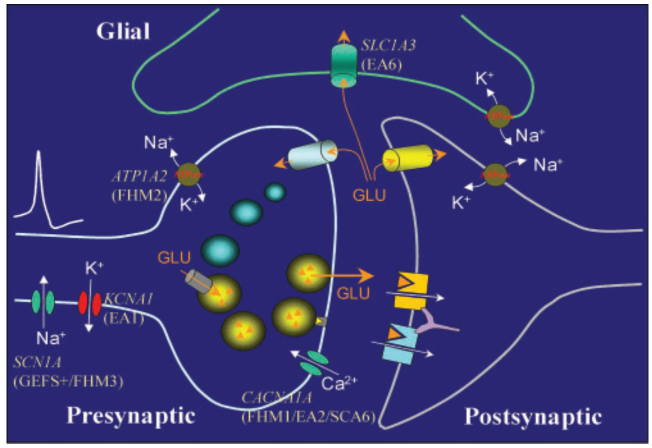

Fig. 3 Mutations in neuronal and glial membrane proteins cause episodic ataxia and hemiplegic migraine. An action potential propagated through *SCNIA* (FHM3)-encoded sodium channels activates presynaptic *CACNAIA* (EA2/FHMI) and *CACNB4* (EA5)-encoded P/Q-type calcium channels. The calcium influx triggers glutamate neurotransmission to activate post-synaptic glutamate receptor channels. K^+ efflux through perinodal *KCNAI* (EAI)-encoded potassium channels repolarizes the membrane potential. Glutamate reuptake by *SLCIA3* (EA6)-encoded glutamate transporters terminates synaptic activity. Electrochemical gradient maintained by *ATPIA2* (FHM2)-encoding Na^+, K^+-ATPase drives glutamate transporters and ion channels.

All of the currently identified genes play an important role in excitatory neurotransmission in the nervous system (Fig. 3). A second hemiplegic migraine syndrome (FHM2) is caused by mutations in *ATP1A2* that codes for the alpha subunit of a Na+/K+-ATPase (De Fusco *et al*., 2003). The ion channel proteins coded by *KCNA1, CACNA1A* and *CACNB4* are important for presynaptic glutamate release. The *SLC1A3*-encoded glial transporter EAAT1 is important for glutamate reuptake from the synaptic cleft. The *ATP1A2*-encoded ion pump is important in maintaining the appropriate electrochemical gradient in neurons and glia. We consider genes coding for other ion channels, pumps, transporters and proteins important in GABAergic neurotransmission as good candidates causing episodic ataxia and hemiplegic migraine syndromes.

Differential diagnosis

The main differential diagnosis of the episodic ataxia syndromes is between other episodic neurological disorders such as epilepsy, paroxysmal dyskinesia and migraine. Complicating matters, epileptic seizures can be seen with both EA1 and EA2. The key to the diagnosis of EA1 and EA2 is to find the characteristic interictal findings of myokymia with EA1 and baseline nystagmus and ataxia with EA2. Occasionally patients with one of the spinocerebellar ataxias syndromes (SCAs) may have episodic fluctuations in their baseline ataxia. This has been best documented with the EA2-allelic disorder SCA6 in which discrete episodes may be responsive to acetazolamide (Jen *et al.*, 1998).

Since EA2 and FHM1 are allelic disorders and since migraine is common with EA2, investigators have questioned whether mutations or polymorphisms in *CACNA1A* or other episodic ataxia genes may be responsible for more common varieties of migraine (Terwindt *et al.*, 2001). In families with FHM1, some members with documented mutations in *CACNA1A* have only migraine headaches (with or without aura). Also, episodic vertigo is a common migraine symptom and vertigo commonly accompanies episodes of ataxia in patients with EA2. However, preliminary studies of patients with migraine with and without aura and of patients with migrainous vertigo have not found polymorphisms in *CACNA1A* that are enriched in patients (Jen *et al.*, 2004b; von Brevern *et al.*, 2006).

Diagnostic testing

Currently diagnostic genetic testing is commercially available for EA1 and EA2, which can also be tested by various research laboratories. The entire coding regions of *KCNA1* and *CACNA1A* are sequenced since mutations occur throughout the genes without any consistent hot spots. *KCNA1* is much easier to screen for mutations than *CACNA1A* since it has only a single exon compared to the 48 exons of *CACNA1A*. Even with sequencing of the entire coding regions of these two genes, deletions, duplications and cryptic mutations in untranslated or intronic regions important for gene expression could be missed. In cases where multiple family members are available, preliminary linkage analysis can help decide whether it is worth sequencing the suspect genes.

Who should be screened for mutations in *KCNA1* and *CACNA1A*?

The majority of patients will present with the characteristic phenotype of these two syndromes (Table 1), however, phenotypic variations have been reported with both syndromes. Age of onset is a key differential, since onset after age 20 years is rare with both EA1 and EA2. Sporadic cases (spontaneous mutations) occur with both EA1 and EA2, therefore, the lack of a family history does not rule out the diagnosis. Patients with later onset and progressive baseline ataxia should be screened for the CAG repeat expansion in *CACNA1A* (SCA6).

Treatment of episodic ataxia

Several different drugs are reported to improve symptoms with EA1 and EA2, but so far there have been no controlled studies documenting or comparing efficacy of these different drugs. Carbamazepine, valproic acid and acetazolamide have been effective for EA1 (Eunson *et al.*, 2000; Klein *et al.*, 2004) and acetazolamide (Griggs *et al.*, 1978), flunarizine (Boel and Casaer, 1988) and 4-aminopyridine (Strupp *et al.*, 2004) have been effective in EA2. The response to acetazolamide is often dramatic with EA2 (Griggs *et al.*, 1978; Jen *et al.*, 2004a). The carbonic anhydrase inhibitors were initially tried in patients with periodic paralysis based on their kaliuretic effect for hyperkalemic periodic paralysis and then, based on an observation made serendipitously, in hypokalemic periodic paralysis. Acetazolamide was used in a single blinded study for treatment of hypokalemic paralysis over 30 years ago, which focused on prevention of attacks (Resnick *et al.*, 1968). A subsequent study even suggested that acetazolamide may improve interictal weakness (Griggs *et al.*, 1970). Acetazolamide was also serendipitously found to be effective in controlling episodes of ataxia with EA2 (Griggs *et al.*, 1978) and there have been multiple reports in the literature since the 1970s reporting excellent results in patients with EA2. Acetazolamide has been shown to increase extracellular proton concentration (Bain *et al.*, 1992), which strongly inhibits ion permeation through open calcium channels. In another study, acetazolamide was found not to directly alter wild type or mutant calcium channel properties, suggesting that acetazolamide may exert its therapeutic effects on other channels (Spacey *et al.*, 2004).

4-aminopyridine was recently found to be effective in stopping attacks in three patients with episodic ataxia, two genetically confirmed to be EA2 (Strupp *et al.*, 2004). Furthermore, 3,4-diaminopyridine was demonstrated in a placebo-controlled study to improve downbeat nystagmus, which is often observed in patients with EA2 (Strupp *et al.*, 2003).

The mouse models of EA2 provide an excellent system to test the efficacy of currently used drugs and the potential to develop new drugs for treating the episodic ataxia syndromes. 4-aminopyridine and 3,4-diaminopyridine were effective in preventing attacks in the mouse model *tottering*, but the drugs did not affect the severity of 'break through' attacks that occurred in the presence of the drug (Weisz *et al.*, 2005). Thus the aminopyridines appear to increase the threshold for attack initiation without mitigating the character of the attack. Drugs that blocked noradrenergic neurotransmission prevented attacks in *tottering* mice but agents that facilitated noradrenergic transmission failed to induce attacks (Fureman and Hess, 2005). Therefore, while noradrenergic transmission is important for attacks, norepinephrine is not sufficient to induce attacks. As noted earlier, Purkinje cell pacemaking is lost in the mouse mutant *leaner*, resulting in a significant degradation of the synaptic information encoded in their activity. This irregular pacemaking is caused by reduced activation of calcium-activated potassium channels (K_{Ca}) which could be reversed by pharmacologically increasing their activity with 1-ethyl-2-benzimidazolinone (EBIO). Infusion of EBIO into the cerebellum of ataxic mice significantly improved motor performance (Walter *et al.*, 2006). Thus drugs that activate K_{Ca} channels might be effective in controlling episodic ataxia in patients with EA2. Interestingly, therapeutic concentrations of acetazolamide activate K_{Ca} channels which could be another mechanism of action of acetazolamide in EA2 (Walter *et al.*, 2006).

Ongoing and proposed clinical trials

A pilot study on 4-aminopyridine in EA2 with a total of 10 patients and a cross-over design was recently completed in Germany (M. Strupp, C. Jahn and T. Brandt, personal communications). As part of the NIH-supported CINCH program, there is an ongoing study of the natural history of the episodic ataxia syndromes. Patients are initially defined phenotypically and genetically and then followed for a minimum of 2 years. Episode rates are carefully monitored and disease progression documented. A controlled pilot study on the safety and tolerability of 4-aminopyridine as an add-on treatment to acetazolamide in EA2 is scheduled to begin soon. We hope to improve diagnosis and understanding of the disease mechanism to stratify patients with episodic ataxia for future clinical trials. Details regarding these and future studies can be obtained at the CINCH website http://rarediseasesnetwork.epi.usf.edu/cinch/index.htm.

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Appendix

This report summarizes the findings presented at the International Conference on Episodic Ataxia Syndromes (Santa Monica, CA, February 5–6, 2006). The conference was generously supported by an NIH conference grant R13 NS054550 (NINDS/ORD).

Participants of the meetings listed alphabetically:

Anthony Amato (Brigham & Women's Hospital), Robert W. Baloh (University of California at Los Angeles), Richard Barohn (University of Kansas Medical Center), K.C. Brennan (UCLA), Stephen Cannon (UT Southwestern Medical Center), Yoon-Hee Cha (UCLA), Andrew Charles (UCLA), James Cleland (University of Rochester), Mark and Jeanine Dias (Patient Representatives), George Ebers (University of Oxford, UK), Timothy Ebner (University of Minnesota), Marina Frontali (Rome, Italy), Tracey Graves (Institute of Neurology, London, UK), Robert C. Griggs (University of Rochester), Angelika Hahn (London Health Sciences Centre, Ontario, Canada), Michael Hanna (Institute of Neurology, London, UK), Kim Hart (University of Rochester), Laura Herbelin (University of Kansas Medical Center), Barbara Herr (University of Rochester), Ellen Hess (Johns Hopkins University), Kate Jacobson (UCLA), Joanna C. Jen (UCLA), Kamran Khodakhah (Albert Einstein College of Medicine), Bethan Lang (Neurosciences Group, Oxford, UK), Y. Joyce Liao (Stanford University), James Maylie (Oregon Health & Science University), Miriam Meisler (University of Michigan), Shree Pandya (University of Rochester), Diane M. Papazian (UCLA), Daniela Pietrobon (University of Padova, Italy), Louis Ptacek (University of California at San Francisco), Ming Qi (University of Rochester), Sanjeev Rajakulendran (Institute of Neurology, London, UK), Goran Rakocevik (NINDS/NIH), Mohammad Salajegheh (Brigham & Women's Hospital), Jeffrey Statland (University of Kansas Medical Center), Michael Strupp (University of Munich, Germany), Shirley Thomas (University of Rochester), Richard W. Tsien (Stanford University), Jeffrey Vance (Duke University), Arn van den Maagdenberg (Leiden University Medical Centre, Netherlands), Shannon Venance (London Health Science Centre, Canada), Barbara Vickrey (UCLA), Ronan Walsh (Brigham & Women's Hospital), Jijun Wan (UCLA), Yunxia Wang (University of Kansas Medical Center), Grace Yoon (University of Toronto, Canada).