

Paroxysmal Disorders and Primary Headaches

Robert W. Baloh, MD, PhD
Department of Neurology
University of California, Los Angeles
Los Angeles, California

EA type 1 (EA1) is characterized by episodes of ataxia lasting seconds to minutes and interictal myokymia.¹ Episodes can be associated with dysarthria and a coarse tremor, and they are usually triggered by physical and emotional stress, startle or sudden movements.² Symptoms resembling aura may also occur. Typical onset of EA-1 is infancy or early childhood; the condition may resolve spontaneously in the teenage years. Most patients with EA1 respond to acetazolamide or antiepileptic drugs. Genetically, EA1 is autosomal dominant or sporadic. Its disease locus was mapped to chromosome 12q.³ Missense mutations in *KCNA1* (encoding Kv1.1, a human homolog of Shaker) have been discovered.^{1,4}

EA2, the most common type of EA, produces episodes of ataxia lasting hours to days, with interictal nystagmus and mildly progressive baseline ataxia.^{5,6} Onset ranges from infancy to early adulthood, and episodes are often triggered by physical and emotional stress. Although presentation varies, vertigo, nausea, and vomiting affect more than half of patients; about half have migraine. During episodes, a spontaneous nystagmus is common; between episodes, a gaze-evoked nystagmus is typical. EA2 can be dramatically responsive to acetazolamide. It is allelic with familial hemiplegic migraine type 1 (FHM1),⁷ and some patients have concurrent episodes of ataxia and hemiplegic migraine.^{8,9} EA2 patients can also have progressive ataxia,^{10,11} fluctuating weakness,¹² epileptic seizures,^{6,13} and dystonia.¹⁴ Genetically autosomal dominant or sporadic, its locus was mapped to chromosome 19p,¹⁵⁻¹⁷ the same as FHM1.¹⁸ A calcium channel gene *CACNA1A* mapped to this locus was described by Ophoff and colleagues,⁷ who also identified missense mutations in FHM1 and truncation mutations in EA2.

EA3 causes episodes of episodic vertigo, tinnitus, and ataxia typically lasting minutes to hours.¹⁹ Onset of EA3 can occur from infancy to age 40. Clinically, patients with EA3 have normal interictal exams, and they respond to treatment with acetazolamide. EA3 resembles migraine-associated vertigo, and it is still unclear whether it classifies as an EA type or a migraine-vertigo syndrome. However, the disease locus was mapped to chromosome 1q42,²⁰ making it genetically distinct from EA1 and EA2.

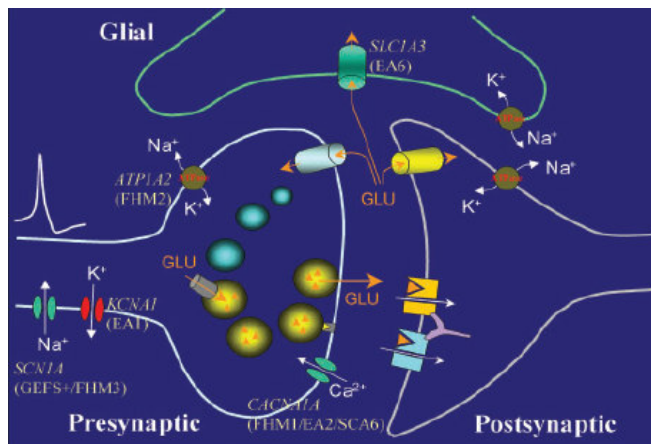
EA4, also called periodic vestibulocerebellar ataxia, was described in families with late-onset vertigo and ataxia as well as interictal nystagmus.^{21,22} The attacks typically last hours and are not relieved by acetazolamide. EA1 and EA2 loci have been ruled out, but no genomewide scan has been reported.

EA5 was identified when a series of families with episodic ataxia were screened for mutations in the calcium channel beta subunit CACNB4.²³ Clinically, EA5 mimics EA2, but it lacks mutations in CACNA1A. Onset occurs before age 20. Nystagmus is present on interictal exam, and acetazolamide has no effect on episodes.

EA6 was identified in a single American child and small Dutch family with episodic and progressive ataxia, episodes of hemiplegia lasting hours to days, seizures, and normal interictal exam. Episodes are nonresponsive to acetazolamide. A *de novo* mutation was identified from a screen of the candidate gene SLC1A3, a glutamate transporter localized to astrocytes.²⁴

EA7, identified in a single American family, produces recurrent episodes of ataxia, weakness, and dysarthria typically lasting a few hours to 3 days that alternate with normal interictal periods. Onset occurs in the teenage years. Episodes of EA7, which are triggered by excitement or exercise, do not respond to acetazolamide. EA7 has an autosomal dominant pattern of inheritance, and its locus has been mapped to chromosome 19q13.²⁵

Mutations in genes associated with episodic ataxia and hemiplegic migraine play an important role in excitatory neurotransmission. An action potential propagated through SCN1A (FHM3)-encoded sodium channels activates presynaptic CACNA1A (EA2/FHM1) and CACNB4 (EA5)-encoded P/Q-type calcium channels. The calcium influx triggers glutamate neurotransmission to activate postsynaptic glutamate receptor channels. K⁺ efflux through perinodal KCNA1 (EA1)-encoded potassium channels repolarizes the membrane potential. Glutamate reuptake by SLC1A3 (EA6)-encoded glutamate transporters terminates synaptic activity. Electrochemical gradient is maintained by ATP1A2 (FHM2)-encoding Na⁺, K⁺-ATPase drives glutamate transporters and ion channels.²⁶



Benign recurrent vertigo (BRV) may be etiologically related to migraine because of similarities in the clinical spectrum of the phenotypes and a high comorbidity within families. Many families have multiple affected genetically related individuals, suggesting familial transmission of the disorder with moderate to high penetrance.

Genetically, BRV is a heterogeneous disorder that is distinct from migraine with aura and is linked to 22q12.²⁷

A genetic mutation has been reported in families with dominantly inherited bilateral vestibulopathy and normal hearing. Affected patients have brief episodes of vertigo lasting seconds to minutes followed by imbalance and oscillopsia; most also have migraine. Typical age of onset is the teenage years, and episodes respond to acetazolamide. In 4 of 5 families with the mutation, a region on chromosome 6q suggestive of linkage to vestibulopathy has been identified.²⁸

References

1. Browne DL, Gancher ST, Nutt JG, Brunt ER, Smith EA, Kramer P, et al. Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, KCNA1. *Nat Genet.* 1994;8:136–140.
2. Brunt ER, van Weerden TW. Familial paroxysmal kinesigenic ataxia and continuous myokymia. *Brain.* 1990;113(Pt 5):1361–1382.
3. Litt M, Kramer P, Browne D, et al. A gene for episodic ataxia/myokymia maps to chromosome 12p13. *Am J Hum Genet.* 1994;55:702–709.
4. Browne DL, Brunt ER, Griggs RC, et al. Identification of two new KCNA1 mutations in episodic ataxia/myokymia families. *Hum Mol Genet.* 1995;4:1671–1672.
5. Baloh RW, Yue Q, Furman JM, Nelson SF. Familial episodic ataxia: clinical heterogeneity in four families linked to chromosome 19p. *Ann Neurol.* 1997;41:8–16.
6. Jen JC, Kim GW, Baloh RW. Clinical spectrum of episodic ataxia type 2. *Neurology.* 2004;62:17–22.
7. Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca²⁺ channel gene CACNL1A4. *Cell.* 1996;87:543–552.
8. Jen JC, Yue Q, Nelson SF, Yu H, Litt M, Nutt J, et al. A novel nonsense mutation in CACNA1A causes episodic ataxia and hemiplegia. *Neurology.* 1999;53:34–37.
9. Ducros A, Denier C, Joutel A, et al. The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. *N Engl J Med.* 2001;345:17–24.
10. Yue Q, Jen JC, Nelson SF, Baloh RW. Progressive ataxia due to a missense mutation in a calcium-channel gene. *Am J Hum Genet.* 1997;61:1078–1087.
11. Denier C, Ducros A, Vahedi K, Joutel A, Thierry P, Ritz A, et al. High prevalence of CACNA1A truncations and broader clinical spectrum in episodic ataxia type 2. *Neurology.* 1999;52:1816–1821.
12. Jen JC, Wan J, Graves M, et al. Loss-of-function EA2 mutations are associated with impaired neuromuscular transmission. *Neurology.* 2001;57:1843–1848.
13. Jouvenceau A, Eunson LH, Spauschus A, et al. Human epilepsy associated with dysfunction of the brain P/Q-type calcium channel. *Lancet.* 2001;358:801–807.
14. Spacey SD, Materek LA, Szczygielski BI, Bird TD. Two novel CACNA1A gene mutations associated with episodic ataxia type 2 and interictal dystonia. *Arch Neurol.* 2005;62:314–316.
15. Kramer PL, Yue Q, Gancher ST, et al. A locus for the nystagmus-associated form of episodic ataxia maps to an 11-cM region on chromosome 19p. *Am J Hum Genet.* 1995;57:182–185.
16. Vahedi K, Joutel A, Van Bogaert P, et al. A gene for hereditary paroxysmal cerebellar ataxia maps to chromosome 19p. *Ann Neurol.* 1995;37:289–293.
17. von Brederlow B, Hahn AF, Koopman WJ, Ebers GC, Bulman DE. Mapping the gene for acetazolamide responsive hereditary paroxysmal cerebellar ataxia to chromosome 19p. *Hum Mol Genet.* 1995;4:279–284.
18. Joutel A, Bousser MG, Biousse V, et al. A gene for familial hemiplegic migraine maps to chromosome 19. *Nat Genet.* 1993;5:40.

19. Steckley JL, Ebers GC, Cader MZ, McLachlan RS. An autosomal dominant disorder with episodic ataxia, vertigo, and tinnitus. *Neurology*. 2001;57:1499–1502.
20. Cader MZ, Steckley JL, Dymment DA, McLachlan RS, Ebers GC. A genomewide screen and linkage mapping for a large pedigree with episodic ataxia. *Neurology*. 2005;65:156–158.
21. Farmer TW, Mustian VM. Vestibulocerebellar ataxia. A newly defined hereditary syndrome with periodic manifestations. *Arch Neurol*. 1963;8:471–480.
22. Damji KF, Allingham RR, Pollock SC, et al. Periodic vestibulocerebellar ataxia, an autosomal dominant ataxia with defective smooth pursuit, is genetically distinct from other autosomal dominant ataxias. *Arch Neurol*. 1996;53:338–344.
23. Escayg A, De Waard M, Lee DD, et al. Coding and noncoding variation of the human calcium-channel beta4-subunit gene CACNB4 in patients with idiopathic generalized epilepsy and episodic ataxia. *Am J Hum Genet*. 2000;66(5):1531–1539.
24. Jen JC, Wan J, Palos TP, Howard BD, Baloh RW. Mutation in the glutamate transporter EAAT1 causes episodic ataxia, hemiplegia, and seizures. *Neurology*. 2005;65:529–534.
25. Kerber KA, Jen JC, Lee H, Nelson SF, Baloh RW. A new episodic ataxia syndrome with linkage to chromosome 19q13. *Arch Neurol*. 2007;64:749–752.
26. Jen JC, Graves TD, Hess EJ, et al. *Brain*. 2007;130:2484–2493.
27. Lee H, Jen JC, Wang H, et al. A genome-wide linkage scan of familial benign recurrent vertigo: linkage to 22q12 with evidence of heterogeneity. *Hum Mol Genet*. 2006;15:251–258.
28. Jen JC, Wang H, Lee H, et al. Suggestive linkage to chromosome 6q in families with bilateral vestibulopathy. *Neurology*. 2004;63:2376–2379.