SECTION EDITOR: DAVID E. PLEASURE, MD

# Channels and Disease

## *Past, Present, and Future*

*Louis J. Ptácek, MD; Ying-Hui Fu, PhD*

Episodic neurological phenotypes make up an interesting and important group of diseases affecting humans. These include disorders of the skeletal and cardiac muscles, peripheral nerves, and brain. They range from episodic weakness syndromes to rare paroxysmal movement disorders. More common episodic phenomena include cardiac arrhythmias, epilepsy syndromes, and headache. Molecular characterization of these disorders is shedding light on their pathophysiologic features and will ultimately lead to better diagnosis and treatment of patients.

### CLINICAL SIMILARITIES AMONG VARIOUS EPISODIC DISORDERS

Disorders such as the periodic paralyses, nondystrophic myotonias, episodic ataxias, paroxysmal dyskinesias, long QT syndrome, migraine headache, and epilepsy all share the feature of being episodic in nature. Affected individuals are often completely healthy between attacks. Stress and fatigue precipitate attacks in all of these diseases, and various dietary factors can also contribute to attack onset. The drugs used to treat these disorders overlap significantly. For example, carbonic anhydrase inhibitors are effective for many patients with periodic paralysis, episodic ataxia, and migraine headache. Mexiletine hydrochloride, an effective antiarrhythmic medication, can be beneficial in treating myotonia in patients with paramyotonia congenita. The anticonvulsant carbamazepine is an extremely efficacious drug for treating the episodic movements of paroxysmal kinesigenic dyskinesia. All of these disorders have a tendency to begin in infancy or childhood and to worsen through adolescence and young adult life. In some cases, they decrease in severity and frequency in middle to late adult life.

**Author Affiliations:** Howard Hughes Medical Institute (Dr Ptácek) and Department of Neurology (Drs Ptácek and Fu), University of California, San Francisco.

Several syndromes with episodic or electrophysiologic phenomena involve more than 1 organ system or combine multiple central nervous system phenotypes within individual patients. For example, Andersen-Tawil syndrome is characterized by episodic weakness, cardiac arrhythmias, and developmental features. Paroxysmal kinesigenic dyskinesia is an episodic movement disorder that is precipitated by sudden movements; these individuals frequently have benign convulsions during infancy prior to the development of their movement disorder.[1] Some patients with episodic ataxia type 1 also manifest attacks of paroxysmal kinesigenic dyskinesia. It has been suggested that migraine headache may be part of the clinical constellation in patients with paroxysmal nonkinesigenic dyskinesia.[2] Finally, for disorders in which electrophysiologic studies can be obtained, a similarity of abnormal but highly organized repetitive action potentials is apparent, as shown in **Figure 1**.

### MOLECULAR CHARACTERIZATION OF EPISODIC NEUROLOGICAL PHENOMENA

The periodic paralyses and nondystrophic myotonias were the first human disorders to be characterized as defects in-voltage-gated ion channels.[3,4] It is now known that



©2004 American Medical Association. All rights reserved.

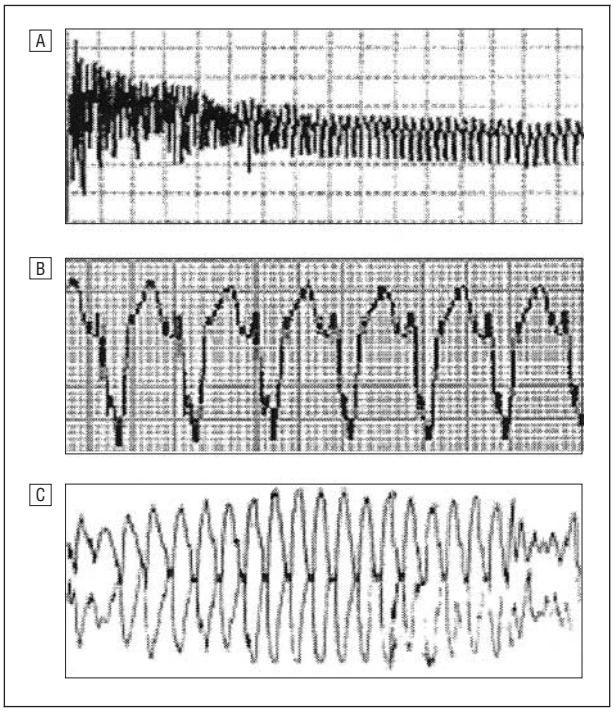


**Figure 1.** Highly organized but abnormal electrophysiologic activity seen in some episodic disorders. A, Myotonia recorded by electromyography in a patient with hyperkalemic periodic paralysis. B, Ventricular tachydysrhythmia on an echocardiogram in a patient with Andersen-Tawil syndrome. C, Seizure recorded by electroencephalography in a patient with epilepsy.

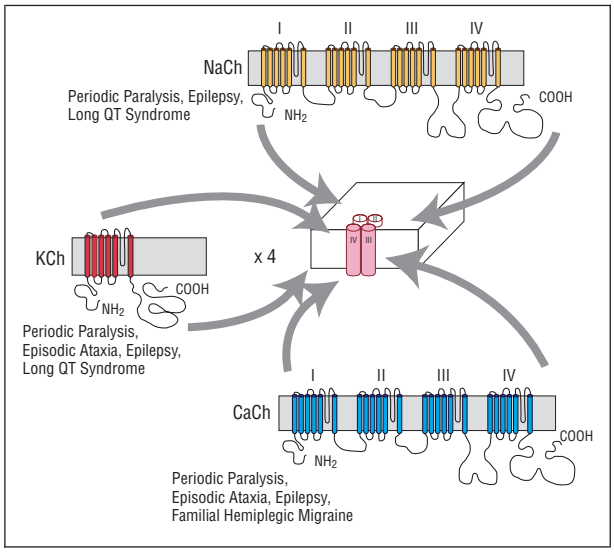


**Figure 2.** Voltage-gated ion channels. Potassium channels (KCh) are polypeptides with 6 transmembrane segments (red cylinders) and a region that lines the inside of the ion-conducting pore (loop between fifth and sixth transmembrane segments). Four such polypeptides must multimerize to form a functional channel. Sodium channels (NaCh) and calcium channels (CaCh) are homologous to KCh but, because of a gene duplication and reduplication sometime during evolution, now have 4 domains (each with 6 transmembrane-spanning segments) that form functional channels as single polypeptides. Many episodic and electrophysiologic disorders affecting the nervous system are known to result from mutations in members of these (and other) ion channel gene families. $NH_2$ indicates N-terminus; COOH, carboxy-terminus.

hyperkalemic periodic paralysis, hypokalemic periodic paralysis, paramyotonia congenita, potassium-aggravated myotonia, Andersen-Tawil syndrome, Thomsen myotonia congenita, and Becker myotonia congenita are caused by mutations in voltage-gated sodium, calcium, potassium, and chloride channel genes (**Figure 2**). Interestingly, mutations in homologs of these channels have subsequently been shown to cause episodic ataxia, long QT syndrome, familial hemiplegic migraine, and mendelian forms of epilepsy. Mutations in these episodic disorders are not limited to voltage-gated channels; they have also been found in ligand-gated channels, transporters, and exchangers.[3,4] The **Table** enumerates the growing list of episodic disorders that have been shown to result from mutations in voltage-gated or ligand-gated channels as well as transporters and exchangers. It is fascinating that multiple phenotypes can result from different mutations in a single ion channel gene and that different ion channel genes, when mutated, can give rise to phenotypes that are clinically indistinguishable.

## NEW DIRECTIONS

### Secondary Channelopathies

A growing body of work demonstrates that antibodies directed against ion channel proteins can cause episodic and electrophysiologic phenotypes in humans. These include Lambert-Eaton syndrome and stiff-person syndrome.[5,6] In these cases, an autoimmune attack against various ion channel proteins has been shown to result in the respective phenotypes.

### Channels in Development

It has previously been demonstrated that mutations in the gene encoding the G protein–coupled inwardly rectifying potassium channel 2 result in the "weaver" phenotype in mice. These mice have multiple problems including a developmental abnormality in which cerebellar granule cells do not migrate normally into the granular cell layer. The only human developmental phenotype now recognized as resulting from ion channel variants is Andersen-Tawil syndrome.[7] These individuals have facial features such as micrognathia, hypertelorism, and high-arched or cleft palate, structures that arise embryologically from neural crest cells. In addition, they have terminal limb features (clinodactyly, brachydactyly, or syndactyly) and may also have short stature. How do inwardly rectifying potassium channels encoded by the potassium channel J2 gene (*KCNJ2*) contribute to developmental processes of the face and distal limbs? This will certainly prove to be an interesting area for future exploration.

### Can New Phenotypes Be Recognized in Some of These Disorders?

Patients with Andersen-Tawil syndrome have a triad of symptoms (muscle, heart, and developmental). Not surprisingly, the *KCNJ2* gene, which causes approximately 60% of all cases of Andersen-Tawil syndrome, is expressed in the embryo, heart, and skeletal muscles. It is also expressed in several other tissues, including the brain. The recognition that *KCNJ2* is the major gene for



©2004 American Medical Association. All rights reserved.

Andersen-Tawil syndrome raises interesting questions, such as whether there is a subtle cognitive or neurobehavioral phenotype in this disease as a result of the mutant channels being expressed in a tissue (brain) in which no phenotype has previously been recognized. These kinds of questions can be formulated and addressed based on discovery of the causative genes and their temporospatial expression patterns.

### Structural Proteins Contribute to Channel Localization and Function

Schwartz-Jampel syndrome was recently shown to result from mutations in the perlecan gene, which encodes the major proteoglycan of basement membranes.[4] This protein may be important for the localization and anchoring of channels in the nerves (eg, causing the neuromyotonia that these individuals manifest clinically). More recently, long QT type 4 cardiac arrhythmia syndrome in a large French family was found to result from mutations in ankyrin B, a membrane adapter that in mutant mice was shown to disrupt organization of the sodium pump, the sodium-calcium exchanger, and the inositol-1,4,5-trisphosphate receptors.[8] These are examples of gene mutations that do not encode ion channels but proteins that affect ion channel function, presumably through localization or anchoring of proteins at the appropriate places in cell membranes of the appropriate tissue.

### A Novel Epilepsy Gene

Audiogenic reflex seizures are well recognized in rodents and (rarely) in humans. One example, the Frings audiogenic seizure–susceptible mouse, is now known to result from mutations in a gene that was initially called *MASS1* (for *monogenic audiogenic seizure susceptible*). This nearly 10-kilobase (kb) gene is expressed at very low levels in the adult brain; therefore, it was hypothesized that this gene might play a role in the development of neuronal circuits that could give rise to epilepsy.[9] Another 10-kb gene identified as a novel G protein–coupled receptor (*VLGR1* for *very large G protein–coupled receptor*) maps close to the *MASS1* locus and shares homologous domains with the MASS1 protein.[10] These 2 approximately 10-kb messages are now recognized to be 2 halves of the same massive gene, which we call the massive G protein–coupled receptor (*MGR1*). How this novel receptor is related to epilepsy remains to be elucidated. In any case, it will certainly be an interesting new chapter in the evolving field of genetic factors underlying this episodic phenomenon.

### Therapeutic Trials Benefit From Molecular Characterization

In the case of periodic paralysis and nondystrophic myotonias, long QT syndrome, paroxysmal dyskinesias, and epilepsies, complex clinical classification schemes have resulted from the work of many physicians who have seen and cared for these patients. As we learn about the molecular basis of these disorders, the classification schemes are being modified.

**Table. Recognized Human Channelopathies**

| Disease | Gene | Ion Channel |
|---|---|---|
| Hyperkalemic periodic paralysis | *SCN4A* | Sodium channel |
| Paramyotonia congenital | *SCN4A* | Sodium channel |
| Potassium-aggravated myotonia | *SCN4A* | Sodium channel |
| Hypokalemic periodic paralysis type 1 | *CACNLA3* | Calcium channel |
| Myotonia congenita | *CLCN1* | Chloride channel |
| Andersen-Tawil syndrome | *KCNJ2* | Potassium channel |
| Congenital myasthenic syndrome | *CHRNA*, *CHRNB*, *CHRNE* | Acetylcholine receptor |
| Episodic ataxia with myokymia (type 1) | *KCNA1* | Potassium channel |
| Episodic ataxia with nystagmus (type 2) | *CACNA1A* | Calcium channel |
| Familial hemiplegic migraine type 1 | *CACNA1A* | Calcium channel |
| Familial hemiplegic migraine type 2 | *ATP1A2* | Sodium-potassium transporter |
| Spinocerebellar ataxia type 6 | *CACNA1A* | Calcium channel |
| Myasthenic syndromes | *CHRNA*, *CHRNB*, *CNRNE* | Acetylcholine receptor |
| Hereditary hyperekplexia | *GLRA1* | Glycine receptor |
| Long QT syndrome type 1 | *KVLQT1* | Potassium channel |
| Long QT syndrome type 2 | *HERG* | Potassium channel |
| Long QT syndrome type 3 | *SCN5A* | Sodium channel |
| Long QT syndrome type 4 | *ANK2* | Ankyrin B |
| Long QT syndrome type 5 | *minK* | Potassium channel |
| Long QT syndrome type 7 | *KCNJ2* | Potassium channel |

Clinical trials for these diseases are often difficult because some of the disorders are extremely rare and because of the genetic heterogeneity that is now known to underlie certain phenotypes. The periodic paralyses represent the first of these disorders for which a clinical trial was enabled by a large database of patients compiled by those characterizing the disorders, as well as the stratification of these patients according to the molecular basis for their disease.[11] The next decade is likely to see many more clinical trials that will benefit from a growing knowledge of the pathophysiologic basis of disease in individual patients.

## COMMENT

Since the molecular characterization of the first channelopathies less than 15 years ago, there has been an explosion of data implicating many different ion channel genes in the pathophysiologic mechanisms of a wide variety of human diseases. These advances underscore the power of human genetics in studying families segregating rare mendelian traits. Multiple genetic factors probably contribute to the pathophysiologic mechanisms in most patients with cardiac arrhythmias, headache, and epilepsy. However, these patients usually do not have a clear pattern consistent with mendelian traits. An exciting question that will be addressed in the next decade is whether subtle genetic variants in the genes mentioned in this article (and many homologous genes) contribute to predisposition to common episodic and electrophysi-



©2004 American Medical Association. All rights reserved.

ologic diseases. What is being learned from rare mendelian disorders will likely guide the search for complex genetic factors contributing to the risk of arrhythmia, headache, and seizure.

**Accepted for Publication:** March 12, 2004.
**Correspondence:** Louis J. Ptácek, MD, Department of Neurology, University of California, San Francisco, Box 2922, 19B Mission Bay, 1550 Fourth St, San Francisco, CA 94143-2922 (ptacek@itsa.ucsf.edu).
**Author Contributions:** *Study concept and design:* Ptácek and Fu. *Drafting of the manuscript:* Ptácek. *Critical revision of the manuscript for important intellectual content:* Ptácek and Fu. *Obtained funding: Ptácek and Fu. Administrative, technical, and material support:* Ptácek and Fu. *Study supervision:* Ptácek.

## REFERENCES

1. Swoboda KJ, Soong B, McKenna C, et al. Paroxysmal kinesigenic dyskinesia and infantile convulsions: clinical and linkage studies. *Neurology*. 2000;55:224-230.
2. Fouad GT, Servidei S, Durcan S, Bertini E, Ptacek LJ. A gene for familial paroxysmal dyskinesia (*FPD1*) maps to chromosome 2q. *Am J Hum Genet*. 1996; 59:135-139.
3. Jen J, Ptácek LJ. Channelopathies: episodic disorders of the nervous system. In: Schriver CR, Beaudet AL, Sly WS, Valle D, eds. *Metabolic and Molecular Bases of Inherited Disease*. 8th ed. New York, NY: McGraw-Hill; 2000:5223-5238.
4. Lenz R, Ptácek LJ. Channelopathies. In: Bradley W, Daroff RB, Fenichel G, Jankovic J, eds. *Neurology in Clinical Practice*. 4th ed. Philadelphia, Pa: Butterworth-Heinemann; 2004:1847-1866.
5. Vincent A, McConville J, Farrugia M, et al. Antibodies in myasthenia gravis and related disorders. *Ann N Y Acad Sci*. 2003;998:324-335.
6. Newsom-Davis J, Buckley C, Clover L, et al. Autoimmune disorders of neuronal potassium channels. *Ann N Y Acad Sci*. 2003;998:202-210.
7. Renner DR, Tawil R, Tristani-Firouzi M, Ptácek LJ. Andersen-Tawil syndrome and Kir2.1. In: Epstein CJ, Erickson RP, Wynshaw-Boris A, eds. *Inborn Errors of Development*. New York, NY: Oxford University Press; 2003:1001-1006.
8. Mohler PJ, Schott JJ, Gramolini AO, et al. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. *Nature*. 2003;421:634-639.
9. Skradski SL, Clark A, Jiang H, White HS, Fu Y-H, Ptácek LJ. A novel gene causing a Mendelian audiogenic mouse epilepsy. *Neuron*. 2001;31:537-544.
10. Nikkila H, McMillan DR, Nunez BS, Pascoe L, Curnow KM, White PC. Sequence similarities between a novel putative G protein–coupled receptor and Na+/Ca2+ exchangers define a cation binding domain. *Mol Endocrinol*. 2000;14:1351-1364.
11. Tawil R, McDermott MP, Brown R Jr, et al; Working Group on Periodic Paralysis. Randomized trials of dichlorphenamide in the periodic paralyses. *Ann Neurol*. 2000;47:46-53.



©2004 American Medical Association. All rights reserved.