Episodic Neurologic Disorders: Syndromes, Genes, and Mechanisms

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Abstract

Many neurologic diseases cause discrete episodic impairment in contrast with progressive deterioration. The symptoms of these episodic disorders exhibit striking variety. Herein we review what is known of the phenotypes, genetics, and pathophysiology of episodic neurologic disorders. Of these, most are genetically complex, with unknown or polygenic inheritance. In contrast, a fascinating panoply of episodic disorders exhibit Mendelian inheritance. We classify episodic Mendelian disorders according to the primary neuroanatomical location affected: skeletal muscle, cardiac muscle, neuromuscular junction, peripheral nerve, or central nervous system (CNS). Most known Mendelian mutations alter genes that encode membrane-bound ion channels. These mutations cause ion channel dysfunction, which ultimately leads to altered membrane excitability as manifested by episodic disease. Other Mendelian disease genes encode proteins essential for ion channel trafficking or stability. These observations have cemented the channelopathy paradigm, in which episodic disorders are conceptualized as disorders of ion channels. However, we expand on this paradigm to propose that dysfunction at the synaptic and neuronal circuit levels may underlie some episodic neurologic entities.

Contents

INTRODUCTION

Whereas many diseases of the nervous system cause progressive deterioration, a sizable fraction of them are predominantly episodic in nature. In this subset of disorders, a patient's neurologic function is impaired during an episode (also known as an attack). Although some patients may suffer from superimposed, chronic neurologic dysfunction, between attacks patients are usually completely normal. Episodes are often triggered by mundane stimuli, such as hunger, fatigue, emotions, stress, exercise, diet, temperature, or hormones. Why these commonplace stimuli trigger episodes of neurologic impairment in some patients but not others is poorly understood.

Many episodic neurologic disorders exist, encompassing a protean range of symptoms. These may include weakness, stiffness, paralysis, arrhythmias, pain, ataxia, migraine, involuntary movements, and seizures. Most episodic neurologic disorders exhibit complex inheritance—that is, disease seems to develop primarily owing to environmental influences rather than genetic ones. In this review, we briefly address the complex disorders that are commonly encountered in clinical practice: transient ischemic attack, syncope, epilepsy, and migraine (**Figure 1**). Aside from these four diseases, which are complex and common, there exist a myriad of symptomatically similar diseases that are complex but rare. Of these, many are in fact progressive neurologic disorders that happen to feature episodic symptoms but are not primarily episodic in nature. However, others are indeed primarily episodic. In this review, we focus on those complex, rare disorders with autoimmune etiology because they have provided substantial pathophysiological insight.

For the same reason, the remaining bulk of our review focuses on episodic neurologic disorders that are Mendelian (**Figure 1**). Each is rare. For these disorders, single gene mutations are sufficient to cause disease. However, even in these genetic diseases, environmental factors can still be important in triggering attacks. Over the past two decades, medical geneticists have extensively clarified the known phenotypes, identified many novel phenotypes, and pinpointed scores of disease genes. In many cases, disease gene discovery has directly led to pathophysiological insight and, in a few cases, even novel treatments. We organize these diverse disorders on the basis of the primary neuroanatomical location affected: skeletal muscle, cardiac muscle, neuromuscular junction (NMJ), peripheral nerve, or CNS. As much as is possible given practical constraints, for each disorder we review the clinical presentation, genetics, and pathophysiology, with particular emphasis on new discoveries and unanswered questions. Finally, in the concluding section we present our view of the field's urgent challenges.

COMPLEX DISORDERS

Complex episodic neurologic disorders develop primarily due to environmental factors, although in most disorders some evidence indicates polygenic inheritance, which remains largely undeciphered (Poduri & Lowenstein 2011, Shyti et al. 2011, Della-Morte et al. 2012). Complex episodic disorders are very common in aggregate. This group includes a legion of causes that are each individually

Complex disorder: a disease that develops primarily due to environmental influences, although polygenic inheritance may increase susceptibility

NMJ: neuromuscular junction

Episodic disorder: a disease in which symptoms occur in discrete paroxysms; between paroxysms, patients appear to be normal or near normal

rare, such as autoimmune episodic disorders (see below). Also, four complex disorders are commonly encountered in clinical practice: transient ischemic attack, syncope, epilepsy, and migraine (**Figure 1**).

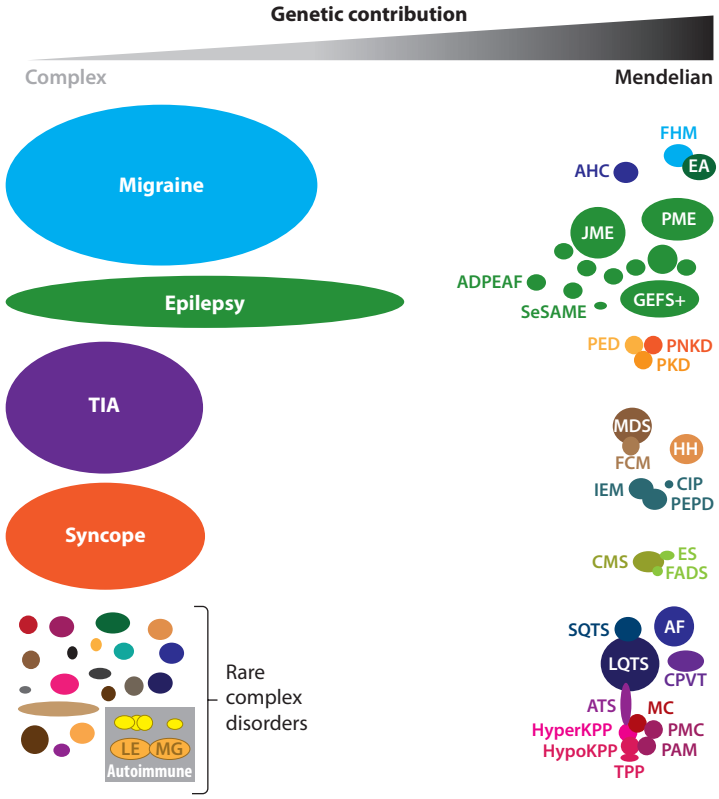
Figure 1

The landscape of episodic neurologic disorders. There are many episodic neurologic disorders, with a vast range in genetic contribution and prevalence. Prevalence is depicted in crude approximation by the size of each ellipse. This fascinating group includes four common complex disorders (*left*), many rare complex disorders including autoimmune (*lower left*), and many rare Mendelian forms (*right*). Some Mendelian phenotypes exhibit profound similarity to particular complex disorders, as depicted by identical coloration (e.g., *light green* for idiopathic epilepsy and for Mendelian epilepsy syndromes). Often, Mendelian phenotypes share phenotypic and/or genetic characteristics, as depicted by overlap and/or similar coloration of each corresponding ellipse. Some complex disorders seem to have a substantial genetic contribution, particularly epilepsy, but most of the complex inheritance remains unexplained (*middle*). Abbreviations: ADPEAF, autosomal dominant partial epilepsy with auditory features; AF, atrial fibrillation; ATS, Andersen-Tawil syndrome; AHC, alternating hemiplegia of childhood; CIP, congenital insensitivity to pain; CMS, congenital myasthenic syndromes; CPVT, catecholaminergic polymorphic ventricular tachycardia; EA, episodic ataxia; ES, Escobar syndrome; FADS, fetal akinesia deformation sequence; FCM, familial cortical myoclonus; FHM, familial hemiplegic migraine; GEFS+, generalized epilepsy with febrile seizures plus; HH, hereditary hyperekplexia; HyperKPP, hyperkalemic periodic paralysis; HypoKPP, hypokalemic periodic paralysis; IEM, inherited erythromelalgia; JME, juvenile myoclonic epilepsy; LE, Lambert-Eaton myasthenic syndrome; LQTS, long QT syndrome; MC, myotonia congenita; MDS, myoclonus-dystonia syndrome; MG, myasthenia gravis; PAM, potassium-aggravated myotonia; PED, paroxysmal exercise-induced dyskinesia; PEPD, paroxysmal extreme pain disorder; PKD, paroxysmal kinesigenic dyskinesia; PMC, paramyotonia congenita; PME, progressive myoclonic epilepsy; PNKD, paroxysmal nonkinesigenic dyskinesia; SeSAME, seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance; SQTS, short QT syndrome; TIA, transient ischemic attack; TPP, thyrotoxic periodic paralysis.

Four Common Complex Disorders

A transient ischemic attack (TIA) results from diminished cerebral perfusion that causes abrupt, focal neurological symptoms in a pattern corresponding to the compromised vascular distribution (reviewed by Della-Morte et al. 2012). Cerebral hypoperfusion usually arises from platelet emboli or thrombi that transiently lodge in a cerebral artery but are dislodged before permanent neurologic injury develops; by definition, TIA symptoms resolve within 24 h. Despite prompt resolution, TIAs typically recur over the course of days to weeks with a stereotypic symptom cluster. These patients should be promptly evaluated and treated, usually by addressing the source of emboli or by anticoagulation, to decrease the risk of progression to ischemic stroke (Della-Morte et al. 2012).

Transient cerebral hypoperfusion also results in syncope (i.e., fainting) (reviewed



in Gauer 2011). Causes of hypoperfusion include orthostatic hypotension, neurovascular disease, decreased cardiac output (usually from arrhythmia), and neural reflexes. For example, a classic scenario is an unpleasant stimulus, such as extreme fright, triggering a vasovagal reflex of bradycardia and hypotension that leads to syncope. The clinical history and premonitory symptoms—fading vision, nausea, pallor, sweating, etc.—are typically diagnostic. Syncopal patients occasionally exhibit brief, mild myoclonic limb jerks or incontinence but are fully oriented upon awakening, distinguishing syncope from the postictal confusion of a true seizure.

Epilepsy is defined as recurrent seizures, which result from episodic cortical hyperexcitability. Generalized hyperexcitability manifests as unconsciousness, tonic-clonic convulsions, cyanosis, reactive hyperventilation, excessive salivation, and postictal confusion. In comparison, when hyperexcitability involves a focal neurologic region, the symptoms reflect the affected cortical region and vary widely depending on the particular epilepsy syndrome (reviewed by Berg et al. 2010, Berg & Scheffer 2011). Epilepsy has manifold pathophysiologies, primarily structural, metabolic, neurodegenerative, idiopathic, and genetic (including some Mendelian forms; see below and **Figure 1**). Seizures can be triggered by stressors such as infection, psychosomatic trauma, or menses.

The final common complex disorder is migraine. Migraine is characterized by episodic severe headache accompanied by nausea, photophobia, and phonophobia. Many patients experience prodromal symptoms hours to days before headache, which vary widely, and about one-quarter of patients experience aura, commonly visual, which immediately precedes the headache. The pathophysiology of migraine remains hotly disputed but probably involves both alterations in cortical excitability (i.e., cortical spreading depression) as well as vasodilatation of cerebral and meningeal vessels (reviewed in Dodick 2008). Like epilepsy, migraine is commonly triggered by stressors (Haut et al. 2006).

A Myriad of Rare Complex Disorders

Episodic neurologic symptoms also occur in a smorgasbord of complex disorders, each of which is individually rare (**Figure 1**). Many are diseases of progressive deterioration that happen to feature episodic symptoms, whereas others are primarily episodic in nature. For a given clinical finding, the differential diagnosis is typically extensive (**Table 1**). For example, myoclonus is a component of more than 200

Table 1 Diagnosis of complex episodic disorders. Episodic neurologic symptoms occur in a variety of complex disorders. The differential diagnosis for a given finding can be very broad. We provide here episodic presentations, along with references containing diagnostic approaches. We have omitted other presentations, such as weakness, stiffness, paralysis, arrhythmia, hemiplegia, pain, and ataxia.

Presentation	Reference(s) with diagnostic approach
Transient ischemic attack (TIA)	Della-Morte et al. (2012)
Syncope	Gauer (2011)
Seizures	Berg et al. (2010), Berg & Scheffer (2011)
Migraine	Haut et al. (2006)
Exaggerated startle	Dreissen et al. (2012)
Dyskinesia	Fahn (2011)
Myoclonus	Caviness & Brown (2004)
Sleep disorder	Sehgal & Mignot (2011)
Ophthalmic disorder	Sheffield & Stone (2011)

disorders that span the spectrum of neurologic disease: structural malformations, infections, storage disorders, spinocerebellar degenerations, dementias, metabolic derangements, toxin/drug exposures, posthypoxia, malabsorption (celiac disease), various epilepsy syndromes, and many more (Caviness & Brown 2004). The differential diagnosis can be just as broad for other episodic presentations (**Table 1**). Usually the diagnosis is suggested by the entire clinical history and examination rather than by episodic symptoms per se. If a diagnosis remains elusive, probability of an autoimmune or Mendelian cause is increased.

Rare complex disorders with autoimmune etiologies have provided special insight into pathophysiology (reviewed in Vincent et al. 2006, Kleopa 2011). Classically, these autoimmune episodic disorders are caused by autoantibodies against ion channels (**Figure 2*b***). For example, ion channels at the NMJ are the targets of autoantibodies that cause muscle weakness in Lambert-Eaton myasthenic syndrome (LEMS) and myasthenia gravis (MG) (Vincent et al. 2006). Clinically, LEMS is characterized by proximal muscle weakness and autonomic dysfunction, whereas MG patients exhibit striking fatigability, particularly of ocular muscles. Both LEMS and MG must be distinguished from congenital myasthenic syndromes (see below), which also present with weakness but are juvenile onset and Mendelian rather than autoimmune in etiology. LEMS is caused by autoantibodies against presynaptic voltage-gated calcium channels, whereas MG is usually caused by autoantibodies against the nicotinic acetylcholine receptor (AChR) on the motor end plate. Recent work has tied AChR-seronegative MG to autoantibodies against muscle-specific tyrosine kinase (MuSK) (Hoch et al. 2001) or low-density lipoprotein receptor-related protein 4 (Lpr4) (Higuchi et al. 2011, Pevzner et al. 2012). Neither of these targets are ion channels; instead, they promote postsynaptic clustering of the AChR channel (**Figure 2*c***).

Another example of an autoimmune episodic disorder is Isaac's syndrome (neuromyotonia). Isaac's syndrome is a disorder of motor nerve hyperexcitability that can present with hyperhidrosis and a range of muscle symptoms including fasciculations, cramps, stiffness, myokymia (quivering), and pseudomyotonia (slow relaxation). For many years, Isaac's syndrome and two related disorders, Morvan's syndrome and limbic encephalitis, were thought to result from autoantibodies against voltage-gated potassium channels (Vincent et al. 2006). However, the data were mixed. Dalmau et al. recently presented strong evidence that these disorders are instead caused by autoantibodies against the Caspr2-Lgi1 complex, which associates with voltage-gated potassium channels on the motor nerve (Lai et al. 2010, Lancaster et al. 2011, Irani et al. 2012, Loukaides et al. 2012). These findings further illustrate an emerging understanding that in addition to targeting channels directly (**Figure 2*b***), autoantibodies may target channel-associated

STIFF-MAN SYNDROME

A compelling, recently elucidated example of autoantibodies interfering with targets other than ion channels to cause episodic disease is stiff-man syndrome (SMS). SMS is characterized by extreme muscle cramps superimposed on progressive, fluctuating muscle rigidity and stiffness. Tragically, these symptoms are so severe that they often cause joint deformities, skeletal fractures, and even muscle rupture. Cramp attacks are triggered by movement, unanticipated somatosensory stimuli, stress, and strong emotions. Solimena et al. (1988) showed that 80% of patients develop autoantibodies against glutamic acid decarboxylase (GAD), but anti-GAD antibody infusion into model animals does not passively transfer SMS symptoms. Recently, Geis et al. (2010) achieved passive transfer in rats by infusing antiamphiphysin antibodies collected from human SMS patients. Furthermore, antiamphiphysin antibodies were internalized into CNS GABAergic neurons where they inhibited GABA (γ-aminobutyric acid) release. This work demonstrates that SMS is caused by autoantibodies directed against not ion channels but intracellular, presynaptic targets (**Figure 2*c***). It seems likely that other autoimmune or idiopathic disorders may be caused by autoantibodies targeting intracellular, synaptic, or even nonneuronal targets (Lennon et al. 2005).

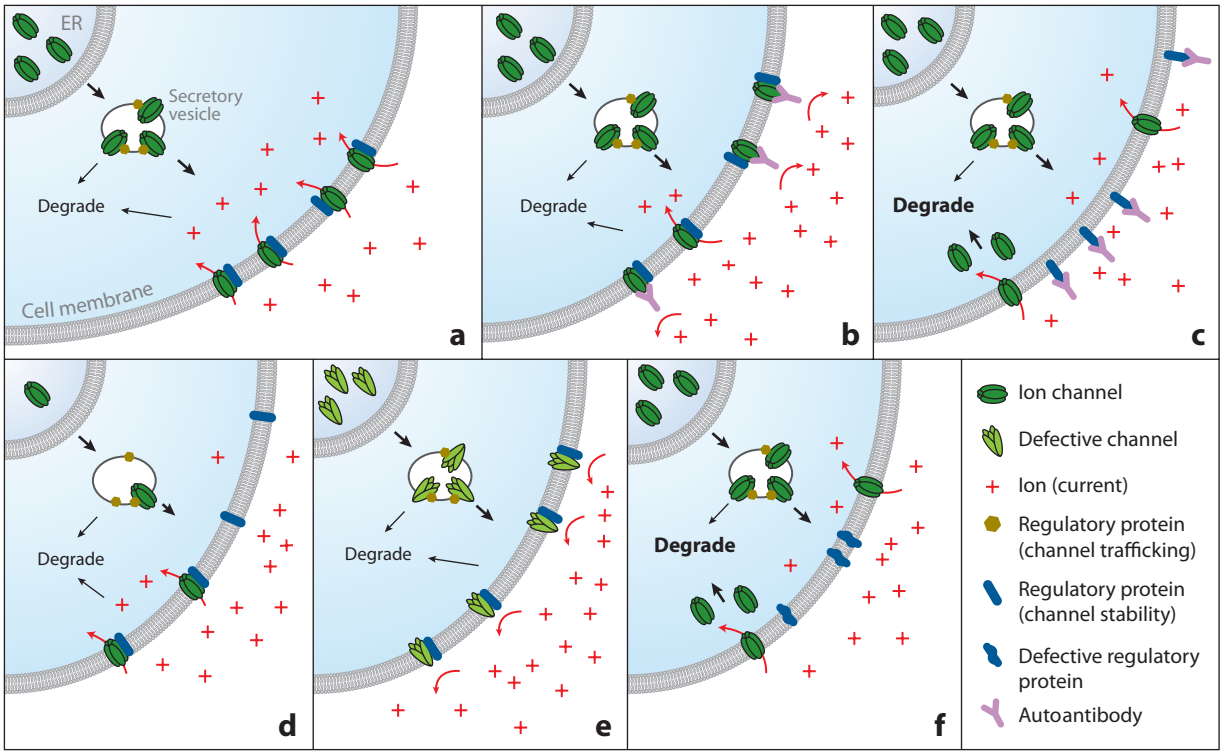


Figure 2

Channelopathy mechanisms. (*a*) Normally, ion channels are trafficked from the endoplasmic reticulum (ER) via secretory vesicles to the cell membrane, where they conduct ions across the membrane to control cellular membrane potential and hence excitability. (*b*) Many autoimmune episodic neurologic disorders are caused by autoantibodies binding to ion channels, which causes defective channel function, such as decreased ion permeability (shown here). (*c*) Investigators have recently associated numerous autoimmune episodic disorders with autoantibodies against targets other than channels. These autoantibodies bind to channel-associated regulatory proteins, thereby indirectly causing defective channel function. Shown here are autoantibodies against a regulatory protein that stabilizes the channel at the membrane. Inhibition of this regulatory protein by autoantibody binding results in decreased channel stability, so more channels are degraded and overall current is decreased. (*d–e*) Most episodic neurologic disorders that exhibit Mendelian inheritance are caused by mutations in ion channel genes. There are many different possible effects of mutations, including absent or decreased expression (*d*), defective trafficking or stability leading to premature degradation, decreased ion permeability (*e*), increased ion permeability, and altered channel kinetics (e.g., delayed inactivation). (*f*) Aside from mutations in ion channels themselves, recent work has identified mutations in genes that do not encode channels. Like the targets of some autoantibodies (*c*), these genes encode regulatory proteins that bind to channels and are critical for channel stability and localization. When mutated, defective regulatory proteins result in aberrant channel trafficking or stability, premature channel degradation, and hence decreased current. For panels *b-f*, see text for examples.

regulatory proteins to cause channel dysfunction indirectly (**Figure 2*c***).

MENDELIAN DISORDERS

General Characteristics

Although each is individually rare, many distinct episodic disorders exhibit Mendelian inheritance. Despite very strong genetic contributions, these diseases share striking similarity with the complex disorders discussed above because patients are often completely normal between attacks, and attacks are often triggered by commonplace environmental stimuli.

We have organized the Mendelian episodic disorders on the basis of the focus of pathology within the nervous system: skeletal muscle,

cardiac muscle, NMJ, peripheral nerve, or CNS (**Figure 1**). Most are juvenile onset and autosomal dominant. The vast majority of known disease genes encode ion channels, which has led to use of the term channelopathies to describe this group of disorders (**Figure 2**) (Kullmann 2010, Ryan & Ptáček 2010). However, this usage is a misnomer for two reasons. First, complex episodic disorders can also result from channel dysfunction, as exemplified by the autoimmune diseases discussed above. Second, some nonneurologic Mendelian diseases are caused by mutations in ion channels (Benoit et al. 2010). Thus, the term channelopathy should be reserved for any disorder, complex or Mendelian, neurologic or nonneurologic, caused by channel dysfunction.

Most Mendelian channelopathies affect primarily a single organ system, presumably because a typical ion channel is expressed in one cell type or a limited number of cell types. The exact pathophysiology depends on the mutation severity (e.g., missense or nonsense) and on the type of channel that is mutated (Kullman 2010, Ryan & Ptáček 2010). Missense mutations are often gain-of-function, causing increased ion flux. However, missense mutations can certainly cause loss-of-function (**Figure 2*e***), and dominant-negative mechanisms are also common because some channels are composed of subunits encoded by separate genes that homo- or heteromultimerize into a functional channel. Nonsense (truncation) mutations are almost always loss-of-function or dominant-negative (**Figure 2*d***). Although exceptions abound, generally mutations in sodium channel genes cause gain-of-function, whereas potassium and chloride channel mutations cause loss-of-function. Sodium, potassium, and chloride channels usually cause myocyte or neuronal dysfunction. In contrast, AChR, $GABA_A$ receptor, glycine receptor, and calcium channel mutations typically disrupt synaptic transmission. In any case, in the PNS the ultimate pathophysiology rests on whether the mutation renders the affected cell hypoexcitable or hyperexcitable. In the CNS, pathophysiology rests on whether inhibitory or excitatory neurons are preferentially affected, thereby resulting in a net hypoexcitable or hyperexcitable network (**Figure 3*b***).

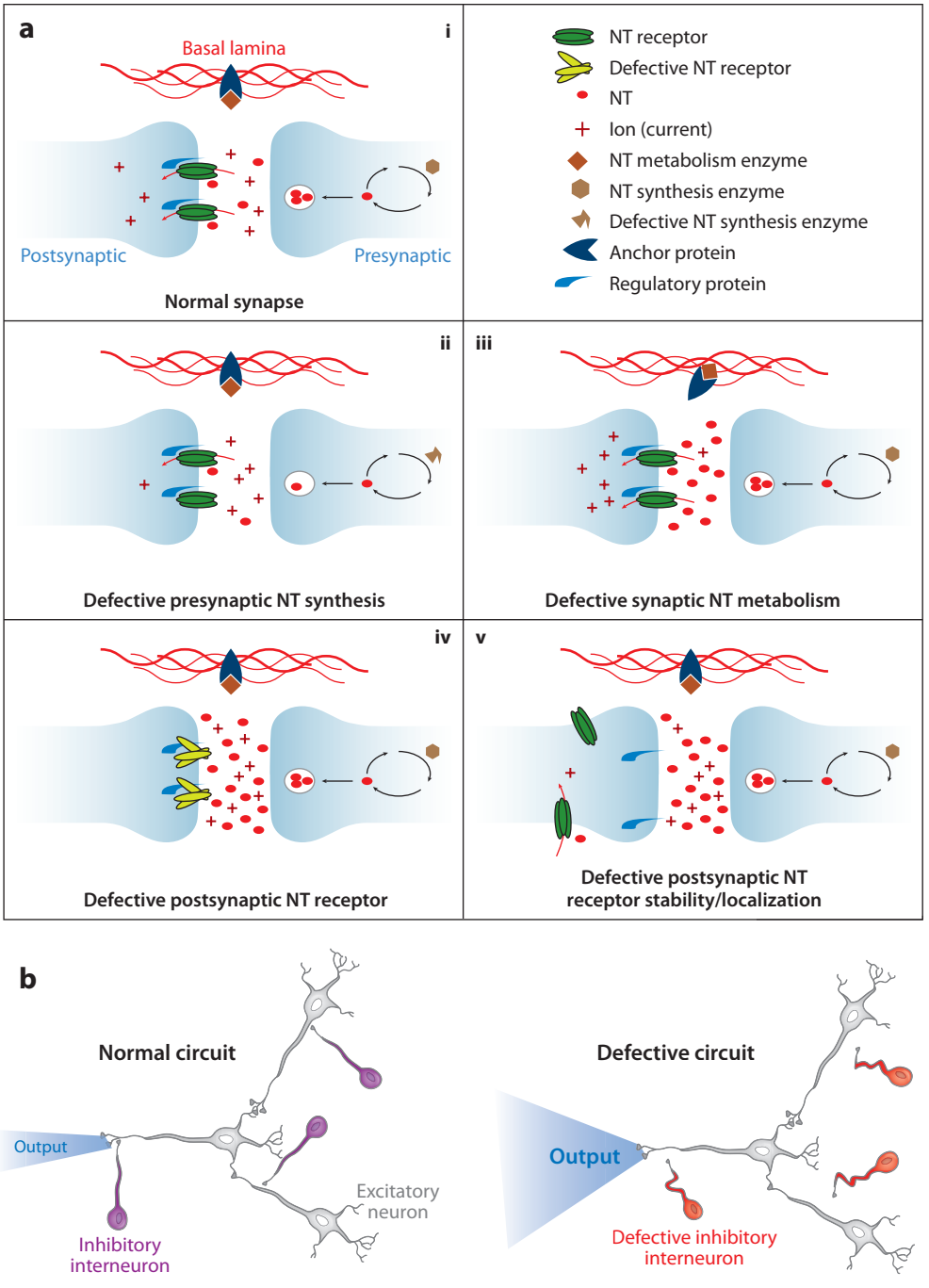
Channelopathy: a disease caused by dysfunction of ion channels; can be inherited (Mendelian) or complex (e.g., autoimmune), neurologic or nonneurologic

Skeletal Muscle

Primary skeletal muscle disorders were the first episodic disorders for which causative mutations were identified (Ptáček et al. 1991, Rojas et al. 1991, McClatchey et al. 1992, Ptáček et al. 1992). These entities were central to establishing the channelopathy paradigm, as all known disease genes encode ion channels. The molecular and cellular pathophysiology has been thoroughly elucidated, and in some cases this insight has led to clinical trials and successful treatments (Tawil et al. 2000). Each disorder falls on a spectrum ranging from muscle hyperexcitability to hypoexcitability. Hyperexcitable muscle presents clinically as myotonia: After contraction, the muscle is slow to relax. In contrast, hypoexcitable muscle presents clinically as weakness or paralysis.

Myotonia congenita (MC) constitutes the far hyperexcitable end of the spectrum. Patients suffer stiffness, particularly after prolonged inactivity, which is relieved by repetitive muscle activity (reviewed by Lossin & George 2008). Mutations in *CLCN1*, the skeletal muscle chloride channel, cause myotonia congenita in either autosomal dominant (Thomsen disease; OMIM 160800) or autosomal recessive (Becker disease; OMIM 255700) forms (Koch et al. 1992). Myotonia in Becker disease tends to be more severe and can even be accompanied by episodic weakness.

Like Becker disease, paramyotonia congenita (PMC; OMIM 168300) is characterized by both myotonia and weakness (reviewed in Jurkat-Rott et al. 2010). PMC can be distinguished from MC because PMC patients exhibit paradoxical myotonia, in which myotonia is exacerbated by exercise and can transition to weakness (whereas myotonia in MC is relieved by exercise). Also, PMC attacks are prominently triggered by cold and mostly affect the upper extremities and face. PMC is caused by mutations in *SCN4A*, a skeletal muscle voltage-gated sodium channel (Ptáček



et al. 1992). Different *SCN4A* mutations cause potassium-aggravated myotonia (PAM; OMIM 608390) (Ptáček et al. 1994b), in which myotonia is instead triggered by potassium. However, in PAM the myotonia never transitions to weakness (Jurkat-Rott et al. 2010).

On the opposite, hypoexcitable end of the spectrum are hyperkalemic periodic paralysis (HyperKPP; OMIM 170500) and hypokalemic periodic paralysis (HypoKPP; OMIM 170400) (Jurkat-Rott et al. 2010). Patients suffer from episodes of weakness or paralysis, triggered by exercise or stress. During attacks, HypoKPP patients are always hypokalemic, whereas HyperKPP patients are often normokalemic. However, for purposes of diagnosis HyperKPP attacks can be induced by a potassium load. Aside from serum potassium levels, the periodic paralyses are clinically distinguishable because HypoKPP never causes myotonia, whereas HyperKPP causes myotonia early in an attack before evolving to weakness/paralysis. Both HyperKPP and HypoKPP patients can develop progressive fixed weakness in those muscles prone to paralytic attacks. Like PMC and PAM, HyperKPP and HypoKPP are caused by mutations in *SCN4A* (Ptáček et al. 1991, Bulman et al. 1999), which highlights the relatedness of these disorders. Other cases of HypoKPP are caused by mutations in *CACNA1S*, which encodes a skeletal muscle voltage-gated calcium channel (Ptáček et al. 1994a). Genotype-phenotype correlations and pathophysiological mechanisms are reviewed elsewhere (Raja Rayan & Hanna 2010).

A variant of HypoKPP is thyrotoxic periodic paralysis (TPP; OMIM 613239) (Jurkat-Rott et al. 2010). TPP patients suffer weakness/paralysis in attacks triggered by thyrotoxicosis. TPP usually afflicts young adult males of Asian ancestry. Ryan et al. (2010) recently demonstrated that some TPP cases are caused by mutations in *KCNJ18*, encoding a skeletal muscle potassium channel. *KCNJ18* mutations have since been discovered in a few patients with nonfamilial HypoKPP but normal thyroid function, so-called "sporadic periodic paralysis" (Cheng et al. 2011). However, *KCNJ18* mutations account for only one-fourth to one-third of TPP cases. We have sequenced many known ion channel genes in *KCNJ18*-mutation negative TPP patients but found no mutations (L.J. Ptáček, unpublished observations), and the genetic basis underlying these cases remains to be elucidated.

Finally, periodic paralysis (either HypoKPP or HyperKPP) is observed in Andersen-Tawil syndrome (ATS; OMIM 170390) (reviewed by Tristani-Firouzi & Etheridge 2010). ATS is a pleiotropic disorder: Periodic paralysis may be accompanied by neurocognitive deficits, skeletal dysmorphisms, and, of paramount clinical importance, long QT syndrome (see below). ATS is caused by mutations in *KCNJ2*, another

Figure 3

Beyond the channelopathy paradigm: mechanisms of synaptopathy and circuitopathy. (*a*) A compelling area for future study is the role of disease genes controlling excitability at the synaptic level, i.e., synaptopathy. In a normal synapse (*i*), a neurotransmitter (NT) is enzymatically synthesized in the presynaptic cell and then released into the synaptic cleft, where it activates postsynaptic NT receptors that then pass current. Regulatory proteins modulate NT receptor stability and localization. NT is metabolized in the synaptic cleft by enzymes that can be anchored to the presynaptic cell, the postsynaptic cell, or the basal lamina (depicted). Defects in these processes can alter synaptic transmission and excitability, as exemplified by defective neuromuscular junction (NMJ) synaptic transmission in the congenital myasthenic syndromes (CMS). CMS can be caused by mutations in a NT synthesis enzyme (*ii*), mutations in proteins that anchor a NT metabolism enzyme to the basal lamina (*iii*), mutations in the NT receptor itself (*iv*), and mutations in proteins that regulate NT receptor stability/localization (*v*). Although this pathophysiology has been heretofore demonstrated only for one type of synapse—the NMJ in CMS—other episodic disorders of the CNS are likely caused by dysfunction of higher-order synapses. Additional mechanisms of synaptopathy are conceivable, such as defects in synaptic vesicle release. (*b*) Another potential mechanism of episodic disease is defective regulation at the circuit level, i.e., circuitopathy. For example, one type of defective circuit is exemplified by GEFS+, which is caused by *SCN1A* mutations that result in decreased GABAergic inhibition by interneurons. Certainly many other types of defective circuits are possible, but whether they can cause episodic neurologic disease is not yet known.

potassium channel (Plaster et al. 2001). *KCNJ2* mutations are found in only 60% of ATS families, suggesting the existence of at least one additional disease gene.

Cardiac Muscle

Numerous Mendelian diseases feature episodic dysfunction of cardiac muscle. These include atrial fibrillation and four ventricular arrhythmias: long QT syndrome, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. Most of the disease genes encode ion channels, but some do not. For example, atrial fibrillation (AF) can be caused by autosomal dominant mutations in five potassium channel genes (*KCNA5*, *KCNE2*, *KCNE5*, *KCNJ2*, *KCNQ1*) and three sodium channel genes (*SCN1B*, *SCN2B*, *SCN5A*) (Mahida et al. 2011). However, monogenic AF can also be caused by mutations in *GJA5*, *NPPA*, or *NUP155*, which encode a gap junction protein, an atrial natriuretic peptide, and a nucleoporin, respectively. Pathophysiological mechanisms for these non-ion channel genes remain elusive (Mahida et al. 2011).

A well-known ventricular arrhythmia, long QT syndrome (LQTS) is defined by an elongated QT interval per EKG. This electrical abnormality reflects delayed cardiomyocyte repolarization, which predisposes to torsades de pointes arrhythmia that manifests clinically as palpitations, syncope, or sudden cardiac death. LQTS presents in four clinical subtypes: Andersen-Tawil syndrome (see above), Romano-Ward syndrome (most common; OMIM 192500), Jervell and Lange-Nielsen syndrome (includes congenital deafness; OMIM 220400), and Timothy syndrome (includes cardiac malformations, syndactyly, and autism spectrum disorders; OMIM 601005) (reviewed by McBride & Garg 2010). Like AF, LQTS is genetically heterogeneous, with 13 known genes, including six potassium channel genes (*KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNJ5*, *KCNQ1*), two sodium channel genes (*SCN4B*, *SCN5A*), one calcium channel gene (*CACNA1C*), and four genes not encoding channels: *AKAP9*, *ANK2*, *CAV3*, and *SNTA1*. Mutations in the four nonchannel genes seem to disrupt trafficking or stability of cardiomyocyte ion channels (**Figure 2*f***) (Mohler et al. 2003, Vatta et al. 2006, Chen et al. 2007, Ueda et al. 2008).

Patients with short QT syndrome (SQTS; OMIM 609620) suffer from a shortened QT interval that, like LQTS, predisposes to ventricular arrhythmia and sudden cardiac death. SQTS is caused by autosomal dominant mutations in three potassium channel genes (*KCNH2*, *KCNJ2*, *KCNQ1*), two of which are also LQTS genes (McBride & Garg 2010). Thus, SQTS and LQTS constitute a spectrum ranging from prolonged to delayed cardiomyocyte repolarization. SQTS can also present in concert with Brugada syndrome (OMIM 601144)—defined by elevation of the ST segment in select EKG leads—in patients with mutations in *CACNA1C* and *CACNB2*, which encode calcium channel subunits. Alternatively, isolated Brugada syndrome results from mutations in three sodium channel genes (*SCN1B*, *SCN3B*, *SCN5A*), one potassium channel gene (*KCNE3*), and *GPD1L*, which encodes a protein that regulates SCN5A phosphorylation and thereby modulates sodium current density (**Figure 2*f***) (Valdivia et al. 2009, McBride & Garg 2010).

Finally, another important cause of sudden cardiac death in children is catecholaminergic polymorphic ventricular tachycardia (CPVT; OMIM 604772). In CPVT, the catecholaminergic surge associated with strong emotions or exercise can trigger ventricular tachycardia. The four disease genes, *RYR2*, *CASQ2*, *TRDN*, and *CALM1*, encode essential components of cardiomyocyte calcium signaling (McBride & Garg 2010, Nyegaard et al. 2012, Roux-Buisson et al. 2012). Recently, Watanabe et al. (2009) elegantly identified flecainide as a potent inhibitor of arrhythmias in a CPVT mouse model. This work was validated in human trials (van der Werf et al. 2011), suggesting an effective treatment for this otherwise lethal disease.

Neuromuscular Junction

Mendelian disorders of the neuromuscular junction (NMJ) are known as congenital myasthenic syndromes (CMS). CMS are distinguished from the complex, autoimmune NMJ disorders LEMS and MG (see above) because CMS cannot be treated by immunosuppression. Although CMS subtypes are clinically and genetically heterogeneous, they are usually characterized by episodic ocular and respiratory weakness (reviewed in Barisic et al. 2011). Weakness results from impaired neuromuscular transmission.

Most CMS subtypes are autosomal recessive, caused by mutations in 1 of 14 known genes. The subtypes/genes are classified by the NMJ component that is primarily affected: presynaptic, synaptic, or postsynaptic (**Figure 3*a***) (Barisic et al. 2011). Presynaptic CMS (OMIM 254210) features prominent episodic apnea and is caused by mutations in *CHAT*, encoding an enzyme critical for acetylcholine synthesis (**Figure 3*a*, *part ii***). Synaptic CMS (OMIM 603034) can be caused by mutations in *COLQ* (Mihaylova et al. 2008) and *LAMB2* (Maselli et al. 2009), which encode proteins that anchor acetylcholinesterase to the basal lamina (**Figure 3*a*, *part iii***). The most common type of CMS, by far, is postsynaptic CMS (OMIM 608931), usually caused by defects in AChR subunit genes *CHRNA1*, *CHRNB1*, *CHRND*, and *CHRNE* (**Figure 3*a*, *part iv***). Mutations in another AChR subunit gene, *CHRNG*, cause Escobar syndrome (OMIM 265000), characterized by joint contractures, pterygia (webbing), and in utero CMS-like respiratory distress that resolves by birth (Hoffmann et al. 2006). Finally, rare cases of postsynaptic CMS are caused by mutations in non-AChR genes, namely *AGRN*, *DOK7*, *GFPT1*, *MUSK*, and *RAPSN*. These genes constitute a molecular pathway essential for AChR aggregation and positioning on the postsynaptic membrane (**Figure 3*a*, *part v***) (Barisic et al. 2011). Mutations in some of these genes (*CHRNA1*, *CHRNB1*, *CHRND*, *DOK7*, and *RASPN*) cause fetal akinesia deformation sequence (OMIM 208150), a perinatal lethal syndrome characterized by developmental anomalies such as pterygia as well as fetal akinesia. Given the clinical and genetic overlap, fetal akinesia deformation sequence is considered an extreme phenotype on a continuum that includes Escobar syndrome and CMS. Identifying which gene is mutated in a CMS patient is critical because certain genetic subtypes respond robustly to otherwise toxic medications (Barisic et al. 2011). About half of CMS cases await genetic diagnosis, suggesting a fruitful area for human genetics to provide further insights into synaptic physiology.

Peripheral Nerve

Recent studies have shown that mutations in *SCN9A* cause an intriguing trio of pain perception disorders. *SCN9A* encodes a sodium channel that is specifically expressed in those peripheral sensory neurons that function as nociceptors. Mutations lead to aberrant excitability of nociceptive nerves and thus alter the patient's sensitivity to painful stimuli. Autosomal dominant, gain-of-function mutations cause hypersensitivity to pain in two disorders: inherited erythromelalgia (IEM; OMIM 133020) and paroxysmal extreme pain disorder (PEPD; OMIM 167400) (Yang et al. 2004, Fertleman et al. 2006). Burning pain occurs in discrete episodes, accompanied by erythema and swelling. IEM affects the extremities and is commonly triggered by exercise, heat, or dietary components, whereas PEPD affects submandibular, ocular, and rectal areas and is triggered by perianal stimulation (e.g., bowel movements).

Autosomal recessive, loss-of-function *SCN9A* mutations cause the opposite phenotype: congenital insensitivity to pain (CIP; OMIM 243000), characterized by complete absence of pain sensation (Cox et al. 2006). Although ostensibly appealing, patients with CIP suffer substantial injuries and early deaths because of inadvertent trauma. Early studies suggested that CIP patients are otherwise normal, but Weiss et al. (2011) recently

Mendelian disorder: a disease in which a mutation in a single gene causes the phenotype; cf. complex genetic disorder

Congenital myasthenic syndromes (CMS): Mendelian disorders of the neuromuscular junction

demonstrated that the patients cannot smell; furthermore, mice with olfactory sensory neuron-specific *SCN9A* knockout also exhibit anosmia (Weiss et al. 2011). Nevertheless, the specificity and degree of pain relief achieved by genetic inactivation of this channel make it a promising target for developing drugs to treat pain (Clare 2010).

Knockin mouse: a mouse engineered to carry a mutation, usually missense, found in humans; the mutant gene is otherwise intact

Central Nervous System

A mélange of Mendelian episodic disorders afflict the CNS, with diverse symptoms depending on which region of the CNS is affected. For example, the cerebellum is the focus of pathology in episodic ataxia (EA). EA is distinguished by attacks of ataxia (imbalance and incoordination) without impaired consciousness (reviewed by Jen et al. 2007, Jen 2008). Sometimes, attacks include weakness or are superimposed on progressive ataxia. Seven subtypes (EA1–EA7) vary in associated symptoms, such as myokymia, nystagmus, tinnitus, vertigo, and hemiplegic migraine. Most subtypes share exertion, emotions, and startle as triggers. Each is autosomal dominant, with mutations in *KCNA1* (EA1; OMIM 160120), *CACNA1A* (EA2; OMIM 108500), *CACNB4* (EA5; OMIM 613855), and *SLC1A3* (EA6; OMIM 612656). Despite demonstrated linkage, the genes for EA3 (OMIM 606554), EA4 (OMIM 606552), and EA7 (OMIM 611907) have proven elusive. *KCNA1* and *CACNA1A/CACNB4* encode subunits of potassium and calcium channels, respectively, that are highly expressed in Purkinje cells of the cerebellum (Tomlinson et al. 2009), and indeed, mice expressing mutant channels exhibit aberrant Purkinje cell activity (Jen et al. 2007). The EA6 gene, *SLC1A3*, encodes a glutamate reuptake transporter expressed in cerebellar astrocytes (Jen et al. 2005), but how mutant *SLC1A3* alters cerebellar output remains unknown.

EA2 features migraine, so it is also termed familial hemiplegic migraine (FHM) type 1 (OMIM 141500). FHM patients suffer from attacks of headache with hemiplegia during aura. Whereas FHM1 is associated with ataxia, two other subtypes, FHM2 and FHM3, are not. For all subtypes, inheritance is autosomal dominant. FHM2 (OMIM 602481) is caused by mutations in *ATP1A2* (De Fusco et al. 2003), which encodes a sodium-potassium ATPase. FHM3 (OMIM 609634) patients carry mutations in the sodium channel *SCN1A* (Dichgans et al. 2005). Knockin mouse models for both FHM1 and FHM2 have increased susceptibility to cortical spreading depression (CSD) (Tottene et al. 2009, Leo et al. 2011), in keeping with the theory that aberrant cortical excitability is at least partially responsible for migraine pathophysiology (see above).

A related disorder is alternating hemiplegia of childhood (AHC; OMIM 104290), characterized by recurrent attacks of hemiplegia (reviewed by Neville & Ninan 2007). AHC often presents with concomitant epilepsy and developmental delay. As a very rare, sporadic disorder, the etiology of AHC has long remained a mystery, but Heinzen et al. (2012) recently showed that AHC is caused by de novo mutations in *ATP1A3*, another sodium-potassium ATPase gene. The mechanism linking sodium-potassium ATPases and hemiplegia in FHM2 and AHC is not clear. Distinct *ATP1A3* mutations cause a quite dissimilar phenotype: autosomal dominant rapid-onset dystonia-parkinsonism (OMIM 128235; de Carvalho Aguiar et al. 2004).

Some families exhibit autosomal dominant migraine without hemiplegia (OMIM 613656). Investigators have proposed two genes so far. The first, *KCNK18*, a potassium channel, was mutated in a single large affected family (Lafreniere et al. 2010). Moreover, the mutant subunit suppressed wild-type channel function in vitro through a dominant negative effect (Lafreniere et al. 2010). However, the same group (Andres-Enguix et al. 2012) later discovered *KCNK18* variants in unaffected controls, variants that also completely abrogate wild-type channel function. How to reconcile these data? One possibility is that *KCNK18* mutation alone is not sufficiently causative and that the single affected family carries additional migraine susceptibility variants. However, it

is extremely unlikely that another locus would cosegregate with the phenotype in the large family (nine individuals affected), which suggests that either the *KCNK18* linkage region itself contains additional susceptibility variants or that *KCNK18* is not causally related to the phenotype. On balance, it is our view that *KCNK18* mutations are likely not causative, although we would happily recant upon identification of additional affected families with *KCNK18* mutations. A stronger case can be made for the second candidate gene, *CSNK1D*, which encodes a kinase, because two independent families carry distinct mutations (Brennan et al. 2013). These mutations alter nearby residues that reside in the highly conserved kinase domain and were shown in vitro to disrupt kinase activity (Xu et al. 2005; K.C. Brennan, E.A. Bates, R.E. Shapiro, J. Zyuzin, W.C. Hallows, H.Y. Lee, C.R. Jones, Y.H. Fui, A.C. Charles, L.J. Ptáček, forthcoming). Furthermore, a mutant mouse model exhibits increased peripheral allodynia, cortical spreading depression, and arterial dilation, all physiological markers of migraine (Brennan et al. 2013). In any case, the overlapping, well-characterized phenotypes of these three families strongly argue for the existence of Mendelian migraine that is distinct from FHM and distinct from migraine with complex inheritance (Eriksen et al. 2004). Heretofore unnamed, we propose the term autosomal dominant migraine (ADM) for this disorder.

Hereditary hyperekplexia (HH) is a disorder of the brain stem, featuring an exaggerated startle reaction (reviewed in Dreissen et al. 2012). Most patients exhibit stiffness at birth that lasts through infancy. Stiffness is exacerbated by handling and is so pronounced that the baby can be held vertically or horizontally without a change in posture. Consciousness is always preserved. Although prolonged stiffness resolves after infancy, throughout the rest of their lives patients suffer from stiffness for a few seconds after an exaggerated startle reaction to unexpected stimuli. HH inheritance can be autosomal dominant, autosomal recessive, or sporadic and is usually caused by mutations in *GLRA1* (OMIM 149400; Shiang et al. 1993). *GLRA1* encodes a subunit of the glycine receptor located in the postsynaptic membrane of glycinergic neurons (**Figure 3*a*, *part iv***) (Dreissen et al. 2012). Less commonly, patients carry mutations in *SCL6A5* (which encodes a presynaptic glycine transporter) (OMIM 614618; Rees et al. 2006) or, very rarely, mutations in *GLRB*, *GPHN*, or *ARHGEF9* (all encode postsynaptic glycinergic proteins; OMIM 138492, 149400, 300607, respectively). These mutations decrease the inhibition exerted by glycinergic neurons in the spinal cord and brain stem, resulting in excessive excitation as reflected by stiffness and exaggerated startle (Dreissen et al. 2012).

Another fascinating group of episodic disorders are the paroxysmal dyskinesias. In these diseases, excessive excitation manifests as attacks of involuntary movements that can include dystonia (sustained contractions), athetosis (writhing), and chorea (small dance-like movements) (reviewed by Bhatia 2011). There are three Mendelian paroxysmal dyskinesias: paroxysmal exercise-induced dyskinesia (PED; OMIM 612126), paroxysmal nonkinesigenic dyskinesia (PNKD; OMIM 118800), and paroxysmal kinesigenic dyskinesia (PKD; OMIM 128200). All three are autosomal dominant with juvenile onset.

PED is usually triggered by exercise and causes dystonia in the heavily exercised muscles. The PED gene, *SLC2A1*, encodes the main glucose transporter in the brain (Suls et al. 2008, Weber et al. 2008). Mutations impair glucose import into the brain such that the increased energy demand after exercise renders the basal ganglia hypoglycemic. However, this defect must not be specific to the basal ganglia because PED often presents with concomitant neurologic illness that may include hemiplegic migraine, developmental delay, and especially epilepsy. Indeed, De Vivo disease, which is also caused by *SLC2A1* mutations, features severe, global developmental delay and epilepsy; PED may not be appreciable (De Vivo et al. 1991, Seidner et al. 1998). Diagnosis of any phenotype along this PED–De Vivo spectrum is

Allodynia: pain resulting from a typically innocuous stimulus; a cardinal symptom of migraine

Pleiotropy: a mutation in a single gene causes multiple phenotypic effects, such as in multiple organ systems

critical because the ketogenic diet is a highly effective treatment (Leen et al. 2010). Ketone bodies use a different transporter to enter the CNS and thereby provide an alternative energy source.

In contrast with PED, PKD attacks are often triggered by startle or sudden movements (hence kinesigenic) (Bruno et al. 2004). PNKD attacks are, by definition, not triggered by movement. Instead, PNKD is induced by ethanol, caffeine, or stress. In both PKD and PNKD, hormones play a role: PKD attacks peak in puberty but decrease in pregnancy, and PNKD attacks increase with menses and thereafter improve with age. However, the exact role of hormones in the genesis of attacks is unclear. PNKD is caused by mutations in the gene *PNKD*, which encodes an enzyme that seems to modulate dopamine release in the striatum in response to ethanol, caffeine, and redox status (Lee et al. 2004, 2012b; Rainier et al. 2004). One hypothesis is that *PNKD* mutations, which alter protein stability and cleavage (Ghezzi et al. 2009, Shen et al. 2011), are gain-of-function, rendering a patient more susceptible to stimuli that trigger dopamine dysregulation in the basal ganglia (Lee et al. 2012b).

Numerous groups recently identified the PKD disease gene, *PRRT2* (Chen et al. 2011, Wang et al. 2011, Heron et al. 2012, Lee et al. 2012a, Li et al. 2012). Within affected families, there is remarkable pleiotropy; some patients suffer from episodic ataxia or hemiplegic migraine (Cloarec et al. 2012, Gardiner et al. 2012, Marini et al. 2012), and others from benign, afebrile infantile epilepsy prior to PKD onset [termed infantile convulsions with choreoathetosis (ICCA)] (Cloarec et al. 2012, Heron et al. 2012, Lee et al. 2012a). In fact, some patients suffer from benign familial infantile epilepsy (BFIE) that resolves in infancy and is never succeeded by PKD (Heron et al. 2012). Given the phenotypic and genetic overlap of these disorders, we have proposed the term PKD/infantile convulsions (PKD/IC) for the diagnosis of any *PRRT2* mutation-positive patient with BFIE, PKD, or both (ICCA) (Cloarec et al. 2012, Lee et al. 2012a). *PRRT2* encodes a transmembrane protein that lacks characteristic ion channel motifs, and its function is not known. Lee et al. (2012a) found that mutations disrupt in vitro binding of PRRT2 to SNAP-25, a synaptic protein integral for neurotransmitter release. However, PRRT2 predominantly localizes to axons rather than to dendritic processes (Lee et al. 2012a), and it is a widespread misconception that individual protein-protein interactions are critical to physiological function (Gillis & Pavlidis 2012). Nevertheless, one possible unifying hypothesis is that PKD and PNKD are both disorders of synaptic regulation (**Figure 3*a***), although this certainly remains unproven.

Two other Mendelian movement disorders are marked by the primary symptom of myoclonus. Myoclonus is defined as sudden, brief, involuntary movements, i.e., twitches. Myoclonus is commonly a component of epilepsy, but in these two disorders seizures do not occur. The first, myoclonus-dystonia syndrome (MDS; OMIM 159900), is characterized by juvenile-onset myoclonus and/or dystonia (Nardocci et al. 2008, Roze et al. 2008). MDS patients suffer severe psychiatric comorbidity, especially depression, although MDS symptoms are clearly ameliorated by ethanol, so depression may simply be a by-product of self-medication by intoxication. MDS is caused by autosomal dominant mutations in *SGCE* (Zimprich et al. 2001), which, like *PRRT2*, encodes a non-ion channel transmembrane protein. Although *SGCE* was cloned in 2001, there has been almost no mechanistic insight since, and its function continues to be obscure.

The second myoclonic disorder, familial cortical myoclonus (FCM), was recently described by our group (Russell et al. 2012). Several features distinguish FCM from MDS: FCM myoclonus is adult onset and slowly progressive, there is neither dystonia nor psychiatric comorbidity, ethanol does not ameliorate symptoms, and FCM exhibits cortical rather than subcortical hyperexcitability. FCM is autosomal dominant and is likely caused by mutation in the gene *NOL3* (Russell et al. 2012). Although we presented substantial

genetic, bioinformatic, and biochemical evidence that *NOL3* is the FCM gene (Russell et al. 2012), we could identify only a single, albeit large, affected family, so definitive assignment of *NOL3* as the disease gene awaits discovery of independent FCM families with *NOL3* mutations and/or validation via a knockin animal model (both of which are in progress). *NOL3* encodes a well-characterized inhibitor of apoptosis (Koseki et al. 1998, Nam et al. 2004, Donath et al. 2006), but the mechanism linking *NOL3* mutations and hyperexcitability, as manifested by myoclonus in patients, remains entirely speculative.

The broadest category of inherited episodic CNS disorders is composed of the Mendelian epilepsy syndromes (reviewed by Poduri & Lowenstein 2011). An illustrative example is generalized epilepsy with febrile seizures plus (GEFS+). Whereas febrile seizures are common and typically benign in young children, their persistence after age six defines GEFS+. Most GEFS+ cases are genetically complex, but ~10% are autosomal dominant. So far, all known disease genes encode ion channels, including three voltage-gated sodium channel genes (*SCN1A*, *SCN1B*, *SCN2A*) and two $GABA_A$ receptor ($GABA_AR$) subunit genes: *GABRG2* and *GABRD* (Wallace et al. 1998, Escayg et al. 2000, Baulac et al. 2001, Sugawara et al. 2001, Dibbens et al. 2004). Thirteen additional loci have been linked to GEFS+ and await gene identification (Morar et al. 2011, Poduri & Lowenstein 2011). Mutations in *SCN1A* are most common. In fact, other *SCN1A* mutations cause more severe phenotypes along the GEFS+ continuum: severe myoclonic epilepsy of infancy (SMEI, also known as Dravet syndrome), borderline SMEI, and intractable epilepsy of childhood (IEC) (OMIM 604403; Stafstrom 2009). *SCN1A* knockout and knockin mice die young from epilepsy, and their hippocampal GABAergic interneurons are hypoexcitable, leading to a net hyperexcitable state (**Figure 3*b***) (Yu et al. 2006, Martin et al. 2010). Given that GEFS+ can also be caused by mutations in $GABA_AR$ subunits, interneuron dysfunction is likely a common mechanism underlying the entire GEFS+ continuum, although to our knowledge this hypothesis remains to be tested in *GABRG2* and *GABRD* knockout mice.

Knockout mouse: a mouse engineered to entirely lack a gene

Predictably, many other Mendelian epilepsy syndromes are caused by mutations in ion channels. These phenotypes and the associated genes are extensively reviewed elsewhere (Helbig et al. 2008, Mantegazza et al. 2010, Nicita et al. 2012). The known genes include two $GABA_AR$ subunits, two AChR subunits, the brain glucose transporter, a sodium-potassium ATPase, four potassium channels, one calcium channel subunit, one chloride channel, and one sodium channel. Two other sodium channel genes, *SCN3A* and *SCN8A*, have been associated with childhood epilepsy (Holland et al. 2008, Estacion et al. 2010, Veeramah et al. 2012), but mutations were each detected in only a single patient; therefore, definitive assignment of these genes will require the discovery of distinct mutations in additional patients.

Recent work has demonstrated that mutations in nonchannel genes can cause Mendelian epilepsy. For example, patients with a phenotype along the GEFS+ spectrum who lack an *SCN1A* mutation and are female sometimes harbor *PCDH19* mutations (OMIM 300088; Depienne et al. 2009, 2011). *PCDH19* encodes a calcium-dependent cell adhesion protein (Morishita & Yagi 2007). Two fascinating unanswered questions are, how do mutations in a cell adhesion protein cause epilepsy, and why do these mutations cause disease only in females?

Another well-characterized epilepsy syndrome caused by mutations in a nonchannel gene is autosomal dominant partial epilepsy with auditory features (ADPEAF; OMIM 600512). The disease gene is *LGI1* (Kalachikov et al. 2002). Lgi1 associates with voltage-gated potassium channels, and autoantibodies to the Lgi1-Caspr2 complex are associated with the autoimmune, peripheral nerve disorder known as Isaac's syndrome (see above). How *LGI1* mutations cause temporal lobe epilepsy without any peripheral nerve hyperexcitability is not

Exome sequencing: a method of sequencing and analyzing all protein-coding sequence from a given patient (that patient's "exome")

clear, and in fact, Lgi1 function is essentially unknown. Recent work suggests that Lgi1 inhibits seizure-induced trafficking of potassium channels in thalamocortical neurons (**Figure 2*c***) (Smith et al. 2012); however, it also seems to function in remodeling of synapses and sensory axons (Zhou et al. 2009, 2012), and it is unclear how these findings can be reconciled into a unifying hypothesis.

Yet another nonchannel epilepsy gene, *EFHC1*, is mutated in one subset of juvenile myoclonic epilepsy (JME; OMIM 254770) (Suzuki et al. 2004). *EFHC1* encodes a microtubule-associated protein that regulates cell division and neuronal migration during cortical development (de Nijs et al. 2009). In fact, many genes that function in neuronal migration are mutated in Mendelian syndromes that feature epilepsy as one symptom along with dramatic, radiologically evident malformations of cortical development (Andrade 2009, Barkovich et al. 2012). For example, severe mutations in a gene essential for interneuron migration, *ARX*, cause gross cortical malformations, but milder mutations result in less severe phenotypes such as early infantile epileptic encephalopathy or even isolated mental retardation (Kitamura et al. 2002, Stromme et al. 2002, Shoubridge et al. 2010). Likewise, severe infantile epilepsy phenotypes are caused by mutations in *CDKL5*, *STXBP1*, and *TBC1D24*, which are nonchannel genes that are clearly essential for normal brain development, although their exact function remains unknown (Weaving et al. 2004, Saitsu et al. 2008, Corbett et al. 2010, Falace et al. 2010). On the basis of these data, it seems likely that many complex cases of epilepsy—which have a substantial genetic contribution (**Figure 1**)—may result from a constellation of more subtle, genetically influenced defects in cortical development.

One last class of Mendelian epilepsies is progressive myoclonic epilepsy (PME): juvenile-onset, myoclonic epilepsy in association with neurodegeneration, dementia, and early death (reviewed by Ramachandran et al. 2009). There are many PME subtypes and causative genes, mostly encoding lysosomal proteins (Ramachandran et al. 2009). Some clinical variants also feature substantial pathology outside the CNS, such as action myoclonus-renal failure (AMRF; OMIM 254900) syndrome (Badhwar et al. 2004). A similar disorder, deemed SeSAME syndrome (seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance; OMIM 612780), is caused by mutations in the potassium channel *KCNJ10* (Bockenhauer et al. 2009, Scholl et al. 2009). Epilepsy in SeSAME syndrome is less severe, does not progress, and is not accompanied by neurodegeneration, so it does not qualify as a PME subtype. We highlight it here to emphasize a somewhat unusual case in which ion channel mutations cause dramatic pleiotropy in diverse organ systems.

Finally, primary episodic sleep disorders, a few of which are Mendelian, are reviewed elsewhere (Sehgal & Mignot 2011, Zhang et al. 2011). Mendelian ophthalmic disorders are extraordinarily diverse and have been very well characterized; however, they are usually progressive rather than episodic, as reviewed by Sheffield & Stone (2011).

BEYOND THE CHANNELOPATHY PARADIGM

We have highlighted the immense progress made in characterizing the phenotypes, genetics, and pathophysiology of episodic neurologic disorders. In our view, four main objectives should be the focus of future work.

The first two objectives are broadly applicable to human genetics. First, we should identify all Mendelian phenotypes and disease genes. This goal is realistic given the advent of inexpensive, high-throughput sequencing (Gonzaga-Jauregui et al. 2012). Many sporadic or seemingly idiopathic cases of severe, stereotyped disorders are likely the result of mutations that are remarkably straightforward to detect via exome sequencing (Choi et al. 2009, Bamshad et al. 2011). On the other hand, many of the disorders described above were characterized in large families with highly significant linkage; yet, cloning of the disease

genes at linked loci remained elusive for years, often because of the sheer number of candidate genes within the critical regions. This problem is now easily circumvented by high-throughput sequencing (Lee et al. 2012b, Russell et al. 2012).

However, there will be challenges. Foremost among them is evaluating whether a rare variant is truly causative. Numerous "disease genes" have been assigned on the basis of a single affected patient carrying a variant (Holland et al. 2008, Veeramah et al. 2012). Although these data certainly represent grounds for functional investigation, the gold standard should continue to be allelic heterogeneity. In fact, every human carries hundreds of rare, novel variants (Tennessen et al. 2012), so even using the identification of two rare variants in the same gene from a large collection of patients to claim causality may be unwarranted (O'Roak et al. 2012, Sanders et al. 2012). Instead, large families with the statistical power to detect linkage will remain valuable because linkage constrains the pool of rare variants that must be considered for causality. Even when the evidence includes a highly penetrant phenotype, large families, linkage, and allelic heterogeneity, some mutations are not sufficient to cause disease in unrelated patients (Klassen et al. 2011). The sobering reality is that determining the causal relationships between mutations and Mendelian diseases may take many years to unravel, particularly for genes of unknown function.

The second main objective is to identify genetic risk factors for related, genetically complex disorders (**Figure 1**). It was hoped that genome-wide association studies (GWAS) would provide an unbiased method for doing so; however, except for a few remarkable early findings (Hageman et al. 2005, Duerr et al. 2006), despite extensive patient collections the calculated effect sizes have been very small. Consequently, the overwhelming majority of GWAS associations have been insufficient to induce researchers to pursue functional biological investigation or, when investigated, are found to have no functional effect. It remains an open question whether high-throughput sequencing will prove fruitful where GWAS was not, although we remain hopeful. In our view, one possibility merits serious consideration: the null hypothesis. Perhaps the "missing heritability" (Eichler et al. 2010) is not missing after all but has instead been grossly overestimated by inherently biased measures of heritability. Only time will tell. Given this history, we are puzzled as to why more resources are not directed toward the tried-and-true approach of applying our comprehension of rare Mendelian disorders to understand pathophysiology of related complex diseases, as exemplified by Brown & Goldstein's (2009) elucidation of familial hypercholesterolemia, which sparked development of the blockbuster statin drugs. This approach has seemingly fallen out of favor. In this regard, episodic neurologic disorders are particularly tantalizing because Mendelian forms exhibit very specific symptoms and symptom clusters (e.g., congenital insensitivity to pain) that may allow for pharmacological treatments with minimal side effects.

A third goal is to understand why these disorders are episodic in nature. Typically, patients appear to be normal between attacks and yet suffer extreme dysfunction during an attack. Furthermore, attacks are triggered by precipitants that are routinely encountered by affected patients and unaffected patients alike, and even in affected patients, these precipitants do not always trigger an attack. The link between the precipitant and an attack is clear for some disorders, such as the primary skeletal muscle disorders in which altered extracellular ion concentrations affect myocyte excitability. Another well-characterized example is PED, in which exercise depletes blood glucose to cause CNS hypoglycemia and hence dyskinesia. However, other triggers remain baffling. For example, strong emotion is a common trigger, but how do psychological factors trigger neurological dysfunction? No one knows.

Finally, the fourth objective is to expand on the channelopathy paradigm (**Figure 3**). Although more mutations in ion channels will likely be found, it has become evident that many

Allelic heterogeneity: distinct mutations in the same gene cause identical/similar phenotypes; the gold standard of establishing causality in genetics

Genome-wide association study (GWAS): method using sets of cases and controls in which polymorphisms across the genome are tested for statistical association with disease

genes that do not encode channels can be mutated to cause episodic disorders. For some, the effect of gene mutation is easily tied to changes in excitability, such as when the genes encode proteins essential for ion channel trafficking, stability, or function (**Figure 2*f***). However, as we have repeatedly noted, for many genes the link to cellular excitability remains poorly understood. We propose that rather than disease genes affecting excitability in a cell-intrinsic way (e.g., ion channel expression or localization on the cell membrane), a compelling area for future study is the role of disease genes in modulating excitability at the synaptic level. This concept of a synaptopathy is certainly not new because the congenital myasthenic syndromes have long been known to be disorders of synaptic regulation (**Figure 3*a***). However, the concept of synaptopathy has, to date, been restricted to the NMJ (**Figure 3*a***), and it seems probable that higher synapses may be dysfunctional in episodic disorders of the CNS. We cannot help but speculate that the lessons learned by investigating synaptic function in Mendelian episodic disorders may apply to various complex disorders such as autism that are known synaptopathies (Grabrucker et al. 2011).

Likewise, disordered regulation of excitability at the circuit level (circuitopathy) likely contributes to episodic disorders of the CNS (**Figure 3*b***). For example, *SCN1A* mutations in GEFS+, in which sodium channel dysfunction results in aberrant interneurons, can be conceptualized as a channelopathy or a circuitopathy because ion channels and also neuronal circuits are defective. Many other types of aberrant circuits are possible, and we anticipate that some nonchannel genes, especially those implicated in brain development and/or mutated in Mendelian epilepsy syndromes, cause disease by altering circuit wiring.

In summary, the past two decades have borne witness to the description of many novel episodic neurologic phenotypes, the identification of causative mutations, and the elucidation of underlying pathophysiology. On all three fronts—syndromes, genes, and mechanisms—much work remains. With the widespread application of high-throughput genomic technology, we expect progress to continue apace. In time, we expect that these fronts will be conquered and the spoils will redound in the form of novel treatments for these tragic diseases. We owe as much to our patients.

SUMMARY POINTS

1. Episodic neurologic disorders cause symptoms in discrete attacks. Between attacks, patients appear to be normal.
2. Attacks are often triggered by commonplace stimuli such as hunger or emotional stress. For most disorders, we do not understand how these stimuli trigger attacks.
3. Episodic neurologic disorders can be caused by a mutation in a single gene (Mendelian). Alternatively, they may be genetically complex: influenced primarily by environmental factors, with some polygenic genetic contribution. The four common complex disorders are transient ischemic attack, syncope, epilepsy, and migraine.
4. Many rare complex episodic neurologic disorders exist. For example, autoimmune episodic disorders are caused mostly by autoantibodies against ion channels or channel-related proteins.
5. Many Mendelian episodic neurologic disorders exist, each of which is rare. Most affect a single anatomical location: skeletal muscle, cardiac muscle, neuromuscular junction, peripheral nerve, or CNS.

6. Most Mendelian episodic disorder genes encode ion channels. Mutant channels are dysfunctional, and ensuing alterations in membrane excitability cause disease.
7. Investigators have recently identified many causative genes that do not encode ion channels. Some alter expression, localization, or function of channels. However, for many others we do not know yet how the mutant gene leads to changes in excitability.
8. Recent progress indicates that episodic neurologic disorders may also be caused by dysfunction at the synaptic and neuronal circuit levels, suggesting an expansion of the channelopathy paradigm.

FUTURE ISSUES

1. Characterize all Mendelian phenotypes, and for each disorder, identify all causative genes.
2. Identify genetic risk factors for related, genetically complex disorders.
3. Investigate why these disorders are episodic in nature.
4. Expand on the channelopathy paradigm: Investigate dysfunction at the level of the synapse and neuronal circuit in episodic disorders of the CNS.

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