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Abstract

Ion channelopathies are caused by malfunction or altered regulation of ion channel proteins due to hereditary or acquired protein changes. In neurology, main phenotypes include certain forms of epilepsy, ataxia, migraine, neuropathic pain, myotonia, and muscle weakness including myasthenia and periodic paralyses. The total prevalence of monogenic channelopathies in neurology is about 35:100,000. Susceptibility-related mutations further increase the relevance of channel genes in medicine considerably. As many disease mechanisms have been elucidated by functional characterization on the molecular level, the channelopathies are regarded as model disorders for pathogenesis and treatment of non-monogenic forms of epilepsy and migraine. As more than 35% of marketed drugs target ion channels, there is a high chance to identify compounds that counteract the effects of the mutations.

Keywords (separated by '-') Epilepsy - Ataxia - Migraine - Pain - Neuromyotonia - Myasthenia - Myotonia - Periodic-paralysis

Chapter 18
Hereditary Channelopathies in Neurology

Karin Jurkat-Rott, Holger Lerche, Yvonne Weber, and Frank Lehmann-Horn

Abstract Ion channelopathies are caused by malfunction or altered regulation of ion channel proteins due to hereditary or acquired protein changes. In neurology, main phenotypes include certain forms of epilepsy, ataxia, migraine, neuropathic pain, myotonia, and muscle weakness including myasthenia and periodic paralyses. The total prevalence of monogenic channelopathies in neurology is about 35:100,000. Susceptibility-related mutations further increase the relevance of channel genes in medicine considerably. As many disease mechanisms have been elucidated by functional characterization on the molecular level, the channelopathies are regarded as model disorders for pathogenesis and treatment of non-monogenic forms of epilepsy and migraine. As more than 35% of marketed drugs target ion channels, there is a high chance to identify compounds that counteract the effects of the mutations.

Keywords Epilepsy · Ataxia · Migraine · Pain · Neuromyotonia · Myasthenia · Myotonia · Periodic-paralysis

18.1 Introduction

The implication that ion channels may play a causal role in disease pathogenesis came first from the observation of abnormal ion conductances from muscle biopsied from myotonic goats [9] and patients with paramyotonia congenital [55] and periodic paralysis [56]. In the 1990s the term ion channelopathies was coined and defined for disorders that are caused by malfunction or altered regulation of ion channel proteins. Therefore, they may be either hereditary (for example by mutations in ion channel genes) or acquired (for example by auto antibodies). In neurology, channels of both the nervous system and skeletal muscle are involved. The channel disturbances result in changes of excitability which one would expect

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to be present constantly in EEG or EMG. However, this is not the case. Clinical symptoms mainly appear episodically, provoked by an out-of-the-normal situation, so-called trigger. Compensatory mechanisms often allow spontaneous and complete remission following an episode. These mechanisms show an age-dependency which causes symptoms to be present mainly in a specific phase of life (only childhood or only adulthood with onset from puberty). In addition to the episodes, progressive manifestations with neuronal or muscular degeneration are present in ∼50% of patients. Main phenotypes include epilepsy, episodic ataxia, migraine, neuropathic pain, myotonias, and muscle weakness including myasthenia and periodic paralyses.

The prevalence of a hereditary neurological channelopathy is only ∼0.1–4 in 100,000 individuals of the general population each. However, because there are so many of them, the total prevalence of channelopathies in neurology is 35 of 100,000. Based on the mechanisms of genetics and pathogenesis of these rare disorders, we can expect that ion channel susceptibilities are involved in the frequently occurring, not strictly hereditary variants of epilepsy, migraine, pain, and muscle weakness. Therefore, at least 5% of the population may either carry a disease-causing or a susceptibility-related mutation in an ion channel of muscle or nerve. Based on this observation, channelopathies are regarded as model disorders for pathogenetic mechanisms [43, 54]. Conveniently, more than 35% of marketed drugs target ion channels, so that channelopathies also provide model disorders for therapeutic strategies.

18.2 Hereditary Channelopathies of the Central and Peripheral Nervous System

18.2.1 Epilepsy

Epilepsy is one of the most common neurological disorders affecting ∼3% of the world's population during lifetime [36]. The disease is characterized by recurring epileptic seizures resulting from synchronized electrical discharges of neurons within the central nervous system. With regard to the complicated nature and the many different functions of the brain, there are a number of clinically differentiable seizure types. The symptoms of a seizure depend on age, the underlying cause and the brain region involved. Accordingly, epileptic semiology can include only mild sensations of the patient himself that are not visible for other individuals (such as seen with an epigastric aura), but also transient black outs (such as known for absence or complex-partial seizures), or severe generalized tonic-clonic convulsions. The most important features used to classify epileptic seizures and epileptic syndromes are (i) the origin of the seizure/epilepsy which can be focal or generalized and (ii) the underlying cause which can be symptomatic (for example due to cortical malformations, brain tumors or stroke) or idiopathic, i.e. genetic. In the following, idiopathic epilepsy syndromes are described for which ion channel mutations have been identified as a genetic cause.

18.2.1.1 Idiopathic Partial Epilepsy

Autosomal dominant nocturnal frontal lobe epilepsy includes frequent brief seizures occurring in childhood with hyperkinetic or tonic manifestations, typically in clusters at night. Ictal video-electroencephalographic studies have revealed partial seizures originating from the frontal lobe but also in parts of the insula, suggesting a defect of a broader network. The penetrance of the disease is estimated at approximately 70–80%. A mutation was identified in the gene *CHRNA4* encoding the α4-subunit of a neuronal nicotinic acetylcholine receptor as the first ion channel mutation found in an inherited form of epilepsy [89]. Altogether, five mutations in *CHRNA4* and two in *CHRNB2*, which encodes the β2-subunit of neuronal nicotinic acetylcholine receptor, have been reported [88]. Recently, another mutation in *CHRNA2*, encoding the neuronal nicotinic acetylcholine receptor α2-subunit, was detected. ~~All these~~ mutations reside in the pore-forming M2 transmembrane segments. Different effects on gating of heteromeric α4β2 channels leading either to a gain- or a loss-of-function were reported when most of the known mutations were functionally expressed in *Xenopus* oocytes or human embryonic kidney cells. An increased acetylcholine sensitivity is thought to be the main common gating defect of the mutations [60, 88].

In one patient with cryptogenic partial epilepsy that was classified as pharmacoresistant because of non-response to carbamazepine or oxcarbazepine, a Nav1.3 mutation, K354Q, was identified that was not present in 295 neurological normal controls [39]. Functional analysis of this mutation demonstrated an increase in persistent current, a gain-of-function. The phenotype was purely focal with no structural brain abnormality to account for the symptoms. The role of Nav1.3 for epilepsy is yet to be established.

18.2.1.2 Idiopathic Secondarily Generalized Epilepsy

Benign familial neonatal seizures (BFNS) are dominantly inherited with a penetrance of 85%. The seizures manifest within the first weeks of life and typically disappear spontaneously after weeks to months. Seizures may have a partial onset, often with hemi-tonic or -clonic symptoms or with apnoe, or may appear primarily generalized. Accordingly, ictal EEGs showed focal and generalized discharges. Interictal ~~EEG~~ are mostly normal. The risk of seizures recurring in adulthood is ∼15%. Although psychomotor development is usually normal, an increasing number of cases with learning disability have recently been described [6]. Mutations have been identified in Kv7.2 and Kv7.3 potassium channels which interact with each other and constitute the so-called "M-current", an important current in the regulation of the firing rate of neurons. Co-expression of heteromeric wild-type and mutant Kv7.2/Kv7.3 channels usually revealed a reduction in the resulting potassium current of ∼20–30%, which is apparently sufficient to cause BFNS [81]. Even subtle changes in channel gating restricted to subthreshold voltages of an action potential are sufficient to cause BFNS, proving the physiological importance of this voltage range for the action of M-channels in a human disease model [62, 108].

Clinically similar epilepsy syndromes that are genetically different from BFNS are BFNIS and BFIS, benign familial (neonatal-)infantile seizures. The phenotype also displays partial epileptic seizures with or without secondary generalization, but they occur between the age of 3 and 12 months (BFIS) or more variable between the neonatal and infantile periode (BFNIS). Ictal EEGs can show focal epileptic discharges in different brain regions. BFIS can be associated with other neurological disorders, such as paroxysmal dyskinesia or migraine. Mutations in the *SCN2A* gene encoding one of the α-subunits of voltage-gated sodium channels expressed in the mammalian brain have been identified in BFNIS [38]. Functional investigations revealed predominant small gain-of-function effects or reduced channel activity predicting increased neuronal excitability. The age dependence of this syndrome could be explained by a transient expression of the respective Nav1.2 channels in axon initial segments of principal neurons in cortex and hippocampus during development, and replacement later on by Nav1.6 at these sites. A few *SCN2A* mutations with severe effects such as non-functional, truncated proteins have been described in patients with intractable epilepsy and mental retardation.

18.2.1.3 Idiopathic Primarily Generalized Epilepsy with Febrile Seizures

Generalized epilepsy with febrile seizures plus (GEFS+) is a childhood-onset syndrome featuring febrile convulsions and a variety of afebrile epileptic seizure types within the same pedigree. The penetrance is ~60%. Two-thirds of affected individuals were diagnosed as having febrile seizures (FS) which may be combined with either FS persisting after the sixth year of life or with afebrile generalized tonic–clonic seizures (FS+). Additional seizure types such as absences, atonic, or myoclonic–astatic, or focal seizures may occur. Vaccination and its associated fever may trigger the first episode of a hitherto unsymptomatic GEFS+ [5]. More than 20 different mutations were subsequently identified in GEFS+ patients, accounting for 10% of cases. GEFS+ is caused by missense mutations in α and β1 subunits of the neuronal sodium channel, encoded by *SCN1A* and *SCN1B* respectively. Mutations may increase persistent sodium current but loss-of-function mutations have been observed as well [2]. Reduced channel function is considered to be more significant than gain-of-function changes [76] ~~and lead~~ to an overall loss-of-function phenotype at the neuronal level. Therefore, sodium channel blockers exacerbate symptoms in many GEFS+ patients.

Next to *SCN1A*, also GEFS+ is associated with mutations in the homologous sodium channel α subunit genes encoded by *SCN2A* in a single family [94] and by *SCN9A* in potentially up to 5% of the patients with febrile seizures [84]. The latter show a high penetrance of 95%. Functional expression has not yet been performed. Finally, several mutations in genes coding for different GABA-A receptor subunits, *GABRG2* and *GABRD*, have been identified. Dominant *GABRG2* mutations produce decrease of GABA-activated chloride currents thus reducing inhibitory currents which results in hyperexcitability. The decrease in inhibition has been observed in the cortex, as shown in a knock-in model carrying one of the human mutations [72].

Severe myoclonic epilepsy of infancy (SMEI) or Dravet syndrome is characterized by ~~hemi- or generalized~~ clonic or tonic–clonic seizures in the first year of life that are often prolonged and associated with fever. During the course of the disease, patients develop afebrile generalized myoclonic, absence, or tonic–clonic seizures, but simple and complex partial seizures also occur. Cognitive deterioration appears in early childhood. In contrast to GEFS+, the syndrome is resistant to pharmacotherapy in most cases, but stiripentol seems to have a significant positive effect in patients with SMEI. Cranial magnetic resonance imaging in patients with SMEI found focal and generalized internal and external atrophy, which is discussed as a result of the brain encephalopathy; the rate of hippocampal sclerosis is not increased. Because patients with SMEI sometimes have a family history of febrile or afebrile seizures, and in some families GEFS+ and SMEI overlap, SMEI may be regarded as the most severe phenotype of the GEFS+ spectrum [85].

Similar to SMEI, intractable childhood epilepsy presents with generalized tonic–clonic seizures (ICEGTC) [31]. Onset and clinical course including learning disability are as in SMEI, except that myoclonic seizures do not occur. Families with some instances of ICEGTC in other family members affected by GEFS+ have been described. Therefore, we may conclude that the GEFS+ spectrum extends from simple febrile seizures to a variety of severe epilepsy syndromes of childhood such as intractable ICEGTC and SMEI, as also confirmed by genetic results described below [60].

For SMEI and ICEGTC, mutations in *SCN1A* encoding Nav1.1 have been identified [13]. Together with GEFS+, more than 100 *SCN1A* mutations have been identified, accounting for 70% of cases [64]. Mutation hotspots, such as sites of CpG deamination, account for 25% of de-novo mutations [48]. Genetic screening for *SCN1A* is standard for diagnosing early-onset childhood seizures. Most SMEI mutations cause loss of function due to nonsense mutations demonstrating that haploinsufficiency of *SCN1A* is pathogenic.

18.2.1.4 Idiopathic Primarily Generalized Epilepsy Without Febrile Seizures

Genetic mutations were also identified in families with classical idiopathic generalized epilepsies, namely childhood or juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic-clonic seizures on awakening (EGTCA). Absence seizures in ECA manifest typically around the sixth year of life are of short duration, ~10 s, and typically occur in clusters of up to 100 seizures a day. In adolescence, generalized tonic–clonic seizures can occur. Myoclonic jerks are the clinical hallmark of EJM, particularly of the upper extremities, which appear without loss of consciousness. They can be clinically subtle and escape clinical recognition. The disease also manifests during puberty, with seizures typically developing after awakening and being provoked by sleep deprivation. Generalized tonic–clonic seizures occur in about 75% of patients. The idiopathic generalized epilepsies may overlap within individuals and are typically associated with generalized spike-wave or poly-spike-wave discharges on EEG. Brain imaging is unremarkable.

For EJM, a mutation in *GABRA1*, the gene encoding the α1-subunit of the GABA-A receptor, was identified in a family with EJM [15]. The mutation leads to loss-of-function of the GABA-A receptor i.e. a decrease of inhibitory chloride currents and hyperexcitability [15]. Larger studies suggest that GABA-A receptor mutations are extremely rare [20]. Two EJM mutations have been described in the calcium channel β subunit gene *CACNB4*, but they were not examined functionally and not much can be deduced about prevelance in the small population studied [26]. Recently, a few EJM mutations were found in the gene *CLCN2* encoding a neuronal voltage-gated chloride channel [34, 78]. This channel may play a role in neuronal inhibition. Owing to its specific gating properties, it constitutes a chloride extrusion pathway keeping the intracellular chloride concentration at low levels, which is important for the inhibitory action of the GABA-A receptor. Because the segregation with the phenotype was incomplete, the role of *CLCN2* as susceptibility gene for EJM is still a matter of debate [66].

For ECA, a mutation in the γ2 subunit of the GABA-A receptor encoded by *GABRG2* has been described [102] which decreased GABA-activated chloride currents. This reduction of inhibitory currents results in hyperexcitability. Due to trafficking changes and endocytosis increase upon temperature elevation in-vitro, and occasional reports of FS in-vivo, the differentiation to GEFS+ is rather difficult (and in agreement with this statement, the features of this family resemble GEFS+). Three ECA mutations were reported in the β3 subunit of the GABA-A receptor encoded by *GABRB3* that showed reduced penetrance and hyperglycosylation-induced reduction of inhibitory chloride current [96]. For completeness of the expression data: a *GABRA1* mutation associated with absence epilepsy revealed a loss of trafficking and a loss of channel current. Functional co-expression of the wild-type suggested that haploinsufficieny is the pathogenetic mechanism [61].

Finally, variants in ECA and other subtypes have been described in *CACNA1H* encoding a neuronal voltage-gated T-type calcium channel. They were suggestive of gain-of-function by several different alterations in channel gating which can explain a neuronal hyperexcitability [72].

18.2.2 Ataxia

Episodic ataxias (EA) are characterized by episodic spells of cerebellar ataxia that can be triggered by stress, startle, or heavy exertion such as exercise. Symptoms can first appear in infancy. There is a phenotypic overlap with migraine, spinocerebellar ataxia, and epilepsy.

EA1 is associated with myokymia (neuromyotonia) i.e. continuous muscle movement and usually presents with paroxysmal truncal and limb ataxia and dysarthria lasting seconds to minutes. Nystagmus is absent. Typically, episodes are triggered by strong emotion or exercise and last seconds to minutes. The syndrome usually presents in childhood or adolescence and often improves spontaneously in the third decade. About 10% of patients also have epilepsy. Inheritance is autosomal dominant. Approximately 20 mutations have been described, almost all of which are missense mutations of the *KCNA1* gene that encodes the voltage-gated potassium

channel Kv1.1 [7]. Most involve highly conserved amino acids such as those in the transmembrane segments. If the functional changes mainly show a slowing of the time course of activation, the phenotype may be primarily neuromyotonia without ataxia, if the threshold of activation is shifted or the current reduced, the ataxia is more prominent. Reduced penetrance can occur.

EA2 is caused by mutations of *CACNA1A*, the gene encoding the neuronal voltage-gated P/Q-type calcium channel α1 subunit, Cav2.1 [67]. The ataxia last longer and mild interictal nystagmus and ataxia are present. Vertigo, nausea and vomiting precede the episodes in over half of the patients. Over 50% have migraine as well. For diagnosis, interictal gaze-evoked nystagmus with features typical of rebound nystagmus may be elicited. Spontaneous vertical nystagmus, particularly downbeat nystagmus, is seen in ∼30% of cases. Penetrance is 80–90%. Acetazolamide and 4-aminopyridine are effective in controlling or reducing the frequency and severity of attacks. More than 50 Cav2.1 EA2 mutations have been described of which the majority represents nonsense mutations leading to premature truncations of the protein with loss of function. The prevalence has been estimated at lower than 1:100,000 population.

EA5 has been described in a single family with a mutation in the calcium channel ß4 subunit encoded by the *CACNB4* gene [26]. This is a subunit that interacts with Cav2.1. The family had clinical features similar to EA2, but mutations in *CACNA1A* were excluded. However, the same mutation was found in a German family with generalized epilepsy without ataxia, so that the associated phenotype must be regarded with care. Functional studies showed only minimal changes in calcium channel function.

Spinocerebellar ataxias (SCA) are characterized by progressive degeneration of cerebellum, brainstem and spinal cord. Of these, SCA6 is a channelopathy that is caused by a CAG repeat expansion in the calcium channel *CACNA1A* gene [110]. It makes up 6% (in Japan) to 30% (in Australia) of SCA cases [80, 91, 103]. In most families, patients show permanent dysarthria, oculomotor deficits, and gait ataxia although there may be a phenotypic overlap with EA2. Depending on the splice variant which is translated into proteins, the mutation elongates a poly-glutamine stretch in the C-term which is thought to form intracellular aggregations. The longer the repeat expansion the earlier is the disease onset. Patients with longer expansions present with disease symptoms at an earlier age.

In a 9-year-old boy with mental retardation, pancerebellar atrophy, and ataxia, a heterozygous nonsense mutation in exon 4 of the *SCN8A* gene was identified [98]. It introduced a stop codon into the pore loop of domain 4 resulting in a prematurely truncated loss-of-function channel. Three additional heterozygous family members exhibited milder cognitive and behavioral deficits, but not the full phenotype. For this reason, *SCN8A* was considered a susceptibility gene for the phenotype.

18.2.3 Migraine

Migraine with and without aura has a 1-year prevalence of 12–15% in North America and Western Europe. Migraine occurs in some 6% of children, and

becomes more common in females after puberty, reaching a peak at age 41 when three times more females than males have migraine [83]. The current pathogenesis models of migraine with aura suggests cortical spreading depression which consists of an initial brief spike of increased neuronal activity followed by long-lasting suppression of excitability spreading across the cortex at 1–3 mm/min. The depression wave is associated with long-lasting depolarization and changes in ion concentration gradients i.e. elevation of extracellular potassium and intracellular sodium. Its progress correlates to the succession of symptoms during the aura initiating the migraine attacks.

Familial hemiplegic migraine (FHM) is a monogenic subtype that enables to study the pathogenesis of the cortical depression wave. FHM presents with characteristic unilateral migrainous headaches accompanied by nausea, phono- and photophobia. Episodes are typically precipitated by an aura with symptoms of both hyper- and hypo-excitability such as aphasia, dysarthria, vertigo, homonymous hemianopsia, cheiro-oral paresthesias, and some degree of mainly unilateral paresis. FHM prevalence has been estimated in Denmark. It is approximately 0.005% with a male to female sex ratio of 1:3. Of the various FHM forms, up to 50% of cases are FHM1 and 20–30% FHM2 [45].

FHM1 includes sporadic hemiplegic migraine with progressive cerebellar ataxia. The aura may be prolonged and confusion and loss of consciousness may occur. In the interval, some families additionally present with epilepsy, retinal degeneration, hypakusis, and persistent cerebellar dysfunction with Purkinje cell atrophy. Over 20 missense mutations have been described, that are primarily located in the pore region or transmembrane segments and result in gain of Cav2.1 function [67].

FHM2 is an autosomal dominant disease, caused by mutations in the *ATP1A2* gene on chromosome 1q21–23 encoding the alpha2 subunit of the astrocytic Na^+/K^+-ATPase 3 [18, 87]. Well over 20 missense mutations have been detected that all lead to loss of ATPase function by blocking ion transport pathways or the Mg-ATP binding region. As FHM2 is not a channelopathy it has not been included in Table 18.1.

FHM3 is caused by mutations in the *SCN1A* gene on chromosome 2q24 encoding the neuronal voltage-gated sodium channel alpha1 subunit, Nav1.1. As just a few families with a Nav1.1 mutation are known, FHM3 is not yet distinct clinically [21]. Functional expression of the three known mutations demonstrated reduced channel activity in two cases and gain-of-function features in the third case [11, 46]. The presence of seizures in addition to migraine in the third family demonstrates the potentially close relationship between these migraine and epilepsy.

18.2.4 Neuropathic Pain

In the peripheral nervous system, Nav1.7 channels are expressed in sympathetic neurons, sensory neurons, and their axons, whereas Nav1.8 and Nav1.9 are exclusively expressed in sensory neurons, including peripheral terminals, axons, and cell bodies. Recent studies have linked Nav1.7 to three pain disorders: inherited

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Table 18.1 Overview of hereditary channelopathies in Neurology. ~~The diseases or the susceptibilities are listed in column 1, the genes and their chromosomal locations in columns 2 and 3, and the ion channels and their specific protein names in columns 4 and 5. The inheritance is given in column 6, and prevalence and population remarks in the two last columns~~

Disease	Acronym	Gene	Locus	Channel	Protein	Trait	Prevalence
Central and peripheral nervous system							
Epilepsy							
Nocturnal frontal lobe epilepsy EFNL	EFNL1 EFNL3 EFNL4	*CHRNA4* *CHRNB2* *CHRNA2*	20q13.3 1q21 8p21	Cation channel	nAChRα4 nAChRβ2 nAChRα2	D	>5 families <5 families <5 families
Cryptogenic pediatric partial epilepsy		*SCN3A*	2q24	Sodium channel	Nav1.3		1 patient
Benign familial neonatal seizures BFNS	BFNS1 BFNS2	*KCNQ2* *KCNQ3*	20q13.3 8q24.22–24.3	Potassium channel	Kv7.2 Kv7.3	D	
BFN/Infantile seizures	BFNIS	*SCN2A*	2q24.3	Sodium channel	Nav1.2	D	
Generalized epilepsy with febrile seizures plus GEFS+	GEFS1 GEFS2 GEFS7 GEFS4 GEFS5	*SCN1B* *SCN1A* *SCN9A* *GABRG2* *GABRD*	19q13.1 2q24 2q24 5q31.1–33.1 1p36.3	Sodium channel GABAAγ2 GABAAδ	Navβ1 Nav1.1 Nav1.7 D	D	
Severe myoclonic epilepsy of infancy	SMEI	*SCN1A*	2q24	Sodium channel	Nav1.1	D	
Childhood absence epilepsy	ECA2 ECA4 ECA5	*GABRG2G* *ABRA1* *GABRB3*	5q31.1–33.1 5q34–35 15q11.2–q12	Chloride channel	GABAAγ2 GABAAα1 GABAAβ3	D	
Susceptibility to ECA	ECA6	*CACNA1H*	16p13.3	Calcium channel	Cav3.2	D	
Juvenile myoclonus epilepsy	EJM5	*GABRA1*	5q34–35	Chloride channel	GABA-A	D	
	EJM6	*CACNB4*	2q22–23	Calcium channel	Cavβ4	D	

Table 18.1 (continued)

Disease	Acronym	Gene	Locus	Channel	Protein	Trait	Prevalence
Central and peripheral nervous system							
Epilepsy							
Susceptibility to EJM	EJM8	*CLCN2*	3q26	Chloride channel	ClC2	D	
Ataxia and migraine							
Spinocerebellar ataxia	SCA6	*CACNA1A*	19p13.1	Calcium channel	Cav2.1	D	
	SCA13	*KCNC3*	19q13.3–4	Potassium channel	Kv3.3		
Episodic ataxia	EA1	*KCNA1*	12p13	Potassium channel	Kv1.1	D	10
Susceptibility to EA	EA2	*CACNA1A*	19p13.1	Calcium channel	Cav2.1		mutations
	EA5	*CACNB4*	2q22–23	Calcium channel	Cavβ4		<1:100,000
							1 patient
Familial hemiplegic migraine	FHM1	*CACNA1A*	19p13.1	Calcium channel	Cav2.1	D	1 family
	FHM3	*SCNA1*	2q24	Sodium channel	Nav1.1		
Susceptibility to ataxia, mental retard.		*SCN8A*	12q13	Sodium channel	Nav1.6	D	1 patient
Neuropathic pain and others							
Inherited erythromelalgia	IEM	*SCN9A*	2q24	Sodium channel	Nav1.7	D	
Paroxysmal extreme pain disorder	PEPD						
Congenital insensitivity to pain	CIP	R	~30 families				
Hyperekplexia	STHE	*GLRA1*	5q31.3	Chloride channel	GlyRα1	D/R	
		GLRB	4q31.3		GlyRβ	R	
Neuromyotonia isolated myokymia	MK1	*KCNQ2*	20q13.3	Potassium channel	Kv7.2	D	3 mutations
		KCNA1	12p13		Kv1.1		3 mutations
Epilepsy,ataxia,deafness,tubulopathy	EAST	*KCNJ10*	1q22–23	Potassium channel	Kir4.1	R	

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Table 18.1 (continued)

Disease	Acronym	Gene	Locus	Channel	Protein	Trait	Prevalence
Central and peripheral nervous system							
Epilepsy							
Paroxysmal dyskinesia	GEPD	*KCNMA1*	10q22.3	Potassium channel	KCa1.1	D	
Dominant deafness		*KCNQ4*	1p34	Potassium channel	Kv7.4	D	
Deafness Jervell and Lange-Nielsen		*KCNQ1*	11p15.5	Potassium channel	Kv7.1	R	
Congenital stationary night blindness		*CACNA1F*	Xp11.23	Calcium channel	Cav1.4	R	
Retinitis pigmentosa		*CNCG1*	4p12–ce	Cation channel	CNCG1	R	
Motor endplate and skeletal muscle							
Congenital myasthenic syndromes	CMS	*CHRNA1* *CHRNB1* *CHRND* *CHRNE*	2q24–32 17p12–11 2q33–34 17p13.2	Cation channel	nAChRα1 nAChRβ1 nAChRδ1 nAChRε1	D/R	
		SCN4A	17q23.1–25.3	Sodium channel	Nav1.4	D	1 patient
Myotonia congenita	MC	*CLCN1*	7q32-qter	Chloride channel	ClC1	D R	1:400,000 1:25,000
	SCM	*SCN4A*	17q23.1–25.3	Sodium channel	Nav1.4	D	1:400,000
Paramyotonia congenita	PMC	*SCN4A*	17q23.1–25.3	Sodium channel	Nav1.4	D	1:200,000
Hyperkalemic periodic paralysis	HyperPP	*SCN4A*	17q23.1–25.3	Sodium channel	Nav1.4	D	1:200,000
Hypokalemic periodic paralysis	HypoPP1 HypoPP2	*CACNA1S* *SCN4A*	1q31–32 17q23.1–25.3	Calcium channel Sodium channel	Cav1.1 Nav1.4	D	1:100,000 1:500,000
Andersen-Tawil syndrome	ATS	*KCNJ2*	17q24.2	Potassium channel	Kir2.1	D	1:1,000,000

Table 18.1 (continued)

Disease	Acronym	Gene	Locus	Channel	Protein	Trait	Prevalence
Central and peripheral nervous system							
Epilepsy							
Susceptibility to thyrotoxic PP	TPP	*KCNJ18*	17p11.1	Potassium channel	Kir2.6	D	0.07%Asian
Central core disease Multiminicore disease	CCD MmD	*RYR1*	19q13.1	Calcium channel	RyR1	D R	
Malignant hyperthermia susceptibility	MHS	*RYR1*	19q13.1	Calcium channel	RyR1	D	1:50,000

erythromelalgia (IEM), paroxysmal extreme pain disorder (PEPD), and Nav1.7-associated congenital insensitivity to pain (CIP) [19, 27, 33]. Dominantly inherited gain-of-function mutations in *SCN9A*, the gene encoding Nav1.7, cause the painful neuropathy IEM, characterized by episodes of burning pain, erythema, and mild swelling in the hands and feet, which are triggered by mild warmth or exercise. Symptoms of IEM can start as early as at age of 1 year or in adulthood, and both types have been described in families and in sporadic cases. Recently, a familial case from Taiwan has been reported with symptoms first appearing in the feet of affected teenagers and with almost a decade delay in the involvement of hands. Although early- and delayed-onset IEM have been linked to mutations in Nav1.7, the etiology of adult-onset IEM remains a mystery.

A different set of gain-of-function mutations has been identified in Nav1.7 in patients with PEPD, previously referred to as familial rectal pain [28]. Severe pain in PEPD patients along with flushing are induced by bowel movement or probing of the perianal areas and are sometimes accompanied by tonic non-epileptic seizures and cardiac deficits. In contrast, recessively inherited loss-of-function mutations in Nav1.7 have been identified in individuals with complete inability to experience pain coupled with impaired sense of smell [16]. These studies provide complementary and compelling evidence for a central role of this channel in pain signaling.

PEPD mutations in Nav1.7 change amino acids that have been implicated in fast inactivation of sodium channels. The voltage dependence of steady-state fast inactivation of PEPD mutant channels is shifted by 20 mV in a depolarizing direction, and inactivation is incomplete, resulting in a persistent and a socalled resurgent current [40]. Impaired channel fast inactivation and the persistent current produced by the mutant channels would be expected to increase frequency of action potential firing. Indeed, expression of PEPD mutant Nav1.7 channels renders neurons of dorsal root ganglia (DRG) hyperexcitable [19]. The favorable response of the patients to carbamazepine, a use-dependent sodium channel blocker, is consistent with the impaired inactivation of the mutant channels.

Loss-of-function mutations invariably truncate the channel protein, resulting in Nav1.7-related CIP and impaired sense of smell [16]. These mutations do not produce functional Nav1.7 channels when expressed in mammalian expression systems [16]. Patients do not experience pain from normally painful acts, such as puncture wounds, bone fracture, tongue and lip biting, or walking on hot surfaces (including burning coals), but do not suffer from other sensory, motor, or cognitive deficits. Heterozygous parents are asymptomatic, indicating that a null mutation on one allele does not lead to haploinsufficiency.

18.2.5 Hyperekplexia

Hyperekplexia, also known as hereditary startle disease or stiff-baby syndrome, is a rare nonepileptic disorder characterized by excessive startle response to acoustic, visual, or other stimuli [109]. Hypertonia and apneic spells, nocturnal myoclonus,

startle-induced falls and accumulation of injuries occur. It is predominantly an autosomal dominant disease with few autosomal recessive and sporadic cases. It mainly affects Northern European descendants, but has been reported from many other countries as well. Of the various responsible genes, those for the inhibitory glycine receptor (GlyR), a hetero-pentameric, ligand-gated chloride channel, are typically affected. Mutations in *GLRA1* encoding the ligand-binding GlyR alpha1 subunit and less frequently those in *GLRB* coding for the GlyR beta subunit cause the syndrome. GlyRs facilitate the fast-response, inhibitory glycinergic neurotransmission in the brainstem and spinal cord. Certain mutations inhibit the occurence of higher conductance states [53].

Symptoms are present from birth, as infants display muscular rigidity, which increases with handling and disappears during sleep. It may lead to potentially fatal spells of apnea (sudden-infant death). The diagnosis is clinically confirmed by demonstrating an exaggerated head-retraction reflex in tapping the infant's nose-bridge or chin. Muscular hypertonia decreases gradually during the first year of life whereas excessive startling persists throughout life. Even so, affected young children and adults tend to walk stiff-legged, with a mildly wide-based gait, but without signs of spasticity. The head-retraction response continues to be readily elicited. Other clinical features are periodic limb movements in sleep and hypnagogic myoclonus. The hallmark is the excessive startling in response to unexpected stimuli, which results in short-lasting generalized stiffness causing the patient to fall forwards "as stiff as a stick" while fully conscious but unable to protect himself. This may result in serious injuries. Clonazepam is the treatment of choice, which potentiates the inhibitory transmitter GABA. During the first year of life infants need to be fitted with an apnea monitor.

18.2.6 Neuromyotonia

It is heterogeneous in terms of symptoms, signs, severity, pattern, and rate of progression and is also termed peripheral nerve hyperexcitability (PNH). Its association with a variety of disorders adds to the diversity. Motor features of spontaneous and continuous skeletal muscle overactivity usually dominate the clinical presentation and are common to all variants. Muscle twitching (fasciculations and/or clinical myokymia – undulation of the muscle causing rippling of the overlying skin) and painful cramps are the commonest, and in many patients the only, presenting features. In the fully developed syndrome, however there can also be stiffness, pseudomyotonia, pseudotetany (for example, Chvostek's and Trousseau's signs with normal calcium homeostasis), and weakness. All of these features tend to be triggered or worsened by muscle contraction. Muscle overactivity characteristically continues during both sleep and general anesthesia. Muscle hypertrophy, usually affecting the calves, can develop in severe cases. Conversely, distal muscle wasting can be seen, especially in those patients with an associated peripheral neuropathy. Growth retardation can occur in severely affected children.

Two of the three hereditary neuromyotonias are channelopathies whereas the third is caused by a mutations in a peripheral myelin protein (PMP22), also called hereditary motor sensory neuropathy type 1a (HMSN type 1a) or hereditary liability to pressure palsies. The two channelopathies are caused by mutations in voltage-gated potassium channels, Kv1.1 and Kv7.2 [17, 107]. Patients with Kv1.1 mutations show continuous muscle overactivity that can be visible as myokymia or detectable only on EMG as regular bursts of high frequency discharges. Only few families only show myokymia while the majority of patients present with additional ataxic episodes (see above EA1). Recently a family with a Kv1.1-N255D mutation revealed hypomagnesemia as a new phenotypic characteristic [32]. Patients with certain Kv7.2 mutations show muscle twitching affecting the limbs and trunk and myokymic discharges on the EMG whereas the majority of patients with present with Kv7.2 mutations present with benign familiar neonatal seizures (see above BFNS).

For the other neuronal channelopathies such as EAST syndrome (epilepsy, ataxia, deafness, and tubulopathy) and the paroxysmal dyskinesias, as well as the sensory diseases such as sensorineural deafness and blindness (dominant deafness, deafness Jervell and Lange-Nielsen, congenital stationary night blindness, and retinitis pigmentosa), we refer to Table 18.1.

18.3 Hereditary Channelopathies of the Motor Endplate and the Skeletal Muscle

18.3.1 Congenital Myasthenic Syndromes (CMS)

CMS are a heterogeneous group of inherited disorders with defective transmission of neuromuscular excitation resulting in muscle fatigue [25]. Weakness is usually evident at birth or within the first year or two of life, and is characterized by feeding difficulties, ptosis, impaired eye movements, and delayed motor milestones. Strength sometimes improves during adolescence, and does not exhibit a progressive course. Reflexes are usually brisk and muscle wasting does not occur. CMS can lead to congenital arthrogryposis multiplex involving reduced fetal movement and multiple joint contractures in the neonate [8]. Electromyography in CMS patients reveals a characteristic decrement of compound action potential amplitude on repetitive stimulation, and single fibre recordings show an increased variability in the synaptic transmission time ("jitter") and transmission blocks [51].

CMS result from defects in presynaptic, synaptic, and postsynaptic proteins. Only postsynaptic CMS are known to be caused by mutations in ion channels like the nicotinic acetylcholine receptor (nAChR) that conducts monovalent cations [24]. Loss-of-function mutations of AChR subunits lead to compensatory expression of fetal δ subunits yielding AChR complexes which differ functionally from the adult type. Rarely mutations alter the kinetic channel properties. These kinetic mutations

result in the slow- or fast-channel syndromes. The low-affinity, fast channel syndrome is caused by loss-of-function mutations that have similar effects as AChR deficiency but is much rarer. Mutations at different sites lead to fewer and shorter channel activations. In contrast to all above CMS, the slow-channel syndrome presents in childhood, adolescence or adult life with upper limb predominance and contractures, does not respond to anticholinesterase, and is progressive. CMS patients with a slow-channel syndrome show increased synaptic response to ACh with characteristic repetitive discharges in response to a single supramaximal stimulus. The syndrome results from gain-of-function mutations in the ion-conducting pore M2 [22]. The leaky AChR exert an excitotoxic effect and cause endplate myopathy via focal caspase activation [99].

18.3.2 Non-dystrophic Myotonia

Myotonia is an involuntary slowed relaxation after a forceful voluntary muscle contraction which is experienced by the patient as muscle stiffness. Situations requiring rapid motor control may provoke severe generalized stiffness causing the patient fall to the ground without being able to protect themselves, and liable to be injured or rendered unconscious. This has previously led to the misdiagnosis of epilepsy, prompting the use of antiepileptic drugs, particularly sodium channel blockers, which improved the myotonia. After making a forceful fist closure the patients are unable to open the hand immediately. Electrical hyperexcitability of the muscle fiber membrane is the basis of myotonia which is apparent in the form of repetitive action potentials in the EMG. Needle insertions in the resting muscle elicit myotonic bursts, i.e. bursts of action potentials with amplitude and frequency modulation that sound like dive bombers). Curare cannot block this activity. This differentiates the symptom from neuromyotonia, which is caused by spontaneous motor unit activity due to hyperexcitability of the terminal motor nerve branches.

18.3.2.1 Myotonia Congenita (MC), A Chloride Channel Myotonia

The two classical forms of myotonia, i.e. dominant myotonia congenita (or Thomsen myotonia) and recessive myotonia congenita (or Becker myotonia) are caused by mutations in *CLCN1*, the gene that codes for the chloride channel of skeletal muscle, ClC1 [49]. For this reason, they are also referred to as chloride channel myotonias. The muscle stiffness slowly progresses during childhood and adolescence whereas it typically decreases with continued exercise, a phenomenon called "warm-up" although it is not really related to temperature. It lasts for several minutes. The usually more severely affected Becker patients often exhibit hypertrophic leg and gluteal muscles and, due to muscle shortening as result of the continuous contractions, tend to toe-walk and develop a compensatory lordosis. The stiff, hypertrophic leg muscles cause gait problems. Very disabling is a peculiar transient weakness which lasts a few seconds following initial contractions [57, 97]. The pathomechanisms of the warm-up phenomenon and the transient weakness remain unclear.

Functionally, the ~15 dominant mutations exert a dominant-negative effect on the homodimeric channel complex as shown by co-expression studies, meaning that mutant/mutant and mutant/wildtype complexes are malfunctional. The most common feature of the resulting chloride currents is a shift of the activation threshold towards more positive membrane potentials almost out of the physiological range [71, 101]. As a consequence of this, the chloride conductance is drastically reduced in the vicinity of the resting membrane potential. Interestingly, both testosterone and progesterone rapidly and reversibly exert a similar effect on the channel [29]. The ~100 recessive mutations do not functionally hinder the associated subunit. This explains why two mutant alleles are required to reduce chloride conductance sufficiently for myotonia to clinically develop in Becker myotonia. Heterozygous carriers of a recessive mutation are healthy but may exhibit some myotonic runs in the EMG.

The prevalence of Thomsen disease is now estimated at ~1:400,000 [57], i.e. much lower than 1:23,000 as thought in the premolecular era [4]. This is owing to the fact that many families with dominant myotonia are now identified with sodium channel mutations which result in a different disease with very similar symptomatology. Other families were found to have Becker myotonia with pseudodominant inheritance. Conversely, the prevalence of Becker myotonia is now thought to be 1:25,000 [57], much higher than Becker's original estimate of 1:50,000 [4].

The frequency of patients carrying two such mutations in Europe may be estimated to be roughly 6:100,000 [3, 95, and our own data]. To deduce the positive predictive value of a *CLCN1* mutation in a myotonic patient, the ratio (true positives)/(true positives + false positives). When considering the fraction of RMC patients with at least one mutation of 67%, the true positives are 67%*0.00006 = 0.00004. Based on our testing, we can say that false positives in non-*CLCN1* myotonic disorders were 5/123 = 4% of patients. The prevalence of non-*CLCN1* myotonias taken together is 1:10,000 = 0.01% [4, 82]. Thus, the rate of false positives is: 4%*0.01% = 0.0000004. We can conclude that the positive predictive value of one recessive *CLCN1* mutation to identify a Becker myotonia mutation is approximately 0.00004/(0.00004+0.000004)~91%.

18.3.2.2 Sodium Channel Myotonia (SCM)

Autosomal dominantly inherited myotonia can be caused by mutations in *SCN4A*, the gene encoding the voltage-gated sodium channel of skeletal muscle, Nav1.4, The channel is essential for the generation of the muscle fiber action potential. SCM includes myotonia fluctuans, myotonia permanens, acetazolamide-responsive myotonia, and painful myotonia, i.e. a spectrum of diseases with overlapping clinical features which have in common that, in contrast to the allelic disorders paramyotonia congenita, hyperkalemic periodic paralysis and hypokalemic periodic paralysis, no weakness occurs [50, 69, 93]. The prevalence of SCM is estimated at ~1:400,000 [57].

At the first glance, *myotonia fluctuans* and moderate SCM are clinically very similar to the well-known Thomsen myotonia, so that this diagnosis usually is made.

However in contrast to Thomsen and Becker patients, SCM patients become stiff 10–30 min after strenuous work. This *delayed* and sometimes painful stiffness may hinder the patient's movements for several hours. It should not be confused with *paradoxical* myotonia, i.e. myotonia worsening with repeated contractions. Usually, most limb muscles show the warm-up phenomenon, and paradoxical myotonia is restricted to the eyelid muscles. Furthermore, potassium and other depolarizing agents (and sometimes cold) aggravate the myotonia, a reaction that is not observed in Thomsen and Becker patients. Therefore we have coined the term *potassium-aggravated myotonia* [37, 65]. SCM responds much better than chloride channel myotonia to sodium channel blockers like the flecainide.

A gating defect of the sodium channels destabilizes the inactivated state so that the channel inactivates slower and incomplete and conducts more sodium [58, 65, 106]. Despite the resulting sustained membrane depolarization, this increased sodium inward current generates repetitive action potentials because the mutant channels show less accommodation.

18.3.2.3 Paramyotonia Congenita (PMC) – Myotonic Stiffness and Flaccid Weakness

Also PMC is caused by *SCN4A* missense mutations with dominant effects on the sodium channel. Signs are present at birth and often remain unchanged throughout life. The cardinal symptom is cold-induced muscle stiffness that increases with continued activity (paradoxical myotonia). In the cold (or even in a cool wind), the face may appear mask-like, and the eyes cannot be opened for several seconds or minutes. On intensive cooling, in most families the stiffness gives way to flaccid weakness or even to paralysis. Families with R1448 substitutions PC also have episodes of generalized periodic paralysis [57]. Such attacks occur spontaneously and can be triggered by rest or potassium. They are of short duration (an hour or less) in comparison to the cold-induced weakness which usually lasts for several hours even when the muscles are immediately re-warmed after a short bout of exposure to cold. During a severe paralytic attack, the muscle stretch reflexes are diminished or absent. Under warm conditions, most patients have no complaints because impaired muscle relaxation improves at higher temperatures. Muscle atrophy or hypertrophy is not typical for the disease. ~~The prevalence is about 1:200,000 [57]. Most of the German families which harbor the R1448H mutation have ancestors in the "Ravensberger Land", an area around and North of the city of Bielefeld.~~

Most PMC mutations are situated in protein parts relevant for channel inactivation, in the inactivation gate itself (i.e. the intracellular loop connecting domains III and IV like T1313M), in the outermost arginine of the voltage sensor in domain IV (R1448H/C/S/P), in intracellular S4–S5 loops of domain III or IV (e.g. F1473S), or in the C-terminus [106]. During cooling to 27°C in-vitro, PMC muscle fibers slowly depolarize from -85 mV to about -45 mV whereas normal muscle fibers depolarize by not more than 5 mV. The depolarization is associated with a long-lasting burst of action potentials which stop as soon as the membrane potential approximates values of –40 to –50 mV [55, 59]. At this voltage, also the mutant sodium channels fibers are inactivated and therefore the muscle fibers become inexcitable

and paralyzed. Functional expression of mutant channels revealed slowed fast inactivation and accelerated recovery from the inactivated state and an uncoupling of *fast* inactivation from activation [12, 54]. As also *slow* sodium channel inactivation should be incomplete to maintain depolarization-induced paralysis [74], several groups examined the effects of temperature on slow inactivation of the mutant channels [10, 75, 104]. The results were not uniform and difficult to interpret since entry into slow inactivation was already changed by the strikingly slowed fast inactivation.

18.3.3 Periodic Paralysis

Patients with muscle paralysis resulting from diseases associated with permanent electrolyte abnormalities are seldom misdiagnosed. In contrast patients with periodic paralysis may not have any interictal signs or symptoms and are often thought to suffer from a conversion reaction, and this may cause them to suffer needlessly. The weakness spells occur episodically with varying intervals of normal muscle function. Apparently, the underlying ion channel defects are usually well-compensated and an additional trigger is often required for channel, cell and tissue malfunction. Two dominant episodic types of weakness with or without myotonia are distinguished by the serum potassium level during the attacks of tetraplegia: hyper- and hypokalemic periodic paralysis. Due to release of potassium from muscle in the hyperkalemic form and uptake of potassium by muscle in the hypokalemic form, the resulting dyskalemia can be so severe that cardiac complications arise. During an attack, death can also occur due to respiratory insufficiency. Independently of the severity and frequency of the paralytic episodes, many patients develop a chronic progressive myopathy in the forties, an age at which the attacks of weakness decrease.

18.3.3.1 Hyperkalemic Periodic Paralysis (Hyperkalemic PP)

The disease is transmitted as an autosomal dominant trait with full penetrance, a male-to-female ratio of 1:1, and a prevalence of 1:200,000 [57]. It is characterized by attacks of flaccid weakness associated with an increase in serum potassium. Potassium-rich food or rest after exercise may precipitate an attack. A cold environment, emotional stress, fasting, and pregnancy provoke or worsen the attacks. Between attacks, the disease is often associated with myotonia, which is mild and does not impede voluntary movements but may exacerbate at the beginning of an attack of weakness. Patients without interictal myotonia are much more prone to develop progressive myopathy and permanent weakness than individuals with myotonia. This becomes especially obvious in individuals with the most common T704M mutation which is not associated with EMG myotonia in half of the patients, and about half of the T704M patients develop permanent myopathy. The second most frequent mutation, M1592V, always is associated with EMG myotonia and permanent myopathy has never been reported.

Also hyperkalemic PP is caused by mutations in the voltage-gated sodium channel Nav1.4 [73]. Most Nav1.4 mutations are situated at inner parts of the transmembrane segments or in intracellular protein loops and affect structures that form the three-dimensional docking site for the fast inactivation particle, and any malformation may reduce the affinity between the "latch bar and the catch". The mutant channels avoid the inactivated state and, in contrast to normal sodium channels, reopen or flicker between the inactivated and the open state, corresponding to a gain-of-function defect [35, 100]. As a result, sodium influx is increased as shown in vitro [56] and in vivo [105]. This inward current is associated with a sustained membrane depolarization that increases the electrical driving force for potassium, and potassium released from muscle elevates the serum potassium level. Sodium influx into muscle is accompanied by entrance of water into the fibers, causing hemoconcentration and further increase in serum potassium. This is a vicious cycle which spreads out and affects the surrounding muscle fibers. Starting point is the elevation of extracellular potassium due to ingestion or exercise.

18.3.3.2 Hypokalemic Periodic Paralysis (Hypokalemic PP)

The disease is transmitted as an autosomal dominant trait with reduced penetrance in women (the male to female ratio is 3 or 4–1) and is the most common of the primary PP (prevalence of 1:100,000) [57]. It differs from hyperkalemic PP in the sense that a spontaneous attack is associated with hypokalemia, potassium is a remedy, and carbohydrate- and sodium-rich food triggers an attack, and the EMG does not show myotonia. In general, the attacks last longer and are more severe. Usually, the patients are weakest during the second half of the night and in the morning, and become stronger as the day goes by.

Hypokalemic PP is caused by voltage sensor mutations in Cav1.1 (hypokalemic PP type 1) and Nav1.4 (hypokalemic PP type 2) [30, 44]. Results on sodium and calcium channels indicate that voltage sensor mutations may create an accessory ion pathway generating a hyperpolarization-activated cation leak independent of the main channel pore [47, 86, 92]. This membrane leak opens under hypokalemic conditions and depolarizes the muscle fibers to -50 mV and renders them inexcitable [47]. As muscle fibers are depolarized at potassium levels in the low normal range, this membrane leak might also be responsible for the progressive myopathy patients with certain mutations suffer from. About 80% of the patients in whom a mutation was identified harbor the R528H or the substitution in Cav1.1 while R1239H seems to predispose to the progressive myopathy in all of them.

18.3.3.3 Dyskalemic Periodic Paralysis Caused by KCNE3/MiRP2 Alteration?

In 2001, an R83H substitution in a K+ channel beta subunit, MiRP2, was suggested to cause dyskalemic periodic paralysis because it showed a loss of function in vitro and was found in 2 of 100 of such patients but in none of 120 unaffected controls [1]. By later studies, the substitution was identified in 1 of 104 and 1 of 138 patients, but also in 8 of 506 and 3 of 321 controls [42, 90]. Taken together, the substitution

is present in 1.17% of patients and in 1.16% of healthy controls, which does not support disease causality and shows that the common lab practice to exclude a novel mutation in approximately 100 healthy controls is insufficient.

18.3.3.4 Andersen–Tawil Syndrome (ATS)

ATS is a periodic paralysis with cardiac arrhythmia and dysmorphic features. The prevalence is estimated to <1,000,000. Patients may experience a life-threatening ventricular arrhythmia independent of their PP, and long QT syndrome is the primary cardiac manifestation. The syndrome is characterized by the highly variable clinical triad of dyskalemic PP, ventricular ectopy, and potential dysmorphic features [79]. The paralytic attack may be hyperkalemic or hypokalemic and accordingly, the response to oral potassium is unpredictable. Mutations of the Kir2.1 potassium channel, an inward rectifier expressed in skeletal and cardiac muscle, are causative of the disorder [70]. Kir2.1 channels are essential for maintaining the highly negative resting membrane potential of muscle fibers and accelerating the repolarization phase of the cardiac action potential. The mutations mediate loss of channel function by haploinsufficiency or by dominant-negative effects on the wildtype allele and may lead to long-lasting depolarization and membrane inexcitability.

18.3.3.5 Thyrotoxic Periodic Paralysis

Thyrotoxic periodic paralysis (TPP) resembles familial HypoPP with respect to changes in serum and urinary electrolytes during attacks and in its response to glucose, insulin, and rest after exertion. However, it differs from familial HypoPP in the adverse effect of thyroid administration and that the male to female ratio in Japanese is about 6:1 and the onset is usually after the age of 20 years. Forty-five percent of the patients develop the syndrome in the third decade, another 35% in the fourth, and the rest in the fifth decade of life. More than 75% of the cases occur in Orientals suggesting a predisposing racial factor (Chinese, Japanese, Korean, Vietnamese). The attacks occur much more frequently in summer than in winter. A geographical component is not likely, because Chinese or Japanese immigrants in North or South America have same disease frequency as in their country of origin. Reports of cases in Caucasians and Blacks indicate that the disease rarely occurs in non-Orientals as well. An unusual association with Hashimoto's thyroiditis has been reported familial in one Chinese family.

The thyrotoxicosis precedes or appears simultaneously with the periodic paralysis in more than 80% of the TPP patients [23] but the thyrotoxic signs are relatively mild at the time of the initial attack (no palpitations, goiter, or exophthalmus). Typical are sudden paralytic attacks of proximal limb muscles after strenuous exercise or at rest following high-carbohydrate meals in the evening or during the night, and hypokalemia during the attacks. The serum potassium falls to levels below 3.5 mM in 80% of the patients. In some patients it may be as low as 1.2 mM and cause life-threatening arrhythmias or sino-atrial block. As the hypokalemia is the

result of an insulin-induced shift of potassium from the extracellular space into the muscle, potassium is released from muscle at the end of an attack to cause rebound hyperkalemia. During an attack, both the arrhythmia and the acute paralytic attack are relieved by administration of potassium.

More than 75% of the cases occur in Asians, suggesting a predisposing racial factor. Statistically, the incidence of thyrotoxic PP in Asian men with hyperthyroidism (Graveś disease) has been estimated at between 13 and 24% [57]. In contrast to TPP, Graves' disease shows a 5:1 female to male predominance with a prevalence of 2% in the general population. In Kir2.6, an inwardly rectifying potassium channel that is transcriptionally regulated by thyroid hormone, mutations were identified in 4 of 30 unrelated TPP patients [77].

18.3.4 Disorders of Excitation-Contraction Coupling

Muscle contractures as well as flaccid weakness are characteristic features of disturbed muscle excitation-contraction coupling. Two allelic forms are well studied: central core disease (CCD) and multiminicore disease.

18.3.4.1 Central Core Disease

Central core disease (CCD) is a congenital myopathy clinically characterized by muscle hypotrophy and weakness and a floppy infant syndrome, often alongside other skeletal abnormalities such as hip displacement and scoliosis. The clinical severity of CCD and the number of cores can vary with age: there is also variability between and within families. The serum CK is normal or mildly elevated. Pathognomonic is the abundance of central cores devoid of oxidative enzyme activity along the predominant type 1 muscle fibers. Usually the mode of inheritance is dominant. The disease is caused by mutations in mutations in the C-terminal region of the ryanodine receptor RyR1 of skeletal muscle which is located in the membrane of the sarcoplasmic reticulum (SR). Some mutations decrease the open probability of the channel so that it loses the ability to release calcium from the SR, thereby causing muscle weakness. Other mutations increase the open probability of the channel, leading to depleted SR calcium stores and weakness.

18.3.4.2 Multiminicore Disease

Multiminicore disease (MmD) is considered a recessively inherited congenital myopathy with a pattern of weakness that differs from central core disease in that there is often severe axial involvement, while respiratory, bulbar and extra-ocular muscles are commonly affected. As with CCD, the condition is stable or minimally progressive, and the serum CK is normal or only mildly elevated. MmD is characterized by cores lacking oxidative enzyme activity on histochemical analysis. However, in contrast to CCD the cores in MmD are usually multiple, are poorly defined and do not extend along the axis of the fiber. Of the four clinical subtypes of MmD, the

moderate form is a channelopathy. It presents with generalized muscle weakness that affects predominantly the pelvic girdle and may lead to scoliosis. This form can involve the hand muscles and lead to amyotrophy and muscle hyperlaxity. This form and another one, associated with ophthalmoplegia, are most often associated with *RYR1* variants [41] which can be homozygous, compound heterozygous or heterozygous with mono-allelic expression and which are spread across the whole RYR1 protein. Furthermore, there are myopathic patients with histological cores in whom mutations of RYR1 and the other MmD-responsible genes such as *ACTA1* and *SEPN1* have been excluded.

18.3.4.3 Susceptibility to Malignant Hyperthermia

Susceptibility to malignant hyperthermia susceptibility (MHS) is an autosomal dominant predisposition of clinically inconspicuous individuals to respond abnormally when exposed to volatile anesthetics, depolarizing muscle relaxants or extreme physical activity in hot environments. During exposure to triggering agents, a pathologically high increase in myoplasmic calcium concentration leads to increased muscle metabolism and heat production resulting in muscle contractures, hyperthermia associated with metabolic acidosis, hyperkalemia, and hypoxia. The metabolic alterations usually progress rapidly and without immediate treatment, up to 70% of the patients die. Early administration of dantrolene, an inhibitor of calcium release from the sarcoplasmic reticulum (SR) has successfully aborted numerous fulminant crises and has reduced the mortality rate to less than 10%.

Malignant hyperthermia occurs worldwide and affects all racial groups. Most cases occur in children and young adults for unknown reason. Incidence of MH crises during general anesthesia varies age-dependently from 1:15,000 in children to 1:50,000 in adults [68]. As the triggering substances elicit an event only in a fraction of anesthesias, the true prevalence of MH susceptibility may be higher than the very low clinical penetrance. In accordance with the varying severity of the clinical picture, non-anesthetic MH-like episodes triggered by overheating, body exertion, and infections have been described. Evidence for a relation to the sudden infant death syndrome is rather weak. MH-like crises have also been observed in patients with myopathies such as myotonia fluctuans, Duchenne/Becker progressive mucular dystrophy, myotonia congenita and myotonic dystrophy. It seems very likely that the molecular mechanisms underlying these MH-like events differ from those of true MH susceptibility, e.g. in the myotonic diseases as increased myotonic reactions to anesthetic agents. This different pathogenesis, of course, does not obviate the need for caution when considering general anesthesia in these disorders.

In up to 70% of MHS families, variants in the skeletal muscle isoform of the ryanodine receptor gene *RYR1* have been identified. In contrast to the CCD mutations, most of the MHS variants are situated at the N-terminus of the protein. Only 29 of the more than 200 sequence variations in *RYR1* have been investigated for their functional effect and meet the criteria to be included in the guidelines for molecular genetic detection of MH susceptibility. In the absence of a “high-throughput”

method to investigate novel variants for being causative, these functional analyses remain laborious and they have not kept pace with the detection rate of novel variants in this large gene. Although it is likely that many of the currently uncharacterized *RYR1* variants associated with MH susceptibility will have pathological significance, until this is proven they have no diagnostic utility. In these circumstances patients with a personal or family history suggestive of MH should be considered at risk of the condition until proven otherwise by normal responses of muscle biopsy specimens to in vitro contracture tests.

18.4 Conclusion

As ion channels constitute one of the only protein families that allow functional examination on the molecular level, expression studies of putative mutations have become standard in supporting the disease-causing nature of mutations. While this is quite helpful, one must not over-interpret functional changes that a mutation produces because these changes may not necessarily indicate a disease-causing mutation but a functional polymorphism instead. Additionally, functional polymorphisms are *not* the equivalent to susceptibility mutations [52]. The confusion of these two does not only lead to circulating errors in the scientific community that take years to correct, but many patients will be falsely diagnosed and treated as well. Therefore, functional studies do not alleviate from the need for the genetic screening of large and adequately matched control populations for the putative mutations. Association analysis is essential to prove disease association or causality. Two reports have proposed the typing of 150–200 controls (300–400 chromosomes) for putative mutations with a prevalence of 1% by power analysis [14, 63]. A more general equation that simply allows to calculate the number of required controls for such studies [42]. The number depends on the prevalence of the change of interest: rare changes require quite a large number of controls. Likewise, scientists must exercise utmost care in the interpretation of genetic epidemiologic results including reviews of the status quo as in the present text.

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Chapter 18

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