Hereditary
Channelopathies in Neurology

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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 phenotypes¹ include certain forms of epilepsy, ataxia, migraine, neuropathic pain, myotonia, and muscle weakness including myasthenia and periodic paralyses. The total prevalence of monogenic² 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 explained 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.

Introduction
The implication that ion channels may play a causal role in disease pathogenesis came first from the observation of abnormal ion conduction from muscle biopsied from myotonic goats [Bryant 1969]; patients with paramyotonia congenita [Lehmann-Horn et al. 1981]; and periodic paralysis [Lehmann-Horn et al. 1983]. In the 1990’s 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

¹ A phenotype is any observable characteristic or trait of an organism: such as its morphology, development, biochemical or physiological properties, behavior, and products of behavior. Phenotypes result from the expression of an organism’s genes as well as the influence of environmental factors and the interactions between the two.

² Pertaining to one gene
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 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, a so-called trigger. Compensatory mechanisms (like what?) 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 [Lehmann-Horn and Jurkat-Rott 1999, Jurkat-Rott and Lehmann-Horn 2005]. Conveniently, more than 35% of marketed drugs target ion channels, so that channelopathies also provide model disorders for therapeutic strategies.

**Hereditary channelopathies of the central and peripheral nervous system**

**Epilepsy**

Epilepsy is one of the most common neurological disorders affecting approximately 3% of the world’s population during a lifetime [Hauser et al. 1996]. 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 different seizure types. The symptoms of a seizure depend on age, the underlying cause and the brain region involved. Accordingly, epileptic signs 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

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3 pertaining to or emanating from a neuron
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.

**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\(^4\), suggesting a defect of a broader network. The penetrance of the disease is estimated at approximately 70 to 80%. A mutation was identified in the gene *CHRNA4* encoding the α4-subunit of a neuronal nicotinic acetylcholine receptor\(^5\) as the first ion channel mutation found in an inherited form of epilepsy [Steinlein et al. 1995]. Altogether, five mutations in *CHRNA4* and two in *CHRNB2*, which encodes the β2-subunit of neuronal nicotinic acetylcholine receptor, have been reported [Steinlein 2004]. Recently, another mutation in *CHRNA2*, encoding the neuronal nicotinic acetylcholine receptor α2-subunit, was detected. Most mutations reside in the pore-forming M2 trans-membrane segments. Different effects on gating of heteromeric\(^6\) 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\(^7\) or human embryonic kidney cells. An increased acetylcholine sensitivity is thought to be the main common gating defect of the mutations [Steinlein 2004, Lerche et al. 2005].

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\(^4\) The insula is located within the cerebral cortex, beneath the frontal, parietal and temporal opercula.

\(^5\) Nicotinic acetylcholine receptors, or nAChRs, are cholinergic receptors that form ligand-gated ion channels in the plasma membranes of certain neurons and on the postsynaptic side of the neuromuscular junction. As ionotropic receptors, nAChRs are directly linked to ion channels and do not use second messengers (as metabotropic receptors do).\(^1\)

\(^6\) Consisting of more than one kind of structural subunit

\(^7\) Xenopus oocytes are very large cells which are easy for scientists to culture and use in experiments

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Like the other type of acetylcholine receptor — the muscarinic acetylcholine receptor (mAChR) — the nAChR is triggered by the binding of the neurotransmitter acetylcholine (ACh). However, whereas muscarinic receptors are also activated by muscarine, nicotinic receptors can be opened by nicotine - hence the name “nicotinic”.\(^2\)

Nicotinic acetylcholine receptors are present in many tissues in the body and are the best-studied of the ionotropic receptors.\(^3\) The neuronal receptors are found in the central nervous system and the peripheral nervous system. The neuromuscular receptors are found in the neuromuscular junctions of somatic muscles; stimulation of these receptors causes muscular contraction.

\(^1\) Consisting of more than one kind of structural subunit

\(^2\) Consisting of more than one kind of structural subunit

\(^3\) Consisting of more than one kind of structural subunit
In one patient with cryptogenic partial epilepsy that was classified as pharmaco-resistant because of non-response to carbamazepine or oxcarbazepine, a Nav1.3 mutation, K354Q, was identified that was not present in 295 neurological normal controls [Holland et al. 2008]. 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.

**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 hemi-clonic symptoms or with apnea, or may appear primarily generalized. Accordingly, ictal EEGs showed focal and generalized discharges. Interictal EEGs are mostly normal. The risk of seizures recurring in adulthood is approximately 15%. Although psychomotor development is usually normal, an increasing number of cases with learning disability have recently been described [Borgatti et al. 2004]. 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 approximately 20-30%, which is apparently sufficient to cause BFNS [Schroeder et al. 1998]. Even subtle changes in channel gating restricted to sub threshold 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 [Maljevic et al. 2008, Wuttke et al. 2008].

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 period (BFNIS). Ictal EEGs can show focal epileptic discharges in different brain regions. BFIS can be associated with other neurological disorders, such as paroxysmal dyskinesia⁸ or migraine. Mutations in the SCN2A gene

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⁸ Paroxysmal dyskinesias are neurologic conditions characterized by sudden episodes of abnormal involuntary movements (hyperkinesias). These may include any combination of involuntary, rapid, randomly irregular jerky movements (chorea); relatively slow, writhing motions that appear to flow into one another (athetosis); increased muscle tone with repetitive, twisting, patterned movements and distorted posturing (dystonia); and uncontrollable flinging movements of an arm, a leg, or both (ballismus). The term paroxysmal indicates that the abnormal movements are sudden and unpredictable, with a relatively rapid return to normal motor function and behavior.
encoding one of the α-subunits of voltage-gated sodium channels expressed in the mammalian brain have been identified in BFNIS [Heron et al. 2002]. 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.

**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 a febrile epileptic seizure types within the same pedigree. The penetrance is about 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 a febrile 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 asymptomatic GEFS+ [Berkovic et al. 2006]. 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 [Barela et al. 2006]. Reduced channel function is considered to be more significant than gain-of-function changes [Rusconi et al. 2007], leading 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 [Sugawara et al 2001]) and by SCN9A in potentially up to 5% of the patients with febrile seizures [Singh et al 2009]. 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

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9. In genetics, a missense mutation (a type of nonsynonymous mutation) is a point mutation in which a single nucleotide is changed, resulting in a codon that codes for a different amino acid (mutations that change an amino acid to a stop codon are considered nonsense mutations, rather than missense mutations). This can render the resulting protein nonfunctional.

10. Homologous chromosomes are chromosome pairs of the same length, centromere position, and staining pattern, with genes for the same characteristics at corresponding loci. One homologous chromosome is inherited from the organism’s mother; the other from the organism’s father.
inhibition has been observed in the cortex, as shown in a knock-in model carrying one of the human mutations [Reid et al. 2009].

Severe myoclonic epilepsy of infancy (SMEI) or Dravet Syndrome is characterized by 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 a febrile 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 a febrile seizures, and in some families GEFS+ and SMEI overlap, SMEI may be regarded as the most severe phenotype of the GEFS+ spectrum [Singh et al. 2001].

Similar to SMEI, intractable childhood epilepsy presents with generalized tonic–clonic seizures (ICEGTC) [Fujiwara et al. 2003]. 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 [Lerche et al. 2005].

For SMEI and ICEGTC, mutations in SCN1A encoding Nav1.1 have been identified [Claes et al. 2001]. Together with GEFS+, more than 100 SCN1A mutations have been identified, accounting for 70% of cases [Meisler and Kearney 2005]. Mutation hotspots, such as sites of CpG deamination, account for 25% of de-novo mutations [Kearney et al. 2006]. 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.

**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, about 10 seconds, 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 \textit{GABRA1}, the gene encoding the α1-subunit of the GABA-A receptor, was identified in a family with EJM [Cossette et al. 2002]. The mutation leads to loss-of-function of the GABA-A receptor i.e. a decrease of inhibitory chloride currents and hyperexcitability [Cossette et al. 2002]. Larger studies suggest that GABA-A receptor mutations are extremely rare [Dibbens et al. 2009]. Two EJM mutations have been described in the calcium channel β subunit gene \textit{CACNB4}, but they were not examined functionally and not much can be deduced about prevalence in the small population studied [Escayg et al. 2000]. Recently, a few EJM mutations were found in the gene \textit{CLCN2} encoding a neuronal voltage-gated chloride channel [Haug et al. 2003, Saint-Martin et al. 2009]. 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 \textit{CLCN2} as susceptibility gene for EJM is still a matter of debate [Niemeyer et al. 2010].

For ECA, a mutation in the γ2 subunit of the GABA-A receptor encoded by \textit{GABRG2} has been described [Wallace et al. 2001] which decreased GABA-activated chloride currents. This reduction of inhibitory currents results in hyperexcitability. Due to trafficking changes and endocytosis\textsuperscript{11} 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 \textit{GABRB3} that showed reduced penetrance and hyperglycosylation-induced reduction of inhibitory chloride current [Tanaka et al 2008]. For completeness of the expression data: a \textit{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 haploinsufficiency is the pathogenetic mechanism [Maljevic et al. 2006].

Finally, variants in ECA and other subtypes have been described in \textit{CACNA1H} encoding a neuronal voltage-gated T-type calcium channel. They were suggestive of gain-of-function by

\textsuperscript{11} Endocytosis is the process by which cells absorb molecules (such as proteins) by engulfing them
several different alterations in channel gating which can explain a neuronal hyperexcitability [Reid et al. 2009].

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 trunk and limb ataxia and dysarthria12 lasting seconds to minutes. Nystagmus13 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 [Browne et al. 1994]. Most involve highly conserved amino acids such as those in the trans-membrane 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 [Ophoff et al. 1996]. The ataxia lasts longer and mild interictal nystagmus and ataxia are present. Vertigo, nausea and vomiting preceds 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 approximately 30% of cases. Penetrance is 80 to 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 β4 subunit encoded by the CACNB4 gene [Escayg et al. 2000]. 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

12 Dysarthria is a condition that occurs when problems with the muscles that help you talk make it difficult to pronounce words.
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 \textit{CACNA1A} gene [Zhuchenko et al. 1997]. It makes up 6% (in Japan) to 30% (in Australia) of SCA cases [Schöls et al. 1997, Watanabe et al. 1998, Storey et al. 2000]. In most families, patients show permanent dysarthria, oculomotor, 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 \textit{SCN8A} gene was identified [Trudeau et al. 2006]. 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, \textit{SCN8A} was considered a susceptibility gene for the phenotype.

**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 [Silberstein et al. 2002]. 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 migraine

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13 Nystagmus means involuntary eye movement

14 a condition that occurs when problems with the muscles that help you talk make it difficult to pronounce words.

15 moving or tending to move the eyeball
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\textsuperscript{17}, dysarthria\textsuperscript{18}, vertigo, homonymous hemianopsia\textsuperscript{19}, cheiro-oral paresthesias\textsuperscript{20}, 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 [Jurkat-Rott et al. 2004].

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, hyperacusis\textsuperscript{21}, and persistent cerebellar dysfunction with Purkinje cell\textsuperscript{22} atrophy. Over 20 missense mutations have been described, that are primarily located in the pore region or trans-membrane segments and result in gain of Cav2.1 function [Ophoff et al. 1996].

FHM2 is an autosomal dominant disease, caused by mutations in the \textit{ATP1A2} gene on chromosome 1q21-23 encoding the alpha2 subunit of the astrocytic Na\textsuperscript{+}/K\textsuperscript{+}-ATPase 3 [De Fusco et al. 2003, Spadaro et al. 2004]. 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 1.

FHM3 is caused by mutations in the \textit{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 [Dichgans et al. 2005]. Functional expression of the three known mutations demonstrated reduced channel activity in two cases and gain-of-function features in the third case [Cestèle et al. 2008, Kahlig et al. 2008]. The presence of seizures in addition to migraine in the third family demonstrates the potentially close relationship between these migraine and epilepsy.

\textsuperscript{17} gross lack of coordination of muscle movements
\textsuperscript{18} impairment of language ability
\textsuperscript{19} visual field loss that respects the vertical midline, and usually affects both eyes, but can involve one eye only
\textsuperscript{20} a feeling of pins and needles experienced in the hand and arm as well as in the nose-mouth area on the same side. The paresthesia may migrate up the arm and then extend to involve the face, lips and tongue
\textsuperscript{21} a health condition characterized by an over-sensitivity to certain frequency ranges of sound
\textsuperscript{22} Purkinje cells send inhibitory projections to the deep cerebellar nuclei, and constitute the sole output of all motor coordination in the cerebellar cortex.
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 erythromelalgia\(^{23}\) (IEM), paroxysmal extreme pain disorder (PEPD), and Nav1.7-associated congenital insensitivity to pain (CIP) [Goldberg et al. 2007, Dib-Hajj et al. 2008, Estacion et al. 2008]. 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\(^{24}\), 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 [Fertleman et al. 2006]. 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 [Cox et al. 2006]. 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 so called resurgent current [Jarecki et al. 2010]. 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 [Dib-Hajj et al. 2008]. 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 [Cox et al. 2006]. These mutations do not produce functional

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\(^{23}\) Erythromelalgia, also known as Mitchell’s disease, acromelalgia, red neuralgia, or erythermalgia is a rare neurovascular peripheral pain disorder in which blood vessels, usually in the lower extremities (or hands), are episodically blocked (frequently on and off daily), then become hyperemic and inflamed. There is severe burning pain (in the small fiber sensory nerves) and skin redness. The attacks are periodic and are commonly triggered by heat, pressure, mild activity, exertion, insomnia or stress.
Nav1.7 channels when expressed in mammalian expression systems [Cox et al. 2006]. 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 haploin sufficiency.

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 [Zhou et al. 2002]. Hypertonia and apnea 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. GlyRαs facilitate the fast-response, inhibitory glycinergic neurotransmission in the brainstem and spinal cord. Certain mutations inhibit the occurrence of higher conductance states [Langosch et al. 1994].

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 nosebridge 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

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24 Erythema is redness of the skin, caused by hyperemia of the capillaries in the lower layers of the skin. It occurs with any skin injury, infection, or inflammation.
25 Hypertonia is a condition marked by an abnormal increase in muscle tension and a reduced ability of a muscle to stretch.
26 Myoclonus is brief, involuntary twitching of a muscle or a group of muscles. GlyR is an ionotropic receptor that produces its effects through chloride current. It is one of the most widely distributed inhibitory receptors in the central nervous system and has important roles in a variety of physiological processes, especially in mediating inhibitory neurotransmission in the spinal cord and brain.
27 GlyR is an ionotropic receptor that produces its effects through chloride current. It is one of the most widely distributed inhibitory receptors in the central nervous system and has important roles in a variety of physiological processes, especially in mediating inhibitory neurotransmission in the spinal cord and brain.
potentiates the inhibitory transmitter GABA. During the first year of life infants need to be fitted with an apnea monitor.

**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\(^2^9\) 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 [Dedek et al. 2001, Wuttke et al. 2007]. Patients with Kv1.1 mutations show continuous muscle overactivity that can be visible as myokymia\(^3^0\) 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 hypo-magnesemia as a new phenotypic characteristic [Glaudemans et al. 2009]. 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\(^3^1\)) and the paroxysmal dyskinesias\(^3^2\), as well as the sensory diseases such as

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\(^{2^9}\) hypnic jerk, hypnagogic jerk, sleep start, or right start, is an involuntary myoclonic twitch which occurs during hypnagogia, just as a person is beginning to fall asleep, often causing him or her to awaken suddenly. Physically, hypnic jerks resemble the “jump” experienced by a person when startled; often accompanied by a falling sensation.

\(^{2^9}\) A rare neuromuscular disorder with onset usually in late childhood or early adulthood, characterized by intermittent or continuous Myokymia, is an involuntary, spontaneous, localized quivering of a few muscles bundles within a muscle, but which are insufficient to move a joint.

\(^{2^9}\) Myokymia, is an involuntary, spontaneous, localized quivering of a few muscles bundles within a muscle, but which are insufficient to move a joint.

\(^{3^1}\) Tubulopathy is a term used to describe a disease affecting the renal tubules of the nephron.
sensorineural deafness and blindness (dominant deafness, deafness Jervell and Lange-Nielsen, congenital stationary night blindness, and retinitis pigmentosa), we refer to Table 1.

Hereditary channelopathies of the motor endplate and the skeletal muscle

Congenital myasthenic syndromes (CMS)

CMS are a heterogeneous group of inherited disorders with defective transmission of neuromuscular excitation resulting in muscle fatigue [Engel et al. 2003]. 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 arthrogryposis33 multiplex involving reduced fetal movement and multiple joint contractures in the neonate [Brownlow et al. 2001]. Electromyography in CMS patients reveals a characteristic decrement of compound action potential amplitude on repetitive stimulation, and single fiber recordings show an increased variability in the synaptic transmission time (“jitter”) and transmission blocks [Kullmann and Hanna 2002].

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 34[Engel et al. 1982]. Loss-of-function mutations of AChR subunits lead to compensatory expression of fetal ß 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

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33 Dyskinesia is a movement disorder which consists of effects including diminished voluntary movements and the presence of involuntary movements, similar to tics or chorea. Dyskinesia can be anything from a slight tremor of the hands to uncontrollable movement of, most commonly, the upper body but can also be seen in the lower extremities.

34 Arthrogryposis, also known as Arthrogryposis Multiplex Congenita, is a rare congenital disorder that is characterized by multiple joint contractures and can include muscle weakness and fibrosis. It is a non-progressive disease.

34 Monovalent Cations: Positively charged atoms, radicals or group of atoms with a valence of plus 1, which travel to the cathode or negative pole during electrolysis.
single supramaximal stimulus. The syndrome results from gain-of-function mutations in the ion-conducting pore M2 [Elenes et al. 2009]. The leaky AChR exert an excitotoxic effect and cause endplate myopathy via focal caspase activation [Vohra et al. 2004].

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 if the head is hit. 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.

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 [Koch et al. 1992]. 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 [Lehmann-Horn et al. 2004, Trip et al. 2009]. The pathomechanisms of the warm-up phenomenon and the transient weakness remain unclear.

Functionally, the approximately 15 dominant mutations exert a dominant-negative effect on the homodimeric\textsuperscript{55} channel complex as shown by co-expression studies, meaning that mutant/mutant

\textsuperscript{55} a protein composed of two polypeptide chains that are identical in the order, number, and kind of their amino acid residues
and mutant/wildtype complexes are dysfunctional. 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 [Pusch et al. 1995, Wagner et al. 1998]. 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 [Fialho et al. 2008]. The approximately 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 about 1:400,000 [Lehmann-Horn et al. 2004], i.e. much lower than 1:23,000 as thought in the pre-molecular era [Becker 1977]. 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 [Lehmann-Horn et al. 2004], much higher than Becker's original estimate of 1:50,000 [Becker 1977].

The frequency of patients carrying two such mutations in Europe may be estimated to be roughly 6:100,000 [Baumann et al. 1998, Sun et al. 2001, 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 myotonia taken together is 1:10,000=0.01% [Becker 1970, Siciliano et al. 2001]. 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+0.0000004)=91%.

**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

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 to 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 [Heine et al. 1993, Mitrovic et al. 1994]. 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 Na⁺ [Lerche et al. 1993, Mitrovic et al. 1994, Wu et al. 2005]. Despite the resulting sustained membrane depolarization, this increased sodium inward current generates repetitive action potentials because the mutant channels show less accommodation.

**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 [Lehmann-Horn et al. 2004]. 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. PMC is considered an extremely rare disorder, though little epidemiological work has been done. Prevalence is generally higher in European derived populations and lower among Asians. Epidemiological estimates have been provided for the German population. Here, it was estimated that the prevalence of PC is between 1:350,000 and 1:180,000 [Meyer-Kleine et al. 1994]. It should be noted, however, that the German population of patients with PC is not uniformly distributed across the country. Many individuals with PC herald from the Ravensberg area in North-West Germany, where a founder effect seems to be responsible for most cases [Becker, 1979; Meyer-Kleine et al. 1994]. The prevalence here is estimated at 1:6,000.

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 [Wu et al. 2005]. 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 [Lehmann-Horn et al. 1987b, Lerche et al. 1996]. 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 [Chahine et al. 1994, Lehmann-Horn and Jurkat-Rott 1999]. As also slow sodium channel inactivation should be incomplete to maintain depolarization-induced paralysis [Ruff 1994], several groups examined the effects of temperature on slow inactivation of the mutant channels [Carle et al. 2009, Ruff 1999, Webb and Cannon 2008]. The results were not uniform and difficult to interpret since entry into slow inactivation was already changed by the strikingly slowed fast inactivation.

**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.

**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 [Lehmann-Horn et al. 2004]. 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 [Rojas et al. 1991]. 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 [Hayward et al. 1996, Wagner et al. 1997]. As a result, sodium influx is increased as shown in vitro [Lehmann-Horn et al. 1987a] and in vivo [Weber et al. 2006]. 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.

**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 to 1) and is the most common of the primary PP (prevalence of 1:100,000) [Lehmann-Horn et al. 2004]. 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) [Fontaine et al. 1994, Jurkat-Rott et al. 2000]. Results on sodium channels indicate that voltage sensor mutations may create an accessory ion pathway generating a hyperpolarization-activated cation leak independent of the main channel pore [Sokolov et al. 2007, Struyk and Cannon 2007]. This membrane leak opens under hypokalemic conditions and depolarizes the muscle fibers to -50 mV and renders them inexcitable [Jurkat-Rott et al. 2009]. 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.

**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.
**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 [Sansone et al. 1997]. 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 [Plaster et al. 2001]. 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.

**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 [Reisin et al. 2000]. An unusual association with Hashimoto’s thyroiditis has been reported familial in one Chinese family [Leung 1985].

The thyrotoxicosis precedes or appears simultaneously with the periodic paralysis in more than 80% of the TPP patients [Engel, 1961] 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 (Grave’s disease) has been estimated at between 13 and 24% [Lehmann-Horn et al. 2004]. 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 [Ryan et al. 2010].

**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.

**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 RYR1 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 RYR1 channel, leading to depleted SR calcium stores and weakness.

**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 [Jungbluth 2007] 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.

**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 [Ording 1985]. 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 [Kalow and Britt 1987]. 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 muscular 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 \textit{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 \textit{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 \textit{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.

\textbf{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 [Kuzmenkin et al. 2003]. 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 to 200 controls (300 to 400 chromosomes) for putative mutations with a prevalence of 1 % by power analysis [Marchuk, 1998; Collins and Schwartz, 2002]. A more general equation that simply allows to calculate the number of required controls for such studies [Jurkat-Rott et al. 2004]. 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.
Table 1. Overview of hereditary channelopathies in Neurology. The diseases or the susceptibilities are listed in column 1, their acronyms in column 2, the responsible genes and their chromosomal locations in columns 3 and 4, and the ion channels and their specific protein names in columns 5 and 6. The inheritance is given in column 7 (D=dominant, R=recessive), and the disease prevalence in the last column.

<table>
<thead>
<tr>
<th>Category</th>
<th>Disease</th>
<th>Acronym</th>
<th>Gene</th>
<th>Locus</th>
<th>Channel</th>
<th>Protein</th>
<th>Trait</th>
<th>Prevalence</th>
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<td><strong>Central and peripheral nervous system</strong></td>
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<td><strong>Epilepsy</strong></td>
<td>Nocturnal frontal lobe epilepsy</td>
<td>ENFL1</td>
<td>CHRNA4</td>
<td>20q13.3</td>
<td>Cation channel</td>
<td>nAChRα4</td>
<td>D</td>
<td>&gt;5 families</td>
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<td></td>
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<td>CHRNB2</td>
<td>1q21</td>
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<td>nAChRβ2</td>
<td>&lt;5 families</td>
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<td>&lt;5 families</td>
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<td></td>
<td>Cryptogenic pediatric partial epilepsy</td>
<td>SCN3A</td>
<td>2q24</td>
<td>Sodium channel</td>
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**Motor endplate and skeletal muscle**

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Elenes S, Decker M, Cymes GD, Grosman C. Decremental response to high-frequency trains of acetylcholine pulses but unaltered fractional Ca2+ currents in a panel of "slow-channel syndrome" nicotinic receptor mutants. J Gen Physiol. 2009;133:151-69.

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