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## REVIEW

## Genetic neurological channelopathies: molecular genetics and clinical phenotypes

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**ABSTRACT**

Evidence accumulated over recent years has shown that genetic neurological channelopathies can cause many different neurological diseases. Presentations relating to the brain, spinal cord, peripheral nerve or muscle mean that channelopathies can impact on almost any area of neurological practice. Typically, neurological channelopathies are inherited in an autosomal dominant fashion and cause paroxysmal disturbances of neurological function, although the impairment of function can become fixed with time. These disorders are individually rare, but an accurate diagnosis is important as it has genetic counselling and often treatment implications. Furthermore, the study of less common ion channel mutation-related diseases has increased our understanding of pathomechanisms that is relevant to common neurological diseases such as migraine and epilepsy. Here, we review the molecular genetic and clinical features of inherited neurological channelopathies.

**INTRODUCTION**

Inherited disorders of ion channel function—the ‘genetic channelopathies’ are a rapidly expanding group of neurological disorders and are implicated in many areas of neurological practice. Although the inherited channelopathies are individually rare, the study of these conditions is contributing to our understanding of pathomechanisms of neurological disease in general.

Ion channels are specialised pore-forming proteins that allow the passage of certain ions across the lipid bilayer of the cell membrane. They are typically divided into two broad categories according to their method of activation—voltage or ligand gated. The ‘gating’ of ion channels by transmembrane voltage changes or specific receptor ligands, such as acetylcholine (ACh), together with their selectivity for distinct ion species, underlies the coordination of ion fluxes during action potentials or following neurotransmitter release.<sup>1</sup>

Most ion channels have a similar basic structure—for example, all voltage-gated ion channels have a large pore-forming subunit—the  $\alpha$  subunit, composed of four homologous domains (I–IV)—each composed of six transmembrane segments (S1–S6). In all cation channels, the S4 segments contain between four and eight positively charged residues conferring voltage dependence, and the S5–S6 loops form the ion pore. Ion channels are also composed of several accessory subunits that may be cytoplasmic or extracellular that have roles in

channel kinetics and membrane stabilisation<sup>2</sup> (figure 1).

Although ion channels are essential for the normal function of all eukaryotic cells, they are particularly important in the nervous system for the generation, repression and propagation of action potentials. Ion channels are often highly selective for a particular ionic species, for example, sodium, potassium or calcium. The opening of sodium channels leads to depolarisation of neurons whereas potassium channel opening leads to hyperpolarisation, as does the opening of chloride channels in adult neurons. The opening of calcium channels causes membrane depolarisation, but calcium ions also have more important roles as second messengers.<sup>3</sup> Hence, loss of function mutations in potassium or chloride channels or gain of function mutations should lead to disorders characterised by hyperexcitability, such as epilepsy. However, the effect of a mutation depends on the specific neuronal circuitry involved. For example, a mutation that causes a gain of function effect in inhibitory interneurons can decrease excitability.<sup>3</sup>

Given their importance in neuronal excitability and synaptic transmission through the central and peripheral nervous systems, it is not surprising that mutations in ion channel genes can lead to disease. Many of the mutations that have been associated with ion channel disorders are missense mutations that affect channel kinetics. However, inherited mutations and chromosomal rearrangements can affect any stage of ion channel biogenesis, including transcription, mRNA processing, splicing, translation, folding and trafficking, as well as subunit assembly.

Inherited disorders of ion channels are typically inherited in an autosomal dominant fashion, although there are exceptions, and can cause a variety of neurological syndromes. Typically, symptoms begin relatively early in life and are paroxysmal or episodic, although a fixed deficit may develop with time. These attacks or paroxysms are often precipitated by various triggers. Stress, of some form, is a frequent trigger, whereas certain triggers are disease specific, such as heat in primary erythromelalgia (PE), or rest after exercise or a carbohydrate load in periodic paralysis. Mutations in ion channels can alter channel function such that homeostasis cannot be maintained in the presence of certain stimuli that would usually be innocuous.<sup>4</sup>

In this review, we describe the clinical characteristics and genetics of inherited channelopathies of the brain, spinal cord, peripheral nerve and muscle (see online supplemental figure S1).

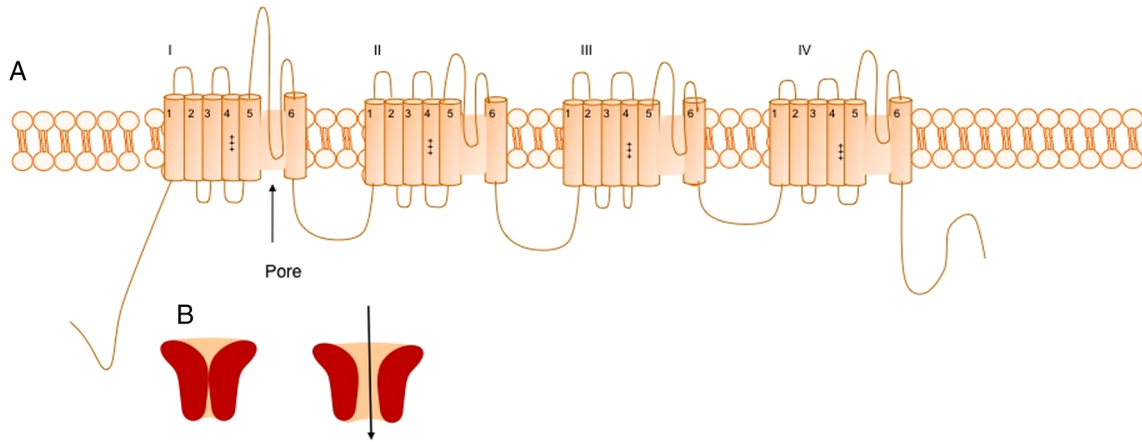


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**Figure 1** (A) Structure of the  $\alpha$  subunit of the voltage-gated sodium channel Nav1.1 encoded by SCN1A. The subunit is composed of four domains (I–IV), which are each composed of six transmembrane subunits (S1–S6)—the positive gating charges in the S4 subunit are marked as is the pore region (between S5 and S6). (B) Schematic representation of ion channel in open and closed states.

### CHANNELOPATHIES OF THE CENTRAL NERVOUS SYSTEM Epilepsy

Although rare, inherited channelopathies account for a substantial fraction of Mendelian epilepsy syndromes and can cause a variety of epilepsy types ranging from severe infantile encephalopathies to relatively benign focal seizures (table 1).

#### Channelopathies associated with epileptic encephalopathies

Early onset epileptic encephalopathies are generally severe epilepsy syndromes that often have a poor neurodevelopmental outcome.

*Severe myoclonic epilepsy of infancy*, also known as Dravet syndrome, manifests as intractable seizures that begin in the first year of life associated with developmental regression and cognitive impairment.<sup>5–6</sup> Missense or nonsense mutations in the SCN1A gene which encodes the pore-forming unit of the fast sodium channel Nav1.1 are present in over 80% of cases and are typically de novo, leading to haploinsufficiency.<sup>7–8</sup> More rarely, mutations in other genes including SCN1B and SCN2A have been found, as well as mutations in the GABA<sub>A</sub> receptor subunit gene GABRG2.<sup>9–11</sup> For some time, it was not understood how a mutation in a sodium channel leading to haploinsufficiency and reduced function could cause hyperexcitability. However, it was subsequently found that Nav1.1 channels have an important role in GABAergic inhibitory neurons, thus loss of function of these channels leads to hypoexcitability of inhibitory networks and consequently hyperexcitability of neuronal networks and in turn, epilepsy.<sup>12</sup>

SCN2A mutations have also been associated with other infantile encephalopathies including *infantile spasms*, *acute encephalitis with refractory repetitive partial seizures*, *Ohtahara syndrome and recurrent encephalopathy*.<sup>13–14</sup> *Intractable childhood epilepsy with generalised tonic-clinic seizures* is a similar disorder to Dravet syndrome and is also associated with mutations in SCN1A.<sup>15</sup> Recently, mutations of GABRA1, GABRB2 and GABRB3 were associated with infantile spasms and Lennox-Gastaut syndrome.<sup>16–17</sup>

*Migrating partial seizures of infancy* is a rare infantile encephalopathy that presents with focal seizures in the first 6 months of life, associated with acquired microcephaly and developmental stagnation or delay. This condition is genetically heterogeneous, with mutations in the KCNT1 gene that codes for a sodium-activated potassium channel and mutations in SCN1A both described.<sup>18–19</sup>

Mutations in SCN8A as well as KCNQ2 have been associated with severe epileptic encephalopathies.<sup>20–22</sup> Some cases of DEND syndrome, (developmental delay, epilepsy and neonatal diabetes) are caused by mutations in KCNJ11 which encodes the Kir 6.2 subunit of the ATP-sensitive potassium channel.<sup>23–24</sup>

#### Generalised epilepsy syndromes

*Generalised epilepsy with febrile seizures plus* is a genetically and clinically heterogeneous familial epilepsy syndrome.<sup>25</sup> Individuals develop febrile seizures early in life that persist beyond the age of 6 years. Numerous different genes have been implicated; namely the sodium channel genes SCN1A, SCN1B, SCN2A and the GABA<sub>A</sub> receptor subunit genes GABRG2 and GABRD.<sup>26–30</sup>

*Benign familial neonatal infantile seizures* is an epilepsy syndrome characterised by sudden onset and subsequent remission of seizures in infancy.<sup>31–32</sup> It is caused by missense mutations in the SCN2A gene.<sup>8</sup> *Benign familial neonatal convulsions* (BFNC) is a similar syndrome characterised by brief seizures, occurring on the second or third day after birth that usually terminate within 6 weeks with normal neurological development.<sup>33–34</sup> It can be caused by loss of function mutations in two potassium channel genes, KCNQ2 and KCNQ3, which code for the potassium channel subunits K<sub>V</sub>7.2 and 7.3, respectively.<sup>35–38</sup> Proteins encoded by these genes co-assemble to form a slowly activating and deactivating potassium channel that plays a critical role in regulating the excitability of neurons.<sup>39</sup>

A syndrome of *generalised epilepsy with paroxysmal movement disorders* has been shown to be caused in one kindred by a dominant missense mutation in the calcium-activated potassium channel gene KCNMA1.<sup>40</sup>

*Absence epilepsy* has been reported in association with mutations in a number of different genes that code for ion channels. Variants in CACNA1H which codes for the  $\alpha$ 1H pore-forming subunit of T-type calcium channels have been reported, in a subset of patients with childhood absence epilepsy.<sup>41</sup> However, mutations have not been found to fully segregate with disease, and the significance of these variants remains unclear.<sup>42</sup> Missense mutations of GABRA1, GABRA6, GABARB3 and GABARG2 which encode various GABA<sub>A</sub> receptor subunits have also been implicated in childhood absence epilepsy.<sup>43–45</sup> Missense mutations of GABRA1 and GABRD have been described in familial *juvenile myoclonic epilepsy*.<sup>30–46</sup> Likewise,

**Table 1** Epilepsy syndromes caused by inherited mutations in ion channel genes

Channel	Gene	Channel	Epilepsy syndrome(s)
Sodium	SCN1A	$\alpha$ subunit of $\text{Na}_v1.1$	Severe myoclonic epilepsy of infancy (SMEI) Intractable epilepsy with generalised tonic-clonic seizures (IEGTC) Migrating partial seizures of infancy (MPSI) Generalised epilepsy with febrile seizures (GEFS+)
	SCN1B	$\beta$ subunit of $\text{Na}_v1.1$	SMEI GEFS+
	SCN2A	$\alpha 2$ subunit of $\text{Na}_v1.2$	SMEI Ohtahara syndrome Benign familial neonatal infantile seizures (BFNIS) West syndrome Infantile spasms GEFS+
	SCN3A	$\alpha 3$ of $\text{Na}_v1.3$	Partial epilepsy
	SCN8A	$\alpha 8$ subunit of $\text{Na}_v1.6$	Infantile epileptic encephalopathy
Potassium	KCNQ2	$\text{K}_v7.2$	Benign familial neonatal convulsions Infantile encephalopathy Myokymia associated with neonatal or early infantile epilepsy Benign familial neonatal convulsions Generalised epilepsy with paroxysmal movement disorder
	KCNQ3	$\text{K}_v7.3$	
	KCNMA1	Calcium-activated potassium BK (Big Potassium) channel	
	KCNA1	$\text{K}_v1.1$	Epilepsy with episodic ataxia
	KCNA2	$\text{K}_v1.2$	Myoclonic epilepsy and ataxia
Calcium	KCNJII	Kir6.2	Developmental delay, epilepsy and neonatal diabetes mellitus (DEND syndrome)
	KCNT1	Sodium-activated potassium channel	MPSI
	CACNA1H	$\alpha$ subunit of t-type calcium channels	Childhood absence epilepsy
	CACNA1A	$\text{Ca}_v2.1$ channel $\alpha$ subunit	Episodic ataxia and childhood absence epilepsy
	CHRNA4, CHRN2 CHRNA2	Subunits of nicotinic AChR receptor	Autosomal dominant familial nocturnal frontal lobe epilepsy
Acetylcholine receptor (AChR)			
GABA	GABRA1	$\alpha$ subunit of GABA receptor	Childhood absence epilepsy Idiopathic generalised epilepsy (IGE) Juvenile myoclonic epilepsy (JME) Infantile spasms, Lennox-Gastaut Absence epilepsy Infantile spasms, Lennox-Gastaut
	GABRB2	B2 subunit of the GABA receptor	
	GABRB3	$\beta 3$ subunit of GABA receptor	
	GABRD	$\delta$ subunit of GABA receptor	GEFS+
	GABRG2	$\gamma 2$ subunit of GABA receptor	JME GEFS+ SMEI Childhood absence epilepsy IGE

mutations in GABRA1 and GABRG2 have been associated with idiopathic generalised epilepsy (IGE).<sup>47</sup>

Recently exome sequencing revealed a mutation in KCNA2 which encodes the potassium voltage-gated channel subfamily A member 2 in a young boy who presented in infancy with ataxia and myoclonic epilepsy.<sup>48</sup>

### Focal epilepsy syndromes

*Autosomal dominant nocturnal frontal lobe epilepsy* (ADNFLE) is a rare syndrome characterised by frequent short-lived motor seizures that typically occur during sleep or on waking.<sup>33 49 50</sup> Mutations in three genes encoding subunits of the nicotinic acetylcholine receptor (AChR), CHRNA4, CHRN2 CHRNA2, have been described in ADNFLE.<sup>49–56</sup> Most mutations of the AChR channel gene are located in the pore-forming domain and are associated with a gain of function effect.<sup>57 58</sup>

A missense mutation in SCN3A, which encodes the  $\alpha$  subunit of  $\text{Na}_v1.3$ , has been described in one patient with *complex partial seizures*. Functional analysis showed that the mutated channel results in prolonged action potentials in neurons expressing  $\text{Na}_v1.3$ .<sup>59</sup>

### Epileptic channelopathies: remaining questions

Epilepsy is a very common condition but monogenic channelopathies only account for a small fraction of the epilepsy seen in clinical practice. Although most epilepsies are not inherited in a Mendelian fashion, it is estimated that about 70% of an individual's risk of developing a disorder such as epilepsy is accounted for by genetic risk factors.<sup>60</sup>

Large-scale exome screening for ion channel variants in epilepsy has led to the identification of mutations/targets in genes that were previously unexpected to have a role in epilepsy. Single nucleotide polymorphisms in the chloride channel genes CLCN1 and CLCN2 were found in three times as many patients with epilepsy compared with controls.<sup>61</sup> CLCN1 was previously thought of as the 'skeletal muscle chloride channel' and was not thought to be expressed in the brain. However, molecular localisation revealed widespread presence of the CLC-1 subunit protein in the mouse and human brain, indicating that it may contribute to the regulation of brain excitability and hence may be implicated in epilepsy syndromes.<sup>61</sup> Further large-scale genetic studies are likely to lead to the identification of other candidate genes.

However, to date, exome sequencing and large-scale genotyping studies of IGE have been disappointing.<sup>62</sup> A possible explanation for the genetics of sporadic epilepsy is that many cases arise from polygenic inheritance, where several variants interact to lower the seizure threshold. Modelling the possible effect of combinations of ion channel mutations in preclinical systems to demonstrate possible pathogenicity is complex and is a major research challenge.

### Treatment of epileptic channelopathies

A complete analysis of treatment in all the various epilepsy syndromes caused by channelopathies is beyond the scope of this review. It is clear however that increased understanding of channel dysfunction in various epilepsy syndromes can lead to an individualised approach to treatment. For example, functional work on mutations in KCNQ2 have shown that the functional changes (decreased voltage sensitivity) can be restored by retigabine, a neuronal K<sub>V</sub>7 activator.<sup>63</sup> It has also been recognised for some time that medications that block sodium channel function can worsen seizures in SMEI.<sup>8</sup> With further research, there is potential for precision medicine in which drugs target specific channels or even target the mechanism by which a channel becomes dysfunctional.

### Cerebellar dysfunction and ataxia

Mutations in ion channels can be associated with both episodic and progressive ataxia syndromes—namely the episodic ataxia syndromes and the spinocerebellar ataxias (SCAs; see online supplemental table S2).

### Episodic ataxias

There are two main forms of episodic ataxia—EA1 and EA2. Both are dominantly inherited. Other rarer forms have been reported in individual families.

EA1 is characterised by brief episodes of ataxia that last seconds to minutes. The attacks begin in early childhood and can be provoked by startle, vigorous activity, illness, hunger and emotion.<sup>64 65</sup> Cerebellar function is normal in between attacks, but there may be persistent neuromyotonia of skeletal muscles which can be confirmed on electromyography (EMG).<sup>65 66</sup> There is an increased incidence of epilepsy associated with EA1<sup>64 67 68</sup> and there also have been reports of an increased risk of hearing impairment.<sup>64</sup> Recently, it has been found that up to 20% of patients accumulate a persistent cerebellar syndrome.<sup>65</sup> EA1 is caused by heterozygous, usually missense mutations in the neuronal voltage-gated delayed rectifier potassium channel (K<sub>V</sub>1.1) gene KCNA1.<sup>64 69</sup> K<sub>V</sub>1.1 channels are fast potassium channels widely expressed in the central nervous system and in peripheral nerve where they regulate axonal excitability.<sup>70</sup> Different EA1-associated mutations of KCNA1 affect channel function via diverse effects.<sup>68 71</sup> Non-invasive excitability studies on motor nerves in patients with EA1 can detect changes specific to loss of fast potassium channel function in vivo with high sensitivity and specificity.<sup>72</sup> Recently, a novel phenotype characterised by long-lasting attacks of jerking muscle contractions associated with hyperthermia, migraine and a short sleep phenotype was described in a patient with a single nucleotide change in KCNA1.<sup>73</sup>

EA2 also presents with episodes of ataxia but these attacks typically last longer than in EA1, lasting hours to days.<sup>74</sup> Approximately 30–50% of patients develop a mild progressive cerebellar ataxia and more than half report migrainous symptoms.<sup>74 75</sup> One kindred with episodic ataxia has been shown to also have absence epilepsy and dystonia has also been

reported.<sup>76 77</sup> EA2 is caused by non-sense, frame shift, splice site and missense mutations in the CACNA1A gene, which encodes the pore-forming  $\alpha$ 1A subunit of Ca<sub>v</sub>2.1—the P/Q-type calcium channel.<sup>78</sup> P/Q-type calcium channels are widely expressed at synapses throughout the central and peripheral nervous systems, and have an important role in triggering neurotransmitter release.<sup>79</sup> Functional analysis has revealed different effects of EA2 mutations including altered channel function with reduced calcium current as well as effects on protein folding and trafficking.<sup>80–82</sup>

### Treatment of episodic ataxia

Acetazolamide is often effective in EA2 and can be tried in EA1, although in our experience it is less effective in EA1.<sup>83</sup> 4- Aminopyridine, a potassium channel blocker, has also been reported in a double-blind randomised trial to have a prophylactic effect on ataxia in EA2.<sup>84</sup> The mechanism of action is incompletely understood, but in animal studies, it was shown to restore the diminished precision of pacemaking in Purkinje cells of EA2 mutant mice by prolonging the duration of the action potential.<sup>85</sup>

### Spinocerebellar ataxias

At least three different ion channel genes have been implicated in various forms of SCA including the calcium channel gene CACNA1A and two potassium channel genes, KCNC3 and KCND3. In contrast to many of the other inherited channelopathies, the symptoms of cerebellar dysfunction in SCAs seem to be predominantly progressive, rather than episodic.

SCA6 is allelic with EA2 and FHM type 1 and is caused by expansions of the CAG repeat sequence in the 3' end of CACNA1A.<sup>86</sup> This is a late onset progressive cerebellar syndrome. Extracerebellar features are less prominent than in other forms of SCA.<sup>87</sup> The pathogenic mechanism of the polyglutamine repeat expansion in SCA6 is poorly understood. The basic function of the P/Q channels are not affected in SCA6 knock in mice, suggesting that the pathogenesis is related to an accumulation of mutant Ca<sub>v</sub>2.1 channels.<sup>88</sup>

Some patients with EA2 have also been found to have small CAG expansions in CACNA1A, thus leading to suggestions that SCA6 and EA2 are a clinical continuum.<sup>89</sup> Recently, mutations in CACNA1A have been reported in three patients with paroxysmal tonic upgaze in association with motor and language delay and cerebellar ataxia, thus widening the phenotype.<sup>90</sup>

Two voltage-gated potassium channel genes have been implicated in other forms of SCA. Missense mutations in KCNC3, which encodes K<sub>V</sub>3.3 have been found in patients with the phenotype of SCA13, which may present as a neurodevelopmental disorder in infancy or an adult onset progressive cerebellar syndrome depending on the causative mutation.<sup>91 92</sup> K<sub>V</sub>3.3 channels are expressed in the cerebellum and have an important role in fast repolarisation of neurons during high frequency repetitive firing.<sup>93</sup>

Mutations in the gene that codes for K<sub>V</sub>4.3, KCND3, have been found in patients diagnosed with SCA19 and SCA22. Most of the patients studied developed cerebellar symptoms around middle age with a variable proportion developing extracerebellar features such as cognitive impairment. Initial functional studies suggest that mutations alter trafficking of channels to the cell membrane and also reduced channel function.<sup>94 95</sup>

No specific treatments have been demonstrated to be effective in patients with progressive SCA.



## Migraine

Familial Hemiplegic Migraine (FHM) is a subtype of severe migraine inherited in an autosomal dominant fashion. Patients have severe auras that include unilateral weakness, as well as visual, somatosensory or dysphasic symptoms, typically followed or accompanied by migrainous headache.<sup>96 97</sup> FHM is genetically heterogeneous and is classified into three types<sup>98</sup> (see online supplemental table S3).

*FHM1* accounts for 75% of genetically confirmed cases and is caused by missense mutations in *CACNA1A*, the same gene that is implicated in EA2 and SCA6.<sup>99</sup> Functional expression studies have shown that FHM mutations result in various gain of function effects, including increased  $\text{Ca}_v2.1$  current density in cerebellar neurons and enhanced neurotransmitter release.<sup>96</sup> *FHM2* is caused by loss of function mutations in the *ATP1A2* gene. This gene encodes the  $\alpha 2$  subunit of  $\text{Na}^+/\text{K}^+$  pumps, which contribute to maintaining transmembrane ion gradients.<sup>100</sup> *FHM3* is associated with heterozygous mutations in the sodium channel gene *SCN1A*.<sup>101</sup> This is the same gene that is associated with seizure disorders. Why some mutations manifest as migraine while others as epilepsy is not understood.

Knowledge of the molecular mechanisms of the different forms of FHM have led to the suggestion that they can be treated with acetazolamide or other agents that target ion channels such as verapamil and flunarizine, which act on some calcium channels, and lamotrigine, which acts on both sodium and calcium channels.<sup>102 103</sup> However, randomised evidence for the efficacy of any particular treatment is lacking.<sup>98</sup>

## Familial hyperekplexia

*Familial hyperekplexia*—also known as hereditary startle disease—is characterised by neonatal hypertonia, hyper-reflexia, myoclonic jerks and an exaggerated startle response to sensory stimuli. The hypertonicity and hyper-reflexia typically improve during infancy but the exaggerated startle response continues into adulthood.<sup>104</sup>

Mutations in *GLRA1* account for 80% of hereditary hyperekplexia and are most commonly inherited in an autosomal dominant fashion, although recessive and compound heterozygous cases also occur.<sup>104</sup> Missense, nonsense, frameshift and splice site mutations, and large deletions have all been described.<sup>50 105</sup> *GLRA1* encodes the  $\alpha$  subunit of the postsynaptic glycine receptor chloride channel which mediates fast inhibition in the brainstem and spinal cord.<sup>104</sup> Mutations impair glycine receptor function, resulting in increased excitability in pontomedullary reticular neurons and abnormal spinal reciprocal inhibition.<sup>104 106</sup> Hyperekplexia can also be caused by mutations in the *GRLB* gene, which encodes the  $\beta$  subunit of the glycine receptor, and in *SLC6A5*, which encodes the presynaptic glycine transporter type 2.<sup>107–110</sup> Clonazepam is the drug of choice as it enhances GABA<sub>A</sub> receptor-mediated inhibition and was shown in a randomised trial to significantly reduce startle activity.<sup>104 111</sup>

## Inherited channelopathies of peripheral nerves

Ion channel disorders have implicated in various inherited diseases of peripheral nerve including pain syndromes and neuropathies (see online supplemental table S4).

## Pain syndromes

Gene mutations in ion channels have been associated with increased pain perception whereas other mutations cause insensitivity to pain. Both ligand-gated and voltage-gated ion

channels have a pivotal role in the detection and transmission of stimuli from nociceptors.

Point mutations in the sodium channel gene *SCN9A* which codes for the  $\alpha$  subunit of  $\text{Na}_v1.7$  channels have been associated with two different pain syndromes associated with gain of function—*primary erythromelalgia* and *paroxysmal extreme pain disorder*.<sup>112</sup> Nonsense mutations in the same gene have been associated with a syndrome causing *congenital insensitivity to pain*.  $\text{Na}_v1.7$  channels are expressed in dorsal root ganglion (DRG) neurons where they regulate excitability of pain fibres. A different phenotype resulting from nonsense mutations in *SCN9A* was described in two Japanese kindreds—*hereditary sensory and autonomic neuropathy type IID*.<sup>113</sup> These patients had adolescent or congenital onset of loss of pain and temperature sensation and autonomic dysfunction with evidence of reduction in sensory nerve action potentials on nerve conduction studies.

## Primary erythromelalgia

*PE* is a rare syndrome characterised by intense burning pain, usually of the extremities, with marked erythema and increased skin temperature.<sup>114</sup> Symptoms usually begin in the first two decades. Precipitating factors for pain include heat, exercise, tight clothing and certain foods. The pain is initially episodic but sometimes can become constant with fluctuations.<sup>115</sup> Mutations in the gene *SCN9A* which encodes the  $\text{Na}_v1.7$  sodium channel are typically inherited in an autosomal dominant fashion and lower the voltage threshold for a sodium current in dorsal root ganglia neurons, increasing their firing frequency in response to stimulation, slowing their activation and increasing their response to slow ramp-like stimuli.<sup>116–119</sup>

## Paroxysmal extreme pain disorder

*Paroxysmal extreme pain disorder* (PEPD) is a distinct syndrome, previously known as familial rectal pain syndrome.<sup>120</sup> The characteristic feature is severe frequently visceral pain that affects various parts of the body including the rectum and genitalia, although the face and limbs can also be involved.<sup>121</sup> The pain can be associated with autonomic features including flushing, lacrimation, rhinorrhea and tonic attacks with apnoea and bradycardia.<sup>122 123</sup> Physical factors such as defecation and eating can trigger attacks, as can emotion.<sup>115</sup>

In contrast to gain of function mutations in *PE*, functional studies have shown that *SCN9A* mutations in PEPD impair the fast inactivation of sodium channels leading to a persistent sodium current.<sup>121</sup>

## Treatment of painful channelopathies

Treatment of the painful channelopathies can be difficult, as patients do not respond to standard analgesics. Oral mexiletine and topical lidocaine, both sodium channel blockers can be effective in *PE*.<sup>124</sup> Mexiletine is a non-selective sodium channel blocker and has been shown to have a normalising effect on the hyperpolarised channels seen in gain of function  $\text{Na}_v1.7$  mutations.<sup>125</sup> Patients often also use physical measures such as immersing feet in cold water. Patients with PEPD may obtain relief from carbamazepine which can help block the abnormal persistent sodium currents due to impaired inactivation of  $\text{Na}_v1.7$  seen in this disorder.<sup>121</sup>

## Congenital insensitivity to pain

In contrast to the above disorders which are autosomal dominant, recessive, loss of function mutations of *SCN9A* result in *congenital insensitivity to pain*.<sup>126</sup> Patients develop repeated

painless fractures and injuries, which although painless can be crippling.<sup>126 127</sup> A mutation in the gene SCN11A which encodes Na<sub>v</sub>1.9, a voltage-gated sodium channel primarily expressed in nociceptors, has also been found in patients with congenital insensitivity to pain; however in contrast to loss of function SCN9A mutations in this condition, SCN11A mutations are associated with a gain of function with sustained depolarisation of nociceptors impeding the generation of action potentials.<sup>128</sup>

### Small fibre neuropathy

The above disorders are rare diseases but recently gain of function missense variants in SCN9A that encodes the Na<sub>v</sub>1.7 channel have been found in approximately 30% of a cohort of patients with *idiopathic small fibre neuropathy*.<sup>129</sup> Mutations in the SCN10A and SCN11A genes which encode Na<sub>v</sub>1.8 and Na<sub>v</sub>1.9, respectively, have also been described in a small number of patients with *painful peripheral neuropathy*, suggesting that inherited channelopathies may play a role in commonly encountered clinical syndromes.<sup>130 131</sup>

### Familial episodic pain syndrome

A different channel type is affected in *familial episodic pain syndrome* (FEPS), a rare dominantly inherited disorder<sup>132</sup> characterised by episodes of severe pain, triggered by cold and hunger, localised principally to the upper body. It is caused by a gain of function missense mutation in the TRPA1 gene, which encodes TRPV1. TRPA1 is part of a family of transient receptor potential (TRP) channels, a large superfamily of cation channels. TRPA1 is expressed in primary afferent nociceptors and plays an important role in response to environmental irritants.<sup>133</sup> A distinct type of FEPS has been described in two large Chinese kindreds who were found to have mutations in SCN11A.<sup>134</sup> Mutations in FEPS cause a gain of function with hyperexcitability of the cells of the DRG.<sup>115</sup>

### Motor and sensory neuropathies

Several inherited neuropathies that present mainly with motor dysfunction are known to be due to ion channel dysfunction.

Three allelic disorders, *Charcot-Marie-Tooth disease type IIC* (HSMNIIIC), *scapuloperoneal spinal muscular atrophy* (SPSMA) and *congenital distal spinal muscular atrophy* (SMA) are caused by mutations in another class of TRP channel—the TRPV4 channels.<sup>135 136</sup> HSMNIIIC is an autosomal dominant axonal neuropathy characterised by progressive distal limb weakness and weakness of the diaphragm laryngeal muscles and vocal cords.<sup>137</sup> SPSMA manifests as progressive weakness of scapular and peroneal muscles, laryngeal palsy and skeletal abnormalities.<sup>138</sup> Congenital distal SMA affects lower motor neurons with variable disease severity ranging from congenital weakness restricted to the distal lower limbs to more severe forms with involvement of pelvic girdle and trunk muscles and arthrogryposis.<sup>135</sup> TRPV4 encodes a channel that is broadly permeable to cations including calcium, and can be activated by mechanical stimuli, heat and endogenous and synthetic agonists. TRPV4 is widely expressed in the brain and spinal cord.<sup>136</sup> There is a lack of consensus regarding the disease mechanism of TRPV mutations causing neurological disease with both gain of function and loss of function effects reported.<sup>137 139 140</sup>

### Peripheral nerve hyperexcitability

*Peripheral nerve hyperexcitability* comprises a heterogeneous group of diseases characterised by spontaneous and continuous muscle activity (myokymia), muscle cramps, stiffness and

fasciculations.<sup>141</sup> It is commonly seen as part of the EA1 phenotype resulting from mutations in K<sub>v</sub>1.1 potassium channels.<sup>69 142</sup> Mutations in the K<sub>v</sub>7.2 potassium channel gene (KCNQ2) associated with BFNC have also been found to cause a genetic form of peripheral nerve hyperexcitability.<sup>141 143</sup>

### Congenital myasthenic syndromes

*Congenital myasthenic syndromes* (CMS) are a heterogeneous group of genetic disorders that affect the neuromuscular junction. They are typically inherited in a recessive fashion and can be caused by mutations in proteins of the neuromuscular junction that are presynaptic, synaptic or postsynaptic. Mutations in over 15 different genes have been identified to date.<sup>144</sup> Of relevance to inherited channelopathies, the most common type of CMS is caused by mutations in various genes encoding the subunits of muscle AChRs. Mutations in any one of the adult subunits of the AChR channel can result in deficiency or kinetic abnormality of the AChR<sup>145</sup> (see online supplemental table S5).

Recessive mutations of CHRNA1, CHRNB1, CHRND and CHRNE, which code for α1, β1, δ and ε subunits, respectively, have all been implicated in *primary AChR deficiency syndromes*. Mutations in the ε (epsilon) subunit are most frequently encountered.<sup>144</sup> Most patients with AChR deficiency syndromes present with feeding problems, ptosis and ophthalmoplegia in early infancy. Patients tend to respond well to pyridostigmine and/or 3, 4-diaminopyridine (DAP), a potassium channel blocker that prolongs the presynaptic action potential, thereby enhancing ACh release.<sup>144 145</sup>

Other mutations can affect the kinetics of AChRs. *Slow channel syndrome* is the only dominantly inherited CMS, and can be caused by mutations in any of the AChR subunit genes. The underlying pathology is a gain of function with sustained activation of the AChR with either delayed channel closure or enhanced ACh affinity. This prolonged channel opening in turn can result in an end-plate myopathy.<sup>146</sup> Symptoms usually present in childhood with delayed motor milestones and ocular signs such as ptosis and ophthalmoplegia. It is important to recognise this syndrome as conventional treatment with pyridostigmine or 3, 4-DAP can worsen symptoms. Treatment is with floxetine or quinidine, both act as open channel blockers.<sup>147</sup>

*Fast channel syndrome* is a rare and severe form of CMS, in which AChRs open for a shorter time than normal. It is associated with loss of function mutations of AChR α1, δ and ε subunits. Children are typically affected from birth with respiratory failure, feeding difficulties with ptosis and ophthalmoplegia. Pyridostigmine and 3, 4-DAP may be beneficial.<sup>144 146</sup>

### Skeletal muscle channelopathies

The skeletal muscle channelopathies are a heterogeneous group of disorders whose clinical manifestations range from flaccid paralysis to myotonia. They are divided into the non-dystrophic myotonias (NDMs) and the periodic paralyses and are caused by mutations in skeletal muscle ion channels that affect muscle excitability (see online supplemental table S6).

### Non-dystrophic myotonias

The NDMs are a group of skeletal muscle channelopathies that present with myotonia (delayed muscle relaxation following voluntary contraction) without systemic features. This group of conditions includes myotonia congenita (MC), paramyotonia congenita (PMC) and the sodium channel myotonias (SCMs).

### Myotonia congenita

MC is the commonest of the skeletal muscle channelopathies<sup>148</sup> and can be inherited in an autosomal dominant (Thomsen disease) or recessive fashion (Becker disease). It is characterised by muscle stiffness that predominantly affects the limbs. Symptoms may be worsened by rest, infection or stress, and can be accompanied by muscle hypertrophy. Patients often exhibit a warm-up phenomenon when muscle stiffness improves with repeated activity. Patients with recessive MC may also have transient weakness on the initiation of a movement.

MC is caused by mutations in the skeletal muscle chloride channel CLCN1, which encodes the channel CIC-1.<sup>149</sup> CIC-1 underlies the majority of the resting conductance of skeletal muscle. Functional expression studies show that pathogenic mutations can reduce the macroscopic chloride current, predisposing to muscle fibre depolarisation and after-discharges.<sup>150</sup> Typically, nonsense, missense and frame shift mutations that do not affect the functional properties for the wild-type subunits in the channel dimer are recessively inherited. Missense mutations that shift the voltage dependence of activation out of the physiological range are often dominantly inherited.<sup>151–154</sup> Recessive mutations generally result in more severe symptoms. Recently, it was found that up to 6% of patients with a recessive family history but only one mutation in CLCN1 carry whole exons or duplications in the CLCN1 gene, thus revealing a novel genetic cause for recessive MC.<sup>155</sup>

### PMC and SCMs

Two other groups of disorders characterised clinically by myotonia are associated with sodium channel mutations—PMC and the SCMs.

PMC presents as muscle stiffness early in life. However, in contrast with MC, symptoms are worsened by exertion (paramyotonia) and cold.<sup>156</sup> PMC is also associated with episodes of weakness, which can last for hours or days. In contrast, SCMs are a subgroup of myotonic disorders that are characterised clinically by pure myotonia without weakness. The severity of SCMs is highly variable varying from a severe form with onset in infancy to mild forms that only cause isolated eyelid myotonia.<sup>157</sup> The infantile forms can be associated with potentially fatal laryngospasm highlighting the importance of genetic counselling in affected adult patients with these disorders.<sup>156 157</sup> The presence of eyelid closure myotonia is specific for mutations in SCN4A and can help to clinically differentiate this disorder from MC.<sup>158</sup>

Both PMC and the SCMs are caused by dominantly inherited mutations in the SCN4A, which encodes the skeletal muscle voltage-gated sodium channel, Na<sub>v</sub>1.4. The same mutation has been shown to cause either condition in different pedigrees.<sup>159</sup> SCN4A mutations cause a gain of function effect on the encoded  $\alpha 4$  subunit of the muscle sodium channel Na<sub>v</sub>1.4. They disrupt fast inactivation or cause a hyperpolarising shift in the voltage dependence of activation.<sup>150</sup> Recently, a small group of patients with myotonia with heterozygous SCN4A mutations and single CLCN1 mutations were described, widening the genetic spectrum.<sup>160</sup>

Treatment of myotonia has improved considerably in recent years. In vitro and animal studies have shown that the sodium channel blocker mexiletine reduces muscle fibre excitability caused by common NDM mutation.<sup>161 162</sup> A recent double-blind, placebo-controlled crossover study of patients with NDM confirmed its efficacy.<sup>163</sup> Acetazolamide, which has been shown to stabilise membrane excitability through a direct effect on the

chloride channel, has also been used and is particularly helpful if there are concerns regarding the proarrhythmogenic side effects of mexiletine.<sup>164 165</sup> Experimental studies have suggested that lacosamide and ranolazine, drugs that are used for epilepsy and angina respectively, enhance slow inactivation of sodium channels and may be an alternative to mexiletine in patients with MC.<sup>166</sup> Other options include carbamazepine and phenytoin, although good-quality evidence is lacking.

### Periodic paralyses

The inherited *periodic paralyses* are a group of disorders comprised of three conditions; *hypokalaemic periodic paralysis* (Hypo PP), *hyperkalaemic periodic paralysis* (Hyper PP) and *Andersen-Tawil syndrome* (ATS).

### Hypokalaemic periodic paralysis

*Hypo PP* is the most common form of periodic paralysis and is characterised by episodes of flaccid muscle weakness that occur in association with a low serum potassium level. Attacks last hours to days and typically affect the limbs; respiratory involvement is rare. Precipitants include carbohydrate meals and rest after exercise.<sup>156</sup> With time, the frequency of attacks may diminish and a fixed proximal weakness may develop.<sup>167</sup> *Hypo PP* is inherited in an autosomal dominant fashion but has a reduced penetrance in women, a feature seen in several muscle channelopathies. Causal mutations were first identified in CACNA1S, which encodes the  $\alpha 1S$  subunit of the skeletal muscle calcium channel Ca<sub>v</sub>1.1.<sup>168 169</sup> These account for approximately 80% of cases. Mutations in the sodium channel gene SCN4A, also associated with the SCMs, account for approximately 10% of cases but up to 10–20% of cases remain genetically undefined.<sup>170</sup>

The overwhelming majority of mutations in *Hypo PP*, whether in calcium or in sodium channels, occur in the voltage-sensing region of the channel.<sup>171</sup> How these lead to attacks of paralysis has been a puzzle for many years. Recently, it has emerged that the mutations open an abnormal cation leak pathway through the voltage sensor itself, separate from the main pore of the channel—the gating pore current.<sup>172 173</sup> The association of attacks with hypokalaemia is thought to reflect the tendency for the inwardly rectifying potassium channel Kir2.1 to fail to conduct when the extracellular potassium concentration is low.<sup>173–175</sup>

Recently, bumetanide, an inhibitor of the Na-K-2Cl co-transporter was shown to prevent this paradoxical depolarisation in hypokalaemic conditions in animal studies and was also shown to prevent attacks in mouse models of sodium and calcium channel mutations.<sup>173 176</sup> Clinical trials of bumetanide for *Hypo PP* are starting.

### Hyperkalaemic periodic paralysis

*Hyper PP* is characterised by episodes of muscle weakness in association with elevated serum potassium. In addition to paralysis, myotonia may also be a feature.<sup>156 170</sup> The attacks of paralysis are typically shorter than *Hypo PP* lasting minutes to hours but can become prolonged with age, lasting up to 2 days.<sup>156 170 177</sup> *Hyper PP* is caused by mutations in the sodium channel gene SCN4A. The mutations in *Hyper PP* tend to impair inactivation of the Na<sub>v</sub>1.4 sodium channel, leading to persistent sodium influx, depolarisation and inexcitability.<sup>178 179</sup> Some *Hyper PP* mutations have also been shown to shift the voltage dependence of activation in the negative direction, allowing channels to open sooner.<sup>180</sup> The association with hyperkalaemia probably reflects in part a positive feedback loop,



whereby depolarisation leads to potassium efflux, which results in a further depolarisation.<sup>181</sup>

### Andersen-Tawil syndrome

ATS is a rare disorder characterised by a triad of periodic paralysis, cardiac defects and skeletal abnormalities, although not every patient will have all three features.<sup>182</sup> The periodic paralysis is typically associated with low levels of potassium but can be associated with normokalaemia or hyperkalaemia. Cardiac abnormalities seen include enlarged U waves, a prolonged QUC interval and ventricular arrhythmias.<sup>183</sup> Cardiac arrest occurs in approximately 10% of patients with ATS and cardiac screening is mandatory.<sup>184–185</sup> Distinctive facial features seen in ATS include micrognathia, low set ears, hypertelorism, clindactyly and syndactyly.<sup>185</sup> ATS is caused by mutations in the coding exon 2 of the KCNJ2 gene which encodes the inward rectifying potassium channel Kir2.1.<sup>186</sup> These channels contribute to the resting membrane potential in the heart, brain and skeletal muscle.

No current through Kir2.1 channels is seen when mutant KCNJ2 channels are expressed in vitro. Co-expression of wild-type channels with mutant channels results in reduction in inward rectifying currents indicating a dominant negative effect of the mutation.<sup>186–187</sup> Up to 10% or 20% of patients will not have a mutations in KCNJ2.<sup>184</sup> Recently, mutations in KCNJ5, the gene encoding Kir 3.4 was found to cause ATS in a patient with typical muscle and cardiac features but without dysmorphism.<sup>188</sup>

### Treatment of the periodic paralyses

Management of periodic paralysis rests on trigger avoidance. Oral potassium can speed attack resolution in Hypo PP whereas ingestion of sweets and mild exercise can hasten attack resolution in Hyper PP. Inhaled salbutamol has also been shown to be effective in treating attacks of Hyper PP.<sup>189</sup> Occasionally, prophylactic treatment is required. Acetazolamide is often a first-line treatment for both Hyper PP and Hypo PP. It has been shown to increase muscle strength and endurance in a small randomised controlled trial.<sup>190</sup> Dichlorphenamide was shown to reduce attack frequency in a double-blind, placebo-controlled trial in Hyper PP and Hypo PP.<sup>191</sup> An additional option in Hypo PP includes potassium-sparing diuretics such as spironolactone or amiloride.<sup>156</sup> Pinacidil, a potassium channel agonist, was found to improve muscle strength in a small randomised controlled trial.<sup>192</sup>

### Electrophysiology in skeletal muscle channelopathies

The functional consequences of ion channel mutations in skeletal muscle can be examined by electrophysiology. Myotonia on needle EMG is seen in all forms of NDM but severity can vary and the duration of myotonic discharges on EMG can be used to distinguish sodium and chloride channel myotonias.<sup>193–194</sup> Measurement of compound action potential amplitudes before and after exercise, the short and long exercise test, helps to distinguish between the different skeletal muscle channelopathies.

### MRI in skeletal muscle channelopathies

MRI has recently been developed for diagnosis and monitoring use in skeletal muscle channelopathies. A hyperintense central stripe in the medial gastrocnemius muscle appears to be specific for NDM, particularly MC.<sup>195</sup> Fatty infiltration of muscles can also be seen on MRI which is consistent with the clinical observation of fixed weakness in some patients over time.<sup>177</sup> Patients with Hypo PP who have permanent weakness are also found to

have fatty muscle replacement on MRI. An increase in <sup>23</sup>Na<sup>+</sup> MRI signal intensity can be seen in patients with Hypo PP suggesting muscle oedema which can be reduced by acetazolamide treatment, indicating that muscle imaging is likely to play an increasing role in therapy monitoring in the future.<sup>175</sup>

### Thyrotoxic periodic paralysis

Thyrotoxic periodic paralysis is a rare condition causing attacks indistinguishable from Hypo PP but in the presence of thyrotoxicosis. The disorder is most common in young Asian and Latin American men in whom 10% of thyrotoxic males develop episodic weakness.<sup>190</sup> Candidate gene sequencing has revealed mutations in KCNJ18 which encodes Kir 2.6, an inwardly rectifying potassium channel that is expressed in skeletal muscle and transcriptionally regulated by thyroid hormones in one-third of patients.<sup>196</sup>

### CONCLUSION

Although individually rare, the inherited channelopathies can be accurately diagnosed by careful clinical assessment and DNA-based diagnosis. An accurate diagnosis is important for genetic counselling and to direct treatment options. Recent molecular genetic advances have provided insights into pathophysiological mechanisms that are potentially relevant to more common paroxysmal disorders such as epilepsy and migraine. Ion channels are an attractive target for investigation of these common diseases with polygenic inheritance. However, to date, genetic association studies have not revealed clear mechanistic understanding, possibly because of the complexity of elucidating the effect of multiple genetic channel variation interactions. The increased use of whole genome sequencing is generating very large amounts of genetic data including variations in ion channel genes. However, extensive biophysical characterisation in representative model systems will be required to determine the contribution of different variants to common paroxysmal neurological diseases.

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