Ion channels and neurological disease: DNA based diagnosis is now possible, and ion channels may be important in common paroxysmal disorders

Ion channels are large transmembrane proteins which are essential for the normal function of all eukaryotic cells. They are especially important in excitable cells because they determine the membrane potential, both at rest and during firing, and also play a critical part in neurotransmitter release. Ion channels may be broadly classified into voltage gated and ligand gated, although many voltage gated channels are also affected by intracellular messengers. It is well recognised that autoimmune attack of the nicotinic acetylcholine receptor underlies acquired myasthenia gravis. Research over the past few years has, however, established that genetic defects in both ligand and voltage gated ion channels also cause some inherited neurological disorders. Collectively, these immunological and genetic conditions have become known as the neurological channelopathies. The genetic channelopathies are listed in tables 1 and 2.

The genetic advances have increased our understanding of the molecular pathogenesis of several relatively rare muscle and CNS diseases. The immediate benefits of this are an improved classification of these disorders and the availability of DNA based diagnosis. However, an important principle has also emerged: permanent ion channel dysfunction can cause a paroxysmal neurological disturbance. By extrapolation, ion channel defects are strong candidates for other paroxysmal disorders. Some of the recently established genetic channelopathies represent rare forms of more common disorders such as migraine and epilepsy. This has led to the suggestion that the genetic susceptibility known to exist in these common disorders

### Table 1 Genetic voltage gated channelopathies

<table>
<thead>
<tr>
<th>Ion channel</th>
<th>Disorder</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal muscle disorders:</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Skeletal muscle sodium channel</td>
<td>HyperPP</td>
<td>Dominant</td>
<td>SCN4A</td>
<td>17q23-25</td>
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<tr>
<td></td>
<td>PMC</td>
<td>Dominant</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>PAM</td>
<td>Dominant</td>
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</tr>
<tr>
<td></td>
<td>NormoPP</td>
<td>Dominant</td>
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</tr>
<tr>
<td>Skeletal muscle DHP sensitive calcium channel</td>
<td>HypoPP</td>
<td>Dominant</td>
<td>CACLN1A3</td>
<td>1q31-32</td>
</tr>
<tr>
<td></td>
<td>MH</td>
<td>Dominant</td>
<td></td>
<td></td>
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<tr>
<td>Skeletal muscle ryanodine calcium channel</td>
<td>MH</td>
<td>Dominant</td>
<td>RYR1</td>
<td>19q13.1</td>
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<td></td>
<td>Central core disease</td>
<td>Dominant</td>
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<tr>
<td></td>
<td>Myotonia congenita</td>
<td>Dominant</td>
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<tr>
<td></td>
<td>Thomsen’s disease</td>
<td>Dominant</td>
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<td></td>
<td>Becker’s myotonia</td>
<td>Dominant</td>
<td></td>
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<tr>
<td>CNS disorders:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Brain and nerve potassium channel</td>
<td>Episodic ataxia type I with myokymia</td>
<td>Dominant</td>
<td>KCNA1</td>
<td>12p</td>
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<tr>
<td></td>
<td>Episodic ataxia type II</td>
<td>Dominant</td>
<td>CACNL1A4</td>
<td>19p13</td>
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<tr>
<td>Brain (P/Q-type) calcium channel</td>
<td>FHM</td>
<td>Recessive</td>
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</tbody>
</table>

Standard gene nomenclature is used for abbreviations. HyperPP=Hyperkalaemic periodic paralysis; HypoPP=hypokalaemic periodic paralysis; NormoPP=normokalaemic periodic paralysis; PMC=paramyotonia congenita; PAM=potassium aggravated myotonia; MH=malignant hyperthermia; FHM=familial hemiplegic migraine; SCA6=spinocerebellar ataxia type 6.

### Table 2 Genetic ligand gated channelopathies

<table>
<thead>
<tr>
<th>Ion channel</th>
<th>Disorder</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuro muscular disorder:</td>
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<tr>
<td>Nicotinic acetylcholine receptor</td>
<td>Congenital myasthenia</td>
<td>Dominant and recessive</td>
<td>CHRNA</td>
<td>2q</td>
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<td></td>
<td></td>
<td>CHRN</td>
<td></td>
</tr>
<tr>
<td>CNS disorder:</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Glycine receptor</td>
<td>Hyperekplexia</td>
<td>Dominant</td>
<td>GLRA-1</td>
<td>5q</td>
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<tr>
<td>Neuronal nicotinic receptor</td>
<td>ADNFLE</td>
<td>Dominant</td>
<td>CHRNA4</td>
<td>20q13.2-13.3</td>
</tr>
</tbody>
</table>

Standard gene nomenclature is used for abbreviations. ADNFLE=Autosomal dominant nocturnal frontal lobe epilepsy.
may be mediated through variations in ion channel function.

In this article we review some of the many recently established genetic neurological channelopathies in which DNA based diagnosis is becoming available. We do not discuss the congenital myasthenic syndromes or hyperekplexia. Also, we speculate on possible future channelopathies and discuss some of the evidence that ion channel dysfunction may be important in common neurological disorders.

**Skeletal muscle channelopathies**

Conventionally, the periodic paralyses would be classified separately from the myotonias. An important result of the genetic progress in this field has been to show that different mutations of the same channel can cause diseases that blur this distinction.

**THE PERIODIC PARALYSES AND PARAMYOTONIA CONGENITA**

The periodic paralyses are disorders of muscle fibre membrane excitability, which are classified on the basis of the serum potassium at or close to the onset of the attack into hyperkalaemic, normokalaemic, or hypokalaemic. During an attack, often precipitated by exercise followed by rest, the muscle fibre membrane enters a partially depolarised inexcitable state. Before molecular genetic advances, electrophysiological work had demonstrated that muscle fibres from patients with hyperkalaemic periodic paralysis (HyperPP) show defective inactivation of sodium channels. When the subunit of the voltage gated sodium channel gene in skeletal muscle was cloned, it was confirmed that mutations in this gene (SCN4A) are the cause of most cases of HyperPP. Different mutations in the same channel are also associated with paramyotonia congenita (either alone or in combination with HyperPP), and with a group of disorders which have become known as congenita (either alone or in combination with HyperPP), and which includes acetazolamide responsive hypokalaemic periodic paralysis (HypoPP). The diagnosis is usually straightforward on clinical grounds. Although DNA based diagnosis is available, it is very time consuming as over 30 point mutations have been described. Treatment with antimyotonic drugs is often needed, of which mexilitene is the drug of choice.

Cloning of the muscle sodium channel has also led to a better understanding of another previously poorly defined group of myotonic disorders. It is now clear that diseases in this group, which has been named “atypical” myotonia congenita, and which includes acetazolamide responsive myotonia, are also due to mutations in the sodium channel SCN4A. A prominent feature of the myotonia in this group is its marked exacerbation after potassium ingestion, which is its marked exacerbation after potassium ingestion, which is not a feature of the chloride channel disorders.

**MYOTONIA CONGENITA AND THE POTASSIUM AGGRAVATED MYOTONIAS**

Myotonia congenita is characterised by generalised symptomatic myotonia from a young age. This is generally milder in the rare dominant form (Thomsen’s disease) than in the much more common recessive form (Becker’s generalised myotonia). Electrophysiological experiments on skeletal muscle preparations from patients (and on the myotonic goat model of the disease) established that the resting chloride conductance of the muscle fibre membranes is reduced. As the chloride conductance plays a major part in determining the resting membrane potential, a decrease in this conductance lowers the threshold for depolarisation and therefore predisposes to myotonia.

When the human skeletal muscle chloride channel CLCN1 was cloned, both forms of myotonia congenita were found to be due to different mutations in this gene. Expression studies have shown that both dominant and recessive mutations result in decreased chloride currents. By contrast with sodium and calcium channels, the functional chloride channel is a homodimer, possibly explaining why the disease can be either dominant or recessive. The recessive mutations result in loss of function. The dominant mutations, on the other hand, may result in haploid insufficiency (50% of the normal gene product is not enough for normal chloride conductance), or have a dominant negative effect, in which mutant and wild-type subunits dimerise to result in abnormal or non-functional channels. The diagnosis is usually straightforward on clinical grounds. Although DNA based diagnosis is available, it is very time consuming as over 30 point mutations have been described. Treatment with antimyotonic drugs is often needed, of which mexilitene is the drug of choice.

**MALIGNANT HYPERTHERMIA AND CENTRAL CORE DISEASE**

Malignant hyperthermia is a rare but serious disorder, generally coming to light when otherwise healthy people undergo general anaesthesia. Exposure to triggering agents, including halogenated volatile anaesthetics and depolarising muscle relaxants, results in hyperthermia, muscle rigidity, and rhabdomyolysis. Without rapid intervention with supportive measures and dantrolene this is often fatal. Malignant hyperthermia is now known to be a disorder of regulation of skeletal muscle calcium. The triggering substances lead to an increased myoplasmic calcium concentration because of excessive release from the sarcoplasmic reticulum. Extrapolation from genetic studies on the porcine model of malignant hyperthermia...
Familial hemiplegic migraine and episodic ataxia type 2 (EA2) are allelic disorders. The causal mutations have been identified in the human ryanodine receptor gene CACNL1A4. This disorder is usually very responsive to acetazolamide, although the precise therapeutic mechanism remains uncertain. An MRS study has shown a disturbance of cerebellar pH in patients with EA2 off treatment. Initially, splice site and frame shift mutations were described in the CACNL1A4 gene in patients with EA2, implying that truncation of the protein may be important in pathogenesis. However, recently the SCA6 CAG repeat has also been described in patients with EA2. One family has, moreover, been reported in which a missense mutation in CACNL1A4 is associated with a severe progressive cerebellar ataxia in one member, whereas other members had episodic ataxia and vertigo, more suggestive of EA2. The genetic distinction between SCA6 and EA2 is thus far from clearcut.

In families with familial hemiplegic migraine patients experience headache preceded by an aura, which includes a hemiparesis lasting hours to days. The onset is usually in childhood, and interictal nystagmus, ataxia, and dysarthria may occur. Four missense mutations in CACNL1A4 have been identified. Up to 50% of families with familial hemiplegic migraine linked to CACNL1A4 exhibit mild cerebellar ataxia and have cerebellar atrophy on imaging. A recent genotype-phenotype correlation study indicates that the presence of cerebellar atrophy may be mutation specific. The same study also identified a CACNL1A4 mutation in a case of “non-hemiplegic” migraine indicating that such mutations may associate with commoner forms of migraine. Interestingly, a missense mutation in the orthologous mouse gene produces the tottering (tg) phenotype which exhibits absence seizures, motor seizures and ataxia. The frame shift and splice site mutations in EA2 are similar to the gene defects in another mouse model, the leaner mouse (tg) which is allelic to the tg mouse but more severely affected, exhibiting absence seizures, severe ataxia and premature death. Abnormalities on EEG are reported in patients with familial hemiplegic migraine and EA2 which, in the light of the findings in the mouse models, raises the question whether CACNL1A4 is relevant to epilepsy in humans.

Recently families with familial hemiplegic migraine not linked to CACNL1A4 have been shown to be linked to 1q31 at or near a different (R type) voltage gated channel α1 subunit gene. The molecular pathogenesis of disease associated with frame shift and splice site mutations of CACNL1A4, and the CAG repeat, has yet to be studied. The four known missense mutations associated with familial hemiplegic migraine have, however, been expressed. Three of the mutations were associated with altered inactivation gating, suggesting that neuronal instability plays a part in migraine attacks.

**EPISODIC ATAXIA TYPE 1**

The most diverse group of human voltage and ligand gated ion channels are the potassium channels, reflecting their early evolutionary origin. Point mutations in the human potassium channel gene KCNA1 cause the dominant disorder episodic ataxia type I (EA1). This channel is expressed widely, but especially in the cerebellum and in peripheral nerve. Patients experience brief attacks of cerebellar ataxia lasting up to minutes, which are not usually accompanied by abnormal eye signs as in EA2. There is no interictal cerebellar dysfunction, and brain imaging is normal. Stress, emotion, or sudden movement may precipitate attacks. Interictally there are continuous spontaneous repetitive discharges on EMG sometimes termed neuro-myotonia, although this is not clinically obvious. The therapeutic response in EA1 is less consistent than in EA2. Many families respond to carbamazepine, and others have a favourable response to acetazolamide, although...
some cases are resistant to both treatments.40 41 Several point mutations are now described, and expression studies indicate that they impair channel function both by reducing the amplitude of the potassium current and by altering its voltage dependent kinetics. These changes would be predicted to increase neuronal excitability, which is the basis of the neuromyotonia and presumably the attacks of ataxia.50 Homozygous deletion of the orthologous gene in the mouse has recently been described to cause severe epilepsy, raising the question whether KCNA1 mutations are involved in human epilepsy. In support of this, there is evidence for an overrepresentation of epilepsy in cases of EA1.51 52 Recently, mutations in two novel potassium channel genes have been shown to associate with benign familial neonatal convulsions, providing more direct evidence that potassium channel dysfunction may cause epilepsy in humans.53 54

**AUTOSOMAL DOMINANT NOCTURNAL FRONTAL LOBE EPILEPSY (ADNFLE)**

This dominant disorder is characterised by clusters of nocturnal frontal lobe seizures, each typically lasting less than 1 minute.53 They usually occur while falling asleep or just before waking. Most patients respond well to carbamazepine. Linkage to chromosome 20q13.2 was established in 1995, followed soon after by the discovery of a point mutation in the a4 subunit of the neuronal nicotinic acetylcholine receptor.54 A second mutation has recently been described.55 The neuronal acetylcholine receptor is a pentameric protein composed of varying combinations of subunits. It is mainly located presynaptically, and influences the release of other neurotransmitters.56 Expression studies of the two known mutations show a loss of channel function, which is thought to be the basis of the epilepsy in these cases.57 It remains to be seen whether other neuronal nicotinic receptor subunits are important in commoner forms of epilepsy.

**Conclusions**

It is now established that genetic defects of both ligand and voltage-gated ion channels can cause diverse neurological disease. To date, these are all relatively rare disorders. The detailed clinical, genetic, and biophysical analysis of neurological channelopathies over the past few years allows common themes to be identified. From a genetic viewpoint it is clear that both dominant and recessive modes of inheritance occur, and in some instances different mutations in the same ion channel gene may exhibit different inheritance. The mutations in CACLN1A4 indicate that different mutations in the same ion channel gene may result in quite different phenotypes, and also suggest that the relation between genotype and phenotype is not always simple. Another interesting finding is that either genetic or immunological insults to the same or closely related ion channels may produce neurological disease. For example, potassium channel antibodies may produce neuromyotonia, which also occurs in association with mutations in the KCNA1 gene.46 47 Some congenital syndromes that mimick acquired myasthenia gravis are also caused by mutations of the peripheral nicotinic receptor.47 This raises the possibility that immunological counterparts may be found for other genetic channelopathies.

Ion channel dysfunction is often susceptible to external factors such as stress and changes in pH, ion concentration, and temperature, and many respond to acetazolamide. The natural history of these disorders is variable. Mutations may produce paroxysmal disorders with normal interictal tissue function (for example, EA1), paroxysmal disorders with progressive tissue dysfunction (for example, EA2), or progressive tissue dysfunction alone, without clear episodic symptoms (for example, SCA6).

It is likely that other neurological channelopathies will be identified. Strong CNS candidate diseases include paroxysmal movement disorders such as paroxysmal dystonic choreoathetosis and familial geniospasm.58 59 Of the skeletal muscle diseases, the myotonic Schwartz-Jampel syndrome is another candidate.60 It is perhaps surprising that genetic channelopathies affecting peripheral nerve have not been described (other than EA1, which includes neuromyotonia in the phenotype).61

Most intriguing is the possibility that ion channels may be important in common neurological diseases such as migraine and epilepsy. The clinical overlap between some of the calcium channel phenotypes and migraine is striking. One study suggests the possibility that CACLN1A4 may be important in commoner forms of migraine, although this requires confirmation.55 The mouse models mentioned above also make CACLN1A4 a good candidate for the genetic susceptibility known to exist in absence epilepsy.56 Ligand gated channels are also strong candidates for commoner forms of primary epilepsy. These include postsynaptic receptors mediating fast excitatory or inhibitory transmission, as well as presynaptic receptors such as nicotinic and kainate receptors, which modulate the release of GABA.62 63 An allelic association has indeed been reported between a kainate receptor subunit and juvenile absence epilepsy.64 It remains to be seen if ion channel dysfunction is important in these common disorders. If it is, a new chapter in pharmacogenetic research with the aim of tailoring therapies to specific genotypes and modes of ion channel dysfunction is likely to follow.

Further information about neurological channelopathy DNA based diagnosis is available from the DNA-laboratory, National Hospital, Queen Square, London, UK. Financial support from the Brain Research Trust and the Medical Research Council is gratefully acknowledged.

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