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: Skeletal muscle sodium channel</td>
<td>HyperPP</td>
<td>Dominant</td>
<td>SCN4A</td>
<td>17q23-25</td>
</tr>
<tr>
<td></td>
<td>PMC</td>
<td>Dominant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PAM</td>
<td>Dominant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NormoPP</td>
<td>Dominant</td>
<td></td>
<td></td>
</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>
</tr>
<tr>
<td>Skeletal muscle ryanodine calcium channel</td>
<td>MH</td>
<td>Dominant</td>
<td>RYR1</td>
<td>19q13.1-13.2</td>
</tr>
<tr>
<td></td>
<td>Central core disease</td>
<td>Dominant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myotonia congenita</td>
<td>Dominant</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Thomsen’s disease</td>
<td>Dominant</td>
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<tr>
<td></td>
<td>Becker’s myotonia</td>
<td>Dominant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS disorders: Brain and nerve potassium channel</td>
<td>Episodic ataxia type I with myokymia</td>
<td>Dominant</td>
<td>KCNA1</td>
<td>12p13</td>
</tr>
<tr>
<td></td>
<td>Episodic ataxia type II</td>
<td>Dominant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FHM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCN1A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain (P/Q-type) calcium channel</td>
<td>Hyperekplexia</td>
<td>Dominant</td>
<td>GLRA-1</td>
<td>5q21</td>
</tr>
<tr>
<td></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. 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>Nicotinic acetylcholine receptor</td>
<td>Congenital myasthenia</td>
<td>Dominant and recessive</td>
<td>CHRNA</td>
<td>2q13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CHRNG</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>CHRN</td>
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<td></td>
<td></td>
<td></td>
<td>CHRNBD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CHRNE</td>
<td></td>
</tr>
<tr>
<td>CNS disorder: Glycine receptor</td>
<td>Hyperekplexia</td>
<td>Dominant</td>
<td>GLRA-1</td>
<td>5q21</td>
</tr>
<tr>
<td></td>
<td>Neuronal nicotinic receptor</td>
<td>ADNFLE</td>
<td>Dominant</td>
<td>CHRNA4</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 were 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 the potassium aggravated myotonias. Also, we speculate on possible future channelopathies and discuss some of the evidence that ion channel dysfunction may be important in common neurological disorders.

**DNA based diagnosis of periodic paralyses is now obviating the need for time consuming and potentially hazardous provocative testing.** In addition to avoiding precipitating factors, drugs which can be effective in both types of periodic paralysis include acetazolamide and thiazide diuretic drugs. A recent placebo controlled trial suggests that dichlorphenamidine (a more potent carbonic anhydrase inhibitor than acetazolamide) is specifically effective in HypoPP. Salbutamol can be useful in HyperPP. Some patients are, however, resistant to all treatments.

**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
Gene, CACNL1A4, coding for the nant disorders are associated with mutations in the same calcium channel glutamine tract located in the C terminal region of the cal-

CNS channelopathies

CALCMI CHANNELOPATHIES: EPISODIC ATAXIA TYPE 2, FAMILIAL HEMIPLEGIC MIGRAINE, AND SPINOCEREBELLAR ATAXIA TYPE 6

Perhaps the most remarkable recent discovery in the field of channelopathies is that three different autosomal domi-
nant disorders are associated with mutations in the same gene, CACNL1A4, coding for the \( \alpha_\text{II}\) subunit of the brain P/Q-type voltage gated calcium channel.\(^{26-29}\) Episodic ataxia type 2 (EA2), familial hemiplegic migraine in some families, and (SCA6) are allelic disorders caused by differ-

In some patients susceptible to malignant hyperthermia central cores are seen in muscle biopsies, and conversely patients with central core disease, a congenital myopathy, are at risk for developing malignant hyperthermia. These findings have recently been explained by the discovery that central core disease and malignant hyperthermia may both be caused by mutations in the ryanodine receptor gene.\(^{24}\) Malignant hyperthermia is, however, genetically heteroge-

Neurological channelopathies

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The mTOR is a serine-threonine kinase located in the cytoplasm of cells and is essential for cell growth and viability.\(^{30}\) It is activated by growth factors and nutrients and plays a critical role in the regulation of cellular metabolism, proliferation, and survival.\(^{31}\) mTOR activation is linked to several disease states, including cancer, diabetes, and neurodegenerative diseases.\(^{32}\) In the context of neuroprotection, the role of mTOR in the regulation of neuronal survival and regeneration is of particular interest.\(^{33}\) mTOR activation leads to the inhibition of autophagy, which is a process that removes damaged organelles and proteins. This inhibition is thought to contribute to neurodegeneration in diseases such as Alzheimer’s and Parkinson’s disease.\(^{34}\) However, recent studies have suggested that mTOR activation may also have beneficial effects, such as promoting neuronal survival and regeneration.\(^{35}\) The therapeutic implications of these findings are currently under investigation.\(^{36}\)

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some cases are resistant to both treatments.40 45 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 EA1.41 45 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.5 54

AUTOSOMATIC 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.55 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 α4 subunit of the neuronal nicotinic acetylcholine receptor.56 A second mutation has recently been described.57 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. 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 CACNL1A4 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 KCNQ1 gene.48 49 Some congenital syndromes that mimick acquired myasthenia gravis are also caused by mutations of the peripheral nicotinic receptor.50 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, SCAs).

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.40 41 Of the skeletal muscle diseases, the myotonic Schwartz-Jampel syndrome is another candidate.61 It is perhaps surprising that genetic channelopathies affecting peripheral nerve have not been described (other than EA1, which includes neuromyotonia in the phenotype).52

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 supporting the possibility that CACNL1A4 may be important in commoner forms of migraine, although this requires confirmation.53 The mouse models above also make CACNL1A4 a good candidate for the genetic susceptibility known to exist in absence epilepsy.54 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.44 45 An allelic association has indeed been reported between a kainate receptor subunit and juvenile absence epilepsy.56

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.

MICHAEL G HANNA
NICHOLAS W WOOD
DIMITRI M KULLMANN

Department of Clinical Neurology, Institute of Neurology, Queen Square, London, UK

Correspondence to: Dr M G Hanna, Muscle and Neurogenetics Sections, Institute of Neurology, Queen Square, London WC1N 3BG, UK. Telephone 0171 837 3611, extension 4231; email Mhanna@ion.ucl.ac.uk

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