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Molecular genetics of human epilepsies

Louise Bate and Mark Gardiner

The term epilepsy encompasses a heterogeneous group of disorders, with a lifetime cumulative incidence of 3%. Genetic factors are thought to contribute to the aetiology in up to 60% of cases. Various molecular and cellular mechanisms give rise to epilepsy, and epilepsy genes fall into several distinct categories. They include genes in which mutations cause abnormal ion-channel function, disordered brain development, progressive neurodegeneration and disturbances of cerebral energy metabolism. In this review, we have focused on current understanding of the molecular genetic bases of human inherited epilepsies. Particular reference has been given to specific idiopathic epilepsies, neuronal migration disorders (cortical dysgeneses) and the progressive myoclonic epilepsies, and how information about this group of disorders might be used to develop new treatment strategies.

Epilepsy describes a diverse group of diseases, the molecular bases of which are as varied as the disorders they produce (Figs 1 and 2). Epilepsy is the commonest chronic neurological disorder, with more than 40 million people affected worldwide. In order to understand the genetics of the epilepsies, a clear understanding of the clinical terminology is required (see below).

Epilepsy and epileptic seizures

Epilepsy is a disorder of the brain that is characterised by recurrent, unprovoked epileptic seizures. An epileptic seizure is a transient episode of abnormal cortical neuronal activity, which is apparent to either the patient or an observer. The abnormal cortical activity can be expressed as a motor, sensory, cognitive or psychic disturbance. A seizure is a clinical diagnosis, although electroencephalogram (EEG) data can be useful in determining the precise seizure type.

Epilepsy can be a feature of a disease process or form part of a syndrome in which a particular pattern of seizures and clinical and investigative findings occurs together. Thus, the term epilepsy should not be used to describe: (1) single epileptic seizures, (2) seizures that occur during an acute illness or (3) occasional provoked seizures (e.g. febrile convulsions or hypoglycaemic seizures).

Seizures occur when there is an excess of excitatory processes in the brain compared with inhibitory processes. Changes in afferent excitation, disinhibition, shifts in extracellular ion concentrations, voltage-gated ion-channel opening and enhanced neuronal synchrony are

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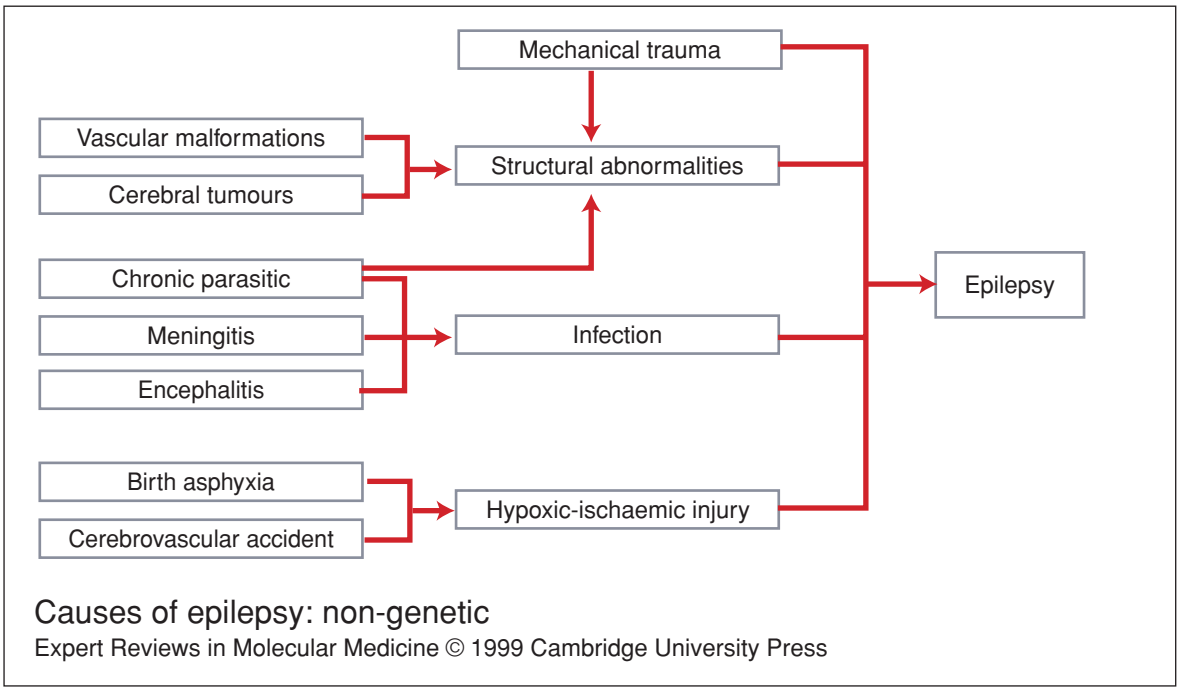

Figure 1. Causes of epilepsy: non-genetic (fig001mgu).

all important in the initiation and propagation of seizure activity (Ref. 1). Neuronal activity is regulated by the concentration of ions in the extracellular and intracellular spaces, and the selective flux of these ions across the neuronal membrane. Voltage-gated or ligand-gated ion-channel genes are, therefore, attractive candidate genes for the epilepsies. It is easy to imagine how mutations in such genes could lead to channel dysfunction, which could alter ion concentrations across the cell membrane, resulting in reduced or increased neuronal excitability.

Clinical classification of epilepsy

Epilepsy can be broadly divided into two groups: (1) partial epilepsy (which is also known as localisation-related or focal epilepsy) and (2) generalised epilepsy. Partial epileptic seizures arise from localised cortical foci. Consciousness can be either retained (as in simple partial seizures) or lost (as in complex partial seizures). If motor disturbance occurs, it is usually localised to a particular group of muscles. The EEG during a seizure (ictal EEG) shows discharges arising from a specific brain area. Generalised epileptic seizures involve both cerebral hemispheres from the onset of the seizure, and consequently any motor manifestations are bilateral. Consciousness might or might not be disturbed.

The epilepsies can be further classified into: (1) symptomatic epilepsies, which have a discernible cause, and (2) idiopathic epilepsies, which do not.

Idiopathic epilepsies

Idiopathic epilepsies (Table 1) are not associated with structural or metabolic abnormalities, and are presumed to have a genetic basis. The pattern of inheritance of such epilepsies is either simple Mendelian or complex. They are age related, each with a specific period of onset, from the neonatal period through to early adulthood. Most types of idiopathic epilepsy respond well to anti-epileptic treatment. Together, the various idiopathic epilepsies account for up to 60% of all epilepsies (Ref. 2).

Idiopathic epilepsies with a Mendelian mode of inheritance

Mendelian idiopathic epilepsies, although rare, have proved an important resource in the genetic analysis of epilepsy. During the past four years, the genes that are mutated in three Mendelian idiopathic epilepsies have been identified. In 1995 and 1997, mutations in the gene *CHRNA4*, which encodes the α4 subunit of the neuronal nicotinic acetylcholine receptor (nAChR), have been found in families that are affected by

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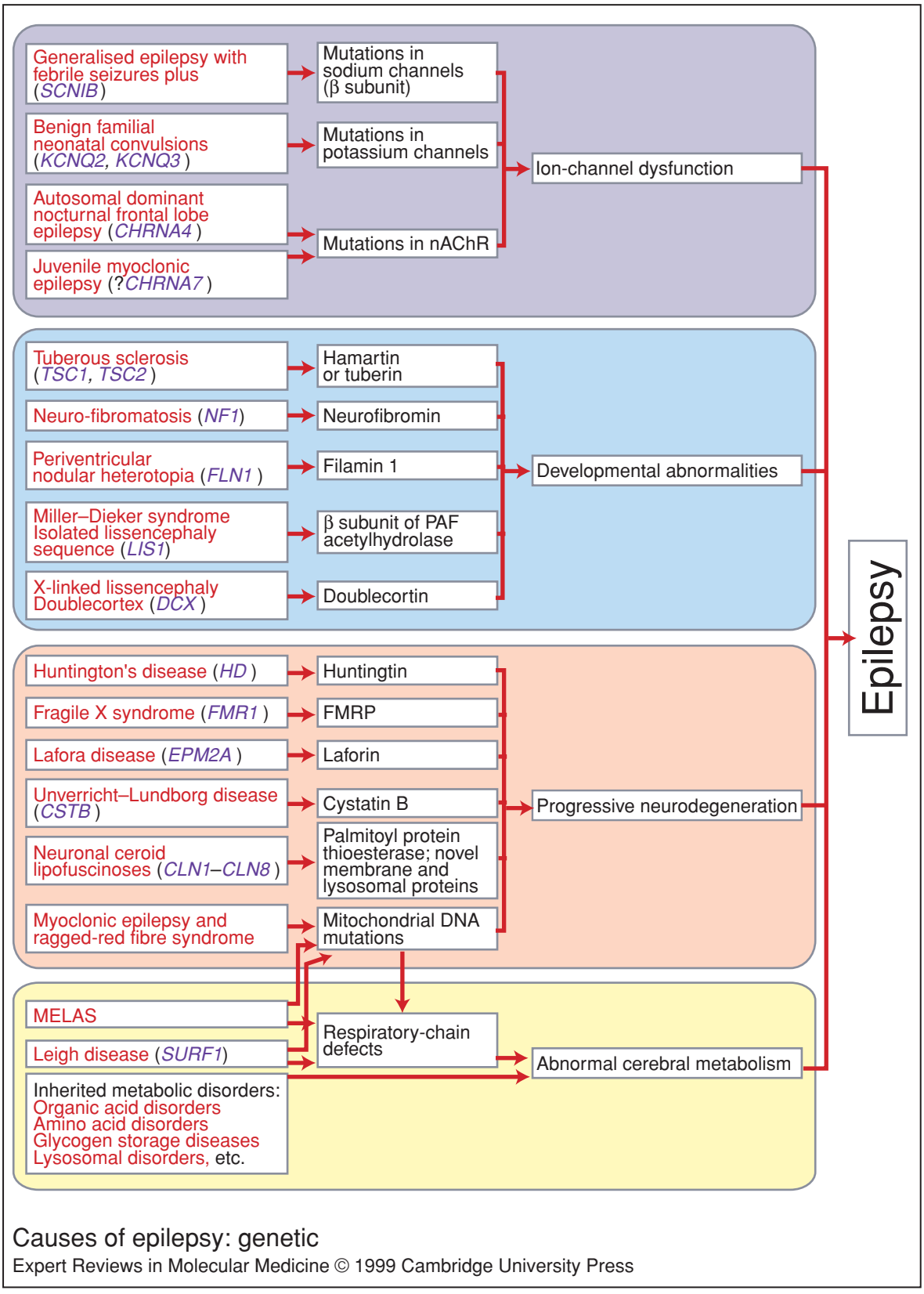

Causes of epilepsy: genetic

Figure 2. Causes of epilepsy: genetic *(see next page for legend)* **(fig002mgu)**.

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Table 1. Genetics of the idiopathic epilepsies (tab001mgu)

Idiopathic epilepsy Mode of inheritance	Phenotype	Gene, chromosomal location (locus name) and gene product	Refs
Benign familial neonatal convulsions (BFNC) Autosomal dominant.	Onset at 2–4 days old; remits at 2–15 weeks; GTCS with ocular signs and motor automatisms.	(1) *KCNQ2*; 20q (*EBN1*); KCNQ2, a voltage-gated K^+ ion channel. (2) *KCNQ3*; 8q24 (*EBN2*); KCNQ3, a voltage-gated K^+ ion channel.	15 16 22
Generalised epilepsy with febrile seizures plus (GEFS+) Autosomal dominant.	Childhood onset but remits by mid-childhood; phenotype includes: (1) 'febrile seizures plus', that is multiple febrile seizures with febrile or afebrile GTCS at >6 years old; (2) febrile seizures and absences, myoclonic seizures or atonic seizures and (3) myoclonic-astatic epilepsy.	(1) *SCN1B*; 19q13 (*GEFS1*); β1 subunit of voltage-gated Na^+ ion channel. (2) Unknown; chromosome 2; unknown.	30 31
Juvenile myoclonic epilepsy (JME) Complex inheritance.	Onset at 7–26 years of age; generalised myoclonic seizures with or without GTCS and absence seizures.	(1) ?*CHRNA7*; 15q14; α7 subunit of nAChR. (2) With or without idiopathic generalised epilepsy: unknown; 6p (*EJM1*); unknown.	41, 42 43, 44 45, 46 47
Childhood absence epilepsy (and/or EEG trait) (CAE) Complex inheritance.	Onset at 3–12 years of age; generalised absences with or without GTCS; EEG characterised by 3–4-Hz spike-wave pattern.	Unknown; 8q24; unknown.	87
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) Autosomal dominant.	Childhood onset; persists in adulthood with brief clustered nocturnal motor partial seizures.	(1) (In minority only) *CHRNA4*; 20q13.2–q13.3; α4 subunit of nAChR. (2) Unknown; 15q24, possibly close to the *CHRNA3–CHRNA5–CHRNB4* region; unknown. (3) Other unknown genes.	4 5 11
Partial epilepsy with auditory symptoms Autosomal dominant.	Onset at 8–19 years of age; infrequent partial seizures with or without non-specific auditory disturbances.	Unknown; 10q; unknown.	88
Benign familial infantile convulsions (BFIC) Autosomal dominant.	Onset at 3.5–12 months of age; partial motor seizures with secondary generalisation.	Unknown; 19q13; unknown.	89
Benign rolandic epilepsy (also known as benign epilepsy with centrotemporal spikes) Complex inheritance.	Onset at 2–14 years of age; partial motor seizures with or without secondary generalisation; inter-ictal EEG characterised by centrotemporal spikes.	Unknown; 15q14 (in the same region as one of the putative JME loci); unknown.	49

Abbreviations used: EEG = electroencephelogram; GTCS = generalised tonic-clonic seizures; Hz = Hertz; nAChR = neuronal nicotinic acetylcholine receptor.

Figure 2. Causes of epilepsy: genetic. The epilepsy syndromes, or diseases that have epilepsy as part of their phenotype, are listed in red at the far left of the figure; these are followed by the genes or disease loci (where known), in blue italics. The proteins that are encoded by these genes or the processes that are affected by the molecular abnormality are listed in the second column of the figure. Abbreviations used: MELAS = mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; FMRP = fragile X with mental retardation protein, PAF = platelet-activating factor; nAChR = neuronal nicotinic acetylcholine receptor **(fig002mgu)**.

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autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). In 1998, mutations in the genes *KCNQ2* and *KCNQ3*, which encode two voltage-gated potassium ion (K^+) channels, were discovered in families that are affected by benign familial neonatal convulsions (BFNC). In the same year, a mutation in the gene *SCN1B*, which encodes the β1 subunit of the voltage-gated sodium ion (Na^+) channel, was found in a large pedigree (collection of related individuals) that is affected by the syndrome generalised epilepsy with febrile seizures plus (GEFS+).

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)

ADNFLE was first described in six families in Australia, Canada and the UK. Patients experience brief, clustered nocturnal motor seizures, and can be misdiagnosed as suffering from sleep disorders or psychiatric disturbance. Its clinical onset is usually in childhood, and the disease often persists throughout adult life. The penetrance of the disease gene is ~ 75%. A locus for ADNFLE has been mapped to chromosome 20q13.2–q13.3, using exclusion mapping. Several regions were tested in an effort to localise the gene, including: (1) regions that contained other epilepsy genes, (2) regions with possible homology to the major gene for partial epilepsy in the mouse model and (3) the rest of the genome (Ref. 3). Mutations were subsequently found in *CHRNA4*, the gene encoding the α4 subunit of the nAChR, which maps to this region. (Refs 4, 5). The nAChRs are heteropentameric ligand-gated ion channels, which comprise various combinations of α and β subunits. Each subunit consists of an N-terminal extracellular domain that is involved in ligand binding, four hydrophobic transmembrane domains and a large cytoplasmic loop between transmembrane domains 3 and 4 (Fig. 3). The commonest configuration comprises two α subunits and three β subunits. They are thought to be predominantly presynaptic and modulate neurotransmitter release. Eight genes for human nAChR subunits have been mapped (Table 2; Refs 6, 7). The gene encoding the α4 subunit is expressed in all layers of the frontal cortex (Ref. 8).

Three mutations in the M2 transmembrane domain (which is thought to be involved in cation selectivity) of the α4 subunit of the nAChR have been found in families with ADNFLE: two non-conservative amino acid substitutions (Ser248Phe and Ser252Leu), and an insertion mutation (776ins3) involving three base pairs. Functional studies have shown that the efficacy of the Ser248Phe mutant channel is reduced by four means: (1) loss of calcium ion (Ca^{2+}) permeability, (2) increased desensitisation, (3) reduced channel opening time and (4) reduced channel conductance, all of which reduce the net flow of ions through the activated channel. Mutant 776ins3 receptors show a 10-fold increase in apparent affinity for acetylcholine (ACh) and a significant reduction in calcium permeability. It has been hypothesised that this mutation, indirectly, causes a loss of function of the α4 β2 channel, although its precise effect on channel gating is not known (Refs 9, 10, 120).

Table 2. Location of genes encoding the neuronal nicotinic acetylcholine receptor (nAChR) subunits (tab002mgu)

nAChR subunit	Chromosomal location
CHRNA2	8p21
CHRNA3	15q24
CHRNA4	20q13.3
CHRNA5	15q24
CHRNA7	15q14
CHRNB2	1p21.1–q21
CHRNAB3	8p11.22
CHRNB4	15q24

In one family, a second ADNFLE locus has been mapped close to the *CHRNA3–CHRNA5–CHRNB4* cluster on chromosome 15q24 (Ref. 11). However, no mutations were found on screening the exons that encode the pore-forming region of *CHRNA3*, *CHRNA5* and *CHRNB4*.

It is now thought that mutations in *CHRNA4* cause ADNFLE in only a minority of affected families. Mutation analysis of seven affected families and seven sporadic cases found no mutations on screening the gene *CHRNA4* or in the exons that encode the pore-forming region of *CHRNB2*, *CHRNA3*, *CHRNA5* and *CHRNB4* (Ref. 11). Mutations in different regions of these genes or mutations in other ion-channel genes might be pathogenic in these cases.

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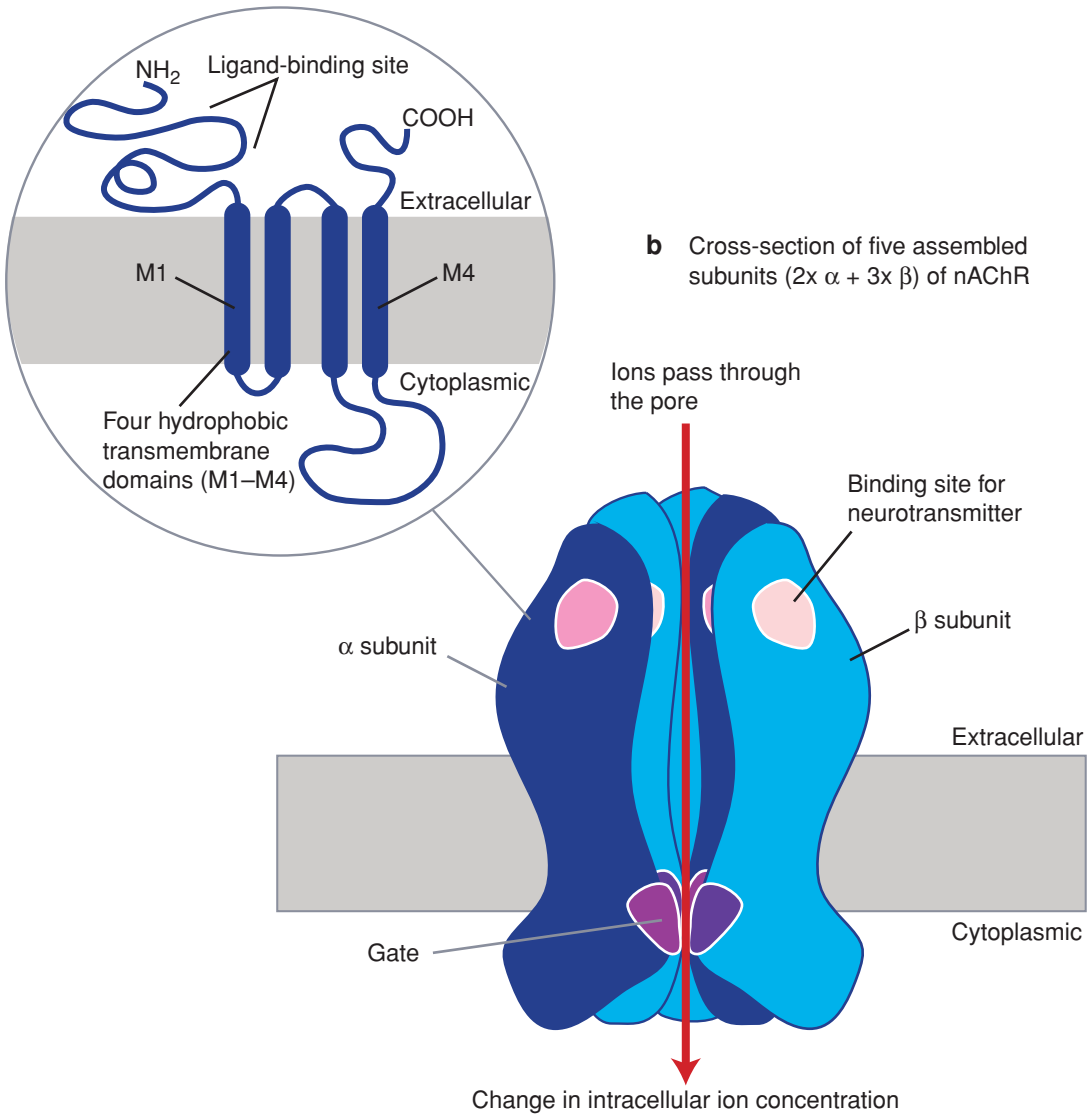

Structure of a neuronal nicotinic acetylcholine receptor (nAChR)

Figure 3. Structure of a neuronal nicotinic acetylcholine receptor (nAChR). The nAChR is a ligand-gated ion channel. Each nAChR is composed of five (α or β) subunits, which can be homomeric (i.e. all α or all β) or heteromeric (i.e. a mixture of α and β, as in this schematic). (a) One subunit of the nAChR comprises: (1) an N-terminal extracellular domain, which is involved in binding to (neurotransmitter) ligands, (2) four hydrophobic transmembrane domains (in dark blue), called M1, M2, M3 and M4, and (3) a long cytoplasmic loop between M3 and M4, and other shorter loops connecting the domains. (b) In cross-section, an assembled nAChR has five subunits, each with a binding site and a gate region. All ligand-gated ion channels bind specific neurotransmitters (in this case, nicotine), which induce a conformational change in the receptor, opening the channel. Charged amino acids line the channel pore and select the ions that can pass through into the cell. The α4 subunit of the nAChR is encoded by the *CHRNA4* gene, which is one of the genes that are mutated in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). (The main part of the figure has been modified from an illustration in Ref. 117, and the insert from an illustration in Ref. 118.) **(fig003mgu).**

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Benign familial neonatal convulsions (BFNC)

BFNC is an autosomal dominant idiopathic generalised epilepsy of the newborn. Seizures begin at 2–4 days of age, and spontaneously remit at 2–15 weeks of age. Seizures typically start with a tonic posture, ocular symptoms and other autonomic features, and can progress to clonic movements and motor automatisms. Affected neonates appear to be normal between seizures, and show normal neurological and intellectual development. Seizures tend to recur later in life in ~16% of patients (Ref. 12). Two susceptibility loci for BFNC have been mapped to chromosome 20 (at locus *EBN1*) and chromosome 8 (at locus *EBN2*) (Refs 13, 14).

EBN1, the BFNC-associated locus on chromosome 20q

The gene for the susceptibility locus *EBN1* was identified using a positional cloning strategy (Refs 15, 16). Positional cloning is the isolation of disease genes on the basis of their chromosomal location, without prior knowledge of the defective protein they encode. The gene locus is initially mapped by linkage analysis. A series of markers from within the candidate interval (ideally <2 cM) is then used to identify overlapping clones that contain genomic DNA from this region. Transcripts (coding sequences) are then identified from the genomic clones. The identified transcripts can then be sequenced, assembled into full-length complementary DNAs (cDNAs) and characterised.

The gene *KCNQ2* encodes a predicted protein comprising 844, 854, 872 or 930 amino acids, depending on the splice variant considered (Ref. 17). *KCNQ2* shows ~50% identity to *KCNQ1*, a gene encoding a voltage-gated delayed rectifying K^+ channel. The protein KCNQ2 displays the hallmarks of a typical voltage-gated K^+ channel, with six transmembrane domains, a pore region, and common charged amino acids in the S2, S3 and S4 domains (Fig. 2). Voltage-gated K^+ channels repolarise neuronal membranes that have been depolarised by Na^+ and Ca^{2+} voltage-dependant channels, following the activation of excitatory neurotransmitter ion channels. Mutations in *KCNQ1* cause two paroxysmal cardiac dysrhythmias, namely long QT syndrome and Jervell–Lange–Nielsen cardioauditory syndrome, in some families (Refs 18, 19).

Mutations in *KCNQ2* have been identified in seven *EBN1*-linked BFNC families (Refs 15, 16). Frameshift, missense and splice-site mutations and a deletion (the breakpoints of which have not been determined) have all been identified. These segregate with disease status, and are all found in the S6 domain, the channel pore and around the C-terminal region of the gene. The S6 domain in the *Shaker*-type K^+ channel subtype, and the C-terminal in inwardly rectifying K^+ channels are involved in the conduction of K^+ ions (Refs 20, 21), and might have the same function in KCNQ2 channels.

EBN2, the BFNC-associated locus on chromosome 8q

The gene for the susceptibility locus *EBN2* was identified by BLAST (basic local alignment search tool) searching the database of human expressed sequence tags (EST) for clones that are homologous to *KCNQ2* (Ref. 22). This novel gene, *KCNQ3*, was mapped to chromosome 8q24, within the *EBN2* critical region. *KCNQ3* encodes KCNQ3, a protein that has been predicted to contain 825 amino acids and have the characteristics of a voltage-gated K^+ channel. The predicted protein is 41–62% identical to KCNQ2 (Refs 22, 23). Mutation analysis of *KCNQ3* in the original *EBN2* family identified a missense mutation in the channel pore, which segregated with affected status. By analogy with mutations in other K^+ channels, this mutation might alter channel gating properties (Refs 24, 25, 26). *KCNQ2* and *KCNQ3* are co-expressed in most areas of the brain, especially the hippocampus, neocortex and cerebellum (Refs 15, 17, 22).

Electrophysiological studies of the wild-type (normal) and mutant KCNQ2 and KCNQ3 channels elicited currents that resembled those of wild-type KCNQ1 channels (Refs 23, 27, 28, 29). It appears that KCNQ2 and KCNQ3 are co-expressed and associate in vivo, and that BFNC is caused by a small loss of function of these heteromeric channels (Ref. 23). These findings could explain how mutations in either *KCNQ2* or *KCNQ3* cause an identical disease phenotype. The heteromeric KCNQ2–KCNQ3 channel did not have a dominant negative effect (i.e. the mutant gene product did not prevent the product of the normal allele from functioning in heterozygotes).

Generalised epilepsy with febrile seizures plus (GEFS+)

GEFS+ is an autosomal dominant idiopathic

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generalised epilepsy (first described in a large Australian pedigree); there is evidence for linkage of this syndrome to chromosome 2 (Ref. 30). Two further GEFS+ loci have been mapped. *GEFS1* has been mapped to chromosome 19q13, in another Australian pedigree (Ref. 31). The candidate gene *SCN1B*, which encodes the β1 subunit of the voltage-gated Na^+ channel, has also been mapped to this region (Refs 32, 33). A third locus has been mapped to chromosome 2q24–q33 in a French pedigree. The candidate region includes a cluster of three sodium channel α subunits (Ref. 121).

Voltage-gated Na^+ channels cause the rapid rise in membrane Na^+ permeability during the initial phase of the action potential in most excitable tissues. They consist of a large α subunit associated with two β subunits (Fig. 4). The β subunits modulate the channel gating properties (Refs 34, 35). *SCN1B* is expressed in the brain, heart and skeletal muscle (Ref. 34). Genes that encode Na^+ channel subunits are attractive candidate genes for epilepsy: anti-epileptic drugs, such as carbamazepine and phenytoin, act by enhancing the inactivation of the Na^+ channels (Ref. 36), and mutations in the α-subunit genes *SCN4A* and *SCN5A* are associated with paroxysmal disorders of skeletal and cardiac muscle (Ref. 37).

Mutation analysis of *SCN1B* in the GEFS+ family identified a point mutation, which segregated with disease status. This mutation disrupts the putative disulphide bond that maintains the extracellular fold motif of the β1 subunit, and might alter the secondary structure of the extracellular domain. Such a disruption has been predicted to cause reduced expression of Na^+ channels, slower inactivation and slower recovery from inactivation (Refs 38, 39).

Electrophysiological studies showed that co-expressed wild-type α and mutant β1 subunits produced Na^+ channels that were inactivated more slowly than wild-type Na^+ channels. This loss of function might be due to altered modulatory effects of the mutant β1 subunit. The observed and predicted functional changes evoked by the mutant β1 subunit might cause persistent Na^+ influx in neuronal cells, resulting in hyperexcitability. The apparent temperature dependence of the GEFS+ phenotype might reflect the effects of temperature on the conductance and gating properties of Na^+ channels.

Idiopathic epilepsies with a complex mode of inheritance

Most idiopathic generalised epilepsies display a complex pattern of inheritance. This common group of epilepsies includes juvenile myoclonic epilepsy (JME), juvenile absence epilepsy (JAE), childhood absence epilepsy (CAE) and epilepsy with generalised tonic clonic seizures on awakening.

The relatives of probands (index cases through whom pedigrees are discovered and investigated) who are affected with idiopathic generalised epilepsies have a 5–8% risk of developing epilepsy (Ref. 40). Frequently, two or more different idiopathic generalised epilepsy phenotypes are found within a single pedigree, which suggests that there might be common susceptibility loci for all idiopathic generalised epilepsies. A common locus, or group of loci, might determine the seizure threshold, with additional loci contributing further phenotypic specificity.

Juvenile myoclonic epilepsy (JME)

JME is an idiopathic generalised epilepsy that has a peak age of onset during adolescence (in the range of 7–26 years). The phenotype is characterised by generalised myoclonic seizures, and can include generalised tonic-clonic seizures and absence seizures. Inter-ictal EEG patterns (i.e. those between seizures) can either be normal or show generalised spike-and-wave or polyspike-and-wave discharges. Affected individuals are otherwise normal, and have no neurological or neuroradiological abnormalities.

Studies have provided evidence both for and against the existence of a locus, *EJM1*, on chromosome 6p, predisposing individuals to JME or related idiopathic generalised epilepsies (Refs 41, 42, 43, 44, 45, 46). However, it has not been possible to refine the localisation of *EJM1* or to determine the exact phenotype to which it confers susceptibility.

Following the identification of mutations in the *CHRNA4* gene in families that are affected by ADNFLE, the genes encoding subunits of the nAChRs have emerged as candidate genes for the inherited epilepsies, including JME. Analysis of regions to which nAChR subunits have been mapped (Table 2) in 34 European families that are affected by clinical JME found significant evidence in favour of linkage in the *CHRNA7* region on chromosome 15q14 (Ref. 47). *CHRNA7* encodes the α7 subunit

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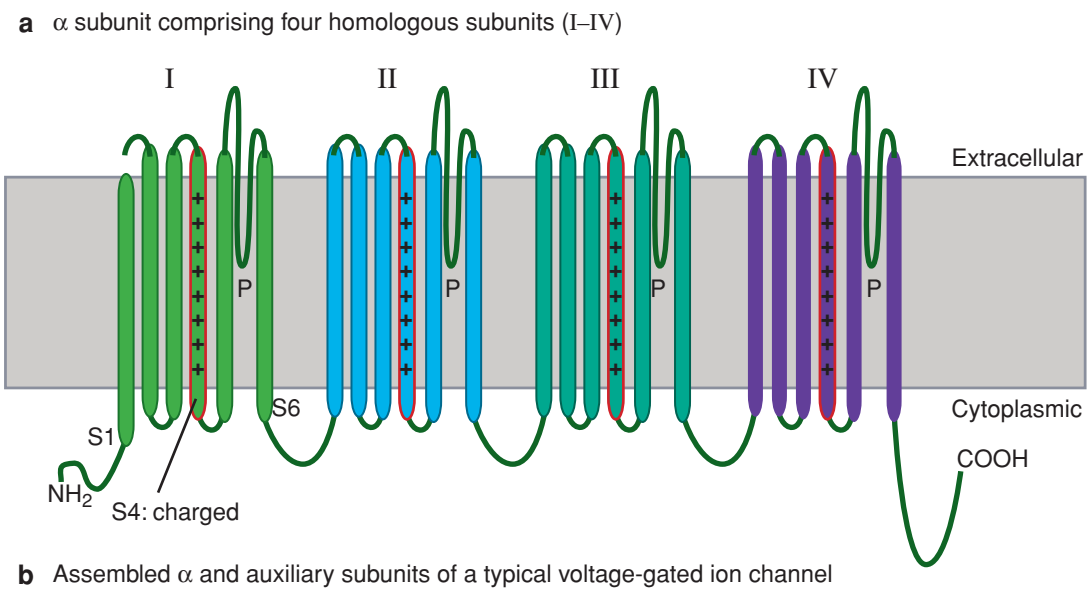

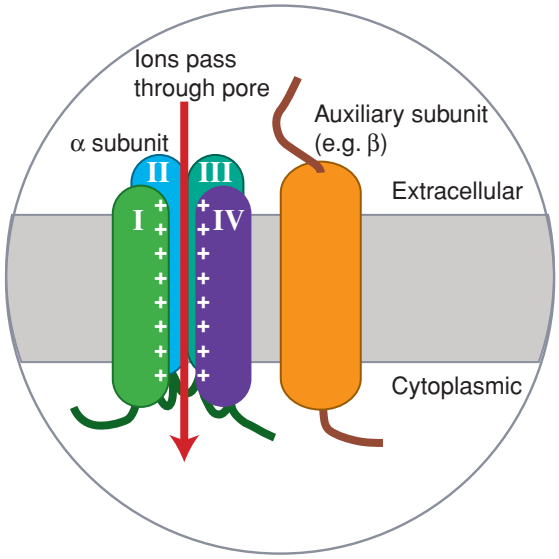

Structure of a typical voltage-gated ion channel

Figure 4. Structure of a typical voltage-gated ion channel. (a) The α subunit of a typical voltage-gated ion channel comprises four subunits [homologous subunits for potassium ions (K^+) channels or homologous repeat domains for sodium ion (Na^+) and calcium ion (Ca^{2+}) channels]. Each domain or subunit is made up of six transmembrane domains (S1–S6); the S4 domain is charged and acts as a voltage sensor. Cations pass through the aqueous pore between the four subunits into the cell. (b) The assembled ion channel has one α subunit plus other auxiliary subunits (β, δ, etc.) that modulate channel function. Mutations in K^+ and Na^+ voltage-gated ion channels are associated with human epilepsies; mutations in Ca^{2+} voltage-gated ion channels are associated with mouse models of spike-wave epilepsies. (The figure has been modified from an illustration in Ref. 119.) **(fig004mgu).**

of the nAChR, which forms homo-oligomeric channels when expressed in oocytes of the frog *Xenopus laevis*. The α7 subunit is expressed throughout the brain (Ref. 48); because of this finding and the suggested modulatory role of the channel, *CHRNA7* (the gene that encodes the α7

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subunit) is viewed as an excellent candidate gene. Mutational analysis of *CHRNA7* is currently being undertaken.

A locus for benign rolandic epilepsy (i.e. benign epilepsy with centrotemporal spikes), an idiopathic partial epilepsy that shows a complex mode of inheritance, has also been mapped to this region (Ref. 49).

Neuronal migration disorders

The neuronal migration disorders are a group comprising more than 25 syndromes that are characterised by the abnormal migration of neurones in the cerebral cortex during embryogenesis, leading to abnormal cortical development. The causes of these disorders are both genetic and environmental, and the observed clinical variability is due to the differences in: (1) their aetiologies, (2) the cortical areas that are affected and (3) the gestational age at which abnormal migration occurred.

Lissencephaly

Lissencephaly (which is derived from the Greek meaning 'smooth brain') is characterised by fewer gyri (folds) over the cerebral surface, owing to the arrest of neuronal migration at 9–13 weeks of gestation. Microscopically, the cortex is poorly organised; it has four primitive layers and diffuse neuronal heterotopia. Affected children have severe mental retardation, subtle facial abnormalities, epilepsy and other neurological abnormalities. Lissencephaly is relatively rare, with an estimated incidence of 1 in 100 000 live births. Improved diagnostic techniques [including magnetic resonance imaging (MRI) and molecular genetic techniques] have increased patient identification, and the true incidence might be ~1 in 13 000–20 000 (Ref. 50).

Classical lissencephaly has been observed in several malformation syndromes, including: (1) Miller–Dieker syndrome (MDS), (2) isolated lissencephaly sequence (ILS) and (3) X-linked lissencephaly (XLIS) and subcortical band heterotopia (SBH) [or 'doublecortex' (DC); Table 3].

Miller–Dieker syndrome (MDS) and isolated lissencephaly sequence (ILS)

Virtually all patients who have MDS and approximately one third of those patients who have ILS have a hemizygous deletion or a mutation in the *LIS1* gene, which encodes a non-catalytic subunit of the platelet-activating factor (PAF) acetylhydrolase, a heterotrimeric enzyme that inactivates PAF (Refs 51, 52).

The role of PAF in neuronal migration is not known. Putative roles include the control of: (1) the differentiation of neuronal cells, (2) the adhesion properties of neural cells and (3) the initiation of migration, via the effects of PAF levels on Ca^{2+} fluxes (Refs 53, 54). Because the LIS1 protein is only one subunit of a trimeric enzyme complex, hemizygosity of the *LIS1* gene might lead to reduced levels of functional enzyme, owing to reduced cellular concentrations of the LIS1 subunit. This, in turn, could result in the accumulation of PAF in the developing brain, causing abnormal migration of neuronal cells by an, as yet, unknown mechanism.

LIS1 protein has been shown to interact with tubulin and affect the dynamic properties of the microtubules (Ref. 54). It might be a component of other multi-subunit enzyme complexes, in which haplo-insufficiency can adversely affect the cellular mechanisms that are involved in neuronal migration.

X-linked lissencephaly (XLIS) and subcortical band heterotopia (SBH)

XLIS causes classical lissencephaly in hemizygous males and a milder phenotype in affected female heterozygotes (which is presumably caused by random X-inactivation). The brains of affected females have a subpopulation of neurones that migrate abnormally and arrest in the subcortical white matter, leading to a 'doublecortex' appearance or SBH (Ref. 55).

Two research groups have cloned the gene that is mutated in XLIS/SBH, namely *DCX*, by assembling a 9–9.5-kilobase candidate contig of overlapping cloned DNA fragments. The consensus sequence of the corresponding cDNA (i.e. that constructed using the commonest base found at each position when comparing a large group of similar DNA sequences) encodes an open reading frame (ORF), which is 1080 base pairs long. This ORF encodes doublecortin (DCX), a novel protein of 40 kDa that has been predicted to comprise 360 amino acids (Refs 56, 57).

Mutation analysis of *DCX* identified missense mutations in nine XLIS pedigrees and two female patients who had sporadic SBH. Frameshift mutations of the *DCX* gene were found in three sporadic females and a novel splice-site mutation was detected in another (Refs 56, 57, 58).

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Table 3. Genetics of the neuronal migration disorders (tab003mgu)

Neuronal migration disorder Mode of inheritance	Phenotype	Gene, chromosomal location (locus name) and gene product and function	Refs
Isolated lissencephaly sequence (ILS) Autosomal dominant.	Classical lissencephaly: severe mental retardation; subtle facial abnormalities; epilepsy and neurological abnormalities.	In ~33% of affected individuals: *LIS1*; 17p13.3 (LIS1); LIS1 protein, which is the non-catalytic subunit of platelet-activating factor (PAF) acetylhydrolase (it interacts with tubulin and inactivates PAF).	51, 52 53, 54
Miller–Dieker syndrome (MDS) Autosomal dominant.	Severe lissencephaly with profound mental and physical disabilities; characteristic facies, mid-line septal calcifications in ~50% of people.	In ~100% of affected individuals: as for ILS.	51, 52 53, 54
X-linked lissencephaly (XLIS) X-linked dominant (males affected).	Classical lissencephaly (see above).	Doublecortin (*DCX*), Xq21–24; doublecortin (DCX), a protein that is associated with the microtubules.	55, 56 57, 58 59, 60
Subcortical band heterotopia (SBH) / doublecortex (DC) X-linked dominant (females affected).	A more subtle phenotype than that for XLIS, including: behavioural problems; epilepsy (GTCS, tonic, atonic and atypical absence seizures, and partial and complex partial seizures); mental retardation (this can develop following the onset of seizures).	As above for XLIS.	55, 56 57, 58 59, 60
Periventricular heterotopia (PH) X-linked dominant (male lethality).	Normal intelligence; partial seizures with or without secondary generalisation; systemic problems including: patent ductus arteriosus, coagulopathies and skeletal dysplasia.	Filamin 1 (*FLN1*); Xq28; filamin 1 (FLN1), an actin-binding phosphoprotein.	61, 62 63

DCX is a neurone-specific phosphoprotein, which is widely expressed in the developing central and peripheral nervous systems of mice. In the human brain, DCX is widely expressed in occipital lobe slices at 22 weeks gestation, with lower levels of expression during early childhood (i.e. at 2 and 4 years of age) and very low levels of expression in adult brain. Apparently, DCX is expressed in both radially and tangentially migrating neurones at the cortical plate, the intermediate zone and the ventricular zone, and also in cerebellar migrating neurones. DCX is localised to the cell bodies and leading processes in migrating neurones, and the axons of differentiating neurones. This expression pattern overlaps that of microtubules; experiments to test the effects of the depolymerisation and hyperpolymerisation of microtubules on the distribution of DCX have shown that DCX is associated with microtubules and can induce the polymerisation of microtubules in vitro. These findings suggest that DCX is a novel microtubule-associated protein and also that it might be involved in the regulation of the organisation and stability of the microtubules (Refs 59, 60).

Periventricular heterotopia (PH)

PH (the existence of normal tissue in an abnormal location) occurs when subsets of neurones in the developing cerebral cortex fail to migrate and remain as nodules lining the walls of the ventricles. It is an X-linked dominant condition, and most affected males die at the embryonic

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stage. Affected females have normal intelligence and present with seizures and other systemic signs (Refs 61, 62).

The locus for PH has been genetically and physically mapped to chromosome Xq28. The candidate region included the gene *FLN1*. *FLN1* encodes the protein filamin 1, an actin-binding protein that binds other cytoskeletal regulators and plays an important role in migration in many cell types. It is expressed in the developing embryonic brains of mice, rats and humans, but only to a limited extent in the adult brain (Ref. 63).

Mutation analysis of the exons that encode the actin-binding domain in 25 affected females (both sporadic and familiar) identified four point mutations and a frameshift mutation. All five mutations have been predicted to cause truncation of the FLN1 protein and affect its critical role in neuronal migration.

Progressive myoclonus epilepsies (PMEs)

The PMEs are characterised by generalised tonic-clonic seizures, stimulus-sensitive myoclonus and progressive neurological dysfunction, including dementia and ataxia. Such epilepsies include: (1) Unverricht–Lundborg disease, (2) Lafora disease, (3) myoclonic epilepsy with ragged-red fibre syndrome (MERRF syndrome), (4) the neuronal ceroid lipofuscinoses (NCLs) and (5) sialadosis. The genetic bases of seven PMEs have been determined.

Unverricht–Lundborg disease

Unverricht–Lundborg disease is an autosomal recessive PME that has a clinical onset of 6–15 years of age. Histologically, the brain shows a marked loss of cerebellar Purkinje cells and also degenerative changes without inclusion bodies or the accumulation of storage material. The disease is rare in the general population, but relatively common in Finland (with an incidence of >1 in 20 000) and the western Mediterranean.

The disease gene locus has been mapped to chromosome 21q22.3 (Ref. 64). *CSTB*, the gene that is mutated in this disorder, has been positionally cloned and shown to encode cystatin B, an inhibitor of cysteine proteases (Ref. 65). Mutations in the coding region of *CSTB* occur in only ~14% of patients. In the majority of patients, the disease is associated with the expansion of a dodecamer repeat in the 5′ untranslated region (Refs 66, 67). Wild-type alleles contain two or three copies of this repeat, whereas mutant alleles contain more than 30 such repeats. A decrease in the level of expression of the messenger RNA (mRNA) that is encoded by this gene seems to be the primary mechanism in the pathology of Unverricht–Lundborg disease.

Cystatin B is ubiquitously expressed. Its role in the development of Unverricht–Lundborg disease is not known. Mice that lack cystatin B (which can be achieved by disrupting the mouse *Cstb* gene) develop myoclonic seizures and ataxia, associated with loss of cerebellar granule cells, and cellular changes that are characteristic of apoptotic (or 'programmed') cell death (Ref. 68). Thus, cystatin B might protect against cerebellar apoptosis. The caspases are a family of cysteine proteases that are involved in the initiation of apoptosis. It is thought that cystatin B might block apoptosis either, directly, by inhibiting caspase activity or, indirectly, by inhibiting the cathepsins, a group of lysosomal proteases that activate the caspases. However, cystatin B might prevent apoptosis even more indirectly, by controlling proteolysis.

Lafora disease

Lafora disease is an adolescent-onset (10–18 years) autosomal recessive form of PME, which is characterised by rapid neurological and cognitive decline. Its diagnosis is established by the presence, on skin biopsy, of characteristic polyglucosan inclusions called Lafora bodies. Lafora bodies are found in various tissues including the skin, liver, striated muscle and brain. Lafora disease is the commonest PME found in southern Europe, the Middle East, northern Africa and the Indian subcontinent.

The locus for Lafora disease has been mapped to chromosome 6q24 (Ref. 69). The gene that is mutated in Lafora disease, namely *EPM2A*, was cloned in 1998, using a positional-cloning approach (Refs 70, 71). It has been proposed that *EPM2A* encodes laforin, an intracellular protein tyrosine phosphatase (PTP). *EPM2A* is expressed in many tissues, including the brain. PTPs act to oppose the action of tyrosine kinases in cell-signalling pathways and regulate levels of phosphotyrosine in cells. Mutation analysis of 30 families that are affected by Lafora disease detected mutations in 10 families, which segregated with disease status. These mutations have been predicted to cause functionally deleterious effects in the enzyme laforin.

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Myoclonic epilepsy and ragged-red fibre syndrome (MERRF syndrome)

MERRF is a mitochondrial disorder that is characterised by progressive myoclonic epilepsy, mitochondrial myopathy, ataxia, deafness and dementia; 'ragged-red fibres' (i.e. the subsarcolemmal accumulation of mitochondria) are seen on skeletal muscle biopsy (Ref. 72). The onset of the disease (from childhood to adult life), the progression of the disease and the pattern of organ involvement vary widely among patients.

The mammalian mitochondrial genome is a circle of double-stranded DNA (dsDNA) consisting of 16 569 base pairs. It includes a non-coding hypervariable loop (of 1000 base pairs) that contains transcription promoters and a control region for replication, and shows a greater propensity to mutate than the coding region. The coding region encodes 37 genes, all of which are involved in the maintenance of mitochondrial bioenergetic function. Of these, 13 genes encode subunits of respiratory-chain enzyme complexes and the H^+-dependent enzyme adenosine triphosphatase (ATPase). Mitochondrial DNA (mtDNA) also contains genes for both ribosomal RNAs (rRNAs) and for a complete set of 22 transfer RNAs (tRNAs), which are sufficient to support mitochondrial protein synthesis. There is no redundancy, with each tRNA being essential for translation, and none of the tRNAs appears to be imported from outside the mitochondrion.

MtDNA is inherited from oocyte mtDNA, probably with no male contribution. Each human cell contains hundreds of mitochondria, each with several mtDNA molecules. At cell division, mitochondria and their genomes are randomly distributed to daughter cells. In normal individuals, all of the mitochondria and their genomes are identical (i.e. homoplasmy). However, the high rate of mutation of mtDNA can produce heteroplasmy, whereby wild-type and mutant genomes co-exist intracellularly. This occurs relatively infrequently, and might not always be pathological.

The commonest pathogenic mutation that is associated with MERRF is an A-to-G transition (i.e. transition of adenine to guanosine) at position 8344 in $tRNA^{Lys}$ (i.e. the tRNA for lysine; Ref. 73). This is a heteroplasmic mutation; the proportion of mutant DNA varies within families, and even among the tissues of the same individual. Carriers of the mutation (i.e. heterozygous individuals) who have only a small proportion of mutant mtDNA can either be unaffected or have a milder phenotype than homozygous individuals. A second mutation in the same gene, at position 8356, is associated with the disorder (Refs 74, 75). Both mutations cause premature termination of the translation of mitochondrial mRNAs, and thus reduced polypeptide synthesis. This can be the result of either ribosomal frameshifting or premature release of peptidyl-tRNA. In pedigrees that have the 8344 mutation, positive correlation has been shown between the severity of the disease, the age at onset, mtDNA heteroplasmy and the reduced activity of respiratory-chain complexes I and IV in skeletal muscle (Ref. 76).

Neuronal ceroid lipofuscinoses (NCLs)

The NCLs are a group of autosomal recessive neurodegenerative disorders that are characterised by the accumulation (in many cell types) of autofluorescent storage material that resembles ceroid and lipofuscin. As a group, they are the commonest cause of childhood neurodegenerative disease (Table 4). The NCLs have a worldwide distribution; however, three subtypes, namely infantile NCL, Finnish variant late infantile NCL and epilepsy with progressive mental retardation, occur predominantly in Finland.

Clinical features that are common to all childhood NCLs are progressive cognitive, motor and visual decline, and seizures. Seizures can be generalised tonic-clonic, myoclonic, astatic or atonic. The age of onset and clinical course vary with each NCL subtype. There are at least ten NCL subtypes, including an adult-onset form (with two subtypes). The commonest form is juvenile NCL, with an incidence of ~1 in 20 000 live births. At least eight genes have been predicted to be responsible for the NCLs, of which six have been mapped and four cloned (see Table 4; Refs 77, 78).

Mendelian disorders associated with epilepsy

Epilepsy is part of the disease phenotype in over 120 simple Mendelian disorders. Most of these disorders are rare, and altogether account for only ~1% of all epilepsies (Ref. 79). Epileptic seizures are a feature of many of the disorders involving an inborn error of metabolism, all of which are individually rare but have a combined incidence of ~1 in 5000 births (Ref. 79). Although discussion of these disorders is beyond the scope of this

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Table 4. Genetics of the neuronal ceroid lipofuscinoses (NCLs) (tab004mgu)

Type of NCL Age of onset and phenotype	Ultrastructure of stored material	Gene locus, chromosomal location and gene product and function	Refs
Infantile 6–18 months; early cognitive decline, early visual failure and late-onset seizures.	GROD	*CLN1*; 1p32; lysosomal palmitoyl-protein thioesterase (PPT), which removes lipid from proteins during their degradation.	90, 91
Late infantile (classical) 2–4 years; early cognitive decline, late visual failure and early-onset seizures.	CVB	*CLN2*; 11p15; lysosomal pepstatin-insensitive protease, a novel enzyme that is homologous to bacterial carboxypeptidases.	92, 93 94
Finnish late infantile 5–7 years; early cognitive decline, early visual failure and late-onset seizures.	FPP or CVB	*CLN5*; 13q21–q32; a novel membrane protein of unknown function.	95, 96
Variant late infantile 2–6 years; early cognitive decline, early visual failure and early-onset seizures.	FPP or CVB	*CLN6*; 15q21–23; unknown.	92
Turkish variant late infantile 2–4 years; early cognitive decline, variable visual failure and variable-onset seizures.	FPP or CVB	*CLN7*; unassigned location; unknown.	97
Late infantile with GROD 2–4 years; early cognitive decline, variable visual failure and early-onset seizures.	GROD and/or CVB	*CLN1*; 1p32; lysosomal PPT, which removes lipid from proteins during their degradation.	98
Juvenile 4–8 years; late cognitive decline, variable visual failure and late-onset seizures.	FPP	*CLN3*; 16p12; a novel membrane protein of unknown function.	99, 100 101
Variant juvenile 4–8 years; late cognitive decline, early visual failure and late-onset seizures.	GROD and/or CVB and/or FPP	*CLN1*; 1p32; lysosomal PPT, which removes lipid from proteins during their degradation.	102, 103
Progressive epilepsy with mental retardation 5–10 years; late cognitive decline, no visual failure and early-onset seizures.	GROD and CVB	*CLN8*; 8p23; unknown.	104
Kufs' disease 20+ years; early cognitive decline, no visual failure and either early-onset seizures or no seizures.	FPP or CVB or GROD	*CLN4*; unassigned location; unknown.	105

Abbreviations used: CVB = curvilinear body; FPP = fingerprint profile; GROD = granular osmophillic deposits.

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Table 5. Genetics of some Mendelian disorders that have epilepsy as part of their phenotype (tab005mgu)

Disorder Mode of inheritance	Clinical phenotype including seizures	Gene locus, chromosomal location and gene product and function	Refs
Tuberous sclerosis complex Autosomal dominant.	Cortical dysplastic lesions, renal cysts or angiolipomata, cardiac rhabdomyomas and hypopigmented skin lesions. Seizures: infantile spasms are characterised by simple and complex partial, myoclonic and GTCS, febrile convulsions.	(1) *TSC1*; 9q34; tuberin, which might be a GTPase-activating protein (it also has a tumour-suppressor role). (2) *TSC2*; 16p13.3; hamartin, the function of which is unknown, but it interacts with tuberin and has a tumour-suppressor role.	106 107 108
Fragile X syndrome X-linked.	Mental retardation, facial dysmorphism, high-arched palate and macro orchidism. Seizures: GTCS and partial with or without secondary generalisation.	*FMR1*; Xq27.3; FRMP, the function of which is unknown, but it might play a role in protein translation.	109
Angelman syndrome Imprinting (loss of maternal information).	Mental retardation, hyperactivity, happy disposition and ataxia. Seizures: absences, myoclonic and GTCS; EEG characterised by a large amplitude spike and slow waves.	Interstitial deletion; 15q11–13; de novo deletion or uniparental disomy. The genes deleted include: *UBE3A*, *GABRB3*, *GABRA5* and *GABRAG3*.	110 111
Rett syndrome Might be X-linked dominant.	Normal infancy but loss of acquired hand and communication skills, and gait apraxia. Seizures: characteristic EEG pattern, with or without GTCS.	Unknown, ?Xq28; unknown.	112
Neuro-fibromatosis Autosomal dominant.	Neurofibromata, gliomas, osseous dysplasia and learning difficulties. Seizures: complex partial infantile spasms, absences and GTCS.	*NF1*; 17q11.2; neurofibromin, which might be a GTPase-activating protein (has a tumour-suppressor role).	113 114
Huntington's disease Autosomal dominant.	Chorea, gait abnormalities, personality changes, dementia and dystonia. Seizures: frequent in early-onset disease, atypical absences, myoclonic and GTCS.	*HD* (or huntingtin); 4p16.3; huntingtin, which might be important in embryogenesis, especially neurogenesis.	115 116

Abbreviations used: EEG = electroencephalogram; GTCS = generalised tonic-clonic seizures; GTPase = GTP phosphohydrolase.

article, some Mendelian disorders for which >10% of patients have seizures as part of their phenotype have been summarised in Table 5.

Research in progress and outstanding research questions

Mutations in four genes that encode voltage-gated or ligand-gated ion channels have been found to be associated with human idiopathic epilepsies. All have been predicted to increase neuronal excitability, either directly or indirectly, leading to seizures. The study of neurological mouse mutants, whose phenotype is characterised by generalised spike-wave seizures, has also provided evidence for epilepsy being an ion-channel disease. Mutations in the pore-forming α subunits and the regulatory β and γ subunits of voltage-gated calcium channels have been identified in tottering, lethargic and stargazer mice (Refs 80, 81, 82). The exact physiological effects of the mutations that are associated with human disease, and the broader question of

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how widespread ion-channel dysfunction leads to a paroxysmal abnormality, which may be localised and age dependent, remain to be fully understood.

Mutations in a gene that encodes an actin-binding protein (which initiates neuronal migration), a gene that encodes a microtubule-associated protein (which may be involved in locomotion or morphogenesis) and a gene that encodes a possible cell-signalling protein (which directs neuronal migration) have been identified in three neuronal migration disorders. Abnormal cortical migration and the resultant abnormal neuronal networks could both generate seizures in the neuronal migration disorders. Studies of the rat hippocampus suggest that, in the developing brain, underlying pathology predisposes to seizure-induced neuronal damage, and the generation of further seizures (Ref. 83). The exact functions of the protein products of these genes, and the pathways of which they are a part, are not yet known.

The genes that are mutated in the PMEs encode proteins that maintain basic cell function by: (1) supplying energy demands, (2) controlling proteolysis and (3) controlling normal cell death. The loss of neuronal cells in the hippocampus and the dentate gyrus in individuals who have temporal-lobe epilepsy is thought to promote further seizures, by the formation of mossy fibre sprouting (the formation of new excitatory synapses by axonal sprouting; Ref. 84). In animal models of kindling-induced seizures, apoptotic cell death can account for some of this neuronal cell loss (Refs 85, 86). The loss of a cytoprotective effect, leading to neuronal cell loss, might induce epilepsy in the PMEs, and research is ongoing into the pathogenetic mechanisms involved in this group of disorders.

Clinical implications and applications

An important aspect of current research is the development of a DNA-based classification of the epilepsies. This would allow more precise diagnosis and prognosis for affected individuals. Knowledge of which of the current drugs in the therapeutic armamentarium is effective for which disorder could then be used to choose the most appropriate therapeutic strategy.

Molecular genetic studies indicate that the inherited idiopathic epilepsies are a group of ion-channel disorders. In the near future, therapies might be developed that are targeted against specific ion channels. It is hoped that these disease-specific agents will have advantages over existing anti-epileptic drugs with regard to their efficacy and reduced profile of side effects.

As our understanding of the pathophysiology of the PMEs increases, new therapies targeted at specific points in the degradation and storage pathways implicated in these disease processes might be developed. As a result of molecular genetic research, new therapeutic targets might also be discovered for other Mendelian disorders that are associated with epilepsy.

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Further reading, other resources and useful contacts

The Lissencephaly Network website includes information about neuronal migration disorders; this site will be of interest to both the general public and clinicians.
http://www.lissencephaly.org/

The American Epilepsy Society has an Internet links page, which includes links to *Epilepsia* (the journal of the International League Against Epilepsy), and to the Epilepsy Foundation of America (EFA), including its gene discovery project.
http://www.aesnet.org/intres/index.htm

The National Society for Epilepsy (UK) website provides useful information about the epilepsies, which has mainly been written for patients.
http://www.erg.ion.ucl.ac.uk/nsehome/open.html

Features associated with this article

Figures

Figure 1. Causes of epilepsy: non-genetic (fig001mgu).
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