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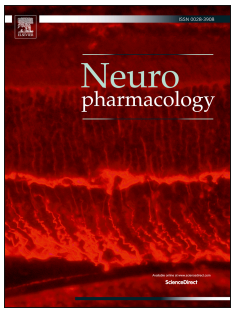

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For channelopathy special issue

Genetics update: monogenetics, polygene disorders and the quest for modifying genes

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Abstract

The genetic channelopathies are a broad collection of diseases. Many ion channel genes demonstrate wide phenotypic pleiotropy, but nonetheless concerted efforts have been made to characterise genotype-phenotype relationships. In this review we give an overview of the factors that influence genotype-phenotype relationships across this group of diseases as a whole, using specific individual channelopathies as examples. We suggest reasons for the limitations observed in these relationships. We discuss the role of ion channel variation in polygenic disease and highlight research that has contributed to unravelling the complex aetiological nature of these conditions. We focus specifically on the quest for modifying genes in inherited channelopathies, using the voltage-gated sodium channels as an example. Epilepsy related to genetic channelopathy is one area in which precision medicine is showing promise. We will discuss the successes and limitations of precision medicine in these conditions.

Keywords

genotype; phenotype; modifier; precision; personalized; epilepsy

Highlights

- The genetic channelopathies are a broad group of diseases which affect multiple organ systems
- Most genetic channelopathies demonstrate marked phenotypic pleiotropy
- Mechanisms that underpin phenotypic pleiotropy include functional effects of specific mutations, the effects of modifying genes, and environmental influences
- Precision medicine treatment of channelopathies has shown early promise, but faces a number of challenges

Introduction

Ion channels are a broad category of transmembrane proteins that share the physiological property of being involved in the regulation of ion flux across cell membranes. In the human genome there are over 400 genes encoding ion channels. Ion channels are expressed in almost all cell membranes, as well as in the membranes of many intracellular organelles, and they are involved in a diverse range of physiological processes. It is therefore no surprise that ion channel dysfunction has been implicated in a wide spectrum of human diseases. The clinical features and age of presentation of diseases related to ion channel dysfunction are dependent on the physiological role of the ion channel in question, as well as the tissue-specific and age-specific expression of its gene(s). Many different mechanisms may lead to ion channel dysfunction, including primary genetic defects in the coding sequence for the channel protein itself, genetic defects in genes and/or noncoding DNA implicated in the expression and regulation of ion channel genes, and acquired ion channel dysfunction as a result of autoimmune destruction of ion channels, which itself is likely to have genetic determinants. Acquired ion channel dysfunction has been observed in rats with chemically-induced seizures, and is likely to involve a mixture of direct toxic/ischaemic damage to ion channels, epigenetic dysregulation of ion channel genes, and intrinsic susceptibility to ion channel dysfunction. In turn, intrinsic susceptibility to ion channel dysfunction is likely to be determined by genetic variants in the ion channel itself, variants in genes that are involved in regulating ion channel genes, and the immune system. Thus, in the channelopathies, as with most human disease, a picture emerges of a complex interplay between genetic, epigenetic, and environmental factors. The case that such complex interplay is likely to underlie all the channelopathies, even those with apparently "monogenetic" causes, is evidenced by the finding that clear genotype-phenotype relationships are rarely observed in these conditions.

Genetic channelopathies

Since ion channels are present in almost all tissues, and they perform a wide range of functions, ion channel disease presents a highly diverse group of conditions. Figure 1 summarises the currently known human channelopathies. Complete details and references are available in the data supplement.

Phenotypic pleiotropy

A brief glance at Figure 1 will immediately reveal that pathogenic variants in many ion channel genes are associated with remarkable phenotypic pleiotropy. For example, heterozygous mutations in the potassium channel gene *KCNQ2* have been identified in three distinct neurological disorders: self-limiting familial neonatal seizures(Singh et al. 1998), early infantile developmental and epileptic encephalopathy(Weckhuysen et al. 2012), and peripheral nerve hyperexcitability(Wuttke et al. 2007). In some cases phenotypic pleiotropy extends beyond a single organ system: *KCNJ5* mutations have been found in long-QT syndrome(Yang et al. 2010), Andersen Tawil Syndrome (a multisystem disorder characterized by periodic paralysis, ventricular arrhythmias, and distinctive dysmorphic facial and/or skeletal features)(Kokunai et al. 2014), and in familial hyperaldosteronism(Choi et al. 2011). In fact, phenotypic pleiotropy is more the rule than the exception in the genetic channelopathies. Now that the extent of phenotype variability associated with ion-channel genes has been widely appreciated, recent scientific efforts have focussed gaining a deeper understanding of *how* any particular mutation may relate to the phenotype seen: the so-called "genotype-phenotype relationship."

Factors influencing the genotype-phenotype relationship

1. Mutation hotspots

In all known ion channel diseases in which non-truncating variants have been implicated, mutational hotspots, regions of the gene where there is clustering of pathogenic variants in association with disease, are seen. These hotspots correspond with functionally important regions of the ion channel, such as the voltage-sensor region, ligand binding site, or the pore-forming region(Zuberi et al. 2011). These regions demonstrate low mutational tolerance across species and within healthy human populations (Swanger et al. 2016). In those channelopathies in which a spectrum of disease severity

is observed, there is a sense that in more severe cases, mutations are more likely to be observed in functionally important regions, though even in one of the most well studied channelopathy genes, *SCN1A*, this remains to be proven(Harkin et al. 2007).

2. Single variant correlations

In a minority of channelopathies certain phenotypes have only ever been observed in association with a single variant, or amino acid change. An example of this is CAPOS (**C**erebellar ataxia, **A**reflexia, **P**es cavus, **O**ptic atrophy, and **S**ensorineural deafness) syndrome, which is caused by heterozygous mutations in the *ATP1A3* gene, encoding the catalytic α_3 subunit of the Na^+/K^+ ATPase. Heterozygous missense mutations in *ATP1A3* have been observed in two other phenotypes: alternating hemiplegia of childhood (AHC) (Rosewich et al. 2012), and rapid onset parkinsonism dystonia (RPD)(de Carvalho et al. 2004). In AHC and RPD, causative mutations have been identified across the length of the gene, though only one variant (p. Asp923Asn) has been found in both AHC and RPD patients(Zanotti-Fregonara et al. 2008, Anselm et al. 2009, Roubergue et al. 2013). However, in CAPOS syndrome, only a single, recurrent, causative variant (p.Glu818Lys) has been identified(Demos et al. 2014, Heimer et al. 2015, Potic, Nmezi & Padiath 2015). It has been postulated that the reason that the p.Glu818Lys mutation leads to a the distinct phenotype of CAPOS syndrome is because this mutation would be predicted to lead to a gain-of-function in the ion channel(Demos et al. 2014), whereas the disease-causing mutations seen in AHC and RPD cause a loss-of-function)(de Carvalho et al. 2004). However, no formal functional studies have been published using a p.Glu818Lys model to back up this theory. With mutations in the potassium channel gene *KCNQ2*, the phenotype seen is of focal tonic seizures beginning in the first days of life. Recently, the single variant (p.Arg198Glyn) has been found in five cases who did not have neonatal seizures, but presented with infantile spasms, hypsarrhythmic EEG, and marked developmental regression between 4 and 6 months of life. Using *in vitro* electrophysiology studies, the authors demonstrated that this variant conferred gain-of-function properties on the ion channel(Millichap et al. 2017). In *SCN2A*, a gene in which mutations

are associated with a wide variety of epilepsy phenotypes, the recurrent p.Arg853Gln variant has been found exclusively in cases presenting with infantile spasms(Wolff et al. 2017, Brain).

3. Predicted pathogenicity of variants

A number of commercially available *in silico* tools (SIFT®, Polyphen®, Mutation Taster®) are frequently used to help geneticists predict the likely pathogenicity of genetic variant that has been identified through sequencing. These tools typically incorporate information about the evolutional conservation of the affected sequence as well as observed mutation rates in healthy populations. Often, in clinical practice, such tools are used in a rather binary fashion to determine whether a genetic variant is causative or not. However, in reality there is likely to be a spectrum of pathogenicity observed with many rare variants. In time, if large shared datasets are collected systematically, *in silico* tools may be used to help define the spectrum of many channelopathies.

The best example of a channelopathy in which the pathogenicity scores have been shown to correlate with phenotype is epilepsy due to *SCN1A* mutations. To date more than 1200 different mutations in the *SCN1A* gene have been identified in association with epilepsy(Djémié et al. 2016). Milder cases of *SCN1A*-related epilepsy are often inherited and cause familial febrile seizures, and genetic epilepsy with febrile seizures plus (GEFS+)(Claes et al. 2001), whereas at the opposite end of the phenotypic spectrum is Dravet syndrome, a severe epilepsy beginning in infancy, in which developmental stagnation is often seen with epilepsy onset(Escayg et al. 2000). Zuberi et al. demonstrated that where *SCN1A* mutations affected the voltage sensing region of the channel, patients with Dravet syndrome had significantly greater *silico* evidence of pathogenicity than patients with GEFS+ (Zuberi et al. 2011).

4. Functional effects of mutations

Defining the functional effects of a genetic variant is gold standard for proving pathogenicity, and requires *in vitro* and/or *in vivo* modelling. The most commonly used models involve transfecting cell

lines (for example human embryonic kidney cells or *Xenopus laevis* oocytes) with the variant being investigated, and then using the patch clamp technique(Neher and Sakmann 1976) to measure the properties of ion currents compared with wild-type cells(Shalaby et al. 1997).

Based on such functional characterisations, ion channel mutations are often referred to as either "loss-of -function" or "gain-of-function," though in reality such terms oversimplify what are often complex alterations in ion channel function(Swanger et al. 2016). Broadly speaking, loss-of-function mutations are associated with reduced channel permeability, and gain-of-function mutations lead to an increase in ion flux.

Loss-of-function:

On the whole, disease causing missense mutations in ion channel genes are more likely to result in reduced permeability (loss-of-function) than increased permeability (gain-of-function). Reduced ion permeability may also result from a whole gene deletion or truncation mutation as a result of halpoinsufficiency. For some ion channels, such as $Na_v1.1$ and $K_v7.2$(Schroeder et al. 1998) normal ion channel function appears to be dependant on biallelic expression of the gene, whilst other ion channels, such as CFTR, entirely tolerate haploinsufficiency without apparent functional consequence. Therefore, in the absence of functional studies, loss-of-ion channel function cannot be inferred from the finding of a nonsense mutation, frameshift mutation, or whole gene deletion (null mutation). Furthermore, even in ion channels that do not tolerate haploinsuffiency, the functional consequences of null mutations may differ from those of loss-of function missense mutations. Compared with null mutations, loss-of-function missense mutations may either result in a functionally less impacted channel, due to residual function of the mutant channel, or conversely in a more severely affected channel, where there is a dominant-negative impact from the mutant on the wildtype channel(Shalaby et al. 1997, Warner et al. 2016). A good example of how loss-of-function can take several different forms, and how this can influence phenotype, is seen with *CHRND*, which encodes the δ polypeptide subunit of the nicotinic acetylcholine receptor expressed

in skeletal muscle. Gain-of-function mutations in *CHRND* cause slow channel congenital myaesthenic syndrome(Gomez et al. 2002), whilst loss-of-function of this channel can take three forms, with each associated with a different phenotype: recessive missense mutations that result in a slowing of channel opening cause fast channel congenital myasthenic syndrome(Gomez et al. 2002); recessive missense mutations that impair co-clustering of the acetylcholine receptor with rapsyn lead to reduced expression of normally functioning receptors, and have been found in association with a more severe congenital myasthenic syndrome(Müller et al. 2006); and recessive truncation mutations (i.e. complete deficiency) cause the most severe phenotype of multiple pterygium syndrome, an embryonically lethal syndrome associated with multiple bone and spinal fusions(Michalk et al. 2009). For some channelopathies distinct phenotypes are seen in the haploinssufficient state compared with the complete deficiency state (as a result of biallelic loss-of-function mutations). With *SCN4A*, heterozygous loss-of-function mutations lead to hypokalaemic periodic paralysis, hyperkalamic periodic paralysis or paramyotonia congenita(Ptáček et al. 1991, Jurkat-Rott et al. 2000, Ptáček et al. 1992), whilst biallelic loss-of-function mutations are associated with a distinct phenotype of congenital myasthenic syndrome(Tsujino et al. 2003).

Gain-of-function:

Even more than loss-of-function mutations, gain-of-function changes are currently very difficult to impute or model *in silico*, and almost always require *in vitro* techniques such as patch clamp to demonstrate. “Gain-of-function” refers to a variety of possible functional changes. Channels may be rendered in a permanently open state, or there may be an increased frequency of channel opening, and increased sensitivity to ligand binding, or delayed channel closure. These different gain-of-function effects demand different techniques to demonstrate. It has been shown in epilepsy related to gain-of-function *KCNT1* and *KCNQ2* variants, that the degree of increased channel permeability correlates with the severity of the phenotype(Millichap et al. 2017, Milligan et al. 2014). To infer GOF in human tissue on the basis of single cell line functional models is problematic. The extent to

which mutant channel subunits are expressed relevant in human brain tissue may not be known, and reduced cell surface expression of apparently functionally enhanced subunits, as a result of impaired trafficking(Swanger et. al 2016) may counteract any gain of function properties(Martin et al. 2010). Demonstration of a gain-of-function mutation can have important therapeutic implications, since it is currently easier to block ion channels with medications than to open dysfunctional ones. This will be discussed in the ***precision medicine*** section of this paper.

Channelopathies with opposing phenotypes:

There are some genetic channelopathies that demonstrate marked differences in the phenotypes observed with loss-of-function mutations versus gain-of-function mutations. The best examples of this are the congenital disorders of pain related to sodium channel mutations, and some of the potassium channel-related cardiac dysrhythmias.

The sodium channel gene *SCN9A* encodes $Na_v1.7$, which is expressed predominantly in dorsal root ganglion cells and sympathetic ganglion neurons(Toledo-Aral et al. 1997). Gain-of-function mutations in *SCN9A* have been found in two conditions characterised by excessive pain perception, primary erythromelagia and paroxysmal extreme pain disorder(Fischer and Waxman 2010) whilst biallelic loss-of-function mutations in the same gene have been found in what could be considered an opposing phenotype, congenital insensitivity to pain(Cox et al. 2006). A similar picture is seen in the cardiac channelopathies caused by *KCNH2* and *KCNQ1* where gain-of-function mutations are found in short QT syndrome(Brugada et al. 2004, Bellocq et al. 2004), whilst loss-of-function mutations are seen in long QT syndrome(Curran et al. 1995, Wang et al. 1996). These could also be considered opposing phenotypes, although both predispose to cardiac arrhythmias.

Complex genotype-phenotype relationships:

Stark contrasts between the phenotypes associated with gain-of-function and loss-of-function in ion channelopathies are in fact quite rare. More commonly a complex relationship between genotype

and phenotype is observed. This is particularly the case with conditions that are known to have complex genetic aetiologies, such as epilepsy and the predisposition to cardiac dysrhythmia, where other genetic modifiers are likely to complicate the relationship between genotype and phenotype. These will be discussed in the section on ***the quest for modifying genes.*** Gain-of-function and loss-of-function mutations of *KCNA2* have both been associated with a severe early-onset epilepsy phenotype, though efforts have been made to delineate the two phenotypes, which may become clearer with the discovery of more cases(Syrbe et al. 2015). Similarly, both gain- and loss-of-function variants have been found in severe early onset epilepsies caused by *KCNB1*(Torkamani et al. 2014), *KCNQ2*(Weckhuysen et al. 2012, Millichap et al. 2017), *GRIN2A*(Carvill et al. 2013), *GRIN2B*(Lemke et al. 2014), *HCN1*(Nava et al. 2014), and *SCN2A*(Wolff et al. 2017), as well as in GEFS+ caused by *SCN1A* mutations(Lossin et al. 2002). These findings suggest that in a state of health neuronal networks expressing these ion channels are poised in a state of equilibrium, the disruption of which, in either direction, can lead to excessive synchronous excitation(Swanger et al. 2016). One of the reasons why disruption of this equilibrium in either direction can predispose to seizures is likely because most of these channels are expressed in both excitatory and inhibitory neurones. This is important to bear in mind when using drugs that act on ion channels to treat epilepsy since some drug classes when used in patients with particular channelopathies may lead to a paradoxical exacerbation of seizures, as is seen with the use of sodium-channel-blocking drugs in *SCN1A*-related epilepsies(Brunklaus et al. 2013, Ogiwara et al. 2007).

In some channelopathy-related epilepsies, a clear genotype-phenotype relationship is seen at one end of the mutational spectrum, but the relationship becomes less clear beyond that. For example in *SCN1A*-related epilepsy a severe phenotype is typically seen with whole gene deletions and truncating mutations compared with missense mutations(Zuberi et al. 2011), whilst in *KCNQ2*-related epilepsies the opposite is true, and whole gene deletions and truncation mutations are associated with self-limiting seizures(Singh et al. 1998, Biervert et al. 1998, Allen et al. 2014, Claes et al. 2004, Miceli et al. 2013, Heron et al. 2007), whilst more severe epilepsies are always associated

with missense mutations, presumably due to gain-of-function, or dominant negative effects(Weckhuysen et al. 2012, Millichap et al. 2017, Miceli et al. 2013, Saitsu et al. 2012, Borgatti et al. 2004).

Such is the complexity of genotype-phenotype relationships in the channelopathies, and the myriad of variables that could potentially influence this, progress in this area will undoubtedly depend on large international data-sharing efforts in which extensive phenotype and genotype data are shared in common databases, as exemplified by the Epilepsy Phenome/Genome project (http://www.epgp.org).

Ion channel-regulating genes

The genetic channelopathies are not restricted purely to conditions caused by mutations in genes encoding the ion channels themselves. Many other genes are likely to play roles in the regulation of ion channels at molecular (e.g. accessory subunits), transcriptional (e.g. chromatin regulating genes), and translational (e.g. microRNA)(Jiang, Zhang and Chan 2012, Wang 2013) levels. Genes encoding ion channel accessory subunits are included in red in the data supplement. Pathogenic mutations in *CNTN2*(Stogmann et al. 2013) and *CNTNAP2*(Strauss et al. 2006), which encode contactin associated protein 2 (CASPR2) have been shown to disrupt clustering of potassium channels at the nodes of Ranvier in myelinated axons(Poliak et al. 2003, Peñagarikano et al. 2012) and cause a childhood-onset epilepsy with associated regression in speech development(Smogavec et al. 2016). *FGF12* and *FGF13* encode fibroblast growth factor proteins which interact with the C-terminus of voltage gated sodium channels(Goldfarb 2012), and mutations in these genes have been found in patients with similar phenotypes to those seen in *SCN1A*-related epilepsy(Puranam et al. 2015, Siekierska et al. 2016, Al-Mehmadi et al. 2016). In cardiology, a large number of genes(Shy, Gillet and Abriel 2013), including *SNTA1*(Wu et al. 2008), *MOG1*(Kattygnarath et al. 2011), and *GP1DL*(Van Norstrand et al. 2007) have been shown to interact with $Na_v1.5$, and have been implicated in causing Brugada and long-QT syndromes. In neuromuscular disease, rapsyn, encoded by the RAPSN gene, is known to play

a major role in the localisation of skeletal muscle acetylcholine receptors(Apel et al. 1995), and RAPSN mutations are associated with congenital myaesthenic syndrome (Ohno et al. 2002) and fatal akinesia deformation sequence (Michalk et al. 2009).

The role of ion channels in complex genetic diseases

The role of ion channel mutations in disease extends beyond rare monogenic diseases. Polymorphisms in ion channel genes have been implicated in susceptibility to several common diseases, including schizophrenia(Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium 2011), common forms of epilepsy(International League Against Epilepsy Consortium on Complex Epilepsies 2014), atrial fibrillation(Ellinor et al. 2012), and diabetes(Reis et al. 2000, Hansen et al. 2005). Genome wide association studies (GWAS) are powered to identify relatively common variants (typically found in ≥5% of the population) that have a moderate impact on disease susceptibility across the population as a whole. Very large sample sizes are needed to detect variants with genome-wide significance, and many relevant genetic contributes to common disease are likely to be missed by current GWAS approaches thanks to said variants being too rare, or too small in effect size. Furthermore, variant signals picked up by GWAS may not necessarily be causative *per se* since all inherited variants in a population segregate to some extent with other variants in nearby genes, a phenomenon known as linkage disequilibrium. Nonetheless it is worthy of note that genome wide significance has been reached for an *SCN1A* variant in a meta-analysis of epilepsy GWAS (total 8,696 cases and 26,157 controls)(International League Against Epilepsy Consortium on Complex Epilepsies 2014), for *CACNA1C* in a schizophrenia GWAS (8,422 cases and 21,397 controls)(Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium 2011), and for both *KCNN3* and *HCN4* in atrial fibrillation(6,707 cases and 52,426 controls)(Ellinor et al. 2012).

An alternative approach to GWAS that can be used to identify rarer variants that may play a role in common disease susceptibility is to compare the number of observed rare variants in any given gene between a disease population and a control population, a technique that is referred to as burden

analysis. Ion channels that have been implicated in type 2 diabetes through this type of methodology have been *KCNJ11*(Hansen et al. 2005) and ABCC8(Reis et al. 2000). With regards to epilepsy, the Epi4K consortium and Epilepsy Phenome/Genome project expanded this methodology to compare the exomes of 1185 individuals with familial epilepsies with 3,877 control subjects. In the epilepsy group there were significantly higher proportions of ultrarare variants in a number of ion channel genes, including *GABRG2, SCN1A*, *ATP1A3, KCNQ2, CACNA1B,* and *GRIN2A*(Epi4K consortium, Epilepsy Phenome/Genome Project 2017). The authors concluded "that genes established as responsible for familial and rare severe epilepsies are also associated with common epilepsies." Atrial fibrillation and epilepsy are examples of common diseases that appear to have both single gene causes and polygenic causes, and yet the very same genes have been implicated in both types of causation. Because these are such commonly observed phenotypes, disentangling the relative contribution of any given gene remains an enormous challenge, if not an impossibility. The genetic aetiology of these conditions is therefore perhaps best conceptualised as part of a spectrum, ***as illustrated in Figure 2.***

The quest for modifying genes

In all but the most severe and highly penetrant single gene channelopathies, genetic modifiers are presumed to exist, since phenotypic variability is observed among those harbouring identical genetic mutations. For example, in affected members of families with genetic epilepsy with febrile seizures plus (GEFS+) due to mutations in *SCN1A*, there are some individuals with a markedly more severe phenotype(Escayg et al. 2000). The same phenomenon is observed in GEFS+ families with *GABRG2* mutations(Harkin et al. 2002), and in families with *KCNQ2* mutations, the majority of whom have self-limiting neonatal seizures, but some of whom continue to have epileptic seizures into childhood and adulthood(Singh et al. 2003). Whilst *SCN1A* truncations are generally found in association with more severe phenotypes, and in patients who experience a seizure-worsening when the anti-epileptic drug Carbamazepine is used, there are isolated case reports of patients with *SCN1A*

truncations who have mild phenotypes and Carbamazepine-responsiveness(Takaori et al. 2017). In some channelopathies entirely different phenotypes can be seen in association with an identical mutation. For example in a family in which the mother and son shared the same missense mutation in *ABCC8* the son presented with congenital hyperinsulinism, whilst the mother had a focal epilepsy but demonstrated completely normal regulation of insulin secretion(Stranks et al. 2016). The concept of genetic modifiers is most compelling in the monogenic forms of epilepsy, autism, and cardiac arrhythmias – conditions where complex polygenic aetiology is already presumed to exist for the majority of cases, and the role of common, low-effect variants is already established(Speed et al. 2014). However, the challenge of identifying genetic modifiers is huge. GWAS requires large sample numbers to identify genomic signals of disease association, so to apply this same methodology to approach the identification of genetic modifiers in a small number of cases where a rare monogenic cause has been identified is an impossibility.

Mouse models of sodium channel related epilepsy have however made some headway in identifying candidate disease modifying genes thanks to the initially serendipitous discovery that *SCN2A* mutants demonstrate a strain-dependant phenotype. Hawkins et al. found that in the *SCN2A*^{Q54} (mice carrying the gain-of-function mutation GAL879-881QQQ) model of epilepsy [B6XSJL/J]F1 mice demonstrated a more severe phenotype than C57BL/6J mice. They used mapping techniques to identify a possible modifying variant on the *HLF* (hepatic leukaemia factor) gene. They then crossed both *SCN2A*^{Q54} and *SCN1A* knockout mice with *HLF* knockout mice and demonstrated that in both *SCN1A* and *SCN2A* models *HLF* deficiency was associated with a more severe phenotype. Because *HLF* haploinsufficiency is believed to result in downregulation of the pyridoxal kinase enzyme which converts pyridoxine to pyridoxal 5' phosphate, they gave the *SCN2A*^{Q54} mice a pyridoxine restricted diet and demonstrated a worsening of seizures(Hawkins and Kearney 2016). Further work by this same group on mouse models has identified candidate genetic modifiers of sodium channel epilepsy in other ion channel genes, including a *GABRA2* variant in an *SCN1A* knockout model, which was

partially rescued by Clobazam(Hawkins et al. 2016), and a *CACNA1G* variant in the *SCN2A*^{Q54} mutant model(Calhoun et al. 2016).

In a parallel story, mouse models have been used to investigate for genetic modifiers of cardiac channelopathies. Remme et al. demonstrated that in an *SCN5A*$^{1798insD/+}$ model, 129P2 mice demonstrated a more severe phenotype than FVB/N mice. They used pan-genomic mRNA expression techniques to uncover a dramatic reduction in *SCN4B* mRNA in the more severely affected strain(Remme et al. 2009).

In humans, evidence for genetic modifiers of channelopathies is largely limited to isolated case reports of patients with pathogenic or possible pathogenic mutations identified in additional genes to the primary ion channel – often referred to as "blended phenotypes." Examples of such blended phenotypes include: a family with *SCN5A*-related cardiac conduction disorder in which the presence of a p.Lys897Thr variant in HERG2 segregated with those members of the family who had a more severe phenotype (Jagodzinska et al. 2016); an individual with a very severe progressive cardiac conduction disorder who was found to have predicated damaging mutations in both *KCNK17* and *SCN5A*(Friedrich et al. 2014); and 2 siblings who had basal ganglia calcifications and generalized epilepsy who were found to have heterozygous damaging mutations in both *CHRNB2* (known to be associated with familial epilepsy) and *SLC20A2* (known to cause primary familial basal ganglia calcification)(Fjaer et al. 2015). There is also increasing evidence that common polymorphisms elsewhere in the same ion channel gene that is believed to be causative of the disease may influence phenotype. This phenomenon has been reported for the c.1059G>A polymorphism in *KCNQ1* which has been associated with further prolongation of the QT interval in patients with long QT syndrome due to pathogenic *KCNQ1* mutations(Kapplinger et al. 2017), and with the *SCN4A* p.Ser906Thr polymorphism which appears to exacerbate the phenotype of patients with hyperkalaemic periodic paralysis caused by p.Iso693Thr mutations in the same gene(Fan et al. 2017).

It is of course equally possible that some genetic variants confer relative protection from channelopathy-related disease, but these are likely to be even harder to identify than deleterious genetic modifiers. In a mouse model of *SCN1A*-related Dravet syndrome, knockout of both Tau alleles resulted in a milder phenotype with reduced epileptic spikes on EEG, and improved learning, memory and executive function(Gheyara et al. 2014). Similarly, knockout of *SCN2A* has been demonstrated to improve survival in a *KCNA1-null* mouse model of SUDEP (Mishra et a. 2017).

Precision medicine

The ion channel-related epilepsies are an area of medicine where precision therapy has shown early promise. The idea that dysfunctional channels can be targeted with drugs acting on them is a highly attractive one, particularly as this has emerged as a possibility in an area of medicine where treatment resistance is common(Berg et al. 2009, Cockerell, Sander and Shorvon 1995), and evidence based therapy is lacking(Marson et al. 2007a, Marson et al. 2007b). Intuitively it is easier to use drugs to block the action of an overactive ion channel than to open up an underactive one, and this has proven to be the case, with the majority of precision medicine successes reported so far being in cases where there is a gain-of-function channelopathy. Due to the extreme rarity of these cases, all evidence base is restricted to anecdotes. Nonetheless these at least provide a proof-of-principle for precision medicine in channelopathies.

Current approaches to precision-medicine begin with identification of the genetic cause of a disease and thereafter take two broad forms: i) rational choice of existing therapies based on established evidence or known mechanisms of action; ii) systematic screening for novel or repurposed drugs using models that incorporate the mutation or genetic mechanism. In future is it possible that precision medicine may not need, nor indeed benefit, from exact knowledge of genetic causation. If high throughput induced progenitor stem cell (iPSC) models can be developed for drug screening, then it may be possible to identify the optimum medication for an individual's disease based on a model that takes into account the full genomic background of an individual, including disease

modifying genes(Avior, Sagi and Benvenisty 2016), though such models would fail to account for the tissue-specific effects of somatic mutations. Another future avenue for precision medicine is the development of non-genomic biomarkers that predict treatment response, such as metabolomic profiles, or functional and spectroscopic imaging(Al Zweiri et al. 2010).

Rational therapy choice based on established evidence/known mechanisms of action

This type of precision medicine is already common practice in some childhood-onset epilepsies. When a patient is found to have an *SCN1A* mutation, most clinicians will withdraw, or avoid using, any sodium channel blocking medications, based on anecdotal reports of seizure-worsening(Brunklaus et al. 2013). This approach can be rationalised by the knowledge that these mutations cause loss-of-function and that $Na_v1.1$ is preferentially expressed in inhibitory interneurons(Ogiwara et al. 2007). Therefore further reducing the excitability of these inhibitory neurones through sodium channel blockade would be expected to promote overall neuronal excitability. Loss-of-function mutations in *KCNQ2* can cause self-limiting familial neonatal seizures as well as a more severe phenotype of early-onset developmental and epileptic encephalopathy. In *KCNQ2* anecdotal evidence supports the use of sodium channel blocking drugs(Pisano et al. 2015). This can be rationalised on the basis that most *KCNQ2* mutations are loss-of-function, and that $K_v7.2$ is preferentially expressed in excitatory hippocampal neurones. Loss of $K_v7.2$ function results in an increased intracellular K^+ concentration. If the resulting reduction in polarisation of the neuronal cell membrane is counteracted by blocking the inwards movement of sodium ions, the increased excitability may be balanced out. Other examples of how the scientific understanding of the action of an ion channel has helped to guide drug choice are the use of Mexilitine in *SCN2A*-related epilepsy(Foster et al. 2016), Retigabine (a potassium channel opener) for *KCNQ2/KCNQ3*-related epilepsies (Millichap et al. 2016), and sulphonylureas in neurodevelopmental disorders related to *KCNJ11* mutations(Slingerland et al. 2008).

In long QT syndrome, beta blockers are thought to be the most rational treatment choice for patients with *KCNQ1* mutations(Barsheshet et al. 2012), whilst medications that preferentially act on the fast inactivation type of sodium channel, are believed to be most effective for those with *SCN5A*-(Moss et al. 2008, Priori et al. 2000).

Using *in vitro* and *in vivo* models to screen for effective drugs

This can be done on a small scale using individual patient genotypes to test a limited number of rationally chosen drugs, or on large scale using high throughput models of genetic channelopathy to test a large number of drugs. The main reported successes of the former approach are with epilepsies due to gain-of-function mutations in *KCNT1, GRIN2A, GRIN2D, and SCN8A.*

Following anecdotal reports of treatment success of quinidine in *KCNT1*-related severe epilepsies (Bearden et al. 2014), Mikati et al. demonstrated *in vitro* that quinidine inhibited h*KCNT1* currents in a *Xenopus oocyte* model. The oocytes expressed the mutations found in two patients with epilepsy of infancy with migrating focal seizures (EIMFS) due to *de novo KCNT1* mutations. Both patients were subsequently treated with quinidine, but only one had a clinically detectable reduction in seizures(Mikati et al. 2015). The reason for these discordant clinical responses to quinidine despite similar *in vitro* evidence for efficacy is unclear, and highlights the need to consider the functional impact of mutations within a more systems-wide context.

Almost identical approaches, involving *in vitro* testing of drugs in *Xenopus oocytes* or human dorsal root ganglion cells expressing the mutations found in real patients, prior to a trial of medication, have been used successfully in *GRIN2A* (Memantine)(Pierson et al. 2014), *GRIN2D* (Memantine and Magnesium sulphate)(Li D. et al. 2016), *SCN8A* (Phenytoin)(Barker et al. 2016), *SCN4A*(Desaphy et al. 2016), and *SCN9A*(Carbamazepine)(Geha et al. 2016).

Whilst these small scale and highly personalised approaches have clearly delivered results to the patients concerned, scaling them up remains a challenge, and the number of drugs that has been tested for *in vitro* effect in each case has been limited. Conversely, high throughput screening of

medications for efficacy in specific genetic channeloapthies using iPSC(Avior, Sagi and Benvenisty 2016) and *in vivo* whole organism models has facilitated the identification of new and repurposed medications. For example, through *in vivo* modelling in zebrafish identified Clemizole (an antihistamine) as a potential treatment for *SCN1A*-related epilepsy(Baraban, Dinday and Hortopan 2013). Whilst whole organism models have the advantage of more accurately reflecting complete neuronal circuitry, they are more expensive to produce, and are not specific for an individual genetic variant.

SCN1A as an example of the challenges facing precision medicine

Whilst in Dravet syndrome knowledge of the *SCN1A* mutation does appear to provide clinicians with immediately tangible information to guide treatment choice,(Brunklaus et al. 2013), in reality the relationship between genotype and treatment response is likely to be highly complex. There are reports of patients who in fact benefit from sodium channel blocking medications, and who experience a deterioration when these medications are withdrawn(Takaori et al. 2017, Dalic et al. 2015). To some extent, variations in medication response may be explained by the location and functional effect of the *SCN1A* mutation. There is some suggestion that those patients with *SCN1A* truncation mutations are more likely to respond to Stiripentol and Topiramate, whilst those with missense mutations are more likely to respond to Clonazepam and Triple Bromide. However these data come from retrospective reports from clinicians and must be viewed with caution(Ishii et al. 2016). As discussed above, dividing mutations into truncating and non-truncating oversimplifies the functional consequences of genetic variants. To truly understand medication response in *SCN1A*-related epilepsy a more complete analysis of the functional effects of specific missense mutations is required, as well as a consideration of the influence of $Na_v1.1$ channel expression and distribution within neuronal networks (which is likely to vary between individuals), and the role of other genetic modifiers.

Many other genetic factors are likely to have an impact on treatment response, besides the particularities of the ion channel mutation. These include: predisposition to specific adverse drug reactions, which is often related to HLA type(Amstutz et al. 2014); genetic variants that affect drug absorption, distribution, metabolism, and elimination(Chen et al. 2014, Shaheen et al. 2014, Löscher et al. 2009, Saygi et al. 2014); and genetic variation at the site of drug targets, which in the case of channelopathy treatment, are often in fact ion channels themselves(Thompson, Kahlig and George 2011). It is important to bear all of these in mind where precision medicine is an objective.

5. Conclusion

We have now entered a very exciting era of genomic medicine, in which obtaining whole genome information on individuals is rapidly becoming the most cost effective way to diagnose rare genetic disease. As the use of Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) becomes more widespread it is almost certain that new ion channel genes will be linked to both monogenic and complex genetic diseases, and that new genotype-phenotype relationships will emerge. Large scale analysis of whole genome data will also provide the opportunity to identify relevant genetic modifiers in “monogenic” channelopathies, some of which may have significant implications for treatment. The emergence of such genetic modifiers will lead to a fundamental reconceptualization of monogenic and complex genetic diseases as existing on a continuous spectrum. The genetic channelopathies are an area where precision medicine has shown early promise, though as yet no model that accurately expresses both genetic modifiers and systems wide context has been developed. To permit widespread application of precision techniques current technical and financial barriers will need to be overcome.

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None of the authors have any disclosures to make in relation to this manuscript.

Ethics statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Legends to table and figure

Figure 1 – Summary of the known human genetic channelopathies

Figure 2 - schematic of how *SCN1A* mutations fit into all models of epilepsy inheritance

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	PHENOTYPE(S)	INHERITANCE	FUNCTIONAL EFFECT	CHANNEL	ACTIVATED BY	ION SELECTIVITY	*GENE*	REFS.
NEUROLOGICAL								
PRESENTING WITH SEVERE EARLY-ONSET EPILEPSY								
SODIUM CHANNELS								
(A)	Dravet syndrome	Dominant	LOF	α subunit of the type 1 neuronal voltage-gated sodium channel ($Na_v1.1$)	Voltage	Sodium	*SCN1A*	(Escayg et al. 2000)
(B)	EOEE	Recessive	LOF	β1 auxiliary subunit for the type 1 neuronal voltage-gated sodium channel	Voltage	Sodium	*SCN1B*	(Patino et al. 2009)
(C)	Early infantile epileptic encephalopathy	Dominant	LOF	α subunit of the type 2 neuronal voltage-gated sodium channel ($Na_v1.2$)	Voltage	Sodium	*SCN2A*	(Ogiwara et al. 2009)
	EIMFS	Dominant	LOF					(Dhamija et al. 2013)
	Autism without other neurological features	Dominant	LOF					(Tavassoli et al. 2014)
(D)	EOEE	Dominant	GOF	α subunit of the type 6 neuronal voltage-gated sodium channel ($Na_v1.6$)	Voltage	Sodium	*SCN8A*	(Veeramah et al. 2012)
(E)	Epileptic encephalopathy with neuromuscular disease	Recessive	LOF	α subunit of the type 8 neuronal voltage-gated sodium channel ($Na_v1.8$)	Voltage	Sodium	*SCN10A*	(Kambouris et al. 2016)
POTASSIUM CHANNELS								
(F)	EOEE	Dominant	LOF and GOF	α2 subunit of Shaker family potassium channels ($K_v1.2$)	Voltage	Potassium	*KCNA2*	(Syrbe et al. 2015)
	EOEE	Dominant	LOF and GOF	Member 1 of the Shab family of potassium channels ($K_v2.1$)	Voltage	Potassium	*KCNB1*	(Torkamani et al. 2014)
	EOEE	Dominant	Unknown	Member 5 of the Ether-a-go-go family of potassium channels ($K_v10.2$)	Voltage	Potassium	*KCNH5*	(Veeramah et al. 2013)
(G)	EOEE	Dominant	LOF	Voltage-gated potassium channel, Q subfamily, member 2 ($K_v7.2$)	Voltage	Potassium	*KCNQ2*	(Weckhuysen et al. 2012)
	Infantile spasms	Dominant	GOF					(Millichap et al. 2017)
(H)	EIMFS	Dominant	GOF	Calcium-activated potassium channel (subfamily T) member 1 ($K_{ca}4.1$)	Calcium	Potassium	*KCNT1*	(Barcia et al. 2012)
CALCIUM CHANNELS								
(I)	EOEE	Dominant	LOF	α1A subunit of the P/Q type voltage-gated calcium channel ($Ca_v2.1$)	Voltage	Calcium	*CACNA1A*	(Damaj et al. 2015)
	Epileptic encephalopathy	Recessive	LOF	α2δ2 auxiliary subunit of the P/Q voltage-gated calcium channel	Voltage	Calcium	*CACNA2D2*	(Pippucci et al. 2013)
GLUTAMATE RECEPTORS								
	Epileptic-dyskinetic encephalopathy	Recessive	LOF	Accessory protein to the neuronal AMPA receptor	Glutamate	Cations	*FRRS1L*	(Madeo et al. 2016)
	EOEE	Dominant	LOF	Subunit 1 of the neuronal NMDA receptor	Glutamate	Cations	*GRIN1*	(Ohba et al. 2015)
	Focal epilepsy + speech difficulties	Dominant	LOF and GOF	Subunit 2A of the neuronal NMDA receptor	Glutamate	Cations	*GRIN2A*	(Carvill et al. 2013)
	Focal epilepsy + speech difficulties	Dominant	LOF and GOF	Subunit 2B of the neuronal NMDA receptor	Glutamate	Cations	*GRIN2B*	(Lemke et al. 2014)
	EOEE	Dominant	GOF	Subunit 2D of the neuronal NMDA receptor	Glutamate	Cations	*GRIN2D*	(Li et al. 2016)
GABA RECEPTORS								

(J)	EOEE	Dominant	LOF	α1 subunit of the neuronal GABA-A receptor	GABA	Chloride	*GABRA1*	(Kodera et al. 2016)
	Epileptic encephalopathy	Dominant	LOF	β1 subunit of the neuronal GABA-A receptor	GABA	Chloride	*GABRB1*	(Janve et al. 2016)
(K)	EOEE	Dominant LOF	LOF	β3 subunit of the neuronal GABA-A receptor	GABA	Chloride	*GABRB3*	(Janve et al. 2016)
(L)	EOEE	Dominant	LOF	γ2 subunit of the neuronal GABA-A receptor	GABA	Chloride	*GABRG2*	(Shen et al. 2016)
OTHER CHANNELS								
(M)	EOEE	Dominant	LOF	α3 isoform of sodium/potassium ATPase	ATP	Sodium/Potassium	*ATP1A3*	(Paciorkowski et al. 2015)
	EOEE	Dominant	LOF and GOF	Hyperpolarization-activated, cyclic nucleotide–gated (HCN) channel, type 1	Hyperpolarisation	Cations	*HCN1*	(Nava et al. 2014)
	EIMFS	Recessive LOF	LOF	Potassium and chloride transporter (KCC2)	Potassium	Potassium and chloride	*SLC12A5*	(Stodberg et al. 2015)
SELF-LIMITING FAMILIAL EPILEPSIES WITH ONSET IN THE NEONATAL OR EARLY INFANTILE PERIOD								
(G)	Self-limiting familial neonatal seizures	Dominant	LOF	Voltage-gated potassium channel, Q subfamily, member 2 ($K_v7.2$)	Voltage	Potassium	*KCNQ2*	(Biervert et al. 1998)
(N)	Self-limiting familial neonatal seizures	Dominant	LOF and GOF	Voltage-gated potassium channel, Q subfamily, member 3 ($K_v7.3$)	Voltage	Potassium	*KCNQ3*	(Charlier et al. 1998)
(A)	GEFS+	Dominant	LOF	α subunit of the type 1 neuronal voltage-gated sodium channel ($Na_v1.1$)	Voltage	Sodium	*SCN1A*	(Claes et al. 2001)
(B)	Genetic epilepsy with febrile seizures GEFS+	Dominant	LOF	β1 auxiliary subunit for the type 1 neuronal voltage-gated sodium channel	Voltage	Sodium	*SCN1B*	(Wallace et al. 1998)
(C)	Self-limiting familial neonatal-infantile seizures	Dominant	LOF	α subunit of the type 2 neuronal voltage-gated sodium channel ($Na_v1.2$)	Voltage	Sodium	*SCN2A*	(Berkovic et al. 2004)
(D)	Infantile convulsions choreoathetosis (ICCA) syndrome	Dominant	LOF	α subunit of the type 6 neuronal voltage-gated sodium channel ($Na_v1.6$)	Voltage	Sodium	*SCN8A*	(Gardella et al. 2015)
(O)	GEFS+	Dominant	Unknown	α subunit of the type 7 neuronal voltage-gated sodium channel ($Na_v1.7$)	Voltage	Sodium	*SCN9A*	(Mulley et al. 2013)
AUTOSOMAL DOMINANT NOCTURNAL FRONTAL LOBE EPILEPSY								
	Nocturnal frontal lobe epilepsy	Dominant	GOF	α2 subunit of the nicotinic acetylocholine receptor	Acetylcholine	Cations	*CHRNA2*	(Combi, Ferini-Strambi & Tenchini 2009)
	Nocturnal frontal lobe epilepsy	Dominant	GOF	α4 subunit of the nicotinic acetylocholine receptor	Acetylcholine	Cations	*CHRNA4*	(Steinlein et al. 1995)
	Nocturnal frontal lobe epilepsy	Dominant	GOF	α4 subunit of the nicotinic acetylocholine receptor	Acetylcholine	Cations	*CHRNB2*	(Phillips et al. 2001)
(H)	Nocturnal frontal lobe epilepsy	Dominant	GOF	Calcium-activated potassium channel (subfamily T) member 1 ($K_{ca}4.1$)	Calcium	Potassium	*KCNT1*	(Heron et al. 2012)
SUSCEPTIBILITY TO IDIOPATHIC GENERALISED EPILEPSIES								
(P)	Susceptibility to IGE	Dominant	GOF	α1H subunit of the T type calcium channel ($Ca_v3.2$)	Voltage	Calcium	*CACNA1H*	(Heron et al. 2007)
(Q)	Susceptibility to JME	Dominant	Unknown	β_4 auxiliary subunit of the P/Q voltage-gated calcium channel	Voltage	Calcium	*CACNB4*	(Escayg et al. 2000)
	Susceptibility to IGE	Dominant	LOF (microdeletions only)	α7 subunit of the nicotinic acetylocholine receptor	Acetylcholine	Cations	*CHRNA7*	(Dibbens et al. 2009)
(R)	Susceptibility to IGE	Dominant	LOF	Type 2 voltage-gated chloride channel	Voltage	Chloride	*CLCN2*	(Saint-Martin et al. 2009)

(J)	Susceptibility to IGE	Dominant	LOF	α1 subunit of the neuronal GABA-A receptor	GABA	Chloride	*GABRA1*	(Lachance-Touchette et al. 2011)
(K)	Susceptibility to IGE	Dominant	LOF	β3 subunit of the neuronal GABA-A receptor	GABA	Chloride	*GABRB3*	(Tanaka et al. 2008)
	Susceptibility to IGE	Dominant	LOF	δ subunit of the neuronal GABA-A receptor	GABA	Chloride	*GABRD*	(Dibbens et al. 2004)
(L)	Susceptibility to IGE	Dominant	LOF	γ2 subunit of the neuronal GABA-A receptor	GABA	Chloride	*GABRG2*	(Lachance-Touchette et al. 2011)
	Familial febrile seizures	Dominant	LOF					(Boillot et al. 2015)
OTHER EPILEPSIES								
	Variable epilepsy phenotype – ranging from epileptic encephalopathy to well-controlled seizures	X-linked recessive	LOF	Type 4 voltage-gated chloride channel	Voltage	Chloride	*CLCN4*	(Palmer et al. 2016)
	Progressive myoclonic epilepsy	Dominant	LOF	Member 1 of the Shaw family of potassium channels ($K_v3.1$)	Voltage	Potassium	*KCNC1*	(Muona et al. 2015)
	Epilepsy and paroxysmal movement disorder	Dominant	GOF	α subunit of the large conductance calcium-sensitive potassium channel (BK)	Calcium	Potassium	*KCNMA1*	(Du et al. 2005)
(N)	Familial focal epilepsy	Dominant	LOF	Voltage-gated potassium channel, Q subfamily, member 3 ($K_v7.3$)	Voltage	Potassium	*KCNQ3*	(Miceli et al. 2015)
	Childhood-onset focal epilepsy	Dominant	LOF and GOF	α subunit of the type 3 neuronal voltage-gated sodium channel ($Na_v1.3$)	Voltage	Sodium	*SCN3A*	(Vanoye et al. 2014)
OTHER NEUROLOGICAL DISORDERS								
MOVEMENT DISORDERS AND RELATED PHENOTYPES								
	Familial hemiplegic migraine	Dominant	LOF	α2 isoform of sodium/potassium ATPase	ATP	Sodium/ Potassium	*ATP1A2*	(Fusco et al. 2003)
	Familial basilar migraine	Dominant	LOF					(Ambrosini et al. 2005)
	Alternating hemiplegia of childhood	Dominant	LOF					(Swoboda et al. 2004)
(M)	Alternating hemiplegia of childhood	Dominant	LOF	α3 isoform of sodium/potassium ATPase	ATP	Sodium/ Potassium	*ATP1A3*	(Rosewich H. et al. 2012)
	Rapid-onset Parkinsonism dystonia	Dominant	LOF					(de Carvalho et al. 2004)
	CAPOS syndrome	Dominant	GOF (unconfirmed)					(Demos et al. 2014)
(I)	Familial hemiplegic migraine	Dominant	LOF	α1A subunit of the P/Q type voltage-gated calcium channel ($Ca_v2.1$)	Voltage	Calcium	*CACNA1A*	(Ophoff et al. 1996)
	Episodic ataxia type 2	Dominant	LOF					(Ophoff et al. 1996)
	Progressive spinocerebellar ataxia (SCA6) – triplet repeat	Dominant	LOF					(Matsuyama et al. 1997)
	Hyperkalaemic periodic paralysis	Dominant	LOF	α1S subunit of the L type voltage-gated calcium channel ($Ca_v1.1$)	Voltage	Calcium	*CACNA1S*	(Ptáček et al. 1991)
	Malignant hyperthermia	Dominant	LOF					
(Q)	Episodic ataxia type 5	Dominant	Unknown	β_4 auxiliary subunit of the P/Q voltage-gated calcium channel	Voltage	Calcium	*CACNB4*	(Escayg A et al. 2000)
(R)	Leukoencephalopathy with ataxia	Recessive	LOF	Type 2 voltage-gated chloride channel	Voltage	Chloride	*CLCN2*	(Depienne et al. 2013)
	Hyperekplexia	Dominant or recessive	GOF	α1 subunit of the spinal glycine receptor	Glycine	Chloride	*GLRA1*	(Thomas et al. 2013)
	Hyperekplexia	Dominant or recessive	GOF	β1 subunit of the spinal glycine receptor	Glycine	Chloride	*GLRB*	(Thomas et al. 2013)

	Episodic ataxia type 1	Dominant	LOF	α1 subunit of the Shaker family potassium channels ($K_v1.1$)	Voltage	Potassium	*KCNA1*	(Zuberi et al. 1999)
(F)	Hereditary spastic paraplegia and ataxia	Dominant	LOF	α2 subunit of the Shaker family potassium channels ($K_v1.2$)	Voltage	Potassium	*KCNA2*	(Helbig et al. 2016)
	Spinocerebellar ataxia	Dominant	LOF	Member 3 of the Shaw family of potassium channels ($K_v3.3$)	Voltage	Potassium	*KCNC3*	(Waters et al. 2006)
(S)	Early-onset cerebellar ataxia, intellectual disability, oral apraxia, and epilepsy	Dominant LOF	LOF	Member 3 of the Shal family of potassium channels ($K_v4.3$)	Voltage	Potassium	*KCND3*	(Smets et al. 2015)
	Spinocerebellar ataxia	Dominant LOF	LOF					(Duarri et al. 2012)
(A)	Familial hemiplegic migraine	Dominant GOF	GOF	α subunit of the type 1 neuronal voltage-gated sodium channel ($Na_v1.1$)	Voltage	Sodium	*SCN1A*	(Dichgans et al. 2005)
NEUROMUSCULAR DISORDERS								
	Slow channel congenital myasthenic syndrome	Dominant	GOF	α1 subunit of the nicotinic acetylcholine receptor	Acetylcholine	Cations	*CHRNA1*	(Engel et al. 1996)
	Fast channel congenital myasthenic syndrome	Recessive	LOF					(Wang et al. 1999)
	Multiple pterygium syndrome	Recessive	LOF (truncation)					(Michalk et al. 2009)
	Slow channel congenital myasthenic syndrome	Dominant	GOF	β1 subunit of the nicotinic acetylcholine receptor	Acetylcholine	Cations	*CHRNB1*	(Engel et al. 1996)
	Congenital myasthenic syndrome associated with Ach receptor deficiency	Recessive	LOF (reduced expression)					(Quiram et al. 1999)
	Slow channel congenital myaesthenic syndrome	Dominant	GOF	δ polypeptide subunit of the nicotinic acetylcholine receptor	Acetylcholine	Cations	*CHRND*	(Gomez et al. 2002)
	Fast channel congenital myasthenic syndrome	Recessive	LOF					(Gomez et al. 2002)
	Congenital myasthenic syndrome associated with Ach receptor deficiency	Recessive	LOF (reduced expression)					(Müller et al. 2006)
	Multiple pterygium syndrome	Recessive	LOF (truncation)					(Michalk et al. 2009)
	Slow channel congenital myasthenic syndrome	Dominant	GOF	ε polypeptide subunit of the nicotinic acetylcholine receptor	Acetylcholine	Cations	*CHRNE*	(Ohno et al. 1995)
	Fast channel congenital myasthenic syndrome	Recessive	LOF					(Ohno et al. 1996)
	Congenital myasthenic syndrome associated with Ach receptor deficiency	Recessive	LOF (reduced expression)					(Ohno et al. 1997)
	Multiple pterygium syndrome (lethal and Escobar variants)	Recessive	LOF	γ subunit of the nicotinic acetylcholine receptor	Acetylcholine	Cations	*CHRNG*	(Hoffmann et al. 2006) (Morgan et al. 2006)
	Dominant myotonia congenita	Dominant	LOF	Skeletal muscle voltage-gated chloride channel	Voltage	Chloride	*CLCN1*	(Koch et al. 1992)
	Recessive myotonia congenita	Recessive	LOF					(Lorenz et al. 1994)
	Dominant central core disease	Dominant	GOF	Skeletal muscle Ryanodine receptor 1	Calcium	Calcium	*RYR1*	(Zhang et al. 1993)
	Recessive central core disease	Recessive	LOF					(Jungbluth et al. 2002, Monnier et al. 2005)
	Malignant hyperthermia	Dominant	GOF					(Monnier et al. 2003)
	Minicore myopathy with external							

	ophthalmoplegia	Recessive	LOF					
	Hyperkalaemic periodic paralysis	Dominant	LOF	α subunit of the type 4 neuronal voltage-gated sodium channel ($Na_v1.4$)	Voltage	Sodium	*SCN4A*	(Ptáček et al. 1994)
	Hypokalaemic periodic paralysis	Dominant	LOF					(Jurkat-Rott et al. 2000)
	Paramyotonia congenita	Dominant	LOF					(Ptáček et al. 1992)
	Congenital myaesthenic syndrome	Recessive	LOF					(Tsujino et al. 2003)
PERIPHERAL NERVE DISORDERS								
(R)	Peripheral nerve hyperexitability	Dominant	LOF	Voltage-gated potassium channel, Q subfamily, member 2 ($K_v7.2$)	Voltage	Potassium	*KCNQ2*	(Wuttke et al. 2007)
(O)	Erythromelalgia and related neuropathic pain syndromes	Dominant	GOF	α subunit of the type 7 neuronal voltage-gated sodium channel ($Na_v1.7$)	Voltage	Sodium	*SCN9A*	(Fischer, Waxman 2010)
	Insensitivity to pain	Recessive	LOF					(Cox et al. 2006)
(E)	Episodic pain syndrome	Dominant	GOF	α subunit of the type 8 neuronal voltage-gated sodium channel ($Na_v1.8$)	Voltage	Sodium	*SCN10A*	(Faber et al. 2012)
	Familial episodic pain syndrome	Dominant GOF	GOF	α subunit of the type 9 neuronal voltage-gated sodium channel ($Na_v1.9$)	Voltage	Sodium	*SCN11A*	(Zhang et al. 2013)
	Hereditary sensory and autonomic neuropathy	Dominant GOF	GOF					(Leipold et al. 2013)
	Familial episodic pain syndrome	Dominant	GOF	Transient receptor potential cation channel, family A, member 1	Various ligands, activated by noxious stimuli	Cations	*TRPA1*	(Kremeyer et al. 2010)
DEAFNESS								
	Hearing loss	Dominant	LOF	Voltage-gated potassium channel, Q subfamily, member 4 ($K_v7.4$)	Voltage	Potassium	*KCNQ4*	(Coucke et al. 1999)
CARDIAC DISEASE								
SODIUM CHANNELS								
(B)	Familial atrial fibrillation	Dominant	LOF	β auxiliary subunit for the type 1 neuronal voltage-gated sodium channel	Voltage	Sodium	*SCN1B*	(Watanabe et al. 2008)
	Brugada syndrome	Dominant	LOF					
	Nonspecific cardiac conduction defect	Dominant	LOF					
	Familial atrial fibrillation	Dominant	LOF	β auxiliary subunit for the type 2 neuronal voltage-gated sodium channel	Voltage	Sodium	*SCN2B*	(Watanabe et al. 2009)
	Familial atrial fibrillation	Dominant	LOF	β auxiliary subunit for the type 3 neuronal voltage-gated sodium channel	Voltage	Sodium	*SCN3B*	(Wang et al. 2010)
	Brugada syndrome	Dominant	LOF					(Hu et al. 2009)
	Familial atrial fibrillation	Dominant	LOF	β auxiliary subunit for the type 4 neuronal voltage-gated sodium channel	Voltage	Sodium	*SCN4B*	(Olesen et al. 2011)
	Long QT syndrome	Dominant	LOF					(Medeiros-Domingo et al. 2007)
	Familial atrial fibrillation	Dominant	LOF and GOF	α subunit of the type 5 neuronal voltage-gated sodium channel ($Na_v1.5$)	Voltage	Sodium	*SCN5A*	(Ellinor et al. 2008, Chen et al. 1998)
	Brugada syndrome	Dominant	LOF					(McNair et al. 2004)
	Dilated cardiomyopathy	Dominant	LOF					(Schott et al. 1999)
	Heart block	Dominant	LOF					(Bennett et al. 1995)
								(Swan et al. 2014)

	Long QT syndrome	Dominant	LOF					(Swan et al. 2014)
	Polymorphic ventricular tachycardia	Dominant	GOF					(Benson et al. 2003)
	Sick sinus syndrome	Recessive	LOF					
POTASSIUM CHANNELS								
(T)	Ventricular tachycardia and dilated cardiomyopathy	Dominant	LOF	ATP-sensitive potassium channel (K_{ATP})	ATP	Potassium	*ABCC9*	(Bienengraeber et al. 2004)
	Familial atrial fibrillation	Dominant	LOF	α5 subunit of the Shaker family potassium channels ($K_v1.5$)	Voltage	Potassium	*KCNA5*	(Olson et al. 2006)
(S)	Brugada syndrome	Dominant	GOF	Member 3 of the Shal family of potassium channels ($K_v4.3$)	Voltage	Potassium	*KCND3*	(Giudicessi et al. 2012)
	Atrial fibrillation	Dominant	LOF					(Olesen et al. 2013)
	Long QT syndrome	Dominant	LOF	Member 2 of the Ether-a-go-go (EAG) type potassium channels ($K_v10.2$)	Voltage	Potassium	*KCNH2*	(Curran et al. 1995)
	Short QT syndrome	Dominant	GOF					(Brugada et al. 2004)
	Jervell and Lange-Nielsen syndrome	Recessive	LOF	Member 1 of the MinK subfamily of potassium channels	Voltage	Potassium	*KCNE1*	(Tyson et al. 1997)
	Long QT syndrome	Dominant	GOF					(Splawski et al. 1997)
	Familial atrial fibrillation	Dominant	GOF	Member 1 of the MinK related peptide subfamily of potassium channels (MiRP1) (membrane subunit which assembles with $K_v10.2$)	Voltage	Potassium	*KCNE2*	(Yang et al. 2004)
	Long QT syndrome	Dominant	LOF					(Abbott et al. 1999)
	Brugada syndrome	Dominant	LOF	Member 2 of the MinK related peptide subfamily of potassium channels (MiRP1) (membrane subunit which assembles with $K_v10.2$)	Voltage	Potassium	*KCNE3*	(Van Norstrand et al. 2007)
	Familial atrial fibrillation	Dominant	GOF	Voltage-gated potassium channel, Q subfamily, member 1 ($K_v7.1$)	Voltage	Potassium	*KCNQ1*	(Chen et al. 2003)
	Jervell and Lange-Neilsen syndrome	Recessive	LOF					(Neyroud et al. 1997)
	Long QT syndrome	Dominant	LOF					(Wang et al. 1996)
	Short QT syndrome	Dominant	GOF					(Bellocq et al. 2004)
(U)	Andersen-Tawil syndrome	Dominant	LOF	Member 2 of the J family of inwardly rectifying voltage-gated potassium channels ($K_{ir}2.1$)	Voltage	Potassium	*KCNJ2*	(Plaster et al. 2001)
	Familial atrial fibrillation	Dominant	GOF					(Xia et al. 2005)
	Short QT syndrome	Dominant	GOF					(Priori et al. 2005)
(V)	Long QT syndrome	Dominant	LOF	G-protein-activated inwardly rectifying voltage-gated potassium channel ($K_{ir}3.4$)	G-protein activation	Potassium	*KCNJ5*	(Yang et al. 2010)
CALCIUM CHANNELS								
	Brugada syndrome	Dominant	LOF	α1C subunit of the L type voltage-gated calcium channel ($Ca_v1.2$)	Voltage	Calcium	*CACNA1C*	(Antzelevitch et al. 2007)
	Timothy syndrome	Dominant	LOF					(Splawski et al. 2004)
	Brugada syndrome	Dominant	LOF	β2 subunit of the L type voltage-gated calcium channel	Voltage	Calcium	*CACNB2*	(Antzelevitch et al. 2007)
	Brugada syndrome	Dominant	LOF	α1δ subunit of the L type voltage-gated calcium channel	Voltage	Calcium	*CACNA2D1*	(Antzelevitch et al. 2007)
	Arrhythmogenic right ventricular dysplasia	Dominant	LOF	Cardiac ryanodine receptor 2	Calcium	Calcium	*RYR2*	(Tiso et al. 2001)
	Catecholaminegic polymorphic ventricular tachycardia	Dominant	LOF					(Priori et al. 2001)
CATION CHANNELS								
	Brugada syndrome	Dominant	LOF	Hyperpolarization-activated, cyclic nucleotide–gated (HCN)	Hyperpolarisation	Cations	*HCN4*	(Ueda et al. 2004)

	Sick sinus syndrome	Dominant	LOF	channel, type 4				(Milanesi et al. 2006)
RENAL DISEASE								
	Barrter's syndrome with sensorineural deafness	Recessive	LOF	β subunit of the renal chloride channel		Chloride	*BSND*	(Birkenhager et al. 2001)
	Dent disease Hypophosphataemic Rickets Nephrolithiasis Hypocalciuric nephrocalcinosis	X-linked recessive	LOF	Type 5 voltage-gated chloride channel	Voltage	Chloride	*CLCN5*	(Lloyd et al. 1996)
	Barrter's syndrome with sensorineural deafness	Digenic recessive	LOF	Renal chloride channel		Chloride	*CLCNKA and CLCNKB*	(Schlingmann et al. 2004)
	Barrter's syndrome	Recessive	LOF	Renal outer-medullar potassium channel ($K_{ir}1.1$)	Voltage	Potassium	*KCNJ1*	(Simon et al. 1996b)
(W)	Liddle syndrome	Dominant	GOF	β subunit of the epithelial sodium channel	Voltage	Sodium	*SCNN1B*	(Shimkets et al. 1994)
	Barrter's syndrome	Recessive	LOF	Type 1 renal sodium/potassium/chloride transporter (NKCC2)		Sodium, potassium and chloride	*SLC12A1*	(Simon et al. 1996a)
	Gitelman syndrome	Recessive	LOF	Type 3 renal sodium/potassium/chloride transporter (NKCC2)		Sodium, potassium and chloride	*SLC12A3*	(Simon et al. 1996c)
ENDOCRINE AND BONE DISEASE								
	Permanent neonatal diabetes mellitus +/- neurologic features	Dominant	GOF	ATP-binding cassette of the sulphonylurea receptor	Sulphonylurea and ATP	Potassium	*ABCC8*	(Proks et al. 2006)
	Transient neonatal diabetes mellitus	Dominant	GOF					(Babenko et al. 2006)
	Persistent hyperinsulinaemic hypoglycaemia of infancy	Dominant and recessive	LOF					(Thomas et al. 1995)
(T)	Cantú syndrome (hypertrichotic osteochondrodysplasia)	Dominant	GOF	ATP-sensitive potassium channel (K_{ATP})	ATP	Potassium	*ABCC9*	(van Bon et al. 2004)
(P)	Familial hyperaldosteronism	Dominant	GOF	α1H subunit of the T type calcium channel ($Ca_v3.2$)	Voltage	Calcium	*CACNA1H*	(Scholl et al. 2015)
	Dominant osteopetrosis	Dominant	LOF	Type 7 chloride channel		Chloride	*CLCN7*	(Cleiren et al. 2001)
	Recessive osteopetrosis	Recessive	LOF					(Kornak et al. 2001)
(V)	Familial hyperaldosteronism	Dominant	LOF	G-protein-activated inwardly rectifying voltage-gated potassium channel ($K_{ir}3.4$)	G-protein activation	Potassium	*KCNJ5*	(Choi et al. 2011)
	Permanent neonatal diabetes, with neurological features (Delay, Epilepsy, Neonatal Diabetes, DEND syndrome) Persistent hyoerinsulinaemic hypoglycaemia of infancy Transient neonatal diabetes Permanent neonatal diabetes	Dominant	GOF	Member 11 of the inward rectifier type of potassium channels ($K_{ir}6.2$)	ATP	Potassium	*KCNJ11*	(Gloyn et al. 2006)

	Maturity-onset diabetes if the young (MODY)							
(W)	Pseudohypoaldosteronism	Recessive	LOF	β subunit of the epithelial sodium channel	Voltage	Sodium	*SCNN1B*	(Chang et al. 1996)
(O)	Osteogenesis imperfecta	Recessive	Unknown	α subunit of the type 7 neuronal voltage-gated sodium channel ($Na_v1.7$)	Voltage	Sodium	*SCN9A*	(Caparros-Martin et al. 2016)
MISCELLANEOUS/MULTISYSTEM DISEASES								
	Primary aldosteronism, seizures, and neurologic abnormalities Sinoatrial node dysfunction and deafness	Dominant Recessive	GOF LOF	α1D subunit of the L type calcium channel ($Ca_v1.3$)	Voltage	Calcium	*CACNA1D*	(Scholl et al. 2013) (Baig et al. 2011)
	Cystic fibrosis	Recessive	LOF	Cystic fibrosis transmembrane conductance regulator	ATP	Chloride	*CFTR*	(Kerem et al. 1989)
	Temple-Baraitser syndrome	Dominant	GOF	Member 1 of the Ether-a-go-go (EAG) type potassium channels ($K_v10.1$)	Voltage	Potassium	*KCNH1*	(Simons et al. 2015)
	Zimmermann-Laband syndrome	Dominant	GOF					(Kortum et al. 2015)
(U)	Andersen-Tawil syndrome	Dominant	LOF	Member 2 of the J family of inwardly rectifying voltage-gated potassium channels ($K_{ir}2.1$)	Voltage	Potassium	*KCNJ2*	(Plaster et al.)
(V)	Andersen-Tawil syndrome (without dysmorphism)	Dominant	LOF	G-protein-activated inwardly rectifying voltage-gated potassium channel ($K_{ir}3.4$)	G-protein activation	Potassium	*KCNJ5*	(Kokunai et al. 2014)
	SESAME (**se**izures, **s**ensorineural deafness, **a**taxia, intellectual disability) or EAST (**e**pilepsy, **a**taxia, **s**ensorineural deafness and **t**ubulopathy) syndrome	Recessive	LOF	Member 10 of the inward rectifier type of potassium channels ($K_{ir}4.1$)	Voltage	Potassium	*KCNJ10*	(Bockenhauer D et al. 2009)
	Familial pulmonary arterial hypertension	Dominant	LOF	Member 1 of the Task family of two pore potassium channels	Voltage	Potassium	*KCNK3*	(Ma et al. 2013)
(W)	Bronchiectasis	Dominant	LOF	β subunit of the epithelial sodium channel	Voltage	Sodium	*SCNN1B*	(Sheridan et al. 2005)
	Nonepidermolytic focal palmoplantar ketatoderma (Olmsted syndrome)	Dominant	GOF	Transient receptor potential cation channel, subfamily V, member 3	Temperature	Cations	*TRPV3*	(Lin et al. 2012)
	Brachyolmia	Dominant	GOF	Transient receptor potential cation channel, subfamily V, member 4, found in ciliated epithelial cells	Various physical, chemical, and hormonal stimuli	Calcium	*TRPV4*	(Rock et al. 2008)
	Familial digital arthropathy-brachydactyly	Dominant	LOF					(Lamande et al. 2011)
	Hereditary sensorimotor neuropathy	Dominant	LOF					(Auer-Grumbach et al. 2010)
	Metatropic dysplasia	Dominant	GOF					(Krakow et al. 2009)
	Parastremmatic dwarfism	Dominant	Unknown					(Nishimura et al. 2010)
	Scapuloperitoneal muscular atrophy	Dominant	LOF					(Auer-Grumbach et al. 2010)
	Spondyloepiphyseal dysplasia	Dominant	GOF					(Krakow et al. 2009)
	Distal spinal muscular atrophy	Dominant	LOF					(Auer-Grumbach et al. 2010)

Table 1 – the known human channelopathies. Abbreviations used: EOEE – early-onset developmental and epileptic encephalopathy; EIMFS – epilepsy of infancy with migrating focal seizures; IGE: Idiopathic generalised epilepsy; JME – juvenile myoclonic epilepsy; CAPOS syndrome - **C**erebellar ataxia, **A**reflexia, **P**es cavus, **O**ptic atrophy, and **S**ensorineural deafness; GEFS+ - genetic epilepsy with febrile seizures plus; GOF – gain-of-function; LOF – loss-of-function

Ion channel physiology

Ion channels can be classified by the mechanism by which they are activated, and/or by the ion(s) that they are permeable to. In the former system, there are three groups of ion channel: 1. Voltage-gated channels; 2. Extracellular ligand-gated channels; and 3. Intracellular ligand-gated channels.

Voltage-gated channels

- Ion permeability varies in association with changes in electrical membrane potential near the channel.
- Important in tissues where rapid conduction of messages is required, such as in nerves, cardiac conduction cells, and skeletal muscle.
- The sequence encoding the voltage-sensing region is highly conserved across evolution, and is intolerant of genetic variation.
- Voltage-gated ion channels are typically composed of tetramers of 4 pore-forming subunits (see Fig. 1).
- Sodium, potassium, and calcium channels are the most prevalent
- There are 9 subtypes of sodium channel, 16 subtypes of calcium channel, and >50 subtypes of potassium channel. Each subtype is encoded by a different gene (e.g. *SCN1A, SCN2A*, *SCN3A* etc.).
- Highly cell-specific expression of ion channel subtypes is critical for physiological function. As an example, $Na_v1.5$ channels, encoded by *SCN5A* are expressed in the heart, whereas $Na_v1.1$ (*SCN1A)*, $Na_v1.2$(*SCN2A)*, $Na_v1.3$(*SCN3A)*, and $Na_v1.6$(*SCN8A)* are expressed in the central nervous system (Grubman et al. 1988).

Extracellular Ligand-gated channels

- Activated by ligand-binding, and may be permeable to chloride (as in GABA receptors) or anions (as in glutamatergic receptors and acetylcholine receptors).

Intracellular Ligand-gated channels

- Open in response to changes in concentration of intracellular substrates, such as ATP (for example pancreatic ATP-sensitive potassium channels).

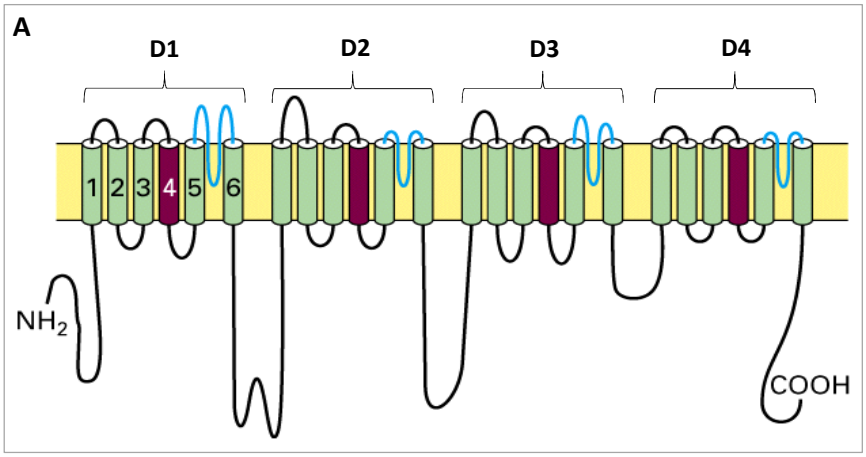
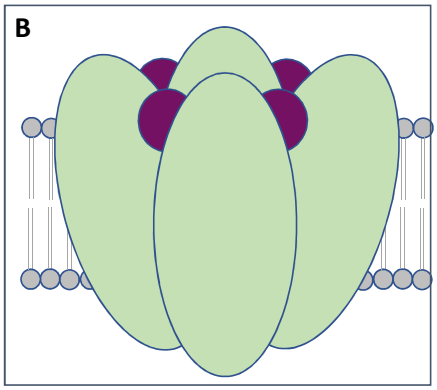
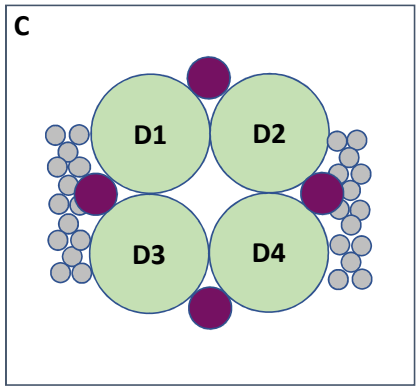


Fig 1. Schematic of the voltage-gated sodium channel: A: momomer; B: transverse; C: axial. Voltage-sensor region coloured purple (no. 4 in A)





- In the brain $Na_v1.1$ subunits localise to inhibitory neurons(Ogiwara et al. 2007) whilst $Na_v1.2$ and $Na_v1.6$ localise to excitatory neurones (Gordon et al. 1987, Chen et al. 2008).
- Time-dependent expression of ion channels is likely to be critical for normal development, and is thought to be responsible for the age-specific presentation of many channelopathies. In the rodent central nervous system, during embryonic life $Na_v1.3$ subunits are most highly expressed sodium channels in the brain, whereas $Na_v1.1$ and $Na_v1.2$ take over from birth. $Na_v1.1$ expression gradually increases through young adulthood (Gordon et al. 1987, Beckh et al. 1989).