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TOPICAL REVIEW

Mutational Consequences of Aberrant Ion Channels in Neurological Disorders

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Abstract Neurological channelopathies are attributed to aberrant ion channels affecting CNS, PNS, cardiac, and skeletal muscles. To maintain the homeostasis of excitable tissues, functional ion channels are necessary to rely electrical signals, whereas any malfunctioning serves as an intrinsic factor to develop neurological channelopathies. Molecular basis of these disease is studied based on genetic and biophysical approaches, e.g., loci positional cloning, whereas pathogenesis and bio-behavioral analysis revealed the dependency on genetic mutations and inter-current triggering factors. Although electrophysiological studies revealed the possible mechanisms of diseases, analytical study of ion channels remained unsettled and therefore underlying mechanism in channelopathies is necessary for better clinical application. Herein, we demonstrated (i) structural and functional role of various ion channels (Na^+, K^+, Ca^{2+},Cl^-), (ii) pathophysiology involved in the onset of their associated channelopathies, and (iii) comparative sequence and phylogenetic analysis of diversified sodium, potassium, calcium, and chloride ion channel subtypes.

Keywords Neurological channelopathies · Ion channels · Nervous system · Therapeutics · Mechanisms · Pathophysiology

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Introduction

Normal functioning of neurological tissues lies in the intricate interplay among ion channels, which is responsible for the membrane excitability. Nonfunctional ion channels are accountable for special class of neurological disorders termed as neurological channelopathies. "Neurological channelopathies" are attributed to the neurological disorders which are provoked due to genetic aberration (mutation) in the ion channels (Kullmann and Hanna 2002). However, its phenotype is covering extensive areas ranging from epilepsies, migraine, and periodic paralysis to pain disorders. Eminent candidates that are responsible for aiding transient neurological disorders are found to be stress, caffeine, and ethanol (Raike et al. 2013).

Genetic neurological channelopathies possess three typical hallmarks, for instance,

- Paroxysmal in nature: It means impaired neurological functional episodes separated by periods of normality are experienced by the patient. Some of these examples include migraine and epilepsy (Kullmann and Hanna 2002; Graves and Hanna 2005; Kullmann and Waxman 2010).
- Environmental onset: Episodes are set off by environmental factors like thermal, physical, and emotional stresses.
- Genetic neurological channelopathy is prone to natural antiquity: Frequency of attack conventionally dwindles with the time, but the patient faces some neurological disability.

Clinical phenotypes include muscle disorders such as periodic paralysis and myotonia (muscle stiffness), disorders of peripheral nerve excitability such as neuromyotonia

and brain disorders like migraine and epilepsy (Graves and Hanna 2005).

Importance of Ion Channels

In an organism, ion channels play an important role for the regulation of cellular homoeostasis. The ion channels are the molecular basis of membrane excitability (synaptic transmission, action potentials, sensory transduction, Pak and Pinto 1976) that has been established for the past five decades but molecular entities are characterized only a decade back. Any alteration or malfunctioning in ion channels is incompatible with life (Graves and Hanna 2005). Ion channels are present in the plasma membrane of the cells and organelles, and monitored a critical role in cardiac, nervous, and immune systems. Several studies proved that ion channels are important target of many clinically used drugs, for instance, amitriptyline targets Na_v1 channels and ziconotide targets $Ca_v2.2$ channel (Kaczorowski et al. 2008).

Ion Channels and Underlying Genetic Diversity

Sodium Ion Channel

Sodium channel allows the inflow of Na^+ ions once excited due to potential difference across the plasma membrane of the cell. Further, depolarization activates the sodium channel which provides a passage of sodium ion into the muscle fiber or neuron, thereby forming the depolarization upstroke of the action potential. With the opening of sodium channel, membrane potential shifted from −70 mV to less negative values due to the influx of positive sodium ions thereby elevating the positive charge inside the membrane. Kariev and Green proposed and provided the evidence that protons constitute the gating current to open the channel (Kariev and Green 2012). Based on the genetic diversity, they are classified into different subtypes (i.e., $Na_v1.1$ to $Na_v1.9$) that are known to be associated with various diseases summarized in Table 1. The multiple sequence analysis of sodium channel subtypes revealed their highly conserved transmembrane regions with 34 glycine(G) and 20 cysteine(C) key residues that are responsible for anchoring in lipid bilayer while 16 highly conserved arginine(R) residues in fourth segment for imparting voltage sensitivity to the channel (Fig. 1a). Their phylogenetic analysis describes that there are two outgroups comprised (SCN5A, SCN10A) and SCN11A proteins. SCN11A protein is more distantly related with other sodium channel proteins, while SCN2A and SCN3A channel proteins are much closely related to each other based on phylogenetic relationship (Fig. 1b).

Potassium Ion Channel

Potassium channel is responsible for conducting K^+ ions level down the electrochemical gradient and involved in various functions, for instance, excitation of neuronal cells, regulation of cell volume, and secretion of hormones (Armstrong and Hille 1998). With the opening of potassium channel in response to membrane depolarization, membrane potential drops down from +30 mV to −70 mV due to the efflux of positive ion, making more negative inside the membrane and therefore proceed toward repolarization of the membrane. Different families of potassium channels exist depending upon the method of gate opening, which are ligand-gated potassium channel which requires binding of an ion and organic molecule and another one is voltage-gated potassium channel that requires voltage stimulus for pore opening (MacKinnon 2003). Mutations in these diverse potassium channel subtypes have been associated with diseases that are elaborated in Table 2. Moreover, multiple sequence alignment of these subtypes indicates that they are greatly divergent among different families proteins during evolution but selectivity filter residues and arginine residues in voltage sensor regions are highly conserved (Fig. 2a). Their phylogenetic relationship (Fig. 2b) by the help of un-weighted pair group method with arithmetic mean identified three major clusters of closely related genes.

Calcium Ion Channel

Calcium channels are responsible for mediating the flow of Ca^{2+} ions in response to either voltage or ligand and therefore designated as voltage-gated or ligand-gated calcium channel (Striggow and Ehrlich 1996). Voltage-gated calcium channel mediates the influx of Ca^{2+} ions along the electrochemical gradient across the plasma membrane and has been classified into transient (T-type), long-lasting (L-type) currents, N-, P/Q-, and R-type according to their inactivation properties (Tsien et al. 1987; Llinas et al. 1992). These diverse channel subtypes associated with diseases have been summarized in Table 3, while their multiple sequence alignment revealed that they are moderately conserved at their ion-traversing region with highly conserved 18 glycine (G) and 5 cysteine(C) key residues that are responsible for membrane attachment with 12 highly conserved arginine(R) residues for providing voltage sensitivity (Fig. 3a). Furthermore, its phylogenetic relationship has been elucidated in Fig. 3b. These calcium channels have been involved in a variety of functions that are triggering gene expression (Morgan and Curran 1989), link membrane depolarization to intracellular signaling (Westenbroek et al. 1990), excitation–contraction coupling,

Table 1 Sodium ion channel subtypes in association with various diseases

Channel name	Subtypes	Genes encoding subtypes	Tissue specificity	Subcellular location	Subunit structure	Physiological role	Involvement in disease	References
Sodium (Na_V) Channel	$Na_V1.1$	SCN1A	Adult brain, especially in Purkinje cells	Cell bodies	Na_v type-1 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Control of action potential generation and propagation	Myoclonic epilepsy	Kalume et al. (2007), Spampanato et al. (2003)
	$Na_V1.2$	SCN2A	Central neurons, peripheral neurons	Axon initial segment of Cerebellar granule cells	Na_v type-2 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Control of action potential generation and propagation	Inherited febrile seizures	Kearney et al. 2001), Shi et al. (2012)
	$Na_V1.3$	SCN3A	Developing CNS, peripheral neurons, and cardiac myocytes	Membrane	Na_v type-3 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Fast activation and Inactivation Kinetics	Hyper excitability in epileptic patient	Estacion et al. (2010)
	$Na_V1.4$	SCN4A	Skeletal muscle	Membrane	Na_v type-4 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Generation and propagation of action potentials that initiate muscle contraction	Several myotonia and periodic paralysis disorders, Arrhythmias	Anyukhovsky et al. (2011)
	$Na_V1.5$	SCN5A	Brain, cardiac muscle	Axon, Co-localized with Neurofilaments	Na_v type-5 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Action potential generation & propagation in cardiac tissue and brain	Syncope, Seizures, Cardiac arrhythmias Long QT syndrome (LQTS), Brugada syndrome, Cardiac conduction disease	Hu et al. (2010), Tan et al. (2007)
	$Na_V1.6$	SCN8A	Cerebellar granule cells	Mature nodes along compact myelinated axons, dendrites	Na_v type-8 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Most prominently expressed and potential generation in various types of tissues	Cognitive impairment with or without cerebellar ataxia (CIAT), Epileptic encephalopathy, early infantile, type 13 (EIEE13)	Trudeau et al. (2006), Osorio et al. (2005)
	$Na_v1.7$	SCN9A	Nociceptors (Nerves transmitting pain signals)	Membrane	Na_v type-9 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Responsible for carrying pain signals to brain	Erythromelalgia, Paroxysmal extreme pain disorder, Congenital insensitivity to pain(CIP)	Cregg et al. (2013), Estacion et al. (2011), Klein et al. (2013)
	$Na_v1.8$	SCN10A	Peripheral sensory nervous system	Membrane	Na_v type-10 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Transmits pain signals to CNS in cold temperature	Pain and Paresthesias	Faber et al. (2012)

Table 1 continued

Channel name	Subtypes	Genes encoding subtypes	Tissue specificity	Subcellular location	Subunit structure	Physiological role	Involvement in disease	References
	$Na_v1.9$	SCN11A	Heart and Dorsal root ganglion neurons	Trigeminal neurones and their axons	Na_v type-11 α-subunit (tetradomain). Each domain consists of internally repeated segments (S1–S6)	Involved in pain related signaling	Mechanical and Heat pain hypersensitivity	Lolignier et al. (2011)
	$Na_V\beta1$	SCN1B	Muscle and Neuronal cells	Membrane	Na_v type-1 β-subunit. Single domain. Auxiliary subunit	Modulate channel gating kinetics	Brugada syndrome, Generalized epilepsy with febrile seizures plus type 1	Audenaert et al. (2003), Patino et al. (2011)
	$Na_V\beta2$	SCN2B	White matter tracts in the cerebellum, Hippocampal, cortical pyramidal neurons, and cerebellar purkinje neurons	At the membrane of Cell bodies and Nodes of Ranvier	Na_v type-2 β-subunit. Single domain. Auxiliary subunit	Modulate channel gating kinetics	Brugada Syndrome	Riuro et al. (2013)
	$Na_V\beta3$	SCN3B	Contractile myocardium	Membrane	Na_v type-3 β-subunit. Single domain. Auxiliary subunit	Modulate channel gating kinetics	Brugada syndrome type 7	Hu et al. (2009), Carmen et al. (2010)
	$Na_V\beta4$	SCN4B	Dorsal root ganglia	Membrane	Na_v type-4 β-subunit. Single domain. Auxiliary subunit	Modulate channel gating kinetics	Long QT-syndrome type 10	Medeiros-Domingo et al. (2007)

rhythmic activity, and excitation-secretion coupling (Bergsman et al. 2000).

Chloride Ion Channel

Chloride channel is the Cl^- ion-conducting channel that can be categorized into five different types depending on the type of activators involved which are cAMP, Ca^{2+}, volume, voltage, and ligand (Suzuki et al. 2006). Presently, three well-known gene families of Cl^- ions are ClC gene family, cAMP-activated CFTR Cl^- channel gene family, and ligand-gated GABA, glycine-receptor chloride channel gene family (Jentsch et al. 2002). Different subtypes of this channel associated with diseases have been summarized in Table 4 whose multiple sequence alignment has described their very little conservation among different families during evolution (Fig. 4a). Their phylogenetic relationship showed two closely related gene families in two major clusters (Fig. 4b). These chloride channels play a variety of roles that are cell volume regulation, transepithelial transport, secretion of fluid from secretory glands, and stabilization of membrane potential (Jentsch et al. 1995).

Molecular Entities of Ion Channels

Sodium Channel Structure

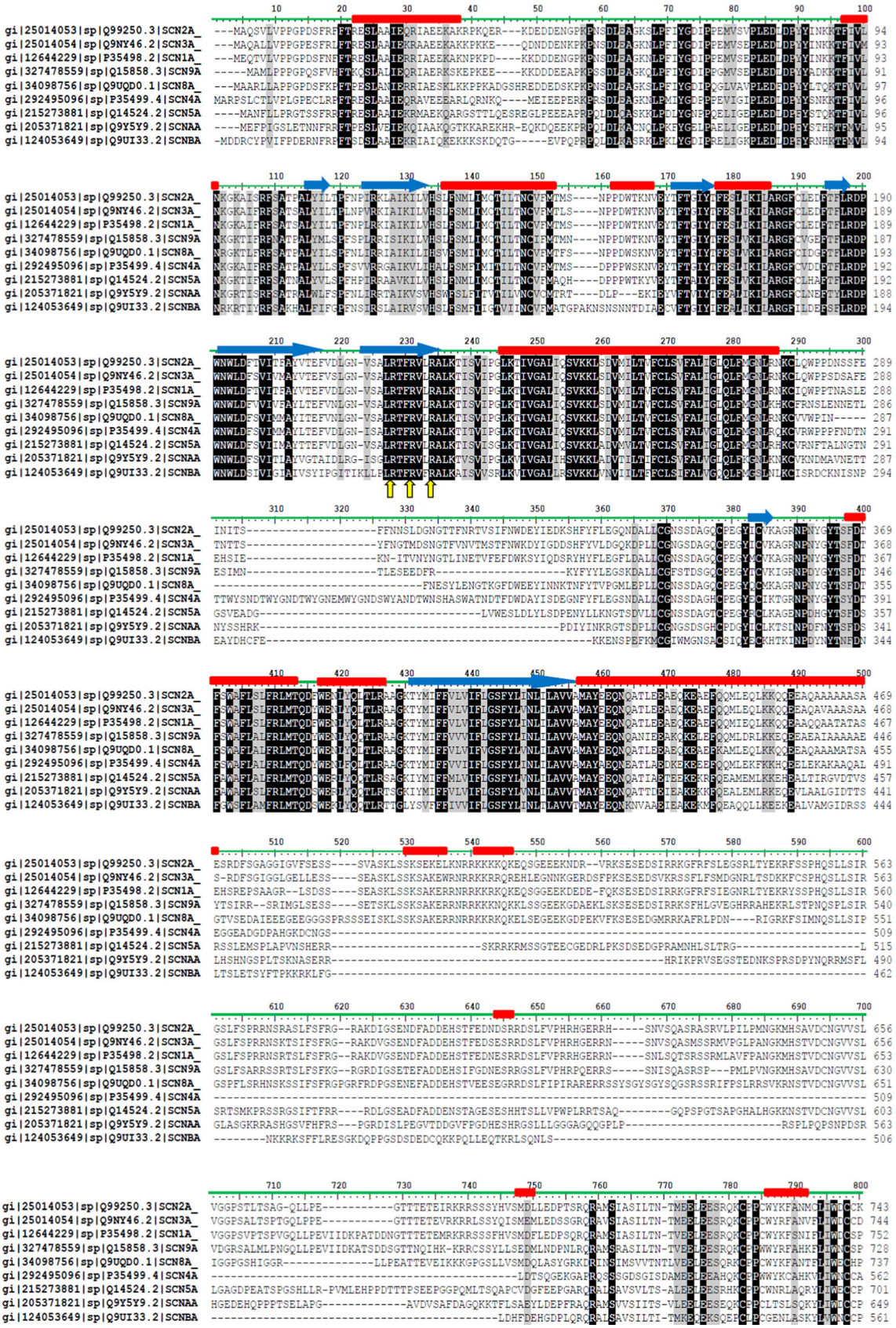
Voltage-gated sodium (Na_v) channel is a complex of a 260 kDa (α-subunit) and 33–36 kDa (β1–β4 auxiliary subunits, Casadei et al. 1986). Pore-forming single α-subunit has been associated with four β-subunits (Fig. 5a). The α-subunit has four internally repeated domains (I–IV) that mold themselves to form an ion-traversing pore. Furthermore, each domain carries six transmembrane helical segments designated as S1–S6 in which uncovered segment (S4) serves as voltage sensor along with a loop between S5 and S6 (Noda et al. 1984; Catterall et al. 2008). Apart from α-subunit that has a role in pore formation, β-subunits have an important role of modulation in the kinetics of gated channels that cause positive or negative shift upon voltage sensitivity of the channel depending on its type. Pore-forming α-subunit mutation is responsible to majority of neurological channelopathies whereas mutations in auxiliary subunit have been known to be responsible in few cases (Fontaine et al. 1990; Rojas et al. 1991; Ptacek et al. 1992).

Potassium Channel Structure

Potassium channels primarily consist of four α-subunits surrounding the central pore region frequently associated with auxiliary β-subunit (Fig. 5b). Each α-subunit of voltage-gated potassium channel (K_v) comprised six transmembrane helical segments (S1–S6) with a cytoplasmic N- and C-termini. N-terminus have T1 domain (tetramerization domain) that assembles the α-subunits into functional channel (Zerangue et al. 2000; Bocksteins et al. 2009), while S4 segment is highly positive and acts as voltage sensor along with the loop between S5–S6 (Yost 1999). Pore region contains the signature sequence GYG (Fig. 2a) which has specificity for conducting K^+ ions (Bocksteins et al. 2009). Auxiliary β-subunit assembles into tetrameric structures and interacts with α-subunit of K_v channel which provides a role in modulating channel gating kinetics (Gulbis et al. 1999). Apart from that, an additional long C-terminal extension in α-subunit has found in case of calcium-activated potassium channels, whereas inward rectifier potassium channel's α-subunit is composed of only two transmembrane segments S1 and S2 which resemble with the S5 and S6 segments of voltage-gated potassium channel (Yost 1999). The β-subunit that associates with α-subunit of calcium-sensitive potassium channel has two transmembrane segments which increases calcium sensitivity of the channel, while β-subunit that associates with α-subunit of inward rectifier potassium channel has comprised of several transmembrane segments (Benatar 2000).

Calcium Channel Structure

Calcium channel consists of a core α_1-subunit and other auxiliary subunits like β-, α_2-, δ-, and γ-subunits (Arikkath and Campbell 2003 (Fig. 5c). Ca^{2+} ion conduction is carried out by a transmembrane protein that is α1-subunit which possesses molecular mass of nearly 200–260 kDa. The α1-subunit consists of four transmembrane repeating units, where each unit is comprised six helical segments S1–S6. S4 helix serves as voltage sensor, while glutamate ions present in the linker region of S5 and S6 are the key residues responsible for providing selectivity filter role to the channel. Besides, this ion conduction tunnel is formed by the combination of S5 segment, linker region between S5–S6, and S6 segment from each of the four transmembrane units (Catterall and Curtis 1987; Campbell et al. 1988; Catterall 1988; Bergsman et al. 2000). The β-subunit is a peripheral membrane unit of nearly 60 kDa which is associated with cytoplasmic surface of membrane and is responsible for differences in major classes of calcium channel (L-, N-, P/Q-type, etc., Takahashi et al. 1987; Bergsman et al. 2000). Moreover, α_2-δ is a 175 kDa dimer which is linked by a disulfide bridge and is responsible for modulating channel gating kinetics (De Jongh et al. 1990; Klugbauer et al. 1999). Another accessory γ-subunit is known to provide the inactivating property in few cases (Eberst et al. 1997; Letts et al. 1998).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gi|327478559|sp|Q15858.3|SCN9A
gi|34098756|sp|Q9UQD0.1|SCN8A_
gi|292495096|sp|P35499.4|SCN4A
gi|215273881|sp|Q14524.2|SCN5A
gi|205371821|sp|Q9Y5Y9.2|SCNAA
gi|124053649|sp|Q9UI33.2|SCNBA

◀**Fig. 1** **a** Multiple sequence alignment of sodium channel subtypes: Highly conserved residues are highlighted in *black,* whereas less conserved residues are highlighted in *light gray*. Moreover, 16 highly conserved Arginine residues of segment 4 are marked with *yellow arrow*, which are responsible for providing voltage sensitivity to the channel. Secondary structure elements of SCN2A predicted by YASPIN are shown on the *top* of amino acid sequence, loop residues are shown in *green line*, α-helices are shown in *rectangles* (*red*), and β-strands are as filled arrows (*blue*). **b** Phylogenetic relationship obtained by UPGMA method using clustalW: There is single major cluster and two closely related subtypes that are SCN2A–SCN3A and SCN5A–SCNAA (SCN10A) along with SCNBA (SCN11A) as an out-group (Color figure online)

Chloride Channel Structure

Different Gene Families of Chloride Channel have Different Structures for Conducting Cl^- Ions.

ClC-chloride channel or voltage-gated Chloride channel has a double-barrel structure (Fig. 5d) (Miller and White 1984; Jentsch et al. 2002). These chloride channels are homodimers, and a pore is formed by each subunit. Each subunit exhibits an anti-parallel architecture. Each subunit contains 18 α-helices (Dutzler et al. 2002).

CFTR chloride channel is comprised two motifs. Each motif contains a membrane-spanning domain (MSD) and nucleotide-binding domain (NBD). R (regulatory) domain acts as a connecting link between these two MSD-NBD motifs (Sheppard and Welsh 1999). MSD usually comprised six transmembrane segments, and NBD has a role in interacting with ATP (Hyde et al. 1990).

Ligand-gated chloride channel consists of five subunits. Each subunit comprised long N-terminal extracellular domain, four putative transmembrane domains (TM), and a short extracellular C-terminal. N-terminal domain has conserved Cys-loop (Maricq et al. 1991; Lindstrom et al. 1995; Vannier and Triller 1997).

Ion Channels and Neurological Diseases

Action potential generation and synaptic transmission in the central and peripheral nervous system depend on the coordinated activity of voltage-gated ion channels. They are found to be present on axon hillock, node of Ranvier in case of myelinated and non-myelinated neurons as well (Debanne et al. 2011). Another salient feature of these channels is related to its highly conserved structure during the evolutionary process. However, synonymous mutation sites in transmembrane region are more conserved than the non-transmembrane region, but mutations in non-transmembrane region are also reported to be non-neutral ultimately causing channel dysfunction (Zhou et al. 2012). Nonfunctional ion channels are incompatible for the cellular entities and lead to the generation of varieties of neurological diseases.

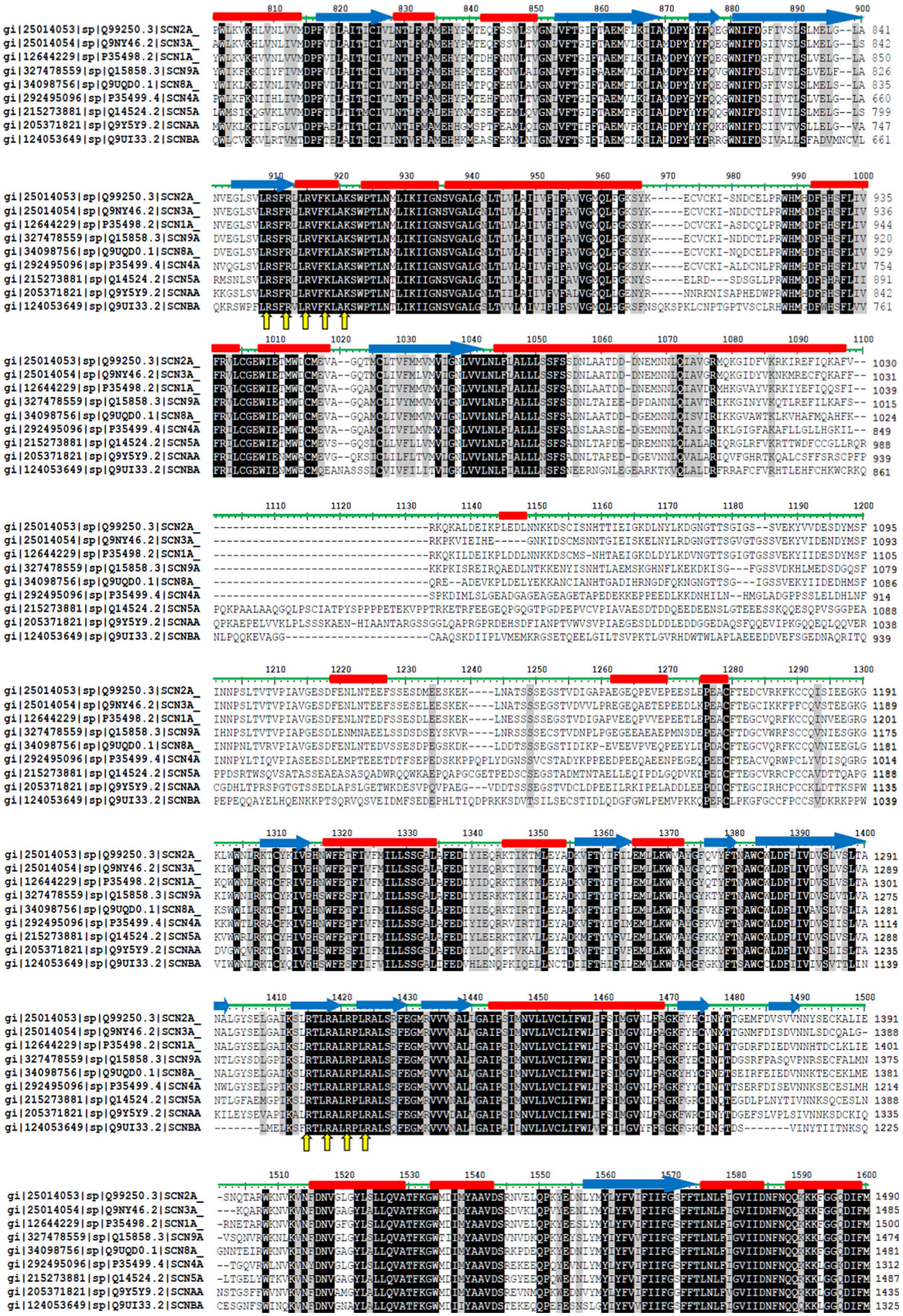
Sodium Ion Channelopathies with Molecular Mechanism

Potassium-Aggravated Myotonia (PAM)

PAM can be categorized into three different clinical phenotypes, myotonia fluctuans, severe myotonia permanens, and acetazolamide responsive myotonia that follow autosomal dominant inheritance pattern (Orrell et al. 1998) and categorized under rare disease by the Office of Rare Diseases (ORD), National Institute of Health (NIH). Myotonia implies muscle stiffness followed by its inability to relax, while in PAM myotonia worsened in the presence of potassium ions. It begins either in childhood or adolescence and known to be caused due to alteration in $Na_v1.4$ channel α-subunit as a result of mutations in SCN4A gene (Heine et al. 1993; Orrell et al. 1998; Vicart et al. 2005). Mutated channel leads to the enhanced influx of sodium ion movement in muscle, and thus prolonged contraction has been observed in PAM. There are multiple factors responsible for its triggering, for instance, fasting, physical exercise, voluntary contraction, cold weather, fever, and potassium-rich food (Ptacek et al. 1992). However, in PAM, potassium ion promotes the muscle contraction, and therefore intake of potassium-rich food is not advisable. Severity of symptoms might be exacerbated when cramps occur in respiratory muscle which could lead to hypoxia. The affected patients exhibit same phenotype with little clinical variation which has been confirmed by electromyography (Lerche et al. 1993). Multiple reasons that have been suggested for the alteration of channel function in several myotonias are reduced fast channel inactivation, enhanced recovery rate from fast inactivation, slowed deactivation or hyperpolarizing shift in steady-state activation (Cummins and Bendahhou 2009). The above phenomenon was also reported in a recent study of $Na_v1.4$ mutation i.e., A799S (Lion-Francois et al. 2010) in a patient suffering with severe neonatal episodic laryngospasm (Simkin et al. 2011). In another study using patch clamp technique, it has been reported that heterozygous mutations (G1306V, G1306A, and G1306E) in same codon of SCN4A gene are very crucial for sodium channel inactivation (Lerche et al. 1993). Apart from fewer intakes of potassium-rich foods, other treatments like physiotherapy (stretching or massaging to aid muscle relaxation) and certain medications such as mexiletine, carbamazepine, or acetazolamide are useful.

Para Myotonia Congenita (PMC)

PMC is a myopathy condition that affects the skeletal muscle contraction and tone that result in stiffness along with sustained weakness for hours. However, the onset of



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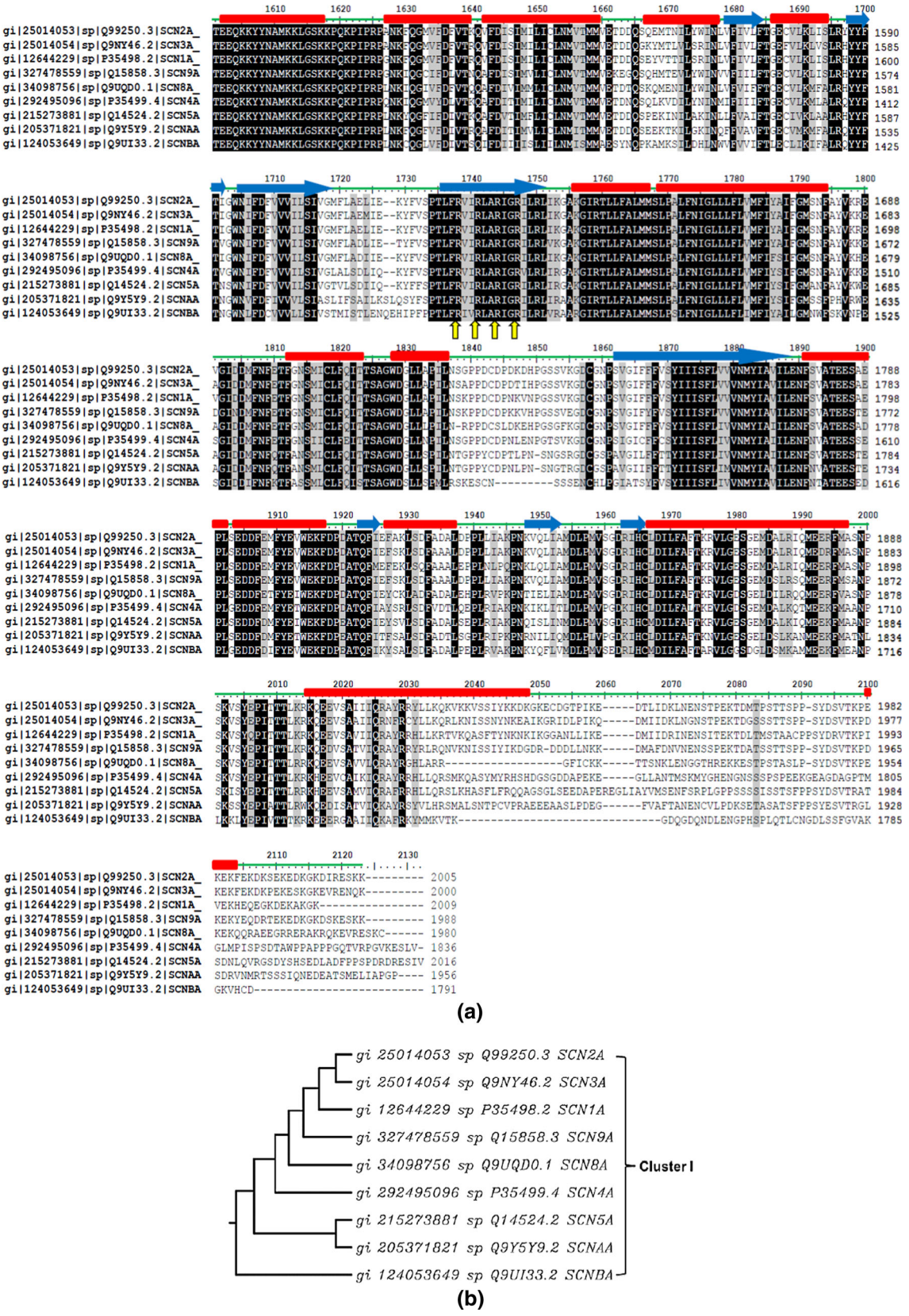


Fig. 1 continued

Table 2 Potassium ion channel subtypes in association with various diseases

Channel name	Subtypes	Genes encoding subtypes	Tissue specificity	Sub cellular location	Structure	Physiological role	Involvement in disease	References
Potassium (Kv) Channel	$K_v1.1$	KCNA1	Unmyelinated Axons, Cell Somas, Axon Terminals, Dendrites	Membrane, Transmembrane	K_v shaker member 1, α-subunit consist of six helical segments (S1–S6)	Circadian Rhythms, Neuronal Firing	Episodic Ataxia Type 1, Myokymia, Periodic Ataxia	Orazio et al. (2012), Brew et al. (2003), Shook et al. (2008)
	$K_v1.2$	KCNA2	Hippocampal Neuron Neocortex, Main olfactory bulb (MOB), and Cerebellum	Membrane, Multi-pass membrane protein	K_v shaker member 2, α-subunit consist of six helical segments (S1–S6)	Regulation of state Transitions and Repetitive activity in Striatal Medium Spiny Neurons	Cerebellar Ataxia, myokymia, and neuromyotonia	Pruss et al. (2009), Lorincz and Nusser (2008)
	$K_v1.3$	KCNA3	Effector memory T-cells	Membrane, Multi-pass membrane protein	K_v shaker member 3, α-subunit consist of six helical segments (S1–S6)	Regulate several physiological functions of Lymphocytes, Cell Proliferation	Down syndrome Neural Progenitors	Wulff et al. (2003), Cidad et al. (2012)
	$K_v1.4$	KCNA4	Heart, Cerebellum	Membrane, Multi-pass membrane protein	K_v shaker member 4, α-subunit consist of six helical segments (S1–S6)	Modulating Electrophysiological Behavior	Chronic Pancreatitis, Hyperalgesia	Chandy et al. (2004), Freedman et al. (1992), Leonard et al. (1992)
	$K_v1.5$	KCNA5	Heart, Brain	Cell membrane, Multi-pass membrane protein	K_v shaker member 5, α-subunit consist of six helical segments (S1–S6)	Physiological processes in Brain and Muscle	Ischemia Affects	Fedida et al. (2003), Gobrit et al. (2007), Vicente et al. (2006), Archer et al. (2001), Stapels et al. (2010)
	$K_v1.6$	KCNA6	Ganglion Cell	Membrane, Multi-pass membrane protein	K_v shaker member 6, α-subunit consist of six helical segments (S1–S6)	Mediates the voltage-dependent potassium ion permeability of excitable membranes	Myokymia and Neuromyotonia	van Poucke et al. (2012)
	$K_v1.7$	KCNA7	Heart, Kidney, Skeletal Muscle	Membrane, Multi-pass membrane protein	K_v shaker member 7, α-subunit consist of six helical segments (S1–S6)	Important Role in the Repolarization of Cell Membranes	Acute myeloid Leukemia	Finol-Urdaneta et al. (2006), Kashuba et al. (2001)
	$K_v2.1$	KCNB1	CNS	Pyramidal Neurons in Cortex	K_v shab member 1, α-subunit consist of six helical segments (S1–S6)	Regulates Neuronal Excitability, Action Potential Duration, and Tonic Spiking	Hyperalgesia	Misonou et al. (2005)
	$K_v2.2$	KCNB2	Trapezoid body neurons	Trapezoid body neurons	K_v shab member 2, α-subunit consist of six helical segments (S1–S6)	Regulate Action Potential Firing	Cardiovascular disease risk	Johnston et al. (2008), Kihira et al. (2010)

Table 2 continued

Channel name	Subtypes	Genes encoding subtypes	Tissue specificity	Sub cellular location	Structure	Physiological role	Involvement in disease	References
	$K_v3.1$	KCNC1	Cortex, Cerebellum, Hippocampus Neurons in the Globus Pallidus, CNS	Hippocampus Neurons in the Globus Pallidus	K_v shaw member 1, α-subunit consist of six helical segments (S1–S6)	Involved in Motor Control	Ataxia with prominent Hypermetria, Constitutive Hyperactivity, Sleep Loss, Impaired Motor performance, Tremor, and Myoclonus	Lewis et al. (2004), Espinosa et al. (2008)
	$K_v3.2$	KCNC2	Cortical GABAergic Interneurons, Hippocampus Somatic, Proximal Dendritic Membrane Axons	Proximal Dendritic Membrane Axons, Cortical GABAergic Interneurons	K_v shaw member 2, Homo- or hetero tetramer, α-subunit consist of six helical segments (S1–S6)	Neurodevelopmental delay Cerebellar Ataxia	Susceptibility to Seizures	Chow et al. (1999), Lau et al. (2000)
	$K_v3.3$	KCNC3	Cortex, Basal Ganglia, and Cerebellum	Membrane, Multi-pass membrane protein	K_v shaw member 3, Homo- or, α-subunit consist of six helical segments (S1–S6)	Involved in Motor Control	Constitutive Hyperactivity, Sleep Loss, Impaired Motor Performance, Ataxia, Tremor, and Myoclonus	Espinosa et al. (2008)
	$K_v4.1$	KCND1	Epithelial Cells, Alveolar and Mammary Epithelial Cells, Adipose Tissue-Derived Stem Cells	Multi-pass membrane protein, Alveolar Mammary Epithelial Cells Adipose Tissue-Derived Stem Cells	K_v shal member 1, Homo tetramer, α-subunit consist of six helical segments (S1–S6)	Contribute to cell Migration and Wound Healing	Gastric Cancer NOS, Malignant Neoplasm of Breast	Sandhiya and Dkhar (2008)
	$K_v4.2$	KCND2	Brain	Localized in the Dendrites near Postsynaptic Regions	K_v shal member 2,, α-subunit consist of six helical segments (S1–S6)	Regulate Synaptic Plasticity	Cardiovascular disease	Jo et al. (2010)
	$K_v4.3$	KCND3	Rat Adult Brain and Heart Tissues	Molecular layer Interneurons	K_v shal member 3,, α-subunit consist of six helical segments (S1–S6)	Internalized in response to Glutamatergic stimulation in Purkinje Cells, Neuronal Somato-dendritic Interactions	Spin cerebellar Ataxia Type 1, Cerebellar Ataxia	Hourez et al. (2011)
	$K_v7.2$	KCNQ2	Peripheral Nerve System	Membrane, Multi-pass membrane protein	K_v KQT like Subfamily member 2, Heteromultimer, α-subunit consist of six helical segments (S1–S6)	Regulate Neurotransmitter Release, Heart Rate, Insulin Secretion Neuronal Excitability, Epithelial electrolyte Transport, Smooth Muscle contraction	Myokymia and Neuromyotonia	van Poucke et al. (2012)

Table 2 continued

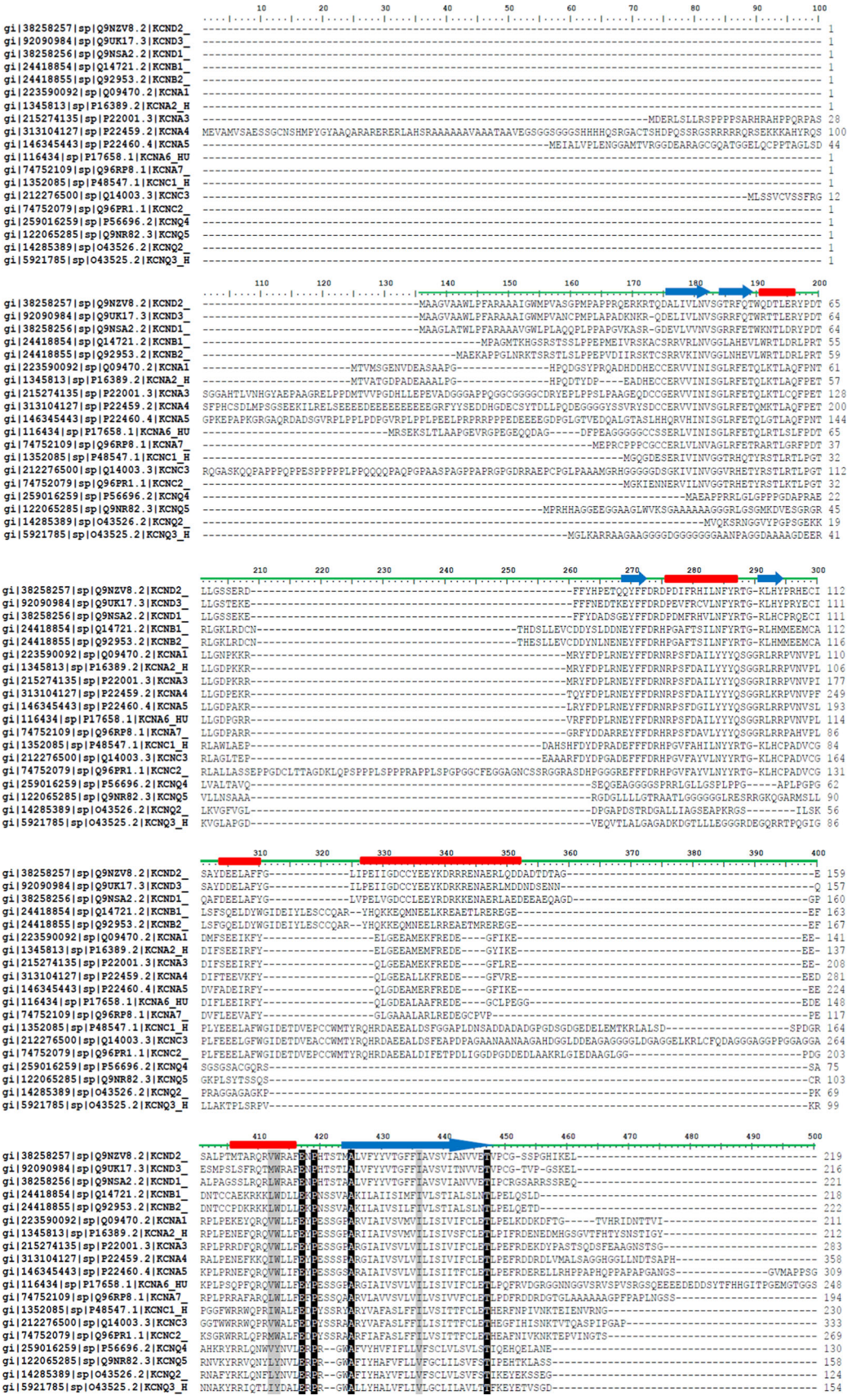
Channel name	Subtypes	Genes encoding subtypes	Tissue specificity	Sub cellular location	Structure	Physiological role	Involvement in disease	References
	$K_v7.3$	KCNQ3	Distributed Broadly in Brain	Membrane, Multi-pass membrane protein	K_v KQT like Subfamily member 3, Heteromultimer, α-subunit consist of six helical segments (S1–S6)	Electrical Hyper excitability in BFNC	Familial Neonatal Convulsions (BFNC), Autosomal Dominant Epilepsy of Infancy, Myokymia	Schroeder et al. (1998), Chung et al. (2006)
	$K_v7.4$	KCNQ4	Almost All Brain Regions	Discrete Nuclei Of Brainstem, Including the Mid- Brain	K_v KQT like Subfamily member 4, Homo/ Hetero tetramer, α-subunit consist of six helical segments (S1-S6)	Participate in both pre- and Post-synaptic Modulation of basal and stimulated excitatory Neurotransmission	Chinese Non-Syndromic Hearing Loss Pedigree	Kharkovets et al. (2000)
	$K_v7.5$	KCNQ5	Neocortex and the Hippocampal	Apical and Lateral Membranes	K_v KQT like Subfamily member 5, Heteromultimer, α-subunit consist of six helical segments (S1–S6)	Controlling Basal Anion Secretion	Epilepsy	Yus-Najera et al. (2003)

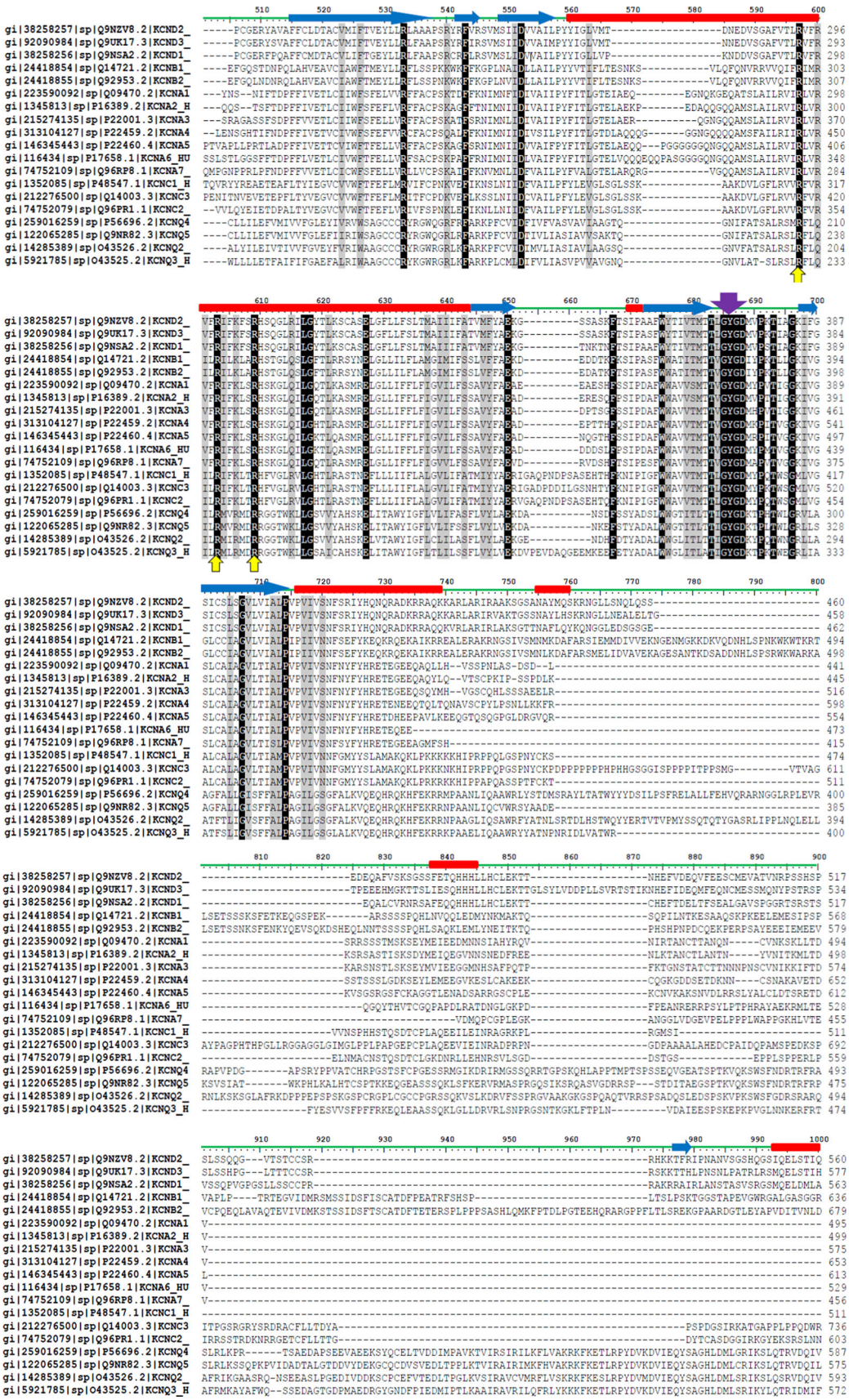
Fig. 2 **a** Multiple sequence alignment of potassium channel subtypes: Highly and less conserved residues have been highlighted in *black* and *light gray* color, respectively, where three highly conserved Arginine residues present in segment 4 impart voltage sensitivity to the channel that has been marked with *yellow arrow*. Moreover, 'GYG' signature sequence has marked with *purple arrow* that provides potassium ion selectivity to the channel. Secondary structure elements of KCND2 (predicted by YASPIN) have shown on the *top* of amino acid sequences that are loop residues (*green line*), α-helices (*rectangles* (*red*)), and β-strands (*filled arrows* (*blue*)). **b** Phylogenetic tree obtained by UPGMA method using clustalW: There are three major clusters where six pairs of subtypes are found to be closely related, which are KCND2–KCND3, KCNB1–KCNB2, KCNA1–KCNA2, KCNA4–KCNA7, KCNC1–KCNC3, and KCNQ4–KCNQ5 (Color figure online)

prolonged muscle contraction begins in infant, while episodes of weakness start at adolescence stage. This disease is also known as Eulenberg disease and comes under rare congenital autosomal dominant neuromuscular disorder (Haass et al. 1981). It is highly cold sensitive and exacerbated due to exercise and cold temperature which affect upper bodily parts, for instance, bulbar, facial, neck, and hand muscles more than the lower limbs (Magee 1966). Prolonged cry in such patients often leads to blepharospasm. Not always but frequently PMC patients are found to be accompanied by Hyperkalemic periodic paralysis with increased level of serum creatine kinase. Voltage-gated sodium channel α-subunit-encoding SCN4A genetic mutation is responsible for PMC (Kim et al. 2002, Pereon et al. 2003), where the cytoplasmic loop region between segment III and IV in sodium channel is hotspot for the mutation (McClatchey et al. 1992; Ptacek et al. 1992; Lerche et al. 1993; Ptacek et al. 1993; Sasaki et al. 1999; Okuda et al. 2001). It has also been studied that R1448H mutation causes cold-induced myotonia that leads to PMC and is responsible for slowed inactivation and faster recovery from inactivation as compared to non-mutant channels (Mohammadi et al. 2003). The problem of myotonia in PAM patients can be relieved by administering mexiletine as a first-line agent, while episodic weakness can be treated with daranide or dianox.

Hyperkalemic Periodic Paralysis (HYKPP)

Hyperkalemic periodic paralysis is a congenital autosomal dominant genetic disorder (Ptacek et al. 1991) with elevated potassium level in blood that causes episodes of muscle weakness (Venance et al. 2006), where intake of potassium-rich foods and rest after exercise are the most prominent factors for triggering of HYKPP. The attack lasts for few hours to a day, where its severity is specified via membrane inexcitability and muscle weakness which affect shoulder, hips more often than hands and legs (Weber et al. 2006; Webb and Cannon 2008). Underlying SCN4A gene mutations affect inner core of transmembrane





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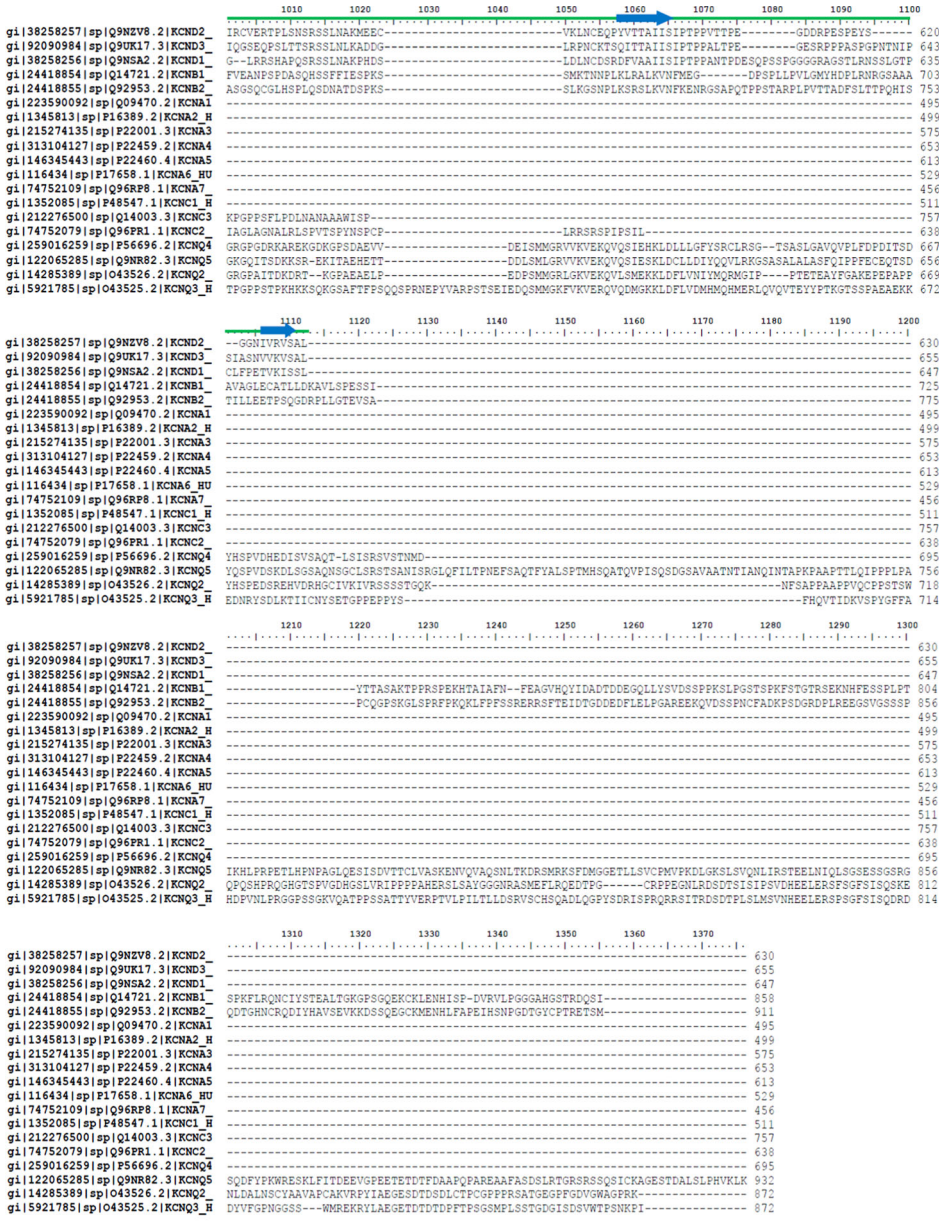


Fig. 2 continued

Table 3 Calcium ion channel subtypes in association with various diseases

Channel name	Subtypes	Genes encoding subtypes	Tissue specificity	Sub cellular location	Subunit structure	Physiological role	Involvement in disease	References
Calcium (Ca_V) Channel	$Ca_v1.1$	CACNA1S	Skeletal Muscle	Located in Muscle Cells triad junctions	Ca_v L-type, α-1S-subunit, Each α_1-subunit consists of 6 helical transmembrane segments (S1–S6)	Functions as a Voltage Sensor in Skeletal Muscle Excitation–Contraction Coupling	Hypokalemic Periodic Paralysis, Thyrotoxic Periodic paralysis, and Malignant Hyperthermia Susceptibility	Kung et al. (2004), Kim et al. (2001)
	$Ca_v1.2$	CACNA1C	Brain, Heart, Ovary Neurons	Membrane, Multi-pass membrane protein	Ca_v L-type, α-1C-subunit, Each α_1-subunit consists of 6 helical transmembrane segments (S1–S6)	Release of Hormones and Neurotransmitters	Vision, Hearing,, and Gene Expression	Kameda et al. (2006), Reuter (1983)
	$Ca_v1.3$	CACNA1D	Auditory Brainstem, Center Auditory Sensory hair Cells, Neuronal Cells, and Some Epithelial Cells	Somato-dendritic Compartment of many Types of Neurones	Ca_v L-type, α-1D-subunit, Each α_1-subunit consists of 6 helical transmembrane segments (S1–S6)	Regulate Intracellular Processes such as Contraction, Secretion, Neurotransmission, and Gene Expression	Deafness	Roberts et al. (1990), Satheesh et al. (2012)
	$Ca_v1.4$	CACNA1F	Retina	Expressed in the Retina and Localizes at Ribbon Synapses in Cone and Rod photoreceptors	Ca_v L-type, α-1F-subunit, Each α_1-subunit consists of 6 helical transmembrane segments (S1–S6)	Synaptic Transmission and Cellular organization in Retina	Congenital Stationary Night Blindness, Syndromic Autism, Schizophrenia	McRory et al. (2004), Klassen et al. (2011), Wei and Hemmings (2006)
	$Ca_v2.1$ (P/Q)	CACNA1A	Presynaptic Terminals Cerebellar Purkinje Cells Granule Cells, Cortex	Somato-Dendritic membranes throughout the brain	Ca_v P/Q-type, α-1A-subunit, Each α_1-subunit consists of 6 helical transmembrane segments (S1–S6)	Mediating Neurotransmitter release in the Nervous System, Postsynaptic Integration, Neuroplasticity, Neural Excitability, and Gene Transcription	Spin cerebellar Ataxia Type 6	Llinas et al. (1992), Mintz et al. (1992), Chen and Piedras-Rentería (2007)
	$Ca_v2.2$ (N)	CACNA1B	Neuron, Retinal Ganglion cell	Multi-pass membrane protein	Ca_v N-type, α-1B-subunit, Each α_1-subunit consists of 6 helical transmembrane segments (S1–S6)	Controls Neurotransmitter Release from Neurons	Episodic Ataxia Type 2, Schizophrenia, and Bipolar Disorder	Yasuda et al. (2004), Zhang et al. (2008)

Table 3 continued

Channel name	Subtypes	Genes encoding subtypes	Tissue specificity	Sub cellular location	Subunit structure	Physiological role	Involvement in disease	References
	Ca_v 2.3 (R)	CACNA1E	Neuronal Tissues (Kidney)	Multi-Pass membrane Protein	Ca_v R-type, α-1E-subunit, Each α_1-subunit consists of 6 helical transmembrane segments (S1–S6)	Modulation of firing patterns of neurons, Muscle Contraction, Hormone or neurotransmitter release, Cell Motility, Cell Division, and Cell Death	Juvenile Myoclinic Epilepsy	Schneider et al. (1994), Williams et al. (1994), Suzuki et al. (2004)
	$Ca_v3.1$	CACNA1G	Neurons and Cardiac tissue	Multi-pass membrane protein	Ca_v T-type, α-1G-subunit, Each α_1-subunit consists of 6 helical transmembrane segments (S1–S6)	Neuronal Firing Activity, Cardiac Pacemaker Activity	Epilepsy, Cardiac Hypertrophy	Hagiwara et al. (1988), Huguenard (1996), Tsakiridou et al. (1995)
	$Ca_v3.2$	CACNA1H	Kidney, Liver, Heart, Brain	Multi-pass membrane protein	Ca_v T-type, α-1H-subunit, Each α_1-subunit consists of 6 helical transmembrane segments (S1–S6)	Secretion of Neuroendocrine Prostate Cancer Cells, Contraction, Secretion Neurotransmission, and gene Expression.	Epilepsy, Idiopathic generalized Type 6, Epilepsy, childhood absence 6 (ECA6)	Splawski et al. (2006)
	$Ca_v3.3$	CACNA1I	Brain Specific	Somato-dendritic Compartment of many Types of Neurones	Ca_v T-type α- 1I-subunit, Each α_1-subunit consists of 6 helical transmembrane segments (S1–S6)	Electrical and Signaling, generate burst firing, and Pacemaker Activity	Hyperalgesia	Talley et al. (1999), Carbone and Lux (1984), Kim et al. (2003)
	Ca_v β_1	CACNB1	Brain, Heart, Spleen, Central Nervous System & Neuro-blastoma Cell	Sarcolemma, Peripheral membrane protein	Ca_v L-type, β-1 (auxiliary)subunit	Modulating G protein inhibition and controlling the alpha-1 subunit membrane targeting	Malignant Hyperthermia susceptibility (Autosomal Dominant Disorder of Skeletal Muscle)	Gregg et al. (1996)
	Ca_v β_2	CACNB2	Heart, Retina	Membrane of smooth Muscle	Ca_v L-type, β-2(auxiliary)-subunit	Hyperpolarizing Shifts	Lambert-Eaton Myasthenic Syndrome, Brugada Syndrome	Perez-Reyes et al. (1992), Pichler et al. (1997), Ball et al. (2002), Reimer et al. (2000), Singer et al. (1991)
Ca_v β_4	CACNB4	Brain, predominantly in the Cerebellum, Kidney	Vestibular, Cerebellar Neuronal membrane	Cav L-type, β-4(auxiliary)-subunit	Shifting the Voltage dependencies of activation and inactivation, Modulating G protein inhibition	Idiopathic generalized Epilepsy, Juvenile Myoclonic Epilepsy	Xu et al. (2011), Ohmori et al. (2008)	

Table 3 continued

Channel name	Subtypes	Genes encoding subtypes	Tissue specificity	Sub cellular location	Subunit structure	Physiological role	Involvement in disease	References
	Ca_v Υ_2	CACNG2	Brain	Multi-pass membrane protein	Ca_v Υ-2 (auxiliary)subunit	Regulates the trafficking and gating properties of AMPA-selective glutamate receptors	Mental Retardation	Hamdan et al. (2011), Shi et al. (2010), Black and Lennon (1999)
	Ca_v Υ_5	CACNG5	Epithelia	Cell Junction, Postsynaptic Cell Membrane	Ca_v Υ-5 (auxiliary)subunit	Modulates gating properties	Schizophrenia and Bipolar Disorder	Chen et al. (2007), Curtis et al. (2011), Chu et al. (2001)

segments or intracellular protein loops which inturn impair the anchoring site of fast inactivation particle thereby leading to persistent Na^+ current through unclosed sodium channel (Bendahhou et al. 2002). The persistent sodium current across non-inactivated channel causes depolarization of cell thereby inactivating other normal sodium channels due to inability of action potential generation (Cannon et al. 1991; Lehmann-Horn et al. 2002). Patients suffering from this disease report abnormal muscle biopsy with high level of creatine kinase in the serum and permanent muscle weakness with aging. The treatment focuses on relieving symptoms and preventing further attacks which could be accomplished with the help of low potassium-high carbohydrate meal and medication of acetazolamide and hydrochlorothiazide drugs which are effective with minimal risks (McArdle 1956; Han and Kim 2011).

Primary Erythro-Melalgia (PEM)

Primary erythromelalgia is an autosomal dominant, peripheral nerve pain disorder which can be characterized by severe burning and bilateral pain with swelling in extremities of the body especially in hands and feet (Dib-Hajj et al. 2005; Waxman and Dib-Hajj 2005a, b). Due to micro-vascular arteriovenous shunting in PEM patients, vasomotor changes such as erythema and oedema take place, resulting in the pain sensation around affected area (Mork et al. 2000). The episodic attacks are found to be triggered or aggravated by increased body temperature, spicy food, and exercise, while cold environment relieves the pain (Michiels et al. 2005). Mutations in SCN9A gene are responsible for pathogenesis of PEM that causes alteration in $Na_v1.7$ α-subunit and lead to increased action potential (Cummins et al. 2004) thereby causing prolonged transmission of pain signals (Yang et al. 2004; Dib-Hajj et al. 2005; Drenth et al. 2005; Dib-Hajj et al. 2007). The patch clamp analysis of mutated sodium channel revealed that there is a hyperpolarization shift toward activation of the channel and slowed inactivation kinetics that makes opening of channel easier and prolonged (Cummins et al. 2004). Various treatment modalities have been tried viz. aspirin, cyclosporine, beta blockers, calcium channel antagonists, but patient should take preventive measures along with medication which include sodium channel blocker like ranolazine and mexiletine with highly promising results (Iqbal et al. 2009).

Paroxysmal Extreme Pain Disorder (PEPD)

PEPD is an autosomal dominant peripheral neuropathy that was earlier known as familial rectal pain and is characterized by excruciating pain and flushing in the submandibular, ocular, and rectal region (Fertleman and Ferrie

2006). Recurrent pain and skin flushing begin in childhood, and pain progresses to ocular and mandibular region with age. Although PEPD is a lifelong disorder, the frequency of attack generally decreases with age. Moreover, it has been observed that attacks are provoked by physical trigger like crying, eating, and defecation (Pett et al. 2013). PEPD is caused due to functional gain mutation in SCN9A gene (Choi et al. 2011; Estacion et al. 2011; Fischer and Waxman 2010) that means mutated channel results in sustained flow of sodium ion and hence maintaining action potential which prolongs transmission of pain signals. It has been reported that mutated channel lowers the threshold for single action potential in dorsal root ganglion neurons that results into increased number of action potential in response to a supra-threshold stimuli which leads to elevated pain signal transmission (Dib-Hajj et al. 2008). To relieve the pain, it is important to take preventive measure from triggering factor like managing constipation and use of anticonvulsants, for instance, carbamazepine has been found to be very effective in many patients (Theile and Cummins 2011).

Congenital Insensitivity to Pain (CIP)

CIP is an autosomal recessive peripheral sensory neuropathy characterized by complete loss of pain sensation in response to injuries (Danziger and Willer 2009) and also known as congenital analgia or congenital analgesia, congenital asymbolia, and congenital indifference to pain (Dyck et al. 1983). Congenital insensitivity to pain has been classified to the family of Hereditary Sensory and Autonomic Neuropathies (HSAN) and it has two common occurring forms that are congenital insensitivity to pain (CIP) and congenital insensitivity to pain with anhidrosis (CIPA) which have been classified as HSAN-V and HSAN-IV, respectively. CIP has been observed to be prevalent in children born to consanguineous marriages, and they generally suffer from accumulated wounds due to repeated injuries as a consequence of imperceptions of pain sensation (Protheroe 1991). Earlier, it was reported that CIP patients possess only nonsense mutations in the SCN9A gene (Dabby 2012; Cox et al. 2006) which were responsible for truncated α-subunit of sodium channel ($Na_v1.7$), but recently missense mutation (R896Q), frame shift deletion mutation (ΔR1370-L1374), and splicing mutation (IVS8-2A > G) have also been observed (Cox et al. 2010; Klein et al. 2013). Recent mutation was reported to be associated with pore regions thereby causing defect in the ion conduction through $Na_v1.7$ channel present on nociceptors that lead to complete loss of pain signal transmission from site of injury to brain (Fischer and Waxman 2010; Lampert et al. 2010, Goldberg et al. 2007). CIP patients not only exhibit loss of pain sensation but also sometimes smell sensation as well because $Na_v1.7$ channel is also present on olfactory receptor neurons that can lead to anosmia (Weiss et al. 2011). Convincing treatment for this disease is remain unclear, but case reports showed promising result with the use of naloxone and naltrexone in reversing the effect of analgesia (Protheroe 1991).

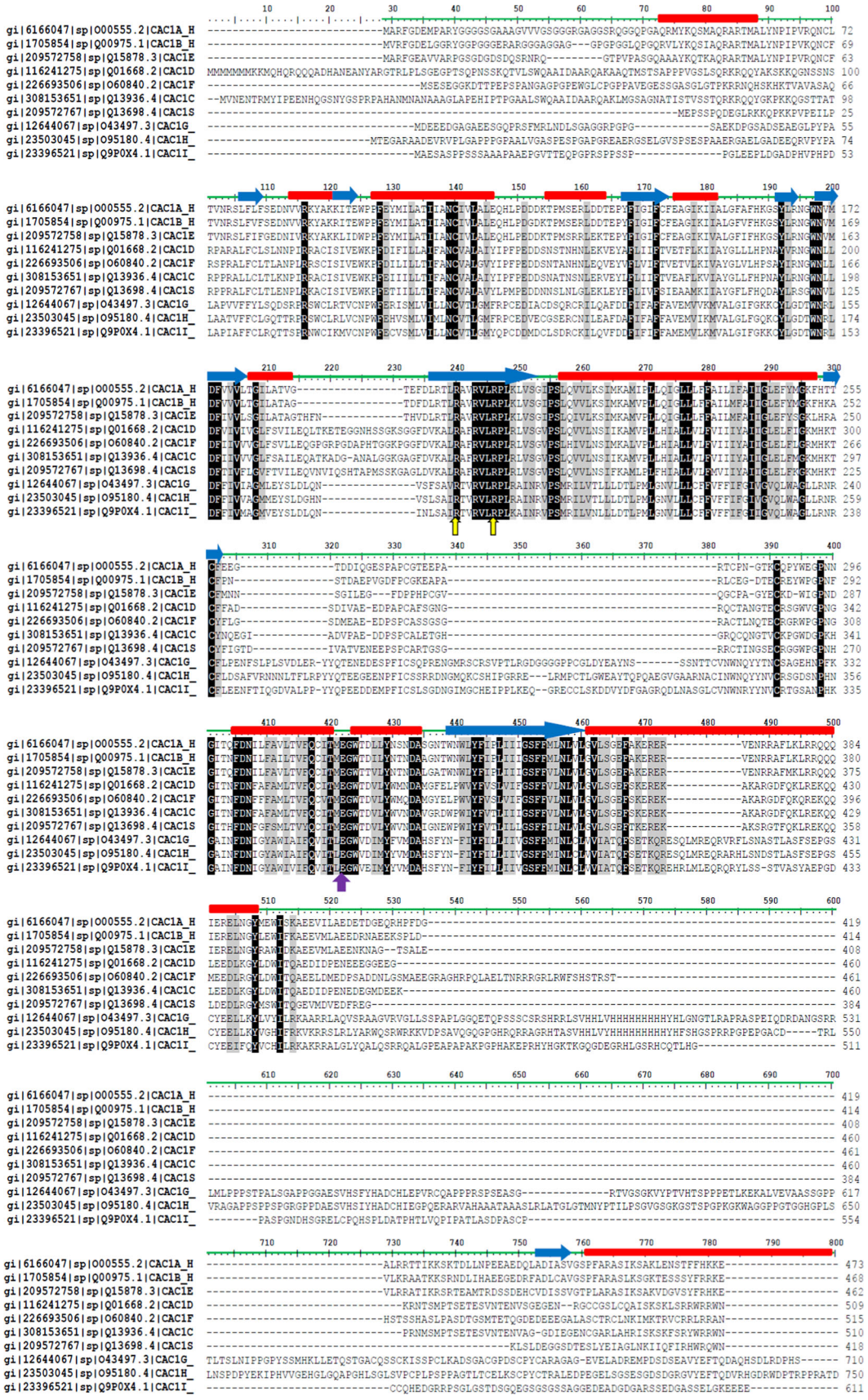
Generalized Epilepsy with Febrile Seizures (GEFS)

Epilepsy is a chronic neurological disorder that can be characterized with the recurrent episodes of convulsions and sensory disturbances due to abnormal electrical signals in the brain. Generalized epilepsy with febrile seizures (GEFS) is a recently described autosomal dominant epileptic syndrome, where convulsions are associated with the elevated temperature of the body (Chang and Lowenstein 2003). It begins in childhood (1 month to 1 year) and may last up to the age of 6 years or sometimes continues till the onset of puberty. GEFS patients exhibit a variety of clinical phenotypes that are typical febrile seizures and other seizure types such as tonic–clonic, myoclonic, myoclonic-astatic, absences, or atonic seizures (Scheffer and Berkovic 1997). Simple febrile seizure generally lasts for 15 min, while complex febrile seizure exhibits episodes that last more than 15 min, and it has also been observed that epilepsies become more prominent in aged people (Brodie et al. 2009). In most of the cases, majorly mutations were found in SCN1A, SCN1B gene, and γ2-subunit of $GABA_A$ receptors (Meisler et al. 2010; Wallace et al. 1998; Wallace et al. 2002; Audenaert et al. 2003; Meisler and Kearney 2005; Fujiwara 2006; Kang et al. 2006), where few mutations in $Na_v1.1$ cause mild epilepsies but several mutations in $Na_v1.1$ channel lead to severe epilepsies (Catterall et al. 2010).The resulting seizures are found to be familial in few cases and sporadic in other cases that imply environmental factors like elevated temperature also play a contributing role. Hyperthermia itself is capable of generating seizures, while resulting mutations are known to aggravate the susceptibility of developing a seizure with fever (Dube et al. 2009). Generally, regular medicines are not prescribed for such patients but for severe cases epileptic medicines like sodium valproate, ethosuximide, clobazam, carbamazepine, and phenytoin drugs are helpful in controlling epilepsies (Tate et al. 2005, 2006; Scheffer et al. 2007; Groot et al. 2012).

Potassium Ion Channelopathies with Molecular Mechanism

Paroxysmal Dyskinesia

Paroxysmal dyskinesia is an autosomal dominant rare episodic movement disorder that exhibits abnormal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gi|23396521|sp|Q9P0X4.1|CAC1I_

◀ **Fig. 3** **a** Multiple sequence alignment of calcium channel subtypes: Highly and less conserved residues are highlighted in *black* and *light gray* color, respectively, where 12 highly conserved Arginine residues of segment 4 have been marked with *yellow arrow*, which provide voltage sensitivity to the channel. Moreover, Glutamate residues in loop region between segment 4 and 5 offer ion selectivity that is marked with *purple arrow*. Secondary structure elements of CACNA1A (predicted by YASPIN) are shown on the top of amino acid sequences that are loop residues (*green line*), α-helices (*red rectangle*), and β-strands (*blue arrows*). **b** Phylogenetic tree obtained by UPGMA method using clustalW: There are two major clusters having four pairs of closely related channel subtypes: CAC1A–CAC1B, CAC1D–CAC1F, CAC1C–CAC1S, and CAC1G–CAC1H (Color figure online)

involuntary movements including chorea, dystonia only during attacks (Demirkiran and Jankovic 1995). It has been classified into four different types on the basis of triggering factors responsible for the episodes that are (i) Paroxysmal kinesigenic dyskinesias (PKD) which is known to be triggered by sudden voluntary movements and unexpected stimulus, (ii) Paroxysmal non-kinesigenic dyskinesias (PNKD) that can be triggered by factors other than movement like stress, fatigue, and alcohol consumption, (iii) Paroxysmal exercise(exertion)-induced dyskinesias (PED) which could be triggered by prolonged exercise, and lastly (iv) Paroxysmal hypnogenic dyskinesias (PHD) in which attack can be triggered during Non-rapid eye movement sleep (Unterberger and Trinka 2008). Increased studies revealed that familial PKD can be caused by channel mutations and it has been identified that coexistence of generalized epilepsy and paroxysmal dyskinesiais caused by mutations in KCNMA1 gene. The resulting mutation in this gene promotes excitability of neurons by inducing rapid repolarization of action potential which allows neurons to conduct at a faster rate thereby causing recurrent attacks (Du et al. 2005). Moreover, recent studies identified that PKD is linked to pericentromeric region of chromosome 16 in a number of families and PNKD is caused due to mutation in myofibrillogenesis regulator 1 gene (MR-1) on Chromosome 2, while PED is caused due to mutation in glucose transporter gene (GLUT1, Mehta et al. 2009).There is no cure for paroxysmal dyskinesia, but symptoms can be relieved to some extent inconsistently with the help of anticonvulsants drugs like acetazolamide, anticholinergics, levodopa, and tetrabenazine along with avoiding the precipitating events like prolonged exercise(Mehta et al. 2009; van Rootselaar et al. 2009).

Benign Familial Neonatal Seizure (BFNS)

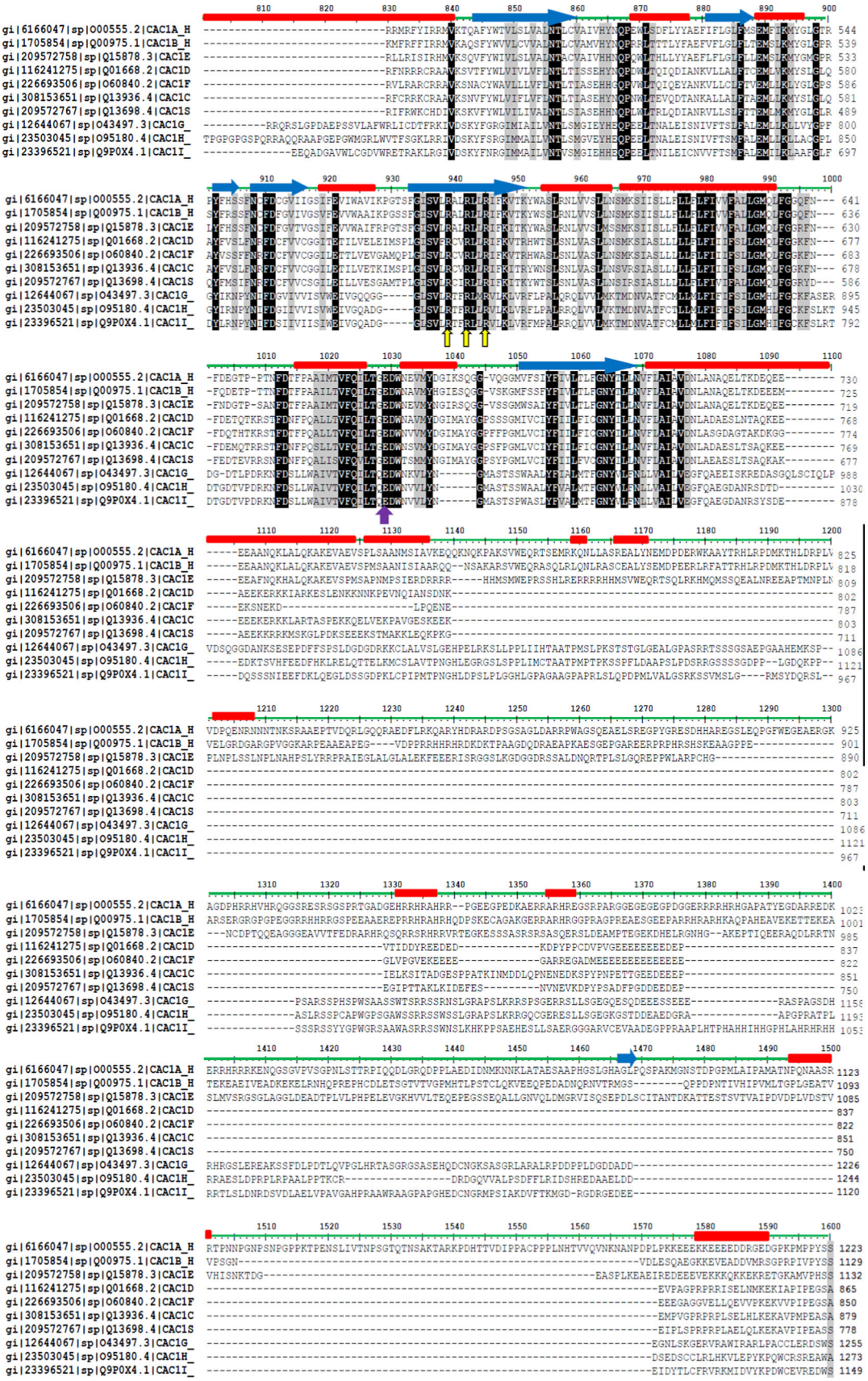
BFNS is an autosomal dominant inherited form of epilepsy which has been characterized by recurrent seizures in new born babies that cause muscle stiffness, convulsions, and loss of consciousness (Biervert et al. 1998). In majority of the suffering neonates, seizures began within the first week of life and disappeared spontaneously within a few months, but some patients showed dysfunctional channel even in adulthood (Tomlinson et al. 2012). Multiple mutations have been reported in KCNQ2 and KCNQ3 gene in the patients suffering with BFNS thereby generating altered M-current (Singh et al. 1998; Castaldo et al. 2002; Singh et al. 2003). However, normal M-current generated by $K_v7.2$ and K_v 7.3 potassium channel repolarizes the cell and hence ensures the inactivation of neurons, while mutated channel generates reduced or altered M-current that causes over-activation of neurons which leads to the seizure development in brain (Wang et al. 1998; Soldovieri et al. 2007; Volkers et al. 2009). Anticonvulsant therapy has been widely used where phenobarbital is effective in majority of individuals, while some individual may require other epileptic drug like carbamazepine, phenytoin, valproic acid, clonazepam, midazolam, or vigabatrin, but treatment has not had a consistent effect on the duration of seizures (Soldovieri et al. 2007).

Andersen Tawil Syndrome (ATS)

ATS is an autosomal dominant genetic disorder that has been characterized by periodic paralysis, ventricular arrhythmias, and developmental abnormalities typically affect head, face, and limbs (Tawil et al. 1994). Based on the genetic causes, ATS has been classified into two types where mutated KCNJ2 gene (Inward rectifier potassium channel $K_{ir}2.1$) was responsible for ATS type 1, while genetic cause for ATS type-2 is still unknown (Plaster et al. 2001). Its onset generally takes place around 20 years and 70 % of KCNJ2 mutations exhibit prolonged QT interval thereby also classified as Long QT syndrome 7 (Tristani-Firouzi et al. 2002) but a distinctive electrocardiogram has been observed in ATS1 patients with prolonged terminal T wave and prominent enlarged U waves (Zhang et al. 2005). Altered $K_{ir}2.1$ inward rectifier potassium channel disrupts PIP2 (phosphatidylinositol-4,5-bisphosphate) binding which has been responsible for inactivating channel thereby leading to sustained action potential and hence causes periodic paralysis and arrhythmias in skeletal and cardiac muscles (Lopes et al. 2002; Seebohm et al. 2012). Treatment of ATS patients requires closely co-ordinated expertise between a neuromuscular specialist and a cardiologist. However, it has been observed that drugs may have beneficial effect on one tissue while detrimental on other, but amiodarone and acetazolamide are effective in many cases (Junker et al. 2002).

SeSAME and EAST Syndrome

SeSAME/EAST is an autosomal recessive disorder whose nomenclature is based on the characteristic symptoms they



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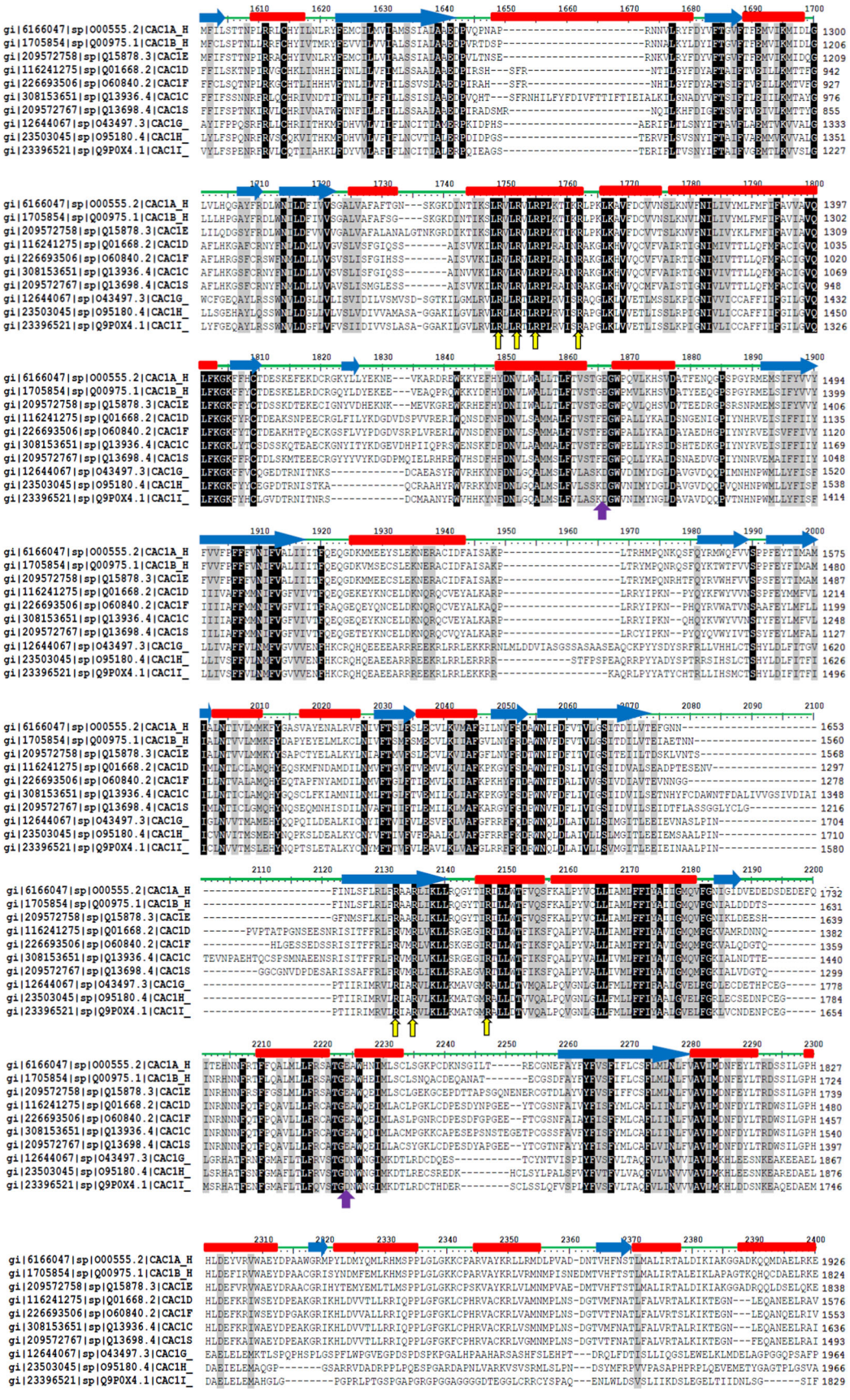

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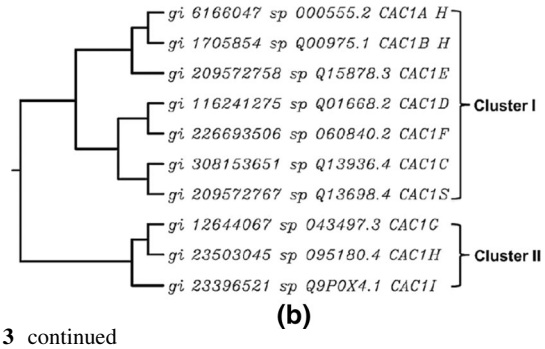

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exhibit, for instance, SeSAME patients are affected with seizures, sensorineural deafness, ataxia, mental retardation, and electrolytic imbalance (hypokalemia, metabolic alkalosis, and hypomagnesaemia, Scholl et al. 2009), whereas EAST patients possess typical symptoms that are epilepsy, ataxia, sensorineural deafness, and tubulopathy (Bockenhauer et al. 2009). Both of them are known to be caused due to mutations in KCNJ10 gene that codes for ATP-sensitive inward rectifier potassium channel 10 (K_{ir} 4.1 channel, Freudenthal et al. 2011). It has been reported that K_{ir} 4.1 channel is expressed in the brain, inner ear, retina, and kidney thereby imparting the functional loss in these organs with mutations. In brain, it contributes potassium buffering for glial cells, controls neuronal excitability, and maintains systemic potassium ion homeostasis, while in kidney it maintains electrolytic balance across distal convoluted tubule (Williams et al. 2010). Multiple mutations in KCNJ10 gene have been reported, which alter inactivation of Kir 4.1 channel via loosing affinity toward channel modulator like PIP2 that results in reduced channel activity with prominent symptoms (Sala-Rabanal et al. 2010). They are lifelong disorders and there is no current treatment that can cure the condition but we can use antiepileptic medicines to relieve symptoms under the guidance of a nephrologist.

Jervell and Lange-Nielson Syndrome (J-LN)

J-LN is an autosomal recessive most severe variant of long QT syndrome that has been characterized by congenital sensorineural hearing loss and cardiac arrhythmia. It begins in childhood and patient suffers with deafness, recurrent fainting, ventricular arrhythmia and sometimes sudden death (Schwartz et al. 2006). Genetic mutations were reported in KCNQ1 and KCNE1 genes that codes for voltage gated delayed rectifier potassium channel's α and β subunit respectively in J-LN patients which is responsible for potassium ion imbalance in the cochlear hair cells and cardiomyocytes (Chen et al. 1999; Tyson et al. 2000). For normal hearing, a continuous flow of endolymph is required into the cochlear hair cells that are known to maintain the voltage gradient for nerve signal transmission (Lasak et al. 2014), thus mutated channel disrupts the voltage gradient required for transmitting signal through auditory nerves thereby causing deafness. On the other hand, mutated channels in cardiomyocytes exhibit delayed repolarization thereby causing prolonged QT wave responsible for cardiac arrhythmia (Lehnart et al. 2007). There is no cure for J-LN but as a relieving therapy beta blockers are being used to keep heartbeat under control with a limited efficacy. Moreover, automatic defibrillator and cochlear implantation techniques are also being used for treating cardiac arrhythmia and hearing loss, respectively, in case medication fails but patients are highly prone to sudden death (Rocha et al. 2013; Broomfield et al. 2012).

Cardiac Arrhythmia

Cardiac arrhythmia is an abnormal heartbeat-related disorder that can be characterized by dizziness, palpitations, syncope, breathlessness, and *angina*. Arrhythmias can be classified on the basis of two factors that are their origin (atria or ventricle) and heart rate where heartbeat might be very slow (bradycardia), very fast (tachycardia), quite early (premature contraction), and quite irregular (fibrillation, Fenton et al. 2008). Voltage-gated ion channels are responsible for the electrical conductivity in the heart and it has been reported that defects in expression and function of ion channels are responsible for certain types of arrhythmias (Kirsch 1999). In most of the studies, KCNE1, KCNE2, KCNH2, KCNQ1, KCNJ2, and SCN5A genetic mutations were identified in the patients suffering from various kinds of cardiac arrhythmia (Schott et al. 1999; Tsuboi and Antzelevitch 2006; Moss et al. 2007; Tsai et al. 2008). These genetic mutations are responsible for altering the inward rectifying voltage-gated potassium channel and voltage-gated sodium channel, respectively, that leads to various phenotypic consequences of these mutations like Brugada syndrome (BrS, a form of idiopathic ventricular fibrillation), Lev-Lenegre syndrome (familial progressive conduction disease), Long QT syndrome (LQTS), Short QT syndrome (SQTS), and Familial atrial fibrillation (AF) (Campuzano et al. 2010). There are three mechanisms that have been proposed by different research groups for explaining the pathogenesis of cardiac arrhythmias (Gaztanaga et al. 2012) that are (i) Automaticity, where enhanced or suppressed firing of impulse takes place by cardiac muscle cells (Weller and Noone 1989), (ii) triggered activity, which involves impulse initiation due to the membrane potential oscillations occurring just after an action potential that results in abnormal transmission of electrical impulse in the heart cell thereby causing aberrant cardiac rhythm. This mechanism has been widely accepted

Table 4 Chloride ion channel subtypes in association with various diseases

Channel name	Subtypes	Genes encoding subtypes	Tissue specificity	Sub cellular location	Subunit structure	Physiological role	Involvement in disease	References
Chloride (Cl_v) Channel	Cl_vC1	CLCN1	Predominantly expressed in Skeletal Muscles	Multi-pass membrane protein	ClvC Type -1. Homodimer. Each monomer consist of 18 helical segments,	Membrane potential stabilization, Signal Transduction and Transepithelial Transport	Autosomal Recessive Myotonia Congenita	Koch et al. (1992), George et al. (1993), Lorenz et al. (1994)
	Cl_vC2	CLCN2	Skeletal Muscle	Multi-pass membrane protein	ClvC Type -2. Homodimer. Each monomer consist of 18 helical segments,	Homeostasis in various Cells	Susceptibility to Epilepsy, Idiopathic generalized, Myoclonic Jerks	Saint-Martin et al. (2009), Lamb et al. (1999), Jeworutzki et al. (2012)
	Cl_vC3	CLCN3	Coronary Vascular Smooth Muscle Cells and Expressed at a Low level in Aortic Endothelial Cells	Multi-pass membrane protein	ClvC Type -3, Homo- or heterodimer. Each monomer consist of 18 helical segments,	Neuronal cells to establish short-term Memory, Myoclonic Jerks	Juvenile absence Epilepsy Type 2, Idiopathic generalized Epilepsy	Cid et al. (1995), Lamb et al. (1999)
	Cl_vC6	CLCN6	Testis, Ovary, Small intestine, Brain, and Skeletal Muscle.	Endosome membrane	–	Antiporter and Contributes to the Acidification of the Lysosome Lumen	Lysosomal storage disease	Ota et al. (2004), Brandt and Jentsch (1995), Eggermont et al. (1997) Lamb et al. (1999), Ignoul et al. (2007), Poet et al. (2006)
	Cl_vC7	CLCN7	Brain, Testis, Muscle, and Kidney.	Lysosome membrane, Multi-pass membrane protein	ClvC Type -7. Heteromers of α-(CLCN7) and β-(OSTM1)subunits.	Antiporter and Contributes to the Acidification of the Lysosome Lumen	Infantile Malignant, Osteopetrosis Type 2, Albers-Schonberg, Disease or Marble Disease	Schroeder et al. (2007), Graves et al. (2008), Leisle et al. (2011) Kornak et al. (2001)
	$Cl_{Ca}1$	CLCA1	Small Intestine, Colon, Goblet Cells Testis, and Kidney	Localized to Microvilli, Basal Crypt Epithelia, Peripheral membrane protein, Extracellular side	–	Goblet cell, Metaplasia, Mucus Hyper secretion, Cystic Fibrosis, and AHR	Biomarker in Chronic Asthma., Chronic Obstructive Pulmonary Disease	Gruber et al. (1998), Bustin et al. (2001), Hoshino et al. (2002), Toda et al. (2002), Lee et al. (2005), Gibson et al. (2005)
	$Cl_{Ca}2$	CLCA2	Epithelium including Cornea, Esophagus, Larynx,	Single-pass type I membrane protein. Basal cell membrane, Single-pass type I membrane protein	–	May act as a Tumor suppressor in Breast and Colorectal Cancer, Cell Adhesion	Leukemia, Breast Tumor Suppressor Gene	Gruber et al. (1999), Bustin et al. (2001), Abdel-Ghany et al. (2001), Connon et al. (2005), Connon et al. (2006)

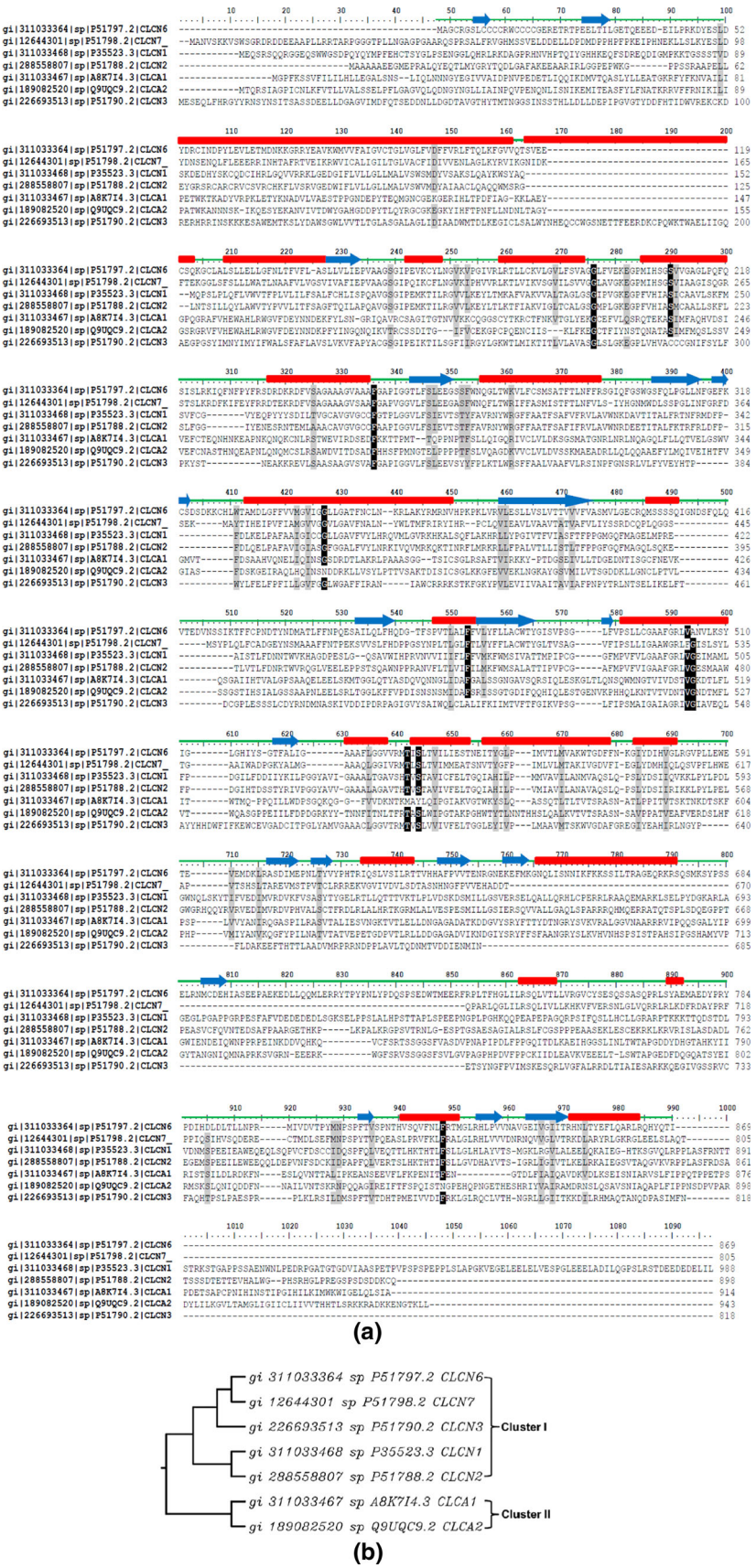
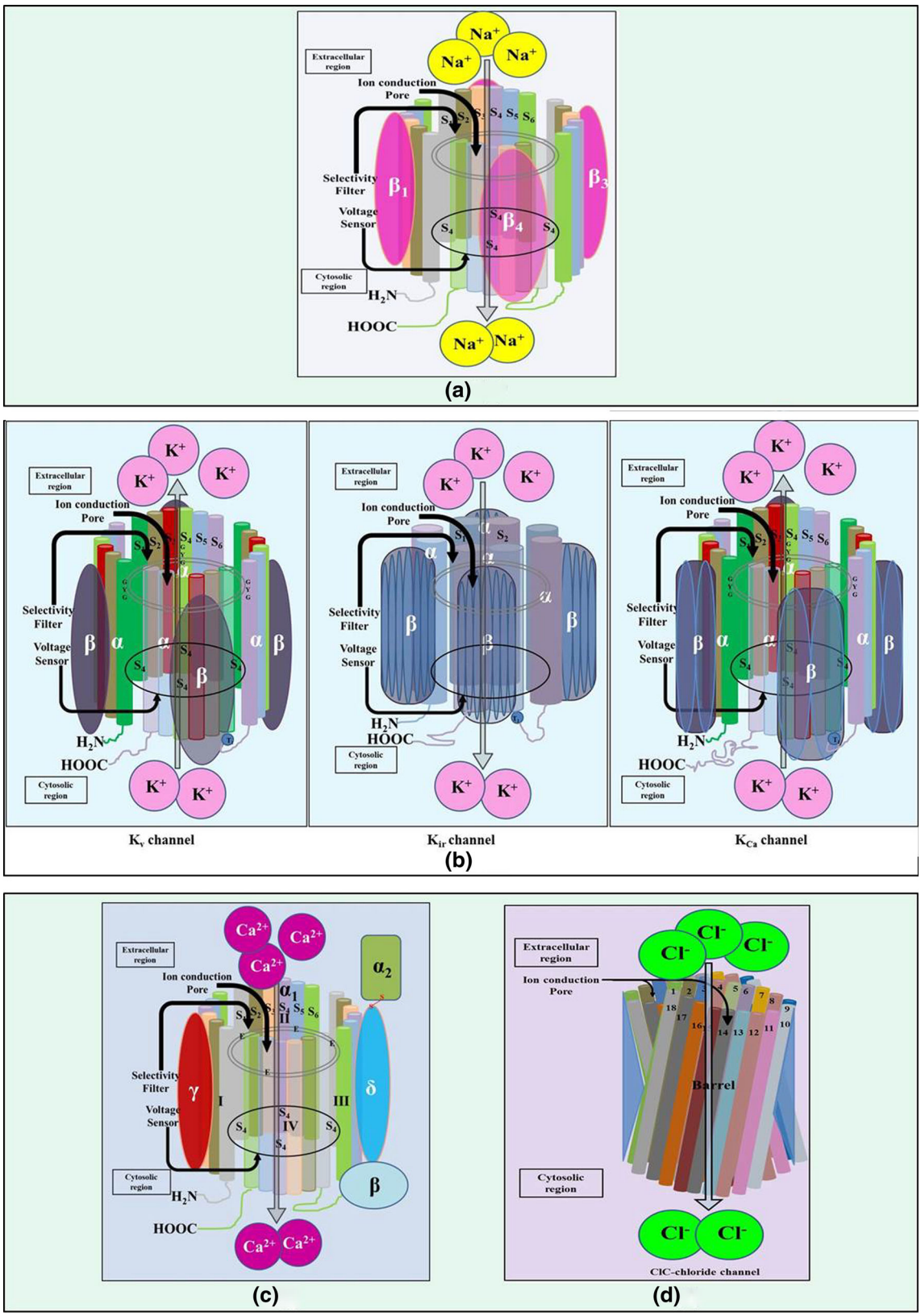


Fig. 4 **a** Multiple sequence alignment of chloride channel subtypes: Highly conserved residues are highlighted in *black,* whereas less conserved residues are highlighted in *light gray* color. Moreover, secondary structure elements of CLCN6 (predicted by YASPIN) are shown on the top of amino acid sequences that are loop residues (*green line*), α-helices (*red rectangle*), and β-strands (*blue arrow*). **b** Phylogenetic tree obtained by UPGMA method using clustalW: There are two major clusters having three pair of subtypes that are closely related, CLCN6–CLCN7, CLCN1–CLCN2, and CLCA1–CLCA2 (Color figure online)


Extracellular region
Ion conduction Pore
Selectivity Filter
Voltage Sensor
Cytosolic region
Na+
K+
Ca2+
Cl-
(a)
Kv channel
Kir channel
KCa channel
(b)
(c)
(d)
ClC-chloride channel

◀**Fig. 5** **a** Sodium channel structure: α-subunit of voltage-gated sodium channel comprised tetradomain, where each domain consists of internally repeated transmembrane helical segments (S1–S6) that is associated with four auxiliary β-subunits. **b** Potassium channel structure: α-subunit comprised transmembrane helical segments that is arranged in a tetramer manner and associated with auxiliary β-subunit. **c** Calcium channel structure: In a voltage-gated calcium channel, α1-subunit arranges itself in a tetradomain manner, where each domain consists of six helical transmembrane segments that is associated with other auxiliary subunits α2-δ (disulfide linkage), β, and γ. **d** Chloride channel structure: Voltage-gated chloride channel has double-barrel anti-parallel structure, where each barrel comprised 18 helical transmembrane segments (Color figure online)

to be related with the ion channel mutations (Charpentier et al. 1991), and (iii) Re-entry, it takes place when isolated fibers have not been activated during initial wave of depolarization but get excited before dying of previous impulse which in turn can re-excite those areas which have already recovered from initial depolarization (Zipes 2003). Beta blockers can relieve the symptoms to some extent depending on the severity of arrhythmia.

Calcium Ion Channelopathies with Molecular Mechanism

Spino-Cerebellar Ataxia Type-6 (SCA6)

There are more than 25 types of spino-cerebellar ataxias that are known to affect cerebellum, brainstem, and other parts of central nervous system but among them SCA6 is one of the most common occurring that affects only cerebellum. SCA6 is an autosomal dominant progressively degenerative pure cerebellar ataxia that is characterized by poor coordination of hands, speech, eye movements, and progressive loss of physical control (Paulson 2009). CACNA1A genetic mutation has been reported (Rajakulendran et al. 2010) where expansion of CAG repeats was found at the 3′ region that generates polyglutamine tract thereby producing abnormally extended α_1-subunit of calcium channel (Ishiguro et al. 2010). These polyglutamine residues have been responsible for abnormal aggregation of calcium channel protein thereby affecting calcium ion transport which imparts toxicity to the neurons, for instance, altered release of neurotransmitters in the brain eventually leads to the neuronal death (Purkinje cells, Kordasiewicz and Gomez 2007). However, very limited clinical trials have been done for disease prevention but a recent study showed the beneficial effect of lithium in treating SCA1 (Watase et al. 2007). Apart from that, acetazolamine can be used to eliminate episodes of ataxia, and RNA antisense approach can also be tried to decrease the expression of mutant gene product (Xia et al. 2004).

Hypokalemic Periodic Paralysis (HypoPP)

Hypokalemic periodic paralysis is an autosomal dominant paralytic disorder that can be characterized by recurrent attacks of extreme muscle weakness associated with low potassium levels in serum. In general, the attacks last for several hours but sometimes it lasts for several days that can be precipitated by a variety of factors, for instance, sodium-rich food, carbohydrate load, cold temperature, infection, stress, anesthesia, and rest after exercise (Sternberg et al. 2002). Major impact (up to 60 %) in the pathogenesis of Hypo PP is contributed by CACNA1S genetic mutations that can be followed by mutations in SCN4A and KCNE3 gene (Jurkat-Rott et al. 1994; Abbott et al. 2001; Sternberg et al. 2001; Matthews et al. 2009). Most of the underlying mutations in sodium channel were reported to nullify the outermost positively charged arginine or lysine residues of a voltage sensor, for instance, multiple mutations in $Na_v1.4$ channel were present in the voltage sensor region (S4) of domain I, II, and III (Jurkat-Rott et al. 2000).The homologous location of S4 missense mutations in $Ca_v1.1$ channel associated with HypoPP has led to the conclusion that abnormal gating pore current is the common underlying mechanism of mutated sodium and calcium channel for the progression of HypoPP (Wu et al. 2012). However, the known mutations affect the voltage sensing capability of these channels which are responsible for the deregulated flow of Ca^{2+} and Na^{+} ions into the muscles that cause reduced contractibility of muscles and ultimately muscle weakness (Sokolov et al. 2007). However, it is quite difficult to treat HypoPP but we can prevent the attacks by regulating sodium and potassium intake. Moreover, acetazolamide has been found to be very effective in preventing paralytic attacks among 50 % of the cases (Matthews et al. 2011).

Episodic Ataxia (EA)

Episodic ataxia is a group of related autosomal dominant disorders that have been characterized by episodes of impaired, uncoordinated bodily movements that can eventually cause muscle stiffness and cramps (Jen et al. 2007). These symptoms generally begin in adolescence and period of attacks usually last from hours to days depending on its severity. EA has been classified into seven types i.e., EA-1 to EA-7 based on their various characteristics which include sign, symptoms, attacking period, and onset age, moreover, out of these seven types only episodic ataxia type 2 and 5 are known to be associated with calcium channel mutations. It has been reported that KCNA1, CACNA1A, CACNB4, and SLC1A3 genetic mutations are responsible for the occurrence of episodic ataxia type 1, 2, 5, and 6, respectively, while genetic cause for EA-3,4, and

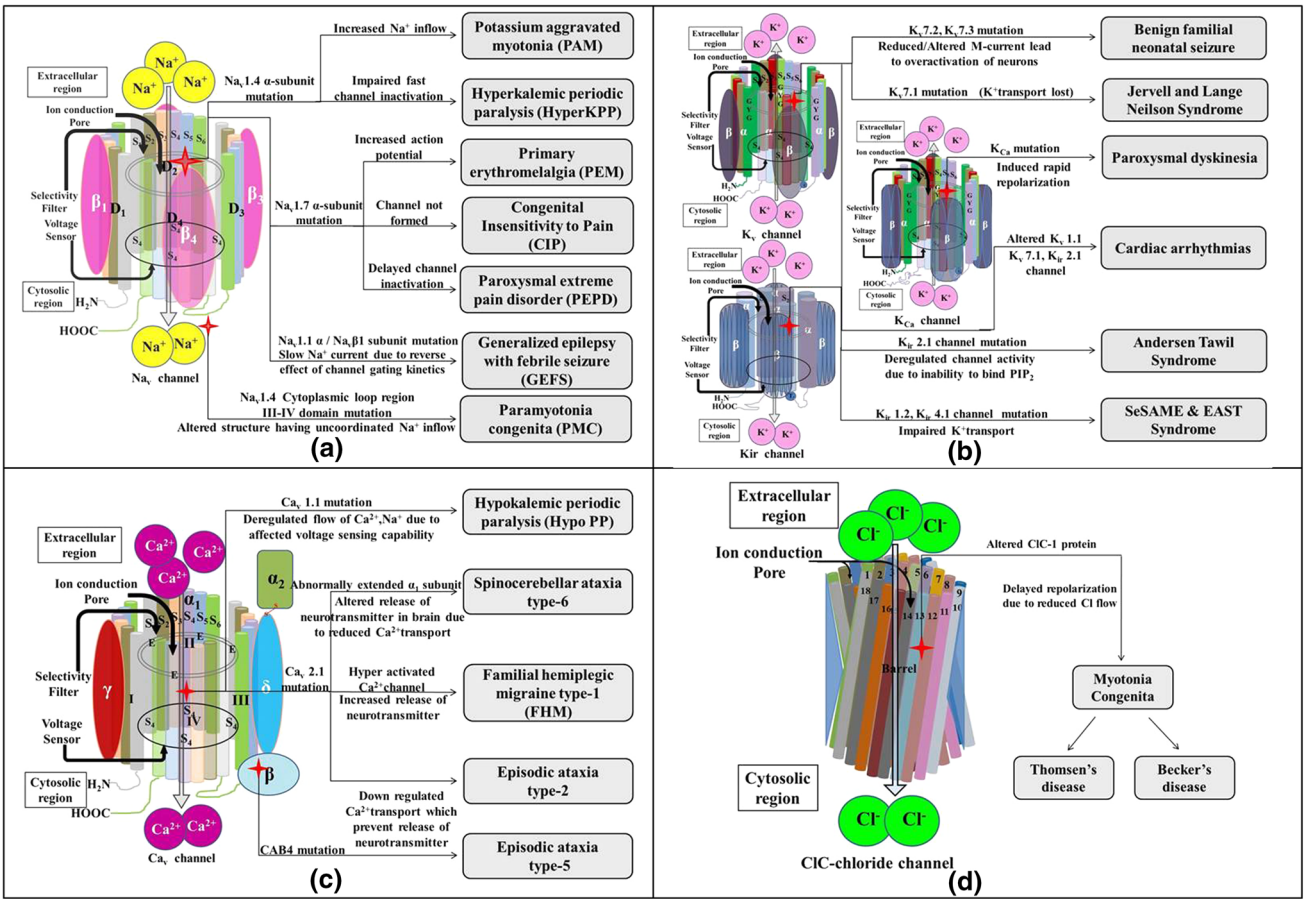


Fig. 6 **a** Sodium ion channelopathies: Mutated $Na_v1.4$ alpha subunit has lead to Potassium-aggravated myotonia (PAM) and Hyperkalemic periodic paralysis, while mutations in $Na_v1.7$ alpha subunit have caused Primary erythromelalgia (PEM), congenital insensitivity to pain (CIP), and Paroxysmal extreme pain disorder (PEPD). Moreover, $Na_v1.1$ alpha and Na_v beta subunit mutations known to cause Generalized epilepsy with febrile seizure, whereas $Na_v1.4$ cytoplasmic loop mutations between domain III and IV have caused Paramyotonia congenita (PMC). **b** Potassium ion channelopathies: Mutated $K_v7.2$ and 7.3 channels resulted in benign familial neonatal seizure, and mutated K_v 7.1 channel leads to Jervell and Lange Nielsen syndrome. Moreover, K_{ca} channel mutation is responsible for Paroxysmal dyskinesia and altered K_v 1.1, K_v 7.1 and K_{ir} 2.1 channel cause Cardiac arrhythmias. Apart from this K_{ir} 2.1 channel mutation leads to Andersen tawil syndrome, while K_{ir} 1.2 and K_{ir} 4.1 channel mutations lead to SeSAME and EAST syndrome. **c** Calcium ion channelopathies: Mutated $Ca_v1.1$ channel is known to cause Hypokalemic periodic paralysis (Hypo PP) and $Ca_v2.1$ channel mutations lead to Spino-cerebellar ataxia type-6, Familial hemiplegic migraine type-1 (FHM-1), and episodic ataxia type-2, while Calcium channel beta subunit CAB4 mutations caused Episodic ataxia type-5. **d** Chloride ion channelopathies: Mutated CLC-1 channel causes Myotonia congenita that can be categorized into Thomsen's and Becker's disease based on symptoms (Color figure online)

7 are still unknown(Adelman et al. 1995; Escayg et al. 2000; Imbrici et al. 2005; Jen et al. 2005). The underlying CACNA1A and CACNB4 genetic mutations have been responsible for down-regulating the Ca^{2+} transport that prevents the release of neurotransmitters into the brain thereby disrupting the signals (Wan et al. 2005). Similarly, decreased transport of K^+ ions due to KCNA1 genetic mutations adds over excitability to the neurons (Maylie et al. 2002), while SLC1A3 genetic mutant glutamate transporter loses its ability to remove glutamate from synaptic region which further provides excitation to the neurons. Thus, altered channels disrupt the normal signaling that triggers episodes of ataxia. The frequency and severity of attacks can be relieved by using anti-epileptic drugs, and carbonic anhydrase inhibitors, for instance, carbamazepine, valproic acid, and acetazolamide, are found to be effective in episodic ataxia type-1 (Eunson et al. 2000; Klein et al. 2004).

Familial Hemiplegic Migraine (FHM)

Familial hemiplegic migraine is an autosomal dominant familial migraine that usually occurs in a particular part of the head preceded by neurological symptoms like double vision, blind spot, or flashing lights (Jen 2001). FHM has been classified into three forms on the basis of clinical or descriptive criteria and can be triggered by emotional stress, certain foods, and minor head injury. It has been

Table 5 Channelopathies associated with various ion channels and their physiology

Tissue affected	Ion channels	Gene	Channel subunit	Disease caused	Symptoms	Mechanism	References
Skeletal muscle	Cl Channel	ClCN1	ClC-1 (chloride channel protein 1)	Myotonia congenita	Muscle stiffness, inability to relax after contraction	Mutated channel either become nonfunctional or open at a more depolarized potential thus losses chloride conductance thereby increasing the time taken for repolarization due to which muscle hyper excitability takes place thus causing myotonia	Lee et al. (2013), Duran et al. (2010), Lossin and George (2008), Koch et al. (1992)
				Thomsen's disease	Proximal muscle weakness, myalgia, and muscular hypertrophy	Mutated channels results in moderate decrease in chloride conduction and following the above-mentioned molecular mechanism it causes mild symptoms	Wu et al. (2002), Kubisch et al. (1998), Koch et al. (1992)
				Becker's disease	Muscle hypertrophy and distal muscle weakness	Mutated channel proteins have not get expressed to the optimum level thereby causing great reduction in chloride conduction and thus causing myotonia by following the above-mentioned mechanism	Graves and Hanna (2005), Wu et al. (2002), (Kubisch et al. (1998)
	Na_v Channel	SCN4A	$Na_v1.4$ (Sodium channel protein type 4 subunit alpha)	Potassium-aggravated myotonia (PAM)	Sustained muscle tension and inability to relax muscle	The altered channels up-regulate the sodium ion influx into the skeletal muscles thereby triggering prolonged muscle contractions due to one or more of the following reasons, for instance, reduced fast channel inactivation, enhanced recovery rate from fast inactivation, slowed deactivation or hyperpolarizing shift in steady-state activation	Orrell et al. (1998) (Cummins and Bendahhou (2009), (Vicart et al. 2005)
				Para-myotonia congenita (PMC)	Cold sensitive myotonia and episodic muscular weakness	Mutated sodium channels exhibit slowed inactivation and faster recovery from inactivation thus causing hyper excitability of muscles (myotonia) and sometimes inexcitability that causes episodic weakness in muscles	Heine et al. (1993), McClatchey et al. (1992), Ptacek et al. (1992), Tamaoka (2003), Vicart et al. 2005)
				Hyper-kalemic periodic paralysis (hyperKPP)	Extreme muscle weakness and increased level of potassium during attacks	Due to altered anchoring site of fast inactivation particle in mutated channel, persistent sodium current takes place that causes depolarization of the cell thereby inactivating other normal sodium channels due to the absence of action potential	(Bendahhou et al. 2002) (Ptacek et al. 1991) (Rojas et al. 1991)
	Na_v & Ca_v Channel	SCN4A and CACNA1S	$Na_V1.4$ (Sodium channel protein type 4 subunit alpha) CaV1.1 (Voltage-dependent L-type calcium channel subunit alpha-1S)	Hypo-kalemic periodic paralysis (hypoKPP)	Extreme muscle weakness associated with low potassium level in serum	Mutated sodium and calcium channels are responsible for abnormal gating pore currents i.e., shift in the resting membrane potential to a more depolarized second stable state (paradoxical depolarization). Moreover, due to their affected voltage sensing capability deregulated flow of Ca^{2+} and Na^{+} ions into the muscles take place thereby causing reduced contractibility of muscles and ultimately muscle weakness	(Sokolov et al. 2010) (Jurkat-Rott et al. 2009) (Sokolov et al. 2007) (Bulman et al. 1999) (Jurkat-Rott et al. 1994) (Ptacek et al. 1994)

Table 5 continued

Tissue affected	Ion channels	Gene	Channel subunit	Disease caused	Symptoms	Mechanism	References
Peripheral Nerve	Na_v Channel	SCN9A	$Na_v1.7$ (Sodium channel protein type 9 subunit alpha)	Primary erythro-melalgia	Burning pain, flushing, and swelling of the feet, hands, and sometimes other areas	Mutated sodium channels exhibit hyperpolarizing shift toward activation and slowed inactivation kinetics that makes opening of channel easier and prolonged. Thus increased inflow of sodium ions enhances transmission of pain signals, leading to the signs and symptoms of erythro-melalgia	(Dib-Hajj et al. 2005) (Waxman et al. 2005a & b) (Estacion et al. 2011)
				Paroxysmal extreme pain disorder (PEPD)	Burning pain and flushing in the submandibular, ocular, and rectal areas	Mutated sodium channels that expressed in nociceptive dorsal root ganglion and sympathetic ganglion neurons cannot be able to close as quickly as usual leading to prolonged transmission of pain signals. Moreover, we can say that gain of function mutations result in increased action potential duration and therefore more synaptic transmission thus causing heightened pain perception	(Fertleman et al. 2007) (Lampert et al. 2010)
				Congenital insensitivity to pain (CIP)	Complete loss of pain sensation	Mutated channel exhibit complete functional loss that leads to an inability to form action potentials and therefore loss of pain sensation	(Cox et al. 2006) (Goldberg et al. 2007)
Central Nervous System	K_v, Ca_v, Channel, and Glutamate transporter	KCNA1, CACNA1A CACNB4 SLC1A3	$K_v1.1$ (Potassium channel subfamily A member 1) Cav2.1 (Calcium channel Subunit alpha), Sodium-dependent glutamate/ aspartate transporter1	Episodic ataxias	Problems with movements, poor coordination and balance	These genes alter the transport of ions and glutamate into the brain that causes certain neurons to become overexcited and disrupts normal communication between these cells. Moreover, it also results in decreased current often due to protein instability. Furthermore, potassium channels are vital in down stroke of action potential and its mutation cause prolonged action potential and altered excitability of different neuronal population	(Jen et al. 2007) (Wan et al. 2005) (Browne et al. 1994) (Zerr et al. 1998)
	K_v Channel	KCNMA1	K_{ca} (Potassium large conductance calcium-activated channel, subfamily M, alpha member 1)	Paroxysmal dyskinesias	Sudden, unpredictable disabling attacks of involuntary movements	Mutated channels formed due to altered KCNMA1 gene promotes excitability of neurons by inducing rapid repolarization of action potential that allows neurons to conduct at a faster rate thereby causing recurrent attacks	(Lee and Cui 2009) (Du et al. 2005)
		KCNQ2 KCNQ3	$K_v7.2$ & $K_v7.3$ (Potassium voltage-gated channel subfamily KQT member 2 & 3)	Benign familial neonatal seizures (BFNS)	Recurrent seizures in newborn babies, muscle rigidity, convulsions, and loss of consciousness	Channels coded by KCNQ2 and KCNQ3 genes transmit M-currents that ensure normal shutting of active neuron, while mutated genes result in reduced or altered M-current which cause excessive excitability of neurons that results in the development of seizures in brain	(Biervert et al,1998) (Singh et al. 1998) (Charlier et al. 1998) (Castaldo et al. 2002)
	Na_v Channel	SCN1A SCN1B	$Na_V1.1$ (Sodium channel type 1 subunit alpha)	Generalized epilepsy with febrile seizures (GEFS)	It is characterized by a long term recurring seizures.	However, it arises from many causes that include metabolic brain disorders, abnormalities of cortical development, brain trauma or structural lesions of the brain (brain tumors), while mutated channel is also one of the prominent factor that causes over excitation of neurons and ultimately epilepsy with seizures	(Catterall et al. 2010) (Tan et al. 2012) (Xu et al. 2012)

Table 5 continued

Tissue affected	Ion channels	Gene	Channel subunit	Disease caused	Symptoms	Mechanism	References
	Ca_v & Na_v Channels	CACNA1A ATP1A2 SCN1A	Ca_v2.1 (Calcium channel Subunit alpha) ATP1A2 (ATPase subunit alpha-2) Na_V1.1 (Sodium channel type 1 subunit alpha)	Familial hemiplegic migraine (FHM)	Intense, throbbing pain in one area of the head, often accompanied by nausea, vomiting, and extreme sensitivity to light and sound.	Altered channels formed by these mutated genes disrupt the normal release and re-uptake of certain neurotransmitters in brain that result in the alteration of signaling between neurons thereby causing hemiplegic migraine. Moreover, these mutated genes cause three different types of Familial hemiplegic migraine that are CACNA1A mutations cause FHM1, ATP1A2 mutations cause FHM2 and SCN1A mutations cause FHM3	(Pietrobon 2010), (Cestele et al. 2008) (Gritz and Radcliffe 2013) (Pelzer et al. 2013) (Ducros et al. 2001)
	Ca_v Channel	CACNA1A	Ca_v2.1 (Calcium channel Subunit alpha)	Spino-cerebellar ataxia type-6 (SCA6)	Progressive pure cerebellar ataxia, poor coordination of hands, speech, and eye movements, Impaired speech, Patient progressively lose physical control	Expansion of CAG repeats were found at the 3′ region that generates polyglutamine tract thereby producing abnormally extended α1-subunit of calcium channel that abnormally aggregate calcium channel protein thereby affecting neurotransmitter's release in the brain eventually causing death of neurons	(Graves and Hanna, 2005) (Denier et al. 1999) (Rajakulendran et al. 2010) (Zhuchenko et al. 1997)
Heart	K_v and Na_v Channels	KCNE1 KCNE2 KCNH2 KCNQ1 KCNJ2 SCN5A	K_v (Voltage-gated potassium channel subfamily E member 1 &2, subfamily H member 2, subfamily Q member 1, subfamily J member 2), Na_v (Sodium channel protein type 5 subunit alpha)	Cardiac arrhythmia	Dizziness, palpitations, syncope, deficits in executive function and abstract reasoning, even cause death	Irregularities in heart rhythm via mutated channel is reported due to triggered activity, which involves impulse initiation due to the membrane potential oscillations occurring just after an action potential that results in abnormal transmission of electrical impulse in the heart cell thereby causing aberrant cardiac rhythm	(Schimpf et al. 2013) (Campuzano et al. 2010)
	Inward Rectifier Potassium (Kir) Channel	KCNJ2	Kir2.1 (Inwardly rectifying potassium channel subfamily J member 2)	Andersen-Tawil syndrome (ATS)	Muscle weakness (periodic paralysis), changes in heart rhythm (arrhythmia), and developmental abnormalities like widespread eyes, cleft palate, and syndactyly of the toes.	Mutations in the KCNJ2 gene alter the usual structure and function of potassium channels that prevent the channels from being inserted correctly into the cell membrane. Moreover, it also prevent binding of PIP2 that disrupt the flow of potassium ions in skeletal and cardiac muscles thus leading to periodic paralysis and irregular heart rhythm	(Plaster et al. 2001) (Tristani-Firouzi et al. 2010) (Donaldson et al. 2004) (Tristani-Firouzi et al. 2002)
		KCNJ10	Kir4.1 (ATP dependent inwardly rectifying potassium channel Kir4.1)	SeSAME syndrome and EAST syndrome	Characterized by generalized seizures with onset in infancy, delayed psychomotor development, ataxia, sensorineural hearing loss, hypokalemia, metabolic alkalosis, and hypomagnesaemia.	Mutated inward rectifier potassium channel disrupts the potassium buffering action of glial cells in the brain and disturbs the homeostasis of potassium ions in various organs like inner ear, retina, and kidney thus exhibiting the symptoms of SeSAME	Bockenhauer et al. 2009) (Scholl et al. 2009)
	K_v Channel	KCNE1 & KCNQ1	K_v (Potassium voltage-gated channel subfamily E member 1,subfamily Q member1)	Jervell and Lange-Nielson syndrome (J-LN)	Cardiac arrhythmia concomitant with deafness	Mutated genes affect potassium channel structure and function thereby preventing the assembly of normal channels. These changes disrupt the flow of potassium ions in the inner ear and in cardiac muscle, leading to hearing loss and an irregular heart rhythm	Schulze-Bahr et al. (1997), Schwartz et al. (2006,) (Wang et al. 2002)

reported that mutations in CACNA1A, ATP1A2, and SCN1A genes are the prevalent causes for FHM type-1, FHM type-2, and FHM type-3, respectively (Ophoff et al. 1996; De Fusco et al. 2003; Dichgans et al. 2005a). Mutated CNCNA1A gene that encodes $Ca_v2.1$ channel gets activated more easily than usual thereby leading to more influx of Ca^{2+} ions which in turn promotes excessive release of neurotransmitters which impart strong signals for severe headache and lead to FHM type-1 (Dichgans et al. 2005b). While in case of FHM type-2, mutated ATP1A2 gene forms either altered or truncated Na^+/K^+ ATPase protein that prevents the flow of K^+ ions out of the neurons thereby causing sustained release of neurotransmitters at the neuronal junction and thus prolongs excitation of pain signals (De Fusco et al. 2003). Moreover, altered $Na_v1.1$ channel encoded by mutated SCN1A gene has also reported to exacerbate headache in a similar fashion as was in case of mutated calcium channel. Thus, resulted mutations in these genes cause FHM due to increased release of neurotransmitters in response to imbalanced ion flow (Pietrobon 2007). Treatment of hemiplegic migraine is quite challenging but apart from anecdotal, verapamil and acetazolamide have shown significant effect in treating FHM (Black 2006).

Chloride Ion Channelopathies with Molecular Mechanism

Myotonia Congenita

Myotonia congenita is a congenital myopathy that can be characterized by muscle stiffness and their inability to relax after contraction which affects the bodily movements. The myotonic attacks may last from seconds to minutes depending on the severity of disease that could range from slightly uncomfortable to complete disability. Cold, sudden pitched sound can trigger the attacks and can affect various body parts, for instance, hands, legs, shoulders, hips, face, feet, tongue, and eyelids (Colding-Jorgensen 2005). Myotonia congenita can be classified into two forms of congenital myopathy based on the inheritance pattern and severity of symptoms, for instance, Thomsen's diseases and Becker's disease have been inherited in an autosomal dominant and autosomal recessive pattern, respectively. It has been reported that mutations in the same ClCN1 gene have been responsible for the occurrence of both Thomsen's and Becker's disease (Zhang et al. 1996; Sun et al. 2001; Pusch 2002). Mutated ClCN1 gene disrupts ClC-1 chloride channel thereby interrupting the normal process of repolarization. Electrophysiological studies in a recessive CLCN1 patient suggested that prolonged repolarization takes place due to reduced inflow of chloride ions into the skeletal muscles thereby causing prolonged muscle contraction in the myotonial patients (Lucchiari et al. 2013). No perfect cure has been reported till now but patients usually learn to adopt preventive measures and can use medicines, for instance, mexiletine, quinine, procanimide, tegretol, and phenytoin to relieve the symptoms (Fazio 1988; Trip et al. 2006).

Thomsen's Disease

It is an autosomal dominant muscle disorder characterized by muscle stiffness and relaxation inability after contraction (Sun et al. 2001). It was first identified by Thomsen in his own family and he himself was also suffering from the same thus named as Thomsen's disease. It exhibits the above-mentioned symptoms but with less severity than Becker's disease with carbamazepine as a potential drug used for relieving against Thomsen's disease (Lyons et al. 2010; Savitha et al. 2006).

Becker's Disease

It is a more common and severe form of myotonia congenita with autosomal recessive pattern of inheritance (Harper and Johnston 1972) that follow the above-mentioned molecular mechanism. Along with the later onset, most of the affected persons feel transient muscle weakness during muscle exertion or after rest and have been encountered by the muscular hypertrophy especially in the region of legs and buttocks, while symptoms can be relieved with the use of sodium channel blocker (Kuhn 1993).

The above-discussed diseases have been defined at either molecular or genetic levels (Fig. 6) that include mutations in the ion channel present in the tissues such as skeletal muscle, brain, and heart (Koopmann et al. 2009) that have been summarized in Table 5. However, disease phenotypes are directly related to the extent of functional deficit in ion channels.

Conclusions

Neurological channelopathies are responsible for a variety of disorders which are threatening to the patient's healthy life. They exhibit three common characteristics that are (i) paroxysmal (i.e., Episodes of impaired neurological function separated by periods of normality), (ii) Triggered by environmental factors, and (iii) tend to share common natural history. Channelopathies must have both a specific molecular lesion (mutation) and inter-current triggering

factor(s) to manifest symptoms. Targeting of these mutated channel protein with drugs became a modern therapeutic approach, and acetazolamide is one of the potential candidate which has been used for treating a variety of channelopathies with promising effects. Scientists have also observed that even synonymous mutations in non-coding regions may lead to dys-functioning of ion channels via altering the process of transcription, splicing, mRNA transport, and translation which is responsible for the occurrence of disease (Goymer 2007). These ion channels differ majorly in their structural and functional aspects. The most diverse type of ion channel is Potassium ion channel (Voltage gated, Inward rectifier, and Calcium mediated) ranging from K_v1–K_v12 gene family. The most complex type of ion channel is Calcium ion channel which consists of α_1-, α_2-δ-, β-, Υ-subunits, whereas least studied ion channel is Chloride ion channel. Apart from their diversity, it has been found that these channels possess highly conserved arginine residues which are responsible for providing voltage sensitivity to the channel, another interesting point is there conserved selectivity filter through diverse subtypes. Sodium channel remained most conserved during evolution in comparison to other channels while due to least study on chloride channel it is difficult to find conserved regions. Mutations in these channels are responsible for various diseases like sodium channelopathies range from muscular disorders to pain disorder (PAM, PEM, Hyper-KPP, CIP, PEPD, GEFS, and PMC), whereas potassium channelopathies range from movement, muscular to heart disorders (Cardiac arrhythmia, ATS, SeSAME & EAST, Paroxysmal dyskinesias, and BFNS). Moreover, calcium channelopathies ranges from muscular disorder to migraine (Hypo-PP, SCA6, FHM1, and EA-2, 5), and chloride channel is likely to cause muscular disorder (Myotonia congenita). Chloride channel is least prone to molecular lesions due to its double-barrel structure. Nowadays molecular lesions are identified with the help of disease loci positional cloning approach. There are still gaps between channelopathies and its cure due to limited knowledge about their mechanisms. Some areas still need to be unraveled for identification and classification of neurological disorders into channelopathies, because there might be possible correlation between ion channel and diseases like Alzheimer's disease, Amyotrophic lateral sclerosis with Calcium channel, Inward rectifier potassium and sodium channel, Huntington's disease with Sodium, Potassium and Chloride ion channel while Parkinson's disease with Calcium, Sodium, and Potassium channel.

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