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Genetic mutations of voltage-gated ion channels associated with channelopathies

By Kit Ying Valeriana Lau

AUTHOR BIO

Kit Ying Valeriana Lau is a junior at the International School of Beijing with passions in microbiology and genetics, especially enjoying lab and research opportunities. In the future, she wishes to further investigate genetic mutations, CRISPR-Cas9, stem cells, and the infectious functions of viruses.

ABSTRACT

This paper explores how mutants of each type of voltage-gated ion channel associated with cardiac channelopathies differ from wildtype genes.

1 in 2000 people is estimated to have Long QT Syndrome (LQTS), a form of cardiac channelopathy that may lead to sudden cardiac death (SCD). Cardiac channelopathies are often caused by mutants that alter voltage-gated ion channels. The main voltage-gated ion channels are sodium, potassium, and calcium-gated ion channels. Structurally, they are composed of proteins that construct ion-conducting pores through the cellular membrane and units influencing their gating and other cellular interactions. Specifically, mutants may cause the formation of abnormal proteins, thus causing deformations in ion channel structure and malfunctioning in electrochemical functions such as supporting normal cardiac activity. Normal cardiac activity is based on action potential phases, with sodium, potassium, and calcium ion influxes and effluxes contributing to this function. Each phase is associated with corresponding intervals and waves, which are evident on an electrocardiogram and reflect a specific normal duration per phase. Structural alterations in ion channels may lead to abnormal repolarization/depolarization durations, which cause various syndromes and symptoms such as SCD or LQTS. Focusing specifically on LQTS, the most prevalent types (LQT1, LQT2, LQT3) result from KCNQ1, KCNH2, and SCN5A mutations, respectively. Each LQTS is caused by a different mutation, different specific ion channels, and varying triggers and symptoms, such as adrenergic stimuli, auditory stimuli, and death during sleep, which target LQT1, 2, and 3, respectively. In conclusion, mutants cause structural deformities that differ from wildtype genes, which lead to cardiac activity abnormalities.

Keywords*:* *channelopathies, ion channels, long QT syndrome, LQTS, cardiac arrhythmia, mutation, voltage-gated, LQT1, LQT2, LQT3*

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INTRODUCTION

Channelopathies can be caused by genetic polymorphisms, altering the structure of ion channels (Badura et al., 2024). Primarily acquired through inheritance, mutations in ion channels can be either autosomal dominant or autosomal recessive, depending on the specific syndrome caused (Behere et al., 2015). Channelopathies are often detrimental, as ion channels are essential in the most fundamental parts of the human body, controlling electrical interactions in the cardiovascular, nervous, and muscular systems. Specifically, in the cardiovascular system, channelopathies can cause arrhythmia and even SCD. Approximately 54% of SCDs are suggested to be caused by channelopathies (Badura et al., 2024).

Ion channels are integral membrane proteins with pores that allow the passage of ions in response to cell excitability. There are two types: ligand-gated – opening in response to ligand signaling – and voltage-gated – opening in response to membrane potential changes (Bernard et al., 2008). Ion channels transport ions across the lipid bilayers of cellular membranes and can switch between open and closed gating states to control ion flows of Ca^{2+}, K^{+}, and Na^{+}, displaying high ion selectivity through the structural conformation of the pores in different ion channels (Roux et al., 2011). Genetic mutation can lead to malfunctioning proteins with abnormal gating, causing either gain-in-function mutations, where too many ions are conducted, or loss-in-function mutations, where too few ions are conducted (Kozlov, 2017). Eventually, these mutations lead to abnormal electrical activity, leading to cardiac arrhythmias (Badura et al., 2024).

A common disorder resulting from channelopathies is LQTS. LQTS is a type of cardiac arrhythmia in which there is a delay in myocardial repolarization, causing a prolonged QT interval, where the QT interval represents the time from the start of the Q wave to the end of the T wave, reflecting ventricular systole and is used to determine the arrhythmia or risk of sudden cardiac death. This increases the risk of seizures and sudden cardiac death, involving symptoms such as cardiac arrhythmia, syncope, and seizures. The voltage-gated ion channels causing LQTS are encoded by genes SCN5A, SCN4B, KCNQ1, KCNH2, and CACNA1C, causing types 3, 10, 1, 2, and 8 LQTS, respectively. Types of LQTS are usually distinguished by the mutation they harbor. Additionally, there are atypical LQTS disorders associated with QT interval prolongation, including Timothy syndrome, Jervell and Lange-Nielson syndrome, and Romano-Ward syndrome. These special LQTS types differ from normal, numbered types by genetic cause, symptoms, and severity; often, they affect other organs/systems than just the cardiovascular system. However, channelopathies can also be induced by drugs and toxins, such as drug-induced LQTS, in which exposure to certain drugs, both recreational and medical, can prolong the QT interval – the time from ventricular depolarization to complete repolarization (Roden, 2005).

VOLTAGE-GATED ION CHANNELS

Ion channels are present in the heart and pump Ca^{2+}, K^{+}, and Na^{+} ions into the heart during diastole and systole, transmitting electricity. They are integral membrane proteins that allow ions to flow through, as ions are charged and cannot diffuse through semi-permeable phospholipid bilayer

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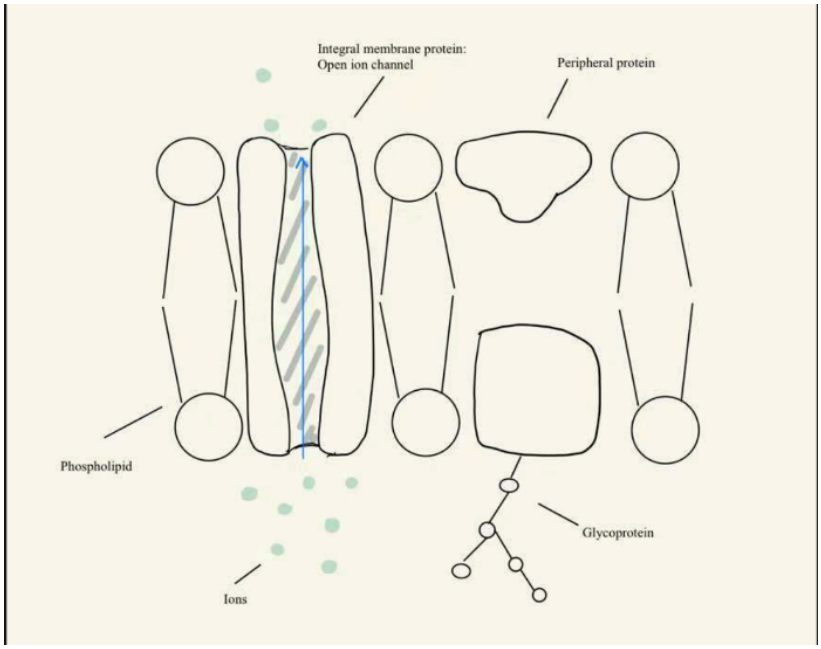
membranes (Fig. 3). When ion channels are in an open state, ions undergo passive transport (facilitated diffusion), flowing from high concentration to low concentration (Terlau et al., 1998).

Figure 1

Model of a part of the cardiac cell membrane with an open ion channel and ions in facilitated transport



When signaled, ion channels open via their gating domains, and ions pass through the pore, going along the electrochemical gradient into the cardiac cell, passing through the membrane (Fig. 1). Specifically, the electrochemical gradient is the primary driving force of ion influx and efflux. It is a combination of the concentration gradient and electrical gradient. The electrochemical gradient causes the influx of ions due to a low concentration within the cell membrane and a high concentration in the exterior environment; there is a tendency for ions to move toward the low-concentration environment. Additionally, due to the negatively-charged environment within cells, cations are attracted and are transported inwards. However, during repolarization, there is a low concentration in the exterior environment and electrostatic attraction is reduced within the cell, since the anions are within cells, thus causing the efflux of cations (Grant, 2009). The influx of ions, sodium influx followed by calcium, into cardiac cells in the systole or rapid depolarization phase causes membranes to depolarize and muscle cell contraction, generating electricity for the heart. During diastole, or resting potential phase, potassium efflux and consecutive closing of sodium and calcium channels occur. This causes membrane repolarization.

NORMAL CARDIAC ACTIVITY

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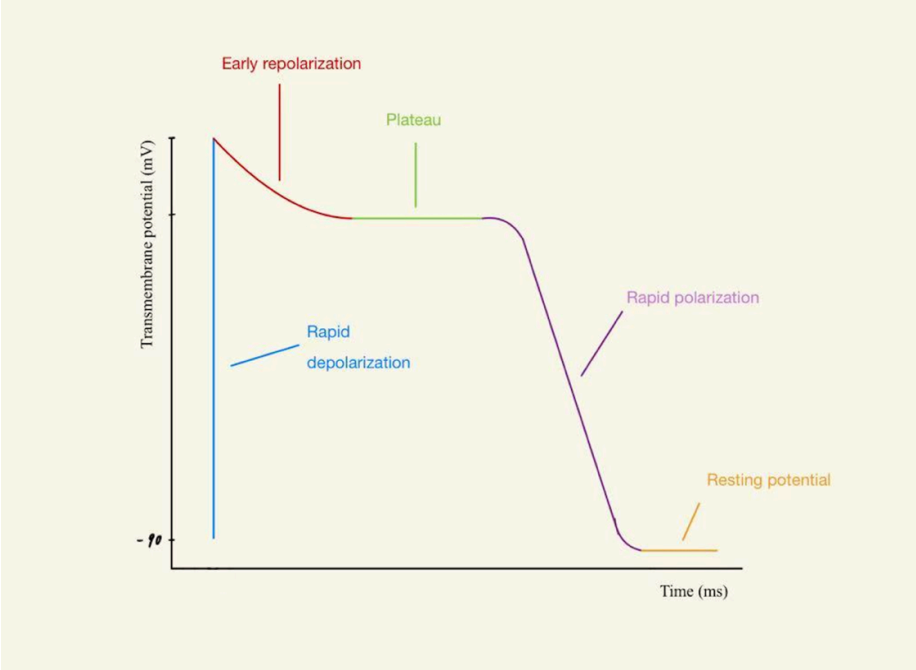
Cardiac activity is maintained through the phases of diastole and systole, controlled by the effluxes and influxes of different ions. A normal cardiovascular system has five cardiac phases: rapid depolarization, early repolarization, plateau, rapid polarization, and resting potential. These phases control the systole and diastole phases of the heart, driven by ion influxes and effluxes. The distinct phases are evident in cardiac action potential diagrams, with different transmembrane potentials controlled by different voltage-gated ion channels (Fig. 2).

Figure 2
Cardiac action potential with phases and transmembrane potential



Note. Adapted from "Cardiac transmembrane ion channels and action potentials: Cellular Physiology and arrhythmogenic behavior, by A. Varró et al., 2021, Physiological Reviews, 101(3), 1083–1176 (https://doi.org/10.1152/physrev.00024.2019).

Systole in the heart is regulated by action potential. Systole starts from sinus nodes, spreading to both atria in the rapid depolarization phase, causing their contraction, while the atrioventricular nodes signal a delay in ventricles for atrium contraction in the early repolarization phase. The AV nodes then stimulate the bundle of HIS and, correspondingly, Purkinje fibers for ventricle contraction in the plateau phase. Ventricular relaxation occurs in the rapid polarization phase. Diastole occurs during the resting potential phase, and membranes are repolarized (Varró et al., 2021). If these phases are delayed or altered, cardiac arrhythmias or even SCD may occur.

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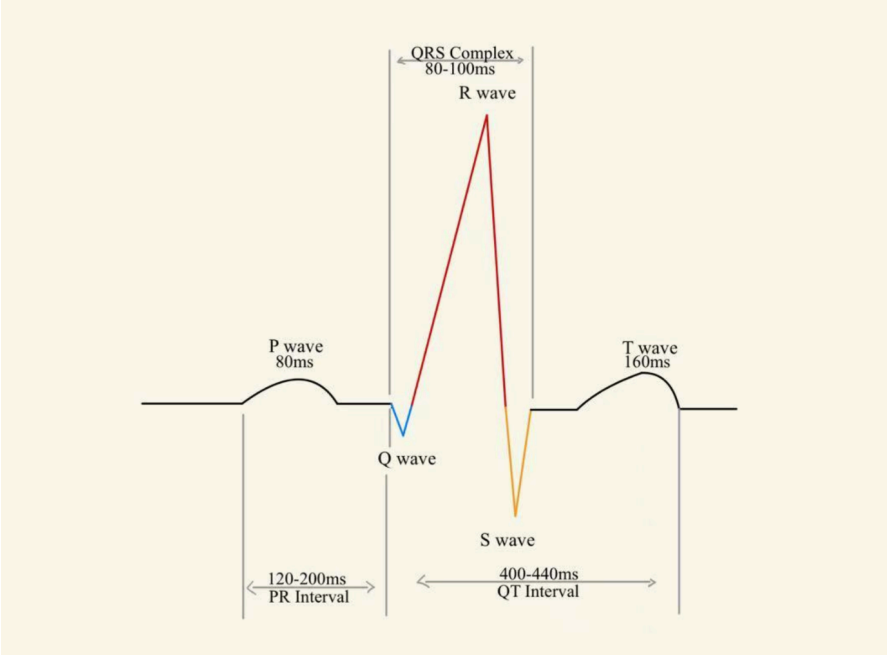
During each cardiac phase, different influxes and effluxes of ions, including Ca^{2+}, K^+, and Na^+, through specific voltage-gated ion channels. In the rapid depolarization phase, sodium channels open, and rapid Na^+ ion influx occurs to induce atrial contraction, increasing the transmembrane potential. Potassium channels open, and sodium channels close in early repolarization. The K^+ efflux causes the transmembrane potential to decrease to around 0 mV. During the plateau phase, K^+ ion efflux is continued, and Ca^{2+} ion influx is created by opening calcium ion channels. K^+ efflux and Ca^{2+} influx balance each other at this stage (Morad et al., 1982). During rapid polarization, K^+ efflux continues; however, the calcium channels close. The transmembrane potential returns to –90 mV through K^+ efflux. The membrane stabilizes at –90 mV during resting potential due to K^+ efflux (Grant, 2009).

Figure 3

An electrocardiogram modeling normal time ranges of each interval



Note. Adapted from "Overview of SCN10A and its role in pain perception," by L. Rosenthal & E. A. Gracia, 2024, Medscape (https://emedicine.medscape.com/article/2172196-overview?form=fpf).

All electrical waves originate from sinoatrial nodes, which initiate sinus impulses. P waves are formed from such sinus impulses, representing both left and right atrial depolarization, and must precede the QRS complex. The PR interval is where electrical activity is transmitted from the atria to the ventricles, passing atrioventricular nodes. At the atrioventricular nodes, ventricular excitation is conducted as the electrical impulse passes to the bundle of His and Purkinje fibers. During the QRS complex, early ventricular depolarization and atrial repolarization occur, forming the T wave, where

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ventricular repolarization occurs. The QT interval represents the duration of ventricle depolarization to repolarization (Rosenthal et al., 2024).

SODIUM-GATED ION CHANNELS

Sodium-gated ion channels are a type of voltage-gated ion channel with ion selectivity, selectively permeable to only conducting Na^+. Sodium-gated ion channels consist of alpha and beta subunits, in which one alpha subunit forms the ion-conducting pore, and two auxiliary beta subunits influence gating, interaction with the extracellular matrix, cellular aggregation, and cell migration. The ion channel also has six transmembrane domains, with S1-S4 primarily participating in voltage-sensing and pore formation and S5-S6 participating in ion conduction and gating (Isom, 2001). Alpha subunits include NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9; encoded, respectively, by genes: SCN1A, SCN2A, SCN3A, SCN4A, SCN5A, SCN8A, SCN9A, SCN10A, and SCN11A. Beta subunits include β1, β2, β3, β4, with corresponding genes: SCN1B, SCN2B, SCN3B, SCN4B (Goldin, 2009).

Table 1
Sodium-gated ion channel genes and disorders associated with mutations

Gene	Associated Disorders	Citations
SCN1A	Dravet syndrome (genetic epileptic encephalopathy giving rise to seizures), febrile seizures plus (GEFS+), congenital arthrogryposis, movement disorder, intellectual disability, familial hemiplegic migraine.	Brunklaus et al., 2022
SCN2A	Benign familial neonatal-infantile epilepsy, autism, intellectual disability, movement disorders, episodic ataxia, developmental and epileptic encephalopathy.	Wolff et al., 2019
SCN3A	Developmental and epileptic encephalopathy, cortical development malformations, infantile hypotonia.	Helbig et al., 2021
SCN4A	Hyperkalemic periodic paralysis, sodium channel myotonias, congenital myasthenic syndrome, non-dystrophic myotonia.	Liu et al., 2015
SCN5A	Brugada syndrome (BrS), LQTS (LQT3), progressive cardiac conduction defect, dilated cardiomyopathy, heart failure, myocardial contractile dysfunction, sick sinus syndrome (SSS), atrial fibrillation, ventricular fibrillation, sudden infant death syndrome (SIDS), progressive familial heart block, Romano-Ward syndrome.	Li et al., 2018. National Library of Medicine, 2025.
SCN8A	Developmental and epileptic encephalopathy, intellectual disability, dyskinesia, ataxia, choreoathetosis, autism, and myoclonus disorders.	Gardella et al., 2020

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SCN9A	Primary erythromelalgia, paroxysmal extreme pain disorder, channelopathy-associated insensitive to pain, seizure, autism spectrum disorders, schizophrenia, bipolar disorder, small fiber neuropathy, genetic epilepsy with febrile seizures plus,	National Library of Medicine, 2025. Li et al., 2021. Cox et al., 2006.
SCN10A	Small fiber neuropathy, arrhythmia, heart block, kidney stone disease, Brugada syndrome.	Wang et al., 2021. Yang et al., 2018. National Library of Medicine, 2025.
SCN11A	Hereditary sensory and autonomic neuropathy type VII, familial episodic pain syndrome, essential tremor.	Huang et al., 2017. NCBI, 2025.
SCN1B	Early myoclonic encephalopathy, developmental and epileptic encephalopathy, genetic epilepsy with febrile seizures plus Dravet syndrome, focal epilepsy, and Brugada syndrome.	Kumar et al., 2022
SCN2B	Arrhythmias, Brugada syndrome, atrial fibrillation, sudden infant death syndrome, Alzheimer's disease.	Sweeney et al., 2019. NCBI, 2025.
SCN3B	Brugada syndrome, sudden infant death syndrome, ventricular fibrillation, and atrial fibrillation.	Wang et al., 2016
SCN4B	Familial atrial fibrillation, ventricular tachycardia, sudden cardiac death, long QT syndrome type 10, sudden infant death syndrome,	Chen et al., 2019. Li et al., 2013.

Genes encoding alpha subunits are generally more specialized to the nervous, skeletal-muscular, or cardiac systems, whereas genes encoding beta subunits could affect a variety of organ systems (Table 1). While SCN5A and SCN11A can affect the cardiovascular system, and the others affect the nervous and skeletal-muscular systems, SCN5A encodes the main cardiac sodium channel NaV1.5 (Li et al., 2018). The following section will focus on the SCN5A and SCN4B mutations responsible for LQTS.

Table 2
LQT3 and LQT10 mutations

Gene & Disorder	**Mutation Type**	**Mutation**	**Citation**
SCN5A (LQT3)	Deletion	ΔKPQ (Delete: Lys1505-Pro1506-Gln1507)	Schwartz et al., 1995 Splawski et al., 2000
SCN5A (LQT3)	Missense	R1644H	Schwartz et al., 1995
SCN5A (LQT3)	Missense	C1717G	Napolitano et al., 2005
SCN4B (LQT10)	Missense	L179F	Medeiros-Domingo et al., 2007

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SCN4B (LQT10)	Missense	S206L	Li et al., 2013

SCN5A mutations that cause LQT3 are mainly composed of missense mutations, with some deletion mutations resulting in gain-in-function (prolonging the duration of sodium current) (Table 2). Other mutations, such as those occurring at the splice site of nonsense mutations, are less common. LQT3 is more lethal than other LQTS types. It is often related to bradycardia-triggered arrhythmias, in which LQT3 increases late sodium currents, prolonging the QT interval and often slowing down heart rates, making patients more prone to lethal arrhythmia due to the prolonged action potential causing risk of early afterdepolarization at a slow heart rate (Pérez-Riera et al., 2017). On the ECG, LQT3 is commonly associated with narrow T-waves and long segments prior (Tester et al., 2014). Point mutations in alpha subunit-encoding chromosomes cause abnormalities and alpha and beta subunit interactions, resulting in the heteromeric channel (potassium channels) deficiency, which also prolongs the QT interval (Chiang et al., 2000). 65% of LQT3 patients experience symptoms/death during sleep (Tester et al., 2014). This is evident in both deletion mutation and point mutation above. Case studies noted that two people with the ΔKPQ mutation died during sleep, and one with the R/H point mutation had multiple cardiac arrests during sleep (Schwartz et al., 1995). However, SCN5A mutations sometimes display incomplete penetrance, meaning that some asymptomatic cases were noted in a few ΔKPQ mutations (Schwartz et al., 1995).

SCN5A mutations are primarily autosomal dominant, where a single mutated allele on any of the 22 non-sex chromosomes leads to the inheritance of LQT3. A form of autosomal dominant LQTS is the Romano-Ward Syndrome, which could also be caused by the SCN5A gene. Many cases of ΔKPQ mutation were also observed to cause the Romano-Ward Syndrome (Splawski et al., 2000), and, similar to LQT3, the Romano-Ward syndrome presents highly lethal symptoms pertaining to the cardiac system, unlike other variants of LQTS such as the Jervell and Lange-Nielson syndrome which interferes with hearing abilities. Romano-Ward syndrome also leads to delayed repolarization, thus differentiating it from LQT3. The RW syndrome is known for its lethal ventricular arrhythmia, as it is associated with left cardiac overactivity and right cardiac activity deficiency; as the right side contains chronotropic fibers; such deficiency has been known to cause heart rate decrease (Vincent, 1986). However, since other genes, such as potassium channel genes, may also cause Romano-Ward Syndrome, identifying a mutation as autosomal dominant is the primary way to distinguish it.

The LQT10 disease caused by SCN4B is generally less common than LQT3; its missense mutation had leucine replaced with phenylalanine at position 179; this position was found to be influencing the transmembrane domains dealing with pore formation and gating, resulting in increased late sodium channel currents, affecting repolarization and leading to a long QT interval (Li et al., 2013). A case study identifying the serine change in position 206 to leucine mutation also noted that SCN4B mutations may also cause LQT10-associated atrial fibrillation and sudden infant death syndrome, which SIDS details that a seemingly healthy infant dies suddenly and unexpectedly, mostly during sleep (Li et al., 2013). The LQT10 association with AF and SIDS was established as the S206L mutation encourages late sodium current and induces ventricular action potential interval (Li et al., 2013).

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POTASSIUM-GATED ION CHANNELS

Potassium-gated ion channels display selective permeability, only permeable to potassium (K^+) ions. There are many varieties of potassium ion channels, with voltage-gated potassium channels (Kv), calcium-activated seven transmembrane potassium channels (Kca), four transmembrane two-pore potassium channels/tandem pore domain potassium channels (K2p), two transmembrane potassium channels/inwardly rectifying potassium channels (Kir) (Tian et al., 2014). Voltage-gated potassium ion channels are composed of 6 subunits with auxiliary beta subunits, in which each subunit has six transmembrane segments of alpha helices S1-S6. Helices S1-S4 form voltage-sensing domains of the channel, and S5-S6 form the porous domain containing a short pore helix and a polypeptide chain with a characteristic sequence forming a selectivity filter (Sands et al., 2005). Voltage-gated potassium channels are divided into families, with corresponding gene families: Kv1 (KCNA1-7, 10), Kv2 (KCNB1-2), Kv3 (KCNC1-4), Kv4 (KCND1-3), Kv7 (KCNQ1-5), Kv10 (KCNH1, 5), Kv11 (KCNH2, 6, 7/hERG), Kv12 (KCNH3, 4, 8/EAG). Special channels Kv5 (KCNF1), Kv6 (KCNG1-4), Kv8 (KCNV1-2), and Kv9 (KCNS1-3) work with Kv2 to function, as they cannot function independently (IUPHA/BPS Guide to Pharmacology).

Table 3
Potassium-gated ion channel genes and associated with mutations

Gene Family	Associated Disorders	Citations
KCNA	Episodic ataxia, epilepsy, hypomagnesemia, paroxysmal dyskinesia, myokymia, developmental epileptic encephalopathy, seizures, intellectual disabilities, atrial fibrillation	Salpietro et al., 2023. Paulhus et al., 2020. Wang et al., 2018
KCNB	Epileptic encephalopathy, hypotonia, seizures, developmental delays, intellectual disabilities, autism, facial dysmorphism.	Bhat et al., 2024. Torkamani et al., 2014
KCNC	Progressive myoclonic epilepsy, epileptogenesis, cerebellar ataxia, developmental epileptic encephalopathy, hypotonia, autism, spinocerebellar ataxia type 13.	Zhao et al., 2024. Clatot et al., 2024. Zhang et al., 2016.
KCND	Spinocerebellar ataxia type 19/22, prominent ataxic syndrome, parkinsonism-dystonia, Brugada syndrome, atrial fibrillation, X-linked neurodevelopmental disorder.	Pollini et al., 2020. Kalm et al., 2024.
KCNF	Possible cognitive disorders, specifically related to the cortex.	Bocksteins, 2016.
KCNG	Migraines, malfunction in Kv2 expression, Hirschsprung's disease, bipolar disorder, type 2 diabetes.	Lacroix et al., 2024. O'Donnell et al., 2018. Pisanu et al., 2019.

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KCNQ	Long QT syndrome type 1, short QT syndrome, Jervell and Lange-Nielsen syndrome, Romano-Ward syndrome, sudden cardiac death, arrhythmia, familial neonatal epilepsy, neonatal seizures, behavioral arrests, self-limited infantile epilepsy, neurodevelopmental disorder, non-syndromic hearing loss, epileptic encephalopathy.	Moreno et al., 2015. Morgat et al., 2024. Wong et al., 2024. Miceli et al., 2014. Lehman et al., 2017. Jung et al., 2019
KCNV	Amyotrophic lateral sclerosis, cell death, nerve degeneration, cone-rod dystrophy, central scotoma, photophobia, red-green axis dyschromatopsia, and nyctalopia.	De Guimaraes et al., 2020. Huang et al., 2024.
KCNS	Essential tremor, cerebellar dysfunction, cerebellar degeneration, reduction in Purkinje cells, schizophrenia,	Georgiev et al., 2014. Liu et al., 2015.
KCNH	Zimmermann-Leband syndrome, Temple-Baraitser syndrome, facial dysmorphia, congenital long QT syndrome type 2, epileptic encephalopathies, autism, developmental disorder, type 2 diabetes.	Fukai et al., 2016. Zhou et al., 2011. Hu et al., 2022. Yang et al., 2018.

Voltage-gated potassium channels span various organ systems, having a significant impact on the nervous, cardiovascular, and skeletal-muscular systems, but also impacting vision and hearing abilities. However, because each gene family has multiple genes, the gene family can cause various disorders in different systems. Specifically, genes KCNQ1 and KCNH2 (hERG) are the primary causes of LQTS. Genes such as the KCNE1 that also cause LQTS will not be included, as its primary function is regulating the KCNQ1 gene, rather than directly affecting a voltage-gated potassium channel.

Table 4
LQT1 and LQT2 mutations

Gene & Disorder	**Mutation Type**	**Mutation**	**Citation**
KCNQ1 (LQT1)	Missense	Y111C	Napolitano et al., 2005
KCNQ1 (LQT1)	Deletion	del584	Peroz et al., 2008
KCNQ1 (LQT1)	Insertion	151-152insT	Peroz et al., 2008
KCNQ1 (LQT1)	Deletion	del451-452	Splawski et al., 2000
KCNQ1 (LQT1)	Insertion	567-568insG	Splawski et al., 2000
KCNH2 (LQT2)	Missense	G2775A	Schwartz et al., 1995
KCNH2 (LQT2)	Missense	G572C	Splawski et al., 2000

All voltage-gated potassium channel LQTS is associated with loss-of-function mutations that reduce repolarization potassium currents, prolonging the QT interval—both KCNQ1 and KCNH2 cause

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two of the three most major and prevalent LQTS types: LQT1 and LQT2. The KCNQ1 gene mutation can also reduce the delayed rectifier potassium current (IKs), which initiates repolarization. Other mechanisms cause LQT1, such as impaired gating/permeability, defective protein tracking, or abnormal channel assembly – meaning that the subunits of the pore are impaired, leading to the gate not opening or not closing according to voltage signaling; misfolding of proteins leading to intracellular trafficking errors; incorrect positioning of the channel; lower channel density leading to a reduction in repolarization of potassium current (Peroz et al., 2008). Based on the studies cited above, it was concluded that most LQT1 mutations were missense mutations when one amino acid is replaced with another; however, there are still some point mutations (deletion, insertion, etc.), with most identifying as either the autosomal dominant Romano-Ward syndrome or autosomal recessive Jervell and Lange-Nielsen syndrome. Table 4 shows a missense mutation, in which tyrosine is replaced by cysteine at position 111; an example of a deletion mutation, deleting the nucleotide at position 1584; and an insertion of thymine between positions 151-152. The stated mutations all reduce the potassium current in charge of repolarization to prolong the QT interval, leading to LQT1. Unlike the other LQTS types, LQT1's symptoms are triggered by adrenergic stimuli (physical exercises, stress, etc.) and usually have a prolonged T wave on the ECG (Tester et al., 2014).

As stated above, both Romano-Ward syndrome and Jervell and Lange-Nielsen syndrome are present in LQT1. The Romano-Ward syndrome only affects cardiovascular functions when caused by KCNQ1 mutation. Otherwise, it encompasses generally similar symptoms and triggers as LQT1. An example of the Romano-Ward syndrome is missense mutation Y111C; however, after observing multiple case studies, Romano-Ward syndrome mostly appears in insertion/deletion mutations. Unlike the Romano-Ward syndrome, the Jervell and Lange-Nielsen syndrome is an autosomal recessive disorder, meaning that a patient needs to have two copies of the mutated gene on a non-sex allele to be able to experience symptoms; patients with only one copy of the mutated gene are considered carriers, but do not exhibit symptoms; thus, for inheritance, both parents must have at least one copy of the mutated gene. People with Jervell and Lange-Nielson syndrome are observed to have congenital deafness or hearing deficiency while also experiencing cardiac disorders such as arrhythmias, sudden cardiac death, or prolonged QT interval (Moss et al., 2007). An example of Jervell and Lange-Nielson syndrome is the insertion of guanine between positions 567 and 568 on the amino acid chain, which affects the transmembrane domains S2-S3 (Splawski et al., 2000). The transmembrane domain is related to voltage sensing, which may lead to impaired gating or abnormal permeability, as it may lead to an atypical reaction reducing the repolarization current.

The KCNH2 gene, otherwise known as hERG (human-ether-a-go-go-Related K^+ Channel), leads to another prevalent LQTS type, LQT2. LQT2 is defined by, similar to LQT1, its loss-of-function mutations, which mutations of IKr rapid delayed rectifier potassium channel also cause the reduction of repolarization potassium current, increasing the QT interval. However, it is triggered by auditory stimuli (loud noises), sudden, surprising events, or emotional stress that induces adrenergic responses. When reflected in the ECG, LQT2 often displays low amplitude notched or biphasic T-waves, meaning that the T waves have low amplitude, two distinct peaks, and both positive and negative deflections, reflecting its instability (Tester et al., 2014). Once again, missense mutations are noticed to be most prevalent in

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LQT2, for instance, in mutation G2775A, where guanine is replaced with adenine on position 2775. A case study on such mutations presented findings that syncope, cardiac arrest, and other related symptoms occurred only during or after emotional stress, further supporting the triggers stated above (Schwartz et al., 1995). LQT2 is also a primarily autosomal dominant mutation, evident in missense mutation G572C, where guanine is replaced with cysteine; such mutations are an example of the Romano-Ward syndrome, which is also autosomal dominant (Splawski et al., 2000).

CALCIUM-GATED ION CHANNELS

Likewise, the calcium voltage-gated ion channels are selectively permeable to Ca^{2+}. Calcium channels are also made from a single, pore-forming alpha subunit and auxiliary subunits α2δ, β, γ; these auxiliary subunits modulate channel folding and trafficking. The calcium channel has three main subtypes, CaV1, CaV2, CaV3. In detail, CaV1 is in charge of conducting gene expression and synapse transmission at ribbon synapses in specialized sensory cells; CaV2 initiates synapse transmission in fast synapses; and CaV3 is responsible for supporting action potential in cardiac myocytes and thalamic neurons (Caterrall, 2011). Each main subtype then has specific channels: CaV1.1 (CACNA1S), CaV1.2 (CACNA1C), CaV1.3 (CACNA1D), CaV1.4 (CACNA1F); CaV2.1 (CACNA1A), CaV2.2 (CACNA1B), CaV2.3(CACNA1E); CaV3.1 (CACNA1G), CaV3.2 (CACNA1I), CaV3.3 (CACNA1H).

Table 5
Calcium-gated ion channel genes and associated with mutations

Gene	Associated Disorders	Citations
CACNA1S	Malignant hyperthermia susceptibility, hyperkalemic periodic paralysis, thyrotoxic periodic paralysis, statin-associated myopathy.	Sangkuhl et al., 2019
CACNA1C	Schizophrenia, bipolar disorder, major depression, autism, long QT syndrome type 8, short QT syndrome, Brugada syndrome, Timothy syndrome, sudden cardiac death, hypotonia, epilepsy, developmental delay, arrhythmia.	Dedic et al., 2017. Napolitano et al., 2006.
CACNA1D	Primary aldosteronism, seizures, autism, sinoatrial node dysfunction, deafness, neurologic abnormalities, hyperinsulinemic hypoglycemia, hypotonia.	Alzahrani et al., 2023. Flanagan et al., 2017.
CACNA1F	Aland Island eye disease, cone-rod dystrophy, X-linked type 3, congenital stationary night blindness type 2.	Alzahrani et al., 2023.
CACNA1A	Developmental and epileptic encephalopathy, episodic ataxia, familial hemiplegic migraine,	Alzahrani et al., 2023.

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	progressive cerebellar ataxia, spinocerebellar ataxia.	
CACNA1B	Seizures, myoclonus dystonia, migraine, epilepsy, non-small cell lung cancer, breast cancer.	Szymanowicz et al., 2024. Zhou et al., 2017.
CACNA1E	Developmental and epileptic encephalopathy, migraine, hypotonia, developmental impairment, hyperkinetic movement disorders, congenital contractures, macrocephaly.	Helbig et al., 2018. Szymanowicz et al., 2024.
CACNA1G	Spinocerebellar ataxia, neurodevelopmental deficits, idiopathic epilepsy, episodic vestibulocerebellar ataxia.	Szymanowicz et al., 2024. Alzahrani et al., 2023.
CACNA1I	Familial hemiplegic migraine, schizophrenia, developmental delay, seizures, hypotonia, epilepsy,	Maksemous et al., 2022. Ghaleb et al., 2021.
CACNA1H	Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis, febrile seizures, myoclonic astatic epilepsy.	Szymanowicz et al., 2024.

CaV1 channels and associated genes commonly affect the nervous and endocrine system, causing sensory and neurological disorders. CaV1 also causes some skeletal-muscular and cardiovascular disorders. This may be related to how each subchannel (CaV1, CaV2, CaV3) plays significant parts in the nervous system and synapses function, whereas there is no direct connection that all channels in each family directly influence cardiac/skeletal-muscular system; only specific channels do. LQTS is present in gene CACNA1C of the CaV1 subtype, encoding the alpha subunit of calcium channel CaV1.2; it is the only gene encoding calcium channel alpha subunits that have been shown to have explicit linkage to LQTS.

Table 6:
LQT8 mutations

Gene & Disorder	Mutation Type	Mutation	Citations
CACNA1C (LQT8/TS)	Missense	G406R	Fukuyama et al., 2014
CACNA1C (LQT8)	Missense	P381S	Fukuyama et al., 2014
CACNA1C (LQT8)	Missense	M456I	Fukuyama et al., 2014

Gain-in-function mutations of the CACNA1C gene cause LQT8, controlling the L calcium channel, an important channel for conducting depolarization currents in cardiomyocytes; mutation results in induced cell surface expression of the calcium ion channel, leading to increased calcium influx, and

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prolonging the QT interval (Mellor et al., 2019). This mutation is displayed on the ECG through late appearing T waves 60% of the time, and the rest experiencing cardiopulmonary arrest, which refers to the sudden loss of cardiac function (Fukuyama et al., 2020). LQT8 is generally rare compared to LQT1, LQT2, and LQT3, with its associated syndrome, the Timothy syndrome, being even more rare and lethal. In addition, LQT8 is often triggered by exercise or emotional fluctuations. For example, missense mutation P381S, where proline in position 381 is replaced by serine; patients with such mutation reported increased QT interval to 548 ms after an exercise stress test, and another patient with the same mutation having syncope during physical exercise (Fukuyama et al., 2014). However, LQT8 can also be asymptomatic; in missense M456I, methionine is replaced with isoleucine, although having an increased prolongation of the QT interval after exercise (from 486 ms to 568 ms), the patient displayed no symptoms (Fukuyama et al., 2014).

Timothy syndrome type 1 is also associated with LQT8 and the CACNA1C gene; it is highly lethal and rarer than LQT8. Timothy syndrome is often associated with early mortality, immune deficiency, congenital cardiac disorders, syndactyly, impairment/dysfunction of the central nervous system, and metabolism abnormalities; however, syndactyly, LQTS, and neurodevelopmental disorders are symptoms that only pertain to type 1 Timothy syndrome (Fukuyama et al., 2020). An example of the Timothy syndrome is missense mutation G406R, where glycine is replaced by arginine at position 406 (Fukuyama et al., 2014).

CONCLUSION

In conclusion, even slight mutations, such as a change in a nucleotide base, could change human physiology, structure, and behavior, leading to malfunction of systems and life-threatening consequences. Specifically, mutants of voltage-gated ion channels Ca^{2+}, K^{+}, and Na^{+} lead to structural changes in either the porous area controlling ion conduction or affecting the gating of ion channels (Isom, 2001). These mutants differ from wildtype genes not only from the changes in nucleotide bases or structural modifications, but also in symptoms and syndromes. A major syndrome prevalent in all three voltage-gated ion channels mutations, under cardiac channelopathies, is LQTS. It is highlighted that abnormalities in cardiac action potential phases, such as the repolarization phase dysfunction may lead to prolonged QT interval. However, as LQTS's specific symptoms vary per type, each mutant causes different variations of LQTS. This syndrome is an adequate reflection of how different mutants may alter different structures, leading to varying disorders. The comparison of LQTS symptoms with normally operating cardiac ion channels reflects how mutants that cause cardiac channelopathies differ from wild-type genes.

This review is limited in that it only analyzes a few mutant genes that appear to be prevalent among LQTS patients, the thoroughness of this review could be improved through inclusivity of more genes. As each gene may affect different structural factors, this would answer my research question more widely. Furthermore, considering more genes involved could widen the range of causes of various syndromes, such as LQTS; this could be used to analyze for trends in mutations, if any. Future discussions on irritation factors of different LQTS or reason behind prevalence in a specific group may

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be beneficial to explaining its difference from wildtype factors in another perspective, while also helping in contrasting between different mutants. Additionally, as many reviews focus on the three main types of LQTS or main strands affecting ion channels, research on rarer mutants may widen the perspective on cardiac channelopathies. Moreover, the primary method of LQTS detection, the Schwartz score, was developed 30 years ago, making it slightly outdated. With novel technology and more application of genetic testing, more LQTS patients may be accurately diagnosed, not only providing adequate, timely treatment, but also possibly discovering more associated genotypes.

As many parts of the pathophysiology of cardiac channelopathies still remain mysterious, and it often causes lethal, life-changing effects, future research on more effective treatment methods is encouraged. Currently, β-blockers remain the dominating treatment method of LQTS, specifically, they are most efficient in reducing symptoms of LQTS 1 and 2. However, we lack data on LQTS 3, and the effects of β-blockers vary per genotype. Further data collection and review on β-blockers is encouraged, especially since it is considered safe to use during pregnancy and its effectiveness is already justified (Krahn et al., 2022).

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