ION CHANNEL DISEASES

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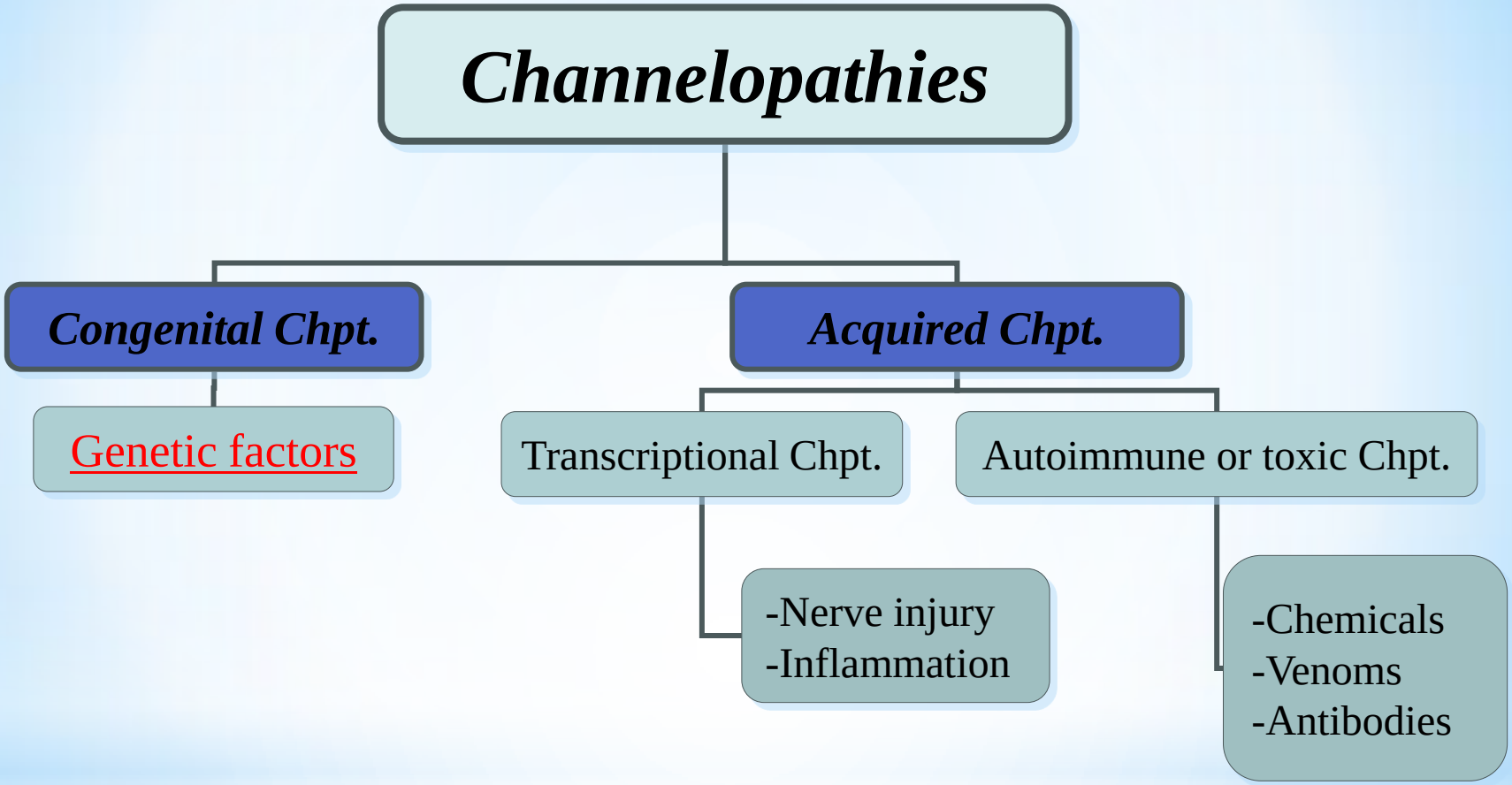
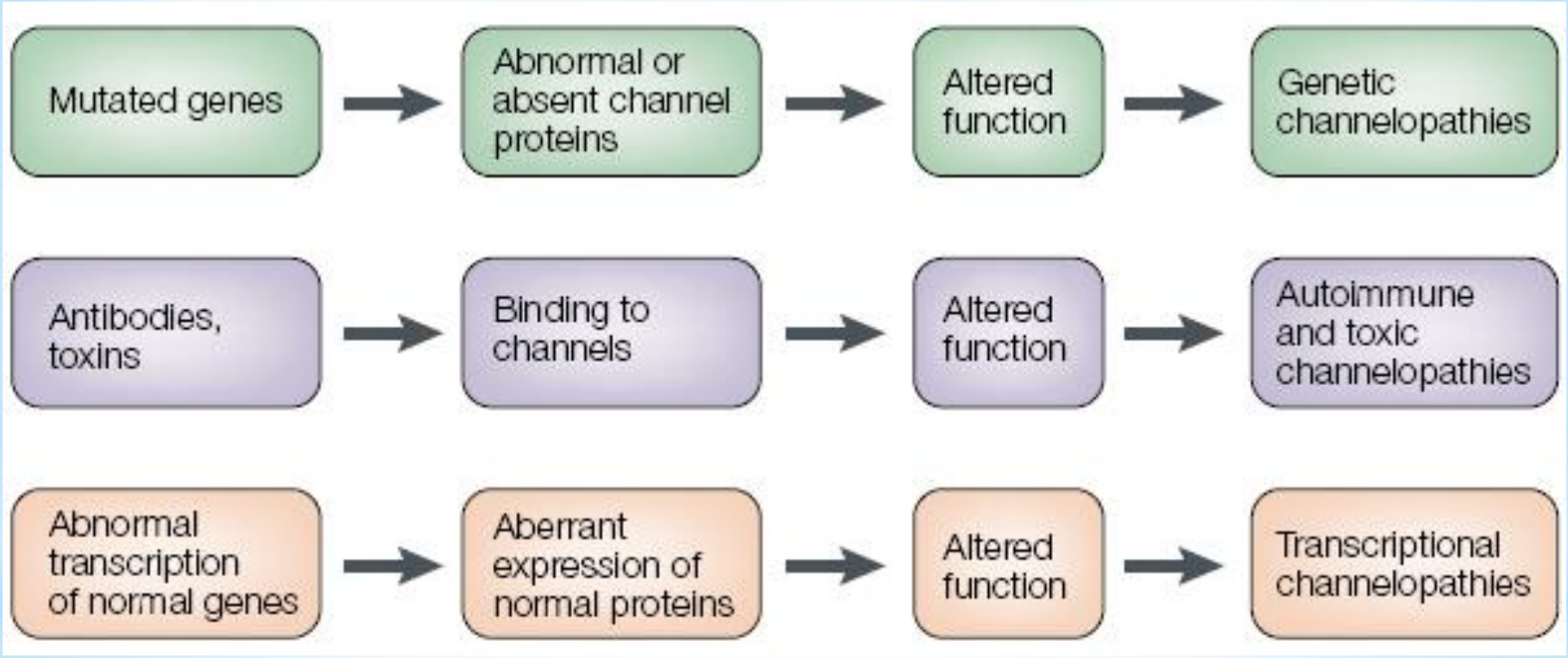
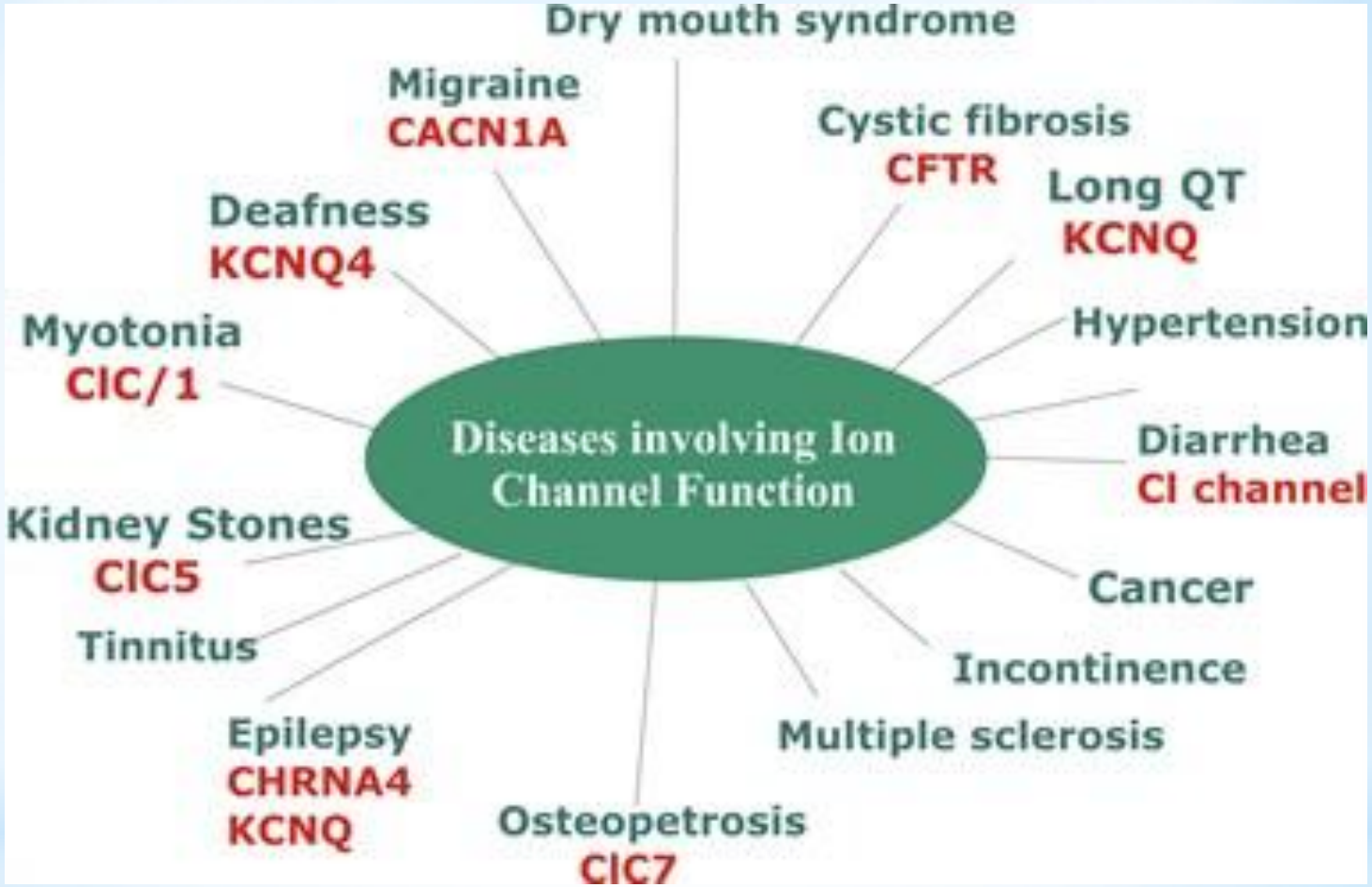
Ion channels are involved in various cellular functions

- Generation of electrical currents
- Transepithelial transport of salt and water
- Regulation of cellular volume and pH
- Acidification of intracellular organelles
- Chemical signalling (role of Ca^{2+})

* *A rapidly growing group of diseases caused by ion channel dysfunction is classified as "channelopathies"*


Channelopathies
Congenital Chpt.
Acquired Chpt.
Genetic factors
Transcriptional Chpt.
Autoimmune or toxic Chpt.
-Nerve injury
-Inflammation
-Chemicals
-Venoms
-Antibodies


Mutated genes
Abnormal or absent channel proteins
Altered function
Genetic channelopathies
Antibodies, toxins
Binding to channels
Altered function
Autoimmune and toxic channelopathies
Abnormal transcription of normal genes
Aberrant expression of normal proteins
Altered function
Transcriptional channelopathies


Dry mouth syndrome
Migraine
CACN1A
Cystic fibrosis
CFTR
Long QT
KCNQ
Deafness
KCNQ4
Hypertension
Myotonia
ClC/1
Diseases involving Ion Channel Function
Diarrhea
Cl channel
Kidney Stones
ClC5
Cancer
Tinnitus
Incontinence
Epilepsy
CHRNA4
KCNQ
Multiple sclerosis
Osteopetrosis
ClC7

General properties of channelopathies

- *A change in the channel*
  - *Structure*
  - *Expression*
  - *Localization*

- *A change in the function of the cell*
  - *"Gain of function"*
  - *"Loss of function"*

* GENETIC DISORDERS OF MUSCULAR ION CHANNELS
* Periodic Paralysis (Hypokalemic OR Hyperkalemic)
* Myotonia Congenita (Paramyotonia Congenita, Potassium-Aggravated Myotonia)
* Andersen-Tawil Syndrome
* Malignant Hyperthermia
* Congenital Myasthenic Syndromes

* GENETIC DISORDERS OF NEURONAL ION CHANNELS

* Familial Hemiplegic Migraine
* Familial Episodic Ataxias
* Hereditary Hyperexplexia
* Primary Erythermalgia

* EPILEPSY

* Familial Focal Epilepsies
* Idiopathic Generalized Epilepsies

* AUTOIMMUNE CHANNELOPATHIES

* Myasthenia Gravis
* Lambert-Eaton Myasthenic Syndrome
* Acquired Neuromyotonia (Isaacs' Syndrome)
* Paraneoplastic Cerebellar Degeneration
* Rasmussen's Encephalitis

Genetic channelopathies

* Loss-of-function
* generally recessive

* Gain of function
* generally dominant

* As a general rule: patients with homozygous recessive mutations are more severely effected than heterozygous dominant mutations, since the latter patients still have residual channel functions.

* CF and Bartter : example of recessive

* Dominant-negative forms can reduce function below 50% (dimers, tetramers) more deleterious than null mutations

* Chloride channel in muscle:

    * Recessive (Becker-type)
    * Dominant (Thomsen-type)

    } myotonia congenita

    * Borderline mutations

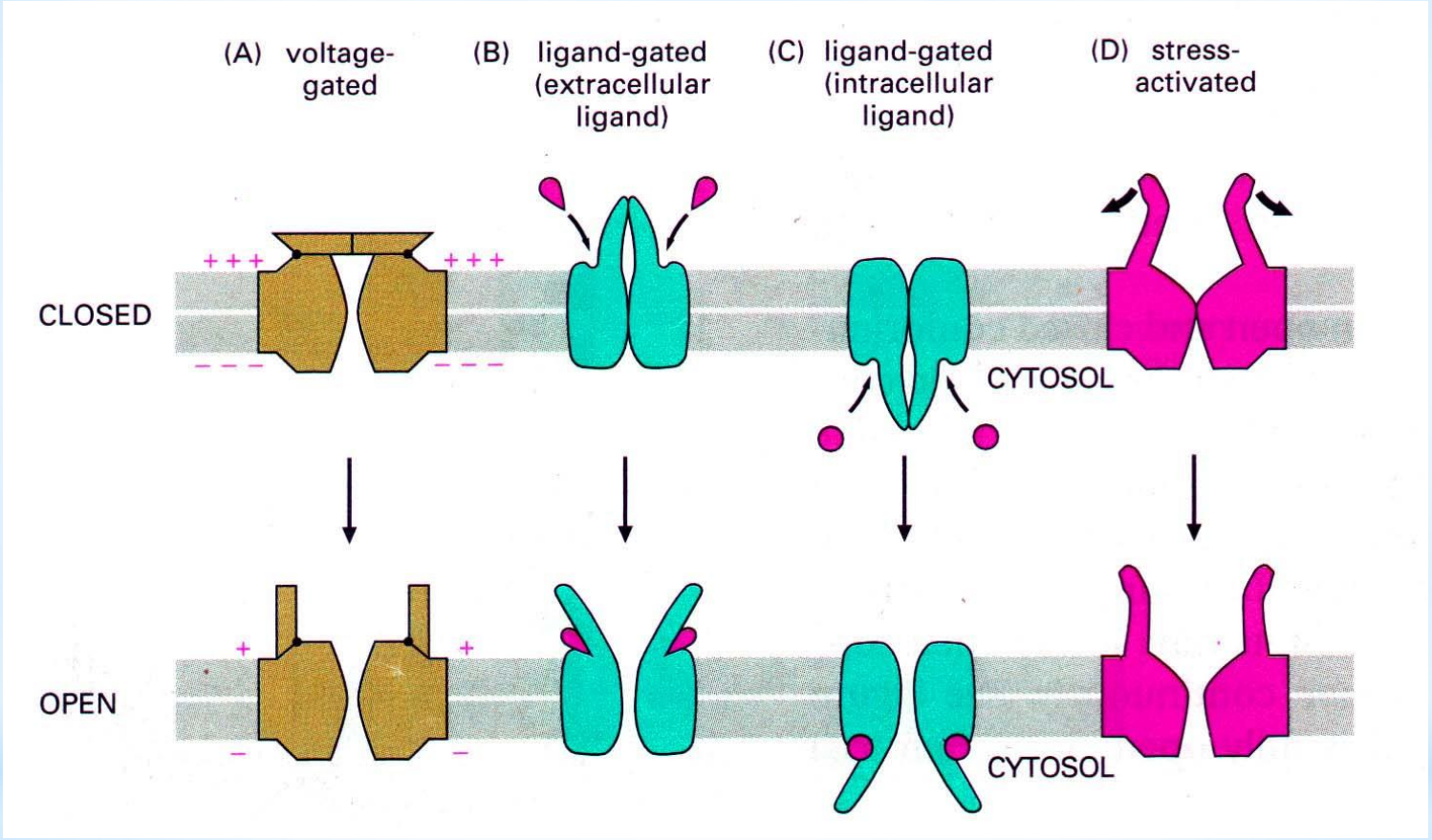

(A) voltage-gated
(B) ligand-gated (extracellular ligand)
(C) ligand-gated (intracellular ligand)
(D) stress-activated
CLOSED
OPEN
CYTOSOL
CYTOSOL

Table 1. Known ion channel diseases

Channel	Gene	Channel-forming unit/ligand	OMIM	Disease
Cation channels:				
CHRNA1/ACHRA	*CHRNA1*	α, ACh	100690	Myasthenia congenita
CHRNA4	*CHRNA4*	α, ACh	118504	Autosomal dominant nocturnal frontal lobe epilepsy
CHRNB2	*CHRNB2*	β, ACh	118507	Autosomal dominant nocturnal frontal lobe epilepsy
Polycystin-2	*PKD2*	α	173910	Autosomal dominant polycystic kidney disease (ADPKD)
CNGA3	*CNGA3*	α, cGMP	600053	Achromatopsia 2 (color blindness)
CNGB1	*CNGB1*	β, cGMP	600724	Autosomal recessive retinitis pigmentosa
CNGB3	*CNGB3*	β, cGMP	605080	Achromatopsia 3
Sodium channels:				
$Na_v1.1$	*SCN1A*	α	182389	Generalized epilepsy with febrile seizures (GEFS+)
$Na_v1.2$	*SCN2A*	α	182390	Generalized epilepsy with febrile and afebrile seizures
$Na_v1.4$	*SCN4A*	α	603967	Paramyotonia congenita, potassium aggressive myotonia, hyperkalemic periodic paralysis
$Na_v1.5$	*SCN5A*	α	600163	Long-QT syndrome, progressive familial heart block type I, Brugada syndrome (idiopathic ventricular arrhythmia)
SCN1B	*SCN1B*	β	600235	Generalized epilepsy with febrile seizures (GEFS+)
ENaCα	*SCNN1A*	α	600228	Pseudohypoaldosteronism type 1 (PHA1)
ENaCβ	*SCNN1B*	β	600760	PHA1, Liddle syndrome (dominant hypertension)
ENaCγ	*SCNN1G*	γ	600761	PHA1, Liddle syndrome
Potassium channels:				
$K_v1.1$	*KCNA1*	α	176260	Episodic ataxia with myokymia
KCNQ1/K_vLQT1	*KCNQ1*	α	192500	Autosomal dominant long-QT syndrome (Romano–Ward) Autosomal recessive long-QT syndrome with deafness (Jervell–Lange–Nielsen)
KCNQ2	*KCNQ2*	α	602235	BFNC (epilepsy), also with myokymia
KCNQ3	*KCNQ3*	α	602232	BFNC (epilepsy)
KCNQ4	*KCNQ4*	α	603537	DFNA2 (dominant hearing loss)
HERG/ KCNH2	*KCNH2*	α	152427	Long-QT syndrome
Kir1.1/ROMK	*KCNJ1*	α	600359	Bartter syndrome (renal salt loss, hypokalemic alkalosis)
Kir2.1/IRK/KCNJ2	*KCNJ2*	α	600681	Long-QT syndrome with dysmorphic features (Andersen syndrome)
Kir6.2/K_{ATP}	*KCNJ11*	α	600937	Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)
SUR1	*SUR1*	β	600509	PHHI
KCNE1/MinK/ISK	*KCNE1*	β	176261	Autosomal dominant long-QT syndrome (Romano–Ward) Autosomal recessive long-QT syndrome with deafness (Jervell–Lange–Nielsen)
KCNE2/MiRP1	*KCNE2*	β	603796	Long-QT syndrome
KCNE3/MiRP2	*KCNE3*	β	604433	Periodic paralysis

Calcium channels:				
$Ca_v1.1$	*CACNA1S*	α	114208	Hypokalemic periodic paralysis, malignant hyperthermia
$Ca_v1.4$	*CACNA1F*	α	300110	X-linked congenital stationary night blindness
$Ca_v2.1$	*CACNA1A*	α	601011	Familial hemiplegic migraine, episodic ataxia, spinocerebellar ataxia type 6
RyR1	*RYR1*	α	180901	Malignant hyperthermia, central core disease
RyR2	*RYR2*	α	180902	Catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia type 2
Chloride channels:				
CFTR	*ABCC7*	α	602421	Cystic fibrosis, congenital bilateral aplasia of vas deferens
ClC-1	*CLCN1*	α	118425	Autosomal recessive (Becker) or dominant (Thomsen) myotonia
ClC-5	*CLCN5*	α	300008	Dent's disease (X-linked proteinuria and kidney stones)
ClC-7	*CLCN7*	α	602727	Osteopetrosis (recessive or dominant)
ClC-Kb	*CLCNKB*	α	602023	Bartter syndrome type III
Barttin	*BSND*	β	606412	Bartter syndrome type IV (associated with sensorineural deafness)
GLRA1	*GLRA1*	α, glycine	138491	Hyperekplexia (startle disease)
GABAα1	GABRA1	α, GABA	137160	Juvenile myoclonus epilepsy
GABAγ2	*GABRG2*	γ, GABA	137164	Epilepsy
Gap junction channels:				
Cx26	*GJB2*		121011	DFNA3 (autosomal dominant hearing loss) DFNB1 (autosomal recessive hearing loss)
Cx30	*GJB4*		605425	DFNA3
Cx31	*GJB3*		603324	DFNA2
Cx32	*GJB1*		304040	CMTX (X-linked Charcot–Marie–Tooth neuropathy)

The third column classifies channel proteins into α, β, and γ subunits, where α subunits are always directly involved in pore formation. Several β subunits are only accessory (i.e. do not form pores), as is the case, for example, with SCN1B and barttin. Others (e.g. of ENaC and GABA receptors) participate in pore formation. For ligand-gated channels, the ligand is given. Note that GABA and glycine act from the extracellular side, whereas cGMP is an intracellular messenger.

Voltage-gated K^+, Na^+ and Ca^{2+} channels

- V-gated channels are evolutionarily related
- They share a fundamental design consisting of six membrane spanning segments (S1–S6).
- Segment four is thought to function as the voltage sensor and contains basic residues at every third or fourth position
- A pore domain allowing selective passage of the ions .
- Mutations in these voltage-gated ion channel genes have been implicated in a number of disorders including non-dystrophic myotonias, periodic paralysis, episodic ataxia, migraine, long QT syndrome and paroxysmal dyskinesia

* GENETIC DISORDERS OF MUSCULAR ION CHANNELS

*The non-dystrophic myotonias (NDM)

- myotonia congenita
- paramytonia congenita
- Na-channel myotonia

*similar to them : periodic paralysis

*All are diseases due to mutations in V-gated ion channel genes

AND

are all clinically distinct autosomal dominant disorders which are (mostly) due to mutations in the α-subunit of the skeletal muscle sodium channel, *SCN4A or in chloride channels CLCN1*

* Myotonia
* is not a disease – but a symptom
* inability to relax after use
* mostly temporary, slight disabling stiffness after a voluntary movement
* sec to min
* strenuous activity OR extended period of rest
* skeletal muscles

* The NDMs

* Nondystrophic myotonias are muscle disorders caused by abnormal muscle cell membrane proteins that affect the control of muscle fiber contraction
* rare
* prolongation of skeletal muscle relaxation time
* leads to hyperexcitability
* two groups:
* the chloride channelopathies (myotonia congenita)
* the sodium channelopathies (paramyotonia congenita)

Myotonia Congenita (MC)

MC : mutations in the skeletal muscle V-gated Cl-channel gene, CLCN1

* Cl conductance plays a major role in repolarization of skeletal muscle.

* Normal muscle requires a high resting chloride conductance for fast repolarization of the t-tubules and stabilization of the electrical excitability of the muscle membrane.
* Cessation of muscle contraction is initiated when Cl channels open and shunt Cl into the muscle to halt contraction. In people with MC , the Cl channel is defective.
* In some mutations, channels are unstable and deteriorate quickly, or a defective ER exists, meaning channel cannot be transported efficiently to the cell surface. In other mutations, the mutated Cl channels are less permeable to chloride ions and more permeable to other ions. The result is prolonged muscle contractions, which are the hallmark of myotonia.

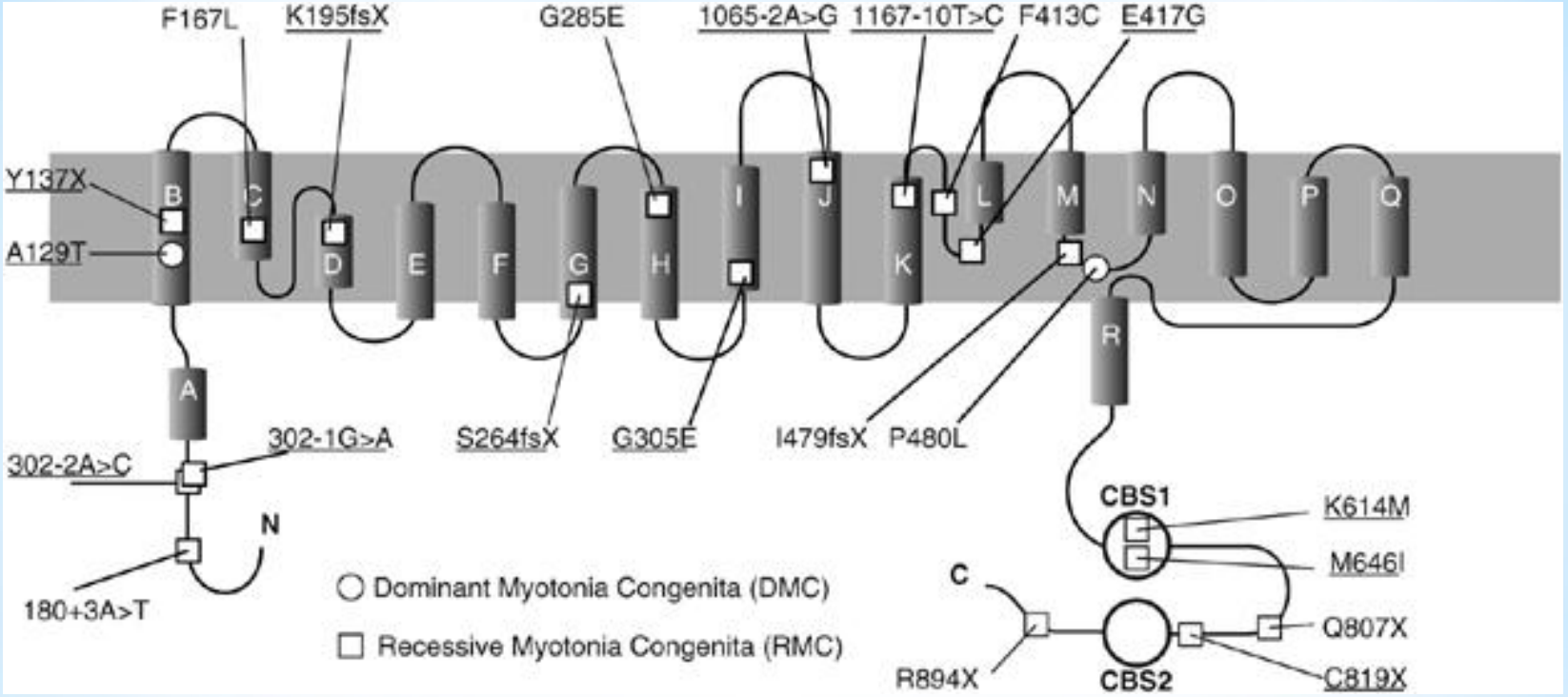
Reduction in Cl current that results in repetitive depolarization:

So a defective muscle relaxation after voluntary contraction.

* two forms: autosomal dominant (Thomsen), and autosomal recessive (Becker)

in both forms muscle stiffness is most pronounced during rapid voluntary movements following a period of rest but improves with repeated activity—the so-called ‘warm-up’ phenomenon

Interestingly, it has recently been found that some recessive mutations may occur in a dominant fashion in some individual. Moreover, different mutations at the same gene locus can also cause both forms of the disease.



The sites of the mutations in the skeletal muscle chloride (ClC-1) channel. Novel mutations are underlined, circles represent dominant myotonia congenita (Thomsen) and squares recessive myotonia congenita (Becker).

Trip et al., European Journal of Human Genetics (2008) 16, 921–929.

* **Paramyotonia congenita**

* Missense mutations of the skeletal muscle V-gated Na channel gene, SCN4A,produce a spectrum of disorders characterized by myotonia and periodic paralysis.

* Paramyotonia congenita (PMC) (Eulenburg's disease) :
* autosomal dominant
* Shows episodic cold- or exercise-induced muscle myotonia in exposed areas (mainly the face, neck, and hands) that lasts for minutes to hours .
* Muscle stiffness (myotonia) is made worse by chilling or activity (contrary to regular myotonia usually eases with physical activity). Thereby *paradoxical* or self-contradictory (gets its name)

* The mutations in SCN4A cause so-called "gating" malfunctions. The sodium pore fails to close.
* But the different mutations cause the pore to malfunction in some way, either not opening enough, remaining open too long or not closing completely, so that sodium ions continue to drip into the cell.
* As a result, the ratios of Na and K become unbalanced.
* At first this imbalance causes the muscle fiber to contract uncontrollably when the signal to contract (move) arrives, but as the imbalance worsens the muscle stops responding to nerve signals and becomes weak or paralyzed.

* **Periodic Paralyses (PPses)**
* The primary PPses : autosomal-dominant disorders of skeletal muscle Na, K and Ca channel genes.
* Episodes of muscle weakness associated with variations in serum potassium concentration.

* **Hyperkalemic periodic paralysis**
* gain-of-function mutations in the α-subunit of the skeletal muscle V-gated sodium channel, Nav1.4 .
* attacks of flaccid limb paralysis or, rarely, weakness of the eye and throat muscles.
* episodes of weakness may last for up to an hour and disappear as the blood K concentration decreases due to elimination by the kidney.
* Triggered by ingestion of K-rich food, rest after exercise, weather changes, certain pollutants (e.g.: Cigarette smoke) and periods of fasting and cold exposure.
* In the presence of high potassium levels, including those induced by diet, sodium channels fail to inactivate properly.

Attacks typically begin in the first decade of life, increase in frequency and severity during puberty, and then decrease in frequency after 40 years of age.

The mutation causes single amino acid changes which are important for inactivation (T704M and M1592V for the majority of cases) .

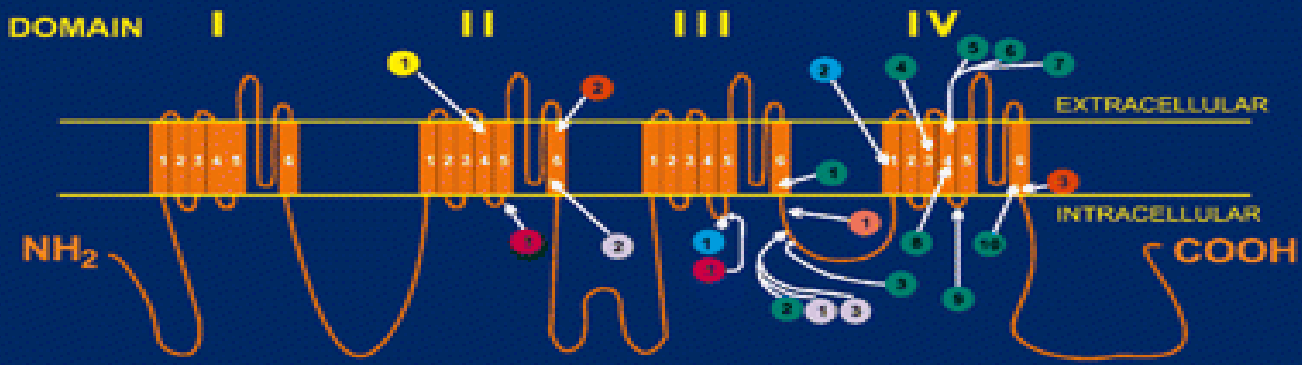
* Some people with HyperPPses have increased levels of K in their blood (hyperkalemia) during attacks; but not all .

* APs from the CNS cause end-plate potentials at the NMJ which causes Na ions to enter via $Na_v1.4$ and depolarise the muscle cells. This triggers the entry of Ca from the sarcoplasmic reticulum (SR) to cause contraction of the muscle. To prevent perpetually contraction, the channel contains a fast inactivation gate.
* In time, K will leave the muscle cells, repolarising the cells and causing the pumping of calcium away from the contractile apparatus to relax the muscle.
* Mutations altering the usual structure and function of this Na channel therefore disrupt regulation of muscle contraction, leading to episodes of severe muscle weakness or paralysis (Mutations in TM III and IV make up inactivation gate and in the cytoplasmic loops between the S4 and S5 helices, the binding sites of the inactivation gate).
* Channel is unable to inactivate and the muscle remains permanently tense.
* Hyperkalemic because a high EC K concentration will make it even more unfavourable for K to leave the cell in order to repolarise it, and this further prolongs Na conductance and keeps the muscle contracted. Hence, the severity would be reduced EC K ion concentrations are kept low.

* **Hypokalemic periodic paralysis (HypoPP)** is caused by mutations in both the α-subunit of the Nav1.4 channel(SCN4A) and the homologous α1-subunit of the skeletal muscle calcium channel, Cav1.1 (CACNA1S) .

* In general, HypoPP is characterized by reversible attacks of muscle weakness concomitant with decreased blood potassium concentrations.
* The attacks may be triggered by rest after strenuous exercise, by a meal rich in carbohydrates, or by exposure to cold. Patients typically wake up paralyzed, and attacks usually last several hours to days
* For the body to move normally, muscles must tense and relax in a coordinated way.
* The CACNA1S and SCN4A proteins form channels that control the flow of positive charged ions.
* Mutations alter the usual structure and function of Ca or Na channels. The altered channels cannot properly regulate the flow of ions into muscle cells, which reduces the ability of skeletal muscles to contract. Because muscle contraction is needed for movement, a disruption in normal ion transport leads to episodes of severe muscle weakness or paralysis.

Skeletal Muscle Sodium Channel (SCN4A)



HYPERKALEMIC PARALYSIS

1. Thr 704 Met
2. Val 783 Ile
3. Met 1592 Val

PARAMYOTONIA CONGENITA WITHOUT PARALYSIS ON EXPOSURE TO COLD

1. Val 1293 Ile

PARAMYOTONIA CONGENITA

1. Val 1293 Ile
2. Gly 1306 Val
3. Thr 1313 Met
4. Leu 1433 Arg
5. Arg 1448 His
6. Arg 1448 Cys
7. Arg 1448 Pro
8. Val 1458 Phe
9. Phe 1473 Ser
10. Val 1589 Met

HYPERKALEMIC & PARAMYOTONIA

1. Ala 1156 Thr
2. Met 1360 Val

ACETAZOLAMIDE RESPONSIVE MYOTONIA

1. Ile 1160 Val

MYOTONIA FLUCTUANS / PERMANANS

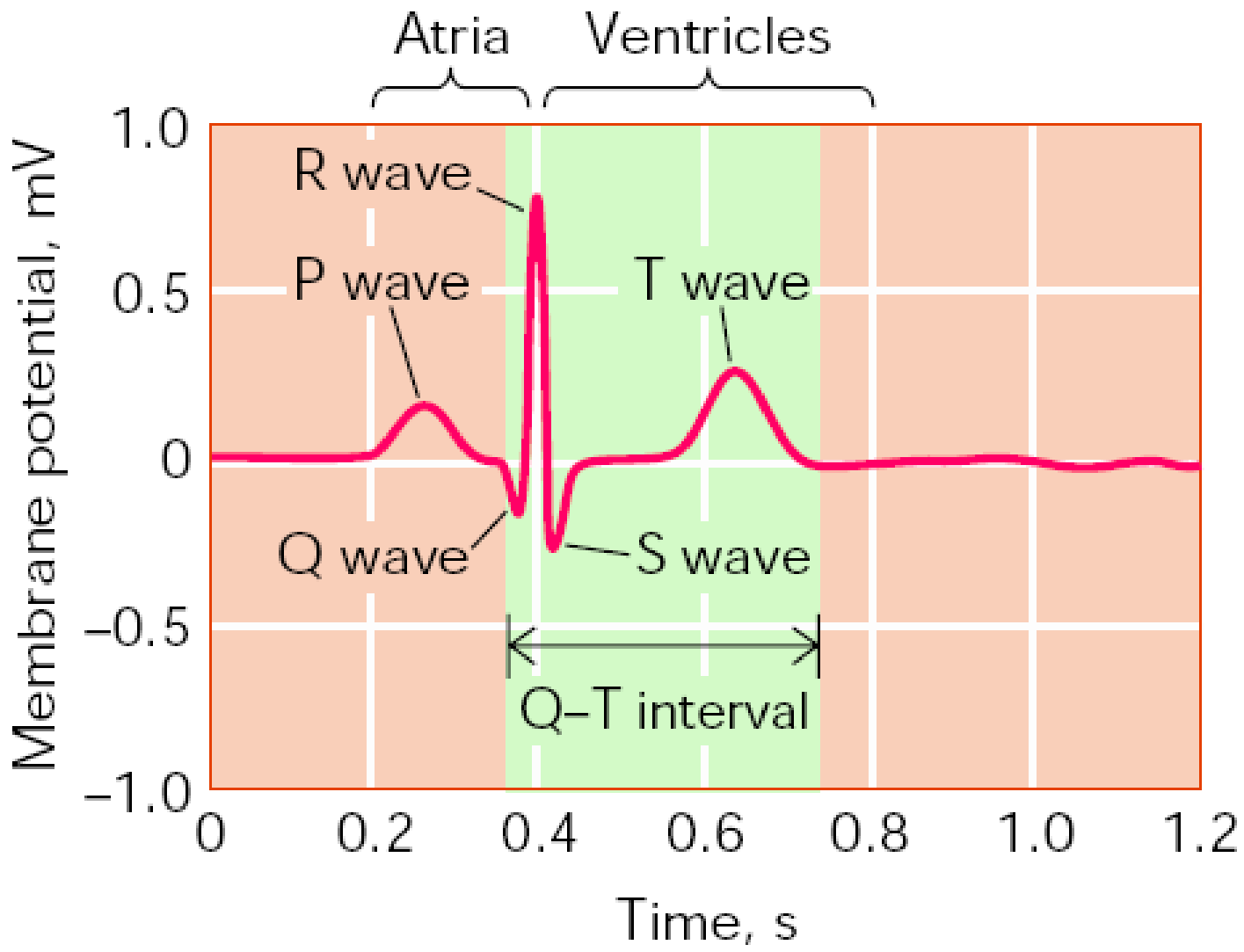
1. Gly 1306 Ala
2. Ser 804 Phe
3. Gly 1306 Glu

HYPOKALEMIC PARALYSIS

1. Arg 669 His

Genetic disorders of Cardiac Arrhytmias

* *Each heartbeat initiated by a depolarization in pacemaker cells spreads through the heart.*
* *Cardiac action potential is much longer than neuronal one due to long lasting opening of the calcium channels.*

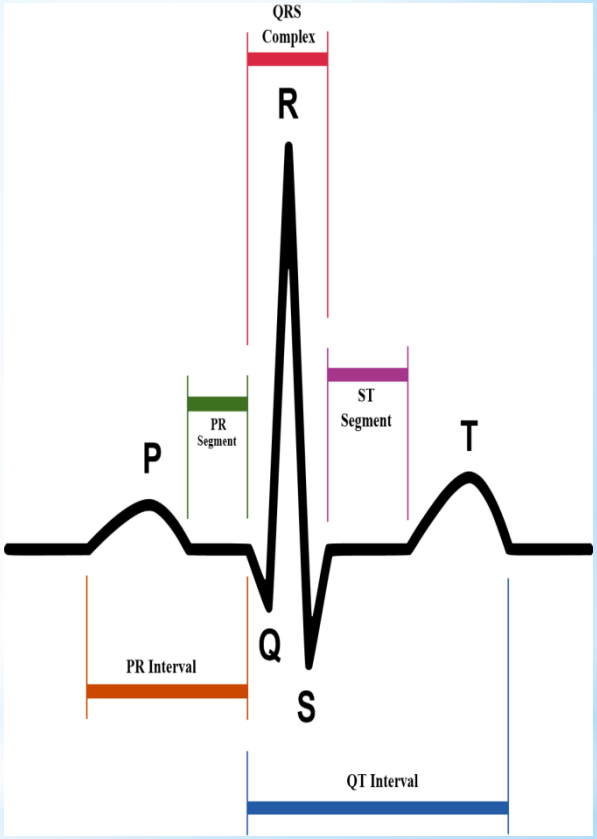

Atria
Ventricles
1.0
0.5
0
−0.5
−1.0
Membrane potential, mV
R wave
P wave
T wave
Q wave
S wave
Q–T interval
0
0.2
0.4
0.6
0.8
1.0
1.2
Time, s

* *The fast initial depolarization is achieved by Nav 1.5 sodium channel coded in SCN5A gene*
* *Mutations leads to sodium channel with incomplete inactivation.*
* *Several different types of potassium channels also contribute repolarization of the cardiac action potentials*
* *KCNQ1/KCNE1 mutation results in long-QT sendrome.*

* LONG QT SYDNROME
* LQTS derives its name from the patients'electrocardiograph which shows a prolongation of the Q and T waves as a result of abnormalities of myocardial repolarization.
* It can cause ventricular arrhythmias, syncope and sudden death in often young and otherwise healthy individuals.
* Mutations in V-gated K channel gene *KCNQ1* were identified as the cause of LQT1-principal delayed rectifying current
* Mutations in an inwardly rectifying potassium channel gene, were identified as the cause of LQT2
* Mutations in the cardiac sodium channel gene *SCN5A*
* were found to cause LQT3

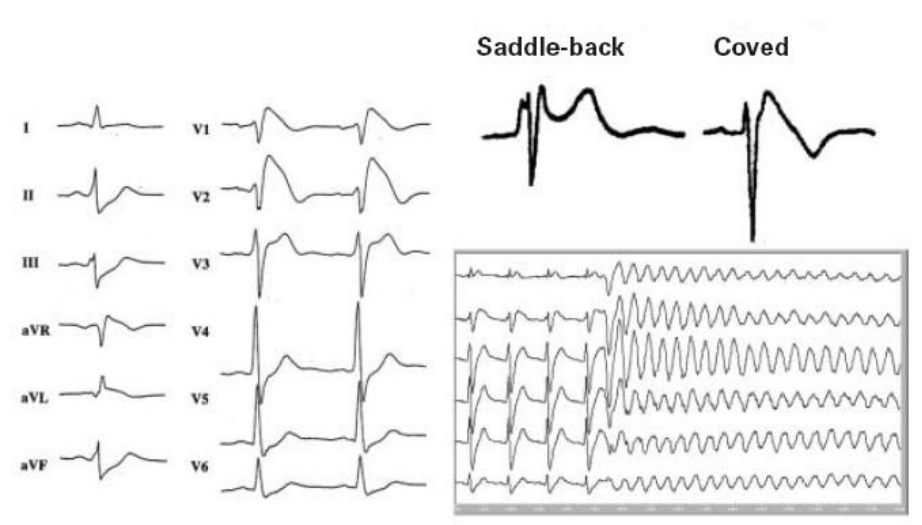
* LQT results from elevated inward depolarizing currents or diminished outward repolarizing currents.
* 1st one is the KCNQ1, slow delayed outward rectifier
* 2nd one is the HERG channel, inwardly rectifying, rapidly activating channel. It effects length of the plateau phase
* 3rd one is the cardiac sodium channel SCN5A

* These mutations tend to prolong the duration of the ventricular action potential (APD), thus lengthening the QT interval.
* LQTS can be inherited in an autosomal dominant or an autosomal recessive fashion.
* The **long QT syndrome** (**LQTS**) is a rare inborn heart condition in which delayed repolarization of the heart following a heartbeat increases the risk of irregular heartbeat and may lead to fainting and sudden death due to ventricular fibrillation



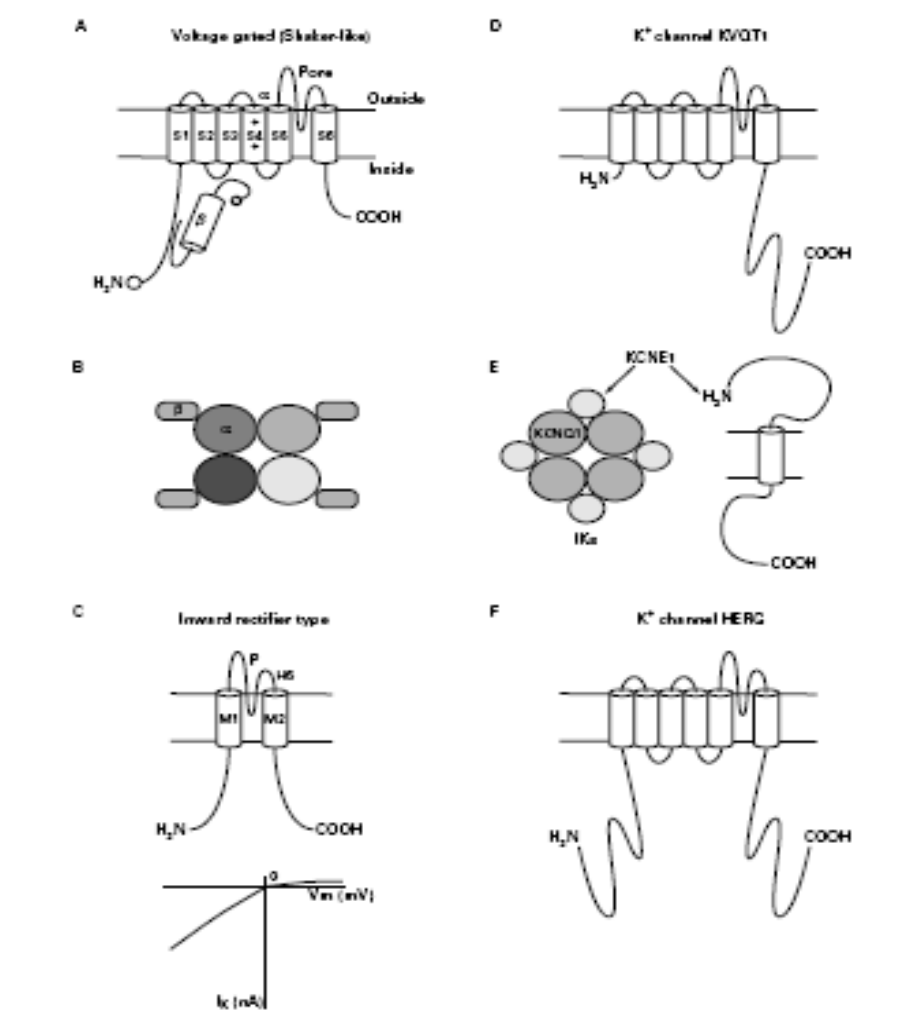
Brugada Syndrome

* *This is an idiopathic cardiac arrhythmia which can lead to a ventricular fibrillation and sudden death*
* *Typical ECG pattern helps diagnosis*
* *Biophysically sodium currents are smaller*
* *20 different genetic mutations has been associated with Brugada syndrome*
* *Recently it was identified that ankyrin-G which anchors Nav1.5 sodium channel*
* *Mutations in ankyrin-G results of loss of binding to sodium channel and results in Brugada syndrome*



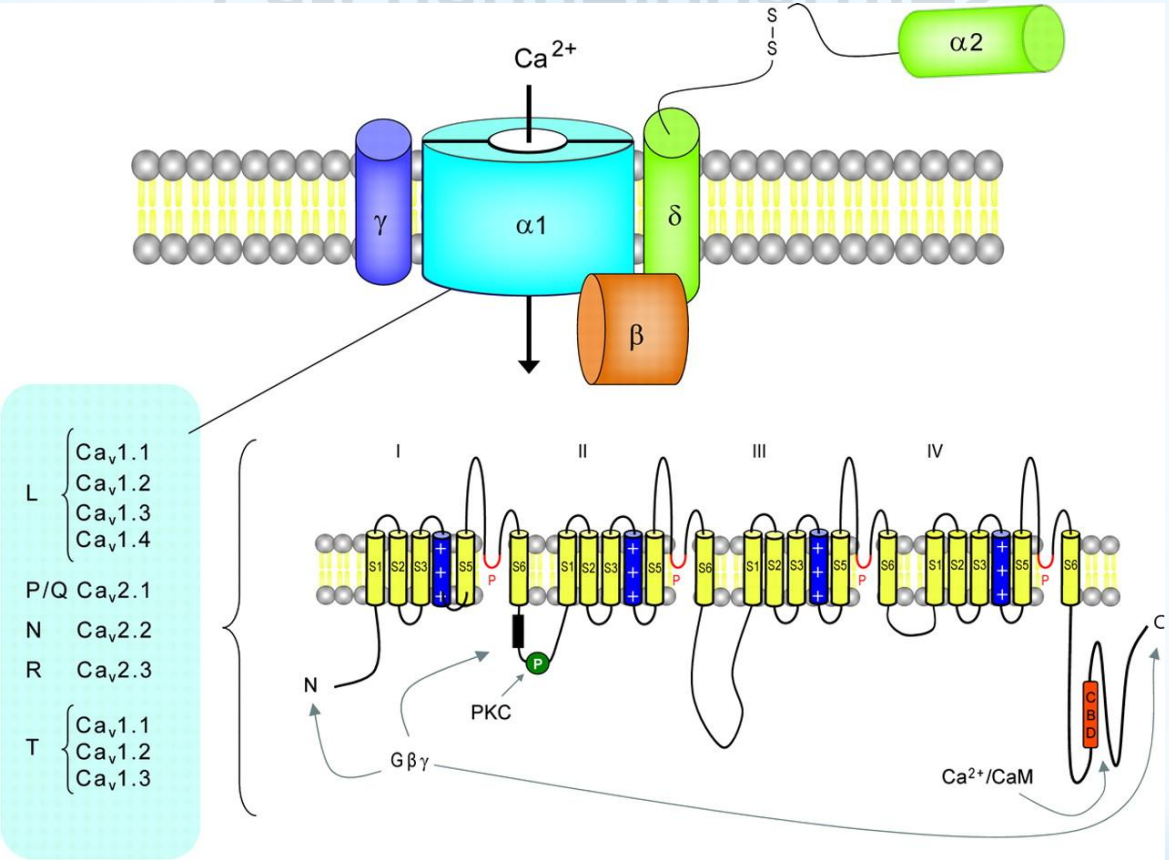
Type	Syndrome	Gene	Protein	Function	Mechanism	Characteristics and triggers	Prevalence in LQTS patients
LQT1	RWS, JLNS	*KCNQ1*	Kv7.1	α subunit I_{Ks}	Loss-of-function	Arrhythmia triggered by exercise, swimming and emotion	40–55%
LQT2	RWS	*KCNH2*	Kv11.1	α subunit I_{Kr}	Loss-of-function	Arrhythmia triggered by sound or emotion	35–45%
LQT3	RWS	*SCN5A*	Nav1.5	α subunit I_{Na}	Gain-of-function	Arrhythmia triggered by sleep, rest and emotion	2–8%
LQT4	RWS	*ANK2*	Ankyrin B	Adaptor ($I_{Na\text{-}K}$, $I_{Na\text{-}Ca}$, I_{Na})	Loss-of-function	Arrhythmia triggered by exercise	< 1%
LQT5	RWS, JLNS	*KCNE1*	minK	β subunit I_{Ks}	Loss-of-function	Arrhythmia triggered by exercise and emotion	< 1%
LQT6	RWS	*KCNE2*	MiRP1	β subunit I_{Kr}	Loss-of-function	Arrhythmia triggered by rest and exercise	< 1%
LQT7	AS	*KCNJ2*	Kir2.1	α subunit I_{K1}	Loss-of-function	Syndromic, arrhythmia triggered by rest and exercise, frequent ectopy	< 1%
LQT8	TS	*CACNA1C*	Cav1.2	α subunit I_{Ca}	Gain-of-function	Syndromic, early onset and death from arrhythmia	< 1%
LQT9	RWS	*CAV3*	M-Caveolin	Adaptor (I_{Na})	Loss-of-function	Rest and sleep triggers arrhythmia	< 1%
LQT10	RWS	*SCN4B*	Navβ4	β subunit I_{Na}	Loss-of-function	Exercise triggers arrhythmia	< 0.1%
LQT11	RWS	*AKAP9*	Yotiao	Adaptor (I_{Ks})	Loss-of-function	Exercise triggers arrhythmia	< 0.1%
LQT12	RWS	*SNTA1*	α_1-Syntrophin	Scaffolding protein (I_{Na})	Loss-of-function	Rest triggers arrhythmia	< 0.1%

Different K-channels



A: V-gated K-channels of Shaker superfamily.
B: A functional tetrameric K-channel
C: Inwardly rectifying K-channels (IRK). H5 and M2 segments are critical for K-permeation
D:V-gated KVLQT1, responsible for long QT syndrome, is expressed in heart
E: V-gated KCNQ1/KCNE1 form the slow cardiac outward delayed rectifier K-current
F: HERG K channel is an inward rectifying voltage dependent channel with rapid and voltage dependent inactivation

* Ca-channelopathies



* Pore forming α_1 subunit (voltage sensing, channel activity), a TM δ subunit disulphide bonded to EC α_2 (membrane localization and modification of ion conducting properties of α_1), an IC β subunit (incorporation of channel to membrane) and in some tissues γ subunit (channel assembly)

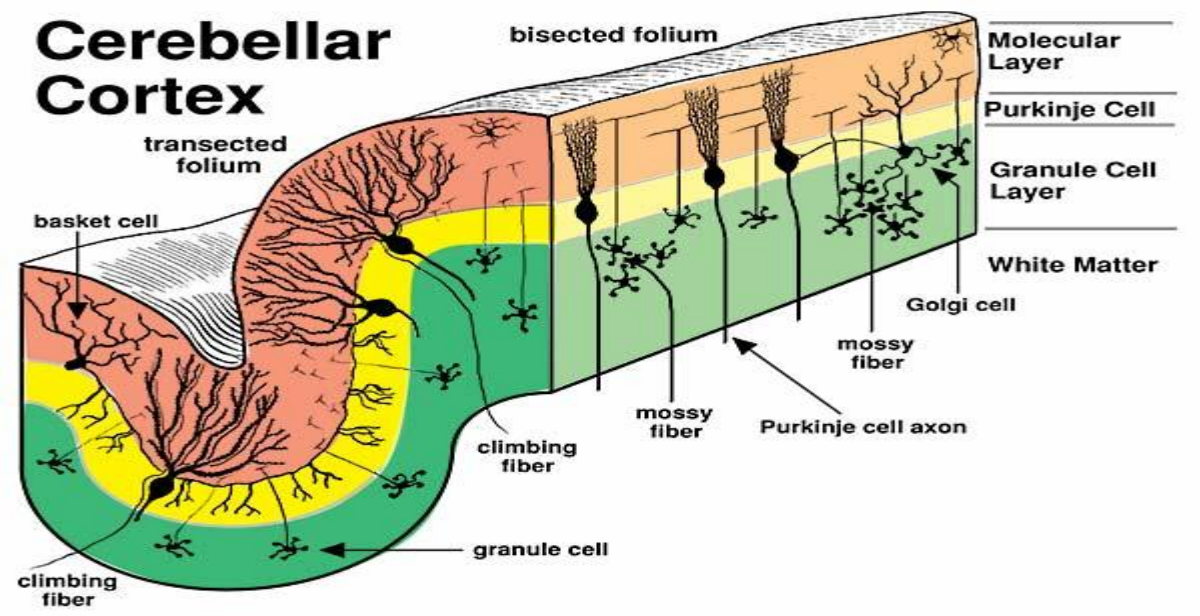
* 6 functionally different types of Ca: L,N,P,Q,R and T.

CACNA1A : episodic ataxia type 2, familial hemiplegic migraine

CACNA1F: X-linked congenital night blindness

CACNA1S: Hypokalemic periodic paralysis

* GENETIC DISORDERS OF NEURAL ION CHANNELS



*The outer molecular layer (brown) has dendrites and axons but few cell bodies. The Purikinje cell layer (yellow) contains large **Purkinje (piriform) neurons**. Axons of Purkinje neurons leave the cerebellar cortex.

Episodic ataxia

* (EA) is an autosomal dominant disorder characterized by sporadic bouts of ataxia (severe discoordination) w/w-myokymia (continuous muscle movements/tremors).
* It is induced by emotion or stress.
* They are a clinically and genetically heterogeneous

* Episodic ataxia with myokymia (EA-1) was the first disorder, that was shown to be due to a mutation in a K- channel gene.
* Attacks last from seconds to minutes. Mutations of the gene KCNA1, which encodes the voltage-gated potassium channel $K_V1.1$, are responsible for Type I episodic ataxia.
* There are currently 17 $K_V1.1$ mutations associated with EA1
* Most of them result in a drastic decrease in the amount of current through $K_V1.1$ channels and slower rates.
* $K_V1.1$ is expressed heavily in basket cells and interneurons that form GABAergic synapses on Purkinje cells.
* It is likely that this mutation results increased and aberrant inhibitory input into Purkinje cells and, thus, disrupted Purkinje cell firing and cerebellum output.

* This abnormality can cause muscle cramping, stiffness, and continuous, fine muscle twitching that appears as rippling under the skin.
* early childhood to adulthood
* can be triggered by environmental factors such as emotional stress, caffeine, alcohol, certain medications, physical activity, and illness

* mutations in the KCNA1, CACNA1A, CACNB4, and SLC1A3 genes alter the transport of ions and glutamate in the brain, which causes certain neurons to become overexcited and disrupts normal communication between these cells.

* Familial Hemiplegic Migraine

* FHM is a rare autosomal dominant subtype of migraine with transient hemiplegia during the aura phase.

FHM type 1 is associated with missense mutations in the CACNA1A gene on chromosome 19p13, encoding the alpha1A subunit of Ca-channels. At least 18 missense mutations identified.

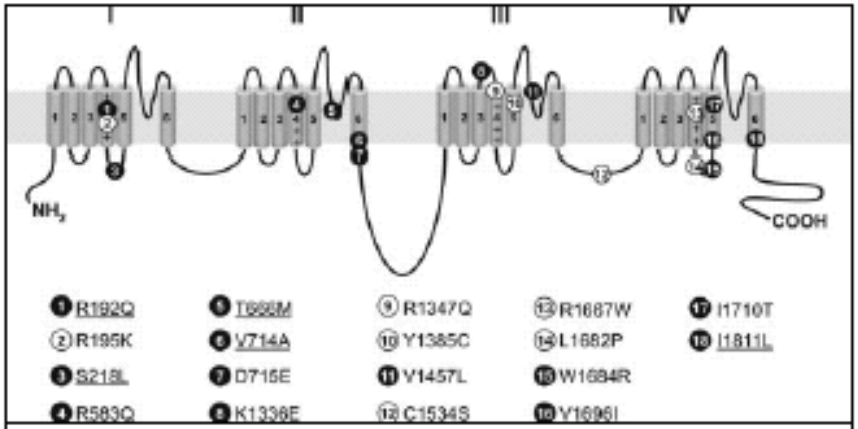


Figure 2

Secondary structure of the Cav2.1 α1 subunit and location of the familial hemiplegic migraine 1 mutations identified so far. In black: mutations whose functional consequences have been studied in heterologous expression systems. Underlined: mutations whose functional consequences have been studied also in transfected neurons from CaV2.1−/− mice, adapted from [6].

* There are 3 types:
* 1- Ca^{2+}-channel work incorrectly time to time
* 2- behaviour of a channel involved in cell energy is changed
* 3- a Na^{+}-channel is altered.

* Paitents will experience a temporary weakness on one side of their body as part of their migraine attack.

* Speech difficulties, vision problems or confusion

* Weakness can last from 1 h to several days

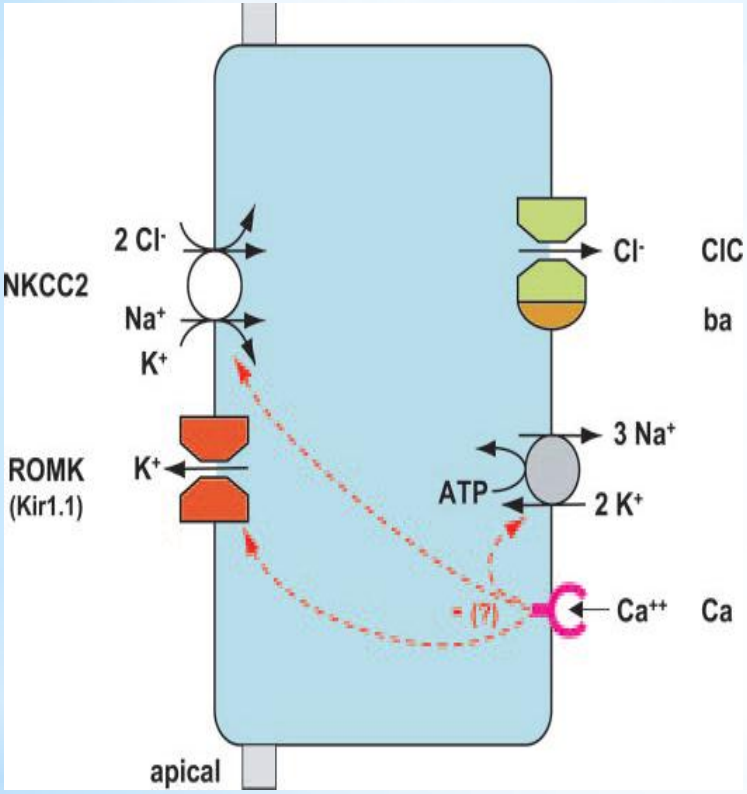
Epilepsy

* In major, pure epilepsies, almost all the genes causing the disease are ion channels
* Several hundred de novo mutations of a single gene, SCN1A, a sodium channel, have already been identified (Kullmann DM, 2010).
* Mainly a severe type in children: severe myoclonic epilepsy of infancy (SMEI).
* Mutations in Na channel, e.g. R1648H, results in altered kinetics in both excitatory and inhibitory neurons
* This leads to aberrant function in the GABAergic interneurons,result in decreased interneuron activity.

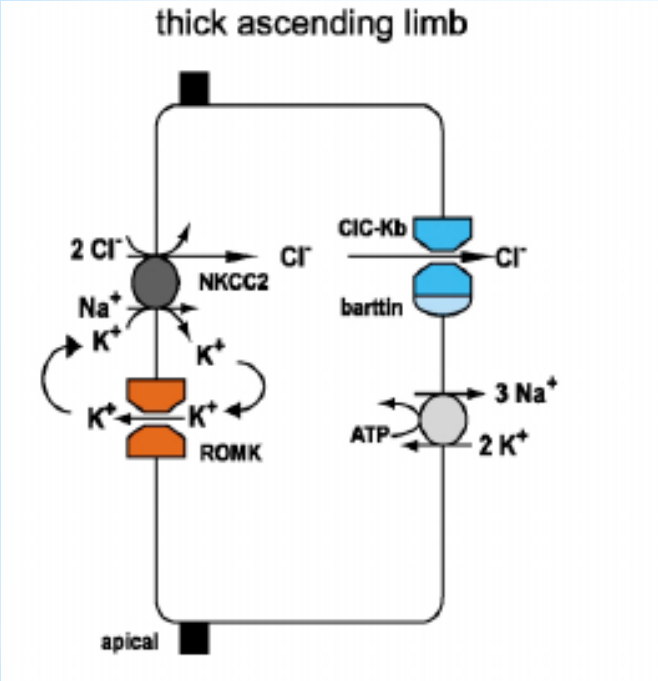
(GABA-mediated inhibition regulates synaptic integration, probability and timing of action potential generation).

GENETIC DISORDERS OF TRANSEPITHELIAL ION CHANNELS

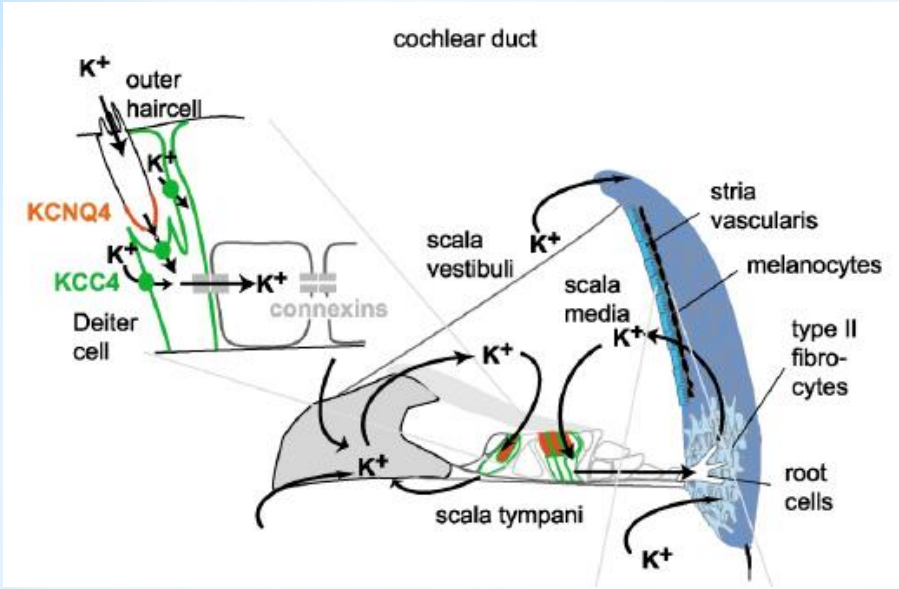
* Bartter syndrome is a group of tubulopathies
* Renal salt wasting, hypokalemic metabolic alkalosis and hyperreninemic hyperaldosteronism with normal blood pressure.
* Autosomal recessive trait:
* A severe antenatal form with or without deafness, and
* Classic Bartter syndromes occur in infancy or early childhood.
* Renal salt loss is caused by impaired transepithelial transport in the thick ascending limb of the loop of Henle.

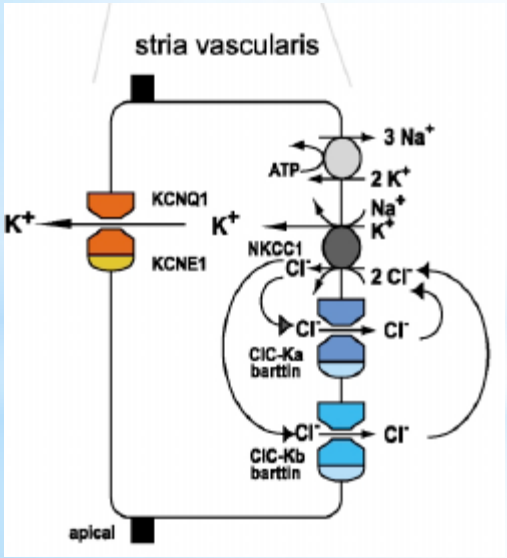


* NaCl reabsorption. Powered by the Na_ gradient established by the basolateral (Na,K)-ATPase, the apical NKCC2 transports Na_, K_, and Cl_ ions into the cell.
* K_ is recycled through apical ROMK (Kir1.1) and Cl_crosses the basolateral membrane through Cl_ channels that are heteromers of pore-forming ClC-Kb subunits and auxiliary barttin subunits. Mutations in the genes encoding NKCC2,
* ROMK, ClC-Kb, and barttin cause Bartter syndrome I to IV.



* Filtered NaCl is taken up through Na-K-2Cl (NKCC2).
* This protein is mutated in severe antenatal forms of Bartter syndrome type I w-/deafness
* K must be recycled over apical membrane ROMK/Kir1.1, and mutations in its gene is the cause of Bartter syndrom type II
* Cl diffuses passively through basolateral ClC-Kb (CLCNKB) . Mutations cause to Bartter syndrome type III





Transport pathway in inner ear:

Hearing depends on high K conc (150 mM) bathing apical membranes of sensory hair cells
During sound stimulation, K enters the hair cells via apical mechanosensitive cation channels, the exit through KCNQ4.
Then this K enters to the strial cells through NKCC1 and the Chloride recycles through ClC-barttin channels.

Loss of KCNQ1, KCNE1, NKCC1 or Barttin causes deafness in humans and mice.

Acquired Channelopathies

* *When peripheral nerve is cut within some days a new family of sodium channel is expressed in the neuronal soma. Neuron becomes more excitable.*
* *Snake, scorpion, anemone, bee, frog, fish venom mediates the toxic effect by severely altering functional properties of various ionic channels.*
* *Inflammation is another factor affecting ion channels.*

Myasthenia gravis

* **Myasthenia gravis** an autoimmune neuromuscular disease leading to fluctuating muscle weakness and fatiguability.
* Weakness is caused by circulating antibodies that block acetylcholine receptors at the postsynaptic neuromuscular junction, inhibiting the excitatory effects of the neurotransmitter acetylcholine on nicotinic receptors throughout neuromuscular junctions.
* Muscles become progressively weaker during periods of activity and improve after periods of rest. Muscles that control eye and eyelid movement, facial expressions, chewing, talking, and swallowing are especially susceptible. The muscles that control breathing and neck and limb movements can also be affected. Often, the physical examination yields results within normal limits.

* In MG, the autoantibodies most commonly act against the nicotinic acetylcholine receptor (nAChR), the receptor in the motor end plate for the neurotransmitter acetylcholine that stimulates muscular contractions.
* In normal muscle contraction, cumulative activation of the nAChR leads to influx of sodium ions. This travels down the cell membranes via t-tubules and, via calcium channel complexes, leads to the release of calcium from the sarcoplasmic reticulum
* Decreased numbers of functioning nAChRs impairs muscular contraction by limiting depolarization.

Lambert Eaton Syndrome

* *Mostly observed in patients with Small cell lung cancer*
* *Progressive weakness is the major symptom*
* *Antibodies against to the presynaptic voltage gated calcium channels in the motor end plate is detected in the blood samples*

Transcriptional channelopathies

* *Results from expression of nonmutated channels*
* *Dysregulated production of normal channel proteins as a result of changes in transcription may perturb the cellular function*

Sodium channels are diverse

* *10 sodium channel genes has been identified in human genome and 9 has been shown to code distinct sodium channels.*
* *They have different voltage-dependence and kinetic properties.*
* *Selective expression of the channels endow the cells with different functional properties.*

Peripheral nerve injury Neuropathic pain

- *The factors triggering changes in sodium channel expression are not fully understood*
- *NGF and GDNF are responsible for expression of Nav1.8 and Nav1.9*
- *Loss of access to peripheral sources of neurotrophic factors is the most probable cause*

Multiple sclerosis

- *Demyelination is the hallmark of MS*
- *Axonal degeneration is also present*
- *Recently a change in sodium channel expression is also observed*
- *In paranodal region sodium channels are present at a low density*
- *Following demylination Nav1.8 expression increases*