Ion Channelopathies

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Human geneticists have revealed a surprisingly large number and diversity of genetic diseases caused by mutations in ion channels. This work began with discovery that paramyotonia congenita and hyperkalemic periodic paralysis are caused by mutations in skeletal muscle sodium channels (Venance et al., 2006), and has expanded to include many different types of diseases (Table below; Ashcroft, 2006). Most often these diseases are dominant, so that only one of the two alleles of the ion channel gene is mutated in patients. These mutations may cause gain or loss of channel function. Moreover, different mutations in the same gene can cause different clinical syndromes because of the different mutational effects. A few examples from sodium channelopathies of the nervous system will serve to illustrate these points.

Three different types of periodic paralysis are caused by different mutations in $Na_V1.4$ channels, the primary sodium channel in skeletal muscle (Venance et al., 2006). Paramyotonia congenita is caused by mutations that have a primary effect of slowing the fast inactivation of sodium channels. The mutations therefore cause these channels to stay open too long and to re-open during repolarization of the action potential, resulting in repetitive firing of action potentials and inappropriately long contractions and re-contractions of skeletal muscle. In contrast, hyperkalemic periodic paralysis is caused by mutations that impair the slow inactivation process of $Na_V1.4$ channels and therefore cause muscle depolarization, action potential block, and paralysis.

Chronic pain is caused by gain-of-function mutations in $Na_V1.7$ channels, which are important for action potential generation and conduction in pain-sensing neurons in dorsal root ganglia (Dib-Hajj et al., 2010). Impairment of the fast-inactivation process of these sodium

channels leads to paroxysmal extreme pain disorder, characterized by intense pain in the rectum, eyes, and mouth. In contrast, mutations that alter the voltage dependence of both activation and slow inactivation of these channels cause inherited erythromelalgia, characterized by burning pain in the extremities. Remarkably, rare families in which both alleles of the $Na_V1.7$ gene have loss-of-function mutations have congenital indifference to pain, in which all sensation of pain is lost. This recessive genetic disease is a serious problem for affected children, who injure themselves without realizing that it is harmful.

Epilepsy is caused by uncontrolled electrical signaling in the brain. Mutations of $Na_V1.1$ channels, one of the three sodium channel types expressed in adult brain, cause multiple clinical forms of epilepsy in children (Catterall et al., 2010). Surprisingly, the most severe form of this group of diseases, severe myoclonic epilepsy of infancy, is caused by loss-of-function mutations that act in a dominant manner. Because sodium channels initiate the action potential, it might be expected that loss-of-function mutations in epilepsy could only reduce electrical excitability. However, studies of this disease in mutant mice have shown that mutation of $Na_V1.1$ channels primarily impairs firing of GABAergic inhibitory neurons (see Chapter 18), which disinhibits action potential firing by excitatory neurons and causes epilepsy (Catterall et al., 2010). In this case, gain-of-function effects on excitability arise at the cellular level because of this failure of inhibitory neuron function.

As the examples from sodium channelopathies of the nervous system shown in the Table below reveal, there is a diversity of mechanisms at both molecular and cellular levels through which mutations in ion channels can cause disease.

Disease Type	Ion Channel Family	Disease Name	Ion Channel Protein	Gene

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Epilepsy	Na_V Channel	Severe myoclonic epilepsy of infancy	$Na_V1.1$	SCN1A
		Generalized epilepsy with febrile seizures plus	$Na_V1.1$	SCN1A
		Benign familial neonatal-infantile seizures	$Na_V1.2$	SCN2A
	K_V Channel	Benign familial neonatal seizures	$K_V7.2$	KCNQ2
			$K_V7.3$	KCNQ3
	K_{Ca} Channel	Generalized epilepsy with paroxysmal dyskinesia	$K_{Ca}1.1$	KCNMA1
Pain	Na_V Channel	Familial erythromelagia	$Na_V1.7$	SCN9A
		Paroxysmal extreme pain disorder	$Na_V1.7$	SCN9A
		Congenital indifference to pain	$Na_V1.7$	SCN9A
Migraine Headache	Na_V Channel	Familial hemiplegic migraine type 2	$Na_V1.1$	SCN1A
	Ca_V Channel	Familial hemiplegic migraine type 1	$Ca_V2.1$	CACNA1A
Ataxia	K_V Channel	Episodic ataxia type 1	$K_V1.1$	KCNA1
	Ca_V Channel	Episodic ataxia type 2	$Ca_V2.1$	CACNA1A
		Spinocerebellar ataxia type 6	$Ca_V2.1$	CACNA1A

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Mucolipidosis	TRP Channel	Mucolipidosis IV	TRPML1	MCOLN1
Blindness	Ca_V Channel	Congenital stationary night blindness	Ca_V1.4	CACNA1F
	CNG Channel	Retinitis pigmentosa	CNGA1	CNGA1
	CNG Channel	Achromatopsia types 2 and 3	CNGA3, CNGB3	CNGA3, CNGB3
Deafness	K_V Channel	Nonsyndromic dominant deafness	K_V7.4	KCNQ4
Periodic Paralysis	Na_V Channel	Paramyotonia congenita	Na_V1.4	SCN4A
		Hyperkalemic periodic paralysis	Na_V1.4	SCN4A
		Hypokalemic periodic paralysis type 2	Na_V1.4	SCN4A
	Ca_V Channel	Hypokalemic periodic paralysis type 1	Ca_V1.1	CACNA1S
Cardiac Arrhythmia	Na_V Channel	Brugada syndrome	Na_V1.5	SCN5A
	K_V Channel	Long QT syndrome type 3	Na_V1.5	SCN5A
		Long QT syndrome type 1 (plus deafness)	K_V7.1	KCNQ1
		Long QT syndrome type 2		KCNH2
	Ca	Timothy syndrome (long QT interval plus developmental defects	Ca_V	CA

Disease Type	Ion Channel Family	Disease Name	Ion Channel Protein	Gene
	$_{V}$ Channel	and autism)	1.2	CNA1C
	Kir Channel	Andersen-Tawil syndrome (cardiac arrhythmia with developmental defects and periodic paralysis)	Kir 2.1	KCNJ2
Kidney Failure	Kir Channel	Bartter's syndrome (salt-wasting)	Kir 1.1	KCNJ1
	TRP Channel	Autosomal dominant polycystic kidney disease	TRPP2	TRPP2
		Focal segmental glomerulosclerosis	TRPC6	TRPC6
Hyperinsulinemia and Diabetes	Kir Channel	Congenital hyperinsulinemia	Kir 6.2	KCNJ11
		Neonatal diabetes	Kir 6.2	KCNJ11