genetic sequence of DNA but rather by postgenomic alterations in DNA and chromatin structure, which influence how, when, and where genes are expressed. DNA methylation and methylation and acetylation of histone proteins that interact with nuclear DNA to form chromatin are key mediators of these events. Epigenetic processes appear to be dynamically active even in postmitotic neurons. *Imprinting* refers to an epigenetic feature, present for a subset of genes, in which the predominant expression of one allele is determined by its parent of origin. The distinctive neurodevelopmental disorders Prader-Willi syndrome (mild mental retardation and endocrine abnormalities) and Angelman's syndrome (cortical atrophy, cerebellar dysmyelination, Purkinje cell loss) are classic examples of imprinting disorders whose distinctive features are determined by whether the paternal or maternal copy of the chromosome of the critical genetic region 15q11-13 is responsible. In a study of discordant monozygotic twins for MS in which the entire DNA sequence, transcriptome (e.g., mRNA levels), and methylome were assessed genome-wide, tantalizing allelic differences in the use of the paternal, compared to maternal, copy for a group of genes were identified. Preferential allelic expression, whether due to imprinting, resistance to X-inactivation, or other mechanisms, is likely to play a major role in determining complex behaviors and susceptibility to many neurologic and psychiatric disorders.

Another advance is the development of transgenic mouse models of neurologic diseases, which has been particularly fruitful in producing models relevant to Alzheimer's disease, Parkinson's disease, Huntington's disease, and ALS. These models are useful in both studying disease pathogenesis and developing and testing new therapies. New transgenic mouse models with conditional expression have fostered investigations in which late gene expression avoids developmental compensation or in which the reversibility of a disease phenotype can be examined by turning a gene off after the disease phenotype has manifested. One can also examine the effects of gene expression in specific subsets of neurons, such as entorhinal cortex, or selectively in neurons, astrocytes, or microglia. Models in both *Caenorhabditis elegans* and *Drosophila* have also been extremely useful, particularly in studying genetic modifiers and therapeutic interventions.

TABLE 444e-1 EXAMPLES OF NEUROLOGIC CHANNELOPATHIES

Category	Disorder	Channe 1 Type	Mutated Gene	Chap. Ref.
Genetic				
Ataxias	Episodic ataxia-1	K	*KCNA1*	450
	Episodic ataxia-2	Ca	*CACNL1A*	
	Spinocerebellar ataxia-6	Ca	*CACNL1A*	
Migraine	Familial hemiplegic migraine 1	Ca	*CACNL1A*	447
	Familial hemiplegic migraine 2	Na	*SCN1A*	
Epilepsy	Benign neonatal familial convulsions	K	*KCNQ2, KCNQ3*	445
		Na	*SCN1B*	
	Generalized epilepsy with febrile convulsions plus			
Periodic paralysis	Hyperkalemic periodic paralysis	Na	*SCN4A*	462e
		Ca	*CACNL1A3*	
	Hypokalemic periodic paralysis			
Myotonia	Myotonia congenita	Cl	*CLCN1*	462e
	Paramyotonia congenita	Na	*SCN4A*	
Deafness	Jervell and Lange-Nielsen syndrome (deafness, prolonged QT interval, and arrhythmia)	K	*KCNQ1, KCNE1*	43
	Autosomal dominant progressive deafness	K	*KCNQ4*	
Autoimmune				
Paraneoplastic	Limbic encephalitis	Kv1	—	122
	Acquired neuromyotonia	Kv1	—	
	Cerebellar ataxia	Ca (P/Q type)	—	
	Lambert-Eaton syndrome	Ca (P/Q type)	—	

ION CHANNELS AND CHANNELOPATHIES

The resting potential of neurons and the action potentials responsible for impulse conduction are generated by ion currents and ion channels. Most ion channels are gated, meaning that they can transition between conformations that are open or closed to ion conductance. Individual ion channels are distinguished by the specific ions they conduct; by their kinetics; and by whether they directly sense voltage, are linked to receptors for neurotransmitters or other ligands such as neurotrophins, or are activated by second messengers. The diverse characteristics of different ion channels provide a means by which neuronal excitability can be exquisitely modulated at both the cellular and the subcellular levels. Disorders of ion channels—channelopathies—are responsible for a growing list of human neurologic diseases (Table 444e-1). Most are caused by mutations in ion channel genes or by autoantibodies against ion channel proteins. One example is epilepsy, a syndrome of diverse causes characterized by repetitive, synchronous firing of neuronal action potentials. Action potentials are normally generated by the opening of sodium channels and the inward movement of sodium ions down the intracellular concentration gradient. Depolarization of the neuronal membrane opens potassium channels, resulting in outward movement of potassium ions, repolarization, closure of the sodium channel, and hyperpolarization. Sodium or potassium channel subunit genes have long been considered candidate disease genes in inherited epilepsy syndromes, and recently such mutations have been identified. These mutations appear to alter the normal gating function of these channels, increasing the inherent excitability of neuronal membranes in regions where the abnormal channels are expressed.

Whereas the specific clinical manifestations of channelopathies are quite variable, one common feature is that manifestations tend to be intermittent or paroxysmal, such as occurs in epilepsy, migraine, ataxia, myotonia, or periodic paralysis. Exceptions are clinically progressive channel disorders such as autosomal dominant hearing impairment. The genetic channelopathies identified to date are all uncommon disorders caused by obvious mutations in channel genes. As the full repertoire of human ion channels and related proteins is identified, it is likely that additional channelopathies will be discovered. In addition to rare disorders that result from obvious mutations, it is also likely that less penetrant allelic variations in channel genes or in their pattern of expression might underlie susceptibility to some apparently sporadic forms of epilepsy, migraine, or other disorders. For example, mutations in the potassium channel gene *Kir2.6* have been found in many individuals with thyrotoxic hypokalemic periodic paralysis, a disorder similar to hypokalemic periodic paralysis but precipitated by stress from thyrotoxicosis or carbohydrate loading.

NEUROTRANSMITTERS AND NEUROTRANSMITTER RECEPTORS

Synaptic neurotransmission is the predominant means by which neurons communicate with each other. Classic neurotransmitters are synthesized in the presynaptic region of the nerve terminal; stored in vesicles; and released into the synaptic cleft, where they bind to receptors on the postsynaptic cell. Secreted neurotransmitters are eliminated by reuptake into the presynaptic neuron (or glia), by diffusion away from the synaptic cleft, and/or by specific inactivation. In addition to the classic neurotransmitters, many neuropeptides have been identified as definite or probable neurotransmitters; these include substance P, neurotensin, enkephalins, β-endorphin, histamine, vasoactive intestinal polypeptide, cholecystokinin, neuropeptide Y, and somatostatin.