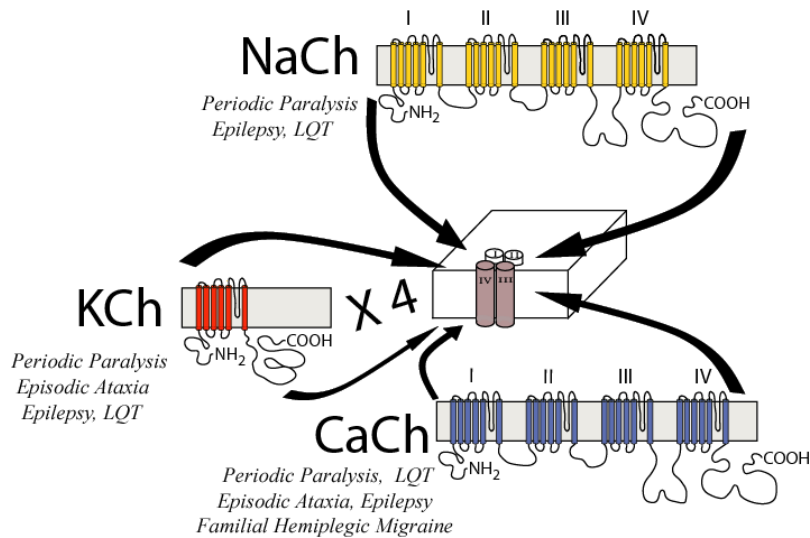


A Gene Causing Migraine with Aura

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Episodic neurological phenotypes—seemingly unrelated disorders, such as the periodic paralyses, nondystrophic myotonias, episodic ataxias, paroxysmal dyskinesias, long QT syndrome, epilepsy, and migraine—have a range of similarities. For example, affected individuals are often healthy between attacks, and stress, fatigue, and various dietary factors frequently precipitate attacks. The conditions tend to begin in infancy or childhood and to worsen through adolescence and young adult life. In some cases, they decrease in severity and frequency in middle to late adult life. They often respond to identical pharmacotherapeutic interventions (eg, carbonic anhydrase inhibitors for periodic paralysis, episodic ataxia, and migraine). Several syndromes featuring episodic or electrophysiologic phenomena involve multiple organ systems or central nervous system phenotypes. Patients with episodic ataxia type 1 can have attacks of paroxysmal kinesigenic dyskinesia, an episodic movement disorder precipitated by sudden movements that frequently affects infants with benign convulsions prior to the development of the disease.² Migraine may be part of the clinical constellation in patients with paroxysmal nonkinesigenic dyskinesia.³

The periodic paralyses and nondystrophic myotonias were the first human disorders to be characterized as defects in voltage-gated ion channels.^{4,5} Many episodic and electrophysiologic disorders affecting the nervous system result from mutations in members of these (and other) ion channel gene families. For instance, hyperkalemic periodic paralysis, hypokalemic periodic paralysis, paramyotonia congenita, potassium-aggravated myotonia, Andersen-Tawil syndrome, Thomsen myotonia congenita, and Becker myotonia congenita are caused by mutations in voltage-gated sodium, calcium, potassium, and chloride channel genes.¹



Mutations in homologs of these channels have subsequently been shown to cause episodic ataxia, long QT syndrome, mendelian forms of epilepsy, and familial hemiplegic migraine (FHM), which has been traced to mutations in *CaCNA1A* (calcium channel), *ATP1A* (Na⁺/K⁺ ATPase), and *SCN1A* (Na⁺ channel). Moreover, these mutations are not limited to voltage-gated channels; they have also been found in ligand-gated channels, transporters, and exchangers.^{4,5} It is fascinating that multiple phenotypes can result from different mutations in a single ion channel gene, and that different ion channel genes, when mutated, can give rise to phenotypes that are clinically indistinguishable.¹

Familial Advanced Sleep Phase Syndrome (FASPS)—a rare, sporadic disorder caused by a mutation in casein kinase 1-delta (*CK1δT44A*)—is characterized by a profound phase advance of the sleep-wake, melatonin, and temperature rhythms associated with a very short tau.^{6,7} Patients routinely fall asleep between 4:00 p.m. and 6:00 p.m. and experience relatively normal sleep duration and architecture. About one third of those with ASPS are older than 65. The trait segregates as an autosomal dominant with high penetrance. Studies of genetic behaviors have been hampered by the complexity of behavioral phenotypes, and FASPS was identified mainly because of a very dramatic advance of the sleep phase that was recognized in a single individual. Subsequent identification of FASPS in a large cohort of FASPS families provided an opportunity to search for genes and variants that cause period alterations as well as phase angle of entrainment variants in the general population, a unique opportunity for genetic analysis of human circadian physiology.⁸

Several lines of evidence support a causative role for *CK1δT44A* in migraine. First, the mutation causes a familial syndrome in which migraine with aura is co-expressed with flushing, myalgias, asthma, and ASPS.^{6,7,9} In addition, mice transgenic for human *CK1δT44A* have a significantly decreased threshold for CSD and a significantly increased number of CSD events per level of stimulus compared with controls.¹⁰ Finally, *CK1δT44A* mice exhibit a dose-dependent and prolonged NTG-induced thermal and mechanical allodynia that is alleviated by sumatriptan.¹¹

Knowledge gained from molecular characterization of rare genetic disorders is informing studies of the genetically and clinically more complex diseases. Molecular characterization of all of these disorders is shedding light on pathophysiology and will ultimately lead to better diagnosis and treatment of patients.

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