TABLE 462e-10 CLINICAL FEATURES OF PERIODIC PARALYSIS AND NONDYSTROPHIC MYOTONIAS

	Calcium Channel	Sodium Channel		Potassium Channel
Feature	**Hypokalemic PP**	**Hyperkalemic PP**	**Paramyotonia Congenita**	**Andersen-Tawil Syndrome[a]**
Mode of inheritance	AD	AD	AD	AD
Age of onset	Adolescence	Early childhood	Early childhood	Early childhood
Myotonia[b]	No	Yes	Yes	No
Episodic weakness	Yes	Yes	Yes	Yes
Frequency of attacks of weakness	Daily to yearly	May be 2–3/d	With cold, usually rare	Daily to yearly
Duration of attacks of weakness	2–12 h	From 1–2 h to >1 d	2–24 h	2–24 h
Serum K^+ level during attacks of weakness	Decreased	Increased or normal	Usually normal	Variable
Effect of K^+ loading	No change	Increased myotonia, then weakness	Increased myotonia	No change
Effect of muscle cooling	No change	Increased myotonia	Increased myotonia, then weakness	No change
Fixed weakness	Yes	Yes	Yes	Yes

[a]Dysmorphic features and cardiac arrhythmias are distinguishing features (see text). [b]May be paradoxical in paramyotonia congenita.

Abbreviations: AD, autosomal dominant; PP, periodic paralysis.

In the midst of an attack of weakness, motor conduction studies may demonstrate reduced amplitudes, whereas EMG may show electrical silence in severely weak muscles. In between attacks, the EMG and routine nerve conduction studies are normal. However, a long exercise test may demonstrate a decrementing amplitude, and myopathic MUAPs may be seen on EMG in patients with fixed weakness.

HypoKPP is caused by mutations in either of two genes. HypoKPP type 1, the most common form, is inherited as an autosomal dominant disorder with incomplete penetrance. These patients have mutations in the voltage-sensitive, skeletal muscle calcium channel gene, *CALCL1A3* (Fig. 462e-8). Approximately 10% of cases are HypoKPP type 2, arising from mutations in the voltage-sensitive sodium channel gene (*SCN4A*). In either instance, the mutations lead to an abnormal gating pore current that predisposes the muscle cell to depolarize when potassium levels are low. It is also now recognized that some cases of thyrotoxic HypoKPP are caused by genetic variants in a potassium channel (Kir 2.6), whose expression is regulated by thyroid hormone.

The chloride channel is envisioned to have 10 membrane-spanning domains. The positions of mutations causing dominantly and recessively inherited myotonia congenita are indicated, along with mutations that cause this disease in mice and goats.

TREATMENT HYPOKALEMIC PERIODIC PARALYSIS

The acute paralysis improves after the administration of potassium. Muscle strength and ECG should be monitored. Oral KCl (0.2–0.4 mmol/kg) should be given every 30 min. Only rarely is IV therapy necessary (e.g., when swallowing problems or vomiting is present). Administration of potassium in a glucose solution should be avoided because it may further reduce serum potassium levels. Mannitol is the preferred vehicle for administration of IV potassium. The long-term goal of therapy is to avoid attacks. This may reduce late-onset, fixed weakness. Patients should be made aware of the importance of a low-carbohydrate, low-sodium diet and consequences of intense exercise. Prophylactic administration of acetazolamide (125–1000 mg/d in divided doses) reduces or may abolish attacks in HypoKPP type 1. Paradoxically the potassium is lowered, but this is offset by the beneficial effect of metabolic acidosis. If attacks persist on acetazolamide, oral KCl should be added. Some patients require treatment with triamterene (25–100 mg/d) or spironolactone (25–100 mg/d). However, in patients with HypoKPP type 2, attacks of weakness can be exacerbated with acetazolamide.

SODIUM CHANNEL DISORDERS OF MUSCLE

Hyperkalemic Periodic Paralysis (HyperKPP) The term *hyperkalemic* is misleading because patients are often normokalemic during attacks.

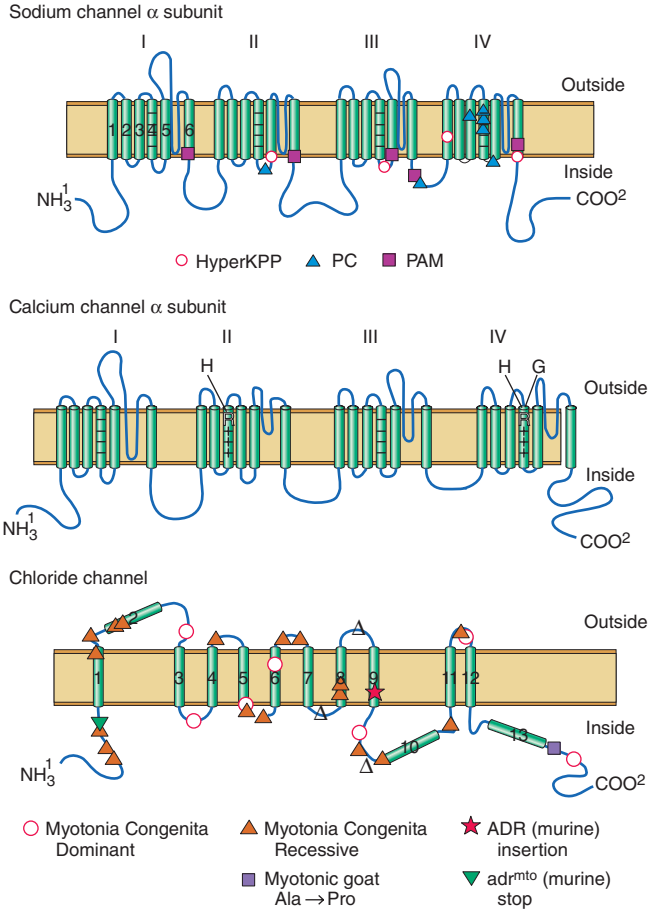

FIGURE 462e-8 The sodium and calcium channels are depicted here as containing four homologous domains, each with six membrane-spanning segments. The fourth segment of each domain bears positive charges and acts as the "voltage sensor" for the channel. The association of the four domains is thought to form a pore through which ions pass. Sodium channel mutations are shown along with the phenotype that they confer. HyperKPP, hyperkalemic periodic paralysis; PC, paramyotonia congenita; PAM, potassium-aggravated myotonia. See text for details.