Paramyotonia Congenita and Skeletal Sodium Channelopathy

Key words: paramyotonia congenita, skeletal muscle sodium channel, hyperkalemic periodic paralysis, sodium channel myotonias

Paramyotonia congenita, the major characteristics of which are cold-induced and exercise-induced myotonia, is an autosomal-dominant muscle disease which is classified into one of a group of muscle diseases, so-called muscle “sodium channelopathies” caused by missense mutations in the gene coding for the skeletal muscle sodium channel α-subunit (SCN4A) (1-4). Such muscle sodium channelopathies share a common abnormality of muscle membrane excitability, which could be expressed as myotonia or weakness. These channelopathies include three allelic disorders, namely paramyotonia congenita, hyperkalemic periodic paralysis and sodium channel myotonias (1-3, 5).

These mutations of the skeletal muscle sodium channel causing sodium channelopathies all exhibit gain-of-function defects. The pathophysiology of sodium channelopathies is currently considered as follows. In the sodium channelopathies of skeletal muscle, the mutant sodium channels pass more Na⁺ current through the muscle membrane than normal, mostly due to an impairment of fast inactivation of the mutant sodium channels, resulting in either slight depolarization with hyperexcitability (myotonia) or sustained depolarization with inexcitability (paresis) (1, 2, 4, 5). In regard to paramyotonia congenita, the mutant sodium channels mostly show abnormalities of channel gating with a slowing of the rate of fast inactivation and with an acceleration of the rate of recovery from inactivation (1, 2, 4, 5), whereby they spend less time in the inactivated state, resulting in a persistent inward Na⁺ current that promotes excessive membrane depolarization and abnormal trains of myotonic potentials (6).

SCN4A contains four repeated domains, designated D1–

![Diagram of the human skeletal muscle sodium channel α subunit showing mutations (1).](image)

Figure 1. Model of the human skeletal muscle sodium channel α subunit showing mutations (1).
D4, each of which occupies a quarter section of the channel. A domain contains six membrane spanning α-helical segments, S1–S6, together forming the structure surrounding the pore through which ion passes. The S4 segments of each domain probably acts as the voltage sensor for opening the gate, and the invaginated stretch of amino acids joining the S5 and S6 segments (P segment) on the outer surface of the membrane likely line the pore itself. All portions spanning the membrane are exclusively or predominantly hydrophobic, except the P segment and every third amino acid in the S4 segment. The channel is designed to open and close in response to an electrical potential change in the cell membrane (‘voltage gating’), and occlusion of the voltage-gated sodium channel probably occurs on the inner membrane surface through folding of the cytoplasmic loop between the third and fourth domains (ID3–4 loop) into the pore (1).

At least 17 different mutations in the SCN4A gene on chromosome 17q23–25 have been found in skeletal sodium channelopathies (1). Although there is generally little correlation between the position of a mutation in the channel and the phenotype, mutations of the inactivation gate (ID3–4 loop) of the channel tend to produce paramyotonia congenita or myotonia fluctuans/permanens (Fig. 1). In this issue, Nakamura et al (7) reported a Japanese family with quite typical clinical features of paramyotonia congenita and Thr1313Met mutation in SCN4A gene, the position of which is located in ID3–4 loop.

See also p 856.

This mutation detected in their patients was described first by McClatchey et al (8), and since then it has been reported exclusively in paramyotonia congenita. The expression of muscle sodium channelopathies depends on the structure and polarity of substituted amino acids at a mutation site, which may partly play a role in phenotypic variability. In addition, there may be other factors influencing disease expression, including genetic polymorphisms elsewhere, effects of other types of muscle ion channels, and so on (1).

It is extremely important to diagnose muscle sodium channelopathies by clinical findings and DNA analysis, not only for treatment but also for prevention of complications during anesthesia and surgery, which load special risks for patients with such diseases mostly by precipitating myotonia. If we realize that the patient is suffering from one of the muscle sodium channelopathies, propofol (6), the effects of which would be expected to decrease the membrane hyperexcitability caused by sodium channel mutations, should be selected as an anesthetic agent rather than the use of depolarizing neuromuscular blocking agents such as succinylcholine or thiamylal which both precipitate generalized myotonia.

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References