

Myotonia Fluctuans

A Third Type of Muscle Sodium Channel Disease

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Objectives: To define a new type of dominant myotonic muscle disorder and to identify the gene lesion.

Design: Case series, clinical examination and electromyography, measurements of grip force and relaxation time, and DNA analysis to probe for mutation in the gene for the skeletal muscle sodium channel.

Setting: Outpatient clinic and home.

Patients: Three families studied; all together, 17 affected and nine unaffected individuals.

Results: The findings in these three families confirm the existence of myotonia fluctuans as we described it previously in another family. Myotonia (prolongation of relaxation time) developed 20 to 40 minutes after exer-

cise. Potassium caused generalized myotonia. Cooling had no major effect on muscle function. Three families had a common mutation in exon 22 and one family had a mutation in exon 14 of the gene for the sodium channel α subunit.

Conclusions: Myotonia fluctuans is a disorder of the muscle sodium channel. There are at present two other distinct clinical muscle disorders associated with mutations in the sodium channel: hyperkalemic periodic paralysis and paramyotonia congenita. The findings in the present report indicate that myotonia fluctuans belongs to a third type of sodium channel disorder. Further work is needed to understand the complex genotype-phenotype correlations in sodium channel disorders.

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IN 1990 WE DESCRIBED an autosomal dominant muscle disorder that had several characteristic features: (1) fluctuating myotonia of varying severity; (2) a "warm-up" phenomenon on days in which myotonia was present; (3) no episodes of weakness and no weakness after potassium loading, after exercise, or after muscle cooling; (4) increased myotonia of delayed onset following exercise; (5) increased myotonia after ingestion of potassium; and (6) no significant increase in myotonia following exposure to cold. We have named this disorder myotonia fluctuans¹ and subsequently others have described a family with this pattern of findings.² In our initial report we presented clinical and laboratory findings to distinguish myotonia fluctuans from myotonia congenita of Thomsen and from paramyotonia. Recently studies localized the gene for myotonia congenita to the segment of chromosome 7 carrying the chloride channel³ and very recently mutations in the gene for the skeletal muscle chloride channel have been shown to cause myotonia con-

genita of Thomsen.⁴ Other investigations have shown that specific mutations in the gene for the α subunit of the skeletal muscle sodium channel appear to account for both hyperkalemic periodic paralysis and paramyotonia congenita.⁵⁻⁸ As a result of these discoveries, we decided to carry out detailed clinical evaluations in three new families with myotonia fluctuans and to perform DNA analysis in these three families and in our original family.¹

In addition to the families described by us previously¹ and to those in the present report, other patients have been described with mutations of the gene for the skeletal muscle sodium channel whose symptoms resemble a mixture of myotonia congenita and paramyotonia.⁹⁻¹² These additional cases combined with those that we have described suggest the existence

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SUBJECTS AND METHODS

DESCRIPTION OF FAMILIES

Family MF-2

Figure 1 presents the family tree in the MF-2 kindred. Sixteen individuals are affected, and 12 of those affected and living have been examined. Eleven have had electromyographic studies and all of them demonstrated myotonia. Eight unaffected family members had electromyographic and clinical examinations. Two affected members have been studied in detail (MF-2 IV-421 and MF-2 IV-407), and findings are presented in the "Results" section.

Three family members initially presented with complications of anesthesia. In one case (MF-2 IV-421) following induction of anesthesia with barbiturate and succinylcholine hydrochloride, the patient had development of increased stiffness of his muscles, especially the masseter muscles. Hypoventilation, hypercapnia, and acidosis developed. The patient received treatment with dantrolene sodium, oxygen, and bicarbonate, and surgery was completed. Two women (MF-2 III-306 and IV-416) had similar difficulties with muscle stiffness provoked by general anesthesia.

Typically the patients complain of variable muscle stiffness. They usually remember the first episodes of muscle stiffness during their teenage years. On many days patients are free of significant myotonic symptoms. On "bad days" patients have troublesome myotonia in many muscles. They note stiffness in the extraocular muscles. Their eyes will occasionally "get stuck" when looking for a period of time in one direction, and they will complain of transient double vision. They may have difficulty with chewing, swallowing, turning their heads, and relaxation of grip. Sometimes the bad days follow a day in which the patient performed an increased amount of exercise or in which the patient had little sleep. Occasionally an infection or minor surgery will precede a bad day. On such days the myotonia worsens after exercise and rest. Once myotonic stiffness develops, patients note that the stiffness decreases with repeated muscle contractions (warm-up). On rare occasions patients may have development of severe generalized stiffness that will immobilize them for several minutes. Patient MF-2 IV-421 recalled an episode of severe delayed-onset myotonia that followed vigorous swimming. After his swim he had rested 10 to 20 minutes. He then started to play soccer, and fell to the ground because of generalized stiffness that lasted several minutes.

Cold weather does not appear to influence the pattern of myotonia. No significant change occurred when patients compared their symptoms during summer and winter. There is variation in severity of symptoms between family members. As an example, patient MF-2 IV-407 has persistent grip myotonia even on "good days" and has episodes of generalized muscle stiffness that have prevented him from his usual participation in soccer. His grandfather, MF-2 II-201, is so mildly affected that he could not recall a single episode in which he was incapacitated by muscle stiffness. In family MF-2, two women reported that pregnancy had no effect on their myotonia while another patient indicated that pregnancy made her muscle stiffness worse.

Family MF-3

Father (MF-3 I-1) and son (MF-3 II-1) are affected, and the daughter is unaffected. The father and son were previously described as having myotonia congenita of Thomson.¹⁴ Their symptoms are similar to those described above for family MF-2. The onset was in high school for the father and in grade school for the son. On many days they had no symptoms. On other days they had prominent myotonia affecting the eyes and grip. On one occasion following an hour of bed rest after nasal surgery (local anesthesia), the son had a bout of marked generalized stiffness in which he could not turn in bed. He gradually recovered over approximately 20 minutes. On another occasion at age 20 years, the son jumped over a creek and after landing became stiff and fell. After several seconds he recovered. The son also thought that his myotonia was worsened by cold.

During World War II, the father performed heavy physical exercise digging trenches for several days in a row. During this activity, the patient had development of severe generalized muscle stiffness. His myotonia was so incapacitating that he was taken from the front lines and given a discharge from the military because of this medical problem.

Family MF-4

In four generations, four individuals have been affected. Three of them are living and have been examined: the grandmother (MF-4 I-1), father (MF-4 II-1), and son (MF-4 III-1). The brother of the father was also examined and he was unaffected. The grandmother recalled that her first episode of stiffness of grip and difficulty opening her eyes occurred during pregnancy. The father first noticed myotonia as a teenager during participation in athletic competition. The son recalls that on one occasion, following a vigorous 15-minute bicycle ride, he became severely stiff after several minutes of rest. More than 1 hour passed before he completely recovered. He also noted that after episodes of infection and after local surgery, generalized stiffness developed. All affected individuals denied that exposure to cold produced any weakness or had any effect on their myotonia.

METHODS

The equipment used for recording the force of isometric muscle contraction and relaxation time of the flexor digitorum profundus muscle and the procedure for carrying out cooling and exercise of forearm muscle are as described previously.^{1,15} Each patient was instructed to make a maximum voluntary contraction and to maintain this effort for 2 seconds. The protocol for "exercise" consisted of maximum contraction for 60 seconds, interrupted by two 20-second rests. Testing of muscle from biopsy samples in patients MF-1 III-3¹ and MF-2 IV-421 for malignant hyperthermia used the standard contracture test protocol.^{16,17}

Genomic DNA was extracted from anticoagulated blood obtained from patients, their relatives, and controls with informed consent. Samples of genomic DNA were amplified by polymerase chain reaction with primers specific for exons 1 to 24 encoding the α subunit of the sodium channel protein.¹⁸ Single-strand conformational polymorphism analysis was performed; aberrant single-strand conformational polymorphism bands were directly sequenced.¹²

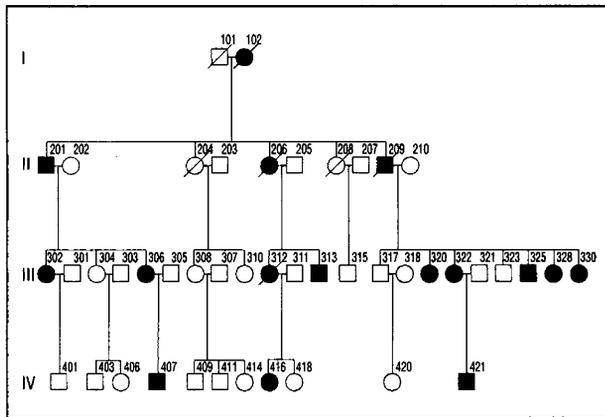


Figure 1. Family tree for family MF-2. Filled squares and circles indicate affected male and female subjects, respectively; open symbols, unaffected individuals; and diagonal line, individuals who have died.

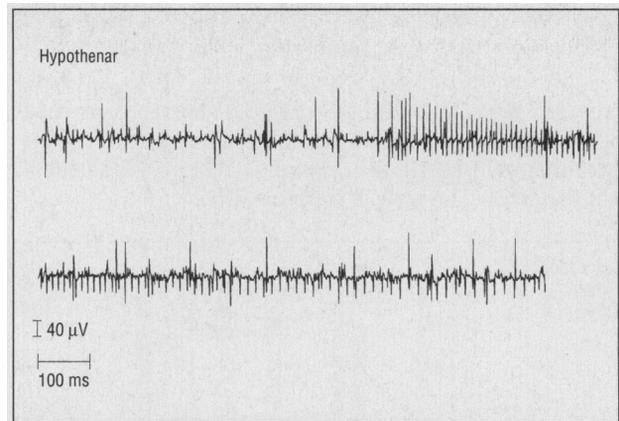


Figure 2. Electromyographic recording of spontaneous muscle fiber activity indicating sodium channel dysfunction at room temperature in hypothenar muscle in patient MF-2 III-306.

Table 1. Forearm Exercise Test*

Family	Patient	Test No.	Relaxation Time of Flexor Digitorum Muscle							
			Baseline	Time After Exercise						
				20 s	2 min	4-7 min	10-15 min	20-40 min	41-60 min	80-90 min
MF-2	IV-421	1	<1	<1	<1	2	1	21	12	17
		2†	13 (4)§	<1	7	...	6	19	8	3
MF-2	IV-407	1	6 (2)§	19 (8)§
		3‡	<1	<1	<1	2	...	2	8	...
MF-3	I-1	1	<1	<1	...	<1	...	8	...	
MF-4	II-1	1	<1	<1	...	2	...	8	6	...
	III-1	1	<1	<1	10	14	...	22	20	...
MF-4	III-1	1	<1	<1	<1	9	...	15	...	<1
		2	2	<1	10	17	...	23	22	7
		3‡	<1	<1	<1	<1	...	<1	<1	...

*Relaxation time is in seconds and is the time required for grip force to return to baseline after a maximum isometric contraction.
 †This test was done in the afternoon on a day on which the patient had already performed exercise during the morning.
 ‡Mexiletine hydrochloride treatment.
 §Numbers in parentheses indicate relaxation times that refer to a second contraction performed 20 to 30 seconds after the initial one.

of a third type of sodium channel disorder, a “sodium channel myotonia.”¹³

RESULTS

CLINICAL SYMPTOMS AND FINDINGS

All patients in families MF-2, MF-3, and MF-4 have fluctuating myotonia and postexercise delayed-onset myotonia. Most of them also experienced myotonia of the extraocular muscles, of eye closure, and myotonia with chewing and swallowing. None had weakness, sensory disturbance, or abnormal tendon reflexes. There was a twofold to fourfold elevation in serum creatine kinase values in those patients studied. Electromyographic recordings were made from hypothenar muscles and occasionally from the flexor digitorum profundus muscle in all patients. All had runs of myotonic discharges, and in many patients there was almost constant fibrillationlike activity (**Figure 2**). There was an increase in density of this fibrillationlike activity following exercise. Motor unit potentials and recruitment were normal.

MUSCLE BIOPSY HISTOLOGIC FEATURES

Muscle biopsies were performed in four patients and no significant abnormalities were found. The findings in one patient (family MF-1) have been reported previously.¹ In two patients (family MF-3) the biopsy findings have been described and listed under the heading of myotonia congenita of Thomsen.¹⁹ Patient MF-2 IV-421 had a biopsy specimen taken of the vastus lateralis muscle that showed a slightly increased variation in fiber diameter, a slight increase in the number of central nuclei, and with myosin adenosine triphosphatase staining at a pH of 4.3 and 4.6, there was an absence of type 2b fibers.

ELECTROPHYSIOLOGIC IN VITRO INVESTIGATIONS

In one patient, MF-2 IV-407, detailed electrophysiologic tests were performed using biopsy tissue obtained from the vastus lateralis muscle. The results have been published elsewhere.¹¹

CONTRACTURE TESTING FOR MALIGNANT HYPERTHERMIA

Patients MF-1 III-3¹ and MF-2 IV-421 had their muscle biopsy samples evaluated using the contracture test as recommended by the European Malignant Hyperthermia Protocol. The results were negative.

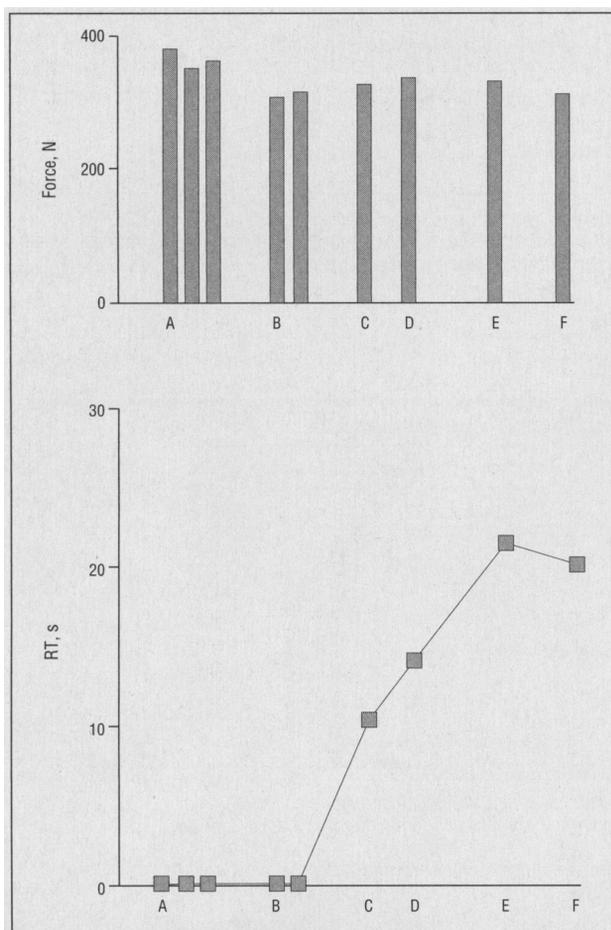


Figure 3. Forearm exercise test in patient MF-4 II-1. Force indicates maximum isometric contraction force of flexor digitorum profundus muscle; RT, relaxation time; A, baseline; B to F, after exercise: B=20 seconds; C=2 minutes; D=7 minutes; E=20 minutes; and F=41 minutes. The maximum of the delayed onset myotonia occurs 20 minutes after exercise.

FOREARM EXERCISE TEST

Maximum isometric contraction force and the relaxation time (degree of myotonia) of the flexor digitorum profundus muscle has been measured in six patients (**Table 1**). **Figure 3** shows an example of the forearm exercise test in one patient. There is delayed-onset post-exercise myotonia with only slight variation in contraction force.

Test 1 in all patients shows delayed-onset postexercise myotonia. The greatest prolongation in relaxation time occurs 20 to 40 minutes following exercise of the flexor digitorum profundus muscle. Five patients had no myotonia at baseline. The patients tended to have "good and bad days" in regard to the severity of their myotonia. Comparison of test 1 to test 2 in patient MF-4 III-1 demonstrates this variation. Test 2 occurred on a bad day and the patient had mild myotonia at baseline, while on a good day (test 1) no myotonia was present. On test 2, he had development of delayed-onset postexercise myotonia within 2 minutes and the prolongation in relaxation time had approached maximum within 4 to 7 minutes. In contrast, on a good day (test 1), the prolongation of relaxation time did not reach a maximum until 20 to 40 minutes postexercise.

In **Table 1** the relaxation times shown in parentheses refer to a second contraction performed 20 to 40 seconds after the initial one. The decrease in relaxation time clearly demonstrates the warm-up phenomenon. There was no significant change in maximum isometric contraction force during these exercise tests.

FOREARM COOLING TEST

Table 2 gives the results of the forearm cooling test in five patients. The test was performed in the opposite arm from the one used for the forearm exercise test and on a separate day except for patient MF-4 III-1. Four patients had no decline in strength following cooling and exercise of the forearm. Patient MF-3 II-1 had a moderate decrease in muscle contraction force. (A decline in force to 80% can be seen in normal subjects.) Three of the five patients had no increase of myotonia with cooling.

Family	Patient	Test No.	Relaxation Time of the Flexor Digitorum Muscle										Force, %†	
			Baseline	Cooling, min		Time After Exercise of the Cooled Muscle								
				15-20	30	20 s	2 min	4-7 min	10-15 min	20-40 min	50-60 min	90-170 min		
MF-2	IV-421	1	8	7	2	6	...	17	6	14	...	4	80	
	IV-407	1	7	...	17	4	22	30	26	...	100	
MF-3	I-1	1	<1	...	<1	<1	...	<1	100	
	II-1	1	6	23	12	24	...	24	8	60	
MF-4	III-1	1	<1	...	<1	<1	8	6	...	1	...	8	100	
		2‡	34	5	2	4	29	10	...	3	100	

*Relaxation time is in seconds and is the time required for grip force to return to baseline after a maximum isometric contraction.

†These are the force values measured at the last time point for each test compared with the baseline force (=100%).

‡This test was done in the afternoon on a day on which the patient had already performed exercise during the morning.

Exercise after forearm cooling led to myotonia of delayed onset in two patients (MF-2 IV-421 and MF-4 III-1, test 1), a pattern typically seen in myotonia fluctuans during testing at room temperature. In two other patients (MF-4 III-1, test 2 and MF-3 II-1) there was a severe increase in myotonia immediately after exercise of the cooled muscle, a pattern typically seen in paramyotonia.

ORAL POTASSIUM LOADING

Oral potassium loading with 80 mmol of potassium chloride was performed in four patients (MF-2 IV-421, MF-2 IV-407, MF-3 II-1, MF-4 III-1). All patients were tested in the afternoon. Within 30 to 60 minutes after potassium ingestion, all four patients observed a significant worsening of myotonia in general, with the most prominent myotonia occurring in the muscles of eye closure and gaze and in the muscles of grip. In comparison, the leg muscles were not as affected by potassium loading as those of the forearm or eyes. In two patients, MF-2 IV-407 and MF-4 III-1, the time required to climb nine steps was 3.4 and 2.9 seconds, respectively, while 1 hour after potassium ingestion, they required 10 and 6.2 seconds, respectively.

Table 3 presents measurements of relaxation time before and after potassium loading in two patients. No exercise was performed. Marked myotonia of grip was present in both patients about 80 minutes after potassium ingestion. No weakness occurred in any of the patients after potassium loading.

BICYCLE EXERCISE TESTING

Patient MF-4 III-1 had baseline measurements of force and relaxation time of the flexor digitorum muscle on the previous evening at 7 PM and in the morning at 9 AM before the bicycle exercise (**Figure 4**). No myotonia was present on either measurement. During the 60 minutes of bicycle exercise (120 W; pedal rate, 40 revolutions per minute), care was taken to keep one arm and hand at rest. There was a significant increase in grip myotonia within 4 minutes following completion of the bicycle exercise. This myotonia lasted for 90 minutes and then gradually declined. Serum potassium level was mea-

sured 20 minutes after completion of exercise, and the value was 3.80 mmol/L.

On another day in the morning this bicycle exercise test was repeated (without measurements of myotonia). Serum potassium values were as follows: baseline, 3.6, 3.7 mmol/L; during exercise, 15 minutes, 4.9 mmol/L, and 60 minutes, 6.0 mmol/L; and postexercise, 7 minutes, 4.2 mmol/L; 25 minutes, 4.2 mmol/L; 60 minutes, 4.1 mmol/L; and 75 minutes, 4.0 mmol/L. Clinically, the patient appeared to have generalized stiffness similar to that observed in the previous bicycle exercise test.

TRIAL OF MEXILETINE

Two patients, MF-4 III-1 and MF-1 case III-3,¹ received mexiletine hydrochloride, 200 mg three times daily. Both patients reported that this treatment prevented the development of myotonic muscle stiffness. Patient MF-4 III-1 performed a standard forearm exercise test. As shown in Table 1, after treatment with mexiletine, relaxation time stayed normal following exercise. Despite the effective-

Table 3. Oral Potassium Loading*

Family	Patient	Relaxation Time of the Flexor Digitorum Muscle					Force, %
		Baseline	Time After Potassium Loading, min				
			30	80	120		
MF-2	IV-421	7†	20	26	12	100	
MF-4	IV-407	6‡	...	38	...	100	

*Relaxation time is in seconds and is the time required for grip force to return to baseline after a maximum isometric contraction.

†Serum potassium level, 4.0 mmol/L at baseline, 4.9 mmol/L at 80 minutes after oral potassium loading.

‡Serum potassium level, 4.1 mmol/L at baseline, 4.6 mmol/L at 80 minutes after oral potassium loading.

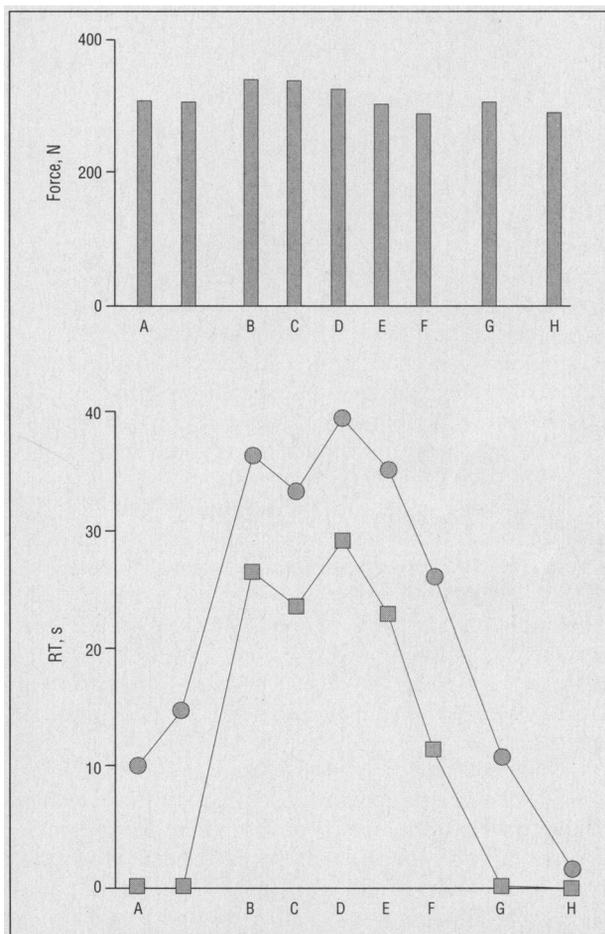


Figure 4. Bicycle exercise test in patient MF-4 III-1. Contraction force and relaxation time of the flexor digitorum muscle (see Figure 3). Square indicates relaxation time (RT) measured between 90% to 10% of maximum force; circle, relaxation time measured between 90% to 3% of maximum force. For further explanation see Ricker et al.¹ A indicates baseline; B to H, time after completion of bicycle exercise; B, 4 minutes; C, 23 minutes; D, 42 minutes; E, 85 minutes; F, 120 minutes; G, 171 minutes; and H, 240 minutes.

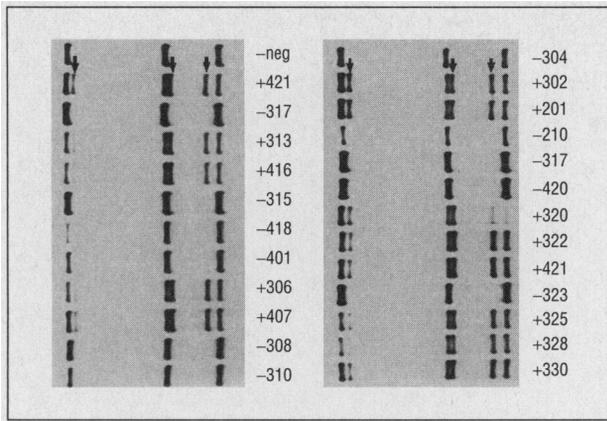


Figure 5. DNA analysis of family MF-2 (see Figure 1). Polyacrylamide gel showing single-strand conformational polymorphism products for exon 22 of α subunit of the skeletal muscle sodium channel. The affected family members had aberrant bands (arrows).

ness of mexiletine in both patients, neither has chosen to continue this treatment. They believe that their symptoms are tolerable most of the time. Both patients described a sensation of increased muscle stiffness and possible weakness of 2 days' duration following discontinuation of the drug therapy.

MOLECULAR GENETIC FINDINGS: LESIONS AFFECTING THE GENE FOR THE SKELETAL MUSCLE SODIUM CHANNEL

DNA from patients in families MF-1,¹ MF-2, and MF-3 showed a similar pattern of abnormal mobility for single-strand DNA fragments containing the transcript SCN4A. **Figure 5** shows data for family MF-2. The abnormality in the gene for the sodium channel in these three families localized to exon 22, which encodes the region of the sodium channel protein containing the cytoplasmic loop between domains III and IV (**Figure 6**). No abnormalities in exon 22 were detected in unaffected family members and in 76 normal controls.

DNA was eluted from the uppermost band on the gels (Figure 5) and underwent sequence analysis. A transposition of guanine to cytosine was found at position 3917 in the α subunit of the adult skeletal muscle sodium channel complementary DNA (**Figure 7**). This finding predicts a substitution of an alanine for a glycine at this location in the protein. No mutations were found in exons 1 to 21 or 23 to 24 of genomic DNA isolated from the patients.

DNA analysis of single-strand fragments in family MF-4 demonstrated abnormalities in exon 14 that codes for the inner portion of the transmembrane segment S6 of domain II and for a part of the cytoplasmic loop that connects domains II and III (Figure 6). No abnormalities of exon 14 were found in the one unaffected family member.

Sequence analysis of the abnormal DNA fragment that contained the alterations in exon 14 showed a transition of thymine for cytosine at position 2411 of the adult skeletal muscle sodium channel complementary DNA. This finding predicts a substitution of phenylalanine for serine in this portion of the protein structure. No muta-

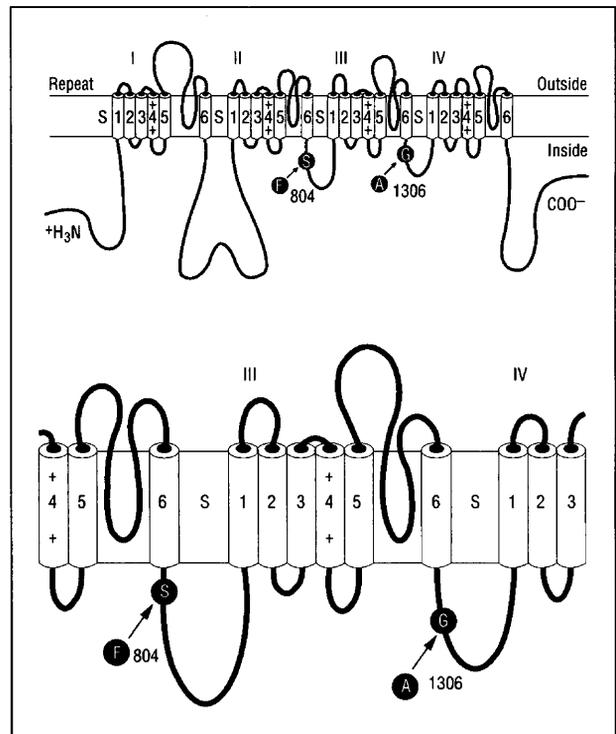


Figure 6. Top, A model of the α subunit of the skeletal muscle sodium channel showing four homologous domains (I to IV), each containing six transmembrane segments. Bottom, A magnified view of the two regions containing the mutations in the sodium channel. The filled circles indicate the abnormality for families MF-1, MF-2, and MF-3 at position 1306 and for family MF-4 at position 804.

tions in exons 1 to 13 and 15 to 24 of genomic DNA have been found in DNA analyzed from patient MF-4 III-1.

COMMENT

This report describes three additional families with myotonia fluctuans.¹ Analysis of DNA in these three families and in the initial family indicates that all those affected have mutations in the gene for the α subunit of the skeletal muscle sodium channel. The mutation in exon 22 is a newly discovered one.¹¹ The mutation in exon 14 had been described previously in a family having "features of paramyotonia and myotonia congenita."⁹

In the past, two families with myotonia fluctuans (MF-3, MF-1) have been diagnosed as having myotonia congenita.^{14,20} The autosomal dominant pattern of inheritance, the absence of paralysis following cold exposure or potassium loading, and the presence of the warm-up phenomenon, all of which are characteristic of myotonia fluctuans, made it difficult to distinguish these patients from those with myotonia congenita. However, myotonic stiffness in myotonia fluctuans varies greatly. It may be almost undetectable on many days. On bad days, patients may experience marked stiffness of the extraocular muscles,² muscles of eye closure, chewing and swallowing muscles, and the muscles of grip. On such days the myotonia following exercise may become so severe as to immobilize the patient.

Mexiletine, an antimyotonia drug structurally similar to lidocaine, is effective in preventing the myotonic

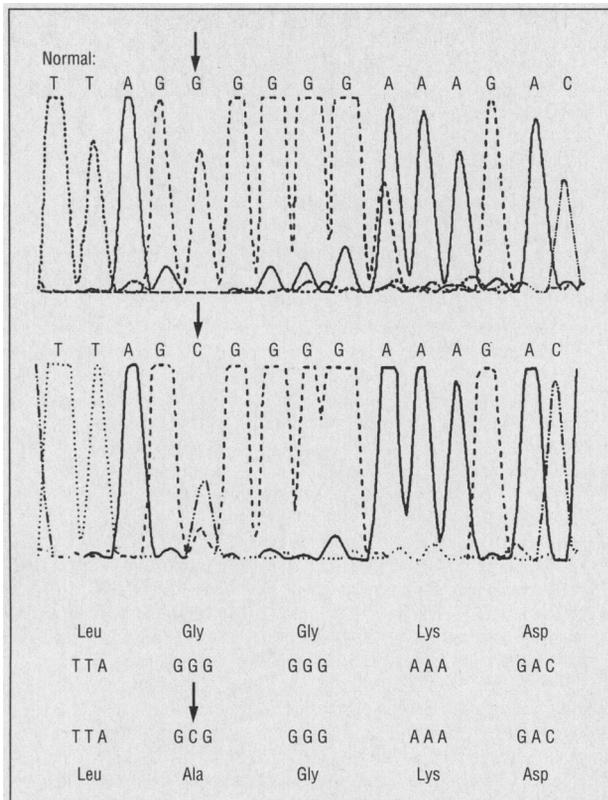


Figure 7. DNA sequencing from the aberrant band in family MF-2. Sequence is from the region corresponding to nucleotide position 3917. G to C transversion is apparent. This predicts a substitution of alanine for glycine at position 1306. T indicates thymidylate; A, deoxyadenylate; G, deoxyguanylate; C deoxycytidylate; Leu, leucine; Gly, glycine; Lys, lysine; Asp, aspartic acid; and Ala, alanine.

stiffness in patients with myotonia fluctuans. It is also effective in paramyotonia.²¹ The patients described herein did not require treatment. However, other patients with more severe symptoms of sodium channel myotonia may have persistent myotonia at rest that may be incapacitating without treatment.^{11,13} One note of caution is necessary. Abrupt cessation of treatment may lead to a transient increase of myotonia and to an unpleasant feeling of weakness in these patients and should be avoided. Acetazolamide was effective in one family with sodium channel myotonia similar to myotonia fluctuans.²²

Patients with myotonic disorders often have development of marked muscle spasms following the use of depolarizing muscle relaxants. Three patients with myotonia fluctuans had stiffness develop during induction of anesthesia and similar complications were reported in two similar families.^{9,12} Patients with myotonia fluctuans will often have no clinical signs of myotonia and yet have an elevation of serum creatine kinase values. However, there is no increased risk of malignant hyperthermia since results of in vitro contracture tests in this and another study¹⁷ were clearly negative. It is sufficient to avoid depolarizing muscle relaxants in these patients.

Electromyographic recordings typically show short-lasting myotonic runs of spontaneous activity in all myotonic muscle disorders. In myotonia fluctuans, there may be, in addition, a fibrillationlike almost constant spontaneous activity at room temperature. A brief period of

exercise of the muscle being recorded is often sufficient to provoke or to increase this activity. This same type of spontaneous muscle fiber activity has been recorded in paramyotonia during muscle cooling.^{15,23} The activity is related to the abnormal functioning of the muscle sodium channel in these disorders. In paramyotonia, the fiber activity leads to sarcolemma depolarization and paralysis while in myotonia fluctuans, the excitability of the membrane is preserved. The underlying reason is not known.^{11,12,21,23}

The mechanism that offers this protection distinguishes the patients with myotonia fluctuans from those with paramyotonia. On the other hand, exercise following cooling of forearm muscle occasionally may lead to increased myotonic stiffness in some patients with myotonia fluctuans. Apparently there may be a shared mechanism for symptoms between some patients with myotonia fluctuans and patients having paramyotonia.

Potassium loading significantly worsens the muscle stiffness in patients with myotonia fluctuans. The mechanism responsible for this increased sensitivity is unclear. The increased sensitivity to potassium is a hallmark also for hyperkalemic periodic paralysis, and the development of weakness after exercise in patients with hyperkalemic periodic paralysis is similar in its time course to that observed for the delayed-onset myotonia in myotonia fluctuans. However, unlike patients with hyperkalemic periodic paralysis, patients with myotonia fluctuans do not have development of weakness after potassium loading and apparently do not show an abnormal rise in serum potassium level following exercise. Fluctuations in extracellular potassium level and other factors, like hormone levels, may play a role in mediating the symptoms in myotonia fluctuans, but more specific studies are necessary to support these possibilities.

Hyperkalemic periodic paralysis, paramyotonia congenita, and myotonia fluctuans are distinct clinical disorders that are all associated with mutations in the gene for the sodium channel,^{13,24-27} but there is no consistent relationship between the location of a specific gene lesion and the type of clinical disorder that will occur. At present, it is not possible to predict if a specific gene mutation will always lead to periodic weakness, muscle stiffness, muscle paralysis after exposure to cold, or to sensitivity to potassium loading. This unpredictability in the relationship between specific mutations in the gene for the sodium channel and the associated clinical disorder emphasizes the need for more standardized evaluation of patients to improve our understanding of the puzzling relationship between genotype and phenotype that exists in disorders of the sodium channel.

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