Correlating phenotype and genotype in the periodic paralyses

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Abstract—*Background:* Periodic paralyses and paramyotonia congenita are rare disorders causing disabling weakness and myotonia. Mutations in sodium, calcium, and potassium channels have been recognized as causing disease. *Objective*: To analyze the clinical phenotype of patients with and without discernible genotype and to identify other mutations in ion channel genes associated with disease. *Methods*: The authors have reviewed clinical data in patients with a diagnosis of hypokalemic periodic paralysis (56 kindreds, 71 patients), hyperkalemic periodic paralysis (47 kindreds, 99 patients), and paramyotonia congenita (24 kindreds, 56 patients). For those patients without one of the classically known mutations, the authors analyzed the entire coding region of the *SCN4A*, *KCNE3*, and *KCNJ2* genes and portions of the coding region of the *CACNA1S* gene in order to identify new mutations. *Results*: Mutations were identified in approximately two thirds of kindreds with periodic paralysis or paramyotonia congenita. The authors found differences between the disorders and between those with and without identified mutations in terms of age at onset, frequency of attacks, duration of attacks, fixed proximal weakness, precipitants of attacks, myotonia, electrophysiologic studies, serum potassium levels, muscle biopsy, response to potassium administration, and response to treatment with acetazolamide. *Conclusions*: Hypokalemic periodic paralysis, hyperkalemic periodic paralysis, and paramyotonia congenita may be distinguished based on clinical data. This series of 226 patients (127 kindreds) confirms some clinical features of this disorder with notable exceptions: In this series, patients without mutations had a less typical clinical presentation including an older age at onset, no changes in diet as a precipitant, and absence of vacuolar myopathy on muscle biopsy.

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The periodic paralyses are rare disorders causing episodic, often disabling weakness. Recognizing the typical presentation avoids the risks and costs of further diagnostic testing and, in many cases, has clear implications for treatment. In addition, while these disorders are rare, episodic disorders affecting the nervous system are not. Further understanding of the genotype and clinical phenotype of these rare disorders will improve our understanding of common diseases such as epilepsy and migraine headaches.

Hypokalemic and hyperkalemic periodic paralysis (HypoKPP and HyperKPP) have been described based on their characteristic phenotype and the serum potassium level during the attack of weakness. In HypoKPP, serum potassium during an attack is low, while in HyperKPP serum potassium is elevated or normal. A third disorder, paramyotonia congenita (PC), is also considered with the periodic paralyses because myotonia and episodic weakness occur both in paramyotonia congenita (PC) and HyperKPP.[1,2] A small group of patients experiences episodic myotonia without attacks of weakness. Patients with this disorder, potassium aggravated myotonia (PAM), respond with an increase in symptoms when challenged with a potassium load. A similar challenge typically provokes weakness in HyperKPP patients. There is also overlap genetically.

In families with dominantly inherited, episodic weakness or myotonia, mutations in ion channel proteins have been identified.[1,2] Abnormal sodium channel inactivation in studies of HyperKPP first implicated sodium channel dysfunction in skeletal muscle as a possible etiology.[3] Subsequent linkage studies, cloning, and functional analysis proved this

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hypothesis correct.[4-6] The majority of cases of HyperKPP are secondary to two mutations in the sodium channel *SCN4A* gene, T704M and M1592V.[7,8] Mutations in the sodium channel are also responsible for PC, especially at residues 1448 and 1313,[9,10] and a small fraction of HypoKPP kindreds, at codon 669[11] and codon 672.[12-15] The majority of cases of HypoKPP are accounted for by two mutations in the calcium channel *CACNA1S* gene, R528H and R1239H.[16-18]

The triad of cardiac arrhythmias, dysmorphic features, and periodic paralysis, recognized as Andersen-Tawil syndrome, has been associated with mutations in an inwardly rectifying potassium channel.[19-21] Potassium channel mutations have also been described in patients with HypoKPP or HyperKPP,[22] though only in two small families. More recently, this same mutation did not segregate with disease in another population investigated[23] raising a question about the role of this variant in causing periodic paralysis. While genetic causes of each of these disorders are well documented, similar phenotypes may be seen in patients with metabolic disturbances. For example, secondary HypoKPP occurs in some patients with chronic potassium wasting[24] or in the setting of hyperthyroidism. There may be overlap between genetic and metabolic causes as in the example of an apparently sporadic case of HypoKPP associated with thyrotoxicosis in which a mutation in the *KCNE3* gene was identified.[25]

The current understanding of the phenotype is based on reports from clinicians with major experience in this area. Thus, we recognize an attack by the generalized weakness of the limbs without other neurologic findings, the common precipitants to an attack, and the laboratory data that help exclude other causes and confirm characteristic features such as low potassium or myotonia on EMG. However, there are no direct comparisons of patients with and without known ion channel mutations and no modern large series focused on the clinical phenotype. Using our large database of patients referred for the initial genetic analysis, we have reviewed the clinical data on patients with the phenotype of HypoKPP (56 kindreds, 71 patients), HyperKPP (47 kindreds, 99 patients), and PC (24 kindreds, 56 patients). In addition, we have screened for mutations in potassium (*KCNE3, KCNJ2*), calcium (*CACN1AS*), and sodium (*SCN4A*) channel genes in this group of patients. We have found important differences in phenotype between those with and without mutations and between the various mutations, including two new *SCN4A* gene mutations. From this analysis, we draw conclusions that we hope will improve our understanding of both the clinical and genetic approach to these disorders.

Methods. *Patients.* Written consent was obtained from all patients and controls in compliance with the Institutional Review Board at the University of Utah Health Sciences Center.

Genetic analysis. In patients for whom a mutation had previously been identified, other genes were not screened. In patients without a known mutation, we expanded the genetic screening to include coding regions of the *SCN4A, KCNE3, KCNJ2* genes. Regarding the calcium channel *CACN1AS* gene, we only included exons encoding the voltage-sensor (S4DI, S4DII, S4DIII, and S4DIV) and the DII-DIII transmembrane domains. These genes were analyzed as described below.

Genomic DNA was extracted from peripheral blood leukocytes using a PUREGENE DNA isolation blood kit (GENTRA Systems, Minneapolis, MN). Specific primer sequences (GenBank accession number NM_000069 for the skeletal muscle calcium gene and NM_000334 for the sodium channel gene), expected PCR product size, and annealing temperature conditions are available on the *Neurology* Web site (see table E-1 at www.neurology.org). Briefly, a standard PCR reaction was performed employing 100 to 200 ng of genomic DNA in 50-μL volume containing 10 mM Tris-HCl (pH 9 at 25C), 50 mM KCl, 0.1% Triton X-100, 200 μmol/L of each deoxy-NTP, 1.5 mM MgCl2, optimized for use with 1 U Taq DNA polymerase and 25 pmol of each specific primer, which were synthesized on a 394 automated DNA synthesizer (Applied Biosystems, Foster City, CA) through the Utah DNA Core Facility. Cycling conditions to generate PCR products included an initial phase of 5 minutes at 94 °C, followed by 35 cycles of 30 seconds at 94 °C, an annealing temperature step of 1 minute and an extension step of 1 minute at 72 °C. PCR products were resolved by electrophoresis in a 2% agarose-ethidium gel and quantified using a DNA mass ladder (Invitrogen; Carlsbad, CA).

PCR products were screened for heterozygous mutation using denaturing high-performance liquid chromatography (HPLC/WAVE DNA Fragment Analysis System, Transgenomic, Omaha, NE) when possible, or purified using QIAGEN QIAquick PCR Purification kit (Valencia, CA) and directly sequenced using either ABI Prism Big Dye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems) or CEQ2000 Dye Terminator Cycle Sequencing kit (Beckman Coulter, Fullerton, CA). Aberrant PCR products (screened) were sequenced to confirm the variations found. All sequences were collected and analyzed through Sequencher Gene Code Corporation (Ann Arbor, MI) software analyzer. Each sample was performed at least twice and in both directions.

Screening for the myotonic dystrophy type 2 (DM2) expansion mutation was done using PCR, Southern analysis, and the repeat expansion assay (RA), as previously described.[26,27]

Clinical chart review. Clinical data from patients with familial periodic paralysis and paramyotonia congenita were collected over the past 15 years as part of an effort to identify the specific genes associated with these disorders. We have reviewed these clinical data in patients with a diagnosis of HypoKPP (56 kindreds, 71 patients), HyperKPP (47 kindreds, 99 patients), and PC (26 kindreds, 57 patients). Two independent reviewers analyzed each chart. The initial diagnostic impression of the referring physician was confirmed during the chart review based on the clinical features as described.[1,2] The completeness of clinical information varied from patient to patient. In cases where the information was incomplete, attempts were made to contact the referring physician (or with permission, the patient) for further details.

Results. We present a summary of the mutation analysis in periodic paralysis and PC, and the clinical data for each of the various disorders with and without mutations. Not all clinical data were available for each patient. Therefore, percentages refer to the percent of patients with a given characteristic among those for whom we had reliable data (N in each box).

Table 1 shows the results of mutation screening for HypoKPP, HyperKPP, and PC patients. In patients with a clinical presentation consistent with HypoKPP, 64% of the kindreds had mutations in either the calcium channel or sodium channel. The majority were secondary to calcium channel mutations with R528H accounting for 42% of the mutations, and R1239H accounting for 42% of the mutations. For HyperKPP, sodium channel mutations were found in 64%. Of these mutations, 33% were T704M, 33% M1592V, 33% other sodium channel mutations. In PC patients, 71% of the kindreds were found to have sodium

Table 1 *Results of mutation analysis in periodic paralysis*

	Kindreds	Patients
All HypoKPP	56	71
HypoKPP without mutations, n (%)	20 (36)	22
HypoKPP with mutations, n (%)	36 (64)	49
R528H (Ca^{++} channel)	15	17
R1239H (Ca^{++} channel)	15	24
R1239G (Ca^{++} channel)	1	1
Na^{+} channel	5	7
All HyperKPP	47	99
HyperKPP without mutations, n (%)	17 (36)	18
HyperKPP with mutations, n (%)	30 (64)	81
T704M (Na^{+} channel)	10	50
M1592V (Na^{+} channel)	10	13
Other Na^{+} channel	10	18
All PC	26	57
PC without mutation, n (%)	7 (29)	7
PC with mutations, n (%)	17 (71)	49

Percent with mutation is the number of kindreds with mutations divided by the total number of kindreds.

HypoKPP = hypokalemic periodic paralysis; HyperKPP = hyperkalemic periodic paralysis; PC = paramyotonia congenita.

channel mutations. Family history of disease was present in three fourths of patients with mutations (88% for PC, 76% for HypoKPP, 77% for HyperKPP) and in one third to one half of those without mutations (30% for PC, 50% for HypoKPP, 50% for HyperKPP).

Table 2 depicts the characteristics found for patients with HypoKPP. The age at onset of the disease is younger for those patients with mutations, 10 vs 22 years. However, there were two noteworthy exceptions in the HypoKPP group. Two patients presented after age 20, one at age 23 and one at age 26. Among patients with (calcium channel) mutations, those with an R1239H mutation presented earlier, average age 7 years vs 14 years for R528H. Although data were limited regarding the age when the disease appeared worst, among those with mutations, teenage years (average age = 15) appear to be the most severe. While the numbers of muscle biopsies were limited in both groups, it is noteworthy that among those with calcium channel mutations, 80% had vacuolar myopathy, 13% had other myopathic changes, and 7% had tubular aggregates. Tubular aggregates may be more frequent among those HypoKPP patients with sodium channel mutations.[12] Myopathic changes were more frequent, 40%, among those without mutations. Clinical myotonia was rarely observed in this group of patients; only two of those without mutations presented with myotonia. Electrical myotonia was reported in one of the patients presenting with clinical myotonia. Residual weakness appears common among those with mutations, 72%, and relatively uncommon among those without mutations, 20%. Hypothyroidism was present in one case among those without mutations. In this case, the patient's hypothyroidism had been treated with appropriate thyroid replacement (150 μg/day) and there was no evidence or suspicion of hyperthyroidism, although laboratory studies to confirm euthyroid status at the time of symptoms were not available. Whether or not an ion channel mutation was found, treatment with acetazolamide appeared beneficial for most patients, 85% of those with mutations, 100% of those without (data not shown). However, five patients reported worsening with acetazolamide, one who had an R528H calcium channel mutation and four of the six patients with sodium channel mutations. In all other patients, potassium restored strength during the attack. The number of patients undergoing anesthesia and details of the anesthesia were difficult to obtain. Four patients, two with mutations and two without, reported an attack of weakness following anesthesia. Exercise was a common precipitant for all HypoKPP patients. Among the usual precipitants "sweets" and salt were also listed among some patients. The average serum potassium level during an attack for patients both with and without mutations was about 2.4 mEq/L.

Table 3 describes the data for patients with HyperKPP. As with HypoKPP, the average age at onset is younger for those with mutations (2 years) than for those without (14 years). Both groups had a younger age at onset than HypoKPP. Those with T704M mutation presented at the earliest age, average 0.8 years, with no patient in this group presenting after 1 year of age. In HyperKPP, attacks of weakness occurred frequently in those with mutations, average 16 attacks per month. Patients with the T704M mutation had attacks, on average, once per day. By contrast, patients with M1592V had about 3 attacks per month. Regarding duration of attacks, T704M patients had much shorter attacks, on average 8 hours, compared with M1592V patients, on average 89 hours. Clinical myotonia was common in all patients referred to us as HyperKPP, in 55% of those without mutations and 74% of those with mutations. These same patients also had electrical myotonia. Fixed proximal weakness not during an attack was also common. Sixty percent of those with mutations and 89% of those without mutations were reported to have weakness. Muscle biopsy showed vacuolar myopathy in 67% of patients with mutations. In patients without mutations, muscle biopsy showed either myopathic change (50%) or was normal (50%). As with HypoKPP, a little less than ¾ of patients with mutations are helped by acetazolamide (data not shown). It is noteworthy that in HyperKPP, all of the non-responders to acetazolamide had T704M mutations. Among the T704M patients receiving acetazolamide, the chance of responding to acetazolamide was only about 50%. For patients without mutations 9 out of 10 found acetazolamide beneficial. In all patients tested, potassium load produced weakness. As opposed to the HypoKPP where there was rare weakness following anesthesia, 20% of HyperKPP with mutations reported weakness after anesthesia. Two of these 10 patients had the double mutation F1480L-M1493I, which had previously been identified in families with periodic paralysis and susceptibility to malignant hyperthermia.[28] No patient without a mutation had an attack following anesthesia. Similar to HypoKPP, rest after exercise was a common triggering factor for an attack both in those with and without mutations. In contrast to HypoKPP, cold was a more common

Table 2 *Clinical data for hypokalemic periodic paralysis (HypoKPP)*

	HypoKPP with mutations				
	Na^+ channel (*SCN4A*)	Calcium channel (*CACNA1S*)			
Summary findings	All mutations (n = 7)	R1239H (n = 24)	R528H (n = 17)	All calcium channel (n = 42)	HypoKPP without mutations (n = 22)
Age at onset, y					
Average ± SD	16 ± 5	7 ± 4	14 ± 5	10 ± 6	22 ± 12
Range	13–27	2–14	8–30	2–26	5–61
	(n = 7)	(n = 21)	(n = 16)	(n = 38)	(n = 18)
Frequency of attacks/mo					
Average ± SD	7 ± 6	10 ± 10	8 ± 10	9 ± 9	1 ± 1
Range	4–14	3.5–30	0.3–10	0.5–30	0.3–2
	(n = 3)	(n = 7)	(n = 7)	(n = 14)	(n = 5)
Duration, h					
Average ± SD	1 ± 0.6	19 ± 12	20 ± 27	20 ± 21	29 ± 23
Range	1–2	2–72	2–72	2–72	1–60
	(n = 3)	(n = 11)	(n = 9)	(n = 21)	(n = 13)
Usual precipitants, %					
Exercise	75	93	50	76	52
Sweets/high carbs	50	43	80	60	18
Salt	0	21	20	24	0
Stress	25	14	0	12	0
Cold		29	20	24	24
	(n = 4)	(n = 14)	(n = 10)	(n = 25)	(n = 17)
Weakness, %					
None	100	40	14	28	80
Mild	0	50	29	39	7
Severe	0	10	57	33	13
	(n = 2)	(n = 10)	(n = 7)	(n = 18)	(n = 15)
Clinical myotonia, %	0	0	0	0	15
	(n = 4)	(n = 11)	(n = 8)	(n = 20)	(n = 13)
EMG/NCS, %					
Normal	100	100	33	56	71
Myopathic	0		67	44	19
	(n = 4)	(n = 2)	(n = 6)	(n = 9)	(n = 7)
Muscle biopsy, %					
Vacuolar myopathy	50	100	71	80	0
Tubular aggregates	50	0	0	7	0
Myopathic changes	0	0	29	13	40
Normal	0	0	0	0	60
	(n = 2)	(n = 7)	(n = 7)	(n = 15)	(n = 5)
Potassium, mEq/L					
Average ± SD	2.2 ± 0.8	1.9 ± 0.4	2.9 ± 0.7	2.4 ± 0.7	2.3 ± 0.5
Range	1.2–3.1	1.6–2.6	1.8–4.2	1.6–4.2	1.4–3.3
	(n = 5)	(n = 8)	(n = 12)	(n = 21)	(n = 15)
Attacks helped by potassium, %	100	100	100	100	100
	(n = 1)	(n = 15)	(n = 9)	(n = 25)	(n = 12)

n = Number of patients for whom data were available.

precipitant to an attack, in 54% of those with and 38% of those without mutations. Hunger and missing meals, or eating potassium-rich foods, were noted as precipitants among those with mutations. The potassium level during an attack was similar in those with and without mutations, approximately 5.3 mEq/L. This is increased compared with the HypoKPP patients.

Table 4 describes the clinical data for patients with PC. The average age at onset of disease for PC was young for both those with (3 years) and without (4 years) mutations.

Table 3 *Clinical data for hyperkalemic periodic paralysis (HyperKPP)*

	HyperKPP with mutations			
	Sodium channel (*SCN4A*)			
Summary findings	T704M mutation (n = 50)	M1592V (n = 13)	All HyperKPP mutations (n = 82)	HyperKPP without mutations (n = 17)
Age at onset, y	0.8 ± 0.8	5 ± 4	2 ± 4	14 ± 14
Average ± SD	0–0.9	0–10	0–16	5–61
	(n = 39)	(n = 13)	(n = 63)	(n = 16)
Frequency of attacks/mo				
Average ± SD	28 ± 12	3 ± 2	16 ± −16	6 ± 6
Range	8–42	5–6	1–42	1–16
	(n = 17)	(n = 4)	(n = 26)	(n = 4)
Duration, h				
Average ± SD	8 ± 28	89 ± 58	24 ± 42	23 ± 18
Range	0.3–168	24–144	2–72	2–48
	(n = 41)	(n = 7)	(n = 56)	(n = 8)
Usual precipitants, %				
Exercise	83	73	80	69
Cold	58	38	54	38
Hunger	29	13	25	6
Stress	46	13	34	19
Illness	0	38	30	
Potassium rich foods	32		21	
Other	25	38	8	13
	(n = 41)	(n = 11)	(n = 64)	(n = 16)
Weakness, %				
None	35	50	40	11
Mild	47	40	43	89
Severe	18	10	17	
	(n = 40)	(n = 10)	(n = 58)	(n = 9)
Clinical myotonia, %	77	90	74	55
	(n = 43)	(n = 10)	(n = 62)	(n = 11)
EMG/NCS, %				
Normal	29		18	44
Myotonia	71	100	72	56
	(n = 14)	(n = 4)	(n = 29)	(n = 9)
Muscle biopsy, %				
Vacuolar myopathy	75	No data	67	
Mild atrophy	25		17	
Other myopathic		100	16	50
Normal				50
	(n = 4)	(n = 2)	(n = 12)	(n = 8)
Weakness with potassium load, %	No data	100	100	100
		(n = 3)	(n = 18)	(n = 6)
Average K+ mEq/L				
Average ± SD	6.1 ± 0.5	5.7 ± 1.5	5.4 ± 1.0	4.9 ± 1.3
Range	5.7–6.7	4.0–6.8	4.0–6.8	3.6–6.1
	(n = 3)	(n = 3)	(n = 20)	(n = 4)

n = Number of patients for whom data were available.

Table 4 *Clinical data for paramyotonia congenita (PC)*

Summary findings	PC mutations (n = 49)	PC without mutations (n = 7)
Age at onset, y		
Average ± SD	3 ± 5	4 ± 5
Range	0–18	0–13
	(n = 41)	(n = 5)
Duration, h		
Average ± SD	15 ± 17	No data
Range	1–60	
	(n = 25)	
Usual precipitants, %		
Cold	91	83
Exercise	46	67
Hunger	26	
	(n = 46)	(n = 6)
Weakness, %		
Mild weakness	47	40
Normal	53	60
	(n = 32)	(n = 5)
Clinical myotonia, %	100	100
	(n = 34)	(n = 6)
EMG/NCS, %		
Myotonia	100	100
Normal		
	(n = 15)	(n = 4)
Muscle biopsy, %		
Myopathic changes	33	
Type 1 predominance		33
Type 2 predominance	33	
Neuroatrophy	17	
Normal	17	67
	(n = 6)	(n = 3)
Response to potassium	70% no weakness 30% weakness 30% myotonia (n = 10)	No data
Objective cold effect	100% increased myotonia 92% decreased CMAP (n = 14)	100% increased myotonia 50% decreased CMAP (n = 2)
Potassium, mEq/L		
Average ± SD	4.0 ± 1.2	3.5
Range	3.3–5.4	
	(n = 3)	(n = 1)

n = Number of patients for whom data were available.

CMAP = compound muscle action potential.

Few patients in this group underwent muscle biopsy; the results were varied in both those with and without mutations. Clinical and electrical myotonia was present in 100% of those with and without mutations. In all cases tested, both with and without mutations, cooling led to increased myotonia and in all but one of the patients with mutations, there was evidence for decreased amplitude of the compound muscle action potential with cooling, i.e., an objective cold effect. In contrast to HyperkPP patients, potassium loading caused increased weakness in only 22% of those with mutations. In addition, 33% of those with mutations experienced increased myotonia as a result of potassium loading. In the patients where CK (creatine kinase) was reported, it was elevated in most patients in both groups, 5 of 7 patients with mutations and 4 of 4 patients without mutations. In most cases, exact CK levels were not available, but were reported as "mildly elevated" or "elevated." Cold precipitated attacks in 91% of those with identified mutations and 86% of those without. Exercise was also frequently reported as a precipitant and in the group with mutations, hunger was a precipitant in 26%. Potassium level during an attack of weakness was infrequently reported, although normal in the cases where data were available. Two new *SCN4A* mutations, E1702K and R672C, were found. Three of four patients with PC "responded well" to Diamox with decreased myotonia. For one patient with PC, myotonia decreased with Diamox, but generalized weakness and attacks of weakness increased. For those PC patients taking mexiletine 7/7 reported decreased myotonia.

Because a large number of patients with clinically evident myotonia remained unexplained by our genetic analysis, we also screened these 21 HyperKPP and PC patients without mutations for the DM2 CCTG expansion. The CCTG expansion mutation in intron 1 of the *zinc finger protein 9* gene (*ZNF9*) causes myotonic dystrophy type 2.[27] In Europe, the disease in these families has been called proximal myotonic myopathy (PROMM).[29] DM2 is an adult onset muscular dystrophy associated with myotonia, proximal weakness, cataracts, cardiac arrhythmias, insulin resistance, and other multisystemic features of adult onset myotonic dystrophy type 1.[26] No DM2 CCTG expansions were found (data not shown).

Discussion. Although not all data were available for all patients, this analysis represents the largest series of such patients with defined mutations. One objective of this analysis was to collate observations gathered by various clinicians regarding the periodic paralyses. We first consider those patients with mutations.

Our data support the current understanding that both familial HyperKPP and PC present in infancy to early childhood, while HypoKPP presents at ages 5 to 20. The clinical axiom that familial periodic paralysis patients do not present over age 20 holds true in patients with mutations with the exception of two HypoKPP patients presenting at age 23 and 26. The general consensus is that HypoKPP patients have longer duration, less frequent, more severe attacks. While our data suggest that this might be true, there was great overlap between the groups. The fact that an "attack" was ill-defined in terms of frequency, severity, and duration in the patient charts may have hampered our ability to make a definitive statement. One typical feature of these episodic disorders is the recognition of precipitants to attacks, as was clearly seen in this data set. Although data regarding when the disorder was most symptomatic were not clear for PC and HyperKPP, patients with HypoKPP believed that their disease was worst during the teenage years (average age worst = 15, data not

shown). Whether this represents hormonal changes or merely reflects the vagaries of a teenage diet in a disease with clear dietary precipitants is unknown.

Myotonia distinguishes HypoKPP vs HyperKPP and PC. One hundred percent of PC and three quarters of HyperKPP patients had evidence of myotonia while no patient with a proven mutation and HypoKPP had evidence of myotonia, either electrically or clinically. Thus myotonia in a patient with presumed HypoKPP should raise suspicion about the diagnosis with the caveat that an exceptional case of sodium channel HypoKPP has been associated with myotonia.[30] Fixed proximal weakness was associated with HypoKPP, HyperKPP, and PC. Thus our data highlight the underappreciated fact that periodic paralyses may also be associated with fixed weakness.[31-33] The etiology of this late onset, proximal myopathy remains undetermined.

Overall, in our data, there was no difference between the male and female patients (data not shown). However, in HypoKPP, 62% of patients were male and 38% female, which likely reflects asymptomatic females in this autosomal dominant disease.[13,34] Whether the other females who presumably carry the gene but did not have paralytic attacks developed a late onset proximal myopathy is unknown. Equal numbers of male/female patients were analyzed for HyperKPP and PC. Interestingly, these same ratios of male/female patients were observed both in those with and without mutations. In HyperKPP males generally have more frequent and more severe attacks.[2] This difference between males and females was not apparent in our data set, which may have been secondary to our imprecise data regarding attacks as discussed above.

Ictal potassium was low among HypoKPP patients, high in HyperKPP, and normal in PC, thus confirming the expected laboratory findings. In keeping with our understanding of the disease, potassium during an attack helped those with HypoKPP and challenging HyperKPP patients led to weakness. However, the kindred carrying the R672C mutation reported worsening after potassium intake. Potassium administration had no effect on most PC patients. When the diagnosis of PC is being considered, an objective cold effect may be a particularly reliable test. One hundred percent of PC patients tested had increased electrical myotonia with cooling of the limb (objective cold effect).

Conspicuously absent from our data are the exercise test, i.e., recording the amplitude of the compound muscle action potential (CMAP) over time following a brief period of sustained exercise of a given muscle.[35] While we endorse this noninvasive, relatively simple test as part of the workup for periodic paralyses, we cannot comment on its utility in our data set, since very few patients had undergone this test.

Who are the patients without demonstrable mutations, but with disease? The patients were referred because they met criteria for periodic paralysis, thus it is not surprising that the clinical data for those with and without mutations were similar. There were, however, several outstanding differences. HypoKPP and HyperKPP without mutations were older at the onset of disease with 13 patients older than 20 years of age. While exercise was a common precipitant for those with and without mutations changes in food intake as a precipitant, either hunger or eating specific foods, was only reported among those with mutations. Another specific finding for those with mutations was vacuolar myopathy on muscle biopsy. While some patients without mutations had non-specific myopathic findings on muscle biopsy, none of these patients had a vacuolar myopathy. These periodic paralysis patients without mutations may be secondary to well-recognized metabolic causes of disease. However, there was no evidence of these disorders in these patients, though how thoroughly they were investigated was not always easily determined. Although only patients who met published criteria for periodic paralyses[1,2] were included in this retrospective chart review, it is possible that some patients without mutations would have been excluded from the study had more extensive clinical and laboratory data been available.

Patients with disease but without mutations may represent mutations in genes that were not screened or a combination of polygenic and metabolic factors. Indeed, the second primary objective of our study was to determine if previously unrecognized mutations in ion channel proteins might account for some of these patients. Our screen did identify several patients with less common mutations, such as sodium channel mutations L689V, L689I, V781I, S906T, I1363T, and L1433R.[15,36,37] In addition, we have identified a novel mutation E1702K in *SCN4A* gene in a family diagnosed with PC whose proband curiously presents with attacks of 10 to 15 seconds duration at several times during the day or night, and ameliorates with oral potassium administration. Another unrelated PC kindred carries the same E1702K mutation but no clinical data were obtained. This variation is the furthest c-terminus mutation found in *SCN4A* gene. For one patient who carries a new *SCN4A* mutation, R672C, interestingly potassium did not help during attacks. Another kindred with a combination of the mutation I1363T with the benign known polymorphism S906T, which was found in 4% of healthy controls, has a classic PC phenotype. Taken all together, these data underscore the particular importance of electrophysiologic study in these cases.

Given our thorough screen of calcium (*CACN1AS*), sodium (*SCN4A*) channel genes and the *KCNJ2* and *KCNE3* potassium channel genes, we doubt that the unexplained patients harbor a mutation in one of those genes. Because of the prominent myotonia in some of the patients without recognized mutations, we also screened for *ZNF9* gene alteration, though no *ZNF9* mutations were identified.

Does genotype make any difference for manage-

Table 5 *Clinical features of the familial periodic paralyses*

	HypoKPP	HyperKPP	PC
Age at onset, y	5 to 20	<10	Infancy
Attacks			
Frequency	Infrequent	Frequent	Frequent
Duration, h	>24	<24	<24
Precipitants	Exercise	Exercise	Exercise
	High carbs	Hunger	Cold
	Salt	Potassium-rich foods	
Myotonia	No	Yes	Always
Weakness	Yes	Yes	Yes
Potassium level	Low	Normal to high	Normal
Response to potassium	Relieves acute paralysis	Causes weakness	No effect
Objective cold effect	None	None	Causes weakness
Muscle biopsy	Vacuolar myopathy	Vacuolar myopathy	Variable

HypoKPP = hypokalemic periodic paralysis; HyperKPP = hyperkalemic periodic paralysis; PC = paramyotonia congenita.

ment options? The difference between HypoKPP, HyperKPP, and PC is usually clear on clinical grounds without genetic testing and thus management guidelines such as avoiding skipping meals in HyperKPP can be easily initiated. There are several further considerations where specific genotype may make a difference. Overall, most patients with HypoKPP and HyperKPP, with or without mutations, respond to acetazolamide. However, patients with HyperKPP caused by a T704M mutation only had a 50% response rate. Some patients with HypoKPP and sodium channel mutations worsened with acetazolamide, as has been previously recognized.[12,15] Second, some families with HyperKPP are also susceptible to malignant hyperthermia when undergoing anesthesia.[28] Knowledge of these particular mutations would have obvious benefit for planning during elective surgeries.

In table 5, we provide a summary of the clinical features. Using this information, clinical experience, and data on laboratory tests we created a simplified flow diagram (figure) for evaluation of patients with episodic weakness. In addition, on the *Neurology* Web site, we have provided a periodic paralyses questionnaire (see E-Questionnaire at www.neurology.org). Collecting this type of data will not only help individual physicians, but will better define the phenotype and thus influence future therapeutic clinical trials. The first such trial demonstrated the efficacy of dichlorphenamide, a carbonic anhydrase inhibitor, for HypoKPP and HyperKPP.[38]

This data set provides the most comprehensive genotype–phenotype correlation for the periodic paralyses. In general, the clinical pearls dispensed by expert clinicians and summarized in table 5 hold up to systematic scrutiny. We have identified a group of familial patients with characteristics similar to those with known ion-channel mutations, but without known causative genes. These provide a fertile area for study of other candidate genes. The detailed clinical analysis presented here may help guide future studies in designing better therapies and in under-

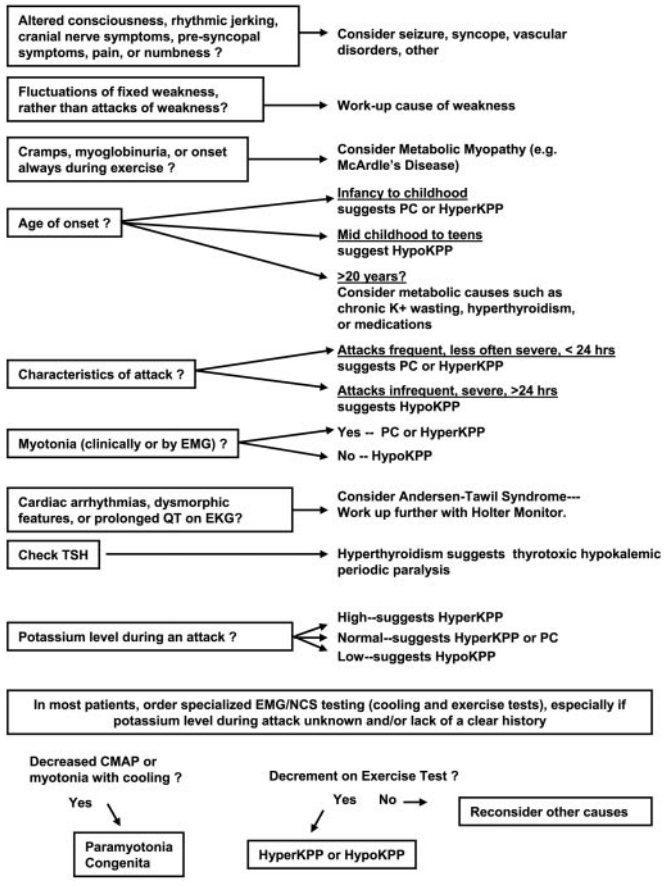

Figure. Diagnosis of periodic paralysis. Periodic paralyses can usually be diagnosed by following the above list of questions and examinations, especially if the patient presents during one of the paralytic episodes.

standing the pathophysiologic consequences of the disease causing mutations.

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