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Hyperkalemic Periodic Paralysis Type 1

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Summary

Disease characteristics. Hyperkalemic periodic paralysis type 1 (hyperPP1) is characterized by attacks of flaccid limb weakness (which may also include weakness of the muscles of the eyes, throat, and trunk), hyperkalemia (serum potassium concentration >5 mmol/L) or an increase of serum potassium concentration of at least 1.5 mmol/L during an attack of weakness and/or provoking/worsening of an attack by oral potassium intake, normal serum potassium and muscle strength between attacks, onset before age 20 years, and absence of paramyotonia (muscle stiffness aggravated by cold and exercise). The attacks of flaccid muscle weakness usually begin in the first decade of life. Initially infrequent, the attacks then increase in frequency and severity over time until approximately age 50 years, after which the frequency of attacks declines considerably. Potassium-rich food or rest after exercise may precipitate an attack. A cold environment, emotional stress, and pregnancy provoke or worsen the attacks. A spontaneous attack commonly starts in the morning before breakfast, lasts for 15 minutes to one hour, and then disappears. Cardiac arrhythmia or respiratory insufficiency usually does not occur during attacks. Between attacks, hyperPP1 is usually associated with mild myotonia (muscle stiffness) that does not impede voluntary movements. Many older affected individuals develop a chronic progressive myopathy.

Diagnosis/testing. Diagnosis is based on clinical findings. In case of diagnostic uncertainty, one of three provocative tests can be employed. HyperPP1 is caused by point mutations in *SCN4A* encoding the voltage-gated skeletal muscle sodium channel. Targeted mutation analysis for nine common mutations detects a mutation in approximately 55% of affected individuals. Sequencing of select exons is also clinically available.

Management. *Treatment of manifestations:* At the onset of weakness, attacks may be prevented or aborted with mild exercise and/or oral ingestion of carbohydrates, inhalation of salbutamol, or intravenous calcium gluconate. *Prevention of primary manifestations:* Hyperkalemic attacks of weakness can be prevented by frequent meals rich in carbohydrates, continuous use of a thiazide diuretic or acetazolamide, and avoidance of potassium-rich medications and foods, fasting, strenuous work, and exposure to cold. *Prevention of secondary complications:* During surgery, avoid use of depolarizing anesthetic agents including potassium, suxamethonium, and anticholinesterases that aggravate myotonia and can result in masseter spasm and stiffness of respiratory and other skeletal muscles, interfering with intubation and mechanical ventilation. *Surveillance:* during prophylatic treatment, determination of serum potassium concentration twice per year to avoid severe diuretic-induced hypokalemia; assessment of neurologic status and MRI of proximal leg muscles every three years. *Agents/circumstances to avoid:* potassium-rich medications and foods, fasting,

strenuous work, exposure to cold. *Testing of relatives at risk:* It is appropriate to test asymptomatic at-risk family members for the disease-causing mutation identified in an affected relative in order to institute preventive measures prior to surgery.

Genetic counseling. HyperPP1 is inherited in an autosomal dominant manner. Most individuals with hyperPP1 have an affected parent; the proportion of cases caused by *de novo* mutations is unknown. Each child of an individual with hyperPP1 has a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing mutation in the family has been identified; however, requests for prenatal testing for conditions such as hyperPP1 that do not affect intellect and have some treatment available are not common.

Diagnosis

Clinical Diagnosis

Diagnostic criteria. The diagnosis of hyperkalemic periodic paralysis type 1 (hyperPP1) is based on the following findings:

- A history of at least two attacks of flaccid limb weakness (which may also include weakness of the muscles of the eyes, throat, and trunk)
- Hyperkalemia (serum potassium concentration >5 mmol/L) or an increase of serum potassium concentration of at least 1.5 mmol/L during an attack of weakness and/or onset/worsening of an attack as a result of oral potassium intake
- Normal serum potassium concentration and muscle strength between attacks
- Disease manifestations before age 20 years
- Absense of paramyotonia (i.e., muscle stiffness aggravated by cold and exercise)
- Absence of cardiac arrhythmia between attacks
- Normal psychomotor development
- Typically, at least one affected first-degree relative
- Exclusion of other hereditary forms of hyperkalemia (See Differential Diagnosis) and acquired forms of hyperkalemia (drug abuse; renal and adrenal dysfunction)

Electromyogram (EMG). The diagnosis is strongly supported by the presence of myotonic signs in the EMG; however, approximately 50% of affected individuals with the most common mutation have no detectable electrical myotonia:

- During the attack, EMG demonstrates a reduced number of motor units or may be silent (no insertional or voluntary activity).
- In the intervals between attacks, EMG may reveal myotonic activity (bursts of action potentials with amplitude and frequency modulation), even though myotonic stiffness may not be clinically present.
- In some individuals, especially in those with permanent weakness, a myopathic pattern may be visible.

Testing

Serum potassium concentration

- During an attack, the serum potassium concentration is elevated by 1.5-3 mmol/L, which is usually sufficient to surpass 5 mmol/L total concentration.

Note: At the end of an attack of weakness, elimination of potassium via the kidney and reuptake of potassium by the muscle can cause transient hypokalemia that may lead to the misdiagnosis of hypokalemic periodic paralysis.

- Even though the serum potassium concentration seldom reaches cardiotoxic levels, changes in the ECG (increased amplitude of T waves) may occur.

Serum creatine kinase (CK) concentration. In the intervals between attacks, serum CK concentration is elevated (sometimes 5-10x the normal range) whereas serum sodium and potassium concentrations are normal.

Provocative tests. In case of diagnostic uncertainty, i.e., in the absence of a measurement of ictal (during an attack) serum potassium concentration and negative molecular genetic studies, a provocative test can be employed to ensure the diagnosis. Systemic provocative tests carry the risk of inducing a severe attack; therefore, they must be performed by an experienced physician and a stand-by anesthetist, with close monitoring of the ECG and serum concentration of potassium:

- The classic provocative test consists of the administration of 2-10 g potassium under clinical surveillance with serum potassium concentration and strength measured at 20-minute intervals. Usually, an attack is induced within an hour and lasts approximately 30 to 60 minutes, accompanied by an increase in serum potassium concentration, similar to spontaneously occurring attacks of weakness. The test is contraindicated in individuals who already have hyperkalemia and in those individuals who do not have adequate renal or adrenal function.
- An alternative provocative test is exercise on a bicycle ergometer for 30 minutes to increase the heart rate to 120-160 beats/min, followed by absolute rest in bed. An affected individual's serum potassium concentration should rise during exercise, decline after exercise, and rise a second time 20 minutes after the conclusion of exercise.
- A local provocative test is measurement of evoked compound muscle action potentials (CMAP). They should have a greater-than-normal increase during two to five minutes of exercise followed by a progressive decline in amplitude that is greater than in normal controls and most rapid during the first 20 minutes after exercise. The decline is the more important parameter [Melamed-Frank & Marom 1999, Fournier et al 2004]. In the authors' experience, the CMAP results are not specific for hyperPP or a given mutation.

Muscle biopsy. Because no specific findings are observed on muscle biopsy and because the results do not influence therapeutic strategies or prognosis, a muscle biopsy is generally not recommended in individuals suspected of having hyperPP1. At onset of the occurrence of attacks of weakness, the muscle fibers do not show morphologic abnormalities even at the ultrastructural level. Further in the course of the disease, but independent of the severity of the attacks of weakness, proliferation, dilation, and degeneration of components of the T tubular system and the sarcoplasmic reticulum occur, leading to the formation of vacuoles resulting in a "vacuolar myopathy" [Jurkat-Rott et al 2002].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

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Gene. HyperPP1 is caused by point mutations in *SCN4A* [Fontaine et al 1990], encoding the voltage-gated skeletal muscle sodium channel.

Clinical testing

- **Targeted mutation analysis.** Molecular genetic testing for nine common mutations (See Table 1) detects a mutation in approximately 60% of individuals with hyperPP1, as defined by the clinical diagnostic criteria [Jurkat-Rott & Lehmann-Horn 2007].
- **Sequence analysis of select exons.** *SCN4A* sequence analysis of select exons may be performed to identify mutations in affected individuals who have tested negative for the nine common mutations.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Hyperkalemic Periodic Paralysis Type 1

Test Method	Mutations Detected [1]	Mutation Detection Frequency by Mutation and Test Method	Test Availability
Targeted mutation analysis	p.Leu689Ile	<1%	Clinical Testing
	p.Ile693Thr	~15%	
	p.Thr704Met	~59%	
	p.Ala1156Thr	<1%	
	p.Met1360Val	<1%	
	p.Met1370Val	<1%	
	p.Ile1495Phe	<1%	
	p.Met1592Val	<25%	
	p.[Phe1490Leu; Met1493Ile]	<1%	
Sequence analysis of select exons	*SCN4A* sequence variants	Unknown	

1. See Table 3.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm the diagnosis in a proband, the following tests are indicated:

- Serum potassium concentrations interictally and, if possible, during a paralytic attack
- ECG recording for the exclusion of a long QT and ventricular arrhythmias
- EMG recording (myotonic activity supports the diagnosis of hyperPP in contrast to HOKPP)
- Serum CK concentration (usually slightly increased)

- Molecular genetic testing of *SCN4A* and, if negative, *KCNJ2* and *CACNA1S*. In contrast, sequencing of *KCNE3* is not required [Jurkat-Rott & Lehmann-Horn 2004].
- In individuals who have atypical clinical features or lack an *SCN4A* mutation, provocative test, Holter recording, and muscle biopsy

Prognostication. Most persons who have the p.Thr704Met mutation develop persistent weakness.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

Several types of myotonia and periodic paralyses (PP) are caused by mutations in the *SCN4A* gene.

Potassium-aggravated myotonias. Individuals with potassium-aggravated myotonia develop severe stiffness following vigorous exercise or oral ingestion of potassium. The spectrum ranges from mild (myotonia fluctuans) to very severe (myotonia permanens):

- **Myotonia fluctuans**, the mildest form, in which the affected individuals either are not aware of muscle stiffness or may experience stiffness that tends to fluctuate from day to day [Ricker et al 1994]. After resting for several minutes, a single contraction may produce such severe stiffness (delayed myotonia) that the individual is unable to move for several hours. This sometimes painful, exercise-induced muscle cramping may be induced by or associated with hyperkalemia or other depolarizing agents [Heine et al 1993, Orrell et al 1998]. The stiffness subsides upon continued exercise (warm-up phenomenon).
- **Acetazolamide-responsive myotonia**, also known as atypical myotonia congenita [Ptácek et al 1994], in which muscle pain may be induced by exercise and the symptoms are alleviated by acetazolamide
- **Myotonia permanens**, a very severe form, in which continuous myotonic activity is noticeable on EMG. The continuous electrical myotonia leads to a generalized muscle hypertrophy (including face muscles) so severe that there has been confusion with Schwartz-Jampel syndrome [Lehmann-Horn et al 2004]. This condition is caused by a specific mutation in the *SCN4A* gene [Lerche et al 1993].

Paramyotonia congenita. The cardinal symptom of paramyotonia congenita is cold-induced muscle stiffness that increases with continued activity (i.e., paradoxical myotonia). Characteristic is the inability to reopen the eyes after several forceful closures in rapid succession. Paramyotonia is usually not induced or aggravated by potassium. In most families, the stiffness gives way to flaccid weakness or even to paralysis on intensive exercise and cooling:

- Families with p.Arg1448Ser, p.Arg1448Cys, p.Arg1448His, and p.Arg1448Pro substitutions also have attacks of generalized hyperkalemic periodic paralysis provoked by rest or ingestion of potassium lasting for an hour or less. In contrast, the cold-induced weakness usually lasts several hours even when the muscles are immediately rewarmed.
- In a Japanese family, the mutation p.Met1370Val resulted in paramyotonia in one family member and in hyperkalemic periodic paralysis in others [Okuda et al 2001].

- In the typical hyperPP-causing mutations such as p.Thr704Met and p.Met1592Val, paramyotonic signs have been reported in single families [Kelly et al 1997, Kim et al 2001, Brancati et al 2003].

Hypokalemic periodic paralysis type 2. Hypokalemic periodic paralysis (HOKPP) is characterized by episodic attacks of flaccid weakness associated with a drop in serum potassium concentration (hypokalemia). The changes in serum potassium concentration are opposite to those seen in hyperPP1, as is the response to certain provocative tests: oral administration of potassium relieves an attack provoked by a carbohydrate-rich meal. No myotonia is detectable in this disease. The recurrent attacks are of longer duration than in hyperPP1; myopathy and permanent weakness also occur [Jurkat-Rott et al 2000]. *SCN4A* substitution mutations at codon 672 (p.Arg672Ser, p.Arg672Gly, p.Arg672Cys, p.Arg672His) and p.Arg669His cause HOKPP2.

Normokalemic periodic paralysis (see also Nomenclature). A type of periodic paralysis with normokalemic episodes of weakness reminiscent of both hyperPP and HOKPP has been reported: potassium sensitivity resembles hyperPP whereas all other features resemble HOKPP. This phenotype, named normokalemic periodic paralysis, is caused by *SCN4A* substitution mutations at codon 675 [Vicart et al 2004]. Codon 675 encodes an arginine in the voltage sensor of domain 2 of the sodium channel next to codons Arg669 and Arg672, which are responsible for HOKPP. It is unclear at present whether the term normokalemic periodic paralysis will continue to be used. Most of the patients in the authors' cohort were hypokalemic during paralytic attacks.

Congenital myasthenic syndrome is associated with fatigable generalized muscle weakness and recurrent attacks of respiratory and bulbar paralysis from birth. Congenital myasthenic syndrome is caused by an *SCN4A* mutation [Tsujino et al 2003].

Clinical Description

Natural History

The attacks of flaccid muscle weakness associated with hyperkalemic periodic paralysis type 1 (hyperPP1) usually begin in the first decade of life and increase in frequency and severity over time. Potassium-rich food or rest after exercise may precipitate an attack [Lehmann-Horn et al 2004]. Also, a cold environment, emotional stress, glucocorticoids, and pregnancy provoke or worsen the attacks.

A spontaneous attack commonly starts in the morning before breakfast, lasts for 15 minutes to an hour, and then passes. In some individuals, paresthesias, probably induced by the hyperkalemia, herald the weakness. During an attack of weakness, the muscle stretch reflexes are abnormally diminished or absent.

Sustained mild exercise after a period of strenuous exercise may postpone or prevent the weakness in the muscle groups being exercised and improve the recovery of muscle force, while the resting muscles become weak.

Usually, cardiac arrhythmia or respiratory insufficiency does not occur during the attacks.

In approximately 50% of individuals with hyperPP1, mild myotonia (muscle stiffness) that does not impede voluntary movements is present between attacks. Myotonia is most readily observed in the facial, lingual, thenar, and finger extensor muscles; if present, it supports the diagnosis of hyperPP1 as opposed to other forms of familial periodic paralysis.

Initially infrequent, the attacks increase in frequency and severity over time until approximately age 50 years, after which the frequency declines considerably. However, many older individuals develop a chronic progressive myopathy [Bradley et al 1990] with permanent weakness that may go unrecognized. The myopathy mainly affects the pelvic girdle and proximal and distal lower-limb muscles.

Genotype-Phenotype Correlations

Given the clinical variability within a single family (i.e., among individuals with the same mutation), mutation differences can be interpreted as causing a tendency to develop a feature, rather than actually causing a discrete feature (see Table 2).

The most notable tendency is that individuals without interictal myotonia are much more prone to develop progressive myopathy and permanent weakness than individuals with myotonia. This becomes especially obvious in individuals with the p.Thr704Met mutation without myotonia, approximately half of whom develop permanent myopathy. Furthermore, some individuals with "normokalemic periodic paralysis" (a term no longer in use: see Nomenclature) have had this common mutation as well [Lehmann-Horn et al 1993].

Table 2. Genotype-Phenotype Correlations in HyperPP1

SCN4A Mutation	Special Features	First Report
p.Leu689Ile	Pain resulting from muscle cramping	Bendahhou et al [2002]
p.Ile693Thr	Cold-induced weakness	Plassart et al [1996]
p.Thr704Met	Permanent weakness, myopathy	Ptácek et al [1991]
p.Ala1156Thr	Reduced penetrance	McClatchey et al [1992]
p.Met1360Val	Reduced penetrance	Wagner et al [1997]
p.Met1370Val	Paramyotonia in one family, hyperPP in others	Okuda et al [2001]
p.Ile1495Phe	Cramping pain, muscle atrophy	Bendahhou et al [1999]
p.Met1592Val	Classic clinical features with EMG myotonia	Rojas et al [1991]
p.Phe1490Leu+ p.Met1493Ile	Malignant hyperthermia susceptibility[1]	Bendahhou et al [2000]

1. The anesthesia-related events could have been exaggerated myotonic reactions as in several other individuals with gain-of-function sodium channel mutations [Klingler et al 2005].

Penetrance

Usually, the penetrance is high (>90%). A few individuals with rare mutations do not present with clinically detectable symptoms but have signs of myotonia detectable by EMG only [McClatchey et al 1992, Wagner et al 1997].

Anticipation

Anticipation is not observed in this disorder.

Nomenclature

Hyperkalemic periodic paralysis was first described in the 1950s. Originally, it was known as "adynamia episodica hereditaria" or Gamstorp disease. Because potassium can provoke an attack of weakness and because a spontaneous attack is usually associated with an increase in serum potassium concentration, the term hyperkalemic periodic paralysis (hyperPP) is recommended [Lehmann-Horn et al 1993].

It has been suggested that the term normokalemic periodic paralysis should be abandoned. The term was originally applied to findings in two reports [Poskanzer & Kerr 1961, Meyers et al 1972]. Normokalemic period paralysis resembles hyperPP in many aspects; the only real differences are the lack of serum potassium concentration increase, even during serious attacks, and the lack of a beneficial effect of glucose administration. The existence of normokalemic PP as a nosologic entity has been questioned because of the potassium sensitivity and the identification of *SCN4A* mutations in families with normokalemic PP, including the original family described by Poskanzer and Kerr [Lehmann-Horn et al 1993, Chinnery et al 2002]. Because the diagnosis of normokalemic PP was often made only as a result of a normal serum potassium concentration during or after an attack of weakness, and because a separate clinical or genetic entity has not been convincingly proven, the term should be abandoned.

A potassium-sensitive type of periodic paralysis with normokalemia and episodes of weakness reminiscent of both hyperPP and HOKPP caused by *SCN4A* mutations at codon 675 was named normokalemic periodic paralysis [Vicart et al 2004] (see Genetically Related Disorders). It is unclear at present whether the scientific community will continue to use the term.

Prevalence

The prevalence of hyperPP1 is approximately 1:200,000.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

In addition to the allelic disorders described in Genetically Related Disorders, hereditary disorders with periodic paralysis or with hyperkalemia to consider when making the diagnosis of hyperkalemic periodic paralysis type 1 (hyperPP1) are discussed below. Adult onset of clinical manifestations points to other diagnoses such as the Andersen-Tawil syndrome or secondary acquired forms of hyperPP.

HyperPP1, caused by mutations in *SCN4A,* accounts for approximately 60% to 70% of hyperPP; the other gene(s) causing hyperPP are unknown:

- At least one other locus, Xp27.3, has been mapped; the causative gene has not yet been identified [Ryan et al 1999]. Potassium levels are near normal but tend to vary within as well as among affected individuals. Episodes of severe muscle weakness, typically precipitated by febrile illness, affect the facial and extraocular musculature as well as the trunk and limbs, and resolve spontaneously over a period of weeks to months. Younger members of the family are normal between episodes but during relapses show generalized weakness, ptosis, and fluctuations in strength. In some cases, fatigability can be demonstrated and late-onset chronic weakness can occur.
- Both hyperPP and hypokalemic periodic paralysis (HOKPP) were reported to be caused by a mutation in another gene, *KCNE3* (reference sequence NP_005463), resulting in a p.Arg83His substitution in a K+ channel beta subunit, MiRP2 [Abbott et al 2001]. Subsequent studies showed that p.Arg83His is a normal allelic variant with a prevalence of more than 1% in the general population, and mutations in *KCNE3* do not cause periodic paralysis [Sternberg et al 2003, Jurkat-Rott & Lehmann-Horn 2004].

Andersen-Tawil syndrome (potassium-sensitive cardiodysrhythmic type of periodic paralysis). Andersen-Tawil syndrome is characterized by the triad of episodic flaccid muscle weakness (i.e., periodic paralysis), ventricular arrhythmias and prolonged QT interval, and common anomalies such as low-set ears, ocular hypertelorism, small mandible, fifth-digit

clinodactyly, syndactyly, short stature, and scoliosis. In the first or second decade, affected individuals present with either cardiac symptoms (palpitations and/or syncope) or weakness that occurs spontaneously following prolonged rest or rest after exertion. Mutations in the potassium channel gene *KCNJ2* are causative [Plaster et al 2001]. Inheritance is autosomal dominant.

Molecular genetic testing, electrocardiogram, and Holter recording obtained between attacks of weakness are very important for distinguishing between hyperPP1 and Andersen-Tawil syndrome.

Hyperkalemic periodic paralysis with multiple sleep-onset REM periods. An individual with sporadic hyperPP and excessive daytime sleepiness with multiple sleep-onset REM periods has been reported. Symptoms were improved by a diuretic that decreased serum potassium concentration [Iranzo & Santamaria 1999]. Genetic analysis has not been performed.

Hereditary disorders characterized by hyperkalemia

- Adrenal insufficiency is characterized by hyperkalemia, hyponatremia, and hypoglycemia. Adrenal insufficiency in infancy may be caused by congenital adrenal hyperplasia (most commonly caused by 21-hydroxylase deficiency) and congenital adrenal hypoplasia including X-linked adrenal hypoplasia congenita. Adrenal cortical hypofunction (Addison disease) can be an autoimmune disorder with familial aggregation or combined with other endocrinopathies, particularly hypoparathyroidism. Addison disease also occurs in X-linked adrenoleukodystrophy.
- Recessive infantile hypoaldosteronism, another hyperkalemic disorder, leads to a rare form of salt wasting that may be life threatening during the first years of life. Recurrent dehydration and severe failure to thrive, associated with mild hyponatremia and hyperkalemia, are typical features. Laboratory tests reveal elevated plasma renin-to-serum aldosterone ratios and serum 18-hydroxycorticosterone to aldosterone ratios [Picco et al 1992].
- Pseudohypoaldosteronism type I is characterized by neonatal salt-wasting resistant to mineralocorticoids. The autosomal recessive form with symptoms persisting into adulthood is caused by loss-of-function mutations in one of the three homologous subunits forming the amiloride-sensitive epithelial sodium channel, ENaC [Chang et al 1996]. The channel is rate limiting for electrogenic sodium reabsorption, particularly in the distal part of the renal tubule. The autosomal dominant or sporadic form shows milder symptoms that remit with age. Truncation of the mineralocorticoid receptor has been identified in one family [Viemann et al 2001].
- Pseudohypoaldosteronism type II, also known as Gordon hyperkalemia-hypertension syndrome, is characterized by hypertension, increased renal salt reabsorption, and impaired potassium and hydrogen excretion resulting in hyperkalemia that may be improved by thiazide diuretics. Mutations have been identified in members of the WNK family of serine-threonine kinases expressed in the distal nephron, a kidney segment involved in salt, potassium, and pH homeostasis [Wilson et al 2001].

Periodic paralysis secondary to acquired sustained hyperkalemia. This type of periodic paralysis can occur in any individual when the serum potassium concentration exceeds 7 mmol/L. Weakness can be accompanied by glove-and-stocking paresthesias. Hyperkalemia can cause cardiac arrhythmia, usually tachycardia, and typical ECG abnormalities (i.e., T-wave elevation, disappearance of P waves). Rest after exercise provokes weakness as in hyperPP1. The diagnosis is suggested by very high serum potassium concentration during the attack, persistent hyperkalemia between attacks, and the underlying disorder. Serum potassium concentrations are far higher than those in hyperPP1. The usual cause is chronic use of medications such as

spironolactone, ACE inhibitors, trimethoprim, nonsteroidal anti-inflammatory drugs, and heparin. Myopathies associated with paroxysmal myoglobinuria (e.g., McArdle disease, carnitine palmitoyltransferase II transferase deficiency) can damage the kidney and thus also lead to potassium retention. Therapy of acquired sustained hyperkalemia involves restriction of dietary potassium intake and treating the underlying cause of the hyperkalemia.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with hyperkalemic periodic paralysis type 1 (hyperPP1), the following baseline examinations are recommended:

- Neurologic status
- ^{1}H MRI (STIR) of proximal leg muscles to identify muscular water accumulation and fatty muscle degeneration [Weber et al 2006]; edema should be extruded with long-term diuretics; evaluate by muscle strength measurement and MRI four weeks after start of treatment.

Treatment of Manifestations

Treatment for hyperPP1 is symptomatic and not curative.

Attacks can often be prevented or aborted by continuing mild exercise and/or oral ingestion of carbohydrates at the onset of weakness (e.g., 2 g glucose per kg body weight). Attacks occur more frequently on holidays and weekends when people rest in bed longer than usual; individuals are advised to rise early and have a full breakfast.

In some individuals attacks can be aborted or attenuated by intravenously injected glucocorticoids or the inhalation of two puffs of 0.1 mg salbutamol.

Calcium gluconate (0.5-2 g taken intravenously) may terminate attacks in some individuals [Lehmann-Horn et al 2004].

Prevention of Primary Manifestations

Preventive therapy for individuals with hyperPP1 consists of frequent meals rich in carbohydrates and avoidance of potassium-rich medications and foods (e.g., fruits, fruit juices), fasting, strenuous work, and exposure to cold.

It is often advisable to prevent hyperkalemic attacks of weakness by the continuous use of a thiazide diuretic or acetazolamide. The diuretics are used in modest dosages at intervals from twice daily to twice weekly. Thiazide diuretics are preferable because of the possible complications of acetazolamide therapy. The dosage should be kept as low as possible (e.g., 25 mg hydrochlorothiazide daily or every other day). In severe cases, 50 mg or 75 mg of hydrochlorothiazide should be taken daily very early in the morning. Individuals should be monitored so that the serum potassium concentration does not fall below 3.3 mmol/L or the serum sodium concentration below 135 mmol/L [Lehmann-Horn et al 2004].

Prevention of Secondary Complications

Preventive measures before surgery including maintaining a normal body temperature, maintaining serum potassium concentration at low level, and avoiding hypoglycemia, help to prevent attacks [Mackenzie et al 2006].

Note: Because the generalized muscle spasms associated with such attacks may lead to an increase in body temperature, individuals with hyperPP1 have been considered to be susceptible to malignant hyperthermia. Most likely, anesthesia-related complications suggestive of a malignant hyperthermia crisis result from severe myotonic reactions [Lehmann-Horn et al 2004, Klingler et al 2005].

Surveillance

During prophylatic treatment, measure serum potassium concentration twice per year to avoid severe diuretic-induced hypokalemia. The value should be between 3.0 and 3.5 mM.

Assessment of neurologic status and MRI of proximal leg muscles every three years is appropriate.

Agents/Circumstances to Avoid

Depolarizing anesthetic agents including potassium, suxamethonium, and anticholinesterases aggravate myotonia. Masseter spasm and stiffness of respiratory and, occasionally, other skeletal muscles can occur and impair intubation and mechanical ventilation. Upon awakening from general anesthesia, individuals with hyperPP1 may be paralyzed for several hours. These agents are therefore strictly contraindicated [Klingler et al 2005].

Testing of Relatives at Risk

It is appropriate to test asymptomatic at-risk family members for the disease-causing mutation identified in an affected relative in order to institute preventive measures prior to surgery.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Whether the spontaneous attacks of weakness usually associated with hyperPP1 are influenced by mexiletine (the drug of choice for several allelic disorders) is unknown.

No data concerning the influence of therapeutic drugs on the development of the myopathy are available.

Cation exchangers are not beneficial in treating hyperPP1.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Hyperkalemic periodic paralysis type 1 (hyperPP1) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals with hyperPP1 have an affected parent from whom they have inherited the disorder.
- A proband with hyperPP1 may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* mutations is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include molecular genetic testing of both parents if the disease-causing mutation has been identified in the proband.

Note: Although most individuals diagnosed with hyperPP1 have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance in family members with the disease-causing mutation.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the parents.
- If a parent has the disease-causing mutation, the risk to the sibs is 50%.
- If a disease-causing mutation is not detected in the DNA of either parent, the risk to the sibs of a proband corresponds to the probability of developing a *de novo* mutation or to the probability of germline mosaicism in a parent. Although these possibilities are unlikely, it is appropriate to consider the sibs to be at risk and to test them for the mutation identified in the proband.

Offspring of a proband. Each child of an individual with hyperPP1 has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents. If a parent is affected or has an *SCN4A* disease-causing mutation, his or her family members are at risk.

Related Genetic Counseling Issues

See Management for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical

evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The *SCN4A* disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions such as hyperPP1 that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Hyperkalemic Periodic Paralysis Type 1

Gene Symbol	Chromosomal Locus	Protein Name
SCN4A	17q23.1-q25.3	Sodium channel protein type 4 subunit alpha

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Hyperkalemic Periodic Paralysis Type 1

170500	HYPERKALEMIC PERIODIC PARALYSIS; HYPP
603967	SODIUM CHANNEL, VOLTAGE-GATED, TYPE IV, ALPHA SUBUNIT; SCN4A

Table C. Genomic Databases for Hyperkalemic Periodic Paralysis Type 1

Gene Symbol	Entrez Gene	HGMD
SCN4A	6329 (MIM No. 603967)	SCN4A

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Hyperkalemic periodic paralysis type 1 (hyperPP1) mutations are situated at several disseminated, intracellularly faced positions potentially involved in the formation of the inactivation apparatus [Lehmann-Horn & Jurkat-Rott 1999]. Therefore, they lead to incomplete or slowed fast inactivation and a pathologically increased sodium current; the result is an increased tendency of the muscle fibers to depolarize.

The degree of depolarization determines the clinical symptoms: slight depolarizations near the sodium channel threshold result in repetitive muscle action potentials (→hyperexcitability = myotonic bursts in the EMG or clinically obvious myotonia); stronger depolarizations beyond the threshold lead to sodium channel inactivation and abolition of action potentials (→ reduced excitability resulting in muscle weakness) [Lehmann-Horn et al 1987]. The myotonia and the paralysis are thus caused by the same mechanism. The dominance of the mutation results from the fact that the mutation is decisive for excitability; i.e., it produces a so-called dominant gain of function. Potassium has no direct effect on the mutant channel but triggers an attack as a result of membrane depolarization that opens the sodium channels [Wagner et al 1997]. Whereas the normal channels properly inactivate, the mutant channels do not.

Usually, a sodium current caused by incomplete fast inactivation should be terminated by slow channel inactivation. However, several hyperPP1-causing mutations also impair slow inactivation [Cummins & Sigworth 1996]. Although not essential for the occurrence of a paralytic attack, this incomplete slow inactivation presumably stabilizes the persistence of the sodium current, making the depolarization of the muscle fibers long enough to be clinically obvious. Several hyperPP mutations are situated in the intracellular S4-S5 loops of the channel that act in a cooperative manner for proper fast inactivation and, dependent on the domain, are important for activation and deactivation [Popa et al 2004], whereas voltage sensor mutations mainly affect channel deactivation [Groome et al 2007].

Normal allelic variants: *SCN4A* contains 24 exons. See Table 3, Normal allelic variants.

Pathologic allelic variants: See Molecular Genetic Testing and Table 3, Pathologic allelic variants.

Table 3. *SCN4A* Allelic Variants Discussed in This GeneReview

Class of Variant Allele	DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence	Reference
Normal	c.737C>T	p.Ser246Leu	NM_000334.4 NP_000325.4	Tsujino et al [2003]
	c.968C>T	p.Thr323Met		Wu et al [2005]
	c.2341G>A	p.Val781Ile		Green et al [1997]
	c.2717G>C	p.Ser906Thr		Kuzmenkin et al [2003]
Pathologic	c.2065C>A	p.Leu689Ile		Bendahhou et al [2002]
	c.2078T>C	p.Ile693Thr		Plassart et al [1996]
	c.2111C>T	p.Thr704Met		Ptácek et al [1991]
	c.3466G>A	p.Ala1156Thr		McClatchey et al [1992]
	c.4078A>G	p.Met1360Val		Wagner et al [1997]
	c.4108A>G	p.Met1370Val		Okuda et al [2001]
	c.4483A>T	p.Ile1495Phe		Bendahhou et al [1999]
	c.4774A>G	p.Met1592Val		Rojas et al [1991]
	c.[4468T>C; 4479G>A] [1]	p.[Phe1490Leu; Met1493Ile] [1]		Bendahhou et al [2000]

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (http://www.hgvs.org).

1. Designates two variants in one allele

Normal gene product: The α subunit of the voltage-gated sodium channel of skeletal muscle comprises 1836 amino acids. The sodium channel of skeletal muscle is decisive for generating the so-called action potential, the signal by which excitation spreads over the muscle fiber in order to initiate a uniform contraction response [Lehmann-Horn & Jurkat-Rott 1999]. The main sodium channel subunit (the so-called α subunit) is mutated in hyperPP1. It is arranged as four homologous domains around a central ion-conducting pore. The α subunit determines the main characteristics of the sodium channel, conveying the properties of ion selectivity, voltage sensitivity, pharmacology, and binding characteristics for endogenous and exogenous ligands. The accessory β subunit has one transmembrane segment and binds to the α subunit with an extracellular immunoglobulin-like fold with a stoichiometry of 1:1. It influences channel expression, trafficking, and gating characteristics.

The voltage-sensitive sodium channel has one open and at least two closed states: one from which the channel can be directly activated (the resting state) and one from which it cannot (the inactivated state) [Lehmann-Horn & Jurkat-Rott 1999]. This implies that at least two gates regulate the opening of the pore, an activation and an inactivation gate, both of which are usually mediated by the α subunit. In addition to the inactivated state produced by depolarizations of short duration, another inactivated state, the so-called slow inactivated state, has been described. It is elicited by long-lasting depolarizations [Ruff 1996]. Recovery from this state requires several seconds, in contrast to recovery from the fast inactivated state, which takes only a few milliseconds.

Abnormal gene product: It is not known which parts of the channel protein are involved in generating the slow inactivated state, but functional studies of the mutations suggest that regions mutated in hyperPP1 are of importance. Because no long-lasting depolarizations physiologically exist (except in the diseased state), changes in the slow inactivated state may

be associated with frequency modulation of the early postsynaptic potential of the neuromuscular endplate. Research has therefore included studies of high frequency-induced changes of inactivation [Richmond et al 1997].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Hyperkalemic periodic paralysis

Periodic Paralysis Association
1024 Royal Oaks Drive #620
Monrovia, CA 91016
Phone: 626-303-3244
Fax: 626-337-1966
Email: inquire@periodicparalysis.org
www.periodicparalysis.org

Periodic Paralysis News Desk
9751 Elbow Drive SW
Calgary, Alberta
Canada T2V 1M4
Phone: 403-244-7213
Email: calexeditor@nucleus.com
www.hkpp.org

Malignant Hyperthermia Association of the United States (MHAUS)
PO Box 1069
11 East State Street
Sherburne, NY 13460
Phone: 800-644-9737 (US and Canada); 607-674-7901; 001-1-315-428-7925 (International)
Fax: 607-674-7910
Email: info@mhaus.org
www.mhaus.org

Muscular Dystrophy Association (MDA)
3300 East Sunrise Drive
Tucson, AZ 85718-3208
Phone: 800-572-1717; 520-529-2000
Fax: 520-529-5300
Email: mda@mdausa.org
www.mdausa.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Author Notes

Applied Physiology - University of Ulm
Voltage-Gated Ion Channels and Hereditary Disease

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Revision History

- 25 April 2008 (me) Comprehensive update posted to live Web site
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- 2 March 2005 (cd) Revision: sequencing of select exons clinically available
- 18 July 2003 (me) Review posted to live Web site
- 27 January 2003 (kjr) Original submission