Hyperkalemic Periodic Paralysis

Synonym: HyperPP

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Author Information

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Summary

Clinical characteristics.

Hyperkalemic periodic paralysis (hyperPP) 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 between attacks, and onset before age 20 years. Although the absence of paramyotonia (muscle stiffness aggravated by cold and exercise) was originally postulated as a means of distinguishing hyperPP from paramyotonia congenita (PMC), approximately 45% of individuals with hyperPP have paramyotonia. In approximately half of affected individuals, attacks of flaccid muscle weakness begin in the first decade of life, with 25% reporting their first attack at age ten years or older. 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 and emotional stress 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, approximately half of individuals with hyperPP have mild myotonia (muscle stiffness) that does not impede voluntary movements. More than 80% of individuals with hyperPP older than 40 years report permanent muscle weakness and about one third develop a chronic progressive myopathy.

Diagnosis/testing.

Diagnosis is based on clinical findings and/or the identification of a heterozygous pathogenic variant in SNC4A. In case of diagnostic uncertainty, one of three provocative tests can be employed.

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 a carbonic anhydrase inhibitor, 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: Periodic assessment of neurologic status; in those with permanent muscle weakness, continuous medication (ie thiazide diuretic) and MRI of proximal leg muscles every one to three years; during prophylactic treatment, determination of serum potassium concentration twice per year to avoid severe diuretic-induced hypokalemia; annual monitoring of thyroid function.

Agents/circumstances to avoid: Potassium-rich medications and foods, fasting, strenuous work, exposure to cold, and use of depolarizing anesthetic agents during general anesthesia.

Evaluation of relatives at risk: It is appropriate to test asymptomatic at-risk family members for the pathogenic variant identified in an affected relative in order to institute preventive measures prior to surgery.

Genetic counseling.

HyperPP is inherited in an autosomal dominant manner. Most individuals with hyperPP have an affected parent; the proportion of cases caused by a de novo pathogenic variant is unknown. Each child of an individual with hyperPP has a 50% chance of inheriting the pathogenic variant. Prenatal diagnosis for pregnancies at increased risk is possible if the pathogenic variant in the family has been identified.

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## Diagnosis

### Suggestive Findings

Hyperkalemic periodic paralysis (hyperPP) **should be suspected** in individuals with the following clinical, family history, electromyogram (EMG), and suggestive laboratory findings:

**Clinical findings**

- History of at least two attacks of flaccid limb weakness (which may also include weakness of the muscles of the eyes, throat, breathing muscles and trunk)
- Onset or worsening of an attack as a result of oral potassium intake
- Disease manifestations before age 20 years
- Absence of cardiac arrhythmia between attacks
- Normal psychomotor development
Family history

- Typically, at least one affected first-degree relative
  Note: Absence of a family history suggestive of hyperPP does not preclude the diagnosis.

Electromyogram (EMG)

- 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 muscle fiber 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.
  Note: Approximately 50% of affected individuals have no detectable electrical myotonia.

Suggestive laboratory findings during attacks

- Hyperkalemia (serum potassium concentration >5 mmol/L) or an increase of serum potassium concentration of at least 1.5 mmol/L
  Note: Serum potassium concentration seldom reaches cardiotoxic levels, but changes in the ECG (increased amplitude of T waves) may occur.
- Elevated serum creatine kinase (CK) concentration (sometimes 5-10x the normal range)

Suggestive laboratory findings between attacks

- Normal serum potassium concentration and muscle strength between attacks
  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.
- Elevated serum CK concentration with normal serum sodium concentration

Establishing the Diagnosis

The diagnosis of hyperkalemic periodic paralysis (hyperPP) is established in a proband with the above suggestive findings in whom other hereditary forms of hyperkalemia (see Differential Diagnosis) and acquired forms of hyperkalemia (drug abuse; renal and adrenal dysfunction) have been excluded and/or by the identification of a heterozygous pathogenic variant in SCN4A by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include single-gene testing, use of a multi-gene panel, and more comprehensive genomic testing.

Single-gene testing

1.

Sequence analysis of SCN4A is performed first.
2. If no pathogenic variant is identified, sequencing of KCNJ2 and CACNA1S may be considered (see Differential Diagnosis).

A multi-gene panel that includes SCN4A and other genes of interest (see Differential Diagnosis) may also be considered. Note: The genes included and sensitivity of multi-gene panels vary by laboratory and over time.

More comprehensive genomic testing (when available) including whole-exome sequencing (WES), whole-genome sequencing (WGS), and whole mitochondrial sequencing (WMitoSeq) may be considered if serial single-gene testing (and/or use of a multi-gene panel that contains SCN4A) fails to confirm a diagnosis in an individual with features of hyperPP. For issues to consider in interpretation of genomic test results, click here.

Table 1.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Test Method</th>
<th>Proportion of Probands with Pathogenic Variants</th>
<th>Detectable by This Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN4A</td>
<td>Sequence analysis</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

4. Ten common pathogenic variants are listed in Table 3; p.Thr704Met alone accounts for 69% of pathogenic variants [Jurkat-Rott & Lehmann-Horn 2007].

5. Authors, personal observation
At least one other locus, Xp27.3, has been mapped but the relevant gene has not yet been identified [Ryan et al 1999].

**Provocative tests.** In case of diagnostic uncertainty (i.e., in the absence of a measurement of ictal (during an attack) serum potassium concentration and normal molecular genetic studies), provocative tests may 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 pathogenic variant.

**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 hyperPP.

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**Clinical Characteristics**

**Clinical Description**

The attacks of flaccid muscle weakness associated with hyperkalemic periodic paralysis (hyperPP) usually begin in the first decade of life and increase in frequency and severity over time, with 25% experiencing their sentinel attack in the second decade of life. Triggers include cold environment, rest after exercise, stress or fatigue, alcohol, hunger, changes in activity level, potassium in food, specific foods or beverages, changes in humidity, extra sleep, pregnancy, illness of any type, menstruation, medication, and potassium supplements [Charles et al 2013].

A spontaneous attack commonly starts in the morning before breakfast, lasts for 15 minutes to an hour, and then passes. In about 20% of affected individuals the attacks last considerably longer, from more than two days to over one week. 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. After an attack, affected individuals report clumsiness, weakness, and irritability, and in 62% muscle pain secondary to the attack. Between attacks, the majority report no or mild symptoms. However, 12% report severe symptoms between attacks that impair activities of daily living.

In more than 50% of individuals with hyperPP, 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 hyperPP as opposed to other forms of familial periodic paralysis. Paramyotonia (muscle stiffness aggravated by cold and exercise) is present in about 45% of affected individuals.

Initially infrequent, the attacks increase in frequency and severity over time until approximately age 50 years, after which the frequency declines considerably. However, more than 80% of the affected individuals older than 40 years report permanent muscle weakness and approximately one third of older affected individuals develop a chronic progressive myopathy [Bradley et al 1990]. The myopathy mainly affects the pelvic girdle and proximal and distal lower-limb muscles.

As shown by a recent observational study, individuals with hyperPP appear to be at higher risk for thyroid dysfunction (relative risk of 3.6) than those in the general population [Charles et al 2013].

Genotype-Phenotype Correlations

Given the clinical variability within a single family (i.e., among individuals with the same pathogenic variant), differences between pathogenic variants 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 pathogenic p.Thr704Met variant, who usually do not have myotonia but in whom permanent myopathy commonly develops (~50% of individuals). Some individuals with "normokalemic periodic paralysis" have also had this common pathogenic variant [Lehmann-Horn et al 1993].

Table 2.

Genotype-Phenotype Correlations in HyperPP
### SCN4A Pathogenic Variant

<table>
<thead>
<tr>
<th>Variant</th>
<th>Special Features</th>
<th>First Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.Asn440Lys</td>
<td>Both hyperPP and paramyotonia and potassium aggravated myotonia</td>
<td>Lehmann-Horn et al [2011]</td>
</tr>
<tr>
<td>p.Arg675Gln</td>
<td>Both hyperPP and normoPP and paramyotonia</td>
<td>Liu et al [2015], Vicart et al [2004]</td>
</tr>
<tr>
<td>p.Leu689Ile</td>
<td>Pain resulting from muscle cramping</td>
<td>Bendahhou et al [2002]</td>
</tr>
<tr>
<td>p.Ile693Thr</td>
<td>Cold-induced weakness</td>
<td>Plassart et al [1996]</td>
</tr>
<tr>
<td>p.Thr704Met</td>
<td>Permanent weakness, myopathy</td>
<td>Ptácek et al [1991]</td>
</tr>
<tr>
<td>p.Ala1156Thr</td>
<td>Reduced penetrance</td>
<td>McClatchey et al [1992]</td>
</tr>
<tr>
<td>p.Met1360Val</td>
<td>Reduced penetrance</td>
<td>Wagner et al [1997]</td>
</tr>
<tr>
<td>p.Met1370Val</td>
<td>Paramyotonia in one family, hyperPP in others</td>
<td>Okuda et al [2001]</td>
</tr>
<tr>
<td>p.Ile1495Phe</td>
<td>Cramping pain, muscle atrophy</td>
<td>Bendahhou et al [1999b]</td>
</tr>
<tr>
<td>p.Met1592Val</td>
<td>Classic clinical features with EMG myotonia</td>
<td>Rojas et al [1991]</td>
</tr>
<tr>
<td>p.[Phe1490Leu;Met1493Ile]</td>
<td>Malignant hyperthermia susceptibility</td>
<td>Bendahhou et al [2000]</td>
</tr>
</tbody>
</table>

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

### Penetration

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

### 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 periodic 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 pathogenic variants in families with normokalemic PP, including the original family described by Poskanzer and Kerr [Lehmann-Horn et al 1993, Chinnery et al 2002].
The name normokalemic periodic paralysis was used to describe a potassium-sensitive type of periodic paralysis with normokalemia and episodes of weakness reminiscent of both hyperPP and hypoPP (also known as HOKPP) caused by heterozygous pathogenic variants in SCN4A at codon 675 [Vicart et al 2004] (see Genetically Related Disorders). However, it has become clear that SCN4A pathogenic variants p.Arg675Gly, p.Arg675Gln, and p.Arg675Trp cause normokalemic PP (see Genetically Related Disorders).

**Prevalence**

The prevalence of hyperPP is approximately 0.17/100,000 (95% CI 0.13-0.20) [Horga et al 2013].

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**Genetically Related (Allelic) Disorders**

Several types of myotonia and periodic paralyses (PP) are caused by pathogenic variants in SCN4A.

**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 with continued exercise (warm-up phenomenon).

- **Acetazolamide-responsive myotonia**, also known as atypical myotonia congenita [Ptáček 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 heterozygous pathogenic variant in SCN4A [Lerche et al 1993].

**Paramyotonia congenita.** The cardinal symptom of paramyotonia congenita is cold-induced muscle stiffness that increases with continued activity (i.e., paradoxic 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 heterozygous pathogenic p.Asn440Lys, 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 pathogenic \texttt{p.Met1370Val} variant resulted in paramyotonia in one family member and in hyperkalemic periodic paralysis in others [Okuda et al 2001].
- In the typical hyperPP-causing pathogenic variants such as \texttt{p.Thr704Met} and \texttt{p.Met1592Val}, the signs of paramyotonia have been reported in single families [Kelly et al 1997, Kim et al 2001, Brancati et al 2003]. In a recent survey, paramyotonic signs were observed in 45.3% of individuals with hyperPP, regardless of the underlying pathogenic variant [Charles et al 2013].

**Hypokalemic periodic paralysis.** Hypokalemic periodic paralysis (hypoPP) 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 hyperPP, 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; the recurrent attacks are of longer duration than in hyperPP; myopathy and permanent weakness also occur [Jurkat-Rott et al 2000]. Heterozygous pathogenic \texttt{SCN4A} variants at codon 672 (\texttt{p.Arg672Ser}, \texttt{p.Arg672Gly}, \texttt{p.Arg672Cys}, \texttt{p.Arg672His}) and \texttt{p.Arg669His} cause hypoPP.

**Normokalemic periodic paralysis** (see also Nomenclature). A type of periodic paralysis with normokalemic episodes of weakness reminiscent of both hyperPP and hypoPP (also known as HOKPP) has been reported: potassium sensitivity resembles hyperPP whereas all other features resemble hypoPP. This phenotype, named normokalemic periodic paralysis, is caused by heterozygous pathogenic \texttt{SCN4A} substitutions at codon 675 [Vicart et al 2004]. \texttt{SCN4A} pathogenic variants \texttt{p.Arg675Gly}, \texttt{p.Arg675Trp}, and \texttt{p.Arg675Gln} generate cation currents that are activated by depolarization [Vicart et al 2004, Liu et al 2015]. This means that the omega currents caused by the pathogenic variant in the S4 (fourth transmembrane segment of each domain that contributes to voltage sensitivity) charges are conducted when S4 is in the activated or inactivated state, but not in the resting state. The associated phenotype differs slightly in the ictal serum potassium levels which can be low or normal (normokalemic periodic paralysis, NormoPP). Also, the reaction to oral potassium administration may be different than for HypoPP, anything from amelioration to worsening of the weakness [Jurkat-Rott et al 2012].

**Congenital myasthenic syndrome** is associated with fatigable generalized muscle weakness and recurrent attacks of respiratory and bulbar paralysis from birth. \texttt{SCN4A}-related congenital myasthenic syndrome is inherited in an autosomal recessive manner.

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**Differential Diagnosis**

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 (hyperPP) are discussed below. Adult onset of clinical manifestations points to other diagnoses such as the Andersen-Tawil syndrome or secondary acquired forms of hyperPP.
**Andersen-Tawil syndrome** (potassium-sensitive cardiodyssrhythmic 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, widely spaced eyes, 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. Heterozygous pathogenic variants 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 hyperPP and Andersen-Tawil syndrome. In the experience of the author, the cardiologic manifestations precede the neuromuscular ones.

**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**.

- Recurrent 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 (OMIM 264350) with symptoms persisting into adulthood is caused by pathogenic loss-of-function variants 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 (OMIM 177735) 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** (PHAII), also known as Gordon’s syndrome or **familial** hyperkalemia and hypertension, is characterized by hypertension, increased renal salt reabsorption, and impaired potassium and hydrogen excretion resulting in hyperkalemia that may be improved by thiazide diuretics. The genes in which **mutation** is known to cause PHAII are: *WNK4* (PHAIIB), *WNK1* (PHAIIC), *KLHL3*.
(PHAIID), and CUL3 (PHAIIE) All types of PHAII are inherited in an autosomal dominant manner; PHAIID may also be inherited in an autosomal recessive manner.

**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 hyperPP. 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 hyperPP. 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 deficiency) can damage the kidneys 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.

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**Management**

**Evaluations Following Initial Diagnosis**

To establish the extent of disease and needs in an individual diagnosed with hyperkalemic periodic paralysis (hyperPP), the following evaluations are recommended:

- Determine neurologic status
- Perform 1H 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.
- Consult with a medical geneticist and/or genetic counselor

**Treatment of Manifestations**

Treatment for hyperPP 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.
  - Both mild exercise and treatment with β2-stimulating agents appear to work by stimulating the Na+K+-pumps [Clausen et al 2011].
- Calcium gluconate (0.5-2 g taken intravenously) may terminate attacks in some individuals [Lehmann-Horn et al 2004].
Prevention of Primary Manifestations

**Diet/environment.** Preventive therapy for individuals with hyperPP consists of frequent meals rich in carbohydrates and avoidance of the following:

- Potassium-rich medications and foods (e.g., fruits, fruit juices)
- Fasting
- Strenuous work
- Exposure to cold

**Diuretics.** It is often advisable to prevent hyperkalemic attacks of weakness by the continuous use of a thiazide diuretic or a carbonic anhydrase inhibitor, such as acetazolamide or the recently approved medication dichlorphenamide. Diuretics are used in modest dosages at intervals from twice daily to twice weekly.

- Thiazide diuretics are preferable because they have fewer side effects than either acetazolamide or dichlorphenamide 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

**General anesthesia.** Opioids or depolarizing agents such as potassium, anticholinesterases, and succinylcholine can aggravate a myotonic reaction and induce masseter spasms and stiffness of respiratory muscles. Intubation and mechanical ventilation may be impaired. Also, alterations of serum osmolarity, pH, and hypothermia-induced muscle shivering and mechanical stimuli can exacerbate the myotonic reaction.

An induction sequence incorporating inhalation of oxygen, cricoid pressure, thiamyal or thiopental, and two times the ED95 dose of an intermediate or short-action non-depolarizing muscle relaxant, followed by intubation, is a reasonable approach to securing the airway in persons with myotonia. Alternatively, inhalational induction may be a possibility for hyperkalemic paralysis and is well tolerated in those undergoing elective surgery.

Following administration of general anesthesia, the affected individual may develop respiratory distress in the recovery room resulting from weakness of respiratory muscles in addition to generalized weakness lasting for hours. The weakness is aggravated by drugs that depress respiration and by the hypothermia induced by anesthesia.

To prevent such attacks, glucose should be infused, a normal body temperature maintained, and serum potassium kept at low level [Klingler et al 2005, Mackenzie et al 2006, Jurkat-Rott & Lehmann-Horn 2007, Barker 2010].

**Note:** Because the generalized muscle spasms associated with such attacks may lead to an increase in body temperature, individuals with hyperPP have been considered to be susceptible to malignant hyperthermia. Most likely, anesthesia-related complications

**Surveillance**

The frequency of consultations needs to be adapted to the individual's clinical features and the response to preventive treatment.

During prophylactic treatment, measure serum potassium concentration twice per year to avoid severe diuretic-induced hypokalemia.

Neurologic examination with attention to muscle strength in the legs should be performed, in order to detect permanent weakness.

Permanent weakness requires continuous medication, eg. with a thiazide diuretic, and MRI of the leg muscles once every one to three years. During treatment, serum potassium concentration should be measured twice per year to avoid severe diuretic-induced hypokalemia. The value should be between 3.0 and 3.5 mmol/L.

Annual monitoring of thyroid function is appropriate.

**Agents/Circumstances to Avoid**

See Prevention of Primary Manifestations and Prevention of Secondary Complications.

**Evaluation of Relatives at Risk**

It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from initiation of preventive measures, particularly those that would decrease the risk of unexpected acute paralysis or anesthetic events.

- Molecular genetic testing can be pursued if the pathogenic variant in the family is known.
- When the results of genetic testing or presymptomatic testing are not known, the related family members must be considered at risk for complications and precautions are indicated, particularly during anesthesia.

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

**Pregnancy Management**

More than 90% of affected women report an increase in attack frequency during pregnancy. While approximately 80% reported improved muscle weakness during attacks, 75% also reported worse muscle stiffness during attacks [Charles et al 2013].

Women who are chronically treated with a diuretic may continue treatment in pregnancy. Human data on prenatal exposure to acetazolamide have not demonstrated an increased risk of fetal malformations. Human data on the use of oral dichlorphenamide therapy during
pregnancy – and whether it leads to an increased risk of malformations in exposed fetuses – are limited.

**Therapies Under Investigation**

A study that compared treatment with dichlorphenamide to treatment with placebo for prevention of episodes and for improvement of strength in individuals with hyperPP and hypoPP has recently been completed; for results, see ClinicalTrials.gov.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

**Other**

Whether the spontaneous attacks of weakness usually associated with hyperPP 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 less beneficial than diuretics in treating hyperPP because they result in more severe side effects.

**Go to:**

**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. —ED.*

**Mode of Inheritance**

Hyperkalemic periodic paralysis (hyperPP) is inherited in an *autosomal dominant* manner.

**Risk to Family Members**

**Parents of a proband**

- Most individuals diagnosed with hyperPP have an *affected* parent.
- A *proband* with hyperPP may have the disorder as the result of a *de novo SCN4A* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is unknown.
- Recommendations for the evaluation of parents of a *proband* with an apparent *de novo* pathogenic variant include *molecular genetic testing* of both parents for the pathogenic variant identified in the proband.
• If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or *germline mosaicism* in a parent (although no instances of germline mosaicism have been reported, it remains a possibility).

• The family history of some individuals diagnosed with hyperPP may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the parents:

- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- The sibs of a proband with clinically unaffected parents are still at increased risk for hyperPP because of the possibility of reduced penetrance in a parent.
- If the SCN4A pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

**Offspring of a proband.** Each child of an individual with hyperPP has a 50% chance of inheriting the SCN4A pathogenic variant.

**Other family members.** The risk to other family members depends on the status of the proband’s parents; if a parent is affected, his or her family members may be at risk.

**Related Genetic Counseling Issues**

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

**Predictive testing** for at-risk asymptomatic adult family members requires prior identification of the SCN4A pathogenic variant in the family.

**Considerations in families with an apparent *de novo* pathogenic variant.** When neither parent of a proband with hyperPP has the pathogenic variant or clinical evidence of the disorder, the SCN4A pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or 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** 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,
allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

**Prenatal Testing and Preimplantation Genetic Diagnosis**

Once the SCN4A pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic diagnosis for a pregnancy at increased risk for hyperPP may be possible options.

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.

Go to:

**Resources**

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **National Library of Medicine Genetics Home Reference**

  Hyperkalemic periodic paralysis

- **Periodic Paralysis Association (PPA)**

  155 West 68th Street

  Suite 1732

  New York NY 10023

  **Phone:** 407-339-9499

  **Email:** lfeld@cfl.rr.com

  [www.periodicparalysis.org](http://www.periodicparalysis.org)

- **Periodic Paralysis News Desk**

  3919 Landry Crescent

  E-23

  Summerland British Columbia V0H 1Z9
**Canada**

**Phone:** 403-244-7213  
**Email:** calexeditor@nucleus.com

hkpp.org

- **Malignant Hyperthermia Association of the United States (MHAUS)**
  
  11 East State Street  
  PO Box 1069  
  Sherburne NY 13460  
  **Phone:** 800-644-9737 (Toll-free Emergency Hotline); 607-674-7901; 315-464-7079  
  **Fax:** 607-674-7910  
  **Email:** info@mhaus.org

www.mhaus.org

- **Muscular Dystrophy Association - USA (MDA)**
  
  222 South Riverside Plaza  
  Suite 1500  
  Chicago IL 60606  
  **Phone:** 800-572-1717  
  **Email:** mda@mdausa.org

www.mda.org

**Go to:**

**Molecular Genetics**

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.*

**Table A.**

Hyperkalemic Periodic Paralysis: Genes and Databases
Table B.

OMIM Entries for Hyperkalemic Periodic Paralysis ([View All in OMIM])

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

Molecular Genetic Pathogenesis

Hyperkalemic periodic paralysis (hyperPP)-causing pathogenic variants 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 pathogenic variant results from the fact that it 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 hyperPP-causing pathogenic variants 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-causing variants are situated in the intracellular S4-S5 loops of the channel that act in a cooperative manner for proper fast inactivation and, depending on the domain, are important for activation and deactivation [Popa et al 2004], whereas voltage sensor variants mainly affect channel deactivation [Groome et al 2007].

Gene structure. SCN4A contains 24 exons. For a detailed summary of gene and protein information, see Table A, Gene.
**Benign allelic variants.** See Table 3, Benign variants.

**Pathogenic allelic variants.** See Establishing the Diagnosis and Table 3, Pathogenic variants.

### Table 3.

*SCN4A* Variants Discussed in This *GeneReview*

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>DNA Nucleotide Change</th>
<th>Protein Amino Acid Change</th>
<th>Reference Sequences</th>
<th>Reference</th>
</tr>
</thead>
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<td>p.Thr323Met</td>
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<td>p.Ser906Thr</td>
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<td>p.Arg672Cys</td>
<td></td>
<td>Kim et al [2007]</td>
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<tr>
<td></td>
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<td>NM_000334.4</td>
<td>Jurkat-Rott et al [2000]</td>
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<td>p.Leu689Ile</td>
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<td>p.Ile693Thr</td>
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<td>Ptácek et al [1991]</td>
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<td>McClatchey et al [1992]</td>
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<td></td>
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<td>p.Met1360Val</td>
<td></td>
<td>Okuda et al [2001]</td>
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<td></td>
<td>c.4108A&gt;G</td>
<td>p.Met1370Val</td>
<td></td>
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<tr>
<td>Variant Classification</td>
<td>DNA Nucleotide Change</td>
<td>Protein Amino Acid Change</td>
<td>Reference Sequences</td>
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<tr>
<td>c.4342C&gt;A</td>
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<td></td>
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<td>p.[Phe1490Leu; Met1493Ile]</td>
<td>2, 3, 4</td>
<td></td>
<td>Bendahhou et al [2000]</td>
</tr>
</tbody>
</table>

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

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

1. See Genetically Related Disorders.

2. See Genotype-Phenotype Correlations.

3. A common pathogenic variant (see Table 1, footnote 4)

4. 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 hyperPP. 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 pathogenic variants suggest that regions mutated in hyperPP 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].

**Go to:**

**References**

**Literature Cited**

7. Brancati F, Valente EM, Davies NP, Sarkozy A, Sweeney MG, LoMonaco M, Pizzuti A, Hanna MG, Dallapiccola B. Severe infantile hyperkalaemic periodic paralysis and paramyotonia congenita: broadening the clinical spectrum associated with the T704M


