<table>
<thead>
<tr>
<th>Disorder</th>
<th>Hyperkalemic periodic paralysis</th>
<th>Paramytonia congenita</th>
<th>Myotonia Congenita</th>
<th>Familial hypokalemic periodic paralysis</th>
<th>Andersen-Tawil Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>Autosomal dominant</td>
<td>Autosomal dominant.</td>
<td>Autosomal dominant (Thomsen) or recessive (Becker)</td>
<td>Autosomal dominant</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Gene and gene locus</td>
<td>SCN4A on 17q23 Sodium channel</td>
<td>SCNA4A on 17q23</td>
<td>CLCN on 7q35</td>
<td>CACNL1A3 on 1q32 Calcium channel</td>
<td>Kir 2.1 (KCNJ2)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Generalized attacks of weakness. Weakness may become gradually permanent.</td>
<td>Muscular stiffness at the beginning of exposure to cold. Muscular weakness on prolonged exposure to cold. Paradoxical myotonia = myotonia worsened by exercise</td>
<td>Stiffness with sudden movement after resting.; warm up phenomenon = decreased myotonia with repeated motion; hypertrophied muscles; lid lag;</td>
<td>Generalized attacks of weakness. Weakness may become gradually permanent</td>
<td>Periodic paralysis (hyper or hypo); cardiac arrhythmia (long QT, ventricular arrhythmia, others); dysmorphic features (microcephaly, clinodactyly, low set ears, others)</td>
</tr>
<tr>
<td>First occurrence of symptoms</td>
<td>At the end of the first decade or beginning of the second decade</td>
<td>At birth</td>
<td>Thomsen – early childhood; Becker – 10 years old or later</td>
<td>Usually in the second decade</td>
<td>Variable</td>
</tr>
<tr>
<td>Frequency of attacks</td>
<td>A few times per year to daily</td>
<td>On every exposure to a cold environment</td>
<td>Daily</td>
<td>Extremely variable: from one to two attacks in a lifetime to daily</td>
<td>Can be daily</td>
</tr>
<tr>
<td>Severity of attacks</td>
<td>Occasionally, generalized paralysis. Frequently moderate weakness, often only in single muscle groups</td>
<td>Stiffness and weakness that become more severe the heavier the work in the cold. The lower the temperature, the more severe the weakness</td>
<td>Legs or generalized</td>
<td>Often, generalized paralysis. Sometimes, moderate weakness (e.g., of the arms or legs)</td>
<td>Often, generalized paralysis</td>
</tr>
<tr>
<td>Duration of attacks</td>
<td>Usually ½ - 1 hour, occasionally several hours</td>
<td>Stiffness only at the beginning of work in a cold environment. Weakness may last for hours after re-warming</td>
<td>Seconds to minutes</td>
<td>Several hours to several days</td>
<td>Minutes to hours</td>
</tr>
<tr>
<td>Time of day when symptoms appear</td>
<td>Early to late morning. Occasionally at any time of day</td>
<td>At any time when exposed to cold environment</td>
<td>Any time, esp. after rest</td>
<td>Second half of night. Early morning. Occasionally, late morning.</td>
<td>Any time</td>
</tr>
<tr>
<td>Triggering factors</td>
<td>Muscular exercise with subsequent rest (attack 20 – 30 minutes later). Cold. Hunger</td>
<td>Cooling and heavy muscular work, particularly in combination</td>
<td>Sudden noise; forceful movement after rest</td>
<td>Muscle exercise with subsequent rest (attack follows several hours later) Carbohydrate-rich meals. Stress. Cold.</td>
<td>Rest after exercise; carbohydrates; cold</td>
</tr>
<tr>
<td>Diagnostic provocation</td>
<td>Muscular exercise (ergometer or running upstairs). Administration of K+</td>
<td>Cooling of lower arm for 30 minutes in water of 12 – 15°C Repeated forceful closure of the fist</td>
<td>Exercise after rest; stair test: rest for 10 minutes in a chair, then climb 10 steps as fast as possible (normal 3 sec., myotonia 30 sec)</td>
<td>Administration of glucose with or without insulin (caution). Muscle exercise and carbohydrate-rich food the evening before the test</td>
<td>Muscular exercise.</td>
</tr>
<tr>
<td>Concomitant symptoms at the beginning of an attack</td>
<td>Myotonia, when present, increased. Cases without myotonia might present lid lag. Paresthesias common</td>
<td>Sensations of tension in the muscle</td>
<td>Muscle pain, sometimes</td>
<td>No myotonia. No sensory disturbance. Sometimes, paresthesias</td>
<td>Paresthesias, muscle discomfort</td>
</tr>
<tr>
<td>K+ in the serum during an attack</td>
<td>4.5 – 8.0 mM</td>
<td>3.5 – 4.5 mM</td>
<td>3.5 – 5.0 mM (i.e., normal)</td>
<td>2 – 3 mM</td>
<td>Variable (low, normal, or high)</td>
</tr>
<tr>
<td>Therapy</td>
<td>Preventive: frequent meals, acetazolamide,</td>
<td>Preventive: keeping the muscles warm, mexiletine. No</td>
<td>Behavior modification; Mexiletine</td>
<td>Preventive: acetazolamide, dichlrophamamide,</td>
<td>Preventative: acetazolamide; dichlrophamamide;</td>
</tr>
</tbody>
</table>
While "classical" descriptions of the diseases are found here, individuals commonly can display a wide range of "non-textbook" signs and symptoms.

Disorders:

**Familial (aka Primary) Hypokalemic Periodic Paralysis:**
- **presentation:** episodic weakness, lasts for minutes to hours
- **triggers:** rest after exercise, high carbohydrate meals, salt
- **treatment acutely:** potassium (orally when possible)
- **treatment chronically:** acetazolamide, dichlorphenamide, eplerenone, spironolactone, triamterene, behavioral modification

**Thyrotoxic Hypokalemic Periodic Paralysis:**
- **presentation:** episodic weakness, lasts for minutes to hours
- **triggers:** rest after exercise, high carbohydrate meals
- **treatment acutely:** potassium (orally when possible)
- **treatment chronically:** treat hyperthyroidism (often with thyroid ablation); propranolol

**Andersen Tawil Syndrome:**
- **presentation:** episodic weakness, lasts for minutes to hours; arrhythmia (long QT interval, ventricular arrhythmia, others); dysmorphic features (microcephaly, clinodactyly, low set ears, others)
- **triggers:** rest after exercise, high carbohydrate meals, salt
- **treatment acutely:** potassium normalization (i.e., potassium for hypokalemia, sugar for hyperkalemia)
- **treatment chronically:** acetazolamide, dichlorphenamide, spironolactone, sometimes beta-blockers or pacemaker for heart arrhythmia
Hyperkalemic Periodic Paralysis:

presentation: episodic weakness, lasts for minutes
triggers: rest after exercise, fasting
treatment acutely: sugar ingestion, albuterol, insulin and glucose, calcium gluconate; some experts feel that there is no role for a potassium binding resin (Kayexalate)
treatment chronically: potassium wasting diuretics, such as hydrochlorothiazide, furosemide

Hyperkalemic Periodic Paralysis with Paramyotonia Congenita:

presentation: episodic weakness preceded by stiffness
triggers: rest after exercise, fasting, cold
treatment acutely: sugar ingestion, albuterol, insulin and glucose, calcium gluconate; muscle rewarming; some experts feel that there is no role for a potassium binding resin (Kayexalate)
treatment chronically: potassium wasting diuretics, such as hydrochlorothiazide, furosemide; rarely, mexiletine

Paramyotonia Congenita:

presentation: episodic stiffness that INCREASES with repeated exercise
triggers: cold
treatment acutely: muscle rewarming
treatment chronically: mexiletine

Myotonia Congenita:

presentation: episodic stiffness that DECREASES with repeated exercise
triggers: exercise after rest; sudden noise
treatment acutely: muscle “warm up”
treatment chronically: mexiletine, sometimes
Some Drugs Used in Ion Channelopathies:

**Diuretics**: agents that cause the kidney to excrete water, often causing salt wasting. Some diuretics spare potassium (i.e., keep potassium in the blood), while others waste potassium (i.e., cause potassium to be spilled into the urine).

**Potassium-Sparing Diuretics**:

- **Spironolactone (Aldactone)**: causes loss of sodium, and thus water, while conserving potassium (blocks aldosterone); *side effects*: breast tenderness in women, gynecomastia (breast enlargement) in men; do not combine with triamterene (two deaths reported)

- **Epleronone (Inspira)**: causes loss of sodium, and thus water, while conserving potassium (blocks aldosterone); less side effects than spironolactone; do not combine with triamterene

- **Triamterene (Dyrenium)**: causes loss of sodium, and thus water, while conserving potassium (works directly on the kidney); *side effects*: avoid non-steroidal anti-inflammatory drugs (such as indomethacin), can worsen gout; do not combine with spironolactone (two deaths reported)

- **Amiloride (Midamor)**: causes mild loss of sodium while conserving potassium

**Potassium-Wasting Diuretics**:

- **Acetazolamide (Diamox)**: for hyperkalemic periodic paralysis, felt to work by wasting potassium; for hypokalemic periodic paralysis, felt to work by making the blood more acidic. When the blood is acidic, it has a lot of hydrogen ions (H+). The muscle buffers excess H+ by absorbing it into muscle. The muscle spits out potassium ions (K+) to the blood in exchange (so that too much + charge does not build up in the muscle).

- **Dichlorphenamide (Daranide)**: about five times more potent than acetazolamide, felt to work the same way as acetazolamide

- **Hydrochlorothiazide (Microzide; Hydrodiuril)**: a water pill used to waste potassium; *side effects*: lowers blood pressure; does not waste calcium; can increase uric acid and make gout worse

- **Furosemide (Lasix)**: a water pill used to waste potassium; *side effects*: low blood pressure; low magnesium; wastes calcium too, so osteoporosis with long term use can be a problem

**Other agents**:

- **Potassium Chloride (Klor-Con; K-Dur; others)**: many forms and types, taken to raise potassium in the blood quickly in the face of attacks of hypokalemic periodic paralysis; some use sustained release preparations for blood level maintenance; *side effects*: diarrhea; stomach upset; stomach lining irritation and ulcer formation

- **Mexiletine (Mexitil)**: a heart rhythm drug that acts on sodium channels and helps to prevent myotonia

- **Clonazepam (Klonopin)**: a muscle relaxant that may help relieve spasms and myotonia in select cases

- **Calcium Gluconate Injection**: stabilizes heart rhythm in the face of high potassium

- **Albuterol (Proventil)**: a “cousin” of epinephrine, it serves to drive potassium from the blood to the muscle by stimulating the Na/K pump

- **Potassium binding resin (Kayexelate)**: given as a rectal suppository, absorbs potassium from the gut