

## **Andersen-Tawil Syndrome (ATS)**

### **A Rare Form of Periodic Paralysis**

**(Genetically diagnosed in about 100 people worldwide)**

**(This is 60% to 70% of ATS cases and this form is known as ATS1)**

**(Clinically diagnosed cases are known as ATS2)**

**(This is 30% to 40% of the cases diagnosed )**

**(Many more remain undiagnosed)**

**(Given a name in 1971)**

### **A Report Compiled**

**By**

**Susan Q. Knittle-Hunter**

**Andersen-Tawil Syndrome (ATS) is an autosomal dominant disorder (usually passed by one parent), and an uncommon cause of periodic paralysis (accounting for approximately 10% of all periodic paralysis cases). It is characterized by three particular components: periodic paralysis, distinctive craniofacial and skeletal anomalies, and prolonged QT interval with a propensity toward malignant ventricular dysrhythmias. However, affected individuals may express only one or two of the three components.**

**Some of these components and symptoms were found in Lahlee Duggins, my mother, possibly through her father, and many of her descendants; specifically, two of her three sons and me, her only daughter. Many of her grandchildren and great grandchildren also have varying degrees of the characteristics and symptoms.**

**Some of the manifestations of this condition are serious and life threatening. Each family member of someone diagnosed with ATS should be well educated about this syndrome, in particular, regarding the episodes of paralysis (full body or partial), the heart complications, the strange effects of most medications and the serious complications of anesthesia.**

**The following articles describe the scope of Periodic Paralysis in the several forms in which it is manifested. Andersen-Tawil Syndrome is a hypokalemic (low potassium) form, though it can also be seen with high potassium or normal potassium levels.**

**An individual is born with Andersen-Tawil Syndrome and symptoms may begin in early childhood or not until later in life. Members of the same family can have varying degrees of it or some of the characteristics without actually having it.**

**During an attack, brought on by many triggers to include: carbohydrates, sugar, medications, exercise, heat, cold, periods of sitting too long, stress (good or bad), etc; potassium leaves the organs it belongs in and goes into the muscles where it**

does not belong and paralyzes the muscles (totally or partially). The depletion of the potassium in the other organs can cause symptoms such as irregular heartbeat, weakness, fainting, numbness, tingling, breathing issues, choking/swallowing problems, exercise intolerance, etc. After many years the body can become permanently weakened.

It is important to get a diagnosis for proper treatment to avoid the permanent disabilities. It is also important so one can avoid the triggers and hopefully control the episodes as much as possible. Most over-the-counter medication, as well as those prescribed by physicians, such as antibiotics and painkillers can cause serious consequences. Many medications can cause an opposite effect such as sleeping aids can keep you awake and agitated.

Executive Functioning (EF) Disorder can accompany ATS. There are three primary layers of executive functions: self-regulation, organization and high order reasoning skills. It is associated with many disabilities: Attention Deficit Hyperactivity Disorder (AD/HD), Learning Disabilities (LD), Tourette Syndrome (TS), Obsessive Compulsive Disorder (OCD), Autism, Depression, Bipolar, etc. It is important to have these conditions diagnosed as early as possible for proper treatment, training, and education.

This report will begin with an overview of the three types of Periodic Paralysis and then proceed to describe Andersen-Tawil Syndrome and its components; to include:

- Alternative Names
- Symptoms & Characteristics
- Management & Treatment
  - How Common Is It?
- Genetics & Inheritance
  - Genetic Testing
- How to get Diagnosed
- More information

# Periodic Paralysis and Related Disorders

## Historical note and nomenclature

Periodic paralysis (Westphal 1885) and the related disorders paramyotonia congenita (Eulenberg 1886) and myotonia congenita (Thomsen 1876) were first described over 100 years ago. During the early part of the twentieth century, an association was recognized between episodic weakness and low serum potassium levels (Biernacki and Daniels 1934), and later, with elevated serum potassium levels (adynamia episodica hereditaria) (Gamstorp 1956). The association between cardiac arrhythmias and periodic paralysis has been noted by several investigators (Klein et al 1963; Lisak et al 1972). Andersen and colleagues described a triad of periodic paralysis, ventricular ectopy, and characteristic physical features (Andersen et al 1971), a phenotype later refined by Tawil and colleagues (Tawil et al 1994; Sansone et al 1997). This syndrome is variously referred to as Andersen syndrome, Andersen-Tawil syndrome, or LQT7.

With molecular technology, mutations have now been identified in multiple voltage-gated ion channels: sodium (hyperkalemic periodic paralysis, paramyotonia congenita, potassium aggravated myotonia, and uncommonly, hypokalemic periodic paralysis), potassium (Andersen-Tawil syndrome), calcium (hypokalemic periodic paralysis), and chloride channels (myotonia congenita) (Catterall 1988). With the degree of overlap between the traditional, clinically-defined syndromes and the degree of genotypic heterogeneity, it is now clear that the traditional classification of the periodic paralyses is too restrictive. Furthermore, although molecular medicine has dramatically enhanced our understanding of these disorders, there remains much work to be done to further characterize the clinical and pathophysiologic features and establish more effective treatments. For example, whereas loci for most of the periodic paralyses have been established and the genes at least partly characterized, a substantial proportion of patients have no mutation in identified genes. Ongoing research is investigating further loci in this unique, complex, and challenging group of disorders.

[Top ↑](#)

## Clinical manifestations

The *sine qua non* for diagnosis of most of these channelopathies is recurrent attacks of weakness (Table 1). Typically, the weakness is generalized and involves the arms and legs together, sparing bulbar and respiratory muscles. Focal weakness of isolated muscles has been described. During attacks, affected muscles are in a state of sustained depolarization and are electrically inexcitable (Engel 1986). This is reflected clinically in weakness, hypotonia, and areflexia. Measurement of serum potassium levels, recognition of precipitating factors, as well as clinical features of myotonia, cardiac arrhythmia, or distinctive craniofacial and skeletal features help in distinguishing variant forms of inherited periodic paralysis. ■ In the related myotonic disorders without periodic paralysis, myotonic stiffness is the major symptom and is typically either improved with exercise (myotonia congenita) or worsened by exercise (paradoxical myotonia of paramyotonia congenita).

**Table 1. Clinical Features of Periodic Paralysis**

	<b>Hypokalemic</b>	<b>Hyperkalemic</b>	<b>Andersen-Tawil syndrome</b>	<b>Paramyotonia congenita</b>
<b>Episodic weakness</b>	Yes	Yes	Yes	Yes (rare)
<b>Onset</b>	Puberty	Infancy	Late childhood	Childhood
<b>Ictal K+</b>	Low	High/normal	Variable	Normal/high
<b>Induces weakness</b>	Carbohydrate meals, insulin, rest after exercise, high-sodium diet	Rest after exercise, fasting, immobility	Exercise	Cold, exercise
<b>Ameliorates weakness</b>	Potassium, sustained exercise, acetazolamide*	Carbohydrates, sustained exercise, acetazolamide	Acetazolamide	Carbohydrates, sustained exercise, acetazolamide
<b>Muscle stiffness</b>	-	++	-	+++
<b>Myopathy</b>	Frequent late Onset	Uncommon late onset	None	Rare
<b>Dysmorphic features</b>	-	-	+	-
<b>Cardiac arrhythmia</b>	-	-	Long QT ventricular arrhythmia	-
<b>Genetic Inheritance</b>	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant
<b>Chromosome</b>	1q or 17q	17q	17q	17q
<b>Gene</b>	CACNLA3 or SCN4A	SCN4A	Kir2.1	SCN4A

\*weakness in patients with hypokalemic periodic paralysis due to sodium channel mutations worsens with acetazolamide (see text).

<b>Disorder</b>	<b>Hyperkalemic Periodic Paralysis</b>	<b>Hypokalemic Periodic Paralysis</b>	<b>Andersen-Tawil Syndrome</b>
<b>Location of problem</b>	sodium channel	calcium channel (most common) sodium channel	potassium channel
<b>Location of gene</b>	chromosome 17	chromosome 1 chromosome 17	chromosome 17
<b>Inheritance pattern</b>	dominant	dominant	dominant
<b>Functional defect</b>	channel does not close properly; prolonged sodium leak into cell	calcium channel on cell surface does not transmit signal for interior calcium release	channel does not open properly; potassium can't leave cell
<b>Average age of onset</b>	before age 10	age 5 to 35	age 2 to 18
<b>Average duration of episodes</b>	30 minutes to 4 hours	2 to 24 hours	1 to 36 hours
<b>Maximum weakness</b>	mild to severe	severe	moderate
<b>Development of permanent weakness</b>	may occur; increases with age	may occur; increases with age	may occur; increases with age
<b>Muscle pain</b>	may occur in exercised muscles	may occur in exercised muscles	may occur in exercised muscles
<b>Episode triggers</b>	high blood potassium; high potassium intake; fasting; cold temperatures; certain anesthetics; depolarizing muscle relaxants	low blood potassium; high carbohydrate intake; rest after exercise; cold temperatures; certain anesthetics; depolarizing muscle relaxants	high or low blood potassium, depending on exact genetic mutation; certain anesthetics; depolarizing muscle relaxants; other triggers consistent with either hyper- or hypokalemic PP
<b>Treatment</b>	<ul style="list-style-type: none"> <li>hydrochlorothiazide, furosemide</li> </ul>	<ul style="list-style-type: none"> <li>potassium supplement</li> </ul>	<ul style="list-style-type: none"> <li>cardiac medications</li> </ul>

- |  |   |  |
|--|---|--|
| <p>acetazolamide or dichlorphenamide; glucose-insulin solution; inhaled albuterol; drugs that bind potassium</p> <ul style="list-style-type: none"> <li>• carbohydrate intake, low-potassium diet</li> <li>• frequent meals, warmth, keep moving</li> <li>• avoid certain anesthetics and depolarizing muscle relaxants</li> </ul> | <p>ts, acetazolamide (can harm some patients), dichlorphenamide, spironolactone or eplerenone</p> <ul style="list-style-type: none"> <li>• high-potassium, low-carbohydrate, low-sodium diet; warmth; keep moving</li> <li>• avoid certain anesthetics and depolarizing muscle relaxants</li> </ul> | <p>such as beta blockers and anti-arrhythmics, implanted pacemaker defibrillator</p> <ul style="list-style-type: none"> <li>• acetazolamide or dichlorphenamide can help or harm</li> <li>• high- or low-potassium diet, depending on mutation</li> <li>• avoid certain anesthetics and depolarizing muscle relaxants</li> </ul> |
|--|---|--|

<http://www.mda.org/publications/Quest/q163infocus.html>

## **Hypokalemic periodic paralysis (hypoPP).**

In hypokalemic periodic paralysis, episodes of weakness are associated with a decrease in serum potassium levels, sometimes dramatically (eg, less than 2.0 mEq/L). Inheritance is autosomal dominant, typically with complete penetrance, although penetrance may be decreased in women. Most patients have mutations in the gene for alpha-subunit of the dihydropyridine-binding voltage-sensitive L-type calcium channel CACNL1A3 (also known as CACNA1S) and are designated hypokalemic periodic paralysis type 1. A minority of families not linked to the CACNL1A3 locus have mutations in the gene for skeletal muscle sodium channel SCN4A, the first resulting in an Arg669His substitution in a highly conserved portion of the channel protein (Bulman et al 1999; Jurkatt-Rott et al 2000), and others identified more recently: Arg672Cys (Kim et al 2004), Arg672His, Arg672Ser (all within the S4 voltage sensing domain of subunit II). Patients with mutations in SCN4A are designated as having hypokalemic periodic paralysis type 2. A third group of otherwise typical periodic paralysis comprises patients who do not demonstrate linkage to either the CACNL1A3 or SCN4A loci. Abbott and colleagues described a missense mutation (R83H) in KCNE3, the gene coding for MinK-related peptide 2 (MiRP2) in 2 families, 1 with hypokalemic periodic paralysis phenotype and the other with hyperkalemic periodic paralysis (hyperPP) (Abbott et al 2001). MiRP2 is an accessory subunit that coassembles with the alpha subunit of the voltage-gated K<sup>+</sup> channel, Kv3.4, which contributes to resting membrane potential in skeletal muscle. A confirmatory study, however, failed to confirm the KCNE3 mutation as a disease-causing mutation as opposed to a benign polymorphism, and a disease-causing mutation in this third group of patients remains to be proven (Sternberg et al 2003; Jurkat-Rott and Lehmann-Horn 2005). It is uncertain whether this is a mutation or a benign polymorphism. An abnormal and pH-dependent reduction in inward ionic current in R83H MiRP2-K3.4 channels has been expressed in Chinese hamster ovary cells, a finding that suggests a pathophysiologic role of KCNE3 mutations in periodic paralysis. This may explain the exercise-induced membrane depolarization in periodic paralysis patients and could arise from a reduced K current with intracellular acidosis following prolonged or intense exercise (Abbott et al 2006).

Periodic paralysis symptoms usually begin around puberty. Men are more severely affected than women. Attacks may be triggered by rest after intense exercise, carbohydrate-rich meals, stress, or alcohol consumption. A typical attack may last for hours or, less often, days. Episodes of weakness are not accompanied by sensory, cardiac, or cognitive symptoms. Slowly progressive and chronic proximal leg weakness in the fourth or fifth decades is typical. Serum CK is usually normal, but may be slightly elevated. Muscle biopsy features include typical myopathic features of abnormal increase in central nuclei and variation of fiber size, and vacuoles. Myotonia does not typically occur in hypokalemic periodic paralysis. Patients with sodium channel mutations may exhibit the following distinctive features: (1) earlier age of onset, (2) postictal myalgia, (3) worsening of symptoms with acetazolamide, (4) prominent tubular aggregates rather than vacuoles on muscle biopsy, and (5) complete penetrance in males and females (Sternberg et al 2001).

. Excessive cooling may lead to muscle depolarization and paralysis that may take hours to reverse on warming, without alteration of serum potassium. Serum CK may be elevated up to 10 times normal. Muscle power remains normal throughout life.

## Andersen-Tawil syndrome (ATS).

Andersen-Tawil syndrome is an autosomal dominant disorder, and an uncommon cause of periodic paralysis (accounting for approximately 10% of all periodic paralysis cases). It is characterized by a triad: periodic paralysis, distinctive craniofacial and skeletal anomalies, and prolonged QT interval with a propensity toward malignant ventricular dysrhythmias. However, affected individuals may express only 1 or 2 of the 3 components ■ (Tawil et al 1994; Sansone et al 1997; Plaster et al 2001). Although the episodic weakness was initially thought to be potassium sensitive, the syndrome has been reported in patients with normokalemia, hyperkalemia, and hypokalemia (Sansone et al 1997). The dysmorphic features are highly variable and include short stature, scoliosis, clinodactyly (permanent lateral or medial curvature of a finger or toe), hypertelorism (wide-set eyes), small or prominent ears that are low-set or slanted, micrognathia (small chin), broad forehead, and dental abnormalities (eg, delayed tooth eruption or missing teeth) (Yoon et al 2006). Cardiac manifestations vary from an asymptomatic long QT syndrome to life-threatening ventricular tachyarrhythmia requiring an implantable defibrillator, but most patients exhibit either a long QTc interval or a prolonged QU interval with characteristic U-wave morphology (Zhang et al 2005; Yoon et al 2006). Episodes of muscle weakness may fluctuate in severity and usually begin before the age of 10 years old or in adolescence. Mild permanent weakness may be seen in some patients. Muscle creatine kinase levels remain normal or slightly elevated. Muscle biopsy may reveal tubular aggregates, variability of fiber size, and central nuclei. Myotonia is not a common feature in Andersen-Tawil syndrome, however, lingual myotonia detected on clinical examination has been reported previously in 2 patients with hyperkalemic periodic paralysis and cardiac arrhythmia (Lisak et al 1972; Gould et al 1985). Recently, Yoon and colleagues described a distinct neurocognitive phenotype associated with ATS, characterized by deficits in abstract reasoning and executive dysfunction (Yoon et al 2007). Most patients (approximately 70%) have mutations in KCNJ2 on chromosome 17q23, the gene encoding the inwardly rectifying Kir2.1, a potassium channel expressed in cardiac and skeletal muscle, and brain (Plaster et al 2001). These cases are designated Andersen-Tawil syndrome type 1. The remaining 30% of patients presumably result from some other as-yet-unidentified mutation, and are designated Andersen-Tawil syndrome type 2.

### Contributors

**Rabi Tawil MD**, author. Dr. Tawil of the University of Rochester in Rochester, New York, has no relevant financial relationships to disclose.

**Paul Twydell DO**, author. Dr. Twydell of the University of Rochester in Rochester, New York, has no relevant financial relationships to disclose.

**Lewis P Rowland MD**, editor. Dr. Rowland of Columbia University has no relevant financial relationships to disclose.

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# Andersen-Tawil Syndrome

## Alternative Names

Andersen cardiodysrhythmic periodic paralysis; Andersen syndrome; ATS; Long QT syndrome 7; LQT7; Periodic paralysis, potassium-sensitive cardiodysrhythmic type

## Symptoms & Characteristics

Several articles are sighted for this section due to the differences in symptoms in some of them. Some personal information has been added for clarity.

Anderson-Tawil syndrome is a disorder that causes episodes of muscle weakness (periodic paralysis), changes in heart rhythm (arrhythmia), and developmental abnormalities. The most common changes affecting the heart are ventricular arrhythmia, which is a disruption in the rhythm of the heart's lower chambers, and long QT syndrome. Long QT syndrome, is a cardiac channelopathy, that causes the heart (cardiac) muscle to take longer than usual to recharge between beats. If untreated, the irregular heartbeats can lead to discomfort, fainting (syncope), or cardiac arrest.

There are two types of Andersen-Tawil syndrome, type 1 and type 2, which are distinguished by their genetic causes.

Physical abnormalities associated with Andersen-Tawil syndrome typically affect the head, face, and limbs. These features often include a very small lower jaw (micrognathia), dental abnormalities, low-set ears, widely spaced eyes, and unusual curving of the fingers or toes (clinodactyly). Some affected people also have short stature and an abnormal curvature of the spine (scoliosis).

## Symptoms

- Widely spaced eyes
  - Short stature
  - Scoliosis
- Webbed toes or fingers
- Unusual short fingers
  - Low set ears

- Broad forehead
- Small jaw
- Protruding jaw
- Broad nasal root

[http://en.wikipedia.org/wiki/Andersen%E2%80%93Tawil\\_syndrome](http://en.wikipedia.org/wiki/Andersen%E2%80%93Tawil_syndrome)

### **Disease characteristics.**

Andersen-Tawil syndrome (referred to as ATS in this entry) is characterized by a triad of episodic flaccid muscle weakness (i.e., periodic paralysis), ventricular arrhythmias and prolonged QT interval, and anomalies such as low-set ears, ocular hypertelorism, small mandible, fifth-digit clinodactyly, syndactyly, short stature, and scoliosis. Affected individuals present in the first or second decade with either cardiac symptoms (palpitations and/or syncope) or weakness that occurs spontaneously following prolonged rest or following rest after exertion. Mild permanent weakness is common. Mild learning difficulties and a distinct neurocognitive phenotype (i.e., deficits in executive function and abstract reasoning) have been described.

### **Executive Functioning (EF) Disorder**

**Relates to difficulty in self regulation, organizing, integration, or high order reasoning skills.**

**"Executive Function disorder, is a disability of not being able to show what you know"**

**Executive Function disorder is associated with many disabilities: Attention Deficit Hyperactivity Disorder (AD/HD), Learning Disabilities (LD), Tourette Syndrome (TS) , Obsessive Compulsive Disorder (OCD), Autism, Depression, Bipolar, etc.**

**Most people with AD/HD also have Executive Function Disorder, but someone can have Executive Function Disorder without being diagnosed with a disability. Executive Function program and services would be needed if the student progress in the general growth in the acquisition of knowledge and skills, are being negatively impacted.**

**Eight Pillars of Executive Control by Dr. Adam J. Cox, Ph.D., January 2009,  
Minuteman Technical High School SEPAC presentation**

<b>1. Initiating Action</b>	<b>being able to organize one’s thoughts well enough to get started on a particular task without having to be asked multiple times.</b>
<b>2. Flexible Thinking</b>	<b>involves learning to adapt by shifting one’s focus and pace as various situations unfold. Imagine how difficult it would be to drive your car if it wouldn’t turn and only went one speed. (About as difficult as parenting a child with only one speed and one direction!)</b>
<b>3. Sustaining Attention</b>	<b>focusing long enough and accurately enough to learn important information. By extension, attention also involves the ability to block distraction. A well orchestrated “executive brain” knows its priorities.</b>
<b>4. Organization</b>	<b>is about managing space. It’s also about taking the emotional impact of chaos seriously. Why? Because chronic disorganization undermines forward momentum – a sense of accomplishment.</b>
<b>5. Planning</b>	<b>is about managing time, and is more important than any other executive pillar when it comes to finishing things on schedule. A planning mind uses time as a tool to clarify priorities and enhance productivity; indispensable skills to 21st century success, beginning with school and, eventually, careers.</b>
<b>6. Working Memory</b>	<b>is the ability to retain information long enough for it to be stored in long-term memory. Our society has a word for this process – learning. Of all the executive controls, working memory is the most pervasive, contributing to the smooth operation of every pillar. (Working memory is the rocket fuel of the modern mind.)</b>
<b>7. Self Awareness</b>	<b>pertains to having both sufficient self-knowledge and an ability to perceive how others see you. This information is essential to making purposeful choices about how to act in situations where one wants to avoid unintended consequences that lead to isolation or ostracism.</b>
<b>8. Regulating Emotions</b>	<b>means expressing one’s feelings in proportion to the events that elicited them. When a child under or over-reacts, she is out-of-sync with people or particular events. Socially, people tend to ignore a silent recluse, and run away from an “erupting volcano.”</b>

From his book: [No Mind Left Behind: Understanding and Fostering Executive Control- The Eight Essential Brain Skills every Child Needs to Thrive](#), by Adam J. Cox, Ph.D. Psychologist

**Executive Function Skills, by Sarah Ward, MS, CCC-SLP , February, 2007 SPED PAC Presentation**

**3 Primary Layers of Executive Functions:**

**1. Self Regulation**

- a. Awareness**
- b. Motivation**
- c. Initiation**
- d. Emotional Control**

**i. Self awareness**

**ii. Self monitor the ability to inhibit or delay responding, which permits impulse control resistance to distraction and delay of gratification)**

**iii. Metacognition (Learning how to learn)**

**2. Organization and Integration**

- a. Integrate details into a bigger picture**
- b. Organize and store information so it can be traced back and retrieved over time (Episodic Memory), (used for planning for the future)**

**3. Higher Order Reasoning Skills**

- a. Analyze**
- b. Draw a conclusion**
- c. Solve a problem**
- d. Predict an outcome**
- e. Reason**
- f. Evaluate**

## Symptoms of Andersen-Tawil Syndrome

- Ventricular arrhythmia
- Abnormal heart rhythm
- Long QT syndrome increased time needed for heart to recharge after each heart beat
- Irregular heartbeat
- Discomfort
- Fainting caused by irregular heart beat
- Small lower jaw
- Dental abnormalities
- Low-set ears
- Widely spaced eyes
- Abnormal curving of fingers
- Abnormal curving of toes
- Short stature
- Abnormal curvature of the spine

[http://www.wrongdiagnosis.com/a/andersen\\_tawil\\_syndrome/symptoms.htm](http://www.wrongdiagnosis.com/a/andersen_tawil_syndrome/symptoms.htm)

### Dysmorphic Features:

**May be very subtle, partial or seen in 'unaffected' family members**

#### Skeletal:

- short stature (often);
- scoliosis

#### Hands/Feet:

- tapering fingers,
- clinodactyly (inward curvature/ 5th fingers);
- brachydactyly (unusually short fingers);
- syndactyly (webbing between fingers or between 2nd and 3rd toes)



An example of webbed toes sometimes seen in ATS.

#### Facial:

- hypertelorism (widely spaced eyes);
- mandibular hypoplasia (small jaw);
- low-set ears;
- broad forehead;
- malar hypoplasia; (underdevelopment of cheekbones)
- broad nasal root;
- micrognathia (short jaw);
- prognathism (protruding jaw);
- ptosis; (an abnormally low position (drooping) of the upper eyelid)
- cleft palate, high arched palate

<http://hkpp.org/physicians/andersens.html>

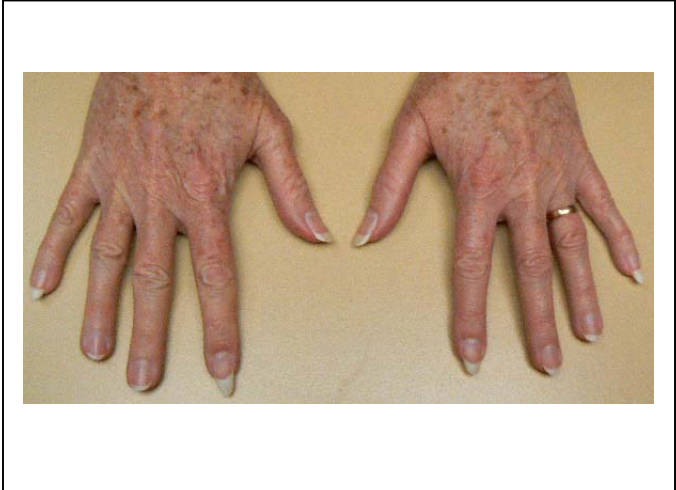
## Andersen–Tawil syndrome

(MIM 170390)

Andersen-Tawil syndrome (ATS), first described in 1971 (Andersen et al., 1971), is characterized by the triad of PP, ventricular ectopy and skeletal anomalies (Tawil et al., 1994; Sansone et al., 1997). Prevalence is unknown but estimated at one-tenth that of HypoPP. Symptomatic onset typically is with episodic weakness in the first or second decade. Intermittent weakness occurs spontaneously or may be triggered by prolonged rest or rest following exertion; permanent proximal weakness often develops. Attack frequency, duration and severity are variable between and within affected individuals and may not correlate with ictal serum K levels, which may be reduced, normal or elevated. ECG manifestations (Fig. 1) include prolongation of the corrected QT interval (QTc), prominent U waves, premature ventricular contractions, ventricular bigeminy and polymorphic ventricular tachycardia. A subset of patients manifests a unique form of ventricular tachycardia, bidirectional ventricular tachycardia, which is characterized by beat-to-beat alternating QRS axis polarity (Fig. 1). While many patients with ventricular ectopy are asymptomatic, others present with palpitations, syncope or rarely cardiac arrest (Tristani-Firouzi et al., 2002). Unlike other forms of arrhythmia-susceptibility syndromes, many ATS patients remain asymptomatic despite frequent runs of tachycardia (Tristani-Firouzi et al., 2002). Furthermore, there appears to be a lower incidence of syncope and sudden death in ATS compared with other long QT (LQT) syndromes (Tristani-Firouzi et al., 2002). Distinctive physical findings (Fig. 2) include a small mandible, ocular hypertelorism, low set ears, clinodactyly, syndactyly and broad nasal root (Donaldson et al., 2003; Tristani-Firouzi et al., 2002). Short stature, unilateral hypoplastic kidney (Andelfinger et al., 2002), vaginal atresia and brachydactyly (Canun et al., 1999) have been reported. Detailed study has also identified microcephaly, short palpebral fissures, thin upper lip, small hands/feet, residual primary dentition and delayed bone age (Yoon and Ptacek, unpublished).

## Developmental Features

### Hands and Feet of Susan Hunter



**Distinctive physical features** recognized initially included low-set ears, ocular hypertelorism, small mandible, fifth-digit clinodactyly, syndactyly, short stature, broad nasal root, and scoliosis [[Andersen et al 1971](#), [Tristani-Firouzi et al 2002](#), [Donaldson et al 2003](#)]. Dental enamel discoloration was noted in two [kindreds](#) with the Gly300Asp and Arg218Trp [mutations](#) [[Davies et al 2005](#)].

Detailed, prospectively collected data in ten individuals with confirmed *KCNJ2* [mutations](#) have expanded the [phenotype](#) to include a characteristic facies and dental and skeletal anomalies [[Yoon et al 2006a](#)].

- Characteristic facies include broad forehead, short palpebral fissures, full nasal bridge with bulbous tip, hypoplasia of maxilla and mandible, thin upper lip, and a triangular shape.
- Dental findings include (among others) persistent primary dentition, multiple missing teeth (oligodontia), and dental crowding.
- Skeletal findings include mild syndactyly of toes 2 and 3 as well as fifth-digit clinodactyly.
- Novel findings include small hands and feet (<10th centile for age) and joint laxity.

[Isolated](#) reports of renal anomalies include unilateral hypoplastic kidney [[Andelfinger et al 2002](#)] and renal tubular defect [[Davies et al 2005](#)].

Andersen-Tawil syndrome (ATS)<sup>1</sup> is a rare autosomal dominant disorder caused by mutations in the inward rectifier potassium channel gene *KCNJ2*, which encodes the inward rectifier potassium channel Kir2.1 protein. Two features of this disease have made this gene of high interest to scientists: (i) patients suffer from both skeletal muscle periodic paralysis and cardiac arrhythmia, a unique feature in ion channel diseases; and (ii) patients exhibit developmental problems such as cleft palate, low set ears, short stature, and development features in the limbs (clinodactyly, syndactyly, brachydactyly) (1-3). While the first feature can be easily understood because of the contribution of Kir2.1 to membrane excitability in both tissues, it is still unknown how this channel contributes to craniofacial, limb, and axial skeletal development.

<http://www.jbc.org/content/278/51/51779.full>

### **Definition of Terms for Symptoms:**

- **characteristic facies** (characteristic appearance of the face in association with a disease or abnormality)
- **brachydactyly** (unusually short fingers)
- **brachydactyly type D** (clubbed thumbs) (characterized by a slightly shorter thumb that is round in section and larger at the end)
- **clinodactyly** (inward curvature/ 5th fingers);
- **syndactyly** (webbing between fingers or between 2nd and 3rd toes)
- **small mandible** (lower jaw in which the lower teeth reside and chin)
- **hypoplasia of maxilla** (small upper jaw)
- **short palpebral fissures** (short opening for the eyes between the eyelids)
- **persistent primary dentition** (still have some baby teeth)
- **ocular hypertelorism** (widely spaced eyes);
- **scoliosis** (curved spine)
- **microcephaly** (abnormal smallness of the head)
- **delayed bone age** (slowed degree of maturation of child's bones)

- **joint laxity** (looseness of the muscles and soft tissue surrounding a joint)
- **broad nasal root** (wide space between the inner corners of eyes)
- **broad forehead** (increased distance between the two sides of the forehead or top to bottom of forehead)
- **malar hypoplasia** (small cheek bones)
- **micrognathia** (short jaw);
- **prognathism** (protruding jaw)
- **ptosis** (an abnormally low position (drooping) of the upper eyelid)
- **cleft palate** (a congenital fissure in the roof of the mouth)
- **high arched palate** (roof of the mouth is high)

### Facial Dysmorphology

In this section, drawings are used to depict terminology and to illustrate certain aspects of facial variation.

[http://www.peds.ufl.edu/divisions/genetics/teaching/facial\\_dysmorphology.htm](http://www.peds.ufl.edu/divisions/genetics/teaching/facial_dysmorphology.htm)

## Management & Treatment

Management of attacks of episodic weakness depends on the associated blood serum potassium concentration.

Prophylactic treatment aims to reduce the frequency and severity of episodic attacks of weakness with lifestyle/dietary modification to avoid known triggers. In addition, the use of carbonic anhydrase inhibitors, daily use of slow-release potassium supplements, and an implantable cardioverter-defibrillator (ICD) in individuals with tachycardia-induced syncope may also be helpful.

Annual screening of individuals who do not display symptoms but have a known disease-causing mutation is important.

Affected individuals should speak with their physician regarding the avoidance of medications thought to exacerbate symptoms or prolong QT intervals.

**The following list/plan was put together after trial and error in my own quest for treatment and management. I had no doctor assisting me and gleaned as much as possible on the internet and in discussion with other people who live with Periodic Paralysis and Andersen-Tawil Syndrome. Each component will be discussed and elaborated on at a later date.**

### How Do I Treat/Manage it?

- Discover your triggers

- Avoid your triggers
- Monitor your vitals  
(obtain medical equipment)

### **Tools and Supplies.**

*Cardy Meter*

*Oximeter*

*Stethoscope*

*Wrist Blood Pressure Device*

*Ear Thermometer*

*PH Monitor*

*Blood Sugar Monitor*

- Gather a team of medical specialists  
(for diagnosis)  
(for treatment)  
(for follow-up)
  - Educate yourself
- Join a Periodic Paralysis Community

### **How Common Is It?**

Andersen-Tawil syndrome is a rare genetic disorder; its incidence is unknown. About 100 people with this condition have been reported worldwide.

Type 1 accounts for about 70% of all cases of Andersen-Tawil syndrome.

Type 2 accounts for the remaining 30% of cases of Andersen-Tawil syndrome.

### **Genetics & Inheritance**

Andersen-Tawil syndrome type 1 is caused by mutations in the KCNJ2 gene. The cause of cases of Anderson-Tawil syndrome type 2 is unknown.

Andersen-Tawil syndrome is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In some cases, a person with Andersen-Tawil syndrome inherits the mutation from an affected parent. Other cases result from new mutations in the KCNJ2 gene. These cases occur in people with no history of the disorder in their family.

## **Periodic paralysis, K<sup>+</sup> sensitive, with cardiac arrhythmias (Andersen Syndrome) 🌟**

- KCNJ2 (Kir2.1) 🌟; Chromosome 17q23; Dominant

- Genetics<sup>3</sup>:
  - Most mutations are missense
  - Some are inframe deletions
- [KCNJ2](#) protein
  - Inwardly rectifying K<sup>+</sup> channel
  - Plays role in hyperpolarization needed for myoblast fusion
  - Mutated protein expression
    - Loss of function
    - Dominant negative
    - Produces reduced inwardly rectifying K<sup>+</sup> current
  - Tissue functions
    - Cardiac & skeletal muscle function
    - Also: Developmental signaling
- Intrafamilial variability
  - Partial manifestations common
  - Arg67Try mutation: Ventricular arrhythmia in females (81%); Periodic paralysis in males (40%)
- Clinical
  - Cardiac: Ventricular arrhythmia may segregate in females
    - Symptoms: Syncope; Sudden death
    - Arrhythmia
      - Bigeminy
      - Bidirectional ventricular tachycardia
      - [Increased Q-T interval](#) (Early)
      - Premature ventricular contractions
      - Polymorphic ventricular tachycardia
      - Heart block
        - [Long QT syndrome 7](#)
    - Other EKG
      - U waves: Prominent
    - Semilunar valve abnormalities
    - Treatment
      - Amiodarone
      - Poor response to classical therapy
    - Cardiac malformation: Occasional
  - [Episodic weakness](#): May segregate in males
    - Onset age: 2 to 18 years
    - Duration of episodes: 1 hour to days
    - Proximal > Distal
    - Precipitants: K<sup>+</sup>; Exercise; None
    - No myotonia
  - Permanent weakness: Occasional
    - Proximal & Distal
  - Skeletal
    - Short stature
    - Clinodactyly: Lateral or medial curvature of finger or toe

- Syndactyly
    - Scoliosis
  - Face
    - Hypertelorism
    - Mandible hypoplasia
    - Low-set ears
    - Broad forehead
    - Malar hypoplasia
  - Kidney, Hypoplastic: Occasional
- Lab
  - Serum K<sup>+</sup> during attack: May be high, low, or normal
- Treatment<sup>5</sup>
  - K<sup>+</sup> Rx
    - Oral K<sup>+</sup> may improve weakness in patients with low K<sup>+</sup>
    - In some families increasing K<sup>+</sup>: Improves arrhythmia; Exacerbates weakness
  - Acetazolamide
- Muscle pathology: [Tubular aggregates](#)

<http://neuromuscular.wustl.edu/mtime/mepisodic.html#andersen>

## **The following is the criteria for making a clinical diagnosis:**

### **Table 3 Diagnostic criteria for ATS**

**(1) A clinically definite diagnosis requires two of the following three features:**

- a. PP**
- b. Prolonged QTc interval or ventricular ectopy (identified on ECG or Holter)**
- c. The typical ATS facies including:  
Low set ears, ocular hypertelorism, small mandible, fifth digit clinodactyly, syndactyly**

**(2) Alternatively, a diagnosis may be made with one of the three features above and an affected family member meeting two of three.**

<http://brain.oxfordjournals.org/content/129/1/8.full.pdf>

The following list/plan was put together after trial and error in my own quest for acquiring a diagnosis. I had no doctor assisting me and gleaned as much as possible on the internet and in discussion with other people who live with Periodic Paralysis and Andersen-Tawil Syndrome. Each component will be discussed and elaborated on at a later date.

## **How Do I Get a Diagnosis?**

In order to get a diagnosis, one must get all the facts together....This is how I did it:

- 1. The proper tests, ruling everything else out...(ie, MRI's, spinal taps, lab work, xrays, emgs)**
  - 2. Lab work showing either low potassium, high potassium and/or paralysis during shifting in normal ranges (I have all three).**
  - 3. Periods of paralysis, either total or partial, which can be documented (I had these in the PCP's office several times and at the hospital on 3 occasions, and in front of at least 5 doctors/specialists as well as a physical therapist and an EMG technician; all of them shrugging their shoulders and sending me on my way when I was able to).**
  - 4. ECGs consistent with "ion channelopathy".**
  - 5. Oximetry (oxygen) recordings indicating, levels dropping during paralysis.**
- (# 1-5 above can give one a "clinical diagnosis")**
- 6. Genetic testing. (Still waiting)**

**#2,4,5 need to be done while in the paralysis....so may need to be done for more than 24 hours until each is documented, during the episodes.**

**#2 may need to be done several times until a baseline is established and then during episodes every 5 to 10 minutes...not just one blood draw....there is no way to see the shifting otherwise. If the shifting is in the normal ranges, it may never show up during tests, unless it is done every few minutes. May need hospitalization to do this.**

**#3 video taping is the best way to do this.**

**Gather all previous medical records and ask for all doctors' records from each appointment you attend. Also, get all lab records, xrays, hospitalizations, etc.**

**It is also important to chart the triggers for the episodes. Documenting an increase of episodes after eating carbs or red meat, after exercising or after taking certain medications is important for being able to control the episodes.**

**Documenting a reduction of episodes when using potassium is good. This can indicate the loss of potassium after shifting.**

**Putting together a team of doctors is helpful for a diagnosis: A PCP who knows about Periodic Paralysis or is willing to learn and a Neurologist, an Electrocardiologist, and a Nephrologist (All knowledgeable about PP or willing to learn).**

**If one suspects Andersen-Tawil Syndrome, gather as much medical information as possible from family members and note the characteristics/symptoms. Create a family flowchart with this information. Adding pictures can be helpful in demonstrating the characteristics.**

### **These conditions can accompany Andersen-Tawil Syndrome**

#### **Malignant Hyperthermia:**

<http://www.mhaus.org/>

<http://www.nlm.nih.gov/medlineplus/ency/article/001315.htm>

<http://www.healthline.com/adamcontent/malignant-hyperthermia>

#### **Neuroleptic Malignant Hyperthermia:**

<http://www.nmsis.org/>

<http://emedicine.medscape.com/article/816018-overview>

[http://www.ninds.nih.gov/disorders/neuroleptic\\_syndrome/neuroleptic\\_syndrome.htm](http://www.ninds.nih.gov/disorders/neuroleptic_syndrome/neuroleptic_syndrome.htm)

**Serotonin Syndrome:**

<http://www.nmsis.org/content.asp?type=education&src=pages/serotoninsyndrome.asp&title=Serotonin+Syndrome>

<http://www.healthline.com/adamcontent/malignant-hyperthermia>

<http://www.mayoclinic.com/health/serotonin-syndrome/DS00860/DSECTION=causes>