Andersen-Tawil Syndrome

Synonym: Long QT Syndrome Type 7 (LQTS Type 7)

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Summary

Clinical characteristics

Andersen-Tawil syndrome (ATS) is characterized by a triad of: episodic flaccid muscle weakness (i.e., periodic paralysis); ventricular arrhythmias and prolonged QT interval; and anomalies including low-set ears, widely spaced eyes, 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.

Diagnosis/testing

The diagnosis of ATS is established in an individual with characteristic clinical and ECG findings and/or identification of a pathogenic variant in *KCNJ2*.

Management

Treatment of manifestations: For episodic weakness: if serum potassium concentration is low (<3.0 mmol/L), administration of oral potassium (20-30 mEq/L) every 15-30 minutes (not to exceed 200 mEq in a 12-hour period) until the serum concentration normalizes; if a relative drop in serum potassium within the normal range causes episodic paralysis, an individual potassium replacement regimen with a goal of maintaining serum potassium levels in the high range of normal can be considered; if serum potassium concentration is high, ingesting carbohydrates may lower serum potassium levels. Mild exercise may shorten or reduce the severity of the attack.

Prevention of primary manifestations: Reduction in frequency and severity of episodic attacks of weakness with lifestyle/dietary modification to avoid known triggers; use of carbonic anhydrase inhibitors; daily use of slow-release potassium supplements; implantable cardioverter-defibrillator for those with tachycardia-induced

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syncope. Empiric treatment with flecainide should be considered for significant, frequent ventricular arrhythmias in the setting of reduced left ventricular function.

Prevention of secondary complications: Cautious use of antiarrhythmic drugs (particularly class I drugs) that may paradoxically exacerbate the neuromuscular symptoms.

Surveillance: Annual screening of asymptomatic individuals with a *KCNJ2* pathogenic variant with a 12-lead ECG and 24-hour Holter monitoring.

Agents/circumstances to avoid: Medications known to prolong QT intervals; salbutamol inhalers (may exacerbate cardiac arrhythmias); thiazide and other potassium-wasting diuretics (may provoke drug-induced hypokalemia and could aggravate the QT interval prolongation).

Evaluation of relatives at risk: Molecular genetic testing if the pathogenic variant is known; if not, detailed neurologic and cardiologic evaluation, 12-lead ECG, and 24-hour Holter monitoring to reduce morbidity and mortality through early diagnosis and treatment of at-risk relatives.

Genetic counseling

ATS is inherited in an autosomal dominant manner. At least 50% of individuals diagnosed with ATS have an affected parent. Up to 50% of affected individuals have ATS as the result of a *de novo* pathogenic variant. Each child of an individual with ATS has a 50% chance of inheriting the disorder. Prenatal diagnosis for pregnancies at increased risk is possible if the *KCNJ2* pathogenic variant has been identified in an affected family member.

Diagnosis

Suggestive Findings

Andersen-Tawil syndrome (ATS) **should be suspected** in individuals with **either** A **or** B:

A. Presence of two of the following three criteria:

- Periodic paralysis
- Symptomatic cardiac arrhythmias or electrocardiographic evidence of enlarged U-waves, ventricular ectopy, or a prolonged QTc or QUc interval
- Characteristic facies, dental anomalies, small hands and feet, AND at least two of the following:
  - Low-set ears
  - Widely spaced eyes
  - Small mandible
  - Fifth-digit clinodactyly
  - Syndactyly of toes 2 and 3

B. One of the above three criteria AND at least one other family member who meets two of the three criteria [Statland et al 2018]

Supportive Findings

Individuals with either episodic weakness or cardiac symptoms require careful evaluation by a neurologist and/or cardiologist as well as measurement of serum potassium concentration (baseline and during attacks of flaccid paralysis), a 12-lead ECG, a 24-hour Holter monitor, and possibly the long exercise protocol.

- **Serum potassium concentration** during episodes of weakness may be elevated, normal, or, most commonly, reduced (<3.5 mmol/U) [Sansone & Tawil 2007, Statland et al 2018].

- **Routine nerve conduction electrophysiology** is normal between episodes. A more sensitive electrophysiologic study, the long exercise protocol, may reveal an immediate post-exercise increment followed by an abnormal decrement in the compound motor action potential amplitude (>40%) [Katz et al 1999] or area (>50%) 20-40 minutes post exercise [Kuntzer et al 2000, Fournier et al 2004]. In a study of 11 individuals with ATS, 82% met long-exercise amplitude decrement criteria for abnormal testing [Tan et al 2011].
- **Electrocardiogram** may reveal characteristic abnormalities including prominent U waves, prolonged Q-U intervals, premature ventricular contractions, polymorphic ventricular tachycardia, and bidirectional ventricular tachycardia [Zhang et al 2005, Delannoy et al 2013, Koppikar et al 2015, Statland et al 2018].
- **24-hour Holter monitoring** is important to document the presence, frequency, and duration of ventricular tachycardia (VT) and the presence or absence of associated symptoms.

Establishing the Diagnosis

The diagnosis of ATS **is established** in a proband with the presence of A or B in Suggestive Findings and/or by identification of a heterozygous pathogenic variant in *KCNJ2* by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of ATS is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with cardiac arrhythmias are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of ATS molecular genetic testing approaches can include **serial single-gene testing** or use of a **multigene panel**:

- **Serial single-gene testing.** Sequence analysis detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis of *KCNJ2* first. If no pathogenic variant is found perform gene-targeted deletion/duplication analysis of *KCNJ2* to detect intragenic deletions or duplications. If no *KCNJ2* pathogenic variant is found, perform sequence analysis of *KCNJ5* (see Table 1, footnote 7).

- **A multigene panel** that includes *KCNJ2*, *KCNJ5*, and other genes of interest (see Differential Diagnosis and Long QT Syndrome) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by cardiac arrhythmias, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Andersen-Tawil Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
KCNJ2	Sequence analysis [3]	~70% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]
KCNJ5	Sequence analysis [3]	See footnote 7.
	Gene-targeted deletion/duplication analysis [5]	Unknown, none reported
Unknown		~30%

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. 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. Plaster et al [2001], Ai et al [2002], Andelfinger et al [2002], Tristani-Firouzi et al [2002], Donaldson et al [2003], Hosaka et al [2003]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Large deletions of KCNJ2 are reported [Lestner et al 2012, Vergult et al 2012, Marquis-Nicholson et al 2014]. The prevalence of large deletions is unknown.
7. One individual with periodic paralysis, ventricular arrhythmias, no history of hypertension, and normal plasma aldosterone levels was found to have a p.Gly387Thr variant in KCNJ5. Of individuals with suspected ATS in whom a KCNJ2 pathogenic variant was not identified, 1/21 had a p.Thr158Ala KCNJ5 variant identified [Kokunai et al 2014].

Clinical Characteristics

Clinical Description

Andersen-Tawil syndrome (ATS) is characterized by a triad of features:

- Episodic flaccid muscle weakness (periodic paralysis)
- Cardiac abnormalities (ventricular arrhythmias, prolonged QTc or QUc intervals, and prominent U waves)
- Distinctive dysmorphic features

Affected individuals present initially with either periodic paralysis or cardiac symptoms (palpitations and/or syncope) in the first or second decade [Tawil et al 1994, Tristani-Firouzi et al 2002]; however, prospective standardized natural history data are not yet available. The phenotype is highly variable. The characteristic triad is present in 58%-78% of individuals with KCNJ2 pathogenic variants [Statland et al 2018].

Weakness. Intermittent weakness occurs spontaneously, or alternatively may be triggered by prolonged rest or rest following exertion. The attack frequency, duration, and severity are variable between and within affected

individuals. Mild permanent weakness is common [Tristani-Firouzi et al 2002]. Affected individuals can develop fixed proximal weakness over time.

Ventricular arrhythmias including bidirectional ventricular tachycardia (VT), polymorphic VT, and multifocal premature ventricular contractions may be asymptomatic, or may manifest (most commonly) as palpitations. Less common symptomatic presentations include syncope, cardiac arrest, or sudden death [Andelfinger et al 2002, Tristani-Firouzi et al 2002, Donaldson et al 2003]. While the ECG may reveal a long QTc (LQT) interval, characteristic T-U patterns including enlarged U waves, a wide T-U junction, and prolonged terminal T-wave downslope distinguish ATS from other LQT syndromes [Zhang et al 2005, Haruna et al 2007]. A large case series found no significant difference in the incidence of ventricular tachyarrhythmias between individuals with typical and atypical presentations of ATS [Kimura et al 2012]. A retrospective multicenter French study of 36 individuals with ATS followed for an average of 9.5 years reported no deaths in follow up; four individuals experienced syncope and one individual had a non-fatal cardiac arrest [Delannoy et al 2013].

Dilated cardiomyopathy was observed in two of three affected individuals in a single kindred with pathogenic variant p.Arg218Trp [Schoonderwoerd et al 2006]. Additionally, cardiomyopathy was documented and reversed by treatment with flecainide in an individual with pathogenic variant p.Arg67Trp [Pellizzón et al 2008], and reversed by bisoprolol in another individual with typical clinical features of ATS and novel variant p.Leu222Ser [Rezazadeh et al 2016]. These reports suggest that dilated cardiomyopathy is a secondary phenotype as a consequence of chronic tachycardia rather than a primary phenotypic manifestation. Additional study is needed to further delineate this clinical feature.

Distinctive physical features recognized initially included low-set ears, widely spaced eyes, small mandible, fifth-digit clinodactyly, second and third toe 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 p.Gly300Asp and p.Arg218Trp pathogenic variants [Davies et al 2005].

Detailed, prospectively collected data in ten individuals with confirmed *KCNJ2* pathogenic variants 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, wide nasal bridge with bulbous nose, hypoplasia of maxilla and mandible, thin upper lip, and a triangular face.
- Dental findings include (among others) persistent primary dentition, multiple missing teeth (oligodontia), and dental crowding.
- Skeletal findings include mild syndactyly of toes two and three as well as fifth-digit clinodactyly.
- Novel findings include small hands and feet (<10th centile for age) and joint laxity.

Note: Isolated reports of **renal anomalies** include unilateral hypoplastic kidney [Andelfinger et al 2002] and renal tubular defect [Davies et al 2005].

Mild learning difficulties have been described [Davies et al 2005]. A distinct neurocognitive phenotype (i.e., deficits in executive function and abstract reasoning) has been recognized in individuals with a *KCNJ2* pathogenic variant despite IQ levels similar to those of their unaffected sibs [Yoon et al 2006b]. Growth restriction and developmental delay have been described as well [Kim et al 2016].

Afebrile seizures occurring only in infancy were reported in 4/23 (17%) of a Japanese cohort with molecularly confirmed ATS [Haruna et al 2007].

Genotype-Phenotype Correlations

Whether a *KCNJ2* pathogenic variant is present or not, individuals with clinically defined ATS are phenotypically indistinguishable [Tristani-Firouzi et al 2002, Donaldson et al 2003].

In a case series that evaluated for *KCNJ2* pathogenic variants in individuals with typical (>2 ATS features) and atypical (only 1 ATS feature or catecholaminergic polymorphic ventricular tachycardia [CPVT]) features of ATS, the proportion of individuals with an identified pathogenic variant was 75% (15/20) in those with typical ATS, 71% (5/7) in those with the cardiac phenotype alone, 100% (2/2) in those with periodic paralysis, and 7% (2/28) in those with CPVT [Kimura et al 2012].

In a single large kindred with the *KCNJ2* p.Arg67Trp pathogenic variant, periodic paralysis was observed only in men, cardiac symptoms only in women, and congenital anomalies in both [Andelfinger et al 2002]. However, this apparent sex-limited bias in clinical presentation has not been confirmed [Donaldson et al 2003, Davies et al 2005].

A large five-generation family was found to have a deletion in *KCNJ2* (c.271_282del12;p.Ala91_Leu94del) and more severe cardiac manifestations, including 4/10 individuals receiving an implantable cardioverter-defibrillator and 5/10 reporting life-threatening ventricular arrhythmias in childhood [Fernlund et al 2013]. These individuals had characteristic mild dysmorphic features, but only one had periodic paralysis.

Two pathogenic variants in *KCNJ2* associated with a reduction in Kir2.1 current but without a dominant-negative effect on normal channels (p.Asn318Ser and p.Trp322Cys) were described in three individuals with an isolated cardiac phenotype: with premature ventricular contractions, ventricular tachycardia, or ventricular fibrillation [Limberg et al 2013].

A recent study examined the predictors of arrhythmias in 11 unrelated families with ATS (11 probands who were all female, 14 unaffected heterozygous family members with the *KCNJ2* pathogenic variant, and 19 family members without the pathogenic variant) and found that a higher risk for arrhythmia, syncope, and/or cardiac arrest was associated with the presence of micrognathia, periodic paralysis, and prolonged duration of the descending portion of T-wave ($T_{peak} - T_{end}$ time) . It was also noted that the ATS clinical manifestations appeared to be more severe in females. The presence of a benign / likely benign variant in *KCNH2* appeared to be associated with a higher risk for syncope [Krych et al 2017].

Penetrance

Non-penetrance is evident in 6%-20% of individuals with an identifiable pathogenic variant [Andelfinger et al 2002, Tristani-Firouzi et al 2002, Donaldson et al 2003].

Nomenclature

Although listed in OMIM, the following names for ATS are no longer in clinical use:

- Periodic paralysis, potassium-sensitive cardiodysrhythmic type
- Andersen cardiodysrhythmic periodic paralysis

Prevalence

The estimated prevalence of ATS is 0.08 – 0.1 per 100,000 [Horga et al 2013, Stunnenberg et al 2018].

Genetically Related (Allelic) Disorders

Familial atrial fibrillation 9 (OMIM 613980). A *KCNJ2* pathogenic missense variant was described in a Chinese family; five affected individuals and two individuals who did not have atrial fibrillation were identified to have the variant.

Short QT syndrome 3 (OMIM 609622). A *KCNJ2* pathogenic missense variant was identified in a female age five years and her father who had short QT intervals and asymmetric T waves on ECG. Pathogenic variants in *KCNH2* and *KCNQ1*, the two genes associated with short QT syndrome, were not identified.

Differential Diagnosis

Andersen-Tawil syndrome (ATS) should be considered in any individual presenting with periodic paralysis and ventricular arrhythmias or prominent U wave or prolonged QTc. Individuals with either episodic weakness or cardiac symptoms require careful evaluation by a neurologist and/or cardiologist as well as measurement of serum potassium concentration (baseline and during attacks of flaccid paralysis), a 12-lead ECG, a 24-hour Holter monitor, and possibly the long exercise protocol. The differential diagnosis depends on the initial presentation and includes the primary and secondary periodic paralyses, thyrotoxic periodic paralysis, and conditions associated with long QT.

Episodes of Flaccid Paralysis

Hypokalemic periodic paralysis is the most common periodic paralysis. Affected individuals may experience paralytic episodes with concomitant hypokalemia (<2.5 mmol/L), and occasionally may develop late-onset proximal myopathy. The paralytic attacks are characterized by reversible flaccid paralysis usually leading to paraparesis or tetraparesis but typically sparing the respiratory muscles and heart. The onset, duration, and severity of attacks, with the associated triggers, are similar to those in individuals with ATS. Weakness is improved with oral potassium ingestion. The cardiac and dysmorphic features of ATS are, however, absent in individuals with hypokalemic periodic paralysis. Molecular testing identifies pathogenic variants in *CACNA1S* or *SCN4A* in approximately 80% of affected individuals after secondary causes such as thyrotoxicosis, diuretic use, and renal (e.g., hyperaldosteronism, distal tubular acidosis) or gastrointestinal (e.g., vomiting, diarrheal illness) causes have been ruled out. Inheritance is autosomal dominant.

Hyperkalemic periodic paralysis is characterized by episodes of flaccid paralysis associated with normal or elevated ictal serum potassium concentrations (>5.0 mmol/U) and aggravated by potassium ingestion. Onset is in the first decade; episodes are briefer than those that occur in individuals with hypokalemic periodic paralysis. Electrical myotonia is evident in 50% of affected individuals. The cardiac and dysmorphic features of ATS are absent. Molecular testing reveals pathogenic variants in *SCN4A* in approximately 80% of individuals. Inheritance is autosomal dominant. Secondary forms of hyperkalemic periodic paralysis to rule out include adrenal insufficiency, hypoaldosteronism, and adverse effects of certain medications (e.g., ACE inhibitors, spironolactone, nonsteroidal anti-inflammatory drugs).

Thyrotoxic periodic paralysis (OMIM 188580, 613239, 614834) is a consideration in any individual with severe weakness and marked hypokalemia. Men, particularly Asians, are affected in greater numbers; however, thyrotoxic periodic paralysis may be seen in individuals of all ethnicities. Diagnosis is established by measurement of serum thyroid-stimulating hormone (TSH), T4, and T3 concentrations. In one series a pathogenic variant in an inwardly rectifying potassium (Kir) channel (encoded by *KCNJ18*) was identified in approximately one third of affected individuals [Ryan et al 2010].

Long QT Syndromes

See Long QT Syndrome, a review of similar phenotypes that are genetically diverse.

Palpitations, Syncope, or Cardiac Arrest

Syncopal episodes are often interpreted as a neurologic problem rather than arrhythmia. Physical examination and ECG should be part of the evaluation of syncope. Bidirectional ventricular tachycardia demonstrated on ECG may be seen with ATS, digitalis toxicity, and catecholaminergic polymorphic ventricular tachycardia

(CPVT). A normal resting ECG with exercise-induced polymorphic arrhythmias is a clue to CPVT. Pathogenic variants in *RYR2* or *CASQ2* are causative. Inheritance is autosomal dominant [Tristani-Firouzi & Etheridge 2010].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Andersen-Tawil syndrome (ATS), the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended:

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with ATS

Organ System	Evaluation	Comment
Cardiovascular	Baseline assessment	Performed by cardiologist familiar w/LQT management
	12-lead ECG & 24-hour Holter monitor	
	Serum potassium concentrations	Performed at baseline & during attacks of weakness
Neurologic	Baseline assessment	Performed by neurologist familiar w/periodic paralysis
	Electrophysiologic studies including long exercise protocol	
Dental	Baseline assessment for dental abnormalities associated w/ATS	Follow up as needed
Musculoskeletal	Baseline assessment & to establish care w/orthopedist / spine surgeon if scoliosis identified	Follow up as needed
Miscellaneous/ Other	Serum TSH concentration	Verification that serum TSH concentration is w/in normal limits
	Consultation w/clinical geneticist &/or genetic counselor	

LQT = long QT
TSH = thyroid-stimulating hormone

Treatment of Manifestations

Management of individuals with ATS requires the coordinated input of a neurologist familiar with the treatment of periodic paralysis and a cardiologist familiar with the treatment of cardiac arrhythmias. To date, no randomized clinical therapeutic trials have been conducted on ATS.

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

- If the serum potassium concentration is low (<3.0 mmol/L), administer oral potassium (20-30 mEq/L) every 15-30 minutes (not to exceed 200 mEq in a 12-hour period) until the serum concentration normalizes often shortens the attack. As dysphagia is almost never a problem during attacks of paralysis, oral potassium replacement is the safest route. If intravenous potassium replacement is needed, a 5% mannitol solution instead of a saline or glucose solution (both of which may exacerbate weakness) is recommended. Close monitoring of serum potassium concentrations and ECG is necessary during potassium replacement therapy in an emergency setting to avoid secondary hyperkalemia.
- Whether a relative drop in serum potassium within the normal range causes episodic paralysis is not clear. If such cases are suspected, affected individuals can work with their physician to devise an individual potassium replacement regimen, with a goal of maintaining serum potassium levels in the high range of normal.

- Attacks of weakness when serum potassium concentration is high usually resolve within 60 minutes. Episodes may be shortened by ingesting carbohydrates or continuing mild exercise. Intravenous calcium gluconate is rarely necessary for management in an individual seen in an emergency setting.

Vasovagal syncope in individuals with ATS mandates a careful cardiology assessment [Airey et al 2009].

Prevention of Primary Manifestations

Prophylactic treatment aimed at reduction of attack frequency and severity can be achieved, as in other forms of periodic paralysis, with the following:

- Lifestyle and dietary modification to avoid known triggers
- Use of carbonic anhydrase inhibitors (acetazolamide: adults 125-1,000 mg daily and children 5-10 mg/kg/day divided 1-2x/day or dichlorphenamide 50-200 mg/1-2x/day). Use of potassium-sparing diuretic should be individualized based on patient needs.
- Daily use of slow-release potassium supplements, which may also be helpful in controlling attack rates in individuals prone to hypokalemia. Elevating the serum potassium concentration (>4 mEq/L) has the added benefit of narrowing the QT interval, thus reducing the risk of LQT-associated arrhythmias.
- An implantable cardioverter-defibrillator in individuals with tachycardia-induced syncope [Chun et al 2004]
- Empiric treatment with flecainide [Bökenkamp et al 2007, Fox et al 2008, Pellizzón et al 2008] should be considered for significant, frequent ventricular arrhythmias in the setting of reduced left ventricular function [Tristani-Firouzi & Etheridge 2010]. A prospective open label study in ten individuals with ATS and a confirmed *KCNJ2* pathogenic variant tested the effect of flecainide, a type 1c antiarrhythmic, for the prevention of cardiac arrhythmias [Miyamoto et al 2015]. Outcomes included a 24-hour Holter monitor before and after treatment and a treadmill exercise test. Flecainide was found to significantly reduce the number of ventricular arrhythmias seen on Holter monitor and to suppress exercise-induced ventricular arrhythmias. Individuals were then followed for a mean of 23 months and no syncope or cardiac arrest was documented. Other case studies have reported beneficial effects with flecainide [Statland et al 2018]. A recent study showed that fleicainide suppresses arrhythmogenicity through Na^+/Ca^{2+} exchanger flux in induced pluripotent stem cells derived from patients with ATS [Kuroda et al 2017]. Thus, flecainide may reduce cardiac arrhythmias in ATS.

Prevention of Secondary Complications

Cardiologists should be aware that some antiarrhythmic drugs (e.g., lidocaine, mexiletine, propafenone, quinidine), particularly Class I drugs, may paradoxically exacerbate the neuromuscular symptoms and should be used cautiously in individuals with ATS.

Although malignant hyperthermia has not been reported in ATS, appropriate anesthetic precautions should be undertaken, as with individuals with other forms of periodic paralysis.

Surveillance

For asymptomatic individuals with a *KCNJ2* pathogenic variant, annual screening including a 12-lead ECG and 24-hour Holter monitoring is desirable, followed by referral to a cardiologist if abnormalities are identified.

Agents/Circumstances to Avoid

Affected individuals should avoid medications known to prolong QT intervals. See CredibleMeds® for a complete and updated list (free registration required).

Salbutamol inhalers, which may be used in the treatment of primary hyperkalemic periodic paralysis, should be avoided because of the potential for exacerbation of cardiac arrhythmias.

Thiazide and other potassium-wasting diuretics may provoke drug-induced hypokalemia and could aggravate the QT interval prolongation.

Evaluation of Relatives at Risk

It is appropriate to evaluate relatives at risk in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures:

- If the pathogenic variant in the family is known, molecular genetic testing can be used to clarify the genetic status of at-risk relatives.
- If the pathogenic variant in the family is not known, detailed neurologic and cardiologic evaluation, 12-lead ECG, and 24-hour Holter monitoring can be used to clarify the disease status of at-risk relatives.

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

Pregnancy Management

The rarity of ATS and the paucity of reports pertaining to pregnancy in women with ATS make an evidence-based approach to pregnancy management difficult to formulate. One case study reported an uneventful pregnancy, with increased episodes of weakness but reduced ventricular ectopy compared to the pre-pregnancy period [Subbiah et al 2008]. However, as data are limited, a multidisciplinary approach to individual care and anticipation of increased risk (as can be seen in those with long QT syndrome) seems reasonable.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Andersen-Tawil syndrome (ATS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- At least 50% of individuals diagnosed with ATS have an affected parent.
- A proband with ATS may have the disorder as the result of a *de novoKCNJ2* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant in *KCNJ2* may be as high as 50%.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include: a detailed neurologic and cardiologic evaluation, 12-lead ECG, 24-hour Holter monitoring, and molecular genetic testing for the *KCNJ2* pathogenic variant identified in the proband.

- The family history of some individuals diagnosed with ATS may appear to be negative because of failure to recognize the disorder in family members, early death of the parent not attributed to the disease, or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless appropriate neurologic and cardiologic evaluations 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 proband's parents:

- If a parent of the proband is affected and/or has the *KCNJ2* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the proband has a known ATS-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Hasegawa et al 2015].
- If the parents have not been tested for the *KCNJ2* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for ATS because of the possibility of reduced penetrance in a heterozygous parent or the possibility of parental germline mosaicism [Hasegawa et al 2015].

Offspring of a proband. Each child of an individual with ATS has a 50% chance of inheriting the *KCNJ2* 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 and/or heterozygous for the *KCNJ2* pathogenic variant identified in the proband, his or her family members are 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.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with ATS has the pathogenic variant or clinical evidence of the disorder, the *KCNJ2* pathogenic variant is likely *de novo*. However, possible 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/preimplantation genetic 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 Testing

Once the *KCNJ2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for ATS are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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**
  Andersen-Tawil syndrome

- **Periodic Paralysis International**
  Canada
  www.hkpp.org

- **Muscular Dystrophy Association (MDA) - USA**
  161 North Clark
  Suite 3550
  Chicago IL 60601
  Phone: 800-572-1717
  Email: mda@mdausa.org
  www.mda.org

- **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

- **Sudden Arrhythmia Death Syndromes (SADS) Foundation**
  508 East South Temple
  Suite #202
  Salt Lake City UT 84102
  Phone: 800-786-7723 (toll-free); 801-531-0937
  Email: sads@sads.org
  www.sads.org

- **International Long QT Syndrome Registry**
  Heart Research Follow-Up Program
  Box 653
  Rochester NY 14642-8653
  Phone: 585-276-0016
  Fax: 585-273-5283
  Email: heartajm@heart.rochester.edu

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. Andersen-Tawil Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
KCNJ2	17q24.3	Inward rectifier potassium channel 2	KCNJ2 database KCNJ2 @ ZAC-GGM	KCNJ2	KCNJ2
KCNJ5	11q24.3	G protein-activated inward rectifier potassium channel 4	KCNJ5 database	KCNJ5	KCNJ5

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Andersen-Tawil Syndrome (View All in OMIM)

170390	ANDERSEN CARDIODYSRHYTHMIC PERIODIC PARALYSIS
600681	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 2; KCNJ2
600734	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 5; KCNJ5

KCNJ2

Gene structure. *KCNJ2* has two exons spanning 5.4 kb. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. See Table A, **Locus-Specific Databases** and **HGMD**. The p.Arg218Trp pathogenic variant is considered a potential mutational hot spot [Davies et al 2005]. The majority of pathogenic variants in *KCNJ2* are missense changes. A small number of in-frame deletions and a duplication have also been reported.

Table 3. *KCNJ2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.199C>T	p.Arg67Trp [1]	
c.271_282del12	p.Ala91_Leu94del [1]	
c.652C>T	p.Arg218Trp [2]	
c.665T>C	p.Leu222Ser [2]	NM_000891.2 NP_000882.1
c.899G>A	p.Gly300Asp [2]	
c.953A>G	p.Asn318Ser [1]	
c.966G>C	p.Trp322Cys [1]	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Genotype-Phenotype Correlations.
2. See Clinical Description.

Normal gene product. *KCNJ2* encodes the inward rectifier potassium channel 2 protein (Kir2.1), with 427 amino acid residues and 48-kd molecular weight. Kir2.1 is expressed primarily in skeletal muscle, heart, and brain. Kir2.1 is involved in setting and stabilizing the resting membrane potential in skeletal and cardiac muscle and has a major role in the terminal repolarization phase of the cardiac action potential [Plaster et al 2001, Tristani-Firouzi et al 2002].

Abnormal gene product. Pathogenic variants in *KCNJ2* cause dominant-negative suppression of Kir2.1 current [Plaster et al 2001, Tristani-Firouzi et al 2002, Lange et al 2003, Donaldson et al 2004, Davies et al 2005, Ballester

et al 2006, Barajas-Martinez et al 2011, Marrus et al 2011] and affect channel-PIP$_2$ interactions [Donaldson et al 2003]. Several pathogenic variants affect trafficking of the mutant channel to the cell surface for reasons that are not clear [Ballester et al 2006]. One study identified loss of an endoplasmic reticulum export motif [Doi et al 2011]. The majority traffic normally to the cell surface but fail to conduct normally [Bendahhou et al 2003]. Phosphatidylinositol 4,5 bisphosphate (PIP$_2$) is an important regulator of Kir2.1 channel function; many *KCNJ2* pathogenic variants alter PIP$_2$ binding [Lopes et al 2002, Donaldson et al 2003].

Flaccid paralysis results from failure to propagate action potentials in the muscle membrane as a result of sustained membrane depolarization [Cannon 2002]. The modestly prolonged QT interval and ventricular arrhythmias are caused by impaired cardiac ventricular repolarization; the reduced inward rectifying potassium current results in distinct T-U wave morphology [Tristani-Firouzi et al 2001, Zhang et al 2005].

While the role of Kir2.1 in skeletal development remains to be clarified, consistent craniofacial, dental, and skeletal anomalies are present [Yoon et al 2006a].

Targeted disruption of Kir2.1 in a knockout mouse is fatal, with complete cleft of the secondary palate [Zaritsky et al 2000].

KCNJ5

Pathogenic variants. One individual with clinical criteria of ATS and a novel pathogenic variant in *KCNJ5* (p.Gly387Arg) has been described. The proband had periodic paralysis and ventricular arrhythmias, with a family history of ventricular arrhythmias on his father's side. A review of 21 individuals in a Japanese cohort (in whom ATS was suspected but a *KCNJ2* pathogenic variant was not found) identified one additional individual with a novel variant in *KCNJ5* (p.Thr158Ala) [Kokunai et al 2014]. The ultimate frequency of *KCNJ5* pathogenic variants in individuals who meet clinical criteria for ATS but do not have a *KCNJ2* variant remains to be determined.

Table 4. *KCNJ5* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.472A>G	p.Thr158Ala [1]	NM_000890.3
c.1159G>C	p.Gly387Arg [1]	NP_000881.3

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

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. See Table 1.

Normal gene product. *KCNJ5* codes a 419-amino-acid G protein-activated inwardly rectifying potassium channel protein 4 (Kir3.4). Expression studies show that *KCNJ5* is expressed in cardiac and skeletal muscle.

Abnormal gene product. Functional studies on the p.Gly387Arg pathogenic variant in *KCNJ5* also demonstrated a dominant-negative effect on Kir2.1 function [Kokunai et al 2014].

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Chapter Notes

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Revision History

- 7 June 2018 (sw) Comprehensive update posted live
- 3 September 2015 (rt) Revision: Treatment of Manifestations
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- 19 March 2007 (me) Comprehensive update posted live
- 27 April 2005 (cd) Revision: prenatal diagnosis available
- 22 November 2004 (me) Review posted live
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