GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Andersen-Tawil Syndrome

[*LQT7, Long QT Syndrome 7, Andersen Syndrome. Includes: Andersen Syndrome Type 1, Andersen Syndrome Type 2*]

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Initial Posting: November 22, 2004.
Last Update: March 19, 2007.

Summary

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.

Diagnosis/testing. The diagnosis of ATS is suspected in an individual with characteristic clinical and ECG findings. *KCNJ2,* encoding the inward rectifier potassium channel 2 protein (Kir2.1), is the only gene known to be associated with ATS. Approximately 70% of individuals with ATS have a detectable mutation in *KCNJ2*. Such testing is clinically available. The presence of a pathogenic *KCNJ2* mutation confirms the diagnosis.

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 until the serum concentration normalizes; if serum potassium concentration is high, ingesting carbohydrates or continuing mild exercise may shorten 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 (ICD) for those with tachycardia-induced syncope. *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 pathogenic *KCNJ2* mutation 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). *Testing of relatives at risk:* molecular genetic testing if the disease-causing mutation is known or clinical diagnostic evaluations to reduce morbidity and mortality through early diagnosis and treatment.

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 cases are caused by *de novo* mutations. Each child of an individual with ATS has a 50% chance of inheriting the disorder. Prenatal diagnosis for pregnancies at risk is clinically available if the disease-causing mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

The diagnosis of Andersen-Tawil syndrome (ATS) is suspected in individuals with two of the following three:

- Periodic paralysis
- Symptomatic cardiac arrhythmias or electrocardiographic (ECG) 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
  - Ocular hypertelorism
  - Small mandible
  - Fifth-digit clinodactyly
  - Syndactyly

OR one of the above three in addition to at least one other family member who meets two of the three criteria [Tawil et al 1994, Sansone et al 1997, Tristani-Firouzi et al 2002].

The presence of a pathogenic *KCNJ2* mutation confirms the diagnosis of Andersen-Tawil syndrome type 1 (ATS1).

Testing

Serum potassium concentration during episodes of weakness may be elevated, normal, or, most commonly, reduced (<3.5 mmol/U) [Tawil et al 1994, Sansone et al 1997, Canun et al 1999, Tristani-Firouzi et al 2002].

Routine nerve conduction electrophysiology is normal between episodes. A more sensitive electrophysiological study, the long exercise protocol, may reveal an immediate post-exercise increment followed by an abnormal decrement in the compound motor action potential (CMAP) amplitude (>40%) [McManis et al 1986, Katz et al 1999] or area (>50%) 20-40 minutes post-exercise [Kuntzer et al 2000, Fournier et al 2004].

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].

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.

Molecular Genetic Testing

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

Molecular Genetic Testing—Gene. *KCNJ2*, encoding the inward rectifier potassium channel 2 protein (Kir2.1), is the only gene known to be associated with ATS1.

Other loci. To date, no other loci have been identified to account for ATS (termed Anderson-Tawil syndrome type 2, or ATS2) in the 30% of kindreds not linked to *KCNJ2*.

Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Clinical testing

- **Sequencing of the entire coding region.** Approximately 70% of individuals with ATS have a missense mutation or a small deletion in the *KCNJ2* gene; more than 20 missense mutations have been described to date [Plaster et al 2001, Ai et al 2002, Andelfinger et al 2002, Tristani-Firouzi 2002, Donaldson et al 2003, Hosaka et al 2003]. R218W is considered a potential hotspot for disease-causing mutations [Davies et al 2005].
- **Mutation scanning.** The detection rate for mutation scanning remains unknown.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Methods	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*KCNJ2* sequence variants	~70%	Clinical Testing
Mutation scanning		Unknown	

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

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

Genetically Related (Allelic) Disorders

No other phenotypes have been associated with mutations in *KCNJ2*.

Clinical Description

Natural History

Andersen-Tawil syndrome (ATS) is characterized by a triad of episodic flaccid muscle weakness, distinctive dysmorphic features, and ventricular arrhythmias and prolonged QT interval [Andersen et al 1971]. 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.

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 [Tawil et al 1994, Sansone et al 1997, Canun et al 1999, Tristani-Firouzi et al 2002].

Ventricular arrhythmias, including bidirectional ventricular tachycardia (VT), polymorphic VT, and multifocal premature ventricular contractions may be asymptomatic or manifest as palpitations most commonly. 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 interval (LQT), characteristic T-U patterns including enlarged U waves, a wide T-U junction, and prolonged terminal T-wave downslope distinguish ATS1 from other LQT syndromes [Zhang et al 2005].

Dilated cardiomyopathy was observed in two of three affected individuals in a single kindred with the R218W mutation [Schoonderwoerd et al 2006]; whether this is an uncommon phenotypic manifestation or a consequence of chronic tachycardia remains to be seen [Tristani-Firouzi 2006].

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 G300D and R218W 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, Oberoi et al 2006].

- 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].

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* mutation despite IQ levels similar to those of their unaffected sibs [Yoon, Quitania et al 2006].

Genotype-Phenotype Correlations

Individuals with clinically defined ATS are phenotypically indistinguishable, regardless of the presence of a *KCNJ2* mutation (ATS1) or absence of a *KCNJ2* mutation (ATS2) [Tristani-Firouzi et al 2002, Donaldson et al 2003].

In a single large kindred with the R67W mutation in *KCNJ2*, 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].

Penetrance

The phenotype is highly variable. Approximately 60% of affected individuals manifest the complete triad of cardinal features and up to 80% express two of the three cardinal features [Tristani-Firouzi et al 2002]. Non-penetrance is evident in 6%-20% of individuals with an identifiable mutation [Andelfinger et al 2002, Tristani-Firouzi et al 2002, Donaldson et al 2003].

Anticipation

Anticipation is not observed.

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 prevalence is not known. ATS represents fewer than 10% of cases of primary periodic paralysis. The incidence of periodic paralysis is also unknown and estimated to be at most 1:100,000.

Differential Diagnosis

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

Andersen-Tawil syndrome (ATS) should be considered in any individual presenting with periodic paralysis and ventricular arrhythmias or enlarged U waves. 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 and thyrotoxic periodic paralysis.

Episodes of flaccid paralysis

- Hypokalemic periodic paralysis is the most common periodic paralysis. Affected individuals have episodes of reversible, flaccid paralysis associated with reduced serum potassium concentrations (<3.5 mmol/U) and/or slowly progressive proximal weakness. The onset, duration, and severity of attacks, with the associated triggers, are similar to those in individuals with ATS. Respiratory muscles are spared. Weakness is improved with oral potassium ingestion. The cardiac and dysmorphic features of ATS are, however, absent in hypokalemic periodic paralysis. Molecular testing identifies mutations in the *CACNA1S* or *SCN4A* genes 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 one of seven common mutations in the *SCN4A* gene in approximately 50% of individuals. 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). Inheritance is autosomal dominant.
- Thyrotoxic periodic paralysis is a consideration in any individual with severe weakness and hypokalemia. Men, particularly Asians, are affected in greater numbers; however, thyrotoxic periodic paralysis may be seen in all races. Diagnosis is established by measurement of serum TSH, T4, and T3 concentrations.

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.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Andersen-Tawil syndrome (ATS):

- Baseline assessments by a neurologist and cardiologist familiar with periodic paralysis and LQT respectively
- Serum potassium concentrations at baseline and during attacks of weakness
- 12-lead ECG and 24-hour Holter monitor
- Electrophysiologic studies including the long exercise protocol [McManis et al 1986, Kuntzer et al 2000, Fournier et al 2004]
- Verification that serum concentration of thyroid-stimulating hormone (TSH) is within normal limits

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.

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

- If the serum potassium concentration is low (<3.0 mmol/L), administration of oral potassium (20-30 mEq/L) every 15-30 minutes until the serum concentration normalizes often shortens the attack. Monitoring of serum potassium concentrations and the ECG in the emergency department may be useful during potassium replacement therapy to avoid secondary hyperkalemia.
- Attacks of weakness when the 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 the emergency department.

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
- The use of carbonic anhydrase inhibitors (acetazolamide: 250-500 mg/1-2x/day or dichlorphenamide: 50-100 mg/1-2x/day)
- The daily use of slow-release potassium supplements, which may also be helpful in controlling attack rates in individuals with a tendency to become hypokalemic. 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 (ICD) in individuals with tachycardia-induced syncope [Chun et al 2004]

Prevention of Secondary Complications

Cardiologists should be aware that some antiarrhythmic drugs, 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

Screening of an asymptomatic individual with a pathogenic *KCNJ2* mutation with an annual 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 www.qtdrugs.org [Woosley 2001] for a complete and updated list.

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.

Testing of Relatives at Risk

It is appropriate to offer molecular genetic testing to at-risk relatives if the disease-causing mutation is identified in an affected family member, so that morbidity and mortality can be reduced by early diagnosis and treatment.

If the disease-causing mutation in the family is not known, it is appropriate to offer clinical diagnostic evaluations to at-risk family members in order to permit early diagnosis and treatment.

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

Therapies Under Investigation

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

Other

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

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

Genetic Counseling

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

Mode of Inheritance

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 novo* gene mutation. The proportion of cases caused by *de novo* mutations may be as high as 50%.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include a detailed neurologic and cardiologicf evaluation, 12-lead ECG, 24-hour Holter monitoring, and molecular genetic testing for the *KCNJ2* mutation identified in the proband.

Note: Although at least 50% of individuals diagnosed with ATS have an affected parent, the family history 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.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected and does not have the KCNJ2 mutation identified in the proband, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.

- If a disease-causing mutation cannot be detected in the DNA extracted from the leukocytes of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.

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

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

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

Prenatal Testing

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

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

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

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

Molecular Genetics

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

Table A. Molecular Genetics of Andersen-Tawil Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
KCNJ2	17q23.1-q24.2	Inward rectifier potassium channel 2

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

Table B. OMIM Entries for Andersen-Tawil Syndrome

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

Table C. Genomic Databases for Andersen-Tawil Syndrome

Gene Symbol	Locus Specific	Entrez Gene	HGMD
KCNJ2	KCNJ2	3759 (MIM No. 600681)	KCNJ2

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

Molecular Genetic Pathogenesis

KCNJ2 encodes inward rectifier potassium channel 2, or Kir2.1 [Plaster et al 2001], expressed primarily in skeletal muscle, heart, and brain [Kubo et al 1993, Raab-Graham et al 1994, Karschin et al 1996]. 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]. The majority of mutations exert a dominant-negative effect on channel current [Lange et al 2003, Donaldson et al 2004, Davies et al 2005, Ballester et al 2006]. Several mutations affect trafficking of the mutant channel to the cell surface for reasons that are not clear [Ballester et al 2006] while the majority traffick 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* mutations 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, Oberoi et al 2006]. Targeted disruption of Kir2.1 in a knockout mouse is fatal with complete cleft of the secondary palate [Zaritsky et al 2000].

Normal allelic variants: *KCNJ2* has two exons spanning 5.4 kb.

Pathologic allelic variants: The 29 mutations described reside in exon 2. They include: R67W, Y68D, D71V/N, T74A, T75R/M, D78G, R82Q, Δ95-98, C101R, V123G, S136F, G144A/S, G146D, P186L, R189I, T192A, N216H, L217P, R218W/Q, G300D/V, V302M, E303K, R312C, and Δ314-315. (For more information, see Genomic Databases table above.)

Normal gene product: *KCNJ2* encodes the inward rectifier potassium channel 2 protein (Kir2.1), 427 amino acid residues, and 48-kd molecular weight.

Abnormal gene product: Mutations in *KCNJ2* cause dominant-negative suppression of Kir2.1 current [Plaster et al 2001, Tristani-Firouzi et al 2002] and affect channel-PIP_2 interactions [Donaldson et al 2003].

Resources

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

National Library of Medicine Genetics Home Reference
Andersen-Tawil syndrome

Cardiac Arrhythmias Research and Education Foundation (CARE)
26425 NE Allen Street Suite 103
P.O. Box 369
Duvall WA 98019
Phone: 800-404-9500; 425-788-1987
Fax: 425-788-1927
Email: care@longqt.org
www.longqt.org

Muscular Dystrophy Association (MDA)
3300 East Sunrise Drive
Tucson AZ 85718-3208
Phone: 800-FIGHT-MD (800-344-4863); 520-529-2000
Fax: 520-529-5300
Email: mda@mdausa.org
www.mdausa.org

Periodic Paralysis Association
1101 Douglas Drive
Tracy CA 95304-5879
Phone: 626-638-3326
Fax: 626-337-1966
Email: inquire@periodicparalysis.org
www.periodicparalysis.org

Sudden Arrhythmia Death Syndromes (SADS) Foundation
508 East South Temple Suite 20
PO Box 58765
Salt Lake City UT 84102
Phone: 800-786-7723; 801-531-0937
Fax: 801-531-0945
Email: sads@sads.org
www.sads.org

Consortium for Clinical Investigations of Neurological Channelopathies (CINCH) Registry
Email: Barbara_Herr@URMC.Rochester.edu
CINCH Registry

References

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

Published Statements and Policies Regarding Genetic Testing

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

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Suggested Readings

Venance SL, Cannon SC, Fialho D, Fontaine B, Hanna MG, Ptacek LJ, Tristani-Firouzi M, Tawil R, Griggs RC. The primary periodic paralyses: diagnosis, pathogenesis and treatment. Brain. 2006;129:8–17. [PubMed: 16195244]

Chapter Notes

Acknowledgments

The authors are funded in part by the Consortium for Clinical Investigation of Neurological Channelopathies (CINCH) supported by NIH 8 U54 NS59065 (NINDS/ORD).

Revision History

- 19 March 2007 (me) Comprehensive update posted to live Web site
- 27 April 2005 (cd) Revision: prenatal diagnosis available
- 22 November 2004 (me) Review posted to live Web site
- 1 June 2004 (rt) Original submission