American Journal of Medical Genetics 140A:312–321 (2006)

Andersen-Tawil Syndrome:
Prospective Cohort Analysis and Expansion of the Phenotype

G. Yoon,[1,4] S. Oberoi,[2] M. Tristani-Firouzi,[3] S.P. Etheridge,[3] L. Quitania,[4] J.H. Kramer,[4] B.L. Miller,[4] Y.H. Fu,[4] and L.J. Ptáček[4,5]***

[1]Department of Pediatrics, Division of Medical Genetics, University of California, San Francisco, California
[2]Department of Orofacial Sciences, University of California, San Francisco, California
[3]Department of Pediatrics, Division of Cardiology, University of Utah, Utah
[4]Department of Neurology, University of California San Francisco, California
[5]Howard Hughes Medical Institute, Department of Neurology, University of California, San Francisco, California

Received 19 September 2005; Accepted 22 November 2005

Andersen-Tawil syndrome (ATS) is an autosomal dominant multisystem disorder characterized by developmental, cardiac, and neuromuscular abnormalities. Approximately 70% of patients have mutations in *KCNJ2*, resulting in dysfunction of the inward-rectifying potassium channel Kir2.1. Variable expression complicates the diagnosis of ATS, which in many cases, is not made until years after the first recognized symptom. To better define the distinctive clinical features of ATS and facilitate earlier diagnosis, we conducted a prospective, standardized evaluation of 10 subjects with confirmed *KCNJ2* mutations. Detailed anthropometric, neurological, and cardiac evaluations were performed. Using this approach, we identified novel skeletal and dental findings and proposed additional diagnostic criteria for ATS dysmorphology. © 2006 Wiley-Liss, Inc.

Key words: andersen-tawil syndrome; channelopathy; inward rectifying potassium channel; periodic paralysis

INTRODUCTION

Andersen-Tawil syndrome (ATS) is an important member of the expanding family of ion channelopathies, for which the genetic bases have only recently been elucidated. Mutations in the *KCNJ2* gene on chromosome 17q23 have been demonstrated to cause the ATS phenotype [Plaster et al., 2001]. *KCNJ2* encodes the inward-rectifying potassium channel protein Kir2.1 and is highly expressed in heart, skeletal muscle, and brain [Raab-Graham and Vandenberg, 1994].

The clinical features of ATS represent a spectrum of phenotypic manifestations encompassing the skeletal muscle and cardiac systems, in addition to craniofacial and skeletal anomalies. The initial case report by Andersen and colleagues in 1971 described a young boy with intermittent muscle weakness, cardiac arrhythmias, and multiple developmental abnormalities. The latter included short stature, dolichocephaly, thin hair, broad nose, low set ears, cleft palate, delayed and incomplete dentition, mandibular hypoplasia, bilateral transverse palmar creases, clinodactyly of the fifth fingers and toes, and incomplete skull mineralization [Andersen, 1971]. However, the triad of cardinal clinical features (periodic paralysis, cardiac arrhythmias, and dysmorphic features) was not universally recognized until multiple patients with similar findings were described in the last decade [Tawil et al., 1994; Sansone et al., 1997; Canun et al., 1999].

ATS is inherited as an autosomal dominant condition with a high degree of phenotypic variability and a clinically significant degree of non-penetrance, ranging from 6% to 20% of mutation-positive individuals [Andelfinger et al., 2002; Tristani-Firouzi et al., 2002]. As the prevalence of *KCNJ2* mutations among patients with the clinical features of ATS is estimated to be approximately 62%, it is likely that

Grant sponsor: Sandler Neurogenetics Center (Y.H.F.); Grant sponsor: Muscular Dystrophy Association (L.J.P); Grant sponsor: NIH (5 U54 RR019482-03, Nervous System Channelopathies: Pathogenesis & Treatment).

*Correspondence to: L.J. Ptáček, M.D., Howard Hughes Medical Institute, University of California San Francisco, Department of Neurology, Box 2922, 19B Mission Bay, Room 548F, 1550 4th Street, San Francisco, CA 94143-2922. E-mail: ptacek@itsa.ucsf.edu

**Correspondence to: G. Yoon, M.D., Department of Pediatrics, Division of Medical Genetics, University of California San Francisco, 505 Parnassus Ave., Room U585 P.O. 0748, San Francisco, CA, 94143-0748. E-mail: gyoon@itsa.ucsf.edu

DOI 10.1002/ajmg.a.31092

genetic heterogeneity exists [Donaldson et al., 2003]. Variable expressivity and non-penetrance render a clinical diagnosis of ATS difficult in many cases, particularly among those individuals who present with isolated muscle weakness or cardiac arrhythmia. In order to better define the distinctive clinical features of ATS and facilitate earlier diagnosis, we conducted a prospective, standardized evaluation of 10 subjects with confirmed *KCNJ2* mutations.

MATERIALS AND METHODS

All study procedures were approved by the Committee on Human Research at the University of California, San Francisco (UCSF). Patients with a *KCNJ2* mutation-confirmed diagnosis of ATS underwent a 3-day admission to the UCSF General Clinical Research Center (GCRC), after giving informed written consent to participate in the study. Study procedures included medical history, genetic/neurologic examination, serum electrolytes, CK level, lipid profile and thyroid studies, 24 hr Holter monitoring, 12-lead ECG, and skeletal survey. A dental panorex was obtained for six subjects. Holter monitors were placed in the same ECG lab (UCSF) using standardized methods. Each Holter included 3-lead real-time recordings and a detailed report. Twelve lead ECGs and Holter recordings were reviewed by pediatric cardiologists (SPE and MTF) blinded to the subject demographics.

Detailed anthropometric examination of all subjects was carried out by a single clinical geneticist (GY). Measurements were obtained according to methods outlined by Hall and colleagues, and compared to standardized normative data [Hall et al., 1989; Jones, 1997].

RESULTS

Demographics

Ten subjects from eight families with identified *KCNJ2* mutations were ascertained at the UCSF GCRC (Table I). All were Caucasian and residents of the United States. The mean age at admission was 24 years (range = 8–45 years), and the mean age at diagnosis of ATS was 19 years (range 5–35 years). Seven patients were female, the remaining three were male.

Family History

Of the 10 subjects, a family history of ATS was present in five, the remaining five were sporadic cases (Fig. 1).

Pregnancy History

There was one case of maternal phenytoin use in pregnancy (Subject 7), otherwise there was no history of teratogenic exposure. There was one case requiring maternal thyroid replacement therapy during pregnancy (Subject 10). One pregnancy was characterized by poor maternal weight gain (5 kg compared to 13–15 kg for other pregnancies; Subject 2). Subjects 2 and 8 were delivered by repeat Cesarean section. The mean gestational age was 40.3 weeks (range 40–42 weeks) and mean birth weight was 3.04 kg (range 2.31–3.63 kg).

General Features

All subjects had normal weight for age; the mean weight was 70th centile for age (range 10–97%). Seven of the 10 subjects had a height at the 10th centile or less for age, one was at the 75th centile, the remaining two were at the 25th centile for age (Table I).

Head Circumference

Head circumference at the lower end of normal was present in five subjects, with three of these individuals having a head circumference just below the 3rd centile for age. The head circumference of the remaining five subjects was within the normal range (50–75%).

TABLE I. Demographic and General Features of ATS Subjects

Subject	Gender	Age	Age at ATS diagnosis	Race	Height (%)	Weight (%)	Mutation
1	F	29	27	Caucasian	5	75	G146D
2	F	8 7/12	5	Caucasian	3	10	del 314-315
3	F	9 11/12	8	Caucasian	10	25	R218W
4	M	21	12	Caucasian	25	90	G300V
5	M	28	22	Caucasian	75	97	G300V
6	F	44	35	Caucasian	25	90	G300V
7	F	14	14	Caucasian	5	75	R218W
8	M	24	20	Caucasian	5	75	R218Q
9	F	25	15	Caucasian	10	75	T75R
10	F	38	34	Caucasian	5	75	D78Y

Craniofacies

Distinctive craniofacial features were observed in all 10 subjects. Broad forehead, short palpebral fissures (length <5%), malar, maxillary and mandibular hypoplasia, thin upper lip, high arched palate, triangular facies, and mild facial asymmetry were observed in all subjects. The lower third of the face was small with prominent narrowing of the jaw, and the nose appeared relatively long compared to the lower third of the face. The nasal root was narrow, with fullness alongside the bridge, just above the tip, and a bulbous or bulky nasal tip. Ocular hypertelorism (interpupillary distance >97%) was present in 8 of the 10 subjects. While ear length was normal in all subjects, low-set ears were observed in five, and pre-auricular pits in three subjects (Fig. 2, Table II).

Dental Findings

Dental anomalies were identified in all subjects. All subjects with the exception of Subject 9 had delayed eruption of permanent dentition. Other findings included multiple missing teeth (oligodontia) and elongated roots with open apices. All subjects for whom a panorex was available had radiographic evidence of hypoplasia of the maxilla and mandible, narrow upper and lower dental arches and antegonial notching of the lower border of the mandible. Six subjects (2, 4, 6, 8, 9, 10) had short rami of which two (9, 10) had condylar resorption, three (1, 3, 10) had enamel hypoplasia, and three (1, 3, 5) had an anterior crossbite (Fig. 3, Table III).

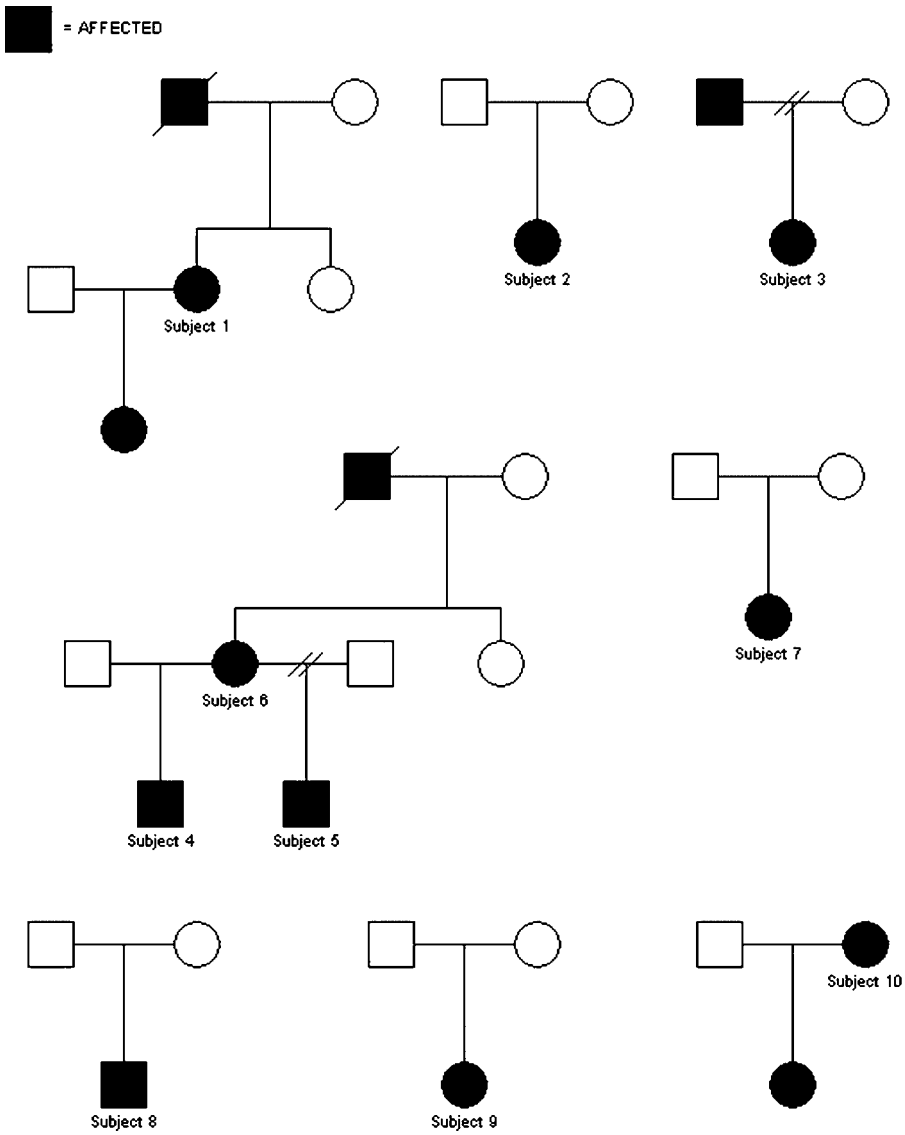

FIG. 1. Pedigrees of all subjects.

TABLE II. Craniofacial Features of ATS Subjects

Subject	HC (%)	IP (%)	PF (%)	LowEar	Pit/Tag	Nose	Palate	Chin	ThinUpperLip
1	2	97	5	No	No	Yes	Yes	Yes	Yes
2	2	25	3	Yes	No	Yes	Yes	Yes	Yes
3	5	97	3	Yes	Yes	Yes	Yes	Yes	Yes
4	75	97	3	Yes	No	Yes	Yes	Yes	Yes
5	75	97	3	No	No	Yes	Yes	Yes	Yes
6	50	97	3	No	Yes	Yes	Yes	Yes	Yes
7	5	97	5	Yes	No	Yes	Yes	Yes	Yes
8	75	97	5	No	No	Yes	Yes	Yes	Yes
9	2	97	3	No	Yes	Yes	Yes	Yes	Yes
10	50	75	3	Yes	No	Yes	Yes*	Yes	Yes

HC, head circumference; IP, interpupillary distance; PF, palpebral fissure length; LowEar, low-set ears; Nose, full nasal bridge with bulbous tip; Palate, high arched palate; *, cleft palate; Chin, mandibular hypoplasia.

Skeletal Findings

Several consistent skeletal anomalies were observed in all members of this cohort. Smallness of the hands and feet was observed in all subjects, with total hand and foot measurements at the 10th centile or less for age. Total hand length measured at or just below the 5th centile in five subjects, while total foot length measured at or just below the 5th centile in eight subjects. Measurements of hand and foot length for the adult patients were plotted at the 16-year level as no standards for adult patients currently exist.

Mild syndactyly of toes 2 and 3 was present in all subjects while syndactyly of the hands was not observed in any subject. Clinodactyly of the toes was observed in all 10 subjects. Seven subjects had 5th finger clinodactyly and all had clinodactyly of the 5th toes. Four of the 10 subjects had scoliosis, with winging of the scapula present in two subjects. Significant joint laxity was a feature of nine subjects. (Fig. 4, Table IV).

FIG. 2. Facial features (AP and lateral) of 10 subjects with ATS. **Top row** (left to right): Patients 1–3, **Second row:** Patients 4–6, **Third row:** Patients 7–9, **Bottom row:** Patient 10)

TABLE III. Dental Features of ATS Subjects

Patient	Delayed eruption	Missing teeth	Abnormal teeth	Crossbite	Mandibular morphology	Antegonial notching
1	Yes	2	Enamel hypoplasia	Edge to edge bite	NA	NA
2	Yes	5	None	None	Short mandibular rami	Yes
3	Yes	2	Enamel hypoplasia	Anterior crossbite	NA	NA
4	Yes	0	Elongated cuspid and bicuspid roots	None	Short mandibular rami	Yes
5	Yes	Unable to assess	None	Edge to edge bite	NA	NA
6	Yes	4	Peg shaped lateral incisors, elongated cuspid roots	None	Short mandibular rami	Yes
7	Yes	Unable to assess	NA	None	NA	NA
8	Yes	2	Elongated cuspid and bicuspid roots	None	Asymmetric and short rami	Yes
9	No	0	Elongated roots	None	Short mandibular rami and condylar resorption	Yes
10	Yes	8	Enamel hypoplasia, discoloration of all teeth	None	Short mandibular rami and condylar resorption	Yes

NA, radiograph not available.

These findings were confirmed by skeletal survey and variable shortening of the metacarpals, metatarsals, and phalanges were also noted. Two subjects (2 and 3) had delayed bone age and an unusual copper-beaten appearance to the skull. Six subjects (1, 4, 5, 6, 7, and 10) had prominent frontal sinuses. Five subjects (2, 3, 7, 9, 10) had gracile ribs and long bones (Fig. 4).

Neuromuscular Findings

The mean age of onset of periodic paralysis was 5 years (range 8 months–15 years). Mean frequency of attacks was three episodes per month (range 1–8) and average duration of attacks was several hours—several days for most subjects. One subject (patient 6) was completely non-penetrant for the neuromuscular phenotype and has never had an episode of periodic weakness or paralysis.

Major triggers for the episodes of periodic paralysis included exercise (5 subjects), rest post exercise (8 subjects), prolonged periods of rest (8 subjects), and stress (8 subjects). Dietary triggers typically seen in other types of periodic paralysis were rarely seen in this cohort of ATS subjects, with no subjects reporting onset of symptoms associated with salt intake and only two subjects reporting symptoms with carbohydrate ingestion. Four subjects reported cold temperature as a trigger for paralysis and one subject reported heat as a trigger. Three of the five adult female subjects reported that menses triggered episodes of paralysis. Of five subjects in whom a muscle biopsy was performed, tubular aggregates were present in four subjects. No subject reported a history of adverse reaction to anesthesia (Table V).

All subjects with the exception of Subject 6 demonstrated proximal muscle weakness of both upper and lower extremities on formal neurological examination (MRC grade 4/5) on admission as well as throughout the 3-day admission. There were no abnormalities of the cranial nerves, deep tendon reflexes, or cerebellar exam. Gait analyses were characterized by truncal lurching due to axial weakness rather than true ataxia.

Pain/Disability

Two subjects in the pediatric age range (Subjects 2 and 3) described excruciating, stabbing pain, which was exacerbated by episodes of paralysis. The pain was graded 20 on a scale of 1–10 and tended to affect the lower extremities more than the upper extremities. It was exacerbated by movement and felt to be a significant barrier to mobility, activities of daily living and function as reported by both the subjects and

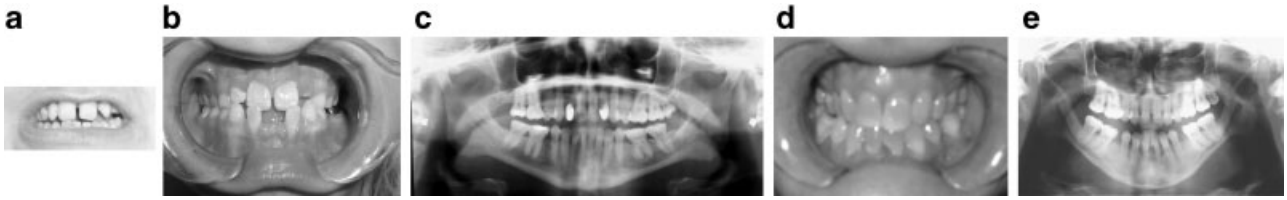

FIG. 3. Dental findings in ATS (left to right): (**a**) Patient 1, age 29 years—Absence of maxillary lateral incisors. **b**: Patient 3, age 9 years 11/12—Markedly delayed eruption of permanent dentition, enamel hypoplasia, and anterior crossbite. **c**: Patient 6, age 44 years—Retained primary maxillary incisors which were prosthetically crowned. There are four bicuspids, two maxillary, and two mandibular teeth missing. The first maxillary bicuspid has two roots instead of one. The cuspid roots are elongated with open apices. The jaw rami were short and antegonial notching of the lower border of the mandible was present. **d** and **e**: Patient 10, age 38 years—Enamel hypoplasia, discoloration of all teeth. Eight congenitally missing teeth: all four-second bicuspids and all four lateral incisors in the maxilla and mandible. The condylar heads were flattened on both sides and there was marked antegonial notching of the lower border of the mandible.

TABLE IV. Skeletal Findings in ATS Subjects

Subject	Scoliosis	ScapWing	JointLax	HandLeng (%)	MidFing Leng (%)	FootLeng (%)	HandSynd	ToeSynd	FingerClino	ToeClino
1	No	No	Yes	3	3	3	No	Yes	No	Yes
2	No	No	Yes	5	10	5	No	Yes	Yes	Yes
3	No	No	Yes	3	10	3	No	Yes	Yes	Yes
4	Yes	Yes	Yes	10	25	3	No	Yes	Yes	Yes
5	No	No	Yes	10	50	10	No	Yes	No	Yes
6	No	No	No	10	25	3	No	Yes	Yes	Yes
7	No	No	Yes	10	25	3	No	Yes	Yes	Yes
8	Yes	No	Yes	5	5	3	No	Yes	Yes	Yes
9	Yes	Yes	Yes	10	10	10	No	Yes	No	Yes
10	Yes	No	Yes	3	3	3	No	Yes	Yes	Yes

ScapWing, scapular winging; JointLax, joint laxity; HandLeng, total hand length; FootLeng, total foot length; HandSynd, hand syndactyly; ToeSynd, 2–3 toe syndactyly; FingerClino, finger clinodactyly; ToeClino, toe clinodactyly.

primary caregivers. Subjects 9 and 10 reported experiencing similar episodes of pain as children, and the affected child of Subject 10 (not evaluated) also reports pain severe enough to limit function.

Disability was grossly quantitated using a modified Rankin score. One subject had no neuromuscular symptoms, one had completely normal function during attacks, four had mild disability, and four subjects were moderately to severely disabled during attacks of paralysis (Table VI).

Cardiac Findings

The average age at cardiac diagnosis was 13 years (range 3 years 8 months–25 years). The cardiac diagnosis was initially ascertained through routine health exams or as part of the investigation of muscle weakness. The most common cardiac symptom was occasional palpitations reported in six subjects. One subject complained of occasional chest pain, however this did not correlate with electrical activity on Holter monitoring. Three subjects (2, 3, and 10) have implanted cardioverter defibrillators (ICDs) due to frequent ventricular ectopy and ventricular tachycardia. One subject (10) experienced three episodes of syncope prior to receiving an ICD.

Review of the 12-lead ECG for all subjects revealed that the QTc interval was normal or only somewhat prolonged with an average QTc interval of 434 ± 31 ms. The heart rate, PR interval, and QRS duration were normal. In three subjects, the QT interval could not be calculated due to bigeminy or frequent premature ventricular contractions (PVCs). The presence of a prominent U wave was common, observed in over half the cohort (Table VII). Similarly, 24-hr Holter monitor recordings demonstrated prominent U waves associated with sinus beats. Frequent episodes of ventricular ectopy were observed in 7 of 10 subjects, ranging from single premature ventricular contractions (PVCs) to non-

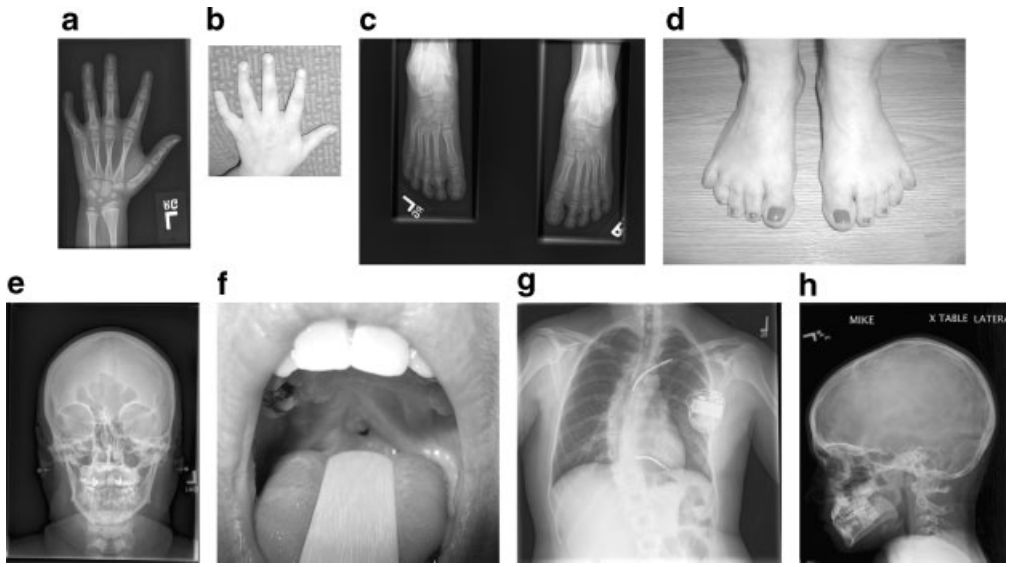

FIG. 4. Skeletal and radiographic findings in ATS. Top row (left to right): (**a**) and (**b**) Patient 2, age 8 years, 7/12—5th finger clinodactyly, short 1st, 4th, and 5th metacarpals, short 5th proximal and middle phalanges. According to the California standard of Greulich and Pyle, the estimated bone age is 5 years and 9 months. **c** and **d**: Clinodactyly of toes 3,4,5, brachydactyly, mild cutaneous 2–3 syndactyly, shortening of metatarsals 1,4,5. Bottom row (left to right): (**e**) Prominent frontal sinuses. (**f**) Residual cleft palate. (**g**) Gracile ribs and scoliosis with ICD in place. (**h**) Copper-beaten skull.

TABLE V. Characteristics of Periodic Paralysis for the ATS Cohort

Subject	AgeOnset	Freq/mo	Duration	Exercise	RestPostEx	Prolong.Rest	NaCl	CHO	Heat	Cold	Menses	Stress	Biopsy
1	8 months	1	Hours	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Normal
2	2 years	1	Hours–days	No	Yes	Yes	No	No	No	Yes	No	No	NA
3	4 years	2	Days	No	Yes	Yes	No	No	Yes	No	No	Yes	NA
4	2 years	4	24hr–days	No	Yes	Yes	No	No	No	No	No	Yes	Tub. Agg.
5	10 years	8	Hours	No	Yes	Yes	No	Yes	No	No	No	Yes	NA
6	None	0	0	No	No	No	No	No	No	No	No	No	NA
7	8 years	4	Minutes	Yes	No	Yes	No	No	No	No	Yes	Yes	NA
8	15 years	2	3–4 days	Yes	Yes	No	No	No	No	Yes	No	Yes	Tub. Agg.
9	5 years	1	Days–weeks	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Tub. Agg.
10	4 years	1	Days	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Tub.Agg.

AgeOnset, age of onset of periodic paralysis; Freq/mo, frequency of attacks per month; duration, duration of attacks; Exercise, exercise as a trigger for episodes of paralysis; RestPostEx, rest post exercise; Prolong.Rest, prolonged rest; NaCl, high salt foods; CHO, carbohydrates; Biopsy, muscle biopsy pathology; Tub Agg., tubular aggregates.
NA, not applicable.

TABLE VI. Disability in ATS

Subject	RankinScore	Pain
1	1	
2	3	Yes
3	4	Yes
4	2	
5	2	
6	0	
7	0	
8	3	
9	3	Yes (as a child)
10	2	Yes (as a child)

Modified Rankin Score: for an average attack.
0, normal.
1, nondisabling symptoms that do not interfere with lifestyle.
2, minor symptoms that lead to restriction of lifestyle but do not interfere with capacity for self care.
3, moderate disability symptoms that significantly interfere with lifestyle or prevent total independence.
4, severely disabled and totally dependent.

sustained ventricular tachycardia (VT). Of interest, the onset of PVCs or runs of VT were typically simultaneous with the U wave (Table VIII). In all seven subjects with ventricular ectopy, PVCs and VT were bi-directional in nature. Bidirectional VT occurred with runs of 3–26 beats in duration at a relatively slow rate (mean 158 ± 27 bpm). Ventricular ectopy and tachycardia burden were quite variable representing an average of $10 \pm 16\%$ (range 0–51%) of heartbeats. There was no consistent relationship between time of day or activity level and ventricular ectopy between members of this cohort. Events occurred with rest and with activity. No correlation was documented between cardiac symptoms and ventricular ectopy/VT. Of note, Subject 1 was entirely asymptomatic despite having ventricular ectopy 50% of the time.

Lab Investigations

All subjects had electrolyte levels drawn during an episode of paralysis. All were in the normal range, with no documented hypo or hyperkalemia. Thyroid function was normal in all subjects. One subject (4)

TABLE VII. Electrocardiographic Findings

Subject	AgeCardiac Diagnosis	HR	PR	QRS	QTc	U	Ectopy
1	12 years	70	88	70	*	*	Bigeminy
2	3 years 8/12	89	148	66	450	+	—
3	7 years	50	152	80	418	+	—
4	13 years	45	146	84	370	−	PVCs
5	None	76	146	88	449	−	—
6	21 years	76	142	82	461	+	—
7	12 years	89	148	102	441	+	—
8	20 years	94	136	106	450	+	—
9	12 years	97	130	66	*	*	Bigeminy
10	25 years	79	152	114	*	+	PVCs

*, Cannot determine due to ectopy; PVCs, premature ventricular contractions.

TABLE VIII. 24-hr Holter Monitor Findings

Subject	PVC	PVC per hr	Couplets	VT	VT Rate	Max length	No. of runs	% time
1	+	1158	+	+	170	26	1000	51
2	+	96	+	+	149	12	181	1.3
3	+	217	+	+	190	11	17	5.3
4	+	528	+	+	150	3	6	12.6
5	+	0.04	−	−	NA	NA	NA	0
6	+	154	+	+	113	3	1	3
7	+	0.08	−	−	NA	NA	NA	0.002
8	+	0.2	−	−	NA	NA	NA	0.004
9	+	80.5	+	+	179	15	354	17
10	+	352	+	−	NA	NA	NA	7

Couplets, two consecutive ventricular beats; VT, ventricular tachycardia defined as three or more consecutive ventricular beats; NA, not applicable.

had a CK level 2.5 times the upper limit of normal, otherwise CK levels were normal in the remaining nine subjects. Three subjects (4, 5, 8) had marked elevations in fasting cholesterol and triglyceride levels.

Mortality

All subjects who participated in this study are alive and well. Two subjects have parents, one with a confirmed *KCNJ2* mutation, who died suddenly of cardiac arrest.

DISCUSSION

The diagnosis of Andersen-Tawil syndrome is complicated by a high degree of clinical variability. The full triad of clinical features (periodic paralysis of skeletal muscle, cardiac arrhythmias, and characteristic dysmorphic features) has been reported present in 58–78% of mutation-positive patients, [Tristani-Firouzi et al., 2002] while between 32% and 81% manifest involvement of two of the three organ systems. [Plaster et al., 2001; Andelfinger et al., 2002; Tristani-Firouzi et al., 2002] Based in part on these data, a clinical diagnosis of ATS has traditionally been made in an individual who has two of the following three cardinal features: periodic paralysis, typical cardiac findings, or typical dysmorphic features. Alternatively, ATS is considered in an individual who has one cardinal feature plus a family history of ATS. [Tristani-Firouzi et al., 2002; Donaldson et al., 2003] Many investigators consider the presence of two or more of the following features to fulfill the dysmorphic criteria for ATS: low-set ears, hypertelorism, small mandible, clinodactyly, or 2–3 syndactyly. [Tristani-Firouzi et al., 2002; Donaldson et al., 2003]. The goal of this study was to quantify the distinctive clinical features of ATS, using a prospective, standardized evaluation of subjects with confirmed *KCNJ2* mutations, with the ultimate aim of facilitating earlier diagnosis for patients with ATS.

We identified a characteristic pattern of craniofacial features, dental and skeletal anomalies that was observed in all members of this cohort. These included broad forehead, short palpebral fissures, relatively long nose with fullness along the bridge and bulbous tip, malar, maxillary and mandibular hypoplasia, thin upper lip, high arched or cleft palate, triangular facies, and mild facial asymmetry. Dental anomalies were identified in all subjects. These consisted of delayed eruption of permanent dentition, oligodontia, and dental root anomalies. Jaw characteristics included small maxilla and mandible, narrow upper and lower dental arches, and antegonial notching of the lower border of the mandible. Finally, skeletal anomalies, specifically hand and foot size at the lower limits of normal, brachydactyly, 2–3 toe syndactyly, and toe clinodactyly, were identified in all subjects. Based on these findings, we propose extending the diagnostic dysmorphology criteria for ATS to include these craniofacial, dental, and skeletal features. (Table IX).

Morphological features supportive of the diagnosis of ATS, present in at least 50% of subjects in this cohort, included hypertelorism, joint laxity, 5th finger clinodactyly, head circumference at the lower limits of normal, ear anomalies, short stature, gracile ribs and long bones, and prominent frontal sinuses on skeletal survey. Scoliosis, scapular winging, copper-beaten skull on skull X-ray, and delayed bone age were less common features, but strengthen the diagnosis if present in addition to the other cardinal features.

The earliest clinical symptom for this cohort of ATS subjects was episodic neuromuscular weakness, with the exception of Subject 6, who has never had an episode. The mean age of onset of periodic paralysis was 5 years (range 8 months–15 years), and predated the cardiac symptoms by at least 2 years; mean age at cardiac diagnosis was 13 years (range 3 years 8 months–25 years). The mean age at diagnosis of ATS was 19 years (range 5–35 years) and time to diagnosis after onset of first clinical symptom ranged from 3 to 30 years. Recognition of the characteristic dysmorphic features of ATS, which are present from birth and apparent in early childhood, is important in making a timely diagnosis of

TABLE IX. Proposed Expansion of the Diagnostic Criteria for ATS Dysmorphic Features

Current dysmorphic diagnostic criteria[a]	Proposed expansion of diagnostic criteria
Two or more of:	Major features[b]:
Low-set ears	Characteristic facies (broad forehead, short palpebral fissures, full nasal bridge with bulbous tip, malar, maxillary and mandibular hypoplasia, thin upper lip, triangular shape, mild asymmetry)
Hypertelorism	Palate (high arched or cleft)
Small mandible	Dental anomalies (persistent primary dentition, oligodontia, or abnormally long dental roots with open apices, narrow upper and lower dental arches, short jaw rami, antegonial notching of the lower mandible, dental crowding)
Clinodactyly	Small hands and feet
2–3 syndactyly	Variable brachydactyly
	Toe clinodactyly and 2–3 toe syndactyly
	Minor features[c]:
	Hypertelorism
	Joint laxity
	5th finger clinodactyly
	Small head circumference
	Ear anomalies
	Short stature
	Prominent frontal sinuses
	Gracile ribs and long bones
	Other Features seen in ATS:
	Scoliosis
	Scapular winging
	Copper-beaten skull
	Delayed bone age

[a][Tristani-Firouzi et al., 2002; Donaldson et al., 2003].
[b]Features seen in all subjects in this cohort.
[c]Features seen in at least 50% of subjects.

ATS in a patient who presents with episodic weakness and/or cardiac arrhythmias.

Rest post exercise, prolonged rest, and stress were consistent triggers for the attacks of periodic paralysis in 80% of subjects. Further studies are required to quantify the relation between these triggers and onset of paralysis. All subjects with the exception of Subject 6 had at least one episode of periodic paralysis during the course of hospital admission during this study and all were associated with normokalemia. Nine patients had undergone some type of surgical procedure prior to admission and none reported complications with anesthesia. Forty percent of subjects had limitation in their activities of daily living, occupation, and overall mobility due to the episodes of weakness. The excruciating neuromuscular pain reported by four subjects has not been previously reported in the literature, and highlights the importance of ascertaining this symptom when evaluating patients with ATS.

An electrocardiographic abnormality was present in all but one of the 10 subjects in this cohort. The 12 lead ECG was sufficient to detect one or more cardiac features of ATS (prolonged QTc, prominent U wave or ventricular ectopy). However, the 24 hr Holter monitor was instrumental in documenting the presence, frequency, duration, and rate of VT. Specifically, the 24 hr Holter monitor confirmed the bidirectional nature of ventricular ectopy in all subjects with frequent PVCs or nonsustained VT. Bidirectional ventricular ectopy is an extremely rare form of ectopy described in only three clinical settings: ATS, digitalis toxicity, and catecholaminergic polymorphic ventricular tachycardia [Kastor, 1973; Francis et al., 2005]. We recommend both a 12 lead ECG and 24 hr Holter monitor as standard tests in the diagnostic work-up of individuals suspected of ATS.

Bidirectional ventricular ectopy was present in 7 out of 10 subjects in this ATS cohort, defining ventricular ectopy as the most common cardiac manifestation. Mild prolongation of the QTc interval was observed in three of the seven subjects in whom a QTc was calculable. This observation is consistent with a recent large scale ECG analysis of *KCNJ2* mutation-positive subjects reporting modest QT prolongation compared to age-matched controls, but a mean value within the limits of normal [Zhang et al., 2005]. One half of the subjects in our cohort demonstrated prominent U waves on the 12 lead ECG. While the underlying cellular mechanism for this observation is unknown, abnormal cardiac repolarization manifested as pathological U waves has been reported as a frequent cardiac finding in ATS [Tristani-Firouzi et al., 2002; Donaldson et al., 2003; Zhang et al., 2005]. Interestingly, no symptoms were reported in any individuals during episodes of ventricular ectopy. Thus as reported in other series [Chun et al., 2004], many ATS patients are remarkably asymptomatic despite a significant tachycardia burden.

Mutations in *KCNJ2* and subsequent Kir2.1 channel dysfunction cause a consistent pattern of skeletal malformations, however the exact mechanism by which this ion channel defect disrupts skeletal development is not known. In mice, targeted deletion of *KCNJ2* results in craniofacial defects, altered cardiac excitability, and neonatal lethality. *KCNJ2* knockout pups universally manifest complete cleft of the secondary palate, which was postulated to account for death shortly after birth [Zaritsky et al., 2000]. The relation, if any, between *KCNJ2* and other genes known to play critical roles in skeletal development has yet to be elucidated. These include the Hedgehog and Hox families, *ROR2*, *GDF5*, *BMPR1A*, and *BMPR1B*, among others [Gao et al., 2001; Johnson et al., 2003; Sammar et al., 2004] Similarly, the role of Kir2.1 in normal tooth development has yet to be elucidated. It is of interest to note that the dental findings in ATS patients, particularly the elongated dental roots with open apices are similar to those reported in two cases of oculofaciocardiodental syndrome [Oberoi et al., 2005].

In summary, we present a detailed study of a cohort of 10 subjects with molecularly confirmed ATS and typical neuromuscular and cardiac findings. In addition, we report a consistent and recognizable pattern of craniofacial, dental, and skeletal malformations, present in all subjects regardless of neuromuscular or cardiac symptoms, which should facilitate an earlier diagnosis of ATS for affected patients.

ACKNOWLEDGMENTS

The authors thank the patients and their families for participating in this research. We thank Paul Keats, Magnus Dias da Silva, M.D., Ph.D., and Michael Kohn, M.D. for technical assistance. We thank Judith Allanson, M.D. for critically reading the manuscript and for her insightful comments. L.J.P. is an investigator of the Howard Hughes Medical Institute. These studies were carried out in part in the General Clinical Research Center, Moffitt Hospital, University of California, San Francisco, with funds provided by the National Center for Research Resources, 5 M01 RR-00079, U.S. Public Health Service.

REFERENCES

Andelfinger G, Tapper AR, Welch RC, Vanoye CG, George AL Jr, Benson DW. 2002. KCNJ2 mutation results in Andersen syndrome with sex-specific cardiac and skeletal muscle phenotypes. Am J Hum Genet 71:663–668.

Andersen ED. 1971. Intermittent muscular weakness, extrasystoles, and multiple developmental anomalies: A new syndrome? Acta Paediat Scand 60:559–564.

Canun S, Perez N, Beirana LG. 1999. Andersen syndrome autosomal dominant in three generations. Am J Med Genet 85:147–156.

Chun TU EM, Dick M 2nd, Andelfinger G, Ballester L, Vanoye CG, George AL Jr, Benson DW. 2004. Polymorphic ventricular tachycardia and KCNJ2 mutations. Heart Rhythm 1:235–241.

Donaldson MR, Jensen JL, Tristani-Firouzi M, Tawil R, Bendahhou S, Suarez WA, Cobo AM, Poza JJ, Behr E, Wagstaff J, Szepetowski P, Pereira S, Mozaffar T, Escolar DM, Fu YH, Ptacek LJ. 2003. PIP2 binding residues of Kir2.1 are common targets of mutations causing Andersen syndrome. Neurology 60:1811–1816.

Francis J SV, Nair VK, Priori SG. 2005. Catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm 2:550–554.

Gao B, Guo J, She C, Shu A, Yang M, Tan Z, Yang X, Guo S, Feng G, He L. 2001. Mutations in IHH, encoding Indian hedgehog, cause brachydactyly type A-1. Nat Genet 28:386–388.

Hall JG, Froster-Iskenius UG, Allanson JE. 1989. Handbook of normal physical measurements. Oxford: Oxford University Press. 504 p.

Johnson D, Kan SH, Oldridge M, Trembath RC, Roche P, Esnouf RM, Giele H, Wilkie AO. 2003. Missense mutations in the homeodomain of HOXD13 are associated with brachydactyly types D and E. Am J Hum Genet 72:984–997.

Jones KL. 1997. Smith's recognizable patterns of human malformation. Philadelphia: W.B. Saunders Company. 861 p.

Kastor J. 1973. Digitalis intoxication in patients with atrial fibrillation. Circulation 47:888–896.

Oberoi S, Winder AE, Johnston J, Vargervik K, Slavotinek AM. 2005. Case reports of oculofaciocardiodental syndrome with unusual dental findings. Am J Med Genet A 136A:275–277.

Plaster NM, Tawil R, Tristani-Firouzi M, Canun S, Bendahhou S, Tsunoda A, Donaldson MR, Iannaccone ST, Brunt E, Barohn R, Clark J, Deymeer F, George AL Jr, Fish FA, Hahn A, Nitu A, Ozdemir C, Serdaroglu P, Subramony SH, Wolfe G, Fu YH, Ptacek LJ. 2001. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. Cell 105:511–519.

Raab-Graham KF RC, Vandenberg CA. 1994. Molecular cloning and expression of a human heart inward rectifier potassium channel. Neuroreport 5:2501–2505.

Sammar M, Stricker S, Schwabe GC, Sieber C, Hartung A, Hanke M, Oishi I, Pohl J, Minami Y, Sebald W, Mundlos S, Knaus P. 2004. Modulation of GDF5/BRI-b signalling through interaction with the tyrosine kinase receptor Ror2. Genes Cells 9:1227–1238.

Sansone V, Griggs RC, Meola G, Ptacek LJ, Barohn R, Iannaccone S, Bryan W, Baker N, Janas SJ, Scott W, Ririe D, Tawil R. 1997. Andersen's syndrome: A distinct periodic paralysis. Ann Neurol 42:305–312.

Tawil R, Ptacek LJ, Pavlakis SG, DeVivo DC, Penn AS, Ozdemir C, Griggs RC. 1994. Andersen's syndrome: Potassium-sensitive periodic paralysis, ventricular ectopy, and dysmorphic features. Ann Neurol 35:326–330.

Tristani-Firouzi M, Jensen JL, Donaldson MR, Sansone V, Meola G, Hahn A, Bendahhou S, Kwiecinski H, Fidzianska A, Plaster N, Fu YH, Ptacek LJ, Tawil R. 2002. Functional and clinical characterization of KCNJ2 mutations associated with LQT7 (Andersen syndrome). J Clin Invest 110:381–388.

Zaritsky JJ, Eckman DM, Wellman GC, Nelson MT, Schwarz TL. 2000. Targeted disruption of Kir2.1 and Kir2.2 genes reveals the essential role of the inwardly rectifying K(+) current in K(+)-mediated vasodilation. Circ Res 87:160–166.

Zhang L, Benson DW, Tristani-Firouzi M, Ptacek LJ, Tawil R, Schwartz PJ, George AL, Horie M, Andelfinger G, Snow GL, Fu YH, Ackerman MJ, Vincent GM. 2005. Electrocardiographic features in Andersen-Tawil syndrome patients with KCNJ2 mutations: Characteristic T-U-wave patterns predict the KCNJ2 genotype. Circulation 111:2720–2726.