Andersen–Tawil syndrome

Definition of a neurocognitive phenotype

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Abstract—*Background:* The Andersen–Tawil syndrome (ATS) is a potassium ion channelopathy caused by mutations in the *KCNJ2* gene. It is characterized by periodic paralysis, cardiac arrhythmias, and distinctive features; the effect of *KCNJ2* mutations on the CNS has never been studied. *Objective:* To define a potential CNS phenotype in ATS using standardized methods. *Methods:* Ten subjects with *KCNJ2* mutations and their unaffected siblings were evaluated at the University of California San Francisco General Clinical Research Center. A comprehensive battery of neurocognitive tests was administered to ATS subjects and their unaffected siblings, followed by pairwise analysis of the resultant differences in scores. An EEG was obtained for all ATS subjects. *Results:* There was no EEG evidence of subclinical seizure activity in any subject. ATS subjects universally had more school difficulties than their siblings, despite similar IQ between the two groups. On formal neurocognitive testing, there was no difference between ATS subjects and their siblings on tests of verbal and visual memory. Assessment of executive functioning revealed ATS subjects scored 1.93 points lower than their siblings on tests of Design Fluency (95% CI −3.46, 0.01; $p = 0.052$) and made 1.9 more errors (95% CI 0.46, 2.54; $p = 0.005$). Subjects with ATS scored an average of 5 points lower than their siblings on tests of matrix reasoning (95% CI −8.67, −1.33; $p = 0.008$). On tests of general ability, ATS subjects achieved much lower scores than their siblings, with an average difference of 9.13 points for reading (95% CI −12.46, 3.21; $p = 0.056$) and 23.4 points for mathematics (95% CI −42.53, −4.22; $p = 0.017$). *Conclusion:* Mutations in *KCNJ2* are associated with a distinct neurocognitive phenotype, characterized by deficits in executive function and abstract reasoning.

NEUROLOGY 2006;66:1703–1710

Andersen–Tawil syndrome (ATS) is a unique member of the neurologic channelopathies, characterized by cardiac arrhythmias and distinctive features in addition to periodic paralysis.[1] Mutations of the *KCNJ2* gene on chromosome 17q23, which encodes the inward-rectifying potassium channel protein Kir2.1, cause reduction in Kir2.1 current and the ATS phenotype.[2] Approximately 70% of patients with ATS have mutations in *KCNJ2,* and the genetic basis of the remaining patients with features consistent with ATS is unknown.[3] ATS is inherited as an autosomal dominant disorder with highly variable expression, although cases arising from de novo mutations are frequent.[4-7]

The Kir2.1 protein is widely expressed but especially prominent in heart, skeletal muscle, and brain.[8] In rats, the brain-specific expression has been localized to the dentate gyrus granule cells of the hippocampus as well as the basal ganglia (caudate putamen and nucleus accumbens) and midbrain (superior colliculus, anterior pretactal nucleus, and deep mesencephalic nucleus).[9] Seizures are not considered part of the clinical presentation of ATS, despite unequivocal evidence of potassium and other ion channel dysfunction as an important cause of epilepsy.[10-13] In addition to the recognized triad of signs in ATS, anecdotal observations by us (L.P.) and others[14] (and R. Tawil, personal communication) suggested possible neurocognitive deficits. To define a potential neurocognitive phenotype associated with ATS, we conducted a prospective, standardized evaluation of 10 subjects with confirmed *KCNJ2* mutations and compared their performance on neurocognitive testing with that of their unaffected siblings.

Methods. All study procedures were approved by the Committee on Human Research at the University of California San Francisco. Subjects with a confirmed diagnosis of ATS by *KCNJ2* mutation analysis, and their unaffected mutation-negative siblings (when available), underwent a three day admission to the University of California San Francisco General Clinical Research Center (GCRC), after giving informed written consent to participate in the study. Clinical characterization of 10 subjects with documented *KCNJ2* mutations (mean age 24 years; range 8 to 45 years) from eight families and eight unaffected siblings (mean age 23 years; range 7 to 48 years) was carried out using a standardized protocol. Study procedures for ATS subjects included medical history, genetic/neurologic examination including clinical photographs, serum electrolytes, creatine kinase level, lipid profile, and thyroid studies, 24-hour Holter monitoring, 12-lead EKG, EEG,

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Supported by grants from the Sandler Neurogenetics Center (Y.H.F.), the Muscular Dystrophy Association (L.J.P), and the NIH (5 U54 RR019482-03, Nervous System Channelopathies: Pathogenesis and Treatment). 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.

Disclosure: The authors report no financial or nonfinancial conflicts of interest.

Received December 1, 2005. Accepted in final form February 22, 2006.

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and skeletal survey, and detailed neurocognitive testing. School reports were reviewed whenever possible. Study procedures for unaffected sibling controls included medical history, physical exam, and neurocognitive testing.

Memory. The California Verbal Learning Test (CVLT-II) was administered to assess verbal episodic memory deficits. It is a widely validated 16-item list learning task with an interference condition, a subsequent short delay recall, and a semantic cuing recall trial.[15] After a long delay of approximately 25 minutes, subjects were administered a free recall trial. The test concluded with semantic cuing and a discrimination trial where subjects were required to recognize the original 16 items among an array of related and unrelated items.

For spatial memory, subjects were administered the Visual Reproductions I and II subtests of the Wechsler Memory Scale (3rd ed.).[16] During the Visual Reproductions I subtest, subjects are shown five increasingly complex figures one at a time. After examining each figure for 10 seconds, the subjects were asked to draw each design from memory. A long delay free recall trial was administered after approximately 25 minutes.

Executive functioning. Executive functioning is referred to as the global cognitive ability to engage in goal-directed behavior. Planning, organization, response inhibition, abstract reasoning, and mental flexibility are components of executive abilities. We assessed executive abilities by administering the Verbal Fluency, Design Fluency, and Trail Making subtests from the Delis–Kaplan Executive Functioning System (DKEFS) battery.[17] The DKEFS is a validated instrument with standardized norms ranging from ages 6 through 89.

Fluency is a widely used neuropsychological task known to be sensitive to frontal dysfunction. We assessed verbal fluency by asking participants to generate as many words beginning with the letters F, A, and S, as possible (excluding proper nouns and similar root words with different suffixes) within the confines of 60 seconds per letter. Design Fluency is considered to be the nonverbal analogue to verbal fluency. The DKEFS evaluates Design Fluency with three conditions. The first two trials are control conditions, presented to subjects with pages containing boxes with five filled (Trial 1) or empty dots (Trial 2). They are required to generate as many different designs as possible in 1 minute using only four lines to connect each dot, making a different design each time. The third condition is a set-shifting task that requires subjects to alternate between empty and filled dots still only using four lines to connect each dot. As with verbal fluency, the numbers of repetitions and rule violations (e.g., failure to shift between empty and filled dots) are tabulated.

Conditions 2, 3, and 4 of the DKEFS Trail Making Test were administered to assess mental flexibility. Conditions 2 and 3 require the subjects to draw lines connecting numbers/letters in order before the 180-second time limit. Condition 4 requires participants to serially alternate between numbers and letters within the confines of a 240-second time limit. Time to completion is then compared against the standardized age-based norms available for age group.

Working memory. We administered the Digit Span and Spatial Span subtest from the Wechsler Memory Scale (3rd ed.)[16] to assess both verbal and nonverbal working abilities. The Digit Span subtest has two components that are administered separately. During the first part, Digit Span Forward, a series of random numbers was read to the subject. The subject was then required to repeat the sequence in the exact same order, with an increase in amount of numbers at the completion of each trial. After failure to repeat the numbers in sequential order after two trials, the second part of the subtest, Digit Span Backward, was then administered. For this task, the subject is required to repeat the sequence in the reverse order. A nonverbal analogue to Digit Span is Spatial Span.[16] Subjects were required to visually track then repeat the sequence of blocks tapped by the examiner in the exact same order. Similar to the Digit Span subtest, after the failure of two trials, the Spatial Span Backward was then administered.

General intelligence. Overall intellectual capacity was assessed using the standardized Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence.[18] A screening measure of academic achievement was assessed by administering the Numerical Operations and Word Reading Subtests of the Wechsler Individual Achievement Test (2nd ed.).[19]

Figure. Subject 1, age 29 (left), with her unaffected sister, age 30 (right). Note the differences in head size and facial features.

Statistical analysis. All data analyses were carried out using Intercooled STATA 8.0 software. The Student t test was used to compare continuous data, and the χ^2 test was used to compare categorical data between ATS subjects and their unaffected siblings for simple descriptive statistical analysis. For the complex neurocognitive data, a pairwise method of analysis was chosen as a means of comparing affected subjects with their unaffected sibling controls. A maximum likelihood mixed effects model was fit for this purpose as it allowed comparison of the two groups, clustered by family. The random effects component of the model enabled adjustment for the effects of inherent differences in cognitive function between families. Analyses were carried out using longitudinal regression techniques.

Case histories. Patient 1. A 29-year-old woman first presented at age 8 months with episodic paralysis. She was diagnosed with cardiac arrhythmias at age 12 following investigations for weakness, but was not formally diagnosed with ATS until age 27. Analysis of the *KCNJ2* gene revealed a G146D mutation. Early motor development was delayed owing to the episodes of weakness; however, speech development was also delayed, and the patient required speech therapy from kindergarten through grade 4. School was a challenge for her, and she repeated kindergarten as well as grades 2 and 5. She had difficulty in all subjects; her average grades were Ds, but she had particular difficulty with math. She completed grade 10 and is currently employed as a factory worker. She had few friends outside her immediate family and describes herself as being shy. She is the single parent of a 3-year-old girl who is also affected with ATS. Family history was significant for her father having periodic paralysis, cleft palate, and sudden death at age 56. Although formal genetic studies were not able to be carried out, it is likely that he had ATS. Neurologic exam was remarkable for joint laxity, mild hypotonia, and mild generalized weakness (proximal greater than distal). Gait analysis was remarkable for slight left truncal lurch due to axial weakness. There was no myotonia, cranial nerve, or cerebellar abnormality. Deep tendon reflexes were normal, and plantar reflexes were flexor. Cardiac investigations revealed marked ventricular ectopy, bigeminy, and ventricular tachycardia, with heart rates of up to 170 beats/min. She had typical ATS facies (hypertelorism, broad forehead, short palpebral fissures, fullness of the nasal base with bulbous tip, malar, maxillary, and mandibular hypoplasia, thin upper lip, high arched palate, and mild facial asymmetry) as well as microcephaly (figure). She also had dental anomalies (oligodontia, enamel hypoplasia, delayed eruption of permanent dentition, malocclusion), small hands and feet, brachydactyly, two- to three-toe syndactyly, and clinodactyly of the toes. Potassium and other electrolyte levels as well as thyroid-stimulating hormone and creatine kinase were normal. EEG (routine and with photic stimulation) was completely normal. A 1-year trial of acetazolamide was carried out at age 12, but this was discontinued because it had no effect on the attacks of paralysis. She was on no medications on admission and had refused all attempts to cardiac management, including medication and consideration of Implantable Cardioverter Defibrillator (ICD) placement.

Patient 2. An 8-year 7-month-old girl presented at age 2 with significant periodic paralysis and was diagnosed with cardiac arrhythmias at age 3 years 8 months. She required placement of an

ICD at age 4 years due to intractable ventricular ectopy and tachycardia. *KCNJ2* mutation analysis carried out at age 5 revealed a del 314-315 mutation. Gross and fine motor development was slightly delayed, but speech development was normal. She had just completed a modified grade 2 program, and review of school reports demonstrated difficulties in answering abstract or inferential type questions, completing assigned work during the allotted time, and processing sequences of events required to complete complex tasks. Prior developmental testing at school revealed her visual motor skills to be within the normal range for age. She had never had overt behavioral problems but developed occasional inappropriate outbursts of anger and frustration during the year prior to admission, attributed to the increasingly complex tasks at school. She had no difficulty with socialization, however, and had many friends. Family history was negative for ATS. Detailed physical examination and cardiac investigations were consistent with a diagnosis of ATS. Lab investigations were normal and whereas routine EEG was significant for nonspecific diffuse increase in theta frequency, there was no epileptiform activity and EEG with photic stimulation was completely normal. Prior CT and MRI studies of the brain were normal. Medications on admission included atenolol, mexilitine, and acetazolamide.

Patient 3. A 9-year 11-month girl developed significant episodic weakness at age 4 and was found to have cardiac arrhythmias during investigation for paralysis at age 7. She was formally diagnosed with ATS at age 8 when analysis of the *KCNJ2* gene revealed an R218W mutation. Early motor development was normal; however, speech development was delayed. She had always struggled in school, particularly with grasping basic math and reading concepts in addition to more complex material. She had a lot of difficulty in first grade, and although her mother requested she be held back a year, this was not done, despite evidence of a potential learning disability. She had completed a grade 4 regular program, achieving grades of Fs, Ds, and Cs for most of the year. She had particular difficulties with math, reading, and science. By parental report, her reading level is at a grade 2 to 3 level. She also had behavioral difficulties over the last 2 years, characterized by immaturity, with inappropriate anger outbursts. She tended to make friends with children who were on average younger than herself. Family history was negative for ATS. Detailed physical examination and cardiac investigations were consistent with a diagnosis of ATS. Lab investigations were normal, as were routine and EEG with photic stimulation. Medications on admission included atenolol, potassium chloride, and acetazolamide.

Patient 4. A 21-year-old man presented with episodic paralysis at age 2, although this was not formally investigated until age 12, when the episodes became more severe. Cardiac arrhythmias were diagnosed at age 13, and analysis of the *KCNJ2* gene revealed a G300V mutation. Early motor development was normal; however, speech development was delayed. He had academic difficulty, particularly in middle school. In grade 6, he manifested difficulties with concentration, as well as retention of reading material, and by high school his grades had deteriorated. There were several subjects for which he received failing grades of Ds and Fs. His best subjects during high school were math and science; his worst subjects were English and English-related subjects. He completed education at the high school level, and since then, he has worked at three different fast food establishments for a period of 1 month each. He worked as a cabinetmaker for 1 month, a plumber for approximately 12 months, and mowed lawns for 6 months. He also spent a year working in a remodeling business. He had been employed during the 14 months prior to admission as a bar manager, but quit 3 weeks prior to admission owing to a dispute at work. He has never had any difficulties with socialization and always had many friends. Family history is significant for a half-brother, mother, and maternal grandfather with ATS. He lived at home with his mother. A trial of verapamil, flecanide, and acetazolamide was started at age 13 but was discontinued at age 18, 3 years prior to admission.

Patient 5. A 28-year-old man, the half-brother of Patient 4, presented with episodic weakness of his arms at age 10 while playing basketball. This was not formally investigated until his entry into the navy at age 18, when he experienced an episode of near total paralysis of both of his upper and lower extremities following a series of anthrax vaccinations. He has never had any cardiac symptoms, and cardiac investigations revealed only mild prolongation of the QTc interval. He was diagnosed with ATS at age 22 when molecular analysis of the *KCNJ2* gene revealed a G300V mutation. Early motor and speech development was normal. He did well in school, with his best subjects being math, history, and science. He occasionally received Cs and Fs in several courses and attributed this to being bored, having problems concentrating on the subject material, or not liking the teacher. He graduated from high school with a 3.2 GPA, joined the navy, and completed an avionics technical training course. He was discharged from the navy on medical leave 4.5 years prior to admission and had been employed as an avionics technician since that time. He never had difficulty with socialization or behavioral problems. He lived in his own home, which he had owned for the past year, with his partner and her four children. He had never been on any medications.

Patient 6. A 45-year-old woman, the mother of Patients 4 and 5, has never had any neuromuscular or cardiac symptoms, other than an irregular pulse. She was diagnosed with ATS at age 35, following the diagnosis of her children, and carries the familial G300V mutation in *KCNJ2*. Early motor and speech development was normal. She disliked school, and average grades achieved were Cs and Ds. She had particular difficulties with math and science. She did not complete high school but did obtain her GED. She has had numerous occupations and is currently working as an auditor of credit card use. She was initially married at age 16 and divorced 2 years later. After obtaining her GED at age 18, she studied as a medical assistant for 1 year. She worked for 1 year as a unit clerk and then for 3 years as a medical assistant. She remarried at age 20 and stayed at home for the 5 years following the birth of her second son. She worked as an insurance coder for a year following her second divorce and then as a secretary for several years until moving to her current position. She was on no medications on admission.

Patient 7. A 14-year-old girl was found to have an irregular pulse on routine physical exam at age 12. Subsequent investigations revealed intermittent bidirectional ventricular tachycardia and premature ventricular contractions. She had had feelings of "heaviness" in her legs since age 8, but only one major episode of periodic paralysis, at age 13, when she experienced almost complete paralysis of her entire left side. She was diagnosed with ATS at age 14, several months prior to admission, and molecular analysis of the *KCNJ2* gene revealed an R218W mutation. Early motor and speech development was normal; however, she had a long-standing history of school difficulties. At the time of admission, she was attending a modified grade 8 program, with a grade 6 math class, and she also had a teacher's aide. The subjects with which she had the most difficulty were math and science; her grades in these subjects were Cs and Ds. She was given a tentative diagnosis of mild learning difficulty but had not yet had a formal educational assessment. She did not have any overt behavioral difficulties, although her mother reported outbursts of inappropriate anger at times. She occasionally got into fights with classmates at school. She had many acquaintances but no close friends by self-report. Family history was negative for ATS. The only medication on admission was flecainide.

Patient 8. A 24-year-old man presented with episodic leg weakness at age 15, while playing soccer. He had never had cardiac symptoms, but cardiac arrhythmias were documented on investigations for weakness. He was formally diagnosed with ATS at age 20 and was found to carry an R218Q mutation in *KCNJ2*. He had mild motor and speech delay, requiring speech therapy during grade 1. He did well throughout elementary and junior high school and graduated high school with a GPA of 3.5. He then started having difficulty in college with his main study subjects (engineering and related courses), and his average grade during freshman and sophomore years was C+. He was formally diagnosed with attention deficit disorder and placed on dextroamphetamine sulfate for 18 months. He reported subsequent marked improvement in concentration, with concomitant improvement in his grades, and he graduated with a bachelor of engineering degree. On admission, he felt he had mild difficulty with concentration and attention, as well as occasional memory lapses, but he did not feel that this interfered with his ability to function in his job as a computer programmer. He had no history of behavioral difficulties. He lived in an apartment with his fiancée. Family history is significant for a father with ATS, who was also diagnosed with attention deficit disorder as an adult. The only medication on admission was acetazolamide.

Table 1 Baseline characteristics of ATS subjects

Subject, age, gender	Mutation	Motor delay	Speech delay	Learning disability	Education (highest level)	Occupation	Age onset periodic paralysis	Age cardiac diagnosis	EEG	Current medications
1, 29 y, F	G146D	Yes	Yes	Yes	Grade 10	Factory worker	8 mo	12 y	Normal	None
2, 8 y 7/12, F	del 314-315	Yes	No	Yes	Grade 2 IEP	N/A	2 y	3 y 8/12	Nonspecific diffuse increase in theta frequency	Atenolol, mexilitine, acetazolamide
3, 9 y 11/12, F	R218W	No	Yes	Yes	Grade 4	N/A	4 y	7 y	Normal	Atenolol, KCl, acetazolamide
4, 21 y, M	G300V	No	Yes	Yes	High school	Unemployed	2 y	13 y	Normal	None
5, 28 y, M	G300V	No	No	No	High school, technical school	Avionics technician	10 y	None	Normal	None
6, 45 y, F	G300V	No	No	Yes	GED	Credit card use auditor	None	21 y	Normal	None
7, 14 y, F	R218W	No	No	Yes	Grade 8 IEP	N/A	8 y	12 y	Normal	Flecainide
8, 24 y, M	R218Q	Yes	Yes	No	BEng	Computer programmer	15 y	20 y	Normal	Acetazolamide
9, 25 y, F	T75R	No	Yes	Yes	3 y of community college	Student	5 y	12 y	Normal	Methazolamide, nadolol, K-Dur
10, 38 y, F	D78Y	No	No	No	MEd	Teacher	4 y	25 y	Normal	Imipramine, pyridostigmine, atenolol, lorazepam

All subjects were Caucasian, had distinctive features typical of ATS, and had no seizures.

ATS = Andersen–Tawil syndrome; IEP = individualized education plan; N/A = not applicable.

Patient 9. A 25-year-old woman presented with episodic weakness at age 5. She was noted to have an irregular pulse as an incidental finding during investigations for the episodic weakness at age 12. She was formally diagnosed with ATS at age 15 and found to carry a T75R mutation in the *KCNJ2* gene. Early motor development was normal; however, she had mild speech delay. She had a longstanding history of school difficulties and recalled having marked problems with clumsiness as well as with learning and memory from a young age. She attended regular classes throughout her primary and secondary education but had global difficulty with academic performance. Her grades in high school were mainly Cs and Ds, and she had particular difficulties with math and sciences. She received extra time to complete school work and for some subjects was placed in a modified program. She underwent a formal educational assessment in 1998, which revealed deficits in several cognitive domains. Testing using the Woodcock–Johnson Psychoeducational Test Battery at age 18 revealed the following: memory for names, age equivalent 5 years; memory for sentences, age equivalent 12 years 3 months; visual matching, age equivalent 12 years 1 month; picture vocabulary, age equivalent 11 years; visual auditory learning, age equivalent 7 years 4 months; broad cognitive ability, age equivalent 10 years 7 months; passage comprehension, age equivalent 13 years; calculation, age equivalent 12 years 11 months; applied problems, age equivalent 11 years 8 months. A teacher assessment carried out at the same time revealed she had difficulty grasping greater than one or two concepts at a time as well as completing tasks requiring planning and complex processing. On admission, she was enrolled as a parttime student at a community college and, other than requiring extra time to complete assignments, was doing well. She never had any overt behavioral issues. She described herself as a "loner" and did not have a wide circle of friends. She spent most of her time socializing with her cousin, as she felt other people become impatient with her very quickly, and preferred the company of younger children to those of her own age. She lived at home with her parents. Family history was negative for ATS. Medications on admission included methazolamide, nadolol, and K-Dur.

Patient 10. A 38-year-old woman presented at birth with cleft palate and severe mandibular hypoplasia, with subsequent respiratory distress requiring admission to the neonatal intensive care nursery for respiratory support. Despite initial difficulties with feeding and growth, early motor milestones were achieved normally and speech development was normal. She required speech therapy from age 6 to 8 as well as multiple surgeries for cleft palate repair, but language function was always normal. She experienced her first episode of periodic paralysis at age 4. An irregular heart rhythm was noted during routine preoperative investigations for surgery at age 14; however, she did not have any other cardiac investigations until age 25, after two episodes of syncope. She had a third episode 1 year prior to admission at age 37 and underwent ICD placement. She was formally diagnosed with ATS at age 34 and found to carry a D78Y mutation in *KCNJ2*. She found it difficult to attend school owing to frequent episodes of periodic paralysis, and in high school her average grades were Cs. She had particular difficulties with mathematics and other subjects that required abstract thought. She graduated from high school and enrolled in an arts program at a local university, where she was able to maintain a B average until her senior year, when she had an episode of depression, and her grades dropped to an average of C. She then obtained a master's degree in education, is currently employed as a special education preschool teacher, and has had held this job for the last 13. She had never had any overt behavioral issues; however, she described herself as being somewhat of a "loner" and shy, especially as a child. She tended to socialize mostly with family and did not have a large circle of friends. She lived with her husband and two children, one of whom had a confirmed diagnosis of ATS. Medications on admission included imipramine, pyridostigmine, atenolol, and lorazepam.

Results. *General features.* Baseline characteristics of the cohort of ATS subjects are summarized in table 1. All 10 subjects had typical distinctive features of ATS,[20] which include hypertelorism, broad forehead, short palpebral fissures, fullness of the nasal bridge with bulbous tip, malar, maxillary, and mandibular hypoplasia, thin upper lip, high arched or cleft palate, mild facial asymmetry, dental anom-

Table 2 IQ and school performance of ATS subjects compared with their unaffected siblings

Subject	ATS IQ	School performance (ATS)	Unaffected sibling IQ	School performance (unaffected sibling)
1	109	Failed kindergarten, grades 2 and 5, completed grade 10 (D average)	108	Completed high school, 2-y teacher training course
2	113	Difficulty with complex tasks, processing information, grade 2 IEP	117	A+ student, grade 6
3	92	Problems with reading, math, science (Fs, Ds, Cs), grade 4	90	As and Bs, grade 2
4	108	Completed high school (Cs, Ds, Fs)	N/A	
5	120	Completed high school (B average, occasional Cs and Fs), avionics technical course	N/A	
6	111	GED (Cs, Ds)	137	A+ student, MSc in biochemistry
7	79	Problems with math, science (Ds, Cs), grade 8 IEP	73	As and Bs, grade 5
8	119	High school GPA 3.5, B.Eng (Cs), diagnosed with ADD, improved with Adderall	96	High school GPA 3.4, college sophomore (B average)
9	94	High school (Cs and Ds), modified community college program	98	BSc in exercise physiology, scholarship student
10	117	High school (Cs), college (Bs and Cs), MEd community college	121	High school A+ student, BA and RN degrees

ATS = Andersen–Tawil syndrome; IEP = individualized education plan.

alies, small hands and feet, brachydactyly, two- to three-toe syndactyly, and clinodactyly of the toes as well as mutations in the coding region of the *KCNJ2* gene. All subjects with the exception of Subject 6 had episodic weakness, and the mean age at onset was 5 years (range 8 months to 15 years). All subjects with the exception of Subject 5 had abnormalities on cardiac monitoring (prolonged QTc, prominent U wave, or ventricular ectopy) (data not shown). There was no significant difference in age between the ATS subjects and their unaffected siblings. The mean age of the ATS subjects was 24 years (SD 11.9), and the mean age of their unaffected siblings was 23 years (SD 13.1) ($p = 0.94$).

EEG findings. No subject had a history of seizures. All subjects, with the exception of Subject 2, had normal routine EEG and EEG with photic stimulation (table 1). A slight increase in theta frequency was found on routine EEG for Subject 2, but this was felt to be nonspecific, and there was no epileptiform activity or lateralizing abnormality. EEG with photic stimulation was normal, as were CT and MRI of the brain carried out prior to admission.

Developmental history. Mild delays achieving gross and fine motor milestones were present in three subjects, but these had resolved by the time they entered school. Five subjects (50% of the cohort) had a history of speech delay in early childhood, which resolved by midchildhood or early adolescence in all cases (table 1).

Educational history and school performance. Seven of the 10 subjects were recognized as being learning disabled or requiring modified educational programs by their respective schools; however, the level of educational support received was extremely variable. There was a striking difference in school performance between ATS subjects and their unaffected siblings, with ATS subjects universally having more difficulty with academic achievement. There was no significant difference in IQ between ATS subjects as a group and their unaffected siblings. The mean IQ for ATS patients was 105.6 (SD 14.9) and mean IQ for control siblings was 105.75 (SD 18.7) ($p = 0.99$) (table 2). In general, subjects with ATS had more difficulties with mathematics and sciences than with language arts, although there were two subjects[5,8] for whom this was not the case. Specific areas of concern reported by teachers or parents included difficulty grasping greater than one or two concepts at a time, completing tasks requiring planning and complex processing, problems with concentration, as well as retention of subject material, solving abstract or inferential type questions, completing assigned work during the allotted time, and processing sequences of events required to complete complex tasks. Six of the seven adult subjects completed high school (one with a GED), four of whom completed 1 or more years of post-secondary or technical education. Five of the seven adults were employed full-time upon enrollment in this study (table 1).

Neurocognitive testing. The results of formal neurocognitive testing are summarized in table 3. A pairwise method of analysis was used to compare affected subjects with their unaffected sibling controls, and results are reported as differences in scores within families between a subject with ATS and the corresponding unaffected sibling.

The average difference in IQ between ATS subjects and their unaffected siblings was −2.25 points ($p = 0.61$). The difference between ATS subjects and their unaffected siblings on testing of visual memory (Wechsler Memory Scale-3 Visual Reproductions) or verbal memory (delayed recall trials of the CVLT-II) did not achieve significance, although the trend was for ATS subjects to perform poorly compared with their unaffected siblings. Subjects with ATS scored an average of 11 points lower than their siblings on the Visual Reproductions 30-minute delay recall test (95% CI −27.5, 5.21; $p = 0.18$); however, the CIs were too wide to provide strong evidence to support this. Similarly, ATS subjects scored 2 points lower than their siblings on the long delay free recall trial of the CVLT-II (95% CI −4.14, 0.14; $p = 0.066$) and made an average of three more intrusive errors than their siblings on delayed free recall trials of the CVLT-II (95% CI −0.29, 6.54; $p = 0.073$). Digit Span Backward and Forward was not significantly different between the two groups, and the score differences between the two groups was less than 1 point. The main measures of executive functioning used were the

Table 3 Results of formal neurocognitive testing

Cognitive domains	Score difference within family (ATS vs unaffected sibling)	*p* Value	95% CI
Memory			
Spatial memory long delay	−11.1	0.18	−27.5, 5.21
Verbal memory long delay	−2	0.066	−4.14, 0.14
Executive functions			
DF set shifting	−1.93	0.052	−3.46, 0.01
DF rule violations	1.9	0.005	0.46, 2.54
Verbal fluency	−4.5	0.27	−12.48, 3.48
Semantic fluency	−1.25	0.46	−4.57, 2.07
CA trails set shifting	−1.5	0.28	−4.23, 1.23
CA trails errors	0.25	0.10	−0.050, 0.55
Working memory			
Digit span forward	−0.63	0.11	−1.39, 0.14
Digit span backward	−0.5	0.48	−1.88, 0.89
Spatial span forward	−0.75	0.63	−3.77, 2.27
Spatial span backward	−0.63	0.29	−1.77, 0.52
IQ	−2.25	0.61	−10.92, 6.42
Vocabulary	1.5	0.81	−10.95, 13.95
Matrix reasoning	−5	0.008	−8.67, −1.33
Achievement			
Numerical operations	−23.4	0.017	−42.53, −4.22
Word reading	−9.13	0.056	−12.46, 3.21

ATS = Andersen–Tawil syndrome; DF = Design Fluency.

Trail Making Test, Design Fluency, and Verbal Fluency subtests of the DKEFS battery. Compared with their siblings, the ATS subjects tended to achieve slightly lower (1.5 points) scaled scores on the Trail Making Test (95% CI −4.23,1.23; $p = 0.28$), as well as make slightly more errors shifting set (95% CI −0.050, 0.55; $p = 0.10$); however, these results did not achieve statistical significance. Tests of Verbal Fluency revealed the ATS subjects generated an average of 4.5 fewer words per minute than their siblings (95% CI −12.48, 3.48; $p = 0.27$) and 1.25 fewer animal names per minute (95% CI −4.57, 2.07; $p = 0.46$); however, the CIs were too wide to support these findings. Tests of Design Fluency revealed ATS subjects obtained scores on average 1.93 points lower than their siblings (95% CI −3.46, 0.01; $p = 0.052$) and made 1.9 more errors (95% CI 0.46, 2.54; $p = 0.005$), which was significant. Subjects with ATS scored an average of 5 points lower than their siblings on tests of matrix reasoning (a measure of abstract reasoning), which was also significant (95% CI −8.67, −1.33; $p = 0.008$). On tests of general mathematical and reading ability, ATS subjects achieved lower scores than their siblings; however, this was less marked for reading ability (−9.13 points; 95% CI −12.46, 3.21; $p = 0.056$) than for mathematical ability where ATS subject scored an average of 23.4 points lower than their siblings (95% CI −42.53, −4.22; $p = 0.017$).

Carbonic anhydrase inhibitor use and neurocognitive function in ATS. The carbonic anhydrase inhibitors as a group are a mainstay of treatment for periodic paralysis; however, they have been implicated in transient episodes of cognitive dysfunction in a randomized controlled double-blinded trial.[21] To measure potential effects of the use of carbonic anhydrase inhibitors on the results of neurocognitive testing for this study, we repeated all analyses, controlling for carbonic anhydrase inhibitor use in the regression model. The resultant adjusted analyses did not change significantly from the unadjusted analyses (data not shown).

Discussion. Mutations in the *KCNJ2* gene, which encodes the inwardly rectifying potassium channel protein Kir 2.1, cause ATS, a recognizable pattern of malformations characterized by periodic paralysis, cardiac arrhythmias, and distinct craniofacial and skeletal features. We present evidence that ATS is also associated with a distinct neurocognitive phenotype, characterized by difficulties completing tasks requiring planning and complex problem-solving skills, problems with attention and concentration, solving abstract problems or answering inferential type questions, completing tasks requiring mathematical skill, and completing tasks within the same time frame as their peers. These tend to manifest as learning difficulties in ATS patients of school age and are not explained by differences in IQ between patients with ATS and their unaffected siblings or peers. The mean IQ of ATS subjects in this cohort was well within the normal range (105.6 [SD 14.9]) and not different from the mean IQ for unaffected siblings (105.75 [SD 18.7]; $p = 0.99$). This finding was confirmed on pairwise multivariate analysis where the average difference in IQ within families between ATS subjects and their unaffected siblings was −2.25 points ($p = 0.61$). This suggests that global measures of overall ability and achievement are not sufficient to describe the ATS cognitive phenotype.

There was an overall trend toward poorer performance for ATS subjects compared with their siblings on tests of verbal and visual memory as well as two tests of executive function, the Trail Making Test and Verbal Fluency. The 95% CIs surrounding these estimates were too wide to provide strong evidence to support these trends, however. Tests of Design Fluency and Matrix Reasoning, nonverbal measures of executive function and abstract reasoning, revealed significant differences in achievement between ATS subjects and their unaffected siblings. The ATS subjects consistently obtained lower scores when required to alternate between two different stimuli during one portion of the Design Fluency test, and they also committed more rule violations while performing this task. Similarly, the ATS subjects consistently achieved lower scores on the Matrix Reasoning test than their unaffected siblings. Tests of general ability in mathematics and reading revealed significantly poorer performance in mathematical ability for ATS subjects compared with their unaffected siblings. We conclude that the ATS neurocognitive phenotype is characterized by relative strength in verbal compared with nonverbal skills, deficits in executive function and abstract reasoning, and IQ, which is within the normal range for the family. This is consistent with areas of difficulty identified on review of school performance as well as

concerns raised by subjects, teachers, and parents. Despite school difficulties, mild behavioral issues, and a tendency to being "loners" and introverted, subjects with ATS in this cohort on average did quite well as adults. Six of the seven adult subjects completed high school (one with a GED), four of whom completed 1 or more years of postsecondary or technical education. Five of the seven adults were employed full-time upon enrollment in this study, and the majority had held the same job for several years.

We also examined the potential confounding effects of carbonic anhydrase inhibitor use on neurocognitive function in ATS. Carbonic anhydrase inhibitors are frequently used for treatment of the periodic paralyses; however, concern regarding possible adverse effects on cognitive function was raised during a randomized controlled double-blinded trial.[21] Specific cognitive deficits reported as adverse effects included confusion, disorientation, slowed mentation, difficulty with memory, and depression; however, these effects were felt to be transient, and usually resolved upon discontinuation of the medication.[21] Repeat analysis of the results of neurocognitive testing while adjusting for carbonic anhydrase inhibitor use did not reveal any significant difference from the unadjusted analysis. This is consistent with the fact that 6 of the 10 subjects were not taking carbonic anhydrase inhibitors on admission or during the time of neurocognitive testing. Of these six subjects, three had attempted a trial of acetazolamide in the remote past; Subject 4 had discontinued acetazolamide use 3 years prior to admission and neurocognitive testing, and Subjects 1 (for 15 years) and 10 (for 20 years) had not used acetazolamide prior to admission. Subjects 5,6, and 7 had never used carbonic anhydrase inhibitors at any time in their lives. These data suggest that mutations in the *KCNJ2* gene cause a neurocognitive phenotype that is independent of carbonic anhydrase inhibitor use in patients with ATS.

The inwardly rectifying potassium channel family is important for a number of crucial functions. These include maintenance of cellular resting conductance and potassium homeostasis, cardiac pacemaker activity, synaptic inhibition, and control of neuronal firing rates.[22] The importance of potassium and other ion channels to the CNS is being increasingly recognized, although the main consequence of ion channel dysfunction appears to be seizure activity,[10-13] which was universally absent in this cohort of subjects with ATS. The reason for complete absence of clinical or subclinical seizures in ATS patients remains unknown. Potassium channel proteins other than Kir 2.1 have been implicated in cognitive function and include those which form SK3 channels and M channels.[23,24] Increased expression of small-conductance calcium-activated potassium channels (SK3 channels) have been implicated in reduced long-term potentiation and impaired performance of hippocampus-dependent learning tasks in mice.[23] Mutations in *KCNQ2* (which encodes a voltage-gated potassium channel protein) lead to reduction in M channel current and, in addition to benign familial neonatal convulsions, cause behavioral hyperactivity and deficits in hippocampus-dependent spatial memory in mice.[24] Whereas deficits in verbal and visual memory were not a prominent feature in this cohort of ATS subjects, it is possible that the study did not have adequate power to detect these differences, and future studies with larger numbers of subjects may be required to investigate this further.

Strengths of this study include the study design and method of statistical analysis, which enabled pairwise comparison of subjects with ATS and their unaffected siblings. This allowed for internal control of factors that would normally confound the analyses, such as parental education, socioeconomic status, geographic location and access to services, nutrition, and genetic factors other than *KCNJ2* mutation status.

Acknowledgment

The authors thank the patients and their families for participating in this research; Paul Keats, Magnus Dias da Silva, MD, PhD, John Neuhaus, PhD, and Michael Kohn, MD, for technical assistance; and Rabi Tawil, MD, for helpful advice and insight.

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