

1 Abstract

2 Andersen Tawil Syndrome (ATS) is a neurological channelopathy caused by mutations in the *KCNJ2* gene
3 that encodes the ubiquitously expressed Kir2.1 potassium channel. The syndrome is characterised by
4 episodic weakness, cardiac arrhythmias and dysmorphic features. However, the full extent of the multi-
5 system phenotype is not well described. In-depth, multi-system phenotyping is required to inform
6 diagnosis, and guide management.

7 We report our findings following deep multimodal phenotyping across all systems in a large case series
8 of 69 total patients, with comprehensive data for 52. As a national referral centre, we assessed point
9 prevalence and showed it is higher than previously reported, at 0.105 per 100 000 population in
10 England.

11 While the classical phenotype of episodic weakness is recognised, we found that a quarter of our cohort
12 have fixed myopathy and 13.5% required a wheelchair or gait aid. We identified frequent fatty
13 infiltration on MRI and tubular aggregates on muscle biopsy emphasising the active myopathic process
14 underpinning the potential for severe neuromuscular disability. Long exercise testing (LET) was not
15 reliable in predicting neuromuscular symptoms. A normal LET was seen in five patients of whom four
16 had episodic weakness. 67% of patients treated with acetazolamide reported a good neuromuscular
17 response.

18 13% of the cohort required cardiac defibrillator or pacemaker insertion. An additional 23% reported
19 syncope. Baseline electrocardiograms were not helpful in stratifying cardiac risk, but holter monitoring
20 was. A subset of patients had no cardiac symptoms, but had abnormal holter monitor recordings which
21 prompted medication treatment. We describe the utility of loop recorders to guide management in two
22 such asymptomatic patients. Micrognathia was the most commonly reported skeletal feature, however
23 8% of patients did not have dysmorphic features and one third of patients had only mild dysmorphic
24 features.

25 We describe novel phenotypic features including abnormal echocardiogram in nine patients, prominent
26 pain, fatigue and fasciculations. Five patients exhibited executive dysfunction and slowed processing
27 which may be linked to central expression of *KCNJ2*. We report eight new *KCNJ2* variants with *in vitro*
28 functional data.

1 Our series illustrates that ATS is not benign. We report marked neuromuscular morbidity and cardiac
2 risk with multi-system involvement. Our key recommendations include proactive genetic screening of all
3 family members of a proband. This is required, given the risk of cardiac arrhythmias among
4 asymptomatic individuals, and a significant subset of ATS patients have no (or few) dysmorphic features
5 or negative LET. We discuss recommendations for increased cardiac surveillance and neuropsychometry
6 testing.

7 **Keywords:** Andersen Tawil syndrome; channelopathy; muscle; cardiac risk; periodic paralysis

8 **Abbreviations:** ATS = Andersen-Tawil Syndrome; CK = creatinine kinase; HSS = highly specialised
9 services; ICD = implantable cardiac device; PPM = pacemaker; LET = Long exercise test; MRC = Medical
10 Research Council; SD = standard deviation; TTE = transthoracic echocardiogram; VT = ventricular
11 tachycardia

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ACCEPTED MANUSCRIPT

1 Introduction

2 Andersen-Tawil Syndrome (ATS) is a rare neuromuscular channelopathy, characterised by a triad of
3 periodic paralysis, cardiac conduction defects and dysmorphic features.¹ The reported point prevalence
4 in England is 0.08 per 100 000.² ATS is caused by mutations in the *KCNJ2* gene, which encodes Kir2.1
5 potassium channels that conduct an inward rectifier potassium current integral to maintaining resting
6 membrane potential. ATS-associated *KCNJ2* mutations cause loss of Kir2.1 channel function.³ The Kir2.1
7 channel is widely expressed, accounting for the multisystem presentation.⁴

8 The morbidity of ATS can be significant. Episodic muscle paralysis makes maintaining employment and
9 education challenging. Cardiac arrhythmias may require medication management or implantable cardiac
10 defibrillator (ICD) insertion and there is a risk of sudden cardiac death.⁵ In addition, ATS patients may
11 show neurocognitive deficits.⁶

12 ATS can present with just one or with all three of the main features, and currently no genotype-
13 phenotype correlations exist. Distinct cardiac electrophysiology findings supported the hypothesis of
14 ATS as distinct from other inherited long QT syndromes.⁷ Further studies illustrated the diagnostic utility
15 of characteristic U waves on ECG.⁸ Recently, the rate of life-threatening arrhythmic events has been
16 defined in one series as 1.24 per 100 person-years.⁹ A small cohort of 11 probands has provided some
17 insights into the dysmorphic features including the presence of micrognathia, low set ears, short stature,
18 clinodactyly and syndactyly but little literature exists in deep phenotyping across all three systems in a
19 single cohort, with severity gradation and genotype correlation.¹⁰

20 We report the multi-system features of a cohort of patients with Andersen-Tawil Syndrome from the
21 United Kingdom (UK) and analyse genotype-phenotype correlations including eight new gene variants
22 with *in vitro* functional data for five. This is the largest reported case series with deep phenotyping
23 across multiple systems, including novel nervous system presentations. Our data improve phenotypic
24 recognition and help to enhance diagnostic rates and the instigation of early appropriate medical
25 therapy to prevent morbidity and potentially mortality.

26 Methods

27 Patients were referred for assessment at the highly specialised service (HSS) for muscle channelopathies
28 funded by NHSE at the National Hospital for Neurology and Neurosurgery (NHNN). Patients were

1 enrolled into a cohort study (Investigation of human neurological ion channel or episodic neurological
2 disorders, REC 07/Q0512/2) which has Ethics approval from the Joint National Hospital for Neurology
3 and Institute of Neurology Research ethics Committee. Written informed consent was obtained for
4 collection of retrospective and prospective clinical data. Prospective data was collected at review by a
5 Neurologist, Geneticist or Cardiologist with expertise in channelopathies. All patients had a
6 neuromuscular examination, creatinine kinase level and electrocardiogram (ECG).

7 Other tests were directed by clinical features. These additional test results were collected
8 retrospectively. They included neurophysiology, holter monitoring, transthoracic echocardiogram,
9 neuropsychology and MRI assessment. Neurophysiology was performed by an experienced
10 neurophysiologist including routine sensory and motor potentials of median, ulnar and tibial nerves as
11 well as EMG of three muscles and a long exercise test (LET). The LET was deemed positive if the
12 decrement in CMAP from the post-exercise peak during the LET was greater than 40%.

13 Neuropsychology testing was performed by a specialist Neuropsychologist. The tests performed were
14 the Wechsler Adult Intelligence Scale Verbal IQ (WAIS-Verbal IQ), Performance IQ (WAIS-PIQ), Recognition
15 Memory Tests (RMT) for words and faces, Tests of naming, Visuo-perceptual testing, Stroop colour and
16 word tests, Fluency testing, Naming Animals, Trail Making test part B and Symbol Digit Modalities Test
17 (SDMT).

18 Patients underwent 3T MRI (Siemens TIM Trio, Erlangen, Germany) examination of the lower limb
19 muscles. A routine imaging protocol was utilised, comprised of axial T1-weighted and axial short-tau-
20 inversion-recovery (STIR) sequences of both thighs and both calves with 5 mm slice thickness and 1 mm
21 slice gap. The images had been reviewed and reported by a radiologist with expertise in neuromuscular
22 MRI.

23 De-identified patient data was also collected from collaborating institutions – St George’s University of
24 London, London; Queen Elizabeth University hospital, Scotland; John Walton Muscular Dystrophy
25 Research Centre, Newcastle.

26 Sanger sequencing of the coding region of *KCNJ2* was carried out as previously described as part of the
27 HSS clinical service.¹¹ Patients with a confirmed genetic diagnosis of ATS were included in the study.
28 Patients with a suggestive clinical phenotype, but negative for *KCNJ2* mutations were excluded.

29 The phenotypes were graded by severity. A mild neuromuscular phenotype is defined as infrequent
30 attacks with a maximum frequency of one attack three to six monthly, no fixed weakness and

1 independent ambulation. Moderate neuromuscular phenotype is defined as monthly or weekly attacks
2 with, at most, intermittent use of a single point stick. A severe neuromuscular phenotype is defined as
3 having fixed weakness or using gait aids or having daily attacks. A mild cardiac phenotype is defined as
4 infrequent (<once per month) arrhythmias not requiring medical treatment; a moderate phenotype is
5 defined as conduction abnormality requiring medical treatment or experiencing syncope; a severe
6 cardiac phenotype is defined as conduction defect requiring an ICD or pacemaker (PPM). A mild
7 dysmorphic phenotype is defined as having fewer than four dysmorphic features. A moderate
8 dysmorphic phenotype is defined as having four or more dysmorphic features.

9 **Xenopus laevis oocytes and molecular biology**

10 Oocytes were removed from *Xenopus laevis* toads in accordance with the Animals (Scientific
11 Procedures) Act 1986. The mutations were introduced into WT *KCNJ2* cDNA (NM_000891.3) by
12 Quikchange site directed mutagenesis (Qiagen). Successful mutagenesis was confirmed for each clone
13 by sequencing the entire insert. The mRNA was transcribed using mMessage Machine T7 kit (Ambion).
14 The oocytes were injected with 2.5 ng WT or mutant mRNA. The oocytes were incubated in Modified
15 Barth's solution (in mM): NaCl 88, KCl 1, MgSO₄ 1.68, HEPES 10, Ca(NO₃)₂ 0.47, NaHCO₃ 2.4, CaCl₂ 0.41,
16 supplemented with penicillin, streptomycin and amikacin for 24-72 hrs at 15-18°C before
17 electrophysiological recordings.

18 **Electrophysiology**

19 Two-electrode voltage clamp experiments were performed using GeneClamp 500B, DigiData 1200 or
20 1550 Interface, and Clampex software (all Axon Instruments) at room temperature in 10K extracellular
21 media (in mM): potassium methanesulfonate 10, sodium methanesulfonate 110, HEPES 10, CaSO₄ 1.8
22 (pH 7.4). Recording electrodes were filled with 3 M KCl and had a tip resistance <1 MΩ. Data were
23 filtered at 1 kHz and sampled at 5 kHz. Holding voltage was 0 mV, Voltage protocol consists of 250 ms
24 steps to test voltages ranging from -190 mV to +100 mV in 10 mV increments. Currents were measured
25 at the beginning of the test pulse. Oocyte data was analysed using Clampfit (Molecular devices), Origin
26 (OriginLab) and Excel software. Leak current was estimated at voltage range 10-30 mV and subtracted
27 from raw current data. Statistical significance was assessed using Kruskal-Wallis ANOVA.

28

1 **Statistical Analysis**

2 For baseline data, mean and standard deviations (SD) were used for normally distributed data and
3 median and range for data that were not normally distributed. Categorical variables were expressed as
4 counts and percentages of the total participants for which comprehensive clinical data was available (52
5 participants). Continuous variables were compared by using the Wilcoxon rank sum test. Proportions for
6 categorical variables were compared using the χ^2 test. All statistical analyses were performed using IBM
7 SPSS Statistics version 22 and Excel version 16.41. The significance threshold was set at a 2-sided P value
8 less than 0.05.

9 **Data Availability**

10 The data that support the findings of this study are available from the corresponding author, upon
11 reasonable request.

12 **Results**

13 **Patient cohort:** A total of 69 patients were identified with a confirmed genetic diagnosis of ATS
14 and mutations in *KCNJ2*. Comprehensive clinical information across all three key domains including
15 cardiac, neuromuscular, and dysmorphic features was available and is described for 52 patients.

16 56% of patients were female. The median age of the cohort was 42 (range 12 – 80). Two patients are
17 deceased.

18 **Development and symptom onset:** No complications in utero were reported. One
19 patient was hypotonic at birth but this had improved at review at age six weeks. Three (5.8%) patients
20 had delayed motor development, including age of walking (18- 24 months) and one child was never able
21 to run.

22 The majority of patients had symptom onset within the first two decades of life. 42.3% had reported
23 symptoms before the age of ten, 23.1% between age 10 and 20, and 9.6% after age 20. The remaining
24 patients could not recall at what age they first had symptoms.

25 In the five patients who presented after the second decade, the oldest presentation was in their 50s
26 with mild muscle symptoms. Diagnosis in this case occurred after a relative was diagnosed with ATS. The

1 five patients with later onset had mild or moderate neuromuscular symptoms, with no fixed weakness.
2 Three of the five patients had mild (less than four) dysmorphic features and one had no distinctive
3 features.

4 The majority of patients presented with muscle symptoms – falls, weakness or paralysis. Five (9.6%)
5 patients presented initially with cardiac symptoms including one patient who presented at age 33 with a
6 cardiac arrest. These patients had a more severe cardiac phenotype over their lifetime. 40% (2 /5
7 patients) required a cardiac device (ICD or PPM), versus 8.7% (4/47 patients) in whom first symptoms
8 were muscle related (Diff 31.3%, CI 11.7-50.9%).

9 All five had abnormal 24-72 hour holter monitor recordings, however, baseline ECGs did not
10 differentiate between those that first presented with cardiac or skeletal muscle symptoms. The ECGs of
11 the five patients that presented first with cardiac symptoms did not demonstrate QU or QT prolongation
12 and had an average corrected QT (QTc) interval of 417 milliseconds. Two of five baseline ECGs had U
13 waves.

14 **Neuromuscular phenotype:**

15 All patients underwent neuromuscular assessment. As a result, MRI investigations were triggered for 10
16 patients. In addition, at the diagnostic stage 23 patients underwent neurophysiological assessment and
17 5 patients had biopsies taken.

18 40 (77%) of patients in our cohort described episodic muscle weakness. Proximal lower limb weakness
19 was the most common attack pattern, followed by more generalised weakness including lower limbs,
20 axial muscles and proximal upper limb muscles. Bulbar and facial muscles were never reported to be
21 affected and neither was respiratory function. Weakness was typically severe enough to affect their
22 ability to perform activities of daily living but very few reported symptoms of complete paralysis. Most
23 patients had monthly attacks, with an equal spread of patients having attacks at either infrequent or
24 very frequent extremes (Figure 1). The majority of patients had attacks of weakness lasting days.
25 However, 9.6% of patients had attacks lasting weeks.

26 25% (13) patients had severe neuromuscular weakness defined by fixed weakness. The ages ranged
27 from 18 to 69. Four patients required a wheelchair for ambulation and a further three required gait aids.
28 The pattern of fixed weakness in these patients was predominantly proximal limb weakness, with lower

1 limbs affected more than upper limbs. Muscles of hip flexion were the most severely affected - graded
2 as low as Medical Research Council (MRC) score 2 in those with the most severe weakness.

3 Additional proximal upper limb fixed weakness, particularly of shoulder abduction, was noted in
4 four/thirteen patients. Upper limb weakness in isolation was not seen. The patients with upper limb
5 weakness had typical attacks with legs affected more than arms. One patient was noted to have isolated
6 bilateral ankle dorsiflexion weakness with no other co-morbidities or explanation for this distal
7 weakness. Of the patients with severe weakness, three (23%) had attacks lasting weeks compared to
8 just two (5.1%) patients in the non-severe group.

9 The majority of patients reported more than one trigger for attacks of paralysis. The most common
10 triggers were exercise and stress (Figure 1). Alcohol was reported as a more specific trigger in three
11 patients that also reported worsening with carbohydrate rich meals. Two patients had attacks
12 temporally associated with the onset of menstruation. Two patients reported attacks being triggered by
13 superimposed infections, these two patients also reported heat as a trigger. Cold was a more common
14 trigger than heat. Only two patients had no identifiable triggers.

15 **Creatinine Kinase (CK)**

16 The CK levels ranged from 59 IU/L to 1379 IU/L. In the majority of patients CK was elevated one to two
17 times the upper limit of normal. Only two patients had CK levels above 1000 IU/L. Both of these patients
18 had fixed weakness and limited ambulation, one required a wheelchair.

19 **Neurophysiology**

20 23 patients had neurophysiological assessment including a long exercise test (LET) used in the diagnosis
21 of periodic paralysis. The remaining patients had a diagnosis made after clinical assessment and genetic
22 analysis. The average decrement in CMAP from the post-exercise peak during the LET was 50% (15SD).
23 Five patients (22%) had a normal LET with no significant decrement, but only one of them reported no
24 attacks of muscle weakness. Those with the highest noted decrement, reaching 72% decrement, did not
25 correspond to those with more severe attack duration or frequency or development of fixed weakness.
26 Although electromyography (EMG) was not performed routinely on all patients, myopathic features of
27 the proximal lower limb muscles was demonstrated in four patients corresponding to a degree of fixed
28 weakness on clinical examination.

1 **Muscle MRI**

2 Ten patients had MRI imaging performed of the lower limb muscles. Three of these MRI scans (at ages
3 33, 47 and 59) were normal and two of these patients did not have any fixed weakness clinically. The
4 third patient had mild (MRC score 65 out of 70) fixed proximal weakness with a normal MRI scan.

5 The seven abnormal MRI scans (average age 44.6, SD10) demonstrated predominant posterior thigh and
6 posterior calf fatty infiltration (Figure 2). The muscles with the most severe fat accumulation were
7 biceps femoris followed by semi-membranosus in the thighs, and gastrocnemius medialis followed by
8 soleus in the calf. Minimal Short-T1 Inversion Recovery (STIR) signal change was noted. When imaged,
9 pelvic muscles also appeared affected by fatty infiltration.

10 **Muscle Biopsy**

11 Five patients underwent clinical muscle biopsies in an external centre prior to diagnosis. Tubular
12 aggregates were seen in two biopsies (Figure 2). Both of these patients had a degree of fixed weakness
13 at the time of biopsy. One of the patients with tubular aggregates had marked fatty replacement in the
14 biopsied muscle on MRI imaging performed nine years later. Small vacuoles with occasional atrophic and
15 angulated fibres were seen in three biopsies with mild or no fixed weakness in these patients.

16 **Symptomatic Treatment for Weakness/Paralysis**

17 34 of 40 patients with episodic weakness or paralysis accepted treatment. Assessment of treatment
18 response was based on patient self-reporting. Acetazolamide was the medication used most often. 30
19 were treated with acetazolamide but ten patients did not have a sufficient clinical response. The
20 average treatment dose was 250mg twice daily. Those that needed a higher dose of acetazolamide
21 (500mg bd) had minimal response to acetazolamide overall and required a second agent. Two patients
22 were changed to dichlorphenamide, three to amiloride, two to spironolactone, one to potassium
23 supplementation and one to daranide. These patients reported response to the second agent.

24 Two patients were commenced initially on treatment with spironolactone and two on amiloride, with
25 good effect in one patient for both drugs. These patients had co-morbidities (e.g. renal stones) that
26 precluded acetazolamide use. One had a pre-treatment screening ultrasound which detected a 6mm
27 right kidney stone and was not treated with acetazolamide.

1 Acetazolamide was generally very well tolerated. One patient developed renal calculi while taking
2 acetazolamide and had a dose reduction to 150mg mane and 125mg nocte as well as lithotripsy. A
3 further patient developed hypokalaemia on acetazolamide and was changed to spironolactone. One
4 patient reported reflux.

5 **Cardiac Phenotype:**

6 39 (75%) of the total cohort reported cardiac symptoms. The most prevalent symptom was palpitations,
7 reported by 46% (Figure 3). 23% of patients reported syncope and a further 15% reported non-specific
8 dizziness.

9 Holter results were attained for 47 patients. Routine 72-hour holter monitoring was abnormal in >90%
10 of cases. Several holter recordings demonstrated more than one arrhythmia. 46% of recordings
11 demonstrated ventricular ectopics (Figure 3) that were polymorphic in character. 25% of recordings
12 showed ventricular bigeminy or trigeminy. 5.77% of recordings had non-sustained ventricular
13 tachycardia (VT) and two recordings demonstrated sustained VT. Two patients reported no cardiac
14 symptoms but did have abnormal holter monitoring in the form of ventricular ectopics, one of these
15 patients had ventricular ectopics for 37% of the duration of the recording.

16 Nine (35%; average age 54.8 SD14) patients had abnormal transthoracic echocardiograms (TTE) out of
17 26 patients who had TTEs. One patient had impaired diastolic dysfunction. The other eight had mild to
18 moderately impaired systolic function due to left ventricular dysfunction; and global hypokinesia was
19 seen in one. No other cause for cardiac dysfunction was identified following Cardiology review and
20 investigation.

21 **Severe cardiac phenotype**

22 Seven (13%) patients had a severe cardiac phenotype requiring device insertion (Table 1). Six had ICD
23 insertion, one of whom had a PPM inserted initially but subsequently upgraded to an ICD, and another
24 had left cervical sympathectomy and then went on to have ICD. One patient required a PPM only for
25 complete heart block, and one additional patient unfortunately died before ICD insertion. Six of seven
26 were female. Two of these patients presented with cardiac features: one suffered a cardiac arrest at age
27 33 and one patient presented with chest pain and ventricular arrhythmias. Admissions prompted
28 genetic testing and diagnosis. Another patient had both neurological and cardiological features at

1 presentation. Four patients with a severe cardiac phenotype presented initially with muscle symptoms
2 (weakness or paralysis) in the first or second decade of life.

3 Baseline ECGs were normal in two of the patients with severe cardiac phenotypes, while holter
4 recordings were abnormal in all patients. One patient had isolated ventricular ectopics only but they
5 were multifocal and polymorphic in character. Three had impaired left ventricular dysfunction and one
6 patient (previously reported) had isolated complete heart block with no other cause identified.¹²

7 Three patients had syncopal episodes and a further two had intermittent dizziness. One patient had loss
8 of consciousness due to VT, resulting in a head strike and consequent intracerebral haemorrhage
9 requiring surgical drainage.

10 One patient had no neurological features at all, presenting with a pure cardiac phenotype. One patient
11 had no dysmorphic features and one patient had only isolated clinodactyly.

12 **Cardiac Treatment**

13 21 patients were on medical treatment for cardiac features. Beta-blockers, bisoprolol in particular, was
14 the most frequently used. Flecainide was used in four patients with a good response and no
15 exacerbation of muscle symptoms.

16 In two patients, loop recorders were helpful in directing treatment. One patient had no cardiac
17 symptoms and a 72-hour holter recording demonstrated only occasional ventricular ectopics. However,
18 sustained tachycardia was noted while having a general anaesthetic for a radial and ulnar fracture at age
19 14. This prompted insertion of the loop recorder which subsequently identified episodes of non-
20 sustained bidirectional ventricular tachycardia, which then prompted treatment. Beta-blockers were
21 trialled initially with no reduction of the arrhythmias seen on loop recorder. This was then changed to
22 flecainide which achieved effective arrhythmia control. In another patient who continued to be
23 symptomatic with palpitations after the initiation of a B-blocker, a loop recorder device confirmed that
24 beta-blockers were ineffective in controlling arrhythmias. A change to flecainide reduced arrhythmias
25 and the frequency of palpitations.

26 **Skeletal Features**

27 32 (62%) patients had definitive dysmorphic features. Micrognathia (38%), clinodactyly (31%) and low set
28 ears (27%) were the most commonly observed (Figure 4). Four (8%) patients had scoliosis. Two patients

1 had cleft palates that were surgically corrected in early childhood. Four (8%) patients had no discernible
2 dysmorphic features. A further 16 (31%) patients had mild dysmorphic features (less than four features
3 in total).

4 Short stature was reported in 13.4%. Height measurements were taken on 17 patients (6 males, 11
5 females). The average height for males was 171.4cm (± 9.02 SD, average height of European male adults
6 is 174cm)¹³. Four patients were taller than the average height for age with heights from 177.8cm to
7 180.3cm. The average height for females was 155.9cm (± 8.5 SD, the average height of European female
8 adults is 161cm). Only one female was taller than the average at 170.1cm. Overall, females appear to be
9 shorter for age, however in both males and females, there are outliers that are tall for age.

10 Nine patients (four males, five females) had hand and foot length measurements taken. Average hand
11 length for females was 17.8cm (± 1.5 SD) which is consistent with a population average (17.3cm)¹⁴.
12 Average hand length for males was 15.92cm (± 0.95 SD) which is shorter than the average (19.3cm).
13 Average foot length for females was 20.6cm (± 1.2 SD) which is smaller than the average UK female shoe
14 size of 6 (24cm). Average foot length for males was 25.6cm (± 1.4 SD) which is comparable to the average
15 UK male size of 27cm. Overall, females tend to have smaller feet while males tend to have smaller
16 hands.

17 Nine patients (four males, five females) had head circumference measured. This was normal for the
18 majority, but two male patients had head circumference below the 25th centile for height¹⁵ and one
19 female patient had head circumference below the 10th centile for height.

20 No definitive correlations were seen between skeletal features and cardiac or neuromuscular
21 phenotypes.

22 **Other Features**

23 **Cognitive Features**

24 Nine patients (17%) reported difficulties with memory and executive function. Four of these patients
25 reported learning difficulties in early education and one patient attended a school with additional
26 learning support. Five of these patients underwent formal neuropsychology assessment, (Table 2) and
27 deficits in executive function were identified in all of them.

1 Scores of intelligence were determined using the Wechsler Adult Intelligence Scale Verbal IQ (WAIS-VIQ)
2 and Performance IQ (WAIS-PIQ). In both scores, there was a mean discrepancy between expected and
3 actual scores - 10.4 for WAIS-VIQ and 10.6 for WAIS-PIQ, suggesting mild-moderate impairment in
4 verbal comprehension, working memory, perceptual organisation and processing speed. The
5 Recognition Memory Test (RMT) was performed well for words but poorly performed for face
6 recognition with three patients performing below the 5th centile. Further tests of executive function,
7 including language tests, were also performed poorly. The Stroop colour and word test, for example,
8 revealed an average performance in the 16th centile. Visuo-perceptual testing was normal.

9 All patients with executive dysfunction had onset of symptoms early in life (<10 years of age), one
10 presenting with hypotonia at birth and another with delayed motor milestones. All nine patients had
11 severe neurological involvement and dysmorphic features.

12 **Newly Described Clinical Features**

13 Among skeletal muscle, cardiac and dysmorphic features we identified otherwise unexplained cardiac
14 dysfunction with abnormal TTE, complete heart block and executive dysfunction as features that to our
15 knowledge have not been described previously for ATS patients. Additional features seen in over 15% of
16 our cohort (8 or more patients) include fasciculations, pain, fatigue and snoring.

17 16 patients (31%) described significant pain. The median age of those reporting pain was 47 (s.d. 13)
18 which is significantly higher than the reported prevalence of chronic pain for this age group in UK -
19 11.2% ($p=0.8 \times 10^{-7}$)¹⁶. Nine patients undertook more detailed pain related assessment using the Brief Pain
20 Inventory Scale.¹⁷ Pain predominantly affected proximal arms, legs and lower back. The degree of pain
21 varied significantly over 24 hours in all patients, from no pain to a score of 7 out of 10 (10 = pain as bad
22 as you can imagine) in one patient. The average pain score was 4.64. Two patients required codeine to
23 manage the pain. The patients reported that pain affected all aspects of life including mood, walking
24 ability, work, relations with other people, sleep and enjoyment of life.

25 10 patients (19%) reported fatigue, significantly higher than the UK general population (49 per 100
26 000)¹⁸. The Modified Fatigue Severity Scale was completed by these patients. Overall, they experienced
27 fatigue 'a lot of the time' with an average score of 5.18 on a 7-point scale (7 = fatigue at all times). For
28 nine patients, fatigue was one of their top three most disabling symptoms. Fatigue significantly
29 interfered with work, family or social life (average score 5.09 out of 7).

1 Nine patients (17%) described fasciculations. Fasciculations were confirmed directly on observation in
2 clinic or from a patient recorded video by a neurologist. The majority complained of visible muscle
3 “twitching” in the arms and legs. One patient additionally described trunk and face muscle
4 fasciculations. The fasciculations were not limited to patients with a severe neurological phenotype and
5 no clear correlation with attacks, triggers or LET testing was seen.

6 Eight (15%) patients or their bed partners reported marked snoring overnight, not significantly higher
7 than the UK general population¹⁹. Three of these patients additionally reported morning headaches and
8 four patients reported excessive daytime sleepiness. Sleep studies did not demonstrate nocturnal
9 hypoventilation. Six of the eight patients who snored, had micrognathia.

10 **Anaesthetic Reactions**

11 The majority of patients did not report any adverse reactions to general anaesthetics. Two patients
12 reported an unspecified “bad” reaction but with full recovery and no specific treatment. Two patients
13 reported an exacerbation of episodic muscle weakness with stress and cold related to the surgical
14 procedure.

15 **Pregnancy and Labour**

16 Detailed evaluation of five pregnancies in the patient cohort was attained. No intrauterine akinesia or
17 prenatal abnormalities were reported. Two pregnancies were delivered by elective caesarean section
18 and another required manual delivery with suction. Three patients had worsening of symptoms during
19 pregnancy and two patients reported improved muscle symptoms. One patient also reported worsening
20 of muscle symptoms post-partum. One patient experienced falls during the pregnancy.

21 **Genetic Data & Genotype-Phenotype Correlation**

22 ATS is caused by mutations in the *KCNJ2* gene. Pathogenic mutations are spread throughout the channel
23 structure. The Kir2.1 channel consists of four subunits. The channel pore consists of the selectivity filter,
24 central cavity and cytoplasmic gate.

25 The most common mutation seen in our cohort was *KCNJ2* Arg218Trp seen in 13.5% of patients,
26 followed by Arg67Trp and Cys122Ser (9.6% of patients each). Only patients with Gly144Asp or
27 Leu193Pro mutations had both severe Neuromuscular and Cardiac phenotypes. However, there is clear
28 variability between patients carrying the same mutation in the severity of phenotype across the

1 different systems. For example, some carriers of Phe99Ser, Arg218Trp, and Arg312Cys variants showed
2 mild and others, severe neurological symptoms. The reason for this variability is unknown but is often
3 seen for other skeletal muscle or cardiac channelopathies.

4 Eight novel mutations were identified in our cohort (Phe99Ser, His110Leu, Cys122Ser, Val126Gly,
5 Ala157Asp, Lys188del, Arg260His and Ala306Val) mapped on the Kir2.2 structure as demonstrated in
6 Figure 5.²⁰ Upon expression in *Xenopus* oocytes Kir2.1 channels carrying Phe99Ser, His110Leu,
7 Val126Gly, Ala157Asp, or Arg260His variants displayed limited, if any currents (Figure 6); confirming
8 pathogenicity of these variants.

9

10 Discussion

11 We demonstrate that patients with ATS have significant neuromuscular morbidity as well as increased
12 risk of severe cardiac events. For this reason, early and accurate diagnosis is important. Mild or absent
13 dysmorphic features as well as clinical heterogeneity may pose challenges to early clinical diagnosis.

14 We show a higher prevalence of ATS than in previous reports with a point prevalence of 0.105 per 100
15 000 compared to 0.08 per 100 000.² The increased prevalence likely represents an increased diagnostic
16 rate achieved with the advent of next generation sequencing as well as a more pro-active
17 recommendation to screen family members in our clinical practice. This recommendation was driven by
18 a greater understanding of the cardiac risk and knowledge that clinically significant arrhythmia requiring
19 medical intervention can occur in the absence of clinical symptoms.

20 The majority of patients reported the onset of symptoms prior to age 20. However, in our UK national
21 channelopathy service, the vast majority of patients are not diagnosed until adulthood. The lack of, or
22 mild spectrum of dysmorphic features in ATS is likely to be a significant contributor to the
23 underdiagnosis or delayed diagnosis of ATS. Improved diagnosis will assist in more accurate prevalence
24 estimates.

25 Importantly, our data reveals that there is significant, previously under recognised, morbidity. The
26 combination of a significant proportion of patients with fixed myopathy, the use of walking aids,
27 elevated CK, abnormal MRI with fat accumulation and muscle biopsy changes indicates that the
28 neuromuscular phenotype in ATS is not benign, and may be progressive.

1 Those reporting attacks lasting weeks were more likely to have fixed weakness. Exploring duration of
2 attacks, not only attack frequency, in patient consultations may be helpful in identifying those more
3 likely to develop fixed weakness. Cold is listed as a more common trigger than heat, but this may
4 represent a bias in a UK cohort.

5 Individual investigations in ATS are not diagnostic e.g. CK levels were not discriminatory and notably a
6 normal LET also did not exclude ATS. While the cause of the muscle biopsy changes seen is unclear,
7 there is a suggestion that vacuoles may be the earliest pathological change, progressing to development
8 of tubular aggregates before end-stage fat accumulation as seen on MRI scans.

9 Pelvic muscle fat accumulation on MRI may explain clinical weakness in some of our patients who have
10 normal imaging of the thighs and calves. Pelvic and axial weakness may be important to consider
11 clinically in these patients and requesting MRI imaging that includes pelvic muscles may be helpful for
12 treating clinicians and physiotherapists. Proximal, peri-girdle weakness may also contribute to the
13 regions of pain that were reported in our cohort.

14 Kir2.1 is widely expressed including in the peripheral and central nervous system.⁴ It is plausible that
15 peripheral nerve potassium channel dysfunction may increase nerve excitability and underlie the
16 fasciculations seen in some of our patients. A neuropsychiatric phenotype has been suggested in the
17 past^{21,22} however this is to our knowledge the first case series with detailed neuropsychological testing.
18 Highlighting the possible neurocognitive deficits may be especially relevant for supporting the education
19 and employment opportunities available to patients. Those with executive dysfunction appear to also
20 have a severe neuromuscular phenotype with fixed weakness, in combination, this may present
21 significant management challenges and will be important to recognise and address.

22 The cardiac phenotype of ATS has often been considered benign, with serious complications reported as
23 a rarity.²³ However our data has shown a real cardiac risk and reflects findings of a recent study focused
24 on cardiac features of ATS.⁹

25 Notably, two of our patients who required ICD or PPM insertion did not report any cardiac symptoms.
26 Therefore, cardiac symptoms cannot be utilised as the sole marker to prompt increased cardiac
27 surveillance or as a predictor of development of a severe cardiac phenotype. Similarly, baseline ECGs
28 were not useful in predicting risk of a severe cardiac phenotype. All 72-hour holter monitor recordings
29 were abnormal in the patients with a severe cardiac phenotype suggesting that a prolonged holter
30 monitor recording would be beneficial in the routine clinical care of those with ATS.

1 In addition, we describe the use of cardiac loop recorders to determine response to medication, which
2 may be a helpful approach in this cohort where not all patients with high cardiac risk were symptomatic
3 prior to needing a cardiac device. They may also be useful in patients with syncope, as this is associated
4 with a higher-risk of life-threatening arrhythmic events in ATS.⁹ Cardiac loop recorders have been used
5 effectively in several conditions to improve the detection rate of arrhythmias.²⁴ We propose a low
6 threshold for the use of loop recorders in patients with a genetic diagnosis of ATS, particularly in those
7 with an abnormal screening 72-hour holter monitor recording, syncope or dizziness. In patients with
8 confirmed cardiogenic syncope or severe arrhythmias captured (e.g. VT, significant ectopic burden), a
9 discussion about ICD insertion with the neurologist, cardiologist and patient is indicated.

10 Additionally, LV dysfunction has not been previously reported in ATS. While the pathophysiology is
11 uncertain, it is likely that the burden of ventricular ectopics/polymorphic ventricular complexes
12 contributes. In general, changes in LV volumes and pressures are seen in asymptomatic patients with
13 frequent ventricular ectopics, and suppression of ectopics may improve cardiac function.^{25,26} As such we
14 recommend a screening TTE in all ATS patients and there may be a role for further monitoring TTEs in
15 those with an uncontrolled ectopic burden. Cardiac MRI may be a useful future research tool to better
16 understand the underlying cardiac muscle structure.

17 Given the cardiac risk associated with ATS, family testing should be offered to all family members of the
18 proband regardless of the presence or absence of cardiac symptoms.

19 Given our relatively young cohort, 31% reporting significant pain is higher than would be expected for
20 this age group¹⁶. Potassium channel dysfunction and consequent pain has been described and may
21 contribute to the presence of pain in a significant proportion of our patients.²⁷

22 Fatigue is a commonly reported symptom in ATS and when present is often described as one of the most
23 disabling symptoms. Currently, no targeted program exists to manage fatigue in patients with ATS.
24 Recognising fatigue as a significant cause of morbidity and referral to a fatigue management program
25 could have significant benefit to a patient's quality of life. While snoring is a reported symptom in ATS
26 patients, which may potentially relate to micrognathia, it is not higher than the general UK population.

27 Four (7.7%) patients had scoliosis that may be a relevant feature of ATS. This is higher than the
28 prevalence of 0.5-5% reported in large scale prevalence studies for idiopathic scoliosis ($p=0.1$).^{28,29}

29 Routine examination of the spine in ATS patients is recommended.

1 In terms of treatment options, the neuromuscular medications commonly include acetazolamide.
2 However, there were a significant subset of non-responders to acetazolamide. Spironolactone or
3 amiloride may be an option in this subset, but further review in larger cohorts is required to determine
4 predictors of acetazolamide non-responders and an optimal second line therapeutic strategy. In
5 contrast, cardiac medication varied considerably between patients and requires further collaborative
6 research to delineate a consensus approach.

7 Genotype-phenotype correlation can be difficult in rare conditions. We did not find any particular
8 clustering for cardiac or dysmorphic phenotypes graded by severity. C-terminal clustering for those with
9 dysmorphic features has been previously described, however in our data no such clustering was seen.⁹
10 No correlation between cardiac, neuromuscular and skeletal features grouped by severity were seen.
11 However, in some subsets, correlations were found as detailed above. For example, in those with
12 cognitive features, the neuromuscular phenotype was more severe.

13 Limitations of our study include the smaller subset of patients who had undergone extra tests such as
14 echocardiogram and MRI. Future natural history studies are indicated with standardised tests performed
15 prospectively to further improve our understanding of ATS. Additionally, while we have endeavoured to
16 include patients who presented to other sub-specialities, our cohort is largely representative of patients
17 who present to and are managed by neurologists, which may introduce some bias in the identified
18 clinical features.

19 Historically, ATS has been characterised as a triad of periodic paralysis, cardiac arrhythmias and
20 dysmorphism. We have demonstrated that the spectrum within these domains, ranges from nil to
21 severe without clear correlation between the severity in different domains. In addition, we show
22 involvement of the peripheral and central nervous system, and both pain and fatigue as key aspects to
23 the neurological features of the syndrome. Importantly, the cardiac and neuromuscular phenotypes are
24 not benign. There is significant risk of life-threatening arrhythmias and progressive muscle weakness
25 that requires proactive management and monitoring.

26 **Key Recommendations:**

- 27 • ATS can cause significant neuromuscular morbidity.
- 28 • Lack of dysmorphic features should not deter from considering the diagnosis of ATS.

- 1 • Genetic testing should be offered to all family members and should not be limited to
2 those who are symptomatic.
- 3 • Cardiac loop recorders should be considered in patients with genetically confirmed ATS
4 and abnormal 72-hour holter monitors regardless of symptoms, and in those with syncope
5 or dizziness to guide management.
- 6 • Discuss ICD insertion with multi-disciplinary input in high risk patients – those with
7 confirmed cardiogenic syncope or severe arrhythmias detected (VT, high burden of VEs).
- 8 • Recommend screening TTE and 72-hour holter monitor for all patients with genetically
9 confirmed ATS and to consider further TTEs for monitoring in patients with an
10 uncontrolled high cardiac ectopic burden.
- 11 • Recommend a low threshold for formal Neuropsychometry evaluation in patients
12 reporting cognitive deficits.
- 13 • Pain and fatigue should be routinely assessed and managed.

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20 for further details contact m.hanna@ucl.ac.uk.

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23 Competing Interests

24 The authors report no competing interests.

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1 **Figure Legends**

2 **Figure 1. Attack Phenotype. (A):** Duration of attacks of periodic paralysis. **(B):** Frequency of attacks of
3 periodic paralysis. **(C):** Reported prevalence of attack triggers.

4 **Figure 2: Muscle MRI and biopsies in ATS. (A)Top:** T1 transverse MRI representative slices
5 demonstrating marked posterior thigh and posterior calf compartment fatty infiltration. **(B)Bottom:**
6 Representative muscle biopsy histology showing subsarcolemmal tubular aggregates appearing
7 basophilic on H&E, which also shows variation in fibre size and occasional internal nuclei in the
8 background (A). The tubular aggregates are also highlighted on Gomori Trichrome (B) and more
9 prominently on oxidative enzyme NADH (C) restricted to pale staining type II (fast) fibres. The tubular
10 aggregates also stained darkly on other enzymes such as phosphofructokinase and aldolase (not shown),
11 but were deficient for COX (D). Abbreviations: H&E – Haematoxylin and eosin; GT – Gomori trichrome;
12 NADH – Reduced nicotinamide adenine dinucleotide-tetrazolium reductase; COX – Cytochrome oxidase.
13 Scale bar in A = 100µ representing all images A-D.

14 **Figure 3: Cardiac Phenotype. (A):** prevalence of reported cardiac symptoms. **(B):** Prevalence of
15 arrhythmias on cardiac holter monitoring (VEs: ventricular ectopics; SVT: supraventricular tachycardia;
16 VT: ventricular tachycardia; HB: heart block). More than one abnormality was seen in some holter
17 recordings.

18 **Figure 4: Prevalence of dysmorphic features.**

19 **Figure 5: Novel variants.** Novel variants are mapped on Kir2.2 structure
20 (www.nature.com/articles/nature10370). Red spheres indicate residues affected by the novel missense
21 mutations, blue spheres indicate K188 that is deleted by a novel mutation, purple spheres indicate the
22 potassium ions. Only two of the four subunits are shown for clarity.

23 **Figure 6: Functional expression of novel variants.** *Xenopus* oocytes Kir2.1 channels carrying Phe99Ser,
24 His110Leu, Val126Gly, Ala157Asp, or Arg260His variants displayed significantly reduced or absent
25 currents compared to the wild type (WT) oocytes.

26

27

1 **Table I Clinical details of patients with a severe cardiac phenotype**

Patient	1	2	3	4	5	6	7
Mutation	Arg218Gln	Arg260His	Leu193Pro	Val126Gly	Arg67Trp	Lys188del	Gly144Asp
Gender	Female	Male	Female	Female	Female	Female	Female
Symptom onset	Age 33	Teenage	Neonate	Early twenties	Teenage	Age 4	Age 6
Presentation	Cardiac arrest	Weakness	Hypotonia	Arm Weakness	Paralysis	Chest pain & arrhythmia	Paralysis
Attack frequency	Nil	4-6 weekly	Frequent	Monthly	Unk	Weekly	Weekly
Fixed muscle weakness	No	No	Yes	Yes	No	Yes	Yes
LET	Not done	26%	Not done	Not done	Not done	33%	61.2%
Treatment for attack	Nil	Acz	Nil	Acz	Nil	Acz, Spiro	Acz
Skeletal features	Nil	Nil	Micrognathia, low-set ears, thin upper lip, missing teeth, cleft palate	Clinodactyly		Micrognathia, low set ears, clindodactyly, syndactyly, small hands & feet cleft palate.	Micrognathia, hypertelorism, low set ears, syndactyly, clindodactyly
Cardiac Symptoms	Syncope, palpitations	Dizziness, dyspnoea	None	None	Syncope, dyspnoea	Chest pain, syncope	Palpitations, dizziness
Prolonged QTc	No	Yes	No	No	Yes	No	Yes
TTE	Normal	Mild impairment. LVEF 49%. Delayed relaxation on transmitral inflow.	Severe impairment, dilated LV	Normal	Mild-Mod LV impairment	Normal	Normal
Holter recording	Frequent VEs, PVCs	Complete Heart Block	Frequent VEs, PVCs	VEs, PVC, SVT	VEs	VT, bigeminy	VEs, NSVT, Sustained VT
Cardiac medication	Bisoprolol		Aspirin, Candesartan, Carvedilol, Furosemide, Spironolactone		Bisoprolol, ramipril	Bisoprolol, amiodarone, sotalol, nodalol	Flecainide, nadolol, propadenone
Cardiac device	ICD	PPM	Awaiting ICD	ICD	PPM then ICD	Sympathectomy then ICD	ICD

2

3

1 **Table 2 Neuropsychology assessment**

	Average	Normal range	<5th centile	5-10th centile	10-25th centile
WAIS-VIQ/PIQ	89				
RMT words		5/5			
RMT face		1/5	3/5	1/5	
Naming	23 rd centile	3/5	2/5		
Visuoperceptual		5/5			
Stroop	16 th centile	1/5	2/5		2/5
Fluency ('S')	51 st centile	3/4			1/4
Animals		5/5			
Trials B		2/4	2/4		
SDMT		1/5	2/5	1/5	1/5

2
3 Summary scores for the patients who underwent formal neuropsychology assessment. (WAIS-VIQ/PIQ: Wechsler Adult Intelligence Scale –
4 Verbal IQ and Performance IQ; RMT: Recognition Memory Test; SDMT: Symbol Digit Modalities Test)

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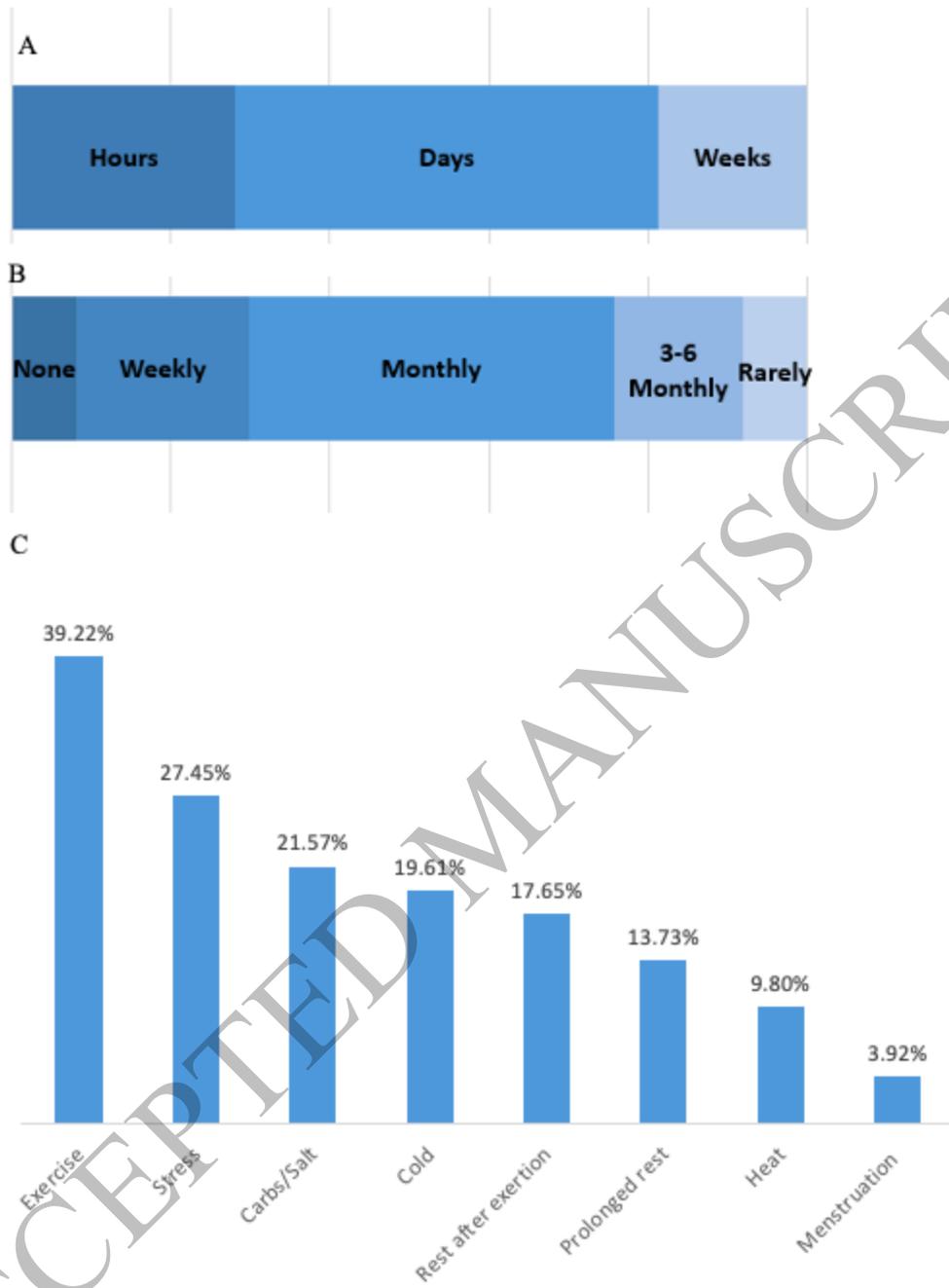


Figure 1
132x177 mm (7.2 x DPI)

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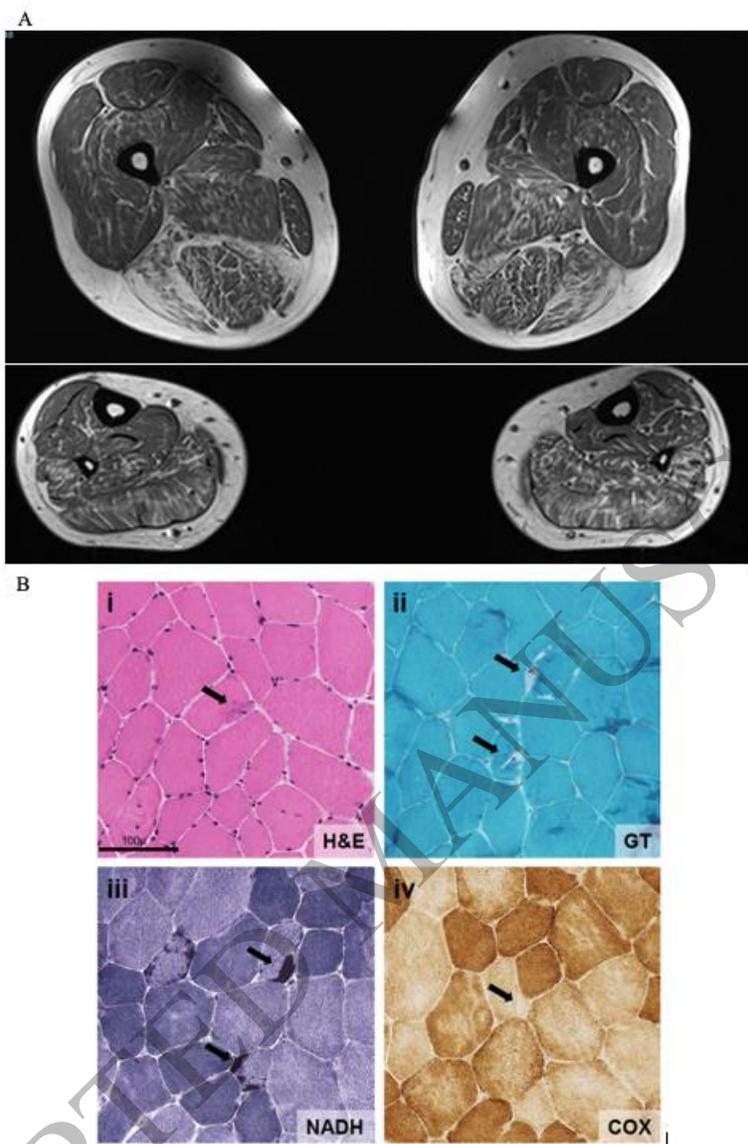


Figure 2
102x153 mm (7.2 x DPI)

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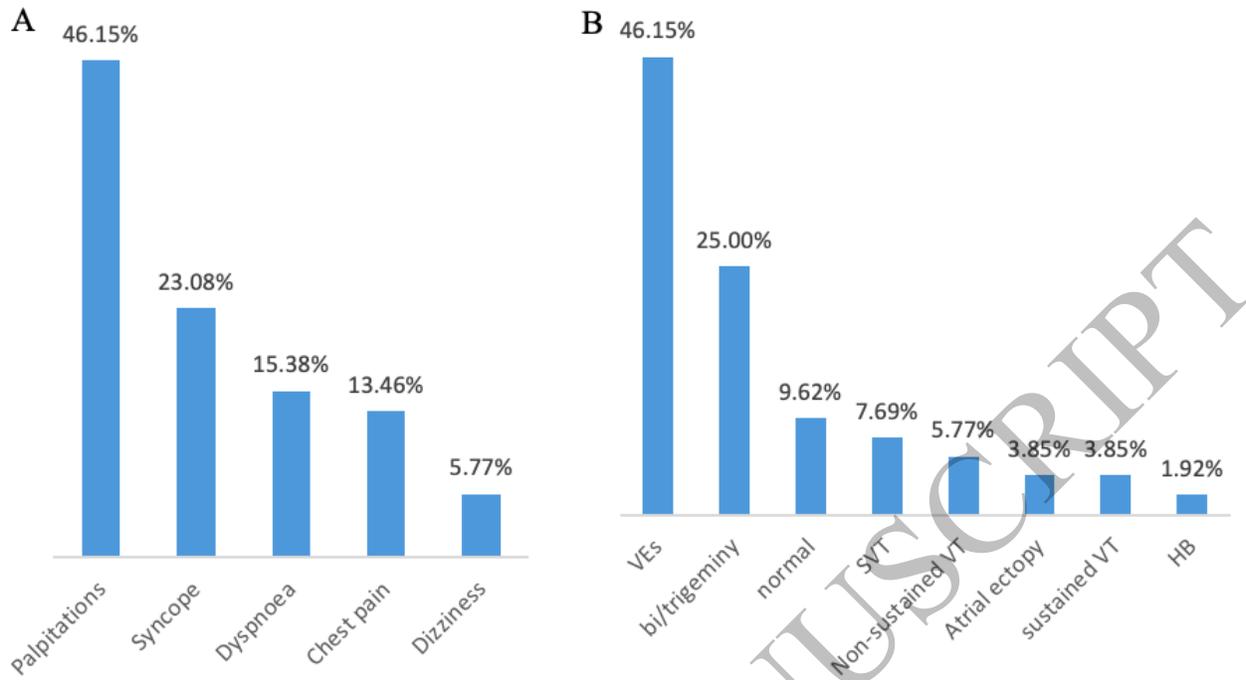


Figure 3
165x92 mm (7.2 x DPI)

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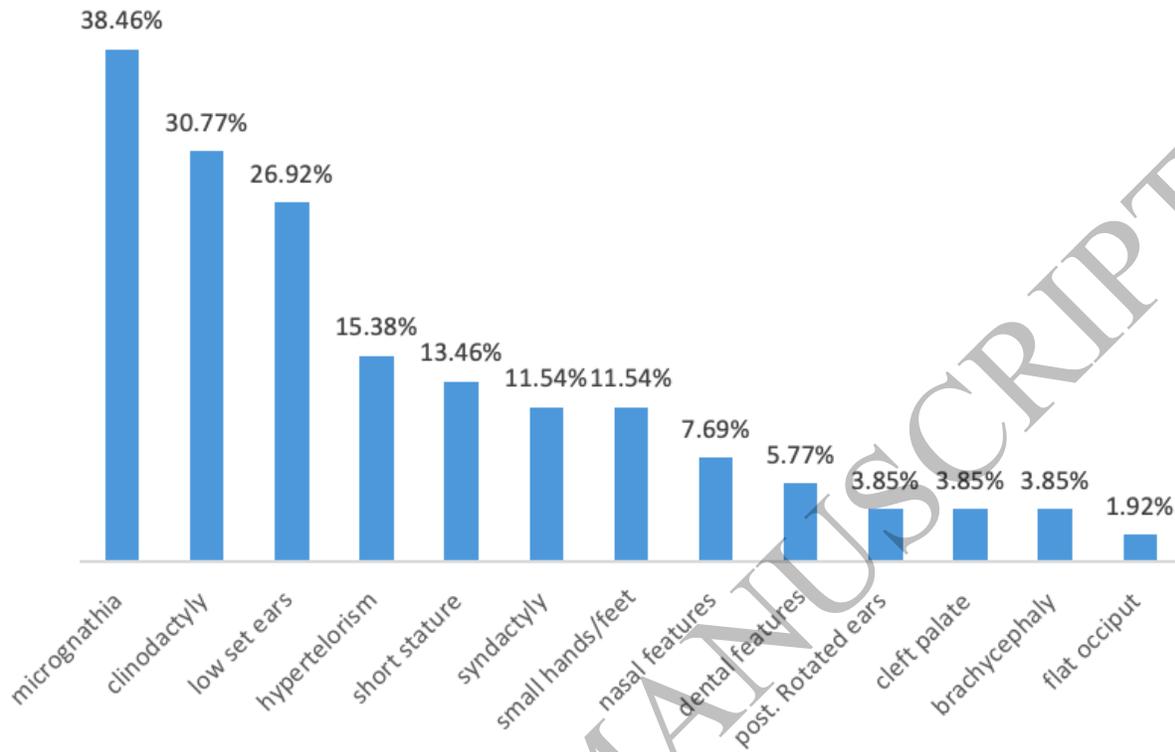


Figure 4
165x113 mm (7.2 x DPI)

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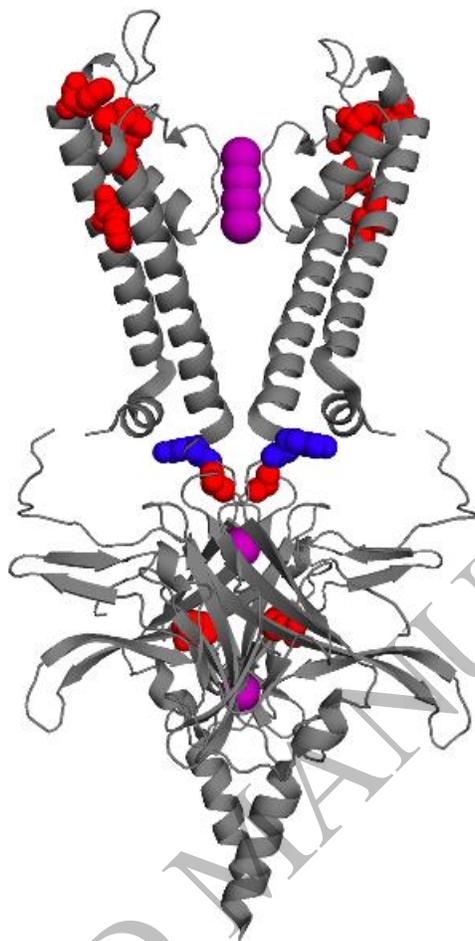


Figure 5
77x129 mm (7.2 x DPI)

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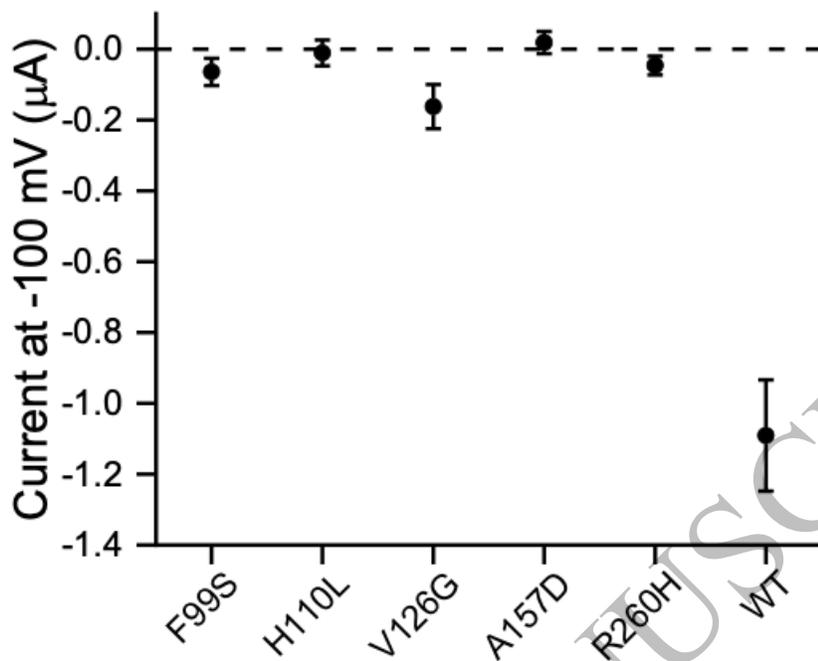


Figure 6
126x99 mm (7.2 x DPI)

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1 Andersen-Tawil Syndrome is a channelopathy characterised by episodic weakness, cardiac
2 arrhythmia and dysmorphic features. Vivekanandam *et al.* perform multi-modal phenotyping on
3 a large case series, and show that 25% of the cohort have fixed muscle weakness and 13%
4 required cardiac device insertion.

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