Andersen-Tawil syndrome: deep phenotyping reveals significant cardiac and neuromuscular morbidity

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Running title: Phenotyping Andersen-Tawil Syndrome

Abstract

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

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

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

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

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

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

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

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

Introduction

Andersen-Tawil Syndrome (ATS) is a rare neuromuscular channelopathy, characterised by a triad of periodic paralysis, cardiac conduction defects and dysmorphic features.[1] The reported point prevalence in England is 0.08 per 100 000.[2] ATS is caused by mutations in the *KCNJ2* gene, which encodes Kir2.1 potassium channels that conduct an inward rectifier potassium current integral to maintaining resting membrane potential. ATS-associated *KCNJ2* mutations cause loss of Kir2.1 channel function.[3] The Kir2.1 channel is widely expressed, accounting for the multisystem presentation.[4]

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

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

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

Methods

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

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

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

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

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

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

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

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

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

Xenopus laevis oocytes and molecular biology

Oocytes were removed from *Xenopus laevis* toads in accordance with the Animals (Scientific Procedures) Act 1986. The mutations were introduced into WT *KCNJ2* cDNA (NM_000891.3) by Quikchange site directed mutagenesis (Qiagen). Successful mutagenesis was confirmed for each clone by sequencing the entire insert. The mRNA was transcribed using mMessage Machine T7 kit (Ambion). The oocytes were injected with 2.5 ng WT or mutant mRNA. The oocytes were incubated in Modified 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, supplemented with penicillin, streptomycin and amikacin for 24-72 hrs at 15-18°C before electrophysiological recordings.

Electrophysiology

Two-electrode voltage clamp experiments were performed using GeneClamp 500B, DigiData 1200 or 1550 Interface, and Clampex software (all Axon Instruments) at room temperature in 10K extracellular media (in mM): potassium methanesulfonate 10, sodium methanesulfonate 110, HEPES 10, $CaSO_4$ 1.8 (pH 7.4). Recording electrodes were filled with 3 M KCl and had a tip resistance <1 MΩ. Data were filtered at 1 kHz and sampled at 5 kHz. Holding voltage was 0 mV, Voltage protocol consists of 250 ms steps to test voltages ranging from -190 mV to +100 mV in 10 mV increments. Currents were measured at the beginning of the test pulse. Oocyte data was analysed using Clampfit (Molecular devices), Origin (OriginLab) and Excel software. Leak current was estimated at voltage range 10-30 mV and subtracted from raw current data. Statistical significance was assessed using Kruskal-Wallis ANOVA.

Statistical Analysis

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

Data Availability

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

Results

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

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

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

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

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

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

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

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

Neuromuscular phenotype:

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

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

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

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

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

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

Creatinine Kinase (CK)

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

Neurophysiology

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

Muscle MRI

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

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

Muscle Biopsy

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

Symptomatic Treatment for Weakness/Paralysis

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

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

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

Cardiac Phenotype:

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

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

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

Severe cardiac phenotype

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

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

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

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

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

Cardiac Treatment

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

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

Skeletal Features

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

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

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

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

Nine patients (four males, five females) had head circumference measured. This was normal for the majority, but two male patients had head circumference below the 25th centile for height [15] and one female patient had head circumference below the 10th centile for height.

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

Other Features

Cognitive Features

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

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

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

Newly Described Clinical Features

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

16 patients (31%) described significant pain. The median age of those reporting pain was 47 (s.d. 13) which is significantly higher than the reported prevalence of chronic pain for this age group in UK - 11.2% ($p=0.8x10^{7}$)[16]. Nine patients undertook more detailed pain related assessment using the Brief Pain Inventory Scale.[17] Pain predominantly affected proximal arms, legs and lower back. The degree of pain varied significantly over 24hours in all patients, from no pain to a score of 7 out of 10 (10 = pain as bad as you can imagine) in one patient. The average pain score was 4.64. Two patients required codeine to manage the pain. The patients reported that pain affected all aspects of life including mood, walking ability, work, relations with other people, sleep and enjoyment of life.

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

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

Eight (15%) patients or their bed partners reported marked snoring overnight, not significantly higher than the UK general population[19]. Three of these patients additionally reported morning headaches and four patients reported excessive daytime sleepiness. Sleep studies did not demonstrate nocturnal hypoventilation. Six of the eight patients who snored, had micrognathia.

Anaesthetic Reactions

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

Pregnancy and Labour

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

Genetic Data & Genotype-Phenotype Correlation

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

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

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

Eight novel mutations were identified in our cohort (Phe99Ser, His110Leu, Cys122Ser, Val126Gly, Ala157Asp, Lys188del, Arg260His and Ala306Val) mapped on the Kir2.2 structure as demonstrated in Figure 5.[20] Upon expression in *Xenopus* oocytes Kir2.1 channels carrying Phe99Ser, His110Leu, Val126Gly, Ala157Asp, or Arg260His variants displayed limited, if any currents (Figure 6); confirming pathogenicity of these variants.

Discussion

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

We show a higher prevalence of ATS than in previous reports with a point prevalence of 0.105 per 100 000 compared to 0.08 per 100 000.[2] The increased prevalence likely represents an increased diagnostic rate achieved with the advent of next generation sequencing as well as a more pro-active recommendation to screen family members in our clinical practice. This recommendation was driven by a greater understanding of the cardiac risk and knowledge that clinically significant arrhythmia requiring medical intervention can occur in the absence of clinical symptoms.

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

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

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

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

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

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

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

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

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

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

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

Given our relatively young cohort, 31% reporting significant pain is higher than would be expected for this age group[16]. Potassium channel dysfunction and consequent pain has been described and may contribute to the presence of pain in a significant proportion of our patients.[27]

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

Four (7.7%) patients had scoliosis that may be a relevant feature of ATS. This is higher than the prevalence of 0.5-5% reported in large scale prevalence studies for idiopathic scoliosis (p=0.1).[28,29] Routine examination of the spine in ATS patients is recommended.

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

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

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

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

Key Recommendations:

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

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

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Competing Interests

The authors report no competing interests.

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Figure Legends

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

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

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

Figure 4: Prevalence of dysmorphic features.

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

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

Table 1 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

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	23rd centile	3/5	2/5		
Visuoperceptual		5/5			
Stroop	16th centile	1/5	2/5		2/5
Fluency ('S')	51st centile	3/4			1/4
Animals		5/5			
Trials B		2/4	2/4		
SDMT		1/5	2/5	1/5	1/5

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

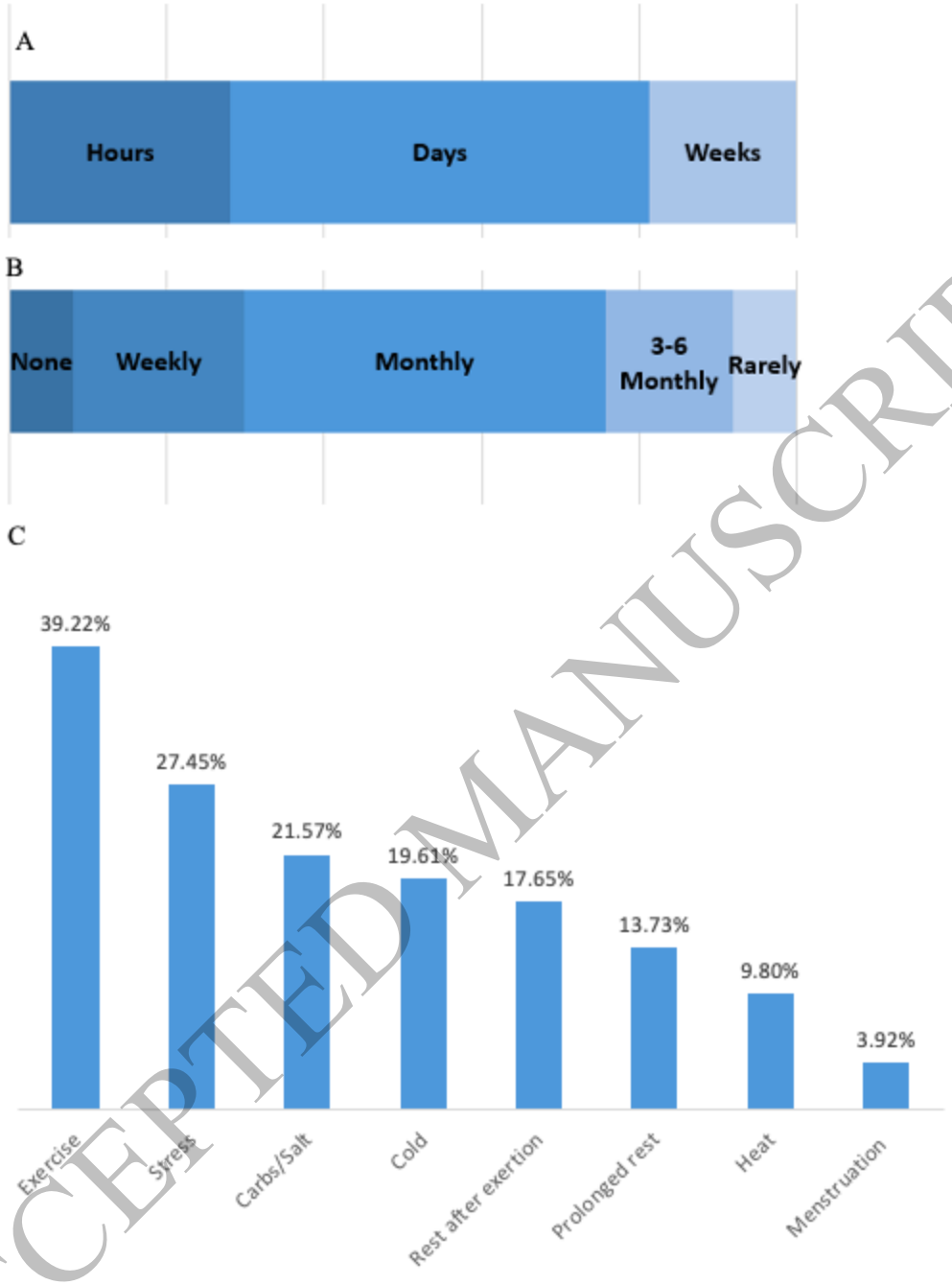

Figure 1
132x177 mm (7.2 x DPI)

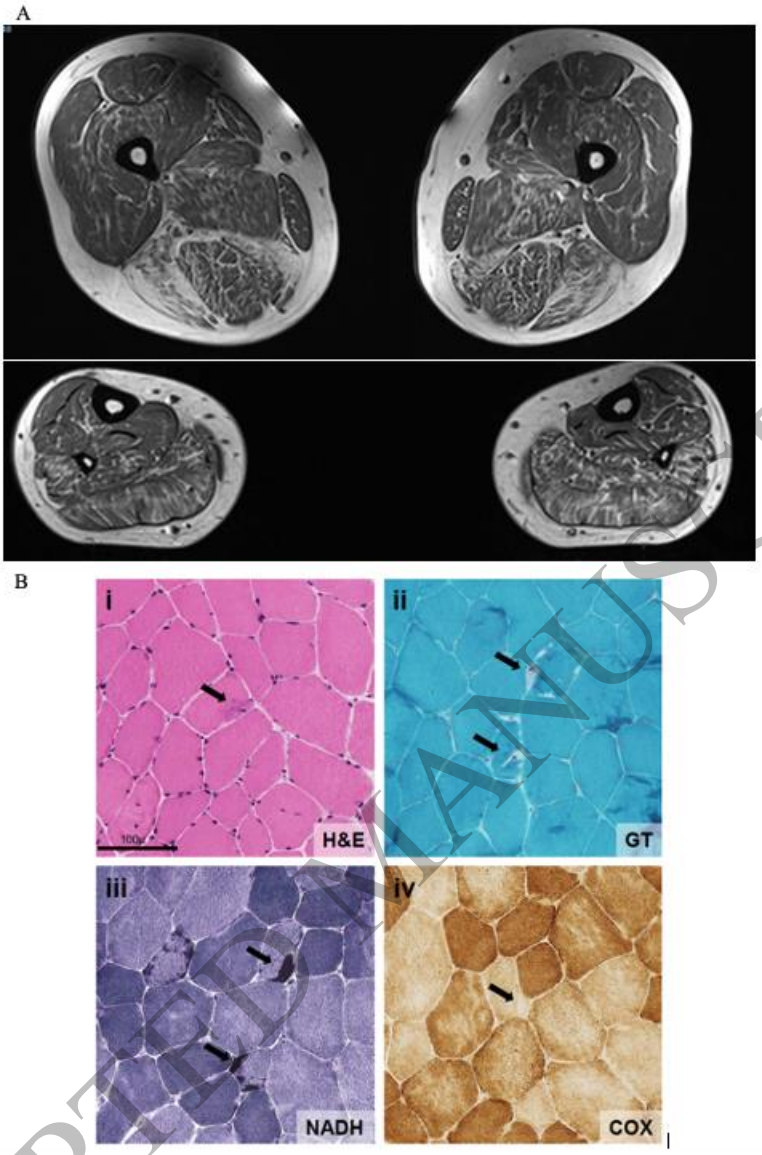

Figure 2
102x153 mm (7.2 x DPI)

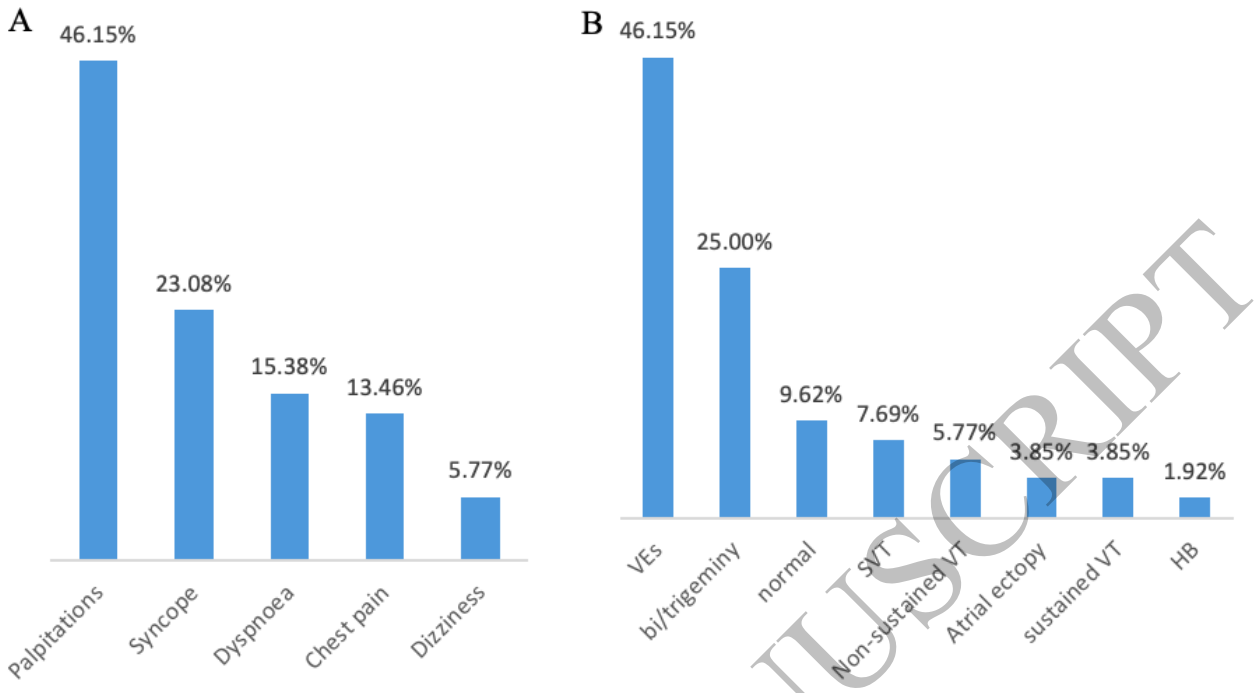

Figure 3
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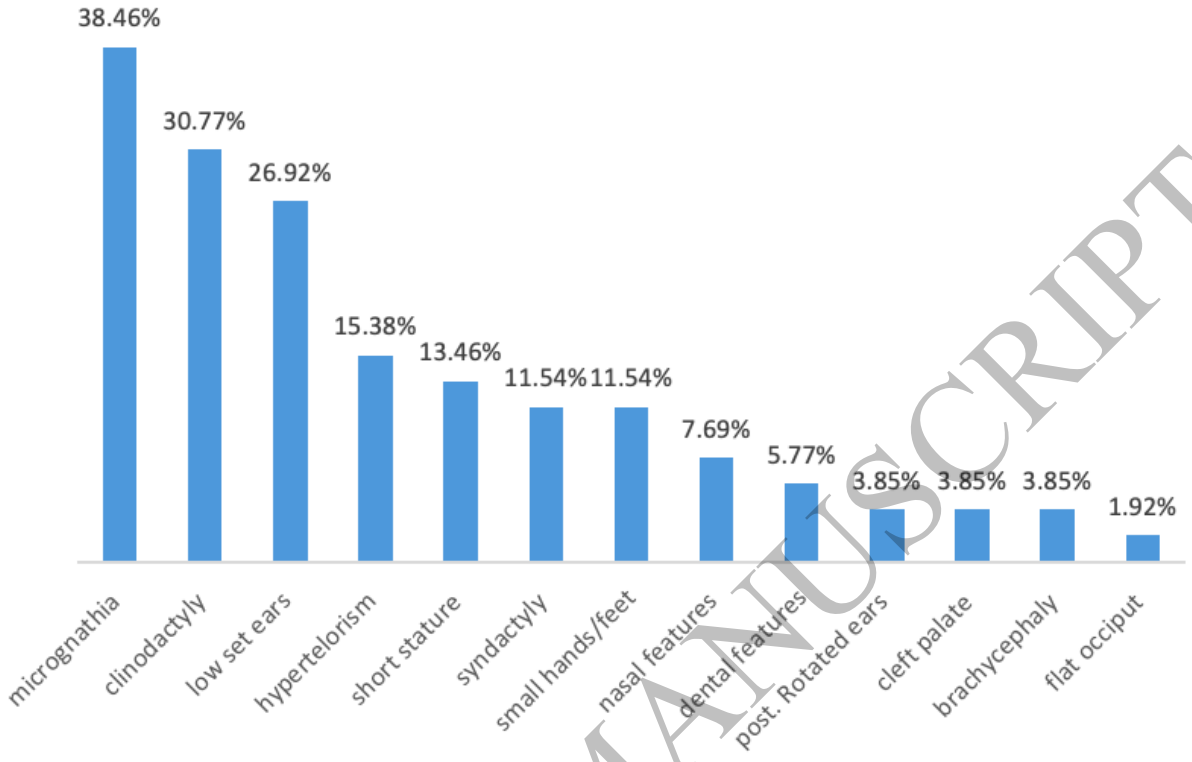

Figure 4
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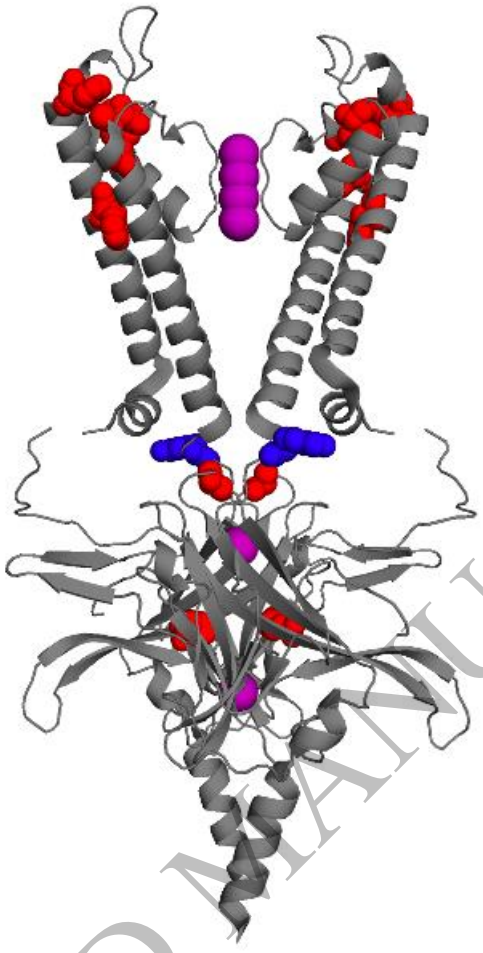

Figure 5
77x129 mm (7.2 x DPI)

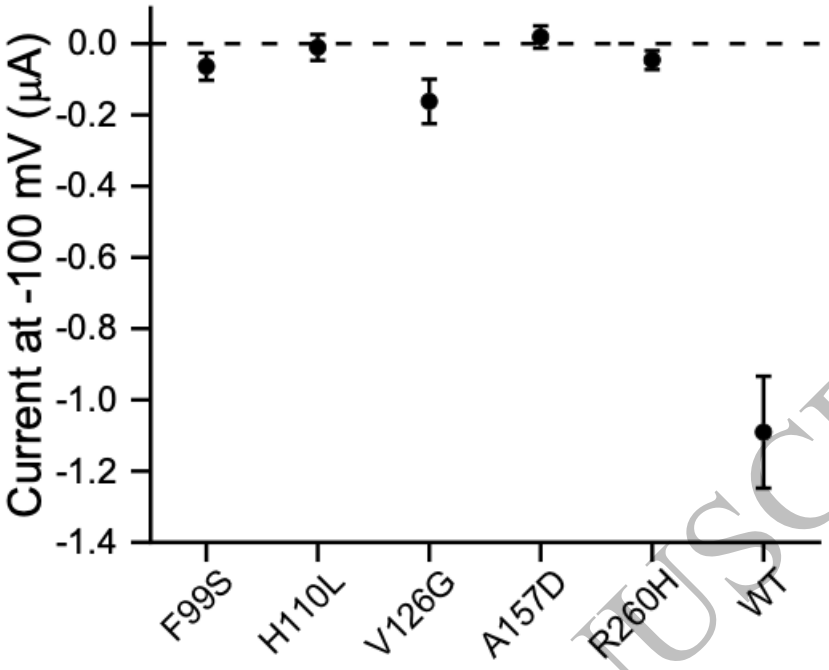

Figure 6
126x99 mm (7.2 x DPI)

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