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CASE REPORT

Case Series of Cerebellar Ataxia with Tremor Due to Heterozygous *STUB1* Variants (SCA48) without *TBP* Expansions: Further Evidence for *SCA48* as a Monogenic Disease

Yan Zochowski[1] · Kishore R. Kumar[2,3,6,7] · Matthew Katz[10] · Paul Darveniza[1,2,8] · Michel Tchan[4,5] · Renee Smyth[3] · Susan Tomlinson[1,3,8,9] · Kathy H. C. Wu[1,2,3,5] · Stephen Tisch[1,2,3,8]

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Abstract

Clinically-relevant variants in the *STUB1* gene have been associated with an autosomal dominant spinocerebellar ataxia 48 (SCA48), a recently described inherited neurodegenerative condition that is characterised by cognitive and psychiatric changes. To describe the clinical phenotype and genetic findings of three new Australian probands with *STUB1* to expand the current understanding of the spectrum of clinical presentation and natural history of SCA48. Clinical and genetic review of patients diagnosed with SCA48 ataxia drawn from our centres. The third case was derived from a collaborating centre (Royal Brisbane Hospital). We identified three unrelated SCA48 patients with heterozygous pathogenic *STUB1* variants. All presented with slowly progressive cerebellar ataxia with tremor and additional findings of dysarthria, parkinsonism, hypertonia, cognitive and psychiatric symptoms. Age of onset varied from 34 to 65 years of age. Brain MRI showed significant diffuse cerebellar atrophy, affecting the vermis and cerebellar hemispheres. We identified two novel pathogenic variants of *STUB1* gene, and one previously reported pathogenic variant. Genetic testing for intermediate expansions of *TBP* (SCA17) identified *TBP* repeats within the normal range of 25–40 in all 3 probands. Our case series expands the clinical spectrum of SCA48. We highlight the importance of tremor as part of the clinical phenotype including upper limb rest tremor and Parkinsonian signs. Our cases lacked pathological *TBP* expansions and provide additional evidence that *STUB1* (SCA48) can manifest as a monogenic disease.

Keywords STUB1 · SCA48 · Monogenic disease · Tremor and Parkinsonian signs

✉ Stephen Tisch
stephen.tisch@svha.org.au

1 School of Medicine, University of Notre Dame, Sydney, NSW, Australia

2 School of Clinical Medicine, Faculty of Medicine and Health, UNSW Medicine & Health, St Vincents Healthcare Clinical Campus, UNSW Sydney, Sydney, NSW, Australia

3 St Vincent´s Clinical Genomics, St Vincents Hospital, Sydney, NSW, Australia

4 Department of Genetic Medicine, Westmead Hospital, Sydney, NSW, Australia

5 Discipline of Genetic Medicine, University of Sydney, Sydney, NSW, Australia

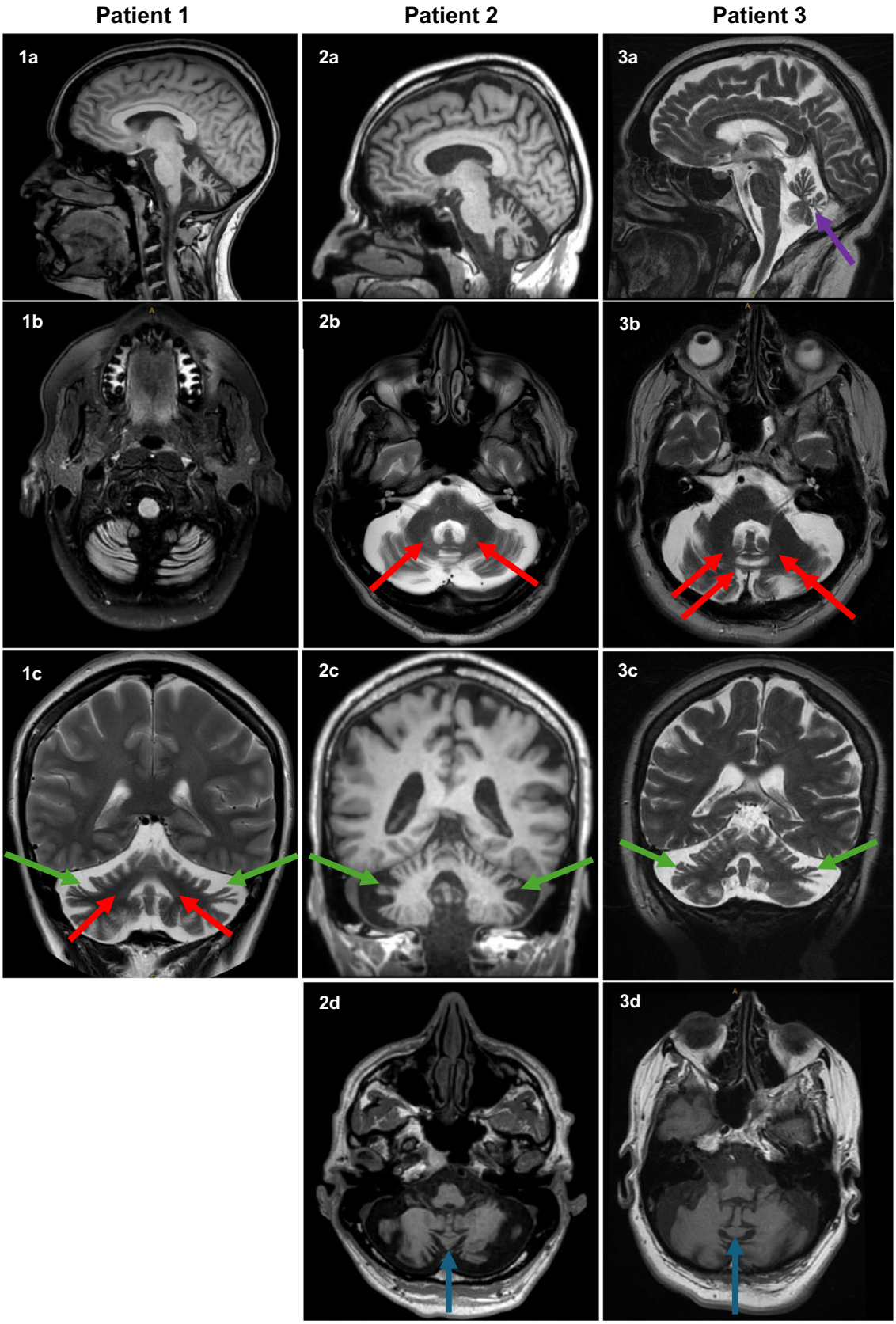
6 Molecular Medicine in Neurology, Concord Repatriation General Hospital and the University of Sydney, Sydney, NSW, Australia

7 Translational Neurogenomics Group, Genomic and Inherited Disease Program, Garvan Institute of Medical Research, Darlinghurst, NSW 2010, Australia

8 Department of Neurology, St Vincent's Health Network Sydney, 390 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia

9 Faculty of Medicine, University of Sydney, Sydney, NSW, Australia

10 Department of Neurology, Royal Brisbane Hospital, Brisbane, QLD, Australia


Patient 1
Patient 2
Patient 3
1a
2a
3a
1b
2b
3b
1c
2c
3c
2d
3d

◂**Fig. 1** Brain T1 weighted sagittal plane (**1a**) and axial (**1b**) and coronal (**1c**) images of patient 1. Advanced diffuse atrophy of the cerebellum with also minor volume loss of the medulla oblongata (1a). Brain T2-weighted coronal MRI of patient 1 showing significant atrophy of the cerebellar hemispheres (green arrows) and hyperintensity affecting dentate nuclei (red arrows) (1c). Brain T1-weighted sagittal (**2a**) and T1-weighted axial images (**2d**) showing diffuse global atrophy of the cerebellum, and atrophy of the vermis (as indicated by the blue arrow). Brain T1-weighted coronal (**2c**) and T2-weighted axial MRI (**2b**) of patient 2 showing significant atrophy of the cerebellar hemispheres, in particular the posterolateral lobules VI-VII (indicated by the green arrows). There is also hyperintensity affecting the dentate nuclei (indicated by the red arrows). T2-weighted sagittal view MRI (**3a**) showing significant cerebellar atrophy (purple arrow), T2-weighted axial view MRI (**3b**) showing subtle hyperintensities in the dentate nuclei (red arrows), T2-weighted coronal view MRI (**3c**) showing cerebellar atrophy, with prominent atrophy of the posterolateral lobes (green arrows), T1-weighted axial view (**3d**) showing vermian atrophy (blue arrow)

Introduction

Spinocerebellar Ataxia 48 (SCA48) is a recently described autosomal dominant inherited degenerative disease that is characterised by late-onset cerebellar ataxia and prominent cognitive and psychiatric changes [1]. It has been associated with disease-causing variants in the *STUB1* gene and encompasses a spectrum of clinical presentations. Typically, SCA48 is characterised by gradual onset of gait ataxia and/or cognitive-affective symptoms in adulthood. Reported clinical syndromes include gait ataxia, dysarthria, dysphagia, and oculomotor abnormalities, as well as cognitive affective symptoms, such as language impairment, depression, anxiety. Rarer clinical features including chorea, Parkinsonism, dystonia, peripheral neuropathies, and epilepsy have been reported. [2–4].

The *STUB1* gene encodes CHIP (C-terminus of Heat shock protein 70 – interacting protein (Hsp70) [5], a dual function protein with a role in ubiquitination as a co-chaperone with heat shock proteins, and as an E3 ligase [6]. The CHIP protein contains several domains, including a tetratricopeptide repeat (TPR) domain, a U-box domain, and a charger linker region each of which has a role in protein homeostasis [7]. The U-box domain of CHIP is located at the C-terminus of the protein and is essential for ubiquitin ligase activity. It functions as an E3 ubiquitin ligase, which tags misfolded or unwanted proteins with ubiquitin for degradation by the proteasome [8]. The ubiquitin system is critical to regulating protein homeostasis as it regulates breakdown of abnormal proteins through their degradation via proteasomes. While the mechanism of *STUB1* variants resulting in neurodegeneration is not fully understood, alterations in the function of the ubiquitin proteasome system have been implicated. It has been proposed that digenic inheritance of *STUB1* variants and *TBP* polyQ expansions explain the incomplete penetrance of SCA17 and SCA48 [9, 10] in response, other groups have suggested that SCA48 is primarily a *STUB1* monogenic disorder [11, 12]. Here, we investigate the clinical and genetic findings of SCA48 in an Australian case series.

Methods

Cases of *STUB1*/SCA48 were identified from our Neurogenomics Clinic databases. Two of the cases were identified from SVH Neurogenomics Clinic [13]. The third case was derived from a collaborating centre (MK). All cases underwent genetic testing utilising gene panels for ataxia causing genes, the specific genes tested are listed in Supplement 1. Testing for SCA17 expansions was performed using triplet repeat primed PCR. All patients were assessed clinically by Neurologists (ST, PD, MK), for phenotyping. The study was ethically approved by University of Notre Dame Human Research Ethics Committee (approval 2021-172S).

Case Series

Patient 1: A 37-year-old female presented with a two-year history of poor balance, incoordination, dysphagia for liquids and generalized fatigue followed by upper limb tremor, mild cognitive decline and dysarthria. Her mother had bilateral hand tremors but no formal diagnosis. Examination revealed dysarthria, gait ataxia, positive Romberg's test, limb hypertonia and dysmetria with upper limb action tremor. Neuropsychological testing found reductions in psychomotor speed, verbal fluency, executive functioning with memory. Brain MRI showed diffuse cerebellar atrophy (Fig. 1—images 1a, 1b, 1c). A 152-gene panel, shown in Supplement 1, with analysis of single nucleotide and copy number variants was performed. It revealed a novel heterozygous variant (c.669 + 1G > A) in *STUB1* which is classified as likely pathogenic according to ACMG criteria [14]. *TBP* gene testing revealed 34 and 35 CAG/CAA repeats, both within the normal range of 25–40.

Patient 2. A 61-year-old right-handed male of Polish descent was referred with four-year history of progressive imbalance, slurring of speech and longstanding foot deformities. His brother and father had been similarly affected at around the same age. Examination revealed dysarthria, impaired upward gaze, right upper limb rest tremor, hammer toes, pes cavus, lower limb muscle wasting, absent ankle jerks and extensor plantar responses, distal sensory loss in the lower limbs with gait ataxia and positive Romberg's test. Nerve conduction studies showed a length-dependent sensorimotor axonal peripheral neuropathy. Brain MRI showed atrophy of the cerebellar hemispheres and vermis with hyperintensity in the dentate nuclei (Fig. 1, images 2a, 2b, 2c, 2d). Testing for triplet repeat expansions associated with SCA1, 2, 3, 6, 7, 12, 17 and Friedreich's ataxia was negative. A 210-gene panel for ataxia, shown in

Supplement 1, with analysis of sequence and copy number variants in both nuclear genes and mitochondrial genome was performed, and a heterozygous frameshift variant *STUB1* c.689_692del, p.(Tyr230Cysfs*9) was identified which is a known pathogenic variant. Genetic testing for *TBP* revealed: 35 and 35 CAG/CAA repeats within the normal range of 25–40.

Patient 3. A 65-year-old female of Scottish descent presented with a three-year history of left-hand rest tremor, gait ataxia with injurious falls, cognitive and motor slowing followed by urinary urgency and incontinence. There was no hyposmia, constipation or dream enactment behaviour. Examination revealed a strained dysarthria, dystonic posturing of the head, upper limb cogwheel rigidity and bradykinesia worse on the left and jerky rest tremor of the left hand with partial action suppression and superimposed finger myoclonus (see Video Supplement). Additional signs included absent ankle jerks, extensor left plantar response and gait ataxia with akinetic features. Brain MRI showed white matter hyperintensities and diffuse cerebellar atrophy (Fig. 1 – image 3a, 3b, 3c, 3d). Testing for triplet repeat expansions associated with SCA 1, 2, 3, 6, 7, 12, 17 was negative. Further testing using a 210-gene panel, shown in Supplement 1, for ataxia with analysis of sequence and copy number variants in both nuclear genes and mitochondrial genome showed a heterozygous loss-of-function variant in the *STUB1* gene: c.327_328insCT, p.(Tyr110Leufs*21), classified as a likely pathogenic variant based on the ACMG criteria. Genetic testing for *TBP* gene disclosed: 34 and 35 CAG/CAA repeats both within the normal range of 25–40.

The clinical and MRI features of the three patients are summarized in Table 1.

Discussion

SCA48 disease was first described by Genis et al. in 2018 with the clinical picture of early cognitive and psychiatric changes and late-onset spinocerebellar ataxia [1]. SCA48 typically displays an autosomal dominant mode of inheritance [1] with evidence of preferential maternal inheritance consistent with sex dependent penetrance [15]. SCA48 disease also manifests with progressive cerebellar ataxia with additional, less common, features including Parkinsonism, tremor, chorea, dystonia and dysmetric saccades [16]. The diagnosis of SCA48 is made after clinical recognition of adult-onset gait ataxia and/or cognitive affective symptoms (these can appear in any order), neuroimaging findings of selective atrophy of the cerebellum, and genetic testing showing causative *STUB1* variants. A family history of a dominantly inherited disorder may help support the diagnosis. Initial case reports of SCA48 disease emerged from multiple areas within Europe including Italy, Spain, Netherlands, and Turkey [1, 3, 4, 17, 18].

Disease progression of SCA48 generally begins with gradual onset of gait ataxia followed by progressive movement impairment, and cognitive and psychiatric symptoms. The three patients in this case series presented

Table 1 Summary of Clinical and MRI features in this *STUB1* case series

	Patient 1	Patient 2	Patient 3	Summary of all patients
Demographic and clinical data				
Sex and age of presentation	F, 34	M, 61	F, 65	
Age at 1st symptom onset	32	57	61	
Age at diagnosis	35	63	66	
Presenting symptoms	Ataxia Dysarthria Dysphagia	Ataxia Dysarthria	Rest tremor	Ataxia (3/3) Dysarthria (2/3) Dysphagia (1/3)
Additional features at follow-up	Cognitive impairment Dysmetria Hypertonia Tremor	Depressed reflexes Impaired upward gaze Muscle wasting Sensory loss Tremor	Bradykinesia Cogwheel rigidity Cognitive impairment Dysarthria Dysmetria Pyramidal signs Bladder incontinence	Tremor (3/3) Cognitive impairment (2/3) Dysarthria (3/3) Dysmetria (2/3) Pathologic reflexes (2/3) Hypertonia (2/3) Abnormal sensation (1/3) Bradykinesia (1/3) Muscle wasting (1/3) Ocular abnormalities (1/3)
Neuroimaging				
MRI	CA	Diffuse CA	Scattered ischemic white matter hyperintensities CA	CA (3/3)

(CA) Cerebellar atrophy

following a similar clinical trajectory in line with what has been described in literature with the slow progressive development of cognitive symptoms and/or cerebellar signs, except for patient three where rest tremor was an initial feature. All developed adult-onset cerebellar ataxia and dysarthria, alongside significant cerebellar atrophy, similar to cases reported in literature. Of note, three patients developed upper limb tremor with rest tremor in patients two and three and action tremor in patient one. In patient three, rest tremor was the presenting feature with later appearance of cerebellar ataxia and Parkinsonism. Cognitive and psychiatric impairment was noted in two of the three patients and are recognized features of SCA48. The extent of these manifestations can range between singular involvement of executive functions to a more global cognitive impairment.

A noteworthy aspect of this series is that tremor was present in all cases. Tremor has been previously described in SCA48 in a minority of cases (Table 2). Tremor (excluding "intention tremor" of limb dysmetria)

Table 2 Comparison of all SCA48 families and case reports in the literature

	Genis et al. 2018 ($n=9$)	De Michele et al. 2019 (Family 1) ($n=5$)	De Michele et al. 2019 (Family 2) ($n=5$)	Palvadeau et al. 2019 ($n=3$)	Lieto et al. 2019 ($n=11$)	Cocozza et al. 2020 ($n=10$)
Mean age of onset	47 (33–56)	31 (5–50)	45 (35–55)	60 (51–70)	43 (30–56)	42 (31–55)
Presenting symptoms	Anxiety (5/8)	Ataxia (6/6)	Ataxia (2/2)	Anxiety (1/1)	Chorea (2/11)	CCAS (1/10)
	Ataxia (1/8)	Dizziness (1/6)		CAS (3/3)	CI (2/11)	Depression (1/10)
	CAS (5/8)	GTCS (3/6)			DYST (8/11)	Dysarthria (6/10)
	Dysarthria (1/8)	Psychiatric symptoms (1/6)			Gait ataxia (5/11)	Gait ataxia (6/10)
		Tremor (1/6)				GTCS (1/10)
Additional symptoms at follow-up	Ataxia (6/8)	Chorea (4/6)	Chorea (1/2)	Apraxia (3/3)	Chorea (7/11)	Anxiety (1/11)
	Cachexia (2/8)	CI (6/6)	Dysarthria (2/2)	Cachexia (3/3)	Dysarthria (11/11)	Bradykinesia (1/10)
	Dysarthria (6/8)	DYSP (3/6)	DYSP (2/2)	CCAS (3/3)	Dysmetria (11/11)	Chorea (4/10)
	DYSP (5/8)	DYST (3/6)	HL (1/2)	Chorea (2/3)	DYST (5/11)	CI (3/10)
	UI (3/8)	HL (1/6)	Psychiatric symptoms (2/2)	Dysarthria (3/3)	EMA (10/11)	Dysmetria (4/10)
		Parkinsonism (5/6)	Tremor (1/2)	DYSP (3/3)	Gait ataxia (10/11)	DYSP (2/10)
		Tremor (2/6)		DYST (3/3)	Parkinsonism (4/11)	DYST (2/10)
		UMNS (5/6)		Gait Ataxia (3/3)	PR (5/11)	Gait Ataxia (10/10)
				Palilalia (3/3)	Tremor (1/11)	GTCS (2/10)
				Parkinsonism (3/3)		Insomnia (1/10)
				PR (1/1)		Nystagmus (2/10)
				PS (1/1)		Postural tremor (2/10)
				UI (3/3)		PR (1/10)
						Psychiatric symptoms (1/10)
						UI (1/10)
Neuroimaging						
MRI	CA (8/8)	CA (5/5)	CA (2/2)	CA (1/1)	CA (10/11)	CA (10/10)
	Mol et al. 2020. (n=9)	Ravel et al. 2021. (n=9)	Pakdaman et al. 2021 Family A (n=4)	Pakdaman et al. 2021 Family B (n=2)	Pakdaman et al. 2021 Family C (n=1)	Current case series (n=3)
Mean age of onset		56 (32–84)	47 (40–52)	50 (30–69)	48	50 (32–61)
Presenting symptoms	N/A	Cerebellar syndrome (1/9)	CI (1/4)	Dysarthria (1/2)	CI (1/1)	Ataxia (3/3)
		CI (3/9)	Depression (1/4)	Gait ataxia (1/2)	Psychiatric symptoms (1/1)	Dysarthria (2/3)
		Gait ataxia (4/9)	Dysarthria (2/4)			DYSP (1/3)
		Psychiatric symptoms (1/9)	Gait ataxia (1/4)			Tremor (1/3)

Table 2 (continued)

Additional symptoms at follow-up	CI (9/9)	Babinski (1/9)	CCAS (1/4)	Dysarthria (1/2)	Dysphagia (1/1)	Abnormal sensation and proprioception (1/3)
	Chorea (5/9)	Chorea (1/9)	CI (2/4)	Encephalopathy (1/2)	Gait ataxia (1/1)	Bradykinesia (1/3)
	Dysarthria (8/9)	CI (8/9)	Dysarthria (3/4)	EMA (1/2)		CI (1/3)
	Gait ataxia (8/9)	Dysarthria (2/9)	Dysphagia (2/4)	Gait ataxia (1/2)		Dysmetria (2/3)
	Gaze palsy (4/9)	DYSP (2/9)	Encephalopathy (1/4)	Gait disturbance (1/2)		EMA (2/3)
	Parkinsonism (3/9)	DYSP (1/9)	EMA (1/4)	Psychiatric symptoms (1/2)		Hypertonia (2/3)
	Saccadic pursuit (4/9)	EMA (3/9)	Gait ataxia (2/4)			Muscle wasting (1/3)
	Upper limb ataxia (3/9)	Gait ataxia (8/9)	PS (1/4)			PR (2/3)
		PR (3/9)	UI (1/4)			Tremor (2/3)
		Psychiatric symptoms (6/9)				
		UI (1/9)				
Neuroimagimg						
MRI	CA (9/9)	CA (8/9)	CA (4/4)	CA (2/2)	CA (1/1)	CA (3/3)

CCAS cerebellar cognitive affective syndrome, *CA* cerebellar atrophy, *CAS* cognitive affective syndrome, *CI* cognitive impairment, *DYSP* dysphagia, *DYST* dystonia, *EMA* eye movement abnormalities, *GTCS* generalised tonic–clonic seizures, *HL* hearing loss, *MRI* magnetic resonance imaging, *PR* pathologic reflex, *PS* pyramidal signs, *UI* urinary incontinence, *UMNS* upper motor neuron signs

is not considered part of the classic cerebellar signs observed in SCAs but is commonly associated with other conditions such as essential tremor (ET) and Parkinson's disease (PD).

In our series rest tremor of a Parkinsonian type, was present in two patients and in case three was combined with mild parkinsonian signs including rigidity and bradykinesia as and upper limb action tremor. De Michele et al. reported patients with Parkinsonism and one case of tongue tremor and one case of mild postural tremor [17], Lieto et al. reported one case of head tremor [3], and Cocozza et al. reported two cases of postural tremor [19], in association with SCA48. We propose that tremor, including Parkinsonian rest tremor should be considered in the clinical spectrum of SCA48. Such patients may easily be misdiagnosed as Parkinson's disease or Multiple systems atrophy.

Brain MRI in all patients showed diffuse cerebellar atrophy, affecting both the vermis and cerebellar hemispheres (Fig. 1 – 1a, 2a, 3a), with the most significant atrophy affecting the posterolateral lobules shown in (Fig. 1 – 1c, 2c, 3c). T2-weighted images showed signal hyperintensities in the dentate nuclei that has been associated with previous SCA48 reports (as shown in Fig. 1 – 2b, 3b) [3, 11, 20]. Neuroimaging findings in our patients are similar to those reported in previous studies [1–4, 17, 19, 20].

There have been several different pathogenic variants of *STUB1* reported in the literature. Frameshift, deletion, missense, nonsense, and duplication variants have all been identified [1–4, 17, 18] either de novo [21] or more commonly inherited from one parent, with no specific region of *STUB1* gene responsible for SCA48 (Fig. 2). Pathogenic *STUB1* variant expression is predominantly in the cerebellum and frontal cortex [22] where impairment in function can lead to the signs seen in patients with SCA48. In our case series, three heterozygous *STUB1* variants were identified, two of which were novel as previously summarised above. The two novel heterozygous variants, 1) a canonical splice variant (c.669 + 1G > A) and, 2) a frameshift variant [c.327_328insCT, p.(Tyr110Leufs*21)] are shown in Fig. 2 in patients one and three respectively. In clinical phenotyping, patients showed clinical features of SCA48 with additional features such as dysarthria, dysmetria, chorea and neuropsychiatric symptoms [3]. The genetic summary for *STUB1* variants is included in Table 3.

Inheritance modes of *STUB1* variants are not fully understood with some evidence suggesting there is autosomal dominant inheritance [1, 18]. Incomplete penetrance associated with SCA48 has been shown where heterozygous carriers of the *STUB1* variants have been unaffected even in old age, but it could also be a reflection

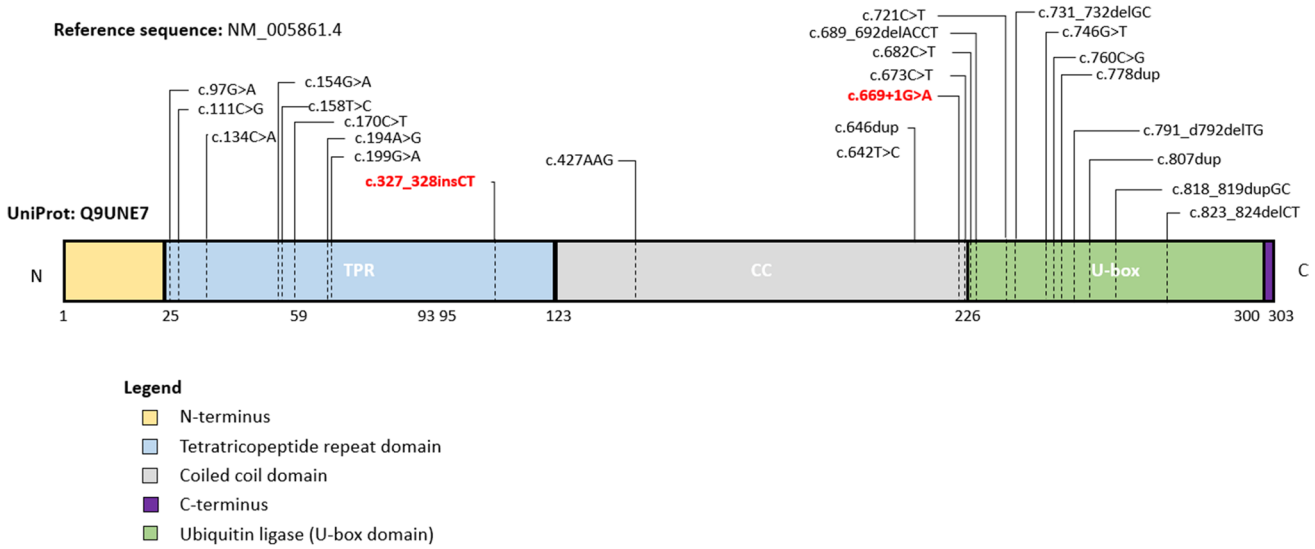


Fig. 2 Scheme of CHIP protein and its major domains; previously reported *STUB1* mutations resulting in SCA48 are in black, whereas the novel mutations discussed in this case series are reported in red; their location in the protein is shown. (De Michele et al., 2019; Landrum MJ, 2018 Jan 4; Lieto et al., 2020; Palvadeau et al., 2020) Adapated from (De Michele & Santorelli, 2021

Table 3 Genetic summary for *STUB1* variants

Patient	Transcript reference	hg38	Codon variant	Amino acid change/ Genomic change	POPmax	ACMG-AMP classification
Patient 1	NM_005861.3	-	c.669 + 1G > A	g.732077G > A	NR	Likely pathogenic
In silico prediction*						
Predicted to disrupt the canonical splice donor site for exon 5 and expected to abolish the canonical acceptor/donor splicing site resulting in alteration of function of the *STUB1* gene product. is a frameshift mutation, which has been thought to cause a loss of function, possibly enhanced by nonsense mediated mRNA decay or through inducing a toxic dominant gain of function in the protein [1]. Additionally, some frameshift mutations are predicted to result in a premature stop codon in the U-box domain. Insertion/deletion mutations are believed to affect the highly conserved resides within the TPR and U-box domains leading to a loss of function [3]						
Patient 2	NM_005861.4	16:732181	c.689_692del	p.(Tyr230Cysfs*9)	NR	Pathogenic
In silico prediction*						
Classified as a pathogenic variant in previous studies as it affected residues in the U-box domain where it is likely to lead a complete loss of protein by nonsense-mediate decay of the mutant mRNA [16]						
Patient 3	NM_005861.4	16:731319	c.327_328insCT	p.(Tyr110Leufs*21)	NR	Likely pathogenic
In silico prediction*						
Located in the TPR domain of CHIP which is essential for ubiquitination. It affects the TPR domain of CHIP that is critical for proteasomal degradation and maintaining CHIP function resulting in alteration of function of the *STUB1* gene product						

ACMG-AMP American College of Medical Genetics and Genomics—Association for Molecular Pathology (version: 8.4.7 from Varsome), *hg38* human reference genome, *NR* allele not previously reported, *POPmax* maximum allele frequency in each reference population from 1000GP, ExAC, gnomAD and ESP

* = Meta SVM, Meta LR and M-CAP in silico prediction ("D" = deleterious, "T" = tolerated)

of diversity in the expression of different variants, given the wide range of age of onset of symptoms [9, 18]. Incomplete penetrance of *STUB1* may also be due to an interaction with expansions of the *TBP* gene responsible for SCA17. It has been shown that the combination of intermediate *TBP* expansions and *STUB1* pathogenic variants is found in almost all manifesting intermediate TBP expansion carriers [9]. This interaction is bidirectional and intermediate *TBP* expansions are found in 40% of probands with *STUB1* variants, with longer TBP repeats predicting faster progression and more cognitive decline [23]. Nevertheless, *STUB1* variants can manifest disease in the absence of *TBP* expansions, as identified in our three cases, supporting the notion that ATX-*STUB1* [24] SCA48 exists as a monogenic disease, albeit with potential for disease modification by *TBP* expansions [23].

In summary, we report the clinical, radiological, and genetic findings of three new unrelated Australian patients with *STUB1* variants, including 2 novel pathogenic variants, without *TBP* expansions, resulting in SCA48. Upper limb resting tremor and Parkinsonian signs are an important feature in SCA48 and may assist in earlier clinical suspicion and subsequent genetic testing. Our cases also highlight the diverse clinical spectrum of SCA48. We also highlight the identification of two novel heterozygous pathogenic *STUB1* variants causing SCA48.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12311-024-01762-2.

Author Contribution Y.Z and S.T. wrote the main manuscript text. S.T., M.K., and P.K. provided clinical notes for the case series. All authors reviewed the manuscript.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics Approval All participants provided written informed consent ($n=3$) and the study was approved by the Ethics Committee at The University of Notre Dame, Australia.

Conflict of Interest The authors declare no competing interests.

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