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Expanding the clinical spectrum of *STIP1* homology and U-box containing protein 1-associated ataxia

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Abstract

Background *STUB1* has been first associated with autosomal recessive (SCAR16, MIM# 615768) and later with dominant forms of ataxia (SCA48, MIM# 618093). Pathogenic variations in *STUB1* are now considered a frequent cause of cerebellar ataxia.

Objective We aimed to improve the clinical, radiological, and molecular delineation of SCAR16 and SCA48.

Methods Retrospective collection of patients with SCAR16 or SCA48 diagnosed in three French genetic centers (Montpellier, Strasbourg and Nancy).

Results Here, we report four SCAR16 and nine SCA48 patients from two SCAR16 and five SCA48 unrelated French families. All presented with slowly progressive cerebellar ataxia. Additional findings included cognitive decline, dystonia, parkinsonism and swallowing difficulties. The age at onset was highly variable, ranging from 14 to 76 years. Brain MRI showed marked cerebellar atrophy in all patients. Phenotypic findings associated with *STUB1* pathogenic variations cover a broad spectrum, ranging from isolated slowly progressive ataxia to severe encephalopathy, and include extrapyramidal features. We described five new pathogenic variations, two previously reported pathogenic variations, and two rare variants of unknown significance in association with *STUB1*-related disorders. We also report the first pathogenic variation associated with both dominant and recessive forms of inheritance (SCAR16 and SCA48).

Conclusion Even though differences are observed between the recessive and dominant forms, it appears that a continuum exists between these two entities. While adding new symptoms associated with *STUB1* pathogenic variations, we insist on the difficulty of genetic counselling in *STUB1*-related pathologies. Finally, we underscore the usefulness of DAT-scan as an additional clue for diagnosis.

Keywords Recessive · Dominant · Ataxia · *STUB1* · SCAR16 · SCA48

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Introduction

Spinocerebellar ataxias (SCA) form a wide family of inherited progressive ataxias characterized by gait impairment, dysarthria, and other cerebellar signs, either in isolation or in combination with the involvement of other parts of the nervous system [1, 2]. Among hereditary ataxias, autosomal recessive cerebellar ataxias (ARCA) represent a heterogeneous group of neurodegenerative disorders. The high diversity of causes is illustrated by the flourishing publications of the last decades [3, 4]. It also led to an urgent need

for diagnostic algorithms to predict the molecular diagnosis based on the clinical phenotype of a patient [5–7]. Next-generation sequencing (NGS) has been of great help to decipher complex pathologies in the last decade. As such, dozens of genes have been associated with spinocerebellar ataxias (SCAs) [8]. The routine diagnostic integration of such technology has also expanded the mutation spectrum and inheritance modalities of less common genes.

In 2013, Shi et al. used whole-exome sequencing to identify homozygous and compound heterozygous pathogenic variations in *STUB1* (coding for CHIP, Carboxy terminus Hsp70 Interacting Protein) in the affected members of three unrelated Chinese families with progressive spinocerebellar ataxia 16 (SCAR16; MIM# 615768) [9, 10]. Patients presented with adolescent-onset ataxia and cerebellar atrophy, sometimes associated with mild cognitive impairment. Subsequently, *STUB1* mutations were found in patients with ataxia and hypogonadotropic hypogonadism, consistent with a diagnosis of Gordon Holmes syndrome (MIM# 212840) [11].

In 2018, *STUB1* was also associated with a dominant form of spinocerebellar ataxia (SCA48), primarily based on the study of a large multigenerational family [12] (SCA48; MIM#618093). Affected members had late-onset, progressive spinocerebellar ataxia associated with cognitive decline. Anxiety was present in half of them. Of note, some had only cerebellar atrophy or cognitive symptoms without symptomatic ataxia. Other groups subsequently reported additional SCA48 cases, revealing a more complex disease with psychiatric and cognitive features, movement disorders such as chorea, parkinsonism and dystonia, sphincter anomalies and epilepsy [13–16].

The existence of a continuum between SCAR16 and SCA48 has been stated but is not firmly established [17]. Specific features seem to distinguish both diseases as, for example, the high frequency of cognitive decline in SCA48. Moreover, as two mode of inheritance exist for the same gene, both diagnosis and genetic counselling are complex. Finally, as the spectrum of *STUB1*-related symptoms appears to be wide, it is unclear what signs are really associated with the diseases and which ones are fortuitous.

Here, we report the clinical, neuroimaging, and genetic study of thirteen additional patients from seven unrelated non-consanguineous French families with spinocerebellar ataxia caused by heterozygous or compound heterozygous pathogenic variations in *STUB1*.

Patients and methods

Clinical and biological analyses

Patients were identified within a cohort of patients with movement disorders who had consulted in neurology departments. We retrospectively collected clinical and radiological data. Patients underwent neurological examination by a neurologist specialized in movement disorders and brain MRI. When necessary, they underwent electroencephalogram (EEG), Positron Emission Tomography scan (PET-scan), and/or dopamine transporter scan (DAT-scan). Functional disability related to ataxia was evaluated with the Spinocerebellar Degeneration Functional Score (SDFS: 0: no functional handicap; 1: no functional handicap but signs at examination; 2: mild, able to run; 3: moderate, unable to run; 4: severe, walking with one stick, unlimited walking; 5: walking with two sticks; 6: unable to walk, requiring a wheelchair; 7: bedridden) [18]. The Scale of Assessment and Rating of Ataxia (SARA, score from 0 to 40) was used to evaluate the severity of cerebellar ataxia [19]. Prior to this study, at least one affected individual per family has had a genetic test for expanded pathological repeats associated with SCAs (SCA1, SCA2, SCA3, SCA6, SCA7) and FRDA (Friedreich's ataxia).

Genetic studies

The proband of families 1, 6 and 7 underwent targeted multi-gene sequencing (NextSeq Sequencing System, Illumina, flow cell) to investigate the coding exons and flanking intronic regions of 392 genes linked to inherited ataxia, alone or associated with other movement disorders anomalies, as previously described using HiSeq 4000 Sequencing System (Illumina) [20].

The affected sister in family 1 (patient 2) underwent clinical exome sequencing using a TruSight One panel (4813 genes) on an Illumina MiSeq platform variant calling and downstream bioinformatic analyses were based on already published pipeline [21–23].

Members of families 2–5 were analysed using the Illumina TruSight One expanded panel (6699 genes) on an Illumina NextSeq 550 platform. Alignment and variant annotation were carried out using an already reported bioinformatics pipeline, based on GATK best practices and ANNOVAR [24]. The software programs “Variantstudio” (www.illumina.com/variantstudio), “Nenufaar” (<https://github.com/beboche/nenufaar>) and “MobiDL” (<https://github.com/mobidic/MobiDL>) were used for in silico analysis.

When available, DNA of family members were then studied by Sanger sequencing.

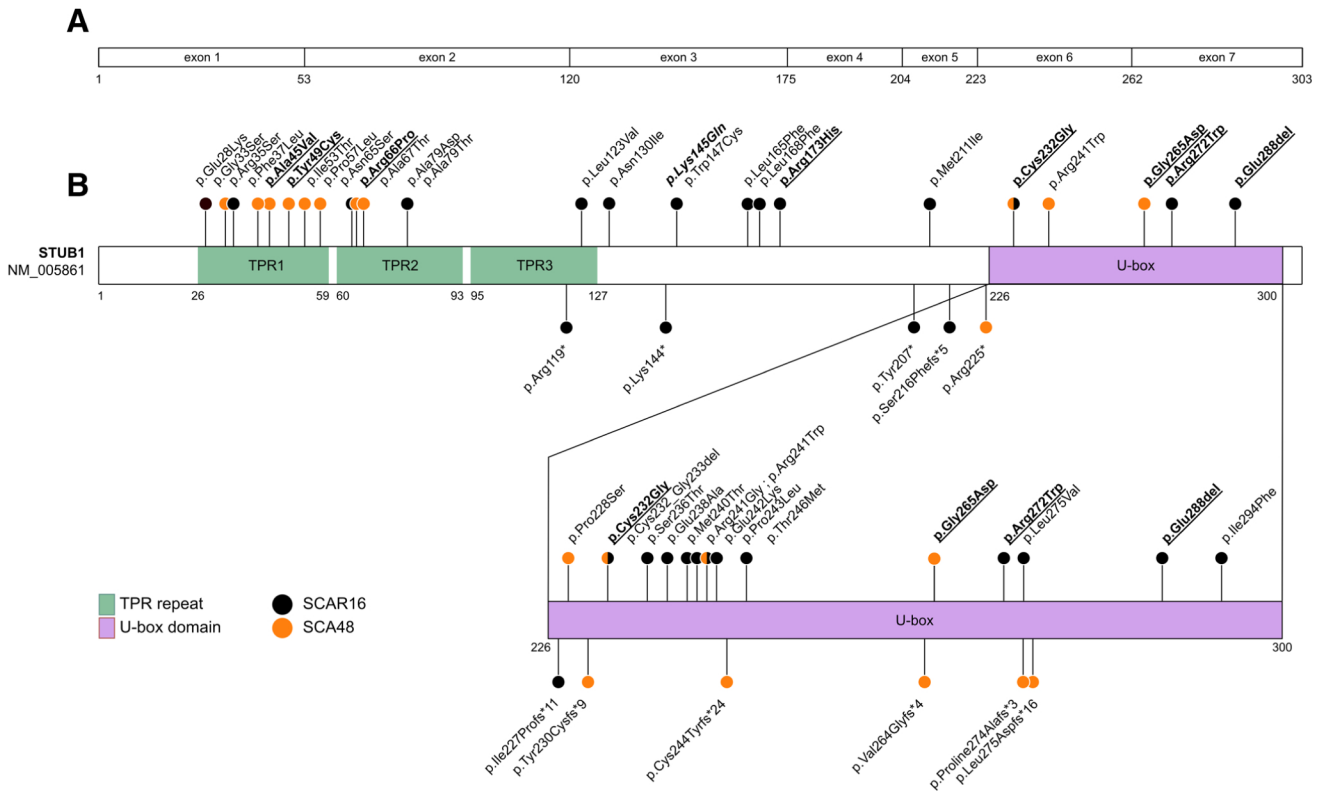


Fig. 1 *STUB1* variations associated with SCA48 and SCAR16. **a** The gene consists of seven exons. **b** Schematic representation of *STUB1* variations based on protein position. Variations underlined are novel variations. Variations in bold are those describe in this study.

The p.(Lys145Gln) and p.(Glu232Gly) variants have already been reported. Orange and black dots represent variations associated with SCA48 and SCAR16, respectively

Results

We identified four SCAR16 and nine SCA48 patients from two SCAR16 and five SCA48 unrelated French families (Table 2, Fig. 1). Clinical features of all our patients are detailed in Table 1 and the pedigrees are shown in Fig. 2a. In all patients, cerebellar ataxia and/or dysarthria was already present at onset, and half presented with ocular movement abnormalities (nystagmus and/or saccadic pursuit, Video 1–5 in Supplementary material). All patients presented a moderate to marked cerebellar atrophy, more prominent in the cerebellar vermis (Fig. 3).

SCAR16

The mean age at onset of symptoms was 30 ± 14.4 years (range 14–45). The severity of ataxia was heterogeneous, ranging from moderate (SARA 12/40, patient 4) to severe (SARA 40/40, patient 2) with a mean SARA score of 23/40.

Family 1

Patient 1, born from healthy unrelated parents, had slowly progressive ataxia, upper limbs dystonia, muscular atrophy of the hands and pyramidal signs. Age at onset was 22 years and the ability to walk was lost at 24. Patient 2, her sister, developed symptoms at 14 years. She had an extremely severe phenotype with generalized dystonia, areflexia, profound hypotonia, amyotrophy and dyskinetic movements. She had no verbal communication and presented with severe intellectual disability and depressive mood. On clinical examination, she also had severe joint contractures, left extensor plantar reflexes and global deep tendon areflexia. She also had pronounced olivo-ponto-cerebellar atrophy. Notably, she presented with mutism and aggressiveness. EEG showed diffuse bilateral slowing between crises whereas rhythmic theta background activity was seen in her sister (Figure S2).

Family 2

Patient 3, also born from asymptomatic and unrelated parents, had mild and slowly progressive gait and upper limb

Table 1 Clinical and imaging findings of STUB1 variations carriers

Family	Family 1		Family 2		Family 3		Family 4		Family 5		Family 6		Family 7	
	SCAR16	SCAR16	SCAR16	SCAR16	SCAR16	SCAR16	SCA48	SCA48	SCA48	SCA48	SCA48	SCA48	SCA48	SCA48
Subject	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	
Sex	F	F	F	F	M	F	M	M	F	M	F	F	F	F
Age at diagnosis, y	33	49	51	48	44	68	32	72	62	73	48	84	53	
Age at first symptom, y	22	14	45	39	31	57	20	60	47	60	48	76	51	
First detected signs/symptoms	Ataxia	Cerebellar syndrome	Dysarthria	Dysarthria	Ataxia	Cognitive dysfunction	Myoclonus	Ataxia	Walking difficulty	Ataxia	Apathy, cognitive dysfunction and behavioural disorder	Cognitive dysfunction	Cerebellar syndrome	
Family history	+	+	+	+	+	+	-	+	+	-	+	+	+	
Intellectual disability	-	+	-	-	-	+	-	-	-	-	-	+	-	
Symptoms during evolution														
Gait ataxia	+	n.a	+	+	+	+	+	+	+	+	+	n.a	+	
Dysarthria	+	n.a	+	+	+	+	-	-	+	+	+	n.a	-	
Cerebellar dysfunction	+	+	+	+	+	+	+	+	+	+	+	n.a	+	
Eye movement abnormalities	Nystagmus, saccadic pursuit	-	Saccadic pursuit	-	Saccadic pursuit	-	Nystagmus, saccadic pursuit	-	-	Nystagmus	-	-	-	
SARA score	33	40	7.5	12	18	n.a	28	24	28	24	8	n.a	33	
SDFS score	4	7	1	1	2	3	3	3	3	3	2	n.a	7	
Dystonia/tremor	Tremor, dystonia (fingers, hands)	Generalized dystonia	-	-	Dystonia (foot, upper limb)	-	-	-	-	-	-	n.a	-	
Chorea	-	-	-	-	+	-	-	-	-	+	-	n.a	-	
Increased tendon reflexes	-	-	+	-	-	-	-	+	+	-	-	n.a	+	

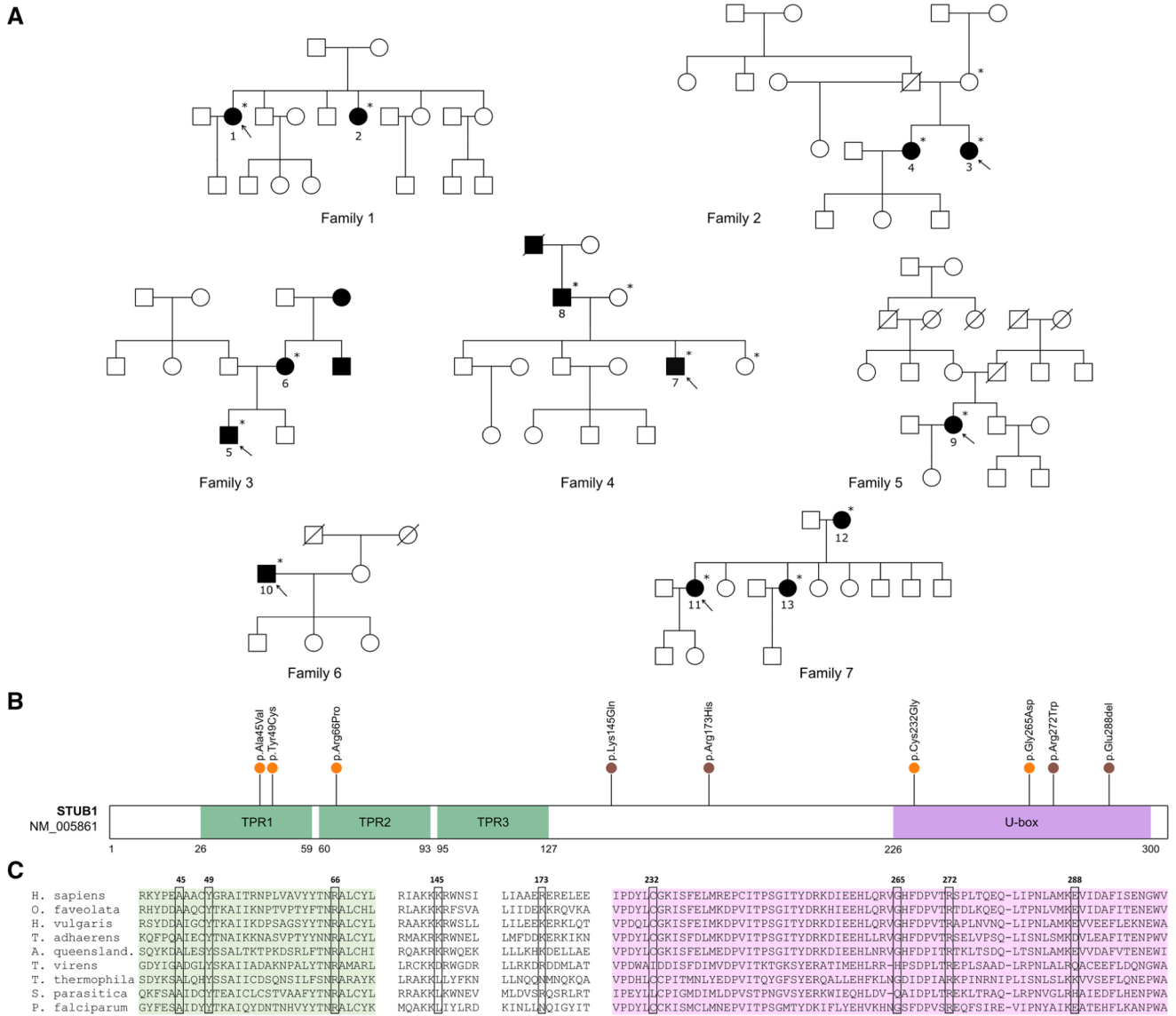


Fig. 2 Pedigrees of *STUB1* index patients, and location and conservation of *STUB1* variations. **a** Affected individuals are represented by black symbols. Index cases are indicated by an arrow. Individuals analysed for presence or absence of the variation are indicated by an asterisk (*). **b** The gene consists of seven exons. The *STUB1* protein (CHIP) harbours three domains: an amino-terminal 3-tetratricopep-

ptide repeat domain (TPR), a highly charged middle domain, and a carboxy-terminal U-box domain. Orange and black dots represent variations associated with SCA48 and SCAR16, respectively. **c** Protein conservation of CHIP in human and other species. *O. faveolata*, *H. vulgaris*, *T. adhaerens*, *A. queenslandica*: distant metazoa; *T. vires*: fungi; *T. thermophila*, *S. parasitica*, *P. falciparum*: protists

family 4. He was primarily considered as a sporadic case with early adulthood onset ataxia associated with myoclonus. Examination of his father, initially reported as unaffected revealed a clear ataxic gait. Sanger sequencing confirmed the presence of the variation in the proband's father. His deceased paternal grandfather was also reported as having late-onset gait ataxia. The missense variation c.146A > G/p.(Tyr49Cys), initially found in the proband of family 7, was also identified in other affected family members (Fig. 2).

Two rare missense variants of unknown significance were also identified (families 5 and 6): c.134C > T/p.(Ala45Val) and c.794G > A/p.(Gly265Asp), respectively. Alanine 45, located in the TPR1 domain, is highly conserved in all eukaryotes, while Glycine 265 of the U-box domain, is conserved up to metazoa (Fig. 2). Both are predicted as pathogenic. Clinical history, while non-specific, was very consistent with SCA48 pathology (ataxia, cognitive decline, behavioural disorder, associated with dysphagia for patient 5 and dopaminergic alteration for patient 6). The segregation

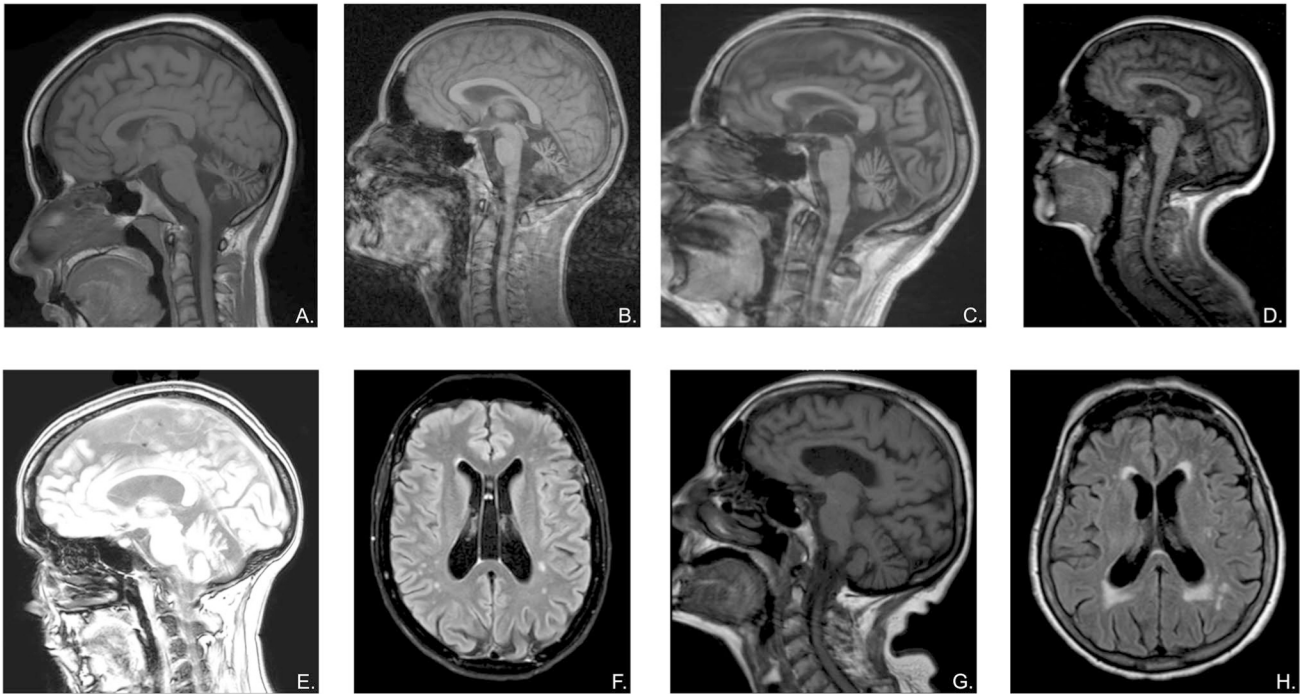


Fig. 3 Cerebral magnetic resonance imaging in *STUB1* ataxia. **a–d** Brain MRI abnormalities in patient 1 (SCAR16), 7, 10 and 13 (SCA48) showing cerebellar atrophy (sagittal T1). **e–f** Brain MRI abnormalities in patient 11 (SCA48). **e** Cerebellar atrophy (T1). **f**

Periventricular white matter hyperintensities (axial FLAIR). **g, h** Brain MRI abnormalities in patient 12. **g** Cerebellar atrophy (sagittal T1). **h** Periventricular white matter hyperintensities (axial FLAIR)

Table 2 *STUB1* variations identified in this study

Family	cDNA change	Exon	Protein change	Proteic domain	Pathogenicity predictions	GnomAD (htz/hom)	ACMG classification	Ref	Pathology
1	c.814C>T	7	p.(Arg272Trp)	U-box	3/3	7/0	Likely pathogenic		SCAR16
	c.863_865delAGG	7	p.(Glu288del)	U-box	–	1/0	Likely pathogenic		SCAR16
2	c.433A>C	3	p.(Lys145Gln)	(helix)	2/3	171/1	Pathogenic	[11, 25, 27]	SCAR16
	c.518G>A	3	p.(Arg173His)	–	2/3	1/0	Likely pathogenic		SCAR16
3	c.694 T>G	6	p.(Cys232Gly)	U-box	3/3	0/0	Likely pathogenic	[25]	SCA48
4	c.197G>C	2	p.(Arg66Pro)	TPR 2	3/3	0/0	Likely pathogenic		SCA48
5	c.134C>T	1	p.(Ala45Val)	TPR 1	3/3	0/0	VUS		SCA48
6	c.794G>A	7	p.(Gly265Asp)	U-box	3/3	0/0	VUS		SCA48
7	c.146A>G	1	p.(Tyr49Cys)	TPR 1	3/3	1/0	Likely pathogenic		SCA48

htz heterozygous, *hom* homozygous, *Ref* Reference, *TPR* tetratricopeptide repeat, *SCA48* spinocerebellar ataxia 48, *SCAR16* spinocerebellar ataxia recessive 16, *VUS* variant of unknown significance

of the variant has not been evaluated as the proband's parents were deceased in both families.

Discussion

Herein, we report thirteen patients (four with SCAR16 and nine with SCA48) affected by spinocerebellar ataxia related to CHIP dysfunction.

STUB1-associated disorders are an emerging group of SCA with a recent estimated frequency of 7% among dominantly inherited cerebellar ataxias [16]. In general, the recessive (SCAR16) and dominant (SCA48) form of *STUB1* pathogenic variations are considered as having different associated phenotype, characterized by a more juvenile and severe disease with complex ataxia in SCAR16 and by a later onset ataxia with cognitive involvement in SCA48.

STUB1 recessive pathogenic variations were reported in patients with a variable age at onset of ataxia, frequently associated with mild cognitive impairment, various degrees of sensory axonal neuropathy, myoclonus, choreoathetosis, dystonia and pituitary dysfunction [25–28]. Dementia has also been reported, both in later stages [29] and as an presenting symptom [30], as well as a variety of different movement disorders [31]. Altogether, these data suggested a phenotypic continuum for SCAR16, from isolated ataxia to multisystemic neurodegeneration and hypogonadism [11, 17, 32]. However, existence of a spectrum shared between SCAR16 and SCA48 remained unclear.

In our series, all patients had ataxia associated with cerebellar atrophy, in agreement with previously reported cases [14–17, 33, 34]. Early mean age at onset and associated features such as dystonia, parkinsonism, increased tendon reflexes, urinary incontinence, and cognitive impairment were consistent with published cases and shared with both the recessive and the dominant forms, suggesting a clinical continuum between SCAR16 and SCA48. In particular, cognitive decline was present in eight out of nine SCA48 patients and was also identified in two SCAR16 patients, one with word-finding difficulties and the other with intellectual disability associated with mutism, suggesting that cognitive decline is not unique to SCA48 patients.

Even if *STUB1*-related diseases should be considered as a single clinical continuum, recurrence of manifestations seems to distinguish SCA48 from SCAR16. In addition to a higher prevalence of cognitive decline in SCA48, and despite mean age at onset is variable in both SCAR16 and SCA48, it appears that onset reaches older ages in SCA48 (up to 76 years in our study). Psychiatric manifestations were frequent in our cohort: depressive mood (2/13), aggressiveness (2/13), and mutism (2/13), but was present (mutism) in only one patient with a recessive form. None of our SCA48 patients had epilepsy or EEG anomalies while two SCAR16 patients had. This is consistent with previous report that epilepsy would be fortuitous in SCA48 patients while part of SCAR16 symptoms [17]. Of note, myoclonus was detected in one of our SCA48 patients.

The families described herein expand the clinical spectrum of the original *STUB1* mutations.

Our study underscores the high interfamilial (e.g. between families 1 and 7) and intrafamilial (e.g. family 3) variability. Also, we report a case of mild ataxia with late age at onset in a SCAR16 family, suggesting wider range of severity than initially described. Moreover, even though psychiatric manifestations are known to be at the forefront of SCA48, we report aggressiveness and mutism as part of the psychiatric spectrum of SCA48 (patient 6 and 13). Of note, periventricular white matter hyperintensities were found in two SCA48 patients, but, as they are non-specific, it is difficult to associate them with the *STUB1*-related spectrum. Finally,

we present two SCA48 patients with marked dopaminergic alteration. Extrapyramidal signs had indeed been reported in previous studies but with few available imaging data [13]. This raises the question of potential intervention by L-dopa treatment in this disease.

The loss-of-function hypothesis does not explain the healthy status of the carrier parents in the SCAR16 families. It is difficult to infer firm genotype–phenotype correlations from our and previous studies, although it appears that pathogenic SCA48 variations are more likely localized in functional domains (TPR, U-box), suggesting a possible loss of function mechanism. Regarding SCAR16, Madrigal et al. proposed that mutations in certain

CHIP domains could bring to specific phenotypic manifestations [32, 35].

In addition, some pathogenic variations may be hypomorphic, such as the p.(Lys145Gln) variation, consistently associated with a later age at onset, and may be modulated by *cis*-variants. Several genes have already been associated with both recessive and dominant forms of ataxia. As an example, *SPTBN2* pathogenic variations lead to both SCA5 and SCAR14 [36]. *KIF1A* and *SPG7* pathogenic variations have also been associated with both recessive and dominant forms of ataxia [37, 38]. Our work now identifies the first *STUB1* variation (p.(Cys232Gly)) associated with two modes of inheritance since we identified this mutation in a three-generation dominant family and it was previously reported by Chiu and collaborators in a SCAR16 family [25]. In their study, the father who carried the pathogenic variation was reported as asymptomatic. As this mutation was identified in compound heterozygosity with the p.(Arg241Trp) mutation in the proband, it would be interesting to confirm that the father will not develop any neurological symptom at an older age. This raises questions about the precise pathophysiology of *STUB1* mutations. Recently, Roux and collaborators suggested a possible synergistic effect with variants in *AFG3L2*, *PRKCG*, and *TBP*, to explain this phenotypic heterogeneity [16].

Following the discovery of the association of the p.Cys232Gly pathogenic variation with both dominant and recessive forms, we insist on the difficulty for the genetic counselling in this disease, in particular in SCAR16 families. Indeed, diagnosis of SCAR16 in a family may lead to pre-symptomatic diagnosis in a parent for certain pathogenic variations. Moreover, as age at onset can be delayed even within a family, segregation analysis of a VUS in non-symptomatic relatives is not recommended since no conclusion will be reached in case he/she is a carrier.

As proposed by Hayer and colleagues, it is increasingly clear that *STUB1* dysfunction leads to a continuum of pathologies consistent with highly selective neurodegeneration [12, 34]. Interestingly, it can result either in isolated ataxia with cerebellar atrophy or in more complex clinical

features with occasional movement disorders, cognitive decline, psychiatric features and hypogonadism.

In summary, the clinical presentation of our cases was consistent with the *STUB1*-related multisystem degeneration. We also extend the clinical spectrum insisting the high intrafamilial variability and recurrent psychiatric manifestations, especially aggressiveness and mutism. We also describe a mild form of SCAR16. Epilepsy seems not to be associated with SCA48. DAT-scan should be considered for SCA48 and SCAR16 patients to assess dopaminergic alteration and to suggest L-dopa intervention. Finally, careful evaluation by a trained neurologist of the proband's family is essential for both variant interpretation and possible care. Moreover, consultation with a trained medical geneticist is highly encouraged to deliver proper genetic counselling.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the local ethics committee.

Consent to participate Written informed consent was obtained from all individuals contributing a blood sample for molecular investigations and the local ethics committees approved the study. A distinct consent form was also signed if videos were recorded.

Consent for publication The final manuscript has been read and approved by all authors who accepted full responsibility for the design and undertaking of the original article. They had access to the data and controlled the decision to publish.

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