

RESEARCH ARTICLE

ATXN8OS Intermediate Expansion Acts as a Genetic Modifier in Spinocerebellar Ataxia Type 48 (SCA48/*STUB1*)

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ABSTRACT: Background: Association between monoallelic *STUB1* variant and expanded *ATXN8OS* alleles was recently reported, suggesting a pathogenic interaction that may influence spinocerebellar ataxia type 48 (SCA48) phenotype.

Objectives: We investigated the frequency and clinical impact of *ATXN8OS* in a large cohort of *STUB1* carriers compared to individuals with other ataxias and controls.

Methods: Ataxic individuals and controls from the SPATAX/BIOMOV cohorts (Paris Brain Institute) were screened for *ATXN8OS* and other CAG expansions using polymerase chain reaction (PCR)/repeat-prime PCR (RP-PCR) and *ExpansionHunter*. *STUB1* carriers underwent whole-genome or exome sequencing.

Results: Our cohort comprised 12 biallelic *STUB1* carriers (SCAR16) and 67 monoallelic *STUB1* carriers (SCA48) without other causative variants. *ATXN8OS* expansions (84–177 CTA/CTG repeats) were identified in seven SCA48 individuals (10.5%) who exhibited earlier onset (median age 28 vs. 47 years, $P < 0.001$) compared to other SCA48 individuals but with similar clinical presentation. *ATXN8OS* expansions were also found in two

healthy controls older than 50 years (2/286, 0.7%) and in eight index cases with autosomal dominant ataxia (8/400, 2%), including four carrying another molecular diagnosis without any effect on the phenotype. Other intermediate expansions were identified in individuals with SCA48: seven (10.5%) carried intermediate *TBP* alleles (40–46 CAG/CAA) without any effect on dementia prevalence; four carried intermediate *HTT* alleles (28–29 CAG); and three carried intermediate *ATXN1* expansions (38 CAG).

Conclusions: *ATXN8OS* intermediate expansion acts as a genetic modifier in SCA48 but not in other ataxias. Moreover, expanded intermediate alleles in neurodegenerative disease genes were present in one-third of SCA48 individuals. These alleles may increase polyglutamine burden, potentially saturating *STUB1* E3 ubiquitin ligase activity. © 2026 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: SCA48; SCA8; cerebellar ataxia; genetic modifier

The *STUB1* gene encodes the CHIP protein, an E3 ubiquitin ligase and co-chaperone implicated in protein quality control by targeting a wide range of chaperone substrates for proteasomal degradation.¹ *STUB1* was

initially associated with autosomal recessive spinocerebellar ataxia type 16 (SCAR16),² a progressive cerebellar ataxia starting in early adulthood and frequently associated with cognitive impairment and sensory

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neuropathy.² More recently, monoallelic pathogenic variants in *STUB1* have been linked to autosomal dominant spinocerebellar ataxia type 48 (SCA48).³ SCA48 is a progressive spinocerebellar ataxia but with a later onset in mid-adulthood (median age at onset ~40 years) associated with cognitive decline and psychiatric symptoms.^{3,4} In SCA48, a digenic inheritance model has been proposed, as *STUB1* variants are frequently reported in association with intermediate allele size of *TBP* (ie, 40–48 CAG/CAA repeats).⁵ *TBP* alleles exceeding 48 CAG/CAA repeats cause spinocerebellar ataxia type 17 (SCA17), a progressive adult-onset ataxia associated with cognitive and psychiatric manifestations.⁶ The co-occurrence of a monoallelic *STUB1* variant with an intermediate allele of *TBP* has been reported to confer a more severe phenotype of SCA48, with increased frequency of cognitive impairment and accelerated disease progression.⁷

A recent study focusing on SCA8/*ATXN8OS* reported that 20% of SCA8 individuals carried a pathogenic heterozygous *STUB1* variants and presented an earlier age at onset compared to the rest of cohort.⁸ *ATXN8OS* is a noncoding RNA gene located on the opposite strand of the *ATXN8* gene, which encodes a nearly pure poly-Q protein with unknown function.⁹ Pathogenic expansions in *ATXN8OS* have been associated with spinocerebellar ataxia type 8 (SCA8)¹⁰ characterized by slowly progressive adult-onset ataxia, cognitive impairment, sensory neuropathy, upper motor neuron involvement, and parkinsonism.¹¹ In SCA8, the pathogenic threshold for CTA/CTG repeat remains poorly defined. Normal alleles typically range from 15 to 50 CTA/CTG repeats.

Based on the reported associations between *STUB1* and repeat expansions in *ATXN8OS* and *TBP*, we systematically screened our *STUB1* cohort for exonic repeat expansions and investigated the cohort for alternative molecular diagnoses.

Patients and Methods

Study Participants

We included all individuals from the SPATAX (NCT00140829) and BIOMOV (NCT05034172) cohorts followed at the Paris Brain Institute (ICM) who presented cerebellar ataxia and carried at least one *STUB1* variant. Transmission mode was determined from pedigree; autosomal dominant inheritance was defined by vertical transmission, with at least one affected first-degree relative in two successive generations. Two additional cohorts from the SPATAX and BIOMOV studies were used to determine the frequency of *ATXN8OS* and CAG repeat expansions: a cohort of 400 index cases of autosomal dominant ataxia, with or without identified genetic cause, and a cohort of 286 healthy controls aged over 50 years.

All participants provided written informed consent, and blood samples were collected in accordance with

local French regulations (Paris Necker Ethics Committee approval [SPATAX RBM 01–29 and RBM 03–48 or BIOMOV NCT05034172]).

Genetic Analyses

The SCA8 locus was amplified by polymerase chain reaction (PCR) using the AccuPrime kit with Buffer A (Thermo Fisher Scientific, Waltham, MA, USA), a final concentration of 0.2 μM of each primer (SCA8-F3: TTTGAGAAAGGCTTGTGAGGACTGAGAATG and FAM-labelled SCA8-R4: FAM-GGTCCTTCATGTGAGAAACCTGGCT), 100 ng of genomic DNA in a 25 μL reaction volume, with 35 cycles of 94°C for 45 seconds, 55°C for 75 seconds, and 72°C for 2 minutes. For repeat-primed PCR (RP-PCR), we used the AccuPrime kit with Buffer A (Thermo Fisher Scientific), 1 μM ATTO565-labelled SCA8-R4 primer (ATTO565-GGTCCTTCATGTGAGAAACCTGGCT), 1 μM SCA8-P4CAG primer (TACGCATCCCAGTTTGAGACGCAGCAGCAGCAGCAGCA), 0.1 μM SCA8-P3R primer (TACGCATCCCAGTTTGAGACG), 100 ng of genomic DNA in 25 μL reaction volume, with 32 cycles of 95°C for 1 minute, 56°C for 1 minute, and 72°C for 2 minutes. Capillary electrophoresis was performed using the ABI 3730xl Genetic Analyzer (Thermo Fisher Scientific). Amplicon sizes were determined using *Peak Scanner* Software 2.0. PCR primers,¹⁰ and RP-PCR primers, as described in Krysa et al.¹² Individuals were first screened using PCR; homozygous and expanded (ie, >50 CTA/CTG repeats) alleles were subsequently confirmed using RP-PCR to verify allele sizes and exclude larger expansions. In controls, RP-PCR was used to detect large alleles, and a subset was tested by PCR to get the size distribution.

Whole-exome sequencing (WES) was performed using the NovaSeq 6000 or X Plus platforms (Illumina, San Diego, CA, USA) with 300 cycles, 150-bp paired-end reads after capture with at least the Twist RefSeq Exome (Twist Bioscience, San Francisco, CA, USA). Whole-genome sequencing (WGS) was performed using the NovaSeq 6000 with 300 cycles, 150-bp paired-end reads (Illumina). Reads were aligned to the hg38 human reference genome using the DRAGEN Germline Pipeline (Illumina). Repeat expansions were sized using *ExpansionHunter* (version 5.0.0) with the default parameters and repeat catalog without off-target regions, targeting the following CAG-repeat-containing genes: *AR*, *ATN1*, *ATXN1*, 2, 3, and 7, *CACNA1A*, *HTT*, and *TBP*; and the GGCCTG repeat in *NOP56*.¹³ *TBP* allele sequences were visualized using *REViewer*.¹⁴ Population reference data for *TBP*, *HTT*, and *ATXN1* repeat lengths were obtained from the STRipy database relying on a 1000 Genomes Project dataset.¹⁵ Variants were classified as pathogenic according to the American College of Medical Genetics (ACMG) classification.¹⁶

Statistical Analyses

Descriptive statistics were used to characterize the study population. Categorical variables (eg, genotype category and inheritance) are reported as frequencies and percentages. Continuous variables are presented as median and interquartile range (IQR) [Q1;Q3]. Group comparisons were performed using the Kruskal–Wallis test for continuous variables and Fisher’s exact test for categorical variables. For significant overall comparisons ($P < 0.05$), post hoc pairwise analyses were conducted using Wilcoxon rank-sum tests (continuous) or Fisher’s exact tests (categorical), with Holm’s correction for multiple comparisons. Associations between age at onset and protein domains were assessed using linear regression models. A threshold of P -value of 0.05 was used to determine statistical significance. Statistical analyses were performed using R (version 4.4.2),¹⁷ with graphs generated using ggplot2.¹⁸

Results

Absence of Alternative Molecular Diagnosis in Monoallelic *STUB1* Variant Carriers (SCA48)

Our cohort comprised 79 individuals from 53 families, including 50 women and 29 men (sex ratio 1.7), who presented cerebellar ataxia and carried at least one pathogenic *STUB1* variant (Fig. 1). Twelve individuals carried biallelic variants (SCAR16) and came from nine families. Geographic origin was predominantly France

($n = 67$) with other European ($n = 10$) and North-African ($n = 2$) ancestries (Table S1).

We investigated the 67 ataxic individuals from 44 families with a monoallelic pathogenic *STUB1* variant (SCA48) by short-read WGS ($n = 43$) or WES ($n = 24$) to exclude a second *STUB1* variant or alternative molecular diagnoses. No other causative variants were identified. Thirteen families exhibited clear autosomal dominant transmission with confirmed segregation of the *STUB1* variant across at least two consecutive generations; 43 families showed autosomal dominant inheritance without genetic documentation of two consecutive generations; 10 cases were isolated, and one suggested a possible autosomal recessive inheritance. Clinical and genetic data are provided in Table S1.

ATXN8OS Expansions in *STUB1* Carriers

The cohort was screened for *ATXN8OS* repeat sizes. *ATXN8OS* expansions were not identified in individuals who carried biallelic *STUB1* variants. However, among monoallelic *STUB1* variant carriers, 10.5% (7/67 individuals from six families) harbored an *ATXN8OS* expansion ranging from 84 to 177 CTA/CTG repeats and normal *TBP* alleles (35–37 CAG/CAA repeats). The frequency of an expanded *ATXN8OS* allele (>50 CTA/CTG repeats) was significantly higher in SCA48 compared to healthy controls older than 50 years (10.5% vs. 0.7%, 2/286, $P = 0.0001$, odds ratio [OR] = 15.6, 95% confidence interval (CI) [3.5–117.8]) (Fig. 3).

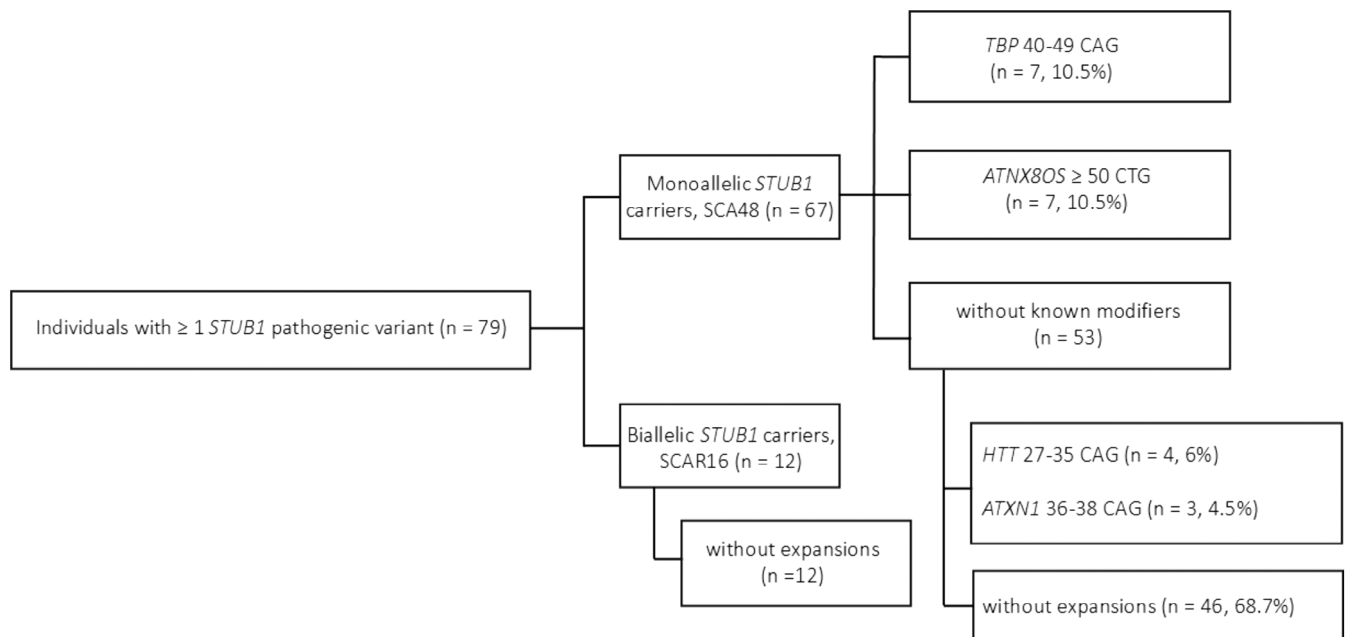


FIG. 1. Study cohort distribution of individuals with *STUB1* pathogenic variants. Seventy-nine individuals had ataxia associated with at least one *STUB1* variant, including 15.2% with biallelic *STUB1* variants and 84.8% with a monoallelic *STUB1* variant. Among monoallelic carriers, 25.3% had a *TBP* allele above 37 repeats, 8.9% had an expanded *ATXN8OS* allele, 8.8% had other expansions, and 41.7% had no repeat expansion.

In the cohort of 400 index cases of autosomal dominant ataxia (102 with molecular diagnoses other than *STUB1* and 298 without molecular diagnosis), 2% (8/400) carried *ATXN8OS* expansion (ranging from 60 to 121 CTA/CTG repeats) (Fig. 3). Thus, *ATXN8OS* alleles (>50 CTA/CTG repeats) were five times more frequent in monoallelic *STUB1* variant carriers than in the ataxia cohort ($P < 0.01$, OR = 5.7, 95% CI [1.9–16.7]).

Other Intermediate Alleles in Monoallelic *STUB1* Variant Carriers

Regarding *TBP* expansions, we found that 10.5% (7/67) of individuals with monoallelic *STUB1* carriers had an intermediate *TBP* allele ranging from 40 to 46 CAG/CAA repeats (Fig. 1). Sequencing of *TBP* alleles greater than 40 CAG/CAA repeats revealed the canonical sequence ((CAG)₃(CAA)₃(CAG)_nCAACAGCAA(CAG)_n) without the loss of CAA interruptions in all cases. Notably, no biallelic *STUB1* variant carriers harbored *TBP* alleles greater than 40 CAG/CAA repeats. Intermediate *TBP* alleles (ie, 40–48 CAG/CAA repeats) were enriched in monoallelic *STUB1* carriers, accounting for 10.5% (7/67) of the cohort compared to 1.4% (19/1368) in the ataxic cohort ($P < 0.001$) and 0.02% (2/763) in controls ($P < 0.001$).

Among the 53 monoallelic *STUB1* variant carriers without *ATXN8OS* or *TBP* expansions, intermediate *HTT* alleles (28–29 CAG repeats) were identified in four individuals from three unrelated families, and an intermediate *ATXN1* allele (38 CAG repeats) was observed in three individuals from a single pedigree. The limited sample size precluded robust genotype–phenotype correlation analyses. No enrichment of intermediate *ATXN1* and *HTT* alleles was observed in monoallelic *STUB1* carriers compared to both cohorts of controls and ataxic individuals. *ATXN1* intermediate alleles were present in 4.5% of monoallelic *STUB1* carriers (3/67), compared to 2.2% (21/984 alleles) in controls ($P = 0.375$) and 4.9% (67/1370 individuals) in other ataxic individuals ($P = 1.0$). Similarly, *HTT* intermediate alleles were detected in 6.0% of monoallelic *STUB1* carriers (4/67) versus 2.9% (29/990 alleles) in controls ($P = 0.375$) and 6.0% (82/1363 individuals) in other ataxias ($P = 1.0$).

Association of *ATXN8OS* Expansions with Earlier Age at Onset in Monoallelic *STUB1* Carriers

We investigated whether age at onset significantly differed among the four groups of *STUB1* carriers: monoallelic *STUB1* carriers with normal *ATXN8OS*/*TBP* alleles: $n = 53$; monoallelic *STUB1* carriers with

expanded *ATXN8OS* alleles: $n = 7$; monoallelic *STUB1* carriers with expanded *TBP* alleles: $n = 7$; and biallelic *STUB1* carriers: $n = 12$. Post hoc comparisons revealed significant younger onset in biallelic *STUB1* carriers and monoallelic *STUB1* carriers with expanded *ATXN8OS* alleles compared to those with one *STUB1* variant and normal *ATXN8OS*/*TBP* alleles or expanded *TBP* alleles ($P < 0.0001$). Specifically, monoallelic *STUB1* variant carriers with normal *ATXN8OS* allele had a median age at onset of 47 years [39.8–53.5], which significantly decreased to 28 years [26–30.0] in individuals carrying *ATXN8OS* expansion ($P < 0.001$) (Fig. 2A; Table 1). Within families sharing identical *STUB1* variants, individuals with *ATXN8OS* expansion exhibited earlier onset than those without. Biallelic *STUB1* variant carriers presented the earliest age at onset, 26 years [20.8–29.0] ($P < 0.0001$), among all groups.

Clinical Features of Monoallelic *STUB1* Variant Carriers

The rest of the phenotypic characteristics were similar between monoallelic *STUB1* carrier groups (Table 1). All seven individuals with *ATXN8OS* expansion presented with ataxia, cerebellar atrophy, and cognitive impairment similarly to more than 95% of monoallelic *STUB1* carriers without *ATXN8OS* expansion. Nearly all individuals without ataxia, cognitive impairment, or cerebellar atrophy had a disease duration of less than 5 years. Other movement disorders were similarly distributed between monoallelic *STUB1* carriers with or without *ATXN8OS* expansions, including mainly parkinsonism (29% vs. 60%, $P = 0.9$) and dystonia (57% vs. 18%, $P = 0.2$). Sensory deficit was reported in 14% of *ATXN8OS* expansion carriers and 35% of non-*ATXN8OS* carriers ($P = 1.0$). Spasticity was rare in both groups, accounting for 14% of *ATXN8OS* expansion carriers and 6% of noncarriers ($P = 1.0$). Dementia or psychiatric syndromes were not identified in *ATXN8OS* expansions group compared to 71% in other monoallelic *STUB1* carriers. Psychiatric features included primarily depression, anxiety, and behavior disturbances. However, disease duration was shorter in individuals carrying *ATXN8OS* expansion (3 years vs. 9 years, $P = 0.41$). No individuals had developmental delay. Epilepsy was reported in 5 cases with normal *ATXN8OS* allele (5/35, 14.2%).

No significant clinical differences were observed between monoallelic *STUB1* carriers with normal and intermediate *TBP* alleles. Dementia prevalence was similar between the two groups (71%, $P = 1.0$), as well as median disease duration to survival endpoint (23 years vs. 33 years, respectively, $P = 1.0$).

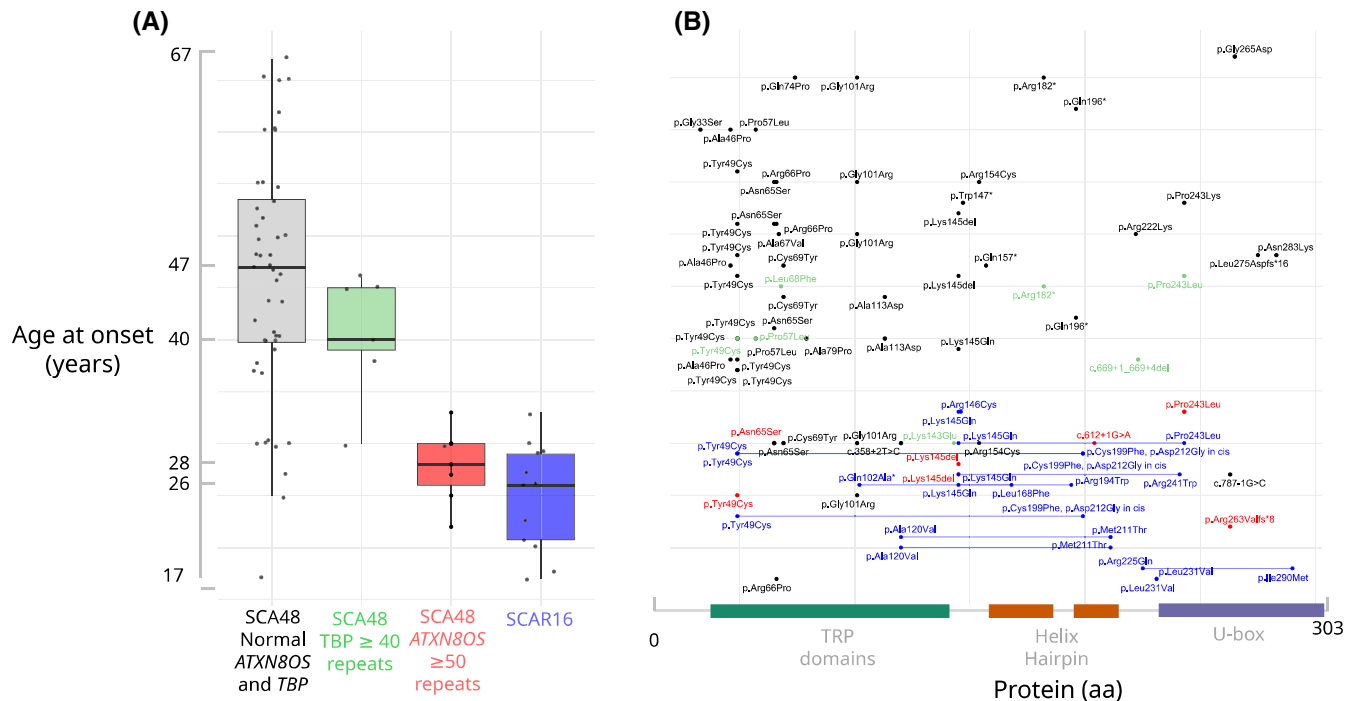


FIG. 2. Comparison of the age at onset between individuals with monoallelic *STUB1* variants not carrying *ATXN8OS* or *TBP* expansions (grey), carrying *TBP* expansion (green), carrying *ATXN8OS* expansions (red), and individuals with biallelic *STUB1* variants (blue). **(A)** *STUB1* variants associated with expansions in *ATXN8OS* are associated with an earlier age at onset. Boxplots represent median, Q1, and Q3 of age at onset in years. **(B)** Age at onset is not associated with the variant position or domain. Points represent individuals. Associated variants in the same individual (compound heterozygous variants) are represented by a blue line. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/mds.27054)]

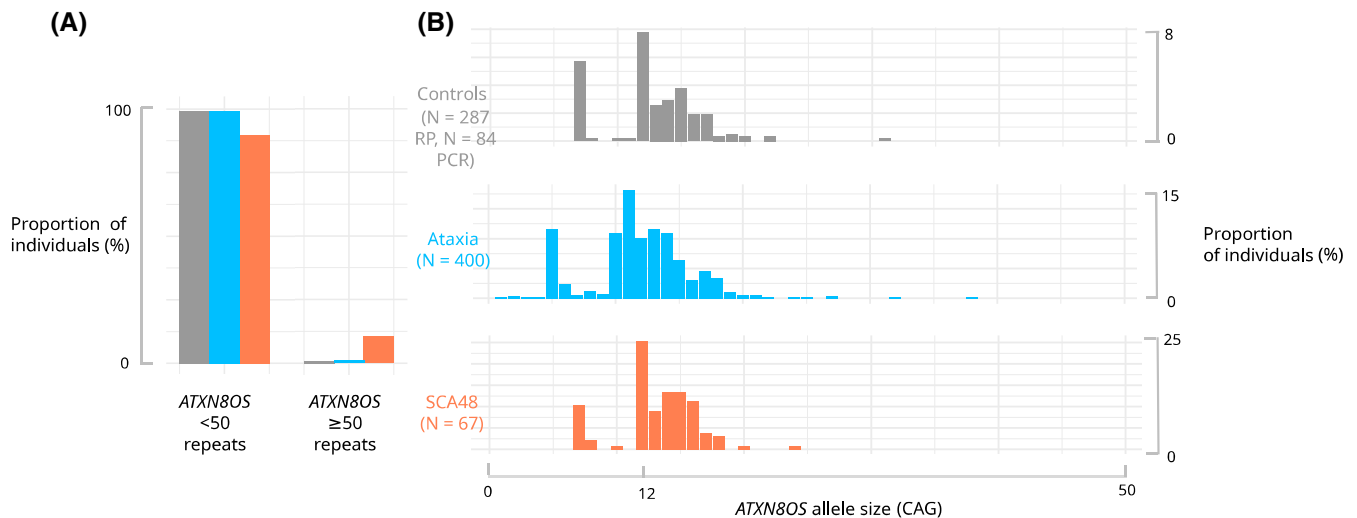


FIG. 3. *ATXN8OS* repeat size distribution in healthy controls (grey), individuals with cerebellar ataxia not related to *STUB1* (blue), and individuals with one *STUB1* variant (orange). **(A)** *ATXN8OS* expansions are present in general population and cerebellar ataxia cohort and enriched in *STUB1* variant carriers' cohort for size ≥ 50 CTA/CTG. **(B)** Distribution of not expanded *ATXN8OS* alleles in the three groups. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/mds.27054)]

Clinical Features of Biallelic *STUB1* Variant Carriers (SCAR16)

In individuals with biallelic *STUB1* variants ($n = 12$), cerebellar ataxia was associated with spasticity (4/12, 33.3%), developmental delay (3/10, 30%), and rapid

disease progression with early age at death (before age 50) in six individuals (Table 1). One SCAR16 patient also carried a pathogenic variant in *PSEN1* (ie, c.236C>T, p.Ala79Val) and developed dementia at age 33, consistent with *PSEN1*-related early-onset dementia.

TABLE 1 Clinical comparison between individuals with monoallelic STUB1 variants carrying or not carrying expansions in ATXN8OS or TBP and individuals with biallelic STUB1 variants

Genotype	Monoallelic STUB1 variants			Biallelic STUB1 variants	
	With normal ATXN8OS and TBP alleles	With expanded TBP allele	With expanded ATXN8OS allele	SCAR16	Adjusted P-value
n	53	7	7	12	
Inheritance					
Autosomal dominant	91% (48/53)	43% (3/7)	71% (5/7)	0% (0/12)	
Autosomal recessive	2% (1/53)	0% (0/7)	0% (0/7)	92% (11/12)	
Isolated case	7% (4/53)	57% (4/7)	29% (2/7)	8% (1/12)	
Age at onset (y)	47.0 (39.8, 53.5); 17.0–67.0, n = 52 ^{c,d}	40.0 (39.0, 45.0); 30.0–46.0, n = 7 ^{c,d}	28.0 (26.0, 30.0); 22.0–33.0, n = 7 ^{a,b}	26.0 (20.8, 29.0); 17.0–33.0, n = 12 ^{a,b}	1.01e–07
Age at examination (y)	56.0 (49.0, 65.0); 22.0–76.0, n = 52 ^d	53.0 (46.0, 56.5); 32.0–69.0, n = 7 ^d	39.0 (29.0, 50.0); 26.0–69.0, n = 7	31.0 (28.5, 34.2); 23.0–59.0, n = 12 ^{a,b}	3.19e–05
Age at death (y)	67.0 (61.8, 72.2); 45.0–85.0, n = 24 ^d	57.5 (49.8, 65.2); 42.0–73.0, n = 2	No death	45.0 (38.0, 56.5); 35.0–71.0, n = 7 ^a	0.0218
Survival (y)	23.0 (18.0, 28.0); 1.0–35.0, n = 53	33.0 (12.0, NA); 2.0–33.0, n = 7	NA (NA, NA); 0.0–39.0, n = 7	20.0 (16.0, NA); 1.0–41.0, n = 12	8e–05
Disease duration (y)	9.0 (5.0, 13.8); 1.0–28.0, n = 51	8.0 (3.5, 14.5); 2.0–29.0, n = 7	3.0 (2.0, 23.5); 0.0–39.0, n = 7	5.0 (3.8, 10.5); 1.0–29.0, n = 12	0.5494
Disability score (0–7)	3.0 (3.0, 5.0); 1.0–7.0, n = 51	3.0 (2.0, 3.5); 1.0–5.0, n = 7	2.0 (2.0, 3.5); 1.0–6.0, n = 7	4.0 (3.0, 6.0); 1.0–7.0, n = 12	0.2335
Severity index (disability score/disease duration)	0.4 (0.3, 0.6); 0.1–4.0, n = 50	0.3 (0.2, 0.6); 0.2–1.0, n = 7	0.4 (0.2, 0.8); 0.1–2.0, n = 7	0.6 (0.5, 1.0); 0.2–3.0, n = 12	0.2179
Cerebellar ataxia	96% (50/52)	100% (7/7)	100% (7/7)	100% (12/12)	1.0
Dysarthria	65% (31/48)	86% (6/7)	57% (4/7)	75% (9/12)	0.6508
Ophthalmological signs	69% (31/45)	86% (6/7)	86% (6/7)	67% (8/12)	0.7829
Nystagmus	20% (9/45)	57% (4/7)	71% (5/7)	50% (6/12)	
Saccadic pursuit	33% (15/45)	29% (2/7)	42% (3/7)	42% (5/12)	
Ptosis	9% (4/45)	14% (1/7)	14% (1/7)	8% (1/12)	
Diplopia	16% (7/45)	14% (1/7)	0% (0/7)	8% (1/12)	
Ophthalmoplegia	11% (5/45)	14% (1/7)	14% (1/7)	0% (0/12)	

(Continues)

TABLE 1 Continued

Genotype	Monoallelic <i>STUB1</i> variants		Biallelic <i>STUB1</i> variants	
	With normal <i>ATXN8OS</i> and <i>TBP</i> alleles	With expanded <i>TBP</i> allele	With expanded <i>ATXN8OS</i> allele	Adjusted <i>P</i> -value
Cognitive impairment	96% (49/51)	100% (7/7)	100% (7/7)	0.7153
Dementia	71% (37/52) ^{c,d}	71% (5/7)	0% (0/7) ^a	7.972e-05
Psychiatric features	34% (13/38)	50% (3/6)	0% (0/7)	0.2359
Spasticity	6% (3/50)	0% (0/7)	14% (1/7)	0.0455
Sensory deficit	35% (17/49)	14% (1/7)	14% (1/7)	0.4397
Parkinsonism	60% (27/45)	67% (4/6)	29% (2/7)	0.0239
Hyperkinetic movement disorders	62% (28/45)	20% (1/5)	57% (4/7)	0.3865
Chorea	31% (14/45)	0% (0/5)	0% (0/7)	0.0585
Myoclonus	16% (7/45)	0% (0/5)	0% (0/7)	0.5488
Dystonia	18% (8/45)	20% (1/5)	57% (4/7)	0.1337
Developmental delay	2.2% (1/45) ^d	0% (0/7)	0% (0/7)	0.0222
Epilepsy	12% (4/33)	17% (1/6)	0% (0/5)	1.00
MRI abnormalities	97% (30/31)	100% (7/7)	100% (7/7)	1.00
Cerebellar atrophy	97% (30/31)	100% (7/7)	100% (7/7)	1.00
Brainstem atrophy	72% (13/18)	25% (1/4)	40% (2/5)	0.0457

Note: Significant pairwise comparisons are shown as ^{a,b,c} and ^d for SCA48 with normal *ATXN8OS* and *TBP* alleles, SCA48 with an expanded *TBP* allele, SCA48 with an expanded *TBP* allele, and SCA48 with an expanded *TBP* allele, respectively.

Absence of Correlation Between Age at Onset or Inheritance and the Affected *STUB1* Domains

In the monoallelic *STUB1* variant carriers' cohort, no association was observed between age at onset and *STUB1* variant protein domain ($P = 0.9666$) (Fig. 2B). Variant details are provided in Table S2. Analysis including biallelic *STUB1* individuals revealed that specific variants (p.Tyr49Cys, p.Pro243Leu, and p.Lys145Gln) were associated with both autosomal dominant and autosomal recessive transmissions (Fig. 2B). Additionally, variants reported only in monoallelic forms in our cohort had previously been described in recessive families (p.Asn65Ser, p.Ala67Val, c.612 + 1G>A, p.Arg241Trp, p.Pro243Leu).^{5,19-23} Twelve variants were exclusively recessive in our cohort, including p.Arg241Trp previously reported in a dominant family.²⁰ Four variants were observed in asymptomatic parents of biallelic *STUB1* individuals and were never reported in dominant forms (p.Gln102Ala*10, p.Cys199Phe, p.Met211Thr, and p.Leu231Val). Moreover, variants were identified across all three protein domains (ie, tetratricopeptide repeat [TRP] domain, helix-hairpin domain, and U-box domain) in both dominant and recessive forms.

Alternative Molecular Diagnoses in Individuals Carrying *ATXN8OS* Expansions Without *STUB1* Variants

As reported above, we identified eight individuals from the cohort of ataxic cases without *STUB1* variants who carried *ATXN8OS* expansion. Four (50%) of them already had a molecular diagnosis of inherited cerebellar ataxia:

1. Family SAL-305: four generations with complex ataxia and cognitive impairment. An *ATXN3* expansion (71–79 CAG repeats) segregated in all 10 affected individuals. The *ATXN8OS* expansion (60–67 CTA/CTG repeats) was present in five affected and six asymptomatic individuals. The *ATXN8OS* expansion was not associated with earlier-onset or additional symptoms.
2. Family SAL-379: four generations with pure cerebellar ataxia and age at onset ranging from 17 to 43 years. All affected individuals harbored a pathogenic deletion of *AFG3L2* (exons 14–16). One affected individual carried an *ATXN8OS* expansion (79 CTA/CTG repeats) and exhibited the latest onset at 43 years.
3. Case AAR-009: an individual with pure spastic paraplegia and age at onset at 41 years, carrying biallelic pathogenic exon 1 deletion in *SPG7* and an *ATXN8OS* expansion (121 CTA/CTG repeats). No

segregation data were available; however, the phenotype was typical for SPG7.

4. Family AAD-271: three generations with complex ataxia and parkinsonism, plus cognitive impairment, chorea, and myoclonus. A pathogenic *NPTX1* missense variant (c.1165G>A, p.Gly389Arg) segregated in eight affected individual.²⁴ The *ATXN8OS* expansion (83–95 CTA/CTG repeats) was present in five affected and two unaffected individuals without association with an earlier-onset or additional symptoms.

Discussion

ATXN8OS Intermediate Expansion Is a Genetic Modifier of Monoallelic *STUB1* Carriers

We screened a large cohort of 67 ataxic individuals harboring monoallelic pathogenic *STUB1* variants to explore the presence of genetic modifiers, including *ATXN8OS*, TBP, and other CAG repeat expansions. After comprehensive genetic workup, including WES and short-read WGS, no alternative molecular diagnosis was identified. Individuals with monoallelic *STUB1* variants exhibited a homogenous phenotype of adult-onset progressive ataxia with cognitive impairment, starting around 47 years of age. We confirmed that co-occurrence of a monoallelic *STUB1* variant and an *ATXN8OS* (>50 CTA/CTG repeats) is associated with an earlier age at onset of about 20 years, with a median age of 28 years. The remaining phenotypic characteristics, including slowly progressive ataxia and cognitive impairment, were similar regardless of *ATXN8OS* size. Additional clinical features included parkinsonism, psychiatric manifestations, and sensory deficit, consistent with previous reports.⁴ *ATXN8OS* expansions were 15 times higher in monoallelic *STUB1* carriers than in controls and 5 times higher than individuals with other inherited ataxias.

Questioning the Pathogenicity of *ATXN8OS* Expansions and Implications for Genetic Counseling

This study further questions the pathogenicity of *ATXN8OS* expansions, as previously suggested.^{25,26} By screening 286 healthy controls with age above 50 years, we confirmed the relatively high frequency (~1%) of expanded alleles (>50 CTA/CTG repeats) in the general population, consistent with previous reports.^{27,28} Moreover, *ATXN8OS* expansions have been frequently reported in other neurological disorders, including ataxia of known causes (Table 2): 2% in SCA2, 2.4% in Friedreich's ataxia,²⁹ 1.9% in SCA6,³⁰ and up to 8.6% in SCA1.³¹ Case reports of individuals with co-occurring *ATXN8OS* expansions and another molecular diagnosis have shown no phenotypic impact.^{32,33,34}

TABLE 2 List of ATXN8OS expansions detected in other neurological diseases, including ataxia from literature and the SPATAX/BIOMOV cohort

Gene/disease	ATXN8OS expanded allele frequency	ATXN8OS expanded allele range (repeats)	Age	References
Psychiatric disorders, including psychosis, borderline personality disorder, or juvenile-onset depression; healthy controls	1.25%; 0.7%	>100	36.8 ± 11.2; 30.2 ± 11.3	Vincent et al (2000) ⁴⁰
Undiagnosed ataxia; diagnosed ataxia, including SCA2 and Friedreich's ataxia; Alzheimer's disease	2.0%; 2.4%; 1.8%	>91	NA, NA, 73.4	Sobrido et al (2001) ²⁹
Celiac disease ataxia	1 case	159	33	Cellini et al (2001) ³²
AVED/ <i>TTPA</i> ataxia	1 case	320	30	Cellini et al (2002) ³³
SCA1/ <i>ATXN1</i>	8.60%	53–116	20–50	Sulek et al (2003) ³¹
SCA31/ <i>BEAN</i>	3 cases	150–250	23–49	Ohnari et al (2008) ³⁴
SCA6/ <i>CACNA1A</i> ; Parkinson's disease, Alzheimer's disease	1.9%; 0.4%; 0.3%	85–399	47 ± 16; 70 ± 10; 61 ± 9	Izumi et al (2003) ³⁰
Late-onset Parkinson's disease	1.50%	75–92	58–81	Wu et al (2004) ³⁵
Juvenile Huntington's disease	1 case	104	29	Bereznai et al (2010) ³⁹
ALS	3%	91–223	65 ± 12	Hirano et al (2018) ³⁷
PSP	0.02%	74–151	76–79	Samukawa et al (2019) ³⁶
Familial essential tremor	1 case	188	57	Zhou et al (2024) ³⁸
SPG7	1 case (AAR-009)	12/121	50	This study
SCA3/ <i>ATXN3</i>	5 affected members; 6 unaffected members (SAL-305 family)	60–67	38–63	This study
SCA28/ <i>AFG3L2</i>	1 affected member (SAL-379 family)	12/79	70	This study
SCA50/ <i>NPTX1</i>	5 affected members and 2 unaffected members (AAD-271 family)	83–95	48–60	This study

Note: Age is represented either as a range or as the mean and standard deviation, depending on the article.
Abbreviations: SCA, spinocerebellar ataxia; ALS, amyotrophic lateral sclerosis; PSP, progressive supranuclear palsy.

ATXN8OS expansions have also been reported in other neurodegenerative disorders, including Alzheimer's disease,²⁹ Parkinson's disease,³⁵ atypical parkinsonism,³⁶ amyotrophic lateral sclerosis,³⁷ essential tremor,³⁸ Huntington's disease,³⁹ and psychiatric disorders.⁴⁰ In our four families with co-occurring ATXN8OS expansions and another molecular diagnosis, the phenotype was consistent with the primary disease-causing gene (ie, typical clinical progression of SCA3 or spastic paraparesis in the SPG7 family), with

incomplete segregation of the ATXN8OS expansion and no apparent phenotypic effect.

We did not identify any ATXN8OS expansions larger than 177 CTA/CTG repeats after screening more than 400 ataxia cases, including *STUB1* carriers, using capillary migration sizing. The pathogenicity of ATXN8OS expansions remains controversial, as the expansion threshold is uncertain, asymptomatic individuals carrying expansions up to 1300 repeats have been reported,²⁷ and reduced penetrance has been

observed across all repeat sizes.²⁷ Moreover, *ATXN8OS* expansions are relatively frequent in aged controls and in other neurodegenerative diseases even with known causes, without a clear effect on phenotype, except for the markedly earlier age at onset observed in monoallelic *STUB1* variant carriers. Taken together, these observations suggest that *ATXN8OS* expansions may not act as fully penetrant disease-causing variants by themselves but rather as genetic modifiers whose effect becomes clinically relevant in specific genetic contexts. One possible explanation for this modifier effect is a pathological interaction between *ATXN8OS*-expanded alleles and monoallelic *STUB1* pathogenic variants. We hypothesize that *ATXN8OS* expansions may promote the accumulation of toxic RNA foci in the context of impaired *STUB1* E3 ubiquitin ligase activity, thereby enhancing neuronal vulnerability and accelerating disease onset. These RNA foci will then lead to sequestration of proteins, including the RNA-binding protein MBNL1, which is a target-specific regulators of pre-messenger RNA (mRNA).⁴¹ Further functional and pathological studies are needed to better characterize the physiopathological processes. Pending further evidence, genetic counseling, particularly prenatal and preimplantation testing for *SCA8*, should be approached with extreme caution.

Other Expansions Associated with Monoallelic *STUB1* Carriers

The other intermediate expansion enriched in the monoallelic *STUB1* cohort was found in *TBP*. Intermediate *TBP* alleles (ie, 40–48 CAG/CAA repeats) were seven times more frequent than in non-*STUB1* ataxic individuals and above 50 times more frequent than in controls. We and others previously reported that intermediate *TBP* alleles in monoallelic *STUB1* variant carriers were associated with more severe clinical outcomes.^{5,7,42} In the present enlarged cohort, longitudinal analyses indicated no difference in the frequency of dementia or shorter survival between individuals with *SCA48* carrying normal or intermediate *TBP* alleles. This could be partly explained by our inclusion of *TBP* alleles from 40 CAG/CAA repeats, whereas certain previous cohorts used a threshold of 41 CAG/CAA repeats.^{5,7,43} We applied the 40-repeat threshold because 40 CAG/CAA alleles are enriched in monoallelic *STUB1* variant carriers compared to the general population and non-*STUB1* ataxic cohort. Recent studies have suggested 39 CAG/CAA as the intermediate *TPB* allele threshold and have reported an enrichment of these alleles in monoallelic *STUB1* carriers.⁴⁴ However, comparisons across studies and cohorts should consider the methods used to size *TBP* CAG repeat expansion. Indeed, the use of *ExpansionHunter* or PCR-based techniques may yield

different repeat length estimates. *ExpansionHunter* is a fast and reliable tool for detecting repeat expansions in spinocerebellar ataxias, as previously demonstrated.⁴⁵ However, sizing is potentially affected by shallow sequencing coverage and the absence of spanning reads, which may not be reliably detected in WGS datasets, including the gnomAD database. The difference between different studies is that CAG repeat expansions were sized either using *ExpansionHunter* or by PCR-based techniques, which appear to differ. Indeed, *ExpansionHunter* seems fast and reliable for detection of repeat expansions in spinocerebellar ataxias, as previously demonstrated.⁴⁵ However, the sizing is potentially affected by shallower coverage and spanning reads, which are not detected in WGS studies, including gnomAD database.

Finally, the longitudinal follow-up of monoallelic *STUB1* carriers showed that almost all developed cognitive impairment and later on dementia. One main limitation of all these studies^{5,7,42,43} is that dementia onset is difficult to define as it is partly subjective, is not always assessed by a neuropsychological evaluation earlier in the disease course, and becomes evident only when the impact on daily functioning is evident.

Additional intermediate alleles in other genes were identified, including four individuals with *HTT* intermediate alleles (28–29 CAG repeats) and three with *ATXN1* intermediate alleles (38 CAG repeats). These intermediate alleles were not more enriched in *STUB1* carriers than other non-*STUB1* ataxic individuals. However, it has been suggested that such alleles may contribute to the pathogenesis of other neurodegenerative disorders or modify the phenotype.^{46,47}

The relatively high frequency of expanded or intermediate alleles of other neurodegeneration-associated genes observed in 27% of monoallelic *STUB1* variant carriers (18% if only significantly enriched expansions are included), along with the absence of disease in heterozygous parents of biallelic *STUB1* variant carriers, raises the question of whether a monoallelic *STUB1* variant alone is sufficient to cause the disease, or whether additional genetic factors are required to trigger the disease. Therefore, large cohorts should be investigated to identify additional genetic factors that may contribute to disease expression.

STUB1 Protein Function and Physiopathology

STUB1 comprises three main domains: the N-terminal TRP domain, the helix-hairpin domain, and the C-terminal U-box domain. Pathogenic variants in TRP domain disrupt chaperone interactions,^{48,49} leading to the accumulation of misfolded protein.^{19,50} Variants in helix-hairpin domain may destabilize the protein or impair homodimers formation.^{50,51} Finally, variants in U-box domain impair ubiquitin ligase

activity.^{50,52} Although biallelic variants lead to the loss of co-chaperone or E3 ubiquitin ligase function or protein instability,^{50,53} monoallelic variants would be expected to exert a dominant-negative effect. However, as identical variants are reported in both biallelic and monoallelic states, differential pathophysiological impacts seem unlikely. Intermediate expansion in *ATXN8OS*, *TBP*, *HTT*, or *ATXN1* may increase poly-Q protein burden, potentially saturating STUB1 E3 ubiquitin ligase activity. Alternatively, stress-induced STUB1 activity, increasing co-chaperone function while decreasing E3 ligase activity,⁵⁰ may contribute, as well as environmental or genetic factors, such as increased misfolded protein burden or mitochondrial dysfunction. Under these conditions, haploinsufficiency due to reduced *STUB1* dosage from monoallelic variants could manifest as later-onset phenotypes. Functional studies incorporating environmental factors and mitochondrial function assessment, combined with long-read sequencing to detect complex noncoding expansions, are needed to characterize monoallelic *STUB1* variant effects on protein activity.

Conclusion

Our study refines the association between monoallelic *STUB1* variants and *ATXN8OS* expansion, showing that the latter acts as a genetic modifier of SCA48 by contributing to an earlier age at onset. Indeed, *ATXN8OS* expansions do not appear to modulate the phenotype of other ataxias or neurodegenerative diseases and may not be sufficient to cause disease on their own. ■

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J.-L.M.: 1C, 1D, 2C, 3B.
C.-S.D.: 1C, 1D, 3B.
L.G.-N.: 1C, 1D, 3B.
E.P.: 2B, 2C, 3B.
Q.T.: 1C, 3B.
A.N.: 1C, 1D, 3B.
A.H.: 1C, 3B.
C.E.: 1C, 3B.
A.B.: 1A, 1E, 3B.
A.D.: 1A, 1B, 1C, 3B.
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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.