Contribution of *ATXN2* intermediary polyQ expansions in a spectrum of neurodegenerative disorders

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**Supplemental data
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ABSTRACT

Objective: The aim of this study was to establish the frequency of *ATXN2* polyglutamine (polyQ) expansion in large cohorts of patients with amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and progressive supranuclear palsy (PSP), and to evaluate whether *ATXN2* could act as a modifier gene in patients carrying the *C9orf72* expansion.

Methods: We screened a large cohort of French patients (1,144 ALS, 203 FTD, 168 FTD-ALS, and 109 PSP) for *ATXN2* CAG repeat length. We included in our cohort 322 carriers of the *C9orf72* expansion (202 ALS, 63 FTD, and 57 FTD-ALS).

Results: We found a significant association with intermediate repeat size (≥ 29 CAG) in patients with ALS (both familial and sporadic) and, for the first time, in patients with familial FTD-ALS. Of interest, we found the co-occurrence of pathogenic *C9orf72* expansion in 23.2% of *ATXN2* intermediate-repeat carriers, all in the FTD-ALS and familial ALS subgroups. In the cohort of *C9orf72* carriers, 3.1% of patients also carried an intermediate *ATXN2* repeat length. *ATXN2* repeat lengths in patients with PSP and FTD were found to be similar to the controls.

Conclusions: *ATXN2* intermediary repeat length is a strong risk factor for ALS and FTD-ALS. Furthermore, we propose that *ATXN2* polyQ expansions could act as a strong modifier of the FTD phenotype in the presence of a *C9orf72* repeat expansion, leading to the development of clinical signs featuring both FTD and ALS. **Neurology® 2014;83:990-995**

GLOSSARY

ALS = amyotrophic lateral sclerosis; **FTD** = frontotemporal dementia; **PD** = Parkinson disease; **polyQ** = polyglutamine; **PSP** = progressive supranuclear palsy; **SCA2** = spinocerebellar ataxia type 2; **TDP-43** = TAR DNA-binding protein 43.

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are considered part of a spectrum of neurologic diseases because they share pathologic hallmarks, consisting of TAR DNA-binding protein 43 (TDP-43) pathology, and a similar genetic background, including *C9orf72* expansion. On the other hand, FTD shares a prominent frontal cognitive syndrome and parkinsonism signs with progressive supranuclear palsy (PSP).

Spinocerebellar ataxia type 2 (SCA2), characterized by cerebellar ataxia, parkinsonism, and mild dementia, is caused by an expanded CAG trinucleotide repeat encoding for a polyglutamine (polyQ) tract in ataxin-2 protein (*ATXN2*; OMIM: *601517). A link between SCA2 and ALS was established in 2010, when *ATXN2* intermediate-length expansions were found to be significantly associated with ALS and it was shown that *ATXN2* protein modifies TDP-43 toxicity.¹ In this study, we analyzed the size of *ATXN2* repeats in a large French cohort of 1,624 patients with ALS, FTD, FTD-ALS, and PSP to evaluate the exact contribution of the *ATXN2* repeat size to

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these neurologic disorders. Furthermore, we tested patients carrying the *C9orf72* mutation to assess whether *ATXN2* could act as a modifier in the presence of a *C9orf72* expansion.

METHODS **Standard protocol approvals, registrations, and patient consents.** The Ethics Committee of Assistance Publique-Hôpitaux de Paris approved this study. All the study participants signed a written informed consent.

Patients and controls. We screened a total of 1,144 patients with ALS (735 sporadic, 409 familial), 203 patients with FTD (124 sporadic, 79 familial), 168 patients with FTD-ALS (97 sporadic, 71 familial), and 109 patients with PSP (107 sporadic, 2 familial) for *ATXN2* repeat length (table 1). The population consisted of index cases of unrelated families. Cases were considered familial when at least a first- or second-degree relative had FTD, PSP, or ALS. Cases were considered sporadic when there was no FTD/ALS spectrum disease or PSP in the family over 4 generations, even though the family history was sometimes incomplete or censored.²

FTD was diagnosed based on international diagnosis criteria,³ ALS was diagnosed based on the El Escorial criteria established by the World Federation of Neurology,² and PSP was diagnosed clinically according to the international consensus diagnostic criteria.⁴ Patients with ALS were evaluated with standardized behavioral procedures for cognitive impairments whenever this was possible, considering the rapid progression of the disease in these patients.

The French Research Network on FTD/FTD-ALS collected DNA samples from patients with FTD and PSP. Patients with FTD were previously screened for mutations in FTD and ALS genes (*PGRN*, *MAPT*, *C9orf72*, *VCP*, *CHMP2B*, *PFN1*, *UBQLN2*, *SQSTM1*, *TARDBP*, *FUS/TLN*, *SOD1*, *ANG*, *TREM2*),^{5–10} and only patients who were found to be negative for known mutations (except for *C9orf72*) were included in this study. Patients with PSP were assessed for variants in *MAPT*, *PGRN*, and *C9orf72*.⁶

Patients with familial ALS were previously screened for mutations in ALS-causing genes (*C9orf72*, *SOD1*, *TARDBP*, *FUS/TLN*, *OPTN*, *ANG*, *VAPB*, *PFN1*, *SQSTM1*, *UBQLN2*, *SS18L1*).^{11–16} Major genes (*C9orf72*, *SOD1*, *TARDBP*, *FUS/TLN*) were also analyzed in patients with sporadic ALS, and all patients with ALS (with or without mutation in these genes) were screened for *ATXN2*.

In this study, we included 322 patients carrying the pathogenic (>23 GGGGCC repeats) *C9orf72* expansion (202 ALS, 63 FTD-ALS, and 57 FTD).^{6,11}

We used DNA samples from 682 unrelated French participants without history of neurodegenerative disorders as controls.

Determination of *ATXN2* CAG repeat size. We determined the polyQ repeat size in exon 1 of *ATXN2* using a fluorescent PCR, as previously described,¹⁷ running PCR fragment on an ABI3730 sequencer (Applied Biosystems, Foster City, CA) with the LIZ-500 size standard (Applied Biosystems). We assessed fragment length using the Peak Scanner Software v1.0 (Applied Biosystems).

Statistical analysis. We compared the frequencies of the different *ATXN2* CAG sizes between each patient group and the control group using the χ^2 distribution test and the Fisher exact test, as appropriate. In all tests performed in this study, we tested the hypotheses separately and considered *p* values below 0.05 significant. We used the SPSS Inc. software (PASW statistic 18, for Windows) to perform statistical analysis.

RESULTS Most of the controls analyzed (99.5%) had fewer than 28 *ATXN2* polyQ repeats, and the majority of them (96.7%) had fewer than 26 triplets. A limited number of controls carried 29 and 30 polyQ repeats (0.4% and 0.1%, respectively). None of the control cases had more than 30 repeats, in agreement with a previous study in the same population.¹⁸

The distribution of the polyQ lengths was different in the 4 cohorts analyzed (table 2 and the figure).

In the FTD-ALS group, the presence of ≥ 29 repeats was associated with the disease. In fact, 6/168 patients with FTD-ALS (3.57%) and 4/682 controls (0.59%) carried more than 29 repeats. Considering familial and sporadic cases separately, only familial cases were different from controls.

We observed an association of *ATXN2* repeat length ≥ 29 in patients with ALS. Thirty-five patients (17 familial ALS, 18 sporadic ALS) had ≥ 29 repeats, and 22 of them (11 familial ALS, 11 sporadic ALS) had ≥ 31 , compared to none in the controls (*p* = 5.599 E-5). The association was stronger when considering the familial cases, but it was still consistent even when considering the sporadic cases by themselves. All patients carrying ≥ 31 repeats had ALS, either with or without FTD.

We did not find any difference in patients with PSP compared to controls (all of them were ≤ 28). In the FTD cohort, only 2 patients had 29 repeats, with a frequency that was very similar to that observed in the controls (0.98% vs 0.59%). No patients with PSP or pure FTD had >29 repeats.

In the cohort of *C9orf72* expansion carriers, overall 3.1% of these patients carried an intermediate *ATXN2* repeat length, detected in 2.5% of patients with ALS, 8.8% of patients with FTD-ALS, and 0% of patients with FTD (table 3 and table 4). In the cohort of patients negative for *C9orf72* expansion, we found the *ATXN2* intermediate allele in 3.6% of patients with ALS, 6.3% of patients with FTD-ALS, and 1.4% of patients with FTD (table 4).

Table 1 Definition of the patient population groups affected by ALS, FTD, and PSP

	Number of cases		
	Total	Familial	Sporadic
ALS	1,144	409	735
FTD	203	79	124
FTD-ALS	168	71	97
PSP	109	2	107
Controls	682		

Abbreviations: ALS = amyotrophic lateral sclerosis; FTD = frontotemporal dementia; PSP = progressive supranuclear palsy. Patients who present clinical signs of ALS and FTD represent the FTD-ALS spectrum, whereas a sufficient number of non-neurologically affected individuals were used as controls in this study.

Table 2 Number of patients with ALS, FTD, FTD-ALS, and PSP and controls (and percentages of total per group) displaying in heterozygosity an allele with expanded polyglutamine (≥ 29) ATXN2 repeat size

Group	Total n	≤ 28 , n (%)	29, n (%)	30, n (%)	≥ 31 , n (%)	p Value
Controls	682	678 (99.5)	3 (0.4)	1 (0.1)	0	
PSP	109	109 (100)	0	0	0	1
Total FTD	203	201 (99)	2 (1)	0	0	0.479
FTD familial	79	78 (98.7)	1 (1.3)	0	0	0.423
FTD sporadic	124	123 (99.2)	1 (0.8)	0	0	0.567
Total FTD-ALS	168	162 (96.4)	2 (1.2)	2 (1.2)	2 (1.2)	0.004 ^a
FTD-ALS familial	71	67 (94.4)	1 (1.4)	1 (1.4)	2 (2.8)	0.003 ^a
FTD-ALS sporadic	97	95 (97.9)	1 (1.05)	1 (1.05)	0	0.164
Total ALS	1,144	1,109 (97)	6 (0.5)	7 (0.6)	22 (1.9)	10.3E-6 ^a
ALS familial	409	392 (95.9)	3 (0.7)	3 (0.7)	11 (2.7)	5.66E-6 ^a
ALS sporadic	735	717 (97.8)	3 (0.4)	4 (0.5)	11 (1.5)	0.001 ^a

Abbreviations: ALS = amyotrophic lateral sclerosis; FTD = frontotemporal dementia; PSP = progressive supranuclear palsy.

^aSignificant value.

Considering the total number of carriers of ≥ 29 ATXN2 repeats (43 patients), 23.2% of them also carried a pathogenic *C9orf72* expansion (10/43 patients). Patients carrying both *C9orf72* and ATXN2 expansions had FTD-ALS (5/10), familial ALS (4/10), and sporadic ALS (1/10) (table 3). None of the patients with ALS with ATXN2 intermediate repeats carried a concomitant mutation in another ALS gene.

DISCUSSION The length of CAG repeats in the ATXN2 gene is quite variable (16–27) depending

on the population, but alleles with 22–23 repeat units are the most common. A stretch of ≥ 34 CAG was identified as causing SCA2.¹⁹

In 2010 it was proposed that intermediate-length expansions, greater than 23 but below the threshold for SCA2, contribute to susceptibility to ALS.¹ This link has been consistently supported by the demonstration that ATXN2 protein associates with TDP-43, modifies its toxicity, and induces its mislocalization in yeast and *Drosophila*.¹ ATXN2 localization is also altered in spinal cord neurons from patients with

Figure Refining the size of the ATXN2 repeats in the spectrum of the FTD-ALS neurodegenerative disorders

Results from our study demonstrate that ≥ 31 ATXN2 repeats are significantly associated with ALS. ALS = amyotrophic lateral sclerosis; FTD = frontotemporal dementia; PSP = progressive supranuclear palsy.

Table 3 ATXN2 intermediary polyglutamine repeats co-occur with C9orf72 hexanucleotide repeat expansions

	Total n	ATXN2 carriers, n (%) ^a	C9orf72 carriers, n (%) ^b	C9orf72 + ATXN2 carriers, n (%) ^c
Total FTD	203	2 (1)	63 (31)	0
FTD familial	79	1 (1.3)	57 (72.1)	0
FTD sporadic	124	1 (0.8)	6 (4.8)	0
Total FTD-ALS	168	7 (4.2)	57 (34)	5 (3, 71.5, 8.8)
FTD-ALS familial	71	5 (7.0)	47 (66.2)	3 (4.2, 60, 6.4)
FTD-ALS sporadic	97	2 (2.1)	10 (10.3)	2 (2.1, 100, 20)
Total ALS	1,144	34 (3)	202 (17.6)	5 (0.4, 14.7, 2.5)
ALS familial	409	16 (3.9)	147 (36)	4 (1, 25, 2.7)
ALS sporadic	735	18 (2.4)	55 (7.5)	1 (0.1, 5.5, 1.8)
Total	1,515	43 (2.8)	322 (21.2)	10 (0.7, 23.3, 3.1)

Abbreviations: ALS = amyotrophic lateral sclerosis; FTD = frontotemporal dementia.

The co-occurrence of repeats was detected solely in familial and sporadic patients displaying both ALS and FTD clinical signs as well as in patients with familial ALS.

^aPercentages of ATXN2 carriers have been calculated on the total number of patients.

^bPercentages of C9orf72 carriers have been calculated on the total number of patients.

^cPercentages have been calculated on the total number of patients, on the total number of ATXN2 carriers, and on the total number of C9orf72 carriers, respectively.

ALS carrying the expanded allele, showing more cytoplasmic accumulation.¹ ATXN2 also modifies FUS pathology in cellular models of ALS, co-localizes with FUS in sporadic ALS patient motor neurons, co-precipitates with FUS in ALS spinal cord lysates, and co-localizes with FUS in the ER–Golgi compartments in neuronal cell lines.²⁰

Because of the presence of TDP-43 inclusions in many neurodegenerative diseases and the heterogeneity of their clinical presentation, a number of studies have evaluated ATXN2 repeat sizes in patients with neurodegenerative diseases.^{17,21–33}

All the studies confirmed a significant association between intermediary repeat lengths and ALS, which is even stronger when familial cases are considered separately from sporadic cases. An association has also been found with PSP.²⁴ No association of ATXN2 repeats has yet been described with FTD,^{24,31} but intermediate repeats are more frequent in Parkinson disease (PD) in a Japanese patient population³³ and ATXN2 polyQ expansions have also been reported in European patients with PD.³⁴

In the present study, we analyzed the size of ATXN2 repeats in a large French cohort of patients and controls. We found no expanded repeats in patients with PSP, in contrast to what has been reported in the past.²⁴ It could be because of the different origin of the patients examined (the association was found in samples from the Mayo Clinic Jacksonville)²⁴ or because of the smaller size of our PSP patient cohort.

Intermediary repeat length was not associated with FTD, as previously reported by other groups.^{24,31} Taken together, these data suggest that ATXN2 does not increase the risk of developing familial or sporadic FTD.

For the first time, the present study describes a significant association between ≥ 29 ATXN2 repeats and FTD-ALS. In particular, the association is stronger when considering familial FTD-ALS cases. Previous studies have thus far reported only 10 familial FTD-ALS cases screened for ATXN2 repeat expansions,³¹ too small a cohort to determine an association in this clinical phenotype. Our results indicate that the ATXN2 intermediary repeats also influence FTD-ALS risk. The highest association with these repeats was found in patients with familial and sporadic ALS.

Of interest, we detected 10 patients concurrently carrying intermediate (≥ 29) ATXN2 repeats and pathogenic C9orf72 expansion. The occurrence of mutations in more than one gene supports the idea that ALS could be considered an oligogenic disease,^{30,35} with some of these genes displaying mendelian inheritance and a number of other genes acting as disease modifiers by influencing penetrance and pleiotropy. Indeed, in support of this view, C9orf72 repeat expansions have also been found to occur in

Table 4 Distribution of ATXN2 intermediate alleles in patients with (C9orf72⁺) and without (C9orf72[−]) C9orf72 expansions in the different subgroups of phenotypes (p values are not significant in the different phenotypes)

	ATXN2 carriers, n (%)		
	FTD	FTD-ALS	ALS
C9orf72 ⁺	0 (0)	5 (8.8)	5 (2.5)
C9orf72 [−]	2 (1.4)	7 (6.3)	34 (3.6)

Abbreviations: ALS = amyotrophic lateral sclerosis; FTD = frontotemporal dementia.

patients carrying variants in a major ALS- or FTD-causing gene, such as *TARDBP*, *SOD1*, *FUS*, *GRN*, *UBQLN2*, *OPTN*, *VAPB*, and *ANG*.³⁶ In our study, only 1/18 sporadic ALS *ATXN2* carriers had the *C9orf72* expansion (and none of them had a mutation in another ALS gene), suggesting that *ATXN2* by itself is a strong risk factor for ALS. Conversely, 4/16 patients with familial ALS and, most importantly, 5/7 patients with FTD-ALS (3/5 familial and 2/2 sporadic) carried both *C9orf72* and *ATXN2* expansions.

Most interestingly, in the cohort of *C9orf72* carriers, we found the co-occurrence of *C9orf72* and *ATXN2* repeats in patients with ALS and FTD-ALS, whereas it was absent in patients with FTD. These results suggest that *ATXN2* polyQ expansions could act as a strong modifier in FTD and ALS, and, in particular, the presence of the *ATXN2* expansion in the context of a *C9orf72* mutation could drive the clinical phenotype toward the ALS side of the FTD-ALS spectrum.

Furthermore, the concomitance of *ATXN2* and *C9orf72* repeats could influence the age at onset, the survival, and/or the phenotype in FTD-ALS cases, but the number of patients carrying both *ATXN2* and *C9orf72* repeat expansions in the present study ($n = 10$) is insufficient to draw any conclusion at this point. Future studies are also needed to confirm that *ATXN2* intermediary repeats act as a risk and/or modifier factor in the FTD-ALS disease spectrum in the presence or absence of *C9orf72* repeat expansions.

AUTHOR CONTRIBUTIONS

Serena Lattante: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision or coordination. Stéphanie Millecamps: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, obtaining funding. Giovanni Stevanin: drafting/revising the manuscript, acquisition of data. Sophie Rivaud-Péchoux: statistical analysis. Carine Moigneu: analysis or interpretation of data. Agnès Camuzat: analysis or interpretation of data. Sandra Da Barroca: analysis or interpretation of data. Emeline Mundwiller: analysis or interpretation of data. Philippe Couarch: acquisition of data. François Salachas: acquisition of data. Didier Hannequin: acquisition of data. Vincent Meininger: acquisition of data. Florence Pasquier: acquisition of data. Danielle Seilhean: acquisition of data. Philippe Couratier: acquisition of data. Véronique Danel-Brunaud: acquisition of data. Anne-Marie Bonnet: acquisition of data. Christine Tranchant: acquisition of data. Eric LeGuern: acquisition of data. Alexis Brice: acquisition of data, obtaining funding. Isabelle Le Ber: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, obtaining funding. Edor Kabashi: drafting/revising the manuscript, study concept or design, study supervision or coordination, obtaining funding.

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It's Time to Plan for ICD-10, and the AAN Can Help

All health care providers are required to transition to ICD-10 on October 1, 2015. Claims for services performed on or after this date with an ICD-9 code will not be processed and payments will be delayed. The AAN provides information and resources to help you make this a smooth transition, and has partnered with Complete Practice Resources to provide you with an affordable online project management tool to help walk you through each phase of the necessary preparation to ensure you're ready. Learn more at AAN.com/view/ICD10 and start your transition today!